Organic Synthesis
Second Edition

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Preface to the 2nd Edition

The new edition of *Organic Synthesis* has been revised and rewritten from front to back. I want to thank all who used the book in its first edition, and thank you for your patience with its many errors. Every effort has been made to correct those problems. Every chapter in this book was revised before any new material was added. Not only were updated examples used when possible, but new material was added that make this edition reflect current synthetic methodology. In addition to correcting errors and deficiencies, the text has been modified in countless places to improve readability and pedagogy. This new edition contains references taken from more than 5600 journal articles, books, and monographs. Of these references, more than 1200 are new to this edition, and most of them were taken from the literature after 1992. About 50% of all new references were taken from literature published in 1999 or 2000. Many new reactions and topics have been added. New topics include combinatorial chemistry, directed ortho metalation, and metathesis reactions. New reactions include Jacobsen-Katsuki epoxidation, the Baylis-Hillman reaction, the Pauson-Khand reaction, Suzuki coupling, Sonogashira coupling, Tamao-Fleming oxidation, Julia-Colonna epoxidation, Ley oxidation, Danheiser annulation, and others. This edition contains references to over 650 natural products, synthetic targets, or other important molecules. It also contains reference to over 270 named reactions, reagents, or processes. Homework in each chapter has been extensively revised. Most of the homework problems are new, although many from the first edition were retained. New homework problems for the new sections and new reactions are also included. Unlike the first edition, most of the homework problems do not contain leading references for the answers. Therefore, they are true homework and thought problems. The answers to all problems from chapters 1-9, and 11-13 are found in the new and updated *Student Solutions Manual* for this book. As in the first edition, a few leading references are provided for the synthesis problems in chapter 10, but most problems do not have answers. The student is encouraged to discuss any synthetic problem with their instructor.

With the exception of scanned figures, all drawings in this book were prepared using ChemDraw or Chem3D from CambridgeSoft. I thank them for providing the software that made this project possible.

I express my gratitude to those who were kind enough to go through the first edition and supply me with lists of errors. It is not possible to list all those who contributed a brief note or an EMail, but let me thank you here for your help. Special thanks to those who assembled an extensive list of errors, which was very useful in revising this edition. They are Gabriel Tojo (Santiago de Compostella), Paul Juvvik (Kjemish Institutt, Universitetet I Bergen), Paris Georghiou (Memorial Univ. of Newfoundland), David Todd (Juniata College), Phil Hultin (Manitoba), Phil Garner (Case Western), Hugh W. Thompson (Rutgers), and Henri Bekolo.

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Finally, I thank my students, who have provided the inspiration over the years for this book. They have also been my best sounding board, allowing me to test new ideas and organize the text as it now appears. I thank my friends and colleagues who have provided countless suggestions and encouragement over the years, particularly Spencer Knapp (Rutgers), George Majetich (Georgia), and Phil Garner (Case Western Reserve).

A special thanks to my wife Sarah and son Steven, whose patience and understanding made the work possible.

If there are errors, corrections, and suggestions, please let me know by EMail or normal post. Any errors will be posted at

http://orgchem.chem.uconn.edu/home/books/orgsyn2.html

Other useful information that relates to organic synthesis may be found at

http://orgchem.chem.uconn.edu/colleges/orgchem.html

Thank you again. I hope this new edition is useful to you in your studies.

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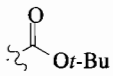
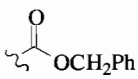
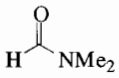
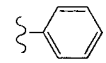
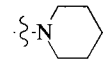
COMMON ABBREVIATIONS

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

Ac	Acetyl	
Acac	Acetylacetonate	
AIBN	*azo-bis*-isobutyronitrile	
All	Allyl	
Am	Amyl	$-CH_2(CH_2)_3CH_3$
aq	Aqueous	
Ax	Axial	
	9-Borabicyclo[3.3.1]nonylboryl	
9-BBN	9-Borabicyclo[3.3.1]nonane	
BINAP	*2R,3S*-2,2'-*bis*-(diphenylphosphino)-1,1'-binapthyl	
Bn	Benzyl	$-CH_2Ph$
Boc	*t*-Butoxycarbonyl	
Bpy (Bipy)	2,2'-Bipyridyl	
Bu	*n*-Butyl	$-CH_2CH_2CH_2CH_3$
Bz	Benzoyl	
CAM	Carboxamidomethyl	
CAN	Ceric ammonium nitrate	$(NH)_2Ce(NO_3)_6$
c-	Cyclo-	
cat.	Catalytic	
Cbz	Carbobenzyloxy	
chap	Chapter(s)	
Chirald	2S,3R-(+)-4-dimethylamino-1,2-diphenyl-3-methylbutan-2-ol	
CIP	Cahn–Ingold-Prelog	
COD	1,5-Cyclooctadienyl	
COT	1,3,5-cyclooctatrienyl	
Cp	Cyclopentadienyl	
CSA	Camphorsulfonic acid	
CTAB	Cetyltrimethylammonium bromide	$C_{16}H_{33}NMe_3^+\ Br^-$

Cy (*c*-C_6H_{11})	Cyclohexyl	
°C	Temperature in Degrees Centigrade	
2D	Two-dimensional	
3D	Three-dimensional	
DABCO	1,4-Diazobicyclo[2.2.2]octane	
d	Day(s)	
dba	Dibenzylidene acetone	
DBE	1,2-Dibromoethane	$BrCH_2CH_2Br$
DBN	1,8-Diazabicyclo[5.4.0]undec-7-ene	
DBU	1,5-Diazabicyclo[4.3.0}non-5-ene	
DCC	1,3-Dicyclohexylcarbodiimide	*c*-C_6H_{13}-N=C=N-*c*-C_6H_{13}
DCE	1,2-Dichloroethane	$ClCH_2CH_2Cl$
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone	
% de	% Diasteromeric excess	
DEA	Diethylamine	$HN(CH_2CH_3)_2$
DEAD	Diethylazodicarboxylate	EtO_2C-N=NCO_2Et
DET	Diethyl tartrate	
DHP	Dihydropyran	
DIBAL-H	Diisobutylaluminum hydride	$(Me_2CHCH_2)_2AlH$
Diphos (**dppe**)	1,2-*bis*-(Diphenylphosphino)ethane	$Ph_2PCH_2CH_2PPh_2$
Diphos-4 (**dppb**)	1,4-*bis*-(Diphenylphosphino)butane	$Ph_2P(CH_2)_4PPh_2$
DIPT	Diisopropyl tartrate	
DMAP	4-Dimethylaminopyridine	
DME	Dimethoxyethane	$MeOCH_2CH_2OMe$
DMF	*N,N'*-Dimethylformamide	
DMS	Dimethyl sulfide	
DMSO	Dimethyl sulfoxide	
dppb	1,4-*bis*-(Diphenylphosphino)butane	$Ph_2P(CH_2)_4PPh_2$
dppe	1,2-*bis*-(Diphenylphosphino)ethane	$Ph_2PCH_2CH_2PPh_2$
dppf	*bis*-(Diphenylphosphino)ferrocene	
dppp	1,3-*bis*-(Diphenylphosphino)propane	$Ph_2P(CH_2)_3PPh_2$
dvb	Divinylbenzene	
e^-	Electrolysis	
EA	Electron affinity	
% ee	% Enantiomeric excess	

EE	1-Ethoxyethyl	EtO(Me)HCO-
Et	Ethyl	$-CH_2CH_3$
EDA	Ethylenediamine	$H_2NCH_2CH_2NH_2$
EDTA	Ethylenediaminetetraacetic acid	
Equiv	Equivalent(s)	
ESR	Electron Spin Resonance Spectroscopy	
FMN	Flavin mononucleotide	
FMO	Frontier Molecular Orbital	
fod	*tris*-(6,6,7,7,8,8,8)-Heptafluoro-2,2-dimethyl-3,5-octanedionate	
Fp	Cyclopentadienyl-*bis*-carbonyl iron	
FVP	Flash Vacuum Pyrolysis	
GC	Gas chromatography	
gl	Glacial	
h	Hour (hours)	
hν	Irradiation with light	
1,5-HD	1,5-Hexadienyl	
HMPA	Hexamethylphosphoramide	$(Me_3N)_3P=O$
HMPT	Hexamethylphosphorus triamide	$(Me_3N)_3P$
^{1}H NMR	Proton Nuclear Magnetic Resonance Spectroscopy	
HOMO	Highest occupied molecular orbital	
HPLC	High performance liquid chromatography	
HSAB	Hard/Soft Acid/Base	
IP	Ionization potential	
i-Pr	Isopropyl	$-CH(Me)_2$
IR	Infrared spectroscopy	
LICA (LIPCA)	Lithium cyclohexylisopropylamide	
LDA	Lithium diisopropylamide	$LiN(i\text{-}Pr)_2$
LHMDS	Lithium hexamethyl disilazide	$LiN(SiMe_3)_2$
LTMP	Lithium 2,2,6,6-tetramethylpiperidide	
LUMO	Lowest unoccupied molecular orbital	
MCPBA	*meta*-Chloroperoxybenzoic acid	
Me	Methyl	$-CH_3$ or Me
MEM	β–Methoxyethoxymethyl	$MeOCH_2CH_2OCH_2$-
Mes	Mesityl	2,4,6-tri-Me-C_6H_2
min	minutes	
MOM	Methoxymethyl	$MeOCH_2$-
Ms	Methanesulfonyl	$MeSO_2$-

MS	Molecular Sieves (3Å or 4Å)	
MTM	Methylthiomethyl	
MVK	Methyl vinyl ketone	$MeSCH_2$-
NAD	Nicotinamide adenine dinucleotide	
NADP	Sodium triphosphopyridine nucleotide	
Napth	Napthyl ($C_{10}H_8$)	
NBD	Norbornadiene	
NBS	*N*-Bromosuccinimide	
NCS	*N*-Chlorosuccinimide	
NIS	*N*-Iodosuccinimide	
Ni(R)	Raney nickel	
NMO	*N*-Methylmorpholine *N*-oxide	
Nu (Nuc)	Nucleophile	
OBs	O-Benzenesulfonate	
Oxone	2 $KHSO_5$•$KHSO_4$•K_2SO_4	
(P) or	Polymeric backbone	
PCC	Pyridinium chlorochromate	
PDC	Pyridinium dichromate	
PEG	Polyethylene glycol	
Ph	Phenyl	
PhH	Benzene	
PhMe	Toluene	
Phth	Phthaloyl	
Pip	Piperidinyl	
PPA	Polyphosphoric acid	
PPTS	*para*-Toluenesulfonic acid	
Pr	*n*-Propyl	-$CH_2CH_2CH_3$
Py	Pyridine	
Quant	Quantitative yield	
Red-Al	$[(MeOCH_2CH_2O)_2AlH_2]Na$	
RT	Room temperature	
sBu	*sec*-Butyl	$CH_3CH_2CH(CH_3)$
sBuLi	*sec*-Butyllithium	$CH_3CH_2CH(Li)CH_3$
s	seconds	
sec	section(s)	

SEM	2-(trimethylsilyl)ethoxymethyl	
SET	Single electron transfer	
Siamyl	*sec*-Isoamyl	$(CH_3)_2CHCH(CH_3)$-
$(Sia)_2BH$	Disiamylborane	
TASF	*tris*-(Diethylamino)sulfonium difluorotrimethyl silicate	
TBAF	Tetrabutylammonium fluoride	n-Bu_4N^+ F^-
TBDMS	*t*-Butyldimethylsilyl	*t*-$BuMe_2Si$
TBHP (*t*-BuOOH)	*t*-Butylhydroperoxide	Me_3COOH
t-Bu	*tert*-Butyl	-CMe_3
TEBA	Triethylbenzylammonium	$Bn(CH_3)_3N^+$
TEMPO	Tetramethylpiperidinyloxy free radical	
TFA	Trifluoroacetic acid	CF_3COOH
TFAA	Trifluoroacetic anhydride	$(CF_3CO)_2O$
Tf (OTf)	Triflate	-SO_2CF_3 (-OSO_2CF_3)
$ThexBH_2$	Thexylborane (*tert*-hexylborane)	
THF	Tetrahydrofuran	
THP	Tetrahydropyran	
TMEDA	Tetramethylethylenediamine	$Me_2NCH_2CH_2NMe_2$
TMS	Trimethylsilyl	-$Si(CH_3)_3$
TMP	2,2,6,6-Tetramethylpiperidine	
Tol	Tolyl	4-$(Me)C_6H_4$
TPAP	Tetrapropylperruthenate	
Tr	Trityl	-CPh_3
TRIS	Triisopropylphenylsulfonyl	
Ts(Tos)	Tosyl = *p*-Toluenesulfonyl	4-$(Me)C_6H_4$
UV	Ultraviolet spectroscopy	
X_c	Chiral auxiliary	

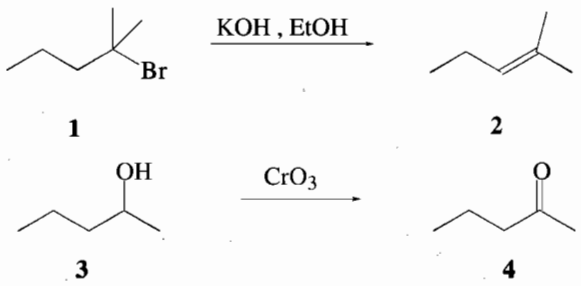
CHAPTER 1

RETROSYNTHESIS, STEREOCHEMISTRY, AND CONFORMATIONS

1.1. INTRODUCTION

Where does one begin a book that will introduce and discuss hundreds of chemical reactions? To synthesize a complex organic molecule, many reactions must be used, and the strategy used for that synthesis must consider different reaction types, as well as how they work. For this reason, a brief introduction to synthetic planning is a useful place to begin. A full discussion of strategies for total synthesis will not be introduced until chapter 10, but the fundamental approach can be useful in understanding how reactions are categorized.

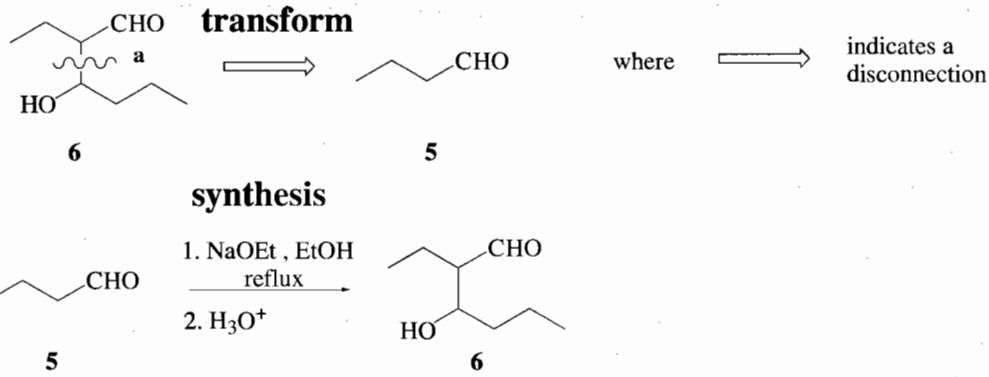
The total synthesis of complex natural products usually demands a thorough knowledge of reactions that form carbon–carbon bonds as well as those that change one functional group into another. Examination of many syntheses, of both large and small molecules, reveals that building up a carbon skeleton by carbon–carbon bond-forming reactions cannot be done successfully unless all aspects of chemical reactivity, functional group interactions, conformations, and stereochemistry are well understood. The largest number of actual chemical reactions in a synthesis, however, are not those that make carbon–carbon bonds but rather those that involve manipulation of functional groups.



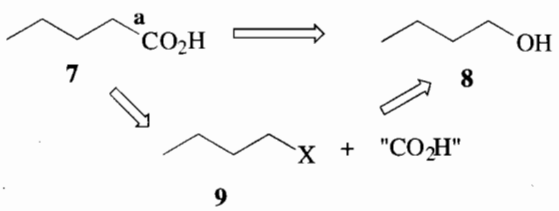
1 **2** **3** **4**

If we change one functional group into another, we define this process as a **functional group interchange** (FGI). Simple examples are the loss of H and Br from 2-bromo-2-methylpentane (**1**) to form 2-methyl-2-pentene (**2**) and oxidizing the alcohol unit in 2-pentanol (**3**) to the carbonyl unit in 2-pentanone (**4**). These reactions can be contrasted with a reaction that brings two reactive fragments together to form a new bond between two carbon atoms, as in the **aldol addition** where two molecules of butanal (**5**) condense under basic conditions to give **6**. carbon–carbon bond-forming reactions such as this one usually require manipulation of key functional groups, or incorporation of a proper functional group prior to the bond-forming reaction, which is one reason that more functional group exchange reactions are required relative to those involved in actually making a carbon–carbon bond. Another reason is that many functional groups are structural units of the molecule being synthesized.

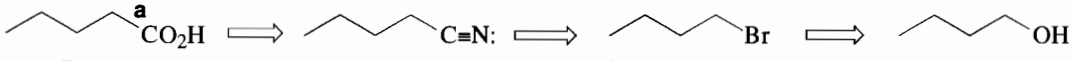
It is common nowadays to show the relationship of two molecules in a synthesis by using a device known as a **transform**. A **transform** is defined by Corey and co-workers[1] as: "the exact reverse of a synthetic reaction to a target structure". The **target structure** is the final molecule one is attempting to prepare. By using the **aldol addition** just mentioned (see sec. 9.4.A) as an example, the synthetic reaction is conversion of butanal (**5**) to hydroxyaldehyde (**6**). The transform for this synthetic step is, therefore, **6** ⇒ **5**. Inspection of **6** and **5** reveals that mentally breaking the highlighted bond (bond ***a***) in **6** (represented by the squiggly line) leads to simplification of the target structure and in this process bond *a* is said to be **disconnected**. An elementary disconnection approach must become an integral part of how one thinks about molecules and that is the real purpose of placing it at the beginning of this book. The focus here, however, is on how molecules are put together. How does the disconnection approach assist us now? Understanding why bond *a* is important has to come from a thorough knowledge of the chemical properties of Compound **6**. When we disconnect bond *a* , we eventually want to make that bond by a chemical reaction. Therefore, if we understand the molecular characteristics of bond *a* in **6** that led us to disconnect it, we will gain information about the chemical reactions required to form it.



Pentanoic acid (**7**) is a simple target that illustrates the utility of the disconnection approach. Disconnection of the carbon–carbon bond marked *a* generates 1-butanol (**8**) as the precursor (the starting material). Analysis of the acid and the alcohol reveals that a change in oxidation state is required, as well as extension of the carbon chain by one carbon. Of the four carbon–carbon bonds in target **7**, bond *a* must be used to attach the carbonyl to the starting material **8**. Disconnection of bond ***a*** leads to the simplified structure **9** and the CO_2H (carboxyl) fragment, which is not a real molecule. These two structures are termed **disconnect products** but **9** contains an unspecified X group, which must be a reactive functional group and could be hydroxyl (as in **8**). The carboxyl fragment does not exist and is considered to be a **synthetic equivalent** for a real but unknown



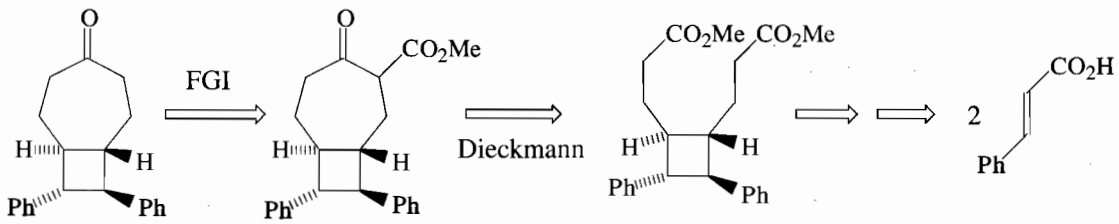
fragment. A synthetic equivalent in this sense is a molecular fragment that reacts to give an actual fragment in a real molecule. Both carbon dioxide (CO_2) and cyanide (C≡N) are reactive fragments that can be converted to CO_2H. Working backward in this manner is termed **retrosynthetic analysis** or **retrosynthesis**,[2] defined by Corey as "a problem-solving technique for transforming the structure of a synthetic target molecule to a sequence of progressively simple materials along a pathway which ultimately leads to a simple or commercially available starting material for chemical synthesis."[2]



7 **8**

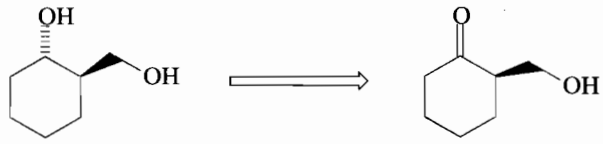
One solution to this synthetic problem is to incorporate a nitrile. It is readily hydrolyzed to an acid and the cyanide (C≡N) group reacts with primary halides via second order nucleophilic substitution (S_N2, see sec. 2.7.A). We first ask if the nitrile can be produced directly from the alcohol starting material. Assume the answer is no, but conversion of the alcohol to a halide or the corresponding *p*-toluenesulfonate ester allows an S_N2 reaction to produce the nitrile. Conversion of an alcohol to a halide is a functional group interchange (FGI) reaction (see sec. 2.8.A). The immediate retrosynthetic precursor of the nitrile is, therefore, a bromide or tosylate and the alcohol starting material is the retrosynthetic precursor. This retrosynthetic map also describes the reactions necessary for the real synthesis starting from **7** but reagents must be added to complete the synthesis. What does this tell us? Analyzing the key bond for disconnection in the target led to the conclusion that the synthesis required a carbon–carbon bond-forming reaction as well as a FGI. We chose the cyanide reaction because the S_N2 process is simple and high yielding in most cases, and the C—OH → C—Br transformation is also well known. Thinking about the synthesis and disconnections led us to analyze and understand reactions, which is the reason why we begin this book with simple synthetic analysis.

When we ask the question of how **7** is prepared from **8**, we are forced to examine the library of reactions that form carbon–carbon bonds as well as those reactions which prepare and interchange functional groups. In other words, it forces a review of organic chemistry. Other important concepts in organic chemistry must also be brought to bear on the problem, including stereochemistry and conformational theory.



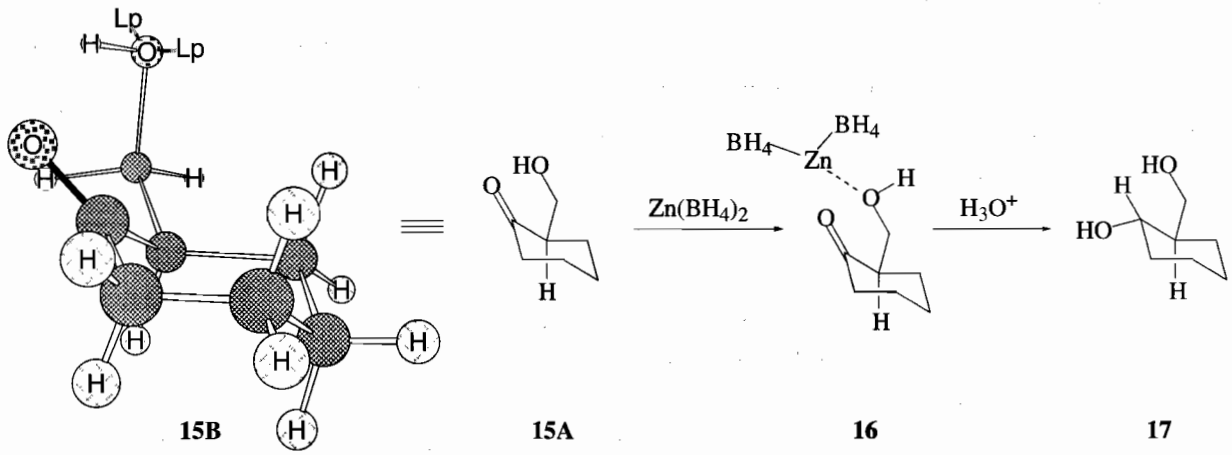
10 **11** **12** **13**

The importance of stereochemistry is illustrated by Corey's disconnection sequence **10**.⇒ **11** ⇒ **12** ⇒ **13**.[3] The second transform involves a **Dieckmann cyclization** (see sec. 9.4.B.ii), and several steps are required to prepared **12** from **13**. Focus your attention on the stereochemical relationship of the various groups and of the ring juncture. We must not only consider methods that make bonds, but also those that form the bond with control of the relative and absolute stereochemistry.



14 **15A**

A third important aspect of organic reactions can be found in the transform **14** ⇒ **15A**. Why does this transform lead to the relative stereochemistry (trans) shown in **14**? The proper relationship of the functional groups must be determined and this is often very difficult with the two-dimensional (2D) structures shown. A three-dimensional representation (3D) of these reactive species will usually give a better understanding, as seen



15B **15A** **16** **17**

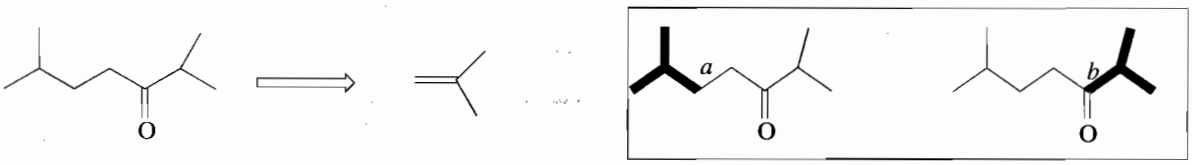
with **15B**, the 3D drawing of **15A** (produced by the computer program Chem3D™; Lp indicates a lone pair of electrons).[4] Representation **15A** provides fewer details than the 3D model. Inspection of both **15B** and **15A** shows the hydroxyl group is positioned on one side of the carbonyl. If a chelating metal such as zinc is used with the reducing step (zinc borohydride, see sec. 4.4.B), coordination with the hydroxyl (**16**) can deliver hydride primarily from the same face as the CH_2OH unit, leading to the observed trans stereochemistry in **17**. In this example, the **conformation** (3D shape) of the molecule is important to the analysis since it provided a model to understand the stereochemistry of the final product.

We will review these three important factors: (1) disconnection and retrosynthesis, (2) stereochemistry, (3) conformational analysis. The aim of this presentation is not to formally introduce synthesis (synthetic theory will be presented in chapter 10)[5] but to focus attention on concepts that help us understand reactions.

1.2. THE DISCONNECTION PROTOCOL

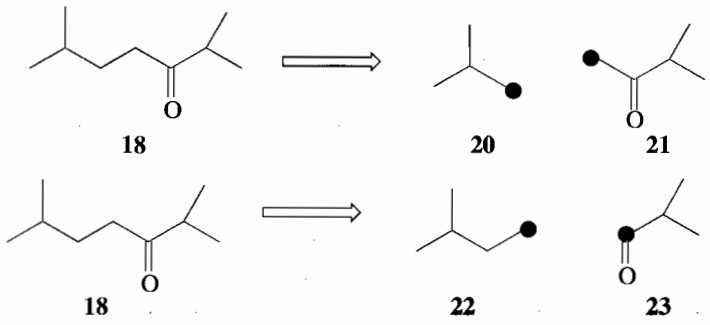
When introducing the disconnection method and synthesis, making the correct disconnection often seems more important than the chemical reactions and concepts required to form the disconnected bond. In reality, the disconnection is dictated by the ability to form the bond in the context of stereochemistry and selectivity, not the other way around. The synthesis of organic molecules dates to the nineteenth century, but the work of

Perkin, Robinson and others in the early twentieth century demonstrated the importance of synthetic planning.[1] In the 1940s and 1950s, Woodward, Robinson, Eschenmoser, Stork and others clearly showed how molecules could be synthesized in a logical and elegant manner. In the 1960s, Corey identified the rationale behind his syntheses, and such logical synthetic plans (termed retrosynthetic analyses) are now a common feature of the synthetic literature.[2] The disconnection approach is now used to teach synthesis and Warren has several books that describe this approach in great detail.[6] Several different strategies for the synthesis of organic molecules are available (see chapter 10) and all are useful. When these strategies are applied to a first synthesis in an introductory course, the most critical issue raised after a disconnection is what to do with the disconnect products. All disconnection approaches assign priorities to bonds in a molecule and disconnect those bonds with the highest priorities, as with Corey's strategic bond analysis (see sec. 10.5).[1,5] Smith described a simple method where the priorities are based only on the relative ability to chemically form the bond broken in the disconnection.[7]



18A **19** **18B** **18C**

In a typical introductory Organic Chemistry course, there are two fundamental types of synthesis problems. In the first, both the starting material and the target are specified. In the second, only the final target is given and the starting material must be deduced by the synthetic chemist; this is usually a more difficult problem. We can illustrate everything we need with the first type of problem and will delay discussion of the second until Chapter 10. In the disconnection **18** ⇒ **19**, 2-butene is the designated starting material, which means that the target (**18**) is to be synthesized from 2-methylpropene (**19**). The four carbons of **19** must be identified in **18**, since ***this will define the carbons that must be disconnected for the synthesis***. The presence of two methyl



18 **20** **21**

18 **22** **23**

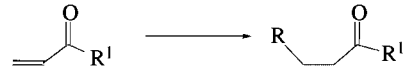
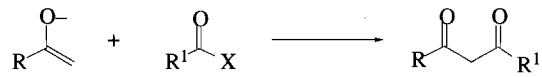
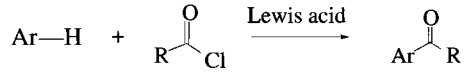
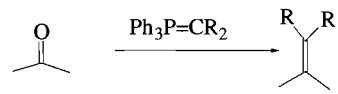
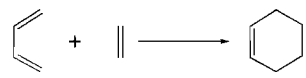
groups in **19** limits the possibilities so that there are two different locations where the four carbons in isobutene may be found (see **18B** and **18C**). If we choose the pattern shown in **18B**, this dictates that bond *a* must be disconnected. If we choose the pattern in **18C**, then bond *b* must be disconnected. Disconnection of bond *a* in **18B** leads to two fragments (**disconnect products**), **20** and **21**. Similarly, disconnection of bond *b* in **18C** leads to disconnect products **22** and **23**. Both disconnections must be considered, but structures **20–23** are not

real molecules so we cannot evaluate the relative merit of each disconnection using these fragments. We must consider a real molecule and a real reaction that will be used to form the disconnected bond in the synthesis. To solve this dilemma, two assumptions will be made. (1) The key bonds will be formed by a small subset of reactions and (2) the bonds will be made by reactions involving ionic intermediates.

The first assumption is based on the observation that a typical introductory organic chemistry course will present the carbon–carbon bond-forming reactions shown in Table 1.1.[7] The second assumption is partly based on the observation that all reactions in the table except entry 10 (the **Diels-Alder reaction**, see sec. 11.4.A) involve ionic or highly polarized intermediates. Based on this, it is reasonable to assume that the disconnections generated from **18** will lead to ionic or polarized intermediates and the new carbon–carbon bond will be formed by one of the reactions found in Table 1.1. We can now convert each disconnect product (**20**-**23**) into an ionic fragment.

The concept of nucleophilic and electrophilic atoms in ionic and polarized intermediates is well known. Polarized bond notation such as $C^{\delta+}$—$Br^{\delta-}$ and $C^{\delta-}$—$Li^{\delta+}$ are commonly used in describing the reactivity of these bonds. The polarizability of various atoms and molecules is also reflected in hard and soft acid and base

Table 1.1 carbon–carbon bond-forming **reactions**

1. Cyanide	R-X + C≡N$^-$ ⟶ RC≡N
2. Acetylides	R-X + R'C≡C$^-$ ⟶ R-C≡C-R'
3. Organometallic reactions	(a) RM + R^1-X ⟶ R-R^1
M = MgX, Li, ZnX,...	(b) RM +
	(c) RM +
4. Organocuprate reactions	(a) R_2CuLi + R'X ⟶ R—R'
	(b) R_2CuLi + 
5. Enolate alkylation	
6. Enolate condensation	
7. Friedel–Crafts acylation	
8. Friedel–Crafts alkylation	Ar—H + R—X ⟶ (Lewis acid) Ar—R
9. Wittig reaction	
10. Diels–Alder cyclization	

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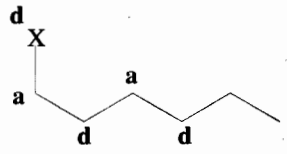
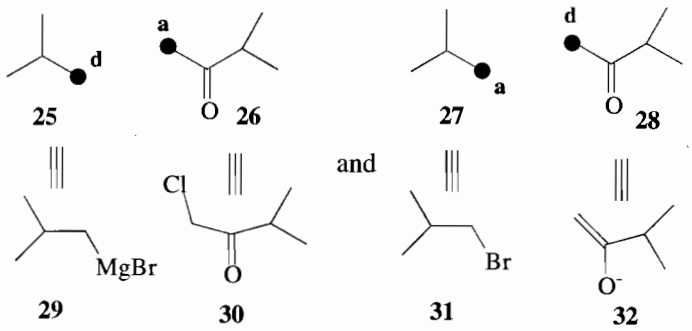
(HSAB) theory (see sec. 2.4).[8] Based on structure **24,** Seebach formalized a bond polarization model.[9] The sites marked d in **24** represent *donor* sites or *nucleophilic* atoms. The sites marked a are *acceptor* sites and correspond to *electrophilic* atoms. If X is oxygen or nitrogen, for example, donation of two electrons from these nucleophilic atoms (X^- or $X^{\delta-}$) to an electrophilic carbon (cation or δ^+ carbon) will generate a C—X bond. Bond polarization induced by the heteroatom extends down the carbon chain due to the usual inductive effects that are a combination of through-space and through-bond effects.[10] The electrophilic carbon adjacent to X (C1) is designated C^a (an acceptor atom) since proximity to the electronegative atom (X) induces the opposite polarity. Similarly, C2 is a donor atom (C^d), but weaker than X (this carbon is further away from the electrons which induce the bond polarization), and C3 is a weak acceptor atom. As a practical matter, the effect is negligible beyond C4 and will be ignored.



24

If this protocol is applied to disconnect fragments **20** → **23**, either carbon at the point of disconnection can be assigned as a donor (d) or an acceptor (a), giving four different possibilities. Disconnect products **20** and **21**, for example, become **25** or **26** and **27** or **28**, respectively. Fragments **25** → **28** are still not real molecules, and another step is required before the best donor–acceptor pair can be chosen; each fragment must be correlated with a synthetic equivalent. Table 1.2[7] provides a list of common synthetic equivalents, leading to a modified definition of **synthetic equivalent**, which is a molecular fragment that is equivalent to a real molecule

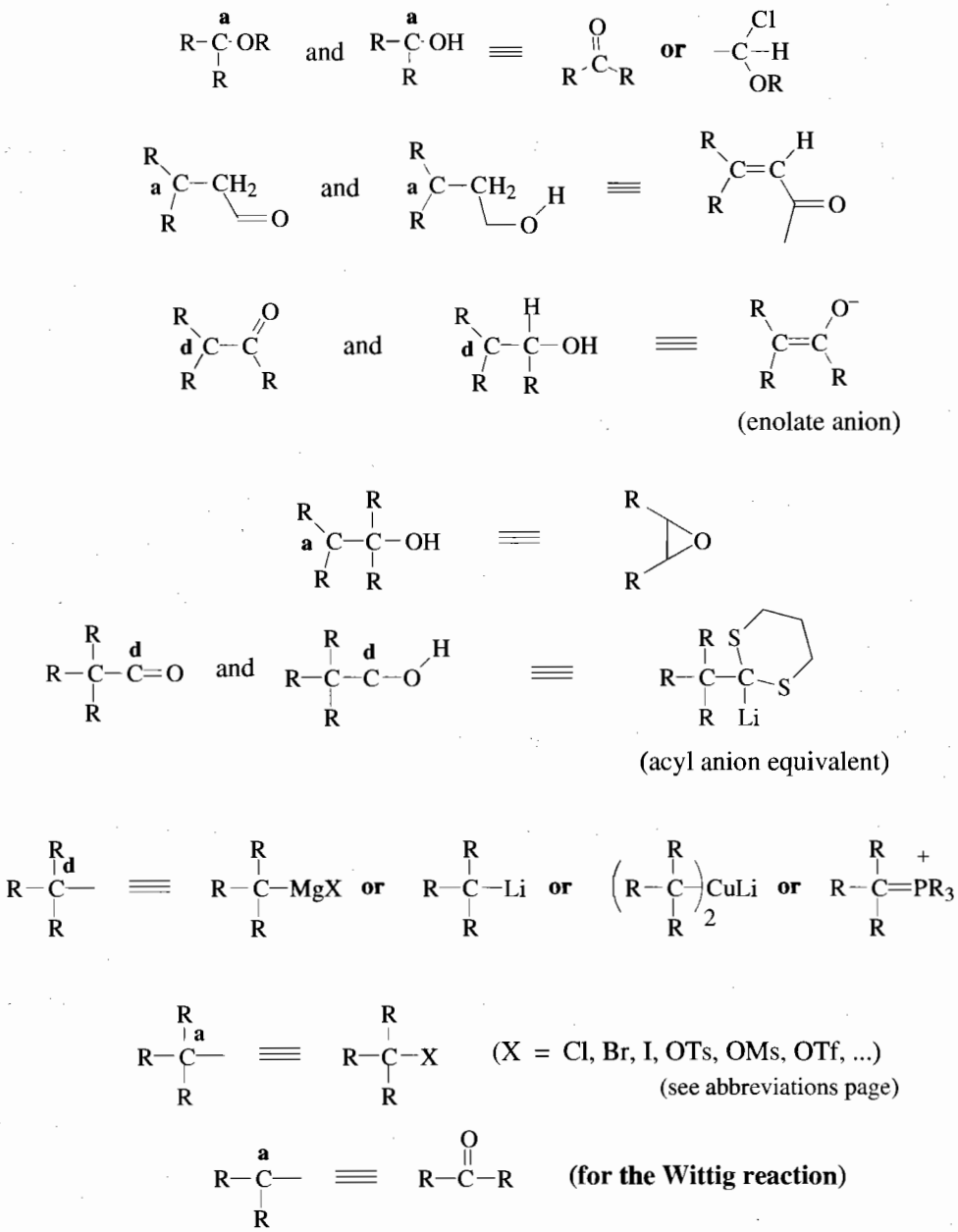


25 **26** **27** **28**

29 **30** **31** **32**

by virtue of its identical chemical reactivity.[11] A C^d site, for example, is equivalent to the $C^{\delta-}$ of a Grignard reagent (see sec. 8.4) and a C^a site is equivalent to the electrophilic carbon on an alkyl halide. Each synthetic equivalent in Table 1.2 is based on a S_N2, first order nucleophilic substitution (S_N1) or nucleophilic acyl addition reaction, which are ionic in nature. Using Table 1.2, fragment **25** is the equivalent of a Grignard reagent, **29** (an organocuprate such as $[Me_2CHCH_2]_2CuLi$ can also be used - see sec. 8.7.A). The equivalent of its partner (fragment **26**) is α-chloroketone **30**. Similarly, the synthetic equivalent of **27** is bromide, **31** (another halide can be used) and the equivalent of **28** is an enolate anion, **32** (see sec. 9.2, 9.3). In the actual synthesis, **29** will react with **30** and **31** will react with **32**, and both reactions will produce **18**. Since it is often

Table 1.2. Common synthetic equivalents for disconnect products



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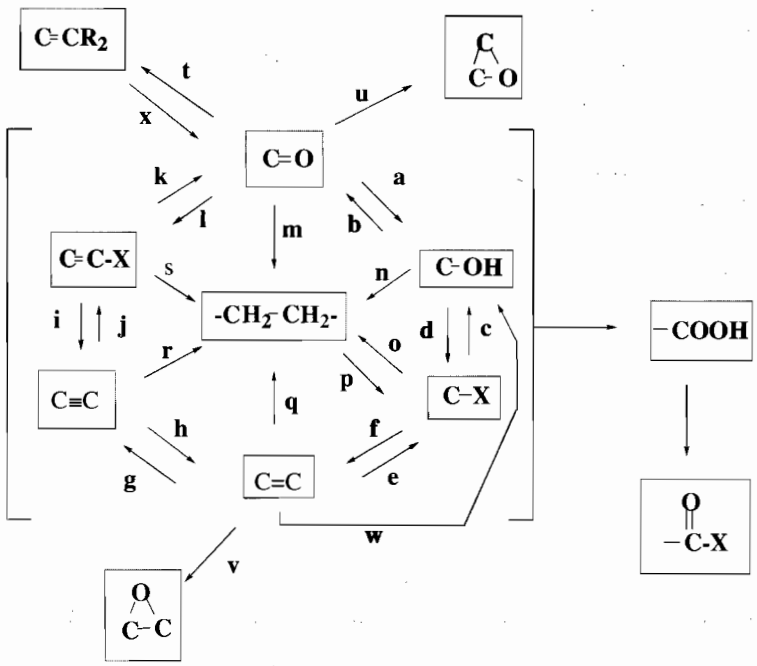
difficult to handle and prepare α-chloroketones, the enolate alkylation reaction of **31** with **32** is probably preferred. Bromide **31** is derived from the 2-methylpropene starting material, but the functional group must be modified. To accomplish this, the chemical relationship of C—C—Br and C=C must be known, that is, how a halide can be chemically transformed into an alkene and vice versa. Figure 1.1[7] provides a functional group reaction wheel that shows how functional groups are interconvertible by known chemical pathways. It is therefore reasonable that an alkene and a halide are chemically related, which means that in a disconnect

product either the halide or the alkene functional group could be incorporated since one can easily be converted to the other at the appropriate time. Similar analysis of disconnect fragments **22** and **23**, but different reactive fragments will be generated, giving a new synthesis.

In most undergraduate organic chemistry textbooks, functional groups are treated as separate entities and the relationship of one functional group to another is sometimes difficult to see. Figure 1.1[7] provides a visual reminder of these relationships, which are often essential to completion of a total synthesis. In the context of this chapter, it illustrates chemical relationships that can be used to understand functional group interchange reactions. A functional group interchange can represent the relationship between a bromide and an alkene

Figure 1.1. Functional group exchange reaction wheel. A visual reminder of the interconvertibility of functional groups.



a. $LiAlH_4$ or $NaBH_4$ or H_2/cat

b. CrO_3

c. $NaOH/H_2O$ or i. PPh_3, RCO_2^-, $MeO_2C\text{-}N{=}N\text{-}CO_2Me$ ii. OH^- iii. H_3O^+ (the Mitsunobu reaction)

d. PCl_5, $SOCl_2$ (X = Cl); PBr_3 (X = Br); i. NaH ii. RX (X = OR); i. PBr_3 or RSO_2Cl ii. K-phthalimide; hydrolysis or NaN_3; H_2/cat. ($X = NH_2$)

e. HX

f. $NaOH/H_2O$ or RO-/ROH

g. i. Br_2 ii. $NaNH_2$

h. H_2/cat or $Na/NH_3/EtOH$

i. $NaNH_2/NH_3$

j. H X

k. H_3O^+

l. PCl_5

m. N_2H_4/KOH or Zn(Hg)/HCl

n. i. RSO_2Cl ii. $LiAlH_4$ (only one carbon reacts)

o. $LiAlH_4$ or H_2/cat.

p. $X_2/h\nu$ or heat

q. H_2/cat

r. 2 H_2/cat

s. excess H_2/cat.

t. $Ph_3P{=}CR_2$

u. $Me_2S^+—CH_2^-$

v. RCO_3H

w. i. B_2H_6 ii. $NaOH/H_2O_2$ or i. $Hg(OAc)_2$ ii. $NaBH_4$

x. i. O_3 ii. Me_2S or H_2O_2

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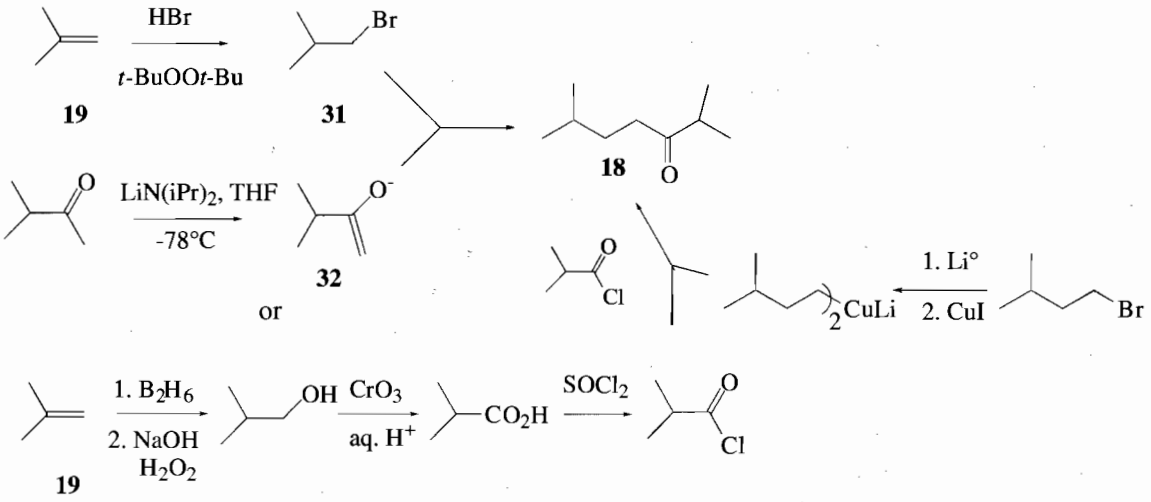
(C-C-Br ⇒ C=C). In the actual synthesis, the required reaction is the reverse of this retroreaction.. It is also possible to write a functional group exchange based on the alkene as C=C ⇒ C—C-Br.

It is important to emphasize that Figure 1.1 is *not* intended as a device to memorize specific reactions, although typical examples are shown. This figure is intended to introduce with the idea of using various functional groups in a synthesis without being distracted by the different forms of disconnect products.



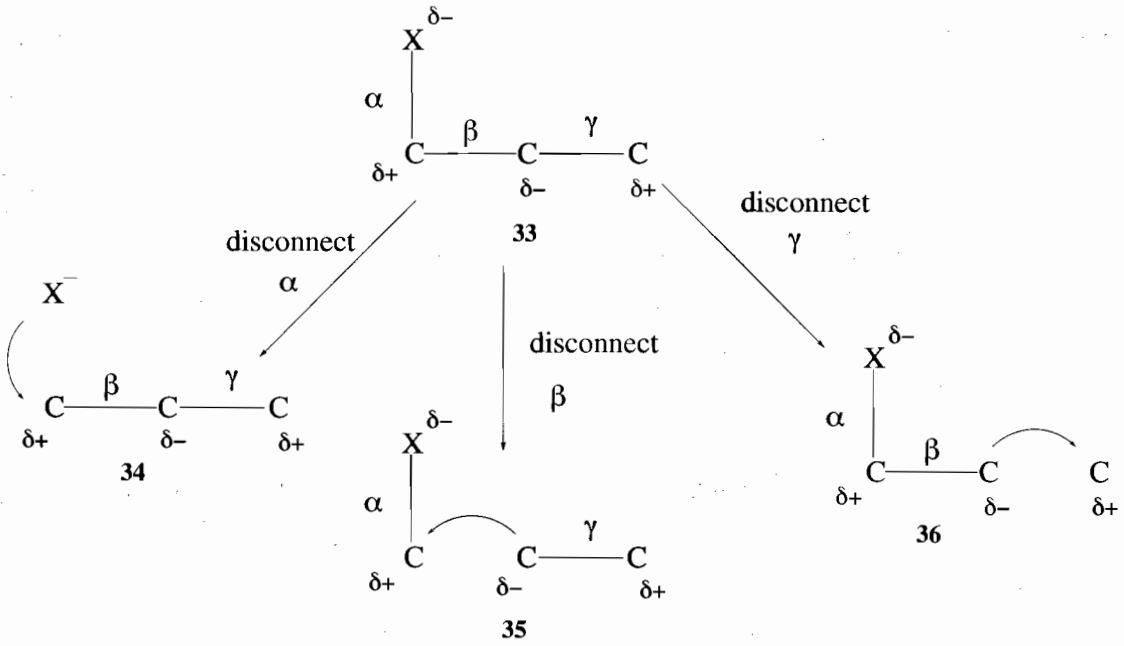
Synthetic sequences for *both* disconnections *a* and *b* are shown. The best route is probably not the one discussed but rather the first one shown in the diagram, which involves conversion of **19** to 1-bromomethyl-propane and reaction with enolate **32** (see sec. 9.2, 9.3.A) derived from 3-methyl-2-butanone. This synthesis is considered to be better than the second one shown (based on disconnection *b*), since it involves simpler reagents and is shorter (fewer chemical steps). The synthetic chemist must make the choice as to which is best, however, based upon his or her own experience and goals. The best route is a subjective judgment, although it usually makes more sense to follow a short and simple route rather than a long and complex one.

1.3. BOND PROXIMITY AND IMPLICATIONS FOR CHEMICAL REACTIONS

How is the synthetic analysis just presented related to a study of chemical reactions? In all of these disconnections, we converted the disconnect products to actual compounds so we could make predictions about which chemical reactions might work. In all cases, one of two bonds was disconnected: the bond connected to the functional group or the one next to it. We can use these observations to understand what reaction types are important for making C—C bonds. From Figure 1.1, it is clear that many functional groups are chemically related. We can use this information to understand chemical reactions that convert one functional group into another.

When a functional group (X) is attached to a carbon atom, the bond polarity is synthetically important out to about the third bond, as indicated in **24**. If we make the *assumption* that most reactions involve ionic intermediates or highly polarized species, then three bonds become very important; the C-X bond (called the α

bond), the adjacent one (the β bond), and the γ bond, as seen in **33**. If we disconnect the α bond we can make it by direct attack of an X group (where X is an heteroatom) on a suitably functionalized carbon, which is illustrated by **34**, where a nucleophilic X group attacks the electrophilic carbon. A simple example is the reaction of azide ion (N_3^-) with 1-iodopropane to give 1-azidopropane. If we disconnect the β bond we obtain **35**, where the natural bond polarization suggests a reaction in which a nucleophilic carbon species attacks the electropositive carbon of the C—X unit. If we modify C—X to become a carbonyl, then the addition of a Grignard reagent to an aldehyde fits this description. Finally, disconnection of bond γ leads to **36**. The carbon atom two removed from X is nucleophilic, and if we again manipulate C—X to be C=O, then this is an enolate anion reacting with an electrophilic species such as iodomethane.



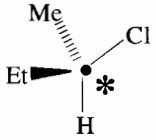
The point of this section is to show how disconnection of generic molecules can be based on natural bond polarization characteristics. Either directly or with manipulation, it offers clues to a variety of common reactions, which is important not only for planning a synthesis, but for understanding how chemical reactions work. This general theme will be elaborated in many chapters to follow.

1.4. STEREOCHEMISTRY

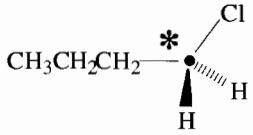
The concept of chirality and absolute configuration is introduced early in undergraduate organic courses. A brief review of elementary concepts will be discussed for simple problems and then applied to larger and more complex molecules in later chapters. This section is intended as a review, and it is assumed the reader has some familiarity with the concepts.

The type of compounds to be discussed in this section must be defined. In one comparison, chlorides **37** and **38** have the same empirical formula but they are clearly different molecules. They are isomers, that is:

two or more molecules that have the same empirical formula. Likewise, cyclopentane and 1-pentene have the same empirical formula (C_5H_9Cl). They are different molecules (see the different carbon marked *) and different chemical types, but they are also isomers. The term isomer does not adequately characterize the relationship between **37** and **38**. They clearly have a closer relationship than 1-pentene and cyclopentane. The term used to define the relationship between **38** and **37** is **regioisomer**: that is, two or more molecules with the same empirical formula but with a different attachment of the atoms (different connectivity).



37

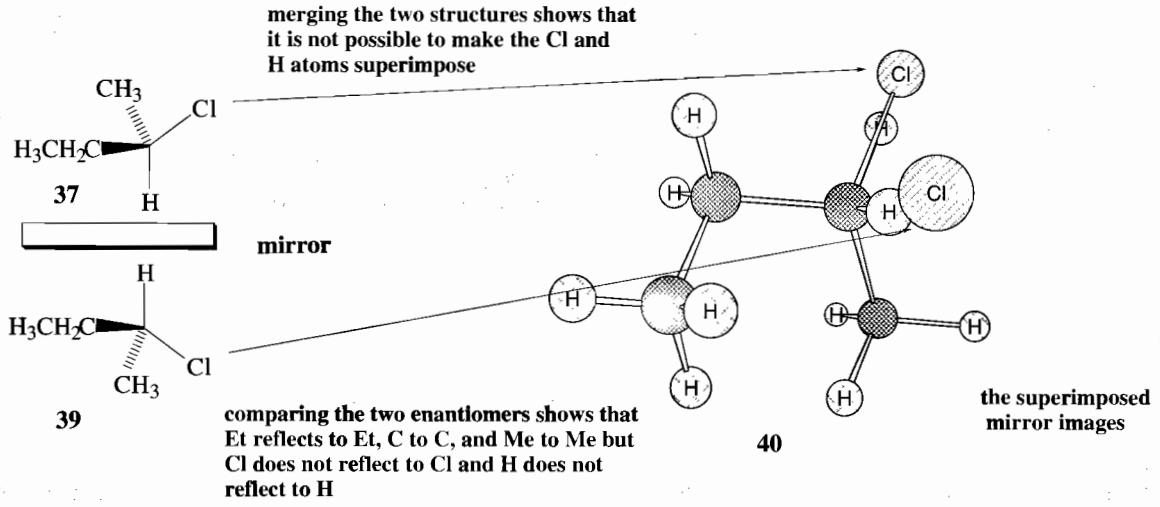


38

Another type of isomerism occurs when two molecules have the same empirical formula and also have the same connectivity of atoms but are different molecules. They differ only in the relative spatial positions of the atoms and are called **stereoisomers**.[12] This section will discuss types and properties of stereoisomers.

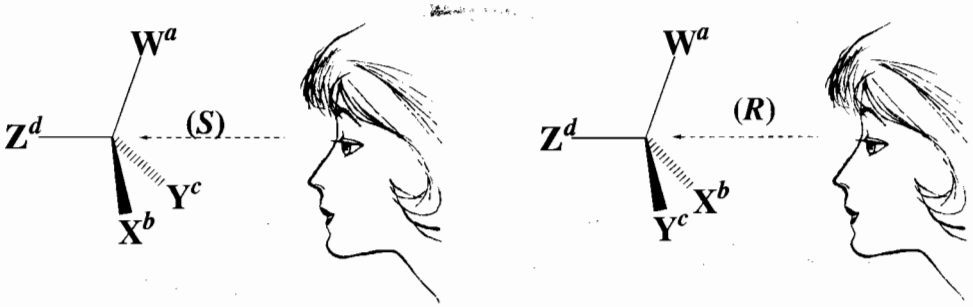
1.4.A. Absolute Configuration in Chiral Nonracemic Molecules

When an atom is bound to four different atoms or groups in a tetrahedral arrangement, that atom is said to be **stereogenic** or chiral. The indicated carbon (C*) in 2-chlorobutane (**37**) is a stereogenic center. The C* in **38** is not stereogenic, since that carbon has two identical atoms (H) attached to it. Why is identification of C* in **37** as a stereogenic center important? The answer is apparent when the mirror image of **37** is drawn (**39**) by reflecting the Cl of **37** to Cl in **39**. Similarly, hydrogen reflects to hydrogen, methyl to methyl, and ethyl to



ethyl and we obtain the two molecules shown. They are ***not superimposable*** by any rotation of bonds or positioning of the molecules and this means that they are different molecules. More precisely, the molecules have no symmetry (they are asymmetric),[13] as can be seen in 3D drawing **40**, [4] that attempts to superimpose **37** and **39**. It is clear that while the Me and Et groups superimpose in **40**, the Cl and H atoms do not. You can confirm this for yourself with any model kit by making both enantiomers and trying to make all groups

superimpose. They do not! Molecules **37** and **39** are different molecules but they are clearly isomers, and they are closely related since they are mirror images. They are not regioisomers because the connectivity of atoms is the same in each molecule. These two molecules are **stereoisomers** (molecules that differ in their spatial arrangement of atoms but have the same point of attachment).[12] Chlorides **37** and **39** are further distinguished as a special type of stereoisomer called **enantiomers**, that is, stereoisomers that are nonsuperimposable mirror images. If a structure and its mirror image are superimposable by rotation or any motion other than bond making and breaking, then they are identical (a single molecule and not enantiomers—**38** is an example). Make a model of **38** and its mirror image and you will find that they are superimposable. When molecules contain more than one stereogenic center, diastereomers (a new type of stereoisomer) will be present (to be discussed in sec. 1.4.B).



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Since **37** and **39** are different molecules, we must be able to identify each with a unique name, and this requires a specialized nomenclature system. The method used is the (*R/S*) system, which employs a set of priority rules developed by Cahn, Ingold, and Prelog.[14] In this system each atom attached to the stereogenic center is assigned a priority (***a*** to ***d***, where *a* is the highest priority atom and *d* is the lowest priority atom). Using the **steering wheel model** (see below) the viewer positions the molecule in such a way that one can sight down the C*-Z^d bond, as shown. An imaginary line $a \rightarrow b \rightarrow c$ is drawn and inspected to see if it rotates around the wheel clockwise (right) or counterclockwise (left). If the $a \rightarrow b \rightarrow c$ sequence is clockwise, the enantiomer is assigned the R configuration. Conversely, if it is counterclockwise, the enantiomer is assigned the (*S*) configuration. When applying this model, the molecule *must* be rotated so that *d* is Z^d prior to sighting down the C*—Z^d bond. Several different molecular representations are shown below, along with the correct orientation for determining the (*R/S*) configuration.

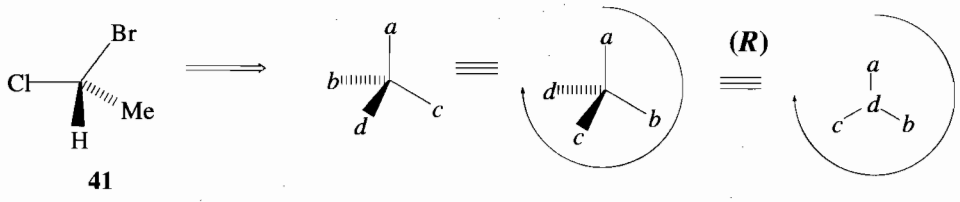
Determining the relative priority (*a* to *d*) is accomplished by a series of rules, the so-called **Cahn–Ingold–Prelog (or CIP) selection rules.**[16,14,15]

1. Atoms with a higher atomic number precede atoms of lower atomic number

O > N > C > H

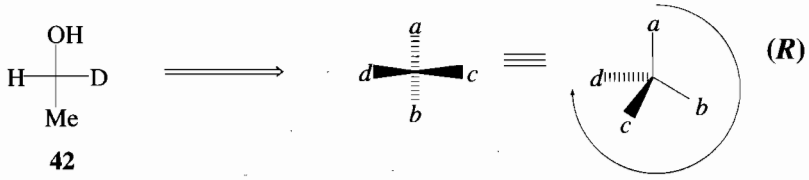
2. Isotopes with a higher mass number precede isotopes of lower mass number

This rule applies to isotopes such as tritium, deuterium and protium ($^3H > ^2H > ^1H$).



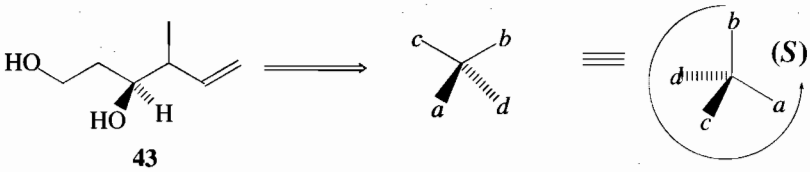
41

These two rules are illustrated first by 1-bromo-1-chloroethane (**41**), where Br > Cl > Me > H and the $a \rightarrow b \rightarrow c$ rotation is clockwise, giving an (*R*) configuration. Similarly, in 1-deuterioethanol (**42**) the priority is O > C > D > H and the $a \rightarrow b \rightarrow c$ sequence is also clockwise for an (*R*) configuration.



42

A problem arises when two of the atoms attached to C* are the same. In 4-methylhex-5-en-1,3-diol (**43**), the priorities of the atoms attached to C* are O > C ≈ C > H. Rules 1 and 2 do not allow us to distinguish the two carbon atoms. A new rule is required to solve this problem.



43

3. When the highest priority atoms are identical, compare the number of priority atoms at the first point of difference to distinguish them.

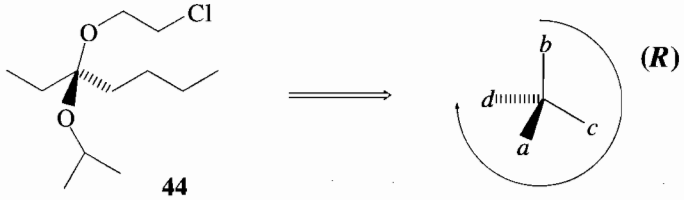
Generic priorities by this rule are: $C^{CCC} > C^{CCH} > C^{CHH} > C^{HHH}$ and

$C^{OOO} > C^{OOC} > C^{OCC} > C^{CCC}$

Examination of **43** reveals that the two carbon atoms attached to C* are C^{CHH} and C^{CCH}. The secondary carbon has a higher priority than the primary carbon. The absolute configuration of **43** is (*S*). Another example is the ketal, **44**. The priority analysis is

[C*—O—C^{CHH} = *b*], [C*—O—C^{CCH} = *a*] and

[C*—C^{CHH}—C^{HHH} = *d*], [C*—C^{CHH}—C^{CHH} = *c*] and the absolute configuration of **4** is (*R*).



44

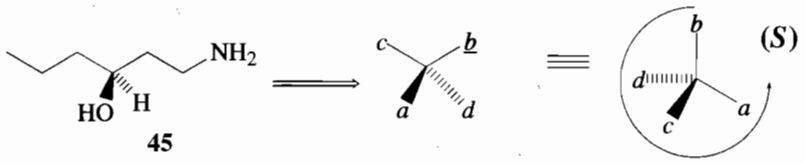
There is another problem in example **44**. As one proceeds down the carbon chain, the carbons (Et and Bu groups) attached directly to C* were identical (no point of difference) and the chain was followed until a point

of difference was reached (C^{HHH} vs. C^{CHH}). Similarly, the oxygen chains were identical at oxygen and the point of difference was reached at the carbon attached to oxygen ($O—C^{CHH}$ vs. $O—C^{CCH}$), leading to a formalized general rule.

4. When the first point of difference contains two or more identical atoms, proceed atom by atom down the highest priority chain to the next point of difference and apply rules 1, 2 or 3 to determine the priority.

Another example where one must proceed down a chain is 3-hydroxy-1-aminohexane (**45**), which shows the following priority for atoms attached to C*: O (*a*) > C ≈ C > H (*d*). Comparing the two chains gives

$[C^*—C^{CHH}—C^{NHH} = b]$ and $[C^*—C^{CHH}—CH^{CHH} = c]$



45

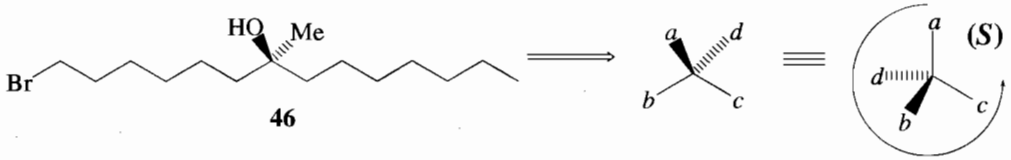
It is necessary to go to the second atom to find a point of difference that will distinguish these groups and **45** is (*S*). Similarly, 1-bromo-7-methyl-7-tetradecanol (**46**) first shows the hydroxyl O and the methyl group to be (*a*) and (*d*), respectively. To determine (*b*) and (*c*) requires analysis to the sixth carbon in each chain to establish the (*S*) configuration.

$O(a) > C \approx C \approx C$

$C^*—C^{HHH} = (d)$

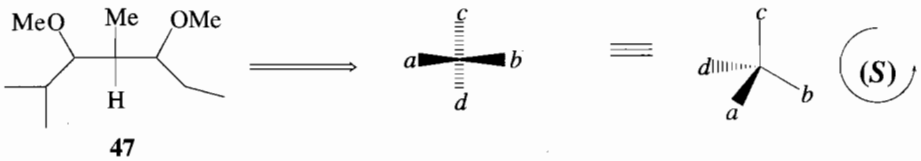
$C^*—C^{CHH}—C^{CHH}—C^{CHH}—C^{CHH}—C^{CHH}—C^{BrHH} = (b)$

$C^*—C^{CHH}—C^{CHH}—C^{CHH}—C^{CHH}—C^{CHH}—C^{CHH} = (c)$



46

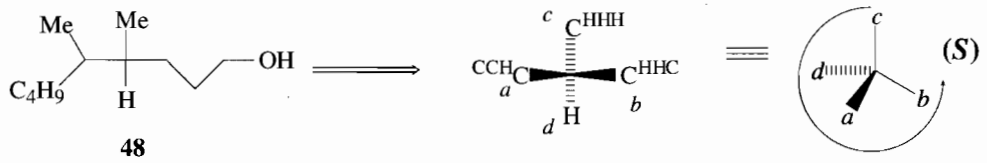
In **47**, the methyl and hydrogen are assigned the priorities (*c*) and (*d*). To determine the *a* and *b* priorities we must focus on the two arms that contain OCH. The highest priority chain is along C-O-C (the oxygen chain), but both groups are $O^C—C^{HHH}$. They are identical and we cannot use them to establish the priority. In such a case, the lower priority carbon chain must be used (in this case, the isopropyl and ethyl groups rather



47

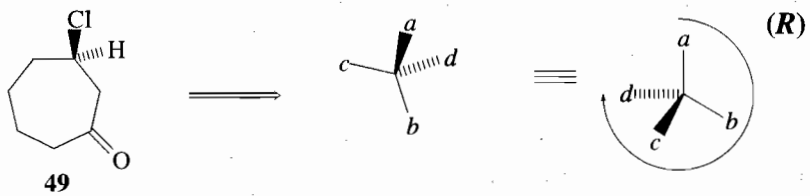
than the methoxy groups), giving $C^*—C^{OCH}—C^{CCH}$ for (*a*) and $C^*—C^{OCH}—C^{CHH}$ for (*b*) and the molecule has the (*S*) configuration.

A common misconception for rules 3 and 4 arises when rules 1 and 2 appear to fail. In **48**, methyl and hydrogen are the (*c*) and (*d*) groups. An analysis by rule 3 predicts $C^{CCH} > C^{CHH}$. In the C^{CHH} chain (—$CH_2CH_2CH_2OH$), however, there is an oxygen. The $CH(Me)CH_2CH_2CH_2CH_3$ (C^{CCH}) chain does not contain a heteroatom. The rules dictate determination of priority at the first point of difference, not the second. The presence of the oxygen is, therefore, irrelevant and the C^{CCH} chain will have priority over the C^{CHH} chain. The absolute configuration of **48** is (*S*).



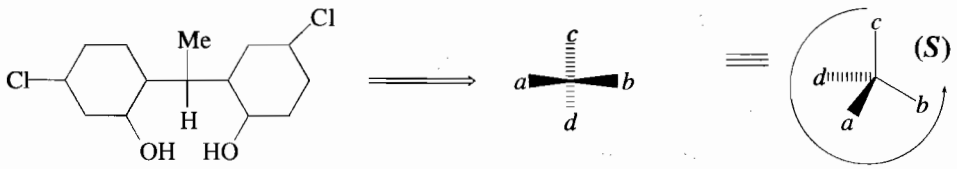
48

Cyclic compounds are treated by the same rules but each arm of the ring is looked on as a different group, using the atom-by-atom comparison. 3-Chlorocycloheptanone (**49**), for example, has Cl(*a*) > C ≈ C > H(*d*). The carbonyl chain is C*—C^{CHH}—$C^{OO°C}$ (*b*) in contrast with the carbon arm, C*—C^{CHH}—C^{CHH} (*c*). The configuration is (*R*).



49

In **50**, the methyl and hydrogen are again (*c*) and (*d*) but the rings pose a problem, one arm of the ring points to chlorine and one to hydroxyl. Since the secondary hydroxy carbon is closest to C*, the bottom arm of each ring is followed rather than the top arm. By this route the left ring is highest priority: (C*—C^{CCH}—C^{COH}—C^{CHH}—C^{ClCH} vs. C*—C^{CCH}—C^{COH}—C^{CHH}—C^{CHH}), absolute configuration is (*S*).



50

Cycloheptanone (**49**) contained a carbonyl and the analysis treated that carbon as C^{OOC}. Where did the second oxygen come from? Multiply bonded atoms such as this are found in alkenes, alkynes, carbonyls ,and nitriles and they require yet another rule.

5. If an atom is attached to another by a multiple bond (double or triple) both atoms are considered to be duplicated. The duplicated atom (X°) is considered to have a valence of zero and has a lower priority than a real atom (X), if that is the only point of difference.

This rule will convert the following common functional groups into their phantom counterparts for consideration in the priority scheme.

$C^*—CH=CH_2 \equiv C^*—C^{HCC^\circ}—C^{C^\circ HH}$

$C^*—C(=O)—C \equiv C^*—C^{OO^\circ C}—O^{CC^\circ\bullet\bullet}$

$C^*—C\equiv C—Me \equiv C^*—C^{CC^\circ C^\circ}—C^{CC^\circ C}—C^{HHH}$

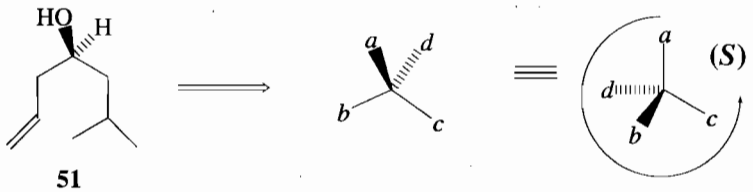
$C^*—CO_2H \equiv C^*—C^{OO^\circ O}—O^{CC^\circ\bullet\bullet}$

$C^*—C\equiv N \equiv C^*—C^{NN^\circ N^\circ}—N^{CC^\circ C^\circ}$

Generally, both X° and X are simply treated as real atoms. If the only choice is between a duplicated atom X° and a real atom (X), however, the duplicated atom has a lower priority (in this case, all other rules have failed to establish the priorities). With the *tert*-butyl fragment, for example, proceeding down the chain to the first point of difference leads to *tert*-butyl with a lower priority than the alkynyl fragment:

$C^*—C\equiv C—Me$ vs. $C^*—CMe_3$ $\qquad$ $C^*—C^{CC^\circ C}—C^{CC^\circ C} > C^*—C^{CCC}—C^{HHH}$

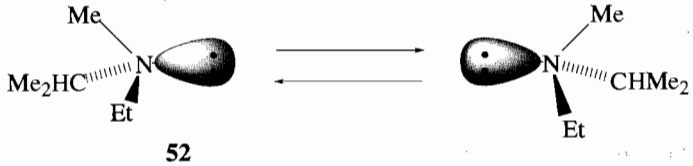
The C and C° are taken as equal in this analysis and rule 4 determines the priority; we compare $C^{CC^\circ C}$ with C^{HHH}, giving the alkyl fragment a higher priority. Another example of this rule is the analysis of 6-methyl-hept-1-en-4-ol (**51**), which shows O(*a*) > C ≈ C > H(*d*). The alkenyl arm is $C^*—C^{CHH}—C^{CHC^\circ}$ and the alkyl arm is $C^*—C^{CHH}—C^{CCH}$. In this case the rules are unable to distinguish the priority of these two fragments. One proceeds to the next atom ($C^{C^\circ HH}$), which is compared with C^{HHH} (=CH_2 vs. CH_3) and the former is higher in priority and becomes group (*b*). The absolute configuration of **51** is (*S*).



51

The International Union of Pure and Applied Chemistry (IUPAC) Commission assembled a list of common substituents in increasing order of sequence rule preference (number 76, iodo, is the highest priority and number 1, hydrogen, is the lowest priority), which is reproduced in Table 1.3.[16] With this table two or more substituents can be evaluated in order to determine their relative priority using the CIP selection rules.[17] Higher numbers have a higher priority. In the table, iodo (76) has a higher priority than bromo (75) and hydrogen (1) has the lowest priority. Similarly, allyl (10) has a higher priority than propyl (4), acetylenyl (21, C≡CH) has a higher priority than *tert*-butyl (19), and hydroxyl (57) has a higher priority than amino (43). This table is provided as a learning aid for studying the rules, not as a tool to be memorized.

When nitrogen is incorporated in a molecule it can, in principle, be a stereogenic center when there are three different alkyl groups on nitrogen (the fourth group is the lone pair of electrons on nitrogen). Although the nitrogen is a stereogenic center, rapid inversion at nitrogen leads to the mirror image (see **52**) being present



52

Table 1.3. Increasing order of sequence-rule preference for common substituents

1. Hydrogen	20. Isopropenyl	39. Methoxycarbonyl	58. Methoxy
2. Methyl	21. Acetylenyl	40. Ethoxycarbonyl	59. Ethoxy
3. Ethyl	22. Phenyl	41. BnOcarbonyl	60. Benzyloxy
4. *n*-Propyl	23. *para*Tolyl	42. *tert*-Butoxycarbonyl	61. Phenoxy
5. *n*-Butyl	24. *para*Nitrophenyl	43. Amino (NH_2)	62. Glycosyloxy
6. *n*-Pentyl	25. *meta*-Tolyl	44. Ammonio (H_3N^{+})	63. Formyloxy
7. *n*-Hexyl	26. 3,5-Xylyl	45. Methylamino	64. Acetoxy
8. Isopentyl	27. *meta*-Nitrophenyl	46. Ethylamino	65. Benzoyloxy
9. Isobutyl	28. 2,5,-Dinitrophenyl	47. Phenylamino	66. Methylsulfinyloxy
10. Allyl	29. 1-Propynyl	48. Acetylamino	67. Methylsulfonyloxy
11. Neopentyl	30. *ortho*-Tolyl	49. Benzoylamino	68. Fluoro
12. 2-Propynyl	31. 2,6-Xylyl	50. BnOCOamino	69. Mercapto (HS-)
13. Benzyl	32. Trityl	51. Dimethylamino	70. Methylthio (MeS-)
14. Isopropyl	33. *ortho*-Nitrophenyl	52. Diethylamino	71. Methylsulfinyl
15. Vinyl	34. 2,4-Dinitrophenyl	53. Trimethylamino	72. Methylsulfonyl
16. *sec*-Butyl	35. Formyl	54. Phenylazo	73. Sulfo (HO_3S-)
17. Cyclohexyl	36. Acetyl	55. Nitroso	74. Chloro
18. 1-Propenyl	37. Benzoyl	56. Nitro	75. Bromo
19. *tert*-Butyl	38. Carboxy	57. Hydroxyl (OH)	76. Iodo

The alkoxycarbonyl groups are RO-(C=O)-.

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at the same time. Because of this facile racemization, such compounds are not optically active unless the interconversion can be inhibited. Approximately 2 x 10^{11} inversions each occur second for ammonia.[18] The energy barrier for this inversion is somewhat higher in amines (see Table 1.4)[20] due the presence of alkyl groups on nitrogen, that are bulkier than the hydrogens in ammonia. Nonetheless, alkyl amines undergo rapid inversion.[19] The magnitude of the energy barrier to inversion in amines is determined by the intergroup

Table 1.4. Energy barrier to inversion of amines and phosphines

Compound	α	$E_{inversion}$ [kcal mol^{-1}	(kJ mol^{-1})]
NH_3	106.77	5.58	23.3[a]
		11	46.0[b]
PH_3	93.3	27	112.9[a]
		47	196.5[b]
NMe_3	109.0	7.46	31.2[a]
		15	62.7[b]
PMe_3	100	20.4	85.3[a]
		57	238.3[b]

[a] Reference 20 [b] Reference 21

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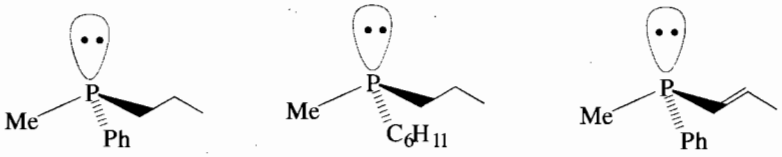
bond angle (α, C1—N—C2) and the corresponding bending force constant.[20] Table 1.4[20] shows values of the parameter (a) for ammonia, trimethylamine, phosphine, and trimethylphosphine, along with an estimate for the energy barrier to inversion. Older estimates of these energy barriers are also included.[21] The inversion at nitrogen in alkyl amines cannot be stopped at the reaction temperatures usually employed in organic chemical reactions. Only when this inversion is impossible due to structural features of a molecule, as in bicyclic and polycyclic amines, is the nitrogen stereogenic and enantiomers observed.

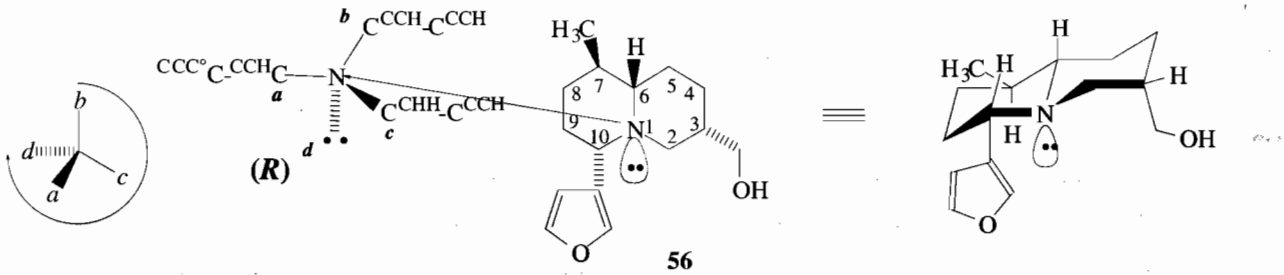
The energy barrier for inversion is low for second row elements (C, O, N) and rapid inversion occurs. With elements in the third row (such as P and S), however, inversion is slow at ambient temperature and those molecules can exist as enantiomers. Methylphenylphosphine (**53**) is configurationally stable at 25°C, although it rapidly inverts at 130°C.[22b] At 130°C this barrier was measured to be 30.7 kcal mol^{-1} (128.4 kJ mol^{-1}),[22a] for a rate of inversion of 3.34 x 10^5 s^{-1}.[23] Similarly, **54** showed a rate of inversion of 0.043 x 10^5 s^{-1} and the rate for **55** was 1.44 x 10^5 s^{-1} [E_a = 32.2 kcal mol^{-1} (134.6 kJ mol^{-1})].[23]



53 **54** **55**

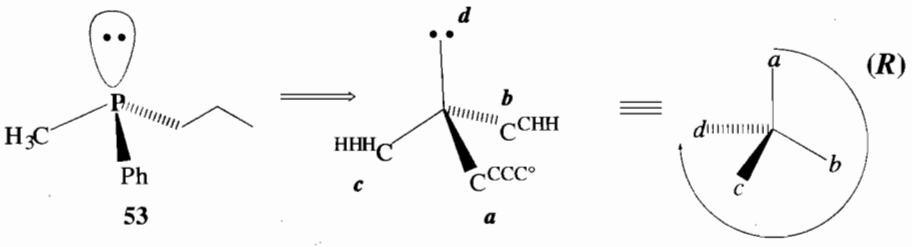
If a molecule contains a nitrogen atom that is determined to be a stereogenic center, it must be assigned a configuration by the CIP selection rules. An example is the bridgehead nitrogen in (–)-castoramine (**56**)[24], which is incapable of inversion at nitrogen because of its rigid bicyclic structure.[25] Castoramine is also drawn to show the trans-orientation of the electron pair, which is preferred to the cis- orientation by ≈2.4 kcal mol^{-1} (10.0 kJ mol^{-1}).[25] This effectively locks the molecule into the trans conformation. In this case, the electron pair is considered to be a group but the first five rules do not allow it to be assigned a priority. The sixth rule is necessary.

6. Lone electron pairs receive an atomic number of zero and are assigned the lowest priority. The duplicated C, O and N atoms from rule 5 have a higher priority rather than an electron pair.

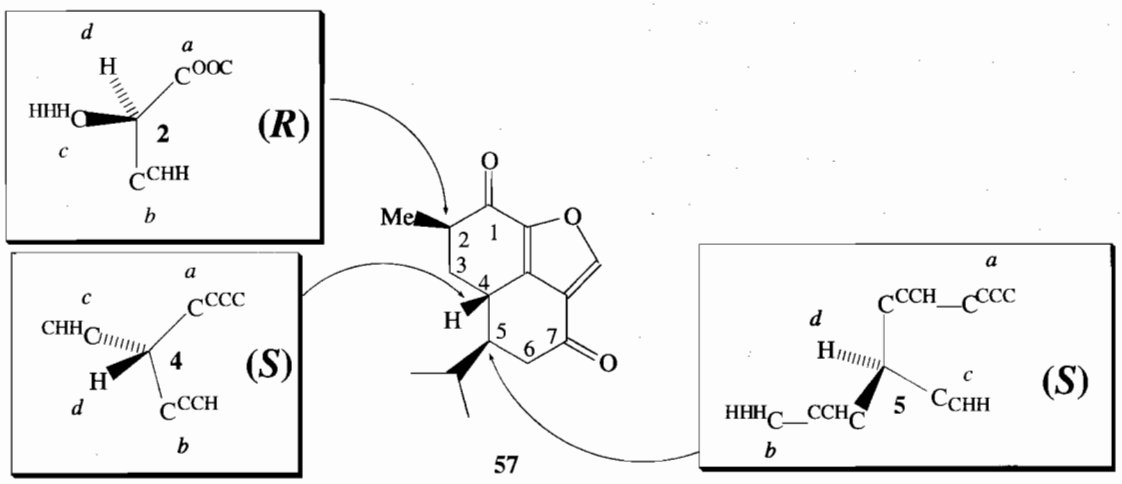


56

For (–) castoramine (**56**) Rule 6 allows a priority determination that assigns the stereogenic nitrogen center as (*R*). Just as a nitrogen atom can be stereogenic, a phosphorus atom in a phosphine such as **53** can be considered chiral since the rate of inversion is negligible at temperatures up to ≈ 130°C, as noted in Table 1.4. The lone pair electrons have the lowest priority by Rule 6 and the absolute configuration is (*R*).



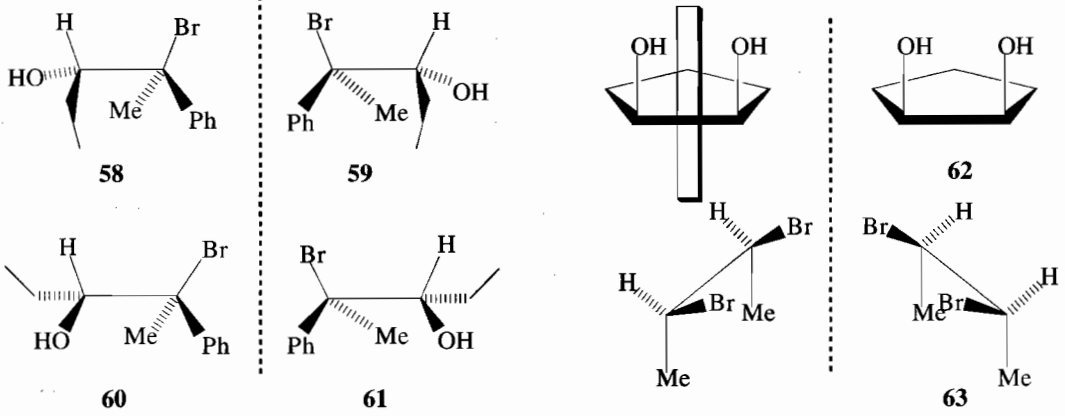
These six rules for determining the priority of groups on stereogenic centers can be applied to any molecule. Natural products are particularly interesting since they are the targets of many synthetic endeavors. As noted above, the absolute and relative configuration of such molecules must be known if they become synthetic targets and this must be factored into the retrosynthetic plan. Hibiscone C (**57**) is an example of a growing class of compounds that contain highly functionalized furan rings.[26] The three stereogenic centers are analyzed to give C2 (*R*), C4 (*S*), and C5 (*S*). Each stereogenic center is treated as if it were an individual and isolated atom. In other words, focus on C2, determine the four attached groups independent of the fact they are all part of one molecule, and then assign priorities. Once this is done, C2 is effectively an isolated tetrahedral carbon, as shown, and it has the absolute configuration (*R*). This fundamental approach is used for all the stereogenic centers, and it can be applied to any molecule, regardless of the complexity. It is also true, however, that in some cases assigning priorities can be tedious and occasionally confusing.



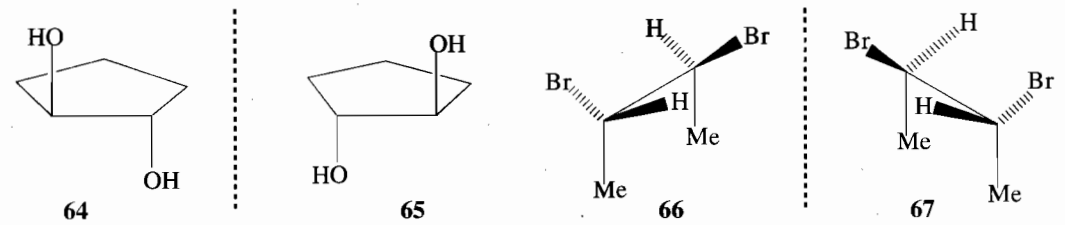
1.4.B. Diastereomers

When there is more than one stereogenic center, the maximum number of possible stereoisomers is predicted by the **2^n rule** (for *n* stereogenic centers there is a maximum of **2^n** stereoisomers). Therefore, when two stereogenic centers are present in a molecule (as in **58**), there are four possible stereoisomers based on the different relative stereochemistry of the groups. For the two stereogenic centers in **58** (C1 and C2) the four possibilities are: C1(*R*)—C2(*R*), C1(*S*)—C2(*S*), C1(*R*)—C2(*S*) and C1(*S*)—C_2(*R*). Bromohydrin **58** is (*SS*) and its enantiomeric mirror image (**59**) is (RR). Likewise, the (RS) compound (**60**) and its mirror image (**61**) with the (SR) configuration are enantiomers. Comparison of **58** and **60** shows them to be stereoisomers, but

they are not mirror images nor are they superimposable. This special type of stereoisomer is given the name **diastereomer**: stereoisomers with two or more stereogenic centers that are not superimposable and not mirror images. By this definition, **59** and **61** are diastereomers.

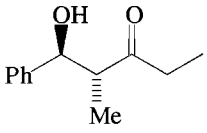


There are cases when a plane of symmetry bisects a diastereomer, as in *cis*-1,2-cyclopentanediol (**62**) and (2*R*,3*S*)-dibromobutane **63**. The mirror image of (2*R*,3*S*)-dibromobutane is (2*S*,3*R*)-dibromobutane—the same compound. In effect, one half of the molecule is the mirror image of the other half so there is symmetry that leads to **fewer** stereoisomers than the maximum predicted by the 2^n rule. Structures **62** and **63** are superimposable upon their mirror images so *they are not enantiomers but are the same compound*, and are called **meso compounds**. Meso compounds occur when the mirror image of a molecule containing more than one stereogenic center is superimposable (when it contains a plane of symmetry). The cis-diol **62** is a meso compound but its diastereomer, the trans-diol, has enantiomers **64** and **65**. Therefore, there are a total of three stereoisomers. Isomers **62** and **64** or **62** and **65** are diastereomers, **64** and **65** are enantiomers and **62** is a meso compound. Similarly, **62** is a meso compound but **66** [(2*S*,3*S*)-dibromobutane] and **67** [(2*R*,3*R*)-dibromo-butane] are enantiomers, giving the three stereoisomers. Notice that changing the configuration of one stereogenic center (2*R* → 2*S*) cannot be done by rotation but by making and breaking bonds. This rotation removes the internal symmetry, making the mirror image nonsuperimposable. Dibromides **63** and **66** are diastereomers, as are **63** and **67**.



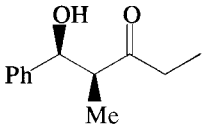
In chapters to come we will see that many different types of organic reactions produce diastereomers. At first glance, these diastereomeric pairs are related to cis and trans isomers, but rotation about the carbon–carbon bond (see sec. 1.5.A) precludes the configurational rigidity necessary for cis- and trans-isomers. A

separate nomenclature system is required based on the relationship of the groups on the stereogenic centers. One system for distinguishing diastereomers labels them threo- and erythro.



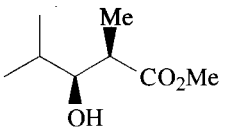
68

erythro



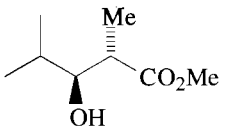
69

threo



70

threo

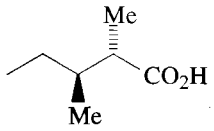


71

erythro

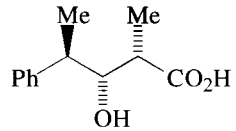
Unfortunately, there is more than one definition for threo- and erythro. Winstein and co-workers gave the following definition of these diastereomers: In a compound with two asymmetric carbons that has two common ligands and a third that differs, the isomers that would be meso if the third ligand were identical are erythro diastereomers.[27] An alternative definition is If two asymmetric carbons have only one ligand in common, then the other four ligands are paired in the same commonsense way and isomers that would have equal pairs eclipsed in any conformation are erythro.[28] Eliel, Mislow and their co-workers[29] defined erythro and threo in terms of Fischer projections. The aldol products (see sec. 9.4.A) **68** and **69**, and the ester–aldehyde condensation products **70** and **71**.[30] are shown with the erythro and threo notation.

To alleviate the confusion of the various uses and perceptions of the erythro/threo notation,[31] Masamune proposed the terms syn and anti to describe the relative stereochemistry of diastereomers.[32] In this notation adjacent groups on the same side of an extended (zigzag) structure are syn and those on opposite sides are anti. This is illustrated with **72–74**.[32,33] This extended structure is used as the basis of the model and it



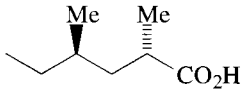
72

C_2C_3 anti



73

C_2C_3 syn; C_3C_4 anti



74

C_2C_4 anti

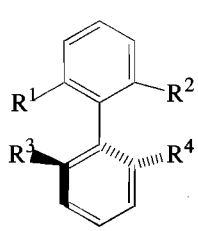
represents the lowest energy conformation of most acyclic molecules (see sec. 1.5.A) in which the interactions of adjacent groups and bonds are minimized. Transforming any given acyclic diastereomer to its low-energy conformation gives a common basis for evaluating the relative stereochemistry of groups on the stereogenic centers.

It is important to note that the clearest way to show differences is to use the absolute configuration (*R*) or (*S*) nomenclature for each stereogenic center in both enantiomers or in enantiomerically pure diastereomers The correct configuration will be cited or the syn- and anti- terminology will be used throughout this book.

1.4.C. Chiral Molecules without a Stereogenic Center (Molecules Containing a Chiral Axis)

A few classes of organic molecules have a chiral axis although they do *not* have a stereogenic center.[34] The mirror image of such a molecule is not superimposable so it is possible to have enantiomers without the

presence of a stereogenic center. Since no chiral atom is present, there is a problem, forcing a modification of the CIP rules. Four important classes of compounds that exhibit this property are biaryls such as **75**, alkylidene cyclohexanes (**76**), substituted allenes such as **77**, and substituted spiranes such as 3,9-diphenylspiro[5.5]tridecane (**78**).[17,34] Chiral biaryls are important as chiral catalysts, used in many reactions



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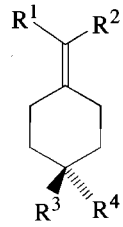

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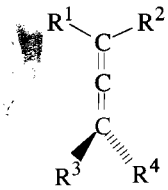

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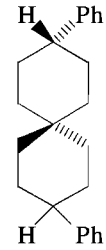
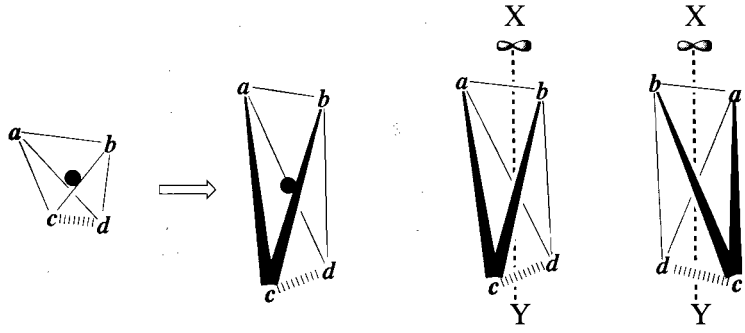


78

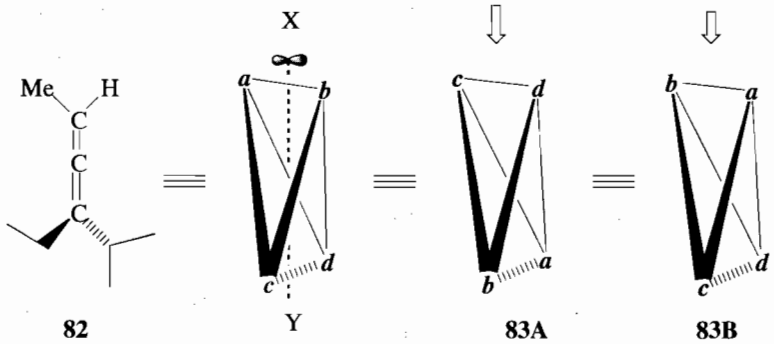
(see sec. 4.8.A, 4.9.G, and sec. 11.9). Obviously, determining the absolute configuration of both the chiral reactants and the asymmetric products resulting from their use is important. Allenes are common partners in pericyclic reactions (see secs. 11.4, 11.10 and 11.11) and they are chiral partners in some of these reactions. Alkylidene cyclohexanes are produced by phosphorus ylids upon reaction with cyclohexanone derivatives (see sec. 8.8.A) and the potential for creating asymmetric products is a key consideration in planning a synthesis of such compounds. It is clearly important to predict the (*R*/*S*) configuration of such compounds.



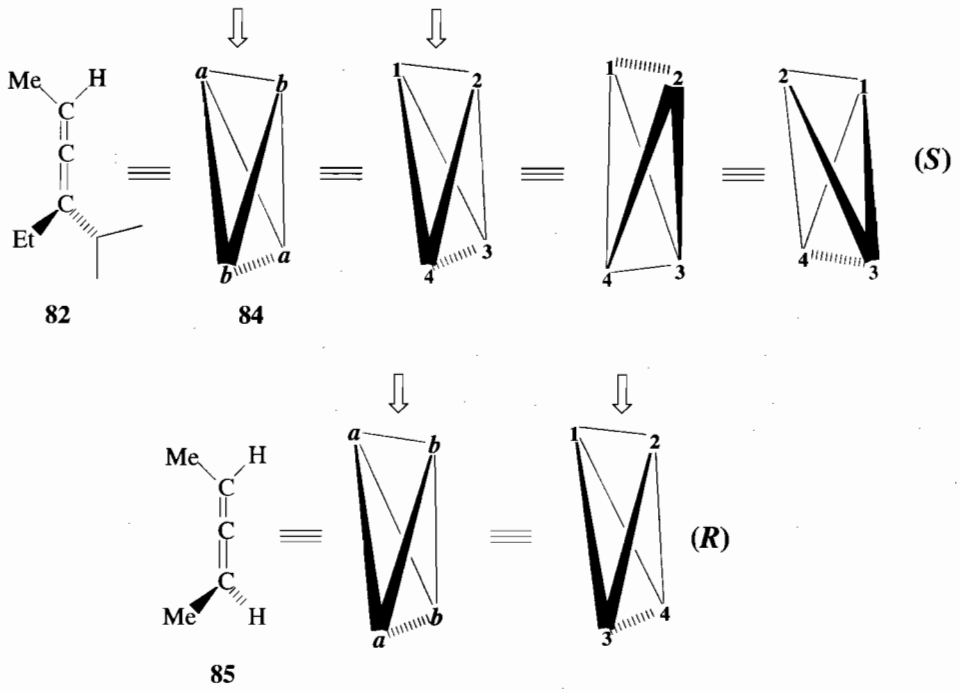
79 **80A** **80B** **81**

These molecules are evaluated by recognizing the presence of an extended tetrahedron (**80A**).[35] A normal tetrahedral atom is represented by **79** and if the atoms *a*→*d* were expanded by grossly extending the bond lengths, an extended tetrahedron such as **80A** would be obtained. Rather than a chiral atom, **80A** contains a **chiral axis** (see X---Y in **80B**) and this can be used to assign priorities. This model requires that **80B** not be interconvertible with its mirror image **81** (i.e., rotation about the chiral axis X---Y must not interconvert **80** and **81**).

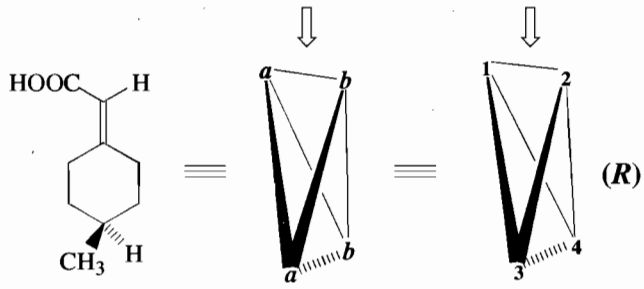
Allene **82** has a chiral axis since there are four different groups at each corner of the extended tetrahedron. These can be assigned priorities a→d (**83A**) by the usual rules and this at first glance suggests **83B** (obtained by rotating **83A** so the a-b-c sequence is in front and the d-atom is to the rear) as the structure to be used for



determining the absolute configuration. This is ***incorrect***. There is nothing here to suggest the appropriate angle from which to view the extended tetrahedron. There is no C*-C^{d} axis from which to view the molecule. The CIP rules were modified as follows to accommodate an extended tetrahedron:[17] (1) The top edge of the extended tetrahedron is prioritized a,b and the bottom edge of the extended tetrahedron is also prioritized a,b. (2) Near groups precede far groups when viewed from the top of the extended tetrahedron. With these rules, **82** is converted to **84** where the top *a,b* pair is associated with 1,2 (a = 1, b = 2). Similarly, the bottom *a,b* pair is assigned 3,4 (a = 3, b = 4) since top has priority over bottom. The model is rotated to put (4) to the rear and 1→2→3 is counter-clockwise, giving an (*S*) configuration. This new model can so be used with allene **85**,

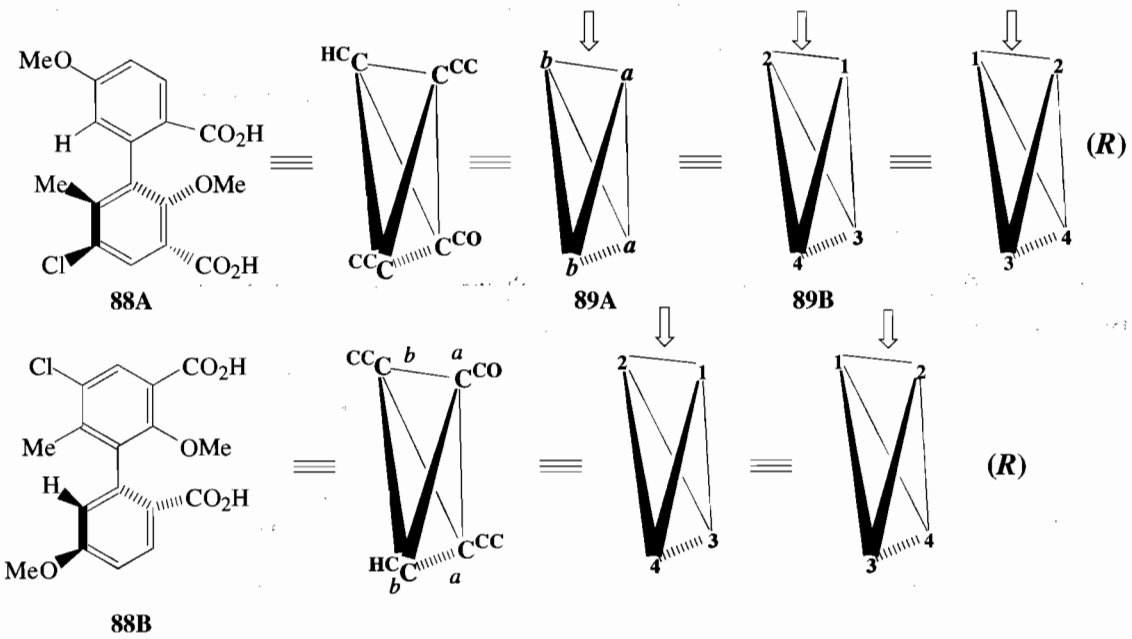


where only two different groups are present. The methyl–hydrogen priorities are shown in **85** and converted to the 1→4 priority scheme, which places (4) to the rear, giving an (*R*) configuration.[17] Molecules such as this can also be evaluated *a priori* using the **Lowe-Brewster rules**.[36] Eliel et al.[37] points out that the configuration of allenes and alkylidenecycloalkanes can be predicted by these rules in most cases but fails for many spirans.



86 **87A** **87B**

A similar situation occurs for cyclic molecules containing an exocyclic alkylidene moiety such as **86**, which has two different groups at C4 of the cyclohexyl system and two different groups attached to the π bond. The C^{OOO} > H priority for CO_2H and H on the alkene is straightforward, and this constitutes the top of the extended tetrahedron. The cyclohexyl arms are in the plane of the π bond, but the methyl and hydrogen at C4 of the cyclohexane ring are in a different plane and they constitute the bottom of the extended tetrahedron. Since the methyl carbon has priority over the hydrogen, the extended tetrahedron is **87A**, which leads to **87B** and the (*R*) configuration.[17]

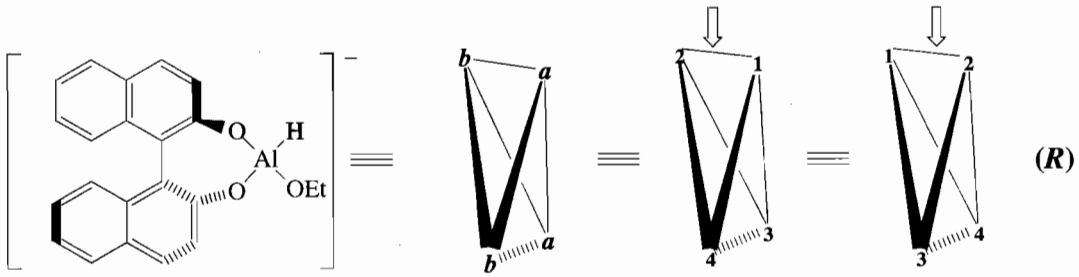


88A **89A** **89B**

88B

Biaryls such as **88A** can be analyzed with this extended tetrahedron rule. The top aromatic ring is prioritized as *a,b* for the 2,6 substituents, as is the bottom ring (see **89A**). The near-far rule leads to **89B** and an (*R*) configuration.[19] A reasonable question is Which aryl ring is on top and which is on the bottom of the extended tetrahedron. Do the rules accommodate these two orientations? Structure **88B** is identical to **88A**, except the former has been rotated by 180°. Analysis of both structures leads to an (*R*) configuration. Prioritizing top and bottom *separately* accounts for rotating the molecule in this manner, but the top must be assigned ***before*** prioritizing the molecule and must ***not*** be changed after the process has begun.

An example of a fused aromatic system used in synthesis is the reducing agent BINAL-H (an abbreviation for **90**, see sec. 4.8.A.).[38] The extended tetrahedron reveals an (*R*)-configuration and it is important to note that binding the aluminum atom into a ring, as shown in **90**, effectively locks the aromatic rings into a single configuration and does not allow racemization unless the C-C-C-C-Al-O- ring is disrupted.



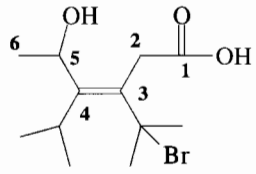
90

1.4.D. (*E*/*Z*) Isomers

Alkenes can exist as stereoisomers. If you are asked to draw the structure of 3-hexene, two different molecules can be drawn (**91** and **92**). They are not superimposable, nor are they mirror images but since rotation is not possible around the C=C moiety, the ethyl groups and the hydrogens have different spatial relationships and cannot be interconverted by rotation. Although no stereogenic center is present, they are stereoisomers and are formally considered to be diastereomers. In this particular case, the C=C unit has identical groups (ethyl) attached and the ethyl groups can be identified as being on the same side of the C=C or on opposite sides. When an alkene contains identical groups and those groups are on the same side, it is called a cis-alkene. When the two identical groups are on opposite sides, it is called a trans-alkene. Alkene **91** is *cis*-3-hexene and **92** is *trans*-3-hexene. These terms are part of the nomenclature and are used to distinguish the stereoisomers.

91

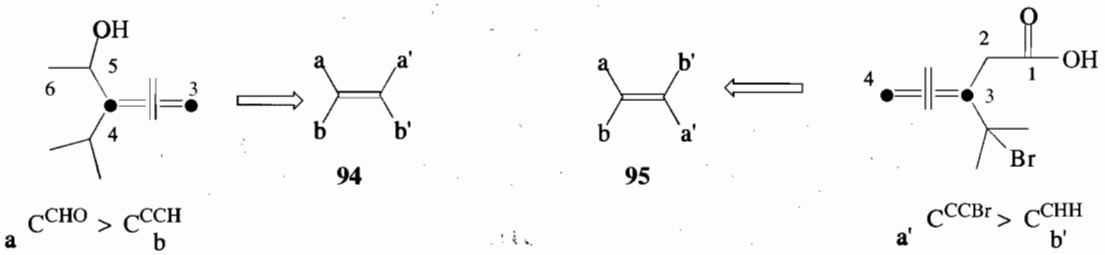
92



93

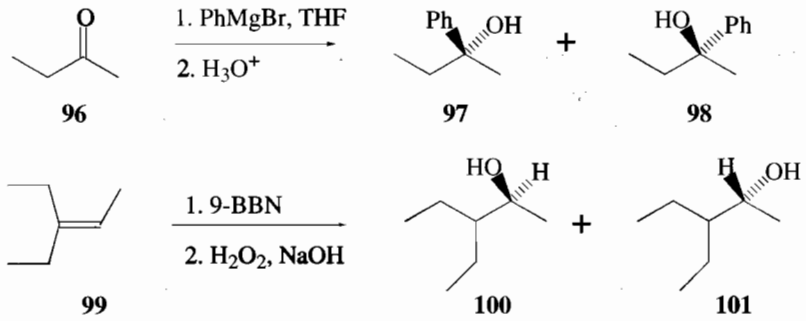
The terms cis and trans are applied in a straightforward manner for simple alkenes such as *cis*- and *trans*-3-hexene (**91** and **92**) or *cis*- and *trans*-1,2-dibromoethene. For 3-(1-bromo-1-methyl-ethyl)-5-hydroxy-4-(1-methylethyl)-hex-3-enoic acid (**93**), however, the cis–trans nomenclature is not obvious. Which of the groups are used to determine sidedness A more general nomenclature system is required, the (*E*/*Z*) system.[16,39] With this system, the CIP selection rules are used to assign priorities to each carbon of the double bond. In **94**, *a* and *a*' have the highest priorities and *b* and *b*' have the lower. Since *a* and *a*' are on the same side of the double bond, they are given the designation (*Z*) (from zusammen = together). Similarly, *a* and *a*' are on opposite sides in **95** and this is assigned the designation (*E*) (from entgegen = opposite). With this system, the

hydroxyl-bearing carbon of C4 in **93** is assigned the highest priority (C^{CHO} vs. C^{CCH} for the isopropyl carbon). Analysis of C3 shows the bromine-bearing carbon to be the highest priority (C^{CCBr} vs. C^{CHH}). This is analogous to **95** and the name of **93** is (*E*)-(1-bromo-1-methylethyl)- 5-hydroxy-4-(1-methylethyl)-hex-3-enoic acid. This nomenclature is generally applicable to all alkenes. 3-Hexene **91** is (*Z*)-3-hexene and **92** is (*E*)-3-hexene. The (*E*/*Z*) system will be used extensively throughout this book, but the cis/trans designations will be used for simple molecules and to describe relative stereochemistry. For example, the carbonyl group and the hydroxyl-bearing moiety in **93** are cis to each other.



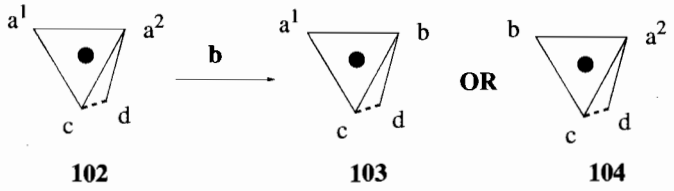
1.4.E. Prochiral Centers

There are molecules that do not possess a chiral center but generate a product with a chiral center after a chemical reaction. In terms of planning a reaction, it is important that we predict whether the product will have an (*R*)- or an (*S*)-configuration. To make this prediction, we must know from which face of the molecule the reagent will approach during the reaction. If it approaches from one face, the (*R*)-enantiomer is generated; if it approaches from the opposite face, the product is the (*S*)-enantiomer.

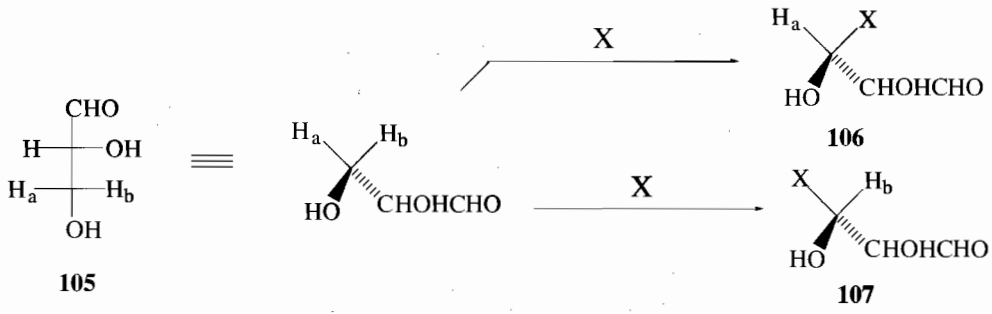


It is obvious that ketone **96** (2-butanone) and alkene **99** do not contain a stereogenic center. If **96** reacts with a Grignard reagent such as phenylmagnesium bromide (PhMgBr), however, the product is a racemic alcohol with enantiomers **97** and **98** (see sec. 8.4.C). Reaction of alkene **99** with a borane such as 9-BBN (9-borabicyclo[3.3.1]nonane) followed by oxidation gives a racemic alcohol, that is, enantiomers **100** and **101** (see sec. 5.4.A). In both cases, the alcohol products contain a stereogenic carbon atom, although they are racemic. The ketone and alkene are described as **prochiral**,[40] and a working definition of **prochirality** is provided by Hanson:[41] "If a chiral assembly is obtained when a point ligand in a finite non-chiral assembly of point ligands is replaced by a new point ligand, the original assembly is prochiral". A ligand is simply a group attached to the prochiral atom (*a, b, c, d*). A point ligand for a prochiral center has two characteristics: "(1)

any two point ligands may be identical or non-identical, and (2) two point ligands may not occupy the same position in space."[41] Addition of a point ligand to a prochiral center creates a new chiral center.[41] If the



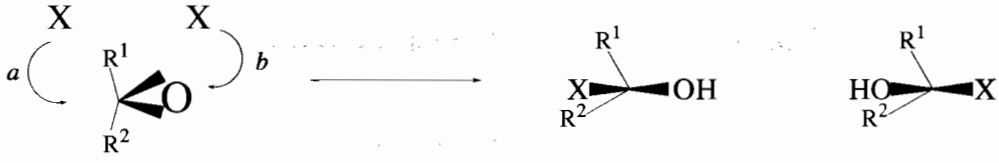
102 **103** **104**



105 **106** **107**

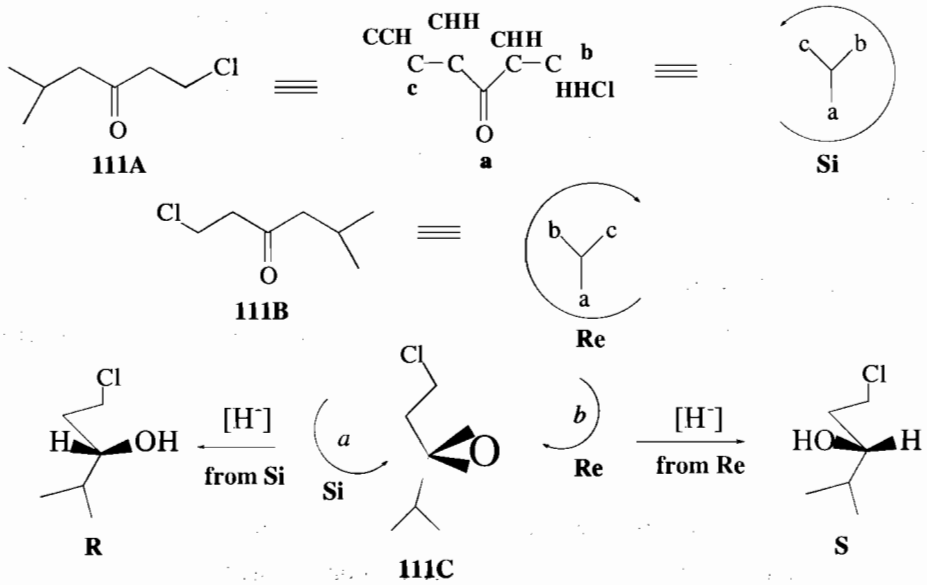
ligands are assigned a priority *a-b-c-d* by the CIP selection rules, configurations for each face of the prochiral center can be obtained. This is illustrated by conversion of the prochiral atom in **102** to either **103** or **104**. In this example, **104** represents an (*S*) chiral center and is formed by replacement of a^1 with b. Similarly, replacing a^2 generates an (*R*) chiral center, **103**. These a^1 and a^2 atoms are described by the terms ***pro-S*** and ***pro-R***, respectively. A *pro-R* center is a point ligand in a prochiral molecule whose replacement leads to an (*R*) center. Analogously, a *pro-S* center is a point ligand in a prochiral molecule whose replacement leads to an (*S*) center. In **102**, ligand a^2 is *pro-R* and a^1 is *pro-S*. An example is D-glyceraldehyde, **105**. The methylene group adjacent to the chiral center is prochiral, and replacement of H_b with a group X gives an (*S*) center in **106** (assuming X has a priority of *c* with H = *d*). Replacement of H_a gives an (*R*) center (in **107**) and that hydrogen is *pro-R*.

Hanson[41] described rules that accommodate most situations observed with prochiral centers. The reader is referred to this work for specific examples that do not yield to a simple analysis. The intent of this section is to familiarize the reader with nomenclature and the uses of *pro-R* and *pro-S* sites in reactions.



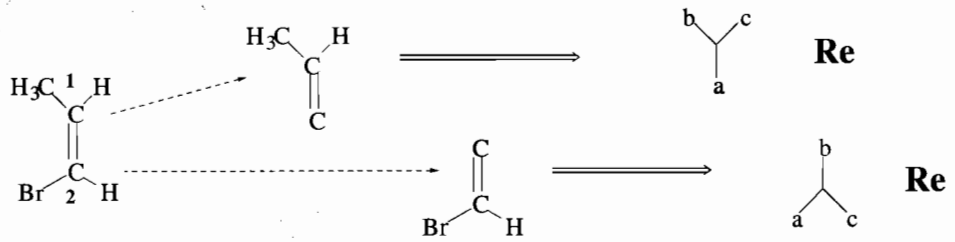
108 **109** **110**

As noted above, synthetically important prochiral centers are the carbonyl of a ketone or aldehyde and the double bond of an alkene. These functional groups do not contain a *pro-R* or *pro-S* group but it is clear that delivery of a fourth point ligand from one face or the other will lead to an (*R*) or (*S*) chiral center, as in conversion of **108** to **109** and/or **110**. If the carbonyl is oriented as in ketone **111A**, priorities can be assigned to the three atoms connected to the prochiral atom, based on the CIP rules. For **111A**, the $a \rightarrow b \rightarrow c$ priority is



counterclockwise and is analogous to (*S*). It is not really an (*S*) configuration, of course, since it is not a stereogenic center but this (*S*) sequence is termed *si*, from the Latin *sinister*[41] When the incoming group approaches the π-bond from this face (with the orientation shown in **111A**) it is called the ***si* face**. If the molecule is given the opposite orientation, as in **111B**, the priority sequence $a \rightarrow b \rightarrow c$ is clockwise or (*R*) and this face is termed *re*, from the Latin *rectus*. That face will then become the ***re* face.**[41] In this example, face ***a*** (see **111C**) is the *si* face and face **b** is the *re* face. Attack of hydride (see secs. 4.2.B, 4.7) from face ***a*** (the *si* face) leads to the (*R*) alcohol and attack from face **b** (the *re* face) leads to the (*S*) alcohol. The configuration of the final product depends, of course, on the priority of the new group added to the prochiral center.

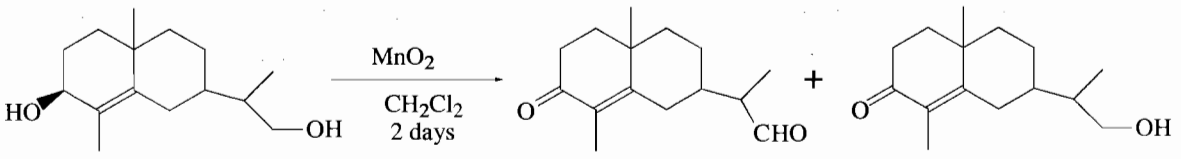
Similar terminology can be applied to alkenes, as with (*Z*)-1-bromo-1-propene (**112**). In this case, there are two prochiral centers to be considered (C1 and C2 of the C=C bond), and *re* or *si* is assigned to each carbon. For **11**, the top faces of both C1 and C2 are *re* (*re–re*) and the bottom faces are *si* (*si–si*)



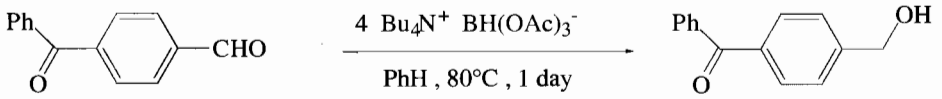
112

1.4.F. Definitions of Selectivity

In the preceding sections, various types of molecules were classified as regioisomers or stereoisomers (diastereomers and enantiomers). When there are two different functional groups in a molecule, a given reagent may react preferentially with one rather than the other. Such a reaction is sometimes termed **chemoselective.** Oxidation of **113** with manganese dioxide (MnO_2, see sec. 3.2.F.iii) gave a 50% yield of **114** and 25% of

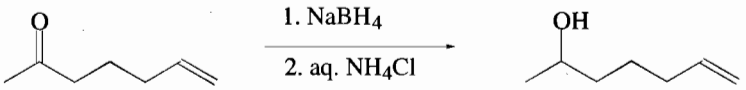


113 **114** **115**



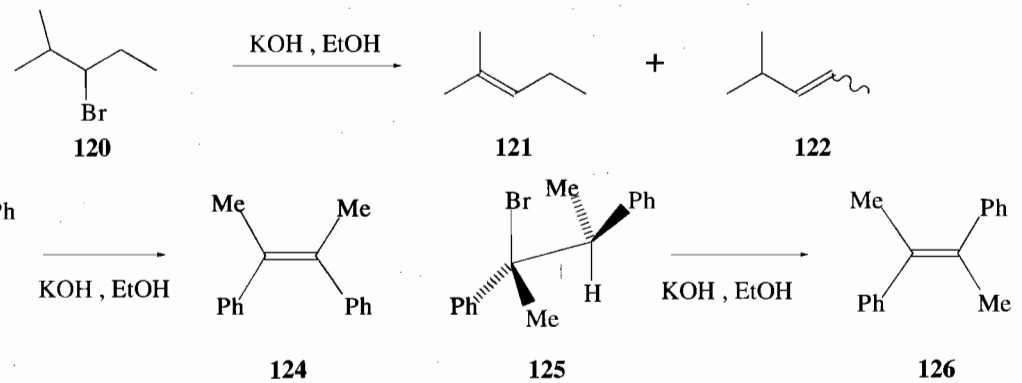
116 **117**

115.[42] Manganese dioxide showed a preference for oxidation of the secondary allylic alcohol at the expense of the primary alcohol. The reagent selected one over the other, which leads to the term **chemoselective** (of two or more reactive functional groups, one reacted preferentially to give the major product in the mixture). When both products are formed but one is formed in greater proportions, the term selective applies. Contrast this reaction with Gribble's reduction of keto-aldehyde **116** with tetrabutylammonium triacetoxyborohydride $[Bu_4N^+ BH(OAc)_3^-$, where Ac = acetate and Bu = butyl, to give **117** in 88%.[43] If the aldehyde carbonyl was



118 **119**

reduced and a portion of the ketone carbonyl was reduced, the reaction would be chemoselective rather than chemospecific. If there had been 100% reduction of the aldehyde but 0% of the ketone, the reaction would be termed **chemospecific**. These terms were defined by Trost: Of two or more reactive functional groups, only one reacts (specific), or one predominates (selective). Reduction of alkenyl ketone **118** gave alcohol **119** and only the carbonyl reacts with sodium borohydride ($NaBH_4$). Since 0% of the alkene reacted, the reaction is chemospecific.



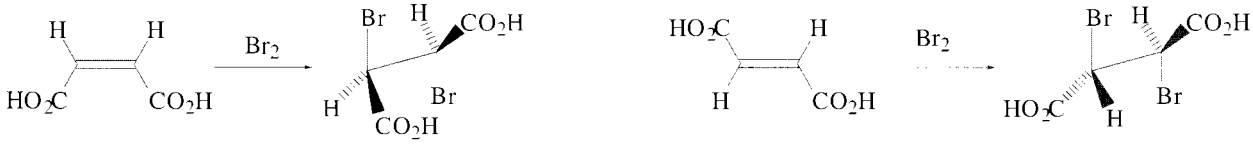
120 **121** **122**

123 **124** **125** **126**

As noted above, the uses of selective and specific for giving a preponderance of a given product or only that product are applied for all selectivities. If a reaction can produce two or more regioisomers it is regioselective or regiospecific The second order (E2) elimination (see sec. 2.9.A) of **120** gives a mixture of **121**

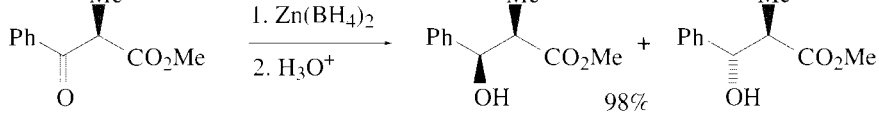
and **122**, with **121** being the major product. The reaction is therefore regioselective. Elimination of the enantiomerically pure (S,S)-diastereomer (**123**), however, gives only the (*Z*)-alkene **124** with none of the (*E*)-isomer and none of the alkene formed by removal of another β-hydrogen (on the methyl). The reaction is regiospecific, and is also stereospecific, which is confirmed by reaction of the (*R,S*)-diastereomer **125** under E2 conditions to give only **126**. If **123** and **125** gave an unequal mixture of **124** and **126**, the reaction would be stereoselective. Since only one product is formed, the reaction is stereospecific.

Similar terminology is applied to formation of diastereomers. March[44] gave the example of maleic acid (**127**) and fumaric acid (**129**) and their reactions with bromine. On addition of bromine to **127**, a racemic mixture of **128** was formed. Addition to **129** gave only *meso*-**130**. In both cases the reaction was diastereospecific. If **127** gave predominantly **128** with only a trace of the diastereomer (**130**), the reaction would be diastereoselective rather than diastereospecific.



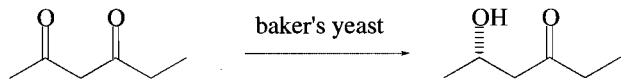
127 **128** **129** **130**

The term stereoselectivity must be explained in terms of a real reaction. If a reaction produces a substance that is not a stereoisomer, that reaction cannot be stereospecific but is at most stereoselective.[45] If stereoisomeric starting materials react to give a single stereoisomeric product, it is a **stereospecific** reaction but if another stereoisomer is also produced (giving a mixture of products), the reaction is **stereoselective**. These terms apply to all types of stereoisomers, including enantiomers (**enantioselective** and **enantiospecific**–see below), diastereomers (**diastereoselective** and **diastereospecific**) and regioisomers (**regioselective** and **regiospecific**). Reduction of keto ester **131** with zinc borohydride [$Zn(BH_4)_2$, see sec. 4.4.B and 4.7.B] gave 98% reduction with a >99:1 preference for **132** over **133**. The reaction produces two diastereomers and it is **diastereoselective**.[45] Since traces of **133** are produced it cannot be diastereospecific.



131 **132** **133**

The final definition concerns formation of enantiomers, and the terms enantioselective and enantiospecific are used. If a reaction produces an unequal mixture of enantiomers it is enantioselective. If it generates only one enantiomer of two possibilities, it is **enantiospecific**. The baker's yeast reduction (see sec. 4.10.F) of **134** gave **135** with >99% ee (S).[46] (Here **% ee** means percent of **enantiomeric excess**.) A 0% ee means a 50:50 mixture (racemic mixture), 50% ee means a 75:25 mixture and 90% ee means a 95:5 mixture. The predominance of the (*S*) enantiomer makes this reaction highly enantioselective.



134 **135**

The selectivity terms introduced in this section will be used throughout the book for reactions that generate stereoisomers. In addition, % ee and % de (diastereomeric excess, defined in the same way as ee but for diastereomers) will be used throughout.

1.5. CONFORMATIONS

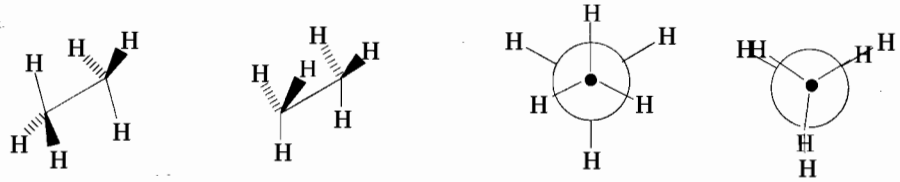
Organic molecules can largely be categorized as having tetrahedral, trigonal or digonal (linear) geometry around each sp^3, sp^2, or sp hybridized carbon atom. When organic molecules absorb energy from the environment they can partially dissipate excess energy by molecular vibrations, including rotation about all carbon–carbon single bonds. Generally, the more energy absorbed, the more facile will be the rotation. The three dimensional nature of carbon compounds and the rotation around carbon–carbon bonds leads to different spatial orientations of molecules called **rotamers**. Different rotamers are not different structures, but different orientations of the same molecule. Analysis of the spatial relationships of the groups can give information about the interactions of the groups as they rotate around the carbon–carbon bond.

The "shape" of a molecule is very important. When we draw the structure of an acyclic molecule, we usually draw the lowest energy rotamer so we draw it with a regular shape rather than as an amorphous shape. For cyclic and polycyclic molecules, the various interactions of the groups will lead to one (sometimes several) energy minima that are drawn to represent the shape of that molecule. In chemical reactions, the shape of the molecule will influence the way an incoming reagent interacts with it and this can have a significant effect on both reactivity and stereochemical induction, especially with the more rigid cyclic and polycyclic molecules. This section will discuss the fundamental conformational preferences of simple acyclic and cyclic molecules. These principles will be applied throughout the book for discussions of chemoselectivity and stereoselectivity.

1.5.A. Conformations of Acyclic Molecules

Ethane is a simple example of an acyclic molecule capable of rotation motion between two carbon atoms. As the molecule absorbs energy from the environment there is rotation about the C—C bond. If one could freeze this motion at different positions, the result would be different rotational isomers referred to above as rotamers. Inspection of rotamer **136** and its **Newman projection** (the dot and circle model used in **138**)[8] reveals that the hydrogen and the bond attaching the hydrogen to carbon are as far removed from each other as possible. This contrasts with **137** (its Newman projection is **139**), where the hydrogen atoms are eclipsing each other and are as close together as possible. This non-bonded interaction between the two eclipsing hydrogens and the electronic repulsion of the C—H bonds destabilizes this rotamer, making it higher in energy. The rotation about C-C therefore has an energy barrier to traverse [measured at 2.9 kcal mol^{-1} (12.1 kJ mol^{-1})][47] if **139** is one of the possible rotamers. If **139** represents the highest energy conformation then

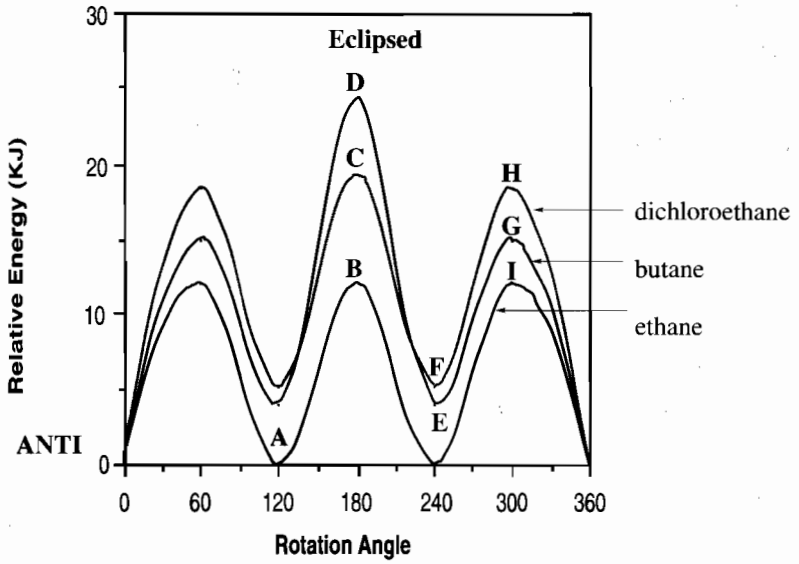
138 will represent the lowest (the energy is 0 kcal mol^{-1} or 0 kJ mol^{-1} ***relative*** **to 139**), since the non-bonded interactions are minimized. To analyze the origins of this barrier, all of the components must be known. A recent review categorizes these as Pauli exchange steric repulsion, hyperconjugation, and relaxation energy changes.[48] In addition, skeletal relaxation effects play a role.[48]



136 **137** **138** **139**

Although rotation of 360° about a carbon–carbon bond can generate an infinite number of rotamers, identification of the highest and lowest energy conformations will reasonably define the energy barrier to rotation about that bond. It is reasonable to assume that of all the possible conformations, there is some preference for the lowest energy rotamer, and ethane will have a higher population of **136** than any other rotamer. An energy curve describing the rotational motion of ethane is shown in Figure 1.2.[47e]

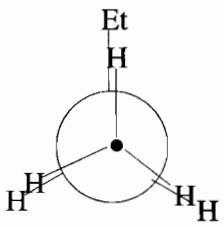
Figure 1.2 also includes the energies for rotamers arising from rotation about the C2—C3 bond in butane. In this analysis, rotamers **140A** and **140B** for the C1—C2 and C3—C4 bonds are ignored. Rotamer **141**, however, has two methyl groups eclipsing and the alkyl substituents impose an energy barrier to rotation (estimated at 4.5–4.9 kcal mol^{-1} = 18.8–20.5 kJ mol^{-1})[49] relative to the H-H interaction in **139** (ethane). This



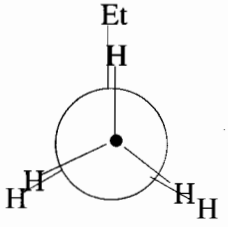
A = 138; B = I =139; C = H =148; D = 141A; E = 144 or **145; F = 149; G = 143** or **146**

Figure 1.2. Conformational energies of ethane, butane and 1,2-dichloroethane. [In part, reprinted with permission from Hine, J. Physical Organic Chemistry, 2nd Ed., McGraw-Hill, New York, ***1962***, p 36. Copyright 1962, McGraw-Hill.]

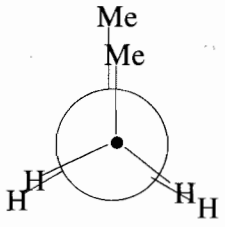
is reasonable because a methyl group is much larger than a hydrogen atom. The methyl–methyl interaction will be higher than the hydrogen-ethyl interaction in the other rotamers (C1-C2 or C3-C4) since the ethyl group is twisted away from the C2-C3 bond as shown in **142A** (a 3D drawing[4] of **140**) and **141A** and **141B** (the 3D drawings[4] of **141**). This means that an ethyl group imposes little more of an energy barrier than a



140A

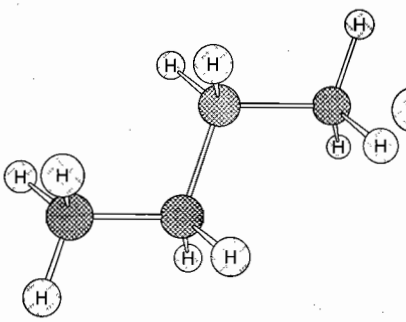


140B

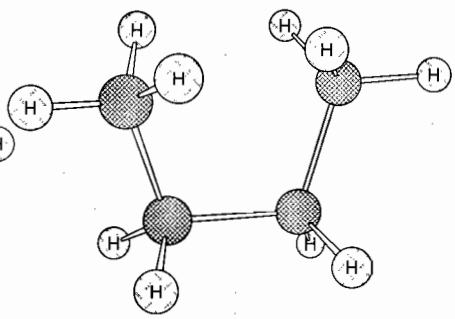


141

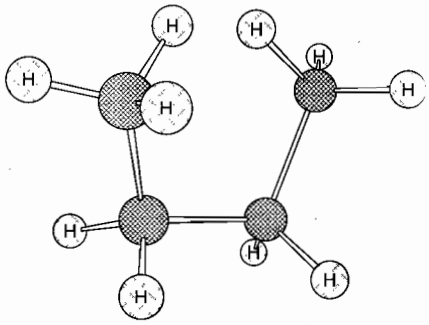
methyl group. It is reasonable to use **141** (see **141A**) to define the energy maximum for rotamers of butane, since this represents the highest energy steric interaction in all of the important rotamers, which are shown in Figure 1.2. As noted above, **141A** and **141B** simply provide different views of the molecule, focusing on different bonds. Rotamer **142B** represents the lowest energy conformation with the two methyl groups anti. The 3D drawings[4] are provided to give a better perspective of the actual steric interactions associated with each



142A



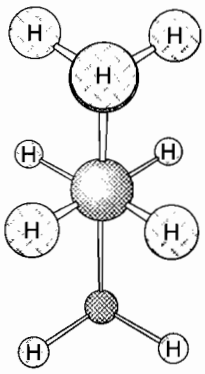
141A



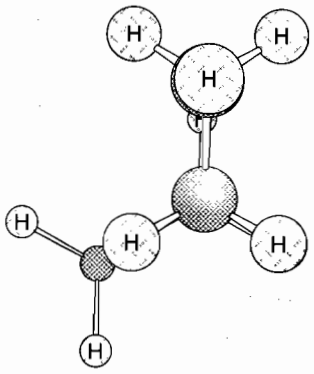
141B

rotamer. Rotamer **141A** represents the highest energy conformation, with the two methyl groups eclipsed. Rotation around the C2–C3 bond generates other high energy rotamers, such as **143** and **146** where there are two Me-H eclipsing interactions (each is 3.59 kcal mol^{-1} = 15 kJ mol^{-1}).[50] Both **144** and **145** (called **gauche** conformations) relieve eclipsing interactions but the methyl groups are closer than in **142B** and, therefore, higher in energy [0.96 kcal mol^{-1} (4 kJ mol^{-1})].[47b] The energy barriers for each conformation are compared with those of ethane in Figure 1.2. It is clear that the free rotation around the C2–C3 bond of butane is significantly more hindered due to the Me-Me interaction, which leads to a higher energy barrier than the one observed in ethane. An eclipsed butane rotamer is also higher in energy than an eclipsed ethane rotamer. Each 120° rotation of ethane generates an identical rotamer, but each 120° rotation of butane gives a different rotamer due to the presence of the methyl groups.

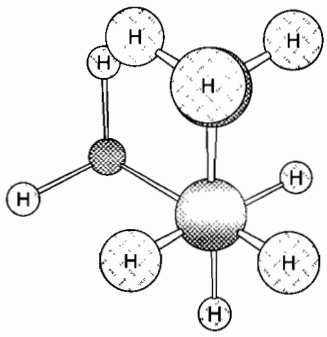
These energy barriers can be quantified in terms of enthalpy (H°), so it is possible to calculate the energy of a given rotamer and the relative population of that rotamer. For butane the calculation must also include



142B



143



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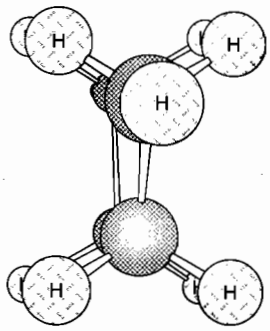
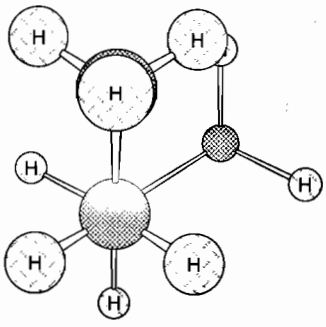


141A



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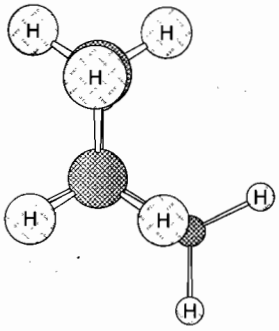
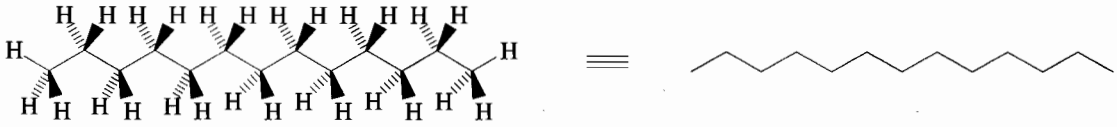


146

rotation about the C1—C2 and C3—C4 bonds. Since **142** is the most populous species, it is drawn to represent the most common conformation of butane. The relative energy of the conformations can be correlated with the relative percentage of each rotamer. An enthalpy difference of 1 kcal mol^{-1} (4.186 kJ mol^{-1}) between the

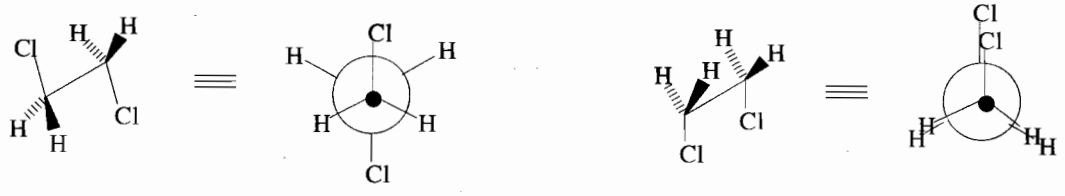


147

anti rotamer and the next most populous rotamer corresponds to about 72% of the anti-isomer being present at room temperature.[51] Note the zigzag, or extended, look of conformation **142**, which is typical of straight-chain alkanes. *n*-Tridecane (**147**), for example, can be represented in this conformation since each all carbon–carbon bonds will assume the lowest energy anti conformation to minimize non-bonded interactions. The sum of all these interactions leads to the extended conformation, and virtually all acyclic hydrocarbon chains will assume this conformation. Note the assumption by Masamune in sec. 1.4.B that the extended conformation of an acyclic molecule will lead to a conformation allowing one to establish syn or anti diastereomers .

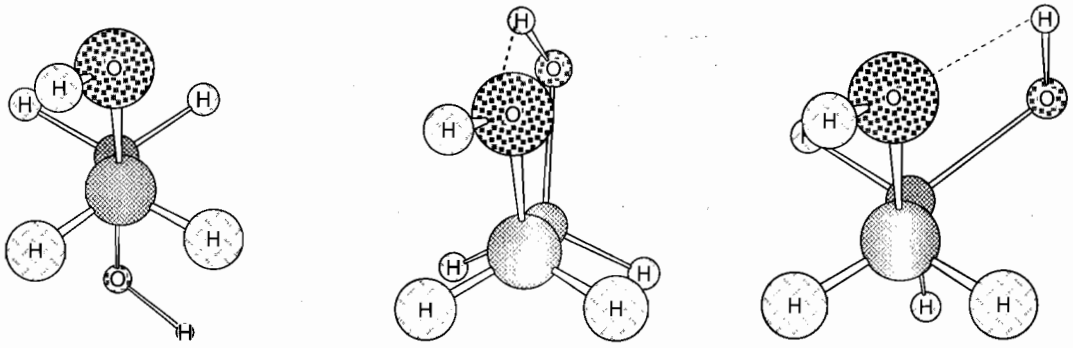
When heteroatoms are added to the chain, the size of the atom plays a role, just as the size of an attached group is important. In addition to this, however, the nonbonded electrons on those heteroatoms interact to influence the rotamer population relative to simple alkanes. In *anti*-1,2-dichloroethane (**148**), the chlorine

atoms are anti but in rotamer **149** they eclipse (the syn conformation). Not only are the chlorine atoms large but they possess three pairs of non-bonded electrons that contribute to severe electronic repulsion in **149**. This Cl–Cl interaction is the dominate energy term and leads to **148** as the lowest energy conformation. The rotamer population of 2,3-dichloroethane, presented in Figure 1.2 for comparison with ethane and butane, reveals that **149** is lower in energy than **141**. This suggests that the energy of a Me–Me interaction is greater than the energy of a Cl–Cl interaction but that the two Cl–H interactions are higher in energy than the corresponding Me–H interactions.



148 **149**

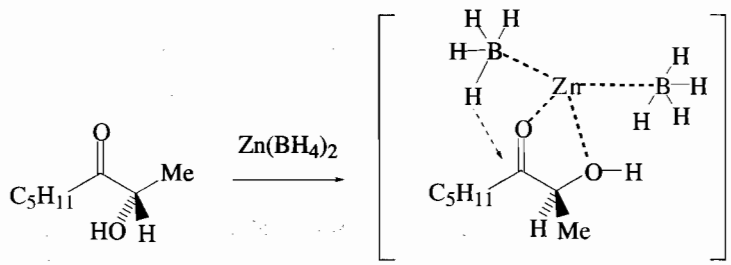
Some groups are capable of hydrogen bonding, providing a stabilizing interaction for a particular rotamer, which contrasts with the destabilizing interaction seen with the electronic repulsion of the chlorines. Examination of 2,3-ethanediol shows the anti conformation to be **150** and the eclipsed conformation to be **151**. The hydroxyl group is capable of hydrogen bonding, however, and the energy gained partially compensates for the strain arising from the eclipsed bonds. Rotating the molecule to the *gauche* conformation **152** relieves the eclipsing interaction but maintains the hydrogen bonding, making **152** the major low-energy conformation *if no hydrogen-bonding solvent is present.* In the presence of hydrogen-bonding solvents, inter-molecular hydrogen bonding tends to stabilize the anti rotamer **150**.



150 **151** **152**

Another way to stabilize an eclipsed or *gauche* conformation is to coordinate heteroatom substituents with a metal ion via chelation. Oishi and co-workers reduction of **153** with zinc borohydride proceeds via a chelated species, **154**.[52] Chelation of zinc to the hydroxyl and carbonyl groups effectively locks the conformation into that shown in the transition state required for reaction. The methyl and hydrogen are held in place, and the hydride is delivered from the less hindered face (over the hydrogen in **154**) to complete the reaction (see secs. 4.4.B and 4.7.B). Since transition metal salts usually behave as Lewis acids, the presence of a heteroatom with

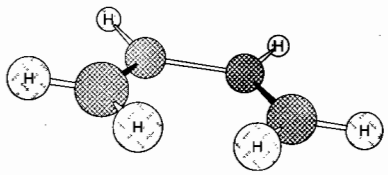
significant Lewis basicity (see sec. 2.3), such as O, S, N, or P will lead to chelation. The most favored acyclic conformation is usually an eclipsed or *gauche* rotamer.



153 **154**

1,3-Dienes are another class of acyclic molecules where conformational mobility can be important to reactivity. Examination of 1,3-butadiene shows that rotation about the C2—C3 single bond generates two rotamers: **155** with the two π bonds cis- to each other and **156** with the π-bonds trans. Rotamer **155** is called the s-cis conformation, and **156** is the s-trans-conformation. In **155**, the planar nature of the π-bond brings the two terminal hydrogens close together, leading to an energy barrier to rotation about C2—C3 of 5 kcal mol^{-1} (21 kJ mol^{-1}).[53] The two conformations are in rapid equilibrium, but **156** represents the major rotamer.

When the diene is substituted, (*E,E*)-, (*Z,E*)- and (*E,Z*)- dienes are possible. The s-cis- conformation of (*Z,Z*)-3,5-hexadiene (**157**) is in equilibrium with the s-trans-conformation, **158**. In **157**, there is a Me–Me interaction which is higher in energy than the H–H interaction in **158**. Although the s-trans conformer (**158**) has two methyl–hydrogen interactions, this is lower in energy than the Me–Me interaction in **157**.



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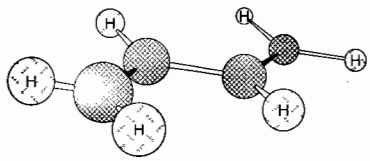

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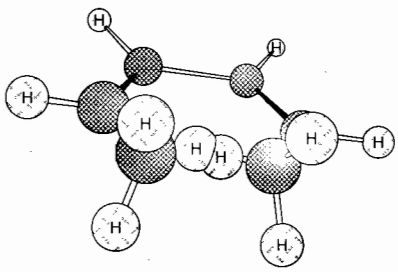

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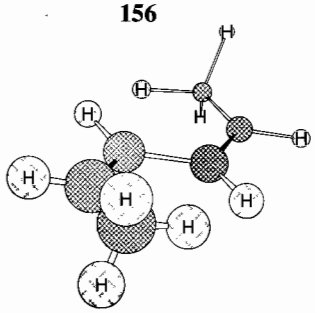


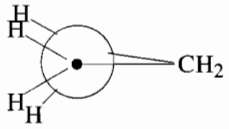
158

1.5.B. Conformations of Cyclic Molecules

Steric and electronic interactions influence the rotation about bonds within acyclic molecules, leading to a relatively small population of low-energy rotamers. Although cyclic compounds cannot undergo complete rotation, they must also dissipate energy absorbed from their environment. In part, this is done by twisting and bending vibrations that have the potential to generate an enormous number of conformations. As with acyclic

compounds, the repulsive energy interaction of adjacent groups and bonds limits the number of conformations actually observed. The cyclic nature of these molecules imposes additional energy barriers to conformational mobility.

A problem peculiar to cyclic molecules is deformation of the bond angles from 109°28' as the molecule attempts to rotate around the C—C bonds., which is particularly problematic when the ring is small. Cyclopropane, for example, exhibits a C—C—C bond angle of ≈ 60°, which induces great strain in the molecule. This type of strain is called **Baeyer** or **angle strain**. It is formally defined as the increase in energy of cyclic compounds that arises from the deformation of the optimum valence angle of 109°28' for sp^3 carbon or 120° for sp^2 carbon. The result of such strain is a higher ground state energy for cyclopropane and a higher energy barrier to forming the molecule by intramolecular cyclization (see below). Formation of three-membered rings is common but the higher ground state energy is important in the reactions of cyclopropane.[53] Deformation of the σ bonds leads to significant p character (the hybridization is $C^{sp^{2.3}}$), and many ring-opening reactions of cyclopropane mimic the chemistry of alkenes. The electron density between the carbon nuclei in cyclopropane is displaced somewhat from linearity between the nuclei.[54] Expansion of the ring by one carbon gives cyclobutane with bond angles of ≈ 90°. In planar cyclopentane, the bond angles are 108°. Cyclobutane has significant Baeyer strain, less than in cyclopropane, but more than in cyclopentane.



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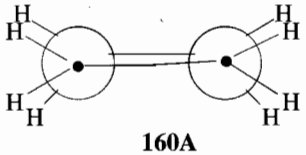
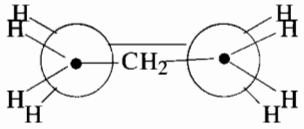
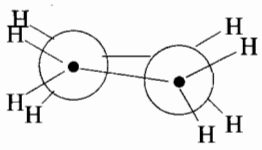


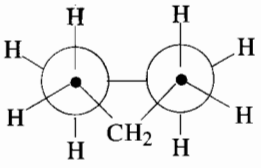
160A



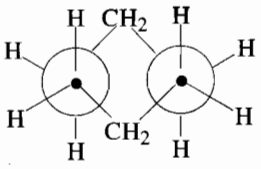
161A



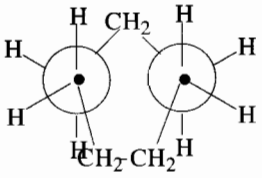
160B



161B



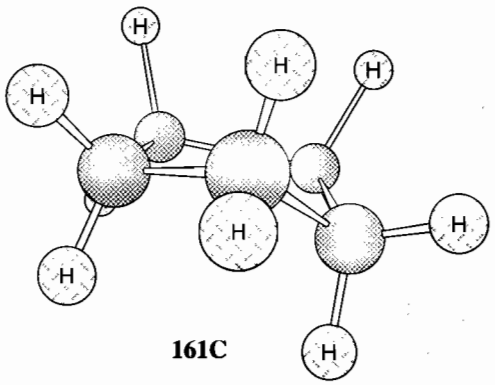
162A



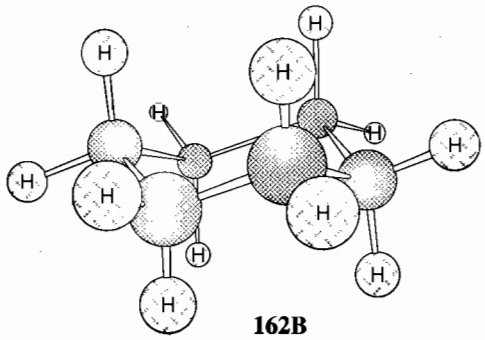
163A

Examination of the Newman projections for cyclopropane (**159**), cyclobutane (**160A**), and planar cyclopentane (**161A**) reveals a second major type of strain, which is the same as that seen in acyclic molecules. All C—H bonds in these planar molecules are eclipsed, with severe nonbonded interactions of the eclipsed hydrogens and electronic repulsion of the eclipsed bonds. This type of strain is called **Pitzer** or **bond opposition strain** and is defined as the increase in energy for a compound arising when adjacent bonds are eclipsed. bringing the attached atoms into close spatial proximity. For cyclic molecules, Pitzer strain occurs in the planar form. Free rotation is not possible, but twisting and bending vibrations of the molecules lead to partial rotations that relieve the Pitzer strain.[54] These motions lead to one or two low-energy conformations that are usually drawn to represent the entire molecule. For cyclobutane, a bent, or puckered conformation (**160B**) results from partial rotation.[55] For cyclopentane, the bent conformation assumes an envelope shape as in **161B** [56] and bending on both ends of planar cyclohexane leads to the familiar chair conformation (**162A**).

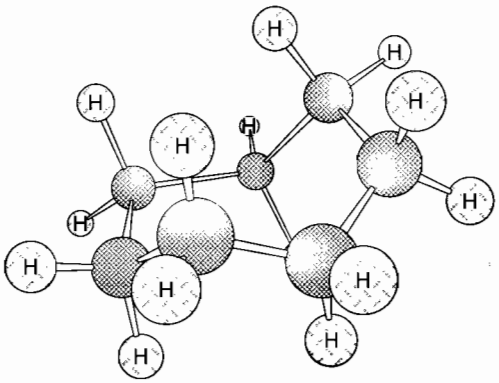
Addition of the extra carbon in cycloheptane allows a chair conformation but two of the carbons eclipse, leading to some Pitzer strain (see **163A**). The 3D drawings[4] of cyclopentane (**161C**), cyclohexane (**162B**), cycloheptane (**163B**), and cyclooctane (**164A**) reveal the C-H bonds in **161C** and **162B** assume a *gauche*-like conformation, relieving virtually all of the Pitzer strain. The smaller ring cavity of the cyclobutane ring allows fewer degrees of freedom in its pseudo rotational motion, and it possesses more Pitzer strain. Bent cyclobutane (**160B**) has less Baeyer strain than the planar form (**160A**).[56] Although Baeyer strain is increased in the envelope conformation (**161C**),[57] the decrease in Pitzer strain more than compensates and **161C** is the low-energy conformation of cyclopentane. Chair cyclohexane has virtually no Baeyer strain since the bond angles are 109°28' and cycloheptane has similar bond angles.[58] Cycloheptane (**163B**) shows at least two of the C—H bonds are fully or partially eclipsed in this low-energy chair conformation, which leads to an increase in Pitzer strain relative to chair cyclohexane.



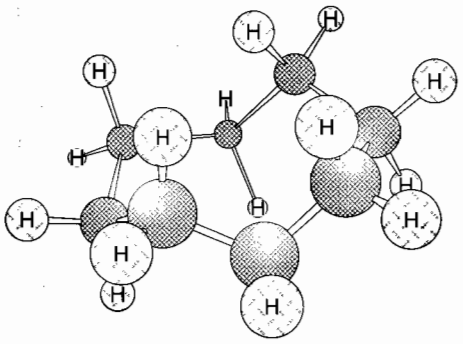
161C



162B



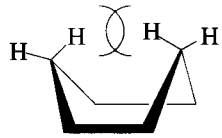
163B



164

Other conformations are accessible to cyclohexane given the available energy. For cyclohexane, a boat conformation (**165**) is higher in energy than the chair (**162B**), due to increased Pitzer strain of the four coplanar carbons. There is also a cross ring (**transannular**) interaction of the 1,4-hydrogens (referred to as flagpole hydrogens). There is a twist conformation (**166**) that is lower in energy than the boat but higher than **162B**. An envelope, or half-chair, conformation (**167**) is very high in energy due to the five coplanar carbons, which greatly increases Pitzer strain. Cycloheptane also has a boat form (**168**) that is actually very close in energy to chair cycloheptane (**163B**).[59]

The molecular conformations induced by relief of Baeyer strain and Pitzer strain are reflected in the energy required for intramolecular cyclization reactions to form each ring. As two reactive ends of the acyclic fragment come together, the strain inherent to the ring product becomes important (see sec. 6.6.B.i). In other



165

166

167

168

words, the acyclic precursor assumes the conformation of the ring that is being formed in the transition state of the reaction. Strain in this transition state is important for the formation of the cyclic product. Figure 1.3(a) shows the relative reactivity for formation of lactones from ω-hydroxy acids of ring size C_3 to C_{17}.[60] There is a reactivity maximum at C_5 and reactivity minima at C_3 and C_8.[60] Figure 1.3(b) shows the enthalpy (ΔH) of

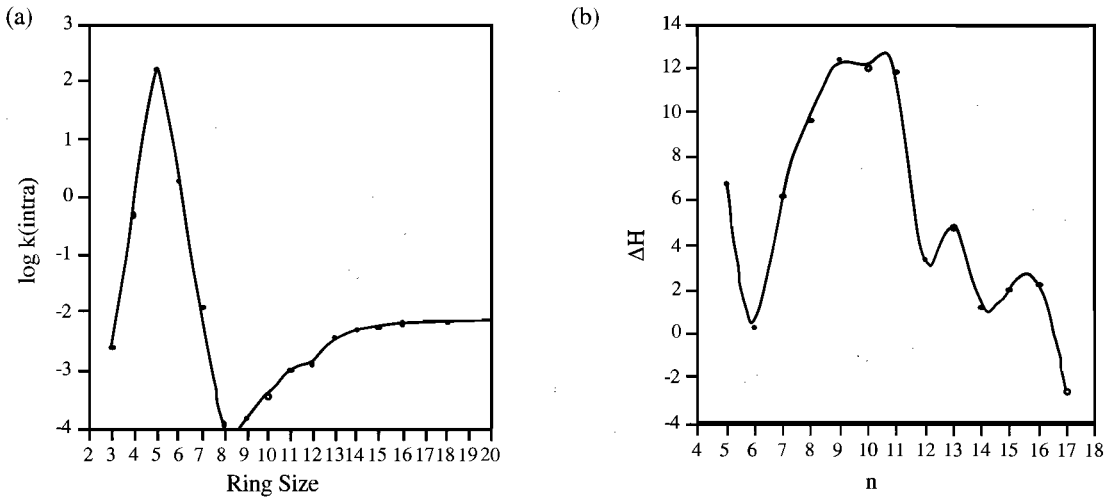
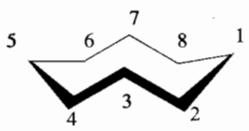


Figure 1.3. (a) Reactivity profile for lactone formation. (b) Enthalpy of cycloalkanes [C_nH_{2n}]. [Reprinted with permission from Illuminati, G.; Mandolini, L. *Acc. Chem. Res.*, *1981*, *14*, 95. Copyright © 1981 American Chemical Society.]

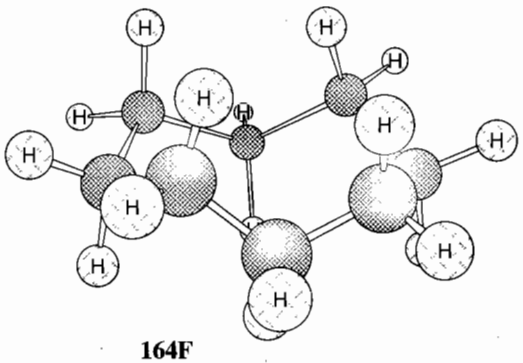
several cyclic alkanes, with a minimum at C_6 and a maximum at C_9.[61] There are two other important features of Figure 1.3 (b). Rings of C_8–C_{13} members are significantly higher in energy than the small rings $C_3 \rightarrow C_7$ and large rings ($\geq C_{14}$). These medium size rings can be formed but only with great difficulty using intramolecular cyclization.[60] The other feature of Figure 1.3(b) is the higher energy required to form rings with an odd number of atoms when compared to the energy required to form rings with an even number of atoms. This difference is best seen by comparing cyclohexane and cycloheptane. The odd carbon in cycloheptane is not easily accommodated by the low-energy chair (all *gauche*) form and will give an increase in Pitzer strain.[61,60] Similar effects are seen for all odd carbon rings.

As the ring size increases, similar Baeyer and Pitzer strain will lead to chair-like conformations. Indeed, an inspection of cyclooctane reveals at least two chair-like conformations, **164B** and **164C**. In **164B**, the two

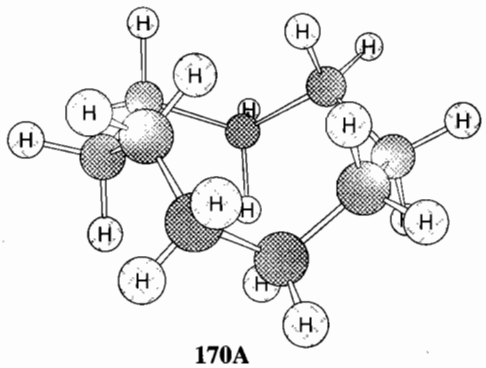


164B **164C** **169A** **164D** **164E**

chairs are the C_1-2-3-7-8-ring and the C_5-4-3-6-7-ring. In **164C**, there is a boat-like interaction that energetically destabilizes **164C** relative to **164B**. Conformation **164B** is usually called the crown conformation and is often taken to be the lowest energy form of cyclooctane. There is a boat conformation for cyclooctane (**164D**)[62,60] and a chair conformation (**164**E),[63] but both are higher in energy than the crown (**164B**).[64] A similar crown conformation is seen for cyclodecane, **169A**.[61b,65] Actually, **169A** conforms to the same extended chair conformation found in diamond (see Fig. 1.4) and cyclodecane fits nicely on this diamond lattice,[62] so it is taken as the lowest energy conformation. The odd-membered ring in cyclononane possesses the twist mentioned with cycloheptane, with the attendant increase in Pitzer strain, which causes an increase in energy and, as seen in Figure 1.4, the molecule cannot superimpose on the diamond lattice. These features are seen in the 3D drawings[4] **164F** (cyclooctane), **170A** (cyclononane), and **169B** (cyclodecane). Even large rings such as cyclooctadecane retain this chair-like or crown-like conformation as the lowest energy form (see **171A**).



164F



170A

This finding does not explain the energy maxima for medium size rings (C_8 to C_{13}), however, and does not explain why the energy falls as the size of the ring increases in Figure 1.3. Another type of strain inherent

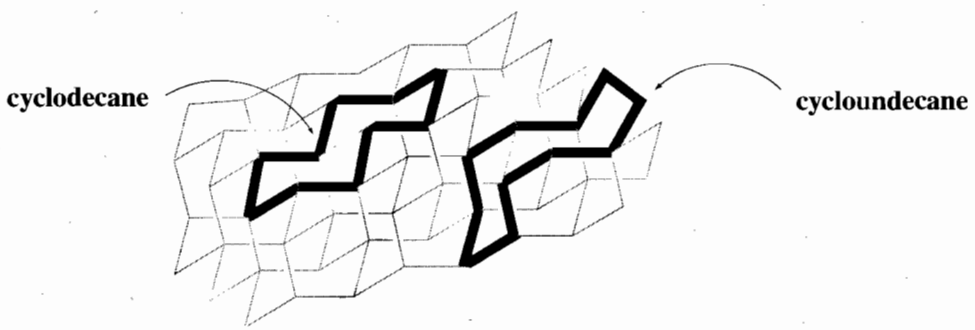
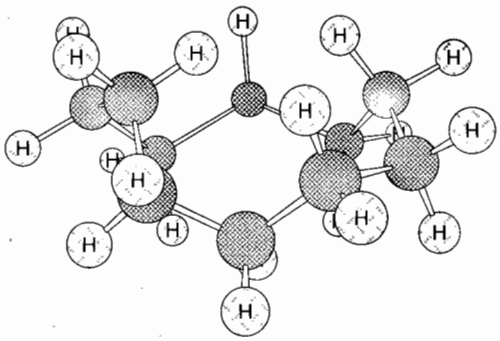
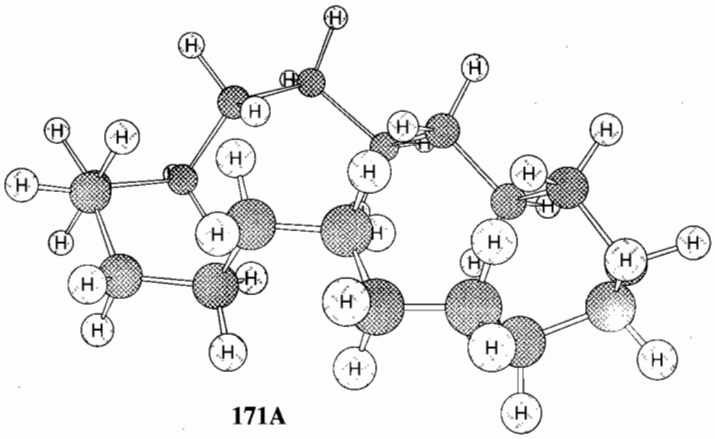


Figure 1.4. Cyclodecane and cycloundecane on a diamond lattice.

in large ring compounds must be introduced Examination of chair conformation **162B** shows that the axial hydrogens are close together in space and as the hydrogen atoms are replaced by alkyl groups, this 1,3-diaxial nonbonded interaction leads to increased strain (see sec. 1.5.D). Closer inspection of **164F** and **169B** also

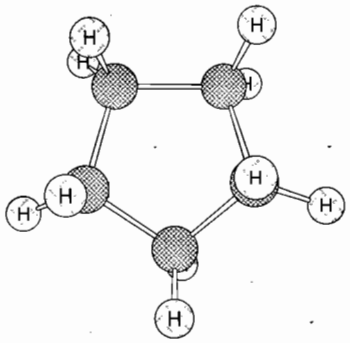


169B

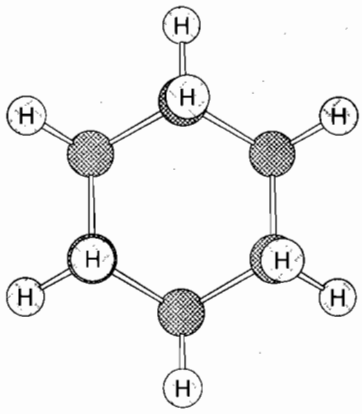


171A

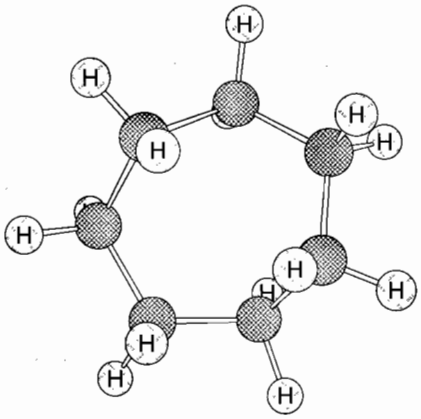
shows that as the degrees of freedom for each ring increases with size, the pseudo-rotational motion increases, bringing the axial hydrogens into close proximity, *within the cavity of the ring*: a **transannular interaction**.[60] To better see this interaction, 3D views of cyclopentane–cyclooctadecane are shown from a new perspective,



161D

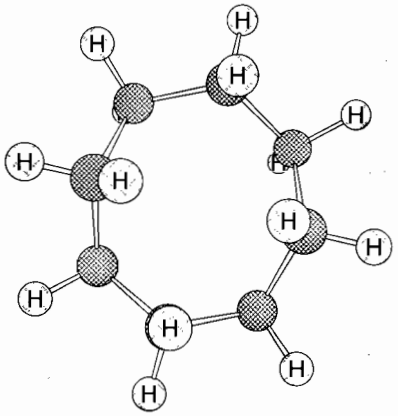


162C

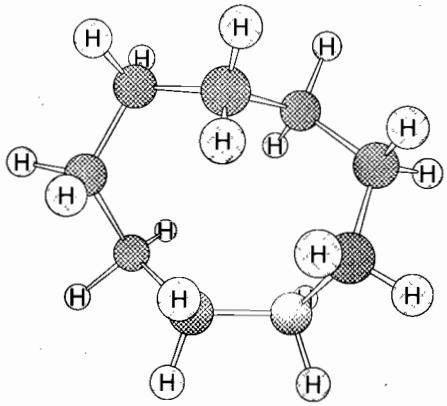


163B

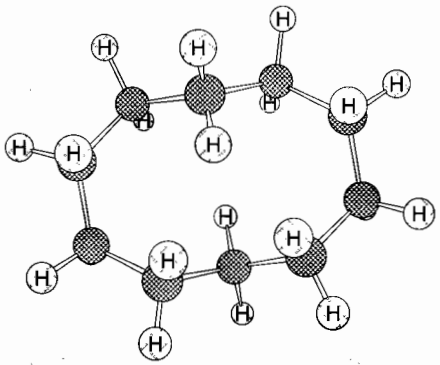
from the top of each ring. The internal cavities of cyclopentane (**161D**) and cyclohexane (**162C**) are empty, revealing no transannular interactions. In cycloheptane (**163B**), two of the hydrogens can approach each other within the cavity, contributing to the higher energy of cycloheptane. In crown-cyclooctane (**164G**), these transannular hydrogens approach much closer within the cavity, leading to an significant increase in the inherent energy for that ring. There is also significant transannular strain in cyclononane (**170B** and crown-cyclodecane (**169C**). As the ring size increases, the cavity becomes larger and the net energy decreases after reaching a maximum at cyclodecane. Although the potential for a transannular interaction is quite high in cyclooctadecane (**171B**), the large cavity and increased degrees of freedom available for vibrational motion allow the transannular hydrogens to sweep past each other. The cavity inside the ring is large enough to accommodate these atoms without generating a large energy gradient.



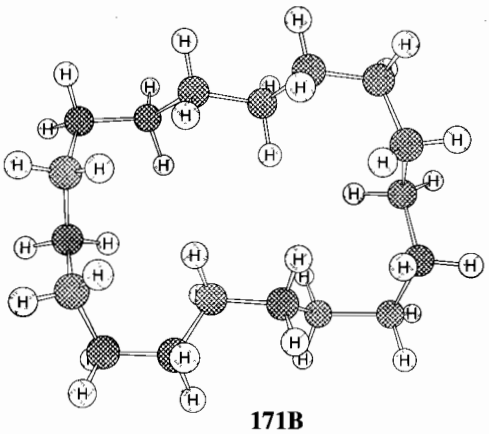
164G



170B

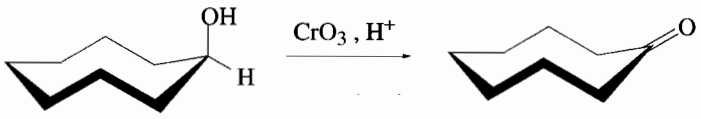


169C



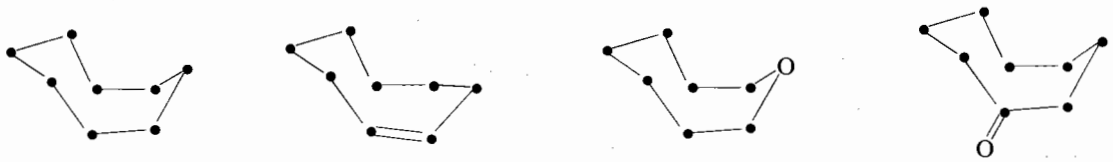
171B

As shown above, the higher energy of medium size rings results from unfavorable dihedral angles.[65] This type of strain has been termed **I-strain** (internal strain).[66] Formally, I strain involves the change in strain when going from a tetrahedral to a trigonal carbon or vice versa (as in changing an alcohol to a ketone). For medium-size rings, tetrahedral bond angles bring the transannular substituents into close proximity. Conversion to a trigonal planar carbon relieves this interaction somewhat and lowers the energy of the system.[67] An example is the oxidation of cyclooctanol (**172**) to cyclooctanone (**173**, see sec. 3.2.A). The reverse process (the reduction, see secs. 4.2.B, 4.8.C, 4.9.B: **173** → **172**) would be more difficult due to the increased *I* strain as well as increased transannular strain in the alcohol.[68]



172 **173**

The presence of a heteroatom, a C=C unit, or a carbonyl influences the conformation of medium-size rings, but the changes are often subtle. The calculated low-energy conformation of cyclooctane (**174**) is compared with those of *cis*-cyclooctene (**175**), the ether oxocane (**176**) and cyclooctanone (**177**). Although **175** is somewhat flattened, the conformations of the other three eight-membered rings are rather similar.[69]

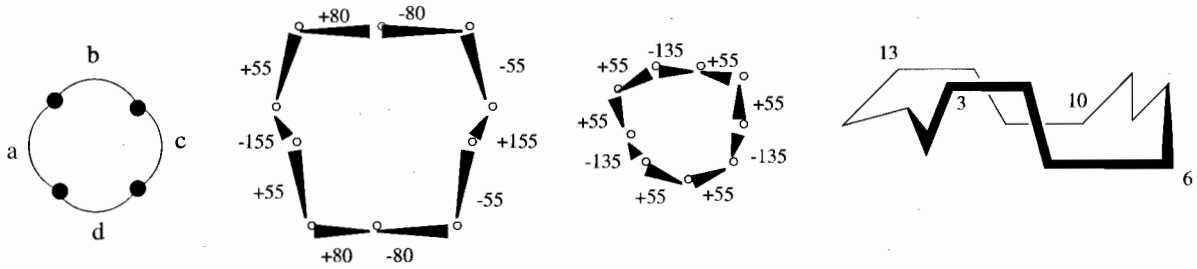


174 **175** **176** **177**

1.5.C. Polar Mapping and Conformational Analysis of Macrocycles

Estimating the conformations of large ring compounds (macrocycles) is more complicated and more difficult than with compounds discussed in the section 1.4. Since this class of compounds includes macrolide antibiotics,[70a] important commercial products such as muscone, and also crown ethers,[70b] there is a great deal of interest in macrocycles.[70] Both the chemical and physical properties of macrocycles depend on the conformations of the large ring.[71] An analysis of conformations of small and medium ring compounds was reported that used an analysis of the sign of torsional angles,[72] and when combined with the use of dihedral maps,[73] Weiler[74] produced a polar map analysis of macrocycles that yielded conformational information. This method has also been applied to the conformational analysis of macrocyclic ethers.[75]

In Figure 1.4, the diamond lattice was taken to be a low -energy conformation of cyclodecane. Another way to represent this conformation is based on Dale's numerical system describing the number of bonds found between corner atoms.[76c] Dale's system is sometimes called wedge notation.[77] Unfortunately, this can be somewhat difficult to calculate, and the method does not seem to be widely used. It is based on the idea that even-membered rings can exist in four quadrangular (four-cornered system) conformations (see **178**). (1) All

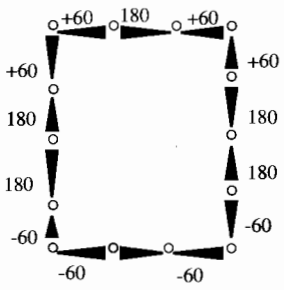


178 **179** **180** **181**

four sides contain an odd number of bonds (a-d = odd). (2) Two adjacent sides are odd with the others even (*ab* odd, *cd* even; or *bc* odd, *ad* even). (3) Two adjacent sides are odd with the others even (*ac* odd, *bd* even: or bd odd, ac even). (4) All sides contain an even number of bonds ($a \rightarrow d$ = even). For odd membered rings. the best conformation arises when there are three (a triangular system) or five corners (a quinguangular system). When there are three corners, all three sets can be odd, or two can be even with one odd and one side must have one or more convex faces. For five corners, all can be odd, two adjacent or next to adjacent can be even with the other three odd, or one can be odd and four even. In this case, there must be one or more concave faces.

The actual notation is illustrated for the diamond form of cyclodecane (see Fig. 1.4) and **179**. The dihedral angles were measured from a Dreiding Model™ (this can also be done with appropriate computer

software) and the corners determined for a given conformation. For **179**, those angles for the four corners are +55/+80 and –55/–80. This method takes the number of bonds on each side, starting with the shorts side and gives the lowest possible combination of numbers. For **179**, there are 2, 3, 2 and 3 bonds, respectively, and this is [2323]-decane. Nonane has an odd number of atoms and has three corners. Conformation **180** represents nonane and it has three corners with angles determined to be +55/+55, leading to the notation [333]nonane. For cyclotetradecane, the lowest energy conformation is **181**, the [3434] conformation (see Fig. 1.5 and the bond angles in **182**). This finding is compared with [3344]-tetradecane (the bond angles are shown in **184**), which leads to the conformation shown in **183**, and is somewhat higher in energy than **181**.



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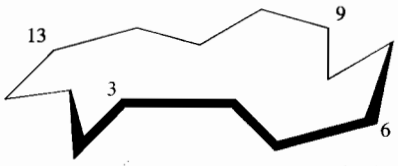

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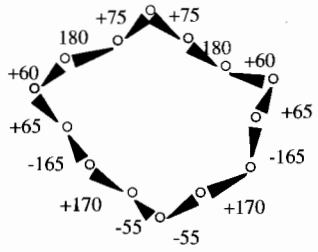
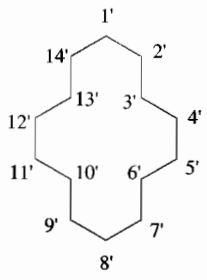


184

When substituents are attached to large rings, they tend to occupy only exterior positions to minimize the large transannular interactions.[78] A fully substituted atom of a macrocycle will usually occupy a corner position since this is the only position where it does not cause severe transannular strain.[76] For both substituted and unsubstituted macrocycles, the conformation of the ring will impose restraints on the torsional angles available to each unit of carbons (four carbons define a torsional angle). If these four atoms are shown



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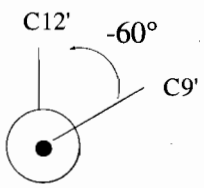

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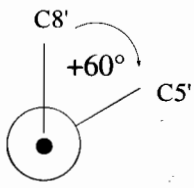

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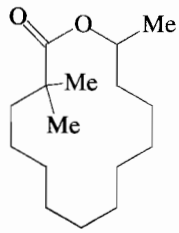


188

in a Newman projection, and if the rotation of the angle from the front plane to the rear plane is clockwise, the torsional angle is positive; counterclockwise is negative. The atoms of cyclotetradecane are numbered as in **185**. Viewing individual torsional angles between C12' and C9' (see **186**) and between C8' and C5' (see **187**) shows a negative torsion angle in **186** and a positive torsional angle in **187**.[74a] The conformation of **181** can be described by a polar map constructed from the torsional angles taken from the model. Ogura et al.[73] were the first to use a polar map of torsional angles to describe the conformation of oleandomycin. Weiler and co-workers[74] used this method to describe the conformations of many macrocyclic molecules, in great detail. One example is conformation **181** ([3434]-cyclotetradecane.), arrived at by plotting the polar map using the

torsion angles from **182** (see Fig 1.5).[74a] This figure has a C_2 axis running through the middle of torsional angles 4 and 11 (bonds C4'—C5' and C11'—C12' in **185** and the molecule has a center of symmetry.

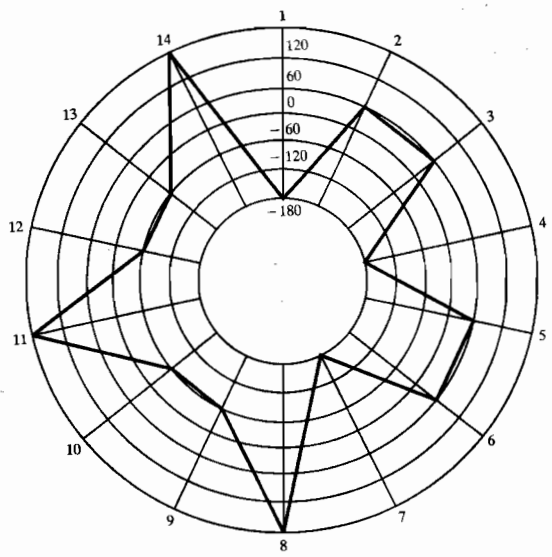


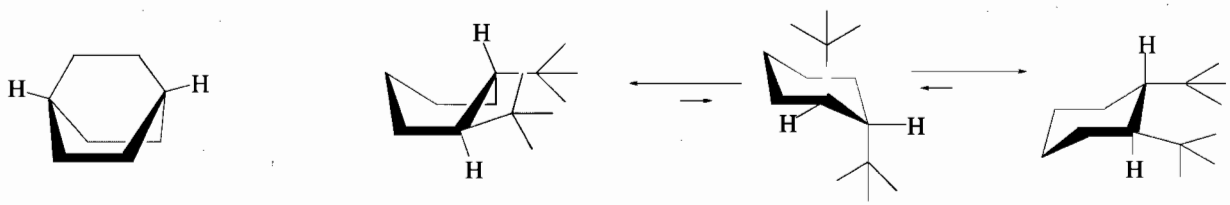
Figure 1.5. Polar map of the torsional angles of the [3434] conformation of cyclotetradecane (181). [Reprinted with permission from Keller, T.H.; Neeland, E.G.; Rettig, S.; Trotter, J.; Weiler, L. *J. Am. Chem. Soc.*, ***1988***, *110*. 7858. Copyright © 1988 American Chemical Society.]

Once Dale's notation is understood and the torsional angles are determined, polar mapping can be used to describe a variety of macrocycles.[74b] As the number of folds in the polar map increases, the relative energy of that conformation increases. Weiler[74b] also presented polar maps and Oak Ridge thermal ellipsoid plots (ORTEP) diagrams for a number of even-membered ring macrolides, which generally assume a [3434] or a [3344] conformation as the low-energy conformation. The use of polar maps of torsional angles may be of great value for determining the conformation of many macrocyclic compounds. Fourteen-membered 3-keto lactones, for example, have been synthesized and their conformations analyzed using this technique.[79] This ability to predict conformational bias is important to the stereochemical outcome of chemical reactions involving macrocyclic rings.

1.5.D. Estimating Conformational Populations

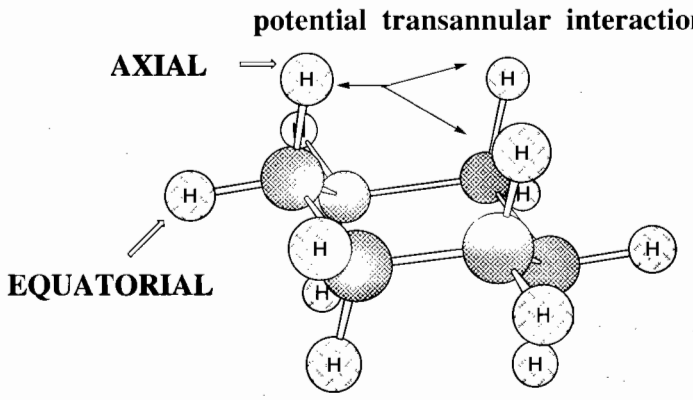
The preceding discussion focused on a low-energy conformation of several ring compounds, but in fact there may be several conformations for each ring that lie close together in energy. To obtain a complete picture, several conformations of equal, close, or higher energy may also have to be considered. The conformational mobility of cyclohexane includes, for example, the two low-energy chair conformations, six degenerate twist–boat conformations, and six degenerate boat conformations.[80,81] It is possible to interconvert the two chairs by deforming one side of the ring to the half-chair, without passing through the planar conformation. The planar conformation shows a great increase in both Pitzer and Baeyer strain, making it quite high in energy. A half-twist of the half-chair gives the so-called twist–boat, which is lower in energy, since Baeyer and Pitzer strain are diminished. Another partial twist gives the higher energy boat, which

possesses a transannular interaction (as shown) analogous to those seen in larger rings and significant Pitzer strain in the four coplanar carbon atoms. Further twisting generates six identical twist–boats, the boat, a new half-chair and eventually the new low-energy chair conformation. If all the energies for the various conformations are known, it should be possible to estimate the percent of each. Since the chair conformation usually



189 **190A** **190B** **190C**

constitutes the majority of this conformer population, the other conformations can be ignored for an initial estimation. This assumption is very reasonable. Eliel et al.[82] estimated that the energy difference between the boat and chair forms is about 4 kcal mol^{-1} (16 kJ mol^{-1}) , and this means "only one molecule in a thousand will be in the boat form", at 298 K (25°C). It is noted that the boat form exists in certain bridged cyclohexane molecules such as bicyclo[2.2.2]-octane (**189**), which is all boat, or it may be forced on the ring by bulky substituents (e.g., *trans*-1,2-di-*tert*-butylcyclohexane), which contains about 12% of the boat **190A**.[82,83] In the chair conformations, one chair form (**190C**) shows significant steric interactions because the two equatorial *tert*-butyl groups are in close proximity, whereas in the diaxial chair (**190B**) those groups do not interact at all. Interestingly, the interaction of the *tert*-butyl groups is somewhat relieved in the twist-boat conformation, which exists alongside the more stable **190A**.[82]



162D

In general, the chair conformations are lower in energy, but **190B** and **190C** reveal two major sources of strain in chair cyclohexanes. In **190B**, each axial *tert*-butyl group interacts with the two axial hydrogen atoms on its side of the ring (a **1,3-diaxial interaction** that is labeled ***A* strain**) and the energy of this interaction (the ***A* value**) is about 12 kcal mol^{-1} (50.2 kJ mol^{-1}), or 6 kcal/*tert*-butyl group.[84] Chair cyclohexane contains both axial and equatorial bonds (see **162D**). Substituents in the axial positions compete for the space above and below the ring, giving rise to a transannular interaction (*A* strain, see Fig. 1.6). In cyclohexane, this

interaction is minimal because hydrogen atoms are relatively small as seen in the space filling model (**162**E). When one hydrogen is replaced with a methyl group (methylcyclohexane, **191**), the steric interaction between methyl and hydrogen is greater, making the transannular interaction much higher in energy, relative to the hydrogen–hydrogen interaction of cyclohexane. ***This is A strain.*** In 1,3-dimethylcyclohexane (**192**) and in 1,3,5-trimethylcyclohexane (**193**) *A* strain increases significantly as the steric interactions increase.

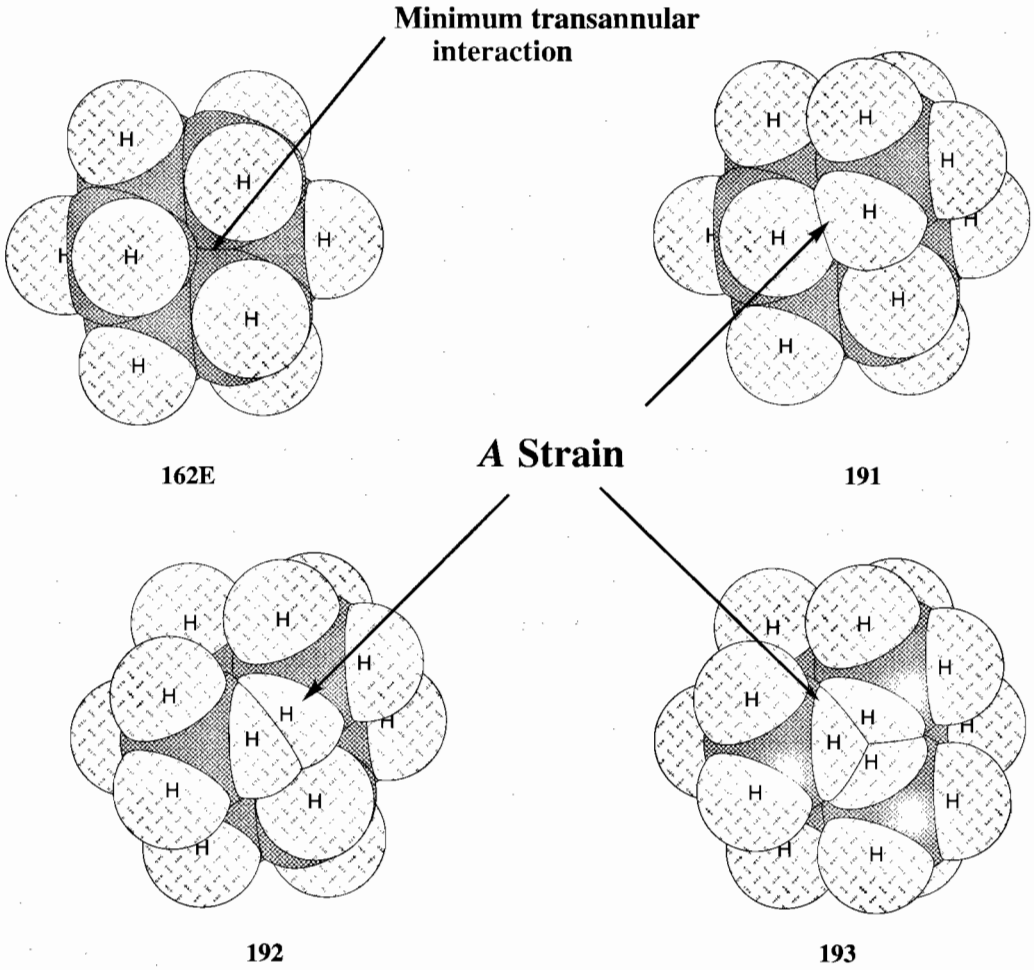


Figure 1.6. *A* Strain in cyclohexane, methylcyclohexane, 1,3-dimethylcyclohexane, and 1,3,5-trimethylcyclohexane.

In **190C**, the 1,2-diequatorial *tert*-butyl groups are in close proximity, producing a new type of strain called ***G* strain** and the energy of the interaction (the ***G* value**)[85] is 2.5 kcal mol^{-1} (10.47 kJ mol^{-1}) per *tert*-butyl group (see Fig. 1.7). This is analogous to the interactions found in the *gauche* butane conformation and is often referred to as a *gauche* interaction. The trans-diequatorial hydrogens in **162**E show little interaction but replacing them with methyl (see *trans*-1,2-dimethylcyclohexane, **194A**) causes significant *G* strain. When the two *tert*-butyl groups in **190** are trans-diequatorial (see **190C**) the interaction is very large and destabilizes that conformation. The space-filling models[4] of 1,2-dimethyl-cyclohexane (**194B**) and 1,2-di-*tert*-butylcyclohexane (**190D**) attempt to show the nature of the *G* strain in cyclohexane derivatives.

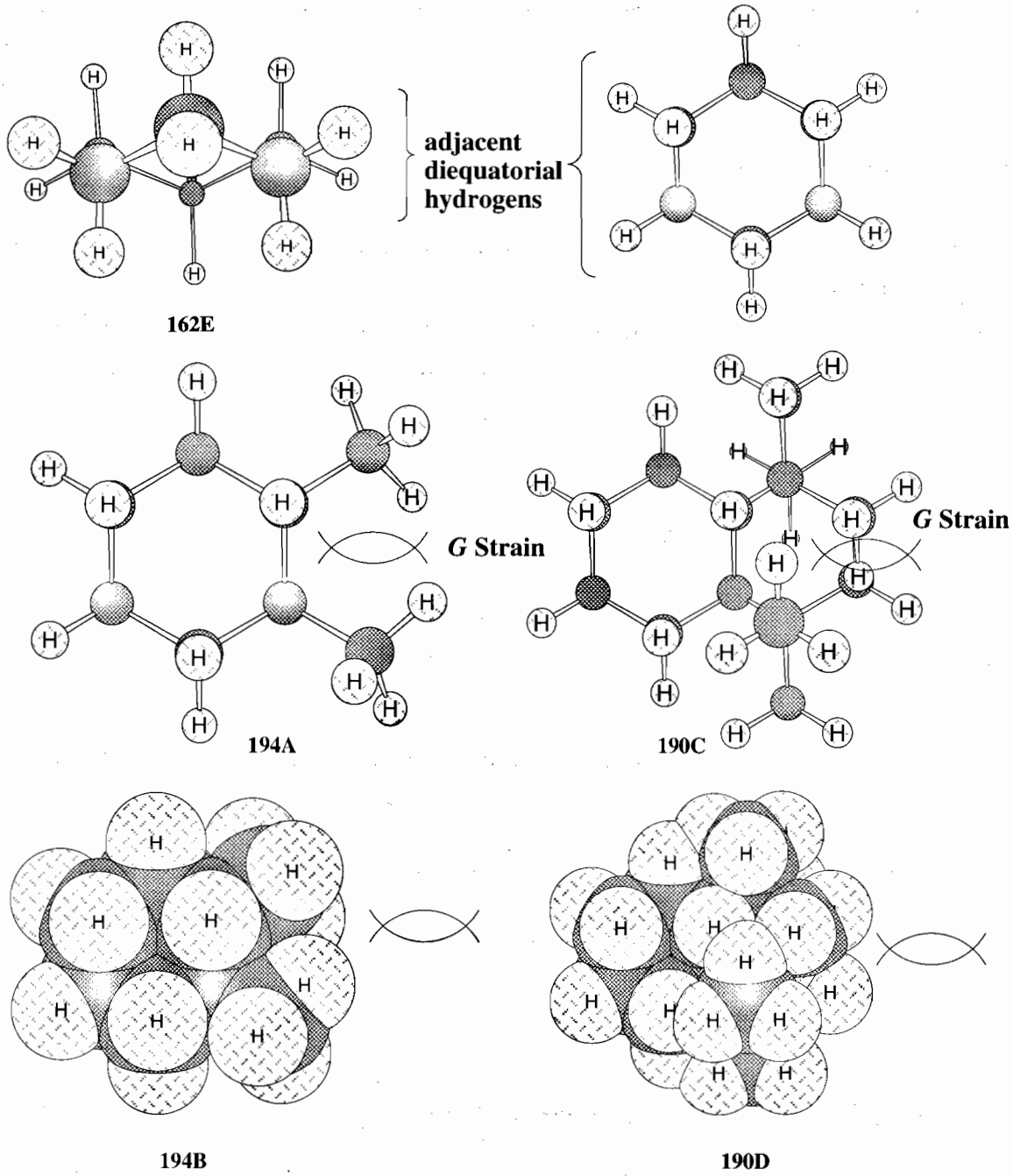
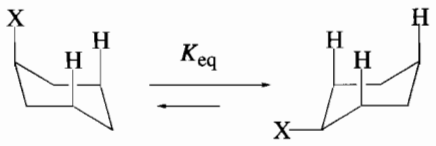


Figure 1.7. *G* Strain in 1,2-dimethylcyclohexane and 1,2-Di-*tert*-butylcyclohexane.

Why are these physical chemistry concepts being discussed in a reactions-synthesis book? It will be apparent throughout this book that the conformation of a molecule has a critical effect on the reactivity and stereochemistry of many reactions (see chapter 6 for examples). In many cases, the various strain energies that influence the conformation of a molecule can be quantified and the percentage of each conformation can be calculated. With such information, more reasonable predictions of reactivity and stereochemistry can be made. The following protocols are therefore presented in an attempt to reinforce the idea that conformational

analysis is a critical part of synthetic analysis and to introduce the most basic approaches to conformational analysis.

We will focus on cyclohexane derivatives to illustrate the fundamental idea When a reagent approaches a cyclohexane ring, the conformation of the ring will influence how the reagent interacts with any functional group on that ring. The populations of the two chair conformations that dominate the conformational population of cyclohexanes can influence the relative rate and the stereochemical outcome of a given reaction. The relative populations of the two chair conformations in cyclohexane derivatives can be predicted with some



195 **196**

accuracy by calculating the *A* and/or *G* values. For a monosubstituted cyclohexane, two chair forms are possible, **195** and **196**, and they are in a dynamic equilibrium. If X ≠ H, the diaxial steric interaction (*A* strain) in **195** will be larger than in **196** and a higher percentage of **196** is expected. This non-bonded interaction can be measured in terms of $F°$, the conformational free energy.[86] Since there are two conformations of differing energies, this difference is represented by ($\Delta F°$),[80a] and it is possible to relate this energy term to the free energy of the system by:

$$\Delta G° = \Delta H° - T\Delta S°$$

For a given temperature, the entropy term will be small relative to $\Delta F°$ (taken to be $\Delta H°$ hereafter) and a second assumption can be made, that $\Delta S° = 0$, leading to

$$\Delta G° \approx \Delta H°$$

The entropy term in not zero, of course, but since the $\Delta S°$ term is usually measured in calories and the $\Delta H°$ term in kilocalories, ignoring $\Delta S°$ will introduce only a small error into the calculation. This difference is demonstrated in Lowry and Richardson's[87] list of $\Delta H°$ and $S°_{298}$ values for a variety of specific bonds. In the C—Me bond, for example, $\Delta H°$ is -10.08 kcal mol^{-1} (42.2 kJ mol^{-1}), whereas $S°_{298}$ is 30.4 cal mol^{-1} (127.2 J mol^{-1}, 0.03 kcal mol^{-1}). Similarly, $\Delta H°$ for cyclopropane is listed as 27.6 kcal mol^{-1} (115.5 kJ mol^{-1}), whereas $S°_{298}$ is 32.1 cal mol^{-1} (134.3 J mol^{-1}, 0.03 kcal mol^{-1}).[87]

The $\Delta H°$ term is related to $\Delta G°$, the free energy, which is related to the equilibrium constant by the expression:

$$\Delta G° = -2.303\ RT \log K_{eq}$$

The conformational equilibrium between **195** and **196** is represented by K_{eq}, which can be calculated from the percentage of the two conformers:

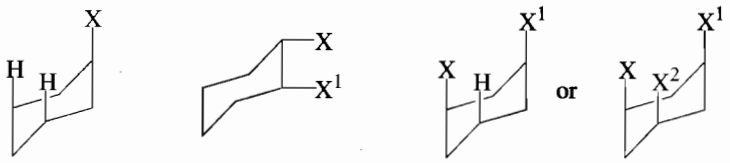
$$K_{eq} = \frac{\%\ \mathbf{196}}{\%\ \mathbf{195}}, \qquad \text{where} \quad \%\ \mathbf{195} + \%\ \mathbf{196} = 100\%$$

It is noted that a general discussion of the Curtin-Hammett principle[86c-f] (product composition is related to the relative concentrations of the conformers)[86i] may be of value in any discussion of this equilibrium reaction.

For this process to work, some estimation of $F°$ (hereafter called $H°$) must be made. In connection with the

development of the interactive synthesis computer program *L*ogic and *H*euristics *A*pplied to *S*ynthetic *A*nalysis (LHASA; sec. 10.4.B),[1,5] Corey developed a protocol for deter-mining the conformational energies of cyclohexane derivatives[85] and assembled a list of *H* values for various substituent interactions in Table 1.5.[85] This table is related to a similar one first assembled by Hirsch and co-workers.[88,89] The energy for a given conformation is taken to be the sums of all monoaxial interactions (*A* values for **195**), any 1,2-diequatorial interactions (*G* values for **197**) and any multiple diaxial interactions (defined by Corey as *U* values[80] and found in the two structures labeled **198**). Simple doubling or tripling of the appropriate *A* value did not give correct results in this latter case and more accurate U-values were required. It is noted that the *A* and *U* values are identical in many cases. They usually differ if the substituent contains unsaturation.

Table 1.5. Corey's *A*, *G* and *U* Values for Calculating Conformational Energies of Cyclohexane Derivatives



195 **197** **198**

Group	*A* (kcal mol^{-1})[a]	*G* (kcal mol^{-1})[a]	*U* (kcal mol^{-1})[a]
H	0	0	0
F	0.2 (0.84)	0	0
Cl	0.4 (1.67)	0.5 (2.09)	0.4 (1.67)
Br	0.4 (1.67)	0.8 (3.35)	0.4 (1.67)
I	0.4 (1.67)	1.0 (4.19)	0.4 (1.67)
PR_3	1.6 (6.7)	1.6 (6.7)	1.6 (6.7)
SR	0.8 (3.35)	0.5 (2.09)	0.8 (3.35)
S(O)R	1.9 (7.95)	2.7 (11.30)	1.9 (7.95)
$S(O_2)R$	2.5 (10.47)	3.5 (14.65)	2.5 (10.47)
OR	0.8 (3.35)	0.2 (0.84)	0.8 (3.35)
NH_3^+	2.0 (8.37)	0.5 (2.09)	2.0 (8.37)
NR_3^+	2.1 (8.79)	0.5 (2.09))	2.1 (8.79)
NHR	1.3 (5.44)	0.3 (1.26)	1.3 (5.44)
N=	0.5 (2.09)	0.1 (0.42)	0.5 (2.09)
N≡	0.2 (0.84)	0.1 (0.42)	1.2 (5.02)
NO_2	1.1 (4.61)	0.3 (1.26)	0.5 (2.09)
C≡	0.2 (0.84)	0	1.2 (5.02)
Aryl	3.0 (12.56)	1.2 (5.02)	0.5 (2.09)
CO_2^-	2.0 (8.37	0.5 (2.09)	2.0 (8.37)
CHO	0.8 (3.35)	0.3 (1.26)	0.8 (3.35)
C=	1.3 (5.44)	0.2 (0.84)	0.9 (3.77)
CR_3	6.0 (25.11)	2.5 (10.47)	6.0 (25.11
CHR_2	2.1 (8.79)	0.8 (3.35)	2.1 (8.79)
CH_2R	1.8 (7.54)	0.4 (1.67)	1.8 (7.54)

[a] The value is parentheses is the energy in kJ mol^{-1}

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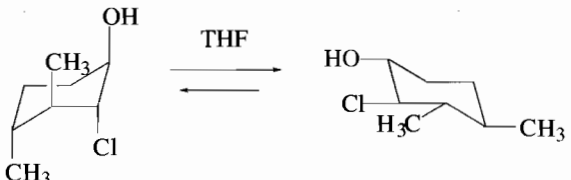


199 **200**

The protocol for calculating the percentage of each conformation is illustrated by the two chair conformations of 2-chloro-3,4-dimethylcyclohexanol, **199** and **200**. Using Table 1.5, the pertinent interactions are U_{OR}, the two U_{CH_2R} and U_{Cl} in **199** and the two G_{CH_2R}, G_{OR} and G_{Cl} in **200**.

$$\begin{aligned}
\Delta H^\circ &= H_{product} - H_{reactant} = H_{\mathbf{200}} - H_{\mathbf{199}} \\
&= (G_{CH_2R} + G_{Cl} + G_{CH_2R} + G_{OR}) - (U_{OR} + U_{CH_2R} + U_{CH_2R} + U_{Cl}) \\
&= (0.4 + 0.5 + 0.4 + 0.2) - (0.8 + 1.8 + 1.8 + 0.4) \\
&= (1.5) - (4.8) = \mathbf{-3.3\ kcal}\ mol^{-1}\ (-13.8\ kJ\ mol^{-1})
\end{aligned}$$

If $\Delta H^\circ \approx \Delta G^\circ$, then *assume* $\Delta G^\circ = -3.3 = -2.303\ RT \log K_{eq}$. At 25°C, $-2.303\ RT = -1.364$. Therefore,

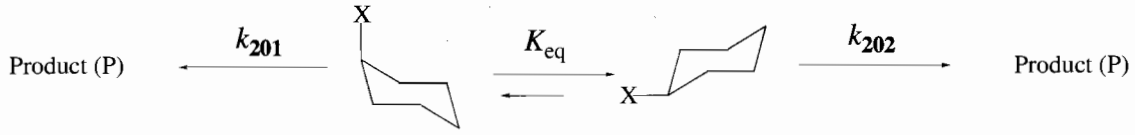
$$\Delta G^\circ = -3.3 = -1.364 \log K_{eq} \qquad \log K_{eq} = \frac{-3.3}{-1.364} = 2.42 \qquad \text{and} \qquad K_{eq} = 10^{2.42} = 262.6$$

Since %**199** + %**200** = 100%, where **200** = 1 – **199**, then $K_{eq} = \dfrac{\mathbf{200}}{\mathbf{199}} = \dfrac{1 - \mathbf{200}}{\mathbf{199}}$

$$\begin{aligned}
K_{eq}\,(\mathbf{199}) &= 1 - \mathbf{199}) \\
262.6\,(\mathbf{199}) &= 1 - (\mathbf{199}) \\
262.6\,(\mathbf{199}) + (\mathbf{199}) &= 1 \\
262.6 + 1\,(\mathbf{199}) &= 1
\end{aligned}$$

thus $(\mathbf{199})\,(263.6) = 1$ and $(\mathbf{199}) = \dfrac{1}{263.6} = 0.0038$

Therefore, %**199** = 0.38%, with 99.62% of **200**. *It is important to reiterate that two major assumptions were made for this calculation*: (1) all conformations other than **199** and **200** were ignored, and (2) ΔS° was assumed to be zero.



201 **202**

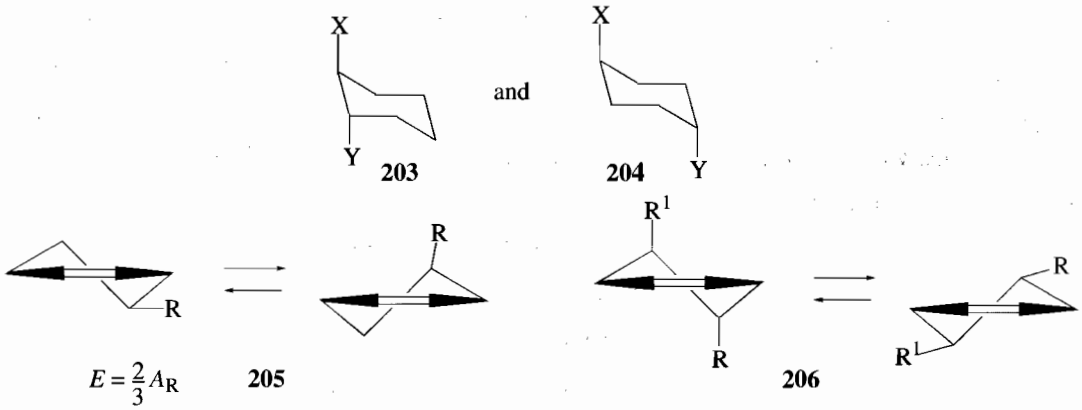
As first shown by Barton,[81] the relative percentage of a given conformation directly influences the rate of a reaction. As summarized by Eliel,[86a] the equilibrium between **201** and **202** is given by the equilibrium constant (K), and the rate of conversion of each conformation to product is given by $k_{\mathbf{201}}$ and $k_{\mathbf{202}}$, as developed by Winstein and Eliel.[86a] The overall rate will then be

$$\text{Rate} = k_{\mathbf{201}}\,[\mathbf{201}] + k_{\mathbf{202}}\,[\mathbf{202}]$$

but Rate = $k\,[C]$, where k is the observed specific rate and $[C]$ is the stoichiometric concentration of the cyclohexane.[86a] The value k is related to the equilibrium constant as

$$K_{eq} = \frac{k_{201} - k}{k - k_{202}} \qquad \text{and} \qquad k = \frac{k_{202} + k_{201}}{K + 1}$$

As mentioned above, the percentage of a given conformation is an essential factor in determining the rate and viability of a given reaction and these calculations allow the synthetic chemist to estimate conformational populations. Just as the minor chair conformation influences the rate, so other conformations (boat, twist-boat, etc.) can also exert an influence, depending on their relative populations.



203 **204** **205** **206** **207** **208A** **208B** **209**

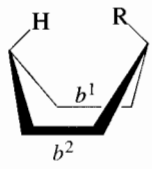
$E = \frac{2}{3}A_R$ $E = G_R + G_{R1}$

$E = \frac{1}{2}A_R$ (R = Me, X=CH_2) $E = \frac{1}{4}A_R$ (n = 3) $E = \frac{1}{2}A_R$

$E = \frac{3}{4}A_R$ (R=Me, X=O) $E = \frac{1}{2}A_R$ (n = 4)

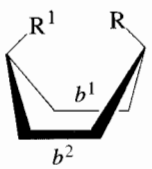
In general, $E = \frac{3-n}{3} A_R$, where n is the number of β sp^2 centers and E is the conformational energy

In addition to the values in Table 1.5 used for calculations of substituted cyclohexane derivatives,[85] Corey also developed formulas for several other cyclic molecules. Incorporation of two halogens with a 1,2- or 1,4-diaxial relationship on a cyclohexane ring led to a higher proportion of the diaxial conformer[90] due to the more favorable electrostatic interactions of the lone pair electrons.[91] Corey's models in this case were **203** and **204**, and the equation used to calculate the conformational energy is $E = \frac{1}{2}(A_X + A_Y)$. Introduction of a π-bond or a heteroatom in the cyclohexane ring changes the energy relationships, as shown for structural types. **205–209** The presence of a π bond flattened the ring and led to a value of $\frac{2}{3}A_R$ for monosubstituted alkenes of the type **205**. The usual U and G values were used for disubstituted derivatives such as **206**. A carbonyl or an aldehyde unit led to a diminished value for A of $\frac{3-n}{3}$, where n is the number of sp^2 centers (see **207**). A spirocyclic or fused ring structure such as **208** also diminished A by three-quarters or one-half, and introduction of an oxygen in the ring (to form a pyran such as **209**) led to the value $\frac{1}{2}A_R$. With the proper parameters, the conformational properties of molecules other than cyclohexane can be determined.



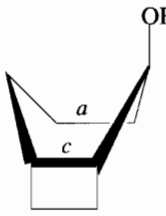
210

$E = (b_1 + b_2) A_R$

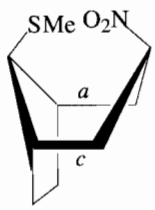


211

$E = (b_1 + b_2) (U_R + U_{R'})$



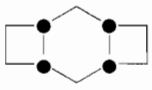
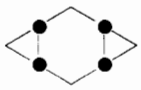
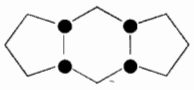
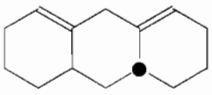
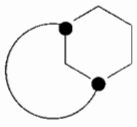
212



213

Corey and co-workers[85] also developed parameters to evaluate boat conformations, which are often important contributors to the conformational population of cyclohexane derivatives (see above). The energies for boat conformations with one or more substituents in the flagpole positions use a new term (*b*) (see **210** and **211**) which is derived from the bowsprit–flagpole interactions (R–H in **210** or R^1–R in **211**). Corey's examples include **212** and **213**. In **212**, the axial hydroxyl group receives a value (A_{OH}) of 0.8 kcal mol^{-1} (3.35 kJ mol^{-1}, see Table 1.5) and $b_1 = 0$ for bond *a* and $b_2 = 0.60$ for bond *c* (see typical ***b*** values in Table 1.6.[85] The conformational energy for **212** is (0.6 x 0.8) = 0.48 kcal mol^{-1} (2.01 kJ mol^{-1}).

Table 1.6. *b* Values for ring flattening structural features

Structure	*b*	Structure	*b*
	0		0.60
	0.25		0.70
	0.50		0.75

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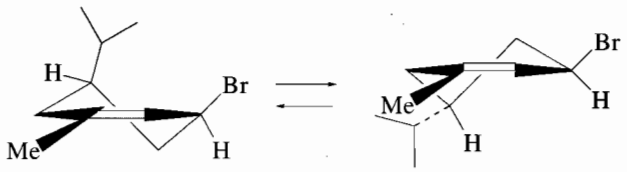
Analysis of **213** requires an explanation of Table 1.6. Introduction of a π bond, a cyclopropane or a cyclobutane ring flattens the boat, leading to increased destabilization. Fused five-membered rings ($b = 0.70$) and larger fused rings do not flatten the ring of interest. Structure **213** does not contain a flattening group, and we have $b_1 = 0.75$ and $b_2 = 0.75$. The energy of **213** is, therefore,

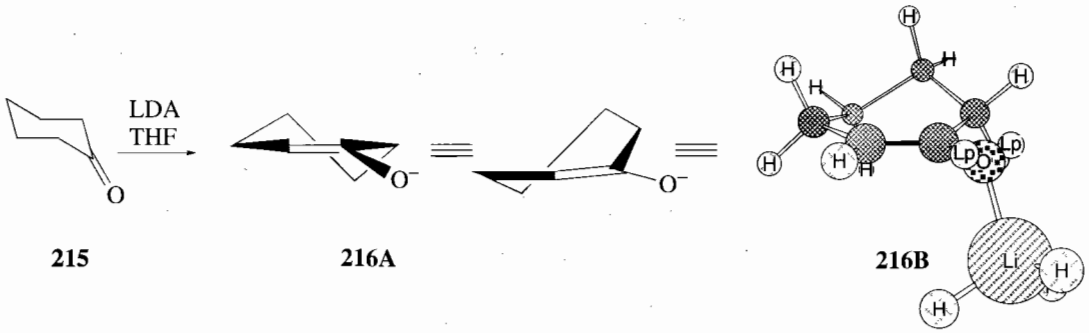
$$E = (0.75 + 0.75)(U_{SR} + U_{NO_2}) = 1.50\ (0.8 + 1.1) = 2.9 \text{ kcal mol}^{-1}\ (12{,}1 \text{ kJ mol}^{-1})$$

These structural types emphasize how important the presence of π bonds and heteroatoms is to the overall conformation. "Flattening" of a ring is often an important structural feature of natural products and other attractive synthetic targets. The π bond in a cyclohexene moiety flattens the ring in **214A** and its other low-energy conformer, **214B**. These are actually half-chair conformations, analogous to **167**.[92] The isopropyl



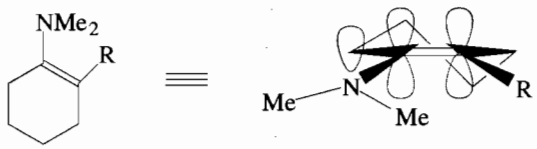
214A **214B**

group (*i*-Pr) is less stable in the pseudo-axial position and more stable in the pseudo-equatorial position.[93] The *i*-Pr↔Br interaction is largely alleviated in **214B**. This effect is compatible with **214B** as the major conformation and higher relative energy for **214A**. It arises in other systems, including reactive intermediates. Conversion of cyclohexanone (**215**) to its enolate (**216A**, see sec. 9.2) flattens the ring and leads to a cyclohexene-like conformation. This flattening is once again easy to visualize with the 3D drawing of the enolate **216B**. Drawing **216A** is clearly analogous to cyclohexene derivative **214A**. The dimethylamino enamine (see sec. 9.6) of cyclohexanone (**217A**) also shows this half-chair conformation (see **217B**). In these latter cases, the lone pair electrons (on oxygen in **216** and on nitrogen in **217**) will overlap with the π bond.



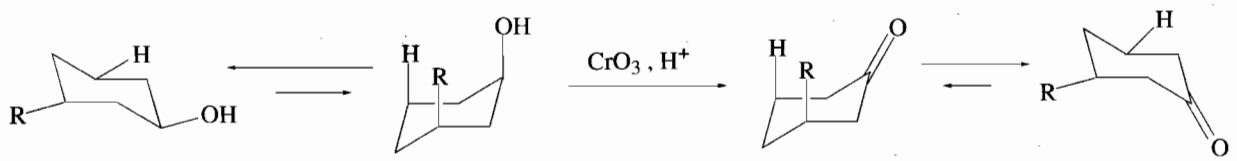
215 **216A** **216B**

When compared to chair cyclohexane, the presence of the trigonal planar carbonyl in **215** removes the 1,3-diaxial hydrogen atom interactions and, as seen in the models for Corey's calculations, partially flattens the ring. The conversion of alcohol **218** to ketone **219** illustrates this point. Although **218** is an equilibrating



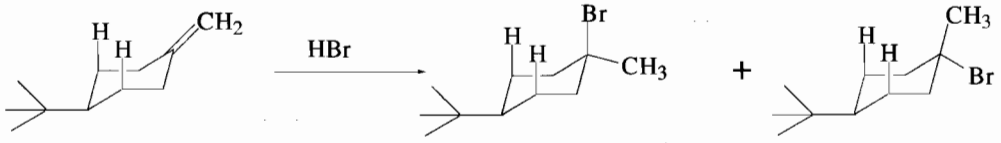
217A **217B**

mixture with an axial or equatorial hydroxyl group, upon oxidation to the ketone the flattening effect of the carbonyl is easy to see. Energetically, the R↔OH interaction (*U* value) in **218** is removed upon oxidation to **219**. In the ketone, the carbonyl effectively eclipses the α-equatorial hydrogens, further lowering the conformational energy.[94] Ketone **219** exists as an equilibrating conformational mixture favoring the R group in an equatorial position.



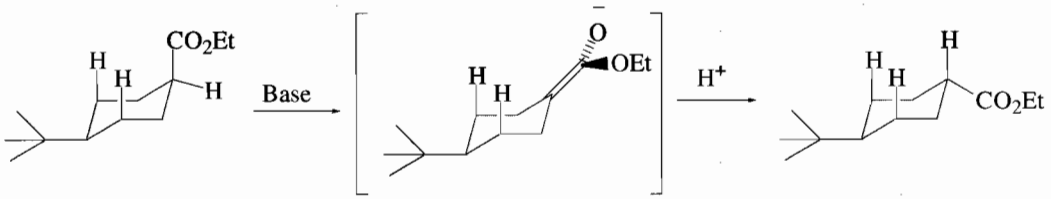
218 **219**

Exocyclic methylene compounds such as **220** will exhibit the same flattening effect observed with the carbonyl group,. An interesting effect is seen in the conversion of **220** to **221** or **222**, where *A* strain is increased in the products, relative to the methylene group. Further, the greater A strain of methyl (1.8 kcal mol^{-1} in Table 1.5 vs. 0.4 kcal mol^{-1} for Br; 7.5 and 1.7 kJ mol^{-1} respectively) suggests that **221** may predominate after addition of HBr to the alkene (see sec. 2.10.A). This analysis ignores the relative trajectories of approach of the reagents (see sec. 6.6.A) and other steric interactions, however.



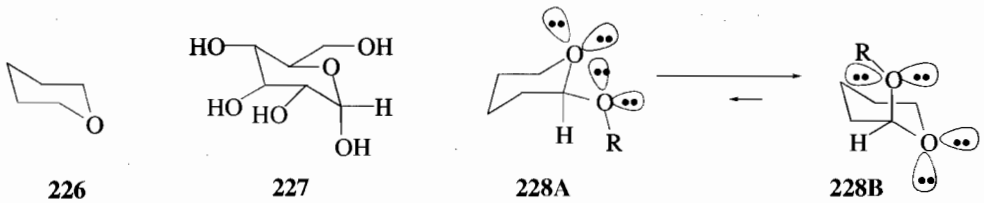
220 **221** **222**

Enolates can be formed that have an exocyclic double bond as well as those formed with the endocyclic double bond in enolate anion **216** (also see sec. 9.5.D). Relief of strain will presumably assist formation of the enolate and may influence the final stereochemistry of groups in the product when the enolate anion reacts with an a suitable reagent (see sec. 9.3.A, 9.4).[95] This effect can also be seen in the equilibration of the cis-ester **223** to the trans-ester **225** via the planar enolate (**224**).[92] This equilibration (accomplished by treating **223** with a proton source) removes the significant *A* strain of the axial carboethoxy group in [A_{COOR} = 1.20 kcal mol^{-1} (4.99 kJ mol^{-1})].



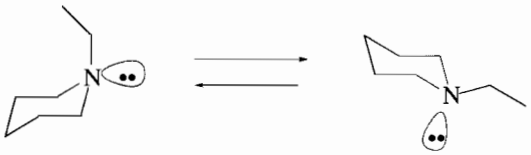
223 **224** **225**

Six-membered rings containing oxygen (such as pyrans, **226**) are an integral part of carbohydrates such as α-D-glucopyranose (**227**). Less substituted pyrans show similar effects. The presence of the α-alkoxy group in **228** leads to a significant effect also seen in α-alkoxy pyrans, the **anomeric effect**.[96] An alkyl group on cyclo-hexane or pyran usually prefers the equatorial position due to increased *A* strain. When an alkoxy group is attached to pyran, however, it prefers the axial position. This effect is probably due to dipolar interactions of the oxygen lone pairs (see **228A** and **228B**).[97] The anomeric effect is evident in glucose, where α-D-glucopyranose (**227**) accounts for a significant portion of the conformational equilibrium.



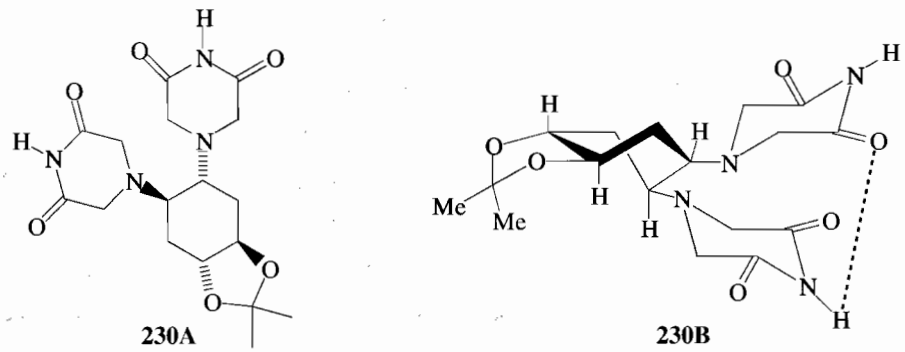
226 **227** **228A** **228B**

The influence of substituents on conformational stability is also evident in amines such as *N*-ethyl piperidine. The chair conformation can be drawn with the ethyl group axial (N lone pair equatorial in **229A**) or equatorial (N lone pair axial as in **229B**). The greater *A* value for ethyl than for the lone pair suggests a predominance of **229B** in this equilibrium mixture. This preference for the larger group being in an equatorial position is analogous to the effects seen in pyrans and cyclohexanes.



229A **229B**

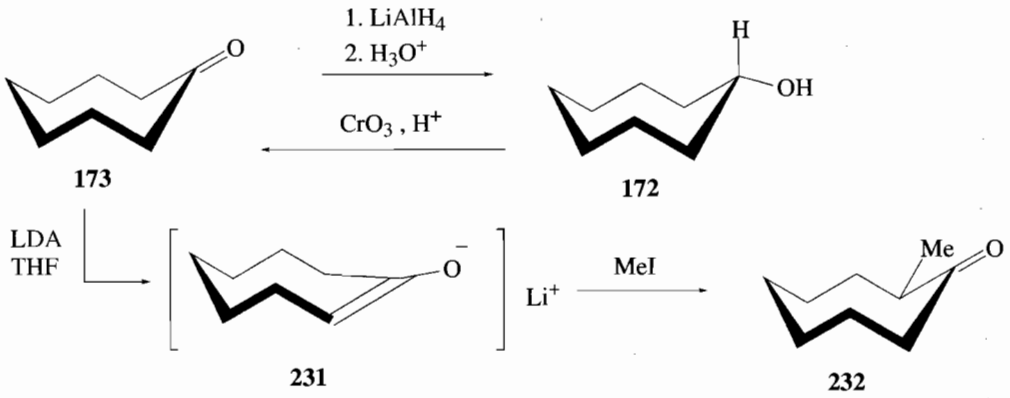
The presence of bulky substituents or substituents capable of chelation or hydrogen bonding can alter conformational populations,[98,99] as first seen with ethylene glycol. In **230A**, there are two effects that influence the conformation.[100] Bulky substituents lead to large *A* and *G* strain in both chair conformations. In addition, internal hydrogen bonding of the glutarimide moieties helps stabilize the twist–boat conformation shown in **230B**, which is the lowest energy conformation of this molecule. The twist–boat conformation is also observed in the absence of internal hydrogen bonding. *cis-,trans-,trans*-1,2,4,4-tetraisopropylcyclohexane, for example, exists as a twist–boat, as confirmed by X-ray crystallography.[101]



230A **230B**

Reduction of cyclooctanone (**173**) provides an example of how conformations influence reactivity. Treatment of with lithium aluminum hydride ($LiAlH_4$, see sec. 4.2.B) generates the alcohol (**172**). The alcohol will have greater transannular and A-strain than the ketone. The reduction may, therefore, be somewhat sluggish relative to similar reduction of cyclohexanone. The oxidation, however, converts **172** to **173** using chromium trioxide (see sec. 3.2.A) and leads to diminished strain as the newly introduced carbonyl flattens the ring slightly. As the product is somewhat more stable than the starting material, the oxidation is more facile.

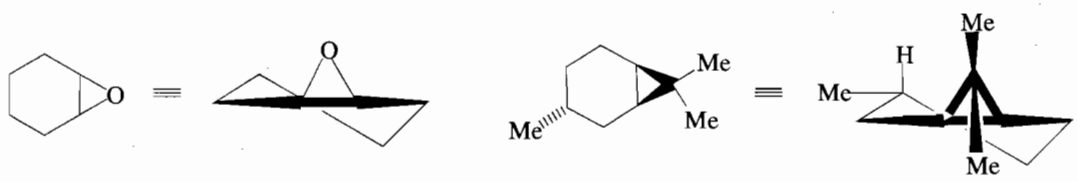
Similarly, formation of the enolate (**173** → **231**) with lithium diisopropylamide (LDA, see sec. 9.2.B) should be facile due to relief of transannular strain for formation of the planar enolate moiety. A subsequent alkylation step (**231** → **232**, see sec. 9.3.A) may be sluggish, however, since the methyl group in **232** will introduce more strain in the product than in the original unsubstituted cyclooctanone (**173**).



173 **172** **231** **232**

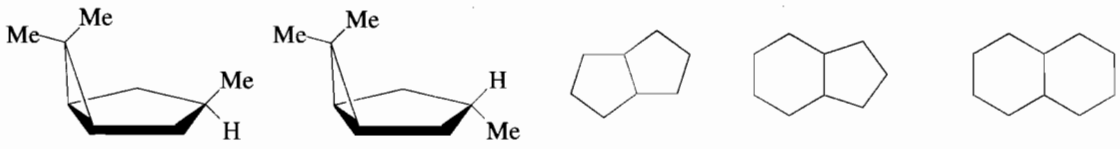
This section has shown the importance of understanding and predicting the conformational preferences for many types of cyclic molecules. The importance of this conformational bias to reactions will be seen throughout most chapters remaining in this book.

1.5.E Conformations in Polycyclic Molecules



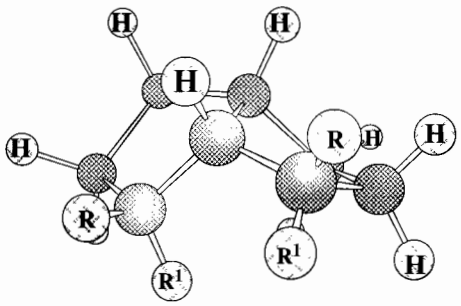
233 **234**

The conformational constraints in monocyclic molecules are magnified in bi-, tri-, and polycyclic molecules. A simple case is cyclohexene oxide (**233**) where the planar three-membered ring flattens the ring. Similar effects are seen in cyclohexene and also occur when cyclopropane is fused to a ring. An example is carane (**234**), which exists primarily in the conformation shown (note that the geminal dimethyl groups are perpendicular to the plane of the cyclopropane ring). Bicyclo[3.1.0]hexanes such as **235** and **234** also show this flattening effect. The cis-isomer (**235**) is expected to show a significant Me–Me interaction which is not present in the trans-isomer, **234** (carane).



235 **234** **236** **237** **238**

The conformational constraints peculiar to [m.n.0]alkanes ($n \neq 1$) can be illustrated by comparing the cis- and trans- isomers of bicyclo[3.3.0]nonane (**236**), hydrindane (**237**), as well as **238** (decalin). Each five- and six-membered ring will assume the envelope conformation for the five-membered rings and a chair conformation for the six-membered rings in their lowest energy form. There are several combinations, however. The cis-isomer (**239**) shows a bent conformation with the two envelope shapes relieving some of the cross ring interactions.[102,86] The two equatorial R groups and the two axial R^1 groups in **239** are unable to move away from each other due to the rigid conformation dictated by the two fused rings. Groups at these positions will maximize the steric interactions. The trans-isomer (**240**) shows a more linear or open structure but requires some distortion of the five-membered ring and is ≈ 6 kcal mol^{-1} (25.1 kJ mol^{-1}) higher in energy than **239**.[103] Both cis- and trans- isomers are easily prepared, however.[104]



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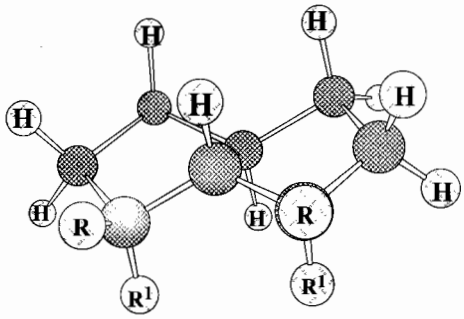
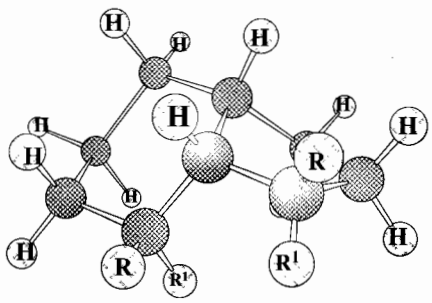
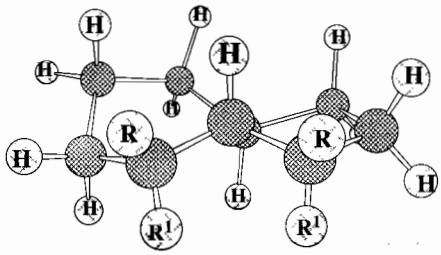


240

Hydrindanes have the five-membered ring in the envelope conformation with the six-membered ring in a chair. The *cis*-indane (**241**) shows a 1,3-diaxial R^1—H interaction and one of the bridgehead hydrogens interacts with the two R groups, giving another *gauche*-like interaction (similar to Corey's G values) Another 1,3-diaxial-like interaction is apparent between R and R^1 on the six- and five-membered rings. In the trans-isomer (**242**), the R–R^1 interaction is lessened, but there is now a R^1—bridgehead hydrogen interaction. The 1,3-diaxial R–H interaction remains, but the extended conformation in **242** is slightly lower in energy (about 1 kcal mol^{-1}, or 4.19 kJ mol^{-1}) than **243**.[105]



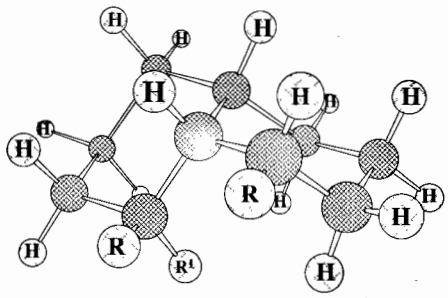
241



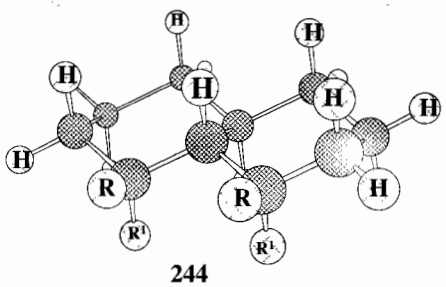
242

In all four cases (**239** → **242**), there is little conformational mobility and steric interactions are more important than in a conformationally mobile system. Similarly, *cis*-decalin (**243**) and *trans*-decalin (**244**) show the same bent and extended forms with both six-membered rings in a chair conformation.[106] There is a

1,3-diaxial R–R^1 interaction in **243** and an axial interaction of R with the bridgehead hydrogens. The R–R^1 groups on adjacent rings are also in close proximity. Examination of **244** shows 1,3-diaxial R–H and R^1–H interactions but the overall energy of **244** is lower due to decreased nonbonded interactions.[107] Eliel describes the conformations of several other bicyclic and polycyclic compounds.[108]

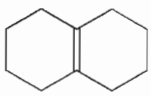


243

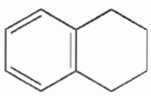


244

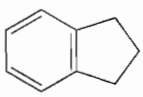
Introduction of a π bond from an alkene or aryl moiety into a bicyclic system leads to significant flattening of the ring. Examples of these systems are **245A** and the aromatic derivatives tetrahydronaphthalene (**246**) and 1*H*-dihydroindene (**247**). The planar nature of the alkene moiety in **245A** (see **245B**) forces the four



245A

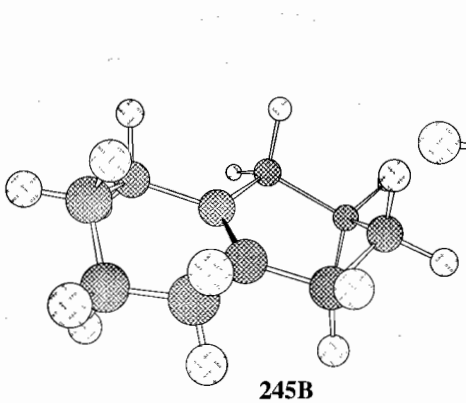


246

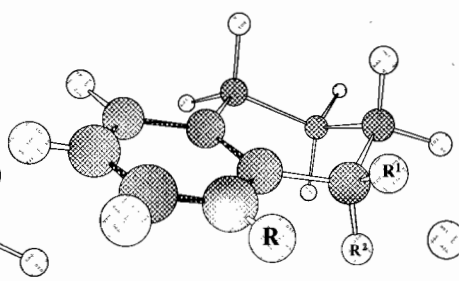


247

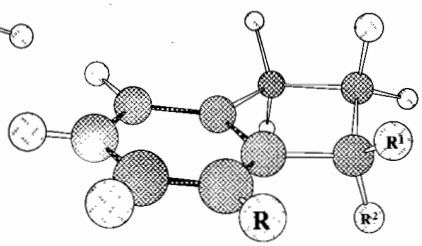
allylic carbons to be coplanar and each ring behaves as if it were cyclohexene. The planar benzene ring in **246** (see **248**) imposes similar conformational constraints and the four carbons of the fused ring assume a



245B

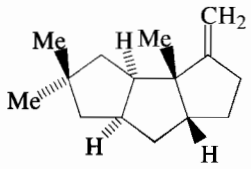


248

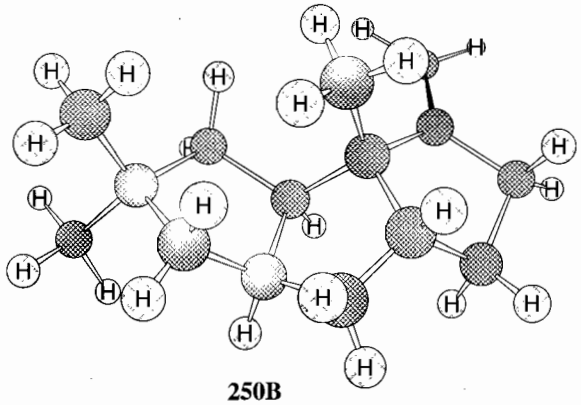


249

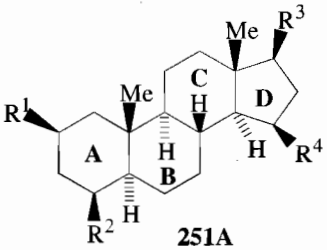
conformation similar to cyclohexene, but the R–R^1 and R^1–R^2 interactions can be significant. In **247** (see **249**), the relatively planar cyclopentane ring brings R and R^1 or R^2 in close proximity for a potential steric interaction. The presence of three or more fused rings is rather common in nature. The natural product hirsutene (**250A**)[109] also shows the conformational bias imposed by three fused five-membered rings (see 3D drawing[4] **250B**).



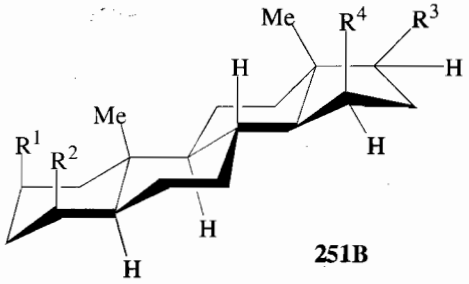
250A



250B

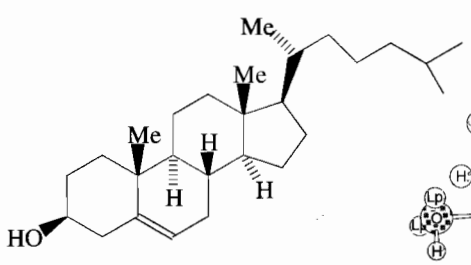


251A

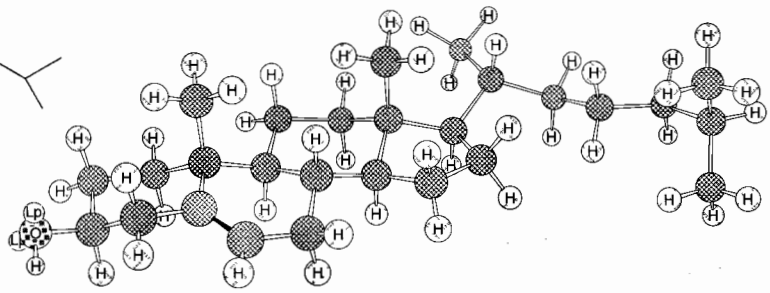


251B

A last example of this phenomenon is seen in the steroid nucleus (**251A**). Each of the cyclohexane moieties will exist in a chair conformation and the cyclopentane will be in an envelope conformation, as seen in **251B**. If a carbonyl or alkene moiety is included, the six-membered ring will be flattened and its conformation will be very similar to that of cyclohexanone or cyclohexene. As seen in conformational drawing **251B**, each trans-fused cyclohexane ring resembles *trans*-decalin and the four fused rings impart great conformational rigidity to the molecule. Only the terminal cyclohexyl and cyclopentyl rings have some mobility. The interaction R^1–R^2–Me of the cyclohexane ring is important, as are the R^3–Me and R–R^4 interaction of the cyclo-pentane ring. Examples of the conformational variations in steroids are seen by examination of cholesterol (**252A**) and β-estradiol (**253A**).[110] When the A ring becomes aromatic, as in estradiol (**253**), the A/B ring system is essentially flattened, inducing significant distortion in the C ring as well (see **253B** relative to **252B**). Relatively minor changes in structure lead to significant changes in conformation and major changes in structure profoundly influence the shape of the molecule. The changes are predictable, however, based on the simple five- and six-ring models discussed in previous sections.

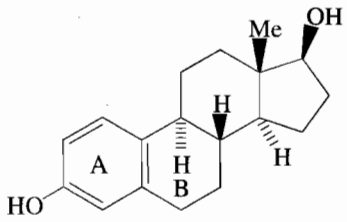


252A

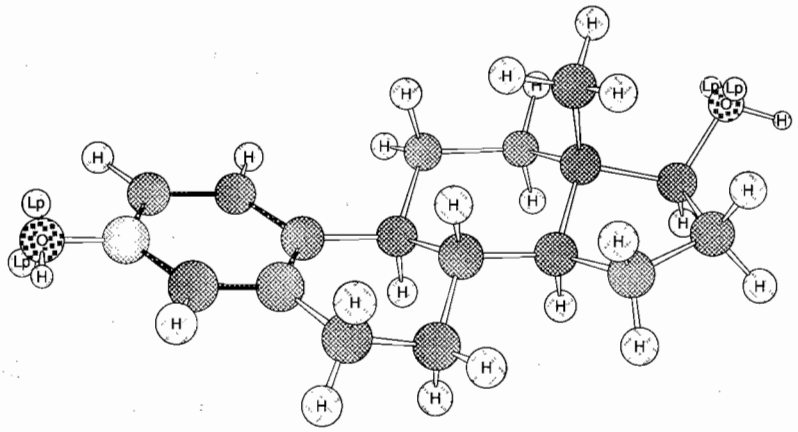


252B

It is reasonable to assume that the simple concepts introduced for monocyclic rings such as cyclopentane, cyclohexane, cyclohexene, and cyclohexanone can be applied, with little change, to complex molecules containing those units. Throughout this book the analysis of simple rings will be used to understand the conformational bias and reactivity of larger and more difficult synthetic targets.



253A



253B

1.6. CONCLUSION

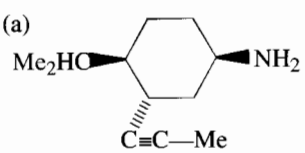
This chapter has reviewed the most fundamental concepts of stereochemistry and conformational analysis, with some applications to more complex problems. For students who have had a good undergraduate organic chemistry course, it is intended as a review, since these concepts are integral to the understanding of organic reactions. The concept of disconnection and retrosynthetic analysis is a prelude to a discussion of synthetic strategies in Chapter 10. The disconnection method and pertinent transforms will, however, be presented in virtually every chapter as new reactions are introduced.

The introduction to organic reactions will be continued in the functional group exchange reactions presented in Chapter 2. That chapter will review the reactions introduced in a typical first organic chemistry course. Some of the concepts will be expanded and updated to include more synthetically useful reactions. Oxidation and reduction will be presented in separate chapters to focus attention on the vast number of reactions that fall under these categories.

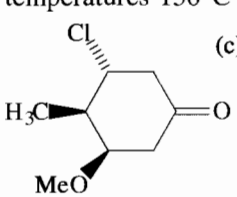
HOMEWORK

1. For each of the following molecules calculate the percentage for both chair conformations using the values in Table 1.5. Calculate using the temperatures 150°C for (a), 35°C for (c) and 25°C for (b) and (c).

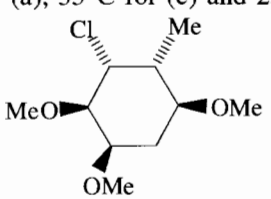
(a)



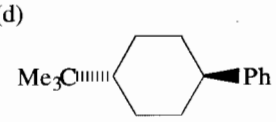
(b)



(c)

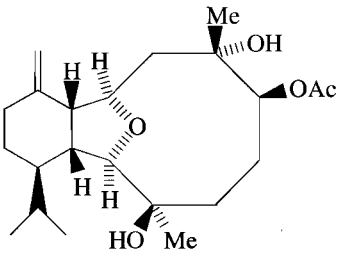


(d)



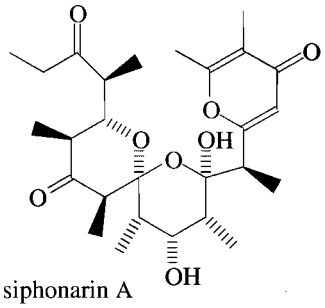
2. Determine the absolute configuration (*R* or *S*) for every stereogenic center in the following molecules:

(a)



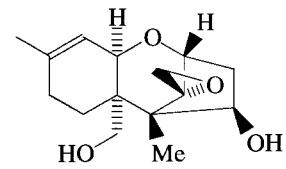
sclerophytin B
see *Org. Lett.*, ***2000***, *2*, 1879

(b)



siphonarin A
see *Org. Lett.*, ***2000***, *2*, 1513

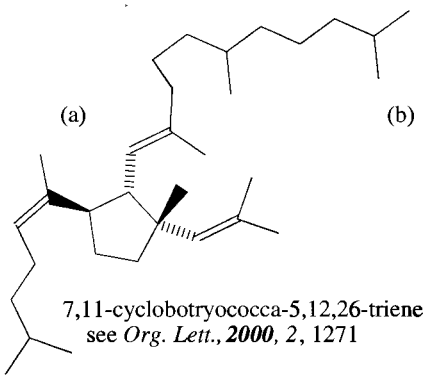
(c)



(–)-verrucarol
see *J. Org. Chem.*, ***1998***, *63*, 2679

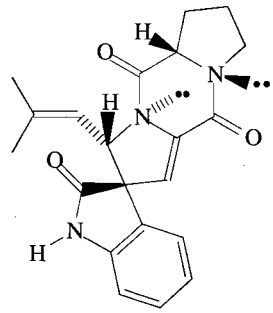
3. Determine the absolute configuration for every stereogenic center in the following molecules:

(a)



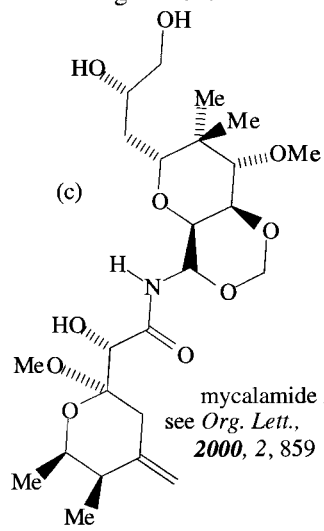
7,11-cyclobotryococca-5,12,26-triene
see *Org. Lett.*, ***2000***, *2*, 1271

(b)



spirotryprostatin B
see *J. Am. Chem. Soc.*, ***2000***, *122*, 5666

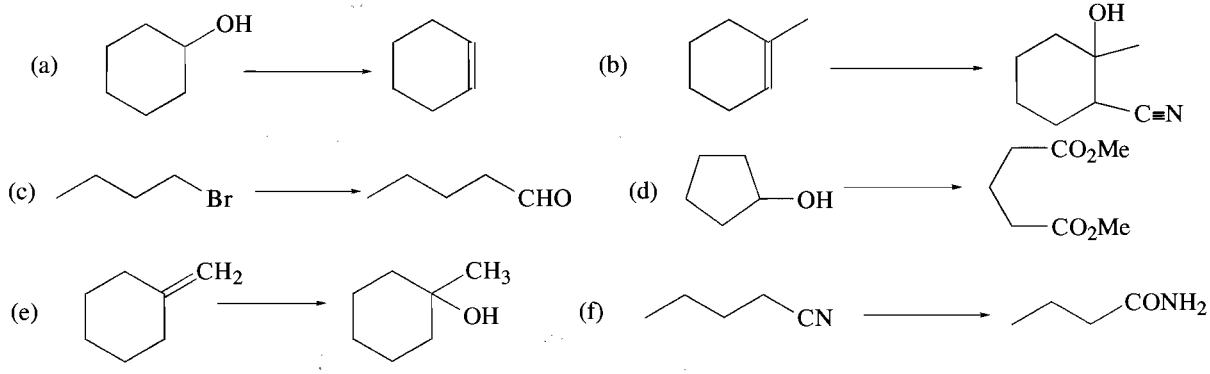
(c)



mycalamide A
see *Org. Lett.*, ***2000***, *2*, 859

4. For disconnect fragments **22** and **23** in Section 1.2, convert each to a real molecule using synthetic equivalents in Table 1.2. Briefly discuss the retrosynthetic and synthetic sequences and show the complete retrosynthetic analysis based on this disconnection.

5. Using the reaction wheel (Fig. 1.1) give reasonable syntheses, including reagents and all intermediates (no mechanisms).

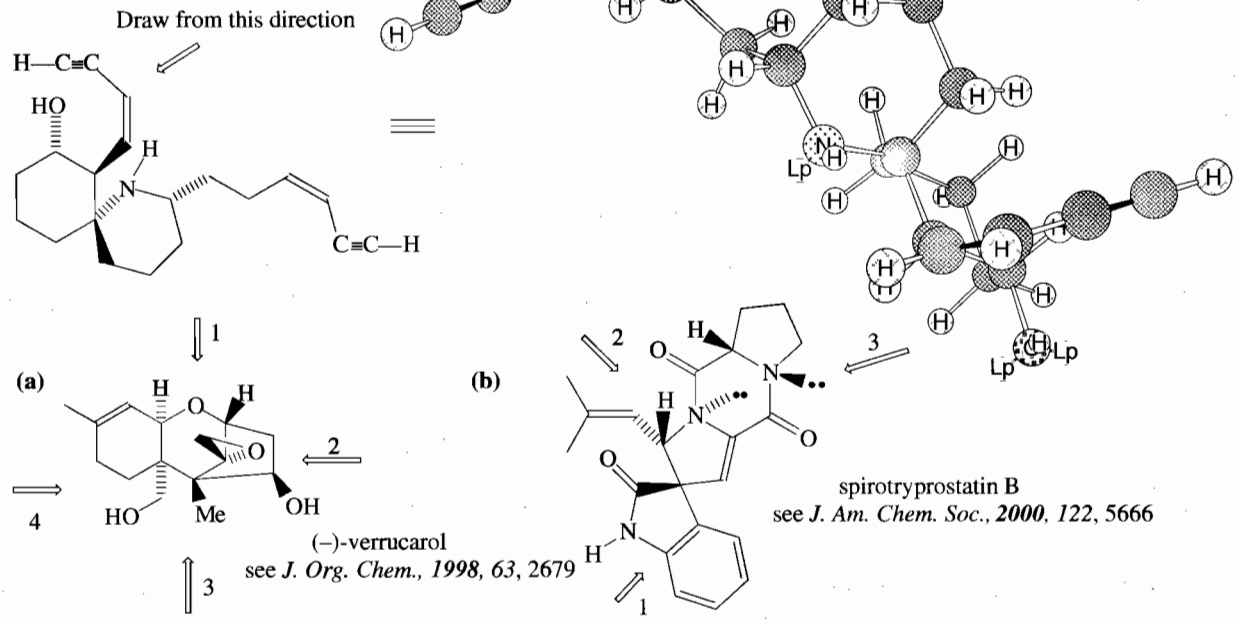


6. Use the *Compendium of Organic Synthetic Methods* (since 1994) to give three *different* reactions (with literature references and reactions) for each of the following:

(a) acids from nitriles
(b) aldehydes from nitriles
(c) amides from halides
(d) amines from nitriles
(e) ethers from halides
(f) halides from amines
(g) ketones from olefins
(h) alkenes from aldehydes

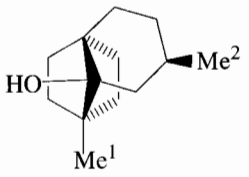
7. Use a 3D computer drawing program such as Chem 3D to draw each molecule in 3D form, from the indicated perspective (see example below).

EXAMPLE



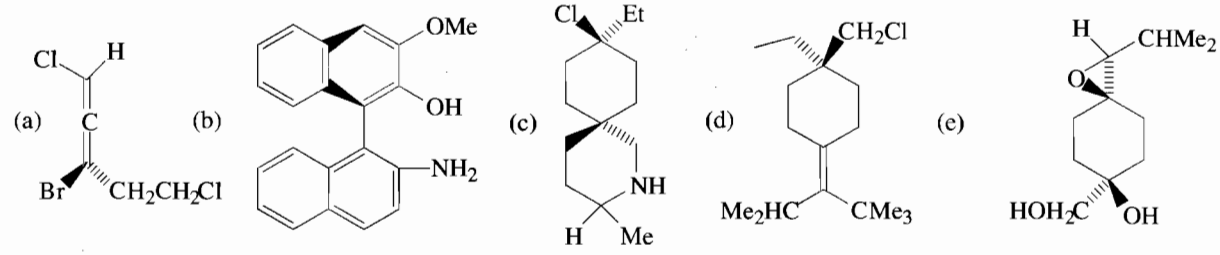
[plus top (above page) and bottom (below page) views]

8. Draw molecule A in what should be the low–energy conformation. Briefly discuss the conformation for the highlighted rings in molecule A. Also discuss the conformational preference (axial or equatorial) for all both methyl groups as well as the hydroxyl.



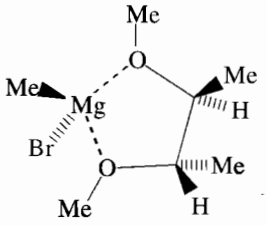
A

9. Determine the absolute configuration (R or S) for each chiral axis in the following molecules:

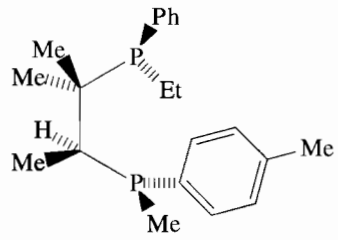


10. Determine the absolute configuration for each chiral center in the following molecules.:

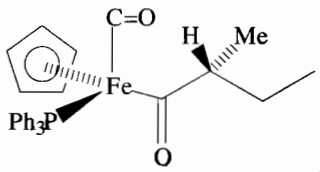
(a)



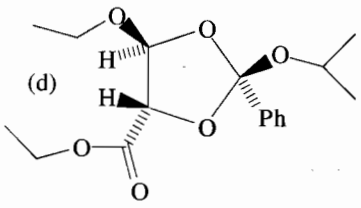
(b)



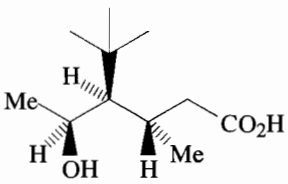
(c)



(d)



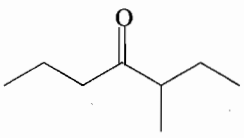
11. The conversion of the hydroxy-acid shown to the corresponding lactone is rather slow. When pushed under aqueous acid conditions, epimerization at the carbon bearing the hydroxyl can occur. Draw the lactone and explain the observations noted in this question.



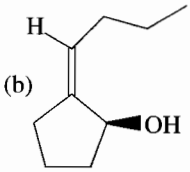
12. Explain why *cis*-1,3-cyclohexanediol exists mainly in the diaxial conformation in aqueous ethanol solution, when by Corey's ΔG calculations (see Table 1.5), the diequatorial conformation should be lower in energy.

13. Determine the correct *re/si* label for each prochiral atom in the following molecules.

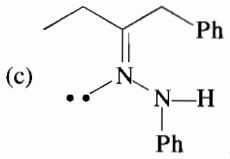
(a)



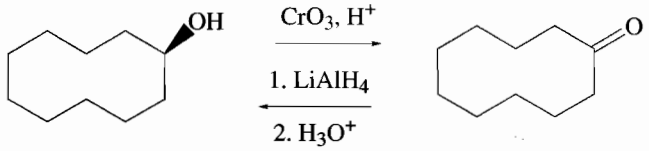
(b)



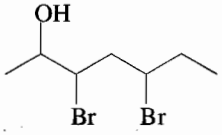
(c)



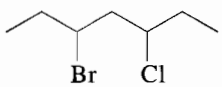
14. Oxidation of cyclodecanol to cyclodecanone is rapid with CrO_3 in acid but reduction of cyclodecanone to cyclodecanol with $LiAlH_4$ is relatively slow (see diagram). Discuss this statement.



15. (a) Draw the (2*S*, 3*R*,4*R*) and the (2*S*, 3*S*, 4*S*) derivative of molecule A. (b) Draw both the erythro/threo and the syn/anti forms of molecule B.

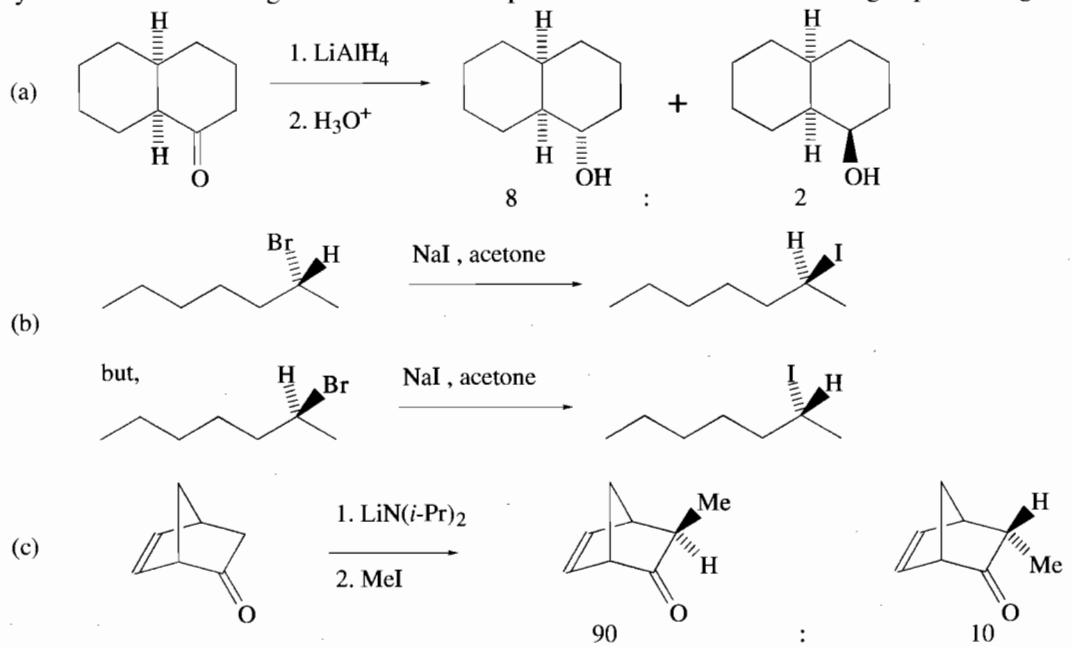


A



B

16. Classify each of the following reactions as stereospecific/stereoselective and/or regiospecific/regioselective.



17. Explain why cyclodecane has a higher ground state energy than does cyclooctadecane. Why is cyclopentadecane higher in energy than cyclohexadecane?

18. Draw the boat conformation of *cis-,trans-,trans*-1,2,3,4-tetraisopropylcyclohexane. See *J. Am. Chem. Soc.*, ***1994***, *116*, 10306.

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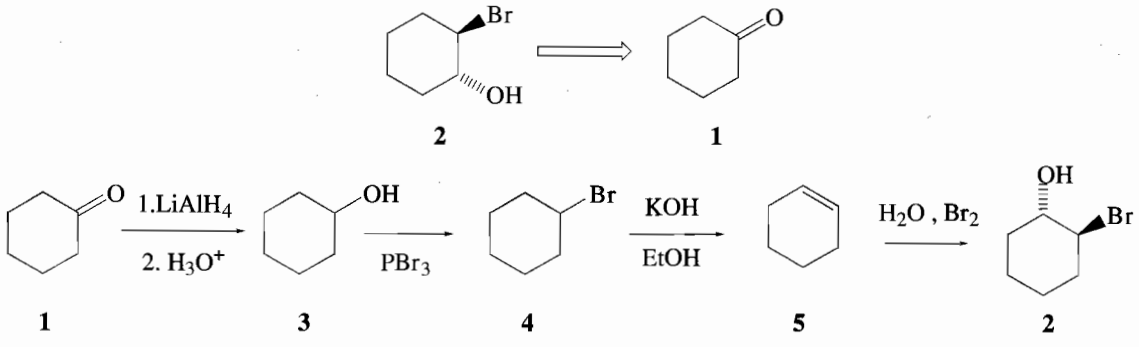
CHAPTER 2

ACIDS, BASES AND FUNCTIONAL GROUP EXCHANGE REACTIONS

2.1. INTRODUCTION

In most syntheses, the main focus is usually construction using carbon–carbon bond forming reactions. Most of the actual chemical reactions in a synthesis, however, are those that incorporate new functional groups. Such reactions are known as functional group exchanges. Because of this, a chapter is devoted to a review of major reaction types involved in functional group exchanges. For all practical purposes, this discussion also constitutes a review of a typical undergraduate organic course.

Figure 1.1 showed that there is a relationship between many functional group interchange reactions. These transformations usually proceed via ionic intermediates and/or polarized C—X bonds or π bonds. A short list of typical reagents was provided in that Figure, but many other reagents are usually available to effect a given transformation. An important synthetic use is to incorporate a given functional group into a molecule. The functional group(s) in a molecule must also be manipulated (transformed) to set it up for a reaction that constructs a carbon–carbon bond. Functional group interchange reactions play a very important role in synthetic organic chemistry. Many different types of reactions are involved in functional group interchanges. Categorizing reactions according to the type of transformation in what is essentially a subset of functional group interchanges is one way to help understand when and how to use a particular reaction. This usually involves grouping by a similar mechanism. In this way, each step can be analyzed according to the transformation before searching for a specific reagent.



This is illustrated by a simple synthetic problem in which bromohydrin **2** is prepared from cyclohexanone (**1**), which requires only functional group transformations. The synthetic relationship between **1** and **2** is represented by the diagram **2**⇒ **1**. This representation is meant to show that the bromohydrin can be formed from the ketone by an as yet unknown number of synthetic steps. Corey and co-workers[1,2] called this representation a transform and used it to define retrosynthetic relationships (sec. 1.2). If we analyze the **2** ⇒ **1**

relationship, it is clear that Br and OH must be incorporated on adjacent carbons, and one possibility is an addition reaction to an alkene. We must somehow convert the ketone to an alkene. One approach would involve reduction of the carbonyl to an alcohol, which could be converted to a leaving group that would allow an elimination reaction to give the alkene. This analysis is based on what must be done to convert **1** to **2** and uses reaction types to give clues regarding what reagents might be necessary. Bringing actual reagents into play brings the synthesis to life. Initial reduction of the ketone with a suitable reducing agent such as $LiAlH_4$ (sec. 4.2.B) gives alcohol **3** and subsequent reaction with phosphorus tribromide (sec. 2.8.A) gives bromide **4** in what is known as a substitution reaction. Base induced elimination gives alkene **5**, which illustrates both an elimination and an acid–base reaction. The final reaction with bromine and water (sec. 2.10.C) gives **2** and illustrates an addition reaction. This sequence used five major reaction types: acid–base, reduction, substitution, elimination, and addition. We will collect the reaction types used for functional group exchanges into seven categories:

1.	Acid - base reactions	$HA + B \longrightarrow HB + A$
2.	Substitution reactions	$RX + A \longrightarrow RA + X$
3.	Elimination reactions	$X{-}C{-}C{-}Y \longrightarrow C{=}C + X{-}Y$
4.	Addition reactions	$C{=}C + X{-}X \longrightarrow X{-}C{-}C{-}X$
5.	Nucleophilic acyl addition	$C{=}O \longrightarrow Nuc{-}C{-}O{-}E$
6.	Oxidation reactions	An example is $H{-}C{-}O{-}H \longrightarrow C{=}O$
7.	Reduction reactions	An example is $C{=}C \longrightarrow H{-}C{-}C{-}H$

Most functional group exchanges and transformations fall into one of these seven categories, and it is useful to classify reagents in them, as in Table 2.1.[3] Many reactions can be placed into more than one of these simple categories. Elimination reactions, for example, involve an initial removal of hydrogen by a base (an acid–base reaction). The second step of many addition reactions involves a substitution. Although these categories are somewhat artificial, they offer a convenient method for describing the most important features of reactions. Oxidation and reduction reactions constitute such a large proportion of functional group exchanges that they will be discussed in separate chapters (chaps. 3 and 4, respectively) to properly examine their synthetic applications. This chapter will focus on the first five reaction types and their application to chemical reactions, synthesis, and functional group transformations. The ultimate goal is to establish a firm base upon which to introduce the reactions required for making important carbon–carbon bonds and techniques employed by the modern synthetic chemist.

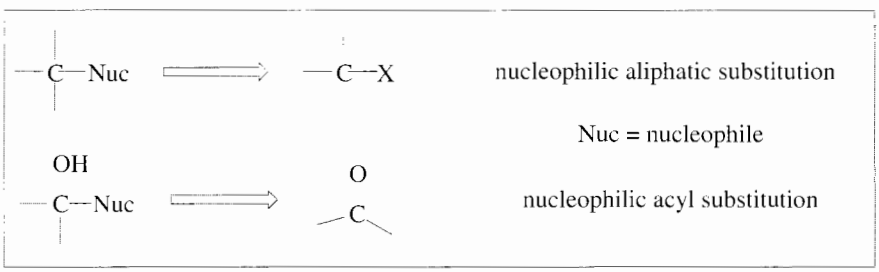
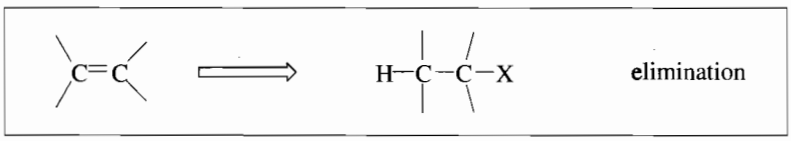


Table 2.1. Correlation of Common Reagents with General Reaction Types

Class of Reagent (Reaction Type)	Reagents
Acids (acid–base;addition)	HCl, HBr, HF, HI, H_2SO_4, HNO_3, H_3PO_4, RCO_2H, RSO_3H, HOH, ROH, AlX_3, FeX_3, ZnX_2, SnX_4
Bases (acid–base; elimination)	NaOH, KOH, LiOH, $Ca(OH)_2$, NaH, KH, RO^-M^+ (*t*-BuO, MeO, EtO; M = Na^+, K^+), RLi, RMgX, NH_3, R_3N, $NaNH_2$, $LiNH_2$, Na NR_2 or $LiNR_2$ (HNR_2 + Na or Li), HOH, ROH, ROR
Nucleophiles (substitution; nucleophilic acyl substitution)	MX (X = Cl^-, Br^-, I^-, CN^-, HO^-, RO^- NH_2^-, NR_2^-, $RC{\equiv}C^-$, $R(CO)O^-$, HS^-, RS^-; M = Na^+, K^+, Li^+, RLi, RMgX, NH_3, NR_3, HOH, ROH, R_2CuLi
Oxidizing agents (oxidation; addition; acid–base)	CrO_3, $K_2Cr_2O_7$, H_2O, ROOR, $HCrO_4$, $KMnO_4$, Cu/heat, MnO_2, SeO_2, HIO_4, O_3, NaOX(NaOH/X_2), NBS, NCS, RCO_3H, HONO ($NaNO_2$/HX), HNO_3, H_2SO_4, Ag^+, Cu^{2+}
Reducing agents (reduction; addition)	Sn/HCl, Fe/HCl, H_2 + catalyst, (Pd, Pt, Ni(R), Ru), $NaBR_4$ (R = H, alkyl, OR), $LiAlR_4$(R = H, alkyl, OR), H_3PO_2, B_2H_6(BH_3), BR_3, M/NH_3 or M/HNR_2 (M = Na, Li)

Substitution (S_N1 or S_N2) is the major reaction of nucleophiles in which one functional group is replaced by another (nucleophilic aliphatic substitution). Nucleophiles can also form a new bond to an acyl carbon (nucleophilic acyl addition). Both of these **retrosynthetic** transforms are represented by the C-Nuc species, where Nuc = CN^-, AcO^-, RO^-, N_3^-, CO_2^-, etc. and X = Cl, Br, I, OAc, OSO_2R, and so on for S_N2 reactions. In nucleophilic acyl substitutions, the nucleophile is usually a carbon, nitrogen or oxygen species.

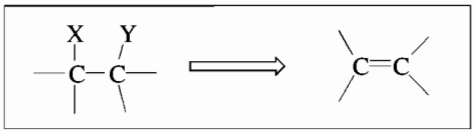
Reagents that are classified as bases can be used with both Lewis and Brønsted–Lowry acids and one application is the elimination of alkyl halides (E2 reactions; sec. 2.9.A) in the presence of a base. Elimination involves conversion of a saturated moiety containing a leaving group to a molecule with a multiple bond. An example of this latter transform is:



where the leaving group (X) is OH, halogen, OTs, and so on. The E2 reaction is discussed in section 2.9.A. It is noted that another class of elimination reactions includes polar species such as sulfoxides, amine oxides, and selenoxides, which undergo thermal syn elimination (sec. 2.9.C).

From a kinetic standpoint, acid–base reactions are among the fastest reactions known, especially in aqueous solvents. They are also used to generate reactive intermediates that can be part of other reaction types. Acids are attacked by Lewis or Brønsted–Lowry bases. Acid–base reactions are integral to many reactions, but they are not always easy to describe by a specific transform since they may be an adjunct to the desired

transformation. An example is the use of conjugate bases of acids as nucleophiles in substitution reactions. Typical nucleophiles are HCN → CN^- and HN_3 → N_3^-. Conjugate bases of weak acids are usually required to initiate E2 type reactions. Some examples are EtOH → EtO^- and $HNEt_2$ → $LiNEt_2$. Many reagents that add to alkenes are acids (HCl, HOBr, etc.) and the reaction mechanism begins with a base (the alkene) attacking the acid (H^+). Addition reactions convert a species containing a multiple bond to one that is saturated. The normal addition reactions of adding HX species to alkenes, as well as those of adding halogens to alkenes, are typically useful addition reactions. The retrosynthetic transform is



As each of these reaction types is discussed in later sections, it will be apparent that virtually all substrates that are functionally transformed are polarized or contain π bonds. Reactions involving carbon radicals (discussed in Chapter 13) are typically an exception, although a polarized species is often required in order to generate the radical. A sufficiently weak bond can undergo homolytic cleavage, with the application of sufficient photolytic or thermal energy. Pericyclic reactions, presented in Chapter 11, are another important exception and will not be included in this chapter. When analyzing a substrate for a functional group transform, the following criteria are usually important.

1. Examine the degree and direction of polarization of a bond. Where will the electrons go?
2. How many bonds away will the polarization be effective?
3. What is the attraction of a given reagent for the polarized bond?
4. Does the polarized bond contain more than one leaving group.
5. If there is a π bond, how efficiently can it donate electrons.
6. If the π bond is polarized, will the δ+ center undergo substitution or will the δ- pole act as an electron donor.
7. Does the reactive center possess special strain or steric hindrance that will modify the reactivity?
8. Is the reactive center conjugated?
   Perhaps most importantly,
9. Is there more than one reactive center in the molecule and can more than one reaction occur competitively?

2.2. ACIDS AND BASES

Many organic molecules react via an initial acid-base reaction. Understanding the properties of acid–base equilibria can lead to an understanding of the mechanistic details of many different reactions.

2.2.A. Acidity in Organic Molecules

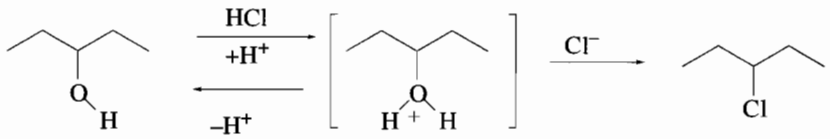
The reaction of HA and B to give BH^+ and A^- is the general expression written for acid–base reactions. The acid (HA) reacts with a base (B:) to give the conjugate acid, HB^+ (CA) and a conjugate base, A^- (CB). The hydrogen is transferred to B: as a proton (H^+). Since the product, HB^+, is also an acid and A^- is a base, this reaction is an equilibrium. The position of the equilibrium is directly related to the acidity of HA and the position of this equilibrium is given by the equilibrium constant K, where K_a is used for acid-base reactions. If the electron pair of the base (B) easily removes the proton from HA, the equilibrium is shifted to the right,

representing an increase in the acidity of HA. Conversely, a low K_a represents little ionization of HA, a shift of equilibrium to the left, and a decrease in the acidity of HA. The position of the equilibrium is dependent on many factors, including the solvent, and the relative stability of the acid (HA) and the conjugate acid (HB^+). A more convenient way to express the relative strength of an acid is pK_a, which allows a large range of changes in K_a to be examined. A large K_a is equivalent to a small pK_a so as the pK_a decreases, the acid strength increases.

$$HA + B: \underset{}{\overset{K_a}{\rightleftharpoons}} BH^+ + A^-$$

$$K_a = \frac{[HB^+]\,[A^-]}{[HA]\,[B:]} \quad \text{where} \quad pK_a = -\log K_a \quad \text{and} \quad K_a = 10^{-pK_a}$$

In many reactions of organic compounds, the acid is much weaker than the familiar mineral acids HCl or H_2SO_4. We must also look at bases other than NaOH and the like. Alcohols are weak acids in the presence of a strong base, for example, but they are amphoteric and can be weak bases in the presence of a strong acid. In the acid–base reaction of 3-pentanol (**6**) and H^+ (HCl) the conjugate acid is oxonium ion (**7**). In this reaction, [HA] is the acid catalyst (HCl) and [B] is the oxygen of 3-pentanol. The chloride ion is [A^-] (the gegenion of the acid catalyst) and [HB^+] is $Et_2CH\text{-}OH_2^+$. The concentration of HB^+ present at equilibrium depends on the presence of an acid catalyst that is strong enough to react with the alcohol, and also the base strength of the alcohol. Following the initial acid-base reaction, oxonium ion **7** has a good leaving group (H_2O), that is displaced by chloride ion to give 3-chloropentane as the final product.



6 **7**

Other oxygenated compounds such as ethers behave as weak bases. The common solvents diethyl ether and THF are weak bases in the presence of a strong acid and THF is a stronger base than diethyl ether. The relative base strength can be seen upon examination of the experimentally determined acidity of the conjugate acid derived from diethyl ether [Et_2OH^+], which has a pK_a = -3.12. This acid is stronger than the protonated form of THF [$C_4H_8OH^+$], which has a pK_a = -2.08.[4] Relative basicity is important in reactions where the ether behaves as a Lewis base, such as Grignard reactions (sec. 8.4.A) or formation of organoboranes (sec. 5.2.A).

Another nontraditional weak acid is the hydrogen on the α-carbon of a ketone such as 2-butanone. When 2-butanone (A) reacts with sodium ethoxide (B), the conjugate base is enolate anion **8** (CB), and ethanol is the conjugate acid (CA). Ethanol is a stronger acid than the ketone and can reprotonate the basic enolate. This shifts the equilibrium back to the left, and the net result is a solution that contains enolate **8**, ethanol, unreacted 2-butanone, and NaOEt (sec. 9.2.E).[5] It is important to note that HA does not function as an acid unless a sufficiently strong base (B) is present to remove and accept the acidic proton. If the base under consideration

is too weak to remove the acidic proton of HA, the equilibrium is shifted almost exclusively to the left (i.e., no reaction).

8

[A] [B] [CB] [CA]

When comparing two acids, several factors can be used to evaluate relative acid strength. In an acid-base reaction where acids are on both sides of the equilibrium (A and CA from above), this information can be useful to estimate the position of the equilibrium, which is essentially an estimation of K_a.

1. In general, a strong acid generates a weak conjugate base and, conversely, a weak acid generates a strong conjugate base.

Comparison of the two acids, HCl and NH_3 indicates that the strong acid HCl generates the weak base, Cl^-:

$$HCl \longrightarrow H^+ + Cl^-$$

Conversely, ammonia is a weak acid that generates the strong base, NH_2^-.

$$NH_3 \longrightarrow H^+ + NH_2^-$$

A strong base will deprotonate a weak acid but a weak base will deprotonate only a strong acid.

2. Across the periodic table, acidity generally increases from left to right.[6]

CH_4	<	NH_3	<	H_2O	<	HF
(≈ 50)		(≈ 31)		(15.7)		(3.17)
weak acid						**strong acid**
CH_3^-	>	NH_2^-	>	HO^-	>	F^-
strong conj. base						**weak conj. base**

A consequence of this trend in acidity is that basicity increases from left to right across the periodic table.

3. Acidity increases going down the periodic table, despite a decrease in electronegativity.

therefore,

	HF	<	HCl	<	HBr	<	HI
pK_a	(3.17)		(-7)		(-9)		(-10)[7]

and,

	H_2O	<	H_2S
pK_a	(15.74)		(7.00)[6]

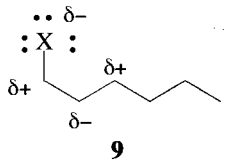
The trend in basicity based on rule 3 is that it increases going up the periodic table. Fluoride is smaller and more electronegative than iodide, has a greater attraction for protons, and forms a stronger bond. These factors make it more difficult to lose a proton from HF than from HI, hence, HF is a weaker acid. Clearly, the increased size of the iodine atom leads to a greater H—I bond distance and, due to the resultant decrease in internuclear electron density, a weaker bond. The acid strength increases, since the weaker I—H bond is more easily ionized, which ignores solvation effects, however, as well as product stability, which are critical to this analysis (see below)

These three concepts allow a quick inspection of a simple acid (HX) for its relative acid strength. Experimental analysis of the acids commonly encountered in organic reactions requires knowledge of at least three factors : (1) electronic effects, (2) resonance effects, and (3) solvent effects.

Incorporation of a hetero-donating or an hetero-withdrawing atom (or group) on a carbon induces bond polarization down the carbon chain, as illustrated by **9**, first introduced in section 1.3.[8] Electron-donating groups release electrons into the carbon chain (inductive or field effect) leading to the so-called *+I* effect. Conversely, an electron-withdrawing group inductively pulls electron density out of the carbon chain and leads to the so-called *–I* effect. The *+I* effect lowers the acid strength whereas the *–I* effect raises it. These electronic effects are generally described by the inductive model[9,10] and the field effect model.[9,11]

The inductive model assumes that substituent effects are propagated by the successive polarization of the bonds between the substituent and the reaction site. This effect is transmitted through both the σ bond network (σ inductive effect) and the π-bond network (π inductive effect).[10] The field effect model assumes that the polar effect originates in bond dipole moments and is propagated according to the classical laws of electrostatics. The appropriate description of this effect is the **Kirkwood–Westheimer model**,[11] in which the molecule is treated as a cavity of low dielectric constant submerged in a solvent continuum.[9a]

Attempts to distinguish inductive and field effects have been frustrated by the lack of a molecule that provides an unambiguous answer.[9b] Such a molecule would require that the low dielectric cavity of the field effect model[12] be occupied by the chemical bonds important to the inductive effect model.[10] If a small attenuation factor is adopted for through-bond transmission of the polar effect, both models predict similar results.[12] For example, *o*-chlorophenylpropionic acid is weaker than expected by the inductive model[13] and is unsuitable.



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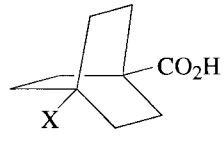

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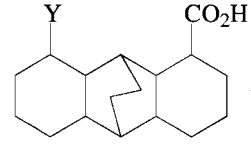
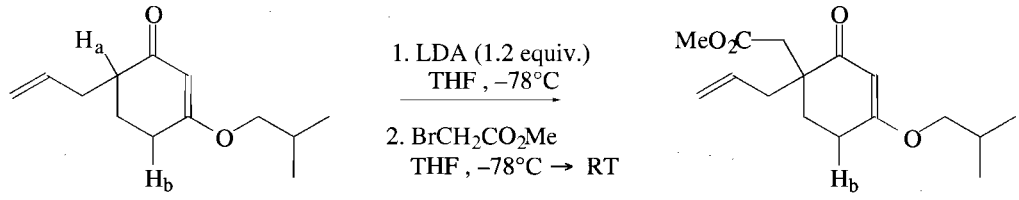


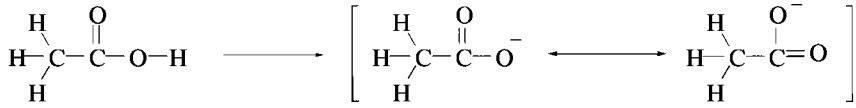
11

Stock reported the pK_a of two systems, **10**[9c] and **11**,[9b] that allow the field effect to be studied. Stock determined that the dominant term associated with the change in pK_a was the positive charge, transmitted through the cavity.[14a] This finding is in general agreement with the Kirkwood–Westheimer model,[11] which suggests that the field effect is the dominant term.[9] Ammonium salts have an *–I* effect,[15] which lowers pK_a (strengthens the acid) relative to acetic acid.[16] Due to the localized character of the σ electrons, the inductive effect diminishes with increasing distance between separation of substituent and reaction center. The change in pK_a is actually due to a combination of inductive, steric and hyperconjugative influences. Chloroacetic acid (pK_a = 2.87)[17] is compared with propionic acid (pK_a = 4.76) since there is no change in the number of α hydrogens, no steric or hyperconjugative effect, and the inductive effect is the only significant contribution to pK_a.[14] The *–I* effect of chlorine induces a significant reduction in pK_a (stronger acid). Electron releasing groups with a *+I* effect will have the opposite effect and lead to a decrease in acidity.[14]



12 **13**

The fundamental concept of inductive and field effects introduced for carboxylic acids can be applied to weaker acids such as the α-hydrogen of ketones. Reaction of **12** with a strong base, in Zoretic's synthesis of megaphone,[18] illustrates this premise. Both H_a and H_b in **12** are acidic, but H_a is preferentially removed by virtue of its proximity to the carbonyl (secs. 9.1, 9.2). Although H_b is acidic by the conjugating effect of the π bond (it is a *vinylogous* acid), the effect is diminished due to the distance from the carbonyl. Formation of the enolate is followed by alkylation (secs. 2.7.A, 9.3.A) to provide **13** in good yield.



14

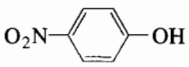
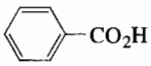
15

One cannot discuss the acidity of a molecule without considering the products formed by the reaction. Remember, this is an equilibrium reaction where the position of the equilibrium (K_a) is determined by the interactions of both A and B as well as CA and CB. Resonance delocalization in the final product is a significant factor that can influence the pK_a of the starting acid in acid–base reactions. Such resonance is due to the existence of low energy molecular orbitals that lead to p electron delocalization transmitted over unsaturated systems. Electron delocalization diminishes the net charge and gives additional stabilization. In the example shown, acetic acid and methanol are compared. Acetic acid (pK_a, 4.76) owes its greater acidity, in part, to the resonance stabilized acetate anion (**14**), whereas methanol (pK_a, 18) generates the methoxide anion (**15**). The charge is *localized* on the p orbitals of oxygen in methoxide but is *delocalized* over three atoms in acetate. Delocalization of charge lowers the net energy of the system, making it more stable (less reactive). Therefore, the conjugate base of acetic acid (acetate anion) is significantly more stable than the conjugate base of methanol (methoxide anion) and this contributes to a lower pK_a for acetic acid relative to methanol.

Resonance effect can also be transmitted via the π bonds of aromatic rings. A comparison of phenol (pK_a, 10.0), 4-nitrophenol (pK_a, 7.2) and 2,6-dinitrophenol (pK_a, 3.6) clearly shows that the presence of a nitro group at these positions enhances acidity, in part by delocalizing electron density in the conjugated phenoxide base. 4-Nitrophenol has one nitro group and its pK_a is measured to be 7.2. In 2,6-dinitrophenoxide, there is more resonance stability due to the second nitro group and the pK_a was measured to be 3.6.[16]

Acidity is strongly influenced by the presence of polar aprotic solvents, as shown in Table 2.2,[19] which compares the pK's of several acids in various solvents.[20] Most reactions take place in solution rather than in the gas phase.[20] The factors that account for the enormous differences between solution and gas-phase chemistry are operationally defined as **solvation**.[19] Protic solvents facilitate charge separation and solvate both the conjugate acid and conjugate base, shifting the equilibrium to favor greater acidity. Aprotic solvents effectively solvate only the cationic product (conjugate base) and the more polar DMSO shows enhanced acidity relative to DMF. Solvating ability is not the only factor however. In the protic solvent methanol, acidity is diminished due to decreased hydrogen-bonding. A comparison of aprotic solvents (DMF, DMSO, and acetonitrile) reveals that the more basic the solvent, the greater the apparent acidity of HA, which is due, in part, to disruption of the internal hydrogen bonding of HA.[21]

Table 2.2. Influence of Solvents on the Acidity of Common Protonic Acids

	p*K*				
	in HOH	in MeOH	in DMF	in DMSO	in MeCN
	7.15	11.2	10.9	9.9	7.0
MeCOOH	4.76	9.6	11.1	11.4	22.3
	4.20	9.1	10.2	10.0	20.7

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The pK_a of carbon acids can depend greatly on the solvent (15.8 for phenylacetylene in diethyl ether, 26.5 in DMSO).[22] This effect is explained by the extent of ion-pairing or ion aggregation. The equilibrium for the deprotonation of phenylacetylene is shifted to the right when the solvent is changed from cyclohexylamine (pK_a = 20.5) to diethyl ether due to increased stability of the ion pair (for the potassium anion, PhC≡C$^-$K$^+$) or the ion aggregate (PhC≡C$^-$K$^+$)$_n$.

It is apparent that acidity in organic molecules is influenced by several factors. Among these, inductive effects, solvent effects, and factors that influence the stability of both the acid and the anionic conjugate base are important. The base is obviously important since the strength of an acid is directly dependent on the strength of the base.

2.2.B. Basicity in Organic Molecules[23]

The relative strength of a base is influenced by the same factors discussed for acids. For common bases, base strength *increases* going to the left and up in the periodic table. An example is

$$F^- > Cl^- > Br^- > I^-$$

Base strength is usually expressed by the pK_a of its *conjugate acid, BH*$^+$ according to the equation

$$BH^+ \rightleftharpoons B: + H^+$$

$$K_a = \frac{[B:]\ [H^+]}{[BH^+]}$$

The inductive and field effects lead to $+I$ (electron donating groups, base strengthening) and $-I$ effects (electron withdrawing groups, base weakening). Examination of amines shows that electron releasing groups intensify the electron density around nitrogen, enhancing the basicity. Electron-withdrawing groups should have the opposite effect. Resonance effects ($+R$) also apply, as described earlier for acids. Resonance effects are also referred to as **mesomeric** effects ($+R$ is $+M$; $-R$ is $-M$), as described in the discussion of aromatic substitution in section 2.11. Electron donating groups can be characterized as having $+R$ effects, and electron-withdrawing groups as having $-R$ effects. When comparing 4-nitroaniline and 4-methylaniline, we note that the methyl group is electron releasing ($+R$) but the nitro group is electron withdrawing ($-R$). The $+R$ effect of the methyl is transmitted through the aromatic ring to intensify the electron density on nitrogen and increase the basicity.

The I and R effects may operate in opposite directions. An example is a slight resonance effect of a group in the meta position of an aromatic nucleus, where the inductive effect is rather large. In the para position, the resonance effect is also large. Table 2.3[24] correlates several substituents with I and R effects.

Table 2.3. $+I$, $+R$, $-I$ and $-R$ Effects in Bases

Effect	Examples
$+I$ (base strengthening)	RO^-, R_2N^-, alkyl
$-I$ (base weakening)	SO_2R, NH_3^+, CF_3, NO_2, CN Cl, Br, CO_2H, CO_2R, I, COR, SR Ph, NR_3^+
$+R$ (base strengthening)	F, Cl, Br, I, OH, OR, NH_2, NR_2 NHCOR, O^-,NH^-, Me, alkyl
$-R$ (base weakening)	NO_2, CN^-, CO_2H, CO_2R, $CONH_2$, Ph COR, SO_2R

Relative base strength is also influenced by two categories of steric encumbrance around the basic atom.

1. In the **primary steric effect**, steric impedance to protonation occurs when bulky groups surround the basic center. When this results in greater strain in the cation (the conjugate acid produced on protonation) than in the neutral molecule, the base is weaker.[25]
2. The **secondary steric effect** occurs when there is hindrance to solvation and it is base weakening. The primary steric effect is credited with the enhanced basicity of aniline, which is more basic than 2,6-dimethylaniline due to greater steric inhibition for reaction with a proton. The secondary effect is probably responsible for the difference in basicity between *N,N*-diethylaniline (pK_a, = 6.65) and *N,N*-dimethylaniline (pK_a, = 5.8). The two ethyl groups inhibit solvation of the protonated conjugated acid,[16] the ammonium salt. Solvation varies with the available space around the basic center. It should be less for pyridine than for aniline. The weakness of tertiary amines relative to secondary amines, in solution, has been attributed to this effect.[24a]

It has been known for many years that the proton acceptor ability of amines in solution and expressed as pK_a of the conjugate acid (BH^+) takes the order:[19]

$$NH_3 \quad < \quad RNH_2 \quad \approx \quad R_2NH \quad > \quad R_3N$$

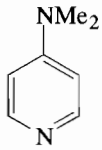
This anomalous order is understood in terms of two opposed influences, one base strengthening and the other base weakening. The base strengthening effect is the electron releasing inductive effects of the alkyl groups on nitrogen. This effect tends to make tertiary amines more basic when compared to secondary or primary amines. As described immediately above, the other major influence is solvation. Solvation is greatest for primary amines, leading to greater stabilization and greater basicity. By using high pressure mass spectrometry (where there are no solvation effects), Munson demonstrated by that the order of gas-phase basicity is:[26]

$$NH_3 \quad < \quad RNH_2 \quad < \quad R_2NH \quad < \quad R_3N$$

It was assumed that the inversion of base strength in solution was primarily a solvation phenomenon. Indeed, this solvation effect is largely the result of hydrogen bonding in an aqueous solvent ($NH_3 \rightarrow NH_4^+$ with four sites for hydrogen-bonding in the ammonium salt vs. $R_3N \rightarrow R_3NH^+$ with only one site for hydrogen bonding in the ammonium salt).

Substitution of alkyl groups for the acidic hydrogen atoms of the ammonium ion reduces the stability induced by hydrogen-bonding with the solvent, and works in opposition to the electron-releasing effect of the increasing number of alkyl groups and dispersal of charge by the inductive effect.[24] Clearly, a discussion of relative acidity must specify the solvent. Ammonia has the greatest solvation effect, since the ammonium ion has four hydrogen atoms capable of hydrogen bonding with the solvent. By this model, tertiary amines generate the least solvated of the amine salts and primary amines give the most solvated amine salt. The salt of a secondary amine is intermediate in solvation stability and, *if* this were the only effect these amines would be intermediate in basicity. The actual order of basicity for amines in solvents, however, is a combination of inductive and solvation effects. Steric hindrance around the electron pair on nitrogen also plays an important role (see above). When all of these factors are accounted for, secondary amines tend to be the most basic, as shown above.

The pK of several common amines used in synthesis have been determined in THF at 25°C.[27] All will be used as bases in reactions used later in this book. 4-*N,N*-Dimethylaminopyridine (DMAP, **16**), proton sponge (**17**), quinuclidine, (**18**), DBU (1,8-diazabicyclo-[5.4.0]-undec-7-ene, **19**), and diazabicyclo-[2.2.2]octane (DABCO, **20**) are shown, along with triethylamine, tributylamine, and tribenzylamine for comparison.[27] The pK values for these compounds are shown in THF, DMSO, and acetonitrile in Table 2.4.[27] These values were determined from proton-transfer ion pairs of the type BH^+ with acidic indicator hydrocarbons in THF. The values obtained in THF differ substantially from the ionic pK_a values for NH^+ in DMSO or acetonitrile. Streitwieser and co-workers[27] states that "at the present time amines cannot be placed quantitatively on any of the ion pair acidity scales currently in use for neutral acids in THF". The realization that it may be necessary to use different bases in different solvents, despite the fact that all are considered to be good bases in organic reactions, makes it clear why a quantitative comparison of bases would be useful.



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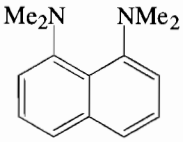

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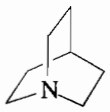

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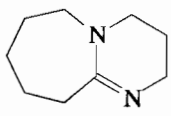

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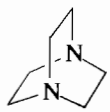

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Table 2.4. pK values of several common amines in various solvents.

Amine	pK_a (THF)	pK_a (DMSO)	pK_a (MeCN)
16	0.61		18.18
17	2.15	7.47	17.28
18	0.15	9.8	19.51
19	-3.78		23.9
20	0.80	8.93	18.29
Et_3N	2.11	9.0	18.70
$(PhCH_2)_3N$	2.41	3.65	12.85
Bu_3N	3.40		18.09

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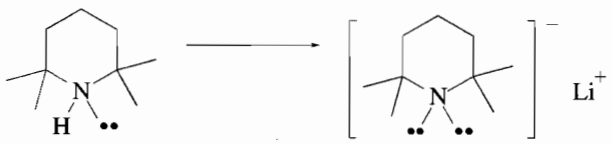
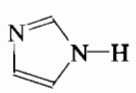
Many different types of bases are used in organic chemistry. Common inorganic bases include the anions of weak bases such as water and ammonia (OH^- and NH_2^-). Similar deprotonation of alcohols leads to the alkoxide bases (RO^-). Methoxide (MeO^-), ethoxide (EtO^-), and *tert*-butoxide ($Me_3C\text{-}O^-$) are very common and are often used in the alcohol solvents from which they were made (methoxide in methanol, *tert*-butoxide in *tert*-butanol, etc.). The bases used to deprotonate water (pK_a = 15.8) or alcohols (p$K_a \approx$ 18) are sodium hydride (NaH), potassium hydride (KH), sodium and potassium hydroxide (NaOH, KOH), sodium metal (Na°),



21 **22**

and sodium or potassium amide ($NaNH_2$ and KNH_2). Amines can be deprotonated by very strong bases such as Grignard reagents and organolithium reagents (secs. 8.4.G.iii and 8.5.G) to give amide bases (R_2N^-). Deprotonation of diethylamine with butyllithium gives lithium diethylamide (Et_2NLi), diisopropylamine gives lithium diisopropylamide (*i*-Pr_2NLi, often called LDA) and 2,2,6,6-tetramethylpiperidine (**21**) gives lithium 2,2,6,6-tetramethylpiperidide (**22**).[28] The parent amines are also common bases but they are used with stronger acids. The most common amine bases are tertiary amines such as triethylamine (NEt_3) or pyridine (C_5H_5N, Py) and those listed in Table 2.4. Imidazole (**23**) is another amine base used in systems that are generally sensitive to strongly basic conditions. The stronger amide bases are used for deprotonation of weak

acids (ketones, alkynes, esters, sulfides, etc. - see Chaps. 8 and 9). The amide bases are often called non-nucleophilic bases due to their poor reactivity as nucleophiles in S_N2 (secs. 9.2.B, 2.6.C)



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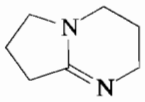

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and in acyl addition reactions (sec. 2.5). Their diminished nucleophilic strength results from the bulky alkyl substituents about the basic nitrogen which inhibits approach to carbon but does not encumber approach to hydrogen. Two other non-nucleophilic bases are 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN, **24**)[191b] and DBU (**19** from above)[191a] in which the bridgehead nitrogen is sterically encumbered. When a very powerful base is required for deprotonation (pK_a of the acid is > 25), carbanion bases such as an organolithium reagent are used most often (sec. 8.5.G). Commercially available reagents such as butyllithium (BuLi), methyllithium (MeLi), and phenyllithium (PhLi) are commonly used in synthesis.

The acid–base concepts described in this section focus on bases that react with protons, the classical Brønsted–Lowry definition of a base. There are other types of electron deficient molecules that function as acids, called Lewis acids. The following section will discuss the relative strength of Lewis acids.

2.3. LEWIS ACIDS

There are two definitions of acidity: a **Lewis acid** is an electron pair acceptor and a **Brønsted–Lowry acid** is a proton donor. For basicity, a Lewis base is an electron pair donor and a Brønsted–Lowry base is a proton acceptor. Section 2.2.B focused primarily on the Brønsted–Lowry definition dealing with reactions of protonic acids (H^+). When a base donates two electrons to an electrophilic center other than a proton, the Lewis acid definition is applied. A Lewis acid is electron deficient relative to the Lewis base. Group 13 (IIIA) atoms such as boron and aluminum are electron deficient since they can form only three covalent bonds and remain neutral. They can satisfy the octet rule by electron donation from a Lewis base, forming an adduct, as shown below. Reaction with the neutral Lewis acid generates a negatively charged complex called an **ate complex**. These will be of particular importance in hydride reductions (sec. 4.2.B) and in hydroboration reactions (see sec. 5.3, 5.4).

Transition metal salts possess a metal atom that is capable of assuming multiple valences. When substituents attached to the metal make it sufficiently electrophilic, the metal derivative functions as a Lewis acid in the presence of a Lewis base. The relative order of Lewis acidity is rarely determined in as straightforward a manner as for protonic acids since the electrophilic metal can have different valences and ligands (the groups or atoms attached to the metal). A number of general statements can be made, however.[29]

Lewis acids usually take the form MX_n, where X is the ligand (a halogen atom, an amine or phosphine or another organic moiety). The metal is M and n is the normal valency of M. The acid MX_n exhibits acidic properties in an equilibrium reaction:

$$MX_n + B \longrightarrow MX_n^- B^+$$

acid base adduct

Formation of a conjugate acid-base adduct ($MX^- B^+$, often called an *ate* complex as mentioned above) is characteristic of Lewis acid–base reactions. If chelation effects and double bond formation between M and any given atom of the base are excluded, three general statements can be made concerning acid strength.[29]

1. In MX_n ($n < 4$) acidity arises from the central atom's requirement for completion of an outer electron octet by accepting one or more pairs of electrons from the base. Acidity is diminished when two electron pairs are required. There is a smaller energy gain upon receipt of the first pair and there is an accumulation of negative charge on M if two pairs are received. The result is that Group 13 (IIIA) acids are more acidic than transition metal acids.

$$BF_3 > AlCl_3 > FeCl_3$$

2. The acidity of M will decrease within any group with increasing atomic volume (effectively, with increasing atomic number) owing to the weaker attraction between nuclear charge and incoming electron pairs (**Fajans' rules**).[29a] The result of these effects leads to the order:

$$BX_3 > AlX_3 > GaX_3 > InX_3$$

3. In general, the energies of different atomic orbitals lie closer together with increasing atomic number, because orbital contractions arising from the electronegativity of the nucleus tend to decrease with increasing atomic number. As a result, there is more effective overlap of hybridized orbitals. The availability of *d* orbitals will be easier (especially with *d* outer orbitals) and more effective, the heavier the element. This leads to a decrease in acidity, as in the series (B→Al→Ga→In) above.

These three statements can be used to estimate the strength of Lewis acids according their Group in the periodic table.[29]

a. Groups 11 (IB) (Cu, Ag, Au) and **12 (IIB**)(Zn, Cd, Hg) usually give covalent species MX_2: ($ZnCl_2$, CdI_2, etc.); M has four electrons in the outer group and needs two additional pairs. By rule 1 these should have only moderate acidity and by rule 2:

$$ZnCl_2 > CdCl_2 > HgCl_2$$

b. Groups 13 (IIIA) (B, Al, In, Tl) and **3 (IIIB)** (Sc, Y, La, Ac) by rule 1 tend to form the most acidic compounds (MX_3). The metal (M) requires only one electron pair to complete the octet (BF_3, $AlCl_3$, $GaBr_3$, etc.). Rule 2 is then applied.

$$BF_3 > AlCl_3 > GaBr_3 > InCl_3 > TlCl_3$$

and,

$$ScCl_3 > YCl_3 > LaCl_3.$$

c. Groups 14 (IVA)(C, Si, Ge, Sn, Pb) and **4 (IVB)** (Ti, Zr, Hf) form covalent species such as MX_4. There are no acidic properties when M = C, and when M = Si only weak acidic properties are observed.

d. Groups 15 (VA) (N, P, As, Sb, Bi) and **5 (VB)** (V, Nb, Ta) usually take the form MX_3 or MX_5. When M is nitrogen, there are no acidic properties, indeed these are bases. When M is phosphorus the molecule is a weak base, but the octet can expand to give weakly acid properties in some reactions. In general, MX_5 compounds

are more acidic than Groups 15 (VA) and 5 (VB) MX_3 compounds due to the expanded octet and the utilization of d orbitals. It is noted that both SbX_5 and NbX_5 are powerful acids.

e. Groups 16 (VIA) (O, S, Se, Te, Po) and **6 (VIB)** (Cr, Mo, W) have the normal covalent character of MX_2. There are close parallels with Groups 14 (IVA) and 4 (IVB). Both OX_2 and SX_2 have virtually no acidity and TeX_2 is very weak. Species arising from abnormal valences, such as TeX_4, can exhibit enhanced acidity since only one electron pair is then required to complete the outer shell of 12.

f. Groups 17 (VIIA) (F, Cl, Br, I, At) and **7 (VIIB)** (Mn, Tc, Re) resemble 14 (IVA) and 4 (IVB) and 16 (VIA) and 6 (VIB) in that the lower members are only weakly acidic. The higher members can expand the octet when attached to electron-withdrawing substituents, and have enhanced acidity (I_3^- and Ph—ICl^-).[30]

With these six general statements as a guide, it is possible to order the more common Lewis acids by decreasing acid strength:

$$BX_3 > AlX_3 > FeX_3 > GaX_3 > SbX_5 > InX_3 > SnX_4 > AsX_5 > SbX_3 > ZrX_4$$

The relative strength of Lewis acids is important to many major classes of organic reactions utilized in synthesis. In sections 11.6.A and 12.4, Lewis acids will be used in connection with several important carbon–carbon bond forming reactions. These include **Friedel–Crafts** type reactions[31] and **Diels–Alder reactions**[32,33,34] (sec. 11.4.A), as well as other pericyclic reactions (chap. 11). Changing the Lewis acids can have dramatic effects on the rate of reaction and the product distribution in both the Diels Alder and Friedel-Crafts reactions.[31] The Lewis acid can also be so reactive that the resulting product is unstable to the reaction conditions. For these reasons, several Lewis acids covering a wide range of acid strengths should be available for a synthesis. Aluminum chloride is a very reactive and unselective catalyst, reacting with virtually all functional groups that have Lewis base properties.[33,35] Zinc chloride ($ZnCl_2$), however, is a mild and selective catalyst in reactions where halides or alcohols are required to react selectively with an olefinic double bond.[31,36] Tin tetrachloride ($SnCl_4$) is a very mild catalyst that can be used for acylation of reactive aromatic nuclei such as thiophene. Catalysis of reactions involving thiophene with $AlCl_3$ is too vigorous and extensive decomposition accompanies the process.[31,37] Tin tetrachloride has also been applied to Friedel–Crafts reactions of active aromatics[31,38] which cannot tolerate vigorous reaction conditions, as with furan derivatives for example.[31,39] These few examples clearly demonstrate that a good working knowledge of the relative acid strength of Lewis acids is essential for understanding many important reactions in synthesis.

2.4 HARD–SOFT ACID–BASE THEORY[40,41]

2.4.A. Hardness and Softness

There is an alternative view of acid-base reactions that relies on the Lewis acid-base definition but has been used to classify a wide range of organic reaction types. Cations are classified as Lewis acids, anions are Lewis bases and salts are viewed as acid-base complexes. When one writes the normal acid–base equation, certain conventions are observed.

$$A' + A\text{-}B \longrightarrow A'\text{-}B + A$$

implies that A' is a stronger acid than A, and

$$B' + A—B \longrightarrow A—B' + B$$

implies that B' is a stronger base than B. For

$$A + B \longrightarrow A—B$$

the equilibrium constant can be defined by $\log K = [S_A]\,[S_B]$

where the S terms represent the strengths of the moieties and are functions of the environment and the temperature. There are strong solvent effects and it is not possible to establish a universal order of acid or base strength[42] due to variations in the parameter S as well as other factors.

For example, if the acid (A) is chromic acid, there is a different basicity order than if A is cuprous ion. Usually, the simple equation shown above is inadequate and requires additional terms

$$\log K = [S_A]\,[S_B] + [s_A]\,[s_B] \qquad 2.1$$

where s is a parameter for the strength of each acid and base, and is called the softness parameter.

The **Edward's equation**[43] (Eqn. 2.2) can be of value for determining the relative strength of Lewis acids and is written as

$$\log \frac{K}{K_0} = \alpha E_n + \beta H \qquad 2.2$$

where H is a proton basicity factor: $H = 2.74 + pK_a$ for water, at 25°C. The term E_n is a redox factor and is equal to E° + 2.60 [E_n = E° + 2.60), where E° is the standard oxidation potential for the base, defined by the reaction:

$$B^- \longrightarrow B^+ + 2\,e^-$$

There are obviously many acids, but the proton (H^+) and an alkyl mercuric ion (RHg^+) have roughly opposite affinities for binding bases. The values of the parameters for the Edward's equation for H^+ are α = 0.000 and β = 2.000 and for $MeHg^+$ the values are α = 5.786 and β = -0.031.[41,44] The reactions of these two acids with Lewis bases define the relative strengths of the Lewis bases, which gives rise to two observations.

1. Bases in which the donor atom is O, N, or F prefer to coordinate to the proton.

2. Bases in which the donor atom is P, S, I, Br, Cl, or C prefer to coordinate to mercury.

In Group 1, the donor atoms are highly electronegative, have a low polarizability, and are hard to oxidize. These are called **HARD BASES** (they bind electrons tightly). In group 2, the donor atoms are of low electronegativity, are highly polarizable and are easy to oxidize.[40c] These are called **SOFT BASES** (valence electrons are loosely bound).[40c] Recognition of these categories forms the basis of the HSAB principle, initially developed by Pearson[40] and also described by Ho.[44]

In separate reactions with hard bases, there are two distinct classes of acids called **HARD ACIDS** and **SOFT ACIDS**. In general,

For **HARD ACIDS**,[40c] acceptor atoms are small in size, are of high positive charge and do not contain unshared pairs of electrons in their valence shell. They are of low polarizability and of high electronegativity.

For **SOFT ACIDS**,[40c] acceptor atoms are large in size, are of low positive charge, and contain unshared pairs of electrons (p or d electrons) in the valence shell. They are highly polarizable and of low electronegativity.

In order to rank these acids according to their relative strength, the criteria of Schwarzenbach[45a] and

Ahrland and co-workers[45b] were used. Hard acids form complexes with the following relative stability:[44]

N >> P > As > Sb
O >> S > Se > Te
F > Cl > Br > I

Similarly, soft acids react in the following manner to produce stable complexes:[44]

N << P > As > Sb
O << S < Se < Te
F < Cl < Br < I

A list of commonly used hard and soft acids is shown in Table 2.5.[41a,46] Lewis acids with large α and β values tend to be soft and Lewis acids with small α and β values are hard. Soft acids form stable complexes with bases that are highly polarizable and good reducing agents (not necessarily good bases toward the proton). Hard acids usually form stable complexes with bases that are good bases toward the proton. A comparison of the ability of Lewis acids to bind donating atoms of Lewis bases is conveniently made by examining the order of the donor atoms as a function of increasing electronegativity:

As, P < C, Se, S, I < Br < N, Cl < O < F

where the atoms on the left form more stable complexes with soft Lewis acids, and those on the right form more stable complexes with hard Lewis acids.

Table 2.5. Classification of hard and soft acids [a]

Hard acids	Borderline cases	Soft acids
H^+, Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, La^{3+}, Ce^{4+}, Gd^{3+}, Ti^{4+}, Cr^{3+}, Cr^{6+}, MoO^{3+}, Mn^{2+}, Mn^{7+}, Fe^{3+}, Co^{3+}, BF_3, BCl_3, $B(OR)_3$, Al^{3+}, $Al(Me)_3$, $AlCl_3$, AlH_3, CO_2, RCO^+, Sn^{4+}, $(Me)_2Sn^{2+}$ RPO_2^+, $ROPO_2^+$, SO_3, RSO_2^+, $ROSO_2^+$, HX (hydrogen-bonding molecules)	Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+} Rh^{3+}, Ir^{3+}, Ru^{3+}, Os^{2+}, $B(Me)_3$, R_3C^+, $C_6H_5^+$, Sn^{2+}, Pb^{2+}, NO^+, Sb^{3+}, Bi^{3+}, SO_2	Pd^{2+}, Pt^{2+}, Pt^{4+}, Cu^+, Ag^+, Au^+, Cd^{2+}, Hg^+, Hg^{2+}, CH_3Hg^+ BH_3, Tl^+, $Tl(Me)_3$, CH_2, carbenes, π acceptors: (chloroanil, quinones, tetracyanoethylene, etc.) HO^+, RO^+, RS^+, RSe^+, Br_2, I_2, O, Cl, Br, I, N, RO, RO_2, M° (metal atoms) and bulk metals

[a] In all cases, the molecules are listed in descending order (the first entry is the hardest or softest).

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In general, hard acids prefer to bind to hard bases and soft acids prefer to bind to soft bases. Several other general comments can be made.

1. Heavier and less electronegative members of a series are usually softer.

R_3P > R_3N

I^- > Br^- > Cl^- > F^-

softer **harder**

2. The more p character, the softer the acid.

$$\underset{\textbf{softer}}{sp^3\ C} > sp^2\ C > \underset{\textbf{harder}}{sp\ C}$$

3. The more electron releasing groups on the moiety, the harder the acid.

$$\underset{\textbf{harder}}{(CH_3)_3C^+} < (CH_3)_2CH^+ < CH_3CH_2^+ < \underset{\textbf{softer}}{CH_3^+}$$

Metals without a minimum of a half-filled outer d shell are not good acceptors,[47] emphasizing the importance of *d* electrons for metal ions. A comparison of the series Ca→Zn suggests that their ions should become harder due to increasing nuclear charge. One also expects an increase in electronegativity and therefore an increase in hardness. In fact, the increase in d electrons leads to increasing softness in this series.

The softness of a base is defined by the equilibrium established in the reaction of $MeHg^+$ and BH^+:

$$MeHg^+_{(aq)} + BH^+_{(aq)} \overset{K}{\rightleftharpoons} MeHgB^+_{(aq)} + H^+_{(aq)}$$

If K is much greater than one, the base is soft. Conversely, if K is ≤ 1, the base is hard. Table 2.6 shows common hard and soft bases.[46,41a,48] The nature of the outer groups on the acceptor atom is important. The hard acid BF_3 possesses hard fluoride ions and readily adds to hard bases. This contrasts with BH_3, which is a soft acid where soft hydride ions readily add to soft anions. Soft bases tend to group together on a given central atom as do hard ligands. There is a mutual stabilizing effect called **symbiosis**.[49]

Table 2.6. Classification of Hard and Soft Bases [a]

Hard Bases	Borderline Cases	Soft Bases
NH_3, RNH_2, N_2H_4, H_2O, OH^- O^{2-}, ROH, RO^-, R_2O, AcO^-, CO_3^{2-}, NO_3^-, PO_4^{3-}, SO_4^{2-}, ClO_4^-, F^- (Cl^-)	$C_6H_5NH_2$, C_5H_5N, N_3^-, N_2, NO^{2-}, SO_3^{2-}, Br^-	H^-, R^-, $CH_2{=}CH_2$, C_6H_6, CN^-, RNC, CO, SCN^-, R_3P, $(RO)_3P$, R_2S, RSH, RS, $S_2O_3^{2-}$, I^-

[a] In all cases, the molecules are listed in descending order (the first entry is the hardest or softest)

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In the case under consideration, the hard fluoride ligands form a complex that makes boron essentially 'B^{+}' and hard. The soft hydride donates negative charge to the central boron by via a covalent bond, or by simple polarization, making the boron more neutral and soft. It appears that the actual charge on the central atom, rather than the formal charge, determines the degree of softness.

As Pearson has pointed out, "while the HSAB principle has proved useful in many ways,[40a] it has been justifiably criticized because of the lack of a precise definition of hardness and the inability to assign numbers to this property".[50] The hardness parameter (η) is now defined in terms of electronegativity, as in Equation 2.3[51]

$$\eta = \tfrac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right) = \tfrac{1}{2}\left(\frac{\partial M}{\partial N}\right) \qquad 2.3$$

where ∂E and ∂N are obtained from the Mulliken electronegativity (χ_M).[52] Pearson used an operational definition of hardness (Equation 2.4).

$$\eta = \frac{I - A}{2} \qquad 2.4$$

In this definition, I is the ionization potential and A is the electron affinity. It was noted that a hard molecule will have a large value of η. For a reaction A + B $\leftrightarrows$ A:B, the following expression can be used to decide which is the acid, A or B:[50]

$$(I_A - A_B) - (I_B - A_A) = 2(X°_A - X°_B) \qquad 2.5$$

If this quantity is positive, transferring an electron from B to A requires less energy than from A to B. The A group is then a Lewis acid. The direction of electron flow can be determined by the difference in absolute electronegativities, whose magnitude is a measure of the driving force for the transfer.[50]

In most cases, there will be electron transfer in both directions, and if the amount of electron transfer in both directions is near unity (≈ 1), the total energy is given by Equation 2.6.

$$(I_A - A_B) + (I_B - I_A) = 2(\eta_A + \eta_B) \qquad 2.6$$

If both A and B are hard, then η_A and η_B will be large and transfer of electrons in *both* directions will be disfavored. If A and B are soft, however, η_A and η_B will be small, favoring electron transfer.[50] Table 2.7[50] provides typical values for electronegativity (X°) and for hardness (η) for several cations, anions and neutrals.

From Table 2.7, it is apparent that Al^{3+} (η = 45.8 eV) is a hard Lewis acid whereas Ag^+(η = 6.9 eV) is a soft Lewis acid. To illustrate neutral molecules, hydrogen (H_2) is harder than iodine (I_2) and chloromethane (η = 7.5 eV) is harder than iodomethane (η = 4.7 eV) Similarly, trimethylamine (η = 6.3) is a harder base than trimethylphosphine (η = 5.9).

Table 2.7. Electronegativity and hardness parameters

Ion/Molecule	X° (eV)	η (eV)	Ion/Molecule	X° (eV)	η (eV)
			Cations		
Na^+	26.2	21.1	Fe^{2+}	23.4	7.3
Ag^+	14.6	6.9	Zn^{2+}	28.8	10.8
I^+	14.8	4.3	Pd^{2+}	26.2	6.8
Mn^{2+}	24.4	9.3	Hg^{2+}	26.5	7.7
Ca^{2+}	31.6	19.7	Al^{3+}	74.2	45.8
			Neutrals		
BF_3	7.8	7.8	C_5H_5N	4.4	5.0
SO_3	7.2	5.5	$CH_2{=}CH_2$	4.4	6.1
N_2	7.0	8.6	H_2S	4.3	6.4
Cl_2	7.0	4.6	C_6H_6	4.0	5.2
SO_2	6.7	5.6	PH_3	4.0	6.0
H_2	6.7	8.7	H_2O	3.1	9.5

O_2	6.3	5.9	MeCl	3.8	7.5
CO	6.1	7.9	NH_3	2.9	7.9
I_2	6.0	3.4	Me_3P	2.8	5.9
Pt	5.6	3.5	Me_2S	2.7	6.0
MeI	4.9	4.7	Me_2O	2.0	8.0
HCl	4.7	8.0	Me_3N	1.5	6.3
			Anions		
F^-	3.40	7.0	Br^-	3.36	4.2
OH^-	1.83	5.7	I^-	3.06	3.7
NH_2^-	0.74	5.3	H^-	0.74	6.8
Me^-	0.08	4.9	MeS^-	1.9	3.1
Cl^-	3.62	4.7	*t*-Bu^-	-0.3	3.6
SH^-	2.30	4.1	$C_6H_5^-$	1.1	4.1
PH^{2-}	1.25	4.3	NO^{2-}	3.1	3.9

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2.4.B. HSAB and Molecular Orbital Theory

Frontier molecular orbital (FMO) theory (sec. 11.2) correlates molecular orbital energies and orbital coefficients with the relative reactivity of molecules. In a molecule, the orbital containing the highest energy bonding electrons is called the highest occupied molecular orbital (HOMO) and the lowest lying orbital that does not contain electrons but can receive them is the lowest unoccupied molecular orbital (LUMO). Both HOMO and LUMO are shown in Figure 2.1.[50] The difference in energy between these orbitals determines the reactivity of many types of reactions. Experimentally, the energy of the HOMO is the ionization potential (I) and the energy of the LUMO is the electron affinity (A), leading to the equations:

$$I = -\varepsilon_{HOMO} \quad \text{and} \quad A = -\varepsilon_{LUMO}$$

In Figure 2.1, the electronegativity (X°) is taken as the midpoint (average) between the HOMO and LUMO energies.[50] If the HOMO is –10 eV and the LUMO is +1 eV, then the midpoint is 5.5 eV and the value of X° is 1 eV –5.5 eV = –4.5 eV. The parameter η will then be 5.5 eV (see Fig. 2.1), which allows one to define a hard molecule or ion as having a large energy gap between the HOMO and LUMO ($\Delta_{HOMO-LUMO}$).[50] A soft molecule or ion will have a small $\Delta_{HOMO\text{-}LUMO}$.[50] Soft acids and bases have properties that lead to a high energy HOMO and a low energy LUMO (a small energy gap). Hard acids and bases have the opposite properties: a low energy HOMO and a high-energy LUMO (a large energy gap). This generalization can be applied to cations, anions and radicals as well as neutral molecules. Radicals contain a singly occupied molecular orbital (SOMO), as shown in Figure 2.2.[50] The electron affinity term in this case arises from adding a second electron to the SOMO and X° is the average energy of the two electrons in that orbital. The quantity I–A is the average value of the interaction energy of the two electrons.[53]

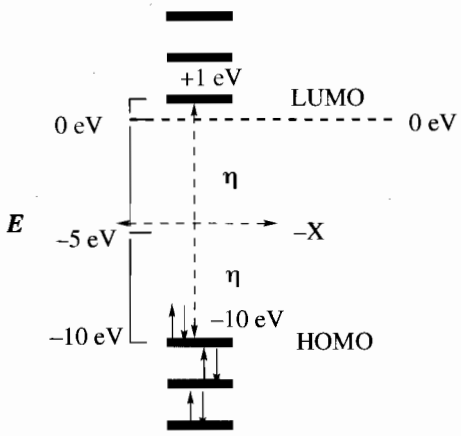

Figure 2.1. Correlation of HOMO and LUMO with electronegativity and hardness

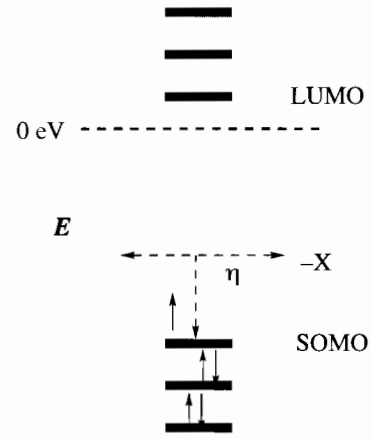

Figure 2.2. Energy diagram For radicals

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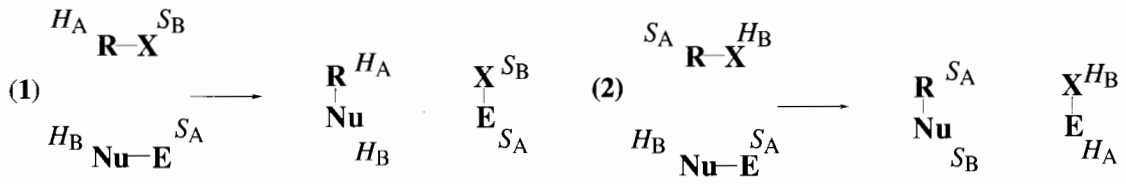
The HOMO–LUMO energy gap is usually the lowest energy electron absorption band. Soft acids and bases tend to absorb light closer to the visible region than do hard acids and bases. Alkenes are chromophoric and it is typical for them to have high–energy HOMOs and low energy LUMOs. In general, unsaturation increases softness. It is also apparent that soft molecules are more reactive than hard molecules (due to a smaller energy gap *I–A*) in unimolecular and bimolecular reactions.

These principles finally allowed Pearson to define hardness (η) as follows:[50] a hard molecule resists changes in its electron charge cloud, both the total amount of charge and the charge distribution in space. A soft molecule has an easily changed electron distribution.

2.4.C. Applications of HSAB Theory

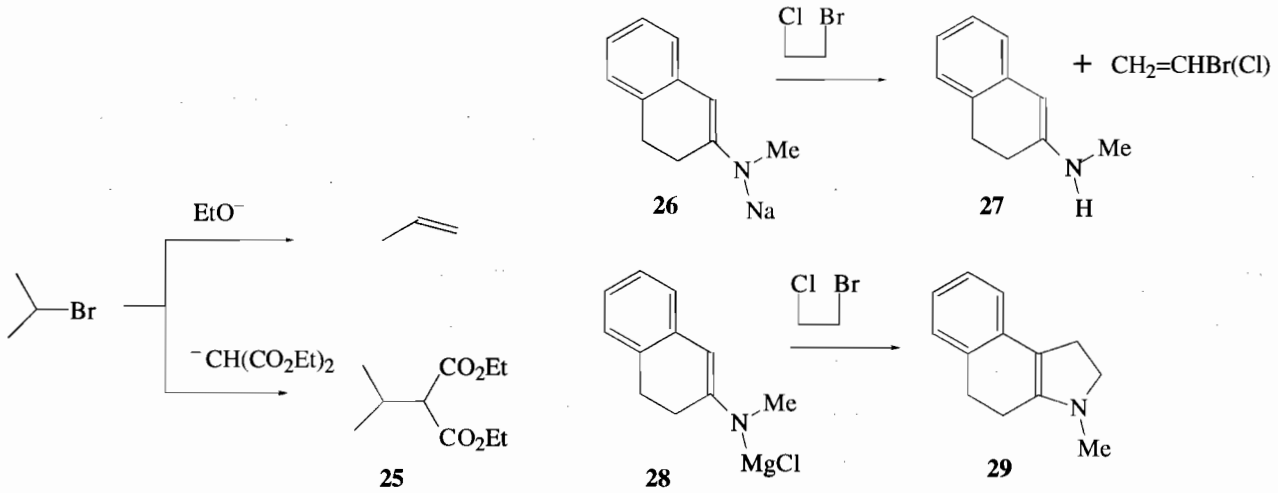
In an attempt to predict product distributions, HSAB theory, has been applied to many chemical reactions not usually classified as acid–base reactions. Care should be exercised in nontrivial cases but this approach may be of value in predicting the likelihood of a number of reactions in a synthetic plan. Several examples are illustrated below.[50]

2.4.C.i. Substitution (also see sec. 2.7). Saville showed that nucleophilic displacement of alkyl halides can be characterized by HSAB theory.[54] In general, the reaction works best when the R group and nucleophile partner are matched. The two major categories are

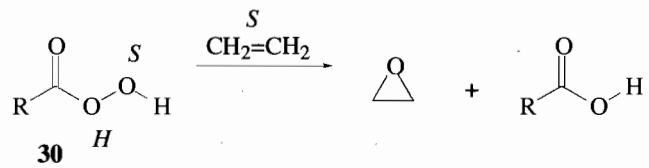


When R—C has a greater differential in hardness and softness, the reaction proceeds best. Table 2.7 shows that chloromethane is harder than iodomethane. Therefore, a hard base such as methoxide will show a larger energy difference for iodomethane, which should react faster.

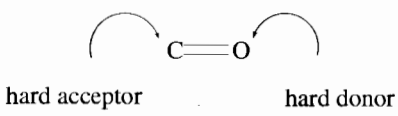
2.4.C.ii. E2 versus S_N2 (see secs. 2.9.A and 2.7.A). Ethoxide and malonate are about equal in basicity,[55] but ethoxide is a much harder base than malonate. Reaction with 2-bromopropane and ethoxide gives primarily elimination, but malonate gives the substitution product (**25**). In general, hard bases give elimination and soft bases substitution. The gegenion has a profound influence on this reaction. Reaction of 1-bromo-2-chloro-ethane with **26** gives only elimination (to bromo or chloroethene), leaving behind the neutral substrate **27**. However, the chloromagnesium salt (**28**) leads to nucleophilic displacement and formation of **29** after a second displacement by the enamine (sec. 9.6) formed in the first substitution.[56]



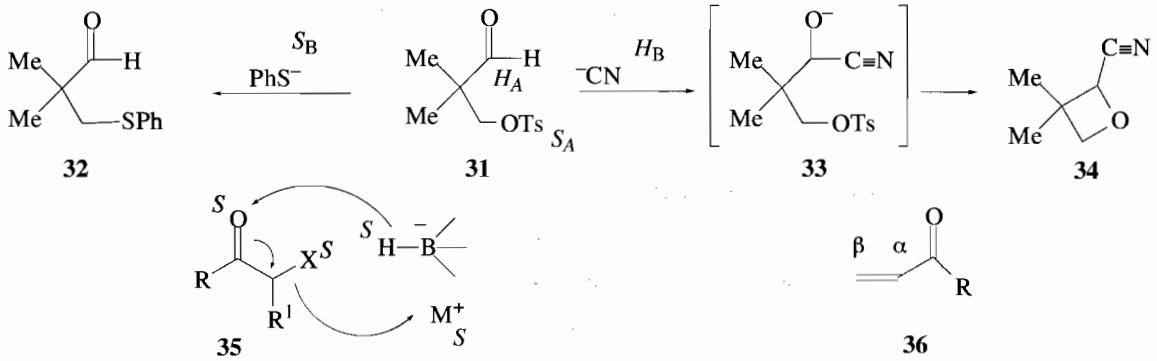
2.4.C.iii. Epoxidation. Peroxyacids such as **30** (sec. 3.4.C) contain an unusual soft–hard combination that leads to attack by a soft alkene (a soft base) on the soft oxygen of the peroxyacid.



2.4.C.iv. Carbonyls. The carbon of a carbonyl is a hard acceptor and the oxygen is a hard donor.



An example is **31**, which reacts with the soft thiophenoxide (PhS) at the tosylate center (C-OTs) to give **32**.[57] Reaction of **31** with the harder cyanide ion, however, gives **33** and subsequent ring closure where the alkoxide unit displaces tosylate generates oxetane **34**.[57] Thiophenoxide is a soft base that reacts with the soft



acid (CH_2OTs), whereas cyanide is a hard base that reacts with the hard acid (the carbonyl). Reductive hydrogenolysis of α-bromoketones (**35**) by some metal borohydrides (not $NaBH_4$, see sec. 4.4.A) is another example. Transfer of the soft base (hydride) leads to loss of the halide (a soft base). The reaction works best when the metal (M^+) is a soft acid.[58] The sodium counterion in sodium borohydride is a hard acid and does not work well in this reaction. A soft acid such as copper or lead, however, will facilitate the reduction.[59,60] Reduction with metal borohydrides will be discussed in section 4.4.B.

Conjugate reduction of α,β-unsaturated ketones (sec. 4.2–4.5) can also be explained by HSAB theory.[61] The β-carbon of a conjugated ketone (**36**) is softer than the carbonyl. A covalent M—H reagent such as hydride is soft and $LiAlH_4$ reduction of cyclohexenone leads to 22% of the conjugate reduction product. Conversely, lithium trimethoxyaluminum hydride (sec. 4.3) suppresses the soft conjugate addition since the alkoxy groups are hard. Only 5% of conjugate addition is observed in this case.[62] The presence of an alkyl group increases the softness of the borohydride. Sodium borohydride gives mainly 1,2-addition but potassium tri-*sec*-butylborohydride (K-Selectride, sec. 4.5.C) gives mainly 1,4-reduction.[63] The B—H bond is more covalent than Al—H and borohydrides are softer than aluminum hydrides, which accounts for observation that BH_4^- is relatively inert to the hard acid H^+. Softer cations such as Na^+ favor 1,4-reduction and it is known that $NaBH_4$ gives more 1,4-reduction than $LiBH_4$.[64]

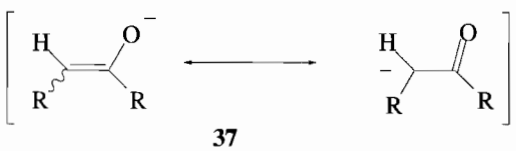
Reaction of enones with organometallics also follows this pattern. Dialkylcuprates (with a soft copper) are soft and give primarily 1,4-addition. When organolithium reagents (with a hard Li atom) react with enones, the major product rises from 1,2-addition. The hardness of common organometallics follows the order:[65]

(**harder**) RLi > RMgX > RCu > R_2CuLi (**softer**)

The alkyl portion also plays an important role. The hardness order of alkyl fragments is:[65]

(**harder**) Me > Et > *i*-Pr > *t*-Bu (**softer**)

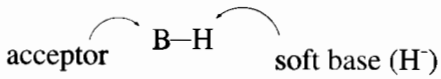
This reactivity order suggests that *tert*-butylmagnesium halides are softer and will give more conjugate addition than methyl-magnesium halides.[66,65] When the alkyl fragment of an organocuprate is hard (such as lithium trialkynyl cuprates) the reagent adds to the carbonyl via 1,2-addition.[67]



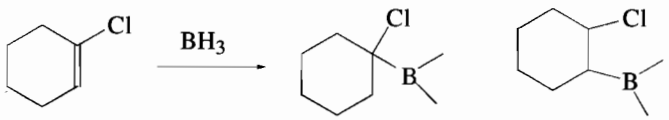
37

2.4.C.v. Enolates. Enolate anions such as **37** are bidentate nucleophiles (the carbanion and alkoxy units can both donate electrons) and bidentate bases. Oxygen is a harder base than carbon and reaction with hard acids tends to give more O alkylation. The hardness of alkyl halides is RCl > RBr > RI, and more C alkylation is expected with R—I but more O alkylation with R—Cl.[41] Reaction of an enolate anion with various alkyl chlorides can lead to more O alkylation than C alkylation, although C alkylation is obtained when the alkyl halide is a bromide or iodide. The product distribution varies as the polarity of the solvent is changed, however.[41] In general, acylation and silylation of enolates (classified as hard acids) give more O alkylation. The ease of C—X bond cleavage parallels the softness of X. In general, the hard Si atoms tend to form strong bonds with oxygenated compounds.

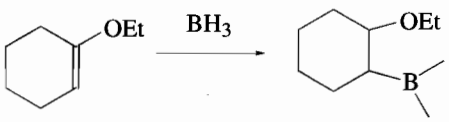
2.4.C.vi. Hydroboration



The reaction between alkenes and boranes forms the basis of hydroboration (see Chap. 5). Borane (B_2H_6, formally known as diborane) is a soft Lewis base and will complex with soft bases such as alkenes. The boron



38 **39** **40**



41 **42**

atom is the acceptor (a soft acid) and hydride is the soft base. When BH_3 (the monomeric form of diborane) reacts with a vinyl chloride, the boron goes primarily to the α-carbon (**38** gave 60% of **39** and 40% of **40**).[68] Reaction with enol ether **41**, however, gave only **42**.[68] Both chlorine and ethoxy are hard bases and influence hardness at the *ipso*-carbon.[69] Ethoxy is harder and accounts for the predominance of **42**. The chlorine substituent leads to resonance stabilization that swamps the increase in hardness. The increased regioselectivity observed in reactions of chloroborane, for example ($ClBH_2$, sec. 5.2.A), is attributed to the heightened hardness of the boron atom,[70] induced by the chlorine.

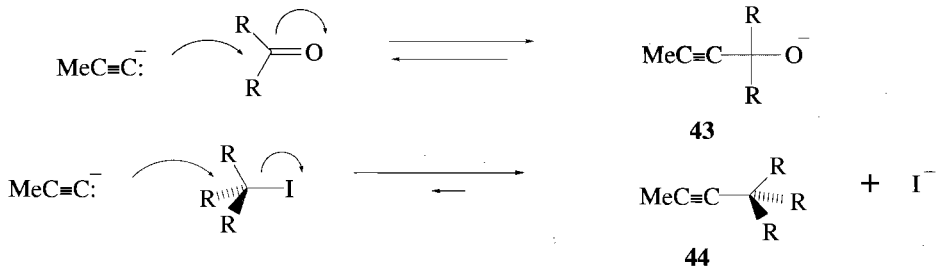
2.5. ACYL ADDITION, SUBSTITUTION AND CONJUGATE ADDITION

A major reaction of nucleophiles is their attack at an acyl carbon (a carbonyl carbon), breaking the π bond and forming a new bond to carbon. This class of organic reactions is called nucleophilic acyl addition. When the carbonyl contains a leaving group, acyl addition is followed by loss of that group to give a substitution

product, which is called acyl substitution. Conjugate carbonyl compounds can also be attacked at the C=C unit in what is called conjugate addition or Michael addition. Both of these types of reactions will be discussed in this section.

2.5.A. Nucleophilic Attack

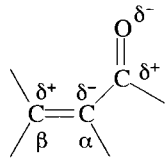
The discussion of Lewis acids made it clear that electrophilic centers other than a proton can react with an electron-donating species. Bond polarization, induced by attached atoms, will polarize atoms and they react with reagents that donate electrons. A simple example is the reaction of carbonyls (C=O) with the nucleophilic



alkyne anion. The carbonyl carbon has a positive dipole ($^{\delta+}$C) because of the electronegative oxygen atom, and that carbon can accept an electron pair (it is termed an **electrophile** or electron loving) from the negatively charged carbon of MeC≡C:$^-$ to give **43**. The carbon of an alkyl halide also has a positive dipole that makes it electrophilic, and attack by the carbanionic carbon will lead to displacement of the iodide (to form **44**) in a S_N2 reaction (sec. 2.7.A). Formation of both **43** and **44** are reasonable extensions of Lewis acid–Lewis base reactions, but the electrophilic center is a carbon atom in both cases. Although the attacking species is formally a Lewis base, it is convenient to designate it as a **nucleophile** (nucleus loving) to emphasize its attack on carbon rather than other electrophilic atoms. A **nucleophile** is therefore defined as a species able to donate two electrons to carbon, forming a new bond to carbon. As we will see in section 2.9.A., if a nucleophile is a relatively strong base as well as a nucleophile, elimination can compete with substitution.

The facility of attack by a nucleophile on an electrophile depends on both the strength of the nucleophile (its ability to donate electrons to carbon) and the nature of the carbonyl substrate. An order of nucleophilic strength for reaction of representative nucleophiles with a carbonyl is[212b]

$$C{=}N{-}O^- > EtO^- > MeO^- > HO^- > N_3^- > F^- > HOH > Br^- > I^-$$



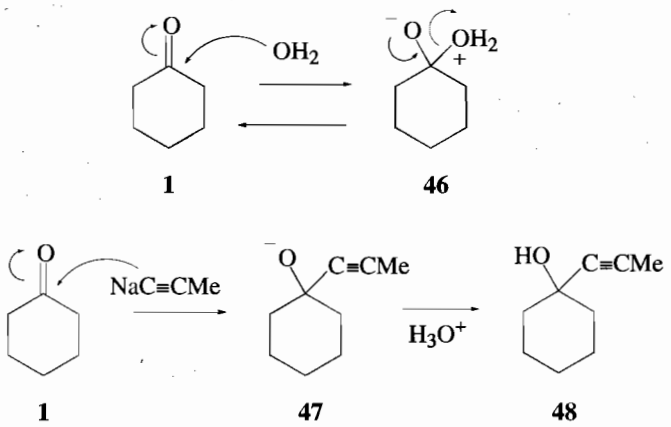
45

A complete discussion of nucleophilic strength will be delayed until sec. 2.7.A, in connection with reactions of nucleophiles and alkyl halides.[71] This section will focus on nucleophilic reactions of carbonyl compounds.

There are two fundamental types of reactions: (1) acyl addition and (2) acyl substitution. A third type of reaction occurs when the carbonyl is conjugated to a π bond. Inductive effects make the β-carbon of the π bond electrophilic (see **45**) and subject to nucleophilic attack. Such conjugate additions will also be presented.

2.5.B. Acyl Addition to Carbonyls[72]

Nucleophilic addition to a carbonyl can be reversible if the attacking nucleophilic species becomes a good leaving group in the product (leaving groups are discussed in sec. 2.6.E). Water and hydroxide, for example, add reversibly. When water adds to cyclohexanone, the product is **46** but H_2O is a good leaving group in the presence of the alkoxide unit, which contributes to making the reaction reversible, as shown. As a practical matter, this occurs with weak nucleophiles. The process becomes effectively irreversible if the nucleophile becomes a poor leaving group in the product. When $Na^+{}^-C{\equiv}CMe$ reacts with a carbonyl, a carbon–carbon bond is formed and the leaving group for the reverse reaction is a carbon group, a very poor one, making the reverse reaction more difficult. For this reason, cyclohexanone reacts with the sodium salt of 1-propyne to give alkoxide **47**. Since it is difficult for **47** to lose acetylide ($^-C{\equiv}CMe$), the addition is essentially irreversible and a hydrolysis step can be done to give the final product, **48**. Clearly, this analysis is overly simplistic and the nucleophilic strength of the incoming reagent as well as the groups attached to the acyl carbon play a major role.



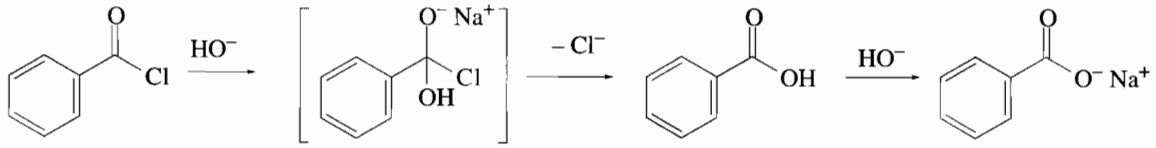
1 **46** **1** **47** **48**

Nucleophilic attack by ethanol (a weak nucleophile) on cyclohexanone is reversible. The reaction can be accelerated and driven to completion by converting the acyl unit of cyclohexanone to a more reactive oxygen-stabilized carbocation, which is usually done by adding an acid catalyst. Protonation of the carbonyl oxygen gives a cation (sec. 2.7.B.i and 12.2) that reacts with ethanol to give a hemi–acetal after loss of a proton. In the presence of the acid catalyst and ethanol solvent, the equilibrium favors formation of the diethyl ketal of cyclohexanone (1,1-diethoxycyclohexane). Ketals and acetals are common protecting groups for the carbonyl group (sec. 7.3.B.i). Other nucleophiles such as water, thiols, and amines can be used in this process with aldehydes and ketones. The acyl addition process is usually reversible, but addition of excess reagent (ethanol) or removal of a product (water) will drive the equilibrium from ketone to ketal (or another addition product). Addition of water or aqueous acid will convert the ketal to a ketone. In general, addition of carbon

nucleophiles to a carbonyl is irreversible (or the equilibrium greatly favors the product) and addition of heteroatom nucleophiles is reversible. Even when the reaction equilibrates, the equilibrium may lie to the side of the products. Heteroatom nucleophiles usually require an acid catalyst in order to establish an equilibrium that can lead to good yields of nucleophilic addition products. All of these reactions are discussed in any undergraduate organic chemistry book, and we will, for the time–being, keep the focus on acyl addition of strong nucleophiles.

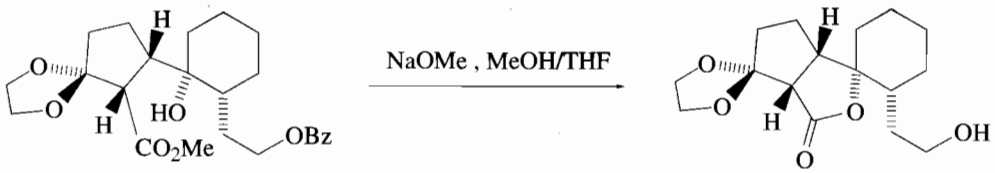
2.5.C. Acyl Substitution to Carbonyl Compounds[73]

Derivatives of carboxylic acids such as acid chlorides and esters have an interesting structural feature relative to a ketone or aldehyde, a carbonyl that bears a chlorine, or an OR group. Nucleophilic addition to such a carbonyl generates an intermediate in which the chlorine or alkoxy group is a leaving group. Both the C—Cl or C—OR bonds are relatively weak (this assumes that the newly formed bond is stronger). If the C—Cl or C—OR bonds are broken, the products are the chloride ion or the alkoxy anion (RO^-), which are rather stable ionic entities. Acyl addition by hydroxide to benzoyl chloride, for example, gives **49** as the initial product. Although it is a reaction product, it is a reactive intermediate and elimination of the chloride ion leads to benzoic acid. The overall result of this process is a substitution reaction where the nucleophile replaces chlorine on the carbonyl; hence, the term **acyl substitution**. Under these basic conditions, the initially formed acid is converted to the carboxylate anion, requiring a neutralization step to recover the acid.



49

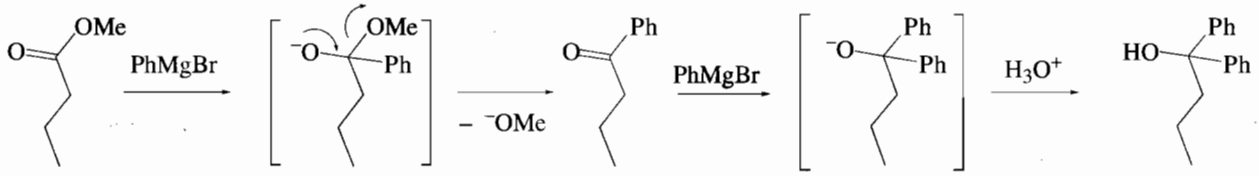
In ketones and aldehydes, addition of a nucleophile leads to a species such as **46** or **47**, where there are strong C—C or C—H bonds, and H or C are not considered to be leaving groups. The presence of a leaving group in acid derivatives leads to the fundamental difference in reactivity between acyl addition and acyl substitution. Acyl addition can be reversible with weak nucleophiles, as in the reaction of ethyl butanoate and sodium methoxide, which generates an alkoxide intermediate bearing both OMe and OEt. In **49**, Cl is a better leaving group than OH, but in this new case, OMe and OEt are close in reactivity. Both are leaving groups.



50 **51**

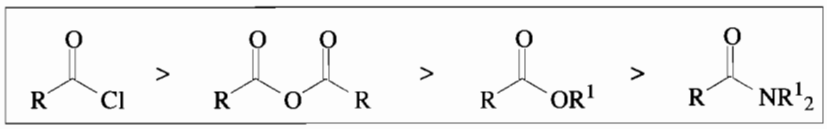
Loss of OMe will regenerate ethyl butanoate but loss of OEt will form methyl butanoate (and sodium ethoxide). This **transesterification** reaction is further complicated by the fact that ethoxide is nucleophilic and

can react with methyl butanoate to give ethyl butanoate. Similar attack on the ethyl ester simply regenerates the starting material. If a large excess of sodium methoxide were used, the equilibrium would favor the methyl ester. Since sodium ethoxide will give both ethyl and methyl butanoate, an excess of sodium ethoxide would favor the ethyl ester. Clearly, this can be a complex process. Transesterification can be useful in synthesis. In Little's synthesis of the phorbol skeleton,[74] hydroxy ester (**50**) with treated sodium methoxide, which generated an alkoxide. Displacement of methanol via acyl substitution (net transesterification) gave an 85% yield of **51**. Also note that the benzoate ester unit was hydrolyzed to the alcohol under these conditions.

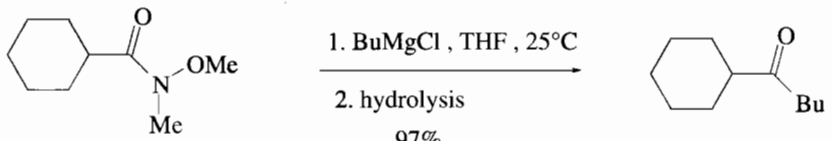


52 **53** **54** **55**

Nucleophilic addition of Grignard reagents to carboxylic acid derivatives is another example of an acyl addition where the newly formed product is subject to further reaction with the reagent.[75] Initial addition to the carbonyl of methyl butanoate gives **52**, which loses methoxide to give the ketone, 1-phenyl-1-butanone (**53**). The ketone is more reactive than the ester and reacts with phenylmagnesium bromide to give **54**. Hydrolysis generates the tertiary alcohol (**55**) (sec. 8.4.C.i). Esters, anhydrides, and amides give similar products via initial nucleophilic addition. The best leaving group is chloride followed closely by carboxylate (acid chlorides and anhydrides, respectively). Amides, with an $^{-}NR_2$ leaving group, are the least reactive. In general, the reactivity of the carbonyl moiety is a function of the leaving group propensity of the ligand attached to carbon. The usual order of reactivity to nucleophilic acyl substitution is:



It is possible that the ketone product formed by reaction of a Grignard with an acid chloride or anhydride is less reactive than those starting materials. If so, significant amounts of the ketone product can be isolated, but the yields are often low. With esters and amides, the ketone product is usually more reactive, very little ketone is isolated from the reaction mixture, and the ketone reacts further to form a tertiary alcohol. If a large excess



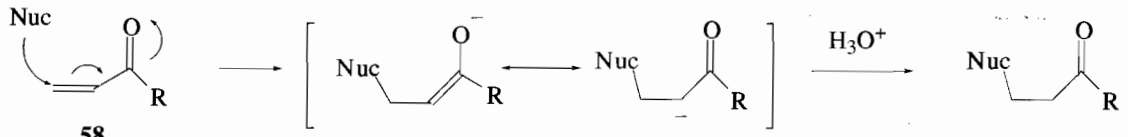
56 **57**

of the nucleophile (such as excess Grignard) is used, the reaction will be driven to give the tertiary alcohol as the major (often the only) product. In later chapters, the problem of reactivity of the ketone product with the organometallic reagents will be circumvented by use of a dialkyl cadmium reagent (sec. 8.4.C.ii).[76] Reaction of acid chlorides with organocuprates will also give the ketone in good yield (sec. 8.7). In some cases,

functionalized amides can give good yields of the acyl addition product. *N*-Methoxy amide (**56**) is referred to as a Weinreb amide, and reaction with butylmagnesium chloride gave a 97% yield of ketone **57**.[77] This reaction will be discussed further in more detail in section 8.4.C.ii.

2.5.D. Conjugate Addition[78]

Conjugated ketones, aldehydes, esters ,and similar molecules have the carbonyl unit connected directly to the π bond of an alkene (as in **58**). Inductive effects make the terminal carbon of the alkene electrophilic and subject to attack by a nucleophile. This type of reaction is referred to as **conjugate addition** or **Michael addition**[79] (sec. 9.7.A) and it is facilitated by formation of a product that is resonance stabilized, the enolate anion (**59**). Hydrolysis gives the final addition product, ketone **60**. In some cases, however, nucleophilic attack at the acyl carbon is faster, which leads to the usual acyl addition product. Acyl addition is usually preferred with conjugated aldehydes but the type of nucleophile is very important as well. When the R group in **58** is hindered, attack at the acyl carbon is difficult and conjugate addition often leads to the major product. When R is small, such as the H in conjugate aldehydes, normal 1,2-addition to the carbonyl (acyl addition) is



usually preferred, as mentioned. Conjugate addition is a key feature of the **Robinson annulation**[80,79] (sec. 9.7.C) in which a ketone enolate reacts with a conjugated ketone to give a cyclohexenone derivative. Another example of a conjugate addition is the reaction of lithium dialkyl cuprates to α,β-unsaturated carbonyl derivatives (sec. 8.7.A.vi).[81,82] Michael additions are common in synthesis.

2.6. CHARACTERISTICS OF REACTIONS INVOLVING NUCLEOPHILES

It is apparent from section 2.5 that many factors influence the course of nucleophilic reactions, including the nature of the nucleophile, its strength, the solvent, the substrate and the nature of the leaving group. When substitution (sec. 2.7.A,B) and elimination (sec. 2.9.A,B) are discussed, it will be noted that they are sometimes competitive when using nucleophiles that are also bases, such as hydroxide. The same factors mentioned above influence the extent of this competition. If the functional groups in a molecule were such that substitution and elimination were competitive processes, then a mixture of products could result. It would be very useful to have a list of parameters for such situations that allow one to make predictions. This section will focus on several factors that influence both nucleophilic and elimination reactions. Analysis of these factors lead to key assumptions and predictions of the major product in many cases.

2.6.A. The Solvent

The solvent is present to solubilize all reactants, of course, and it also absorbs excess heat that may be liberated by the reaction. A very important property of a solvent is polarity, which largely determines its

ability to solvate and separate ions (solvation). Solvation is the key to most nucleophilic reactions and is very important in acid–base reactions, as seen in sec. 2.2. A good measure of this ability of a solvent to separate ions is the dielectric constant.[83,84] Table 2.8[83,84] shows the dielectric constants for several common solvents.

Table 2.8 is further divided into two classes of solvents, those that contain an acidic proton (X—H, **protic**) and those that do not possess an acidic proton (**aprotic**). With each class, the higher the dielectric constant, the more polar the solvent. The essential difference between protic and aprotic solvents is the ability of protic

Table 2.8[84] Dielectric Constants and Relative Polarity of Common Organic Solvents

Solvent Protic	Dielectric Constant		Solvent Aprotic	Dielectric Constant
		(polar)		
HOH	78.5		$H(C{=}O)NH_2$	109.0
DOD	78.25		DMSO	46.68
80% a. EtOH	67		DMF	36.71
HCO_2H	58.5		MeCN	37.5
MeOH	32.7		$MeNO_2$	35.87
EtOH	24.55		HMPA	30
n-BuOH	17.8		Acetone	20.7
NH_3	16.9		Ac_2O	20.7
t-BuOH	12.47		Pyridine	12.4
Phenol	9.78		*o*-Dichlorobenzene	9.93
$MeNH_2$	9.4		CH_2Cl_2	9.08
$MeCO_2H$	6.15		THF	7.58
			Ethyl acetate	6.02
			Chlorobenzene	5.71
			Ether	4.34
			CS_2	2.64
			NEt_3	2.42
			Benzene	2.28
			CCl_4	2.24
			Dioxane	2.21
			Hexane	1.88
		(nonpolar)		

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solvents to solvate *both* cations and anions, whereas aprotic solvents efficiently solvate *only* cations. The polarized OH unit in the protic solvents listed is not sterically encumbered, which allows the $^{\delta-}$O end to solvate cations and the $^{\delta+}$H end to solvate anions (via hydrogen bonding). The negative dipole of aprotic solvents can participate in the solvation of cations but the positive dipole is sterically hindered and anion solvation is poor.

If the solvent is water, or contains water, the bimolecular (collision) processes between a neutral substrate and a charged nucleophile (such as nucleophilic acyl addition reactions and nucleophilic displacement with alkyl halides) are generally slow due to solvation effects and unimolecular processes may be competitive. A unimolecular process involves ionization of the substrate, usually to a carbocation (sec. 2.7.B.i). If the solvent is anything but water, the faster bimolecular processes probably dominates., which is obviously an *assumption.*

It is not entirely correct since ionization can occur in ethanol, acetic acid, and so on, but ionization is slow in these solvents relative to the same reaction in water. Thus, other more competitive processes (such as bimolecular substitution or elimination) often predominate. This simple assumption allows one to begin making predictions about nucleophilic reactions. Even if those predictions are shown experimentally to be incorrect, one begins to understand the factors that are important to each reaction. In those cases where the assumption fails and the products are different from the one predicted, the analysis will lead to a better understanding of the overall process. It must always be remembered, however, that the various devices used in this section to predict the major product are *assumptions*.

The solvation effect of water is based on its ability to surround the nucleophilic and electrophilic centers (by hydrogen bonding to the electrophilic H or the nucleophilic O: HO—H----X^- and H_2O----X^+), making collision more difficult in a bimolecular process. For ionization to complete with bimolecular processes, the counterion should be a weak nucleophile and/or a weak base in most cases. If the counterion is too basic, it can induce elimination that can be faster than ionization. If the counterion is too nucleophilic, bimolecular substitution processes will be faster.

In an ionization reaction involving water, the charges on the $^{\delta+}C$ and the $X^{\delta-}$ group become greater. Water will first solvate and then separate the developing charges, which accelerates the ionization process and helps stabilize the products, which further accelerates the rate of ionization. Similar reaction in the aprotic solvent diethyl ether shows that solvation of the cation is possible but the anion is not solvated very well. In practical terms, the solvent does *not* help to pull the leaving group away in the rate determining step so ionization is much slower. Even in protic solvents such as ethanol, the dielectric is so small that charge separation is incomplete, again slowing the ate determining ionization reaction.

In nucleophilic substitution reactions with alkyl halides a pentacoordinate transition state (see **62**) will be formed at the midpoint of this bimolecular process. If water is the solvent, the developing charge on both sides of the central carbon will be separated, hindering formation of the transition state. Both bimolecular substitution and elimination reactions are slowed since nucleophiles are usually negatively charged or are polarized (δ^-). Water solvates these polarized atoms and partially solvates the electrophilic center in neutral substrates. The solvated nucleophile must penetrate its own solvent sheath as well as that of the electrophile to reach the carbon for collision in a bimolecular process, which effectively reduces its nucleophilicity. Nucleophilic strength is therefore dependent on the solvent. Aprotic solvents solvate cations but the nucleophile is not well solvated due to the greater steric demands of the aprotic solvent as it approaches the nucleophilic atom. The nucleophile has virtually no solvent sheath and can approach the electrophilic center with greater ease, effectively increasing the nucleophilicity and leads to the maximum rate possible for the bimolecular process. In all cases, the more polar the solvent, protic or aprotic, the more pronounced will be the solvation effect.

2.6.B The Substrate

It was clear in section 2.5 that the group connected to a carbonyl unit played a significant role in the course of nucleophilic acyl addition reactions. Bimolecular processes in general are dependent on the nature of the substrate (the molecule containing the electrophilic center). For reactions of primary alkyl halides, bimole-

cular processes usually lead to the major product. The low lying transition state available for bimolecular substitution (secs. 2.7.A,B) is responsible for this, combined with the high energy required to form a primary cation (sec. 2.7.B.i). Substitution reactions tend to be faster than elimination for primary halides, even in protic solvents. Exceptions occur when a very hindered base (or nucleophile) such as DBN or DBU is used (**24** and **19**, respectively), since approach of those reagents to the carbon bearing the leaving group is difficult.

In reactions of tertiary halides, unimolecular processes dominate in protic solvents (especially water and aqueous solvent mixtures) where substitution is usually faster than elimination. Substitution involves nucleophilic attack directly at a cationic center, whereas elimination involves removal of an acidic hydrogen two bonds removed from the cationic atom, explaining the difference. Clearly, a nucleophilic species is strongly attracted to the most positive center and that should lead to the major product. In aprotic solvents, bimolecular substitution is not observed for tertiary halide due to the high energy required to form the pentacoordinate transition state (sec. 2.7.A.i). Under conditions that favor bimolecular reactions and in the presence of a suitable base, elimination is the dominant process.

For secondary halides in aqueous solvents, unimolecular and bimolecular processes compete, and the result is usually a mixture of products. With strong bases and protic solvents other than water, bimolecular elimination is usually faster than substitution, although this is only an assumption and accurate predictions can be difficult with secondary substrates. In polar aprotic solvents, bimolecular processes are usually faster. If a strong base is present and a protic solvent is used, bimolecular elimination is usually preferred to bimolecular substitution, but this is another assumption. If ethanol is used as a solvent and sodium ethoxide is a nucleophilic base, Table 2.9[85] shows the competition between bimolecular substitution (S_N2) and bimolecular elimination (E2) for a series of alkyl bromides. The preference for E2 reactions of secondary and tertiary halides in this protic solvent is clearly shown.

Table 2.9. Relative Rates of Substitution vs. Elimination for Alkyl Bromides

Halide	k (S_N2)	k (E2)	% Alkene
EtBr	172	2.6	0.9
n-PrBr	54.7	5.3	8.9
iPrBr	0.058	0.237	80.3
t-BuBr	0.1	4.17	97

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2.6.C. The Nucleophile–Base

The stronger the nucleophile, the greater the attraction for $^{\delta+}C$, and this makes bimolecular processes more favorable. Bimolecular processes are usually favored in aprotic solvents due to enhanced nucleophilicity, as well as the greater energy demands required to generate cations. As base strength increases, the rate of elimination will increase relative to substitution, but substitution reactions compete when the base is also a good

nucleophile. In general, high nucleophilicity and/or high basicity leads to a competition between S_N2 and E2, and the S_N2 reaction is usually the faster process. If the attacking species is a strong nucleophile but a weak base, the reaction will proceed almost entirely by S_N2 when primary and secondary substrates are involved, but tertiary substrates show elimination or no reaction at all if the nucleophile is not basic enough. With low nucleophilicity, high basicity species, E2 dominates for tertiary and secondary substrates. Even primary halides can undergo elimination with a nonnucleophilic base such as DBN (**24**) or DBU (**19**).

For unimolecular reactions, unimolecular substitution (S_N1, sec. 2.7.B.ii) is favored with strong, nonbasic nucleophiles in aqueous media. Unimolecular elimination (E1, sec. 2.9.B) processes are favored with bases of weak to moderate strength that are also poor nucleophiles. In general, S_N1 is faster than E1 since the cationic carbon is most strongly attracted to the electron rich center.

2.6.D. Concentration of the Reacting Species

For bimolecular processes, the rate of reaction is given by the expression:

$$\text{Rate} = k\ [\text{nucleophile or base}]\ [\text{RX}]$$

where k is the rate constant. Increasing the concentration of the nucleophile, halide, or base leads to an increase in rate. Decreasing the concentration will decrease the rate. To ensure a rapid and complete reaction, an excess of base or nucleophile is often used.

For unimolecular processes, the rate of the reaction should be given by the expression:

$$\text{Rate} = k_1\ [\text{RX}] + k_2\ [\text{nucleophile or base}]$$

because this is a two-step process. The two steps (two reactions) are (1) ionization of the substrate to form a cation (rate = k_1 [RX]) and (2) reaction of the cation with the nucleophile or base to produce the product (rate = k_2 [R^+] [nucleophile or base]). For the unimolecular reaction, the overall rate is actually shown to be

$$\text{Rate} = k\ [\text{RX}]$$

where the rate constant (k) assumes that the first process (k_1) is very slow and that the second (k_2) is so fast that changes in k_2 have little or no effect. An increase or decrease in the concentration of nucleophile or base, therefore, has only a minor effect on the overall rate of the reaction in most cases. An increase in the concentration of RX will increase the rate and a decrease in concentration will decrease the rate. Unimolecular reactions are commonly done in an aqueous solvent mixture (aq THF, aq acetone, etc.) with as a high a concentration of substrate and nucleophile or base as is possible in the aqueous medium.

2.6.E. The Leaving Group

The leaving group (X) is the atom or group of atoms displaced in a substitution or elimination reaction. A good leaving group should have a relatively weak and polarized C—X bond. After departure, X^- should be a very stable ion. If this ion can be effectively solvated, its leaving group ability is enhanced. In general, gegenions derived from strong acids are good leaving groups and those derived from weak acids are poor leaving groups. Typical good leaving groups are Br, I, OTs, OMs, and Cl and typical poor leaving groups are OAc, OH and NH_2, although acetate is a common leaving group for many reactions and is significantly better than hydroxyl or amino. What this really says is that more vigorous conditions are required for OAc to leave than would be required for Br to leave. In general, this is true.

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Halides are probably the most common leaving groups. A general order of leaving group ability for halides is (I > Br > Cl >>> F). Large atoms such as iodide result in a longer bond than C-F. With less electron density between the nuclei, the longer bond is generally weaker and easier to break (it is actually displaced by the nucleophile). After the halide departs, the larger iodide is better solvated by the solvent, diminishing the net charge of the ion and making it more stable, which assists the overall reaction. Iodides role as a leaving group is complicated by the fact that it is a better nucleophile than fluoride (sec. 2.7.A.i). If an excess of iodide is used in a nucleophilic displacement reaction with a chiral allylic iodide, the iodide functions as both a leaving group and a nucleophile. In this case, iodide displaces iodide and successive S_N2 inversions can lead to racemic product. Good leaving groups tend to give stable ions or a neutral molecule after their departure. The less basic the group, the more easily it departs. Table 2.10[86] provides a limited rate comparison of leaving group ability in a specific S_N2 reaction.

Table 2.10. Leaving group ability in the reaction of haloethanes and ethoxide:

$$EtX + EtO^- \longrightarrow EtOEt + X^-$$

X	Relative Rate (k_X/k_{Br})
Cl	0.0024
Br	2.0
I	2.9
OTs	3.6

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The problems of nucleophilic leaving groups such as iodide (see above) could be alleviated if the leaving group were not nucleophilic. Tosylate [—OSO_2—C_6H_4(4-Me)] and mesylate (—OSO_2—CH_3) groups are derived from sulfonic acids and they are good leaving groups. However, the resonance stabilized anion (RSO_3^-) has a diffuse charge and is a poor nucleophile. Indeed, sulfonate esters possess several qualities of a good leaving group: (1) resonance stabilization of the departed ion; (2) relief of steric strain upon leaving due to the bulk of the group; (3) the relative weakness of the C—O (sulfonate) bond

Groups involving second—row elements are usually better leaving groups than comparable first row element groups. Charged species (which generate neutrals after departure) are better leaving groups than neutral leaving groups (which generate charged species after departure). These preferences are illustrated by

$$RS > RO \qquad \text{and} \qquad R_2O^+ >>>>> RO$$

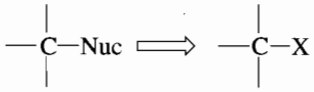
In general, good leaving groups are large, of low nucleophilicity, more stable after departure, and of low electronegativity. High polarizability with large atoms such as iodide or sulfur is usually associated with weaker bonds and better leaving group ability. Poor leaving groups are small, very nucleophilic, and highly electronegative.

2.7. SUBSTITUTION REACTIONS

Replacement of one atom or functional group for another is referred to as substitution. The two major types of substitution discussed to this point involve reaction at an sp^3 carbon (nucleophilic aliphatic substitution) or at sp^2 carbonyl carbon (nucleophilic acyl substitution). Substitution reactions at an sp^3 carbon can be mechanistically categorized as bimolecular or unimolecular. Bimolecular substitution formally refers to the fact that it follows second–order kinetics, but as a practical matter these reactions usually involve collision of a nucleophile with the carbon of a substrate bearing a leaving group. Unimolecular substitution is again derived from the rate expression that follows first–order kinetics, but involves initial ionization of a substrate bearing a leaving group to form a carbocation intermediate, followed by reaction with a nucleophile. The former reaction is labeled S_N2 and the latter is labeled S_N1. Both S_N2 and S_N1 reactions are extremely useful for the introduction of heteroatom and carbon functional groups into a carbon skeleton.

2.7.A. Bimolecular Nucleophilic Substitution

When a nucleophile collides with a carbon that is part of a polarized bond bearing a leaving group (an electrophilic carbon), it leads to the transform:



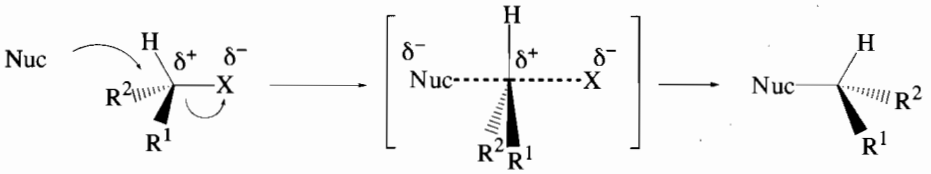
and the experimental reaction required to accomplish this transform is

where X is a suitable leaving group and the reaction is called **nucleophilic aliphatic substitution**.[87]

2.7.A.i. The S_N2 Reaction. In reactions where the substrate (see **61**) has a leaving group (X) connected to a sp^3 carbon, displacement by a nucleophile leads to a product in which X has been replaced by the nucleophile to give **63**. This process can be described as a bimolecular (it follows second order rate equation) substitution that involves a nucleophile. The mechanistic descriptor is, therefore, S_N2. Reactions labeled as S_N2 may be observed in several different functional group exchange reactions and the substrate and the reagent can be either simple or complex. All S_N2 reactions can be represented by the simple reaction sequence: **61** → **63**, which proceeds by a pentacoordinate transition state (**62**).[84b] This scheme arises from many experimental observations in a wide variety of S_N2 type reactions. The primary features of the reaction, as determined by many years of experiments are (1) it follows second order kinetics, (2) inversion of configuration at the stereogenic center in chiral molecules and (3) the dependence of the reaction rate on the structure of the halide.

Approach of the nucleophile from the side of the molecule bearing the group X is unfavorable due to electrostatic as well as steric repulsion. Approach from the side opposite X (backside or anti attack) will minimize these repulsive forces and is energetically preferred. To initiate the reaction, the nucleophile collides with

the δ^+ carbon, and transfers two electrons to that carbon. These two electrons are used to form a new bond and the C—X bond is broken with both of those electrons being transferred to the more electronegative heteroatom leaving group, completing the substitution process.



61 **62** **63**

The experimentally observed characteristics of many of these substitution reactions led to a mechanism that explained the observations. The reaction requires a five-coordinate transition state such as **62**, and the transition state structure is taken to be the logical midpoint of the reaction. At this transition point, the nucleophile–carbon bond is partially formed and the C—X bond is partially broken. This transition state is consistent with the following observations:

1. Backside attack dictates that inversion of configuration must occur in the final product, relative to the starting material. Inversion can be detected when the starting halide possesses a stereogenic carbon bearing a leaving group, as in the conversion of **61** → **63** (R^1, R^2 = H, alkyl, aryl).
2. Since the reaction requires a collision of the nucleophile and the halide,[84a] the rate of reaction is proportional to the concentrations of both reactants and the nature of the solvent. An S_N2 reaction is termed bimolecular because it is described by the rate expression: (Rate = k [N] [halide]). The rate of reaction is also dependent upon the strength of the nucleophile (see above).[84] Protic solvents slow reaction and aprotic solvents are the preferred reaction medium.
3. The rate of reaction is fast with MeBr and slower with secondary halides. Tertiary halides such as *tert*-butyl bromide, Me_3C—Br, do not undergo substitution via this mechanism at any reasonable rate.

The structure of the halide is critically important because for a S_N2 reaction, as shown in Table 2.11.[88] This table gives the rate for reaction for the reaction of alkyl halides with potassium iodide. As the steric bulk around the carbon being attacked by iodide increase, the rate of reaction slows, which can be directly correlated with an increase in activation energy required to achieve the pentacoordinate transition state, **56**. With tertiary halides, the steric bulk imposes a large energy barrier for formation of **56**, making the rate of S_N2

Table 2.11. Reaction Rates of Alkyl Halides with Potassium Iodide

RBr + KI ⟶ RI + KBr

Relative Rate	R–X
1	MeBr
3.3×10^{-2}	EtBr
8.3×10^{-4}	Me_2CHBr
5.5×10^{-5}	Me_3CBr
3.3×10^{-7}	Me_3CCH_2Br
2.3	CH_2=$CHCH_2Br$
4.0	$PhCH_2Br$

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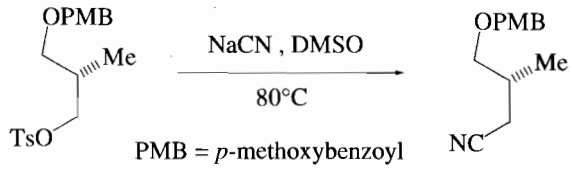
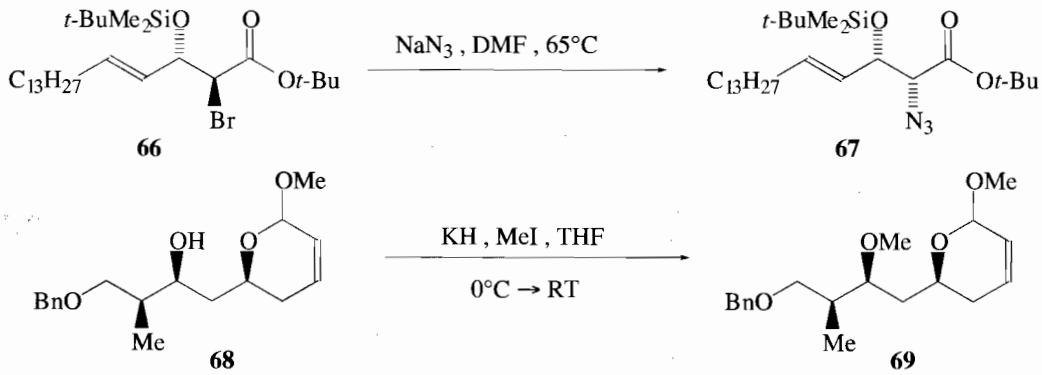
so slow, they are not observed. The neopentyl system, which appears to be primary, is in fact so sterically hindered that the rate of S_N2 reactions is slower than that of a tertiary halide. Unhindered methyl halides easily attain the necessary transition state and give facile S_N2 type reactions. In allyl and benzyl halides, the π-bond participates in removal of the leaving group in the transition state, and both of these halides react faster than bromomethane. in the structure of the halide.[88]

The S_N2 reaction is a powerful method for inserting functional groups into a carbon skeleton. There are several important synthetic considerations. The poor reactivity of sterically hindered halides dictates that primary or secondary substrates be used. A typical example is the S_N2 reaction of cyanide ion with the primary tosylate unit in **64**, which gave nitrile **65** in Mulzer's synthesis of the C1–C12 segment of the antitumor



64 **65**

agent laulimalide.[89] An S_N2 reaction with azide is another good way to introduce nitrogen into a molecule, with control of stereochemistry and usually without the complications often accompanying the use of amine



66 **67**

68 **69**

nucleophiles (elimination, salt formation, reversibility). An example is the conversion of (*S*)-bromide **66** into azide **67** with clean inversion of configuration, allowing Corey to synthesize sphingosine enantioselectively.[90] Note that polar aprotic solvents were used in both cases to maximize the yield of S_N2 products and suppress side reactions such as elimination (secs. 2.6, 2.9.A). Many S_N2 reactions involve functional group transforms such as Br → OMe, OTs → N_3 → NH_2, and Cl → I. Many other types of nucleophilic reactions are possible, including reactions of enolate anions with alkyl halides (sec. 9.3.A), which proceed via an S_N2 pathway.[91] A classical reaction that involves a S_N2 reaction is the **Williamson ether synthesis**,[92] illustrated by the conversion of the OH unit in **68** to the anion with KH. This alkoxide reacted with iodomethane by S_N2 displacement of iodide to give the methyl ether unit in **69**.[93] The aprotic solvent THF was also used in this reaction, which was a part of Miyashita's synthesis of the C9–C17 segment of the swinholides A–C.[93] The use of microwaves in conjunction with phase transfer catalysis is also quite effective in these types of reactions.[94]

The reactions involving **64**, **66**, and **68** used three different types of nucleophiles, cyanide, an azide, and an alkoxide. The ability to evaluate the relative strength and effectiveness of various nucleophiles is obviously as important for S_N2 reactions as it was for nucleophilic acyl substitution reactions. A general list of nucleophiles in order of their ability to form bonds to sp^3 carbon in a S_N2 reaction is:

RS^-	>	ArS^-	>	$S_2O_3^-$	>	$(H_2N)_2CS$	>	I^- >
CN^-	>	SCN^-	>	HO^-	>	N_3^-	>	Br^- >
ArO^-	>	Cl^-	>	Pyridine	>	AcO^-	>	HOH

where the dominant factor is assumed to be polarizability.[96]

Nucleophilic strength depends on two factors, the nature of the substrate (*s*) and the strength of the nucleophile, measured by its nucleophilicity (*n*). Nucleophilic strength for a given species is given by the Swain–Scott equation[95a] [$\log(\frac{k}{k_0}) = (s)\ (n)$] where $n = 0$ for water at 25°C, $s = 2.00$ for methyl bromide[96a] and *n* is a reagent parameter measuring nucleophilic power in a particular system. The parameter *s* is the susceptibility of the substrate (here an halide) to being attacked (it measures the power of a substrate to discriminate between various nucleophiles). An electrophlicity index has been established based on electronegativity divided by chemical hardness.[95b,c] The important qualitative message of this equation is that nucleophilic strength varies with the substrate and that a given nucleophile will react differently not only with a carbonyl and with a halide, but differently with different halides. Table 2.12 gives a partial list of nucleophiles,[96] ordered by use of the Swain-Scott equation[92] for their reaction with bromomethane, which constitutes a general order of nucleophilic strength for S_N2 reactions. It is known that the nucleophilicity order differs for S_N2 reactions when compared with acyl addition to a carbonyl (secs. 2.7.A,B, 2.5), and tends to follow more closely the order established for basicity [the carbonyl carbon is a harder acid than saturated carbon (sec. 2.4.C)].

There are obviously several parameters contributing to nucleophilic strength. A few general statements can be made concerning the relative orders of nucleophilic strength.

Table 2.12. Nucleophilic Strength with Bromoethane as Ordered by the Swain–Scott Equation

Nucleophile	n	Nucleophile	n	Nucleophile	n
$S_2O_3^{2-}$	6.35	SO_3^{2-}	5.67	CN^-	5.13
PO_4^-	5.06	I^-	4.93	SCN^-	4.80
CO_3^{2-}	4.36	HO^-	4.23	PhO^-	4.16
Br^-	4.02	N_3^-	3.92	*p*-$ClPhO^-$	3.86
NO_2^-	3.71	HPO_3^-	3.52	$B_2O_7^{2-}$	3.45
pNO_2PhO^-	3.08	Cl^-	2.99	AcO^-	2.76
HCO_2^-	2.62	HSO_3^-	2.3	$H_2PO_4^-$	2.2
F^-	1.88	SO_4^{2-}	2.1	NO_3^-	2.1
HSO_4^-	2.1	ClO_3^-	2.1	ClO_4^-	2.1
HOH	0.01				

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1. A nucleophile with a negative charge is stronger than its conjugate acid.

$$NH_2^- > NH_3 \quad \text{and} \quad HO^- > HOH$$

2. In the same row, nucleophilicity parallels basicity, and

$$R_3C^- > R_2N^- > RO^- > F^-$$

Rules 1 and 2 predict the following order for nucleophilic strength:

$$NH_2^- > RO^- > HO^- > R_2NH > ArO^{-*} > NH_3 > C_5H_5N > F^- > HOH > ClO_4^{-**}$$

* less nucleophilic due to resonance delocalization ** charge spread out due to resonance, less nucleophilic

Nucleophilic strength for a given substituent can be measured in terms of the rate of the S_N2 reaction or in reactions with carbonyl derivatives.[97] The relative rates of several nucleophiles were determined by reaction with iodomethane and are shown in Table 2.13.[98] As mentioned previously, several factors contribute to nucleophilic strength. Electronic effects are important, as illustrated by the electron releasing methyl group, which should make methoxide more nucleophilic than hydroxide. The rate of the S_N2 reaction of sodium hydroxide with iodomethane is 1.3×10^{-4} $M^{-1}s^{-1}$ whereas the rate with sodium methoxide with iodomethane is 2.51×10^2 $M^{-1}s^{-1}$.[98]

Table 2.13. Relative Rates of Reaction of Nucleophiles with Iodomethane

Nucleophile	k ($\times 10^3$ M^{-1} s^{-1})
MeO^-	0.251
F^-	0.00005
Et_2NH	2.2
PhO^-	0.073
NH_3	0.041
Pyridine	0.022

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It was noted that nucleophiles are less nucleophilic if they that can delocalize electrons by resonance. An example is the phenoxide anion, where electron density is delocalized away from oxygen by the adjacent phenyl ring, meaning that oxygen cannot donate electrons to carbon as effectively and is less nucleophilic. It should also be noted that nucleophilic reactions are usually under kinetic control, whereas acid–base reactions are under thermodynamic control. Under kinetic control, the most nucleophilic species will react faster and dominate the substitution reaction.

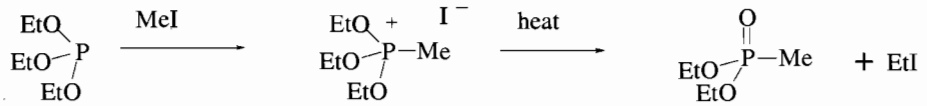
3. Going down the periodic table, nucleophilicity increases but basicity decreases [$I^- > Br^- > Cl^- > F^-$ (this ordering is solvent dependent) and ($RS^- > RO^-$)].

Comparing the rate of reaction of MeI with $PhSe^-$ [7000×10^3 $M^{-1}s^{-1}$], PhS^-, [1070×10^3 $M^{-1}s^{-1}$] and PhO^- [0.073×10^3 $M^{-1}s^{-1}$] shows this trend.[98] Likewise, trialkylphosphines are more nucleophilic than

trialkylamines (R_3P > R_3N). The rate of reaction of Et_3P with iodomethane is 1.29 x 10^3 $M^{-1}s^{-1}$ whereas the rate for Et_3N is 0.595 x 10^3 $M^{-1}s^{-1}$.[98] These latter reactions are particularly useful in organic synthesis. Phenoxide is commonly used in S_N2 reactions for the preparation of phenyl (or aryl) ethers, a structural unit found in many naturally occurring molecules. Thiophenol is used to generate phenyl sulfides via the thiophenoxide anion, and phenyl selenides can be formed from the phenyl selenide anion. Oxidation of the sulfide or selenide generates the corresponding sulfoxide (S-oxide) or selenoxide (S-oxide) which are subject to thermal syn elimination to form the corresponding alkene[99] (secs. 2.9.C.v, 2.9.C.vi). These transformations can also be used to introduce an alkenyl unit, especially an α,β-unsaturated carbonyl, into the molecule. Thioalkyl groups are also used to enhance the acidity of the adjacent hydrogen and the chemistry of sulfur stabilized carbanions is important for reactions that generate carbon–carbon bonds, including many of the Umpolung reagents (sec. 8.6.B).

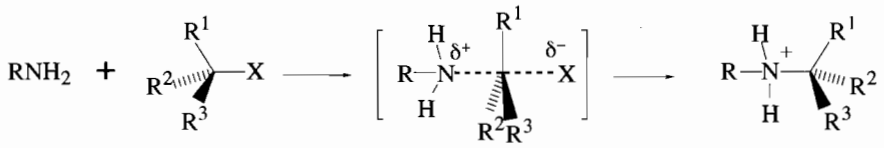
The reaction of trialkylphosphines, especially triphenylphosphine, with alkyl halides is particularly useful since the resultant phosphonium salts are easily converted to the phosphonium ylid on treatment with a suitable base (sec. 8.8.A). Ylids are, of course, the reactive species in the well-known **Wittig olefination** reaction,[100] which will be discussed in section 8.8.A.i. A related S_N2 process involves reaction of a trialkylphosphite with an alkyl halide, the **Arbuzov reaction** (sometimes called the **Michaelis–Arbuzov reaction**).[101] Triethylphosphite (**70**) reacts with iodomethane to give the phosphonium salt, **71**. Heating generates the monoalkyl phosphonic ester (**72**). This type of phosphonic ester can be converted to an ylid and used in the well–known **Horner–Wadsworth–Emmons olefination**[102] (sec. 8.8.A.iii).

The analogous, but slower, reaction with amines can be used to form ammonium salts, which are useful in the **Hoffmann elimination** sequence (sec. 2.9.C.i).[103] Triphenylamine, for example, reacts with iodomethane to give methyltriphenylammonium iodide ($MePh_3N^+$ I^-). This reaction also generates alkyl ammonium salts that can be used as phase–transfer catalysts,[104] especially useful in substitution and elimination reactions. These reagents often contain large alkyl groups (dodecyl, hexadecyl, and octadecyl), although small groups are commonly used and tetrabutylammonium chloride is a useful phase–transfer reagent.



70 **71** **72**

Substitution by amines or phosphines on an alkyl halide is clearly an S_N2 type process. Normally, the presence of water in the reaction medium suppresses the rate of S_N2 reactions because they usually involve a charged nucleophile and a neutral substrate. An exception can occur, however, if both starting materials are neutral but the products are charged, as in the reaction of amines with alkyl halides. This reaction generates transition state **73** with a δ+ nitrogen and a δ- halogen. A protic solvent will separate the developing charge in this transition state, ultimately leading to the solvent separated ions $^+NRH_2R'$ and X^-. Solvation and ion separation therefore accelerates the S_N2 process in this preparation of ammonium salts.

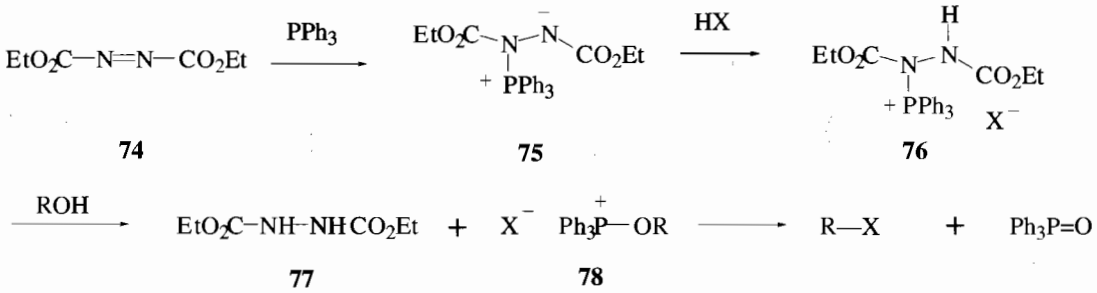


73

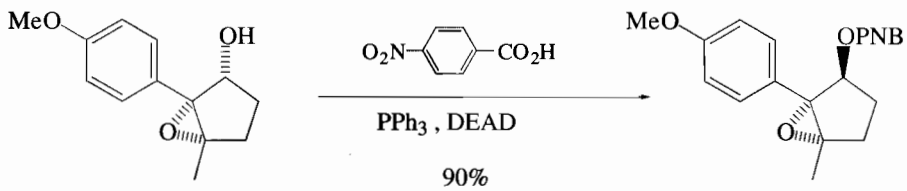
4. Greater steric encumbrance diminishes nucleophilicity. Reactions involving the nitrogen atom of pyridine and of 2,6-dimethylpyridine (2,6-lutidine) as nucleophiles illustrate this point. The rate of reaction of pyridine with methyl iodide is 0.022 x 10^3 $M^{-1}s^{-1}$. The two methyl groups around the nitrogen atom in 2,6-lutidine sterically encumber approach of nitrogen to the carbon of methyl iodide and the rate declines to 0.00042 x 10^3 $M^{-1}s^{-1}$, ≈ 50 times slower.[98] As pyridine approaches the electrophilic carbon, the ortho hydrogens interact with the alkyl groups on that carbon, but this represents a minimal steric interaction. When lutidine approaches the carbon, however, the ortho-methyl groups provide a large steric interaction with the alkyl groups on the electrophilic carbon, impeding close approach of the nucleophilic nitrogen and the electrophilic carbon, and diminishing the rate of the collision reaction. The effect of this steric hindrance is to make lutidine less nucleophilic than pyridine.

A key feature of S_N2 reactions is inversion of configuration at the electrophilic center (see the transformation **66** → **67** above). Alcohols are convenient synthetic intermediates but the OH moiety is a poor leaving group (sec. 2.6.E). If an alcohol moiety that is attached to a stereogenic center is converted to a derivative that possesses a weaker C—O bond with a greater tendency for displacement (such as an ester, sulfonate ester or phosphonate derivative), S_N2 type displacement is possible with inversion of that stereogenic center. The S_N2 reaction can an effective method for inversion of the stereocenter with insertion of a different functional group. If the goal is to invert the chiral center in (*S*)-2-pentanol to produce (*R*)-2-pentanol, however, a problem arises. Formation of (*R*)-2-pentanol requires reaction with hydroxide or methoxide (to produce the methyl ether, followed by cleavage of the O-methyl group with trimethylsilyl iodide (sec. 7.3.A.i).[105]. Both hydroxide and methoxide are strong bases, however, and tosylate is a good leaving group. Under these conditions, significant elimination will accompany the substitution reaction and give 2-pentene (sec. 2.9.A). Although the use of highly polar, aprotic solvents such as DMF or DMSO will maximize the substitution, elimination will remain a competitive side reaction, and it may be the major process.

2.7.A.ii. The Mitsunobu Reaction. There are many times when a nucleophile is too weak for facile S_N2 displacement. Substitution is also difficult if the substrate contains a poor leaving group,. A successful and highly useful solution to this problem is the **Mitsunobu reaction**.[106] In this procedure, a poor leaving group is converted to an excellent leaving group. As initially formulated, the process involved reaction of diethylazodicarboxylate (DEAD, **74**) with triphenylphosphine (Ph_3P) to form **75**. This dipolar ion reacts with HX, which is present in the initial reaction, to give phosphonium salt **76**. An alcohol is then added and the subsequent reaction generates alkoxyphosphonium salt **78** and diimide **77**. The X group displaces triphenylphosphine



oxide (a neutral leaving group) to give the substitution product, R—X. The X moiety in HX can be a variety of groups, including carboxylate ($RCO_2H \rightarrow$ ester), azide ($-N_3 \rightarrow RN_3$), imido (imides → *N*-alkyl imides), and R (an active methylene compound such as malonate or an α-cyanoester).[106] A typical transformation is esterification of alcohol **79** to *p*-nitrobenzoate (OPNB) ester **80** in 90% yield[107] The reaction proceeded with complete inversion of configuration, and the inverted alcohol unit can be unmasked by simple hydrolysis of the ester.

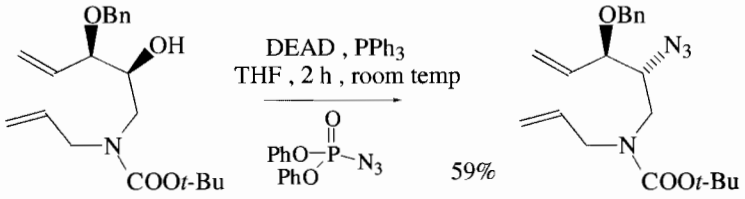


79 **80**

The conversion of **79** to **80** illustrates what is probably the most common application of the Mitsunobu reaction, inverting the stereogenic center of a chiral alcohol (the problem described in sec. 2.7.A.i). The alcohol is first converted to an ester in most cases, however, because that reaction is more efficient than using the free alcohol. Formation of **80** proceeded with inversion of the (*R*)-alcohol and isolation of the (*S*)-alcohol requires only hydrolysis of the ester, as mentioned above.

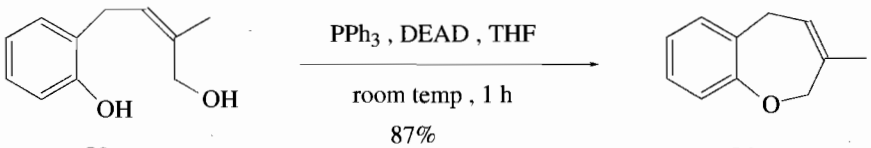
The reaction is not limited to coupling alcohols and acids to form esters. The reaction of succinimide with 2-propanol under Mitsunobu conditions gave *N*-isopropyl succinimide in 73% yield.[108] Hydroxyl can also be replaced with other functional groups using this method. Mitsunobu coupling can be used to prepare esters that might be difficult to prepare under other conditions by using an appropriate alcohol and an acid,[109] illustrated in Fürstner's synthesis of (–)-balanol,[110] in which (*R*)-alcohol **81** was converted to (*S*)-azide **82** in 59% yield using Mitsunobu conditions. In this synthesis, the azide unit was later reduced to a primary amine by catalytic hydrogenation over Pd/C, illustrating that the Mitsunobu can be used to convert an alcohol to an amine, with inversion of configuration, in a two-step process. It is interesting to observe that the phosphonate azide reagent used was more efficient that the usual reagents KN_3 or NaN_3.[111] An alternative method reacts alcohols with phthalimide under Mitsunobu conditions to give the N-substituted phthalimide, which can be unmasked to the primary amine by reaction with hydrazine.[112] The reaction of phthalimide with alkyl halides followed by treatment with hydrazine constitutes the classical **Gabriel synthesis.**[113] The use of hydrazine in this manner is called the **Ing–Manske modification**[114] of the Gabriel synthesis. The use of Mitsunobu

conditions simply expands that reaction to include alcohols. The same transformation has been accomplished using TsNHCO$_2t$-Bu (abbreviated TsNHBoc) to incorporate the nitrogen moiety.[115]



81 **82**

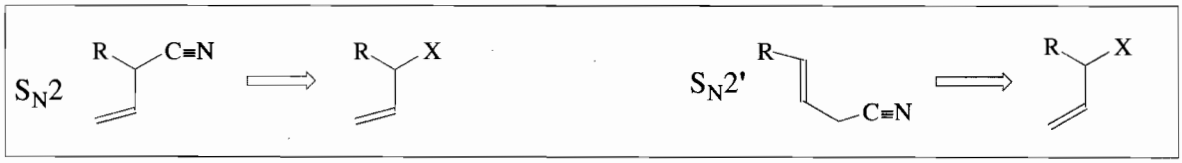
Another modification illustrates two features that can be useful in synthesis. When **83** was treated with triphenylphosphine and DEAD (Bn is benzyl), cyclization occurred to give benzoxepin (**84**) in 87% yield.[116] This shows that Mitsunobu conditions can be used for intramolecular reactions and also that an alcohol can be coupled with another OH unit. This transformation was used by Yamaguchi in a synthesis of radulanins.[116]



83 **84**

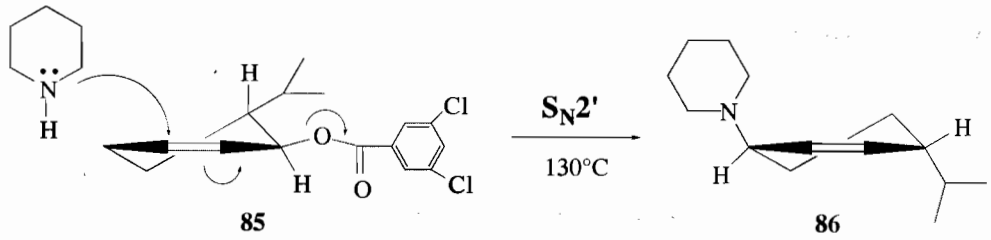
The Mitsunobu reaction is a clever and highly useful exploitation of the S_N2 reaction that allows one to control the stereochemistry of a given stereogenic center (see Chap. 6). It also allows one to correct the stereochemistry if an alcohol is produced that has the opposite stereochemistry from that desired.

2.7.A.iii. The S_N2' Reaction. Normal S_N2 reactions were illustrated in the previous sections. In general, allylic halides react faster with nucleophiles than do simple alkyl halides (see above) because the π bond can



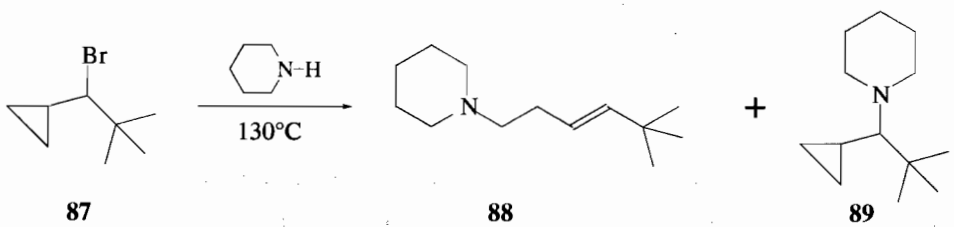
participate in expulsion of the leaving group. If the leaving group bearing carbon becomes too sterically hindered in the allylic system, the normal S_N2 path is inhibited and an alternative mode of attack occurs, at the end of the π system. Such attack is termed an S_N2' **reaction** (nucleophilic bimolecular substitution with allylic rearrangement).[117] The retrosynthetic analysis of each reaction, using cyanide as the nucleophile, offers a useful comparison, especially for regiochemical differences in the product distribution. The two pathways often compete and can lead to annoying mixtures of regioisomers, although the reaction can be synthetically useful. Formation of piperidine derivative **86** via the S_N2' displacement of the allylic 3,5-dichlorobenzoate (**85**) is an excellent example of this process.[118] The nucleophile attacks the π bond since the O-benzyl carbon is sterically encumbered. The π bond assists the removal of the leaving group in an S_N2' reaction.

The S_N2' reaction proceeds with a high degree of stereochemical control, as in the nucleophilic displacement **85** → **86**. Bordwell described the S_N2' reaction with amines as second order, but invoked a tight ion



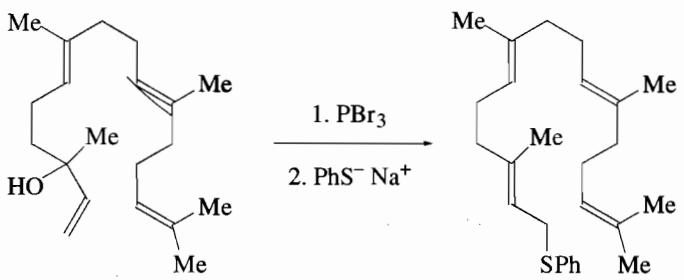
85 **86**

pair to explain the process.[119] A tight ion pair will have significant ionic character but the ions are not separated by solvent. The work with cyclopropylcarbinyl halides supports this mechanistic rationale. Reaction of piperidine with the *tert*-butyl derivative (**87**) gave the expected **88** in 88% yield but also 8% of **89**.[120] This



87 **88** **89**

latter product is not compatible with a simple S_N2 displacement due to the great steric hindrance imposed by the neopentyl-like structure, but the tight ion pair mechanism explains the presence of **83** very well. When it can be applied as the major process, stereochemical and regiochemical control makes the S_N2' reaction a useful tool in synthetic planning. With other allylic substrates, the possibility of this reaction as a competitive side reaction must be acknowledged as a process that can diminish the yield of the S_N2 product.



90 **91**

A synthetic example of an S_N2' reaction is the conversion of **90** to a tertiary bromide with phosphorus tribromide. Subsequent reaction with the sodium salt of thiophenol gave an S_N2' displacement to **91** in Itô's synthesis of neocembrene.[121]

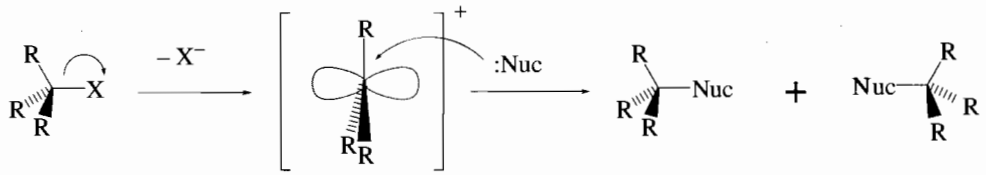
Organocuprates (sec. 8.7.A) react via an S_N2' type process in some cases. One example is the displacement of an ester group in **85** by dialkyl cuprates.[122] The organocuprate reaction may actually proceed by copper stabilized radical intermediates, rather than a formal S_N2' mechanism.[123] An S_N2' like reaction has

also been observed in reactions of organocuprates with cyclopropylcarbinyl halides, where the strained cyclopropane ring behaves similarly to the π bond of an alkene.[124]

2.7.B. Unimolecular Nucleophilic Substitution

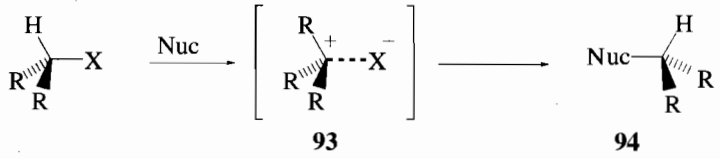
The most synthetically useful nucleophilic substitution reaction is the bimolecular S_N2 reaction, shown in the section 2.7.A. A unimolecular substitution (ionization followed by substitution) is less useful in synthesis in a general sense, but is often the best specific reaction to effect a particular functional group exchange. In Chapter 12 we will see many examples where cationic reactions are very useful. Unimolecular substitution also occurs as a side reaction in aqueous media and can influence both the yield, stereochemistry, and regiochemistry of the final product.

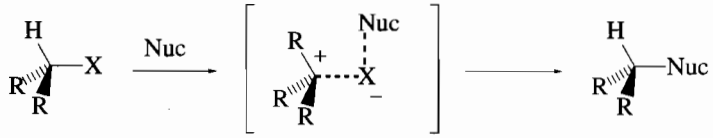
2.7.B.i. Carbocations. A carbocation is an electron-deficient species bearing an sp^2 hybridized carbon that is, in effect, an empty p orbital. Such species are also called carbenium ions. Carbocations are electrophilic and key intermediates in many ionization reactions, as will be discussed in Chapter 12. They react with virtually any nucleophile, although the cation tends to react fastest with the strongest nucleophile if more than one is present in the reaction medium. From a kinetic standpoint, this is a unimolecular process since the rate deter-mining step is not collision of two molecules but rather slow ionization of the C—X bond with loss of the leaving group X. This ionization reaction leads to cation **86** and X^-. Carbocation **92** will react with the best available nucleophile, which can be X^-, a heteroatom of the solvent, or an added nucleophile. The overall substitution reaction is a two-step process (ionization followed by substitution) that is termed S_N1 (a unimolecular nucleophilic substitution).[125] There is great mutual attraction between the positive carbon of the carbocation and the (–) or (δ-) site of the electron-rich nucleophile, so the second reaction (coupling) is much faster than the initial ionization reaction. In the context of an ionization, leaving group is a bit of a misnomer since it does not simply leave, but is pulled off, usually by the solvent, which assists the process by solvation and separation of the resulting ions.



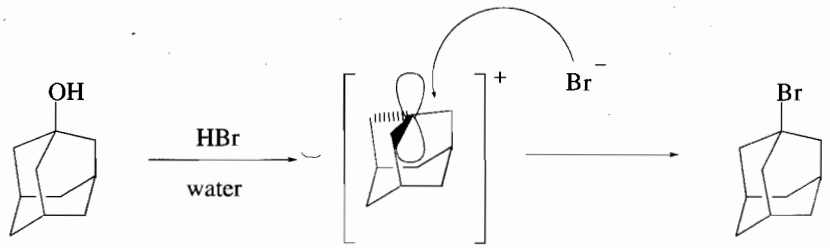
92

The central carbon of the carbocation is sp^2 hybridized and planar and as mentioned above, **92** is conveniently viewed as having a trisubstituted carbon atom with an empty p orbital. The relative stability of carbocations is briefly discussed below, and again in section 12.2.A in connection with forming carbon–carbon bonds via carbocation intermediates. Since the carbocation has an sp^2 carbon, **92** has a trigonal planar shape and an attacking nucleophile can approach from either face, in a model that predicts a racemized substitution product. This simple model is misleading, however, because stereochemical retention or inversion is often observed in S_N1 reactions. If the initial ionization generates a tight ion pair (represented by **93**), then the leaving group (X) provides some steric hindrance to the attacking nucleophile and the inverted substitution





product (**94**) will predominate, but is usually not the exclusive product. If the leaving group (X) can chelate to or otherwise coordinate with the nucleophile, then an ion pair such as **95** may result and delivery of the nucleophile will be from the same face as the leaving group. Such ion-pairing will lead to a product with retention of configuration (see **96**). These cases do not occur with great regularity, and in general, the S_N1 reaction proceeds with significant if not complete racemization at the electrophilic center. Polycyclic molecules can be an exception, however, since the conformational constraints of the ring system usually offer only one face to an attacking nucleophile. An example is adamantyl alcohol (**97**), which gives carbocation **98** upon treatment with aqueous HBr. The rigid skeletal structure of **98** limits approach of the nucleophilic bromide to the cationic center to the top of the molecule as the bottom is sterically blocked. The result will be selective formation of **99**.[126] In general, cationic reactions of this type can be highly stereoselective in substitution reactions if there is steric bias for one face over the other. In the absence of such steric bias, these reactions often show poor to moderate stereoselectivity.



2.7.B.ii. The S_N1 Reaction. The mechanistic rationale described above results from many years of experimental observations about the S_N1 reaction (statements 1–6 below).[125] In general, the S_N1 process occurs in those cases where water is present as a solvent or co-solvent, there is a good leaving group and the substrate is tertiary or secondary. A S_N1 reaction can occur in any polar protic solvent such as methanol, ethanol, or acetic acid, but ionization is much slower in these solvents relative to water because they are not as efficient for the separation of ions (sec. 2.7.B). If ionization is relatively slow, faster reactions (S_N2 or elimination processes) often predominate. It is convenient to ***assume*** that S_N1 reactions occur only in aqueous media and use this assumption to predict product distributions for a given set of reaction conditions. *As with any*

assumption, this one fails to accurately predict the products in many cases, but it provides a good working model to begin analyzing reactions. The ultimate test, of course, is the actual experimental result. The S_N1 process is characterized by the following:

1. The rate of reaction with tertiary halides that is much faster than with primary halides,[127] which is shown in Table 2.14 for reaction of bromoalkanes with potassium iodide in aqueous media.[127]

Table 2.14. Reaction of Alkyl Halides with Potassium Iodide in Aqueous Media

RBr	Relative Rate
MeBr	1.0
EtBr	1.0
Me_2CHBr	11.6
Me_3CBr	1.2×10^6

2. The rate equation can be described using only the concentration of the halide and not that of the nucleophile. The rate determining (slow) step is ionization of the C—Br bond and the fast second step does not greatly influence the overall rate. The rate expression is, Rate = k [RX], for this unimolecular reaction.[122]

3. Reaction with chiral halides proceeds with significant racemization rather than with inversion (see above).

4. A cationic intermediate is formed rather than the transition state noted for an S_N2 reaction (see **56**).

5. The reaction often proceeds with rearrangement of the carbon skeleton of the organic substrate.

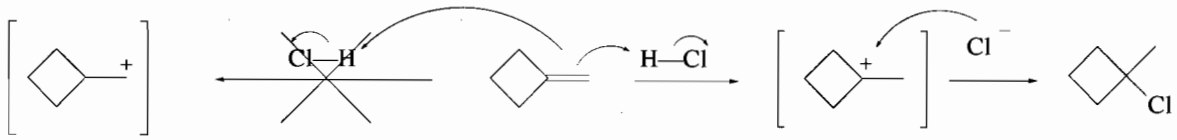
6. Unless water is a solvent or co-solvent, the initial ionization reaction is rather slow and is usually not competitive with other possible reactions.

Stability of the carbocation intermediate in this ionization reaction is critical to the overall rate of the S_N1 process.[128] A general ranking of carbocations by their relative stability is[128]

$$R_3C^+ > H_2C{=}CHCH_2^+ \approx PhCH_2^+ > R_2CH^+ > RCH_2^+ > CH_3^+$$

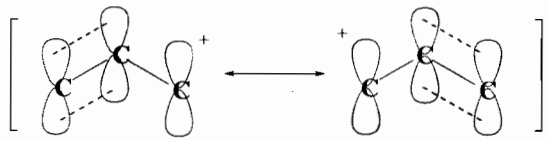
It is based on the electron-releasing inductive properties of the carbon groups attached to the positive center. The three alkyl groups on the tertiary cation release electrons to partially diminish the point charge of the cation, leading to greater stability of the tertiary cation relative to the primary, which has only one electron releasing group. Both allyl and benzyl cations disperse the charge by resonance and are more stable than primary alkyl or secondary alkyl cations. Tertiary alkyl cations are usually more stable than a primary allylic cation, although a secondary or tertiary allylic cation will be more stable than a tertiary alkyl. Cation stability is also discussed in section 12.2.A)

With cations ranked according to their relative stability, we then assume that given a choice, the more stable cation will be formed in a reaction because it is lower in energy. The addition of HCl to methylenecyclobutane (**100**) illustrates this point, where the final product is 1-chloro-1-methylcyclobutane (**103**), used by Fitjer in a synthesis of cuparene.[129] The π bond reacts as a base, donating a pair of electrons to the acid (H^+ = HCl). When the new C—H bond is formed, a carbocation is generated at the other carbon of the π bond, leading to



102 **100** **101** **103**

two possible cations, **101** and **102**. The electron-releasing effects of the alkyl groups make the tertiary cation (**101**) more stable than the primary cation (**102**). The reaction will therefore show a preference for **101**, which then traps the nucleophilic bromide (generated from HBr) to give the major product, **103**. The stability of the intermediate cation is a critical parameter that will largely determine the course of unimolecular reactions. As mentioned, allylic and benzylic cations are more stable than secondary alkyl cations. This stability is due to participation of the π bond in the ionization process and also by stabilization of the cationic intermediate by resonance. The resonance delocalization in both the allyl cation (**104**) and the benzylic cation (**105**) diminishes the net charge at the cationic carbon, making them more stable and easier to form. Although they are more stable, they are highly reactive intermediates and easily react with nucleophiles in a S_N1 reaction.



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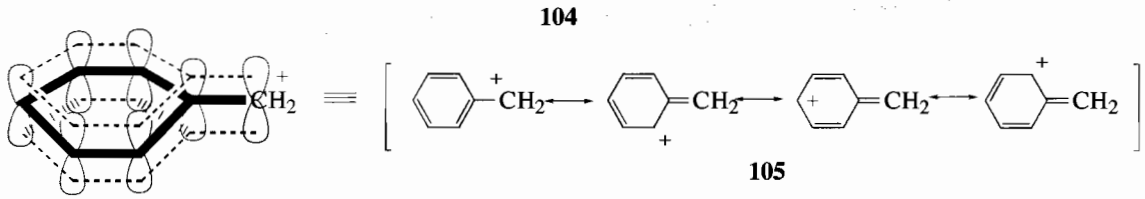
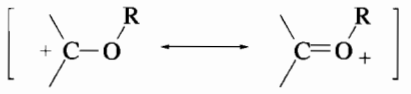


105

When heteroatoms are attached to the positive carbon, the cation gains added stability via donation of electrons (back donation) to the electron deficient center, which leads to greater stability, often by resonance delocalization of the charge on the heteroatom. Two common examples of this are oxo-stabilized cations such as **106** and sulfur-stabilized cations such as **107**. In both cases, back donation from the heteroatom leads to resonance stabilized cations. Both **106** and **107** are more stable than a simple tertiary cation bearing three



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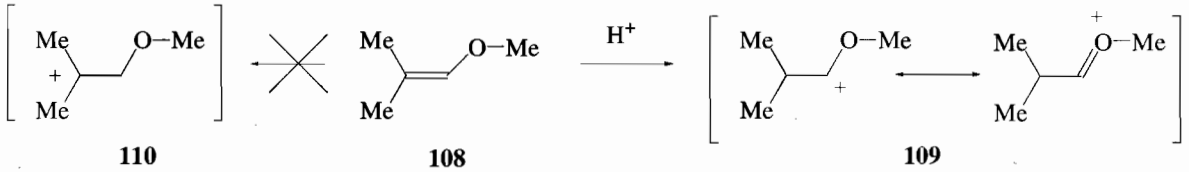


110 **108** **109**

alkyl groups. The most common method for generating oxo-stabilized cations is protonation of a carbonyl, which is also important for the formation of enamines and imines from ketones and aldehydes by reaction with

amines.[130] Another method for generating this cation is by addition of acid to a vinyl ether. Reaction of **108**, for example, gives only **109** rather than the tertiary cation **110**, an indication of the greater stability of the oxygen-stabilized cation. Similar results are observed upon protonation of thiocarbonyls or thioenol ethers.

Relief of steric strain also influences the rate of S_N1 reactions, although the effect is usually relatively small. When R is large there is more steric hindrance in the tetrahedral precursor than in the planar carbocation, accelerating the ionization process. A comparison of the chlorides in Table 2.15[131g] illustrates that as the steric crowding increases, the rate of ionization is accelerated.[131g] Such crowding was called **back strain** by Brown[131d] and it contributes to the increased rate of ionization observed with hindered halides.[132d]

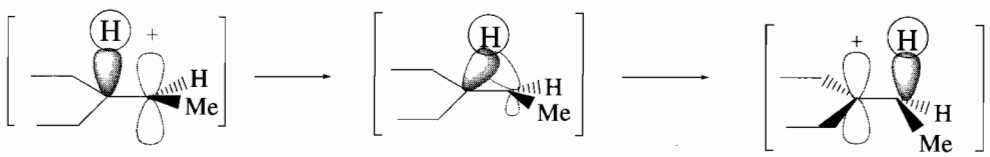
Table 2.15 Increased Rate of Ionization Due to Back Strain

Chloride	Relative Rate of Ionization
Me_3C—Cl	1.0
Me_2EtC—Cl	1.7
$MeEt_2C$—Cl	2.6
Et_3C—Cl	3.0

[Reprinted with permission from Harris, J.M.; Wamser, C.C. *Fundamentals of Organic Reaction Mechanisms*, Wiley, New York, *1976*, p 118. Copyright © *1976* by John Wiley and Sons, Inc.]

In general, S_N2 reactions are faster than S_N1 for primary and secondary halides, tertiary halides do not give S_N2 reactions but do give S_N1 reactions in protic solvents. In reactions with nucleophiles, primary halides give only S_N2 reactions and tertiary halides undergo S_N1 processes. Secondary halides give a mixture of bimolecular and unimolecular products in aqueous solvents, and the relative amounts of each type of product is dependent upon the nucleophile, the substrate, and (of course) the ionizing power of the solvent.

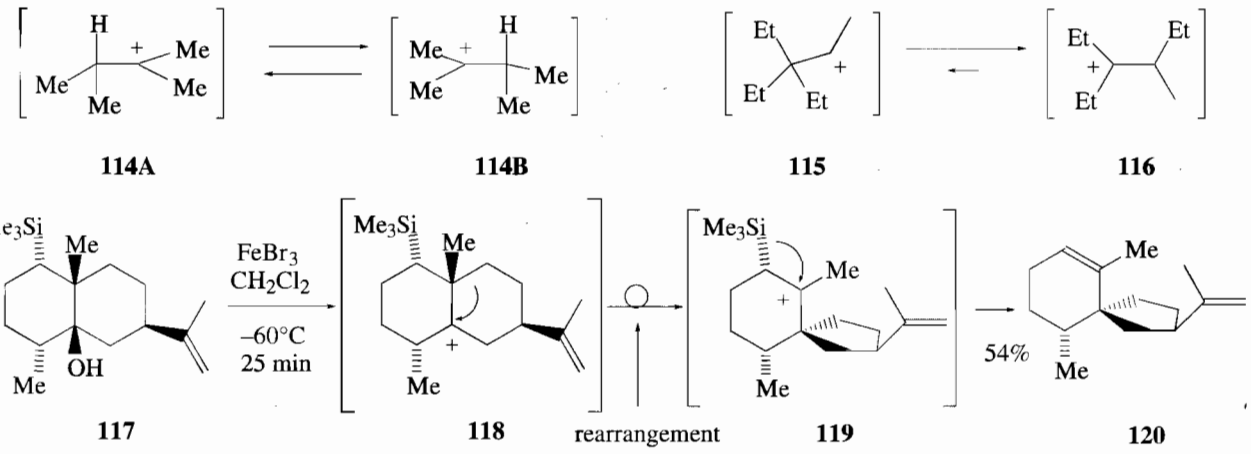
2.7.B.iii. Cationic Rearrangements. Reactions that generate cationic intermediates have a potential liability that makes the choice of an S_N1 reaction unsuitable for many syntheses. Carbocations can undergo skeletal rearrangement to give an energetically more stable cation, *prior* to trapping the nucleophile . This means that $k_{rearrangement} > k_{trapping}$ for this type of reaction. If a σ bond is adjacent to the cationic center and parallel to the p-orbital, as illustrated in **111**, electron density is donated from the σ-bond. As the electrons distort toward the positive center, the C—H σ bond weakens and the adjacent orbitals begin to share electron density, as illustrated in **112**. As the electrons in the σ bond shift, the atom attached to carbon (H in the case of **111** but it can also be another carbon group) is transferred to the adjacent carbon via transition state **112**. As this occurs, a new cation is formed and a new C—H bond (see **113**) to complete a molecular rearrangement



111 **112** **113**

(1,2- shift). If we examine **111** and **113**, the product of the rearrangement is a more stable tertiary cation generated from a less stable secondary cation. The driving force for this rearrangement is the energy gained in forming a more stable cation. A tertiary cation is more stable than a secondary by 11-15 kcal mol^{-1} (46.0–62.7 kJ mol^{-1}) and a secondary cation is more stable than a primary by about the same amount.[133] The substituent can only be transferred (a 1,2–hydrogen shift for **111** → **112**) if the electrons in the σ bond are parallel to the p orbital of the cation.[134] As mentioned above, alkyl groups (called 1,2-alkyl shifts) and also aryl groups (called 1,2–aryl shifts) can be transferred in addition to a hydrogen atom. The energy barrier to transfer of hydrogen is lower than that for alkyl or aryl shifts, but the energy barrier for a 1,2-methyl shift is estimated to be < 5 kcal mol^{-1} (20.9 kJ mol^{-1}).[135] For the degenerate rearrangement of **114A** to **114B**, the energy barrier for a 1,2-hydrogen shift was shown to be 3.4 kcal mol^{-1} (14.2 kJ mol^{-1}).[136] Although the difference in energy for a hydrogen versus a methyl shift appears to be small, hydrogen will migrate preferentially in virtually all cases. Cationic rearrangements include 1,2–hydride shifts, 1,2–alkyl shifts and 1,2–aryl shifts, which all occur with great facility,[128] giving a more stable carbocation.

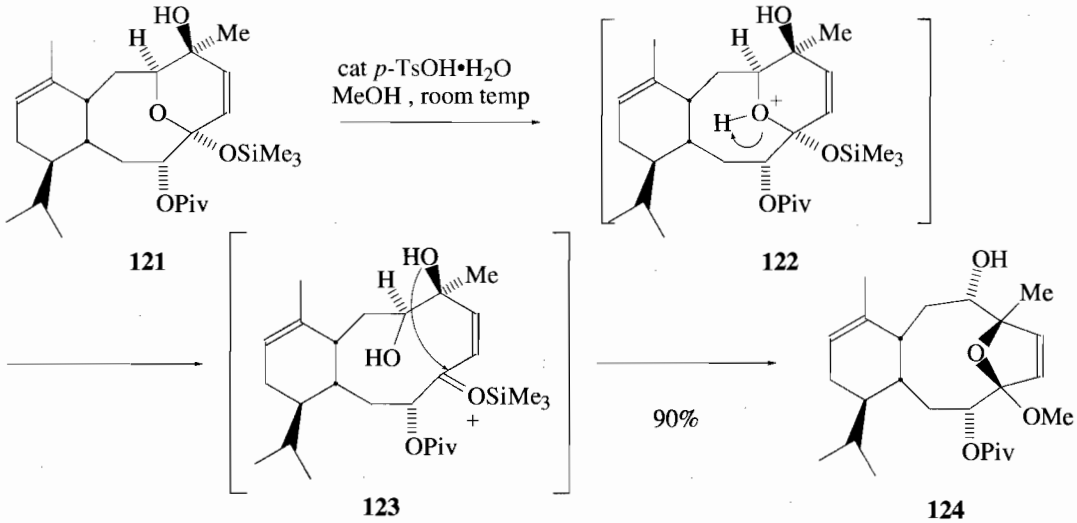
Another example is the rearrangement of **115** to **116**. In **114**, a hydrogen was shifted in preference to a bulkier ethyl group. but in **115** only ethyl groups are available for migration so a 1,2–ethyl shift occurs to give **116**. In general, the smaller substituent migrates preferentially. Such rearrangements usually occur faster than the coupling reaction[137] between a nucleophile and the carbocation. The chemistry of carbocations, including rearrangements is discussed in more detail in section 12.2.B.



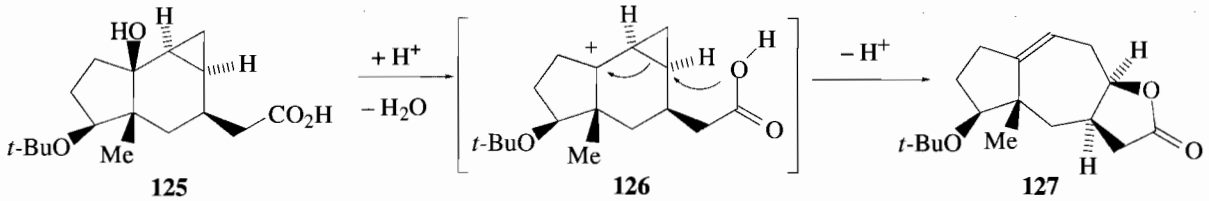
A synthetically useful example of this process is the conversion of **117** to **120**, which involves a 1,2-alkyl shift, and was part of Hwu's synthesis of (–)-solavetivone.[138] The alkyl fragment is actually part of the bicyclic ring system, one arm of the bicyclo[4.4.0]decane ring system. Reaction of the OH unit with the Lewis acid resulted in formation of the tertiary cation **118**, which was followed by a 1,2-alkyls shift to give **119**, where the new cation is stabilized by the adjacent silicon of the trimethylsilyl group.[139] Loss of the trimethylsilyl group from **119** gives spiran (**120**).

A second synthetic example illustrates several useful features of cation rearrangements. When **121** (OPiv is a pivaloyl ester) was treated with *p*-toluenesulfonic acid in methanol, protonation occurred at the more basic

ether oxygen, as shown, to give **122**. Since this is a simple acid–base reaction, this is to be expected. The adjacent C—O bond is broken to generate the resonance stabilized acyl cation **123**. Once again, formation of the more stable cation drives the reaction. There are two reactive hydroxyl groups and if they react with the acyl cation in **123**, a six-membered ring can be formed by attack of one and a five-membered ring by attack of the other. The latter is lower in energy and **124** was isolated in 90% yield from this reaction, as a part of Danishefsky's synthesis of elutherobin.[140]



Marshall's transformation of the [4.1.0]bicycloheptane unit in **125** to the cycloheptene unit in **127**[141] is an example of a reaction that raises mechanistic questions. After protonation of the alcohol unit in **125**, loss of water generates carbocation **126**. Subsequent rearrangement and trapping of carboxylate would give lactone **127**. Alternatively, nucleophilic attack by the carboxyl oxygen on the cyclopropane ring would open the ring with concomitant expulsion of the leaving group (water) to give **127** without invoking the presence of cation **126**, since this transformation could proceed by a synchronous pathway. This alternative cannot be ruled out based on the formation of the observed product. A tight ion pair in which the ions are not solvent separated offers another reasonable pathway, where the carboxylate anion would react with the cationic center in the same manner as described above. It is important to note that cyclopropylcarbinyl cations (such as **126**) rapidly open to homoallylic derivatives or cyclobutane compounds,[142] and the cyclopropane ring probably assists in expulsion of the leaving group (in this case an $—OH_2^+$ moiety).



The presence of a free cation or the operation of a synchronous mechanism is an important mechanistic consideration when planning any sequence involving cations. Since divergent mechanisms can have different

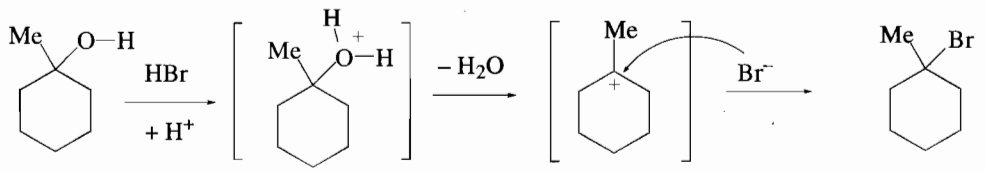
influences on the product distribution and stereochemistry of a reaction, it is important to understand what is happening. A detailed kinetic study would presumably answer the question of whether a reaction was concerted, stepwise, or a mixture of both. Mechanistic studies can be found by examining the literature or by experimental methods if a synthetic outcome is at all in doubt. Indeed, many synthetic organic chemists regularly publish mechanistically oriented papers. This information will usually answer questions concerning the planned transformation in a retrosynthesis.

2.8. SUBSTITUTION BY HALOGEN

Halogen can be introduced into a molecule is several ways. An important method involves replacement of the OH unit of an alcohol with halogen. The hydrogen atom of an alkyl fragment, particularly an allylic or benzylic fragment can be replaced with halogen by a free-radical mechanism. Both of these transformations will be examined in this section.

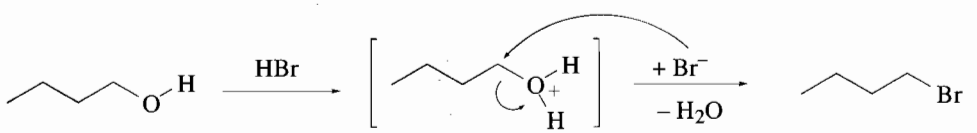
2.8.A. Halogenation of Alcohols

In Section 2.7.B, the reaction of a tertiary alcohol with HBr or HCl gave a halide via a carbocation intermediate. This is a very general reaction in which alcohols react with mineral acids (HCl, HBr, and HI) to give the corresponding alkyl halide.[143] We can explain the process by a simple example in which 1-methyl-1-



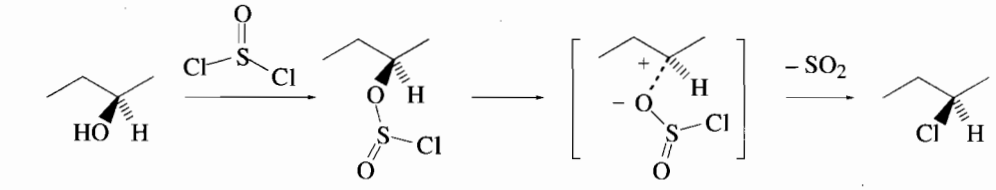
128 **129** **130** **131**

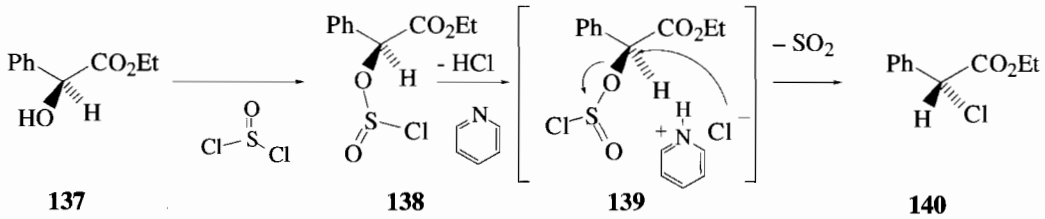
cyclohexanol (**128**) reacts with HBr to initially give oxonium ion **129**, which loses H_2O to produce tertiary methylcyclohexyl cation **130**. This cation traps the gegenion of the acid (Br^- in this case) to give **131**. Reaction of 1-butanol with HBr also gives the expected primary halide but the reaction follows an S_N2 mechanism, with bromide displacing $^+OH_2$ in the sequence **132** → **133** → **134**. The high energy barrier for ionization of **125** to the relatively unstable primary cation, coupled with the low energy demands to the S_N2 transition state lead to this preference. For secondary alcohols, both mechanisms can operate simultaneously and competitively. In aqueous media, the cationic mechanism usually dominates for secondary substrates, but if no solvent is used (neat) or if the reaction occurs in aprotic solvents, the S_N2 mechanism dominates. The mechanism obviously depends on the specific substrate and the reagents used, as well as on the reaction conditions. In terms of the functional group exchange, however, reaction of primary, secondary, and tertiary alcohols with HBr or HCl is an excellent method for the preparation of alkyl bromides or chlorides.



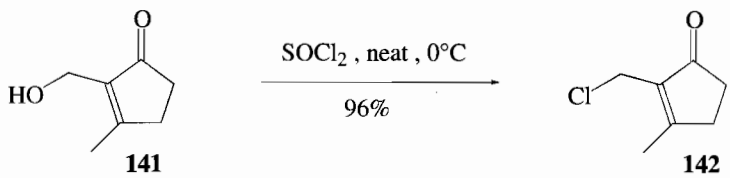
132 **133** **134**

Several halogenating reagents other than HBr, HCl, or HI have been developed that convert alcohols to halides.[143] These reagents are usually sulfur or phosphorus halides or oxyhalides. Two of the most common are thionyl chloride ($SOCl_2$) and thionyl bromide ($SOBr_2$). Thionyl chloride reacts with an alcohol to form an alkyl chlorosulfite (**135**). Loss of $ClSO_2^-$ generates a cation that dissociates to a tight ion pair (represented by **136**), and chloride is transferred to carbon intramolecularly with complete retention of configuration.[144] The chlorine is unable to approach the rear of the cation, and the ion pair does not dissociate sufficiently to allow a normal cation reaction. In this case, (*R*)-2-butanol was converted to (*R*)-2-chlorobutane. The mechanistic designator for this process is (Substitution Nucleophilic Internal) **S_Ni** and requires that the leaving group possess an atom capable of being transferred to the carbon substrate.[145]

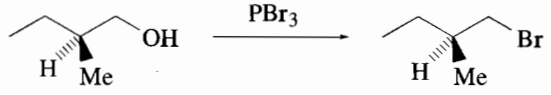




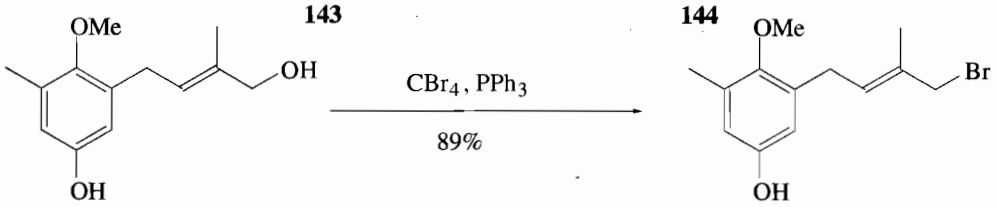
If a basic amine such as pyridine is added to this reaction mixture, the stereochemistry of the final product is different. Initial reaction with alcohol **137** gives **138**, but pyridine (or another tertiary amine) coordinates the HCl byproduct to give pyridinium hydrochloride (see **139**). The nucleophilic chloride ion is now in solution rather than being lost as HCl, and it displaces the chlorosulfite unit in an S_N2 reaction that gives alkyl chloride **140** with complete inversion of configuration. Reaction of an alcohol with thionyl chloride and pyridine is called the **Darzens' procedure**[146] in the *Merck Index*.[146b] A modification that improves the stereoselectivity premixes the alcohol with thionyl chloride and pyridine, and the resulting sulfinate is treated with thionyl bromide.[147] Thionyl bromide also converts alcohols to the bromide,[148] but the extent of inversion or retention is not as clean as with thionyl chloride. Thionyl chloride is the reagent of choice for the transformation R—OH → R—Cl, in most cases. An acid by-product is produced, however, and sensitive systems (particularly allylic alcohols) may be subject to acid catalyzed rearrangements and side reactions. With primary alcohols, stereo-chemical considerations are not important, and simple treatment with thionyl chloride gives the chloride, as in the conversion of **141** to **142** in Ziegler's studies for a synthesis of FS-2[149]



Phosphorus halides give the ROH → RX transformation for primary, secondary, and tertiary alcohols. The most common reagents are phosphorus trichloride (PCl_3), phosphorus pentachloride (PCl_5), phosphorus oxychloride (phosphoryl chloride, $POCl_3$), phosphorus tribromide (PBr_3), and phosphorus pentabromide (PBr_5). The chloride reagents give less rearrangement in reactions with alcohols than is observed with HBr or HI. Secondary alcohols usually give some rearrangement, even with the phosphorus reagents.

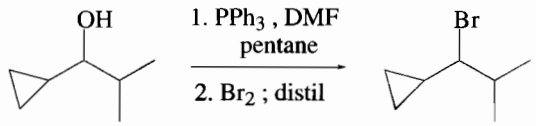


143 **144**



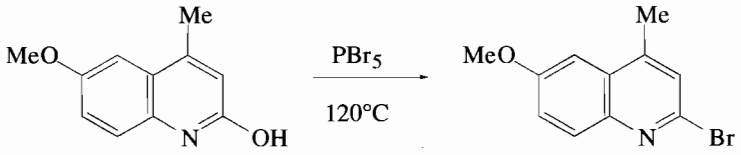
145 **146**

Phosphorus trichloride is used for the preparation of acid chlorides[150] but less often for the conversion of alcohols to chlorides because other reagents are more practical. Phosphorus tribromide is a common reagent for conversion of alcohols to bromides, however.[151] A typical reaction is the conversion of **143** to **144** with PBr_3, where the adjacent chiral center in (*S*)-2-methyl-2-butanol was not disturbed,[152] implying that the reaction does not proceed via an intermediate with significant ionic character. A mixture of carbon tetrabromide and triphenylphosphine, is a mild and convenient method for converting alcohol to bromides, as illustrated by the conversion of **145** to **146** in 89% yield, in Díez and Urones' synthesis of an analog of usneoidol E.[153] Triphenylphosphine and *N*-chlorosuccinimide (NCS, see **173** below) converts allylic alcohols to allylic chlorides.[154] Conversion of an alcohol to a mesylate followed by treatment with LiBr is a mild method for preparing bromides[155] and treatment with LiCl allows formation of the chloride.[156] Carbon tetrachloride and hexamethylphosphorus triamide (HMPT) has been used to convert alcohols to chlorides.[157]



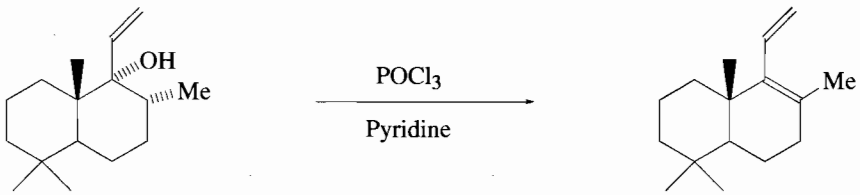
147 **148**

The bromination method mentioned above that uses triphenylphosphine and either CBr_4 or elemental bromine is a particularly mild method for this transformation. Cyclopropylcarbinyl alcohols are acid sensitive substrates, for example, usually giving ring-opening products or cyclobutane derivatives on treatment with acid (see above).[145,158] The reaction of **147** with PPh_3 and bromine gave a 79% yield of **148**.[159,160] It was essential that the bromide–triphenylphosphine–alcohol complex be heated in order to generate this bromide since mixing the reagents without distillation led only to isolation of the starting material.[159]

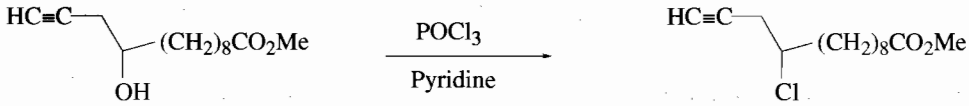


149 **150**

Phosphorus pentachloride is commonly used for the preparation of acid chlorides,[161] along with thionyl chloride.[162] Phosphorus pentabromide has been used to brominate aromatic rings, as in the conversion of **149** to **150** in 42% yield,[163] but more vigorous conditions are required.



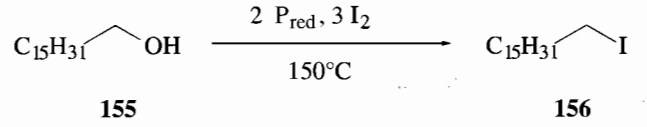
151 **152**



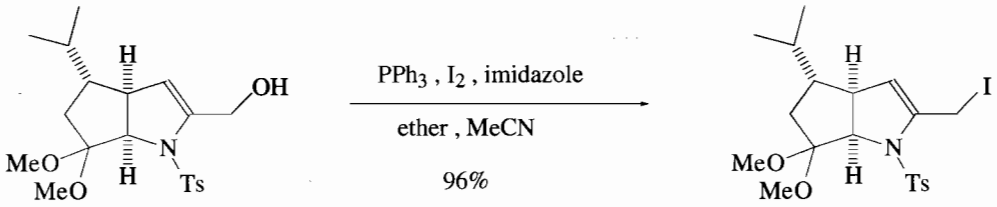
153 **154**

In combination with pyridine, phosphoryl chloride ($POCl_3$) reacts with alcohols to form an intermediate that eliminates to give an alkene (see sec. 2.9.A for elimination reactions). The tertiary alcohol in **151** was converted to the alkene unit in **152** by treatment with $POCl_3$ and Pyridine, for example.[164] Substitution by chloride ion sometimes competes with elimination when secondary alcohols are substrates. Treatment of alcohol **153** with $POCl_3$ and pyridine, for example, gave chloride **154** rather an the conjugated ene–yne.[165] As with other halogenating agents, primary alcohols react to give mainly the substitution product, the alkyl halide. Phosphorus pentabromide can be used with secondary alcohols in place of PBr_3 since much less rearrangement occurs.[161]

Although most phosphorus chlorides and bromides are commercially available, it is sometimes necessary to prepare fresh reagents. In the case of phosphorus iodides, the reagents have poor shelf-lives (they are unstable and decompose under mild conditions) and are commonly prepared *in situ*, or immediately prior to use by reaction of red phosphorus with iodine. Phosphorus bromides can also be prepared this way. Reaction of 1,2,3-propanetriol with red phosphorus and bromine, for example, gave 1,3-dibromo-2-propanol.[163] Iodides are similarly prepared from red phosphorus and iodine, as in the conversion of cetyl alcohol (**155**) to cetyl iodide (**156**) in 85% yield.[166] Using P and I_2 is a common method for the conversion of aliphatic alcohols to aliphatic iodides. Another popular method is illustrated by treatment of **157** with triphenylphosphine, iodine, and imidazole,. In this case, taken from Hiemstra's synthesis of roseophilin,[167] the primary alcohol unit was converted to iodide **158** in 96% yield.

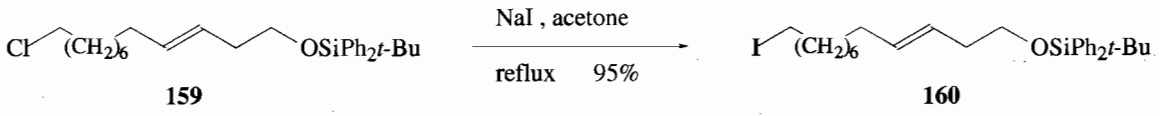


155 **156**

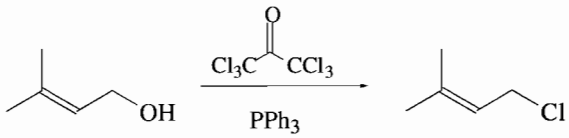


157 **158**

An old but still useful alternative is the **Finkelstein reaction,**[168] which involves treatment of an alkyl chloride, bromide, mesylate, or tosylate with sodium or potassium iodide to produce alkyl iodides via an S_N2 reaction. Refluxing chloride **159** with sodium iodide, in dry acetone, for example, gave a 95% yield of iodide **160** in Baldwin's synthesis of haliclamines A and B.[169] Similarly, Shirai and co-workers converted a tosylate to an iodide using the Finkelstein reaction, in a synthesis of dysidiolide.[170]



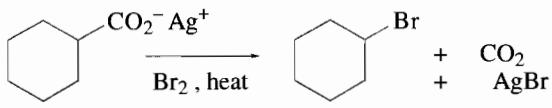
159 **160**



161 **162**

Allylic alcohols are often a problem for functional group interchanges since acidic conditions generate the allyl cation and normal S_N2 conditions can be accompanied by polyalkylation or S_N2' reactions. For allylic alcohols, most of the halogenating reagents described above induce rearrangement or other deleterious side reactions due to acid byproducts. Magid showed that allylic alcohols such as **161** are converted to the allylic chloride (**162**) by the reaction of a mixture of triphenylphosphine (PPh_3) and hexachloroacetone, which generates the chlorinating species chlorotriphenylphosphonium chloride ($Cl—PPh_3^+Cl^-$).[171] The reaction of triphenylphosphine with bromine or carbon tetrabromide (CBr_4) similarly converts an alcohol into the corresponding bromide, as we have seen above.

There are other functional group transformations that lead to alkyl halides. A classical transformation converts carboxylates to allyl bromides ($C—CO_2^- \rightarrow C—Br$). This transformation is called the **Hunsdiecker reaction**[172] (it has also been called the **Borodin reaction**)[173] and it is most useful for the preparation of secondary halides. The silver salt of a carboxylic acid is heated with bromine to give the bromide via decarboxylation. An example is conversion of the silver salt of cyclohexane carboxylic acid (**163**) to bromocyclohexane.[174] Phosphorus and bromine also react with acids in the **Hell–Volhard–Zelinsky reaction.**[175] An example is the conversion of amido acid **164** to the α-bromo acid bromide **165.**[175] Quenching with water generates the α-bromo acid **166.**



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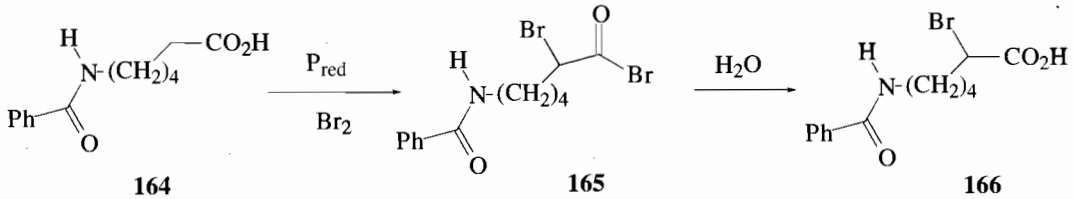
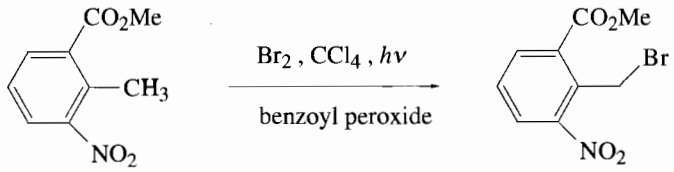


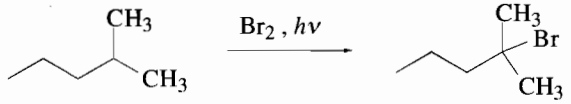
164 165 166

2.8.B. Allylic and Benzylic Halogenation

In addition to cation intermediates, radical intermediates can be used to introduce bromine or chlorine into a molecule.[176] Both allylic and benzylic moieties form resonance stabilized free radicals that react with bromine or chlorine to give the corresponding halide. Allylic radicals are easily accessible from the corresponding allylic halides, particularly allyl iodides (secs. 13.3–13.5). Benzylic radicals are available from benzylic halides and also directly from the hydrocarbon, if it bears a benzylic hydrogen. Addition of bromine to **167** (in the presence benzoyl peroxide and photochemical initiation) gave benzylic bromide **168 in high**



167 168

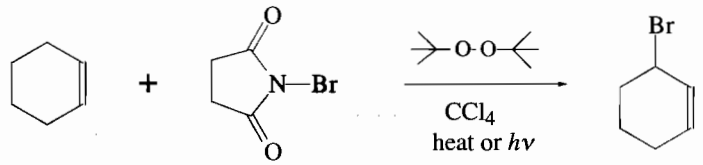


169

yield in a synthesis of indole alkaloids.[177] It is well known that radicals can be produced by reaction of alkenes with a radical initiator, and alkanes react with chorine or bromine in the presence of light ($h\nu$) or heat. The selectivity is not always very good, unless the radical formed by this process is an allylic or a benzylic radical. Free radical chlorination of alkanes by chlorine is unselective, converting virtually all C—H bonds in the molecule to C—Cl. Bromination is more selective, showing a great propensity to react with tertiary positions (tertiary C—H) to give tertiary bromides, as in the conversion of 2-methylpentane to **169**. The poor selectivity of the chlorination reaction limits its utility in synthesis. Formation of tertiary bromides, as well as allylic and benzylic radicals, is synthetically useful in radical bromination reactions.

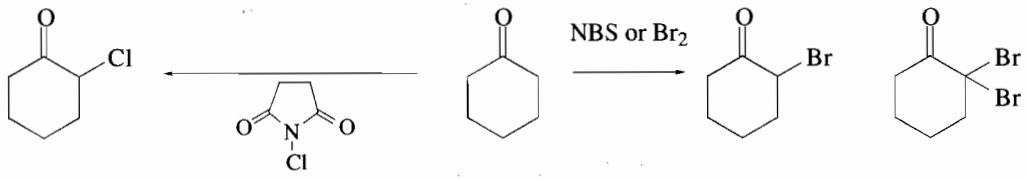
A more convenient method for halogenation of allylic and benzylic C-H moieties uses the readily available *N*-bromosuccinimide (NBS, **170**) or NCS (**173**) with heat and/or light,[178] in what is called the **Wohl-Ziegler reaction.**[178f,g,h] Reaction of NBS with cyclohexene in refluxing carbon tetrachloride gives bromocyclohexene (**171**) if an incandescent lamp is held close to the reaction or a catalytic amount of radical initiator

[such as azo-bis-isobutyronitrile (AIBN) or benzoyl peroxide - sec. 13.3] is added. Heating AIBN leads to homolytic cleavage and formation of a cyano radical ($Me_2C^{\bullet}$—CN), which initiates the radical chain process (sec. 13.3). This chain process generates the allylic (or benzylic) radical that reacts with bromine (or additional NBS) to give the allylic or benzylic bromide product and another radical chain carrier.[178] Reaction with NCS proceeds by a similar mechanism.



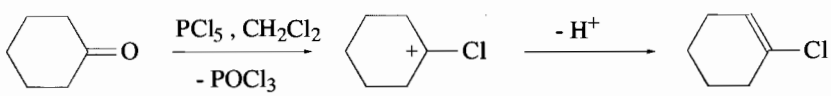
170 **171**

Ketones containing an enolizable hydrogen can be halogenated at the α position (the carbon adjacent to the carbonyl) with bromine, chlorine, NBS, or NCS.[179] The reaction probably proceeds via addition of X_2 to the enol form of the carbonyl (secs. 9.2.A, 9.8.A). Elimination of HX from the addition product generates another enol, which tautomerizes to the α-haloketone.[179] Reaction of cyclohexanone with bromine, for example, would give 2-bromocyclohexanone (**174**) and a similar reaction with NCS (**173**) would give 2-chlorocyclohexanone (**172**).



172 **173** **174** **175**

Halogenation of carbonyl compounds is often accompanied by secondary reactions. The initially formed α-halo carbonyl can react with another equivalent of halogen, for example, to give the α,α-dihalo carbonyl. In the bromination of cyclohexanone, 2,2,-dibromocyclohexanone (**175**) was also produced. Usually the mono-halogenated product predominates with ketones, but this depends on the substrate and the reaction conditions. Halogenation of lactams using this method often gives an α,α-dihalide.. 2-Pyrrolidinone, for example, reacts with NCS or PCl_5, to give a mixture of 3-chloro- and 3,3-dichloro-2-pyrrolidinone.[180] With phosphorus halides the dichloride is usually the major product, but the monochloride can be formed in reasonable yield using NCS.

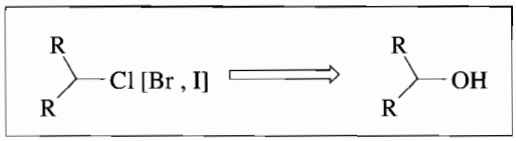


176

Halogenation usually occurs preferentially at the more highly substituted α position of unsymmetrical ketones. Regioselectivity can be a problem in the halogenation of unsymmetrical ketones, but heating a ketone with *tert*-butyl bromide and DMSO at 65°C is a mild and selective solution to the problem,[181] and it

usually gives the more substituted bromide. Another problem in halogenation reactions of carbonyls is elimination ($POCl_3$ is produced as a side product when PCl_5 is used). When cyclopentanone reacts with PCl_5, for example, the main product is 1-chlorocyclopentene via elimination of a proton but 1,1-dichlorocyclopentane is also formed by addition of chloride ion to the chloro-cation.[182] Similarly, cyclohexanone reacts to give 1-chlorocyclohexene (**176**).[183]

Incorporation of halogen into a molecule is important because halides are often precursors for substitution or elimination reactions. The ability to convert alcohols to halides is therefore an important functional group transformation. The transform is

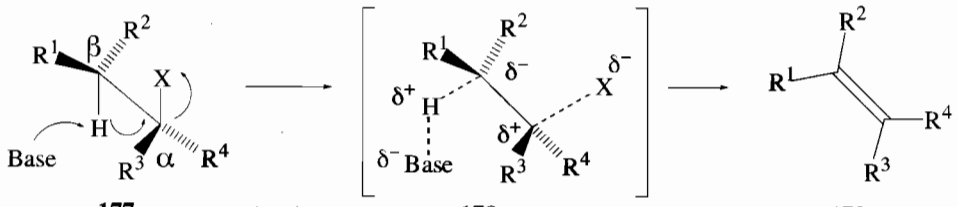


2.9. ELIMINATION REACTIONS

There are several types of reactions in which a halogen, a sulfonate ester, or another functional group is lost from the molecule, along with a hydrogen or sometimes another functional group to generate a carbon–carbon double bond. Both alkenes and alkynes can be formed. This section will examine methods for the formation of such molecules via elimination reactions.[184] A recent monograph describes several different preparations of alkenes.[185]

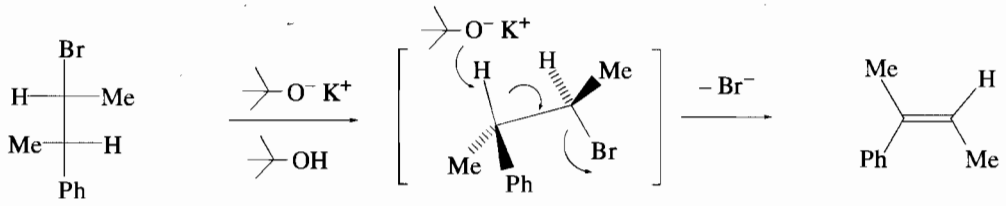
2.9.A. Bimolecular 1,2-Elimination

Elimination is a major class of functional group exchange reactions in which a H atom and a leaving group are removed from a molecule, leaving behind a π bond. However, it relies on acid–base chemistry to initiate the elimination process. Mechanistically, elimination is characterized by removal of a proton by a base, followed by expulsion of an atom or group (the leaving group, X) to form the π-bond. The reaction eliminates the elements of H—X, which leads to the name. We have discussed the characteristic features of nucleophiles and their reactions. In many cases, the nucleophile used in a substitution reaction is also a good Brønsted–Lowry base. Although there is strong attraction between the δ^+ dipole on the carbon bearing the leaving group and the base, collision with this carbon is unproductive in tertiary substrates due to the high energy of activation for the S_N2 transition state. The bond polarization induced by the halide extends down the carbon chain to the β-hydrogen, which has a δ^+ dipole. Collision of the base with this β-hydrogen is an acid–base reaction that removes the hydrogen as shown in **177**. As negative charge develops on the β-carbon (the base provides two electrons to the hydrogen, leaving behind two electrons on the carbon), the electron migrate toward the δ^+ dipole of the carbon bearing X, forming a new π-bond as the leaving group is expelled. The overall process generates a new π bond in the alkene product (**178**) as the elements of H and X are lost from the starting material. The reaction is given the designation of **E2 reaction** (bimolecular elimination) because it follows second-order kinetics. The elimination process is synchronous rather than stepwise,[186] and all experimental observations can be explained by a transition state such as **179**.



177 **178** **179**

Since the elimination sequence begins with an acid-base reaction in which the halide is treated with a base, an acid must be present in the alkyl halide. The acid is a hydrogen atom attached to the β-carbon relative to the leaving (the β-hydrogen—see **177**) and bond polarization resulting from the presence of X makes that hydrogen δ^+ so it functions as a weak, acid. As the base reacts with the β-hydrogen, the orientation of the leaving group and that hydrogen must be anti (i.e. 180° apart).[186] This is due to electronic repulsion between



180A **180B** **181**

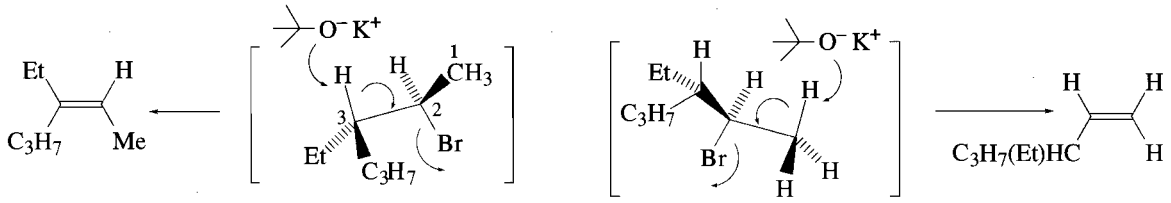
the developing charge (electron pair) on the β-carbon and the leaving group, which is minimized in an anti-transition state. This anti-relationship makes the stereochemistry of the alkene product predictable. In **178**, the relative position of the alkyl groups in the anti transition state (note that R^1 and R^3 are on the same side) is retained in the alkene (**179**) when the π bond is formed. When halide **180A** is treated with a base such as *tert*-butoxide, only the (*Z*)-alkene (**175**) is formed via E2 elimination. Halide **180A** is the (2*R*,3*S*) diastereomer of 2-bromo-3-phenylbutane and the only rotamer that has the bromine leaving group and the β-hydrogen in an anti conformation is **180B**. The relative positions of phenyl and methyl are cis in **180B** and after elimination of HBr, the (*Z*)-isomer (**181**) is formed. Similar reaction with the 2R,3R diastereomer of 2-bromo-3-phenyl-butane will give only the (*E*)-alkene.

Using the Hammet postulate, the transition state for this reaction is product-like (a late transition state), so that factors stabilizing the alkene product will have a strong influence on the transition state. Alkyl groups that are attached to an sp^2 carbon release electrons to the π bond and enhance the strength of the π bond. A more highly substituted alkene is therefore more stable and a relative order of alkene stability is:[187]

$R_2C{=}CR_2$ > $R_2C{=}CHR$ > $RCH{=}CHR$ > $R_2C{=}CH_2$ > $RCH{=}CH_2$ > $H_2C{=}CH_2$

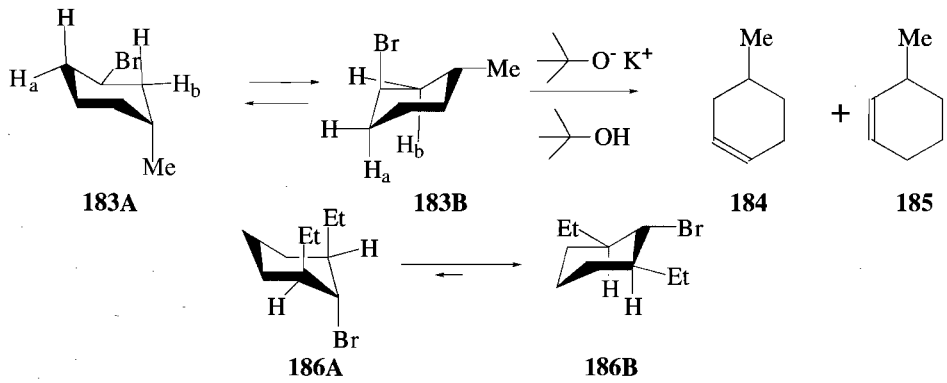
When there are two different β-hydrogen atoms, there is the possibility of forming two different alkene products. Removal of hydrogen in **176A** will lead to a double bond between C2—C3 in (*Z*)-3-ethyl-2-hexene but removal of hydrogen from **176B** will lead to a double bond between C1—C2 in 3-ethyl-1-hexene. Transition state **176A** leads to a more highly substituted alkene (3-ethyl-2-hexene) than does **182B** (which

leads to 3-ethyl-1-hexene). A trisubstituted alkene is thermodynamically more stable than a monosubstituted alkene. Since the Hammet postulate assumes a product-like transition state, transition state **182A**, which leads to the more stable product must be energetically more accessible relative to **182B**. Acid-base reactions are best viewed as equilibrium processes and when under thermodynamic control, formation of the lowest energy product is favored. The initial step of the E2 reaction is an acid-base reaction, and removal of the hydrogen that gives the transition state leading to the more stable product is favored, 3-ethyl-2-hexene. Formation of the more stable alkene is characteristic of E2 reactions and is usually termed **Saytzeff (Zaitsev) elimination.**[188] Formation of the more substituted alkene and this term is also associated with E1 reactions.



182A **182B**

The anti orientation of the β-hydrogen and the leaving group required for the E2 reaction can lead to problems when the reaction is attempted with cyclic structures.[189] In cyclohexane systems, an E2 reaction can occur only if the β-hydrogen and the leaving group must have a trans- diaxial relationship. Elimination of bromine in *trans*-1-bromo-3-methylcyclohexane (both chair conformations **183A** and **183B** must be considered) upon treatment with base can give two regioisomeric alkenes, **184** and/or **185**. Both alkenes have a disubstituted C=C unit and are approximately equal in stability. Based only on stability of products, we predict a 1:1 ratio. If the methyl group partially hinders removal of H_b, it will be a little easier to remove H_a and **184** will be favored. In cyclohexane systems, both equilibrating chair conformations (**83A** and **183B**) must be

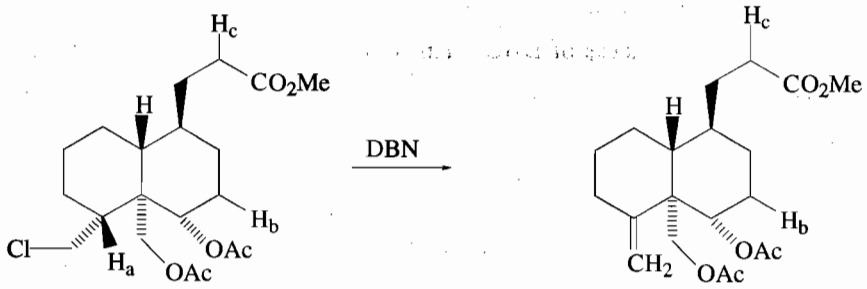


183A **183B** **184** **185**

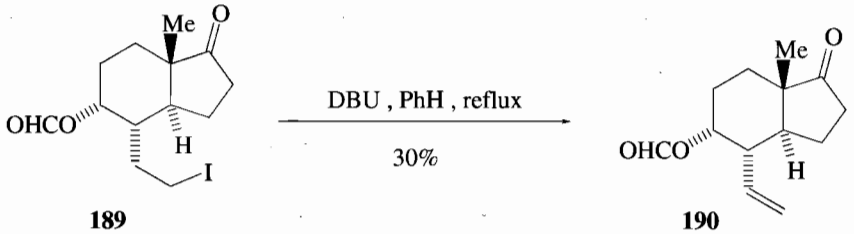
186A **186B**

examined for reaction with the base. In **183A**, the bromine is equatorial and there are no β-hydrogens that can attain an anti conformation relative to the bromine. An E2 elimination cannot occur from **183A**. In **183B**, however, both H_a and H_b are anti to the axial bromine and elimination leads to **184** and **185**, respectively. Another example is halide **186**, where there are two β-hydrogens. There are two chair conformations (**186A** and **186B**), and **186B** is the thermodynamically more stable due to decreased *A* strain (sec. 1.5.D). In **186A** the two ethyl groups are axial and the β-hydrogens are equatorial and, therefore, not susceptible to base

induced elimination. In **186B** the hydrogens are axial and the bromine is equatorial, again preventing an E2 elimination. We therefore predict that treatment of **186** with base will *not* lead to an E2 reaction. The conformational characteristics of a cyclohexane or other ring system must be evaluated carefully because they may have a significant influence on reactivity in an E2 reaction.

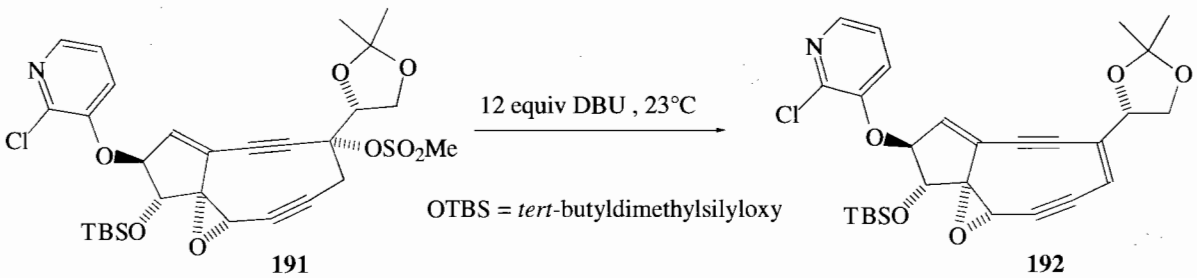


The leaving group in an E2 reaction can be a halide as with alkyl chlorides, bromides, iodides, or a sulfonate ester such as a mesylate (—OSO_2Me), a tosylate (—OSO_2p-Me-C_6H_4), or a triflate (—OSO_2CF_3). Elimination of the tertiary chloride from alcohols upon treatment with thionyl chloride and pyridine, as noted previously for the conversions **151** → **152** and **153** → **154** (see above), is a typical synthetic example. The previously mentioned nonnucleophilic base DBN (**24**)[190a] can be used to induce an E2 type reaction with primary halides. The DBN selectively removes H_a from **187** to form the exo-methylene group shown in **188**.[191] It does not remove H_b with elimination of acetate (an E2 process) nor H_c to generate the ester enolate (sec. 9.2). Nitrogen in the sterically hindered base DBN is a poor nucleophile, retarding the normal nucleophilic acyl addition to a carbonyl group in an ester. Note that **188** contains the relatively unstable exocyclic double bond and that the alkene formed is significantly less stable than others that would be more thermodynamically stable. The related base DBU (**19**)[190a] gives reactions that are analogous to DBN.[190b] The two nonnucleophilic bases give moderate to good yields of alkene in E2 reactions with alkyl halides, and little or no substitution products. Even primary halides, which give mostly S_N2 reactions with nucleophilic bases, usually give an alkene in good yield. An example is the conversion of primary iodide **189** to **190** in 30% yield, taken from Rigby's synthesis of (+)-estradiol.[192]



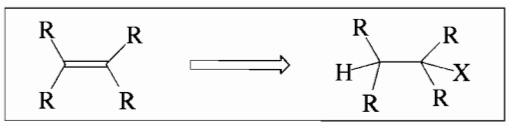
Although DBN and DBU are very selective, the most common bases used in E2 reactions are hydroxide (in water) or alkoxides in alcohol solvent (sodium methoxide in methanol, sodium ethoxide in ethanol, potassium *tert*-butoxide in *tert*-butanol).[186] Amide bases such as sodium amide or lithium diethylamide can be used in ammonia or amine solvents. In these latter cases, the bases are also good nucleophiles and in reactions with

tertiary halides the elimination process dominates. With secondary halides, substitution can compete and with primary halides, S_N2 is the major reaction. Other sterically hindered amines such as 2,2,6,6-tetramethylpiperidine have been used and the weaker base imidazole is important for elimination reactions with sensitive substrates. Sulfonate esters are also good leaving groups, as mentioned above, and are commonly used in elimination reactions. A synthetic example of the E2 reaction with a mesylate derivative is the conversion of **191** to **192** upon treatment with an excess of DBU. This alkene was an intermediate in Myer's synthesis of the kedarcidin core structure.[193]



191 **192**

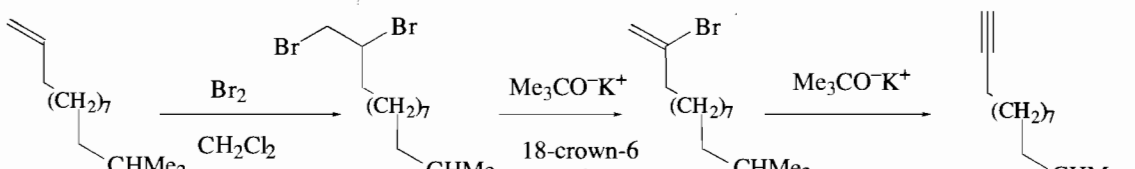
It is clear that a variety of substrates with different leaving groups can be converted to alkenes via elimination. β-Elimination of sulfones is also known.[194] A general transform for the important E2 reaction is



where X = halogen, OH, OR, OSO_2R

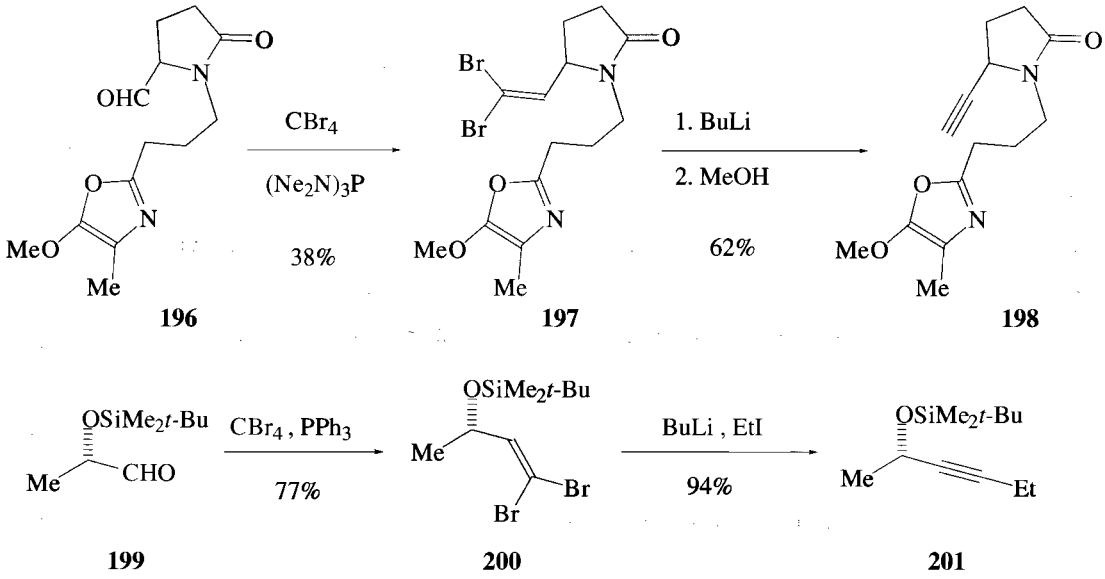
It is noted that vicinal dibromides can be treated with base in such a way that *both* bromine atoms are lost to generate an alkene. Many different reagents have been used for this transformation.[195] Recently, indium metal was shown to be an effective reagent.[196]

The E2 reaction can also be applied to the synthesis of alkynes. When a vinyl halide is treated with a strong base, loss of HX by what is essentially an E2 process leads to formation of a triple bond. In a simple example, 12-methyltridec-1-ene was treated with bromine in dichloromethane to give dibromide **193**. When this was treated with potassium *tert*-butoxide in petroleum ether, in the presence of 18-crown-6, initial elimination gave vinyl bromide **194** but this reacted again with the base, and an E2 reaction gave alkyne **195** in 72% yield for both chemical steps. Alkyne **195** was used in Mori's synthesis of the sphingosine derivative sulfobacin B.[197]

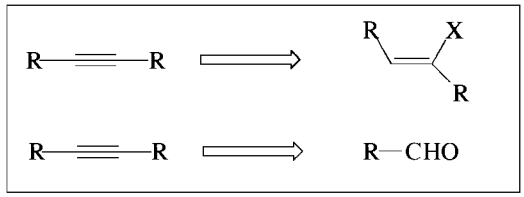


193 **194** **195**

An alternative method for preparing vinyl bromides can be incorporated into a synthesis of alkynes when combined with an E2 reaction. In Jacobi's synthesis of (-)-stemoamide,[198] aldehyde **196** was treated with



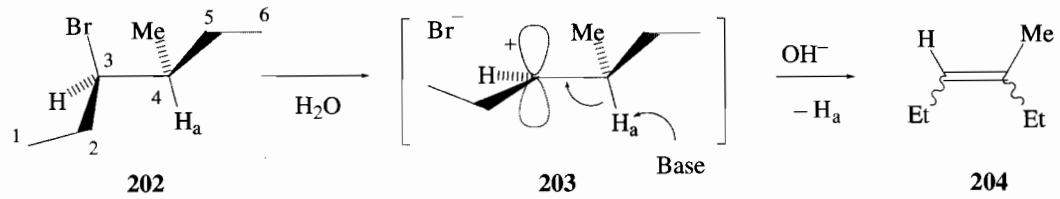
carbon tetrabromide and HMPT to give vinyl dibromide **197** in 38% yield via an olefination reaction (see sec. 8.8.A). When this was treated with butyllithium, elimination occurred to give an alkyne anion, which was quenched with methanol in a second step to give alkyne **198** in 65% yield. This sequence could be modified to produce internal alkynes as well. In the synthesis of callystatin A by Marshall and co-workers,[199] aldehyde **199** was treated with carbon tetrabromide and triphenylphosphine to give vinyl dibromide (**200**) in 77% yield. When this was treated with butyllithium and then iodoethane, alkyne **201** was formed in 94% yield. It is clear that extending the E2 reaction to prepare alkynes is quite useful as well or as versatile. The E2 disconnections to prepare alkynes are



where X = halogen, OH, OR, OSO_2R

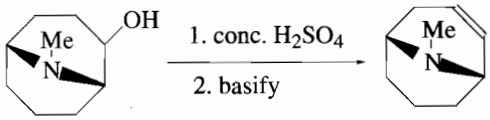
2.9.B. Unimolecular 1,2-Elimination

The E2 reaction follows second-order kinetics and this is usually associated with a collision between the base and the β-hydrogen. The rate is proportional to the concentration of both the halide and the base. Under certain conditions, the reaction follows first-order kinetics and involves an ionization step. In those cases (1) water is present, (2) a good leaving group is present, (3) a weak base is used, and (4) molecular rearrangements are often observed. In this mechanism, there is no dependence on the concentration of the base since the slow step is ionization of the halide, with assistance of the solvent to give a carbocation, as we saw in an S_N1 reaction. A simple example based on the generic mechanism involves heating bromide **202** in aqueous media, which generates a solvent separated ion pair (**203**) as the water assists in breaking the C—Br bond and then solvating the bromide ion, as well as **204**. The β-hydrogen (H_a in **202**) is polarized to a greater extent in the carbocation (**203**) than in **202** since a hydrogen is adjacent to a full positive charge. A base must



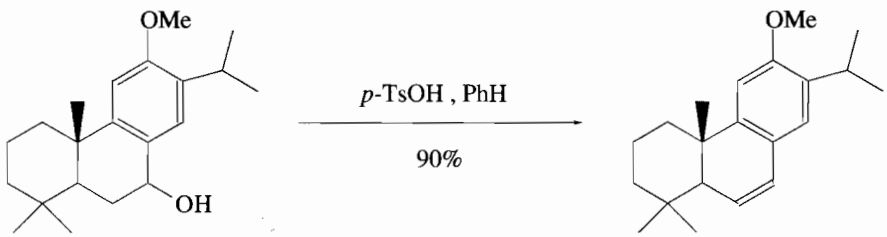
202 **203** **204**

be present in the medium to remove H_a (the oxygen of water is strong enough in this case) and migration of the electron pair to the electrophilic center generates the π bond of the alkene product **204**. The C—C bond connecting the positive carbon to that bearing H_a can rotate so **203** exists as a mixture of rotamers, leading to **204** as a mixture of (*E*/*Z*)- isomers. The intermediacy of the planar carbocation prevents formation of an alkene with the stereospecificity observed in the E2 reaction, but the thermodynamically more stable product will predominate (**Saytzeff elimination**). The reaction is unimolecular since the slowest step in this process is loss of the leaving group to form the cation, and it is termed an E1 **reaction** (unimolecular elimination).[200,201]



205 **206**

The S_N1 reaction usually competes with the E1 process in aqueous media since most bases used in this reaction are nucleophilic. Only when the gegenion is a very weak nucleophile will the E1 process dominate and produce substantial amounts of alkene product. Formation of an alkene when alcohols react with concentrated sulfuric acid or perchloric acid is an example, as when **205** was treated with concentrated sulfuric acid to give alkene **206**.[201] Milder conditions can be used, as in the treatment of **207** with *p*-toluenesulfonic acid in benzene to give a 90% yield of **208** in Pan's synthesis of (–)-6,7-dehydroferruginyl methyl ether.[202] As with any reaction involving a carbocation, rearrangements are possible. In the case of **208**, formation of the conjugated alkene unit biased the reaction to proceed with high selectivity. Although sometimes useful, as shown in these examples, the E1 reaction is often an important side reaction in S_N1 processes, and it is important that the possibility of E1 reactions be considered when carbocation intermediates are generated.



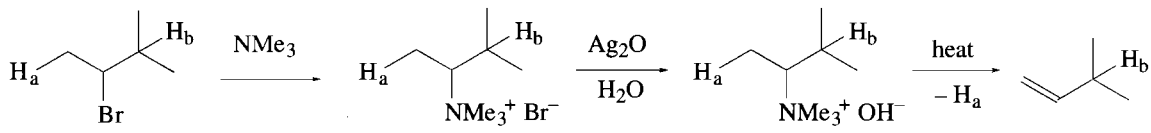
207 **208**

2.9.C. Syn-Elimination Reactions

Both E2 and E1 reactions require a base, and that base is usually a separate molecule added to the reaction medium; that is., they are intermolecular processes. In those reactions, the hydrogen removed by the base

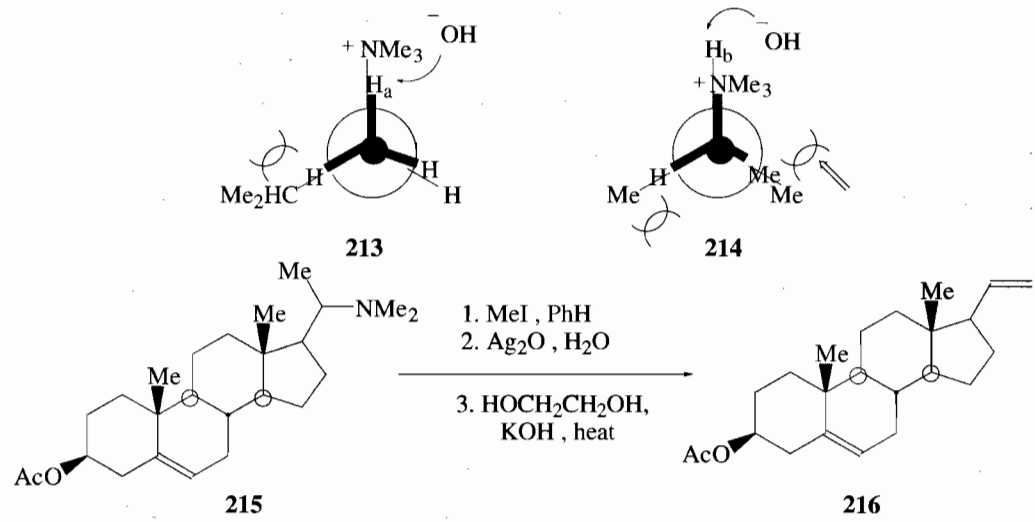
must have an anti relationship to the leaving group. Another type of elimination process is possible if the basic atom were part of the same molecule that contains the leaving group. If the base were part of or tethered to the substrate, however, the β-hydrogen could only be removed if it eclipsed the basic atom in a syn conformation. This process requires that the acidic hydrogen be removed by the base in an **intramolecular** reaction. If the tethered base were also a leaving group, removal of the syn β-hydrogen is possible, but it would require higher reaction temperatures since the higher energy eclipsed conformation is necessary for reaction (sec. 1.5.A). Such reactions are termed **syn elimination**.[99] There are several examples of this reaction involving different tethered bases that can also serve as leaving groups, and several are named reactions.

2.9.C.i. Hofmann Elimination. In a syn elimination, the experimental observation is that the less stable alkene is formed and that the reaction is under kinetic control rather than thermodynamic control. The thermodynamically controlled E2 reactions require an anti-transition state. The kinetically controlled syn-elimination, however, requires a syn-transition state in which the β-hydrogen and the leaving group assume an eclipsed conformation. In general, the lowest energy syn-eclipsed rotamer will be important for syn-eliminations. A classical example of this process is the **Hofmann elimination**,[103,99] illustrated by conversion of 2-bromo-3-methylbutane (**209**) to 3-methyl-1-butene (**212**). The secondary bromide is first converted to ammonium bromide **210** by an S_N2 reaction with trimethylamine. Ammonium salt **210** does not possess a basic atom or group, because the bromide counterion is not very basic. For the elimination to occur, bromide must be replaced to a stronger base, such as hydroxide, before elimination can occur. Reaction with silver



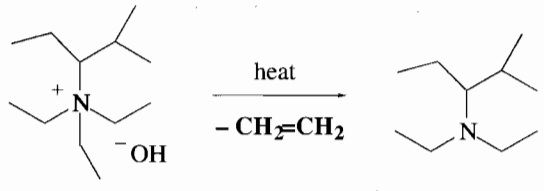
209 **210** **211** **212**

oxide (Ag_2O) in the presence of 1 equivalent of water (water cannot be the solvent or a cosolvent) gives the corresponding trimethylalkylammonium hydroxide (**211**). If water is present in excess the ionic base would be solvent separated from the ionic ammonium moiety by the solvent and an E2 reaction would result. In the absence of an ion separating solvent, however, the basic hydroxide is tethered to the ammonium ion by ionic bonding. Hydroxide can react with the β-hydrogen only when that C—H bond eclipses the C—NMe_3^+ OH^- bond. When hydroxide reacts with this hydrogen, water is formed along with a π bond via expulsion of trimethylamine. In some cases, there is evidence that a nitrogen ylid intermediate is generated,[203] (sec. 8.8.C) but direct removal of hydrogen by hydroxide accounts for the product in most cases.[204] Closer analysis of **211** reveals there are two removable β-hydrogens, H_a and H_b. Since removal of either hydrogen is an intramolecular process requiring a syn conformation, **213** and **214** are the two important eclipsed conformations that must be considered for the elimination transition state. The methyl–methyl and methyl–hydrogen interactions in **214** (see ⇐) are significantly higher in energy than the hydrogen–hydrogen and isopropyl–hydrogen interactions that arise in **213** (see sec. 1.5.A). Removal of H_a from the lower energy **213** is favored and leads to the observed major product **212**.

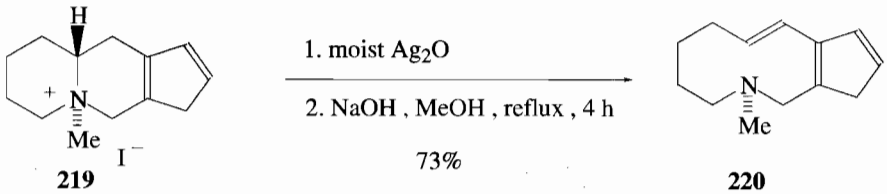


A typical synthetic transformation using the Hofmann elimination also illustrates an alternative synthetic approach to this reaction. Reaction of iodomethane with the dimethylamino moiety in **215** leads to the trimethylammonium salt. This ammonium leaving group allows the usual Hofmann elimination sequence, with thermal syn-elimination giving the vinyl derivative, **216**.[203,204] This variation is important since using an amine as a Hofmann precursor is often more convenient than relying on an S_N2 reaction of an amine and a halide to produce the requisite ammonium salt (sec. 2.7.A).

Vital to the success of the Hofmann elimination is the use of amines such as trimethylamine or triphenylamine to generate the quaternary ammonium salt, since they do not possess β-hydrogens. When an amine such as triethylamine, which has β-hydrogens, reacts with 3-iodo-2-methylpentane, ammonium salt **217** is the product and there are four β-hydrogens that can be removed by a base. Elimination via the most energetically favorable conformation will lead to the smallest and least substituted alkene, ethylene.[203a,b] The other product is the tertiary amine, **218**. However, if one of the β-hydrogens is more acidic, such as that in the benzylic position of **219** relative to the thiophene ring, Hofmann elimination leads to selective deprotonation and formation of a single alkene, in this case **220**.[205] This example also illustrates the use of this reaction to open a bicyclic ring system to give a 10-membered ring, which is difficult to form using cyclization techniques (see sec. 6.6.B).



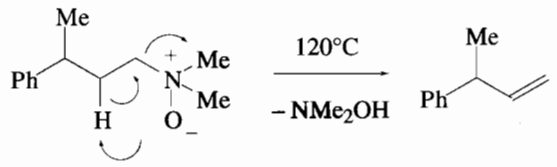
217 218



219 220

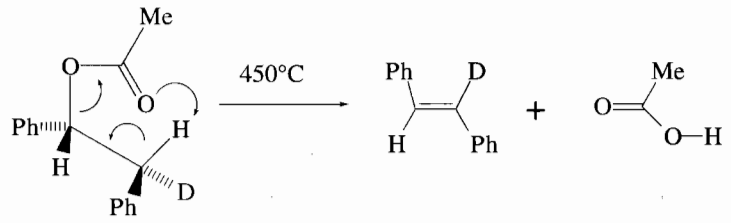
In the most general application, syn-elimination requires the presence of a basic atom that is part of a molecular fragment that is also a leaving group. The elimination step requires heating and the basic end of the molecule is often negatively charged or at least negatively polarized. If the tethered base is a negatively charged ion such as hydroxide, ion pairing with the cation is required if the syn-elimination is to occur, and this places stringent solvent requirements on the system. A polar protic solvent such as water will ionize the ammonium hydroxide, leading to S_N2 reactions rather than syn-elimination. For this reason, the reaction is often done neat (this means no solvent). As the polarization of the Lewis base end of the dipole increases, the attraction for the δ^+ proton should increase, leading to greater facility of the syn elimination via transfer of hydrogen to the basic atom. Typically, this means that the reaction should occur at a lower reaction temperature. Perhaps more importantly, the leaving group ability of the base will influence the reaction temperature and facility of the syn elimination. The combination of a strong internal base and a good leaving group leads to lower reaction temperatures. If the leaving group is unstable to the reaction conditions as it departs and fragments to other products, this will usually drive the reaction to completion under milder conditions. There are a number of syn elimination reactions commonly used in synthesis that illustrate this trend.

2.9.C.ii. Amine Oxide Pyrolysis (Cope Reaction). A useful modification of the Hofmann elimination replaces the hydroxide ion that is coordinated via an ionic bond to the cationic ammonium salt with an atom or group that is part of the leaving group. Cope found that changing the $R_4N^+OH^-$ group to an amine *N*-oxide (R_3N—O) satisfied this new criterion (see **215**). These polar amine oxides function as bases and removal of the β-hydrogen via a syn conformation allows expulsion of the neutral leaving group, *N,N*-dimethylhydroxylamine. Since the base is part of the molecule and *not* a separate molecule, competitive E2 elimination is not much of a problem. Syn-elimination from an amine oxide requires somewhat lower temperatures than those observed with the Hofmann elimination (see above). Pyrolysis of amine oxides to produce alkenes is usually referred to as the **Cope elimination**,[206,103d,99] and a typical reaction temperature is 120°C, as shown for the conversion of **221** to **222**.[103d] Pyrolysis of **221** did not lead to 2-phenyl-2-butene as the major product, although it is the thermodynamically more stable conjugated isomer.[103d] The Cope elimination requires the synthesis of *N*-oxides, and these are usually formed by oxidation of the corresponding amine with hydrogen peroxide or *m*-chloroperoxybenzoic acid[207] (sec. 3.9.B). It is noted that alkenyl-*N*-methylhydroxylamines can undergo a reverse Cope elimination to give pyrrolidine or piperidine *N*-oxides.[208]

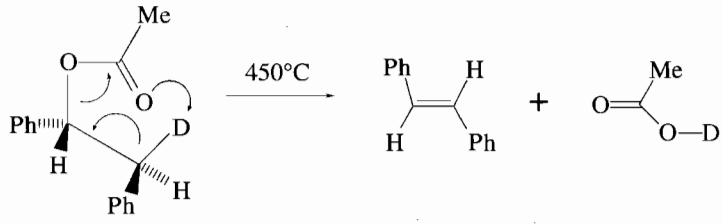


221 **222**

2.9.C.iii. Ester Pyrolysis.[209,99] If the structural components required for syn-elimination in the Hofmann and Cope elimination could be modified to use more readily available synthetic precursors, the reaction might have wider applicability. One possibility is to replace the amino group with an oxygen moiety so there is a



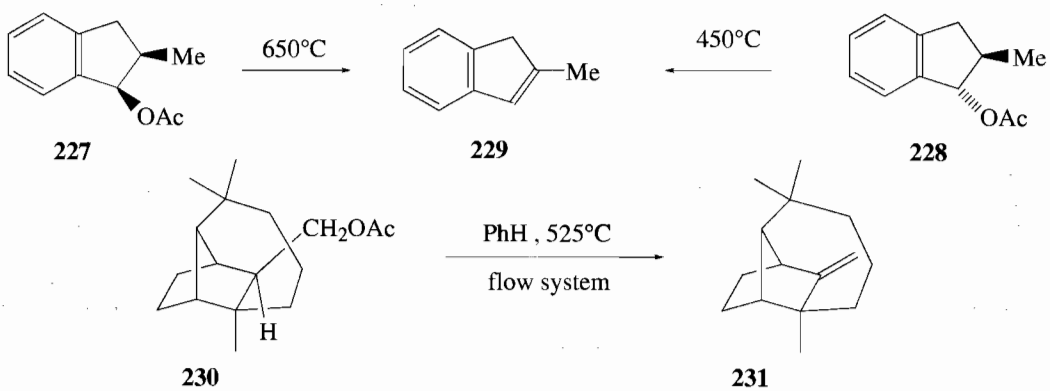
223 **224**



225 **226**

basic atom that can function as a leaving group. A simple choice is acetate (—OCOMe), which is a moderate leaving group, and the carbonyl oxygen of the ester could function as a tethered base. Clearly, this oxygen is a weak base and acetate is a poorer leaving group than ammonium or an amine oxide. For these reasons, syn elimination of acetates is expected to require more vigorous conditions than observed in Hofmann elimination or Cope elimination. Acetates are readily available, however, by reaction of an alcohol with acetic anhydride or acetyl chloride and pyridine (or another base). Thermolysis of an acetate group leads to syn elimination via expulsion of acetic acid (the leaving group), but the temperature requirements for ester pyrolysis are quite high. In **223**, heating to 450°C was required for elimination to the alkene product (**224**), where the deuterium was retained.[209b,105] Similar pyrolysis of the syn acetate (**225**) gave alkene **226** in which the deuterium was lost. This finding is completely consistent with a syn- transition state for removal of hydrogen or deuterium from the β-carbon by the acetoxy group.[209c,99]

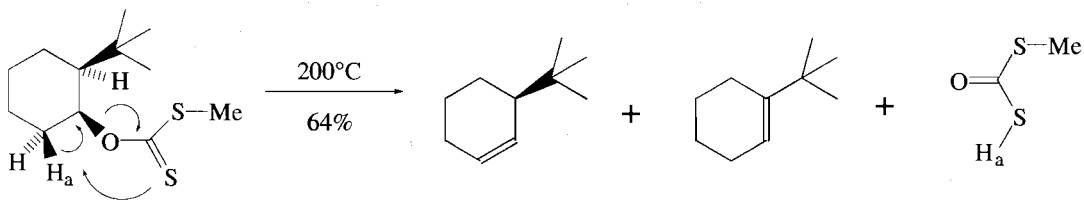
The importance of the syn relationship of hydrogen and the leaving group is seen in hydrindanes **227** and **228**, which produced **229** upon pyrolysis. The cis-derivative (**227**) required temperatures at least 200°C higher than the trans-acetate (**228**).[209b] A synthetic example that involves ester pyrolysis is taken from Fallis' synthesis of (+)-longifolene (**230**), formed in 56% yield by pyrolysis of **231**.[210]



227 **229** **228**

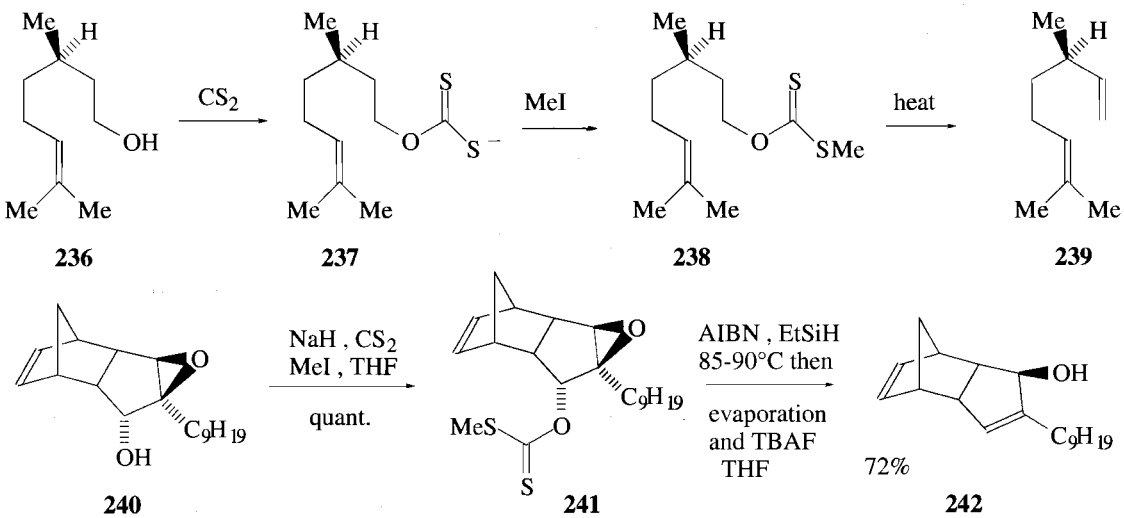
230 **231**

2.9.C.iv. Xanthate Ester Pyrolysis.[211,99,209a,b] The high temperatures required for acetate pyrolysis could be diminished if there were a better leaving group and/or a stronger base. If the product formed after departure of the leaving group were more stable and/or if it decomposed after its departure, the elimination would also be more facile. These goals were accomplished by changing the ester moiety to the sulfur analog of a carbonate [O—(C=O)—OR], specifically the xanthate group [O—(C=S)—SR]. Upon heating a xanthate



232 **233** **234** **235**

ester, a syn-elimination proceeded under relatively mild conditions. The xanthate group is a better leaving group than acetate but sulfur is a poorer base than oxygen, although it is a better nucleophile.[212,89,96,97] The elimination proceeded at significantly lower temperatures, however (≈ 200°C), and it is important to note that the neutral molecule **235** was lost as a byproduct. This product fragmented to COS and methanethiol, making the elimination an essentially irreversible process. In a specific example, the thiocarbonyl group of xanthate **232** fragmented to **233** and **234**, with the less substituted **233** being the major isomer. This reaction is one step of the **Chugaev elimination**[213,211] used for conversion of alcohols to alkenes.[211] An alcohol such as **236** reacts with carbon disulfide to give a thioanion (**237**) which reacts as a nucleophile when added to iodomethane. The product of this reaction is a xanthate ester (**238**). Heating generates alkene **239**, which was an intermediate in Mori's synthesis of the German cockroach sex pheromone.[214] There are alternative elimination routes that involve xanthate esters, including conversion of epoxy-alcohol **240** to xanthate ester **241** in



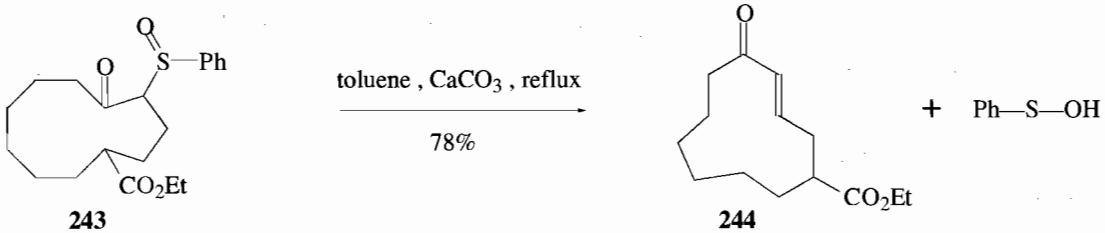
236 **237** **238** **239**

240 **241** **242**

quantitative yield using standard conditions. The elimination step required the use of triethylsilane (Et_3SiH), a radical initiator such as AIBN, and treatment with tetrabutylammonium fluoride (TBAF). Under these condi-

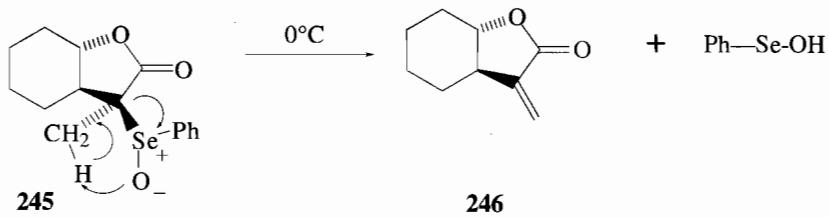
tions, opening of the epoxide ring was accompanied by elimination to give **242** in 72% yield in Ogasawara's synthesis of (+)-frontalin.[215] This elimination is related to the Barton–McCombie reaction involving reduction of xanthates under radical conditions (see sec. 4.9.H).

2.9.C.v. Sulfoxide Pyrolysis.[216] Another change in the syn elimination precursor continues the theme of changing sulfur for oxygen but incorporates the polarized oxygen found in Cope elimination. If a sulfide is oxidized with peroxide or with sodium *meta*-periodate ($NaIO_4$), the resulting sulfoxide has a highly polarized S—O bond (sec. 3.9.A). The negatively polarized oxygen of sulfoxides (S-oxides) can function as a tethered base with the O—S—R moiety serving as a leaving group. If the β-hydrogen and the S—O moiety assume an eclipsed conformation, the basic oxygen removes the hydrogen in a syn transition state to generate PhS—OH (benzenesulfenic acid where sulfur is bonded to a phenyl group). This product is unstable to the reaction conditions and decomposes, facilitating the elimination. A typical example is elimination of the sulfoxide unit in **243**.[217] Sulfoxides are often obtained by oxidation of the corresponding sulfide with sodium periodate ($NaIO_4$) or peroxy acids (as discussed in sec. 3.9.A).[218] Heating gave the α,β-unsaturated ketone (**244**). In addition to phenyl sulfoxides, methyl sulfoxides (—S(O)Me) can also be prepared and they undergo syn-elimination when heated, but the temperature required for pyrolysis is ≈ 150°C. When R is phenyl, elimination usually can often be observed by heating to only 80°C, although refluxing toluene was used here.



243 **244**

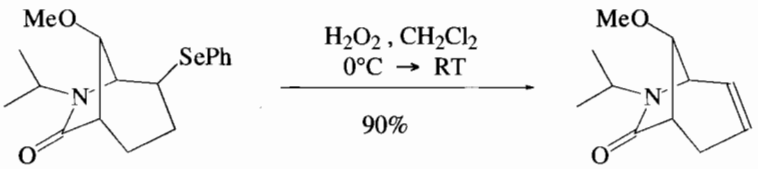
2.9.C.vi. Selenoxide Pyrolysis.[218] Just as sulfides are oxidized to sulfoxides, selenides (R—Se—R) can be oxidized to selenoxides. It is reasonable to assume, therefore, that replacing the sulfoxide with a selenoxide will also lead to thermal syn-elimination to the less substituted alkene. The increased polarity of the Se-O bond of the selenoxide, relative to the S-O bond of the sulfoxide, and the loss of the unstable R—Se—OH allows even lower temperatures for thermal syn-elimination (typically 0-25°C). Elimination of PhSeOH from **245** is clearly analogous to the sulfoxide pyrolysis of **243**, and the exocyclic-methylene derivative (**246**) rather than



245 **246**

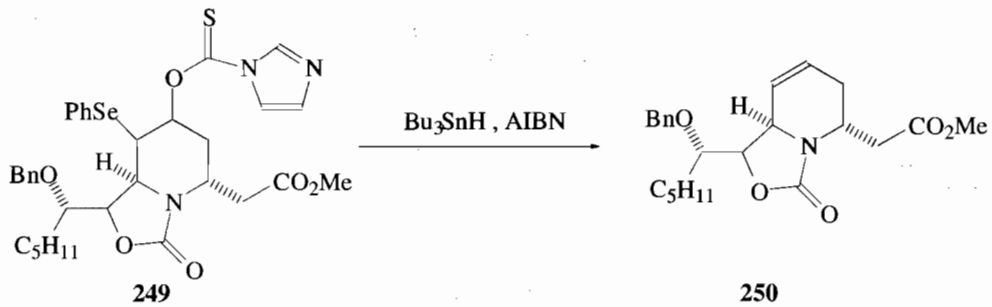
the endocyclic alkene is the major product.[225a] This elimination occurred at 0°C, making it a particularly attractive method for the generation of sensitive alkenes, in this case, the less stable exocyclic methylene

lactone (**237**). This contrasts with the rearrangement to the endocyclic alkene observed in the sulfoxide pyrolysis. Lower reaction temperatures certainly contribute to this outcome, although the steric constraints for isomerization of the bicyclic selenoxide **236** are probably important as well. It is noted that *selenium compounds are* ***toxic*** and great care should be exercised in the handling and disposal of all materials.



247 **248**

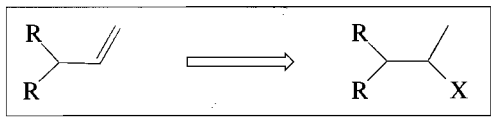
There are many synthetic examples that use this technique in addition to the simple case of **245**. In a typical one, Weinreb and co-workers oxidized selenide **247** with hydrogen peroxide, inducing syn-elimination to **248** in a synthesis of peduncularine.[219] There are also useful modifications of the reaction. Selenides can undergo another type of elimination reaction when they are on a carbon adjacent to a thiocarbamate group, as in **249**. Radical induced elimination with AIBN in the presence of a hydrogen atom donating species such as tributyltin hydride (see sec. 13.3) gave the elimination product **250**, which was used in Comins' synthesis of (+)-cannabisativine.[220] It is noted that **249** was generated *in situ* from an alcohol precursor and the theocarbamate formation–elimination steps were done in a one-pot reaction.



249 **250**

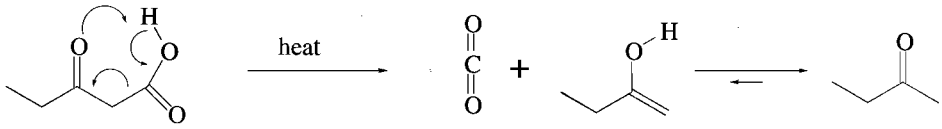
Bond polarization and leaving group ability are not the only factors that influence the ease of thermolysis, which can be illustrated by xanthate ester pyrolysis. DePuy and King state "the much greater ease of xanthate pyrolysis as compared to the pyrolysis of esters must be due to an added driving force as a consequence of conversion, in the transition state, of the system —O—C=S into the system O=C—S—. Examination of the relative bond energies shows that conversion should be exothermic to the extent of nearly 20 kcal mol^{-1}".[99] Bond polarization is, however, a convenient handle for predicting the relative ease of syn elimination in many cases, although it accounts for only part of the difference in actual reactivity and product formation. It is also known that *n*-alkyl aryl selenides that have an ortho-substituent on the aromatic ring are superior reagents for oxidation and syn-elimination when compared to those compounds having a para-substituent.[221] Structural effects therefore play a role in the reaction.

The retrosynthetic transform for syn elimination is that shown for the anti elimination reactions except that the less substituted alkene is the target:



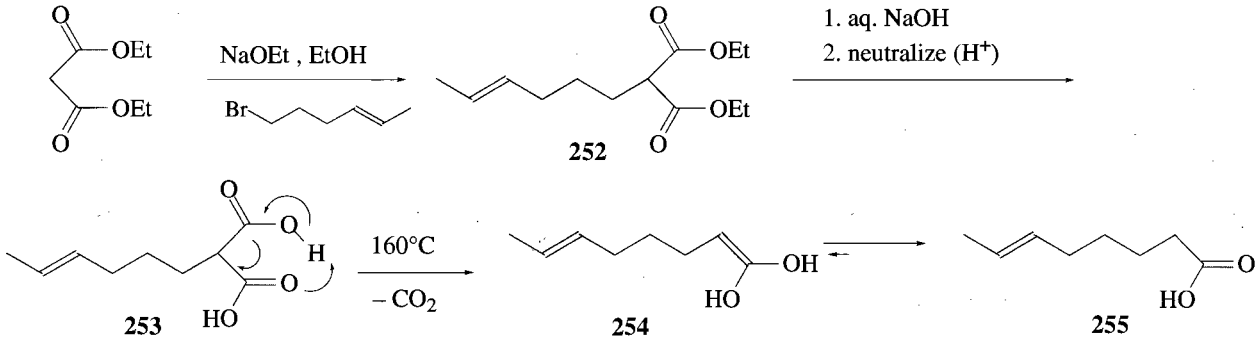
2.9.D. 1,3-Elimination (Decarboxylation)

Sections 2.9.A–C focused on 1,2-elimination reactions. The syn elimination reactions just discussed showed that an acidic hydrogen could be removed by a basic atom in the same molecule, leading to loss of a leaving group and formation of a π-bond. This principle can be applied to systems where an acidic hydrogen and a leaving group are separated by three atoms in what is termed 1,3-elimination. When a carboxyl carbon is β to a π-bond (a carbonyl, alkene or aryl) the acidic hydrogen of the acid can be transferred to the oxygen of the carbonyl (or to the sp^2 carbon of alkenes or aryls) via a six-center transition state. This requires a syn-



251

orientation of the carbonyl oxygen and the carboxyl hydrogen, as was observed in syn 1,2-elimination. This thermal process results in cleavage of the bond connecting the carboxyl carbon, loss of carbon dioxide, and formation of a new π bond. The 1,3-elimination process just described is called **decarboxylation**. Decarboxylation is most common with β-keto-acids, β-carboxyl esters and 1,3-diacids (malonic acid derivatives). Simple examples are the elimination of carbon dioxide from 3-oxopentanoic acid (**251**) to give an enol, which tautomerizes to 2-butanone. The way in which structure **251** is drawn implies that transfer of hydrogen

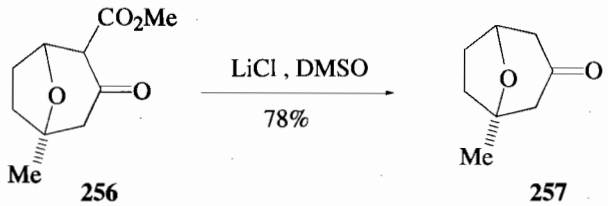


252 **253** **254** **255**

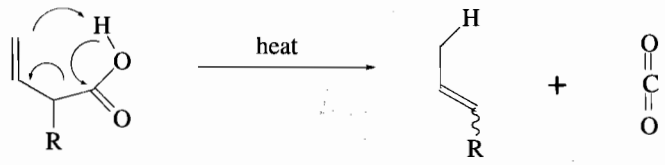
to the oxygen of the ketone moiety occurs via a six-center transition state. The malonic acid synthesis (sec. 9.3.A) generates substituted malonic esters that can be saponified to diacids such as **253**. Treatment of diethyl malonate with sodium ethoxide and then 6-bromo-(2*E*)-hexene gave a 72% yield of **255**. Saponification with aqueous KOH gave a 99% yield of **253**, which upon heating to 160°C for 5 h gave a 94% yield of **255**, which was part of Clive's synthesis of brevioxime.[222] Heating these 1,3-diacids leads to decarboxylation via a similar six-center transition state, and the initially formed product of decarboxylation is an enol, in this case **254**. This enol form of the acid tautomerized to the isolated product, **255**. In these reactions, the acidic hydrogen is the

O–H moiety of the carboxylic acid and the base is the oxygen of the carbonyl β to the acid moiety. Both decarboxylations occur under rather mild conditions (50–150°C is typical) and the overall reaction is assisted by loss of a neutral leaving group, carbon dioxide.

A mild decarboxylation procedure was developed by Krapcho.[223] When methyl ester **256** was treated with LiCl in DMSO, decarboxylation occurred to give a 78% yield of **257** in the Molander and Hass synthesis of davanone.[224] This mild procedure is referred to as **Krapcho decarboxylation**.

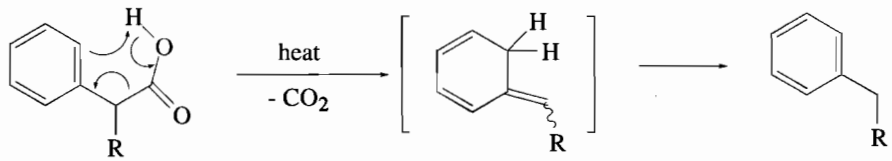


256 **257**



258 **259**

A similar reaction is observed with allylic acids such as **258**. The acid proton is once again in the O—H unit of a carboxylic acid, but now the base is the alkenyl π bond. The π bond of an alkene is a much weaker base than the oxygen of a carbonyl so the hydrogen transfer is less efficient. As a practical matter, this means



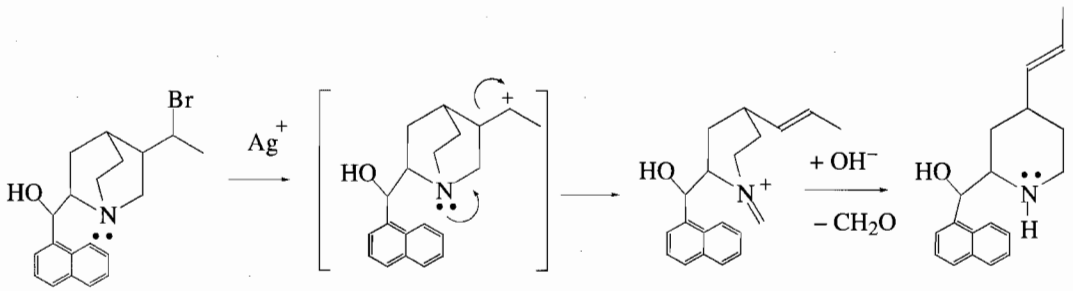
260 **261** **262**

the decarboxylation requires higher temperatures. Decarboxylation proceeds with bond migration, as shown, to give **259**. Migration of the double bond is an important feature in the decarboxylation of alkenyl acids and must be accounted for in any synthetic plan. Another source of π bonds are aromatic rings. transfer of the acidic hydrogen of the acid to the π-bond of an aryl carbon is more difficult than with simple alkenes. First, the π bond is a weaker base due to resonance delocalization and second, accepting the hydrogen requires that the aromatic nature of the benzene ring be disrupted. For both reasons, higher energy is required for the reaction, which means higher reaction temperatures for thermolysis of **260** relative to systems such as **258**. The decarboxylation proceeds by the usual six-center transition state to give benzylidene intermediate **261**, which is unstable to the thermal conditions of the reaction and quickly aromatizes to **262**.

.E. 1,3-Elimination (Grob Fragmentation)

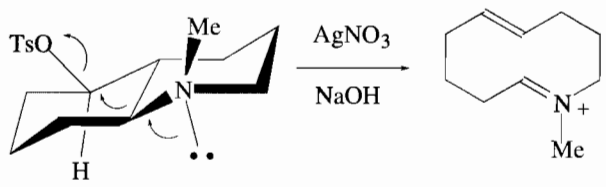
Both syn-1,2-elimination and decarboxylation reactions require transfer of electrons to an acidic hydrogen, and the concomitant bond cleavage releases a leaving group and forms a π bond. An elimination reaction is

possible in systems where the base is not a second molecule but rather part of the molecule containing the leaving group *but it is not on the β-carbon*. In this new reaction, the basic atom and the leaving group must be separated by at least three carbons to assume the requisite anti relationship for elimination. If these criteria can be met, 1,3-elimination will occur. An example of this type of reaction was first observed by Prelog in work that solved the structure of quinine and other Cinchona alkaloids. This work involved degradation studies that included treatment of **263** with KOH and silver nitrate. Silver ion generated a cation (**264**) and the nitrogen lone pair induced a 1,3-elimination ring–opening reaction to iminium salt **265**.[225] In the presence of aqueous

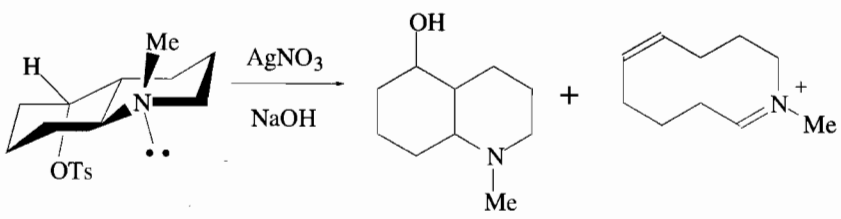


263 **264** **265** **266**

hydroxide, formaldehyde was lost to give the final product, **266**. The nitrogen acts as the internal base, transferring electrons toward the leaving group (or the carbocation center) in a process requiring the nitrogen lone pair and the leaving bromine to be anti. This concept of an anti relationship is taken from Prelog's proposed synchronous mechanism for this 1,3-elimination, which demands that "both the Cα—X bond and the orbital of the nitrogen lone pair be antiperiplanar to the Cβ—Cγ bond".[226,227] This 1,3-elimination was later expanded by Grob et al. to include amino halides and amino sulfonates.[228] The synchronous nature of the reaction was confirmed by Grob, as illustrated by the elimination of the tosylate leaving group in **267** to give **268**.[227] The 5β-isomer (**267**) undergoes elimination to the (*E*)-isomer (**268**) whereas the 5α-isomer gave the (*Z*)-isomer. These stereochemical results are best explained if the pertinent orbitals are antiparallel in the transition state leading to the elimination. The reaction rates for both of these substrates are rather high but it was observed



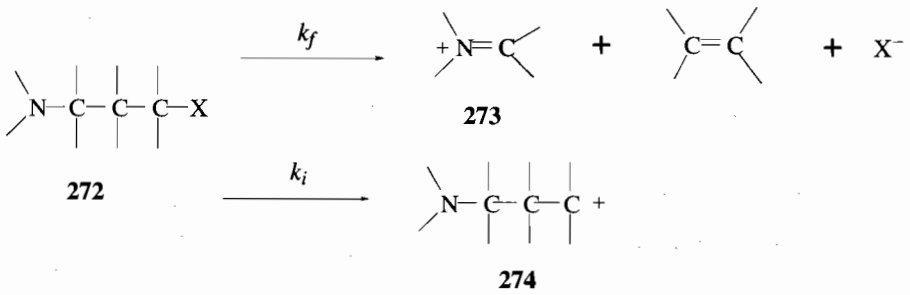
267 **268**



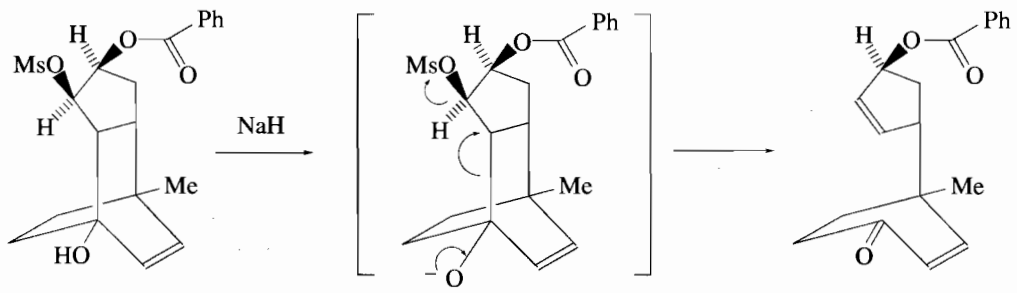
269 **270** **271**

that the 5α-isomer (**269**) reacted much slower and gave a mixture of the substitution product (**270**) in addition to the elimination product (**271**). This latter result indicates that the usual S_N2 reaction expected with a tosylate and a nucleophile such as hydroxide will occur unless the rate of the synchronous elimination is fast. Although the reaction was discovered by Prelog, Grob's contributions to this reaction led to its bearing his name, the **Grob fragmentation**.

Both ionization and elimination processes are possible in these systems as illustrated by generic structure **272**, which gives the elimination products (iminium ion **273** and the alkene) with a rate constant k_f and the ionization product to **274**, with a rate of k_i. This latter pathway leads to substitution. The synchronous fragmentation can occur only if the k_f of this process is comparable with or greater than the rate of ionization

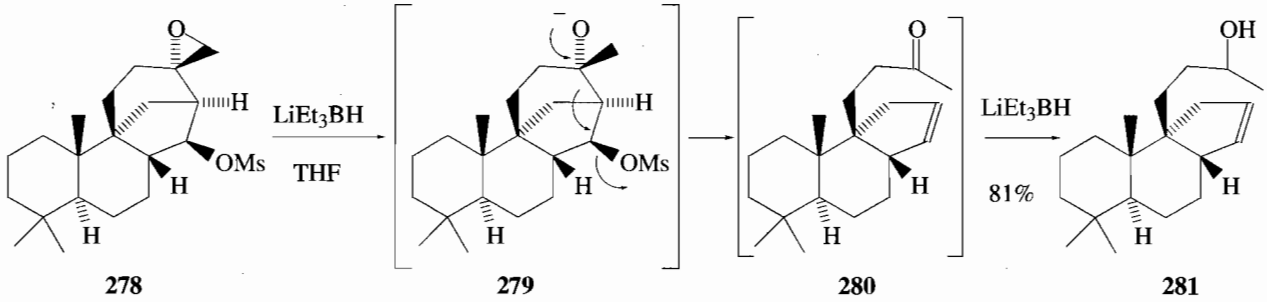


k_i for the γ-amino carbon ($k_f \geq k_i$).[228] If the stereochemical requirements are satisfied, k_f is the dominate term. This increase in reactivity due to synchronous fragmentation is referred to as the **frangomeric effect**, and expressed by $f = k_f / k_i$. This effect is not limited to amines or carbocations derived from alkyl halides and ether salts. Suitable derivatives of 1,3-diols also undergo this fragmentation.[229] When an alkoxide moiety has the proper orientation relative to a leaving group, as in **276** (generated from the alcohol **275**), the synchronous 1,3-fragmentation leads to an alkenyl ketone (**277**), which was used by Still in a synthesis of trichodermol.[230]



The alkoxide required to initiate Grob fragmentations can be generated in several ways. Direct acid–base reaction with an alcohol to form the alkoxide is only one way. Carbanion addition to a carbonyl followed by a Grob fragmentation was used in Magnus' synthesis of hinesol.[231] Yet another synthetic variation for the Grob fragmentation is apparent in White's synthesis of 2-desoxystemodinone,[232] where reduction of an epoxide unit in **278** with lithium triethylborohydride led to alkoxide **279**, and Grob fragmentation gave **280**. Under the reaction conditions, the ketone unit in **280** was reduced by the hydride (see sec 4.5.B) and this gave the final

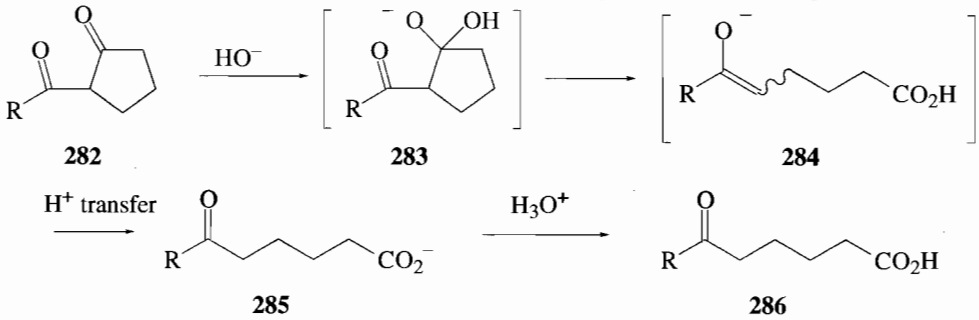
product (alcohol **281**) in an overall yield of 81%. A radical-induced Grob-type fragmentation has also been reported in connection with the synthesis of terpenoids.[233]



278 **279** **280** **281**

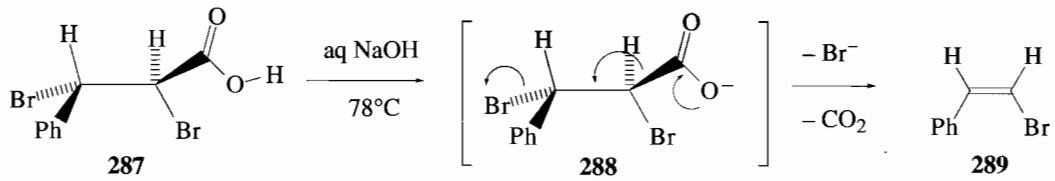
2.9.F. Other 1,3-Elimination Reactions

A number of 1,3-elimination processes other than those described above have been observed. Treatment of diketone **282** with hydroxide initially formed **283**, but the ring opened to give the enolate anion (**284**). Proton transfer gave **285** and hydrolysis led to keto-acid **286**.[234] This particular fragmentation relied on an equilibrium that favored the resonance stabilized enolate anion, and a proton transfer to give the keto-carboxylate.



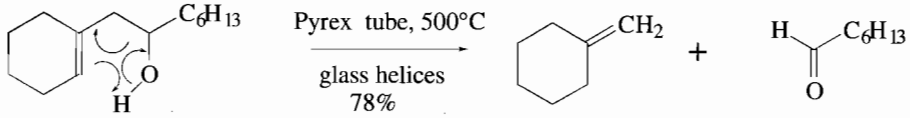
282 **283** **284** **285** **286**

Elimination of carbon dioxide (CO_2) has been observed with β-halo carboxylates. Fragmentation of the carboxylate anion of β-halo acrylic acids (see **288**) can lead to alkenes, as in the conversion of cinnamic acid



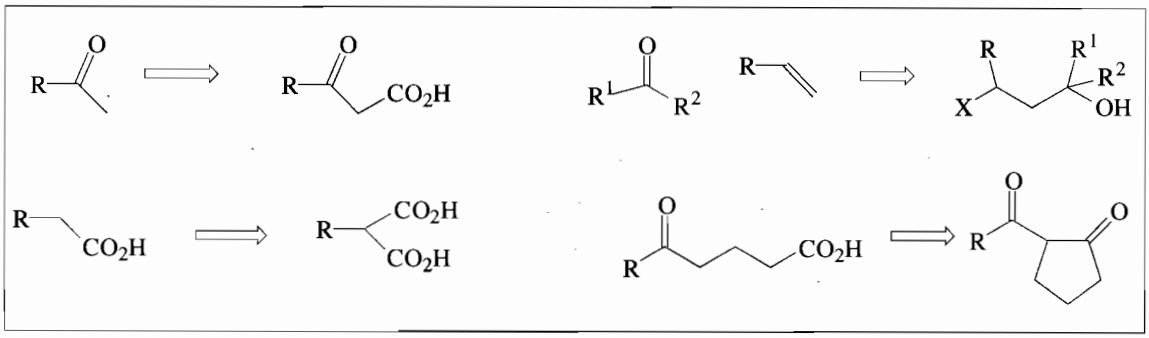
287 **288** **289**

dibromide (**287**) to **289**.[235] In this case, the carboxylate anion displaced the bromide on the β-carbon. In some cases, homoallylic alcohols can eliminate an aldehyde moiety. An example is the pyrolysis of **290** at 500°C to give methylenecyclohexane (**291**) along with the aldehyde heptanal. This fragmentation occurs via the six-center transition state indicated in **290**,[236] although it could be described as a retro-ene reaction.



290 **291**

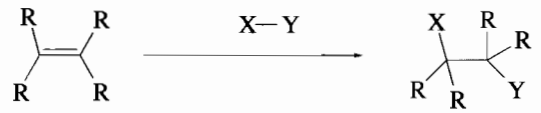
This section has described several synthetically important 1,2- and 1,3-elimination processes. In both cases, substitution can be a competitive reaction, but proper choice of reaction conditions will maximize formation of the elimination products. Several interesting disconnections that are possible with substrates capable of undergoing 1,2- and 1,3-eliminations are shown.



10. ADDITION REACTIONS

Acids and bases have figured prominently in all of the sections of this chapter. The concept of an alkene functioning as a base has also been explored. In this section, the π bond of an alkene or an alkyne will be used as a base, both with protonic acids, Lewis acids, and with other electrophilic centers. When an alkene donates an electron pair (acts as a base) to a proton, the π bond breaks and forms a new C—H bond to one carbon of the old C=C unit. The other carbon of that unit becomes an electron deficient center (a carbocation), which reacts further, usually by substitution or elimination. When the alkene donates the electrons to a Lewis acid, the resulting complex will react to give other products. In all cases, recognizing the Lewis basicity of alkenes and alkynes will help explain the addition reactions discussed in this section.

The elimination reactions presented in Section 2.9 are important in synthesis and usually involve conversion of an alcohol or alkyl halide to an alkene or alkyne. There are many functional group interchange reactions that involve the reverse transformation: an alkene or alkyne being converted to an alkyl halide, an alcohol or another functional group. If two new atoms or groups are transferred, or added, to the π bond during this process, the reaction is called an **addition reaction**.[237] The general reaction for addition of a reagent to an alkene is shown for the conversion of **292** to **293**, in which the electrons of the π-bond are used to form a new σ bond. Formation of a second sigma bond between Y and the other carbon of the former π-bond completes the addition of X—Y, generating two sp^3 hybridized centers from the sp^2 hybridized centers.



292 **293**

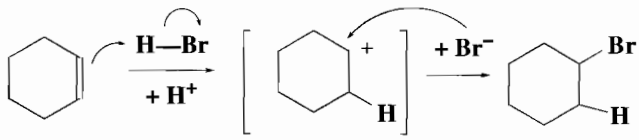
This addition process encompasses many reaction types, but for synthetic planning, it is convenient to classify addition reactions into four mechanistic categories:

1. Those involving free and metal stabilized ions as intermediates.
2. Those involving symmetrically bridged ions as intermediates.
3. Addition via a four-center transition state.
4. Nucleophilic acyl addition, discussed previously in sec. 2.5.

Nucleophilic acyl addition was discussed in sec. 2.5. The main examples of four-center transition state additions are hydroboration, which will be discussed in chapter 5, and hydride reduction of carbonyls, which will be discussed in section 4.2-4.5. This section will focus on categories 1 and 2.

2.10.A. Addition That Generates Carbocation Intermediates

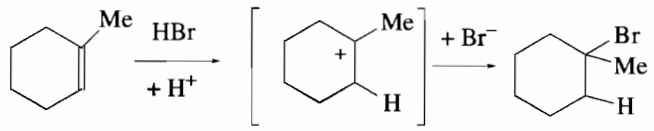
This type of reaction begins when a π bond of an alkene donates an electron pair to an acid (H^+)—an acid–base reaction where the alkene is a weak base. The π bond is broken as the new Br—H bond is formed, and the remaining carbon of the former double bond becomes a carbocation. The reaction of cyclohexene with acid to form secondary cation **294** illustrates this process. The cationic center then reacts with the nucleophilic gegenion (Br^- from HBr) to produce bromocyclohexane. The latter portion of this sequence is analogous to the second step (coupling) of an S_N1 reaction. The initial reaction usually involves formation of a solvent separated carbocation intermediate, but this depends on the solvent. A tight ion pair intermediate can react in the substitution step to give the same product. The net result of this cationic reaction is addition of H and Br across the π bond.



294

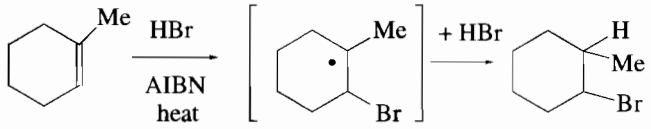
Alkenes are rather weak bases and will react only with strong acids. This limits the reaction to strong acids HX (such as HCl, HBr, H_2SO_4, HNO_3, etc.), which react with alkenes to form an alkyl halide, sulfate, nitrate, and so on. Alkyl sulfates and nitrates are often unstable and undergo elimination reactions or decompose. In many cases, they cannot be formed at all. Secondary reactions after their formation (including elimination and ionization) usually make isolation of sulfates and nitrates very difficult. When $HClO_4$ or HBF_4 are used, ClO_4^- and BF_4^- are very weak nucleophiles and react slowly with the cation intermediate. In such a case, another nucleophile can be added that will react with the cation. If water is present (it may come from the use of an aqueous solvent), it will add to the carbocation intermediate to give an alcohol product. If a more nucleophilic reagent such as KCN is added to the reaction, a nitrile can be formed. From a synthetic viewpoint, this option greatly expands the utility of the reaction, allowing introduction of a nucleophilic unit (Y) that is not a part of the initial acid (HX). Since a carbocation is formed during the addition process, it is subject to the rearrangement problems inherent to such species (sec. 2.7.B.iii) with accompanying loss of stereoselectivity. This process is under thermodynamic control and tends to give the more stable ion and the more stable final product. Before the mechanistic nature of this reaction was understood, it was observed that reactions of alkenes and acids always produced the more substituted product, which is the so-called

Markovnikov addition,[238,239] of simple alkenes. In other words, addition of HCl, HBr, or HI to substituted alkenes will lead to an alkyl halide where the nucleophile is attached to the more substituted carbon of the π-bond. The basis of this regioselectivity is, of course, formation of the more stable carbocation, **295**, which is attacked by bromide ion to give 1-bromo-1-methylcyclohexane (**296**). This is the normal course of all reactions with acid and an alkene if the intermediate is a cation. In section 2.7.B.ii, the reaction of **100** with HCl is an example of this type of reaction.

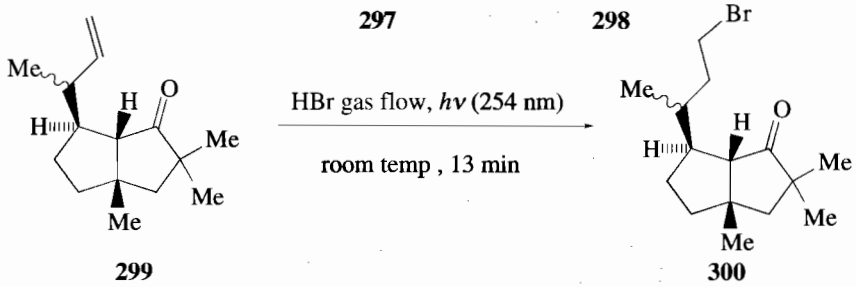


295 **296**

There is an alternative reaction pathway that is more-or-less specific for HBr and alkenes. This pathway gives the less substituted bromide, which immediately shows reaction cannot proceed by a cation intermediate, and it further work has shown that it proceeds by a radical intermediate. When an alkene reacts with HBr in the presence of a peroxide, the initial reaction is homolytic cleavage of the peroxide to give a radical (see the discussion of allylic halogenation with NBS and NCS in secs. 2.8.B, 13.3-13.7). This radical reacts with HBr to generate a bromine radical (Br•), which is attacked by the π-bond of methylcyclohexene to give a carbon radical (**297**).[239] The bromine atom rather than hydrogen adds first (hydrogen added first to form cation **295**) to produce the more stable tertiary radical. The tertiary radical is more stable than the secondary



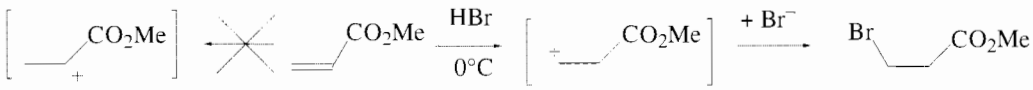
297 **298**



299 **300**

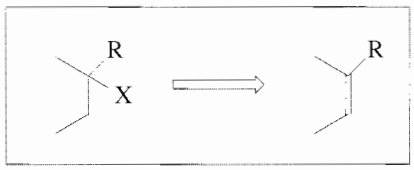
radical for essentially the same reasons as a tertiary cation is more stable than a secondary cation. This radical intermediate reacts with HBr to give the final product (1-bromo-2-methylcyclohexane, **298**) and generates a new bromine radical in a chain propagation step. The net result is addition of H and Br, but the bromine resides on the less substituted position of the double bond; this is referred to as anti-**Markovnikov addition.**[239] This reaction is limited to HBr, however, and reaction with alkenes requires initiation by exposure light or the presence of a peroxide or another radical initiator such as AIBN (see sec. 13.3).[238] Despite this limitation, the reaction can be quite useful in synthesis. Reaction of **299** with HBr under photolysis conditions, for example, gave a 73% yield of primary bromide **300** in Coates synthesis of cameroonanol.[240]

In a normal reaction of alkenes and acids such as HX, the key to predicting the regiochemistry is to identify the more stable cation (or radical) intermediate. There are cases when this is not always at the more substituted carbon. When HBr is added to the conjugated π bond of methyl acrylate, the resulting anti-Markovnikov addition appears to be anomalous, giving methyl 3-bromopropionate (**302**) as the final product.[241] The course of the reaction is predictable, however, by examination of the possible cation intermediates. Addition of H^+ to the π bond generates cation **301** as the precursor to **302**. Addition to give the alternative cation (**303**) would place the positive charge adjacent to a δ^+ carbon of the carbonyl, so that intermediate is destabilized and is not formed under these conditions. The greater stability of **301** relative to **303** suggests a preference for the observed product, **302**. In all cases, therefore, the carbocation mechanism for addition of acids such as HX to an alkene will result in the most stable carbocation and the most substituted product. These intermediate cations are, of course, subject to rearrangement as seen with S_N1 reactions in sec. 2.7.B.ii.



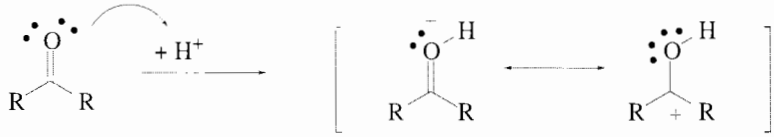
303 **301** **302**

The disconnection for carbocation addition with strong acids HX is:



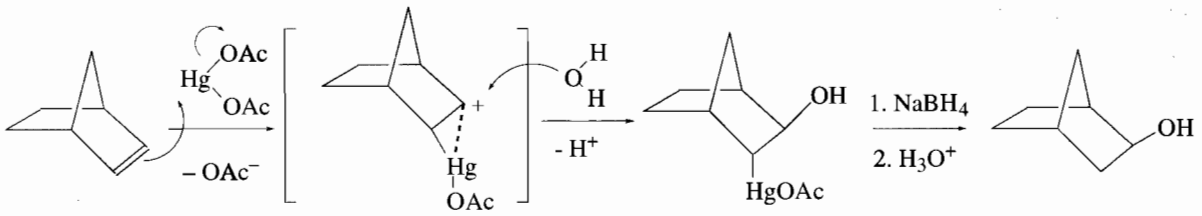
2.10.B Addition to Generate Metal-Stabilized Cations

As mentioned in previous sections, carbocation intermediates are subject to rearrangement to a more stable ion (sec. 2.7.B.iii). If the cation were stabilized in some manner, rearrangement would be much less likely, as when a heteroatom is attached to the electrophilic carbon. An example is the oxygen stabilized cation (**304**) generated by reaction of a ketone with an acid catalyst. The electrons on the heteroatom are donated to the positive center leading to resonance stabilization (this is called back donation). Such a cation is usually



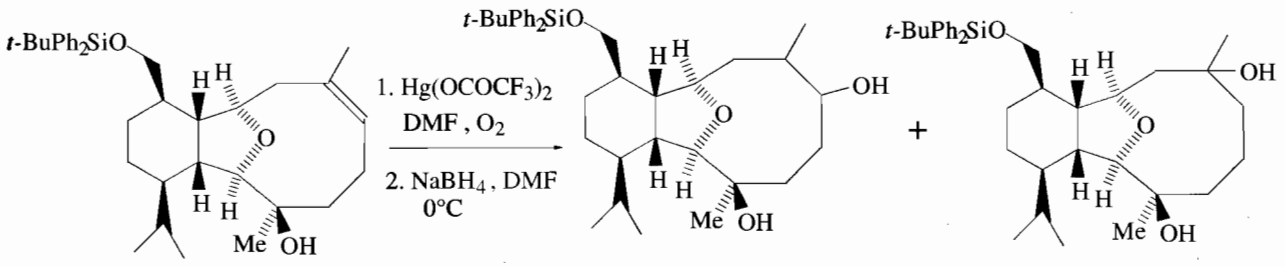
304

more stable than the secondary or tertiary cations that might form after a rearrangement that does not have the stabilization provided by the heteroatom. In this case, the rearrangement does not occur. Some Lewis acids, such as the mercuric ion, interact with a cation in a similar manner, generating a bridge-like intermediate in which the carbocation is stabilized by the back-donation from the metal atom. This type of intermediate is observed in the reaction of norbornene (**305**) and mercuric acetate [$Hg(OAc)_2$] to give the mercury-stabilized cation **306**. This cation does not undergo the norbornyl rearrangement (sec. 12.2.B) which is very facile, and

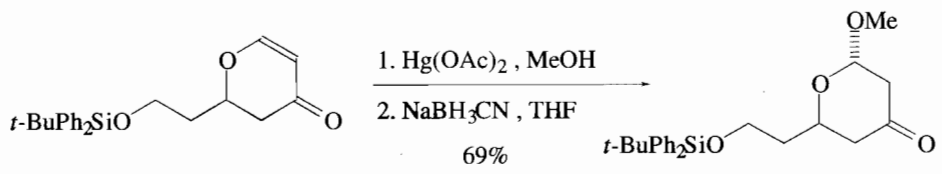


305 **306** **307** **308**

the observation illustrates the additional stabilization imparted by the mercury. Indeed, cations stabilized by mercury in these reactions are remarkably free of the rearrangements that plague other cationic reactions,[242] This cation behaves like any other cation in terms of its substitution reactions, however, reacting with water, which is in the reaction medium, to give mercuric alcohol **307**. In this sequence, reduction of the Hg (II) intermediate (**307**) with sodium borohydride is required to remove the mercury by hydrogenolysis (sec. 4.4.A and 4.8.E) and give the final alcohol product, **308**.[243] This overall process is known as **oxymercuration-demercuration**.[244] This reaction also proceeds with high regioselectivity for the product with the hydroxyl at the more substituted position (the norbornyl structure also leads to formation of >99% exo alcohol in **273**), as with any other cation. Such reactions are not regiospecific, however, and in some cases significant amounts of isomeric alcohols are produced. The reaction is stereoselective but it is not stereospecific. When **309** was treated with mercuric bis-(trifluoroacetate) (the less nucleophilic trifluoroacetate ion is less prone to competitive substitution reactions) in the presence of molecular oxygen it gave a mixture of 54% of **310** and 18% of **311** after reduction with sodium borohydride.[245] In addition, **310** was isolated as a 3:7 mixture of α:β diastereomers. Paquette et al. then converted the β isomer to the structure reported for sclerophytin A.[245]



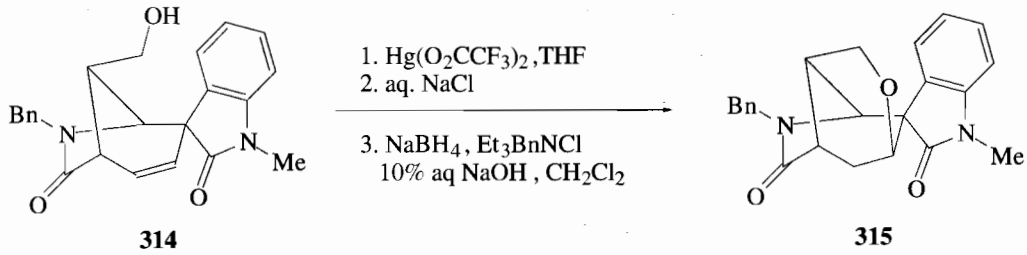
309 **310** **311**



312 **313**

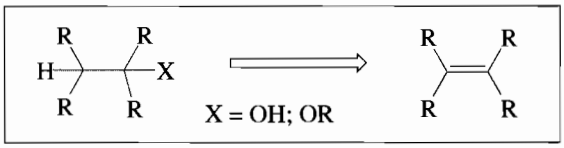
The use of an alcohol rather than water as the nucleophilic solvent will lead to formation of an ether, and is a simple variation of oxymercuration.[243,246] In Donaldson's synthesis of the C3–C15 segment of phorboxazole, pyrone **312** was treated with mercuric acetate in methanol.[247] Subsequent reduction with sodium cyanoborohydride (sec. 4.5.D) gave a 69% yield of **313** with high selectivity. The intramolecular

variation of this reaction is quite useful, as illustrated by Hiemstra's conversion of **314** to **315** in 88% yield as part of a synthesis of ent-gelsedine.[248]



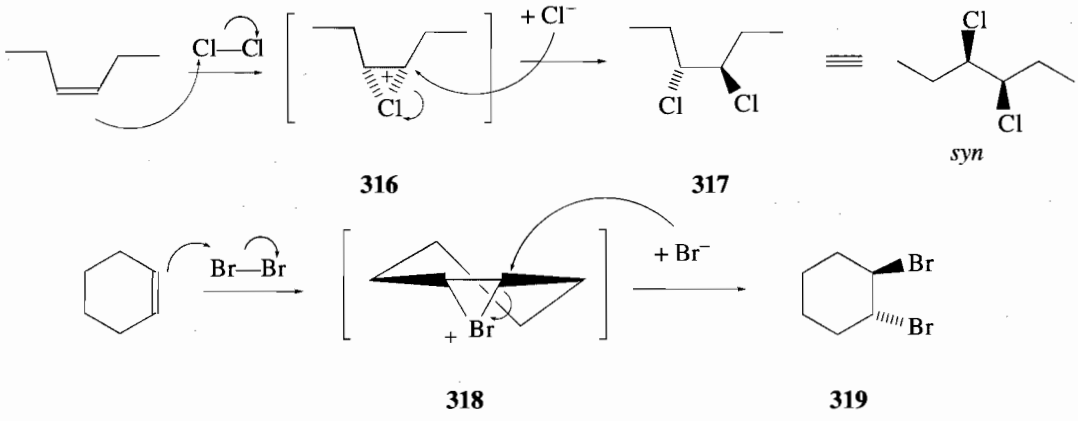
314 **315**

The functional group transform for this reaction type is shown.



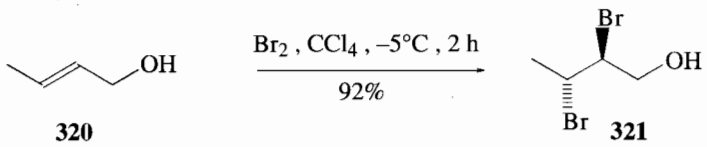
2.10.C. Addition Involving Symmetrically Bridged Cationic Intermediates

In reactions with HX, alkenes behave more or less as Brønsted–Lowry bases. Alkenes can also function as Lewis bases in reactions with electrophilic halogens. Symmetrical reagents such as bromine or chlorine are not usually polarized, but when they are brought into proximity with a π bond, a dipole is induced in the X—X bond [C=C→X⁺X⁻]. This type of structure is sometimes called a charge transfer complex. It is important to note that this occurs only with reagents such as diatomic chlorine, bromine, or iodine that are polarizable. Molecules that are not polarizable, such as diatomic hydrogen , do not react in this way, and actually require



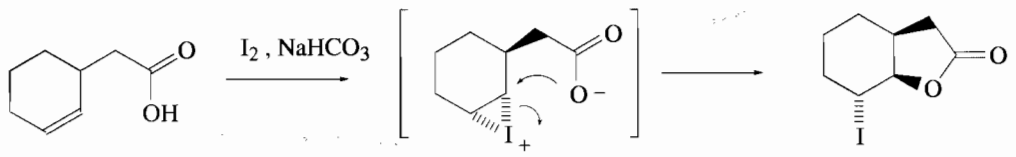
the presence of a transition metal to first break the H—H bond before it can react. With polarizable species, the positively polarized halogen can function as a Lewis acid in reactions with an alkene, which donates electrons to X^+, displacing X^-. The cationic center generated by this reaction is adjacent to the newly formed C—X bond. Since the X group contains unshared electrons, they can be back donated to the cation center, forming a symmetrically bridged (three membered ring) intermediate. This is *not* a stepwise process. The three-mem-bered ring intermediate is formed directly and is called a **halonium ion** (chloronium, bromonium

or iodonium). Subsequent S_N2 type attack by the X^- gegenion (i.e., backside attack) gives the final addition product. The experimentally observed trans (anti) relationship of the two halogen atoms in the addition product means there must be an anti-relationship between X^+ and X^- in the transition state. Anti-addition of X^- (backside attack) is required to minimize electronic repulsion between the X in the halonium ion and the nucleophilic X^- group. The stereochemistry of groups attached to the C=C unit in the alkene starting material is maintained in the diastereospecific ring opening, and overall addition of X_2 is diastereospecific. Addition of chlorine to *cis*-3-hexene generates **316** and displacement by chloride gives the product, **317**. Similarly, addition of bromine to cyclohexene gives **318** as an intermediate and anti-attack by bromide leads to **319**. Anti attack gives the trans product in **319** where the cyclic nature of the product makes the trans relationship easy to see. This trans addition is difficult to see in **317**, the product formed by adding chlorine to *cis*-3-hexene. When a stereochemically pure alkene (such as *cis*-3-hexene) is used, the stereochemical positions of the ethyl groups and the incoming chlorides are fixed in the anti-transition state and, therefore, in the final product. The addition is stereospecific. The trans addition of the chlorines is shown in the dichloride product **307**, and if this product is redrawn in the extended conformation used by Masamune et al.[249] (sec. 1.4.B), the stereochemical relationship of the two chlorines is anti, as shown. If this reaction proceeded via a planar free ion, such facial specificity would not be expected. A typical synthetic application of this reaction is reaction of *trans*-crotyl alcohol (**320**) with bromine in carbon tetrachloride at –5°C to give **321** in 92% yield.[250] This transformation was used to prepare the C14-C20 fragment in Lee's synthesis of amphidinolide B1.[250]



320 **321**

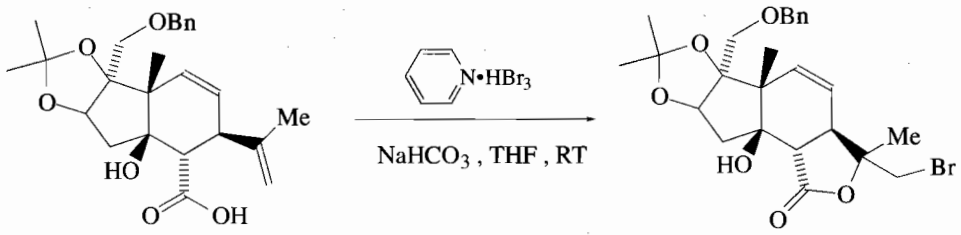
The diastereoselectivity that arises from the intermediacy of a halonium ion has been exploited in a new type of reaction that produces lactone products. When **322** was treated with iodine and sodium bicarbonate, the initially formed iodonium ion (**322**) was opened by the carboxylate anion, generated by the reaction of bicarbonate with the acid moiety.[16] Backside displacement of the iodonium ion led to the trans-relationship between the lactone ring and the iodide moiety in iodolactone **324**. This reaction is commonly referred to as **iodolactonization**.[251] This reaction can be extended to include bromolactonization and chlorolactonization.



322 **323** **324**

The use of liquid bromine or gaseous chlorine can be problematic, however. A modification that avoids the problems of liquid bromine is shown in Trost's synthesis of picrotoxinin,[252] in which **325** was treated with pyridinium bromide perbromide, in THF, to give bromolactone **326** in 85% yield.

Another addition reaction involves reaction of alkenes with aqueous solutions of bromine or chlorine rather than the anhydrous conditions noted above. The reaction can proceed by formation of a cation under aqueous

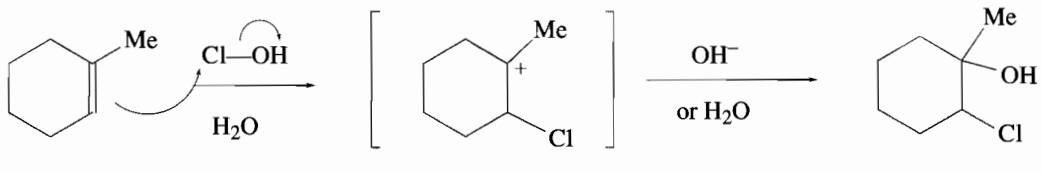


325 **326**

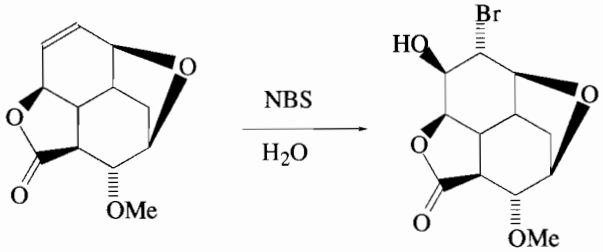
conditions, but it is complicated by the fact that dissolution of chlorine or bromine in water results in formation of a hypohalous acid (XOH, X = Cl, Br), represented by the reaction:

$$X_2 + HOH \longrightarrow XOH = X^+OH^-$$

When pure XOH (ClOH or BrOH) is used in an aprotic medium, the X^+ portion of this reagent is electrophilic and reacts with an alkene to generate the same halonium ion observed with bromine and chlorine additions. The OH^- gegenion is the nucleophilic partner and opens the halonium ion to produce a halohydrin, completely analogous to the reactions of bromine or chlorine. It is more typical for these reagents to be used in water, however, and the initially formed halohydrin will exist primarily as the ring–opened cation, and the hydroxide nucleophile would then attack the cationic center and be incorporated at the more substituted position.[253] Indeed, with relatively simple systems, reactions of alkenes with aqueous chlorine or bromine usually gives the halohydrin with the hydroxyl at the *more* substituted position.[251,253] When methylcyclohexene reacts with HOCl in water, the chloronium ion opens to give the tertiary cation **327**. Reaction with water (or hydroxide) leads to the usual Markovnikov product, in this case chlorohydrin (**328**).



327 **328**

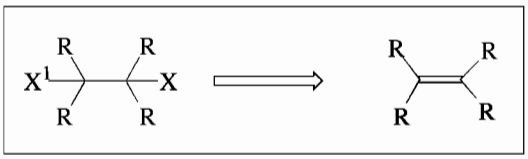


329 **330**

Reaction of NBS or NCS with a minimal amount of H_2O in DMSO is a convenient method for the preparation of HOBr or HOCl, respectively.[254] Subsequent reaction with an alkene leads to a chlorohydrin or

a bromohydrin. The reaction is usually selective for the trans product, and this suggests the presence of the halonium ion intermediate. This reaction is one that can be mechanistically ambiguous in some cases since the outcome depends on the solvent, the nature of the substrate, and the concentration of the reagents. An synthetic illustration of this reaction is addition of hypobromous acid (formed in aqueous solution with NBS to **329**. This reaction generated a single product (**330**) with the trans-geometry shown, an intermediate in Woodward's synthesis of reserpine.[255]

These reactions give the retrosynthetically useful transform:



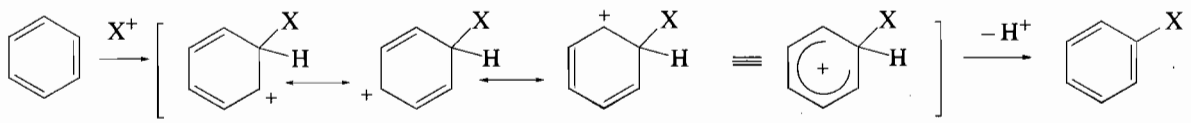
$X = X^1 = Br, Cl, I$ or $X = Br, Cl, I$; $X^1 = OH$

2.11. AROMATIC SUBSTITUTION

In many ways, the principles of substitution, elimination, and addition converge in aromatic systems in what is generically called aromatic substitution.[256] Addition to electrophilic centers, substitution of carbocations, nucleophilic displacement, and elimination of leaving groups are all mechanistic features of various aromatic substitution reactions.

2.11.A. Defining Aromatic Substitution

The substitution reactions discussed in previous sections occurred at a sp^3 hybridized carbon. Addition reactions, however, occurred at sp^2 hybridized carbons in the presence of acids. When the atom being replaced in a substitution is an hydrogen or halogen attached to an aromatic ring, the mechanistic explanations given for substitution at aliphatic carbon are unsatisfactory. The unimolecular S_N1 process described for aliphatic carbon compounds is not very attractive for these stated substitutions because it would require formation of an unstable and high energy aryl cation (the positive charge would reside on a sp^2 carbon atom). A more useful approach is to invoke a mechanism seen in addition reactions where one of the π bonds of the aromatic ring behaves as a Lewis base, in the presence of a suitable Lewis acid, to produce a cationic intermediate that can then react with an appropriate nucleophile. This will effect the Ar—C—H → Ar—C—Nuc transformation.

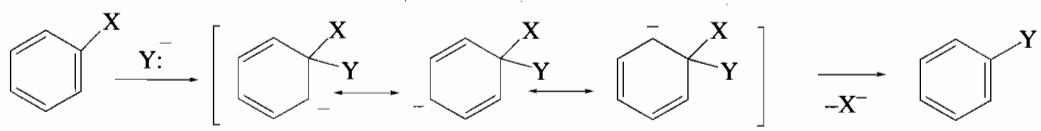


331 **332** **333**

For this process to occur, benzene must act as a base, but benzene does *not* react with HCl or HBr when they are mixed together so it is clear that it is too weak a base for even these strong acids. A way to solve this problem is to generate a formal cation (X^+) where benzene might be a strong enough Lewis base to react, forming a new C—X bond as the aromatic ring is disrupted. This is shown for the reaction of benzene with an

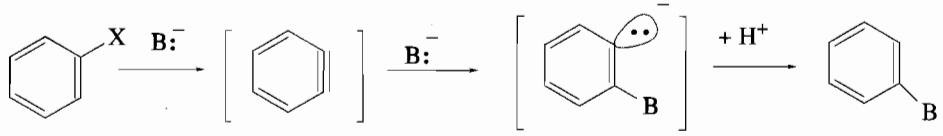
electrophilic species (X^+) where the new cation (**331**) is resonance stabilized (as shown). Loss of a proton to form **333** will be very rapid because the stable aromatic ring will be regenerated. The intermediate cation **331** is sometimes referred to as a benzenonium ion,[257] but old terminology called a **Wheland intermediate**. especially when drawn as the delocalized cation **332**.[258] Clearly, this is a viable process or we will not discuss it. The electrophilic species (X^+) has replaced an aromatic hydrogen via an electrophilic process. This reaction is termed electrophilic aromatic substitution[259] but involves an initial addition reaction followed by an elimination (of H^+) to complete the process.

For alkenes, nucleophilic attack at a sp^2 carbon is quite difficult because in contrast to a carbonyl carbon it is not polarized. Nucleophilic attack on unsubstituted benzene rings is also very difficult, but if a good leaving group is attached to one of the sp^2 carbons, the reaction is possible although reaction conditions can be harsh. Nucleophilic attack on an aryl halide (**333**) by reaction with a nucleophile (Y^-) would produce a resonance stabilized anion (**334**) as an intermediate. The transition state for the formation of **335** is high in energy and it is formed only with vigorous reaction conditions (high temperatures, high pressures, long reaction times). If the intermediate is stabilized by groups that can disperse the charge by resonance, such as nitro groups, the reaction is much easier and reaction conditions are much milder. Elimination of X^- then gives the final substitution product, **335**. The intermediate carbanion **334** results from nucleophilic attack on an aromatic ring and the overall reaction is called **nucleophilic aromatic substitution**. The actual sequence involves initial nucleophilic attack followed by an elimination reaction from the intermediate.



333 **334** **335**

When an unactivated aryl halide (**333**) is treated with a very strong base, an elimination reaction is possible that generates an intermediate called a benzyne (**336**). Benzyne is electron deficient and will be attacked by nucleophiles in a reaction that opens the π bond not part of the aromatic cloud, and produces a new carbanion (**337**). Protonation completes the sequence to give the aromatic substitution product **338**.

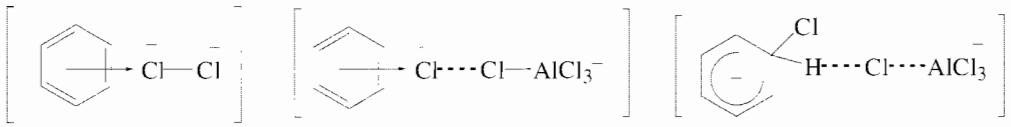


333 **336** **337** **338**

Section 2.11.B will deal with the most fundamental aromatic substitution reactions. This subject is usually presented in detail in undergraduate textbooks. The treatment varies greatly with the text, however, and leading references are usually absent. This discussion is intended only as a brief review.

2.11.B. Electrophilic Aromatic Substitution

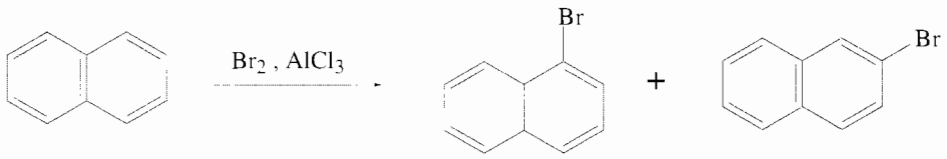
The π bonds in benzene are poor electron donors because, in part, this would disrupt the stable aromatic sextet. This means that benzene is a weak base and addition of an electrophilic species such as HCl gives no reaction, as mentioned above. Although benzene can form a weak charge transfer complex with chlorine (see **339**), mixing benzene and chlorine does *not* give a reaction. When a strong Lewis acid such as $AlCl_3$ is added, however, a charge transfer complex such as **340** is formed *between the Lewis acid and chlorine rather than with benzene*. In this complex, the chlorine–chlorine bond is weakened sufficiently so that it can be attacked by benzene, transferring one chlorine to benzene (with disruption of the aromatic system) and transfer of the other chlorine to $AlCl_3$ (see **341**). The stronger the Lewis acid (see sec. 2.3) the faster will be the reaction between halogen and benzene. The result is formation of a Wheland intermediate, which loses a proton to give chlorobenzene.[260] Reaction of chlorine with the Lewis acid transformed the poorly reactive diatomic chlorine into a highly reactive electrophile that reacts with benzene to give a substitution reaction. It is important to note that the charge–transfer complex mechanism may not be valid for chlorination of alkyl benzenes and is solvent dependent.[260a]



339 **340** **341**

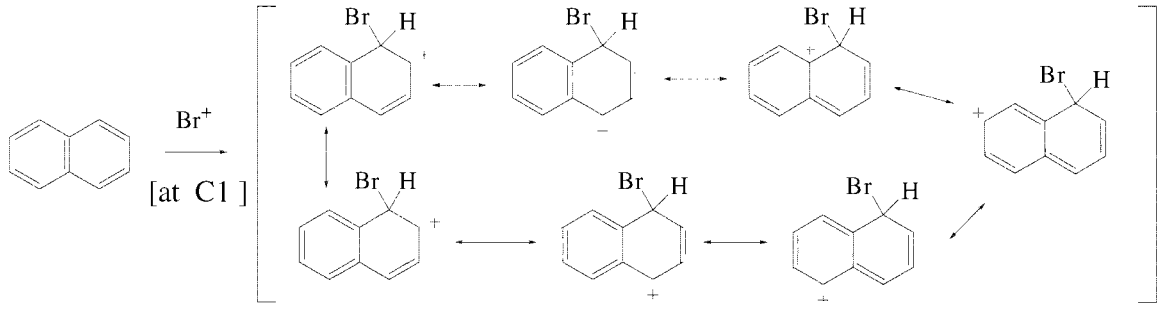
Two charge–transfer complexes are formed during the course of this reaction.[261] The first will be **340** and the second (**341**) is generated during loss of the proton in the aromatization process. In the chlorination reaction, the rate–determining step (the slowest) is conversion of the charge transfer complex to the Wheland complex (**340** → complex).[259] Formation of **340**, conversion of the Wheland complex to **341,** and elimination of the proton are all fast processes.

Bromine reacts in a manner identical to chlorine,[262,260b] producing Br^+ as a reactive intermediate (in the charge–transfer complex). Reaction of bromine, benzene, and aluminum chloride, therefore, generates bromo-benzene. Typical Lewis acid catalysts for this reaction are iodine, $AlCl_3$, $SbCl_3$, PCl_3, PCl_5, and $SnCl_4$.[263] When benzene is treated with a mixture of nitric and sulfuric acids, nitrobenzene is the product,[264] via a nitronium ion (NO_2^+).[265] Benzene also reacts with sulfuric acid [or sulfuric acid saturated with sulfur trioxide (SO_3), which is known as fuming sulfuric] to give benzenesulfonic acid.[266] Benzenesulfonic acid is also formed by reaction of benzene with chlorosulfonic acid ($ClSO_3H$)[267] or fluorosulfonic acid (FSO_3H).[268]



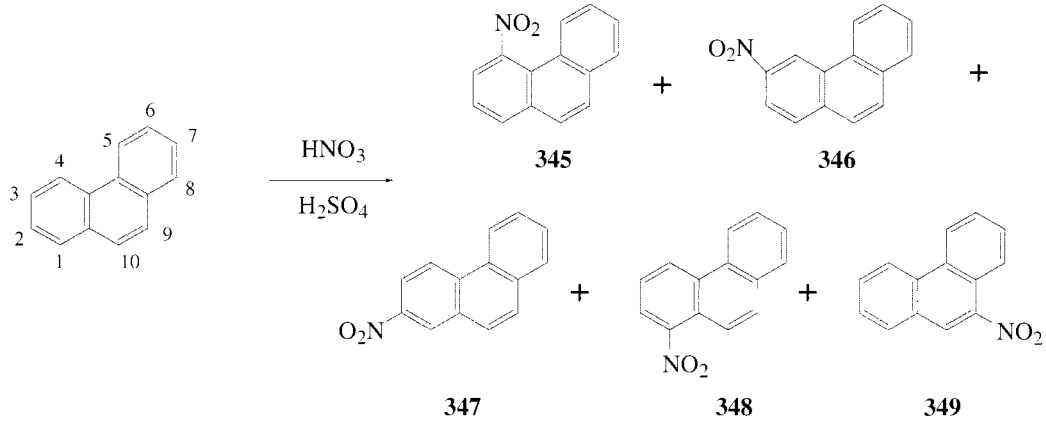
342 **343**

It is also possible to use these reagents for electrophilic aromatic substitution with aromatic derivatives other than benzene. Naphthalene, for example, reacts with a mixture of bromine and aluminum chloride to give 99% of 1-bromonapthalene (**342**) with only 1% of 2-bromonapthalene (**343**). Substitution at the 1-position of naphthalene is greatly preferred,[269] and this can be explained by examining the reactive intermediate. Reac-tion of naphthalene and Br^+ at the C1-position generates the resonance stabilized Wheland type intermediate. There are a total of seven resonance structures (see **344**) and an important feature is the presence of a fully aromatic (intact benzene ring) structure in four of those resonance intermediates. Similar analysis of the intermediates for attack at C2 reveals there are six structures, but only two of them have fully aromatic rings. This simple analysis predicts **344** to be more stable than the intermediate resulting from attack at C2 and the experimentally major product from bromination of naphthalene is **342** in a 99:1 ratio (**342/343**).



344

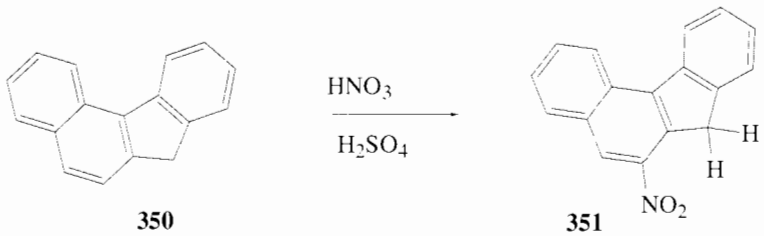
If the cationic intermediates for a substitution are close in energy, little selectivity is expected and a mixture of products is predicted. An illustration is the nitration reaction of phenanthrene, which gave five products: **345** (6%), **346** (23%), **347** (7%), **348** (27%) and **349** (37%).[270] Although substitution at C9 is preferred, a complex mixture is obtained that may be very difficult to separate. Substitution at several positions is a common occurrence for substitution reactions of polycyclic aromatic derivatives, although the product distribution is usually influenced by the nature of the catalyst and by the reaction conditions that are used.



345 **346** **347** **348** **349**

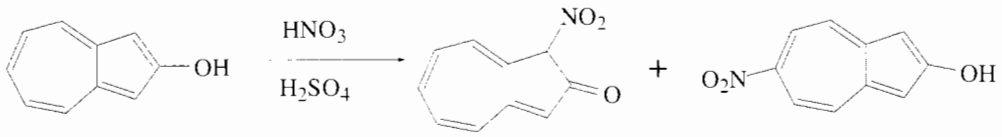
Despite the many products produced in the previous example, electrophilic substitution of complex aromatic molecules can proceed with great selectivity. An example is the nitration of benzo[*c*]fluorene (**350**), which

gave a good yield of the 5-nitro derivative (**351**).[271] Another example is the nitration of 2-hydroxyazulene (**352**), which gave a mixture of 1-nitroazulen-2-one (**353**) and 6-nitro-2-hydroxyazulene (**354**).[272]



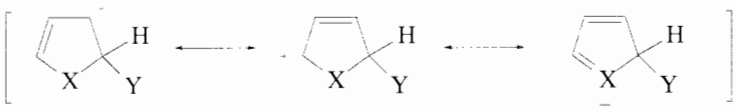
350 **351**

Heterocyclic aromatic derivatives also undergo electrophilic aromatic substitution reactions. Pyrrole, for example, reacts with nitric acid in acetic anhydride, at 0°C, to give 50% of 2-nitropyrrole and 15% of 3-nitropyrrole. Pyrrole is more reactive in these reactions when compared to benzene, and the mild reaction conditions described are sufficient. One caution is that the products may decompose with prolonged exposure to a powerful Lewis acid. The preference for substitution at C2 in pyrrole is seen in other five-membered ring



352 **353** **354**

heterocycles such as furan and thiophene. This preference can be explained by the relative stability of the cationic intermediates, just as in substitution reactions with benzene derivatives. Inspection of the cation resulting from attack at C2 (**355**) shows that the lone pair electrons on the heteroatom participates in resonance delocalization, giving a total of three resonance structures. Since attack at C3 (see **356**) will lead to only two structures, attack at C2 is preferred. If there are substituents at C2 and C5, however, attack will occur at C3. Pyrrole, with the more basic nitrogen, should be better able to stabilize the cationic intermediate than furan or thiophene, and is expected to be more reactive than either of them.



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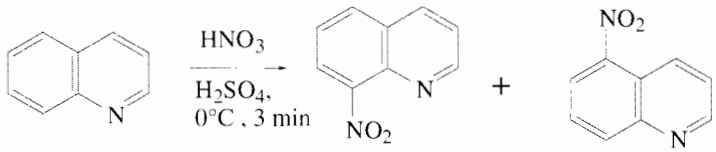
356

Pyridine, unlike five-membered ring heterocycles, undergoes substitution with difficulty and at the C3 position, as illustrated by its reaction with mercuric sulfate ($HgSO_4$) and H_2SO_4 (at 220°C) to give pyridine 3-sulfonic acid. Pyridine, in contrast to pyrrole, is rather unreactive as can be seen by the vigorous conditions that are required for the reaction. The same arguments for C2 substitution in five-membered rings apply the

preference for C3 substitution in six-membered ring heterocycles. Reaction of the electrophile at C3 generates a more stable cationic intermediate.

Other heterocyclic ring systems react with the reagents in this section, including bicyclic and tricyclic compounds. In some cases, one aromatic ring contains a heteroatom while the other does not, as in quinoline or isoquinoline. The aromatic ring in quinoline (**357**) that does not contain nitrogen undergoes electrophilic aromatic substitution preferentially. It is known that pyridine is less reactive than benzene, so it is reasonable that the pyridine portion of quinoline should also be less reactive than the benzene portion. The two pro-ducts of this reaction (HNO_3, H_2SO_4, 0°C, 3 min.) are 8-nitroquinoline (**358**) and 5-nitroquinoline (**359**, the nitrogen is atom No. 1), formed in roughly equal amounts. The preference for attack at C5 and C8 is explained by the usual stability arguments for the cationic intermediates.



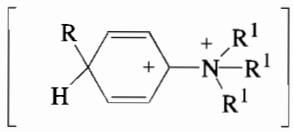
357 **358** **359**

The products arising from nitration of quinoline clearly show that one ring reacts faster than another, although the isomer distribution depends on reaction conditions. The deactivated pyridine ring in **357** lowers the rate of electrophilic substitution relative to the other aromatic ring. This general phenomenon can be applied to monocyclic heterocycles, polycyclic heterocycles, poly-cyclic aromatic hydrocarbons, and benzene derivatives. For quinoline, attack in the heterocyclic ring will place a positive charge *on* the nitrogen, which is very destabilizing. Quinoline shows a rather dramatic effect but such effects can be far more subtle.

360 **361** **362**

The presence of electron–withdrawing or electron–releasing groups on an aromatic ring will deactivate or activate that ring to electrophilic aromatic substitution, which suggests that the primary effect is inductive. It is also true that the inductive effect will be transmitted to or from the aromatic ring at the carbon bearing the substituent, the ***ipso*** carbon. When a substituent is electron rich (a negative charge or a δ- dipole attached to the ipso carbon) an electron releasing effect will occur in the cationic intermediate resulting from reaction with X^+. Obviously, inductive effects will occur in the neutral aromatic molecule, but this discussion will focus attention only on the reactive intermediates as a convenient method for predicting reactivity. If the substituent releases electrons (as in **360**) that substituent is said to have a positive inductive effect (+I) and it should stabilize the cation intermediate. A negative inductive effect (*–I*) occurs when the substituent at the ipso carbon is electron withdrawing (a positive charge or δ^+ dipole attached directly to the ipso carbon), as in **361**. An *–I* effect will remove more electron density from the cationic intermediate, further destabilizing it, and

aking its formation more difficult. A second factor has a profound influence on the course of electrophilic omatic substitution reactions. If the group at the ipso carbon is capable of dispersing the positive charge of e intermediate by resonance delocalization, that intermediate will be more stable. This resonance effect is ten called a mesomeric effect and labeled *+M* or *–M*. The OR group in **362** exhibits a +M effect since the ectrons on oxygen can be donated to the positive charge at the ipso carbon, which results in transferring the arge to oxygen, as shown, by resonance. It is reasonable to assume, therefore, that a substituent at the ipso rbon with unshared electrons (such as oxygen, sulfur, nitrogen, halogen) will have a *+M* effect and stabilize e cationic intermediate of electrophilic aromatic substitution. Conversely, a group bearing a positive charge r a partially positive dipole will not be able to delocalize a positive charge, and indeed, the two like charges on adjacent atoms will destabilize that intermediate by electronic repulsion, as in **363**. An intermediate such as **362** should be more easier to form and since formation of that cation is the rate determining step (see above), the substitution should be faster. Anisole, for example, is very reactive in electrophilic aromatic substitution, often not requiring a Lewis acid. Toluene, on the other hand, has a *+I* effect (see **364**) but no mesomeric effect. The substitution should be faster than for benzene (with no activating substituents) but slower than for anisole with both a *+I* and a *+M* effect (see **365**).



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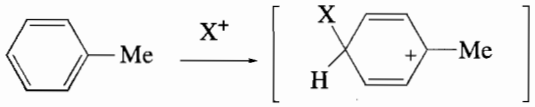

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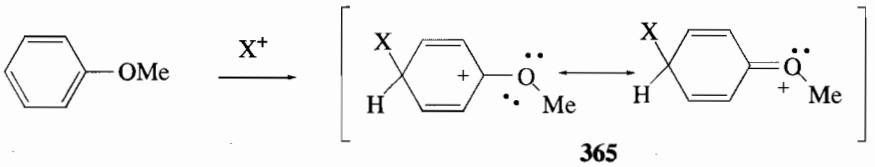

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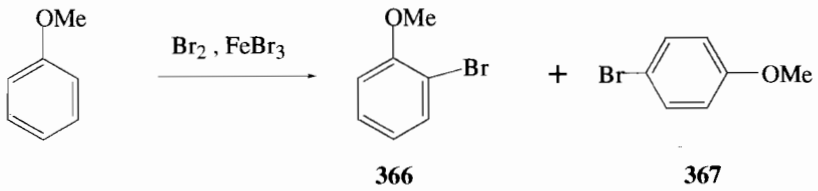
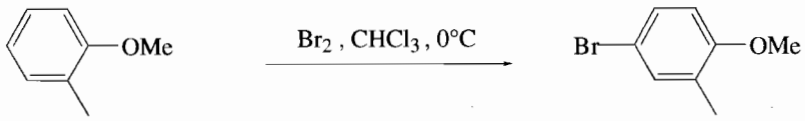
It is important to note that the *+M* effect observed with anisole occurs only with ortho and para substitution. In those cases the positive charge in the intermediate can be transferred to the ipso carbon and thereby to the oxygen. The presence of an extra resonance form is indicative of increased stability for those intermediates because delocalization occurs over more atoms. This greater stability means that the cation is formed with greater ease and electrophilic aromatic substitution is faster. Attack at the meta position generates a cation that cannot transfer the charge to the ipso carbon and no *+M* effect is available. For substituents such as OR, therefore, ortho/para substitution should be faster than meta substitution, and bromination of anisole will give, primarily, 2-bromoanisole (**366**) and 4-bromoanisole (**367**), in roughly equal amounts.

Those substituents with a *+I* effect or a *+I* and a *+M* effect increase the rate of electrophilic aromatic substitution relative to benzene and are said to be activating substituents.[273] Since ortho and para products should predominate with these activating groups, activators are also said to be ortho/para directors. When 2-methylanisole was treated with bromine in chloroform, for example, a 94% yield of **368** was obtained as part of Vyvan's synthesis of heliannuol D.[274] Note that the presence of two activating groups allowed the reaction to proceed without adding a Lewis acid, which is typical of very activated benzene derivatives.

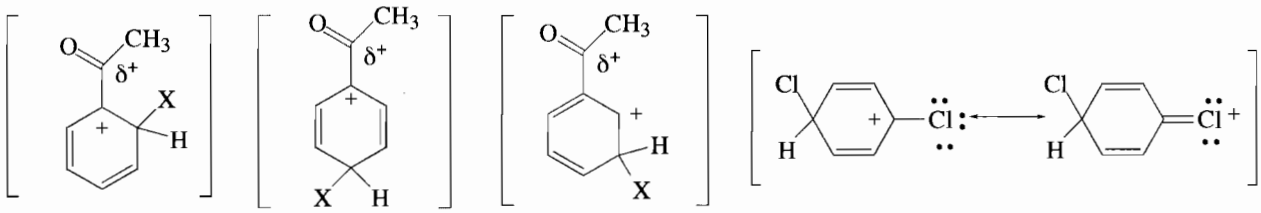


366 **367**



368

If a substituent has a *–I* effect or a *+I* effect, and a *+M* effect increases the rate of electrophilic aromatic substitution relative, to benzene, and that substituent is said to be deactivating.[273] This occurs when the substituent at the ipso carbon is electrophilic (SR_2, NO_2, CO_2R, SO_3R, NR_3, C=O or C≡N) and reaction with an aromatic ring would generate a reactive intermediate that places a positive charge adjacent to the electrophilic center. The key resonance structures for ortho, para and meta attack are shown in **369**, **370**, and **371**, atom (S, N, C, etc.). In **369** and **370,** a distinct *-I* effect is seen, as the positive charge of the intermediate resides on the ipso carbon, adjacent to the δ^+ dipole of the carbonyl. This interaction will destabilize these intermediates, making them more difficult to form in this rate-determining step and slowing the overall reaction. Attack in the meta position (see **371**) cannot put the positive charge at the *ipso* carbon. The two electrophilic centers are relatively close together and this is destabilizing, but less destabilizing than having the charges on adjacent atoms. Intermediate **371** is, therefore, less destabilized than **369** or **370** and will form faster in this particular reaction, leading to a predominance of the meta substitution product. Such groups are deactivating and meta-directors. Deactivating groups of this type slow the overall reaction relative to benzene and lead to meta products. This analysis leads to the correct observation that nitration of nitrobenzene gives primarily 1,3-dinitrobenzene. Analysis of many types of substituents led to Table 2.16,[275] which shows activating and deactivating groups, classified by their I and M effects. The table also shows if the substituent is an ortho/para or a meta director.



369 **370** **371** **372**

Halogenated benzenes show a deactivating effect similar to that for the deactivating groups listed, but give primarily ortho and para substitution products, as in the formation of 1,2-dichlorobenzene and 1,4-dichlorobenzene from the reaction of chlorobenzene with Cl_2 and $AlCl_3$. This is explained by the fact that chlorine has a *–I* effect (making it deactivating) but a *+M* effect, making it an ortho/para director. This mesomeric

effect is seen in **372** for para substitution. When the *I* and *M* effects are in conflict, as in chlorobenzene, the reaction is generally slower than if a pure *+I* and/or *+M* effect is possible.[273]

Table 2.16. Substituent Effects in Electrophilic Aromatic Substitution

Substituent Type	Effect	Directing Effect	Example
+I, +M	Activating	ortho/para	Alkyl groups, O^-
+I, -M	Activating	ortho/para	$SiMe_3$, CO_2^-
-I, +M	Activating	ortho/para	NMe_2, $NHCO_2Me$, OMe, Ph
-I, +M	Deactivating	ortho/para	Cl, Br, $CH{=}CHNO_2$
-I	Deactivating	meta	Me_3N^+
-I, -M	Deactivating	meta	NO_2, C≡N, COR

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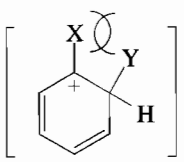
There are other effects that influence the rate of electrophilic aromatic substitution. Both steric hindrance and strain play a significant role.[276] When a substituent (X in **373**) is physically large, ortho substitution is inhibited due to significant steric hindrance in the transition state which, in principle, makes it more difficult for that intermediate to form. This effect is observed when X is an alkyl group (see Friedel-Crafts alkylation - sec. 12.4.B). Many of the groups encountered in this section have heteroatoms, and the steric effect is often less important because the X group can coordinate with the incoming group. This type of coordination (or chelation) effect is represented in **374** and the result is an increase in the amount of the ortho product. With the heteroatom substituents discussed in this section, this model is more important and the increase in ortho products at the expense of para products is called the **ortho effect**. Steric hindrance does play a significant role in substitution reactions of aromatic derivatives such as **375**, where the 1,3-relationship of the substituents makes approach along path c sterically difficult. Paths *a* and *b* are accessible and substitution of **375** will lead to products resulting from attack along paths *a* and *b*.



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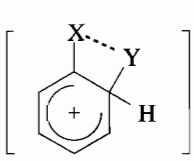

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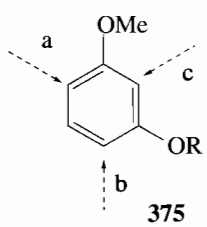
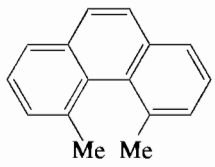


375

Strain arises in molecules when an aromatic ring is deformed out of planarity. This occurs in 4,5-dimethylphenanthrene (**376**), where the two methyl groups interact and the net result of this interaction is that the molecule is more reactive.[277] Strain also occurs in molecules such as β-hydroxyindane (**377**), which is brominated at the γ-position to give **378**.[277] The strain imparted by the five-membered ring makes the α-

position less susceptible to electrophilic aromatic substitution. Formation of resonance intermediate **379** demands a shortened bond for the sp^2 hybridized carbon, and this increases the strain at that position. When this reaction occurs in a six-membered ring such as β-hydroxytetralin (**380**), however, the strain in the intermediate is greatly diminished and bromination gives primarily the α-product, **381**. The explanation for this selectivity is known as the **Mills–Nixon effect**.[278]



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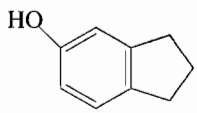

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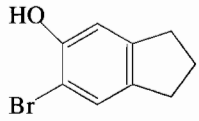

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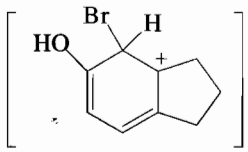

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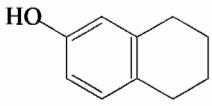

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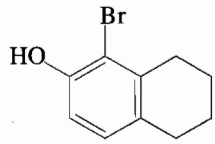
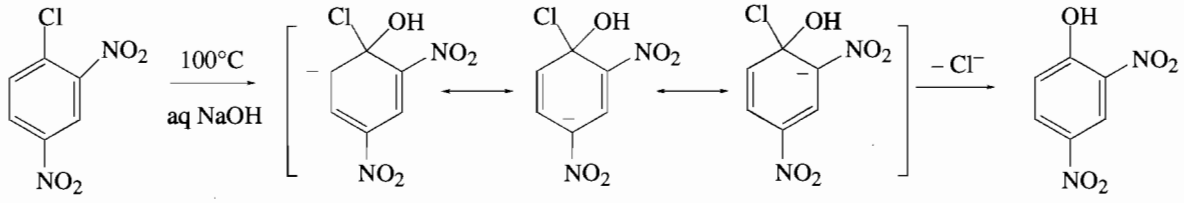


381

All of these effects are observed when comparing the rates of various electrophilic aromatic substitution reactions. Activating substituents increase the rate of reaction relative to benzene. The rate of reaction for the nitration of anisole, for example, was 9.7 x 10^6 times faster than nitration of benzene. The reaction of anisole with nitric and sulfuric acids, gave 44% of *o*-nitroanisole, 56% of *p*-nitroanisole and < 1% of *m*-nitroanisole.[279] This contrasts with reactions involving deactivating substituents, where selectivity for the meta -product is usually very good. Nitration of nitrobenzene, for example, gave 1,3-dinitrobenzene in 94% yield, with only 6% of the ortho product and < 1% of the para product.[279]

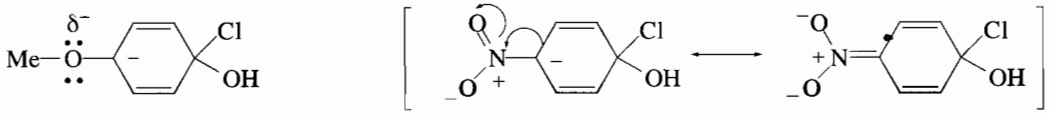
2.11.C. Nucleophilic Aromatic Substitution

An aromatic ring is electron rich and nucleophilic attack on that ring is expected to be slow if not impossible under normal reaction conditions. Nucleophilic aromatic substitution[280] does occur, however, and is synthetically useful with a variety of substituent and nucleophiles. When dinitrochlorobenzene, for example, is treated with sodium hydroxide in aqueous media, or neat, no reaction occurs. If that mixture is heated to ≈100°C, however, a substitution reaction occurs transforming 2,4-dinitrochlorobenzene into 2,4-dinitrophenol.[281] Indeed, this is a commercial method for the production of phenol derivatives, despite the harsh reaction conditions. The fact that such harsh conditions are required indicate that this nucleophilic substitution reaction has an high activation energy for initial attack of the aromatic ring (although in this case the ring is activated by the nitro groups–see below). The reaction must occur by attack of the nucleophilic hydroxide at the *ipso* carbon, generating the resonance stabilized carbanion intermediate **382**. The chloride is a leaving group, expelled by the negative charge (two electrons) in **382** and assisted by rearomatization of the ring to



382

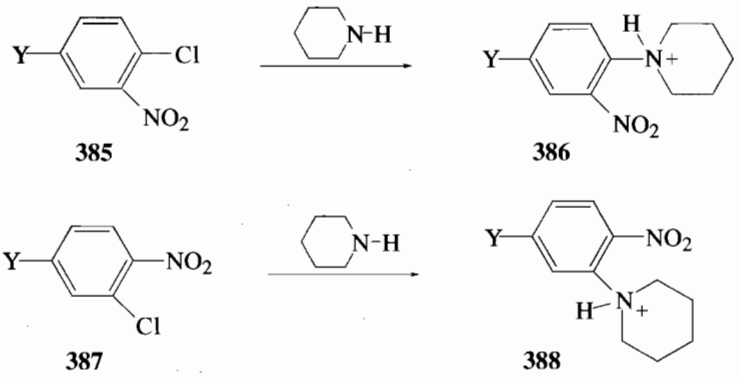
give the phenol derivative. The rate-determining step is the initial collision to form **382**, and factors that make this collision more favorable will increase the rate of the overall substitution process. The *I* and *M* effects noted with electrophilic aromatic substitution are operative but their effect will be the exact opposite for nucleophilic attack on **382** since the charges are different (the donor or acceptor properties of each group remains unchanged). A correctly positioned electron withdrawing group, for example, will delocalize the negative charge and stabilize that intermediate. Conversely, an electron releasing group will destabilize the intermediate.



383 **384**

Inspection of intermediate **383** (which arises by nucleophilic attack of hydroxide on 4-chloroanisole) places the negative charge on the carbon adjacent to the OMe moiety. The electron rich oxygen will repel the negative charge and destabilizing this intermediate. The reaction conditions for nucleophilic substitution of 4-chloroanisole should be more vigorous than those required for chlorobenzene. The intermediate arising from reaction of 4-chloronitrobenzene and hydroxide (**384**) has a negative charge on the carbon adjacent to the positive nitrogen of the nitro group. The charge can be delocalized out of the ring and onto the nitro oxygen, leading to an additional resonance structure and a more stable intermediate. Stabilization of the anionic intermediate by a nitro group will be most effective at the ortho and para positions and much less effective when the substituents are in the meta position, all relative to the *ipso* carbon. For nucleophilic aroma-tic substitution, electron-withdrawing groups stabilize the reactive intermediates and enhance the rate of the reaction. These effects are shown in Table 2.17,[282] which compares the relative rates of nucleophilic substitution of chlorobenzene derivatives with piperidine. Electron-donating substituents destabilize the reactive intermediate and diminish the rate of the reaction, which is dramatically illustrated by the reaction of 2,4,6-trinitrochlorobenzene with dilute hydroxide, which gave trinitrophenol upon simple warming and did not require high temperatures or pressures. In Table 2.17, rate enhancement is greatest when the substituent (Y) is in the para position, although some rate enhancement is observed for the meta substituent as well. The para substituent in **385** led to formation of **386** and showed a large rate effect for electron withdrawing substituents. The derivative with a meta substituent (**387**) generated **388** and showed a smaller rate effect. Electron withdrawing groups exerted the largest influence (the reference compound was the Y = H compound [k_H = 1] in all cases.

Table 2.17. Influence of substituents on nucleophilic aromatic substitution.

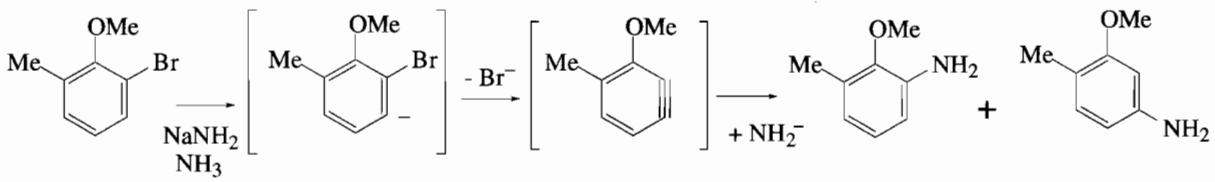


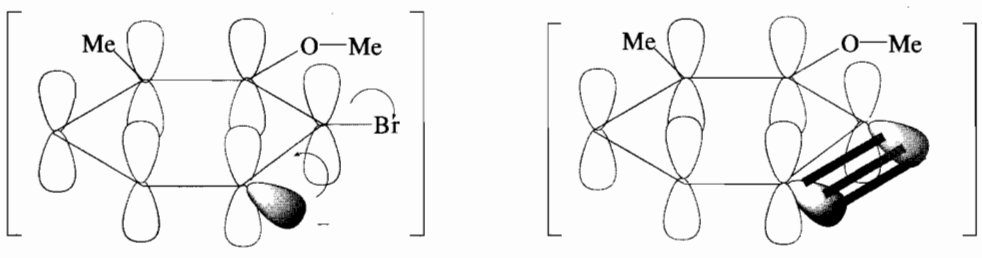
Y	k/k_H for 385	k/k_H for 387
NO_2	41000	
CN	6000	5
CO_2Et	920	5
Br	10	35
Cl	6	32
OMe	0.025	4
H	1	1
Me	0.2	0.9

[Leon M. Stock, AROMATIC SUBSTITUTION REACTIONS, ©1968, pp. 87. Reprinted by permission of Prentice Hall, Englewood Cliffs, New Jersey

2.11.D. Benzyne Derivatives

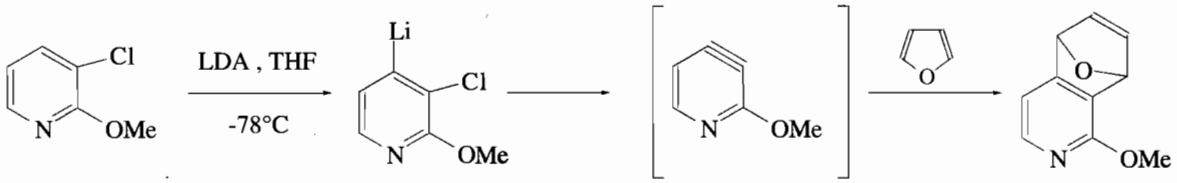
When relatively unreactive (unactivated) aryl halides are treated with powerful bases such as potassium amide (KNH_2) or *tert*-butyllithium (sec. 8.5.B), a hydrogen atom is removed from the aromatic ring in an acid-base reaction. The presence of the halogen makes the ortho hydrogens more acidic. Removal of the





ortho hydrogen generates a carbanion, but this filled orbital is perpendicular to the plane of the aromatic π-cloud (see **391B**). In this unstable intermediate, the charge resides on the carbon next to the halogen, which is a good leaving group. Elimination of the halide forms a new π bond that is perpendicular to the π-cloud of the benzene ring in a highly reactive species (**391** and see **336**) called a benzyne. When **389** was treated with sodium amide, for example, deprotonation gave **390A** and the bromide was expelled to give the benzyne intermediate, **391A**.[283] When **390A** is redrawn as **390B**, it is clear that the carbanionic center is perpendicular to the aromatic π cloud and parallel to the C—Br bond. Expulsion of this adjacent leaving group forms the new π bond of the benzyne intermediate **391B**. This π-bond is subject to nucleophilic attack, and the nucleophilic amide will react with **391A** to produce a mixture of **392** and **393**, the result of attack at both carbons of the double bond. One substitution product (**393**) has the new amino substituent adjacent to the carbon that bore the bromide leaving group, which is often called **cine substitution**.

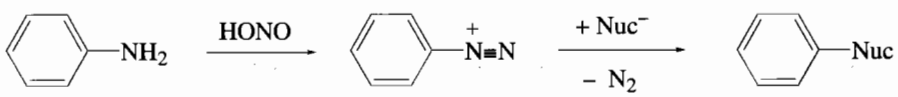
Benzyne formation and their reactions are not limited to simple benzene derivatives. Heterocyclic molecules can also be used for benzene reactions. One important use of benzyne derivatives is in the Diels–Alder reaction (see sec. 11.4.A). When 3-bromo-2-methoxypyridine (**394**) was treated with LDA at -78°C, for example, lithium–hydrogen exchange occurred to give **395**. Loss of LiBr led to benzyne (**396**), which reacted with furan to give the Diels–Alder product (**397**) in 74% yield.[284]



394 **395** **396** **397**

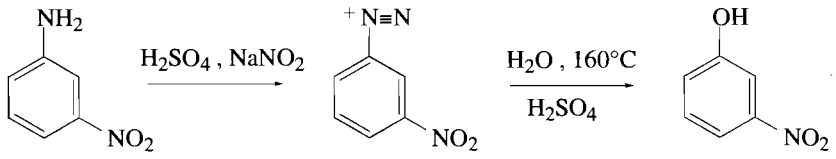
11.E. Substitution Reactions of Aryl Diazonium Salts

When a primary aromatic amine such as aniline is treated with nitrous acid (HONO), usually generated by the reaction of sodium nitrite and HCl or H_2SO_4,[285] an aryl diazonium compound is formed, in this case benzenediazonium chloride (**398**).[286] The nitrogen fragment of a diazonium ion (Ar—N_2^+) is one of the best leaving groups known[286ab] and it can be displaced by a variety of nucleophiles to give the substitution product **399**).[287]



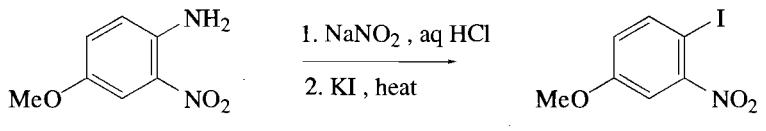
398 **399**

Many different nucleophiles can react with aryl diazonium salts, often by different mechanisms that range from S_N1 type processes to those involving radicals.[288] Heating **398** in aqueous acid generates phenol.[289] This reaction is also illustrated by the conversion of 3-nitroaniline (**400**) to the diazonium salt (**401**), which was followed by heating in aqueous sulfuric acid to give 3-nitrophenol (**402**).[290]

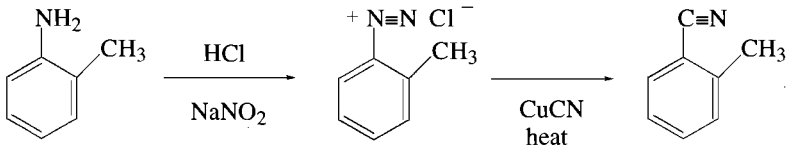


400 **401** **402**

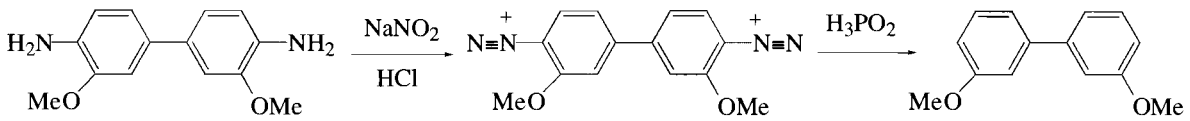
Treatment of diazonium salts with cuprous, Cu(I), salts generates aryl halides. When **398** reacts with CuCl (cuprous chloride) or CuBr (cuprous bromide), the products are chlorobenzene or bromobenzene via what is probably a radical reaction.[291] This conversion is known as the **Sandmeyer reaction**.[292] The use of copper powder rather than cuprous salts for this transformation is often called the **Gattermann reaction**.[293,292b,c] Aryl iodides are also produced from diazonium salts by reaction with potassium iodide (KI) but the actual reactive species may be I_3^-.[294,295] Treatment of aniline derivative **403** with sodium nitrite and HCl followed by treatment with KI, for example, gave a 89% yield of **404**.[296] Aryl nitriles are generated under Sandmeyer conditions using cuprous cyanide (CuCN), as in the conversion of **405** to benzonitrile derivative **407** via diazonium chloride, **406**.



403 **404**

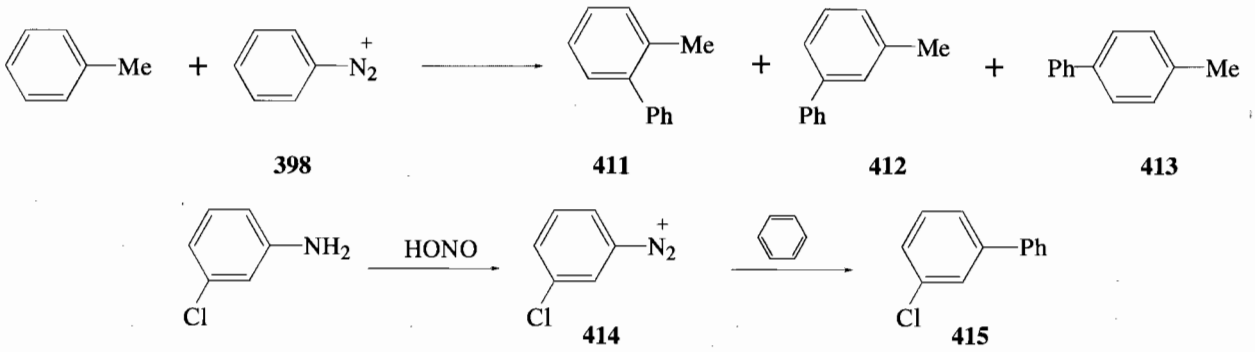


405 **406** **407**



408 **409** **410**

Nitrogen can be completely removed from a diazonium salt by reduction with H_3PO_2 (hypophosphorus acid).[297] This technique is often used in conjunction with using the electron withdrawing properties of a nitro group to positioning another group. Reduction to an amine, diazotization and then reduction resulted in loss of nitrogen and removal of nitrogen from the molecule. The amine moiety itself can be used to position groups, and this is very useful since the amine unit is electron releasing. Diazotization and reduction removes nitrogen as before. The deamination process is illustrated by the conversion of aryl diamine **408** to the bis-(diazonium) salt **409** and subsequent reduction to the biaryl **410**.[298]



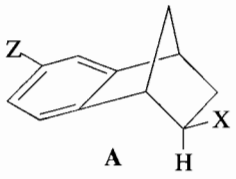
In basic solutions, of an activated aromatic substrate, diazonium salts decompose and couple to give biaryls (Ar-Ar).[299] Reaction of benzenediazonium ion (**398**) and toluene gave a 67% yield of **411**, along with 19% of **412** and 14% of **413**.[299] This result suggests the coupling is rather unselective. Selectivity is observed only when the substituent is part of the aryl diazonium ion, as in the conversion of **414** to **415**.[299]

2.12. CONCLUSION

This chapter has attempted to show a few reaction types that dominate much of the chemistry used by organic chemists on a daily basis. It is also meant as a review of the fundamental functional group transformations encountered in a typical undergraduate organic chemistry course. Chapters 3 and 4 will discuss the place of oxidation and reduction reactions in organic chemical transformations, which will be followed by hydroboration in Chapter 5 and a discussion of protecting groups in chapter seven. Chapter 6 will discuss cyclization reactions and methods for controlling stereochemistry and regiochemistry. Some of the important concepts in Chapter 6 will be introduced in Chapters 3-5 and Chapter 6 will attempt to tie those concepts together.

HOMEWORK

1. From the rate data given for compound **A** (in the table below), it is clear that the presence of a methoxy group significantly enhances the rate of solvolysis of **A**. Offer a reasonable mechanistic explanation of this solvolysis reaction that is consistent with the observed rate data.



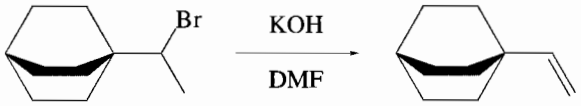
see *J. Org. Chem.*, ***1985***, *50*, 821.

Assume that differences in the rate due to changing the leaving group is insignificant for this question.

Z	X	Relative Rate
H	OTs	1
MeO	Cl	130
Me	OTs	4.96
Cl	Cl	0.15

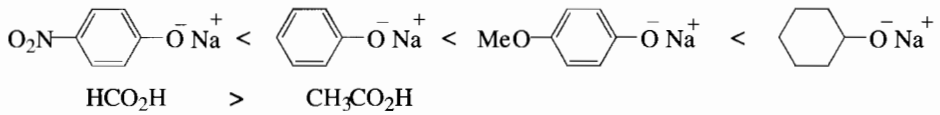
2. Reaction of 3-pentanol with potassium iodide in aqueous ethanol gave no reaction under several different reaction conditions. If one adds a catalytic amount of *para*-toluenesulfonic acid, however, the reaction proceeds to give 3-iodopentane. Explain these observations.

3. Explain why the obvious S_N2 conditions shown in the following reaction give only elimination and no substitution with this secondary bromide.



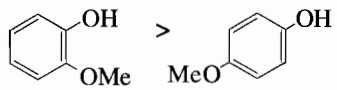
4. Explain each of the following trends.

(a) Order of basicity.



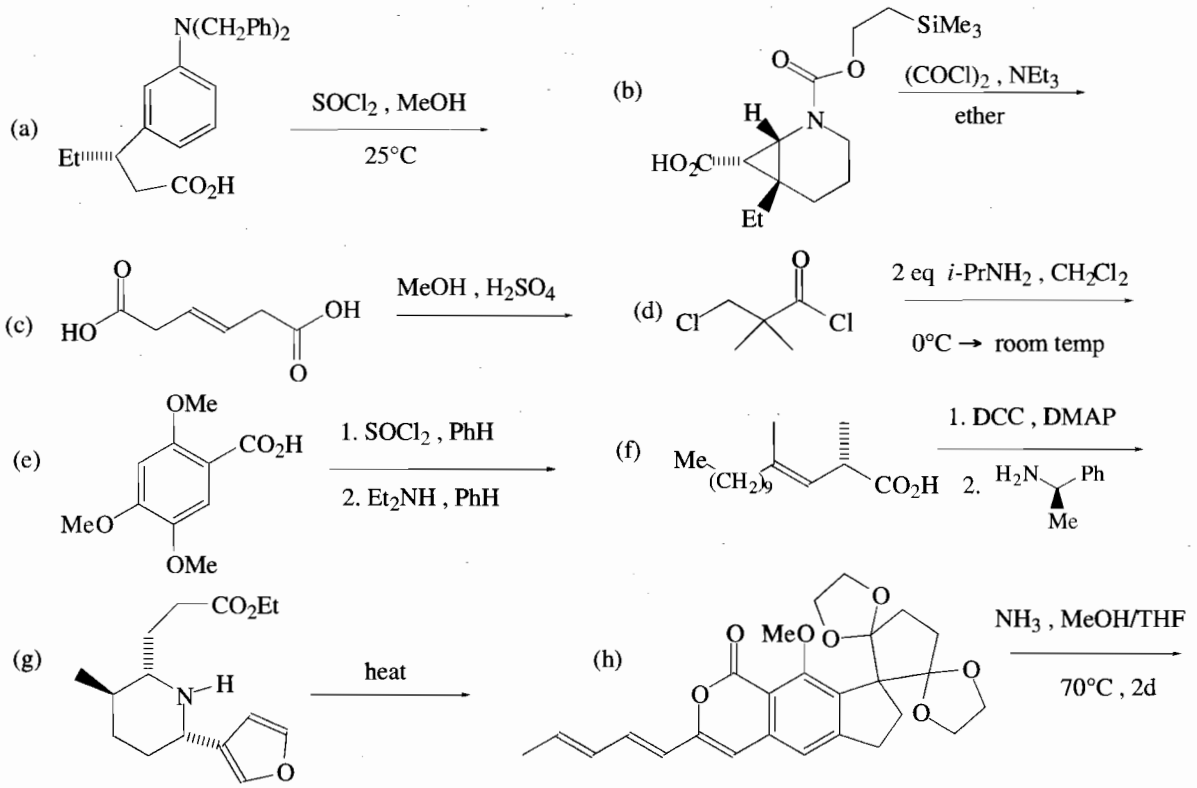
HCO_2H > CH_3CO_2H

(b) Order of acidity.

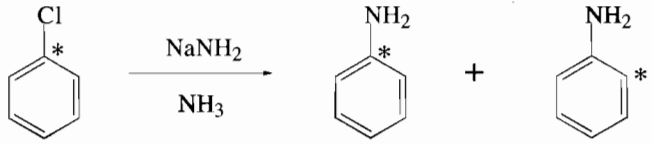


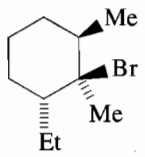
CH_3CO_2H in water > CH_3CO_2H in THF

5. Give the major product for each of the following transformations involving conversion of a carboxylic acid or a derivative into another acid derivative.

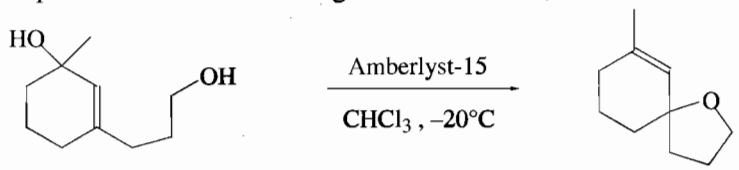


6. Taken from Stock, L.M., *Aromatic Substitution Reactions*, Prentice-Hall, Englewood Cliffs, N.J., ***1968***, p. 91. Explain why the ^{14}C label is found at both C1 and C2 in the aniline product despite the fact that the label is localized on C1 in the chlorobenzene precursor. The * indicates the position of the ^{14}C label.



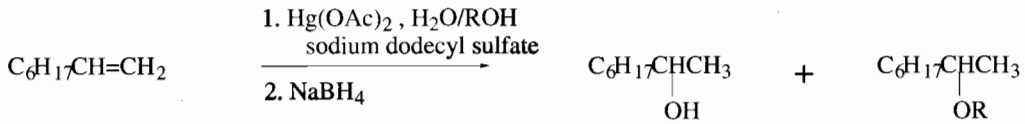
7. Does the bromide shown undergo an E2 reaction?  If so, draw the major product(s) If not, why not?

8. Offer a mechanistic explanation for the following transformation: (*Tetrahedron Lett., **2000**, 41,* 3411)



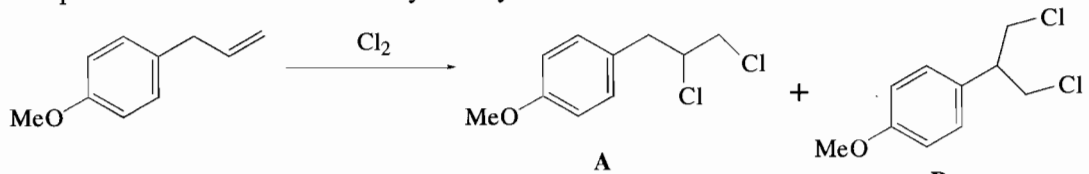
Amberlyst is an acidic resin

9. Taken from *J. Org. Chem., **1987**, 52,* 5039. The following reaction gives a mixture of the alcohol and the ether, in the proportions given later in this question. Only 0.03 eq of 1-octene were used. In each case, a 1:1 ratio of water to alcohol was used.



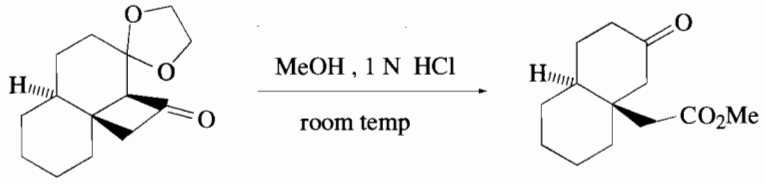
Reaction with 1.0 equivalent of 1-octanol (to 0.03 eq of 1-octene) gave a 98:2 mixture of alcohol/ether in 50% aq THF. The use of 10 equivalents of 1-octanol in 0.3 M THF in water gave a 52:48 mixture of alcohol/ether. Explain what the 52:48 mixture tells you about the relative nucleophilicity of water and 1-octanol. Explain why increasing the amount of 1-octanol leads to more ether product.

10. Two products are formed in the following reaction, A and B. (a) Offer a reasonable explanation of how B could arise in this reaction. (b) Would the use of the 4-chlorophenyl derivative rather than the 4-methoxy derivative help or hurt formation of B? Why or why not?

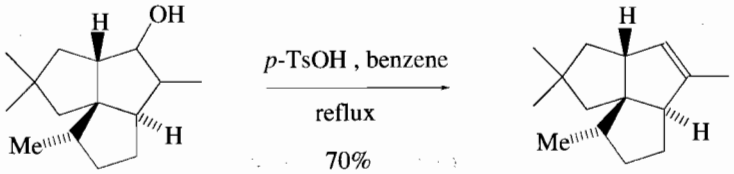


see *J. Org. Chem., **1987**, 52,* 260 and *J. Org. Chem., **1984**, 47,* 4855.

11. Offer a mechanistic explanation for the following transformation: see *Tetrahedron Lett.*, ***1997***, *38*, 3469.

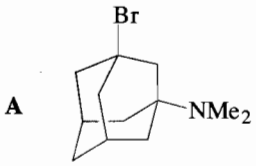


12. Treatment of alcohol A leads to B in 70% yield (see *Tetrahedron Lett.*, ***2000***, *41*, 403). Explain this product in terms of a mechanism and comment on why the C=C unit is generated between C2-C3 rather than between C2-C1 [hint, see sec. 6.3.B].

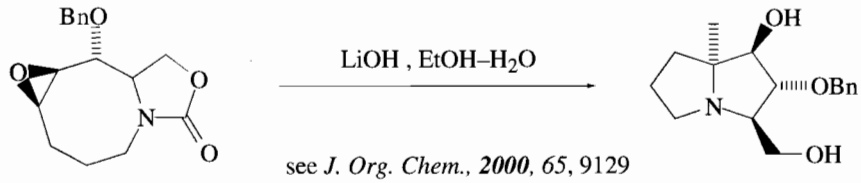


A **B**

13. Solvolysis of A leads to an alkene–iminium salt. Draw this product and suggest a mechanism for its formation. See *Angew. Chem. Int. Ed. Engl*, ***1990***, *29*, 188.



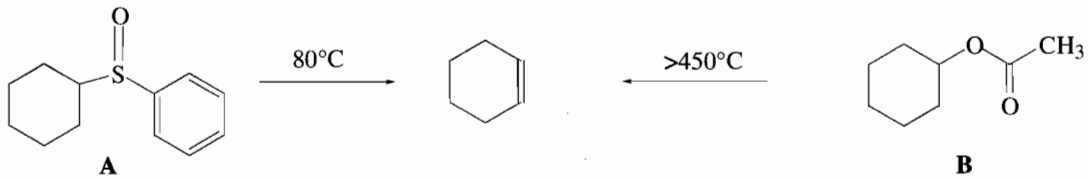
14. Suggest a reasonable mechanism for this reaction.



15. Explain each of the following.

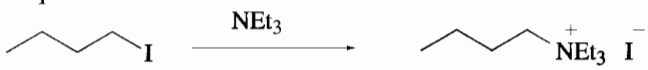
(a) Heating 2-*N,N,N*-triethylammonium)butane gives ethene rather than 1-butene. Explain!

(b) The elimination of **A** requires lower temperatures than the elimination reaction of **B**.

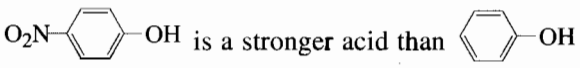


A **B**

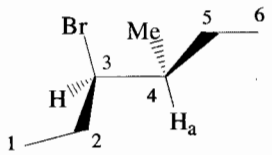
(c) This reaction is faster in aqueous ethanol than in 100% ethanol:

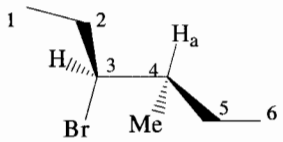


(d) $H_3N^+CH_2CO_2H$ is a stronger acid than $H_3N^+(CH_2)_4CO_2H$.

(e)  is a stronger acid than

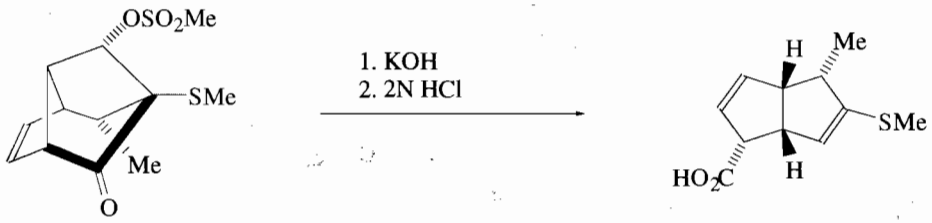
16. 3-Bromo-4-methylhexane is drawn in two different orientations, A and B. Using an E2 reaction, remove H_a and convince yourself that the two orientations lead to the same alkene. Explain this and why an E2 reaction of this molecule leads to one alkene but an E1 reaction leads to a mixture of (*E*) and (*Z*) isomers.

A 

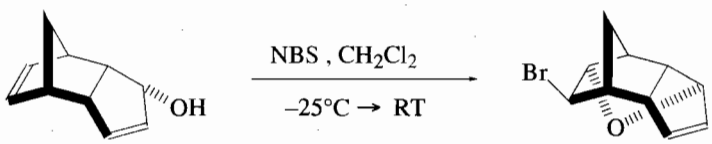


B

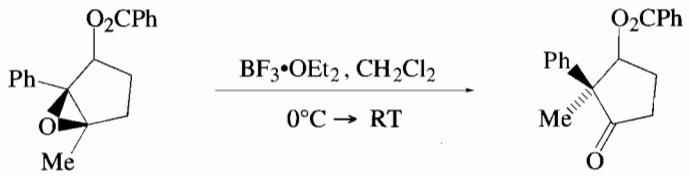
17. Offer a mechanistic explanation for the following transformation: See *J. Org. Chem.*, ***1997***, *62*, 641.



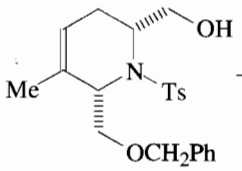
18. Offer a mechanistic explanation for the following transformation. See *Synthesis*, ***1996***, 219.



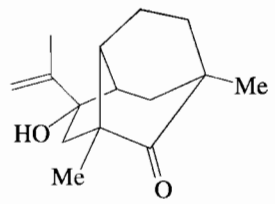
19. Offer a mechanistic explanation for the following transformation. See *Tetrahedron Lett.*, ***2000***, *41*, 2133.



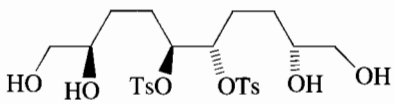
20. For each of the following give the major product, with all appropriate stereochemistry. If there is no reaction, indicate by N.R.

(a) 

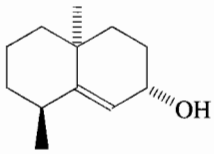
1. $MeSO_2Cl$, NEt_3
2. KCN , DMSO

(b) 

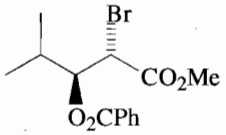
p-TsOH , $ClCH_2CH_2Cl$
heat

(c) 

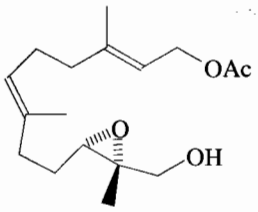
NaH , THF
0°C , 4 h

(d) 

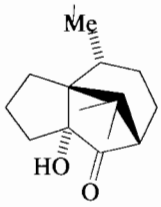
PPh_3 , DEAD
KOH , aq MeOH

(e) 

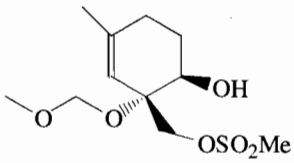
NaN_3
DMSO

(f) 

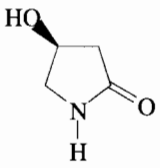
1. $MeSO_2Cl$, NEt_3
2. LiBr , acetone ,50°C

(g) 

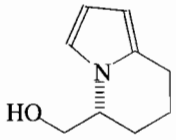
$SOCl_2$, Pyridine
40°C

(h) 

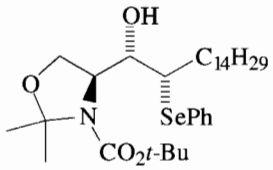
NaH , ether , reflux

(i) 

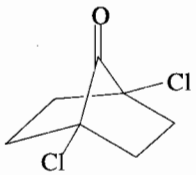
DEAD , PPh_3

(j) 

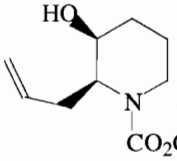
1. $MeSO_2Cl$, NEt_3
2. NaCN

(k) 

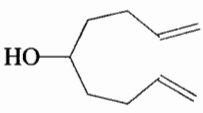
30% H_2O_2
room temp

(l) 

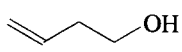
1. aq NaOH
2. H_3O^+

(m) 

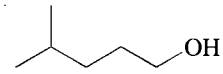
NBS , MeCN
room temp , 30 min

(n) 

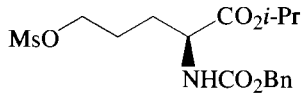
$TsNHCO_2t$-Bu
i-$PrO_2CN{=}NCO_2i$-Pr
PPh_3 , room temp

(o) 

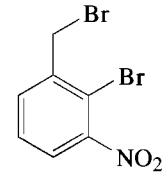
1. NaH ,THF
2. $BrCH_2CO_2Na$, THF

(p) 

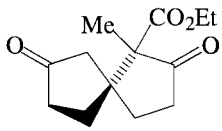
PBr_3

(q) 

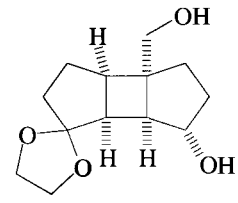
NaH , DMF

(r) 

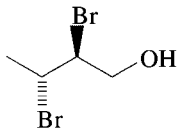
H^+ , H_2O , heat

(s) 

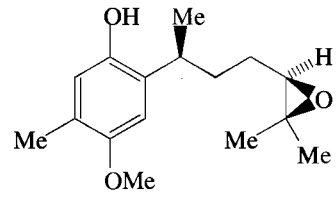
HCl , AcOH
reflux , 14h

(t) 

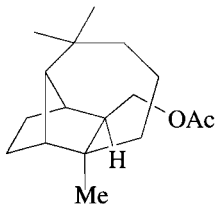
PPh_3 , I_2
imidazole

(u) 

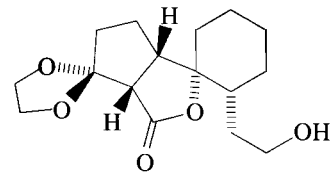
$LiN(i\text{-}Pr)_2$, HMPA
THF , –78°C

(v) 

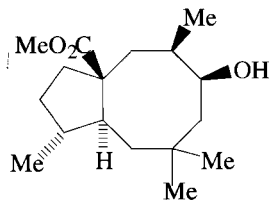
powdered KOH
DMSO , 70–100°C

(w) 

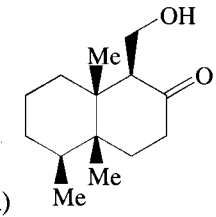
525°C , flow system

(y) 

, THF
I_2 , PPh_3

(z) 

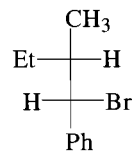
1. $POCl_3$, HMPA
Pyridine
2. aq KOH ; neutralize

(aa) 

1. MsCl , $i\text{-}Pr_2NEt$
CH_2Cl_2
2. DBU , THF

21. (a) Draw the transition state for the following reaction.

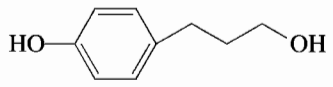
(b) Give the major product



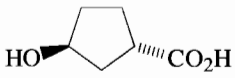
KOH , EtOH

(c) what type of reaction is this?

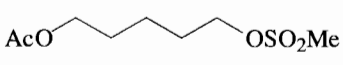
22. In each case, predict the major product and explain your answer.

(a) 

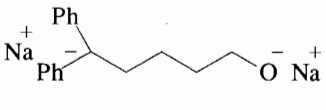
1. 1 equiv NaH
2. MeI

(b) 

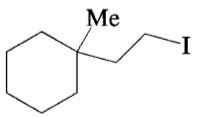
1. 2 equiv NaH , THF
2. 1 equiv allyl bromide
3. H_3O^+

(c) 

1 equic NaCN
DMF

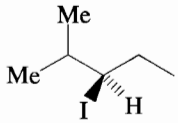
(d) 

1. MeI
2. H_2O

(e) 

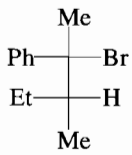
DBU

23. For the following reaction, predict the product and show the correct stereochemistry. Use Newman projections to indicate how you chose your product and to justify your answer.

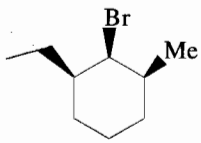


1. $PhS^- Na^+$, DMF
2. $NaIO_4$
3. 120°C

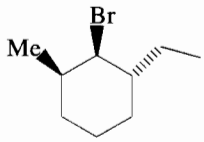
24. For each of the following, show the major product. Explain your choice.

(a) 

KOH
EtOH
heat

(b) 

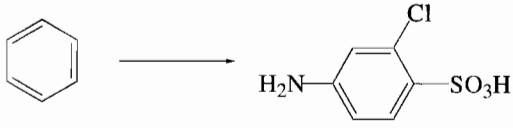
KOH
EtOH
heat

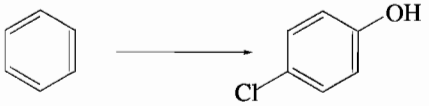
(c) 

KOH
EtOH
heat

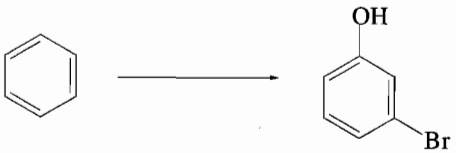
25. For each of the following provide a suitable synthesis. Show all intermediate products and all reagents.

(a)

(b) 

(c) 

(d)

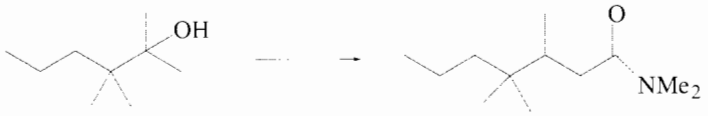
(e) 

(f)

(g)

(h)

(i)



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CHAPTER 3

OXIDATION

3.1. INTRODUCTION

Oxidation in organic chemistry has historically been defined in terms of reactivity. A broad definition by Sheldon and Kochi states, "oxidation in Organic chemistry refers to either (1) the elimination of hydrogens, as in the sequential dehydrogenation of ethane, or (2) the replacement of a hydrogen atom bonded to carbon with another more electronegative element such as oxygen in the following series of oxidative transformations of methane:"[1]

$$CH_4 \longrightarrow CH_3OH \longrightarrow CH_2O \longrightarrow HCO_2H \longrightarrow CO_2$$

Oxidation can also be defined as reaction of an element with oxygen,[2] analogous to the second criterion stated above. A more general definition, applied most often in inorganic chemistry, involves the loss of one or more electrons from an atom or group.[2] In an attempt to identify an oxidation process for a given organic reaction, Soloveichik and Krakauer[3] listed five criteria that could be used to arrange compounds by their ability to be oxidized.

1. Pauling's electronegativity scale.[4]
2. The oxidation number of the parent substance of each homologous series under consideration.
3. The ratio of bond moment to bond length, μ /l (net charge).[5]
4. Hammett's sigma function as revised by Taft (Taft's σ^*).[6]
5. Chemical reactions of the substance involved, particularly hydrolysis, which does not provide basic . changes in oxidation stage if certain conventions are maintained.[3]

With these criteria, the **oxidation state** of the molecule can be determined and this is useful for categorizing a reaction as an oxidation or a reduction. Soloverchik and Krakauer also listed rules for determining the oxidation state of a molecule:[3]

1. The oxidation state of carbon in hydrocarbons of the methane series is zero
2. The oxidation state is increased by one for each bond with a hydrogen atom or an alkyl group replaced by a bond with a more strongly electron attracting atom or group (—NH_2, SH, halogen, CO_2, etc.) for every removal of a pair of hydrogen atoms from two adjacent carbon atoms.
3. The group on a carbon is defined by its substituent carbons bearing the same substituents belonging to the same group. Groups within an oxidation state are arranged in order of increasing induced electron deficiency of the function bearing carbon. ($CH_3X > RCH_2X > R_2CHX > R_3CX$).

These rules can be used to determine if a starting material and a product are in a higher or a lower oxidation state. There are several structural types and an oxidation is defined as conversion of a group at a lower stage to a higher stage (I → II, II → III, etc.).[3] Examples are $R_3CNH_2 \rightarrow R_2C{=}NH$ (I → II); $RCONH_2 \rightarrow (H_2N)_2C{=}O$ (III → IV); and, $AcCR_3 \rightarrow R_2C{=}O \rightarrow RCl_3 \rightarrow Cl_3CCO_2H$ (I → II → III → IV).[3]

As mentioned, oxidation involves a loss of electrons, and this definition has been applied to organic as well

as inorganic molecules. Loss of electrons is associated with the change in oxidation state of an atom, and this electron loss can be determined by a device known as **oxidation number**. Holleran and Jespersen[7] listed several rules to determine the oxidation number or each atom within a molecule. The change in the numbers between starting material and products shows the loss or gain of electrons and the change in oxidation state.

1. The sum of the oxidation numbers of all the atoms in a molecule or ion must equal the total charge (0 for a neutral molecule).
2. Metallic atoms of groups 1 (IA) and 2 (IIA) have oxidation numbers of +1 and +2, respectively.
3. H and F are assigned oxidation numbers of +1 and –1, respectively, when part of a molecule.
4. Oxygen is assigned an oxidation number of -2 in its compounds except for peroxide, where it is –1, and for OF_2, where it is +2.
5. Atoms of group 7 (VIIB) are assigned oxidation numbers of -1 in their binary compounds.
6. In binary compounds, atoms from groups 16 (VIA) and 15 (VA) are assigned oxidation numbers of –2 and –3, respectively.
7. If two rules conflict, the rule that occurs first takes precedence.
8. If a conflict occurs within the same group, the lighter element takes the charge (I is +1 in ICl).

Oxidation numbers can be assigned to any atom, as shown in the following examples:

H_2O_2 (1 for O) BrO_3 (+5 for Br) OF_2 (+2 for O) LiO_2 ($-\frac{1}{2}$ for O)

If an element is not included explicitly in one of the rules, its oxidation number is found by difference, as in the case of the nitrite ion. The symbol Σ below refers to the net charge for the molecule, as determined by the usual formal charge calculations. For the N in NO_2^-,

NO_2^- (each O = -2, Σ = -1, therefore, N = +5)

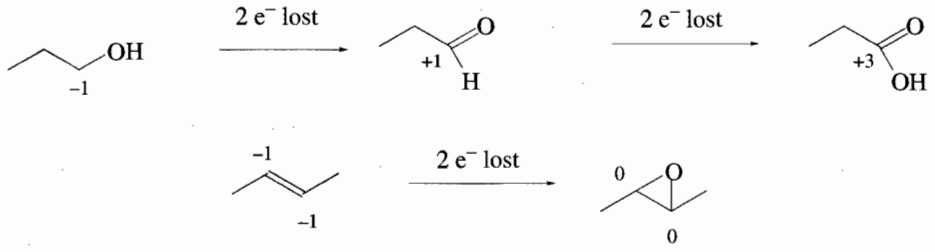
A simplified version of this methodology was used by Hendrickson, Cram and Hammond[8] and later by Pine,[9] in their undergraduate organic textbooks. The rules shown above were applied only to those atoms most commonly encountered in simple organic molecules, H, O, C, N, and the halogens. Hendrickson, Cram, Hammond, and Pine used the following convention for assigning oxidation numbers.[8,9]

–1	for hydrogen
0	for carbon (bonds to same atom)
+1	for a covalent bond to a heteroatom (usually oxygen or halogen)

Determining the oxidation number for all atoms in a molecule is unnecessary. Only those atoms that are modified or changed during the reaction require examination. If the sums of the oxidation numbers of the various atoms in the starting material and in the product are compared, the change in oxidation number can be calculated and determination made if the reaction is an oxidation or reduction.

In the first example, 1-propanol is oxidized to propanal, and this is further oxidized to propanoic acid in a second step. In 1-propanol, the carbon bearing the hydroxyl group has an oxidation number of -1 (C is 0, each H is –1, and O is +1). The oxidation number of that carbon in propanal is +1 (C is 0, H is –1, O is +1, and O, from the second bond to the carbonyl, is +1). The change in oxidation number is –1 → +1, for a net **loss** of two electrons and an oxidation (remember that as the net charge becomes more positive, this is associated with loss of electrons, which have a negative charge). Similarly, the carbon of interest in propanoic

acid has an oxidation number of +3 (C is 0, the three bonds to oxygen total +3). Conversion of propanal to propanoic acid involves *loss* of two additional electrons (+1 → +3) and is an oxidation. Each of these two electron oxidations is a one stage oxidation but a direct conversion of 1-propanol to propanoic acid would be a four electron, two-stage oxidation. Only the carbon bearing the oxygen atoms was examined in this example since the other carbons are not changed during the course of the reaction.



The oxidation of 2-butene to the corresponding epoxide involves modification of two carbons (sec. 3.4). The oxidation number of each carbon comprising the π bond is -1 (C,C is 0, and H is –1) and the oxidation number of each epoxy carbon in the product is 0 (C,C is 0, O is +1 and H is –1), for a change of one electron (–1 → 0) for *each* of those two carbons. The *net* change for each molecule is loss of two electrons for a one-stage oxidation.

If there is a choice of more than one reagent for a particular oxidation reaction, the relative strength of those reagents is important. It is also important to determine whether a given reagent will induce a one or two-stage (two electron or four electron) oxidation (1-propanol to propanal or 1-propanol to propanoic acid, for example). Oxidation and reduction are linked together since an oxidation of one species is accompanied by reduction of another. The reduction potential is obtained from polarographic (electrolysis) experiments that involve transfer of electrons between electrodes.[10] "An electrode process is a heterogeneous transfer of electrons between electrodes and an organic molecule".[11] The potential of the electrode controls the availability of electrons in the medium. The tendency toward electron loss or electron gain in the reduction system is given by the reaction

$$M \rightleftharpoons M^{2+} + 2\,e^-$$

It can be measured as an electrical driving force, expressed as the electrode potential.[11] As written, this equation represents a loss of two electrons from M and is an oxidation. If written as the reverse reaction, it is a reduction. Both oxidized and reduced species must be present in this equilibrium, and changes in potential occur as one changes to the other. It is important to note that the electron transfer process shown above does not always correlate with the functional group transformation associated with oxidation of organic substrates. It does allow comparisons of the relative strengths of various oxidizing agents, however. For selected electrolysis reactions (generically referred to as electrochemistry) for organic substrates , see section 4.9.J.

If the electrode potential in an electrolysis reaction is made more positive, oxidation (with loss of electrons) will compensate for this positive change in potential.[12] A more negative potential will be compensated for by addition of electrons to the oxidized form. The equilibrium potential of a reversible system of this type can, therefore, be given by the equation

$$E = E_o - \frac{RT}{nF} \ln \frac{[Ox]}{[Red]} \qquad 3.1$$

where E_o is the standard reduction potential and F is Faraday's constant (96,400 Coulombs per equivalent). Ox and Red refer to the oxidized and reduced forms, respectively. Electrode potential is always expressed relative to an arbitrary standard and the zero electrode potential is usually taken as that of "the reversible equilibrium between hydrogen gas at one standard atmosphere pressure and hydrogen ions at unit activity" (the normal reversible hydrogen electrode potential).[13] For the reaction,

$$M \rightleftharpoons M^+ + e^-$$

the metal (M) is assumed to be coupled with a metal having less tendency to ionize, generating a negative potential in the electrolytic cell. The electrode potential (ε) is proportional to the free energy (ΔG) of the reaction by

$$\Delta G = -z\,F\,E \qquad \text{for the cell} \qquad 3.2$$

$$\Delta G = -z\,F\,\varepsilon \qquad \text{for a single electrode} \qquad 3.3$$

where E is the electromotive force, F is the Faraday constant and z is the number of electrons involved in the overall cell reaction. If ε is negative, ΔG is positive and the reaction is *not* spontaneous. Using the **European convention**,[14,15] $\varepsilon°$ for a metal is taken as negative when the polarity of the metal in that cell is negative. Therefore, the expression $\Delta G = -[-z\,F\,\varepsilon]$ will be used for the reaction. An example is

$$Na \longrightarrow Na^+ + e^-$$

where $\varepsilon°$ is negative, ΔG is negative and this ionization (a one-electron oxidation) is a spontaneous reaction.

The oxidation potential represents the ability of a metal atom (M) to be ionized to an ion (M^+) with loss of an electron. For the oxidation of organic molecules, transition metal compounds containing chromium, manganese, ruthenium, selenium, silver, or cerium are often used. The oxidation potential is therefore a useful method for examining the oxidizing power of these reagents.

Permanganate (MnO_4^-) is a powerful oxidizing agent used in many organic oxidations but there are several other oxidation states available to manganese, including manganate (MnO_4^{2-}) and hypomanganate (MnO_4^{3-}). Their reactivity toward reductants (the organic substrate) varies inversely with the charge on the oxidant,[16a] and the relative order of oxidizing power is

$$MnO_4^- > MnO_4^{2-} > MnO_4^{3-}.$$

The reduction potentials for these species are known to be[16a]

$$MnO_4^- + e^- \longrightarrow MnO_4^{2-} \qquad (\varepsilon = +0.558\ V)$$

$$MnO_4^{2-} + e^- \longrightarrow MnO_4^{3-} \qquad (\varepsilon = +0.285\ V)$$

These reactions are shown as the standard reduction potential (see below) since reduction potential reflects the propensity of a metal or metal salt to be reduced, with concomitant oxidation of an organic substrate. The larger reduction potential for permanganate is correlated with its stronger oxidizing ability. The point of this example is that the oxidizing agents used in this chapter are not always metals but are often metal derivatives. Their oxidizing power varies with the derivative and it is important to understand the oxidizing power of each when they are used for the oxidation of an organic substrate. Oxidizing power varies with the reaction medium. Permanganate, for example, shows different reduction potentials in acidic and basic media:[16a]

$$MnO_4^- + 3\,e^- + 4\,H^+ \longrightarrow MnO_2 + 2\,H_2O \qquad (\varepsilon = +1.679\ V)$$

$$MnO_4^- + 3\,e^- + 2\,H_2O \longrightarrow MnO_2 + 4\,OH^- \qquad (\varepsilon = +0.59\ V)$$

From Table 3.1,[17] it is clear that the pH of the media plays an important role in the oxidizing power of a given reagent. Acidic, neutral, and basic media will be employed in the following sections for the oxidation of different substrates and a variety of oxidizing agents will be used. The choice of reagent and conditions will

Table 3.1. Standard Reduction Potentials of Common Oxidizing Systems

Reaction	Potential(V)[a]
$O_3 + 2\,H^+ + 2\,e^- \rightarrow O_2 + H_2O$	2.07
$H_2O_2 + 2\,e^- + 2H^+ \rightarrow 2\,H_2O$	1.77[18]
$HIO_5 + H^+ + 2\,e^- \rightarrow IO_3^- + 3\,H_2O$	≈ 1.7
Pb (IV) + $2\,e^- \rightarrow Pb^{3+}$	1.69[18]
$MnO_4^- + 4\,H^+ + 3\,e^- \rightarrow MnO_2 + 2\,H_2O$	1.679
$MnO_4^- + 8\,H^+ + 5\,e^- \rightarrow Mn^{2+} + 4\,H_2O$	1.491
$Ce^{4+} + e^- \rightarrow Ce^{3+}$ (0.5N H_2SO_4)	1.4587
$Ce^{4+} + e^- \rightarrow Ce^{3+}$	1.4430
$Cr_2O_7^{2-} + 14\,H^+ + 6\,e^- \rightarrow 2Cr^{3+} + 7\,H_2O$	1.33
$O_3 + H_2O + 2\,e^- \rightarrow O_2 + 2\,HO^-$	1.24
$O_2 + 4\,H^+ + 4\,e^- \rightarrow 2\,H_2O$	1.229
$MnO_2 + 4\,H^+ + 2\,e^- \rightarrow Mn^{2+} + 2\,H_2O$	1.208
$HCrO_4^- + 7\,H^+ + 3\,e^- \rightarrow Cr^{3+} + 4\,H_2O$	1.195
$Cr^{6+} + 3e^- \rightarrow Cr^{3+}$ (2N H_2SO_4)	1.10
$OsO_4 + 8\,H^+ + 8e^- \rightarrow Os + 4\,H_2O$	0.85
$Ag^+ + e^- \rightarrow Ag$	0.7996
$Fe(CN)_6^{3-} + e^- \rightarrow Fe(CN)_6^{4-}$ (1N H_2SO_4)	0.69
$O_2 + 2\,H^+ + 2\,e^- \rightarrow H_2O_2$	0.682
$2\,AgO + H_2O + 2\,e^- \rightarrow Ag_2O + 2\,OH^-$	0.599
$RuO_4 + e^- \rightarrow RuO_4^{2-}$	0.59
$MnO_4^- + 2\,H_2O + 3\,e^- \rightarrow MnO_2 + 4\,HO^-$	0.588
$MnO_4^- + e^- \rightarrow MnO_4^{2-}$	0.564
$Cu^+ + e^- \rightarrow Cu$	0.522
$Ag_2CO_3 + 2\,e^- \rightarrow 2\,Ag + CO_3^{2-}$	0.4769
$Fe(CN)_6^{3-} + e^- \rightarrow Fe(CN)_6^{4-}$ (0.01N NaOH)	0.46
$Ag_2O + H_2O + 2\,e^- \rightarrow 2\,Ag + 2\,OH^-$	0.342
$Cu^{2+} + 2\,e^- \rightarrow Cu$	0.3402
$O_2 + e^- + H^+ \rightarrow HO_2^-$	–0.32[18]
$Cu^{2+} + e^- \rightarrow Cu^+$	0.153
$CrO_4^{2-} + 4\,H_2O + 3\,e^- \rightarrow Cr(OH)_3 + 5\,HO^-$	–0.12

[a] All values from Reference 17 unless otherwise noted.

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influence the overall reaction and determine if the oxidation is a two electron (one-stage) or a four electron (two-stage) oxidation.

A list of reduction potentials for various metals and metal salts known to oxidize organic substrates is presented in Table 3.1.[17] In most compilations of reduction potentials, the reaction is shown as the reduction potential ($M^+ + e^- \rightarrow M$) and this convention is followed in Table 3.1. The potential given is also the oxidation potential for the reverse of the reaction shown. In general, the larger the reduction potential as presented in Table 3.1, the greater the oxidizing power of that reagent. From the Table 3.1 it is apparent that ozone, hydrogen peroxide, oxygen, lead [Pb(IV)], silver (Ag^+), chromium [Cr(VI)], permanganate (MnO_4^-), and periodic acid are strong oxidizing agents. These reagents are probably the most important for the oxidation of organic molecules and will figure prominently in this chapter.

Reduction potential can also be correlated with ionization potential (I), which is defined by

$$M_{gas} \xrightarrow{I} M^+ + e^- \qquad 3.4^{19}$$

The primary difference between I and the reduction potential (ε) is that I is defined for a gas-phase reaction whereas ε is measured in solution. The solvent has a great influence on the course of the oxidation. It is difficult to directly correlate ε and I, but the latter can be used for a general comparison of the ability of a molecule or reagent to be oxidized or reduced. In general, larger ionization potentials are correlated with greater oxidizing power. Osmium tetroxide (I = 12.97 eV)[20] is a stronger oxidizing agent than ruthenium tetroxide (I = 12.33 eV)[20] by this criterion. It would be useful to know the reduction potentials of the organic substrates that are being oxidized but these are difficult to obtain, since the reduction potential will be different for each type of oxidation. For this reason, comparison of one electron oxidations (the usual first half-wave potential reported for most organic molecules) can be misleading. The ionization potential offers a useful alternative but suffers from the same problem since it represents loss of one electron to form the ion. Table 3.2[20] gives a list of common organic substrates that can be oxidized. Most of these will be discussed in this chapter. It is presented only as an introduction to the relative ability of an organic substrate to be oxidized: The reader is cautioned to remember that the ability of an alkene to be oxidized will depend on whether the reaction involves epoxidation, hydroxylation, halogenation, or oxidative cleavage. With that caution in mind, the data in Table 3.2 suggest that primary alcohols are more easily oxidized than secondary alcohols (the lower value of I represents a substrate that is more easily oxidized) and alkenes are more easily oxidized than alkynes. The ionization potentials also suggest that sulfides and tertiary amines are easily oxidized. Table 3.2 also contains the ionization potentials for a few common oxidizing agents.

In the following sections, the emphasis will be on oxidation reactions that transform one functional group into another. The important transformations in this section will be oxidation of alcohols to carbonyls; oxidation of alkenes to diols or epoxides; and oxidative cleavage of alkenes to carbonyl derivatives. A few methods will be discussed for the oxidation of alkyl fragments, such as oxidation of a methyl group to hydroxymethyl, an aldehyde, or a carboxylic acid. The oxidation of sulfur and nitrogen compounds will also be briefly discussed. Any attempt to classify organic reactions by the oxidizing power of the reagent is

Table 3.2. Ionization potentials of common oxidizable organic substrates.

Molecule	*I* (eV)	Molecule	*I* (eV)
MeC≡CH	10.36	2-Butene	9.13
Benzene	9.24	$EtNH_2$	8.86
Me_3N	8.82	Et_2NH	8.01
O_2	12.06	O_3	12.3
H_2O_2	11.0	MeCHO	10.2
EtOH	10.49	EtCHO	9.98
1-Propanol	10.1	Acetone	9.69
2-Propanol	10.15	Cyclohexanone	9.14
Phenol	8.51	MeCOOH	10.36
$MeCO_2Me$	10.27	Me_3P	8.60
Me—S—Me	8.68	Et—S—Et	8.43
Cl_2	11.48	Br_2	10.54
I_2	9.28	RuO_4	12.33
OsO_4	12.97		

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difficult, since the classification depends on both reaction and reagent. Similarly, classification by organic substrate is difficult, since there are oxidations involving transfers of different numbers of electrons, giving different products. The choice of classification by functional group transform is intended to convey a general sense of the use of oxidation in organic synthesis and is specifically correlated with the disconnection-transform theme of this book. The reader is referred to the excellent monograph by Hudlicky[16b] for a thorough synthetic discussion of oxidation reactions.

3.2. ALCOHOLS TO CARBONYLS (CH—OH → C=O)

One of the most important oxidations in organic chemistry converts alcohols to aldehydes, ketones, or carboxylic acid derivatives. Alcohols are oxidized to carbonyl derivatives by a variety of oxidizing agents but the particular product formed depends on the structure of the alcohol as well as the reagent.[21] Primary alcohols are initially oxidized to aldehydes, which can be isolated, but it is possible to further oxidize that aldehyde to a carboxylic acid. Each of these oxidations is a two-electron process. It is also possible to convert a primary alcohol directly to an acid via a four-electron oxidation, although it likely proceeds by initial formation of an aldehyde. Secondary alcohols can be oxidized to ketones via a two electron process but harsher conditions can lead to oxidative cleavage (this would be a four-electron oxidation). These transformations correlate with one- and two-stage oxidations (see above). The discussion of alcohol oxidation must focus on the relative strength of the reagent, the conditions under which it is used, and structural variations of the alcohol substrate. This section will begin with the most common alcohol oxidizing reagent, Cr(VI). A discussion of other reagents, including the use of DMSO reagents, the Dess–Martin Periodinane reagent (sec. 3..D), the tetrapropylammonium perruthenate (TPAP, $Pr_4N^+RuO_4^-$), and others will follow.

3.2.A. Oxidation with Chromium (VI)

As seen in Table 3.1, Cr(VI) is a strong oxidizing agent. In sulfuric acid, the reaction of Cr(VI) has a reduction potential of 1.10 V but several chromium species may be present:

$Cr^{6+} + 3\,e^- \rightarrow Cr^{3+}$ (2N H_2SO_4)	1.10 V
$Cr_2O_7^{2-} + 14\,H^+ + 6\,e^- \rightarrow 2\,Cr^{3+} + 7\,H_2O$	1.33 V
$HCrO_4^- + 7\,H^+ + 3\,e^- \rightarrow Cr^{3+} + 4\,H_2O$	1.195 V

3.2.A.i. Chromium Reagents. Oxidation of an alcohol is accompanied by reduction of the chromium [Cr (VI) → Cr(III)]. As implied by the reduction potentials of the three chromium species shown, there are many Cr(VI) reagents,[22,23] but the most common is the inorganic reagent chromium trioxide, a polymeric species usually written as $(CrO_3)_n$. In aqueous media, chromium trioxide exists in equilibrium with several other Cr(VI) species, including H_2CrO_4, $HCrO_4^-$, CrO_4^{2-}, HCr_2O_7, $Cr_2O_7^{2-}$, $H_2Cr_2O_7$, and $HCr_2O_7^-$.[24] Of the Cr(VI) species listed in Table 3.1 dichromate is the strongest. Since oxidation of alcohols requires that both alcohol and chromium oxidant are soluble or partly soluble in the medium, most oxidations are carried out in aqueous media, where several Cr(VI) species are present. At high dilution, the excess of water shifts the overall equilibrium dichromate.[24,25] At higher concentrations (less water), polymeric chromium trioxide (polychromates) and chromic acid are the predominate species.[25] Dichromate is generated by "complex formation between the two acid chromate ions to give a dichromate anion".[26] Formation of this complex and its relative concentration are dependent on the pK_a of the acid. In dilute solution, the concentration of Cr(VI) is independent of the acid, but only if the acidity is below the apparent pK_a of chromic acid.[26] As the acid is changed, the pK_a of the complex increases with decreasing electron withdrawing power of the acid. The electrons on the oxygen atoms attached to chromium are less available for protonation,[26] leading to a larger dissociation constant,[27] which suggests that the position of the equilibrium depends on the acid. If a different acid (HA) is added to the mixture, it will influence the position of the overall equilibrium according to the reaction:[28]

$$HCrO_4^- + 2\,H^+ + A^- \longrightarrow HCrO_3A + H_2O$$

If the acid is more effective at withdrawing electrons from the complex ($HCrO_3A$), the pK_a for the reaction increases. There is, therefore, a correlation with the strength of the mineral acid and the $HCrO_3A$ species:[26,27]

$$H_3PO_4 < HCl < H_2SO_4 < HClO_4$$

The nature of the oxidizing species is obviously important for determining the mechanism of oxidation of an alcohol to a carbonyl with chromium (VI). As mentioned above, in aqueous solutions, CrO_3 generates CrO_4^{2-}, $HCrO_4^-$ and $HCr_2O_7^{2-}$ as the primary oxidizing species, along with several other chromium species.[29] At pH ≥ 1, CrO_3 is almost completely ionized.[29] Since organic molecules are being oxidized with chromium reagents, the focus tends to be on the organic molecule (the alcohol in this case) and Wiberg presented the following scheme to represent the oxidation of a secondary alcohol to a ketone:[30]

$$R_2CHOH + Cr(VI) \longrightarrow R_2C{=}O + Cr(IV)$$

$$R_2CHOH + Cr(IV) \longrightarrow R_2\dot{C}OH + Cr(III)$$
$$R_2\dot{C}OH + Cr(VI) \longrightarrow R_2C{=}O + Cr(V)$$
$$R_2CHOH + Cr(V) \longrightarrow R_2C{=}O + Cr(III)$$
$$3\ R_2CHOH + 2\ Cr(VI) \longrightarrow 3\ R_2C{=}O + 2\ Cr(III)$$

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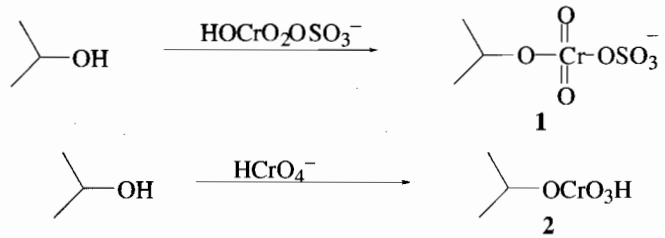
This mechanism shows that Cr(VI), Cr(IV) and Cr(V) species are involved in the overall oxidation process. Clearly, this is not a balanced equation, and the Cr species are undefined. The Cr(VI) species are usually $HCrO_4^-$ and CrO_3, the Cr(V) is usually $HCrO_4^-$ and the Cr(IV) is usually $HCrO_3^-$.[30] The actual oxidation involves both water (H_2O) and acid catalyst (H^+), and a balanced equation for the oxidation of 2-propanol is[2c]

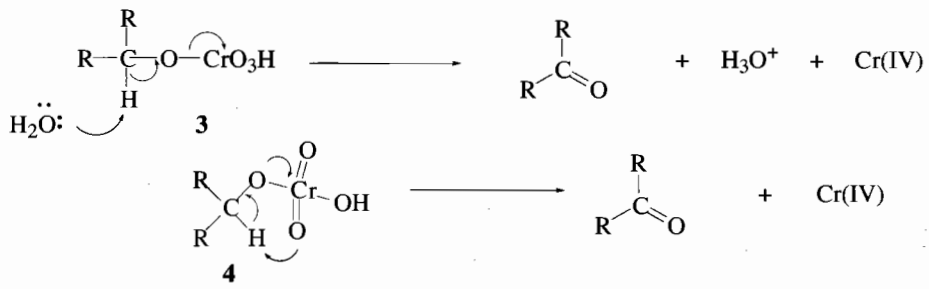
There is strong evidence that the oxidation begins by formation of a chromate ester,[31] which collapses t the carbonyl compound and a Cr(IV) species in the rate-determining step.[29,32,33] The driving force of th reaction is reduction of Cr(VI) to Cr(IV).[34] Westheimer determined that the rate term for the oxidation of 2- propanol was[33]

$$v = k_a\,[HCrO_4^-]\,[R_2CHOH]\,[H^+] + k_b[HCrO_4^-]\,[R_2CHOH]\,[H^+]^2$$

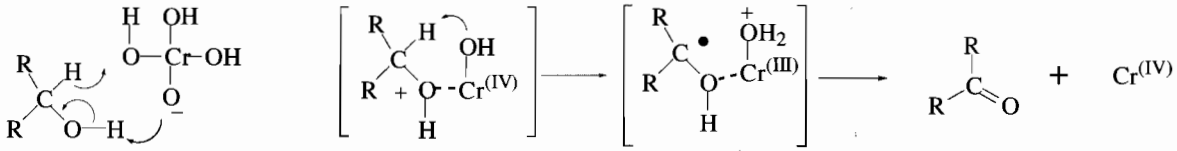
If sulfuric acid is used as the acid in an aqueous medium containing chromium trioxide and 2-propanol, the initial chromate ester is probably **1**, which arises from reaction of $HCrO_4^-$ and H_2SO_4 (HA in the abov equation).[26] In water containing no external acid, the chromate ester probably takes the form of **2**.[35]



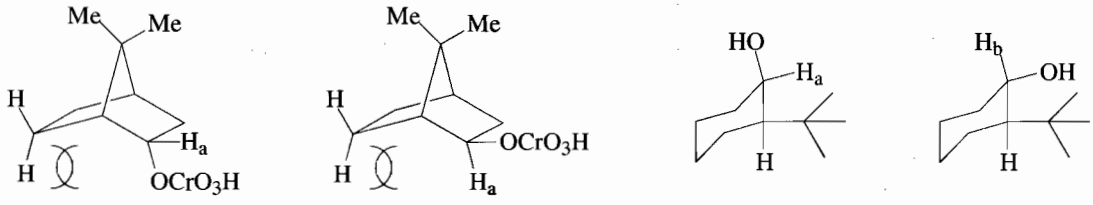
Decomposition of chromate ester **2** involves removal of the proton attached to the oxygen-bearing carbo Westheimer initially proposed that water behaves as a base to remove this hydrogen,[32,33,36c] although lat work showed that addition of pyridine to the reaction (a stronger base than water) did *not* enhance the rate o oxidation.[36] At least two mechanisms have been proposed for this step. Westheimer proposed an inte molecular attack by water, as mentioned (see **3**) but later retracted this proposal.[36c,37] Kwart and Franc proposed an intramolecular reaction for removal of the proton (see **4**), by an oxygen on the chromate ester. Roček discounted both mechanisms for several reasons, including the important observation that protonati should *not* lead to rate enhancement with a species such as **4**, but in fact it does. Roček proposed a mechanis



startng as shown in **5**,[36b] in which oxygens from the chromic acid removed hydrogens both from carbon and from oxygen. Roček later proposed[38] formation of a coordination complex such as **6**, presumably formed from Cr(IV) in a similar way to **6** (shown exactly as reported in the paper), that decomposed to a radical species (**7**). Further oxidation of **7** generated the products.



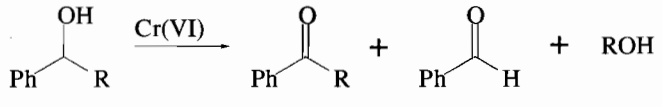
There is a steric component to this reaction. As the steric bulk around the carbon bearing the OH group increases, removing that hydrogen becomes increasingly difficult and the overall rate of oxidation will be diminished.[39] *endo*-Borneol (see **8**), for example, exhibits a relative rate of oxidation of 25.0:49.1 relative to *exo*-borneol (see **9**).[40a] This can be correlated with the more facile removal of H_a from chromate ester complex **8** (where H_a is on the exo face) than from complex **9** (where is H_a is on the more hindered endo face). Another example of steric hindrance can be seen in cyclohexyl derivatives by comparing *cis*-2-*tert*-butylcyclohexanol (**10**, relative rate 50.6) and *trans*-2-*tert*-butylcyclohexanol (**11**, relative rate 10.7).[40a] In both **10**



and **11**, the bulky *tert*-butyl group will occupy an equatorial position in the lowest energy conformation (sec. 1.5.D). The equatorial H_a on the hydroxyl-bearing carbon in **10** reacts with relative rate of 50.6. The chromate ester from reaction of **11** (an axial H_b) with chromic acid (relative rate 10.7), has a large steric interaction with the adjacent *tert*-butyl group (*G* strain - sec. 1.5.D). This rate difference is also observed with modified chromium reagents such as pyridinium chlorochromate (sec. 3.2.B.ii).[40b] Although there is little steric hindrance for the removal of H_b, formation of the chromate ester is inhibited. The chromate ester in **10** will occupy an axial position and there will be no *G* strain, although there will be *A* strain (sec. 1.5.D). Approach to H_a is somewhat hindered, and formation of the requisite chromate ester is energetically favorable.

From this discussion, it is apparent that oxidation of alcohols with Cr(VI) depends on several factors. The solvent and any acidic additives (or acidic solvents) will influence the rate of the oxidation as will the structure of the alcohol. It is therefore not surprising that there are many variations in reaction conditions for Cr(VI) oxidations of alcohols. As the substrate and the oxidizing requirements of the chromium are changed, the reaction medium will be changed.

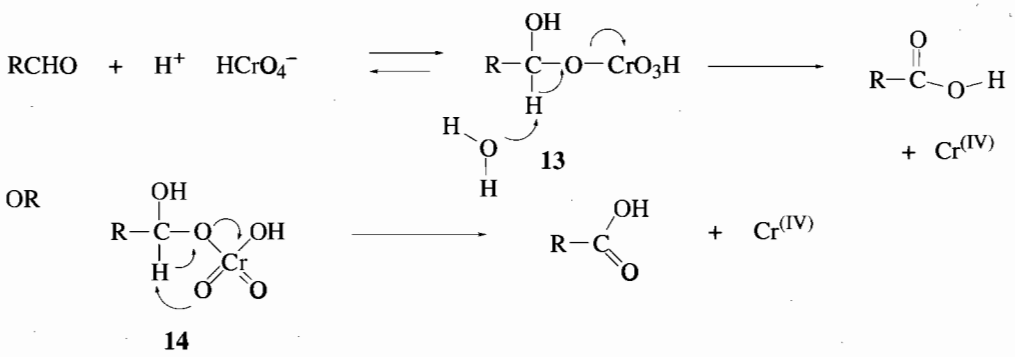
A common way to change reaction conditions for the oxidation of alcohols is to modify the acid that is added to the medium. Indeed, chromium trioxide will have different oxidizing abilities in different acids. Since most organic compounds are insoluble in water, a cosolvent is usually required to dissolve not only the chromium reagent but also the alcohol substrate. This solvent must be resistant to oxidation, and acetic acid or acetone are commonly used. For the alcohol → carbonyl conversion several Cr(VI) reagents can be used, including chromium trioxide in water or aqueous acetic acid catalyzed by mineral acid, sodium dichromate in aqueous acetone catalyzed by mineral acid, sodium dichromate in acetic acid, the CrO_3•pyridine complex, and *tert*-butyl chromate.[41] Both primary and secondary alcohols can be oxidized to the aldehyde or ketone, respectively. Aldehydes may be oxidized to the carboxylic acid under some conditions.



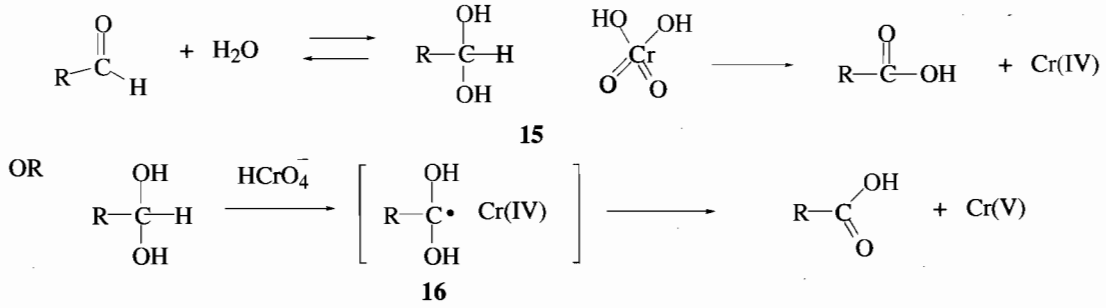
12

3.2.A.ii. Chromium Trioxide in Water or Aqueous Acetic Acid. Low molecular weight alcohols are usually sufficiently soluble in water that no cosolvent is required for oxidation with chromium reagents. 2-Propanol gives excellent yields of acetone in water, although the miscibility of acetone in water makes its isolation difficult. The presence of other oxidizable groups on the organic substrate such as alkenes, sulfides, phenolic, and amines often lead to side reactions in the oxidation of water soluble alcohols, significantly lowering the yield of carbonyl products. Sulfides are oxidized to sulfoxides, amines to hydroxylamines, and phenols to quinones, for example. Phenylalkyl carbinols are subject to oxidative cleavage with chromium trioxide in aqueous acid, as observed in the oxidation of **12**.[42] When the R group in **12** is isopropyl (*i*-Pr), only 6% cleavage was observed but changing R to *tert*-butyl led to 60% cleavage, presumably due to greater facility for generating a tertiary cation in the latter case.[42] Cleavage of this type is greatly suppressed by addition of manganous ion. Small amounts of cleavage products can be observed with hindered carbinols but this is a problem only when a stable carbocation can be produced.[43]

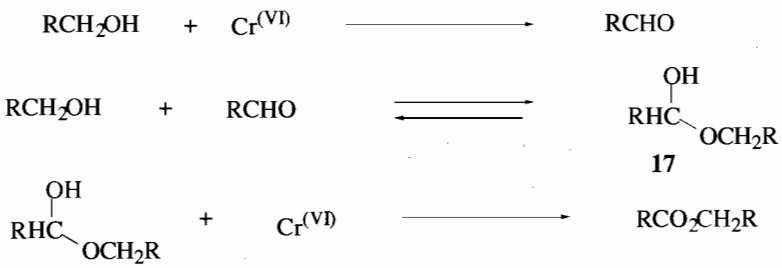
Oxidation of primary alcohols leads to aldehydes in moderate to good yield. Aldehydes are relatively easy to oxidize to the corresponding carboxylic acid. In most cases, the oxidation stops at the aldehyde, but small amounts of the acid are a common byproduct. Heating and long reaction times lead to increased amounts of the acid, and in some cases, the aldehyde is the minor product. Where feasible, removal of the aldehyde as it forms will minimize side reactions. When the reaction is pushed to give the carboxylic acid, there are at least two reasonable mechanistic rationales for this conversion.[44] These two approaches involve formation of a chromate ester such as **13**. Removal of the α-hydrogen (analogous to the alcohol to aldehyde conversion)



either intramolecularly (as in **14**) or by an external base (as in **13**) generates the acid. Oxidation to the acid may also occur by initial formation of a hydrate followed by removal of the α-hydrogen from **15**. This gives the acid moiety, although a radical process that generates **16** is also possible.[44]



With some primary alcohols, it is possible to establish an equilibrium between the initially formed aldehyde and the precursor alcohol in which unreacted alcohol is converted to an hemiacetal (**17**), which can be further oxidized to an ester.[45] This often accompanies the oxidation of lower molecular weight primary alcohols. Oxidation of 1-butanol to butyl butyrate with Cr(VI), for example, is an *Organic Syntheses* preparation.[46]

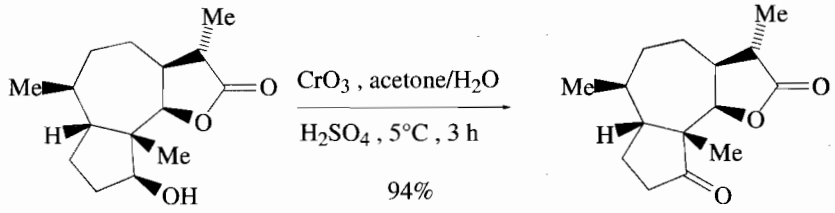


Some of the problems that accompany oxidation in water can be alleviated or moderated by using an organic cosolvent. Oxidations in aqueous acetic acid suppresses the oxidative cleavage to some extent as well as greatly improving the solubility of the organic substrate. It is possible to oxidize a wider variety of alcohols in this solvent. Bowman found that CrO_3 in anhydrous acetic acid was superior to CrO_3 in aqueous acetic acid for the oxidation of saturated alcohols. Oxidation of allylic alcohols in anhydrous acetic acid gave yields that were comparable to those obtained in aqueous media.[47] This improvement may be due to formation of an acetyl chromate ion ($AcOCrO_3^-$), analogous to chromate complexes formed with other acids (see $HCrO_3A$ see

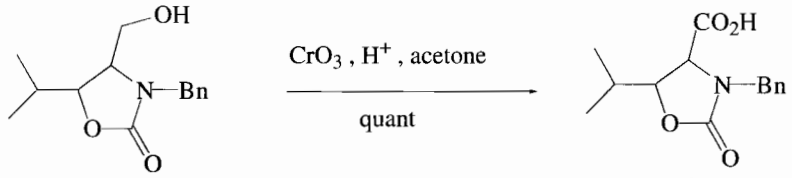
above). Such a species may increase the electron accepting power of chromium.[26,48]

$$H_2CrO_4 + AcOH \rightleftharpoons AcOCrO_3^- + H_2O$$

3.2.A.iii. Chromium Trioxide in Acetone: Jones Oxidation.[49] Organic solvents other than acetic acid can be used with aqueous chromium trioxide. Jones used acetone as a cosolvent in a dilute sulfuric acid solution, and found that oxidation of alkynyl carbinols was improved when compared to other known procedures. Secondary alcohols can be oxidized to ketones, and primary alcohols can be oxidized to either an aldehyde or a carboxylic acid. An example is the oxidation of **18** to give ketone **19** in 94% yield, taken from

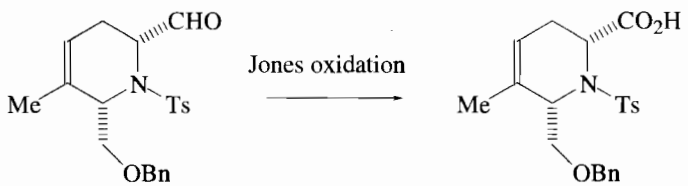


18 **19**



20 **21**

Ando's synthesis of hymenolin.[50] This chromium trioxide/acetone/sulfuric acid reagent is often referred to as the **Jones reagent**, and oxidation of alcohols with this reagent is called **Jones oxidation**. Direct conversion of a primary alcohol to an acid is seen in the oxidation of **20** to **21**, quantitatively, in Ōmura, Smith and coworker's synthesis of (+)-lactacystin.[51] Jones oxidation is especially useful for molecules that contain alkenyl or alkynyl groups.[52] Oxidation of alcohols is usually faster in acetone than in acetic acid, and using a large excess of acetone protects the ketone product from further oxidation.[53] Many primary alcohols are oxidized



22 **23**

to aldehydes with this procedure,[54] but the reaction conditions are strongly acidic and the final product is sometimes a carboxylic acid. However, there are many examples in which Jones oxidation has been used in the presence of reactive functional groups. If the starting material is an aldehyde rather than an alcohol, Jones oxidation can give the carboxylic acid. An example is seen in Weinreb's synthesis of cylindrospermopsin in which aldehyde (**22**) was oxidized to the acid, **23** in 82% yield.[55] Jones oxidation is compatible with complex

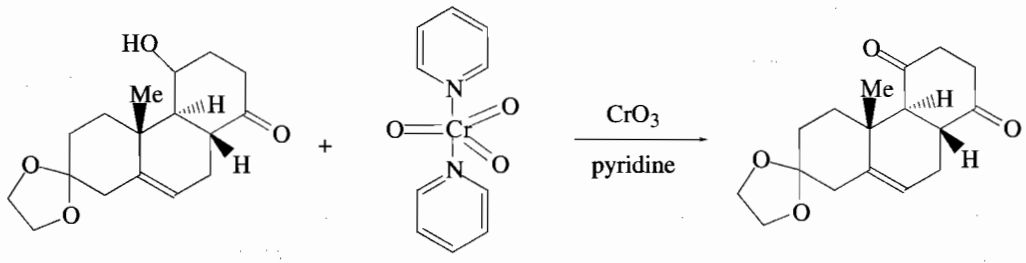
molecules that contain a variety of functional groups such as alkenes, tertiary alcohols, esters, ketones, oxetanes and amides.[56]

3.2.B. Modified Chromium (VI) Oxidants

Apart from changing the solvent, additives can be included in the reaction medium to create a new oxidizing reagent *in situ*. The fundamental Cr(VI) reagent can also be chemically modified prior to being used as an oxidizing agent. This section will examine both of these approaches.[57a]

3.2.B.i. Chromium Trioxide–Pyridine. In 1948, Sisler and co-workers isolated and characterized a stable complex from the reaction of chromium trioxide and pyridine.[57b] Sisler did not use this reagent for the oxidation of organic molecules but Sarett and co-workers recognized its utility in the synthesis of steroids. In this connection, alcohol **24** was oxidized to **26** in 89% yield.[58] The reagent, which probably has the trigonal bipyramidal structure shown in **25**, proved useful for the general oxidation of primary and secondary alcohols, even in the presence of double bonds and thioethers,. The oxidation usually requires pyridine as a solvent and was referred to as **Sarett oxidation** for many years. Care must be exercised in preparing the reagent.

The solution "must always be prepared by cautious addition of chromium trioxide to pyridine which has been carefully purified by distillation from potassium permanganate."[59] *Reversing this order of addition may cause the mixture to ignite spontaneously.*[60]

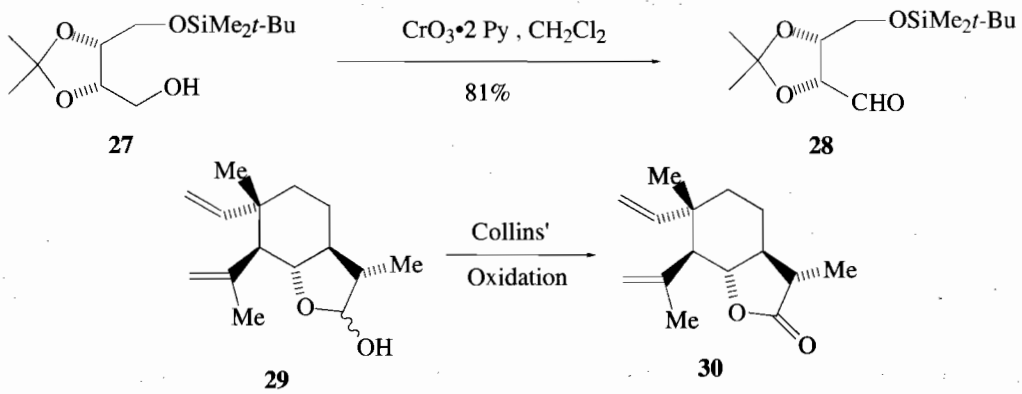


24 **25** **26**

A second problem with Sarett oxidation is the difficulty in isolating the products from a pyridine solution. An advantage of the technique, as mentioned above, is that alkenes, ketals, sulfides, and tetrahydropyranyl ethers are oxidized much slower than alcohols and rarely give competitive side reactions.[61] Oxidation of secondary alcohols proceeds in good yield, but oxidation of primary aliphatic alcohols often gives low yields of the aldehyde.[62] Benzylic and allylic alcohols give good yields, however.

A modification was introduced by Collins et al.,[63] and when applied to the oxidation of alcohols it has come to be known as **Collins oxidation**. This modification was developed to circumvent the danger inherent in preparing the reagent, deal with the problem of poor yields in the oxidation of primary alcohols to aldehydes, and facilitate isolation of the carbonyl products. The Sisler-Sarett reagent formed by reaction of chromium trioxide and pyridine was first removed from the pyridine solvent and added to dichloromethane, and this mixture was then treated with the alcohol. The oxidation typically required a 5:1 or 6:1 ratio of complex/alcohol, and reaction occurred at ambient temperatures.[47] Cyclohexanol was oxidized to

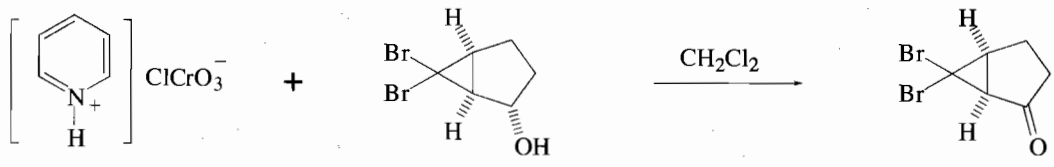
cyclohexanone in 98% yield by this method and 1-heptanol was oxidized to heptanal in 93% yield. The yield of aldehyde products from primary alcohols was significantly better, but a large excess of the reagent was required and the isolation problems persisted. Nonetheless, Collins oxidation has become a mainstay of organic synthesis. An example is Piccialli's oxidation of **27** to the aldehyde **28** in a synthesis of pinolidoxin.[64] Allylic alcohols are easily oxidized to the corresponding conjugated ketone or aldehyde with this reagent, and Urones used this type of oxidation in a synthesis of (–)-hyrtiosal.[65] This reagent can be used with groups that are more sensitive to hydrolysis or to over-oxidation. These include lactols, as illustrated by Ando's conversion of lactol **29** to lactone **30**.[66]



27 **28** **29** **30**

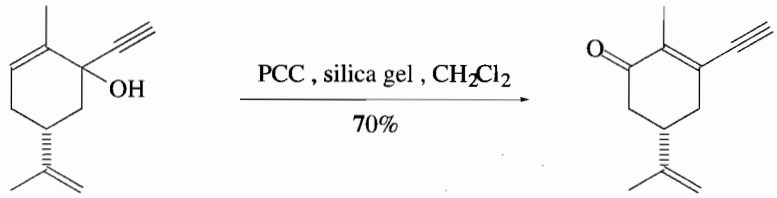
Ratcliffe and co-workers further improved this procedure by preparing dichloromethane solutions of the chromium trioxide–pyridine complex directly.[67] Addition of chromium trioxide to a solution of dichloromethane and pyridine was followed by the alcohol, which is the procedure typically used today, but it is still referred to as Collins oxidation.

3.2.B.ii. Pyridinium Chlorochromate. The need for improved oxidation of primary alcohols and greater ease for isolation of products prompted further research into the nature of Cr(VI) reagents. Corey found that addition of pyridine to a solution of chromium trioxide in aqueous HCl allowed crystallization of a solid reagent characterized as **31**, pyridinium chlorochromate (**PCC**).[68] This reagent was superior for the conversion of primary alcohols to aldehydes in dichloromethane but less efficient than the Collins oxidation when applied to allylic alcohols.[69] Oxidation of 1-heptanol with PCC in dichloromethane gave 78% of heptanal, for example. As stated by Corey, PCC is an effective oxidant in dichloromethane although aqueous chlorochromate species are not very effective oxidants.[69] Oxidation of secondary alcohols to ketones is straightforward, as in Banwell's synthesis of γ-lycorane, in which **32** was oxidized by PCC to the ketone (**33**).[70]



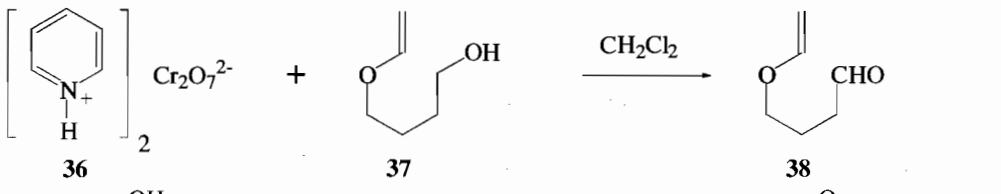
31 **32** **33**

A drawback to the use of pyridinium chlorochromate is its mild acidity. It is inferior to Collins oxidation when the oxidation products or the starting alcohol is acid sensitive. This acidity can be used to synthetic advantage, however, and Corey described its use to promote oxidative cationic cyclizations.[71] Reaction of citronellol with PCC in dichloromethane was accompanied by cationic cyclization reaction to give (-)-pulegone as the final product.[72a,68] Rearrangements such as oxidative transpositions can also occur.[72b] When **34** was treated with PCC on silica gel, in dichloromethane, a 70% yield of conjugated ketone **35** was isolated, which was part of Sarikrishna's synthesis of 1a,25-dihydroxyvitamin D_3.[73] Oxidations using PCC on alumina[74] have also been reported, presumably to minimize acid-catalyzed rearrangement. The PCC reagent has also been used in the synthesis of dihydropyranone derivatives from 2-furyl alcohols,[75] in the conversion of oximes to ketones,[76] and in the direct oxidation of tetrahydropyranyl protected alcohols to aldehydes.[77]

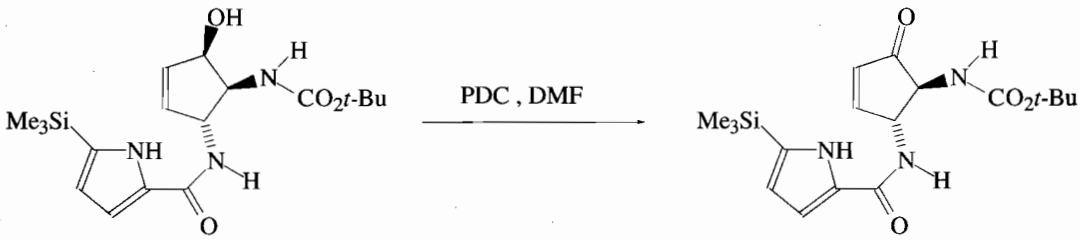


34 **35**

3.2.B.iii. Pyridinium Dichromate. Problems caused by the acidity of PCC can be largely eliminated by using the more neutral reagent pyridinium dichromate (**PDC**), **36**. Although first used by Coates and



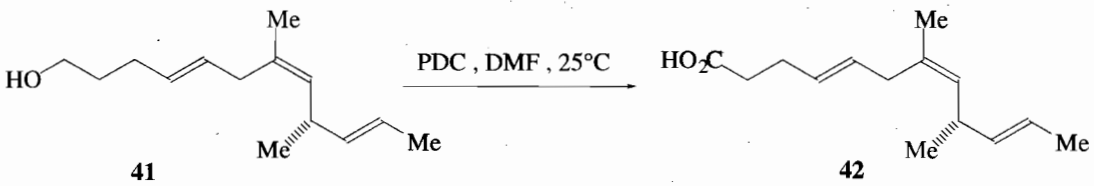
36 **37** **38**



39 **40**

Corrigan[78] it was not exploited synthetically until Corey prepared the reagent by addition of pyridine to neutral chromium trioxide solutions and used it for the oxidation of alcohols to aldehydes, ketones, and acids.[79] The reagent is not acidic and the neutral conditions required for the oxidation are superior for the oxidation of allylic alcohols. In dichloromethane (nonaqueous workup) the oxidation is similar to that of PCC. Addition of catalytic amounts of pyridinium trifluoroacetate in dichloromethane significantly increases the rate of oxidation. Allylic alcohols are oxidized faster than aliphatic alcohols, making PDC the reagent of choice for this transformation. Cyclohexenol, for example, is oxidized 10 times faster than cyclohexanol with

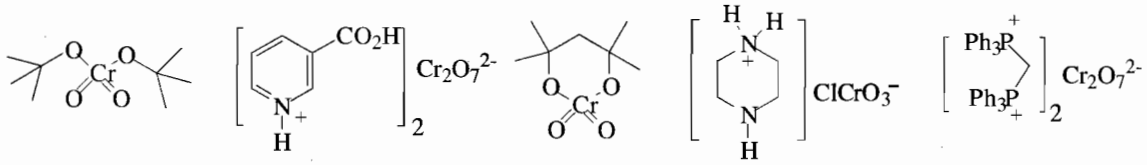
PDC in dichloromethane at 25°C.[79] Primary aliphatic alcohols are also oxidized, however, under very mild conditions.[80] This oxidation occurs under essentially neutral conditions, as shown by the reaction of **37** with PDC to give aldehyde **38** in 92% yield, despite the presence of the acid sensitive enol ether.[79] This reagent is very effective for many types of alcohols,. In Yokokawa's synthesis of (–)-hennoxazole A,[81] alcohol **41** was converted to carboxylic acid **42** in 72% yield.



41 **42**

In the oxidation of **39**, the solvent was changed from dichloromethane to DMF, which can sometimes be necessitated by solubility problems. However, when the solvent is DMF there is a significant difference between the oxidation of aliphatic primary alcohols and that of allylic primary alcohols. Cyclohexenol is oxidized to cyclohexenone in 86% yield with PDC in DMF at 0°C.[79] Similarly, geraniol was oxidized to geranial in 92% yield. It is important to note that treatment of non-conjugated primary alcohols with PDC in DMF at ambient temperatures often give carboxylic acids rather than an aldehyde. For example, oxidation of **41** with PDC in DMF, at 25°C, gave acid **42** in high yield.[82] It is also interesting to note that Smith reported the oxidation of an aldehyde to the corresponding carboxylic acid with PDC in DMF in a synthesis of (+)-thiazinotrienomycin E.[83]

3.2.B.iv. Structurally Modified Chromium Reagents. The literature is full of chromium trioxide complexes that have been developed by adding amine or phosphine bases, usually with the goal of varying the

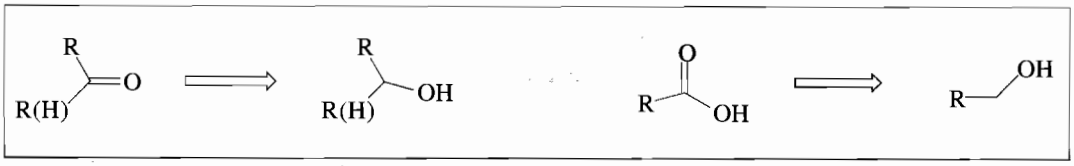


43 **44** **45** **46** **47**

specificity of the oxidation. Alternatively, stabilized chromate esters have been prepared and found to be effective oxidizing agents. If the oxidizing power of these modified reagents can be generalized at all, it may be said they behave similarly to PCC or PDC. Some examples are **43**,[84] **44**,[85] **45**,[86] and **46**,[87] and **47**.[88] The reasons for developing modified reagents varies with the application. In many instances, they were developed to alleviate problems with isolation of products or with the use of large excess of the oxidizing reagent (as with Sarett and Collins oxidations). In other cases, the need for decreased acidity, for improved solubility in low-boiling aprotic organic solvents, or for increasing (or decreasing) the relative oxidizing power of the chromium reagent provided the driving force for developing the new reagent. In the cases of **43** and **45**, chromyl chloride (CrO_2Cl_2) was the chromium precursor rather than chromium trioxide. Another modifi-

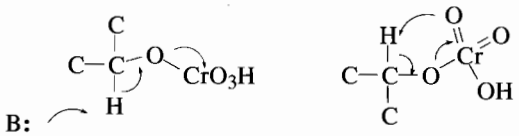
cation used amine bases other than pyridine, giving the PDC analog **44** and the PCC analog, **46**. Another approach involved changing the amine base to a phosphine and **47** used a bis-phosphine (1,1-bis-triphenyl-phosphinomethane) to generate this PDC analog. Oxidation with modified chromium reagents proceeds in a manner similar to PCC and PDC oxidations. Reagent **45** was developed by Corey, and is of particular interest in that it can be used as a *catalytic* oxidizing agent (only 2% of **45** was required for the oxidation of cyclooctanone from cyclooctanol) in the presence of peroxyacetic acid (in dichloromethane).[86]

The functional group transforms for the oxidations in this section are



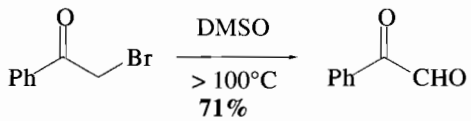
3.2.C. Dimethyl Sulfoxide Oxidations[89]

Section 3.2.B.iv discussed the oxidation of alcohols using derivatives of the transition metal Cr(VI), many of which required acidic conditions. Many alcohols, especially those bearing sensitive functional groups, require neutral oxidizing conditions. The development of PDC and related reagents helped to solve



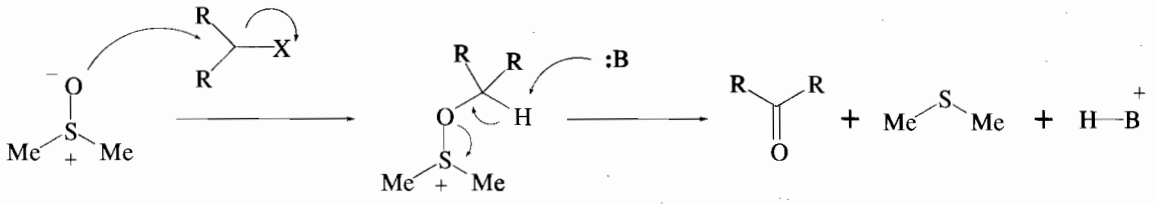
48 **49**

this problem, but there are cases where PDC or PCC give poor yields, primarily with hindered alcohols. The key to Cr(VI) oxidations was formation of a chromate ester and removal of the acidic α-hydrogen (as in **48**). In one sense, the chromate ester behaved as a leaving group and removal of the hydrogen that is β to the chromium makes the reaction *conceptually* analogous to an E2 reaction (sec. 2.9.A). The problem with this analogy is, of course, that there is no direct evidence for removal of that hydrogen in **49** by an external base (see above).[35,36] The evidence suggests removal of the hydrogen via an intramolecular process, as in **49**, which is formally analogous to the syn-elimination discussed in section 2.9.C. One way to design a new method for oxidizing alcohols is to replace the chromate ester with another leaving group such that the β-hydrogen to that leaving group could be removed intramolecularly or intermolecularly. It has been shown by a number of workers that DMSO is capable of forming exactly this type of group, where dimethyl sulfide (Me_2S, abbreviated DMS) functions as the leaving group from a sulfoxonium intermediate. Treatment with mild base leads to removal of the appropriate hydrogen and expulsion of DMS generates ketones and aldehydes from alcohols. There are many variations of this reaction.



50 **51**

Dimethyl sulfoxide functions as both a solvent and a reactant for a variety of alcohol substrates. The nucleophilic oxygen can react with electrophilic centers to form a sulfoxonium salt, which can be converted to ketones or aldehydes under neutral conditions. Kornblum et al. first observed this process, but with halides rather than with alcohols,. He reported that reaction of α-halo ketones with DMSO at elevated temperatures gave good yields of the corresponding glyoxal (an α-keto-aldehyde).[90] By this procedure, phenylacetyl bromide (**50**) was oxidized to **51** in 71% yield.[90] The contact times were usually very short and it was often difficult to isolate high boiling glyoxals from DMSO. If the glyoxal could be removed from the reaction medium by distillation as it was formed, however, the reaction was very efficient. This transformation is not limited to α-halo ketones. Both primary[91] and secondary[92] alkyl iodides or tosylates can be converted to aldehydes or ketones, although they are much less reactive than α-halo ketones. Reaction of 1-bromooctane with DMSO and $NaHCO_3$ at 100°C, for example, gave octanal in 74% yield after 5 minutes[91] and can be compared with the conversion of an alkyl tosylate to a ketone, which requires temperatures of 150–170°C and an acid receptor such as sodium bicarbonate to be present. Elimination is a serious side reaction and oxidation of secondary α-halo ketones often gives poor yields.[93] The mechanism probably involves nucleophilic displacement of halides by DMSO to form an alkoxysulfoxonium salt, **52**. Removal of the α-proton, probably by DMSO, leads to the carbonyl product and DMS(which functions as the leaving group).[94]



52

A similar type of oxidation was observed when alcohols reacted with DMSO. Traynelis and Hergenrother showed that benzylic and allylic alcohols were converted to the aldehyde in high yield by refluxing them in DMSO with air bubbling through the medium.[95] In this case, air was a reagent and cinnamyl alcohol was oxidized in this manner to cinnamaldehyde in 90% yield.[95] Air is the oxidant and DMSO probably functions as a solvent.

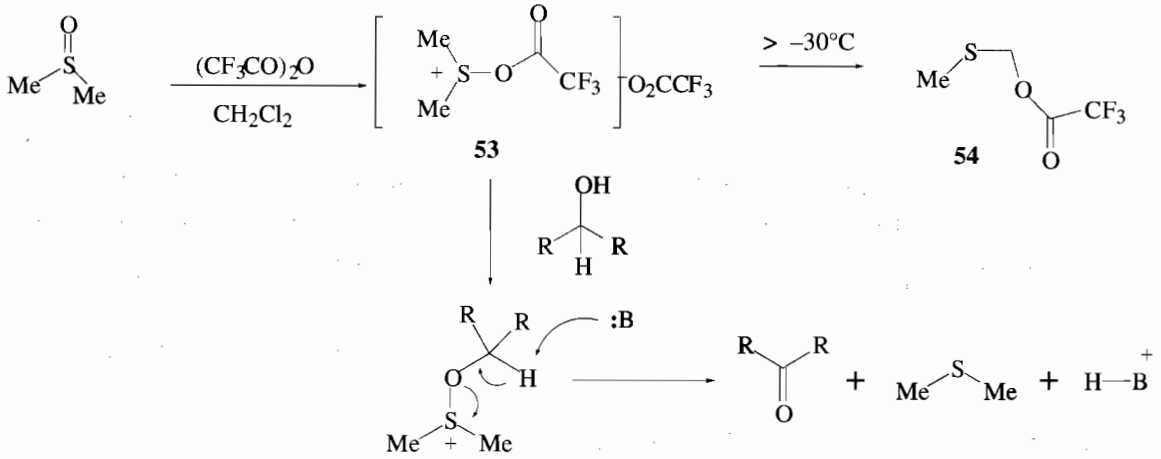
There are several variations of this basic reaction involving DMSO. In each case, another reagent is added to activate the DMSO–alcohol oxidation reaction. Several variations will be presented.

3.2.C.i. Swern Oxidation. The variation that is probably the most common in synthesis was discovered by Swern, who found that DMSO can be activated for the oxidation of alcohols by addition of trifluoroacetic anhydride.[96] The reaction is usually done in dichloromethane at temperatures below –30°C. The initially

In the absence of a moderating solvent, admixture of DMSO and trifluoroacetic anhydride proceeds explosively.

formed trifluoroacetyl derivative (**53**) is stable below -30°C but at higher temperatures undergoes a **Pummerer**

rearrangement to give **54**.[97] At lower temperatures, the initially formed sulfoxonium intermediate (**53**) reacts with an alcohol to form **52** and then loses DMS to form the ketone or aldehyde. This mechanism is common

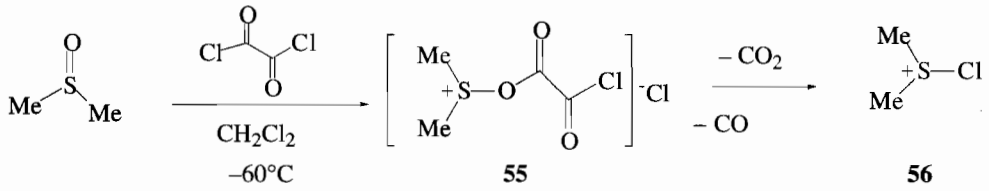


for virtually all of the oxidations presented in this section, where the reagent used to generate **52** varies. Both primary and secondary alcohols are converted to the corresponding aldehyde or ketone. An important and interesting feature of Swern oxidations is their low sensitivity to steric encumbrance. Oxidation of the moderately hindered alcohol 2,4-dimethyl-3-pentanol gave 2,4-dimethyl-3-pentanone in 86% yield.[96] Oxidation of a primary alcohol to the corresponding aldehyde is also facile. Amines are commonly added to facilitate decomposition of the initially formed complex that results from addition of the alcohol to **53**. Oxidation of 1-decanol under the original Swern oxidation conditions gave a 56% yield of decanal when triethylamine was added. Addition of diisopropylamine rather than triethylamine increased the yield to 81%.[98] Swern oxidation can be used in molecules containing quite a bit of functionality, and as mentioned it tolerates alcohols that are somewhat sterically hindered.

Swern also found that oxalyl chloride activates DMSO for the oxidation of alcohols.

The reaction is violent and exothermic at ambient temperatures.

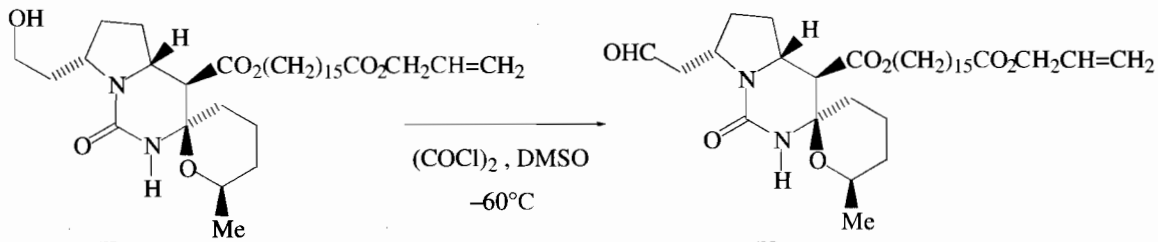
The resulting reagent is superior to the DMSO–trifluoroacetic anhydride reagent.[99] The reaction probably proceeds via intermediate complex (**55**), which is unstable above -60°C. The reaction is, therefore, performed



at temperatures at or below –60°C, and it proceeds with loss of carbon dioxide and carbon monoxide to give chlorosulfonium salt **56**.[96] Subsequent reaction with the alcohol and deprotonation in the usual manner gives the carbonyl and dimethyl sulfide. Cyclododecanol was oxidized to cyclododecanone in 97% yield with this

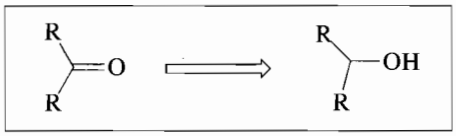
reagent, and hex-2-en-1-ol was oxidized to the conjugated aldehyde 2-hexenal in good yield.[96] Oxidation with DMSO and oxalyl chloride is often called **Swern oxidation** although this term can also be used with the DMSO–trifluoroacetic anhydride oxidation.

A typical synthetic use is the conversion of **57** to aldehyde **58** (87% yield), taken from Overman's synthesis of ptilomycalin.[100] In many synthetic sequences, one will find the term Swern oxidation or simply Swern over a reaction arrow rather than giving the reagents. This is quite common, forcing the reader to recognize certain named reactions, hence the highlighted names for many reactions in this book.

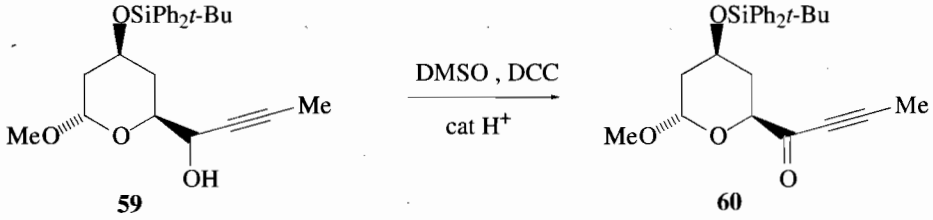


57 **58**

The functional group transform for DMSO-type oxidations is



3.2.C.ii. Moffatt Oxidation. In order to oxidize the alcohol with DMSO the oxygen of DMSO must displace the hydroxyl group, which is inherently a poor leaving group. Moffatt 's solution to this problem was

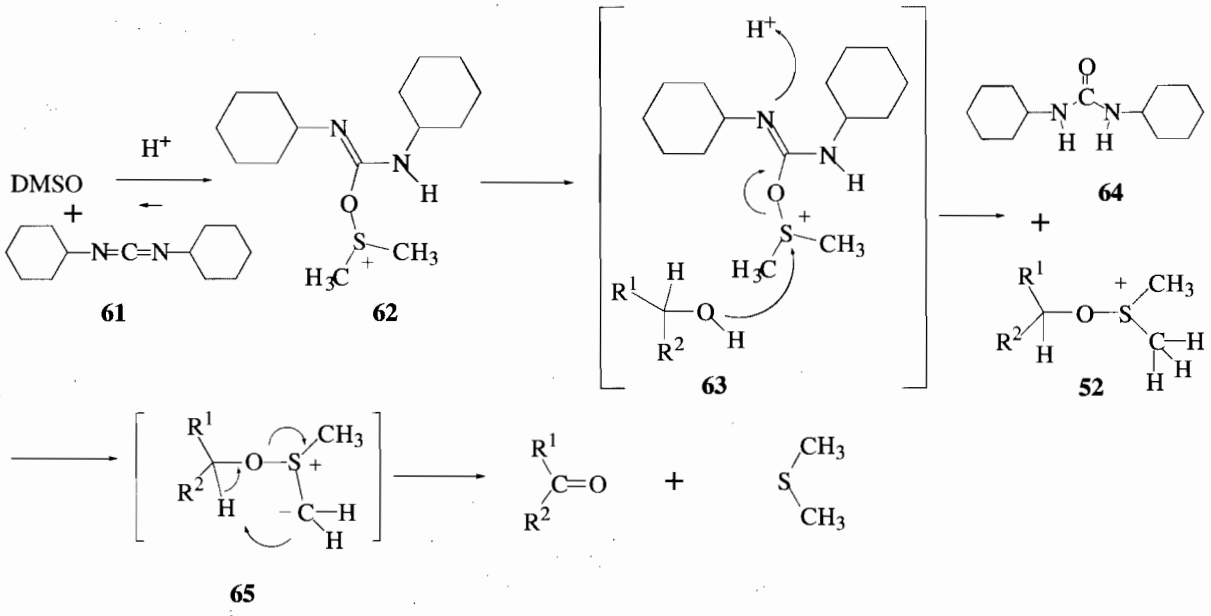


59 **60**

to turn the problem around. Rather than DMSO behaving as a nucleophile to displace a functionalized alcohol, Moffatt functionalized the DMSO, enabling the oxygen of the hydroxyl group to attack sulfur and generate an intermediate such as **52**. This work *predated* the Swern oxidation. A mixture of DMSO and dicyclohexylcarbodiimide (DCC, **61**), in the presence of an acid catalyst, was shown to be a mild and efficient oxidizing reagent for alcohols.[101] This type of reaction has come to be known as **Moffatt oxidation** and an example is the conversion of **59** to **60** (83% yield), used in Smith's synthesis of (+)-acutiphycin.[102] DMSO-based oxidants such as the Moffatt oxidation is also the reagent of choice for the synthesis of nucleoside aldehydes.

A mechanistic rationale for this oxidation was provided by Moffatt,[103,101] where the driving force of the reaction is formation and separation of the highly insoluble dicyclohexylurea (**64**). An alkoxysulfonium

intermediate (**63**) provides a conceptual link to other DMSO based methodology. The DMSO reacts with DCC (**61**) to form sulfoxonium intermediate **62**, which now contains a urea leaving group (see **63**), allowing the alcohol to attack the sulfur. Dicyclohexylurea (**64**) is displaced, generating the requisite sulfoxonium salt, **52**. Deprotonation of the sulfoxonium salt is probably an intermolecular process and occurs with bases as weak as the acetate ion. Deprotonation generates a sulfur ylid (**65**; sec. 8.8.B), which is stabilized by the d orbitals of sulfur.[104] A result of this interpretation is that the carbanion center in the sulfur ylid removes the α-hydrogen intramolecularly (as shown in **65**). The alternative is to have that proton removed from **65** by the base in an intermolecular reaction, as shown above for **52**. By either mechanism, the carbonyl product and DMS are liberated. An alternative mechanism could involve reaction of the alcohol and DCC to form a complex prior to its reaction with DMSO, but this has not been observed.[105] Removal of the appropriate hydrogen as in **65** is formally analogous to the syn-elimination mechanism discussed in section 2.9.C.

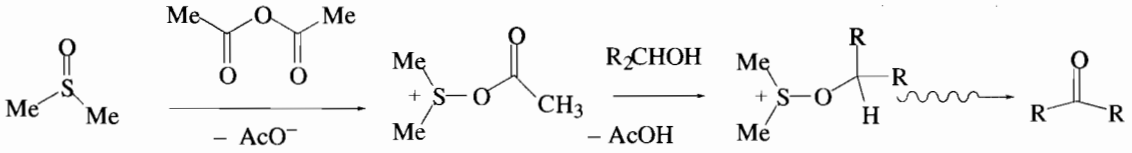


The initial reaction with DMSO is usually fast but overall oxidation is quite slow unless mineral acids or strong organic acids such as dichloroacetic acid or trifluoroacetic acid are added to the reaction.[106] The pyridinium salts of strong acids are also good catalysts, exemplified by the pyridinium salts of orthophosphoric acid and trifluoroacetic acid. Reagents formed in the presence of these acid gave clean and rapid oxidation of primary and secondary alcohols in the Moffatt oxidation. *o*-Phosphoric acid,[107] dichloroacetic acid, and pyridinium trifluoroacetate are the most common acids used in this oxidation.[108]

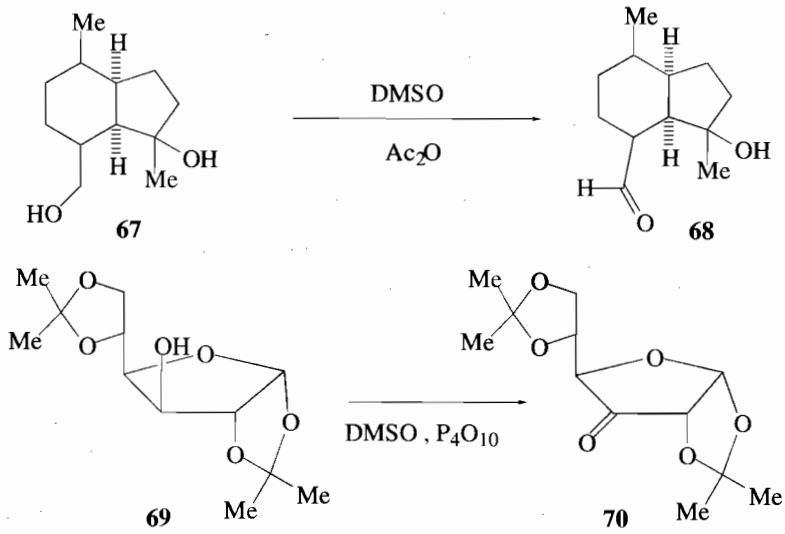
Moffatt oxidation has several problems associated with it. One is formation of the urea product **64**, which can be very difficult to remove. Treatment with oxalic acid is the most common method employed for the removal of the last vestiges of the dicyclohexylurea byproduct.[109] Oxidation of homoallylic alcohols is sometimes accompanied by isomerization of the double bond into conjugation with the carbonyl group. This can be minimized or prevented by addition of pyridinium trifluoroacetate. A threefold excess of DCC and an excess of DMSO are usually required for Moffatt oxidation and these must be removed from the product. The

DMSO need not be the solvent, however, and cosolvents such as ethyl acetate often give better results. Many applications are possible due to the neutral oxidizing conditions and lack of side reactions, and a variety of functionalized substrates containing alcohol moieties have been oxidized. Tertiary alcohols are, of course, resistant to Moffatt oxidation and dehydration has been observed in such systems,[110] giving the alkene and regenerating DMSO.[110] Some steroidal allylic alcohols dehydrate to a heteroannular diene under these conditions.[111]

3.2.C.iii. Other DMSO Oxidations. Albright and Goldman developed a reagent using DMSO and acetic anhydride that formed an active sulfoxonium complex.[112] In the initial work, yohimbine was oxidized to the ketone (yohimbinone) in 85% yield, at ambient temperatures in 24 h.[112] As with DCC, DMSO initially reacts with acetic anhydride to form sulfoxonium salt **66**, which then reacts with the alcohol. Acetate is the leaving



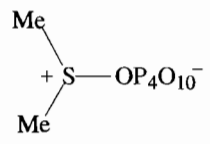
group attached to sulfur, and reaction with an alcohol generates **52**. Removal of the α-proton by acetate gives **65** as before (see above), the precursor to the ketone or aldehyde. A major advantage of this method is the production of water soluble byproducts. It is especially effective with hindered alcohols. With unhindered alcohols the products are often acetate esters and thiomethoxymethyl esters. Conversion of **67** to aldehyde **68**[113] illustrates the oxidation of a primary alcohol.



Onodera et al. developed a reagent for the oxidation of alcohols that used DMSO and phosphorus pentoxide. It is very efficient for the oxidation secondary alcohols, particularly those found in carbohydrates.[114] The alcohol moiety in **69**, for example, was converted to ketone **70** in 65% yield.[114] The

initial intermediate was probably the sulfoxonium derivative (**71**), which was attacked by the alcohol. Deprotonation of the alkoxy-sulfoxonium ion in the usual manner gave the ketone. Virtually all examples of oxidation with this reagent involved carbohydrates.

The complex formed by pyridine-sulfur trioxide was shown to activate DMSO for oxidation, when a base such as triethylamine is present.[115] The presumed intermediate is **72**. Reaction of the alcohol generates the usual complex (**52**). Deprotonation by triethylamine gives **65**, and this gives the carbonyl product. Stereo-



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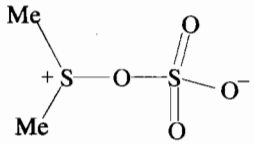

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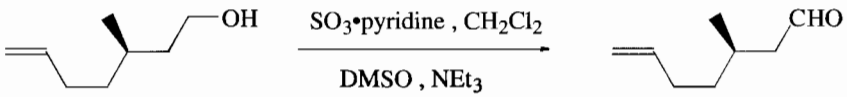
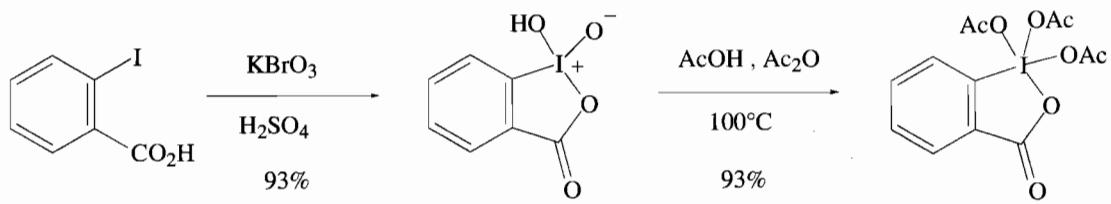


73 **74**

chemical differences in the alcohol are important with this reagent. Alcohols with different stereochemical and conformational properties can have great differences in the rate of their oxidation, which leads to differences in the selectivity for the oxidation of related alcohols. This modification is found in several syntheses of natural products. In one example, the primary alcohol unit in **73** was oxidized to aldehyde **74** in 85% yield, as part of Hagiwara's synthesis of (*R*)-(–)-muscone.[116]

3.2.D. Dess–Martin Periodinane Oxidation

The search for mild oxidizing reagents that convert alcohols to aldehydes or ketones under neutral or near neutral conditions has produced a new type of reagent that contains a hypervalent iodine.[117] Dess and Martin showed that 2-iodobenzoic acid (**75**) reacted with $KBrO_3$ in sulfuric acid to give a 93% yield of **76**. Subsequent heating (100°C) with acetic anhydride and acetic acid produced **77** in 93% yield, the so-called **Dess–Martin periodinane**.[118] This reagent converted alcohols to ketones or aldehydes, illustrated by the transformation of cyclohexanol to cyclohexanone in 90% yield, in dichloromethane at 25°C.[118] In this particular

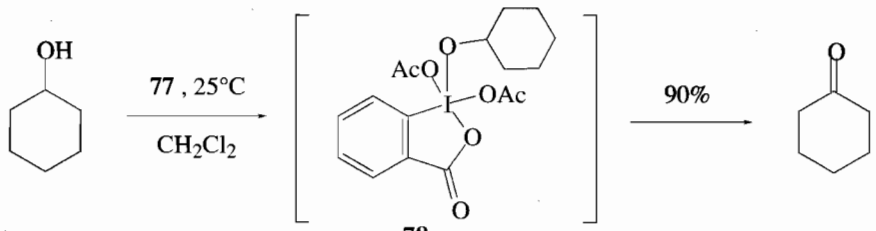


75 **76** **77**

reaction, an intermediate was trapped and its structure shown to be **78**.[118] The reagent appears to have an indefinite shelf-life in a sealed container but hydrolysis occurs upon long-term exposure to atmospheric moisture.

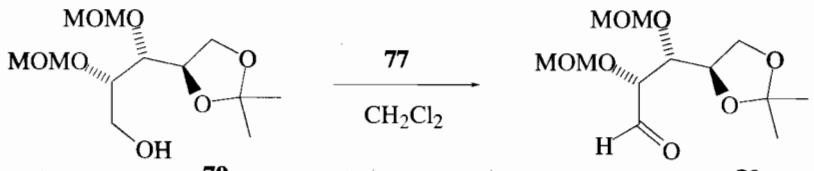
The Dess–Martin reagent can be shock sensitive under some conditions and it explodes above 200°C.[119] An improved procedure for its preparation is available.[120]

Hypervalent iodine reagents are well-known oxidizing agents,[121] and they can oxidize the α-position of methyl ketones to give the corresponding α-hydroxyketone.[122] Oxidation with this reagent does not require an inert atmosphere but a catalytic amount of trifluoroacetic acid can be added to accelerate the oxidation, although the catalyst is not required. It has also been shown that a Dess–Martin intermediate can be generated in aqueous media and used for oxidation.[123] Dess and Martin prepared several other periodinane reagents that can also be used to oxidize alcohols,[124] as well as a chiral hypervalent organoiodinane derived from a binaphthyl.[125]



78

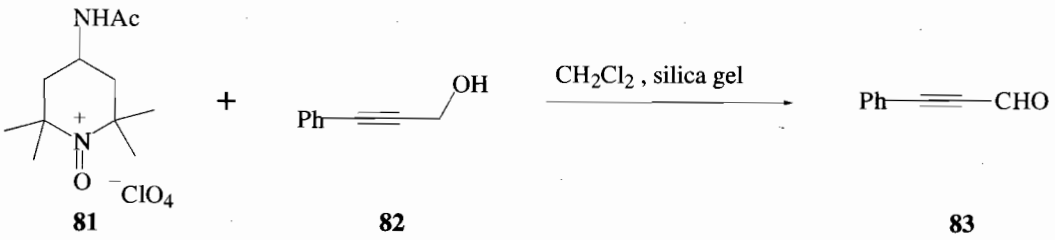
There are many synthetic applications in the recent literature. The most common application is the oxidation of primary alcohols where the substrate can tolerate only a narrow range of reaction conditions or is part of a highly functionalized molecule.[126] Secondary alcohols can also be oxidized under very mild conditions. A synthetic example is taken from Tadano's synthesis of (–)-mniopetal E,[127] in which the primary alcohol unit in **79** was oxidized to the aldehyde unit in **80**.



79 **80**

3.2.E. Oxidation with Oxammonium Salts

Oxammonium salts such as **81** are new and powerful oxidizing agents for the selective oxidation of alcohols to aldehydes or ketones.[128] Such salts can be generated catalytically from small amounts of a nitroxide in the presence of a secondary oxidation procedure, either chemical or electrochemical,.[129] or with two equivalents of acid and 2 equivalents of a nitroxide.[130] When **81** was mixed with acetylenic alcohol **82** in dichloromethane, aldehyde **83** was isolated in 93% yield.[131] The reaction can be monitored as the initial yellow slurry changes to a white slurry and the presence of unreacted oxidant can be checked with starch.[131] It is not necessary to use anhydrous conditions, and it was discovered that the rate of reaction was enhanced by the presence of silica gel. This reagent is compatible for the mild oxidation of many alcohols, including aliphatic primary and secondary as well as allylic and benzylic alcohols.

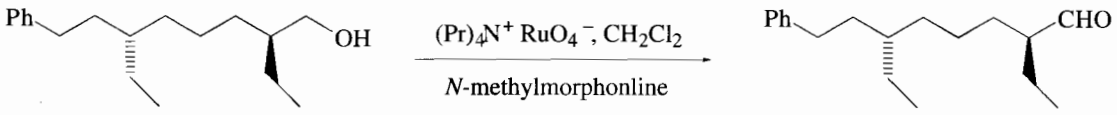


81 **82** **83**

3.2.F. Oxidation with Other Metal Derivatives

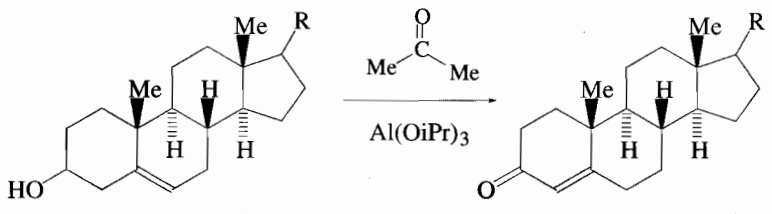
The oxidation of alcohols is not limited to chromium derivatives, DMSO derivatives, or hypervalent iodine compounds. There are several metal-based reagents that can be very effective, particularly with sensitive functionality. This section will examine several of the more important regents.

3.2.F.i. Tetrapropylammonium Perruthenate–Ley Oxidation. Ruthenium derivatives have been used for oxidation reactions. A particularly useful one is TPAP, introduced by Ley for the oxidation of alcohols and called **Ley oxidation**.[132] It is a very mild oxidizing agent that is compatible with many sensitive functional groups. An example of its use is the oxidation of **84** to **85** in 85% yield, as part of Meinwald's synthesis of components from a crocodile exocrine secretion.[133]



84 **85**

3.2.F.ii. Oppenauer Oxidation. In oxidation reactions involving both Cr(VI) and DMSO reagents, the alcohol is converted to a complex in which the α-hydrogen of an alcohol can be removed as an acid. A classical and alternative method for the oxidation of alcohols focuses on the reversible reaction between ketones and metal alkoxides, which is especially effective when the metal is aluminum[134] The reversibility of the aluminum alkoxide reaction was first demonstrated by Verley[135] and Ponndorf[136] for the reaction of a ketone with an aluminum alkoxide, which led to formation of a new aluminum alkoxide and a new ketone. In

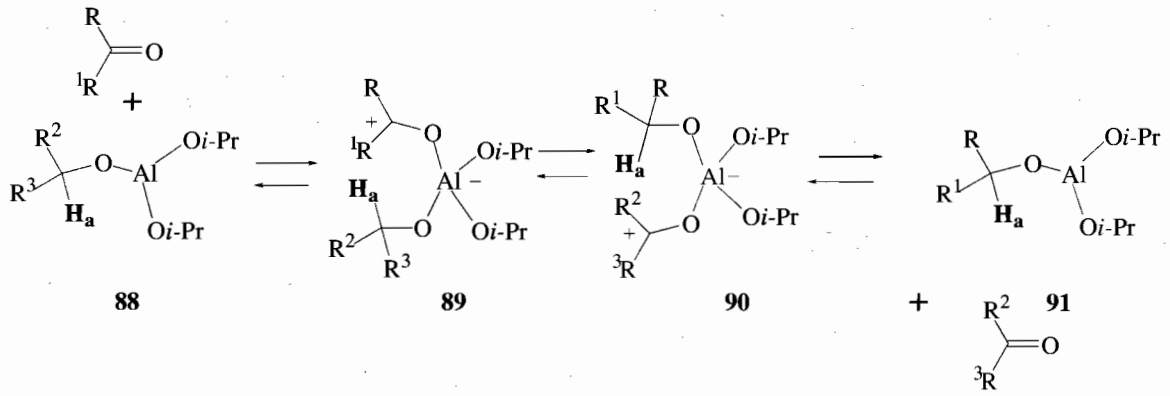


86 **87**

1937 Oppenauer applied this reaction to the oxidation of unsaturated steroidal alcohols using aluminum triisopropoxide [$Al(O\textit{i}\text{-}Pr)_3$] in acetone.[137] The acetone acts as a hydrogen acceptor and the presence of excess acetone drives the reaction toward the oxidation product. Oppenauer used this method to oxidize the alcohol

unit of Δ^5-3-hydroxy steroids such as **86** to the Δ^4-3 ketone (**87**).[137] The observed shift of the double bond into conjugation is very common when the alkene moiety is in close proximity to the reactive center. This reaction has been applied to a wide variety of oxidations involving steroids and simple alcohols, and has come to be called **Oppenauer oxidation.**[134,138] It is noted that this reaction is the reverse of the **Meerwein–Ponndorf–Verley reduction** discussed in section 4.9.I.

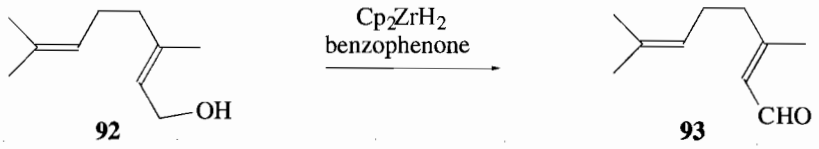
The reaction proceeds via an aluminum coordination complex (**88**), with transfer of hydrogen between the two alkoxy carbons to give **91**.[134,139] The aluminum in the initially formed alkoxide complex (**88**) functions as a Lewis acid, reacting at the carbonyl oxygen of the ketone to form an *ate* complex (**89**). Formation of the *ate* complex is followed by transfer of H_a from the alkoxide carbon of **89** to the alkoxy unit from the ketone carbon (giving **90**), via a six-center transition state. Transfer of H_a between **89** and **90** is a reversible process. Just as **88** and **89** are in equilibrium, so the new *ate* complex **90** is in equilibrium with a new alkoxide (**91**) and a new ketone. If an excess of the original ketone ($RCOR^1$) is added, the equilibrium is shifted toward **91** and formation of the new ketone (R_2COR_3). The original ketone ($RCOR^1$) acts as a **hydrogen acceptor** in the intermediate *ate* complexes. If the goal is oxidation of an alcohol, acetone is used as a solvent and aluminum triisopropoxide is the reagent. In the previously cited example, the secondary alcohol added to the reaction medium was **86** and the new ketone formed was **87**.



Oppenauer oxidation of saturated alcohols is often sluggish, but this problem can be overcome by changing the structure of the metal alcoholate or the hydrogen acceptor or by changing the solvent. Aluminum tri-*tert*-butoxide, triisopropoxide, or tri-*n*-propoxide is used most often but aluminum triphenoxide gave better yields with saturated hydroxy steroids.[140] Acetone (often with benzene as a cosolvent) is the most commonly used hydrogen acceptor, although cyclohexanone in a solution of toluene or xylene is also used. The latter conditions allow higher reaction temperatures and shorter reaction times.[96] Ideally, the ketone that serves as the hydrogen acceptor should have a high reduction potential (sec. 3.1), but a large excess of the ketone can compensate for a low reduction potential, as with acetone.[141] Benzophenone is used occasionally because it is resistant to condensation reactions (Chaps. 8 and 9) that can compete.

Nonsteroidal alcohols can, of course, be oxidized by this method.[142,143] In general, Oppenauer oxidation of primary alcohols gives low yields of aldehydes. Although oxidation of benzyl alcohol gave about 60% of

benzaldehyde, geraniol (**92**) gave only 35% of geranial (**93**).[144] Schinz and co-workers found that aldehydes are effective hydrogen acceptors when used for the oxidation of primary alcohols to aldehydes. If the boiling point of that aldehyde was ≥50°C *higher* than the expected product, the aldehyde product could be distilled as it was formed.[145,144b]



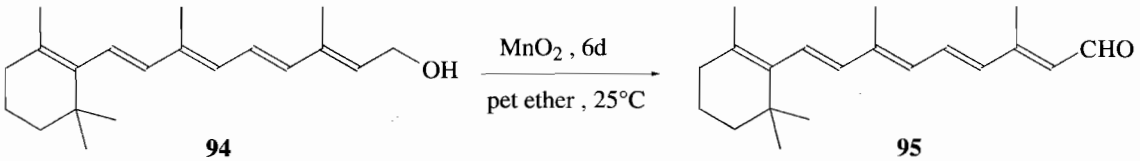
92 **93**

There are two common side reactions that were mentioned previously. One is migration of a non-conjugated double bond into conjugation, and the other is condensation of the aldehyde product with the carbonyl hydrogen acceptor (this is an acid catalyzed **aldol condensation** – sec. 9.4.A).

In recent years, metal catalysts other than aluminum have diminished the occurrence of these side reactions. Ishii et al.[146] showed that a cyclopentadienyl zirconium reagent (Cp_2ZrH_2) was an effective catalyst in the Oppenauer oxidation using a 1:1 ratio of alcohol to hydrogen acceptor and giving excellent yields of aldehydes from primary alcohols. The reaction used only a catalytic amount of the zirconium reagent but required heating in an autoclave, without solvent. Geraniol (**92**) was oxidized to geranial (**93**) in 92% yield by this method using benzophenone as the hydrogen acceptor. Magnesium catalyzed Oppenauer oxidations are observed in other reactions. In Grignard alkylation reactions with aldehydes (sec. 8.4.C), direct oxidation of the magnesium alkoxide generated during the reaction prior to hydrolysis is possible.[147]

3.2.F.iii. Oxidation with Manganese Dioxide. Although manganese dioxide (MnO_2) is a common form of Mn(IV), it is rather insoluble in most organic solvents. Manganese dioxide is the usual end-product of permanganate oxidations in basic solution (sec. 3.5.A). In Table 3.1, the reduction potential of MnO_2 was shown to be 1.208 volts for the following reaction.

$$MnO_2 + 4\,H^+ + 2\,e^- \rightarrow Mn^{2+} + 2\,H_2O \qquad 1.208\ V$$

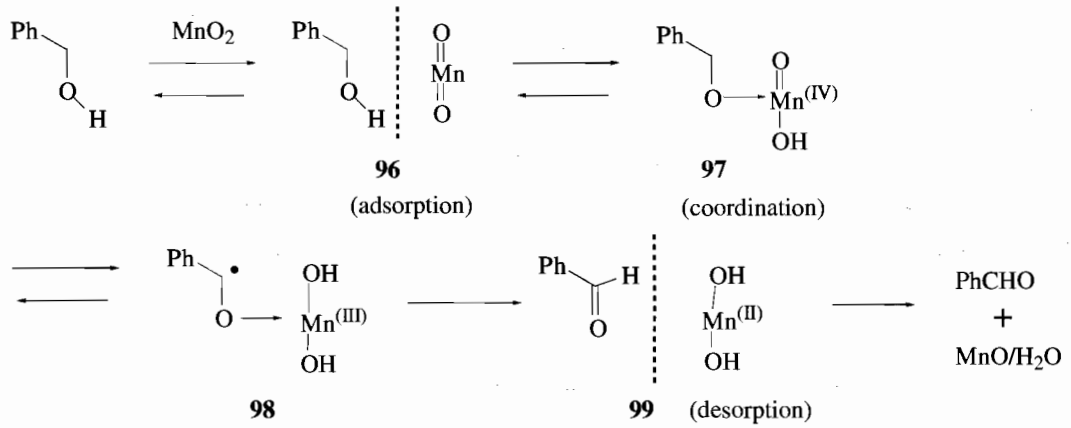


94 **95**

Manganese dioxide is capable of oxidizing alcohols to ketones or aldehydes. The reaction proceeds via a radical intermediate (see below), producing MnO (which is Mn^{2+}) as the byproduct. Manganese dioxide is an important reagent in organic synthesis since it oxidizes primary and secondary alcohols to the aldehyde or ketone, respectively, in neutral media.[148] This reaction was discovered by Ballet al when they precipitated manganese dioxide and used it to convert vitamin A (**94**) to retinal (**95**) in 80% yield.[149]

There are several ways to prepare this reagent, and its oxidizing power is strongly influenced by the method of preparation.[148] One of the more common methods involves precipitation of MnO_2 from a warm aqueous

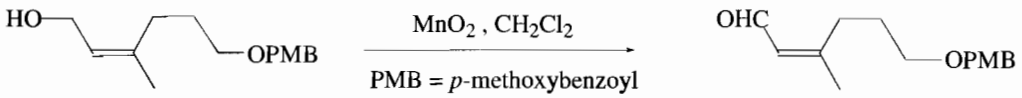
solution of $MnSO_4$ and $KMnO_4$ at a particular pH. The precipitated reagent is then activated by heating to 100–200°C or higher[150] for several hours. The solvent used for the oxidation is important, since the reaction proceeds by coordination of both substrate and reagent. The solvent can influence the degree of adsorption and desorption of the alcohol on the manganese dioxide. If a primary or secondary alcohol is used as the solvent, competition for adsorption sites with the alcohol will diminish the yield of oxidation products. Many other solvents can been used, however, including alkanes (petroleum ether, cyclopentane), chlorinated hydrocarbons (CH_2Cl_2, $CHCl_3$), ethers (diethyl ether, THF), acetone, acetonitrile, DMSO, DMF, and Pyridine. Reaction times range from a few min. for allylic alcohols to several hours for saturated alcohols. The oxidation of **94** required 6 days, an indication that activating the manganese dioxide prior to addition of organic substrate is important.



[Reprinted with permission from Goldman, I.M. *J. Org. Chem.*, ***1969***, *34*, 3289. Copyright © 1969 American Chemical Society.]

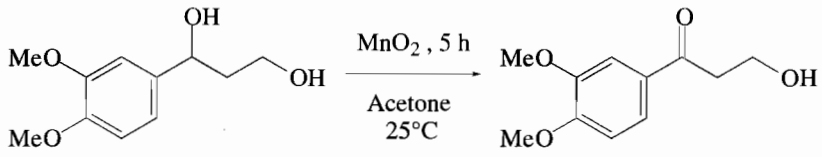
Both Goldman[151] and Henbest et al.[152] proposed a radical intermediate in oxidations using manganese dioxide. Goldman's mechanism is shown for reaction with benzyl alcohol and involves adsorption of the alcohol on manganese dioxide (see **96**) followed by formation of a coordination complex (**97**). Coordination in this manner allows electron transfer, which generates a radical (**98**) in a process that is accompanied by reduction of Mn(IV) to Mn(III). A second electron transfer generates the carbonyl product adsorbed on $Mn(OH)_2$ as in **99**. The product is desorbed, with loss of water, to complete the oxidation. An alternative ionic mechanism was proposed by Hall and Story for oxidation which invoked formation of a manganate ester.[153]

Manganese dioxide is probably most useful for the oxidation of allylic and benzylic alcohols. Williams and co-workers oxidized **100** to aldehyde **101**, for example, as part of a synthesis of the AB ring system of norzoanthamine.[154] Oxidation of alcohols by manganese dioxide is influenced by the steric encumbrance around the carbon bearing the hydroxyl moiety. In general, there is no significant difference in the rate of oxidation of cis- and trans- isomeric alkenes, and there appears to be little or no cis/trans isomerization during the oxidation. React-ion of *cis*- or *trans*-2-methyl-2-penten-1-ol with MnO_2 led to either the cis- or the trans-aldehyde in 64 or 83% yield, respectively.[155] Boehm et al. noted, however, that some cis–trans isomerization occurred in similar oxidation of pentadienols and pentenynols.[156]



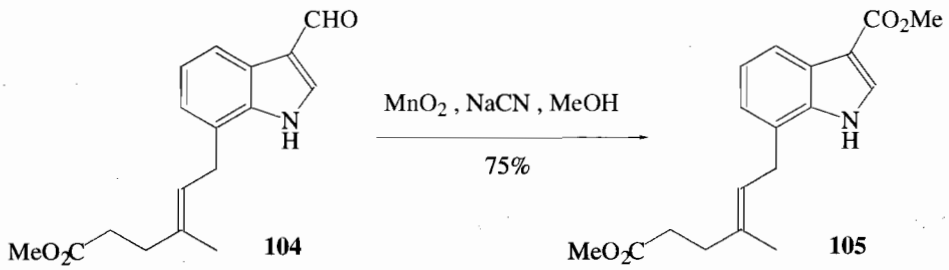
100 **101**

Manganese dioxide oxidizes allylic and benzylic alcohols faster than primary saturated alcohols, but primary and secondary allylic alcohols react at about the same rate. This use of manganese dioxide is particularly important.[157] Oxidation of benzylic alcohols is also facile and a secondary benzylic alcohol is oxidized faster than a primary saturated alcohol. The secondary benzylic alcohol group in **102** was oxidized to give aryl ketone **103** (94% yield) in preference to reaction at the primary aliphatic hydroxyl.[158]



102 **103**

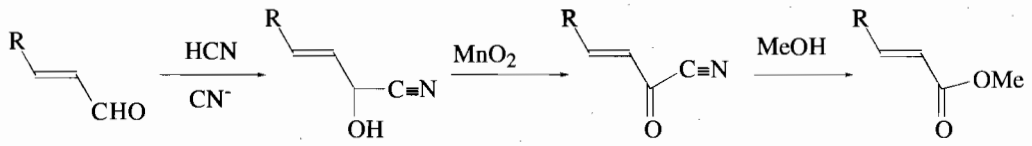
Although the oxidation of allylic and benzylic alcohols is faster, saturated alcohols do react with manganese dioxide. Their oxidation requires a neutral medium, freshly prepared and activated manganese dioxide, the proper solvent, and long reaction times. Simple examples are the oxidation of 2-propanol to acetone and 2-methyl-1-propanol to 2-methyl-propanal, both in 50% yield.[159] The conditions are not too vigorous, however, and complex molecules are easily oxidized with manganese dioxide. Even saturated secondary alcohols, which are relatively unreactive,[159] can be oxidized if there are no allylic or benzylic alcohols present.[160] There is little difference in rate between secondary allylic alcohols and primary saturated alcohols, but steric and/or conjugative effects may have an influence on the reaction. Primary allylic and secondary allylic alcohols are often oxidized with essentially the same rate of reaction, leading to poor selectivity.[161] If oxidation of an allylic or benzylic alcohol is in competition with an aliphatic alcohol moiety that is present elsewhere in the molecule, however, the selectivity for the allylic or benzylic alcohol can be very high. If a large excess of MnO_2 is used, it is possible to oxidize more than one alcoholic position without affecting other labile functionality.[162]



104 **105**

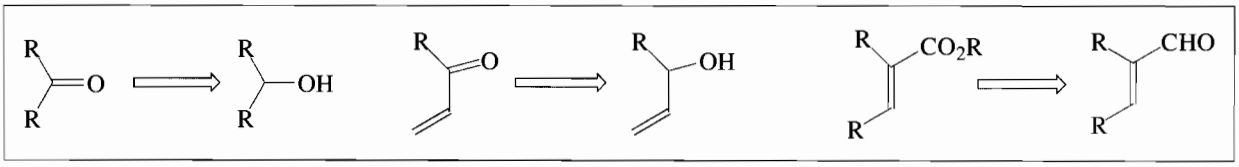
Allylic alcohols can react with MnO_2 under certain conditions to give the conjugated acid or ester (in alcoholic solvents). When indole aldehyde (**104**) was treated with MnO_2 in the presence of NaCN and methanol, for example, a 75% yield of methyl ester (**105**) was obtained.[163]

The purpose of cyanide in this oxidation is to convert the conjugated aldehyde to a conjugated ester. In a related reaction using HCN, Corey showed that HCN/CN^- reacts with a conjugated aldehyde to form a cyanohydrin such as **106**.[164] Subsequent oxidation with MnO_2 gave the cyanoketone, **107**, which reacted with the alcoholic solvent (methanol) to give the methyl ester.



106 **107**

The functional group transforms available from reactions of MnO_2 are

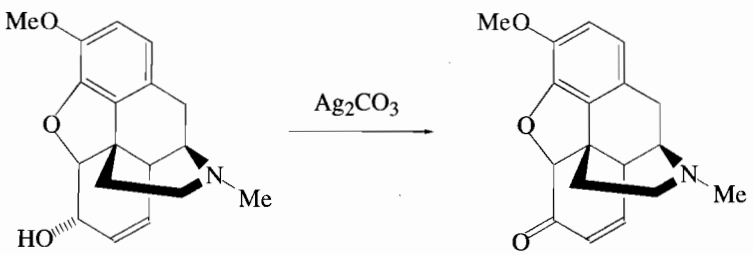


3.2.G. Oxidations with Silver (Silver Carbonate and Silver Oxide)

Silver ion is an excellent oxidizing agent. Table 3.1 shows that the reduction potentials for several silver reagents rank them among the more potent of reagents. The most common reagents are silver carbonate (Ag_2CO_3, reduction potential = 0.4769 V), silver(I) oxide (Ag_2O, reduction potential = 0.342 V), and silver(II) oxide (AgO, reduction potential = 0.599 V), where the reduction potentials are taken from the following reactions:

$Ag_2CO_3 + 2\,e^- \rightarrow 2\,Ag + CO_3^{2-}$	0.4769 V
$Ag_2O + H_2O + 2\,e^- \rightarrow 2\,Ag + 2\,OH^-$	0.342 V
$2\,AgO + H_2O + 2\,e^- \rightarrow Ag_2O + 2\,OH^-$	0.599 V

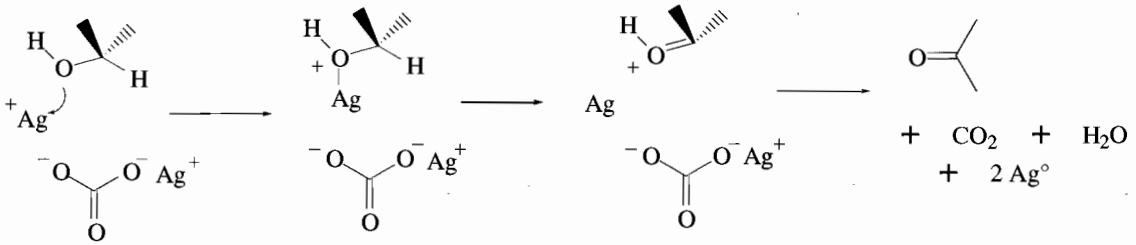
3.2.G.i. Silver Carbonate. Silver carbonate (Ag_2CO_3) is not a powerful oxidizing agent but it is extremely useful in organic chemistry. Rapoport et al. were probably the first to use silver carbonate for the oxidation of alcohols to carbonyl derivatives. Rapoport refluxed codeine (**108**) with silver carbonate in benzene and obtained a 75% yield of codeinone (**109**).[165] In later work King et al. oxidized codeine with silver carbonate in refluxing toluene or xylene and obtained an 85% yield of **109** with a much shorter reaction time.[166]



108 **109**

Fétizon et al. examined the scope of this oxidation and modified the reagent by condensing silver carbonate on Celite. He found that reaction of primary alcohols with excess silver carbonate on Celite gave excellent yields of the corresponding aldehyde, illustrated by the conversion of geraniol (see **92** above) to geranial (**93**) in 97% yield using four equivalents of Ag_2CO_3 on Celite, in refluxing benzene.[167] This modified reagent has come to be known as **Fétizon's reagent**. Saturated primary alcohols are converted to aldehydes in excellent yields and, as seen with Rapoport's work, secondary alcohols are also oxidized to ketones.

Fétizon proposed a mechanism by which involved adsorption of the alcohol on silver carbonate gave a species such as **110**. One-electron transfer via the silver ion in **111** liberated the protonated carbonyl and carbonic acid (see **112**), which decomposed to carbon dioxide and water.[168] This mechanism involved four distinct processes:[169]



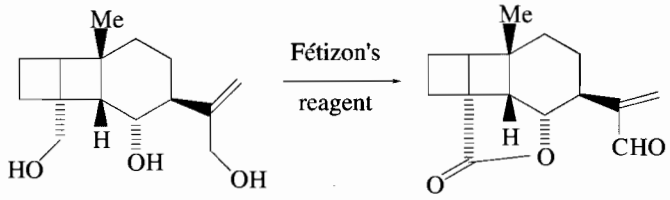
110 **111** **112**

1. Reversible adsorption of alcohol on the surface of the oxidizing medium with the electron of oxygen forming a coordinated covalent bond with the silver ions.
2. Oxidation of the C—H bond so the HCOH group is *coplanar* and *perpendicular* to the silver carbonate/Celite surface.
3. A concerted irreversible homolytic shift of electrons to generate reduced silver atoms, hydrogen ions , and a protonated carbonyl.
4. Collapse to products with carbonate ion acting as a hydrogen ion acceptor, generating carbonic acid, which decomposes to carbon dioxide and water.

Polar solvents inhibit the reaction, presumably by interfering with the adsorption process as noted in the mechanism proposed for manganese dioxide oxidations. Oxidation of 1-heptanol to heptanal with Fétizon's reagent was quantitative when the solvent was 35% hexanes. When benzene was used as a solvent, the yield of heptanal dropped to 90% and was < 1% in ethyl acetate, methyl ethyl ketone, or acetonitrile.[169] Since the oxidation is a heterogeneous reaction, requiring adsorption of the alcohol substrate, as the surface area of the reagent increases (increased by precipitation on Celite), the rate of oxidation increases. An optimum ratio is reached beyond which increasing the silver carbonate/Celite ratio slows the oxidation.[169]

The reaction does not have carbocation intermediates and even optically pure 1,2,2-triphenylethanol, which is known to have a strong tendency toward rearrangement,[170] undergoes oxidation without racemization or rearrangement.[169] There is a significant steric effect that is seen in the oxidation of hindered alcohols, since the alcohol must be adsorbed on the surface of the reagent. All groups undergoing a bond change must be coplanar in the transition state and perpendicular to the plane of the solid surface. Any combination of steric and conformational factors that inhibit this transition state will slow the reaction. 5α-Androstan-6α-ol, for

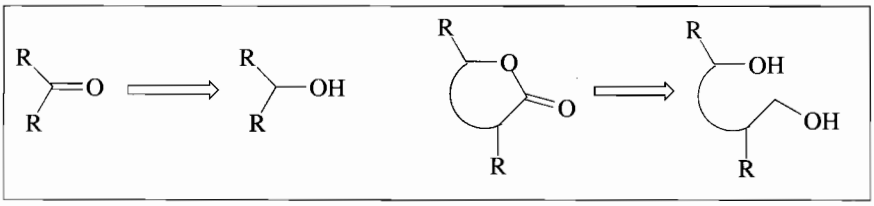
example, is extremely unreactive with silver carbonate. The diminished rate is attributed to the difficulty in adsorption to the silver, which is hindered by the C19 methyl and the C4 methylene group.[169] This contrasts sharply with 5α-androstan-6β-ol, which is not sterically impeded and undergoes rapid oxidation. The accessibility of the hydrogen attached to the carbon bearing the hydroxyl group is also important. endo-2-Norbornanol is oxidized about 50 times faster than *exo*-2-norbornanol, for example.[171]



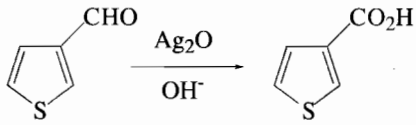
113 **114**

It is possible to run a controlled over-oxidation reaction with silver carbonate. Fétizon discovered that 1,3- and 1,4-diols are smoothly oxidized to butyrolactone and valerolactone derivatives in good yield.[172] Oxidation of a diol can be accomplished in the presence of a variety of functional groups, even another alcohol. A primary alcohol, for example, will be oxidized faster than a secondary alcohol, as illustrated by the conversion of **113** to **114**.[173]

The functional group transforms for silver carbonate are



3.2.G.ii. Silver(I) Oxide. Silver(I) oxide (Ag_2O) is the weakest of the three silver oxidizing agents introduced in this section. It is used primarily for the selective oxidation of aldehydes to carboxylic acids. It



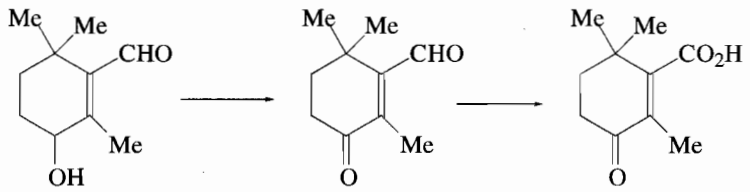
115 **116**

is usually very easy to oxidize an aldehyde to a carboxylic acid, but there are cases where the substrate bearing the aldehyde moiety is also susceptible to oxidation. In such cases, a mild and selective oxidant is required and Ag(I) oxide is often the reagent of choice. Silver(I) oxide was used by Campaigne and LeSuer in the oxidation of 3-thienaldehyde (**115**) to 3-thienoic acid (**116**) in 97% yield.[174] The silver oxide was prepared *in situ* by mixing a solution of silver nitrate ($AgNO_3$) and excess sodium hydroxide.[175] In a synthesis of strigol, Pepperman examined the oxidation of **117** to keto aldehyde **118** with the goal of converting **118** to **119**. A variety of oxidizing agents were used (see Table 3.3).[176] In all cases the secondary alcohol in **117** was oxidized to the ketone but further oxidation to acid **119** was a problem because extensive decomposition

occurred, lowering the yield. Pepperman found that oxidation of **118** followed by treatment with silver (I) oxide gave excellent yields of **119**, in a fast reaction with few byproducts.

Despite the good yield of **119** eventually obtained in Table 3.3, oxidation of an α,β-unsaturated aldehyde usually gives a poor yield of the acid. Oxidation of **118** had previously given a maximum of 40% yield of **119**.[177] Frank[178] found that oxidation of β-cyclocitral, another conjugated aldehyde, gave only 23% conver-

Table 3.3. Oxidation of 118 to Keto Acid 119



117 **118** **119**

Reagent	% 119[a]
$KMnO_4$–H_2SO_4	13.5
Air (bubbled)	37
Air (thin film)	46
Ag_2O	72
MnO_2-NaCN	80 (as Me ester)
Jones	55

[a] Based on keto aldehyde **118**

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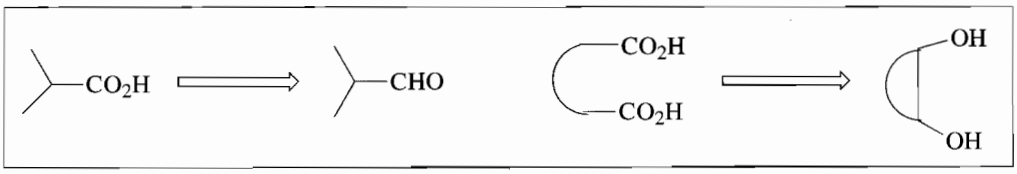
sion to β-cyclogeranic acid with silver oxide. In **118**, the extended π configuration seemed to facilitate oxidation under the conditions used and it behaves differently than conjugated aldehydes. The oxidation of saturated aldehydes is straightforward.[179]

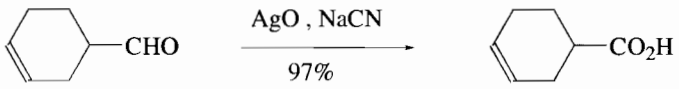
Silver oxide can also oxidize primary alcohols directly to the acid, as in the oxidation of 1-dodecanol to dodecanoic acid.[180] Oxidation of 1,2-diols is accompanied by cleavage to the diacid (sec. 3.7.C), as in the conversion of 1,2-cyclohexanediol to adipic acid in 89% yield.[180]

The functional group transforms available to silver (I) oxide are



3.2.G.iii. Silver(II) Oxide. Silver(II) oxide (AgO) is the most powerful of the three oxidants presented in this section. Although it is not widely used, Ag(II) oxide converts aldehydes and alcohols to carboxylic acids

or ketones.[181] The reagent can be prepared by oxidation of silver nitrate with potassium peroxydisulfate ($K_2S_2O_8$) in an alcoholic solvent.[182] Benzyl alcohol was oxidized to benzaldehyde in aqueous solutions of AgO,[182a] and in neutral or alkaline solution further oxidation gave benzoic acid in 57% yield.[182b] Corey found that a mixture of AgO and sodium cyanide converted aldehydes such as **120** to the acid (**121**) in 97%



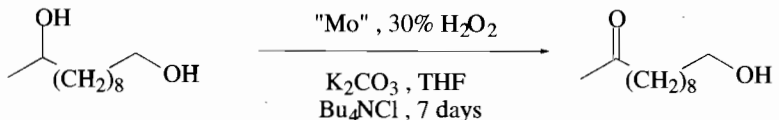
120 **121**

yield, without isomerization of the double bond into conjugation.[164] Oxidation with manganese dioxide and sodium cyanide in acetic acid gave the ethyl ester.[164] Corey observed little or no oxidation with cinnamaldehyde, but oxidation of **118** with this reagent gave 80% of **119**.

3.2.H. Other Common Transition Metal Oxidants

This section contains several oxidizing reagents that do not easily fall into a single category. The intent is to show some of the variety in reagents which convert alcohols to ketones and aldehydes. These reagents are not as widely used as the reagents presented above. The main purpose of this brief discussion is to show that there are alternative reagents (sometimes they are exotic) currently available or in development that may solve a difficult oxidation problem. The reader is encouraged to conduct a thorough search of the literature since several alternative reagents will probably be found that may solve a given synthetic problem. Most of these alternative reagents use transition metal derivatives.

It is known that potassium permanganate tends to overoxidize primary and secondary alcohols to the acid, and sometimes oxidative cleavage accompanies the reaction. This oxidizing power can be moderated by complexing permanganate ion with another cationic species. Trimethylcetylammonium permanganate,[183] bis-(bipyridylcopper) permanganate (bpy_2CuMnO_4)[184] and *n*-butyl permanganate[185] have all been used in the oxidation of alcohols. Molybdenum reagents have also been used for oxidations, and there are many variations in the ligands that can be used, including: $(NH_4)_6Mo_7O_{24}$•2 H_2O,[186,187] $Mo(CO)_6$•Py-cetyl,[188,189] $Mo(N_2)_2(dpe)_2$,[190] and $BnNMe_3^+$ $OMoBr_4^-$.[191] Many of these reagents have been shown to be selective for the oxidation of secondary alcohols, as in the oxidation of 1,10-undecanediol (**122**) to keto alcohol, **123**.[186]



122 **123**

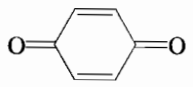
Cerium(IV) has been used extensively,[192] and the two most common reagents are ceric ammonium sulfate [$Ce(SO_4)_2$•2$(NH_4)_2SO_4$•2 H_2O] and ceric ammonium nitrate [$Ce(NH_4)_2(NO_3)_6$].[193] Modified cerium reagents such as $Ce(OH)_3O_2H$[194] and $[(NO_3)_3Ce]_3H_2IO_6$[195] have been used by Firouzabadi et al. or the oxidation of primary alcohols, especially benzylic and allylic alcohols.

3.3. FORMATION OF PHENOLS AND QUINONES

In addition to the oxidation of aliphatic hydroxy compounds, aromatic derivatives that contain hydroxyl groups (phenol derivatives) can also be oxidized.[196] The course of the oxidation differs in that the aromatic ring is disrupted, leading to quinones, important components in a variety of natural products.[197] It is also possible to convert aromatic hydrocarbons to phenols by oxidation. Quinones are obtained by oxidation of phenols and a phenol can be very loosely viewed as an enol. Inclusion of this chemistry immediately after discussing the oxidation of alcohols to ketones, aldehydes, or acids is done with the goal of providing some continuity in studying the oxidation of hydroxyl compounds.

3.3.A. Quinones

The quinone structure is incorporated in a wide variety of naturally occurring compounds called *quinoids*. The most common quinoids are the 1,4-quinones (*p*-quinones, **124**) and the 1,2-quinones (*o*-quinones, **125**).[198] Quinoids can be prepared by many methods, including oxidation of non-quinoid precursors, cyclization methods, condensation methods, and annulation methods.[199] This section will focus only on oxidation reactions, which constitute the only completely general methodology.[199]



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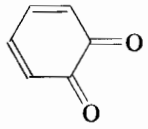


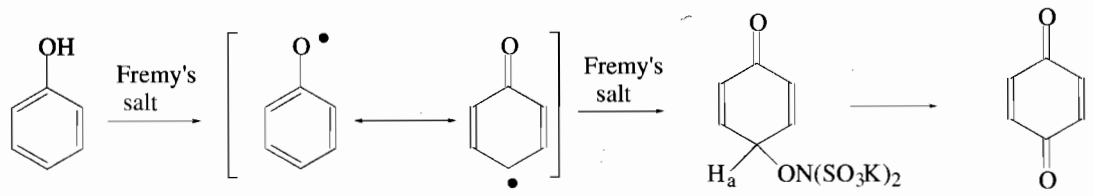
125

One of the most common reagents for oxidizing phenolic derivatives to quinoids is **Fremy's salt** (potassium nitrosodisulphonate $[(KO_3S)_2NO\bullet]$.[199,200] This reagent was prepared as the disodium salt in 1845 by Fremy,[201] but Raschig prepared the potassium salt, which was more effective and remains the reagent of choice.[202] Acidic solutions are very unstable and the salt also decomposes in aqueous solutions at pH greater than 10.

Fremy's salt sometimes undergoes violent, spontaneous decomposition but this appears to be due to the presence of catalytic amount of nitrite ion.

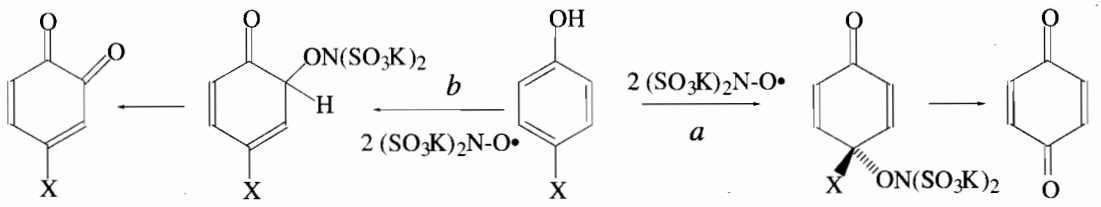
The most common solvents are aqueous alcohol and aqueous acetone and the reaction is usually buffered with phosphate or acetate. The reaction is rapid and may be monitored by disappearance of the purple color of the radical. A simple mechanism for the oxidation was proposed by Teuber and Rau.[203] Electron transfer from Fremy's salt to phenol generates a radical species (**126**), and this reacts with excess Fremy's salt to give an addition product, **127**. Loss of the hydrogen α to the oxygen moiety in **127** leads to formation of the quinone (**124**) and potassium aminodisulfonate $[\ HN(SO_3K)_2\ ]$.

The steric demands on the reaction sometimes lead to low yields of ortho-quinones, and in such cases the less hindered *p*-quinone is usually the major product. If the para- position is blocked, the yield of *o*-quinone can be low. When both the ortho- and para-positions are not sterically hindered and can be attacked,



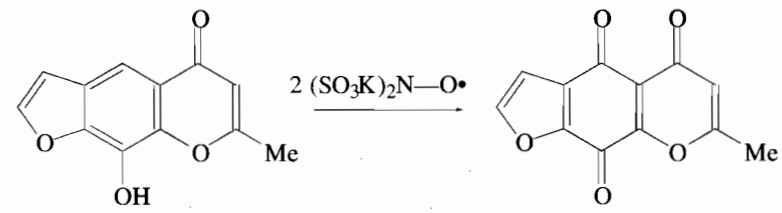
126 **127** **124**

the *p*-quinoid is usually the major product. If the para position is blocked and there is no steric hindrance, *o*-quinones will be formed exclusively. When X = H in **128**, oxidation follows *path a* to give the 1,4-quinone. Formation of **129** is consistent with para-attack, and loss of the X group will give **124**. When X in **128** is alkoxy (X = OR) or alkyl (X = R), however, *path b* is preferred. Since the para-position is blocked, the ortho-intermediate (**130**) is formed and loss of the bis-(disulfonate) in the usual manner (see above) gives the 1,2-quinone, **131**. When X = Cl in **125**, the chlorine is usually lost with formation of the 1,4-quinone.[199]

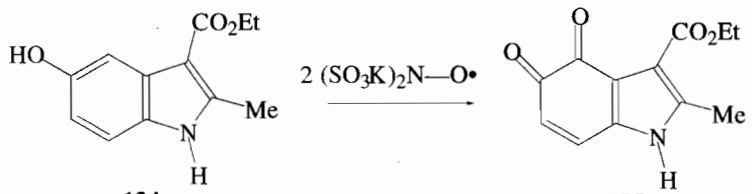


131 **130** **128** **129** **124**

There are two important factors that influence the oxidation. One is electronic stabilization of the incipient phenoxy radical and the other is the steric requirements that are connected with the formation of the cyclohexadiene intermediate. The presence of electron-withdrawing groups can cause the oxidation to fail or at least lead to a poorer yield.[199,200,204] Oxidation of phenols with Fremy's salt can be applied to more sophisticated derivatives such as **132**, which gave 1,4-quinone (**133**).[199,205]



132 **133**



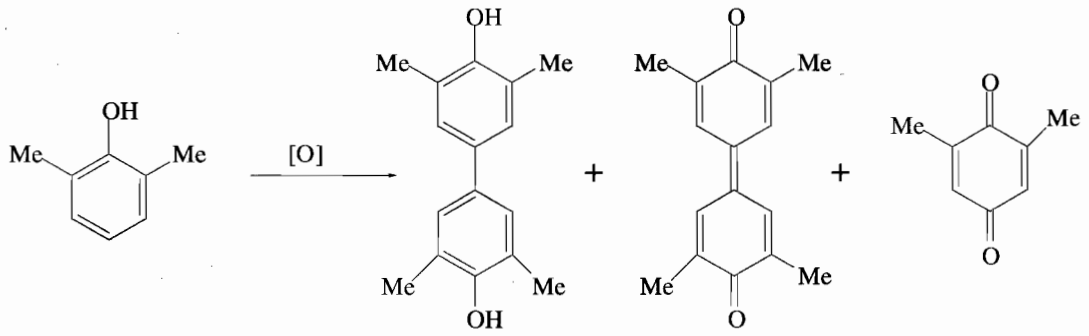
134 **135**

Oxidation of phenols with Fremy's salt requires a buffered medium, since the salt is stable in only a limited pH range, as previously mentioned. Many *o*-quinones are unstable to acidic conditions and may give other

products if the pH exceeds 7. Oxidation of **134** gave **135** in 85% yield under standard conditions, for example, but in acid solution that product dimerizes completely.[206] When the phenyl ring of the phenol contains a *p*-chlorine[199,207] or a *tert*-butyl group,[208] these groups can be eliminated from the intermediate, generating a quinone.[207,208] Oxidation of aniline derivatives with Fremy's salt is often accompanied by elimination of the amino moiety to give a quinoid. Oxidation of 3-ethoxy-5-methylaniline, for example, gave 3-ethoxy-5-methyl-1,4-benzoquinone in 93% yield.[209]

Many other oxidizing agents convert phenols to quinones, including Cr(VI). In general, most other oxidizing agents give lower yields of quinone and higher percentages of dimerized products. Chromic acid is an effective oxidant for the conversion of phenols to quinones only when a para- substituent such as halogen, hydroxyl, or amino is present. The yields are often poor,[210] but not always.[211] Anodic oxidation of phenols to quinones[212] can be very efficient. Bacon and Izzat described the oxidation of 2,6-xylenol (**136**) with a variety of oxidizing agents.[213] In most cases, oxidation gave not only the expected quinone (**139**) but also dimerized products such as the coupled phenol (**137**) and the coupled quinone (**138**) as well as polymeric material.[213] Table 3.4[213] shows the product distribution obtained with different oxidizing agents. Clearly, Fremy's salt is the superior reagent in this list for preparation of the quinone (**139**). It is also clear that the coupled quinone predominates with most oxidizing agents and that polymerization is an ever-present problem. Table 3.4 shows the most common reagents used for the oxidation of phenols, including Fremy's salt, ferric ion, copper(II), titanium(III), and titanium(IV), as well as manganese dioxide,[214] selenium dioxide, and sodium periodate.

Table 3.4. Oxidation of 2,6-Xylenol (136)



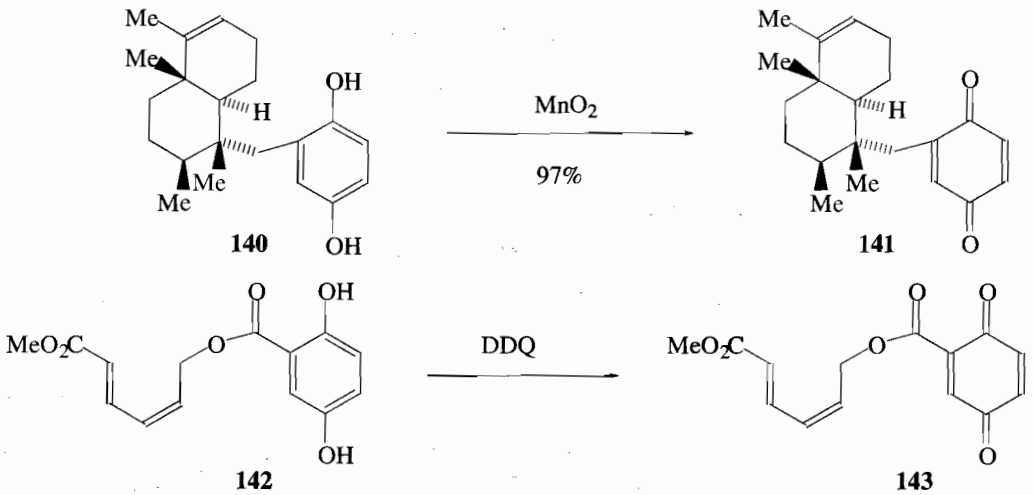
136 **137** **138** **139**

Reagent	% 137	% 138	% 139	% Polymer
$AgNO_3/K_2S_2O_8$	27	51	5	5
$CuSO_4/Na_2S_2O_8$	1	47	27	15
Cu (III) ClO_4		30		45
$CuSO_4$ /NaOCl		17	26	60
$CuSO_4$ /air stream		3	9	20
$FeCl_3$		54	14	15
$K_3Fe(CN)_6$/NaOH		52		25
MnO_2/4M H_2SO_4			16	50

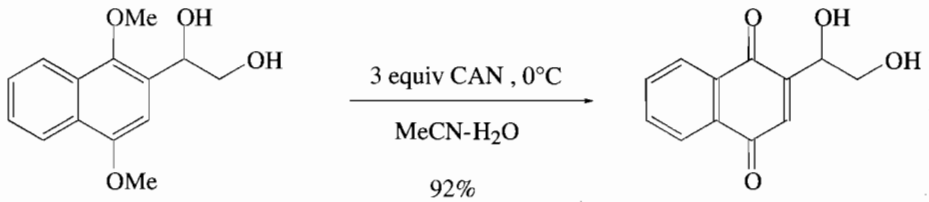
MnO_2		53		40
$CuSO_4$ /H_2O_2		33	9	40
$FeSO_4$ /H_2O_2		22	3	55
$TiCl_3$/H_2O_2	9	20	51	5
$TiCl_4$ /H_2O_2		50	38	10
SeO_2/H_2O_2	4			
$NaIO_4$		0.3	9	
NaClO	13	8		75
$NO(SO_3K)_2$			**74**	

Note that catechols (1,2-dihyroxybenzenes) are readily oxidized to *o*-quinones,[215] but the products are often sensitive to the electrophilic or nucleophilic species in the reaction medium. Catechol itself gives **125**. Dimerization is as much a problem with catechols as with monophenols (see Table 3.4).[216] The conversion of catechol to **125** used silver carbonate and it is noted that silver salts are the classical oxidation reagent for such transformations.[217] Other reagent have been used to oxidize catechol derivatives, including ceric sulfate, lead tetraacetate, DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone),[218] iodate, and periodate.[219]

There are many syntheses of molecules containing a quinone unit and in most cases, the quinone is oxidized late in the synthesis from a resorcinol or catechol derivative. In some cases, the quinone unit is used in a Diels–Alder reaction (see sec. 11.4.A), and the quinone is unmasked immediately prior to its being used. In Theodorakis' synthesis of avarone, avarol (**140**) was synthesized and treatment with MnO_2 gave the final target quinone, avarone (**141**) in 97% yield.[220] An example of the quinone being unmasked immediately prior to its use is in Danishefsky's synthesis of myrocin C,[221] in which **142** was oxidized to quinone **143** with either DDQ (2,3-dichloro-5,6-dicyano-1,4-quinone) or with argentic oxide (silver oxide, AgO). The oxidation was followed by heating to give an intramolecular Diels–Alder reaction (see sec. 11.8).

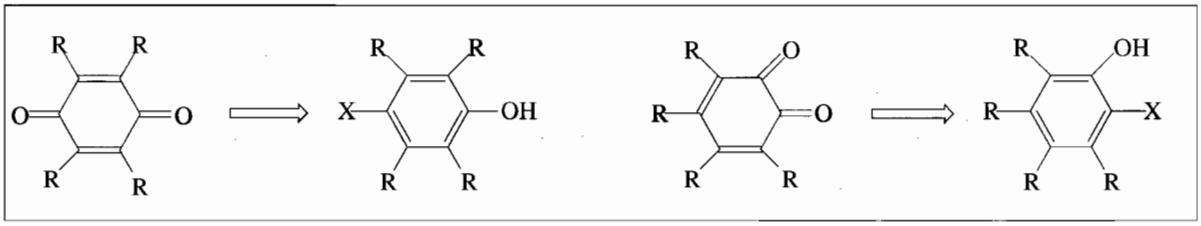


As mentioned above, quinones can be formed from derivatives of resorcinol or catechol as well as from the parent hydroxyl compounds. When dimethoxy compound **144** was treated with ceric ammonium nitrate (CAN), for example, a 92% yield of quinone **145** was obtained as part of De Kimpe's synthesis of isagarin.[222]



144 **145**

Oxidation of phenol leads to several interesting functional group transforms, including

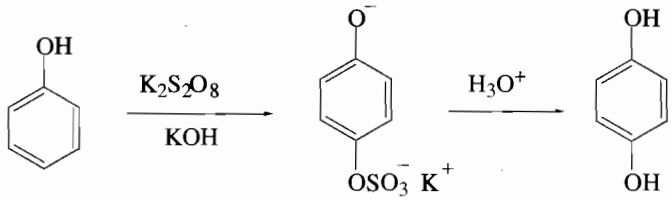


3.3.B. Phenols

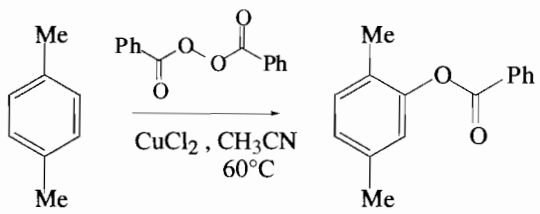
As discussed in section 2.11.E, phenols are conveniently prepared by hydrolysis of diazonium salts. There are also several oxidative methods that convert aromatic derivatives to phenols.[223] Direct hydroxylation can be accomplished by free radical reagents such as a mixture of H_2O_2 and ferrous ion (Fe^{2+}) (**Fenton's reagent**).[224] The yields are usually poor, in the 5–20% range, and there are usually large amounts of biphenyls (a coupling product). Oxidation of benzene, for example, gave a low yield of phenol but a relatively large yield of biphenyl, and this is not a very useful synthetic method for preparing phenols. A modification was introduced by Udenfriend et al. as a model for the biogenic hydroxylation of tyramine, and it used an oxygen–ferrous ion–ascorbic acid system in the presence of ethylenediaminetetraacetic acid (EDTA) (**Udenfriend's reagent**).[225,224a] This reagent gave good yields of ortho- and para-phenolic derivatives from phenyl acetamide. An electrolytic version of this oxidation uses anodic oxidation in the presence of Undenfriend's reagent and oxygen to convert tyramine to a mixture containing 21% hydroxytyramines and dihydroxytyramine (DOPA).[226]

Alkyl benzenes react with hydrogen peroxide, Lewis acid catalysts (such as boron trifluoride),[227] or strong protonic acids such as trifluoroperoxyacetic acid[228,224a] to give the corresponding phenol. Chambers et al. used trifluoroperoxyacetic acid to oxidize mesitylene (1,3,5-trimethylbenzene) to 2,4,6-trimethylphenol in high yield, based on consumed mesitylene (only a 17% conversion based on the peroxyacid).[228] Similarly, McClure and Williams reported the oxidation of anisole to phenolic products in low yield (ortho- derivative in 27% yield and para- derivative in 7% yield), and with a conversion of only 44%.[229] Hart and co-workers found that the yield of 2,4,6-trimethylphenol from 1,3,5-trimethylbenzene was greatly improved (88% yield with good overall conversion) by using a mixture of boron trifluoride (BF_3) and trifluoroperoxyacetic acid (in dichloromethane at –7°C).[227] This modification is probably the best method for peroxyacid oxidation of aromatic hydrocarbons to the corresponding phenol. Aluminum chloride is also an effective catalyst in this transformation, giving primarily a mixture of ortho- and para-hydroxy derivatives.[230]

Phenol can be hydroxylated with potassium persulfate ($K_2S_2O_8$) in alkaline media (the **Elbs persulfate oxidation**).[231] In 1893 Elbs used ammonium persulfate to oxidize 2-nitrophenol to nitroquinol.[232] Later workers used the potassium salt,[233] which is now the reagent of choice, in order to obtain synthetically useful yields of para- hydroxy phenols. The initial oxidation product is the persulfate (**146**) which is hydrolyzed to hydroquinone (**147**), as shown.[234] The ortho-product (a pyrocatechol derivative) is formed if the para-position is blocked, but the reaction is slower and the yields are in the 30–50% range.[235] The presence of electron–withdrawing groups on the aromatic ring improves the yield but electron releasing groups such as methoxy (OMe) can also be tolerated.[236]



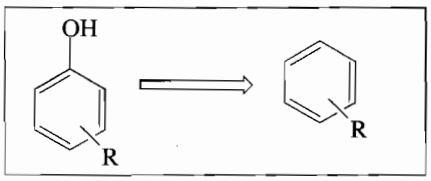
146 **147**



148

An attractive alternative to direct hydroxylation is the thermal or photochemical decomposition of diacyl peroxides. Aryl derivatives react to give an acyloxylation reaction.[237] The conversion of *p*-xylene to **148** in the presence of cupric chloride is an example,[238] although the yield was only 24%. The benzoate ester in **148** was easily hydrolyzed to the phenolic derivative. Lead tetraacetate [$Pb(OAc)_4$, abbreviated LTA, see sec. 3.7.C.i] gives a similar reaction, but this reagent generates the O-acetyl derivative from aryl derivatives. Polycyclic aromatics and aryl derivatives containing electron–releasing groups give the best yields of oxidation products.[239,240]

The functional group transform for this reaction is



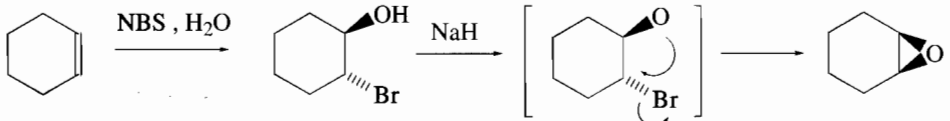
3.4. CONVERSION OF ALKENES TO EPOXIDES

The previous sections focused attention on the oxidation of a C—OH moiety to a C=O (carbonyl) group. Other functional groups are subject to oxidation, including the π bond of alkenes. There are several different

oxidative functional group transformations that involve alkenes, including incorporation of one oxygen (epoxidation), incorporation of two oxygens (hydroxylation) or one oxygen and a nitrogen (aminohydroxylation), and oxidative cleavage (usually to carbonyl derivatives). Sections 3.4.A–D will discuss various methods for the conversion of alkenes to epoxides (oxiranes)[241] and the other functional group transformations will be discussed in succeeding sections.

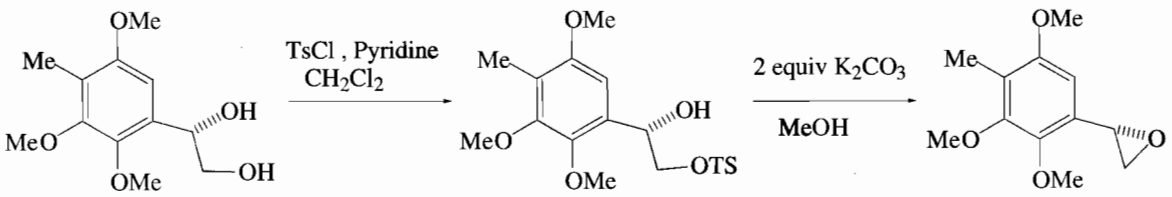
3.4.A. Epoxides from Halohydrins

This section will begin with a simple method for producing epoxides that uses the reaction of alkenes and hypohalous acids (generated by the reactions $Cl_2 + H_2O \rightleftharpoons HOCl$ or $Br_2 + H_2O \rightleftharpoons HOBr$) to give the trans-(or anti-) halohydrin as the major product. An example is the conversion of cyclohexene to bromohydrin **149** (sec. 2.10.C). Subsequent treatment with a base such as sodium hydride generates the alkoxide (**150**), which is anti- to the adjacent bromine, which anti- orientation leads to displacement of halide



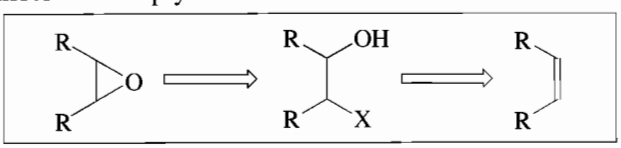
149 **150** **151**

to give cyclohexene oxide (**1515**) via an S_N2 process, which is actually an *intramolecular* **Williamson ether synthesis** (sec. 2.7.A.i). The S_N2 nature of the cyclization restricts the reaction to primary and secondary halides and the halogen must be trans- to the hydroxyl group for epoxide formation. The halohydrin is often generated with aqueous NBS (see sec. 2.10.C). Alternatively, 1,2-diols can be converted to a mono-sulfonate ester (a monomethanesulfonate or *p*-toluenesulfonate). Subsequent reaction with potassium hydroxide from either the halohydrin[242] or the hydroxysulfonate leads to an alkoxide that displaces the leaving group to give the epoxide. A typical synthetic example is taken from Danishefsky's synthetic studies aimed at the saframycin–eceinascidin series.[243] Treatment of diol **152** with *p*-toluenesulfonyl chloride gave the tosylate (**153**) in 95% yield, and subsequent treatment with methanolic potassium carbonate gave epoxide **154**, also in 95% yield.[243]



152 **153** **154**

The functional group transform is simply:

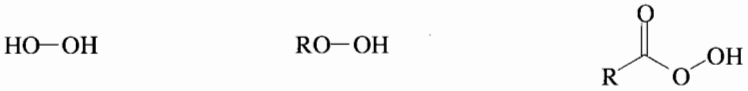


3.4.B. Peroxide Induced Epoxidations

The reaction of peroxides with alkenes is probably the most common method for the preparation of epoxides (oxiranes). Peroxides are a source of electrophilic oxygen when they react with the nucleophilic π bond of an alkene. In Table 3.1, hydrogen peroxide (H_2O_2) was shown to be a powerful oxidizing agent, with a reduction potential of 1.77 V[18] for the following reaction:

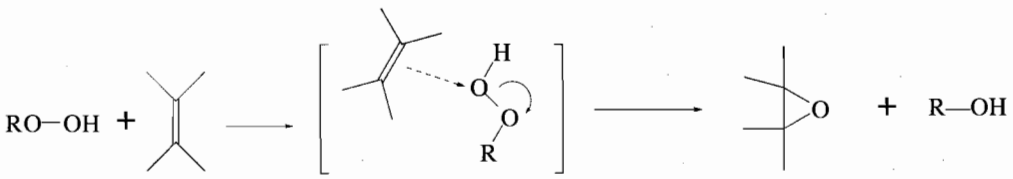
$$H_2O_2 + 2\,e^- + 2\,H^+ \rightarrow 2\,H_2O \qquad 1.77\ V$$

While most peroxide reactions involve homolytic cleavage of the O—O bond, generating free radicals (sec. 13.3), H_2O_2 and its monosubstituted derivatives can react with alkenes via either a concerted or ionic mechanism.[244] Three categories of peroxides are used for epoxidation: H_2O_2, alkyl hydroperoxides (**155**),



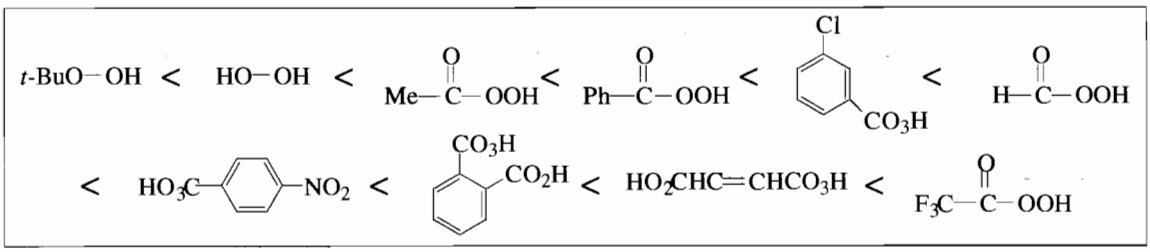
155 **156**

and peroxyacids (**156**). The alkene reacts as a Lewis base and coordinates with the electrophilic oxygen of a peroxide, as in **157**, to generate a positively charged oxygen. Heterolytic cleavage transfers that oxygen to the alkene and subsequent proton transfer liberates the byproduct (water from hydrogen peroxide, an alcohol from an alkyl hydroperoxide, and a carboxylic acid from a peroxy acid). This sequence involves backside attack at oxygen in what is essentially an S_N2 process (sec. 2.7.A.i).[245] The relative rate of oxidation for



157

various peroxide reagents is largely determined by the nature of the OR group in **153**, which behaves as a leaving group. The oxidizing power of the peroxide is inversely related to the pK_a of the conjugate acid generated by loss of the leaving group (ROH).[246] It is difficult to compare different types of reagents but a useful ranking of peroxides by their ability to convert alkenes to epoxides is as follows:[246,245]



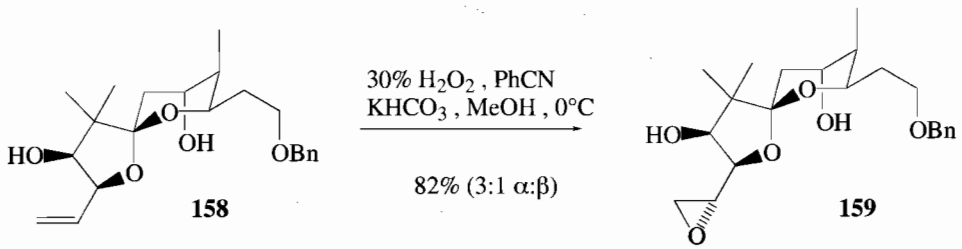
The strength of the peroxide reagent correlates more or less with its reactivity with alkenes. In the following sections, the emphasis will be on the synthetic utility and generality of peroxide induced reactions.

3.4.B.i. Hydrogen Peroxide. Table 3.1 showed the reduction potential of oxygen in the following reactions:

$$O_2 + 2\,H^+ + 2\,e^- \rightarrow H_2O_2 \qquad 0.682\ V$$
$$O_2 + 4\,H^+ + 4\,e^- \rightarrow 2\,H_2O \qquad 1.229\ V$$

Hydrogen peroxide is used in water or water miscible solvents but epoxidation of alkenes is slow unless metal ion catalysts are used. Vanadium pentoxide,[247] tungsten trioxide,[248] and molybdenum trioxide[249] are common catalysts. With allylic alcohols, oxidations of the hydroxyl moiety can be faster than the oxidation of the alkene moiety. Excellent yields of crotonaldehyde have been obtained when crotyl alcohol was treated with hydrogen peroxide in an attempted epoxidation reaction. Hydrogen peroxide oxidation of alkenes is not used very often since other peroxide reagents are more effective, unless the alkene is soluble in aqueous media. Many of the comments presented in the following section also apply to hydrogen peroxide.

There is an exception to the poor reactivity exhibited by hydrogen peroxide. When **158** was treated with 30% hydrogen peroxide, in the presence of benzonitrile and potassium hydrogen carbonate, epoxide **159** was formed in 86% yield,[250] in what is known as the **Payne epoxidation**.[251] The reagents shown generate peroxybenzimidic acid *in situ*. This transformation was taken from Smith's synthesis of (+)-calyculin A.[250] *The Payne epoxidation is known to give a diastereofacial preference that is opposite to epoxidations with peroxyacids.* In this particular example, the epoxide **159** was a 3:1 (α:β) mixture of isomers at the epoxy carbon.



3.4.B.ii. Alkyl Hydroperoxides. Alkyl hydroperoxides are prepared by reaction of tertiary alcohols or alkenes with hydrogen peroxide in the presence of sulfuric acid.[252] Alkyl hydroperoxides are also prepared by the autoxidation of alkanes with oxygen,[253] which is also a potent oxidizing agent. The relatively stable reagent *tert*-butyl hydroperoxide (*t*-BuOOH, TBHP), for example was prepared in 75% yield (8% conversion) by reaction of isobutane with oxygen.[254] In this case, the reaction was carried out in the liquid phase with di-*tert*-butyl peroxide as an initiator (see sec. 13.3). This oxidation is a general reaction for most tertiary alkanes[255] and probably involves a radical intermediate that reacts with oxygen.[255] Subsequent reaction with the alkane gives the hydroperoxide and regenerates the radical carrier (sec. 13.3).

Tertiary alkylhydroperoxides are used most often as oxidizing agents with alkenes since primary or secondary alkylhydroperoxides are susceptible to rearrangement and decomposition. Alkylhydroperoxides are relatively soluble in organic solvents, are more stable, and are easier to handle than hydrogen peroxide.[256] Both TBHP and cumyl hydroperoxide are commercially available and widely used. As with hydrogen peroxide, reaction of alkenes with hydroperoxides usually requires transition metal catalysts in order to form

an epoxide.[257] Several common catalyst systems are given in Table 3.5.[258] Epoxidation with hydroperoxide gives racemic products in most cases. An important variation is the **Sharpless asymmetric epoxidation** which generates chiral epoxides, and will be discussed in sec. 3.4.D.i.

Table 3.5. Alkene Epoxidation by Transition Metal Catalyzed Reaction with Alkyl Hydroperoxides[258]

R	Alkene	Solvent	M	% M	Conditions	% Epoxide
H	Cyclohexene	dioxane	MoO_3	10	50°C, 10 h	38
t-Bu	Cyclohexene	dioxane	MoO_3	12	80°C, 8 h	99
t-Bu	Cyclohexene	neat	$MoO_2(acac)_2$	2	70°C, 1 h	86
cumyl	Cyclohexene	PhEt	V-naphth.	0.03	90°C, 1 h	97
sec-Bu	Cyclopentene	neat	V-octoate	1	46°C, 6 h	98
t-Bu	1-Octene	EtOAc	Na_2MoO_4			
t-Bu	1-Octene	EtOAc	$Na_4(PMo_{12}O_{40})$	8	135°C, 2 h	89
Cumyl	1-Octene	cumene	MoO_3	19	100°C, 6 h	84
tert-amyl	1-Propene	neat	Mo-naphth.	2	130°C, 2 h	78
cumyl	2-Methyl-	neat	Na_2MoO_4			
	2-pentene	neat	$Na_4(PMo_{12}O_{40})$	1.5	110°C, 0.75 h	97

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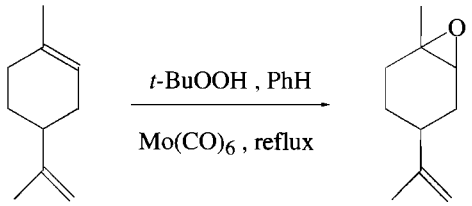
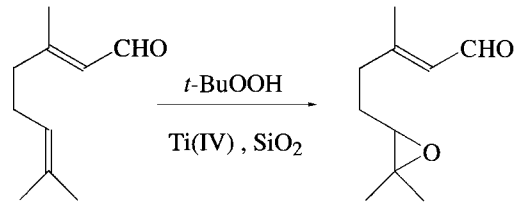
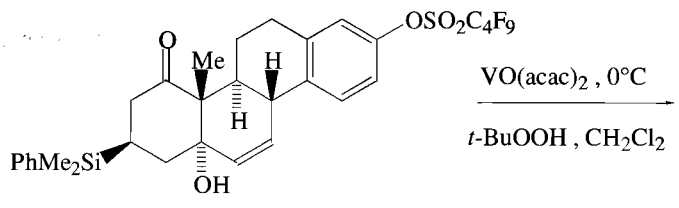
In the epoxidation reaction, more highly substituted alkenes react faster than less substituted alkenes.[259] Reaction of **160** with TBHP and molybdenum hexacarbonyl selectively gave oxidation of the trisubstituted alkene, leading to **161**.[260] Electron deficient alkenes are less reactive, as illustrated by the epoxidation of



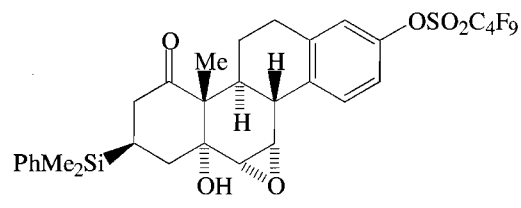
160 **161**



93 **162**

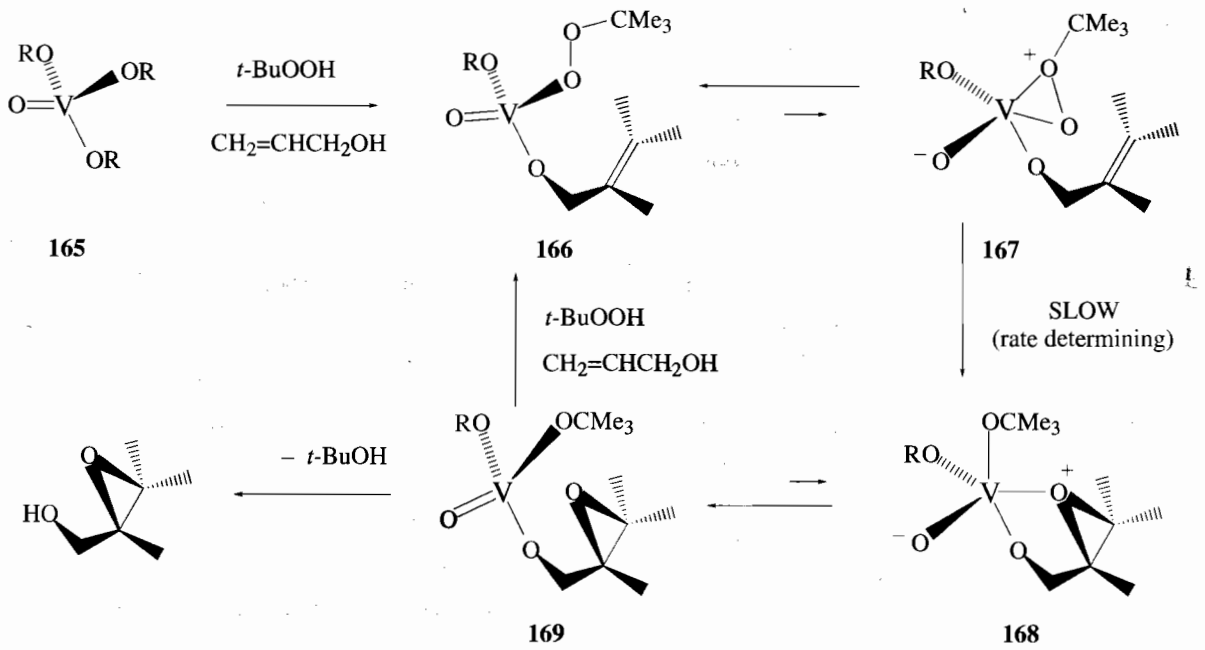


163

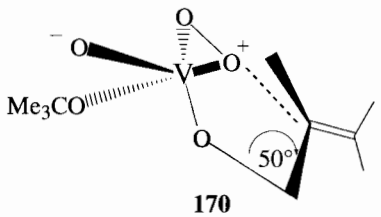


164

geranial (**93**), which was epoxidized selectively at the unconjugated alkene moiety to give **162**.[261] A neighboring group effect is observed when a coordinating group is present, as in allylic alcohols. Epoxidation of allylic alcohol **163** in Corey's synthesis of nicandrenone,[262] gave a 76% of epoxide **164**, with high selectivity for the epoxy-oxygen syn- to the alcohol unit. Such reactions involve initial coordination of the metal to both the allylic alcohol and the hydroperoxide, followed by displacement at the peroxy group by the alkene moiety.[263] Although free radicals are not formally involved in the epoxidation, small amounts of radical decomposition products are sometimes observed.[264] Sharpless proposed a mechanism for the vanadium-catalyzed epoxidation[265a] that explains the stereoselectivity and provides insight into metal-catalyzed epoxidations



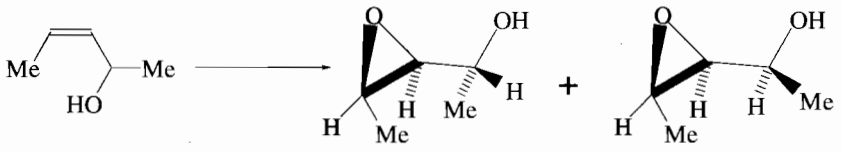
in general. A vanadium(V) species such as **165** reacts with the allylic alcohol and TBHP to give **166** via displacement of two alkoxy ligands. Coordination of the second oxygen of the peroxide generates a metal peroxide (**167**). The rate determining step of this process is the epoxidation (**167** → **168**), where the stereochemistry of the epoxide is determined. Displacement of the epoxide probably proceeds via **168** with



170

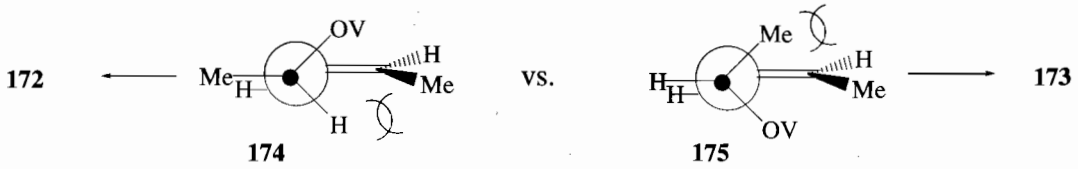
loss of *tert*-butyloxy and the OR ligand to regenerate the vanadium catalyst. In **167**, the alkene π bond will attack the peroxide moiety from the rear, along the axis of the O—O bond.[265a] In order to achieve backside attack, the allylic portion of the complex must deform as in **170**, giving an **O—C—C**=C bond angle of ≈ 50°. This model predicts the diastereoselectivity for the epoxidation of acyclic allylic alcohols such as **171**, which

gave a mixture of **172** and **173** in a ratio of 71:29.[265a] Examination of the transition states for the epoxidation of **171** (**174** and **175**) show a destabilizing interaction between methyl and hydrogen as compared to a hydrogen–hydrogen interaction. However, **175** has a severe steric interaction between the alkenyl methyl



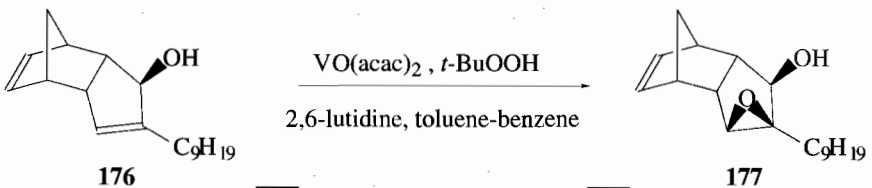
171 **172** **173**

and the methyl on the adjacent carbon as well as the oxygen–vanadium complex. In **174**, the lower energy destabilizing interaction of the hydrogen and oxygen–vanadium complex suggests that it is lower in energy. If **174** is lower in energy, **172** is predicted to be the major product. The energy difference between **174** and **175** is not great, however, and significant amounts of the minor isomer **173** are observed.

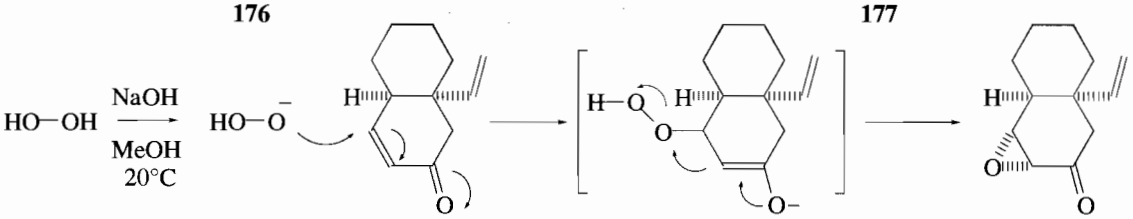


174 **175**

Another synthetic example illustrates both the epoxidation capabilities of this reaction as well as the stereochemical influence of neighboring alcohol unit noted above with the transformation **163→164**. In a synthesis of (–)-malyngolide by Ogasawara and co-workers, allylic alcohol **176** was treated with $VO(acac)_2$ and *t*-BuOOH, in the presence of 2,6-lutidine, and a 66% yield of **177** was obtained.[266] The hydroxyl unit directed the epoxidation to the exo face of the bicyclic system, as shown. Also notice that the *more substituted alkene* was epoxidized rather than the less substituted one, which is also typical of epoxidation reactions of this type, and will be discussed in more detail below, in connection with peroxyacid reactions.



176 **177**

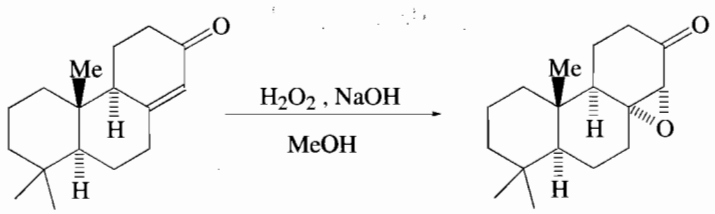


178 **179** **180**

In basic media, peroxides are deprotonated and the product is a peroxy anion, which reacts with conjugated carbonyl derivatives at the C-terminus (1,4-addition, conjugate addition). Hydrogen peroxide, for example, reacts with base to give the hydroperoxide anion (HOO^-), which adds to α,β-unsaturated ketones, aldehydes

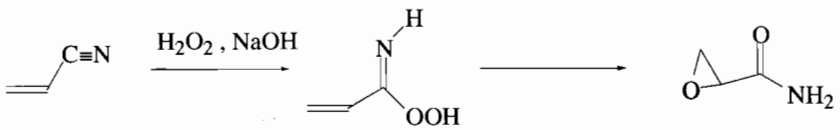
and esters.[267] Treatment of conjugated ketone **178** with basic hydrogen peroxide converted it to the corresponding epoxide (**180**) as part of Heathcock's synthesis of vernolepin[268] This reaction undoubtedly proceeds by an intermediate such as **179** in which the enolate displaces the hydroxyl group to yield the epoxide. This example also illustrates the selectivity of the hydroperoxide anion for conjugated alkenes over unconjugated alkenes. Note that the conjugate addition proceeded exclusively from the less hindered bottom face of the molecule.

For α,β-unsaturated aldehydes and ketones, the presence of a single carbonyl group is sufficient to activate the double bond to conjugate addition with hydroperoxide anions. This reactivity does not extend to α,β-unsaturated esters, however, and epoxidation does not occur unless two ester groups are present [such as is found with alkylidene malonate derivatives, $CH_2=C(CO_2)_2$].[269] Peroxide anion epoxidation is usually stereoselective but rarely stereospecific.[270] The hydroperoxide anion also reacts with α,β-unsaturated carbonyls to give an α,β-epoxyketone.[271,272] This can be seen in the epoxidation of **181** with basic hydrogen peroxide,, which gave a 92% yield of **182** in the Abad et al. synthesis of (–)-borjatriol.[273] The epoxidation occurred from the less hindered bottom face of the molecule.

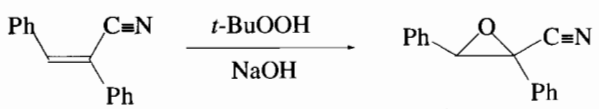


181 **182**

Alkyl hydroperoxides react with a suitable base to give a hydroperoxide anion (ROO^-), directly analogous to the reactions of hydrogen peroxide. The reaction with conjugated carbonyl derivatives is virtually the same for both HOO^- and ROO^-, except for reactions with α,β-unsaturated nitriles.[274] Alkaline hydrogen peroxide converts such nitriles to epoxy amides,[275] as in the reaction of acrylonitrile to give **183**, via initial formation of **184**.[275] The related reaction of **185** with *tert*-butylhydroperoxide in basic solution, however, gave good yields of the epoxy-nitrile (**186**) rather than the amide.[275]



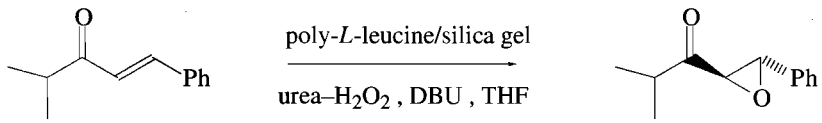
183 **184**



185 **186**

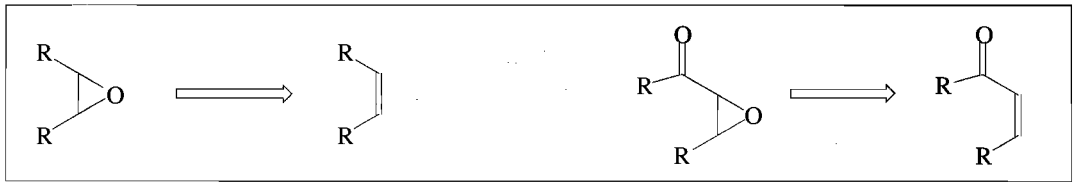
3.4.B.iii. Juliá–Colonna Epoxidation. A new and useful innovation involving the hydroperoxide anion epoxidation of conjugated carbonyl compounds modified the procedure so the reaction is done in the

presence of a polyamino acid such as poly-*L*-alanine or poly-*L*-leucine. This modification is now called the **Juliá–Colonna epoxidation reaction**.[276] Originally, the reaction was done in a water-immiscible solvent such as toluene, in which the substrate was treated with an aqueous NaOH–H_2O_2 solution containing the polyamino acid. In general, harsh reaction conditions are required, including long reaction times, and there was often difficulty in recovering the product from the gel-like catalyst as well as the catalyst itself.[277] These problems were diminished by using a biphasic system that used a urea–hydrogen peroxide complex as the peroxide donor, in an organic solvent containing DBU, along with the polyamino acid.[278] This diminished the reaction time and alleviated the problems caused by the use of an aqueous base, and the product was easily recovered.[277] The problem of catalyst recovery remained, however.[277] Gellar and Roberts modified the reaction by using silica gel as a solid carrier for the poly-*L*-leucine, and performed the reaction in THF.[277] An example is the epoxidation of **187** to **188** in 93% yield, an improvement in both yield and reaction time when compared to the same reaction without the use of silica gel.[277]



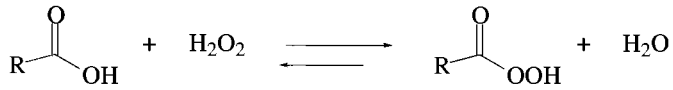
187 **188**

The functional group transforms for this section are



3.4.C. Organic Peroxyacids

Perhaps the most common method for the epoxidation of simple alkenes is their reaction with peroxyacids, which has occasionally been referred to as the **Prilezhaev (Prileschajew) reaction**.[279,280] This reaction does not require transition metal catalysis and the yield of epoxide is often high. Peroxyacids such as **156** are prepared by reaction of carboxylic acids with hydrogen peroxide. An equilibrium is established during the reaction that favors the peroxyacid, although several alternative methods are available.[279] In general, strong

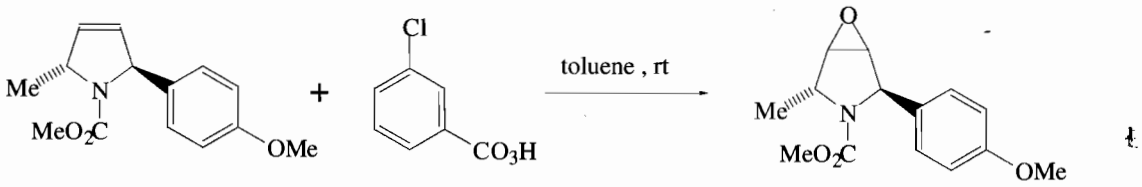


156

acids such as formic and trifluoroacetic acid generate useful equilibrium concentrations of the peroxyacids upon reaction with hydrogen peroxide (the equilibrium is shifted to the right, forming **156**). Most other alkyl and aryl acids. however, require catalytic amounts of strong mineral acids or *p*-toluenesulfonic acid to give the corresponding peroxyacid, however.[281] Several peroxyacids are commercially available, including peroxyformic, peroxybenzoic, trifluoroperoxyacetic, and *m*-chloroperoxybenzoic (MCPBA, **190**). Peroxyacids are

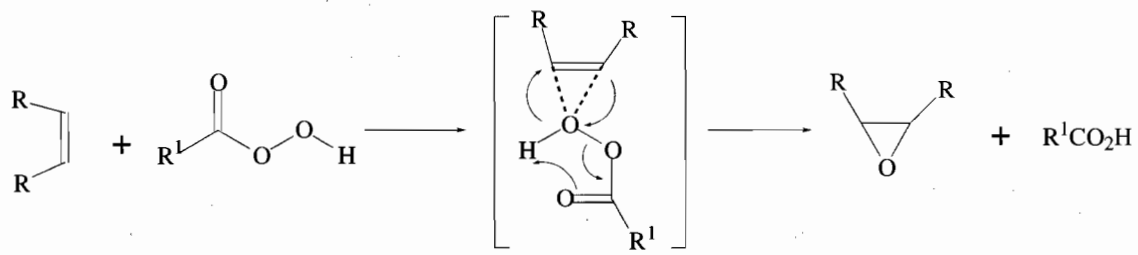
significantly less acidic than their carboxylic acid counterparts,[282] making them less likely to initiate acid–base reactions. The major byproduct of the alkene epoxidation reaction, however, is the carboxylic acid precursor to the peroxyacid (see below). If necessary, this acid can be neutralized during an epoxidation reaction by addition of sodium acetate (or another buffering agent).

A simple example of alkene epoxidation is taken from Correia's synthesis of (–)-codonopsinine,[283] in which **189** was converted to epoxide **191** with MCPBA in toluene, as a 93/7 mixture of α/β diastereomers. Although MCPBA is one of the more popular epoxidizing agents, shortages of concentrated hydrogen peroxide sometimes make high purity MCPBA difficult to obtain, although less pure reagent is usually available. Development of alternative reagents has therefore been an ongoing process. The peroxyacid magnesium monoperphthalate (abbreviated MMPP,[284] see the parent peroxy acid **223** below) was prepared by Brougham et al. and is an efficient reagent for the conversion of alkenes to epoxides in aqueous media.[285]



189 **190** **191**

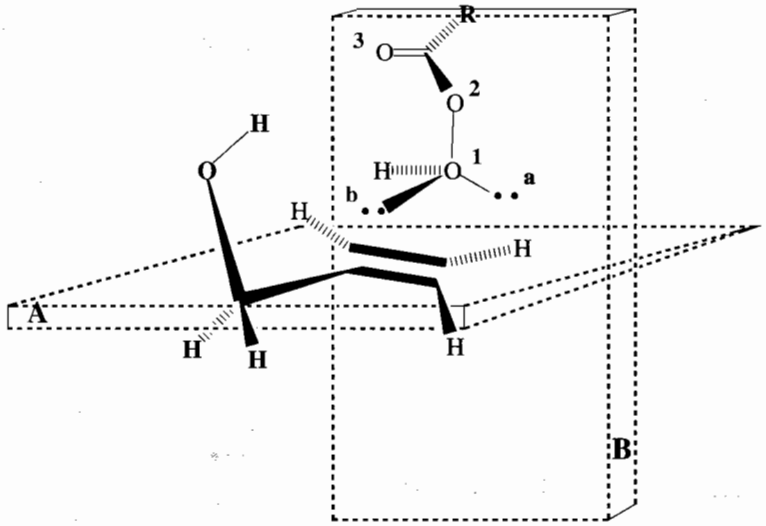
A major advantage of using peroxyacids is the rapid epoxidation of unfunctionalized alkenes, which are normally unreactive with hydrogen peroxide or alkyl hydroperoxides without the presence of transition metal catalysts.[286] The reaction probably proceeds via a concerted mechanism, as proposed by Bartlett,[287] in which the alkene and the electrophilic peroxy oxygen in **156** coordinate, with concomitant expulsion of the carboxylic acid and release of the epoxide. Other mechanisms have been proposed as well.[288] The transition state for this reaction has been analyzed using computational methods[289] but it is usually represented by a complex such as **192**. The geometry of the transition state facilitates loss of the R^1CO_2H byproduct and also dictates a syn delivery of oxygen, without changing the geometry of the alkene.



156 **192**

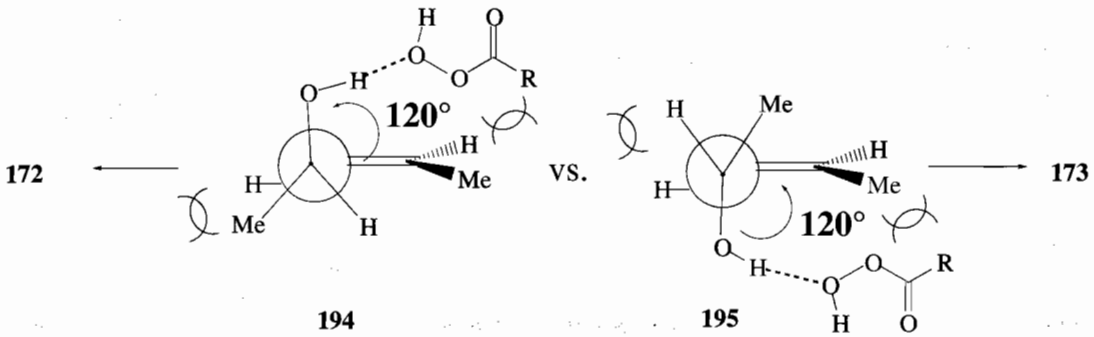
Neighboring group effects are important in reactions of peroxyacids, as they were with reactions of hydroperoxides. Reexamination of the epoxidation of **171** using MCPBA rather than TBHP reveals that the peroxyacid gave a 95:5 mixture of **172** and **173**. Using MCPBA rather than TBHP led to a slight increase in diastereoselectivity for the reaction, although this depends on the substitution pattern of the alkene. Sharpless

and co-workers proposed an intermediate based on **193**,[265] in which one plane (defined by the peroxyacid molecule in plane B) is oriented at an angle of ≈ 60° to the plane of the π bond (plane A). One of the non-bonding electron pairs on oxygen (pair a) lies in plane B and is properly situated to begin bonding with the



193

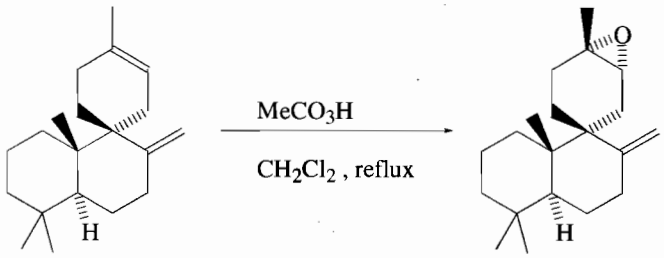
alkene carbon. The other lone pair electrons (pair b) is positioned so it can hydrogen bond with the allylic hydroxyl group, as in **194** or in **195**. The selectivity of epoxidations involving peroxy acids was previously explained by hydrogen bonding to O^2 or O^3 in **193**.[290] If backside displacement of the peroxy bond is required, hydrogen bonding to O^2 or O^3 is not possible. A hydrogen bond to O^1, however, will have a dihedral angle for the **O—C—C**=C bond from ≈ 50-130°, with 120° predicted as optimal (shown in **194** and **195**).[265a] In **194**, the destabilizing methyl-hydrogen interaction is less than the methyl–alkenylmethyl interaction in **195**. The peroxy moiety will interact with the alkenylmethyl moiety in both cases. The greater destabilizing interaction in **195** leads to a predominance of **172** (from **194**) with only small amounts of **173** (from **195**).



194 **195**

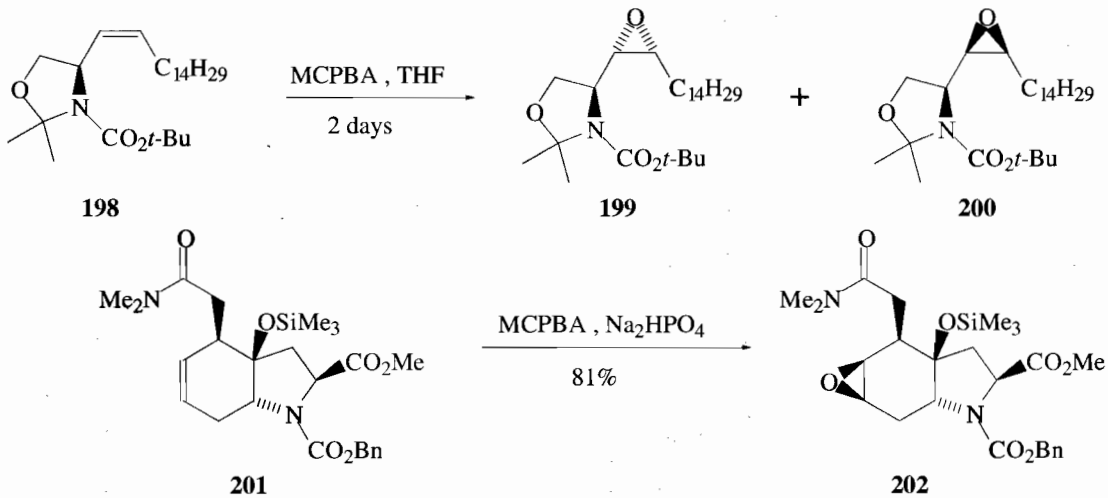
More highly substituted alkenes are electron rich and react faster with peroxyacids than do less substituted alkenes. In general, the relative rate of epoxidation increases with the nucleophilic character of the alkene[291] (CH_2=CH_2 has a relative rate of 1, RCH=CH_2 = 24, RCH=CHR = 500, R_2C=CH_2 = 500, R_2C=CHR = 6500,

and $R_2C{=}CR_2$ = >>6500).[292] Tri- and tetrasubstituted double bonds are rapidly epoxidized with both peroxyalkanoic acids and peroxybenzoic acids, but peroxybenzoic acids are more effective. If a molecule contains two alkene moieties, the more highly substituted alkene is epoxidized faster. 1,2-Dimethyl-1,4-cyclohexadiene, for example, gave primarily the tetrasubstituted epoxide upon reaction with MCPBA.[293] This preference is also seen in White's synthesis of 2-desoxystemodinone, in which the trisubstituted alkene in **196** was epoxidized in preference to the exocyclic disubstituted alkene, giving **197** in 62% yield.[294]



196 **197**

Epoxidation of monosubstituted alkenes, which are generally less reactive, often requires the use of a strong peroxyacid such as trifluoroperoxyacetic acid, although MCPBA is usually effective.[295] For most alkenes, MCPBA is a good all-purpose peroxyacid. Even highly hindered alkenes can be epoxidized with little difficulty.[296] If there is no possibility of hydrogen bonding, the peroxyacid usually approaches the alkene from the least hindered face,[297,298] and such reactions are diastereoselective. Diastereoselectivity usually depends on the peroxy acid used, as well as the reaction conditions. Epoxidation of **198** with MCPBA in THF, for example, gave an 84% yield of epoxide **199** with only 4% of **200**, in an example taken from the Azuma et al. synthesis of sphingosine.[299] When done in benzene, the reaction was complete in only 4 h, but the ratio of **199/200** was 82:18. Although **199** was the major product in all cases, diastereo-selectivity varied with solvent and reaction time.



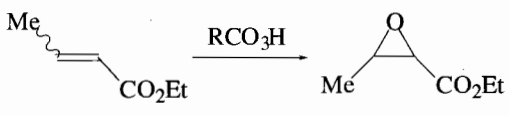
198 **199** **200**

201 **202**

A buffer is often added to epoxidation reactions involving peroxyacids. The byproduct of the reaction is a carboxylic acid, as mentioned several times above. If trifluoroperoxyacetic acid (CF_3CO_3H) is used as the

oxidizing agent, the byproduct is the strong organic acid, trifluoroacetic acid (CF_3CO_2H). This acid is strong enough to catalyze rearrangement or other reactions of the epoxide product. Addition of an acid salt ($RCO_2^-M^+$) to the reaction medium will usually buffer the reaction and prevent deleterious side reactions. Reactions with peroxybenzoic acid, for example, would use sodium benzoate, and sodium trifluoroacetate is used with trifluoroperoxyacetic acid. Both sodium and potassium acetate are used as generic buffers and sodium or potassium hydrogen phosphates can also be used. An example of a buffered reaction is the conversion of **201** to **202** in 81% yield, in Wipf's synthetic studies for a synthesis of the tuberstemonone ring system.[300]

The presence of electronegative substituents on the double bond lowers the nucleophilicity of the alkene and decreases the rate of epoxidation.[301,282] Vinyl chlorides,[302] vinyl acetates,[303] and vinyl ethers[304] are all oxidized, but vinyl acetates react slower than unsubstituted double bonds.[305] Glycidic esters (epoxy esters) such as **203**, for example, can be formed from conjugated esters such as ethyl 2-butenoate, using MCPBA[306] or trifluoroperoxyacetic acid, with a disodium phosphate or a sodium or potassium hydrogen phosphate buffer.[307] The epoxides resulting from epoxidation of these substrates are often labile, however, and can rearrange to an α-halo or α-carboalkoxy ketone in unbuffered reactions.[308]

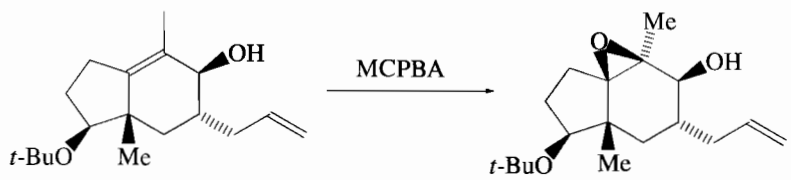


203

204 **205**

Conjugation diminishes the reactivity of an alkene in epoxidation reactions. Conjugated esters, for example, are less reactive than simple alkenes due to the electron-withdrawing effect of the carbonyl. Isolated (unconjugated) alkenes are usually epoxidized before conjugated alkenes, as seen in the reaction of **204** to give **205**, in Hiyama's synthesis of β-sinesal.[309]

The neighboring group effect observed in the reaction of allylic alcohols and hydroperoxides is also observed with peroxyacids. The so-called **Henbest rule** states that allylic alcohols exert a strong directing influence upon epoxidation when peroxyacids are used.[310] However, it is known that this effect does not operate in medium sized rings, and rings with significant flexibility tend to give the trans-product.,[311] The Henbest rule can be exploited synthetically, however, and Marshall used it in a synthesis of confertin.[312] The less hindered face of allylic alcohol **206** is the bottom (α) face, but the ability of the hydroxyl-to-hydrogen bond with MCPBA directed epoxidation from that face to give the observed β-epoxide, **207**.[312] The net result of this neighboring group effect is epoxidation on the more sterically hindered face of the molecule.

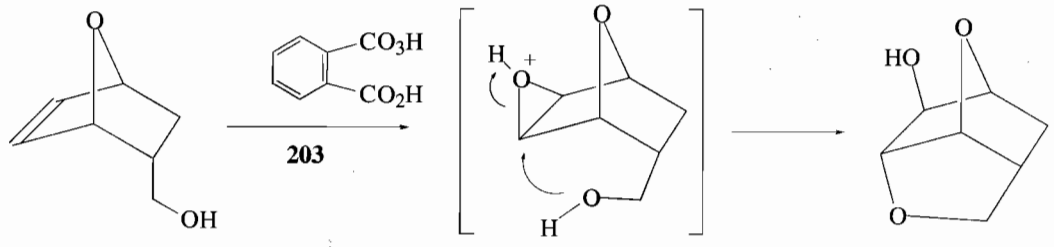


206 **207**

The presence of other groups can also lead to a neighboring group effect. The relative ability of a group adjacent to a double bond to coordinate with a peroxy acid and give syn delivery of the epoxide oxygen is[313]

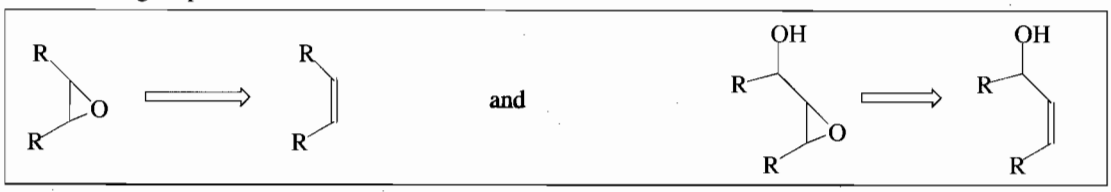
OH	>	CO_2H	>	CO_2R	>	OCOR

Occasionally, the proximity of the alkene to another reactive group can lead to a competing reaction. In the case of **208**, the hydroxyl does not show a significant neighboring group effect and epoxidation with perphthalic acid (**203**) proceeds from the *exo*-face.[292,314] The acid byproduct of the epoxidation is trifluoroacetic acid, a strong acid that can protonate the exo-epoxide (see **209**. The hydroxyl unit on the other side of the molecule can now participate in the reaction, opening the epoxide ring to give alcohol–ether **210** as the final product.[292,314] To avoid such secondary reactions, protection of the offending group is required (sec. 7.3.A) or, in some cases, buffering will minimize acid-catalyzed secondary processes .



208 **209** **210**

The functional group transforms are

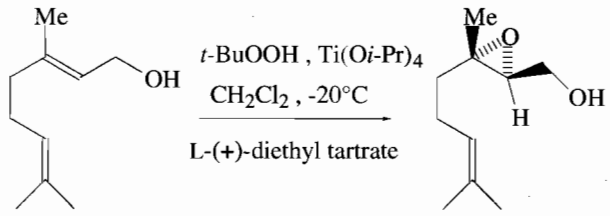


3.4.D. Asymmetric Epoxidation Reactions

The previous section described metal catalyzed epoxidation of allylic alcohols by alkyl hydroperoxides, and **193** was proposed as a model to predict the diastereoselectivity of these reactions,. In the cases presented, the reaction was diastereoselective but not enantioselective (sec. 1.4.F) and those epoxidation reactions generated racemic epoxides. To achieve asymmetric induction one must control both the relative orientation of the alkene relative to the peroxide and also the face of the substrate from which the electrophilic oxygen is delivered. Control of this type can be accomplished by providing a chiral ligand that will also coordinate to the metal catalyst, along with the peroxide and the alkene unit. There are two major asymmetric epoxidation reactions, one that can be applied only to allylic alcohols and is the prototype for asymmetric induction in these systems. The other is a procedure that can be applied to simple alkenes. Both procedures use a metal-catalyzed epoxidation that employs alkyl hydroperoxides, introduced in section 3.4.B.ii.

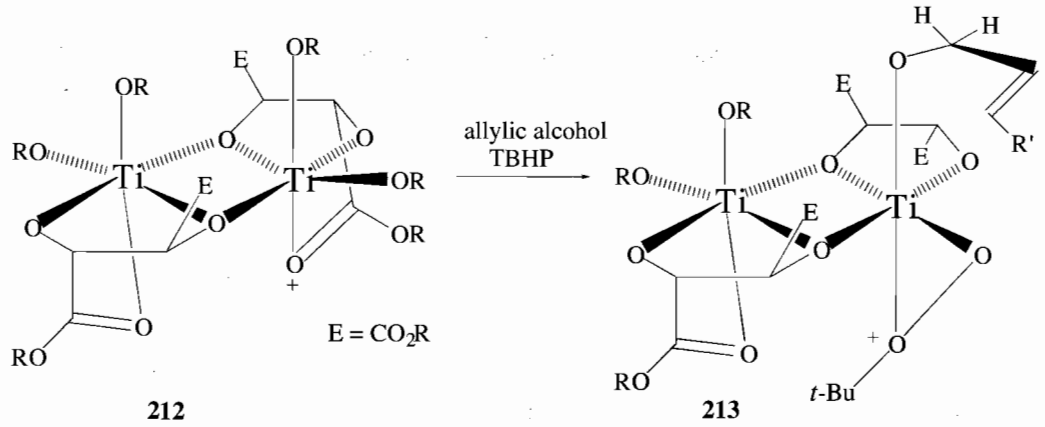
3.4.D.i. Sharpless Asymmetric Epoxidation. The epoxidation reactions described heretofore generated racemic products even when they were highly diastereoselective. The reagents presented simply did not

provide the facial bias required for asymmetric induction. That changed in 1980, when Sharpless reported that epoxidation of allylic alcohols with *tert*-butyl hydroperoxide, catalyzed by tetraisopropoxy titanium (IV) [Ti(O*i*-Pr)$_4$], gave the epoxy alcohol with high enantioselectivity when (+)- or (–)-diethyl tartrate was added to the reaction medium.[315,316,265] Reaction of geraniol (**92**) under these conditions, in the presence of L-(+)-diethyl tartrate (DET), gave **211** in 77% yield with 95% ee for the (2S,3S) stereoisomer.[315] It is noted that the natural isomer of diethyl tartrate [L-(+)-] is readily available as is the *unnatural* tartrate [(D-(–)-], although it is significantly more expensive. When the epoxy alcohol product is water soluble, a decrease in optical activity and yield was observed.[315]



92 **211**

When the previously cited transition structure **193** is applied to the asymmetric epoxidation of allylic alcohols, it must be modified to include binding of the peroxide, the allylic alcohol, and also the chiral tartrate. The metal in the new model is titanium rather than vanadium, and tetraisopropoxy titanium was found to react with 2 equivalents of diethyl tartrate to form a species such as **212**, where OR = O*i*-Pr and CO_2R = CO_2Et.[317,318] The tartrate can bind to titanium from either the bottom or the top face.[318] The nature of the



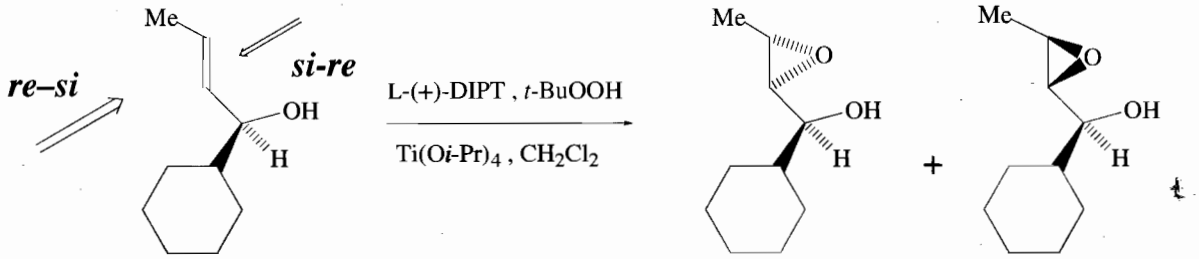
212 **213**

[Reprinted with permission from Burns, C.J.; Martin, C.A.; Sharpless, K.B. *J. Org. Chem., 1989, 54*, 2826. Copyright © 1989 American Chemical Society.]

OR and E groups will determine the facial preference and, thereby, the selectivity of the epoxidation. When **212** reacted with TBHP and an allylic alcohol, 2 equivalents of 2-propanol were displaced to generate **213**. The peroxide linkage and the allylic alcohol in **213** are closely related to the orientation described in **193** (see above). Backside attack of the alkene moiety along the axis of the O—O bond will lead to the epoxide. The titanium metal, serves as a template for the reaction and the presence of the chiral tartrate converts **213** into a

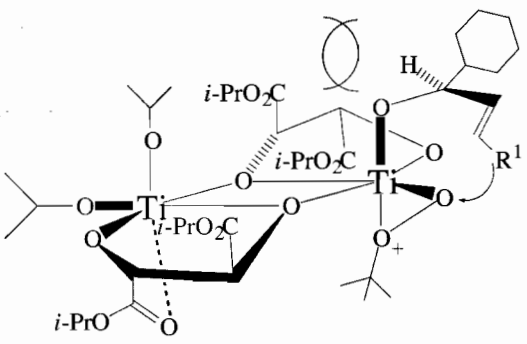
chiral template. If the groups that are shown as E in **213** were not present, the allylic alcohol could bind to titanium on both the top and the bottom. When the metal binds tartrate (the source of the E groups in **212** and **213**), this creates a pocket where the allylic alcohol and peroxide can attach. The face opposite this pocket is too sterically hindered for efficient binding and the usual backside attack leads to a single enantiomer. The extent of this enantioselectivity is determined by the extent to which binding of the allylic alcohol and peroxide is limited to a single face. Sharpless showed that this process proceeds by a series of reversible (equilibrium) steps for binding alcohol, alkoxy groups, and peroxide to titanium.[318]

Sharpless provided an empirical model that enables one to predict the stereochemistry of the epoxide formed in this reaction. When using the natural L-(+)- (2*R*, 3*R*) tartrate, the allylic alcohol should be oriented as shown for **214**, with the hydroxyl group in the plane of the double bond and to the right.[316c] With this



214 **215** **216**

orientation the (+)- tartrate (in this case diisopropyl tartrate, DIPT) delivers oxygen (remember it is the alkene that attacks the peroxide) from the face bearing the hydroxyl (the *re–si* face) to give primarily the anti-product (**215**) with trace amounts of the syn-isomer, **216**.[316c] If the model in **214** is redrawn as **217** and **218** for the reaction that forms **215** and **216**, the source of this selectivity can be determined. In **217**, the CO_2i-Pr↔H interaction is small compared to the cyclohexyl↔CO_2i-Pr interaction in **213**. This steric preference for **217** leads to binding of the allylic alcohols and a relative orientation for backside attack of the peroxide linkage that lead to approach of peroxide oxygen to the si face of the alkene. In **217**, the (*S*)-chiral center of the allylic alcohol gives a better fit with the chiral center of the tartrate (the chirality is matched) than does the (*R*)-chiral center of the alcohol in **218**. Such matching of chiral centers is referred to as **consonance** (as in **217**) whereas the interaction of mismatched chiral centers (in **218**) is called **dissonance**.



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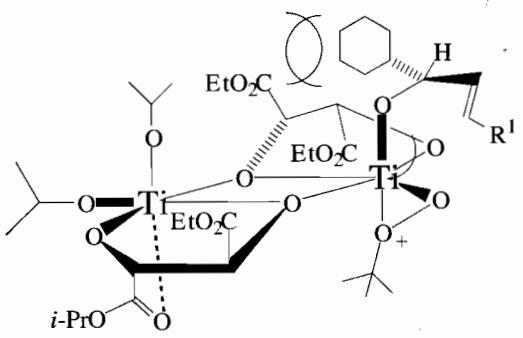

218

This is further illustrated in Figure 3.2[318] for DET, which shows the propensity for (+)-DET to give the anti-product from the *re–si* face and for (–)-DET to give the syn-product from the *si–re* face. Figure 3.2 illustrates consonance when the chirality of natural (+)-DET leads to faster reaction from the *si* face to give the anti-product. Conversely, the chirality of (–)-DET is mismatched to the *si* face making that reaction slower, although it is matched to the *re* face and that epoxidation is faster. Allylic alcohol (**214**), for example, reacts

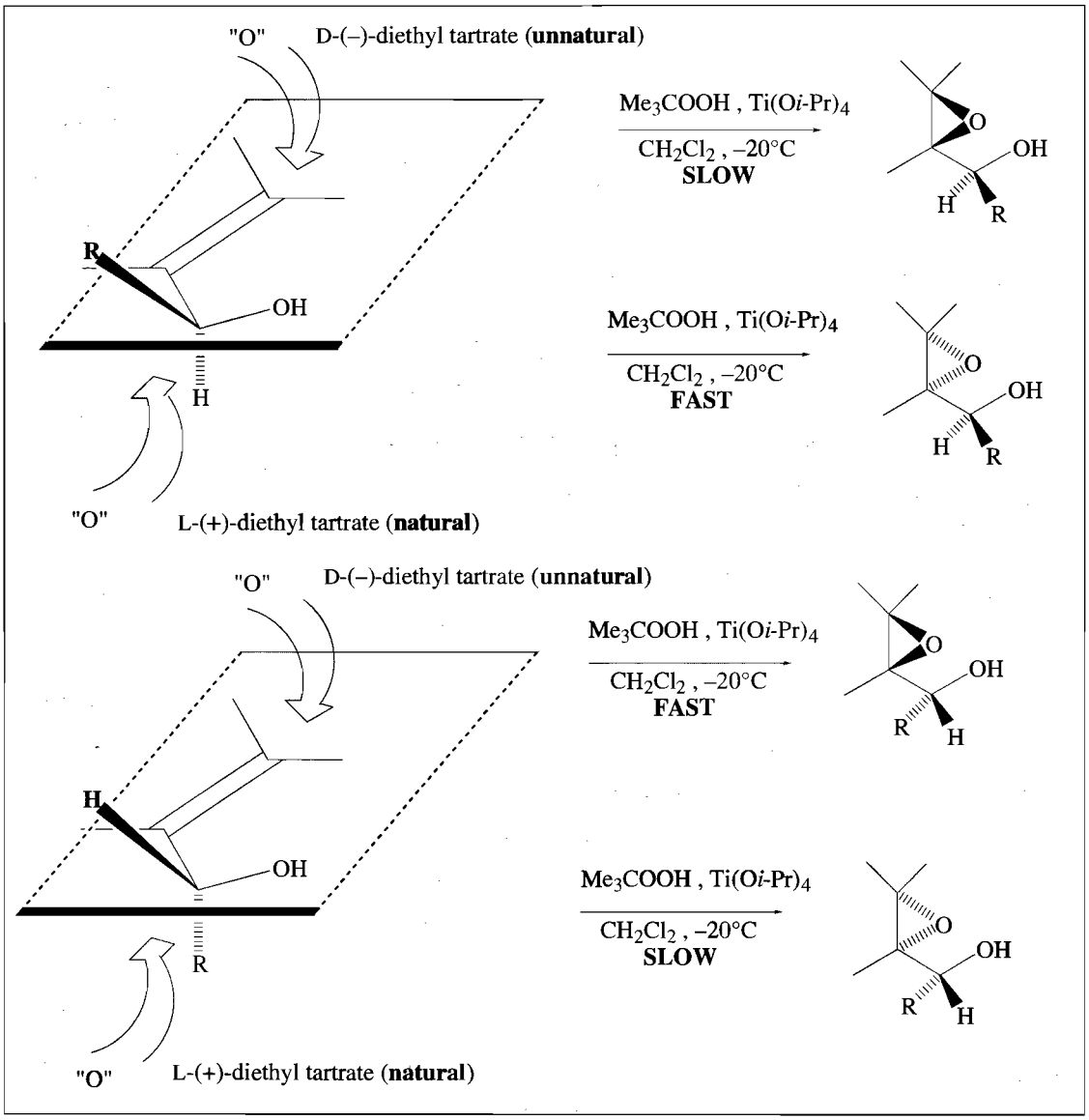

Figure 3.2. Facial selectivity on allylic alcohols for (+) and (–)-diethyl tartrate.

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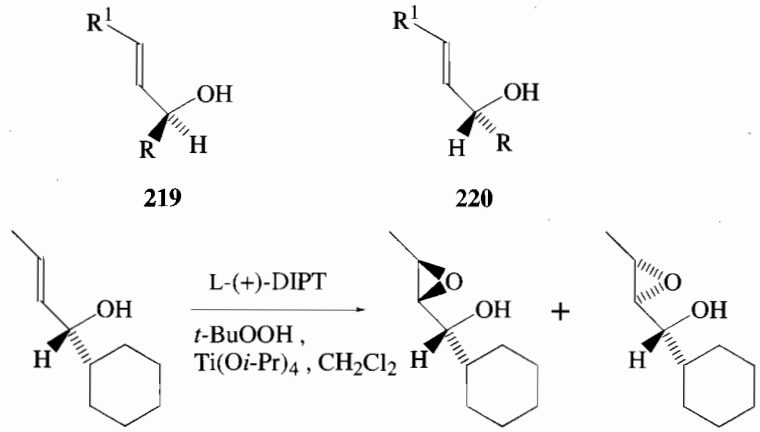
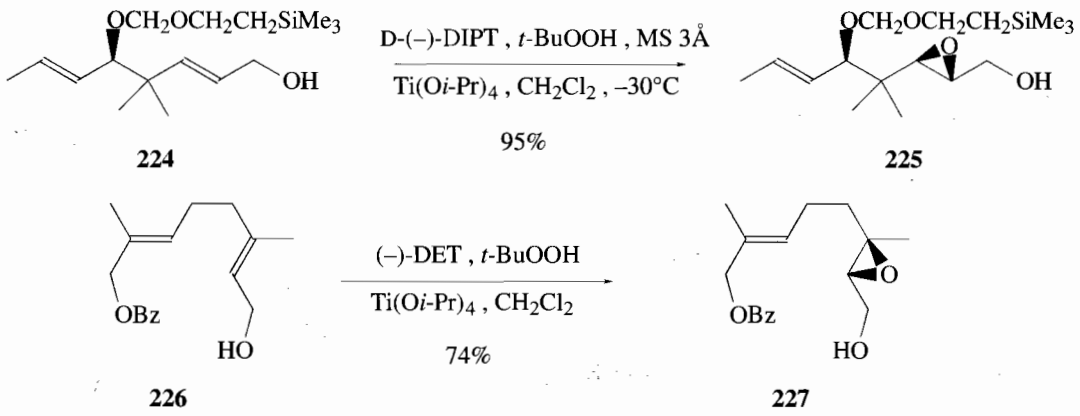
104 times faster than **221** with (L)-(+)-DIPT due to the consonance with the (*S*)-enantiomer (and the corresponding dissonance of this tartrate with the (*R*)-enantiomer). This led to **kinetic resolution** (one enantiomer reacts faster to give a predominance of that epoxide) of the allylic alcohols.[316c] In general, the

additive (L)-(+)-DIPT reacts best with allylic alcohols of the type represented by generic structure **220**, where (D)-(–)-DIPT would be the choice for **219**. The (*R*)-enantiomer of alcohol **214** is **221**, and it reacts with (L)-(+)-DIPT to give a mixture of diastereomers (**222** and **223**) with the syn-isomer (**223**) predominating (38:62).

As the size of the alkyl group on tartrate increases (Me → Et → *i*-Pr) the rate for reaction of one enantiomeric allylic alcohol increases in comparison with the other.[318] Inspection of **222**/**223** reveals that changing the tartrate ester from methyl to ethyl and then to isopropyl increases the steric preference for one enantiomer

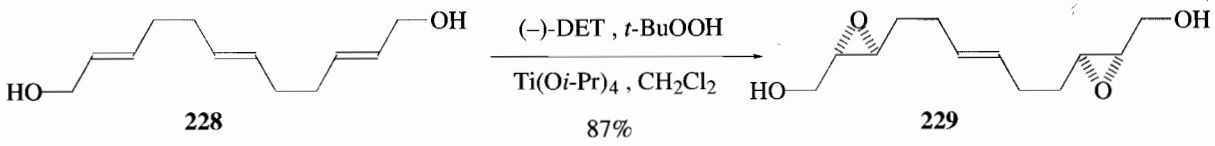


(see above). The CO_2R'cyclohexyl interaction is greater when R^1 is isopropyl than when R^1 is methyl, which will lead to faster binding of **214** than of **221** and faster epoxidation. Figure 3.2 also illustrates the source of kinetic resolution in the matched and mismatched interaction of (+)- or (–)-DET with a chiral allylic alcohol. This methodology can be applied in a variety of synthetic manipulations.[319,320]



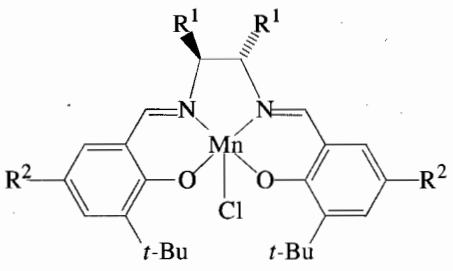
Sharpless asymmetric epoxidation is the first example of a reaction where an achiral precursor is converted to a chiral substrate with high enantioselectivity. This discovery triggered a flurry of activity, applying the basic principles of asymmetric epoxidation to a variety of other reactions. Sharpless asymmetric epoxidation is very important in the synthesis of natural products since this reaction offers an asymmetric route to many important synthons. One example is the conversion of **224** to **225**, in 95% yield (> 15:1 de), in Meyer's synthesis of disorazole C_1, where MS indicates the use of molecular sieves.[321] In a second example, taken

from Liang's synthesis of chrysotricine, **226** was converted to **227** in 74% yield.[322] In this example, the selectivity for the allylic alcohol unit, even in the present of the allylic ester is striking. A last example is taken from Hoye's synthesis of (+)-parviflorin,[323] and it is included to show that a double-Sharpless epoxidation can be accomplished, as in the conversion of **228** to **229** in 87% yield in ≈ 97% ee.



228 **229**

3.4.D.ii. Jacobsen–Katsuki Asymmetric Epoxidation. The Sharpless asymmetric epoxidation only works with allylic alcohols, as was illustrated by the conversion of **224** to **225**. By changing the catalyst, it is now possible to convert simple alkenes to the corresponding epoxide with high asymmetric induction. In independent work, Katsuki and Jacobsen showed that manganese–salen complex catalyzed asymmetric epoxidation in the presence of *tert*-butylhydroperoxide, where salen = bis(salicylidene)ethylenediamine. A typical catalyst is **230** where R^1 can be an aryl group or cycloalkyl, bromine, trialkylsilyloxy and other groups. The manganese–salen catalyst **231** {the chemical name is [*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine]manganese(III)] chloride} is known as the **Jacobsen catalyst** and is very useful. In addition, metals other than manganese have been used. Mechanistically, it has been established that the order of mixing of the components is important.[324] Although Mn^{IV}–salen complexes are formed in the absence of alkenes, in the common epoxidation conditions, Mn^{IV}–salen complexes play a minor role.[324]



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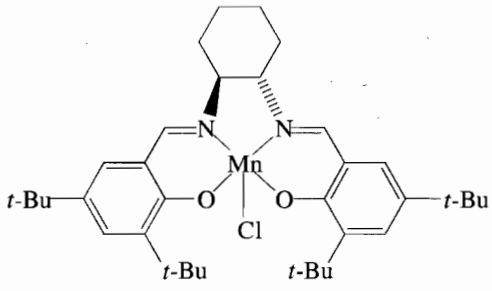

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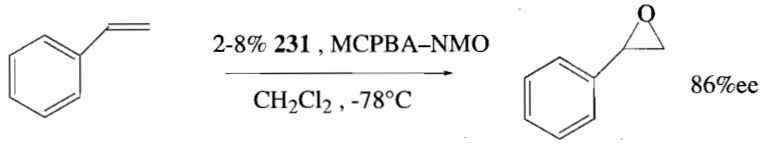
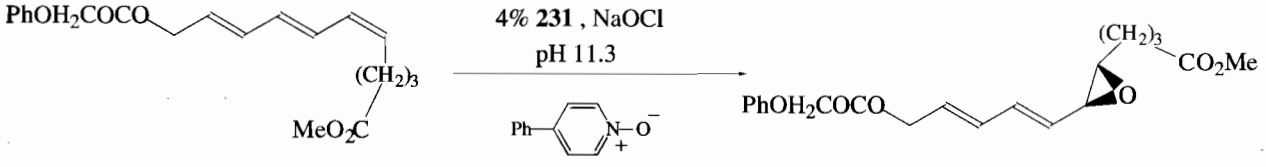


232

Perhaps the most interesting feature of this reaction is that simple alkenes were oxidized with high asymmetric induction, in what is now called the **Jacobsen–Katsuki reaction.**[325] In a typical transformation, styrene was converted to styrene oxide (**232**) in 89% yield and 86% ee using 2–8 mol% of **230** (R^1 = Ph, R^2 = $OSi(i\text{-}Pr)_3$, with the combination of MCPBA and *N*-methylmorpholine *N*-oxide (NMO) as the oxidizing agent.[325k] Jacobsen used this procedure in a synthesis of leucotrine A_4 (LTA_4).[325d] In this synthesis, **233** was

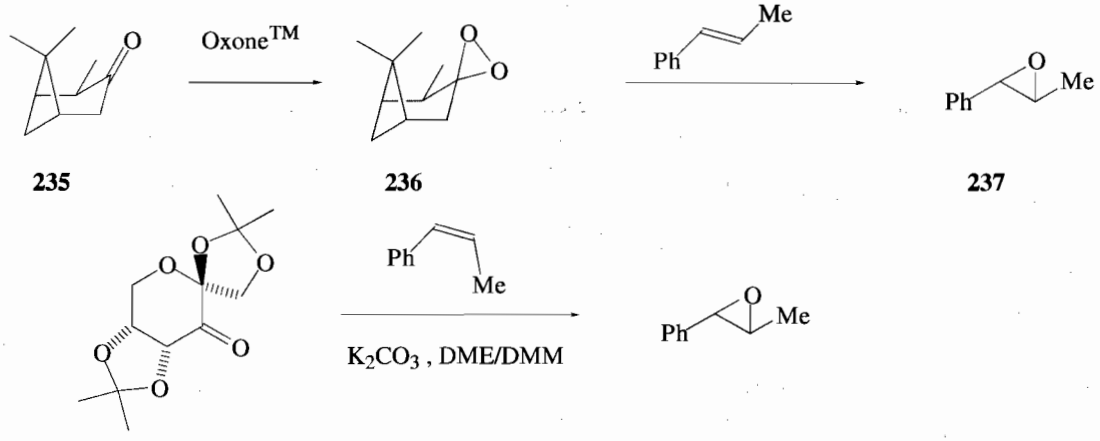
oxidized with sodium hypochlorite (NaOCl and 20% 4-phenylpyridine *N*-oxide, at pH 11.3, using 4% of the **231** catalyst). Epoxide **234** was obtained in 62% yield (82% ee and a trans/cis ratio of 8:1).[325d] Katsuki found that the degree of enantioselection is some of the later Mn–salen complexes depends on the conformation of the ligand and the nucleophilicity of the substrate,[326] which is explained by enthalpy and entropy factors.



233 **234**

This epoxidation reaction is useful for disubstituted alkenes and also for trisubstituted alkenes.[325h] Epoxidation of trisubstituted alkenes proceeds with absolute asymmetric induction that was opposite to that observed with cis- or trans-disubstituted alkenes.[325h] Jacobsen suggested a general, skewed side-on approach transition state model,[327] for the epoxidation that proceeds by a stepwise mechanism involving radical intermediates.[327b] Song et al. has introduced a variation in which catalyst **231** is used in an ionic liquids consisting of 1,3-dialkylimidazolium cations, with a PF_6^- counterion,[328] which allows the manganese–salen catalyst to be easily recycled. The mechanism of this reaction has been discussed elsewhere[329] and, as mentioned above, radical intermediates have been postulated.[330] There is no doubt that this reaction will increase in importance in syntheses. It should be noted that manganese–salen catalysts have been used in epoxide ring-opening reactions.[331]

3.4.D.iii. Epoxidation with Dioxiranes. Dialkyl dioxiranes (see **236**) are versatile oxidizing agents that can be generated from Oxone™ (potassium peroxymonosulfate) and ketones.[332] When generated in the presence of an alkene, an epoxide is the product and, if done in the presence of a chiral ketone a chiral epoxide is formed.[333] Curci was the first in 1984 to report this chiral epoxidation, using (+)-isopinocamphone (**235**) as a catalyst and converting (*E*)-β-methylstyrene to epoxide **237**, but in only ≈ 12% ee. (1*R*,2*R*)[334] This is an



235 **236** **237**

238 **237**

excellent alternative for asymmetric epoxidation to the Sharpless and Jacobsen–Katsuki procedures described above. Many chiral ketones can be used and significantly better enantioselection can be achieved. A recent example by Shi used a fructose-derived ketone (**238**), which reacted with (*Z*)-β-methylstyrene to give an 87% yield of **237** in 91% ee (1*R*,2*S*).[335] In this reaction, the abbreviation DMM refers to dimethoxymethane.

3.5. CONVERSION OF ALKENES TO DIOLS (C=C → CHOH—CHOH)

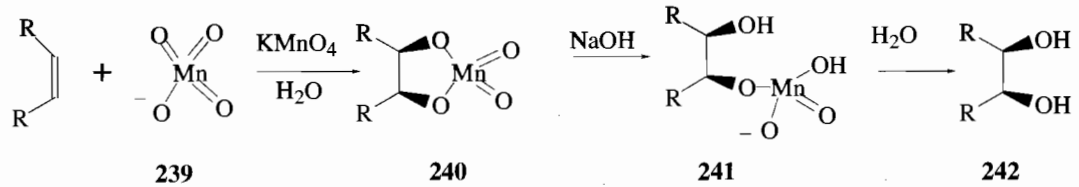
Just as one oxygen can be added to an alkene to form an epoxide, two oxygens can be added to generate 1,2-diols.[336] 1,2-Diols and polyols containing several contiguous hydroxyl moieties are important structural features of many natural products, particularly macrolide antibiotics. 1,2-Diols are usually formed by the syn-addition of manganese or osmium reagents to an alkene. The mechanistic aspects of this type of syn- dipolar addition will be discussed in section 11.11, but a cursory introduction will be given here. If a dipolar reagent has an oxygen at each pole, reaction with an alkene will deliver oxygens across the π bond. Subsequent reaction of this cycloadduct can liberate a 1,2-diol. Both potassium permanganate and osmium tetroxide react with alkenes in this manner. These two are the most common reagents used to prepare 1,2-diols. An alternative route to 1,2-diols is available using silver salts of carboxylic acids will conclude this section.

3.5.A. Dihydroxylation with Potassium Permanganate

In Table 3.1, it was noted that permanganate (MnO_4^-) is a powerful oxidizing agent in basic, acidic and neutral media. In acidic solution, the reduction potential is 1.679 V or 1.491 V, but it is 0.588 V in basic solution, according to the following reactions.

$MnO_4^- + 4\,H^+ + 3\,e^- \rightarrow MnO_2 + 2\,H_2O$		1.679 V
$MnO_4^- + 8\,H^+ + 5\,e^- \rightarrow Mn^{2+} + 4\,H_2O$		1.491 V
$MnO_4^- + 2\,H_2O + 3\,e^- \rightarrow MnO_2 + 4\,HO^-$		0.588 V

In this section, permanganate [principally potassium permanganate ($KMnO_4$)] will be used to oxidize alkenes to 1,2-diols. It is apparent from preceding discussions that alkenes can donate an electron pair to an electrophilic center. The structure of permanganate (MnO_4^-, **239**) is best viewed as the 1,3-dipolar molecule (δ^+ O and an negative O). Reaction occurs between an alkene, which donates electrons to the electrophilic oxygen of the dipole. As the π-bond breaks, positive character develops on one carbon, which is attacked by

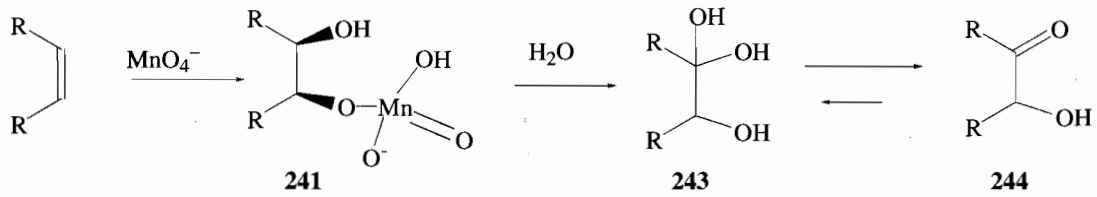


239 **240** **241** **242**

the negative oxygen of the dipolar molecule. It is likely that this is a concerted process, controlled by the frontier orbital energies of the alkene and the dipole (see sec. 11.2, 11.11.A). The product of this reaction is a

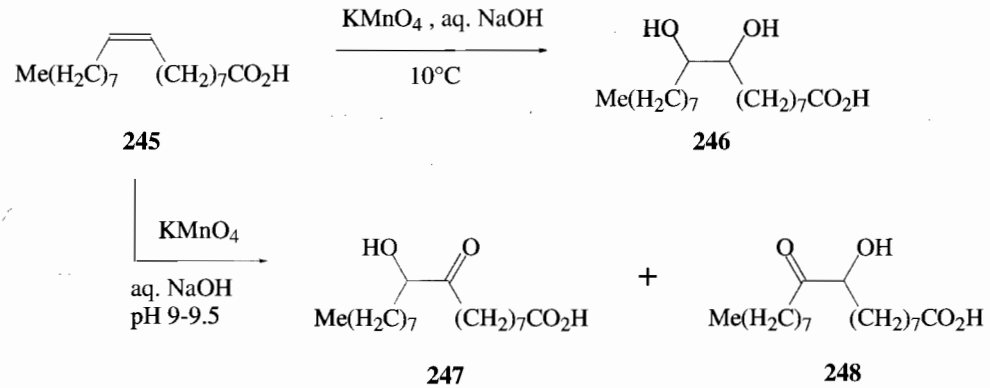
cyclic manganate ester (**240**).[337] Formation of **240** is accompanied by reduction of Mn(VII) to Mn(VI).[337] Subsequent decomposition generates a 1,2-diol (**242**) so that the overall reaction is an oxidation of the alkene. The cis geometry of the oxygen atoms is fixed at the time of the dipolar addition. The timing for forming each C—O bond must be close, if is not concerted (sec. 11.11.A).[338] Under alkaline conditions cis diols are produced by attack of hydroxide at manganese in **240** to form **241**. Subsequent reaction with water liberates the diol and the Mn(V) byproduct disproportionates to Mn(VII) [MnO_4^-] and Mn(IV) [usually MnO_2].

Reaction of permanganate with an alkene is an exothermic process.[339] This oxidation with $KMnO_4$ is very facile in several solvents (aqueous EtOH, acetone, *t*-BuOH), under acidic, basic, or neutral conditions.[340] Under dilute conditions, permanganate oxidizes alkenes to the 1,2-diol. Under vigorous conditions (75°C, 0.2 M KOH) extensive carbon–carbon bond cleavage occurs[341] (sec. 3.7). In neutral media (and very low hydroxide concentration) large quantities of α-hydroxy ketone (ketols such as **244**) are formed.[342] Under these conditions the alkene is oxidized by permanganate to **241** with Mn^{6+} as the byproduct. Aqueous hydrolysis generates **243** before hydroxide can attack manganese a second time, leading to the ketol and MnO_2. If strongly basic conditions are used to decompose **241**, the diol is the major product. Henbest showed that the presence of electron-withdrawing groups reduce the rate of diol formation and promoted the formation of diketones and cleavage products.[343]



241 **243** **244**

Swern showed that the permanganate oxidation of oleic acid (**245**) was pH dependent. Earlier, Lapworth and Mottram oxidized oleic acid to 9,10-dihydroxy stearic acid, **246**,[344] in essentially quantitative yield by what might be considered standard conditions for hydroxylation: 0.1% oleic acid, no more than 1% $KMnO_4$, short reaction time (5 min), slight excess of alkali and a reaction temperature of 0–10°C.[344] Swern found that



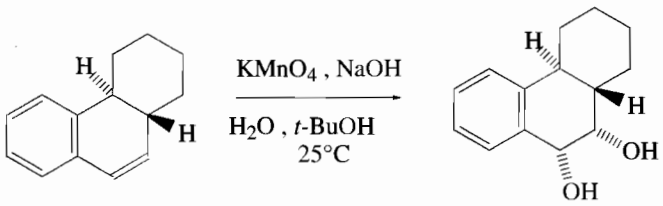
245 **246**

247 **248**

reaction of **245** with potassium permanganate and sodium hydroxide without pH control gave 45% of a mixture of 9-keto-10-hydroxystearic acid (**247**) and 10-keto-9-hydroxystearic acid (**248**), along with 30% of

246.[345] If the pH of the reaction medium was controlled to pH 9–9.5 (by addition of sulfuric acid to the hydroxide solution), a 45% yield of a mixture of **247** and **248** was produced along with 20% of **246**.

The ability to generate the cis- diol stereoselectively is important in synthesis, where the ability to position functional groups with complete control is essential. One example is the oxidation of 1,2,3,4,4a,10a (*trans*-4a,10a)-hexahydrophenanthrene (**249**) to octahydrophenanthrenediol (**250**) in 66% isolated yield.[346] The selectivity observed in this reaction clearly indicates the bottom face of **249** to be hindered. The source of the steric hindrance is the interaction of the axial hydrogens in the adjacent ring with the incoming reagent.



249 **250**

Potassium permanganate oxidation in the presence of phase transfer catalysts permits non-aqueous solvents such as dichloromethane to be used, and this generally leads to an increase in yield of the oxidation products.[347] A solution of dichloromethane and aqueous sodium hydroxide (+ alkene) uses a phase transfer agent such benzyltriethylammonium chloride to solubilize the reactants.[348] When potassium permanganate was added to this mixture, oxidation of *cis*-cyclooctene to *cis*-1,2-cyclooctanediol was observed in significantly higher yields than could be obtained under standard permanganate oxidation conditions.[349]

3.5.B. Dihydroxylation with Osmium Tetroxide

In Table 3.1, osmium tetroxide (OsO_4) had a relatively high reduction potential (0.85 V) in acidic media, with OsO_4 being reduced to osmium metal.

$$OsO_4 + 8\,H^+ + 8\,e^- \rightarrow Os + 4\,H_2O \qquad 0.85\ V$$

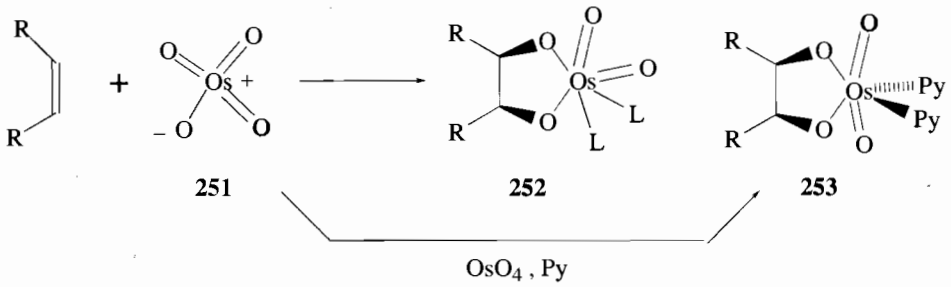
For applications to organic chemistry, osmium tetroxide is most often used in neutral, aqueous media and the primary use is for the conversion of alkenes to 1,2-diols.

3.5.B.i. Dihydroxylation of Alkenes. Criegee found that osmium tetroxide (**251**) is reduced by alkenes to give the cis-diol, via an intermediate osmium complex that must be decomposed.[350]

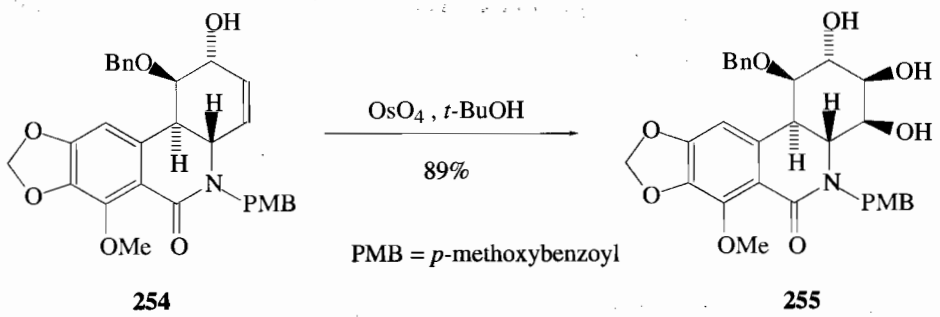
> *Osmium tetroxide vapors are poisonous and result in damage to the respiratory tract and temporary damage to the eyes.*[351] *Use OsO_4 powder only in a well-ventilated hood with extreme caution.*

In the absence of tertiary amines, osmium tetroxide reacts with alkenes via 1,3-dipolar addition to generate a monomeric Os(VI) ester such as **252**,[352] where L is a **ligand** that can be a solvent molecule or an added substrate such as pyridine. Sharpless et al. proposed that hydroxylation proceeds by an allowed [2+2]- cycloaddition reaction, producing an Os(VII) intermediate, followed by reductive insertion of the Os—C bond into an Os=O bond.[353] This complex can be decomposed in aqueous or alcoholic solution, but the hydrolysis is

reversible. The presence of a reducing agent is usually required to drive the reaction to the cis-diol by reducing Os(VI) to osmium metal, preventing reformation of the ester.[351] When the reaction is done in the presence of a base such a pyridine, an ester complex such as **253** is formed by coordination with 2 equivalents of the ligand (pyridine) and it can sometimes be isolated.[352] In most osmylation reactions of alkenes, the osmium ester is not isolated but decomposed with a reducing agent, producing the cis-1,2-diol. A variety of reagents can be used to decompose the osmium ester, including bisulfite ion in pyridine,[354] sulfite, or bisulfite in aqueous ethanol,[355,356,350] mannitol in alkaline solution,[349] or potassium chlorate ($KClO_3$) under acidic conditions.[349]

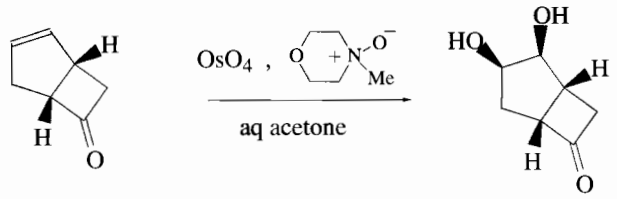


The relatively bulky osmium complex is sterically demanding and osmylation generally involves reaction at the less hindered face of an alkene. Osmylation of **254** to **255** by Rigby, in a synthesis of (+)-pancratistatin, shows the cis-delivery of the reagent and the selectivity for delivery from the less hindered face.[357] In this case, the osmium complex formed on the top of the molecule despite the free hydroxyl group on the bottom face. A conformational drawing of **254** will show that the alkene unit and the lactam unit effectively flatten the two rings, and the top face is more accessible.



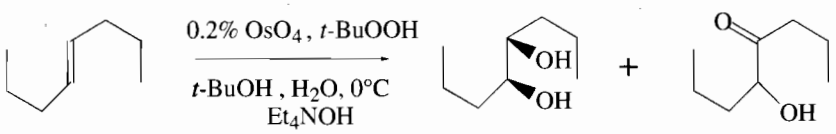
Alkenes bearing electron-withdrawing groups react more slowly with osmium tetroxide.[343,358] Although this is one of the most effective methods for syn-diol formation from alkenes, when stoichiometric amounts are required the toxicity and expense of OsO_4 have limited its applicability to small scale reactions and/or reactions with precious compounds.[359] For this reason, procedures have been developed where osmium tetroxide can be used catalytically.[360] Metal chlorates, hydrogen peroxide, *t*-BuOOH, and amine *N*-oxides are effective catalysts in this reaction. One of the more effective catalysts was developed by Van Rheenan et al. at Upjohn,[361] who used a tertiary amine N-oxide such as NMO as both a catalyst for the reaction and an agent to decompose the osmylate ester. Osmylations with NMO can be accomplished with about 1 mol % of OsO_4 at

ambient temperatures. This procedure is superior to other syn-hydroxylation procedures since only small amounts of osmium tetroxide are used.[362] Relatively unsubstituted alkenes react quickly but the oxidation failed with several highly substituted alkenes.[363] It is noted that a trisubstituted alkene was successfully oxidized using this reagent.[364] The reaction is usually run in aqueous acetone, THF, or *tert*-butanol as a one or two-phase reaction. The use of trimethylamine *N*-oxide often gives better results than NMO in reactions with hindered alkenes.[365] The NMO variation was used by Willis in a synthesis of pseudomonic acids in which **256** was oxidized to **257**.[366] Note the delivery of the two hydroxyl units from the exo-face of **256**.



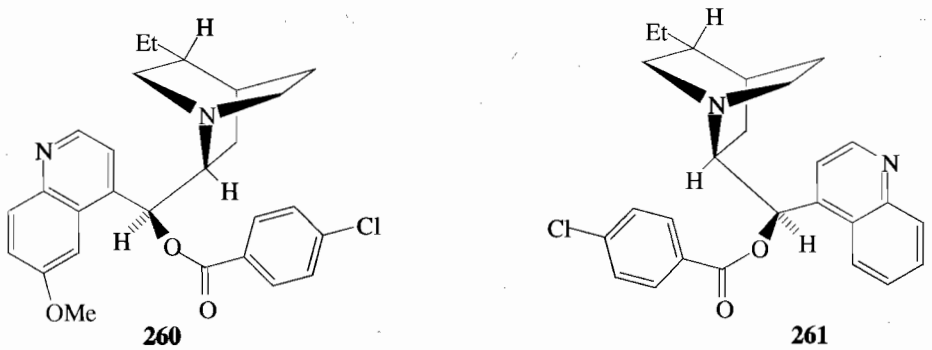
256 **257**

As with permanganate oxidations, α-hydroxy ketones can be formed as side products. In some cases, structural features make the osmium complex relatively unstable, and in an aqueous medium it can react with water to give a hydroxy–hydrate, which is then converted to an α-keto alcohol. Sharpless et al. developed a procedure that used *tert*-butyl hydroperoxide with a catalytic amount of osmium tetroxide,[367] in the presence of tetraethylammonium hydroxide (Et_4N^+ OH^-). The procedure gave improved yields of the cis-diol and a little α-hydroxyketone, as shown in the conversion of oct-(4*E*)-ene to a mixture of **258** and **259** in 73% yield. This method is more reliable for oxidation of tri- and tetrasubstituted alkenes than the Upjohn procedure. The reaction was not suitable for base sensitive alkenes, but later work showed that changing the solvent to acetone allowed the use of tetraethylammonium acetate (Et_4NOAc)[368] for the hydroxylation of sensitive alkenes such as ethyl crotonate.



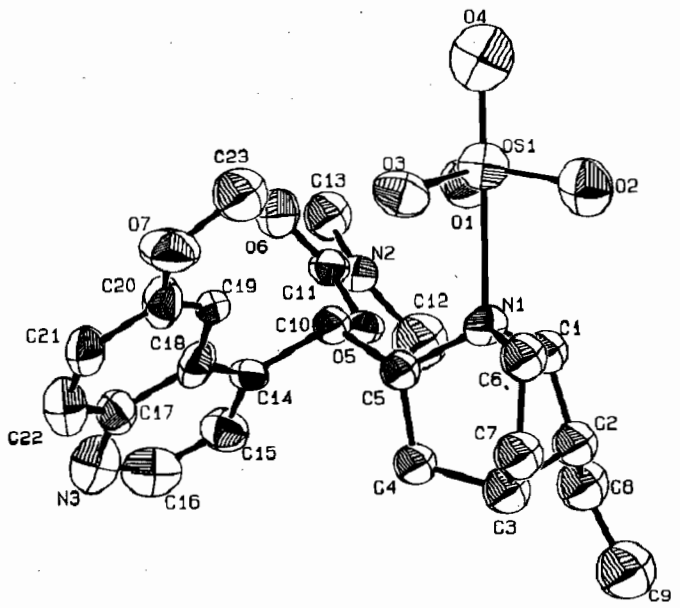
258 **259**

3.5.B.ii. Sharpless Asymmetric Dihydroxylation. Although osmylation is an attractive method for the conversion of alkenes to 1,2-diols, the reaction generates racemic products. Sharpless attempted to solve this problem by adding a chiral substrate to the osmylation reagents, with the goal of generating a chiral osmate intermediate. The most effect chiral additives were found to be the Cinchona alkaloids, especially esters of dihydroquinidines such as **260** and **261**.[369] The % ee of the diol product is good-to-excellent with a wide range of alkenes in what is called the **Sharpless asymmetric dihydroxylation**. The chiral alkaloid forms a complex with the osmium and the alkene, directing attack from the *opposite* enantioface of the alkene.[369] The cis-addition imposed by the cyclic osmium intermediate is very important in reactions of acyclic alkenes, because the two hydroxyl moieties in the product will be syn- to each other, making the reaction highly



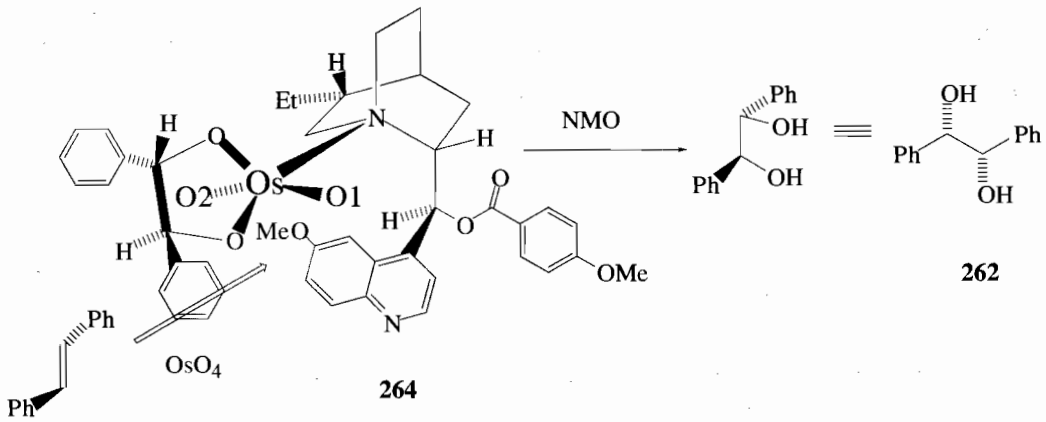
diastereoselective. This selectivity is also dependent on the geometry of the alkene precursor, and high diastereoselectivity is obtained only with regiochemically pure alkenes. This selectivity is illustrated by the reaction of trans-stilbene with OsO_4 and NMO, which gave the diol **262** with 99% ee in the presence of **260**. In general, the % ee in the asymmetric hydroxylation procedure are lower than those observed in the asymmetric epoxidation reaction (sec. 3.4.D).

The source of enantioselectivity can be discerned from the structure of the osmium complex.[370] An X-ray crystal structure of the OsO_4 complex of (dimethylcarbamoyl) dihydroquinidine (**263**) has been published.[371] Using **263** as a guide, the osmium complex of stilbene can be represented as **264** (the *p*-methoxy ester was used in this case), which may not be the active complex but it illustrates how selectivity arises in the reaction.



[Reprinted with permission from Svendsen, J.S.; Markó, I.; Jacobsen, E.N.; Pulla Rao, Ch.; Bott, S.; Sharpless, K.B. *J. Org. Chem.*, ***1989***, *54*, 2263. Copyright © 1989 American Chemical Society.]

Stilbene coordinates with osmium in a manner that minimizes any interaction of the phenyl groups with the azabicyclo[2.2.2]octane moiety and/or with the methylquinoline ring. As seen in **264**, O1 appears to be significantly more hindered than O2. The phenyl rings of the stilbene molecule are oriented so that those rings are



away from O2 and the azabicyclooctane ring. If stilbene binds in this way, the threo (syn) isomer (**262**) will be the major diol product. The chirality of the Cinchona alkaloid is important since it provides facial selectivity for complexation of the alkene as well as orientational control via the steric interactions described above. Figure 3.3[318] provides a graphic similar to Figure 3.2 (which showed a model for Sharpless asymmetric epoxidation) that illustrates the facial selectivity of Sharpless asymmetric dihydroxylation. If the alkene

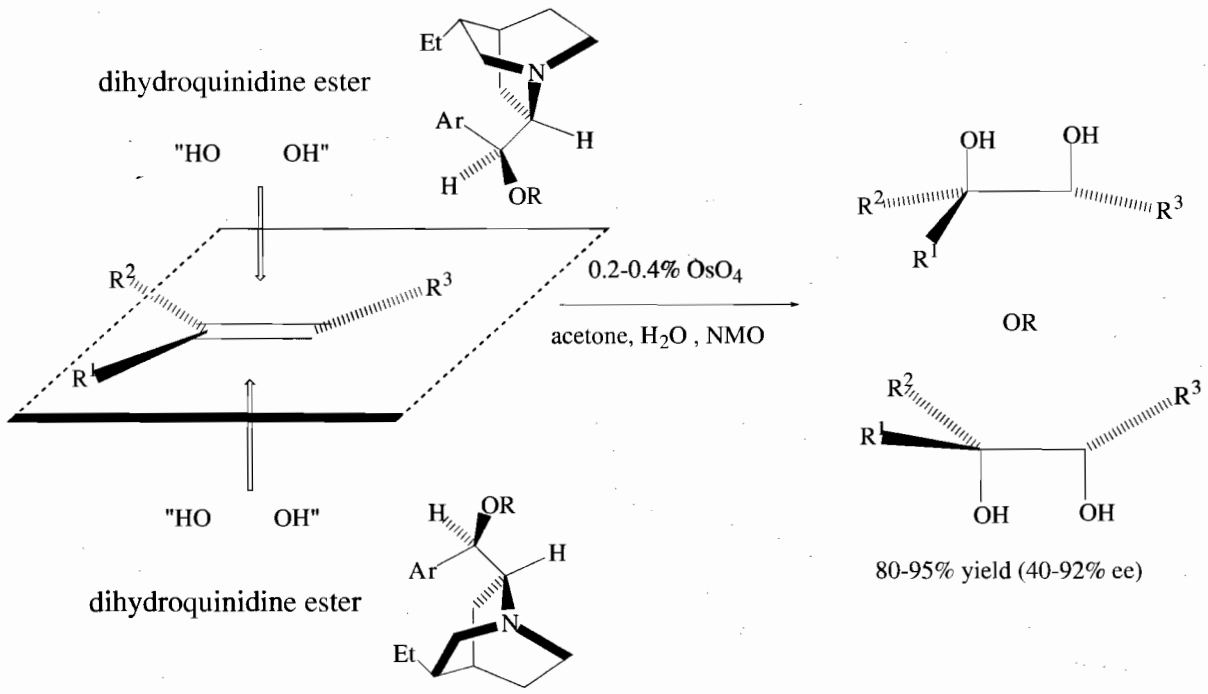


Figure 3.3. Facial selectivity in the Sharpless asymmetric dihydroxylation.

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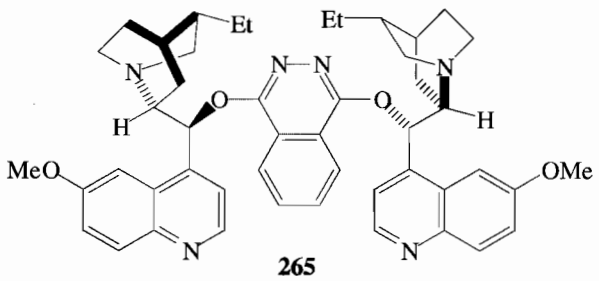
is oriented as shown in Figure 3.3, the natural dihydroquinidine ester forces delivery of the hydroxyls from the top face. Conversely, dihydroquinoline esters deliver hydroxyls from the bottom face. Highest % ee values (70–90%) are obtained with trans 1,2-disubstituted alkenes.[318] The lowest % ee values are obtained with cis-1,2-disubstituted alkenes.[284] Trisubstituted and monosubstituted alkenes show greater variation in asymmetric induction (30–80% ee and 25–60% ee, respectively).[318] As with Sharpless asymmetric epoxidation, asymmetric hydroxylation is an important addition to reactions that convert achiral precursors to chiral molecules.

New catalysts are available for this reaction that improve the efficiency and ease of use. Two phthalazine derivatives,[372] $(DHQD)_2PHAL$ (**265**) and $(DHQ)_2PHAL$ (**266**) have been used in conjunction with an osmium reagent that has resulted in two commercial catalysts, AD-mix-β[373] (using **265**) and AD-mix-α[373] (using **266**). The abbreviations shown here refer to the reagents used to make each catalyst. Catalyst **265** is prepared from dihydroquinidine (DHQD) and 1,4-dichlorophthalazine (PHAL). Similarly, **266** is prepared from dihydroquinine (DHQ) and PHAL. The actual oxidizing medium labeled AD-mix α or β- uses **266** or **265**,



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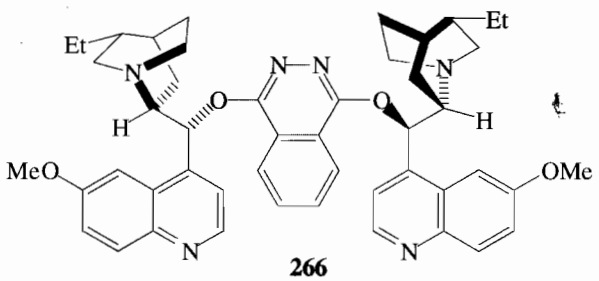


266

respectively, mixed with potassium osmate $[K_2OsO_2(OH)_4]$, powdered $K_3Fe(CN)_6$, and powdered K_2CO_3 in an aqueous solvent mixture.[372] These mixes have become standard catalysts for dihydroxylation. Sharpless introduced a model, shown in Figure 3.4,[372] to predict the enantioselectivity of each catalyst. With the R_L, R_M, and R_S substituents of the alkene arranged as shown, the AD-mix-β catalyst gives dihydroxylation from the top, whereas the AD-mix-α catalyst gives dihydroxylation from the bottom, as shown.

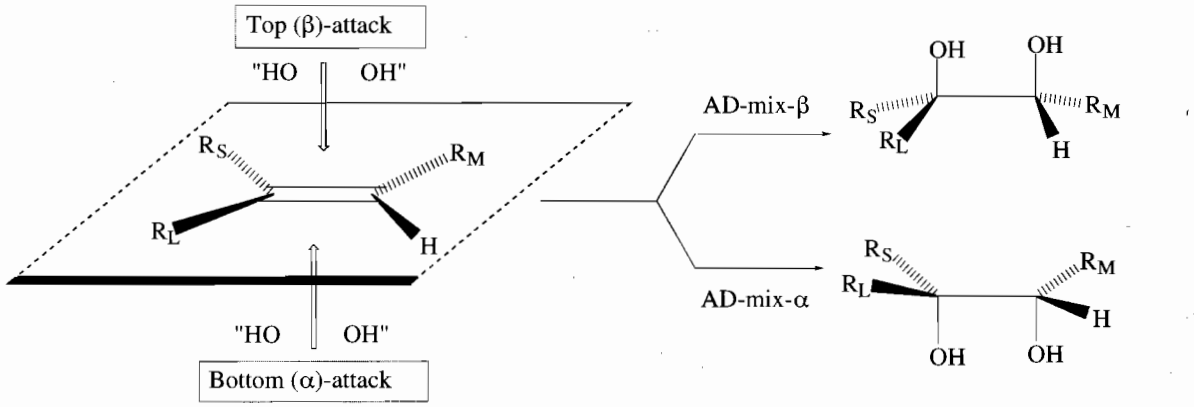
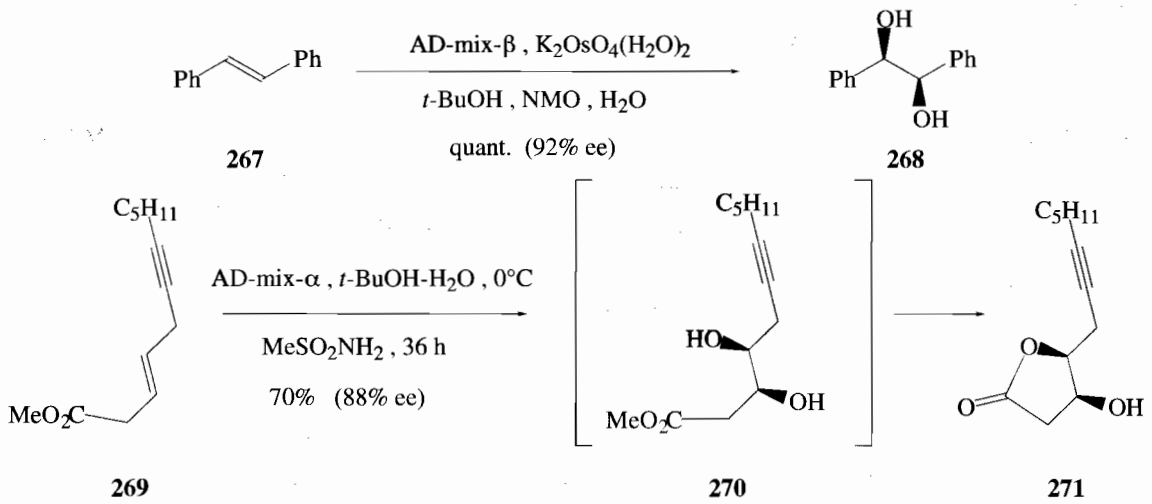


Figure 3.4. Facial selectivity in asymmetric dihydroxylation using AD-mix-α and AD-mix-β.

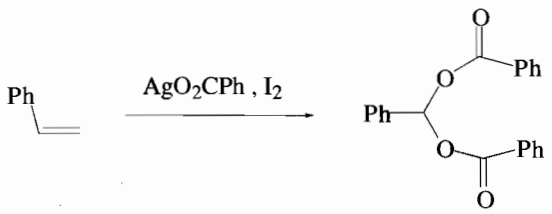
[Reprinted with permission from Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.*, ***1992***, *57*, 2768. Copyright © 1992 American Chemical Society.]

In a simple synthetic example, Jung used AD-mix-β[373] to convert **267** to **268** in quantitative yield and 93% ee, as part of study using dialkyl aminals in asymmetric induction.[374] Similarly, Corey used AD-mix-α[373] with **269** as part of synthesis of eicosanoid (11*R*,12*S*)-oxidoarachidonic acid,[375] but the initial diol (**270**) was not isolated. Internal transesterification led to the hydroxy-lactone **271** in 70% yield and 88% ee. After crystallization, **271** was obtained in 86% yield and 94% ee after crystallization. A comparison of **268** and **271** shows that the different catalysts have produced diols with the opposite absolute configuration.



3.5.C. The Prévost Reaction

An alternative route to 1,2-diols reacts alkenes with a mixture of silver carboxylate and iodine rather than with peroxides. Prévost found that silver benzoate and iodide converted styrene to 1,2-dibenzoate **272**, which could be saponified to the 1,2-diol.[376a,358] The transformation is called the **Prévost reaction**.[376] This



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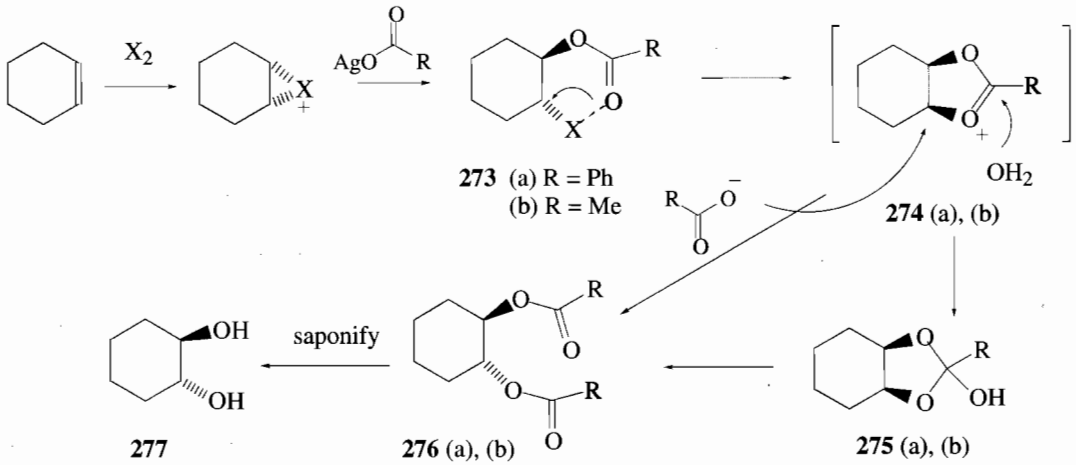
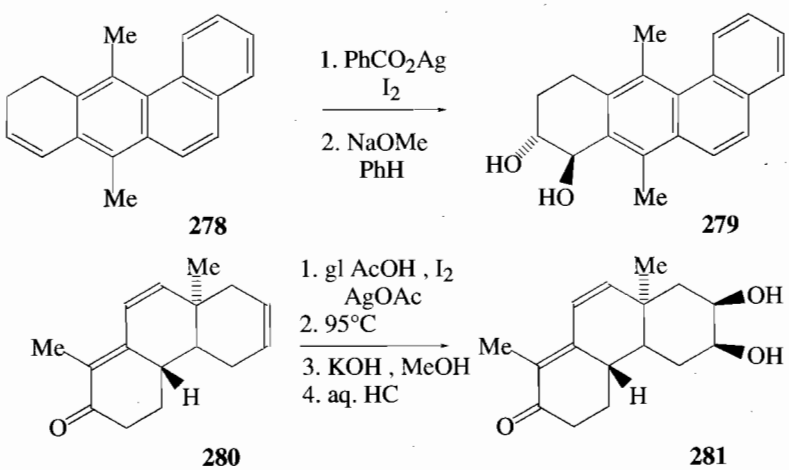
reaction is related to the **Hunsdiecker reaction**[376b] (described in sec. 2.8.A). Birkenbach et al. reported a similar reaction of alkenes and silver carboxylates in which cyclohexene was treated with silver acetate and iodide to give 2-iodocyclohexanol.[377] Brunel had earlier reported a related reaction using iodine and mercuric acetate.[378] In the Prévost reaction, water is not involved in the transformation, which can be illustrated using cyclohexene. Initial formation of an iodonium salt from reaction of cyclohexene and iodine is followed by reaction with silver benzoate to give **273a**.[376] Attack by a second molecule of benzoate gives the trans diacetate, **276a**, presumably via a cyclic species such as **274a**, which is opened by benzoate to give the trans diester. Saponification generates the trans-diol (**277**). The Prévost reaction therefore generates trans

diols, in contrast to permanganate and osmium hydroxylation reactions, which give cis diols. Alternatively, water can attack **274** to give **275**, which is attached by the carboxylate anion to give **276**. An example is the conversion of **278** to **279** in 94% yield.[379]



As mentioned, the Prévost reaction proceeds via initial formation of an iodonium salt that is opened by the silver carboxylate. Winstein studied reactions of silver acetate and bromine with alkenes, and showed that initial formation of the bromonium ion was followed by formation of a bromoacetate (**273b**), which is analogous to **273a**.[380] In aqueous media, attack by the neighboring acetate generates an oxonium salt (**274b**) that reacts with water to form **275b**. Reaction with additional silver acetate gives the final product, a trans 1,2-diester (**276b**). The presence of water in the reaction apparently changed its course from an intermolecular displacement of **274** which gave the trans-product, to attack by water with ring opening, which preserved the cis stereochemistry. This is called the **Woodward modification**[381] of the Prévost reaction and gives the cis-diol rather than the trans-diol. Woodward used this modification in the conversion of **280** to the cis acetate, which was saponified to give diol **281** in 65% overall yield.[381]

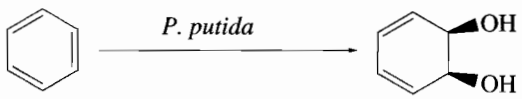


It is noted that an alternative route to trans diols is available by hydrolysis of epoxides. Reaction of cyclohexene with MCPBA gives cyclohexene oxide and hydrolysis (acid or base) gives *trans*-1,2-cyclohexanediol.

The functional group transforms for all of the hydroxylation reactions in this section are

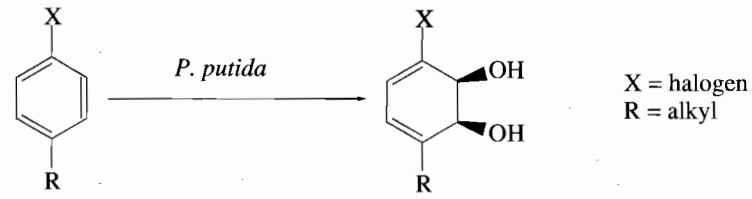
3.5.D. Dihydroxylation of Aromatic Rings

Enzymatic transformation of organic molecules is an increasingly important source of chiral, nonracemic products. Transformations in previous sections focused on π bonds of alkenes, but these techniques did not work with aromatic rings. It is now possible to convert one π-bond of an aromatic ring (benzene, for example) into racemic or chiral, nonracemic cyclohexadiene 1,2-diols using the organism *Pseudomonas putida*.[382,383] Early work by Gibson et al. established that racemic **282** could be formed in good to moderate yield by reaction of benzene with this organism[384] based on earlier work by Marr and Stone[385] and by Walker and Wiltshire.[386] In even earlier work, Ballard et al. had postulated **282** as an intermediate in the oxygen assisted oxidation of benzene derivatives in the presence of *P. putida*.[387]



282

Gibson showed that this transformation is not limited to benzene. The reaction can be generalized to give products such as **283**. In specific cases, chlorobenzene gave **284**,[388] bromobenzene gave **285**, 4-chlorotoluene gave **286**,[389] and toluene gave **287**,[389] for example, all with excellent asymmetric induction since the aromatic ring contains a substituent and introduction of the hydroxyl groups generates a chiral molecule. In



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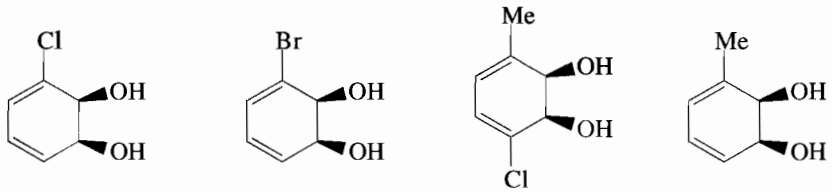
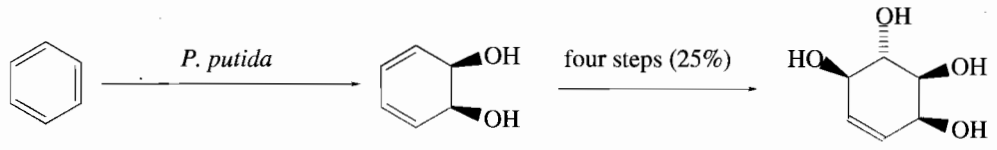


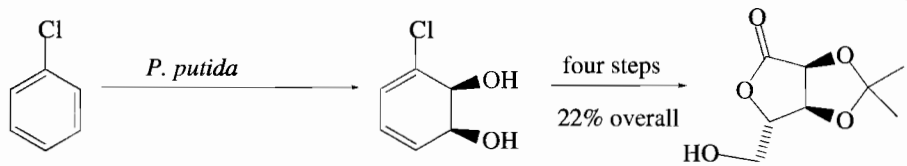
284 **285** **286** **287**

one sense, this oxidation belongs in section 2.11, which described various transformations of benzene derivatives. Since this reaction formally involves the conversion of a π bond in a benzene ring to a cis diol, it is placed in this section for the sake of continuity.



282 **288**

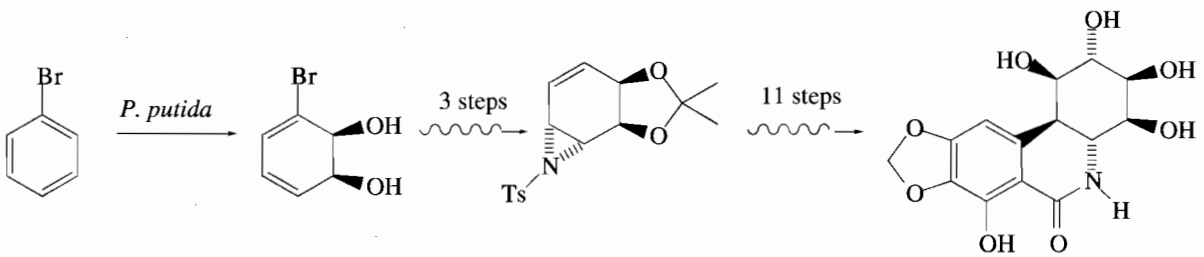
Recently, this transformation has been used in a variety of interesting syntheses, particularly by Ley and Hudlicky. Ley showed that **282** could be converted to conduritol F (**288**) in four steps (25% overall yield).[390] Carless and Hensley also prepared conduritol A and D using similar methodology.[391] In other work, Ley et al. converted **284** to myoinositol-1,4,5-triphosphate (IP_3)[392] and **282** to pinitol, an antidiabetic agent.[393] Hudlicky et al. prepared (+)-pinitol in an enantiodivergent synthesis that used the chiral derivative **285** as a starting material.[394] This latter example illustrates the true power of this method, since chiral nonracemic synthetic targets can be produced from readily available starting materials.



284 **289**

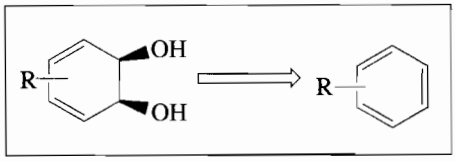
A wide range of chiral nonracemic targets can be prepared using aromatic rings as precursors to diols. Hudlicky prepared **284** in >99.9% ee,[395] and used this diol to synthesize 2,3-isopropylidene (*L*)-ribose γ-lactone (**289**) in four steps (18% overall yield).[395,396] Once the diol is available, it can be transformed in many interesting ways. Diol **285** was used as the diene partner (sec. 11.4) in a Diels–Alder reaction for the synthesis of amino cyclitols.[397] After oxidation of styrene with *P. putida*, the resulting diol led to the synthesis of zeylena via a Diels–Alder reaction.[398] The methyl derivative (**286**) was used for the preparation of terpene and prostanoid synthons.[399] Johnson used **284** as a precursor for the synthesis of prostaglandin PGE_2, resolving the starting material to provide the asymmetric precursor required for the synthesis.[400]

The synthesis of nitrogen-containing natural products is also possible via diols such as these. Hudlicky and co-workers prepared the bicyclic alkaloid (+)-kifunensine, for example, from **284**.[401] More complex molecules can also be prepared, as illustrated by the conversion of **285** into (+)-pancratistatin (**291**),[402] via synthetic intermediate **290**. Banwell et al. reported an asymmetric synthesis of (–)-patchoulenone from **287** using this basic approach.[403]



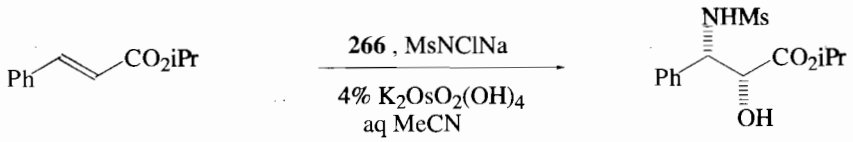
285 **290** **291**

The use of **284–287** as well as other diol derivatives derived from functionalized aromatic compounds is clearly an important method for the preparation of molecules that can be used in asymmetric synthesis. This process provides an important source of diol starting materials that can be manipulated to form a variety of important natural products. This interesting oxidation leads to the functional group transform:



3.5.E. Aminohydroxylation

This section has focused on dihydroxylation of alkenes, and section 3.5.B.ii discussed asymmetric dihydroxylation. A relatively new modification of this process allows the synthesis of amino alcohols.[404] Sharpless introduced what is now called the **Sharpless asymmetric aminohydroxylation reaction**.[405] When cinnamate **292** was treated with nitrogen reagents in the presence of $(DHQ)_2PHAL$ (**266**) using what is effectively the AD-mix-α, chiral, nonracemic amino alcohols were formed. The nitrogen sources include TsNClNa,[405] MsNClNa,[406] CbzNClNa,[407] and BocBNClNa.[408] In a typical example, cinnamate **292** was treated with **266**, 4% $K_2OsO_2(OH)_4$ and MsNClNa, in aqueous acetonitrile, and a 65% yield of **293** was obtained, in 94% ee.[404]



292 **293**

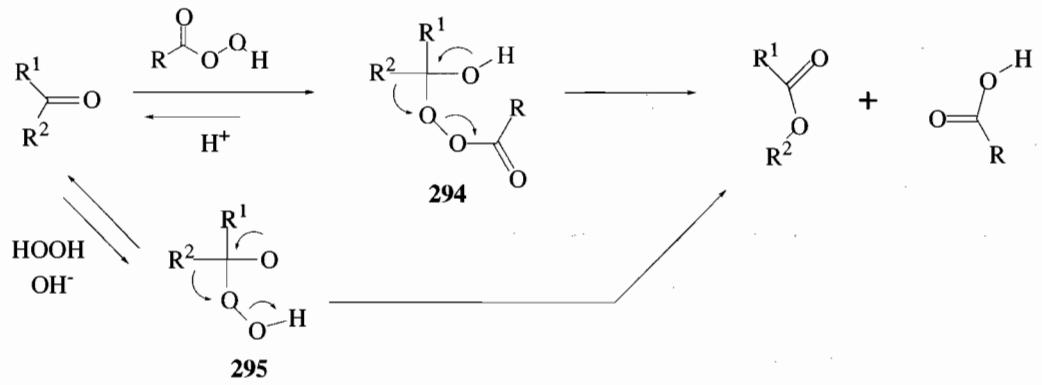
3.6. BAEYER–VILLIGER OXIDATION ($RCOR' \rightarrow RCO_2R'$)

3.6.A. Peroxide Induced Baeyer–Villiger Oxidation

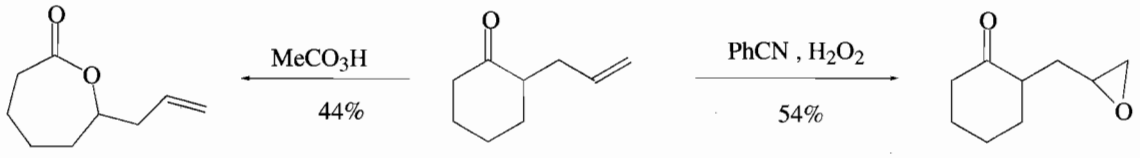
We have just seen that the π bond of an alkene reacts with peroxides. The π bond of a carbonyl group can also react with peroxides, but the reaction is accompanied by a rearrangement. Ketones react with peroxyacids or hydrogen peroxide to give esters via a C → O rearrangement known as the **Baeyer–Villiger reaction**.[409] Both acid and base catalyzed mechanisms have been proposed. The acid catalysis mechanism[410] for reaction with a peroxyacid proceeds via **294**,[411] and the proposed base catalyzed reaction with hydrogen peroxide[412] proceeds via **295**.[411] A solid-state variation of this reaction has been reported in which hexagonal mesoporous silica supported peroxy acids are used to induce the Baeyer–Villiger reaction.[413]

In all cases, the R_2 group migrates to the electrophilic oxygen with concomitant loss of the acyl or hydroxyl leaving group. Since hydroxyl is a poorer leaving group than acyl, the base–catalyzed reaction is "inferior to the peroxyacid route."[414] An obvious reaction that can compete with the Baeyer–Villiger reaction is the conversion of alkenes to epoxides with peroxyacids. Ketones react with peroxyacids more slowly than do alkenes, usually requiring long reaction times, strong acid catalysts and highly reactive peroxyacids.[415] As

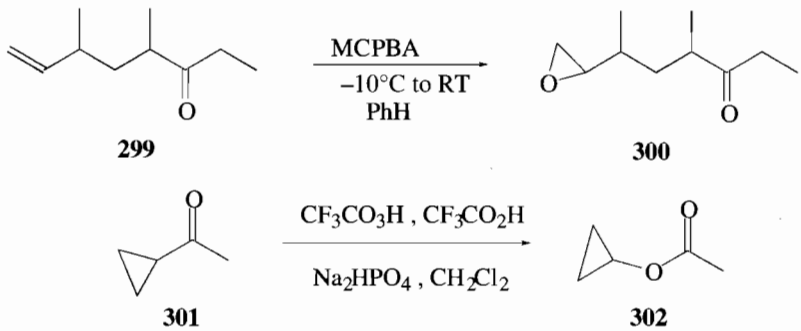
stated by Lewis, however, "this rate difference is not large with isolated carbon–carbon double bonds and Baeyer–Villiger oxidation can be competitive with epoxidation."[416] Lewis illustrated this by oxidation of **296**



with peroxyacetic acid to form lactone **297** in 44% yield and observed no epoxide products. Changing to hydrogen peroxide (benzonitrile was the solvent) led to epoxide **298** in 54% yield rather than the lactone. When an alkene and a carbonyl are present in the same molecule, the presence of an acid catalyst leads to preferential attack at the carbonyl. Selective epoxidation is best accomplished in a reaction medium that does

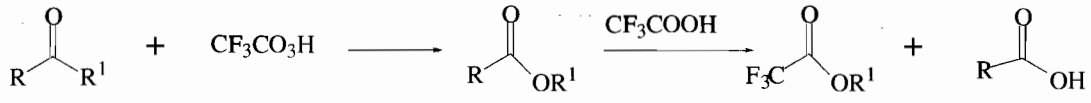


not contain acid, and MCPBA (in an inert solvent at low temperature) usually gives selective epoxidation.[354] This selectivity was exploited by Silverstein and co-workers for the conversion of **299** to **300** in a synthesis of α-multistriatin.[417] Conjugated ketones react with MCPBA to give mixtures of products, and steric hindrance is a significant factor. Oxidation of 3-hydroxycholesten-4-en-6-ones, for example, gave mixtures of an epoxide and a lactone whose proportions varied with the stereochemistry of the hydroxy group (α or β).[418] Glotter and co-workers concluded that for this system, the Baeyer–Villiger reaction was faster than epoxidation.[418]



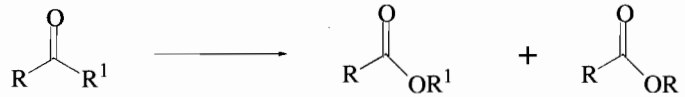
Although most peroxyacids can be used in the Baeyer–Villiger reaction, trifluoroperoxyacetic acid is one of the more efficient reagents for this rearrangement.[419] House gave an example in which **301** was selectively

converted to the acetate ester (**302**).[420,419] The reaction conditions and the specific product formed raise several interesting points about this transformation. First of all, the reaction is buffered with disodium phosphate (Na_2HPO_4). As shown previously, the byproduct of the reaction is the carboxylic acid precursor of the peroxyacid (sec. 3.4.C). With relatively weak acids such as acetic acid (from peroxyacetic acid), acid-catalyzed side reactions are less important. The powerful acid trifluoroacetic acid (from trifluoroperoxyacetic acid) often causes problems, however. In the generalized reaction of **303**, the final product is an ester (**304**) and a carboxylic acid (CF_3COOH), and the presence of both compounds in solution raises the possibility of transesterification reactions. Transesterification of **304** would give a trifluoroacetyl ester (**305**) and acid **306**.[423] Addition of a buffer to the initial reaction minimizes transesterification and other acid catalyzed reactions. Typical buffers include disodium phosphate and the salt of the original acid ($RCO_2^-Na^+$ for example). In the case of **304**, $CF_3CO_2^-M^+$ might be a suitable buffer, or even sodium acetate.



303 **304** **305** **306**

Another point learned from the transformation of **301** to **302** is that the cyclopropyl group is selectively transferred in preference to the methyl group. When unsymmetrical ketone **303** is treated with a peroxyacid,

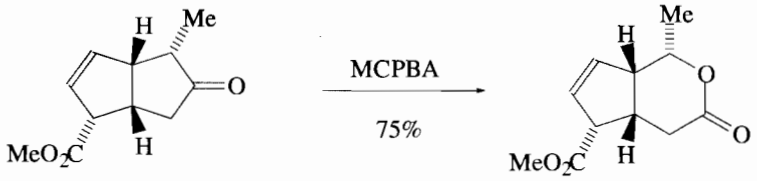


303 **304** **307**

two esters are possible (**304** and/or **307**). Different groups (R and R^1 in **303**) will show different migratory aptitudes in the Baeyer–Villiger reaction. Both Lewis[421,411] and House[422] reported the migratory aptitude of alkyl groups (R) in **303** to be

tert-alkyl	>	cyclohexyl	≈	2° alkyl	≈	benzyl	≈	phenyl >
vinylic[423,421]	>	1° alkyl	>	cyclopropyl	>	methyl		

This migratory preference is clear in Chang's oxidation of **308** to **309** in 75% yield, taken from a synthesis of sarracenin.[424] Although there may be some correlation between migratory ability and the ability of that

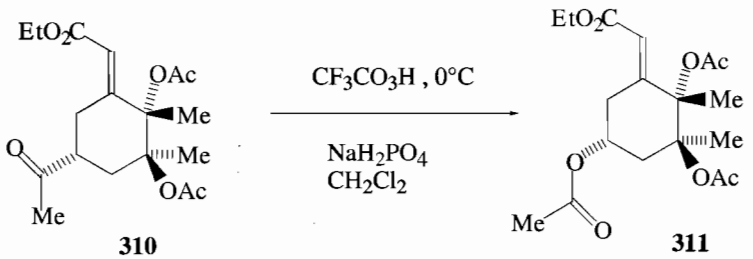


308 **309**

group to stabilize a δ^+ charge, but as stated by House "this property, arising from the electron distribution in the migratory group, cannot be the only factor determining migratory aptitude".[425] Electron–releasing

groups on aromatic derivatives accelerate the rearrangement, and electron–withdrawing groups slow it. Aryl groups generally migrate in preference to alkyl groups.[426] Although the reaction is usually selective, other products are formed and they can sometimes be difficult to separate.

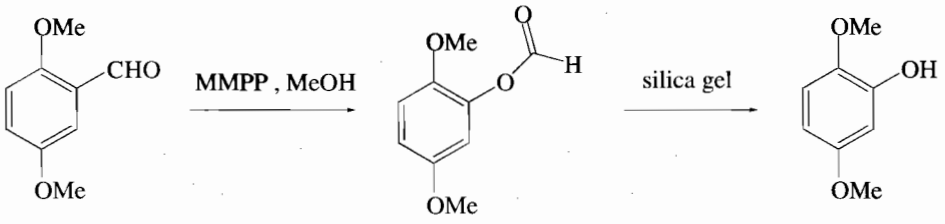
Simple dialkyl ketones are not easily oxidized by less reactive peroxyacids and usually require the more powerful trifluoroperoxyacetic acid.[427] Since most groups migrate in preference to methyl, "the Baeyer–Villiger reaction of methyl ketones serves as a stereospecific source of optically active alcohols by way of the acetate",[428] as seen in the conversion of **310** to **311** in 85% yield.[429] This example also illustrates that the stereochemical integrity of the migratory group is retained, which appears to be a general phenomenon.[430]



310 **311**

Saponification of the ester product from the Baeyer–Villiger reaction is easily accomplished, leading to the alcohol and the interesting functional group transform (C—C=O → C—OH) for acyclic ketones. Cyclic ketones (such as **296** and **308**) are more reactive than their acyclic counterparts and oxidation with a variety of peroxyacids leads to good yield of the corresponding lactone, as in the conversion of cyclopentanone to δ-valerolactone in 81% yield[431] (also see **308** → **309**). Hydrolysis of the lactone leads to an ω-hydroxy acid but the facility of the ring opening depends on the size of the lactone ring. Aqueous hydrolysis is an equilibrium process that favors the closed ring in five-membered ring systems, but favors the open chain compound with seven-membered and higher lactones. In these cases, the peroxyacid reaction should be buffered to prevent unwanted acid-catalyzed ring opening.[432] Six-membered ring lactones are intermediate in stability between those just cited and hydrolysis will usually give a mixture of the lactone and the open-chain acid. The migratory aptitude of the alkyl moieties in mono- and disubstituted cyclic ketones is the same as that observed with acyclic ketones.

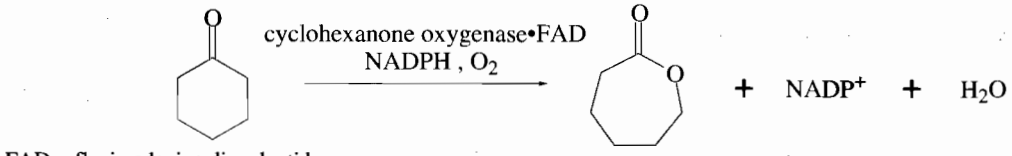
Other carbonyl derivatives react with peroxyacids. 1,2-Diketones, *o*-quinones, and α-keto-esters react with cleavage of the bond between the two carbonyls.[433,426] Similarly, 1,3-dicarbonyl compounds react with peroxyacids to give 2-hydroxy-1,3-dicarbonyls (enediols)[434] but 2,2-disubstituted-1,3-dicarbonyl compounds are resistant to such oxidations.[435] Ethyl acetoacetate is an example of the first type, and it gives a glycidic ester upon treatment with a peroxyacid.[434,435] Aldehydes are easily oxidized, and reaction with peroxyacids or hydrogen peroxide usually gives a carboxylic acid (the transformation is RCHO → RCO_2H) with little or no rearrangement. Exceptions are electron-rich aldehydes such as functionalized benzaldehyde derivatives. In these cases, formation of the formate ester is facile and is called the **Dakin reaction**.[436] A synthetic example is taken from de Koning's synthesis of γ-rubromycins,[437] in which aldehyde **312** was treated with MMPP and the Baeyer–Villiger reaction gave formate ester **313**. Hydrolysis was accomplished on moist silica gel to give a 94% yield of phenol **314** after both steps.



312 **313** **314**

3.6.B. Enzymatic Baeyer–Villiger Oxidation

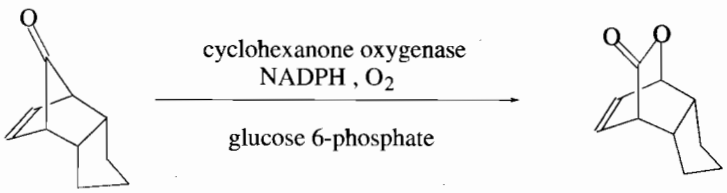
Enzymatic conversion of ketones to esters is very common in microbial degradations.[438] A synthetically important as well as typical transformation is the enzymatic Baeyer-Villiger oxidation, reported by Walsh,



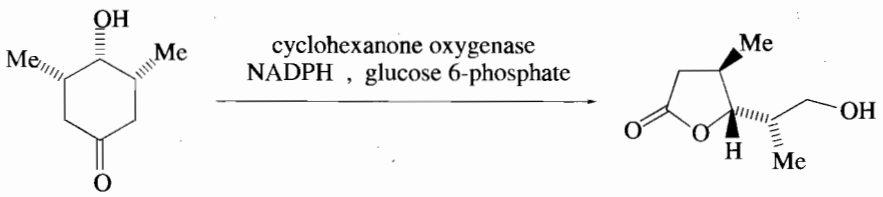
FAD = flavin adenine dinucleotide
NADPH = reduced nicotinamide adenine dinucleotide phosphate

315

which gives lactone **315** from cyclohexanone,[439] using a purified cyclohexanone oxygenase enzyme.[440] Walsh studied the mechanism of this reaction, and also showed that this enzyme converted phenylacetaldehyde to phenylacetic acid (65% yield) accompanied by only a 12% yield of benzyl formate ($PhCH_2OCHO$).[441] The rearrangement induced by this enzyme proceeds with completely stereochemical retention, as shown by Schwab,[442] analogous to the Baeyer–Villiger rearrangement that used *m*-chloroperoxybenzoic acid. There are only a few examples where this reaction has been used in synthesis, but this is an interesting addition to the well-known Baeyer–Villiger rearrangement.



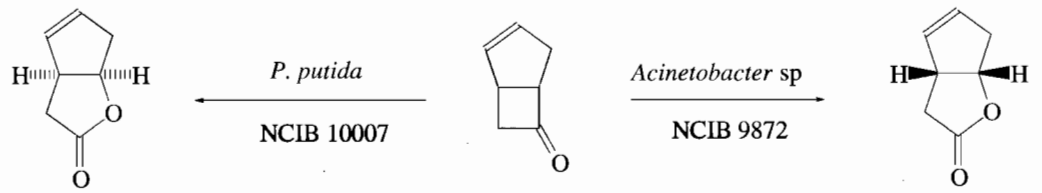
316 **317**



318 **319**

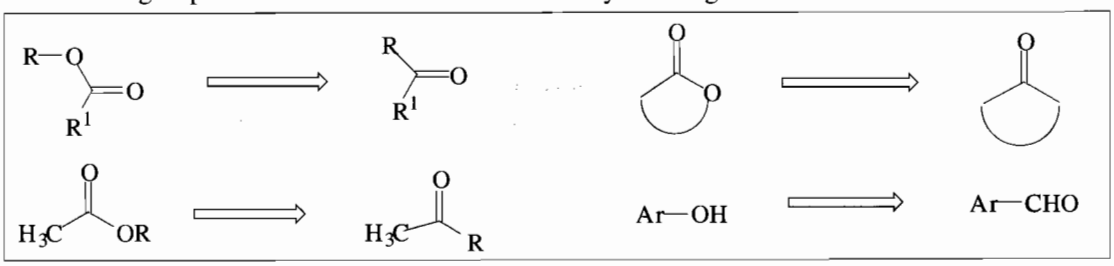
Taschner showed that cyclohexanone oxygenase, obtained from *Acinetobacter* NCIB 9871,[442b] converted 4-methylcyclohexanone to the corresponding γ-methyl caprolactone in 80% yield with >98% ee.[443a] In

another example, lactone **317** was prepared from bicyclic ketone **316** in 80% yield and 97% ee.[442b] It is clear that the formation of chiral, nonracemic lactones via the enzymatic Baeyer–Villiger reaction will be of great value in synthesis as an extension of the better known peroxide induced Baeyer–Villiger.[442c] The enzymatic reaction appears to proceed in a predictable manner using the peroxide induced reaction as a model, although the enantioselectivity of the final product is influenced by the concentration of the substrate.[444] Taschner et al. found that **318** was converted to **319** in 80% yield, and in >98% ee.[443] This rearrangement is easily related to similar rearrangements using MCPBA.[445] Other enzymatic systems have been found that give a Baeyer–Villiger reaction. An enzymatic Baeyer–Villiger reaction using myristic acid and hydrogen peroxide was catalyzed by *Candida anatarctica* lipase.[446] The absolute stereochemistry of the lactone product can sometimes be con-trolled by changing the enzymatic system. Oxidation of **320** with *Acinetobacter sp.* NCIB 9872 gave lactone **322**.[447] Oxidation with *P. putida* NCIB 10007, however, gave lactone **321**.[448] This type of stereochemical control expands the utility of the asymmetric Bayer–Villiger reaction.



321 **320** **322**

The functional group transforms available from the Baeyer–Villiger reaction are

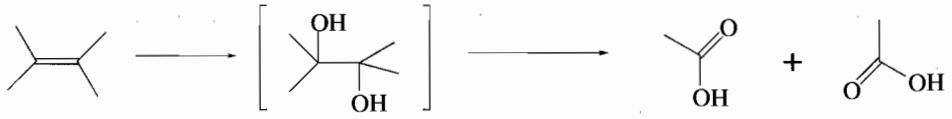


3.7. OXIDATIVE BOND CLEAVAGE (C=C → C=O + O=C)

3.7.A. Cleavage of Alkenes by Transition Metals

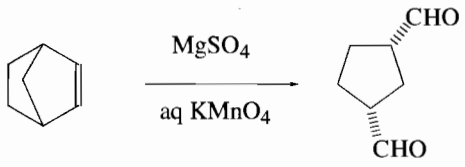
Alkenes can be oxidized to both epoxides and 1,2-diols by various reagents.[449] These transformations represent one-stage (two-electron) oxidations relative to the alkene. If more powerful oxidizing agents are used, however, the C=C moiety can be cleaved into two carbonyl derivatives. This section will discuss the various reagents that effect this transformation.

3.7.A.i. Potassium Permanganate. In Section 3.5.A, treatment of alkenes with dilute solutions of potassium permanganate was shown to give a one-stage oxidation to 1,2-diols in excellent yield. More concentrated solutions and more vigorous conditions, usually in acidic media, leads to cleavage of the alkene to a diacid via oxidation of the intermediate diol (**323**).[450] Typical oxidative cleavage conditions are hot and concentrated



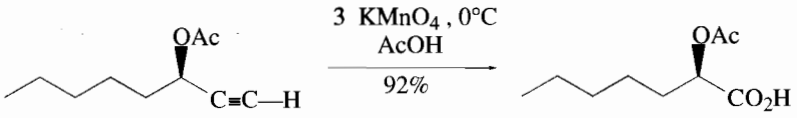
323

but these ambiguous terms can mean concentrations that range from a >10% solution of permanganate to 10 M solutions and temperatures that range from ambient to > 100°C. An important modification that increases the synthetic utility of the reaction mixes periodic acid (HIO_4)[451] with a catalytic amount of permanganate (called the **Lemieux–von Rudloff reagent**).[452] The stoichiometric oxidant HIO_4 oxidizes the manganate product back to permanganate, allowing oxidative cleavage of alkenes under catalytic conditions. A solution of potassium permanganate in benzene with the well–known potassium complexing agent dicyclohexyl-18-crown-6 is very effective for cleaving alkenes to acid products,[453] as illustrated by the cleavage of cyclohexene to adipic acid.



324 **325**

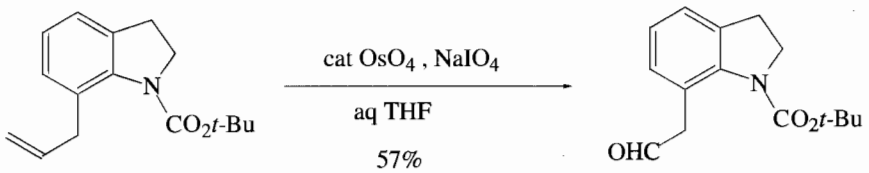
Oxidation of disubstituted alkenes leads to aldehydes, but if the alkenyl carbon has a hydrogen attached to it (i.e. C=C-H), the product is usually a carboxylic acid. Isolation of the aldehyde in this powerful oxidizing medium can be difficult, although oxidation of bicyclo[3.3.1]hept-2-ene (norbornene, **324**) with aqueous permanganate and magnesium sulfate gave dialdehyde **325** in up to 66% yield.[454] It is also possible to obtain aromatic aldehydes from aryl substituted alkenes by permanganate oxidation in aqueous media, but good yields are obtained only when the aromatic ring has ortho- or para-electron withdrawing substituents.[455,456] The presence of the conjugating groups on the alkene increases the rate of oxidation but bulky groups on the alkene greatly reduce the yield of aldehyde products. It is also possible to oxidize alkynes with permanganate. Midland showed that **326** was oxidized to 2-acetoxyheptanoic acid (**327**) in 92% yield with excess permanganate in acetic acid.[457]



326 **327**

Potassium permanganate is a very powerful reagent and can oxidize alkyl fragments (sec. 3.8) as well as alkenes. Straight-chain alkyl groups attached to aromatic rings are oxidized with concentrated permanganate to give benzoic acid derivatives, as in the oxidation of 2-chlorotoluene to 2-chlorobenzoic acid.[458] Similarly, 2-methylpyridine was oxidized to pyridine 2-carboxylic acid.[459]

3.7.A.ii. Osmium Reagents. When alkenes are oxidized with a mixture of OsO_4 and $NaIO_4$ (the **Lemieux-Johnson reagent**),[460] oxidative cleavage leads to aldehydes and ketone products. This technique requires only 1–5 mol% of osmium tetroxide, which is important given the expense and toxicity of osmium compounds. Lai and Anderson used this reagent to cleave the alkene moiety in **328** to the aldehyde moiety in **329** as part of the synthesis of indole analogs of mycophenolic acid.[461] *N*-Methylmorpholine *N*-oxide is sometimes added to the reaction. Paquette et al. used this variation in a synthesis of (–)-polycavernoside A.[462]

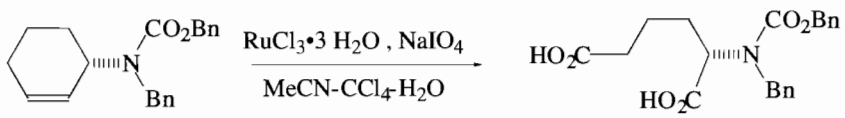


328 **329**

3.7.A.iii. Ruthenium Reagents. Ruthenium compounds are powerful oxidizing agents that are capable of cleaving alkenes. In Table 3.1, ruthenium tetroxide (RuO_4) showed a reduction potential of 0.59 V in the following reaction:

$$RuO_4 + e^- \rightarrow RuO_4^{2-} \qquad 0.59\ V$$

Ruthenium tetroxide cleaves alkenes to give ketones, aldehydes, or carboxylic acids.[463] Halogenated solvents such as dichloromethane are commonly used, since ether, benzene, and pyridine *react violently* with ruthenium tetroxide.[464] The yield of cleavage products is variable and sometimes low (cyclohexene, for example, gave adipaldehyde in only 10% yield).[465,463] Yields of the oxidative cleavage products were greatly improved by addition of sodium periodate ($NaIO_4$) to the reaction.[466] A disadvantage of the $RuO_4/NaIO_4$ reagent is that alkenyl carbons bearing a hydrogen atom are usually oxidized to the acid rather than the aldehyde.[467] Other ruthenium salts also give excellent yields of cleavage products, particularly when mixed with sodium periodate.



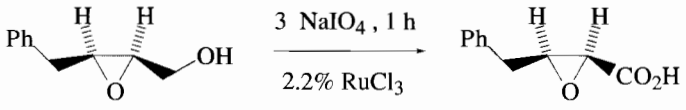
87%

330 **331**

In its initial formulation, Sharpless used RuO_2 and $NaIO_4$ for the oxidation, but he also showed that ruthenium trichloride ($RuCl_3$) and sodium periodate give selective oxidative cleavage to the acid in good yield.[468] It is relatively easy to oxidize tetrasubstituted alkenes, as in Mehta's synthesis of precapnelladiene using a mixture of RuO_2 and $NaIO_4$ to oxidize a bicyclic alkene to a cyclooctadione derivative.[469] Similarly, Takano and Ogasawara used $RuCl_3$ and $NaIO_4$ to convert **330** to (*S*)-glutamic acid derivative **331** in 87% yield.[470]

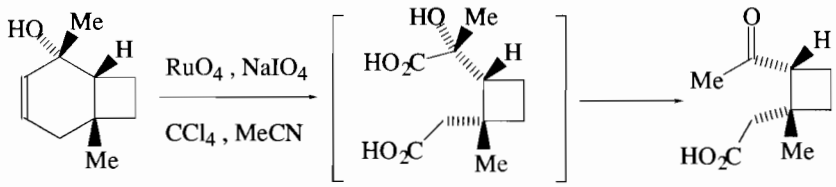
A key ingredient in the $RuCl_3/NaIO_4$ oxidation appears to be the choice of solvent, with acetonitrile being preferred. Under these reaction conditions, alkenes such as 1-nonene are cleaved to acids (nonanoic acid, 89% yield).[468] Alcohols (see **332**) can be oxidized to the acid (in this case forming **333** without disturbing the

adjacent epoxide) and 1,2-diols are cleaved to the acid in high yield.[468] The oxidations are not accompanied by racemization or rearrangement, even when adjacent to a chiral center as in **330** or **332**.[468]



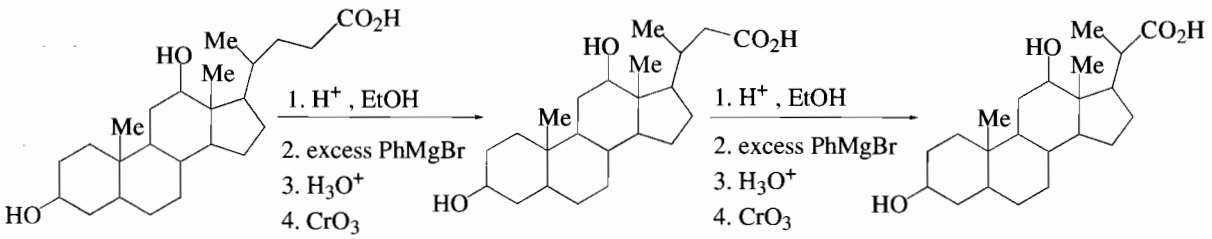
332 **333**

In some cases, secondary reactions can accompany the oxidation. In Silverstein's synthesis of optically pure grandisol,[471] **334** was opened to the diacid (**335**), which gave ketone **336** after oxidative decarboxylation under the reaction conditions.



334 **335** **336**

3.7.A.iv. Chromium Reagents. It is clear from this chapter that Cr(VI) is a powerful oxidant. A striking example is the observation that Cr(VI) can cleave alkenes to ketones and acids. It is often difficult to limit the extent of oxidation, however, and the products often include "epoxides, ketols, and acids and ketones arising from cleavage or rearrangement reactions".[472] Chromium oxidation of 1,1-diphenylalkenes, however, is the basis of the classical **Barbier–Wieland degradation**, which removes one carbon from the starting molecule.[473] Wieland used this method for the conversion of desoxycholic acid (**337**) to nordesoxycholic acid (**338**) in which two carbons are cleaved (one at a time) from the carboxylic acid chain by sequential Barbier–Wieland degradations.[474] The first sequence (esterification, reaction with phenylmagnesium bromide and then oxidative cleavage) gave **338** and the second sequence gave **339**.

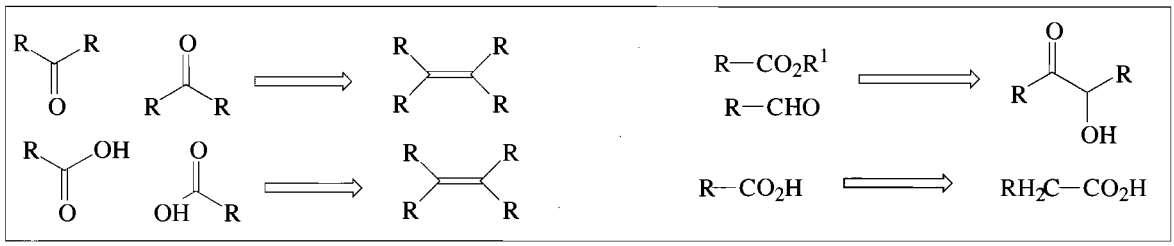


337 **338** **339**

The **Gallagher–Hollander degradation**[475] is a related oxidative cleavage sequence that removes two carbons from the original molecule. The original acid is converted to a diazoketone (see sec. 13.9.B.iii for other applications of diazoketones). Hydrolysis generates a methyl ketone that is brominated. This step is followed by elimination (induced by collidine), which generates a conjugated ketone. Oxidative cleavage with chromium trioxide completes the sequence, giving a new acid with a net loss of two carbons.[475]

A modification of the Barbier–Wieland degradation allows removal of three carbons and is called the **Miescher degradation.**[476] Initial reaction converts the acid to an ester and reaction with phenylmagnesium bromide generates the diphenylalkylidene intermediate that was important to the Barbier-Wieland sequence. Subsequent treatment with NBS (sec. 2.8.B) gives an allylic bromide and elimination with methanolic potassium carbonate (K_2CO_3) leads to a conjugated diene. Oxidative cleavage with chromium trioxide cleaves three carbons from the original molecule. With these oxidative techniques, a long chain carboxylic acid can be shortened by one, two or three carbons in a convenient manner.

The functional group transforms for oxidative cleavage with metals are

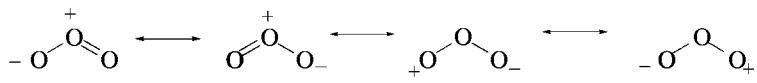


3.7.B. Cleavage of Alkenes with Ozone

Ozone (O_3) is a powerful oxidizing agent. The reduction potential is high in both acidic and basic media, as was shown in Table 3.1 (2.07 and 1.24 V, respectively) for the following reactions.

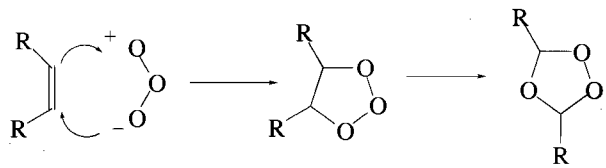
$$O_3 + 2\,H^+ + 2\,e^- \rightarrow O_2 + H_2O \qquad 2.07\ V$$
$$O_3 + H_2O + 2\,e^- \rightarrow O_2 + 2\,HO^- \qquad 1.24\ V$$

Ozone occurs naturally in the atmosphere but in too low a concentration for convenient use. In the laboratory, ozone is produced by electric discharge in oxygen. Ozone is best viewed as a resonance species with four



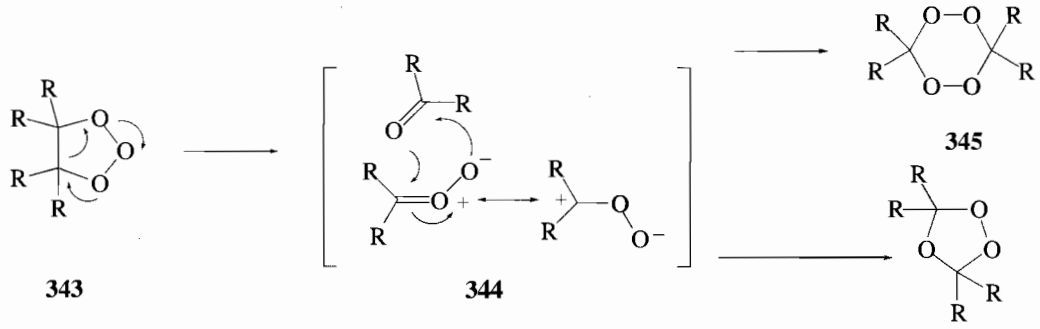
340A **340B**

contributors. Contributors **340A** and **340B** are important for understanding how many reactions work,[477] including that with alkenes. Alkenes react via a 1,3-dipolar addition[478] mechanism (discussed in sec. 11.11.A) to give a 1,2,3-trioxolane product (**341**). This trioxolane is thermally unstable, even at low temperatures, and rapidly rearranges to a 1,2,4-trioxolane, better known as an ozonide (**342**).[477,478] The accepted mechanism of this rearrangement was proposed by Criegee,[479b] in which cleavage of an O—O bond in trioxolane (**343**) gives a ketone (or aldehyde) and a carbonyl oxide (**344**). A second dipolar addition (see **344**) with the ketone (or an aldehyde) leads to the ozonide, **346**. Other reaction pathways are possible with the carbonyl oxide. When



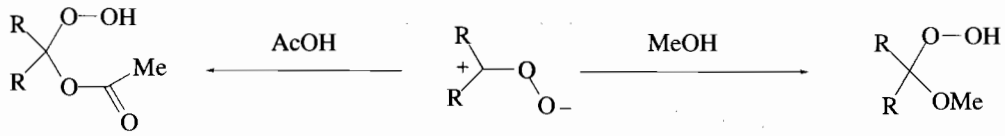
341 **342**

the carbonyl partner is an aldehyde, ozonide formation is preferred in virtually all cases. When the partner is a ketone, however, **344** can dimerize to the tetraoxone (**345**) or polymerize to polyperoxides.[480] If methanol or acetic acid are used as a solvent, Criegee showed that alkoxyhydroperoxides (**347**) or carboalkoxyhydroperoxides (**348**) may result.[481]



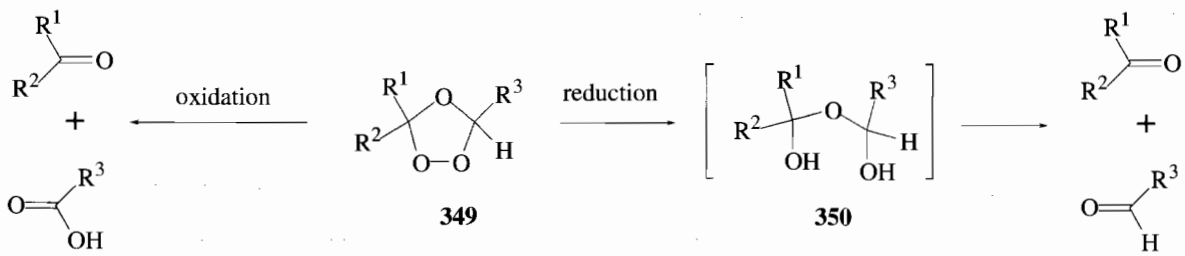
343 **344** **345** **346**

Several studies have examined cis/trans isomerism in the ozonide[482] but this section will focus only on products derived *from* the ozonide (aldehydes, ketones, and acids). The geometry of the alkyl groups on the ozonide will not be discussed except to say that cis-alkenes give both cis- and trans-ozonides, with the cis generally predominating. Similarly, trans-alkenes give higher yields of the trans-ozonide. In many cases, however, the cis/trans ratio is close to 1:1.[483]



348 **344** **347**

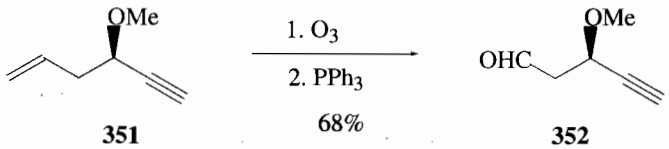
An ozonide (such as **349**) can be decomposed by four methods: (1) reduction, (2) hydrolysis, (3) oxidation, and (d) thermolysis.[484] If the ozonide carbons bear a hydrogen (=CHR^3 in **349**), reductive decomposition usually gives the corresponding aldehyde whereas an acidic or oxidative workup will yield the acid.[485] When that carbon bears two carbon groups (CR^{1}R$_2$ in **349**), the product is a ketone by either oxidative or reductive methods. It is likely that reduction of the peroxide linkage in **349** first yields a bridged hemiacetal (**350**),[486] which fragments to the carbonyl derivatives with loss of water. Hydrolysis of the ozonide apparently occurs at a O—C—O linkage and the peroxide linkage (C—O—O—C) to give the peroxy hemiacetal (structurally related to **347** but with an OH rather than OMe).[486]



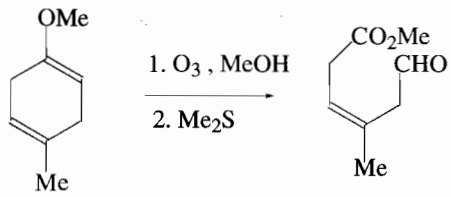
349 **350**

Reducing agents can be used, but most convert the ozonide to an alcohol rather than to a carbonyl.[487] Reduction of the ozonide with lithium aluminum hydride or sodium borohydride generates the alcohol products, as expected, by further reducing the intermediate carbonyl products. It is noted that 1 mol of $LiAlH_4$ is required per mole of ozonide and the temperature is usually maintained below –10°C.[488] The most common reagents that decompose an ozonide to produce aldehyde and ketone products are zinc/acetic acid and DMS in methanol.

A typical example of an application of ozonolysis in synthesis is the cleavage of the alkene unit in **351** to give aldehyde **352**, with loss of formaldehyde, a part of Smith's synthesis of (+)-thiazinotrienomycin E.[489] In this case, the reductive workup used triphenylphosphine. Ozonolysis of **353** gave aldehyde **354**, an intermediate in Corey's synthesis of the Cecropia Moth Juvenile hormone,[490] via a reductive workup with DMS. Note that the electron rich vinyl ether moiety reacted in preference to the simple alkene moiety. The ozonolysis product of the methyl vinyl ether was a methyl ester. This method is particularly useful for the preparation of protected acids. In general, electron rich alkenes are oxidized faster than electron-poor alkenes.

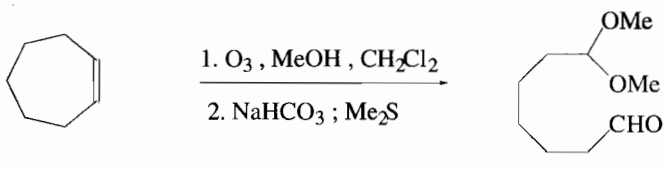


351 **352**



353 **354**

It is possible to trap an aldehyde product of ozonolysis as an acetal using what is called the **Schreiber protocol.**[491] In Fürstner's synthesis of (*R*)-(+)-lasiodiplodin, cycloheptene was ozonized in the presence of methanol at –78°C,[492] which was followed by neutralization with bicarbonate and DMS to give aldehyde-acetal **355**. This method is effective to chemically differentiate the two aldehyde units that result from simple ozonolysis of the cyclic alkene.

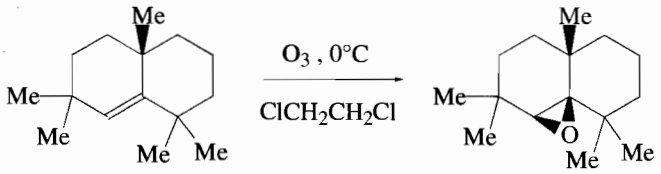


355

The oxidative workup used to produce acids from ozonides such as **349** uses reagents such as hydrogen peroxide, peroxy acids, silver oxide, chromic acid or permanganate. The conversion of cyclohexene to adipic acid by treatment with (1) O_3 and (2) H_2O_2 is a simple example[493] of a typical oxidative workup. When the ozonide is disubstituted (two carbon groups on the initial carbon of the alkene), the product is a ketone and

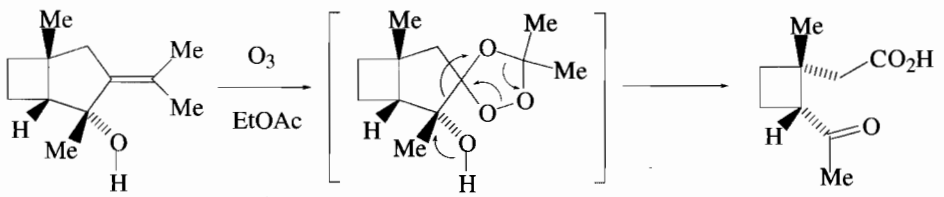
either oxidative and reductive workups can be used. If that carbon bears an hydrogen, the oxidative workup will produce an acid and a reductive workup of the aldehyde, as discussed above.

Sterically hindered alkenes react with ozone approximately as fast as do unsubstituted alkenes. Ozonolysis of 2,2,5,5-tetramethyl-3-(1,1-dimethylethyl)-3-hexene, for example, gave pivalaldehyde and di-*tert*-butyl ketone, using trimethyl phosphite as a reducing agent.[494] Steric hindrance is a factor in some cases, however, as in the ozonolysis of **356**, which gave an epoxide (**357**) in 70% yield, rather than oxidative cleavage.[495a] This is what Bailey and Lane call partial cleavage, which is sometimes observed with highly hindered alkenes.[495b] The product distribution depends upon the solvent that is used.[495,496,497]

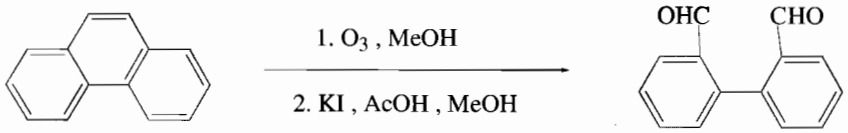


356 **357**

An ozonide can rearrange prior to cleavage if a reactive functional group is adjacent to the carbon bearing the ozonide oxygen. Cargill and Wright used this abnormal reaction in a synthesis of grandisol,[498] where ozonolysis of **358** initially formed the expected ozonide (**359**). Fragmentation of **359**, initiated by the adjacent hydroxyl group, gave keto acid **360** as shown.



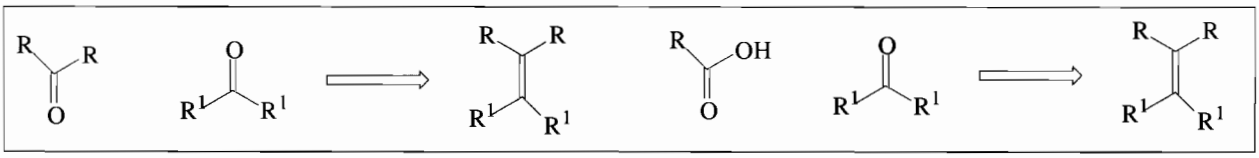
358 **359** **360**



361 **362**

Some aromatic compounds can also react with ozone, although most simple aromatic rings such as benzene derivatives and naphthalene do not. Anthracene reacts with ozone to give anthraquinone in 73% yield after an oxidative workup.[499] Indeed, quinone formation is a more typical example of the reaction of ozone with aromatic compounds (for other oxidative cleavage reactions see sec. 3.8 and for oxidation to phenols and quinones see sec. 3.3). Only a reactive π bond, such as the 9,10 bond of phenanthrene, will oxidatively cleave, and phenanthrene (**361**) was oxidized to dialdehyde **362** upon treatment with ozone in methanol followed by a workup with potassium iodide in acetic acid.[500]

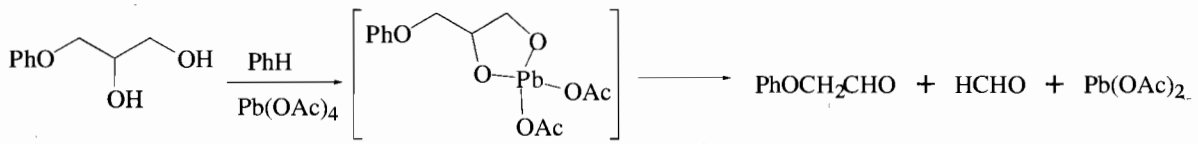
The functional group transform for ozonolysis of alkenes and all oxidative cleavage reactions of alkenes can be summarized by



3.7.C. Cleavage of 1,2-Diols

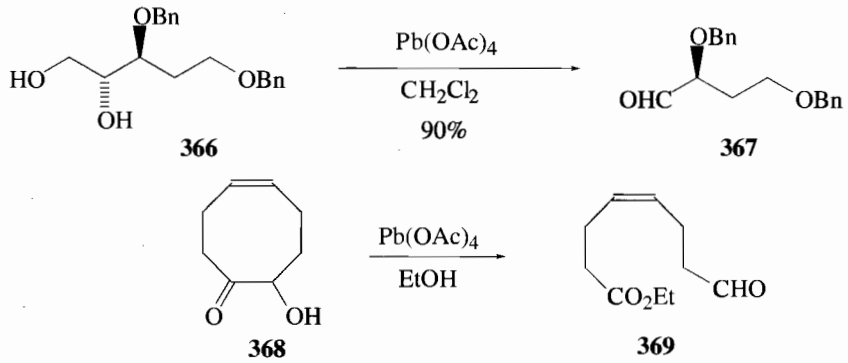
Sections 3.7.A and 3.7.B showed that alkenes are oxidatively cleaved by transition metal oxidants. With certain reagents, 1,2-diols can also be oxidatively cleaved, usually to aldehydes or ketones.[501]

3.7.C.i. Lead Tetraacetate. The reduction potential of lead compounds was not included in Table 3.2, but lead tetraacetate [$Pb(OAc)_4$, LTA] is a common reagent for oxidizing organic compounds. The reduction potential for LTA in perchloric acid has been reported to be 1.6 V,[502] making it one of the more powerful



363 **364** **365**

oxidants examined in this chapter. For organic substrates, LTA is used in solvents such as acetic acid or benzene primarily for the oxidative cleavage of 1,2-diols, α-hydroxy ketones, 1,2-diketones, and α-hydroxy acids.[503] Cleavage of diols probably proceeds via a cyclic intermediate such as **364** as in the conversion of

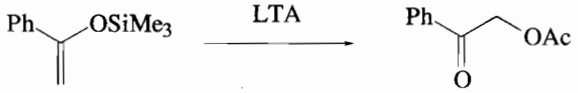


366 **367** **368** **369**

363 to **365**.[504] The diol displaces the acetate ligands, allowing fragmentation to formaldehyde, **365** and lead (II) acetate, $Pb(OAc)_2$. Formation of this complex (**364**) is analogous to similar complexes that were observed in reactions of alkenes with permanganate and osmium tetroxide. A cyclic intermediate such as **364** is formed faster with syn-than with anti-diols,[505] and syn-diols are, therefore, oxidized faster. Similar results are observed in the oxidative cleavage of diols with periodic acid. A typical application is the oxidative cleavage of the diol in **366** to give aldehyde **367** in Mulzer's synthesis of hastanecine.[506] Unfunctionalized alkenes are unaffected by the reagent.[507] α-Hydroxy ketones are also cleaved with LTA, as in the oxidation of ketol **368** to give **369**, taken from Henrick's synthesis of gossyplure.[508] Note that the alkene was not oxidized by LTA.

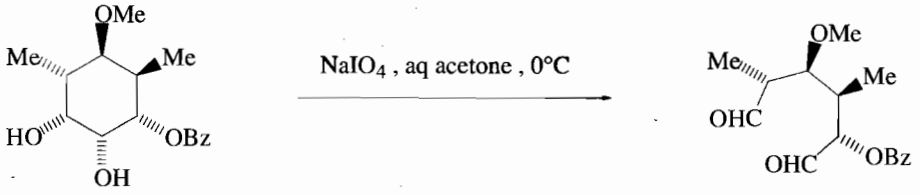
Functionalized alkenes are oxidized with LTA and a variety of interesting transformations are possible.[509]

Ethyl vinyl ether, a typical vinyl ether, gave a diacetate (2-ethoxy-1,2-ethanediol diacetate) upon treatment with LTA in acetic acid.[510] Vinyl esters can also give α-acetoxy ketones.[511] Oxidation of silyl enol ethers leads to α-acetoxy ketones, illustrated by the conversion of **370** to **371** in good yield.[512] Ketones and aldehydes exist, in part, in an enol form and this enol an be oxidatively cleaved with LTA to give an α-acetoxy ketone.[513] The yields of the α-acetoxylation product derived from methyl ketones can be improved by the addition of boron trifluoride, which acts as a catalyst.[514] Unsymmetrical dialkyl ketones react selectively at the less substituted position, presumably via the kinetic enol (sec. 9.1, 9.2.E). Oxidation of 2-butanone, for example, gave exclusively 1-acetoxy-2-butanone.[515] It is interesting to note that oxidation of α-epoxy alcohols give α-acetoxy ketones,[516] and enamines undergo cleavage by LTA to form an α-acetoxy ketone, but the yields are often low.[517]



370 **371**

3.7.C.ii. Sodium Periodate In section 3.7.A.ii, a mixture of osmium tetroxide and periodic acid oxidatively cleaved alkenes. Sodium periodate can cleave diols directly. In the Chida et al. synthesis of pironetin, for example, **371** was cleaved to dialdehyde **372** using an aqueous acetone solution of $NaIO_4$.[518] Sodium periodate in dichloromethane, in the presence of sodium bicarbonate, has also been used.[519]



372 **373**

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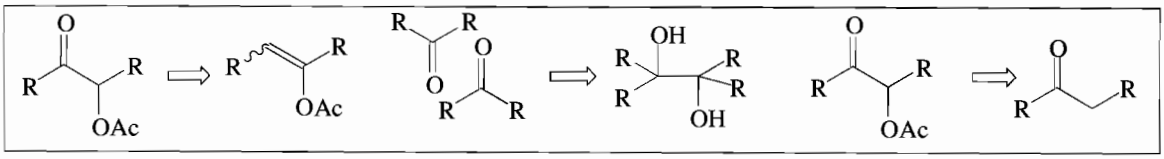


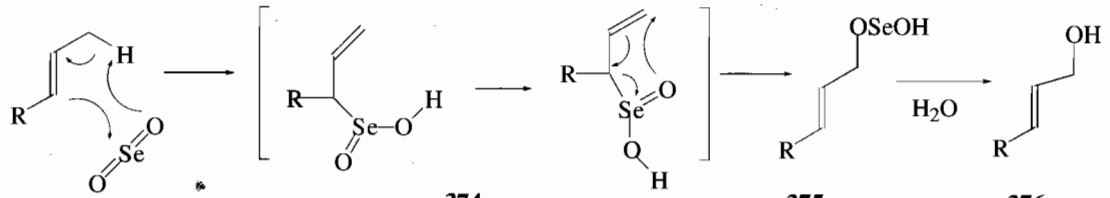
3.8. OXIDATION OF ALKYL OR ALKENYL FRAGMENTS (CH → C=O OR C-OH)

When relatively powerful oxidizing agents are employed with *alkane* fragments that are activated by the presence of a π bond (allylic, benzylic, α-carbonyl compounds), that fragment can be oxidized to an alcohol, aldehyde, or ketone or it can be oxidatively cleaved.[520] The most common reagents for these transformation are selenium dioxide (SeO_2), chromium trioxide (CrO_3), chromyl chloride (CrO_2Cl_2) and LTA. Cleavage of silanes of the type R—$SiMe_2Ph$ can be included in this section, due to a new method has been developed that converts the silyl unit to an alcohol (R—OH). It has also been shown that *t*-BuOOH and CuI oxidizes the allylic carbon of alkenes to conjugated ketones.[521]

3.8.A Selenium Dioxide

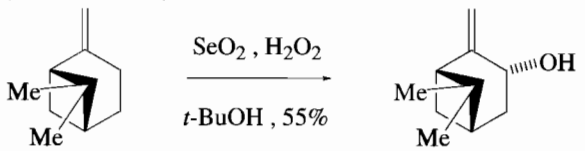
Selenium dioxide is probably the most common reagent used to selectively oxidize an alkyl fragment, and is particularly effective for converting allylic or benzylic C—H fragments to the corresponding allylic alcohol.[522] In the most common applications, carbonyl derivatives are oxidized to 1,2-dicarbonyl compounds and allylic hydrocarbons to alcohols or esters.[523]

The reaction of SeO_2 and allylic molecules proceeds via an initial **ene reaction** (sec. 11.13) to give **374**. A 2,3-sigmatropic shift (sec. 11.12.A) affords **375**, which is hydrolyzed to the allylic alcohol **376**.[524] It is important to note that the reaction shows an overall transformation that appears to be a direct conversion of



374 375 376

C—H to C—OH, but in fact the reaction is accompanied by two migrations of the π bond, as shown. An illustration is the preparation of *trans*-pinocarveol (**377**) from β-pinene (**378**) in 55% yield.[525] When the reaction in done is the presence of acetic anhydride, the allylic alcohol product is converted to the corresponding acetate.[526]



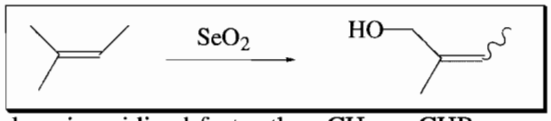
377 378

Guillemonat assembled a set of rules that predict the oxidation products for different alkenes.[527] Trachtenberg[528] expanded the discussion of these rules to include general statements concerning oxidation with selenium dioxide and these are listed below.

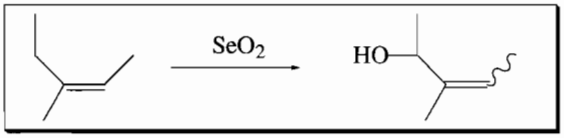
1. Oxidation always occurs on the disubstituted side of a double bond if there is a nonbridged alkenyl hydrogen available there.
2. Oxidation of 1-alkylcyclohexenes occurs in the ring rather than in the side chain.
3. Oxidation never occurs at bridgehead positions in bicyclic systems falling within the limits of **Bredt's rule** (sec. 6.3.B).
4. All other things being equal relative to the above rules, the preferred order of reactivity is $CH_2 > CH_3 > CH$
5. If the preferred allylic position is tertiary, a diene will generally be produced in preference to a tertiary alcohol.
6. Allylic rearrangement products can and will be formed.
7. Skeletal rearrangement can occur if the preferred allylic position is adjacent to a quaternary carbon or a cyclopropyl ring.

Rabjohn summarized these rules with pertinent examples.[523]

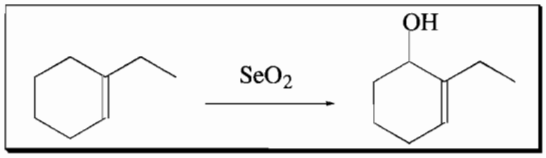
a. In trisubstituted alkenes, oxidation occurs on the more highly substituted side of the double bond.



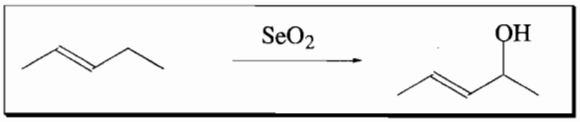
b. By rule (4) above, methylene is oxidized faster than CH_3 or CHR_2:



c. By rule (2) above, oxidation of cyclic alkenes usually occurs in the ring.

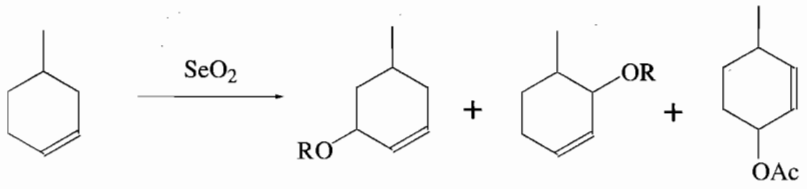


d. Disubstituted alkenes are oxidized in the α-position and methylene is oxidized faster than methyl or methine (rule 4) and example (b).



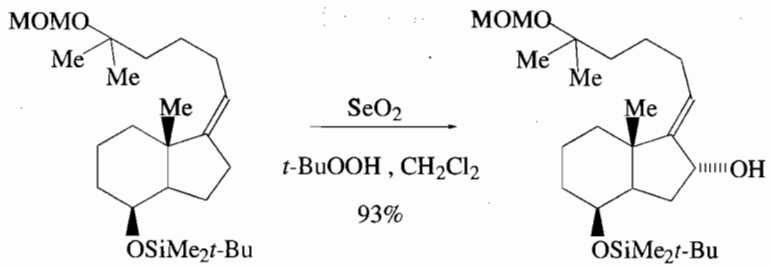
If the alkene is flanked by two methylene groups, both are oxidized.

e. With terminal monosubstituted alkenes the problem of allylic rearrangement is marked. 1-Butene gives a mixture of 2-buten-1-ol and 3-buten-3-ol.[529] Terminal disubstituted alkenes have at least two allylic positions, as do terminal disubstituted alkenes and both are subject to oxidation. Oxidation of the unsymmetrical 4-methylcyclohexene, for example, gives different products as the reaction conditions are changed (**379–381**).



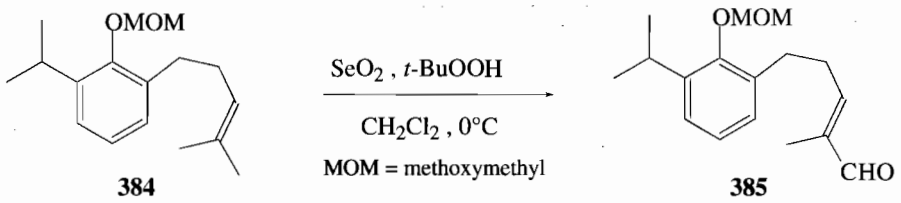
379 **380** **381**

Mouseron and Jacquier showed that **379** (R = H) was the major product when 4-methylcyclohexene was oxidized with selenium dioxide in acetic acid.[530] When Guillemonat changed the solvent to a mixture of acetic acid and acetic anhydride, **370** (R = Ac) was the major product with trace amounts of **381**. The combined yield of **379–381**, however, was only 19%.[527]



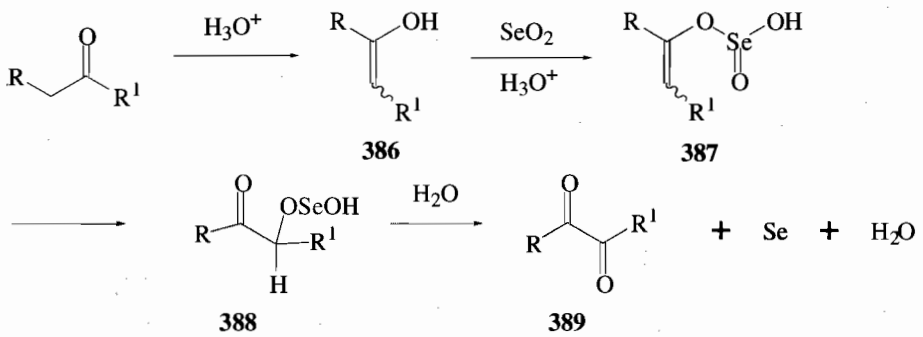
382 **383**

The seven rules listed above suggest good selectivity. In many cases, alcohol products are obtained, as in the Mouriño's synthesis of vitamin D_3 analogs,[531] where **382** was converted to **383** in 93% yield. Notice the high selectivity of this reaction despite the fact that there are two allylic sites. When an electron-withdrawing group is attached to a double bond, the reaction with SeO_2 is slow relative to an unconjugated double bond. Benzylic positions are unaffected, as seen in the conversion of the allylic site in **384** to alcohol **385**, in Yang's synthesis of (–)-triptolide.[532] Notice that in this reaction, the product is an aldehyde.



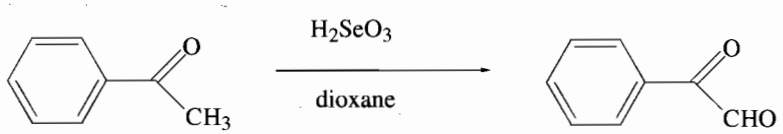
384 **385**

A second major application of selenium dioxide is the oxidation of aldehydes and ketones to the corresponding 1,2-dicarbonyl.[533] This conversion proceeds by reaction of the enol form of the carbonyl (**386**) with selenium dioxide to give the selenous enol ester, **387**. Oxidative rearrangement to **388** is followed by loss of



386 **387** **388** **389**

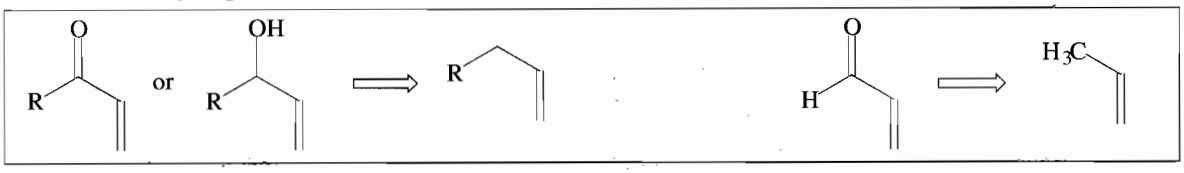
selenium and water to give the dicarbonyl (here a diketone, **389**).[534] Cyclohexanone was converted to cyclohexane-1,2-dione in 60% yield with SeO_2,[535] and similar oxidation of aldehydes led to glyoxals in good yield. Methyl ketones can be oxidized to glyoxals, as in the conversion of acetophenone to **383** in 72% yield.[536] In unsymmetrical ketones, oxidation occurs preferentially at the less sterically hindered position,[537] which is probably related to the relative stability of the enol, which is the reactive intermediate (as in **390**). The hydrogen on the carbon β to the oxoseleno moiety can be removed in some cases, forming an aldehyde by an E2 type elimination.[538] Such aldehyde formation is an important reaction only when the α-hydrogen is sterically hindered[539] and is especially important in reactions with ketones.[540]



390

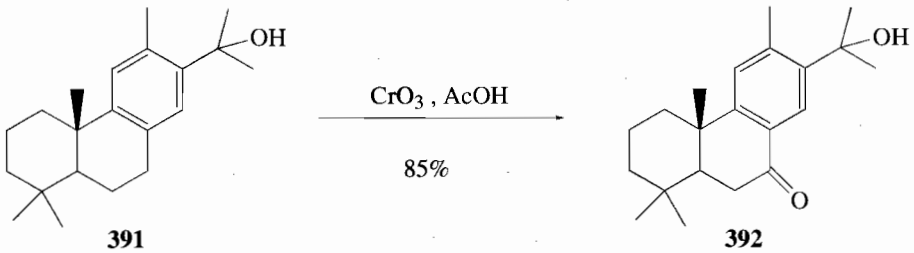
In addition to oxidizing an allylic CH unit or positions α to a carbonyl, selenium dioxide can also oxidize benzylic positions to a carbonyl derivative, without oxidizing the aromatic ring.

The functional group transforms available from selenium dioxide oxidations are



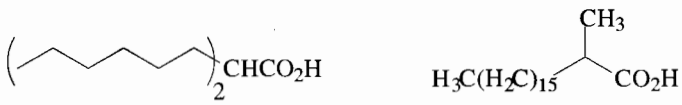
3.8.B. Chromium Trioxide Oxidation

As first noted in section 3.2.A, Cr(VI) is a powerful oxidizing agent. In addition to oxidizing alcohols to aldehydes, ketones, or carboxylic acids and effecting oxidative cleavage of alkenes, it is capable of oxidizing the C—H bond of certain hydrocarbons. In general, tertiary C-H is cleaved before secondary and secondary before primary. The initial product of this oxidation is usually an alcohol, which can be eliminated to give an alkene or be further oxidized to a ketone or acid. It is also possible to oxidize ketones to acids by oxidative cleavage. In the reactions just mentioned, it is difficult to control overoxidation and this method has little synthetic value, although methyl ketones can be oxidized to the acid [$R_2CH(C{=}O)Me \rightarrow R_2C{-}CO_2H$], with CrO_3. Chromium oxide can also oxidize benzylic positions., as in the **Étard reaction** (see sec. 3.8.E). When **391** was treated with chromium trioxide in acetic acid, an 85% yield of **392** was obtained, as part of Pan's synthesis of (–)-6,7-dehydroferruginyl methyl ether.[541]



391 **392**

Another use, which is somewhat dated, is the classical **Kuhn–Roth oxidation**.[542] This method allows one to determine the number of methyl groups present in a molecule. Oxidation with chromium trioxide in concentrated sulfuric acid oxidatively cleaves methyl groups to acetic acid, and titration with standard base gives the number of equivalents of acid formed, which is also the number of methyl groups in the original molecule. Kuhn–Roth oxidation of 2-methylpyridine, for example gave about one equivalent of acetic acid.[543b] and oxidation of fatty acids or alcohols (with chain lengths up to 20 carbons)[543] will give one or more equivalents

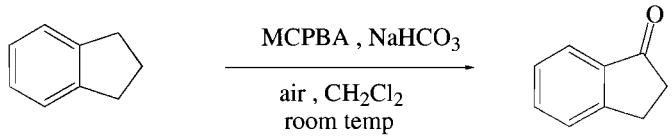


393 **394**

of acetic acid. Modification of the oxidation step allows determination of the number of methyl groups in fatty acids of > 20 carbons.[544] For fatty acids of > 20 carbon atoms, poor solubility of the organic compound led to incomplete oxidation and too few equivalents of acetic acid were observed. Prior dissolution of the acid or alcohol in sulfuric acid, followed by addition of chromium trioxide, gave improved yields and reduced

decomposition. Kirste and Stenhagen[544] showed that **393** released ≈ two equivalents of acetic acid. Ginger[543] observed 1.65 equivalents from α-methylstearic acid (**394**) in what is probably a typical experimental result for a Kuhn–Roth oxidation.

3.8.C. Oxidation with Peroxyacids and Oxygen. In the presence of air (oxygen), benzylic oxidation is possible using peroxy acids such as *m*-chloroperoxybenzoic acid. Ma and co-workers found that oxidation of indane (**395**) using a mixture of MCPBA, $NaHCO_3$, and air gave an 88% yield of 1-indanone (**396**).[545] When the reaction was carried out under a nitrogen atmosphere, no indanone was formed. The peroxyacid–oxygen oxidation has the potential to be a new type of benzylic oxidation that can be synthetically useful.

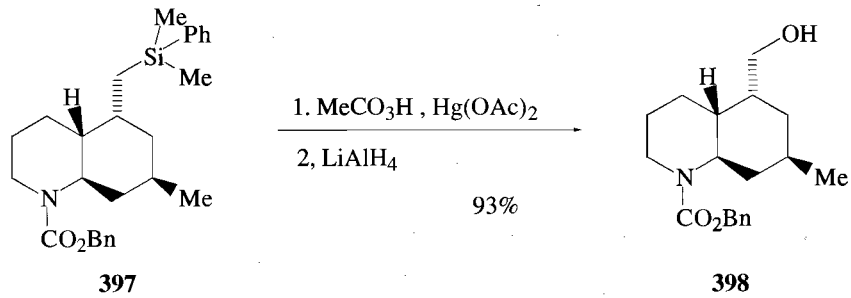


395 **396**

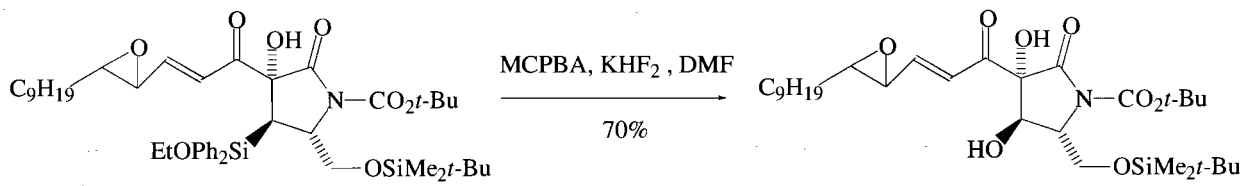
3.8.D. Tamao–Fleming Oxidation

Just as carbon-based alkyl groups can be oxidized, a silicon-based silane unit can be oxidized under certain conditions. Alkylsilanes can be converted to a hydroxy unit, but either an aryl group[546] (R—SiR'_2Ar) or another silyl group[547] (RSi—SiR'_3) must be attached to silicon. In an early version of this reaction, Fleming used a two-step process to transform the silane unit to an alcohol unit, treatment with mercuric acetate and peroxyacetic acid, followed by reduction with lithium aluminum hydride (see sec. 4.2.A for reductions with $LiAlH_4$). Comins et al. used this procedure to convert dimethylphenylsilane (**397**) to alcohol **398** in 93% yield for the two steps,[548] which was part of a synthesis of *N*-acetyl-*N*-methylphlegmarine.[548]

There were several cases when this original procedure failed, but it was discovered that if the silane units are treated with a fluorinating agent such as TBAF or CsF, the Ar or SiR'_3 unit is replaced with F.[549] Subsequent treatment with hydrogen peroxide or a peroxy acid gave the alcohol. This sequence is often called the



397 **398**



399 **400**

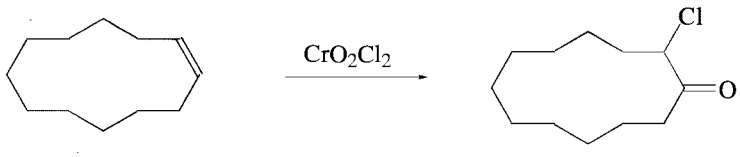
Tamao–Fleming oxidation.[546] Barett found the original procedure failed with several derivatives aimed at the synthesis of (+)-pramanicin, but the Tamao-Fleming procedure, using MCPBA-KHF_2, converted **399** to **400** in 70% yield.[550] One of the more attractive features of this oxidation is that the absolute stereochemistry of the C—Si bond in **399** is retained in the C—O bond of **400**. In other words, the reaction proceeds with retention of stereochemistry of the silyl group. Another variation uses KF and hydrogen peroxide for the oxidation, a reaction used by Overman for one step of a synthesis of (+)-aloperine.[551]

Incorporation of the silyl unit can be done in several ways,[552] including conjugate addition of silylcuprates to conjugated carbonyl compounds (see sec. 8.7.A.vi.). A brief discussion of silane carbanions will be presented in section 8.10.

3.8.E. Alkene Oxidation (C=C → C—C=O)

Several transition metal derivatives convert alkenes into a carbonyl derivative with rearrangement, but *without* bond cleavage.[553] This section will briefly discuss several of these reagents and their reactions. A common one is chromyl chloride (CrO_2Cl_2), which reacts with 1,1-disubstituted terminal alkenes [$R_2C{=}CH_2$] to give the corresponding aldehyde.[554] Oxidation of 1,1-diphenylethene with chromyl chloride required a reductive workup with zinc (to reduce the chromium intermediate) but gave diphenylacetaldehyde in 63% yield.[555] This interesting conversion is a synthetically useful method for the preparation of α,α-disubstituted aldehydes.

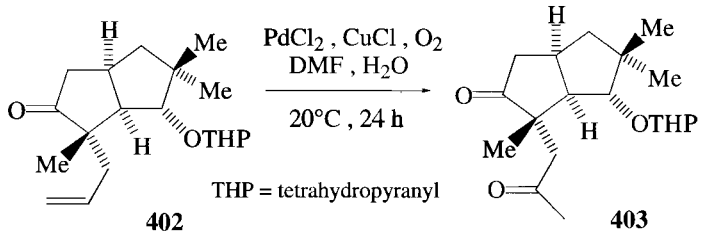
This reagent can also be used for the oxidation of methylated aryl derivatives to the corresponding aryl aldehyde, in what has become known as the **Étard reaction.**[556] Tillotson and Houston found that the Étard reaction is catalyzed by small amounts of alkene, added to or present in the reaction medium.[557] The reaction involves addition of chromyl chloride to a carbon disulfide or carbon tetrachloride solution of the arene. A dark brown, insoluble, and ***explosive*** intermediate usually precipitates. Dilute sulfurous acid is added to decompose the precipitate to the aldehyde. Toluene is converted to benzaldehyde and ethylbenzene was oxidized to phenylacetaldehyde with this reagent.



401

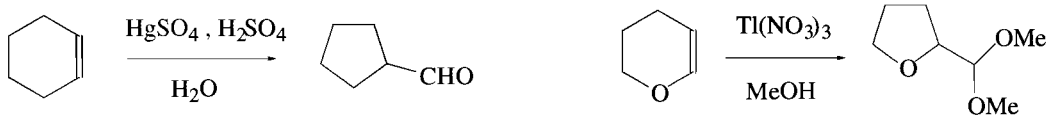
Chromyl chloride can also produce ketones, but a common side reaction is formation of an α-chloro ketone, as in the conversion of cyclododecene to α-chlorocyclododecanone (**401**) in 79% yield.[558] In a subsequent reaction, the chloride moiety in **401** was reduced to give cyclododecanone in 95% yield with zinc and acetic acid. Chromyl chloride also reacts with alkenes to give a trans-chlorohydrin rather than a carbonyl compound (see sec. 2.10.C for the preparation of chlorohydrins), as in the conversion of cyclohexene to *trans*-2-chlorocyclohexanol.[559] It is interesting that in this particular case (the temperature was maintained at –78°C in dichloromethane), the cis-chlorohydrin was formed.[560]

Lead tetraacetate initiates a similar type of oxidation with terminal alkenes, in the presence of acid, to give an aldehyde by selective oxidation of the terminal carbon.[561] An example is the conversion of styrene to phenylacetaldehyde in 98% yield.[562] Palladium chloride ($PdCl_2$) reacts with terminal alkenes, in the presence of oxygen and copper salts, to give a methyl ketone (this reaction is called the **Wacker process** and is discussed in sec. 12.6.A). It is more useful than the LTA oxidation. Oxidation of terminal alkenes with LTA leads to the aldehyde, whereas oxidation with $PdCl_2$ leads to the methyl ketone. The $PdCl_2$ oxidation is illustrated by conversion of **402** to **403** in 77% yield, in Ikegami's synthesis of coriolin.[563]



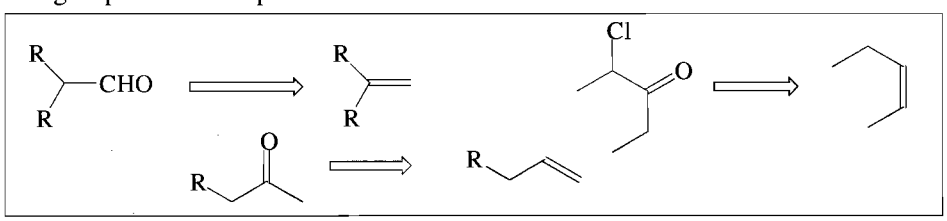
402 **403**

Mercuric salts induce oxidative rearrangement of cyclic alkenes and give cycloalkane carboxaldehydes.[564] Cyclohexene, for example, gave cyclopentane carboxaldehyde (**404**) in 53% yield.[565,561] Acyclic alkenes such as 2-butene can also be oxidized with mercuric sulfate and sulfuric acid, giving 2-butanone in this case.[566] Thallium nitrate [$Tl(NO_3)_3$] is an important reagent for the oxidative rearrangement of cyclic alkenes.[567] The reaction is not restricted to carbocyclic compounds, but can also be applied to heterocyclic compounds as shown by the oxidation of 3,4-dihydro-*2H*-pyran (**405**) to the dimethyl acetal (**406**) in 65% yield.[568]



404 **405** **406**

The functional group transforms presented in this section are



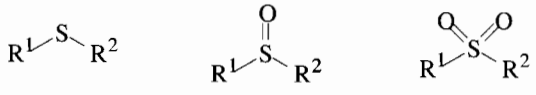
3.9. OXIDATION OF SULFUR, SELENIUM, AND NITROGEN

It is possible to oxidize atoms other than carbon. Sulfur, selenium and nitrogen are easily oxidized by many of the oxidizing agents presented in this chapter. Several oxidation stages are available, leading to an interesting array of functional groups. Sulfur, for example, can be oxidized from a sulfide to a sulfoxide, which is turn can be oxidized to a sulfone. Sulfonic acids and sulfonate esters represent even higher oxidation levels for sulfur. Selenium behaves similarly to sulfur. Nitrogen can be oxidized to hydroxylamines, nitrones,

N-oxides or nitro compounds. These groups figure prominently in many synthetic transformations. In section 2.9.C, *N*-oxides, sulfoxides and selenoxides were important intermediates for syn-elimination reactions. In this chapter (sec. 3.5.B), *N*-oxides were used to catalyze osmylation reactions with alkenes. In sections 8.6 and 8.8.B, sulfoxides and sulfones will be used to stabilize carbanions, which react to form carbon–carbon bonds. It is therefore fitting that this chapter conclude with a brief survey of the methods for oxidizing these important synthetic intermediates.

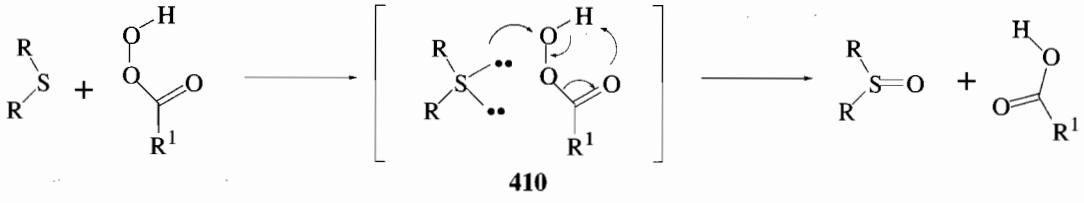
3.9.A. Oxidation of Sulfur Compounds

3.9.A.i. Oxidation of Sulfides to Sulfoxides. Sulfides (thioethers, **407**) are readily oxidized to sulfoxides (**408**) by a variety of oxidizing agents. Further oxidation of sulfoxides to sulfones (**409**) requires more vigorous conditions but is straightforward.[569] Treatment of sulfides with peroxyacids, hydrogen peroxide or alkyl hydroperoxides will generate the corresponding sulfoxide. The overall mechanism for oxidations with peroxy acids and alkyl hydroperoxides is shown.[569] In the reaction with peroxyacids, the sulfide attacks the O—O bond along an S_N2 trajectory (see **410**). The O—O bond is broken, and the hydrogen is transferred to the carbonyl group, liberating a carboxylic acid and the sulfoxide.[568] This type of reaction with alkyl hydroperoxides usually requires acid catalysis. When the sulfide attacks the O—O bond of a hydroperoxide, hydrogen transfer liberates an alcohol and the acid catalyst, as shown in **411**.[569]



407 **408** **409**

Sulfides react faster with hydrogen peroxide and alkyl hydroperoxides than do alkenes. For this reason, transition metal catalysts are rarely necessary, but these reactions are acid catalyzed and first order in both sulfide and peroxide. The acid (HX) can be as weak as alcohol or water but the "effectiveness (of the oxidation) is determined by the pK_a of the acid."[570] Sulfides also react faster with peroxides than do ketones (see the Baeyer–Villiger reaction, sec. 3.6). Formation of the sulfone in these reactions is straightforward, but requires more vigorous reaction conditions. It is usually easy to isolate the sulfoxide from oxidation of a sulfide. Direct conversion of a sulfide to a sulfone requires excess peroxide and vigorous reaction conditions (heating, long reaction times, more concentrated peroxide).



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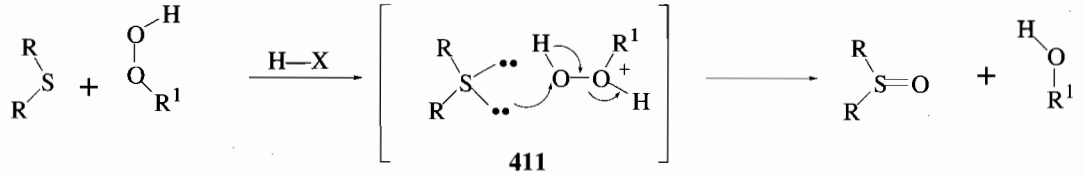
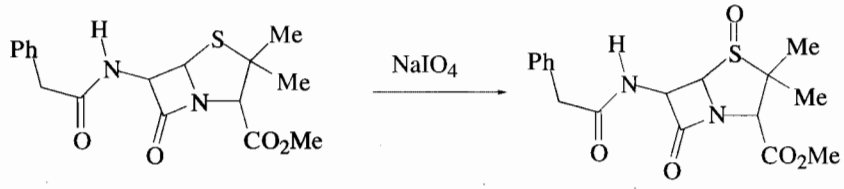
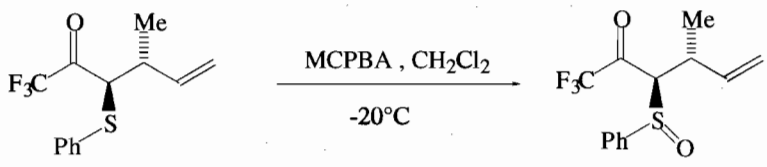


411

Another common oxidizing agent is sodium *m*-periodate ($NaIO_4$). Leonard used sodium periodate to oxidize methylphenyl sulfide to the sulfoxide in near-quantitative yield.[571] In that report, many methods were summarized for oxidizing sulfides, including nitric acid, hydrogen peroxide, chromic acid, ozone, peroxyacids,



412 **413**

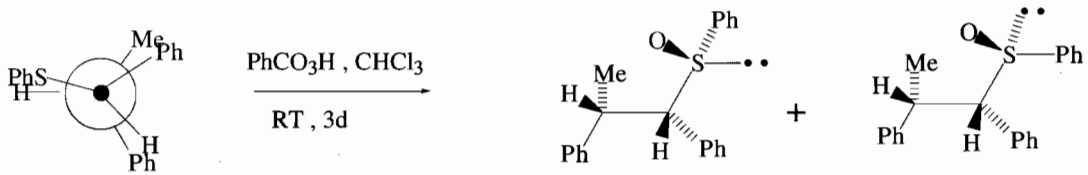


414 **415**

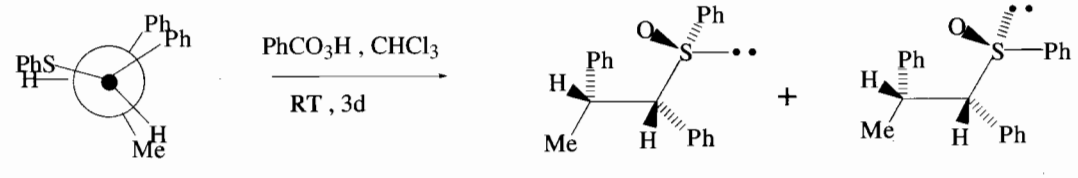
manganese dioxide, and selenium dioxide.[572] Sykes and Todd were apparently the first to use sodium periodate with sulfides, oxidizing benzylpenicillin methyl ester (**412**) to the corresponding sulfoxide (**413**).[573] Sodium periodate is often the reagent of choice for the oxidation of sulfides to sulfoxides, but MCPBA can also be used, as in the oxidation of sulfide **414** to sulfide **415**.[574]

3.9.A.ii. Preparation of Chiral Sulfoxides. The sulfur atom in a sulfoxide has four different groups (R, R^1, O, and the lone pair electrons). There is virtually no inversion at sulfur (in contrast to nitrogen) so the sulfur can be a stereogenic center under these circumstances, which raises two points when using unsymmetrical sulfoxides. The first is the presence of diastereomers that can complicate separation and identification. The second is the ability to resolve the enantiomeric sulfoxides or produce one enantioselectively, and use this material as a chiral auxiliary or as a chiral template (sec. 10.9).

Cram reported an example that illustrates both the oxidation of sulfides to sulfoxides and the formation of diastereomers.[575] Oxidation of erythro- or threo-1-alkylthio-1,2-diphenyl-propane with peroxybenzoic acid gave syn- and anti- sulfides. The erythro-sulfide (anti-sulfide **416**) gave two erythro- (anti) sulfoxides, **417** and **418**.[575] Similarly, the threo- sulfide (syn-sulfide **419**) gave two threo-(syn-sulfides, **420** and **421**. The two

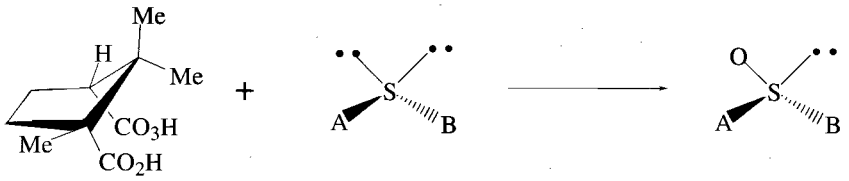


416 **417** **418**



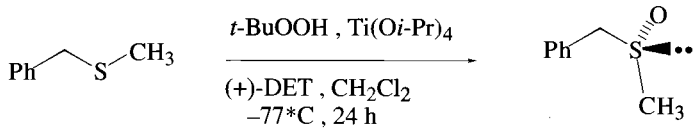
419 **420** **421**

stereogenic carbons retain their absolute configuration during the oxidation but the oxygen is delivered to different faces of sulfur to generate the observed diastereomers. In general, the achiral A-S-B sulfide (**423**) is converted to the chiral sulfoxide **424**. When (+)-peroxycamphoric acid (**422**) was used, the configuration of the predominant optical isomer was the same as in **424**, if A was bulkier than B. Later work by Folli et al. confirmed this preference.[576] Approach of sulfur to the peroxyacid occurs in the direction of the lone pair of electrons on sulfur (an S_N2 like trajectory toward the O—O bond of the peroxide; *vide supra*) and can lead to either the (*R*) or the (*S*) enantiomer. As the difference between A and B became larger, or the chiral peroxyacid was made bulkier, greater selectivity was observed. The optical yields (% ee) were in the range of 1.2–4.5% ee but this is dependent upon the nature of the solvent.[576] Oxidation of phenylmethyl sulfide with (+)-monoperoxycamphoric acid gave the chiral, nonracemic sulfoxide with a 1.2% ee in acetonitrile, and similar oxidation gave 1.7% ee in 2-propanol, 3.8% ee in chloroform, 4.5% ee in ether, 3.6% ee in benzene, and 3.1 % ee in dioxane.[577,576]



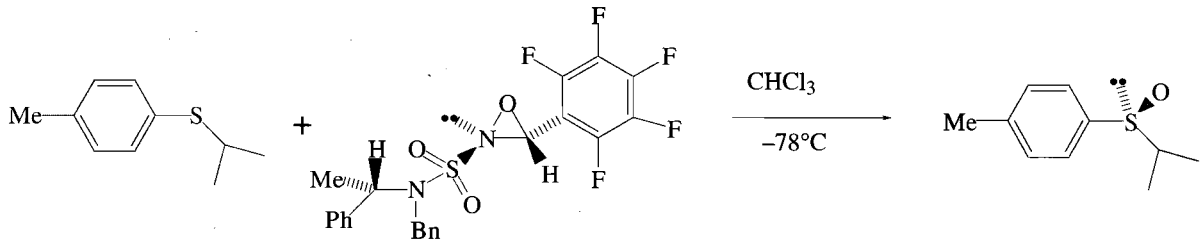
422 **423** **424**

A greater percentage of asymmetric induction has been achieved by procedures that generate a reactive complex where the sulfide and the oxidant are tightly bound. Kagan and Duñach,[578] as well as DiFuria et al.,[579] used titanium tetraisopropoxide [Ti(OiPr)4] and optically active diethyl tartrate (DET) to catalyze the



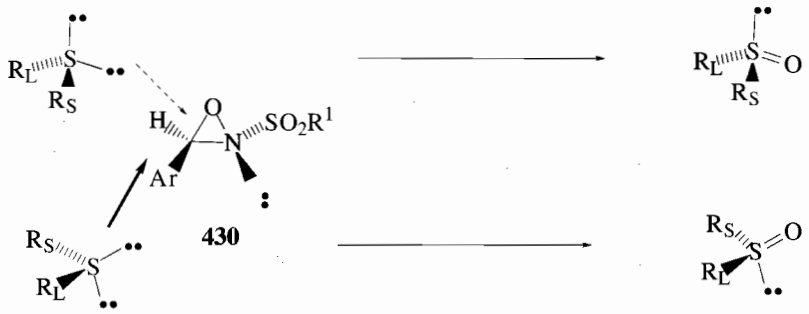
425 **426**

reaction, analogous to the **Sharpless asymmetric epoxidation** discussed in section 3.4.D.i. DiFuria oxidized benzylmethyl sulfide (**426**) to **426** in dichloromethane with 46% ee.[579] Kagan and Duñach oxidized methylphenyl sulfide to the corresponding (*S*)-sulfoxide in water with 89% ee under similar conditions.[578]



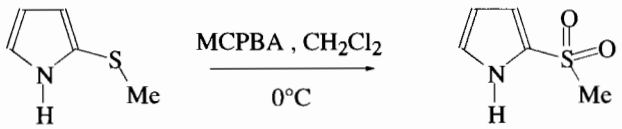
427 **428** **429**

Davis et al. used a chiral oxaziridine for the asymmetric oxidation of sulfides to sulfoxides.[580] Oxidation of isopropyl-*p*-tolyl sulfide (**427**) with oxaziridine **428**, for example, gave 60.3% ee (S) of **429** (at –78°C in chloroform).[580] The absolute configuration of the sulfide is determined by approach of the sulfide to the oxaziridine oxygen, as illustrated by **430**. Steric factors appear to be the primarily reason for the chiral recognition.[581] In this model, attack by sulfur minimizes the R_L and R_S interactions with the oxaziridine



moiety ($R_S \leftrightarrow SO_2R^1$ and $R_L \leftrightarrow$ Ar or $R_S \leftrightarrow$ Ar and $R_L \leftrightarrow SO_2R^1$). When R^1 in **430** is (+)-10-camphor, the resulting oxaziridine derivative reacted with sulfide to give the (+)-(*R*)-sulfoxide whereas the adduct derived from (–)-camphor gave the (–)-(*S*)-sulfoxide.[580] Davis reported several other chiral oxaziridine reagents that gave good to excellent asymmetric induction for the oxidation of sulfides to sulfoxides. These regents are a mild and excellent alternative to oxidation with chiral peroxyacids.

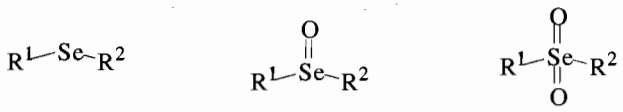
3.9.A.iii. Oxidation of Sulfides or Sulfoxides to Sulfones and Oxidation of Selenium Compounds. As noted above, the oxidation of sulfoxides to sulfones is facile, but slower than the sulfide → sulfoxide conversion. The mechanism is probably similar to that for oxidation of sulfides,[582] but sulfoxides are less nucleophilic than sulfides and the reaction slower.[583] Sulfoxides are oxidized to sulfones using the same oxidants that converted the sulfide to a sulfoxide, but longer reaction times and/or more vigorous conditions are usually required. Direct oxidation of a sulfide to a sulfone is also easily accomplished in many cases. Oxidation of sulfide **431** with MCPBA gave sulfone **432** directly, without oxidation of the sensitive pyrrole unit.[584] It is noted that the sulfur in a sulfone is achiral due to the presence of two oxygen atoms.



431 **432**

The selenium analogs of the sulfide, sulfoxide and sulfone are known, and the generic structures are **433**, **434**, and **435**, respectively. The oxidation of these compounds is virtually identical to those observed with sulfur. The main drawback to their use is the toxicity of the selenium compounds. Selenoxides are relatively unstable and decompose at ambient temperatures, usually leading to syn-elimination. This selenoxide elimination reaction is more facile than the analogous sulfoxide elimination (0°C vs. 120°C) and is often preferred

in organic synthesis (secs. 2.9.C.v, 2.9.C.vi). The thermal instability of the selenoxide, relative to the sulfoxide, is also reflected in the selenone, which is labile and rarely used.

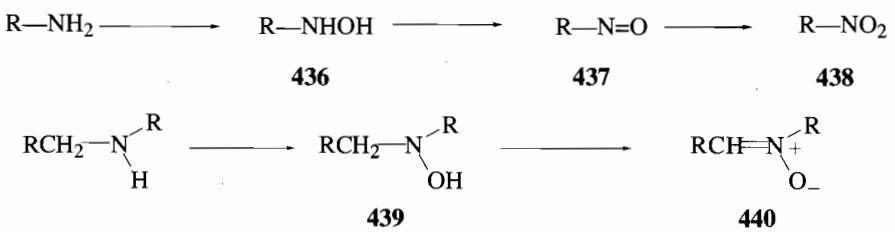


433 **434** **435**

3.9.B. Oxidation of Amines

The oxidation of nitrogen compounds is also common in organic chemistry, particularly with nitro compounds. Aromatic nitro compounds are very important commercial compounds and their preparation was discussed in section 2.11.B. The reader is referred to the references found here and to specific applications for the preparation of oxides of nitrogen. Two categories of nitrogen compounds that are subject to oxidation are amines and amides. Amides "do not react well with hydrogen peroxide or peroxyacids but most other nitrogen compounds react readily."[585] Oxidation of primary amines gives the nitroso (**437**) and the nitro compound (**438**) via the hydroxylamine derivative (**436**).[586] Ozonolysis of phosphinimines also produces nitro compounds.[587] Secondary amines are also oxidized via the hydroxylamine (**439**) but eliminate to give the nitrone (**440**).

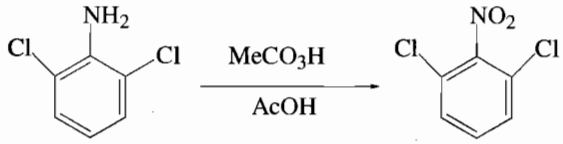
As mentioned above, nitro compounds are obviously of great importance in organic chemistry and aryl nitro compounds are an important source of aniline derivatives (secs. 4.2.C.v, 4.8.D). Both amine oxides and nitrones have been synthetically exploited. Alkyl nitroso derivatives, however, usually cannot be isolated since they decompose in solution, although the aromatic derivatives are more stable in solution and can be used in synthesis (sec. 2.11.E). Treatment of a primary amine with excess peroxyacid is a useful preparative route to alkyl nitro compounds.[588] Yields are highest for tertiary alkyl primary amines; next come secondary, followed by primary alkyl. Peroxyacid oxidation of oximes also provides a route to alkyl nitro compounds.[589] This method is convenient for preparing aromatic nitro compounds as in the oxidation of 2,6-dichloroaniline to 2,6-dichloronitrobenzene (**441**).[590] Nitrones are 1,3-dipoles and have been used in 1,3-dipolar cycloaddition reactions (sec. 11.11.D).



436 **437** **438**

439 **440**

Tertiary amines tend to give N-oxides directly and in high yield. The chemistry of heterocyclic N-oxides has been described by Katritzky.[591] Thermal elimination of N-oxides is the basis of the classical Cope reaction. (sec. 2.9.C.ii).[592]



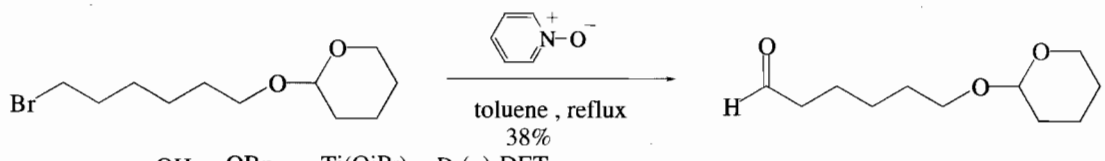
441

3.10. CONCLUSION

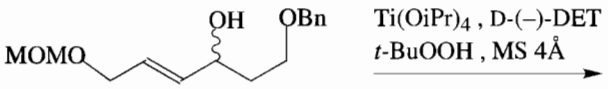
This chapter has focused on synthetically useful oxidation reactions for a variety of functional group transformations. This treatment is not comprehensive, but illustrates the various oxidation methods and reagents. These techniques will resurface in many syntheses and as part of other methodology in succeeding chapters. In Chapter 4, the reverse process, reduction, will be presented, emphasizing synthetically useful reactions and reagents.

HOMEWORK

1. The following reaction was reported in the synthesis of niphatoxin B. Give the product and suggest a mechanistic rationale for this reaction.



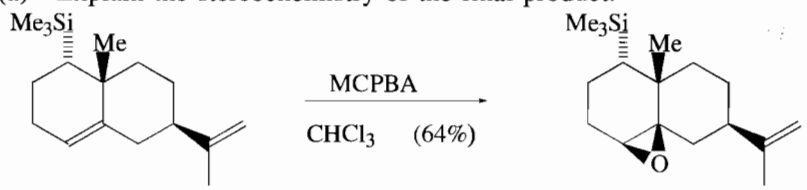
2.



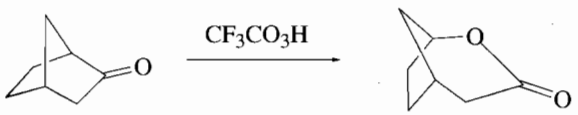
The product of this reaction was expected to be a diol-acid, and the infrared (IR) showed an OH peak and a strong carbonyl, but there was no apparent CO_2H absorption. Likewise, the ^1H NMR showed there was no CO_2H group. Show the actual product and explain why the anticipated diol-acid was not isolated.

3. Explain each of the following:

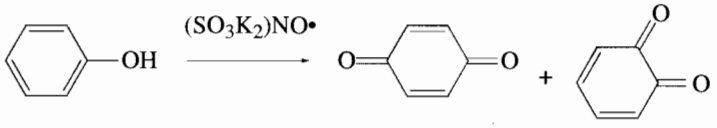
(a) Explain the stereochemistry of the final product.



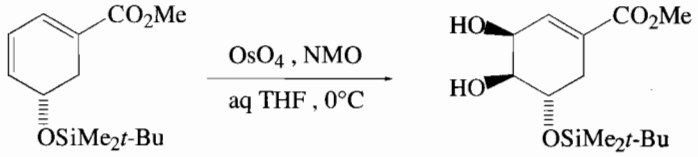
(b) Explain the regioselectivity of this reaction.



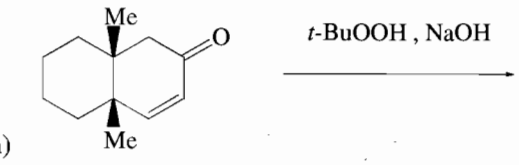
(c) Explain why *p*-quinone is the major product.



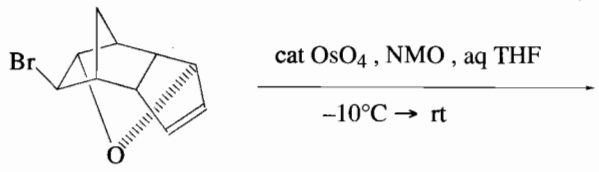
(d) Explain why the nonconjugated alkene reacts preferentially.



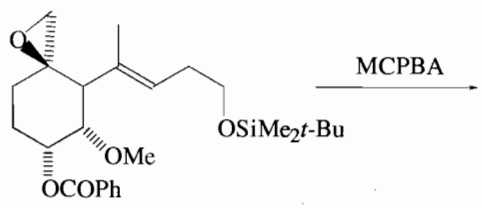
4. Give the major product of each reaction and explain the regiochemistry and/or stereochemistry where applicable.



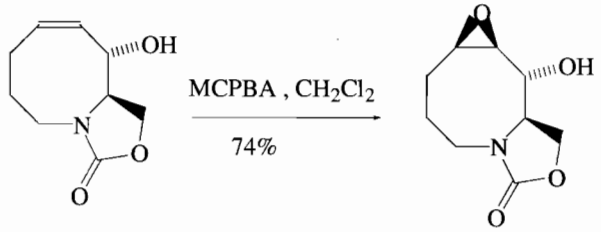
(a)



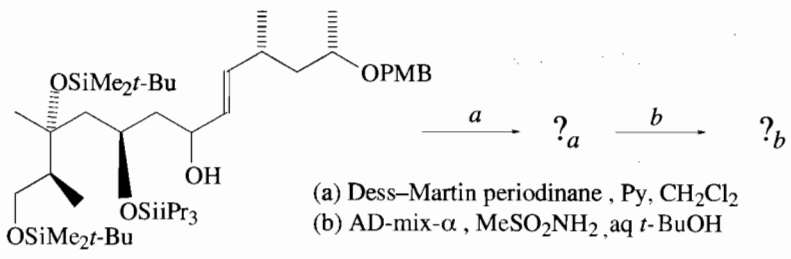
(b)



(c)

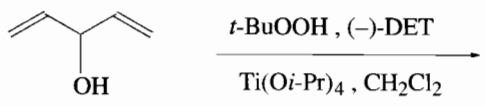


(d)

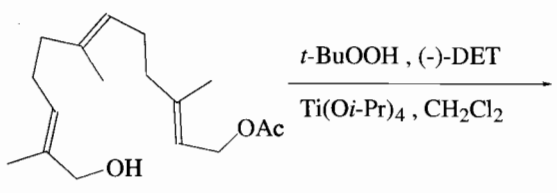


(e)

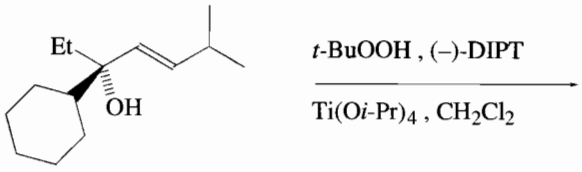
5. Predict the major product. Draw an appropriate transition state for each reaction.



(a)

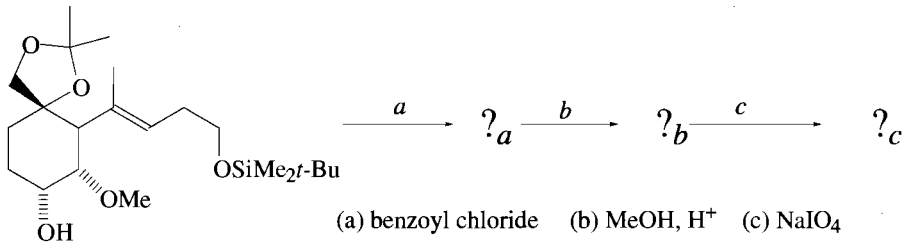


(b)



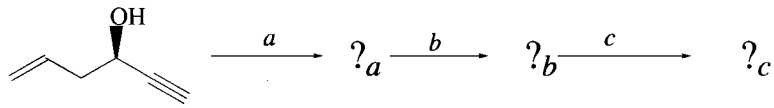
(c)

6. (a) Identify each product (?$_a$, ?$_b$, and ?$_c$) in the following sequence. It is taken from Taber's synthesis of (–)-fumagillin.



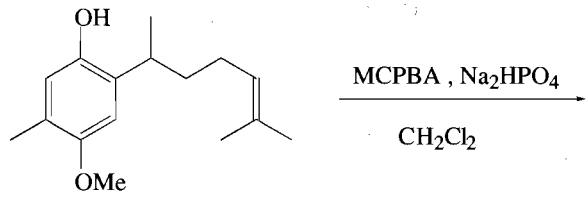
(a) benzoyl chloride (b) MeOH, H^+ (c) $NaIO_4$

(b) identify each product (?$_a$, ?$_b$, and ?$_c$) in the following sequence, taken from Smith's synthesis of (+)-thiazinotrienomycin E.

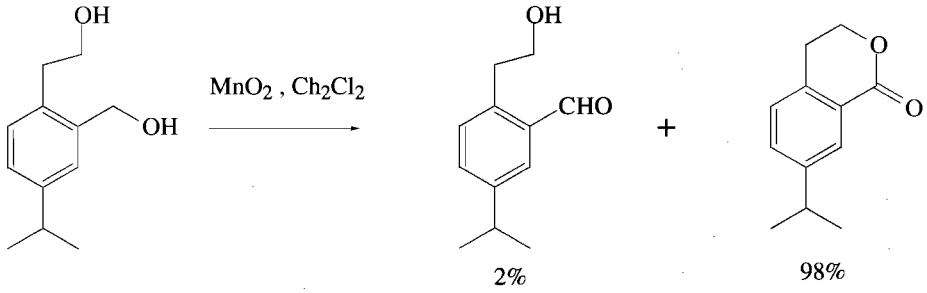


(a) BuLi , ether-DMSO ; MeI (b) O_3 ; PPh_3 (c) PDC , DMF

7. Briefly explain why treatment of the alkene shown with MCPBA in dichloromethane, and Na_2HPO_4, gave a 1:1 mixture of the two diastereomeric epoxides (draw them). This is taken from Vyvyan's synthesis of heliannuol D.

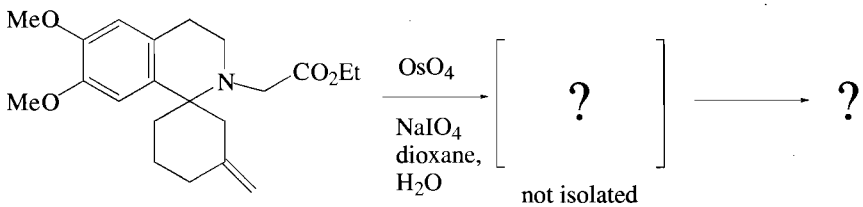


8. Provide a mechanism to explain the following transformation.

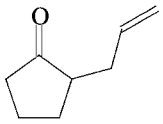


9. Give the major product for each reaction.

(a)



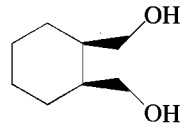
(b)



MCPBA , 5% $Sc(OTf)_3$

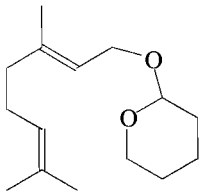
CH_2Cl_2 , rt

(c)



Ag_2CO_3 , Celite

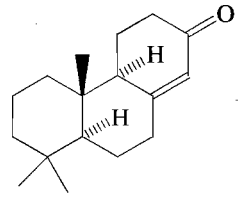
(d)



SeO_2 , SiO_2

t-BuOOH

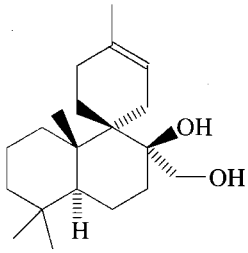
(e)



H_2O_2-NaOH

MeOH

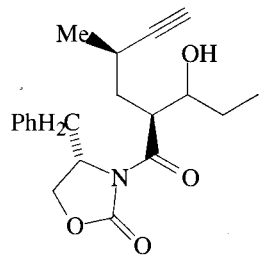
(f)



DMSO , $(COCl)_2$

NEt_3 , CH_2Cl_2

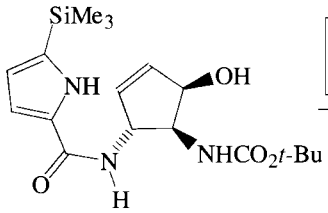
(g)

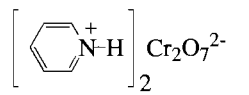


SO_3•pyridine , *i*-Pr_2NEt

DMSO , CH_2Cl_2

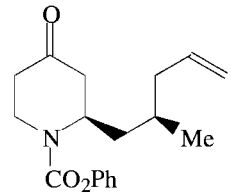
(h)





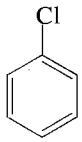
CH_2Cl_2

(i)



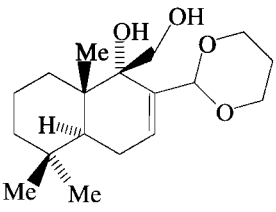
1. O_3 , MeOH
2. Me_2S

(j)



P. putida 39D

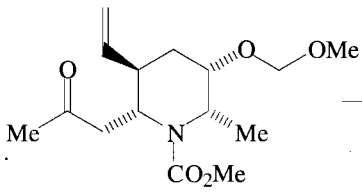
(k)



DMSO , DCC

NEt_3 , reflux

(l)

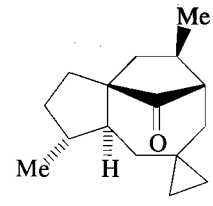


OsO_4 , $NaIO_4$

dioxane–H_2O

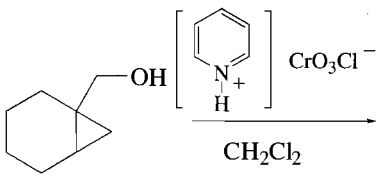
room temp

(m)



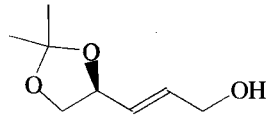
MMPP , DMF

(n)



CH_2Cl_2

(o)

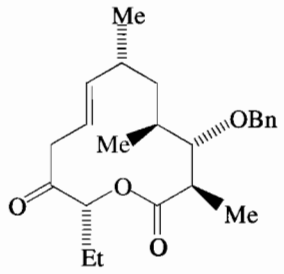


t-BuOOH , (+)-DIPT

$Ti(Oi\text{-}Pr)_4$, CH_2Cl_2

–30°C

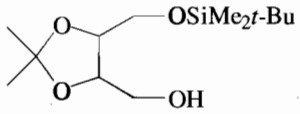
(p)



mCPBA

CCl_4

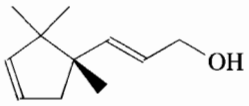
(q)



CrO_3•2 Py

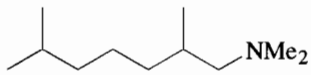
CH_2Cl_2

(r)



MnO_2

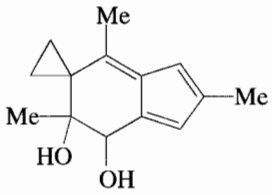
(s)

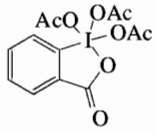


1. 30% aq H_2O_2
MeOH

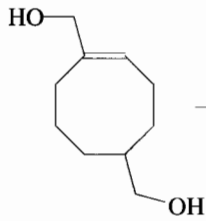
2. Py/KOH
105°C

(t)



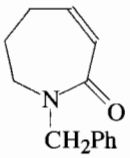


(u)



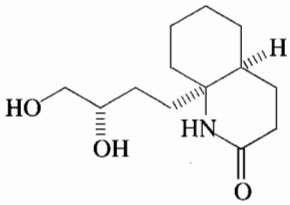
MnO_2

(v)



OsO_4 , NMO

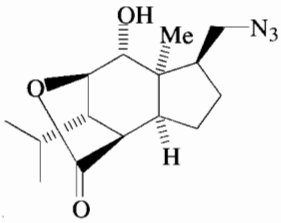
(w)



1. MsCl , collidine

2. NaOH , THF–MeOH

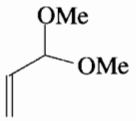
(x)



CrO_3 , H_2SO_4

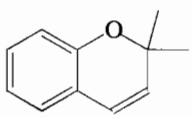
H_2O , acetone

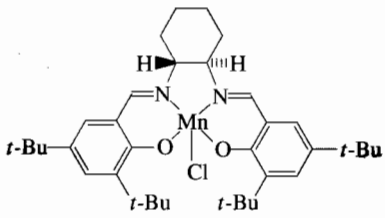
(y)



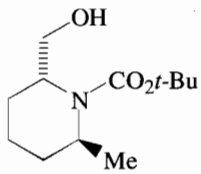
HOCl , NaOH

(z)





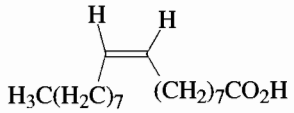
(aa)



Pr_4N^+ RuO_4^-,

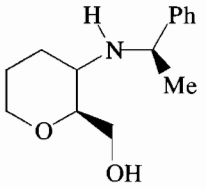
, CH_2Cl_2

(ab)



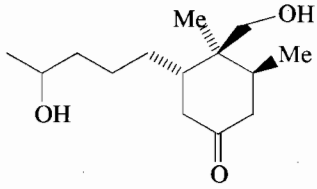
1. $KMnO_4$, dil aq NaOH
10°C
2. dil aq H_3O^+

(ac)



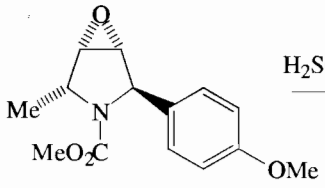
$(COCl)_2$, DMSO , NEt_3
CH_2Cl_2 , –78°C

(ad)



1. CrO_3 , H_2SO_4
aq acetone
2. K_2CO_3 , EtI

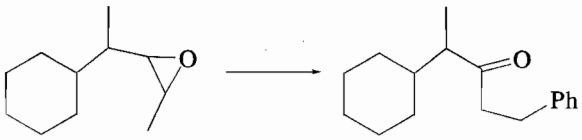
(ae)



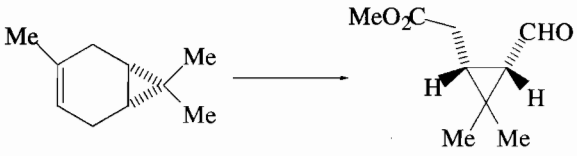
H_2SO_4 , aq dioxane
95% , 9 h

10. In each case, provide a suitable synthesis. Give all reagents that are necessary and show all intermediate products.

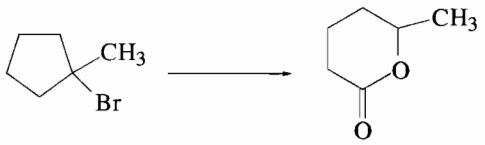
(a)



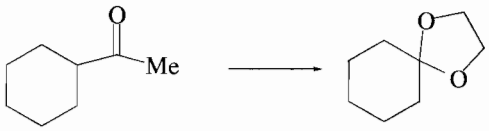
(b)



(c)



(d)



(e)

(f)

(g)

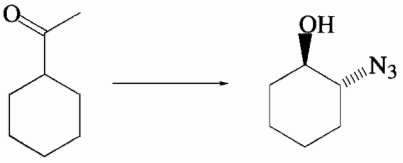
(h)

(i)

(j)

(k)

(l)



(m)

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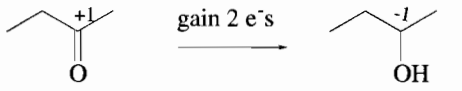
CHAPTER 4

REDUCTION

4.1. INTRODUCTION

The introduction to section 3.1 briefly reviewed oxidation reactions. Reduction reactions are equally important and many different classes of organic molecules can be reduced. If an oxidation reaction proceeds with an increase in oxidation state and a loss of electrons,[1] then a reduction reaction proceeds with a decrease in oxidation state and a gain of electrons. The concept of oxidation stage that was introduced in section 3.1 is also useful for reduction, since reduction can be defined as conversion of an atom in a higher oxidation stage to a lower one (III → II, IV → II or II → I), as in the transformation RCH=NH → RCH_2NH_2.[2] The oxidation numbers of Holleran and Jespersen,[3] and the modified method of Hendrickson, Cram, Hammond[4] and Pine[5] are useful for analyzing reduction reactions. It is also convenient to view organic reductions as the addition of hydrogen to the molecule. Examples are the reduction of 2-butanone (**1**) to 2-butanol and of propanenitrile (**2**) to butanamine, which is, of course, is not always mechanistically correct, but it is conceptually useful.



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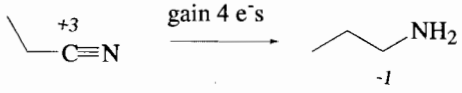

2

One measure of the ability of a reagent to reduce molecules is the reduction potential, (sec. 3.1). The standard reduction potentials for several metals and metal salts commonly used in synthesis are listed in Table 4.1.[6] For a metal to behave as a reducing agent, the reverse reaction (Li → Li^+, for example])must be facile. The high reduction potential of Li^+ → Li indicates that the Li → Li^+ reaction is favored, and lithium metal is an excellent reducing agent (by contrast, Li^+ is a very poor oxidizing agent). Conversely, Sn^{4+} → Sn^{2+} has a positive reduction potential (indicating a facile reaction), and Sn^{2+} is a reducing agent. The standard hydrogen electrode is taken as zero (0) V, (see Table 4.1), but this does not really represent the reducing power of hydrogen gas in the presence of a suitable catalyst. Hydride reducing agents are not represented in this table, although they are among the most potent reducing agents known. Since the reagents used for reduction cannot be correlated with the relatively simple metal and metal salt reagents presented in Chapter 3, no attempt will be made to use reduction potentials to illustrate the reducing power of each reagent. Only reductions that use electrolysis techniques or those that use dissolving metal conditions (sec. 4.9) are correlated with the data in Table 4.1. This table is useful, however, to reinforce the concept of gaining electrons in

organic molecules during a reduction process by showing the standard reduction potentials of metals such as lithium and sodium.

Chapter 3 was organized by functional group changes and the various reagents and techniques for each transformation were discussed. Most of the reduction techniques, despite their differences in mechanism and reagents, accomplish the same or similar functional group changes. There are, of course, differences in functional group reactivity as well as chemoselectivity (a term used by Trost) and stereochemistry for the

Table 4.1. Standard Reduction Potentials for Metals and Metal Salts

Reaction			ε (V)
Li^+	→	Li	–4.045
Ca^+	→	Ca	–4.02
K^+	→	K	–2.924
Na^+	→	Na	–2.711
Mg^{2+}	→	Mg	–2.375
Ti^{2+}	→	Ti	–1.63
Ti^{3+}	→	Ti^{2+}	–2.0
Te	→	Te^{2-}	–0.92
Zn^{2+}	→	Zn	–0.763
Zn^{2+}	→	Zn(Hg)	–0.763
Fe^{2+}	→	Fe	–0.409
Sn^{2+}	→	Sn	–0.136
$2\ H^+$	→	H_2	0.000
Sn^{4+}	→	Sn^{2+}	+0.15
Fe^{3+}	→	Fe^{2+}	+0.770

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various reagents. This chapter is organized by type of reduction with a discussion of applicable functional group transformations. The monograph on reduction by Hudlicky[7] categorizes reductions as catalytic hydrogenation, reduction with complex hydrides, electroreduction, reduction with metals and reductions with nonmetals and includes an extensive survey of specific organic functional group reductions. The reader is referred to this monograph for an excellent survey of reduction and reduction types. The order of topics in this chapter attempts to correlate a type of reduction with its relative utility in organic synthesis. This chapter will begin with hydride reductions since they are probably the most widely used, followed by catalytic hydrogenation. Reduction by various metals, including reduction by electrolysis and reduction with nonmetals will follow. The final sections will deal with miscellaneous nonmetal reductions, including photoreduction and enzymatic or microbial reductions.

Reduction of prochiral centers (sec. 1.4.E) can generate enantiomers and diastereomers. It is therefore important to introduce the models that are used to predict the diastereoselectivity or enantioselectivity of a

reduction. These stereochemical explanations are applicable to many reactions in organic chemistry. This information will be presented again in Chapter 6, but it is important that stereoselectivity be viewed as a *part of the reaction* and **not** as a separate topic. For that reason, stereoselective reactions are discussed in each chapter where they are pertinent. It will be seen that reduction includes a wide range of functional group interchanges and important synthetic processes.

4.2. REDUCTION WITH COMPLEX METAL HYDRIDES

4.2.A. Lithium Aluminum Hydride

Gaylord's monograph with the title shown for this section,[8] as well as his contemporary review,[9] describes hydride reducing agents that were used until 1957. The two most common hydride reducing agents are lithium aluminum hydride ($LiAlH_4$), and sodium borohydride ($NaBH_4$, to be discussed in sec. 4.4).[10] The synthesis and initial applications of $LiAlH_4$ for reduction of organic compounds were reported by Schlesinger and co-workers[11] and Brown and co-workers[12] in 1947. Lithium aluminum hydride was prepared by reaction of lithium hydride (LiH) with aluminum chloride ($AlCl_3$).[13] Sodium borohydride was first prepared by reaction of sodium hydride (NaH) with trimethylborate, $B(OMe)_3$.[13,14]

$$4\ LiH + AlCl_3 \xrightarrow{\text{ether}} LiAlH_4 + 3\ LiCl$$

$$4\ NaH + B(OMe)_3 \longrightarrow NaBH_4 + 3\ MeO^- Na^+$$

Further studies showed that replacement of the hydrogen in $LiAlH_4$ or $NaBH_4$ with alkyl or alkoxy groups led to a variety of reducing agents with modified reducing abilities, chemoselectivities, and stereoselectivities. Lithium aluminum hydride is one of the most powerful reducing agents known for organic substrates bearing a polarizable functional group. This reagent is stable at ambient temperatures but reacts violently with moisture, giving hydrogen gas, lithium hydroxide ,and aluminum hydroxide (hydrated alumina), as shown in the following reaction:[9]

$$LiAlH_4 + 4\,H_2O \longrightarrow LiOH + Al(OH)_3 + 4\,H_2$$

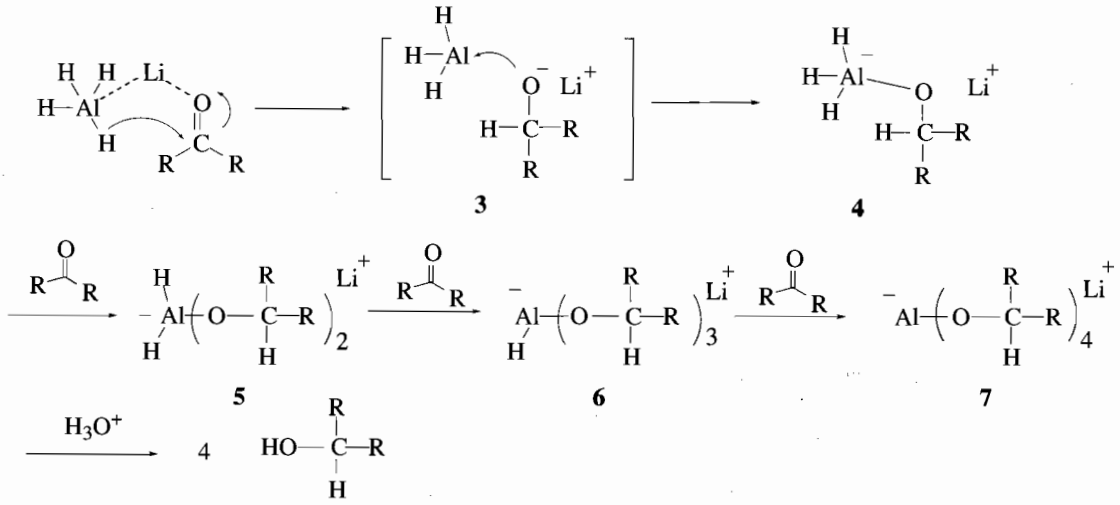
This moisture does not have to be inadvertently added water. It can arise from "inadequately dried apparatus, fingerprints, and perspiration-soaked gloves", leading to ignition.[15] Although this reagent is commercially available as a powder, lumps are also available. *"Lumps are best crushed by cautious pounding with a hard rubber hammer in a tray with an aluminum foil liner. Grinding with a mortar and pestle should be done in a dry box in an atmosphere of nitrogen or argon.... If ground too vigorously in the presence of air the hydride may take fire."*[15] The purpose of these quotations from Fieser is to emphasize the reactivity of $LiAlH_4$ and the danger of mishandling this reagent.

Lithium aluminum hydride has some solubility in ether solvents but tends to form a slurry when relatively large amounts of the reagent are used. The solubility of $LiAlH_4$ in ether is 35–40 g/100 g of ether but obtaining this solubility requires concentration of a more dilute solution.[14] The solubility is 13g/100 g in THF

and 0.1 g in dioxane,[14] which are also commonly used solvents. The reagent is usually represented as $Li^+[AlH_4^-]$ and exists as aggregates of solvated lithium ions and aluminohydride ions in diethyl ether.[16] Such slurries of $LiAlH_4$ are capable of reducing virtually all polarized organic functional groups, as described by Gaylord.[9,8] Molecules with an acidic hydrogen such as acids, alcohols, amines, etc. may react with lithium aluminum hydride in an acid–base reaction to generate hydrogen gas with destruction of the active hydride.

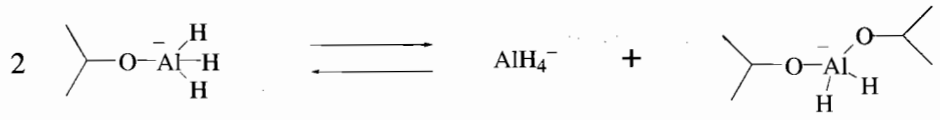
4.2.B. Reduction of Carbonyl Compounds

Lithium aluminum hydride rapidly reduces most carbonyl compounds, including aldehydes and ketones,[17] carboxylic acids, acid anhydrides, acid chlorides, esters, lactones, amides, carbamates, imides, and lactams.[18] Most $LiAlH_4$ reductions of carbonyl compounds begin by coordination to the carbonyl oxygen followed by transfer of the nucleophilic hydride (oxygen is polarized δ– relative to aluminum) to the electrophilic carbonyl (carbon is polarized δ+ relative to oxygen). House illustrated this mechanism for the $LiAlH_4$ reduction of acetone, showing the stepwise formation of alkoxyaluminate intermediates.[16] Initial transfer of hydride to the carbonyl generates **4**, possibly via direct coordination of aluminum to oxygen and transfer of hydride to the carbonyl carbon. Complex **3** has also been proposed as an intermediate. Since **4** contains three active hydrides, a second equivalent of carbonyl can react to give **5**. Similarly, a third equivalent gives **6** and a fourth



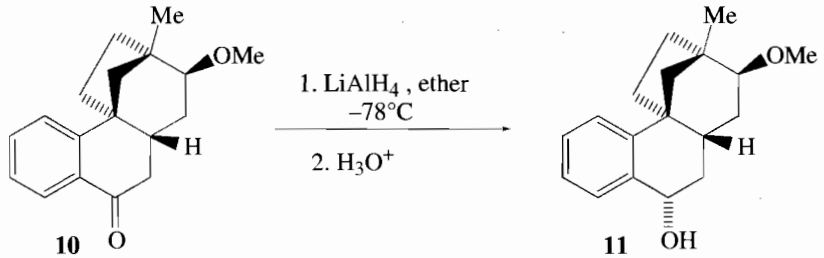
gives **7**. The reactivity of each new hydride intermediate with the carbonyl substrate decreases with the increasing number of electronegative alkoxy substituents.[15] It is not always obvious how many carbonyl units add to $LiAlH_4$ for a given substrate. In principle, 1 mol of acetone reacts with 4 equivalents of hydride (which is $\frac{1}{4}$ mole of $LiAlH_4$) to give **7** (R = Me). A very bulky ketone such as 2,4-dimethyl-3-pentanone (diisopropyl ketone) gives a different result. It reacts with $LiAlH_4$ to give **4** or **5** (R = *i*-Pr). Addition of the carbonyl compound to $LiAlH_4$ (a 1:1 molar ratio), followed by titration of the complex with water or aqueous acid will release hydrogen gas from the unreacted hydrides. The hydrogen gas can be trapped, allowing an exact determination of the number of carbonyl molecules that reacted with the tetrahydroaluminate. In general, at least 1 M equivalent (four equivalents of H^-) or more are added to the carbonyl moiety to ensure complete

reduction. A complicating factor is that alkoxyaluminate intermediates are subject to disproportionation, as in the reversible interconversion of **8** to **9**,[16,19] which is more of a problem with increasing steric bulk around the carbonyl carbon (ketone > aldehyde; 2° carbon > 1° carbon). Disproportionation regenerates the tetrahydroaluminate anion that can cause problems of overreduction, loss of functional group specificity, and stereoselectivity.[16]



8 **9**

The final alcohol product from the reduction of $R_2C{=}O$ is released by treatment of **7** (or any other alkoxyaluminate product) with acid or base. The net reaction involves protonation of the alkoxide base but reaction at aluminum occurs in both acidic and basic media. In many cases, titration with water is sufficient to release the alcohol, but saturated ammonium chloride or dilute hydrochloric acid are sometimes necessary. Aqueous or acidic workup of a $LiAlH_4$ reaction is exothermic and evolves hydrogen gas, which leads to frothing. Since volatile ether solvents are usually employed, isolation of the alcohol can be difficult and sometimes dangerous with large scale reactions. If excess water is added, the alumina salts formed during the hydrolysis can form a paste, which is difficult to filter. Fieser and Fieser described[20a] Mićović and Mhailović's basic workup procedure,[20b,c] which has several advantages. It produces a granular precipitate that is easily filtered [for *n* grams of $LiAlH_4$ *n* mL of water, then n mL of 15% NaOH followed by 3*n* mL of water]. Although this information is best found in a lab manual, in fact, the choice of a reducing agent is often dictated by the relative ease of isolation of a given product and this discussion is offered with that in mind.



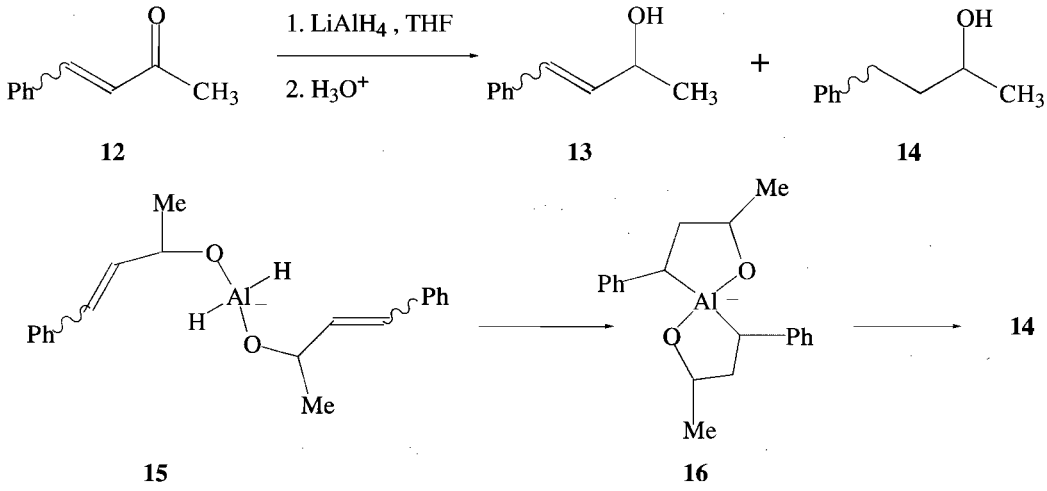
10 **11**

The rate of reduction of aldehydes is faster than that of ketones, because there is less steric hindrance for delivery of hydride to the carbonyl carbon. In extreme cases, reduction of highly hindered ketones may have a half-life that measures in days, but rarely does reduction fail to occur in contrast to results obtained with other reducing agents such as sodium borohydride[21] (sec. 4.4), which reduces only selected functional groups. A typical synthetic use of this reaction is reduction of the ketone moiety in **10** to give alcohol **11** (quantitative yield) in Overman's synthesis of scopadulcic acid B.[22] The conversion of heptanal to 1-heptanol (ether, reflux, 15 min) in 86% yield is an example of the reduction of aldehydes with $LiAlH_4$.[12]

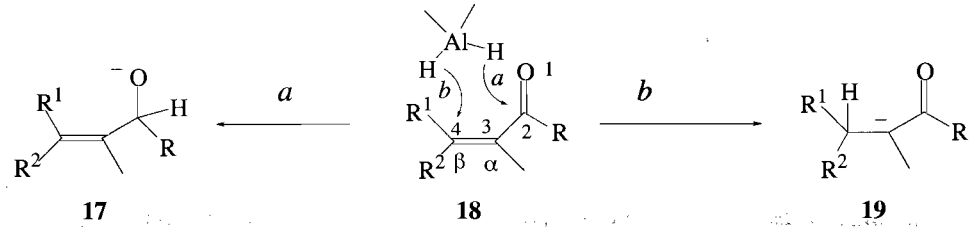
One of the more important characteristics of carbonyl reduction with $LiAlH_4$ is the diastereoselectivity of the reaction when reduction introduces a second stereogenic center. As a general rule, hydride is delivered to

the less sterically hindered face of the molecule, *unless* special chelation or coordination effects are present. Reduction of **10** to **11** illustrates this principle.[22] We will discuss this concept in detail in section 4.7.

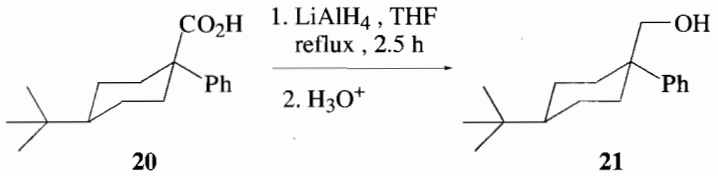
Reduction of α,β-unsaturated carbonyl derivatives poses a potential problem. Reduction of benzalacetone (**12**) can lead to either the allylic alcohol (**13**), via normal 1,2-addition of hydride to the carbonyl, or to the saturated alcohol (**14**) via 1,4-reduction (delivery of hydride to the alkenyl carbon).[23] Initial 1,2-reduction leads to a bis-(alkoxyaluminate) (**15**), which is apparently converted to an intermediate such as **16**[24] as generalized in **18**. If reduction proceeds via coordination of the aluminum to the carbonyl oxygen, 1,2-reduction occurs via path *a* (to give **17**), which is the usual transition state (see **3** and **4**). The β-carbon in **18** is polarized with a positive dipole, however, and hydride can also be delivered to the β-carbon via path *b* (a six-center transition state). This path leads to conjugate (1,4) addition and enolate **19** as the product. If the R group in **18** is small (such as a hydrogen in conjugated aldehydes), 1,2-addition predominates. As the R^1 and/or R^2 groups increase in size, delivery to the β-carbon is sterically inhibited (giving more **17**). Conjugate reduction is common for conjugated ketones, where the β-carbon is relatively unhindered. Conjugate reduction is rare for conjugated aldehydes, although there are a few reagents that give this product in high yield (see the discussion for aluminum hydride in sec. 4.6.B).



House pointed out that **16** can disproportionate (as mentioned above) or that another mechanism may be operative in this reduction.[24] Inverse addition of the hydride (a slurry of $LiAlH_4$ is added to the carbonyl compound), short reaction times, and low reaction temperatures generally give moderate to good yields of the conjugate reduction product.[24] Good yields of allylic alcohols can often be obtained from α,β-unsaturated aldehydes, however, when the reaction is done at low temperatures with strict control of the stoichiometry.



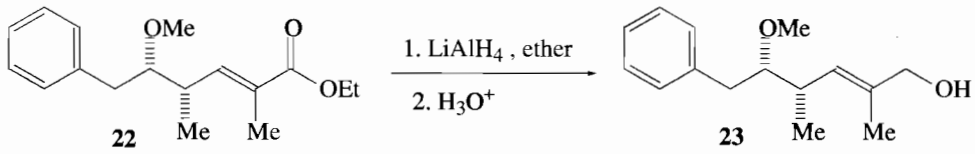
Reduction of carboxylic acids with 1 mole of $LiAlH_4$ consumes three of the four hydrides that are available,[25] and the reduction product is an alcohol. The acid has the acidic hydrogen of the OH unit, and this reacts first. Subsequent reduction of the carbonyl unit leads to the usual alkoxyaluminate, which is hydrolyzed to the alcohol. Reduction of acid **20** to alcohol **21** in 87% yield is a useful example.[26] Reduction of acids to alcohols bearing a heteroatom at the α-position is also possible.



20 **21**

Acid derivatives are also reduced by $LiAlH_4$. Reduction of the highly reactive acid chlorides[12] and acid anhydrides[27] is rapid. Partial reduction of aromatic anhydrides to lactones has been reported by controlling the stoichiometry of $LiAlH_4$ and the anhydride.[28] In most cases, however, complete reduction to the diol occurs.[27,12,28]

Reduction of esters to hydroxymethyl derivatives is straightforward and both nitrogen and oxygen containing substituents can be tolerated in the reduction. A commonly used reduction involves acetates, which are converted to the alcohol ($RCH_2OAc \rightarrow RCH_2OH$, where the acetate serves as a protecting group for the alcohol

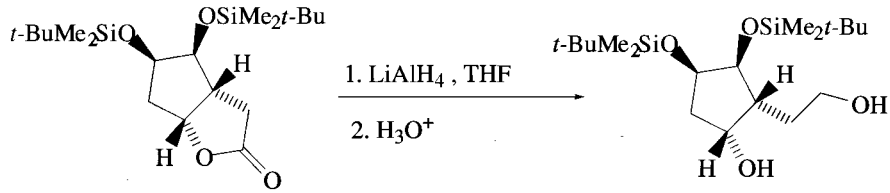


22 **23**

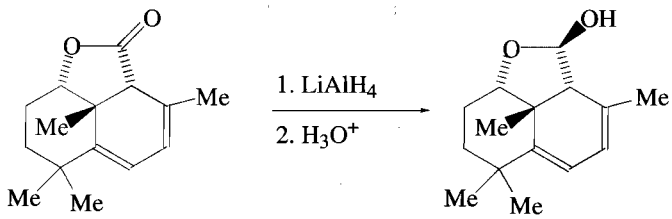
and is removed by reduction – sec. 7.3.A.ii). The reduction proceeds without loss of stereochemistry at the adjacent carbon. Readily available amino esters (derived from naturally occurring amino acids) serve as a source for the preparation of chiral amino alcohols, which have a variety of uses in synthesis.[29] The 1,2-reduction of conjugate esters leads to allylic alcohols, under the proper reaction conditions. 1,4-Reduction of conjugated esters is often a problem, as it is with conjugated aldehydes and ketones, but selective 1,2-reduction is easily attained as shown by the conversion of **22** gave **23**, taken from Armstrong's synthesis of motuporin (also known as nodularin-V).[30]

The related reduction of cyclic esters (lactones) leads to a useful synthesis of diols. Reduction of δ-valerolactone, for example, gave an 85% yield of 1,5-pentanediol.[31] The number of carbons separating the hydroxyl units is determined by the size of the lactone ring.[32] Stereogenic centers adjacent to the oxygen and carbonyl of the lactone are not compromised during the reduction.[33] The conformational bias of the lactone ring can be used to control the relative stereochemistry of substituents as they are incorporated on the ring (Chap. 6). Ring opening by $LiAlH_4$ reduction occurs with retention of the relative and absolute stereochemistry of the substituents, allowing control of their stereochemistry in the acyclic system (sec. 6.5). Lactone **24**, for example, was reduced to diol **25**.[34] This diastereomer was required for Willis' synthesis of the pseudomonic acids.[34] In some cases, it is possible to achieve partial reduction of a lactone with $LiAlH_4$. When the

lactone carbonyl is sterically hindered, as in **26**, partial reduction is possible. In this case, lactol **27** was formed in > 80% yield.[35] . In general, however, partial reduction of lactones with $LiAlH_4$ is *difficult* and one normally expects that $LiAlH_4$ reduction will give a diol.

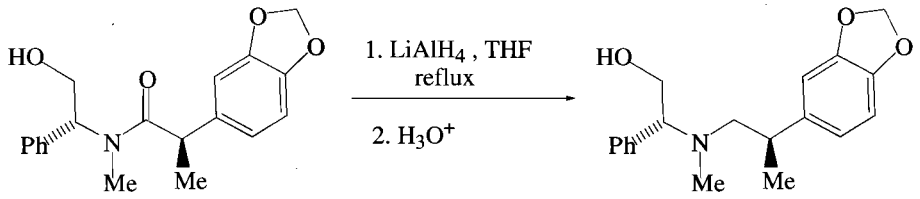


24 **25**



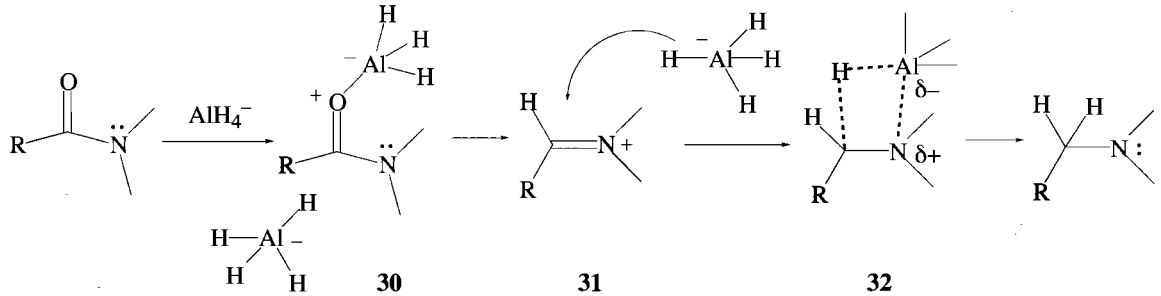
26 **27**

Amides react with $LiAlH_4$ differently than do other carbonyl derivatives. Reaction with $LiAlH_4$ gives an intermediate iminium salt, which is further reduced to an amine as the final product. The net result of this two–step process is complete removal of oxygen from the molecule, illustrated by the reduction of amide **28**, which gave amine **29** in ≈ 85% yield from Quirion's asymmetric synthesis of 1,4-disubstituted tetrahydroisoquinolines.[36] The reaction proceeds by initial transfer of hydride to the amide, forming a complex such as



28 **29**

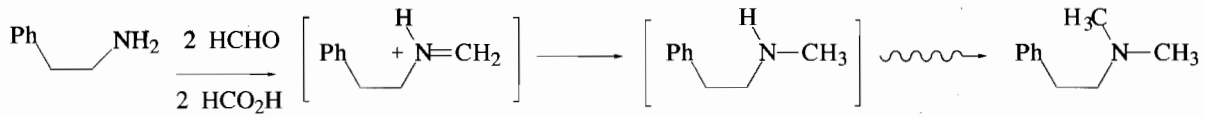
30. Further reduction and subsequent elimination of the alkoxyaluminate leads to an intermediate iminium salt (**31**). Addition of another hydride (as in **32**) and hydrolysis gives the amine.[37] As the steric hindrance on



30 **31** **32**

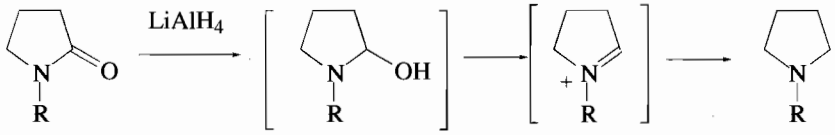
nitrogen increases coordination, and delivery of hydride is more difficult. Cleavage of the C—N bond can occur to give an aldehyde (which is reduced to the alcohol) and an amine. This is usually observed when the electron-donating ability of the nitrogen is diminished by substituents, but the yields are often poor.

Reduction of an amide provides a route to amine derivatives since the oxygen atom is removed. Formamide derivatives are easily synthesized by reaction of amines with ethyl formate, for example, and subsequent reduction provides an effective method for monomethylation and dimethylation of amines. Reaction of 2-phenylethanamine with formaldehyde and formic acid gave iminium salt **33** as a reactive intermediate, which



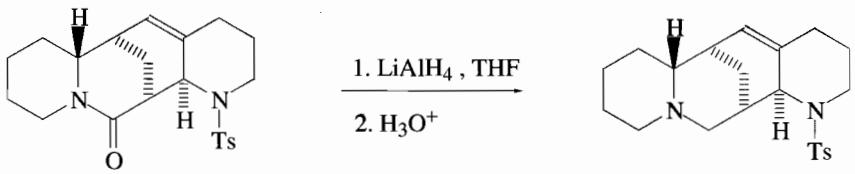
33 **34** **35**

was reduced by formic acid to the *N*-methyl derivative (**34**). Further reaction with formaldehyde and reduction with formic acid led to the dimethylamino product (**35**) in 83% yield.[38] Formic acid reductions are also discussed in section 4.10.D. A related reaction is the reduction of benzamide derivatives to the *N*-benzyl derivative.[39] Benzamides are easily prepared by reaction of an amine with benzoyl chloride or bromide. For all practical purposes, imides can be considered as cyclic amides, and $LiAlH_4$ reduction usually proceeds with cleavage to give an amine and an alcohol fragment.



36 **37** **38** **39**

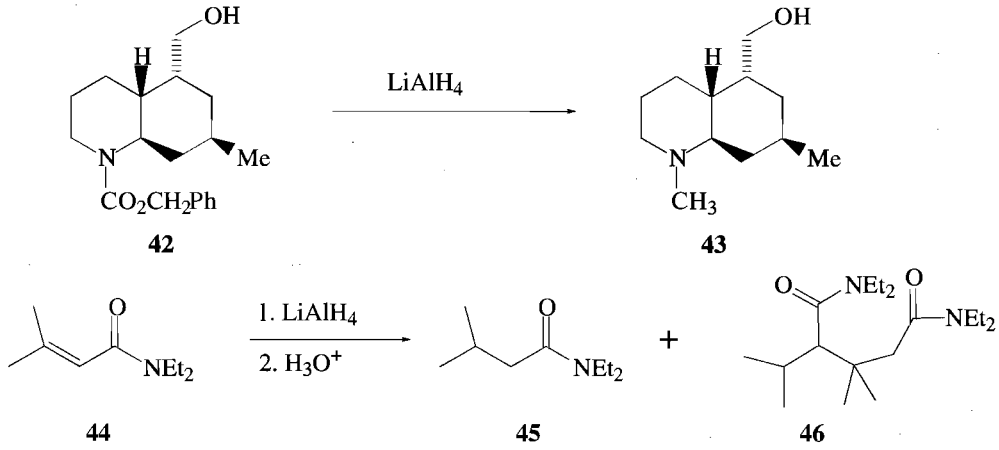
Lactams are cyclic amides and they are reduced by $LiAlH_4$ to the cyclic amine. The reduction of a typical lactam such as 2-pyrrolidinone derivative **36** presumably proceeds via initial formation of the α-amino alcohol (**37**), followed by elimination to an iminium salt (**38**), and then reduction by hydride to give the amine (**39**). This reaction is very useful in the synthesis of alkaloids, as seen in the reduction of **40** to **41** in 88% yield as part of Overman's synthesis of (+)-aloperine.[40] The lactam nitrogen is significantly less basic than the corresponding amine and cyclic amines are often protected as the lactam. The amine is then unmasked late in the synthetic sequence by hydride reduction.



40 **41**

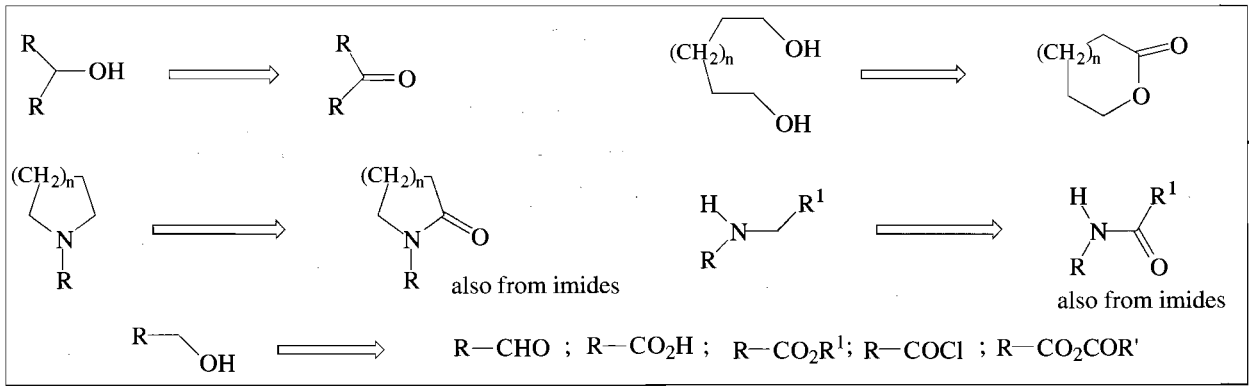
Carbamates are characterized by a O—CO—N group, which has an electron withdrawing ester unit on the nitrogen. Amines are easily converted to carbamates (sec. 7.3.C.iii) and reduction usually proceeds with

cleavage of the C=O bond to give a methylated amine.[41] An example is the reduction of **42** to **43**, as part of Comins' synthesis of *N*-acetyl-*N*-methylphlegmarine.[42] This protocol is an alternative to the direct methylation of amines seen in section 2.7.A.i, which commonly gives polymethylated products upon reaction with iodomethane. It is also possible to reduce the alcohol portion of the carbamate. Reduction of a benzyl carbamate gives a benzylic alcohol, for example (this is called a Cbz protecting group; see sec. 7.3.C.iii).[43]



Conjugated amides can undergo both 1,2- and 1,4-addition with hydrides, but there is another competing side reaction. Reductive coupling is possible via generation of an intermediate amide enolate.[44] Reduction of the relatively hindered *N,N*-diethyl-3,3-dimethylacrylamide (**44**) gave a 47% yield of the expected conjugate reduction product **45**, but also 12% of the enolate condensation product **46**.[44] Enolate condensations are discussed in Chapter 9.

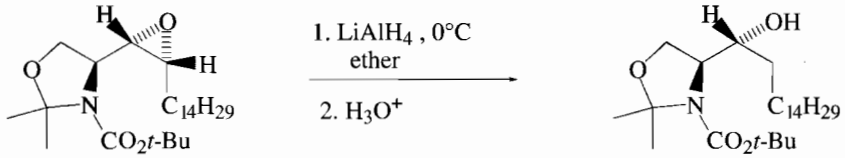
It is clear that the principal reduction product of carbonyl derivatives is an alcohol. Succeeding sections will discuss the reduction products observed for functional groups that do not contain a carbonyl group. The functional group transforms for this section include:



4.2.C. Lithium Aluminum Hydride Reduction of Non-Carbonyl Heteroatom Functional Groups

As shown by Gaylord,[8] lithium aluminum hydride reduces virtually every heteroatom containing functional group known. This section will explore the reduction of several heteroatom-containing functional groups that are commonly seen in synthesis.

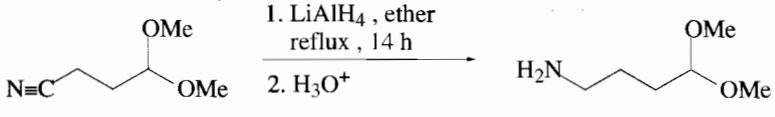
4.2.C.i. Epoxides. Epoxides are easily generated from alkenes[45] (sec. 3.4) and also from ketones and aldehydes[46] (sec. 8.8.B). They are one of the most useful of all oxygenated functional groups. Reduction of epoxides leads to alcohols.[47] Lithium aluminum hydride delivers hydride to the less sterically



47 **48**

encumbered carbon of an epoxide,[48] and often proceed with excellent selectivity. An example is the reduction of **47** to alcohol **48** (86% yield) in Azuma and Ogino's synthesis of sphingosine.[49] If the attacking reagent has a choice of primary versus secondary or secondary versus tertiary, there is selectivity for the less hindered carbon. Epoxides can give products where delivery of hydride is to the more substituted carbon[50] when the epoxide oxygen can coordinate with the aluminum (via an *ate* complex). Delivery of hydride can occur intramolecularly to the most electropositive carbon, although intermolecular delivery is also possible.[51]

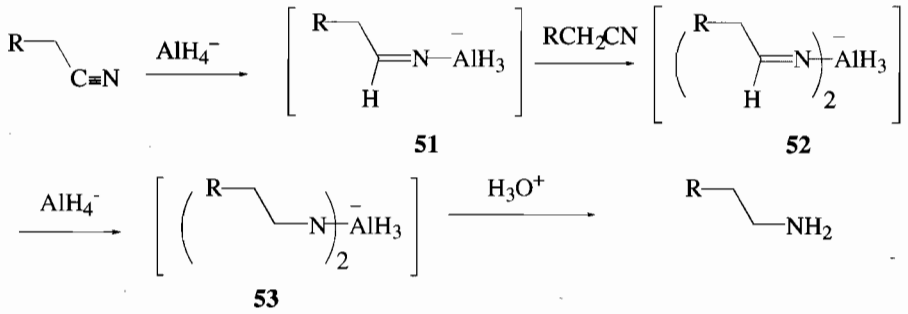
4.2.C.ii. Ozonides. Ozonolysis is a powerful method for cleaving alkenes to carbonyl products (sec. 3.7.B). Ozonolysis of alkenes initially generates an ozonide that can be reduced by a variety of reagents. Dimethyl sulfide or zinc in acetic acid are the most common reagents for the reduction of an ozonide to an aldehyde or ketone. Reduction of the ozonide with the more powerful lithium aluminum hydride, however, gives direct conversion to the alcohol.



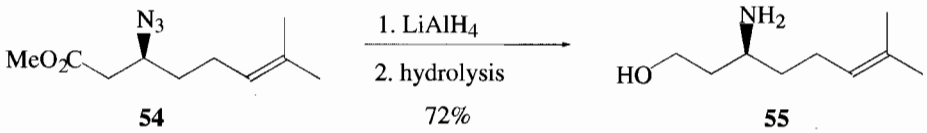
49 **50**

4.2.C.iii. Nitriles. Nitriles are synthetic precursors for both functional group transformation and carbon-carbon bond forming reactions (secs. 8.2, 9.4.B.iv). They are usually formed by a S_N2 substitution reaction in which cyanide displaces a leaving group from an alkyl halide or sulfonate ester but dehydration of amides (secs. 2.7.A.i, sec. 8.2) is also an important synthetic route. Once the nitrile has been formed, reduction of the cyano group with $LiAlH_4$ usually gives a primary amine,[52] allowing nitriles to function as protected (latent) aminomethyl groups, as in the conversion of **49** to **50**.[53] The amine product is sometimes trapped (protected, sec. 7.3.C) by reaction with an acyl halide to give an amide, since this allows further synthetic manipulation. The reaction proceeds via initial reduction to an iminium salt (**51**), which is converted to a bis-(iminoaluminate)(**52**).[54] The literature is rather vague concerning the specific structure of this intermediate, but reduction of **52** with additional hydride leads to **53**, as reported by Soffer and Katz.[54] The hydrogens in the final amine product probably come from hydrolysis although the nature and substitution pattern of the nitrogen in **53** was not specified. The aluminum in **53** may be coordinated by solvent (usually ether or THF) or a second

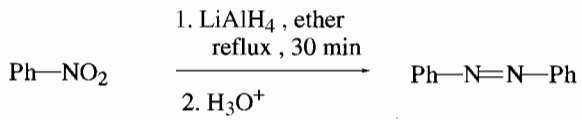
aluminum species. In some cases, removal of the α-proton occurs to give the α-lithio nitrile (sec. 9.4.B.iv), especially when a hydride slurry is added to the nitrile solution (inverse addition).[54] A dimeric product is formed, indicative of an enolate condensation. Addition of butanenitrile to lithium aluminum hydride gave butanamine in 79%, for example, but inverse addition in ether gave only 34% of that amine. Inverse addition also led to 26% of 2-ethyl-1,3-hexanediamine, presumably via a **Thorpe condensation**[55] (sec. 9.4.B.iv) of an intermediate nitrile carbanion.[54]

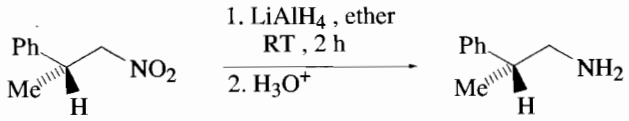


4.2.C.iv. Azides. Azides are important precursors to amines.[56] The azide anion (N_3^-) is an excellent nucleophile and S_N2 displacement of primary and secondary halides (or alkyl sulfonates) with sodium azide (sec. 2.7.A.i) gives the corresponding alkyl azide. Lithium aluminum hydride reduction of the azido group in **54** gave a primary amino group (R—N_3 → R—NH_2), and the ester group was simultaneously reduced to an alcohol, giving **55** in 72% yield. This transformation was part of Overman's synthesis of ptilomycalin A.[57]



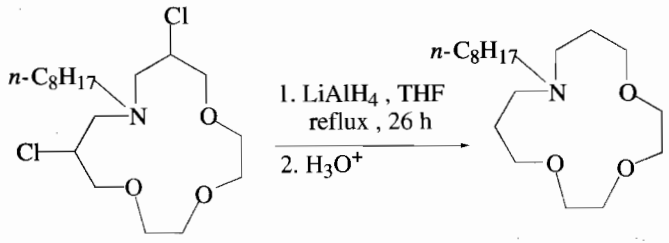
4.2.C.v. Nitro Compounds. Aliphatic nitro compounds can be reduced to amines,[58] so they also function as amine surrogates. Aliphatic nitro compounds are reduced to primary amines in excellent yield. Reduction of nitriles or azides is usually the preferred method to introduce an amino group since reactions that introduce the nitro group often require strong acid. Aromatic nitration (sec. 2.11.B) is relatively easy, however, and reduction to aniline derivatives would be a very attractive synthetic route to this important class of amines. Hydride reduction is not straightforward, however, as seen in the $LiAlH_4$ reduction of nitrobenzene, which does not give aniline but rather an azo compound, **56** (in 84% yield).[59] This fundamental difference in reactivity is illustrated by comparing formation of **56** with reduction of primary nitro compound **57** to the amine (**58**, in quantitative yield).[60] Catalytic hydrogenation (see sec. 4.8.D) is the best method for the reduction of aromatic nitro compounds to aniline derivatives.





57 58

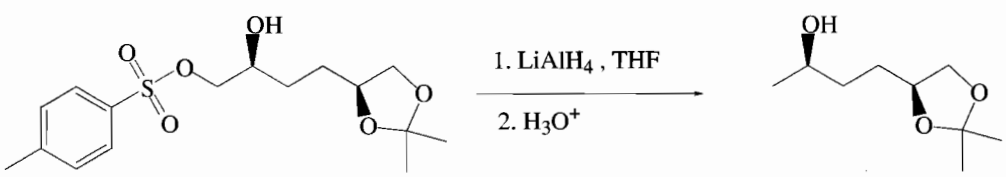
4.2.C.vi. Alkyl Halides. Alkyl halides are reduced by lithium aluminum hydride to give a hydrocarbon in what is known as a **hydrogenolysis** reaction ($R_3C—X \rightarrow R_3C—H$; sec. 4.8.E).[61] Reduction of 1-bromobutane



59 60

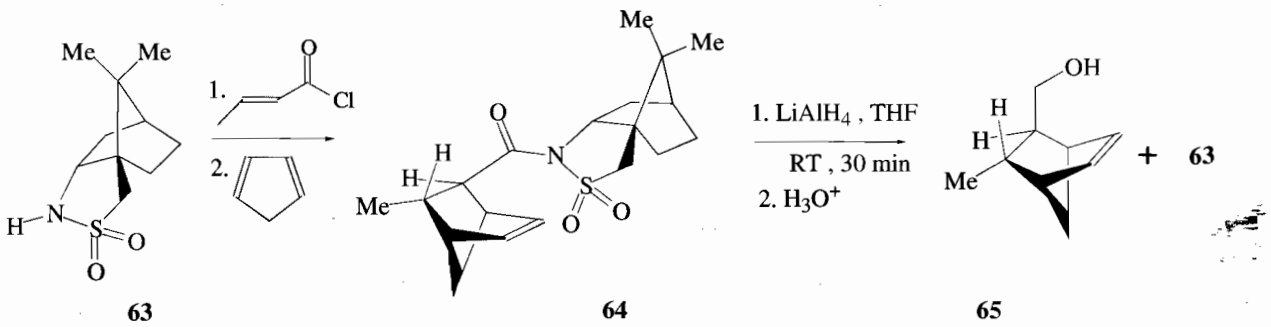
in ether, di-*n*-butylether, or THF gave yields of *n*-butane in the 30–96% range.[59,31] The reduction of **59** to **60** in 72% yield is an example of this reduction.[62] Benzylic halides are relatively easy to reduce when compared to aliphatic halides and only require treatment with $LiAlH_4$ in ether solvents.[63] Electronic effects can influence the yield, as seen in the reduction of trityl chloride [$Ph_3C—Cl$] to triphenylmethane [$Ph_3C—H$] in 98% yield. Aryl halides are resistant to reduction with $LiAlH_4$,[64] but activated halides such as 2-chloro-1-iodobenzene can be reduced (40% yield of chlorobenzene was obtained upon reaction with $LiAlH_4$). Electron-releasing groups such as methyl or methoxy enhance the yield of reduction products,.[65] Hydride reduction of allylic halides is sometimes plagued by reductive elimination as a competitive side reaction.

4.2.C.vii. Sulfonate Esters. Sulfonate esters are readily formed by reaction of alcohols with sulfonyl halides and are reduced to the hydrocarbon with $LiAlH_4$, via cleavage of the C—O bond.[61] Reaction of the tosylate group in **61** with $LiAlH_4$ via hydrogenolysis of the C—O bond gave **62** in high yield in Kibayashi's synthesis of (–)-(*3R,6S,9R*)-decarestrictine C_2.[66] Despite the success of this experiment, low yields (<50%) are common in this reaction. Alkyl sulfonate groups are also reduced with $LiAlH_4$,[67] and cleavage of the C—O bond in primary tosylates (—CH_2OTs) or mesylates (—CH_2OMs) to a methyl group is probably the most common application.[68,69] Formation of an alcohol (via S—O bond cleavage) is often observed, accounting for the low yields mentioned above. Cleavage of the S—O bond most often occurs when the C—O bond (the alcohol group) is sterically hindered.



61 62

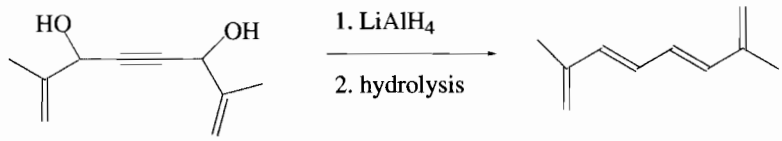
4.2.C.viii. Sulfonamides. Reduction of sulfonamides does *not* give an alcohol and an amine. Primary sulfonamides resist reductive cleavage with $LiAlH_4$; secondary sulfonamides are cleaved, but the reaction requires



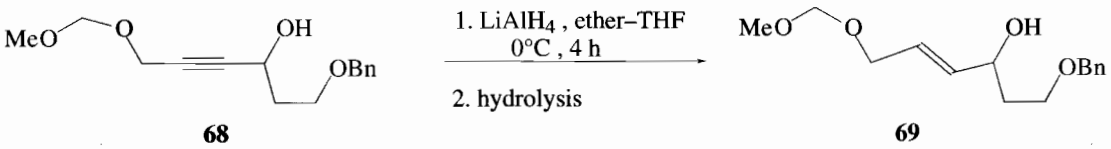
63 64 65

temperatures of 120°C in dibutyl ether.[70] Exceptions to this sluggish reactivity occur when the sulfonamide is conjugated to a carbonyl moiety. Oppolzer et al. developed a chiral sulfonamide auxiliary (sultam **63**) derived from camphor,[71] and attachment of this auxiliary allows high asymmetric induction in a variety of reactions. In a synthesis of loganin, **Diels–Alder reaction** (sec. 11.4.A) of an acrylate derivative of **63** and cyclopentadiene gave sulfonamide **64**.[72] Reductive cleavage of the sulfonamide with lithium aluminum hydride removed the auxiliary to give, in this case, alcohol **65**. It is noted, however, that complete removal of this group is sometimes a problem that limits the utility of this auxiliary.

4.2.C.ix. Alkyne-Alcohols. This elimination process can be turned to an advantage when propargylic alcohols are reduced.[73] The so-called **Whiting reaction**[74] reduces an alkynyl diol such as **66** with $LiAlH_4$ to give a diene (**67**, cosmene) via addition of four hydrogen atoms followed by formal elimination of 2 equivalents of water. In general, alkene and alkynyl moieties are not reduced by lithium aluminum hydride, but as noted in the Whiting reaction, propargylic alcohol derivatives ($C{\equiv}C{-}CH_2{-}OH$) are important exceptions.[75,76] Alkyne alcohols as well as diols can be reduced by this method. Reduction of alkynyl alcohols, readily formed via condensation of alkyne anions with aldehydes and ketones (sec. 8.3.C), generally gives the trans-allylic alcohol. Alkynyl-alcohols can also be reduced to allylic alcohols, as in the conversion of **68** to **69** in 90% yield, in a synthesis of hastanecine by Mulzer and Scharp.[77]

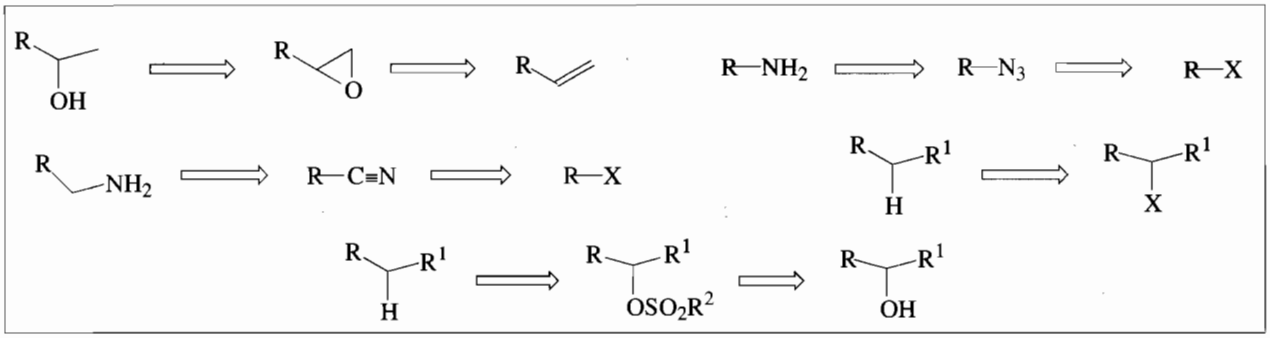


66 67



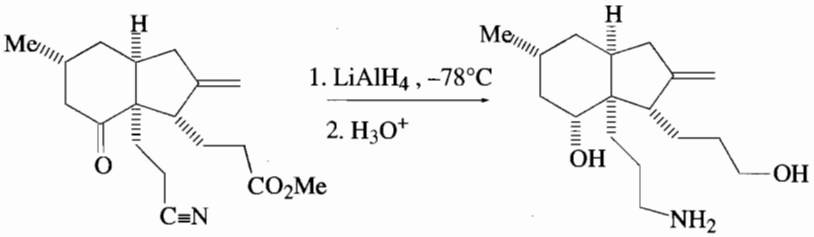
68 69

The functional group transforms in this section are summarized as



4.3. ALKOXYALUMINATE REDUCING AGENTS

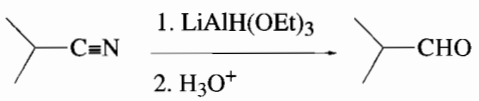
Lithium aluminum hydride is a powerful reducing agent that can reduce many functional groups and it is common for the reduction to span several oxidation stages (—CO_2Et → —CHO → —CH_2OH, for example), albeit in a mechanistically stepwise manner. There are many instances, however, when it is desirable to reduce a functional group by a single oxidation stage (such as —CO_2Et → —CHO), without overreduction. It is also important to selectively reduce one functional group in the presence of others because multifunctional molecules may contain several reducible functional groups (i.e., lactone + ester + aldehyde) and lithium aluminum hydride tends to reduce all of them. An example of this poor selectivity is the reduction of **70** to **71**, in which the ketone, cyano and ester groups were reduced at –78°C (95% yield in Heathcock's synthesis of fawcettimine).[78] A chemoselective reaction (a term introduced by Trost) will reduce a single functional group in high yield, in the presence of the other functional groups. This section will examine reagents that exhibit chemoselectivity for selected functional groups.



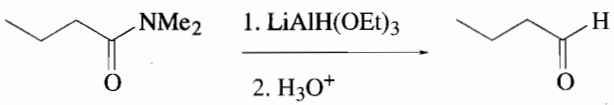
70 **71**

Is it possible for a reagent to react faster with one functional group than with another? The answer may be yes, but in **70** reaction with $LiAlH_4$ rapidly reduces all three functional groups so any rate differences are probably imperceptible. If the hydride reagent were structurally modified so that its reducing power was diminished, however, small differences in rates of reduction for various functional groups might be exploited, allowing selective reduction of one functional group in the presence of another. It was shown previously that reaction of lithium aluminum hydride with carbonyls led to alkoxyaluminates and that each successive reaction with the carbonyl was slower, demonstrating that the alkoxyaluminates are increasingly less reactive. If the Al—H unit remains in the molecule, however, that species can function as a reducing agent. A more

efficacious method for preparing these reagents is required since one cannot rely on adding excess of the carbonyl compound. An alternative and controllable method for preparation of alkoxyaluminates [$LiAlH_n(OR)_{4-n}$] is the direct reaction of lithium aluminum hydride with an appropriate alcohol. Addition of *n* equivalents of ROH leads the alkoxyaluminate with *4–n* H remaining on aluminum. Brown showed that many alcohols could be used to prepare alkoxyaluminum hydrides. Four equivalents of methanol, for example, react with $LiAlH_4$ to form lithium tetramethoxyaluminum [$LiAl(OMe)_4$] but 3 equivalents (in ether, THF, or glyme) gave $LiAlH(OMe)_3$ [lithium trimethoxyaluminum hydride].[79] Three equivalents of ethanol gave lithium triethoxyaluminum hydride ($LiAlH(OEt)_3$). Brown first showed that treatment of $LiAlH_4$ with 4 equivalents of the hindered *tert*-butanol led to the release of only 3 equivalents of hydrogen gas (i.e., only 3 equivalents of hydride reacted), generating lithium tri-*tert*-butoxy aluminum hydride, $LiAlH(Ot\text{-}Bu)_3$.[80] This hydride failed to react with the excess *tert*-butyl alcohol at ambient temperatures (although it did react upon prolonged heating at elevated temperatures).[80] This reagent is significantly less reactive than $LiAlH_4$ or the other alkoxyaluminum hydrides. Brown went further, and compared the reducing power of lithium aluminum hydride, lithium tri-*tert*-butoxyaluminum hydride and lithium trimethoxyaluminum hydride with a variety of functional groups.[81] Trimethoxyaluminum hydride is about as strong a reducing agent as lithium aluminum hydride.[82] Although the solid reagent is stable and sold commercially, ether solutions of the solid reagent are not very stable. It is often preferable to prepare the reagent as needed by addition of methanol to a THF slurry of lithium aluminum hydride.[82] Reduction of epoxides, nitriles, and tosylates was slow and nitriles gave mixtures of amines and aldehydes in poor yield.[83] Lithium triethoxyaluminum hydride is also unstable in solution and is usually prepared *in situ* by addition of 3 equivalents of ethanol to $LiAlH_4$ in ether at 0°C.[82] It is a powerful reducing agent but shows good selectivity for reduction of nitriles and amides. Both aliphatic nitriles such as **72**, which gives isobutyraldehyde, as well as aromatic nitriles are reduced to aldehydes in good yield.[83] Tertiary amides such as *N,N*-dimethylbutanamide (**73**) are also reduced to the aldehyde (in this case butanal).[84] As the steric bulk of the alkyl groups attached to the nitrogen of a tertiary amide increased, the yield of aldehyde was diminished. Reduction of the *N,N*-diethyl- analog of **73**, for example, gave only 47% of the aldehyde and similar reduction of the *N,N*-diisopropyl- analog gave no aldehyde at all.[84] Trimethoxyaluminum hydride and lithium aluminum hydride gave significantly lower yields of aldehydes with both nitriles and tertiary amides.

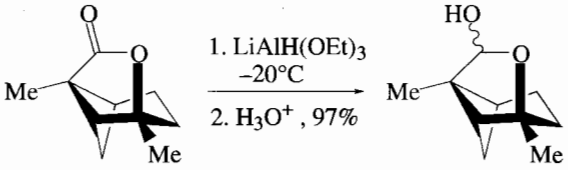


72



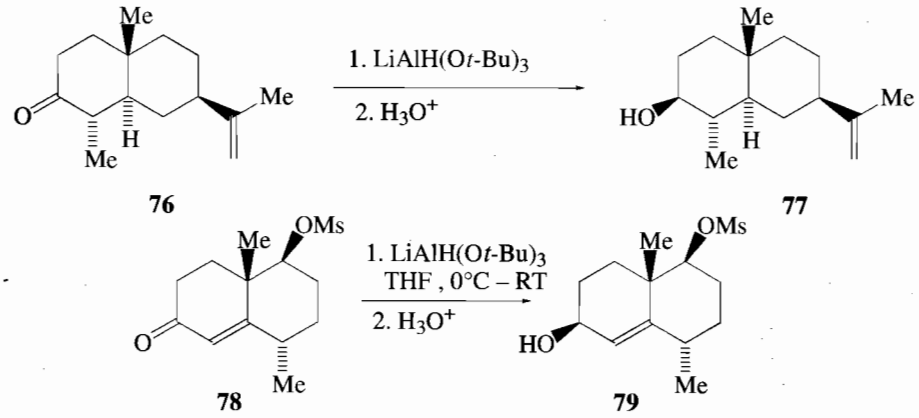
73

These relatively mild reducing agents can reduce the carbonyl of a lactone to give a lactol. In one example, **75** (an intermediate in Magnus' synthesis of grandisol)[85] was isolated in 97% yield when **74** was reduced with lithium triethoxyaluminum hydride at –20°C. It is known that trialkoxyaluminum hydrides will reduce aldehydes, ketones, esters and acid chlorides before reducing nitriles and amides.



74 **75**

Lithium diethoxyaluminum hydride [$LiAlH_2(OEt)_2$][86] and the monoethoxy derivative [$LiAlH_3(OEt)$][87] have been used in syntheses. It is clear, however, that $LiAlH(O\textit{t}\text{-}Bu)_3$ is one of the more commonly used reagents. It is stable in solution, gives useful concentrations in ether solvents (36 g/100 g of solvent in THF, 2 g/100 g in diethyl ether and 41 g/100 g in diglyme),[80] and reacts with organic substrates faster in solutions where it is in higher concentration. It is also thermally stable. Heating to 165°C for five h. followed by titration with acid showed that 92% of its active hydrogen was retained.[80] It is apparent that lithium tri-*tert*-butoxyaluminum hydride is less reactive than the other alkoxyaluminum hydrides discussed (see above), but it easily reduces aldehydes, ketones, some esters, anhydrides, and acid chlorides. Epoxides are reduced very slowly; nitriles and dimethyl amides are not reduced at all. The use of this reagent is a preferred method for the selective reduction of acid chlorides to aldehydes. The best yields of aldehydes are realized

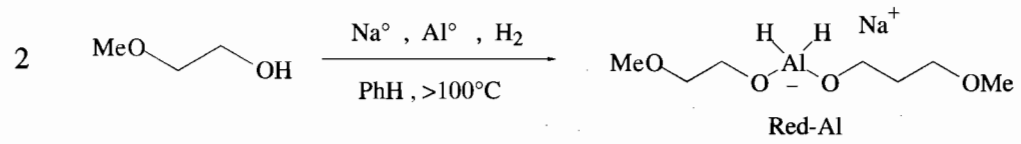


76 **77**

78 **79**

from aromatic acid chlorides, as in the reduction of *p*-nitrobenzoyl chloride to *p*-nitrobenzaldehyde in 80% yield.[80] The yield of aldehyde from aliphatic acyl chlorides is generally in the 40–60% range. Alkyl esters do not react, allowing some selectivity for the reduction of ketones and aldehydes in the presence of esters and other functional groups. Li and co-workers reduced the ketone moiety in **76** to alcohol **77** in 92% yield with excellent diastereoselectivity, in a synthesis of (+)-chyrsanthemol.[88] Although alkyl esters are inert to this reagent, many phenyl esters are reduced to the aldehyde, as in the conversion of methyl *p*-chlorobenzoate to *p*-chlorobenzaldehyde (–22°C, 8 h) in 77% yield.[89] The presence of the *p*-chlorine undoubtedly enhances the ability to reduce the ester.

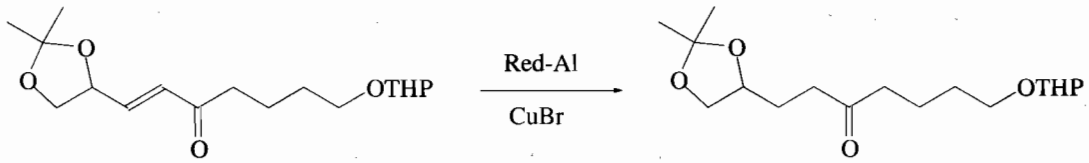
Reaction of conjugated carbonyls with $LiAlH(O\textit{t}\text{-}Bu)_3$ gives primarily 1,2-reduction, as in the quantitative reduction of **78** to **79** in Marshall's synthesis of globulol.[90] Both sulfonate esters such as the mesylate group in **78**, and halides[91] are resistant to reduction with $LiAlH(O\textit{t}\ Bu)_3$.



Red-Al

Sodium *bis*(2-methoxyethoxy)aluminum hydride (Red-Al®, Vitride®) was prepared by Vit in 1967.[92c] It was prepared in benzene, as shown, under a hydrogen atmosphere at temperatures > 100°C,[92] and its reducing power is close to that of lithium aluminum hydride. An important advantage of this reagent is its stability to dry air (it does not ignite in even moist air or oxygen), and it is thermally stable up to 200°C, unlike $LiAlH_4$, which can detonate at elevated temperatures. Perhaps the greatest utility of Red-Al is its solubility in aromatic hydrocarbon and ether solvents, which allows it to be conveniently used for applications that require inverse addition of hydrides.

The reactivity profile of Red-Al is essentially the same as $LiAlH_4$, reducing aldehydes, ketones[93] and acid derivatives to alcohols.[92b] Ketones and aldehydes are reduced with Red-Al at –78°C to the alcohol.[94] The analogy to $LiAlH_4$ reduction also applies to the reduction of carboxylic acids with Red-Al.[95] Reduction of conjugated carbonyls gives primarily 1,2-reduction to an allylic alcohol.[96] Red-Al reduces esters to alcohols in a manner identical with $LiAlH_4$.[97] The selectivity for 1,2-reduction can be changed to selectivity for 1,4-reduction by the addition of cuprous bromide (CuBr) to Red-Al, as in the conversion of **80** → **81** in 72% yield.[98] The active reducing agent is probably copper hydride. It is well known that addition of cuprous salts (Cu^+) promotes conjugate addition (see organocuprates in sec. 8.7.A.vi).[99] Reaction of cuprous bromide (CuBr) and Red-Al gave a sodium complex whereas reaction of CuBr and $LiAlH(OMe)_3$ gave a lithium complex.[100,101]

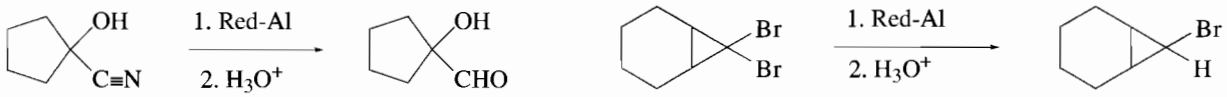


80 **81**

Other functional groups can be reduced, leading to interesting transformations such as epoxides to alcohols,[102] and lactams to amines.[103] Epoxides are reduced at the less hindered carbon.[104] The product distribution can vary with the solvent, especially when the steric hindrance is similar at each carbon of the epoxide. As with $LiAlH_4$, Red-Al reduces aromatic nitriles to amines although aliphatic nitriles typical are difficult to reduce and give poor yields.[105] Some interesting differences in selectivity, relative to $LiAlH_4$, are observed when Red-Al is used for reduction. Cyanohydrin **82**, for example, was reduced to α-hydroxy-aldehyde **83**,[106] rather than to the amino-methyl compound obtained with lithium aluminum hydride.

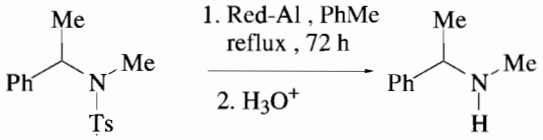
Hydrogenolysis of C—X bonds is usually faster than with $LiAlH_4$, and Red-Al is preferred to $LiAlH_4$ for reduction of aliphatic halides and many aromatic halides.[107] Primary aliphatic monohalides are reduced to the hydrocarbon (1-bromoheptane is reduced to heptane, for example, in 99% yield).[107] Aromatic halides are also reduced, as in the conversion of bromobenzene to benzene in 99% yield.[107] Under similar conditions,

however, chlorobenzene gave only 15% of benzene. It is possible to obtain selective reduction when more than one halide is present. Reduction of the gem-dibromide moiety in **84**, for example, gave the syn-monobromide (**85**) as the major product.[108]



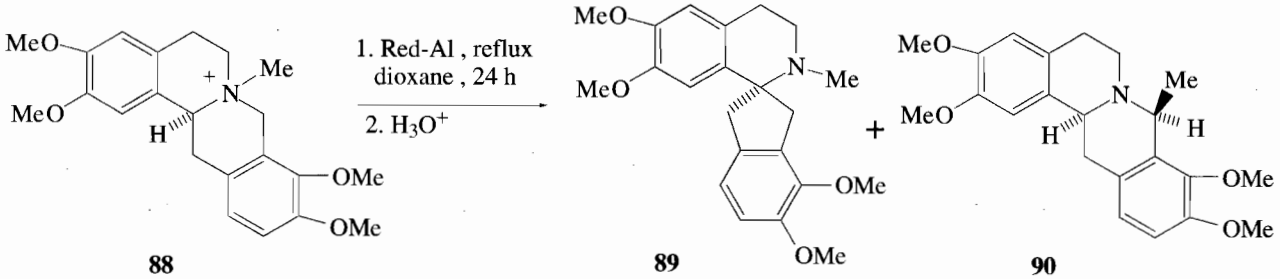
82 **83** **84** **85**

Sulfonate esters are reduced via C—O cleavage, as with $LiAlH_4$. Primary tosylates and mesylates are reduced to the methyl derivative.[109] Analogous to reaction with $LiAlH_4$, sterically hindered sulfonate esters often give significant amounts of S—O cleavage during the reduction. Although $LiAlH_4$ does not readily reduce sulfonamides to the corresponding amine (sec. 4.2.C.viii, *vide supra*),[110] cleavage of the N—S bond with Red-Al is relatively easy, as illustrated by the conversion of *N*-tosyl deoxyephedrine (**86**) to deoxyephedrine (**87**) in 64% yield.[110] It was assumed that the sulfonate fragment lost from **88** was reduced to the thiol.



86 **87**

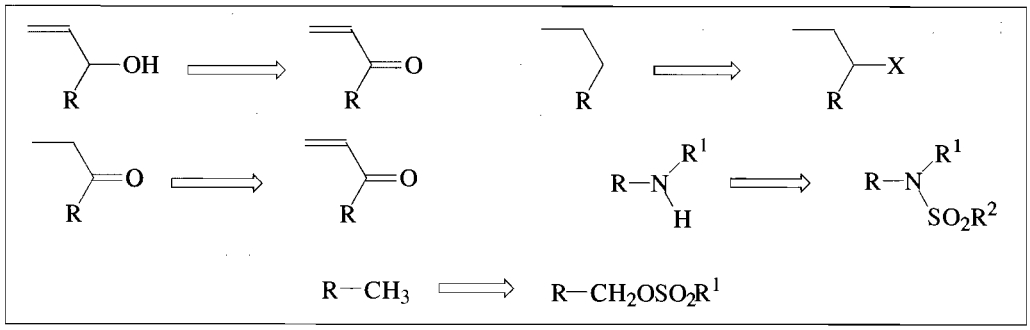
Red-Al can reduce benzylic alcohols to the hydrocarbon at elevated temperatures. The reaction occurs more readily when the aromatic ring contains an electron releasing group in the ortho- or para-position, but the temperatures required can be > 140°C.[111] Amino groups also activate a benzylic position to hydrogenolysis. Even at these higher reaction temperatures, reduction to the alcohol can compete with formation of the hydrocarbon, but usually as a minor process. An example is the reduction of 4-(*N,N*-dimethyl-amino)benzaldehyde with Red-Al at 141°C, which gave a mixture of 4-hydroxymethyl-*N,N*-dimethylaniline (63% yield) and 4-methyl-*N,N*-dimethylaniline (8%).[112] Similar reduction of 4-aminoacetophenone gave only toluidine, however, in 90% yield.[112] As with $LiAlH_4$, propargylic alcohols are reduced to allylic alcohols[113,114]



88 **89** **90**

Red-Al behaves as a base in certain applications, *if* a readily reducible functional group is *not* present in the molecule. Kametani used Red-Al to induce a **Steven's rearrangement** (sec. 8.8.C.ii) of berbine methiodide (**88**) to spirobenzylisoquinoline (**89**) (9.4%) plus **90** (22.5%).[115] The yield of rearranged products was poor, which is typical for this application of Red-Al.

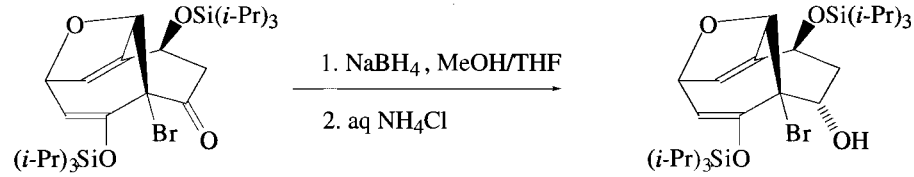
The functional group transforms most useful with Red-Al are:



4.4. REDUCTIONS WITH BOROHYDRIDE

4.4.A. Sodium Borohydride

Sodium borohydride ($NaBH_4$) was discovered by Schlesinger and Brown in 1943,[116] but details of its preparation were not reported until the 1950s.[117] Its discovery predated that of lithium aluminum hydride but the security regulations of World War II ($NaBH_4$ was important for the separation of uranium salts as part of the Manhattan project) delayed its disclosure.[117] Sodium borohydride is less reactive than lithium aluminum hydride, making it a very selective reagent, reducing aldehydes, ketones and acid chlorides in the presence of other reducible functional groups,[118] as reflected in the solvents used for the reduction. Aqueous and alcohol solvents are preferred due to the excellent solubility of sodium borohydride (25 g/100 g of solvent in water at 0°C [88.5 g/100 g at 60°C], 16.4 g /100 g in methanol, 4g /100 g in ethanol).[116a] Sodium borohydride reacts with water to form hydroxyborohydride intermediates but these also function as mild reducing agents. Similar reaction with alcohols is relatively slow and the most common reaction solvents are ethanol and 2-propanol. Sodium borohydride is relatively insoluble in ether solvents (0.1 g/100 g of THF, 5.5 g/100 g in diglyme and 0.8 g/100 g in DME), and these are rarely used for borohydride reductions. In most cases aqueous ammonium chloride, aqueous acetic acid, or dilute mineral acids are used for hydrolysis.

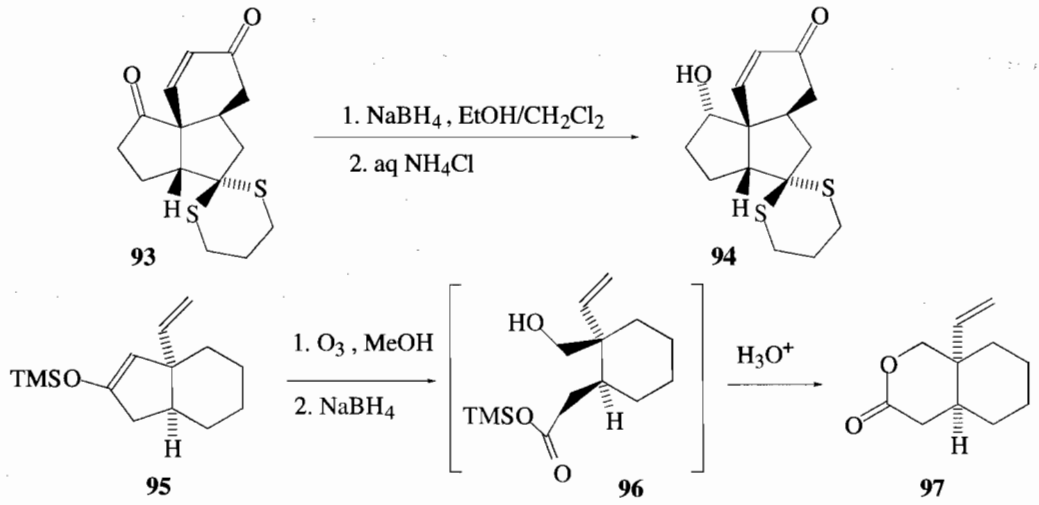


91 **92**

Ethanolic solutions of sodium borohydride reduce aldehydes and ketones in the presence of epoxides, esters, lactones, acids, nitriles, and nitro groups.[116a,119] The reaction is very selective for reactive functional groups such as acid chlorides, aldehydes or ketones, and the yields are commonly > 80%. The reduction of simple aldehydes or ketones that are part of more complex structures is perhaps the most prevalent use of sodium borohydride. The reduction of the ketone moiety in **91** to give the secondary alcohol in **92** (88% yield)[120] is a typical application involving sensitive functionality. Sodium borohydride often gives the 1,2-

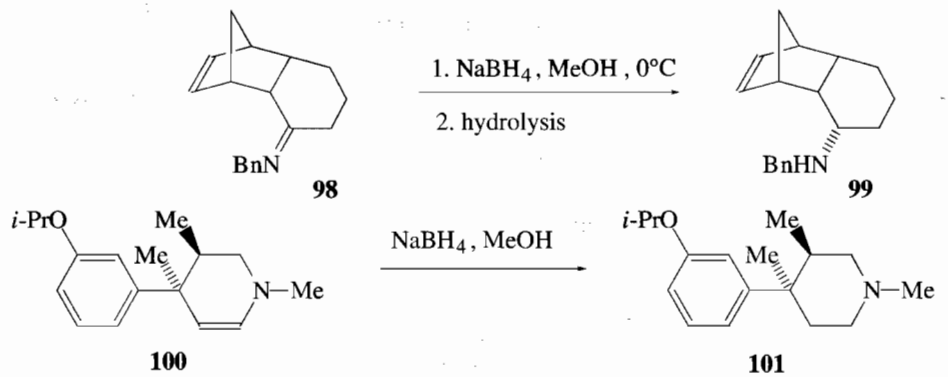
reduction product from conjugated carbonyl derivatives, and this is especially true when the terminal carbon of the conjugated system is sterically hindered. Conjugated ketones also give 1,2-reduction. In general, sodium borohydride is an excellent reagent for the reduction of ketones or aldehydes in the presence of esters,[121] hydroxyl groups α to the carbonyl,[41] a carbohydrate residue,[122] or halogens in the α position.[123] Aryl ketones[124] or aldehydes[125] are also easily reduced.

Unconjugated ketones and aldehydes are rapidly reduced, usually in preference to a conjugated carbonyl that may be present elsewhere in the molecule. Paquette treated **93** with $NaBH_4$ and obtained **94** in good yield, without reduction of the conjugated ketone unit, as part of a synthesis of magellanine.[126] Similar reduction with $LiAlH_4$ would reduce both carbonyl groups and probably give a mixture of 1,2- and 1,4-reduction products from the conjugated ketone.



93 **94** **95** **96** **97**

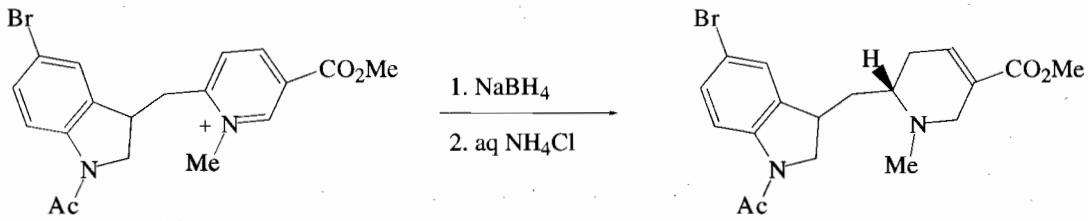
In section 4.2.C.ii, $LiAlH_4$ was used to reduce ozonides to the alcohol (sec. 4.2.C.ii). Sodium borohydride can be used in an identical manner,[127] as seen in the ozonolysis of **95**, where borohydride reduction gave **96** without reduction of the sensitive trimethylsilyl ester.[128] Subsequent hydrolysis gave lactone **97**, a key intermediate in Heathcock's synthesis of vernolepin.[128]



98 **99** **100** **101**

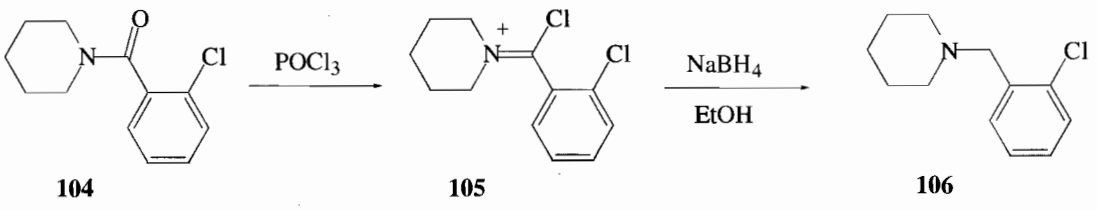
One of the more important uses of sodium borohydride is the reduction of enamines, imines, and iminium salts, particularly useful in alkaloid and amino acid syntheses. Imine **98** was reduced to amine derivative **99** in

74% yield in the Takano et al. enantiocontrolled synthesis of *(S)*-2-aminoadipic acid.[129] In a similar manner, Werner used sodium borohydride to selectively reduce enamine **100** at the 1,2-position, giving **101** in a synthesis of Opioid antagonists.[130] Pyridinium salts can also be reduced, and this is illustrated by the conversion of **102** to **103** as part of Julia's synthesis of lysergic acid.[131] In this reaction, initial reduction of the iminium salt generated a dienamine and 1,2-reduction gave the final product, **103**.

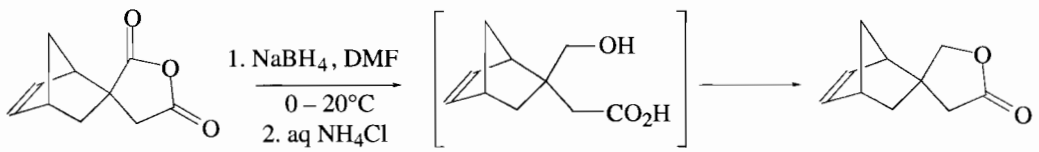


102 **103**

Amides are not reduced directly by $NaBH_4$, but if they are first converted to an iminium salt, this is readily reduced to give an amine. Reaction of **104** with phosphorus oxychloride ($POCl_3$) gave the **Vilsmeier–Haack complex**[132] (**105**) and this was reduced to the piperidine derivative **106**.[133] Primary amides are converted to nitriles by this procedure. Vilsmeier complex **105** is related to an intermediate generated in what is known as the **Vilsmeier reaction**,[132] which converts aromatic derivatives to aryl aldehydes. In a typical Vilsmeier reaction, $POCl_3$) and DMF react to form $Me_2N{=}CHCl^+$, and this reacts with an aromatic compound to form an aldehyde, after hydrolysis. It is noted that imides react with sodium borohydride under mild conditions to give a 2-hydroxylactam.[134]



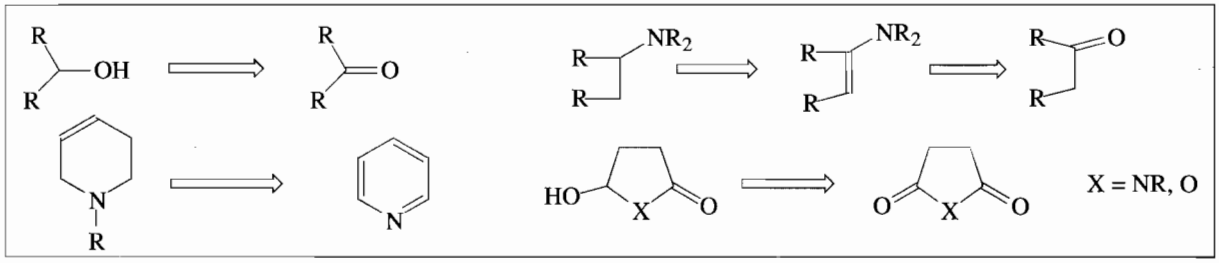
104 **105** **106**



107 **108** **109**

Anhydrides are related to lactones as imides are related to lactams. Partial reduction of an anhydride directly to an hydroxylactone is difficult, but reduction (with ring opening) to a hydroxy acid and subsequent ring closure can generate a lactone when $NaBH_4$ is used. An example is the reduction of anhydride **107**, in DMF, to give lactone **109** in 55% yield.[135] As discussed in Section 1.5.E, norbornyl systems usually react via the exo face, accounting for the selectivity of this reduction. In this particular example, reduction of the exo carbonyl gave alcohol **108**, which closed to the lactone (**109**) in the presence of the carboxyl group.

The functional group transforms for this section are

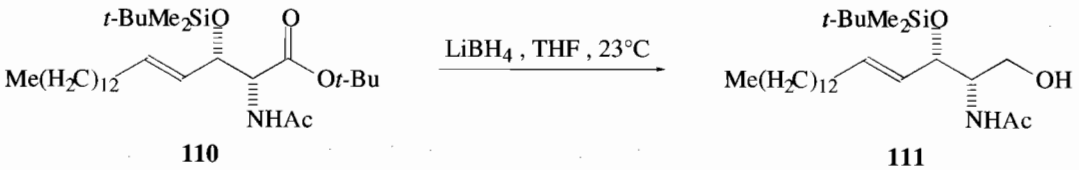


4.4.B. Alternative Metal Borohydrides (Li, Zn, Ce)

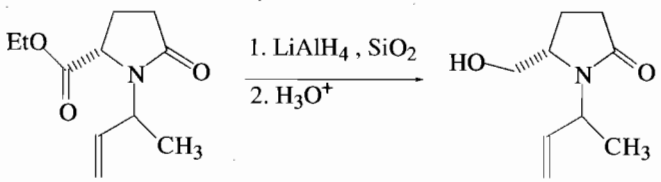
In previous sections, the metal counterion for hydride reducing agents has been largely restricted to sodium, lithium, and potassium. When different metal hydrides are used, there can be a significant effect on

$$NaBH_4 \quad + \quad LiBr \longrightarrow LiBH_4 \quad + \quad NaBr$$

the course of the reduction. Lithium borohydride ($LiBH_4$), for example, prepared by reaction of sodium borohydride and lithium bromide,[136] is a more powerful reducing agent than $NaBH_4$, reducing not only aldehydes, ketones, and acid chlorides but also epoxides, esters, and lactones. It does not reduce acids, nitriles or nitro compounds, however.[137] Lithium borohydride is soluble in ether (4 g/100 g) and THF (21 g/100 g) unlike $NaBH_4$, which is insoluble in the former and sparingly soluble in the latter. The major use of $LiBH_4$ is



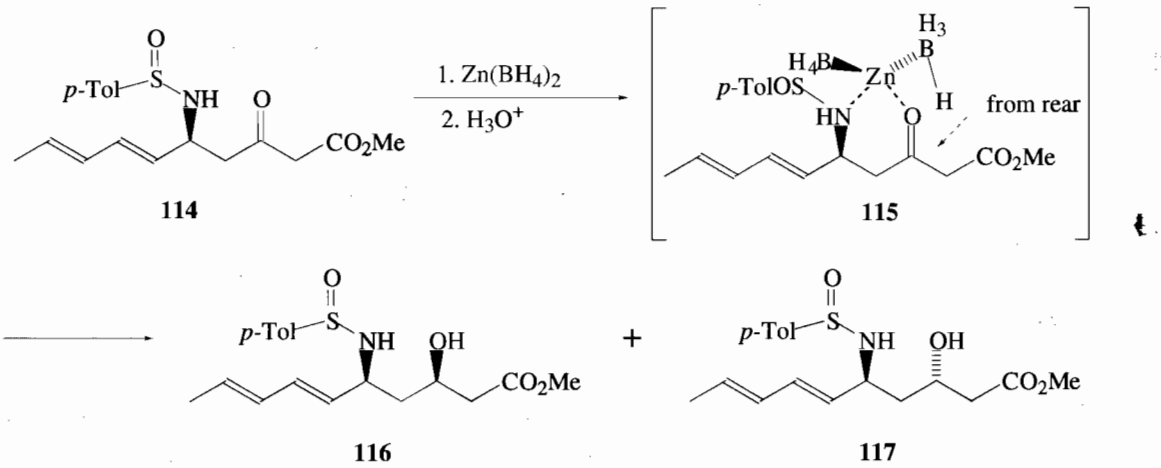
110 **111**



112 **113**

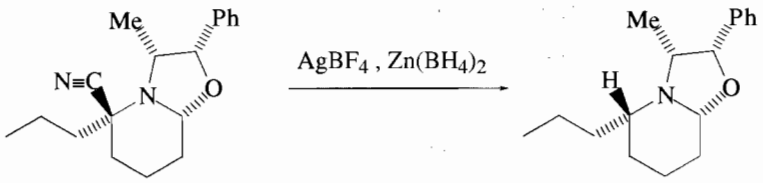
the selective reduction of esters, when the ester is the most reducible group in the molecule. An example is the reduction of amide-ester **110** to amide-alcohol **111**, in Corey's synthesis of sphingosine.[138] Lithium borohydride usually reduces lactones to the corresponding diol.[139] It is also important to note that $LiBH_4$ reduces an ester in the presence of a carboxylic acid.[140] There are some cases where $LiBH_4$ fails to reduce esters. For example, attempts to reduce the *N*-allylic pyroglutamate **112** with $NaBH_4$ or $LiBH_4$ failed.[141] This problem was solved by using Hojo's reagent (lithium aluminum hydride preadsorbed on silica gel), which showed great selectivity for reduction of the most reducible group in multifunctional group molecules.[142,143] This reagent was used to reduce **112** to the hydroxymethyl derivative (**113**) in 91%, without racemization of the stereogenic center at C5, taken from Smith's synthesis of pyrrolizidine alkaloids.[141] Hojo showed that silica gel is an effective catalyst for several other reactions.[144]

Metal hydrides with metal ions of higher ionic potential (such as Mg, Ca, Ba, and Sn) are also effective for the reduction of esters.[145a,136b] Magnesium borohydride is prepared *in situ* from $NaBH_4$ and magnesium chloride ($MgCl_2$) in diglyme at 100°C, and readily reduces esters.[144b] Addition of aluminum chloride ($AlCl_3$) to 3 equivalents of sodium borohydride generates aluminum borohydride [$Al(BH_4)_3$], which is a very powerful reducing agent, reducing lactones, epoxides, carboxylic acids, tertiary amides and nitriles as well as ketones, aldehydes, and esters.[146] Zinc borohydride [$Zn(BH_4)_2$] is prepared from zinc chloride ($ZnCl_2$) and sodium borohydride in ether. It is most useful[147] for selective reduction of α,β-unsaturated aldehydes and ketones, as in the reduction of 2-cyclohexenone to 2-cyclohexenol in 96% yield (only 4% of cyclohexanol was formed).[148]



114 **115** **116** **117**

One of the most useful applications of zinc borohydride is the diastereoselective reduction of hydroxycarbonyl derivatives (sec. 4.4.B).[149,150] The selectivity is explained by coordination (chelation) of the zinc with the carbonyl oxygen and the proximate hydroxyl oxygen, forming a cyclic species such as **115**. Hydride from the BH_4^- ion is delivered to the carbonyl carbon from the less sterically hindered face of the molecule (see **153**). The excellent diastereoselectivity possible with this reagent is illustrated by formation of a 76:24 mixture of **116** and **117** from the zinc borohydride reduction of **114** taken from Davis' synthesis of the piperidine alkaloid (–)-SS20846A.[151] The origins of the diastereoselectivity of this reduction are represented in **115**, where **116** is generated by delivery of hydride from the less hindered rear face. The origin of diastereoselectivity in all hydride reductions will be explained in Section 4.7.

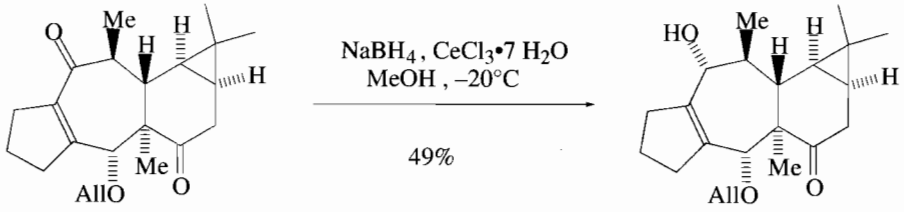


118 **119**

It is possible to reduce epoxides at the more substituted position, with high selectivity, by using zinc borohydride supported on silica gel.[152a] When 1-nonene oxide (2-heptyloxirane) was treated with this reagent, an

88% yield of 1-nonanol was obtained. In general, however, epoxides can be difficult to reduce with $Zn(BH_4)_2$.[152b] When 1-nonene oxide was treated with $Zn(BH_4)_2$ in THF, only a small amount of reduction occurred and a mixture of regioisomeric products was obtained.[152a] Reductive cleavage of a nitrile group has also been observed when a mixture of zinc borohydride and silver tetrafluoroborate ($AgBF_4$) was used, as in the conversion of **118** to **119** in Husson's synthesis of dihydropinidine.[153]

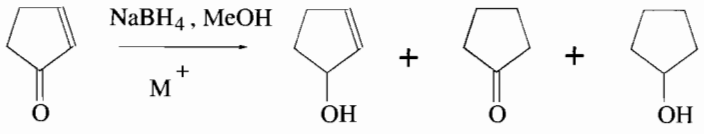
Addition of cerium salts to sodium borohydride leads to a reagent giving very selective 1,2-reduction of conjugated aldehydes and ketones.[154] The carbonyl of a conjugated ketone is reduced faster than that of a normal ketone, as in the conversion of **120** to **121** in 49% yield, taken from Yamamura's synthetic study of euphoreppinol.[155] Gemal and Luche examined the extent of 1,2- versus 1,4-reduction of conjugated ketones when $NaBH_4$ was mixed with various metal salts.[156] These results are shown in Table 4.2[156] and it is clear that the lanthanide salts, including cerium, show a marked preference for 1,2-reduction. Lithium and copper salts



120 **121**

give complete reduction of both the carbonyl and the alkene moiety, whereas the other salts give mixtures of 1,2- (**122**) and 1,4-reduction products (**123** and **124**), although they are significantly less reactive. Addition of salts such as Ni^{2+} or Co^{2+} give reduction of the alkene without disturbing the carbonyl, but it is possible that these reactions proceed by a completely different mechanistic pathway and large amounts of unreacted ketone often remain. The selectivity for the formation of **122** in Table 4.2, obtained when cerium salts are mixed with $NaBH_4$, can be explained by a chelated intermediate such as **125**. In such a complex, the borohydride moiety is held by the carbonyl carbon and transfer of hydride to the alkene is difficult unless the complexation is

Table 4.2. 1,2- vs. 1,4–Reduction of Cyclopentenone with Sodium Borohydride Admixed with Metal Salts



122 **123** **124**

Metal Salt	% Cyclopentenone	% 122	% 123	% 124
La^{3+}	0	90	0	10
Ce^{3+}	0	97	0	3
Sm^{3+}	0	94	0	6
Eu^{3+}	0	93	0	7
Yb^{3+}	0	89	0	11

Y^{3+}	0	86	0	14
Li^{+}	0	1	0	99
Cu^{+}	2	6	4	88
Ba^{2+}	2	6	11	76
Zn^{2+}	90		7	3
Fe^{2+}	19	12	9	60
Fe^{3+}	33	5	12	50
Tl^{3+}	86	2	8	4
Ni^{2+}	18	0	76	6
Co^{2+}	27	0	61	12

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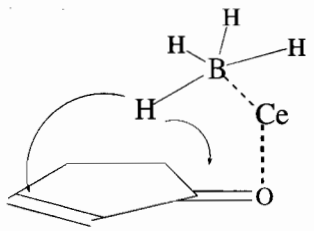
reversible. If the complex is formed irreversibly, hydride transfer to the carbonyl (1,2-addition to give **122**) is under kinetic control. If the complex forms reversibly (thermodynamic control), 1,4-reduction (to give **123** or **124**) predominates. The sodium borohydride/cerium reagent is now referred to as the **Luche reagent**.



125

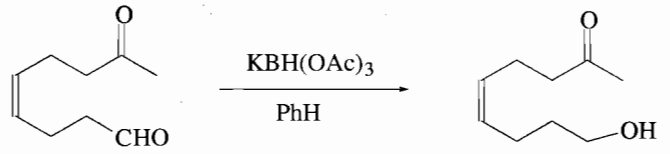
4.5. ALKOXY- AND ALKYLBOROHYDRIDES

Alkoxyborohydrides and alkylborohydrides are not as well known as metal alkoxyaluminum hydrides. In general, alkylborohydrides are more reactive than $NaBH_4$. Since $LiAlH_4$ is such a powerful regent, there is little need for alkylalumium hydrides, and we will not discuss them. Alkoxyaluminates are less reactive than $LiAlH_4$ and alkoxyborohydrides are less reactive than $NaBH_4$. Some derivatives are unstable in ether solvents. Sodium trimethoxyborohydride [$NaBH(OMe)_3$], for example, disproportionates in solution.[157] The triisopropoxyborohydride derivative [$NaBH(OiPr)_3$] is very stable in THF, however, and is prepared in THF by treatment of $B(O\textit{i}\text{-Pr})_3$ with sodium or potassium hydride.[157,158] This reagent reduces only aldehydes and ketones, reacting with virtually no other functional group.[159] An interesting class of alkoxyborohydrides are the acyloxy derivatives, and we will begin with them.

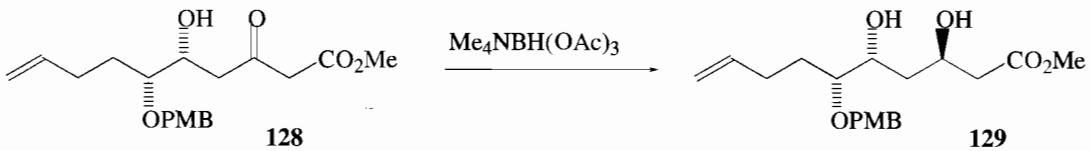
4.5.A. Acyloxyborohydrides

Acyloxyborohydrides [$NaBH_{4-n}(O_2CR)_n$] are remarkably selective,[160] as illustrated by the reduction of the aldehyde unit in **126**, in the presence of a ketone moiety.[161] Reduction with potassium triacetoxyborohydride (generated by dissolving potassium borohydride in acetic acid) gave **127** in 60% yield. It can also reduce

ketones in the presence of esters, as in the reduction of **128** to **129** in 90% yield (>10:1 diastereoselectivity), taken from Evan's synthesis of (+)-miyakolide.[162] Sodium triacetoxyborohydride has also been used for selective 1,4-reduction of conjugated esters[163]. Another important use of acetoxyborohydride is for reduction of imines and enamines, which is useful for the synthesis of alkaloid precursors. Imines are also reduced by this reagent.[164]

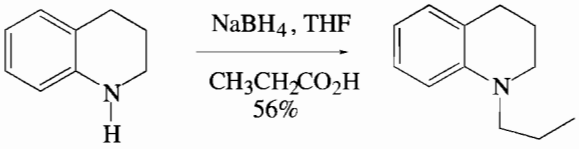


126 **127**



128 **129**

Reductive alkylation is possible when an amine unit is present in the substrate (sec. 4.10.D). The acid fragment is transferred to nitrogen, and an *N*-alkyl amine is the final product. An example is the conversion of tetrahydroquinoline (**130**) to the *N*-propyl derivative (**131**) in 56% yield.[165] When hydroxyl groups are present in the organic substrate, acetoxylation occurs if no other reducible functional group is present. An example is the reduction of 4-ethoxybenzyl alcohol to the O-acetyl derivative, in 95% yield.[166] Although these latter reactions can compete with the reduction of other functional groups, acyloxyborohydrides are important chemoselective reducing agents.



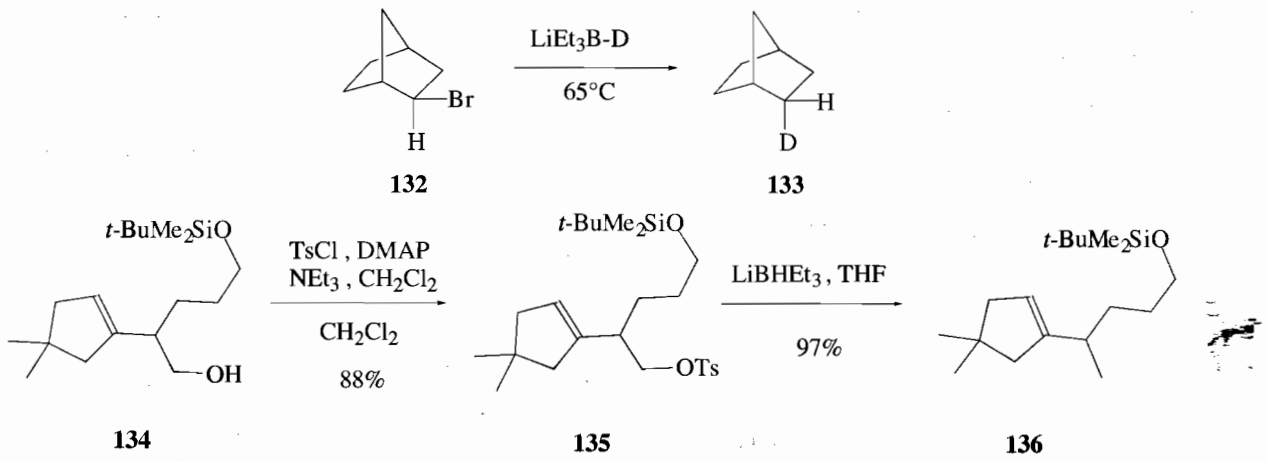
130 **131**

4.5.B. Super-Hydride

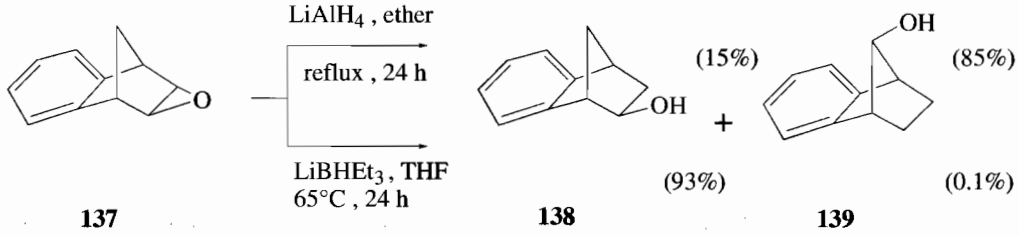
Alkyl groups are known to be electron releasing relative to boron. Therefore, when alkyl groups are attached to the boron of a borohydride reagent, the reducing power of that reagent is enhanced.[119a,167] An extremely useful reducing agent has been developed using this idea, lithium triethylborohydride ($LiBHEt_3$),

$$BEt_3 + LiH \xrightarrow{THF,\ 65°C,\ 15\ min} LiBHEt_3$$

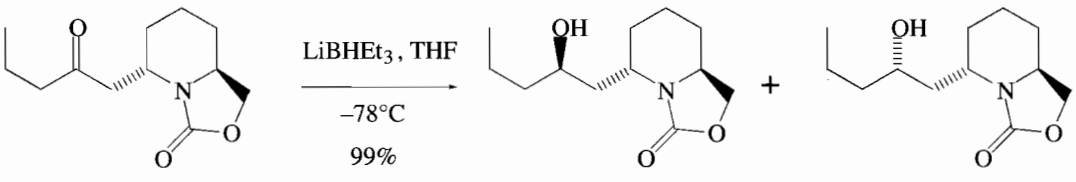
which referred to as Super-Hydride.™ It is prepared by reaction of lithium hydride with triethylborane in THF.[168] Super-Hydride is more powerful than $LiBH_4$ and is probably the most powerful hydride nucleophile available,[169] giving reactions that mimic S_N2 behavior. The most common use of Super-Hydride is probably for the reductive dehalogenation of alkyl halides, which illustrates its nucleophilic nature. As shown in the



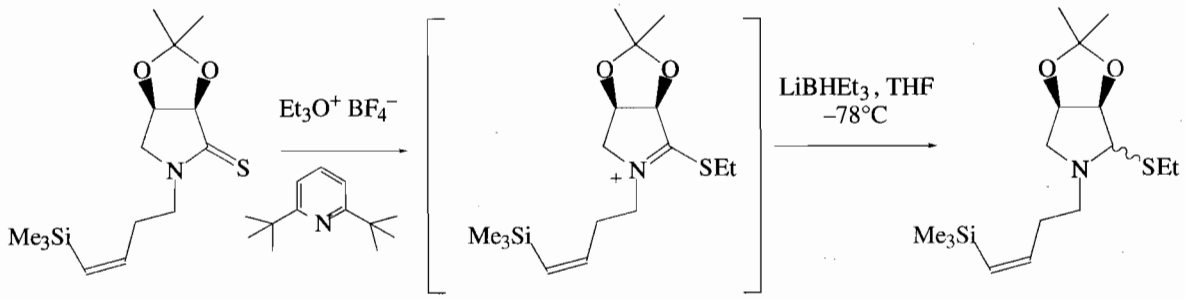
conversion of 2-*exo*-bromobicyclo[2.2.1]heptane (**132**) to the endo-(*D*)-derivative (**133**), deuteride displacement proceeds with inversion, analogous to an S_N2 process.[169,170] Sulfonate esters such as mesylates, tosylates, and triflates are reduced with $LiBHEt_3$ via C—O cleavage. The alcohol moiety in **134** is first converted to the corresponding tosylate (**135**), and this was reduced to a methyl group in **136** in 97% yield, as part of Pattenden's synthesis of pentalenene.[171] The highly nucleophilic nature of the reagent allows epoxides to be opened regioselectively. Super-Hydride attacks electrophilic centers at the less sterically hindered site, as in the reduction of 1-methyl-1,2-epoxycyclohexane to 1-methyl-cyclohexanol in 99% yield.[172] In reactions with substrates that are sensitive to rearrangement, $LiBHEt_3$ is superior to $LiAlH_4$. Reduction of **137** gave 15% of **138** and 85% of the rearranged alcohol **139** when treated with $LiAlH_4$.[172] Reduction with Super-Hydride, however, gave 93% of **138** with < 0.1% of **139**.[172]



Super-Hydride will reduce ketones and aldehydes, of course, but it is not used extensively unless the stereochemistry of the alcohol product can be influenced by this reagent and there are no other groups in the molecule that are reduced by this reagent. In Lhommet's synthesis of (–)-porantheridine, reduction of the ketone unit in **140** gave a 4:1 mixture of **141** and **142**, in 99% yield.[173] Esters are also reduced to alcohols, even in the presence of a lactam.[174] The nucleophilicity of Super-Hydride usually leads to 1,2-reduction of



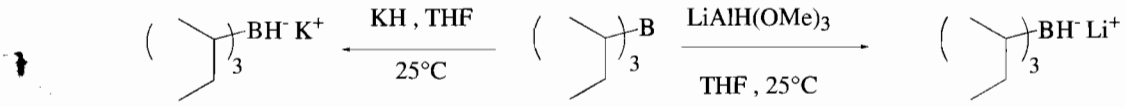
conjugated carbonyl compounds.[175] The nucleophilic nature of $LiBHEt_3$ makes it attractive for the reduction of iminium salts, as in Overman's reduction of iminium salt intermediate **144** (derived from thiolactam **143**) to the ethylthio derivative (**145**) in 84% overall yield.[176]



143 **144** **145**

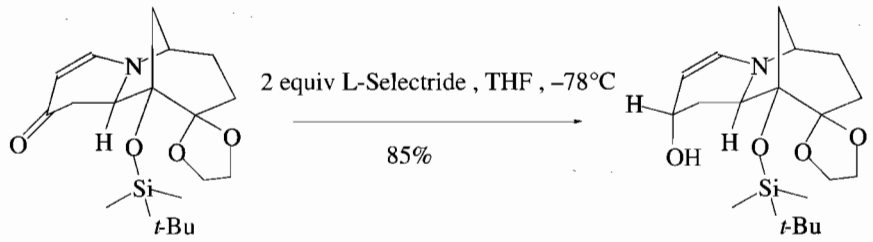
4.5.C. The Selectrides

It was established in Section 4.5.B that adding alkyl groups to a borohydride unit increased the reducing power, which can be modulated if the alkyl groups are sterically bulky, since it is more difficult for the B—H unit to approach a substrate. In addition, the presence of large groups that provide significant steric hindrance can lead to greater diastereoselectivity in the reduction of prochiral carbonyls. Two commonly available reagents that exploit this concept are prepared by the reaction of tri-*sec*-butylborane (**147**,



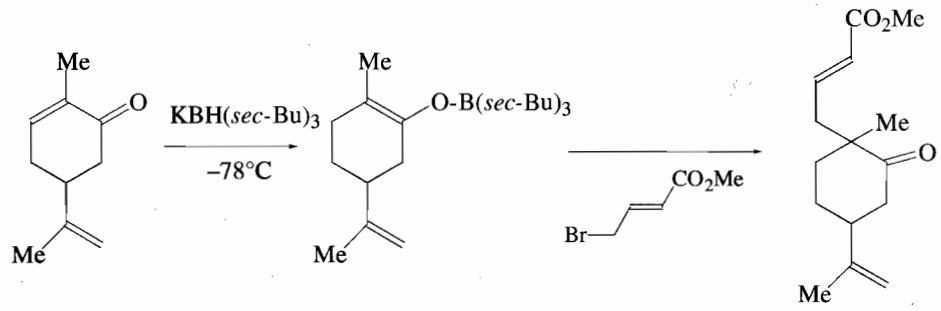
146 **147** **148**

sec. 5.2.A) with potassium hydride or lithium trimethoxyaluminum hydride to give potassium tri-*sec*-butylborohydride (**146**, called K-Selectride™) or lithium tri-*sec*-butylborohydride (**148**, called L-Selectride™).[119a,177,158,168] Both reagents reduce aldehydes and ketones to the corresponding alcohol, even at temperatures as low as –78°C. Both the potassium and lithium derivatives are effective for reductions although, by analogy to other borohydrides, the lithium derivative may be somewhat stronger. L-Selectride reduced the conjugated ketone moiety of **149** selectivity to alcohol **150**, for example, in 85% yield as part of Weinreb's synthesis of (–)-norsecurinine.[178] The excellent diastereoselectivity achieved in this reduction is the primary reason for using Selectride rather than another hydride reducing agent.



149 **150**

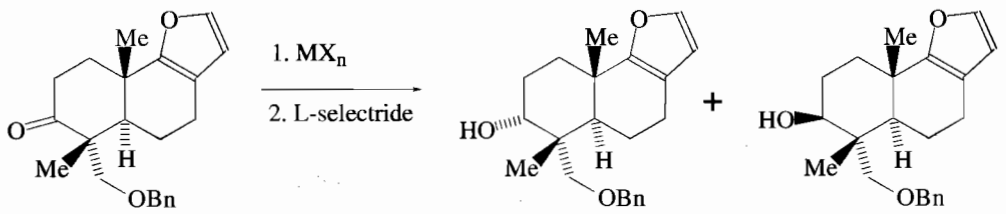
α,β-Unsaturated ketones can sometimes be converted to an enolate anion that is trapped with Selectrides as a boron enolate via 1,4-reduction.[119a] This enolate can be alkylated by addition of an alkyl halide (sec. 9.3.A), as in Ganem's reaction of carvone (**151**) to give enolate **152**, which reacted with methyl 4-iodo-2-butenoate to give **153**.[179] If the normal 1,4-reduction product is the desired product, it can be obtained by simple treatment of the enolate with aqueous acid rather than with an alkyl halide.[180,179c]



151 **152** **153**

The selectivity of a Selectride reagent can be influenced by the addition of metal salts, just as the reactivity of $NaBH_4$ was modified in Section 4.4.B. Tanis showed that **154** gave a mixture of **155** and **156** upon treatment with L-Selectride and added transition metals,[181] via a chelated intermediate complex. Addition of magnesium bromide ($MgBr_2$) favored **155** (8.5:1, 95% yield) and the influence of magnesium bromide, zinc iodide (ZnI_2) and tetravalent titanium is shown in Table 4.3.[181] Magnesium salts gave the best results in Table 4.3, consistent with the chelating properties of that metal. The preference for **155** over **156** is due to delivery of hydride from the less hindered face of **154**.

Table 4.3. Influence of Metal Salts on L-Selectride Reduction of 197



154 **155** **156**

MX_n	No. Equiv MX_n	Ratio 155/156	Yield (%)
None	0	2.8:1	99
$ZnI_2 \cdot OEt_2$	1.5	1.2:1	93
$MgBr_2 \cdot OEt_2$	1.5	7.0:1	95
$MgBr_2 \cdot OEt_2$	2.0	8.5:1	95
$Ti(O\textit{i}\text{-}Pr)_3Cl$	1.5	4.0:1	96
$Ti(O\textit{i}\text{-}Pr)_4$	1.5	5.7:1	93

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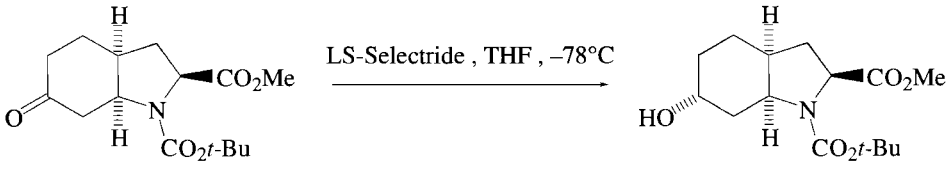
Alkyl borohydrides with even greater steric hindrance but with similar reactivity and selectivity to the Selectrides, were prepared from trisiamylborane (siamyl = Me_2CH_2CHMe- ≡ tri-*sec*-isoamyl, sec. 5.2.A). Lithium trisiamylborohydride [$LiBH(CHMeCHMe_2)$] and the potassium salt [$KBH(CHMeCHMe_2)$], are similar to the L- and the K-Selectrides and are called LS-Selectride and KS-Selectride, respectively.[182] In Bonjoch's synthesis of aeruginosin 298-A, LS-Selectride reduction of **157** gave **158** in 53% yield.[183]

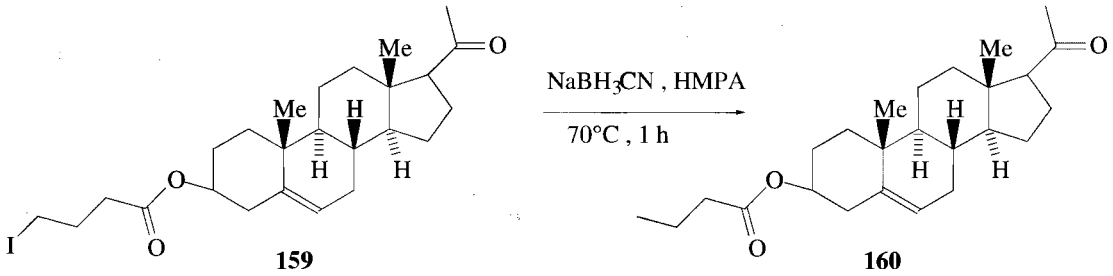


157 **158**

4.5.D. Sodium Cyanoborohydride

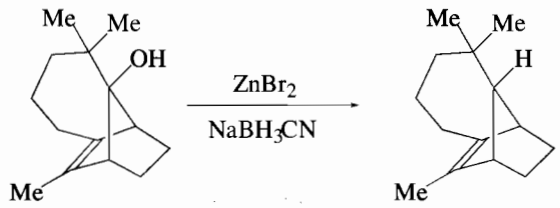
Alkyl groups are not the only substituents that can be attached to boron in order to generate new borohydride derivatives. Reaction of $NaBH_4$ with HCN gives sodium cyanoborohydride ($NaBH_3CN$),[184] for example. a remarkably stable reagent that does not decompose in acid solution (the pH should be less acidic than pH 3). It is soluble in THF, MeOH, H_2O, HMPA, DMF and sulfolane and is unreactive, making it very

selective.[185] Cyanoborohydride readily reduces iodides, bromides, and tosylates to the hydrocarbon in excellent yield when HMPA is the solvent,[186] even in the presence of carbonyl groups. The reduction of the iodo group in **159** gives **160** without disturbing the ester or ketone moieties illustrates this selectivity.[187] Alcohols are similarly reduced if zinc bromide ($ZnBr_2$) is added to the reagent, as in the reduction of **161** to **162** in Johnson's synthesis of longifolene. This reduction presumably proceeds via formation of an intermediate bromide or via a carbocation.[188]

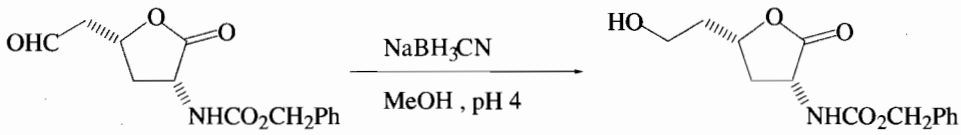


159 **160**

Ketones and aldehydes are reduced in acidic media, but *not* at neutral pH. Sodium cyanoborohydride is stable at pH 3–4 and in this acid medium, a carbonyl is converted to the protonated form ($C{=}OH^+$) which is susceptible to reduction. At pH 3–4, ketones and aldehydes are rapidly reduced,[189] as illustrated by the reduction of the aldehyde unit in **163** to give **164** in 89% yield (at pH 4 in this case), in Varela's asymmetric synthesis of 4-hydroxypipecolic acid.[190] Note that neither the lactone moiety or the benzyl carbamate were reduced under these conditions.

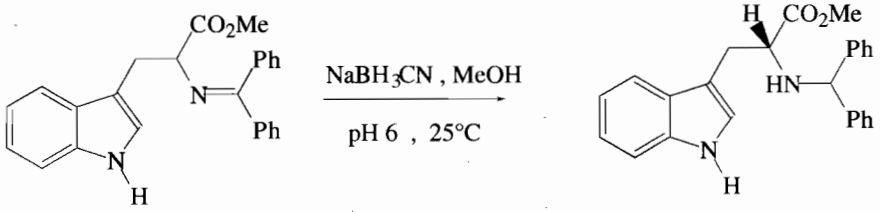


161 **162**



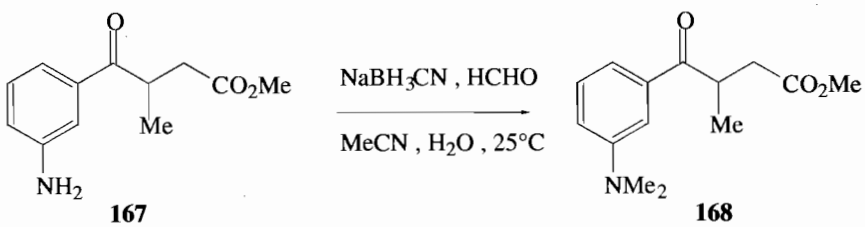
163 **164**

The ability to reduce compounds under acidic conditions is ideal for the reduction of enamines. Protonation of nitrogen gives an iminium salt in acidic media that is then reduced with cyanoborohydride to an amine.[189,191] Imines can be reduced in acidic media in the presence of many other functional groups, as shown by Cook's reduction of imine **165** to give **166** in 79% yield in a synthesis of substituted tetrahydro-β-carbolines.[192] This reagent is excellent for the reduction of iminium salts at neutral pH as well,[193] and it is also useful for the reductive alkylation of amines.[194] Dimethylamino derivatives such as **168** can be prepared from the amine (**167** in this case) by treatment with formaldehyde and cyanoborohydride, even in the presence



165 **166**

of functional groups such as the conjugated ketone and the ester in **167**.[195] Apart from the actual $NH_2 \rightarrow NMe_2$ conversion, the selectivity for a specific group shown in this example is the major advantage in using cyanoborohydride rather than other reducing agents.



167 **168**

4.5.E. Selected Usage of Hydride Reducing Agents

Several hydride reducing agents were discussed in preceding sections. It is reasonable to ask which is preferred in a given situation. This question is not easy to answer, especially in natural product synthesis. The

best reagent is the one that gives the highest yield with the fewest side reactions, but identifying this reagent often requires experimentation in the specific system being examined. Table 4.4 is presented as a simple guide to the various hydrides and their preferred use. It is very general and should be used to only give a *first estimation* of relative reactivity.

Table 4.4. Typical reductions with selected hydride reagents

Hydride	Applications	Special Considerations
$LiAlH_4$	General. Reduces most groups: aldehydes, ketones, acids and acid derivatives ,nitriles, aliphatic nitro, halides and propargyl alcohols	aromatic nitro reduced to diazo. Sulfonate esters give mixtures of C-O and S-O cleavage. Conjugated carbonyls often give mixtures of 1,2- and 1,4-reduction.
$LiAlH(OMe)_3$	Milder than $LiAlH_4$. Generally used for aldehydes, ketones and conversion of acid chloride or esters to aldehydes.	Esters are reduced more slowly than ketones and aldehydes. Conjugate carbonyls give mostly 1,2-reduction. Amides, nitriles are reduced to aldehydes.
$LiAlH(O\textit{t}\text{-}Bu)_3$	Mild and selective. Good for converting acid derivatives to aldehydes.	Esters are reduced more slowly than ketones and aldehydes. Conjugate carbonyls give mostly 1,2-reduction. Amides, nitriles are reduced to aldehydes.
Red-Al	Similar to $LiAlH_4$. Good for carboxylic acids. Nitriles can be converted to aldehydes and aromatic aldehydes to aromatic methyl.	Conjugate carbonyls give 1,2- reduction (1,4-when Cu^+ is added). Soluble in organic solvents - excellent for reverse addition experiments.
$NaBH_4$	General but mild. Good for ketones, aldehydes, acid chlorides, imines and iminium salts	Esters and most acid derivatives reduce slowly or not at all. Conjugate carbonyls give mostly 1,2-reduction, but 1,4-reduction is common. Halides are not reduced very well and epoxides reduce very slowly.
$LiBH_4$	Good for esters. Stronger than $NaBH_4$– less selective	Similar to $NaBH_4$, except for esters.
$Zn(BH_4)_2$	Generally similar to $NaBH_4$ - gives higher diastereoselectivity	Similar to $NaBH_4$.
$NaBH_4 \cdot CeCl_3$	Gives primarily 1,2-reduction with conjugated carbonyls	Similar to $NaBH_4$.
$MBH(O_2CR)_3$	Good for imines and enamines.	Reducing power is dependent on solvent and the nature of the R group (of RCO_2H precursor). Alkylation can occur with amines and hydroboration can occur with alkenes.
Super Hydride ($LiBHEt_3$)	Strong reducing agent. Good for halides (S_N2 type reactions), halides and sulfonate esters (C—O cleavage).	Similar to $LiAlH_4$.

Selectride [$MBH(sec\text{-}Bu)_3$]	Used primarily with aldehydes and ketones when higher diastereoselectivity is required.	Similar to $LiBH_4$.
$NaBH_3CN$	Excellent for reduction of halides at neutral pH and alcohols (if a Lewis acid is added).	Generally unreactive with most groups at neutral pH. Reduces aldehydes and ketones at pH 4 and lower. Acid derivatives are generally unreactive.

4.6. BORANE, ALUMINUM HYDRIDE, AND DERIVATIVES

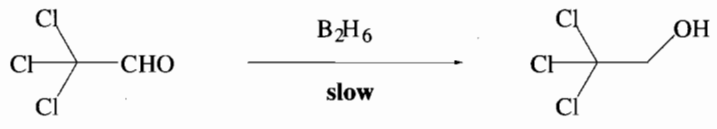
4.6.A. Borane

$$6\ LiH + 8\ BF_3{\bullet}OEt_2 \xrightarrow{\text{ether}} B_2H_6 + 6\ LiBF_4$$

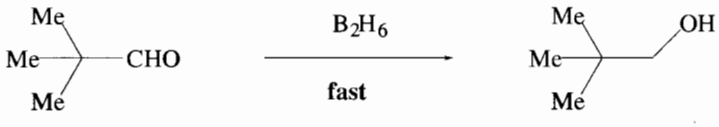
$$3\ NaBH_4 + 4\ BF_3{\bullet}OEt_2 \xrightarrow{\text{ether}} 2\ B_2H_6 + 3\ NaBF_4$$

Brown and Schlesinger first reported the preparation and use of diborane as a reducing agent in 1939.[196] This finding began the exploration of hydrides and boranes as reducing agents and borane reagents are discussed after hydrides only because hydride reagents are now used more often. Borane and its derivatives remain the reagent of choice for many applications. Diborane is usually generated by reaction of $BF_3{\bullet}OEt_2$ with LiH[197] or by reaction of $NaBH_4$ and BF_3 (sec. 5.2.A) .[198]

Diborane (the stable dimer is B_2H_6, but it is usually represented as BH_3—an unstable monomeric form) is a potent reducing agent for aldehydes, ketones, lactones, epoxides, acids, tertiary amides and nitriles. It is ineffective for the reduction of esters and reacts with alkenes in ether solvents, forming the basis of hydroboration chemistry (sec. 5.2). The primary difference in reactivity between borane and metal hydride reagents is that borane is a good Lewis acid and coordinates to atoms of high electron density, as illustrated by a comparison of the reduction of trichloroacetaldehyde (**169**) to give the alcohol **170**, and similar reduction of pivalaldehyde (2,2,-dimethylpropanal, **171**) to give **172**. Sodium borohydride reduced **169** faster than **171**. Diborane, however, reacted faster with **171**, which possessed the more electron-rich carbonyl oxygen.[199]

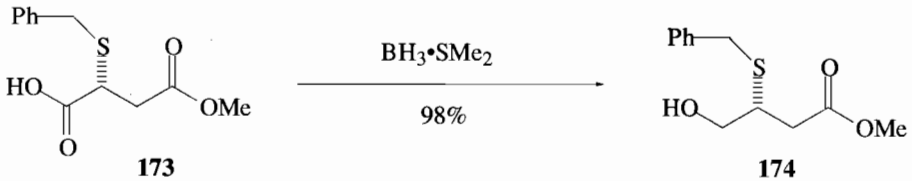


169 **170**



171 **172**

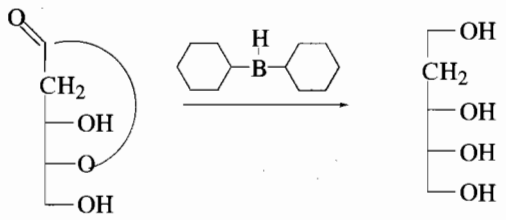
Borane reduces esters very slowly and ketones or aldehydes are selectively reduced in the presence of esters. The most widely used application of borane is for the selective reduction of carboxylic acids, even in the presence of halides, esters, nitriles, and ketones.[200] Since $LiAlH_4$ reduces both acids and esters and $NaBH_4$ does not reduce acids (and often reduces esters with difficulty), borane is the reagent of choice for selective reduction of carboxylic acids in the presence of an ester group. The reduction occurs without racemization of adjacent chiral centers, as in the borane reduction of (–)-malic acid to generate *(S)*-1,2,4-butanetriol in 92% yield.[201] Seki and Kondo's reduction of the acid moiety in **173** to alcohol **174** (in a synthesis of orally active carbapenams), without reduction of the benzylthio or ester groups also demonstrates this selectivity.[202] Borane can reduce imides to give an amine.[203] Borane also reduces epoxides at the less hindered carbon when mixed with catalytic amounts of sodium borohydride.[204]



173 **174**

The flammability and difficulties[205] in handling gaseous borane led to development of several stable Lewis base complexes that are easier to use. One of the more useful is the borane complex of dimethyl sulfide (DMS; $H_3B{\bullet}SMe_2$), used in the reduction of **173**, is prepared by bubbling DMS into a THF solution of diborane. This reagent is very soluble in most organic solvents, including benzene and toluene, and gives all the selectivity expected for borane.[205] Borane is useful for the conversion of α-amino acids to α-amino alcohols, as in the reduction of phenylalanine to phenylalaninol in 77% yield.[206] Lactams are also reduced to cyclic amines.[207]

Other boranes such as bis(1,2-dimethylpropyl)borane (disiamylborane), and 9-borabicyclo[3.3.1]nonane (usually referred to as simply 9-BBN), both discussed in section 5.2.A, reduce organic functional groups in a manner similar to borane.[208] There are interesting differences in selectivity, however. Dialkylboranes reduce esters and lactones whereas similar reduction with borane are very slow. Dicyclohexylborane, for example, reacted with **175** to give 4-deoxyerythropentose (**176**).[209] Tertiary amides are reduced by dialkylboranes to the corresponding aldehyde.[208a] Disiamylborane reduced *N,N*-dimethylbenzamide to benzaldehyde in 89% yield, for example. The increased steric hindrance of the reagent can have a significant effect on the selectivity in the reduction of prochiral ketones, relative to reduction with $LiAlH_4$ or $NaBH_4$.



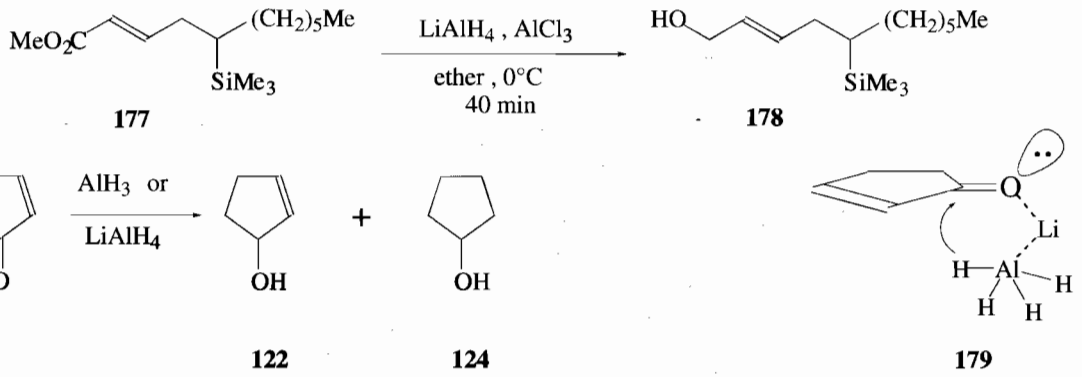
175 **176**

4.6.B. Aluminum Hydride

Borane (BH_3) is considered to be a Lewis acid when compared with borohydride (BH_4^-), which is an *ate* complex of borane. Similarly, AlH_4^- has an electrophilic analog, aluminum hydride (AlH_3). This reagent

$$3\ LiAlH_4 + AlCl_3 \longrightarrow 4\ AlH_3 + 3\ LiCl$$

is capable of selective reduction for many organic functional groups and is usually prepared by reaction of 3 equivalents of $LiAlH_4$ with aluminum chloride ($AlCl_3$).[210] Aluminum hydride prepared in this way is not always pristine since mixed chloroaluminum hydrides can be formed, depending on the proportions of lithium aluminum hydride and aluminum chloride.[211] The most common mixed hydrides are Cl_2AlH and $ClAlH_2$ and adjusting the stoichiometry of the reagents can produce either as the major product. When properly prepared, aluminum hydride reduces aldehydes, ketones, acid chlorides, epoxides, acids, tertiary amides, and nitriles with ease. Its most common use, however, is the selective 1,2-reduction of conjugated aldehydes, ketones, and esters, as in the reduction of the conjugated ester in **177** to the allylic alcohol moiety in **178** (94% yield) in Wilson's synthesis of the melon fly pheromone.[212] Similar selectivity is observed with conjugated ketones as shown by the AlH_3 reduction of 2-cyclopentenone to **122** (90% yield), with **124** as a minor product.[213] It is sometimes possible to control the 1,2- versus 1,4-selectivity of $LiAlH_4$, however, by changing reaction conditions. Reduction of cyclopentenone with $LiAlH_4$ in diethyl ether at –70°C gave an 85% yield of **122**.[213]

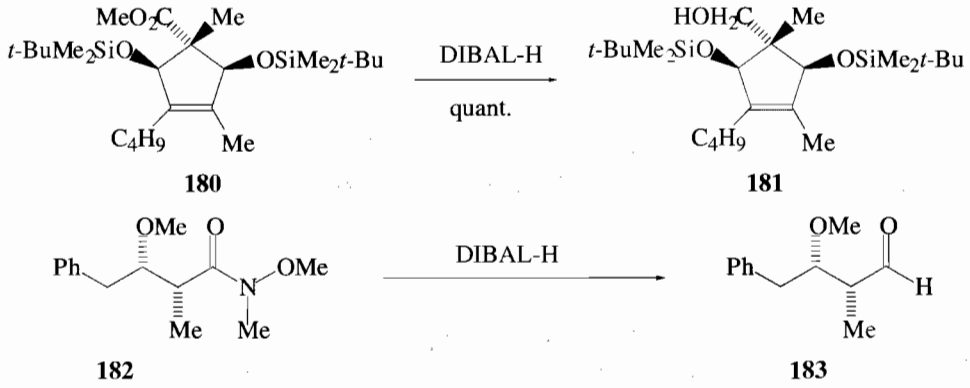


The preference for 1,2-reduction is explained by the Lewis acidity of AlH_3. Aluminum hydride first complexes with the carbonyl (as in **179**), making it difficult for the hydride to be delivered to the end of the alkene moiety via a six-center transition state. The four-center transition state required for delivery of hydride to the carbonyl carbon is, by comparison, very easy to attain. If the complexation is strong, as with AlH_3, then 1,2-reduction predominates. When the coordination is relatively weak, as with $LiAlH_4$, both 1,2- and 1,4-reduction are observed.

4.6.C. Diisobutylaluminum Hydride

It is often difficult to generate pure AlH_3 and this can cause problems in reactions with sensitive substrates. It has been possible to develop alkyl alanes that are analogous to the alkylboranes, and these have proven to be

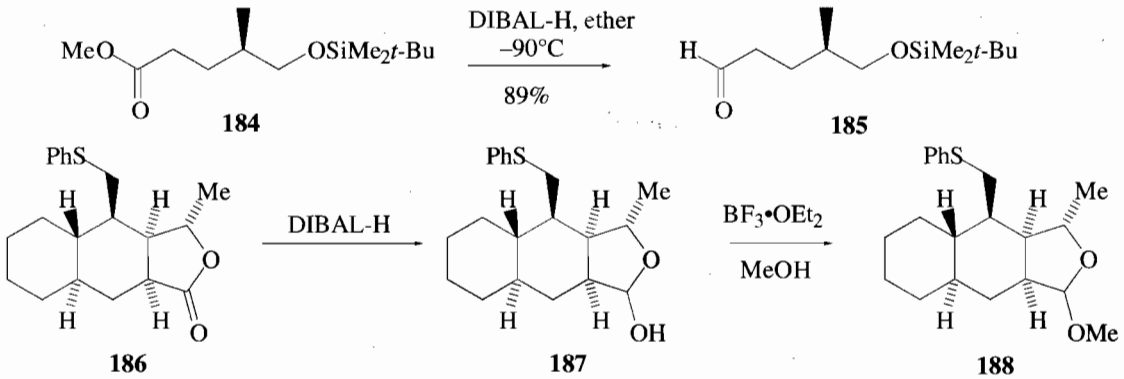
quite useful. A commercially available and commonly used alkyl derivative is diisobutylaluminum hydride ($[(CH_3)_2CHCH_2]_2AlH$, **Dibal**; sometimes called DIBAL-H), prepared by refluxing triisobutylaluminum in the solvent heptane, but other solvents can also be used.[214] It is a pyrophoric liquid when used neat, so it is commonly used as a heptane or ether solution. DIBAL-His a strong reducing reagent, reducing most functional groups. Its synthetic utility lies in three areas: reduction of esters, reduction of lactones, and reduction of nitriles. Esters are commonly reduced to the alcohol, analogous to $LiAlH_4$, as illustrated by reduction of the ester unit in **182** to the hydroxymethyl group in **183** in quantitative yield as part of Ōmura and Smith's synthesis of (+)-madindoline A.[215] Another quite useful reduction involves the conversion of a Weinreb's amide (see sec. 2.5.C) to an aldehyde, as in the reduction of **182** to **183** in Rinehart's synthesis of *N*-Boc Adda (where Adda is (*2S,3S,8S,9S*)-3-amino-9-methoxy-2,6,8-trimethyl-1-phenyl-4,6-decadienoic acid.[216] The Boc group [—NCO_2t-Bu]) will be discussed in Section 7.3.C.iii.



180 **181**

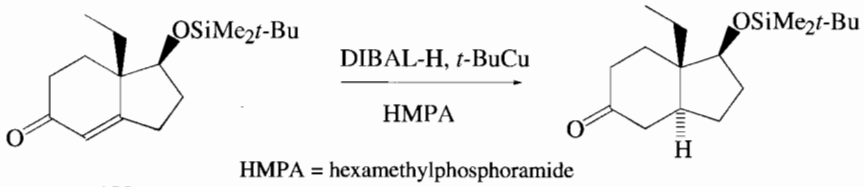
182 **183**

In some cases, it is possible to limit the reduction to a single oxidation stage (specifically, the ester → aldehyde conversion).[217] Ester **184** was reduced at –90°C to give aldehyde **185**, in 89% yield as part of Mulzer's synthesis of tartrolon B.[218] Notice that the reaction was run at low temperature, which is usually required for reduction to the aldehyde rather than the alcohol. In many cases, however, significant amounts of alcohol are formed, even at low temperatures. A popular use of DIBAL-H is reduction of lactones to lactols. This reduction can be done to protect the lactone, as in the reduction of **186** to lactol **187**, which was not isolated but reacted with BF_3 and methanol to give methoxy derivative **188** in 94% overall yield, as part of the Hart et al. synthesis of (+)-himbeline.[219]



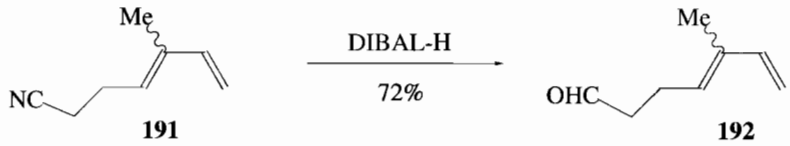
184 **185**

186 **187** **188**



189 **190**

When mixed with alkylcopper reagents (MeCu or *t*-BuCu are the most common), DIBAL-H gives selective 1,4-reduction of conjugated carbonyl compounds. An example, taken from Corey's synthesis of desogestrel, is the conversion of **189** to **190** in 91% yield, using HMPA as a solvent.[220] DIBAL-H is also an effective reagent for the reduction of nitriles to aldehydes, as in the reduction of **191** to **192** in 72% yield[221]



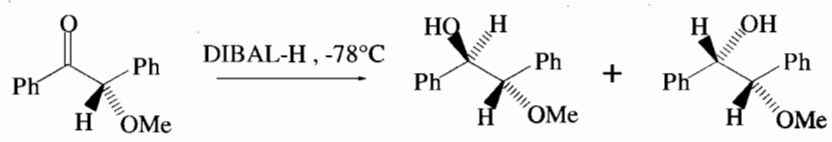
191 **192**

It is clear that borane and aluminum hydride, along with their alkyl derivatives, offer significant advantages for the reduction of many functional groups. Borane is often the reagent of choice for reduction of acids in the presence of esters, aluminum hydride for selective 1,2-reduction of conjugated carbonyls, and DIBAL-H for partial reduction of lactones and conversion of esters and nitriles to aldehydes. It should be pointed out that DIBAL-H also reduces ketones and aldehydes. Reduction of chiral ketone **193** in Table 4.5,[223a] which has a methoxy group α- to the carbonyl that is subject to hydrogenolysis, was reduced to a 99:1 mixture of the anti-alcohol (**194**) and the syn-alcohol (**195**).[222] This example was included to raise a specific question. Why is DIBAL-H so selective that **194** is formed as the major product (why is it so diastereoselective)? That question is addressed in Section 4.7.

4.7. STEREOSELECTIVITY IN HYDRIDE REDUCTIONS

As seen in the reduction of **193**, hydride reduction of prochiral ketones led to alcohol products with good diastereoselectivity but each diastereomer was racemic. In Table 4.5,[223a] the diastereoselectivity (anti/syn

Table 4.5. Diastereoselectivity with Different Reducing Agents for the Reduction of 193



193 **194** **195**

Reducing Agent	Conditions (h)	Yield (%)	194/195
$LiAlH_4$	THF, 0°C (5 h)	89	94.5:6.5
	THF, −78°C (1 h)	85	95:5

	THF, HMPA, 0°C. (5 h)	82	90.4:9.6
	ether, 0°C (0.5 h)	84	97:3
	ether, –78°C (1 h)	83	98:2
DIBAL-H	toluene, –78°C (2.5 h)	78	87:13
	THF, –78°C (2.5 h)	85	99:1
KBH_4	aq MeOH, 0°C (0.5 h)	86	90:10
K-Selectride	THF, –78°C (1 h)	79	98:2
	ether, –78°C (3 h)	68	98:2
$PhSiMe_2H$, Bu_4NF	HMPA, 25°C (32 h)	0	
H_2/Pd	EtOH, 25°C (5 h)	98	76:24

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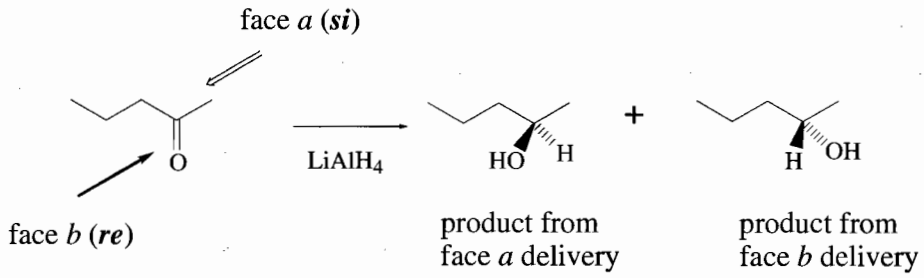
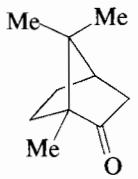
selectivity) for reduction of such substrates is shown to depend on the reducing agent as well as the reaction conditions. This table shows not only a variety of reducing agents (some will be discussed later in this chapter), but also their selectivity for the reduction of this prochiral center (sec. 1.4.E). When diastereomers are formed by reduction of carbonyl groups, how can the relative stereochemistry of such reductions be predicted and what is the absolute stereochemistry of the reduction? The following sections will attempt to answer these questions.

4.7.A. Chiral Additives in Acyclic Systems

The previous discussion focused on the functional group changes that are possible when hydride reducing agents are used and, when appropriate, their regiochemical preferences. A major aspect of hydride reduction is the stereochemistry of the reduction, as introduced in Table 4.5. A simple example is 2-pentanone, which is reduced to 2-pentanol. The carbonyl is a prochiral center (sec. 1.4.E) since addition of hydride from the two



faces (*a* or *b*) of the carbonyl generates enantiomers.[223b] Since both faces are equally susceptible to attack (as shown), the alcohol product is racemic. There is no facial bias in the reaction and most hydride reagents discussed previously generate racemic products. If a stereogenic center is present in the molecule prior to



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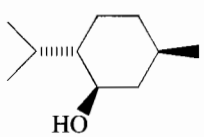
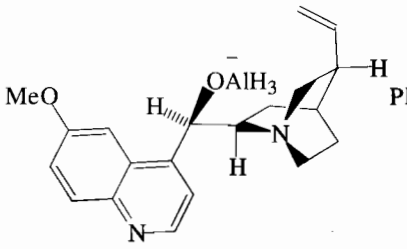


197

reduction, diastereomers are formed, and the first center can influence the stereochemistry of the one being formed. Acyclic ketones or aldehydes without a pendant chiral center will also give racemic alcohols. If the reaction gave only one enantiomer it would be classified as enantiospecific (100% ee, sec. 1.4.F). If it gave a predominance of one enantiomer it would be classified as enantioselective (> 0% ee but < 100% ee, where 0% ee represents a 50:50 mixture). Development of chiral reducing agents has led to enantioselective reductions.



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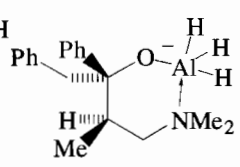

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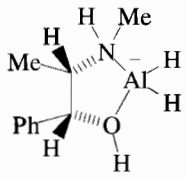

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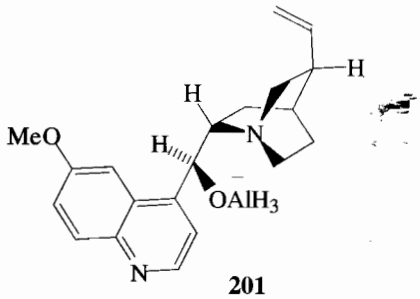
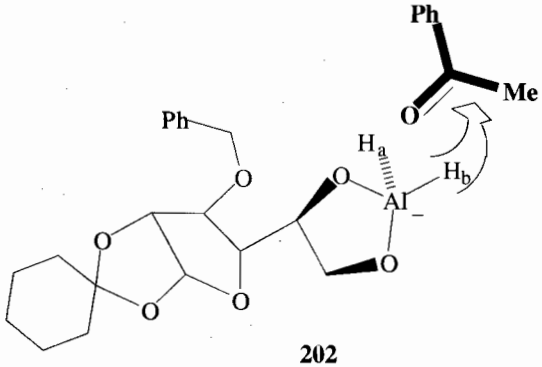


201

This technique was described in the monograph by Morrison and Mosher that covered the literature up to ≈ 1970.[224] Early work in this area attempted to prepare chiral reagents by reacting hydride reagents with natural products that contained chiral centers of known absolute stereochemistry, such as (–)-camphor (**196**),[225,226] or (–)-menthol (**197**).[226b] Reaction of these molecules with $LiAlH_4$ prior to addition of a substrate with a prochiral carbonyl led to a reagent capable of reducing the carbonyl with modest asymmetric induction. These reagents were not very effective, however. Reduction of methyl *tert*-butyl ketone (3,3-dimethyl-2-butanone), for example, showed no asymmetric induction when the product (3,3-dimethyl-2-butanol) was analyzed. Other chiral natural products have been attached to $LiAlH_4$ and their use has led to



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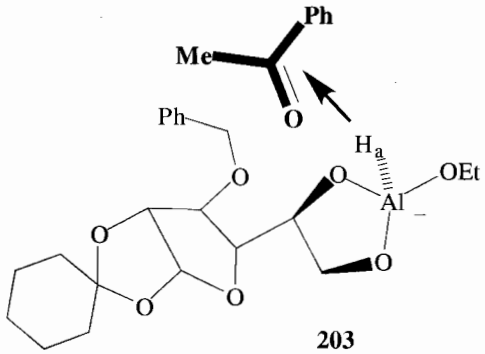
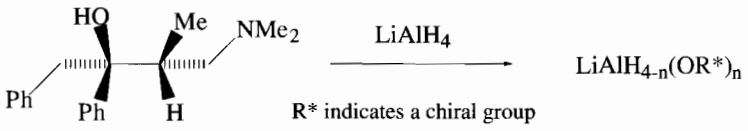


203

moderate-to-good enantioselectivity. Quinine reacts with $LiAlH_4$ to give **198**, (+)-(*2S,2R*)-1,2-diphenyl-3-methyl-4-dimethylamino-2-butanol (Darvon alcohol; Darvon is the O_2CEt ester of this alcohol) gave **199**, and ephedrine gave **200**. In addition, (+)-quinidine (**201**, a diastereomer of quinine) and (+)-cinchonine (the derivative of quinidine without the OMe group on the quinoline unit) are chiral reducing agents.[224] *Cinchona* alkaloids such as these were used by Sharpless as chiral additives in the **Sharpless asymmetric dihydroxylation** reaction discussed in Section 3.5.B.ii. Acetophenone reacted with **198** to give the (*R*)-phenethyl alcohol in 48% ee.[227] Similar reduction of acetophenone with **199** gave the alcohol with 45% ee, **200** gave 13% ee (*R*)-

and **201** gave 23% ee (*S*).[217] Lithium aluminum hydride derivatives of monosaccharides have been used to give moderate % ee in reduction of cyclic ketones. The bis(alkoxy) derivative of lithium aluminum hydride - 3-*O*-benzyl-1,2-cyclohexylidene α-*D*-glucofuranose (**202**), and the analogous 1:1 ethanol adduct (**203**) gave enantioselective reduction of acetophenone.[228] Reducing agent **202** reacted with acetophenone to give *(S)*-phenethyl alcohol with 33% ee. Adduct **203** showed greatly improved but opposite selectivity, giving 71% ee in the product *(R)*-phenethyl alcohol when reacted with acetophenone.

The structural features that lead to asymmetric induction usually vary with the reagent, making generalization difficult. Landor found that H_b in **202**, for example, was transferred to a carbonyl group during reduction faster than H_a. Acetophenone was reduced to give the (*S*)-alcohol, and this demands that the ketone approach H_b in **202** away from the protruding O-benzyl group, as shown. This model corresponds to approach of the reagent from the *re* face. Presumably, the methyl–oxygen lone–pair interaction is less than the phenyl–oxygen lone pair interaction. This difference is not great and the observed enantioselectivity was only modest. When ethanol was incorporated into the reagent (see **203**), H_b was replaced with an ethoxy group, making H_a the only source of hydride. The carbonyl must now approach on the same face of the carbohydrate as before, but to reduce steric interactions the orientation of the ketone relative to H_a places the larger phenyl group up and away from the sugar moiety (the *si* face). This approach leads to reduction that generates the *(R)*-alcohol.[228]

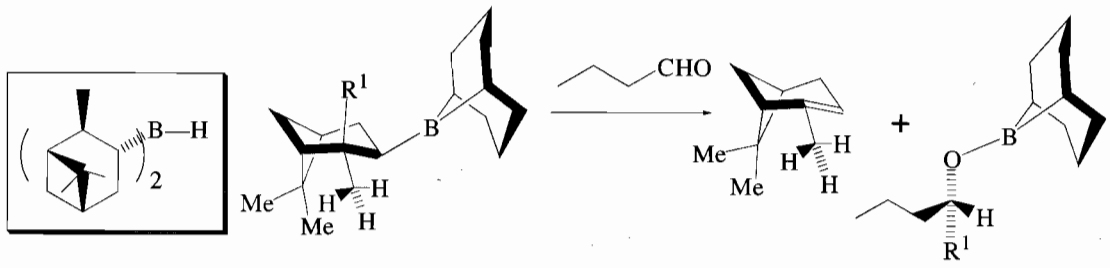


204 **205**

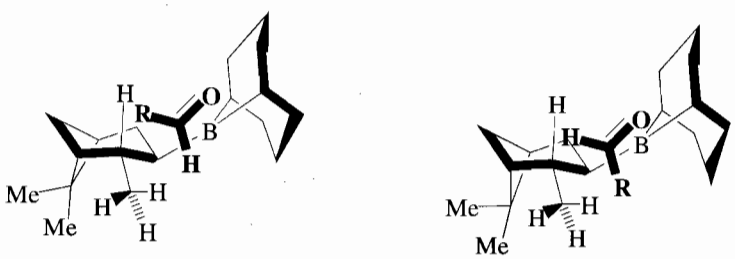
Although this steric analysis is attractive, it does not apply to reagents such as the lithium aluminum hydride-Darvon alcohol reagent (see **199**), prepared by Mosher (Darvon alcohol is **204**).[229] First of all, the hydride reacts to form an alkoxyaluminate (**201**) where the value of *n* may be 1, 2, or 3 (although *n* was shown to be 1 in **205** and is probably 2 after the initial reaction of $LiAlH_4$ with **204**). Second, the coordination state of the aluminum is unknown (both tetrahedral and octahedral coordination complexes are possible). Finally, the age of the reagent is important. Freshly prepared reagent is insoluble in ether solvents and reacts selectively to give the *(R)*-phenethyl alcohol from acetophenone. If the reagent is allowed to age, it becomes soluble and gives the *(S)*-alcohol on reduction, which is probably not due to formation of a tris-alkoxyaluminate ($n = 3$), however. These ambiguities preclude the simple steric analysis that was possible with the structurally well-defined **202** and **203**. When the structure of the active reducing agent is known, steric and facial arguments can predict approach to the carbonyl from the less hindered face with an orientation that minimizes steric interactions (generating the major diastereomer or enantiomer).

Chiral boranes can be used as reducing agents for carbonyl compounds.[230] Brown prepared a variety of chiral boranes in connection with extensive studies of hydroboration reactions (sec. 5.4.B). Reaction of diborane and α-pinene, for example, gave (–)-(1*R*,2*S*,3*R*,5*R*)-diisopinocampheylborane (**206**), which reduced carbonyl derivatives to alcohols with high asymmetric induction.[231] Trialkylboranes are also capable of

reducing carbonyls, but by a different mechanism (i.e. hydride comes from C-H rather than Al—H or B—H). Boranes such as Midland's (–)-(1*R*,2*S*,3*S*,5*S*) complex between pinene and 9-BBN [**207** (R' = H), B-3-pinanyl-9-borabicyclo-[3.3.1]nonane = Alpine borane®] are chiral and can be used for the asymmetric reduction of aldehydes and ketones.[232] Alpine borane® reduced *d*-butanal to d_1-1-butanol with high enantioselectivity.[233] The source of hydride in Alpine borane® (and generally in trialkylboranes) is the tertiary hydrogen (R' = H)

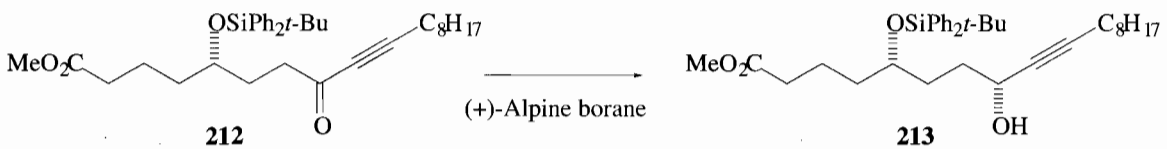


206 **207** **208** **209**



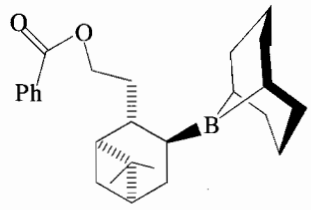
210 **211**

that has been replaced by deuterium in **207** (R' = *d*). Reduction of butanal gave the *(R)*-deuterobutanol (**205**, where R' = *d*) and pinene (**208**).[224] The first important consideration is the observation that tertiary β-hydrogens in these boranes are removed much faster than the secondary or primary β-hydrogens.[234,232a] Approach of the carbonyl to this hydrogen must occur from the face (**210**) nearest the tertiary β-hydrogen (R' = D in **211**). It might appear at first that the R= group in the aldehyde (R = *n*-propyl) would prefer to be oriented away from the pinanyl ring, but in fact the opposite is true. Examination of **210** shows the R group is over the pinanyl ring but away from the protruding bridgehead hydrogen, which is the required approach for reduction (the *re* face of the aldehyde) and there is minimal steric interaction.[233] When the aldehyde approaches with the opposite orientation (the *si* face as in **211**) the R group interacts with the hydrogens on the methyl group, sterically destabilizing **211**.[233] The orientation in **210** is preferred, leading to the *(R)*-alcohol in this case. The extent of selectivity observed in the reduction of ketones depends on the relative size and nature of the groups attached to the carbonyl. An example is the reduction of alkynyl ketone **212** to **213** in up to 86% yield (>93% ee) in Nakanishi's synthesis of PsiAβ.[235] In this case, the alkynyl group is considered the small group in the steric analysis.



212 **213**

With all reagents generated by addition of chiral materials to $LiAlH_4$, their exact structure must be determined before facial and orientation preferences can be determined for a given substrate. As illustrated by Alpine borane®, the mechanism of hydride transfer must also be known. When these parameters are known, careful examination of models (Dreiding® models or computer generated modeling) should determine the actual steric interactions. A casual inspection is usually insufficient for accurate predictions however.



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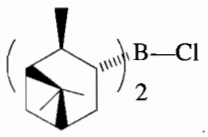

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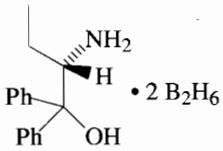

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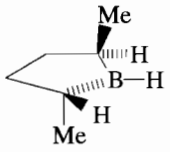

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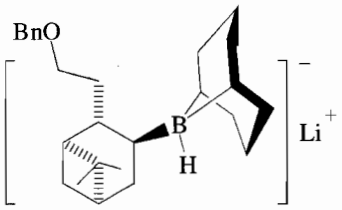

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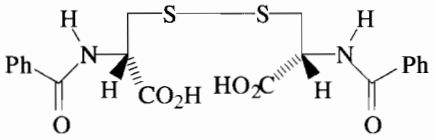

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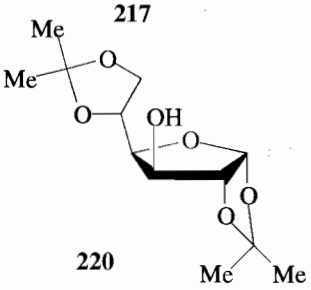

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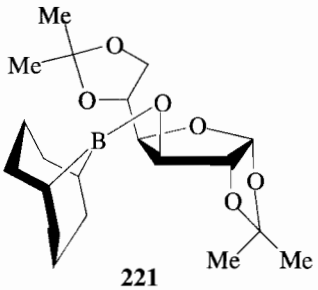
Morrison and Mosher collected data for asymmetric induction in the reduction of several acyclic ketones and this monograph is an excellent source when one must choose an asymmetric reducing agent.[236] The use



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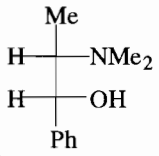

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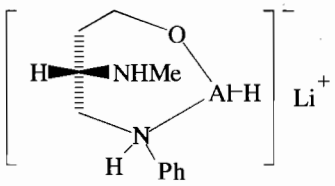

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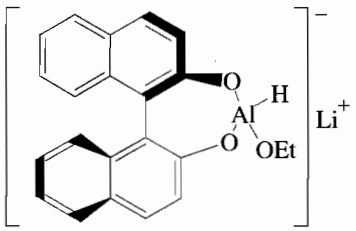

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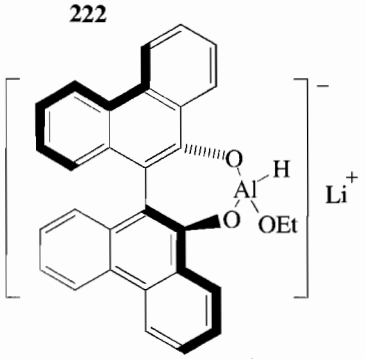

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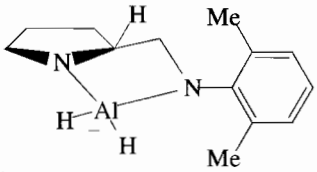

226

of (–)-**206** for reduction of acetophenone in diglyme, for example, gave 14% ee [(*R*)-phenethyl alcohol]. Similar reduction of ethyl isopropyl ketone (2-methyl-3-propanone) gave 62% ee of the (*S*)- alcohol in

THF.[236] Many new reagents have been developed and used in organic synthesis. Brown compared several chiral boranes with other chiral complexes for the reduction of several cyclic and acyclic ketones.[237] Several reagents have already been discussed, including **206** and **299**. Other reagents include enantrane (**214**),[238] diisopinylcamphenyl chloroborane (Ipc_2BCl, **215**),[239] the mixture of diborane and AMDPB (**216**),[240] (2*R*,5*R*)-dimethylborolane (**217**),[241] NB-enantride (**218**),[242] (*S,S'*)-*N,N'*-dibenzoylcystine and (**219**) and lithium borohydride,[243] 1,2,5,6-di-O-isopropylidene-*D*-glucofuranose (**220**) and sodium borohydride,[244] K-glucoride (**221**),[245] a mixture of $LiAlH_4$ and *N*-methylephedrine (**222**) in the presence of 3,5-dimethylphenol,[246] a mixture of $LiAlH_4$ and (*S*)-2-(2,6-xylidinomethyl)-pyrrolidine (**223**),[247] the lithium aluminum hydride-(*S*)-(4-anilino)-3-(methylamino)-1-butanol complex (**224**),[248] Binal-H (**225**),[249] the lithium aluminum hydride-ethanol-(*S*)-(−)-10,10'-dihydroxy-9,9'-biphenanthryl complex (**224**),[250] the lithium aluminum hydride-**222**-*N*-ethylaniline complex,[251] the lithium aluminum hydride-**222**-2-(ethylamino)-pyridine complex,[252] and an enzymatic reduction (sec. 4.10.F) with *Thermoanaerobium brockii* alcohol dehydrogenase (**227**).[253] Brown collected these data into Table 4.6,[237] in which the preferred chiral reducing agents were chosen for different classes of ketones. Table 4.6 provides general data and it is not exhaustive, but the term effectiveness presumably refers to the order in which the reagents appear. The reagent

Table 4.6. Preferred Asymmetric Reducing Agents

Class of Ketones		Preferred Reagents (in decreasing order of effectiveness)
I. Acyclic	a. Unhindered	**217**. 2,5-dimethylborolane
		206. B-Ipc-9-BBN, 6 Kbar
		227. *T. brockii*
	b. Hindered	**217**. 2,5-dimethylborolane
		215. Ipc_2B-Cl
		216. BH_3-AMDPB (2:1)
II. Cyclic		**215**. Ipc_2B-Cl
		216. BH_3-AMDPB (2:1)
		221. K-Glucoride
III. Aralkyl	a. Unhindered	**206**. B-Ipc-9-BBN, 6 Kbar
		215. Ipc_2B-Cl
		223. $LiAlH_4$-DBP-EtOH
		224. Binal-H
		226. $LiAlH_4$-diamine
		216. BH_3-AMDPB (2:1)
	b. Hindered	**221**. K-Glucoride
		226. $LiAlH_4$-diamine
		215. Ipc_2B-Cl
IV. Heterocyclic		**206**. B-Ipc-9-BBN, 6 Kbar
		206. B-Ipc-9-BBN, neat
		215. Ipc_2B-Cl
V. α-Halo		**206**. B-Ipc-9-BBN, neat
		216. BH_3-AMDPB (2:1)
		215. Ipc_2B-Cl
		224. Binal-H
VI. α-Keto esters		**206**. B-Ipc-9-BBN, neat
VII. β-Keto esters		**219**. $LiBH_4$-DBC-t-BuOH

	215. Ipc_2B-Cl
VIII. Acyclic conjugated enones	**224**. Binal-H
	A. $LiAlH_4$-MEP-NEA[a]
	223. $LiAlH_4$-aminobutanol
IX. Cyclic conjugated enones	**223**. $LiAlH_4$-aminobutanol
	B $LiAlH_4$-MEP-EAP[b]
X. Conjugated ynones	**224**. Binal-H
	214. NB-Enantrane
	222. $LiAlH_4$-MEP-ArOH
	206. B-Ipc-9-BBN, THF

[a]**A**. **222** + $LiAlH_4$ + 2-ethylaminopyridine[251] [b]**B**. **222** + $LiAlH_4$ + 2-ethylaminopyridine[252] (*R*)- for 2,2-dimethylcyclopentanone to 16% ee (*S*) for 2-chloroacetophenone to 71% ee (*S*) for 2-cyclohexen-1-one.[254]

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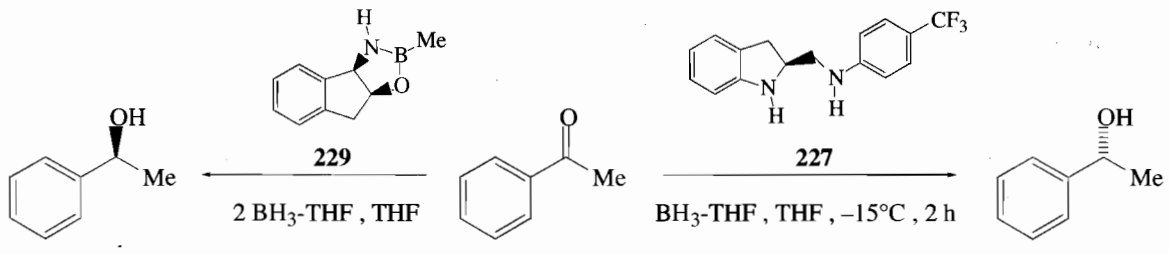
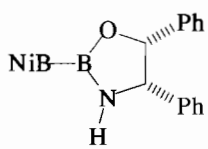
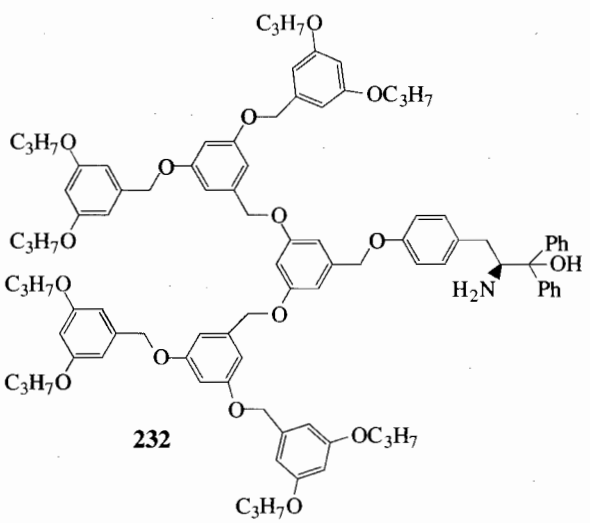
giving the highest % ee with good yields of the reduction products appears at the top of the list with the following reagents being less effective. This table allows one to choose a chiral additive and reducing agent for reduction of a given type of ketone. Brown also described a series of chiral *ate* complexes from boronic esters that showed high diastereoselectivity for the reduction of ketones.[254]



230 **228**



231



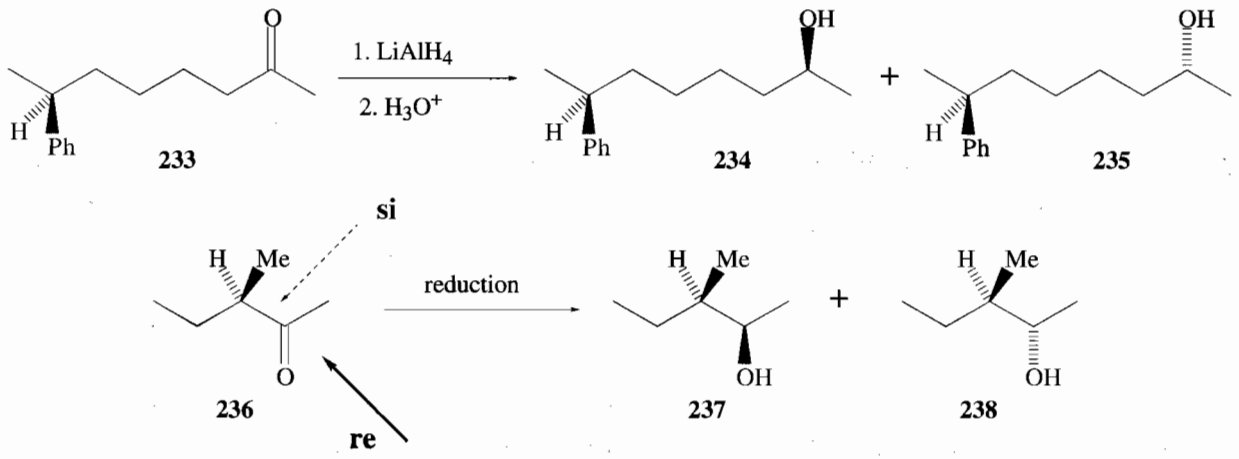
232

Development of chiral additives for asymmetric reduction is an on-going area of research. A sampling of some newer reagents include the reduction of acetophenone with a **227**–borane complex, giving **228** in 88%

yield and 92% ee (*R*).[255] Reduction of acetophenone and 0.1 equivalents of oxazaborolidine **229** in the presence of borane gave a >95% yield of the (–)-enantiomer [**230**; 84% ee, (*S*)].[256] When oxazaborolidine–nickel boride complex (**231**) was mixed with borane, acetophenone was reduced to **230** with 94% ee.[257] It is noted that the use of oxazaborolidine reagents for the enantioselective reduction of ketones was previously described.[258] Oxaborolidines derived from amino alcohols of (1*R*)-camphor have also been used as catalysts.[259] Bolm et al. showed that hyperbranched dendritic amino acids such as **232** (much more highly branched dendrimers were also used) gave reduction when mixed with a borane-dimethyl sulfide complex. Dendritic amino acid **232**, for example, reduced acetophenone under these conditions to **228** in 78% yield and 89% ee (*R*).[260]

4.7.B. Selectivity in the Reduction of Carbonyl Derivatives Containing a Chiral Carbon

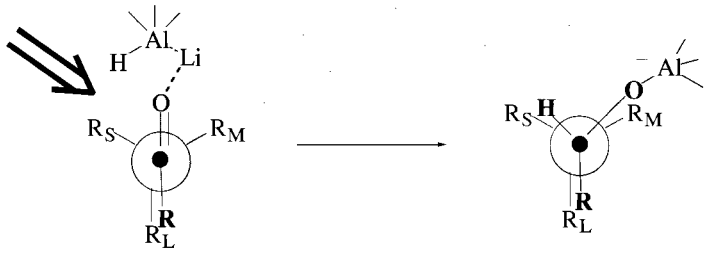
As seen in Section 4.7.A, the preparation of chiral reagents from hydrides gave reasonable diastereoselectivity, but the % ee was often poor to moderate. A different situation arises when the prochiral center is in a molecule that already contains a stereogenic center, because reduction generates diastereomers, as in the reduction of **233** and **236**. In the former case, **233** contains a stereogenic center but it is too far removed from the prochiral center to exert much influence. Reduction of this compound will be, more or less, the same as reduction of a ketone with no stereogenic center, and the resulting mixture should be close to a 1:1 mixture of syn and anti diastereomers (**234** and **235**). The absolute configuration of the stereogenic center at C7 in **233**



is unchanged in both **234** and **235** and does not influence the reduction of the carbonyl moiety. Ketone **236**, however, has a stereogenic center adjacent to the carbonyl and its chirality will exert an influence on the approach of the incoming reagent. Reagents will approach from the face presenting the least amount of steric hindrance. In **236**, approach over the hydrogen face (the *si* face) will give **237** but approach over the more hindered methyl face (the *re* face) will give **238**. Note that alcohols **237** and **238** are diastereomers. This ketone and similar acyclic systems are not locked into a single conformation and the carbonyl can be down (as shown) or up. This means that reduction occurs from both the *re* and the *si* face to give a mixture. Interaction with the reducing agent can, however, influence the conformation of the reactive carbonyl compound and,

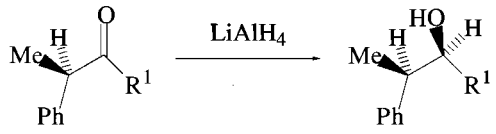
thereby, the diastereoselectivity. It is entirely reasonable that the conformation of the carbonyl compound is locked in the transition state leading to products. If one is to control diastereoselectivity, not only must facial and orientation bias be addressed, but the conformation of the reactant in the transition state must be known.

The extent of asymmetric induction in systems containing an adjacent stereogenic center has been discussed by Morrison and Mosher.[261] Cram suggested a model for asymmetric induction in ketones such as **236** that has come to be known as **Cram's open chain model** (**Cram's model**), or simply **Cram's rule**.[262,263] This model assumes a kinetically controlled reaction (nonequilibrating and noncatalytic) for asymmetric 1,2-addition to aldehydes and ketones. The three groups attached to the chiral center are R_S (small substituent), R_M (middle-sized substituent), and R_L (large substituent). Determining the relative size of the substituents is



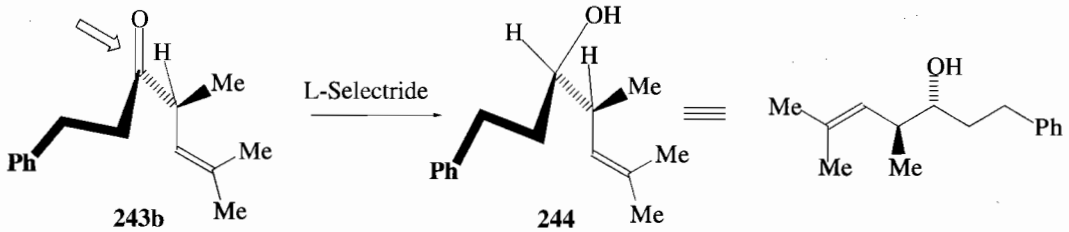
239 **240**

not always straightforward, since the *largest* group is defined as the most sterically demanding group relative to the other substituents and the incoming reagent. A typical Cram model is shown as its Newman projection (**239**) and assumes that there is a predominant rotamer in which the large substituent (R_L) is syn- to the R^1 group attached to the carbonyl. The hydride is delivered from the less sterically hindered face (over the smallest substituent R_S) to give **240** as the major diastereomer. Stereoselectivity is determined by the extent of

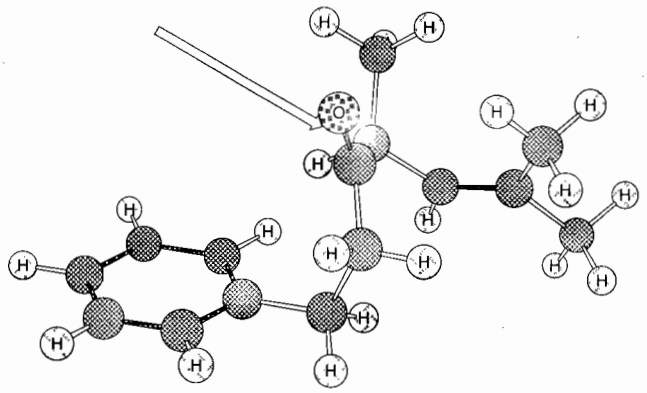


241 **242**

the O↔R_S or O↔R_M interaction with the metal hydride. The greater the difference in steric bulk between R_S and R_M, the greater the selectivity. If R_S and R_M are close in size, this model predicts little or no selectivity. This model also assumes the R_L↔R^1 interaction is minimal, which is not entirely correct.[264,291] The proportion of the anti- product (**242**) produced by $LiAlH_4$ reduction of chiral ketone **241** increases as the steric bulk of R^1 increases (48% when R^1 = Me; 52% for R^1 = Et; 70% for R^1 = *i*-Pr; 96% for R^1 = *t*-Bu). This suggests that the R_S-R_M↔R^1 rather than the R_S-R_M↔O interaction is important in this model. A synthetic example is the L-Selectride reduction of **243b** to give more than 99% of the anti-diastereomer (**244**).[265] From the Cram model (see 3D drawing[266] **243a**) the large group (C=CMe_2) is syn- to the 2-phenylethane moiety on the carbonyl, and delivery of hydride over the small group (H) predicts the threo-(anti-) selectivity in the product (**244**).

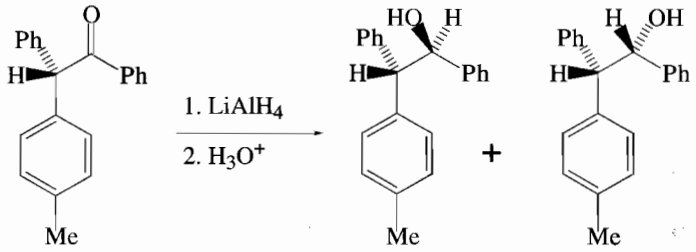


243b 244



243a

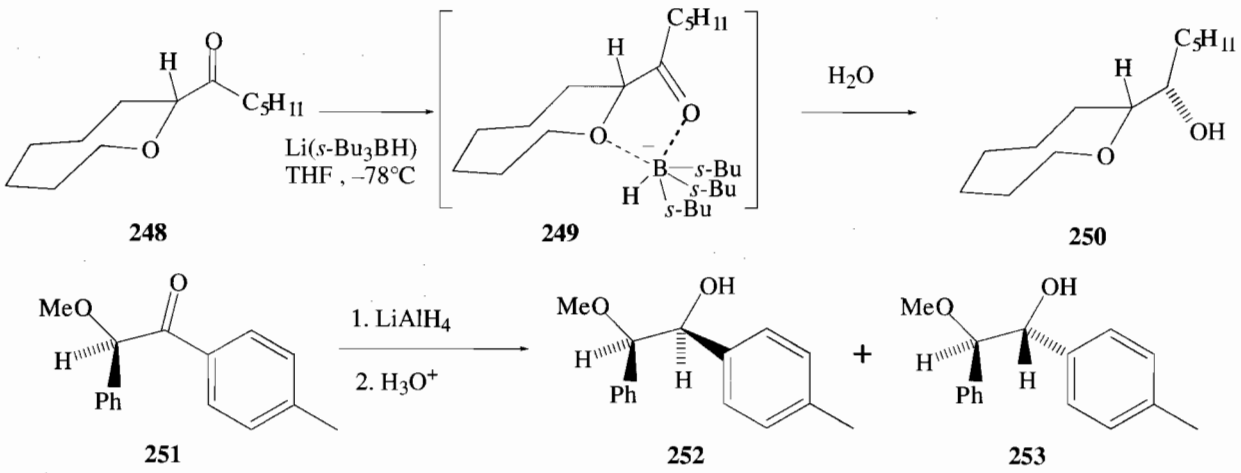
When the relative difference in size of the groups is negligible, little or no diastereoselectivity is observed. Reduction of **245**, for example, gave a 1:1 mixture of syn- and anti-diastereomers, **246** and **247**.[267] We are comparing phenyl with 4-methylphenyl. At the reactive center (the carbonyl), the methyl group of the *p*-tolyl moiety is rather far away, which means that phenyl and tolyl are essentially identical from a steric viewpoint and in their ability to make a meaningful difference in facial selectivity. To the approaching hydride reagent, phenyl and tolyl are virtually identical in size when analyzed by the Cram model.



245 246 247

When an oxygen, sulfur, or nitrogen is attached to the carbon α to the carbonyl, the metal of the hydride can coordinate (chelate) to both the heteroatom and the carbonyl oxygen, which leads to a cyclic structure that effectively locks the molecule into a single rotamer. The Cram designations of large, medium and small no longer have the same meaning. When such a cyclic chelated structure can be formed, the model is changed to the **Cram cyclic model** (more commonly called the **Cram chelation model**).[267,268] When an hydroxyl group, an ether, amino, amide, thiol or thioether group is in the α-position chelation to that group makes it eclipse the carbonyl, as shown in complex **249**. Delivery of hydride from the less hindered face (over R_S)

predicts the major diastereomer. In this example, the ether oxygen in the eight-membered ring in **248** is the chelating atom, and **250** was isolated in 48% yield as the single diastereomer shown, as part of Holmes synthesis of (+)-laurencin.[269] The selectivity in this model will depend on the reagent, the chelating ability of the



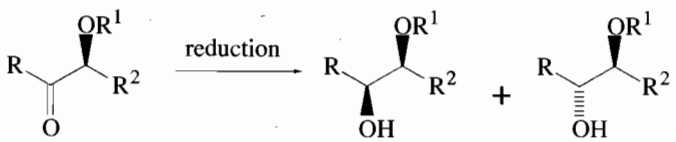
248 **249** **250**

251 **252** **253**

substituent, the coordinating ability of the solvent as well as the relative size of the substituents (R_S and R_L). Morrison and Mosher presented data for these systems,[270] that included reduction of **254** to an 88:16 mixture of **255** and **256**.[267] The presence of the methoxy group in **254** led to a chelated intermediate, and the Cram cyclic model predicts the correct diastereoselectivity. In derivatives where the hydroxyl is blocked (protected - chap. 7), the reduction proceeds with normal Cram selectivity.[271] In general, a hydroxyl substituent is capable of coordinating via a hydrogen bond and should be more tightly bound than when the hydroxyl is blocked (as in an OMe group). The distance between the chelating group and the carbonyl is an important consideration.

Oishi[272] and co-workers studied the diastereoselectivity of several reducing agents that reacted both with α-alkoxy and α-hydroxy ketones (**254**–see Table 4.7).[272] These results indicate a distinct preference for the anti (erythro) diastereomer **256** when $Zn(BH_4)_2$ was used for reduction of the keto-alcohol. More anti product was obtained with $LiAlH_4$, but the reaction was less selective. The Cram chelation model for the anti transition state (**257**) to give **256** was favored over the model for syn selectivity (delivery over the methyl

Table 4.7 Diastereoselectivity in Reduction of α-Alkoxyketones



254 **255** **256**

R	R^1	R^2	Reducing agent	255/256
n-C_5H_{11}	H	Me	$LiAlH_4$	36:64
n-C_5H_{11}	H	Me	$Zn(BH_4)_2$	23:77
n-C_4H_9	H	Et	$Zn(BH_4)_2$	11:89
n-C_3H_7	H	*n*-C_3H_7	$Zn(BH_4)_2$	<1:>99

Et	H	*n*-Bu	$Zn(BH_4)_2$	13:87
Me	H	*n*-C_5H_{11}	$Zn(BH_4)_2$	15:85
			$LiAlH_4$	30:70
i-Pr	H	Me	$Zn(BH_4)_2$	15:85
			$LiAlH_4$	42:58
Me	H	*i*-Pr	$Zn(BH_4)_2$	4:96
			$LiAlH_4$	27:73
Ph	H	Me	$Zn(BH_4)_2$	2:98
			$LiAlH_4$	13:87
Me	H	Ph	$Zn(BH_4)_2$	10:90
			$LiAlH_4$	20:80
n-C_5H_{11}	$SiPh_2tBu$	Me	Red-Al	61:39
Et	$SiPh_2tBu$	*n*-Bu	Red-Al	93:7
i-Pr	$SiPh_2tBu$	Me	Red-Al	46:54
Me	$SiPh_2tBu$	*i*-Pr	Red-Al	96:4
Ph	$SiPh_2tBu$	Me	Red-Al	91:9
Me	$SiPh_2tBu$	Ph	Red-Al	76:24

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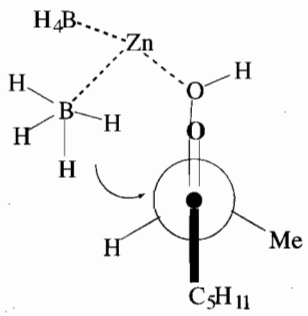
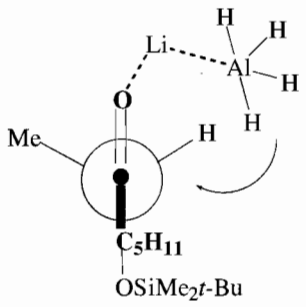
group to give **255**). When hydroxyl was replaced with a bulky silyl ether, the selectivity changed from anti to syn. Chelation was diminished and Cram's rule (**258**) is used to predict the correct syn-selectivity. In Section 4.4.B excellent diastereoselectivity was obtained in the zinc borohydride reduction of **114**, giving **116** as the

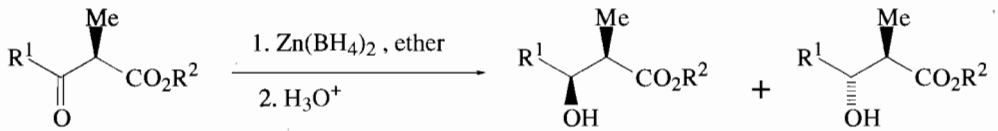


257



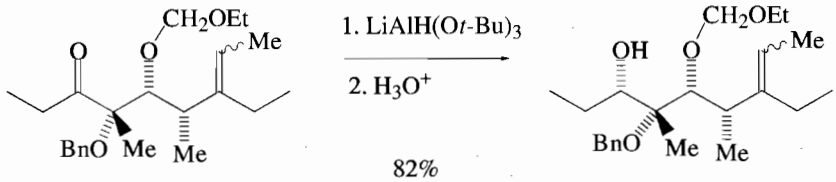
258

major product. Oishi examined the reduction of β-keto esters such as **259** (R^1 = Ph, R^2 = Me) with zinc borohydride and found a preference for the syn-product (**260**, R^1 = Ph, R^2 = Me) over the anti-product (**261**), by more than 99:1 (98% yield).[149] The analogous methyl ketone (**259**, R^1 = Me, R^2 = Bn) gave only a 2:1 mixture of **260/261** under identical reaction conditions.[149] The zinc coordinates both the carbonyl of the ester moiety and the oxygen of the prochiral carbonyl group. Hydride is delivered from the less hindered face (over hydrogen), which is the *si* face when R^1 is phenyl and the *re* face when R^1 is methyl (referring to **259**).



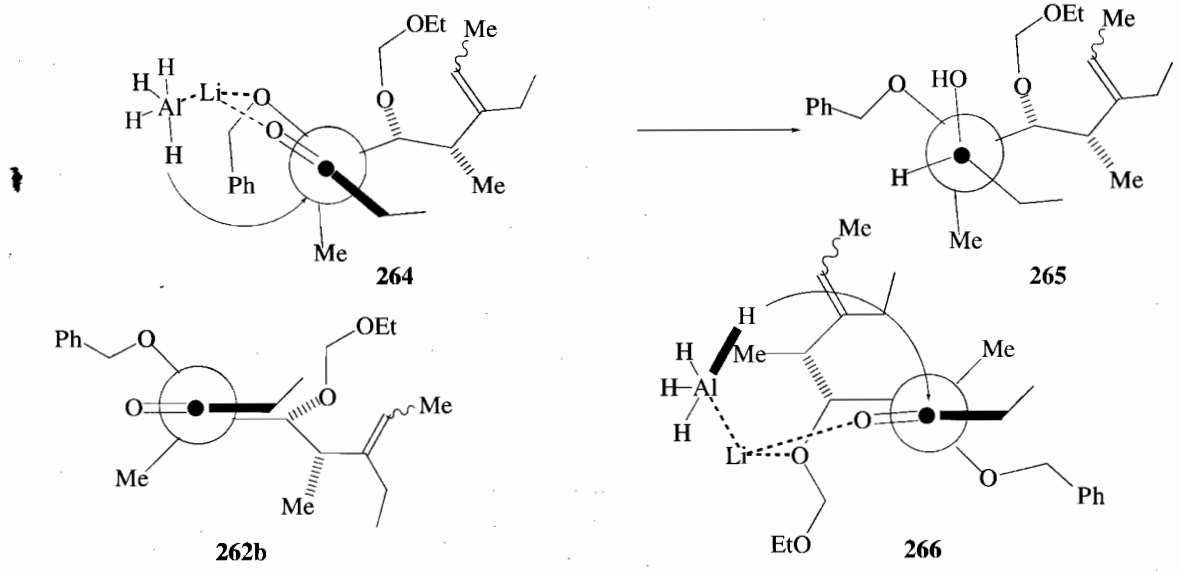
259 **260** **261**

The presence of an α-alkoxy substituent does not always lead to Cram selectivity. Reduction of **262a** gave 82% of the syn diastereomer, **263**.[273] Analysis of the Cram cyclic model for **262** (see **264**) leads to an incorrect prediction of the anti-diastereomer (**265**) as the major product. The normal Cram model (see **262b**) predicts the correct syn-diastereomer (**263**) but in reality, the solution to this problem requires that the alkoxy substituent at the C3 position be coordinated with the metal of the reducing agent. In **264**, a five-membered



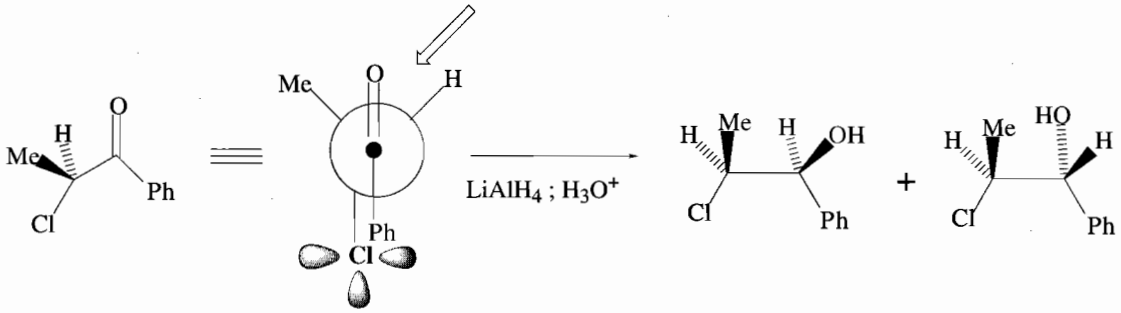
262a **263**

cyclic transition state is possible via coordination with the benzyloxy group. In **266**, coordination of the reagent to the 3-alkoxy substituent leads to a six-centered cyclic transition state, with delivery of hydride from the less hindered methyl face, leading to **263**. With hindered reducing agents such as tri-*tert*-butoxyaluminum hydride, **266** is preferred to **264**. With several alkoxy substituents, it is clear that the model required to predict the major diastereomer becomes more complex.



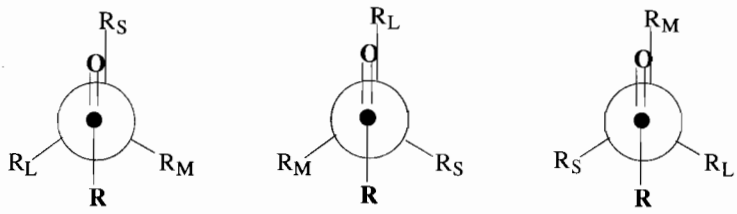
262b **264** **265** **266**

The reduction of **262a** illustrated that chelating substituents at the carbon β to a carbonyl can influence the diastereoselectivity of hydride reductions, which is particularly important for the reduction of 1,3-diketones and β-ketoesters. When the α-substituent is a halogen, however, the open-chain model does not predict the correct results nor does the chelation model. Cornforth et al. suggested that the electron pairs on the carbonyl oxygen and on the halogen will repel and assume an anti-conformation,[274] as in **267**. In effect, the halogen becomes R_L, with delivery of hydride over the smallest group, which has come to be called the **Cornforth model**. Reduction of **267** gave a 75:25 mixture of **268** and **269**, with the major product predictable by the Cornforth model.[275]



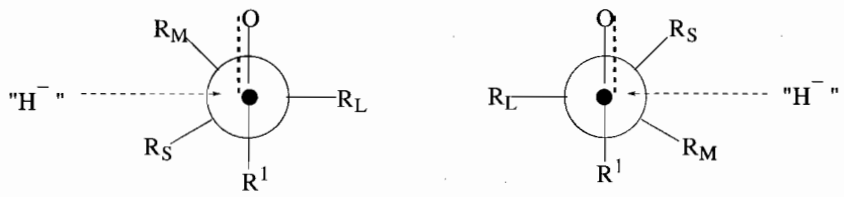
267 **268** **269**

The Cram open-chain model assumed the presence of a reactive species that led to a higher energy eclipsed conformation in the final product. The Cram open-chain model fails to predict the correct diastereoselectivity for many acyclic molecules that contain heteroatom substituents.[276] The Cram model also fails to predict the correct diastereomer when the relative size R_S and R_M are close. One attempt to correct the deficiencies of the



270 **271** **272**

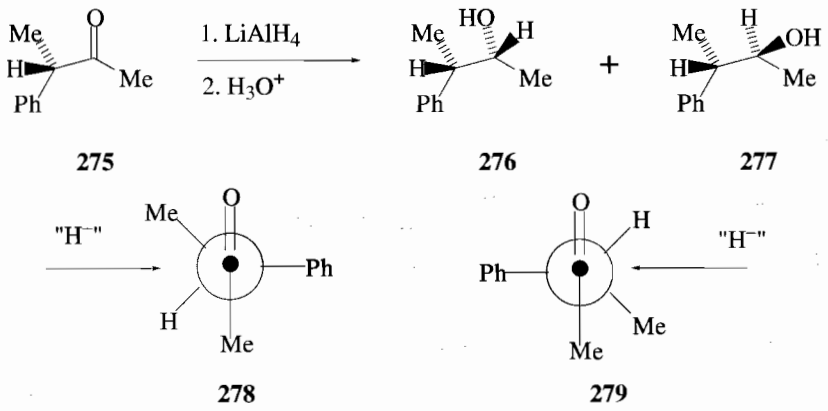
Cram model was a modification introduced by Karabatsos.[277] He assumed a *reactant-like transition state* that showed little bond breaking or bond making. The rotamer chosen for the model showed the groups on the chiral carbon to be aligned as in a normal sp^3–sp^2 bond, which led to three rotamers that were considered by the **Karabatsos model** (**270**–**272**), where the R_S group was assumed to be closest to the incoming reagent in each.[278] It is noted that reaction via all three rotamers lead to an anti-conformation in the product. Karabatsos showed that **272** was favored over **270** by 0.8 kcal mol^{-1} (3.35 kJ mol^{-1}) when R_S = H and R_M = Me. The selectivity of a reduction was assumed not to be dependent on the higher energy of **270** but only on rotamers **271** and **272**. The destabilizing O↔R_L and O↔R_M energy interactions in these two rotamers determine the diastereoselection for the reaction. This model does not adequately solve the problems when R_S is large or when applied to cyclic molecules. It offers advantages over the Cram model in some applications.



273 **274**

Felkin and Ahn proposed an alternative model that gave somewhat better results in these systems.[279,280] The model was based on several assumptions. (1) the transition states are reactant-like; (2) the previous

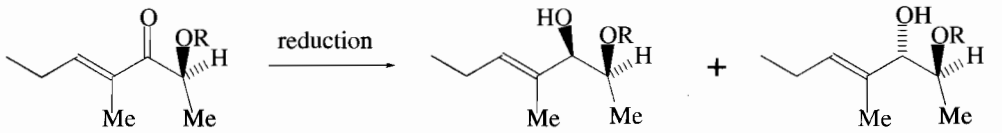
eclipsed models introduce significant torsion strain in the partial bonds of these transition states; (3) the important steric interaction in these transition states involves the group attached to the prochiral center and the incoming group; (4) polar effects stabilize the transition states in which the separation of the incoming group and any electronegative substituent at the α-carbon is greatest and destabilize the others. Felkin concluded that models **273** and **274** were the most important. The use of these structures to predict diastereoselectivity is called the **Felkin–Ahn model**.[279] When R_M is small relative to R_S, there is little difference in the destabilizing $R_M \leftrightarrow O, R_S \leftrightarrow O$ interaction or the destabilizing $R_S \leftrightarrow R^1$, $R_M \leftrightarrow R^1$ interaction and modest to poor selectivity is predicted. As R_M or R^1 increases in steric bulk, the increased $R_M \leftrightarrow R^1$ destabilizing interaction in **274** will favor **273**.[281] Reduction of **275** with $LiAlH_4$ was shown to give a 2:1 mixture of **276** and **277**.[282] For an analysis of this reduction, the two models of interest are **278** and **279**. The destabilizing Me↔Me interaction in **279** is greater than the analogous H↔Me interaction in **278** and delivery of hydride will be via **278**, which predicts **267** as the major product.



The Felkin–Ahn and Cram models are best applied to acyclic systems. Problems arise when any of these models are used to predict the products generated by the reduction of cyclic ketones. These problems will be analyzed and new models for predicting diastereoselectivity in the reduction of cyclic molecules will be discussed in Section 4.7.C.

Somewhat different problems occur when attempting to apply one of these models to 1,2-reduction of a conjugated aldehyde or ketone (such as **280**). Overman studied this system, which showed a preference for the syn product (**281**) over the anti product, **282** (see Table 4.8).[283] The silyloxy derivative shows very high Cram selectivity, possibly due to "destabilization of the minor Felkin–Ahn transition state (**283**) as a result of steric interactions between the α-methyl group and the β-hydrogen of the enone system."[283] Such steric interactions make **284** the preferred conformation and leads to the syn product. Note that in **283** and **284**, the alkenyl group attached to the carbonyl imposes a larger steric interaction on the adjacent carbon than when a sp^3 hybridized carbon is attached to the carbonyl.[149,150] The planar nature of the alkenyl moiety forces the hydrogen in **283** and **284** to come close to the substituents on the α-carbon. The model for conjugated carbonyl derivatives is usually taken to be **285**, where the destabilizing $R \leftrightarrow R^3$, R↔X and $R \leftrightarrow R^4$ interactions will determine which rotamer is preferred.

Table 4.8. Diastereoselectivity in the Reduction of Conjugated Ketone 280



280 **281** **282**

R	Reagent	Conditions	281/282
$SiPh_2t$-Bu	DIBAL-H		94:6
$SiPh_2t$-Bu	$LiAlH_4$	-20°C	95:5
H	$LiAlH_4$	-10°C	40:60
CH_2OBn	DIBAL-H	pentane, 25°C.	70:30
CH_2OBn	DIBAL-H	pentane, -22°C	55:44
CH_2OBn	$LiAlH_4$	THF, -10°C	30:70
CH_2OBn	$LiAlH_4$	ether, -10°C	2:98
Ac	DIBAL-H	pentane, 25°C	45:55
$SiMe_3$	DIBAL-H	pentane, 25°C	43:57

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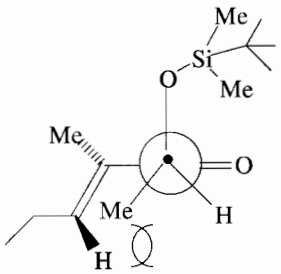
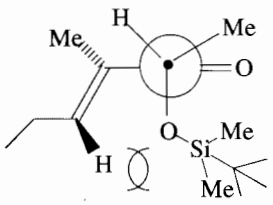
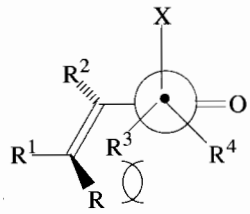
A transition state similar to **285** also explains the syn-selectivity observed with the DIBAL-H reduction of the benzyloxymethyl ether derivative of **280** (see Table 4.8). It does not explain, however, the anti-selectivity observed with $LiAlH_4$ or when other substituents are present, as seen in Table 4.8. For these cases, a chelation model (**286**) must be invoked to explain the erythro (anti) selectivity, where path *b* is less hindered. Chelation



283

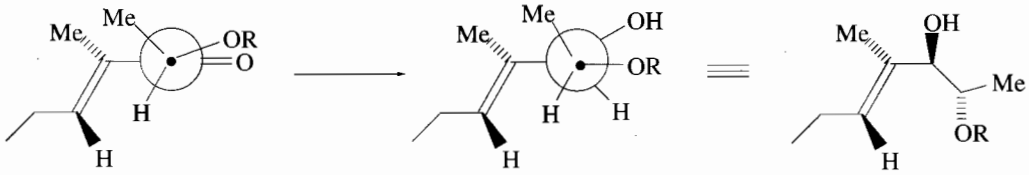


284



285

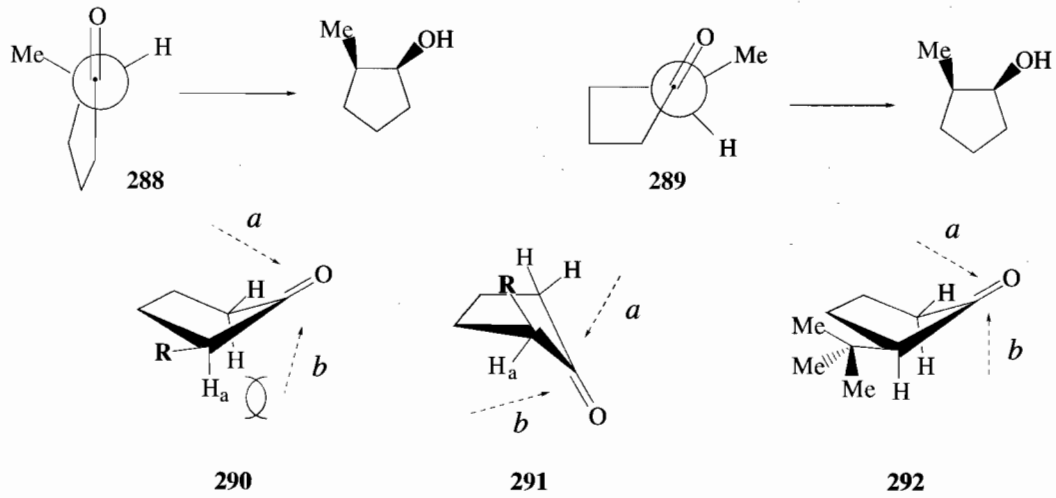
of the carbonyl and the α-alkoxy oxygen positions the methyl group away from the β-alkenyl hydrogen, leading to formation of **287**. As seen in **286**, the Felkin–Ahn model easily accommodates a chelated intermediate and appears to give a clearer picture of selectivity for 1,2-addition in conjugated systems.



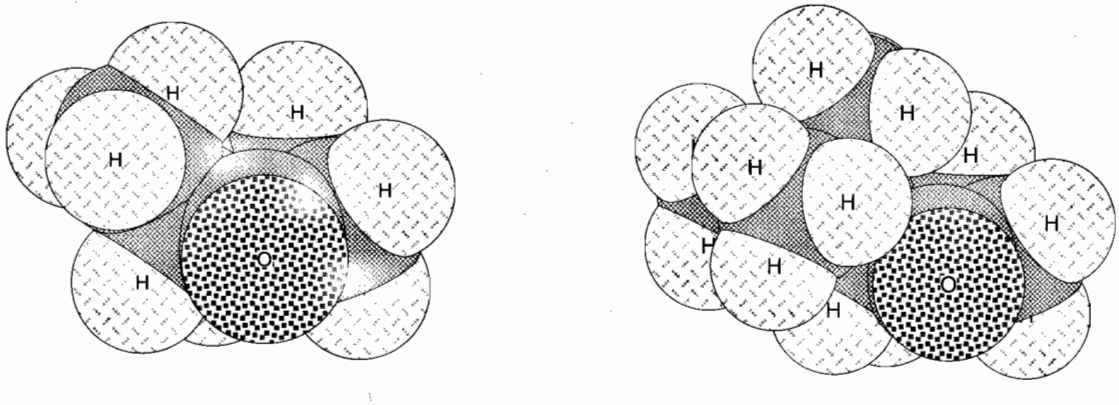
286 **287**

4.7.C. Selectivity in Reduction of Monocyclic Molecules

In general, stereochemical predictions for *cyclic* ketones using the models described in Section 4.7.B are unreliable. Reduction of 2-methylcyclopentanone, as shown in Table 4.9,[284] illustrates the difficulty. Model **288** is an approximation of the Cram model for 2-methylcyclopentanone and it predicts the cis isomer to be the major product of hydride reduction. Analysis of cyclohexanone derivatives shows that fitting them to the Cram model requires severe distortion of the ring away from the low energy chair conformation to a half-chair or a planar form. The Felkin–Ahn model for 2-methylcyclopentanone (**289**) also predicts the cis product although there is less distortion of the ring. When reductions of actual molecules are compared to predictions from the models (as in Table 4.9), it is clear that the trans isomer is favored except when very bulky borohydride reagents are used. Both the Cram and Felkin–Ahn models gave incorrect predictions.

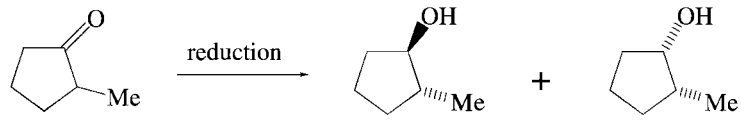


The actual experimental results can be explained by using models **290** and **291**, the two envelope conformations available to 2-substituted cyclopentanones (sec. 1.5.B). In **290**, approach of a reagent to the carbonyl at an angle of ≈ 110° (the **Bürgi–Dunitz trajectory**–sec. 6.6.A)[285] leads to an interaction with H_a (path *b*), making path *a* preferred and this leads to the trans product, which appears to be contradicted by inspection of **291**, where approach via path *a* is inhibited by the R group. Since the R group will be pseudo-equatorial in the



lowest energy conformation (as in **290**), this is the model used to predict the major diastereomer in reactions of cyclopentanone derivatives. Inspection of the 3D space-filling model[266] of 2-methylcyclopentanone (**293**) shows that approach over the methyl is only slightly more hindered than approach over hydrogen on the bottom face. As the α-substituent in **290** increases in size, path *a* becomes less favored and lower selectivity

Table 4.9. Hydride Reduction of 2-Methylcyclopentanone



295 **296**

Reagent	% 295	% 296
$NaBH_4$[a]	74	26
$LiAlH_4$[b,c]	76	24
B_2H_6[d]	69	31
$LiAlH(OMe)_3$[a,b]	56	44
$LiAlH(OEt)_3$[b]	77	23
$LiAlH(OtBu)_3$[a,b]	72	28
$Li(mesityl)_2BH_2$[e]	2	98
L-Selectride[d]	1.5	98.5
$Li(siamyl)_3BH$[d]	0.5	99.5

[a] Ref. 286 [b] Ref. 287 [c] Ref. 288 [d] Ref. 289 [e] Ref. 290

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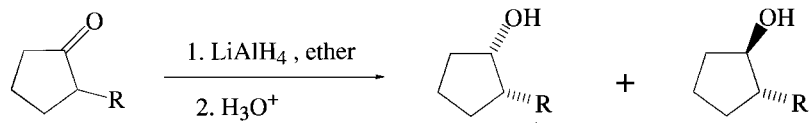
is observed, as in Table 4.10.[290] The reason for this is shown for the *tert*-butyl derivative (see **292**). where the methyl groups impose greater hindrance to approach via path *a*. The 3D model (see **294**) for the *tert*-butyl

Table 4.10. Lithium Aluminum Hydride Reduction of 2-Substituted Cyclopentanones

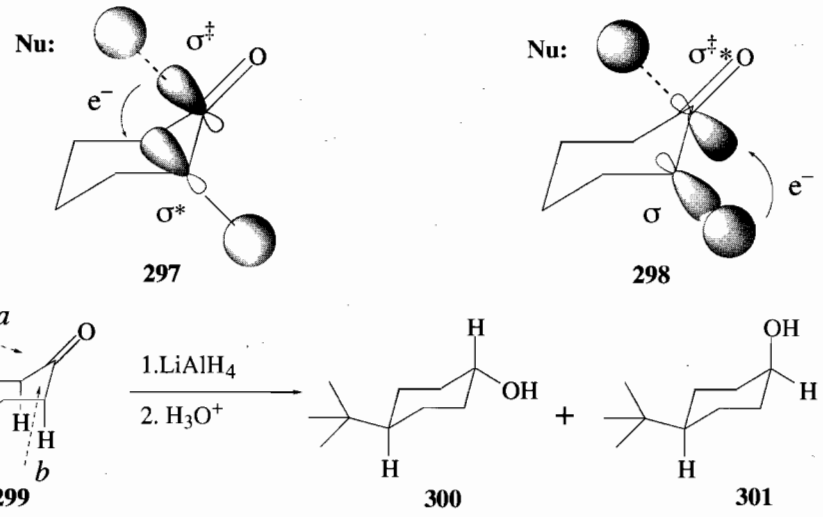


290 cis trans

R	% cis	% trans
Me	24	76
Et	27	73
i-Pr	47	53
t-Bu	54	46
Ph	40	60
c-C_6H_{11}	42	58

derivative shows somewhat increased hindrance to approach along path *a*. Even with this very bulky *tert*-butyl group, however, essentially a 1:1 mixture of stereoisomers is obtained upon reduction. For clarity, it must be emphasized that **290–292** are somewhat distorted in a stylized envelope conformation. Note that the actual structures of these cyclopentanone derivatives are more planar than is represented in **291–292** (see 3D drawings[266] **293** and **294**).

The Cram model does not predict the correct stereochemistry of reduction products derived from cyclohexanone derivatives. anti-Periplanar hyperconjugative effects have been invoked to explain the observed results. The Felkin–Ahn model suggests an interaction such as that shown in **297**.[291] An alternative proposal was put forth by Cieplak, shown in **298**,[292] and it was found that the incipient bond (the one being formed) was electron deficient, in line with Cieplak's proposal. Cieplak's model has led to some controversy, and a



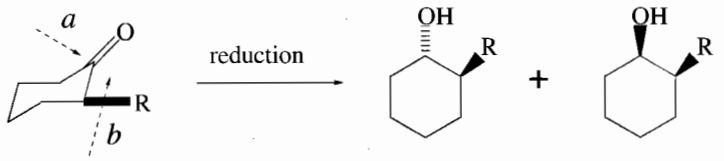
so-called exterior frontier orbital extension model has been proposed to explain the selectivity.[293] The actual stereo-selectivity can be shown using the reaction of 4-*tert*-butylcyclohexanone (**299**) with lithium aluminum hydride or sodium borohydride, which gives the trans-alcohol (**300**) as the major product (92 and 80%, respectively) via axial attack (path *a*).[294] The bulky *tert*-butyl group at C4 in **299** effectively locks the molecule into that chair conformation (sec. 1.5.D). An attempt to use the Cram model or the Felkin-Ahn model predicts path *b* as the major pathway (to give **301**), which is incorrect. A more useful perspective for this analysis is a model represented by **299**, which suggests that approach via path *b* is encumbered by the axial hydrogens on the bottom face of the molecule. An important aspect of these models is the trajectory of approach for the hydride. The angle of approach will be close to 110° (see above)[285] and over the π bond of the carbonyl (as seen in **299**). This angle of approach will exacerbate the steric problems posed by the axial hydrogens at C2 and C6 for path *b* and the axial hydrogens at C3 and C5 for path *a*. In simple cyclohexanone derivatives, path *a* is preferred. When the α-carbon is substituted, as in **302**, path *a* (to give **303**) is still preferred to path *b* (which gives **304**) unless R is very large, as shown in Table 4.11.[290,288] The 3D drawing[266] of 2-methylcyclohexanone (**305**) shows that the equatorial methyl imparts little impedance to path *a*. As the steric bulk at C2 is increased, approach from path a is somewhat inhibited, leading to increasing

amounts of the cis-product (via path *b*). It is interesting to note that $LiAlH(OMe)_3$ gives more cis-product than $LiAlH(Ot\text{-}Bu)_3$. Generally, smaller reagents give more axial attack (path *a*) and larger reagents give more equatorial attack (path *b*). In their monograph, Morrison and Mosher arranged the relative size of hydride reagents as follows.[295]

$LiAlH_4$ < $LiAlH(OtBu)_3$ < $NaBH_4$ < KBH_4 < $LiAlH(OMe)_3$* < Ip_2BH**

* see Section 4.3 ** see Section 5.4.B

Table 4.11. Hydride Reduction of 2-Substituted Cyclohexanone Derivatives, 302



302 **303** **304**

R	Reagent	% 303 (ax attack)	% 304 (eq attack)
Me	$LiAlH_4$/THF	76	24
	$NaBH_4$/*i*-PrOH	70	30
	$LiAlH(Ot\text{-}Bu)_3$/THF	70	30
	$LiAlH(OEt)_3$/THF	74	26
	$LiAlH(OMe)_3$/THF	31	69
Et	$NaBH_4$/*i*-PrOH	65	35
i-Pr	$LiAlH_4$/THF	63	37
	$NaBH_4$/*i*-PrOH	50	50
t-Bu	$LiAlH_4$/THF	42	58
	$NaBH_4$/*i*-PrOH	50	50
	$LiAlH(OMe)_3$/THF	36	64
	$LiAlH(OtBu)_3$/THF	46	54

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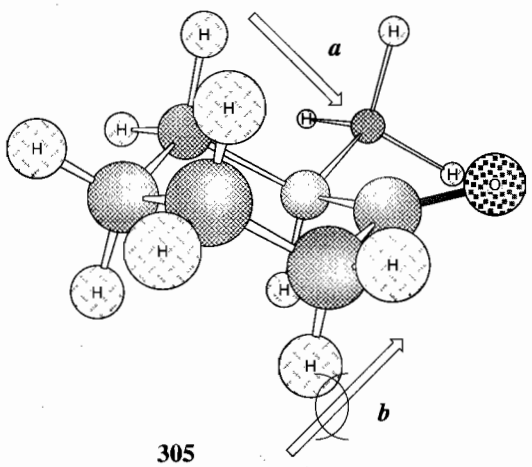
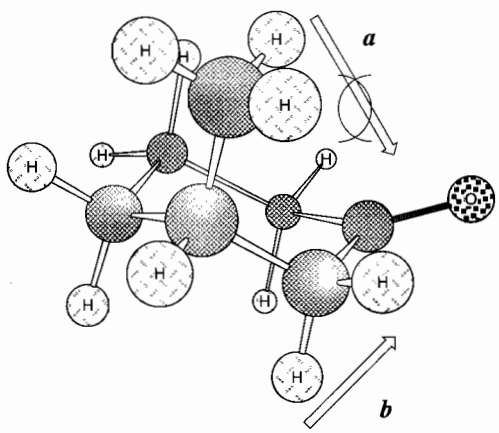


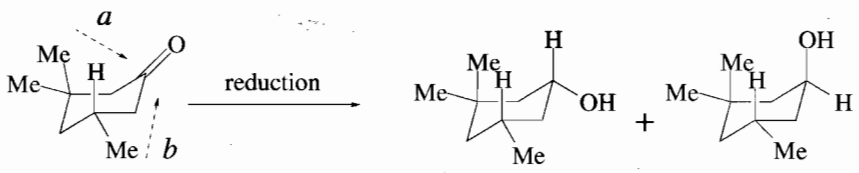
305



306

Substituents at C3 or C5 also have a significant effect on the approach of reagents to the carbonyl of cyclohexanone derivatives. As shown in Table 4.12[288,296] for 3,3,5-trimethylcyclohexanone (**307**), an *axial* methyl group at C3 of a cyclohexanone blocks path *a* (see 3D drawing **306**) and the product is not, therefore, **308**. The preferred mode of attack is path *b* to give the trans alcohol, **309** As the size of the hydride reagent increases, path *b* is favored to an even greater degree.

Table 4.12. Selectivity in Hydride Reductions of 3,3,5-Trimethylcyclohexanone (307)



307 **308** **309**

Reagent	% 308	% 309
$LiAlH_4$	52	48
$LiAlH(OMe)_3$	75	25
$LiAlH(OEt)_3$	83	17
$LiAlH(OtBu)_3$	73	27
$NaBH_4$/EtOH	67	33
$NaBH_4$/aq MeOH	71	29
KBH_4/aq MeOH	71	29
$NaBH(OMe)_3$/aq MeOH	65	35
$NaBH(OiPr)_3$/diglyme	77	23

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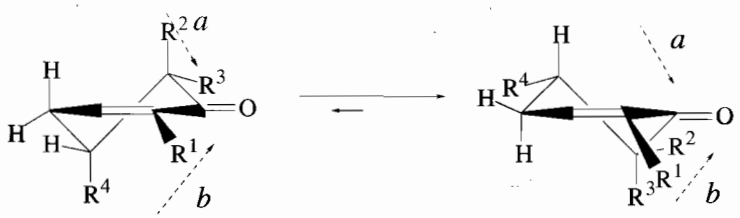
Recently, De Maio et al. studied the stereochemistry and relative rates of k_{ax} and k_{eq} for acyl addition reactions of 5-substituted adamantan-2-ones.[297] This kinetic data did not fit with current theories of π face diastereoselection. Their studies suggest that k_{ax}/k_{eq} measurements do not adequately indicate what is happening on the two sides of a stereogenic center. In addition, they found that axial reactivities always increase with increasing electronegativity of the substituted at C5 and that k_{eq} changes depend on the conformation of that group and on reaction conditions. In their words: "Simple theories such as those based on dipole–dipole interactions are unable to explain such as behavior, nor can theories based on ground state MO calculations."[297]

4.7.D. Stereoselectivity in the Reduction of Cyclohexenone Derivatives

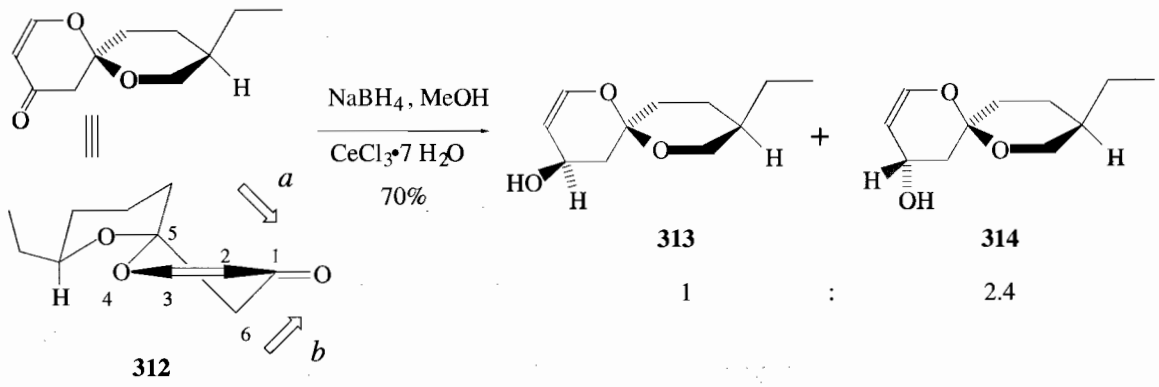
The conformational problems of cyclohexene derivatives are somewhat different than those observed with cyclohexanone or cyclohexane derivatives. The presence of the alkene moiety effectively flattens four carbons of the ring, which changes the different steric effects for substituents with an incoming reagent, relative to cyclohexanone derivatives. The most abundant conformations of cyclohexenone derivatives are **310** and **311**. The first problem that arises in conjugated derivatives is the competition of 1,2- with 1,4-addition for

many reducing agents, discussed in previous sections. In this section only products arising from 1,2-reduction will be discussed. It appears that the C2 group (R^1) offers little interference to either path *a* or *b* unless it is very large. The R^2 group, however, can inhibit approach by path *a* if sufficiently large and a large R^4 may inhibit approach by path *b*.



310 **311**

The sodium borohydride-cerium chloride reagent (**Luche reagent**) was shown to give selective 1,2-reduction of conjugated ketones in Section 4.4.B. Reduction of **312** gave **314** as the main product,[298] and this illustrates that the cyclohexenyl system is sensitive to steric blocking when substituents are present at C5 or C6. In this case C5 poses some steric encumbrance to path *a* and the major product of the reduction is via path *b*. This model predicts that **314** results from attack via path *b* and **313** results from attack via path *a*. It is clear from the 2:1 ratio of products favoring **314** that the steric encumbrance at C5 is less important in **312**. This may be due to the increased ability of the cerium reagent to chelate with the carbonyl.

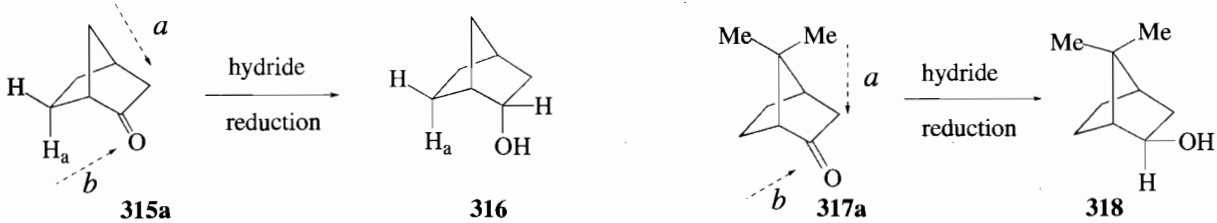


312 **313** **314**

1 : 2.4

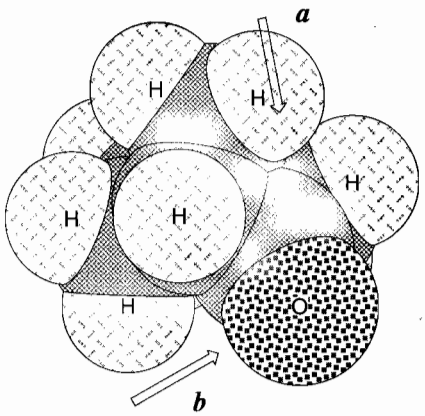
4.7.E. Selectivity in the Reduction of Bicyclic and Polycyclic Derivatives

As with monocyclic ketones, bicyclic ketones show excellent diastereoselectivity upon reduction with hydride reagents. A typical example is the selectivity observed in the reduction of bicyclo[2.2.1]heptan-2-one (**315**, norbornanone) and 7,7-dimethylbicyclo[2.2.1]heptan-2-one (**317**). The exo face (path *a* in **315a**) is

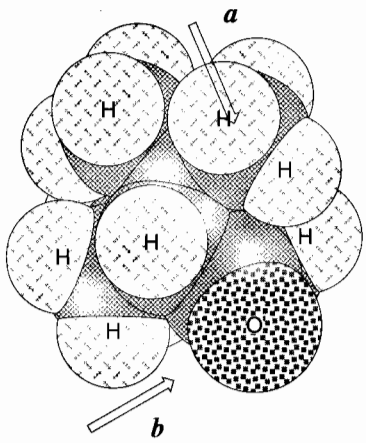


315a **316** **317a** **318**

usually preferred, leading to the endo alcohol **316**. The endo hydrogens (H_a in **315a**) provide the major source of steric encumbrance (see 3D drawing[266] **315b**). Approach of a reagent to the carbonyl at an angle of 110° brings the reagent into close proximity to this hydrogen. The exo face appears somewhat hindered but is actually less hindered than the endo face. When the exo face (path *a*) is blocked by a methyl group (see 3D drawing **317b**), attack by path *b* is preferred and the exo alcohol (**318**) is the major product. In all [2.2.1], [2.1.1], and [2.2.2] bicyclic ketones of this type, the major product is predicted by the extent of steric hindrance at the exo face (exo attack with no substituents on the bridge, as in **315**).[299,288,289] When the bridge has substituents (as in **317**), endo attack is generally preferred.



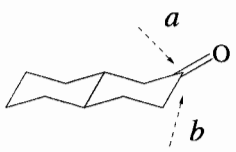
315b



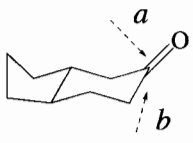
317b

When edge-fused bicyclic (bicyclo[*m.n.*0]) systems are examined, as shown in Table 4.13,[290] they behave very similarly to monocyclic ketones. Reduction of decalone (**319**) and indanone (**320**), for example,

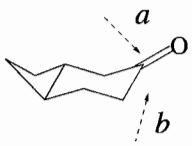
Table 4.13. Selectivity in Hydride Reduction of Bicyclic Ketones



319



320



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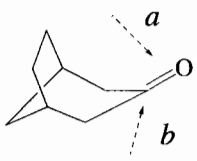

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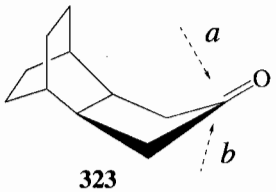
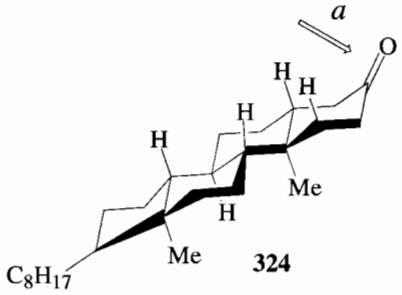


323

Bicyclic Ketone	Reagent	% ax Alcohol[b]	% eq Alcohol[a]
366	$NaBH_4$	15	85
	$LiAlH_4$	13	88
367	$NaBH_4$	11	89
	$LiAlH_4$	10	90
368	$NaBH_4$	6	94
	$LiAlH_4$	6	94
369	$NaBH_4$	40	60
370	$NaBH_4$	72	28

[a] Axial attack, path *a*. [b] Equatorial attack, path *b*.

occurred primarily from path a, as shown. In this table, the axial alcohol results from equatorial attack by the hydride and the equatorial alcohol results from axial attack by the hydride. These results show that axial attack (path *a*) is preferred in [m.n.0]-bicyclic ketones **319**, **320** and **321**, as in cyclohexanone since the trajectory of attack is the same. The presence of the bridging carbon inhibits path *a* somewhat in **322** and to a greater extent in **323**. There is also a preference for path *a* in complex compounds such as 3-cholestanone (**324**). Coprostanone (**325**) is an isomer of **324** and it also gives axial attack as shown (via path *a*) although the conformation of the molecule is slightly different.[300] Bicyclic and polycyclic systems appear to be more complex than cyclohexanone, but the major diastereomeric product can be predicted with little or no modification of the simple cyclohexanone and cyclopentanone models presented above.



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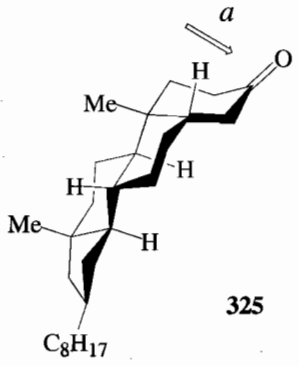
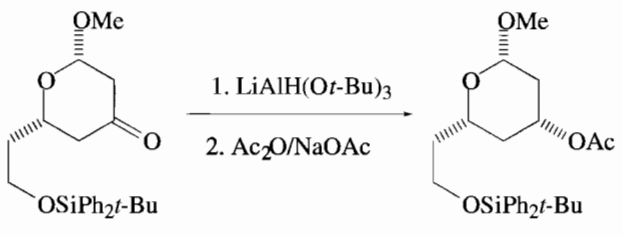


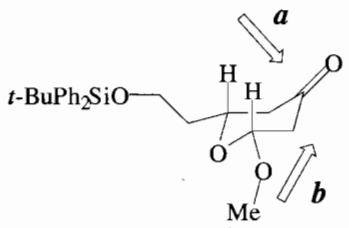
325

4.7.F. Selectivity in the Reduction of Natural Products

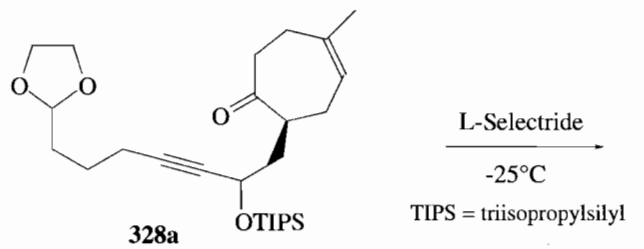
There are many synthetic examples where hydride reduction of complex molecules proceeds with high diastereoselectivity. Reduction of **326a** to alcohol **327** with lithium tri-*tert*-butoxyaluminum hydride is taken from Donaldson's synthesis of the C_3–C_{15} bis(oxane) segment of phorboxazole.[301] The conformational drawing (**326b**) reveals that path *a* is preferred in the more stable chair conformation with the two substituents in the equatorial position. This model predicts the major alcohol product, which was converted as the acetate.



326a **327**

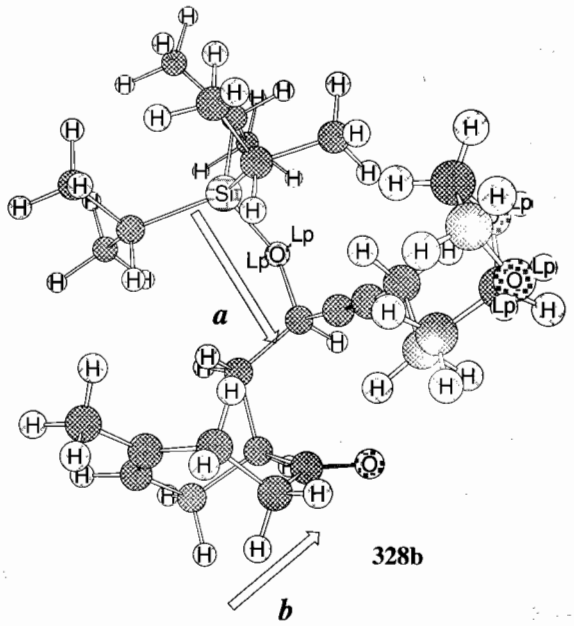


326b

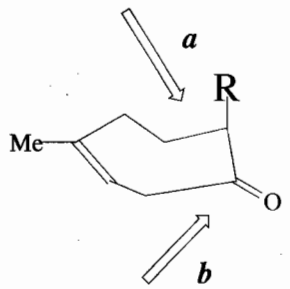


328a **329**

Another example is Overman's reduction of **328a** to give **329** in 92% yield with L-Selectride, as part of a synthesis of (+)-scopadulcic acid A.[302] The 3D model[266] (**328b**) shows the seven-membered ring with a large substituent that is in essentially an axial position. Since **328b** may be difficult to interpret due to the small size of the atoms, it is shown again as **319c** with the alkynyl unit represented as R. It is clear that path *a* is blocked by "R", and delivery of hydride via path *b* leads to the observed syn-diastereomer **329**.

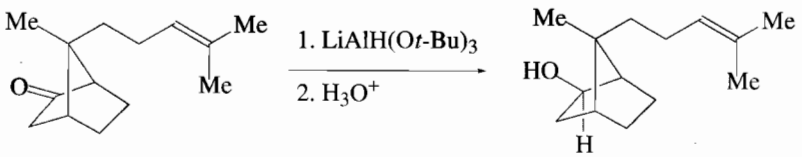


328b

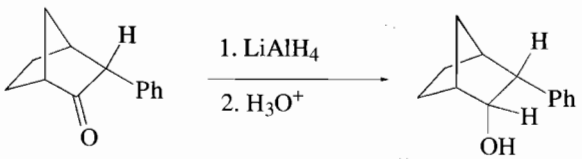


328c

Reduction of norbornane-like precursors to natural products is also predictable. Reduction of the ketone unit in **330**, in Money's synthesis of β-santalene for example, gave the exo-alcohol **331** via attack from the less hindered endo face.[303] Conversely, removal of the steric encumbrance at C7 (as in **332**) gave attack via the exo face to give **333** (in about a 4:1 ratio favoring the endo alcohol shown).[304]



330 **331**



332 **333**

There are many more examples of selectivity in reduction. These few are simply meant to illustrate that the simple principles discussed in this section, and the models used, can be applied to more complex systems with reasonable success.

4.8. CATALYTIC HYDROGENATION

Reduction of functional groups with hydrogen gas is one of the most important reactions in organic chemistry, dating to the first hydrogenation of ethene to ethane by von Wilde in 1874.[305] As stated by Hudlický,[7] "true widespread use of catalytic hydrogenation did not start until 1897 when Sabatier and his co-worker developed the reaction between hydrogen and organic compounds to be a universal reduction method (Nobel Prize, 1912)."[306,307] In addition to Hudlický's book, two monographs that describe synthetic applications of catalytic hydrogenation are available from Rylander[308] and Freifelder,[309] Additional information concerning the application of catalytic hydrogenation to organic chemistry is found in the series *Catalysis in Organic Reactions*.[310] Catalytic hydrogenation is used to reduce alkenes,[311] alkynes,[312] ketones and aldehydes,[313] nitriles,[314] nitro compounds,[315] and aromatic rings.[316]

4.8.A. Catalytic Activity and Reactivity

The method involves addition of hydrogen gas to an organic molecule. The reaction requires a catalytic amount of a transition metal (see Table 4.14)[317] for reaction to occur and proceeds by adsorption of hydrogen and the substrate on the surface of the metal. The mechanistic rationale for this type of reduction will be discussed in Section 4.8.B. There are two major types of catalysis: **heterogeneous** (catalyst insoluble in the reaction medium) and **homogeneous** (catalyst soluble in the reaction medium). Heterogeneous hydrogenation can be **supported** (both slurry processes and fixed gel operations)[308] and **unsupported** (primarily solution reactions). The functional group that is reduced, the extent of reduction, and the product distribution depend on the nature and amount of the catalyst as well as the type of hydrogenation procedure employed. Laboratory scale reductions of most organic functional groups containing a π bond usually involve a slurry

Table 4.14. Typical hydrogenation catalysts.

Platinum Oxide[a]	Platinum black[b]
Pt/C[c,319b]	Pt/Rh oxide[d]
Pd oxide[e]	Pd/$BaCO_3$[f]
Pd/$SrCO_3$[g]	Pd/C[f]
Pd hydroxide/C[h]	Rh/C[f]
Ni boride-P1[i]	Ni boride-P2[j]
Ni (NiC)[k]	Ni—Cu[l]
Ni-Kieselguhr[m]	Urushibara Ni[n]
Raney Ni [Ni(R)][o]	Ni(R) W1[p]
Ni(R) W2[f]	Ni(R) W3[q]
Ni(R) W4[332a]	Ni(R) W5[r]
Ni(R) W6[s]	Ni(R) W7[r]
Ni(R) W8[t]	Raney cobalt[u]
Copper chromite[v]	

[a] Ref. 318 [b] Ref. 319 [c] Ref. 320 [d] Ref. 321 [e] Ref. 322 [f] Ref. 323 [g] Ref. 324 [h] Ref. 325 [i] Ref. 326 [j] Ref. 327 [k] Ref. 328 [l] Ref. 329 [m] Ref. 330 [n] Ref. 331 [o] Ref. 332 [p] Ref. 333 [q] Ref. 334 [r] Ref. 335 [s] Ref. 336 [t] Ref. 337 [u] Ref. 338 [v] Ref. 339

process involving heterogeneous catalysis. Industrial (large scale–kilogram or ton scale) applications often use fixed-bed heterogeneous catalysis or homogeneous catalysis. Homogeneous hydrogenation in synthesis has been reviewed by Birch and Williamson.[340]

The first variable in catalytic hydrogenation is the catalyst. The most commonly used heterogeneous catalysts are platinum, palladium, nickel, rhodium, nickel, and ruthenium. Rylander gave references for the preparation of the most common catalysts, shown in Table 4.14.[317] In some cases, salts of transition metals are used rather than the metal itself although the pure metal adsorbed on a support (see above) is also commonly used. Hudlický presented an order of relative reactivity with propene for groups 8–10 (VIII) transition metal catalysts,[341] based on the work of Mann and Lien.[342] The order given is:

Rh	>	Ir	>	Ru	>	Pt	>	Pd	>	Ni	>	Fe	>	Co	>	Os
14.0		15.0		6.5		16.0		11.0		14.0		10.0		8.1		7.4

In this series, rhodium is the most active catalyst. The activation energy for the reaction of hydrogen with propene is also shown, and it is noteworthy that the catalytic activity does not correlate with the activation energy for the hydrogenation reaction (numbers below the metal). These catalysts are used for the reduction of many functional groups and Table 4.15[343] correlates functional groups commonly reduced with hydrogen with recommended reaction conditions and catalysts. No single catalyst gives excellent results for all functional groups and there are significant differences in chemo- and stereoselectivity. Note that most hydrogenations are done at ambient temperature and pressure. Only a few of the catalysts indicated in Table 4.15 require high pressures and then only for selected functional groups. In most cases, < 10 mol% of the catalyst is required per mole of the compound. Both Raney nickel and rhodium catalysts appear to require greater amounts of the catalyst. The purpose of this table is to provide a quick guide to the reduction of common functional groups and to show the most common catalysts used. These catalysts and the functional groups reduced will be the focus of this section.

In the context of hydrogenation, the **support** is an inert material on which the catalyst is adsorbed or admixed. Common supports are carbon (platinum black and palladium on carbon, for example) and alumina (rhodium is often adsorbed on alumina) and both calcium sulfate ($CaSO_4$) and barium sulfate ($BaSO_4$) are used. In part, the support dilutes the expensive transition metal catalyst, which allows one to control the rate of reaction as well as making it cost effective. Typically 1–10 mol % of the catalyst (see Table 4.15) is added to the support (sometimes called a carrier). The support can diminish the reactivity of the catalyst. For many applications, too active a catalyst will lead to overreduction and/or poor selectivity. If the activity of the metal catalyst is too high, addition of compounds that bind to the metal will usually diminish the activity. Such compounds displace hydrogen atoms or the organic substrate being reduced. This process is referred to as **poisoning** of the catalyst and it can greatly diminish the reducing power of that catalyst. In essence, when the poison is bound to the catalyst, hydrogen and the organic substrate cannot be bound, hence poor reactivity. Common poisons include metal cations, halides, Hg°, divalent sulfur compounds, carbon dioxide, amines and phosphines.[344] In many cases, the organic molecule being reduced or a minor reaction product can poison the catalyst.[345]

Table 4.15. Recommended Reaction Conditions for Catalytic Hydrogenation of Selected Functional Groups

Functional Group	Product	Catalyst	(mol %)	Temp. (°C)	Pressure (atm)
Alkene	Alkane	A	5–10%	25	1–3
		B	0.5–3%	25	1–3
		C	30–200%	25	1–3
Alkyne	Alkene	D	8%	25	1
		E	2% + 2% quinoline	20	1
		F	10% + 4% quinoline	25	1
	Alkane	B	3%	25	1
		C	20%	25	1–4
Carbocyclic aromatic	Hydroaromatic	B	6–20%, AcOH	25	1–3
		G	40–60%	25	1–3
		C	10%	75–100	70–100
Heterocyclic Aromatic	Hydroaromatic	B	4–7%, AcOH or HCl/MeOH	25	1–4
		H	20%, HCl/MeOH		
		C	2%	65–200	130
Aldehyde, ketone	Alcohol	B	2–4%	25	1
		A	3–5%	25	1–4
		C	30–100%	25	1
Halide	Hydrocarbon	A	1–15%, KOH	25	1
		E	30–100%, KOH	25	1
		C	10–20%, KOH	25	1
RNO_2, azide	Amine	B	1–5%	25	1
		A	4–8%	25	1
		C	10–80%	25	1–3
Oxime, nitrile	Amine	B	1–10% AcOH or HCl/MeOH	25	1–3
		A	5–15%, AcOH	25	1–3
		C	3–30%	25	35–70

A = 5% Pd(C); B = PtO_2; C = Raney Ni; D =0.3% $Pd(CaCO_3)$; E = 5% $Pd(BaSO_4)$;
F = Lindlar catalyst; G = 5% $Rh(Al_2O_3)$; H = 5% Rh (C)

[Reproduced with permission from Reductions in Organic Chemistry by M. Hudlický published in 1984 by Ellis Horwood, Chichester.]

Many other factors influence the reduction. These include the tendency of the catalyst to agglomerate, addition of a promoting substance, synergism between two catalysts, the temperature of the reaction, the ratio of hydrogen to compound being reduced, the pressure of hydrogen gas, the preparation method, and the age of the catalyst and the number of times it has been recycled.[308,7,309]

A hydrogenation reaction is rather complex. The surface of the metal catalyst is very porous, allowing adsorption of hydrogen gas, organic substrates, and various poisons. As the number of **active sites** (regions of the catalyst that can accommodate and bind hydrogen atoms and/or organic substrates) increases, the rate of hydrogenation increases. A poison will bind to the active site in preference to the substrate or hydrogen, preventing their adsorption.[346] Gases such as carbon dioxide (CO_2) and carbon monoxide (CO) can fill up

the active sites as well. Measurement of active sites in a catalyst is difficult. The position of the metal at the surface or just below the surface has a major influence on chemisorption. In many cases, metal salts are used as catalysts and a change in oxidation state during the reaction can deactivate the catalyst.[346]

Heterogeneous catalysis is a surface phenomenon, and it is known that there are different types of metal particles on the surface. Maier suggested the presence of **terrace-**, **step-**, and **kink**-type atoms (in Fig. 4.1)[347] on the surface of a heterogeneous catalyst. These terms refer to different atom types, characterized by the number of nearest neighbors[347] which correspond to different transition metal fragments as well as to different coordination states of that metal.[348] A terrace type atom (A in Fig. 4.1) typically has eight or nine neighbors and corresponds to a geometry such as **334**. The step type of atom (B) usually has seven neighbors and can be correlated with structure **335**. Finally, the kink type atom (C) has six neighbors and corresponds to structure **336**. As the number and type of neighboring atoms around each type of atom changes, the binding capacity (active sites) will change. In general, as the particle size increases, the relative concentration of terrace atoms will increase, whereas small particle size favors the kink type of surface atoms. Since the **terrace** atoms

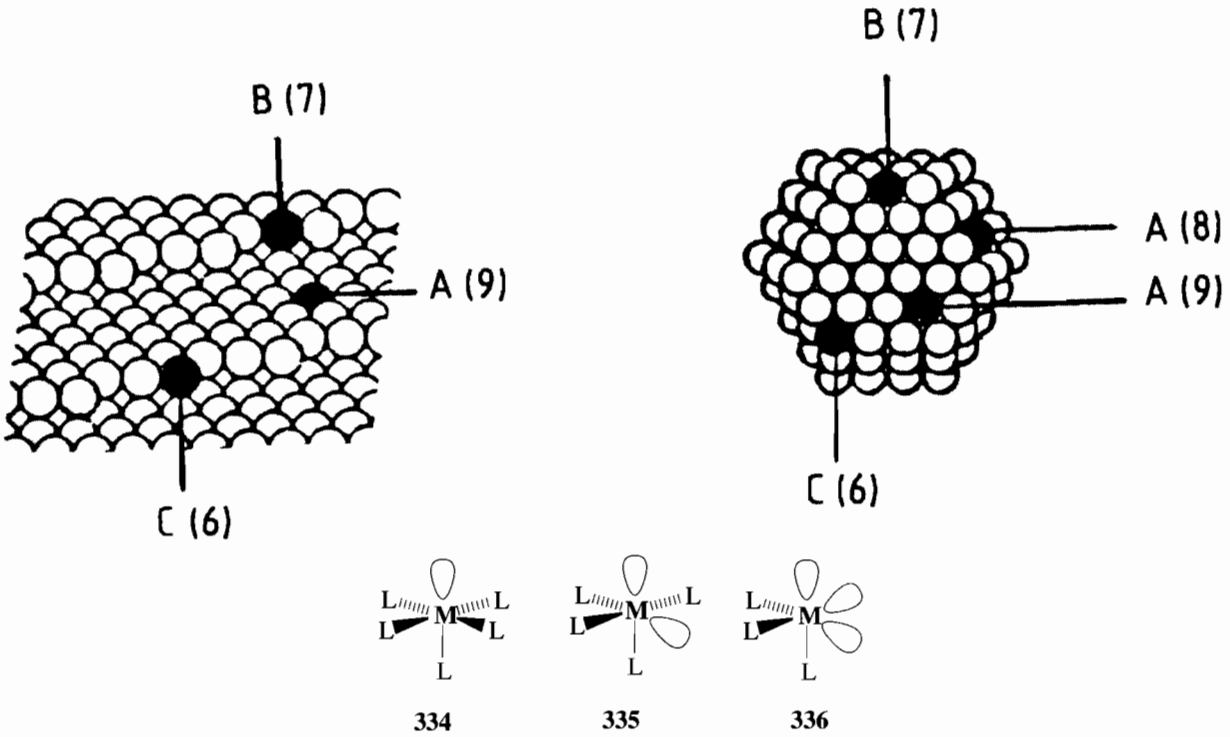


Figure 4.1. The principal surface and particle sites for heterogeneous catalysts.

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correspond to ML_5 transition metals, the **step** to ML_4 and the **kink** to ML_3, they should exhibit distinctly different reactivity.[347] Other factors can influence the way each type of atom will interact with an organic substrate, but it is clear the surface of the catalyst is important. Indeed, Maier suggested the ideal catalyst would be "a material with the right surface structure rather than an empirical mixture of ingredients".[348] It is likely that the use of modifiers, poisons, and special reaction conditions will change the shape, size, and surface

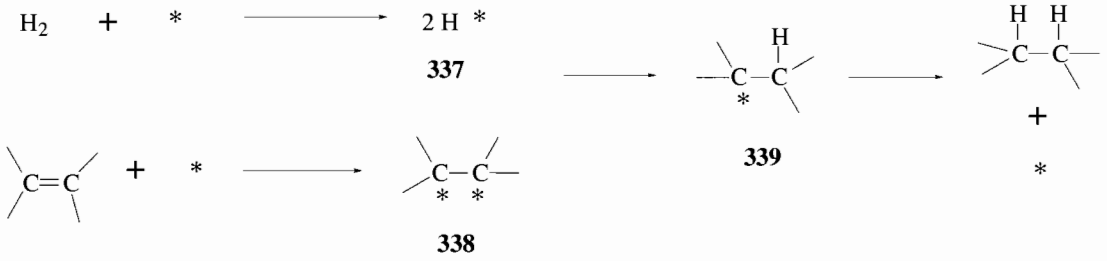
structure of the catalyst. This will, of course, influence the selectivity and reactivity. With palladium, both "hydrogenation and hydrogenolysis were found to be sensitive to the surface structure and morphology of the catalyst."[347] It is important to emphasize that Maier states he does not believe this analysis applies to homogeneous catalysis.[348] A mechanistic evaluation of the reduction of alkenes with homogeneous catalysts will be presented in Section 4.8.B.

There are several interesting differences between homogeneous and heterogeneous catalysis. The soluble homogeneous catalysts usually have a dissociated ligand and/or a coordinating solvent that compete with the organic substrate for active metal sites. Heterogeneous catalysts act essentially as an insoluble matrix, whereas the homogeneous catalyst is soluble in the reaction solvent and functions as a discreet molecules Because heterogeneous catalysts are insoluble, only those metal atoms at the surface of the matrix are thought to be important for hydrogenation, as noted for **325–327**; much of the catalyst is *within* the matrix and inaccessible. The soluble homogeneous catalyst allows each molecule of catalyst to be accessible (sec. 4.8.B). Thus, homogeneous reactions require less catalyst. The matrix nature of heterogeneous catalysts often means poor chemoselectivity, bond migration, hydrogenolysis, and so on (see below). Prediction of stereochemistry in the final product is usually difficult due to the requisite chemisorption for reaction. Since heterogeneous catalysts often require polar solvents, problems can arise due to the poor solubility of hydrogen gas in the solvent. The surface nature of heterogeneous catalysts make them susceptible to poisoning, as discussed above, but homogeneous catalysts are soluble and many of the problems arising from chemisorption at a surface disappear. Homogeneous catalysts tend to be significantly more selective for alkenes and alkynes, show less reactivity with heteroatom-containing functional groups and are less prone to poisoning.[317] Nonpolar solvents (such as benzene, and methylene chloride) can be used with homogeneous catalysts, which is important because such solvents can dissolve more hydrogen gas, facilitating the reduction. Reaction with an organic substrate occurs with more or less discreet catalyst molecules of known coordination states. The stereochemistry of the reduction product is often predictable by analysis of the geometry of substrate binding around the metal (the binding of hydrogen, solvent and other ligands must also be known). Typical homogeneous catalyst include **Wilkinson's catalyst**, $(Ph_3P)_3RhCl$ (**328**)[349] and the iridium complex, $[Ir(cod)(Py)PCy_3]^+ PF_6^-$, which is related to **Vaska's catalyst** (see **329**).[350] It is also clear that the main difference between an homogeneous and heterogeneous catalyst is the presence of an organic substrate called a ligand [pyridine (Py), cyclooctadiene (COD), tricyclohexylphosphine (PCy_3), triphenylphosphine, bis(phosphine) ligands, and mono and diamines] in the homogeneous catalyst. These ligands bind to the metal whereas heterogeneous catalysts typically consist of transition metals (M°), metal halides or metal oxide salts (MX_2, MX_4, and so on where X is Cl or O.

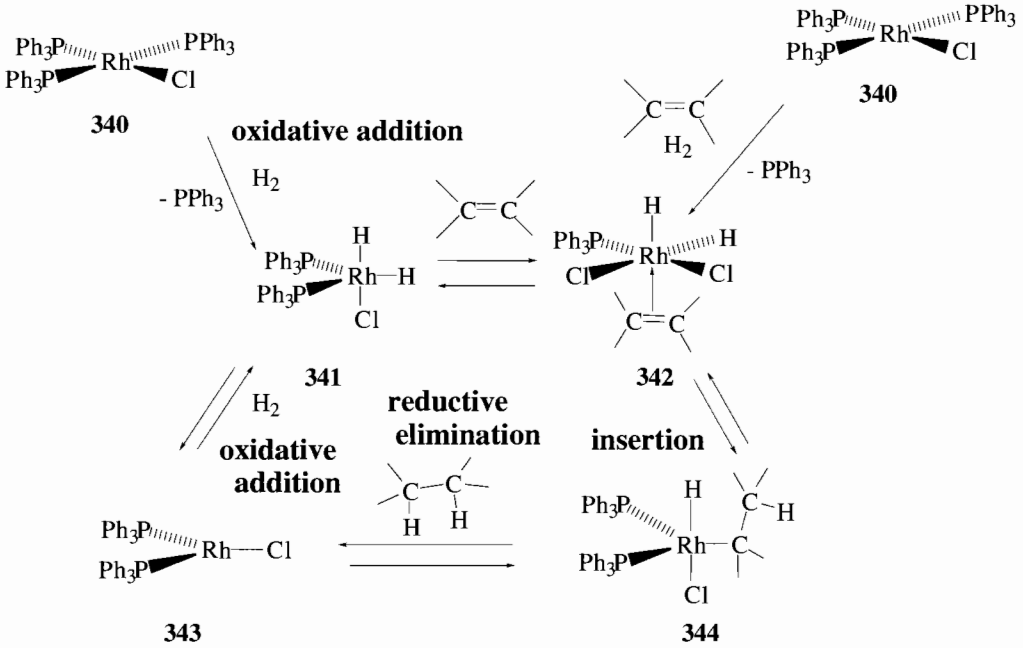
.8.B. Hydrogenation of Alkenes and Alkynes

Catalytic hydrogenation is commonly used for the reduction of alkenes, alkynes, aromatic hydrocarbons, and aromatic heterocycles, carbonyl derivatives, nitriles, and nitro compounds. The reaction with alkenes proceeds on the surface of a heterogeneous metal catalyst, via cleavage of diatomic hydrogen and adsorption

of the hydrogen atoms. Horiuti and Polanyi proposed a mechanism in 1934 for the reduction of ethene with hydrogen on nickel.[351] In each step, (*) refers to an undefined nickel atom or complex. Hydrogen gas is cleaved to hydrogen atoms that are bound to the nickel (represented by **337**). An alkene is also bound to the surface of the metal (represented by **338**), allowing the reaction to proceed, with transfer of hydrogen to the carbon (in **339**), which is misleading, since the surface is porous and contains metal atoms in more than one coordination state for heterogeneous catalysts (see above). Discreet catalyst molecules function as the catalyst



in homogeneous hydrogenations and binding to a particle of catalyst is relatively well understood. The exact mechanism of heterogeneous catalysis is not well understood since it is a surface phenomenon. It is clear that the catalyst ruptures the H-H bond to generate a metal—H (H*) species where hydrogen is adsorbed at an active site on the surface of the catalyst. The differing ability of metals to bind hydrogen and to transfer that hydrogen to an organic substrate is a critical factor that leads to differences in reduction for different catalysts.



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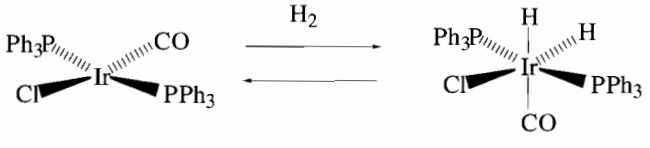
As mentioned, the hydrogen adsorption process is better understood for the reduction of alkenes with homogeneous catalysts, and Wilkinson's catalyst (**340**) has been studied extensively. Wilkinson's catalyst

$[(Ph_3P)_3RhCl]$ is usually prepared from rhodium chloride ($RhCl_3$) and triphenylphosphine in ethanol (88% is a typical yield of **340**).[352] The mechanism of activation when used for hydrogenation of alkenes is hydrogen activation, substrate activation, and hydrogen transfer.[353] A mechanistic picture of the reaction is shown for the reaction of the square planar catalyst (**340**) with hydrogen gas to form a trigonal bipyramidal species, **341**.[354] Subsequent reaction with the alkene will replace a phosphine ligand to give a species such as **342**. It is also possible that the alkene binds to the catalyst first, followed by hydrogen. Hydrogen is transferred from rhodium to carbon in a stepwise manner, generating a species such as **344**. Release of the alkane generates a trigonal species (**343**) that reacts with additional hydrogen to regenerate **341**. Cotton and Wilkinson used this cycle to illustrate the hydrogenation of alkenes.[355]

There are many other homogeneous catalysts, involving several different transition metals. **Vaska's catalyst** (**345**) is one of the more important and it also reacts with hydrogen, converting the square planar catalyst to the octahedral **346**.[356] Reduction appears to involve replacement of the triphenylphosphine ligand with hydrogen or an alkene in a reversible process.[317]



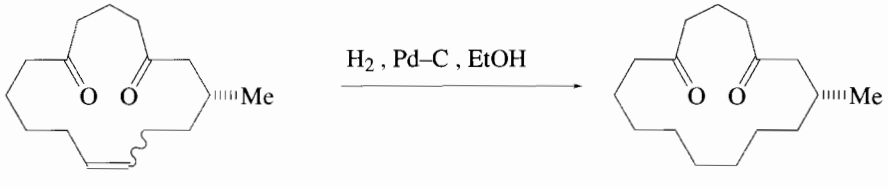
345 **346**

As shown above, the mechanism of hydrogenation involves coordination of the organic substrate to the metal, usually through the π bonds or lone pairs of electrons on heteroatom functional groups. The ability to bind the substrate, how it is bound (π complex or metal–carbon bond) and its reactivity to metal-bound hydrogen are the other factors determining differences in catalysis. Rylander's book[308] examines the reduction of many functional groups, and finds that palladium is preferred for reduction of alkenes, platinum for carbonyl, and rhodium for selective reduction of aromatic rings. The following order of reactivity is useful for general applications:

Pt	C=O	>>	C=C	>	**(H)**	>	Ar
Pd	C=C	>	**(H)**	>	C=O	>	Ar
Ru	C=O	>	C=C	>	Ar	>	**(H)**

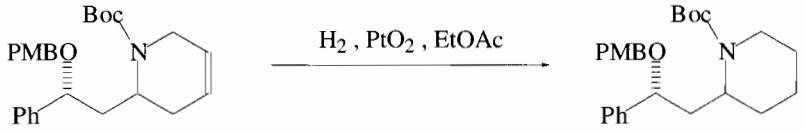
where **(H)** = hydrogenolysis

With proper choice of catalyst, high chemoselectivity can be achieved. In the Hagiwara et al. synthesis of (*R*)-(+)-muscopyridine, for example, hydrogenation of **347** was a Pd-C catalyst gave a 98% yield of diketone



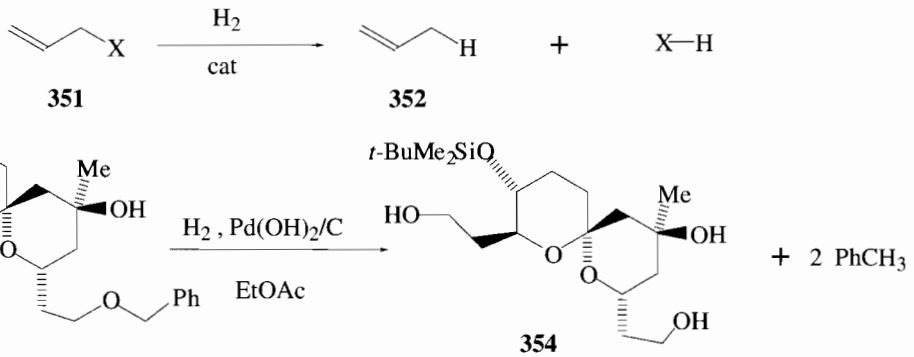
347 **348**

348, with no reduction of the ketone units.[357] Alkenes can be reduced in the presence of benzylic substituents without hydrogenation. In the Cossy et al. synthesis of (+)-sedamine, hydrogenation of **349** was a PtO_2 catalyst gave a 94% yield of **350** without hydrogenolysis of the benzylic ester group.[358]



349 **350**

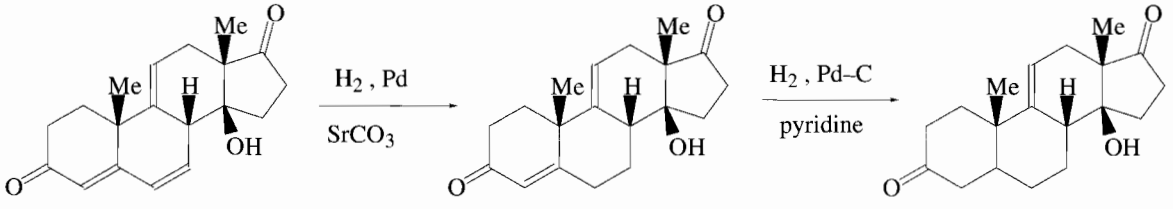
The phenomenon of ***hydrogenolysis*** (cleavage of a C—X bond, where X is an heteroatom) was introduced with the discussion of $LiAlH_4$ reduction and involves cleavage of carbon-heteroatom bonds. This process is particularly facile when the C—X bond is allylic or benzylic to a π-bond. Reaction with hydrogen cleaves the C-X bond (see **351**) to give the hydrocarbon (**352**). The ability of a catalyst to effect hydrogenolysis is indicated by (H) in the comparison of catalyst reactivity for Pt, Pd and Ru. The group X can be halogen, alcohol, ether, amine, and so on. A synthetic example of hydrogenolysis is cleavage of the two O-benzyl units in **353** to give diol **354** in quantitative yield, as part of Heathcock's synthesis of the C_1-C_{28} portion of spongistatin.[359] As shown in this example, hydrogenolysis of the $PhCH_2O—CH_2—$ unit leads to the alcohol and toluene ($PhCH_2—H$).



351 **352**

353 **354**

The order of catalytic ability shown above for platinum, palladium, and ruthenium is most useful when a catalyst must be chosen for hydrogenation of a multifunctional molecule. In molecules containing an alkene and a ketone or aldehyde, platinum catalysts selectively reduce the carbonyl. There are also differences in

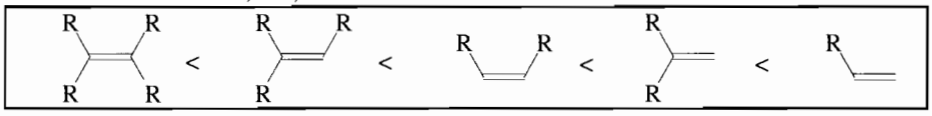


355 **356** **357**

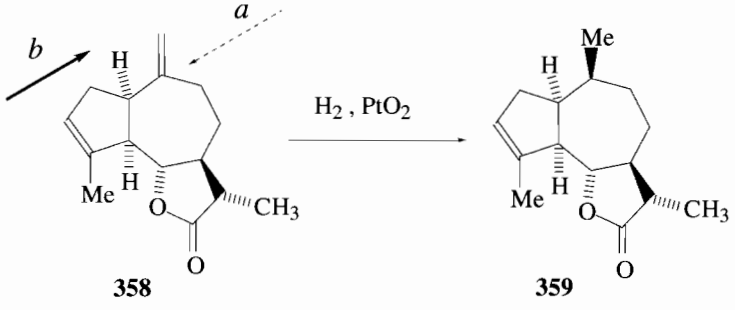
conjugated vs. nonconjugated alkenes. An example of this selectivity is the reduction of **355** with palladium and strontium carbonate ($SrCO_3$), which gave selective reduction of one alkene unit to **356** without reducing

either the conjugated carbonyl or the cyclopentanone moiety. Changing to a palladium on carbon catalyst allowed selective reduction of the conjugated double bond to give **357** in 87% yield.[360]

In general, more highly substituted alkenes do not adsorb on the catalyst as effectively and are not readily reduced, which implies that vinyl groups are easily reduced but tetrasubstituted alkenes are very sluggish. The relative order of reduction for mono, di-, tri- and tetrasubstituted alkenes is:



Unfortunately, this selectivity for reduction of the less hindered double bond is not always observed and varies considerably with the catalyst and reaction conditions (see Table 4.15).[343,361] When a double bond is highly strained, it is more easily reduced.[361] The reduction of the exo-methylene group in **358** to **359** illustrates this selectivity.[362] The exocyclic methylene group is more strained than the internal double bond, which is part of the cyclopentene moiety. Although the methylene is only disubstituted and the cyclopentene unit is trisubstituted, selective reduction of the methylene unit was observed.

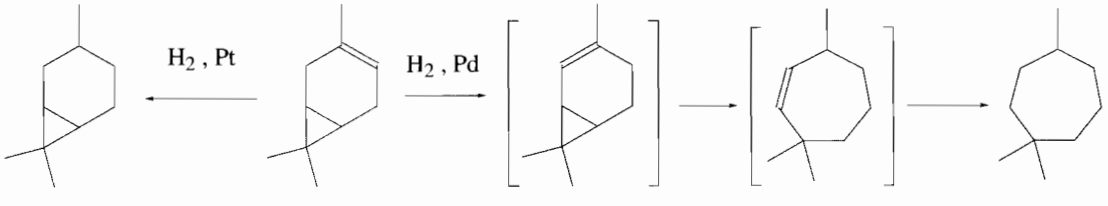


358 **359**

Isomerization of the double bond and even rearrangement are problems with some catalysts, and catalysts vary widely in their ability to induce isomerization. An order of ability to promote double bond migration was reported by Rylander, based on work by Gostunskaya et al.[363]

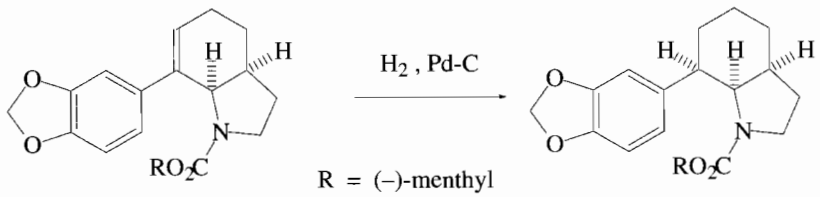
Pd	>	Ni	>>	Rh	≈	Ru	>	Os	≈	Ir	>	Pt

This relative order of bond migration is the same as the relative ability of these metals to absorb hydrogen gas. Rhodium does not show significant isomerization at low temperatures, but at temperatures > 80°C, isomerization is facile.[364] Reduction of car-3-ene (**360**) with a platinum catalyst gave carane (**361**), but using a palladium catalyst led to **364**. The initial reaction was a bond isomerization to give **362**, but this was followed by opening of the cyclopropane ring to form **363**. The final product (**351**) was generated by reduction of the double bond in **364**.[365]



361 **360** **362** **363** **364**

One way to explain the observed results in the reduction of **360** is that palladium binds alkenes reversibly, whereas platinum binds them more tightly and essentially irreversibly. If true, this has consequences for the stereochemistry (cis/trans-) of the final product. Banwell's synthesis of γ-lycorane involved reduction of **365** to



365 **366**

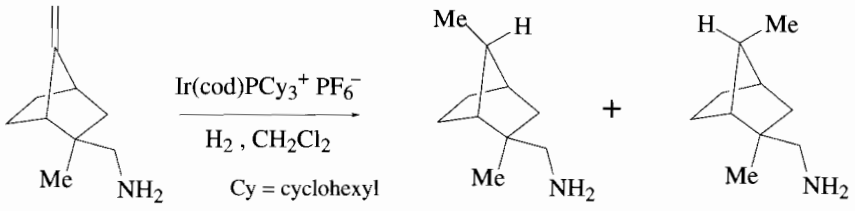
366,[366] where the cis-relationship of the 6-5 ring juncture led to delivery of hydrogen selectively from the bottom of **365** to give the observed stereochemistry in **366**. This experiment suggests that binding of hydrogen atoms and the alkene unit to palladium is such that delivery of both hydrogens is from the same face. Clean formation of predominantly one stereoisomer also suggests that the alkene is bound tightly to the metal. If the alkene isomerizes prior to delivery of hydrogen, or if the alkyl moiety is not bound tightly to the metal after the first hydrogen is delivered, the alkyl-metal intermediate will equilibrate *prior* to delivery of the second hydrogen. Such an event usually favors the trans-product or, in general, the thermodynamically more stable product. When either a cis- or a trans-product can be produced, catalysts differ significantly in their ability to give the cis-product. The ability of the catalyst to give primarily cis-products on hydrogenation is[367,365]

Ir	>	Os	>	Pt,Ru,Rh	>>	Pd

Platinum is an excellent choice to give the cis adduct (the reduction is essentially under kinetic control) and palladium will usually give primarily the trans adduct (the reduction is essentially under thermodynamic control). If the selectivity observed in the hydrogenation of **358** is examined more closely, one sees that the platinum probably does not isomerize the alkene prior to delivery of hydrogen nor lead to thermodynamic control. Face *b* is probably not the less hindered face for coordination to the catalyst. The oxygen atoms of the lactone ring may play a role, holding the catalyst and facilitating reduction from that face (a neighboring group effect –see the discussion of haptophilicity below). It is important to note, however, that if **358** gives a highly stereoselective reduction product, other molecules with similar structures may show the same stereochemistry. It *may* therefore be possible to predict the major product of hydrogenation reactions by examining the literature for reduction of alkenes with a similar structure. For all reductions, a thorough search of the literature for relevant examples is important.

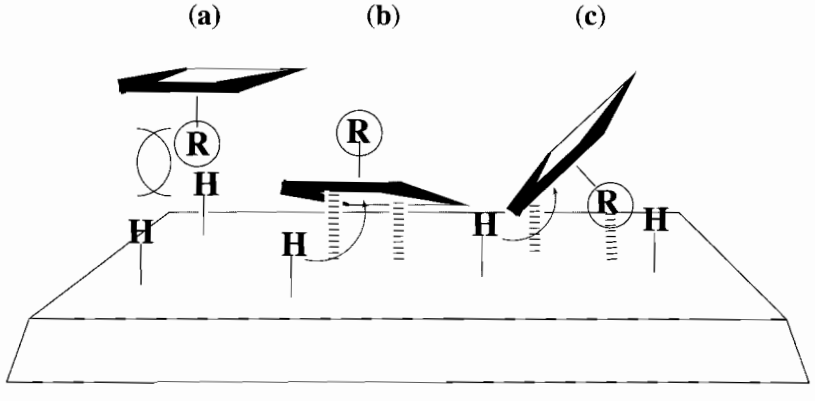
Predicting the stereochemistry of reduction is, as shown above, difficult in many cases and identification of the less hindered face can also be difficult. As Rylander pointed out, adsorption may occur to minimize steric interaction but this may not be the step that controls the stereochemistry of the final product. The example of **345** seems to reinforce this statement. Stereochemistry can vary with the degree of isomerization, the catalyst, reaction conditions, and the purity of the alkene.[368,369] Norbornene systems usually give exclusively exo-(cis)-addition of hydrogen unless there is significant steric encumbrance at the C7 position.[370]

Another phenomenon that influences the stereochemistry of reduction in alkene systems is **haptophilicity**, which is an anchoring effect in which a functional group binds to the surface of the catalyst and directs delivery of hydrogen from that side of the molecule.[371] This is analogous to the neighboring group effects encountered in previous sections and chapters. As with other neighboring group effects, the extent of its importance greatly depends on the hydrogenation solvent. Hydrogenations that used heterogeneous catalysts are usually explained in terms of "approach, fit and binding of the reducible molecule to the surface of the catalyst".[371,372] This is especially true when the geometry of a molecule or substituent hinders approach or fit.[373] The presence of a chelating group often produces stereochemistry opposite to that predicted by steric effects.[374] Different modes for adsorption of a haptophile on the surface of a catalyst are illustrated in Figure 4.2.[371] Reduction of amine **367** illustrates haptophilicity. The aminomethyl group is bound to the catalyst[375] and directs the hydrogen from the same face as the aminomethyl, to give **368**, with formation of only 10% of the syn diastereomer (**369**).[376]



367 **368** **369**

The first mode illustrated in Figure 4.2[371] suggests that a neighboring group can interfere with the haptophilic effect, presumably by preventing the required hydrogen bonding or dipole interaction. In most cases, hydrogenation of 3β-substituted Δ^5 steroids [such as 3β-cholesteryl methyl ether (**370**)] yields the saturated derivative with a trans-A/B ring juncture (H is trans to the bridgehead methyl).[377] Catalytic hydrogenation of



(a) Failure of adsorption cis to a hindering group
(b) Adsorption trans to a hindering or haptophilic group
(c) Adsorption cis to a haptophile

Figure 4.2. Adsorption of a haptophile on the surface of a catalyst.

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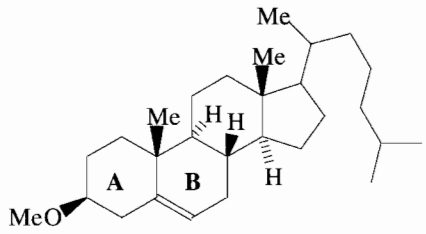
3α-substituted steroids such as epicholesteryl methyl ether (**371**), however, gave a cis-A/B ring juncture.[378] This latter reduction required the addition of catalytic amounts of perchloric or sulfuric acid and failed when done in ethanolic potassium hydroxide.[379] The α-methoxy group prevented adsorption on the α face. Binding therefore occurred on the β face, leading to a cis-A/B ring juncture (H is cis to the bridgehead methyl), which illustrates the first case in Figure 4.2.



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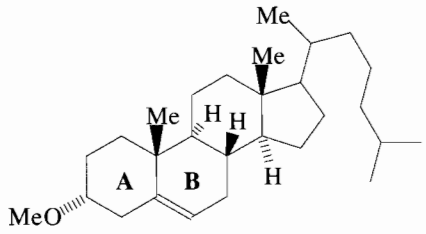
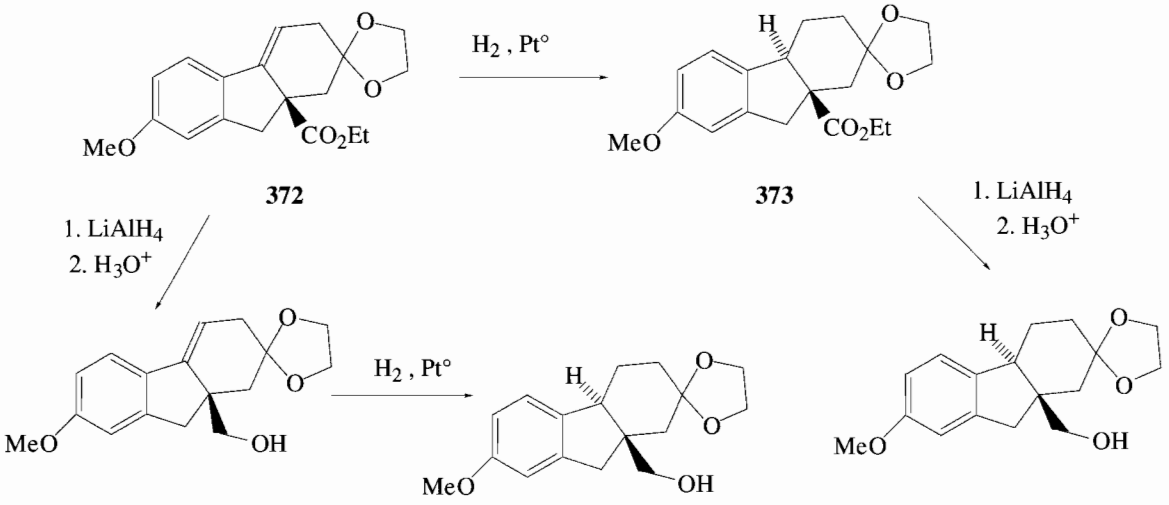


371

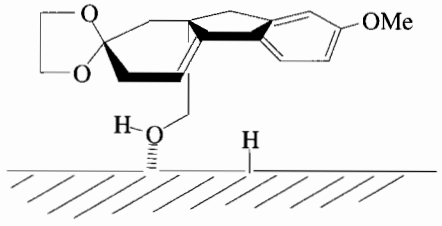
The second and third binding modes shown in Figure 4.2 can be illustrated by the reduction of **372**. The ester group in **372** functions as a poor haptophile and does not bind very well to the metal. Steric hindrance leads to the alkene moiety binding to a catalyst particle from the opposite face, and the product (**373**) has the trans-stereochemistry for the ring juncture.[378,371b] Hydrogenation was followed by lithium aluminum hydride reduction of **373** and gave **376**. If the order of reactions are reversed and **372** is first reduced with $LiAlH_4$ (to give **374**) and then subjected to catalytic hydrogenation, a haptophilic effect of the alcohol (see **377**) delivers hydrogen to that face, giving **375**. The presence of the hydroxymethyl group in **375** led to the opposite stereochemistry upon hydrogenation when compared to that observed with the ester group in **372**, illustrating the difference between the second and third cases in Figure 4.2.



372 **373** **374** **375** **376**

Alkynes contain π bonds, of course, and catalytic hydrogenation is quite easy. There are two significant problems with hydrogenation of alkynes, however. Hydrogenation of the triple bond first gives an alkene, but

overreduction can occur to give an alkane moiety (a two-stage reduction–sec. 4.1). Initial formation of an alkene product also gives rise to stereochemical control problems. Hydrogenation of alkynes can produce both cis and trans isomers. Both problems must be addressed.



377

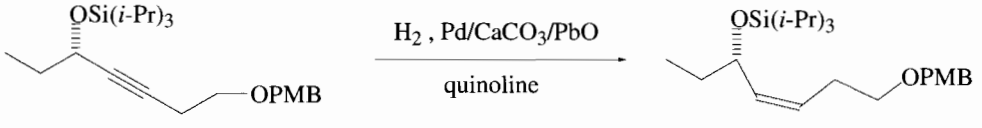
Selective reduction to the alkene without overreduction requires that the alkyne be adsorbed to the catalyst more tightly than the alkene. To selectively generate a cis alkene also requires that double bond migration and cis–trans isomerization of the alkene product be minimized. Palladium is usually a poor choice since both of these processes are faster than transfer of a hydrogen atom to the alkene. An order has been established for selectivity in the reduction of 2-pentyne to 2-pentene[380] without reduction of the C=C moiety in 2-pentene.

Pd	>	Pt	>	Ru	>	Rh	>	Ir

Selectivity for formation of the cis alkene (usually 91–98%) was

Pd	>	Rh	>	Pt	>	Ru	≈	Ir

The best reagent for selective reduction of alkynes to the cis alkene is the **Lindlar catalyst**.[381] Palladium chloride ($PdCl_2$) was precipitated on calcium carbonate ($CaCO_3$) in acidic media and deactivated with lead tetraacetate [$Pb(OAc)_4$] to give the named Pd–$CaCO_3$–PbO catalyst. Reduction of alkynes will stop at the cis alkene with little or no cis–trans isomerization. A variation uses quinoline as a poison, and this catalyst was used by Overman and co-workers to convert alkyne **378** to cis-alkene **379** as part of a synthesis of

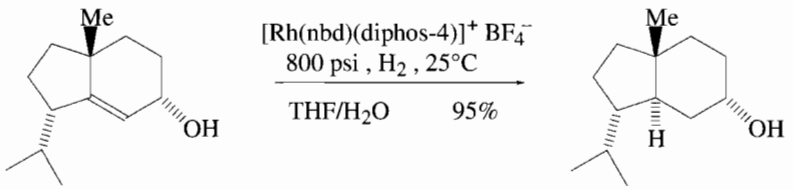


378 **379**

ptilomycalin A.[382] Cram and Allinger used a palladium on barium sulfate ($BaSO_4$) catalyst poisoned with quinoline[383a] (sometimes called the **Rosenmund catalyst**),[383b-d] to achieve the same selectivity. The poison is required to deactivate the catalyst (quinoline coordinates to the active sites on the metal), reducing the propensity for overreduction and bond migration. This Cram–Allinger catalyst is widely used in organic synthesis, and is commonly called a Lindlar catalyst. A mixture of nickel boride (Ni_2B) on borohydride exchange resin also gives cis alkenes upon hydrogenation of alkynes.[384]

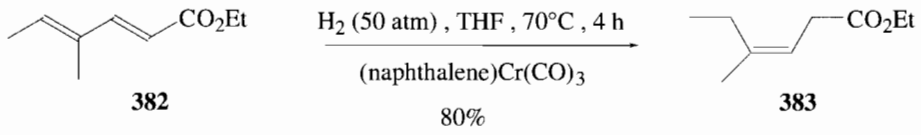
Homogeneous catalysis for the reduction of alkenes is an increasingly useful synthetic tool. The stereoselectivity of the reduction is significantly better than with heterogeneous catalysts,[385] which can be illustrated by the hydrogenation of **380** to the trans fused derivative **381** in 95% yield.[386] Reduction of ω-halo alkenes

such as 6-bromo-1-hexene to 1-bromohexane in 78% yield shows the selectivity for reduction of the alkene moiety over hydrogenolysis of the C—Br bond.[387] The reduction of **380** and 6-bromo-1-hexene used a homogeneous rhodium catalyst (nbd = norbornadiene and diphos = diphenylphosphinoethane).



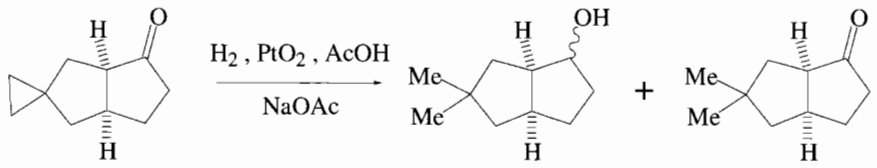
380 **381**

Dienes are hydrogenated to give alkenes, but over-reduction is a problem, as it was with alkynes. Homogenous catalysts can be of value here. The diene unit in **382** was hydrogenation to give the non-conjugated alkene unit in **383** (80% yield) in the Serebryakov et al. synthesis of faranal.[388] Both 1,2- and 1,4-reduction are possible, and the major product depends on the catalyst used, as well as the substituents on the C=C units of the diene.



382 **383**

It is possible to reduce cyclopropane rings by catalytic hydrogenation, using even a heterogeneous catalyst such as platinum oxide (PtO_2, often called the **Adams' catalyst**). Cyclopropane rings often react similarly to alkenes and with active catalysts, are opened during hydrogenation to a geminal dimethyl group. In one example, **384** was reduced to a 10:82% mixture of **385** and **386** in Cossy's synthesis of hirsutene.[389] The use of a platinum catalyst maximized the hydrogenolysis and minimized reduction of the carbonyl.

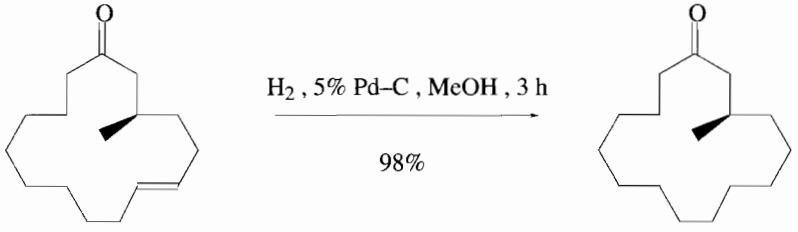


384 **385** **386**

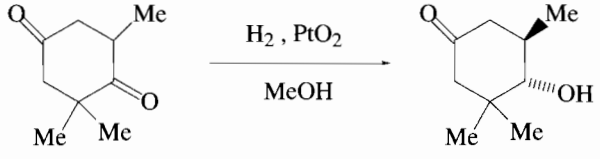
4.8.C. Hydrogenation of Carbonyl Compounds

The π bond of a carbonyl can reduced by catalytic hydrogenation to give an alcohol in the case of aldehydes or ketones. Problems of chemoselectivity and stereoselectivity are common with these compounds as they were with alkenes and alkynes. Hydrogen, in the presence of palladium catalysts, reduces alkenes faster than carbonyls and platinum is usually the preferred catalyst for carbonyls, which is apparent in the hydrogenation of **387** to (–)-muscone (**388**), the final step in Hagiwara's asymmetric synthesis.[390] It is noted, however, that in the reduction of **384**, reductive cleavage of the cyclopropane ring was faster than reduction of the ketone so care must be exercised. With alkenyl aldehydes, platinum reduces the aldehyde preferentially when adsorbed on carbon or calcium carbonate but not when adsorbed on barium sulfate or alumina (Al_2O_3).[391]

Platinum-catalyzed hydrogenation of **389** to the trans alcohol **390** illustrates a reduction with PtO_2.[392] Note that the more hindered carbonyl was reduced, which is surprising, as is the trans geometry of the product. This example is a reminder of the difficulties encountered in predicting selectivity in products obtained by catalytic hydrogenation, including ketones. The proliferation of readily available, easy to use and highly selective hydride and borane reducing agents often makes catalytic hydrogenation a second choice for reducing heteroatom containing functional groups, particular carbonyl derivatives.

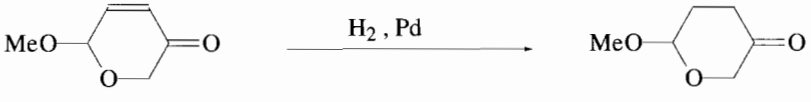


387 **388**



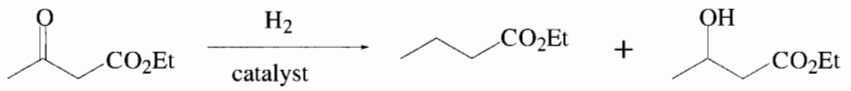
389 **390**

Hydrogenation of conjugated carbonyl compounds can give either 1,2- or 1,4-reduction, or a mixture, but the product distribution can usually be controlled by changing the catalyst. Hydrogenation of **391** with palladium, for example, cleanly reduced the alkene unit to give **392** in 96% yield.[393] Hydrogenation of similar compounds using a platinum catalyst generally reduces the carbonyl unit preferentially.



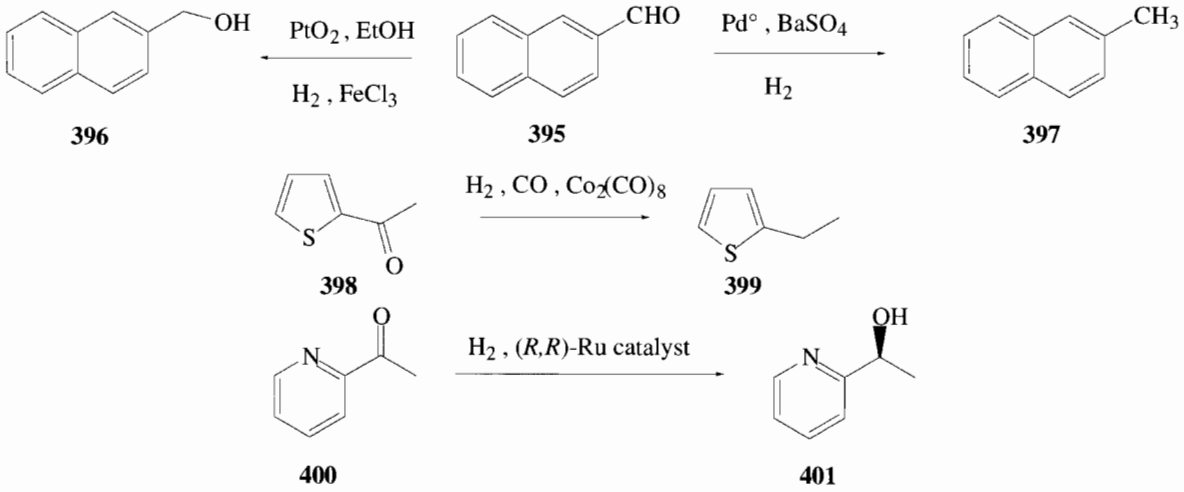
391 **392**

Hydrogenolysis (reductive cleavage) of the C—O bond is rarely a problem in hydrogenation reactions involving aliphatic carbonyl compounds, and new catalysts[394] are being developed all the time. The presence of an heteroatom substituent can lead to significant hydrogenolysis, however, as in the reduction of the ester ethyl 3-oxobutanoate (**393**).[395] Reduction gave the expected alcohol product [ethyl 3-hydroxybutanoate, **394**)], but hydrogenolysis of the C—O bond in **394** gave ethyl butanoate as a side product. It is important to note, however, that it is possible the alcohol moiety in **394** eliminated under the reaction conditions and the resultant alkene moiety was further reduced. Hydrogenolysis *may* not be involved in this transformation at all but it probably is. In the case of **393**, platinum black gave the greatest amount of reductive cleavage (90% ethyl butanoate and 10% of **394**). The use of additives and of platinum oxide (100% **394**) led to reduction of the ketone without hydrogenolysis.



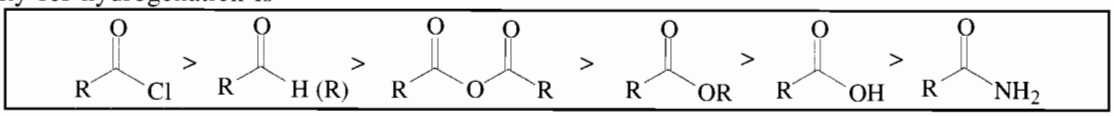
393 **394**

When the carbonyl of ketones or aldehydes is conjugated to aromatic systems, hydrogenolysis products are often the major isolated products. Catalytic hydrogenation of 2-naphthaldehyde (**395**) with palladium on barium sulfate, gave only 2-methylnaphthalene (**397**).[396] When the **Adam's catalyst** (PtO_2) was used, with ferric chloride ($FeCl_3$) as a promoter, an 80% yield of alcohol **396** was obtained although addition of excess promoter induced further hydrogenolysis to **397**.

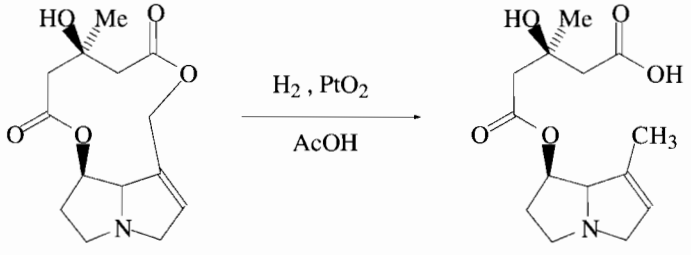


Hydrogenolysis was also observed in the reduction of 2-acetylthiophene (**398**) when the homogeneous catalyst cobalt octacarbonyl [$Co_2(CO)_8$] was used, and 2-ethylthiophene (**399**) was isolated in 52% yield.[397] The homogeneous catalyst was necessary to minimize poisoning by the sulfur compound. As mentioned earlier, homogeneous catalysts are usually less susceptible to poisoning.[398] In general, reduction to the alcohol is rapid with aromatic aldehydes using palladium, but slow with ruthenium. The reverse is observed with aliphatic aldehydes. Hydrogenolysis can occur in acidic media or with vigorous reaction conditions. Catalysts are available, however, that allow hydrogenation of a ketone unit that is attached to heterocyclic rings, giving the alcohol without significant hydrogenolysis. An example is a homogeneous ruthenium catalyst used to hydrogenate **400** to **401** in 96% yield, and with high enantioselectivity (see below).[399]

Some acid derivatives are reduced by catalytic hydrogenation, *but not all*. There is a clear difference in reactivity, apart from specificity for the metal catalyst. The ability of hydrogen to reduce acid derivatives follows the expected order and acid chlorides will be reduced faster than esters, for example. Aldehydes and ketones are reduced significantly faster than all acid derivatives except acid chlorides.[400] The general order of reactivity for hydrogenation is



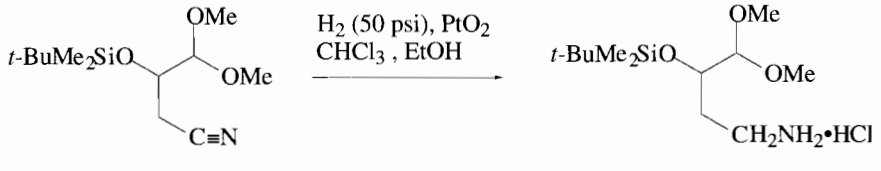
Esters are difficult to reduce and the reduction of alkenes, alkynes, aldehydes, and ketones in the presence of esters and amides is usually facile. Hydrogenation of carboxylic acids is very difficult. The use of ruthenium oxide (RuO_2) or ruthenium on carbon (Ru/C) at high pressure and temperatures is the preferred method for reduction of acids to alcohols. Hydrogenolysis can be a problem with esters possessing an allylic or benzylic C—O bond, as in the cleavage of one ester linkage in the diolide dicrotaline (**402**) to give **403**.[401]



402 **403**

8.D. Hydrogenation of Other Heteroatom Functional Groups

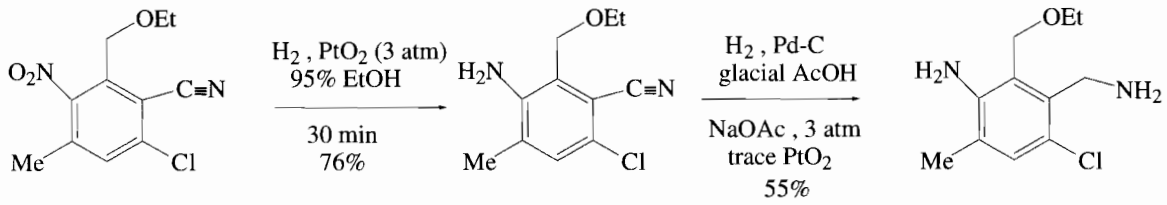
Most functional groups that contain a π bond can be reduced by catalytic hydrogenation, and groups such as halides can be reduced as well. Many problems can accompany reduction, however, including poor reactivity, overreduction, or competing side reactions, particularly with nitriles and halides. It is noted, however, that nitriles are usually reduced to the amine in good yield. Hydrogenation of nitriles usually generates an imine intermediate, and nucleophilic addition of unreacted amine leads to dimers or polyalkylated species as the final product. Reduction of propanenitrile with a rhodium catalyst gave dipropylamine, for example, after hydrogenolysis of the initially formed condensation product.[402] Reduction of propanenitrile with platinum or intermediate, and nucleophilic addition of unreacted amine leads to dimers or polyalkylated species as the final product. Reduction of propanenitrile with a rhodium catalyst gave dipropylamine, for example, after hydrogenolysis of the initially formed condensation product.[402] Reduction of propanenitrile with platinum or palladium catalysts gave the trisubstituted amine (tripropylamine) but rhodium oxide (Rh_2O_3) gave primarily the monoamine. Nickel, nickel boride (NiB), and cobalt are the best catalysts for conversion of low molecular weight nitriles to primary alkyl amines.[410,403] Isolation of the amine product can sometimes be problematic, and it is often isolated as its hydrochloride salt. Clive[404] found that hydrogenation of **404** in the presence of several equivalents of chloroform, which served as a controlled source of HCl,[405] gave amine **405** in high yield, as part of a synthesis of brevioxime.[404]



404 **405**

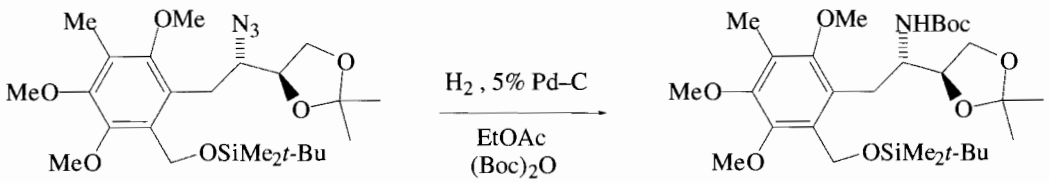
Aromatic nitriles can give mixtures of the primary amine and dibenzylamines (via the condensation reaction), but this depends on the catalyst.[402] Rhodium hydroxide [$Rh(OH)_3$] is very effective for production

of aminomethyl derivatives, with repression of the condensation reaction. Hydrogenation of **406** with platinum reduced the nitro group, but not the nitrile, to give **407**. Subsequent reduction with palladium gave the amino-methyl group in **408** (and also reduced the chloro moiety) in Folker's synthesis of pyridoxine.[406]



406 **407** **408**

Hydrogenation of nitro compounds is rather straightforward, and palladium, platinum, and nickel catalysts have been used. Palladium is the most common catalyst for both aromatic and aliphatic nitro compounds. The poor results obtained for reduction of aromatic nitriles with hydride reagents (sec. 4.2.C.iii) make catalytic hydrogenation the preferred method. Reduction of **407** involved conversion of the aromatic nitrile moiety to the benzylamine derivative when palladium and a trace of platinum oxide was used.[406] Hydrogenation using platinum oxide converts aromatic nitro compounds to aniline derivatives,[407] even in the presence of other reducible groups.[408]

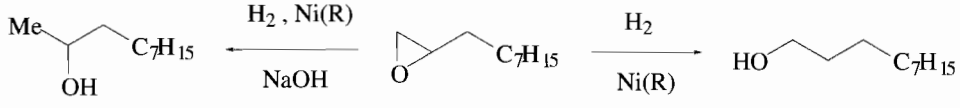


409 **410**

Catalytic hydrogenation is commonly used for reduction of azides, which are important compounds used in [3+2]-cycloaddition reactions (sec. 11.11.H) and in rhodium-catalyzed carbene chemistry (sec. 13.9.B.ii). Platinum, palladium, and nickel have been used for this reduction but hydrazine is sometimes added to limit the extent of hydrogenolysis. Azides are important precursors to amines since the N_3 moiety can be incorporated into a molecule via an S_N2 reaction more easily than an amine, in most cases (secs. 2.7.A, 2.7.B), but a second step (reduction) is required to give the amine. Hydrogenation to the amine can be carried out with retention of the original configuration of the azido group. An example is the palladium catalyzed reduction of **409** to **410** in the Danishefsky and co-workers synthesis of saframycin subunits.[409] Note that hydrogenation occurred without inversion of the C—N bond so the relative stereochemistry of the amino unit in **410** is the same as that of the azide unit in **409**. In this case, the hydrogenation was performed in the presence of Boc anhydride to trap the amine as the *N*-Boc derivative (-$NHCO_2t$-Bu–see sec. 7.3.C.iii).

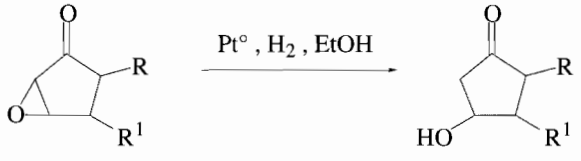
Epoxides react with hydrogen and a catalyst by a hydrogenolysis reaction, but it is relatively slow and many functional groups can be reduced preferentially, which means that epoxides can be reduced if there is little or no other functionality. If reduction of the epoxide is to be avoided, rhodium on carbon (Rh/C)[410] or Wilkinson's catalyst[411] is preferred. Predicting the direction of ring opening (regioselectivity in the reduction)

in epoxides is a difficult problem. Symmetrical epoxides typically show delivery of hydrogen to both carbons of the oxirane ring and Rylander discussed the various factors that influence this delivery.[412] Prediction is usually difficult, but it has been observed that addition of hydroxide to the reaction medium influences the regioselectivity of the reduction. Hydrogenation of 1-octyloxirane (**411**) with Raney nickel gave 1-decanol (**413**) but hydrogenation using Raney nickel mixed with NaOH gave 2-decanol (**412**).[413]



412 **411** **413**

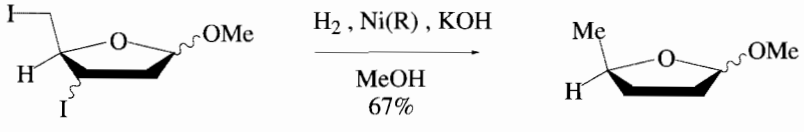
Reduction of α,β-epoxyketones is usually accompanied by hydrogenolysis at the α-position, and the product is a β-hydroxy ketone,[414] as in the conversion of **414** to **415**.[415] If other substituents (electron releasing or withdrawing) are attached to the β-position, the direction of reduction is less predictable. Reduction of aziridines by hydrogenolysis is similar to that of epoxides and usually occurs at the less hindered C—N bond.[416,417]



414 **415**

3.E. Synthetically Useful Hydrogenolysis Reactions

Halides are common components of organic molecules, and in many cases they must be removed. One way to do this is reduction to the corresponding hydrocarbon by hydrogenolysis. A nickel catalyst (usually

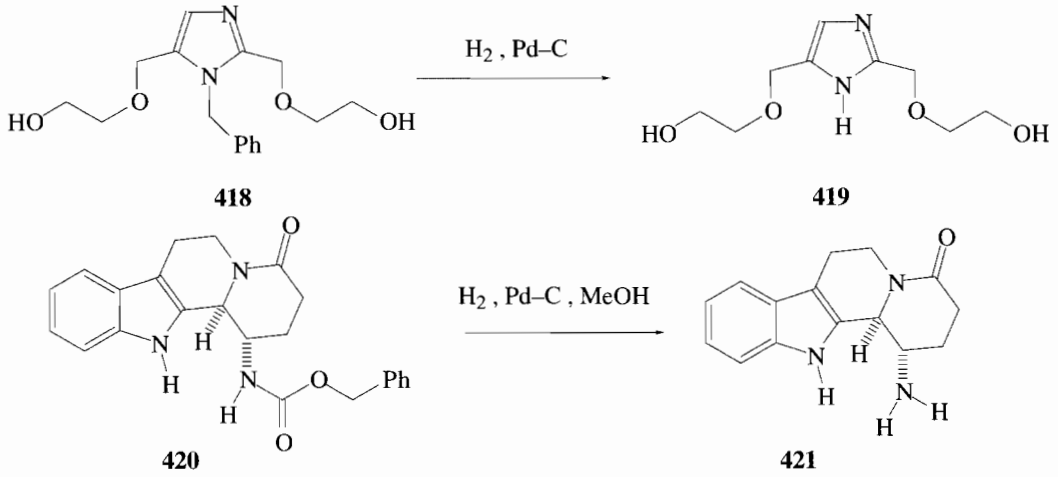


416 **417**

Raney nickel) can be used, as in reduction of the iodomethyl furanose derivative **416** to the methoxy lactol, **417**[418] which is sometimes a problem since reduction of alkenyl and carbonyl functional groups with palladium catalysts commonly removes halogen along with the target functional group. If the halogen is to remain in the molecule, platinum is the preferred catalyst.

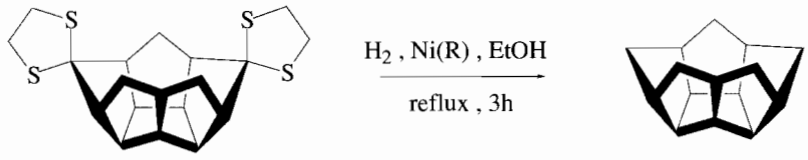
The hydrogenolysis reaction is an important part of many syntheses that involve protection of functional groups (secs. 7.3.A, 7.3.C). The benzyl group is commonly used to protect alcohols and amines (secs. 7.3.A, 7.3.C.i).[419] Palladium shows a propensity for hydrogenolysis, and it is commonly used to cleave $PhCH_2$-//-O or $PhCH_2$-//-N bonds. Hydrogenolysis of these protected functional groups leads to toluene and the alcohol or amine. Removal of the O-benzyl groups in the hydrogenation of **353** (see sec. 4.8.E) is an example of this

reaction. Other groups are often reduced faster than the O-Bn bond, or competitively with it however.[420] Hydrogenation of benzyl amines leads to hydrogenolysis and cleavage of the C—N bond. The N-benzyl group of imidazole **418** was cleanly removed with hydrogen (Pd–C) to give **419** in 87% yield.[421] Hydrogenolysis is the common method for removal of the benzyloxycarbonyl (Cbz; benzyl carbamate) group, a carbamoyl protecting group often used to protect amines (sec. 7.3.C.iii). This reaction is illustrated by deprotection of the amine in **420** to give **421** in quantitative yield, as part of Lee's synthesis of amino-indolo[2,3-*a*]quinolizidines.[422]



418 **419** **420** **421**

Dithianes and dithiolanes are generated from the reaction of dithiols with aldehydes and ketones, and they are commonly used as sulfur stabilized carbanions (sec. 8.6) or as carbonyl protecting groups (sec. 7.3.B.ii), making them very useful synthetic intermediates. In addition, sulfur compounds such as sulfoxides and sulfones are important for C—C bond forming reactions via the sulfur carbanions (sec. 8.6.A). In many cases, after the sulfur group has been used it must be removed from the molecule. Bivalent sulfur is a common poison of heterogeneous catalysts, but the affinity of sulfur for nickel makes Raney nickel an effective reagent for hydrogenolysis of the C—S bond. The utility of this reagent can be illustrated by Eaton's use of it to reduce the bis(dithiane) moieties in **422**, giving [5]-peristylane (**423**) in 90% yield.[423] In contrast to the reactions conditions shown for **422**, there are many instances in which the dithiolane is simply heated with Raney nickel in ethanol or methanol without adding hydrogen gas.[424]



422 **423**

4.8.F. Hydrogenation of Aromatic and Heteroaromatic Hydrocarbons

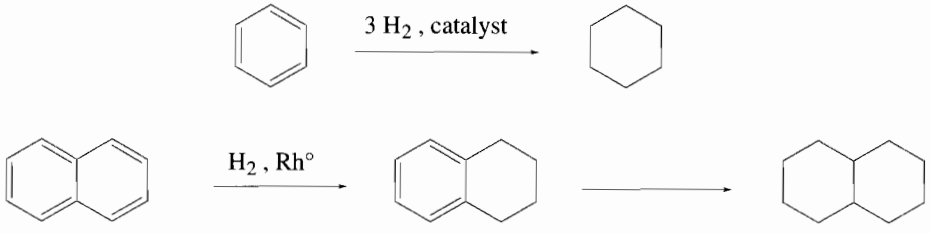
Aromatic hydrocarbons and heterocycles are important in many natural products and reduction of the aromatic ring is very important from a synthetic viewpoint. Clearly, the most simple example is reduction of

benzene to cyclohexane, and it requires vigorous reaction conditions unless rhodium catalysts are used. Rylander showed the order of various catalysts for the reduction of benzene to be

Rh	>	Ru	>>	Pt	>	Pd	>>	Ni	>	Co

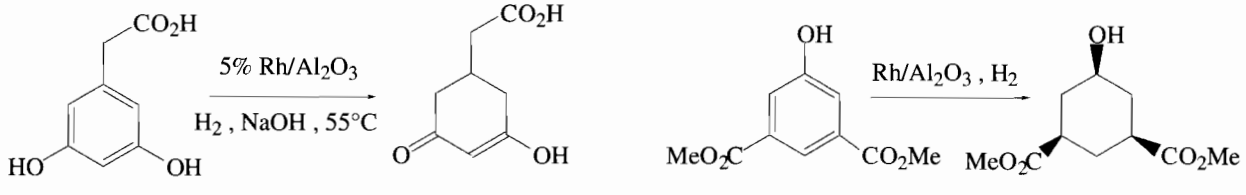
Rhodium and ruthenium are used if hydrogenolysis is to be avoided. The catalyst of choice changes somewhat with fused ring aromatic hydrocarbons. The relative order for reduction of naphthalene to tetralin (**424**) is[425]

Pd	>	Pt	>	Rh	>	Ir	>	Ru

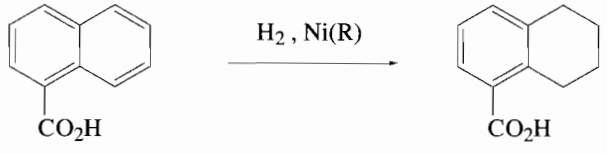


424 **425**

This order is due, in part, to the slowness of palladium to further reduce the aromatic ring in **424**. Rhodium initially reduces naphthalene to **424**, but further reduction to decalin (**425**) is so rapid that **424** is a minor constituent of the final product mixture.



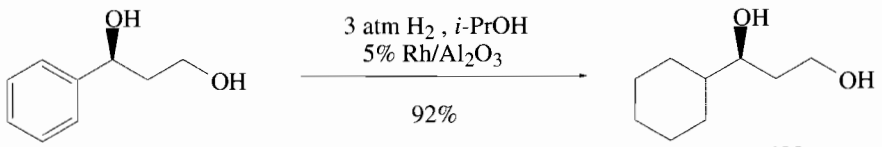
426 **427** **428** **429**



430 **431**

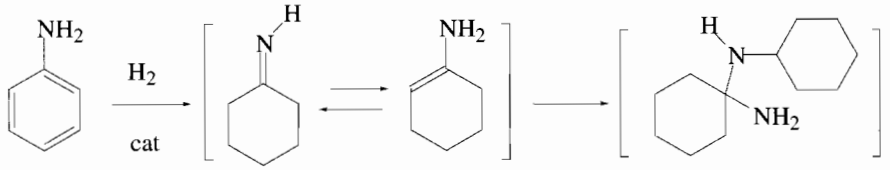
When the aromatic ring is substituted, catalytic hydrogenation can be complicated by side reactions. Reduction of phenols initially gives enol products, but these are usually converted to cyclohexenone or cyclohexanedione derivatives, as in the reduction of **426** to **427**,[426] which stands in contrast to the reduction of **428**, which gave the cyclohexane derivative **429** in the presence of excess hydrogen.[427] Note the selectivity of the reduction for the all cis geometry in **429**. The use of palladium or platinum catalysts show significantly less stereoselectivity in this type of reduction. Catalytic hydrogenation is usually very selective for electron-rich aromatic rings when aromatic rings are also in the molecule that have electron-withdrawing substituents. A simple benzene ring is reduced faster than a ring with an electron withdrawing group attached to it, for example. Reduction of 1-naphthalenecarboxylic acid (**430**) with Ni(R) led to selective reduction of the more

electron-rich ring to give **431**.[428] An example of hydrogenation of a benzene rings in a synthetic sequence is the conversion of **432** to **433** in 92% yield, as part of Werner's synthesis of the opioid antagonist LY255582.[429]

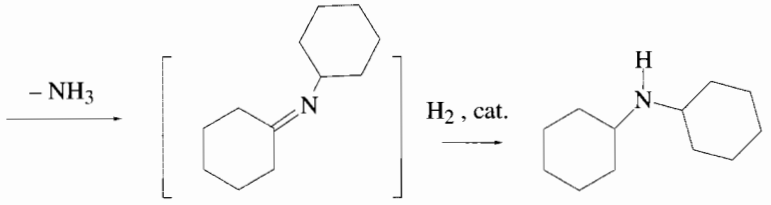


432 **433**

Catalytic hydrogenation of aniline derivatives is often accompanied by disubstituted amine products, as in the formation of dicyclohexylamine (**435**) from aniline.[430] The reactive intermediate in the reduction is an



434 **435**



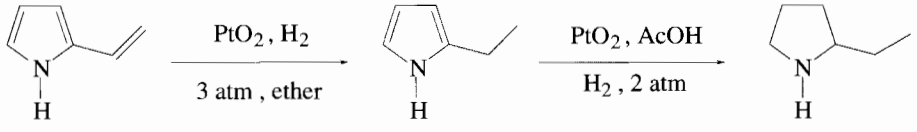
436

initially formed imine **434** (which is in equilibrium with the enamine under the reaction conditions). Reduction of **434** can give cyclohexylamine, which reacts with **434** to give **435**. Under the reaction conditions, **435** loses cyclohexylamine to give an imine (or an iminium salt). This intermediate then reacts with additional hydrogen to give the isolated product, **436**. This process is analogous to the dimerization reactions observed in the $LiAlH_4$ reduction of aliphatic nitriles (sec. 4.2.C.iii for the formation of dipropylamine from propanenitrile). This side reaction can usually be limited to a small percentage by the use of ruthenium or rhodium catalysts, allowing isolation of the amine. It is noted that enamines can be directly reduced to the amine by catalytic hydrogenation.[431] The order of least coupling (with Ru) to most coupling (with Pt) is[430]

Ru	<	Rh	<<	Pd	<	Pt

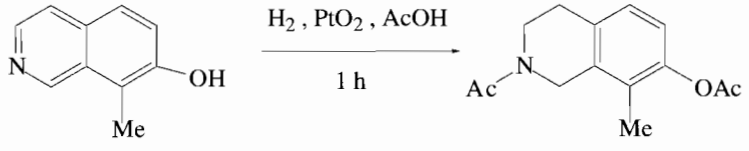
The product(s) formed by reduction of heterocyclic aromatic compounds varies with the number of rings, the heteroatom and its position in the molecule, as well as the catalyst. For pyridine and pyrrole derivatives, rhodium is the most common catalyst, and acidic media are used to form the corresponding salt which is more easily reduced. Hydrogenation of pyrrole is more difficult., which is illustrated by the observation that hydrogenation of 2-vinyl pyrrole (**437**) with 3 atmospheres of hydrogen gave 2-ethyl pyrrole (**438**) in 81% yield without reduction of the pyrrole ring.[432] Hydrogenation of the pyrrole ring is possible under acidic

conditions, which is illustrated by hydrogenation of the previous reaction product, (**438**) to give **439**.[432] Rhodium catalysts are usually preferred in low-pressure hydrogenations to reduce heterocyclic aromatic rings.



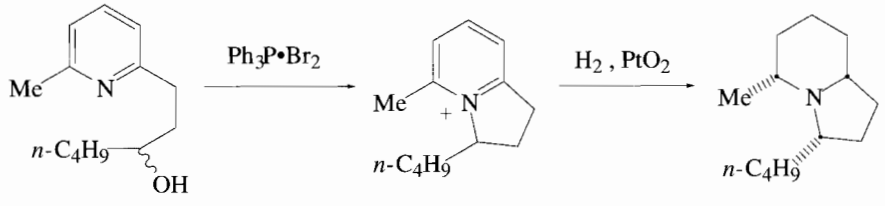
437 **438** **439**

Both platinum and palladium catalysts can be used for the hydrogenation of heteroaryl derivatives, although platinum is more common. Selective reduction of the heterocyclic ring in 8-methyl-7-hydroxy isoquinoline (**440**) gave **441** in 67% yield, in Woodward and von E. Doering's synthesis of quinine.[433]



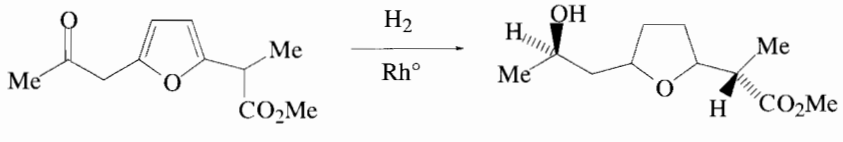
440 **441**

Reductive alkylation of heteroaromatic rings is possible using catalytic hydrogenation.[434] Cyclization of the substituted pyridine **442** was induced by treatment with triphenylphosphine•bromine, and generated pyridinium salt **443**. Isolation of **443** by Sonnet was followed by hydrogenation with platinum, generating the trail pheromone of the Pharaoh ant (3-butyl-5-methyloctahydroindolizine, **444**).[435]



442 **443** **444**

Oxygenated heterocycles are reduced with hydrogen but are prone to hydrogenolysis, especially when platinum is used. Hydrogenation of furan derivatives uses palladium, rhodium, or ruthenium catalysts to minimize this problem. When the reaction is done at higher temperatures and under acidic conditions, however, ring cleavage can occur via hydrogenolysis. Hydrogenation of furan to THF is straight-forward when a mixed catalyst, 70% rhodium + 30% platinum, is used.[436a] The reduction of disubstituted furan **445** to

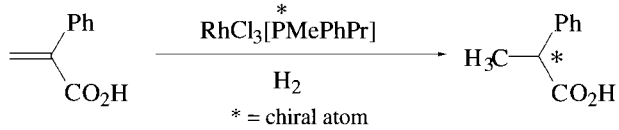


445 **446**

446 in the Gerlach et al. synthesis of 8-*epi*-nonactic acid used a rhodium catalyst.[436b,c] Reduction of thiophene derivatives can be accompanied by serious problems since bivalent sulfur is a common poison for heterogeneous catalysts. This problem can be circumvented or diminished by using a large excess of a heterogeneous catalyst. As an example, thiophene was reduced to perhydrothiophene in 71% yield, but only when the molar ratio of palladium to thiophene was 2:1 or greater.[437]

4.8.G. Asymmetric Catalytic Hydrogenation

Substituted alkenes can have prochiral carbons, and hydrogenation leads to stereogenic centers. Therefore, we must address the issue of stereoselectivity. Asymmetric induction during hydrogenation is possible if a chiral catalyst is used. With heterogeneous systems this usually involves addition of a metal catalyst to a chiral coordinating molecule or a chiral medium[438] such as silk fibroin,[439] (a natural structural protein from silk), which gave reduction in up to 70% ee (see sec. 1.4.F for a definition of % ee). Other chiral additives include palladium on poly-(*L*)-leucine,[440] Pd/C with (*S*)-methionine,[441] palladium on silica gel in the presence of a chiral alkaloid such as narcotine,[442] and platinum with *l*-menthoxy acetate or tartaric acid.[443] Hydrogenation of a chiral substrate with a heterogeneous catalyst can show enantioselectivity during reduction but problems associated with chemisorption sometimes lead to racemization and bond migration and is less of a problem with homogeneous catalysts. Indeed, soluble homogeneous catalysts offer the best route for asymmetric induction in catalytic hydrogenation, especially for alkenes. The occasionally poor activity of homogeneous catalysts with heterocyclic functional groups limits their utility to some extent.

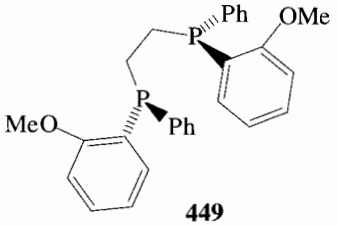


447 **448**

A common way to generate a chiral catalyst involves a modification of Wilkinson's catalyst (**340**) in which an optically active tertiary phosphine, bis- or tris-phosphines are used as ligands in place of triphenylphosphine. If the phosphorous atom of the added phosphine is the stereogenic center, the optical yields are usually 4–22%, as in the conversion of atropic acid (**447**) to hydratropic acid (**448**) with 22% ee.[444] An example of this type of phosphine is (–)-methylpropylphenylphosphine. bis(Phosphines) are commonly used, including **449** (called dipamp)[445] and **450** (called R-camp).[446]

As noted in Section 1.4.A, phosphines are configurationally stable if the temperature is *below* ≈ 130°C, which is in sharp contrast to amines. These amines show fluxional inversion at both ambient and very low temperatures. This configurational stability allows the preparation, isolation and even the resolution of chiral phosphines, but they are not always easy to synthesize. A useful alternative is to attach a chiral molecule to a phosphine with an achiral phosphorus atom. When the ligands are used to form homogeneous catalysts, the enantioselectivity can be very good, if the alkene substrate is properly chosen. In addition to **435** and **436**, some of the more popular chiral phosphine ligands include **451** (called diop),[447] **452** (called chiraphos),[448] **453** (called prophos),[449] the ferrocenyl derivative **454**,[450] and **455** (called bppm).[451] Most of these are based

on the achiral phosphine ligand 1,2-diphenylphosphinoethane (called diphos or dppe, **456**). These bis-(phosphine) ligands are most commonly coordinated to rhodium[452] to prepare modified Wilkinson's catalysts.



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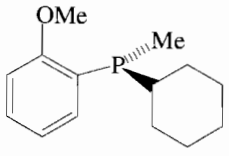

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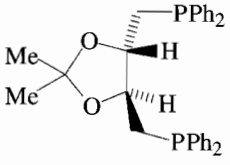

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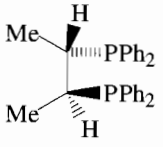

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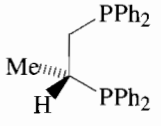

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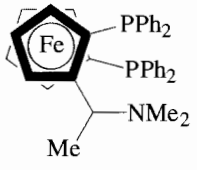

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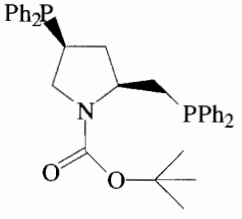

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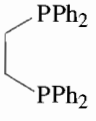
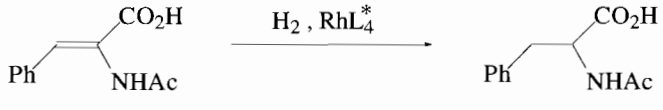


456

One of the more important applications of chiral hydrogenation catalysts is the preparation of chiral α-amino acids. Koenig correlated the % ee for the reduction of **456** to **457** with rhodium catalysts prepared from several chiral phosphine ligands (see Table 4.16).[452] In general, reduction of **457** gave the enantiomer of **458** with the absolute configuration opposite that of the chiral phosphine [i.e., (*RR*) → (*S*); (*SS*) → (*R*); (*R*) → (*S*); (*S*) → (*R*)]. One complicating factor is that some isomerization (*E*)→(*Z*) occurs in **457** during hydrogenation, depending on the solvent and the catalyst. Reduction of **457** in THF with **456** showed 23% isomerization. Reduction with (*RR*)-diop (**451**) gave 20% isomerization but dipamp (**449**) showed 0% isomerization. Isomerization was more extensive in ethanol (28% with diphos, 35% with diop, and 6% with dipamp). When benzene was used, no isomerization was observed with any of these catalysts.[453b]

When these catalysts react with rhodium salts, many intermediate metal complexes can be formed, including Rh(diphos)cod$^+$, Rh(diphos)Ac, Rh(dipamp)$_2$, Rh(diop)NBD$^+$, and Rh(camp)$_2$COD$^+$. In work by Halpern,

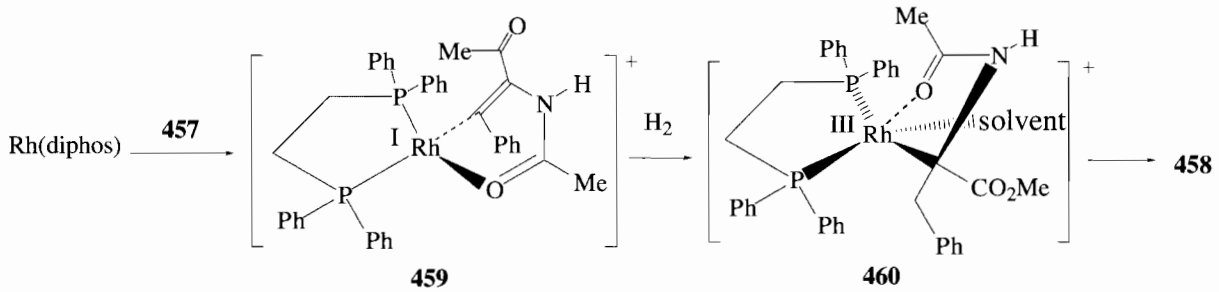
Table 4.16. Effect of Chiral Phosphine Ligands on the Asymmetric Hydrogenation of 457



457 **458**

Ligand	% ee (*R* or *S*)
(*RR*) **451**	85 (*S*)
(*SS*) **452**	95+ (*R*)
(*RR*) **453**	90 (*S*)
454	93
(*SS*) **449**	91 (*R*)
(*RR*) **450**	94 (*S*)
(*R*) **436**	15 (*S*)

several intermediates in the hydrogenation of **457** with rhodium catalysts were characterized.[448a] An initial square planar Rh(I) coordination complex (**445**) was detected by NMR (^{1}H, ^{13}C, ^{31}P) and its tetrafluoroborate salt was isolated and identified by X-ray crystallography.[454] Lowering the temperature and using the same NMR techniques allowed observation of a square-planar Rh(III) intermediate (**446**), generated after transfer of hydrogen to the π bond.[448a,454] Halpern presented a mechanistic rationale for the reduction of **443** with this catalyst, based on these intermediates.[455] Halpern and co-workers suggested transformation of a square planar complex to an octahedral complex as the hydrogens are transferred from rhodium to carbon, in a stepwise manner.[448,454] Chiral ligands generate facial selectivity in the complex during the hydrogen transfer.



[Reprinted with permission from Chan. A.S.C.; Halpern, J. *J. Am. Chem. Soc.*, ***1980***, *102*, 838. Copyright © 1980 American Chemical Society.]

4.9. DISSOLVING METAL REDUCTIONS

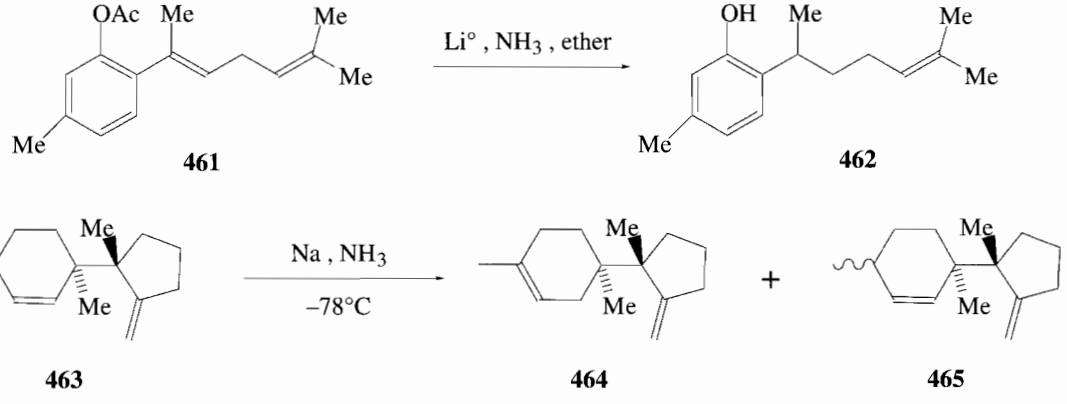
Reduction involves the gain of electrons by an organic species, as described in this chapter. There are many metals and metal salts that can transfer electrons to an organic substrate, reducing them, with concomitant oxidation of the metal. This section will describe the more common metals used for this purpose as well as the functional groups that are reduced by them. Electron transfer in an electrolytic cell accomplishes essentially the same reactions as treatment with alkali metals, but there are some interesting differences.

4.9.A. Reduction with Alkali Metals

Metals can be used to reduce organic molecules in the presence of a proton transfer agent, which is very different from the metal-catalyzed hydrogenations discussed above. Alkali metals can transfer an electron to some organic molecules, but an acidic solvent (with an X—H bond) is required to deliver a hydrogen to the resulting reactive intermediate. Transfer of an electron to an organic molecule generates a metal cation along with the radical anion derived from the organic fragment. The acidic solvent used as the hydrogen source to quench the radical anion is usually water, alcohol, or ammonia, but primary or secondary amines can also be used. The ability of a metal to reduce organic molecules is directly related to its ability to release electrons (reduction potential)and Hudlický tabulated these for several alkali and transition metals ,[456] A list of standard reduction potentials for common reducing metals was presented in Table 4.1. It was apparent in that table that lithium and potassium, followed closely by sodium, were the most effective electron transfer metals in this series. It is therefore not surprising that these metals are used most often for reduction of organic molecules.

Metal reduction is most useful for polarized organic substrates containing multiple bonds (C=O, C=N, C≡N). Isolated alkenes are not easily reduced, which is a major difference from the obviously related electrolytic reductions to be discussed in Section 4.9.J. Alkenes and alkynes that are conjugated to a phenyl ring, another double bond or an aromatic ring are reduced quite easily, however, as in the conversion of **461** to **462** in 97% yield.[457] Aromatic rings, halides, and sulfur derivatives are also reduced and alkynes are generally converted to the trans alkene. Complete reduction of the aromatic ring is also possible, especially with hetero-cyclic rings, including pyridine derivatives and furan derivatives.

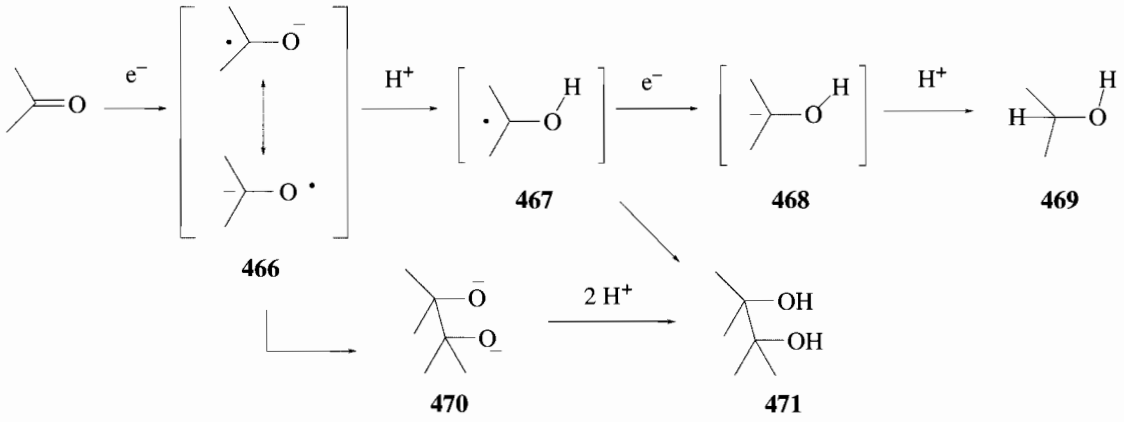
Conjugated dienes are also reduced, usually via 1,4-addition to give an alkene. When the diene unit in **463** was treated with sodium metal in ammonia, a 65% yield of **464** was obtained, as part of Meyer's synthesis of (–)-trichodiene.[458] As expected, a mixture of 1,4-reduction (to give **464**) and 1,2-reduction (to give **465**) was observed (in a ratio of 85:15), which is common with this type of reduction. Note that the nonconjugated exo-methylene group in **450** was not reduced under these conditions.



Dissolving metal conditions are capable of reducing many organic functional groups and excellent chemo-, regio-, and stereoselectivity are commonly observed. The choice of solvent is important to the reaction, often changing it course, and having a great influence of the yield and ease of isolation of the products. Liquid ammonia is commonly used, often in conjunction with alcohols. Low molecular weight amines and ethylenediamine can be used in reductions with lithium metal.[459] The most common applications for this reaction include reduction of alkynes, conjugated carbonyls, and Birch-type reductions of aromatic rings.

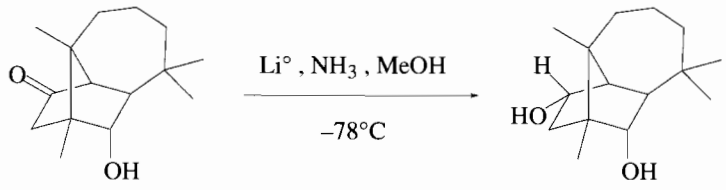
.9.B. Reduction of Carbonyl Compounds

Metal reduction of ketones and aldehydes begins with electron transfer from the metal to the carbonyl, forming a ketyl (a radical anion). If we use acetone as a typical example, the mechanism involves transfer of an electron from the metal to the carbonyl π bond giving a radical anion with two canonical forms (**466**).[460] There are two competing pathways for the ketyl, reduction or radical coupling to give **470**, which gives diol **471** after protonation. If we want to facilitate reduction, a protonic solvent such as alcohol or water is added to transfer a proton to the oxygen in an acid–base reaction (giving **467**), which is followed by a second electron transfer from the metal to give the carbanionic species **468**. A second proton is transferred from the solvent to give 2-propanol (**469**).



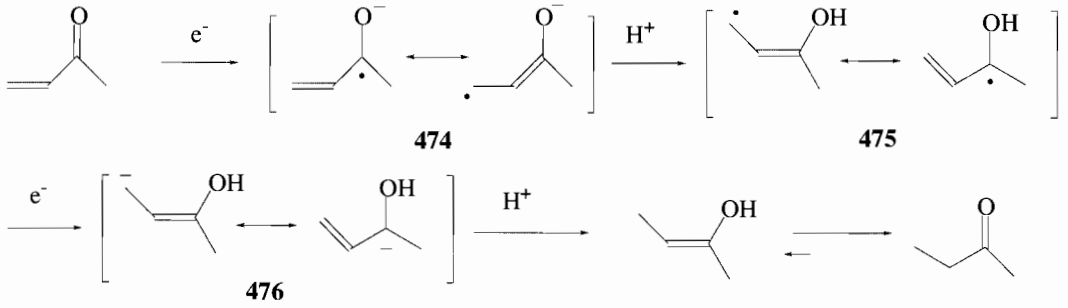
466 467 468 469 470 471

When a ketone or aldehyde is part of a molecule bearing another stereogenic center, reduction can proceed with good diastereoselectivity. Reduction of **472** from the exo- face led to a quantitative yield of **473**, in Takasu and Ihara's synthesis of culmorin.[461] Conjugated ketones are reduced selectivity at the alkene moiety and there is usually a preference for the product with a trans-ring juncture.[462]



472 **473**

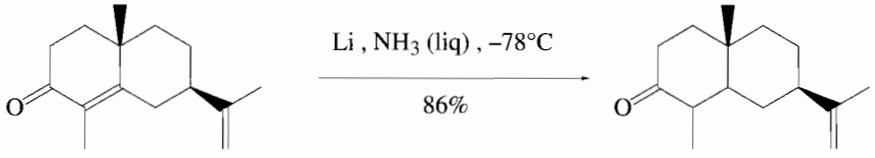
The competing side reaction mentioned above is radical coupling of **456** to give **470**, or of **467** to give diol **471**. Protonation of **470** also gives diol **471** and this coupling reaction is a useful method for the synthesis of 1,2-diols,[463] with aromatic ketones giving the best yields. This reaction is called the **pinacol coupling** (see sec. 13.8.D for a more complete description).[540] Reductive coupling with a mixture of magnesium and magnesium iodide (Mg + MgI_2) is the preferred method for inducing a pinacol coupling reaction, although magnesium amalgam (Mg/Hg) can also be used.[464a] Pinacol coupling of acetone leads to a diol called pinacol (2,3-dimethyl-2,3-butanediol), which gives the reaction its name.



474 **475** **476**

The electron transfer/proton transfer mechanism of ketone reduction is under thermodynamic control and not surprisingly leads to the more stable alcohol, usually a trans- alcohol.[364b] Conjugated ketones react to

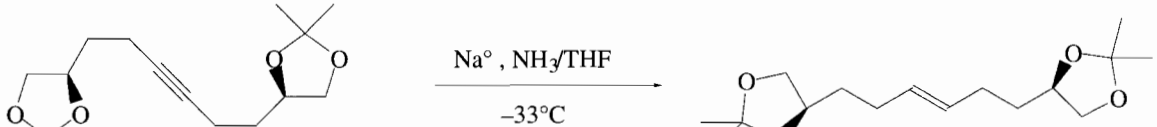
give alcohols via 1,4-reduction,[364b] and this is explained by the ketyl mechanism. Transfer of an electron gives a very stable, resonance delocalized ketyl (**474**). Protonation gives an allylic enol radical (**475**), and transfer of a second electron gives **476**. Proton transfer generates the enol, which tautomerizes to the ketone product. An example is the dissolving metal reduction of **477** to give an 86% yield of **478**, in Li's synthesis of (+)-chrysanthemol.[465] Pinacol coupling is also a competing side reaction with conjugated ketones.[466] Conjugated reduction of α,β–unsaturated esters has been reported using Mg in methanol.[467]



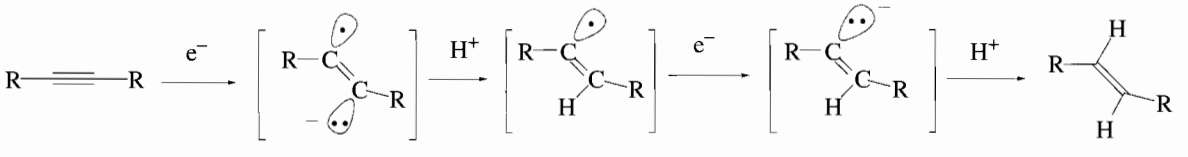
477 **478**

9.C. Reduction of Alkynes

An important use of metal reduction is to convert alkynes to trans-alkenes, as illustrated by the conversion of **479** to **480** in 92% yield as part of Koert's synthesis of squamocin A.[468] In the general case, the reaction is initiated by electron transfer to the alkyne (see **481**) to give a radical anion (**482**). Electron repulsion of the radical orbital and the carbanion orbital dictates that they be as far apart as possible, hence the trans-geometry. Protonation of **482** from either ammonia or an added alcohol cosolvent gives a vinyl radical, **483** and a second electron transfer leads to vinyl carbanion **484**. A second protonation step gives the final trans alkene product. Reduction using either lithium or sodium in liquid ammonia gives primarily the trans alkene,[466b] but increasing amounts of the cis alkene are observed in protonic solvents such as ethanol. Reduction of terminal

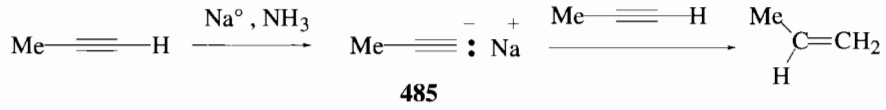


479 **480**



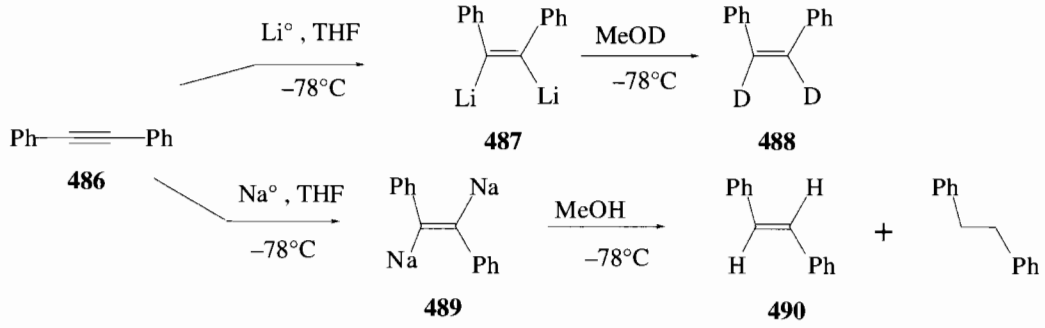
481 **482** **483** **484**

alkynes is complicated by the acidity of the alkyne hydrogen, which reacts with sodium or lithium to form an acetylide anion (secs. 2.2.A, 8.3.B). Reduction to the alkene is possible, however, by controlling the stoichiometry of the reagent. Reaction of propyne with sodium initially generates the acetylide (**485**), and in the presence of additional alkyne **485** is reduced to 1-propene, as shown.[469] If sodium becomes the limiting reagent, reduction to the alkene is possible. An example is the reduction of 1-octyne to 1-octene in 90% yield (ratio of alkene/sodium = 11.5/1).[466b]



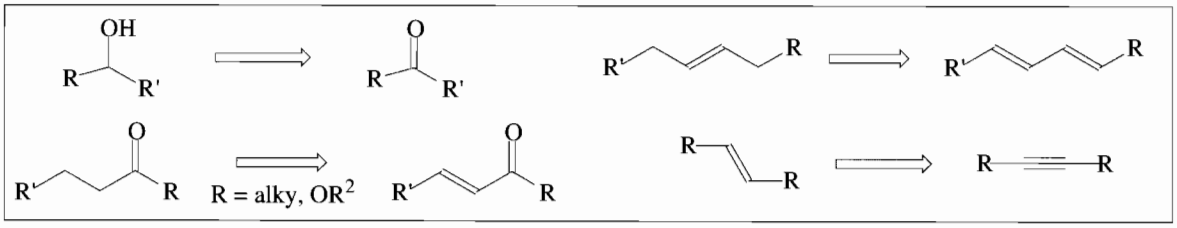
485

Low molecular weight amines such as ethylamine and methylamine are often substituted for ammonia when higher reaction temperatures are required (i.e., > –33°C). Changing to an ether solvent also leads to interesting differences in reactivity. As House pointed out,[470] reduction of diphenylacetylene (**486**) with sodium in THF (–78°C) gave only 25% of the expected *trans*-stilbene (**490**) along with 30% of the completely reduced 1,2-diphenylethane and unreacted starting material. Similar reduction with lithium in THF gave a quantitative yield of the deuterated cis alkene **488** upon quenching with *d*-methanol, presumably due to the greater stability of the dimeric dilithio species (**487**) relative to the disodio species **489**.



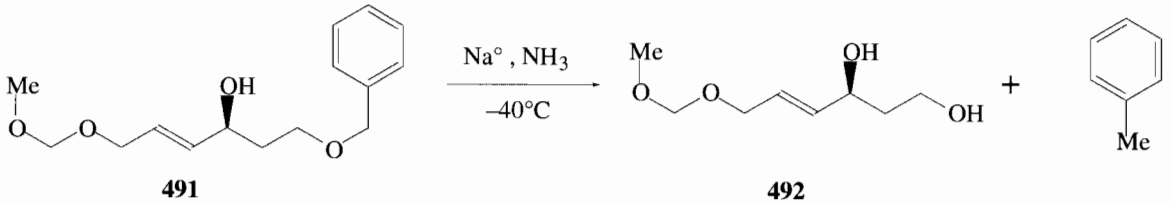
486 **487** **488** **489** **490**

The functional group transforms possible are:

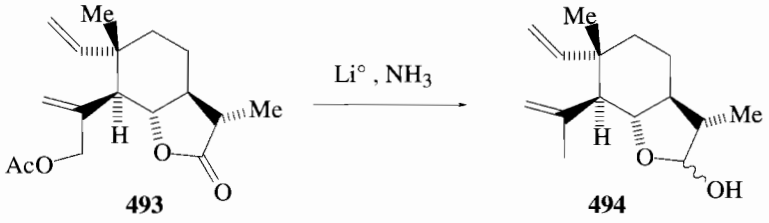


4.9.D. Hydrogenolysis

Hydrogenolysis can occur using dissolving metal conditions, and is particularly useful for the cleavage of O-benzyl and N-benzyl derivatives. It is widely used as a useful alternative to catalytic hydrogenation. Treatment with sodium in ammonia cleaves the O-benzyl group, as in the conversion of **491** to **492** (in 90% yield), in Mulzer's synthesis of hastanecine.[471] Note that the byproduct is toluene. It is also possible to cleave other reactive C—O (or C—N) bonds. Allylic acetates, for example, are cleaved to the hydrocarbon, as shown by the reaction of **493** with lithium and ammonia to give an 81% yield of **494**.[472]

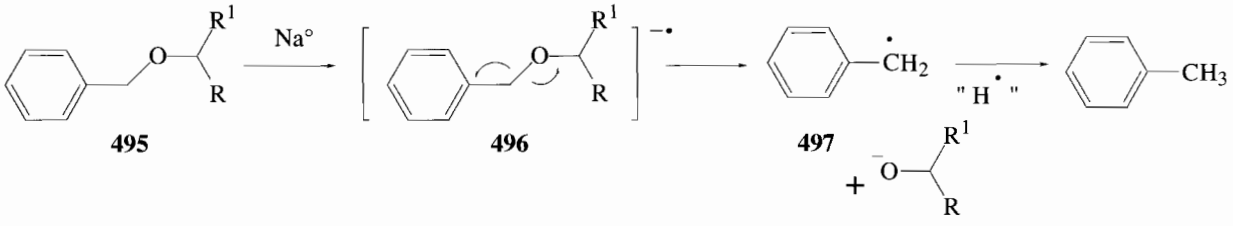


491 **492**



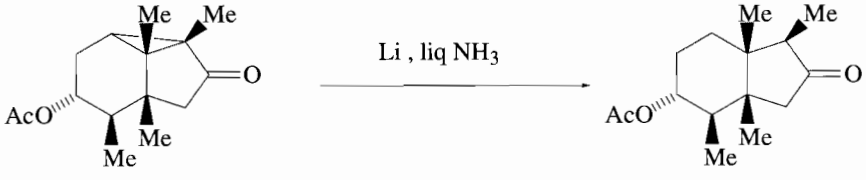
493 494

The hydrogenolysis reaction with metals in ammonia involves transfer of an electron to the heteroatom with cleavage of the C—X bond. Electron transfer to benzyl ether (**495**), for example, generates a radical anion such as **496**. Homolytic cleavage liberates an alkoxide and the benzyl radical (**497**). This benzyl radical removes a hydrogen atom from a hydrogen donor in the medium (solvent, starting ether, etc.) to give toluene as the other reduction product. One could also invoke cleavage to an alkoxy radical and a benzyl carbanion, although formation of the resonance stabilized benzyl radical is a more reasonable mechanistic rationale.



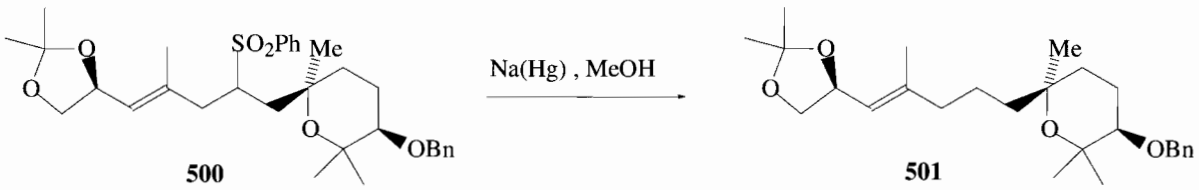
495 496 497

Since the mechanism involves electron transfer to a heteroatom rather than carbon, vinyl, and aryl derivatives can be easily reduced under these conditions. Many functional groups can be reduced, depending on their ability to accept an electron. Cyclopropane rings are opened under these conditions. The bridging cyclopropane moiety in **498**, for example, was opened with lithium and ammonia to give **499** in 85% yield, as



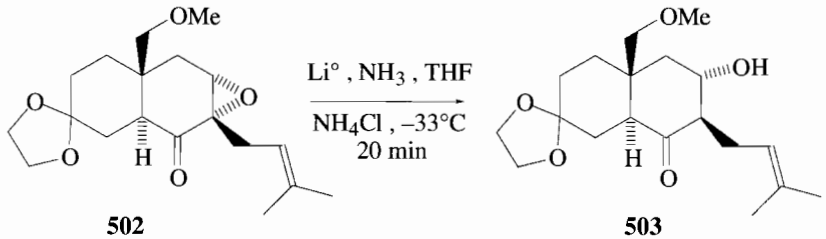
498 499

part of Srikrishna's synthesis of (+)-pinguisenol from (*R*)-carvone.[473] Cyclopropane rings can also be opened to give methyl derivatives.[474] Halides undergo hydrogenolysis with alkali metals, and both alkyl[475] and vinyl halides give good yields. Since unfunctionalized alkenes are relatively unreactive under these conditions, dissolving metal reduction is a powerful method for the conversion of vinyl halides to alkenes. Hydrogenolysis of the C-S bond is rapid, and sulfides, sulfones, and sulfoxides are reduced to the hydrocarbon moiety by this method.[479,476] Since sulfur usually poisons hydrogenation catalysts, reduction with metal is a preferred method for chemoselective cleavage of the C—S bond. The sulfone group in **500** (—$CHSO_2Ph$) was cleaved to the hydrocarbon (—CH_2— in **501**) with sodium amalgam in methanol (83% yield) in the Díez et al. synthesis of usneoidol E.[477] Sulfides are similarly reduced.[478] Both sulfoxides and sulfones are important in alkylation and condensation reactions of their respective sulfur-stabilized carbanions (sec. 8.6).



500 **501**

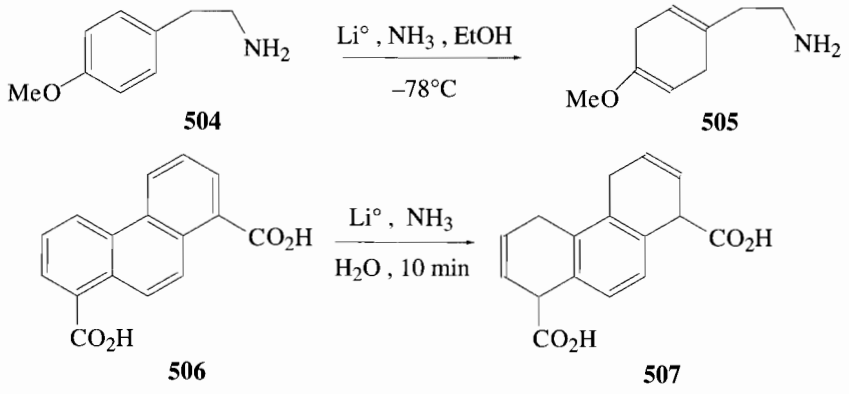
Epoxides are opened by dissolving metal reductions to give an alcohol, usually with good stereoselectivity and regioselectively favoring the product with oxygen at the less hindered carbon. Reduction of **502** with lithium in ammonia gave a 76% yield of **503**.[479] The radical anion intermediate usually leads to the more stable trans alcohol. Epoxides are also subject to pinacol type coupling reactions, but the yields are very low and reduction is the major process.[480] Esters and lactones are usually reduced to the alcohol or diol. Anomalous reactions can occur, however, as in the reduction of a lactone to a lactol,[481] but this is common only with carbohydrates and hindered lactones.



502 **503**

4.9.E. Birch Reduction

Partial reduction of aromatic rings with alkali metals is an important synthetic method because it allows one to use aromatic substitution reactions to set functionality, and reduction to a nonaromatic system then allows transforms to other compounds.[482] When a dissolving metal reduction is carried out on an aromatic ring containing electron releasing groups (alkyl, alkoxy, etc.) these groups will be found on a vinylic carbon (sp^2 carbon) in the final cyclohexadiene product,[483] as in the reduction of **504** to **505** in 95% yield as part of Bonjoch's synthesis of deethylibophyllidine.[484] Conversely, reduction of an aromatic ring that has an electron

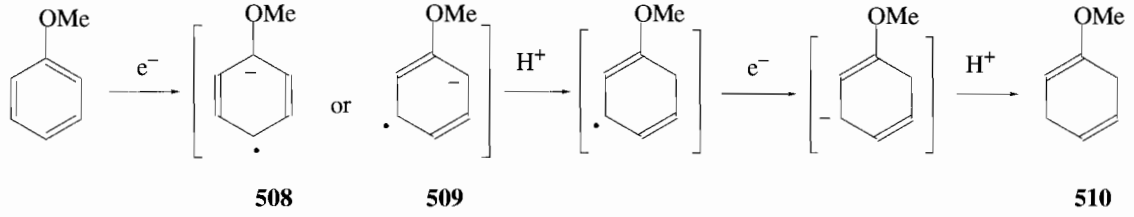


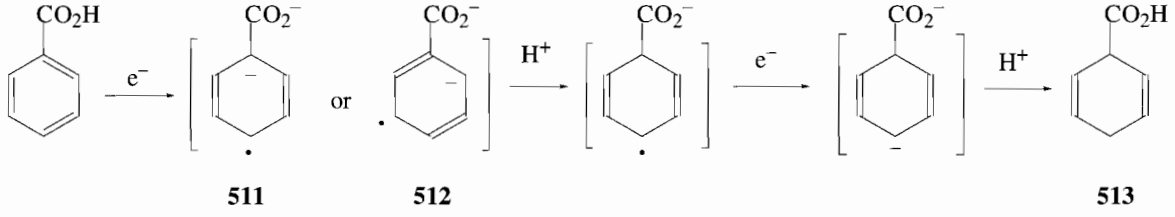
504 **505**

506 **507**

withdrawing group on the ring will generate a product with that group on the sp^3 carbon. Reduction of **506**[485] led to **507** where the electron-withdrawing COOH groups are on saturated carbon atoms. The electron

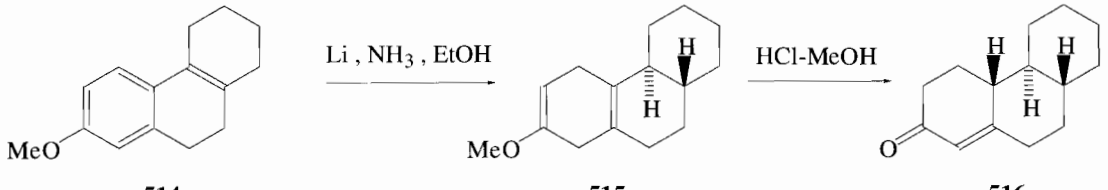
transfer mechanism invoked for reduction of alkynes and carbonyls also explains these results. Transfer of an electron to anisole is slower due to the OMe, and leads to **508** or **509**. The proximity of the negative charge to the electron-rich oxygen in **508** destabilizes it, which leads to a preference for **509**. Protonation and a second electron transfer will lead to vinyl ether **510**. When the substituent on the aromatic ring is changed to an electron-withdrawing group (such as carboxyl), the selectivity changes. Electron transfer to benzoic acid leads to **511** or **512**. The electron-withdrawing carbonyl group stabilizes the developing negative charge in **511** and it is preferred to **512**. The usual sequence leads to **513** as the final product. This partial reduction of aromatic rings is known as the **Birch reduction.**[486] Complete reduction of the aromatic ring is also possible, especially with those molecules that contain heterocyclic rings such as pyridine or furan derivatives.



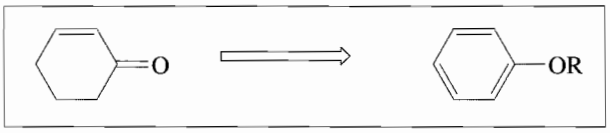


This leads to the functional group transforms:

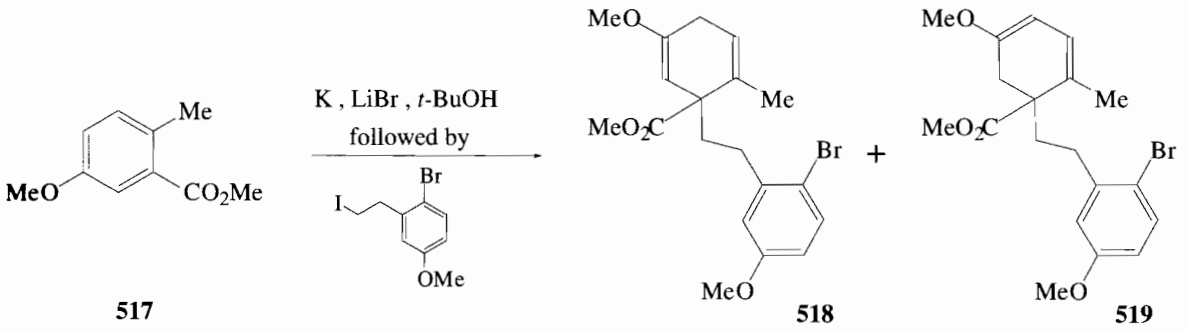
There are a wide variety of synthetic applications of this chemistry, making it one of the most powerful reactions in organic chemistry (sec. 10.5.B.vi). An example is the Birch reduction of the methoxybenzene portion of **514**, which gave **515**.[487] Subsequent treatment with methanolic HCl converted the vinyl ether moiety in **515** to the ketone unit (via the enol) found in **516**. Note that Birch reduction formed a trans ring juncture in **515** from the conjugated C=C unit in **514**. Initial hydrolysis of **515** led to a nonconjugated ketone, but under the acidic conditions the conjugated systems found in **516** was formed. However, it is



possible to prevent the double bond from migrating into conjugation,[488] if hydrolysis is done under very mild conditions. Treatment with oxalic acid, $(CO_2H)_2$, is commonly used for this purpose. Reduction of anisole derivatives is an important route to cyclohexenone derivatives and the functional group transformation is

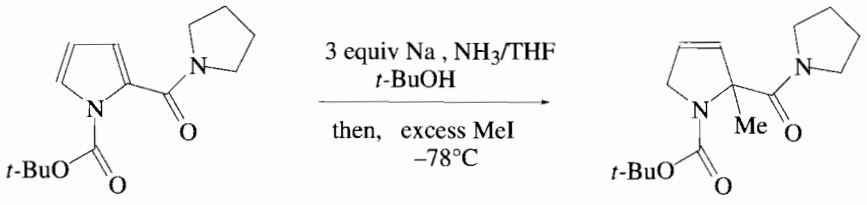


It is possible to form partially reduced bicyclic and tricyclic aromatic derivatives by this method.[489] One of the more interesting synthetic features of the Birch reduction is the ability to alkylate the carbanionic intermediate generated by the electron-transfer reaction. Birch reduction of **517**, for example, gave a mixture of **518** and **519** in 96% yield upon addition of 2-(2-bromo-5-methoxyphenyl)-1-iodoethane to the initially produced anion.[490]



517 **518** **519**

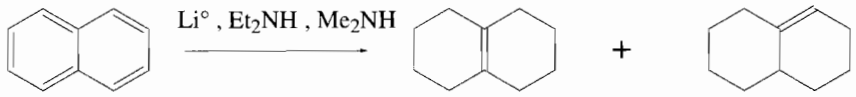
As mentioned briefly above, Birch reduction is an important method for reducing heterocyclic aromatic rings. Although Birch reduction of pyrroles tends to give poor yields, reduction of the *N*-Boc derivatives can give quite good yields. When **520** was treated with sodium in ammonia/THF and then iodomethane, for example, an 85% yield of **521** was obtained. Reduction of pyridine rings to the piperidine derivative has been reported, but the yields tend to be low.[491] Partial reduction of a furan ring is also possible.[492]



520 **521**

4.9.F. The Benkeser Reduction

The preeminence of lithium and sodium in metal reductions has been challenged by the use of calcium in amines, developed by Benkeser. In the initial work, naphthalene was reduced to an 80:20 mixture of Δ^9-octalin (**522**) and $\Delta^{1(9)}$-octalin (**523**) with lithium in diethylamine-dimethylamine.[493] Replacing lithium with calcium gave a 77:23 mixture of **522** and **523** in 92% yield.[494,495] This method has come to be called the **Benkeser reduction**. This has become an important modification because Birch reductions with sodium are

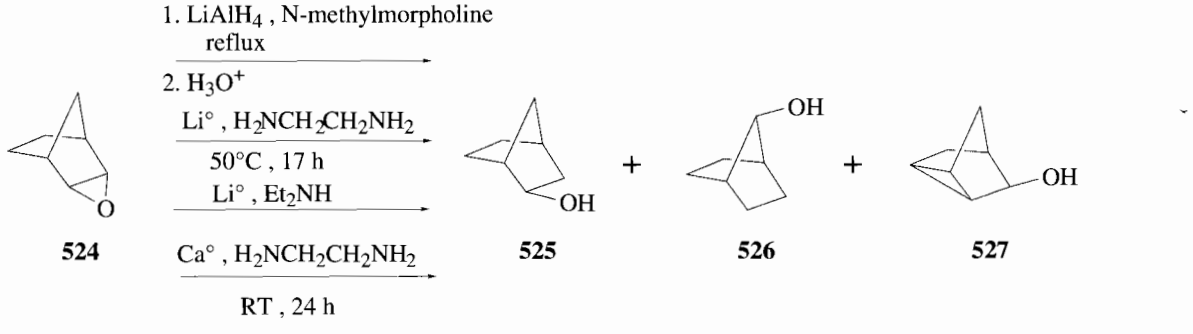


522 **523**

difficult when run at medium scale (kilogram range), whereas the Benkeser reduction gives good yields of products. Addition of the proton source *tert*-butanol allows reduction of benzene rings to stop at the diene stage, and this is useful for Birch reduction of aromatic rings.[496] Reduction of anisole with calcium under these conditions gave 86% of **510**, in addition to minor amounts of other reduction products.

Just as lithium and sodium can be used in low molecular weight amines for reduction of alkynes,[497] calcium is an effective reducing agent in amine solvents. Reaction of 2-nonyne with a calcium–methylamine–ethylenediamine mixture gave 87% yield of an 86:8:4 mixture of *trans*-2-nonene/*trans*-3-nonene/*trans*-4-nonene, the latter two products arising by bond isomerization.[498]

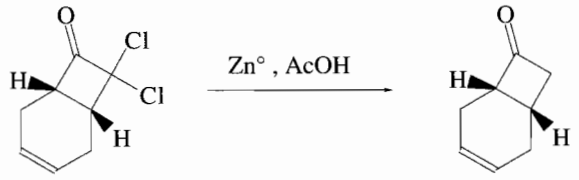
This reagent is also effective for reduction of epoxides. Lithium aluminum hydride reduction of **524** was very sluggish and required refluxing in *N*-methylmorpholine to obtain an 84% yield of **525**. Along with **525**, 16% of the rearranged alcohol **526** was isolated.[499] Brown showed that reduction with lithium in diethylamine gave 64% of **525** and 35% of **526** after addition of **524** to the amine solution after 1 min.[500] If **524** was added after 5 min, however, only 10% of **525** and 3% of **527** was obtained, along with unreacted starting material.[501] When lithium was used with ethylenediamine, 87% of a 99.3:0.2:0.5 mixture of **525/526/527** was obtained.[501] Benkeser showed that reduction of **524** with calcium in ethylenediamine gave an 89% conversion to **525** at ambient temperatures.[501] This method is preferred for reduction of epoxides when treatment with $LiAlH_4$ fails or is very slow.



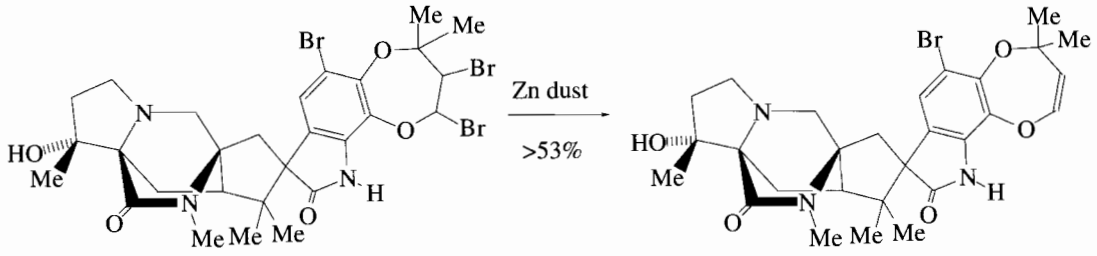
524 **525** **526** **527**

4.9.G. Reduction with Zinc

For many years, zinc has been an important metal for reduction of organic molecules.[502] The most common reducing medium is zinc dust in acetic acid or HCl.[503] Zinc in acetic acid is a very effective reagent for reduction of α-haloketones, as with α,α-dichloro ketone **528**, which was converted to **529**.[504] Alkyl bromides and chlorides react with zinc and acetic acid very slowly when the halogen is *not* conjugated to a carbonyl. Reduction of primary iodides is relatively fast, and this method is commonly used to insert methyl groups in a synthetic target.[505] Another reaction is observed when a molecule contains two halogen atoms on adjacent



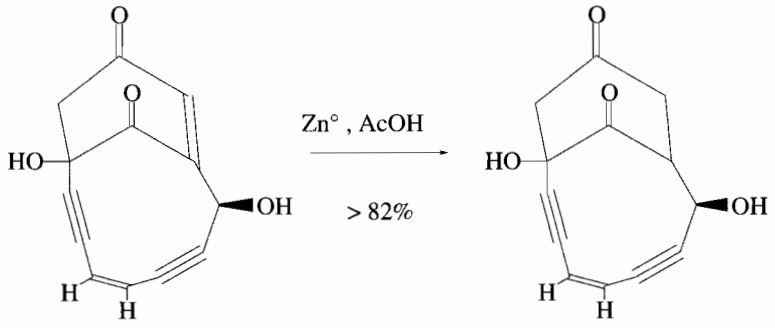
528 **529**



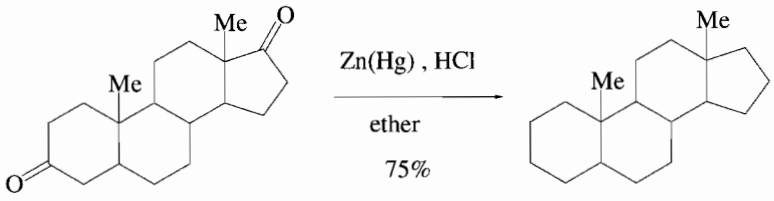
530 **531**

carbon atoms (a vicinal dihalide). Reductive dehalogenation to the alkene is a useful process, as seen in the conversion of **530** to **531** in > 53% yield.[506] A similar reaction was observed when sodium and ammonia[507] or a zinc–titanium tetrachloride ($TiCl_4$) reagent was used.[508]

Zinc in acetic acid leads to 1,4-reduction of conjugated ketones such as **532**, in this case giving the saturated ketone **533** in Danishefsky's synthetic studies on calicheamicin.[509] This conjugated system is quite sensitive but Zn/AcOH gave > 82% of the desired conjugate reduction product, **533**.



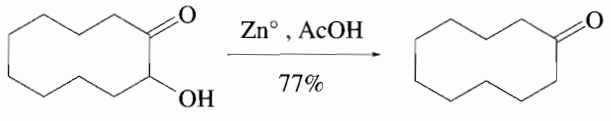
532 **533**



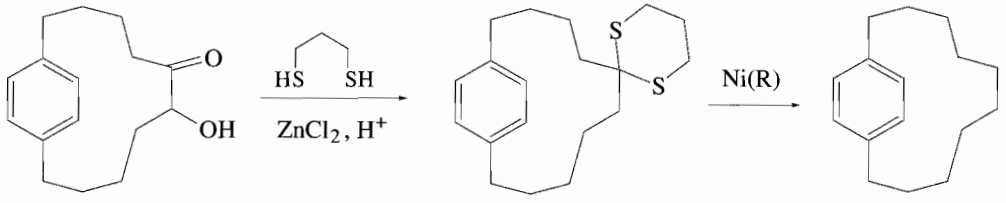
534 **535**

Zinc is the classical reagent for removing a ketone carbonyl via reaction with zinc amalgam (Zn/Hg) in HCl, the **Clemmensen reduction**.[510] Reduction of ketone **534** to **535** is an example of this conversion.[511] The effectiveness of using zinc in acid for reduction is seen in the removal of a hydroxyl group from an acyloin such as **536** (sec. 13.8.E) to give cyclodecanone, **537**.[512] A useful modification of this reaction was

introduced by Cram. Reaction of the acyloin **538** with acidic zinc chloride, in the presence of 1,3-propanedithiol, reduced the alcohol via hydrogenolysis and converted the carbonyl to a dithioketal (**539**) in 82% yield.[513] The dithiane moiety was reduced to **540** (85% yield with Raney nickel) in Cram's example, but it could also be hydrolyzed to the ketone in the presence of water and mercuric salts (sec. 7.3.B.ii).

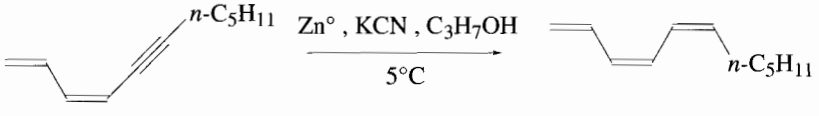


536 **537**



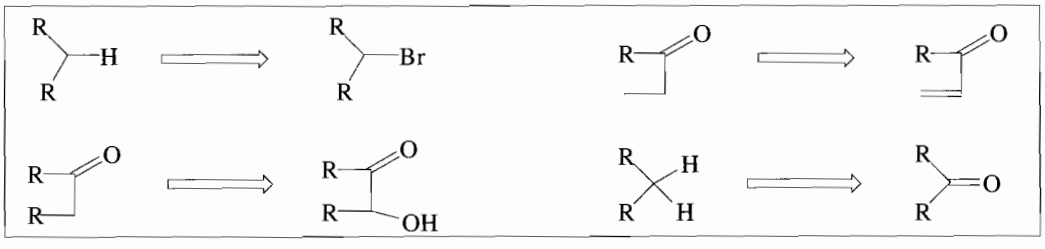
538 **539** **540**

It was previously mentioned that zinc reduces alkynes to alkenes. Näf showed that reduction of the conjugated alkyne (**541**) to the conjugated cis alkene (in **542**) occurred with zinc in the presence of potassium cyanide (KCN). This reduction was not possible by hydrogenation with a Lindlar catalyst, due to the poor selectivity for reaction with only the alkyne, without reduction of any alkenes.[514] The yields obtained by zinc reduction were not always reproducible, however.[514b]



541 **542**

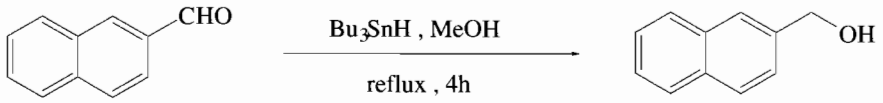
The functional group transforms available with zinc are



4.9.H. Reduction with Tin and Tin Compounds

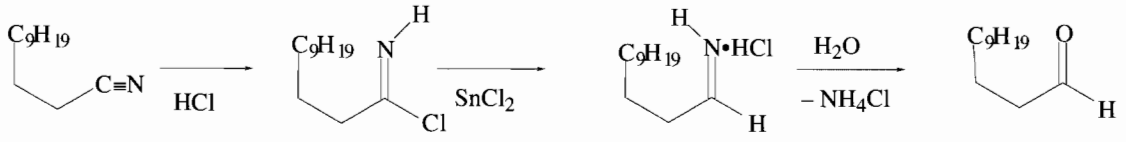
Tin metal is used sparingly as a reducing metal in modern organic synthesis, which contrasts with tin derivatives such as tributytin hydride, which are common. Aldehydes, for example, are readily reduced with tributyltin hydride (Bu_3SnH) in aqueous media. An example is the reduction of 2-naphthaldehyde to the alcohol (**396**) in 93% yield in refluxing methanol.[515] When this reaction was done in water, and 85% yield of **396** was obtained.

For the reduction of other functional groups, heating with HCl is often required and in such cases other reducing methods are usually more convenient. Typical applications include reduction of acyloins and aromatic nitro compounds.[516] A classical use of tin, and one still used occasionally, is the so-called **Stephen reduction**, where a nitrile is converted to the corresponding aldehyde.[517] An example is the reduction of lauronitrile (**543**) to give lauraldehyde (**546**) when treated with a stannous chloride ($SnCl_2$) solution that is saturated with anhydrous HCl.[518] The reaction proceeds by initial addition of HCl to the nitrile, to give **544**.



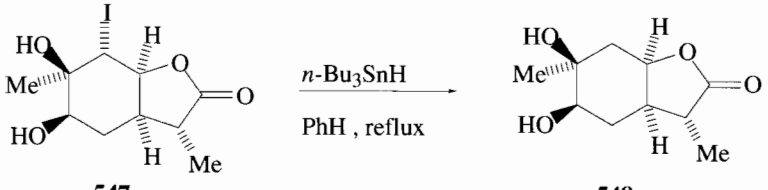
396

This intermediate is reduced by stannous chloride to give **545** and $SnCl_2$ is converted to tin tetrachloride ($SnCl_4$). Subsequent treatment with aqueous HCl converts imine **545** to the aldehyde (**546**) via hydrolysis, in 73% overall yield. Stannous bromide ($SnBr_2$) often gives better yields of aldehyde than stannous chloride. Most aromatic nitriles give good yields of the aromatic aldehyde.[519]



543 **544** **545** **546**

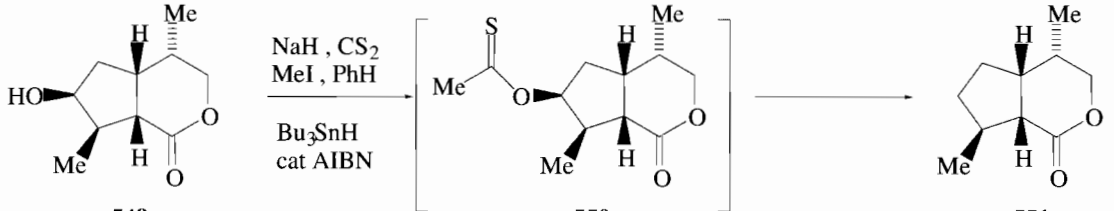
Tin derivatives are more useful than tin metal in synthetic applications. Trialkyltin hydrides, for example, are important for radical hydrogen transfer in reductions of alkyl, alkenyl, and aryl halides.[520] In one example, taken from Bäckvall's synthesis of paeonilactone A, the CHI moiety of **547** was reduced to —CH_2— in **548** using tri-*n*-butyltin hydride.[521] Corey and Suggs showed that this reaction can be catalytic[522] when the tin hydride is generated *in situ* by photolysis of a mixture of trimethyltin chloride and ethanolic sodium borohydride. Tributyltin chloride can be used as well. The reaction is not restricted to aliphatic derivatives, and vinyl bromides are reduced to the alkene with tin hydride.[523] One of the more common uses of tin hydride is as a hydrogen transfer agent in radical cyclization reactions[524] (sec. 13.7). A number of other functional group reductions have been reported with tributyltin hydride, including reduction of nitro groups[525] and reduction of azido groups[526] to amines.



547 **548**

A variation of the tributyltin hydride reduction is available that can be applied to alcohols. The alcohol is converted to a thionocarbonate and then reduced with Bu_3SnH and AIBN, which circumvents the need for

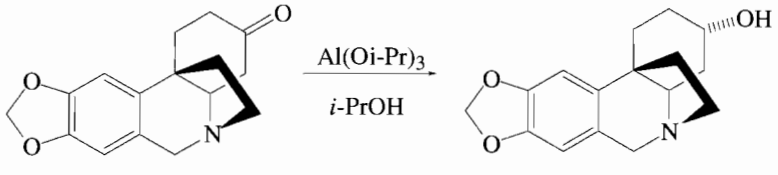
con-version of the alcohol to a halide, which can have many side reactions with sensitive substrates, and proceeds in good yield. This transformation is known as the **Barton deoxygenation** or the **Barton-McCombie reaction**.[527] An example from Lee is the reduction of the OH unit in **549** to **551**, (+)-dihydronepetalactone.[528] Treatment with sodium hydride and then carbon disulfide, in the presence of iodomethane gives a xanthate ester (**550** - a thionocarbonate). When generated in the presence of tributyltin hydride and AIBN, reduction occurs with cleavage of the C—O bond to give **551** in 75% yield. Fu has shown that the reaction can be done in the presence of polymethylhydrosiloxane using a catalytic mount of tributyltin hydride.[529]



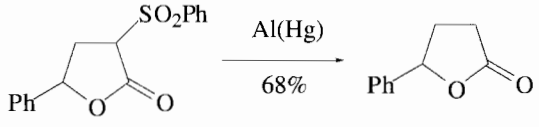
549 **550** **551**

4.9.I. Reduction with Aluminum and Aluminum Compounds

A classical reduction that involves metals is the **Meerwein–Ponndorf–Verley reduction**,[530] the reverse of the **Oppenauer oxidation** discussed in Section 3.2.E.ii.[531] The mechanistic details of this reversible reaction are presented in that section. The major difference between reduction or oxidation is the use of an alcohol solvent rather than a ketone solvent (usually 2-propanol rather than acetone). A ketone is treated with an aluminum alkoxide such as triisopropoxyaluminum in the presence of an hydrogen-donating solvent such as 2-propanol. Refluxing conditions are usually required to initiate transfer the hydrogen to the ketone, reducing it and generating acetone from 2-propanol. The final step in the Irie et al. synthesis of dihydrocrinine (**553**) from **552**. they used this reduction with Al(O*i*-Pr)$_3$ in isopropanol to give exclusively the α-alcohol shown.[532] Reduction of **552** with lithium aluminum hydride gave only the β-alcohol.[532]



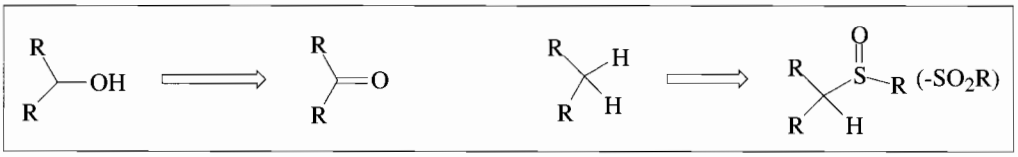
552 **553**



554 **555**

Aluminum amalgam (Al/Hg) is also a useful reagent that is most commonly employed for hydrogenolysis of sulfur compounds.[533] Reduction of sulfoxides is an important application,[534] as is reduction of sulfones. Aluminum amalgam reduces the α-phenylsulfonyl moiety in **554** to give lactone **555** in 68% yield.[535] Aluminum amalgam has also been used for reduction of nitro compounds to the amine,[536] and reduction of azides to the amine.[537]

The functional group transforms for reductions with aluminum compounds are

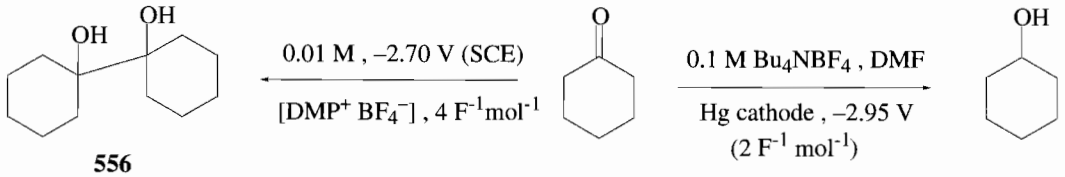


4.9.J. Electrolytic Reductions

As shown in Table 4.1, the reduction reaction of alkali metals involves a single electron transfer.[538] Electron transfer can also be done in an electrolytic cell, as described in Section 3.1. Electrolysis of acetone is an example where an electron is transferred to the carbonyl, generating a radical anion (a ketyl - see sec. 4.9.B). We have seen that the fate of these reactive species depends on the solvent, and in the case of electrolysis whether or not the electrode potential allows an additional electron transfer and what reactive species may be present in the reaction medium. There are at least two major types of reaction products available to the ketyl as introduced in Section 4.9.B. It can undergo radical coupling or it can remove a hydrogen atom from an acidic solvent (such as ethanol or ammonia) and be reduced. The radical coupling of acetone described is formally known as **pinacol coupling** (the **pinacol reduction**)[539,464a] and is described in Section 13.8.D.

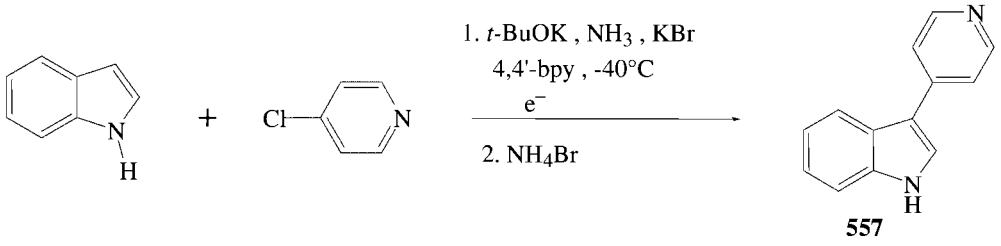
Aldehydes usually undergo reductive dimerization upon electrolysis, as in the formation of 4,5-octanediol in 55% yield from butanal.[540] Small chain aldehydes (such as acetaldehyde) give significant amounts of reduction to the alcohol but the proportion of dimer increases as the chain length increases, which is probably due to increased hydration of the small aldehydes and the alcohol products.

The electrochemical properties of many functional groups have been described in reviews by Steckhan,[541] Degner (industrial uses of electrochemistry),[542] Kariv-Miller,[543] and Feoktistov.[544] The synthetic applications of anodic electrochemistry has also been reviewed.[545] There are interesting differences between dissolving metal reductions (secs. 4.9.B–G) and electrochemical reactions. Cyclohexanone, for example, can be reduced to cyclohexanol (sec. 4.9.B) or converted to the 1,2-diol (**556**) via pinacol coupling by controlling the reduction potential, the nature of the electrode and the reaction medium.[546] Presumably, the more concentrated conditions favor formation of cyclohexanol via reduction of the carbanion. More dilute solutions appear to favor the radical with reductive dimerization to **556**. More important to this process, however, is the difference in reduction potential (–2.95 vs. –2.700 V) and the transfer of two Faradays per mole in the latter.



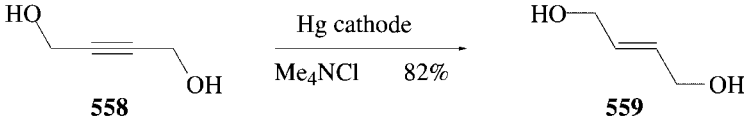
556

Coupling between two different species is possible under some conditions, particularly when an aryl halide is one of the partners. When indole was treated with 4-chloropyridine, for example, under electrolytic conditions, a 60% yield of **557** was obtained[547] when 4,4'-bipyridyl (bpy) was used as a redox mediator.



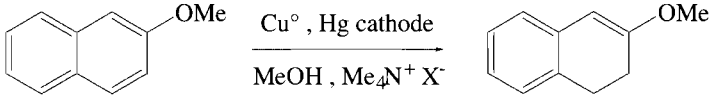
557

Reduction of alkynes to the trans-alkene proceeds via a radical anion such as **485**, and is virtually identical to similar reduction involving alkali metals (sec. 4.9.C). Electrolytic reduction of but-2-yn-1,4-diol (**558**) gave an 82% yield of *(E)*-but-2-en-1,4-diol (**559**).[548] Electrolytic reduction of alkynes is sensitive to reaction conditions. Although the trans alkene is usually formed, Hudlicky cited Campbell and Young's work[549] in which electrolysis of alkynes (in 95% EtOH + H_2SO_4) on a spongy nickel cathode gave 65–80% of the cis alkene. Similar reaction in a methylamine solution containing LiCl gave the trans alkene. The sensitivity to reaction conditions is apparent in the reduction of conjugated carbonyl systems, which are reduced electrolytically to give the 1,4-reduction product.[550] It is noted that electrolysis of cyclohexenone did not give reduction products, but rather reductive coupling products. A difference between electrolysis and dissolving metal reductions is the ability to reduce simple double bonds, as in the electrolytic reduction of 1,5-cyclooctadiene to cyclooctene.[551] Another difference is noted in the electrolysis of conjugated acid derivatives, which give reductive coupling products.



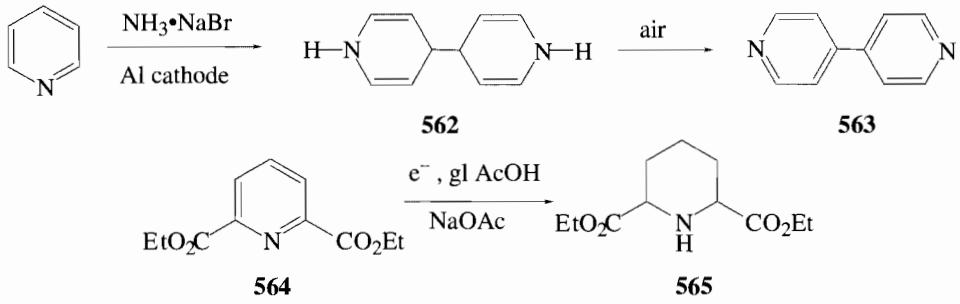
558 **559**

Electrolysis of conjugated ketones also generates a radical anion by addition of an electron to the conjugated system, but dimerization usually occurs by coupling at the end of the conjugated system.[552] Such dimerizations can occur even with significant steric hindrance at the terminal alkene carbon.[553] Conjugated nitriles and esters show a preference for coupling at the end of the conjugated system. 2-Methylpropenenitrile, for example, was dimerized in high yield to 2,5-dimethyladiponitrile,[554] and ethyl acrylate was coupled to an aldehyde to give a γ-hydroxy ester (which cyclized to the lactone).[555]

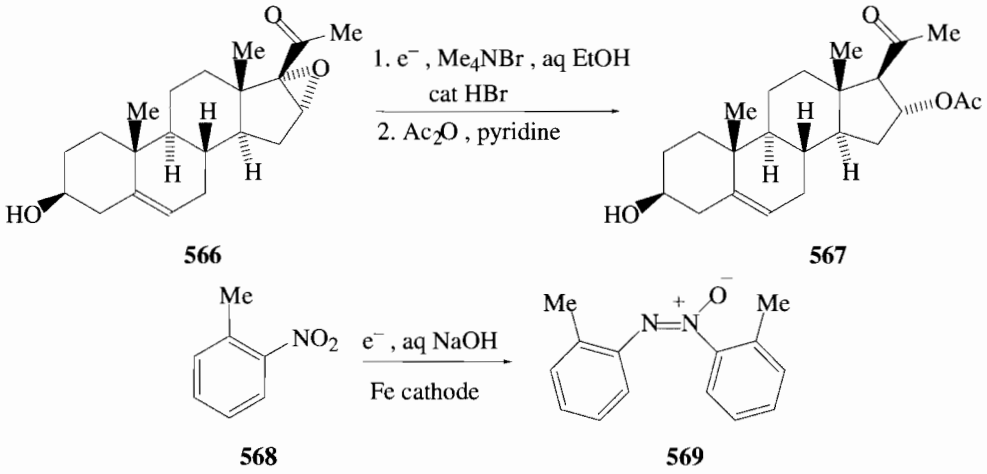


560 **561**

Electrolysis can be used to achieve Birch reductions (sec. 4.9.E),[556] as in the reduction of 2-methoxynaphthalene (**560**) to give **561** in 95% yield.[557] Electrolysis of heterocycles leads to interesting reduction products. Pyridine, for example, gave the reductive dimerization product **562**, but air oxidation rapidly converted this to **563**.[558] In addition to partial reduction, it is also possible to completely reduce a heteroaromatic ring, as in the conversion of **564** to **565** in 95% yield, in glacial acetic acid.[559]



Electrochemical processes can be used for the reduction of many other functional groups. Halogen is removed, as in the reduction of 6-chloro-1-hexene to 1-hexene in 23% yield (in DMF).[560] Aryl halides are similarly reduced electrochemically. 2-Chloroaniline, for example, was reduced to aniline in 85% yield.[561] If the electrodes and solvent are changed reductive coupling can occur.[562] Elimination is possible in some cases.[563] Epoxides are opened electrochemically, and hydrogen is often delivered to the more substituted carbon, as in the quantitative conversion of **566** to **567**.[564] Azides are reduced to the amine.[565]



Nitro compounds are reduced to the corresponding amine. Unlike hydride reductions, both alkyl nitro compounds (2-methyl-2-nitro-1,3-propanediol was reduced to 1-amino-2-methyl-1,3-propanediol in 95% yield)[566] and aromatic nitro derivatives [nitrobenzene was reduced to aniline with $Ti(SO_4)_3$ in sulfuric acid and cetyltrimethylammonium bromide] are electrolytically reduced.[567] If conditions are modified, reductive coupling can give azoxy compounds such as **568** (from **569**)[568] or diazo compounds.[569] A variety of acid derivatives are reduced under electrochemical conditions, including nitriles (to amines),[570] acids (to alcohols),[571,572] esters (to alcohols),[573] and amides (to alcohols).[574] It is possible to selectively reduce a cyclic imide to a lactam.[575]

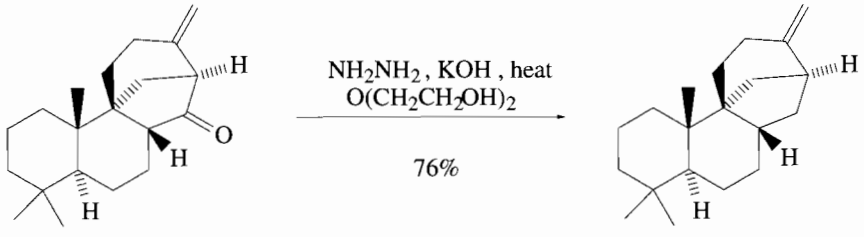
4.10. NONMETALLIC REDUCING AGENTS

There are several methods for reducing organic functional groups that use nonmetallic reagents. The mechanism of reduction varies with each reagent and each has a rather specific and useful application. This

section is presented as a survey of these methods and is not intended as an in-depth analysis. The intent is to offer alternatives for the reduction of functional groups when more traditional methods fail. In the case of enzymatic reductions (sec. 4.10.F), this technique is quickly becoming an important reduction method in asymmetric synthesis.

4.10.A. Reduction with Hydrazine (Wolff–Kishner)

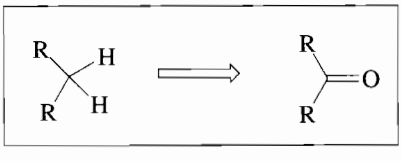
When a carbonyl group must be removed from a molecule, the acidic conditions of the **Clemmensen reduction** are not always compatible with other functional groups. An alternative method of reduction was developed in basic media that relied on the reaction of carbonyls with hydrazine to form a hydrazone. In the presence of base, a hydrazone anion intermediate (sec. 9.4.F) can be formed that removes a proton from the acidic solvent, leading to reduction. This process has been termed the **Wolff–Kishner reduction**.[576] A variety of modifications have been introduced for this procedure, including isolation of the hydrazone and using an



570 **571**

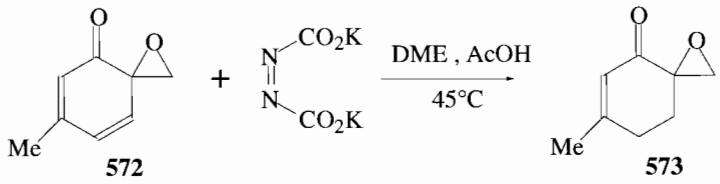
alkoxide base.[577] Perhaps the most important change in this reaction is the **Huang–Minlon modification**, which uses refluxing diethylene glycol as the solvent and has been shown to be much more efficient for this transformation.[578] Reduction of the ketone unit in **570** using this modification gave **571** in 76% yield as part of White's synthesis of 2-desoxystemodinone.[579] Note the use of bis(2-hydroxyethyl) ether as the solvent in a slight modification of the Huang–Minlon method. Hydrazine hydrochloride (N_2H_4•HCl) has been shown to be effective for the reduction of sterically hindered ketones.[580] Hydrazine is also used to convert an alkyl phthalimide to an alkyl amine by replacing the H_2C—NR—CH_2 moiety with a O=C—NHNH—C=O unit, in what is often called the **Ing–Manske procedure**.[581]

The functional group transform for reduction with hydrazine is



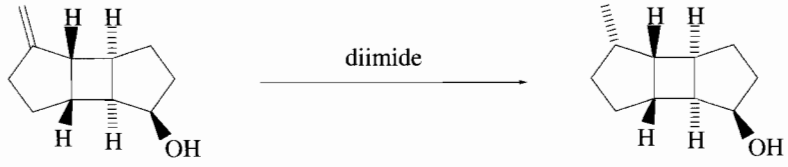
4.10.B. Reduction with Diimide

Diimide (NH=NH) is a transient species generated by reaction of acids with potassium azodicarboxylate,[582] by thermolysis of anthracene-9,10-diimine,[583] from hydrazine derivatives[530] or tosylhydrazone.[584] Diimide reduces isolated C=C units to the corresponding saturated derivatives (i.e., C=C → —CH_2CH_2—).[585] It is



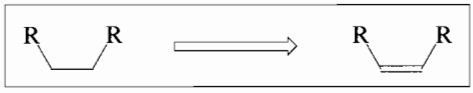
572 **573**

known that diimide gives primarily cis reduction of alkenes[586] and *reduces symmetrical π bonds faster than polarized π bonds*.[587] Generation of diimide with potassium azodicarboxylate gave selective reduction at the least conjugated alkene in **572**, giving **573** in 77% yield, an important intermediate in Corey's synthesis of ovalicin.[588] The conjugated ketone and exocyclic epoxide were not reduced. Corey also showed that the course of a reduction with diimide could be altered by addition of cupric salts [such as cupric acetate, $Cu(OAc)_2$].[589] This new reagent is highly selective for the reduction of conjugated alkenes, with specificity for the less substituted double bond of the diene.[590] A typical use is the conversion of the exo-methylene unit in **574** to a methyl group in **575**, taken from Dauben and co-workers synthesis of the spatane nucleus.[591]



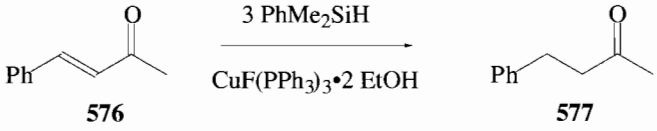
574 **575**

The functional group transform is



4.10.C. Reduction with Silanes (Hydrosilylation)

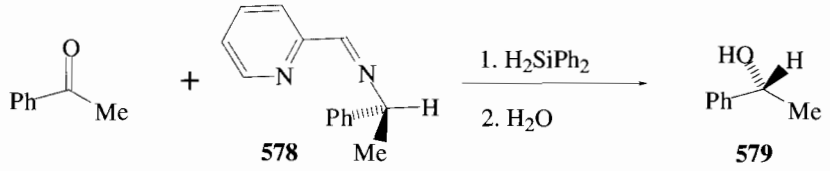
Silane hydrides can be used for the reduction of carbonyls and alkenes. Reaction of methylcyclohexene with a mixture of triethylsilane (Et_3SiH) and trifluoroacetic acid (CF_3CO_2H) reduced the alkene moiety to give methylcyclohexane in 72% yield.[592] Under the same conditions, however, 1-pentene was not reduced. More commonly, this reagent is used for reduction of conjugated carbonyls, probably via formation of a silyl enolate (secs. 9.2, 9.3.B) as in the reduction of cyclohexenone to cyclohexanone in 85% yield with Ph_2SiH_2.[593] Addition of transition metals such as $ZnCl_2$, or copper salts to the silane facilitates the reduction,[594] as in the conversion of **576** to **577** in 96% yield.[595]



576 **577**

Ketones and aldehydes are reduced by silanes in acid media, as in the reaction of cyclohexanone with Et_3SiH and trifluoroacetic acid to give cyclohexanol in 74% yield.[592] The reaction is selective for 1,2-reduction of aldehyde moieties, as in the reduction of 3-phenyl-prop-(2*E*)-enal to 3-phenylprop-(2*E*)-en-1-ol in

95% yield).[596] Another example of such selectivity is the reduction of the ketone unit in 2-bromo-1-phenylpropanone to give 2-bromo-1-phenyl-1-propanol in 70% yield.[543] Ketones are usually reduced faster than epoxides.[597,598]

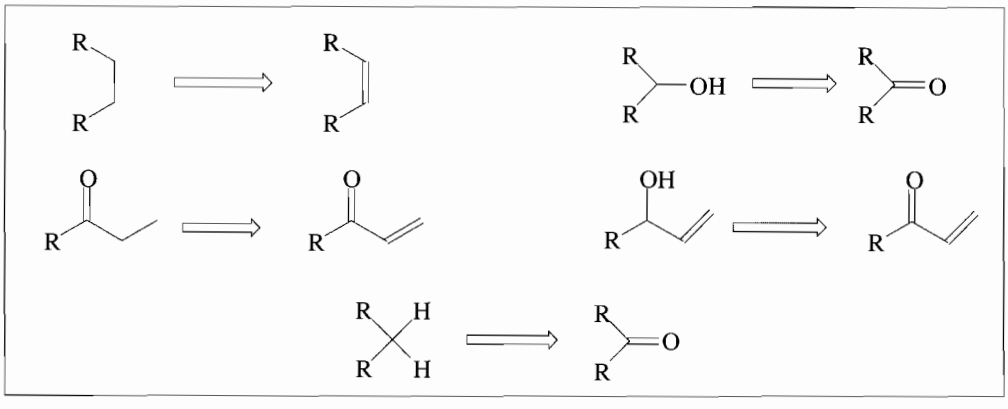


578 **579**

Asymmetric reduction involving silanes is possible when a chiral additive is used. An example is reduction of acetophenone to *(R)*-phenethyl alcohol (**578**) in 99% yield and 84.2% ee in the presence of **579**.[599]

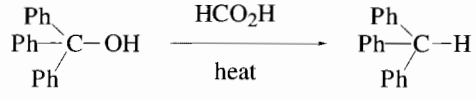
Reductive cleavage of carbonyls or alcohols is possible, analogous to the Wolff–Kishner or Clemmensen reduction, which is illustrated by conversion of cyclohexanone to cyclohexane in 90% yield,[600] using a silane•BF_3 complex. Other modifications in the reducing power of silanes are possible, such as addition of cesium fluoride to give reduction of an ester moiety.[601] Hydrosilylation provides a powerful and selective method for the reduction of many functional groups and is increasingly important in organic synthesis.

The functional group transforms observed in this section are



4.10.D. Reduction with Formic Acid

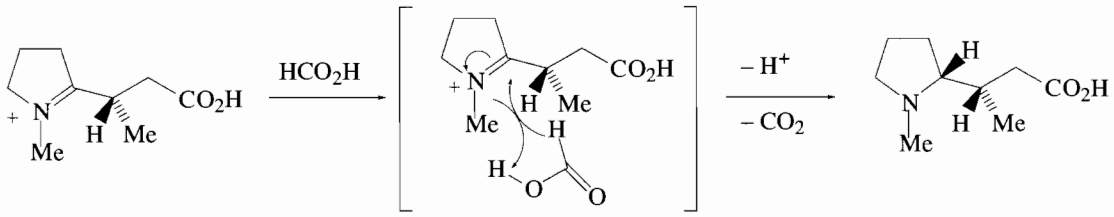
Formic acid has been used in a variety of rather specific reductions. Heating triphenylcarbinol (**580**) in formic acid, for example, led to triphenylmethane (**581**).[602] The most common application of formic acid reduction involves enamines, presumably via conversion to an iminium salt, which is the actual species reduced



580 **581**

by formic acid.[603] Reduction of iminium salts proceeds by hydride transfer, with formation of carbon dioxide.[604] Reduction of 3-(–)-*erythro*-2-(*N*-methyl)pyrrolidiniminiumbutanoic acid (**582**) to **584** illustrates that the reaction is stereoselective. The hydride transfer process is represented by **583** and the stereochemistry

of **584** is predicted by analysis with Cram's rule (sec. 4.7.B).[605] The hydride approaches from the more sterically accessible face. A proton catalyzed tautomerization converts enamines to iminium salts, which are then reduced to the corresponding amine.[606] Reduction of iminium salts is apparently responsible for the classical reductive methylation procedure of amines and formaldehyde in the presence of formic acid.

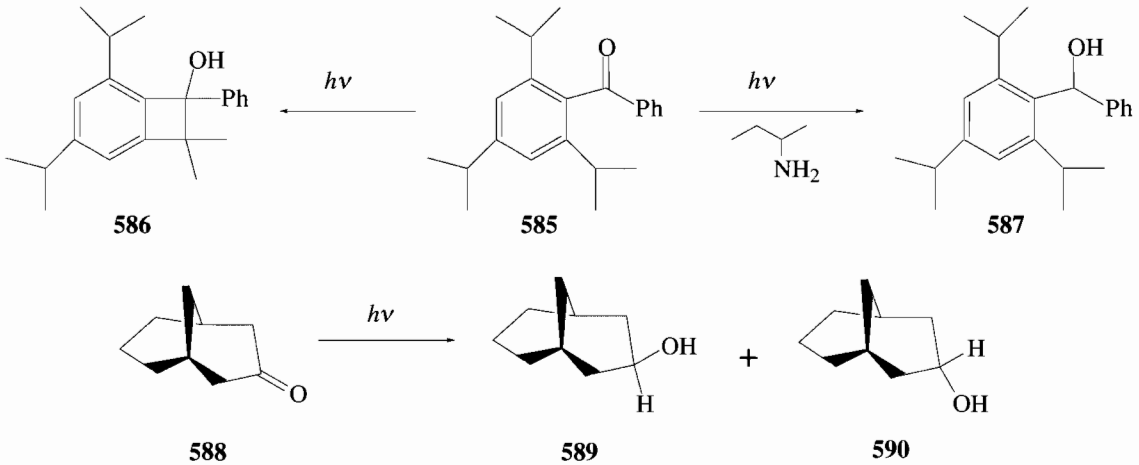


582 **583** **584**

Several modifications of this reduction involve formates and are effective for reduction of various functional groups. A mixture of formic acid and ethyl magnesium bromide was used to reduce decanal to decanol in 70% yield.[607] Decanal was also reduced to decanol in 69% yield by using sodium formate in *N*-methyl-2-pyrrolidinone as a solvent.[608] Functional groups other than carbonyl derivatives can be reduced under relatively mild conditions with formate derivatives. Ammonium formate, in the presence of palladium on carbon was used to reduce an azide to a primary amine.[609] Aliphatic nitro compounds are also converted to an amine with this reagent.[610]

4.10.E. Photoreduction

Electron transfer to certain functional groups can be induced by irradiation with light. When combined with a sensitizer and a hydrogen atom donor, reductions are possible. The basics of photochemical techniques and the use of sensitizers are discussed in Sections 11.10.B and 13.4.



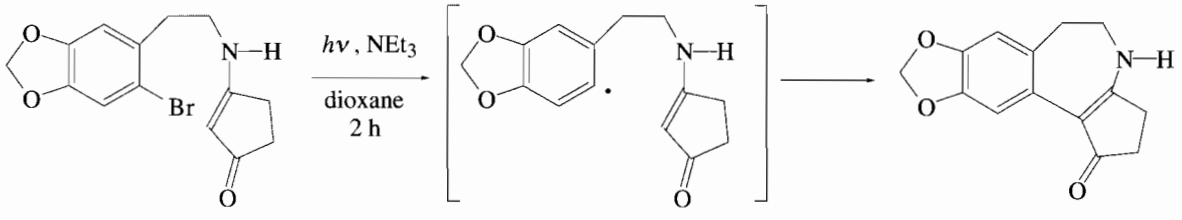
586 **585** **587**

588 **589** **590**

In the presence of a hydrogen atom donor (usually an alcohol or an amine), carbonyl derivatives and halides can be photochemically reduced. Photolysis of ketone **585** gave the benzocyclobutane **586**[611] but photolysis in the presence of *sec*-butylamine gave alcohol **587** as the product. Photoreduction is often less

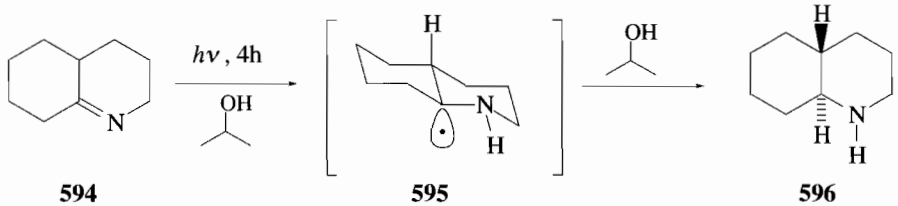
stereoselective than other techniques. Both metal hydride reduction and catalytic hydrogenation of **588** gave exclusively the endo-alcohol **590**, whereas dissolving metal reduction gave 47% of the exo-isomer **589**.[612] Photoreduction of **588** gave a 54% yield of a 4:1 mixture of **589** and **590**.[612]

A disadvantage in using photoreduction is competition from other photochemical pathways (sec. 13.4), including coupling, isomerization and migration of multiple bonds. Functional groups with larger quantum yields will react preferentially but this is very dependent on the wavelength of the light used for irradiation (sec. 11.10.B and sec. 13.4).



591 **592** **593**

Reduction of halides is a useful application of this process and there are variations that make it more useful. Mariano and co-workers showed that the bromide in **591** is removed to give a radical, and this cyclizes (via **592**) in the presence of the enaminone moiety to give a mixture of several products on irradiation with Pyrex™ filtered light.[613] When a Vycor™ filter (secs. 11.10.B and sec. 13.4) was used to limit the incident light to >220 nm [130 kcal mol^{-1}, 544.2 kJ mol^{-1}] (required for the enaminone moiety), radical cyclization was the major process (sec. 13.7 for a discussion of radical cyclization), giving **593** in 85% yield.



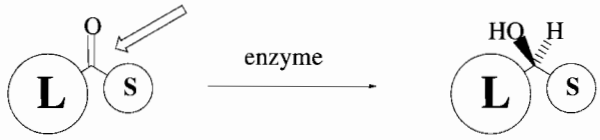
594 **595** **596**

Photoreduction of imines has been used in the synthesis of various alkaloids. Irradiation of $\Delta^{1,9}$-octahydroquinoline (**594**) led to a 98% yield of *trans*-octahydroquinoline (**496**). Hydrogen is transferred to the nitrogen (2-propanol is the hydrogen transfer agent), leading to the thermodynamically more stable radical (**595**).[614] A second hydrogen transfer delivers the hydrogen to the bottom face of **595**, giving **596**.

.10.F. Enzymatic and Microbial Reductions

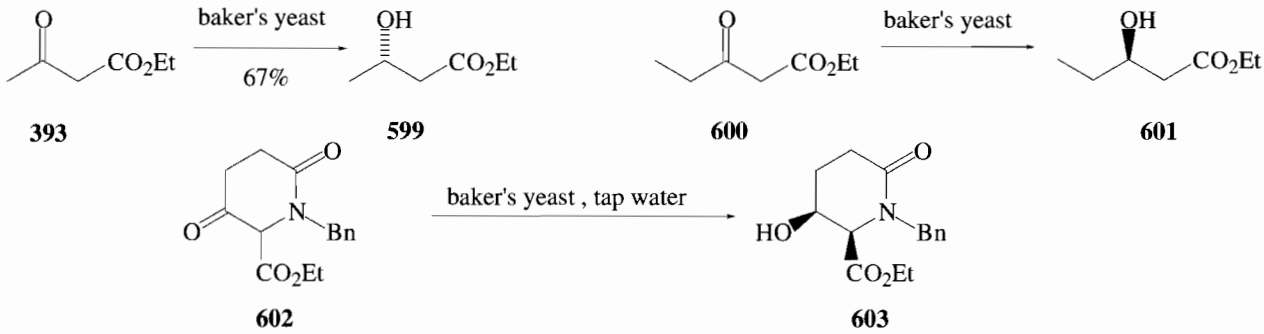
Enzymes are an increasingly available and important tool in the arsenal of the synthetic chemist. Enzymatic reductions are often straightforward and highly stereoselective. There are now many enzymatic transformations that are compatible with the use of organic solvents.[615] Other solvents can be used as well, illustrated by the enzyme alcohol dehydrogenase from *Geotrichum candidum*, which is active in supercritical carbon dioxide.[616] Prelog studied the reduction of ketones with several enzymatic systems. Reduction of

ketones with *Curvularia fulcata*, for example, gave predictable stereochemical induction based on identifying Large (L) and Small (S) groups around the carbonyl (this method is sometimes called **Prelog's rule**).[617] If the steric difference between (L) and (S) in **597** is large enough, the enzyme delivers hydrogen from the less hindered face (over S in **597**) to give **598**. Two of the most common enzymatic systems are yeast alcohol dehydrogenase (YAD) and horse liver alcohol dehydrogenase (HLADH). This former reagent is usually obtained from yeast and is a protein with a molecular weight of ≈ 80,000, containing four subunits. This information is given to illustrate that the exact structure of the enzyme is not always correlated with the exact portion of that structure required for reduction (the active site). Such ambiguities of structure make exact mechanistic arguments difficult. An important part of the selectivity observed with these enzymes, however, is "determined by nonbonded interactions of substrate and enzyme in the hydrogen transfer transition state".[617] Prelog argued that compounds that can assume a diamond lattice (sec. 1.5.B) gave higher selectivities.



597 **598**

A very common reagent is baker's yeast (*Saccharomyces cerevisiae*) and it is important for the selective reduction of β-keto esters and β-diketones. In the Sih and co-workers synthesis of (*L*)-carnitine,[618] a dependence on the size of the ester group was discovered. Reduction of ethyl acetoacetate (**393**) with baker's yeast gave the (*S*)-alcohol (**599**) but reduction of ethyl β-ketovalerate (**600**) gave the (*R*)-alcohol (**601**).[618] Sih showed the selectivity of reduction changed from (S)-selectivity with small chain esters to (*R*)-selectivity with long chain esters.[618] The break point for selectivity occurred at a chain length of four to five carbons



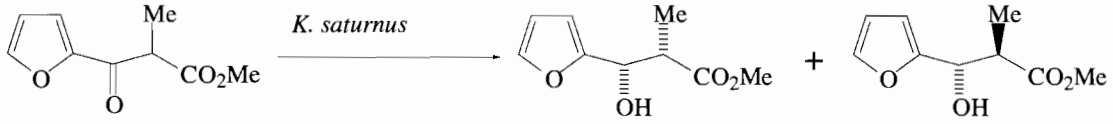
393 **599** **600** **601**

602 **603**

[RC(=O)—O(CH$_n$)H, n = 4, 5]. Baker's yeast has been used in many synthetic applications. Hydroxyester (**599**), for example, was used in Mori's synthesis of (*S*)-(+)-sulcatol.[619] More complex systems can be reduced, as in the reduction of **602** to **603** (88% yield and >99% ee).[620] The selectivity is consistent with the (*S*)-selectivity predicted by Prelog's Rule. 1,3-Diketones are usually reduced to the β-keto alcohol. 2,4-Hexanedione, for example, was reduced to (*S*)-5-hydroxy-3-hexanone quantitatively [>99% ee].[621]

Oishi encountered problems in the reduction of aryl β-keto esters such as the furan derivative **604**, where baker's yeast was unable to reduce the ketone moiety.[622] Oishi examined other selected yeasts including

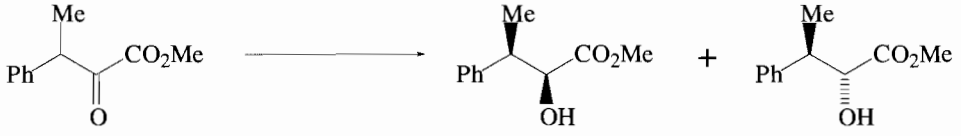
Kloeckera saturnus, which converted **604** in 47% yield to a 47:53 mixture of the syn- (**605**) and anti- (**606**) diastereomers in 87% ee and 53% ee respectively.[622] Another yeast (*Saccharomyces delbrueckii*) gave 43% reduction with a syn/anti ratio of 39:61. Reduction with *S. delbrueckii* gave 99% ee of **605** and 94% ee of



604 **605** **606**

606.[622] Oishi examined the selectivity for reduction of **607** with a variety of organisms, as shown in Table 4.17.[623] In all cases, the organism produced an excess of either the syn- or the anti-diastereomer (**608** or **609**). The chemical yields were poor in some cases and the reduction proceed with modest to good diastereoselectivity in other cases. The enantioselectivity of the reaction was good to excellent with 60–99% ee

Table 4.17. Diastereoselective reduction of 607 by selected yeasts.



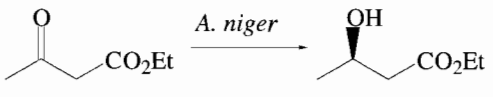
607 **608** **609**

Yeast	Yield (%)	591/592
Endomycopsis fibligera	72	48:52
Hansenula anomala	44	43:57
Hansenula anomala NI-7572	44	40:60
Kloeckera saturnus	46	18:82
Lipomyces starkeyi	15	85:15
Pichia farinosa	40	15:85
Pichia membranaefaciens	51	53:47
Rhodotorula glutinis	46	68:32
Saccharomyces acidifaciens	14	44:56
Saccharomyces debrueckii	63	28:72
Saccharomyces fermentati	70	28:72
Candida albicans	26	17:83

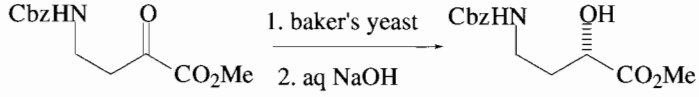
observed for both the syn- and the anti-diastereomers produced. In other work, Oishi and co-workers found that selected yeasts showed different diastereoselectivity and enantioselectivities when the aryl group was changed from phenyl to thiophene.[623a] Several strains of yeast were used but the yields were poorer than the analogous reduction of **604**, and although the diastereoselectivity was similar, changes in enantioselectivity were very pronounced.

Other organisms have been used to reduce β-keto esters. Indeed, either the *(R)*- or the *(S)*- alcohol can be obtained. Bernardi et al. showed that **393** was reduced to *(S)*-alcohol **599** in 96% yield, 7:93 *(R/S)*- with *G. candidum*.[624] The reaction medium is quite important. Nakamura et al. found, for example, that reduction of

ketones with this enzyme in the presence of the hydrophobic polymer Amberlite™ XAD gave the (*S*)-alcohol in high enantiomeric excess, whereas low enantioselectivity was obtained in the absence of the polymer.[625] Reduction of **393** with *Aspergillus niger* gave 98% of a 75:25 mixture favoring the (*R*)-alcohol **610**.[624] α-Keto esters (glyoxalates) are reduced with yeast, as illustrated by the conversion of **611** to (*S*)-alcohol **612** in 47% yield (in 49% ee in this case).[626] Aryl glyoxalates are usually reduced to the (*R*)-alcohol.[626] It has also been shown that using acetone powder of a microorganism such as *G. candidum* led to improved stereoselectivity.[627] Trifluoromethyl ketones are reduced with opposite stereochemistry relative to methyl ketones with this organism.[628] Bioreduction using methanol as a cosolvent and the fungus *Curvularia lunata* CECT 2130 gave chemoselective reduction of aromatic β-keto nitriles to the corresponding (*S*)-β-hydroxy nitriles with high enantioselectivity.[629]

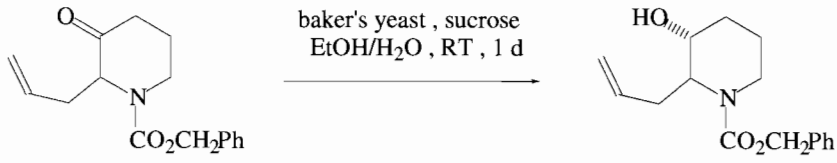


393 **610**



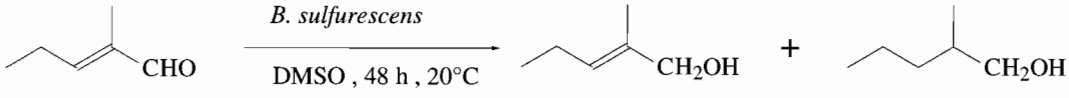
611 **612**

Simple ketones can also be reduced with baker's yeast.[630] In a synthetic example, ketone moiety of the piperidone unit in **613** was reduced with baker's yeast to give a 40% yield of **614** (98% ee) in Takeuchi's synthesis of isofebrifugine.[631]



613 **614**

Veschambre used *Beauveria sulfurescens* for the reduction of conjugated carbonyls. *trans*-Crotonaldehyde was reduced to but-(2*E*)-en-1-ol in 80% yield.[632] 2-Methyl-2-pentenal (**615**), however, gave a mixture of 31% of the conjugated alcohol (**616**) and 69% of the completely reduced alcohol (2-methyl-1-pentanol, **617**).[632] Later work showed this microbial reduction gave the (*S*)-alcohol by a stepwise process in which the

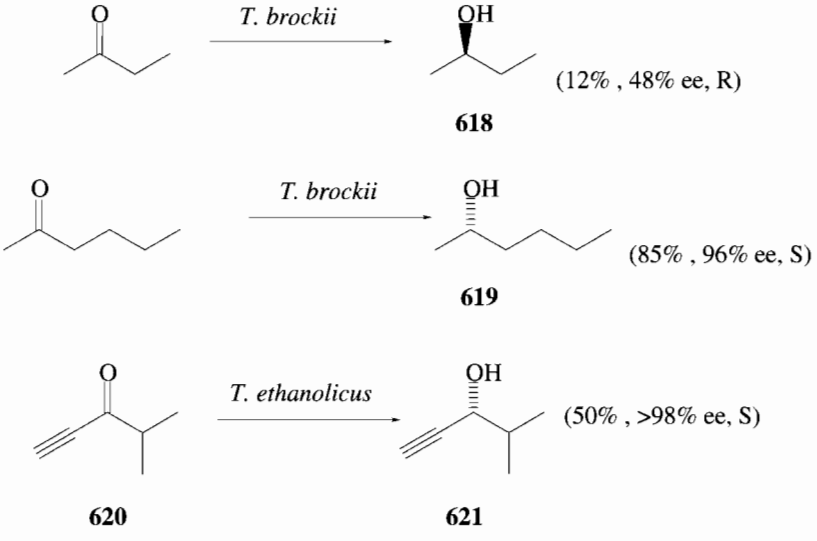


615 **616** **617**

conjugated double bond was reduced first, establishing the (*S*)-stereochemistry, followed by reduction of the aldehyde moiety to the alcohol.[632b] Veschambre established a rule for this reduction. The hydrogen is delivered to the double bond α to the carbonyl from the front or back depending on the relative bulk of R^1 and R^2, which is simply a modification of Prelog's Rule. Reduction of geranial with baker's yeast gave (*R*)-citronellol, consistent with the prediction. The (*Z*)-isomer neral was predicted to give the (*S*)-isomer, but

reduction with baker's yeast gave a 6:4 *(R/S)* mixture, possibly due to isomerization of the double bond in neral prior to delivery of hydrogen.[632b]

Another common organism for reduction of the carbonyl group is *Thermoanaerobium brockii* (**227**), first mentioned in Section 4.7.A in Table 4.6. Keinan et al. showed that small ketones such as 2-butanone are reduced by *T. brockii* to give the *(R)*-alcohol [2-butanol, **618** in 12% yield and 48% ee, *(R)*] but large ketones such as 2-nonanone are reduced to the *(S)*-alcohol [**619**, 85% yield and 96% ee, *(S)*].[253] An alcohol dehydrogenase found in *Thermoanaerobacter ethanolicus* reduces ethynyl ketoses such as **620** to **621** in good yield and high enantioselectivity [in this case **621** was isolated in 50% yield and >98% ee, *(S)*].[633] These



simple examples illustrate typical enantioselectivity of the reduction and that the selectivity depends on the size and nature of the groups around the carbonyl. These changes in selectivity are explained by a knowledge of the active site of the enzyme. The carbonyl is bound close to a nicotinamide moiety in the coenzyme. Two alkyl sites are also present with the smaller alkyl group lying closer to the nicotinamide having the greater affinity.[253] Keinan and Lamed[253] suggested the small alkyl site can accommodate groups smaller than *n*-propyl. For methyl–alkyl ketones, if the alkyl is methyl, ethyl, isopropyl, or cyclopropyl, the *(R)*-alcohol predominates but if the alcohol group is larger than *n*-propyl, the *(S)*-alcohol predominates. For internal ketones (alkyl–alkyl) the *(S)*-alcohol is usually the major product.[634] It appears that various yeast preparations and *T. brockii* are the most commonly used reducing organisms. The low cost and high selectivity of such enzymatic and microbial reagents foretell an increasingly important role in organic synthesis.

4.11. CONCLUSION

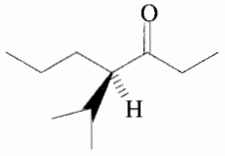
It is obvious from this chapter that reductive processes are wide ranging and important to organic synthesis. The diastereoselectivity and enantioselectivity of many reducing agents are important for fixing stereogenic centers in synthetic targets. An attempt has been made to show how reagents were developed as well as their chemoselectivity.

Chapter 5 will introduce reactions associated with hydroboration. This important synthetic methodology is a logical extension of the borohydride and borane reductions seen in this chapter. Chronologically, the reductive capabilities of boranes preceded the alkene addition reaction, which is the heart of hydroboration. In part, this is why hydroboration is presented after reduction.

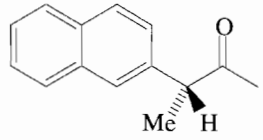
It is also noted that the stereochemical models introduced in this chapter will be used continuously in succeeding chapters. Addition of Grignard reagents and other organometallics to carbonyls generally follow Cram's rule or the Felkin–Ahn model. Chelation control will be important in many reactions including enolate alkylation reactions. This chapter has therefore been a vehicle for introducing not only reduction but the stereochemical basis for all of organic chemistry.

HOMEWORK

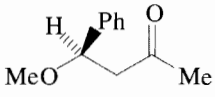
1. Predict the correct diastereomeric product using (a) the appropriate Cram model and (b) the Felkin–Ahn model. In each case, draw the model for that specific reaction.

(a) 

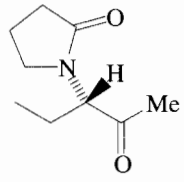
1. $LiAlH_4$
2. dil H_3O^+

(b) 

1. $LiAlH(Ot\text{-}Bu)_3$
2. dil H_3O^+

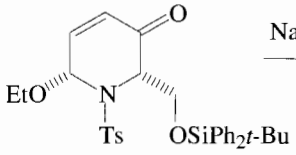
(c) 

1. $Zn(BH_4)_2$
2. dil H_3O^+

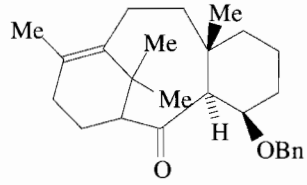
(d) 

1. $Zn(BH_4)_2$
2. dil H_3O^+

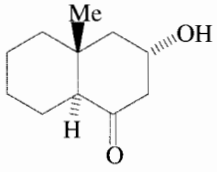
2. In each case, predict the major diastereomer. Explain your answer.

(a) 

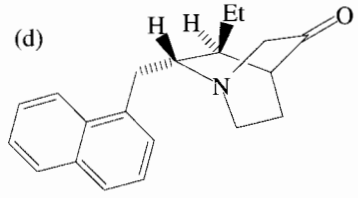
$NaBH_4 \bullet CeCl_3$

(b) 

$LiAlH_4$, THF
0°C

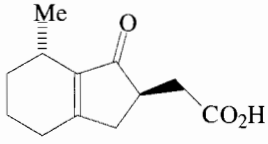
(c) 

1. $Zn(BH_4)_2$
2. dil H_3O^+

(d) 

1. $NaBH_4$
2. dil H_3O^+

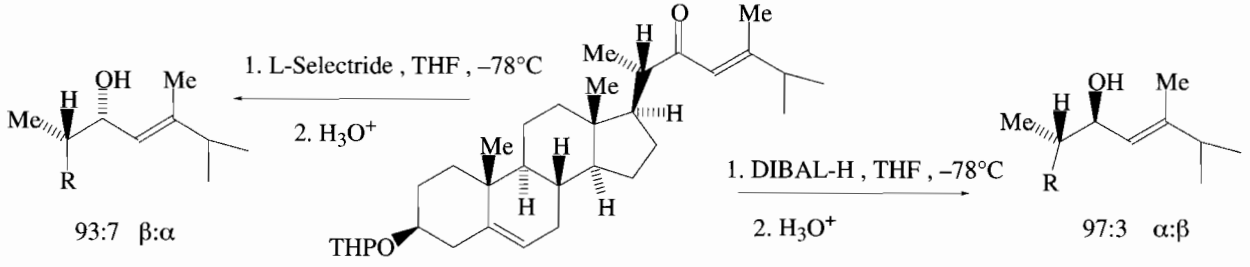
3. Predict the major product and explain the stereochemistry for that product.



$NaBH_4$, $CeCl_3$

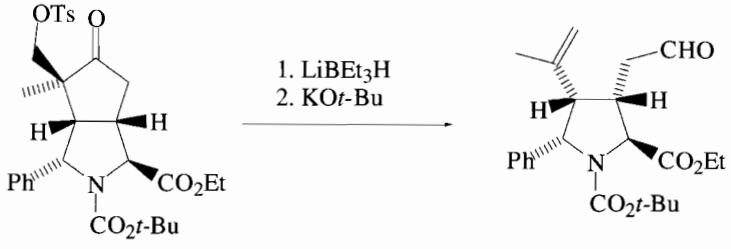
see *J. Org. Chem.*, ***1998***, *63*, 1259

4. Explain why there is such a difference in selectivity for reduction of this conjugated ketone when the reducing agent is changed.

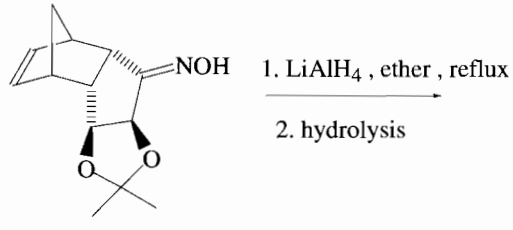


Tetrahedron Lett., ***1985***, *26*, 69

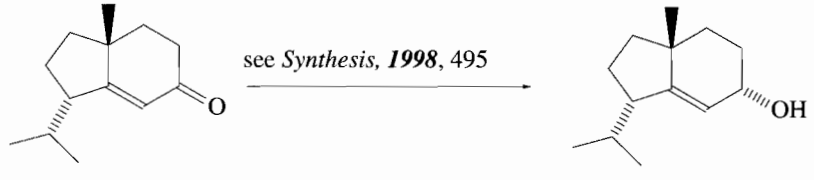
5. Briefly discuss this transformation.



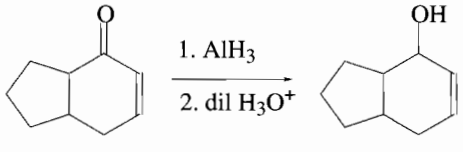
6. Predict the major product, and predict the stereochemistry of that product.



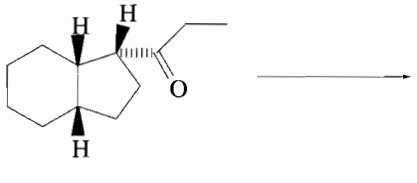
7. Briefly discuss the following transformation, particularly focusing attention on the stereochemistry.



8. Explain each of the following observations or products.



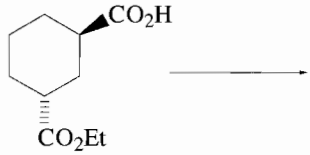
(a) The major process is 1,2-reduction.
(b) L-Selectride gives greater diastereoselectivity in this reduction than does sodium borohydride. Predict the major product.



(c) Treatment of benzene with $Na/NH_3/EtOH$ gives 1,4-cyclohexadiene, whereas similar treatment of cyclohexene with this reagent gives no reaction.

(d) Birch reduction of anisole leads to 1-methoxy-1,4-cyclohexadiene but reduction of benzoic acid give 3-carbalkoxy-1,4-cyclohexadiene.

(e) Reduction with $LiAlH_4$ gives a diol but reduction with diborane gives a hydroxy ester.



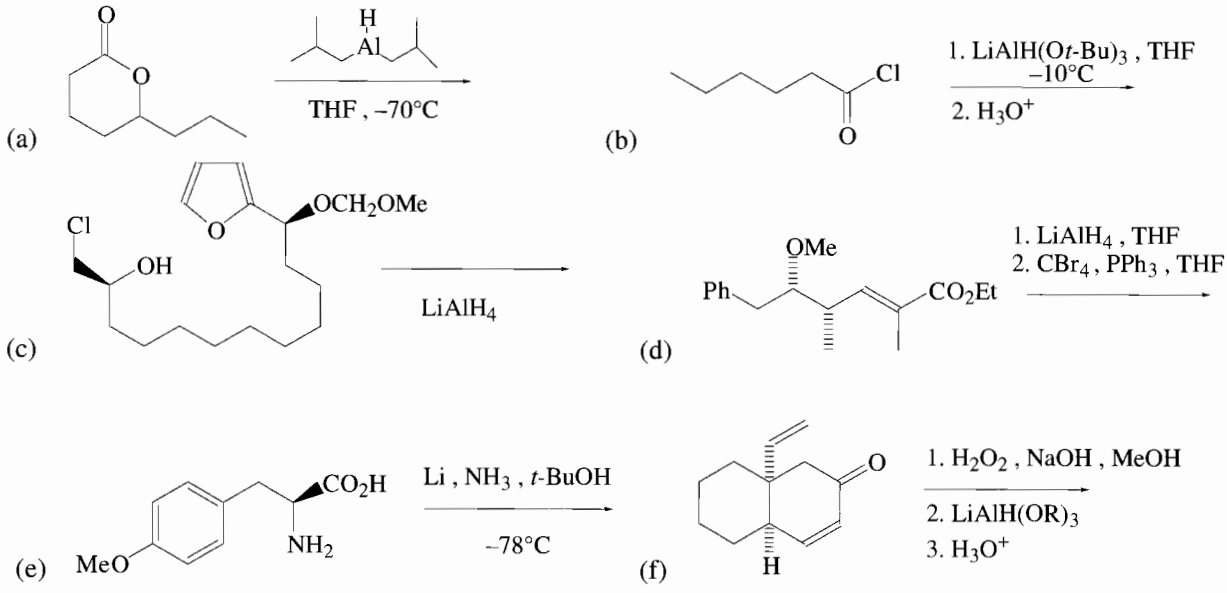
(f) Diimide reduces unconjugated alkenes faster than conjugated alkenes.

(g) Reduction of A and B with zinc borohydride leads to opposite stereochemical results.

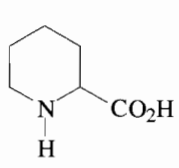
(h) Cerium borohydride gives primarily 1,2-reduction upon reaction with cyclohexenone but sodium borohydride gives a mixture of 1,2- and 1,4-reduction.

9. For each transformation, give two <u>different</u> reagents that will successfully complete the given conversion.

10. In each case, predict the major product of the reaction shown.



(g)



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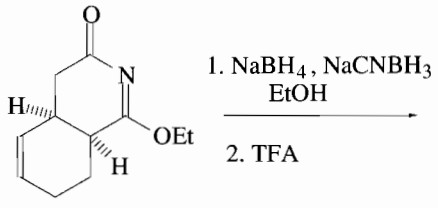

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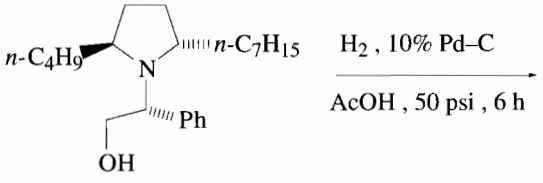

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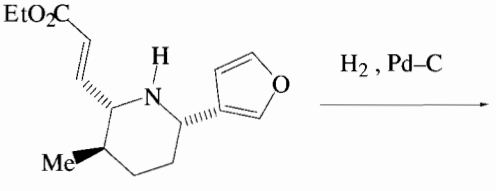

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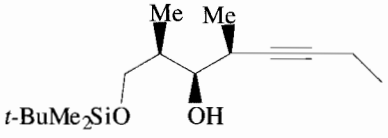

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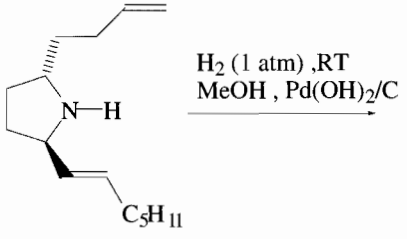

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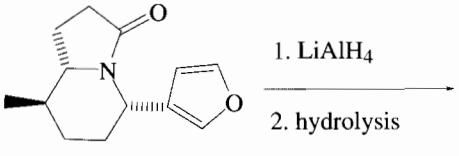

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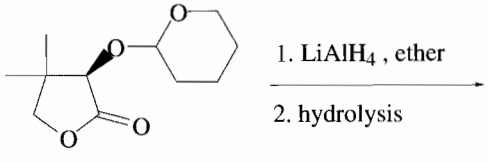

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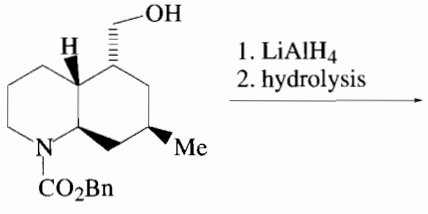

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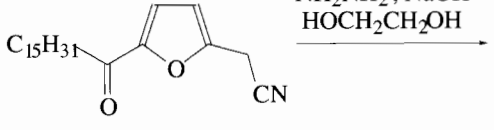

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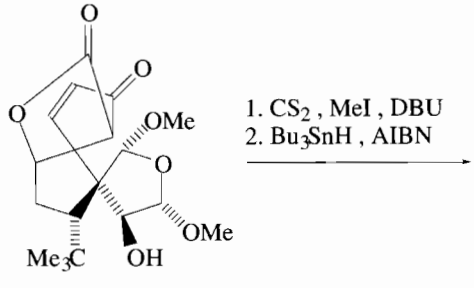

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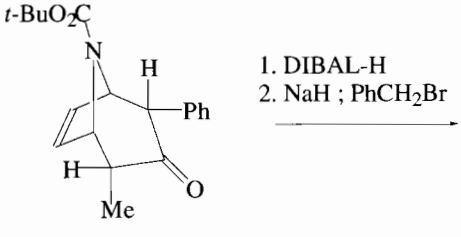

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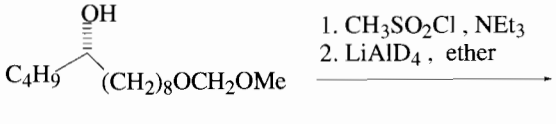

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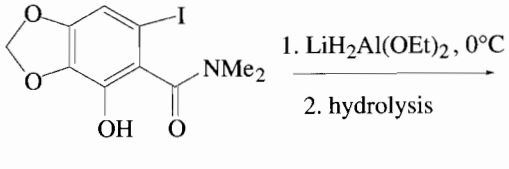
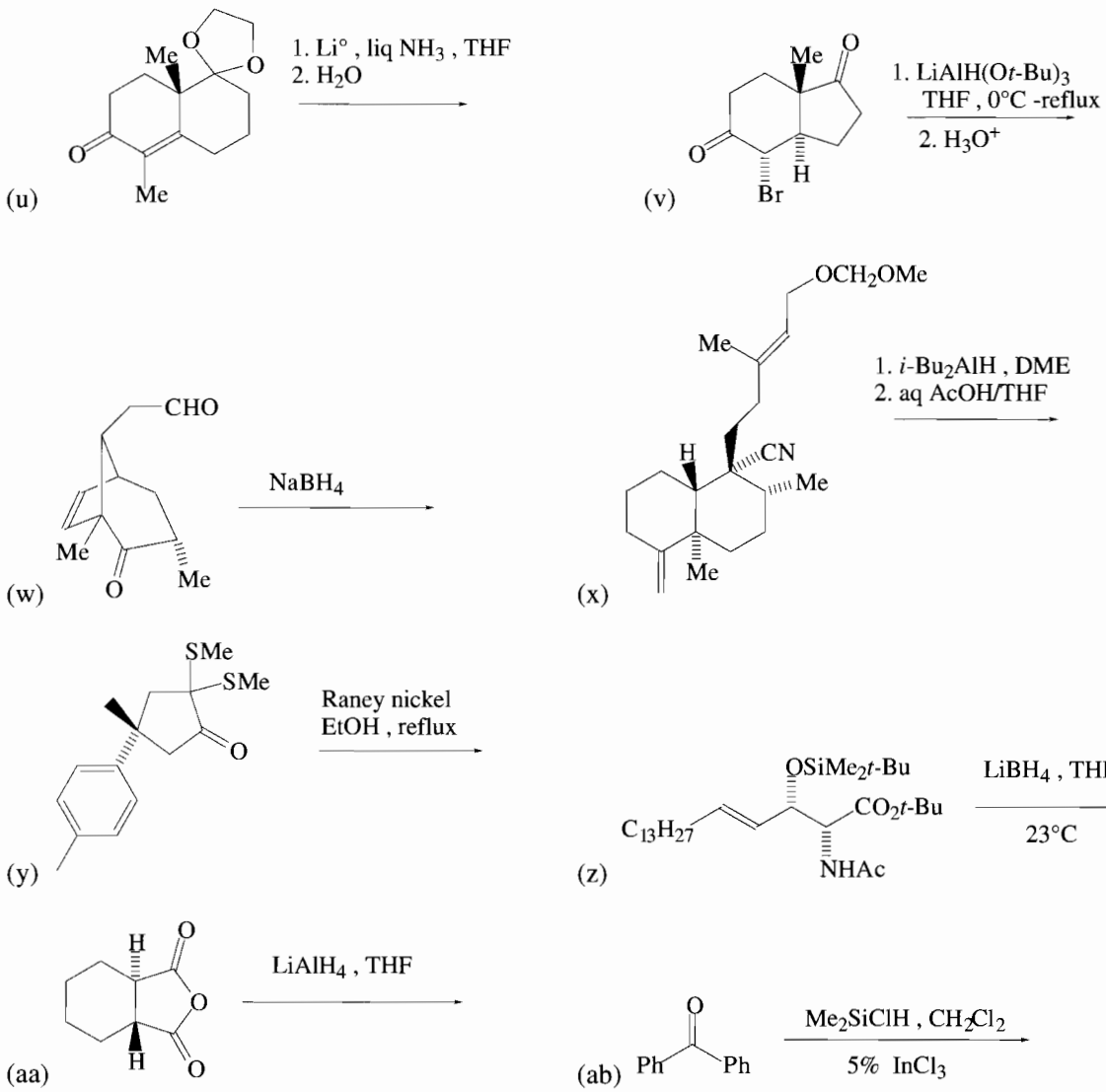
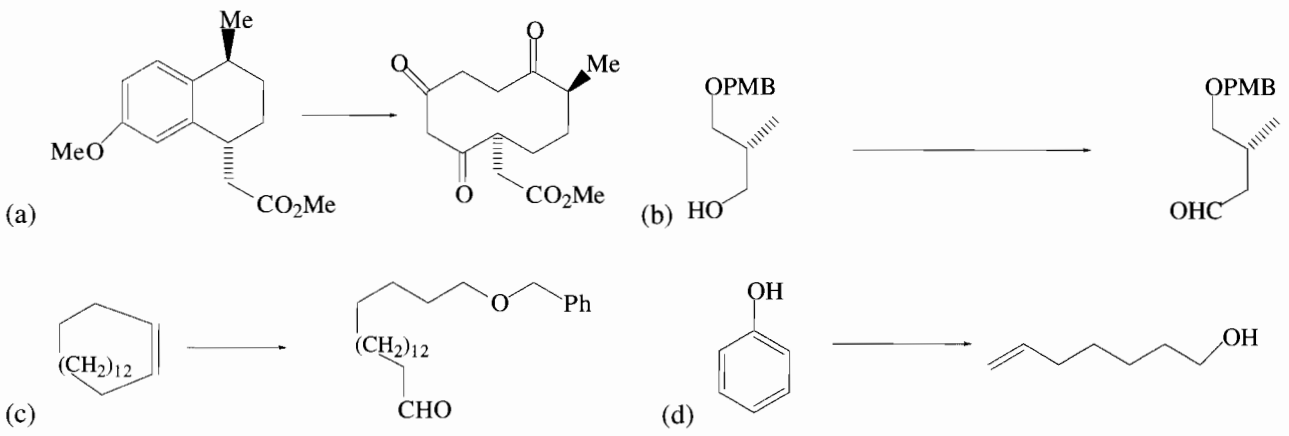
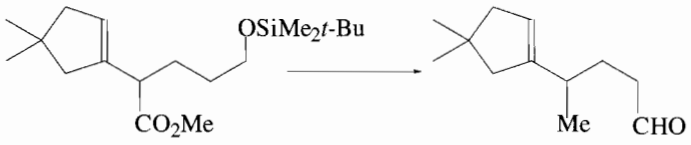
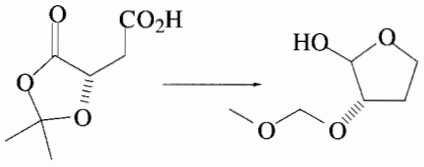


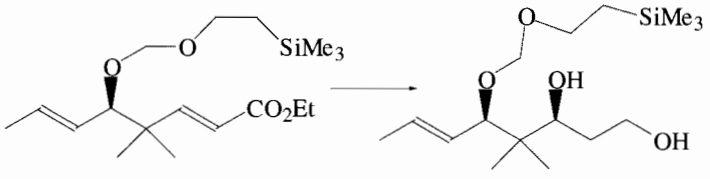


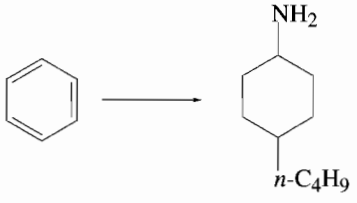
11. In each case, provide a suitable synthesis showing all intermediate products and all reagents.

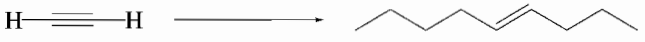


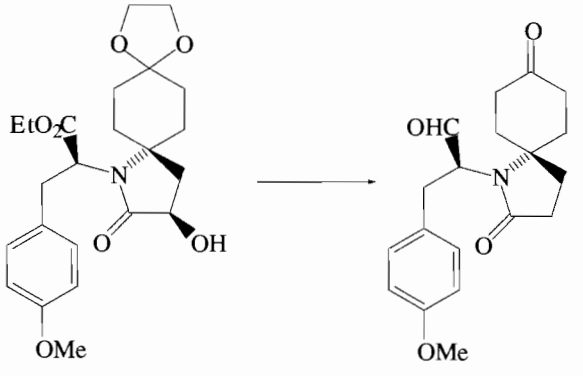
(e) 

(f) 

(g) 

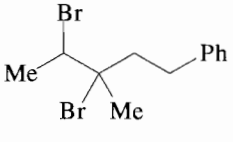
(h) 

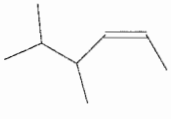
(i) 

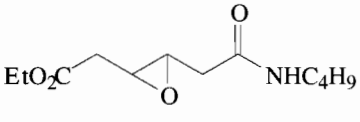
(j) 

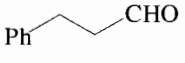
(k)

12. Show a complete synthesis for each of the following. Use any starting material of your choosing that contains six carbons or less but you must find it in a current catalog from a chemical company (give the source and price of your starting material). Show a retrosynthetic analysis and synthesis for each molecule.

(a) 

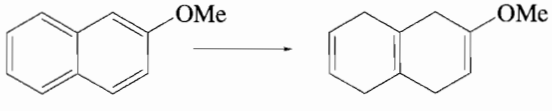
(b) 

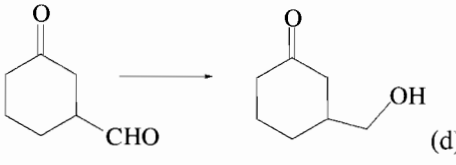
(c) 

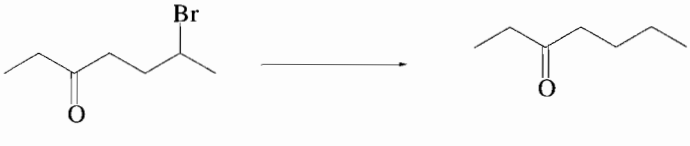
(d) 

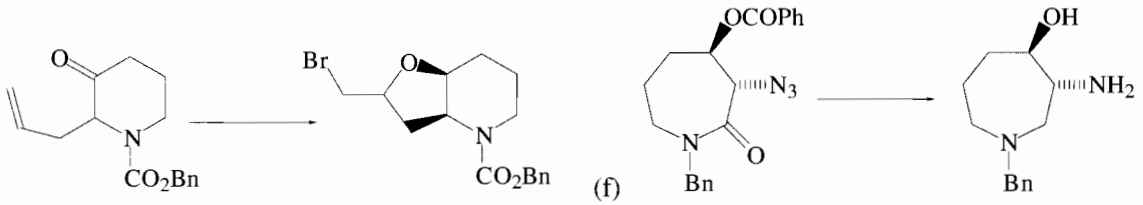
13. Give reagents that will accomplish each of the following selective transformations.

(a)

(b) 

(c) 

(d) 



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9 Gaylord, N.G. *J. Chem. Educ.*, ***1957***, *34*, 367.
10 For a review of 60 years of hydride reductions, see Brown, H.C.; Ramachandran, P.V.. in *Reductions in Organic Synthesis. Recent Advances and Practical Applications*, Abdel–Magid, A.F (Ed.), ACS Symposium Series 641, American Chemical Society, Washington, DC, ***1996***. pp 1–30.
11 Finholt, A.E.; Bond, A.C.; Schlesinger, H.I. *J. Am. Chem. Soc.*, ***1947***, *69*, 1197.
12 Nystrom, R.F.; Brown, W.G. *J. Am. Chem. Soc.*, ***1947***, *69*, 1197.
13 Reference 7, p 14.
14 Schlesinger, H.I.; Brown, H.C.; Finholt, A.E. *J. Am. Chem. Soc.*, ***1953***, *75*, 205.
15 Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis, Vol. 1*, Wiley, New York ***1967***, pp 581–595.
16 House, H.O. *Modern Synthetic Reactions*, 2nd ed, Benjamin, Menlo Park ***1972***, p 49 and citations 5, 12 and 14 therein.
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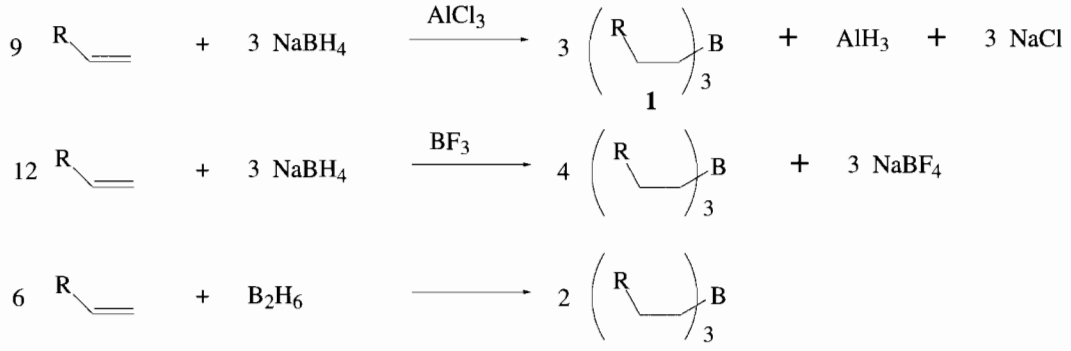
CHAPTER 5

HYDROBORATION

5.1. INTRODUCTION

In chapter 4, borane and alkylborane reagents were introduced as powerful and selective reducing agents. The Lewis acidity of borane (BH_3) led to interesting differences in reducing power when compared to $LiAlH_4$ and $NaBH_4$ derivatives. An example of this Lewis acidity is Brown's discovery that diborane (B_2H_6) reacted with alkenes in ether solvents to form trialkylboranes (**1**).[1] Brown's monograph on hydroboration described three methods that generated diborane in the presence of the alkene.[2]



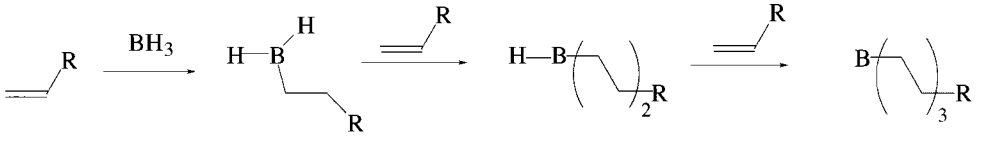
Continuing interest in this reaction led to development of a large number of functional group transformations and carbon–carbon bond-forming reactions that utilized mono-, di-, trialkyl, and alkenylboranes. This work contributed to Brown's award of the Nobel Prize for Chemistry in 1979 and is continuing to this day. The inclusion of hydroboration in organic synthesis and some unique transformations made possible by it are detailed in this chapter. A discussion of hydroboration following the discussion of the reducing properties of boranes (in Chap. 4) is both historically correct and conceptually useful. Where appropriate, the diastereoselectivity and the enantioselectivity of hydroboration reactions will be discussed. In addition to the functional group transformations that are available via hydroboration, the reactions presented in this chapter are a useful review of many reaction types encountered in earlier chapters.

5.2. PREPARATION OF ALKYL AND ALKENYL BORANES

5.2.A. Alkyl Boranes

Diborane reacts with alkenes to form alkylboranes in ether solvents. This important finding apparently resulted from an observation by Brown that reduction of ethyl oleate, in ether solvents and in the presence of a Lewis acid, consumed 2.4–2.5 hydrides per mole and 3 equivalents when a larger excess of the reagent was used.[3] Brown discovered that borane had *added* to the π bond of the alkene moiety generating a monoalkyl-

borane (**2**), and this is a general reaction. If a sufficient quantity of alkene is present, one of the active hydrogens on **2** can react with a second equivalent of alkene to give the dialkylborane (**3**) and with a third equivalent to give the trialkylborane (**1**).[2] The reaction of diborane with unsaturated molecules had been reported earlier by Stock and Kuss,[4] in the explosive reaction of acetylene and diborane at 100°C. In 1948, Hurd reported that alkenes reacted with diborane at elevated temperatures to form a trialkylborane,[5] but the reaction was slow at 100°C (24 h) and even slower at ambient temperatures. This earlier work with borane did not use ether as a solvent, but Brown's work showed that ethers had a catalytic effect on the addition of borane to alkenes. Although the "reaction of diborane with pure olefins is indeed quite slow, addition of mere traces of ether changed the initially slow reaction to a fast one."[6] This rate acceleration allowed alkylboranes to be readily formed[1a,7] under relatively mild conditions, allowing them to be used in synthesis.

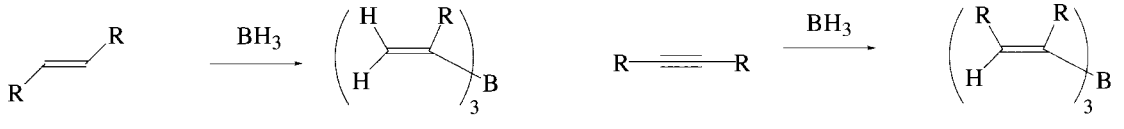


2 **3** **1**

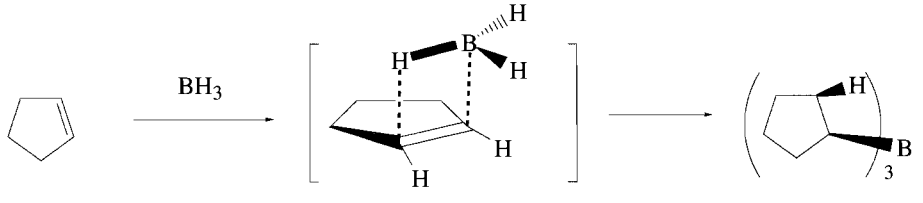
An excellent *in situ* preparation of diborane results from the reaction of boron trichloride (BCl_3) or boron trifluoride (BF_3) with sodium borohydride in the presence of alkenes, as shown above. This reagent gave virtually instantaneous conversion of an alkene to a trialkylborane at ambient temperatures, when done in a ether solvent.[8] When diborane was isolated and purified it also reacted with alkenes, rapidly and quantitatively in ether solvents.

5.2.A.i. General Properties of Boranes. When borane reacts with alkenes there are several predictable characteristics.[9]

1. Borane reacts with alkenes and alkynes rapidly and quantitatively (in most cases) by addition of the hydrogen–boron moiety to the π- bond of an alkene or an alkyne, to give an alkylborane or an alkenylborane, respectively.[2,10]

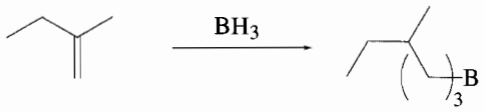


2. The reaction proceeds by cis addition of hydrogen and boron, probably via a four-center transition state such as **4**.

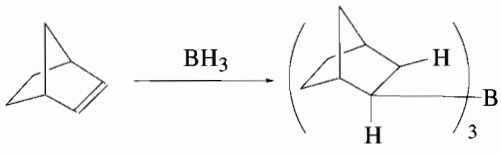


4

3. The boron adds regioselectively at the less sterically hindered position, as shown in the reaction with 2-methyl-1-butene.

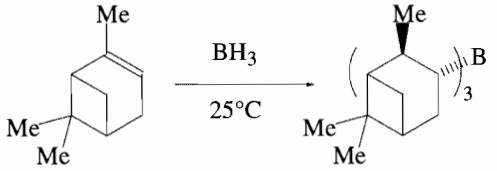


4. The boron adds stereoselectively to the less sterically hindered face of the alkene. Reaction with norbornene, for example, gave 99.6% of the exo-borane (**5**) with only 0.4% of the endo- borane.[11] This is consistent with the normal addition of reagents to the exo face of norbornyl derivatives (sec. 1.5.E).



5

5. Hydroboration proceeds without skeletal rearrangement, at normal temperatures, as in the hydroboration of α-pinene (**6**) to give **7**.[2,10]



6 **7**

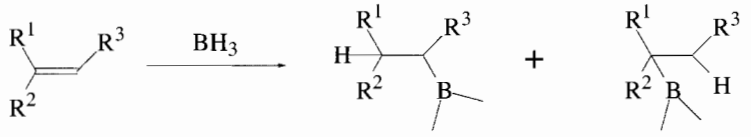
6. In ether solvents, a wide range of other functional groups can be tolerated, even reducible ones such as esters, if the stoichiometry of the reagent is controlled.

7. The organoborane product can be oxidized, eliminated, rearranged, protonated and aminated, leading to a large number of functional group transformations.

As noted in (3), borane adds selectively to the less sterically hindered carbon of the alkene or alkyne, but *mixtures* of Markovnikov product (addition of boron to the most hindered carbon) and anti-Markovnikov (addition of boron to the less hindered carbon) product are usually observed. This selectivity is best understood by examining the four-center transition state required for the addition (see **4**). When borane approaches the alkene unit of 2-methylpropene, two orientations are possible (**8** and **9**). In **8**, the BH_2 moiety is positioned over the less hindered carbon bearing the hydrogen atoms [$BH_2 \leftrightarrow H_2C=$] because this minimizes the destabilizing steric interactions with the methyl groups on the alkene [$BH_2 \leftrightarrow Me_2C=$] found in the other orientation (**9**). In other words, this interaction destabilizes **9** and leads to selective delivery of boron to the less hindered carbon via **8**. Table 5.1[12] shows the relative proportions of alkylborane formed by addition of diborane to several representative alkenes.

8 **9**

Table 5.1. Directive Effects in Reactions of Alkenes with Borane



10 **11**

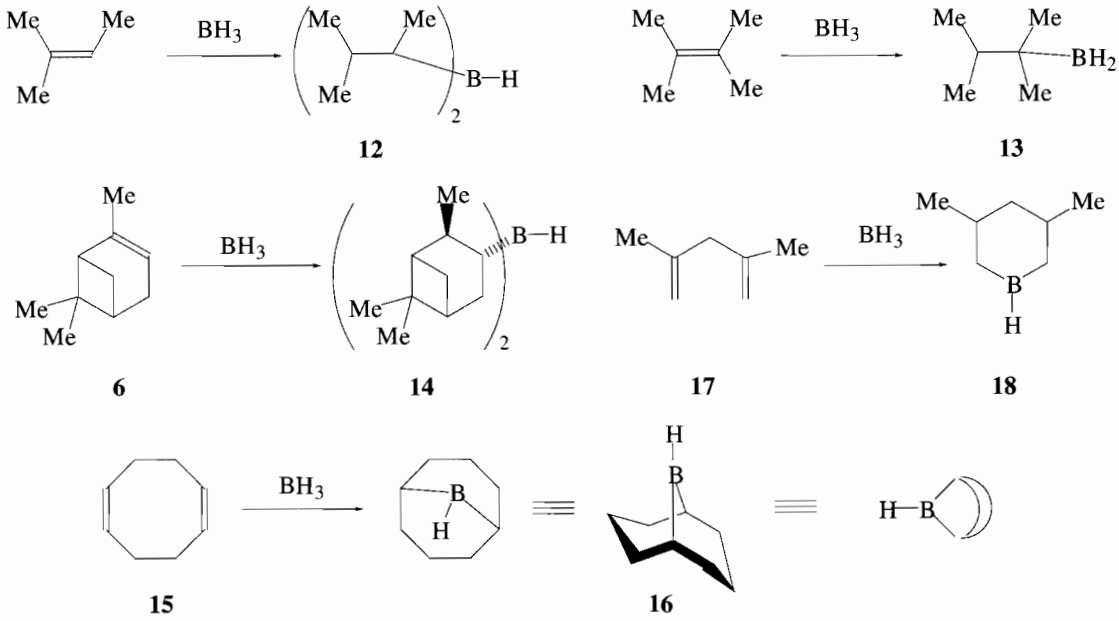
R^1	R^2	R^3	%10	%11
Et	H	H	93	7
Bu	H	H	94	6
i-Pr	H	H	94	6
t Bu	H	H	94	6
Ph	H	H	80	20
CH_2Ph	H	H	90	10
Et	Me	H	99	1
Ph	Me	H	100	trace
Me	H	Me[a]	55	45
Et	H	Me[b]	51	49
Me	H	*i*-Pr[b]	43	57
Me	H	*t* Bu[b]	42	58
Me	Me	Me	98	2
Me	Me	*t* Bu	98	2

[a] cis- [b] trans-

With monosubstituted alkenes, the steric interaction between the BH_2 moiety of the borane and the single alkyl group on the π bond is sufficient to give >90% selectivity for the anti-Markovnikov product **10**, over **11** (93:7 for R^1 = Et, R^2,R^3 = H) With di- and trisubstituted alkenes the increased steric interaction between the boron and alkyl groups on the alkene lead to extremely high selectivities (R^1 = Ph and R^2 = Et in **10**, for example). Electronic effects are also a factor in the reaction of styrene, which gives only 80% selectivity for **10**. This electronic effect diminishes with distance (as when R^1 is benzyl, which behaves as if it were a simple alkyl group). When there is little steric difference between two groups in disubstituted alkenes (the B—H↔R^1 and B—H↔R^3 interactions are about the same, as when R^1 = Et and R^3 = Me), poor selectivity is observed and close to a 1:1 mixture of **10** and **11** is observed. cis Alkenes with large groups attached to the π-bond often give good selectivity for the anti-Markovnikov borane, but cis alkenes with small groups show poor selectivity. In trans alkenes, large differences in the size of substituents were less important, although there is some selectivity for addition of boron to the carbon bearing the smaller substituent. With trisubstituted alkenes, addition of boron occurred preferentially at the monosubstituted carbon (note the selectivity observed with 2,4,4-trimethyl-2-pentene in Table 5.1 [R^1 = R^2 = Me, R^3 = *t*-Bu]).

The boron–alkyl interactions in the four-center transition state (**8** or **9**) largely control the reaction, but destabilizing steric interactions between alkyl substituents attached to the boron, in the alkylborane products, are also important. There are three B—H bonds in borane and therefore three equivalents available to react

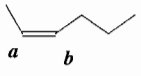
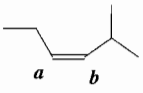
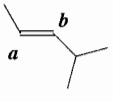
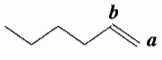
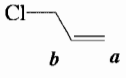
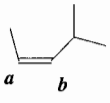
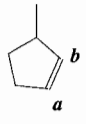
with 3 equivalents of alkene, which would give a trialkylborane. Terminal alkenes (such as 1-decene) and relatively unsubstituted alkenes (such as 2-butene or cyclohexene) usually react with borane to give trialkylboranes (R_3B).[13] Relatively unhindered trisubstituted alkenes such as 2-methyl-2-butene usually give a dialkylborane (R_2BH),[13] and hindered alkenes such as *tert*-butylcyclohexene or 2,4,4-trimethyl-2-butene lead to a monoalkylborane (RBH_2).[13] In general, as the steric bulk of the alkyl substituent on the π bond increases, the rate of addition of the initially formed organoborane product to unreacted alkene decreases.



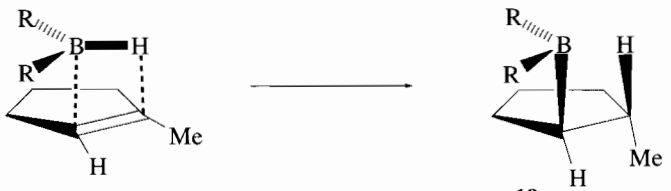
Borane can react with an alkene to give a monoalkylborane. The reactive unit of borane is B—H, and a monoalkylborane has two B—H unit available. It is therefore reasonable that a monoalkylborane can also react with an alkene, forming a dialkylborane. Since the dialkylborane has one B—H unit, it can react with an alkene to form a trialkylborane. Monoalkyl and dialkylboranes are less reactive than diborane itself in reactions with alkenes because alkyl groups are electron releasing, diminishing the Lewis acidity of the boron. The mono-alkylborane derived from 1,2-dimethylcyclopentene, for example, does not react with additional 1,2-dimethyl-cyclopentene but it reacts rapidly with a less hindered alkene such as 1-butene to give a mixed alkyl trisubstituted borane. Similarly, disubstituted boranes react with 1 equivalent of a new alkene to give a mixed trialkylborane, but they are less reactive than monoalkylboranes. The point of these observations is that mono- and dialkylboranes function as new hydroboration reagents, reacting with alkenes in a manner analogous to borane. If a trialkylborane is formed, no hydrogen remains on boron and it cannot react with additional alkene. Brown used this premise to generate several important organoboranes[14] that have become commercially available. Reaction of 2-methyl-2-butene gives **12**, diisoamylborane (diisoamylborane = disiamylborane = Sia_2BH), 2,3-dimethyl-2-butene gives **13** (*tertiary* hexylborane = thexylborane, $ThexBH_2$), and α-pinene (**6**) gives **14** (diisopinocampheylborane = Ipc_2BH). Dienes form cyclic boranes, as with the reaction of 1,5-cyclooctadiene (**15**) with borane to give **16** (9-borabicyclo[3.3.1]nonane = 9-BBN) and the reaction of 2,4-dimethyl-1,4-pentadiene (**17**) to give **18** (3,5-dimethylborinane).

5.2.A.ii. Regioselectivity and Diastereoselectivity. There are two stereochemical advantages in using hindered alkylboranes as hydroboration reagents: increased anti-Markovnikov selectivity and enhanced cis selectivity. This selectivity can be seen in Table 5.2,[15] which compares reactions of borane, disiamylborane and 9-BBN with several alkenes. Hindered boranes show greater selectivity for delivery of boron to the less sterically hindered carbon of terminal alkenes (to $=CH_2$) than does diborane. Perhaps the most dramatic increase in selectivity is observed with internal alkenes since they show poor selectivity with borane, whereas the hindered 9-BBN delivers hydrogen selectively to the less hindered carbon in such systems. Borane gave only 80% addition to the terminal carbon of styrene upon reaction, despite the electronic effects of the phenyl (see Table 5.1). When the bulky 9-BBN added to styrene, however, >98.5% addition to the terminal carbon was observed. It is clear from Table 5.2 that 9-BBN and disiamylborane react with alkenes to give extremely high yields of the anti-Markovnikov addition product. These reagents are more expensive, but 9-BBN is more stable than the pyrophoric diborane, which is almost always used in solution or generated *in situ*.

Table 5.2. Enhanced Anti-Markovnikov Selectivity with Bulky Boranes

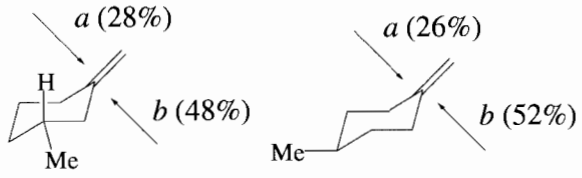
Alkene[a]	BH_3		Sia_2BH		9-BBN	
	a	*b*	*a*	b	*a*	*b*
	45	45	57	33		
	56	43	87	3	90	3
	51	39	86	5		
			98	2	94	1
	94	6	99	1	99.9	0.1
	60	40	98	2		
	57	43	97	3	99.9	0.1
	81	19			98.5	1.5
	48	40	60	40		

[a] C_a is always the less sterically hindered carbon. For disubstituted alkenes, C_a is the carbon distal (most distant from) a pedant substituent. ***a*** and ***b*** refer to the points of attachment of the boron atom.



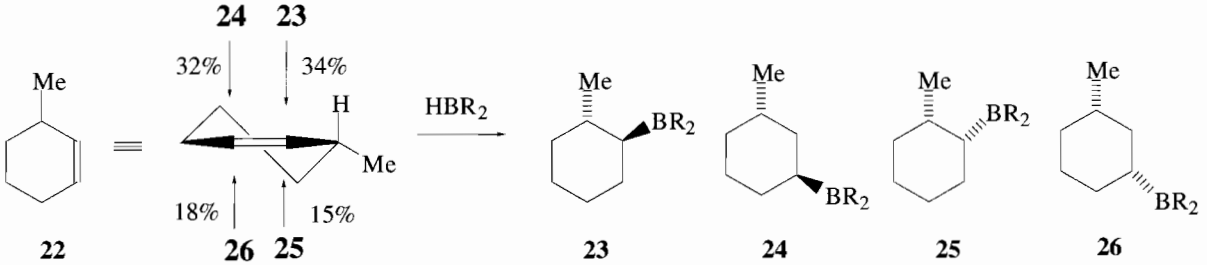
19

Diborane as well as mono- and dialkylboranes give cis addition in reactions with alkenes, as noted above, which is a result of the four-center transition state in which the boron and hydrogen are delivered from the same face, illustrated by hydroboration of 1-methylcyclopentene with R_2BH to give **19.** The methyl-bearing



20 **21**

sp^2 carbon of the alkene is a prochiral center and addition of the borane will generate the (*R*) and (*S*) enantiomers of the trans-isomer. Hydroboration produces only the *trans*-borane (**19**) via cis-addition of BR_2 and H (see *2* in sec. 5.2.A.), making the addition highly diastereoselective. When the compound contains a substituent, diast-ereoselectivity is determined by approach of the borane from the less sterically hindered face of the alkene (secs. 5.2.A.ii, 5.4.B). In general, boranes containing bulky substituents give greater selectivity. Similar factors were discussed for hydride reductions (sec. 4.7.B). For cyclic molecules possessing an exocyclic methylene group, attachment of boron occurs almost exclusively at the terminal alkene carbon.[16,15] As seen for the reaction of **20** and **21** with diborane (the values in parentheses are percentage yields of each organoborane product obtained by reaction from that face), the preferred face of attack is path ***b*** (with the major product resulting from attack at the terminal carbon of the alkene). The borane is sufficiently bulky that the diaxial interaction of the axial hydrogens at C3 and C5 inhibits path ***a*** (opposite the effect seen with hydride reduction of cyclohexanone derivatives –sec. 4.7.C, where path *a* is preferred). As the size of the borane increases, the selectivity for path *b* will also increase

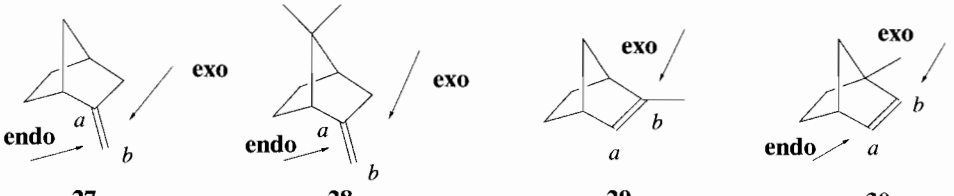


22 **26** **25** **23** **24** **25** **26**

When the alkene is internal and unsymmetrical, as in 3-methyl-1-cyclohexene (**22**), the reaction is more complicated. In addition to the two faces (top and bottom) of the molecule, there are two different and reactive sp^2 carbons of the alkene. Hydroboration leads to four products, **23**, **24**, **25**, and **26**. With diborane

there is virtually no regioselectivity (32:34 for top attack to give **23** and **24** but also 18:15 for bottom attack to give **25** and **26**). There is a preference for delivery of the boron to the face opposite the methyl group (32:18 and 34:15), making **23** and **24** the major products.[15] Similar results were observed when 1,6-dimethylcyclohexene reacted with borane.[17]

Stereoselectivity in addition reactions of borane with bicyclic alkenes is similar to that observed for reduction of bicyclic ketones with hydride reducing agents. Boranes add to norbornene derivatives from the exo face (**27** gave 85% exo attack upon reaction with diborane). In **27–30**, all values are percentage yields of the organoborane products obtained by reaction from that face. Interestingly, only 80% exo attack was observed when **27** reacted with disiamylborane,[15] and the size of the borane appears to have little effect on selectivity.

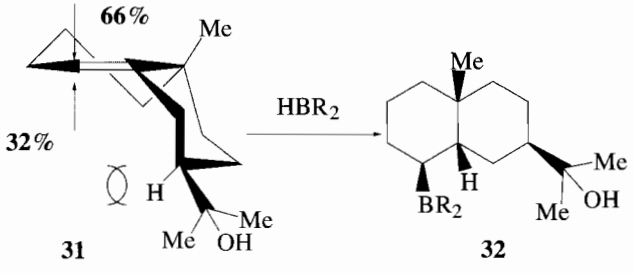


27 **28** **29** **30**

diborane	(a) 85% exo , 15% endo	(a) 10% exo , 56% endo	(a) 99% exo	(a) 47% exo , 1% endo
disiamylborane	(b) 80% exo , 8% endo	(b) 10% exo , 85% endo		(b) 50% exo , 2% endo

Substituents at the 7-position block the exo face and reaction of **28** with diborane gave 56% of the endo product, with only 10% of the exo product. In this case, reaction of **28** and disiamylborane gave 85% of the endo product, showing enhanced selectivity.[15] Similar results were observed when the C=C unit is within the ring.[18] Reaction of 2-methylbicyclo[2.2.1]hept-2-ene (**29**) with diborane shows the expected exo selectivity and also a preference for attack at the less hindered carbon. The C=C unit in **30** has no steric features to distinguish one carbon from the other, and reaction with diborane gives essentially a 1:1 mixture of regioisomers, although there is a marked preference for exo delivery of boron.

When the alkene is part of an edge fused bicyclic system (bicyclo[*m.n.*0] systems), the regio- and stereoselectivity is influenced by the conformation of the molecule and the relative stereochemistry of the substituents. Hydroboration of **31,** in Heathcock's synthesis of eudesmanes, led to a 66:34 mixture of boranes with attack from the top face predominating (giving **32**).[19,15]

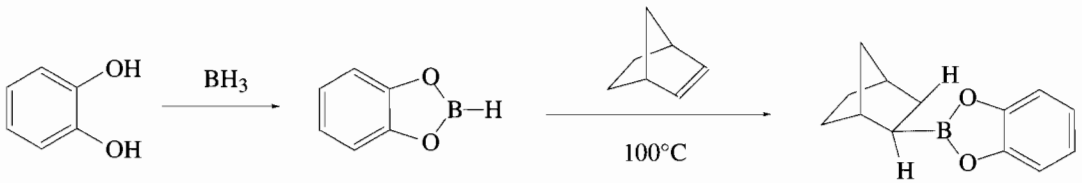


31 **32**

Dialkylboranes can disproportionate, although hindered alkylboranes are relatively stable, and this limits their utility in reactions with alkenes. One solution to this problem was the discovery that boranes containing heteroatoms stabilize the borane and are easy to prepare. Diborane reacts with alcohols such as methanol to

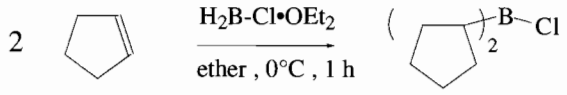
$$2\ \text{MeOH} \xrightarrow{BH_3\ ,\ THF} (MeO)_2B\text{-}H + 2\ H_2$$

form dimethoxyborane [$(MeO)_2BH$].[20] Similarly, alkyl glycols react to give cyclic dialkoxyborates,[21] but these are somewhat unreactive in subsequent reactions with alkenes. Catecholborane [(**34**), formed by the reaction of borane with catechol, (**33**)] reacts with alkenes to give an alkoxyborinate,[22] but requires heating to ≈ 100°C. An example is the reaction of **34** with norbornene to form the exo-alkoxyborinate (**35**).[22] An advantage in using catecholboranes is that the boronic acid byproducts are more easily hydrolyzed than the corresponding dialkylboranes (sec. 5.4.A).



33 **34** **35**

Chloroboranes are another class of heteroatom-substituted boranes. Dichloroborane (Cl_2BH) and monochloroborane ($ClBH_2$) are formed by the reaction of diborane with varying proportions of boron trichloride etherate (BCl_3•OEt_2). In ether solvents, both reagents are formed as the etherate.[23] An alternative synthesis was the reaction of HCl with borane•THF,[24] but reduction of boron trichloride with lithium borohydride in ether proved to be the most useful route.[23]

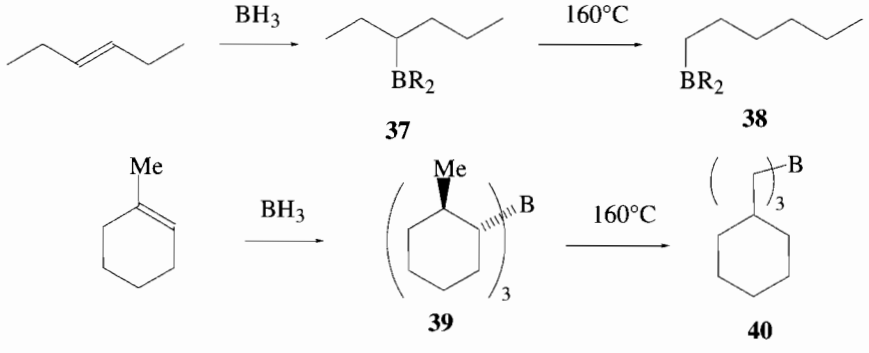


36

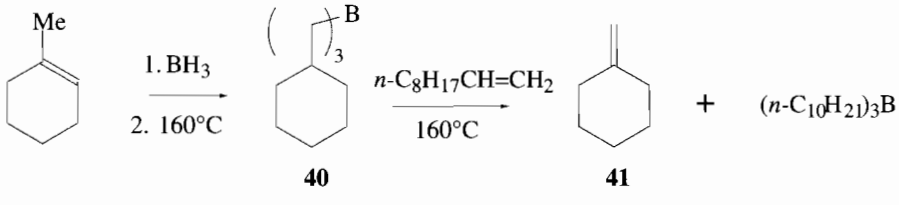
In contrast to catecholborane, chloroborane reacts with alkenes at 0°C to give a dialkyl chloroborane, as in the formation of **36** from cyclopentene.[25] Chloroboranes show great regioselectivity for attachment of boron at the terminal carbon of 1-alkenes (anti-Markovnikov addition).[26] 1-Hexene gave 99.5% of the terminal borane, for example, whereas similar reaction with diborane gave only 94%.[15b] Similarly, styrene reacted to give 96% of the terminal borane compared with 81% from diborane, despite the electronic effects of the phenyl group. Internal alkenes show less selectivity as in the reaction of 4-methyl-2-pentene, which gave only 60% delivery of boron to the 2-position. 2,3-Dimethyl-2-butene, however, reacted to give 99.7% of product with the boron moiety at the 2-position. The addition of chloroborane to alkenes is less influenced by steric factors than the similar addition of mono- or dialkylboranes, accounting for the generally poorer selectivity exhibited by chloroborane in its reactions with internal alkenes.

5.2.A.iii. Isomerization of Alkylboranes. One of the early discoveries of organoboranes was their tendency to undergo isomerization if the temperature approached 160°C. This isomerization involves migration of the boron from a more to a less substituted position, usually giving the terminal alkylborane as the predom-

inant isomer.[27] Reaction of 3-hexene with borane initially gave 3-boranylhexane **37**), but heating induced rearrangement to hexylborane (**38**). This isomerization can be used to advantage in subsequent reactions of boranes, such as oxidation to alcohols (sec. 5.4.A). If the initial hydroboration occurs ***on*** a ring (as in **39** from the cyclic alkene), isomerization will put boron at the terminal position of an alkyl side chain, as in the conversion of 1-methylcyclohexene to **40** via heating **39**.[28,29b]

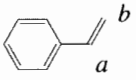
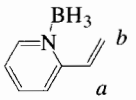
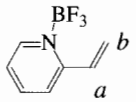
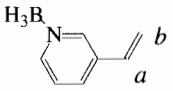
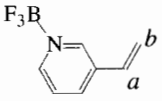
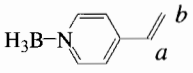
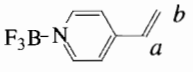
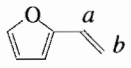
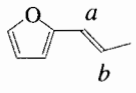
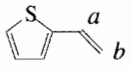
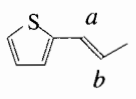


This process is synthetically important because a sacrificial alkene such as 1-decene or 1-hexadecene can be added to bias the overall reaction toward a specific target alkene. Mechanistically, thermal isomerization apparently involves a series of reversible elimination reactions of borane followed by re-addition in an anti-Markovnikov manner.[2] If the sacrificial alkene has a significantly higher boiling point, then the desired alkene can be distilled from the reaction medium.[27a] The sacrificial alkene must not boil < 160°C, however, which is the temperature required for borane isomerization. This process makes it possible to isomerize the double bond of an alkene to a less substituted isomer, a process that Brown termed **contrathermodynamic isomerization**.[29,30] In this way, methylenecyclohexane (**41**) was prepared from 1-methylcyclohexene by addition of 1-decene to the dominant borane species, **40**.[28] α-Pinene was converted to β-pinene in 54% yield[28] by contrathermodynamic isomerization. Significant amounts of endocyclic isomers often accompany this hydroboration-bond migration process with exocyclic alkenes and separation of these isomeric by-products can be difficult, limiting the utility of this process.



5.2.A.iv. Hydroboration of Dienes and Heteroatom-Containing Alkenes. Hydroboration has also been reported with a variety of heteroaryl alkenes.[31] The regioselectivity of hydroboration with several heterocyclic alkenes is summarized in Table 5.3.[31] Styrene shows the expected selectivity for addition of boron to the terminal carbon. The presence of nitrogen in the pyridyl derivatives changes the selectivity for addition from the terminal carbon (the β-carbon) to the α-carbon, even when the reagent is not sterically hindered. Nitrogen releases electrons to the π-bond and the carbon closest to nitrogen receives the most

Table 5.3. Hydroboration of heterocyclic alkenes[a]

Alkene	$BH_3 \cdot SMe_2$		9-BBN		$(CH_2)_4BH$		Sia_2BH	
	a	*b*	*a*	*b*	*a*	*b*	*a*	*b*
	19	81	2	98			2	98
	67	33	37	63	83	17	85	15
	83	17	44	56	84	16	88	12
	50	50	8	92	23	77	17	83
	40	60	14	86	29	71	13	87
	100	0	69	31	42	58	57	43
	85	15	74	26	59	41	53	47
	16	84	3	97	0	100	0	100
	96	14	88	12	98	2	95	5
	12	88	2	98	0	100	0	100
	89	11	94	6	95	5	96	4

[a] The labels **a** and **b** refer to the point of attachment of the boron atom.

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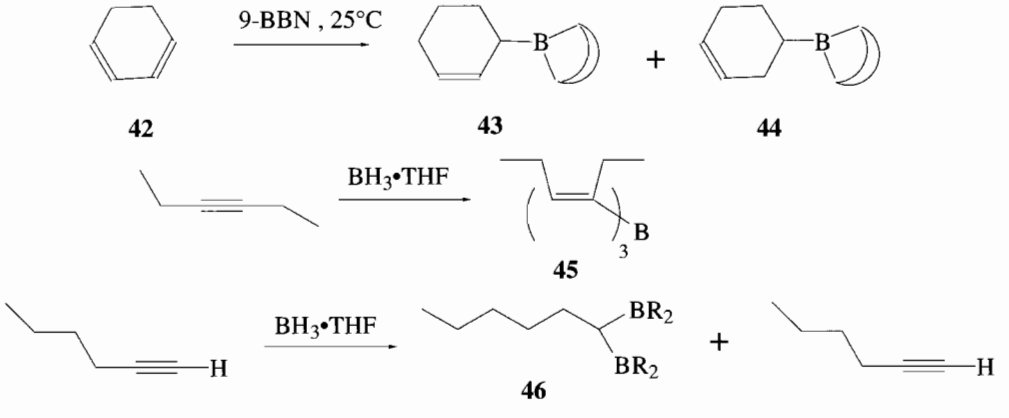
electron density. With diborane, this electronic effect makes attack at C_a preferred when the nitrogen is ortho (2-pyridyl) or para (4-pyridyl). The meta compound (3-pyridyl) does not transmit electrons through the π-system as effectively, and the selectivity is poorer. When excess borane is used, the first equivalent coordinates to nitrogen and the second to the alkene. Addition of BF_3 has the same effect, allowing the use of a single equivalent of borane. The bulky reagent 9-BBN usually shows high selectivity for attack at C_b with 2-pyridyl and 3-pyridyl substituted alkenes, but the electronic effect of the aromatic groups also leads to significant amounts of attack at C_a. When the nitrogen is further away (as in 4-pyridyl), the steric and electronic effects are less important and attack at C_a is preferred. An analogous effect is seen with furan and thiophene derivatives.

Hydroboration of conjugated dienes raises the usual issue, 1,2- versus 1,4-addition. Conjugated dienes such as 1,3-cyclohexadiene (**42**) gave mainly 1,4-addition (85:10 **43**:**44** with 9-BBN is a typical example). Reaction with dibromoboranes, however, favors the dihydroboration product.[32] In the case of the symmetrical dienes **42**–**44** could result from 1,2-addition to different carbons of one C=C moiety. In this example, however, **43** is considered to be a 1,4-addition product and **44** is considered to be a 1,2-addition product. As the size of the ring increases, dihydroboration increases at the expense of mono-hydroboration. Six-membered rings are less reactive in hydroboration reactions relative to larger and smaller rings.[33] Nonconjugated dienes such as 1,4-cyclohexadiene show the expected independence of the double bonds, giving a mixture of mono-hydroboration and dihydroboration products.[33]

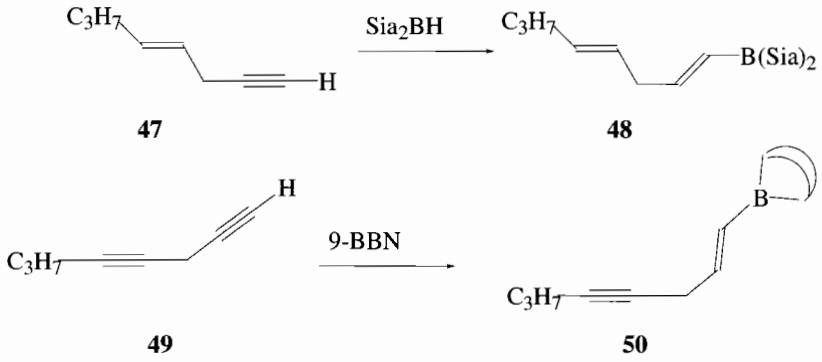


5.2.B. Alkenylboranes

Boranes add to one π bond of an alkyne just as they add to the π bond of an alkene, and the product is the corresponding alkenyl (vinyl) borane, which undergoes many of the same reactions as alkylboranes.[34] Internal alkynes such as 3-hexyne react with diborane to give the trialkenylborane (**45**) in moderate yield, but terminal alkynes such as 1-hexyne give predominantly the 1,1-diboranyl derivative (**46**) plus unreacted alkyne,[35] which occurs because hydroboration of the alkene product competes with reaction of the starting, and is the dominate reaction when terminal alkynes are involved. This secondary reaction can be moderated by the use of hindered boranes such as 9-BBN or Sia_2BH[36] since these reagents react faster with alkynes than with vinylboranes. This rate difference is apparent in the reaction of octa-4-ene-1-yne (**47**) with Sia_2BH to

give the (*E,E*)-dienyl-borane, **48.**[35] Unhindered terminal alkenes react with organoboranes faster than do alkynes, or at least competitively, especially with unhindered boranes such as diborane.

9-BBN reacts with terminal alkynes to give the trans-alkenylborane but significant amounts of 1,1-diborane are also formed, due to the secondary addition to the alkene mentioned above.[37] Brown suggested this was due to the accessibility of the boron to one face of 9-BBN, which can be corrected by addition of a large excess of the alkyne, which is easily recovered, although this is a poor choice for the hydroboration of expensive alkynes. The alkenylborane derived from 9-BBN is stable enough for isolation and can be conveniently purified, in contrast to most other alkenylboranes. The 9-BBN reagent reacts faster with terminal alkynes[38] than it does with internal alkynes, as shown by the conversion of octa-1,4-diyne (**49**) to **50**.[34] Terminal alkynes react with boranes to give the trans-alkenylborane and 9-BBN reacts with internal alkynes to give the (*Z*)-alkenylborane (with the alkyl groups cis-).[36]



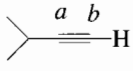
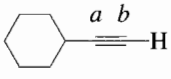
Catecholborane (**34**) reacts with alkynes but requires reaction temperatures that are higher than those used for reaction of alkynes and alkylboranes, as noted earlier. Phenylethyne, for example, reacts with **34** to give excellent yields of vinyl borane, but the reaction must be done in refluxing THF.[39] Alkenylborinates derived from catecholborane are stable and can be isolated by distillation or recrystallization.[34]

Thexylborane has two active hydrogens on boron, allowing reaction with two equivalents of an alkyne. Reaction of thexylborane with 2 equivalents of 1-nonyne gave primarily (but not exclusively) the *trans-, trans*-dialkenylborane **51.**[40] Reaction of thexylborane with relatively hindered terminal alkenes or internal alkenes gave only the monoalkyl derivative. These vinylboranes can react with terminal alkynes (just as dialkylboranes react with additional alkene) to give unusual mixed (alkyl-thexyl-alkynyl) boranes that can be used in other transformations (secs. 5.3, 5.4).[40] Reaction of monochloroborane etherate with alkynes gives a dialkenyl-borane.[41] Significant amounts of the 1,1-diborane are usually formed in reactions with terminal alkynes, but using a 40% excess of the alkyne leads to nearly quantitative yields of the dialkenylborane.[42] A more attractive alternative is to use dibromoborane•methylsulfide ($HBBr_2$•SMe_2),[43] which reacts by simple addition with internal alkynes but reacts with terminal alkynes to give the dialkenylborane, without formation of the 1,1-diborane byproduct.[44]

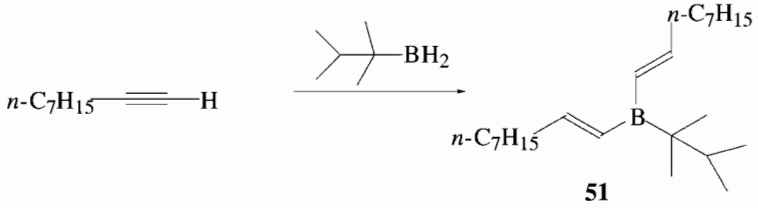
Internal alkynes react with boranes to form the cis-alkenylborane. This, of course, is due to the four-center transition state leading to the vinylborane product. The reaction is selective for the less hindered of the two

available alkynyl carbons due to the steric demands of the hydroboration reagent as well as the size and electronic characteristics of the alkynyl substituents. These results are similar to those observed with alkenes when steric factors are the primary influence on the reaction, but the linear nature of alkynes leads to less selectivity than similar reactions with alkenes. When electronic factors dominate, selectivity in the hydroboration reaction is diminished and mixtures of alkenylboranes are formed.[34] The regioselectivity for reaction of several terminal alkynes with hydroboration reagents is shown in Table 5.4.[34] The reagents of choice for selectivity in the hydroboration of alkynes depends largely on steric factors with most hydroboration reagents, as seen in Table 5.4. When electronic factors are involved, the selectivity is diminished and can be reversed, depending on the choice of organoborane reagent.

Table 5.4. Directive Effects for Hydroboration of Substituted Internal Alkynes[a]

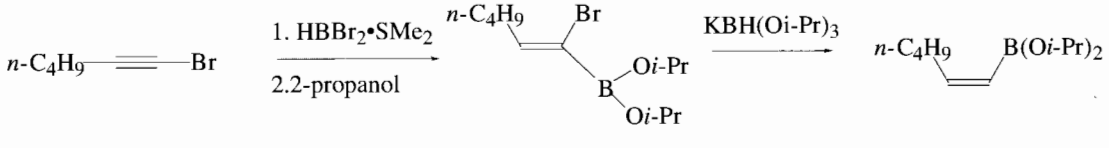
Reagent	n-C_3H_7–C≡C–H (a / b)		 (a / b)		 (a / b)		Ph–C≡C–H (a / b)	
	a	**b**	**a**	**b**	**a**	**b**	**a**	**b**
Diborane	40	60	25	75				
Thexylborane	39	61	19	81				
Disiamylborane	39	61	7	93	9	91	19	81
Dicyclohexylborane	33	67	8	92	8	92	29	71
$HBBr_2$•SMe_2	25	75	4	96	9	91	64	36
9-BBN	22	78	4	96	4	96	65	35

[a] The labels **a** and **b** denote the point of attachment of the boron.



51

An alternative route to vinylborinates adds the dimethyl sulfide complex of $HBBr_2$ to 1-bromo-1-alkynes. Reaction of 1-bromo-1-hexyne (**52**) gave **53** in 87% yield, after treatment with an alcohol (2-propanol in this case).[45] Subsequent reduction of the bromide with potassium triisopropoxyborohydride [$KBH(Oi\text{-}Pr)_3$] generated cis-vinylborane (**54**) in 89% yield.



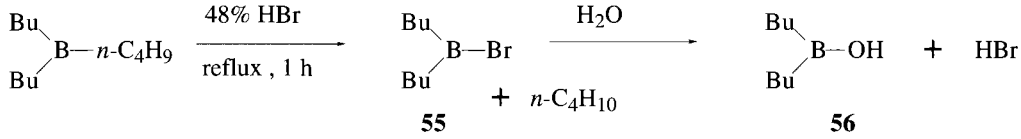
52 **53** **54**

5.3. SYNTHETIC TRANSFORMATIONS

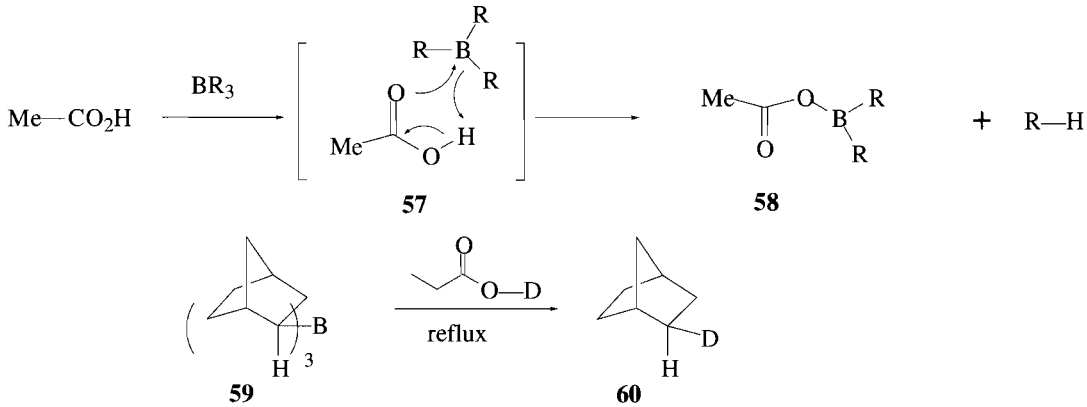
Sections 5.1 and 5.2 described methods for preparing organoboranes and discussed the regio- and stereoselectivity associated with their formation from alkenes and alkynes. The synthetic value of organoboranes, however, lies in their ability to serve as intermediates for the transformation of alkenes and alkynes into other useful functional groups. The discussion will begin with the reactions of organoboranes to generate functional groups that do not contain heteroatoms. Heteroatom functional groups will be discussed in Sections 5.4–5.5.

5.3.A. Protonolysis

Alkylboranes react with oxygen and are pyrophoric (the lower alkylboranes burn with a green flame). The product of this reaction is an alkylborinate (R_2BOR). Although tri-*n*-butylborane (and higher analogs) do not spontaneously burst into flame, they remain sensitive to oxygen, and hydroboration reactions should be protected from air.[46] Exceptions are 9-BBN and catecholborane, which are much less reactive with oxygen. This



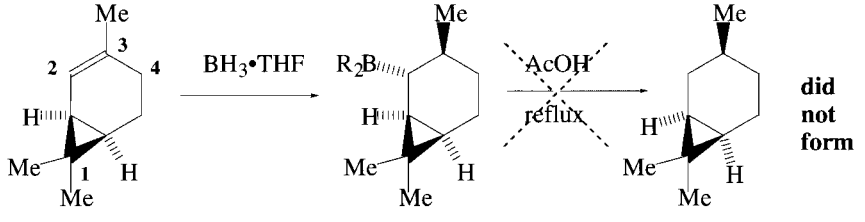
sensitivity to oxygen stands in contrast to the relative insensitivity of alkylboranes to water and alcohol. Trimethylborane, for example, reacts with water at 180°C after 7 h to give only 69% of dimethylborinic acid.[47] Not only is the reaction with water, alcohols, and phenols slow, but addition of aqueous alkali actually stabilizes trialkylboranes to hydrolysis.[48] Alkylboranes can be hydrolyzed with aqueous mineral acids, but only under vigorous conditions. Conversion of tri-*n*-butylborane to di-*n*-butylboronic acid (**56**) required heating with 48% HBr at reflux for 1 h and proceeded through the intermediate bromoborane, **55**.[49] A more useful method for protonolysis is the reaction of alkylboranes and carboxylic acids at temperatures near 100°C.[50]



In a typical reaction, two of the alkyl groups of the trialkylborane are removed at ambient temper-ature on treatment with propionic acid.[51] Protonolysis of the third alkyl group requires refluxing in diglyme, although the yields of hydrocarbon derived from the alkyl portion of the borane are excellent.[51] Primary alkyl groups

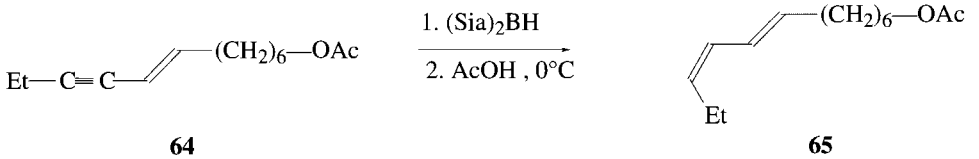
undergo protonolysis faster than secondary alkyl. Protonolysis proceeds even in the presence of oxygen, nitrogen, chlorine and sulfur substituents. The mechanism of protonolysis begins with coordination of the boron to the carbonyl oxygen of the acid, followed by transfer of hydrogen to the carbon of the alkyl group via a six-center transition state, **57**.[52] Synfacial transfer of hydrogen leads to retention of configuration when boron is transferred to oxygen and hydrogen is transferred to carbon, leading to R—H and **58**. This retention of configuration during the reaction is easily observed in the reaction of tri-exo-norbornyl-borane (**59**) with refluxing deuteropropionic acid. The product is exo-deuteronorbornane (**60**), where the transfer of deuterium proceeded with complete retention of configuration.[53]

The protonolysis reaction is sensitive to steric effects, presumably due to steric interactions in the transition state (see **57**). This sensitivity to steric hindrance can be seen in organoborane **62**, formed by hydroboration of (+)-Δ^2-carene (**61**).[54] Protonolysis with glacial acetic acid at room temperature ***failed*** to give carane (**63**), and heating the borane in refluxing acetic acid gave 16 different products.[55] The failure of the reaction is due to the increased steric bulk around the boron, inhibiting transfer of the hydrogen, which contrasted with the reaction of the borane of (+)-Δ^3-carene (double bond between C3 and C4 leading to the product with the boron at C4), which reacted with propionic acid at 150°C to give carane in 45% yield.[56]



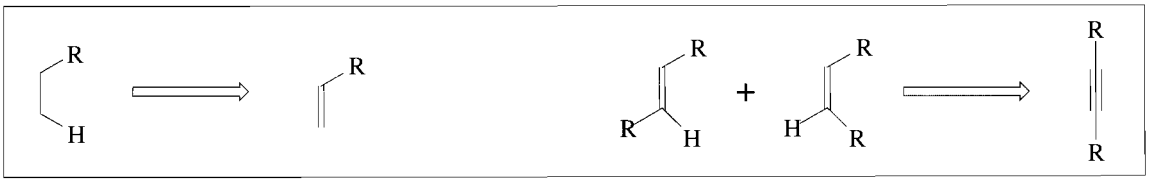
61 **62** **63**

Protonolysis of alkenylboranes generates an alkene and this reaction is faster than the analogous protonolysis of alkylboranes.[57] Once again, protonolysis proceeds stereospecifically with retention of configuration. In Negishi's synthesis of the sex pheromone of *Lobesia botrana* (**65**), hydroboration of **64** was followed by protonolysis with acetic acid at 0°C to give **65**, for a net conversion of an alkyne to an alkene.[58] As with alkylboranes, protonolysis of vinylboranes with deuteroacetic acid allows the synthesis of deuterated alkenes.



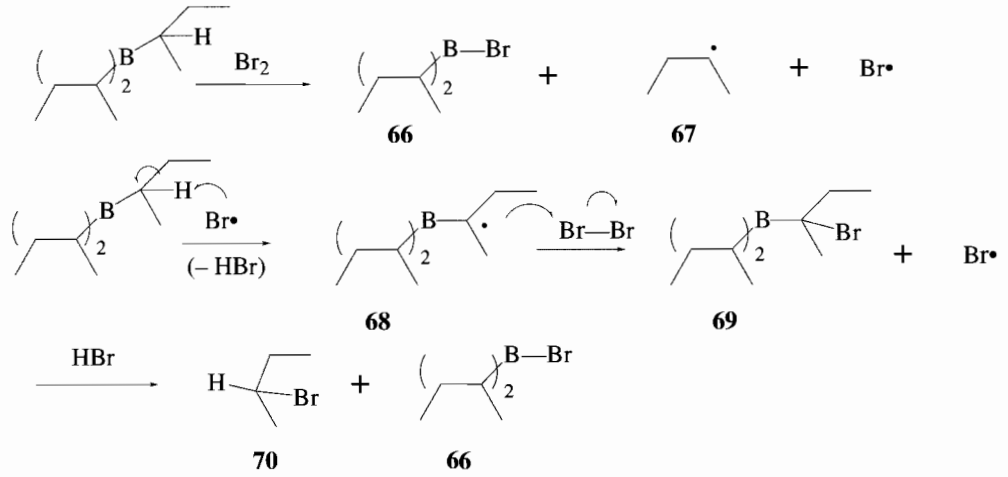
64 **65**

The functional group transforms pertinent to protonolysis are

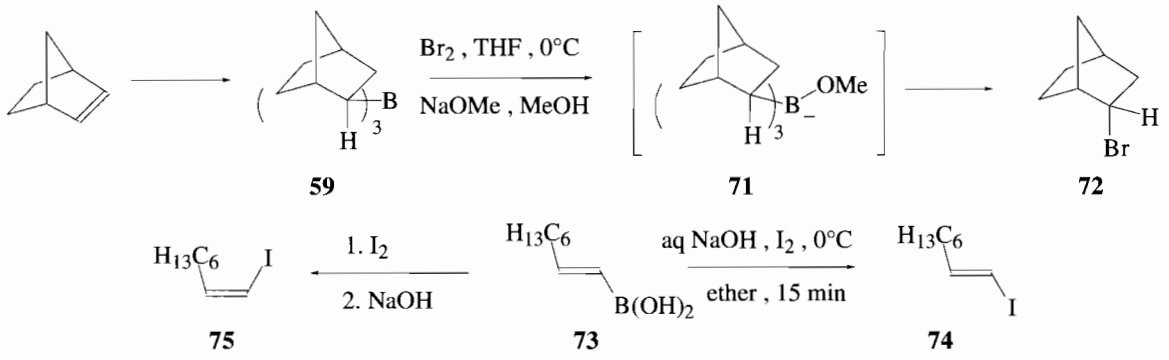


5.3.B. Halogenation

If boron of an alkylborane could be replaced with a halogen, the product would be an alkyl halide. However, reaction of alkylboranes (neat) with chlorine, bromine, or iodine is very difficult.[49a] When halogenation is done with bromine or iodine dissolved in dichloromethane, however, the reaction is fast and is synthetically useful.[59] A simple example is the reaction of alkenes with boranes followed by addition of bromine, which leads to the alkyl bromide. An example is taken from the synthesis of 2-bromobutane (**70**) from 2-butene in 88% yield.[60] The bromination occurs by a free radical mechanism. Initial reaction with bromine generates a



bromine radical (Br•), bromoborane (**66**), and 2-butyl radical (**67**). Subsequent reaction with tri-*sec*-butylborane generates the radical at the carbon α to the boron (**68**), and reaction with bromine generates α-bromoborane (**69**). The final reaction is between **69** and HBr to generate the observed products, **70** and **66**.[59] There are many cases where an organoborane does not react very well with bromine, but addition of bases such as sodium hydroxide or sodium methoxide catalyzes the reaction, allowing it to proceed at temperatures as low

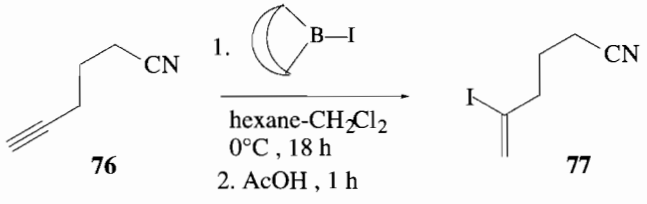


as 0°C.[61] With this modification, formation of bromides (such as **70**) and iodides via hydroboration is synthetically useful. Hydroboration of norbornene initially gives the exo-borane (**59**), but subsequent reaction with bromine and the borane is slow. Addition of NaOMe converts **59** to an *ate* complex, **71** and this reacts rapidly with bromine to give endo-2-bromonorbornane (2-bromobicyclo[2.2.1]heptane, **72**) in 75% yield.[62] It is interesting to note that the halogenation reaction proceeds with net inversion of configuration at

the carbon bearing the boron, suggesting backside attack by bromine. Formation of the *ate* complex and reaction with bromine involves ionic intermediates, not free radical intermediates as noted in reactions of **66**.

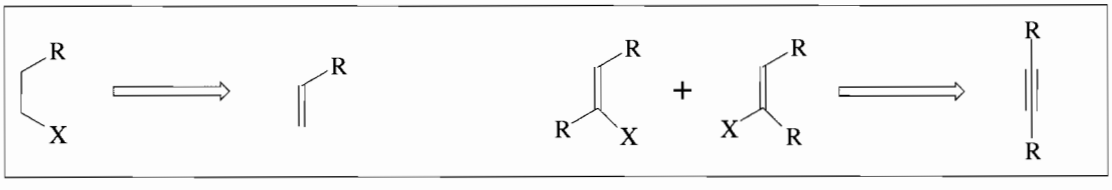
Halogenation of vinylboranes generates vinyl halides. Both cis and trans halides are available by modification of the reaction conditions. When trans-alkenyl boronic acid (**73**, derived from 1-octyne) was treated with iodine and sodium hydroxide, trans-1-iodo-1-octene (**74**) was formed in 90%.[63] When the boronic acid was treated with iodine and then with base, the (*Z*)-alkenyl iodide (**75**) was produced.[64] Vinylboranes derived from internal alkynes lead to cis–trans mixtures with both of these procedures. Boronic acids derived from alkynes and catecholborane give the (*Z*)-bromide on addition of bromine followed by sodium hydroxide.[65]

There is an alternative method for converting alkynes to vinyl iodides using B-iodo-9-BBN.[66] Reaction of cyano alkyne **76** with reagent, followed by protonolysis with acetic acid gave a 74% yield of **77** in Hodgson's synthesis of (–)-periplanone B.[67] This procedure is more direct and avoids some potential problems with previous procedures.



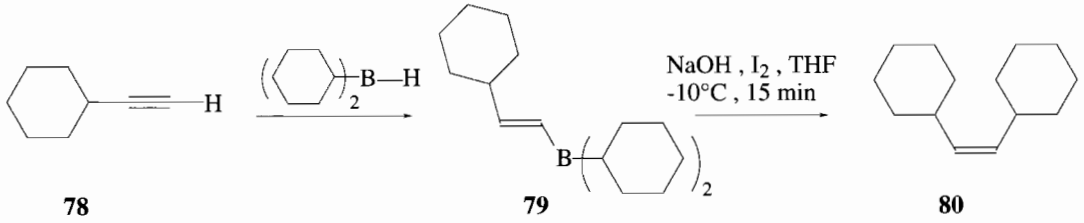
76 **77**

The halogenolysis reaction makes possible the following transformations:



5.3.C. Alkene, Diene, and Alkyne Synthesis

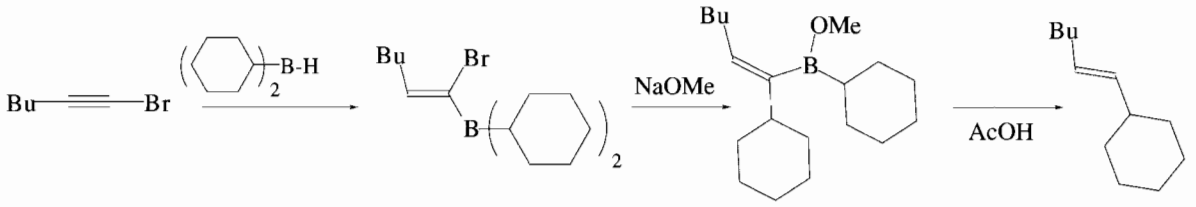
Vinylboranes are versatile intermediates, and there are modifications that convert them to alkenes. Hydroboration of a terminal alkyne such as cyclohexyl acetylene (**78**) with dicyclohexylborane gave (*E*)-alkenylborane (**79**). Subsequent treatment with iodine and sodium hydroxide resulted in transfer of an alkyl group from boron to the alkenyl carbon, generating *cis*-1,2-dicyclohexylethene (**80**) in 77% yield (92% isomeric



78 **79** **80**

purity)].[68] Although iodine and base are used, the product is an alkene and not a vinyl iodide. The differences in reaction conditions for halogenation and elimination are subtle and care must be taken to direct the reaction one way or the other. Conversion to the alkene is believed to proceed via initial coordination of base

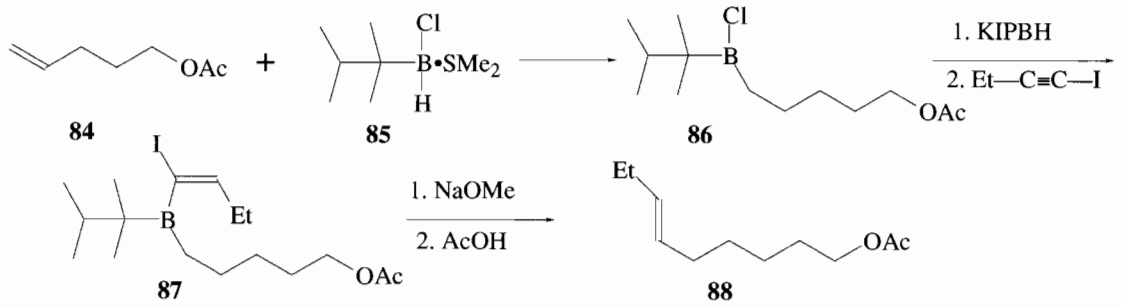
to the boron (to form an *ate* complex), followed by formation of an iodonium (or halonium) ion. This positively charged intermediate facilitates a 1,2-B→C alkyl shift, which is followed by trans elimination of iodine and boron.[9] A major limitation to this procedure is that it is successful only with symmetrical dialkylboranes. Mixed boranes such as those formed from thexylborane and alkynes lead to migration of both the thexyl group and the alkyl group, giving isomeric mixtures. Halogenation can compete with the elimination reaction, as expected, and this led to development of an alternative cis-alkene synthesis, illustrated by the reaction of 4-octyne and 9-BBN. The product of this reaction was *cis*-4-octene in 98% yield, after protonlysis in refluxing methanol.[69] *cis*-4-Octene was also obtained (in 99% yield) in < 15 mi. at 25°C, if 1% acetic acid was added to the reaction.



52 **81** **82** **83**

trans Alkenes can be formed by manipulating the intermediate vinylborane. This new sequence involves hydroboration of a 1-bromoalkyne, treatment with base to induce the B→C alkyl shift, and then protonolysis to give the trans alkene.[70] The conversion of 1-bromo-1-hexyne (**52**) to **81** shows that a borane can be used that has alkyl groups different from those found in the alkyne starting material. Treatment with sodium methoxide induced rearrangement to **82** and protonolysis with acetic acid gave the final product, (*E*)-1-cyclohexyl-1-hexene (**83**).

In both of these alkene syntheses, the B→C alkyl shift proceeded with retention of configuration.[71] Both alkene-forming reactions have been used for the synthesis of prostaglandin intermediates, in which the stereoselectivity of the processes is valuable.

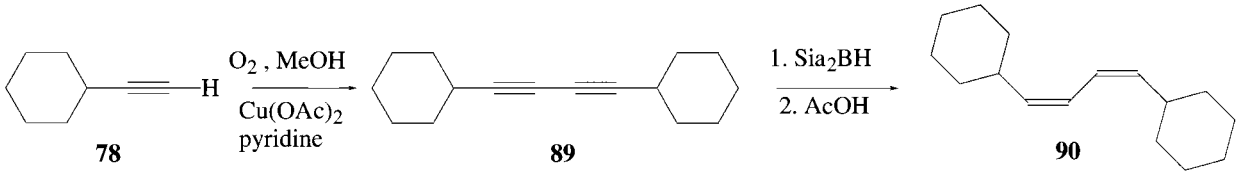


84 **85** **86** **87** **88**

The dimethyl sulfide complex of chlorothexylborane (see **85**) can be used to generate alkenes from alkynes. Alkenes and alkynes can be coupled using this reagent, as illustrated by the reaction of O-acetylpent-4-en-1-ol (**84**) and **85**, which gave chloroborane **86** as the initial product. Subsequent reaction with potassium triisopropoxyborohydride (KIPBH) generated an *ate* complex which reacted with 1-iodo-1-butyne to give **87**. Final treatment with sodium methoxide followed by protonolysis gave *trans*-5-octenyl ethanoate (**88**).[72] An

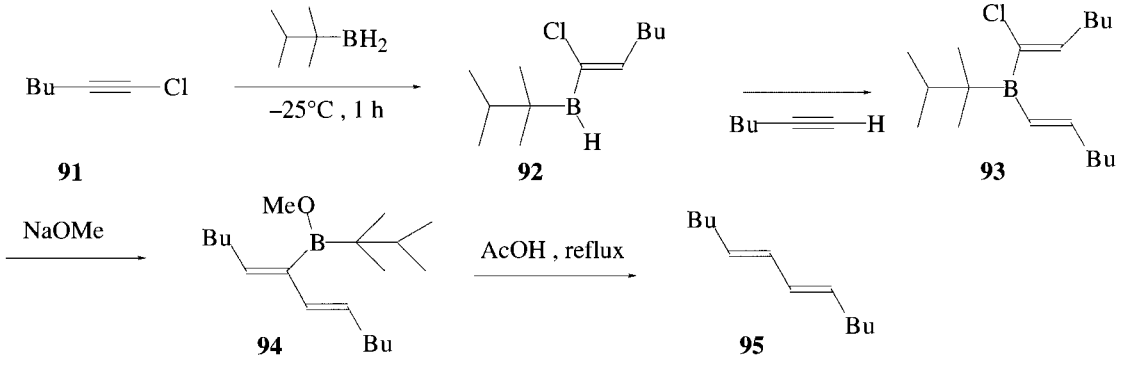
alternative synthetic route to (*E*)-alkenes from alkenyldialkyl-boranes has been developed using cyanogen bromide (BrCN).[73]

Related techniques have been developed to prepare (*Z*-,*Z*)-; (*Z*-,*E*)- and (*E*-,*E*)- dienes. Hydroboration of diacetylenes followed by protonolysis is a convenient route to (*Z*-,*Z*)-dienes, as in the conversion of **89** to **90**.[74] The requisite symmetrical diacetylenes are prepared by oxidative coupling with oxygen and cuprous chloride, as in the conversion of 1-cyclohexylethyne (**78**) to **89**.[75] Unsymmetrical conjugated dienes can be prepared by formation of a diacetylene *ate* complex, prepared from disiamylmethoxyborane by sequential reaction with different acetylides.[76] A similar borane route to unsymmetrical diacetylenes uses dicyclohexyl methyl-thioborane.[77]



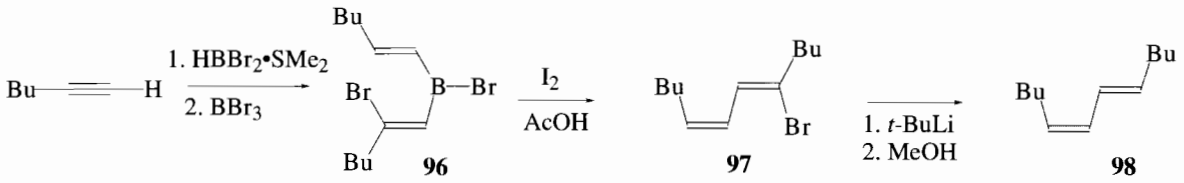
78 **89** **90**

(*E*-,*E*)-Dienes are prepared by a different route. Hydroboration of a 1-chloroalkyne such as 1-chloro-1-hexyne (**91**), with thexylborane, gives addition product **92**. Treatment of **92** with 1-hexyne leads to a second addition to give alkyldialkenylborane **93**,[78] and when this reacts with sodium methoxide a B→C shift gives **94** and final protonolysis generated the (*E*-,*E*)-diene [**95**, (5*E*,7*E*)-dodecadiene].[78] Since the two alkyne units are incorporated in different steps, this technique is suitable for the preparation of both symmetrical and unsymmetrical dienes. An alternative route to symmetrical (*E*-,*E*)-dienes involves treatment of dialkenylchloroboranes with methylcopper.[79,44] Dienes can also be prepared from dialkyl-alkenylboranes by reaction with sodium methoxide and then cuprous bromide-dimethyl sulfide ($CuBr{\bullet}SMe_2$).[80]

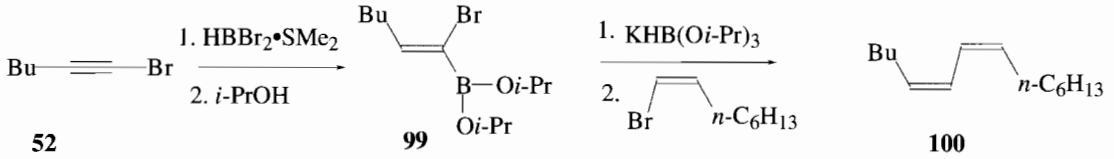


91 **92** **93** **94** **95**

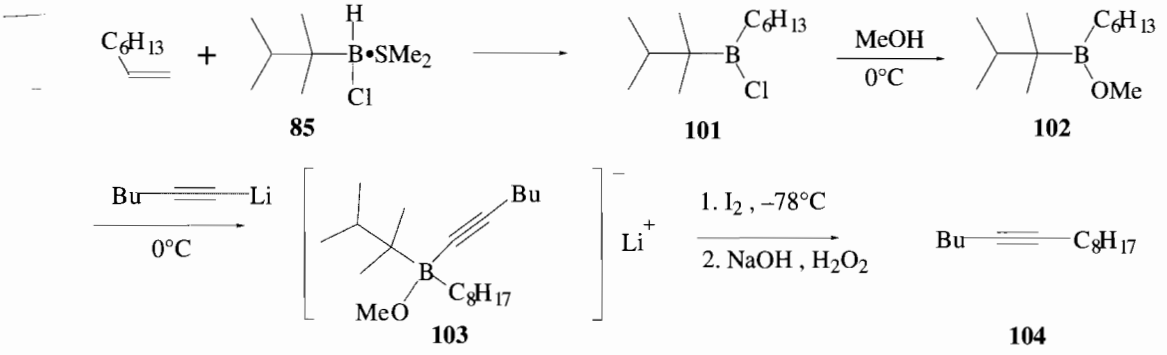
(*Z*-,*E*)-Dienes can be prepared by the reaction of alkynes with dibromoborane. Initial reaction of 1-hexyne with the dimethyl sulfide complex of $HBBr_2$ required addition of boron tribromide (BBr_3) to give the borane that was free of dimethyl sulfide.[81] In the subsequent reaction with additional 1-hexyne, divinylborane (**96**) was formed, which was treated with iodine/acetic acid to give bromodiene (**97**). Bromine–lithium exchange was induced by the addition of *tert*-butyllithium, leading to the vinyllithium reagent (secs. 8.5.A, 8.5.B), and quenching with MeOH gave **98**.



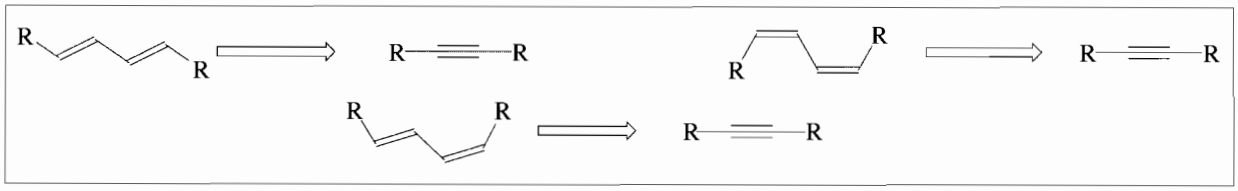
(*Z,Z*)-Dienes can be formed by a different sequence. Reaction of 1-bromo-1-hexyne (**52**) and the complex $HBBr_2{\bullet}SMe_2$ was followed by reaction with potassium triisopropoxyborohydride to form vinylborane **99**. Subsequent coupling with *cis*-1-bromo-1-octene gave the (*Z*-,*Z*)-diene (**100**) in 87% (>99% *ZZ*).[82] Internal alkynes can also be coupled to give dienes using this procedure,[83] and terminal alkynes lead to (*E,Z*)-dienes, but the regioselectivity of this latter reaction is poor.[83,84] Two different alkynes can also be coupled to form unsymmetrical dienes.[85]



A synthetic route to unsymmetrical alkynes has been reported, which essentially couples an alkene to a terminal alkyne.[86] Reaction of chlorothexylborane (**85**) and 1-octene gave **101** and quenching with methanol gave **102**. An *ate* complex (**103**) was generated when this borane reacted with 1-lithio-1-hexyne and iodination, and oxidation led to a 75% yield of 5-tetradecyne (**104**).[86] Two alkyne byproducts were formed, however, resulting from transfer of different alkyl groups to carbon and causing isolation problems for the alkyne of interest. Synthetic applications of this reaction are limited by the common observation that different alkyl groups are transferred from species such as **103** to give mixtures of alkyne products.[87]

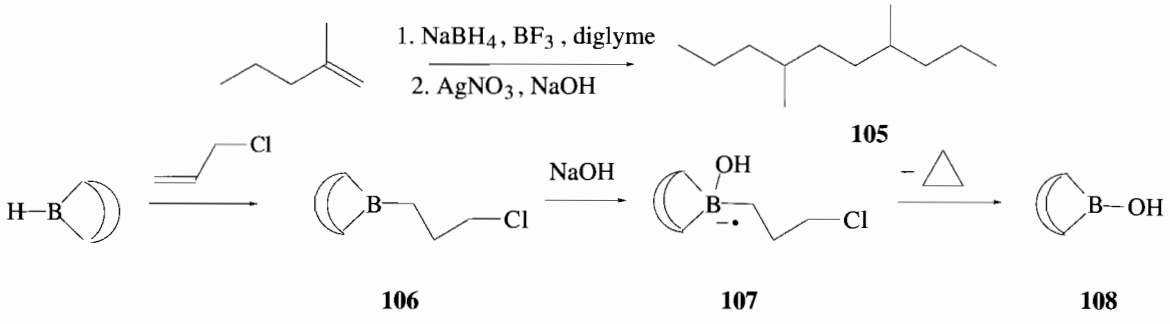


The variety of reactions illustrated in this section shows the range of alkyne–diene transforms.



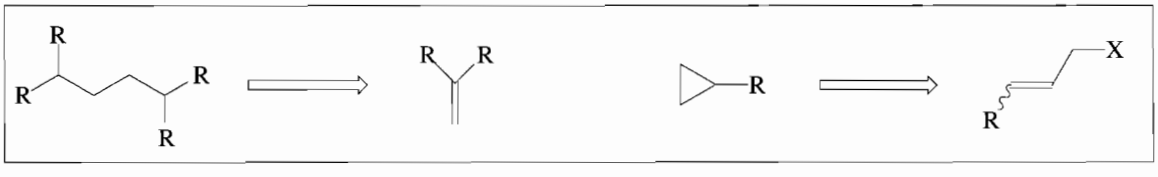
5.3.D. Coupling, Isomerization, and Displacement

Organoboranes can be used as synthetic intermediates to make carbon–carbon bonds. As a practical matter, this reaction couples two alkene moieties. Both symmetrical and unsymmetrical coupling products can be formed, although the method is most useful for symmetrical coupling. Initial hydroboration is followed by treatment with basic silver nitrate ($AgNO_3$), to oxidatively remove boron from the molecule with concomitant coupling of the two alkyl fragments, generating an alkane. A typical example is taken from the hydroboration of 2-methyl-1-pentene, which gave the symmetrical coupling product 4,7-dimethyldecane (**105**) in 61% yield on treatment with silver nitrate and NaOH.[88] The reaction probably proceeds via an alkyl silver intermediate. When this reaction is applied to two different alkenes ($RCH{=}CH_2$ and $R^1CH{=}CH_2$, for example), statistical coupling leads to a mixture of $RCH_2CH_2CH_2CH_2R$, $R^1CH_2CH_2CH_2CH_2R^1$ with only 50% of the cross coupled alkane, $RCH_2CH_2CH_2CH_2R^1$.[89] This process is useful for the preparation of large, symmetrical alkanes.



Another variation in the hydroboration sequence utilizes allylic halides to generate cyclic alkanes. Reaction of 9-BBN with allyl chloride, for example, generated the ω-chloroborane (**106**). Treatment with hydroxide initially formed **107**, but cyclopropane was formed by internal displacement of chloride, with **108** as the byproduct.[90] Variations of this process can generate many different substituted and functionalized cyclopropane derivatives. If propargyl bromides are used rather than allylic chlorides, cyclopropylboranes can be formed.[91] Extending the methylene spacer between the alkynyl moiety and the halide (or other leaving group such as tosyl, mesyl, etc.) allows larger rings to be generated in like manner. The constraints against forming rings of eight atoms and larger (secs. 1.5.B, 6.6.B) is a limiting factor.

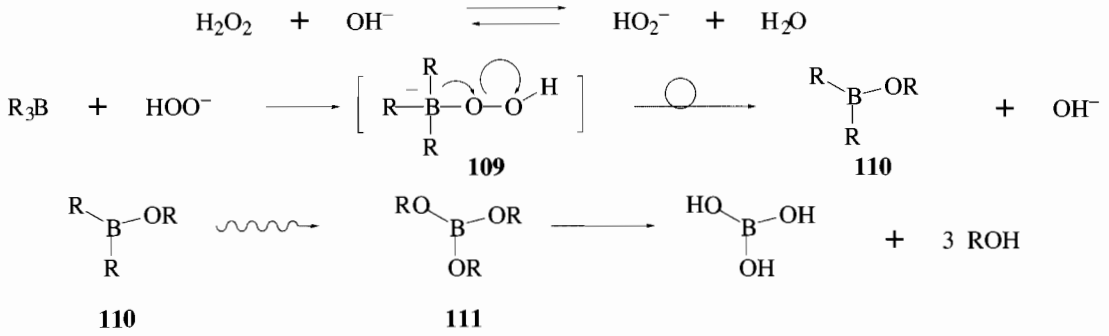
The functional group transformations seen in this section lead to the interesting transforms:



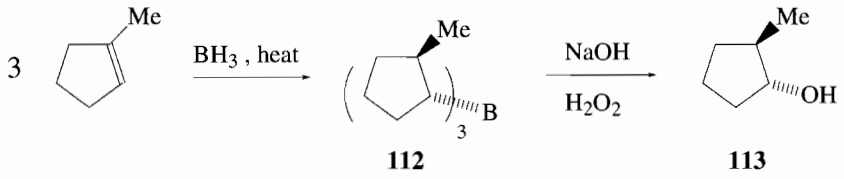
5.4. TRANSFORMATIONS THAT GIVE OXYGEN-CONTAINING FUNCTIONAL GROUPS

5.4.A. Oxidation of Boranes to Alcohols

Perhaps the most utilized transformation of organoboranes is their oxidation to alcohols, accomplished with basic hydrogen peroxide (H_2O_2, NaOH). The *active* reagent is the hydroperoxide anion (HOO^-). Alkenes are converted to alcohols with a Markovnikov orientation (the OH group is on the more substituted carbon of the C=C moiety) of the OH group via either acid catalyzed addition of water or oxymercuration (sec. 2.10.A,B).

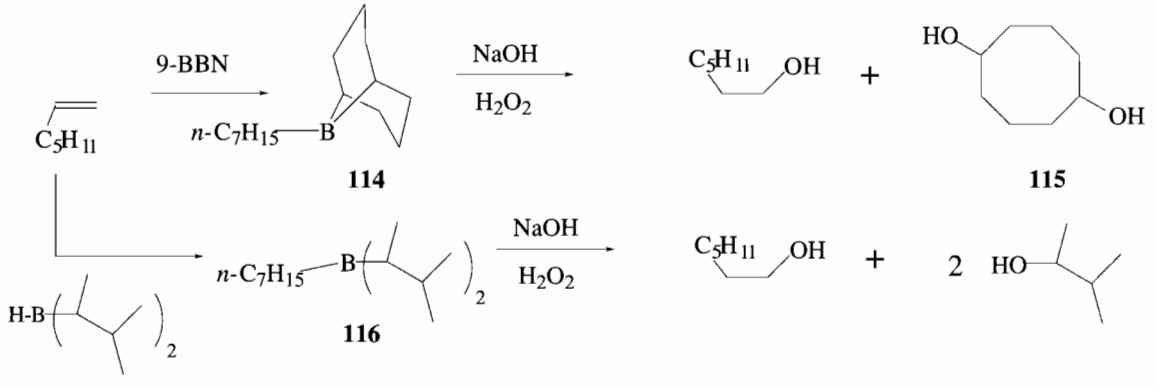


Both reactions proceed via the more stable carbocation intermediate. Hydroboration, followed by oxidation, gives the alcohol resulting from anti-Markovnikov addition of borane and oxidation places the OH group on the less substituted carbon of the C=C moiety. This two-step hydroboration–oxidation sequence is a superb method for conversion of alkenes to the less substituted alcohol.[2] The oxidation with basic hydrogen peroxide is quantitative and proceeds by initial attack at the boron to give the *ate* complex (**109**), followed by a rapid B→O alkyl shift to form borinate (**110**). Attack by additional hydroperoxide anion leads to transfer of the other R groups, generating **111**. Final hydrolysis liberates the alcohol.[92] The power of this oxidation sequence is amply demonstrated by the conversion of 1-methylcyclopentene to trans-trialkylborane (**112**). Oxidation with basic hydrogen peroxide gave *trans*-2-methylcyclopentanol (**113**) in 86% yield.[93]

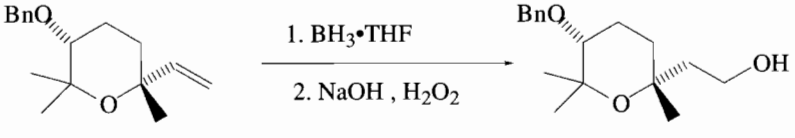


The mechanism shown above implies that the oxidative rearrangement (the B → O shift) proceeds with complete retention of configuration at the boron-bearing carbon and this is generally true, as in the conversion of **112** to **113**. For retention to occur, the hydroperoxide anion must attack boron rather than carbon and this is followed by a synfacial migration of the alkyl group to oxygen, without rearrangement, epimerization, or racemization. Conversion of an alkene to an alcohol in this manner is most efficient when all three of the groups on the trialkylborane are the same, as with **112**. Oxidation will give 3 equivalents of the desired alcohol. Since 9-BBN or disiamylborane are commonly used in hydroboration reactions, the trialkylborane being oxidized has at least two sites for formation of a C—OH bond. Reaction of 1-heptene with 9-BBN, for example, generated **114** and oxidation generated not only the desired target 1-heptanol, but also 1,5-cyclo-

octanediol (**115**). Separation of these two alcoholic products can be a problem and can limit the utility of hydroboration reactions. The monoalcohol can sometimes be distilled from the product mixture but more com-monly chromatographic separation of the monoalcohol from the diol is required. If disiamylborane were used rather than 9-BBN, the trialkylborane intermediate (**116**) would generate 1-heptanol as well as 2 equivalents of 3-methyl-2-butanol. The separation of the desired alcohol (1-hexanol in this case) from the secondary monoalcohol byproduct (3-methyl-2-butanol in this case) is a potentially serious problem. The choice to convert an alkene to an alcohol via hydroboration requires that one weigh the factors of selectivity and reactivity against the ease of isolating the targeted product. When the alcohol product contains many carbons and functional groups, as is common in natural products, the separation problem is probably minimal and selectivity is the major concern. With lower molecular weight alcohol products, ease of isolation may outweigh small increases in selectivity, and diborane is probably the reagent of choice.

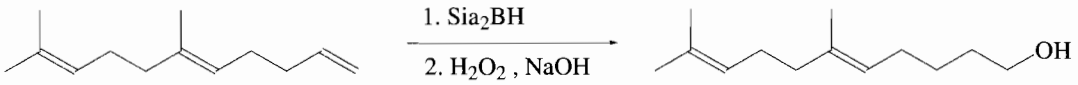


This alcohol-forming hydroboration reaction figures prominently in many natural product syntheses. It is facile and highly regioselective, and sometimes diastereoselective.[94] In a synthesis of a usneoidol E analog, Díez et al. reacted **117** with a borane-THF complex, which led to incorporation of the OH group on the less



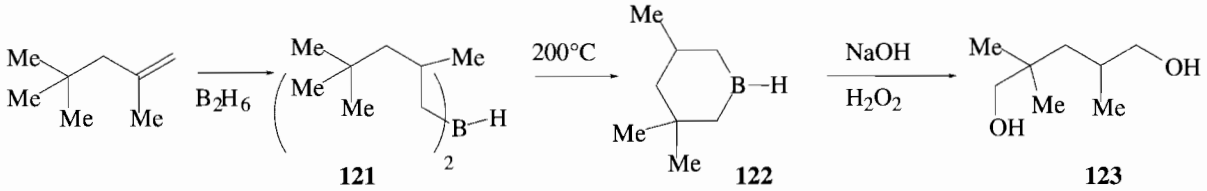
117 **118**

substituted carbon (an 80% yield of alcohol **118**)[95] with high regioselectivity. Note the high regioselectivity even with borane. Less sterically hindered alkenes react faster than more substituted alkenes, as is apparent in the conversion of **119** to **120**.[96] The hydroboration–oxidation sequence is both highly regioselective but also highly stereoselective. Alcohol **118** should be easily separable from the alcohol byproducts generated from diborane but it is possible that **120** might be more difficult to separate from the disiamyl–borane alcohol by-products (see above). For this reason, formation of an alcohol using hydroboration for complex and/or multi-functional molecules may be experimentally easier than for simple alkenes of lower molecular weight.



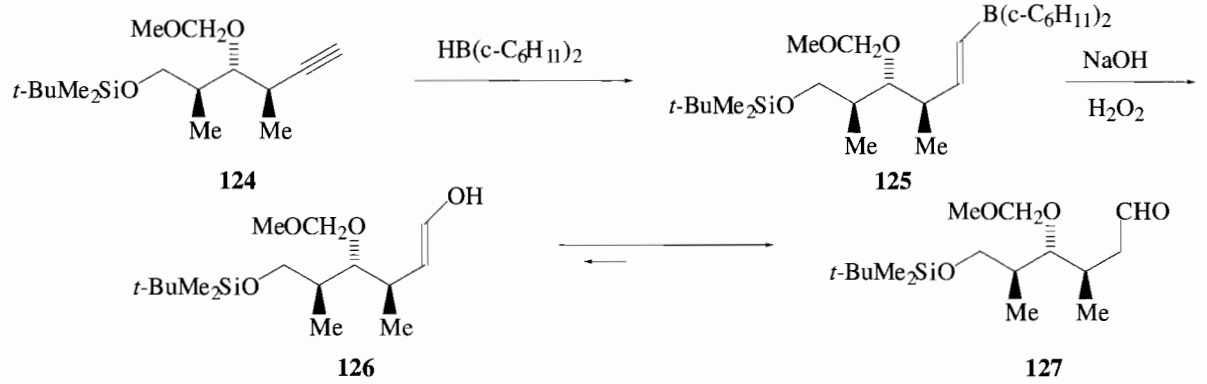
119 **120**

One of the interesting reactions of alkylboranes that was not discussed in Section 5.3 is cyclization. When the alkyl portion of the borane contains a carbon at the C5 position and when an intermediate dialkylborane possess a B—H bond, cyclization occurs upon vigorous heating (typically 200–400°C).[97] Hydroboration of 2,4,4-trimethyl-1-pentene gave **121** and heating to 200°C led to 3,3,5-trimethylborinane (**122**). In general, oxidation of borinanes leads to a diol product. The reaction of **122** with basic hydrogen peroxide, for example, gave an 80% yield of 2,2,4,-trimethyl-1,5-pentanediol (**123**).[97]



121 **122** **123**

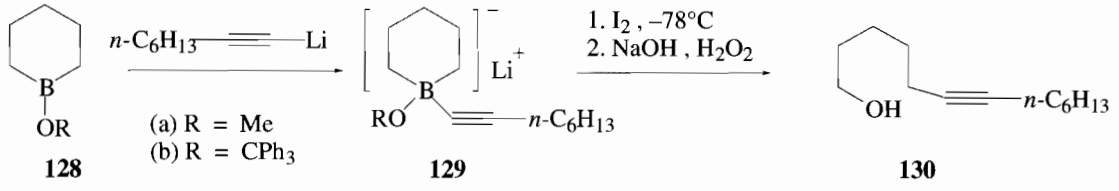
When alkynes are subjected to the hydroboration–oxidation sequence, the alcohol product is actually an enol and it tautomerizes to a carbonyl derivative (a ketone from internal alkenylboranes and an aldehyde from terminal alkenylboranes). An example is taken from Marshall's synthesis of subunits of aplyronine, in which the reaction of alkyne **124** with dicyclohexylborane gave vinylborane **125**. Subsequent oxidation gave the enol (**126**), which tautomerized to produce aldehyde **127** in 86% yield.[98] Similarly, reaction of the terminal alkyne 3,3-dimethyl-1-butyne with dibromoborane gave a 77% yield of 3,3-dimethyl-1-butanal.[99] The synthesis of aldehydes requires that the hydrolysis solution be buffered to pH 7 to minimize aldehyde condensation reactions (such as the **aldol condensation**, sec. 9.4.A). The reaction is regioselective with the position of the carbonyl fixed by the position of the boron in the initially formed alkenylborane. An interesting variation of this reaction uses 1-trimethylsilylalkynes where hydroboration and oxidation leads to a silyl-ketone, which gives a carboxylic acid upon treatment with basic hydrogen peroxide.[100]



124 **125** **126** **127**

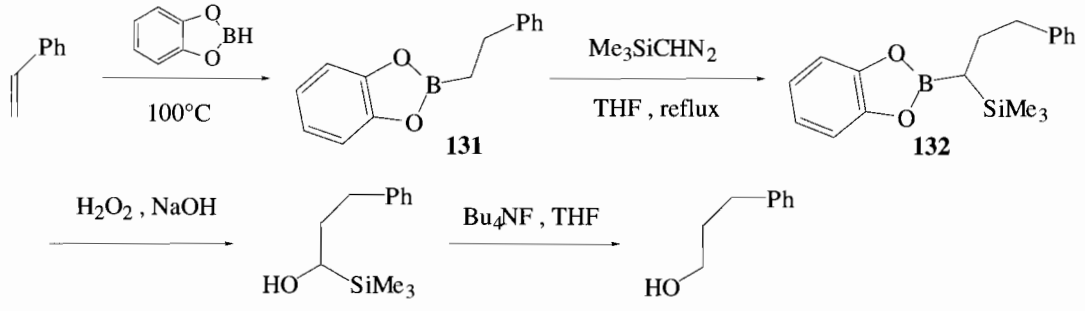
Cyclic boranes can also be used to generate alcohols in a chain extension reaction. The length of the chain is controlled by the ring size of the borinane. B-Methoxyborinane (**128a**) reacted with 1-lithio-1-octyne to

give an *ate* complex (**129a**). Iodination and oxidation cleaved the borinane to give 22% of alkynyl alcohol **130**.[101] A similar reaction with B-triphenylmethoxyborinane (**128b**) gave **130** in 85% yield.[101] A variation of this sequence couples cyclic boranes with iodoalkynes, leading to acyclic alkenyl alcohol products.[102]



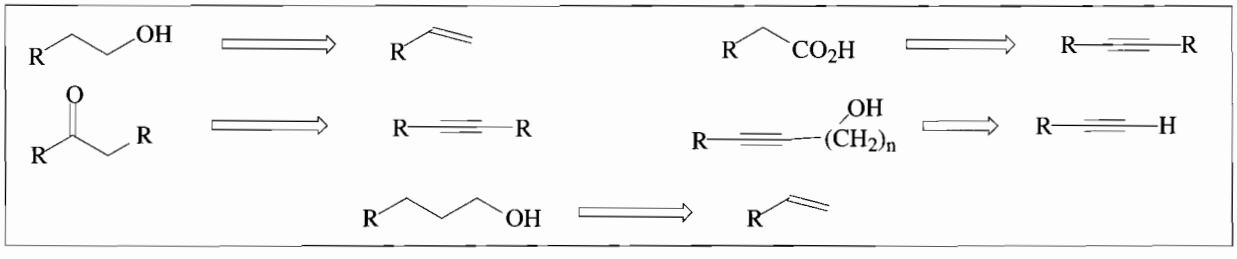
128 **129** **130**

Another chain extension reaction uses diazosilylalknes. The reaction of styrene with catecholborane at 100°C gave **131**. Subsequent reaction with Me_3SiCHN_2 gave **132** and oxidation in the usual manner gave silyl alcohol **133**. The silyl group is removed in another step using tetrabutylammonium fluoride, giving 3-phenyl-1-propanol (**134**) in 60% overall yield from styrene.[103]



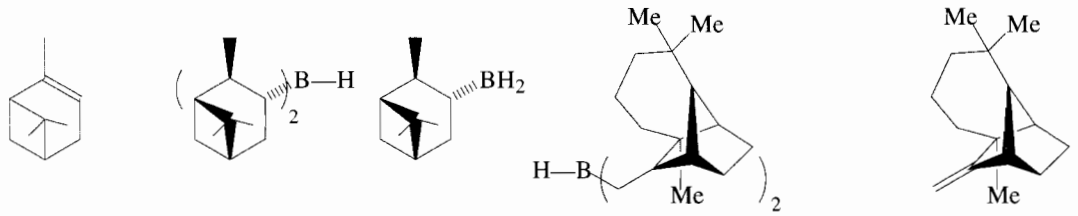
131 **132** **133** **134**

The functional group transformations possible with these reactions are:



5.4.B. Asymmetric Hydroboration

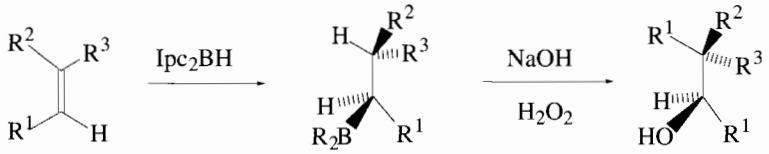
Optically active products can be produced via hydroboration if an optically active borane is used, and if the C=C moiety of the alkene precursor is prochiral (sec. 1.4.E). Several chiral alkylboranes have been developed, by Brown and by others, by reaction of borane or achiral organoboranes with naturally occurring chiral alkenes such as pinene or longifolene. These chiral organoboranes react to give hydroboration products with good asymmetric induction and diastereoselectivity. The most common synthetic application is to prepare chiral alcohols from alkenes, using diisopinocampheylborane (**14**, Ipc_2BH) or monoisopinocampheylborane (**135**, $IpcBH_2$), both derived from α-pinene (**6**), as well as dilongifolylborane (**136**, Lgf_2BH) which is derived from longifolene, **137**.[104]



6 **14** **135** **136** **137**

Diisopinocampheylborane is prepared by reaction of either(*R*)- or (*S*)-α-pinene (**6**) with diborane,[105] and this dialkylborane product exists largely as a dimer. The product can also be formed by slow reaction of borane and pinene (3 days in THF) with the major isomer precipitating from solution.[102a] This chiral non-racemic reagent reacts with alkenes in the usual manner and gives a chiral, non-racemic alcohol after oxidation with basic hydrogen peroxide. As usual, hydroboration of an alkene (**138**) occurs from the less hindered side of the molecule via cis addition (to give **139**) and the oxidation proceeds with complete retention of configuration (to give **140**). The stereogenic center of the newly formed alcohol usually has the *opposite* chirality relative to the organoborane [(–)-IpC$_2$BH gives the (*R*)-alcohol and (+)-IpC$_2$BH gives the (*S*)-alcohol].[104] Hydroboration of *cis*-2-butene with (*S*)-**14**, for example, gave (*R*)-(--)-2-butanol with 87% ee (in diglyme; 78% ee in THF). The percentage asymmetric induction (% ee) for the synthesis of several alcohols from the appropriate alkene is shown in Table 5.5.[104]

Table 5.5. Asymmetric Induction with (–)-Diisopinocampheylborane (14)



138 **139** **140**

R^1	R^2	R^3	% ee of 140[a]
Me	Me	H	87 (*R*)
Et	Et	H	95 (*R*)
Me	H	Me	13 (*R*)
Me	Me	Me	14 (*R*)
—(CH$_2$)$_3$—		Me	22 (1*R*,2*R*)
H	Et	Me	21 (*R*)
H	*i*-Pr	Me	30 (*R*)
H	*t*-Bu	Me	13 (*R*)
n-C$_4$H$_9$	^{2}H	H	42 (*R*)
n-C$_4$H$_9$	H	^{2}H	86 (*S*)[b]
H	H	*n*-C$_3$H$_7$	48 (*R*)

[a] The (*S*)-configuration was obtained with (+)-diisopinocampheylborane [b] Antipode of **140**.

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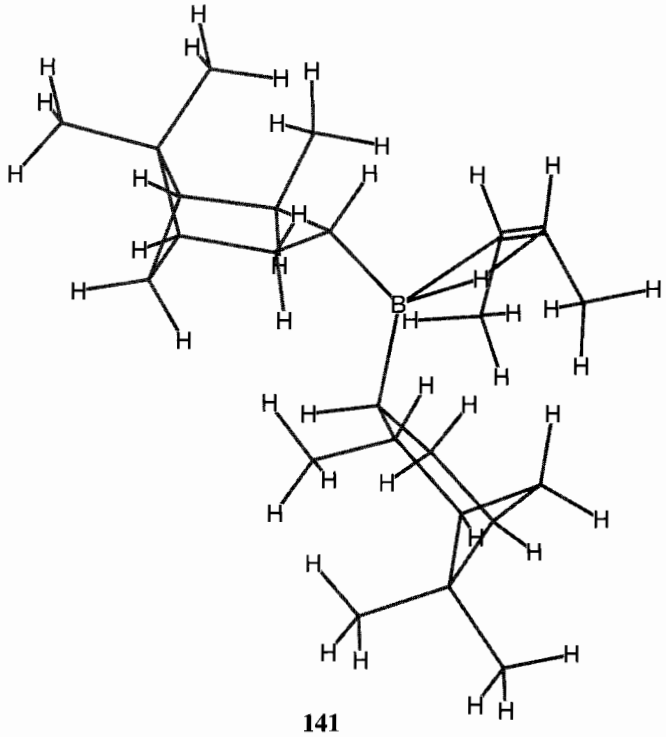
It is apparent from Table 5.5 that hydroboration of cis alkenes using **14** leads to an alcohol with higher enantioselectivity than obtained from trans alkenes or hindered terminal alkenes. This can be explained by examination of two proposed structures where the borane approaches the alkene in the hydroboration step (shown as 3-D[106] representations), **141** for cis alkenes and **142** for trans alkenes.[104] The lowest energy conformation for the reagent positions the two pinanyl rings orthogonal to each other, as shown. When a cis alkene approaches, the favored transition state will minimize all steric interactions. The chirality of the pinanyl rings dictates approach from the right face (as drawn in structures **141-144**). If the chirality of this reagent



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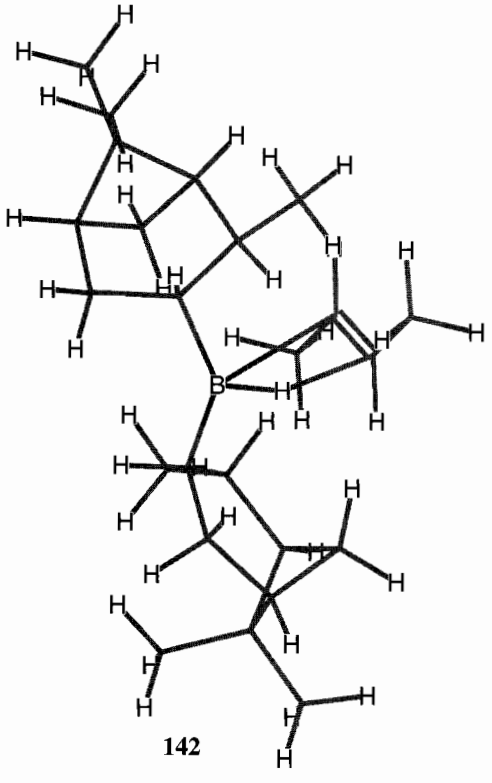
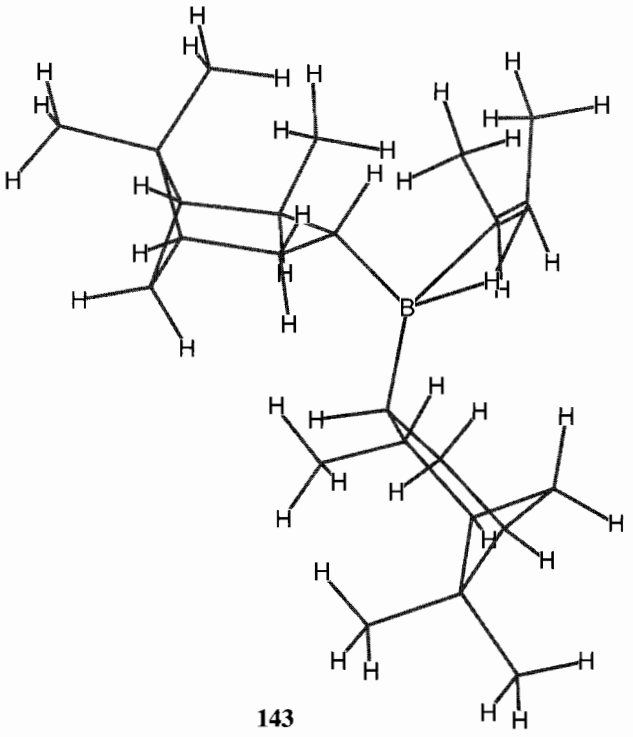


142

were the opposite of that drawn, approach would be from the left face. The orientation of the alkene is also important in determining enantioselectivity, and this orientation is largely dictated by steric interactions of the alkyl groups on the alkene with one pinanyl ring. The second pinanyl ring is effectively on the other side of the borane and out of the way of the groups on the alkene. If the alkene approaches from only one face (here the right face), there is a pocket that can accommodate groups on the alkene. In **141**, *cis*-2-butene approaches the right face of the pinanyl reagent and is oriented so that the methyl groups are down. This orientation minimizes steric interactions between the methyl groups and the pinanyl group that is on top of the pinanyl reagent (top and bottom are relative in this discussion since the pinanyl borane reagent possesses C_{2v} symmetry). Approach from the same face but with the methyl groups up, as in **143**, has a greater steric interaction and is disfavored relative to **141**. Therefore, this particular analysis suggests that **141** is the model that should be used to predict stereochemistry for cis alkenes.



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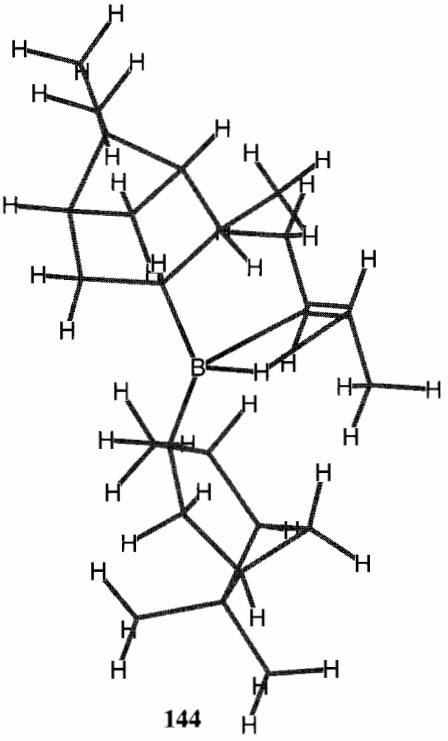
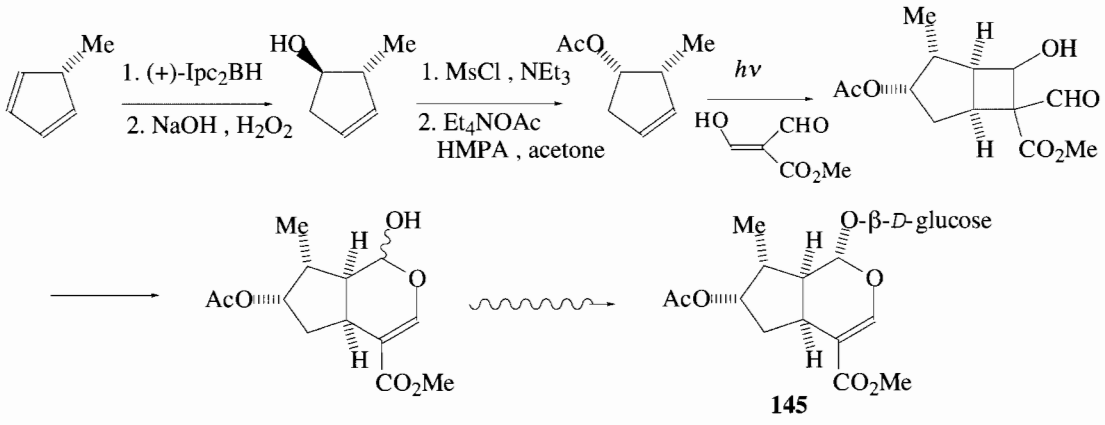


144

When *trans*-2-butene reacts with the pinanyl borane reagent, approach from the right face leads to a situation where one methyl group is up and interacts sterically with the pinanyl ring, but the other methyl group is down and in a pocket (see **142**). The steric interaction of the single methyl group in **142** is greater than the interactions observed in **141** but similar to those observed in **143**. The trans alkene should therefore show poorer selectivity than the cis alkene. Rotation of *trans*-2-butene by 180° along the C=C bond axis (to give **144**) also brings one methyl group up and in close proximity to the boranylpinane group that protrudes on top in **144**, which suggests that **144** is not significantly lower in energy in **142**. There is no orientation that leads to significantly less severe steric interactions for trans alkenes, as seen with cis alkenes, and diminished enantioselectivity for the hydroboration–oxidation sequence. If the two substituents on the trans alkene are sufficiently different in size, however, increased selectivity for reaction at the less sterically hindered carbon is possible. With 1,1-disubstituted alkenes, there is little selectivity in the hydroboration–oxidation sequence. Diisopinocampheylborane apparently forms a trimer rather than react with a severely hindered alkene, and this further complicates the reaction.[104] When the borane intermediate of the initial alkene reaction is treated with O-sulfonylhydroxylamine (sec. 5.5.A), enantioselectivity in the chiral amine product is similar to that observed in the alcohol forming sequence.[104] Diisopinocampheylborane was used by Partridge and Uskoković in a synthesis of loganin (**145**).[107] This synthesis is outlined in Scheme 5.1.[107]

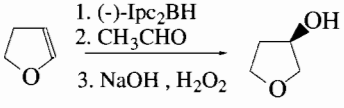
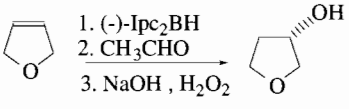
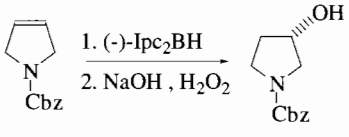
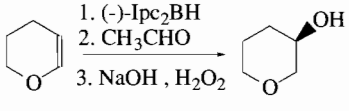
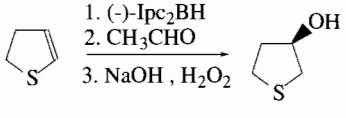
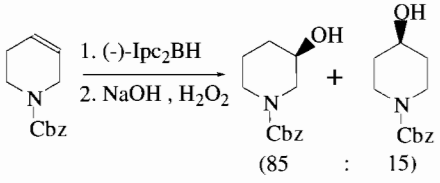
Asymmetric induction has been observed in the hydroboration of heterocyclic rings such as dihydrofuran, dihydropyrrole, dihydropyran, and dihydrothiophenes.[108] Table 5.6[108] shows the hydroboration-oxidation sequence that gives heterocyclic alcohols in good yield and with excellent % ee from heteroatom containing



145

Scheme 5.1. Synthesis of loganin

Table 5.6. Asymmetric Hydroboration of Heterocyclic Compounds with Diisopinocampheylborane.

Reaction	Yield (%)	% ee
	92	100, (*R*)
	68	100, (*S*)
	92	89, (*S*)
	81	83, (*R*)
	80	100, (*R*)
 (85 : 15)	68	70, (*R*)

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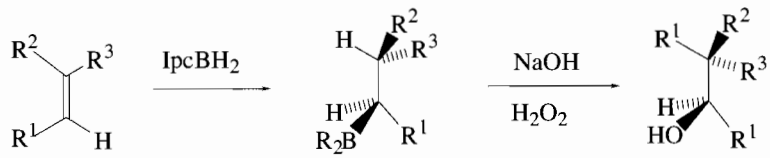
alkenes. It is important to note that these reactions required addition of acetaldehyde to displace α-pinene prior to oxidation of the borane. The hydroboration reaction is highly regioselective for placement of the boron on the alkene carbon distal to the heteroatom.

Monoisopinocampheylborane (**135**) is another important chiral borane, formed by reaction of α-pinene with the triethylamine complex of thexylborane,[109] which gives the monoisopinylcamphylborane•triethylamine complex. It is necessary to release monoisopinocampheylborane by treatment with borane•THF or boron trifluoride etherate.[110] This reagent is obviously less hindered than the diisopinocampheyl derivative and reacts faster, even with hindered and polysubstituted alkenes. As shown in Table 5.7[104], the highest enantioselectivity is observed with trans alkenes (see **146**). Initial reaction generates a chiral organoborane (**147**) and oxidation gives the alcohol (**148**) with high asymmetric induction.

Table 5.7. Enantioselectivity with Monoisopinocampheylborane



146 **147** **148**

R[1]	R[2]	R[3]	% ee of 148[a]
Me	H	Me	72
Me	Me	H	24
t-Bu	H	*t*-Bu	92
Me	Me	Me	53
Et	Me	Me	58
—$(CH_2)_3$—		Me	66
—$(CH_2)_3$—		Ph	100
—$(CH_2)_4$—		Et	88
—$(CH_2)_4$—		Ph	72

[a] The stereochemistry of the stereogenic center in **148** bearing the OH group is shown as the (*R*)-configuration but the absolute configuration of **148** depends on which antipode of $IpcBH_2$ is used.

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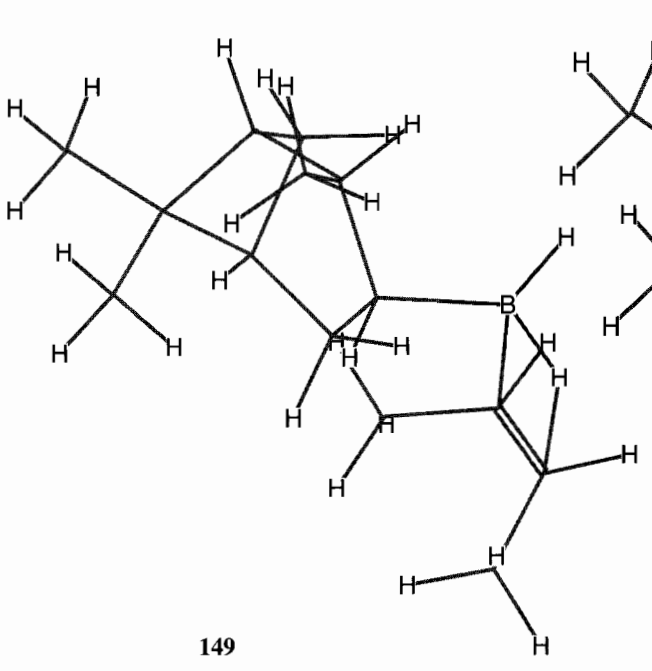
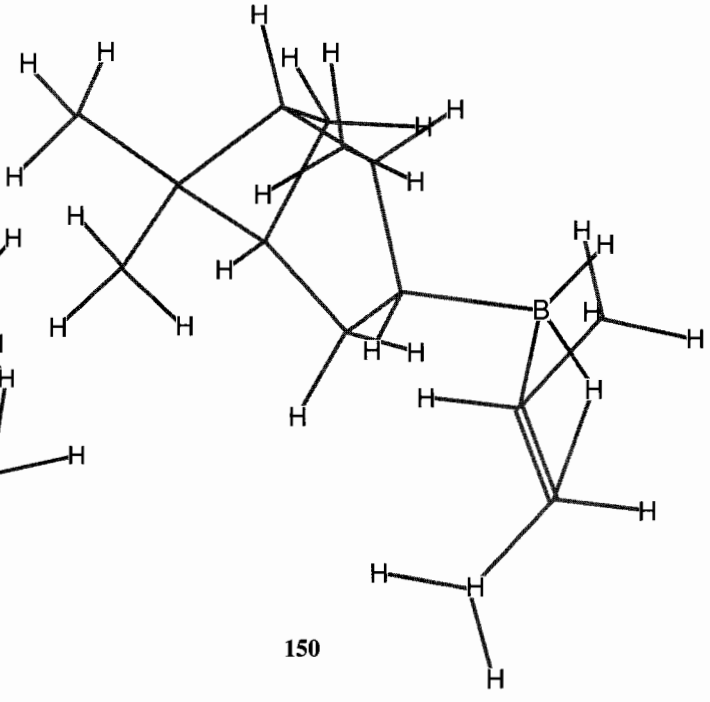
Asymmetric induction increases with increasing steric demands of the alkene, and cis alkenes show the *worst* selectivity. This can be explained by three-dimensional drawing **149**, which shows approach of *re,si* face of *cis*-2-butene with the less sterically hindered case of the methyl groups down (when the methyl groups are up there is a severe interaction). If *cis*-2-butene is rotated by 180° along the axis which *bisects* the C=C bond (C=/=C), the other face (the *si,re* face) of the alkene is exposed to reaction. There is no facial bias for approach of the cis alkene and, therefore, little or no enantioselectivity in the hydroboration reaction. Examination of **150** for approach of *trans*-2-butene from the left face of the pinanyl borane reagent shows

that there is a pocket where one methyl can be accommodated, and there is only minimal steric interaction with the other methyl group. Rotation of 2-butene by 180° along the axis that *bisects* the C=C bond (C=/=C) places the up methyl to the rear and causes one methyl to have severe steric interactions with the pinanyl ring.



149



150

This difference in steric hindrance leads to good enantioselectivity for trans alkenes. 2-Butene shows outstanding selectivity because it is symmetrical. Unsymmetrical alkenes show good selectivity only when there are significant differences in the size of substituents. 1,1-Disubstituted alkenes show good selectivity *if* both groups are large, and particularly if one group is significantly larger than the other.

Although **14** shows good selectivity for cis alkenes and **148** shows good selectivity for trans-alkenes, there was no reagent that showed good selectivity with both cis and trans alkenes. A solution to this problem was found when dilongifolylborane (**136**) was prepared by reaction of the dimethyl sulfide complex of borane with (+)-longifolene (**137**), which is readily available [the (–) antipode is rare however].[111] Compound **136** is a dimeric, high–melting white crystalline solid that is stable in ether solvents and can be stored several weeks without decomposition. Examination of Table 5.8[104] shows that this reagent gives good enantioselectivity with both cis and trans alkenes, as well as 1,1-disubstituted alkenes. The enantioselection is due to the pocket which the longifolyl group provides in the borane. Inspection of **151**, that shows the approach of *cis*-2-butene to **136**, reveals an orientational bias for cis alkenes. The protruding ring substituents will sterically interact with the alkene substituents when the alkene is oriented with the methyl groups up, but when the methyl groups are down there is a pocket (which can accommodate small to moderately sized substituents in the general case). This pocket also allows good selectivity in reactions with 1,1-disubstituted alkenes. The pocket can also accommodate trans alkenes, and rotation does not significantly increase steric interactions (as seen in **152** for approach of *trans*-2-butene). As the steric size of unsymmetrical trans alkenes increases, the

Table 5.8. Enantioselectivity in Hydroboration Reactions of Dilongifolylborane (136)

Alkene	% ee of Alcohol
cis-2-butene	78
trans-2-butene	
cis-3-hexene	71
trans-3-hexene	
2-methyl-2-butene	70
2-methyl-2-pentene	75
1-methylcyclopentene	63

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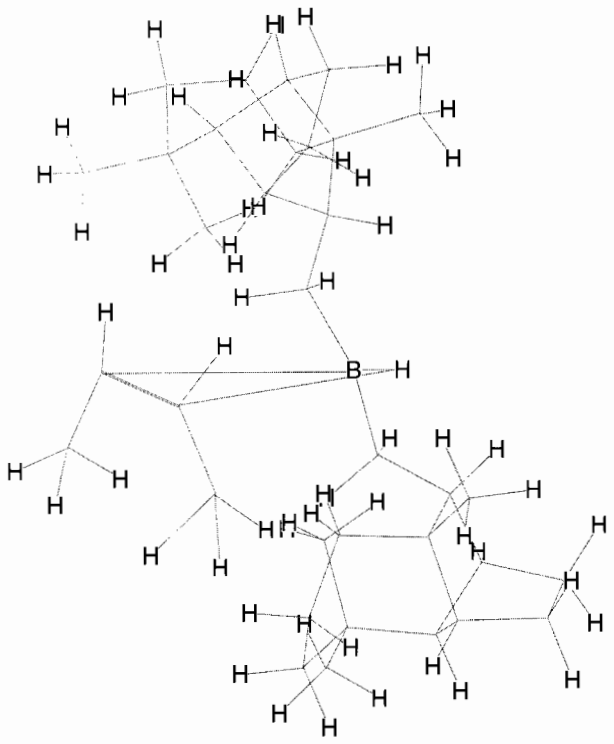
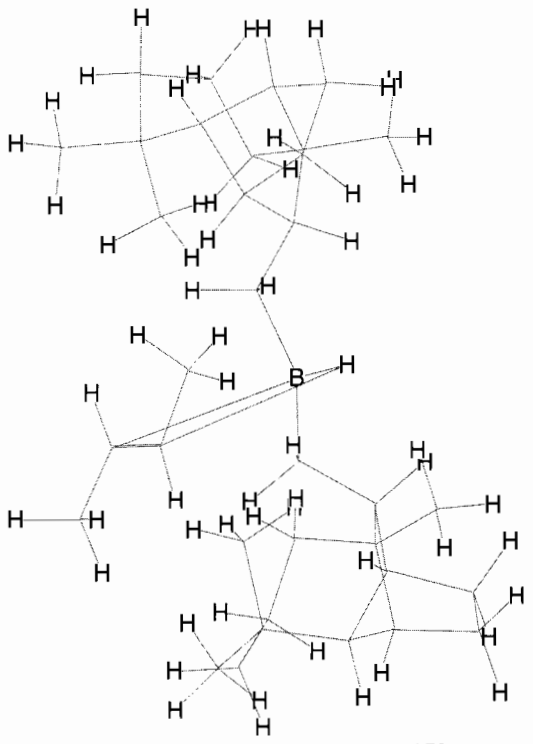
selectivity will increase. Both **151** and **152** are drawn to represent the lowest energy approach of 2-butene to the B—H bond of the borane.

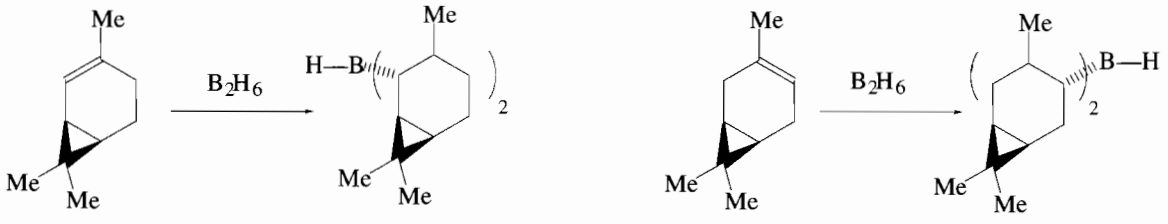


151



152

Another class of chiral boranes has been prepared from Δ^2-carene (**61**) and Δ^4-carene (**154**). The first reagents of this class to be widely used are (1*S*)-di-2-isocaranylborane (**153**, 2-$^{d}Icr_2BH$) and (1*S*)-di-4-isocaranylborane (**155**, 4-$^{d}Icr_2BH$).[112] These reagents behave in a similar manner to Ipc_2BH but are less reactive and their relative reactivity is: $Ipc_2BH > 2^{d}Icr_2BH > 4\text{-}^{d}Icr_2BH$. Table 5.9[112] illustrates the selectivity and asymmetric induction of **153** and **155** upon reaction with a variety of alkenes. These reagents showed good selectivity with cis alkenes but trans alkenes and terminal alkenes react slowly and show poor selectivity.



61 **153** **154** **155**

These five reagents show that chiral boranes can induce moderate to good enantioselectivity in the conversion of alkenes to alcohols (or to amines, sec. 5.5.A). These reagents are a powerful addition to the growing list of enantioselective reactions used in organic synthesis.

Table 5.9. Asymmetric Hydroboration with Carene Based Reagents

Alkene	Reagent[a]	Time (h)	Alcohol	Yield, %	% ee
cis-2-Butene	2-Icr$_2$BH	12	2-Butanol	63	93 (*S*)
	4-Icr$_2$BH	72		58	50, (*R*)
trans-2-Butene	2-Icr$_2$BH	150		69	30, (*R*)
	4-Icr$_2$BH	72		62	40, (*S*)
2-Methyl-1-butene	2-Icr$_2$BH	3	2-Methyl-1-butanol	61	15, (*S*)
	4-Icr$_2$BH	4		72	5, (*R*)
2-Methyl-2-butene	2-Icr$_2$BH	240	3-Methyl-2-butanol	61	37, (*S*)
	4-Icr$_2$BH	120		75	0
trans-3-Hexene	4-Icr$_2$BH	72	3-Hexanol	65	32, (*S*)
1-Methylcyclopentene	2-Icr$_2$BH	240	2-Methyl cyclopentanol	65	3, (1*R*2*R*)
	4-Icr$_2$BH	26		72	3, (1*R*2*R*)

[a] 0°C, THF

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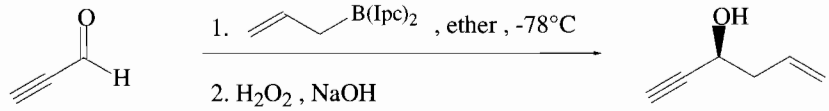
5.4.C. Addition of Allylboranes to Carbonyl Compounds

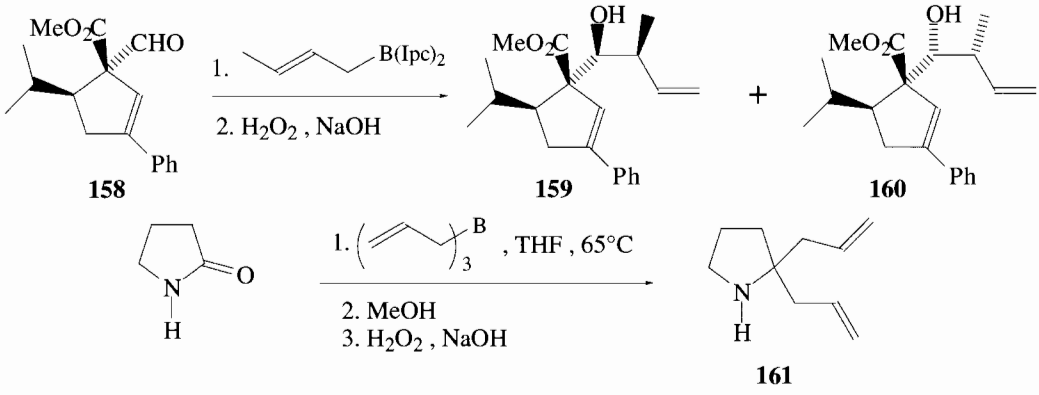
A particularly useful borane is the chiral reagent (–)-B-allyl(diisopinocampheyl)borane.[113] Although the chemistry of acyl addition to aldehydes and ketones to give alcohols will not be formally discussed until Section 8.4.C, the addition of this chiral allylborane to carbonyl compounds will be presented here. In a simple example taken from Smith's synthesis of (–)-macrolactin A,[114] **156** was treated with (–)-B-

allyl(diisopinocampheyl)borane in ether at -78°C. The usual oxidation gave **157** in high yield and 90% ee, which illustrates both the reaction and the synthetic utility, an asymmetric synthesis of alcohols from aldehydes and ketones.



156 **157**

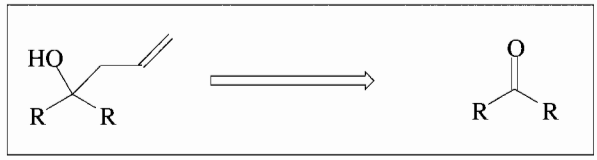
The reaction proceeds with excellent enantioselectivity as shown, but in some cases the diastereoselectivity is modest, which is true when the allylborane reagent is substituted, as in crotylborane derivatives. In the Ōmura,, Smith and co-workers synthesis of (+)-lactacystin, for example, reaction of the B-crotyl derivative shown with aldehyde **158** gave a 4:1 mixture of **159** and **160** in high yield.[115] Each diastereomer was formed with high enantioselectivity.



158 **159** **160** **161**

Although this reaction is most useful for aldehydes, other carbonyl compounds can be used as well. It is known that carboxylic acids,[116] esters,[116a,b,117] anhydrides,[117] and amides[117] react with allylic boranes to give the corresponding alcohols. In one example, 2-pyrrolidinone reacted with triallylborane. Following treatment with methanol followed by basic hydrogen peroxide, a 90% yield of 2,2-diallylpyrrolidine (**161**) was obtained.[118] This transformation is believed to proceed by initial addition to the carbonyl followed by elimination to give an imine. The imine reacts with a second equivalent of triallylborane to give the 2,2-disubstituted derivative. The methanol cleaves the N—B bond and the oxidation step removes the remaining borane derivatives.

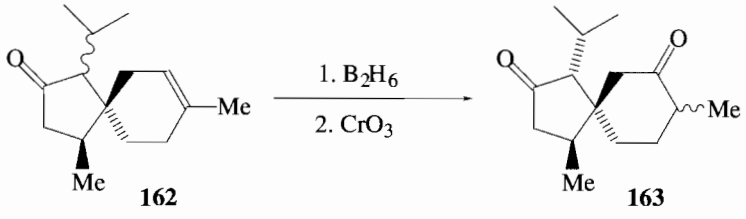
The disconnection for this reaction is



The reader is also directed to Section 12.7.C for a palladium–catalyzed coupling reaction involving boronic acids called **Suzuki coupling**.

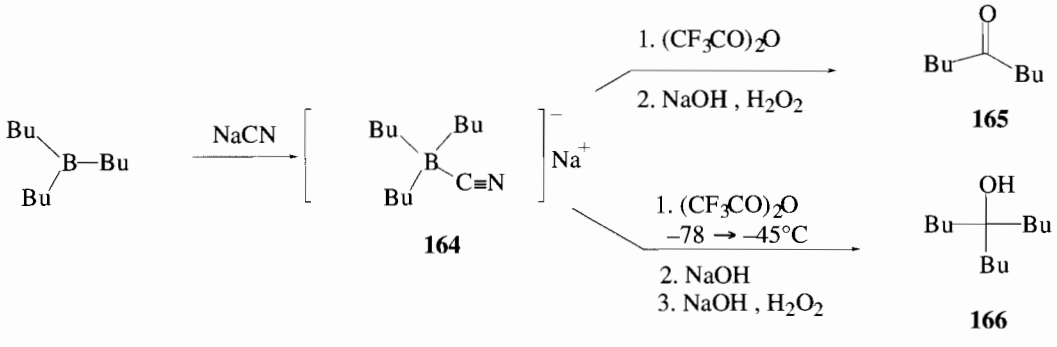
5.4.D. Oxidation to Aldehydes and Ketones

The alcohols that were formed via hydroboration and oxidation in Section 5.4.A can be oxidized to aldehydes or ketones with an appropriate oxidizing agent (see Chap. 3) after they are isolated from the hydroboration–oxidation sequence. It is possible, however, to combine these steps and oxidize organoboranes directly to ketones by treatment with chromic acid. Hydroboration of cyclohexene, for example, generated tricyclo-hexylborane and oxidation with chromic acid rather than basic hydroperoxide gave a 65% yield of cyclo-hexanone directly. Initial oxidation of tricyclohexylborane likely gave the alcohol, which was oxidized to the ketone (cyclohexanone) *in situ*, .[119] The oxidation to the alcohol proceeds by a chromate ester of boron and the rate of oxidation is sensitive to steric effects,[120] analogous to the chromic acid oxidation of secondary alcohols (sec. 3.2.A). Using diethyl ether as a solvent facilitates isolation of the final ketone product. When the alkyl substrate is sensitive to acid rearrangement, chromic acid oxidation can facilitate that rearrangement.[121] As with oxidation of organoboranes to form alcohols, there are many synthetic examples of direct oxidation to carbonyls. In Martin's synthesis of acorone, alkene **162** was converted to the borane and oxidized directly with chromium trioxide to give **163** as a mixture of epimeric methyl ketones.[122]



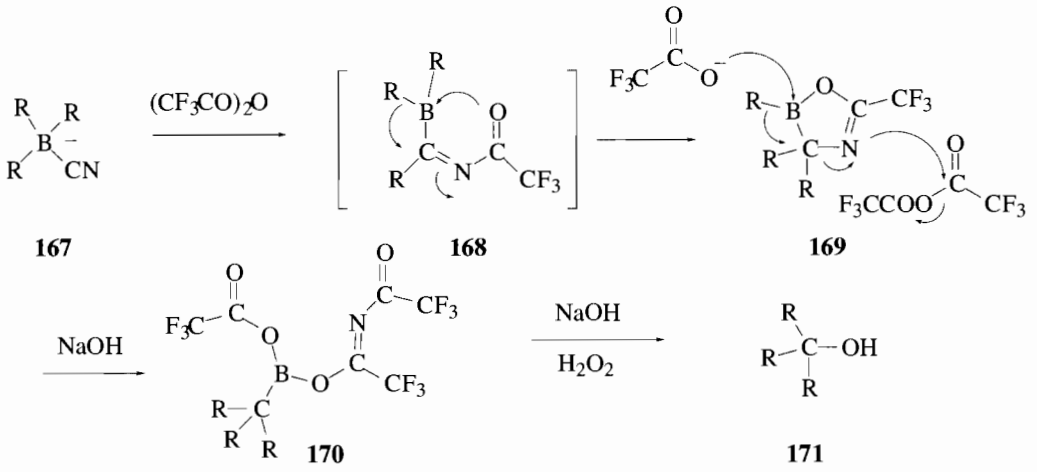
162 **163**

An alternative method for the preparation of ketones from organoboranes uses cyano *ate* complexes. Formation of the ketone requires transfer of two alkyl groups from the boron. Treatment of tri-*n*-butylborane with sodium cyanide (NaCN) gave the cyano *ate* complex (**164**). An electrophilic reagent such as trifluoroacetic anhydride [$(CF_3CO)_2O$] was added to initiate migration of the alkyl groups from boron to carbon, allowing oxidation with basic hydrogen peroxide to give the symmetrical ketone, 5-nonanone (**165**) in 94% yield.[123] Treatment of the cyano-*ate* complex with sodium hydroxide and then basic hydrogen peroxide in the usual oxidation sequence leads to a tertiary alcohol. Tri-*n*-butylborane was converted to 5-butyl-5-nonanol (**166**) in 85% yield by this procedure, along with 15% of **165**.[124] The mechanism of tertiary alcohol formation is postulated to be initial formation of an imine such as **168** from the cyano *ate* complex (**167**).

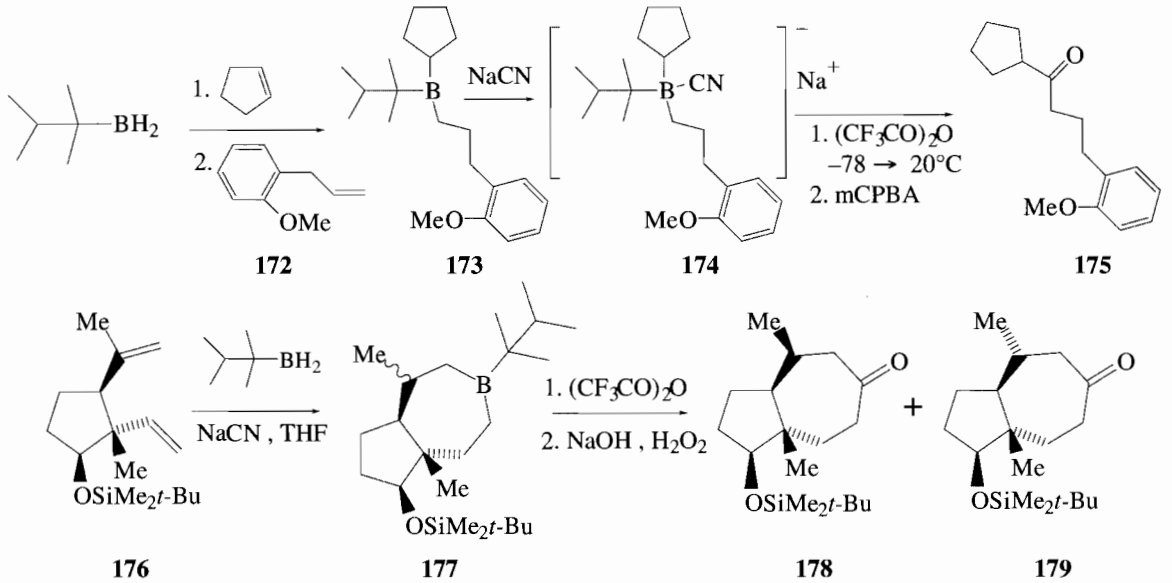


164 **165** **166**

Cyclization via attack at boron in **168** led to **169**, which was opened by reaction with trifluoroacetate anion to give **170**. Oxidation of the **170** gave the tertiary alcohol, **171**. The ketone product is formed by oxidation of the intermediate **169**, although oxidative cleavage of **170** is also possible.[125]



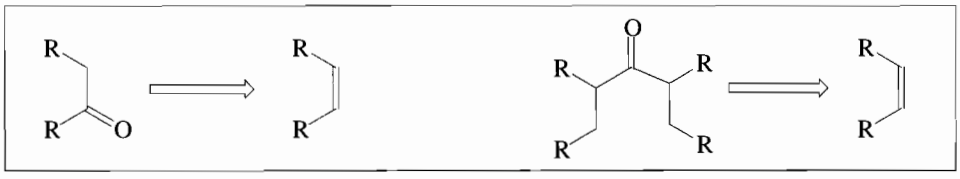
While this method is applicable to symmetrical alcohols or ketones, formation of unsymmetrical ketones is difficult unless selective transfer of the alkyl groups can be achieved. Thexylborane provides a solution since it can react sequentially with two different alkenes to generate an unsymmetrical trialkylborane. Reaction of thexylborane with cyclopentene and then arylalkene **172**, for example, gave **173**. Subsequent reaction with sodium cyanide gave the unsymmetrical *ate* complex (**74**) and this generated unsymmetrical ketone **175** upon treatment with trifluoroacetic anhydride followed by oxidation.[120b]



Unsymmetrical cyclic ketones can be formed by the hydroboration of dienes followed by the oxidation sequence just described. In a typical example, Bryson reacted **176** with thexylborane but sodium cyanide was present (*in situ*) and this mixture generated **177**. When this product was treated with trifluoroacetic anhydride

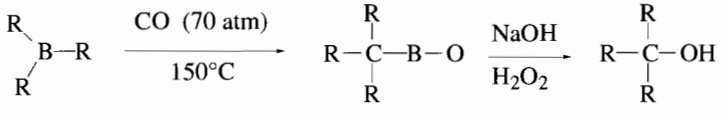
and then oxidized with basic hydrogen peroxide, a 70:30 mixture of **178** and **179** was obtained in 48% yield.[126] This **boron annulation sequence** was used in Bryson's synthesis of confertin[126] and it has been applied to the synthesis of several bicyclic alkaloids.[127]

The functional group transforms for the alkene to ketone conversion are:



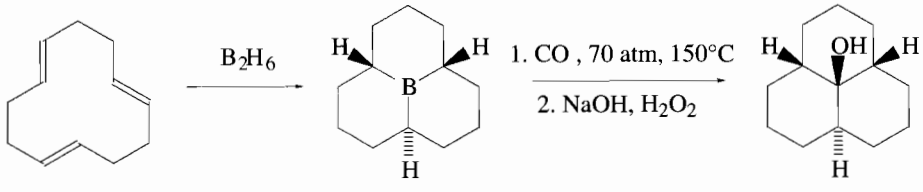
5.4.E. Carbonylation: Formation of Alcohols, Aldehydes and Ketones

There is an alternative method for converting organoboranes into alcohols or carbonyl derivatives that requires more vigorous reaction conditions. Organoboranes react with CO in a reaction that transfers the three alkyl groups of a trialkylborane from boron to carbon,[128] which requires relatively high pressures of carbon monoxide and high temperatures (typically 70 atmospheres and 150°C). Subsequent oxidation induces the usual B→O shift in **180**, which leads to a symmetrical tertiary alcohol (**181**). A simple example of this reaction involves the hydroboration product of cyclohexene, tricyclohexylborane. Reaction with CO gave **180** (R = cyclohexyl) and oxidation generated tricyclohexylcarbinol (**181**, R = cyclohexyl) in an overall yield of 86%.[129]



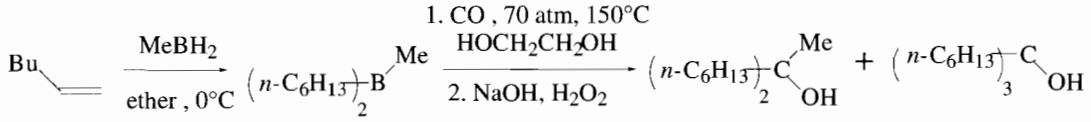
180 **181**

This sequence is useful for the preparation of symmetrical tertiary alcohols, even highly hindered ones, that would be difficult to prepare by other routes. It is limited to an organoborane derived from a single alkene, however, since a mixed borane will lead to several alcohol products. Hydroboration of dienes and trienes lead to cyclic, bicyclic, and tricyclic tertiary alcohols, structures that are commonly found in natural products. The method is illustrated by reaction of diborane with 1,5,9-cyclododecatriene (**182**), which gave tricyclic borane **183** with a bridgehead boron. Carbonylation and oxidation as before incorporate the carbon group and led to the tricyclic alcohol (perhydrophenalenol, **184**) where the carbinol carbon bridges all three rings.[130] This compound was produced in 70% yield in three chemical steps and would be difficult to prepare by other synthetic methods.



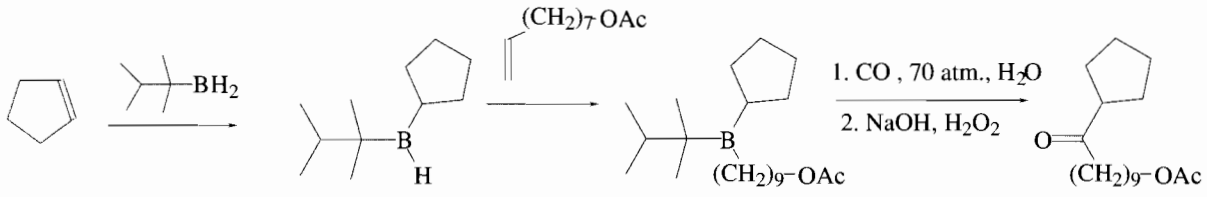
182 **183** **184**

Another route to tertiary alcohols involves monomethylborane ($MeBH_2$), which can be prepared from lithium methylborohydride ($LiMeBH_3$).[131] Reaction of $MeBH_2$ with 2 equivalents of 1-hexene gave **185**. Carbonylation and oxidation gave a 1:1 mixture of **186** and **187**.[131] When 10 equivalents of 1-hexene were used and the hydroboration was done at –25°C (in THF), carbonylation and oxidation gave **186** in 96% yield.[131] Ketones rather than alcohols can be synthesized if the carbonylation step is done in the presence of



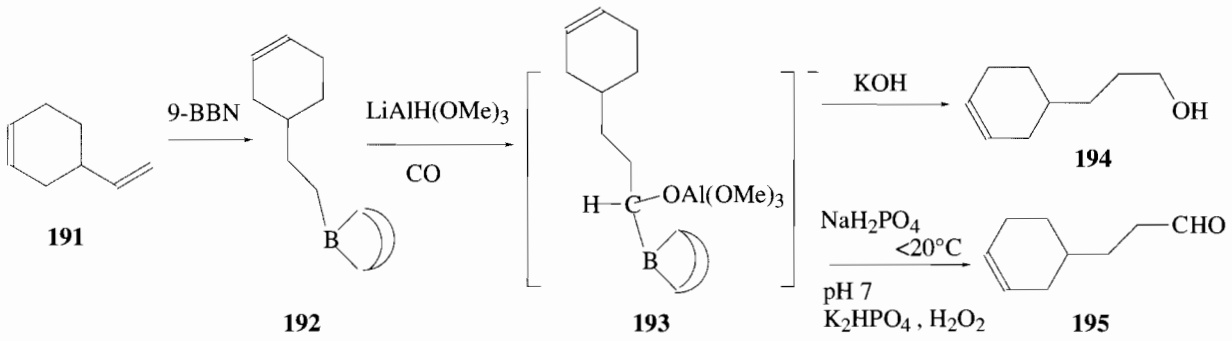
185 **186** **187**

water. In this modification, an OH group is transferred to carbon but only two of the alkyl groups are transferred. Oxidation leads directly to an intermediate that decomposes to a ketone rather than an alcohol.[132]



188 **189** **190**

A pressure of 70 atmospheres of CO is required since hindered boranes, especially thexylborane, react sluggishly at atmospheric pressure. However, thexylborane reacted with cyclopentene to generate **188**, and subsequent reaction with O-acetyl-hept-6-en-1-ol gave the trialkylborane (**189**). Carbonylation in the presence of water followed by oxidation gave the mixed ketone (**190**) in 73% yield.[133] In a similar manner, dienes can be transformed into the corresponding cyclic ketones.[134,135]

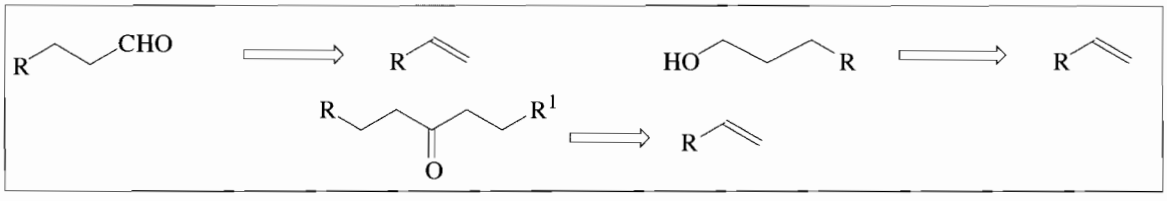


191 **192** **193** **194** **195**

Another modification of the carbonylation sequence adds a single carbon to a substrate and generates an aldehyde. When 4-vinylcyclohexene (**191**) was treated with 9-BBN, the usual borane (**192**) was formed. Carbonylation in the presence of lithium trimethoxyaluminum hydride [$LiAlH(OMe)_3$, sec. 4.3], gave an α-boranyl alkoxyaluminate (**193**). Cleavage of **193** with hydroxide liberated the alcohol (**194**) but oxidation of **193** with buffered hydrogen peroxide gave the aldehyde, **195**.[128,136] The use of a complex hydride with **192** increased the rate of CO uptake by the trialkylboranes (this is a general phenomenon).[137] Indeed, a small

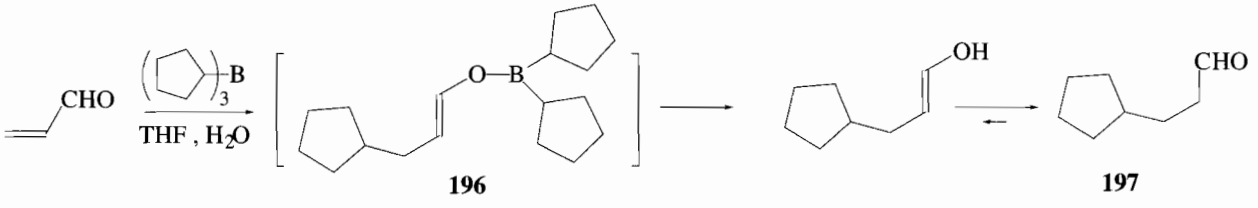
amount of free trialkylborane must be present in the reaction medium or carbonylation does not occur at a reasonable rate.[138] Trialkylborohydrides are probably the active reducing agents in this reaction.[139] When sodium borohydride or lithium tri-*tert*-butoxyaluminum hydride was used, complex side reactions accompanied carbonylation. For this reaction, lithium trimethoxyaluminum hydride or potassium triisopropoxyborohydride is the preferred reagent.

The functional group transforms in this section are quite useful and are outlined below:



5.4.F. Conjugate Addition

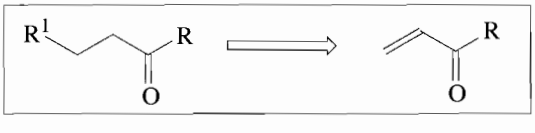
Borane, monoalkylboranes and dialkylboranes (such as thexylborane and 9-BBN) were shown to be powerful reducing agents for carbonyl derivatives (sec. 4.6.A). When the B—H unit is removed, as in trialkylboranes, addition to the alkene moiety of α,β-unsaturated ketones or aldehydes occurs. An alkyl group of the borane is transferred to the terminal position of the alkene moiety (1,4-addition) and boron is transferred to the oxygen, giving a boron enolate (sec. 9.4.D). Initial hydroboration of acrolein with tricyclopentylborane gave boron enolate **196**.[140]



196 **197**

Hydrolysis of **196** generates an enol and thereby the aldehyde (**197** in 88% yield).[141] Conjugated ketones react in a similar manner to give substituted ketone products.[142] Brown and co-workers noted that the reaction with acrolein was a useful method for the ***three–carbon extension*** of a carbon chain. It was also observed that the reaction was inhibited by addition of free radical inhibitors such as galvinoxyl, which implies that initial addition to the conjugated system probably proceeded by a free radical chain mechanism.[143]

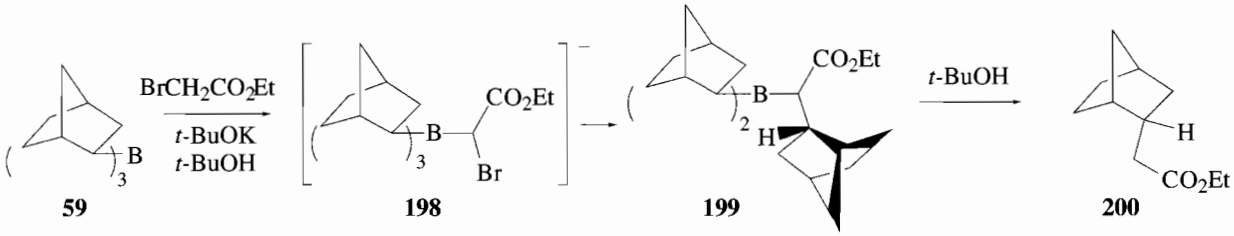
The relatively simple functional group transform for this reaction is:



5.4.G. Carbanions Containing Boron, Boron Enolates, and Enolate-Like Derivatives

Organoboranes react with bromine to form brominated boranes,[144] but they also react with brominated substrates. α-Bromo esters, for example, react with organoboranes to give coupling products if a base is added to the bromination reaction.[145a] Adding a base suppresses radical bromination, allowing an ionic reaction to

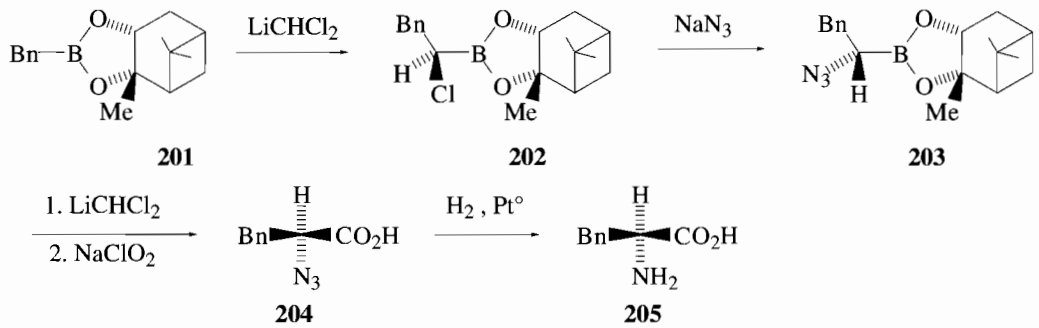
predominate. This transformation has been successfully applied several different classes of molecules, including α-bromoketones, α-chloro-nitriles, α-bromosulfoxides, and 4-bromocrotonates.[9] If phenyl or arylboranes are used as the organoborane partner, bromoesters can be arylated.



59 **198** **199** **200**

If an α-bromo carbonyl compound such as ethyl α-bromoacetate is treated with base, an enolate is formed (secs. 9.2, 9.4.B) and it can react with a trialkylborane to give an *ate* complex such as **198**, formed from ethyl bromoacetate and trinorbornylborane (**59**). The *ate* complex rearranges via a B→C shift that transfers an alkyl group from boron, replacing the bromine and giving **199**.[145a] The protonated base (the conjugate acid in this case is *tert*-butanol) generated by the initial enolate forming reaction is a sufficiently strong acid to initiate loss of boron. The resulting enol tautomerizes to ester **200** in 85% yield.[145a]

A related azide reaction was used to prepare phenylalanine.[146] Chiral borinane **201** reacted with lithium dichloromethane ($LiCHCl_2$) to give **202**. Subsequent reaction with sodium azide gave **203**. Reaction with a second equivalent of $LiCHCl_2$ was followed by oxidation with $NaClO_2$ to give azido acid **204**. Catalytic hydrogenation (sec. 4.8) gave phenylalanine (**205**) in 63% overall yield.[146]



201 **202** **203**

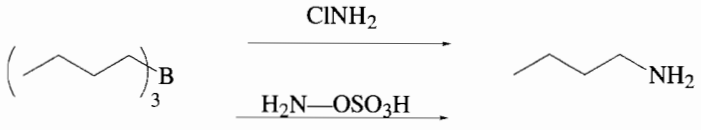
204 **205**

The transforms possible by these reactions are

5.5. AMINES AND SULFIDES VIA HYDROBORATION

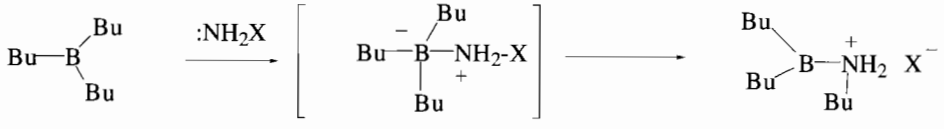
Hydroboration reactions can be modified to incorporate both nitrogen and sulfur into organic molecules. The most common heteroatom is nitrogen but there are a few examples where sulfur or even metals have been inserted into organic molecules.

5.5.A. Nitrogen–Containing Compounds

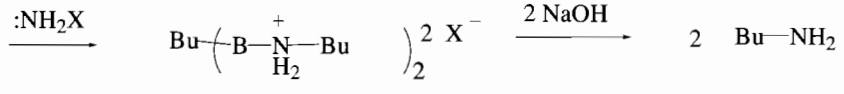


206

Trialkylboranes are converted to primary and secondary amines in a convenient manner.[147] Reaction of chloramine ($ClNH_2$) or hydroxylamine *O*-sulfonic acid (H_2N-OSO_3H) with trialkylboranes give primary amines.[148] Treatment of tributylborane with either reagent, for example, gave 1-aminobutane (**206**). The reaction proceeds via attack by nitrogen at the boron to give *ate* complex **207**. A B→N alkyl shift proceeds with expulsion of the leaving groups (X^- or HSO_4^-) to give **208**. The initially formed **208** can react with a second equivalent of amine to give **209**, and subsequent treatment with NaOH leads to cleavage that generates the alkylamine (**206**). Hindered organoboranes require temperatures of ≈ 100°C for this reaction.[149]

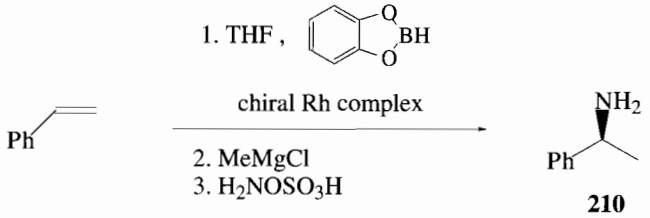


207 **208**



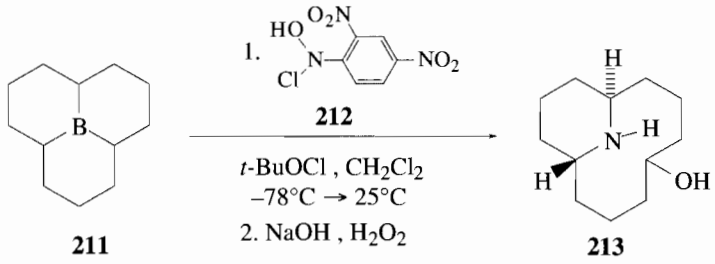
209 **206**

Aromatic boranes usually give poor yields of amines, although this can be improved by using Lewis acids. Lewis acids promote the rearrangement (there is a favorable intramolecular reaction) because of the proximity of the aromatic nucleus to the aminating species. Asymmetric hydroboration is possible in these reactions, giving chiral, nonracemic amines. When styrene was treated with catecholborane in the presence of a chiral rhodium catalyst, and then treated with MeMgCl (Et_2Zn can also be used), a complex is formed that generates a chiral borane. Subsequent treatment with H_2NOSO_3H gave a 54% yield of **210** in 87% ee.[150]

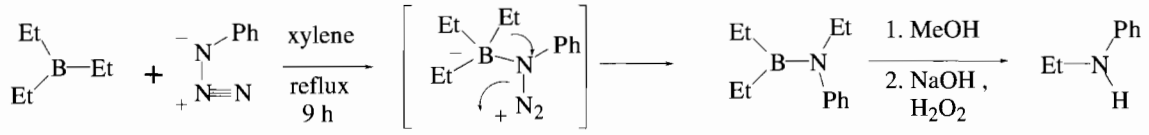


210

It is also possible for two alkyl groups to migrate from boron to an intermediate such as **207**.[151] When borane **211** was treated with *N*-chloro-*O*-(dinitrophenyl)hydroxylamine (**212**), a double migration of the alkyl groups led to amino alcohol **213** upon oxidation.[152]

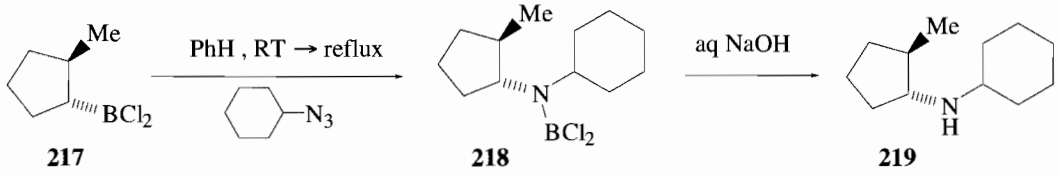


Azides react with trialkylboranes and the resulting intermediate can be converted to an amine but the initial reaction requires high temperatures. Secondary amines are produced by this reaction.[153] In the example shown, the boron in triethylborane is attacked by a nitrogen of phenyl azide (**214**), to form the usual *ate* complex, **215**. A B→N shift of an ethyl group generated **216** via expulsion of nitrogen. Methanolysis and oxidation gave the secondary amine (*N*-ethylaniline), in 78% yield.[153] The oxidation step was required only



214 **215** **216**

to destroy excess borane. Alkyldichloroboranes react with azides to give secondary amines,[154a] and dialkylchloroboranes give the same reaction.[154b] Dichloroborane reacted with 1-methylcyclopentene to give **217**. Reaction with cyclohexyl azide generated a new chloroborane (**218**) and this was treated with aqueous hydroxide to give an unsymmetrical secondary amine (**219**) in 90% yield. The rearrangement and oxidation proceeded with complete retention of the trans geometry in the cyclopentane ring.[154a] When trialkylboranes react with chlorodimethylamines, the products are tertiary dimethylamines, but a radical scavenger such as galvinoxyl must be added to suppress competing radical reactions.[155]



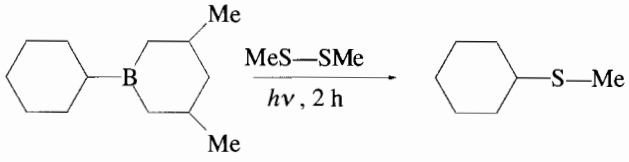
217 **218** **219**

5.5.B. Sulfur

Trialkylboranes react with organic disulfides to give thioethers (sulfides) but air or light is required because the reaction proceeds by a radical chain process.[156] This reaction is very slow in the dark and ultraviolet (UV) light is required for reasonable reaction rates. Trioctylborane reacts with dimethyl disulfide under these conditions to give methyl 1-octyl sulfide in 95% yield.[156] The mixed borane B-cyclohexyl-3,5-dimethylborinane (**220**), gave 94% of cyclohexyl methyl sulfide (**221**) under the same conditions.[156]

This section illustrates several specific transformations of organoboranes that are synthetically useful. The preparation of unsymmetrical sulfides is increasingly important since chiral sulfoxides can be prepared (sec.

3.9.A) and used in organic synthesis. α-Lithio sulfides give useful carbanion reactions and sulfur ylids can be formed (secs. 8.6, 8.8.B). The difficulties in preparing primary and secondary amines by traditional methods (from halides or tosylates via reaction with imides or azides, sec. 2.7) make the hydroboration–amination sequence a mild and useful alternative for the synthesis of amines.



220 **221**

The functional group transforms available in this section are

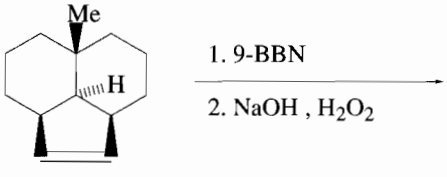
5.6. CONCLUSION

This chapter concludes the discussion of functional group exchange reactions that are used most commonly in organic synthesis. Hydroboration provides alternatives to many of the transformations described in chap. 1, and adds many unique ones. Hydroboration also provides new examples of controlling asymmetric induction by proper design of reagents. This idea will be reviewed in chap. 6 and it will include general methods for controlling selectivity. Problems unique to forming cyclic compounds will also be discussed.

HOMEWORK

1. Virtually all of the functional group transforms associated with organoboranes involve conversion to an *ate* complex. Explain why this is the case.

2. Give the major product of the reaction shown, and discuss all forms of selectivity that apply to it.



3. Predict the structure of each product, A–F.

A + NH_2OSO_3H ⟶ **B**

A + CH_3CO_2D, diglyme, 100°C ⟶ **C**

A + H_2O_2, KOH ⟶ **D**

A + I_2, NaOH ⟶ **E**

A + (1) CO, H_2O (2) NaOH, H_2O_2 ⟶ **F**

4. For each of the following, draw an appropriate transition state and predict the major product(s).

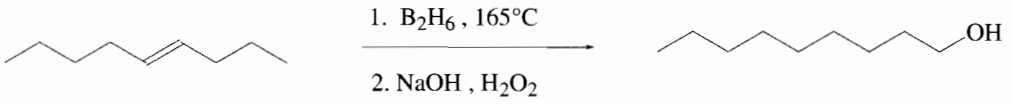
(a) (–)-IpC_2BH + (3*Z*) hexene

(b) (–)-IpC_2BH + 6-methyl-(3*E*)-octene

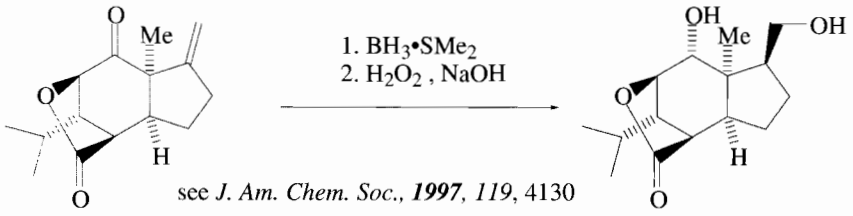
(c) (+)-$IpCBH_2$ + (3*E*)-hexene

5. Give three different examples of carbon–carbon bond–forming reactions involving boranes. Show all starting materials, reagents, and product(s).

6. Provide a mechanistic rationale for the following transformation:

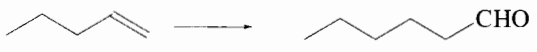


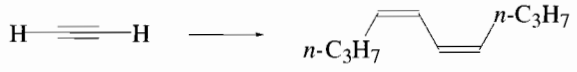
7. Provide a rationale for formation of the indicated product, paying particular attention to the stereochemistry of the secondary alcohol.



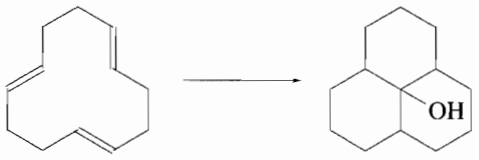
see *J. Am. Chem. Soc.*, ***1997***, *119*, 4130

8. The following transformations are very convenient using a hydroboration strategy. Discuss the possibility of alternative synthetic routes that do <u>not</u> involve hydroboration.

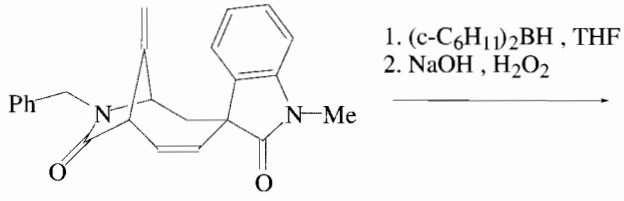
(a) 

(b) 

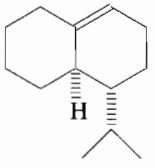
(c)

(d) 

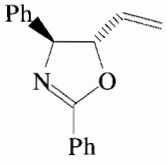
9. Predict the major product of this reaction and justify the stereochemistry of the final product.



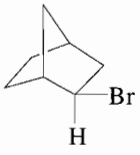
10. In each case, give the major product or products. Remember stereochemistry where it is appropriate.

(a) 

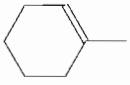
1. B_2H_6
2. CrO_3 , pyridine

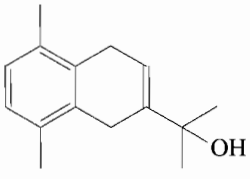
(b) 

1. 9-BBN , THF
2. NaOH , H_2O_2

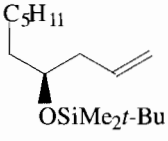
(c) 

$Et_3B—D^-Li^+$
THF , reflux

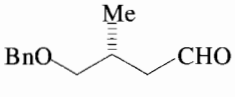
(d) 
B_2H_6 , 160°C
1-decene

(e) 

1. B_2H_6
2. H_2O_2 , NaOH

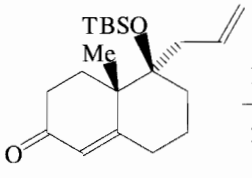
(f) 

1. 9-BBN , THF
2. H_2O_2 , NaOH

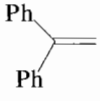
(g) 

1.

THF , –100°C
2. NaOH , H_2O_2

(h) 

1. 9-BBN , THF
2. NaOH , H_2O_2

(i) 

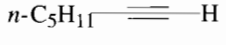
1. catecholborane , 100°C
2. Me_3SiCHN_2 , THF
3. NaOH , H_2O_2
4. Bu_4NF , THF

(j)

1. $HBBr_2•SMe_2$
2. BBr_3
3. HC≡CBu
4. I_2 , KOAc
5. *t*-BuLi
6. MeOH

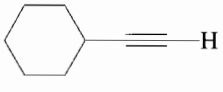
(k)

1. disiamylborane
2. HC≡CPh
3. NaOMe
4. 2-methylpropanoic acid
100°C

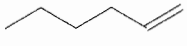
(l) 

1.

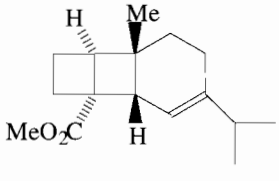
2. PhI , NEt_3 , cat Pd

(m) 

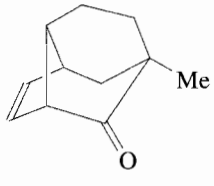
1. 9-BBN
2. PhCHO

(n) 
1. B_2H_6
2. CO , ethylene glycol
heat
3. NaOH , H_2O_2

11. Predict the major product. Explain the selectivity of each reaction.

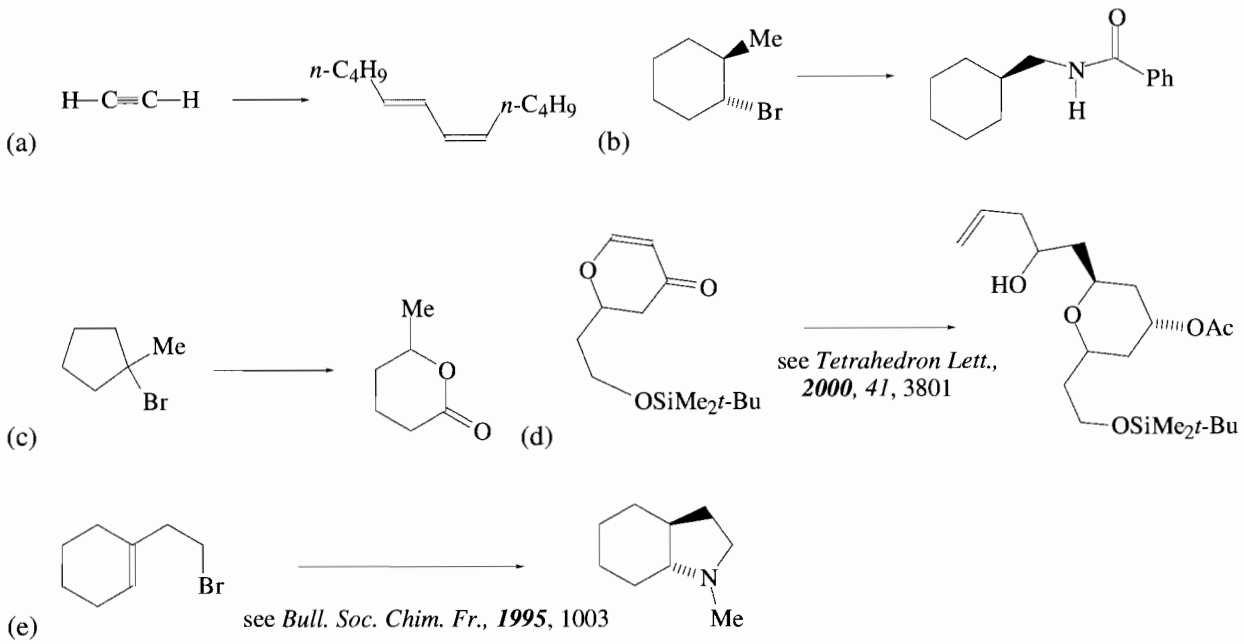
(a) 

1. B_2H_6
2. NaOH , H_2O_2

(b) 

1. 9-BBN
2. H_2O_2 , NaOH

12. In each case, provide a suitable synthesis. Show all reagents and intermediate products.



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CHAPTER 6

STEREOCONTROL AND RING FORMATION

6.1. INTRODUCTION

Chapters 1–5 contain many examples of regioselective, diastereoselective, and enantioselective reactions involving both acyclic and cyclic molecules. The chelating effect of certain heteroatom containing substrates was also discussed, with examples of how chelation control could override the effect of nonbonded interactions. There were examples that illustrated the ability to influence, and sometimes control, the facial selectivity of a reaction in both acyclic and cyclic systems. Conformational preferences (orientations) in the substrate were also shown to be important. The purpose of this chapter is to focus attention on methods for either controlling the conformational effects in a molecule or exploiting unalterable conformational effects to achieve a specific synthetic purpose. This chapter provides a review that will summarize key concepts and focus attention on stereoselectivity prior to discussing carbon–carbon bond-forming reactions.

Section 6.5 in this chapter will summarize methodology for controlling the stereochemistry of acyclic molecules by taking advantage of the conformational bias of cyclic molecules. The cyclic carrier is manipulated and then opened to give a certain stereochemical pattern in the acyclic molecule. Another section deals with intramolecular cyclization reactions for generating small, medium, and large ring compounds. The limitations and synthetic value of these ring forming reactions will also be discussed. This chapter will present the fundamental ways an organic chemist recognizes the conformational and topological features of a molecule and uses that information to give the desired result. This strategy includes recognition of those molecular features that will prevent the desired reaction or lead to incorrect stereochemistry, allowing the chemist to design alternatives.

6.2. STEREOCONTROL IN ACYCLIC SYSTEMS

Reactions of acyclic molecules can generate diastereomers and the term controlling stereochemistry usually refers to an attempt to generate one diastereomer in preference to another as the major product of a reaction. This section will classify various stereocontrol problems and outline general methodologies that are available to solve each problem. The types of situations where attempts to control stereochemistry are important include:

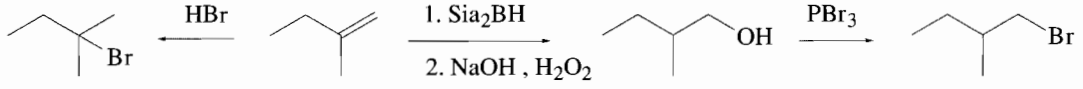
1. Regioselectivity (Markovnikov/anti-Markovnikov)
2. Retention versus Inversion of configuration
3. cis–trans Selectivity
4. syn–anti Selectivity
5. Heteroatom chelation effects

Reactions where these effects are important were presented in previous chapters. The carbon–carbon bond forming reactions in succeeding chapters contain many additional examples. The purpose of this chapter is

not to solve specific synthetic problems (diastereoselective enolate alkylation and condensations, selectivity in the Claisen rearrangement, etc.) but rather to define the problems in a general sense. Approaches for solving these problems will be discussed, but specific solutions are usually postponed to later chapters.

6.2.A. Regioselectivity

A typical reaction that illustrates Markovnikov addition is the reaction of HBr with 2-methyl-2-butene to give 2-bromo-2-methylbutane (**1**, sec. 2.10.A). This reaction proceeds by formation of the more stable carbocation, which reacts with the nucleophilic bromide ion. If the anti-Markovnikov bromide (the bromine resides on the less substituted carbon) is desired, a different mechanistic pathway must be followed. A typical anti-Markovnikov addition reaction is addition of borane to the alkene, giving primary alcohol (**2**) after oxidation of the intermediate alkylborane (sec. 5.4.A).[1] This alcohol can be converted to the anti-Markovnikov bromide, **3**, by treatment with PBr_3. The key to controlling such reactions is a fundamental



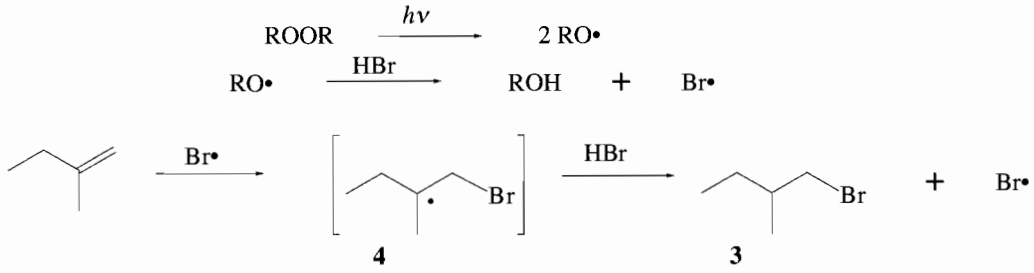
1 **2** **3**

understanding of the different mechanisms leading to their formation. Addition of HBr generates a carbocation, with the charge residing on the more substituted carbon. The three alkyl substituents attached to the positive center provide more electronic stabilization to the p orbital of the cation than is possible in the other possible intermediate, the primary carbocation. Trapping with the nucleophilic bromide ion generates **1** as the major product. If a reaction generates a cation, Markovnikov orientation is sure to result. If anti-Markovnikov addition is desired, *a change in reaction mechanism must occur.*

The hydroboration reaction with alkenes to produce alkylboranes[1] (sec. 5.2) proceeds by a four-center transition state rather than a cationic intermediate . The regiochemistry of the final alkylborane product is controlled by the nonbonded steric interactions of the groups attached to boron (in this case *sec*-isoamyl from the disiamylborane) and the groups on the alkene. Oxidation with basic hydrogen peroxide converts the borane to the anti-Markovnikov alcohol (**2**). The difference in regiochemistry between **1** and **2** arose because the mechanism for generating each relied on difference factors.

The previous example changed the regiochemistry by changing the reagent as well as the fundamental type of reaction. An example of changing regiochemistry by changing the mechanism of a reaction involving similar or the same reagent is illustrated by the anti-Markovnikov addition of HBr to alkenes in the presence of peroxides (secs. 2.10.A, 13.5.B).[2] This reaction generates a carbon radical (**4**) by initial addition of a bromine radical to the alkene. Bromine radical is formed by homolytic cleavage of an added peroxide (sec. 13.3), followed by reaction with HBr. The accepted mechanism suggests that the more stable radical is formed upon addition of Br•, also the result of electronic stabilization by the three alkyl groups in **4** rather than the alternative primary radical. It is also possible that the addition occurs at the less hindered site and that there is a kinetic component to the reaction. Reaction of **4** with HBr gives the primary bromide (**3**) and generates

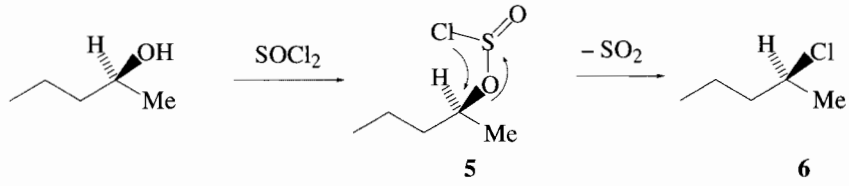
another bromine radical in a chain propagation step. Since the bromine adds first to give the more stable tertiary radical, hydrogen is transferred to that radical, which is a net reversal of the regioselectivity of addition relative to the cationic reaction. This radical reaction works well only for HBr additions and not for HCl or HI,[2b] although RSH adds with an anti-Markovnikov orientation under radical conditions It follows, however, that radical type addition reactions will proceed in an anti-Markovnikov fashion[3,4] (secs. 13.3–13.6).



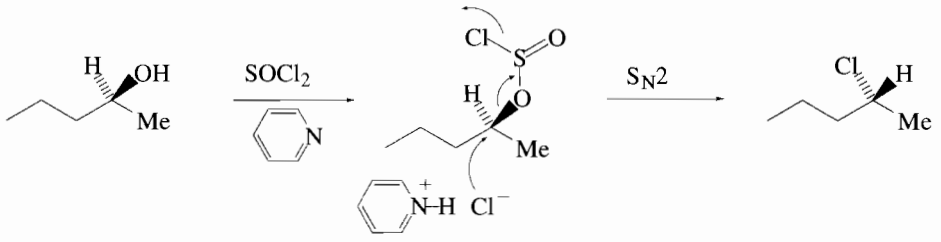
In general, cation and radical addition reactions generate reactive intermediates and reaction products are determined by the relative stability of the intermediate and the order in which the adding elements were delivered, assuming the reaction is not under kinetic control. With hydroboration, no intermediate is involved and although electronic factors are important, steric factors largely control the regiochemical outcome of the reaction. Control of regioselectivity is predictable by understanding the mechanism of the addition.

6.2.B. Retention versus Inversion of Configuration

A classical example of controlling the configuration of a stereocenter is conversion of a chiral secondary alcohol to the corresponding secondary chloride with thionyl chloride,[5] and it is also another example of changing stereochemistry by modifying the mechanism of the reaction. Both retention of configuration (neat $SOCl_2$) and inversion ($SOCl_2$ + pyridine) are possible (sec. 2.8.A).[5] Thionyl chloride reacts with (*S*)-2-pentanol to produce a chlorosulfinate ester (**5**). The HCl byproduct escapes from the reaction medium and an intramolecular delivery of chloride in what is called a S_Ni mechanism (see **5**),[5,6] with concomitant loss of

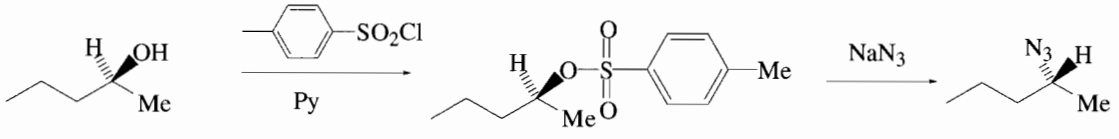


sulfur dioxide (SO_2) gives (*S*)-2-chloropentane (**6**). The synfacial delivery of chlorine generates the chloride with retention of configuration of the original hydroxyl moiety. If pyridine (or another basic tertiary amine) is added, then the HCl byproduct is trapped as the pyridinium hydrochloride salt and nucleophilic chloride ion is in the medium. Displacement of the chlorosulfinate ester by chloride in an S_N2 reaction (see **7**) gives chloride **8** with net inversion of configuration.[7] The presence or absence of a nucleophilic chloride ion allows one to control the stereochemistry of the reaction.



7 8

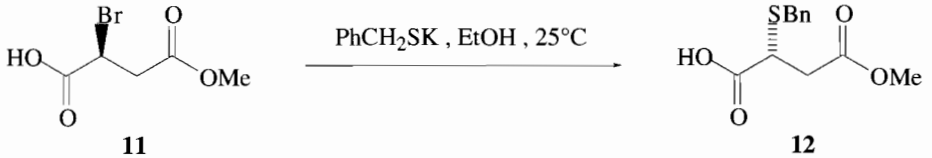
Formation of **8** shows that conversion of the OH unit to a leaving group allows an S_N2 reaction to occur. In general, both the hydroxyl and amine units are poor leaving groups. If the alcohol is converted to a



9 10

derivative with a weaker C-O bond and a greater tendency for displacement (such as an ester, sulfonate ester or phosphonate derivative), S_N2 type displacement is possible with inversion of that stereogenic center. A simple example of this process is conversion of *S*-2-pentanol to the corresponding tosylate (**9**) that can be displaced by nucleophiles such as azide to give **10**, with complete control of the stereogenic center. This sequence is an effective method for inversion of the stereocenter with attachment of a different functional group but not all nucleophiles are effective. If a nucleophile such as methoxide is used, the S_N2 reaction with **9** would give a methyl ether. Nucleophiles such as methoxide are strong bases, however, and elimination can occur to give an alkene via the E2 reaction (sec. 2.9.A). If the S_N2 reaction occurs the methyl ether can be isolated and in a subsequent step, the O—Me bond can be cleaved with iodotrimethylsilyl[8] (sec. 7.3.A.i) to give an alcohol. The use of highly polar, aprotic solvents such as DMF or DMSO can sometimes increase the yield of substitution product (secs. 2.6.A, 2.7.A.i) and minimize elimination by-products. Although feasible for simple molecules, reaction conditions and side reactions cause problems for complex molecules.

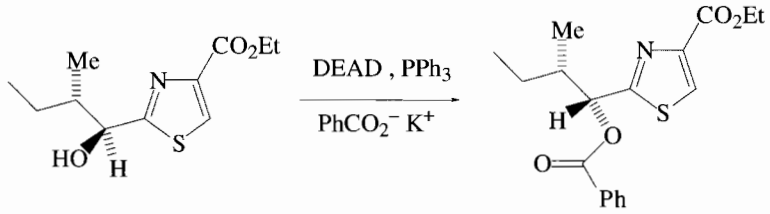
The ability to control a stereogenic center is illustrated by a simple S_N2 reaction in which (*S*)-bromide **11** was treated with the potassium salt of benzylthiol to give thioether **12** in 77% yield and 98% ee as part of the Seki et al. synthesis of an orally active 1-β-methylcarbapenam, TA-949.[9] The importance of solvent in this reaction is illustrated by differences in % ee. When THF was used, **12** was isolated in only 12% ee. It was raised to 48% *ee* in DMF and to 72% ee in water.[9]



11 12

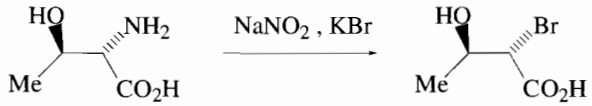
A successful and highly useful S_N2 reaction that is commonly used to change the stereochemistry of a reactive center is the **Mitsunobu reaction** (sec. 2.7.A.ii).[10] As initially formulated, the Mitsunobu reaction

involved mixing diethylazodicarboxylate (DEAD) and triphenylphosphine (Ph_3P) with an alcohol and nucleophiles such as carboxylic acid salts.[10] An example is the reaction of chiral alcohol **13** with the Mitsunobu reagents and potassium benzoate. The presence of an acid or acid salt (such as potassium benzoate) led to nucleophilic displacement with clean inversion to generate an ester, in this case **14**. Hydrolysis liberated the inverted alcohol, in Schmidt's synthesis of ulicyclamide[11]. The (*S*)-alcohol was inverted to the (*R*)-alcohol after initial formation of the acetate ester (NaOAc was used rather than potassium benzoate), using a parallel sequence of reactions.[11] Other nucleophiles can be used in the Mitsunobu reaction.



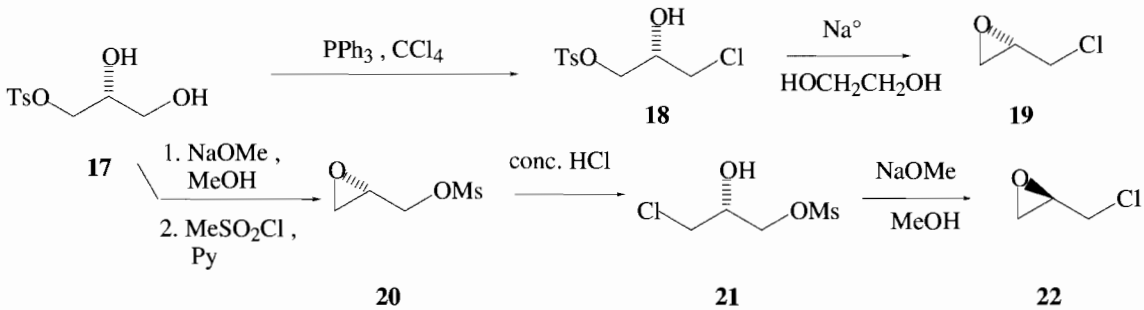
13 **14**

Methods other than the Mitsunobu reaction are available for controlling relative stereochemistry. An amino group, of course, can be converted to other functional groups and an interesting conversion is the NH_2 → Br transformation, with complete retention of configuration. Reaction of amino acid **15** with sodium nitrite ($NaNO_2$) and potassium bromide (KBr) gave the α-bromo acid (**16**) with complete retention of configuration,[12] a reaction first observed by Walden.[12b–d] This reaction was taken from Salzmann's synthesis of the potent carbapenam antibiotic thienamycin.[13] It is noted that this is a special case where the carboxylate unit participates in the reaction.



15 **16**

Another method for inverting or controlling stereochemistry is illustrated by conversion of (*D*)-mannitol to (*R*)- or (*S*)-epi-chlorohydrin.[14] Stereocontrol was obtained by manipulating differences in reactivity. Tosyl diol **17** (obtained from (*D*)-mannitol) was chlorinated selectively at the more reactive primary alcohol to give



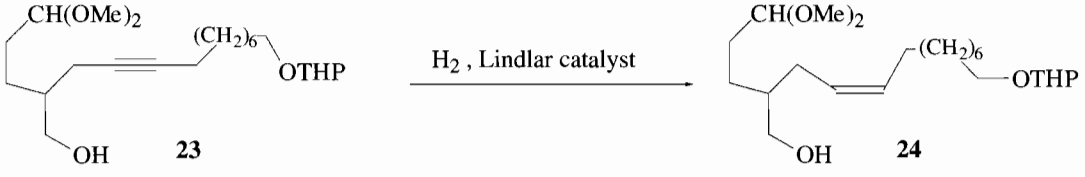
17 **18** **19** **20** **21** **22**

18. Treatment with sodium gave the epoxide (*S*)-epi-chlorohydrin (**19**).[14] Reaction of **17** with base, however, took advantage of the presence of the leaving group (tosylate) to form a hydroxy oxirane. Upon treatment of

this hydroxy epoxide with methanesulfonyl chloride, mesylate **20** was formed. Subsequent treatment with HCl opened the epoxide and gave chlorohydrin **21**, which gave (*R*)-epi-chlorohydrin (**22**) upon treatment with sodium methoxide (the OMs in **20** is a better leaving group than Cl in **18**). This example shows that understanding reactivity differences in a molecule can lead to control of the stereochemistry in chemical manipulations.

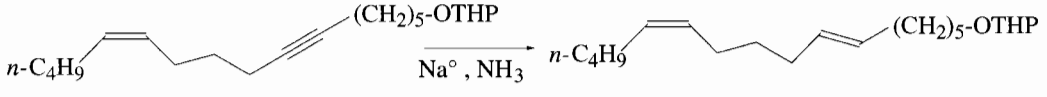
6.2.C. cis–trans Selectivity

Control of cis–trans-geometry is well illustrated by catalytic hydrogenation or alkali metal reduction of alkynes, as discussed in Sections 4.8.B and 4.9.C, respectively. The Lindlar catalyst (sec. 4.8.B) allows selective reduction of alkynes to the cis-alkene, as in the conversion of **23** to **24** in Kaiser's synthesis of niphatoxin B.[15] This contrasts sharply with treatment of an alkyne with alkali metals (sec. 4.9.C) to give the



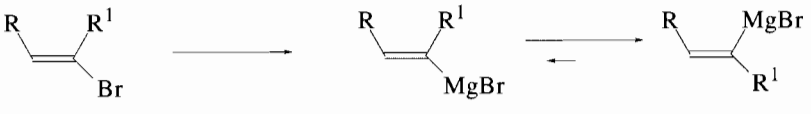
23 **24**

trans alkene, as in the conversion of **25** to **26**.[16] Once again, a fundamental understanding of the difference in these two reaction mechanisms allowed control of the cis–trans geometry of the final product. Control of cis–trans-geometry (diastereoselectivity) in cyclic systems will be discussed in Section 6.3.D.



25 **26**

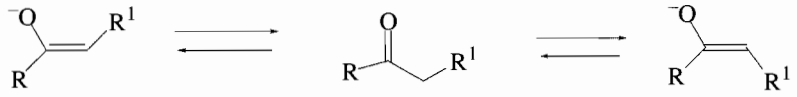
There are two other reactive species whose cis–trans isomerism can be important to the distribution of products, organometallics derived from vinyl halides, and enolate anions. The configurational stability of these species will be discussed in detail in Sections 8.4.F, 8.5.D and in Sections 9.2.C, 9.5, respectively. The



27 **28** **29**

problems that are associated with cis–trans isomerism, however, will be introduced here. When (1*E*)-bromo-1-propene (**27**) reacts with magnesium, Grignard reagent 1-propenylmagnesium bromide **28** (R = CH_3, R^1 = H, secs. 8.4.A, 8.4.F) is formed. Isomerization led to a mixture of the (*E*)-isomer (**28**) in 60–70% yield with 30–40% of the (*Z*)-isomer (**29**),[17] and this is reflected in the subsequent reactions of the Grignard reagent. Reactions of trans alkenyl organometallics usually give predominantly the trans alkenyl product and cis alkenyl halides give the corresponding cis alkenyl product. Significant amounts of isomerization accompany these reactions, and when this Grignard mixture reacts with carbon dioxide mixtures of the conjugated acid are produced.[17b]

When a ketone reacts with a suitable base (secs. 9.1, 9.2) an enolate anion is formed by removal of the α-proton. In the case of an unsymmetrical ketone such as **30**, a mixture of (*Z*)-enolate (**31**) and (*E*)-enolate (**32**) usually results (secs. 9.2.E, 9.5.A). This mixture influences the diastereoselectivity and enantioselectivity of enolate condensation reactions (sec. 9.5). Such a mixture of geometrical isomers generates both syn- and anti-products upon reaction with aldehydes so it is important to control or at least identify the geometry of the enolate. Several solutions to this problem have been developed, including formation of stable and separable enolate isomers and controlling reaction conditions to maximize production of one isomer.

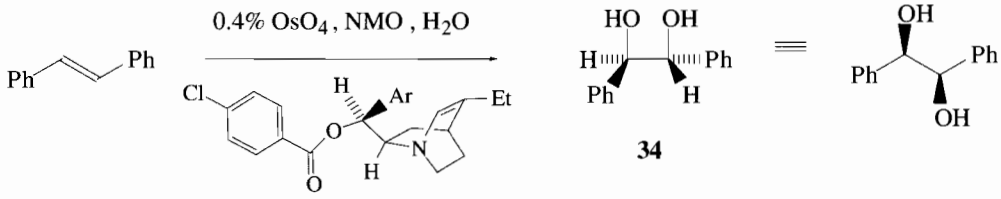


31 **30** **32**

These techniques will be discussed in Section 9.2, but an example is conversion of 3-pentanone to a 77:23 mixture of (*E*)- and (*Z*)-enolates by reaction with lithium diisopropylamide.[18] When the enolate was formed by treatment with lithium 2,2,6,6-tetramethylpiperidide (LTMP), only slightly greater amounts of the (*E*) -enolate were observed (86:14 *E/Z*). Addition of HMPA) to this reaction medium, however, led to a reversal of selectivity, favoring the (*Z*)-enolate (8:92). Under the best conditions, this (*E/Z*)-mixture will lead to a similar mixture of diastereomers in the products formed by reaction of the enolates. Some isomerization can occur in the deprotonation or condensation steps, and the product may isomerize under the reaction conditions.[19]

6.2.D. syn–anti Selectivity

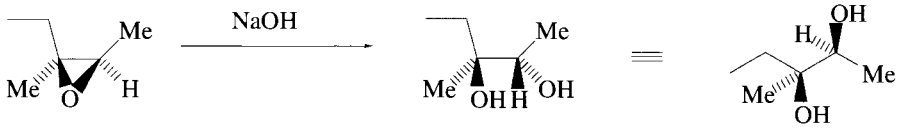
There are many reactions that generate a mixture of syn and anti diastereomers, and if the reaction is diastereoselective, one predominates. In Chapter 9, we will see many examples of this in connection with enolate anion condensation reactions. An example is the conversion of alkenes to 1,2-diols. Reaction of



33 **34**

alkenes with aqueous permanganate or osmium tetroxide (secs. 3.5.A–C) lead exclusively to a cis diol via the syn hydroxylation mechanism. It is a diastereospecific reaction. Sharpless developed a protocol for high asymmetric induction by adding quinidine (**33**), with either *N*-methylmorpholine oxide (NMO) or *tert*-butylhydroperoxide with osmium tetroxide (OsO_4).[20] As seen in the hydroxylation of *trans*-stilbene, the syn-diol **34** is the major product.[20] An alternative method for stereoselectivity generating diols begins with an epoxide (**35**), formed by oxidation of an alkene (sec. 3.4), which is opened to the diol with hydroxide (or another oxygen nucleophile). In this example, the syn diol (**36**) is formed via backside approach of the

nucleophilic hydroxide to the less hindered carbon of **35**. Epoxide **35** is assumed to be optically active so the enantiopurity of the diol product can be determined and this is used as a measure of the stereoselectivity of the ring opening. Both **34** and **36** are syn diols but they result from different mechanistic pathways. In some cases it is possible to influence the direction of epoxide ring opening. In 85% aqueous DMSO, 1-phenyl cyclohexene oxide reacted with KOH to give the trans diol. As in previous sections, changing to a different

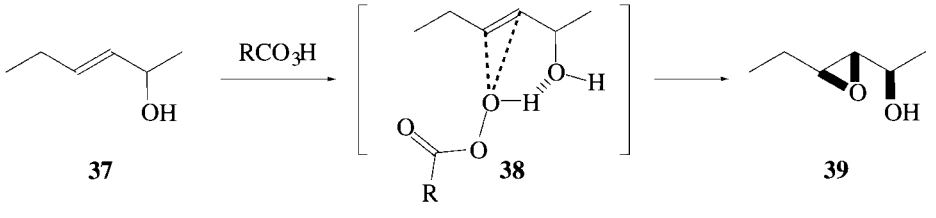


35 **36**

mechanistic process can modify the selectivity. Treatment of this epoxide with a catalytic amount of perchloric acid or sulfuric acid (in 90% aqueous DMSO), for example, gave a mixture of cis and trans diols in roughly equal amounts, although there was a slight excess of the trans.[21] In this latter case, acid catalyzed ring opening proceeds via a carbocation, which reacted with water to give a mixture of diastereomers. When ring opening was initiated by KOH in the nonaqueous environment, an S_N2 like mechanism led to formation of a single diastereomer via backside attack.

6.2.E. Heteroatom Chelation

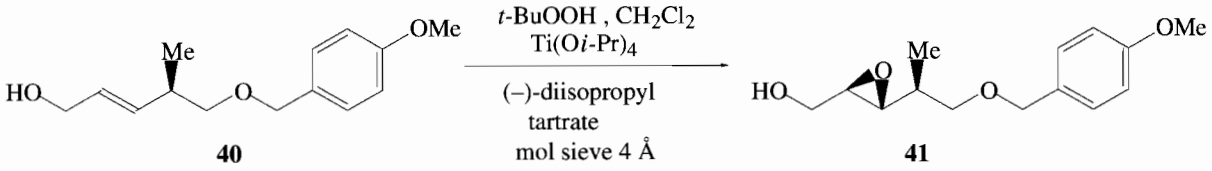
One major way to control diastereoselectivity is to take advantage of the chelating effect of neighboring heteroatom groups (neighboring group effects) with certain reagents, which can be illustrated by reaction of chiral allylic alcohol **37** with a peroxyacid. Coordination with the oxygen (see **38**) and delivery of the electrophilic oxygen from that side[22] gave epoxy-alcohol **39** as the major diastereomer, which means that coordination directs the stereochemical course of the reaction. In Chapter 3 and especially in chapter 4, the neighboring group effects of heteroatoms on epoxidation, hydride reduction and hydroboration, as well as haptophilic effects in catalytic hydrogenation (sec. 4.8.B) were important for the observed diastereoselectivity.



37 **38** **39**

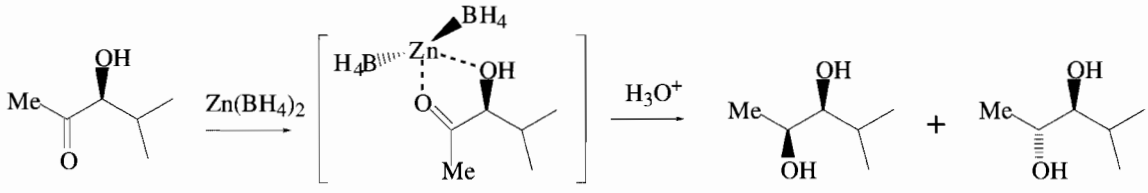
The **Sharpless asymmetric epoxidation** (sec. 3.4.D.i) exploits this chelation effect because its selectivity arises from coordination of the allylic alcohol to a titanium complex in the presence of a chiral agent. The most effective additive was a tartaric acid ester (tartrate), and its presence led to high enantioselectivity in the epoxidation.[23] An example is the conversion of allylic alcohol **40** to epoxy-alcohol **41**, in Miyashita's synthesis of the C_8-C_{15} segment of (+)-discodermolide.[24] In this reaction, the tartrate, the alkenyl alcohol, and the peroxide bind to titanium and provide facial selectivity for the transfer of oxygen from the peroxide to the alkene. Binding of the allylic alcohol to the metal is important for delivery of the electrophilic oxygen and

also for controlling orientation of the alkene relative to the epoxidation agent. In this example, coordination with the chiral tartrate led to preferential delivery from the opposite (*si*) face. The reaction is not only enantioselective, but diastereoselective, and syn–anti-selectivity can be controlled by the coordination of the substrate to the (+) or (-) tartrate.

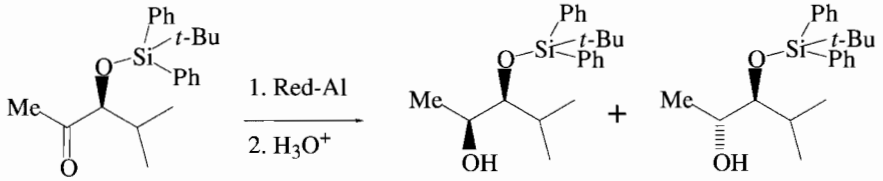


40 **41**

The **Cram chelation model** (sec. 4.7.B) is an example where the chelation effects of the heteroatom influence the rotamer population and, thereby, the selectivity of the reduction. Zinc borohydride [$Zn(BH_4)_2$], effectively chelates the carbonyl oxygen and alcohol oxygen atoms in the reduction of **42** and leads to intermediate **43**. Transfer of hydride to the carbonyl gave primarily the anti diastereomer, **45** (4:96, **44/45**). When the chelating hydroxyl group was blocked as a *tert*-butyldiphenylsilyl ether (in **46** - sec. 7.3.A.i), reduction with Red-Al (sec. 4.3) led to a reversal in selectivity (96:4, **47/48**).[25] The ability to chelate a heteroatom varies with the reagent used. Lithium aluminum hydride shows less selectivity, due in part to poorer coordination with the heteroatom and reduction of **42** gave a 27:73 mixture of **44** and **45**, respectively.[25]



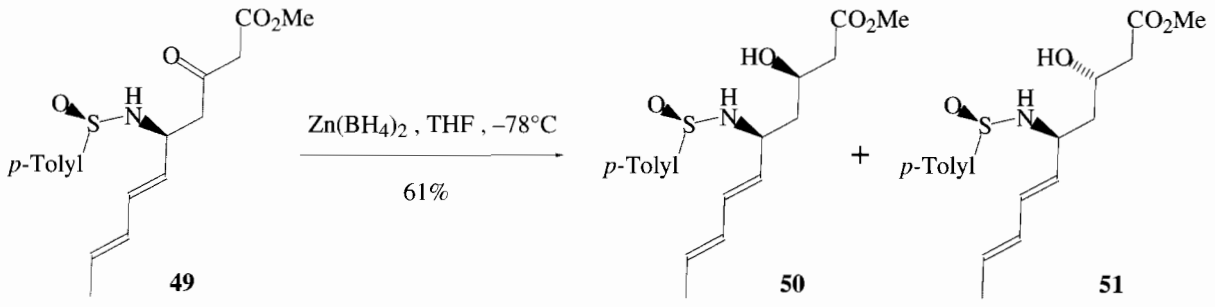
42 **43** **44** **45**



46 **47** **48**

Other heteroatoms can coordinate with reducing agents to afford high selectivity. Reduction of **49** with zinc borohydride, for example, gave a 76:24 mixture of **50** and **51** (61% yield), which was eventually converted by Davis to (–)-SS20846A,[26a] which is (4*S*)-hydroxy-(2*S*)-(1-pentadienyl)piperidine and a proposed intermediate in the biosynthesis of the potent antimicrobial agent streptazolin.[26b,c]

The examples in Sections 6.2.D and 6.2.E show that chelation effects can be controlled by the nature of the heteroatom (alcohol vs. ether, amine vs. amide vs. sulfonamide vs. azide) and the choice of reagent (changing the metal in metal hydrides for example). Such chelating effects have also been used extensively in cyclic systems, and those applications will be discussed in Sections 6.4 and 6.5.



6.3. STEREOCONTROL IN CYCLIC SYSTEMS

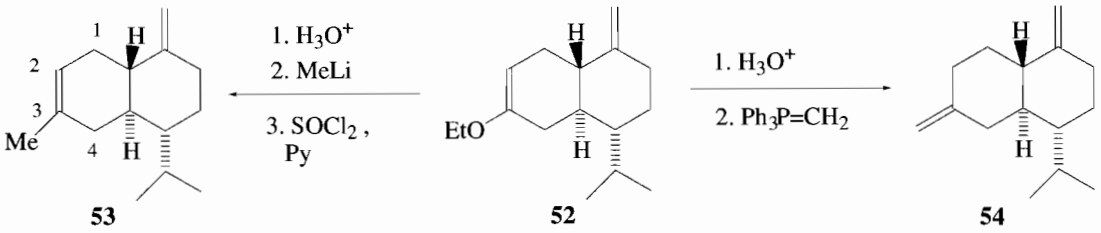
Many of the problems encountered in acyclic systems also arise in cyclic systems. The methods for controlling Markovnikov and anti-Markovnikov regiochemistry and retention or inversion of the configuration are essentially the same as in acyclic systems. It is difficult to separate regiochemical (mode of addition) effects and retention versus inversion effects from cis–trans isomerism in cyclic molecules. Addition to a substituted π bond leads to geometrical isomers, and in most cyclic systems control of the absolute configuration of a stereogenic center is associated with cis–trans isomers and/or with diastereomer formation. The terms syn and anti have no meaning in cyclic systems, and only three discussions fundamental to cyclic molecules will be presented: control of diastereoselectivity, inversion of configuration of a stereogenic center, and the chelating effects of heteroatoms.

An important and differentiating feature of cyclic systems is the relatively rigid conformations assumed by these molecules (sec. 1.5.B). In both Chapters 3 and 4, conformational bias had a profound effect on reaction pathways and also on the trajectory of attack. These effects provide the tools to control selectivity.

6.3.A. Regioselectivity

The problems associated with regioselective addition to cyclic molecules are essentially the same as those noted in acyclic molecules. Reaction of HBr with methylcyclopentene, for example, is highly regioselective for the Markovnikov product, giving the tertiary bromide, 1-bromo-1-methylcyclopentane. Hydroboration of methylcyclopentene, however, gave an 86:14 mixture of *trans*-2-methyl-2-cyclopentanol and 1-methyl-1-cyclopentanol, favoring the former.[27] As with acyclic systems, increasing the steric bulk of the hydroboration reagent led to increased regioselectivity. Reaction with 9-BBN followed by oxidation gave an almost quantitative yield of *trans*-2-methyl-2-cyclopentanol.[28] As with acyclic molecules, regioselectivity is controlled by selecting a reaction with a different mechanism.

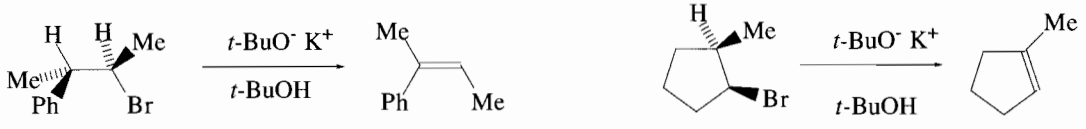
Alkene positional isomerism is a problem that arises from time to time. It is conceptually related to regiochemistry and is presented here. Careful synthetic planning is usually required to solve this problem, as illustrated by the Burk–Soffer synthesis of ε-cadinene (**53**) and γ_2-cadinene (**54**).[29] Conversion of **52** first to the ketone, then to the tertiary alcohol, and finally to the tertiary chloride allows E2 elimination to give **53**. Conversely, Wittig olefination (sec. 8.8.A) of the ketone gave the exo methylene derivative, **54**. It is important to note that formation of the C2–C3 C=C unit is favored for *trans* decalin derivatives over the C3–C4 unit.



53 **52** **54**

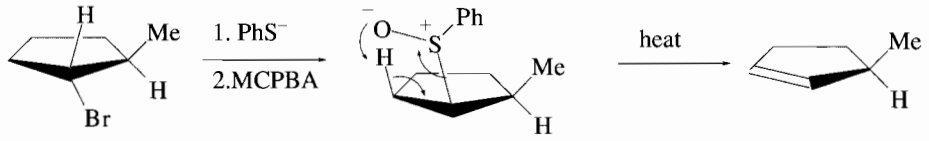
6.3.B. Bredt's Rule

As we have just seen in the formation of **53** or **54**, regioselectivity is important is the formation of double bonds in elimination reactions. In Chapter 2 both E2 (anti) elimination (sec. 2.9.A) and syn elimination (sec. 2.9.C) processes were discussed. Regiocontrol in the elimination was achieved by binding the base to the



55 **56** **57** **58**

molecule (an internal base for syn elimination) or by allowing the base to attack the molecule in a bimolecular reaction (an external base for anti elimination). Treatment of a halide such as **55** with potassium *tert*-butoxide in *tert*-butanol led to anti elimination and formation of the more substituted alkene (**56**), which is due to the late transition state of the reaction, invoking the Hammond postulate, and the electronic requirements that position the leaving group anti to the hydrogen being removed, effectively locking the conformation in that transition state. The same effect is observed in cyclic halides such as *cis*-2-bromo-1-methylcyclopentane (**57**), which gives methylcyclopentene (**58**) upon treatment with base. The major difference, of course, is the

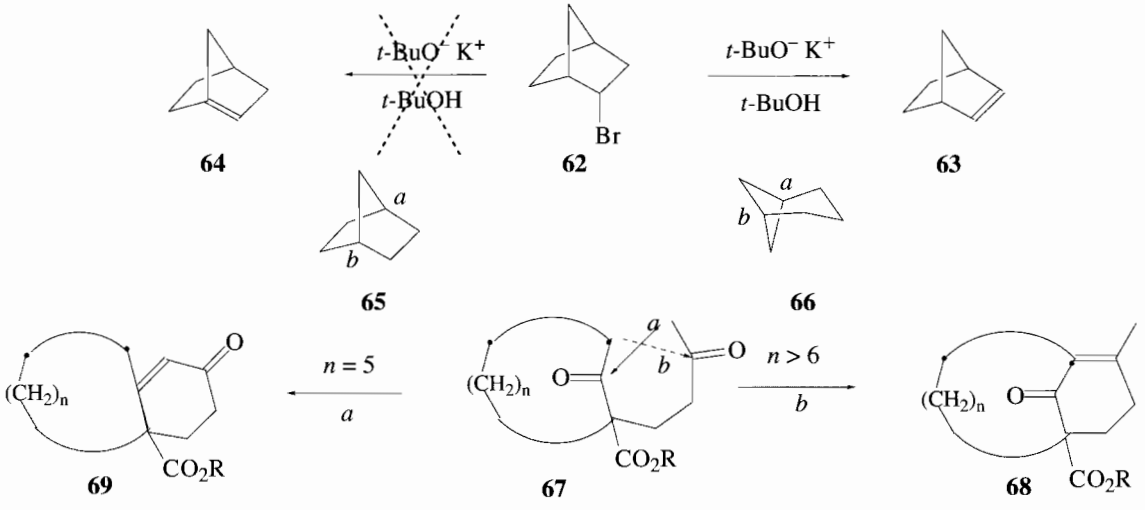


59 **60** **61**

inability of the ring to rotate about the carbon–carbon bonds. Nonetheless, the more highly substituted (more stable) alkene is also produced. For both syn and anti elimination, the β-hydrogen and the leaving group are fixed by the regiochemistry of the halide. Syn-Elimination involves intramolecular attack of base, dictating removal of the β-hydrogen that is syn to the leaving group. The steric demands of this syn transition state make approach and removal of the less substituted β-hydrogen energetically more favorable. Conversion of **59** to sulfoxide **60**, therefore, gives the less substituted alkene (3-methyl-1-cyclopentene, **61**) upon thermolysis.

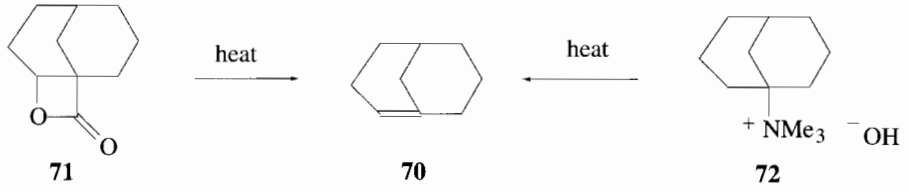
A unique regiochemical problem arises in small bicyclic compounds. Elimination of the bromine and H in 2-bromonorbornane (**62**) gave exclusively the Δ^2-norbornene (**63**) and none of the Δ^1-norbornene (**64**). To form an alkene such as **64** would require that bridgehead carbon atoms be compressed toward planarity, but the π overlap required for a planar C=C unit would be diminished due to structure-imposed twisting. The

transition state energy required for elimination to a bridgehead carbon in small systems is very high, and small bicyclic systems *cannot* accommodate this great increase in strain. The observation that carbon–carbon double bonds cannot be formed to bridgehead atoms in small bicyclic rings is formally called **Bredt's rule**.[30] As originally stated by Bredt, "in systems of the camphane (**65**) and pinane (**66**) series and related compounds, the bridgehead carbons (*a* and *b*) cannot be involved in a carbon double bond."[30b,c] As a corollary, "reactions which should lead to such compounds will be hindered or will take a different course."[30a] It has been noted that small bridgehead systems that tolerate a trans double bond will violate Bredt's rule.[31,30]



How large must ring systems be before they fail to comply with Bredt's rule? For [2.2.1], [2.1.1], and [1.1.1] bicyclic systems, Bredt's rule is applied. Prelog established that cyclization of **67** gave **68** when $n > 6$.[32,30e] When $n = 5$, both **68** and **69** were formed, but **68** was not formed when $n < 5$.

Fawcett attempted to correlate the lower limit of Bredt's rule by calculating the sum of the numbers of the bridged atoms [m + n + o = *S*] in systems such as **65** and **66** with three bridges.[30d] For **65**, $S = 2 + 2 + 1 = 5$, and for **66**, $S = 3 + 1 + 1 = 5$. In Prelog's example (**67**), this [6.3.1] system has $S = 9$ when $n = 5$, and Bredt's rule does not apply. When the values of n are < 5, however, Bredt's rule applies for **67**. Relatively small bridgehead alkenes with a [3.3.1] system such as **70** ($S = 7$) can be prepared by pyrolysis of β-lactone **71** or ammonium salt **72**.[33] Figure 6.1[30e] shows several small bicyclic ring systems for $S = 2$ to $S = 7$, and analysis of these alkenes suggests that the constraints upon Bredt alkenes are important when *S* is 7 or less.



Köbrich established three guidelines[30e] that govern the application of Bredt's rule.

1. For homologs with different *S* values, the ring strain varies inversely with *S*.
2. For a given *S*, the ring strain varies inversely with the size of the larger of the two rings with respect to

which the bridgehead bond is endocyclic.

3. For a given bicyclic ring skeleton, the ring strain varies inversely with the size of the bridge containing the bridgehead double bond.

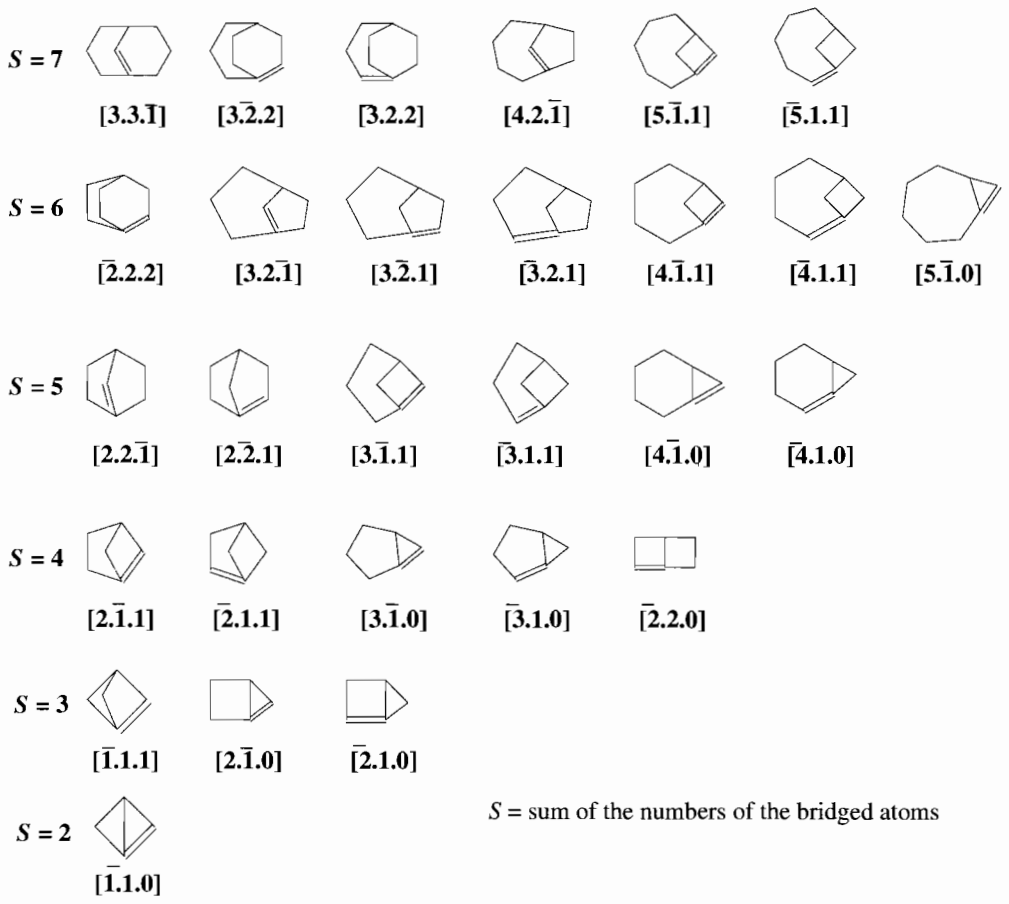


Figure 6.1. Typical Bredt alkenes.

[Reproduced with permission from Köbrich, G. *Angew. Chem. Int. Ed. Engl.*, ***1973***, *12*, 464. Copyright 1973 VCH Weinheim.]

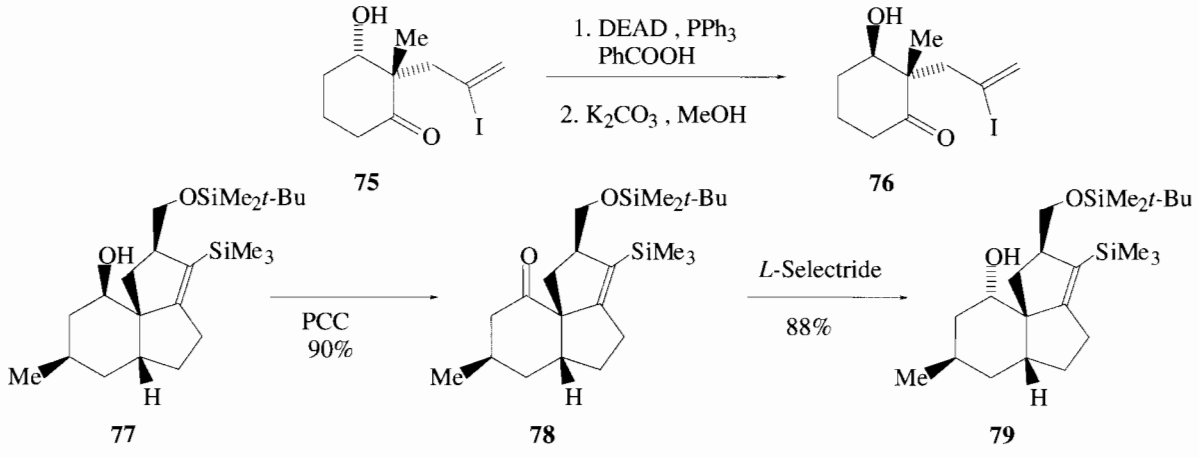
For example, these rules predict that **73** is more stable than **74**.[34] These three rules do not allow direct comparison in every case, but are generally applicable. Köbrich presented a list of carbocyclic Bredt's compounds[30e] and states that many heteroatom and polycyclic analogs can be included in the Figure 6.1 list.[30e]

73 **74**

6.3.C. Retention versus Inversion (Diastereocontrol)

As mentioned previously, reactions of cyclic molecules that involve formation of stereogenic centers are similar to those of acyclic systems in that they can proceed with clean retention or inversion of configuration, or a mixture of the two. Reaction of sodium azide (NaN_3) and *cis*-4-*tert*-butyl-1-bromocyclohexane gives

trans-4-*tert*-butylazidocyclohexane with complete inversion of configuration via an S_N2 pathway. A synthetic example of a reaction that proceeds with inversion is the Mitsunobu reaction that featured chiral alcohol **75**. The presence of an acid or acid salt (such as potassium benzoate) in the reaction medium leads to nucleophilic displacement with clean inversion to generate an ester. Subsequent treatment with methanolic potassium carbonate liberated alcohol **76** with the inverted hydroxyl, in Mori's synthetic work toward poitediol.[35]

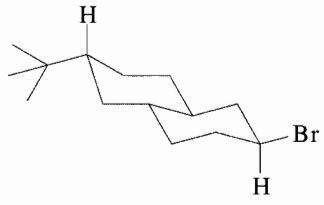


In Section 1.5.B, we saw that many cyclic systems exit primarily in one or two low energy conformations, which can be used to control stereochemistry, if other groups are present that sterically block approach of a reagent. In Section 4.7.C, the angle of approach of a reducing agent to a cyclohexanone derivative, for example, was strongly influenced by the substituents on the ring. In **77**, the stereochemistry of the secondary alcohol is incorrect for the synthetic target. In order to invert the stereochemistry, **77** was oxidized with PCC to give ketone **78**. Subsequent reduction with L-Selectride gave an 88% yield of **79** with the correct stereochemistry.[36] This transformation was taken from Sha's synthesis of (+)-paniculatine. This inversion is possible because the approach of the hydride reagent to the carbonyl unit in **78** is restricted by the presence of the tricyclic system and other substituents. Oxidation followed by reduction of a carbonyl is a simple, yet powerful tool for modifying stereochemistry in many systems.

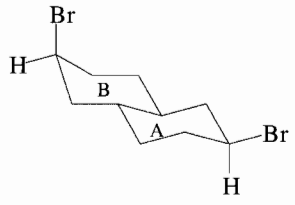
One major difference between cyclic and acyclic systems is the inability of cyclic systems to undergo rotation about carbon–carbon bonds, leading to relatively well-defined conformations. If *trans*-4-*tert*-butyl-1-bromocyclohexane is used as an example, there is the usual equilibrating population of the two chair conformations (sec. 1.5.D). The diequatorial conformer is significantly more stable and accounts for the major portion of the equilibrium (sec. 1.5.B). According to Corey's calculations[37] from Section 1.5.D, the equatorial form predominates (>99.99:<1, diequatorial/diaxial). To predict the major product, nucleophilic backside attack on both conformations must be considered, and the less sterically hindered pathway is usually preferred. In this case, the diequatorial conformation is more reactive.

In a conformationally anchored system such as **80**, S_N2 displacement of the equatorial bromine may be extremely slow. If the reaction is too slow, the temperature can be raised and a more polar solvent (DMF, DMSO, etc.) can be used (secs. 2.6.A, 2.7.Ai). In some cases, the more vigorous reaction conditions will lead

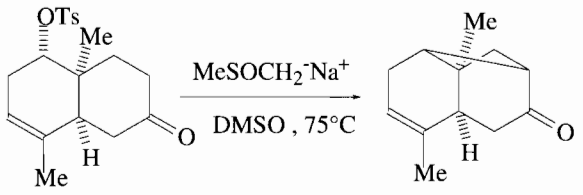
to an alternative reaction (such as elimination or thermal decomposition) rather than the desired S_N2 displacement. Similarly, dibromide **81** is expected to undergo nucleophilic substitution in ring B since displacement of the bromide in ring A is very slow.



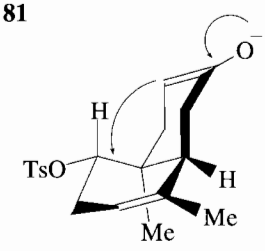
80



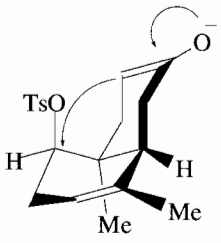
81



82 **83**

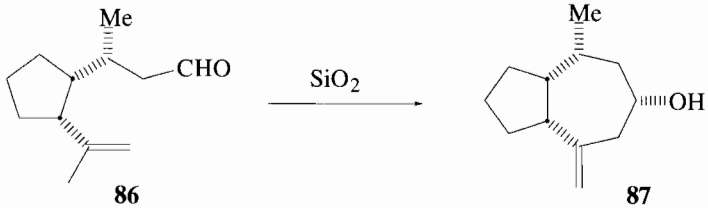


84

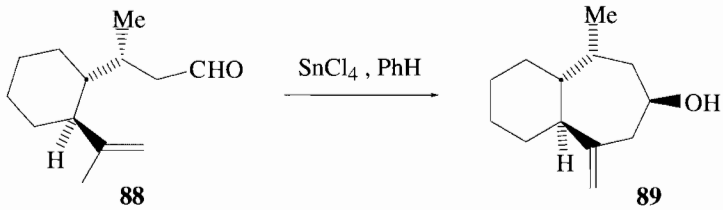


85

For intramolecular reactions, the relative stereochemistry of the leaving group is very important, which can be seen in Corey's synthesis of α-copaene and α-ylangene.[38] This synthesis involved displacement of the tosyl group in **82** by the nucleophilic carbon of the enolate anion (formed with dimsyl sodium - sec. 9.2.A and 9.3.A) to give the bridged product (**83**) characteristic of the ylangene natural products. Examination of the conformational drawing for **82** (see **84**) reveals that the enolate carbon is properly oriented to attack the tosyl carbon from the rear, so displacement of the OTs group is possible only when it is in the equatorial position and is syn to the bridgehead methyl group. The isomeric axial tosylate (shown in **85** where the tosyl group is anti to the bridgehead methyl group) cannot be displaced via backside attack, since the enolate carbon cannot approach the tosyl carbon from the rear. Therefore, **82** will react as shown to give **83**, but the isomeric tosylate will not.



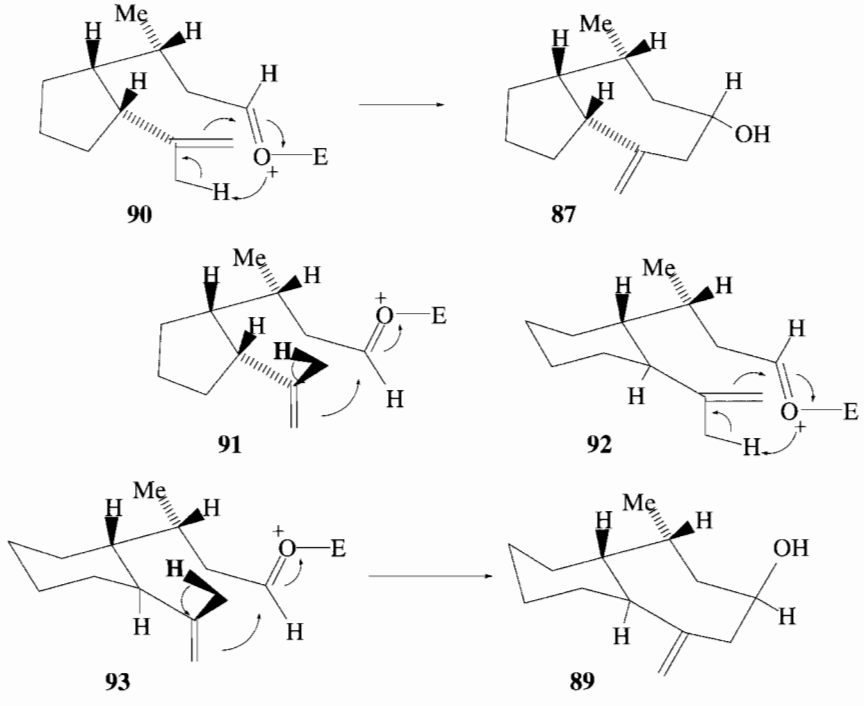
86 **87**



88 **89**

Marshall et al. showed that alkenyl aldehydes can be cyclized on acidic silica gel, and the stereochemistry of the bicyclic alcohol product is controlled by the cis or trans geometry of the monocyclic precursor.[39] This

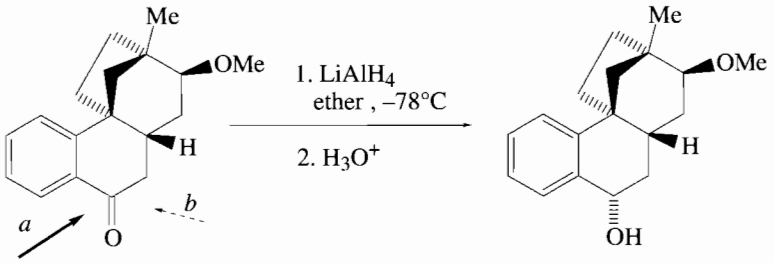
trans-formation proceeds by an **ene reaction** (sec. 11.13), which is particularly effective when catalyzed by Lewis acids.[39c,d] The cis precursor **86** was cyclized to **87**, whereas the trans aldehyde **88** was cyclized to **89**. Formation of a seven membered ring requires a seven-membered chair-like ring for the ene reaction to occur (see **90**) in order to form **87**. If the oxygen is in the axial position (as in **91**) rather than the equatorial position (as in **90**), then the alkenyl group is further removed from the acylium cationic center, and transfer of the hydrogen and attack by the π bond to accomplish the ene reaction is more difficult. Cyclization of **88** requires transition state **93**. This transition state brings the alkenyl moiety close to the acylium cation, and the oxygen is in the axial position for efficient transfer of hydrogen and attack by the alkene, leading to **89**. The opposite conformation (**92**), with the equatorially disposed oxygen, has a greater transannular steric interaction and is also a higher energy boat-like transition state that disfavors the ene reaction in this particular system.



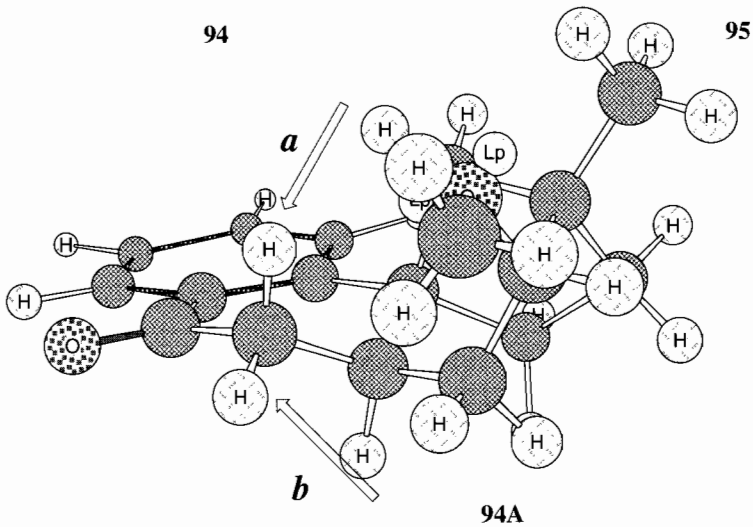
6.3.D. Diastereoselectivity

If one stereoisomer can be produced when more than one is possible (a diastereoselective reaction), this is desirable and obviously related to the concepts discussed in previous sections in the context of acyclic systems. In cyclic systems, the conformation of the ring, conformational preferences in the transition state, and stability of the final product are critically important for predicting and controlling stereochemistry. We saw this above in the conversion of **77** to **78**. In Chapter 4, many examples were given in which the conformation of a cyclic molecule dictated the approach of a reducing agent to control the stereochemistry of the final diastereomer. Reduction of 4-*tert*-butylcyclohexanone showed a marked preference for delivery of hydride from lithium aluminum hydride to give the trans alcohol.[40] The preference for delivery of hydride from one face of a molecule is seen in the Overman et al. synthesis of scopadulcic acid B.[41] In this case, **93** was reduced with $LiAlH_4$ to give **94**,, with high selectivity for delivery of hydride from the top face (β face, **path *a***). Inspection

of 3D drawing **94A** suggests that the bottom face is blocked by the hydrogen atoms and despite the fact that the bicycloheptanone unit is essentially on the top it does not interfere, and path *a* is relatively unhindered.

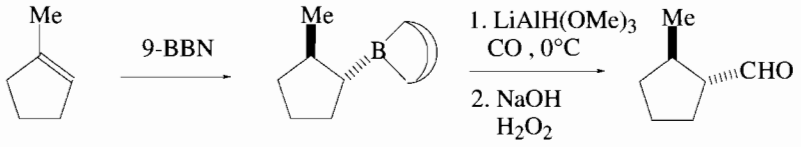


94 **95**



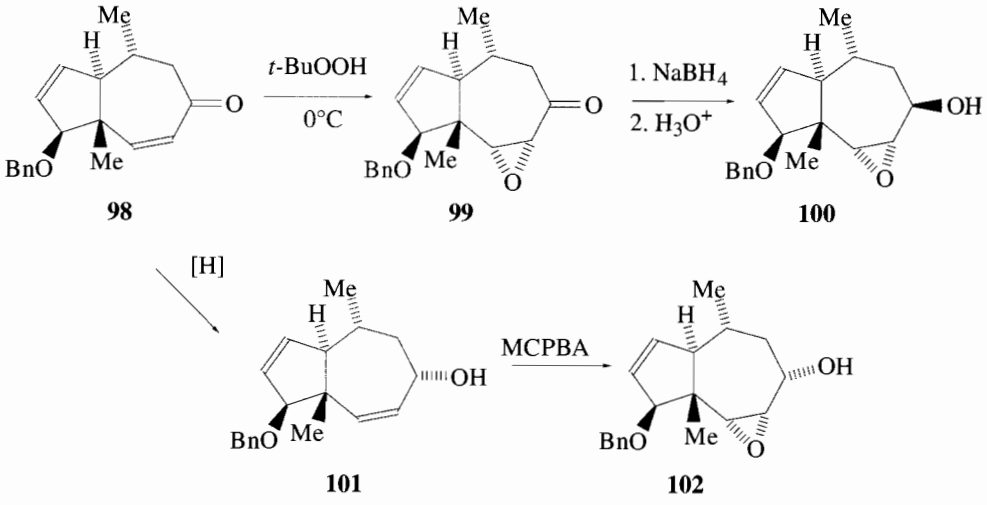
94A

In Chapter 5, the cis addition inherent to hydroboration is the result of a four-center transition state (sec. 5.2.A.ii), which delivered boron and hydrogen from the same face. Subsequent transformations that involve boron lead to a new group on the same face as boron. Reaction of methylcyclopentene with 9-BBN, for example, gave exclusively the trans borane (**96**), and that was converted to aldehyde **97** by carbonylation.[42] The addition of the boron dictated the stereochemical relationship of the methyl group and the 9-BBN moiety. The carbonylation and oxidation reactions proceeded with net retention of configuration, maintaining the trans geometry in the isolated product.

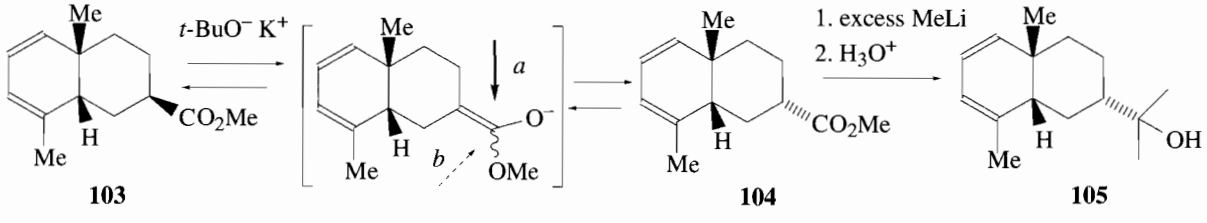


96 (racemic) **97** (racemic)

In some cases, the natural selectivity of a reaction leads to a product that has the incorrect stereochemistry required for a given target. The synthetic chemist is not always forced to accept that stereochemistry. There are at least two options: (1) change the synthetic pathway to generate a compatible intermediate that can produce the desired stereochemistry, or (2) change the stereocenter in the final product.



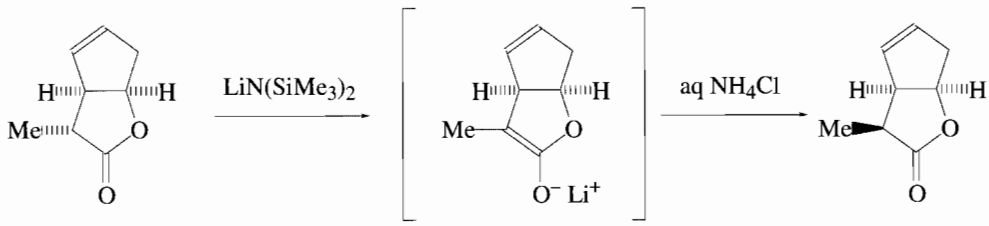
An example of the first process is epoxidation of **98** from the less hindered α face to give **99**. Subsequent reduction from that same face gave **100**.[43] The relative stereochemistry was different, however, when initial reduction of **98** (hydride is delivered from the β-face) gave alcohol **101**. Subsequent epoxidation proceeded via coordination of the alcohol with the epoxidation agent (MCPBA–sec. 3.4.C) to give **102** with the epoxide and alcohol cis (syn) to each other.[43] Simply changing the order of reactions allowed Grieco to target one diastereomer or the other.



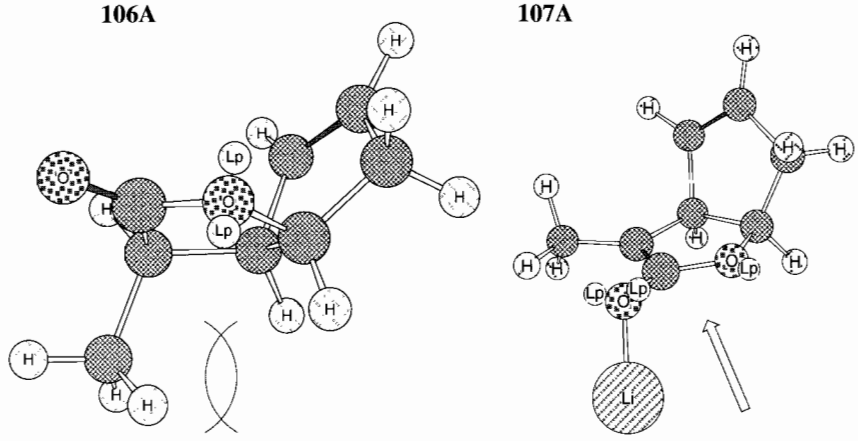
less stable *more stable*

There are many methods available to correct the relative stereochemistry of a stereogenic center that is incorrect for a given target. In the transformation of **13** to **14**, the Mitsunobu reaction was shown to be very effective for acyclic molecules, and it can be used with cyclic systems. Another type of stereocenter that can be corrected is a CHX moiety, where X is an electron-withdrawing group and the H can be removed by treatment with base to form a planar enolate anion (secs. 9.1, 9.2). When **103** was treated with a base, protonation of the resultant enolate anion gave **104** in which the stereocenter was inverted. This inversion of configuration can be explained by examining the planar enolate, where the hydrogen can be delivered from the top face or from the bottom face. The CO_2Me is axial and that it sterically interacts with the axial hydrogens (*A* strain, sec. 1.5.D), which contrasts with **104**, where the equatorial CO_2Me group has minimal *A* strain and it has little effect on the relative stability of **103** and **104**. Delivery of the proton from the bottom (face *b*) of the flattened enolate anion leads to **103** in which there will be greater *A* strain than if the proton is delivered from the top (face *a*). For this reason, the product of this reaction is the lower energy **104**. In this example, taken from Hortmann's synthesis of occidentalol[44] treatment of **103** with *tert*-butoxide followed by

in situ protonation by *tert*-butanol (sec. 9.2.E) led to a 25:1 mixture of **104/103** favoring epimer **104**. Subsequent treatment with methyllithium gave occidentalol (**105**).[44,45] Exploiting such differences in product stability allows one to change the diastereomer population.



106A **107A** **108**

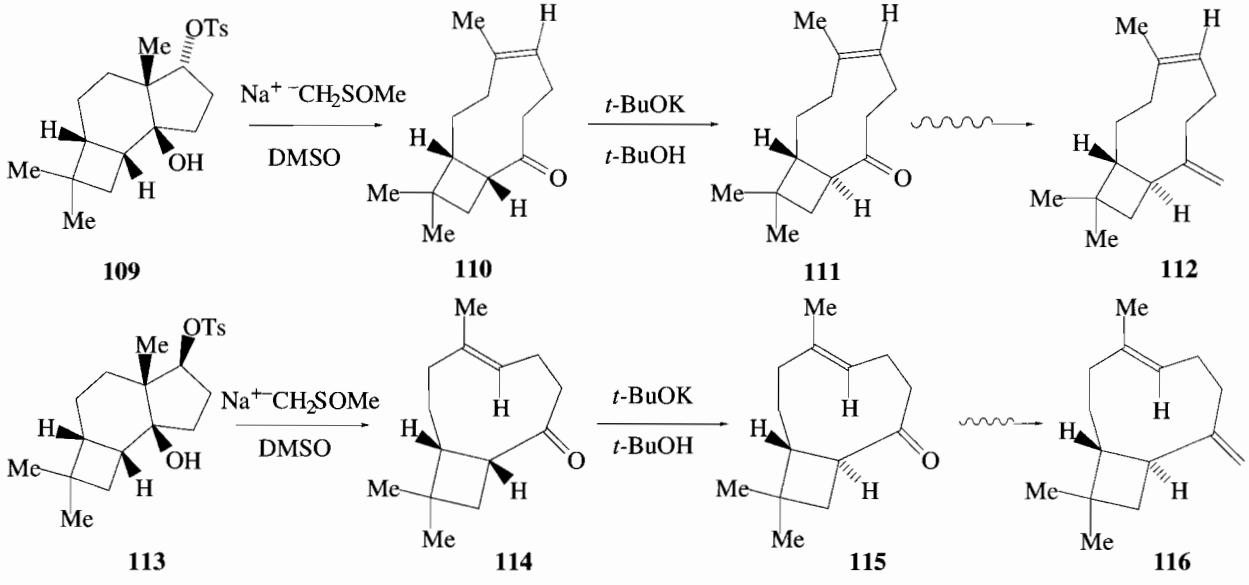


106B **107B**

Another example is the inversion of stereochemistry of the proton α-to the carbonyl in **106A**, giving **108** in the Olivo and co-workers synthesis of callipeltoside-A.[46] Treatment of **106A** with base gives planar enolate **107A**. The enolate reaction is under kinetic control, and protonation from the less hindered bottom face (indicated with the arrow in **107B**) leads to **108**. Although there is a steric interaction in **106B**, this is alleviated in **107B**, opening up the bottom face for reaction.

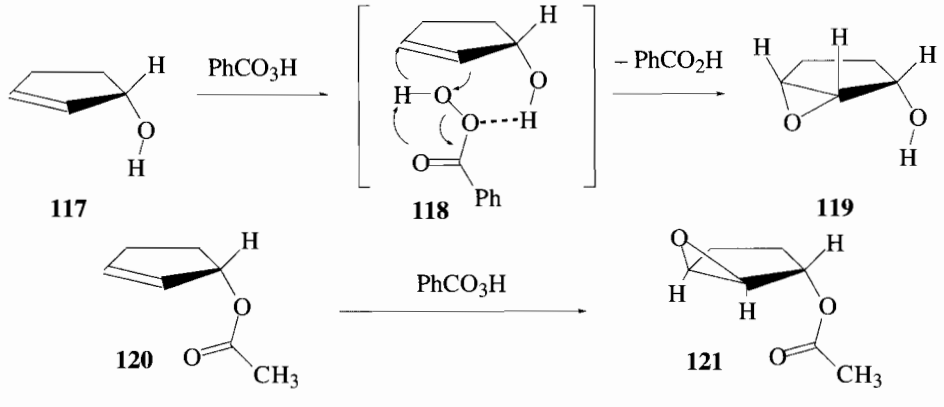
When an alkene unit is the product of a reaction, there is the potential for both (*E*) and (*Z*) isomers. The examples previously cited for E2 and syn elimination are illustrative. In both cases, the stereochemistry (*E*) or (*Z*) of the double bond is important. In acyclic systems, this is often controlled by using resolved chiral precursors, knowing that the E2 elimination is stereospecific. Controlling cis–trans isomers for alkene derivatives is also possible in medium and large ring molecules. Corey's synthesis of caryophyllene (**112**) and isocaryophyllene (**116**) illustrates this type of control.[47] Double-bond geometry is controlled by changing the stereochemistry of the carbon bearing the leaving group in the cyclic precursor (see further discussion of this technique in sec. 6.5). A **Grob fragmentation**[48] (sec. 2.9.E) in **109** led to the (*Z*)-double bond in **110**, required for **112**. Once the (*Z*)-double bond had been incorporated, the α-hydrogen was equilibrated (via enolization with potassium *tert*-butoxide) from the initially formed cis ring juncture (in **110**) to the more stable trans ring juncture in **111**. To obtain the other geometric isomer (in **116**) the relative stereochemistry of the OTs group had to be changed to that shown in **113**. A Grob fragmentation of **113** gave the (*E*)-double bond

in **114**, characteristic of **116**.[48] As before, the cis-ring juncture in **114** was equilibrated to the more stable trans (in **115**) by enolization prior to conversion to **116**. The strong statement from these examples is that the *(E/Z)*-stereochemistry of the alkene products was determined by the relative stereochemistry of the tosylate precursors, once the reaction to generate the double bond in those alkenes was chosen.



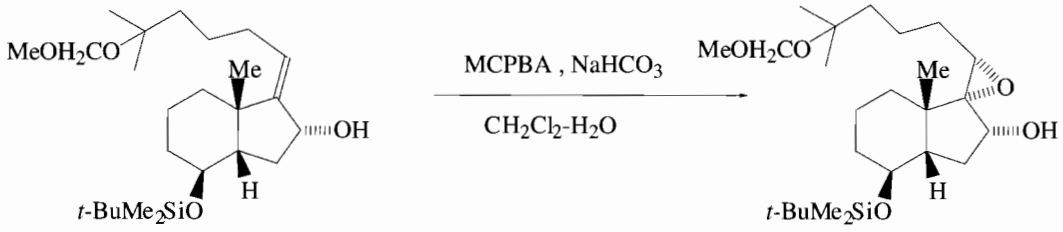
6.4. NEIGHBORING GROUP EFFECTS AND CHELATION EFFECTS

The influence of heteroatom substituents in directing reactions to one face or another has been noted in this as well as several preceding chapters. In Chapter 3, a neighboring group effect influenced delivery of oxygen to the double bond of an allylic alcohol, described by Henbest and by Sharpless (secs. 3.4.B, 3.4.C), which is

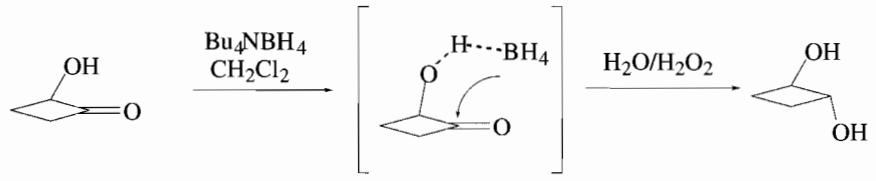


identical to the effect described for acyclic control in Section 6.2.E (see above). Peroxyacid epoxidation of **117** proceeded via coordination of the peroxyacid to the alcohol (see **118**), delivering the electrophilic oxygen from that face to give **119**,[23] which contrasts with epoxidation of allylic acetate **120**, which gave primarily **121** via delivery from the less sterically hindered face. The acetate group inhibits coordination with the peroxy-acid, and delivery of the electrophilic oxygen is from the less sterically hindered face so the epoxide unit is on

the opposite side of the ring. A synthetic example of this effect is taken from Mouriño's synthesis of vitamin D_3 analogs in which allylic alcohol (**122**) was treated with MCPBA. Coordination with the hydroxy group directed the epoxidation from the bottom face, giving an 86% yield of **123**.[49] It is noted that this effect was seen in the conjugate epoxidation of ketone **98** versus the alcohol-directed epoxidation of **101** (see above).[43] Such neighboring group effects are due to a chelating effect of an heteroatom substituent with the reagent. The chelation effects of oxygen substituents with zinc borohydride [$Zn(BH_4)_2$] in the reduction of β-keto esters and β-diketones (secs. 4.4.B, 4.7.B, 6.2.E) is another familiar example.[25] This chelation effect is also seen in the reduction of 2-hydroxycyclobutanone (**124**) with tetrabutylammonium borohydride, which leads to the trans diol **126** via a complex such as **125**, where the borohydride is held on the same side as the hydroxyl.[50] Neighboring group effects can be more subtle, however, and can direct the stereochemistry of a reaction.

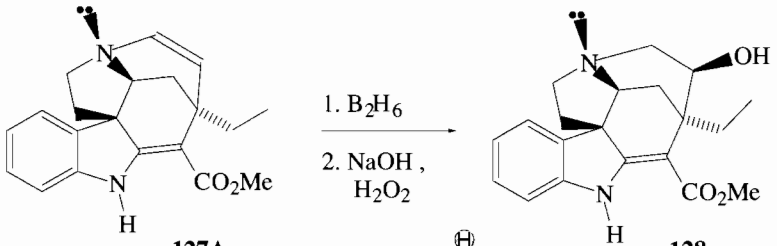


122 **123**

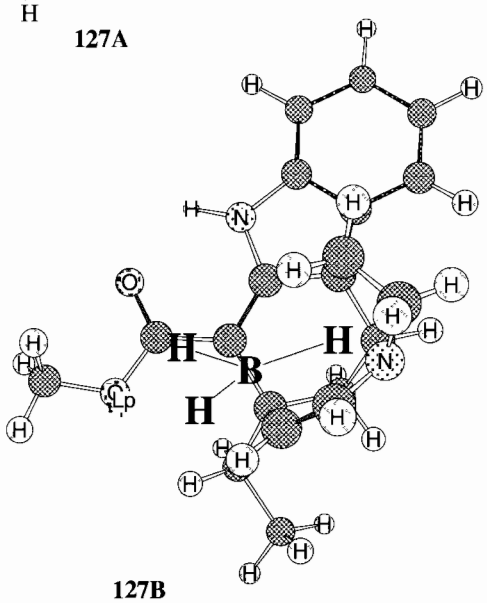


124 **125** **126**

Hydroboration of alkenes to give alcohols typically follows an anti-Markovnikov orientation (sec. 5.2.A). There are many cases where the reactive carbons of an alkene have the same substitution pattern, however. The product distribution can sometimes be controlled by chelation effects, but the mere presence of a heteroatom does not always mean this will be the case. Hydroboration of **127** (tabersonine) is an example where the hydroboration–oxidation sequence (sec. 5.4.A) gave **128** in 90% yield, as a mixture of diastereomeric secondary alcohols (4:1 β/α mixture favoring **128**). This reaction was part of the Caron-Sigaut et al. synthesis of 14-hydroxyvincadifformine,[51] but they showed that chelation was *not* an important factor, contrary to what might be suspected from a cursory examination of the starting materials. The enamine unit in **127** is part of a bicyclic system where the exo face is more accessible, leading to the stereochemistry in **128** (secs. 1.5.E, sec. 4.7.E). As suggested in the 3D representation **127B**, the regiochemistry of the alcohol unit in **128** probably results from steric interactions as borane approaches the C=C unit. Coordination of boron in a four-center transition state to the sp^2 carbon from the face shown leads to the major product after oxidation. This reaction site is less sterically encumbered than coordination of boron to the other sp^2 carbon.

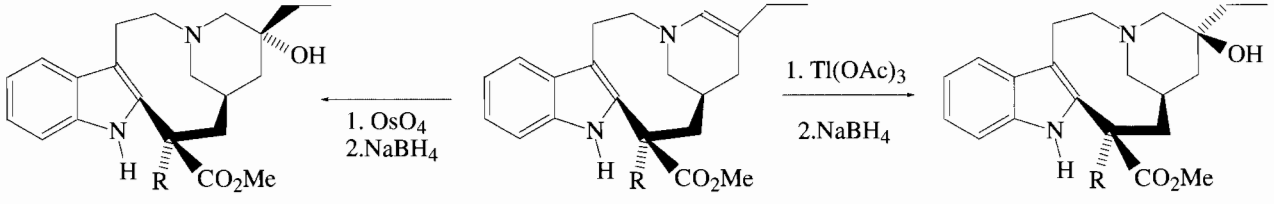


127A **128**



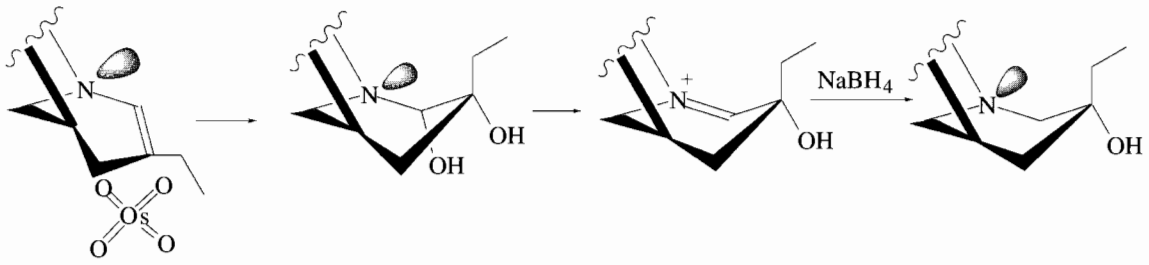
127B

Brown showed that electronic and chelation effects can be important in the hydroboration of allylic amines (sec. 5.2.A.iv), but in this system, steric factors control the reaction, with delivery of boron to the carbon shown.

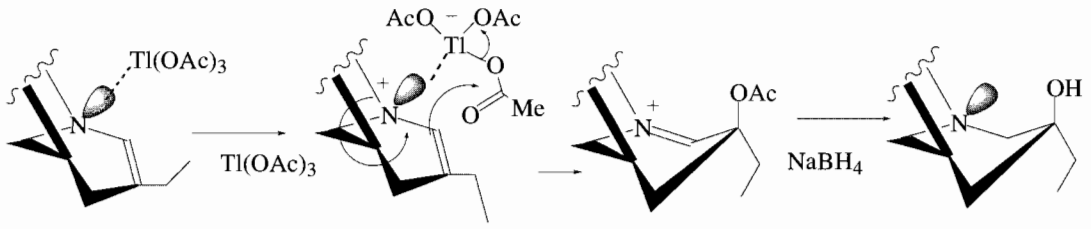


130 **129** **131**

An example of a subtle neighboring group effect where chelation is important is the hydroxylation of **129**. Dihydroxylation via osmium tetroxide (sec. 3.5.B) and reduction gave **130**, an intermediate in a synthesis of $\Delta^{20'}$-20'-deoxyvinblastine.[52b] This transformation is compared with the reaction of **129** with thallium acetate, where reduction gave the epimeric alcohol, **131**.[52a] The nitrogen lone pair is responsible for the reversal of diastereoselectivity. Osmium tetroxide (OsO_4) does *not* coordinate well to the nitrogen and the osmate ester is formed on the less hindered α face of **132**, and this leads to diol **133**. Elimination of the α-hydroxyamine gave an iminium salt (**134**) that was reduced with hydride to **135** (product **130**). Thallium (III), however, coordinates quite well to the nitrogen lone pair of **136** to give **137**, and oxygen of one acetate unit is transferred to the enamine moiety (secs. 9.6.A,B) from the β face to give **138**. Reduction gave **139** (product **131**).

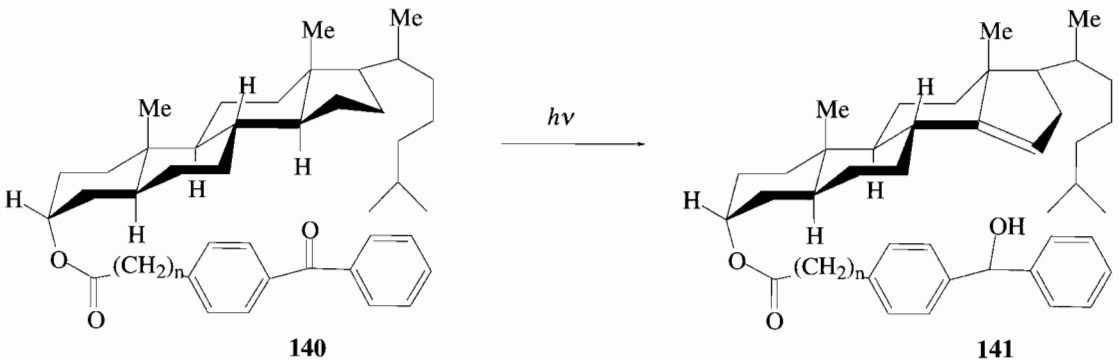


132 **133** **134** **135**



136 **137** **138** **139**

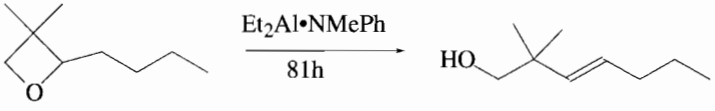
Neighboring group effects usually influence stereo- and regiochemistry of the functional group close to the chelating atom or group. There are examples of such effects that can influence a reaction at sites distant from the coordination point.[53] An example of a neighboring group effect with consequences at a remote site is the photochemical isomerization of **140** (n = 1) to **141** in 55% yield (sec. 13.5.E for a brief discussion of this concept).[54] The β-C3 hydroxyl group was converted to an ester, with a chain of methylene units that positioned a benzophenone moiety on the β face of the molecule. Irradiation generated the benzophenone triplet (see secs. 13.4, 11.10.B for a brief introduction to photochemical techniques), and with an appropriate methylene spacer [$(CH_2)_n$] the hydrogen at C14 was selectively removed to give the $\Delta^{14\text{-}15}$ alkene (**141**, n = 1). With this particular spacer, the C8 hydrogen on the α face of the molecule is inaccessible and not removed. Longer or shorter methylene spacers (n = 0, n > 2) led to diminished yields of **141**.



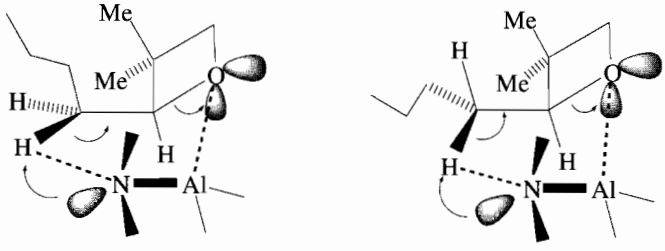
140 **141**

Neighboring group effects can compete with steric effects, as illustrated by treatment of oxetane **142** with diethylaluminum-*N*-methylaniline. This elimination reaction gave a 99% yield of (*E*)-alkene **143** in a synthesis of humulene.[55] The aluminum coordinated to the oxetane oxygen on the less hindered β face in **144** and **145**, the two key rotamers. Rotamer **144** is lower in energy due to the severe nonbonded interaction

of the propyl group and the oxetane methyl in **145**. Removal of the indicated hydrogen by the basic nitrogen, in a six-center transition state as seen in rotamer **144**, led to the (*E*) isomer, **143**. Removal of that hydrogen in **145** would give the (*Z*) isomer, but the relatively high energy of that species favored the observed trans selectivity via **144**.



142 **143**

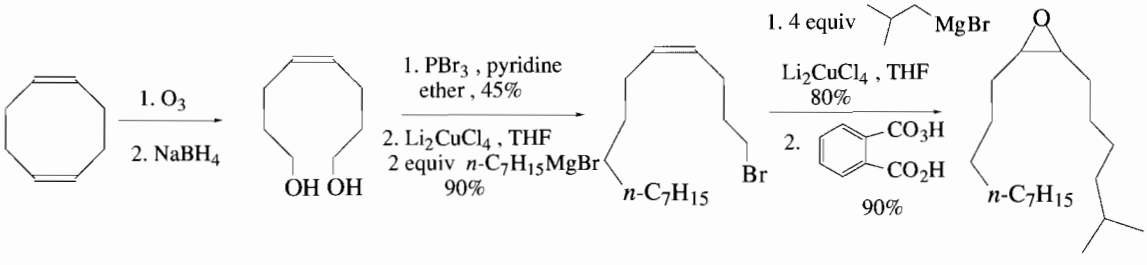


144 **145**

In planning a reaction, not only the obvious effects of α or β hydroxyl, alkoxy, and amino groups must be considered, but also the more subtle effects of nearby nitrogen, oxygen, and sulfur lone pairs. These chelating effects are apparent both in directing stereochemistry or regiochemistry and in slowing or stopping a desired reaction. These effects can be used synthetically to direct attack of a reagent, as shown above. If one wishes to prevent the chelating effect, the offending group must be blocked or removed. Alternatively, the planned synthetic sequence can be accomplished before the chelating atom is present. Careful analysis of all synthetic intermediates is required to use or avoid these effects.

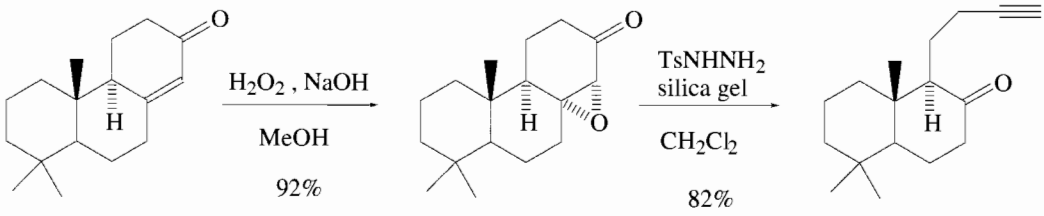
6.5. ACYCLIC STEREOCONTROL VIA CYCLIC PRECURSORS

It is apparent from preceding sections that stereocontrol in cyclic systems is much easier than in acyclic systems, which is due, of course, to the conformational bias inherent in cyclic systems. Synthetic chemists have exploited this fact for many years. A cyclic system can be used to position functional groups, often with control of regio- and stereochemistry. The ring is then opened to give an acyclic system and the regiochemistry and stereochemistry of the substituents has been fixed. There are many examples.



146 **147** **148**

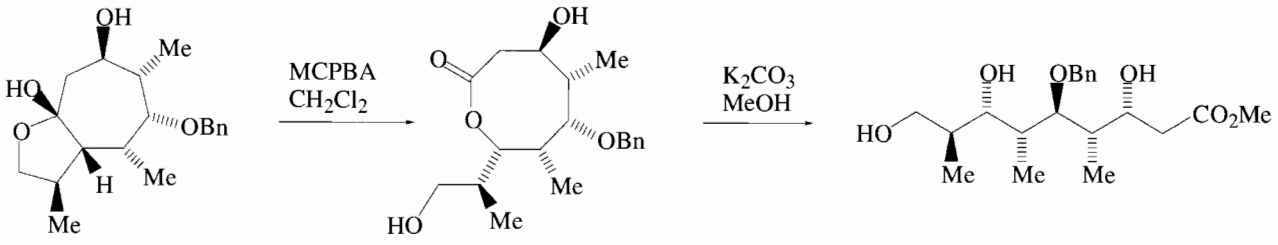
In Chapter 3, ozonolysis (sec. 3.7.B) of cyclic alkenes was shown to generate α,ω-functionalized systems. The utility of the process is demonstrated by the ozonolysis of 1,5-cyclooctadiene to give diol **146** in 85% yield.[56] Conversion to the dibromide and two copper assisted displacements (sec. 8.7.A) followed by epoxidation led to the racemic sex pheromone of the female face fly, **148**.[56] An excess of the organocuprate reagent (Li_2CuCl_4/RMgX) was required for reasonable yields of the coupling products (sec. 8.7.A.ii) due to decomposition and disproportionation of the copper reagents. Examining the overall sequence shows that the requisite functional groups at the α-and ω-positions were inserted by the sequential alkylation reactions, first to **146** giving **147** and then to **147** to give the alkene precursor to **148**.



149 **150** **151**

Another example of inserting and positioning a functional group is the conversion of **149** to **151**.[57] Treatment of the conjugated ketone in **149** with basic hydrogen peroxide gives the epoxide, **150**. Subsequent reaction with tosylhydrazine in dichloromethane led to **Eschenmoser ring cleavage**[58] and the product **151** (this named reaction transforms an epoxy-ketone to a keto-alkyne). This particular transformation is taken from the Abad et al. synthesis of (–)-borjatriol.[57]

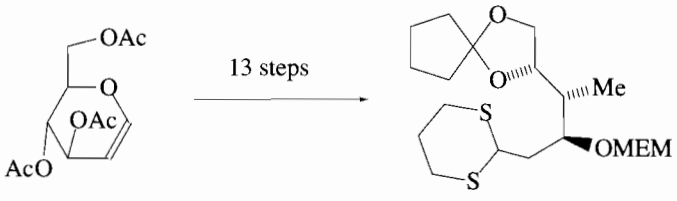
The diastereoselectivity obtained for reactions on a ring makes it possible to use a cyclic molecule to fix a stereocenter in an acyclic target, as seen in the formation of **154** from **152**. Diol **152** had been prepared by a multistep sequence, with control of the stereocenters. When this diol was subjected to oxidation with MCPBA lactone **153** was formed. Subsequent ring opening with methanolic potassium carbonate led to the acyclic fragment **154**, with six contiguous stereogenic centers whose stereochemistry had been fixed in the cyclic compound.[59]



152 **153** **154**

Macrocyclic ring compounds (sec. 6.6.B) possess functionality and stereochemistry that can be as difficult to control as in acyclic systems. The use of cyclic precursors is of value here also. In the Corey synthesis of (–)-*N*-methylmaytansine,[60] a sugar derivative, tri-*O*-acetyl-*D*-glucal (**155**), was used as a precursor to **156**. This precursor contained the correct stereochemistry and functionality for elaboration of the eastern

hemisphere of *N*-methylmaytansine. In this sequence, **155** served as a chiral template for the synthesis, and MEM is 2-methoxyethoxymethyl (sec. 7.3.A.i). This synthetic strategy will be described in section 10.9.

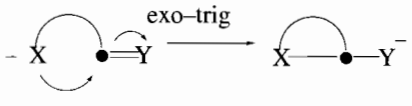


155 **156**

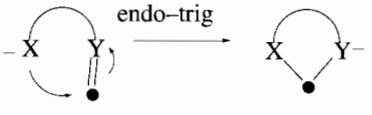
6.6. RING–FORMING REACTIONS

6.6.A. Baldwin's Rules

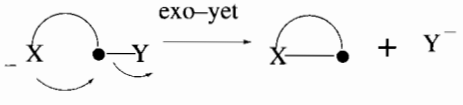
From the preceding discussion, it is clear that cyclic compounds play an important role in organic synthesis. The desired compound is not always commercially available, however, and must often be prepared by cyclization reactions from acyclic precursors, which is particularly true for large ring (macrocyclic) compounds and poly-cyclic molecules. In the latter case, a cyclic molecule acts as a template and the other rings are built onto the template (this is called **annulation**). This section will discuss the salient features of ring-forming reactions commonly encountered in synthesis.



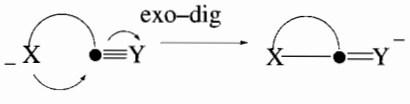
157 **158**



159 **160**



161 **162**



163 **164**

An introduction to cyclization reactions is best begun with a discussion of **Baldwins rules for ring closure** or simply **Baldwin's rules**. Baldwin studied many nucleophilic, homolytic, and cationic ring–closing processes and found a predictable pattern of reactivity. This approach is based on the stereochemical requirements of both reagent and substrate as well as the angles of approach that are allowable when two reactive centers come together. To form a ring, the two reactive centers are connected by a tether of atoms (usually carbon atoms but not always) and this imposes constraints on angles from which they can approach one another, and on the stereochemistry of the product. If the length and nature of the chain (tether) linking terminal atoms X and Y allows this geometry to be attained, ring formation is possible (**favored**) and we make the predication that the reaction will succeed. If the proper geometry cannot be attained, ring formation is difficult (**disfavored**). In this latter case, alternative but competitive processes usually dominate. Baldwin classified ring closing reactions

into two categories: exo (the electron flow of the reaction is external to the ring being formed [**158** from **157**] and endo [the electron flow is within the ring being formed (**160** from **159**)].[61] Baldwin further classified reactions according to the hybridization of the atoms accepting the atom in the ring closing process. If the atom being attacked is sp^3 hybridized, as in **161**, the reaction is termed tet and an exo-tet reaction will generate a ring such as **162**. Attack at an sp^2 atom (**157**) is termed trig (forming the ring **158** or **160**). Attack at an sp hybridized atom (**163**) is dig, and an exo-dig reaction will generate ring **164**.

It is therefore possible to describe ring forming reactions by the number of atoms in the cyclic product, whether the reaction is exo or endo, and whether it involves **tet**, **trig**, or **dig** intermediates. A **5-exo-tet** reaction represents formation of a five-membered ring by displacement at sp^3 carbon by X, where Y is exo to the ring being formed. The cyclization reactions that form 3–7 membered rings, along with all **exo/endo**, and **tet/trig/dig** possibilities are shown in Figure 6.2.[61]

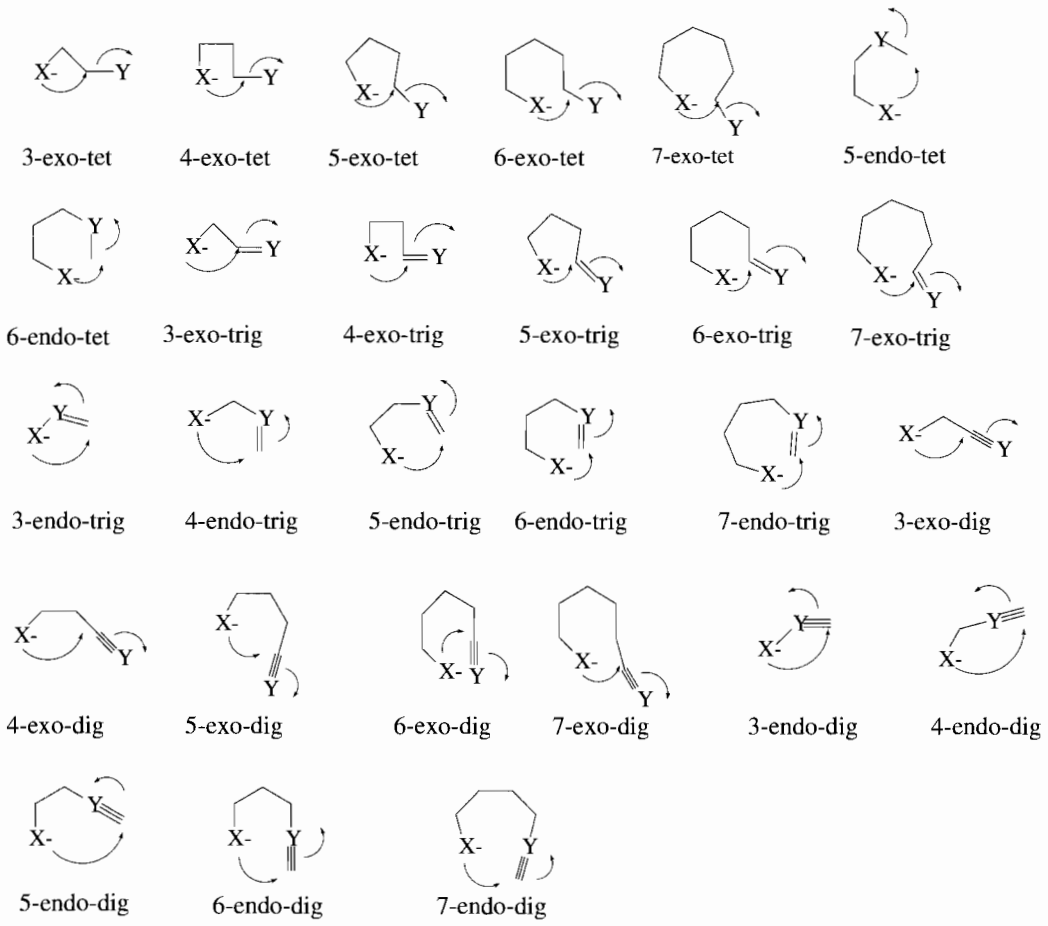
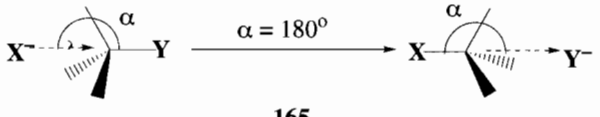


Figure 6.2. Ring closures categorized by Baldwin's rules.

When two reactive ends of a molecule come together, they can approach each other only from certain trajectories, called the angle of attack. Before discussing Baldwin's rules, it is first necessary to establish what angles of attack are possible. Elliot and Graham-Richards described a method for predicting the preferred approach angles based only on the substrate.[62] Displacement at a sp^3 carbon generally requires backside

attack (see **165**) and the incoming group (**X**) must approach the **Y**-bearing carbon at an angle close to 180°. For exo processes, this is usually easy but for endo processes it can be difficult. Reactions at double bonds (trig) are controlled by the planar nature of alkenes, imines, and carbonyls. The bond angles are ≈ 120°, but upon reaction the sp^2 atom is converted to a sp^3 atom. Since sp^3 atoms are tetrahedral (with bond angles of



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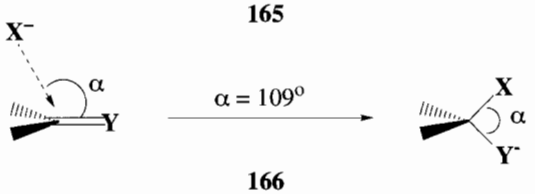
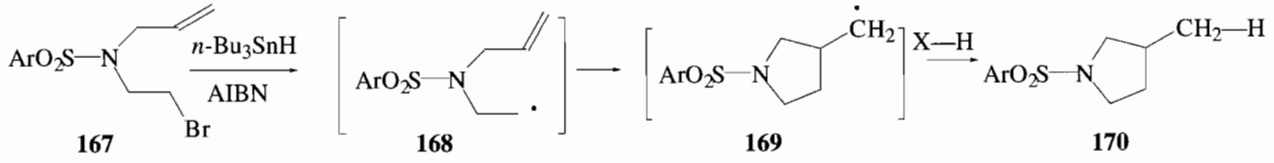


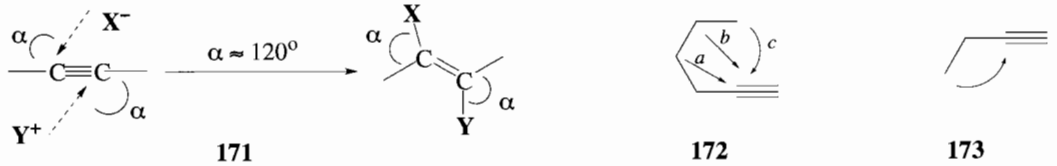
166

≈ 109°–sec. 4.7.C), the best trajectory for attack of a sp^2 atom (a carbonyl, for example) is about 109° (the Bürgi-Dunitz trajectory;[63] see **166**). Treatment of **167** with *azobis*-isobutyronitrile and tributyltin hydride leads to a radical intermediate (**168**)[64] (see sec. 13.7 for a discussion of radical cyclization). Attack at the alkene unit easily allows approach at 109° and this cyclization gives **169**. Hydrogen transfer to **169** form Bu_3SnH completes the reaction and generates the product, **170**. Formation of large rings is not a problem with respect to Baldwin's rules since there is sufficient flexibility in the tether to attain virtually any approach angle that is required.[65]



167 **168** **169** **170**

In molecules containing a triple bond there is a linear geometry, so the bond angles are 180°. Conversion of the sp atom to an sp^2 atom generates the 120° bond angle characteristic of alkenes. Using the same analogy as for the sp^2–sp^3 conversion, an incoming atom should approach the triple bond at an angle of ≈ 120° (see **171**).[66] Ring closure is difficult for reactions where the chain is small (***a*** in **172**). With longer chains (***b*** and ***c*** in **172**) the process may be more facile. For intramolecular reactions, attack at an angle of 120° or greater is possible in most cases (see **173**).



171 **172** **173**

These discussions led Baldwin to establish several rules for ring closure, known as **Baldwin's rules**:[61]

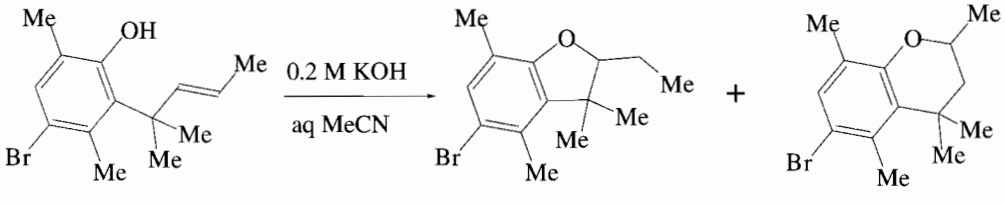
1. For **tet** systems: **3-7 exo-tet** are *favored*
5-6 endo-tet are *disfavored*

2. For **trig** systems:
3-7 exo-trig are *favored*
6-7 endo-trig are *favored*
3-5 endo-trig are *disfavored*

3. For **dig** systems:
5-7 exo-dig are *favored*
3-7 endo-dig are *favored*
3-4 exo-dig are *disfavored*

The disfavored reactions are not impossible, ***simply more difficult*** and usually slower than other competing reactions (inter- or intramolecular). Although many of the reactions show here will not be presented until Chapters 8, 9, 12 and 13, several examples of carbon–carbon bond forming reactions will be given to illustrate these rules.

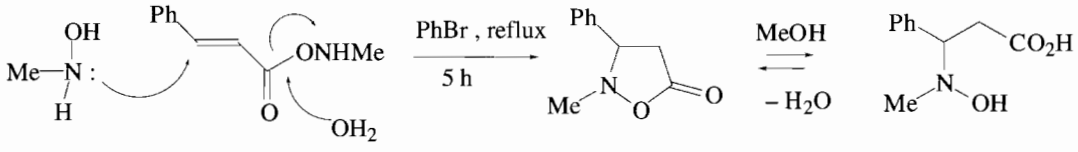
When **174** reacted with KOH in aqueous acetonitrile, the 5-exo-trig product (**175**) was favored over formation of the 6-endo-trig product (**176**) by a ratio of 18:1.[67] The alkynyl derivative (**177**) reacted 10^3 times slower than **174** and gave *only* the 5-exo-dig product (**178**). The 6-endo-dig product (**179**) was ***not*** isolated from the reaction, although the actual product distribution was probably > 100:1 favoring **178** over **179**. It was suggested that sp atoms generally prefer the exo mode of attack to the endo mode.[67]



174 **175** **176**

179 **177** **178**

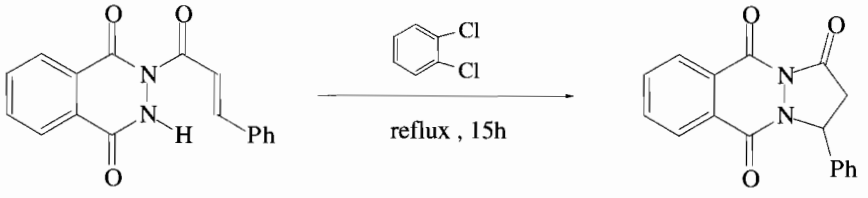
There are reactions that seemingly contradict Baldwin's rules. Fountain showed that *N*-methyl-*O*-cinnamoyl hydroxylamine gave 5-phenyl-3-pyrazolidinone (**180**, which exists as the two valence tautomers shown) under forcing conditions (15 h in refluxing dichlorobenzene), via the disfavored 5-endo-trig pathway.[68] This simply illustrates that the rules say favored or disfavored, not allowed or forbidden. It does point out, however,



180

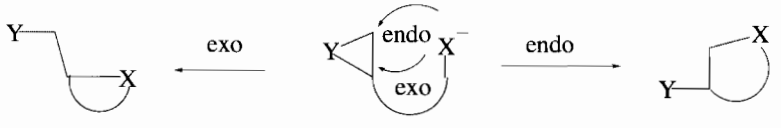
that factors other than geometry and stereochemistry must be considered. Fountain also suggested that electronic factors must be considered.[69] Anselme showed that cyclization of **181** to **182** occurred via a 5-endo-trig

process,[68] but under more vigorous conditions than noted by Fountain for cyclization of **179**. Presumably, the nitrogen lone pair electrons in **181** are more nucleophilic than in CO_2NHMe precursor to **180**.[69]



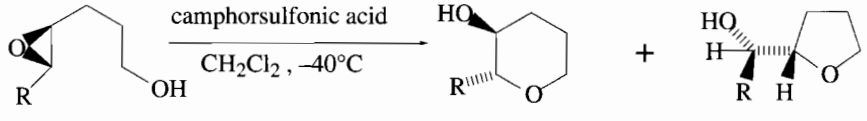
181 **182**

Epoxides and other three-membered rings present special problems since they are in between tet and trig systems. Generally, three membered rings prefer the exo mode of attack (see **183**) to give **184**.[70] The endo



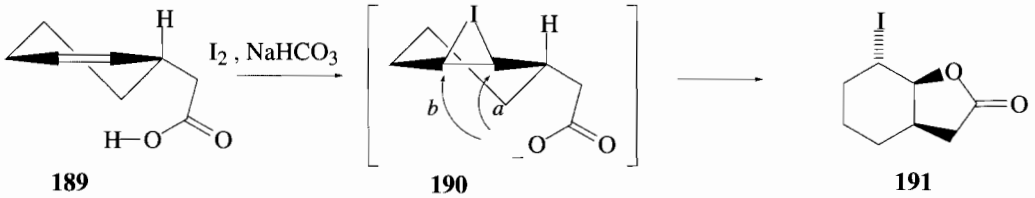
184 **183** **185**

mode of attack generates **185**. If we use **186** as an example, protonation of the epoxide oxygen with an acid (camphorsulfonic acid) followed by attack by the OH unit and ring opening gave the observed products.[71] When R was $CH_2CH_2CO_2Me$,, the 5-exo product **188** was the only one (94 yield), which is typical. When the R substituent in **186** was changed from alkyl to alkenyl (vinyl), however, the course of the ring opening was changed to give only the 6-exo product (**187**) in 90% yield. In general, the 5-exo mode of attack is preferred.



186 **187** **188**

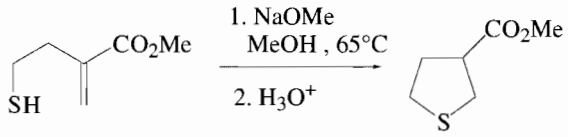
Three-membered rings other than epoxide follow the same ring opening pathways. An example of such an opening is the iodolactonization reaction discussed in Section 2.10.C. Reaction of **189** with base in the presence of iodine likely gives a carboxylate anion–iodonium intermediate (**190**). Displacement of iodide by carboxylate, (**path *a***) is a 5-exo process and is favored over the analogous 6-endo process (**path *b***). The final product is iodolactone **191**.[72] It is noted that this reaction may not proceed by discreet iodination to give **190**.



189 **190** **191**

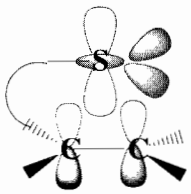
Third-row elements are difficult to analyze by Baldwin's rules because the atomic radii are larger and the bond lengths are large. Conformations can be attained that are unavailable to molecules that contain only

second-row atoms. The constraints on approach angles are therefore less stringent. Thiol **192**, for example, was cyclized to **193** by a 5-endo-trig process (an internal Michael addition).[60b,73] The sulfur atom has 3d orbitals and can receive electrons via back donation from the occupied p orbitals (see **194**). This reduces the requisite angle of attack from 109° to 90° or less, facilitating the endocyclic ring closure.



192 **193**

Baldwin's rules also apply to ketone enolates,[74] but Baldwin and Lusch modified the rules to make the terminology more specific.[75] The special angular requirements of enolates are shown for the exo-tet -process (**195**) and the exo-trig process (**196**). The p orbitals of the enolate must approach the reactive center at an angle of about 180° or 109°, respectively. It is the orientation of the orbital, not just the nucleophilic atom (C or O) that must be considered for determining the correct angle of approach (sec. 9.2.B).



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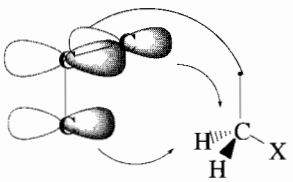

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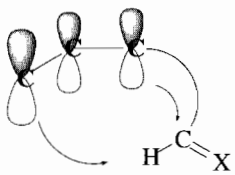
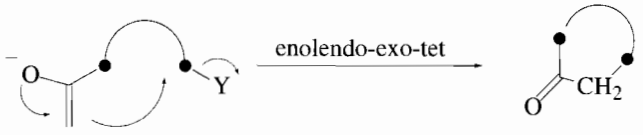


196

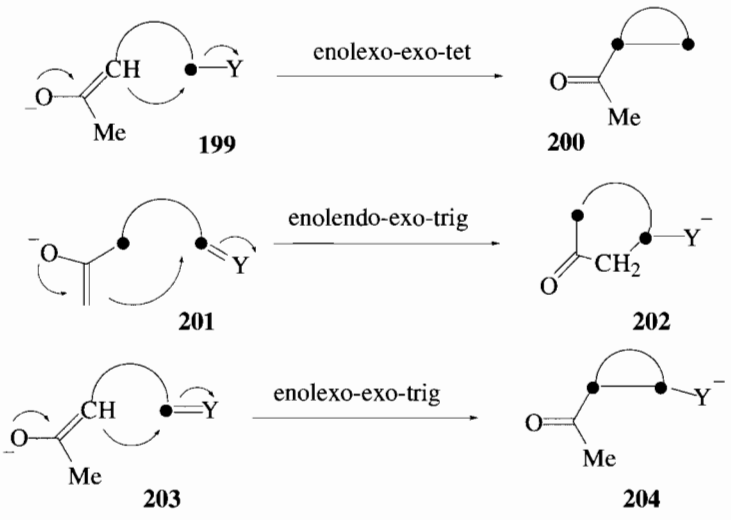
There are two ways to view the ring closure. A kinetic enolate (less substituted: derived from removal of the most acidic proton–sec. 9.2.E) such as **197** will close via exo displacement of Y to give **198**. A thermodynamic enolate (more substituted: resulting from equilibration to the most stable enolate product - sec. 9.2.E) such as **199** also undergoes an exo displacement of Y but gives **200**. Conversion of **197** to **198** was termed enolendo-exo-tet, and conversion of **199** to **200** was termed enolexo-exo-tet. Similarly, exo-trig reactions can be classified in this manner. The kinetic enolate (**201**) gives **202** in an enolendo-exo-trig process. Cyclization of the thermodynamic enolate (**203**) gives **204** via an enolexo-exo-trig reaction.

The rules are somewhat different for ring closure with enolates.

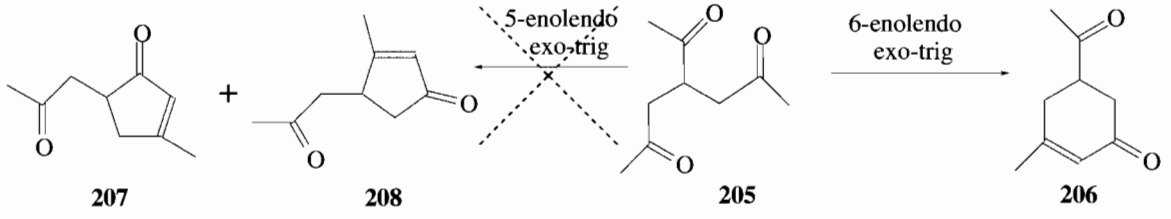
6-7 enolendo-exo-tet	*favored*
3-5 enolendo-exo-tet	*disfavored*
3-7 enolexo-exo-tet	*favored*
3-7 enolexo-exo-trig	*favored*
6-7 enolendo-exo-trig	*favored*
3-5 enolendo-exo-trig	*disfavored*



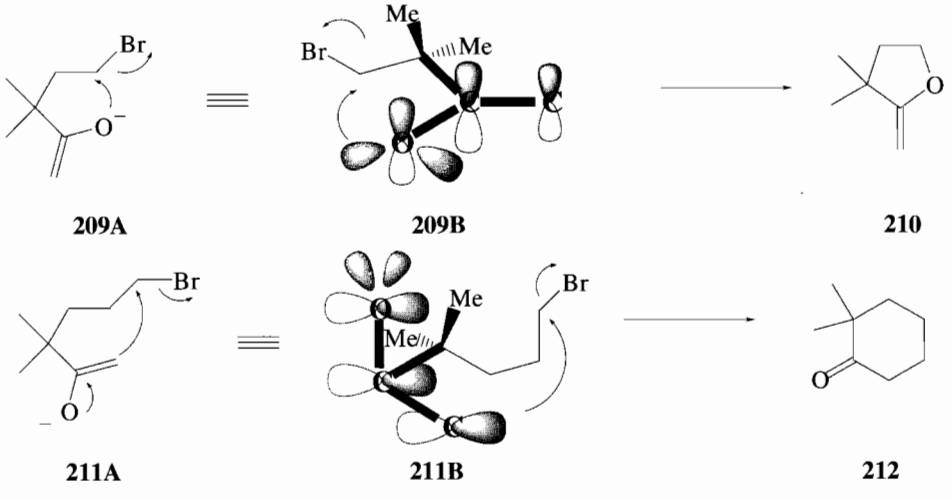
197 **198**



Two competing intramolecular cyclizations (see the aldol condensation–sec. 9.4.A.ii) are illustrated for triketone **205**.[75] In this case, only the favored 6-enolendo-exo-trig product (**206**) was obtained and not the disfavored 5-enol-endo-exo-trig products (**207** and **208**). Enolates generally tend to undergo 5-exo-tet reactions at oxygen, whereas 6-enolendo-exo-tet reactions prefer carbon. In order to form a five-membered



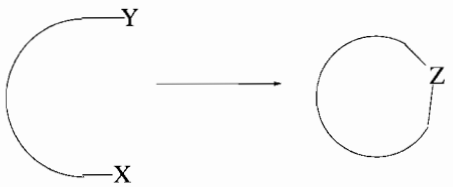
ring from 209, the oxygen lone pair must be at the correct angle for displacement of bromine in **209** (the product is tetrahydrofuran **210**). Another view of **209A** shows the positioning of the orbitals that will allow displacement (see **209B**). In order to generate a six-membered ring, however, the orbitals of the enolate carbon in **211** must be at the correct angle for displacement (see **211B**) and the product will be **212**.



6.6.B. Macrocycles

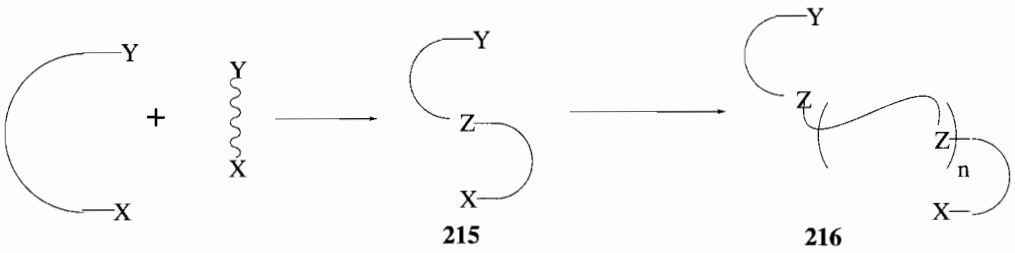
6.6.B.i. Macrocyclic Ring Closures. Baldwin's rules explain most of the cyclization reactions for small- and medium-sized rings encountered in previous chapters and those that are seen in succeeding chapters. An exception is the formation of large rings. Formation of carbocyclic rings will be discussed in later chapters in connection with the appropriate carbon–carbon bond-forming reactions. Macrolactonization, however, is a functional group exchange process, and large lactone rings are also an important feature of many natural products. This section will discuss the problems and solutions for macrocyclic cyclizations. The principles discussed here for preparing large ring lactones are applicable to most other macrocyclizations.

Illuminati and Mandolini described the ring-closing reactions of bifunctional chain molecules.[76] In the 1920s and 1930s Ruzicka et al.[77] and Ziegler et al.[78] studied macrocyclic reactions. Macrocyclic ring formation requires an intramolecular cyclization reaction of a bifunctional molecule such as **213**, where cyclization gives the monocyclic product, **214**. In this model, X and Y are reactive functional groups that generate a new



213 **214**

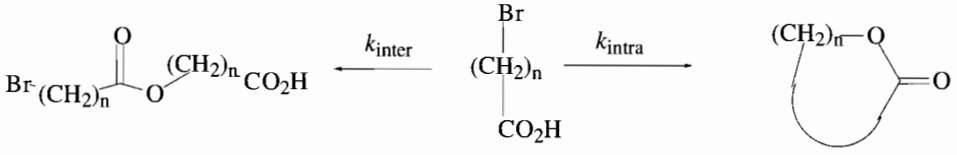
group, Z (which may contain X, Y, or both). An important reaction that competes with cyclization is the intermolecular reaction where initial coupling generates the dimeric **215**. Repeated intermolecular reactions give the oligomers or polymers (**216**). Ruggli discovered that high substrate concentrations favor polymerization while low concentrations favor cyclization.[79] The rate of cyclization is a function of the structure of the open-chain precursor and that of the product-like transition state. The activation energy for ring closure is largely determined by the strain energy of the final ring.[80] As shown in Sections 1.5.A, 1.5.D, strain energy is



215 **216**

due to "(1) bond opposition forces due to imperfect staggering (**Pitzer strain**), (2) deformation of ring bond angles (**Baeyer strain**), and (3) transannular strain due to repulsive interactions between atoms across the ring when they are forced close to each other."[76,81] As the chain length increases for a cyclization reaction, the probability of the chain termini approaching each other decreases ("negative $\Delta S^{\ddagger}$ due to less freedom of internal rotation around single bonds of the molecular backbone when the disordered, open-chain precursor is converted into the ring shaped transition state").[76] In general, the ring product is a good model of the

transition sate of cyclization for all but the shortest chains.[82] When large, stainless rings are formed, no strain energy shows up in the transition states. In short chains, there is an advantage in terms of entropy but it is offset by enthalpy due to extremely large strain energies. Ziegler first used this principle of a ring-shaped transition state to generate large membered rings by is known as the **high dilution method**.[83] Cyclization of **215** to **217**, for example, was accomplished by slow addition (6.6 x 10^{-4} mol $L^{-1}day^{-1}$) of bromo-acid to a solvent containing potassium carbonate (K_2CO_3) or hydroxide.[84] For n = 9, a 77% yield of **217** was obtained.[84] The main side product of this process was the dimeric ester **216**.



218 **217** **219**

Bromocarboxylate **215** can be cyclized to a lactone and this simple reaction will be used to illustrate cyclization processes in general. An intramolecular cyclization reaction of **215** (governed by k_{intra}) will generate the lactone (**217**), but an intermolecular reaction (k_{inter}) will give the dimeric ester (**216**).[76] The relative preference of a reaction is given by the effective molarity (**EM**) = k_{intra}/k_{inter}.[85] The EM is supposed to be the first-order rate constant for ring closure times the second order rate constant for reaction between chain ends (if they were not connected) but EM for five and six-membered rings exceeds the real concentration.[76] Two parameters similar to EM are useful for predicting conditions under which a ring can be synthesized, free of significant polymerized byproducts.[86] The first is the parameter $C\alpha/M_o$ (see Eqn. 6.1), where k_R is the rate of ring formation of cyclic monomer and k_P is the rate of formation of cyclic dimer. If the initial concentration is less than unity ($\alpha < 1$), the yield is not less than 55%. For medium rings, k_R/k_P should be < 0.1 M.[87]

$$\frac{C_\alpha}{M_o} = \frac{1}{2\alpha} \ln (1 + 2\alpha) \qquad 6.1$$

where $\alpha = \dfrac{M_o}{(k_R/k_P)}$ and k_R and k_P are defined by:

$$\text{monomer} \xrightarrow{k_R} \text{monomeric complex}$$

$$2 \text{ monomer} \xrightarrow{k_P} \text{dimer}$$

Similarly, the parameter η_c/η_m (the yield of cyclic substance obtained under high dilution conditions) can be used, where η_m is the total number moles of bifunctional substrate, η_c is the number of moles of monomeric ring product produced, and v_f is the constant feed rate in that is measured in moles per liter per second (mol L^{-1} sec^{-1}).[86] The dimensionless parameter β is a measure of the feed rate, and the relative formation of cyclic monomer is a function of the feed rate.[86]

$$\frac{\eta_c}{\eta_m} = \frac{2}{1 + \sqrt{1 + 8\nu_f\, k_P/k_R 2}} = \frac{2}{1 + \sqrt{1 + 8\beta}} \qquad 6.2$$

The dependence on ring size for lactone formation is illustrated by Figure 6.3(a)(the reactivity for lactone formation), Figure 6.3(b) (the $\Delta H^{\ddagger}$ profile for lactone formation) and Figure 6.3c (the $\Delta S^{\ddagger}$ profile for lactone formation).[76] The quantity $\Delta H^{\ddagger}_{intra} - \Delta H^{\ddagger}_{inter}$ is a useful measure of the strain energies involved in ring formation for lactones. As the chain length increases, $\Delta H^{\ddagger}$ decreases.[88] For very large rings (C_{18}–C_{23}), $\Delta H^{\ddagger}_{intra} \approx \Delta H^{\ddagger}_{inter}$ and the intramolecular reaction is nearly strain free. In the C_3–C_{16} region, ring formation is strain dependent with $\Delta H^{\ddagger}$ maximal at C_3 and C_8 (≈ 8 kcal/mol^{-1} mol^{-1}; 33.5 kJ mol^{-1}). For C_3–C_8, the cis conformation predominates due to the increased strain inherent to a trans conformation.

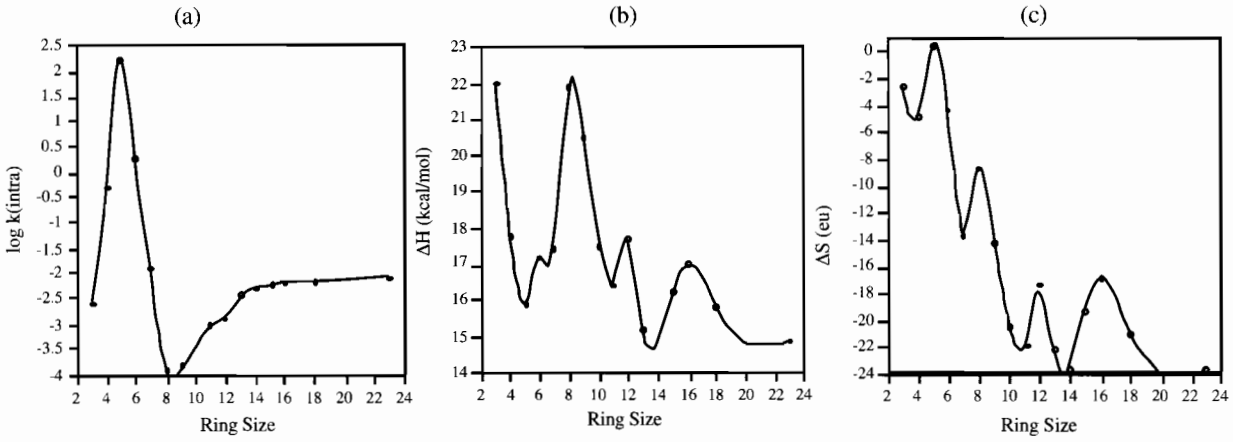


Figure 6.3. For lactone formation: (a) Reactivity profile, (b) $\Delta H^{\ddagger}$ profile, and (c) $\Delta S^{\ddagger}$ profile.

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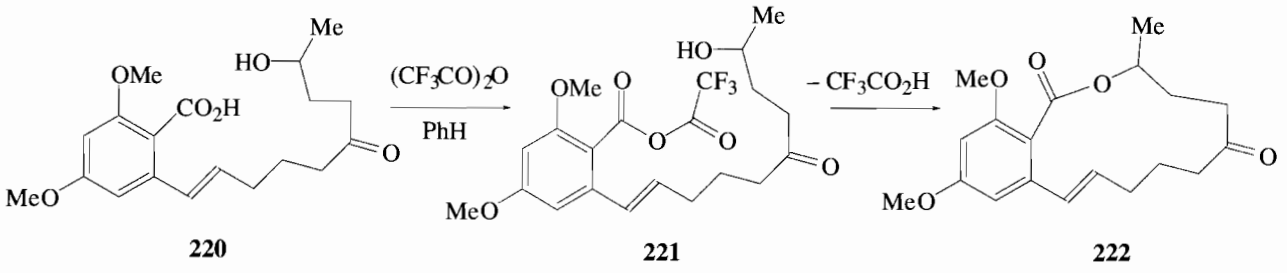
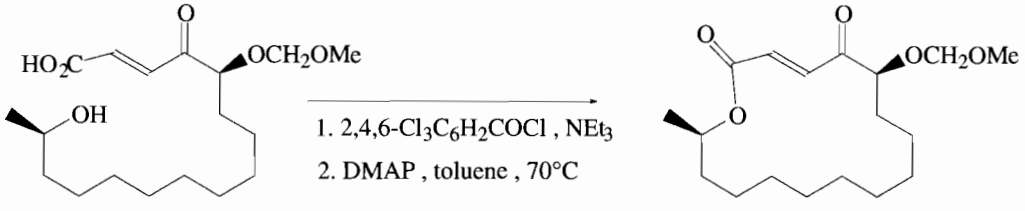
As shown in Figure 6.3(c), $\Delta S^{\ddagger}$ does not show a regular pattern but tends to level off for large rings because of a "looseness in the ring due to low frequency out of plane bending motions".[76,89] The variation in $\Delta S^{\ddagger}$ indicates the importance of individual ring features, with maxima occurring at ring sizes of C_8, C_{12}, and C_{16}. For ring sizes of C_3–C_6, the $\Delta S^{\ddagger}$ values are relatively insensitive to ring size. Solvation around the reactive end plays a major role in C_3 and C_4 rings, but for C_5 rings and larger, such solvation is less important.

6.6.B.ii. Synthetic Approaches to Macrocyclic Lactones. There are many examples of biologically important, naturally occurring lactones. A variety of cyclization techniques have been developed, but all are based on the idea that the carbonyl end of an ω-substituted acid is activated to facilitate attack by or at the other functionalized end. Trifluoroacetic anhydride, for example, was used to convert **220** to **222** in 31% yield.[90] The initially formed mixed anhydride (**221**) activated the carbonyl to attack by the hydroxyl moiety, leading to **222** in the Taub et al. synthesis of zearalenone.[90] An alternative synthetic route required a macrocyclization reaction but it involved Friedel–Crafts acylation (sec. 12.4.D). Cyclization has also been observed using a mixture of trifluoroacetic acid and trifluoroacetic anhydride.[91]



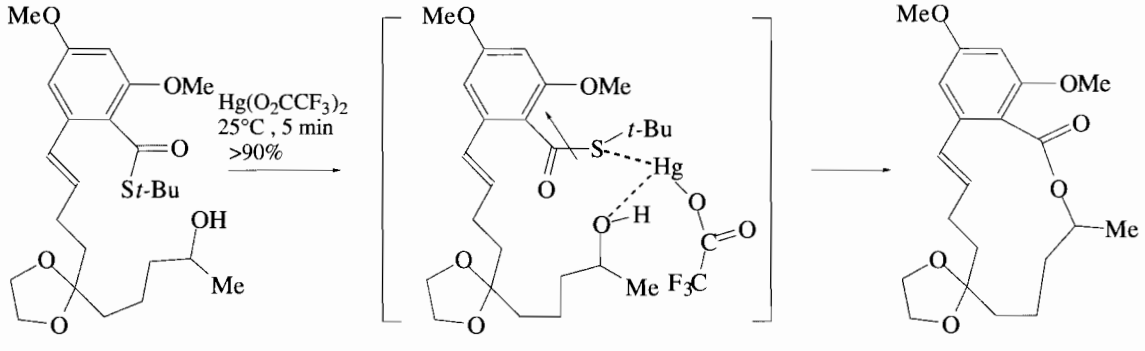
220 221 222



223 224

Another macrocyclization technique has been developed based on formation of a mixed anhydride. In the **Yamaguchi protocol**[92] a seco acid is treated with 2,4,6-trichlorobenzoyl chloride, and the resulting mixed anhydride is heated with DMAP (4-*N*,*N*-dimethylaminopyridine) in toluene. A synthetic example shows that other functional groups can be tolerated in this reaction. In Kobayashi and Okuii's synthesis of the antibiotic (–)-A26771B, seco acid (**223**) was converted to lactone **224** in >66% yield using the Yamaguchi protocol.[93] A variation of this procedure prepares the mixed anhydride by reaction of the seco acid with Boc anhydride, followed by heating with DMAP in toluene.[94]

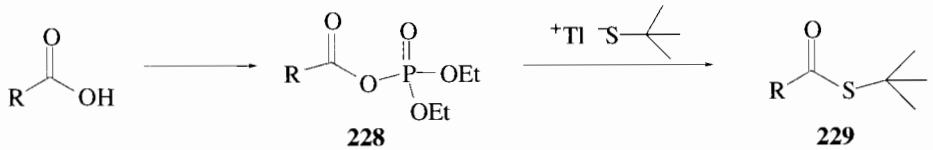
Mercuric trifluoroacetate [$Hg(OCOCF_3)_2$] is an effective reagent for the cyclization of hydroxy thioesters.[95] This cyclization procedure was used by Masamune et al. for the conversion of **225** to **227** (in 90% yield) in a synthesis of zearalenone dimethyl ether.[96] Masamune developed this procedure to complete the total synthesis of methymycin, where one step involved treatment of a thioester with mercuric salts.[97,96] Mercury(II) has an affinity for bivalent sulfur and it binds the thioester unit as well as the terminal hydroxyl



225 226 227

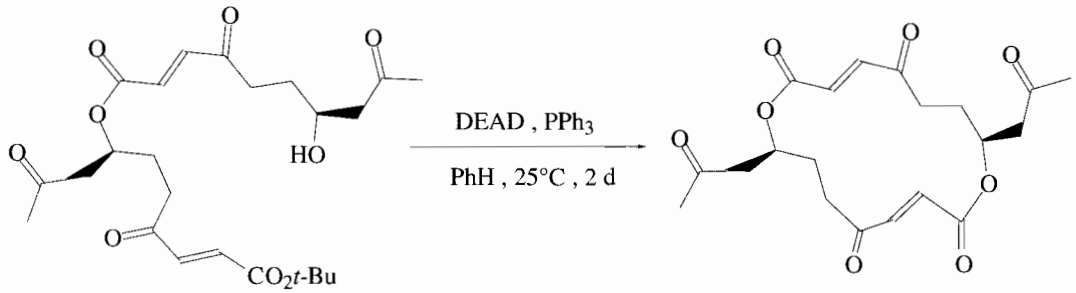
group, as represented by **226**, which brings the reactive termini [HO—S(R)C=O] into close proximity where the hydroxyl oxygen can attack the carbonyl carbon of the thioester to give cyclized product, lactone **225**.

The thioester moiety in **225** (see **229**) is formed by reaction of the phosphonate ester of the appropriate acid (see generic structure **228**) with the thallium salt of 2-methyl-2-propanethiol [TlSC(Me)$_3$], which is a mild and general procedure for the preparation of thioesters.



228 **229**

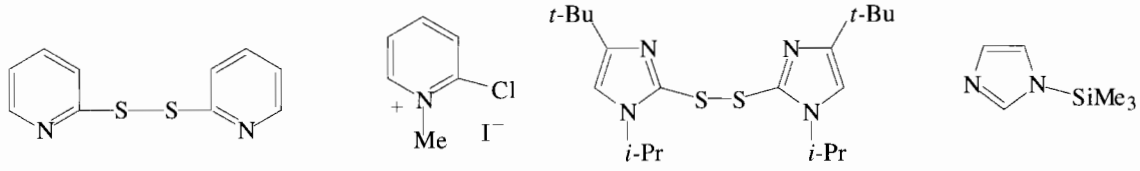
Diethyl azodicarboxylate (EtO_2C-N=N-CO_2Et, DEAD) is a key reagent in the **Mitsunobu reaction** (sec. 2.7.A.ii) and has also been used for macrolactonization.[98] Reaction of **230** with DEAD gave 15% of **231** in White's synthesis of the antibiotic vermiculine.[99]



230 **231**

A variety of specialized reagents have been developed for macrolactonization reactions. Two of the more important are the **Corey–Nicolaou reagent**, 2,2'-dipyridyl disulfide (**232**)[100] and the **Mukaiyama reagent**, which is 2-chloro-1-methylpyridinium iodide (**233**).[101] A number of related reagents have been developed, including imidazole disulfide **234** [2,2'-dithio-(4-*tert*-butyl-1-isopropylimidazole)][102] and imidazole **235** [*N*-(trimethylsilyl)imidazole].[103] All of these reagents are effective for the cyclization of ω-hydroxy acids, as shown in Table 6.1. For comparison, available cyclization results with DEAD and **234** are included. In this table, a hydroxy acid is converted to a lactone (**219**).

As seen in Table 6.1, diolide (**236**) can be formed during cyclization, by reaction of an initial intermolecular coupling product, the ω-substituted carboxylate [X—$(CH_2)_n$—CO_2—$(CH_2)_nCO_2^-$]. The

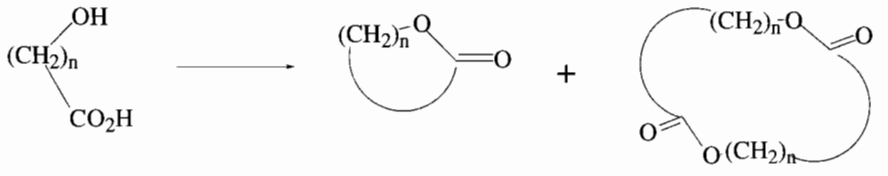


232 **233** **234** **235**

nucleophilic oxygen anion of the carboxylate group displaces the X leaving group in a macrolactonization process to give the diolide (see **236**). Diolides are most commonly observed during the formation of medium size lactones where transannular interactions leads to poor yields. Cyclization of a 10-membered lactone, for example, is difficult, and under high dilution conditions the formation of the 20-membered diolide is usually

favored, following the initial coupling. Diolides are common contaminants in reactions that form 6- to 11-membered ring lactones.

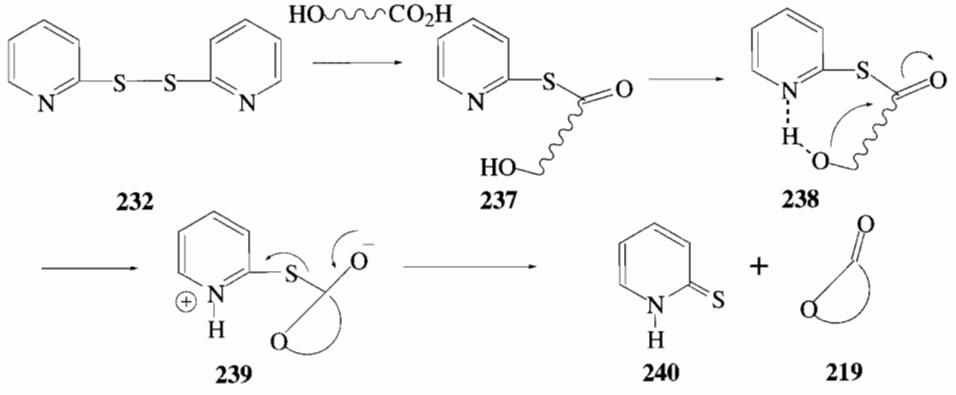
Table 6.1. Macrolactonization of ω-Hydroxy Acids



219 **236**

n	Reagent	% 219	% 236
5	**232**	71	7
	233	89	0
	DEAD	40	53
6	**232**		
	233	0	93
7	**232**	8	41
	233	13	34
	DEAD	0	20
10	**232**	47	30
	233	61	24
11	**232**	66	7
	233	69	14
	234	87	
	DEAD	60	17
12	**232**	68	6
13	**234**	90	
14	**230**	80	5
	233	84	3
15	**234**	96	

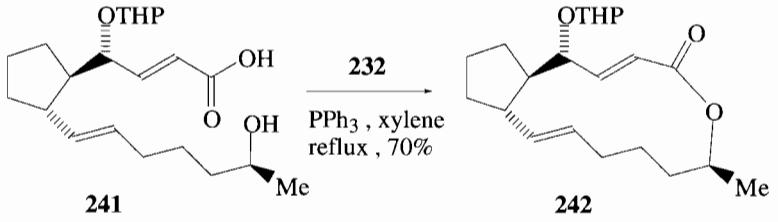
The Corey–Nicolaou procedure reacted **232** with a seco acid to form a thioester (**237**), which is in equilibrium with the protonated form, **238**. The template effect is achieved via hydrogen bonding (see **238**),



232 **237** **238**

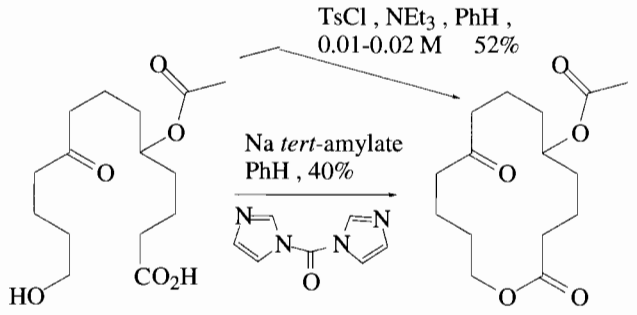
239 **240** **219**

allowing nucleophilic acyl attack by the hydroxy group to give **239**. Displacement of thiopyridone (**240**) gives the lactone (**219**). A synthetic application is the conversion of **241** to **242** in 70% yield by using **232** to initiate cyclization. Lactone **242** was an intermediate in Corey's synthesis of brefeldin A.[104] A similar cyclization was used in Schmidt's synthesis of nonactin.[105]



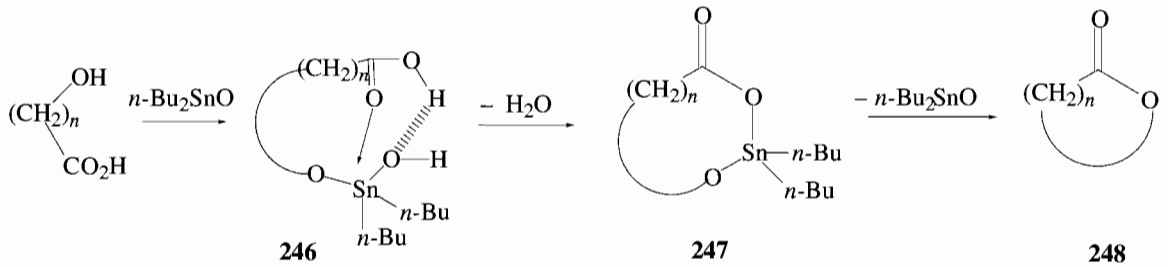
241 **242**

Another useful reagent is 1,1'-carbonyldiimidazole (**244**). Hydroxyacid **243** was converted to **245** (40% yield) in White's model studies for a synthesis of erythromycin B.[106] This reagent promotes formation of an initial imidazolium intermediate to activate the carbonyl to attack. White also cyclized **240** by treatment with tosyl chloride and triethylamine under dilute conditions (0.01–0.02 M) and obtained a 52% yield of **245**.[106]



243 **244** **245**

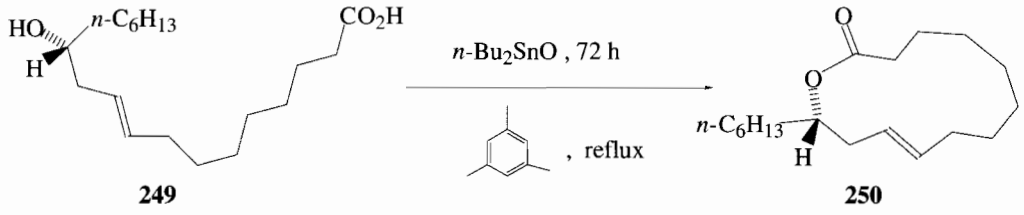
Finally, dibutyltin oxide (n-Bu_2SnO) has been reported as a tin template driven extrusion lactonization reagent.[107a,b] This reagent effects cyclization in refluxing mesitylene with an ω-hydroxy acid, giving 22–63% of the corresponding 13–17 membered ring lactone (0% for n = 7, 63% for n = 14 and 60% for n = 15). The reaction works via conversion to **246**. The tin reagent complexes the carbonyl unit and the hydroxyl



246 **247** **248**

group (as in **247**). Thermally induced loss of water is accompanied by extrusion of n-Bu_2SnO to give the lactone **248**. The reaction requires stoichiometric amounts of dibutyltin oxide to ensure reasonable reaction times. The reaction is amenable to asymmetric macrolactonization since the reagent does not induce racemiza-

tion at the stereogenic center bearing the hydroxyl group. Cyclization of **249** to **250**, for example, proceeded in 44% yield and was used in Hanessian and co-workers synthesis of ricinelaidic lactone.[107]



249 **250**

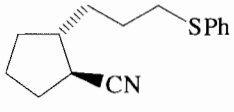
6.7. CONCLUSION

The intent of this chapter is to tie together many of the principles introduced in earlier chapters. In addition, many of the principles used in the important chapters dealing with making carbon–carbon bonds have been discussed. If there is a theme to this chapter, it is that organic chemists can exercise a significant amount of control over synthetic reactions, which is possible by understanding the mechanism of the transformations and the various interactions of heteroatoms and reagents. A thorough understanding of the conformational aspects of reactivity is essential. With knowledge of these principles a useful plan can be assembled for the synthesis of even complex molecules. Without this understanding, syntheses beyond a very few simple steps will be doomed to failure.

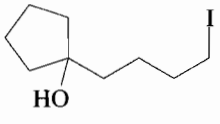
One last piece of information is required for synthesis in order to manipulate functional groups. In those cases where a heteroatom functional group interferes with a transformation and cannot be removed, modified, or inserted earlier or later in a synthesis, methods are available to temporarily block it. This method is termed protection and the moiety used to block the reactive fragment is called a protecting group, which will be the focus of Chapter 7.

HOMEWORK

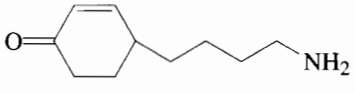
1. In each of the following, give the major product and classify each reaction according to Baldwin's rules:

(a)


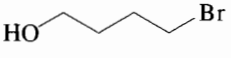
1. BuLi , THF
2. H_3O^+

(b)


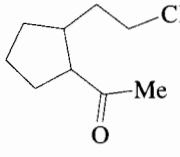
NaH

(c)


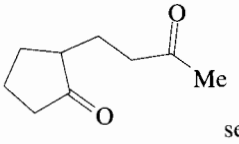
heat

(d)


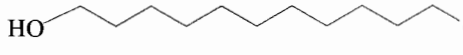
NaH

(e)


1. $LiN(i\text{-}Pr)_2$, THF , –78°C
2. H_3O^+
see Chapter 9

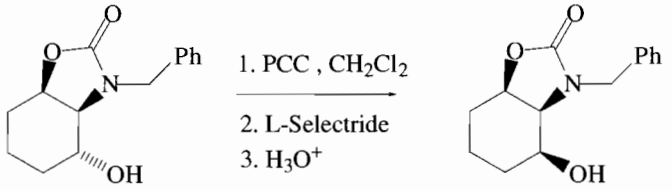
(f)


1. NaOEt , EtOH , reflux
2. H_3O^+
see Chapter 9

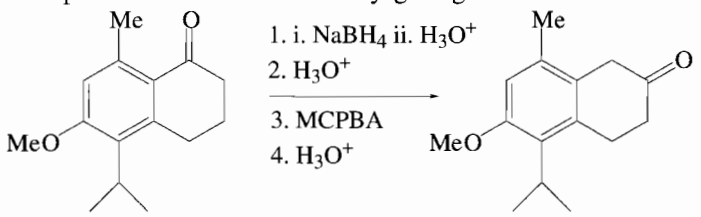
(g)


1. $t\text{-BuS}^- Tl^+$
2. $Hg(OAc)_2$

2. Explain why the following sequence results in inversion of configuration of the hydroxyl group:

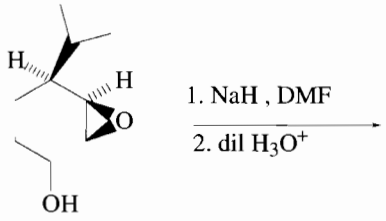


3. Explain this transformation by giving the three intermediate products.

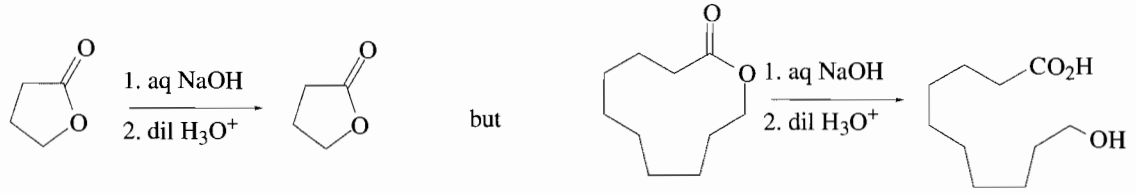


For related reactions see (a) Fieser, L.F.; Fieser, M. *Advanced Organic Chemistry,* Reinhold, New York, **1961**, pp 897–898; (b) *Technol. Repts. Osaka Univ., **1958**, 8,* 455 [*Chem. Abstr., **1959**, 53*: 18920i].

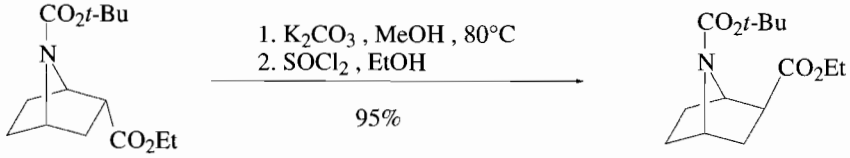
4. Draw the major product of this reaction and predict the correct stereochemistry. Briefly explain your answer.



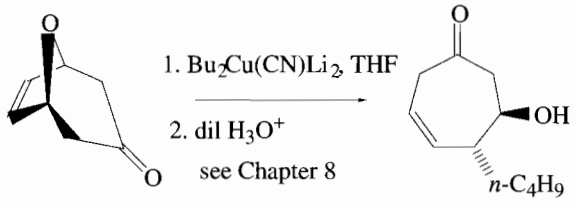
5. Explain why these two saponification reactions lead to different products (ring closed vs. ring opened).



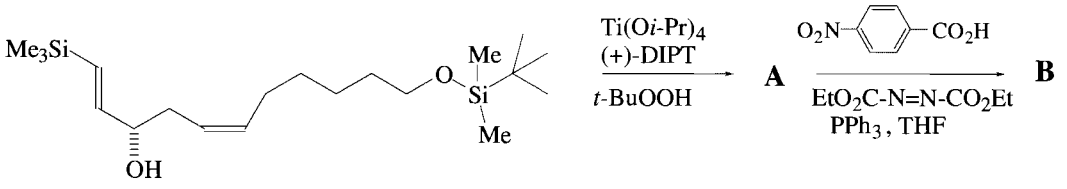
6. Suggest a reason why the carboethoxy group epimerizes upon treatment with potassium carbonate. Why is the second step required?.



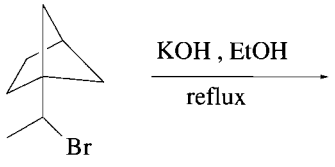
7. Offer a mechanistic rationale for the following conversion that explains the stereoselectivity of the reaction.



8. Show the structure of both A and B. Each of these reactions has a name associated with it. Give the name of each reaction and look up one recent review of each.

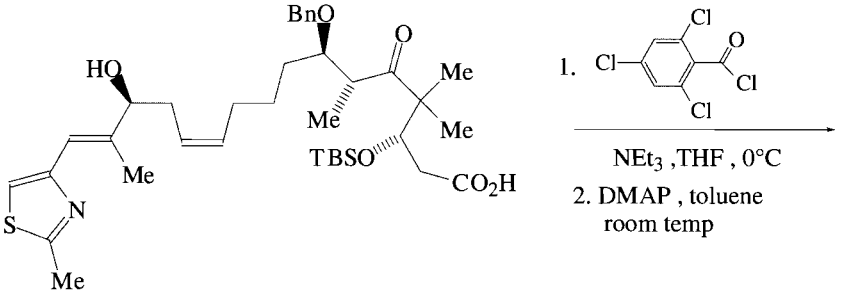


9. Predict the major product of this reaction. Explain your answer in the context of other possible products.

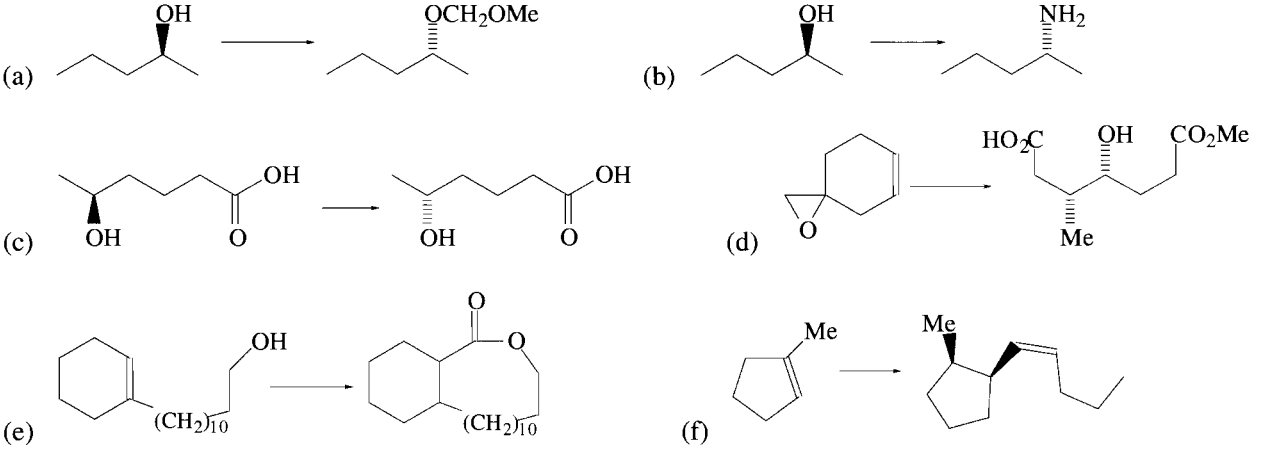


10. Inspection of Table 6.1 suggests that the Mukaiyama reagent gives better yields of lactone with simple ω-hydroxy acids than the Corey–Nicolaou reagent. Offer an explanation that accounts for this observation.

11. Give the major product of the following reaction:



12. In each case provide a suitable synthesis. Show all intermediate products and all reagents.



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CHAPTER 7

PROTECTING GROUPS

7.1. INTRODUCTION

Many problems arise during a synthesis. Some synthetic targets contain more than one functional group and if they interact with each other or if one group reacts with a reagent competitively with another group, the synthesis can be in serious trouble. The presence of a ketone and an aldehyde in the same molecule is an obvious point of concern since they react similarly with nucleophilic species such as a Grignard reagent. The presence of an alcohol and an amine in the same molecule will also cause problems since reactions with acids, bases, and nucleophiles are possible for both functional groups. One practical solution to such problems is to temporarily block a reactive position by transforming it into a new functional group that will not interfere with the desired transformation. That new blocking group is called a **protecting group**. This process requires at least two chemical reactions. The first reaction transforms the interfering functional group into a different one, which will not compete with the desired reaction, which is termed **protection**. The second chemical step transforms the new functional group (i.e. the protecting group) back into the original group at a later stage of the synthesis. This latter process is termed **deprotection**.

Is the use of a protecting group a desirable feature that should always be incorporated into a synthesis? *No*, it should always be avoided if possible. In many cases, however, it ***cannot*** be avoided and a discussion of where to anticipate the use of a protecting group in a synthesis is necessary.[1] As mentioned above, the process of protection–deprotection adds two steps to a synthesis. If there are four interfering functional groups and each requires protection, as many as eight steps may be added. Planning the order for insertion of a given functional group can usually minimize the use of protecting groups, but not always. If an aldehyde group can be inserted into a molecule after a ketone–Grignard reaction has been done, for example, there is no need to protect the aldehyde and two synthetic steps are saved. When a protection step is necessary, the first question is what transformation can be done that blocks the reactivity of a given group, but provides a chemical pathway back to the original group in high yield. The protecting group must be relatively inert and, ideally, react with a specific reagent to unmask it (regenerate the original group).

The most important functional groups that cause reactivity problems are alcohols, ketones and aldehydes, and amines. Carboxylic acids contain the COOH group, which can also cause problems, but this is usually blocked as an ester. For alcohol groups, the acidic hydrogen of the O—H causes problems, and a protecting group must remove that hydrogen. The most common methods for temporarily removing the acidic hydrogen are to convert the alcohol to an ether, an acetal, or an ester. Ketones and aldehydes are subject to nucleophilic acyl addition, and the carbonyl moiety is usually protected by conversion to an acetal or a ketal, a thioacetal or a thioketal, or a hydrazone derivative. The interfering part of an amine is the basic, lone pair of

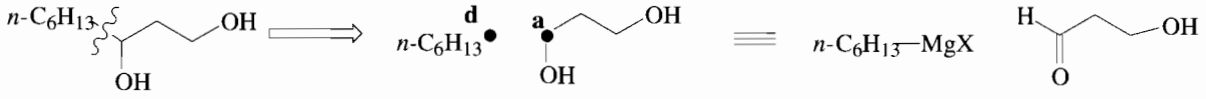
electrons. These electrons can be tied up by conversion to a quaternary ammonium salt but such salts are not always easy to use in synthetic sequences. The lone pair is not usually removed, but electronically delocalized by conversion to an amide or a sulfonamide. In some reactions, the N—H group is acidic and a protecting group must block the acidic hydrogen.

If a protecting group is described, methods are known to protect the functional group in high yield and the deprotection can be done with some selectivity, also in high yield. Greene and Wuts' excellent monographs describe these functional groups as well as many others in great detail.[2] The series *Compendium of Organic Synthetic Methods*[3] also provides some examples of recently used protecting groups and there are reviews.[4]

Two essential questions remain. When does one use a protecting group and how is that group chosen? When to use a protecting group is not an easy question to answer. Greene and Wuts' books are an excellent source for choosing a protecting group, and they provide many examples. Section 7.2 will outline problems where the best solution was to use a protecting group, and Section 7.3 will give a brief review of common protecting groups. It is important to note that there are other uses of the groups here labeled protecting groups. They can be used to provide directing effects, influence solubility and other physical properties, make it easier to isolate certain products, and they can increase the crystallinity of a compound. In addition, protected functional groups are common in the pharmaceutical industry as prodrugs. They are useful for solid-phase attachment of functional groups (see sec. 10.12), and for tagging molecules (fluorescence tagging for example). Some of these uses will be touched upon in later chapters, but here we will focus on classical uses for protecting groups.

7.2. WHEN ARE PROTECTING GROUPS NEEDED?

It is not easy to give a set of rules for when to use protecting groups. Each synthesis is different and the requirements vary with the reaction sequence and functional groups that are present. In this section, a series of common synthetic problems will be presented where protection–deprotection was a viable solution.

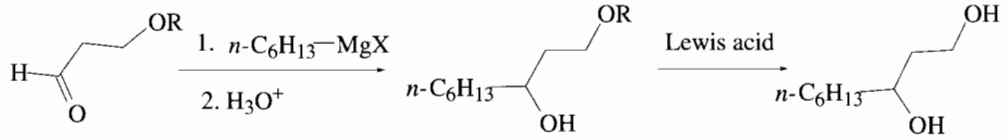


1 **2** **3** **4** **5**

The place to begin this discussion is with a synthesis. An analysis of diol **1** shows that there are several possible disconnections, but we will focus on only the bond connected to the hexyl group. Disconnection of the indicated bond leads to disconnect products **2** and **3**. Using the concept of synthetic equivalents introduced in chapter 1, the disconnect products are converted to hexylmagnesium halide (**4**, sec. 8.4.C) and a β-hydroxyaldehyde (**5**). If this synthetic route is chosen, protecting groups are necessary.

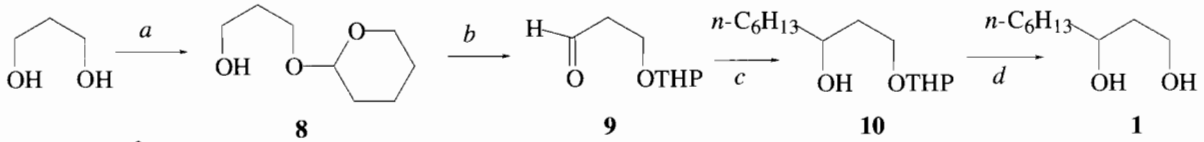
Why is it necessary to use a protecting group? Grignard reagent **4** is a base as well as a nucleophile, and attempts to react it with **5** will have problems because the acidic hydroxyl group reacts faster than the carbanionic center adds to the carbonyl. It is possible that the alkoxide could react with a second equivalent of

Grignard reagent, of course, but there are solubility problems with this polar product and it is probably easier to block the OH to prevent the deprotonation. In other words, the Grignard reagent, the hydroxyl and the carbonyl moiety should not be present in the molecule at the same time. The O—H unit of **5** must be replaced with a functional group that can tolerate the Grignard reaction, but be converted back to a hydroxyl afterward. If the hydroxyl group is converted to an ether, as in **6**, the key Grignard reaction can proceed to give **7**. In a subsequent step, the R group can be removed to regenerate the hydroxyl moiety in **1**. In this case, the hydroxyl group was protected, allowing the desired reaction to proceed, which is one instance where protecting groups should be used.



6 **7** **1**

An actual synthetic solution for the preparation of **1** was taken from Kitching's synthesis of a gland secretion of fruit flies in which 1,3-propanediol was converted to the monotetrahydropyranyl (THP) derivative (**8**) by reaction with dihydropyran.[5] The identical nature of the two hydroxyls made protection of one very easy, by simply controlling the stoichiometry of the reagent. Oxidation of the unprotected alcohol (to aldehyde **9**) was followed by addition of hexylmagnesium bromide to give **10**, deprotection with acidic methanol gave the product, 1,3-nonanediol (**1**). This particular sequence was used to prepare an authentic sample of a synthetic intermediate for purposes of comparison, and no yields were reported. When a disubstituted molecule is symmetrically functionalized (as with 1,3-propanediol), the two groups are chemically equivalent and protection of one of them is rather easy. The choice of protecting group will be determined by which reagents are to be used to modify the unprotected alcohol.



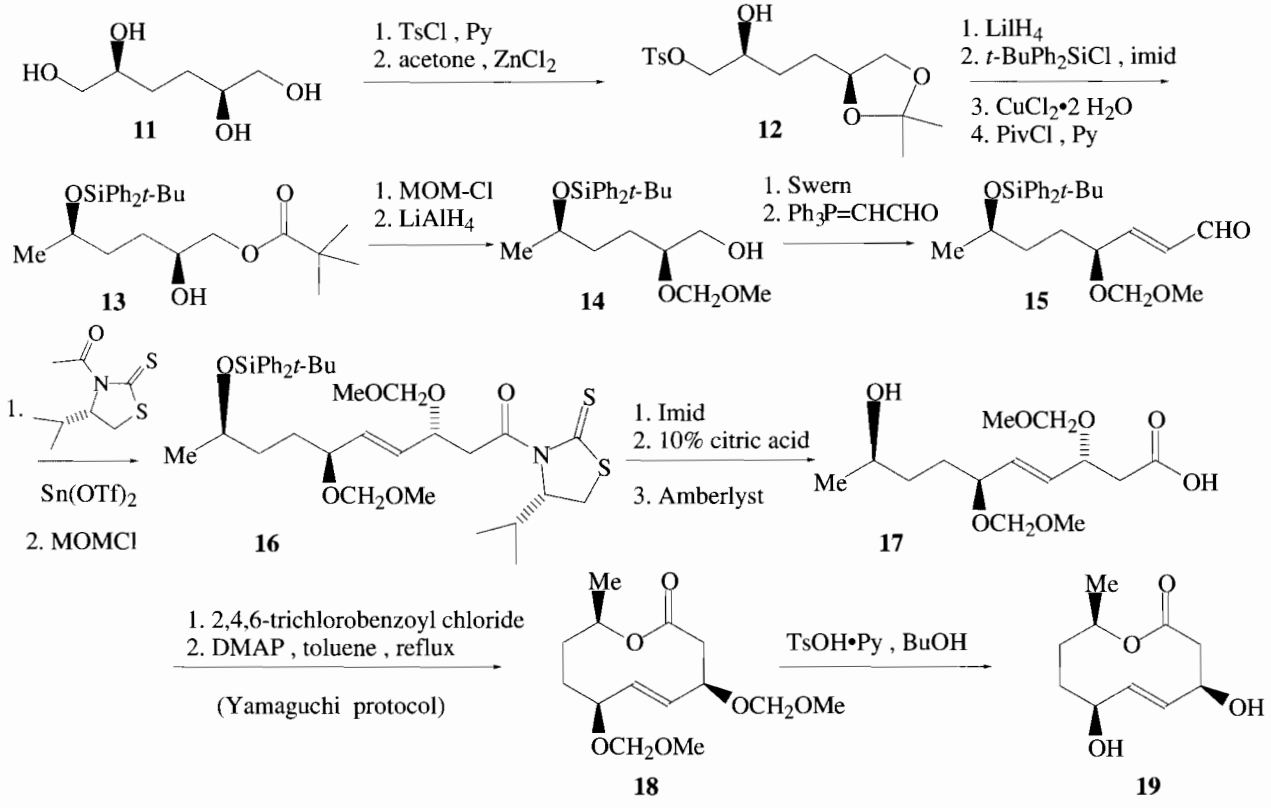
8 **9** **10** **1**

(*a*) H^+, (*b*) PCC , NaOAc (*c*) i. n-$C_6H_{13}MgBr$ ii. H_3O^+ (*d*) MeOH , H^+

What are the consequences of using protecting groups in synthesis? First of all, protection must be used or the sequence will not work. However, the price to be paid is at least two more synthetic steps (insertion and removal of the protecting group), and the overall yield of the synthesis will suffer. The ability to generate a target directly versus the loss of material that accompanies the use of protecting groups must be weighted in the context of the specific synthesis. Usually, protecting groups are used because there is no direct way to solve the problem without them.

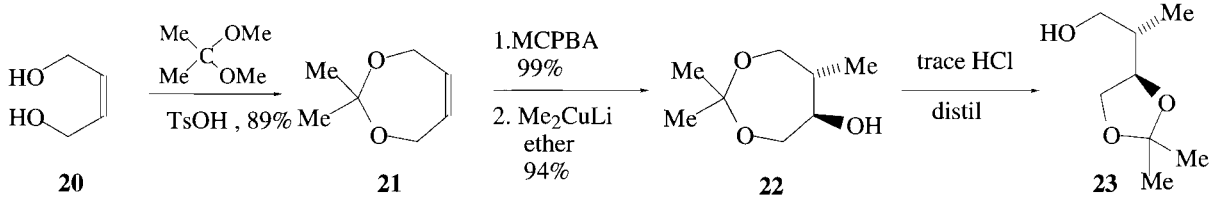
In complex synthetic targets, it is common for two or more identical functional groups to be present. It is unlikely that all of those groups can be incorporated simultaneously, and there is a chance that once two groups are incorporated, one will interfere with reactions aimed at another. An example where several alcohol

moieties are incorporated in a molecule is in Kibayashi's synthesis of (–)-(3*R*,6*S*,9*R*)-decarestrictine C_2 (**19**) from tetraol **11**.[6] Although most of these specific protecting groups will be described in this chapter, an analysis of the synthesis will illustrate how their use led to the desired target. One primary alcohol in the symmetrical starting material is converted to a tosylate, allowing the diol unit to be blocked as an acetonide (**12**). The remaining alcohol unit was protected as the silyloxy group and after converting the acetonide protecting group back to the diol, the terminal OH was converted to a pivaloyl ester (**13**). The secondary alcohol was protected as the OCH_2OMe (MOM) group, which differentiated the two secondary alcohols of **11**. This sequence also differentiated the two primary alcohol units so that reduction with lithium aluminum hydride reduced the tosylate to a methyl group and the ester back to a primary alcohol (see **14**). Swern oxidation followed by a Wittig reaction (see sec. 8.8.A) gave conjugated aldehyde **15**. Condensation with the 1,3-thiazolidine-2-thione (also see sec. 12.9.A for related metal condensation reactions) and protecting the resulting

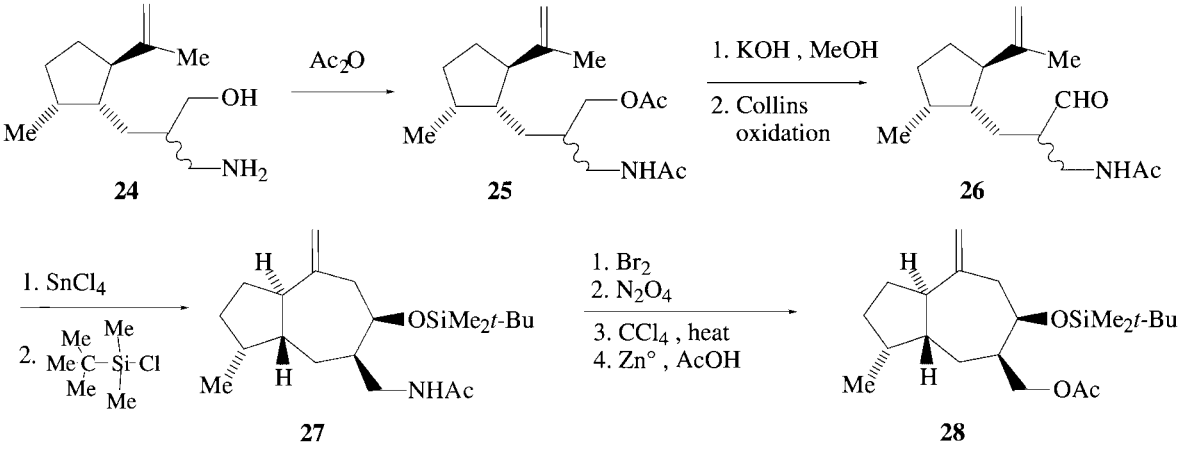


secondary alcohol with the MOM group gave **16**. Conversion of the amide unit back to the carboxylic acid and deprotection of the silyloxy unit gave **17**, allowing a Yamaguchi protocol (see sec. 6.6.B) to give lactone **18**. Removal of the two MOM protecting groups gave the final target **19**. This sequence illustrates that a symmetrical tetraol, with two primary and two secondary alcohol units can be manipulated in such a way that two of the alcohols can be elaborated to other functionality, and the final product still contains the one original secondary alcohol while the other is part of the lactone ring. Despite the need for protection and deprotection, this sequence allowed Kibayashi to target specific functional groups in a controlled manner, one of the positive aspects of using protecting groups. The abbreviations mentioned above are defined in section 7.3.A.

If protecting groups must be used in a synthesis, the goal is to be efficient and keep the number of steps to a minimum. It is often necessary to protect a group, deprotect it, and then later protect it a second time. If these steps could somehow be combined, it could save on the total number of steps in the synthesis and make the overall process more efficient. An example of this is seen in the conversion of **20** to **23** in Silverstein's synthesis of α-cubebane.[7] In this case, the starting material is **20**, which contains two primary hydroxyl groups that are first protected as a ketal in **21**. This choice allows manipulation of **21** to give **22**, where a third hydroxyl group has been incorporated. The next step in the sequence required manipulation of the -CH_2OH unit that is adjacent to the methyl group. Rather than deprotect **22** and then re-protect the resulting triol, **22** was treated with acid, inducing deprotection of the seven-membered ring ketal and formation of the more stable five-membered ring ketal moiety in **23**. This trick maximizes the utility of the protecting group and minimizes the number of actual steps required for its use.

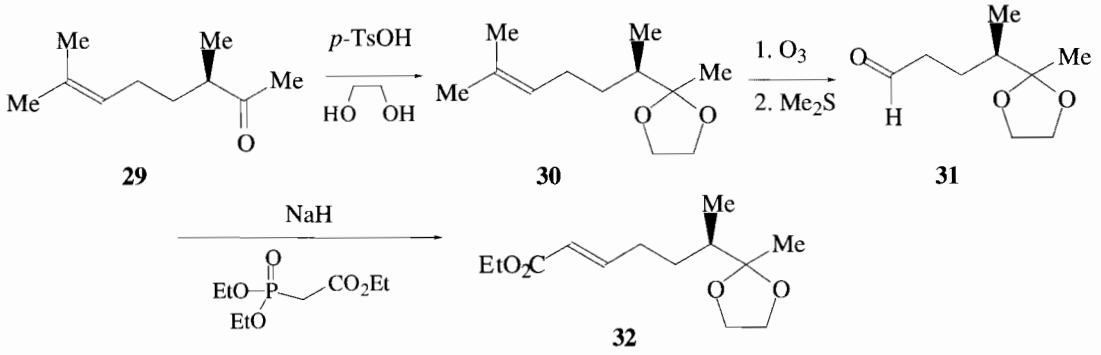


There are occasions when it is impossible to avoid placing two like functional groups in a molecule, yet one of them is to be selectively transformed and the other must be protected, which can be done *if* one functional group reacts at a different rate in the protecting group reaction. The conversion of **11** to **19** illustrated this concept. Amino alcohol **24** is another example of a molecule containing two functional groups that can interfere with each other, and it was necessary to incorporate both at the same time (from an amino acid precursor). The functional groups are different, an amino group and a hydroxyl group, and it is necessary to chemically differentiate them. In this case, the hydroxyl was to be converted to an aldehyde (**26**) and then cyclized with $SnCl_4$ to give **27**. Unfortunately, a free amine could react with the aldehyde and would also be



subject to competitive oxidation. An amine might also react with the Lewis acid ($SnCl_4$), interfering with the cyclization reaction. The NH_2 group must be protected. This example was taken from Andersen's synthesis of

kessanol,[8] where an acetyl group was chosen for protection, but both the amine and the alcohol formed their respective acetate derivative in **25**. The ester is more easily hydrolyzed than the amide, however, and treatment of **25** with aqueous KOH gave the alcohol, which was oxidized to the aldehyde in **26** by Collins oxidation (sec. 3.2.B). Ring closure was initiated by $SnCl_4$, and the hydroxyl group was then protected as its *tert*-butyldimethylsilyl ether (see **27**). The final synthetic sequences gave **28** as the final product. It is interesting to observe that bromination of **27** was done to protect the C=C unit, allowing the amide unit to be manipulated. Heating with zinc and acetic acid regenerated the double bond, so the dibromide is an alkene protecting group.



A final example illustrates the use of planning a synthesis such that groups that might interfere with each other are incorporated in a protected form. The synthesis of **32** from **29** involves conversion of the $Me_2C{=}C$ group to an aldehyde that can undergo an olefination reaction. Clearly, the presence of the ketone moiety in **29** would interfere with this sequence. For this reason, the aldehyde group in **31** was incorporated early in the sequence in the form of an alkene, knowing that the aldehyde can be unmasked by ozonolysis. Before this step, however, the ketone unit is protected as the ketal (**30**), allowing ozonolysis to give **31**. **Horner-Wadsworth-Emmons olefination** of this aldehyde (sec. 8.8.A.iii) gave **32**. Knowing that an aldehyde unit and a ketone unit must be present in the same molecule allowed them to be synthetically incorporated at different times and in a manner where one would not interfere with the chemistry of the other. This sequence was taken from Chiang's synthesis of inhibitors of cholesterol biosynthesis.[9]

7.3. PROTECTING GROUPS FOR ALCOHOLS, CARBONYLS, AND AMINES

This section will introduce the actual functional group modifications used for protecting groups. The monographs by Greene and Wuts[2] describe protecting groups for many different functional groups. This section is not exhaustive, but rather representative. Most of the protecting groups used in synthesis involve alcohols, ketones, aldehydes, and amines, and only common protecting groups will be examined. The intent is to introduce protecting groups and to provide a few simple tools that may solve a synthetic problem.

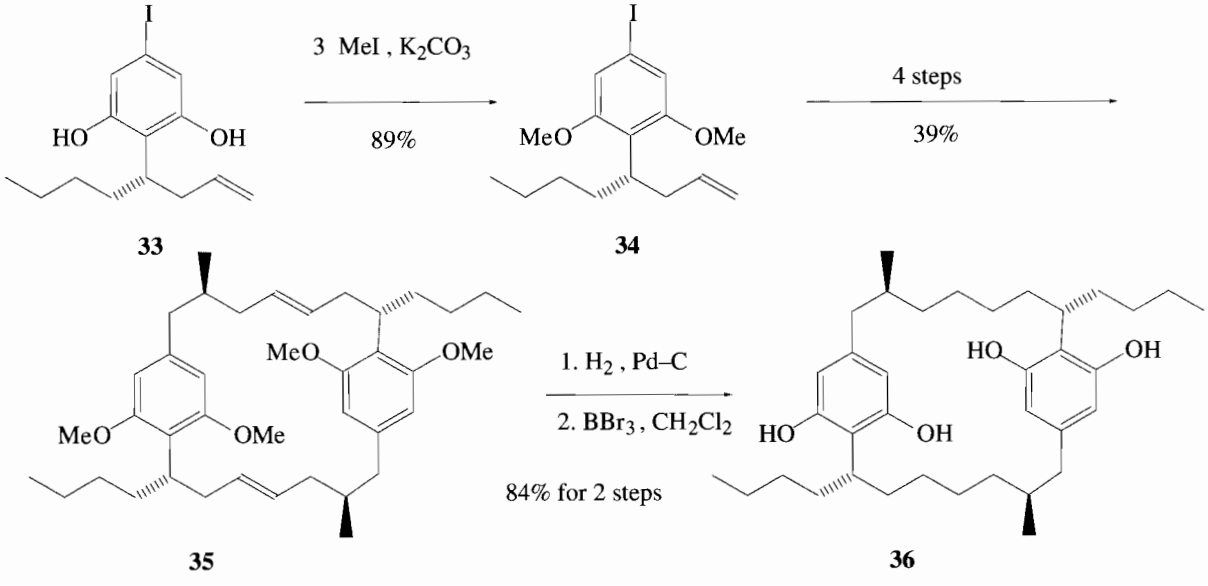
7.3.A. Protection of Alcohols

The first task in developing a protecting group for a given functional group is to identify the interfering part of that group. In the case of alcohols, this is almost always the acidic hydrogen of the O—H group. If an

alcohol moiety interferes with a planned reaction, the OH must be converted to O—X (another functional group), but this reaction must proceed in high yield and under mild conditions. The new functional group (now called the **protecting group**) must be impervious to all reagents used in succeeding synthetic steps but must be easily removed, in high yield, under conditions that do not disturb other functionality. All of this chemistry must be done within the limitations of reactivity imposed by the given functional group.

Alcohols give two major reactions that largely fit these criteria. Conversion of alcohols to ethers usually proceeds in high yield to give a relatively inert product. Due to this inertness, the reaction conditions required for cleavage of the ether may be very harsh. Specialized ether protecting groups have there-fore been developed that can be removed under mild and selective conditions. Another solution is to convert alcohols to acyclic acetals or ketals. These groups maintain much of the inertness of ethers but are easily converted back to the alcohol. It is also possible to convert alcohols to esters under mild conditions, and hydrolysis easily converts them back to the alcohol. There is a problem if an ester group is used, however, since many reagents react with its acyl carbon. A few examples of ester protecting groups will be discussed, but ethers and acetals constitute the vast majority of alcohol protecting groups.

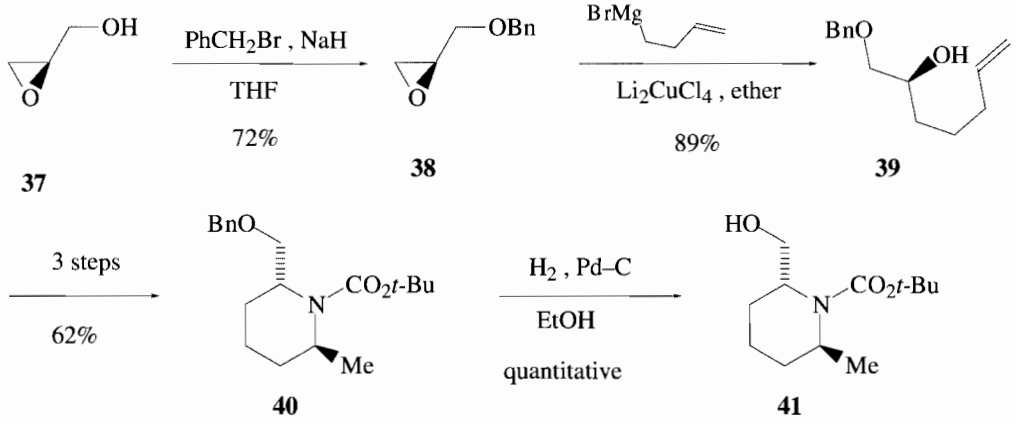
7.3.A.i. Ether and Acetal Protecting Groups. A simple way to protect the OH of an alcohol is as its methyl ether (-OMe). Reaction of an alcohol with a base [often sodium hydride (NaH) in THF or DMF] gives an alkoxide. Subsequent reaction with iodomethane gives the methyl ether via an S_N2 reaction (sec. 2.7.A.i) . Formation of dialkyl ethers via reaction of an alkoxide with an alkyl halide is called the **Williamson ether**



synthesis.[10] Methyl ethers can also be prepared by treatment of an alcohol with dimethyl sulfate (Me_2SO_4), a base, and a phase-transfer agent (such as tetrabutylammonium iodide)[11] or by reaction of an alcohol with trimethyloxonium tetrafluoroborate (**Meerwein's reagent**).[12] Methyl ethers are stable to strong bases, nucleophiles, organometallics, ylids, hydrogenation [except for benzylic ethers (see below)], oxidizing agents, and hydride reducing agents.[13] They are stable in the pH range 1→14. Methyl ethers can be cleaved with

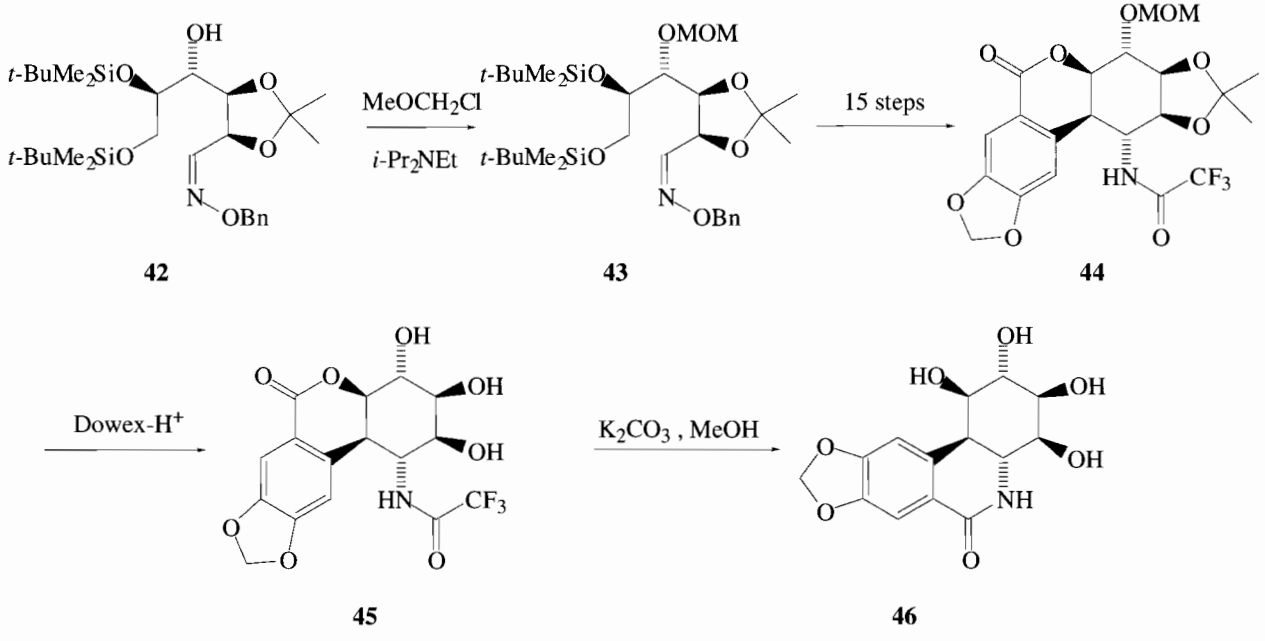
concentrated HI, but trimethylsilyl iodide unmasks the alcohol in chloroform at ambient temperatures.[14] Lewis acids such as boron tribromide (BBr_3) also cleave methyl ethers to alcohols. The use of this group is illustrated in a synthesis of (–)-cylindrocyclophane F (**36**), in which Smith prepared bis(methyl ether) (**34**) from bis(phenol) (**33**) via reaction with potassium carbonate and iodomethane.[15] With the phenolic units blocked, four steps were required to prepare the cyclophane unit in **35**. Catalytic hydrogenation of both alkene units was followed by deprotection with BBr_3 to give the final target **36**.

Another common protecting group is the benzyl ether (—OCH_2Ph, **O—Bn**), prepared by reaction of the nucleophilic alkoxide of an alcohol with benzyl bromide or chloride.[16] Benzyl ethers are stable to a wide range of reagents, including pH 14, carbanions, and organometallics, nucleophiles, hydrides, and some oxidizing agents (RuO_4 will give benzoates, for example).[17] The two best methods for removing the benzyl group involve cleavage of the O—CH_2Ph bond by hydrogenolysis (secs. 4.8.E, 4.9.D). The most common method is probably catalytic hydrogenation, usually with a palladium catalyst.[18] Hydrogenolysis by dissolving metals (sodium or potassium in ammonia–sec. 4.9.D) is also used.[19] The O—benzyl group was used in the De Clercq and co-workers studies directed towards the synthesis of (+)-himbacine,[20] in which epoxy alcohol **37** was converted to benzyl ether (**38**) by treatment with sodium hydride (KH) and benzyl bromide. The epoxide was opened by the Grignard reagent derived from 4-bromo-1-butene to give **39**, and this was converted to **40** in three steps. Deprotection of the alcohol was accomplished with hydrogen with a Pd–C catalyst to give **41** in quantitative yield.



Alcohols can be converted to a *tert*-butyl ether [O—$C(CH_3)_3$] by reaction of the alcohol with 2-methyl-2-propene (isobutylene) and an acid catalyst (sulfuric acid or BF_3).[21] This procedure takes advantage of the facile formation and relative stability of a tertiary cation, which allows subsequent reaction with the alcohol in a S_N1 type reaction to give the ether. A limitation on this reaction is that other functionality in the molecule must be compatible with acidic conditions. As a protecting group, *tert*-butyl is sensitive to strong acid, but is actually stable to pH 1 → 14, as well as to nucleophiles, organometallics, hydrides, catalytic hydrogenation, oxidations, and dissolving metal reductions.[22] The group can be removed with strong aqueous acid, as mentioned above, as well as with Lewis acids. Two common methods for removal of the *tert*-butyl group are treatment with anhydrous trifluoroacetic acid (CF_3COOH, **TFA**)[21a] or with trimethylsilyl iodide.[14]

In many cases, the incorporation or removal of methyl, benzyl, *tert*-butyl and other simple ether protecting groups is not compatible with the presence of other sensitive functional groups which may be present. Similar problems arise in molecules containing several hydroxyl moieties that require protection and subsequent deprotection in a specific order (such as those in the (–)-(3*R*,6*S*,9*R*)-decarestrictine C_2 synthesis, **11** → **19**). Alternative ether protecting groups have been developed that show greater selectivity in reactions with acids or Lewis acids, allowing more latitude in the choice of a method to remove them. These alternatives have been classified by Greene and Wuts as substituted methyl ethers[23] but their RO—CHR^1—O—R^2 structure shows them to be acetals. There are many possible derivatives, but only a few are used with great frequency.



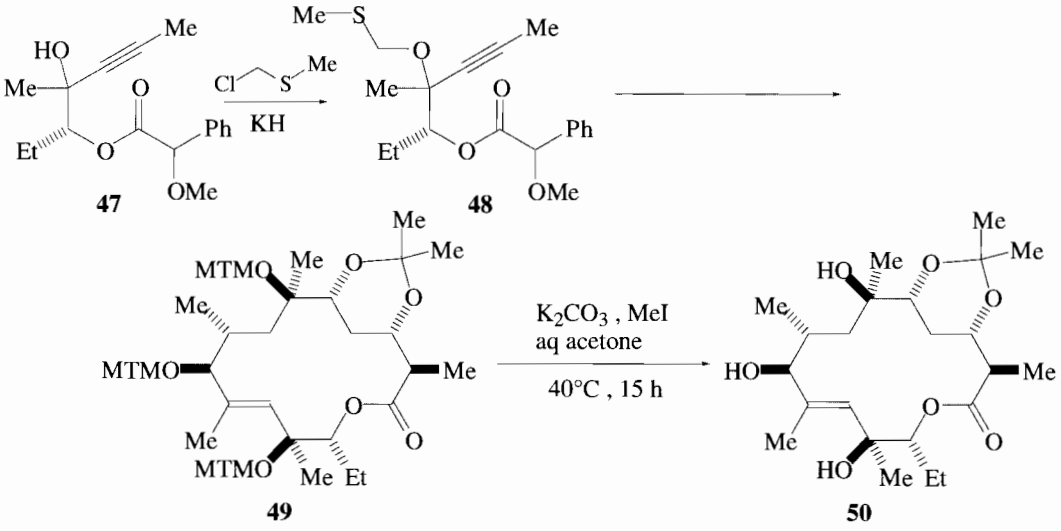
42 **43** **44**

45 **46**

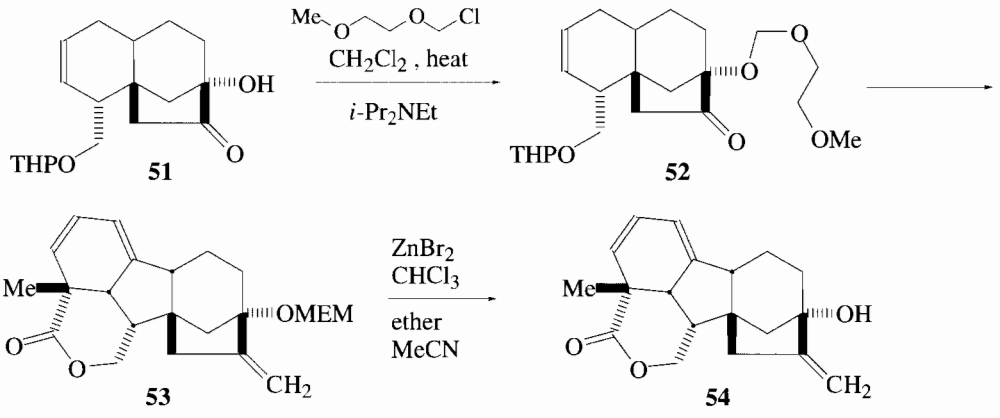
The first of these acetals is methoxymethyl ether (O—CH_2OMe O-**MOM**), formed by reaction of the alcohol with a base (such as NaH in THF) and then with $ClCH_2OCH_3$ (chloromethyl methyl ether).[24] The MOM group is somewhat sensitive to acid, but is generally stable in the pH 4–12 range. It is important to note that HCl in an aqueous THF solution (pH ≈ 1) does not cleave the BnO group whereas it does cleave the OMOM group. It is stable to nucleophiles, organometallic reagents, hydrides, catalytic hydrogenation (except with platinum catalysts in acidic media) and to oxidation,[25] but reacts with acidic media to give the alcohol. Sensitivity to acid is the key to removing this group, and 50% aqueous acetic acid with a sulfuric acid catalyst is commonly used for deprotection,[26] as is HCl in MeOH.[27] An example is taken from Keck's synthesis of 7-deoxypancratistatin (**46**),[28] in which the free hydroxyl group in **42** was converted to the MOM protected unit in **43**. Manipulation of over 15 chemical steps resulted in **44**, and treatment with Dowex resin (an acid resin commonly used as a controlled source of acid) not only removed the MOM group, but also cleaved the acetonide and generated triol **45**. When treated with methanolic potassium carbonate, the *N*-trifluoro-acetyl group was removed (see sec. 7.3.C.ii) to give a primary amine, which was accompanied by attack at the lactone unit to give the lactam in the target compound, **46**.

A variation on the MOM protecting group replaces the oxygen with sulfur to generate the methylthiomethyl ether (O-CH_2SMe, O-**MTM**). The target alcohol is converted to the alkoxide with sodium hydride or another suitable base and then treated with chloromethylmethyl sulfide ($ClCH_2SMe$).[29a] An alternative method uses DMSO and acetic anhydride in acetic acid.[29b] This thioether protecting group is stable to pH 1-12 but it is sensitive to very strong aqueous acid and to Lewis acids (especially mercuric salts). It reacts with many hydrogenation catalysts (bivalent sulfur is a poison–sec. 4.8.A) and can be oxidized to a sulfoxide with many oxidizing agents (sec. 3.9.A).[30] The group is stable to reaction with nucleophiles, organometallics, and hydrides. It can be removed by treatment with Lewis acids, and mercury salts are especially effective.[29] This group can also be removed by treatment with iodomethane in mildly basic solution, in some cases.[30]

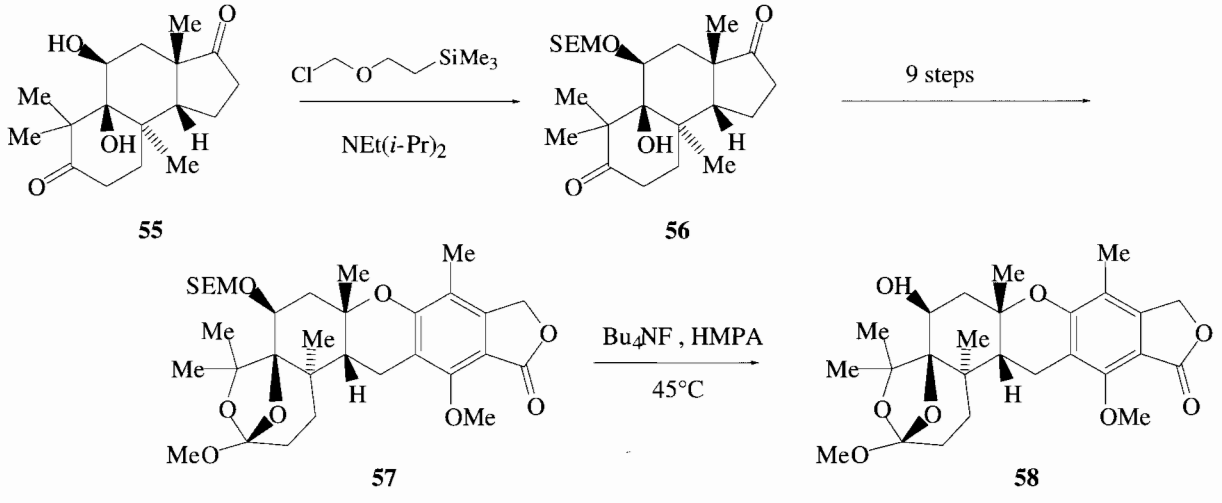
The MTM group was used to protect several of the alcohol groups in Corey's synthesis of erythronolide A.[31] Alcohol **47** contains a sensitive OH group, and it was converted to the MTM derivative (**48**). This allowed the construction of the tris-MTM lactone (**49**). Treatment with potassium carbonate (K_2CO_3) and iodo-methane in aqueous acetone (40°C, 15 h) gave the triol (**50**) in 80% yield, which was converted to erythronolide A.



Another common acetal protecting group is the 2-methoxyethoxymethyl ether (—O—$CH_2OCH_2CH_2OMe$, O—**MEM**). The MEM group is attached by the usual conversion of the target alcohol to an alkoxide (usually with NaH in THF or DME, although diisopropylethylamine (**Hünig's base**) can be used in dichloromethane), and then reaction with methoxyethoxy chloromethyl ether.[32] It is stable to pH 1–12, oxidizing agents, hydrogenation, hydrides, nucleophiles, and organometallics,[33] but is cleaved in strong aqueous acid (pH <1) and is sensitive to Lewis acids. This latter observation is the key to deprotection. Either zinc bromide ($ZnBr_2$) or titanium tetrachloride ($TiCl_4$) in dichloromethane can be used for deprotection.[32] Corey used the OMEM group to protect the tertiary alcohol in **51** in a synthesis of gibberellic acid.[34] This OH group could cause problems in the manipulation of other hydroxyl groups in several synthetic intermediates that were important to the synthesis. Alcohol **51** was converted to MEM ether (**52**) with MEM chloride and Hünig's base. Elaboration of the gibberellic acid intermediate gave **53**, and deprotection with zinc bromide gave alcohol **54**.



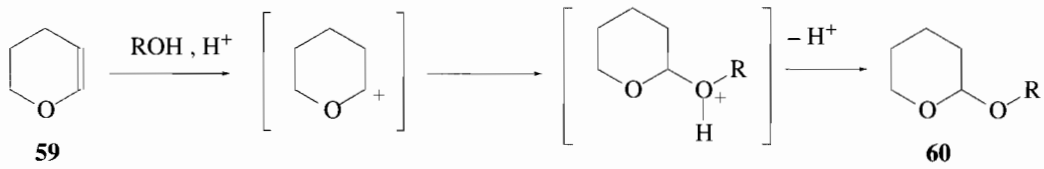
A variation of the OMEM group is the 2-(trimethylsilyl)ethoxymethyl ether (O-$CH_2OCH_2CH_2$-$SiMe_3$, O—**SEM**), developed by Lipshutz.[35] The trimethylsilyl group is used as a trigger for facile deprotection of



the alcohol. The O—SEM group is attached to an alcohol by reaction with Hünig's base and 2-(trimethylsilyl)ethoxymethyl chloride ($Me_3SiCH_2CH_2OCH_2Cl$). It is stable in a pH range of 4-12. Some nucleophiles and many Lewis acids react with this group,[36] but it is generally stable to hydrides and to many organometallics (such as butyllithium) as well as most oxidizing agents. The presence of silicon makes the group sensitive to fluoride [as with silyl protecting groups - see below], and treatment with tetrabutylammonium fluoride (n-$Bu_4N^+F^-$, TBAF) usually regenerates the alcohol, but not always. Indeed, the OSEM group can be difficult to remove. In Paquette's synthesis of (–)-australide B,[37] the secondary alcohol unit in **55** was protected as the SEM derivative (**56**). Significant synthetic manipulation over nine steps resulted in **57**, and the SEM group was removed with tetrabutylammonium fluoride to give **58**.

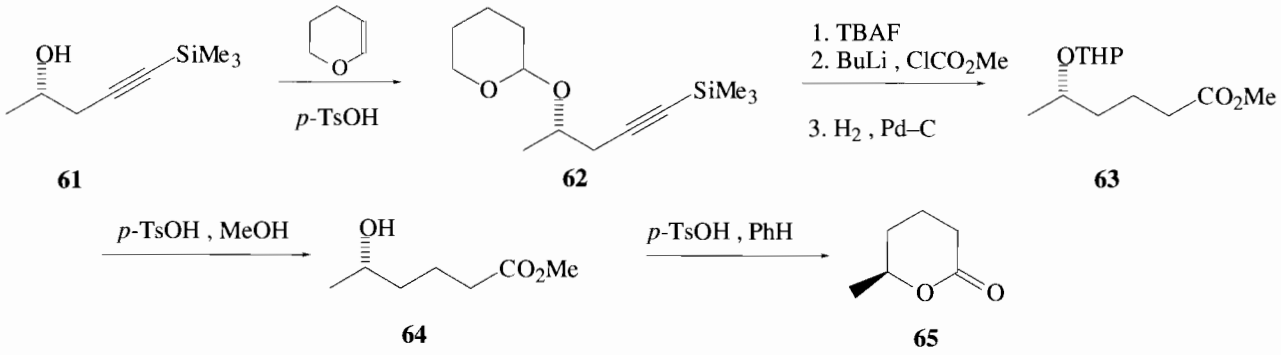
A cyclic acetal protecting group, the tetrahydropyranyl ether (—O—2—c-C_5H_9O, **THP**), has been a mainstay of older organic synthesis. An alcohol reacts with dihydropyran (**59**), in the presence of an acid such as p-toluenesulfonic acid, to give the THP derivative (**77**) via an oxygen stabilized cation.[38] One problem with this protecting group is the fact that a new stereogenic center is created when **60** is formed. If ROH is chiral,

60 will exist as diastereomers, which may make identification, isolation, and purification difficult if this protecting group is carried through many synthetic steps. This group is stable to base (pH 6–12) but unstable to aqueous acid and to Lewis acids.[39] It is relatively stable to nucleophiles and organometallics. It is also



59 **60**

stable to hydrogenation, hydrides, and oxidizing agents.[38] It is removed with aqueous acid or methanolic tosic acid.[40] Greene reported[38] that explosions have occurred when tetrahydropyranyl ethers are treated with diborane - basic hydrogen peroxide[41] or with 40% peroxyacetic acid.[40] An example involving this protecting group is White's work in which the absolute configuration of C_{34}-botryococcene was determined.[42] Alkyne-alcohol **61** was treated with dihydropyran and tosic acid to give the tetrahydropyranyl ether **6**, Removal of the trimethylsilyl group form the alkyne, conversion to the alkyne anion, and reaction with methyl chloroformate gave the ester. The alkyne was hydrogenated to give **63**. At this point, the THP protecting group was removed with methanolic toluenesulfonic acid to give **64**. A second treatment with tosic acid under more vigorous conditions, converted the ester to the acid, allowing the molecule to cyclize to lactone **65** via an intramolecular transesterification.

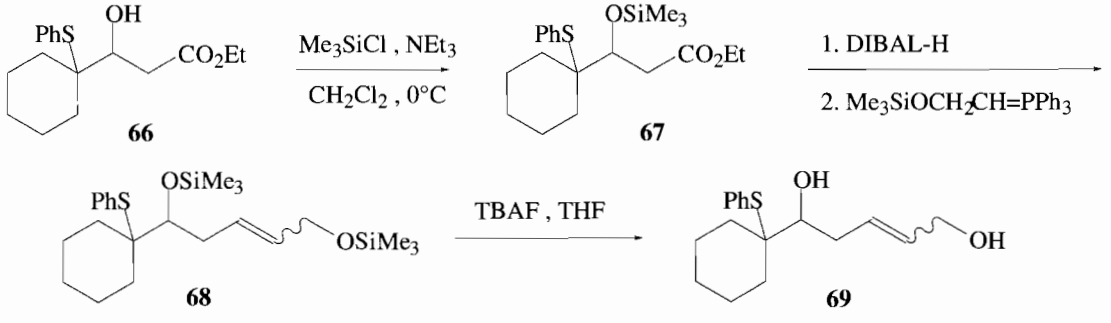


61 **62** **63** **64** **65**

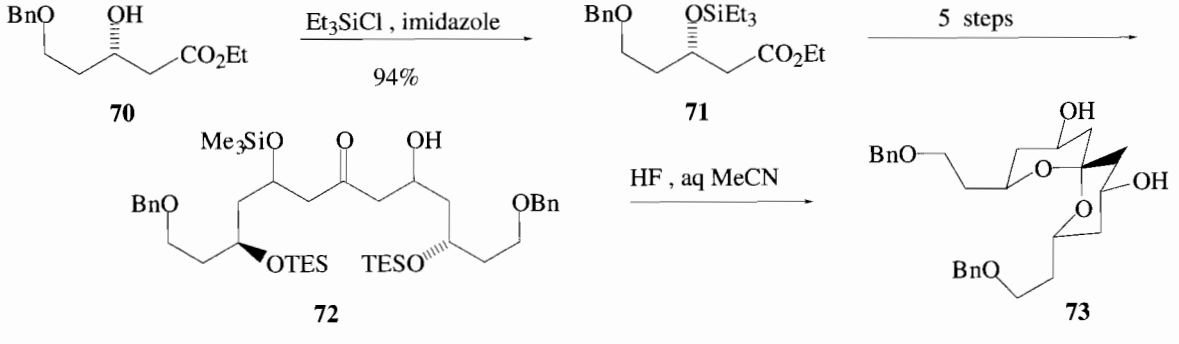
Another generic type of acetal protecting group is classified by Greene as a substituted ethyl ether.[43] A common member of this group is 1-ethoxyethyl ether [O—CH(OCH_2Me)Me, O—**EE**]. As with the O—THP group, diastereomers can be generated when the OEE group is incorporated in a molecule, with the same problems. The protected derivative will exist as diastereomers, since there are two stereogenic centers. The group is usually attached to the alcohol via reaction with ethyl vinyl ether under acid conditions (HCl or tosic acid).[44] The group is stable to a relatively narrow pH range of 6–12, but it is compatible with reactions of nucleophiles, organometallics, hydrogenation, hydrides, and most oxidants.[45] It is sensitive to acid conditions and to Lewis acids. Treatment of the O—EE ether with aqueous acetic acid[44a] and with aqueous HCl in THF[44b] are the most common methods of cleavage to the alcohol.

Silyl ethers have become extremely important for the protection of alcohols, having the generic structure $OSiR_3$. Variation in the R group leads to significant differences in the stability of the protecting group. In

general, silyl ethers can be cleaved with aqueous base or acid, but the rate of hydrolysis for a secondary silyl ether is significantly slower than that of a primary silyl ether.[46] In addition, alkyl alcohols are more reactive than phenolic derivatives, and the order of reactivity for other silane groups is $COOSiR_3$ > $NHSiR_3$ > $CONHSiR_3$ > $SSiR_3$.[47] Steric factors play a major role in the relative stability of the $OSiR_3$ group in cleavage reactions. The prototype of this class of protecting groups is the trimethylsilyl ether [O—Si(Me)$_3$, O—**TMS**]. The group is usually attached to the alcohol by reaction with chlorotrimethylsilane (Me_3SiCl) and an amine base such as triethylamine or pyridine,[48] although Greene and Wuts list several other methods.[49] This group is sensitive to many aqueous conditions and the TMS group is sometimes cleaved in an aqueous workup procedure.[50] The group is not very stable to organometallics such as Grignard reagents, or to nucleophiles, hydrogenation or hydrides, but it can be used with some oxidants. The sensitivity of OTMS to these reagents is often the result of the aqueous or acid workup procedures that are required for a given reaction. If strictly anhydrous conditions are used, the TMS group can be used for short term protection. Under aprotic conditions, fluoride ion (such as tetrabutylammonium fluoride) readily attacks silicon and cleaves the O—Si bond.[46a] A synthetic example is the protection of the alcohol in **66** using chlorotrimethylsilane and triethylamine, giving **67**.[51] This allowed reduction of the ester to the aldehyde (sec. 4.6.C) and Wittig olefination (sec. 8.8.A.i) to give **68**, with two OTMS protected alcohol units. When this was treated with tetrabutylammonium fluoride in THF, diol **69** was obtained.



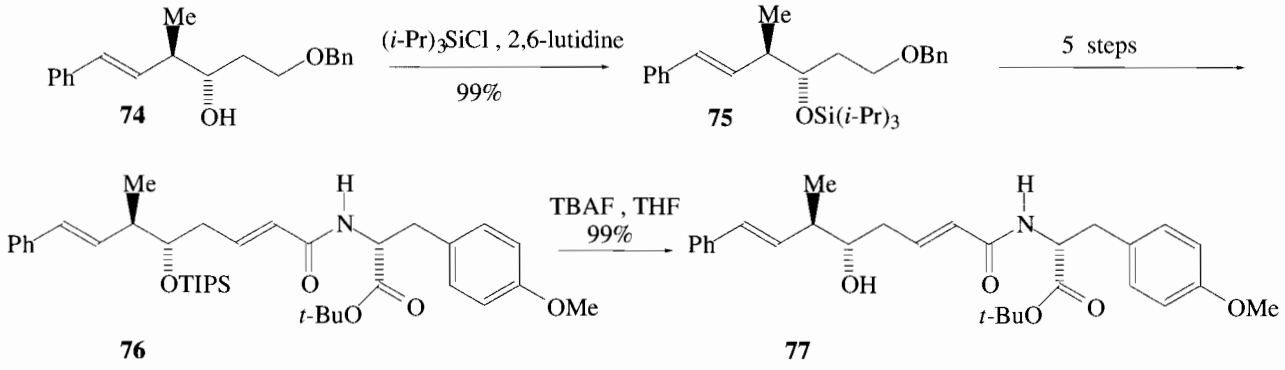
The fact that hydrolysis of the OTMS group is so facile makes it unsuitable for most alcohol moieties that require long-term protection. A more stable silyl derivative is the triethylsilyl group (O—$SiEt_3$, O—**TES**).



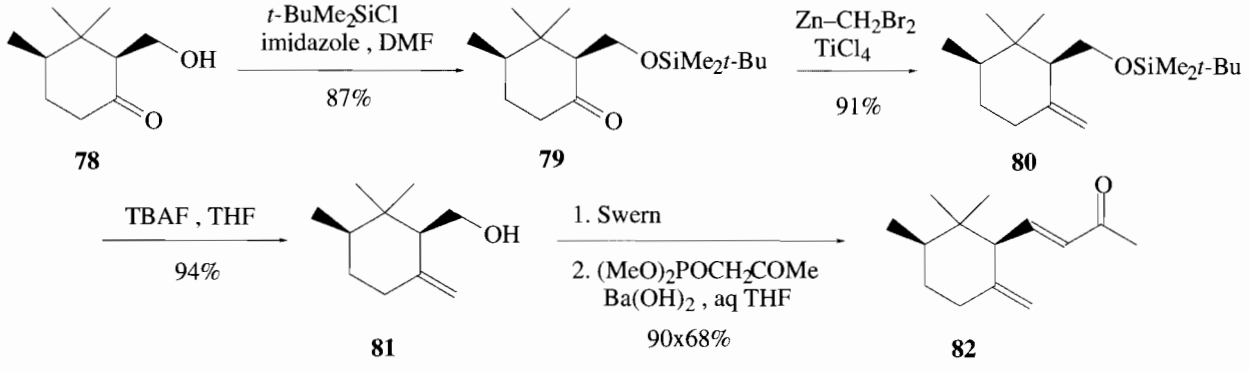
The group is attached by reaction of the alcohol with chlorotriethylsilane (Et_3SiCl) and pyridine.[52,53] The O—TES group is generally more stable than O—TMS, and in particular it is less sensitive to water. Aqueous

acetic acid cleaves O-TES[53] and fluoride is also effective for removing it. In the Heathcock and co-workers synthesis of the C1–C28 portion of spongistatin 1,[54] **70** was converted to **71** with chlorotriethylsilane and imidazole, in 94% yield. This fragment was coupled in five steps to give **72**, and treatment with HF in aqueous acetonitrile deprotected the OTES groups, along with the OTMS group, and promoted cyclization to give **73**.

Another popular protecting group is the triisopropylsilyl ether [O—Si(CH(Me)$_2$)$_3$, O—**TIPS**], attached in the usual manner via triisopropylchlorosilane (*i*-Pr$_3$SiCl) and imidazole.[55] The group is stable in the pH 2-14 range and it is generally impervious to nucleophiles, organometallics, hydrogenation (except in acetic acid), hydride and oxidizing agents.[56] It is usually removed with fluoride (tetrabutylammonium fluoride or aqueous HF). In Ghosh's synthesis of (+)-cryptophycin B,[57] alcohol **74** reacted with triisopropylchlorosilane in the presence of 2,6-lutidine to give the O—TIPS derivative **75** in 99% yield. Elaboration to **76** in five steps was followed by deprotection with tetrabutylammonium fluoride to give a 99% yield of **77**.



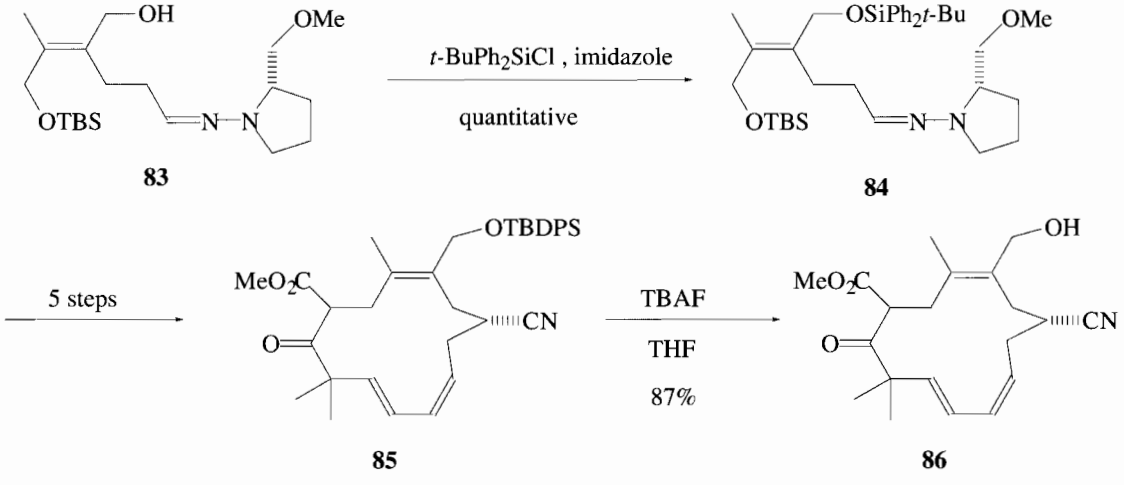
One of the most used silyl ether protecting groups is *tert*-butyldimethylsilyl [O—Si(Me)$_2$*t*-Bu, abbreviated as O—**TBDMS** although it is also abbreviated as O—**TBS**]. The most common method for attaching this group reacts the alcohol with *tert*-butyldimethylsilyl chloride using imidazole[58a] or dimethylaminopyridine[58b] as the base. The analogous silyl triflate (*t*-BuMe$_2$Si—OSO$_2$CF$_3$) is also useful for generating this ether from alcohols, with 2,6-lutidine as the base.[58c] The group is stable to base and reasonably stable to acid (pH 4→12) than the other silyl protecting groups. It is also stable to nucleophiles, organometallics, hydrogenation (except



in acidic media), hydrides, and oxidizing agents.[59] It can be removed with aqueous acid but the most common method of cleavage uses fluoride (tetrabutylammonium fluoride,[58] tetrabutylammonium chloride, and KF,[60]

and also aqueous HF[61]). This group was used for short-term protection in Monti's synthesis of (+)-*cis*-γ-irone (**82**).[62] The resolved hydroxy-ketone **78** was protected with *tert*-butyldimethylsilyl chloride and imidazole to give an 87% yield of **79**. Olefination using the reagent shown (see sec. 8.8.D) gave **80**, and this was followed by deprotection with tetrabutylammonium fluoride (in 94% yield) to give **81**. Swern oxidation (sec. 3.2.C.i) and Horner–Wadsworth–Emmons olefination (sec. 8.8.A.iii) led to the final target **82**.

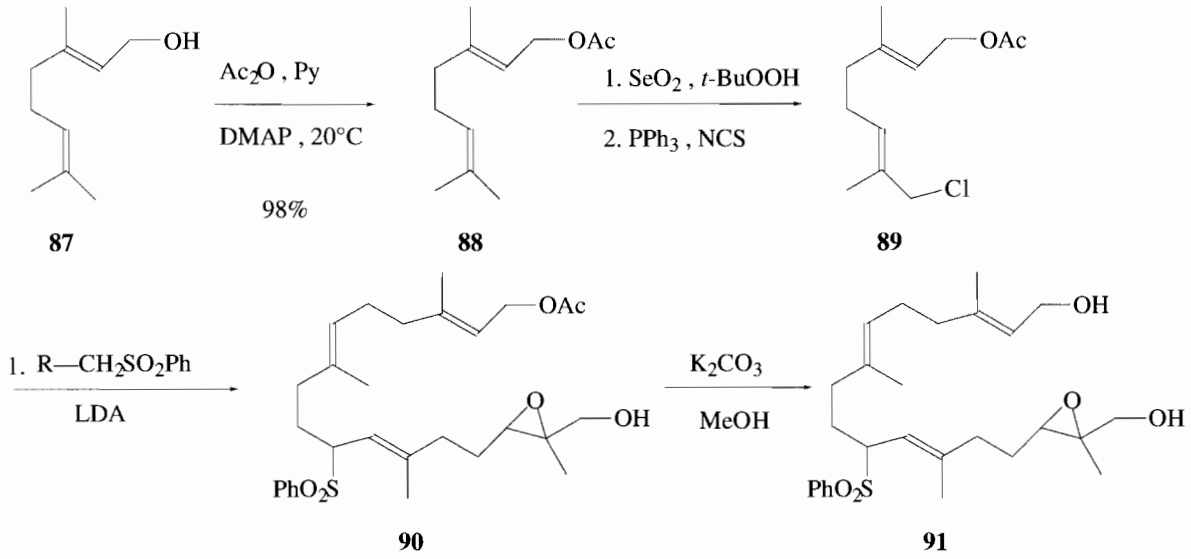
A final silyl ether protecting group that is used with great regularity is the *tert*-butyldiphenyl group [O—$SiPh_2C(Me)_3$, O—**TBDPS**]. This protecting group was developed by Hanessian when it was discovered that the O-TBDMS group was sensitive to hydrogenation.[63] The TBDPS group is attached to the alcohol by reaction with *tert*-butyldiphenylsilyl chloride (*t*-$BuPh_2SiCl$) and imidazole.[63] It has stability characteristics similar to dimethyl-*tert*-butyl derivatives, but is more stable to Lewis acids.[64] An example is the synthesis of (+)-martimol by Deslongchamps, who protected the allylic alcohol in **83** as the OTBDPS derivative **84**.[65] A five-step sequence led to macrocycle **85** and deprotection with $Bu_4N^+F^-$ gave an 87% yield of **86**.



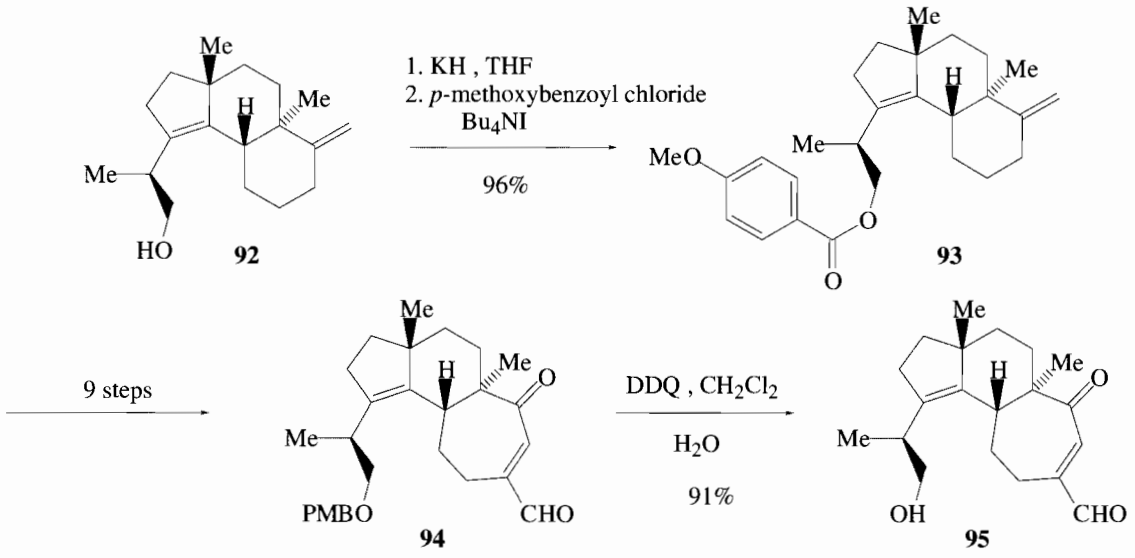
83 **84** **85** **86**

7.3.A.ii. Ester Protecting Groups. The second major class of alcohol protecting groups are the O-esters (O—COR), where COR is an acyl group. Ester protecting groups are limited in scope due to their susceptibility to nucleophilic acyl substitution, hydrolysis, and reduction. Several esters are commonly used in synthesis, however, including acetates, benzoates, and mesitoates. Although there are many esters which can, and likely have, been used in synthesis, this discussion will focus only on the more common derivatives.

Acetates (**OAc**) are formed by reaction of an alcohol with acetic anhydride or acetyl chloride in the presence of pyridine or triethylamine. Acetates are stable to pH from 1 up to 8, organometallics such as ylids and organocuprates, catalytic hydrogenation, borohydrides, Lewis acids, and oxidizing agents.[66] Hydrolysis with acid or base (saponification) cleaves the ester to the alcohol and an acid. Reaction with $LiAlH_4$ reductively cleaves the acetate to the alcohol and ethanol. Acetates have found wide-spread use in synthesis. In the Li and co-workers synthesis of (–)-sinulariol-B,[67] geraniol (**87**) was acetylated to give **88** in 98% yield. Allylic oxidation with selenium dioxide (sec. 3.8.A) gave an alcohol, which was converted to chloride **89** with NCS and triphenylphosphine (sec. 2.8.B). Coupling with the appropriate sulfone anion gave **90** and deprotection with methanolic potassium carbonate gave alcohol **91**.



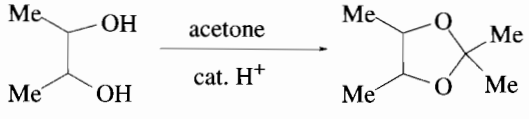
Alcohols also react with benzoyl chloride (PhCOCl) or benzoic anhydride [$(PhCO)_2O$], usually in the presence of pyridine or triethylamine, to give the benzoyl derivative (benzoate ester, O-**Bz**). Benzoates are more stable to hydrolysis than acetates, with a pH stability from pH 1 up to 10-11. Treatment with 10% K_2CO_3 (pH 11), for example, will hydrolyze the O—Bz group. Benzoyl esters are more stable to reactions with nucleophiles such as cyanide and acetate, ylids, and organocuprates. Benzoate esters also resist catalytic hydrogenation, and reaction with borohydrides and with oxidizing agents.[68] The group is usually cleaved by basic hydrolysis or $LiAlH_4$ reduction.



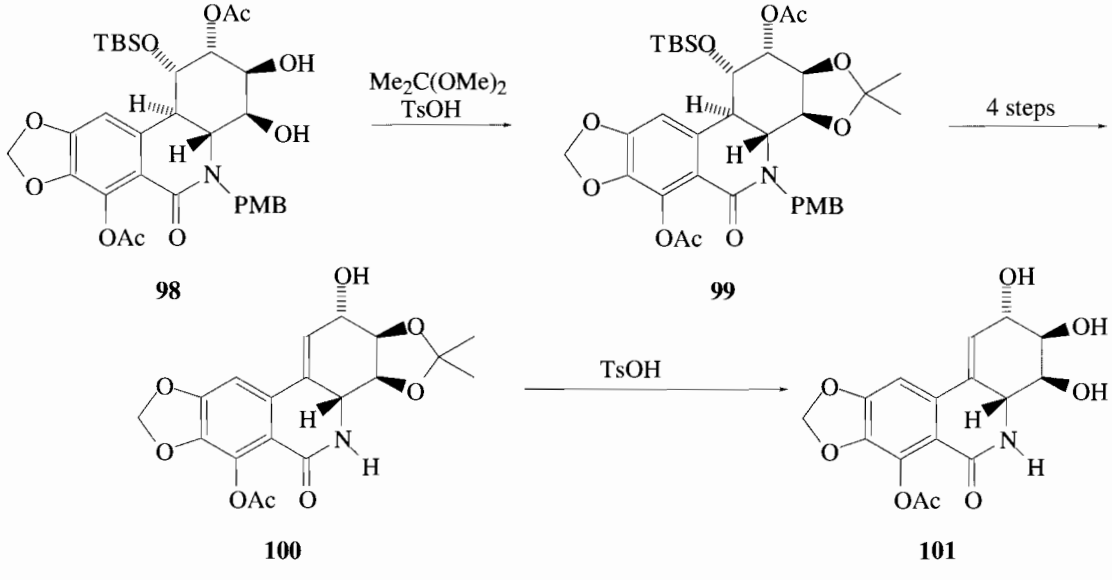
Three additional protecting groups in this category are the mesitoate ester ($OCOC_6H_22,4,6$-trimethyl, O—**Mes**), the pivaloyl ester (OCO—*t*-Bu),[69,70] and the para-methoxybenzoyl ester (OCO—C_6H_4-4-Me). The mesitoate ester is formed by reaction of an alcohol with mesitoyl chloride in the presence of pyridine or triethylamine.[71] The main advantage of this ester is its stability to hydrolysis (pH 1–12), nucleophilic attack,

organometallics, catalytic hydrogenation; reaction with boranes, borohydrides, Lewis acids; and oxidation.[72] This stability results from the presence of two ortho methyl groups, which effectively block the acyl carbon to attack. The group can be cleaved by reduction with $LiAlH_4$[72] (cleavage of the C—O bond is only occasionally a problem),[73] or with concentrated alcoholic potassium *tert*-butoxide.[74,72] The *p*-methoxybenzyl group appears to be rather popular in the recent literature, and an example is taken from Piers synthesis of sarcodonin G.[75] Formation of the alkoxide from **92** followed by treatment with *p*-methoxybenzoyl chloride gave **93**. This allowed conversion of the six-membered ring into the cycloheptenone unit in **94** in nine steps. Deprotection by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave **95** in 91% yield.

7.3.A.iii. Protection of Diols. 1,2-Diols are obviously alcohols, but the vicinal nature of the hydroxyls allows them to be protected as cyclic ketals. When a 1,2-diol such as 2,3-butanediol (**96**) reacts with a ketone such as acetone, in the presence of an acid catalyst, a 1,3-dioxolane (**97**) is formed. Ketals such as **97**, which



96 **97**



98 **99**

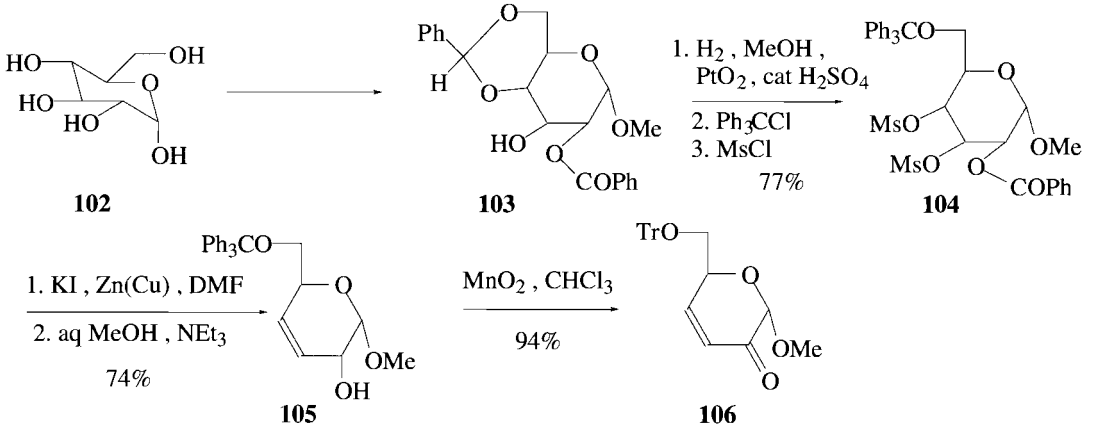
100 **101**

are derived from acetone, are often called **acetonides** (isopropylidene ketals). A 1,3-diol will generate a six-membered ring acetonide, which is a 1,3-dioxane derivative. Common methods for acetonide formation are reaction of the diol with 2-methoxy-1-propene in the presence of an acid such as anhydrous HBr[76] or reaction of acetone with an acid catalyst.[77] The group is stable to base but not to acid (pH 4→12). It is stable to nucleophiles, organometallics, catalytic hydrogenation, hydrides, and oxidizing agents.[78] It can be cleaved with aqueous HCl, with acetic acid[79] or with *p*-toluenesulfonic acid in methanol.[80] This group has been used

extensively in the manipulation of carbohydrates. Acetonides are useful in other synthetic applications , as in the protection of the 1,2-diol unit found in **98**, which was converted to **99** by reaction with the dimethyl acetal of acetone and tosic acid as part of Rigby's synthesis of (+)-narciclasine (**101**).[81] This step allowed the double bond to be incorporated in **100**, which was followed by deprotection with tosic acid to give **101**.

Reaction of diols with other aldehydes or ketones will lead to a wide array of ketals or acetals. Two of the more common are derivatives of benzaldehyde (benzylidene acetals) and cyclohexanone (cyclohexylidene ketals). Hanessian's synthesis of the **Prelog–Djerassi lactone**[82c,d] converted (*D*)-glucose (**102**) to the benzylidene acetal, **103**,[82a] which was followed by conversion to dimesylate (**104**),[82a,b] involving removal of the benzylidene group by catalytic hydrogenation. Formation of the alkene in **105** and removal of the benzoyl group allowed oxidation with MnO_2 (sec. 3.2.E.iii) to give **106**. Several of these steps were incorporated in Weiler's synthesis of (–)-α-multistriatin.[83]

Greene and Wuts[2] discuss many other ketal protecting groups that have been used in synthesis, but acetonide is probably the most common. Discussions of methods for protecting alcohols in this section have been extensive, due to the wide range of alcohol protecting groups. Since the hydroxyl is capable of being transformed into a wide range of other functional groups, its protection is of particular importance. Since more than one hydroxyl moiety is commonly incorporated into a molecule, the requirement for several selective protecting groups is obvious. The following sections will deal with protection of the other two key functional groups, the carbonyl group found in ketones and aldehydes and also the nitrogen found in amines.



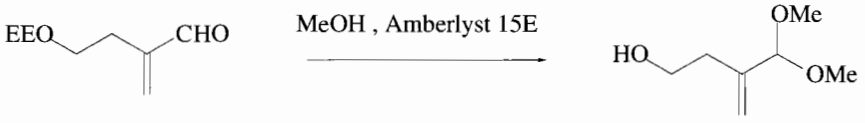
7.3.B. Protection of Aldehydes and Ketones

As with alcohols, developing methods to protect ketones or aldehydes must begin with identification of the interfering portion of these molecules. It is the carbonyl. The main reaction of a carbonyl is nucleophilic acyl addition but the oxygen of the carbonyl can also function as a base in the presence of a suitable acid, leading to oxygen-stabilized carbocations (secs. 2.7.B.i, 12.2.A) and substitution reactions. To prevent these reactions, the electrophilic carbon and the π bond of the carbonyl must be removed, but conversion to a new functional group must be easily converted back to the carbonyl. One method is to reduce the C=O unit to an alcohol (see Chap. 4) and then protect the OH unit as described in sec. 7.3.A. When it is appropriate in the synthesis, the alcohol is deprotected, and then oxidized back to the aldehyde or ketone. In general, the procedures described

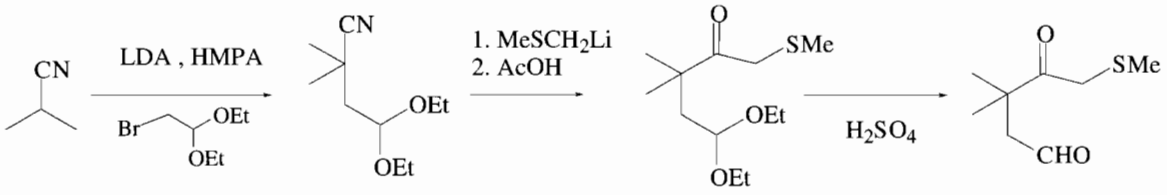
in this section for protection of the C=O require only two steps: protection and deprotection. An alternative and indeed the major method for protecting carbonyls is its conversion carbonyl to a ketal or acetal, using alcohol or diol reactants. A variation of this reaction uses thiol or dithiol reactants to generate dithioketals or dithioacetals. In both cases, the acyl moiety is transformed and removed, but treatment with acid (or Lewis acids with the dithio derivatives) readily converts the ketals or acetals back to the ketone or aldehyde. It is important to note that in previous sections, alcohols were protected as ketals or acetals by reaction with ketones or aldehydes, but in this section the carbonyl group will be protected as the ketal or acetal by reaction with alcohols. The group is the same; the difference is which functional group is the object of attention and isolation.

7.3.B.i. Ketals and Acetals. When a molecule contains few other functional groups, ketals and acetals are formed by reaction of the carbonyl with methanol or ethanol under anhydrous conditions, in the presence of an acid catalyst. In general, dry HCl (gas), sulfuric acid,[84] BF_3•OEt_2,or *p*-toluenesulfonic acid (PPTS) is the catalyst of choice for the formation of dimethyl (or diethyl) ketals or acetals from ketones or aldehydes. The addition of molecular sieves to adsorb water usually improves the yield of ketal or acetal.[85] Diethyl and dimethyl ketals and acetals are generally stable in a pH range of ≈ 4–12, but they are sensitive to aqueous acid and to Lewis acids. They are stable to nucleophiles, organometallics, catalytic hydrogenation, hydrides and most oxidizing agents (they do react with ozone, for example).[86] Conversion of the ketal or acetal back to the ketone or aldehyde is accomplished by treatment with aqueous acids such as trifluoroacetic acid[87] or oxalic acid (HOOC—COOH).[88] A popular alternative for regenerating the carbonyl from a ketal or acetal is trans-ketalization, whereby acetone is added along with PPTS (or another acid catalyst). Acetone generates a new ketal (2,2-dimethoxypropane) in this reaction, liberating the originally protected carbonyl derivative.[89] Other acetals or ketals can be used as well.

It is obvious that many alcohols can be used to generate acetals and ketals, but methanol and ethanol are probably the most common ones used. The yields of product with this reagent are high, the lower molecular weight alcohol byproducts are easily removed after deprotection. Another attractive feature of the methoxy unit is that it gives simple singlets in the ^{1}H NMR spectrum, that usually do not obscure important signals from the remainder of protected substrate. In Kuwahara's synthesis of a sesquiterpene isolated from the pheromone gland of a stink bug, *Tynacantha marginata* Dallas,[90] conjugated aldehyde **107** was treated with methanol in the presence of an acidic resin to give the dimethyl acetal **108**. Under the reaction conditions, the O—EE unit was deprotected back to the alcohol. Diethoxy acetals are also quite useful. A synthetic example using an diethyl acetal is taken from Tanino and co-workers synthesis of (–)-coriolin.[91] Formation of the anion from 2-methylpropanenitrile and reaction with the diethyl acetal of 2-bromoacetaldehyde gave **109**. The nitrile unit was elaborated to the methylthioketone unit in **110**, and treatment with sulfuric acid regenerated aldehyde **111**.

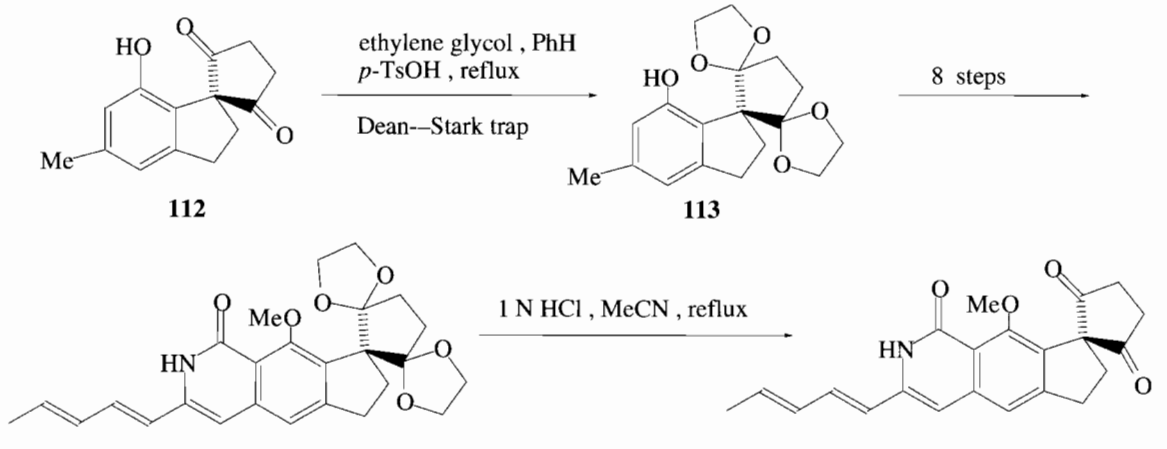


107 **108**



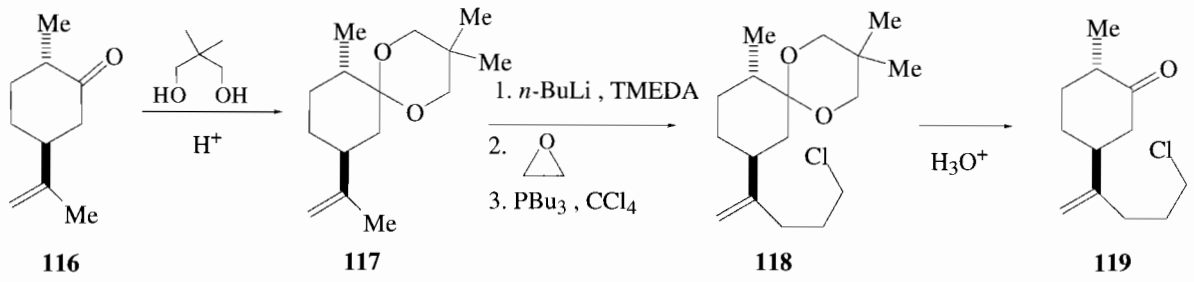
109 **110** **111**

The 1,2- and 1,3-diols, which form cyclic ketals or cyclic acetals [1,3-dioxolanes or 1,3-dioxanes as discussed for protection of diol - see above], are particularly important for the protection of aldehydes and ketones. 1,3-Dioxolane derivatives are formed by reaction of the carbonyl with 1,2-ethanediol and 1,3-dioxanes are formed by reaction with 1,3-propanediol. Dioxane protected ketones are usually hydrolyzed back to the carbonyl faster than the analogous dioxolane protected derivatives but dioxolane protected aldehydes are hydrolyzed faster than dioxane protected.[92] Despite this difference in reactivity, dioxolanes appear to be the most commonly used protecting group. The carbonyl group is reacted with 1,2-ethanediol (ethylene glycol) and PPTS, BF_3•OEt_2, or oxalic acid.[93] Reaction of the carbonyl with 1,3-propanediol (propylene glycol) under similar conditions generates the dioxane. Cyclic ketals are sensitive to acid and are generally stable to pH 4–12 and to reactions with nucleophiles, organometallics, hydrogenation (except in acetic acid), hydrides and oxidizing agents, but they do react with Lewis acids.[94] The most common method for cleavage of the dioxane or dioxolane derivatives is treatment with aqueous acid, including HCl in THF[95] and aqueous acetic acid.[96] In Bach's synthesis of fredericamycin A,[97] diketone **112** was treated with ethylene glycol to give the bis(dioxolane) (**113**). The lactam ring was elaborated in eight steps to **114**, and HCl in acetonitrile converted the dioxolane units back to the ketone units in **115**.



112 **113** **114** **115**

A variation in ketal protection introduces alkyl substituents on the diol moiety. Money, for example, used 2,2-dimethyl-1,3-propanediol to protect the ketone in **116** (forming **117**). Use of this protecting group allowed the reaction of the allylic unit in **117** with butyllithium and also conversion of the resulting alcohol product to chloride **118**. Deprotection of the carbonyl gave **119** in a synthesis of camphorenone.[98]

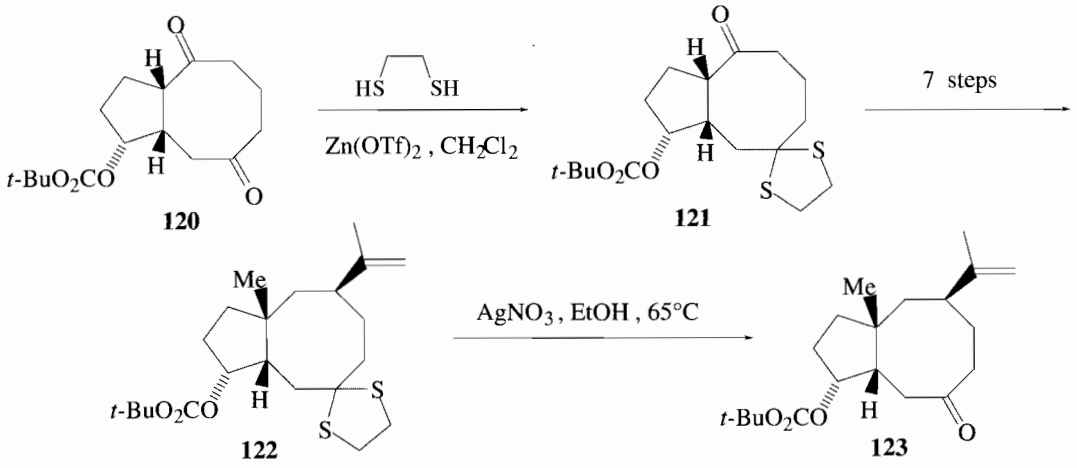


116 **117** **118** **119**

7.3.B.ii. Dithioketals and Dithioacetals. The use of cyclic ketals and acetals in conjunction with acyclic carbonyl derivatives offers some selectivity for protection of more than one carbonyl. Expanding the methodology to include the sulfur analogs [dithioketals and dithioacetals, $R_2C(SR')_2$] gives even more flexibility. Both cyclic and acyclic dithio derivatives are known and used, but cyclic dithioketals and acetals are more common. A ketone or aldehyde reacts with 2 equivalents of a thiol (mercaptan) under acidic conditions (HCl and BF_3 are typical acids).[99,102a] The main advantage of these groups is their stability to acid. They are stable from pH 1–12, and compatible with nucleophiles, organometallics, hydrides and oxidizing agents, although CrO_3 can oxidize the sulfur.[100] Dithioacetals and ketals are particularly reactive with mercuric and silver salts, and are relatively unreactive with many other Lewis acids.[94] Mercuric chloride under aqueous conditions is the most commonly used method for conversion back to the carbonyl.[101] As with the oxygenated analogs, the use of cyclic dithioketals and acetals is very prevalent. Reaction with 1,2-ethanedithiol generates 1,3-dithiolanes, and 1,3-propanedithiol gives 1,3-dithianes.

The most common acid catalyst used to form dithianes and dithiolanes from ketones and aldehydes is boron trifluoride etherate (BF_3•OEt_2).[102] These protecting groups are similar in their stability to the acyclic derivatives. Cyclic dithioketal and dithioacetal derivatives are relatively insensitive to acid, showing stability from pH 1–12. They are stable to nucleophiles, organometallics, hydrides, and many oxidizing agents.[100] They are subject to hydrogenolysis and the bivalent sulfur atoms in dithianes can poison heterogeneous hydrogenation catalysts (sec. 4.8.A). They are also sensitive to strong Lewis acids such as aluminum chloride ($AlCl_3$) and mercuric salts. This latter reaction is the basis of the most common cleavage reaction, the **Corey–Seebach procedure**,[103] other cleavage reagents include Vedejs' use of boron trifluoride etherate in aqueous THF containing mercuric oxide (HgO),[103c] *N*-Bromosuccinimide,[104] iodine in DMSO,[105] ceric ammonium nitrate [$Ce(NH_4)_2(NO_3)_6$, **CAN**],[106] and iodomethane in aqueous media.[107] One of the best cleavage procedures is Corey's use of *N*-chlorosuccinimide and silver nitrate in aqueous acetonitrile.[108] There are many synthetic examples that use this sort of protection. In Trost's synthesis of 11-hydroxyjasionone,[109] diketone **120** was converted to the monodithiolane derivative **121**. Seven steps were required to transform **121** to **122**, and final treatment with silver nitrate in hot ethanol regenerated the ketone unit in **123**.

Many derivatives of 1,2- and 1,3-dithiols have been used as protecting groups, but those discussed are the most common. Greene and Wuts[2] discuss other methods for protection of ketones and aldehydes, including cyanohydrins, hydrazones, oximes, oxazolidines, and imidazolidines.[110] Most of these are rather specialized and will not be discussed in this general presentation.

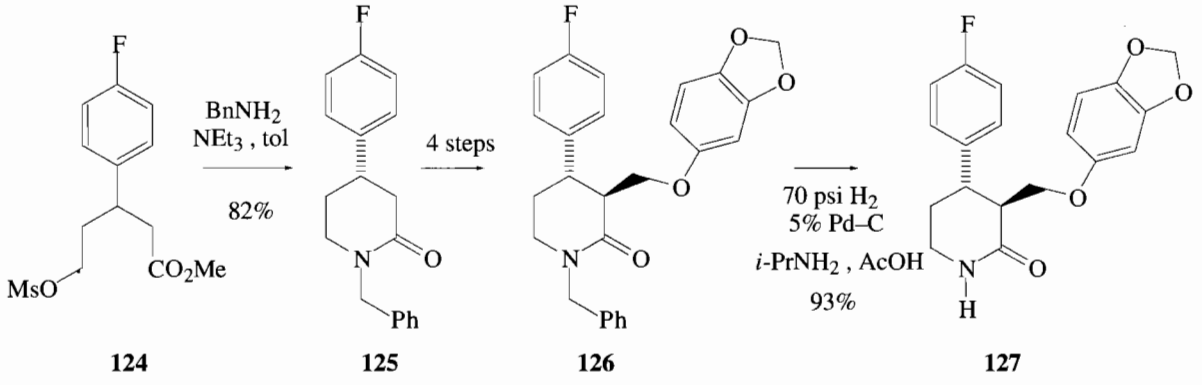


7.3.C. Protection of Amines

The last major type of functional group to be discussed will be amines. The interfering portion of this group is the basic and nucleophilic lone pair of electrons on nitrogen. If those electrons are tied up with alkyl groups (forming an ammonium salt), the usual reactions involving amines (alkylation, basicity, and oxidation) are not possible. Ammonium salts are not often used as protecting groups, however, since these charged species are incompatible with many reactions. In addition, ammonium salts are good leaving groups for substitution and elimination reactions. A more useful protection method generates a derivative in which the electron pair is completely or partially delocalized, reducing the basicity and nucleophilicity of the nitrogen. The three most common methods of amino group protection involve conversion of primary and secondary amines to a tertiary amine (usually benzyl or trialkylsilyl), conversion to an amide (or a carbamate), and to a lesser extent, conversion to specialized sulfonamides.[111] Only the first two of these methods will be discussed.

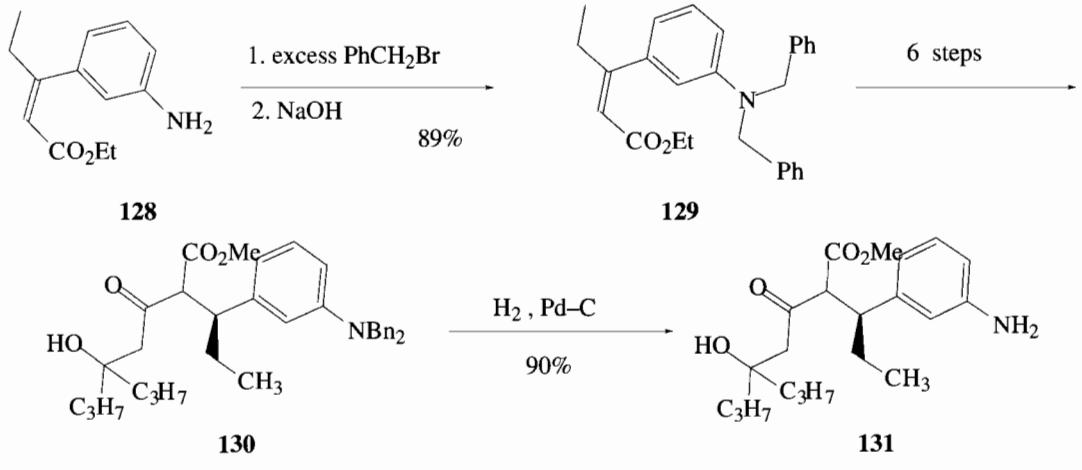
7.3.C.i. N-Alkyl and N-Silyl Protecting Groups. Benzyl (N—CH_2Ph, **N—Bn**) is a very common alkyl protecting group for nitrogen. An amine is treated with benzyl chloride or benzyl bromide, usually in the presence of a base such as potassium carbonate (K_2CO_3) or hydroxide.[112] This group is stable to acid and base (pH 1–12) and to nucleophiles, organometallics, hydrides, but reacts with Lewis acids (as a Lewis base).[113] The N—C bond is subject to hydrogenolysis by catalytic hydrogenation or dissolving metals. Treatment with hydrogen and palladium on carbon[114] (sec. 4.8.E) and with sodium in liquid ammonia[115] (sec. 4.9.D) are the two most commonly used methods of cleavage. Most of the other alkyl groups used are less general and rarely seen.[116]

A synthetic example using the N-benzyl protecting group is taken from Yu's synthesis of (+)-paroxetine.[117] When the mesylate group in **124** was displaced by benzylamine in a S_N2 reaction, the resultant amine reacted with the methyl ester to produce N-benzyl lactam **125**. After four synthetic steps that generated **126**, catalytic hydrogenation removed the protecting group to give (+)-paroxetine (**127**). It is interesting to see that the *N*-benzyl group was removed without hydrogenolysis of the benzylic ether unit. It is also known that *N*-benzyl can be removed in the presence of O-benzyl, by catalytic transfer hydrogenation in the presence of a hydrogen donor, 1,4-cyclohexadiene.[118]



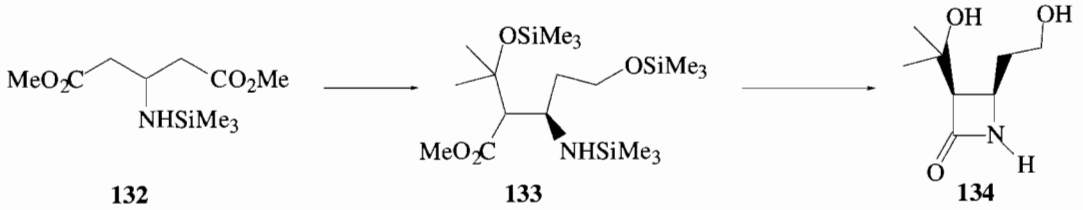
124 **125** **126** **127**

The benzyl protection group can be applied to primary amines. In the Romero et al. synthesis of HIV-1 (human immunodeficiency virus) protease inhibitors, the aniline unit in **128** was treated with excess benzyl bromide to give the *N,N*-dibenzyl derivative **129** in 89% yield.[119] The alkyl fragment was elaborated in six steps to give **130**. Catalytic hydrogenation with a palladium on carbon catalyst removed both benzyl groups to give aniline derivative **131** in 90% yield.



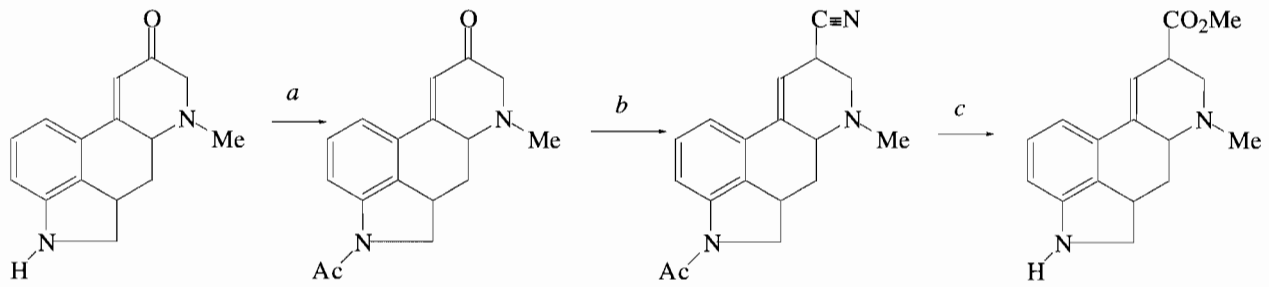
128 **129** **130** **131**

In one sense, a N-silyl derivative (N—SiR_3) can be considered to be an analog of an N-alkyl derivative (N-CR_3). A simple silyl protecting group is trimethylsilyl (N-$SiMe_3$, **N-TMS**), which is formed by reaction of the amine with chlorotrimethylsilane and triethylamine or pyridine. The trimethylsilyl group is sensitive to water, as seen by the reaction of Me_3SiNEt_2 and alcohols to give $ROSiMe_3$. It is therefore used under anhydrous conditions.[120] Ohno and co-workers[121] used *N*-trimethylsilylamine (**132**) as an intermediate in the synthesis of **133**. Removal of the protecting group under aqueous conditions gave the primary amine, which cyclized with the ester group to give the β-lactam (**134**) in a synthesis of carpetimycin A.



132 **133** **134**

7.3.C.ii. N-Acyl Protecting Groups. Amides are common protecting groups for amines. N-Acetyl is the best known of the amide protecting groups, and N-acylamines are known as acetamide derivatives (N—COMe, **N-Ac**). Reaction of acetic anhydride or acetyl chloride with an amine, in the presence of a base such as pyridine or triethylamine, will generate the acetamide.[122] Acetamides are sensitive to strong acid and base but are stable in the pH range 1→12. Nucleophiles and many organometallics react with the N-acetyl group (organolithium reagents do not react very well, although reactive Grignard reagents do). This group is also

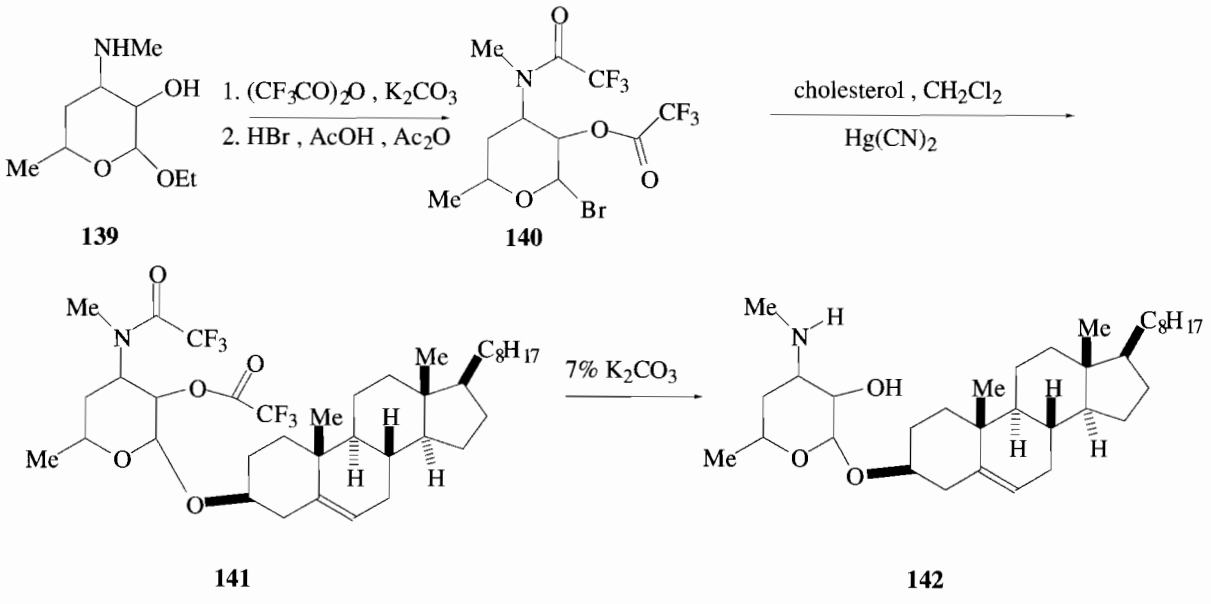


135 **136** **137** **138**

(*a*) Ac_2O (*b*) 1. $NaBH_4$ 2. $SOCl_2$ 3. NaCN (*c*) 1. MeOH , H_2SO_4

subject to reduction by catalytic hydrogenation, borane, and borohydride reducing agents (not $LiAlH_4$) and can be oxidized by many oxidizing agents.[123] Reactions that use Lewis acids, such as glycosylation, can also cause problems if this protecting group is present. The two major methods for cleavage of N-acetamides to regenerate the amine are treatment with aqueous acid[124] and treatment with triethyloxonium tetrafluoroborate[125] ($Et_3O^+BF_4^-$, **Meerwein's reagent**[126]). Reduction with $LiAlH_4$ gives the ethylamine derivative and this hydride can also be considered as a cleavage reagent in some cases.[127] A synthetic example is taken from Woodward's synthesis of lysergic acid,[128] using the N-acetyl group to protect **135** as acetamide **136**. Reduction, chlorination and conversion to the nitrile (**137**) was followed by methanolysis that generated a methyl ester and as well as giving the amine (**138**) from the acetamide to complete the sequence.

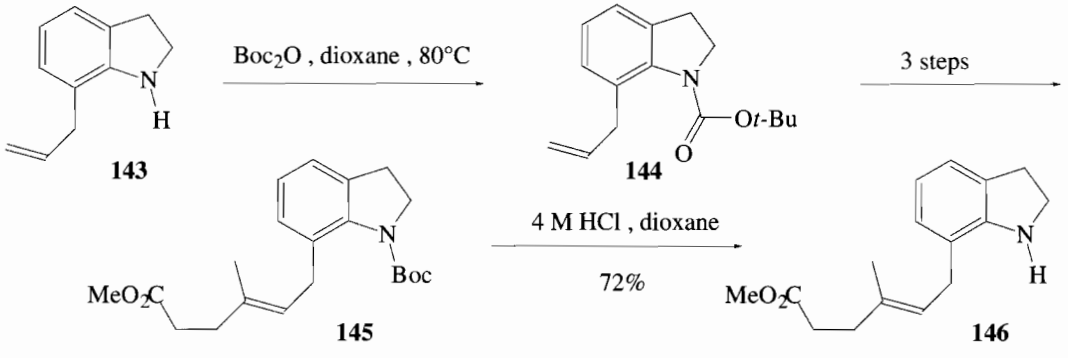
A simple modification of this technique has dramatic effects on the stability of the protecting group. If trifluoroacetyl is used rather than acetyl, the trifluoroacetamide (N-$COCF_3$, **N-TFA**) is generated. Trifluoroacetyl is usually attached by reaction of the amine with trifluoroacetic anhydride [$(CF_3CO)_2O$] in the presence of triethylamine or pyridine.[122,129] This group retains its stability to acid but is more sensitive to base (pH 1-10) than the acetamide analog. It is stable to anhydrous bases or tetraalkylammonium hydroxides because deprotonation occurs. It reacts with most nucleophiles, organolithium reagents, $LiAlH_4$, and borohydrides via nucleophilic acyl substitution but is stable to oxidation, Lewis acids, borane, and most catalytic hydrogenation.[130] It is usually removed with potassium carbonate in aqueous methanol,[131] by reduction with sodium borohydride,[132] or by ammonia in methanol.[133] Newman prepared N,O-bis(trifluoroacetyl) tetrahydropyran (**140**) from the alcohol precursor (**139**), and this allowed a synthesis of cholesterol glycoside **141**.[131,134] Subsequent deblocking with 7% potassium carbonate (K_2CO_3) gave the amino glycoside, **142**.



139 **140** **141** **142**

Benzamides (N—COPh, **N—Bz**) are formed by reaction of amines with benzoyl chloride in pyridine or triethylamine.[135] This group is stable to pH 1–14, nucleophiles, organometallics (except organolithium reagents), catalytic hydrogenation, hydrides (except $LiAlH_4$, and borane), and oxidizing agents.[136] The group is removed with 6 N HCl or HBr in acetic acid[137] or by hot, concentrated aqueous NaOH.[138] Reduction with diisobutylaluminum hydride (DIBAL-H, sec. 4.6.C) also cleaves the benzamide group.[139]

7.3.C.iii. N-Carbamate Protecting Groups. A related class of protecting groups for nitrogen are the carbamates (N—COOR).[140] Many of these groups were developed for protection of amino acids in peptide synthesis. One of the most popular is the *tert*-butyl carbamate (*tert*-butoxycarbonyl, [NCOC(Me)$_3$], N-**Boc**). Commercially available BOC-ON® [$(Me)_3C$—O—CO-CO_2N=C(CN)Ph] reacts with amines, in the presence



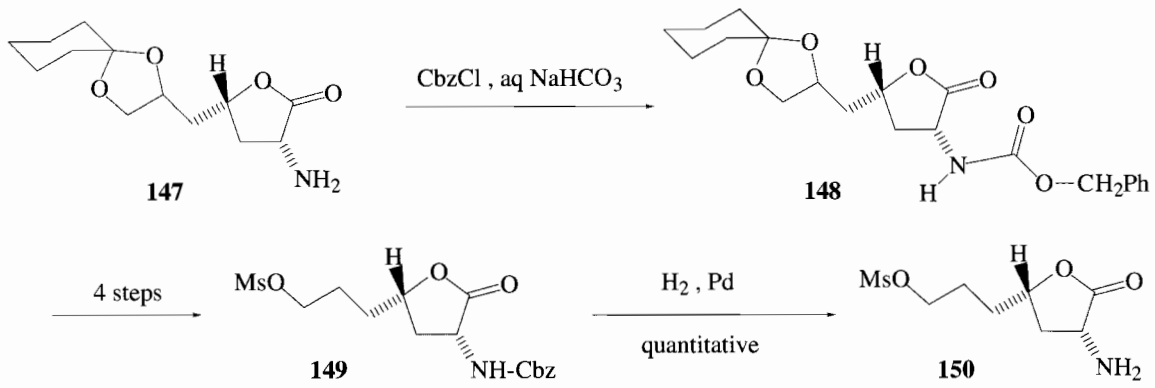
143 **144** **145** **146**

of another base such as triethylamine, to give the NBoc derivative.[141] Similarly, reaction with di-*tert*-butyldicarbonate ($[(CH_3)_3CCO]_2CO$) under basic conditions gives the BOC-protected amine.[142] This group is sensitive to strong anhydrous acid (stable to pH 1→12) and trimethylsilyl triflate (Me_3Si-OTf), but it is stable to nucleophiles, organometallics (including organolithium reagents although Grignard reagents can react by nucleophilic acyl addition), hydrogenation (except under acidic conditions), hydrides, oxidizing agents (not

Jones' conditions), aqueous acid, and mild Lewis acids.[143] The Boc group is usually removed by treatment with aqueous HCl[144] or with anhydrous trifluoroacetic acid.[145] In Lai's synthesis of indole analogs of mycophenolic acid, indole derivative **143** was converted to the N-Boc compound (**144**) using Boc anhydride.[146] Elaboration of the side chain in three steps was followed by deprotection with HCl in dioxane, giving **145** in 72% yield. Trifluoroacetic acid in dichloromethane converted **145** to **146** in 60% yield.[146]

Another very popular carbamate is the benzyl carbamate (N—CO_2CH_2Ph, N—**CBz**, benzyloxy carbonyl), which Greene points out has been used since 1932.[147] The group is attached by reaction of an amine with benzyl chloroformate ($PhCH_2O_2CCl$) in the presence of base (aqueous carbonate or triethylamine). The group is very stable to acid and base (pH 1–12), to nucleophiles, to milder organometallics (it reacts with organolithium reagents and Grignard reagents), to milder Lewis acids, and to most hydrides (it reacts with $LiAlH_4$).[148] The group is sensitive to hydrogenolysis by catalytic hydrogenation, which is the primary means of cleaving this group (Pd on carbon is the usual catalyst).[141,149]

In a synthesis of 4-hydroxypipecolic acid, Varela and co-workers protected the primary amine unit in **147** as the benzyl carbamate (**148**).[150] Manipulation of the protected diol led to the primary mesylate in **149**, and catalytic hydrogenation removed the Cbz group to give the primary amine in **150**.



7.4. CONCLUSION

It is obvious that the preceding discussions are not exhaustive, but they are representative of the methods used by synthetic chemists to protect key functional groups. The monographs by Greene and Wuts[2] also discuss methods for protection of carboxylic acids,[151] and amides,[152] as well as thiols,[153] and other functional groups. These monographs also contain detailed discussions of other protecting groups that can be used for alcohols, amines, ketones, and aldehydes.

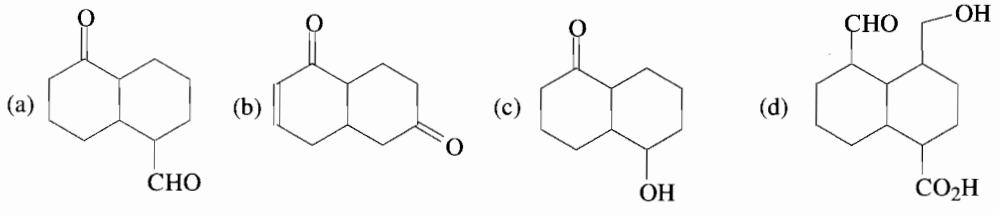
The synthetic problems presented in this chapter are typical, and representative of the need for protecting groups. There are obviously other situations that demand a protecting group but the cases presented give a useful arsenal of such groups and a sample of the situations that require their use. One should always be cautious with protecting groups, remembering that each protection-deprotection sequence adds two steps to a synthesis that diminishes the overall yield. By their nature, protecting and deprotecting steps usually involve

the use of an excess of reagents. These reagents are also often quite cheap. Thus, the yields are usually high. Also, one-pot and simultaneous deprotection saves steps. New protecting groups for specific and general situations are always being developed and a search of the current literature is always useful. Secondary sources that usually include references for new protecting groups are the *Compendium of Organic Synthetic Methods*.

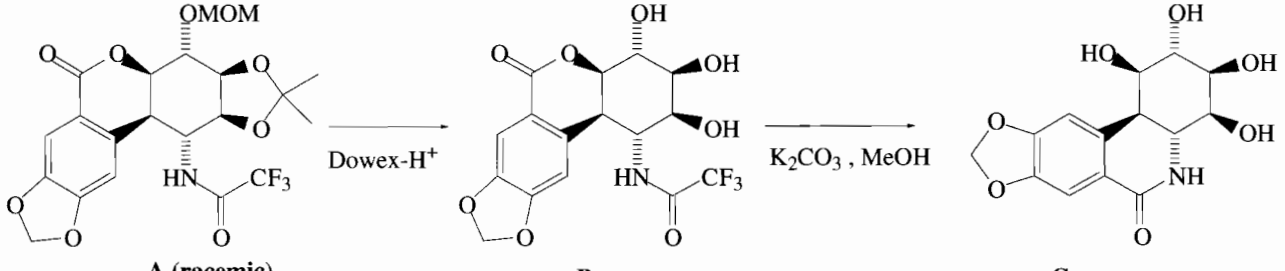
With this chapter, the first part of this book is complete. Functional groups have been introduced, and the manipulation and interchange of functional groups and their protection have been discussed. All of the fundamental concepts for organic synthesis have also been introduced: stereochemistry, chirality, conformational control, chelation effects and various problems in selectivity. The remaining chapters will deal with formation of carbon–carbon bonds, but the basic principles introduced in Chapters 1–7 will be invoked throughout. Since functional group manipulation is required to set up a molecule for formation of a carbon bond, the functional group exchange reactions in Chapters 2–5 will be used again and again.

HOMEWORK

1. In each of the following, discuss the relative merits of protecting functional groups or finding a chemoselective reagent for: (i) reduction with hydrides, (ii) oxidation with Jones or PCC, (iii) catalytic hydrogenation, and (iv) reaction with MeMgBr (Chap. 8).

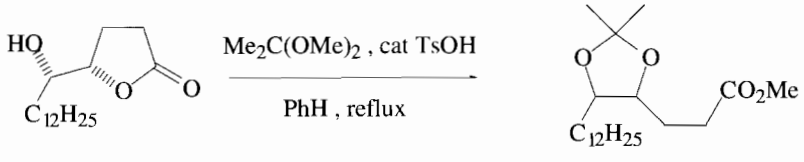


2. In the transformation of **A** to **B** and then to **C** from the synthesis of 7-deoxypancratistatin, in Section 7.3.A.i., deprotection was followed by conversion of a lactone to a lactam. Provide a mechanism for the deprotection of both the O—MOM group and the dioxolane, giving a triol, and also for the lactone–lactam conversion in the second step.



A (racemic) **B** **C**

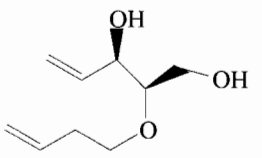
3. Explain the following transformation.



see *J. Org. Chem.*, ***1999***, *64 7067*

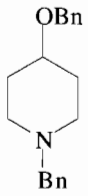
4. In each of the following, give the major product. If there is no reaction, indicate by N.R. Show stereochemistry where it is appropriate.

(a)



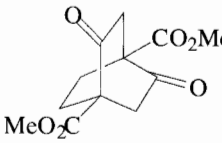
excess Ac_2O

(b)



10% Pd–C , EtOH
22°C

(c)



2 HS SH

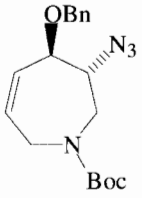
BF_3

(d)

1. 1,3-propanedithiol
BF_3•OEt_2

2. DMSO , $(COCl)_2$, NEt_3

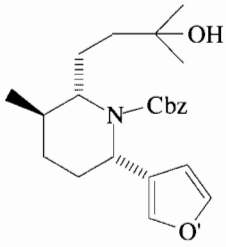
(e)



excess H_2 , Pd–C

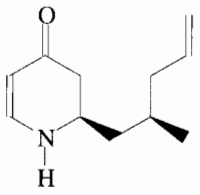
CF_3SO_3H

(f)



Pd black , HCO_2NH_4

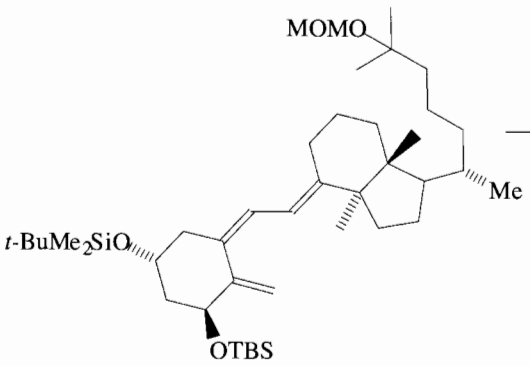
(g)



1. BuLi

2. PhOCOCl

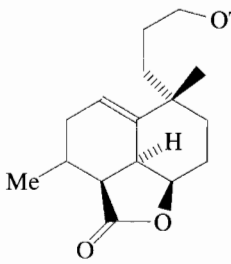
(h)



1. Bu_4NF , THF

2. AG50W-X4
MeOH

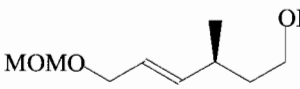
(i)



1. Bu_4NF , THF

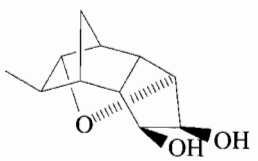
2. NaH , THF–DMF
$PhCH_2Br$

(j)



Na , NH_3 , –40°C

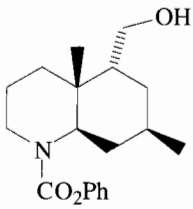
(k)



MeO OMe

cat *p*-TsOH
DMF

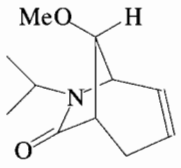
(l)



1. $LiAlH_4$

2. hydrolysis

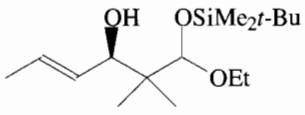
(m)



BBr_3, CH_2Cl_2

–78°C → –20°C

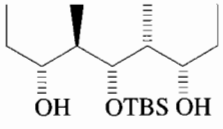
(n)



1. $Me_3SiCH_2CH_2OCH_2Cl$
Hünigs base , CH_2Cl_2

2. 80% AcOH

(o)

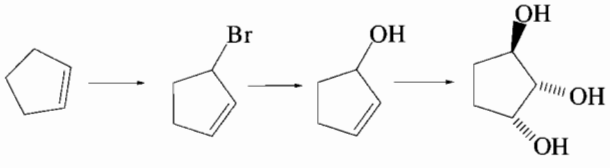


1. $(COCl)_2$, DMSO

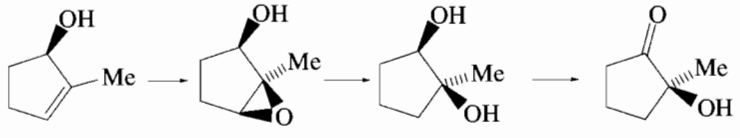
2. HF•pyridine , THF

5. For each of the following, determine if protection is required in the given sequence. If so, choose the protecting group(s), explain your choice(s), and provide all necessary reagents for the entire sequence.

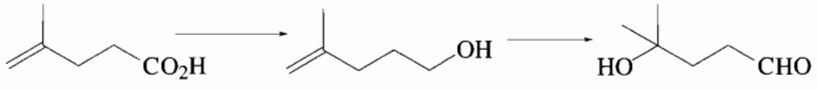
(a)



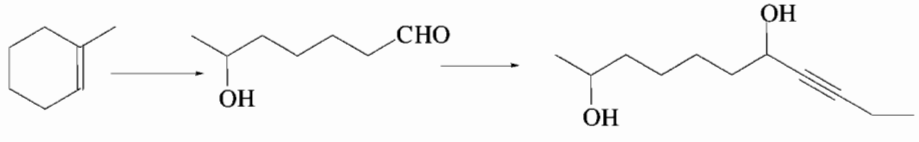
(b)



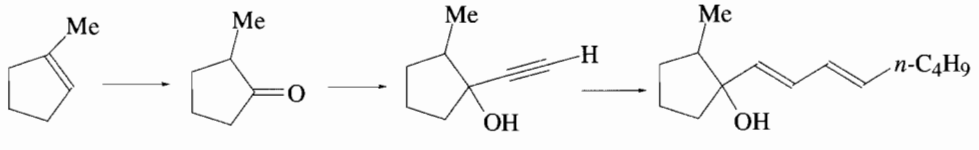
(c)



(d)

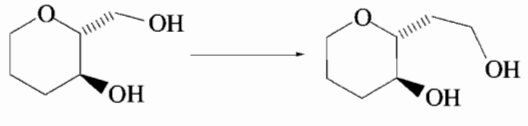


(e)

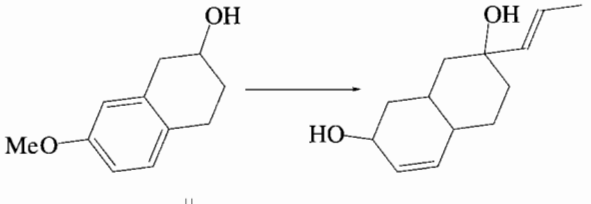


6. In each case, complete the synthesis showing all reagents and all intermediate products.

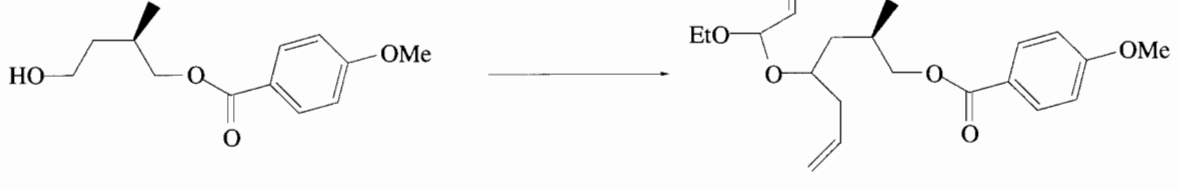
(a)

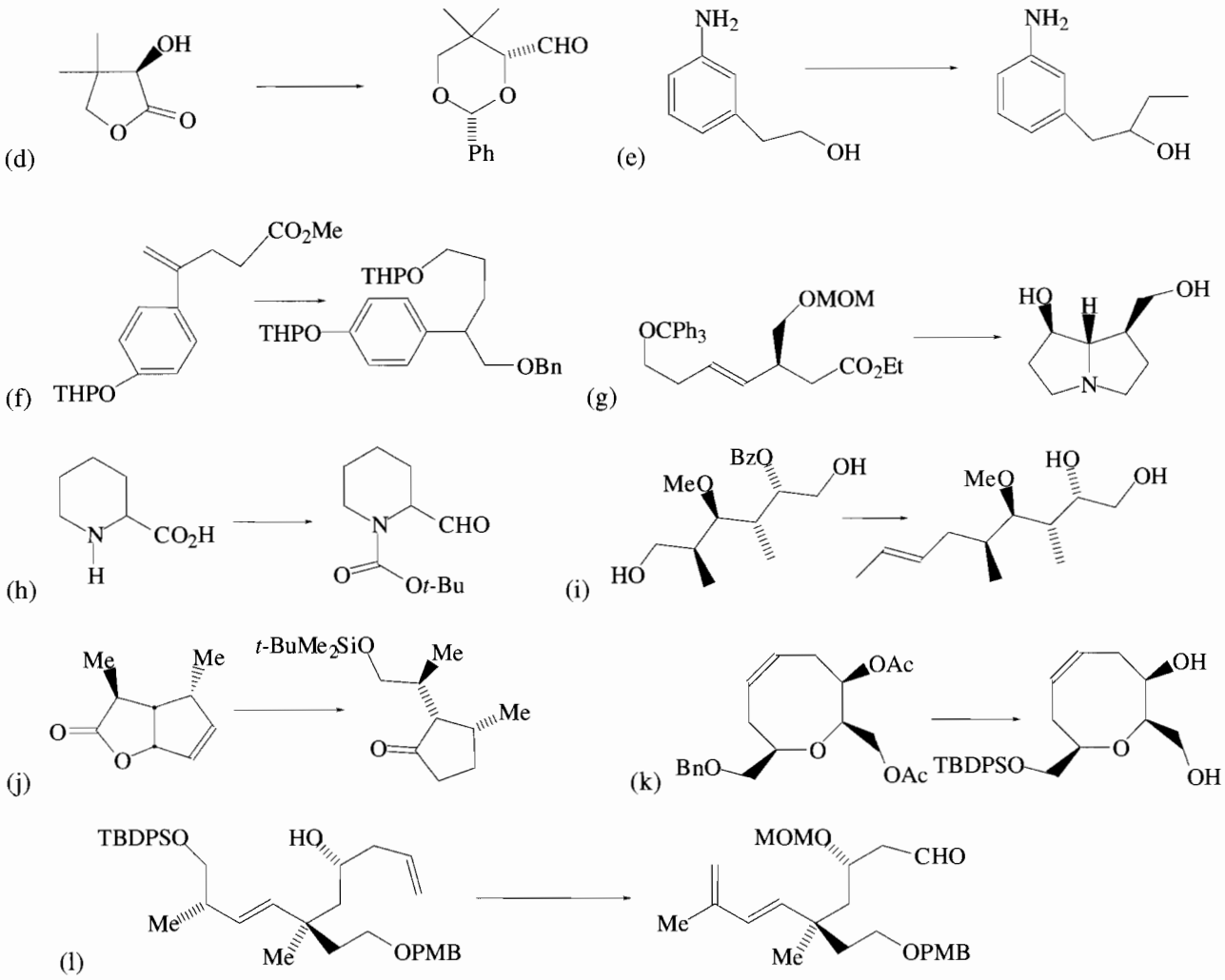


(b)



(c)





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CHAPTER 8

C^d DISCONNECT PRODUCTS: NUCLEOPHILIC SPECIES THAT FORM CARBON–CARBON BONDS

8.1. INTRODUCTION

The formation of new carbon–carbon bonds poses a major challenge in any synthesis since a complex carbon skeleton must usually be constructed from a relatively simple one. Introduction of new functional groups that are compatible with existing functional groups and also with the reagents that are necessary to complete the transformation further complicates the problem. Finally, the problems of regioselectivity, stereoselectivity, chemoselectivity, and absolute configuration of the chiral centers must be addressed in a reasonable manner. As an introduction, the major reactions that build new carbon–carbon bonds have been classified into four major types: nucleophilic, electrophilic, pericyclic and radical reactions. This chapter will focus on those reactions that employ a nucleophilic carbon species. Referring back to Chapter 1, disconnection of a bond generated two fragments (R—C^a and R—C^d), where R—C^d was a donor or nucleophilic fragment and R—C^a was an acceptor or electrophilic fragment (sec. 1.2). The main purpose of this chapter is to identify those types of molecules that function as C^d, and especially to expand on the number of reactions that were presented in Chapter 1. In most cases the nucleophilic carbon is an organometallic derivative where the metal is magnesium, lithium, sodium, potassium or a transition metal.

8.2. CYANIDE

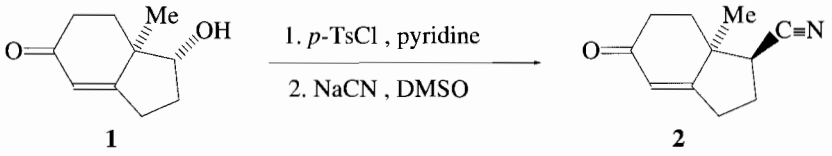
8.2.A. Formation of Nitriles

Cyanide ion is a simple but convenient and powerful nucleophile for generating carbon–carbon bonds. When it displaces a leaving group in a S_N2 reaction, the carbon chain is extended by one. The resulting nitrile

$$\text{R—X} + \text{NaCN} \xrightarrow{\text{DMSO}} \text{R—C}\equiv\text{N} + \text{NaX} \qquad \text{X = Br, Cl, I, OSO}_2\text{R}$$

is easily converted to a variety of other functional groups,[1] making it an excellent synthon. The displacement reaction of ethyl halides or sulfonate esters by cyanide ion to give propanenitrile ($CH_3CH_2CH_2CN$)[1] was reported in 1854 by Williamson;[2] but the first nitrile had been synthesized by Wöhler and Liebig in 1832.[3] Since this is an S_N2 process (sec. 2.7.A.i) and the best yields of nitrile are obtained with primary and secondary substrates, whereas tertiary halides such as 2-chloro-2-methylbutane react to give elimination to the alkene (sec. 2.9.A).[4] Cyanide displacement of secondary halides often gives poor yields, however. The best yields of nitriles such as hexanenitrile (capronitrile), formed in 97% yield after only 20 min. (sec. 2.7.A.i), are obtained in polar, aprotic solvents such as DMSO, DMF, or THF.

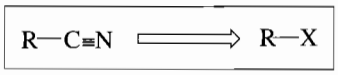
Sulfonate ester leaving groups can also be used, as in the conversion of alcohol **1** first to the tosylate group and then to nitrile **2** with NaCN in DMSO.[5a] The S_N2 reactions proceed with the expected inversion of configuration. Another common reagent that generates a nitrile is tosylmethylisocyanide ($TsCH_2N{\equiv}C$, also called TosMIC),[5b] which reacts with ketones or aldehydes to generate a nitrile ($R_2C{=}O \rightarrow R_2CH\text{-}C{\equiv}N$).[5b]



1 **2**

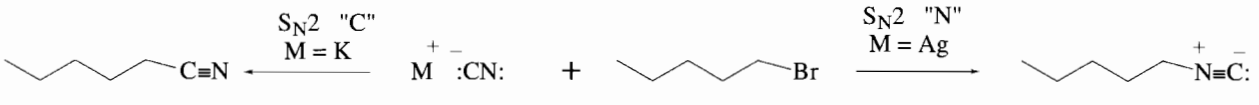
When a cyano group is incorporated into a molecule, one carbon is added to that molecule. Nitriles are versatile synthetic intermediates since they can be converted to several other functional groups. Three important reactions of nitriles are hydrolysis to acid derivatives,[6] reduction to amines (secs. 4.2.C.iii , 4.8.D), and reduction to aldehydes[7] (secs. 4.3, 4.6.C, 4.9.H). In this chapter, we will see that nitriles react with Grignard reagents (sec. 8.4.C.iii) and organolithium reagents (sec. 8.5.E) to form ketones. Treatment of nitriles containing an α-proton with strong bases such as lithium diisopropylamide generates the α-carbanion, which can react with alkyl halides, aldehydes, or ketones or another nitrile (see the Thorpe reaction in sec. 9.4.B.iv). Reactions of cyanide are not limited to alkylation of halides and sulfonate esters. Epoxides are also opened by cyanide via an S_N2 process, which means that attack occurs primarily at the less sterically hindered carbon of the epoxide.[8]

Disconnection of a C—CN bond is particularly attractive when the CN unit is attached to a primary or a secondary carbon, which reflects the relative ease of formation of this bond by the S_N2 reaction and the variety of functional group transformations available. The disconnection for nitriles can be simplified as:



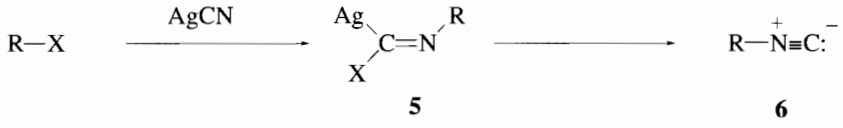
8.2.B. Isonitriles: Formation and Reactions

Both potassium and sodium cyanide react with alkyl halides to give excellent yields of the nitrile in the solvent DMSO. When the reaction is done in refluxing alcohol or when certain other metal cyan-ides are used, an isomeric product (see **4**) is often observed called an isonitrile (isocyanide).[9] Isonitriles were first reported



3 **4**

by Gautier and Hofmann.[10] Cyanide is a bidentate nucleophile (see **5**) and in general C^- is a better nucleophile than N^- but this depends on the metal counterion. If M^+ in MCN is sodium or potassium, (they form ionic compounds), cyanide reacts primarily at carbon. If M^+ is a metal such as silver that forms relatively covalent bonds, the electrons on the carbon are tied up and cyanide reacts primarily at nitrogen, which is illustrated by the reaction of MCN with 1-bromopentane to give **3** or **4**. Reaction with potassium



5 6

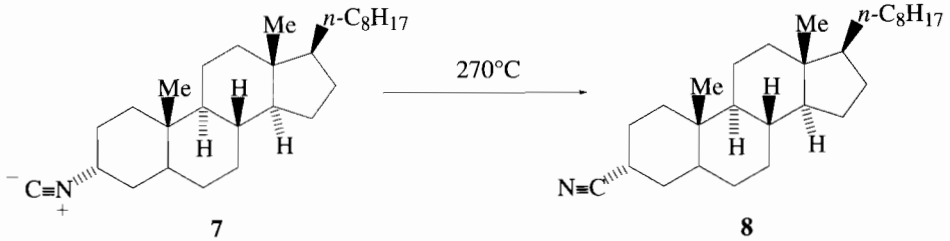
cyanide (KCN) generates hexanenitrile (**3**) whereas silver cyanide (AgCN) gives the isomeric isonitrile **4**. If the reaction is done is alcoholic solvents, which minimizes the nucleophilicity of ionic species, the yield of isonitrile is improved. The relationship between ionic and covalent metal cyanides and formation of isonitriles upon reaction with alkyl halides is shown in Table 8.1.[1] The best yields of isonitrile are observed with silver cyanide and copper cyanide, which form highly covalent metal cyanides, which is due, in part, to the formation and stability of intermediates such as **5**. Reaction of an alkyl halide with silver cyanide is a preparative route to isonitriles, **6**, but they can also be formed by dehydration of formamide derivatives.[11]

Table 8.1. Preparation of isonitriles from alkyl halides and metal cyanides.

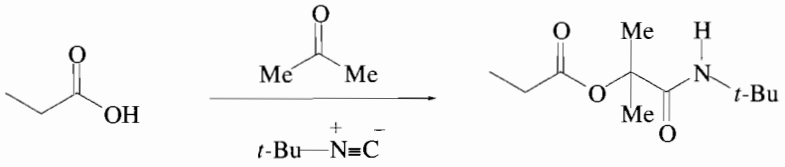
6

Metal Cyanide	RN≡C (%)
AgCN	Quantitative
CuCN	56
$Cd(CN)_2$	11
$Ni(CN)_2$	8
$Zn(CN)_2$	2.6
KCN	Trace

Hydrolysis of isonitriles with cold, dilute aqueous acid leads to an amine and formic acid. If the reaction of cyanide with an alkyl halide gives a mixture of nitrile and isocyanide, mild hydrolysis with aqueous acid affects only the isocyanide, allowing isolation of the nitrile. Isocyanides can also be converted to the nitrile by thermal rearrangement, requiring typical temperatures of between 140° and 240°C.[1] Heating 3-α-isocyano-cholestane **7** to 270°C, for example, gave 3-α-cyano-cholestane (**8**). Interestingly, the reaction proceeded with >99% retention of configuration.[12] If the isonitrile does not contain functionality that would be damaged by heating, good yields of the nitrile can be obtained. Not that isocyanates[13] are easily formed from isonitriles by reaction with halogens.[13b]

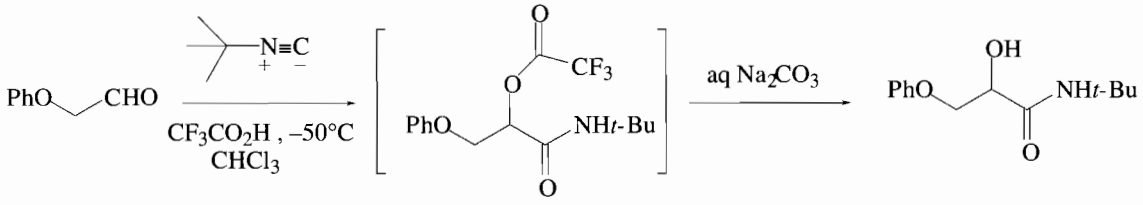


7 8



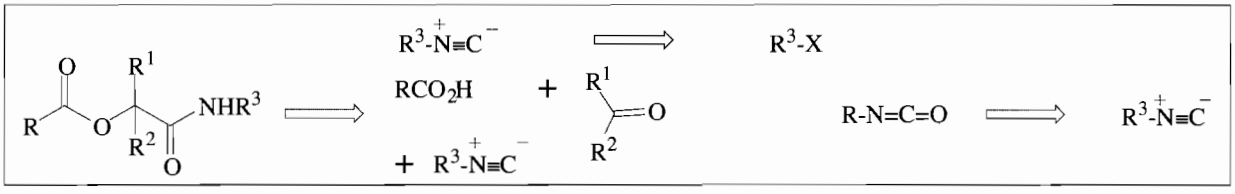
9

Isonitriles can be used for a few useful synthetic transformations.[9,14] The **Passerini reaction**[15] is a convenient route to amide esters. When propionic acid was heated with acetone and *tert*-butylisonitrile, for example, the product was α-propanoyloxy amide **9**.[15a] A useful modification of the Passerini reaction used trifluoroacetic acid rather than a normal aliphatic carboxylic acid. When α-phenoxyacetaldehyde (**10**) reacted with *tert*-butylisonitrile and trifluoroacetic acid (TFA), **11** was formed. Hydrolysis of this trifluoroacetyl ester with aqueous sodium carbonate led to isolation of the α-hydroxyamide (**12**) in 69% yield.[16] This modification has the advantage that hydrolysis conditions for trifluoroacetate esters are milder than for normal esters.



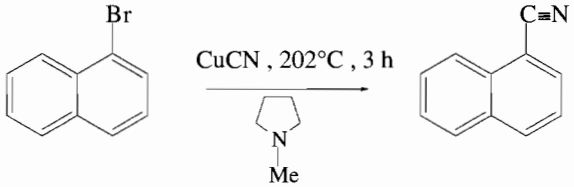
10 **11** **12**

Isonitriles are somewhat limited in their synthetic utility, but they have some interesting disconnections:



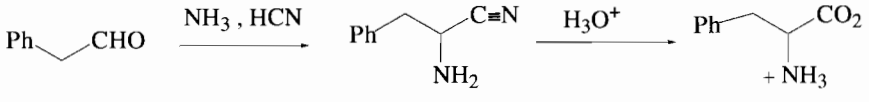
8.2.C. Other Nitrile-Forming Reactions

Aryl halides are inert to reaction with cyanide ion under normal S_N2 conditions (chap. 2, sec. 2.11), but they do react when heated with cuprous salts like cuprous cyanide (CuCN). Reaction of 1-bromonaphthalene (**13**) with CuCN at 202°C gave an 89% yield of the aryl nitrile (**14**).[17] This transformation is called the **Rosenmund–von Braun reaction**[18] and can be applied to a wide range of aryl halides . The aryl nitriles produced can be used in a variety of reactions.[19] This transformation does *not* work when potassium or sodium cyanide is used. An amine base is usually added to facilitate the reaction.



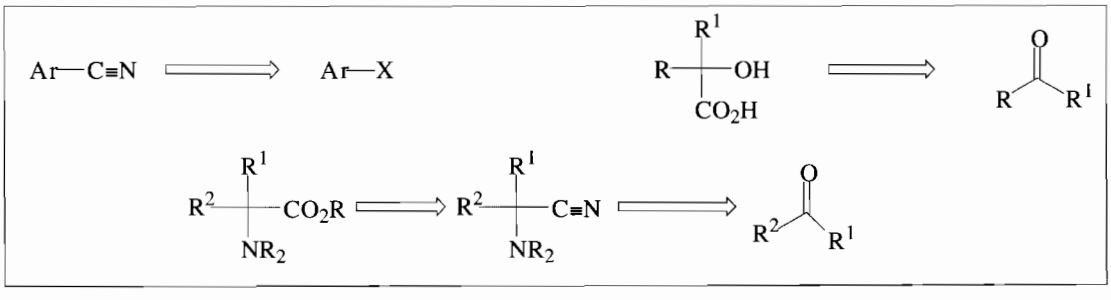
13 **14**

Aliphatic or aromatic carboxylate salts can also be nitrile precursors. For example, fusion (250–300°C) of sodium propionate with cyanogen bromide[20] gave propanenitrile.[21,20b] Cyanide is a nucleophile and it reacts with carbonyl derivatives via acyl addition, although this is usually a reversible reaction. The addition can be controlled in many cases, however, and the product is a cyanohydrin [RCHCN(OH)], which forms the basis of the classical **Strecker synthesis**.[1,22] This synthesis is used to prepare racemic α-amino acids. When phenylacetaldehyde (**15**) was treated with NH_3 and HCN, for example, the product was the amino nitrile, **16**. Hydrolysis of the nitrile generated the amino acid, phenylalanine (**17**).[22] There are many modifications of the Strecker synthesis, including those by Erlenmeyer, Tiemann, Zelinsky and Stadnikoff and Knoevenagel and Bucherer.[1] In all cases, the reaction produces racemic amino acids but newer methodology introduces enantioselectivity into the process. One modification of the original Strecker procedure uses a chiral amine



15 **16** **17**

and produces amino acids with good asymmetric induction.[23] Other acid derivatives can also be prepared with HCN and carbonyl derivatives. Addition of HCN to a ketone or aldehyde leads to a cyanohydrin in a reversible reaction, and hydrolysis gives the α-hydroxy acid,[1,24] which is an equilibrium process favoring the cyanohydrin for aliphatic aldehydes and ketones. The yields are usually poor with aryl and diaryl ketones, however. These reactions add the following disconnections to those previously shown for nitriles:

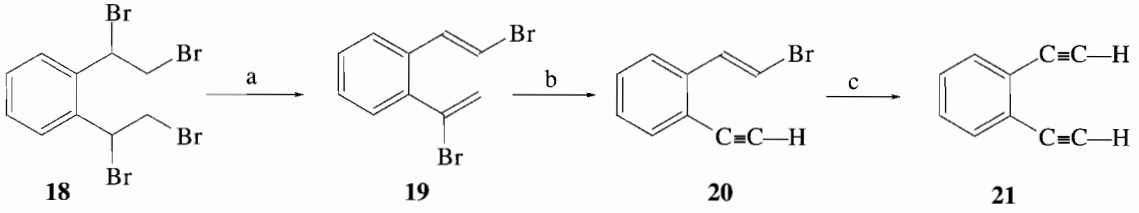


8.3. ALKYNE ANIONS (R—C≡C:⁻)

The conjugate base of an alkyne is an alkyne anion (older literature refers to them as acetylides), and it is generated by reaction with a strong base and is a carbanion. It functions as a nucleophile (a source of nucleophilic carbon) in S_N2 reactions with halides and sulfonate esters. Acetylides react with ketones, with aldehydes via nucleophilic acyl addition and with acid derivatives via nucleophilic acyl substitution. Acetylides are, therefore, important carbanion synthons for the creation of new carbon–carbon bonds. Some of the chemistry presented in this section will deal with the synthesis of alkynes and properly belongs in Chapter 2. It is presented here, however, to give some continuity to the discussion of acetylides.

8.3.A. Preparation of Alkynes and Alkyne Anions

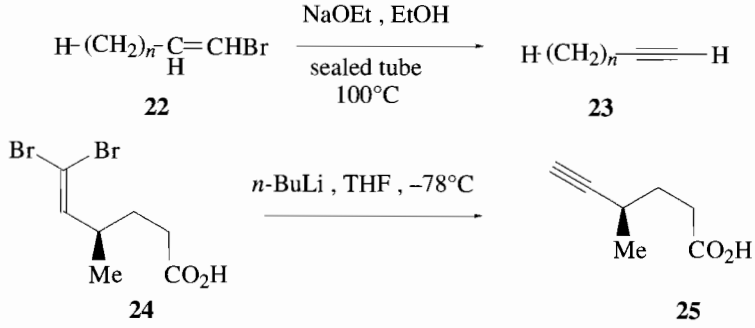
Alkynes have been thoroughly studied over many years[25] and numerous methods are available for their preparation.[26] One of the most useful is dehydrohalogenation of dihalides. This method works best for aryl derivatives when trans elimination is possible.[27] Tetrabromide **18** underwent the usual E2 elimination with potassium *tert*-butoxide (sec. 2.9.A) to give **19**. Base induced dehydrohalogenation gave mono-alkyne **20** since only one trans elimination was possible.[28] Treatment of **20** with a second equivalent of base did give bis(alkyne) **21** but required a cis elimination pathway. This second elimination was more difficult, requiring excess base and more vigorous conditions.



18 **19** **20** **21**

(a) 2 *t*-BuOK , dioxane (b) *t*-BuOK , *t*-BuOH , dioxane (c) *t*-BuOK , PhH , reflux

As the chain length of the vinyl halide increases, the yield of terminal alkyne product generally decreases.[23,29] Vinyl bromide **22** (n = 0) gave 61% of acetylene **23** (n = 0), for example, but 1-bromo-1-hexene (**22**, n = 4) gave only 18% of the corresponding alkyne (**23**, n = 4).[29] Alkynes can also be formed from non-terminal (internal) vinyl halides (such as 3-bromo-3-heptene), but when alkoxide bases are used, the vigorous conditions usually required for elimination of the halogen can cause the triple bond of the product to migrate to the terminal position.[30]

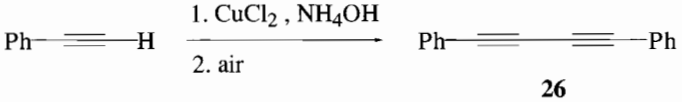


22 **23** **24** **25**

A useful source of terminal alkynes are 1,1-dibromoalkenes such as **24**. When this was treated with *n*-butyl-lithium in THF at –78°C, alkyne **25** was formed in 83% yield.[31] This example was taken from Evans' synthesis of (+)-miyakolide. Dibromides such as **24** can be formed from aldehydes or ketones via a variation of the Wittig olefination reaction (see sec. 8.8.A).

Coupling is an important reaction of alkynes that leads to di-ynes. It occurs under a variety of conditions,[32] but is particularly important when alkynylcopper derivatives are involved. Two classical alkyne coupling reactions involve copper derivatives. In the **Glaser reaction**,[33] where an alkyne such as phenylacetylene reacts with basic cupric chloride ($CuCl_2$), subsequent air oxidation gives a diyne (in this case **26** in 90% yield).

This reaction has also been reported to give a quantitative yield of **26** in the presence of $CuCl_2$ and NaOAc, using supercritical CO_2 as the solvent.[34] The second important reaction is the **Cadiot–Chodkiewicz coupling**,[35] in which a bromoalkyne such as **28** reacts with a monoalkyne (such as **27**) in the presence of cupric chloride and an amine to give the diyne (a 90% yield of **29**).[35a] Glaser-type coupling of alkynes can be accomplished with other copper derivatives and bases other than hydroxide. Cupric acetate and pyridine is also an effective reagent.[36] Internal coupling reactions are also possible. It has been shown that indium metal can be used to couple alkynes with allyl bromide with an anti-Markovnikov regiochemistry.[37]



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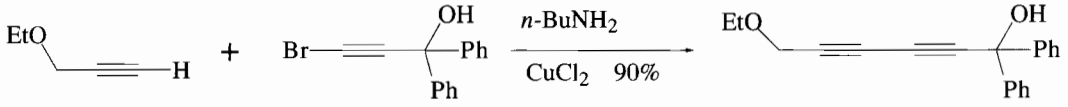
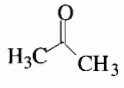
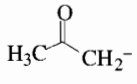


27 **28** **29**

8.3.B. Acidity of Alkynes

Acetylene and other terminal alkynes have an acidic hydrogen attached to the triple bond (C≡C—H), but they are weak acids. A strong base is required to remove that proton to give an alkyne anion such as **30**, which behaves as a carbon nucleophile. It reacts with alkyl halides or sulfonate esters (R^1—X where R^1 = Me, 1°, 2° alkyl, and X = halogen or OSO_2R) via an S_N2 sequence to give disubstituted alkynes such **31**. As shown in Table 8.2,[38] the acidity of a proton is enhanced (lower pK_a) as the **s character** of the carbon to which it is attached increases.[39] Despite the fact that alkynes are rather weak acids, a variety of bases (sodium hydride, lithium, sodium, or potassium amide, lithium dialkyl amides, organolithium reagents, or Grignard reagents) will generate an alkyne anion.[40] 1-Octyne reacted with methylmagnesium bromide, for example, to give methane and the magnesium salt of the acetylide.[40] This must be taken into account if a Grignard reaction is one step of a planned synthesis (secs. 8.4.A, 8.4.F.i).[41]

Table 8.2. Relative Acidity of Common Weak Acids

Alkyne	Conjugate Base	pK_a
RC≡CH	$RC{\equiv}C^-$	25
$R_2C{=}CH_2$	$R_2C{=}CH^-$	36
		20
ROH	RO^-	17

The acidity of the alkynyl hydrogen is strongly influenced by the nature of the group on the other side of the triple bond, as shown in Table 8.3.[42] When the R group is electron releasing (e.g., an alkyl group such as

butyl) the acidity of the proton decreases. Likewise, an electron withdrawing R group increases the acidity.[42] In Table 8.3, the acetylide was trapped with D_2O to give the *d*—alkyne (**32**). Strong bases such as MNH_2 (M = Li, K, Na) or *n*-butyllithium in ether (sec. 8.5.G) abstract the proton rapidly at –80°C. Ethylmagnesium bromide is less basic so alkyne deprotonation is slower (30-90 min. at reflux).[42] Conjugation enhances the

$$R{-}C{\equiv}C{:}^{-}\ M^{+} \xrightarrow{R^1{-}X} R{-}C{\equiv}C{-}R^1$$

30 **31**

acidity[43] (see Table 8.3), and *n*-PrC≡C—C≡CH reacts instantaneously with ethylmagnesium bromide in refluxing ether. This contrasts with *n*BuC≡CH which shows no reaction after 15 min under the same reaction conditions, although it reacts slowly when longer reaction times are used.[42] At higher reaction temperatures, dilithiation [HC≡CH → HC≡C—Li → Li-C≡C—Li] can be a problem with acetylene, although when *n*-butyllithium (ether, < –10°C) is used this is not a significant problem. Attempts to form HC≡C—M with either *n*-butyllithium (M = Li) or Grignard reagents (M = MgBr) in ether led to M—C≡C—M due to the instability of M—C≡C—H. In THF, however, both HC≡CMgBr and HC≡CLi are sufficiently stable to be used as nucleophiles in an S_N2 reaction, if the temperature is maintained below 35°C.

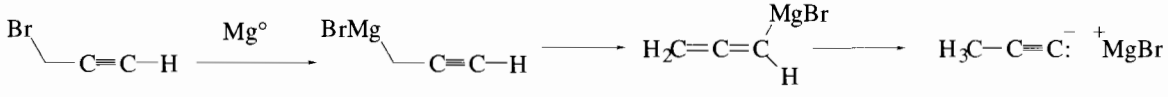
Table 8.3. Effect of Substituents on Alkyne Acidity

$$R{-}C{\equiv}C{-}H \xrightarrow[D_2O]{NEt_3,\ DMF} R{-}C{\equiv}C{-}D$$

32

R	Relative Acidity
Ph	1.0
H	0.73
n-Bu	0.058
$Cl(CH_2)_4$—	0.033
$HC{\equiv}C(CH_2)_4$—	0.076
MeO	2.0

When one attempts to form the Grignard reagent of propargyl bromide (**33**), the acidity of the alkyne hydrogen causes problems. The initial magnesium insertion reaction generates a Grignard reagent but migration of the MgBr moiety generates an allene structure (**34**), which forms the propynylmagnesium salt (**35**) at temperatures below 0°C.[44] Attempts to use the bromomethyl carbon atom in alkyne **33** as a nucleophile should therefore be approached with caution.

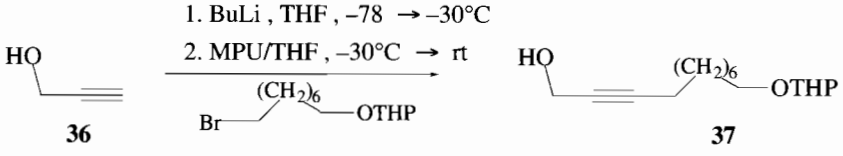


33 **34** **35**

When an alkyne possesses an α-proton (like 1-butyne), vigorous heating can induce a rearrangement to an internal alkyne (2-butyne) under basic conditions.[45] This rearrangement is usually not a problem in S_N2 alkylation reactions involving alkyl halides, at reaction temperatures from ambient to ≈ 120°C (rearrangement requires much higher temperatures). If the alkylation is sluggish and the reaction requires refluxing in DMF or DMSO however, such rearrangements may be competitive.

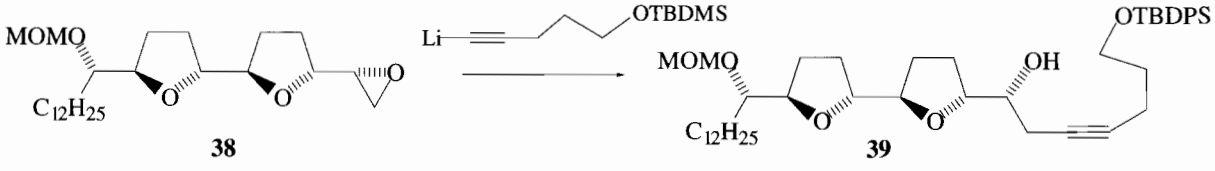
8.3.C. Reactions of Alkyne Anions

As noted above, alkyne anions are very useful in S_N2 reactions with alkyl halides, and in acyl addition reactions to a carbonyl.[46] Alkyl halides[47] and sulfonate esters (tosylates and mesylates primarily) serve as electrophilic substrates for acetylides. A simple example is taken from Kaiser's synthesis of niphatoxin B, in which propargyl alcohol (**36**) is treated with butyllithium and then the OTHP derivative of 8-bromo-1-octanol to give a 47% yield of **37**.[48]



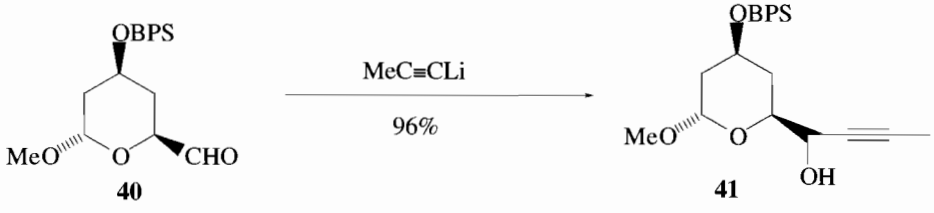
36 **37**

As with cyanide, S_N2 reactions of alkyne anions can be done with substrates other than halides or sulfonate esters. Epoxides are opened by acetylides at the less sterically hindered carbon to give an alkynyl alcohol. A synthetic example is the reaction of epoxide **38** with the indicated lithium alkyne anion gave an 85% yield of **39**, an intermediate in the Sinha et al. synthesis of squamotacin.[49]



38 **39**

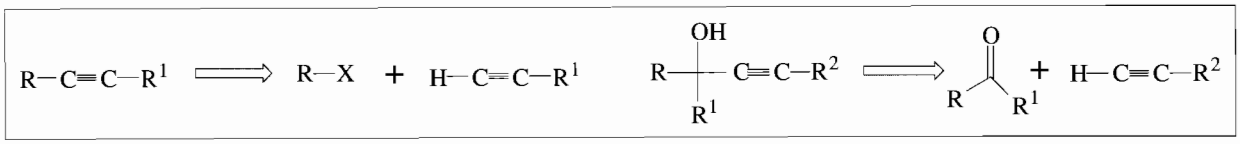
The other major synthetic use of alkyne anions is their reaction with ketones and aldehydes to give an alkynyl alcohol via nucleophilic acyl addition. The lithium salt of 1-propyne, for example, reacted with aldehyde **40** to give alcohol **41** as part of Smith's synthesis of (+)-acutiphycin.[50] The reaction is selective for ketones and aldehydes in the presence of acid derivatives, if the acetylide is not present in large excess.[51]



40 **41**

The reaction is not limited to simple alkynes, of course. Terminal alkynes in general give the reaction and a variety of polar substituents can be incorporated.[52] Acetylides show some propensity for 1,2-addition in conjugated systems, especially if the β-carbon of the double bond is hindered.

The reactions of acetylides with carbonyls and halides lead to the following disconnections:

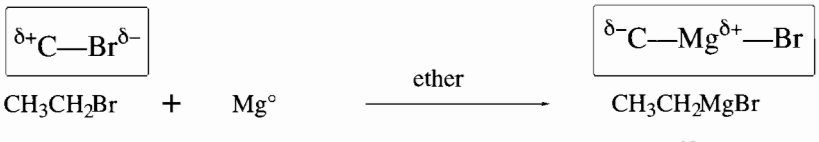


Disconnection of the C-//-C≡C bond is a high priority when the C≡C unit is attached to a primary or secondary carbon, reflecting the facile formation of that bond via the S_N2 reaction. The alkyne moiety is easily converted to a variety of other functional groups, including reduction to alkenes, oxidation to ketones and aldehydes, and addition of halides and acid derivatives. Two-carbon or multiple-carbon chain extensions are characteristic of this reaction, and the functional group transforms that are available from alkynes make them highly useful synthons. The ability to reduce alkynes to either the (*E*) or (*Z*) alkene is also of great synthetic value, as discussed in Section 4.9.B for cis reduction and Section 4.10.D for trans reduction. Addition reactions (with HX or X_2) were discussed in Sections 2.10.A, 2.10.C. There are several copper-catalyzed coupling reactions of aliphatic and aromatic alkynes, but these are primarily radical mediated reactions and will be discussed in Chapter 13.

8.4 GRIGNARD REAGENTS (C—Mg)

8.4.A. Preparation and Properties of Grignard Reagents

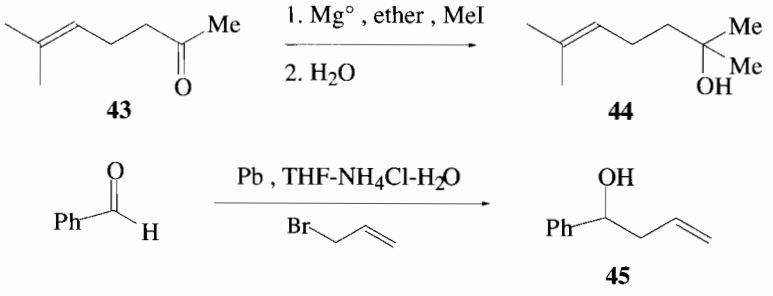
What we now call the **Grignard reaction** was reported by Victor Grignard in 1900.[53a] He was awarded the Nobel Prize in 1912 for this work. The Grignard reaction is now one of the most important and powerful in all of organic chemistry and it set the stage for much of the organometallic chemistry that is so important in modern organic chemistry.[53b] The so-called **Grignard reagent** (RMgX) is formed by the reaction of magnesium (Mg°) with an alkyl or aryl halide, usually in an ether solvent. A simple example is the reaction of bromoethane with magnesium in ether to give **42**. The importance of the Grignard reagent is seen when the C—Br bond is contrasted with a C—Mg-—Br bond. The normal bond polarization in the C—Br bond generates an electrophilic carbon. The C—Mg bond in the Grignard reagent, however, generates a nucleophilic carbon (see **42**). This ability to *invert* the polarity of a carbon atom means the Grignard reagent can function



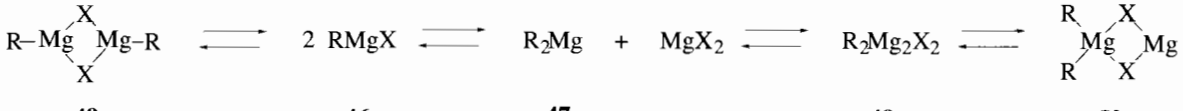
42

as a carbon nucleophile, usually in reactions with a carbonyl derivative. The reaction was first discovered in 1899 by Barbier, who was Grignard's mentor, although its nature was not well understood at the time. Barbier discovered that a ketone (such as **43**) reacted with magnesium metal (Mg°) in the presence of iodomethane, in ether, to give an alcohol (**44**, after hydrolysis) that resulted from coupling of the two organic fragments.[54] This conversion is now known as the **Barbier reaction** or **Barbier coupling**.[54] Its utility is somewhat limited

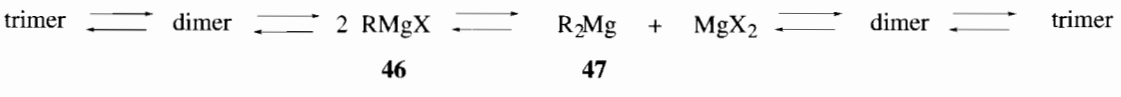
by the requirement that all reagents be mixed together. In subsequent work, Grignard took the reaction much further. He premixed magnesium metal and the halide, characterized the resulting product as RMgX, and showed how RMgX reacted with many functional groups (particularly with ketones and aldehydes).



Note that there are several modern versions of the Barbier reaction that use transition metals or their derivatives.[55] Examples include indium metal, samarium iodide, and lead. An example using lead reacted benzaldehyde with allyl bromide in the presence of lead metal to give a 99% yield of **45**.[56] A retro-Barbier fragmentation has also been reported in which an alcohol was treated with 10 equivalents of bromine and 15 equivalents of potassium carbonate in chloroform to give a bromo ketone.[57]

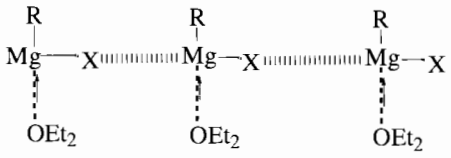


When organomagnesium compounds are formed using the Grignard protocol, the reagent is not isolated but used in solution. In solution, a Grignard reagent (see **46**) is not the simple monomeric species RMgX. Ashby reviewed their composition and discussed the mechanism for their formation.[58] Ashby's conclusion was that the reaction proceeds by a single electron transfer (SET) process. Recent work involving the formation of aromatic Grignard reagents, however, indicate that no freely diffusing radicals were detectable.[59] The RMgX structure usually drawn for a Grignard reagent (**46**) is in equilibrium with dimethylmagnesium (**47**) and $MgBr_2$, as well as **48** in what is called the **Schlenk equilibrium**.[60] The term Grignard reagent really refers to this equilibrium. It was later reported that dimers such as **49** and **50** were present in ether solutions. The Grignard reagent equilibrium is more complex in ether than it is in THF.[61] Smith et al. verified that the equilibrium favored RMgBr in ether, although there is a mixture.[62] In THF, all species (**46–50**) were present and the RMgBr concentration was diminished relative to similar solutions in ether.[63] The Grignard reagent (RMgX) can associate into dimers and trimers in many solvents via a solvent dependent interaction with the halogen.[64]



In other work, Ashby and co-workers concluded[65] that the RMgX species exists in ether, THF, and triethylamine but the composition varies in each solvent. In ether, the monomeric species is largely of RMgX with

lesser amounts of R_2Mg and MgX_2. Association is extensive > 0.3 M and the dimers are assumed to be **49** and **50**. The trimeric structure can be represented as **51**. Ether solutions of Grignard reagents are stable if protected from moisture and air. A 2 N solution of CH_3MgI in ether was stored in a sealed tube for 20 years and shown to have virtually the same concentration of Grignard reagent as when originally sealed.[66]



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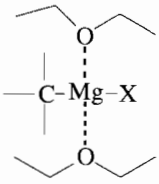

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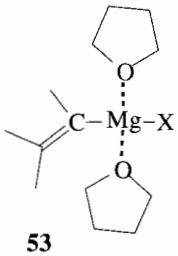


53

In THF, relatively little association occurs and the most abundant monomeric species include both RMgX and $R_2Mg + MgX_2$, as mentioned above. In triethylamine (rarely used as a solvent for Grignard reactions), the only species observed is RMgX for simple alkyl magnesium bromides and chlorides. The amine functions as a Lewis base and will coordinate with RMgX, leading to a monomeric species. The solution is more complex for alkyl magnesium iodides or aryl magnesium halides. In hydrocarbon solvents, alkyl halides and Mg° react at temperatures >100°C[67] to give a mixture of insoluble organomagnesium and inorganic magnesium compounds ($R_2Mg + MgX_2$ + highly associated combinations).[68,67]

Grignard reagents can be formed from primary, secondary and tertiary halides. Alkyl chlorides, bromides, and iodides can be used. In all cases, an ether solvent stabilizes the Grignard reagent by forming a Lewis acid–Lewis base charge-transfer complex such as **52**. Coordination with ether also assists in the initial magnesium insertion reaction and minimizes decomposition of the Grignard reagent via disproportionation. Aryl and vinyl halides react with magnesium to form aryl magnesium halides such as phenylmagnesium bromide (PhMgBr) or vinyl Grignard reagents such as 1-propenylmagnesium bromide ($CH_3CH{=}CHMgBr$). In both cases, the C—Br bond of the aryl or vinyl bromide is stronger than the analogous C—Br bond of an alkyl halide. A stronger Lewis base is therefore required both to assist the insertion and to stabilize (see **53**) the organometallic. Formation of aryl or vinyl Grignard reagents is usually done using the more basic THF. The reaction can work in ether, but formation of the Grignard may be sluggish and the yields can be poor.

Grignard reagents react as carbanions and they are also very basic. The conjugate acid of the Grignard is an alkane (Me—H ⇒ MeMgX), which is a very weak acid (pK_a = 25-40),[69] which means that the Grignard reagent is a very strong base. Chevrot et al. showed that methylmagnesium halides are more basic than other straight-chain alkyl or aryl Grignard reagents.[69] Vinyl Grignard reagents and allylic Grignard reagents are slightly more basic than alkylmagnesium halides, and organomagnesium chlorides (RMgCl) are more basic than organomagnesium bromides (RMgBr). This finding may be due to displacement of the Schlenk equilibrium towards RMgX.

The basicity of Grignard reagents is an important factor in their reactions with electrophilic compounds. Grignard reagents react with the electrophilic hydrogen of water[70] to give the hydrocarbon (R—H) and a magnesium hydroxide. Other electrophilic reagents react with Grignard reagents, including molecular oxygen

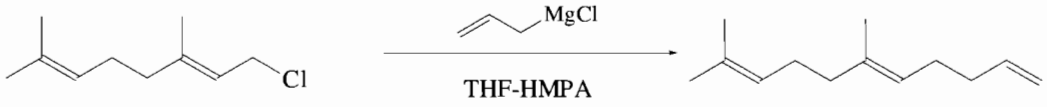
which gives a hydroperoxide anion (**54**) as an initial product. This reacts with additional Grignard reagent to give an alkoxide (**55**)[70] and hydrolysis liberates the alcohol as the final product. The use of anhydrous solvents and exclusion of air is essential for optimum yields in formation and reactions of Grignard reagents on small scale, but on large scale with relatively simple reactants less care need be taken.

$$RMgX + HOH \longrightarrow R{-}H + HOMgX$$

$$RMgX + O_2 \longrightarrow \underset{\mathbf{54}}{ROOMgX} \xrightarrow{RMgX} \underset{\mathbf{55}}{2\ ROMgX} \longrightarrow 2\ ROH$$

8.4.B. The Reaction with Alkyl Halides

Although the nucleophilic Grignard reagent might be expected to displace an alkyl halide in an S_N2 reaction ($RMgX + R^1Y \rightarrow R{-}R^1$), by analogy to cyanide or acetylides. In fact, the yield of coupling product ($R{-}R^1$) is usually poor. Indeed, if Grignard reagents readily coupled with alkyl halides, Grignard reagents would be difficult to prepare. Only reactive Grignard reagents such as allylmagnesium halides react with alkyl halides that are also highly reactive (iodomethane, allyl bromide, benzyl bromide) to give good yields of a coupling product.[71] It is important to note that highly reactive Grignard reagents intended for uses other than coupling are usually prepared in dilute solution, with excess magnesium and via slow addition of the halide to avoid coupling. An example of a successful coupling reaction involves reaction of allyl chloride (**56**) with allylmagnesium chloride to give **57**.[72]



56 **57**

8.4.B.i. The Kharasch Reaction. Normal alkyl halides are not very reactive in coupling reactions with Grignard reagents. In general, good yields of coupling are obtained only by addition of transition metal catalysts.[73] Kharasch showed (Table 8.4)[74] the effectiveness of several transition metals to promote the

Table 8.4. Transition Metal Catalyzed Coupling of Phenylmagnesium Bromide and Benzal Bromide

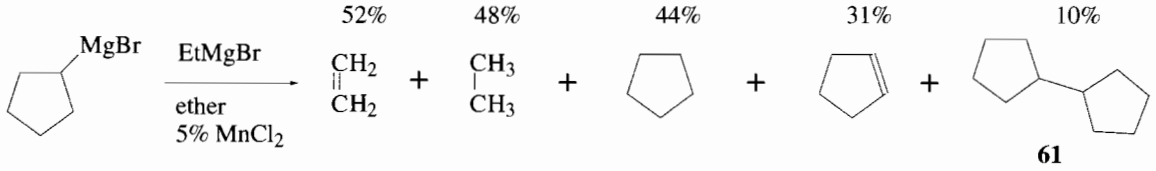
$$PhMgBr + \underset{\mathbf{58}}{Ph_2CH{-}Cl} \xrightarrow{M} \underset{\mathbf{59}}{Ph_2CH{-}Ph} + \underset{\mathbf{60}}{Ph_2CH{-}CHPh_2}$$

M	% 59	% 60
No catalyst	0	90
$CoCl_2$	82	6
$FeCl_3$	63	17
Cu_2Cl_2	30	47
$MnCl_2$	0	82

[Reprinted with permission from Sayles, D.C.: Kharasch, M.S. *J. Org. Chem.*, ***1961***, *26*, 4210. Copyright © 1961 American Chemical Society.]

coupling reaction of phenylmagnesium bromide and chlorodiphenylmethane (**58**). It is clear that cobalt chloride ($CoCl_2$) is very effective and it has been widely used. As shown in Table 8.4, the products of this reaction are the cross coupling product (**59**) as well as the symmetrical coupling product (the Wurtz product, **60**–sec. 8.5.B.ii). This transition metal catalyzed coupling reaction is known as the **Kharasch reaction**.

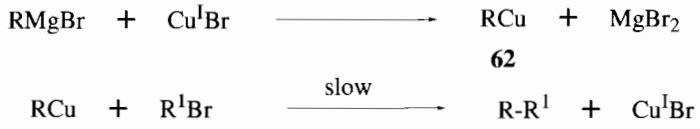
Disproportionation is a serious problem in transition metal catalyzed coupling reactions. Metal–hydrogen exchange followed by Wurtz coupling (sec. 8.5.B.ii) is also a problem. Iron, cobalt, manganese, and nickel salts catalyze disproportionation as shown for the reaction of cyclopentylmagnesium bromide and ethylmagnesium bromide.[75] The latter reagent disproportionated to give ethane and ethene, and similar disproportionation of cyclopentylmagnesium bromide gave cyclopentane and cyclopentene. Only a 10% yield of a coupling product (**61**) was observed, and there no cross-coupling was observed. The reaction of phenylmagnesium and ethylmagnesium bromide behaved similarly, giving 81% of biphenyl.[76]



61

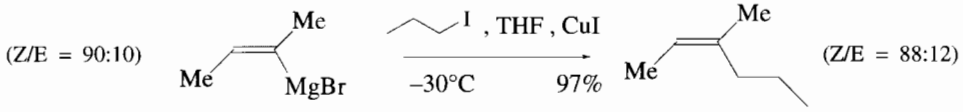
Silver salts are effective catalysts for coupling alkyl Grignard reagents and alkyl halides. The reaction of ethylmagnesium bromide and 1-bromopropane, for example, gave 47% of butane, 12% of hexane, and 37% of the cross-coupled product, pentane.[77] Disproportionation is less of a problem, but the statistical coupling seen in this example is typical, which clearly limits the synthetic utility of the reaction if the cross-coupling product is the desired target. When the target is the symmetrical coupling product (the alkyl groups are the same in the halide and the Grignard reagent), however, product yields can be good. Indeed, reaction of ethylmagnesium bromide with bromoethane gave a 92% yield of butane.[77]

Cuprous [Cu(I)] salts are readily available and when mixed with Grignard reagents give excellent yields of cross-coupled products with very little disproportionation.[77,78] This reaction will be discussed in greater detail in Section 8.7.A. However, a simple example is the reaction of isopropylmagnesium bromide with bromoethane in the presence of cuprous bromide (CuBr) to give 2-methylbutane.[77] The origins of this reaction date



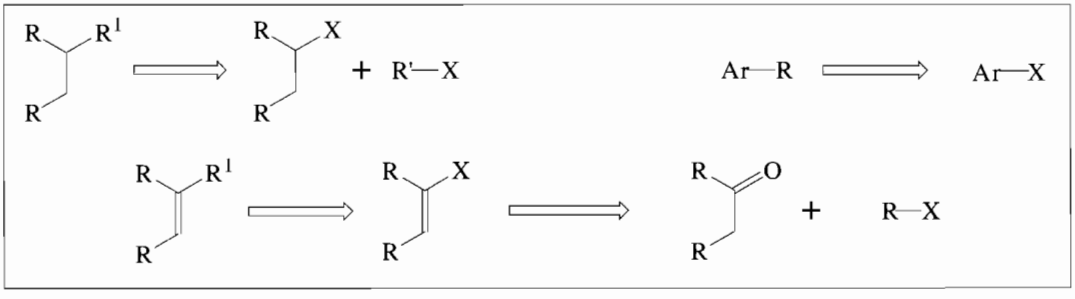
to 1936 and work by Gilman et al.[79] with later work by Cotton et al.[78] and by Noller and co-workers.[80] Kochi and co-worker studied the mechanism of the reaction[77] and proposed an alkylcopper(I) species such as **62** as an intermediate, which reacted with the alkyl halide to give the coupled product (R-R') in the rate-determining (slowest) step of the sequence.[77] The reaction is straightforward with primary alkyl halides,[81] but secondary and tertiary halides do not react as well. If the concentration of Cu(I) is too high with secondary and tertiary halides, disproportionation occurs. The Grignard reagent, however, can be primary, secondary, tertiary, aryl, or vinyl. A useful example of this is the conversion of the Grignard reagent of 2-bromo-2-

butene (**63**) to (3*Z*)-methyl-2-hexene (**64**) by the Cu(I) catalyzed reaction with iodopropane.[82] Grignard reagent **63** was enriched in the (*Z*) isomer and the reaction proceeded with high stereoselectivity to give predominantly the (*Z*)-isomer of **64**. Organocuprates of this type will be discussed in Section 8.7.A.



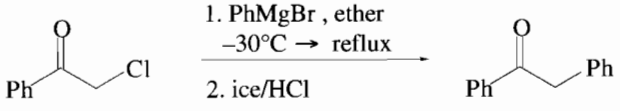
63 **64**

Kochi and co-worker used a different copper catalyst (Li_2CuCl_4, prepared by reaction of LiCl and $CuCl_2$ in THF) to catalyze the coupling of Grignard reagents and alkyl halides. An example is the reaction of hexylmagnesium bromide with bromobutane to give a 73% yield of decane.[83] Metal-catalyzed coupling reactions lead to the disconnections:



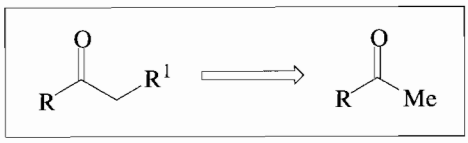
The coupling reaction of Grignard reagents and cuprous salts does not work well with secondary and tertiary halides, as mentioned above. Similar reagents can be prepared with cuprous salts and organolithium reagents that are much more reactive and give better yields of coupling products. These organocuprate reagents will be discussed in Section 8.7.

8.4.B.ii. Reaction with α-Halocarbonyls. α-Haloketones give good yields of coupling products with Grignard reagents, even without a transition metal catalyst. These compounds have two electrophilic sites, the carbonyl carbon and the halogen-bearing carbon, but the two are easily differentiated. The halogen-bearing

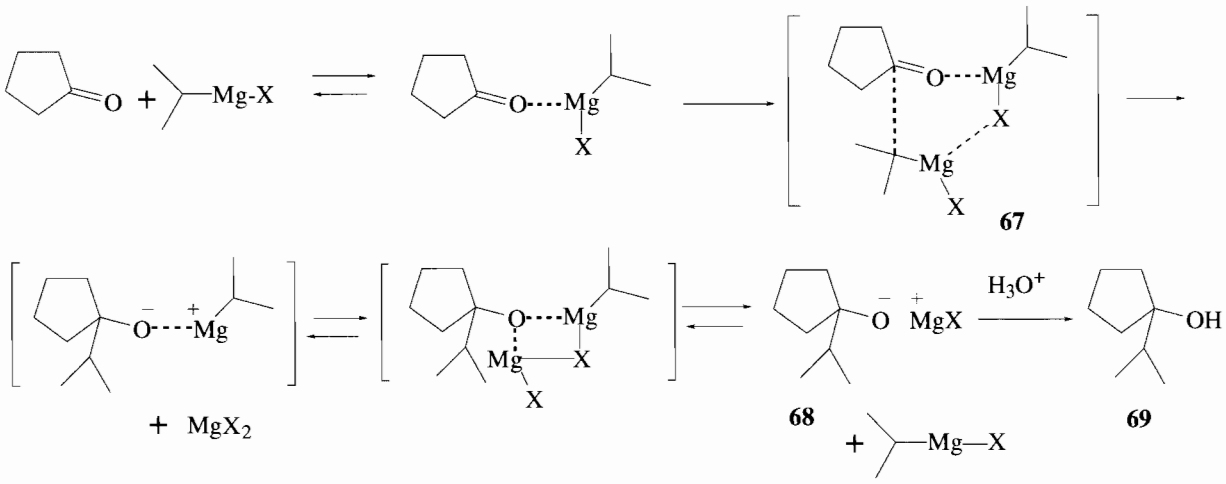


65 **66**

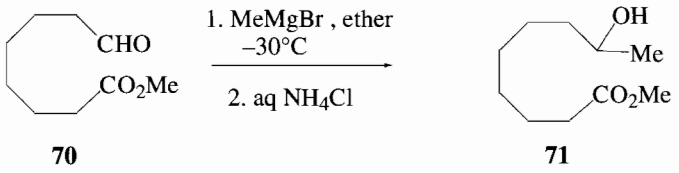
carbon is more susceptible to attack by Grignard reagents, and this coupling reaction occurs without the need of a transition metal catalyst. α-Chloro ketone (**65**) can be prepared by treatment of a ketone with NBS, NCS, Cl_2, $SOCl_2$, and so on,[84] and subsequent reaction with phenylmagnesium bromide gave **66**.[85] This method is superior for the preparation of α-arylketones, but the yields are often poor if the carbonyl is not conjugated to an aromatic nucleus (i.e., with simple alkylketone derivatives). The disconnection for substitution of an α-halo-ketone is



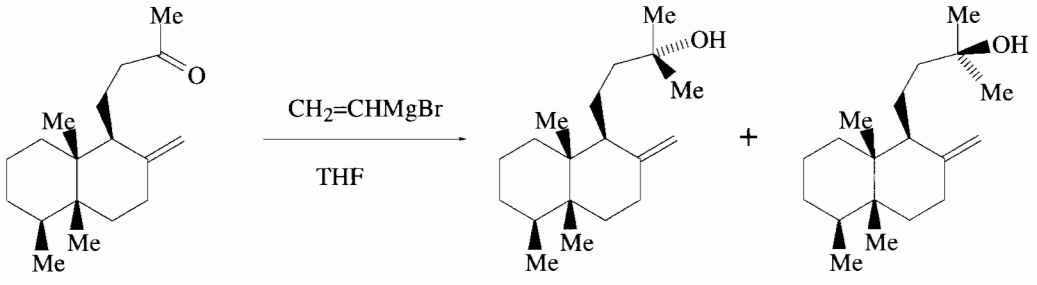
8.4.C. Reactions with Carbonyl Derivatives



8.4.C.i. Acyl Addition. Grignard reagents react with aldehydes and ketones to give alcohols in what is probably the most common use of a Grignard reaction.[86] This reaction is shown for cyclopentanone, which reacts with the nucleophilic isopropylmagnesium bromide at the electrophilic carbonyl carbon to give alkoxide **68**. Hydrolysis is required to liberate the alcohol product **69**. The mechanism shown below was suggested by Ashby.[87] It invokes a cyclic transition state **67** to transfer the alkyl group from magnesium to oxygen, forming the alkoxide and may involve a single electron transfer (SET). This cyclic transition state has stereochemical implications for the alcohol product, since steric and electronic effects will be more important in a cyclic than an acyclic transition state.



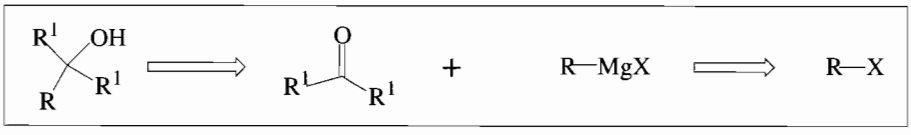
70 **71**



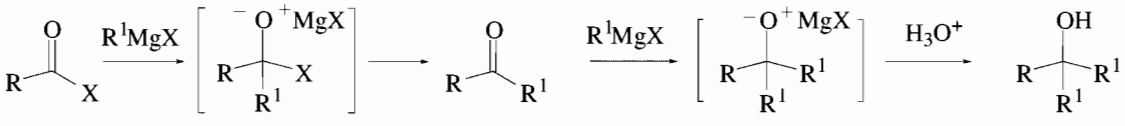
72 **73** **74**

The Grignard reaction is one of the best methods to prepare secondary alcohols from aldehydes, since it generates a carbon–carbon bond during the reaction (RMgX + R^1CHO). With ketones, the reaction generates tertiary alcohols (RMgX + $R^1{}_2$C=O). A simple example is the reaction of methylmagnesium bromide and aldehyde **70** to give alcohol **71** in 83% yield.[88] This reaction was taken from Doyle's synthesis of patulolide A and also illustrates that aldehydes react much faster than esters (see sec. 8.4.C.ii). The low temperature used was to maximize reaction of the aldehyde rather than the ester. An example of a reaction using a ketone is taken from Bonjoch's synthesis of nakamurol-A,[89] where **72** reacted with vinylmagnesium bromide to give a 45% yield of a 1.2:1 mixture of **73** and **74**.

The disconnection for this process is

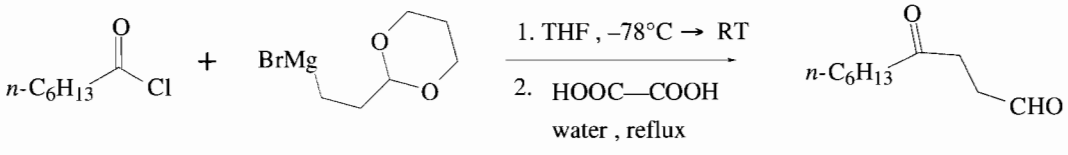


8.4.C.ii. Acyl Substitution. In addition to their reaction with aldehydes and ketones, Grignard reagents also react with most other carbonyl derivatives.[90] As we saw in Section 2.5.C acid derivatives contain a leaving group such as Cl, O_2R, OR, or NR_2 and react with nucleophiles via acyl substitution. Initial addition of a Grignard reagent to the acyl carbon generates an alkoxide intermediate (**75**), and displacement of the leaving group (X) leads to a ketone. If the ketone is more reactive than the initial acid derivative, further reaction with the Grignard can give tertiary alcohol **77** via alkoxide **76**.[91] The competition between ketone product and acyl starting material can lead to mixtures of products and significant amounts of unreacted starting material.



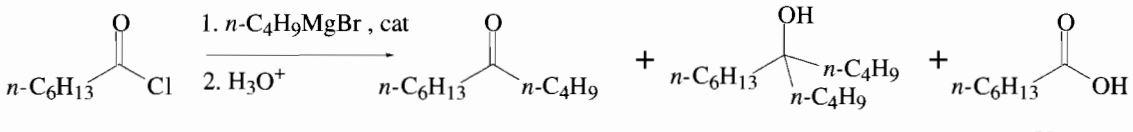
75 **76** **77**

The most reactive acid derivatives are the acid chlorides, where chlorine is the leaving group.[92] Reaction of Grignard reagents with acid chlorides gives excellent yields of the tertiary alcohol when an excess of the Grignard reagent is used, especially with vigorous reaction conditions. When the reaction is done at low temperatures and/or when metal catalysts are added, isolation of the ketone product is often possible.[93] Reaction of heptanoyl chloride and **78**, for example, gave an 89% yield of keto-aldehyde **79**.[93] This reaction was carried out at –78°C to maximize ketone formation and minimize reaction with **75** as well as inhibit decomposition of **75**. The second step is hydrolysis using oxalic acid that converted the dioxane protecting group back to an aldehyde (sec. 7.3.B.i).



78 **79**

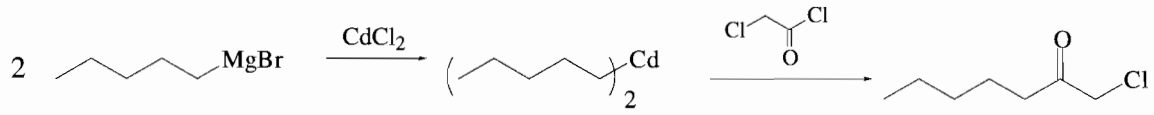
An excellent method for converting an acid chloride to a ketone employs transition metal catalysts such as ferric chloride in conjunction with low reaction temperatures.[94] Reaction of butylmagnesium bromide with octanoyl chloride at –60°C gave a mixture of 13% of **80**, 4% of **81** (from the secondary reaction of butylmagnesium bromide and **80**), and 60% of **82**.[94] When a catalytic amount (2 mol %) of ferric chloride ($FeCl_3$) was added, however, a 76% yield of ketone **80** was obtained, along with 3% of the over alkylation product, **81**.[94] If the intermediate ketone is unreactive to nucleophilic substitution due steric hindrance or peculiar electronic factors (diisopropyl ketone and phenyl-*tert*-butyl ketone are both sterically hindered) the ketone can usually be isolated (sec. 8.4.G for problems with hindered ketones). In many instances, however, even dry ice temperatures and reverse addition techniques give poor yields of the ketone.[95]



80 **81** **82**

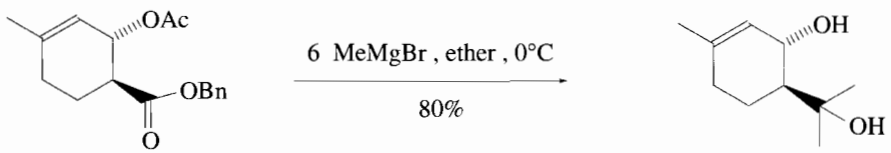
catalyst = NONE , –60°C	13%	4%	60%
catalyst = 2% $FeCl_3$, –60°C	76%	3%	15%

An alternative method for isolating the ketone is to change the metal from magnesium to one that gives a less reactive organometallic. It is known that a Grignard reagent reacts with cadmium chloride ($CdCl_2$) to give a dialkylcadmium reagent (R_2Cd), which reacts with carbonyl derivatives,[96] a reaction that was discovered by



83 **84**

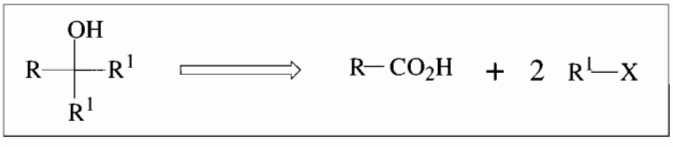
Gilman et al.[97] This reaction is rather slow, however, and in many cases it is not clear that a pure dialkylcadmium reagent is the active reagent in the reactions described.[98] Dialkylcadmium reagents are readily formed from primary Grignard reagents but secondary and tertiary organocadmium reagents are relatively unstable,[99] and the likely decomposition pathway is dissociation to radicals, which disproportionate to give alkane and alkene products. Reagents such as di-*n*-pentylcadmium (**83**) are formed by reaction of a Grignard reagent (pentylmagnesium bromide) and anhydrous cadmium chloride ($CdCl_2$). Such reagents react rapidly with acyl halides but very slowly or not at all with ketones, aldehydes, esters, or amides. The yields of ketone products obtained by reaction with acid chlorides are moderate to good.[100] In general, dialkylcadmium reagents do not react with the ketone products, but there are exceptions when highly reactive ketone products are formed.[97] When **83** reacted with α-chloroacetyl chloride, a 46% yield of **84** was obtained.[100]



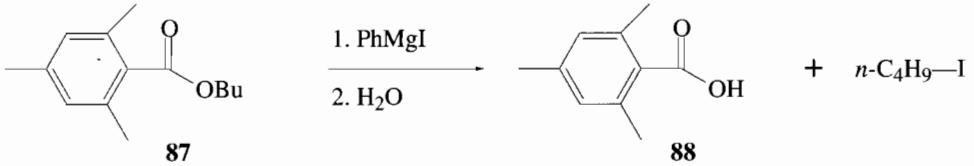
85 **86**

Although esters are much less reactive than acid chlorides (ethoxy is a poorer leaving group than Cl), they are only slightly less reactive than the ketone products resulting from reaction with a Grignard reagent. A Grignard reaction with esters rarely gives the ketone in good yield. A mixture of ester, ketone, and tertiary alcohol is often observed when only 1 equivalent each of Grignard reagent and ester are used. Two or more equivalents of Grignard reagent gives the alcohol as the only product.[101] The tendency for over reaction of some acid derivatives can have useful synthetic applications. The reaction of **85** with an excess of methylmagnesum bromide illustrates the reaction at hand, but introduces an interesting feature.[102] If we focus on the benzyl ester, addition of 2 equivalents of Grignard reagent lead to the tertiary alcohol in **86**. The acetate group in **85** is also an ester and reaction with MeMgBr leads to the alcohol unit in **86** and *tert*-butanol (via loss of acetone from initial addition of MeMgBr and subsequent reaction of acetone to give the alcohol). We have previously seen another application of this reaction in the **Barbier–Wieland degradation** (sec. 3.7.A.iv.),[103] used to decrease the chain length of carboxylic acid esters by one carbon.

The usual disconnections for reaction with esters and acid chlorides are

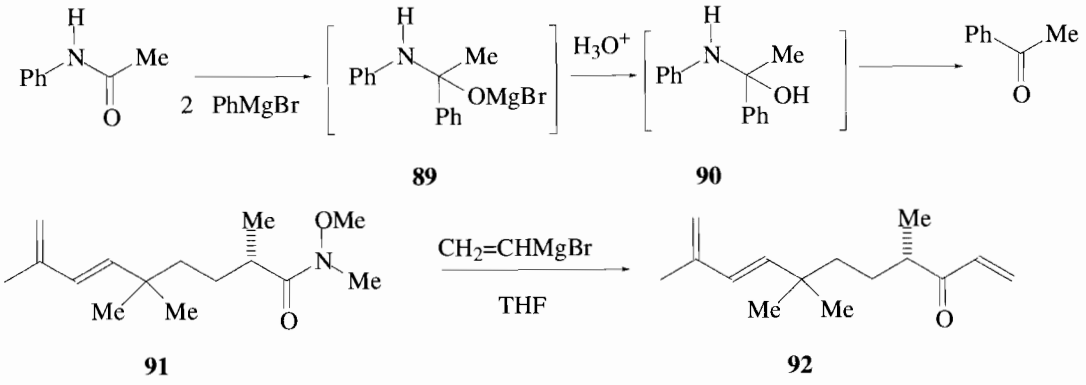


Alkyl esters such as *n*-butyl mesitoate (**87**) resist the acyl addition reaction because the acyl carbon is sterically hindered by the ortho methyl groups. When **87** reacted with phenylmagnesium iodide, for example, the products were mesitoic acid (**88**) and iodobutane.[104] Since acyl addition is inhibited by the presence of

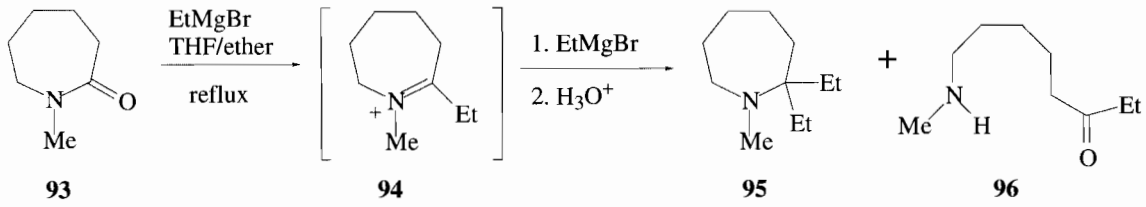


87 **88**

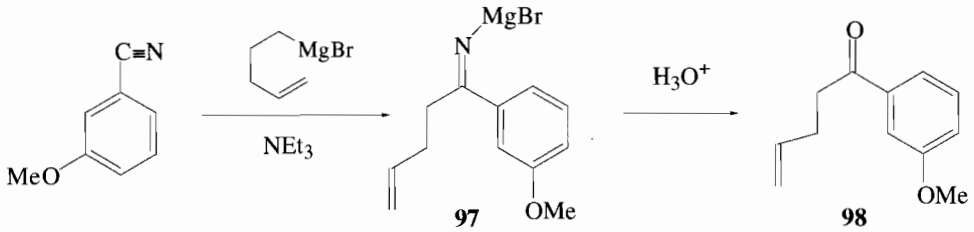
the methyl groups, iodide (assisted by Mg^{2+} complexation with the carbonyl) attacks the O—C group (O—Bu in **87**) in an S_N2 reaction that displaces the carboxyl moiety (which functions as a leaving group). Grignard reactions with lactones are interesting in that ring opening accompanies acyl addition, giving a diol in which the two ends are differentiated. Valerolactone, for example, reacted with butylmagnesium iodide to give 5-methyl-1,5-hexane-diol. Amides are less reactive than esters (NR_2 is a poorer leaving group than OR) and the ketone product can often be isolated, although the yields are usually poor. Reaction of *N*-methylacetamide with two equivalents of phenylmagnesium bromide gave alkoxide **89**.[105] Hydrolysis led to loss of the amine (via **90**) and formation of the ketone product. Since **89** cannot react with additional Grignard, the product is the ketone. N,N-dialkyl amides also react with Grignard reagents to give a ketone, but as mentioned above, the yields are usually poor.[106] An exception is the reaction of Grignard reagents with Weinreb's amide , which we have seen previously (see sec. 2.5.C). This activated amide (—CONMe(OMe) is an excellent leaving group and the reaction stops at the ketone. In the Mori et al. synthesis of (1*S*,3*S*,7*R*)-3-methyl-α-himachalene, amide **91** was converted to conjugated ketone **92** by reaction with vinylmagnesium bromide.[107]



The reaction with lactams follows a somewhat different pathway than that just described for amides. The final product is an amine, or an amino ketone. 2-Pyrrolidinone and 2-piperidone derivatives give primarily the amine, with minor amounts of ring cleavage products (amino ketones). Larger ring lactams give mainly the amino ketone, which is illustrated by N-methyl caprolactam (**93**). This compound reacted with ethylmagnesium bromide to initially form an iminium salt (**94**). This iminium salt is not isolated, but rather reacted with additional Grignard to give a mixture of the dialkylamine (**95** in 42% yield) and the ring-opened amino ketone (**96** in 23% yield).[108]

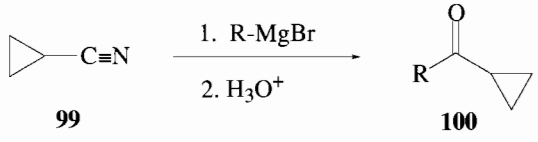


8.4.C.iii. Reaction with Nitriles. Nitriles are carboxylic acid derivatives and react with Grignard reagents (also sec. 8.2.C).[109] Initial attack generates an intermediate iminium salt that can be hydrolyzed (with loss of ammonia) to the corresponding ketone.[110] The best yields are obtained with aryl nitriles, and this is illustrated



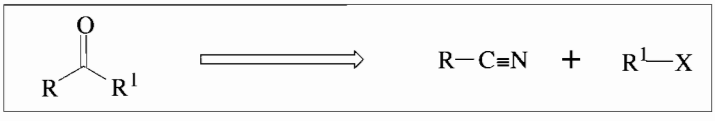
by the addition of the Grignard reagent derived from 4-bromo-1-butene to 3-methoxybenzonitrile. The initial reaction generates iminium salt **97**[111] and subsequent hydrolysis produced ketone **98**. When an alkyl nitrile reacts with a Grignard derived from an hindered alkyl halide, the yield of ketone is often poor, which is not always the case, however. Reaction of cyclopropanecarbonitrile (**99**) and isopropylmagnesium bromide gave > 80% of ketone **100** (R = *i*-Pr).[112] The intermediate iminium salt is not usually isolated since hydrolysis to the ketone is rapid. Hindered iminium salts can resist hydrolysis due to steric blocking of the imino carbon,

however, and vigorous exposure to aqueous acid can be required to give even modest yields[113] Reaction of **99** with *tert*-butylmagnesium bromide, followed by heating at reflux with 1 N HCl, gave only 35% of **100** (R = *t*-Bu).[112a]. Hindered nitriles often give no reaction at all when they are reacted with very hindered Grignard reagents. Reaction of *tert*-butylmagnesium chloride with cyanomethyl-2,4,6-trimethylbenzene, for example, gave 0% of the ketone.[114]

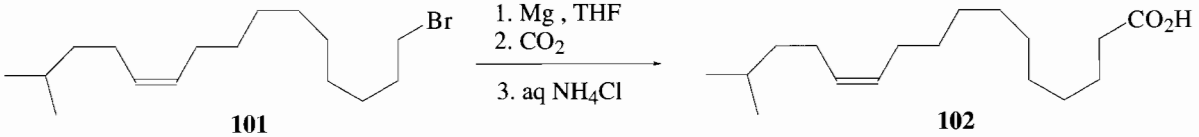


99 **100**

The disconnection for the nitrile-Grignard reagent reaction is:



8.4.C.iv. Reaction with Carbon Dioxide. Carbon dioxide (CO_2, O=C=O) is actually a carbonyl derivative and as such can react with a nucleophilic Grignard reagent.[115] The reaction product is a carboxylate salt that gives the acid upon hydrolysis.[116] Conversion of benzylmagnesium bromide to phenylacetic acid[117] is an example of this transformation. This functional group interchange of a halide to an acid proceeds with a one carbon extension of the chain. Carballeira and co-workers used this protocol in a synthesis of (*Z*)-15-methyl-hexadec-11-enoic acid, in which primary bromide **101** was converted to the corresponding Grignard reagent, reacted with carbon dioxide, and hydrolysis generated a 60% yield of the target **102**.[118]



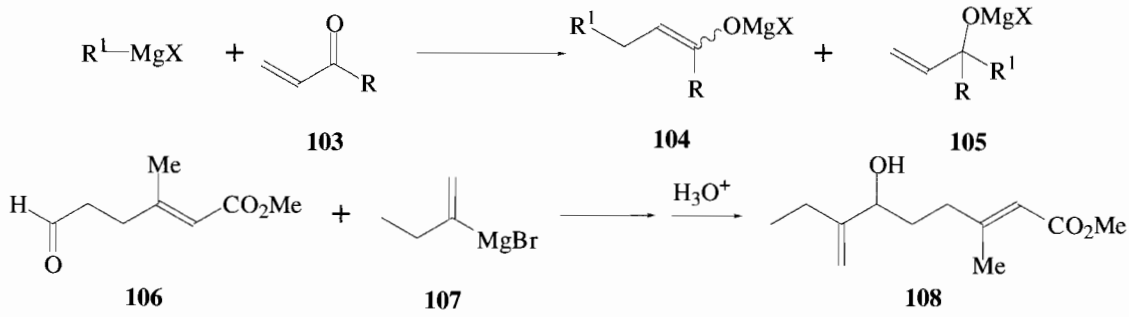
101 **102**

The disconnection for the carboxylation reaction is

8.4.D. Conjugate Addition

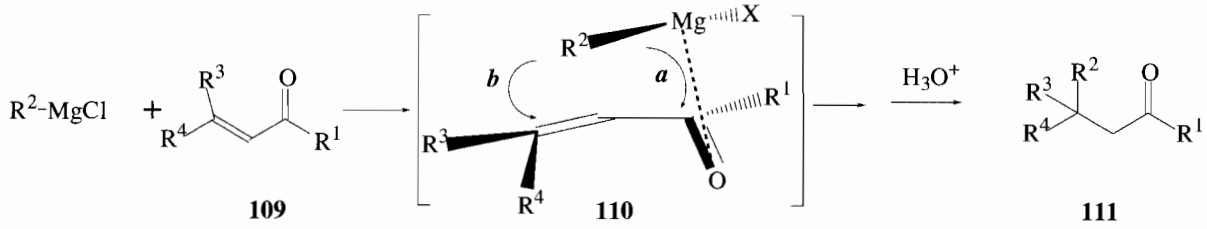
α,β-Unsaturated carbonyl derivatives have two reactive sites and nucleophilic addition of a Grignard reagent can occur at either the acyl carbon (1,2-addition) or the alkenyl carbon (1,4-addition). When a Grignard reagent reacts with a conjugated carbonyl such as **103**, the 1,4-addition product is an enolate anion (**104**–sec. 9.2). The 1,2-addition product is the usual alkoxide **105**. The course of this reaction varies with the steric bulk of R^1 in the Grignard and R in the carbonyl compound. As the size of R increases, the amount of 1,4-addition increases, although α,β-unsaturated aldehydes usually give only 1,2-addition.[119] Conversely, as the R^1 group of the Grignard increases in size, less conjugate addition is observed for a given R. The reaction of Grignard reagents with simple aldehydes and ketones is usually faster than conjugate addition with

unsaturated esters, which are somewhat less reactive than conjugated ketones. Aldehyde **106**, for example, reacted with vinyl Grignard **107** to give **108** rather than attacking the conjugated system.[120]



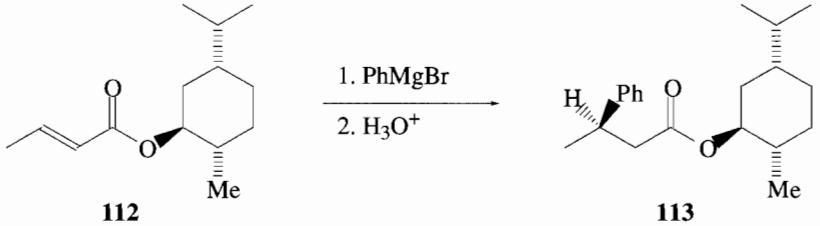
In Table 8.5[121] the influence of R^2 (from the Grignard reagent) and R^1 (attached to the carbonyl) on the percentage of conjugate addition is shown for reaction of alkyl Grignard reagents with **109**. It is noted that the phenyl group in **109** (R^3 = Ph, R^4 = H) has a significant influence on the reaction (see below), which proceeds by a six-center transition state (see **110**) to give the conjugate addition product, **111**. As R^1 in **109** becomes larger, attack at the carbonyl (path *a*) in a four-center transition state induces a large and destabilizing $R^2 \leftrightarrow R^1$ interaction leading to preferred attack at the end of the planar conjugated system (path *b*). When R^1 is small, R^2 is easily transferred to the carbonyl by the usual four-center transition state (path *a*).[123] Increasing the size of R^3or R^4 increases the magnitude of the $R^3(R^4) \leftrightarrow R^2$ interaction in the six-center transition state (path *b*), diminishing the amount of 1,4-addition. Removing the Lewis acid byproduct (MgX_2) facilitates formation of **110** with an increase in 1,4 addition product **111**.[123] When two electron–withdrawing groups are attached to the alkene moiety, conjugate addition is very facile. With alkylidene malonates and related compounds, virtually no 1,2-addition is observed.[122]

Table 8.5. Effect of Steric Hindrance on 1,4- vs. 1,2-Addition to α,β-Unsaturated Ketones



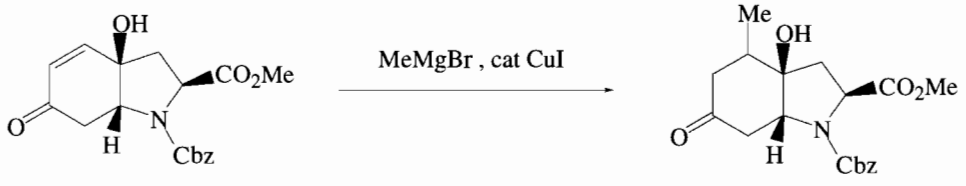
R^1	R	% 111
Me	*i*-Pr	50
Me	*t*-Bu	33
t-Bu	*i*-Pr	60
t-Bu	*t*-Bu	48
Ph	*i*-Pr	66
Ph	*t*-Bu	67
PhCH=CH—	*i*-Pr	70
PhCH=CH—	*t*-Bu	93

A similar transition state can be drawn for reaction of Grignard reagents and α,β-unsaturated esters, where steric hindrance in the ester moiety partially blocks the acyl carbon and leads to more 1,4-addition.[123] An example is the reaction of butylmagnesium bromide with *sec*-butylcrotonate to give *sec*-butyloctanoate.[124] Asymmetric induction is possible in these reactions, as illustrated by the reaction of the (–)-menthyl ester[125] of crotonic acid **112** to give the (*S*)-(+) enantiomer] of 3-phenyl derivative **113** in 46% yield.[126] Interestingly, addition of Cu_2Cl_2 to the reaction gave the (*R*)-(–) enantiomer.



112 **113**

In general, addition of cuprous [Cu(I)] salts to a Grignard facilitates conjugate addition, partly because a more highly reactive species (R_2MgCu or RCu) is formed, and partly because copper coordinates better to the carbonyl, which facilitates the six-center transition state. The organocuprates derived from organolithium reagents (R_2CuLi–sec. 8.7.A) are extremely useful in conjugate addition reactions. [127] Organocopper



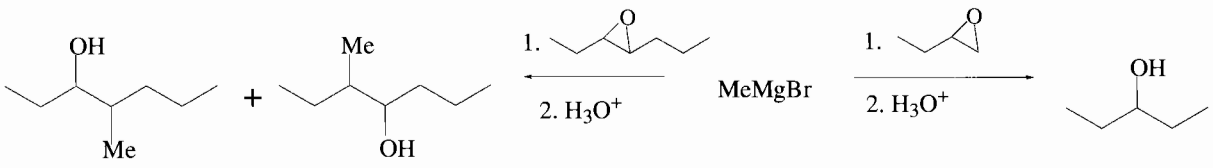
114 **115**

reagents derived from the reaction of a Grignard reagent with a cuprous salt, however, are also very useful. The reaction of methylmagnesium bromide with conjugated ketone **114** in the presence of a catalytic amount of cuprous iodide, for example, gave a 60% yield of the conjugate addition product **115** in Wipf's synthesis of the tuberstemonone ring system.[128] This example is typical in that cuprous salts generally lead to 1,4-addition, despite the usual propensity of conjugated aldehyde to give 1,2-addition with nucleophiles. A variety of conjugated carbonyl derivatives undergo 1,4-addition with Grignard reagents. Conjugate addition to α,β-unsaturated amides is known and proceeds with little variation from the results observed for conjugated ketones or esters.[129] As mentioned above, the organocuprates derived from lithium will be discussed in greater detail in Section 8.7.A.

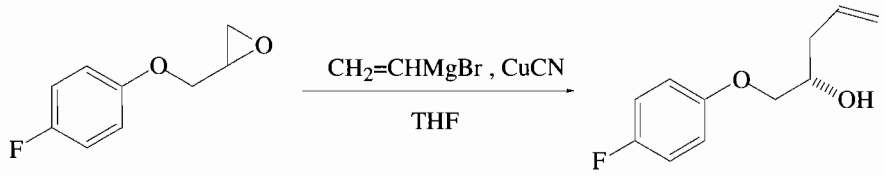
8.4.E. Reaction with Epoxides[130]

Grignard reagents react with epoxides to form a new carbon–carbon bond and open the three-membered ring, but there are two electrophilic carbon atoms. The final product after hydrolysis is an alcohol. The Grignard reagent attacks the less hindered carbon in an S_N2 like reaction.[131] If the carbons of the epoxide moiety are primary or secondary, attack can occur at either carbon leading to a mixture of alcohol products.

When 2-ethyloxirane reacts with methylmagnesium bromide, attack at the primary carbon gave 3-pentanol with only trace amounts of attack at the secondary carbon. When the epoxide has substituents that provide

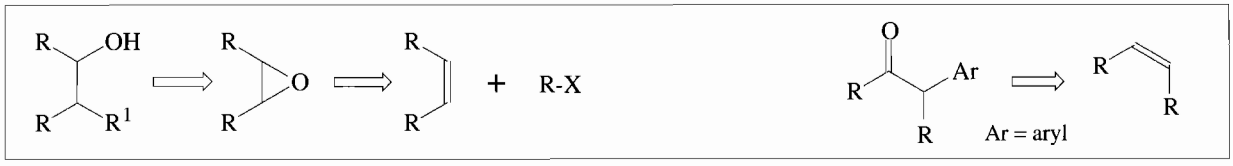


equal or close to equal steric hindrance at each carbon, as in 2-ethyl-3-propyloxirane the reaction produces a mixture of regioisomeric alcohol products. In this case, reaction of this epoxide and methylmagnesium bromide gave a mixture of 4-methyl-3-heptanol and 3-methyl-4-heptanol. When a Grignard reagent opens an epoxide, the new substituent is on the β-carbon, relative to the OH.



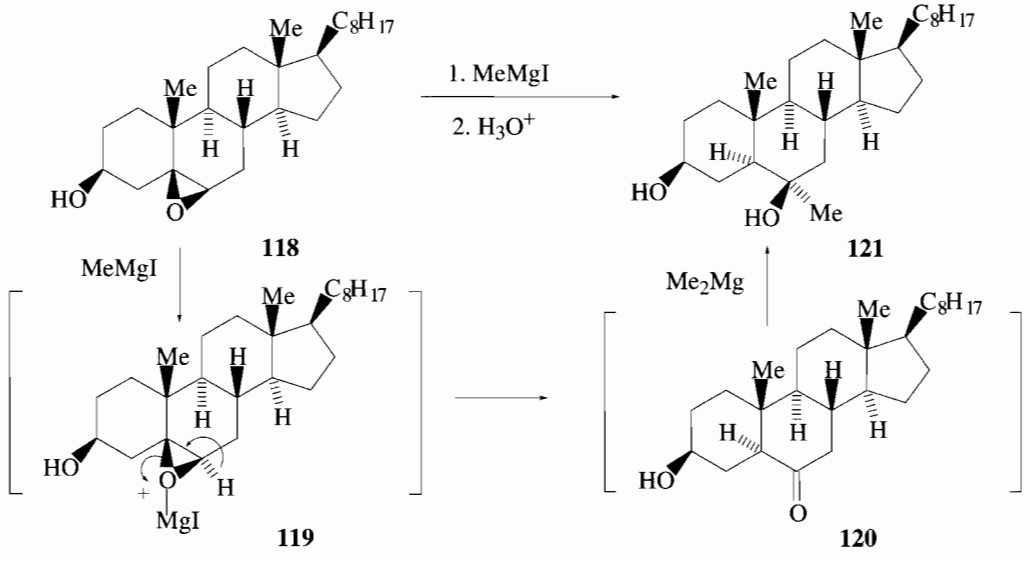
116 **117**

Metal salts such as cuprous ion promotes the ring opening reaction of epoxides, which is particularly useful for directing the incoming Grignard reagent to a particular carbon (to make the reaction more regioselective). An example is taken from Gurjar's synthesis of the antiasthmatic compound CMI-977, in which reaction of epoxide **116** with vinylmagnesium bromide and cuprous cyanide,[132] gave **117**. Note that the Grignard reagent added to the less substituted carbon. Synthetically, the Grignard–epoxide reaction is a very effective route to α-aryl ketones. Epoxidation of cyclohexene with *m*-chloroperoxybenzoic acid (sec. 3.4.B.iii) gave cyclohexene oxide. Reaction with phenylmagnesium bromide and hydrolysis led to 2-phenylcyclohexanol. Oxidation of the secondary alcohol moiety with chromium trioxide (or with another oxidizing agent as in sec. 3.2) gave the targeted 2-phenylcyclohexanone. This sequence generates the useful disconnections:

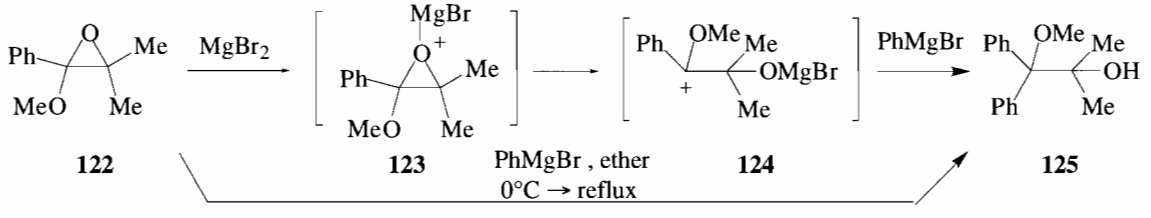


Looking back to the Schlenk equilibrium (see above), Grignard reagents contain the mild Lewis acid MgX_2 even if no other reagent is added. It is part of the reagent, and it can induce acid catalyzed rearrangements of acid-sensitive epoxides, complicating the normal product distribution. When 5,6β-epoxycholestane (**118**) was treated with methylmagnesium iodide, the product was 4aα-methyl-A-homo-β-norcho-lestan-4aβ-ol, **121**,[133] and it is explained by reaction of the epoxide with MgI_2 to give **119**. A 1,2-hydride shift (secs. 2.7.B.iii, sec. 12.2.B) generated ketone derivative **120**, and this reacted with additional methylmagnesium iodide to give the alcohol (**121**). The involvement of MgI_2 in the conversion of **118** to **121** was later substantiated by similar

reaction of a cholestan-3-one derivative with methylmagnesium iodide.[134] The yield was low, since cationic rearrangement was slower than nucleophilic attack in the aprotic solvent used for this Grignard reaction.



If the epoxide moiety is attached to a tertiary carbon, cationic rearrangements can lead to significant amounts of rearranged product. The cationic intermediate generated from the epoxide and MgX_2 does not

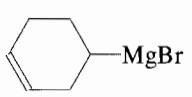


always rearrange to a ketone derivative, but can give S_N1 type reactions if a tertiary center is present. Reaction of phenylmagnesium bromide with epoxide **122**, for example, led to a coordination complex of the magnesium and oxygen in **123**. The oxonium salt opened to generate an oxygen-stabilized cation (**124**), which is particularly stable. When this intermediate reacted with the nucleophilic PhMgBr reagent, the product was the alcohol (**125**) (after hydrolysis).[135] It should be noted that in epoxy-ketones or epoxy-aldehydes, opening the epoxide ring is usually slower than addition to the carbonyl.[136]

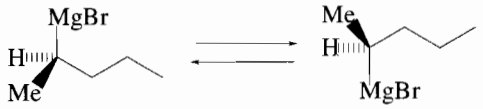
8.4.F. Selectivity in Grignard Reactions

8.4.F.i. Configurational Stability of Grignard Reagents. In principle, replacing a halogen with a MgX unit can generate a stereogenic center, and this has important stereochemical implications for any reaction. *When the C—Mg bond of a Grignard reagent is formed, however, the stereochemical integrity of that bond is poor*. For this reason, the generation and use of chiral Grignard reagents is ***not*** a synthetically useful option in most systems. The NMR studies by Roberts [137] and Fraenkel[138] on Grignard regents in ether established that the C—Mg has significant ionic character and undergoes rapid inversion at the magnesium-bearing carbon

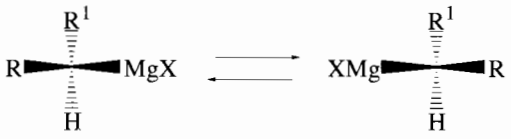
atom. 3-Cyclohexenylmagnesium bromide (**126**), for example, undergoes inversion of configuration at the C-Mg position. The rate of inversion decreased when the solvent was changed from ether to THF.[139] Fraenkel et al. also showed that 2-butylmagnesium bromide (**127**) undergoes rapid inversion at ordinary temperatures,[138,140] thereby making a Grignard reagent derived from chiral 2-butyl bromide effectively racemic.



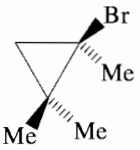
126



127

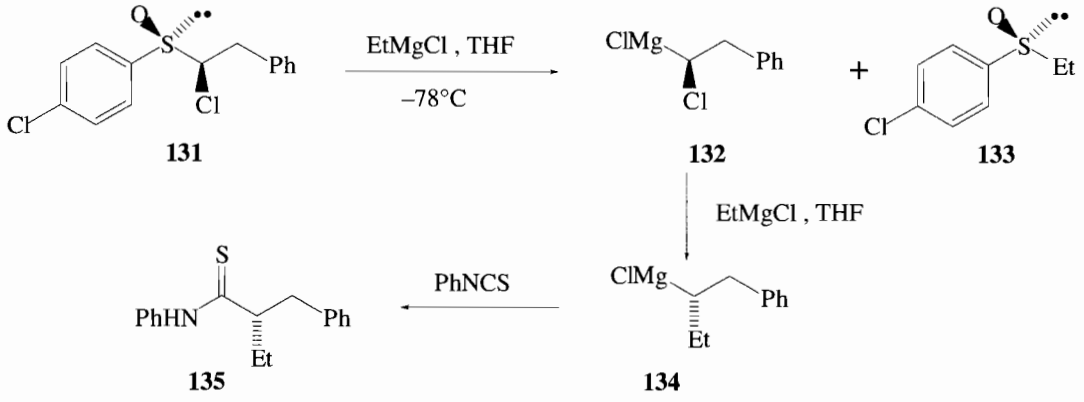


128 **129**



130

Since the carbon–magnesium bond is stereochemically unstable, the enantiomers generated from an asymmetric halide (**128** and **129**) are in rapid equilibrium (**128** ⇄ **129**)[141] suggesting that a Grignard derived from this halide will give racemic products. However, there are some exceptions to this configurational instability. Walborsky et al. reported that the Grignard reagent derived from **130** reacts with carbon dioxide to give the corresponding carboxylic acid. Formation of the Grignard and subsequent reaction proceeds with some retention of configuration, but with only 14% ee in 38% yield.[142] The % ee can be as high as 80%, however, when the reactions are carried out in ether.[142] Better selectivity is possible with menthol-based Grignard

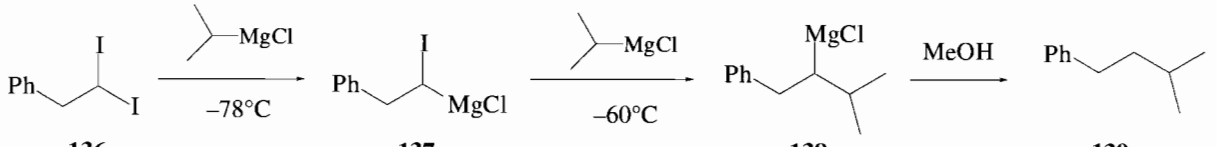


131 **132** **133**

135 **134**

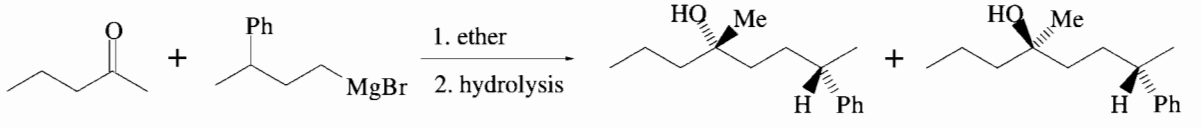
reagents.[143] Cyclopropyl derivatives tend to give better selectivity than acyclic or larger ring Grignard reagents. α-Halo-Grignard reagents have been shown to be excellent precursor to chiral Grignard reagents. Hoffmann showed that ethylmagnesium chloride reacted with α-halosulfoxide **131** to give **132**, along with sulfoxide **133**.[144] When **132** was treated with more ethylmagnesium chloride between –50 to –30°C, Grignard reagent **134** was formed in solution. When this reacted with phenylisothiocyanate, thioamide **135** was isolated in 56% yield and 83% ee. Hoffmann observed that racemization of the Grignard reagent **134** was slowest in the presence of chloride, an anion of low nucleophilicity.[145] The use of ethylmagnesium chloride was important because the reaction was least complicated by formation of a rearranged Grignard product.[146]

As just mentioned, certain Grignard reagents can rearrange. When an α-halo Grignard reagent is treated with another organometallic reagent (such as another Grignard reagent), a new Grignard reagent is generated by a carbon–carbon bond-forming reaction.[146] This appears to be a rearrangement product but actually arises by formation of a carbenoid species (sec. 13.8.D) that undergoes a C—H insertion reaction. Reaction of diiodide **136** with isopropylmagnesium chloride, for example, generates the iodo Grignard reagent **137** at –78°C. As this warms up, it reacts with additional isopropylmagnesium chloride to give **138**, and quenching with methanol gives the observed product **139**.[146] For most of the reactions listed in this section, this process should not be a major problem.



136 **137** **138** **139**

8.4.F.ii. Diastereoselectivity and Enantioselectivity. When a Grignard reagent reacts with unsymmetrical ketones or aldehydes (these will contain a prochiral carbonyl carbon), a new stereogenic center is produced. If another stereogenic center is present in either the Grignard reagent (but not at the carbon bearing the Mg) or the carbonyl substrate, diastereomers result. If 2-pentanone reacts with the Grignard reagent derived from 3-phenyl-1-bromobutane (**140**), the resulting alcohol will be a mixture of syn and anti diastereomers (**141** and **142**, respectively). Each diastereomer will be racemic. In light of the previous discussion, in Section 8.4.F.i., it may be possible for one diastereomer to predominate (the reaction would be diastereo-selective), but it should not be enantioselective.

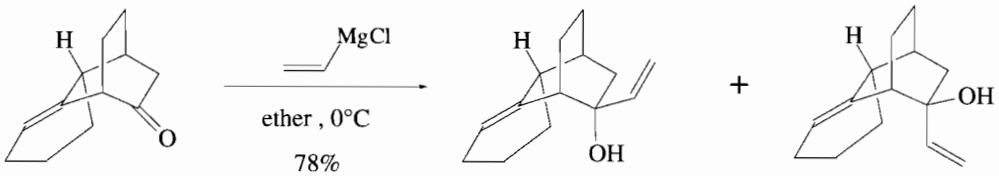


140 **141**-*syn (racemic)* **142**-*anti (racemic)*

The products formed from such a reaction can be organized into four categories that reflect four simple combinations of chiral and achiral Grignard reagents reacting with chiral or achiral carbonyl derivatives: (1) Mixing an achiral Grignard reagent and a carbonyl derivative that does not possess a substituent attached to a chiral center generates one new chiral center; (2) mixing a chiral Grignard reagent and a carbonyl derivative that does not possess a substituent attached to a chiral center generates diastereomers; (3) mixing an achiral Grignard reagent and a carbonyl derivative that has a substituent attached to a chiral center leads to diastereomers with possible diastereoselectivity; (4) mixing a chiral Grignard reagent with a carbonyl derivative that has a substituent attached to a chiral center will lead to good diastereoselectivity.

If there is steric bias in a molecule and if the addition of a Grignard reagent generates diastereomers, the products will be formed with good diastereoselectivity in many cases. The rationale for diastereoselectivity discussed for reduction in section 4.8 generally applies to reaction of Grignard reagents and carbonyl

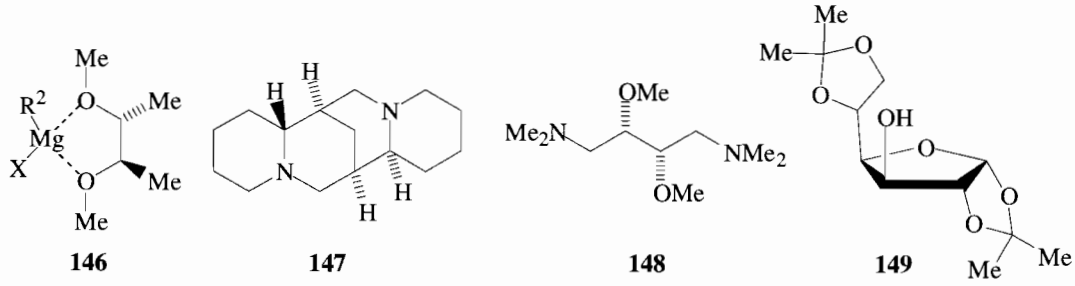
derivatives. Bicyclic ketones such as **143**, for example, are known to give products resulting from attack at the less hindered exo face (sec. 1.4.E). When this ketone reacted with vinylmagnesium chloride, a 7:1 mixture of **144/145** was formed in 78% yield. This example was taken from Hanna's synthetic studies directed toward vinigrol.[147] When the exo- face in a typical bicyclic system is blocked by substituents (as in seven-substituted bicyclo[2.2.1]heptan-2-ones), attack occurs via the endo ace.[148]



143 **144** **145**

Assuming that Grignard reagent addition to a carbonyl is a diastereoselective reaction that produces racemic products, it is important to ask if it is possible for the reaction to be enantioselective. If we rely on the carbon bearing the magnesium atom, the answer is no. If we incorporate a stereogenic center elsewhere in the molecule, however, the answer may be yes. For purposes of this discussion, the relative merits of the four cases listed above will be discussed.

Case 1 involves an achiral Grignard reagent reacting with a prochiral ketone to give a racemic alcohol. Some asymmetric induction[149] has been achieved by forming asymmetric complexes of the Grignard reagent with solvents such as (2*R*, 3*R*)-(+)-dimethoxybutane.[150] The two oxygens of this chiral ether coordinate with the Grignard reagent to form a monomeric species such as **146**.[141] In **146,** the magnesium becomes asymmetric by its coordination with the oxygens and reaction with a prochiral ketone will generate an diastereomeric transition state for the acyl addition.[141] If the reaction is diastereomeric in the transition state, an excess of one enantiomer will result. Since R^2 in **146** is actually the equilibrium mixture **128** and **129**, complex **146** represents four stereochemically distinct solvated species, not necessarily present in equal amounts, and each can react with a prochiral substrate at different rates.[141] The extent of induced stereoselectivity is generally low, perhaps 2–3%,[141] even in an asymmetric solvent. When phenylmagnesium bromide reacted with 2-octanone in the optically active solvent 2-methyltetrahydrofuran, 2-phenyl-2-octanol was formed in only 11–18% ee.[151]

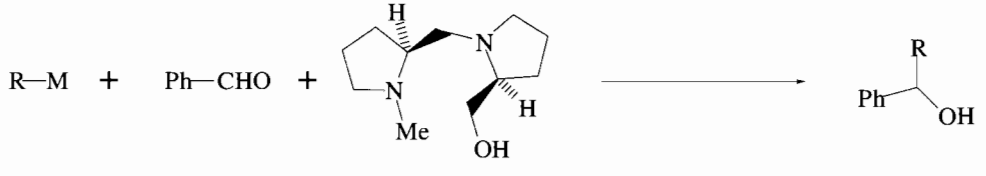


146 **147** **148** **149**

In some cases, it is possible to form a chiral, nonracemic alcohol from a prochiral ketone and a Grignard reagent by adding an asymmetric ligand (a chiral additive) to the reaction mixture, which is differentiated from

the reaction of Grignard reagent with a carbonyl species that has a stereogenic center present in the same molecule (case 3 above—a Cram's rule type system —see sec. 4.8.B for a discussion of Cram's rule). Presumably, the Grignard reagent forms a chiral complex with these additives, promoting facial selectivity in the addition reaction with the carbonyl. In work by Nozaki, addition of (–)-sparteine (**147**) to the reaction of ethylmagnesium bromide and benzaldehyde gave (*R*)-(+)-1-phenyl-1-propanol in 15% yield and 22% ee.[152] Under the same conditions reaction with acetophenone gave racemic 2-phenyl-2-butanol in 11%. Seebach showed that addition of **148** to benzaldehyde gave 1-phenyl-1-propanol in 6-8% ee.[153] Inch et al. added furanose **149**[154] to a mixture of methylmagnesium bromide and 1-phenyl-1-heptanone and found a 95% yield of (*R*)-(+)-2-phenyl-2-octanol with 70% ee. Under similar conditions, however, ethylmagnesium bromide reacted with acetophenone to give a 48% yield of (*S*)-(–)-2-phenyl-2-butanol with 27% ee.[154] Chiral amino alcohols were used as additives by Battioni and Chodkiewicz but gave optical yields of only 0–20%.[155] Mukaiyama obtained good results with the chiral ligand **150** in reactions of organolithium reagents, dialkylmagnesium reagents, and Grignard reagents with benzaldehyde, as shown in Table 8.6.[156] The optical yields of alcohol **151** when **150** was added to the reaction are dependent on both the solvent and the temperature of the reaction. In case (2), the chiral center of the Grignard might be expected to give some selectivity for the syn or anti diastereomeric product. The configurational instability of the C-Mg bond[139-141] at the putative stereogenic carbon, however, leads to an equilibrating mixture that is effectively a chiral, racemic Grignard reagent, with poor syn–anti selectivity in the diastereomeric alcohol mixture.

Table 8.6. Asymmetric Induction in Organometallic Reactions of Benzaldehyde in the Presence of 150



150 **151**

RM	Solvent	Temp °C	% 151	% ee
n-BuCu	Ether	–78	22	0
Et_2Zn	Ether	–78	76	0
n-BuMgBr	Ether	–78	90	47 (*R*+)
n-Bu_2Mg	Ether	–78	93	68 (*R*+)
n-Bu_2Mg	Ether	–123	89	73 (*R*+)
n-Bu_2Mg	MeOMe	–123	84	43 (*R*+)
n-Bu_2Mg	THF	–110	91	59 (*R*+)
n-Bu_2Mg	DMM	–78	87	51 (*R*+)
n-Bu_2Mg	DME	–78	96	28 (*R*+)
n-Bu_2Mg	PhMe	–78	93	60 (*R*+)
n-Bu_2Mg	PhMe	–110	94	88 (*R*+)

DMM = dimethoxymethane DME = dimethoxyethane

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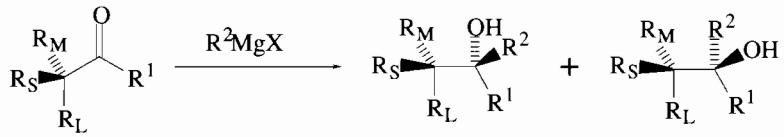
If the carbonyl partner contains a chiral carbon, as in case (3), the asymmetry of that center should exert an influence when the Grignard reagent reacts with the prochiral carbonyl (the faces of the carbonyl are diastereotopic), leading to some diastereoselectivity in the alcohol product. This is the system that formed the basis of the Cram model,[157] the Cornforth model,[158] the Felkin-Ahn model[159] and the Karabatsos model,[160] all discussed in Section 4.8.B. In general, addition of Grignard reagents to a prochiral carbonyl, where the α- or β- carbons are chiral, are best predicted by the Cram model, the Cram chelation model, or the Felkin-Ahn model. The presence of a chiral center in one of the reactive partners induces facial bias on approach of the two reagents, leading to moderate to good diastereoselection for either the syn or the anti isomer. Examples taken from Mosher and Morrison's compilation are shown in Table 8.7,[161] and they show that Cram's open chain model predicts the diastereoselectivity of Case (3) reactions. In Table 8.7, ketone **152** reacted with various Grignard reagents (R^2MgX) to give a mixture of diastereomeric alcohols, **153** and **154**.

Table 8.7. Cram Selectivity for Carbonyls with an Adjacent Stereogenic center (152)



152 **153** **154**

R_S	R_M	R_L	R^1	R^2	X	153/154
H	Me	Ph	H	Me	Br	2.4:1
				Me	I	2.0:1
				Et	Br	3.0:1
				Ph	Br	>4.0:1
H	*i*-Pr	Ph	H	*i*-Pr	Br	1.9:1
Me	Et	Ph	H	Ph	Br	2.9:1
H	Et	Ph	H	Me	I	2.5:1
				Et	Br	3.0:1
H	Me	Et	H	Me	Br	1.5:1
H	Me	Et	Me	*i*-$PrCH_2$	Br	1.8:1

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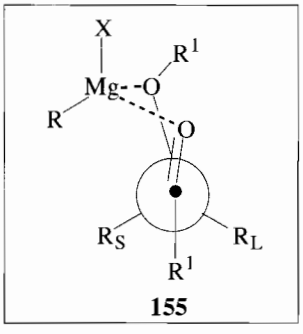
As discussed in Chapter 4, the Cornforth dipolar model (sec. 4.7.B) is the best one for predicting the stereoselectivity for α-chloroketones, and the Cram cyclic (chelation) model (**155**)[162] is preferred for ketones with heteroatoms in the α-position. The chelation model is very common in Grignard reactions and it assumes that the magnesium of the Grignard is coordinated to both the heteroatom and the carbonyl oxygen, as shown in **155**. For this reason, coordination of an organometallic with carbonyls that have a heteroatom in the α- and β- positions has been termed **chelation control** when it results in formation of products with high diastereoselectivity.[163] Part of this model assumes that the incoming group in **155** (R attached to magnesium) is delivered from the less hindered face (over the smallest group, R_S). In this model, the R^1 group could be H

or alkyl. An example of chelation control is the reaction of α-benzyloxy ketone (**156**) with vinylmagnesium bromide, a key step in Williams' synthesis of (±)-citreoviridin.[164] In this case, diastereomer **158** was formed exclusively and the chelated intermediate (**157**) correctly predicts the observed stereochemistry.



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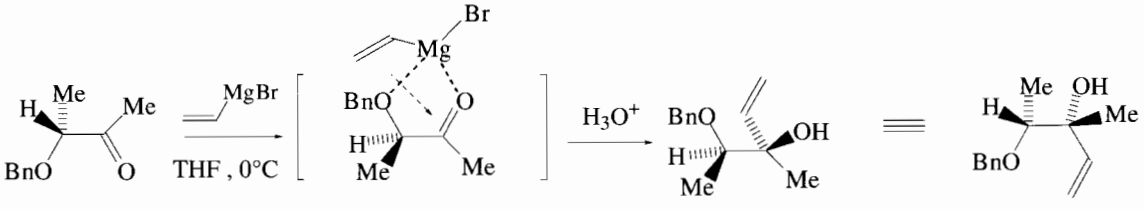


156 **157** **158**

Case 4 (see above]) should give the best diastereoselectivity. The instability of the C—Mg bond, however, leads to the same poor diastereoselectivity for the carbon bearing the magnesium, as observed in case 2. The chiral center on the carbonyl substrate remains intact, and it influences the reaction, leading to good diastereoselectivity in the alcohol product upon reaction with a prochiral carbonyl derivative (for all practical purposes, this is a case 3 situation except that there is loss of diastereoselectivity due to the inability to control the configuration of the stereogenic center in the Grignard reagent).

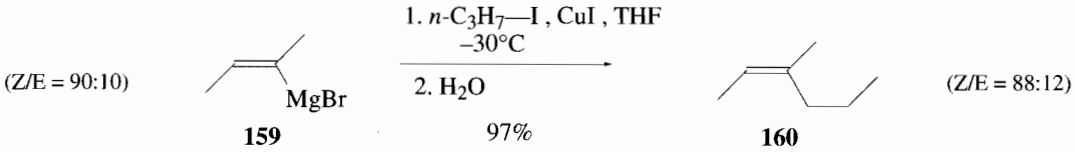
8.4.F.iii. Stereochemical Integrity of Alkenyl Grignard Reagents. A different stereochemical problem arises when vinylmagnesium halides are formed from alkenyl halides. Both (*E*) and (*Z*) isomers can be formed. Reaction of stereochemically pure (*E*) or (*Z*) alkenyl halides with magnesium gave a mixture of (*E*) and (*Z*) vinyl Grignard reagents.[165] Subsequent reaction with carbonyl derivatives reflect this (*E*/(*Z*) mixture in the final products. Martin et al. reported that reaction of pure (*E*)- or (*Z*)-1-bromo-1-alkenes with magnesium metal and then with CO_2 gave stereospecific conversion to the corresponding acid. Although (*E*) halide gave mainly the (*E*) product, this is *misleading*. In fact, severe loss of stereochemical integrity was observed and a mixture of both (*E*) and (*Z*) isomers was always obtained, as in Table 8.8.[166] It is important to note that there are significant differences between the stereochemical ratio of the Grignard reagent and that of the acid product. Table 8.8 shows a comparison of bromopropenes and bromohexenes, where loss of stereochemical integrity is more pronounced in the longer chain alkenes. In addition, greater loss of stereochemical integrity is apparent when these longer chain Grignard reagents react with the electrophile

(CO_2). A partial solution to this problem is reaction of the vinyl Grignard reagent with alkyl halides in the presence of cuprous iodide [Cu(I)I], which does little for the initial loss of stereochemistry upon formation of

Table 8.8. Stereoselectivity in the Formation of Grignard Reagents from Stereochemically Pure Vinyl Halides and Subsequent Reaction with CO_2

Halide	(*Z*/*E*)	RMgBr (*Z*/*E*)	RCOOH (*Z*/*E*)
(*Z*)-1-Bromo-1-propene	98.5:1	80–90:20–10	85–95:undetected
(*E*)-1-Bromo-1-propene	5:95	30–40:70–60	15–5:85–95
(*Z*)-1-Bromo-1-hexene	97:1	75–85:25–15	45–55:55–45
(*E*)-1-Bromo-1-hexene	1:99	40–50:60–80	35–45:65–55

the Grignard, but in subsequent reactions, greater retention of stereochemistry is observed.[167] An example is the reaction of **159** with iodopropane in the presence of cuprous iodide, giving a 97% yield of **160**. The original 90:10 (*Z*/*E*) mixture in **159** was retained (88:12 *Z*/*E*) in the final product **160**.



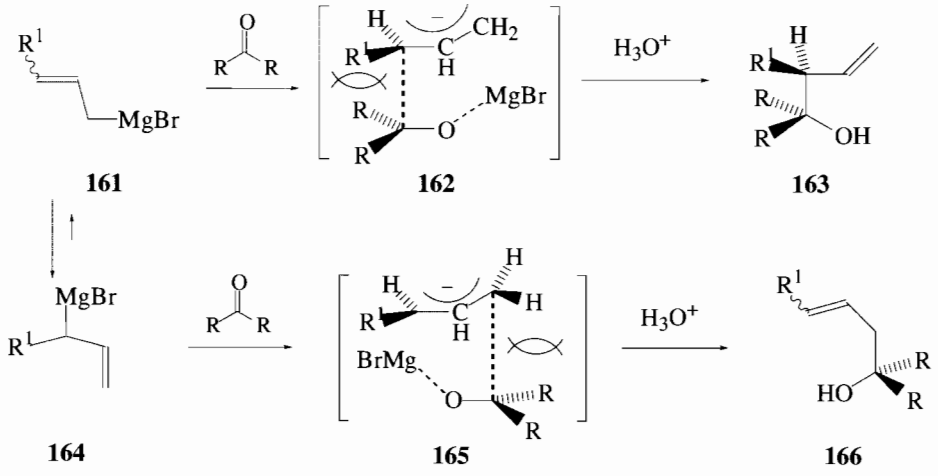
Another problem arises with allylic Grignard reagents. When the magnesium halides derived from (*E*)-1-bromo-2-butene were quenched with water (see Table 8.9),[168] the double bond had isomerized and the products were a mixture of 1-butene, (*Z*)-2-butene, and (*E*)-2-butene. This allylic rearrangement is well known[169] in reactions of Grignard reagents. Increasing the solvating power of the solvent, as in changing from diethyl ether to THF, increased the lability of the C—Mg bond and gave more racemization.

Table. 8.9. Isomerization of Crotylmagnesium Halides

		Isomerization (%)		
Crotyl Mg(X)	Solvent	1-Butene	(*Z*)-2-Butene	(*E*)-2-Butene
Br	Ether	75	11	14
Cl	Ether	80	9	11
I	Ether	80	10	10
Cl	THF	60	15	25
I	THF	55	20	25

Reaction of an allylic magnesium halide with an electrophile can give a new bond at either carbon of the allylic carbanion, with two possible isomeric products.[170] Felkin and co-workers described the reaction with

ketones as a non-cyclic S_E2' rearrangement and it is sensitive to steric encumbrance at the carbonyl carbon.[171] Allylic Grignard **161**, when generated from either the (*E*)- or the (*Z*)- bromide, forms an equilibrating mixture (**161** and **164**). When this mixture of Grignard reagents reacts with a ketone (via **162** and **165**, respectively), the isomeric alcohols **163** and **166** are formed. Increasing the steric bulk of R^1 and R destabilizes **162** relative to **165**, favoring **166** over **163**. The 2-butenyl derivative (R^1 = Me) reacted primarily as the crotyl derivative (**161**),[172] but this was in equilibrium with a small amount of **164**.[173]

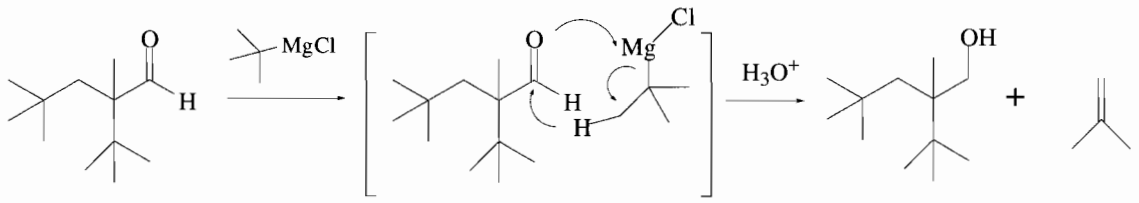


When **161/164** reacted with aldehydes[174] or unhindered ketones,[175] α-methallyl alcohol **163** was formed (**166/163** ratio is < 0.01). With diisopropyl ketone (R = *i*-Pr) the **166/163** ratio was 0.5[176] and with di-*tert*-butyl ketone **166** was the major product.[176a,177] *tert*-Butylalkylmagnesium bromide (R^1 = *t*-Bu)[172] increased the strain in **162** to the extent that even the unhindered substrate acetone gave predominantly **166** (R = Me), although similar reaction with acetaldehyde gave only **163** (**166/163** ratio is <0.01). In all cases **166** was isolated predominantly as the (*E*) isomer [(*E*/*Z*) ratio is > 20:1]. Cyclic ketones such as cyclopentanone showed the greatest selectivity for **166** [cyclopentanone: **166:163** = 65:1, R = R^1 = —$(CH_2)_4$—] and cyclohexanone gave a 3:1 ratio (R=R^1 = —$(CH_2)_5$—). Miginiac, Prévost and co-workers noted that 1-bromo-2-pentene reacted with magnesium and various electrophiles to give primarily the 3-alkyl derivatives.[178] A minor side reaction is sometimes observed when attempting to prepare the Grignard reagent of an ω-haloalkene. The Grignard reagent derived from reaction of 6-bromo-1-hexene and magnesium gave ≈ 5% of 1-methylcyclopentane via addition of the Grignard reagent to the alkene double bond.[179] The analogous organolithium reagents can give excellent yields of cyclization under similar conditions (RX + Li°), as discussed in Section 8.5.F.ii.

8.4.G. Reduction, Organocerium Reagents, and Enolization

8.4.G.i. Reduction. Although Grignard reagents react with ketones and aldehydes to give alcohols in good yield, there are some side reactions that can compete with the normal reactions including reduction and enolization. Reduction of carbonyl compounds is most common when both the carbonyl unit and the magnesium-bearing carbon of the Grignard reagent are sterically hindered.[180] Reaction of **167** with *tert*-

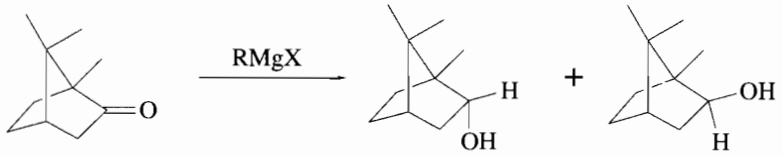
butylmagnesium chloride, for example, gave >90% of the reduction product, alcohol **169**, with none of the carbonyl addition product.[181] In order for reduction to occur, however, the Grignard must possess a β-hydrogen. This is similar to the transition state observed in the **Meerwein–Ponndorf–Verley reduction**[182] (sec. 4.10.J) and the **Oppenauer oxidation** (sec. 3.2.E). Magnesium easily coordinates with the carbonyl oxygen, leading to a complex such as **168** where hydrogen transfer gives the alcohol **169**. Elimination of H and MgX from the Grignard leads to an alkene (in this case isobutylene). Hamelin[181b] showed that even an unhindered aldehyde such as propanal can be reduced with a small Grignard reagent such as ethylmagnesium



167 **168** **169**

bromide. A Grignard reaction between hindered ketones and aldehydes often leads to reduction as a synthetically useful process. Camphor (**170**) can be reduced to borneol (**171**) and isoborneol (**172**) upon reaction with Grignard reagents, with some selectivity for isoborneol as seen in Table 8.10.[183]

Table 8.10. Reduction of Camphor with Grignard Reagents.

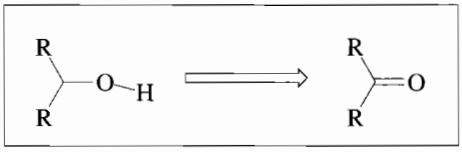


170 **171** **172**

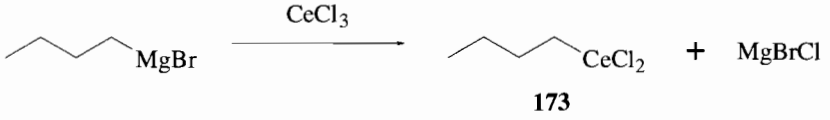
RMgX	% 171	% 172
EtMgBr	35	29
i-PrMgBr	45	45
n-PrMgBr	34	48
$Et_2CHMgBr$	29	55

When chiral Grignard reagents and asymmetric solvents are employed, varying degrees of asymmetric induction can be achieved in the reduction process.[184] In most cases, the % ee for reduction is small. Nasipuri and coworkers[185] described the asymmetric reduction of phenylalkyl ketones.[186] A cyclic model[187] and an acyclic model[188] were proposed. Asymmetric induction was higher with phenylalkyl ketones than with cyclohexylalkyl ketones or *tert*-butylalkyl ketones.[189]

Since the Grignard reduction can be used synthetically, the appropriate functional group transform is

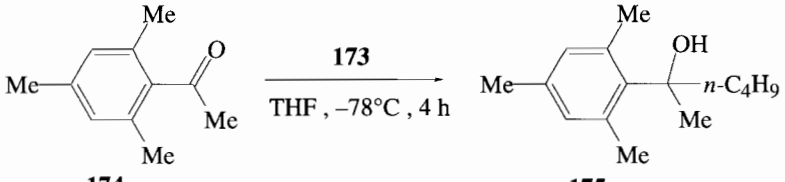


8.4.G.ii. Organocerium Reagents. Reduction in Grignard reactions of hindered ketones can severely limit a carbonyl alkylation reaction. This limitation can be circumvented, however, by the converting the Grignard



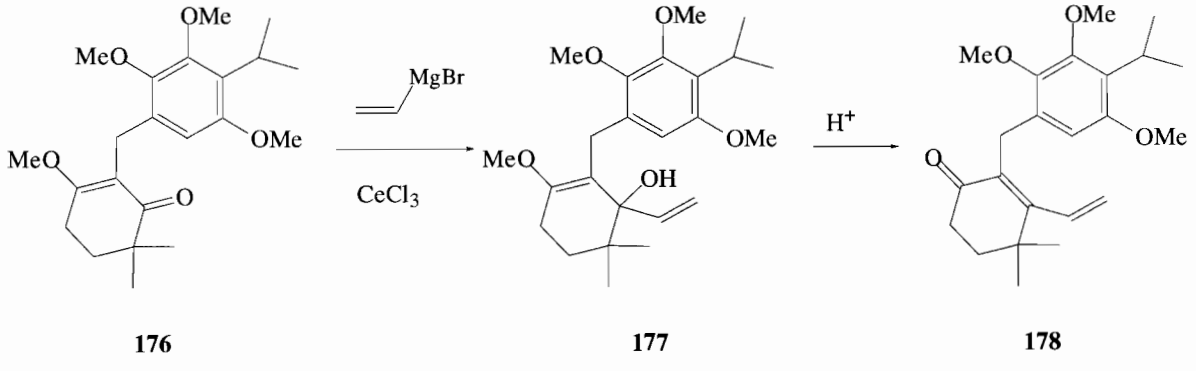
173

reagent to an organocerium reagent. Imamoto and coworkers showed that methyl mesityl ketone (**174**) gave only 10% of the acyl addition product (**175**) upon reaction with butylmagnesium bromide.[190] A mixture of butylmagnesium bromide and cerium chloride ($CeCl_3$), however, gave organocerium **173** and a 57% yield of **175**.[190] A synthetic example using an organocerium reagent is taken from Majetich's synthesis of perovskone,

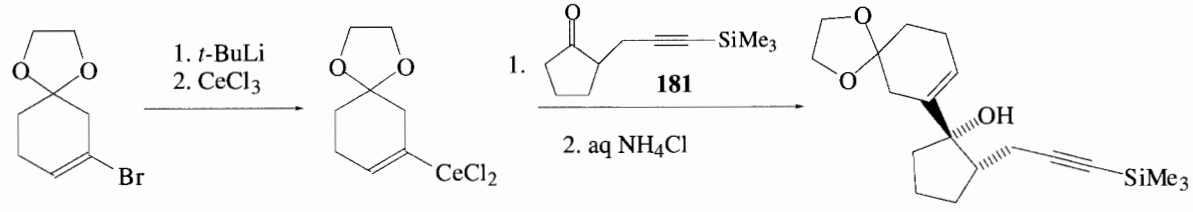


174 **175**

in which sterically hindered ketone **176** reacted with the organocerium reagent derived from vinylmagnesium bromide to give the 1,2-addition product **177**.[191] In this example, mild acid hydrolysis led to elimination of water and formation of the extended conjugated ketone **178** in an overall yield of 90%.



176 **177** **178**

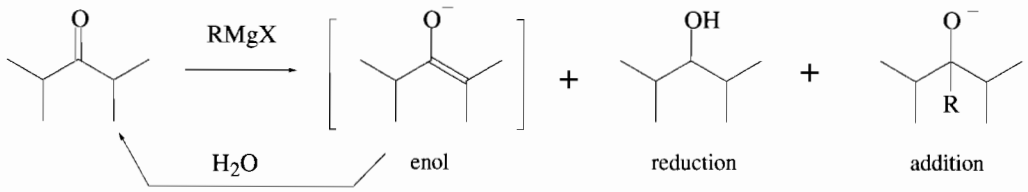


179 **180** **182**

Organolithium reagents (sec. 8.5) are also useful precursors. Vinylcerium reagent **180** was prepared from vinyl bromide **179** in Ovaska's synthesis of fused polycyclic ring systems.[192] When this reacted with **181**, alcohol **182** was isolated in 61% yield after hydrolysis.

8.4.G.iii. Enolization. Aldehydes and ketones have acidic protons on the α-carbon, which can be removed by the basic Grignard reagent to generate an enolate anion (sec. 9.2.A). Formation of the enolate anion can sometimes compete with nucleophilic addition to the carbonyl. If there are no secondary reactions, hydrolysis of the enolate product regenerates the starting ketone and the net result is unreacted starting material. Nucleophilic addition to the carbonyl is usually faster than deprotonation, but small amounts of enolization can be observed as shown in Table 8.11.[193] With unhindered Grignard reagents, enolate anion formation is insignificant and reduction is the major reaction that competes with nucleophilic addition. With the hindered isopropylmagnesium halide, steric interactions completely suppressed addition, and reduction accounted for 69% of products, with only 2% enolization. Similar reactivity was observed by Hamelin in reactions with ethylmagnesium bromide,[194] in which the effect of solvent and temperature on reduction and enolization was probed. Increasing the size of the groups attached to the carbonyl increased the amount of reduction but only slightly increased the amount of enolization. Increasing the size of the group attached to magnesium, in the presence of a hindered carbonyl derivative, greatly increases the amount of enolate that is formed.

Table 8.11. Competition for Nucleophilic Addition, Reduction, and Enolate Formation in Reactions of Diisopropyl Ketone with Grignard Reagents



RMgX	RMgX/Ketone	% Enolate	% Reduction	% Addition
EtMgBr	1.3	1	21	78
	1.5	1	19	80
	2.5	1	15	80
	1.2	2	21	77
n-PrMgCl	1.2	2	51	46
	2.5	1	37	62
n-PrMgBr	1.2	1	64	35
	1.4	2	60	36
n-PrMgI	1.2	2	69	30
i-PrMgCl	1.2	28	72	0
i-PrMgBr	1.2	29	65	0
	1.4	30	65	0
i-PrMgI	1.4	30	70	0

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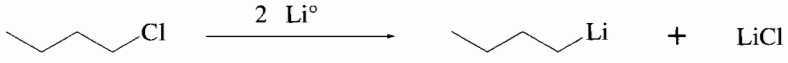
8.5. ORGANOLITHIUM REAGENTS (C—Li)

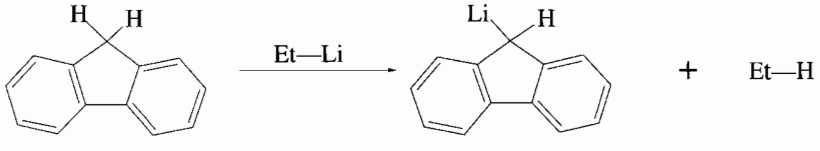
Grignard reagents are clearly important in synthesis. If MgX is replaced with Li, another class of organometallic reagents is available, the organolithium reagents. These are also potent nucleophiles and they are more basic than Grignard reagents. Both of these features can be exploited in synthesis.

8.5.A. Preparation, Structure, and Stability

Organolithium reagents, characterized by a C—Li bond, are as important in organic synthesis as the Grignard reagents. Lithium is less electronegative than carbon, and the carbon of the C—Li bond is polarized δ–, as in Grignard reagents.[195] Organolithium reagents are expected to behave both as a nucleophile and as a base. It is important to understand the chemical properties of organolithium reagents and note differences with Grignard reagents before discussing their reactions.[196]



Ethyllithium was discovered by Schlenk and Holtz in 1917,[197] but it was not until 1930 that Ziegler and Colonius[198] discovered that organolithium reagents could be prepared by direct reaction of lithium metal and an alkyl halide,[199] as in the reaction of lithium and chlorobutane to give *n*-butyllithium ($CH_3CH_2CH_2CH_2Li$, abbreviated as BuLi) shown above. Two years prior to this work, Schlenk and Bergmann had reported that ethyllithium (CH_3CH_2Li, abbreviated as EtLi) reacted with fluorene (**183**) with exchange of the acidic hydrogen with Li to give fluorenyllithium (**184**).[200] These two reactions describe the main methods for preparing organolithium reagents and the latter also describes the most useful synthetic application—removal of an acidic hydrogen to generate a new organolithium species.



183 **184**

Organolithium reagents are usually written as R—Li but this does not begin to describe their actual structure.[196,199,201] Some physical data suggest that the C—Li bond in an organolithium is highly covalent.[199] It is known that organolithium reagents exist as associated aggregates, due in part to this covalent character. Both methyllithium[202] and ethyllithium[203] have been obtained in crystalline form and their crystal structure determined by X-ray crystallography. The structure in Figure 8.1[204] is that of crystalline isopropyllithium reported by Siemeling, which exists as a hexamer, $(i\text{-PrLi})_6$.

Methyllithium and ethyllithium are tetrameric in the solid state,[203,205] and most organolithium reagents are highly associated in solution as well.[195,196] The degree of association is related to the solvent and structure of the organolithium, but tends to be higher for straight-chain than for branched (secondary and tertiary)

organolithium reagents. The extent of association of the organolithium is important since it can affect the rate of metal–halogen or metal–hydrogen exchange as well as the product distribution. Table 8.12[199,206,201a] shows the degree of association of several common organolithium reagents in various solvents, which decreases

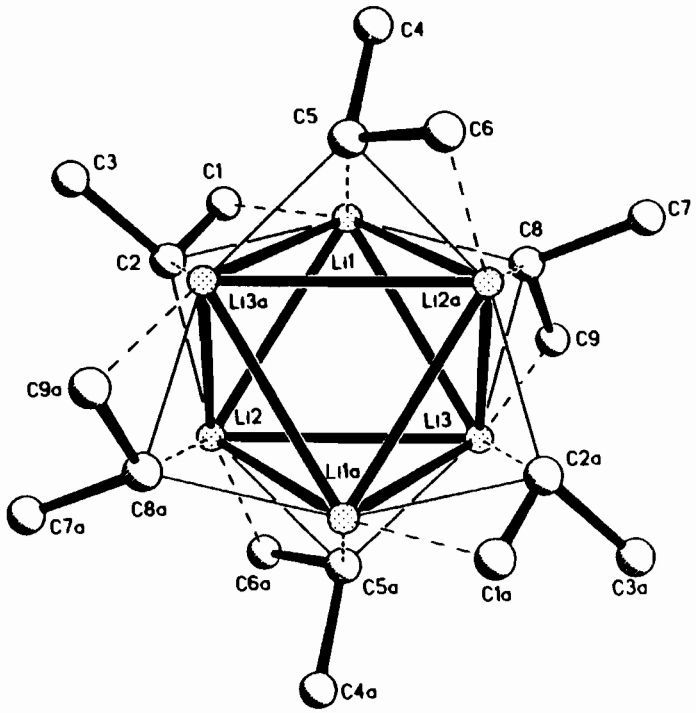


Figure 8.1. X-ray crystal structure of isopropyllithium.

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Table 8.12. Association of Organolithium Reagents in Common Solvents

$$\text{R-Li} \longrightarrow (\text{R-Li})_n$$

R	Solvent	n
Et	Cyclohexane	6
	Hexane	6
	Et_2O	2
	Benzene	6,2
n-Bu	Cyclohexane	6
	Benzene	6,2
	Et_2O	6
n-Bu + TMEDA	Hexane	1
t-Bu	Hexane	4
	Benzene	4
Ph	Et_2O	2

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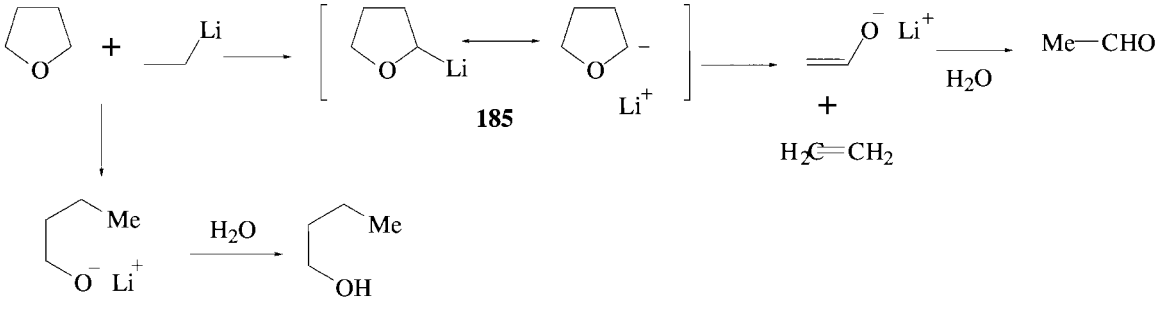
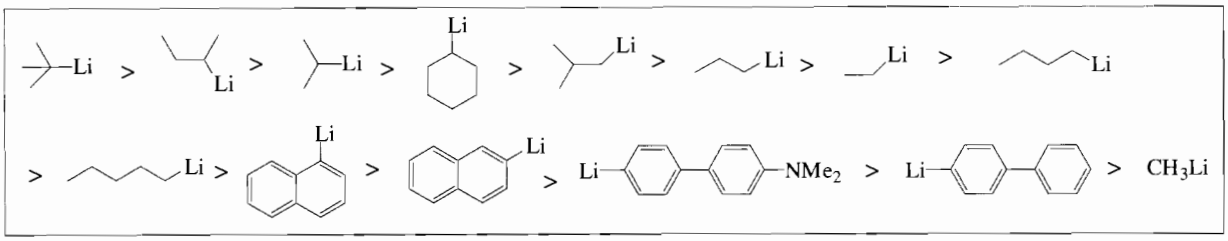
as the coordinating ability of the solvent increases. This can loosely be compared with increasing solvent polarity. The most commonly used solvents are ether, THF, pentane, and hexane.[207] This increased solvation reduces the ability of the organolithium reagent to associate and thereby form solvated oligomers.[207] Williard has determined the X-ray structures of butyllithium–TMEDA, –THF, and –DME complexes. and shown that they are tetramers.[208] Complexing also increases the ionic character of the relatively covalent C—Li bond, lowering the energy requirements for the transition state leading to reactions.[209]

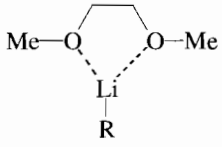
Although ethers are attractive solvents for reactions of organolithium reagents, they also react with them. They are Lewis bases and coordinate to lithium, stabilizing the organometallic and participating subsequent reactions, although the ether fragment does not appear in the final product in most cases.[210,195] Organolithium reagents are basic, removing the α-hydrogen of an ether via Li—H exchange (acid–base reaction). Disproportionation of the lithio-ether derivative (**185**) generates an alkoxide and an alkene when tetrahydrofuran is the solvent.[211] The acidity of the α-proton varies with the ether and the organolithium reagent. It is not surprising, therefore, that organolithium reagents have different stabilities in different solvents. The half-life of *n*-butyllithium in diethyl ether at 25°C is 153 h., whereas that of ethyllithium is 54 h and that of cyclohexyllithium is 30 min.[212] This stability to reaction of *n*-butyllithium can be used as an approximate



reaction order for Li—H exchange. Primary organolithium reagents exhibit better stability (they are less reactive than the secondary or tertiary reagents). It has also been determined that *n*-butyllithium decomposes in THF in 2 h at 25°C.[213] Its stability can be increased by the addition of a less acidic co-solvent such as diethyl ether or tetrahydropyran (THP). Solutions of *n*-butyllithium are stable for 24 h. in an ether-THF mixture and up to 1 week in an ether-THP solution.[213] Addition of a hydrocarbon co-solvent such as pentane, hexane or cyclohexane to the ether also extends the lifetime of the organolithium reagent. Lowering the temperature of the reaction from 25 to 0 or to –78°C significantly reduces the rate of the cleavage reaction, extending the lifetime of the organolithium in solution, and as noted above the solvent plays a critical role. In DME, the half-life of *tert*-butyllithium is 11 minutes at -70°C but <2 minutes at -40°C, whereas in THF the half life is 338 minutes at -40°C and only 42 minutes at --20°C.[214] In THF, *n*-butyllithium has a half life of 1039 minutes at 0°C but only 38 minutes at 20°C, and in DME at –20°C the half life is 11 minutes. In ether, however, *n*-butyllithium has a half life of 9180 minutes (153 hours) at 20°C and 1860 minutes (31 hours) at the reflux temperature of 35°C.[214] The general reactivity of organolithium reagents in cleavage reactions of diethyl ether via Li—H exchange is[215]



The reactivity of organolithium reagents in ethers can be increased by addition of a Lewis base that is stronger than diethyl ether or THF. When dimethoxyethane is used as a solvent, for example, the reactivity is greatly increased.[216] The two oxygens in dimethoxyethane coordinate to the lithium of the organolithium reagent and generate what is essentially a monomeric organolithium species (**186**). Such coordination may also increase the polarity of the C—Li bond and thereby the carbanionic character. Similar effects are observed when stoichiometric amounts of nitrogen bases such as DABCO (1,4-diazabicyclo[2.2.2]octane, **187**)[217] and TMEDA (**188**)[217,195] are added. Alkoxides such as potassium *tert*-butoxide have also been used,[218] but are less effective. The effects of these additives are apparent in the reaction of benzene with *n*-butyllithium.[218] A solution of *n*-butyllithium in benzene is relatively stable even at reflux, giving < 5% of phenyllithium. Addition of TMEDA, however, led to a 76% yield of phenyllithium in three h at ambient temperatures.[218] The structure of a 1:1 complex between allyllithium and TMEDA was determined by NMR at low temperature.[219] With unsymmetrical alkyl substitution at the termini, the allyl C—C bond to the more substituted terminus is of higher bond order than to the less substituted terminus.



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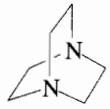

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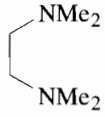
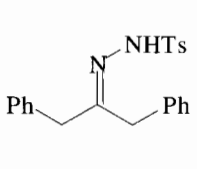


188

Many of the organolithium reagents used for reactions are commercially available, usually packaged in bulk ether or hydrocarbon solvents, and the latter often contains many hydrocarbon impurities, which is not a problem for most applications unless the reaction products are alkanes or alkenes. Ether solvents suffer from contamination caused by the deprotonation reaction, which reduces the amount of organolithium and also generates alkoxides in solution. Once a bottle of commercial reagent has been opened, it reacts with moisture and oxygen to further reduce the molarity of the solution and generate additional alkoxide. For these reasons organolithium reagents should always be standardized prior to each use. A variety of methods have been developed for this purpose, each taking advantage of the basicity or complexing ability of the organolithium reagent.

Gilman titration[220] gives the total alkali (organolithium + alkoxide) when one aliquot is titrated first with water and then with standardized HCl. Quenching a second aliquot with benzyl chloride and followed by titration with H_2O and then standardized HCl gives the alkoxide concentration. The difference in these values is the molarity of the organolithium. 1,3-Diphenylacetone tosylhydrazone (**189**),[221] 2,5-dimethoxybenzyl

alcohol (**190**),[222] and diphenylacetic acid (**191**)[223] have all been utilized for standardization, each relying on removal of an acidic proton to generate a colored anion. The use of 1,10-phenanthroline (phen, **192**) as a titration reagent relies on complexation between the organolithium and the two nitrogens, leading to a colored and reversible charge transfer complex.[224] Titration with 2-butanol destroys the complex, and the resultant color change allows the molarity to be determined. Recently, salicylaldehyde phenylhydrazone (**193**) has been used as an indicator where deprotonation of the phenolic OH leads to a yellow alkoxide anion.[225] More than 1 equivalent of the organolithium reagent removes the hydrazone NH to give a red dianion, which is the endpoint for the titration.



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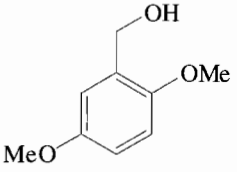

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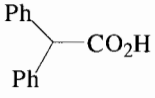

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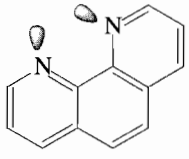

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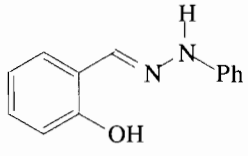

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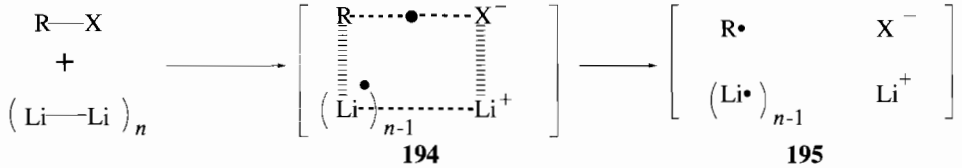
8.5.B. Metal–Halogen Exchange

For applications where the organolithium reagent is not commercially available, it is most often prepared by direct synthesis (by reaction of lithium metal with the appropriate alkyl halide). The reaction between one organolithium reagent and an alkyl halide generates a new organolithium reagents, along with a new halide. This reaction can be used to prepare many reagents that can be used in subsequent reactions.

8.5.B.i. Preparation of Organolithium Reagents. When an alkyl halide reactions with lithium metal, a new organolithium reagent is produced, along with a new alkyl halide, which is an exchange reactions and it probably proceeds by a one-electron transfer from lithium to the halide (via **194** or **195**).[195,196] Using highly purified lithium leads to a dramatic decrease in formation of the organolithium reagent, and it was discovered that the lithium must contain at least 0.02% of sodium for the reaction to proceed normally.[226]

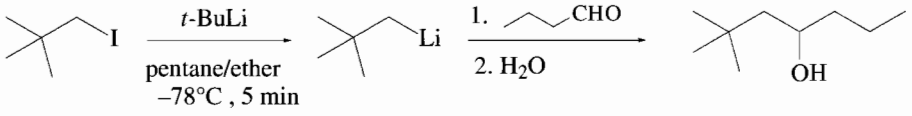


194 **195**

A related and useful process is the **Wittig–Gilman reaction**, in which an organolithium (R'—Li) reacts with an alkyl halide to produce a new organolithium (R—Li) via metal-halogen exchange.[227] Several mechanisms

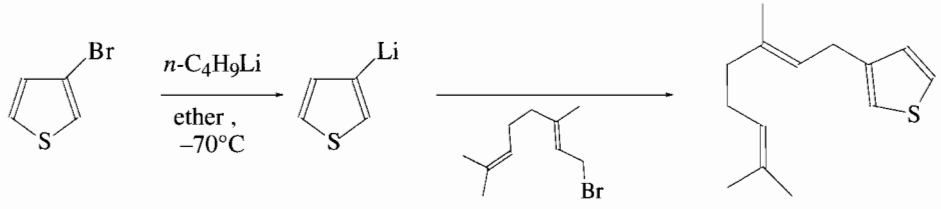
have been proposed for this exchange.[228] It is reversible and the equilibrium favors the organolithium possessing the group best able to stabilize the carbanionic center. If R—X is more susceptible to nucleophilic

displacement than R^1—X, the reaction proceeds to the right. An alternative view is to recognize that the pK_a of RH is less than that of R^1H (RH is more acidic than R^1H). The reaction can be reversible in the sense that exchange of the newly formed organolithium with the newly formed alkyl halide can lead to a mixture of organolithium reagents.[229] Proper choice of initial halide and organolithium can usually shift the equilibrium toward the desired organolithium reagent and minimize the reverse reaction. This exchange reaction is very rapid when *tert*-butyllithium is used with primary alkyl halides. Bailey showed that *tert*-butyllithium reacted with neopentyl iodide (**196**), in a mixture of pentane and ether, to give **197** in < 5 min at –78°C.[230] In this case, **197** was treated with butanal to give an 89% yield of alcohol **198** (sec. 8.5.C). It should be noted,



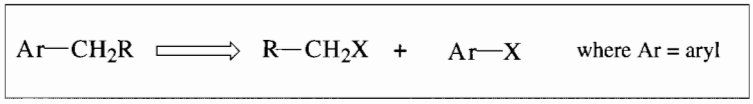
196 **197** **198**

however, that this particular reaction gives good results only with primary iodides. Halides that react with the organolithium reagent should generate a new organolithium that is much less reactive, which is apparent when an aryl halide or a vinyl halide is used to generate an aryllithium (such as 4-lithiotoluene)[231] or a vinyllithium reagent.[232,230] Heteroaryllithium reagents such as 3-lithiothiophene (**199**),[233] generated from 3-bromothiophene, are formed rapidly in ether solvents.[227a] When the relatively stable aryllithium reagents are prepared, coupling with alkyl halides is a very important reaction, as in the reaction of **199** with geranyl bromide (**200**) to give **201**.[234]



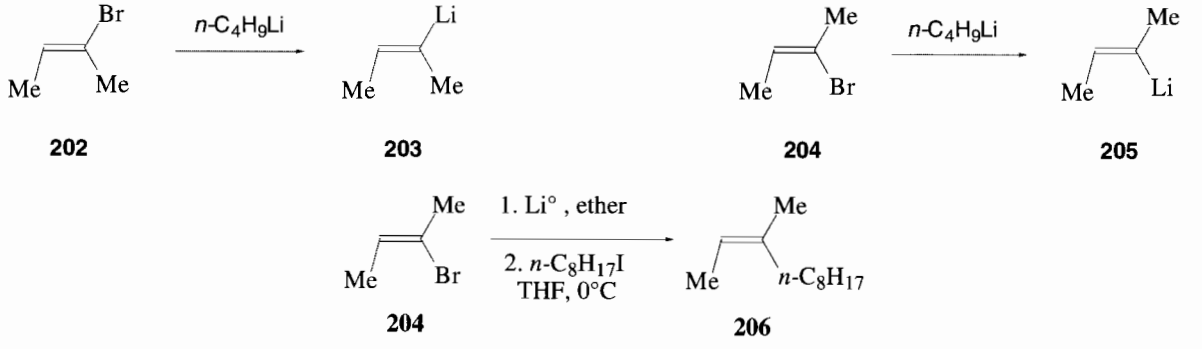
199 **200** **201**

The disconnection for aryl alkylation is



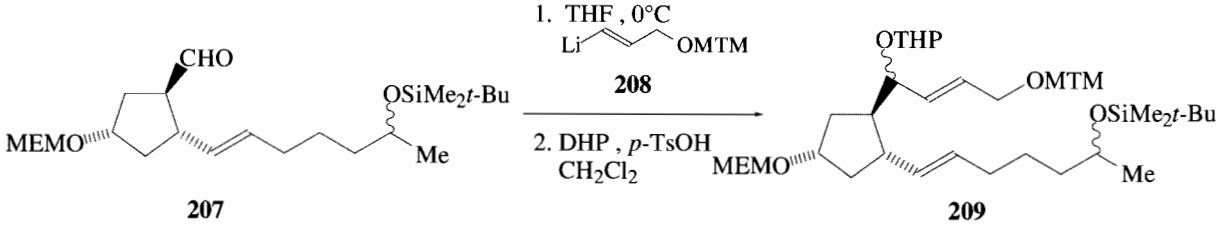
The lithium–halogen exchange is particularly useful for the preparation of stereodefined alkenyllithium reagents.[235] Two equivalents of the an organolithium reagent are necessary. In the reaction of **202** and *n*-butyl-lithium, one equivalent of *n*-butyllithium exchanges to form **203**, forming 1-bromobutane. A second equivalent of *n*-butyllithium reacts with 1-bromobutane to form butene and butane. This is typical of RLi/R^1X exchange reactions. In this particular example, the geometric configuration of the 2-bromo-2-butenes **202** and **204**, for example, is retained on metal-halogen exchange to give the corresponding lithiobutenes (**203** and **205**, respectively).[236] There is less isomerization of the alkenyl group during Li—H exchange than is observed with formation of the analogous Grignard reagent with magnesium. Stereodefined organolithium

reagents are important for coupling reactions with alkyl halides. Wurtz coupling (*vide infra*, sec. 8.5.B.ii) is minimized when aryllithium and vinyllithium reagents are formed by metal–halogen exchange. An example is the reaction of vinyl bromide **199** with lithium, and subsequent reaction with iodooctane to give a 77% yield



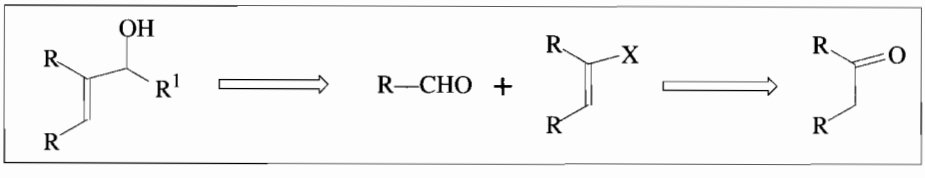
202 **203** **204** **205** **204** **206**

of **206** (94% *Z*).[237] Alkenyllithium reagents react with aldehydes and ketones as well, and the ability to control the stereochemistry of a vinyllithium reagent is important in synthesis. Corey prepared (*E*)-vinyllithium (**208**) and reacted it with aldehyde **207** to give **209** in a synthesis of (±)-brefeldin-A.[238] The various protecting groups shown in **209** were discussed in Section 7.3, but DHP is dihydropyran.



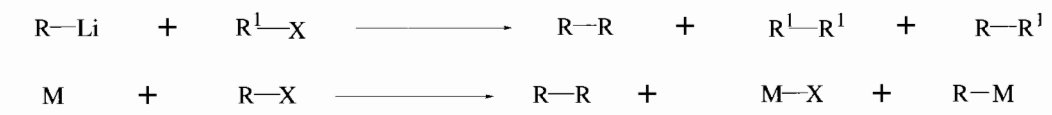
207 **209**

The alkenyllithium-alkyl halide disconnection is:

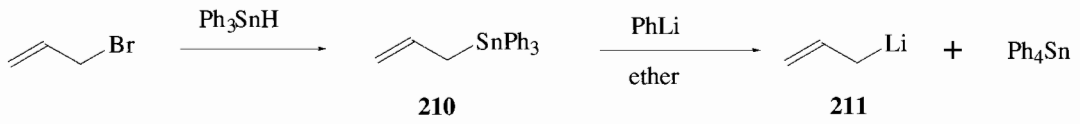


8.5.B.ii. Wurtz Coupling. There are two major side reactions in a metal–halogen exchange reaction between an organolithium reagent and an alkyl halide, coupling (the **Wurtz reaction**,[239,240] which generates R-R, R^1-R^1, and R-R^1) and α-metalation. The halogen is electron withdrawing, making the proton on the α-carbon acidic, and facilitating its removal by the basic organometallic. As noted for the **Kharasch reaction** with Grignard reagents (sec. 8.4.B.i), this sort of exchange leads to two organolithium reagents and two halides, and this can give direct coupling products R—R and R^1—R^1 or a cross coupling product, R—R^1. Wurtz coupling also occurs during metal-halogen exchange reactions forming R—R.

Wurtz coupling can be avoided by using an organotin compound as a precursor to the organolithium reagent.[241] Allyllithium (**211**) is often difficult to prepare by the usual metal–halogen exchange methods. Allyl bromide reacted with triphenyltin hydride (Ph_3SnH) to give allyltriphenyltin (**210**). Subsequent metal–



metal (Sn—Li) exchange induced by the addition of phenyllithium gave an excellent yield of the desired allyllithium reagent (**211**) along with tetraphenyltin (Ph_4Sn).[239] This route is useful when the organolithium reagent is very reactive or when the halide does not undergo exchange at a reasonable rate (as with vinyl bromide to give vinyllithium).[242]

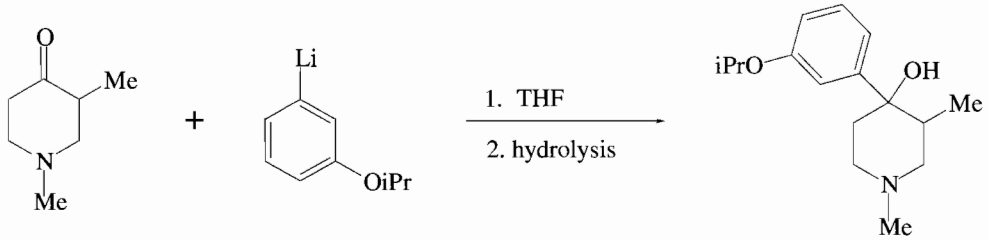


210 **211**

Reactive halides, such as allyl or benzyl halides, usually give Wurtz coupling during lithium-halogen exchange, leading to low concentrations of organolithium. Less reactive alkyl halides often fail to react at all. Addition of cuprous salts greatly enhances the reaction with alkyl halides but this generates a new reagent, a lithium dialkylcuprate. This important class of reagents will be discussed in Section 8.7.A.

8.5.C. Reactions with Aldehydes and Ketones

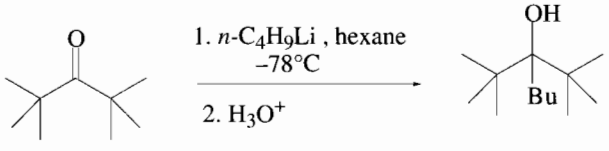
The reactions of organolithium reagents (RLi) parallel those of Grignard reagents (RMgX) in many ways.[86] Williard's *ab initio* study of the reaction of methyllithium aggregates with formaldehyde in aqueous media indicated polar solvation comprising one formaldehyde and one water around lithium ions, coordinating the reactive methyl group.[243] Addition occurred according to a concerted mechanism involving a four-membered ring transition state, but hydrophobic solvents and low substrate concentrations promoted a nonconcerted mechanism involving ring opening of the dimers and the trimer. Acyl addition of the nucleophilic carbanionic center (C—Li) to the electrophilic carbonyl of aldehydes and ketones is the normal reaction, as when piperidone **212** reacted with aryllithium reagent **213**.[244] Hydrolysis is required as a second step to give alcohol (**214**), isolated in 69% yield in Werner's synthesis of opioid antagonists.



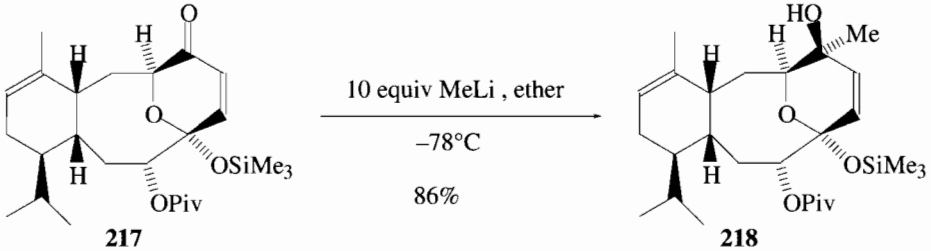
212 **213** **214**

Unlike similar reactions with Grignard reagents reduction is not a serious problem.[245] Organolithium reagents such as *n*-butyllithium easily add to hindered ketones such as di-*tert*-butyl ketone (**215**). The product is the alcohol by direct addition to the carbonyl, **216**.[245b] Simple organolithium reagents that are commercially available can be added to carbonyl derivatives and often provide the most efficient route to substituted

alcohols. It is also possible to prepare organolithium reagents that are not commercially available, such as organolithium reagents **208** or **213**.



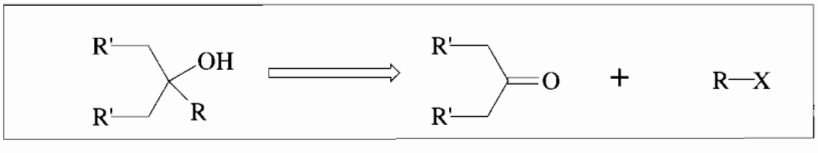
215 **216**



217 **218**

Organolithium reagents usually prefer 1,2-addition in conjugated systems due primarily to their enhanced nucleophilicity and poor coordinating ability relative to Grignard reagents. The reaction of methyllithium with **217**, for example, gave **218** in the Danishefsky and co-workers synthesis of eleutherobin.[246] Note that an excess of methyllithium was used and that even under these conditions the pivaloyl ester did not react. Conjugated ketones give primarily 1,2-addition upon reaction with organolithium reagents. Reaction of methyllithium with 3-penten-2-one gave < 1% of conjugate addition, with 2-methyl-3-penten-2-ol being the major product.[247] It is noted that addition of cuprous iodide to the reaction led to > 99% of conjugate addition[247] (sec. 8.7.A.vi).

The disconnection for organolithium addition is

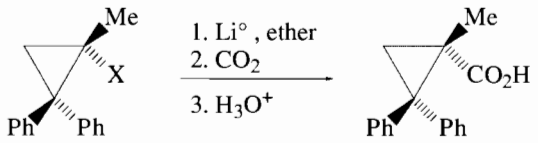


8.5.D. Stereoselectivity in Organolithium Reactions

8.5.D.i. Configurational Stability. As with Grignard reagents, it is important to know if an organolithium reagent with a chiral carbon at the C—Li unit is configurationally stable in subsequent reactions with prochiral substrates. In general, such stereogenic centers are not very stable and undergo racemization[248] unless cyclopropyl halides are used as precursors, similar to the diastereoselectivity noted with cyclopropyl Grignard reagents (sec. 8.4.F.i). Reaction of halide **219** (X = Cl, Br, I) with lithium metal and quenching with CO_2 gave the acid **220**.[142] The amount of racemization varied as the halide was changed. Table 8.13[142] shows the % of racemization observed when the organolithium reagent is generated from R—X. It follows the order: I > Br > Cl, where R is a cyclopropyl group. Reaction of **219** [X = I, 1% sodium (25 microns)] gave 64% racemization, but decreasing the sodium concentration to 0.002% gave 87% racemization. An increase in the particle size of the sodium increased the amount of racemization. Both results are consistent with a complex heterogeneous

surface reaction. The nature of the halide, the percentage of Na, and the particle size all contribute to the relative rate of formation of the organolithium as well as the stereoselectivity of the reaction.[249] It is important to note that the choice of solvent can also influence the stereochemistry of organolithium reactions. There is some evidence that organolithium reagents have greater stereochemical stability in hydrocarbon solvents than they do in ether.[250]

Table 8.13. Racemization of Cyclopropyllithium with Changes in Halide



219 **220**

X	Time (min)	% 220	Optical Purity (%)	Racemization (%)
Cl	40	73	71	29
Cl	60	76	66	34
Br	32	60	46	54
Br	42	70	42	58
I	33	42	36	64
I	41	60	36	64

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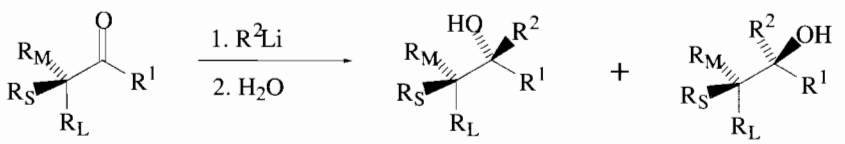
8.5.D.ii. Diastereoselective Addition Reactions. Acyl addition of organolithium reagents to ketones and aldehydes usually follows Cram's rule (sec. 4.8.B), as seen in Table 8.14.[251] Since lithium does not coordinate as readily as magnesium in reactions with carbonyls, chelation effects are somewhat diminished relative

Table 8.14. Cram Selectivity in Reactions of Organolithium Reagents with Ketones and Aldehydes



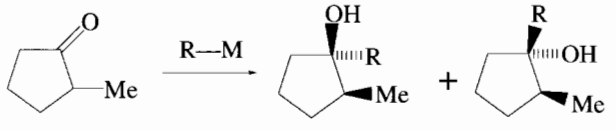
221 **222** **223**

R_S	R_M	R_L	R^1	R^2	222/223
H	*i*-Pr	Ph	H	*i*-Pr	1:1
Me	Et	Ph	Me	Et	2.3:1
Me	Et	Ph	Et	Me	10:1
H	Me	Cyclohexyl	H	Me (in pentane)	1.5:1
H	Me	Cyclohexyl	H	Me (in ether)	1.2:1

[Reprinted by courtesy of Professor James D. Morrison from Morrison, J.D.; Mosher, H.S. *Asymmetric Organic Reactions*, American Chemical Society, Washington, D,. ***1976***, pp. 92–93.]

to Grignard reagents and the Cram cyclic model is not as useful for predicting the selectivity. When complexing agents are added to the reaction, however, the cyclic model does predict the major diastereomer. Table 8.14, taken from Mosher and Morrison's work, shows the usual Cram selectivity for ketone **221** with a variety of organolithium reagents. The products are diastereomeric alcohols **222** and **223**. Reaction with cyclic ketones usually favors formation of the syn diastereomer as shown in Table 8.15.[252] As with Grignard reagents, attack at a carbonyl occurs at the less sterically hindered face of the molecule. 2-Methylcyclopentanone, for example, gave a mixture of cis- (**224**) and trans- (**225**) alcohols, generally favoring **224**.

Table 8.15. Selectivity in Reactions of 2-Methylcyclopentanone with Organolithium Reagents and Grignard Reagents

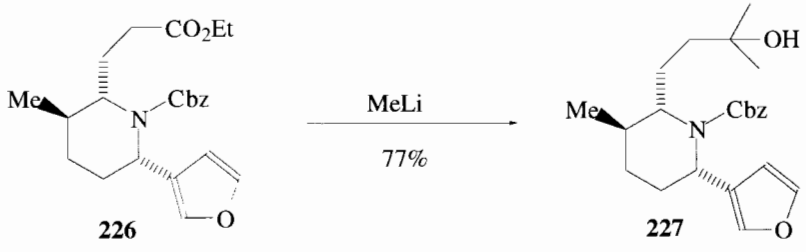


224 **225**

RM	Solvent	224/225	Yield (%)
MeLi	Ether	70:30	53
MeMgI	Ether	45:55	95
EtMgBr	THF	75:25	68
n-PrMgBr	Ether	80:20	50
$C_6H_{13}MgBr$	Ether	80:20	53
PhLi	Ether	95:5	53
PhMgBr	THF	99:1	60

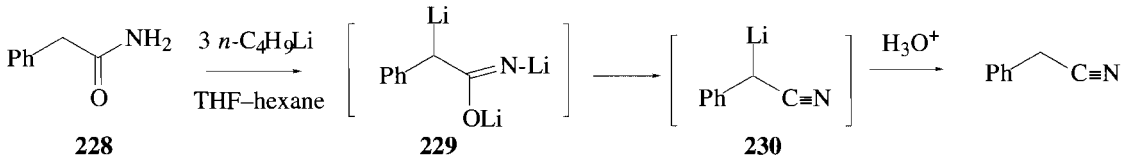
8.5.E. Reactions with Other Functional Groups

Organolithium reagents react with carbonyl compounds other than aldehydes and ketones more or less the same way as do Grignard reagents.[90] Esters usually react to give a tertiary alcohol[253] and acid chlorides give mixtures of unreacted starting material and tertiary alcohol.[254] Adding an excess of the organolithium reagent gives the tertiary alcohol exclusively, which is formally analogous to acyl substitution reactions of Grignard reagents (sec. 8.4.C.ii). If an ester is treated with excess methyllithium, a tertiary dimethyl carbinol results, as in the conversion of **226** to **227** in Barluenga's synthesis of (–)-nuphramine.[255] Careful selection of the organolithium reagent and of the reaction conditions often allows the synthesis of ketones rather than tertiary alcohols, however.[256]



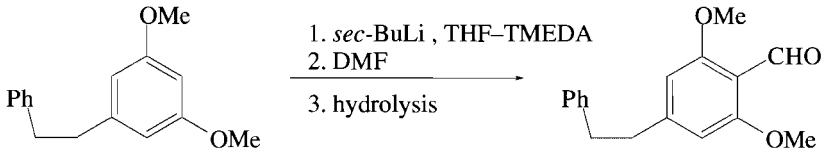
226 **227**

Reaction with amides can give a ketone,[105,257] but removal of the proton on the α-carbon of amides or lactams by the basic organolithium to form an enolate anion is a common side reaction. For this reason, non-nucleophilic bases such as lithium diisopropylamide are commonly used (sec. 9.2.B).[258] Organolithium reagents react with Weinreb's amide (see sec. 2.5.C) to give ketones, just as it was noted for Grignard reagents in Section 8.4.C.ii.[259] Primary amides react with excess organolithium to give a nitrile, as in the conversion of phenylacetamide (**228**) to benzonitrile in 72% yield.[260] Reaction of **228** with 3 equivalents of butyllithium gave trilithiated species **229**, fragmentation gave **230**, and hydrolysis gave benzonitrile.[260]



228 **229** **230**

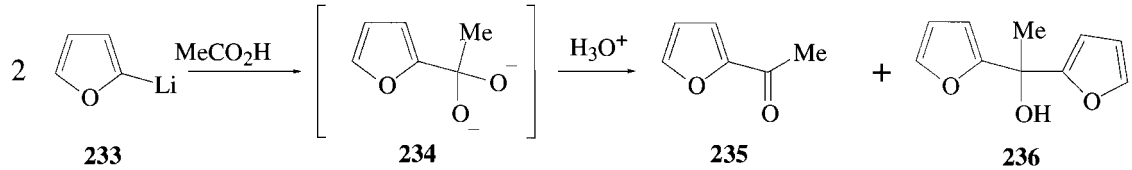
There is a rather useful reaction with amides. Organolithium reagents react with DMF to give aldehydes.. An example is the reaction of **231** with *sec*-butyllithium to give the aryl-lithium reagent (see sec. 8.5.F for directed ortho metalation reactions). Subsequent reaction with DMF and hydrolysis gave a 91% yield of aldehyde **232** in Yamaguchi's synthesis of the radulanins.[261]



231 **232**

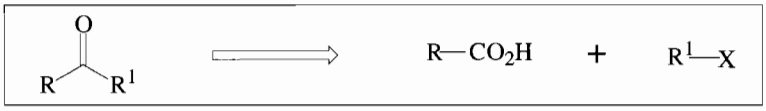
Organolithium addition to acid derivatives gives the disconnections:

Organolithium reagents are more reactive than the corresponding Grignard reagent. Reaction of an organolithium reagent with a carboxylic acid gives the expected carboxylate salt, but a second equivalent can add to the lithium carboxylate to give a ketone. Similar reaction with Grignard reagents would give only the carboxylate salt. 2-Furyllithium (**233**) reacted with a variety of acids, including acetic acid, to give the dianion (**234**).[262] Hydrolysis of **234** gave the hydrate, which was converted to the ketone (**235**) under the reaction conditions. Since the ketone was generated directly by reaction with the acid, it was subject to further reaction with excess furyllithium to give alcohol **236** as a byproduct.[262]

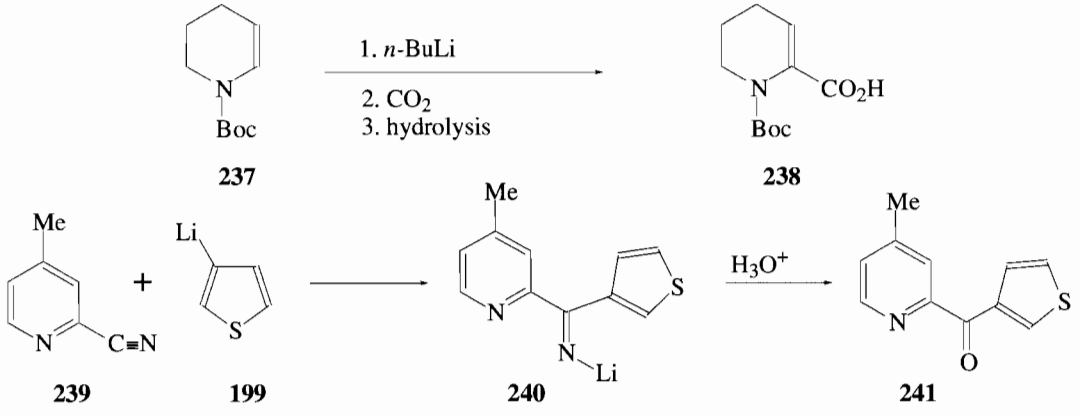


233 **234** **235** **236**

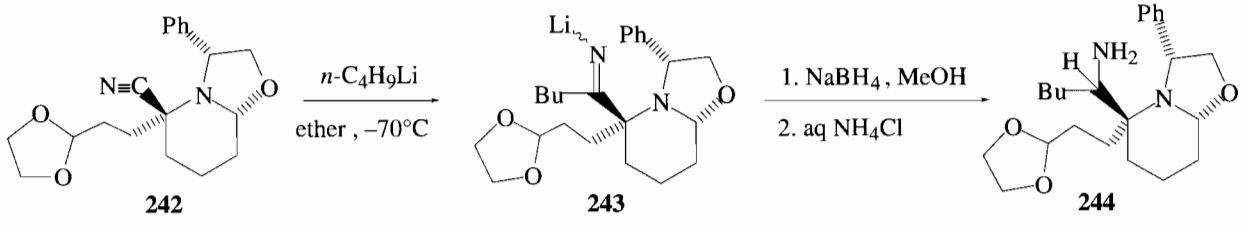
The disconnection for ketone formation from the acid is:



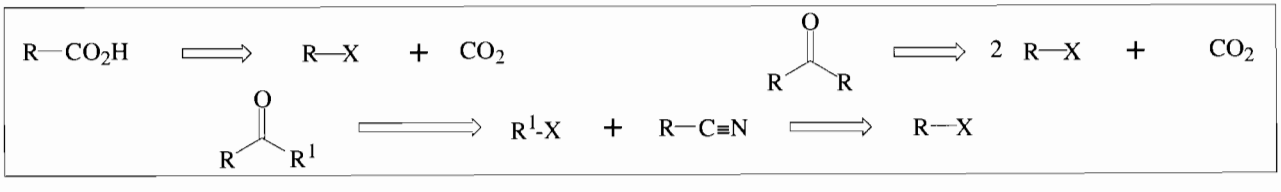
Organolithium reagents react vigorously with carbon dioxide to give the corresponding carboxylic acid after hydrolysis. The reaction is usually accomplished by carefully pouring the organolithium solution onto dry ice. An example is taken from Beak's synthesis of (–)-coniine in which carboxylic acid **232** was prepared from the lithium derivative of N-Boc enamine **233**.[263] We saw this reaction earlier when cyclopropyllithium reagent **219** was quenched with CO_2.



Nitriles are acid derivatives because they can be hydrolyzed to or prepared from carboxylic acids, and possess an electrophilic carbon that can be attacked by nucleophiles.[264] 3-Thienyllithium (**199**) reacted with 4-methylpyridine carbonitrile (**239**), for example, to give an iminium salt (**240**), analogous to the reaction of Grignard reagents. Subsequent acid hydrolysis converted the initially formed imine to the ketone, **241**.[265] Addition of an organolithium reagent initially generates an imine, so reduction to an amine (secs. 4.2.C.iii, 4.4.A, 4.5.A) is also possible. Reaction of butyllithium with nitrile **242**, for example, gave an 84% yield of lithiated imine, **243**,[266] and reduction with methanolic sodium borohydride gave a 90% yield of amine **244**.

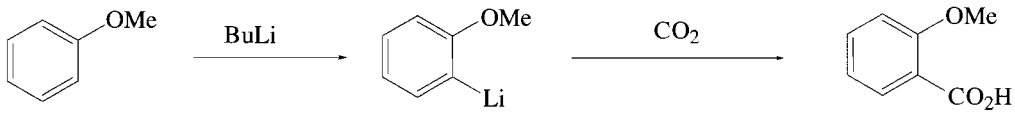


The disconnections for these two reactions are

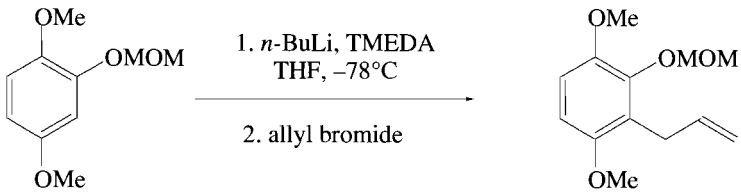


8.5.F. Directed Ortho Metalation

When an aromatic ring has an attached heteroatom or an heteroatom-containing substituent, reaction with a strong base such as an organolithium reagent usually leads to an ortho lithiated species.[267] Subsequent reaction with an electrophilic species gives the ortho substituted product. This was discovered independently by Gilman and by Wittig in 1939–1940 when anisole was found to give ortho deprotonation in the presence of butyllithium and subsequent ortho substitution.[268] This reaction generated ortho-lithiated anisole (**245**), and subsequent reaction with carbon dioxide gave 2-methoxybenzoic acid (**246**).[268a] Hauser and co-workers greatly contributed to this reaction.[269] Several categories of functional groups are capable of this ortho-directing effect, and Snieckus provides a table of relative directing abilities of various groups.[270] When two directing metalation groups have a 1,3-relationship on the aromatic ring, they can react cooperatively to enhance the ortho selectivity,[271] which is illustrated by the reaction of **247** with butyllithium and TMEDA in THF. Subsequent treatment with allyl bromide gave a 97% yield of **248** in de Koning's synthesis of the bis(benzannelated) spiroketal core of the γ-rubromycins.[272] Another example is taken form the synthesis of erythrolaccin, reported by Snieckus and co-worker.[273] When **249** was treated with bromine, ortho-bromo amide **250** was formed in good yield. Conversion to the ortho lithiated compound and treatment with 3,5-dimethoxybenzaldehyde gave an alcohol, and treatment with tosic acid led to lactone **251** in 94% overall yield.[273] This sequence was followed by several synthetic steps that gave erythrolaccin tetramethyl ether, **252**. Collum's rate studies of the butyllithium–TMEDA mediated lithiations of five arenes suggest that the lithiations do not necessarily rely on a complex-induced proximity effect.[274] Collum and co-worker[274] proposes a triple-ion based model, that depends largely on inductive effects promoted by Schlosser. and co-worker.[275]



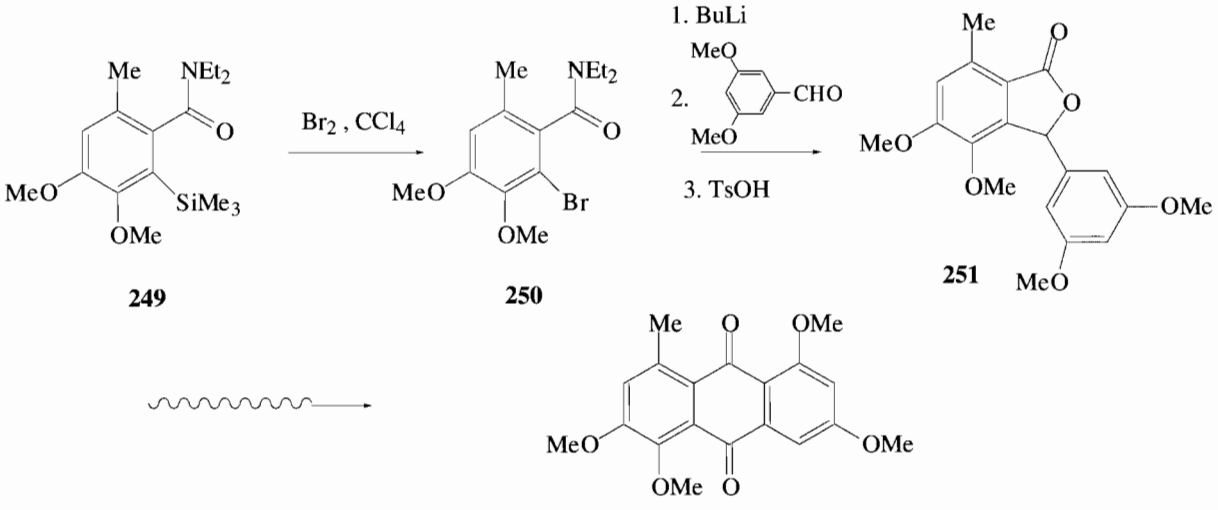
245 **246**



247 **248**

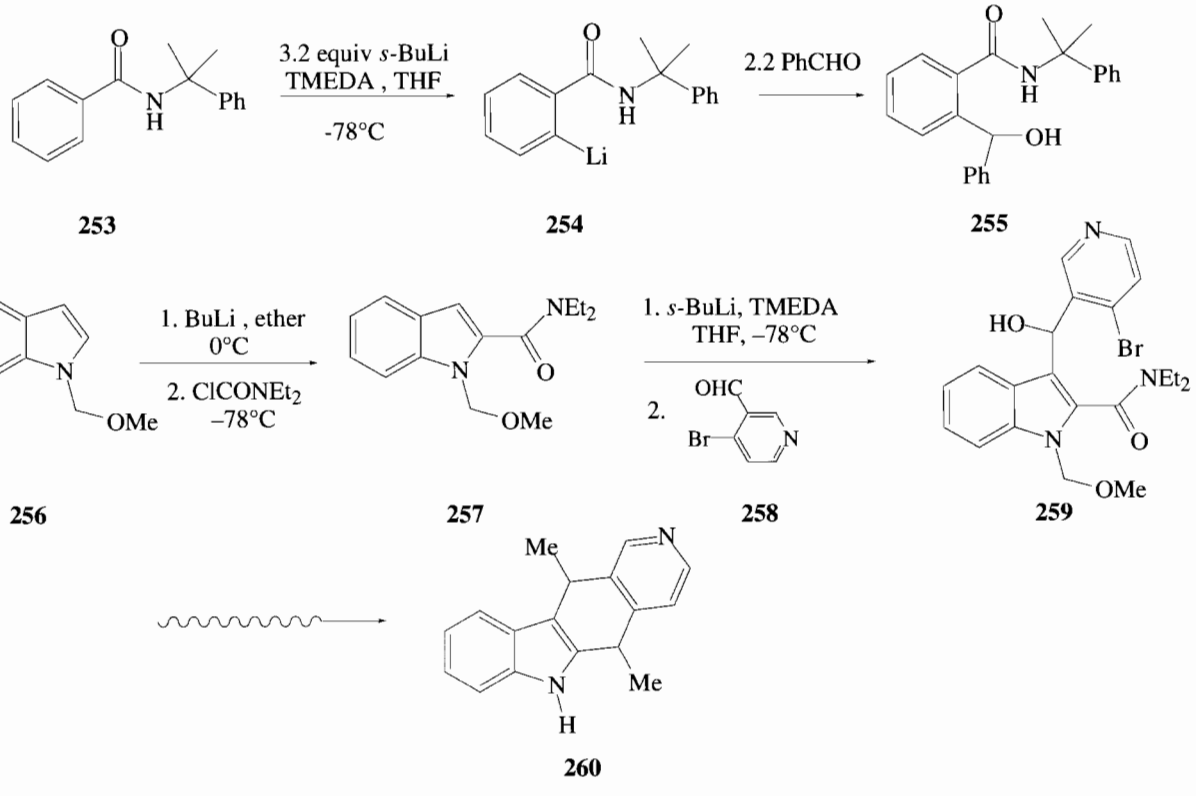
As a rule, the powerful organolithium bases should be used with organic solvents in which they are highly soluble, due to their association into aggregates (see sec. 8.5.A).[267a] Additives such as TMEDA are usually important because they effectively break down the aggregates (see sec. 8.5.A) to generate monomers and dimers in solution.[274] The premise that ortho lithiated species are stabilized by coordination was proposed by Roberts and Curtin many years ago,[276] and Snieckus summarized the early evidence pointing to the idea that the directed ortho-lithiation process is a three-step sequence.[267a] These are coordination of the organolithium

aggregate to the heteroatom-containing aromatic compound, deprotonation to give the coordinated ortho-lithiated species, and finally, reaction with an electrophile to give the final product as with any organolithium reagent.



249 **250** **251** **252**

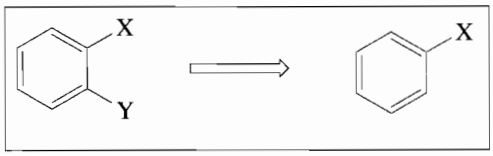
As mentioned, many groups are capable of directed ortho metalation, which is illustrated by the reaction of *N*-cumylbenzamide (**253**) with 3.2 equivalents of *sec*-butyllithium in the presence of TMEDA, to give **254** as a reactive intermediate.[277] When treated with benzaldehyde, an 86% yield of **255** was obtained. The reaction is



253 **254** **255** **256** **257** **258** **259** **260**

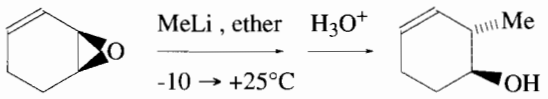
not limited to simple aromatic rings. Snieckus treated indole **256** with butyllithium and then with Et_2NCOCl to give the C2-substituted amide (**257**).[278] When this was treated with *sec*-butyllithium and TMEDA, ortho-lithiation was followed by treatment with pyridine-aldehyde **258** to give **259**. This two-step process constituted a tandem directed ortho-metalation sequence. Compound **259** constituted a key intermediate for the antitumor alkaloid ellipticine (**260**) in several subsequent steps. There are many examples of this approach being used in synthesis. The conversion of **231** to **232** above, for example, exploited this chemistry. It is clear that this regioselective approach to preparing functionalized aromatic rings will grow in importance in coming years.

A disconnection for these reactions is generalized as



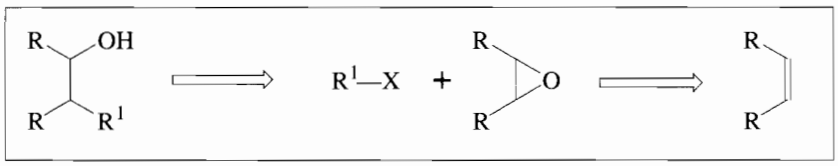
8.5.G. Addition to Epoxides, Alkenes, and Alkynes

8.5.G.i. Reactions with Epoxides. Epoxides are opened to the alcohol as expected, untroubled by the MgX_2 catalyzed rearrangements often observed with Grignard reactions. Methyllithium reacted with epoxide **261** to give the alcohol (**262**) in 68% yield.[279] The methyllithium added selectively to the allylic position to give the (*E*)-carbinol. In general, the organolithium attacks the epoxide at the less sterically hindered (less substituted) carbon, as with any nucleophile.

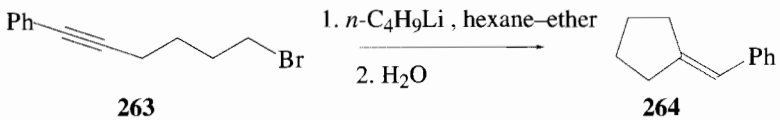


261 **262**

The epoxide ring opening gives the disconnection:



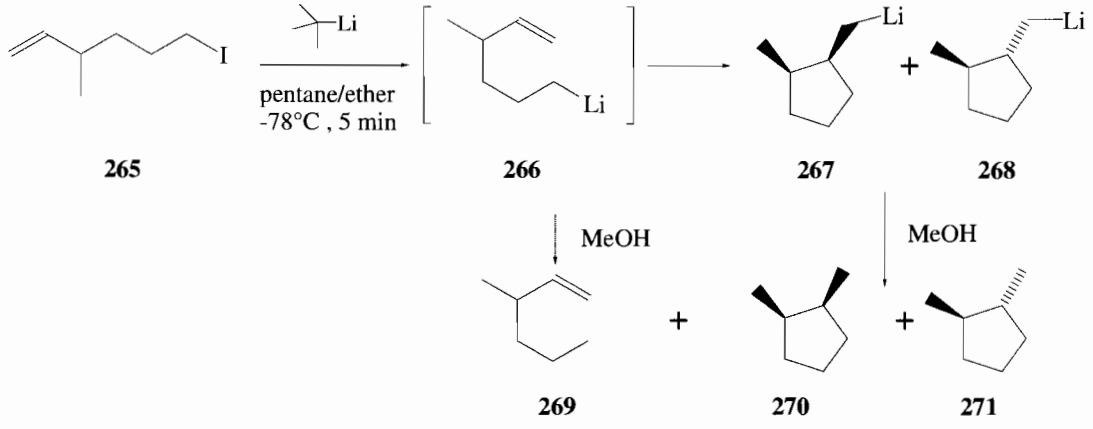
8.5.G.ii. Intramolecular Addition to Alkenes and Alkynes. Organolithium reagents can react with alkenes or alkynes in an intramolecular reaction, although both are relatively inert to the analogous intermolecular reaction. Ward treated alkynyl bromide **263** with *n*-butyllithium and observed a 60% yield of



263 **264**

the alkylidene cyclopentane **264**.[280] There were several other products produced in this reaction, and the mechanistic pathway for the cyclization was not well understood. Bailey et al. showed that the *tert*-butyllithium

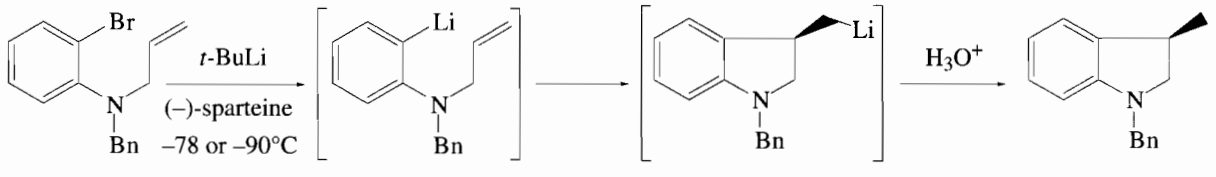
exchange reaction and the cyclization reaction are rapid at low temperatures. Reaction of 6-iodo-3-methyl-1-hexene (**265**) gave **266**, which cyclized to a mixture of **267** and **268**. Quenching with methanol at -78°C gave a mixture of 76% of **270**, 5.6% of **271** , and 14.2% of uncyclized product, **269**.[281] Bailey et al. also showed the initially formed organolithium product could be trapped with a variety of electrophiles, including aldehydes.[282] Cooke has shown that alkyllithium and alkenyllithium derivatives containing an ester moiety can be



265 **266** **267** **268**

269 **270** **271**

cyclized to form ketone products by direct addition or by Michael addition.[283] Both bicyclic and spirocyclic molecules can be prepared by addition of TMEDA to the initially formed organolithium, because it induces a second cycliza-tion reaction. As before, these organolithium products could be trapped with various electrophiles.[284] This reaction can proceed with good enantioselectivity in the presence of (–)-sparteine. The reaction of **272** with *tert*-butyllithium and (-)-sparteine (**147**), for example, gave **273**, which cyclized to give **274**. Quenching with water led to **275** in 60% yield (65% ee) in ether and 85% yield (87% ee) in toluene.[285] When the reaction was done in THF, however, an 80% yield of obtained but with 0% ee.

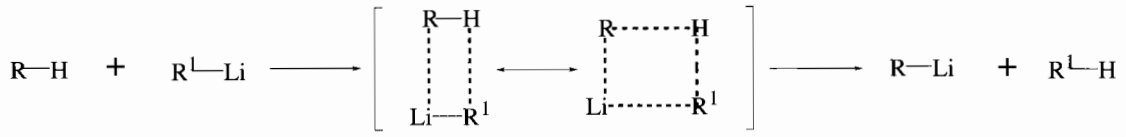


272 **273** **274** **275**

8.5.H. Basicity: Metal–Hydrogen Exchange

Organolithium reagents are stronger bases than Grignard reagents. In reactions with carbonyl derivatives, removal of the α-hydrogen to form an enolate anion can be more of a problem. Addition to the carbonyl of ketones and aldehydes is still the faster process, however. Lithium triphenylmethide tends to give selective deprotonation, which illustrates that the extent of enolate formation with organolithium is dependent on many factors.[286] Formation of the enolate occurs by an exchange of an acidic hydrogen with the lithium of the organolithium reagent.

Because organolithium reagents are powerful bases,[287] the metal–hydrogen exchange reaction with functionalized substrates plays an important role in many syntheses.[288] This acid–base reaction is believed to



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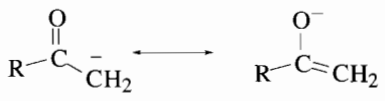
proceed via a four-center transition state such as **276**, generating a new organolithium (R—Li) from the acid (R—H + R^1—Li).[197,289] For this reaction to occur, R—H must be a stronger acid than R^1—H, and R^1—Li must be a stronger base than R—Li. Initial coordination of the lithium atom with the atom bearing the most acidic hydrogen[287,290] is the rate-determining step in cleavage of the C—H bond.[291] In general, the more acidic the proton being removed in R—H, the more facile the reaction with R^1—Li. Six factors influence the acidity of a C—H bond.[292]

1. The first factor is the percentage of **s character**.[292a] As the s character of a bond increases, the attached proton becomes more acidic because the 2s orbital lies closer to the nucleus than the 2p orbitals. When the proton is removed, increased electron density in the 2s orbital gives greater stability to the carbanion. As shown in Table 8.16,[292a] this leads to enhanced acidity of the alkynyl C-H relative to the analogous alkenyl C—H. Reducing the C—C—C bond angle, as in cyclopropane, increases the % s character, and a cyclopropane C—H is more acidic than a normal alkane hydrogen. The percentage of s character can be determined from ^{13}C NMR nuclear spin-spin coupling constants.[293]

Table 8.16. The pK_a as a Function of % s Character

Compound	Bond Hybridization	% s Character	pK_a
HC≡CH	sp	50	25
CH_2=CH_2	sp^2	33	36.5
Cyclopropane	$sp^{2.28}$	30	39
Ethane	sp^3	25	42



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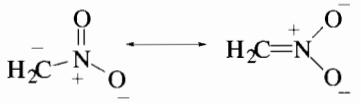

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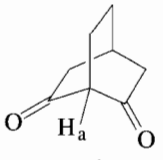
2. Conjugative effects enhance the acidity of certain hydrogens.[292a] When the proton on a C—H bond is on an atom bearing a substituent that can delocalize electron density toward a more electronegative atom, that proton is more acidic. The conjugate base (the carbanion) formed after its removal is more stable because the

electrons can be delocalized over several atoms. Carbonyl groups provide some delocalization in the resonance stabilized enolate anion (**277**). Aryl and alkenyl groups also provide conjugative stabilization, as in the benzyl anion (**278**). Conjugating groups such as nitro and cyano are excellent stabilizing substituents, as shown for **279** and **280**, respectively. The alkene bond linkage in an enolate anion (**279**) is usually planar, but steric interactions, reduction of bond angles in small rings, and solvent interactions can inhibit formation of the planar enolate. The stabilizing effects of conjugation are diminished in an enolate anion as a result of these factors[294] (sec. 9.2). The proton H_a in diketone **276**, for example, is much less acidic when compared to H_a in dione **281**,[294] which has been attributed to poor overlap of the carbanion orbital with the p orbitals of the carbonyl in **282**, due to the steric constraints of the bicyclo[2.2.2]octane ring system. The diminished acidity is therefore not entirely due to the difficulty that arises when forming a planar enolate.



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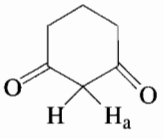

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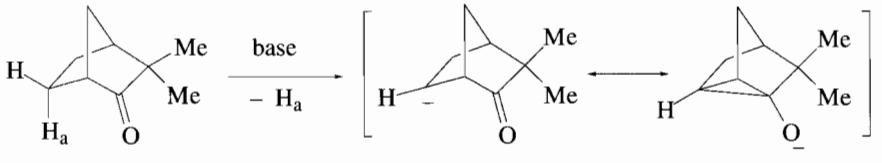
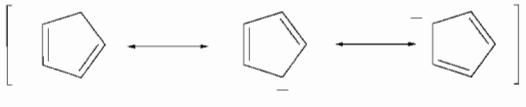
3. Inductive effects[292a] involve both through bond transmission of electrons, and field (through space) effects (sec. 2.2.A). As the electronegativity of a substituent increases, the central atom diverts increasing amounts of s character to the orbital occupied by the unshared electron pair.[292a] Methoxyacetic acid (pK_a 3.57) is more acidic, for example, than acetic acid (pK_a 4.75).[295] Most carbanion stabilizing groups act through a mixture of inductive and conjugative effects that are difficult to separate. The fluoride anion and quaternary ammonium cations are the only common substituents that stabilize ions by pure inductive effects.



283 **284** **285**



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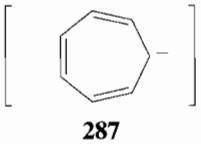

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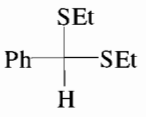
4. Homoconjugative effects[292a] occur when the position adjacent to a group that induces acidity (called the α-carbon) is blocked but the β-carbon bears an hydrogen. Removal of the β-hydrogen of certain ketones (called β-enolization) can give a stabilized carbanion when its p orbital is held rigidly at the proper angle and distance to the p orbital of the carbonyl. The effect is usually limited to a compound where an acidic proton is disposed β to the carbonyl and the α-position does not possess hydrogen atoms.[296] A **homoenolate** (first reported by Nickon)[297] is believed to be resonance stabilized by species such as **284** and **285**, derived from treatment of **283** with base.[298] The net result is enhancement of the acidity of H_a in **283**.[299]

5. Aromatic character[292a] is an important consideration when comparing the conjugate bases of several weak acids. If one of the conjugate bases is a resonance stabilized anion, the acid precursor will be more acidic than the acid that generates a nonaromatic conjugate base. The pK_a of cyclopentadiene is ≈ 15, due in part to removal of a proton that leads to the very stable, aromatic cyclopentadienyl anion (**286**), in sharp contrast with cycloheptatriene (pK_a of ≈ 36), where loss of the hydrogen would give the antiaromatic 8 π electron cycloheptatrienyl anion **287**.



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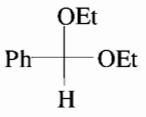

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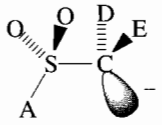

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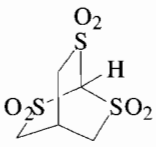

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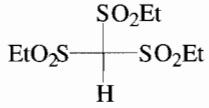


292

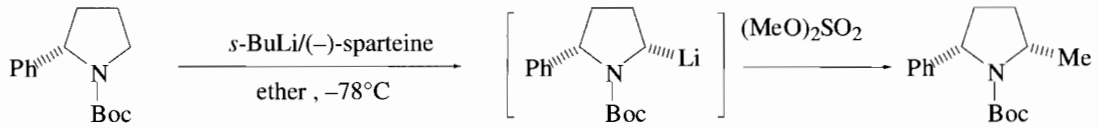
6. d-Orbital effects[292a] are important only when atoms are present that are not in the second row of the periodic chart, such as sulfur, phosphorus, and transition metals. Carbanions can be stabilized by overlap of the electron pair with 3d orbitals of third row elements such as phosphorus and sulfur.[300] Dithioacetal **288** is more acidic than acetal **289** by 5–6 pK_a units. The carbanionic p orbital aligns itself to minimize electrostatic repulsion, as in **290**.[301] Forcing these orbitals into close proximity by confining them to a polycyclic system significantly decreases the acidity. Tris-sulfone (**291**) is less acidic than **292**, but in this case solvation effects contribute to the difference in acidity.[300,301]

In summary, all six factors described above contribute to the following order of acidity, based on the ability of that functional group to enhance the acidity of an α-proton:

NO_2	>	CO	>	SO_2	>	CO_2H	>	CO_2R	≈	CN
	≈	$C(=O)NH_2$	>	X	>	H	>	R		

The pK_a values of several common functional groups are presented in Table 8.17 to show the effect on acidity of carbonyl substituents in the context of other organic acids. In reactions with an appropriate acidic molecule, the organolithium removes the acidic proton to give the new organolithium. In general, an organolithium will exchange with an acidic hydrogen of another molecule if the conjugate acid of the organolithium is a *weaker* acid than its reactive partner. According to this rationale, methyllithium (pK_a of methane is 40) will remove the acidic hydrogen in phenylacetylene (pK_a is 21) (see Table 8.17). This carbanion can be used as a nucleophile in addition reactions or for substitution reactions. Enolization of carbonyl derivatives is usually accomplished with lithium dialkylamide bases rather than alkyllithium reagents, as discussed in Section 9.2.B.

Metal–hydrogen exchange is useful for the preparation of allylic and alkyl[302b], aryl,[302a] and heteroaryl lithio derivatives. We have seen several examples of this in previous syntheses, including the conversion of **231→232** and **237→238**. Asymmetric deprotonation is possible using *sec*-butyllithium and (–)-sparteine (**147**, and see the reaction of **272** above). The reaction of Boc pyrrolidine derivative **293**, for example, gave **294** and subsequent reaction with the methylating agent dimethyl sulfate gave a 45% yield of **295** in a ratio of 93:7 syn/anti diastereomers.[303] It is also possible to generate allyllithium derivatives from allylic hydrocarbons.[304]



293 **294** **295**

The disconnections for the aryl substitution reactions are

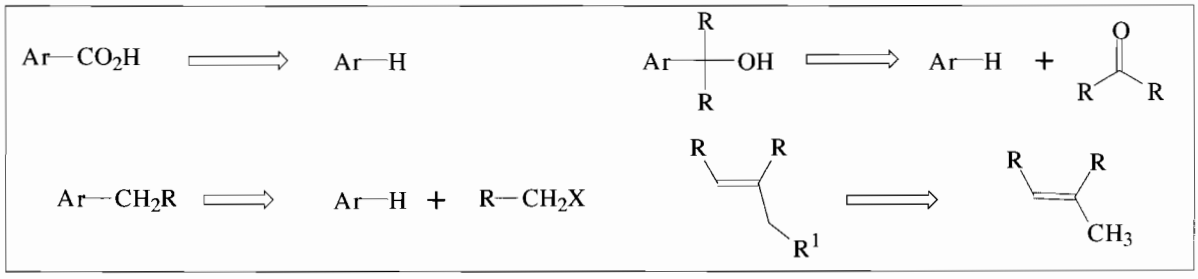
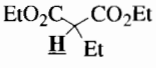
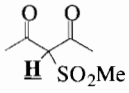
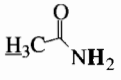
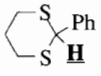
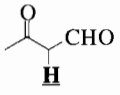
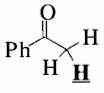
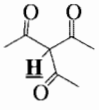
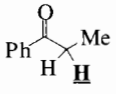
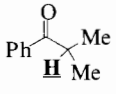
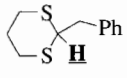
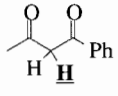
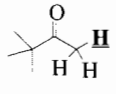
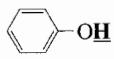
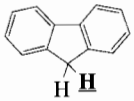
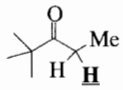
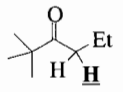
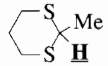
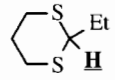
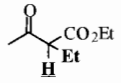
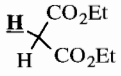
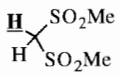
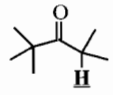
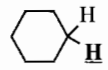
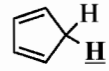


Table 8.17. pK_a Values of organic acids[305,306,307,308,309,310,311,312,313]

ACID	pK_a	ACID	pK_a	ACID	pK_a
	3.6[a]		15[a]	H—C≡C—H	25[b]
Ph—CO2H	4.2[a]	H—OH	15.7[b]	H-CH2CO2Et	25.6[h]
	4.7[b]	H3C-OH	16[b]		25[a]
Me—CO2H	4.8[b]		16.5[a]	Ph—NH2	27[b]
	5.0[a]	Et-OH *t*-Bu-OH	18[c]		29.6[c]
	5.9[a]		18.6[b,d]		31.3[c], 36.5[i]
	5.85[a]		19.1[d]	Ph3C—H	32.5[b]
	8.6[a]		19.5[d]		34[c]
	9.4[a]		20[a]		35[b]
	9.8[a]		20.8[d,e]		35[b][41][f]

	9.9[a]		21[b]		36[b]
	10.2[a]	Ph-C≡C-<u>H</u>	21[b]		36.5[b][44][f]
	10.5[j]		21.3[d]		37[b][44][f]
	11[a]		21.6[d]		38.3[c]
	12[a]	Ph_2N—<u>H</u>	23[b]		38.6[c]
	12.7[a]	Et_2N—<u>H</u>	23[b]		39[b]
	13.3[a]	<u>H</u>$_3$C—SO_2Me	23[a]	<u>H</u>—CH_3	40[b]
	14[a]		23.5[d,e]		45[b][51][f]
	14-15[b]	<u>H</u>$_3$C—CO_2H	24[g]		

[a] Ref. 310, [b] Ref. 305, [c] Ref. 306, [d] Ref. 309, [e] Ref. 307, [f] Ref. 308, [g] Ref. 251 [h] Ref. 311 [i] Ref. 312 [j] Ref. 313
The acidities of ketones has also been measured in DMSO[314]

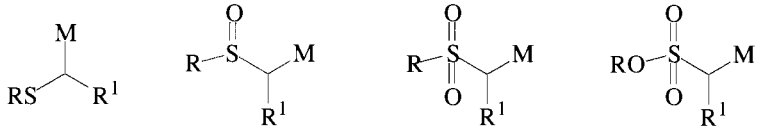
8.6. SULFUR STABILIZED CARBANIONS AND UMPOLUNG

Introducing a heteroatom (X) into an organic molecule enhances the acidity of the proton adjacent to the heteroatom (H—C—X). A sulfur group makes the proton more acidic due to electron-withdrawing effects as well as by stabilization of the resulting carbanion by the d orbitals (see above).[300,301] Several different sulfur-stabilized carbanions are known and have been used extensively in organic synthesis.[315,316] Sulfur stabilized carbanions react with alkyl halides or with aldehydes and ketones in the same manner as other carbanions.

8.6.A. Sulfur Carbanions

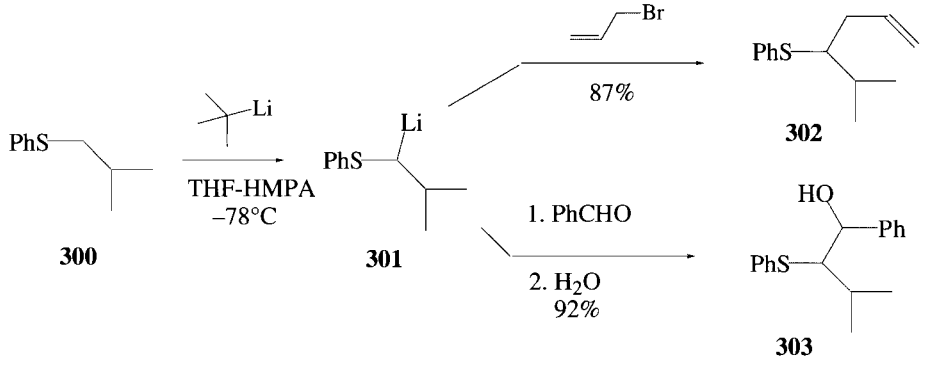
Thioethers (sulfides)[319] can be converted to their α-carbanion derivative (**296**, M = Li, Na, K) by treatment with strong bases such as *n*-butyllithium, sodium amide ($NaNH_2$) or potassium amide (KNH_2). The hydrogen atom α-to the sulfur atom of sulfides is a weaker acid than that α-to a carbonyl, nitrile or nitro group and stronger bases are required for deprotonation. Sulfides are stronger acids, than the allylic, vinyl, and aromatic hydrocarbons discussed above, however. The various oxides of sulfur can also be converted to α-carbanions. The most important derivatives are the α-carbanions derived from sulfoxides (**297**), sulfones (**298**), and

sulfonate esters (**299**). Increasing the number of oxygens on the sulfur atom generally increases the acidity of the α-proton. Bordwell studied the acidity of various sulfur derivatives using DMSO as a solvent.[317,38b] Anders and co-workers studied the structure of sulfur-stabilized allyllithium compounds in solution, and found that they were monomers in THF.[318]



296 **297** **298** **299**

Oxidation of a sulfoxide to a sulfone places a second oxygen on sulfur (RSO_2R–sec. 3.9.A.iii) and this increases the relative acidity of the α-hydrogen. Dimethyl sulfone is more acidic than the corresponding sulfoxide (RSOR, DMSO) by 6.1 pK_a units. The presence of an electron-releasing methyl group ($PhSO_2CH_3$ vs. $PhSO_2CH_2CH_3$)[317c] causes a reduction of acidity by two pK_a units. As the group attached to the sulfur becomes more electron withdrawing, the acidity increases ($Me_3CSO_2CH_3$ = 30.3, $MeSO_2CH_3$ = 31.1, $PhSO_2CH_3$ = 29.0, $CF_3SO_2CH_3$ = 18.8).[317c,g] A similar trend is observed for the thio-analogs of acetonitrile (Me_3CSCH_2CN = 22.9, Me_2CHSCH_2CN = 23.6, $CH_3CH_2SCH_2CN$ = 24.0, CH_3SCH_2CN = 24.3, $PhSCH_2CN$ = 20.9).[317g] Two sulfur groups significantly increase the acidity of the proton ($CH_3SO_2CH_3$ = 31.1, $CH_3CH_2SO_2CH_2SO_2CH_2CH_3$ = 14.4, $CH_3SCH_2SOCH_3$ = 29.0),[317g] and another electron withdrawing group leads to an increase in acidity ($CH_3SO_2CH_2CN$ = 13.6, CH_3SCH_2CN = 24.3).[317g]

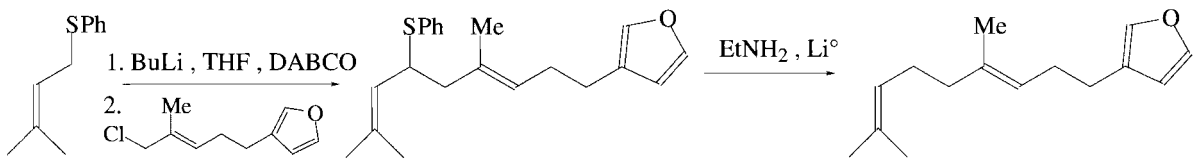


300 **301** **302** **303**

As mentioned, the proton on the α-carbon of a sulfide[319] is a very weak acid and its removal requires a strong base. Organolithium reagents are commonly used for this purpose. Phenylisopropyl sulfide (**300**) reacted with *tert*-butyllithium (THF, HMPA) to give the α-lithio derivative **301**. Alkyl sulfides often require addition of HMPA or TMEDA to facilitate Li—H exchange. Organolithium reagent **301** reacted with allyl bromide to give **302** in 87% yield or with benzaldehyde to give **303** in 92% yield.[320a]

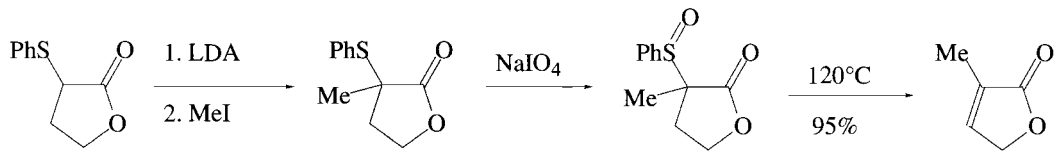
There are many synthetic applications for sulfide carbanions. Sulfide **304** required the addition of DABCO to facilitate deprotonation by butyllithium, but the resulting anion coupled readily with allylic chloride **305** under these conditions to give **306**. The sulfide moiety was removed by a dissolving metal reduction (for example, see secs. 4.9.D, 4.9.F) to give dendrolasin, **307**.[320b] The ability to remove the sulfur after activating

a carbon for nucleophilic attack is one of the most attractive features of organosulfur chemistry. Coupling of allylic halides and allylic thiocarbanions is sometimes called **Biellmann alkylation.**[321] Intramolecular reactions occur readily and reaction with epoxides or alkyl halides is possible.



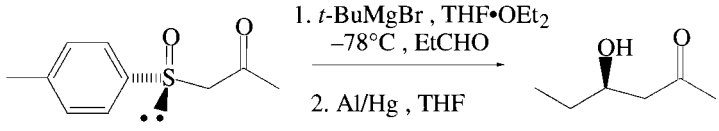
304 **305** **306** **307**

When a sulfide group is attached to the α-carbon of a molecule an electron-withdrawing group such as a carbonyl (the sulfide is β to the carbonyl), the acidity of the α-proton is greatly enhanced (see Table 8.17). When α-phenylthio lactone (**308**) was treated with lithium diisopropylamide (LDA, sec. 9.2.B) the 2-lithio derivative was formed. Subsequent treatment with methyl iodide gave **309**.[322] The sulfide was especially useful for this purpose, since it was easily oxidized to the corresponding sulfoxide (**310**) and subsequent heating induced syn-elimination to alkene **311** (sec. 2.9.C.v). The sulfide-alkylation sequence can be applied to many systems, including some where highly functionalized molecules are prepared.



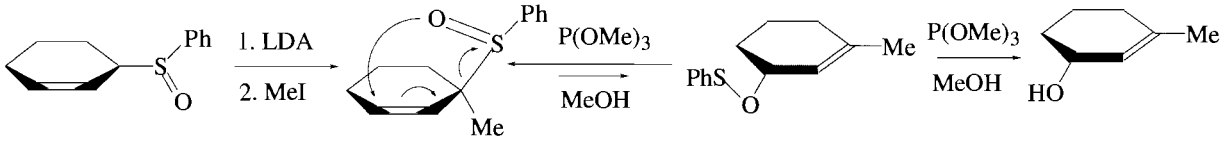
308 **309** **310** **311**

Sulfoxide carbanions formed by deprotonation of sulfoxides are common in alkylation reactions.[323] It is possible to prepare chiral sulfoxides (sec. 3.9.A.ii) and generation of the corresponding organolithium derivatives followed by condensation with aldehydes or ketones generates diastereomeric products. Once the organolithium derivative is generated, the stereochemical integrity of the C—Li bond is remarkably stable, possibly due to interactions with the adjacent functional groups. Conversion of the asymmetric keto-sulfoxide (**312**) to the carbanion, followed by condensation with propanal gave an alcohol-sulfoxide. The sulfoxide group was removed by treatment with aluminum amalgam to complete the asymmetric synthesis of 3-hydroxy-ketone **313** in 67% yield and 64% ee.[324] It is noted that *tert*-butylmagnesium bromide was used as the base. The reductive cleavage of the sulfoxide with aluminum amalgam (sec. 4.9.I) is one of the most common methods for removing a sulfur moiety.



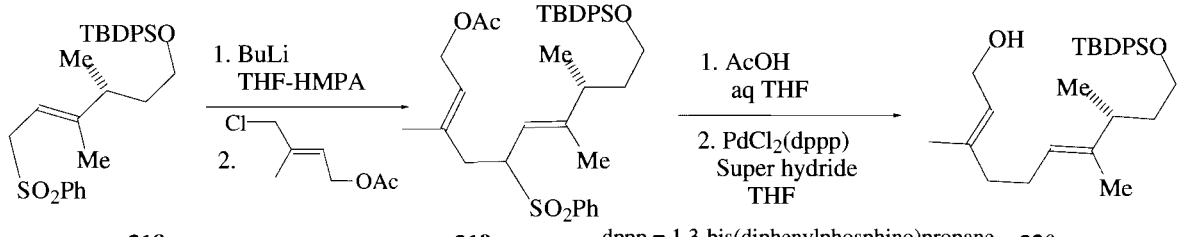
312 **313**

Another variation in sulfoxide reactivity is shown after an initial conversion of **314** to **315** via reaction with LDA and alkylation with methyl iodide.[325b] In this case, removal of the sulfur moiety allowed access to a new functional group, an allylic alcohol. Heating allylic sulfoxide **315** induced a facile [2,3]-sigmatropic rearrangement (sec. 11.12.A) to give **316**. Trimethyl phosphite [$P(OMe)_3$] was added to trap a minor isomer of the equilibrium. Hydrolysis of **316** gave cyclohexenol derivative **317**. This reaction is called the **Mislow–Evans rearrangement**.[325] The [2,3]-sigmatropic rearrangement that occurs with allylic sulfoxides is useful and predictable, since it proceeds with high stereoselectivity.[325c] This rearrangement is useful for introducing functional groups other than allylic alcohols into a molecule, as in the Otera and co-workers use of this reaction to generate conjugated aldehydes.[326] Selenoxides also give this reaction.[327]



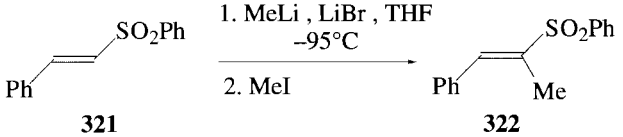
314 **315** **316** **317**

Sulfones are useful organosulfur compounds.[328] In Pickett's synthesis of 9-methylgermacrene-B, sulfone **318** was treated with *n*-butyllithium to generate the α-carbanion.[329] Alkylation with the allylic chloride shown gave **319**.[330] Hydrolysis of the acetate to an alcohol was followed by treatment with a palladium catalyzed Super–Hydride reduction of the sulfone to give **320** in 82% yield. Alternatively, sodium amalgam and Raney nickel [Ni(R)] can be used to remove sulfur from organic molecules (sec. 4.9.D). [331]



318 **319** dppp = 1,3-bis(diphenylphosphino)propane **320**

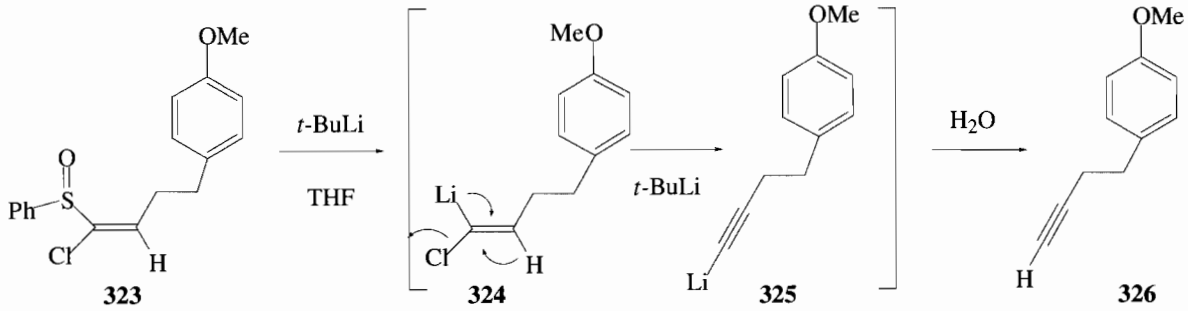
In 1-lithio vinyl sulfides (sec. 8.6) the sulfur atom stabilized the carbanion, allowing either alkylation or condensation reactions. The sulfonyl moiety can also stabilize a vinyllithium derivative. Vinyl sulfone (**321**), for example, was converted to the 1-lithio derivative with methyllithium.[332] This organometallic reacted in the usual manner with alkyl halides (methyl iodide) to give the coupling product, **322**.



321 **322**

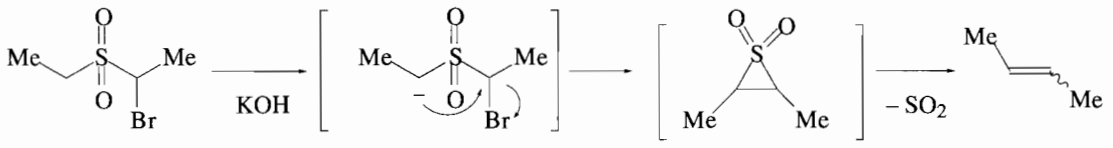
Vinyl sulfoxides undergo an unusual elimination reaction when a leaving group such as chloride is also present on the double bond. When **323** was treated with *tert*-butyllithium, exchange occurred to give **324**.[333] In the presence of additional *tert*-butyllithium, chloride is lost and a lithio alkyne (**325**) is formed in what is

known as the **Fritsch–Buttenberg–Wiechell rearrangement.**[334] Hydrolysis led to the final product, alkyne **326** in 74% yield. A similar reaction was observed when **323** was treated with Grignard reagents.



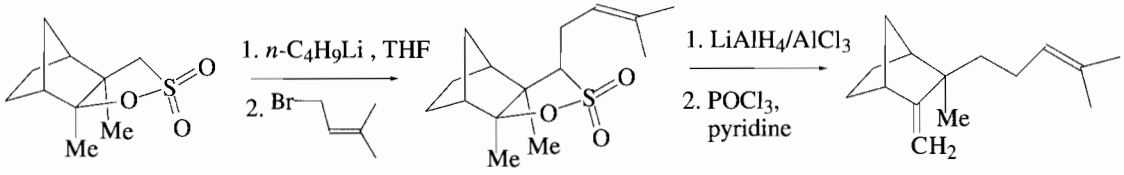
323 **324** **325** **326**

When the sulfone has an α-halo substituent, formation of the carbanion is often accompanied by loss of the SO_2 moiety via the so-called **Ramberg–Bäcklund reaction.**[335] An illustration is the conversion of 1-bromoethyl ethyl sulfone (**327**) to 2-butene.[336] Initial reaction with potassium hydroxide generated the sulfone carbanion (**328**), which displaced bromide intramolecularly to give an episulfone (**329**). Under the reaction conditions, **329** lost sulfur dioxide (SO_2) to give the alkene. Meyers introduced a modification of this reaction in which the sulfone was converted directly to the alkene without isolating the α-halosulfone, using KOH in CCl_4.[337,338] Sulfuryl chloride and bromine can also be used.[338]



327 **328** **329**

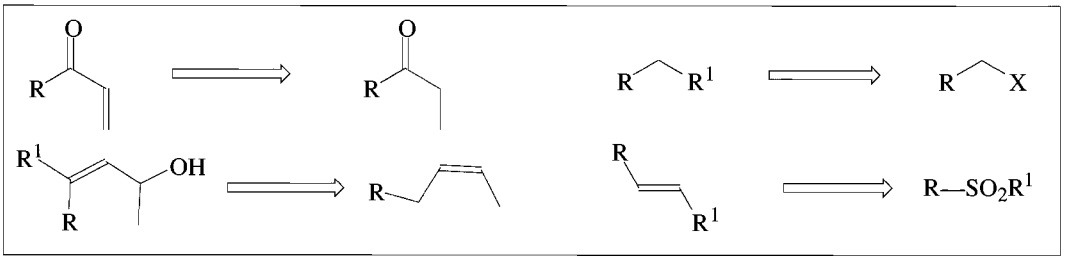
Sulfonate carbanions have been used less extensively than sulfone, sulfoxide, and sulfide carbanions. Sulfonates are good leaving groups and subject to nucleophilic displacement or elimination in the presence of the bases required to generate the carbanion. Cyclic sulfonates (sultones such as **330**) have been alkylated via



330 **331** **332**

reaction with *n*-butyllithium and alkyl halides.[339] Sultone (**330**) was used in Wolinsky's synthesis of the terpene β-santalene (**332**), via alkylation with 1-bromo-3-methyl-2-butene to give **331**.[340] The sulfur was removed by reduction with aluminum hydride (AlH_3, sec. 4.6.B) and treatment with $POCl_3$ and pyridine generated the exo-methylene group (secs. 2.8.A, 2.9.A).[340] It is noted that reductive cleavage of the sultone can give the thioalcohol via S—O cleavage and/or the alcohol via C—O cleavage.[339a] Sultones and sulfonate esters are rarely used in synthesis but sulfides and sulfones are common. Sulfoxides, especially chiral sulfoxides, are now very common.

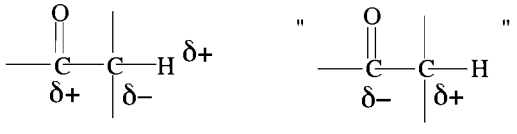
The disconnections for these compounds are



8.6.B. Umpolung

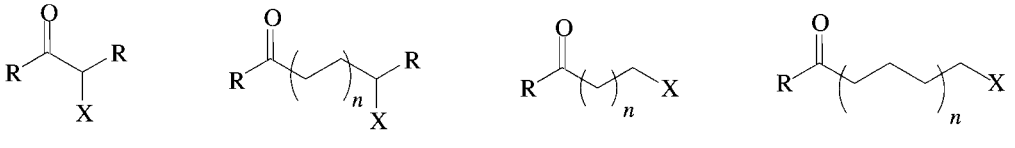
We are used to seeing a certain kind of reactivity associated with a given functional group. In some cases, it is possible to reverse the reactivity, in effect making an electrophilic center in to a nucleophilic one and vice versa. This section will explore reactions that allow this reversal.

8.6.B.i. Definition of Umpolung. Under normal conditions, a carbonyl group is polarized as shown in **333**. The carbonyl carbon is electrophilic and the α-carbon nucleophilic, as in an enolate anion (**277**). It would be very attractive from a synthetic viewpoint if the polarity of a carbonyl could be reversed, as in **334**.



333 **334**

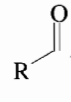
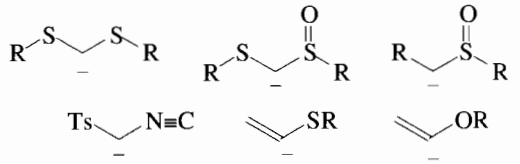
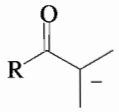
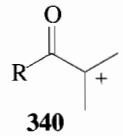
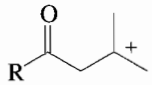
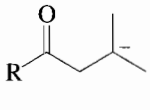
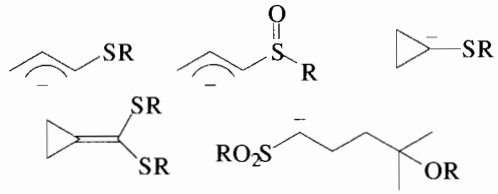
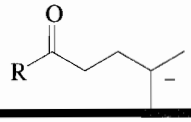
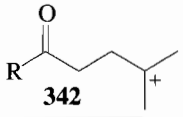
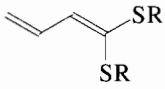
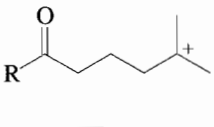
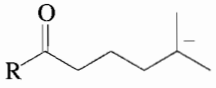
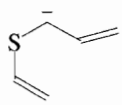
In **334**, the acyl carbon would be nucleophilic. To attain this reversal, it is necessary to change the carbonyl into another functional group such that the carbon becomes nucleophilic. If this transformation can be accomplished, the carbonyl must be easily regenerated when the desired reactions have been carried out. Seebach termed this process **umpolung**.[341] There is umpolung (reversal of reactivity) whenever one observes



335 **336** **337** **338**

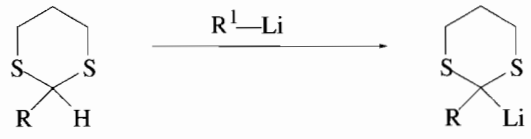
a 1,2-*n* relationship of the functional groups in a carbonyl compound, where *n* is the number of carbon atoms separating the functional groups. For umpolung, there are an even number of carbons separating the carbons bearing the functional groups (0, 2, 4, ... as in **335**, where no carbons separate the groups, and in **336** where two carbons separate the groups),[341a] which contrasts with normal reactivity, where an odd number of carbons separate the carbonyl bearing functional groups (1, 3, 5, ... as **337** where one carbon separates the groups, and in **338** where three carbons separate the groups).[341a] Table 8.18[341c] shows several umpolung equivalents, along with the reactivity of the normal fragment and typical reagents that give the umpolung reactivity.

Table 8.18. Typical Umpolung Equivalents and Reagents

Normal	Desired Umpolung	Umpolung Reagents
a_1	 **339** d_1	
 d_2	 **340** a_2	
 a_3	 **341** d_3	
 d_4	 **342** a_4	
 a_5	 **343** d_5	

[Reprinted from Gröbel, B.-T.; Seebach, D. *Synthesis*, ***1977***, pp. 357. Copyright 1977 by Georg Thieme Verlag.]

8.6.B.ii. Acyl Anion Equivalents. The most common umpolung equivalent is that for acyl anion **339**, and dithianes **344** are the most common reagent used for this purpose. Dithiane **344** is prepared from an aldehyde, but ketones are also precursors (sec. 7.3.B.ii). Removal of the hydrogen adjacent to the sulfur requires a base such as *n*-butyllithium and the product is α-lithiodithiane (**345**). The acidity of this hydrogen is largely

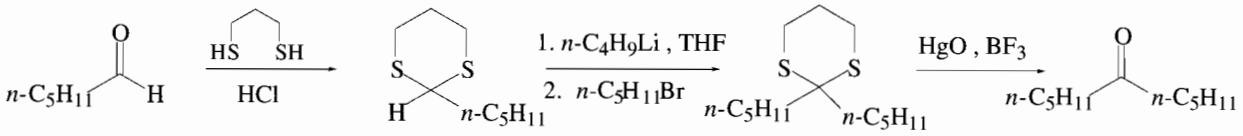


344 **345**

due to greater polarizability of the sulfur and the greater C—S bond length rather than to the presence of the d orbitals.[342] The pK_a of 1,3-dithiane (**344**, R = H) is 31.1.[307] 2-Methyl-1,3-dithiane (**344**, R = Me) has a pK_a of 38.3, however, and 2-phenyl-1,3-dithiane (**344**, R = Ph) has a pK_a of 29.6.[307] The acidity is clearly

dependent on the electronic effect of the R group. There are many dithioacetal derivatives (dithioketals do not posses an acidic hydrogen) including both acyclic and cyclic species. For reasons of stability, availability, and ease of preparation, dithianes are used most often.

A typical application is the reaction of hexanal with 1,3-propanethiol and an acid catalyst to give dithiane **346** (sec. 7.3.B.ii). Subsequent treatment with *n*-butyllithium to give corresponding lithio derivative (**347**, R = pentyl) followed by addition of 1-bromopentane gave the alkylation product, **348**.[343] To complete the reversal of reactivity, the carbonyl must be unmasked, which is usually done with a Lewis acid that has a high

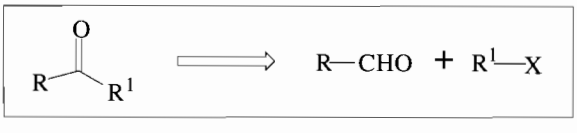


346 **347** **348**

Other electrophiles include H^+, RX, RCOX, epoxides, ketones, aldehydes, etc.

affinity for sulfur, such as mercuric oxide with boron trifluoride in aqueous THF.[343] Treatment of **347** with this reagent gave an 82% yield of **348**.[343] Many different oxidants have been employed to unmask dithianes, including Cl_2, Br_2, *t*-BuOCl, NBS, $Pb(OAc)_4$, $Ce(NH_3)_6(NO_3)_4$, $Tl(O_2CCF_3)_3$, and so on.[344] The choice of reagent depends on the facility of the hydrolysis and the sensitivity of the molecule to further reaction. The lithiated dithiane reacts best with primary and secondary alkyl halides,[345] acyl halides, ketones and aldehydes.[346] Nitriles and amides react only if they have no acidic protons. Dithiane anions also react with aldehydes and ketones as well as with epoxides.[347] An important synthetic use of this reaction is the preparation of highly functionalized aldehydes using **344** (R = H) as a starting material.[348] This is an important route to β-hydroxy and alkoxy aldehydes and a variety of substituents can be incorporated in the epoxide.

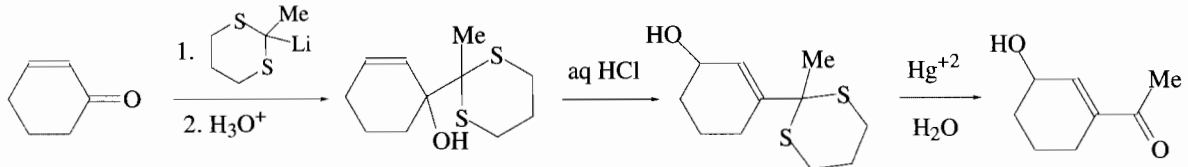
The disconnection for the acyl anion umpolung is



Although conjugate addition is known, dithiane anions most often give 1,2-addition with conjugated systems. Cyclohexenone reacted with **345** (R = Me) to give the 1,2-addition product **349** in 99% yield.[349] In this case, treatment with aqueous acid led to a rearrangement, giving **350** in 83% yield. Unmasking the carbonyl with mercuric salts led to an 80% yield of **351**.[349] With stabilized carbanions of this type, 1,4-addition products are observed in some cases and this may be due to a kinetic–thermodynamic phenomenon in which the initially formed 1,2-addition product equilibrates to a 1,4-adduct.[350] This equilibration can be induced by treatment with base. For example, Wilson showed that treatment of **349** with 1–1.5 equivalents of KH (in HMPA/THF) led to a 23% yield of the 1,4-adduct (the 3-dithianylcyclohexanone).[351] The extent of 1,2- versus 1,4-addition observed in these systems is therefore dependent on the reaction conditions employed.

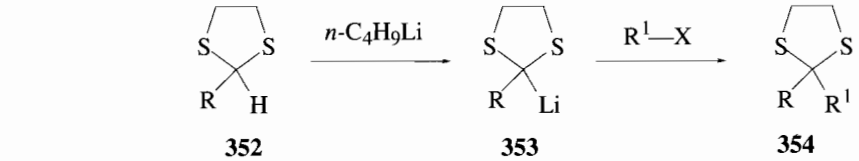
As mentioned above, many reagents have been used for hydrolysis, which is due, in part, to variations in reactivity of the dithiane as the nature of the 2-alkyl group changes. Several problems can arise during

hydrolysis. The reaction becomes acidic so $BaCO_3$, $CaCO_3$, or HgO are often added to maintain neutrality. Hydrolysis of dithianes derived from aldehydes often give acetals in neutral media. When an alkenyl group is present, addition of mercuric ion can give a competitive oxymercuration reaction (sec. 2.10.B). In general, $HgO/BF_3{\bullet}OEt_2$ in aqueous organic solvents is used for hydrolysis of sensitive substrates.[349]

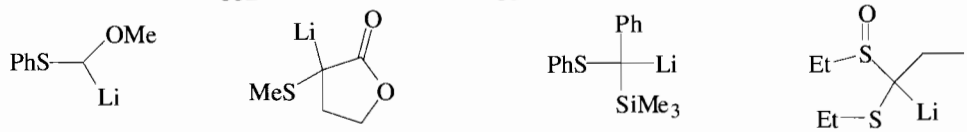


349 **350** **351**

Acyl anion equivalents are not limited to dithianes: virtually any dithioketal or dithioacetal can be used. Another common reagent is dithiolane (**352**).[352] This reagent is prepared from an aldehyde and 1,2-ethanedithiol. Dithiolane (**352**) reacts with organolithium reagents to give the 2-lithio-1,3-dithiolane derivative (**353**), and reaction with an alkyl halide in the usual manner generates **354**. The reaction conditions are very important since lithio dithiolanes such as **353** can fragment (see below) and, for this reason, dithiane derivatives are more commonly used as umpolung reagents. The same reagents that unmasked a dithiane to give back a carbonyl will convert a dithiolane to a carbonyl. Other reagents that function as acyl anion equivalents include **355**,[353] **356**,[354] and **257**.[355]



352 **353** **354**

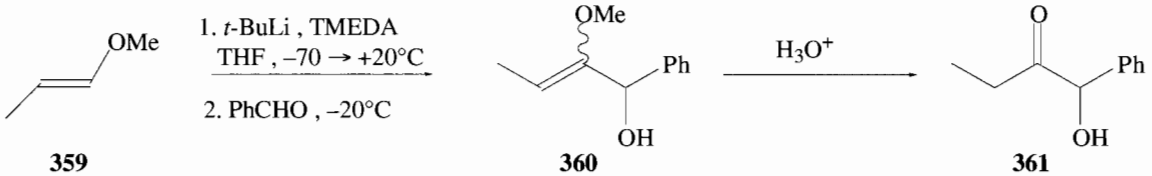


355 **356** **357** **358**

Schlessinger and co-workers used a mixed sulfide–sulfoxide derivative (**358**) to achieve the umpolung. The advantages of this reagent include ease of generation (the proton is more acidic and NaH, KH, LDA can be used), greater stability of the anion, and lower cost. Since the anion is more stable, it is less reactive, and the alkylation reactions generally require higher temperatures.[356] The diethyl derivative is superior to the dimethyl.[357] Acid hydrolysis is more facile, which is important, since dithiane hydrolysis can be sluggish with highly substituted derivatives. The lithio-derivative **358** gave primarily Michael addition (1,4- or conjugate addition) in conjugated systems rather than the 1,2-addition usually observed with dithiane anions.[358] These examples are meant to show that many possible acyl anion equivalents. The exotic reagents are used to fine tune an umpolung reaction when other reagents fail or give poor yields. In general, relatively simple dithiane and dithiolane derivatives are used.

A major drawback to using dithiolane anions is their relative instability when compared with dithiane anions (see discussion of **349**, see above). Lithio-dithiolanes are stable only when R in **353** is an anion stabilizing

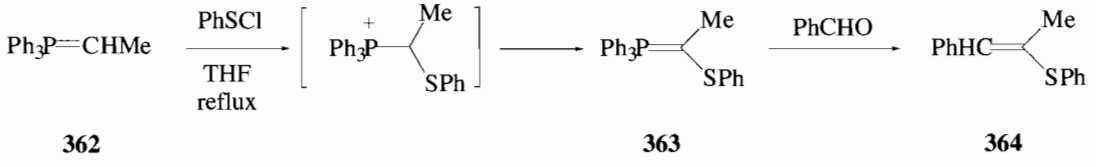
group such as COR or CO_2R, but when used in conjunction with such electron-withdrawing groups, the dithiolane becomes very useful.



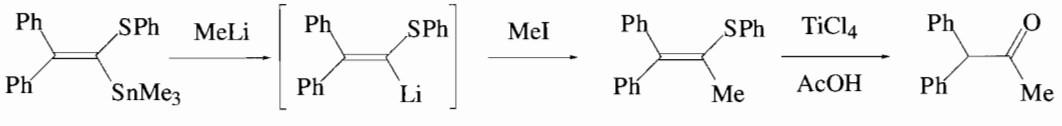
359 **360** **361**

A second major class of acyl anion equivalents are the enol ethers such as methyl 1-propenyl ether (**359**). When **359** was treated with *tert*-butyllithium (note the need for a stronger base with the less acidic vinyl hydrogen) and then condensed with benzaldehyde, the product was **260**.[359] Lithiation of vinyl derivatives was described in Section 8.5. Facile hydrolysis with aqueous acid liberated the corresponding ketone (**361**), completing the acyl anion equivalency. Schlosser co-workers found that a mixture of *sec*-butyllithium and potassium *tert*-butoxide could be used to generate the lithium anion of *O*-tetrahydropyranyl enol ethers.[360] This modification generates a product that is more easily hydrolyzed to the ketone.

Vinyl sulfides can also function as acyl anion equivalents but their preparation has not as yet been discussed. In one common synthesis, a Wittig reagent (**362**, sec. 8.8.A) reacted with benzenesulfenyl chloride to produce a new ylid (**363**), which condensed with benzaldehyde to give a 79% yield of the vinyl sulfide, **364**.[361,364] When **364** was treated with mercuric salts, a 73% yield of phenylacetone was obtained. In the second approach, a vinyl tin compound (**365**)[362] was treated with methyllithium, and lithium–metal exchange provided **366**.[241] Alkylation with iodomethane gave a 91% yield of **367** and treatment with titanium tetrachloride led to a 75% yield of 1,1-diphenylacetone.[241]

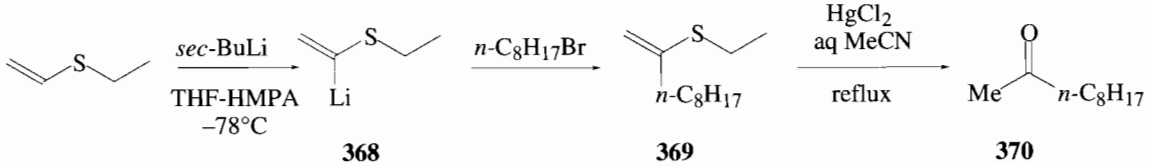


362 **363** **364**



365 **366** **367**

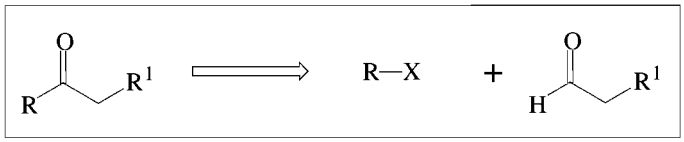
In both cases, sulfur stabilized the lithium derivative and reaction with alkyl halides proceeded in a manner analogous to other vinyllithium reagents. Hydrolysis required mercuric salts or another Lewis acid to give the ketone, as in the preparation of $Ph_2CHCOMe$ from **367**. Another preparation involves direct treatment of an



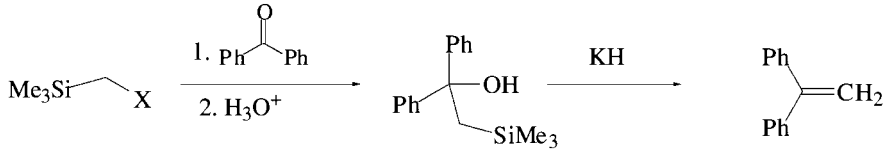
368 **369** **370**

alkylvinyl sulfide, such as ethylvinyl sulfide, with *sec*-butyllithium to give alkenyllithium (**368**). Subsequent treatment with an alkyl halide such as 1-bromooctane led to **369** and hydrolysis with mercuric salts (see sec. 7.3.B.ii for a related reaction with dithioketals and dithioacetals) gave ketone **370** in 90% yield.[363]

The disconnection for vinyl sulfides and enol ethers is

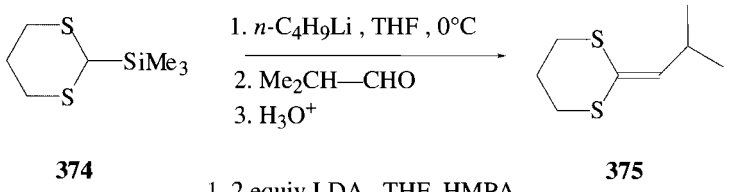


8.6.B.iii. A R(CO)CH$_2^+$ Umpolung Equivalent. Reagents that reverse the usual nucleophilic character of the α-carbon to give **340** (see Table 8.18) are ketene dithioacetals (see **375**, **377,** and **381** below). These compounds can be prepared by several synthetic routes One of the more useful preparations is the **Peterson olefination**,[364] which is an alternative to the Wittig reaction (sec. 8.8.A) in which either trimethylsilylmethyllithium (**371**, X = Li) or its Grignard analog (X = MgBr, MgCl, etc.) reacts with aldehydes or ketones to give a β-silyl alcohol (**372**). Subsequent treatment with base induces elimination of the hydroxyl and the silyl

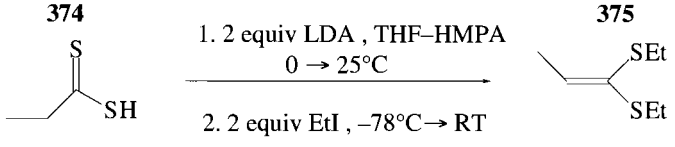


371 **372** **373**

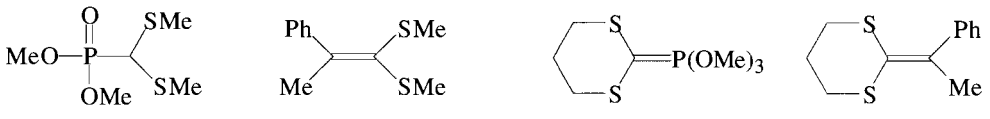
group to give an alkene (in this case 1,1-diphenylethene, **373**).[364] Ketene dithioacetals can be prepared by Peterson olefination with 2-trimethylsilyl-1,3-dithiane (**374**) followed by reaction with an aldehyde (such as isobutyraldehyde to give **375** in 44% yield).[365]



374 **375**



376 **377**

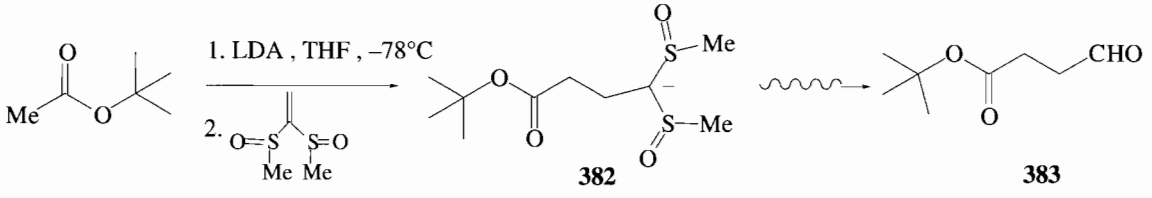


378 **379** **380** **381**

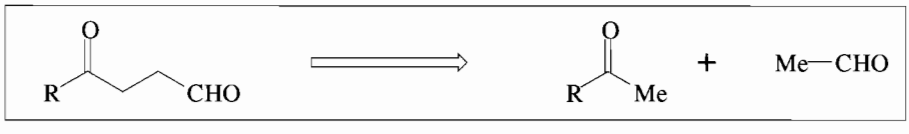
Dithiocarboxylic acid derivatives also provide a useful route to dithioketene acetals (another name for ketene dithioacetals).[366] Treatment of dithiopropionic acid (**376**) with excess LDA (for O-alkylation reactions

see sec. 9.3.B), followed by reaction with excess iodoethane, led to a 97% yield of ketone dithioacetal **377**.[367] Ketene dithioacetals can be prepared by reaction of an aldehyde or ketone with dithioalkyl phosphonate esters such as **378**, which gave excellent yields of the dithioketene acetal upon reaction with aldehydes or ketones.[368] Reaction of **378** with acetophenone, for example, gave **379** in 81% yield. Corey and Märkl showed that phosphonate ylids such as **380** also react with compounds such as benzaldehyde to give the desired product, in that case **381**.[369]

The actual umpolung reaction that allows a ketene dithioacetal to function as if it had an electrophilic carbon α to a carbonyl is achieved by conjugate addition of nucleophiles to the ketene dithioacetal, followed by hydrolysis. Both sulfide and sulfoxide ketene derivatives can be used. Conjugate addition of an ester enolate derived from *tert*-butyl acetate (secs. 9.2, 9.4.B, 9.7.A) to the ketene dithioacetal [CH_2=C(SOMe)$_2$] gave the stable dithioacetal anion (**382**). Conversion of the dithioacetal to the bis(sulfoxide) enhanced the ability of that species to function as a Michael acceptor. Subsequent transformation of **382** gave the aldehyde-ester (**383**).[370]



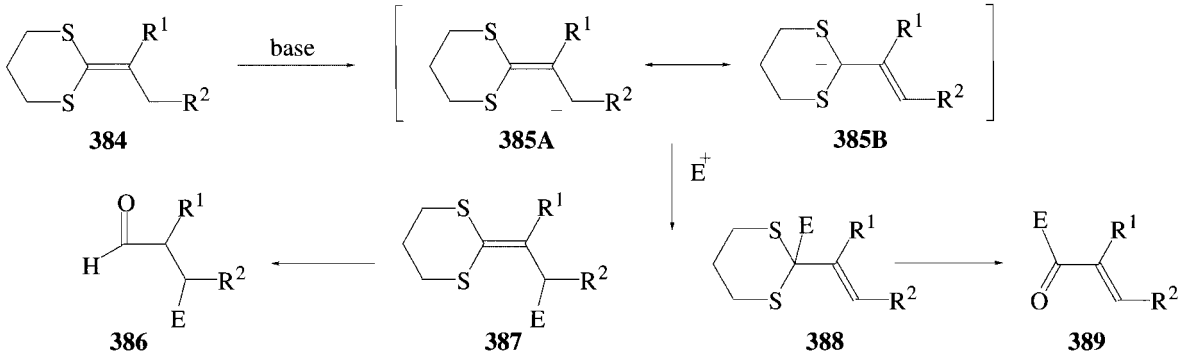
The disconnection for this process is:



8.6.B.iv. R(CO)$CH_2CH_2^-$ Umpolung Equivalents. In this umpolung equivalent (**341**–see Table 8.18), the reactive center is more distant from the carbonyl, making it more difficult to generate the umpolung reagent. Ketene dithioacetals can be used for the umpolung equivalent of **341**, although the yields tend to be low. When the ketene dithioacetal possesses an allylic hydrogen (as in **384**), treatment with a strong base generates a resonance stabilized anion (**385**). Alkylation with an appropriate reagent (E—X) generates two products (**387** and **388**) from each of the two carbanionic centers. Since the carbanion in **385B** is stabilized by two sulfur atoms, **388** usually predominates unless R^2 in **384** is an electron withdrawing group. In that case, **385A** may be stabilized to a greater extent giving **387** as the major product. Hydrolysis of **388** generates **389**. Only **387** will yield the umpolung product (**386**) upon hydrolysis, suggesting that the umpolung is observed as the major process only when R^2 is an electron-withdrawing group. These principles are illustrated by the reaction in Table 8.19.[341c,371] Reaction of the ketene dithioacetal (**384**) with *n*-butyllithium gave a resonance stabilized anion, which could be alkylated at either the α- (**388**) or the γ-position (**387**). It is apparent that R^2 = alkyl, the anion adjacent to the sulfur atoms is the most prevalent and dominates alkylation reactions. As mentioned above, the desired umpolung equivalent is obtained only when the anion (which gives **387** in Table 8.19) is

stabilized by electron-withdrawing groups at R^2 or when a hindered electrophile is used.[371] When R^2 is cyano, the major product was **387**, but when R^2 was *n*-propyl, the major product was **388**.[371]

Table 8.19. Ketene Dithioacetal 385 as a Nucleophilic Umpolung Reagent

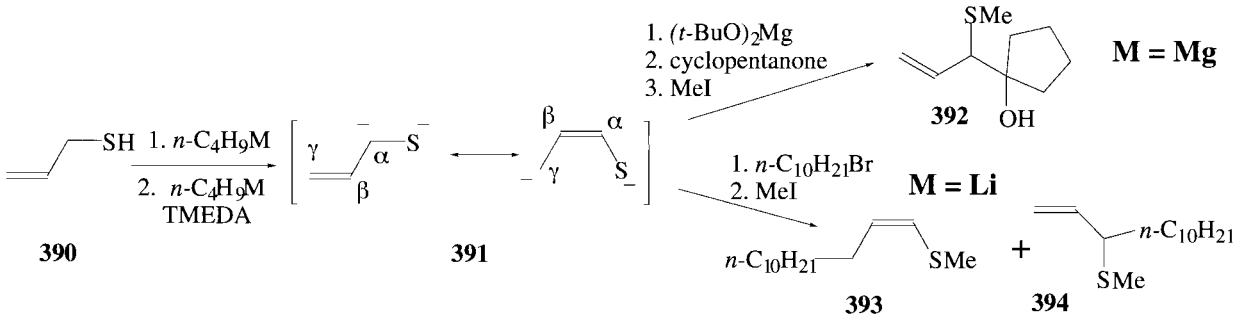


R^1	R^2	E^+	% 388	% 387
H	*n*-Pr	MeI	90	
H	CN	EtI		31–75
Me	I	*i*-PrCl	92	
—$(CH_2)_2$—		$PhCH_2Br$	80	
—$(CH_2)_3$—		C_7H_{15}	75	
—$(CH_2)_4$—	CH_2=$CHCH_2Br$		86	
—$(CH_2)_4$—	PhC(=O)Ph			50

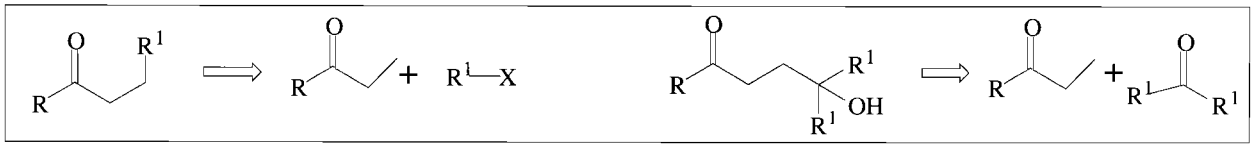
[Reprinted from Gröbel, B.-T.; Seebach, D. *Synthesis, 1977*, pp. 357. Copyright 1977 by Georg Thieme Verlag.]

A more efficient method to generate this umpolung equivalent is via the dianion of allyl thiols. Treatment of allylthiol (2-propene-1-thiol, **390**) with base removes the acidic hydrogen from sulfur, and a second equivalent of strong base removes the hydrogen from the α-carbon to give **391**. The course of the subsequent alkylation reaction depends on the metal counterion of the base.[372] When M = Li (from *n*-butyllithium), alkylation occurs at both the α and γ carbanionic centers (to give **393** and **394**, respectively), but γ-alkylation predominates (a 68:31 mixture favoring **393** in 93% yield).[372,373] When M = Mg (magnesium *tert*-butoxide is added to effect the Li—Mg exchange reaction), substitution occurs predominantly at the carbon α to sulfur, giving **392**.[374] Hydrolysis of **393** with mercuric salts liberated the aldehyde. In general, there is a great preference for reaction at the α-position unless that position is sterically hindered. The solvent, the nature of the R group on sulfur, and the nature of the electrophile play a role as well. Allylic sulfides are used more often than allylic thiols. The monoanion derived from an allylic sulfide also gives α and γ substitution.[375,325b]

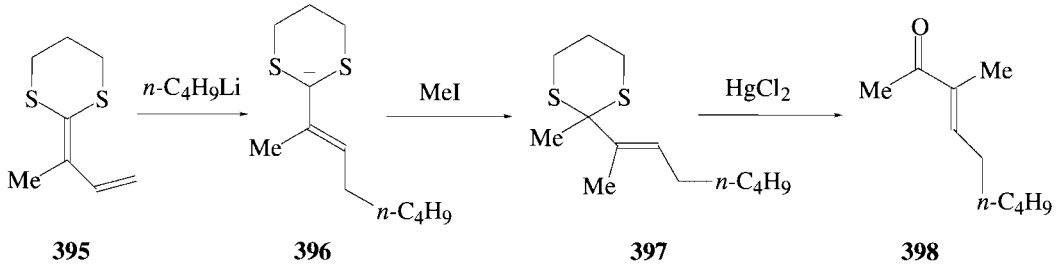
In THF, γ-substitution predominated in reactions of **391** and addition of DABCO increased that yield, presumably by coordination near the sulfur to sterically block that position. Addition of HMPA favors more α-substitution, and addition of a strongly coordinating species such as cryptate blocks the γ-position, which leads to α-substitution as the sole product.



Reasonable disconnections for this process are

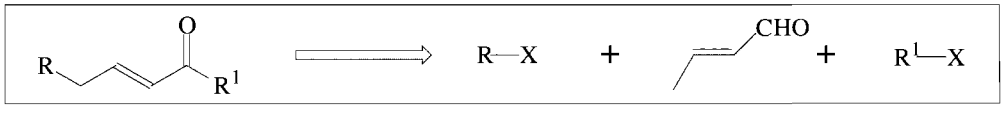


8.6.B.v. A R(C=O)CH$_2$CH$_2$CH$_2^+$ Equivalent. In this umpolung equivalent, the potentially positive center is even further removed from the carbonyl (see **342** in Table 8.18). This umpolung equivalent is best achieved by reaction of a nucleophile with a vinylogous ketene dithioacetal such as **395**.[376] Initial reaction of



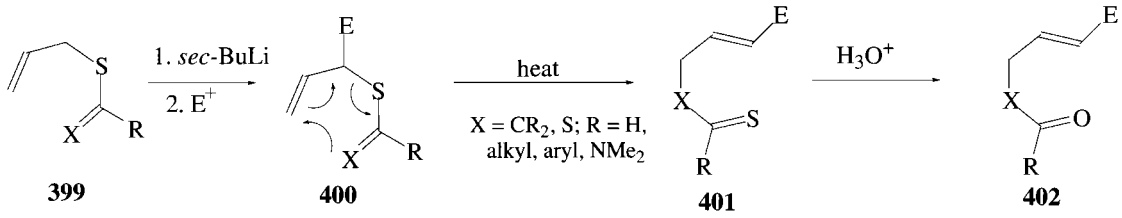
395 with *n*-butyllithium proceeds via Michael type addition rather than deprotonation (there are no acidic hydrogens) to give the ketene dithioacetal anion (**396**). In order to achieve this umpolung equivalent, the ketene dithioacetal *cannot* have an acidic hydrogen present in the dithioacetal unit, since it would be selectively deprotonated. Addition of an alkyl halide such as iodomethane leads to alkylation at the dithiane carbon (to give **397**) and hydrolysis of the dithiane with mercuric chloride leads to the conjugated ketone, **398**.[376] As mentioned earlier, this umpolung reagent is somewhat limited in utility by the requirement that the initial substrate not have acidic hydrogens. It is important to mention what is becoming a pattern. As the umpolung center is removed further from the carbonyl, preparation of the requisite reagents becomes more difficult.

The disconnection is

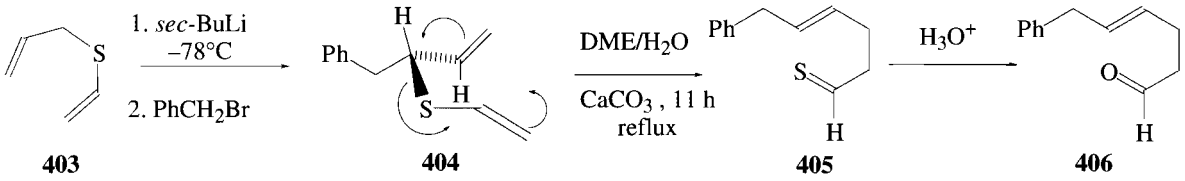


8.6.B.vi. An R(C=O)CH$_2$CH$_2$CH$_2$CH$_2^-$ Equivalent. The final umpolung equivalent in Table 8.18 is **343**, where the reactive center is separated from the carbonyl by three carbons. This umpolung equivalent is

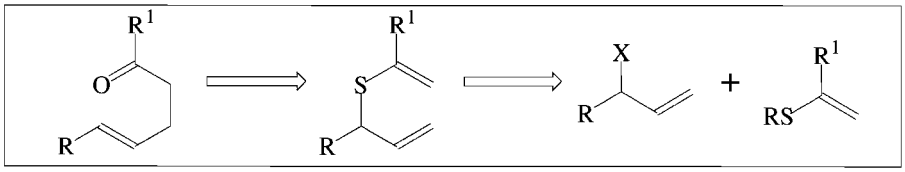
relatively easy to obtain, however, by the use of an allyl vinyl sulfide such as **399**. Upon heating, a thio-Claisen rearrangement (sec. 11.12.D.iii) accomplishes the desired umpolung transformation.[377] A



generalized example is treatment of **399** with base and quenching with an electrophile (E^+) to give **400**. Heating gives the thio-Claisen rearrangement and thiocarbonyl derivative **401**. Subsequent hydrolysis converts the thiocarbonyl to the aldehyde unit in **402**. A simple example is the reaction of allyl vinyl sulfide **403** with *sec*-butyllithium to give the reactive α-lithio sulfide, and this reacted with benzyl bromide to give **404**. Heating in aqueous dimethoxyethane led to the thio-Claisen product **405**, and hydrolysis provided aldehyde **406** in 62% overall yield.[378] The specificity for the trans alkene in **405** arises from the chair-like transition state (see **404**, secs. 11.12.C, 11.12.D), in which the benzyl group is equatorial in the lowest energy conformation leading to product.



The disconnection for this Umpolung is:



The ability to alter normal reactivity patterns of carbonyl derivatives allows a variety of carbon–carbon bond forming processes to proceed. The products derived from these reactions can often be obtained by no other route and provide great flexibility in synthetic planning.

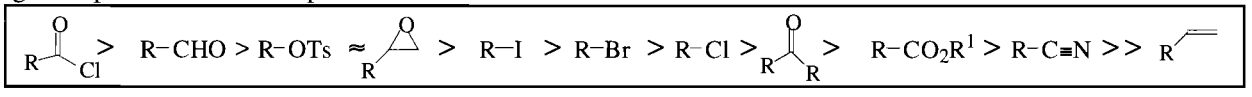
8.7 ORGANOCOPPER REAGENTS (C—Cu)

In all previous sections, the C^d reagent used as a nucleophilic source of carbon was an organometallic derived from sodium, potassium, magnesium, or lithium reagents. In this section the focus will be on a class of reagents that contains a carbon–copper bond, the lithium dialkylcuprates (R'_2CuLi).

8.7.A. Lithium Dialkylcuprates

8.7.A.i. Preparation of Gilman Reagents. Gilman et al. was the first to observe that reaction of cuprous salts, Cu(I), with 2 equivalents of an organolithium reagent generated an organocuprate such as lithium di-*n*-butyl-cuprate (Bu_2CuLi).[379,79] The reagent formed in this way is usually called a **Gilman reagent** and is drawn as R_2CuLi.[379,79] The mechanism[380] of the reaction probably involves an intermediate and transient Cu(III) species, and it may proceed via one-electron transfer.[381] The stability of organocopper species varies considerably with their structure. Dimethylcuprate (Me_2CuLi), for example, was shown by Whitesides and House to be stable in ether for hours at 0°C under nitrogen.[382] Secondary and tertiary cuprates, however, rapidly decompose in ether above –20°C.[382] Disproportionation is the primary decomposition route for organocuprates, and the halide also plays a role in the stability of the cuprate. Cuprous iodide gives better results than cuprous bromide,[382] but the dimethyl sulfide–cuprous bromide complex (Me_2S•CuBr) has been used with success.[383]

There are two major reactions of organocuprates, and both give products reminiscent of a carbon nucleophile: (1) reaction with alkyl halides and (2) conjugate addition with α,β-unsaturated ketones. Conjugate addition to α,β-unsaturated ketones is promoted when ether is used as a solvent.[381] The substitution reaction is promoted by the use of THF or ether–HMPA as a solvent.[381] As mentioned earlier, the mechanism of these reactions probably involves a one-electron transfer, although other mechanistic proposals are in the literature,[384] but the synthetic result is that expected of a carbon nucleophile.[385] The general reactivity of organocuprates with electrophiles follows the order:[381]



The R groups can be primary, secondary, tertiary alkyl, aryl, or heteroaryl and can bear remote functionality such as ethers, acetals or ketals, sulfides, or other labile groups.[381]

8.7.A.ii. Coupling Reactions. In previous sections, Grignard reagents and organolithium reagents usually gave poor yields of coupling products in a reaction with an alkyl halide, unless catalyzed by transition metals. Cuprous salts were used with Grignard reagents to catalyze coupling reactions (sec. 8.4.B.i). Addition of cuprous salts to organolithium reagents give organocuprates (R'_2CuLi), the active species in the coupling reaction and this has become the preferred method for the formation of coupled products (R—R') from alkyl

$$R\text{—}X \quad + \quad R^1{}_2CuLi \xrightarrow[-20°C]{\text{ether}} R\text{—}R^1$$

halides.[386] The reactivity of the cuprate is due in large part to the low ionic character of the Cu—C bond; the low oxidation potential (0.15 eV) separating Cu(I) and Cu(II) ions, the tendency for Cu to form polynuclear Cu clusters, and the formation of mixed-valence Cu compounds.[381] Reaction of organocuprates with alkyl halides, tosylates, or acetates is straightforward in terms of the coupling products that are obtained, but the mechanistic details of this coupling have been a source of some controversy. The reaction of an organocuprate and a primary alkyl halide generally gives good yields of the coupling product (R—R^1) in a

Wurtz-type process[387] (sec. 8.5.B.ii). Table 8.20[382] shows the relative reactivity of di-*n*-butylcuprate with various organohalides to give the alkane R—R'. The reaction proceeds faster and in higher yield in THF than in ether. From this study the order of reactivity of the halide substrate was determined to be RI > RBr > RCl. The secondary halide gave reduced yields and tertiary halides gave virtually no reaction under conditions that produced large amounts of product from primary halides. Sulfonate esters such as mesylates or tosylates and also acetates are susceptible to displacement by organocuprates.[388]

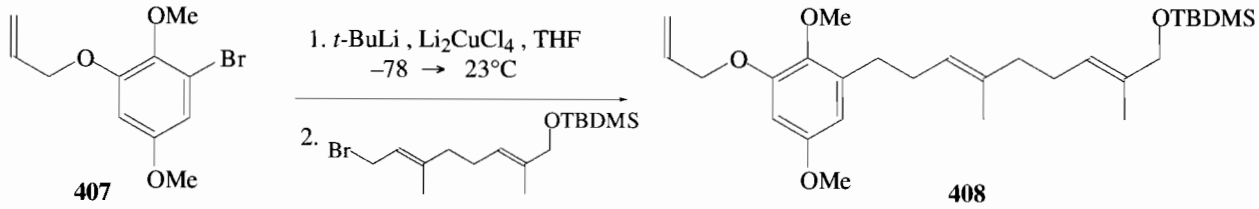
Table 8.20. Relative Reactivity of Lithium Di-*n*-butyl Cuprate with Alkyl Halides

$$R{-}X + n\text{-}Bu_2CuLi \xrightarrow{\text{ether, } -20^\circ C} R{-}n\text{-}Bu$$

RX	Solvent	Time (h)	% R—*n*-Bu
1-Iodopentane	Ether	1	68
		26	70
	THF	1	98
1-Bromopentane	THF	1	98
1-Chloropentane	THF	1	80
	Ether	1	10
		26	10
2-Bromopentane	THF	1	12
		26	12
2-Bromo-2-methylpentane	THF	1	<10

[Reprinted with permission from Whitesides, G.M.; Fischer Jr., W.F.; San Filippo Jr., J.; Bashe, R.W.; House, H.O. *J. Am. Chem. Soc.*, ***1969***, *91*, 4871. Copyright © 1969 American Chemical Society.]

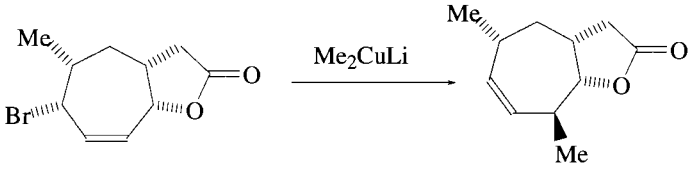
The coupling reaction is extremely useful for joining alkyl fragments or alkyl–aryl, aryl–aryl, or heteroaryl fragments by reaction with alkyl halides or sulfonate esters.[389] In a typical synthetic application, the cuprate derived from **407** (via Li–Br exchange with *tert*-butyllithium and reaction with Li_2CuCl_4 to form the aryl cuprate) reacted with the allylic bromide shown to give a 74% yield of **408** in the Overman and co-workers synthesis of the kinesin motor protein inhibitor adociasulfate 1.[390] It is noted that organocuprates react with secondary bromides with inversion whereas the identical reaction with a secondary iodide proceeds with racemization. In this synthesis, TBDMS is *tert*-butyldimethylsilyl (see sec. 7.3.A.i).



407 **408**

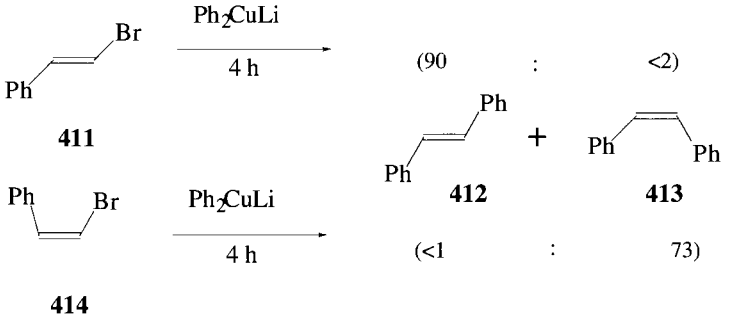
Organocuprates can react with compounds containing an allylic leaving group even when there is steric hindrance, but if the steric encumbrance becomes too great it can also proceed by a S_N2' like pathway (sec. 2.7.A.iii).[391] The reaction of dimethylcuprate and **409** to give the methyl derivative (**410**) illustrates this

process.[392] Allylic halides are not the only substrates susceptible to S_N2' displacement. Cyclopropylcarbinyl halides react with organocuprates such as di-*n*-butylcuprate to give the (*E*)-homoallylic compound.[393]

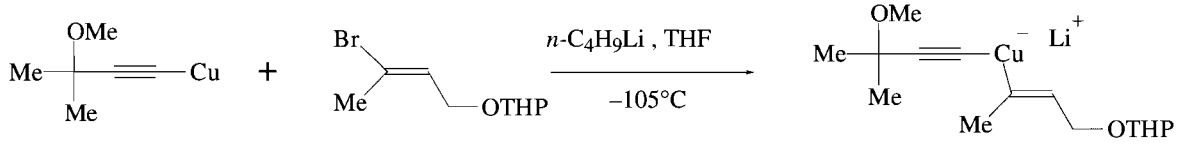


409 **410**

In addition to the expected displacement of alkyl halides, organocuprates react with vinyl halides and aryl halides to give good yields of the coupled product.[394] This alkenyl halide coupling reaction proceeds with high stereoselectivity, in contrast to the Grignard and organolithium coupling reactions. (*E*)-2-Bromostyrene (**411**) reacted with diphenylcuprate to give a 90:<2 mixture of (*E*/*Z*) stilbenes (**412/413**).[387] Similarly, the (*Z*)-bromide (**414**) gave a <1:73 mixture of **412/413**.[387] It is apparent that the coupling proceeded with little or no loss of stereochemical integrity of the vinyl bromide. Vinyl sulfonate esters such a triflate derivatives [triflate = OTf = $—SO_2CF_3$] also react with organocuprates to give the coupling product.[395]



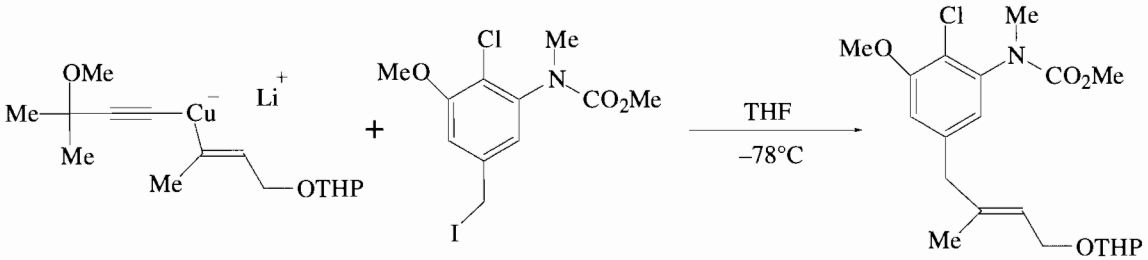
Coupling reactions with alkyl halides often use large excess of cuprate, as mentioned above, which can be a severe limitation if the halide precursor to the organocuprate is difficult to prepare or unavailable from commercial sources. A solution to this problem is to prepare a cuprate with a ligand that is less reactive, allowing selective transfer of the substituent of choice. An example is the use of **417** in a reaction with **418** that



415 **416** **417**

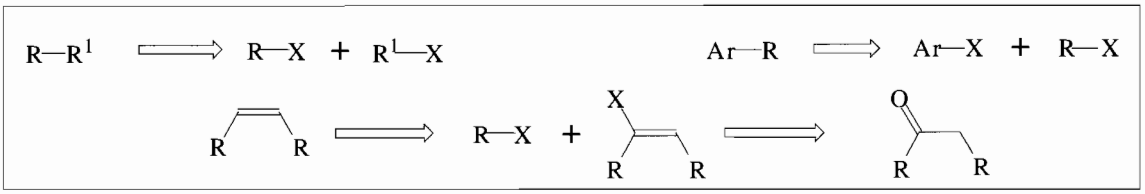
gave **419**, an intermediate in Corey's synthesis of *N*-methylmaytansine.[396,347] The alkynyl–copper bond in species such as **417** is very stable relative to alkyl–copper and alkenyl–copper bonds. When an alkyl-alkynyl cuprate or an alkenyl–alkynyl cuprate is prepared, the alkyl or alkenyl group will be transferred selectively. Cuprate **417** was prepared by reaction of the Cu(I) species **415** with vinyl bromide **416** in the presence of *n*-butyllithium.[396] It is noteworthy than only the alkenyl group was transferred to the benzylic iodide and not

the alkynyl moiety. In general, this method allows a synthetically prepared halide such as **416**, which may be difficult to obtain in pure form, to be coupled to another halide with greater efficiency.

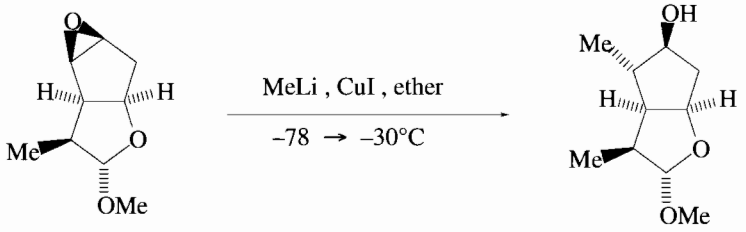


417 **418** **419**

The alkyl or aryl halide –organocuprate coupling disconnection is

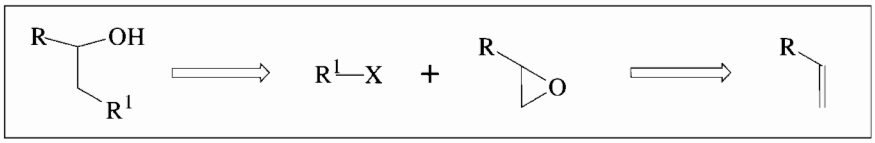


8.7.A.iii. Reaction with Epoxides. Organocuprates also react with epoxides,[397] with addition occurring at the less sterically hindered carbon, typical of a nucleophilic addition. In the Olivo and co-workers synthesis of the C1-C9 fragment of cappipeltoside-A, dimethylcuprate was formed *in situ* and reacted with epoxide **420** to give **4221** in 73% yield, .[398] The ring opening was highly selective for the alcohol shown.

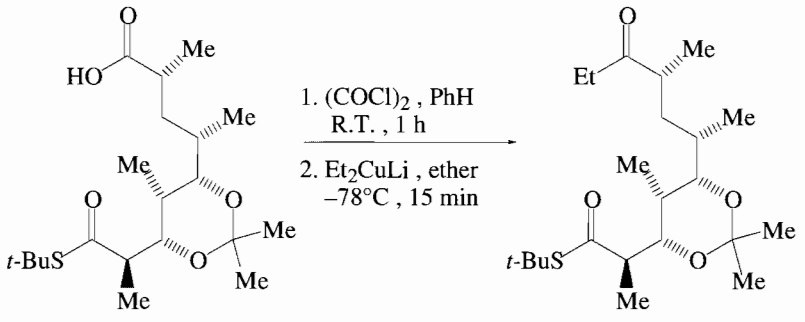


420 **421**

The epoxide –organocuprate disconnection is

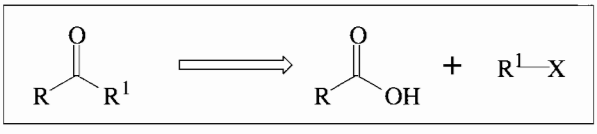


8.7.A.iv. Reaction with Acid Chlorides. As briefly mentioned in Section 8.4.C.ii, the reaction of a dialkyl cuprate and an acid chloride is a preferred method to synthesize ketones.[399,400] The reaction with acyl halides usually requires low temperatures to isolate the ketone product.[388,387] This method is usually preferable to and more general than one that uses dialkylcadmium reagents (sec. 8.4.C.ii). Masamune et al. used this reaction to convert acid **422** to ketone **423** in a synthesis of erythronolide.[401] In this case, oxalyl chloride was used to prepare the requisite acid chloride because of the sensitive nature of the molecule.

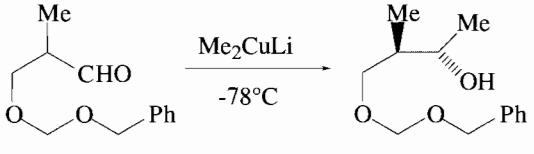


422 **423**

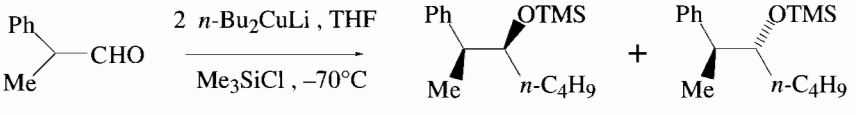
The acid chloride–organocuprate disconnection is



8.7.A.v. Reaction with Aldehydes and Ketones.[402] The reaction of organocuprates with aldehydes is fast. Dimethylcuprate reacted with benzaldehyde to give phenylethyl alcohol at < –90°C,. Ketones react more slowly as illustrated by the reaction of dimethylcuprate and 5-nonanone, which occurred at about –10°C to give 5-methyl-5-nonanol.[403] No reaction occurred at lower temperatures. Higher temperatures are often required for reaction of hindered aldehydes, leading to significant decomposition of the organocuprate via disproportionation before the addition reaction occurs. Still showed a typical cuprate addition to an aldehyde



424 **425**



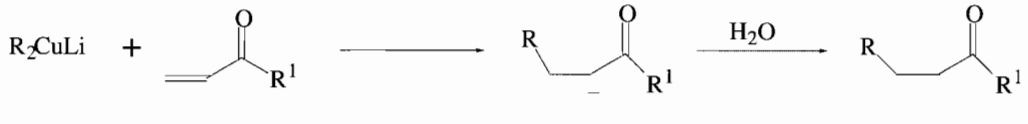
426 **427** **428**

when dimethylcuprate reacted with **424** (at –78°C) to give **425**.[404] In this case the excellent diastereoselectivity (30:1 anti:syn **425**) was the result of chelation control (secs. 4.7.B, sec. 6.2.E). The cuprate addition usually follows Cram's rule (sec. 4.7.B) in the absence of chelation effects. Di-*n*-butylcuprate reacted with **426** in the presence of chlorotrimethylsilane to give a 6.4:1 mixture of **427/428** (**428** is predicted by Cram's rule, the Cram product).[405] As mentioned above, ketones react very slowly with cuprates. This problem can be alleviated by adding chlorotrimethylsilane to the reaction (this was used in the reaction of **426**). With conjugated ketones, addition of chlorotrimethylsilane enhances the rate of 1,2-addition. It also enhances Cram diastereoselectivity when an organocuprate reacts with a chiral aldehyde.[405] There is a clear

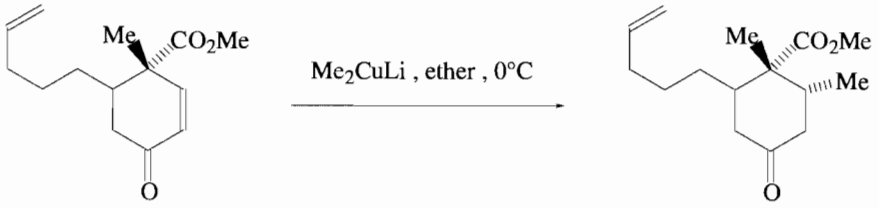
enhancement of rate and this is probably not just a consequence of trapping the enolate anion that results from conjugate addition. The precise mechanism is unclear but may be related to an equilibration reaction for organocuprate conjugate additions.[404]

8.7.A.vi. Conjugate Addition. Organocuprates react with α,β-unsaturated conjugated aldehyde and ketone derivatives such as **429** to give almost exclusive 1,4-addition.[406] Initial conjugate addition generates an enolate anion (**430**–secs. 9.2.A, 9.7.A), and hydrolysis gives the ketone **431**. A straightforward synthetic example is the reaction of conjugated ketone **432** with dimethylcuprate to give a 93% yield of **433**, taken from Maier's synthesis of dysidiolide.[407]

After the initial addition of a cuprate to a conjugated system, an enoate anion is formed. When the mixed cuprate showed a reaction with cyclopentenone, for example, the product is enolate anion **434**. This

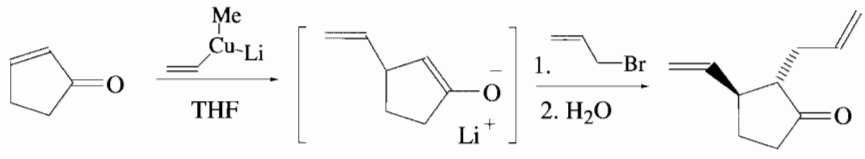


429 **430** **431**



432 **433**

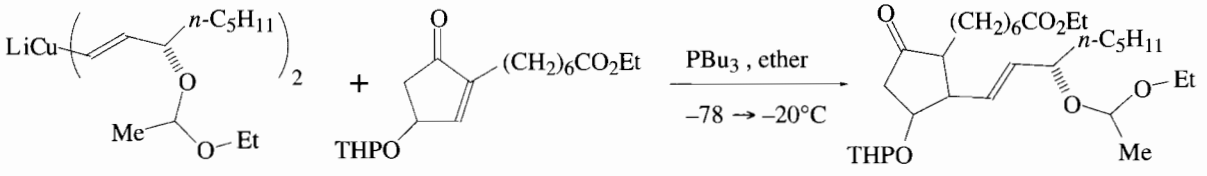
nucleophilic enolate anion can react with an alkyl halide that is added to the reaction, generating an alkylated ketone as the product (sec. 9.3.A). In this particular case, treatment with allyl bromide gave 3-vinyl-2-allylcyclopentanone (**435**) in 69% yield. Addition of water or aqueous acid to **434**, gave 3-vinylcyclopentanone.[408] The ability to add two alkyl substituents via conjugate addition and then alkylation with an alkyl halide (a double alkylation) is one of the more powerful applications of conjugate addition with organocuprates. In general, the two groups have a trans relationship,[407] but the cis–trans ratio in products such as **435** varies with the organocuprate.



434 **435**

The reaction is not limited to the use of simple organocuprates: very complex cuprates can be prepared and then reacted with complex carbonyl partners, leading to products with very sophisticated structures. Mixed cuprate **417** was one example. Another example that used an unsymmetrical organocuprate is Sih's reaction of

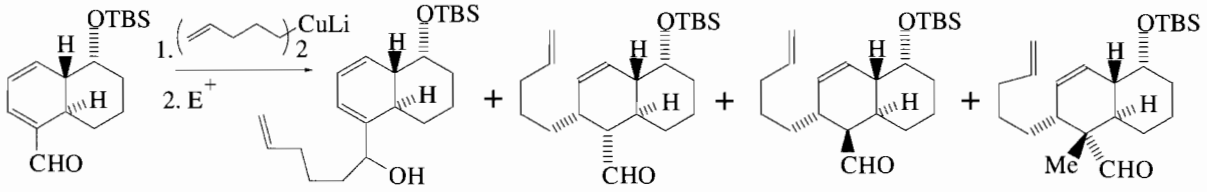
(–)-dialkenylcuprate (**436**) with **437** to give **438**, an intermediate in a prostanoid synthesis.[409,410] As with all Michael-type additions, the reaction of organocuprates is somewhat sensitive to steric effects at the reactive π bond. Addition usually occurs to the less sterically hindered position. Steric hindrance also plays a role in the diastereoselectivity of the reaction. Heathcock et al. showed that the position of the substituent relative to conjugated system is a significant factor in the formation of (*E*) or (*Z*) isomers from cycloheptenones.[411] The larger the group on the ring and the closer to the β-carbon, the greater the stereoselectivity.



436 **437** **438**

Because of the reactivity of aldehydes with cuprates (sec. 8.7.A.v), 1,2-addition to α,β-unsaturated aldehydes can compete with 1,4-addition, although the former usually predominates. α,β-Unsaturated ketones normally give 1,4-addition. In Table 8.21,[412] Marshall showed how the copper reagent and proportion of RLi to Cu influenced the ratio of 1,2- to 1,4-addition with **439** and di(4-pentenyl)cuprate. Reaction with this

Table 8.21. Organolithium/Cuprous Halide Ratio in 1,2 versus 1,4-Addition of Organocuprates to 439



439 **440** **441** **442** **443**

Conditions	E^+	% 440	% 441	% 442	% 443
2RLi, CuI, Me_2S 2:1 ether/THF, 14 h	MeI	17	37	19	7
2RLi, CuBr•SMe_2 2:1 ether/THF, 14 h	MeI	17[a]	20	16	8
1.8 RLi, CuI, Me_2S 1.6:1 ether/THF, 14 h	MeI	0	30	22	33
1.8 RLi, CuI, Me_2S 1.8:1 ether/THF, 10 h	H_3O^+	0	65		
1.6 RLi, CuI, Me_2S 1.6:1 ether/THF, 14 h	H_3O^+	0[b]	0		
1.8 RLi, CuI, Me_2S 1.6:1 ether/THF, 14 h	1. TMSCl 2. H_3O^+	0	91		

[a] + 10% of **439**. [b] + 92% of **439**.

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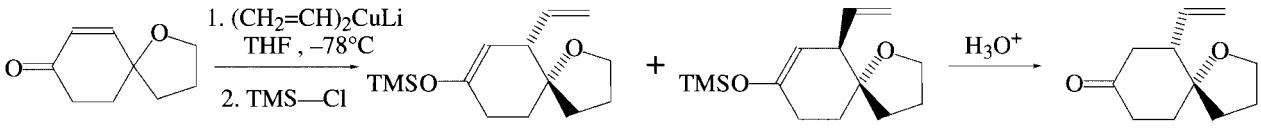
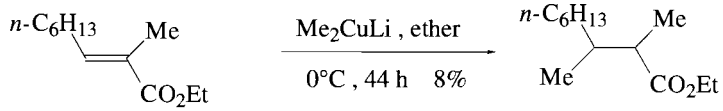
cuprate gave the 1,2-addition product **440**, the 1,4-addition products **441** and **442** and the dialkylation product **443** when the initial addition product was quenched with iodomethane. Diminishing the RLi/Cu ratio to <2:1 suppressed 1,2-addition. The best yields were obtained when the intermediate enolate was trapped with chlorotrimethylsilane, which was mentioned above with the reaction of **426** with di-*n*-butylcuprate. The improvement in yield is presumably due to its rate accelerating influence.[413,414] The enhanced diastereoselectivity can be seen in the addition of divinylcuprate to **444**, which gave two racemic enol silyl ethers, **445** and **446**. In the absence of chlorotrimethylsilane the ratio of enolates was 56:44 (this is also the diastereomeric ratio of **445/446**, although the silyl enol ether cannot be formed without addition of chlorotrimethylsilane). The addition of chlorotrimethylsilane to the cuprate addition product increased this ratio to >99:1 (**445/446**).[414] Isolation of **441** was followed by hydrolysis to give **447** as the major product.

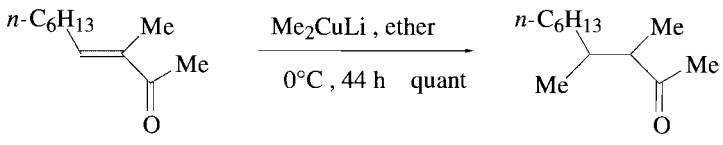


444 **445** **446** **447**

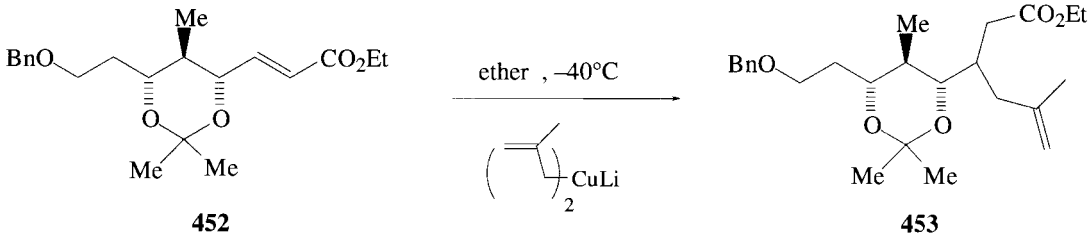
Conjugated esters are less reactive than the corresponding ketones.[415] Conjugate addition to ester **448** gave only 8% methylated product **449** after reaction with dimethylcuprate for 44 h. The analogous ketone (**450**) gave a quantitative yield of **451** under the same conditions. Although conjugated esters usually react slower than conjugated ketones, they do give conjugate addition products unless a more reactive group is present in the molecule. Addition of the diallylcuprate shown to ester **452**, for example, gave the alkylated ester (**453**), an intermediate in Nicolaou's synthesis of tylosin.[416] It is important to note that conjugated esters show greatly enhanced reactivity when RCu•BF_3 is used as the organocopper reagent.[417] With highly hindered systems, especially β,β-disubstituted conjugate esters, RCu•BF_3 is the reagent of choice.[418]



448 **449**

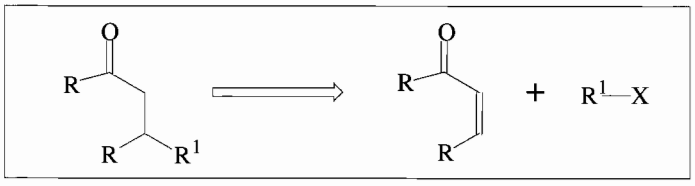


450 **451**

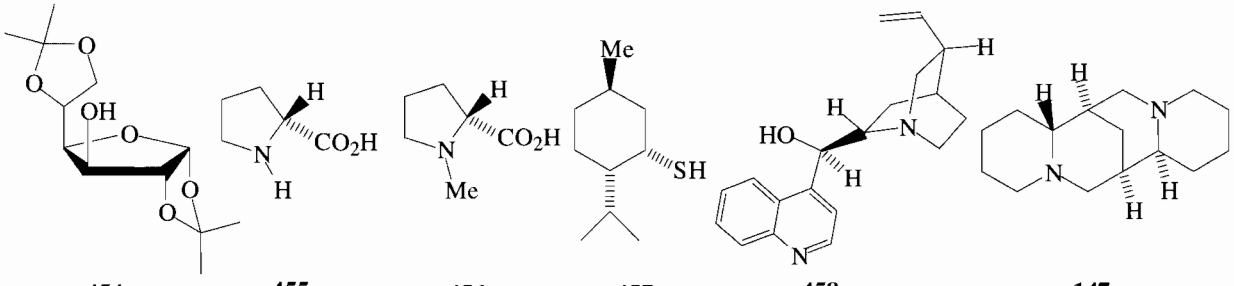


452 **453**

The disconnection for cuprate conjugate addition is

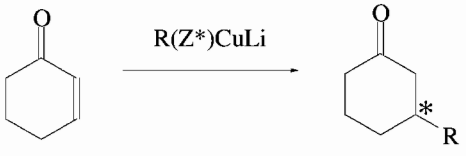


8.7.A.vii. Asymmetric Induction. Addition of an organocuprate to a conjugated system often creates a new stereogenic center, so a discussion of diastereoselectivity and possible enantioselectivity is appropriate. Controlling asymmetric induction in organocuprate addition reactions has been done principally by using organocuprates whose chirality has been modified.[419] In Table 8.22[419] there are several examples that use chiral groups, including 1,2,5,6-di-*O*-isopropylidene-α-*D*-glucofuranose (**454**), (*S*)-proline (**455**), (*S*)-*N*-methylproline (**456**), and neomenthyl thiol (**457**). Addition of the organocuprate that possessed a chiral ligand to cyclohexenone gave the chiral ketone, **459**.[419] It can also be seen in this table that this is a generally poor method for achieving asymmetric induction when simple chiral additives are used.



454 **455** **456** **457** **458** **147**

Table 8.22. Asymmetric Induction in Conjugate Addition of Organocuprates Containing Chiral Ligands to Cyclohexenone



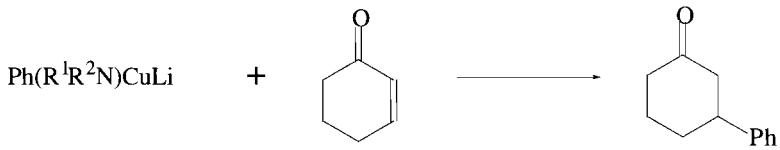
459

R	Z*	Solvent	Temp. (°C)	% 459	% ee
Me	**454**	ether	0	-	6.5, (*S*)
Me	**455**	ether	–5	-	15.5, (*S*)
Bu	**456**	ether	–70	26	4.7
Bu	**457**	THF	–90	66	15.3
Me	**455**	PhH	0	61	26, (*S*)

In acyclic systems, Mukaiyama and co-workers found that addition of chiral magnesium cuprate R(A*)CuLi derived from **456** gave good asymmetric induction.[420] Lithium cuprates derived from **458**,

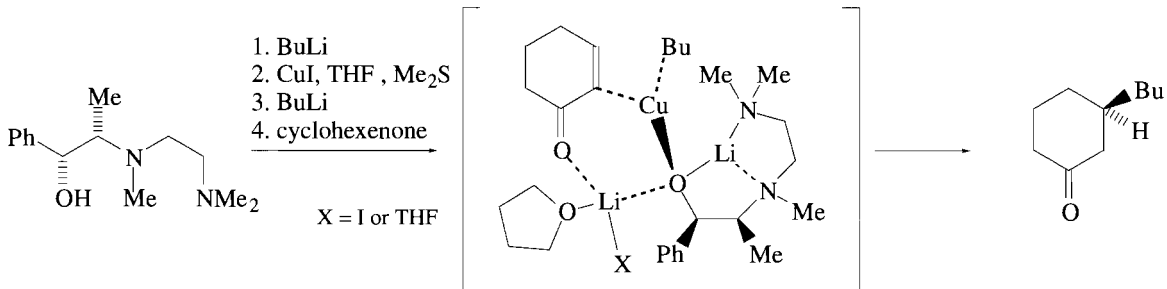
however, gave the addition product in poor yield and in very modest % ee.[421] Kretchmer also used the alkaloid (–)-sparteine (**147**) as a complexing agent with magnesium cuprates ($RCuMgX_2$), but observed < 10% optical purity upon addition to α,β-unsaturated ketones.[422] Langer and Seebach observed products with up to 27% optical purity when the co-solvent for the reaction was (*R,R*) or (*S,S*)-1,4-(dimethylamino)-2,3-dimethoxybutane.[423] Gustafsson used cuprates containing an asymmetric ligand (RR*CuLi) where R* = (–)-[1-(dimethylamino)ethyl] phenyl[424] or *o*-[cyclohexyl(dimethylamino)methyl]-phenyl,[425] but these gave < 5% ee in organocuprate reactions.

Bertz showed that cuprates such as **460** added to cyclohexenone to give the 3-phenyl derivative (**46`1**) in optical yields of 0–50%.[426] Typical examples are R^1R^2N = (4*S*,5*S*)-(+)-5-amino 2,2-dimethyl-4-phenyl-1,3-dioxane (the reaction proceeded in 62% yield, 50% ee); (R) or (S) α-methylbenzylamine (70% yield, 30% ee); (*R*) or (*S*) α-(1-naphthyl)ethylamine (70% yield, 30% ee); and (–) α-2-naphthylethyl-amine (50% yield, 40% ee).[426]



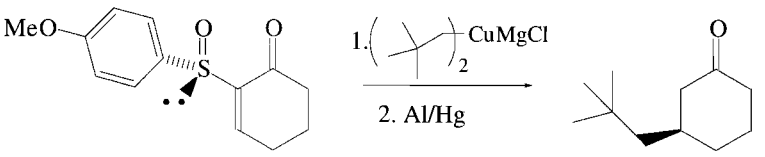
460 **461**

This discussion is intended to show the various approaches used to achieve asymmetric induction and the generally poor results that were observed. More recently, good-to-excellent asymmetric induction has been achieved with a new generation of chiral additives or chiral ligands.[427] Corey et al. achieved enantioselectivities in the 75–95% range with the chiral controller ligand **462**, obtained from (+) or (–)-ephedrine.[428] This chiral ligand was converted to the asymmetric copper complex (**463**) upon reaction with cyclohexenone and transfer of the butyl group gave 3-butylcyclohexanone (**464**) in 80% yield (80% ee).[428] Similar reaction with ethyllithium gave the ethyl derivative in 66% yield with an optical purity > 95% ee. If the organolithium reagent was heavily contaminated with alkoxides, however, the optical purity was as low as 9% ee.



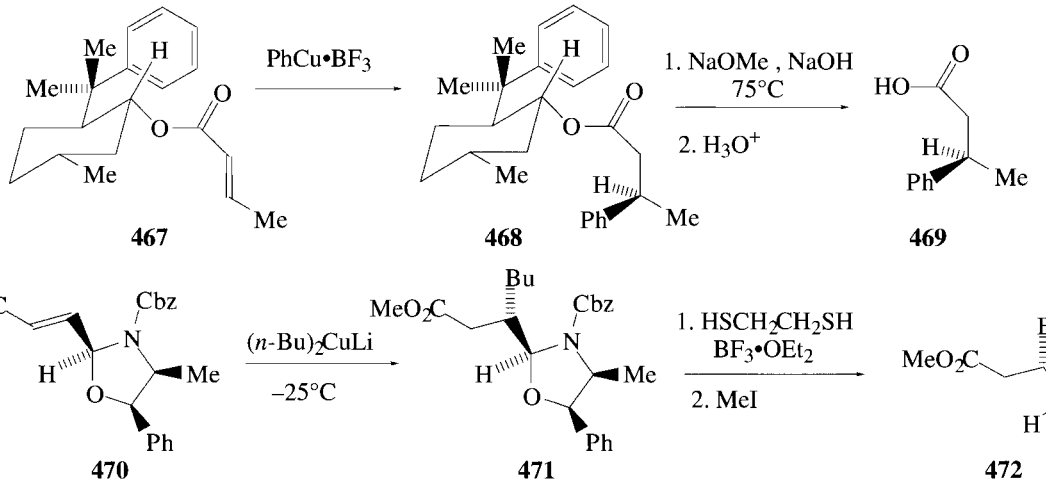
462 **463** **464**

A different approach to solving this problem is to attach a chiral auxiliary to the enone substrate. The auxiliary is a chiral material that is attached to an achiral substrate. The asymmetry of the auxiliary controls the selectivity of the reaction and is then removed in a separate chemical step. Posner studied the use of optically pure α-carbonyl-α,β-ethylenic sulfoxides (**465**, see sec. 3.9.A.ii for the preparation of optically active sulfoxides).[429] Conjugate addition of di-(2,2,-dimethylpropyl)magnesium cuprate to the chiral



465 **466**

sulfoxide was followed by reductive cleavage of the C—S bond of the sulfoxide with aluminum amalgam to give a 7:1 (*R*/*S*) mixture of 3-(2,2-dimethylpropyl)cyclohexanone (**466**) in 99% yield.[429] Oppolzer and Löher used a different auxiliary, preparing (–)-(8*E*)-phenylmenthyl acrylates such as **467**.[430] The conformational stability of the cyclohexyl ring in **467** ensured that the phenyl group blocked one face of the α,β-unsaturated ester, leading to excellent facial selectivity during the addition. Conjugate addition (here with phenylcopper–boron trifluoride–see the previous discussion in sec. 8.7.A.vi) followed by saponification of the ester (**468** was formed in 76% yield) gave the acid **469** in > 99% ee. Oppolzer et al. also reported excellent diastereoselectivity for addition of organocopper derivatives to α,β-unsaturated sulfonamides derived from camphor (see sec. 11.9.A for further discussion of chiral auxiliaries).[431]

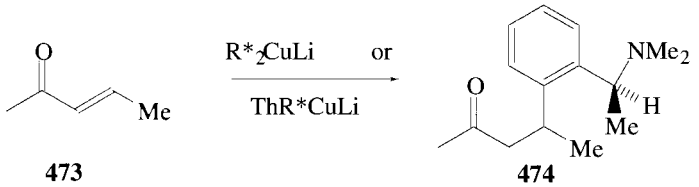


467 **468** **469**

470 **471** **472**

Other asymmetric substrates can be used with organocuprates. One example is Scolastico's report that reaction of **470** with di-*n*-butylcuprate gave a 70% yield of **471** (78–98 % ee).[432] Using this auxiliary, alkylated ester **471** was converted to aldehyde **472** in 80% yield with 91% asymmetric induction.[432]

A less general method involves transfer of a chiral group from the cuprate to the enone. The chiral Gilman reagent [R*$_2$CuLi, R = (*R*)-2-(1-dimethylamino)phenyl] reacted with (4*E*)-methyl-3-penten-2-one (**473**) to give **474** in 30% yield and 80% ee.[433] Reaction of the mixed cuprate [ThR*CuLi where Th = 2-thienyl and R* = (*R*)-2-(1-dimethylamino)phenyl] gave **474** in 70% yield (82% ee).[433]



473 **474**

8.7.B. Higher Order Cuprates

Cuprates are very useful but there are a few problems associated with them. In an attempt to circumvent these problems, Lipshutz developed the so-called *higher order mixed cuprates* ($R_2Cu(CN)Li_2$),[434] prepared by reaction of 2 equivalents of organolithium reagent with cuprous cyanide (CuCN).[435] Mixed cuprates react

$$2\ R\text{—}Li + CuCN \longrightarrow R_2Cu(CN)Li_2$$

faster than Gilman reagents with alkyl halides, even secondary halides, and are considered to be the reagent of choice for this purpose, which is illustrated in Table 8.24[436a] for the reaction of alkyl halides with the higher order cuprate derived from butyllithium and cuprous cyanide to give the alkane, R-*n*-Bu. It is noted that Bertz questioned the validity of structure of cuprates such as $R_2Cu(CN)Li_2$, citing ^{13}C NMR evidence that the reagent actually existed as $R_2CuLi{\bullet}LiCN$ in THF.[437] This conclusion was contradicted by Lipshutz[438] who compared the ^1H and ^{13}C NMR spectra of the higher order cuprate $Me_2Cu(CN)Li_2$ with those of $Me_2CuLi{\bullet}LiBr$ and $Me_2CuLi{\bullet}LiI$ and concluded that the spectra were not at all similar. Lipshutz concluded that the spectra proved the presence of a Cu—CN bond and a higher order cuprate structure. *Ab initio* evidence,[439a] as well as kinetic evidence[439b,c] by Bertz again calls these structures into question and suggests their structure is best described as cyano-Gilman reagents, as does additional NMR evidence by Bertz.[440]

Table 8.24. Reaction of Higher Order Cyanocuprates with Alkyl Halides

$$R\text{—}X + 2\ n\text{-}Bu_2Cu(CN)Li_2 \longrightarrow R\text{—}n\text{-}Bu$$

Halide	Temp (°C)	Time (h)	% R—*n*-Bu
Iodocyclopentane	–78	2	82
Bromocyclopentane	0	6	86
Iodocyclohexane	–78	1	100
Bromocyclohexane	RT	6	41
2-Iodopentane	—50	2	99
2-Bromopentane	0→RT	2	94
2-Chloropentane	RT	11	28
2-Tosyloctane (10 equiv cuprate)	RT	8	>80

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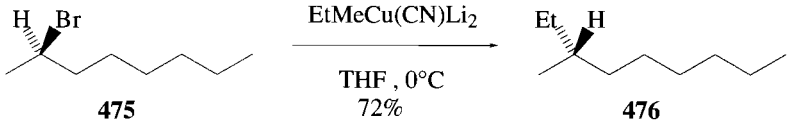
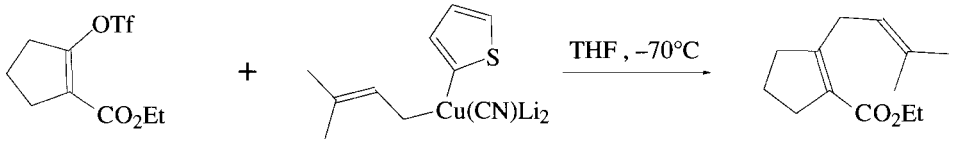
Organocuprates react with chiral halides to give chiral coupling products. When (*R*)-2-bromooctane (**475**) reacted with the mixed-cuprate [$EtMeCu(CN)Li_2$], a 72% yield of (*R*)-3-methylnonane (**476**) was obtained,[436b,c] which is the result expected of a nucleophilic S_N2 like displacement of the bromide. As mentioned in Section 8.7.A, the reaction probably proceeds via single electron-transfer process, but the stereochemistry of this reaction mimics nucleophilic substitution. The extent of inversion is very dependent on the nature of the reacted organocuprate, however. 2-Iododecane derivatives showed virtually no inversion of configuration when with Gilman-type reagent or with higher order cuprates.[436a] Bromides, on the other hand,

gave virtually complete inversion with both reagents.[436a] The smallest amount of inversion was obtained with symmetrical cuprates, and the largest amount with mixed cuprates.



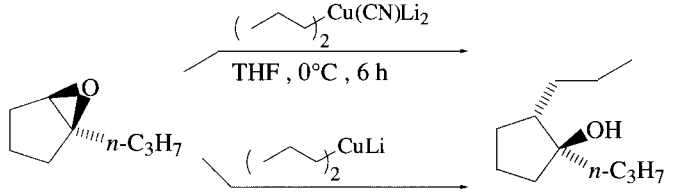
475 **476**

This displacement reaction is not limited to allyl derivatives or to substrates bearing halide leaving groups. Both vinyl and aryl derivatives can be reacted with higher order cuprates, as with Gilman reagents. Lipshutz and Elworthy found that vinyl triflates are particularly useful in cuprate coupling reactions. The reaction of vinyl triflate **477** reacted with the mixed cuprate **478**, gave **479** in 87% yield.[441] An interesting feature of

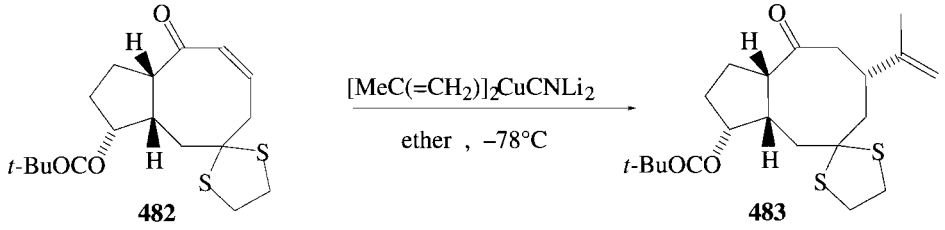


477 **478** **479**

cuprate **478** is the presence of 2-thienyl as an unreactive ligand (see **417**). Lipshutz et al. found this to be most effective in for the selective transfer of the group other than thienyl,[442] which is, of course, analogous to the use of alkynyl groups as unreactive substituents in Gilman reagents. The mixed-alkyl cuprates are easily prepared by sequential addition of two different organolithium reagents to cuprous cyanide. In general, for reagents such as R(Me)Cu(CN)Li_2 (R > Me), the R group is transferred selectively for both the halide displacement and the conjugate addition.



480 **481**

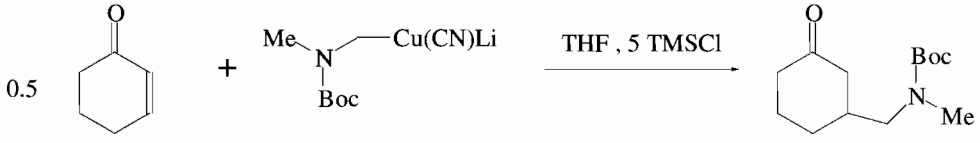


482 **483**

Epoxide ring opening is more efficient with the higher order cuprate than with Gilman reagents, and attack is at the less sterically hindered carbon.[436a] Reaction of **480** with di-*n*-propylcuprate, for example, gave only 15–30% of **481**. Similar reaction with $Pr_2Cu(CN)Li_2$ gave an 86% yield of **481**.[443,444] Higher order cuprates

give excellent yields of conjugate addition with α,β-unsaturated compounds, analogous to results with Gilman reagents.[445] In the Trost and Paquette synthesis of 11-hydroxyjasionone,[446] conjugated ketone **482** reacted with the higher order vinyl cuprate shown to give a 90% yield of **483**.

Dieter et al. developed an α-aminoalkylcuprate, that allows nitrogen to be incorporated into a substrate. When cyanocuprate **484** reacted with cyclohexenone, for example, in the presence of chlorotrimethylsilane, a 98% yield of the conjugate addition product **485** was obtained.[447a]

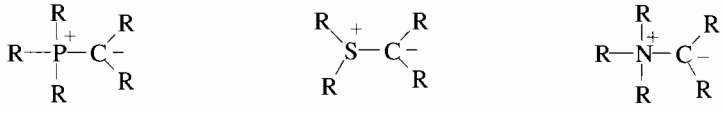


484 **485**

The disconnections for the higher order cuprate are identical to those observed with Gilman reagents.

8.8. YLIDS

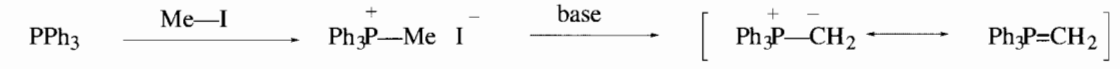
In this section, ylids are defined as compounds in which a carbanionic carbon is immediately adjacent to an atom bearing a positive center. Many atoms can support a positive charge but phosphorus, sulfur and nitrogen lead to particularly useful and interesting compounds. This section will deal with ylids and their reactions, focusing on phosphorus ylids such as **486**, sulfur ylids such as **487,** and nitrogen ylids such as **488**. Of these three classes of ylids,[448] the phosphorane ylids (**486**) and other phosphorus ylids are the best studied due to their relative stability and ability to generate alkenes from carbonyl compounds. The sulfur ylids (**487**) are also well known,[449] and generally react as carbanions with carbonyl derivatives to give oxiranes or cyclopropane derivatives. The nitrogen ylids (**488**) are not as well known as isolable entities, but have a few synthetic applications.[450]



486 **487** **488**

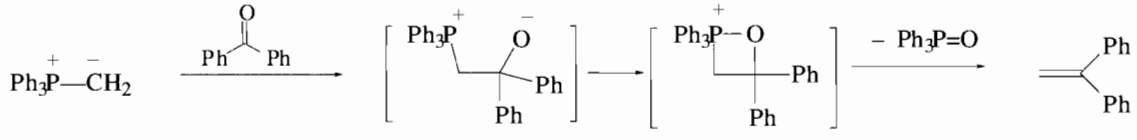
8.8.A. Phosphorus Ylids

8.8.A.i. Wittig Reagents. Phosphorus ylids have a history dating to the 1890s and to the pioneering work of Michaelis and Gimborn.[451] The reactivity of ylids was first exploited by Wittig who found that phosphonium salts (**489**) were generated by an S_N2 reaction of a trialkylphosphine with an alkyl halide. These phosphonium salts were shown to react with strong bases to give the corresponding ylid (**490**), a resonance stabilized species. Wittig was attempting to make pentavalent phosphorus by this synthetic route, and the discovery of these phosphorus ylids may have been serendipitous.



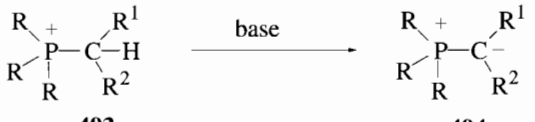
489 **490**

In earlier work, Staudinger and Hauser found that phosphazines ($R_3P{=}N{-}N{=}CR_2$) generated $R_3P{=}CR_2$ upon heating and he examined some of the chemistry of these phosphorus ylids,[452] but Wittig discovered that they reacted with aldehydes and ketones to form an alkene product. This reaction has come to be called the **Wittig olefination reaction** or simply the **Wittig reaction.**[453] In early papers, it was postulated that the elimination proceeded via a labile intermediate called a betaine **491**, which collapsed to an oxaphosphetane (**492**). Either of these intermediates can decompose to give an alkene (reaction of benzophenone, for example, led to 1,1-diphenylethene, **373**) and a trisubstituted phosphine oxide (in this case, triphenylphosphine).[453] The P—O bond is particularly strong, with a bond dissociation energy of 130–140 kcal mol^{-1} (544.2-586.0 kJ mol^{-1}),[454] and formation of this strong bond is largely responsible for decomposition of the intermediate betaine or oxaphosphetane to give the alkene.



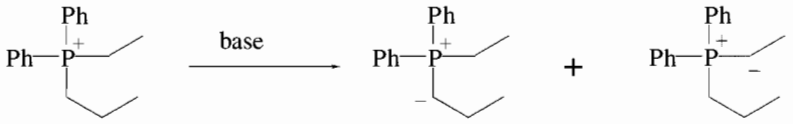
490 **491** **492** **373**

Betaine or oxaphosphetane intermediates are not usually isolable, although an oxaphosphetane derived from a highly specialized ylid was isolated as an stable solid and its structure was determined by X-ray crystallography.[455] The existence of betaine derivatives as discrete intermediates has been called into question and this issue will be addressed in connection with mechanistic discussions of the Wittig reaction in Section 8.8.A.ii.



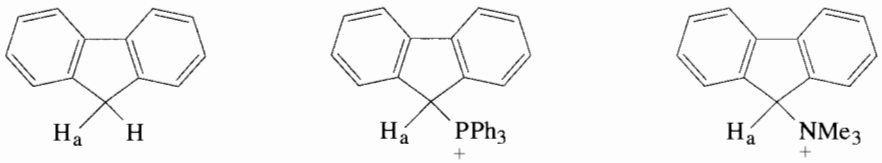
493 **494**

Examination of the generalized structure **494** (generated from phosphonium salt **493**) shows the formal charge on phosphorus is positive. When R^1 and/or R^2 are alkyl, the positive charge on phosphorus decreases due to the inductive effect of the alkyl groups. Such ylids are more reactive with a ketone or aldehyde, but decomposition of the resulting oxaphosphetane is more difficult. The R groups on the phosphorus should not be a group that contains α-protons, since deprotonation would lead to a mixture of isomeric ylids. Reaction of **495** with *n*-butyllithium, for example, gives two ylids, **496** and **497**. To prevent this problem, all the R groups in **493** should be the same and not possess α-hydrogens, which accounts for the fact that Ph_3P and other triaryl phosphines are used in the Wittig reaction. If R^1 in **493** is electron-withdrawing (COR, CO_2R, CN, etc.) the negative charge of the ylid is delocalized by that group, decreasing both the nucleophilicity and reactivity of the carbanionic carbon. Such ylids usually react well with aldehydes, but ketones are less reactive.



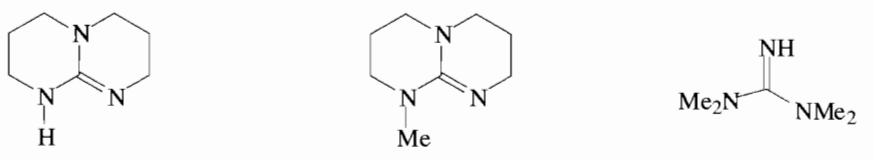
495 **496** **497**

The strength of the base required for deprotonation of the phosphonium salt (to form the ylid) depends on the relative acidity of the α proton, which depends not only on the alkyl or aryl group attached to that carbon (—CHR^1R^2 in **494**) but also on the nature of the groups attached to the phosphorus. The α-hydrogen of a phosphonium salt such as **493** is much more acidic than that of the analogous structure without the phosphorus atom. Fluorene (**183**) has a pK_a for H_a of 25,[456] for example, but H_a in the triphenylphosphonium derivative **498** has a pK_a of <10.[457] The proton (H_a) in the corresponding ammonium salt (**499**) has a pK_a slightly less than that of fluorene.[458] In general, electron-releasing groups such as alkyl ($R^1 = R^2 =$

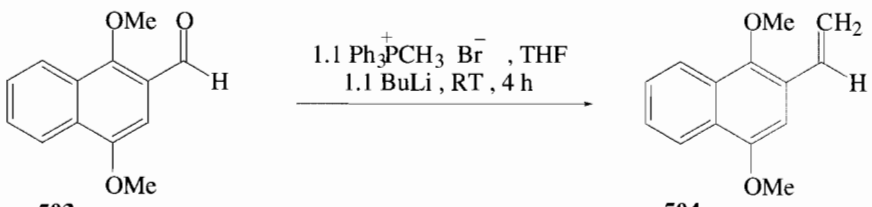


183 **498** **499**

alkyl in **493**) tend to make the α-hydrogen less acidic. Conversely, electron-withdrawing groups (R^1 and/or R^2 = COR, CO_2R, CN, etc. in **493**) make that hydrogen more acidic. The wide range of acidity for hydrogens in phosphonium salts leads to a range of different bases that can be used. Both sodium hydride and potassium hydride have been used as bases, as has dimsyl sodium (sodium salt of DMSO) in DMSO. It is more common to use *n*-butyllithium, *tert*-butyllithium, or *sec*-butyllithium in ether or THF. It has recently been shown that guanidine bases promote the Wittig reaction, as well as the Horner–Wadsworth–Emmons reaction discussed in Section 8.8.A.ii, under mild conditions with high efficiency and facile isolation of products.[459] These bases include 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, **500**), its methyl derivative MTBD (**501**), which were ≈ 100 times more effective than tetramethylguanidine (TMG, **502**). It is also noted that Wittig reactions can be done using stable phosphorus ylids in the presence of silica gel, in hexane.[460]

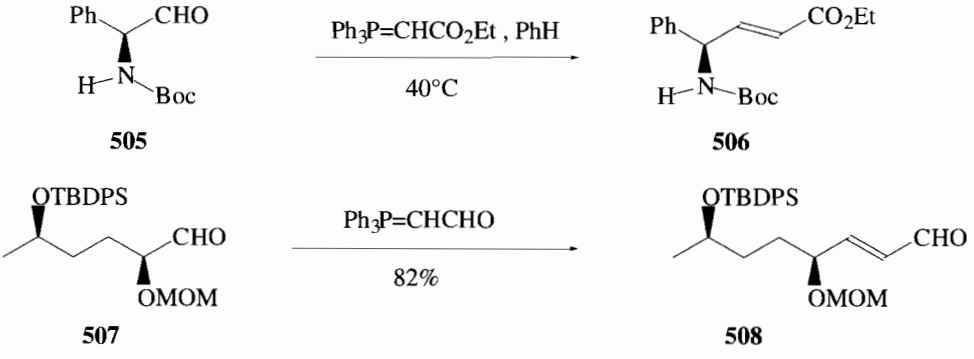


500 **501** **502**



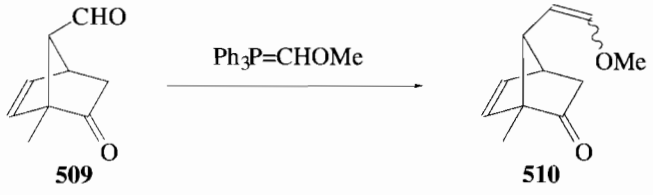
503 **504**

As mentioned, the use of triarylphosphonium ylids to form alkenes via reaction with aldehydes and ketones is known as the **Wittig reaction**,[453c,461] which is one of the more important synthetic methods in organic synthesis,[462] particularly for incorporating exocyclic methylene groups.[463,464] For this and other work, Wittig was awarded the Nobel prize in 1979. The synthetic applications are straightforward but very powerful. In De Kimpe's synthesis of isagarin, aldehyde **503** was treated with methyltriphenylphosphonium bromide and butyllithium in THF.[465] Triphenylphosphonium methylid ($Ph_3P{=}CH_2$) was generated *in situ* and reacted to give a 77% yield of **504**. A wide variety of substituents (R^1 and R^2 in **494**) can be attached to the carbanionic carbon in phosphorus ylids.[466] Arylalkyl ylids ($Ph_3P{=}CRAr$)are commonly used in synthesis. Even reactive groups such as esters and nitriles can be used. The N-Boc aldehyde **505** reacted with $Ph_3P{=}CHCO_2Et$, for example, to give an 83% yield of **506**.[467] Clearly, the ester unit is compatible with formation of the ylid, and the carbamate unit in **505** did not interfere. Even an aldehyde group can be incorporated, as in the conversion of **507** to **508** in Kibayashi's synthesis of (–)-(3*R*,6*S*,9*R*)-decarestrictine C_2.[468] In general, an ylid that contains an electron withdrawing group at the carbanionic carbon is less reactive, but they still react with carbonyl



505 **506** **507** **508**

derivatives. The phosphorane can even possess another acidic proton, although 2 equivalents of base are required to generate the anion ylid. An example is $Ph_3P(CH_2)_3CO_2H$, which was converted first to the carboxylate anion and then to the ylid by treatment with base.[469] The resulting ylid reacted with aldehydes in the usual manner to give an alkene. The anionic centers should be separated by several carbons, however. Protected alcohols can also be incorporated as part of the ylid.[469] It is even possible to do the Wittig reaction in aqueous media with water-soluble phosphonium salts developed by Warren and co-workers.[470] There are other nonclassical applications of the Wittig reaction that are useful in synthesis,[471] and intramolecular versions are known.[472] Poor stereocontrol is sometimes a problem in Wittig olefination reactions (see sec. 8.8.A.ii).

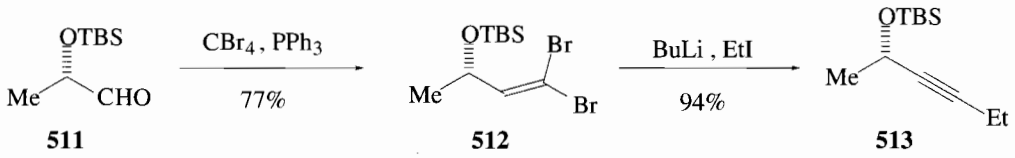


509 **510**

It is also possible to incorporate electron rich groups other than alkyl on the ylid. Chang et al. reacted **509** with the methoxy ylid to give vinyl ether **510** in a synthesis of 2-pupukeanone.[473] In many reactions of this

type, it is possible to isolate the aldehyde that is formed initially by hydrolysis of the vinyl ether. Vinyl sulfides can also be formed by Wittig methodology.[474]

The presence of halogen atoms in a molecule is compatible with formation of an ylid and subsequent Wittig reaction. Carbon tetrabromide and triphenylphosphine have been used to give vinyl dibromide products, which are rapidly converted to the corresponding alkyne. Indeed, this is an important synthetic route to alkynes called the Corey–Fuchs procedure.[475] The reaction of **511** with this reagent gave vinyl dibromide **512** in 77% yield as part of Marshall's synthesis of callystatin A.[476] When **512** was treated with butyllithium and ethyl iodide, alkyne **513** was isolated in 94% yield.

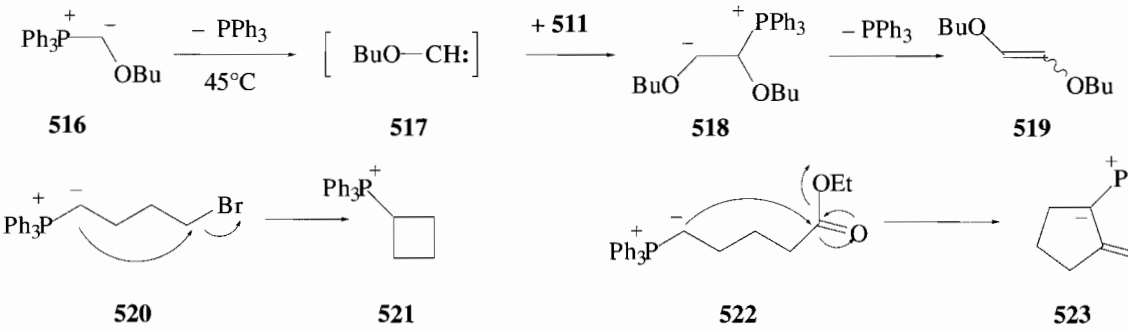


511 **512** **513**

For use in the Wittig reaction, it is important that the R^1 and R^2 groups on the ylid (see **494**) not be subject to spontaneous fragmentation when the carbanion is formed. This is illustrated by bis(phosphonium) salt (**514**), which upon treatment with phenyllithium did not give the ylid but rather decomposed to triphenylphosphine and the vinyl phosphonium salt **515**.[477] Such fragmentation occurs most often when a leaving group is β to the phosphorus atom. When the two phosphorus groups are separated by three or more methylene groups, conversion to the bis-ylid is straightforward.[477]

514 **515**

Another side reaction can occur in ylids that bear a heteroatom substituent, decomposition to a carbene intermediate (sec. 13.9.B). Butoxymethyl ylid **516** spontaneously fragmented to triphenylphosphine and carbene **517**, for example. This carbene reacted with an additional molecule of the ylid (**516**) to give the bis(enol)ether (**519**) via the zwitterion **518**.[478]



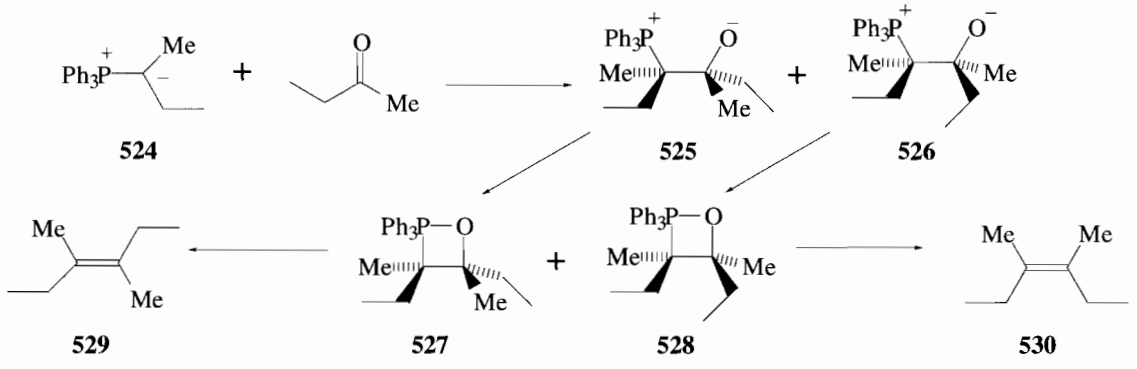
516 **517** **518** **519**

520 **521** **522** **523**

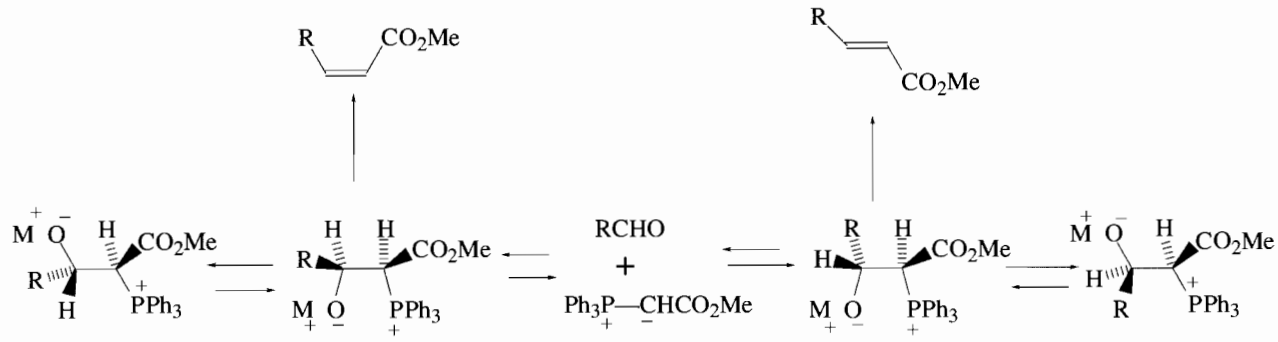
Phosphorus ylids rarely rearrange, but the presence of a reactive group such as a halide[479] or ester[480] can lead to anomalous products. In one example, the carbanionic carbon of **520** displaced the bromide to give

triphenylcyclobutylphosphonium bromide (**521**), via an internal S_N2 reaction.[477] In the second case, nucleophilic attack of the carbanionic carbon in **522** at the ester moiety generated an α-keto ylid, **523**.[478]

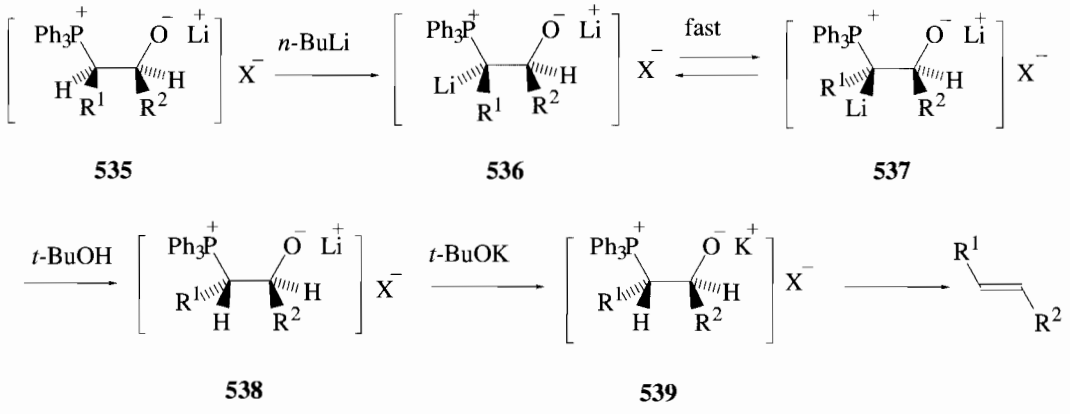
8.8.A.ii. (*E*/*Z*) Isomers in Wittig Reactions. When a phosphorus ylid reacts with an aldehyde or ketone, the alkene that is formed is a mixture of (*E*) and (*Z*) isomers.[481] Initial postulations suggested that the stereochemistry of the alkene products was controlled by the stereochemistry of the betaine, which rapidly collapsed to an oxaphosphetane. Subsequent fragmentation to the alkene occurred via a syn-elimination pathway.[448] An example of this postulate is shown by addition of ylid **524** to 2-butanone to generate betaine **525** and the anti-oxaphosphetane, **527**.[448] Syn elimination led to the (*E*)-alkene, **529**. The reaction mixture also contained betaine **526**, the precursor to the syn oxaphosphetane (**528**) which led to the (*Z*) alkene, **530**.



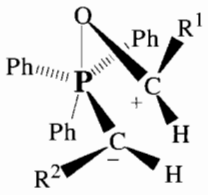
Resonance stabilized ylids such as $Ph_3P{=}CHCO_2Et$ and $Ph_3P{=}CHPh$ give predominantly the (*E*) alkene, whereas nonstabilized ylids such as $Ph_3P{=}CHEt$ give predominantly the (*Z*) alkene.[482] These results are also rationalized in terms of a betaine intermediate. For resonance stabilized ylids, formation of the betaine is reversible and equilibration favors formation of the thermodynamically more stable anti-betaine. The anti-betaine may also collapse faster than the syn-betaine.[483] If elimination of triphenylphosphine oxide is slow, the possibility of equilibration to the anti-betaine is maximized and there will be increased amounts of the (*E*) alkene. Tricyclohexylphosphine ylids are less electrophilic than triphenyl ylids, and they show greater selectivity for formation of the (*E*) alkene.[484] Addition of a protic solvent or a Lewis acid to coordinate the oxygen atom of the betaine leads to more (*Z*) isomer.[481,484] If, after reaction of an aldehyde and $Ph_3P{=}CHCO_2Me$, the metal coordinates with the betaine (or the oxaphosphetane), this coordination slows down the interconversion of **533** and **534** and diminishes the stereoselectivity. The equilibrium concentration of **531** and **532** is not the same as the concentration of **533** and **534**. The complexed form shows some preference for the anti conformation **534**, which gives a slight preference for the (*Z*) isomer. These arguments refer only to stabilized phosphoranes and ignore the stereochemistry of the groups around the phosphorus atom, which are stable throughout the reaction.[485] When the ylid is not stabilized (as when it possesses alkyl substituents), betaine and oxaphosphetane formation is essentially irreversible. Reaction of unsaturated ylids with aromatic aldehydes or α,β-unsaturated aldehydes show some reversibility, however.[486] Lithium salts are usually present in the reaction medium, and this can lead to poor yields of alkene products. Under salt free conditions, the reaction appears to be under kinetic control leading to the syn betaine and the (*Z*) alkene.[487]



Schlosser et al. found that the (*E*/*Z*) selectivity can be controlled by manipulating the solvent and the concentration of salt and rationalized his observations in terms of a betaine intermediate.[488] Betaine **535** can react with unreacted *n*-butyllithium to form a dilithio species (**536**), which rapidly establishes an equilibrium with **537**.[488] If lithium salts are added to this equilibrium, oxaphosphetane formation and elimination from the kinetic syn betaine **535** is inhibited. Further addition of excess butyllithium leads to **536** and **537**. This equilibrium favors the anti species **537**. Protonation leads to betaine **539** (or the potassium salt, **538**) and thereby to an oxaphosphetane which collapses to the anti alkene. This study suggests that excess base and excess salt promotes equilibration and formation of the anti *(E)* alkene.



To obtain the (*Z*) alkene, salt free conditions are required. The syn betaine is relatively hindered and as the carbonyl reactant becomes more hindered there is a greater preference for the (*Z*) alkene.[489] Schneider explained this effect by considering the importance of the substituent configuration around the phosphorus atom during reaction.[490] The intermediate **540** (apical oxygen and equatorial ylid carbon) must rotate at the O—C bond to form the betaine (**541** or **542**). The Ph↔R^2 steric interaction is maintained throughout, but the R^1↔Ph interaction in **540** inhibits formation of **542** and favors **541** (the syn betaine), leading to the (*Z*) alkene. With protic solvents or polar additives, the configuration of the phosphorane may change, and this model does not apply. For stabilized ylids, the pre-betaine intermediate is represented by **543** and is oriented so that the positive-end is attracted to the nucleophilic acyl carbon and forms the anti betaine and the (*E*) alkene.[484] The R^1 group rotates to form the betaine, and this rotation minimizes the R^1↔CO_2Et interaction.



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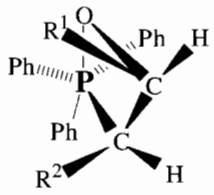

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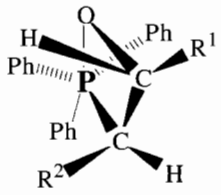

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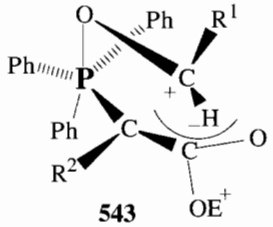
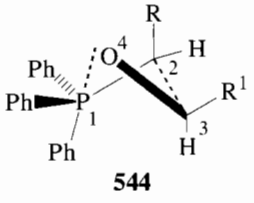


543

The intermediacy of the betaines used in the mechanistic discussions of the Wittig reaction has been questioned and Vedejs has proposed an alternative explanation. The Wittig reaction is subject to solvent effects that indicate a nonpolar transition state for stabilized ylids.[491] There appears to be no direct evidence for the presence of betaines, and none have been isolated. Alternatively, Vedejs and Snoble detected oxaphosphetanes as the only observable intermediates in several Wittig reactions of nonstabilized ylids,[492] using ^{31}P NMR.[493] In more recent work, Vedejs devised a test for the betaine mechanism based on changes in phosphorus stereochemistry in the proposed intermediates (betaine vs. oxaphosphetane).[494] The results of this test suggested that "the conventional betaine mechanism[495,461e] can play at most a minor role in the Wittig reaction".[494] Vedejs points out that the "stereochemical test does not necessarily disprove mechanisms via intermediates with lifetimes that are short compared to the time scale of bond rotation."[494]

Vedejs proposes two oxaphosphetane models to predict the stereochemistry in the Wittig reaction. For systems that give primarily cis alkenes, a cis-oxaphosphetane is required based on the assumption that the reaction proceeds by an early transition state (like starting materials) and the oxaphosphetane has a puckered conformation (**544**).[496] Similarly, for systems that give trans alkenes as the major product, a trans-oxaphosphetane is required, the reaction is assumed to proceed by a late transition state (product-like), and the oxaphosphetane has a planar structure (**545**). In general, the trans-oxaphosphetane is more stable than the cis-oxaphosphetane, and under equilibrium conditions, the trans product is favored. Kinetic control conditions (which appear to dominate Wittig reactions) would lead to the cis-product using this analogy.[492] Vedejs and co-workers suggest that there is no single, dominate Wittig transition state geometry but rather a continuum of related mechanistic variants.[493] Examination of **544** and **545** suggests that the interplay of 1,2-steric interactions (interactions of substituents on P and C2 in **544** and also on C2-C3) and 1,3-steric interactions (interactions of substituents on P and C3 in **545**) will determine cis or trans selectivity.[494] When large groups at the α-carbon provide increasing 1,3-steric interactions, puckered transition states become more important. For stabilized ylids, 1,2-interactions dominate the transition state, leading to trans selectivity.



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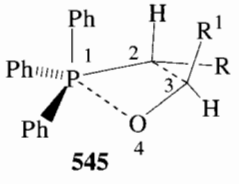
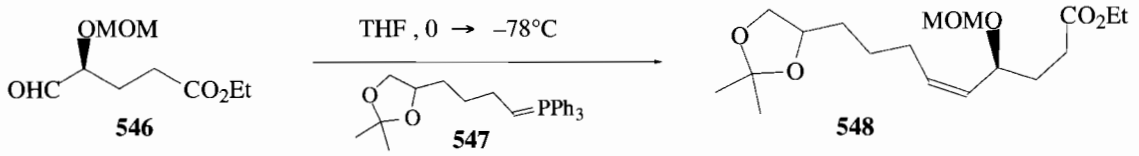


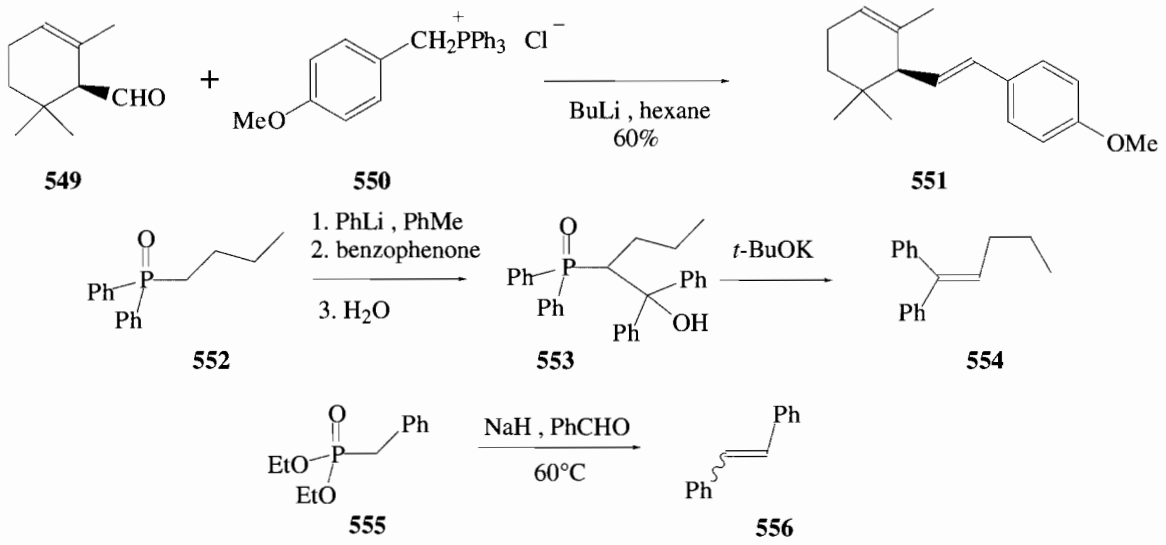
545

Maryanoff et al. also studied this problem, and found a prevalence of (*Z*)-alkene and cis-oxaphosphetane in the salt-free Wittig reaction, which forms the alkene by syn elimination of $Ph_3P{=}O$.[497] His work also suggests

a very slow equilibration of cis- and trans-oxaphosphetanes relative to the rate of alkene formation. There is a significant concentration dependence on the stereochemistry of the reaction. Increasing concentration favored the trans-oxaphosphetane.[497] At high dilution, alkenes were generally formed with (Z)-selectivity in THF with LiBr present. The concentration effect may be associated with sequestration of lithium by THF. The ability of lithium soluble salts to promote formation of (*E*)-alkenes from nonstabilized ylids is well known (see above), but it is clearly concentration dependent in THF. Based on studies with many types of phosphorus ylids, Maryanoff et al. concludes that betaines can have a "meaningful, albeit transient, existence,[497]" despite the lack of direct evidence for their existence. Since kinetic experiments demonstrated that cis-oxaphosphetanes undergo reversal to the ylid and an aldehyde faster than does the trans-oxaphosphetane (see above), the degree of stereochemical drift in Wittig reactions is probably due to the relative rates of oxaphosphetane reversal.

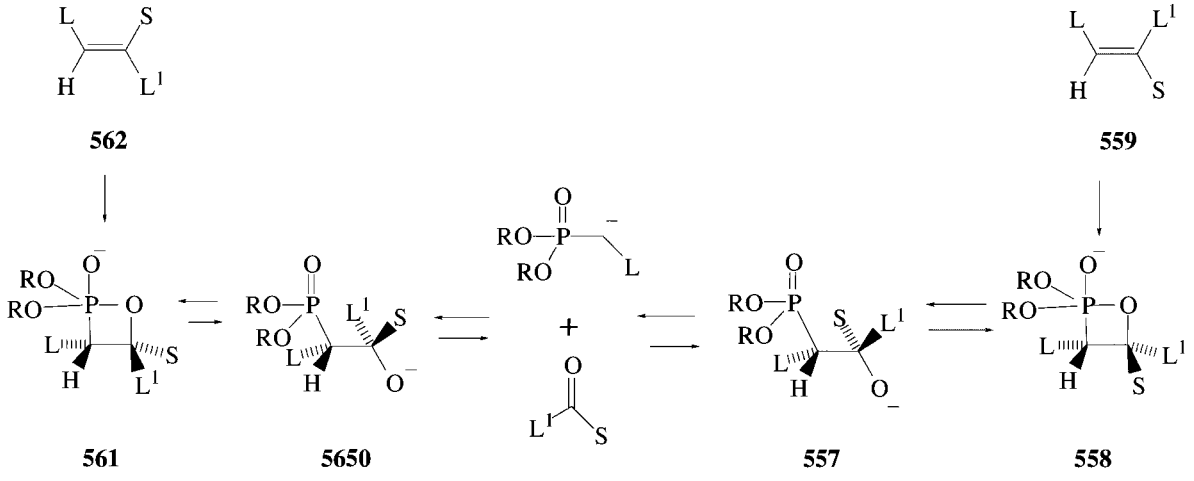


The ability to control the stereochemistry of a Wittig reaction is seen in Wu's synthesis of annonacin, in which aldehyde **546** was treatment ylid **547** to give an 81% yield of **548**.[498] A trans specific reaction is shown as a contrast in Pan's synthesis of (–)-6,7-dehydroferruginyl methyl ether.[499] Aldehyde **549** reacted with the ylid generated from phosphonium chloride **550** to give the trans alkene (**551**) in 60% yield.



8.8.A.iii. Phosphine Oxides and Phosphonate Esters.[500] Many extensions of the Wittig reaction have been introduced that improve or modify the reactivity and/or stereoselectivity of the ylid. Horner et al. showed that α-lithiophosphine oxides such as that derived from **552** react with aldehydes or ketones to give a β-hydroxy phosphine oxide (**553**) as an isolable species.[501] Subsequent treatment with base liberates the alkene, (**554**). Wadsworth and Emmons modified the Horner reaction to use phosphonate ester derivatives such as

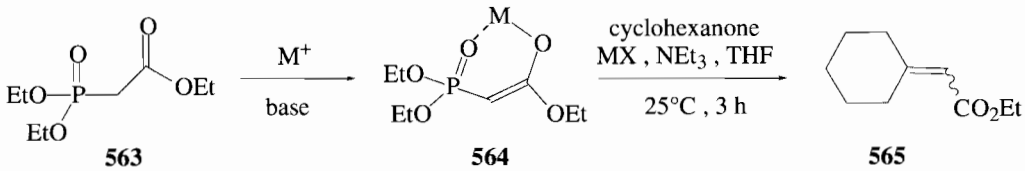
555. Reaction with aldehydes or ketones (such as benzaldehyde) in the presence of base gave the olefination product **556** (in 84% yield).[502] These variations have come to be called the **Horner–Wadsworth–Emmons modification** of the Wittig reaction, or **Horner–Wadsworth–Emmons olefination**.[503] It is sometimes called **Horner–Emmons olefination**.



The major product of olefination with phosphonate carbanions is usually the (*E*)-isomer.[504] However, a (*Z*)-selective reaction has recently been developed that uses sodium iodide and DBU as the base.[505] Speziale and Ratts suggested that increased amounts of (*Z*) alkene were obtained by increasing the steric bulk of the L and L^1 groups in **557** and **560**, formed by reaction of the phosphonate ester ylid with a carbonyl compound. This equilibrium favors the anti conformation(**557** over **560** and elimination gives more of the (*Z*) product, **559**.[506] This model assumes that steric encumbrance is more important in **557** and **560** than in oxaphosphetanes **558** and **561**, respectively, that are required for syn elimination to the alkene. This equilibrium generally favors **559** over **562** due to the stereochemical preferences in the initially formed ylid products.

Normally, bases such as *n*-butyllithium, potassium *tert*-butoxide, or sodium hydride are required to generate the phosphonate carbanion.[507] Once generated, the nature of the metal ion influences the nucleophilicity of that anion. Addition of a metal ligand to the reaction mixture also influences the relative ease with which the α-proton is removed by the base. With some metals a weaker base can be used to generate the carbanion.[508] Addition of metal salts to **563**, for example, led to chelation and promoted carbanion formation (**564**) by stabilizing it.[509] Tables 8.25[509] and 8.26[509] show the influence of metal additives and solvent on the olefination reaction with phosphonate ester carbanions. Addition of complexing Lewis acids such as LiBr or $MgBr_2$ allowed the ylid to be formed with a base as weak as triethylamine. In Table 8.25, the carbanion derived from **558** reacted with cyclohexanone to give the alkylidene product **565**. Magnesium bromide was the most efficient metal additive for producing this product.[509] In Table 8.25, botli the metal additive and the solvent were varied in the reaction of **563** and triethylamime (to form carbanion **564**) with benzaldehyde to produce the conjugated ester **566**.[509] In this study, only (*E*)-**566** was isolated with no (*Z*)-**566** detected. The best results were obtained in ether solvents or acetonitrile, with lithium halides, although magnesium bromide was also effective.

Table 8.25. Influence of Metal Salts on the Horner-Wadsworth-Emmons Olefination

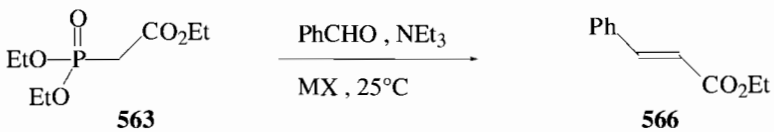


563 **564** **565**

MX	Concentration	% 565
none		0
LiCl		19 (50)[c]
LiBr		39 (85)[c]
$MgCl_2$		52 (86)[c]
$MgBr_2$	5 mmol	50 (48)[c]
	10 mmol	62 (85)[c]
	20 mmol	70
	10 mmol[a]	90
	10 mmol[b]	0
NaI		0
$ZnCl_2$		0.5
$AlCl_3$		0
$FeCl_3$		0
$CuCl_2$		0

[a] 2 equiv NEt_3. [b] no NEt_3 added. [c] % **565** after a reaction time of 24 h.

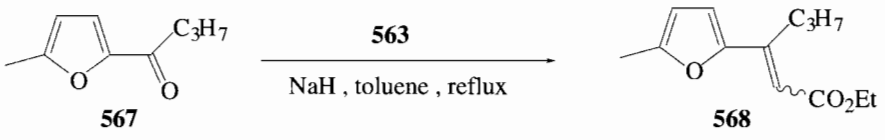
Table 8.26. Effect of Solvents and Added Metal Salts on the Horner-Wadsworth-Emmons Olefination



563 **566**

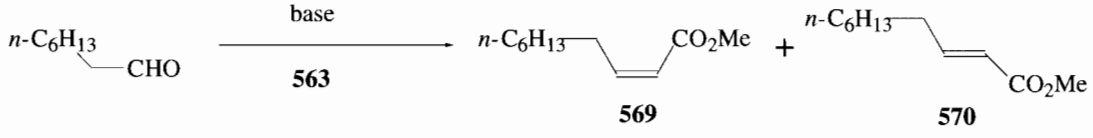
Solvent	MX	% 566
MeCN	LiCl	77
	LiBr	93
	$MgCl_2$	15
	$MgBr_2$	71
Ether	LiCl	77
	LiBr	71
	$MgBr_2$	80
THF	LiCl	86
	LiBr	96
	$MgBr_2$	81
CH_2Cl_2	LiCl	56
	LiBr	70
	$MgBr_2$	47
DMF	LiBr	25
	$MgBr_2$	10

[Tables 8.25 and 8.26 Reprinted with permission from Rathke, M.W.; Nowak, M. *J. Org. Chem.*, ***1985***, *50*, 2624. Copyright © 1985 American Chemical Society.]



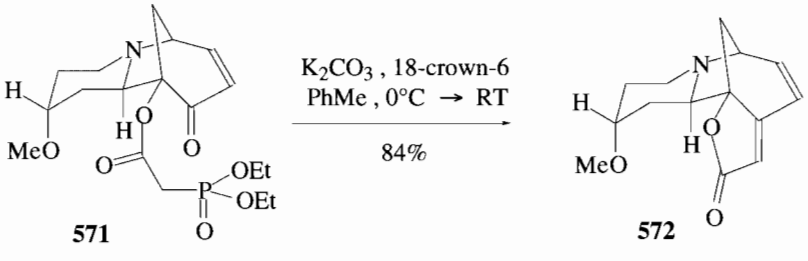
567 **568**

There are many applications of phosphonate ester methodology in organic synthesis. An asymmetric olefination has been reported using a benzopyranoisoxazolidine auxiliary, generating alkylidene cyclohexane derivatives with good asymmetric induction.[510] Föhlisch and co-workers reacted furanyl ketone **567** with **563** and NaH to give an 83% yield of **568** in a synthesis of lasidiol.[511] Still showed that octanal reacted with the carbanion derived from **563** to give a mixture of **569** and **570**.[512] Using $KN(TMS)_2$ (potassium hexamethyldisilazide) as a base (sec. 9.2.B) in THF in the presence of 18-crown-6, gave an 8:1 mixture of **569/570** in 81% yield when OR = OMe in **563**. Changing OR to OCH_2CF_3 led to isolation of a 12:1 mixture of **569/570** in 90% yield.[512] Reaction of **563** (R = CH_2CF_3) with benzaldehyde, under the same conditions, gave a >50:1 mixture of (*Z*/*E*) alkenes in >95% yield.[512] When Triton B ($PhCH_2NMe_3^+OH^-$) was used in THF with **563** (R = CH_2CF_3) a 7:1 mixture of **569/570** was obtained (84%) but the use of KO*t*-Bu in THF gave a 2:5 mixture of **569/570** in 70% yield.[512] It is clear from these studies that the preference for the (*Z*)-alkene product can be strongly influenced by the reaction conditions and phosphonate carbanion chosen for the reaction.



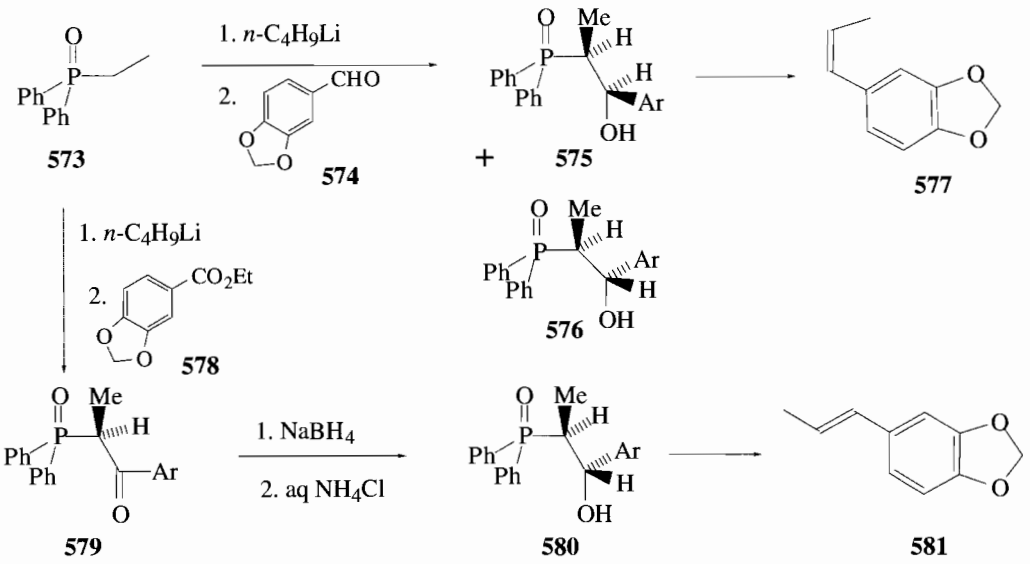
569 **570**

Intramolecular olefination reactions are possible using phosphonate carbanions because they are relatively stable. This type of cyclization is also possible with Wittig reagents, but it is more facile with phosphonate carbanions. One example is Weinreb's treatment of phosphonate **571** with potassium carbonate and a crown ether to give a 84% yield of **572** in a synthesis of phyllanthine.[513]



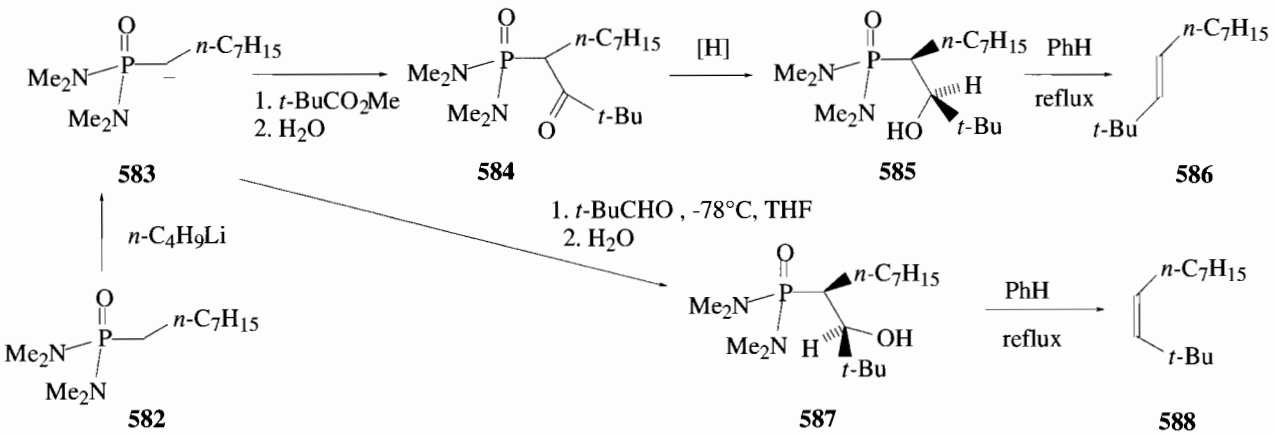
571 **572**

Warren showed that olefination of ketones and aldehydes, or even esters, with phosphine oxide carbanions allows some control of stereochemistry in the alkene products. Reaction with an aldehyde or ketone generates diastereomeric β-hydroxyphosphine oxide products, which can be isolated and then chromatographically separated. Reaction of **573** with *n*-butyllithium was followed by addition of 3,4-methylenedioxybenzaldehyde (**574**, known as piperonal) to give a 9:1 mixture of **575/576**, the syn and anti alcohol, respectively.[514] The pure syn alcohol **575** was isolated in 75% yield by chromatography on silica gel.



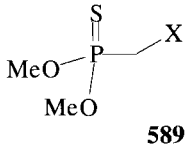
Subsequent treatment with sodium hydride in DMF gave the (*Z*)-alkene, α-isosafrole (**577**). If **573** reacted first with butyllithium and then with the analogous ester (**578**), the keto-phosphine oxide **579** was produced. Reduction of the ketone with sodium borohydride gave predominantly (≈ 6:1) the anti isomer **580**, which gave the (*E*)-alkene **581** upon reaction with sodium hydride. An interesting application of this methodology is to extend the chain of an aldehyde by one carbon (R—CHO → RCH_2CHO).[515]

The use of phosphine oxide ylids and phosphonate ester carbaions just described is very similar to Corey's use of α-lithiophosphonic acid bis(amides) for olefination reactions. Corey showed that reaction of **582** with *n*-butyllithium gave the lithio derivative **583**.[516] Subsequent reaction with methyl 2,2-dimethylpropanoate (methyl pivaloate) gave the corresponding ketone, **584**. Reduction with $LiAlH_4$ and quenching with water led to isolation of alcohol **585**. Heating in refluxing benzene, in the presence of silica gel, liberated the alkene **586** in 71% yield.[515]



Corey also showed that the stereochemistry of the alkene could be controlled. Reaction of **582** with butyllithium and then pivalaldehyde, for example, gave **587**. Thermal elimination gave a 3:1 (*Z*/*E*) mixture of **588**

and **586**, favoring **588**.[517] By comparison, the triphenylphosphonium carbanion from 1-bromooctane reacted with pivalaldehyde to give a 98.5:1.5 mixture of **588/586**, which clearly favored the (*Z*)-isomer.[517] Good yields of (*E*) or (*Z*) alkenes were obtained by oxidation of the alcohol intermediate derived from reaction with aldehydes or ketones, with manganese dioxide in chloroform. Sodium borohydride was used for reduction of this ketone, as shown above, allowing one to control the relative stereochemistry of the intermediate product.



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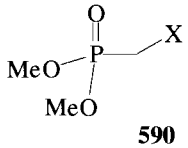
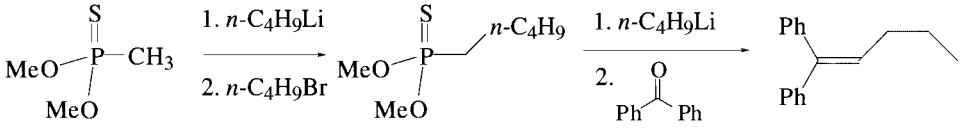


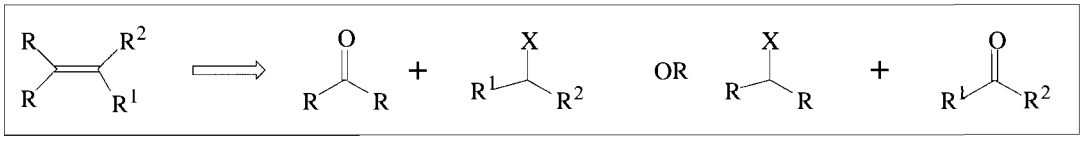
590

Corey and Kwiatkowski developed phosphonothioate derivative **589**[518] and phosphonate derivative **590**, and showed the corresponding ylids gave good yields of alkene products upon reaction with aldehydes and ketones when X = Cl, C(=O)R, or Ar. When X = H or alkyl in **590** (the ylid is not stabilized), formation of the lithio derivative was difficult and elimination to the alkene was also sluggish. The thio derivative (**589**), however, reacted with carbonyl derivatives and decomposed to alkene products at temperatures ranging from ambient to 65°C. An example is the reaction of **591** with *n*-butyllithium and then 1-bromobutane to give the alkylated product, **592**. This result is very interesting since Wittig-type reagents do not undergo alkylation reactions in good yield. Addition of more base to **592** led to a new ylid and condensation with benzophenone at 25°C, gave **593**. Higher temperatures (65°C) for elimination were required when the carbonyl component was a nonconjugated aldehyde or ketone.



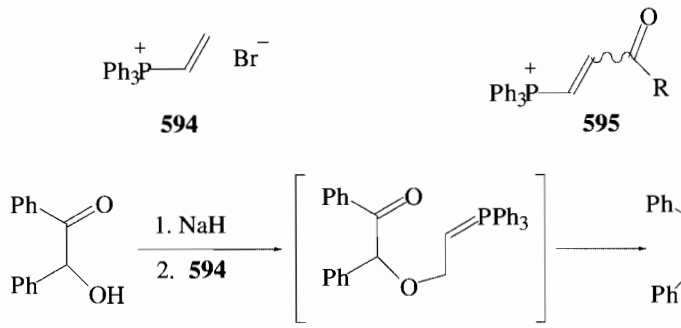
591 **592** **593**

The disconnection for the Wittig type reactions is

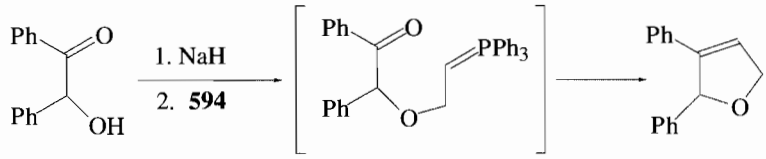


8.8.A.iv. Alkenylphosphonium Salts. Alkenylphosphonium salts are known and they react with carbonyl compounds to form heterocyclic compounds. Phosphonium salt (**594**) was generated by reaction of 1-phenoxy-2-bromoethane with PPh_3, followed by heating.[519] Phosphonium salt **595** was formed from the corresponding β-chloro-α,β-unsaturated ketone by reaction with PPh_3 and **594**, followed by reaction with aqueous KBr.[520] The most common use of these phosphonium salts is in a reaction with carbonyl compounds that possess a nucleophilic atom at the β- or γ-position. Treatment of **596** with sodium hydride generated an alkoxide and conjugate addition to **594** generated ylid **597**. The subsequent intramolecular olefination reaction gave dihydrofuran derivative **598** in 50% yield.[521] α-Thioketones react with vinyl phosphonium salts

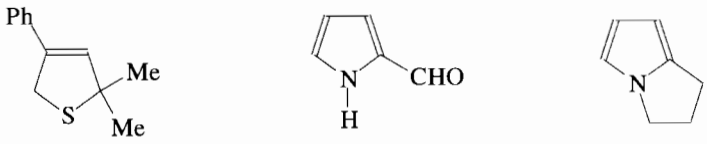
to give dihydrothiophenes. When 3-mercapto-1-phenyl-2-propanone reacted with $Ph_3P{=}CMe_2$, for example, the product was **595**.[522] In a similar manner pyrrole-2-carboxaldehyde (**600**) reacted with vinylphosphonium salts to give a 1,2*H*-pyrrolizine derivative (**601**).[523]



594 **595**

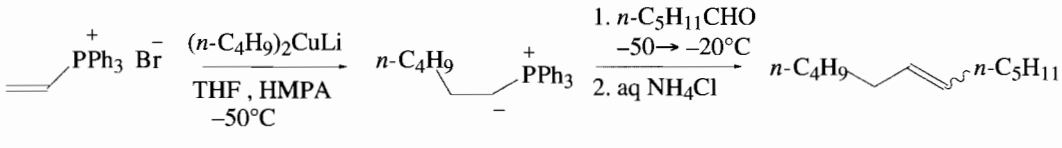


596 **597** **598**

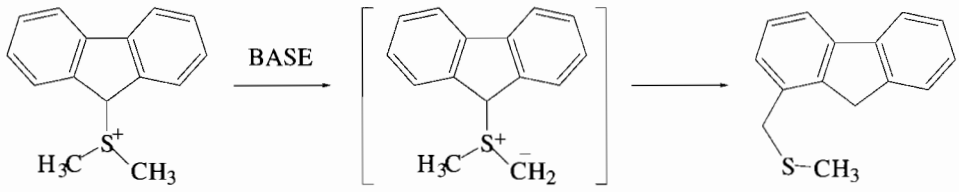


599 **600** **601**

An interesting modification of this reaction generates a normal Wittig reagent by reaction of **594** with an organocuprate (sec. 8.7.A). Addition of dibutyl cuprate to **594** generated ylid **602**. Subsequent reaction with hexanal gave the expected alkene **603** as a 1:4 mixture of (*Z*/*E*) isomers.[524]



594 **602** **603**

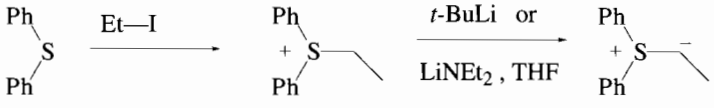


604 **605** **606**

8.8.B. Sulfur Ylids

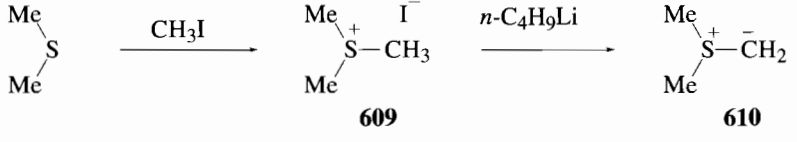
8.8.B.i. Sulfonium and Sulfoxonium Ylids. Just as phosphines react with alkyl halides to give the corresponding phosphonium salt, sulfides (thioethers) react with alkyl halides to give the corresponding sulfonium salt.[449,525] Ingold and Jessop first reported observation of sulfonium ylid **605** in 1930 (from the fluorene derivative, dimethylsulfonium salt **604**), but this initially formed ylid rearranged to give **606**[526] in a sulfur analog of the **Sommelet–Hauser rearrangement**[527] (sec. 8.8.C.ii). Sulfur ylids are formed by reaction with a

strong base (such as RO^-/ROH, NaH/DMSO, RLi, or $LiNR_2$ in THF or ether) with the appropriate sulfonium salt.[528] The sulfonium salt is formed by reaction of a dialkylsulfide or a diaryl sulfide (R_2S) with primary, allyl or benzyl halides[529] A typical example is the reaction of diphenyl sulfide and iodoethane to give sulfonium salt **607**.[530] Subsequent reaction with *tert*-butyllithium generated the ylid (**608**), which contains the Ph_2S^+ moiety, a good leaving group for S_N2 displacement by a nucleophile. The gegenion of the sulfonium salt is iodide, which can displace Ph_2S, and this means the reaction that generates the sulfonium salt is reversible.[531] The use of relatively nonnucleophilic gegenions such as tetrafluoroborate or perchlorate will minimize this side reaction and is usually a necessity. When highly electrophilic species are used, such as silver salts, other complicating reactions are possible. Rearrangements can occur by reaction of $AgBF_4$ with the alkyl halide to form the secondary cation (sec. 12.2.B). In general, the straight-chain sulfonium salt is the major product.[532]

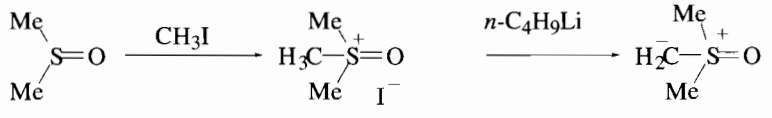


607 **608**

Dimethyl sulfide is a useful precursor to sulfur ylids, reacting with iodomethane to give trimethylsulfonium iodide (**609**). When this salt was treated with *n*-butyllithium, deprotonation of the hydrogen on the α-carbon led to dimethylsulfonium methylid (**610**). Dimethyl sulfoxide also reacts with alkyl halides to give a sulfoxonium salt. When DMSO reacted with iodomethane, trimethylsulfoxonium iodide (**611**) was formed. As with the dimethyl sulfide derivative, treatment with a strong base such as *n*-butyllithium generated the corresponding ylid, dimethylsulfoxonium methylid (**612**).

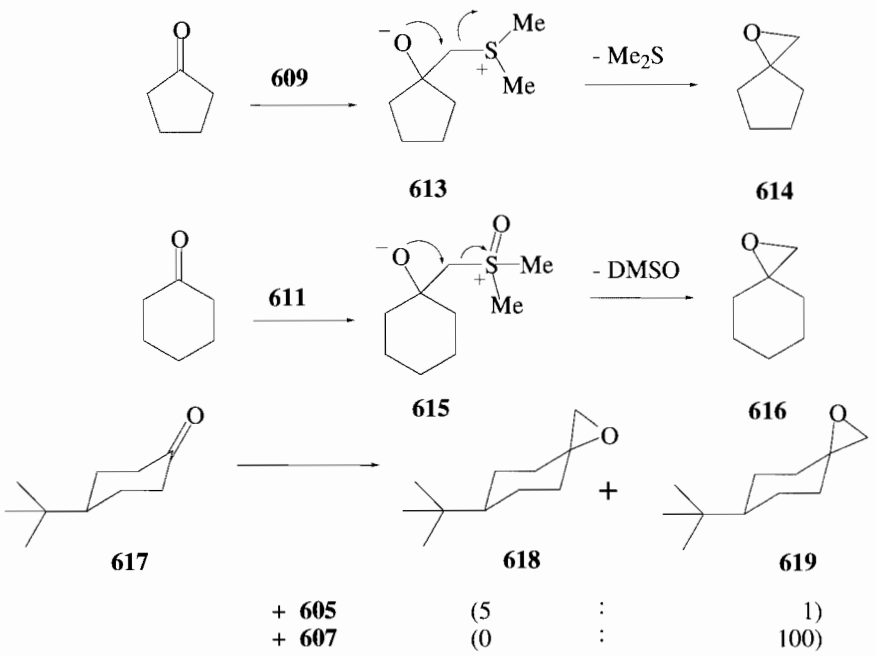


609 **610**

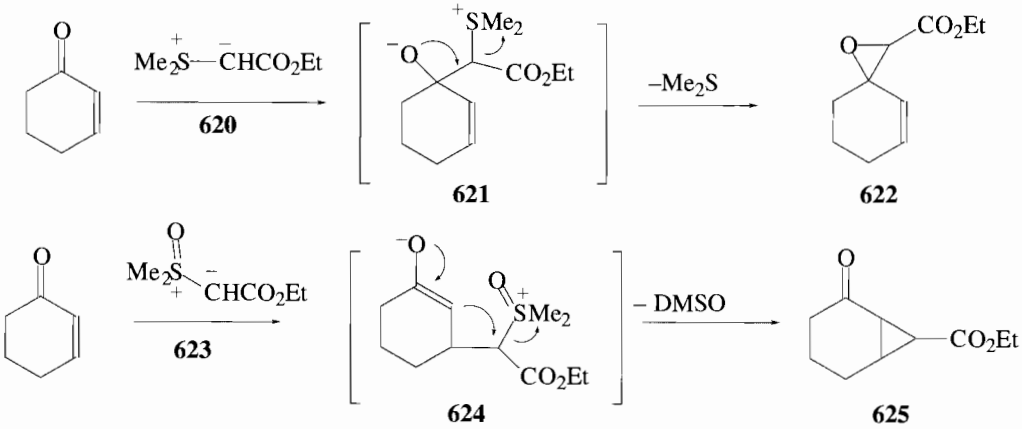


611 **612**

When **610** reacts with carbonyl derivatives, it behaves as a carbanion rather than an ylid. The reaction of dimethylsulfonium methylid with cyclopentanone, for example, gave the acyl addition product **613**. Since dimethyl sulfide (Me_2S) is a good leaving group, the nearby alkoxide displaces Me_2S to give an oxirane, **614**. Epoxide formation and *not* alkene formation is the normal reaction of sulfur ylids when they react with aldehydes or ketones.[533] Dimethylsulfoxonium ylid **612** also reacts with carbonyl compounds to give an intermediate (**615**) that contains a leaving group, DMSO, and displacement by the adjacent alkoxide gives the same oxirane as before (**616**).[529] Initial generation of intermediates such as **613** or **615** is probably irreversible. An intermediate such as this was generated independently and shown to form an epoxide.[534]

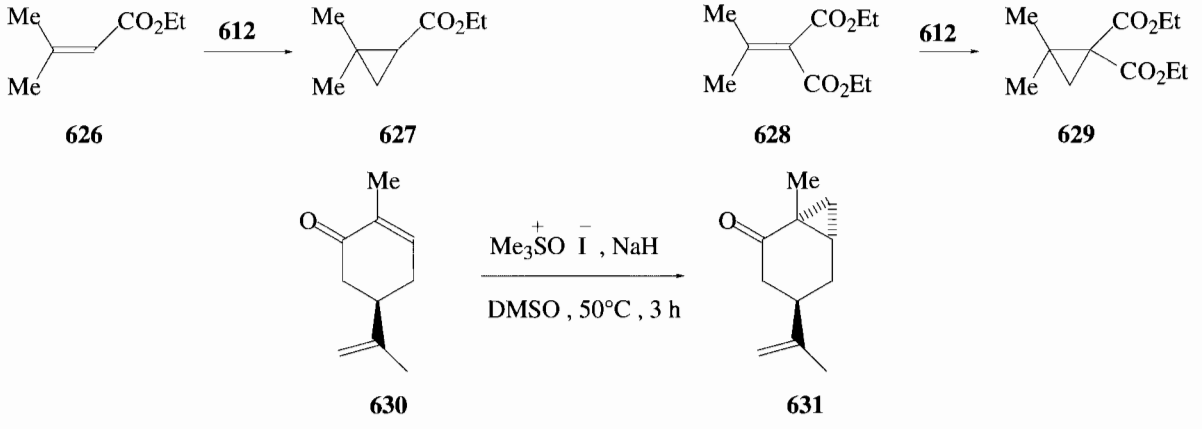


It is known that dimethylsulfonium methylid (**610**) generally adds irreversibly to ketones and aldehydes. On the other hand, dimethylsulfoxonium methylid (**612**) adds reversibly to a carbonyl. This difference is reflected in their reactivity with cyclic ketones such as 4-*tert*-butyl cyclohexanone (**617**). Dimethylsulfonium methylid (**610**) reacted with **617** to give the oxirane with an axial exocyclic C—C bond (**618**), which is less stable than the product with an axial C—O bond (**619**).[535] When **612** reacted with **617**, however, the oxirane with the more stable equatorial exocyclic C—C bond (**619**) was formed.[536] This is attributed to the reversibility of the addition of **612** to the ketone leading to the more stable oxirane, whereas **610** generated the intermediate salt irreversibly in what is essentially a kinetic process.



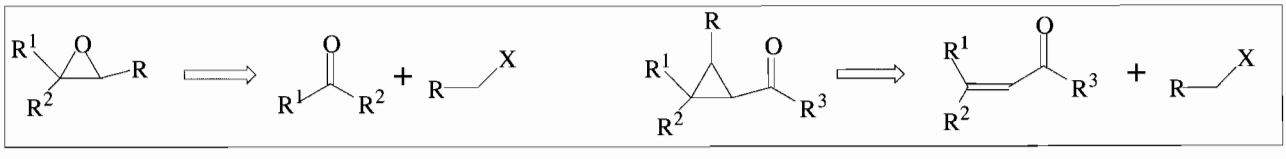
Another difference in the reactivity of these two ylids is reflected in their reactions with α,β-unsaturated ketones. The carboethoxy dimethylsulfonium methylid **620** reacted with cyclohexenone to give the usual alkoxy sulfonium salt **621**. Intramolecular displacement of dimethyl sulfide led to the expected oxirane (**622**) analogous to the formation of **614**. Dialkylsulfonium ylids react via 1,2-addition with displacement of the

sulfide to give an allylic oxirane.[534] When carboethoxy dimethylsulfoxonium ylid **623** reacted with cyclohexenone, however, the 1,2-addition adduct is formed reversibly, and 1,4-addition becomes competitive. The conjugate addition product **624** is an enolate anion (secs. 9.2, 9.3, 9.7) and intramolecular displacement of DMSO

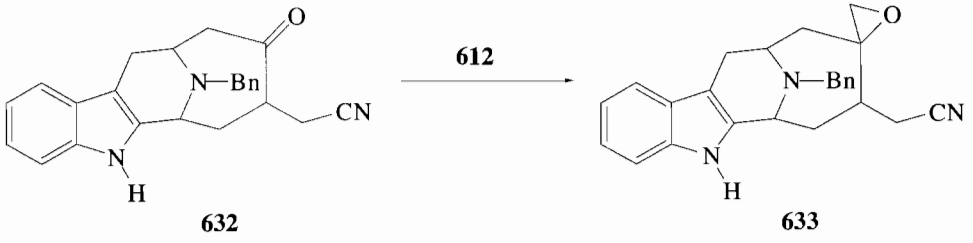


generates a cyclopropane ring, as in **625**.[536] In general, dimethylsulfonium methylid reacts with conjugated ketones to give an allylic oxirane but dimethylsulfoxonium methylid reacts to give the cyclopropyl ketone. The latter reaction is facilitated as the conjugate system becomes more amenable to Michael addition. Acrylate **626**, for example, gave only a 9% yield of **627** after 1 h, whereas **628** gave a 91% yield of **629** under the same reaction conditions.[537] The reaction is synthetically useful despite the limitations, as shown by the conversion of *R*-(–)-carvone (**630**) to **631** in 96% yield as part of Brocksom's synthesis of guaiane–sesquiterpenes.[538]

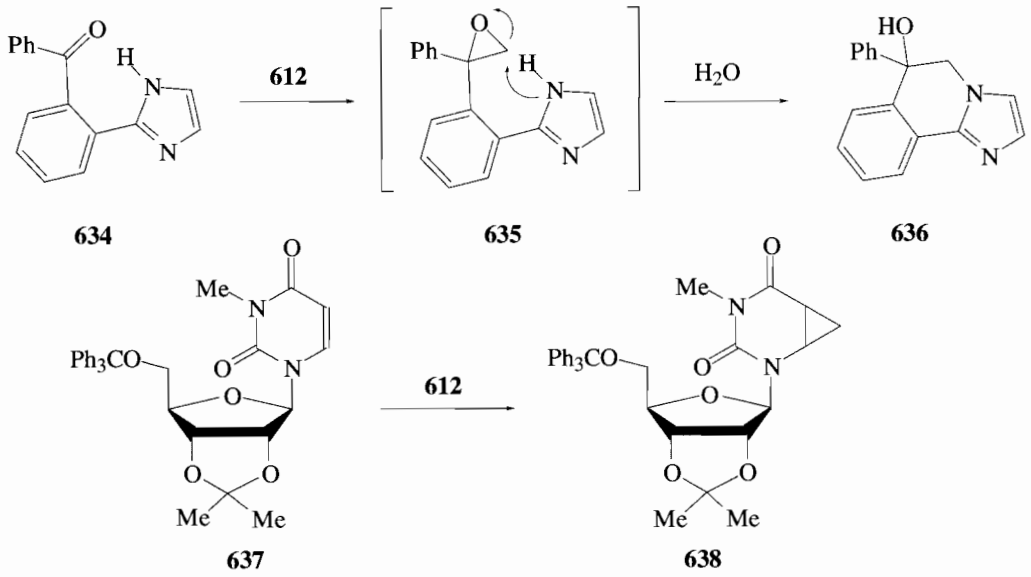
Disconnections for reactions of these sulfur ylids are



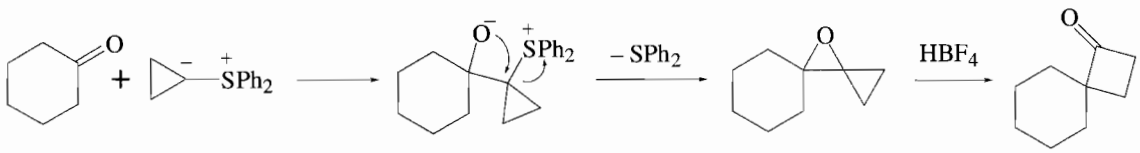
This methodology has been applied to a variety of syntheses.[539] Keto-nitrile **632** reacted with **612** to give the oxirane moiety in **633**, in 70% yield, a key step in Mashimo and Sato's synthesis of ajmaline.[540] When the oxirane product is generated in the presence of a nucleophile, further reaction is possible. Initial reaction of the ketone moiety of **634** with **612** gave the oxirane **635**. The nucleophilic nitrogen of imidazole opened the oxirane, however, to give **636**.[541] The cyclopropanation reaction can be useful in many synthetic applications. Cyclopropanation of the protected *N*-methyluridine moiety in **637** with **612** generated the bicyclic species **638** in 80% yield (7:3 β/α).[542]



632 633

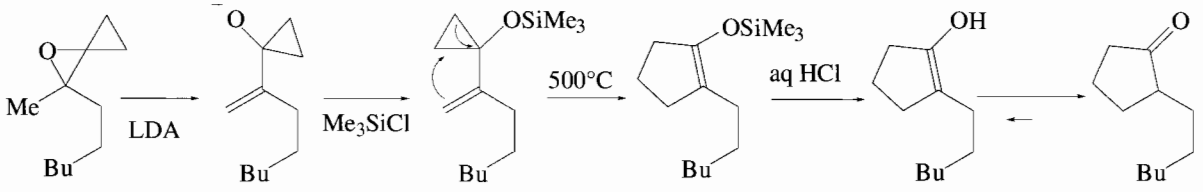


8.8.B.ii. Diphenylcyclopropylsulfonium Derivatives. Trost and Bogdanowicz showed that diphenylcyclopropylsulfonium ylids such as **639** reacted with ketones and aldehydes in a manner similar to **610**. Attack at the carbonyl generated the expected intermediate **640**, and intramolecular displacement of diphenyl sulfide by alkoxide gave the oxirane **641**. This oxirane, however, is an oxaspiropentane derivative and is susceptible to several additional synthetic manipulations.[543,546a] A useful transformation is the conversion of the oxaspiropentane moiety to cyclobutanone derivative (**642**) by treatment with Lewis acids such as HBF_4, $LiClO_4$, or $Eu(fod)_3$, where fod = tris-(6,6,7,7,8,8,8)-heptafluoro-2,2-dimethyl-3,5-octanedionate.[544] Such products arise via a cationic rearrangement of an oxonium ion (sec. 12.2.B), formed by protonation of (or coordination to) the oxiranyl oxygen. Ring opening generated a cyclopropylcarbinyl cation, which rearranged to the oxo-stabilized cyclobutyl cation (sec. 12.2.B), and this gave the cyclobutanone product. When better coordinating Lewis acids are used [$LiClO_4$ or $Eu(fod)_3$], there is a chelation effect that further stabilizes the intermediate cation.



An alternative reaction pathway is available when a carbon adjacent to the oxiranyl moiety possesses a hydrogen. Reaction of **643** with lithium diisopropylamide (sec. 9.2.B) removed the hydrogen on the carbon α to the oxiranyl carbon and formed **644** via opening of the oxaspiro moiety. When this was done in the presence of chlorotrimethylsilane, the alkoxide was trapped as the trimethylsilyl ether **645** (sec. 7.3.A.i). Subsequent heating (flash vacuum pyrolysis at ≈ 300–500°C) led to a rearrangement, that generated **646**.[545] This so-called **vinyl cyclopropane rearrangement** is a well-known sigmatropic rearrangement and it will be

discussed in Sections 11.12.B, 13.9.C.iii. Silyl enol ether (**646**) is simply a protected enolate (secs. 9.2.B, 9.2.D) and aqueous hydrolysis liberated the unstable enol, **647** (sec. 7.3.A.i). Tautomerization favored the final product, ketone **648**.[545] Trost et al. applied this methodology to a synthesis of allamandin.[546]

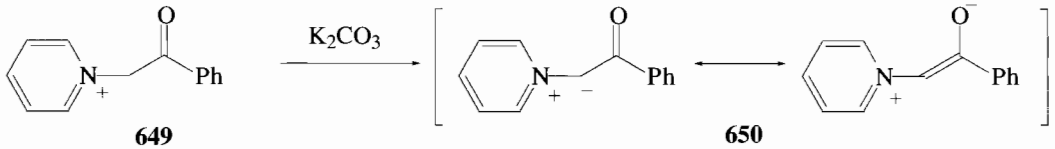


643 **644** **645** **646** **647** **648**

The disconnections for the cyclopropyl sulfide reactions are

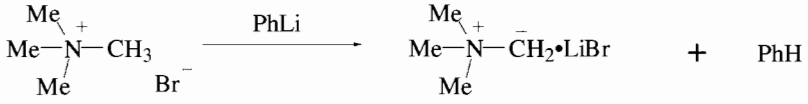
8.8.C. Nitrogen Ylids[445,547]

8.8.C.i. Formation of Nitrogen Ylids. The first report of a nitrogen ylid was probably by Krohnke in 1935, who prepared the resonance stabilized pyridinium ylid **649** by reaction of pyridinium salt **650** with potassium carbonate (K_2CO_3).[548] Wittig Wetterling found that phenyllithium reacted with tetramethylammonium bromide (**651**) to give the corresponding ylid (**652**).[549] The ylid was shown to be the lithium bromide complex. Complexation with added or generated metal salts or other reagents is very important for the stability of nitrogen ylids. Ylid **652** decomposed to carbene (CH_2:) (see sec. 13.9) in solvents that strongly



649 **650**

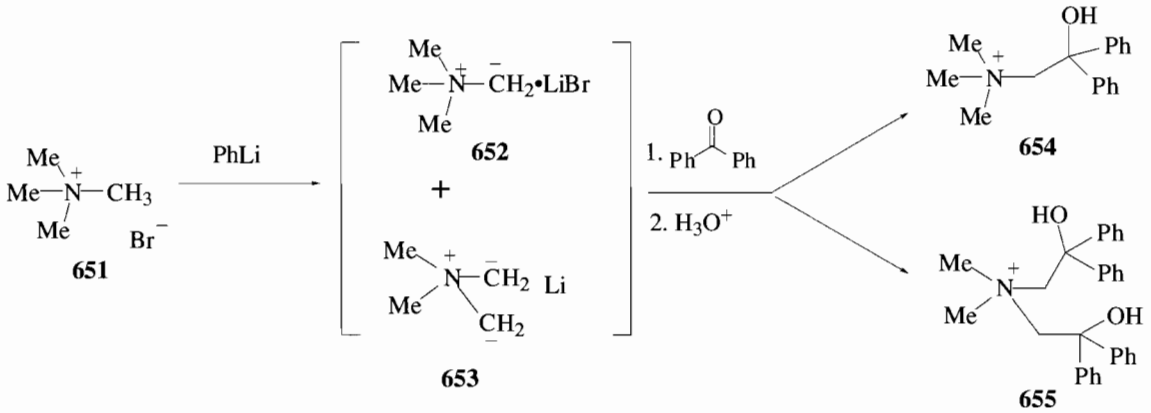
coordinate lithium bromide, and this carbene polymerized to polymethylene under the reaction conditions. In ether (ambient temperatures for 90 h), reaction of tetramethylammonium bromide and phenyllithium gave 20% trimethylamine and 12% polymethylene. In dimethoxyethane (DME), which forms a strong complex with LiBr, polymethylene was formed in 74% yield, which suggested that the free (uncomplexed) ylid was rather unstable.



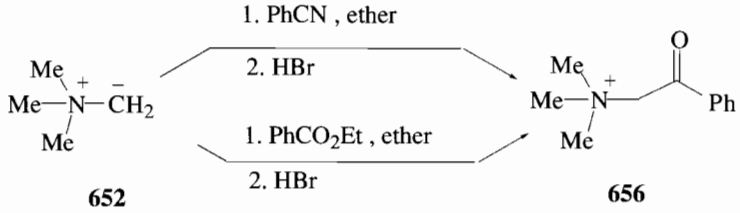
651 **652**

Wittig showed that tetramethylammonium bromide (**651**) reacted with 2 equivalents of phenyllithium to form a species (**652** and/or **653**) that gave 18% of monosubstituted product (**654**) and 20% of the bis-adduct

(**655**) on reaction with benzophenone followed by hydrolysis.[550] Although nitrogen ylids behave as carbanions, alkylation of **652** in THF is difficult because the carbanion is also basic and participates in an elimination reaction with an alkyl halide by losing trimethylamine. Reaction of **652** with bromocyclohexane, for example, gave a 92% yield of cyclohexene.[551] Ylid **652** does behave as a carbanion if the substrate does not possess a leaving group. Reaction with either benzonitrile or ethyl benzoate gave the ammonium ketone **656**.[551] Similar reaction with benzoyl chloride gave a mixture of the usual ketone product (**656**) and a secondary product resulting from *O* alkylation of the enol form of the acid chloride. Nitrogen ylids behave as both a stronger base and a stronger carbanion than any of the phosphorus or sulfur ylids encountered in previous sections.

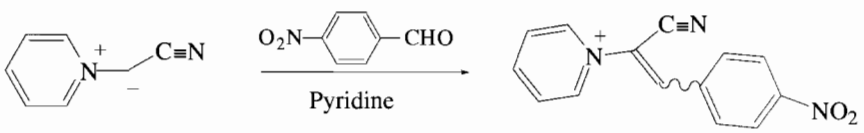


651 **652** **653** **654** **655**



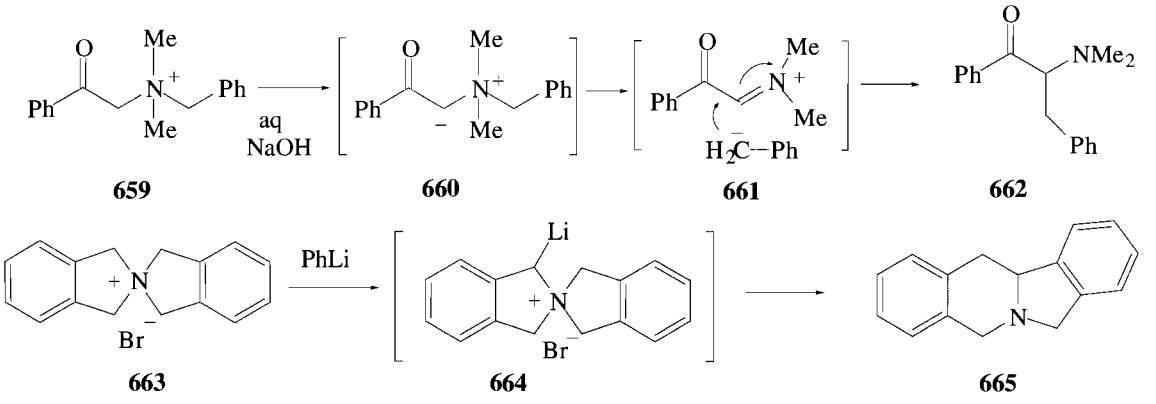
652 **656**

Pyridinium ylids such as those discovered by Krohnke (see above) and simple *N*-alkyl derivatives generally undergo nucleophilic reactions as carbanions. Pyridinium ylids react with aldehydes in a Knoevenagel reaction (sec. 9.4.B.iii) rather than as an ylid. Carbanion **657**, for example, reacted with 4-nitrobenzaldehyde to give **658**, after elimination of water from the initial alcohol product.[549,550a,552] Pyridinium ylids undergo Michael addition on reaction with conjugated carbonyl systems.[553] Another class of nitrogen ylids is azomethine ylids, which are useful synthetic intermediates. They are often formed by thermal ring opening of aziridine derivatives.[554] The main synthetic use of azomethine ylids is in [3+2]-cycloadditions and this will be discussed in Section 11.11.F.[555]

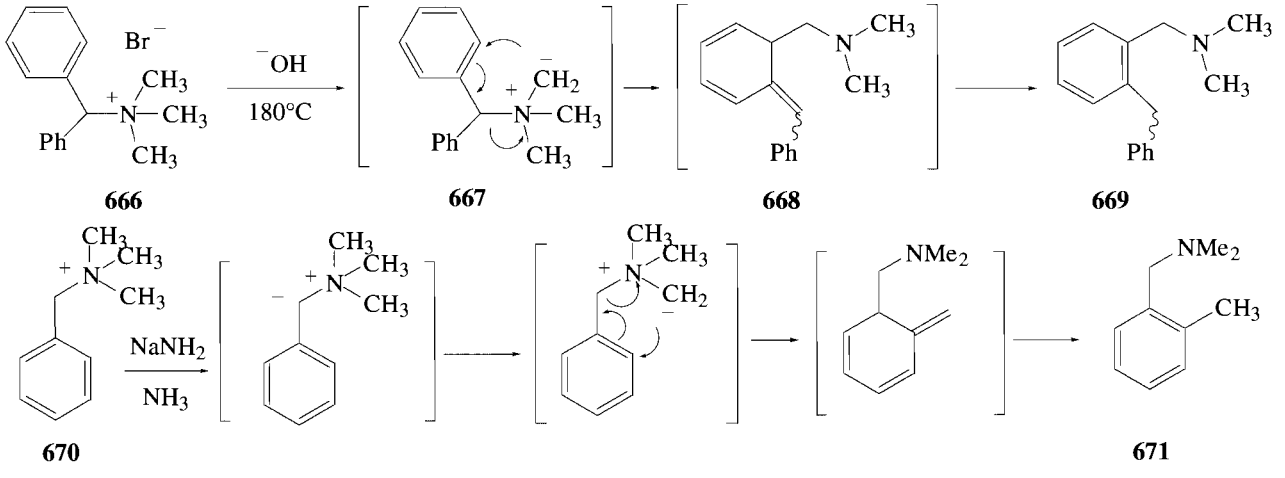


657 **658**

8.8.C.ii. The Stevens' Rearrangement and the Sommelet Rearrangement. The intermediacy of nitrogen ylids has been suggested for two classical reactions, the **Stevens' rearrangement**[556,527c] and the **Sommelet–Hauser rearrangement** (sometimes called the **Sommelet rearrangement**).[557] Stevens found that

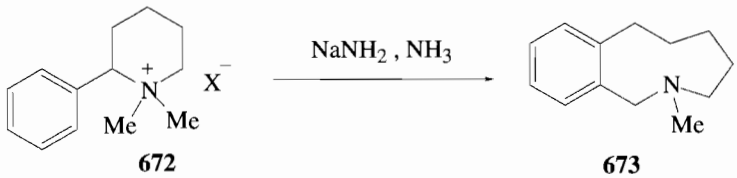


treatment of phenacylbenzyldimethylammonium bromide (**659**) with aqueous hydroxide gave amino ketone **662** The reaction probably proceeds via hydrogen abstraction from the ammonium salt (**659**) to give the ylid **660**. A N→C 1,2-benzyl shift occurs via a carbanionic intermediate **656** to give amine **662**.[556d] The mechanism involves a [2,3]-sigmatropic rearrangement of the ylid followed by proton migration to restore aromaticity.[558] The preparation of complex alkaloids is a common synthetic application of the Steven's rearrangement. The reaction of bis(α,α-*o*-xylylene) ammonium bromide (**663**) with phenyllithium led to the α-lithio compound **664**. This nitrogen ylid was unstable and rearranged, with loss of LiBr, to **665**.[559]



The original Sommelet rearrangement was the formation of *o*-benzylbenzyldimethylamine (**669**) from benzhydryltrimethylammonium bromide (**666**) on heating to 180°C with concentrated hydroxide.[557] Initial deprotonation probably occurs at the benzylic site but equilibrium conditions generated ylid **667**. Nucleophilic attack at the proximal benzene ring gave **668** via cleavage of the C—N bond. Subsequent aromatization gave the final product **669**. Evidence suggests the mechanism is a [1,2]-shift of the ylid through a caged radical pair intermediate.[558] Steric effects are believed to be less significant than electronic effects for ylid

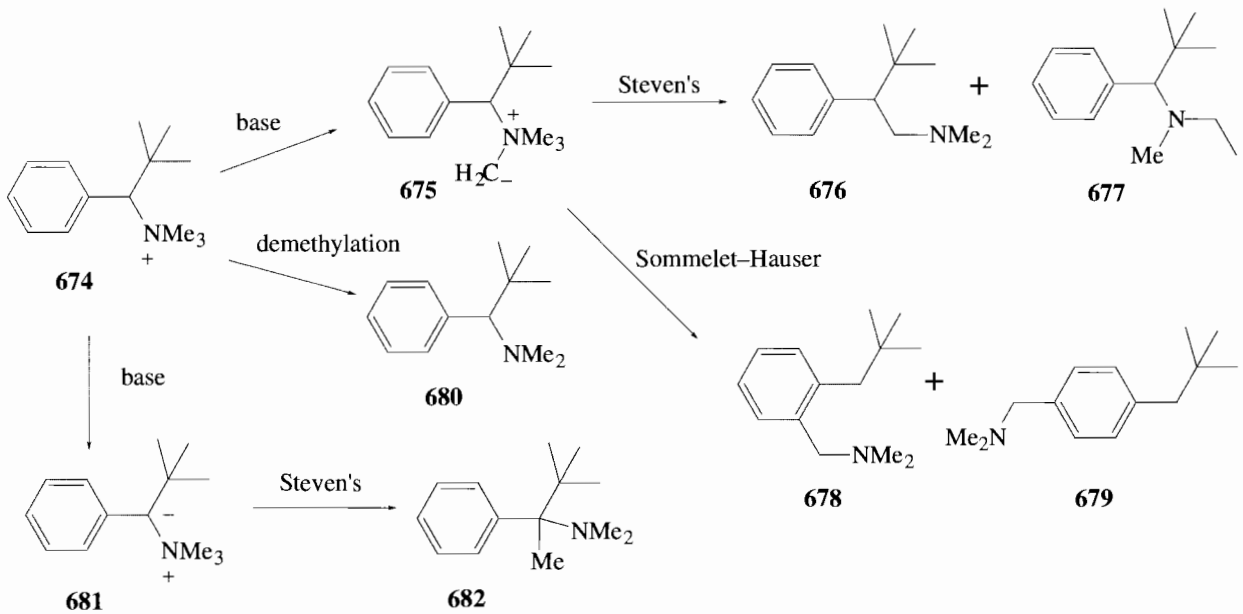
stability.[560] The **ortho substitution rearrangement** of Hauser, involving reaction of benzyltrimethylammonium salt **670** with $NaNH_2$ to give 2-dimethylaminomethyl toluene (**671**) is either the same reaction or closely related.[561] Hauser and co-worker showed that this rearrangement could be used for a ring expansion reaction. Reaction of dimethylammonium salt **672** with sodium amide gave an 83% yield of **673**.[562]



672 **673**

The Sommelet and Stevens rearrangements compete with each other in some cases, as shown in Table 8.27.[563] The major products from reaction of **674** with base are the Stevens products **676** and **677**, and the

Table 8.27. Competition Between the Sommelet and Stevens Rearrangements



Solvent	Base	Temperature (°C)	680	678	679	677	%
NH_3	$NaNH_2$	–33[a]	6	81	0.8	12	75
DMSO	Li/DMSO	51[b]	49	31	1.2	18	
HMPT	$NaNH_2$	25[a]	2	60	3.0	35	65
HMPT[c]	*n*-BuLi	25[a]	1.5	63	3.5	32	
Hexane	*n*-BuLi	51[b]	1.1	13	5.9	80	73
t-BuOH	*t*-BuOK	51[b]	97	1.5	0.3	1.7	68
MeOH	MeOK	90[d]	100				10

[a] 6 h. [b] 47 h. [c] 41 h. [d] + hexane.

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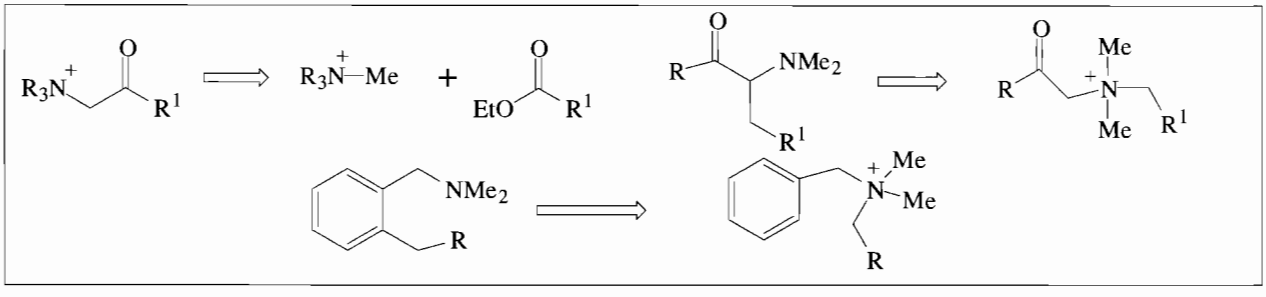
Sommelet–Hauser product **678**. Small amounts of the para rearrangement product (**679**) and the direct displacement product (**680**) are also present. The ammonium salt precursor to the ylid (**674**) can generate either ylid (**675** or **681**), but formation of **681** is sterically inhibited relative to **675**. The Stevens product of **681** (amine **682**) is more sterically crowded than **676** or **677**. In polar aprotic solvents the major product is the Sommelet–Hauser product **678**, but in nonpolar solvents (hexane) the Stevens product **676** predominates. In DMSO, the enhanced nucleophilicity of the base causes the displacement product **680** (base attacks the methyl carbon and displaces the amine) to be formed in high yield. Alkoxide bases are not strong enough to generate the ylid from **674**, and the displacement reaction (to give **680**) dominates in those cases.

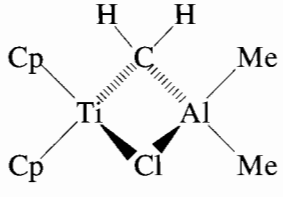
It is noted that a nitrogen ylid has been invoked in the **Hofmann elimination reaction** (sec. 2.9.C.i).[564] This ylid mechanism is highly questionable for many substrates that proceed via β-elimination with a coordinated hydroxide.[565] In those cases, removal of the hydrogen directly by hydroxide appears more likely. The ylid mechanism probably operates when PhLi is used as a base[566] and when there is steric inhibition of the usual β-elimination process.[567]

The useful disconnections of nitrogen ylids are



8.8.D. Transition Metal Olefination Reagents

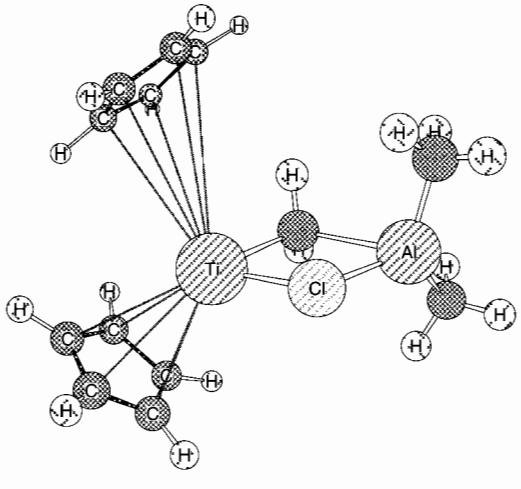
There are other organometallic derivatives that give Wittig-type olefination reactions, with titanium derivatives being the most commonly used.[568] The initial addition reaction to the carbonyl gives a transient metalated alcohol that leads to an alkene. An example is the **Tebbe reagent**, which exists as a bridged methylene species (see **683**), where Cp is cyclopentadienyl.[569] The aluminum species can be varied to include chloride



$(Cp_2TiCH_2{\cdot}AlClMe_2)$

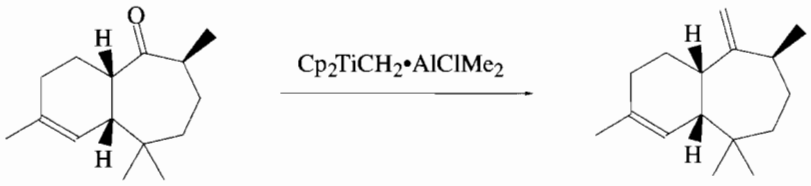
683

≡

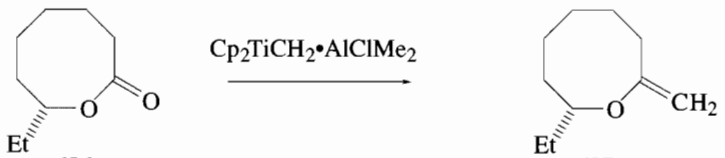


($AlCl_3$), triperdeuteromethyl aluminum [$Al(CD_3)_3$] or trimethylsilyl [$AlCl(CH_2SiMe_3)_2$]. The most common reagent is the aluminum dimethylaluminum chloride compound shown. The Tebbe reagent reacts with ketones to give an olefination product, analogous to the Wittig reagent. In a synthesis of (1S,3S,7R)-3-methyl-α-himachalene, Mori et al. converted ketone **684** to diene **685** using the Tebbe reagent.[107]

The Tebbe reagent is quite useful in that it reacts with the carbonyl of esters to give vinyl ethers. Pine showed that **683** reacted with methyl benzoate to give an 81% yield of 1-methoxy-1-phenylethene.[570] Similar reaction of lactone **686** with **683** gave the exo-methylene vinyl ether **687** in Holmes' synthesis of (+)-laurencin.[571] The Tebbe reagent also reacts with conjugated esters via 1,2-addition to give the vinyl ether.[569]



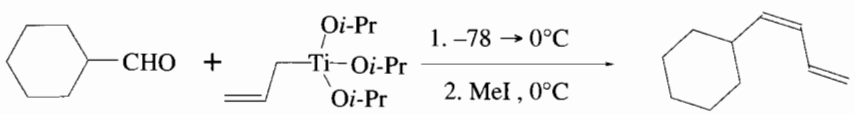
684 **685**



686 **687**

Other titanium-based olefination reagents have been developed. Eisch used a zinc analog of the Tebbe reagent (**688**) in a reaction with benzophenone to give 1,1-diphenylethene in 78% yield.[572] Similarly, Clawson et al. used **689** in olefination reactions with ketones and aldehydes.[573] Alkoxytitanium reagents such as **690** have been employed, as in the conversion of cyclohexane carboxaldehyde to 1-cyclohexyl-1,3-butadiene (**691**), in 86% yield.[574] In this olefination reaction, the (*Z*)-isomer predominated over the (*E*) (96:4 *Z*/*E*).

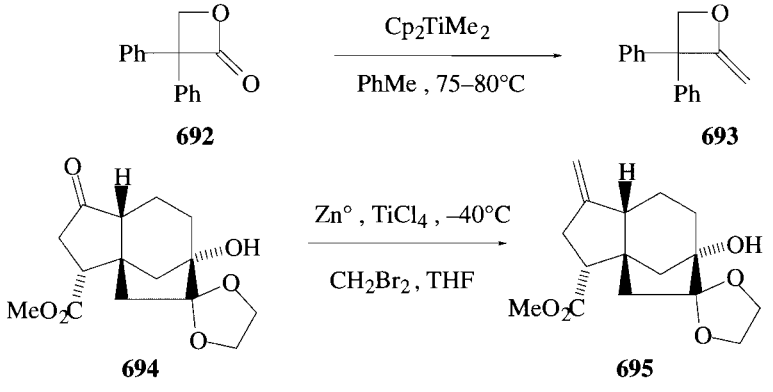
688 **689**



690 **691**

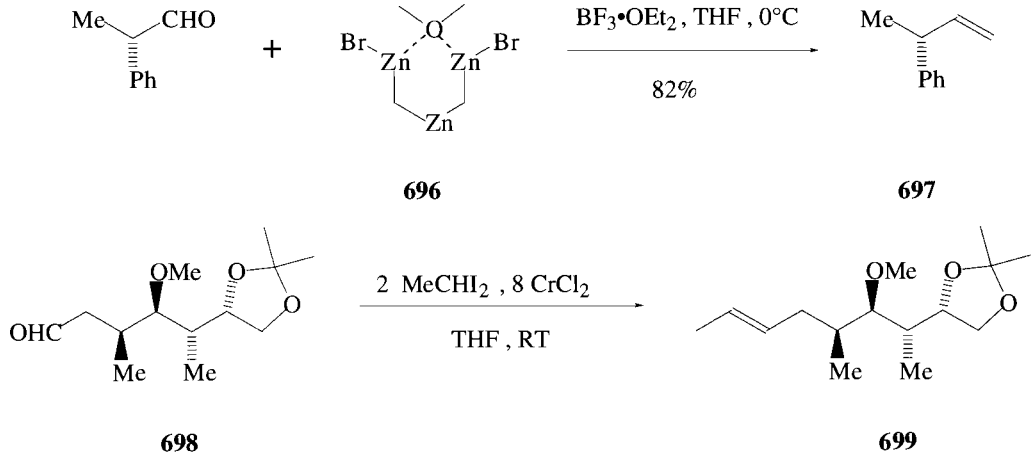
Two additional titanium reagents that have been used for olefination reactions are Cp_2TiMe_2, developed by Petasis,[575] and Lombardo's use[576] of Oshima's reagent ($Zn—CH_2Br_2—TiCl_4$).[577] The Cp_2TiMe_2 reagent is now called the **Petasis reagent**. It is prepared by reaction of methyllithium with titanocene dichloride [(Cp_2TiCl_2)], which avoids some of the difficulties of **683** (high cost, long preparation times, short shelf-lives, extreme sensitivity to air and water, residual aluminum reagents) and is particularly attractive for synthetic

applications. Although ketones and aldehydes are more reactive, in the absence of the ketone moiety, an ester moiety can react. An example of its use is Howell's conversion of **692** to **693** in 76% yield.[578] Similar reaction with β-lactams leads to 2-methyleneazetidines.[579] A Petasis-like reagent has also been reported that gives the same reaction, using $CH_2(ZnI)_2$, $TiCl_2$, and TMEDA in THF.[580] Lombardo used the Zn—CH_2Br_2—$TiCl_4$ reagent in synthetic studies of C_{20} gibberellins (GA_{38}).[576] Attempts to use $Ph_3P{=}CH_2$ or $Me_2S(=O){=}CH_2$ with **694** led to the 8*a*-α isomer, where that hydrogen had epimerized. Oshima's reagent is electrophilic and should suppress the tendency of the ketone to enolize, but its initial use led to the destruction of **694**. Lombardo developed a more active form of this reagent (add $TiCl_4$ dropwise to a stirred suspension of zinc dust in CH_2Br_2 and THF at –40°C, and then allow the mixture to warm to 5°C and *stir for 3 days*),[576] and treatment of **694** with this modified reagent led to a 90% isolated yield of **695**. Lombardo's modified reagent is clearly important when the ketone or aldehyde to be used in the olefination reaction is sensitive to basic reagents. Another variation of this reagent uses CH_2Br_2, Zn, $TiCl_4$ and a catalytic amount of $PbCl_2$.[581]



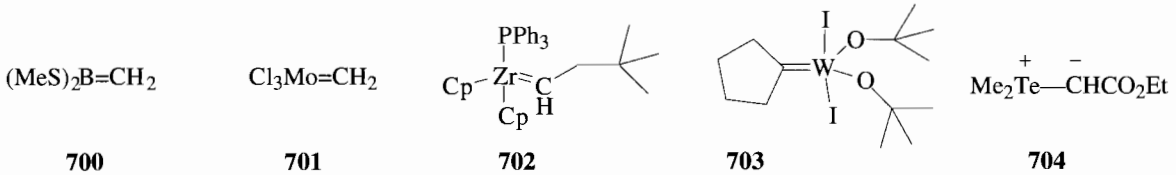
692 693 694 695

The **Nysted reagent** (**696**)[582] is commercially available, and it reacts with aldehydes or ketones in the presence of BF_3•etherate to give an alkene. Reaction with 2-phenylpropanal, for example, gave an 82% yield of **697**.[583] The **Takai reaction**[584] uses $MeCHI_2$ in the presence of $CrCl_2$ to generate the alkene. An example is taken from Chida's synthesis of pironetin in which aldehyde **698** was converted to **699** in 74% yield as an 11:1 mixture of (*E*/*Z*) isomers.[585]



696 697 698 699

Other organometallic reagents have been reported to give Wittig-type olefination reactions with ketones and aldehydes. Typical examples are **700**,[586] **701**,[587] **702**,[588] **703**,[589] and **704**.[590] This list is certainly not exhaustive and is probably not completely representative. It does, however, illustrate some of the reagent types that have appeared and continue to appear.



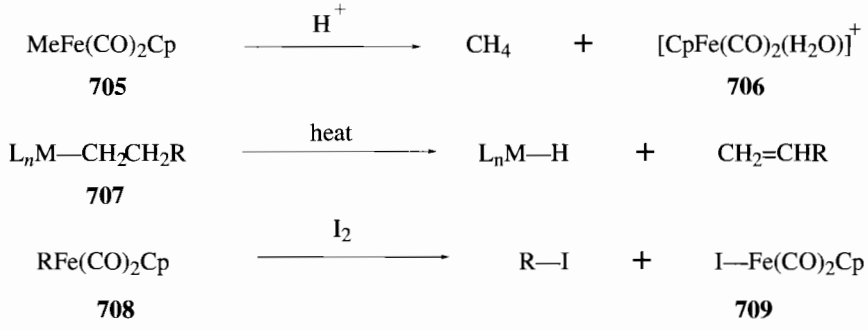
700 **701** **702** **703** **704**

The disconnections for these reagents are identical to those in sec. 8.8.A for the Wittig reagents.

8.9. OTHER ORGANOMETALLIC CARBANIONIC COMPOUNDS

8.9.A. Organoiron Compounds

8.9.A.i. Formation and Stability. A few organoiron compounds have found their way into organic synthesis.[591] In general, Fe—C bonds are sensitive to homolytic cleavage, producing organic radicals and the metal in a lower oxidation state. This instability is due to small energy differences between the filled *d* orbitals and the valence *s* and *p* anti-bonding orbitals of the Fe—C bond. This bond can be stabilized in at least two ways. The first involves addition of a ligand possessing acceptor properties (CO, cyclopentadienyl, phosphines, amines, etc.). The second involves alteration of the effective electronegativity of the carbon (induce a different hybridization state) or attachment of strongly electronegative groups such as fluorine to the carbon.

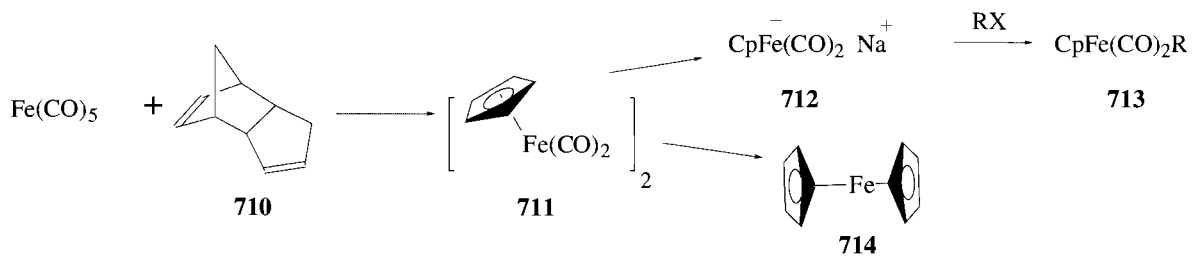


705 **706** **707** **708** **709**

To be useful in organic synthesis, the iron must eventually be removed from the molecule. The Fe—C bond can be broken in several ways. Cleavage by a proton source is very common.[592] Reaction with either water or an alcohol is usually sufficient, although a catalytic amount of acid is sometimes required.[592] This process simply protonates the alkyl fragment in an organoiron compound such as **705** to give methane and **706**.[592] Some organoiron complexes are thermally labile, generating an alkene via β-elimination.[593] Thermal disproportionation is also observed and the thermal stability of simple alkyl groups in $RFe(CO)_2Cp$ was reported to be R = Me ≈ Ph >> Et > *i*-Pr. An example of the disproportionation reaction is the fragmentation of **707** to the alkene. Reaction of the organoiron complex with an halogen[592] also cleaves the

C—Fe bond. When **708** was treated with iodine, an alkyl halide (R—I) and the iron iodide (**705**) were formed. The two most common methods for converting an organoiron to the alkyl fragment are protonolysis and halogenation. Both of these techniques will be used in the following sections.

8.9.A.ii. Cyclopentadienylirondicarbonyl (Fp) Compounds. A common organoiron reagent is cyclopentadienylbis(carbonyliron) (Fp, **711**).[594] This derivative can be converted to an alkyl derivative (**713**, where R = alkyl) by reaction with an alkyl halide, or to the protio derivative (**713**, R = H) by reaction with an acid.[595] The anionic reagent **712** is prepared by reaction of iron pentacarbonyl with the dimer of cyclopentadiene (**710** - sec. 115.B) at 200°C to give the dimeric species **711**. Treatment of **711** with base leads to loss of cyclopentadiene and formation of **712**. A byproduct of this process is ferrocene (**71`4**) formed by extrusion of carbon monoxide from **711**.[595]

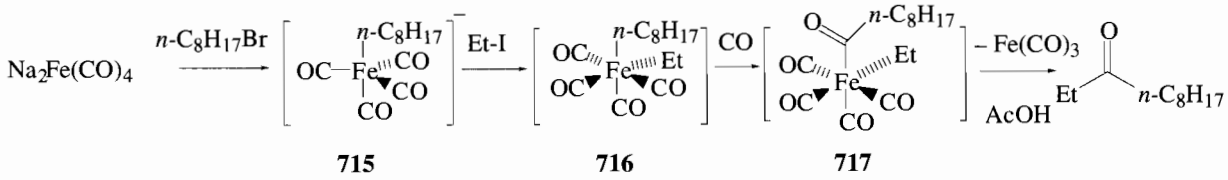


The protonated form of Fp can add to conjugated carbonyl derivatives such as acrylonitrile[596] and also with conjugated dienes.[597] Both SO_3[598] and carbon monoxide can be inserted into the Fe—C bond of FpR.[598] Protonolysis provides a synthetic route to substituted nitriles or alkenes. In each case the Fp unit can also be removed photochemically, thermally, or by treatment with triphenylphosphine. Hydride extraction to give an alkene or a diene is also known.[599]

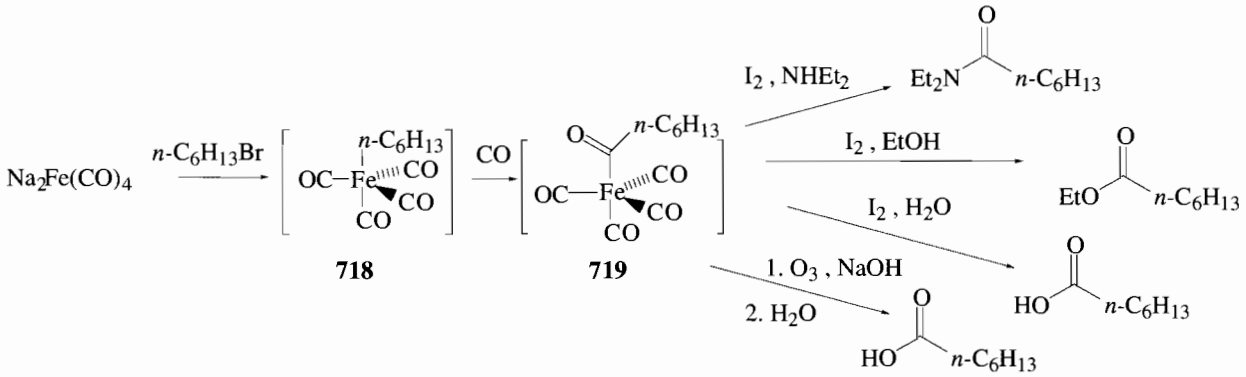
8.9.A.iii. Sodium Tetracarbonyl Ferrate. An extremely useful organoiron reagent is sodium tetracarbonyl ferrate [$Na_2Fe(CO)_4$],[600] usually prepared by reduction of iron pentacarbonyl. The synthetic utility of this reagent lies in its ability to react with alkyl halides in a stepwise manner, including the reaction with two different alkyl halides, as reported independently by Cooke and by Collman and co-workers.[600,601] When sodium tetracarbonyl ferrate reacted with 1-bromooctane, a trigonal bipyramidal complex (**715**) was formed

$$Fe(CO)_5 \xrightarrow{1\%\ Na(Hg)} Na_2Fe(CO)_4$$

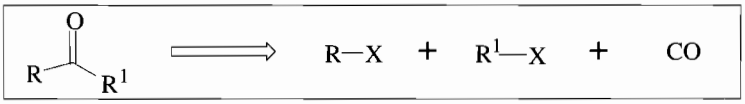
by insertion of the alkyl fragment. Subsequent treatment with iodoethane led to a second insertion and expansion of the coordination shell to an octahedral species (**716**). When the reaction was pressurized with carbon monoxide, CO inserted itself in the C—Fe bond to give an acyl derivative **717**. Protonolysis with acetic acid cleaved the Fe—C bond and concomitant migration led to coupling of the alkyl and acyl fragments to produce 3-undecanone, along with iron tricarbonyl [$Fe(CO)_3$]. If **716** was treated with triphenylphosphine, then CO insertion occurred via an intramolecular migration and protonolysis also led to 3-undecanone.



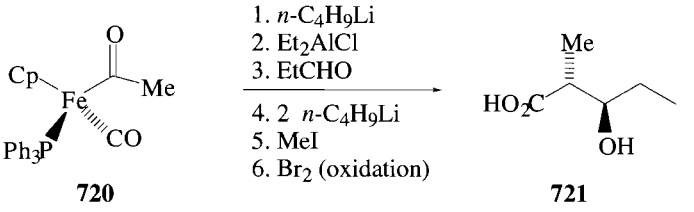
The final product of the sequence shown above is an unsymmetrical ketone. A modification of this reaction involves addition of only one alkyl halide to sodium tetracarbonyl ferrate, followed by pressurization with carbon monoxide. Reaction with 1-bromohexane gave the expected complex, **718**. When treated with carbon monoxide, carbonyl insertion gave **719** and subsequent oxidation with oxygen in the presence of a base led to heptanoic acid.[602] Iodination in the presence of water also gave the acid but when the reaction was done in ethanol, ethyl heptanoate was formed. Similarly, *N,N*-diethylheptanamide was generated by reaction with iodine and diethylamine.[602] In general, the yields of ketone are higher with primary aliphatic halides and tosylates. Secondary substrates give significant amounts of elimination although this can be minimized if THF is used as a solvent.



The disconnection for this process is

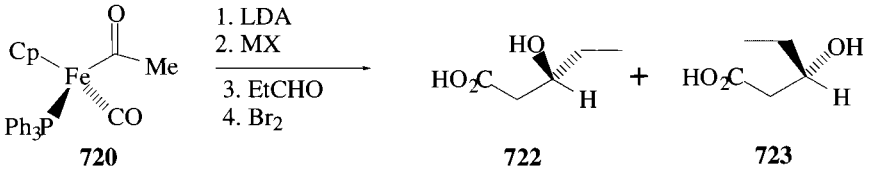


8.9.A.iv. Chiral Organoiron Species. In work reported independently by Davies and by Liebeskind, iron reagents such as **720** were prepared, shown to be chiral, and resolved into the (*R*) and (*S*) antipodes. One of the phenyl groups in **720** effectively blocks one face of the carbonyl moiety, inducing high diastereoface selection in reactions at that carbonyl or at the adjacent carbon. The carbonyl partner of the iron species can undergo enolate reactions similar to those of an acid derivative (secs. 9.2, 9.3). Oxidation with iodine or bromine, as shown above,[602] cleaves the C—Fe bond and generates the acid derivative. Davies et al.[603] showed that the asymmetric acetyl derivative **720** can be deprotonated to form an enolate and condensed with an aldehyde (such as propanal) or alkylated (as with iodomethane). When **720** was reacted with butyllithium and condensed with propanal, reacted with excess butyllithium, subsequent alkylation with iodomethane and oxidation of the C—Fe bond with bromine gave **721** with high asymmetric induction.[603,604] Similarly,



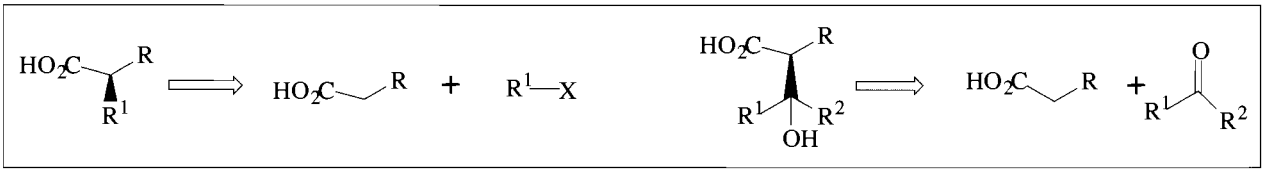
720 721

Liebeskind and Welker reacted **720** with lithium diisopropylamide (sec. 9.2.A) and propanal, showing the enantioselectivity in the final β-hydroxy acids (**722** and **723**) to be dependent on the conditions used to form the enolate.[605] If diisobutylaluminum chloride (*i*-Bu_2AlCl) was used, a 5.2:1 mixture of **722** and **723** was reversed (to 1:11.6) in 66% yield. Good enantioselectivity was observed in this reaction also. The acyl iron derivative behaves essentially as a protected acid, where the iron group is a chiral auxiliary.[606] The chiral iron moieties are useful variation of enolate condensation chemistry (sec. 9.4.B). In addition to the formation of the condensation product, the high asymmetric induction will prove valuable.



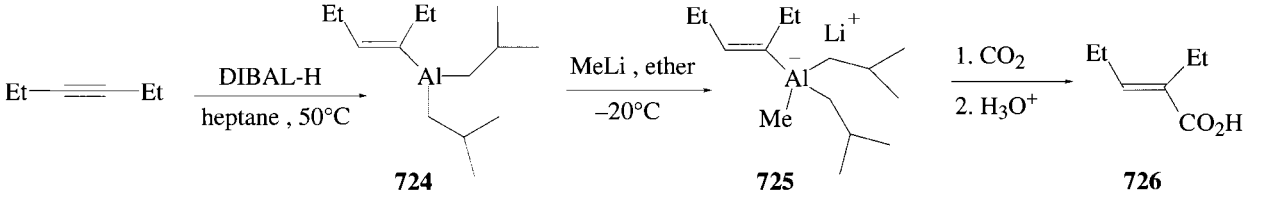
720 722 723

The disconnections possible with these organoiron compounds are



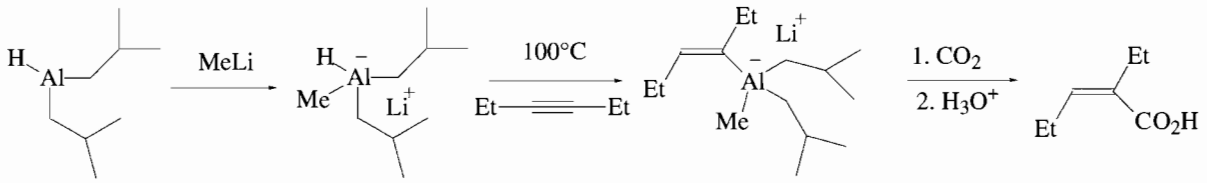
8.9.B. Organoaluminum Compounds

The chemistry of organoaluminum compounds is electrophilic in nature. Zweifel and Whitney, however, showed that conversion of an organoaluminum to its *ate* complex[607] changed it into a nucleophilic species. Examples of this reaction have been largely confined to the vinyl alanates, which react with electrophiles to give the (*E*) or the (*Z*) isomer, depending on the reaction conditions. Treatment of an alkyne such as 3-hexyne with diisobutylaluminum hydride (DIBAL-H) gave the vinyl alanate, **724**. When this reacted with methyllithium, the aluminum formed in 73% yield. If tin chloride ($SnCl_2$) was used, however, the ratio of **722** to **723** was found to be *ate* complex **725** was formed. Subsequent reaction with an electrophile such as carbon dioxide led to a transfer of the vinyl group to the carbonyl, forming the (*E*)-acrylic acid derivative **726**. The



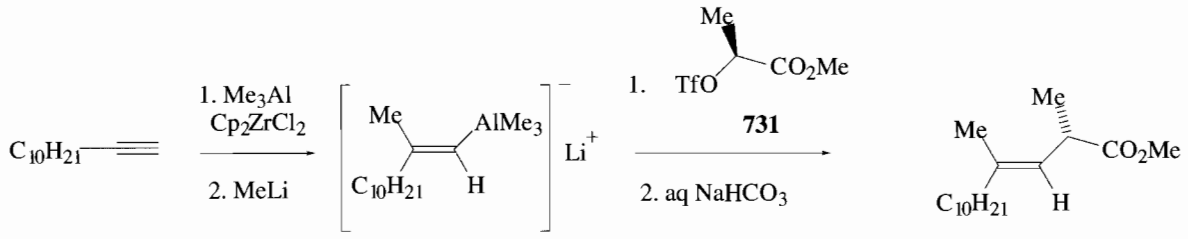
724 725 726

geometry of the intermediate alanate and the final product was changed by first reacting methyllithium with DIBAL-H, to give the aluminate **727**. When this *ate* complex reacted with the alkyne (3-hexyne), a new *ate* complex **728** was formed. Subsequent trapping with carbon dioxide gave the (*Z*)-acrylate, **729**. The aluminum *ate* complex also reacted with alkynes and hydrolysis converted the aluminum intermediates into substituted 1,3-butadienes.[608] Reaction of the *ate* complex with halogens gave the corresponding vinyl halide, with retention of the geometry.[607] Similar reaction with alkyl halides gave the substitution product.[609]



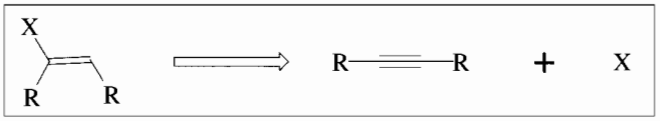
727 **728** **729**

Another way to generated vinyl alanes is the transition metal catalyzed addition of trialkylaluminum reagents to alkynes. In Hoye's synthesis of elenic acid,[610] 1-dodecyne was treated with Me_3Al in the present of Cp_2ZrCl_2 and then MeLi. The resulting *ate* complex **730** was then reacted with triflate **731** to give a 96% yield of the alkene, **732**.



730 **732**

The disconnection for the alkyne–alanate reaction is

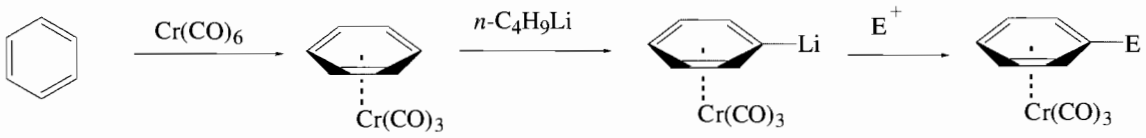


8.9.C. Organochromium Reagents

Benzene and its derivatives react with chromium hexacarbonyl [$Cr(CO)_6$] to give an arylchromium complex **733**.[611] Chromium resides in a position perpendicular to the plane of the ring, as shown. Semmelhack found that the chromium activated the benzene ring to metal–hydrogen exchange with organolithium reagents (sec. 8.5.G) and these new lithium reagents reacted with alkyl halides to give the alkyl substitution product. As shown in Table 8.28,[612] reaction of **733** with butyllithium generated **734** via lithium–hydrogen exchange. Subsequent reaction with an electrophile gave **735** in good yield.

Arylchromium complex **733** reacts with carbon nucleophiles via nucleophilic aromatic substitution. As shown in Table 8.29,[613] organolithium reagents and enolates add to **733** to generate a carbanionic complex

Table 8.28. Li—H Exchange in Arylchromium Complex 733 and Substitution Reactions with Electrophiles



733 734 735

E^+	E	% 735
CO_2	$—CO_2Me$	72
Acetone	$—C(OH)Me_2$	29
$MeOSO_2F$	$—CH_3$	91
PhCHO	—CH(OH)Ph	0
Me_3SiCl	$—SiMe_3$	94
I_2	—I	76

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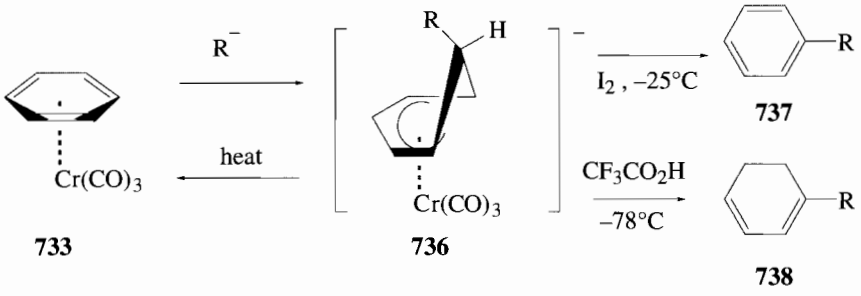
736. Several important characteristics of this reaction are shown. First, the nucleophilic addition can be reversible if complex **736** is heated. Second, the complex can be decomposed by reaction with iodine (to give **737**) or by protonolysis (with trifluoroacetic acid, TFA) to give cyclohexadiene derivative **738**. The reagents used to remove the metal are similar to those used with organoiron complexes (sec. 8.9.A).

When the benzene ring is functionalized, ortho, meta, or para isomers are possible upon reaction of the chromium complex with nucleophiles. In general, the meta substitution product predominates[614,615] but all

Table 8.29. Nucleophilic Aromatic Substitution of 733 by Organolithium Reagents and Enolate Anions



733 736 737 738

R^-	% 736
$LiCH_2CN$	68
$LiCMe_2CN$	94
2-Lithiodithiane	93
$LiCMe_3$	97
$LiCH_2CO_2CMe_3$	87

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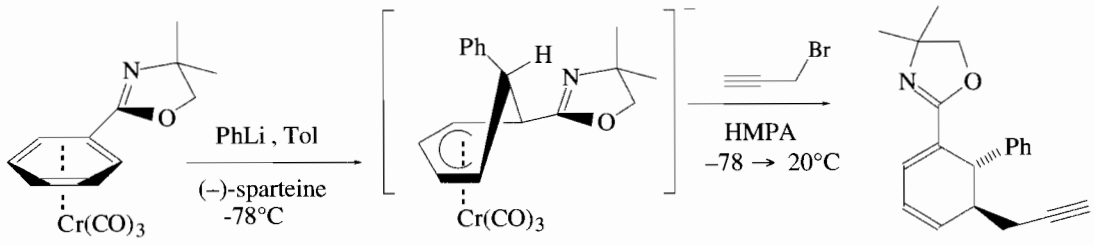
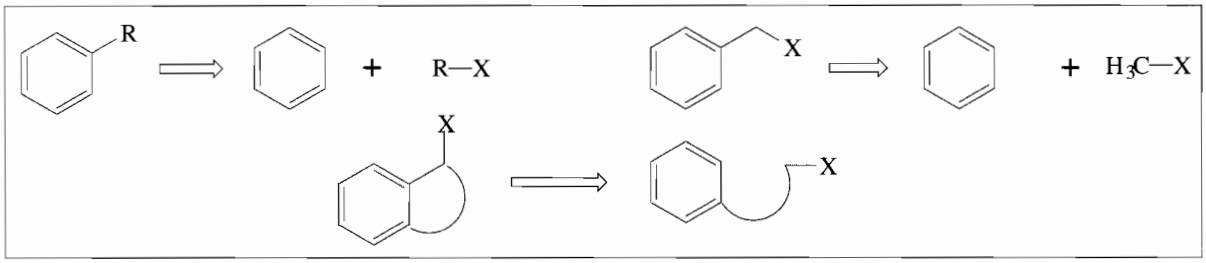
three isomeric products are formed These transformations have been used in synthesis, as when Semmelhack used an arylchromium complex for a synthesis of acorenone,[616,614] and also in a synthesis of (±)-frenolicin which exploited the lithium–hydrogen exchange reaction.[617] Semmelhack also showed that chromium complexes of polynuclear aromatic molecules undergo nucleophilic substitution, but not on the ring complexed to



739 **740** **741**

chromium.[618] Asymmetric induction is possible when chiral ligands are used in conjunction with the organolithium addition reactions. An example is the reaction of **739** with phenyllithium in toluene, and in the presence of (–)-sparteine for example. The resulting complex **740** was then treated with propargyl bromide, and a 72% yield of **741** was obtained with 54% ee.[619]

The disconnections available from organochromium chemistry are:



In general, nucleophilic aromatic substitution reactions are rather difficult with unsubstituted aryl derivatives or when the aromatic ring contains a strongly electron-releasing group. Formation of the chromium complex activates such aromatic compounds to nucleophilic substitution. Since the nucleophiles are carbon nucleophiles, this technique offers a route to carbon bonds that would be very difficult to form by other methods.

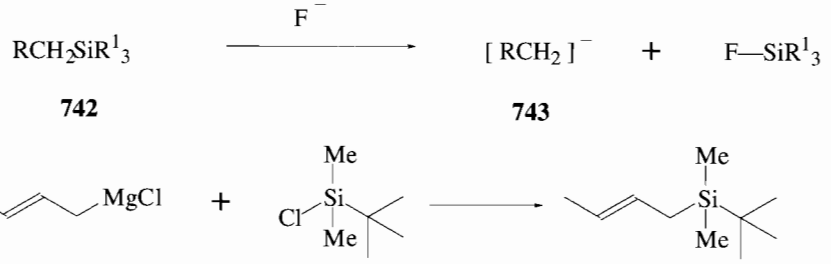
8.10. SILANE CARBANIONS AND AROMATIC CARBANIONS

There are additional methods for generating carbanionic centers that are not classified in previous sections. Two of the more useful are treatment of organosilanes with fluoride and formation of resonance stabilized aromatic carbanions. These two methods will be presented in this section, with an emphasis on the more synthetically useful versions of each reaction.

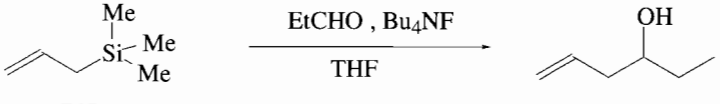
8.10.A. Silane Carbanions

Allylic silanes are synthetically useful compounds that are usually prepared by reaction of chlorotrialkylsilanes and allylic Grignard reagents, as with the preparation of the *tert*-butyldimethylsilane **744**.[620]

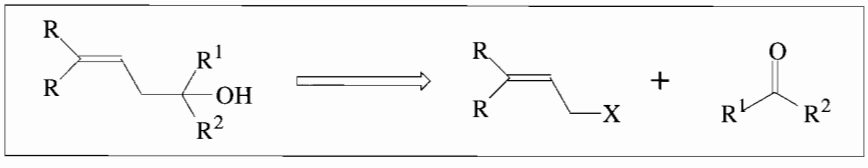
When a silane such as **742** is treated with fluoride ion, fluoride attacks the silicon and displaces the carbanion **743**. If the anion is generated in the presence of an electrophile, typical carbanion reactions occur. It is unlikely that the carbanion (**743**) has a significant lifetime as a discrete entity. Indeed, it need not exist at all,



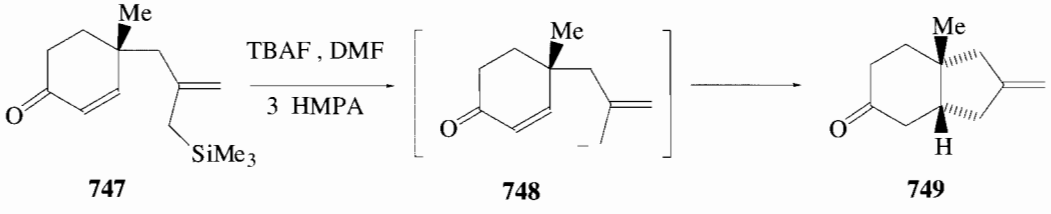
since the carbanionic character of that carbon increases as the fluoride departs, forming a transient hypervalent silicon species. Sakurai showed that allylic silanes react with ketones or aldehydes upon treatment with tetra-*n*-butylammonium fluoride (TBAF) in THF. Allyl silane **745** reacted with butanal in the presence of TBAF to give an 83% yield of alcohol **746**.[621] Similar reaction of allylic silanes with TBAF in the presence of benzophenone gave the acyl substitution product.[621]



The disconnection for silane carbanion addition to carbonyls is

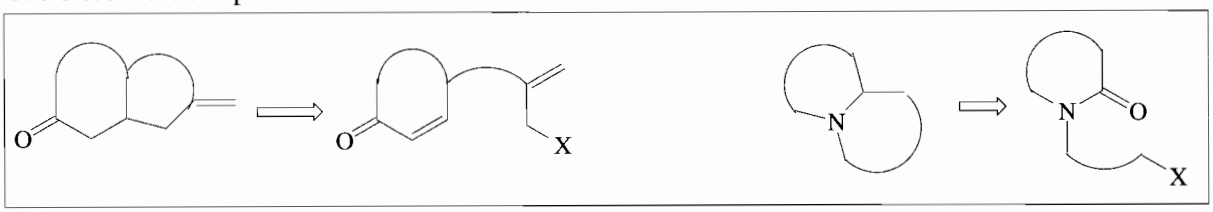


Majetich showed that fluoride generated carbanions undergo Michael-type additions.[622] To achieve conjugate addition with carbanions generated from silanes usually requires the use of DMF as a solvent, and HMPA is often added to obtain satisfactory yields. In this example, **747** was treated with TBAF to generate the carbanion **748**. Intramolecular Michael addition and hydrolysis led to the bicyclic product **749**.[622]



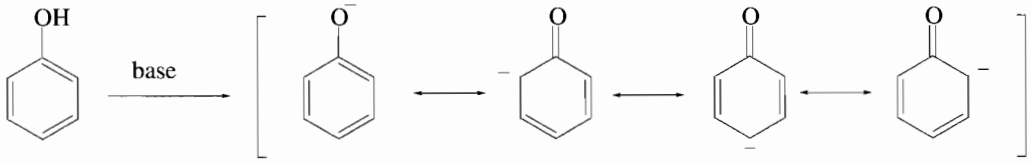
It is noted that Vedejs used the fluoride/silane carbanion reaction to generate a novel imidate ylid that was used in a [3+2]-cycloaddition reaction with ethyl acrylate (sec. 11.11.F).[623]

The disconnections possible with these latter reactions are



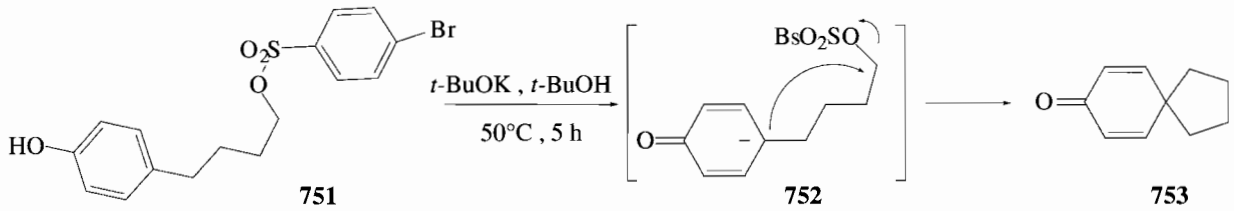
8.10.B. Phenolic Carbanions

When phenols are treated with base, the resulting phenoxide ion (**750**) has four resonance contributors



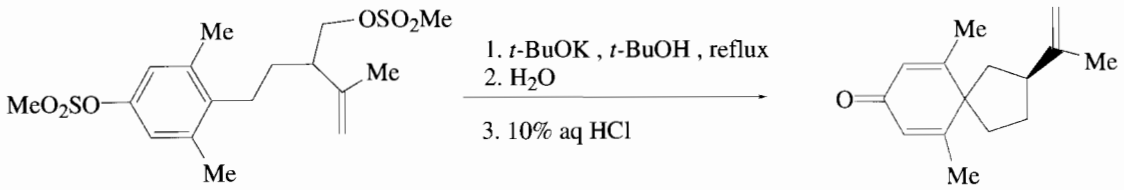
750

as shown. If an electrophilic species were added to **750**, the ether product (O-alkylation) predominates via the Williamson ether synthesis (sec. 2.7.A.i). If an electrophilic center is tethered to the phenolic moiety, however, it is possible to trap the carbanion center intramolecularly. Winstein showed that *p*-bromophenylsulfonyl (OBs) derivatives such as **751** reacted with potassium *tert*-butoxide to give the reactive carbanion intermediate **752**.[624] This resonance contributor gives a carbanionic center that can displace a leaving group such as bromine, iodine, or a sulfonate ester. Displacement of the bromobenzenesulfonyl leaving group in **752** by the aromatic carbanion proceeded via an Ar_1^--5 mechanism[625] to give the spirocyclic ketone **753**.



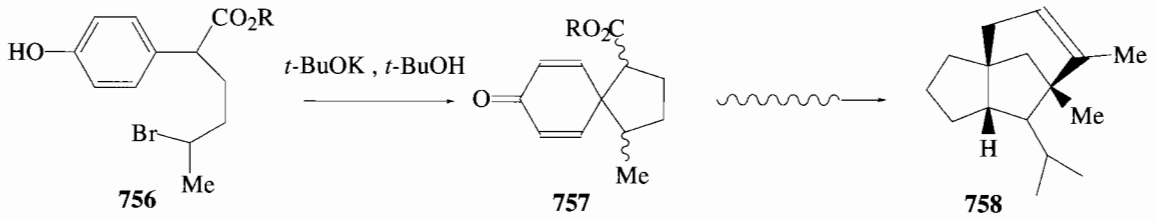
751 **752** **753**

A phenol need not be used directly, as long as a phenoxide anion can be formed easily. Spirocyclization of the bis(methanesulfonate) **754** to **755** is a useful example where the requisite phenolic anion is generated *in situ*.[626] Spirocyclization was used by Corey as well as by Crandall and Lawton to construct the spirocyclic portion of cedrene, **758**. In independent syntheses, phenolic ester **756** was cyclized to **757** in good yield. Corey used the methyl ester[627] and obtained a 53:47 mixture of (*Z*/*E*) isomers of **757**. Corey also found



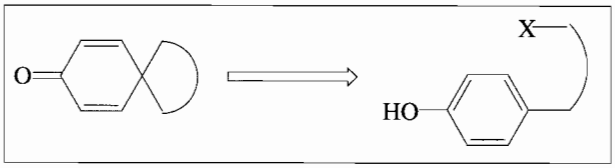
754 **755**

that treatment of **756** with sodium methoxide in methanol induced epimerization to give the (*E*)-isomer as the predominant product. Crandall and Lawton used the ethyl ester of **756** but employed cyclization conditions similar to those of Corey.[628] Conversion to cedrene (**758**) was straightforward in both cases.



756 **757** **758**

This spirocyclic disconnection is



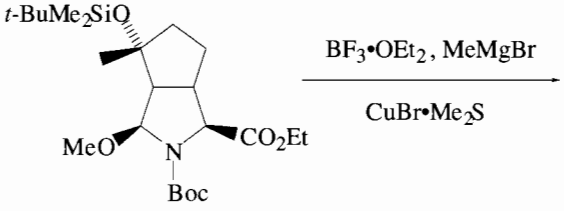
8.11. CONCLUSION

This chapter has shown how incorporation of a metal or an appropriate electron withdrawing group or atom gives carbanions that can be used to form new carbon–carbon bonds. The great variety of nucleophilic species, the range of electrophilic species with which they react, and the high degree of stereoselectivity which accompanies many of the reactions show why these are among the most powerful disconnections in organic synthesis.

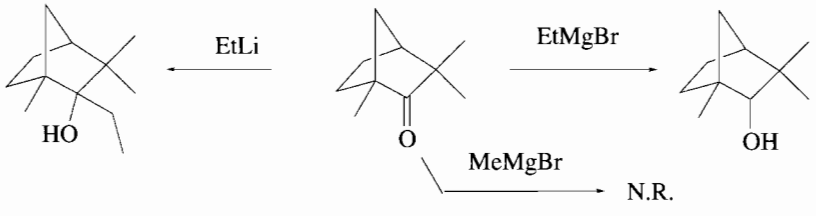
Perhaps the most useful of nucleophilic carbanion reagents are the carbonyl stabilized carbanions, the enolates. Enolate anions will be discussed in Chapter 9.

HOMEWORK

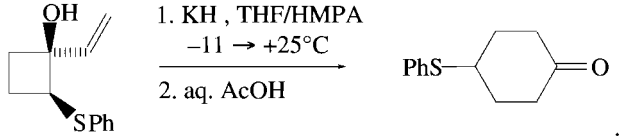
1. Predict the major product and explain the stereochemistry of the following reaction.



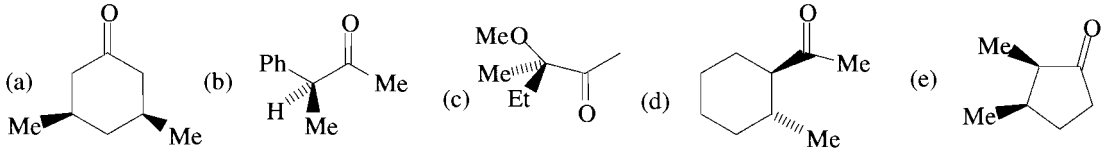
2. Explain the difference in reactivity for the reaction of this ketone with ethylmagnesium bromide, with ethyllithium, and with methylmagnesium bromide, as shown.



3. Given the reaction sequence , give a mechanistic rationale for formation of the cyclohexanone product

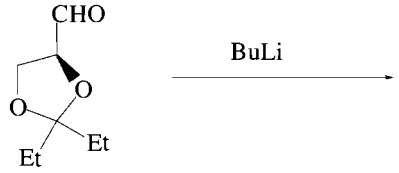


4. In each case, draw the transition state for the Cram, Karabatsos and Felkin–Ahn models of the reaction of each molecule with (1) MeMgBr (2) PhMgCl (3) $CH_3C{\equiv}C{:}^{-}Na^{+}$ (4) EtLi (5) 2-lithio-1,3-dithiane

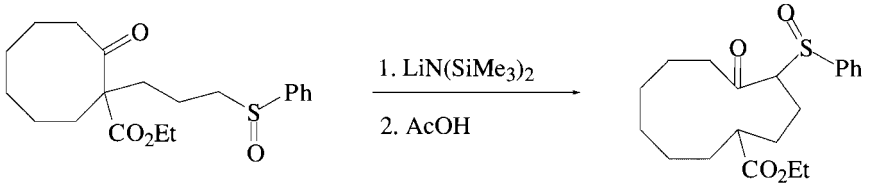


Draw the major product(s) that result from each reaction, after hydrolysis.

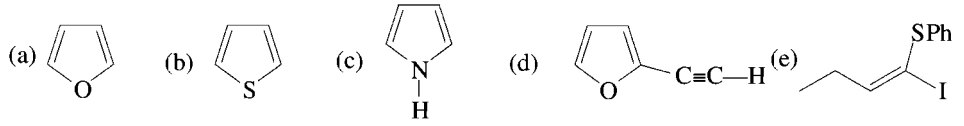
5. The following reaction gives a diastereomeric ratio of about 3:1. Draw both of these products, and predict the major product..



6. Give a mechanistic explanation for the formation of the product shown from the designated starting material.



7. Give the major product for (a–e) when treated with (1) *n*-BuLi/THF/-78°C; (2) MeI/–78→0°C; (3) aq NH_4Cl.

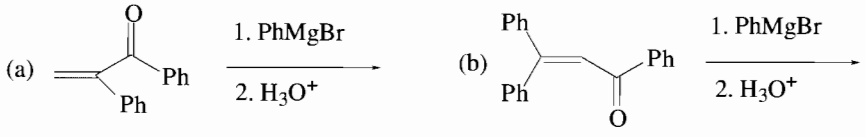


8. For each of the following give a complete reaction that illustrates its use for the formation of a carbon–carbon bond:

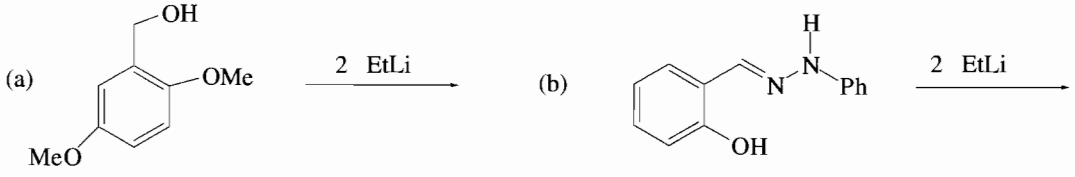
(a) $CdCl_2$; (b) Cp_2TiMe_2 ; (c) $CeCl_3$ (d) lithium 2,2,6,6-tetremethylpiperidide ; (e) CO; (f) CuCN;

(g) *N,N,N′,N′*-tetramethylethylenediamine; (h) $FeCl_3$; (i) NaCN; (j) $NaNH_2$; (k) BF_3; (l) $Na_2Fe(CO)_4$; (m) *i*-Bu_2AlH; (n) PPh_3; (o) NaH; (p) $(MeO)_2POMe$; (q) DMSO.

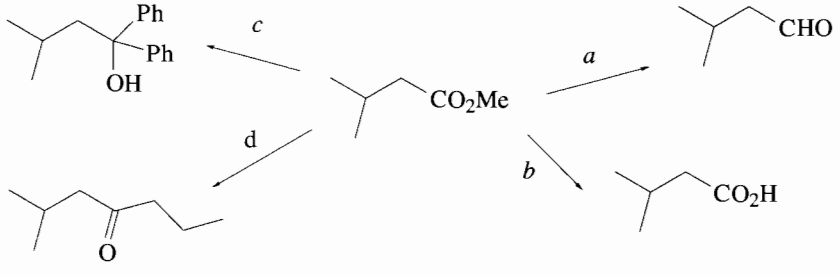
9. Discus and compare the differences in reactivity for the reactions



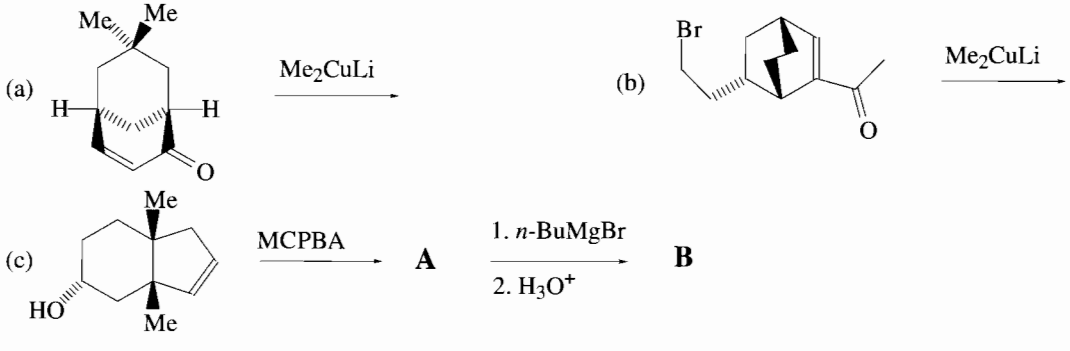
10. Each of the following molecules can be used to standardize a solution of an organolithium reagent. Describe, with reactions, the acid–base chemistry involved in each reaction.



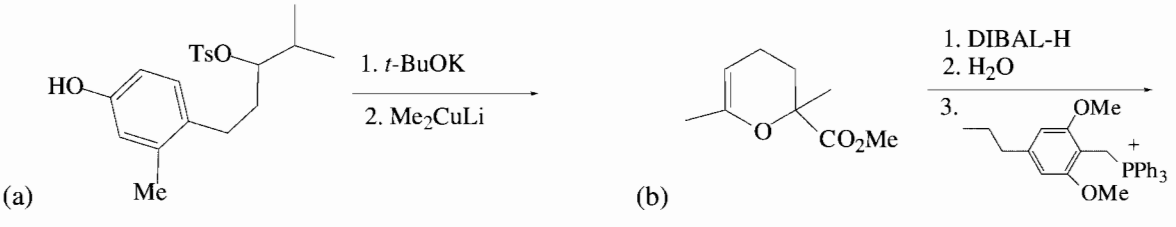
11. Provide a suitable synthetic sequence for each transformation (a–d).

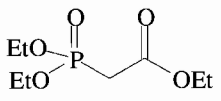


12. For (a–c) give the major product of each reaction, with correct stereochemistry, and justify your choice.

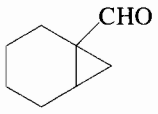


13. In each of the following reactions, predict the major product, with the correct stereochemistry where appropriate:

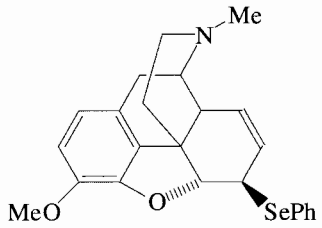


(c) 

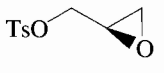
1. NaH ,THF , 25°C
2. Me_2CHCHO , THF
3. hydrolysis

(d) 

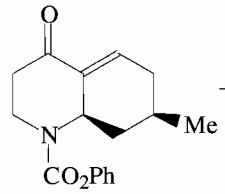
1. PPh_3 , CBr_4 , CH_2Cl_2
2. BuLi , pentane

(e) 

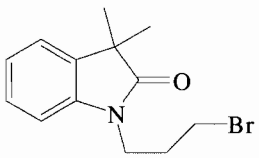
1. H_2O_2
2. aq. KOH

(f) 

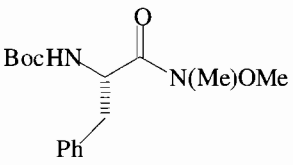
1. BuLi , 1,3-dithiane , THF
2. CH_2=CHMgBr , CuI, THF

(g) 

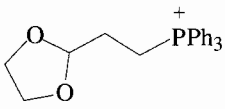
$PhMe_2SiCH_2MgCl$
CuI , ether

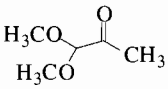
(h) 

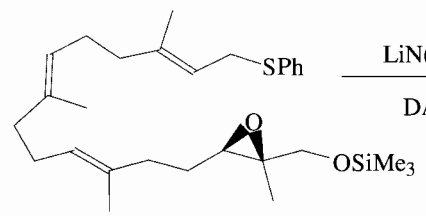
1. *t*-BuLi , ether , –78°C
2. $LiAlH_4$, ether

(i) 

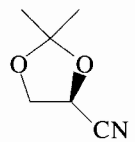
1. $LiC{\equiv}CC_9H_{19}$
2. hydrolysis

(j) 

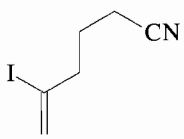
1. BuLi , THF , –20°C
2. 

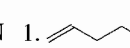
(k) 

$LiN(iPr)_2$, THF
DABCO

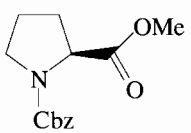
(l) 

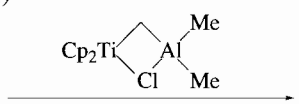
1. BuMgBr
2. $NaBH_4$

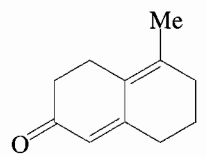
(m) 

1. 

2. 2 M HCl

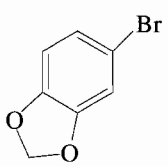
(n) 



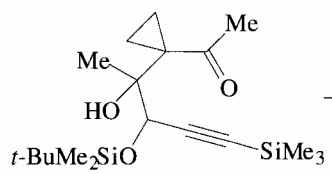
(o) 

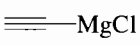
Me_2CuLi

J. Am. Chem. Soc., ***1980***, *102*, 4274

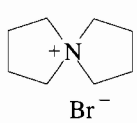
(p) 

1. Mg° , THF
2. CO_2
3. H_3O^+
4. $SOCl_2$
5. iPr_2Cd
6. H_3O^+

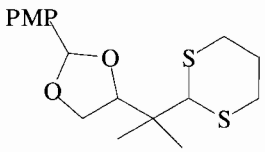
(q) 



$CeCl_3$

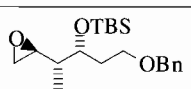
(r) 

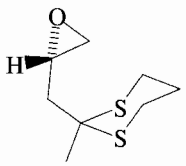
PhLi

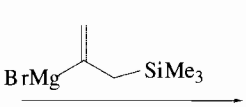
(s) 

PMP = *p*-methyoxyphenyl

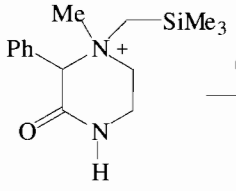
BuLi , HMPA/THF



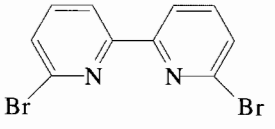
(t) 



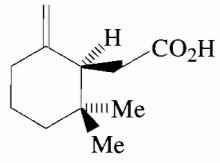
0.15 CuI , THF
–50°C

(u) 

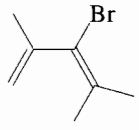
CsF , DMF

(v) 

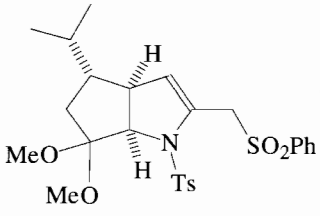
1. 2 BuLi , THF
2. excess CO_2
3. hydrolysis

(w) 

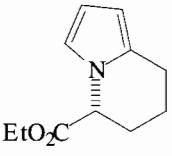
1. $LiAlH_4$; H_2O
2. $MeSO_2Cl$, NEt_3
3. NaI , acetone
4. 3-lithiofuran , HMPA

(x) 

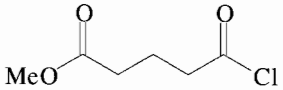
1. *t*-BuLi , THF , –78°C
2. ethylene oxide
3. DMSO , $(COCl)_2$, NEt_3
CH_2Cl_2 , –78°C

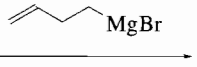
(y) 

1. BuLi , HMPA-THF , –78°C
2. 1-bromohex-5-ene

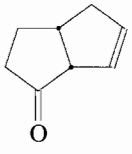
(z) 

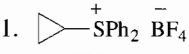
1. $LiAlH_4$
2. $MeSO_2Cl$
3. NaCN
4. aq, NaOH/MeOH

(aa) 

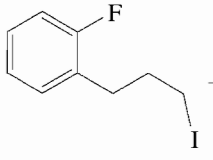


CuI

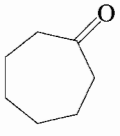
(ab) 

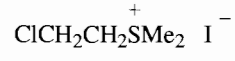
1. 

KOH , DMSO
2. LDA , THF , –78°C
3. H_3O^+

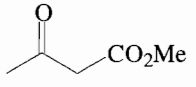
(ac) 

1. 3.2 *t*-BuLi ,–78°C , pentane–ether
2. THF , warm
3. MeOH

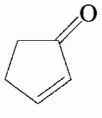
(ad) 

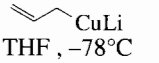


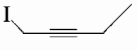
t-BuOK , *t*-BuOH

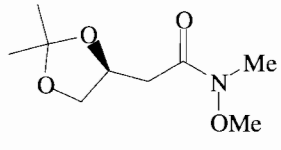
(ae) 

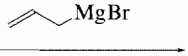
1. NaH
2. *n*-BuLi , THF , –78°C
3. $MOMOCH_2Br$

(af) 

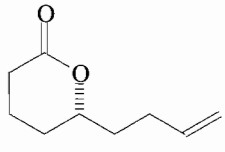
1. 

THF , –78°C
2. TMEDA
3. 

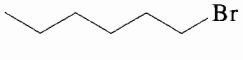
(ag) 

1. 

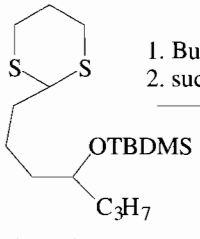
2. hydrolysis

(ah) 

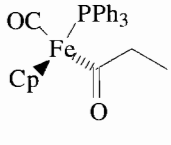
1. excess MeLi
2. H_3O^+

(ai) 

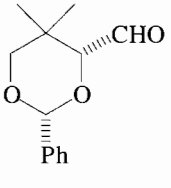
1. $Na_2Fe(CO)_4$
2. MeI
3. CO
4. I_2 , AcOH

(aj) 

1. BuLi , TMEDA-THF
2. succinic anhdyride , THF

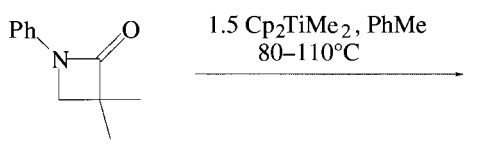
(ak) 

1. LDA , THF , –78°C
2. MeI
3. Br_2

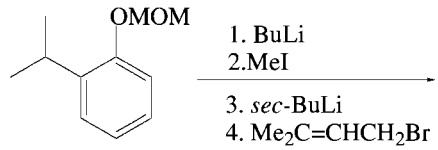
(al) 

Zn , CH_2Br_2
$TiCl_4$, THF
CH_2Cl_2 ,RT

(am)



(an)



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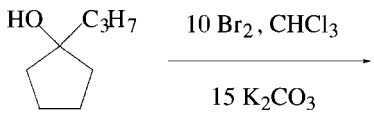
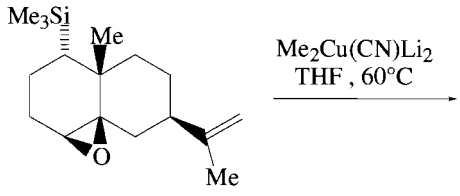
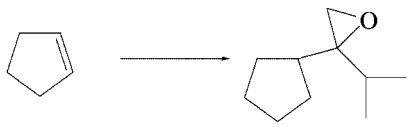


(ap)



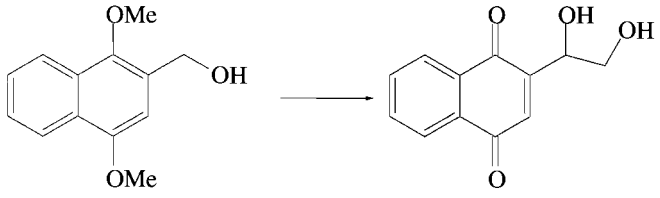
14. Provide a suitable synthesis for each of the following transformations. Show all reagents and intermediate products.

(a)

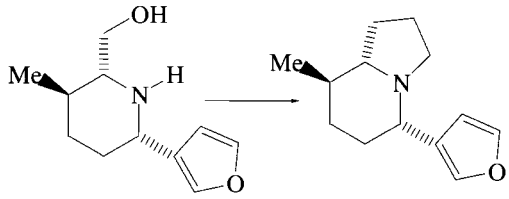


(b)

(c)

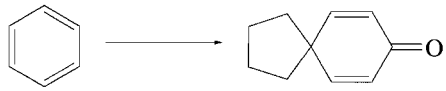


(d)

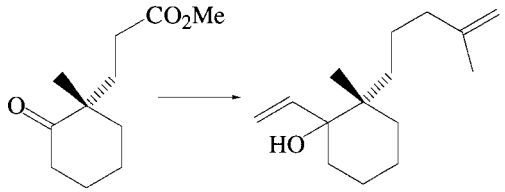


(e)

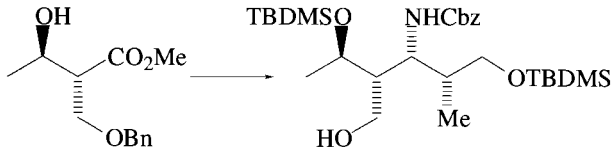
(f)



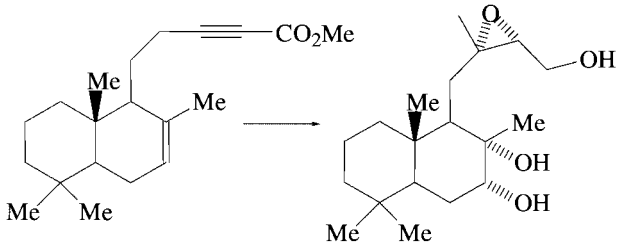
(g)



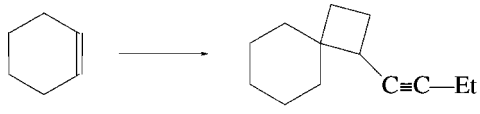
(h)



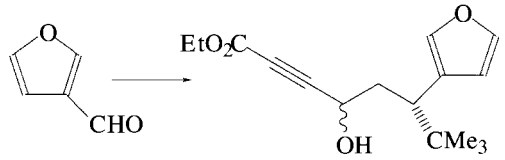
(i)



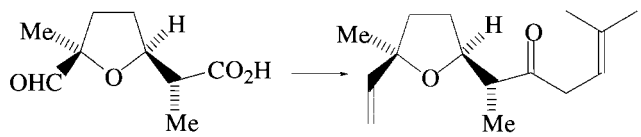
(j)

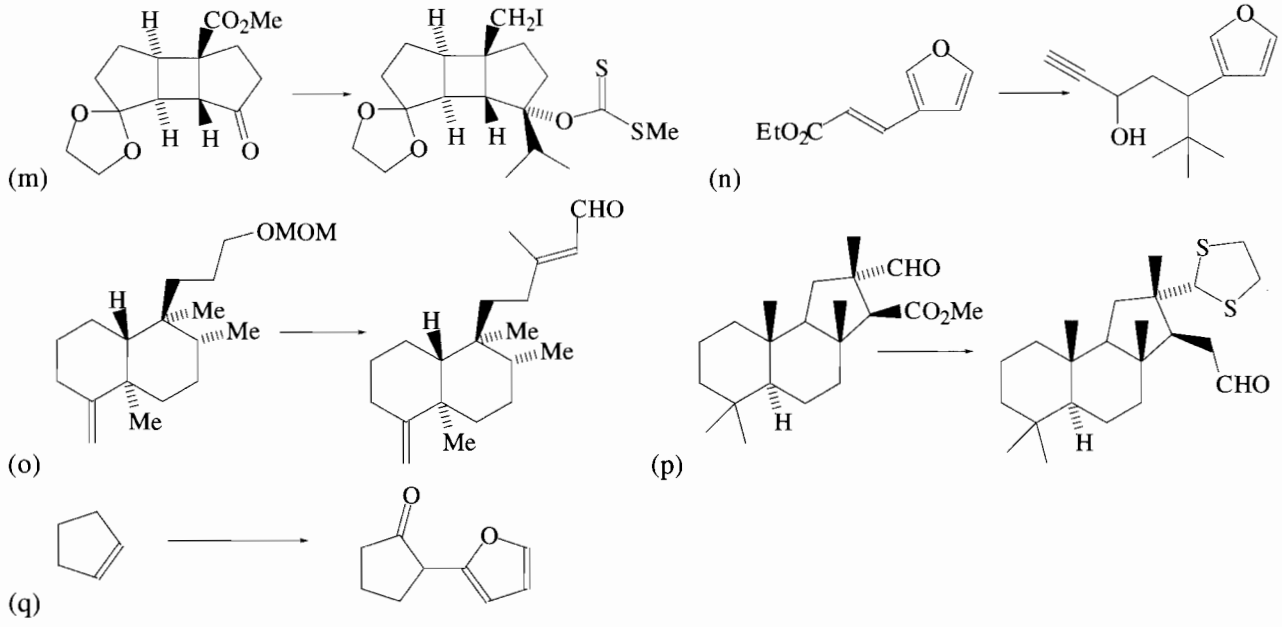


(k)

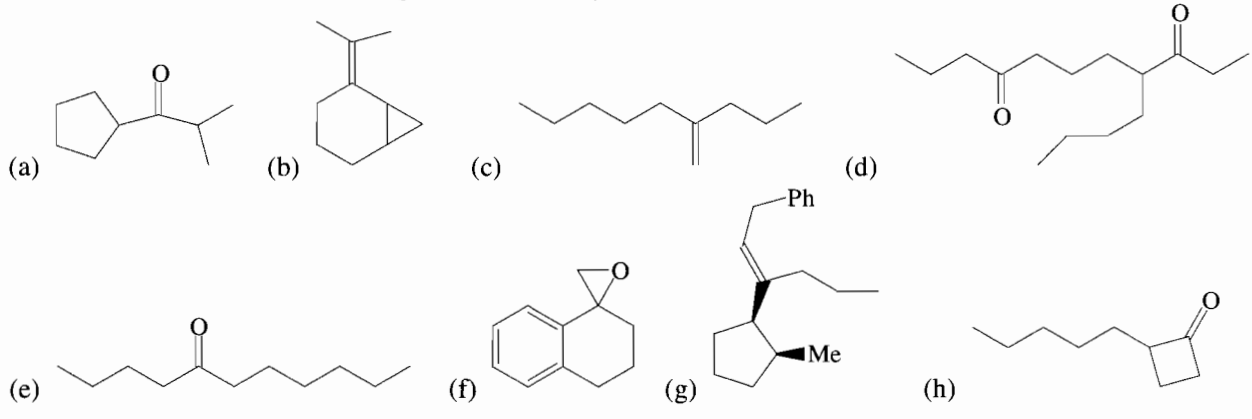


(l)





15. Synthesize each of the following molecules from a starting material of no more than six carbons. That starting material must be commercially available from a chemical company. Show your retrosynthetic analysis and all reagents and intermediate products of the synthesis.



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6 For an example taken from a synthesis of *R*–(+)–myrmicarin 217, see Sayah, B.; Pelloux–Léon, N.; Vallée, Y. *J. Org. Chem.*, ***2000***, *65*, 2824.

7 For an example taken from a synthesis of laulimalide, see Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.*, ***2000***, *41*, 33.

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CHAPTER 9

C^d DISCONNECT PRODUCTS: NUCLEOPHILIC SPECIES THAT FORM CARBON–CARBON BONDS: ENOLATE ANIONS

9.1. INTRODUCTION

In Chapter 8, the presence of a proton on a carbon α to an electron-withdrawing group gave a carbon acid. Removal of that proton by a base generated several synthetically useful reagents that contained a carbanion center, and functioned as a C^d disconnect product (sec. 1.2). When the electron–withdrawing group is a carbonyl group (ketones, aldehydes, esters, etc.) the pK_a of the adjacent protons are in the range pK_a 20–24.[1] As discussed in Section 8.5.G, the effects of the carbonyl group are due to (1) the inductive electron-withdrawing ability of the unsaturated substituent but mainly due to (2) the ability of these substituents to delocalize the negative charge remaining after a proton has been removed.[2] With the enhancement in acidity induced by the carbonyl, weaker bases can be used for deprotonation when compared to sulfides, sulfoxides, and so on (introduced in Chapter 8).[2] Alkoxide and hydroxide ions, as well as amines, are basic enough to remove protons adjacent to a carbonyl (see Table 8.17 in sec. 8.5.H), generating a resonance stabilized **enolate anion**. The bases used in previous chapters are all rather nucleophilic and when dealing with aldehydes, ketones, or carboxylic acid derivatives, acyl addition to the carbonyl may compete with deprotonation. Acyl addition must be suppressed or diminished if an enolate anion is to be generated and used in subsequent reactions, which can be achieved by decreasing the nucleophilicity of the base while maintaining or enhancing its basicity. This chapter will introduce enolate anions and discuss solutions to the problems posed, as well as present synthetically useful reactions.

9.2. FORMATION OF ENOLATES

9.2.A. Preparation and Properties

The attachment of an electron-withdrawing carbonyl on a C—H moiety enhances the acidity of that hydrogen, the so-called α-hydrogen. Reaction of a carbonyl derivative such as 3-methyl-2-butanone (**1**) and a suitable base leads to an acid–base reaction in which H_a is removed (as H^+), leaving an electron pair on the α-carbon (in **2**). The enolate anion is resonance stabilized, with the electrons delocalized on the carbon (a carbanion) and on the oxygen. If the carbanion center is the preferred site for reaction, an enolate anion will behave like any other nucleophilic center when mixed with a molecule containing an electrophilic center. Therefore, an enolate anion can behave as a carbon nucleophile. Table 9.1 reproduces a portion of Table 8.17 in Section 8.5.H. Several things are apparent from the data in Table 9.1. In **1**, there are two chemically different types of α-hydrogen atoms. There are three identical hydrogen atoms on the methyl group and one

(labeled H_a) on C3. The presence of the methyl group on the α-carbon (an electron-releasing alkyl group) diminishes the acidity of H_a; that is, the C—H_a bond less polarized and less acidic. This trend can be seen in Table 9.1 by comparing **3** (acetone) with **4** that has a pK_a of 20.8. They are obviously close. However, when **4** is compared to **5**, with a pK_a of 21.3, and **6** with a pK_a of 23.5, the presence of the alkyl substituents leads to a higher pK_a (less acidic proton). Since deprotonation is an acid-base reaction, and we know that alkyl groups

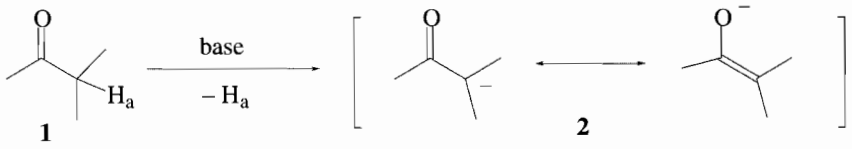
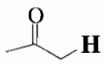
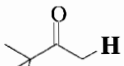
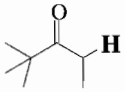
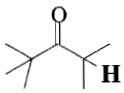
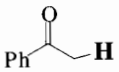
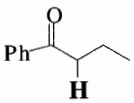
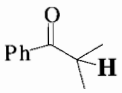
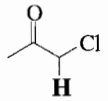
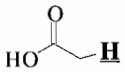
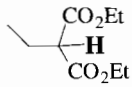
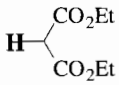
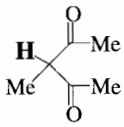
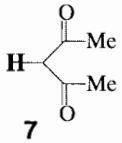
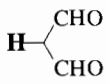
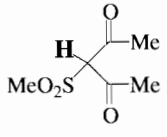
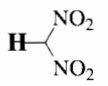
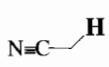
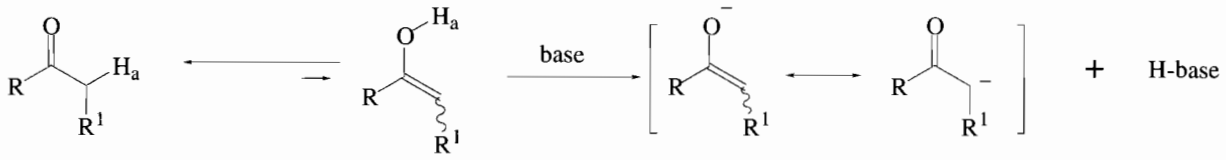


Table 9.1. pK_a values of Typical Carbon Acids

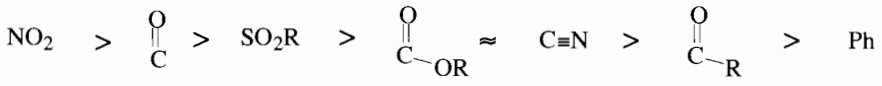
Carbon Acid	pK_a	Carbon Acid	pK_a
 **3**	20[3]	 **4**	20.8[4,5]
 **5**	21.3[4]	 **6**	23.5[4,5]
	19.1[6,4]		18.6[4]
	19.5[4]		16.5[3]
	24[3]		15[3]
	13.3[3]	 **8**	11[3]
 **7**	9.0[3]	 **10**	5.9[3]
 **9**	4.7[3]		3.6[3]
	25[3]		

are electron-releasing, the effect on the equilibrium is that the carbanionic center in the enolate anion is destabilized and the C—H_a bond is stronger (see **1**). These factors shift the acid-base equilibrium to the left (toward **1**) and contributes to a decrease in the acidity of the hydrogen. Comparing the α-hydrogen of acetone to the α-hydrogen of acetic acid (pK_a of 20 vs. 24) shows that the α-hydrogen of the ketone is more acidic. If acetone is compared with acetylacetone (**7**, pK_a of 9.07 in Table 9.1) it is clear the presence of the second carbonyl group greatly enhances the acidity of H_a. The presence of an electron-releasing methyl group in **8** diminishes the acidity (pK_a of 11). If a sulfonyl group, which is an electron-withdrawing species, is attached (see **9**) the acidity is enhanced (pK_a of 3.6). The α-hydrogen of an aldehyde is more acidic than that of a ketone, as seen by comparing malonaldehyde (**10**, pK_a of 5.9) with acetylacetone (**7**, pK_a of 9.0).



11 **12** **13**

The enol content of carbonyl derivatives is an important factor in the acidity of the α proton. By taking a ketone such as **11** as an example, the acidic proton of the enol (**12**) is attached to oxygen rather than carbon (from the keto form, **11**). Removal of H_a from **12** generates the enolate anion (**13**). Removal of H_a from **11** simply generates the other resonance form of **13**. In general, monoalkylated ketone derivatives such as **11** exist primarily in this keto form, but 1,3-dicarbonyl derivatives (such as **7–10** for example) have relatively high concentrations of enol (see **12**) and this contributes to the greater acidity of the proton on the α-carbon. The relative enol content of a molecule is strongly dependent on the solvent, as observed with ethyl acetoacetate.[7] For ethyl acetoacetate, the enol content is 0.4% in water, 2.2% in 50% aqueous ethanol, 6.9% neat, 11% in ethanol, 27% in ether, and 46% in hexane.[7] There is a clear dependence on hydrogen-bonding ability and polarity. The extensive hydrogen-bonding that is possible in water minimizes intramolecular stabilization of the enol, whereas aprotic solvents such as ether or hexane maximize the intramolecular hydrogen bonding, which stabilizes the enol. Removal of a proton connected to oxygen is expected to be more facile than similar removal from a carbon, and one expects that as the enol content increases, the acidity should increase. Although it is tempting to correlate enhanced acidity with increased enol content, inductive effects play a major role in the increased acidity of H_a for 1,3-dicarbonyl derivatives such as **11** (where $R^1 = CO_2Et$; sec. 2.2.A). The carbonyl group is a typical electron-withdrawing substituent but there are many others. In chapter 8, the ability to increase the acidity of a proton was shown to follow the order:



and this is reflected in Table 9.1. It is important to note that recent studies of X-ray structures of enolate anions and amide bases suggests that the enolate anion may be formed by direct removal of the proton from the α-carbon via an intermediate tetrameric lithium complex involving the base and the carbonyl starting material (sec. 9.2.D). Whether the α-hydrogen is removed directly from carbon or from the O—H of an enol,

one electron-withdrawing group enhances the acidity of that hydrogen. The presence of two or more groups enhance the acidity of an α-proton even more, but the effect is not strictly additive, as shown in Table 9.2.[8,3]

Table 9.2. Enhancement of Acidity with Increasing Number of Electron-Withdrawing Groups

Compound	pK_a	Compound	pK_a
CH_3NO_2	11	CH_3COCH_3	20
$CH_2(NO_2)_2$	4	$CH_2(COCH_3)_2$	9
$CH(NO_2)_3$	0	$CH(COCH_3)_3$	6
$CH_3SO_2CH_3$	23	CH_3CN	25
$CH_2(SO_2CH_3)_2$	14	$CH_2(CN)_2$	12
$CH(SO_2CH_3)_3$	0	$CH(CN)_3$	0

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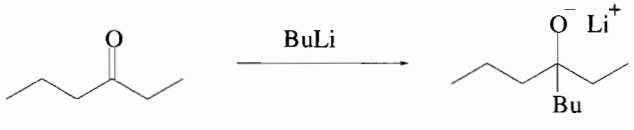
9.2.B. Non–nucleophilic Bases

Although the carbonyl group enhances the acidity of the α-proton, it also causes problems with the base used for the deprotonation. Although organolithium or Grignard reagents are powerful bases, they react with carbonyl derivatives primarily by nucleophilic acyl addition to the carbonyl, as in the reaction of 3-hexanone and *n*-butyllithium to give **14**. This acyl addition reaction can be suppressed somewhat by lowering the reaction temperature to –78°C, –100°C or even lower, but nucleophilic addition remains a major process. Removal of the α-proton is obviously an acid–base reaction and other bases can be used to remove the protons of mono-ketones, aldehydes, and esters. Ideally, the base would not be very nucleophilic, which would have the result of suppressing nucleophilic attack at the carbonyl, but it must be sufficiently basic to remove a relatively weak acidic proton.



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Hydroxide and alkoxides (formed from reaction of alcohols with NaH, NaOH, etc.) are strong enough bases to deprotonate most ketones. Sodium hydroxide (NaOH) in water or alcohol can be used, as well as MeOH/MeO^-,EtOH/EtO^-, or *t*-BuO^-/*t*-BuOH. These are nucleophilic reagents, however, and their use depends on the reversibility of the nucleophilic addition reaction, allowing the deprotonation to compete. The bases NaH and KH are poor nucleophiles, and they are very useful for generating enolates, although not kinetically active enough for a wide range of applications. Sodium and potassium hydride are used most often with malonate derivatives, acetoacetic esters, or 1,3-diketones.

Amines are weak acids, and are deprotonated only in the presence of a strong base. Treatment of a secondary amine with a strong base will generate a strong conjugate base (R_2NH + base → R_2N^- M^+), the amide

anion (R_2N^-. It is more basic than the alkoxide obtained from similar reaction with an alcohol, and is better able to remove the α-proton of a ketone or aldehyde. Generation of $NaNH_2$ from ammonia is well known but reaction of a secondary amine with a basic molecule such as *n*-butyllithium is required to give the analogous lithium dialkylamide. Lithium diisopropylamide (**15**, LDA)[9] is formed by reaction of diisopropylamine and *n*-butyllithium.[10] At first glance, it appears that LDA has a nucleophilic nitrogen atom. In reactions with carbonyl derivatives, however, nucleophilic attack at the acyl carbon is sterically blocked, as illustrated in Figure 9.1, which represents the approach of LDA to 2-butanone. As the nitrogen approaches the carbonyl,

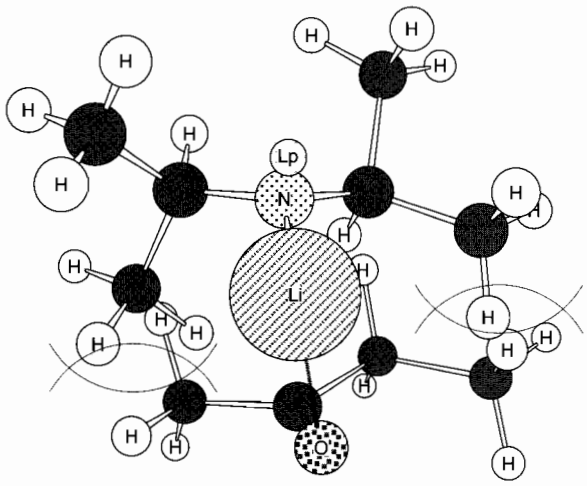
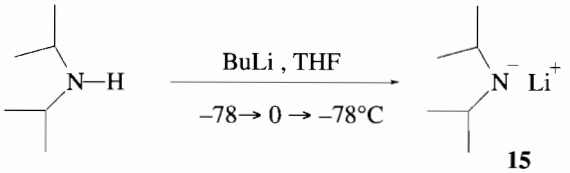


Figure 9.1. Steric hindrance that inhibits nucleophilic acyl addition of LDA (top) as it approaches 2-butanone (bottom) where Lp are lone pair electrons.

the methyl groups of the isopropyl units are sterically repelled by the methyl and ethyl groups, inhibiting nucleophilic attack. If nitrogen cannot react at the acyl carbon due to steric hindrance, it is considered to be a poor nucleophile. Since approach to an α hydrogen is not sterically encumbered, LDA reacts as a base. There is steric hindrance to acyl addition and removing an acidic proton is facile, so dialkylamides can be categorized as nonnucleophilic bases. All this really means is that nucleophilic acyl addition is slow relative to the acid base reaction that removes the α-proton. Virtually any secondary amine can be converted to the corresponding amide base (R_2NLi), including lithium diethylamide (**16**), lithium tetramethylpiperidide (**17**),[11] and lithium hexamethyldisilazide (**18**),[12,13] although **15** is probably the most commonly used amide base. In



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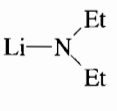

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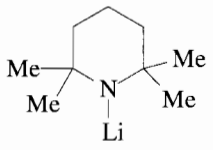

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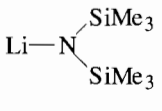

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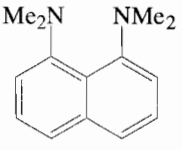
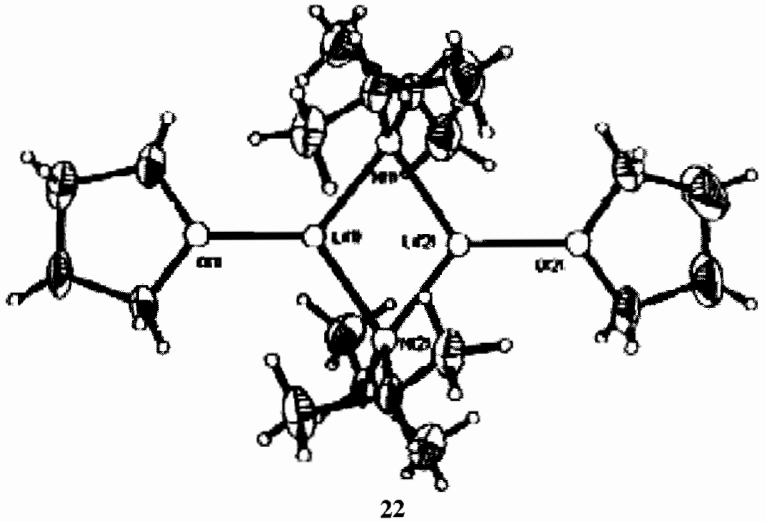


19

17, the four methyls interact with groups flanking the carbonyl, and this inhibits approach of nitrogen to the acyl carbon. In **18** [a bis(*s*ilyl)amide], the bulky trimethylsilyl groups sterically block the nitrogen, and in this case it is so hindered it does not deprotonate all carbonyl species, although common ketones, aldehydes, and esters react to form the enolate anion without major problems. The hindered chelating base 1,8-bis(dimethylamino)naphthalene (**19**) is a very poor nucleophile but extremely efficient at removing protons.[14] It is sold under the name Proton Sponge.™

The structure of LDA (**15**) is not the monomeric species suggested by structure **15**, but rather an aggregate. Jackman,[15a,29] and later Seebach and co-workers studied the colligative properties of LDA as a solution in THF and concluded that dilute solutions exist as both dimers (**20**) and monomers (**21**).[15b] The structure of LDA is assumed to be the THF solvated dimer shown by Williard's X-ray structure, **22**,[15c] which shows that the nitrogen may be more sterically encumbered than is suggested in the representation in Figure 9.1.



22

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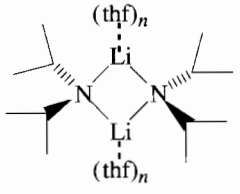
Collum and co-worker studied the solution structure of lithium diethylamide (**16**) in THF and in ether. Not only dimers and trimers, but also four-, five-, and six-rung ladder structures such as **22** were detected.[16]



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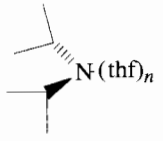

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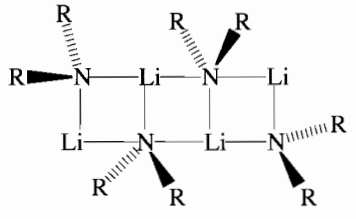
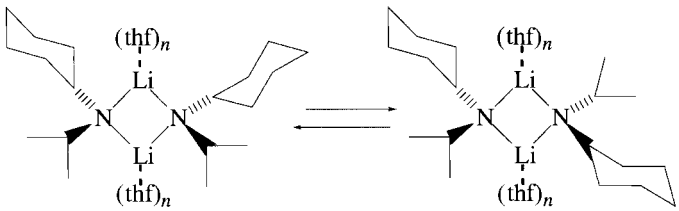


22

Collum also investigated the aggregation state of LDA in solution during the metalation of *N,N*-dimethylhydrazones (sec. 9.4.F.ii) using ^{6}Li and ^{15}N NMR.[17] The NMR data also suggested a solvated, dimeric

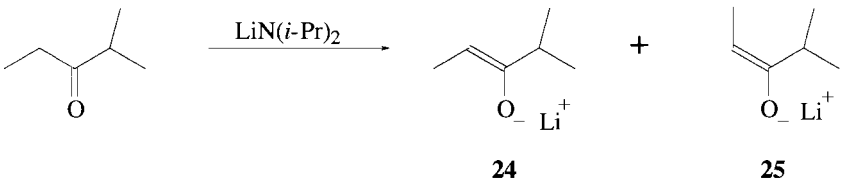
structure such as **20**. Collum found evidence that the solution structure of lithium isopropylcyclohexylam (LICA) was an equilibrating set of stereoisomeric dimers, cis-**23** and trans-**23**.[18] Collum's studies found no evidence for monomeric species in solution and concluded that **21** was not a significant species in ether solutions of LDA.[17,18a]



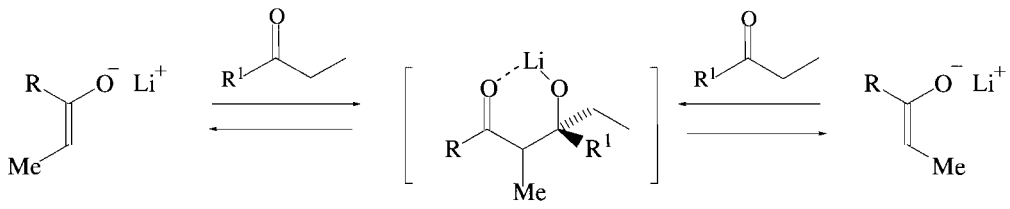
23

9.2.C. (*E*/*Z*) Geometry in Enolate Formation

There are many cases when formation of an enolate anion from a ketones is accompanied by formation of (*E*) and (*Z*) isomers. Treatment of 2-methyl-3-pentanone with LDA (THF, –78°C), for example, gave a 60:40 mixture of the (*Z*) and (*E*) enolates (**24** and **25**)[19] Subsequent reaction of **24** and **25** with a carbonyl



24 **25**

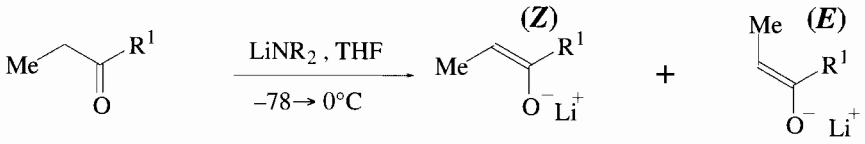


26

compound (sec. 9.4.A) could lead to different stereochemical consequences even if the orientation and facial bias of the reaction is controlled. It is therefore important to understand the factors that control regioselectivity in enolate forming reactions. Evans' review[20] includes a compilation of several studies of selective enolization. Table 9.3.[21] shows the influence of structure and base on enolate geometry.

Only moderate variations in kinetic (*E*/*Z*) ratios are observed except for LHDS, which favored the thermodynamically more stable (*Z*) enolate. The sterically demanding LTMP favored formation of the kinetic E enolate.[22] An equilibration process is clearly occurring, possibly by an aldol addition — retro-aldol process that was suggested by Rathke and co-workers (via **26**).[22] The **aldol condensation** will be discussed in Section 9.4.A. Addition of HMPT (hexamethylphosphorus triamide) destabilizes and deaggregates aldolate **26**, promoting equilibration.

Table 9.3. The Influence of Ketone Structure and Base on Enolate Geometry.

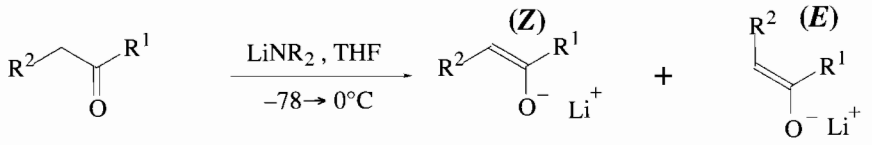


R^1	$LiNR_2$[a]	(Z/E)
Et	LTMP	14:86
Et	LTMP/HMPA	92:8
Et	LDA	23:77
Et	LICA	35:65
Et	LHDS	66:34
Et	$(Me_2PhSi)_2NLi$	100:0
iPr	LDA	60:40
iPr	LICA	59:41
iPr	LHDS	>98:2
iPr	LTMP	32:68
t-Bu	LDA	>98:2
Ph	LDA	>98:2
mesityl	LDA	5:95
mesityl	LICA	4:96
mesityl	LHDS	87:13

[a] **LDA** = lithium diisopropylamide (**15**). **LICA** = lithium isopropylcyclohexylamide (**23**). **LTMP** = lithium 2,2,6,6-tetramethylpiperidide (**17**). **LHDS** = lithium hexamethyldisilazide (**18**).

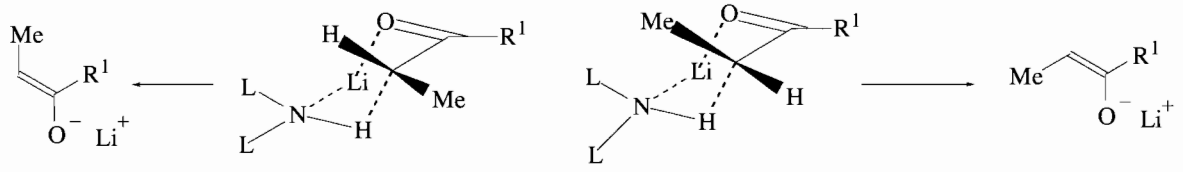
The (*E*/*Z*) trends observed for ketones can be seen in enolates of esters and amides, as shown in Table 9.4.[23] The kinetic (*E*) ester enolate predominates with esters in most cases unless HMPT is added,[24] although the thermodynamic (*Z*) isomer predominates with amides.[25] It is unlikely that the equilibration observed with ket-ones is responsible for reversal in enolate geometry in esters on addition of HMPT. Such equilibration would show great preference for formation of the (*Z*)-enolate with both LDA and with *sec*-butyllithium lead to significant amounts of **Claisen condensation** (sec. 9.4.B.i). As mentioned earlier, amide derivatives showed the influence of the carbonyl structure on the (*E*/*Z*) enolate ratio can be rationalized by the so-called **Ireland model**,[24,26] where the two important steric factors are taken to be R^1 versus Me in **28** and Me versus L in **30** (see Table 9.5).[27] Since enolates actually exist as aggregate dimers, tetramers, or hexamers (sec. 9.2.D), this model is best used as a mnemonic device. It was actually developed as a model to predict stereochemistry in the anionic accelerated Claisen rearrangement (sec. 11.12.D.ii) and was used for predicting stereo-chemistry in ester enolates. It is also a useful tool for predicting (*E*) and (*Z*) isomers for enolate anions. When R^1 is not sterically demanding (as in OR) the H ↔ L interaction in **27** is much smaller than the Me ↔ L interaction in **29** and more of the (*E*) isomer (**28**) is produced. When R^1 is large (such as *tert*-butyl) the large Me ↔ R^1 interaction in **27** is larger than the H ↔ R^1 interaction and usually larger than the Me ↔ L interaction in **29**. In this case, **29** is favored, leading to an increased amount of the (*Z*) isomer (**30**). It is possible that addition of HMPT disrupts the pericyclic transition states represented by **27** and **29**.

Table 9.4. Enolate Geometry of Esters and Amides



R^1	R^2	$LiNR_2$	(Z/E)
OMe	Me	LDA	5:95
OCH_2OMe	Me	LDA	<2:98
O*t*-Bu	Me	LDA	5:95
OMe	Et	LDA	9:91
OMe	Et	LDA, HMPT	84:16
O*t*-Bu	Et	LDA	5:95
O*t*-Bu	Et	LDA, HMPT	77:23
S*t*-Bu	Me	LDA	10:90
NEt_2	Me	LDA	>97:3
NEt_2	Me	*sec*BuLi	75:25
Pyrrolidino	Me	LDA	>97:3
Pyrrolidino	Me	*sec*BuLi	80:20

Table 9.5. (*E*) and (*Z*) Enolates by the Ireland Model



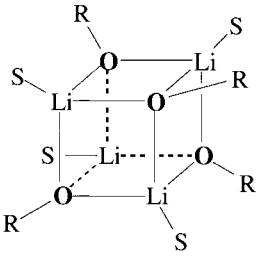
28 **27** **29** **30**

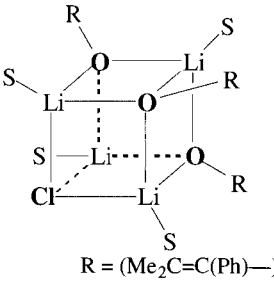
R^1	% (*E*)	% (*Z*)
OMe	95	5
O*t*-Bu	95	5
Et	77	23
i-Pr	40	60
Ph	0	100
t-Bu	0	100
NEt_2	0	100

9.2.D. Structure and Aggregation State of Enolate Anions

Any discussion of enolate geometry must include the structure of the enolate. It is well known that metal enolates exist as dimers[28a] or other aggregates in ether solvents[28] (see Section 9.2.C. for a discussion of aggregate formation with LDA).[28d] Jackman and Szeverenyi suggested that the lithium enolate of isobutyrophenone exists as a tetramer (**31**) in THF solution[29] but exists as a dimer (**32**) in DME.[30] Such aggregates were proposed by House et al.,[31] who found that ketone enolates of groups 1 (IA), 2 (IIA), and 3 (IIIA) metals

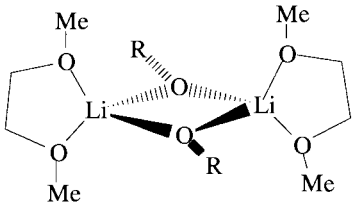
exist primarily as the O—metal enolate.[32,30] For lithium enolates, increasing the donor properties of the solvents from ether → THF → DME increases the Li—O bond polarization, enhancing the α-carbon π-electron density.[33] An increase in π-electron density is also observed for the series: Li → Na → K. Increasing π-electron density is associated with greater reactivity of carbon in the enolate alkylation reactions.[34]





R = $(Me_2C{=}C(Ph)—)$ S = solvent

31



32

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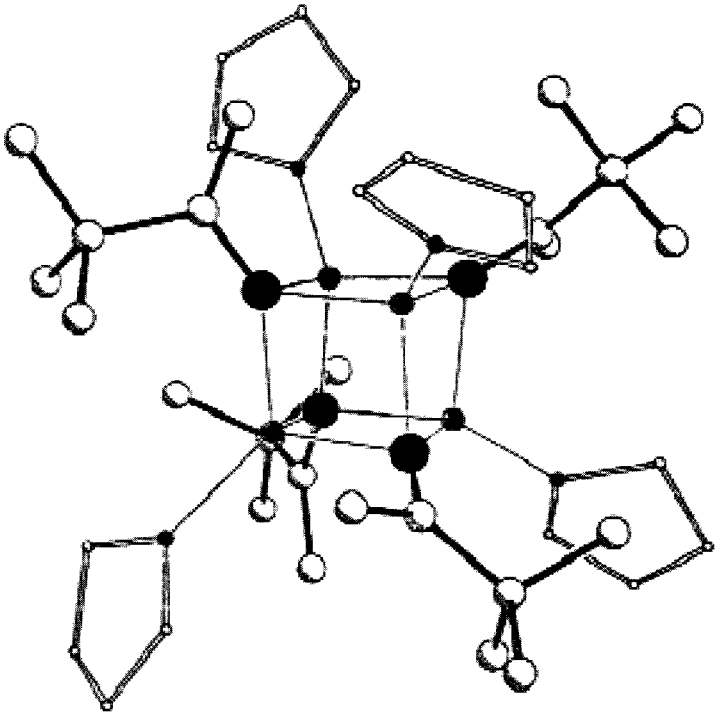
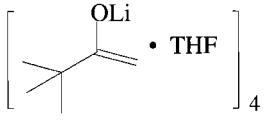
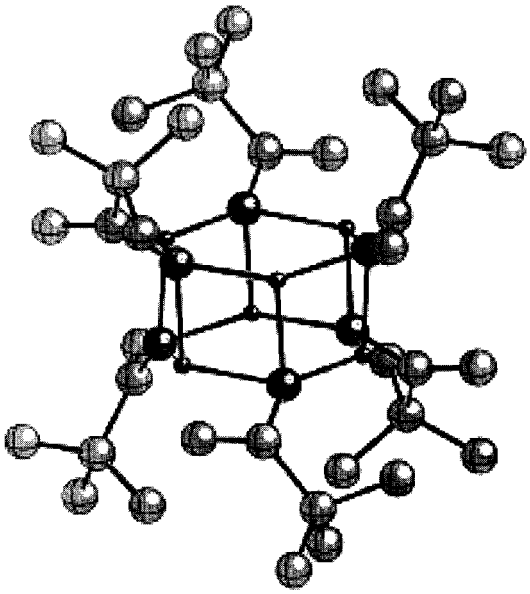
Lithium enolates of ketones exist as aggregates in solution.[29-31,34d,35] Mixed aggregates between the enolate anion and the amide base are also possible.[36] In 1981, Seebach and co-workers confirmed by X-ray crystallography that the lithium enolates of pinacolone and cyclopentanone form a tetrameric aggregate in the solid state, and it was assumed that a similar species exited in solution.[37] A THF solvated tetramer of lithium pinacolonate is shown (see **33**), as it was reported by Seebach.[37] Williard et al. reported the X-ray structure of



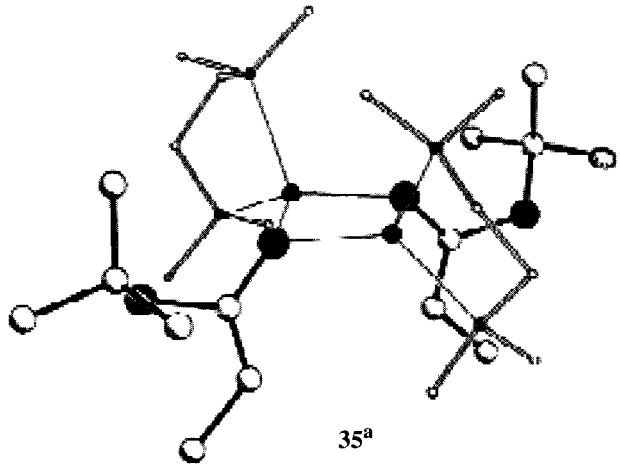


33[a]

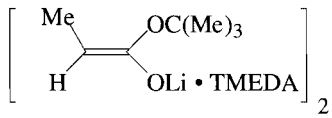
[a] Provided through the courtesy of Professor Dieter Seebach, E.T.H., Zurich, Switzerland.



34[b]



35[a]



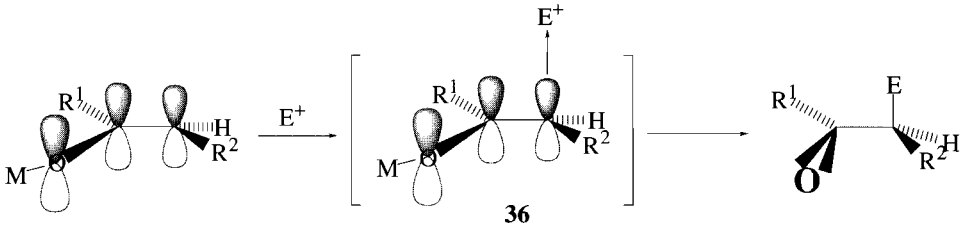
[b] Provided through the courtesy of Professor Paul Williard, Brown University, Providence, RI.

the unsolvated lithium enolate of pinacolone to be a hexamer (**34**).[38] They also reported that the structure of the potassium enolate of pinacolone was a hexamer, although the sodium enolate was a tetramer. The tetramer was composed of a cubic cluster of four enolized ketone molecules, four sodium atoms, and four *unenolized* solvating ketones units, which contrasts with **34** in which each oxygen atom is coordinated to three lithium atoms and each enolate double bond is almost antiperiplanar to one lithium atom. A variety of X-ray crystal structures for organolithium derivatives confirm the presence of aggregates in the solid state.[39] There is also evidence that the aggregate structure is preserved in solution and is probably the actual reactive species.[37b]

Seebach et al. showed that lithium enolates derived from esters are aggregates. The lithium enolates of (*Z*)-*tert*-butyl propionate (**35**) and of *tert*-butyl-2-methylpropionate are dimers in the solid state.[40] In both cases, the crystal contains two coordinated TMEDA molecules (see **35**). The lithium enolate of (*Z*)-methyl 3,3-dimethylbutanoate was found to be a dimer containing four THF molecules. Focusing on colligative properties rather than X-ray analysis, Collum and co-workers determined that lithium 2-carbomethoxycyclohexanone dimethylhydrazone (sec. 9.4.F.ii) is a dimeric THF solvate in the solid state.[41] *Perhaps the most important implication of this work is that the reactivity of enolate anions in alkylation and condensation reactions (see below) will be influenced by the aggregate state of the enolate.* If the enolate anion is are attached to (or a part of) a tetrameric or hexameric complex, then simple steric and electronic arguments for reactivity and selectivity are flawed if they are based only on examining monomeric species. Another important implication is that the relative proportions of (*E*) and (*Z*) enolate anions will be influenced by the extent of solvation and the aggregation state.

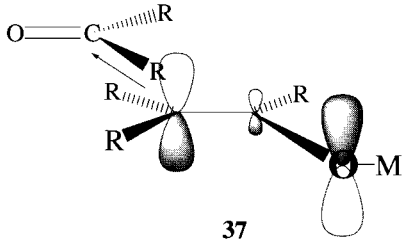
The solvent plays a significant role in the aggregation state of enolate anions, and this directly influences their reactivity. Streitwieser et al. found that selected lithium enolate anions have lower aggregation states in

dimethoxyethane than in THF, and that aggregation is much higher in methyl *tert*-butyl ether.[42] He found that alkylation and acylation of the enolate anions was extremely slow in methyl *tert*-butyl ether. These reactions apparently require additional solvation of the lithium cation, which is ineffective in this solvent.

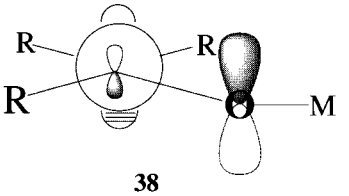


36

Once formed, an enolate anion can react with a variety of electrophiles. The approach of the electrophile is usually assumed to be perpendicular (as in **36**), in reactions with alkyl halides and epoxides, to maximize overlap of participating orbitals.[43] This model also applies to the deprotonation reaction. The LUMO of the electrophile is important for this reaction and Dunitz and co-workers[44] showed that a nonvertical approach (represented by **37** or **38**)[45] is preferred when nucleophiles attack carbonyl centers. The angle of approach (as discussed in secs. 4.7.C, sec. 6.6.A) is ≈ 110° and is called the **Bürgi–Dunitz trajectory**.[46,44] Models **37** and **38** imply that the angle at which the enolate nucleophile approaches the carbonyl carbon is somewhat restricted, and this enhances the steric effects between R and the approaching electrophile. Since the geometry of the enolate will influence the approach of the electrophile, geometric constrictions must be considered when examining stereoselectivity. It appears that enolate–alkyl halide transition states are essentially reactant-like, and that the product stereochemistry is determined largely by steric factors.



37



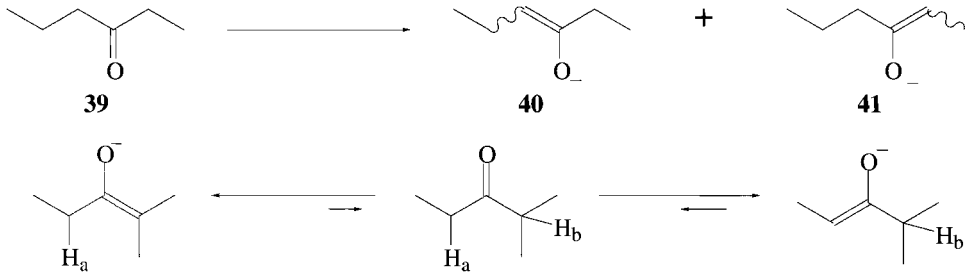
38

Lithium enolates exist as large aggregates and their approach to the electrophile is restricted by steric and electronic considerations, as well as by the relative geometry of the molecule. Despite the structural complexity remarkably good predictions for reactivity and diastereoselectivity can be made based on the steric requirements that would be present in a monomeric system. For example, in most reactions of enolate anions the electrophile will be delivered to the less hindered face of the enolate to give the major product. In all models used to describe reactivity (secs. 9.5.A.iii–9.5.A.v), a monomeric enolate will be shown but the facial and orientational bias of the enolate is clearly influenced by the state of aggregation in solution.

9.2.E. Kinetic versus Thermodynamic Control

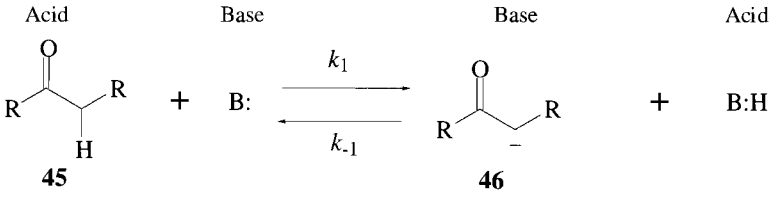
The protons on both sides of the carbonyl in an unsymmetrical ketone are acidic. If the substitution pattern at those carbons is not identical, the pK_a values of the hydrogens are different. When such a ketone is

treated with an appropriate base, removal of the different protons will lead to different regioisomeric enolates. 3-Hexanone (**39**), for example, reacted with LDA to give a mixture of **40** and **41**. In many cases, however, ketones have different substitution patterns on the α- and α'-carbon. These α–protons have slightly different pK_a values, with the less substituted position being the more acidic. As noted in Table 9.1, ketone **4** has a pK_a of 20.8 and **5** has a pK_a of 21.7. In general, the difference in pK_a for monosubstituted versus disubstituted positions is typically only about 1 pK_a unit. 2-Methyl-3-pentanone (**42**) has two acidic protons, H_a and H_b. The methyl group releases electrons to the carbon bearing H_b, reducing the acidity of H_b by about 1 pK_a unit relative to H_a. Removal of H_a leads to enolate **43**, and loss of H_b leads to enolate **44**. Enolate **43** results from loss of the most acidic proton, which is removed faster in an acid–base reaction, and this product is referred to as the **kinetic** enolate. Enolate **44** is the most thermodynamically stable enolate, but it is formed more slowly and is called the **thermodynamic** enolate, which raises the question if it is possible to form one enolate or the other regioselectively. It is noted that **43** can be formed as a mixture of (*E*) and (*Z*) isomers. The (*E*/*Z*) ratio is one of the parameters that can be controlled to influence selectivity in diastereoselective aldol condensation reactions, discussed in Section 9.5.



The enolate–forming process is an acid–base reaction and, as such, an equilibrium reaction (sec. 2.2.A). The key to forming one enolate or the other regioselectively is to control this equilibrium. As with any acid–base reaction, the equilibrium is controlled by the relative strengths of the acid–conjugate acid and the base–conjugate base pairs. A strong acid reacting with a strong base that generates a weak conjugate acid and a weak conjugate base will have an equilibrium shifted to the right (K_a is large). When the conjugate acid and conjugate base formed are stronger than the acid and base starting materials, the equilibrium is shifted to the left (K_a is small). A typical equilibrium reaction of a ketone and a base is shown for the reaction of **45** to give **46**. Kinetic control (formation of the kinetic enolate as the major product) is achieved when K_a is large ($k_1 >> k_{-1}$). If K_a is near unity, thermodynamic or equilibrium control (formation of the thermodynamic enolate as the major product) predominates.[2] This equilibrium is controlled by the choice of solvent, base, cation, and temperature. ***Kinetic control*** is favored by several factors,[2] including (1) aprotic solvents: (2) strong bases that are weakly nucleophilic, **and generate a weak conjugate acid**: (3) cations such as Li which complex oxygen: (not Na^+ or K^+) (4) low temperatures: and (5) short reaction times. The conditions that favor thermodynamic control must be the opposite of those described for kinetic control.[2] ***Thermodynamic control*** conditions include (1) protic solvents, (2) nucleophilic bases, **that generate a strong conjugate acid**, (3) cations that form

ionic M—O bonds, (4) higher temperatures, and (5) long reaction times. These parameters can be explained by examining the three species involved in the equilibrium, **42**–**44**. For kinetic control (formation of **43**), the reaction should be essentially irreversible and the reaction conditions should suppress the equilibrium.

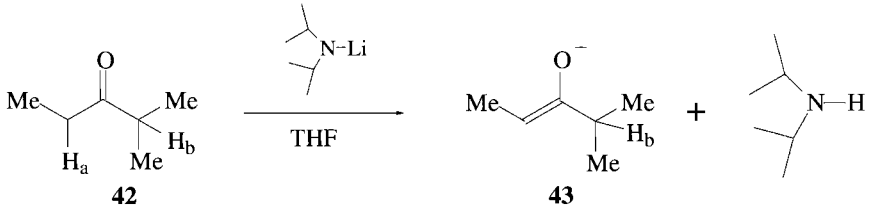


45 **46**

$K_a = \frac{k_1}{k_{-1}}$ and $pK_a = -\log K_a$

Solvents can be grouped according to whether or not they have an acidic proton. Protic solvents (solvents containing an acidic hydrogen, usually O—H, S—H or N—H) promote equilibrium conditions and aprotic solvents favor irreversible conditions. In the reaction of **45**, the ketone is the acid ($pK_a \approx 21$) and a protic solvent such as ethanol ($pK_a \approx 17$) or water ($pK_a \approx 15.8$) will be a stronger acid. Once the conjugate base (the enolate anion) is formed, it reacts with the protic solvent to regenerate the ketone, driving the equilibrium to the left (small K_a). Aprotic solvents such as THF do not have an acidic proton and the enolate anion cannot react with them, meaning that once formed, the enolate anion will be relatively stable (equilibrium shifted to the right–large K_a). This discussion can be summarized by saying that aprotic solvents such as ether or THF favor kinetic control, and protic solvents such as ethanol, water, methanol, or *tert*-butanol favor thermodynamic control.

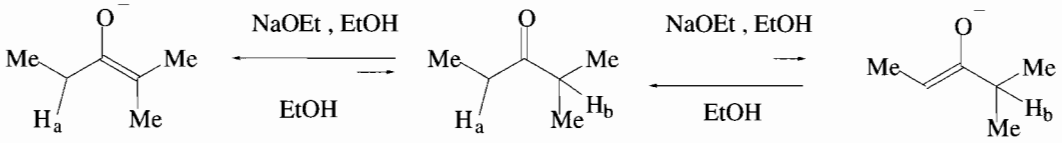
The base plays two roles in this reaction. First, it must react with the acid (**42**) quickly and efficiently (it must be a strong base). The base also generates a conjugate acid after deprotonation that plays a significant role in the position of the overall equilibrium. If the conjugate acid is more acidic than **42**, it will reprotonate the conjugate base (the enolate anion), which drives the equilibrium back toward **42** and promotes the



42 **43**

equilibrium process. When LDA deprotonates **42** to form **43** *in an aprotic solvent,* the only acids in the equilibrium are **42** ($pK_a \approx 21$) and diisopropylamine ($pK_a \approx 25$), the conjugate acid formed by reaction with LDA. Since diisopropylamine is a weaker acid than the ketone, reaction with the enolate anion (the conjugate base) is relatively slow, which shifts the overall equilibrium to the right (large K_a), which favors irreversible enolate formation and kinetic control. If the reaction is done in THF with sodium ethoxide as the base, enolate **43** is also formed since H_a is the most acidic proton. The pK_a of this ketone acid is ≈ 21 (as mentioned – see Table 9.1) but as ethoxide reacts with **42** it generates ethanol as the conjugate acid with a pK_a of about 17. Ethanol easily reacts with the enolate anion, shifting the equilibrium to the left so that **42**, ethoxide, ethanol,

and some **43** are all in solution. Although H_b in **42** is less acidic than H_a, it is acidic enough to be removed by ethoxide. If the conversion of **42** to **43** is slow and/or reversible, there will be time to remove the less acidic H_b, generating enolate anion **44**. The conjugate acid (ethanol) will reprotonate **44**, establishing a second equilibrium between **42** and **44**. If the solvent is the acidic ethanol, this equilibrium is favored and as mentioned, **42**–**44**, ethanol, and NaOEt will all be in solution. The C=C unit of enolate anion **44** is more highly substituted so it is thermodynamically more stable. Therefore, once the equilibrium is established, it will shift to favor the most stable enolate **44** (hence the term thermodynamic control). This discussion can be summarized by saying that strong bases such as $LiNH_2$ or $LiNR_2$ favor kinetic control, since they generate weak conjugate acids but strong bases such as NaOH, NaOMe, NaOEt, or NaO*t*-Bu will favor thermodynamic control, since they generate strong conjugate acids. Since the amide bases ($LiNR_2$) are stronger bases than the alkoxide bases (NaOR), the initial acid–base reaction (deprotonation) will be faster with the former reagents, also favoring kinetic control.



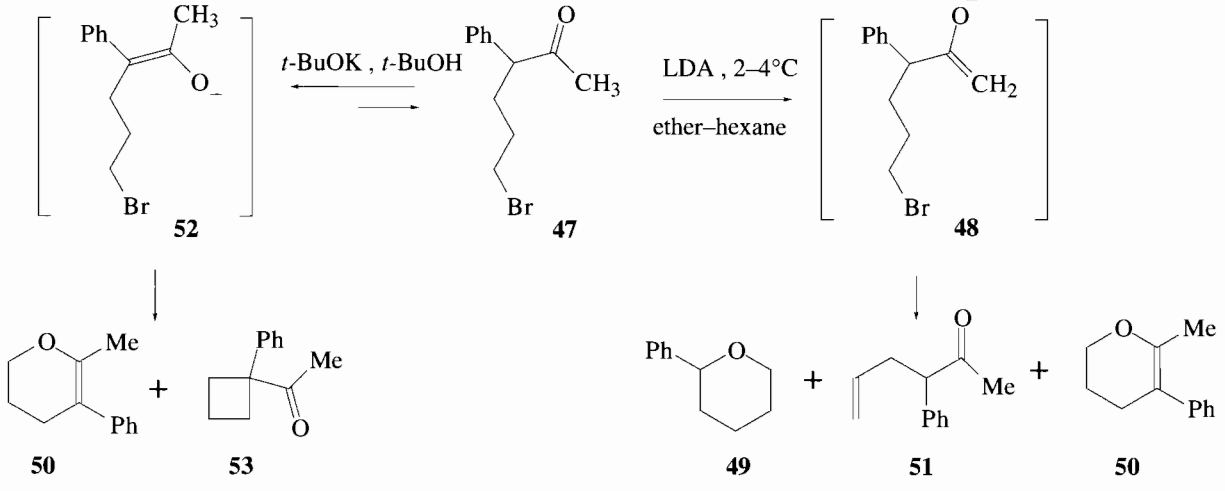
44 **42** **43**

The counterion (M^+) of the base ($M^+NR_2^-$) will be the counterion of the enolate, unless another metal ion is added. The covalent character of the M—O bond in the enolate plays a role in the kinetic versus thermodynamic equilibrium. If the M—O bond is relatively covalent (as with the Li—O bond), the initially formed enolate (**43**) will form more easily and be less likely to react with an acid to give **42**, which favors the kinetic process. If the M—O bond is more ionic (M = Na, K), the ionic character of the enolate increases and it becomes increasingly easier to reprotonate the anionic oxygen to give **43** (this promotes the equilibrium). This relationship is summarized and reinforced by noting that sodium and potassium enolates equilibrate readily, whereas magnesium, lithium, zinc, copper, or aluminum enolates give largely irreversible reactions.[47]

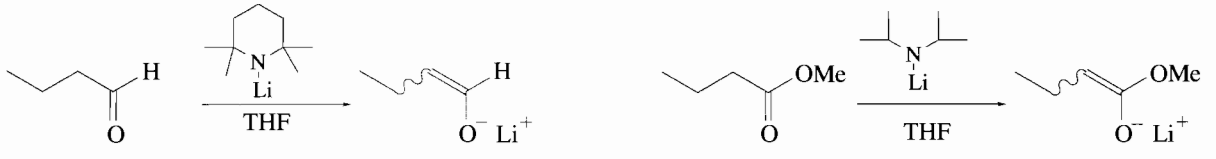
Reaction temperature is another important variable. If the reaction is kept cold, all reactions (including the forward and reverse reactions that constitute the equilibrium) are slowed. If there is enough energy at low temperatures to convert **42** to **43**, the subsequent acid–base reactions (that will promote the equilibrium) will be slower and this favors kinetic control. The common reaction temperatures are –78°C (CO_2 in acetone or 2-propanol) and –100°C. (ether in CO_2).[48] Conversely, high reaction temperatures promote the equilibrium process. In most cases, the temperatures observed with thermodynamically controlled reactions are the reflux temperatures of the solvent (refluxing ethanol, water, methanol, *tert*-butanol).

The final parameter in this process is the length of time the molecules are allowed to react. If the reaction time is short (typically min to h), it is more difficult for the equilibration process to develop. If the reaction is allowed to go for a long time (typically hours to days, although minutes can be a long time in some reactions), equilibration and thermodynamic control is more likely. The time factor is linked to the presence or absence of an acid in the system. When **43** is formed by reaction of LDA and **42**, its conjugate acid is

diisopropylamine. Diisopropylamine is a weak acid, and when given a sufficiently long contact time with a strong base (the enolate anion is a strong base), some acid–base equilibration can occur. Few reactions are quantitative and virtually none are instantaneous. If the conversion of **42** to **43** occurs in only 90%, then 10% of unreacted ketone remains. With a pK_a of ≈ 21, **42** is acidic enough to reprotonate **43** and establish the equilibrium required for thermodynamic control, if given sufficient time. If the reaction itself is slow, enolate **43** is being formed in the presence of unreacted **42** and there is the possibility of a reaction. The terms short and long are obviously relative and vague, and caries with the electrophile for a particular enolate. In general, short reaction times favor kinetic control and long reaction times favor thermodynamic control.

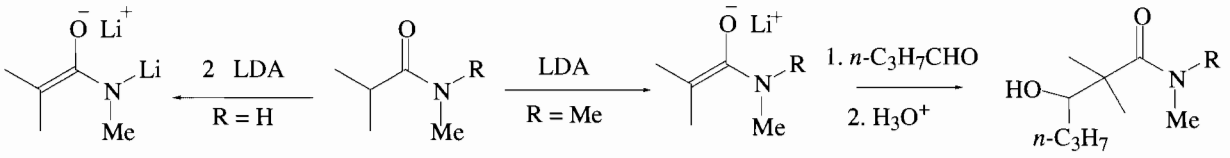


The intramolecular cyclization reaction of bromoketone **47**[49,83] illustrates how changing reaction conditions can influence formation of the kinetic or thermodynamic enolate. The reaction of **47** with LDA (ether, 0°C) generates the kinetic enolate (**48**). Subsequent intramolecular displacement of the bromide by the enolate anion gives cyclohexanone **49**. Some elimination of **48** under the reaction conditions occurred, giving **51**. A complicating factor in this example is that the oxygen in **48** is also a nucleophile and O-alkylation (this will be discussed in sec. 9.3.B) gave the pyran product **50**, although **49** is the major product. When **47** was treated with *tert*-butoxide in *tert*-butanol, the thermodynamic enolate (**52**) was formed and this cyclized to the dihydropyran **50** via O-alkylation. A four-membered ring product (**53**) would be the normal enolate alkylation product that is analogous to **49**, but its formation has a relatively high activation barrier and it was a minor product (secs. 1.5.B, 6.6.B).



Carbonyl compounds other than ketones readily form enolates. It was noted in Table 9.1 that the α-hydrogen of an aldehyde was more acidic than that of a ketone. When aldehydes are used, however, there is only

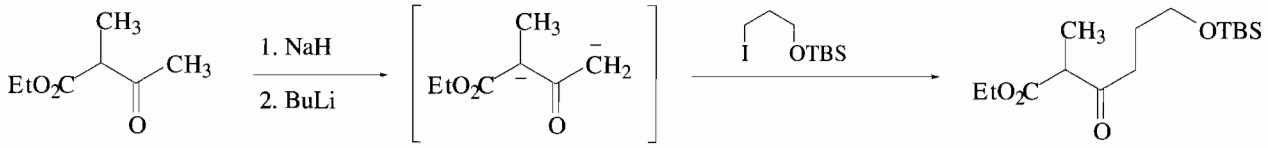
one acidic proton and either kinetic or thermodynamic control conditions can be used. Formation of (*E*) or (*Z*) isomers of **54** remains a problem, however. It may be desirable to use kinetic control conditions to control geometry or minimize secondary reactions such as nucleophilic addition of the conjugate base to the carbonyl or an aldol-type condensation, which is more facile with aldehydes than with ketones (sec. 9.4.A). Using a nonnucleophilic base such as LTMP usually maximizes formation of the enolate. Acid derivatives such as esters and *N,N*-disubstituted amides also have only one acidic proton and deprotonation gives a single isomeric enolate. Reaction of methyl butanoate with LDA, for example, gave enolate **55**, as a mixture of (*E*) and (*Z*) isomers.



57 **56** **58** **59**

When primary or secondary amides are treated with a base, there is a complicating reaction that was not possible with esters, ketones, or aldehydes. The N—H moiety is acidic enough to react with the bases used for deprotonation. Treatment of **56** with base gave the *N*-lithio derivative, but the α-lithio derivative (**57**) can be generated by addition of two equivalents of base.[50] Enolate anion formation is straightforward with tertiary amides, such as dimethylisobutyramide (**56**, R = Me) and the resultant enolate anion (**58**) reacted with butanal to give amido-alcohol **59** in 68% yield[50] (see sec. 9.4.B).

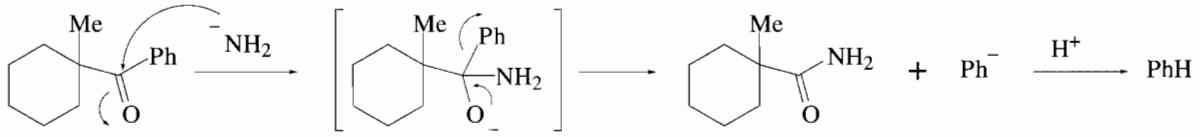
When an ester has another carbonyl group at the β-position (such as in keto-ester **60**), it is possible to form a dianion. Initial treatment of **60** with NaH leads to removal of the more acidic proton between the two carbonyl groups, and subsequent reaction with *n*-butyllithium gives the dianion **61**.[51] When **61** reacts with the iodide shown, alkylation occurs at the methyl group, the site of the least acidic proton in **60** and the more nucleophilic carbon in **61**. The final product (**62**) was obtained as part of the Vedejs and Duncan synthesis of C(16),C(18)-bis-*epi*-cytochalasin D.[51]



60 **61** **62**

All ketones, aldehydes, and esters mentioned so far have had an α-carbon that can lead to an enol, which means that there was a hydrogen on that carbon that could be removed by base. When a ketone does not have such a proton (it is a non-enolizable ketone), treatment with strong base can lead to a C—C bond cleavage reaction. Discovered by Semmeler,[52] Haller and Bauer[53] developed the reaction illustrated by reaction of **63** with $NaNH_2$ to give amide **65**. Acyl addition of the amide anion to the carbonyl of the ketone led to **64**, and loss of the anion Ph^- gave the amide product. Workup protonates the anion to give, in this case, benzene. This

reaction is now known as the **Haller–Bauer reaction**.[54]



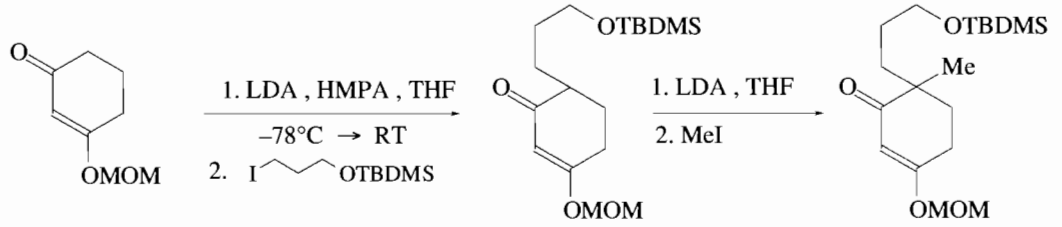
63 **64** **65**

9.3. REACTIONS OF ENOLATE ANIONS WITH ELECTROPHILES

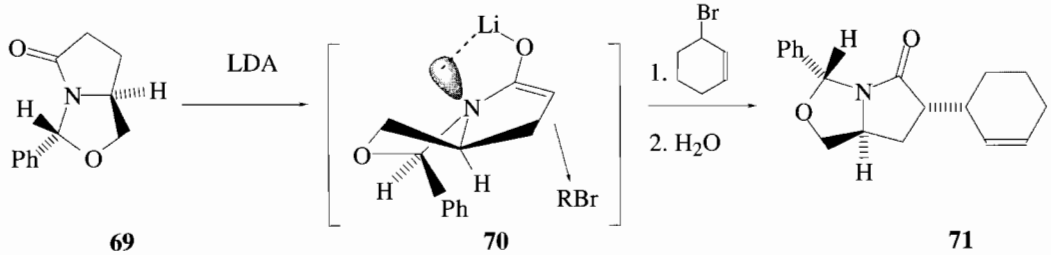
There are two major reactions of enolates: (1) displacement reactions with alkyl halides or other suitable electrophiles and (2) nucleophilic addition to carbonyl compounds. Reaction of **58** with butanal to give **59** and reaction of **61** with bromopentane to give **62** are simple examples of each process. Enolate anions function as carbon nucleophiles and their reactions are fundamentally the same as those discussed in Section 8.3.C for acetylides. Although there are interesting differences, treating an enolate anion as a carbon nucleophile is very reasonable.

9.3.A. Enolate Alkylation

An enolate anion is a nucleophile and, unlike Grignard reagents and organolithium reagents, reacts easily with the electrophilic carbon of an alkyl halide.[55] Although both the oxygen and the carbon are nucleophilic (sec. 9.3.B), the carbon is usually the most nucleophilic site in the enolate. As with other carbon nucleophiles, such as acetylides (sec. 8.3), the electron rich carbon attacks the electrophilic carbon of the halide to form a new carbon–carbon bond, with lithium iodide (LiI) as the byproduct.



66 **67** **68**



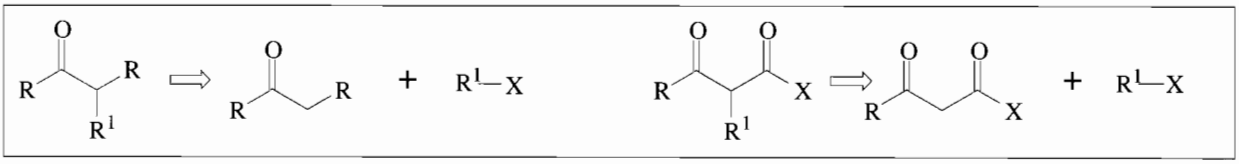
69 **70** **71**

There are many synthetic applications that involve enolate alkylation. In the Yamada and co-workers synthesis of dysidiolide, cyclohexenone **66** was treated with LDA to generate the enolate anion.[56] Addition of TBDMS protected 3-iodo-1-propanol gave the alkylated product **67** in 76% yield. Notice that HMPA

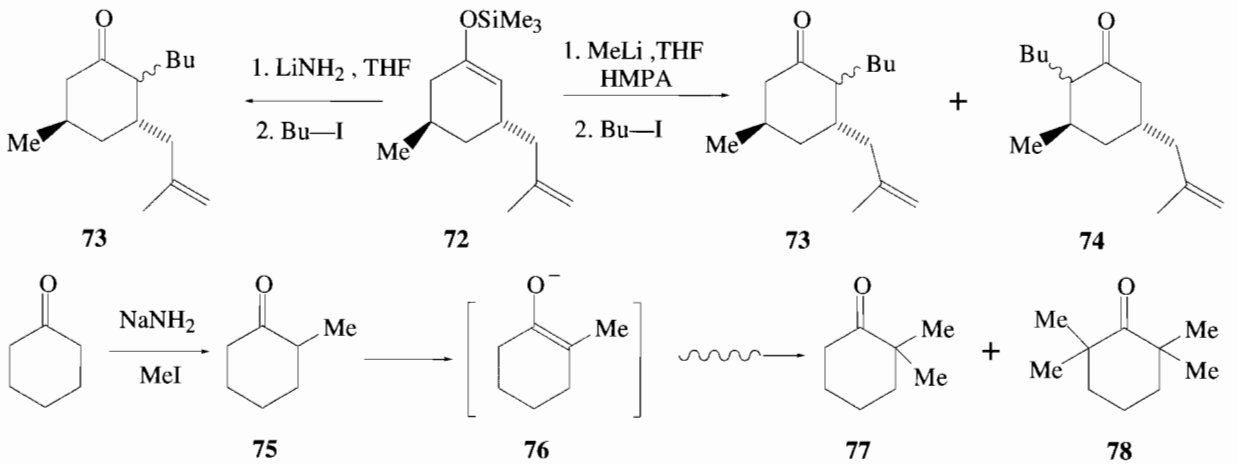
[hexamethylphosphoramide, $(Me_3N)_3P{=}O$] was added to facilitate formation of the anion and also the alkylation step. In this particular example, **66** was treated with LDA and then iodomethane to give the doubly alkylated **68**. Another example is the reaction of **69** with LDA to give enolate **70**, where the lithium is chelated with the nitrogen lone pair electron. The asymmetric centers in the lactam and the relatively rigid conformation of **70** led to reaction from the bottom face (the α face in steroid nomenclature). Addition of 1-bromo-2-cyclohexene from this less sterically hindered face led, therefore, to **71** with high diastereoselectivity (>95:<5 favoring the stereochemistry shown for **71**).[57]

In the conversion of **66** to **67**, we saw that HMPA was used as an additive. Another useful ingredient in many alkylation reactions is hexamethylphosphorus triamide [HMPT, $(Me_2N)_3P$], which coordinates with the enolate anion, diminishing the aggregate state and increasing reactivity. This additive also enhances the polarity of the solvent and thereby enhances the facility of the S_N2 alkylation step (sec. 2.7.A.i). The use of an additive such as HMPA or HMPT is very common when the enolate anion reacts slowly and/or the halide is relatively unreactive. Other acid derivatives such as lactones can react with LDA to give an enolate anion, which then reacts with alkyl halides in the usual manner.

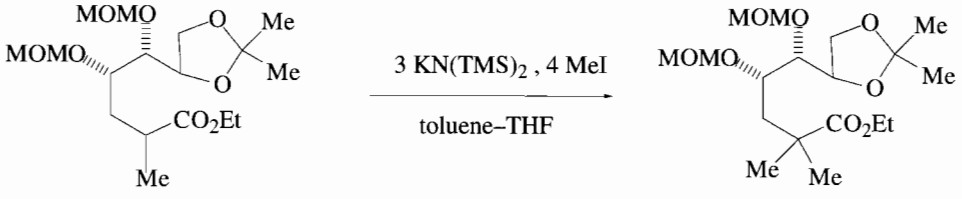
The general disconnections for enolate alkylation are



Alkylation reactions with unsymmetrical ketones that have essentially the same pK_a for both α-hydrogens often show poor regioselectivity and over-alkylation can be a problem. Partial equilibration can occur under some reaction conditions, as shown for reactions of **72**, leading to poor regioselectivity.[58] When $LiNH_2$ was used as a base in THF, and then quenched with iodobutane, a single alkylation product was obtained in 95% yield (**73**, the kinetic product since equilibration is minimal under these conditions). In the presence of excess base and a complexing agent such as HMPA, however, equilibration occurred and alkylation gave a mixture of **73** and **74** (52% and 14% yield, respectively, along with dialkylation products).[58] Polyalkylation is a problem



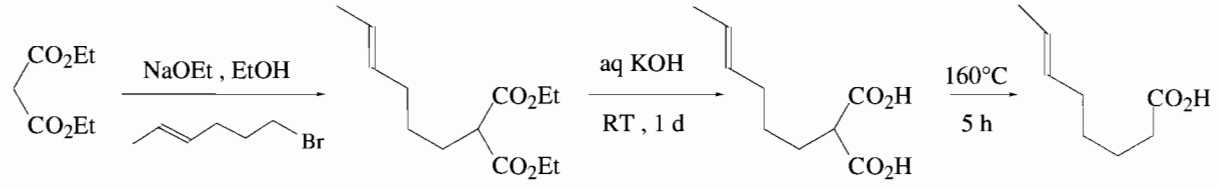
when a very reactive halide such as iodomethane is used under equilibrating conditions. Treatment of cyclohexanone with sodium amide and then iodomethane gave the expected 2-methylcyclohexanone (**75**), but this α-alkyl derivative can enolize under the reaction conditions (to **76**) and a second methylation occurs under the reaction conditions to give **77**. If an excess of iodomethane is present, the tetramethylated cyclohexanone derivative (**78**) can be formed. The 2,6-dimethyl and the 2,2,6-trimethylcyclohexanone derivatives are also possible products from this reaction. Indeed, it is usually very difficult to prepare and isolate **77** by this method.



79 **80**

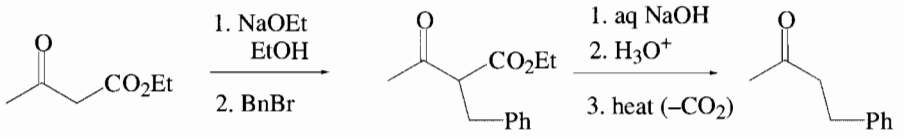
Enolates derived from acid derivatives can also be alkylated. When ester **79** was treated with 3 equivalents of $KN(TMS)_2$ in a toluene–THF mixture, in the presence of 4 equivalents of iodomethane, a quantitative yield of **80** was obtained, as part of Tadano's synthesis of (–)-mniopetal E.[59]

There are two classical reaction sequences in organic chemistry that rely on enolate alkylation. One is the **malonic ester synthesis**.[60,61] In a synthetic example taken from the Clive and Hisaindee synthesis of brevioxime,[62] diethyl malonate was treated with a base such as sodium ethoxide, under thermodynamic control conditions. The resulting enolate anion is treated with the indicated alkyl halide to give the alkylated product **81** (in 72% yield).[62] Saponification of **81** to the dicarboxylic acid (**82**, in 99% yield), was followed by decarboxylation (sec. 2.9.D) and formation of the substituted acid **83**, in 94% yield.[62]



81 **82** **83**

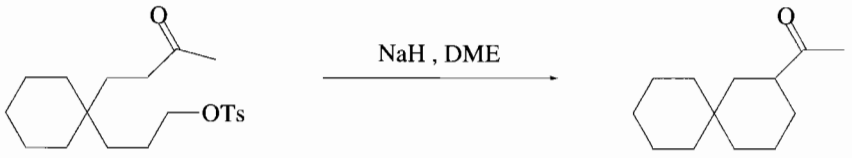
The second classical reaction mentioned above is the **acetoacetic ester synthesis**.[58b,63] In this reaction, an ester of acetoacetic acid (3-oxobutanoic acid) such as ethyl acetoacetate is treated with base under thermodynamic control conditions and alkylated, as with the malonic ester synthesis. Reaction with sodium ethoxide in ethanol (since an ethyl ester is being used) generated the enolate and quenching with benzyl bromide led to **84**. Saponification and decarboxylation (as above) gave a substituted ketone (**85**). Although the malonic ester synthesis and the acetoacetic ester synthesis are fundamentally similar, the different substrates lead to formation of either a highly substituted acid or a ketone. The reaction is not restricted to acetoacetate derivatives, and any β-keto-ester can be used (ethyl 3-oxopentanoate for example).[64]



84 **85**

The key to all of these reactions is the enhanced acidity of the hydrogen on the carbon between the two carbonyls. As noted in Table 9.1, 1,3-dicarbonyl derivatives have a pK_a in the range of 8–12 for that proton. The enolate anion formed from a 1,3-dicarbonyl compound is somewhat less reactive because the enolate is more stable due to resonance delocalization. For this reason, higher reaction temperatures are usually (but not always) required. A typical experiment will use the reflux temperature of the alcohol solvent being used. Another alternative is to use a complexing agent such as HMPT or HMPA (see above), or DABCO (azabicyclo[2.2.2]octane).

86 **87**

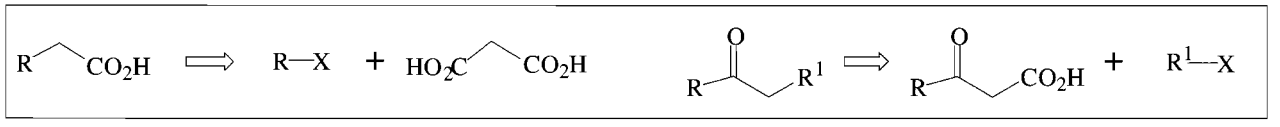


88 **89**

This general technique of using a doubly activated enolate anion can be applied intramolecularly to generate cyclic compounds. In the Deslongchamps and co-workers synthesis of (+)-martimol,[65] keto-ester **86** was treated with the basic cesium carbonate and intramolecular displacement of the allylic chloride gave the macrocycle **87**, in 75% yield. There is a related ring-forming process called the **Perkin alicyclic synthesis**.[66] In general, this useful modification of the malonic ester synthesis condenses an α,ω-dihalide with a malonic ester (although other 1,3-dicarbonyl derivatives can be used). This particular reaction converts malonic acid derivatives to cyclic compounds having a carboxylic acid substituent (cyclopentanecarboxylic acid or cyclohexanecarboxylic acid, for example). Notice that this is an intramolecular alkylation reaction, which is quite common. Another example is treatment of keto-tosylate **88** with NaH in DME, which gave a 77% yield of spiroketone **89**.[67] Presumably the product results from the thermodynamic enolate since that leads to a six-membered ring, whereas the kinetic enolate would have to form an eight-membered ring. In this example, the leaving group was a tosylate rather than a halide. Since they are readily formed from the corresponding alcohol, this is a very attractive synthetic approach.

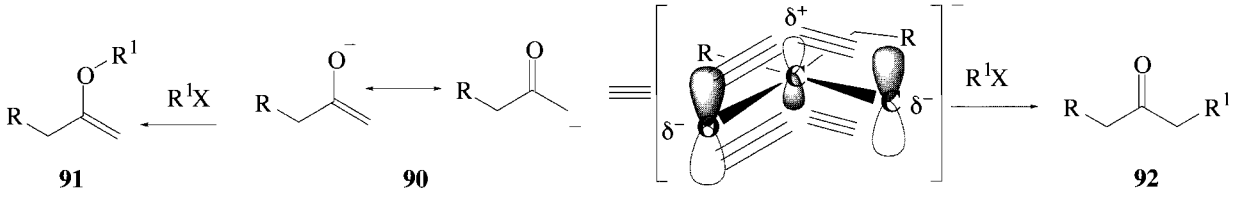
Variations of the malonic ester and acetoacetic ester sequences lead to many useful synthetic opportunities. In the examples quoted, the base–solvent pair used was ethanol–sodium ethoxide, where the alkoxide is the conjugate base of the solvent. If NaOEt–EtOH were used with a methyl ester, transesterification[68] would give a mixture of methyl and ethyl esters as products. For both malonic ester and acetoacetic ester removal of the most acidic proton (α to both carbonyls) also gives the more thermodynamically stable enolate. Either NaOEt–EtOH or LDA–THF will generate the desired enolate. The malonic ester synthesis is most useful for the synthesis of highly substituted monoacids, and the acetoacetic ester synthesis is used to prepare substituted methyl ketones.

The disconnections for the malonic and acetoacetic ester syntheses are



9.3.B. O versus C Alkylation of Enolate Anions

Cyclization of **47** discussed in Section 9.2.E showed an intramolecular alkylation reaction of enolates to give **49**, but the formation of **50** illustrated an important competing reaction in the alkylation of enolates. An enolate anion is a bidentate nucleophile because it contains *two* nucleophilic centers, the carbanionic center and the oxygen, as illustrated by **90**. Reaction of the O nucleophile in **90** with an alkyl halide leads to the vinyl ether **91**. Reaction at the C nucleophile of **90** generates the usual alkylation product **92**. Since a carbanion is usually more nucleophilic than an alkoxy anion for common electrophiles, **92** tends to be the major product. There are several factors that can influence the relative proportion of these products, however. When



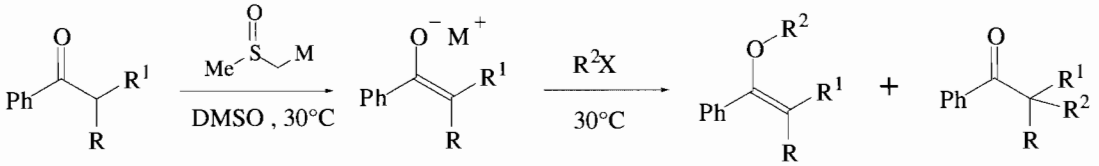
91 **90** **92**

92 is the major product, the process is referred to as C-alkylation, and it is greatly preferred in ether solvents when lithium enolates are used. Ether promotes the nucleophilic nature of the enolate, favoring the carbanion. The lithium enolate forms a relatively covalent O—Li bond, again favoring C-alkylation. When very reactive halides (iodomethane, allyl bromide) react with sterically unhindered enolates (usually with a potassium or sodium gegenion), O-alkylation (formation of product **91**) is preferred. The highly ionic O—Na or O—K bond effectively increases the nucleophilic character of the oxygen. When the alkylation occurs intramolecularly, O-alkylation can be a much more serious problem. Approach of the carbon nucleophile to the electrophilic center is sometimes restricted due to the nature of the tether (see sec. 6.6.A for **Baldwin's rules**). When the highly polar solvent DMSO is used, the enolate is largely monomeric, and this increased reactivity favors O-alkylation. The product distribution depends on the substitution pattern of the enolate and the nature of the counterion, as in Table 9.6.[69]

Treatment of ketone **93** with dimsyl anion generates enolate **94**, but this can potentially form a mixture of (*E*)- and (*Z*)-isomers. Reaction of **94** with various alkyl halides led to the O-alkylation product (**95**) and the C-alkylation product (**96**). In DMSO, the ratio of O- to C-alkylation is relatively insensitive to changes in the gegenion (the metal), suggesting that the enolate is an unencumbered anion in this cation solvating medium. Note that C-alkylation is preferred except when the steric bulk at the nucleophilic carbon becomes too great (R, R^1 = Ph, Ph or Et, Et). For $PhCOCHPh_2$ (**93**, $R^1 = R^2$ = Ph), O-alkylation is effectively the only process.

This reaction can sometimes be useful in synthesis. In the Honda et al. formal synthesis of securinine,[70] *N*-benzylamino-ketone (**97**) was treated with lithium hexamethyldisilazide and then sorbic anhydride. This gave dienyl ester **98** by O-alkylation of the initially formed enolate anion. When the nitrogen protecting group was

Table 9.6. O versus C Alkylation for Phenyl Ketones in DMSO



93 **94** **95** **96**

R	R^1	M	R^2X	95/96	95/96
H	Ph	Na	*n*-PrCl	0.27	1:3.7
			i-BuCl	0.21	1:4.8
			n-Amyl-Cl	0.28	1:3.6
			n-Amyl-Br	0.14	1:7.1
H	Et	Li	*n*-PrCl	1.1	1:0.9
			n-PrBr	0.44	1:2.3
			i-BuCl	0.52	1:1.9
			n-Amyl-Cl	1.3	1:0.77
			n-Amyl-Br	0.5	1:2
			n-Amyl-I	0.20	1:5
		Na	*n*-PrCl	1.3	1:0.77
			i-BuCl	0.52	1:1.9
			n-Amyl-Cl	1.2	1:0.8
			n-Amyl-Br	0.64	1:1.6
			n-Amyl-I	0.23	1:4.4
		Cs	*n*-Amyl-Cl	1.3	1:0.77
Me	Me	Li	*i*-BuCl	0.73	1:1.4
			n-Amyl-Cl	2.2	1:0.45
		Na	*n*-PrCl	1.3	1:0.77
			i-BuCl	0.68	1:1.5
			n-Amyl-Cl	2.1	1:0.48
Et	Et	Na	*n*-PrCl	7.1	1:0.14
			i-BuCl	3.6	1:0.28
			n-Amyl-Cl	9.2	1:0.11
Ph	Ph	Li	*n*-PrCl	>100	1:<0.01
			n-Amyl-Cl	>100	1:<0.01

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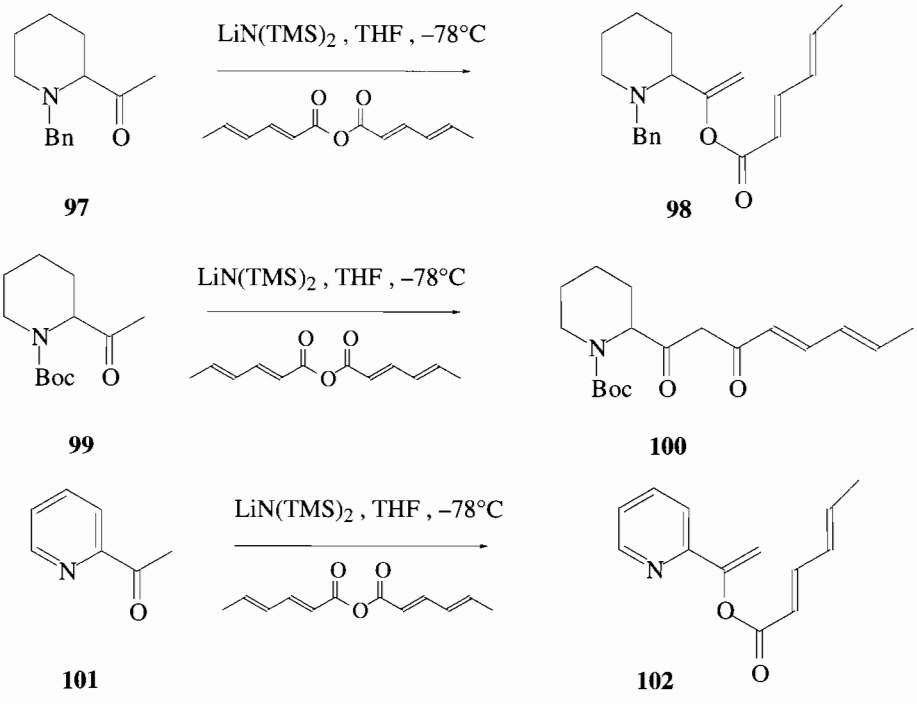
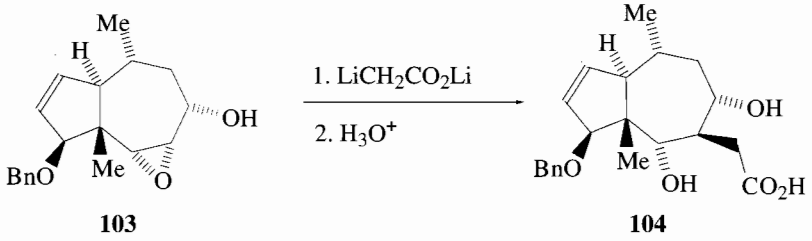
changed to N-Boc (see **99**), however, the identical reaction gave C-alkylation and the product was **100**. Neither of these products was suitable for the synthesis, but the reaction with 2-acetyl pyridine (**101**) gave **102** and this was transformed into securinine. This example shows that O- versus C-alkylation is very dependent on the local environment and electronic effects within the enolate anion.



In ether and THF, O-alkylation is a much less serious problem in reactions with alkyl halides. With the possible exception of iodomethane, the use of lithium enolates in ether solvents leads to C-alkylation as the major product in virtually all cases. When the enolate carbanion center is sterically hindered, however, O-alkylation can be a problem, even in THF or ether. There are some reagents that prefer O-alkylation, with silyl halides, and anhydrides being the most common. Both of these O-alkylation reactions will be discussed in Section 9.3.C.

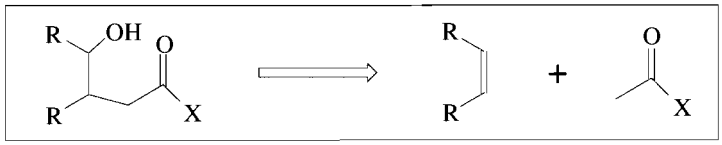
9.3.C. Enolate Reactions with Non-Carbonyl Electrophiles

Enolates can react with many electrophilic species other than alkyl halides, analogous to the reactions of other carbanions (Chap. 8). Nucleophilic ring opening of an epoxide to give alcohols is very common, occurring at the less sterically hindered carbon.[71] Grieco et al. used the dilithio salt of acetic acid ($LiCH_2CO_2Li$,

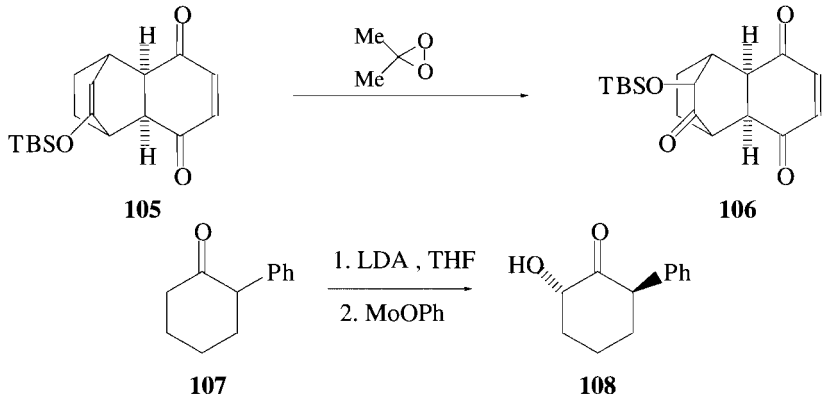


sec. 9.4.B.vii) in a reaction with epoxide **103** to give **104** in a synthesis of bigelovin.[72] The regioselectivity in the ring opening is probably due to a combination of neighboring group effects with the adjacent hydroxyl group and steric blocking of one carbon by the bridgehead methyl.

The epoxide ring opening gives the interesting disconnection,



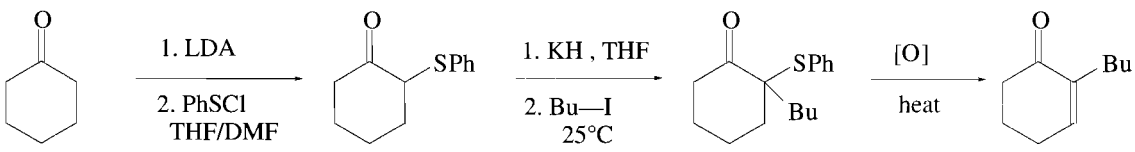
It is also possible to oxygenate an enolate to give the corresponding acyloin (an α-hydroxy ketone) or alkoxy derivative. Reaction of an enolate anion with oxygen and trimethylphosphite [$(MeO)_3P$], for example, gives an α-hydroxy derivative.[73] Reaction of an enol ether such as **105** with 3,3-dimethyldioxirane leads to the protected α-hydroxy ketone (**106**), in an example taken from Danishefsky's synthesis of myrocin C.[74] An effective oxygenation reagent for enolate anions is MoOPh, and a typical use is taken from work by Vedejs to



105 **106** **107** **108**

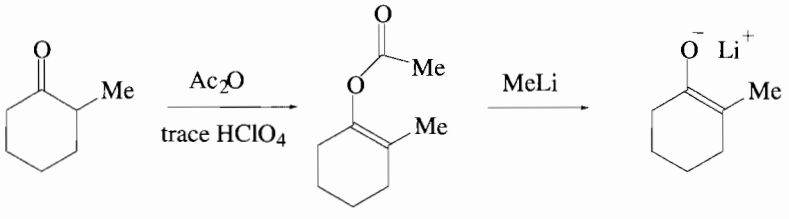
prepare **108** from 2-phenylcyclohexanone (**107**) in 70% yield.[75] The structure of MoOPh is actually MoO_5•Py•HMPA.[76] Nozoe and co-workers showed that 2-phenyl-2-*p*-toluenesulfonyloxazidine (see Davis' work in sec. 3.9.A.ii) could convert the enolate derived from a 2-pyrrolidinone derivative to the 3-hydroxy derivative (α-hydroxylation) in good yield.[77]

Enolates react with sulfenyl halides to give an α-alkylthio ketone. As shown for cyclohexanone, reaction with LDA followed benzenesulfenyl chloride (PhSCl) produced phenylthio derivative **109**. The proton adjacent to both the carbonyl and the sulfur (the α-proton) was more acidic and it was deprotonated with potassium hydride, forming the enolate, and alkylation with iodobutane gave a 91% yield of **110**.[78] As mentioned in Chapter 2, the sulfide moiety can be oxidized to a sulfoxide and thermally eliminated (syn elimination, sec. 2.9.C.v) to give an alkene.[79] Similar methodology can be applied to selenides, R—Se—R1.[80]



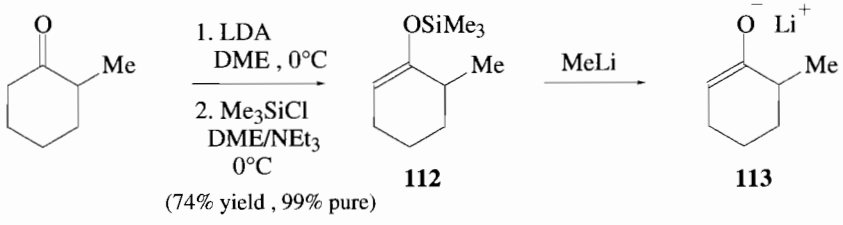
109 **110**

In addition to the methods described for controlling the ratio of thermodynamic and kinetic products, other techniques have been developed to trap the enolate, based on reactions with reagents that prefer O-alkylation. Reaction of a ketone with acetic anhydride, usually in the presence of a catalytic amount of perchloric acid, generates the thermodynamic enol acetate **111**.[81] When this is treated with methyllithium, the acyl carbon of the acetyl group is attacked, displacing the thermodynamic enolate (**76**) in high yield. Once **76** is available, it can be treated with an alkyl halide or a carbonyl derivative in the usual manner. Some isomerization occurs on treatment with methyllithium, but the major product of this process is that resulting from alkylation of the thermodynamic enolate.



111 **76**

Trialkylsilyl halides show a great propensity to react with the oxygen rather than the carbon of enolate anions. Stork showed that O-alkylation allows enolates to be trapped as the trialkylsilyl enol ether, which is most useful for kinetic enolates in which a lithium enolate (such as the kinetic enolate derived from 2-methylcyclohexanone and LDA) is reacted with trimethylsilyl chloride to give an isolable intermediate, **112**.[82] The enolate is trapped with high efficiency, and conversion to the enolate is readily accomplished by treatment with methyllithium, which generates the kinetic enolate (**113**) and the volatile trimethylsilane (Me_3SiH).[83] This



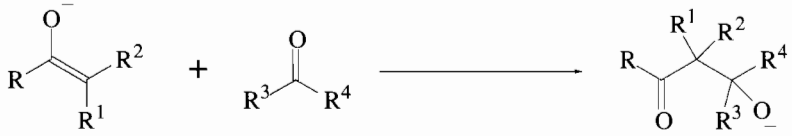
112 **113**

latter reaction is subject to some equilibration, but gives the kinetic alkylation product in good yield. O-Silyl enolates can be generated by other reagents from a variety of starting materials.[84] With kinetic enolates, the trapping proce-dure is especially useful since the isomeric silyl enol ethers can be isolated and separated from amine by-products and unreacted ketone. Unmasking and alkylation can be accomplished under controlled conditions that minimize equilibration, maximizing the yield of kinetic product.

9.4. ENOLATE CONDENSATION REACTIONS

The condensation reaction of enolate anions and carbonyl derivatives is one of the most useful of all reactions in organic chemistry. The condensation is nothing more than an acyl addition reaction of the nucleo-

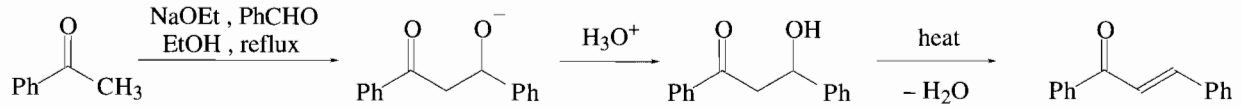
philic enolate to the electrophilic carbonyl carbon.[85] The generalized reaction is represented by enolate **114** reacting with carbonyl derivative **115** (an aldehyde or a ketone in this case) to give the acyl addition product **116**. The reaction is straightforward unless R^1 and/or R^2 are very large and sterically hinder approach to the carbonyl. If R^3 and/or R^4 in the carbonyl partner was very large, acyl addition may also be slow. If the carbonyl is an aldehyde or a ketone, the reaction proceeds to give **116**. If the carbonyl partner is an acid derivative, however, R^3 or R^4 is a leaving group (Cl, O_2CR, OR, NR_2) and **116** reacts further to produce a 1,3-dicar-bonyl compound (sec. 9.4.B) via acyl substitution (see below). There are many synthetic variations and, to further complicate matters, the enolate may be generated under kinetic or thermodynamic conditions. A wide range of keto-alcohols and 1,3-diketones are generated with formation of a new carbon–carbon bond. The more common variations of this reaction are well known, and usually have a name associated with them, as shown below.[86,61,87,88]



114 **115** **116**

9.4.A. The Aldol Condensation

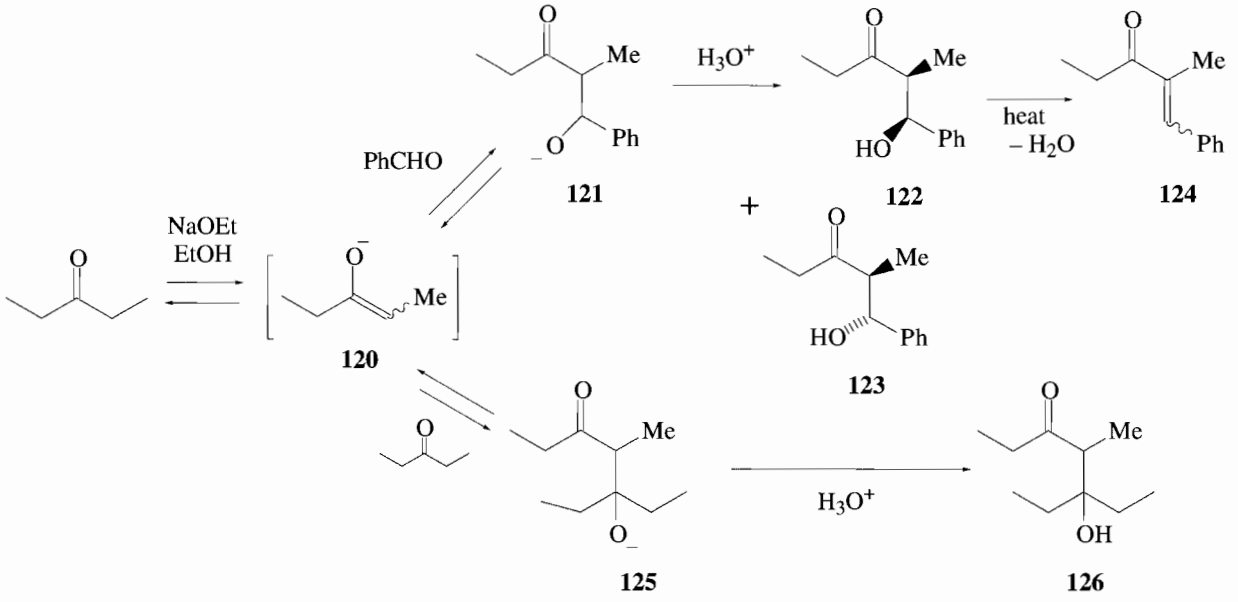
9.4.A.i. Intermolecular Reactions The **aldol condensation**[89] is one of the classical reactions in organic chemistry, apparently first reported by Chiozza in 1856[89a] and later expanded by Wurtz[89b] and Perkin.[89c] In its earliest version, an aldehyde was mixed with a base and an aldehyde that did not contain an enolizable hydrogen (such as benzaldehyde), under what we now categorize as thermodynamic conditions. Ketones were also used. If acetophenone reacted with benzaldehyde in the presence of sodium ethoxide (in ethanol), the initial product was alkoxide **117**. Hydrolysis provided the β-hydroxy ketone product (an aldol), **118**. In general, the hydrolysis step provides the aldol, but sometimes elimination of water (dehydration) accompanies the acid treatment to give a conjugated ketone (**119**), although heating is often required before this is the major product. When an aromatic aldehyde (such as benzaldehyde) is the reaction partner, the aqueous acid workup almost always leads to elimination of water from the aldol product. If an aliphatic aldehyde is used, the aldol product is usually easy to isolate. When an aromatic aldehyde is condensed with an enolate of an aliphatic aldehyde or ketone to give the α, β-unsaturated ketone, the reaction is called the **Claisen–Schmidt condensation**.[90,89d]



117 **118** **119**

A major drawback of the reaction as originally formulated is self-condensation. The enolate derived from 3-pentanone (see **120**) exists in an equilibrium with the ketone and benzaldehyde under these conditions.

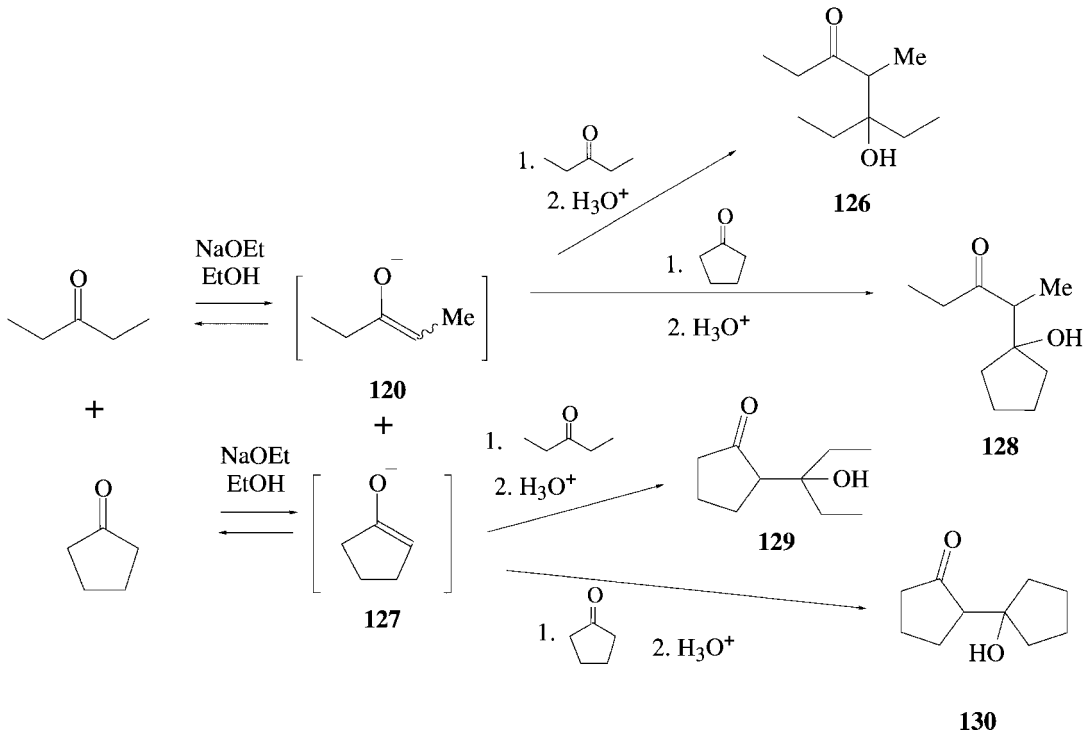
Enolate **120** can react with benzaldehyde to give the aldolate product **121** and hydrolysis gives the alcohol. In this case, diastereomers are formed, **122** and **123** and, at this point, we cannot predict one or the other as a major product. For the time being, we will assume that the reaction produces close to a 1:1 mixture of the two products. If this mixture is heated, conjugated ketone **124** is formed. The problem with this approach is clear when we recognize that enolate **120** can also react with unenolized 3-pentanone to produce the self-condensation aldol product (**125**) and hydrolysis provides **126**. Therefore, this reaction could produce three different aldol products.



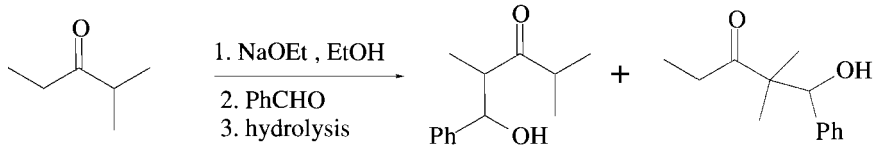
This latter point introduces the disadvantages of the traditional aldol condensation, but there are also advantages. The main advantage is the construction of a relatively complex carbon skeleton from simple precursors. In addition, this carbon–carbon bond forming reaction generates new stereogenic (but racemic) centers, sometimes from achiral precursors and, as will be seen in Section 9.5.A, good-to-excellent diastereoselectivity is possible in many cases. The reaction conditions used for the aldol condensation of 3-pentanone described above are rather harsh and this is a disadvantage if elimination of water from the aldol product occurs or if self-condensation occurs under these equilibrating conditions. Aldehydes that do not contain an enolizable proton can be added to the enolate of a ketone to give a cross-coupling product, but a large excess of the aldehyde is required to minimize self-condensation.

There are certainly cases when we want a crossed-aldol condensation between two reactive partners that have an enolizable position, as in 3-pentanone with cyclopentanone. If 3-pentanone and benzaldehyde, which has no enolizable protons, can lead to three products, what will happen in this new case? If an aldol condensation occurs under thermodynamic conditions, 3-pentanone reacts with sodium ethoxide to give enolate **120**. This enolate can condense with either unenolized 3-pentanone (to produce **126**) or with unenolized cyclopentanone (to produce **128**). Both of these ketones are symmetrical, and there is no opportunity for additional enolates, which would further complicate the reaction (see below). The pK_a of 3-pentanone and cyclopentanone are not

very different. Under equilibrium conditions, both enolates (**120** and **127**) will be formed and will be available for reaction. In addition to the formation of **126** and **128**, enolate **127** can condense with either the unenolized 3-pentanone (to produce **129**) or with unenolized cyclopentanone (to produce **130**), giving a total of four aldol products in this reaction. The possibility of diastereomers will increase the actual number of aldol products. If these products are produced in equal amounts, both the low yield of the desired aldol and problems that will arise when attempts are made to isolate it make the reaction unattractive. Even if one aldol is produced in greater amount, the problems of poor yields and isolation of the desired product remain. It is clear that this mixed aldol is not a synthetically useful reaction as described above.

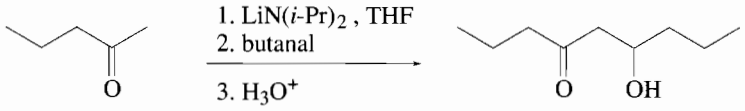


If an unsymmetrical ketone is used in this reaction, the problem is exacerbated. Reaction of **42** with sodium ethoxide, under thermodynamic control conditions, generates two different enolate anions. When reacted with an aldehyde with no α-hydrogens (benzaldehyde), two aldol products are formed (**131** and **132**). When **42** reacts with sodium ethoxide under thermodynamic conditions in the presence of an unsymmetrical ketone such as 2-butanone, the kinetic and thermodynamic enolates of both ketones are formed, which means that four different enolate anions are formed, and each one reacts with two different ketones. Therefore, the attempted mixed aldol condensation of 2-butanone and **42**, therefore, produces eight different aldol products.



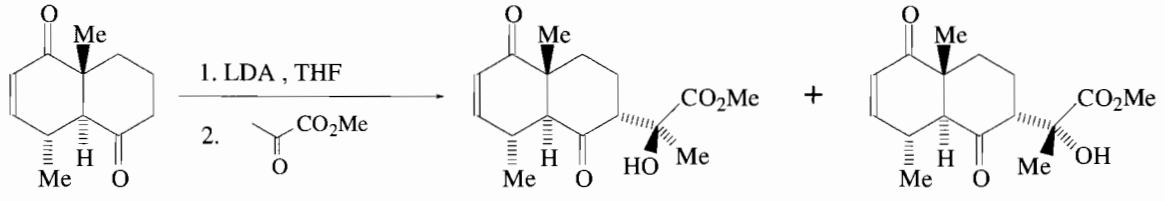
42 **131** **132**

One solution to this problem lies in changing from thermodynamic control conditions to kinetic control conditions. If 3-pentanone, for example, were treated with LDA in THF at –78°C, enolate **120** would be produced irreversibly and in high yield. In a subsequent step, cyclopentanone (or **42**) could be added to give a single aldol condensation product. The advantage of kinetic control is the essentially irreversible formation of the enolate, which minimizes self-condensation products. A kinetically controlled mixed aldol condensation is shown for the reaction of 2-pentanone with LDA and subsequent condensation with butanal to give **133**.[91] This technique will only give the kinetic aldolates, however. If the thermodynamic aldolate is desired, the thermodynamic enolate must be trapped as the enol acetate (see above) and then treated with an appropriate carbonyl derivative after unmasking with methyllithium.



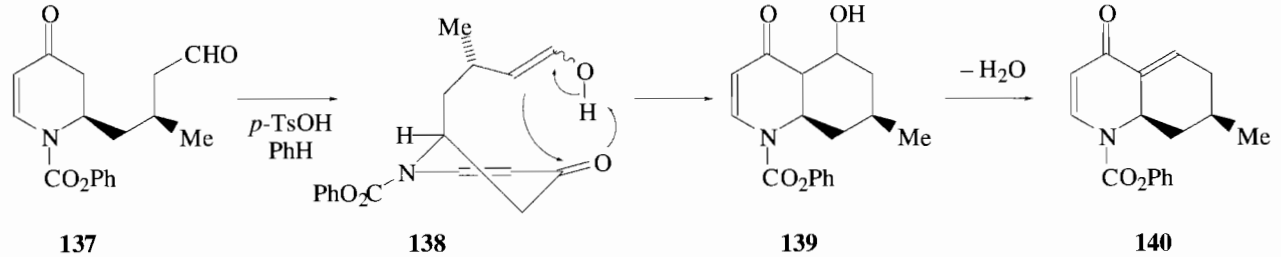
133

There are countless synthetic examples of the aldol condensation. In one example taken from Massanet's synthesis of eudesmanolides,[92] diketone **134** was converted to the enolate anion with LDA. In a second step, methyl pyruvate was added to give a 98% yield of **135** and **136** in about a 1:1 ratio.

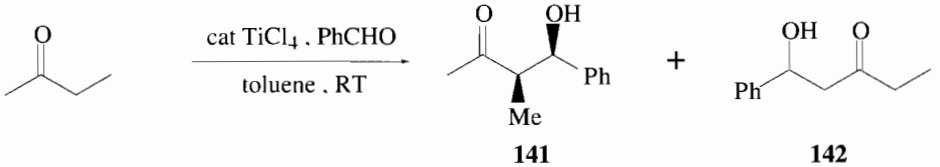


134 **135** **136**

It is also possible to induce aldol condensation reactions under acidic conditions. When **137** was treated with tosic acid in hot benzene (40–50°C), the normal keto–enol tautomerism equilibrium was shifted to favor enol **138**. The enol attacked the carbonyl on the pyridone in an intramolecular aldol cyclization, producing aldol **139**. Elimination of water under the reaction conditions gave an 84% yield of **140** in Comins' synthesis



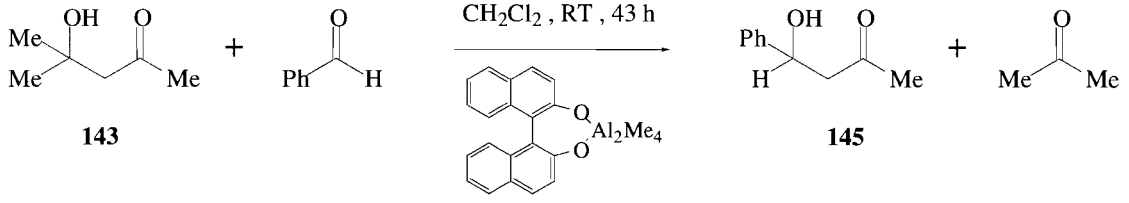
137 **138** **139** **140**



141 **142**

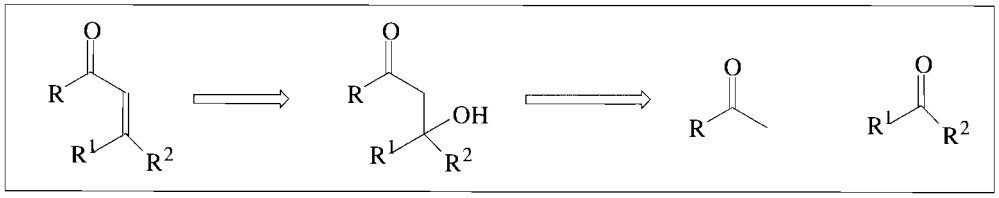
of *N*-acetyl-B-methylphlegmarine.[93] The actual cyclization reaction proceeded via the transition state arising from the conformation shown for **138**, where the enol hydrogen is transferred directly to the oxygen of the carbonyl to generate **139** directly. Lewis acids also catalyze the aldol condensation. When 2-butanone was condensed with benzaldehyde in the presence of a catalytic amount of $TiCl_4$ in toluene, an 83% yield of **141** and **142** was obtained in a 97:3 ratio.[94] Under these conditions, the reaction was highly regioselective for the thermodynamic product. In addition, **141** was obtained as a 95:5 mixture of syn/anti diastereomers, making the reaction highly diastereoselective as well.

Another variation of this classic reaction is called the aldol-transfer reaction, reported by Nevalainen. In the presence of a suitable catalyst, usually an aluminum compound, an aldol product reacts with an aldehyde, gen-erating a ketone and a new aldol.[95] An example is the reaction of benzaldehyde with aldol **143** in the pres-ence of 5% of aluminum catalyst (**144**). In dichloromethane at ambient temperatures, a 62% yield of aldol **145** was obtained after a reaction time of 43 h. The other product of this reaction was acetone, which was readily removed. This transformation involves a retro-aldol reaction of **143** (see sec. 9.5.A.vi.) and the resul-tant enolate anion reacts with benzaldehyde. This reaction has been done with several aldehydes and **143** is particularly attractive (the aldol condensation product of acetone), because acetone is the second product.

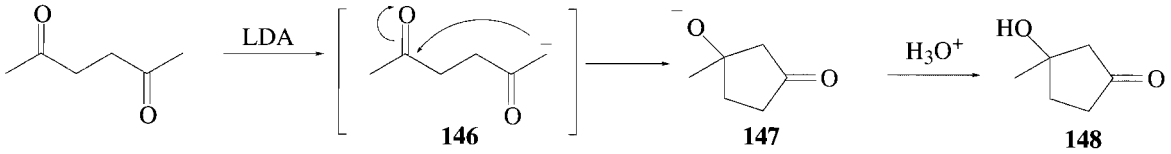


143 **144** **145**

The aldol disconnection is



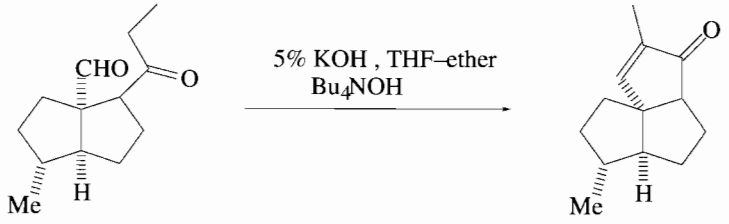
9.4.A.ii. Intramolecular Reactions. The intramolecular aldol condensation is one of the most important synthetic methods known, illustrated by the simple reaction of 2,5-hexanedione with LDA to first give kinetic enolate **146**. This enolate could condense with a second molecule of dione to give an aldol product, but



146 **147** **148**

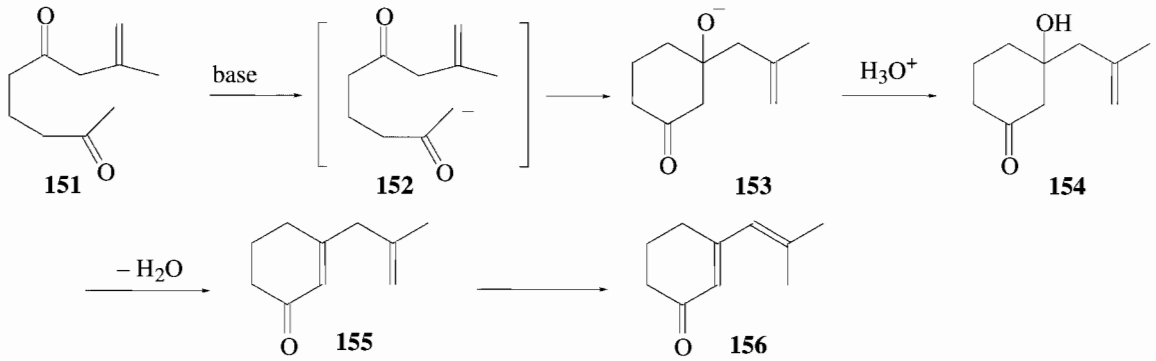
intramolecular attack of the second carbonyl group is much faster and leads to the cyclic aldol product, **147**, which gives **148** upon hydrolysis. The synthesis of (–)-5-oxosilphiperfol-6-ene by Sha et al,[96] in which keto-

aldehyde **149** was treated with aqueous sodium hydroxide under phase-transfer conditions, is a typical synthetic application. The intramolecular aldol led to **150** after elimination of water upon workup.



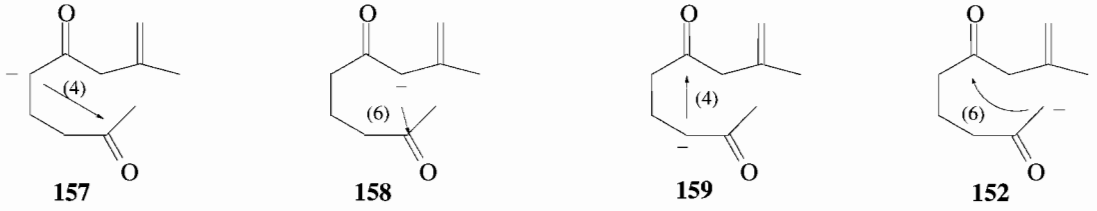
149 **150**

Another example illustrates some the problems inherent in the intramolecular reaction that do not arise with the intermolecular version. Deprotonation of **151** with sodium ethoxide under thermodynamic control conditions gives enolate anion **152** and isolated product **156** (water was lost from the initial aldol product), which



151 **152** **153** **154** **155** **156**

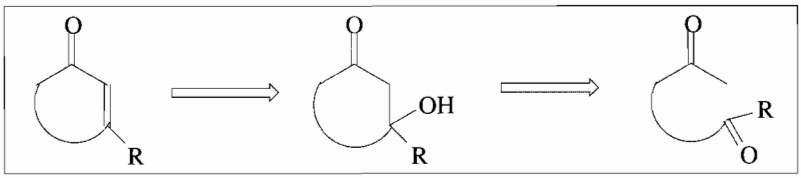
was used in Rouessac's synthesis of isoshyobunone.[97] Under these reaction conditions, **151** can generate four different enolate anions, **152** and **157–159**. The intramolecular aldol condensation reaction with **157** and **159** would generate four-membered rings, which is energetically less favorable (secs. 1.5.B, 6.6.B) than formation of the six-membered rings that can be formed from the other enolates, **158** and **152**. Another product is



157 **158** **159** **152**

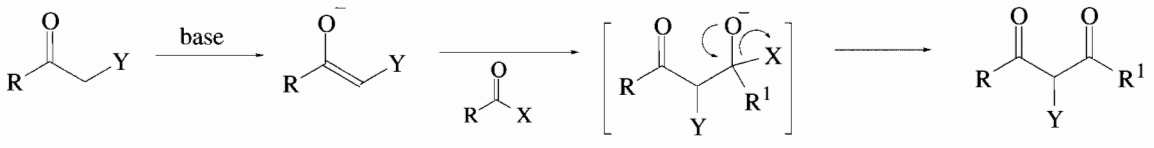
formed in the enolate condensation reaction of **151**, dienone **156**, which is the kinetic product, relative to cyclization via **158**. To produce **156**, enolate **152** closes to form **153** and hydrolysis generates the aldol **154**. Dehydration gives the conjugated ketone (**155**), where the isopropenyl double bond remains out of conjugation. Under the acidic conditions of the workup, that double bond moves into conjugation to give the final product **156**. Despite several possible reaction pathways, this intramolecular aldol cyclization proceeded with high selectivity for a single product. The cyclization is governed by the factors discussed in Section 6.6 for ring closures, which poses problems not encountered with the intermolecular aldol condensation.

The disconnection for an intramolecular aldol condensation is:

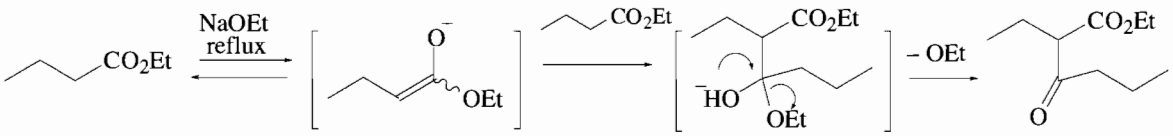


9.4.B. Condensation Reactions of Acid Derivatives

Just as ketone and aldehyde enolates react with ketones and aldehydes, they can also react with esters and other acid derivatives.[98] Similarly, esters and other acid derivatives can be converted to their enolate anions and then react with another acid derivative or with an aldehyde or ketone. There are many variations of this reaction. When an acid derivative is attacked by a nucleophile, the alkoxide product contains a leaving group that can give other reactions, as described for reactions of acid derivatives and Grignard reagents (sec. 8.4.C.ii) and organolithium reagents (sec. 8.5.E). Conversion of a carbonyl derivative (**160**) to the enolate (**161**) allows reaction with an acid derivative (**162**). Attack at the acyl carbon produces the usual alkoxide (**163**), but the X group is a leaving group (Cl, O_2CR, OR, NR_2) and expulsion of X leads to a 1,3-dicarbonyl compound **164**,, which is, of course, the normal acyl substitution sequence. This section will examine those reactions where the carbonyl partner is an acid derivative and, in many cases, the enolate partner will also be an acid derivative.



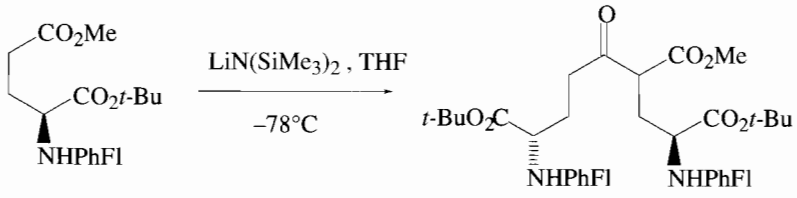
160 **161** **162** **163** **164**



165 **166** **167**

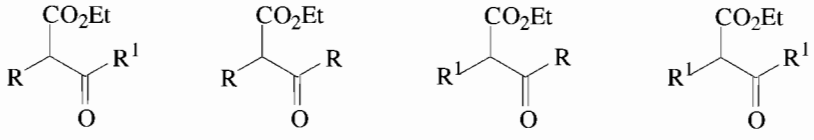
9.4.B.i. The Claisen Condensation. A classical reaction is the condensation of an ester enolate with an ester, illustrated by the self-condensation of ethyl butanoate in the presence of sodium ethoxide to give β-keto-ester **167**. Initial reaction with the base, under thermodynamic control in this case, generates the enolate anion (**165**). This anion attacks the carbonyl of a second molecule of ethyl butanoate to give **166**. Displacement of ethoxide generates ketone **167**. As shown here, this reaction is known as the **Claisen condensation**.[99] A synthetic example is taken from Lubell's synthesis of indolizidine alkaloids, in which diester **168** was treated with $LiN(SiMe_3)_2$ in THF at –78°C to give the self-condensation product **169**, in 52% yield.[100]

The reaction described for ethyl butanoate is a self-condensation, but as with the aldol condensation, Claisen condensation of two different esters can result in a mixture of products under thermodynamic control conditions. The reaction of two different esters is called the **crossed-Claisen** (or a **mixed Claisen**) condensation . A generalized reaction involving RCO_2Et and R^1CO_2Et can lead to at least four different condensation



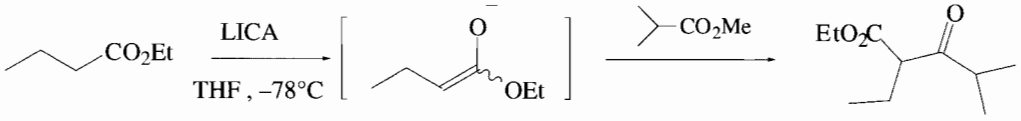
168 **169**

products. One ester (RCO_2Et) can condense with itself to give **170** or with R^1CO_2Et to give **171**. Similarly, ester R^1CO_2Et can condense with itself to give **172** or with RCO_2Et to give **173**. As with the aldol condensation, if a particular crossed Claisen product is desired, kinetic control conditions are preferred to convert the



170 **171** **172** **173**

ester to the enolate anion, irreversibly, prior to treatment with the second ester. A simple example is the reaction of ethyl butanoate with LICA to give **165**. Subsequent addition of methyl isobutanoate led to the β-keto-ester **174**. Self-condensation of the lithium enolate with the parent ester is a problem when LDA is used as a base[101] but this is minimized with LICA.[102] Forming the ester enolate under kinetic control conditions gives greater flexibility in the condensation, allowing the lithium enolate to be condensed with a variety of other esters. It is noted that a full equivalent of base is required to form the enolate anion.

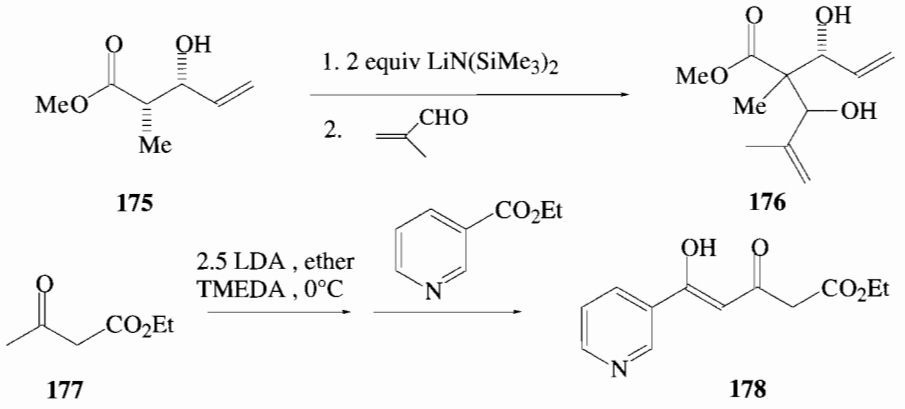


165 **174**

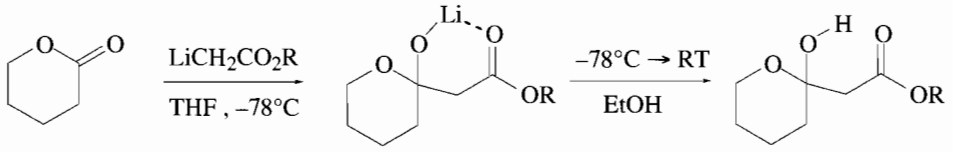
The α-proton in a normal Claisen product, such as **174**, is more acidic than in the starting ester since it is adjacent to two carbonyls (see Table 9.1). Reaction with base under thermodynamic conditions will give the 1,3-dicarbonyl enolate and under thermodynamic control conditions, deprotonation of **174** is certain. The resulting anion is relatively stable, however, due to the increased resonance delocalization possible when two carbonyl groups are present (sec. 9.2.A). Therefore, this enolate shows greater resonance delocalization, it is less nucleophilic and less reactive. This means that the enolate of **174** is *less reactive* than the enolate derived from the ester starting material and should not be a significant competitor in most condensation reactions. The thermodynamic conditions that employ an alkoxide base require that the alcohol solvent be the conjugate acid of that base (methanol and sodium methoxide, for example), or transesterification will give two different esters for all products.

There are two important variations of this condensation. In the first, an ester enolate is condensed with a ketone or aldehyde. This has been called the **Claisen reaction**.[103] An example is taken from the Ōmura co-

workers synthesis of (+)-madindoline A by reaction of the enolate derived from **175** and lithium hexamethyldisilazide with methacrolein to give the condensation product **176,** as a mixture of diastereomers in 70% yield.[104] When the reaction is modified to use an aldehyde or ketone enolate rather than an ester enolate but the reactive partner is an ester, it is still referred to as the Claisen reaction. In this variant, a ketone or aldehyde enolate reacts with an ester to give a 1,3-diketone. In a synthesis of tetrahydro-1-oxpyranobenzopyrans, Hua et al. generated the enolate anion at the methyl ketone unit of **177** and condensation with ethyl pyridine-3-carboxylate gave an 88% yield of **178**.[105] In this case, the product exists largely in the enol form shown.

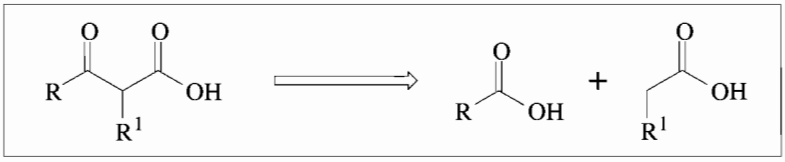


Reaction of an ester enolate with an acid chloride will also generate a β-keto-ester and is a useful alternative to the Claisen condensation. Ketone enolates can also be condensed with acid chlorides.[106] An ester enolate can be trapped with trimethylsilyl chloride, as with aldehydes and ketones. An interesting variation of this



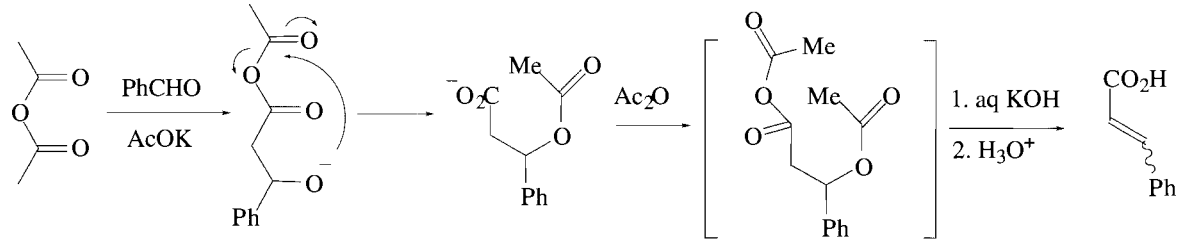
condensation involved lactone **179**, which was condensed with a lithio acetate (R = *t*-Bu, Et) in a modified Claisen condensation to give **180**.[107] Rather than the normal loss of alkoxide to give the β-diketone, **180** was hydrolyzed under mild conditions to give alkoxy hydroxy-ester **181**.

The Claisen disconnection is



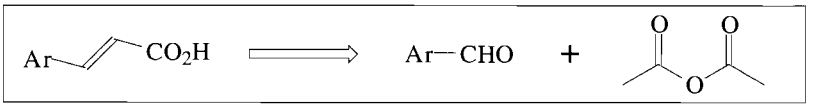
A variation of this condensation involves reaction with aldehydes, and it is called the **Perkin reaction**.[108] Condensation of an aldehyde (having no enolizable protons) with the enolate of an acid anhydride leads to an acetoxy ester such as **182**.[108a] Internal acyl substitution by the alkoxide forms the O-acetyl ester and liberates the carboxylate anion (**183**). Subsequent reaction with more acetic anhydride generates a new mixed

anhydride **184**. Saponification leads to the β-hydroxy acid, which eliminates water in the acid hydrolysis step to give the final product, the aryl acrylic acid derivative (**185**; cinnamic acid).

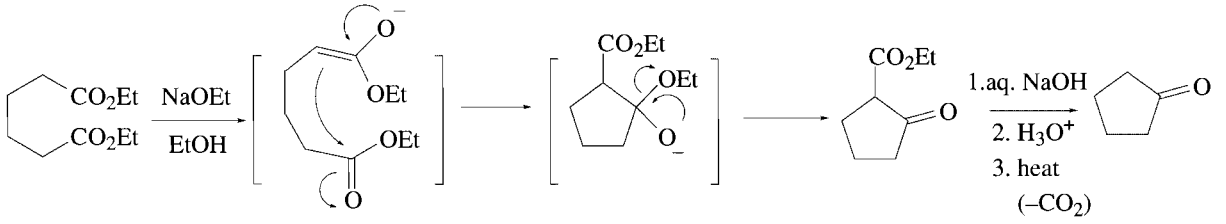


182 **183** **184** **185**

The Perkin disconnection is

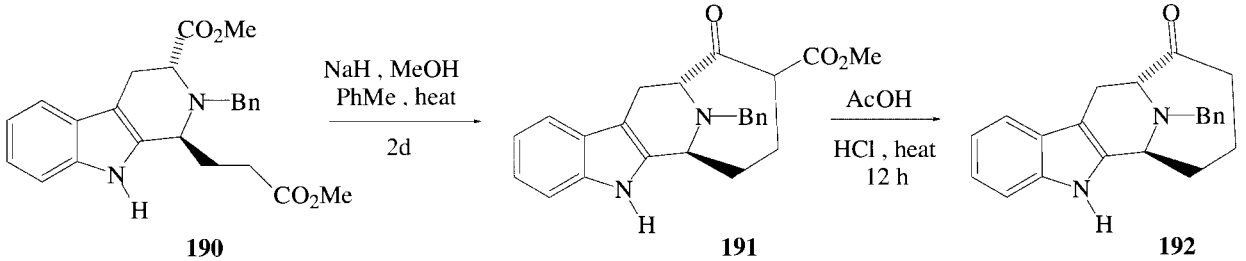


9.4.B.ii. The Dieckmann Condensation. Just as there is an intramolecular version of the aldol condensation, there is an intramolecular version of the Claisen condensation but it has been given a different name, the **Dieckmann condensation**.[109,110] This reaction involves intramolecular cyclization of an α, ω-diester such as **186**. The reaction is usually done under equilibrating conditions, although kinetic control conditions can also



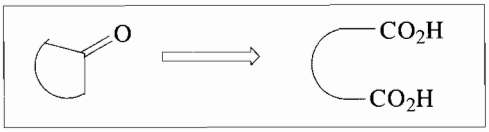
186 **187** **188** **189**

be used, and the initially formed enolate (**187**) attacks the ester group on the opposite side of the molecule to give a ring (alkoxide **188**). Loss of ethoxide gave β-keto-ester (**189**). Hydrolysis and thermally induced decarboxylation gave the cyclic ketone, cyclopentanone.[109] In Cook's synthesis of (+)-ajmaline, diester **190** was treated with NaH in methanol and cyclization gave **191**.[111] When this keto-ester was heated with acetic acid and HCl, hydrolysis and decarboxylation gave the ketone **192**. Note that the enolate is formed by removing the proton from the α-position of the less substituted ester. There are many synthetic applications of the Dieckmann cyclization.[112,113]

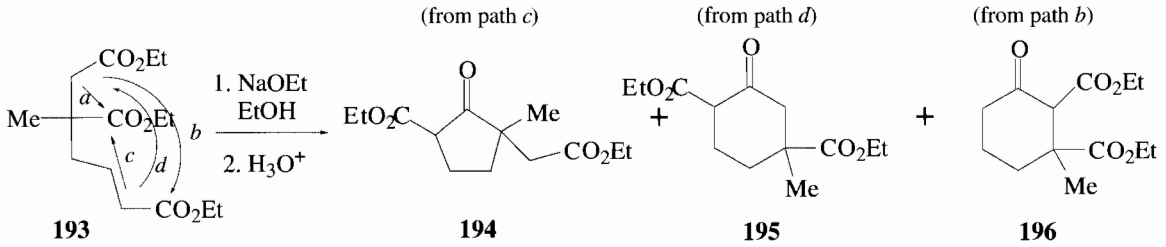


190 **191** **192**

The Dieckmann disconnection is

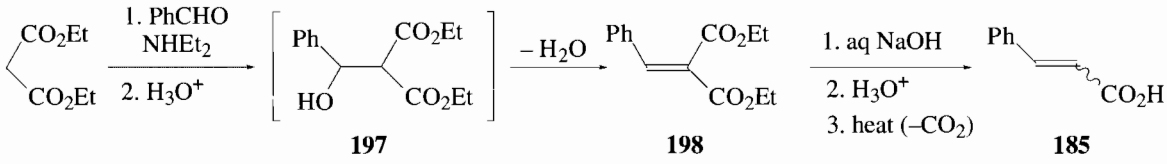


The size of the ring being formed has a great influence on the course of the reaction. When **193** was treated with sodium ethoxide, three isomeric Dieckmann products were possible, **194–196**. Reaction of the enolate via path *a* could generate a three-membered ring but this is energetically less favorable. Attack

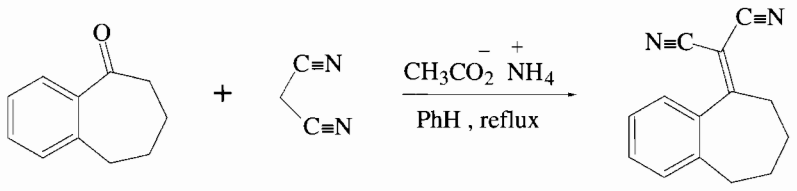


of the enolate via path *b* would generate **196** but this is disfavored due to the sterically hindered center adjacent to the enolate carbon. This leaves reaction paths *c* (to give **194**) and *d* (to generate **195**) as viable possibilities. What is the product? Reaction of **193** under these conditions gave **195** as the only product.[114] The yield of this product varied with the base used to initiate enolate formation.[114] The presence of the methyl group in **193** influences the course of the reaction and similar cyclization with the triester lacking that methyl gave a different major product.[115]

9.4.B.iii. The Knoevenagel Condensation. Another classical reaction called the **Knoevenagel condensation**[116,108b] involves malonate enolates in a condensation reaction with aldehydes, usually a non-enolizable aldehyde. An aldehyde or ketone can be condensed with an active methylene compounds such as a malonic

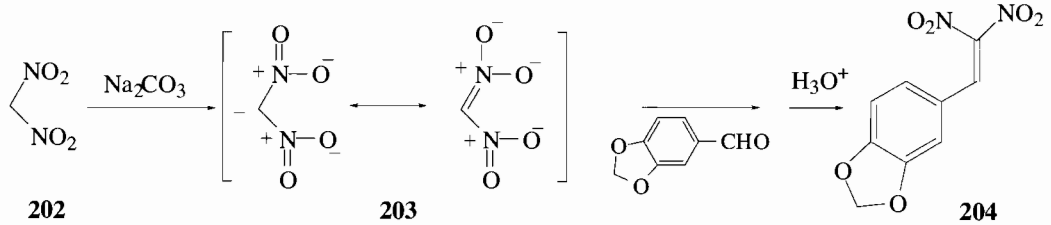


ester using a primary or secondary amine as the base. To avoid a competing aldol condensation, the aldehyde should have no α-protons. Diethyl malonate and benzaldehyde were condensed to form **197**, for example. Spontaneous elimination of water gave the alkylidene product (**198**) and saponification followed by decarboxylation gave the final Knoevenagel product, the conjugated acid (**185**). Contrary to the aldol condensation, elimination commonly occurs upon hydrolysis of these products. This reaction sequence is a facile route to substituted methylene malonic acids [$RCH{=}C(CO_2H)_2$] and acrylic acid derivatives. When the base is pyridine with a trace of piperidine (rather than diethylamine) and malonic acid is the enolate precursor, the reaction is called the **Doebner condensation** or the **Doebner modification**.[117] Kwon and co-workers showed that microwave irradiation facilitates the Knoevenagel condensation with aldehydes.[118]



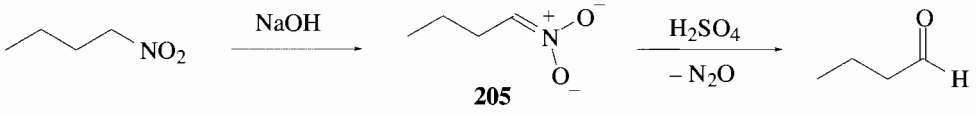
199 **200** **201**

Other derivatives containing two electron-withdrawing groups can be used in the reaction, including malononitrile (**200**). When condensed with 2,3-benzocycloheptanone (**199**), the dicyanoalkylidene product (**201**) was isolated in 46% yield.[119] Cyanoacetic acid derivatives (such as ethyl 2-cyanoacetate) are also common partners in the Knoevenagel condensation.[120]



202 **203** **204**

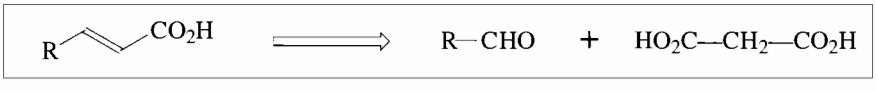
A related reaction involves nitro compounds. As noted in Table 9.1, dinitromethane (**202**) has a pK_a of 3.6. Amines or even sodium carbonate are excellent bases for the deprotonation of **202** to give the resonance stabilized nitro-enolate **203**. When this reacted with piperonal, the dinitroalkylidene product **204** was formed in good yield. The **Henry reaction**[121] (also known as the **Kamlet reaction**) is closely related to this condensation and is often called a nitro aldol reaction. The Henry reaction involves condensation of nitromethane (or another nitroalkane) with aldehydes or ketones. An example is the condensation of nitromethane with benzaldehyde to give a 75% yield of 1-nitro-2-phenylethene via the nitro enolate ($^-CH_2NO_2$).[122] Mononitro compounds such as nitrobutane can also react with a suitable base to generate an enolate anion and then react with aldehyde or ketones.[123] Several variations of this reaction have appeared, including using microwave irradiation to assist the reaction,[124] using Mg—Al hydrotalcites to induce condensation,[125] using powdered KOH without solvent,[126] and using proazaphosphatranes [$P(RNCH_2CH_2)_3N$] to promote the reaction.[127]



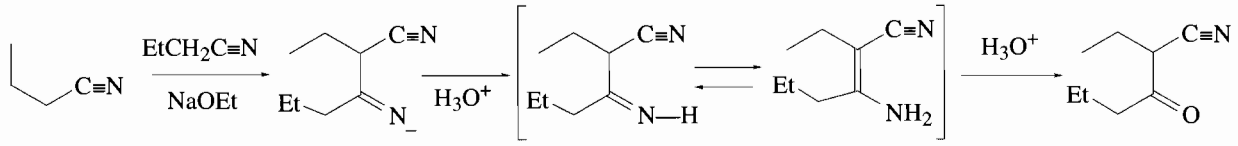
205

Note that nitro enolates have other synthetic uses. When nitrobutane was treated with sodium hydroxide, nitro-enolate **205** was formed. Rather than addition of an aldehyde or a ketone, **205** was treated with concentrated sulfuric acid to form butanal, with loss of N_2O, in what is known as the **Nef reaction**.[128] Modern versions of this reaction use bases such as LDA and less vigorous oxidizing agents such as MoOPh.[129]

The Knoevenagel disconnection is:

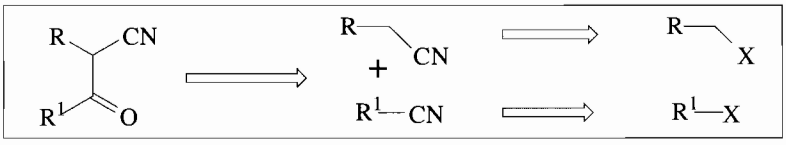


9.4.B.iv. Nitrile Enolates. Nitrile enolates are formed by reaction of a nitrile with LDA or another suitable base. Both alkylation[130] and condensation reactions with aldehydes[131] or ketones are known.[132] In addition to alkyl halides and carbonyl derivatives, condensation can occur with another nitrile. The base-catalyzed condensation of two nitriles to give a cyano-ketone, via an intermediate cyano enolate, is known as the **Thorpe reaction**.[133,109e] Reaction of butanenitrile with sodium ethoxide gave a nitrile enolate, which reacted with a second molecule of butanenitrile at the electrophilic cyano carbon to give **206**. Hydrolysis gave an intermediate imine-nitrile (**207**), which is in equilibrium with the enamine form (**208**, sec. 9.6.A). Hydrolysis led to the final product of the Thorpe reaction, an α-cyano ketone, **209**.[133] Mixed condensations are possible when LDA and kinetic conditions are used to generate the α-lithionitrile (a mixed Thorpe reaction). When pentanenitrile was treated with LDA and condensed with benzonitrile, 2-cyano-1-phenyl-1-pentanone was the isolated product after acid hydrolysis. Nitrile enolates can also be alkylated with a variety of alkyl halides.[134]

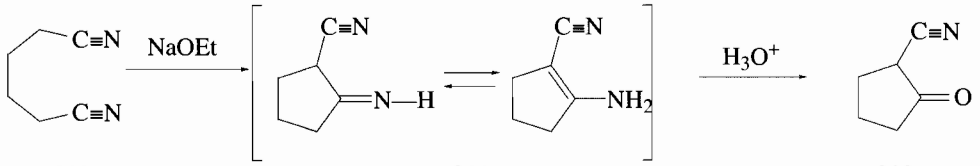


206 **207** **208** **209**

The Thorpe disconnection is:

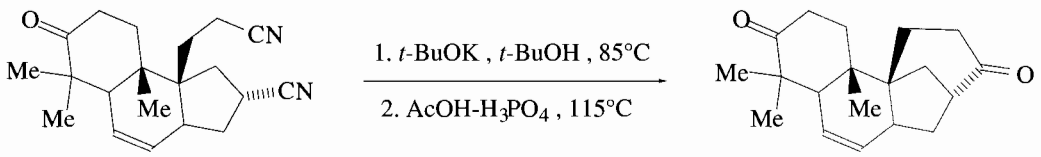


There is an intramolecular version of the Thorpe reaction called the **Thorpe–Ziegler reaction**.[135] When an α,ω-dinitrile is treated with base, formation of the enolate is followed by cyclization. When adiponitrile (**210**)



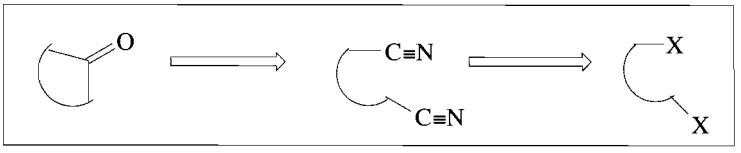
210 **211** **212**

was treated with sodium ethoxide, cyclization gave the usual imine-enamine mixture (**211**). Hydrolysis gave the cyano-ketone (2-cyanocyclopentanone, **212**).[135b] In Deslongchamp's synthesis of (+)-martimol,[65] dinitrile **213** was treated with potassium *tert*-butoxide in *tert*-butanol at 85°C, and after heating to 115°C with acetic acid-phosphoric acid ketone **214** was obtained in 68% yield.

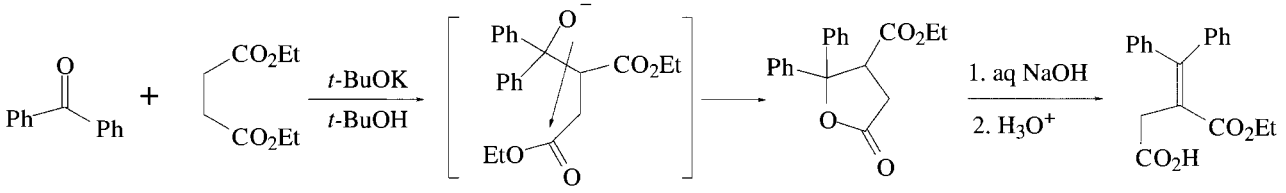


213 **214**

The Thorpe-Ziegler disconnection is

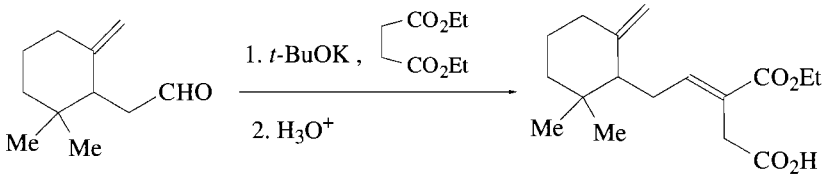


9.4.B.v. The Stobbe Condensation. When succinic ester derivatives (such as diethyl succinate, **215**) are condensed with non-enolizable ketones or aldehydes in the presence of base, the initial condensation product is **216**. The alkoxide reacts with the distal ester via acyl substitution to give a lactone intermediate (**217**). In the original version of this reaction, saponification of **217** gave the α-alkylidene monoester, **218**. The reaction is not completely general and is limited to those α, ω-diesters for which the Dieckmann condensation is not a



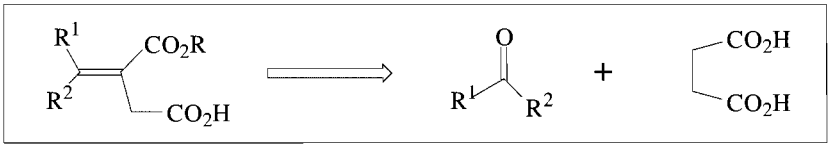
215 **216** **217** **218**

competitive reaction. Succinic acid derivatives are therefore the most common substrate, and this transformation is known as the **Stobbe condensation.**[136] The aldehyde or ketone substrate is not limited to non-enolizable derivatives, however. A synthetic example is the reaction of **219** with diethyl succinate (*tert*-butoxide was used as a base), which gave a 68% yield of **220**.[137]



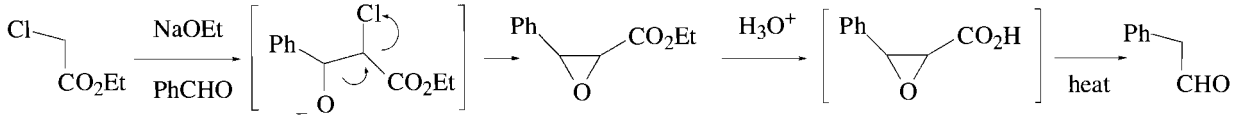
219 **220**

The Stobbe disconnection is

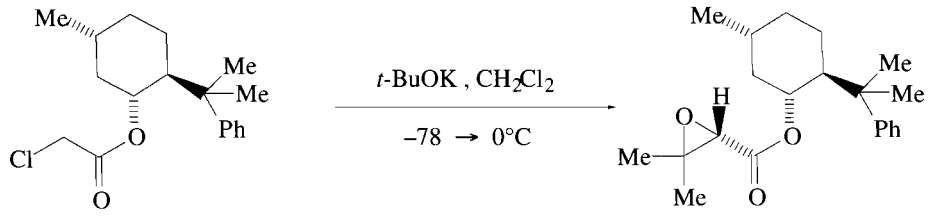


9.4.B.vi. The Darzens' Glycidic Ester Condensation. When an α-halo ester is treated with base and the resulting enolate anion condensed with a carbonyl derivative, the product is an alkoxide. This nucleophilic species can displace the halogen intramolecularly to produce an epoxide, which forms the basis of a classical reaction known as the **Darzens' glycidic ester condensation.**[138] Reaction of ethyl α-chloroacetate and sodium ethoxide, in the presence of benzaldehyde, generated the usual alkoxide (**221**). Intramolecular displacement

of chloride, however, gave the glycidic ester (**222**). Saponification gave the epoxy acid (**223**), which was unstable and lost carbon dioxide to generate a substituted aldehyde or ketone such as phenyl acetaldehyde in this case. This sequence is a useful **chain extension reaction** in which an aldehyde (PhCHO) is converted to a longer chain aldehyde homolog ($PhCH_2CHO$). A ketone is similarly converted to a longer chain aldehyde.



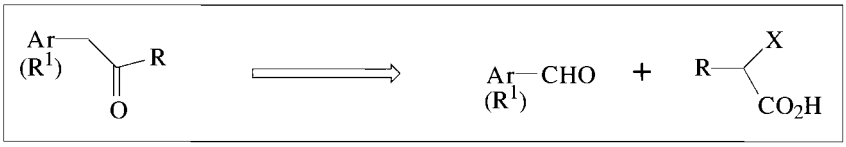
221 **222** **223**



224 **225**

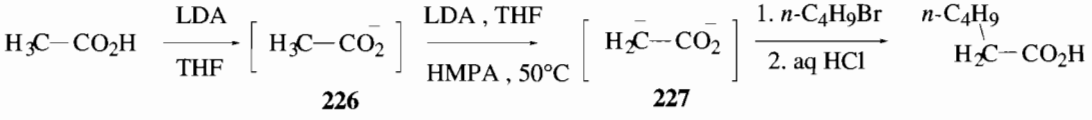
Cyclohexanone, for example, reacted with ethyl α-chloroacetate in the presence of *tert*-butoxide to give cyclohexane carboxaldehyde via hydrolysis of the initially formed glycidic ester.[139] Using an α-alkyl-α-chloroester in this sequence leads to a ketone as the final product. An asymmetric version of this reaction has been recently reported, in which (–)-8-phenylmenthyl ester of chloroacetic acid (**224**) reacted with acetone to give a 64% yield of **225** in 87% de.[140] A catalytic asymmetric Darzens condensation has been reported using a chiral phase transfer agent.[141] It is noted that a Wittig reaction that produces a vinyl ether ($Ph_3P{=}CHOR$ + ketone → $R_2C{=}CHOR$) also converts a ketone to a chain extended aldehyde (sec. 8.8.A.i) when the vinyl ether is hydrolyzed to the aldehyde. It is an attractive alternative to the Darzens' glycidic ester condensation.

The Darzens' disconnection is



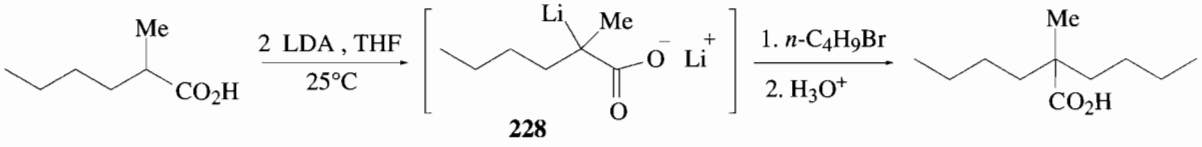
9.4.B.vii. Acid Dianions. All of the named reactions discussed in Section 9.4 constitute relatively minor variations of the fundamental condensation reaction of aldehydes, ketones, or acid derivatives with another aldehyde, ketone, or acid derivative. The ability to produce kinetic enolates from acid derivatives has made possible another useful modification of the enolate reaction. Carboxylic acids have an acidic proton that is removed by 1 equivalent of base to first give a carboxylate (see **226**). Addition of a second equivalent of a powerful base such as a dialkylamide leads to the dianion (**227**). Subsequent reaction with an electrophilic species, in this case 1-bromobutane, occurred first at the more nucleophilic α-carbon to give hexanoic acid.[142] The carboxylate is usually generated with *n*-butyllithium and the enolate with LDA, although 2 equivalents of LDA can be used. As discussed in Chapter 8, treatment of a carboxylic acid with an excess of an organo-

lithium reagent usually gives the ketone, via reaction of the carboxylate (**226**) with the second equivalent of an organolithium reagent (sec. 8.5.E).[143] For this reason, dialkylamides are employed for the second



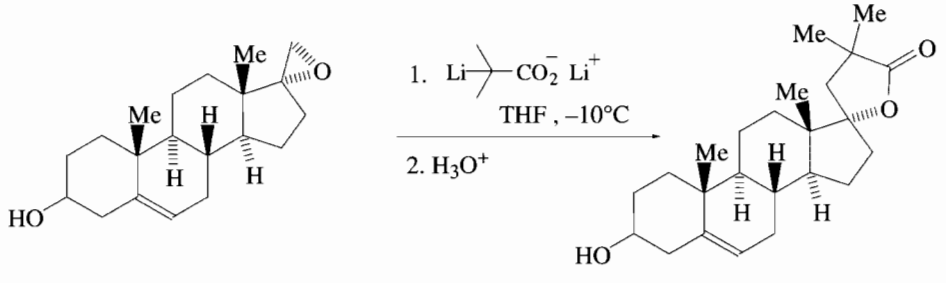
226 **227**

deprotonation. An acid dianion gives all of the reactions of enolates derived from acid derivatives.[144] When 2-methylhexanoic acid was treated with 2 equivalents of LDA, dianion **228** was formed. The least acidic hydrogen (the α-hydrogen) was removed last and generated the most nucleophilic center in **228**. Subsequent reaction with bromobutane occurred exclusively at the α-position, and hydrolysis gave an 85% yield of the substituted acid, 2-butyl-2-methylhexanoic acid.[144a]



228

Dianions of this type react with ketones,[145] epoxides,[146] and esters[147] as well as a wide variety of other electrophiles. As an example, the dilithio anion of 2-methylpropionic acid was condensed with the epoxide moiety in **229** to form an hydroxy acid, which cyclized to form the lactone ring in **230**.[146] Since most of the enolates of acid derivatives contain a leaving group, the alkoxide resulting from reaction with an epoxide often displaces that leaving group to give the lactone.



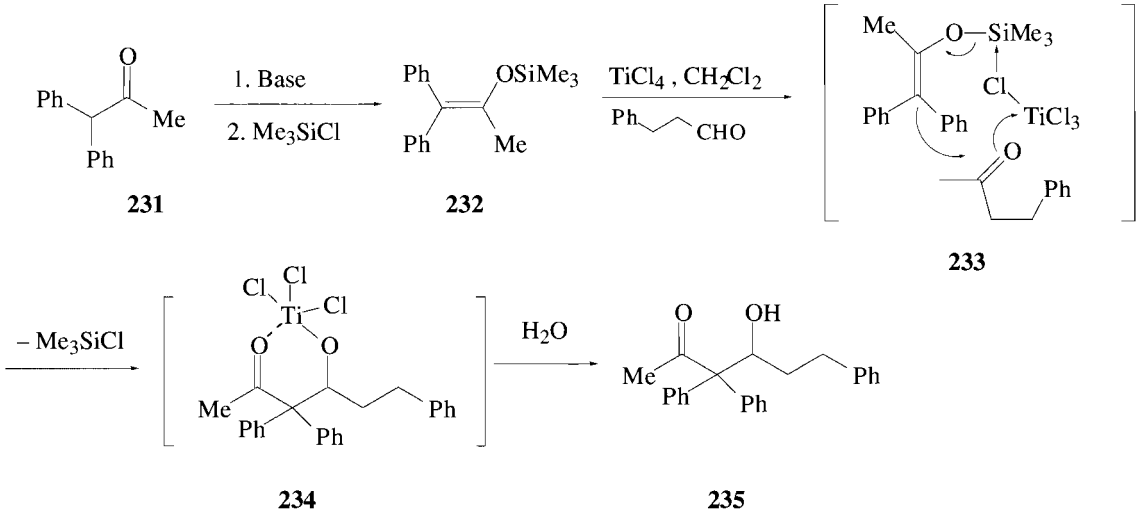
229 **230**

The condensation of enolates with alkyl halides or other carbonyl derivatives allows a wide variety of synthetic and functional group transformations in the carbon–carbon bond-forming process. Enolates are, therefore, among the most powerful synthetic intermediates known. In addition to generating a new carbon–carbon bond, the reaction proceeds with high diastereoselectivity in most cases, making it even more useful.

9.4.C. The Mukaiyama Aldol Reaction

The acid–catalyzed aldol condensation was mentioned briefly in Section 9.4.A.i, including a reaction catalyzed by $TiCl_4$. Using traditional Brønsted–Lowry acids generates the aldolate product, but the acidic conditions make the process reversible and poor yields can result, as well as deleterious cationic side reactions.

For these reasons, this variation is not as widely used as the anionic reaction (the aldol condensation). The base catalyzed reaction often leads to dimers, polymers, self-condensation products or α,β-unsaturated carbonyl derivatives, as described in Section 9.4.A. Mukaiyama and co-workers modified the acid-catalyzed reaction to include silyl enol ethers. He found that they react with carbonyl compounds to produce aldol-like

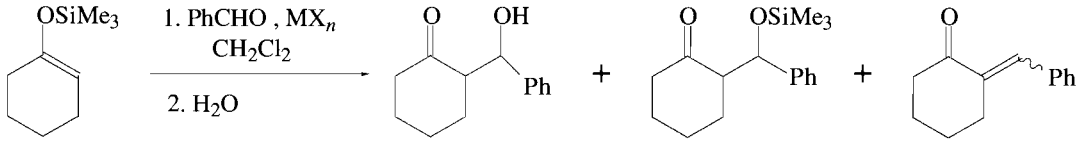


231 **232** **233** **234** **235**

products, in the presence of titanium tetrachloride ($TiCl_4$) and other Lewis acids (e.g. BF_3•OEt_2, TMS-OTf).[148] The requisite silyl-enol ether is prepared by treatment of a ketone such as diphenylacetone (**231**) with base and trapping the thermodynamic enolate with chlorotrimethylsilane, to give **232**. The concept of trapping enolates with chlorotrimethylsilane was briefly introduced in Section 9.3.B. When **232** was mixed with an aldehyde such as 3-phenylpropanal, in the presence of $TiCl_4$, a condensation occurred via a transition state such as **233** to produced the titatnium aldolate **234** via loss of chlorotrimethylsilane. Hydrolysis provided the aldol product **235**. The reaction proceed without self-condensation and at –78°C. This reaction is now called the **Mukaiyama aldol reaction** (or just the **Mukaiyama reaction**).[149] Other Lewis acids can initiate this coupling, including tin tetrachloride ($SnCl_4$) and boron trifluoride etherate (BF_3•OEt_2).

Mukaiyama et al. showed that the reaction of **236** with benzaldehyde, in the presence of various Lewis acid, generated three products, the aldolate (**237**), the trimethylsilyl alkoxide (**238**) and the alkylidene elimination product (**239**).[150] These results are shown in Table 9.7,[150] and it is clear that titanium tetrachloride ($TiCl_4$) and tin tetrachloride ($SnCl_4$) are the best catalysts, although boron trifluoride (BF_3•OEt_2) also gave good results. In general, $TiCl_4$ is the most common catalyst, and its use is illustrated by a reaction taken from Heathcock's synthesis of spongistatin 1.[151] Silyl enol ether **240** (prepared from the corresponding ketone by treatment with Hünigs base and TMSOTf) reacted with aldehyde **241** in the presence of boron trifluoride etherate, to give the aldol product **242** in high yield. The silyl-enol ether shows good selectivity, reacting preferentially with aldehydes, even in the presence of a ketone moiety.[150,152] Condensation does occur with ketones, however, if no aldehyde carbonyl is available and ketones react faster than esters.[160,153] Denmark and Stavenger showed that trichlorosilyl enolates are very competent aldol reagents, even in the absence of additives.[154]

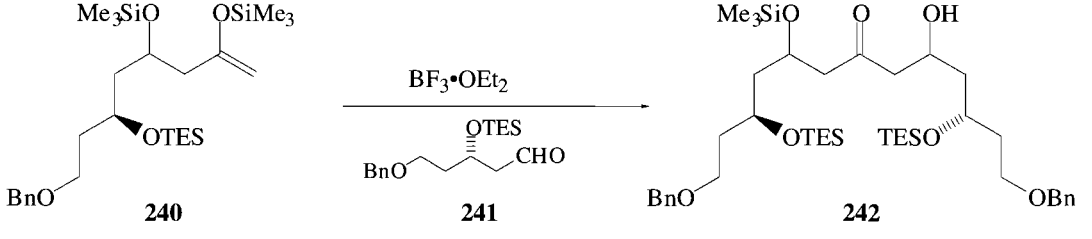
Table 9.7. Reaction of Silyl Enol Ethers with Benzaldehyde in the Presence of Lewis Acids



236 **237** **238** **239**

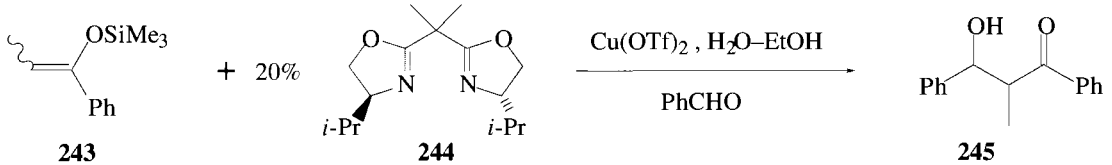
Lewis Acid	Temperature (°C)	Time (h)	% 237	% 238	% 239
$TiCl_4$	RT	2	82	trace	2
$TiCl_4$	-78	1	92	0	0
$SnCl_4$	RT	1	33	trace	28
$SnCl_4$	-78	1	83	trace	trace
$FeCl_3$	RT	1	0	0	12
$AlCl_3$	RT	1	55	trace	trace
BCl_3	RT	1	26	0	0
BF_3•OEt_2	-78	1	80	12	0
$ZnCl_2$	RT	10	69	8	3
$SnCl_2$	-78	12	trace	0	0
Bu_3SnCl	RT	24	0	0	0
$MgCl_2$	RT	24	0	0	0
$CdCl_2$	RT	24	0	0	0
LiCl	RT	24	0	0	0

[Reprinted with permission from Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc., **1974**, 96,* 7503. Copyright © 1974 American Chemical Society.]



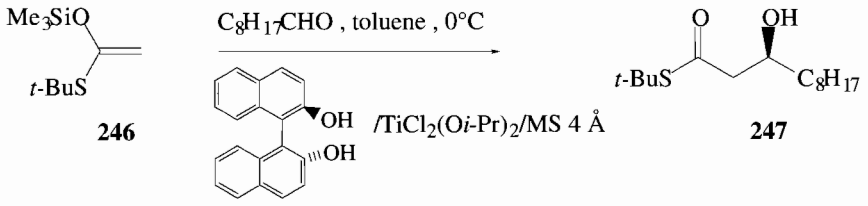
240 **241** **242**

As originally formulated, the diastereoselectivity of the Mukaiyama reaction is not very good, often giving a mixture of syn-and anti- diastereomers in approximately a 1:1 ratio. When complexing agents are added to the reaction medium, however, good diastereoselectivity can be obtained (sec. 9.5.A.v–see below). Improved diastereoselectivity and some asymmetric induction is possible when chiral catalysts are used in conjunction with complexing agents. The reaction of benzaldehyde with **243**, for example, gave a 74% yield of **245** (3.2:1 syn/anti) in the presence of cupric triflate and catalyst **244**.[155] Interestingly, this reaction was done in aqueous media. A water-accelerated reaction of ketene silyl acetals has also been reported.[156]



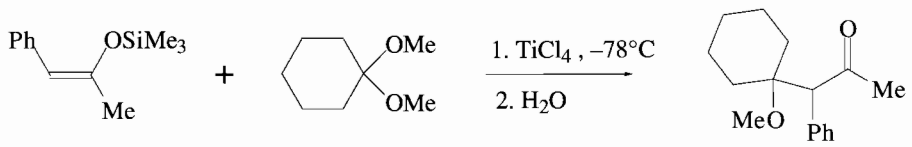
243 **244** **245**

The reaction can be applied to silyl enol esters as well. Good asymmetric induction can be achieved in the Mukaiyama aldol reaction. The reaction of silyl enol thioether **246** and nonanal, for example, gave **247** in 60% yield and in ≈ 93% ee when the (*R*)-BINOL–titanium catalyst shown was used.[157] In this work, the reaction was also done in supercritical fluoroform and in supercritical carbon dioxide. A similar reaction was reported using catalysts closely related to **244** and dichloromethane as the solvent.[158] Chiral oxazaborolidine catalysts have also been shown to be effective for enantioselective Mukaiyama aldol reactions.[159]



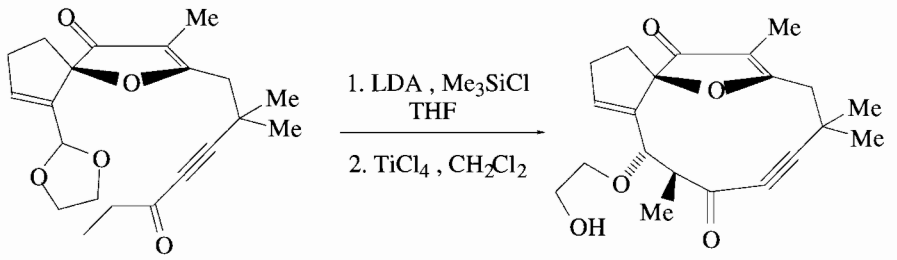
246 **247**

Silyl enol ethers also react with acetals in the presence of $TiCl_4$.[160] An example is the reaction of silyl-enol ether **248** with 1,1-dimethoxycyclohexane (**249**, a protected cyclohexanone–sec. 7.3.B.i) to give **250** in 91% yield.[161,162,163]



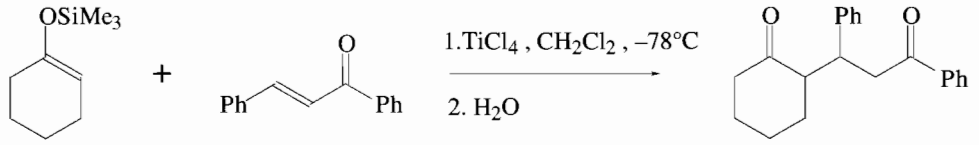
248 **249** **250**

Mukaiyama conditions were used intramolecularly for the successful closure of an 11-membered ring in Smith's synthesis of normethyljatrophone.[164] Conversion of the alkynyl conjugated ketone in **251** to the silyl-enol ether was followed by reaction with $TiCl_4$, leading to reaction with the dioxolane moiety and ring closure (sec. 7.3.B.i for formation of dioxolanes) to give **252** in 47% yield.[164]



251 **252**

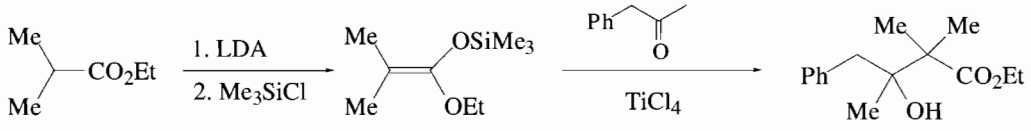
Conjugated ketones react with silyl-enol ethers under Mukaiyama conditions to give the 1,4-addition product in high yield. Reaction of **236** with **253**, for example, gave a 95% yield of the 1,4-product (**254**).[165] Aldol condensations with conjugated systems often lead to 1,4-addition of the enolate anion (sec. 9.7.A). Since the aldol condensation is usually done under basic conditions, further reaction of the products, including self-condensation of the starting materials, is commonly observed. Mukaiyama conditions are relatively mild, and the 1,4-addition proceeds in good yield with few deleterious side reactions.



236 **253** **254**

The Mukaiyama reaction can also be applied to ketene acetals such as **255**, derived by trapping the enolate of an ester such as ethyl isobutanoate. Reaction of ketene acetal **255** with phenylacetone and $TiCl_4$ produced the condensation product **256**.[149a] This variation is very useful since esters can be used as ketene acetal precursors, greatly expanding the utility of the reaction.

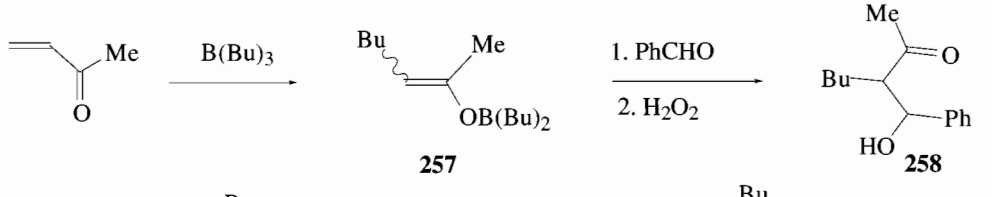
The disconnections are identical to those shown for the aldol condensation.



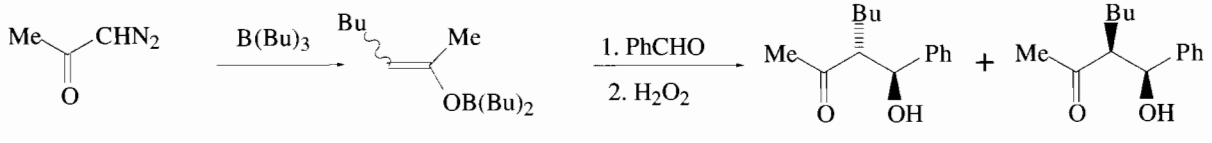
255 **256**

9.4.D. Boron Enolates

Vinyl boronates (borinic esters such as **257**) have become important intermediates in directed aldol condensations, particularly when they are derived from aldehydes. The importance of boron enolates is apparent in the reaction of **257** with benzaldehyde (room temperature, 10 min), to give a 92% yield of the aldol (**258**) after treatment with water.[166] Regiochemical problems in enolate formation can be solved by trapping the enolate as the boronic ester and separating the desired isomer. Subsequent condensation proceeds with excellent diastereoselectivity (sec. 9.5). Mukaiyama is probably the first to have discovered this reaction, in the conjugate addition of tri-*n*-propylborane (sec. 5.2.A) with methyl vinyl ketone to give **245**. Subsequent reaction with benzaldehyde gave a 91% yield of a 33:1 mixture of diastereomers (**260/261**).[167,148] The conjugate addition method used by Mukaiyama for the preparation of **257** was first reported by Brown.[168] Masamune also prepared **257** via reaction of diazoketone **259** with tributylborane (sec. 13.9.C for the preparation and other reactions of diazoketones).[166] Other methods for the preparation of boron enolates include the reaction of borane derivatives with ketones, thioesters, and with ketone enolates (see below).

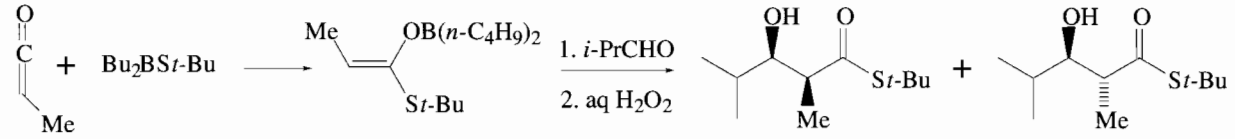


257 **258**



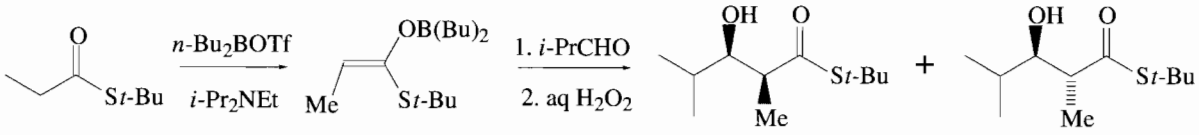
259 **257** **260** **261**

There are several interesting features of the boron enolate aldol condensation. The condensation reaction that produced **260** and **261** clearly proceeded with good diastereoselectivity. The selectivity in the boron enolate reaction is analogous to that observed in base-catalyzed enolate condensations (sec. 9.5). It is important to note that the boron aldolate product was treated with an oxidizing agent to remove boron (just as boranes were oxidized in Chap. 5). The two most common oxidants are H_2O_2 and MoOPh.[171] This oxidation did not degrade the diastereoselectivity of the initial condensation. Several factors



262 **263** **264** **265**

can be used to control or at least influence the diastereoselectivity of this reaction. The first is the geometry of the boron enolate. The (*E*)-isomer of boron enolate **257** predominates in most methods for its preparation. This isomer led to the diastereoselectivity shown for the preparation of **260**. Masamune found that treatment of **257** with lithium phenoxide led to isomerization of the (*E*)-isomer to the (*Z*)-isomer,[166] and subsequent condensation with benzaldehyde gave a 90% yield of **260** and **261** (>2:1 ratio). Masamune also found that the geometry of the boron enolate was greatly influenced by its method of preparation. Reaction of tributylborane with methyl vinyl ketone (MVK) gave predominantly the (*E*)-isomer, as shown. Ketene **262** reacted with sulfide Bu_2BSt-Bu to give the (*E*)-enolate (**263**) as the major isomer. Condensation with isobutyraldehyde gave a 75% yield of **264** and **265** in a ratio of 5:>95 favoring **265**.[169] Masamune also showed that

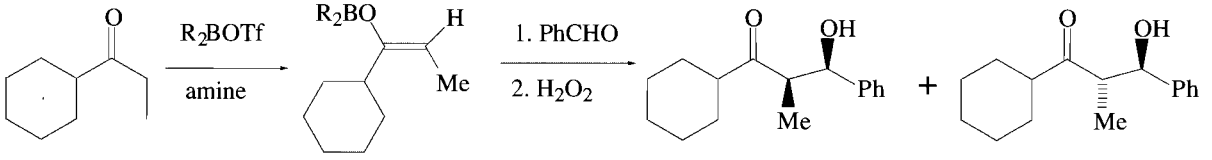


266 **267** **268** **269**

boron enolates could be generated by reaction of a thioester such as **266** with dibutylboryl triflate and Hünigs base (diisopropylethylamine). The product of this reaction was boron enolate **267**, and subsequent condensation with isobutyraldehyde gave **268** and **269**, although the diastereomeric ratio was reversed to give a >95:5 ratio (79% yield) favoring **269**.[169] A similar reaction occurs with enolizable ketones such as **270**, as shown in Table 9.8.[170] The syn/anti ratio of the aldolate products resulting from reaction of the boron enolate (**271**) varied as Hünigs base or 2,6-lutidine was used as the base. The best selectivity for the syn-diastereomer (**268**) was observed with 9-BBN derivatives, and the best anti- diastereoselectivity (to give **269**) occurred with dicyclopentylboranes and Hünigs base.

The diastereoselectivity of the aldol condensation varies with the substituents on the carbonyl precursor to the boron enolate. The boron enolates derived from ketone **274** are shown in Table 9.9.[171] The lithium enolate of **274** reacted with a boron triflate to give the (*Z*) enolate **275** and the (*E*) enolate **276**. Reaction with an aldehyde gave the syn boron aldolate (**277**) and the anti boron aldolate (**278**). The boron aldolates were

Table 9.8. Diastereoselectivity in the Directed Aldol Condensation of Boron Enolates as a Function of Borane and Base.



270 **271** **272** **273**

R	Amine	% 271	272/273
n-Butyl	Hünigs base		43:57
	2,6-Lutidine	82	82:18
Cyclopentyl	Hünigs base	88	14:86
	2,6-Lutidine	79	54:46
9-BBN	Hünigs base	79	>97:<3
	2,6-Lutidine	84	91:9

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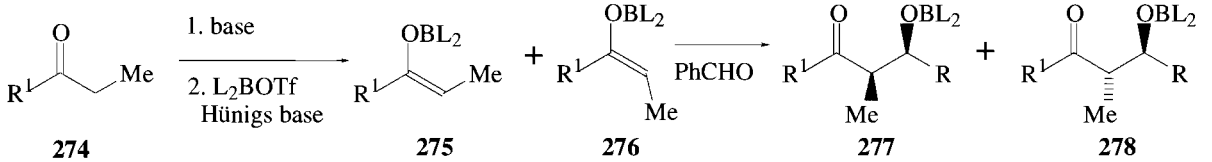
Table 9.9. Selectivity in Boron Enolate Aldol Condensations.



274 **275** **276** **277** **278**

R'	275/276	277/278	Yield (%)
Et	> 99:1	> 97:3	77
Ph	> 99:1	> 97:3	82
i-Bu	> 99:1	> 97:3	82
i-Pr	45:55	44:56	92
t-Bu	> 99:1	> 97:3	65

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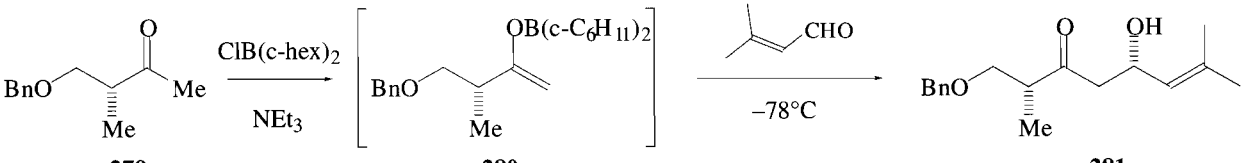
converted to the aldol by treatment with H_2O_2 or MoOPH.[171] The results were similar to those observed by Masamune. The best selectivity was obtained in an ether solvent with the enolate and product ratios a function of the base. Hünigs base gave a (*Z*/*E*) ratio of >99:1 whereas lutidine gave a 69:31 ratio. The ligand (L) was important and L = *n*-Bu led to a (*Z*/*E*) ratio of 99:1, whereas L = cyclopentyl gave 84:16.[171,172,220]

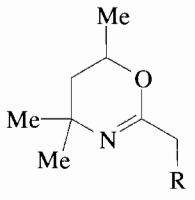


279 **280** **281**

A synthetic example of this reaction is taken from Evan's synthesis of (+)-miyakolide.[173] Ketone **279** was treated with B-chlorodicyclohexylborane in the presence of triethylamine, and this generated boron enolate **280**. 4-Methylbut-2-enal was also present in the reaction and they condensed to give a 98% yield of **281**, with a diastereoselectivity of 88:12.

9.4.E. The Meyers Aldehyde Synthesis

Groups other than a carbonyl can stabilize a carbanion. Meyers[174] described the preparation of α-lithio derivatives of dihydro-1,3-oxazines (**282**) and 2-oxazolines (**284**) and their use in alkylation and condensation reactions via α-lithio derivatives such as (**283**). Meyers treated the commercially available **285** with *n*-butyllithium to form the α-lithio derivative (**286**), stabilized by chelation with the nitrogen. When iodomethane was added, a carbanion displacement reaction occurred to give **287**.[174] The imine unit in **287** was reduced with borohydride (sec. 4.4.A) to give amine **288**, and hydrolysis produced the aldehyde (in this case propanal).



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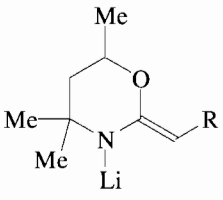

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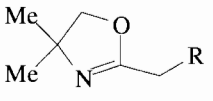

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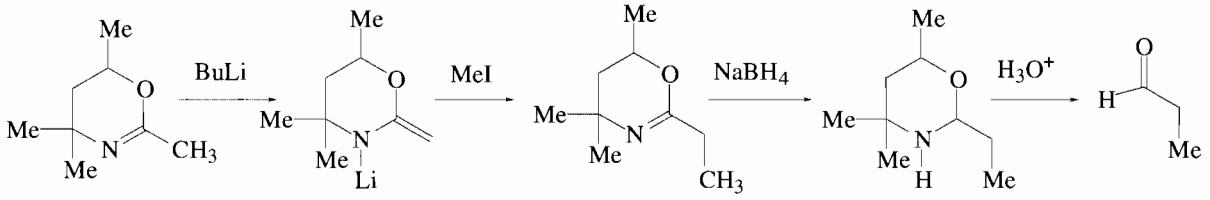
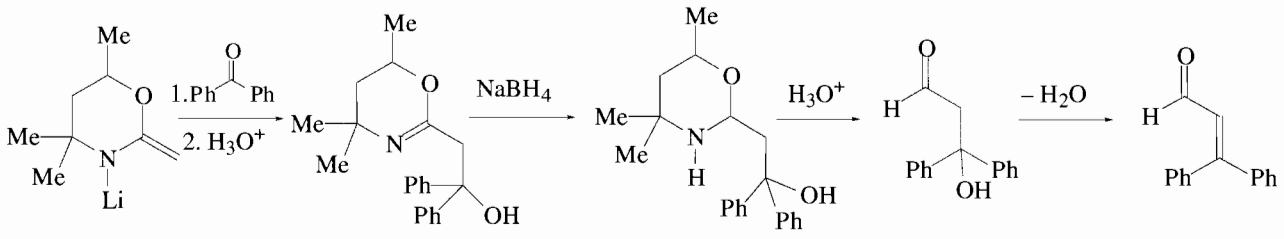


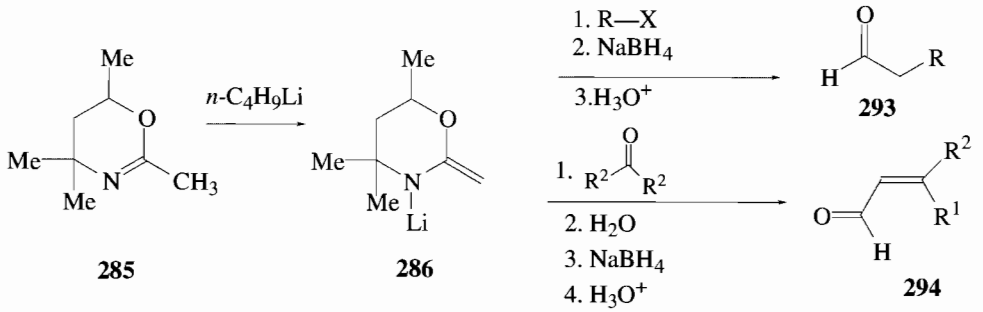
285 **286** **287** **288**

When **286** was treated with benzophenone, the initial condensation product, after hydrolysis, was the alcohol (**289**). Reduction of the imine moiety provided **290** and hydrolysis led to conversion of the oxazolidine to an aldehyde in **291**. but this eliminated water under the hydrolysis conditions to give the conjugated aldehyde (**292**).[175] This sequence is known as the **Meyers' aldehyde synthesis**.[174,176] Table 9.10[174,175] shows formation of both the alkylation product and the condensation products when **286** reacts with alkyl halides or carbonyl derivatives, respectively.



286 **289** **290** **291** **292**

Table 9.10. Aldehyde Formation via Alkylation and Condensation with Dihydro-1,3-oxazine (285)[a]



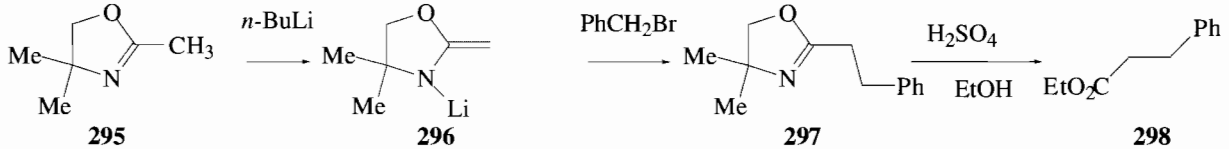
285 286

R	X	R^1	R^2	% 293	% 294
Me	I			60	
n-Pr	I			65	
n-Bu	Br			67	
CH_2=$CHCH_2$—	Br			53	
iPr	I			47	
$PhCH_2$	Br			54	
		C_3H_7	H		61
		C_6H_{13}	H		48
		Ph	H		64
		Me	Me		50
		—$(CH_2)_5$—			53
		Et	Et		62
		Ph	Me		50
		Ph	Ph		62

[a] overall yield from **285**.

[Reprinted with permission from Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Politzer, I.R. *J. Am. Chem. Soc.*, ***1969***, *91*, 763 and Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Fitzpatrick, J.M.; Malone, G.R.; Politzer, I.R. *J. Am. Chem. Soc.*, ***1969***, *91*, 764. Copyright © 1969 American Chemical Society.]

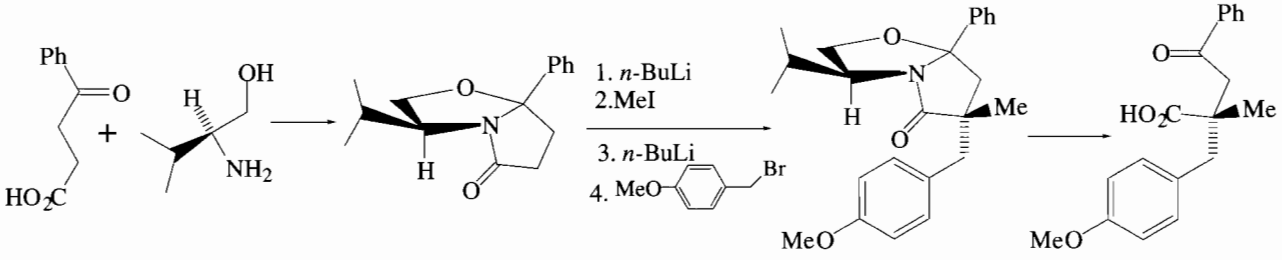
Meyers and others[177] showed that 2-oxazolines such as **295** are useful carbanionic synthons when they are converted to their α-lithio derivative. Reaction of **295** with *n*-butyllithium, for example, gave **296**. Addition of benzyl bromide gave the alkylated product **297**, and heating that product in ethanolic sulfuric acid gave an 84% yield of the ethyl ester, ethyl 3-phenylpropanoate (**298**).[178] Ketones react in a similar manner and the product is usually a conjugated acid derivative.



295 296 297 298

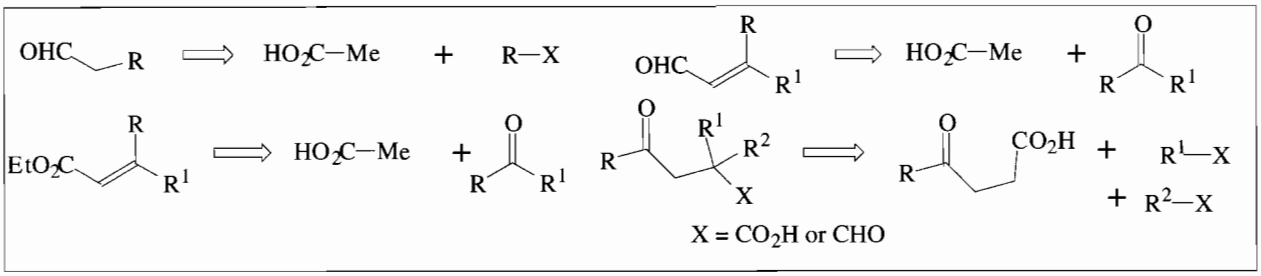
These reactions are not limited to the simple oxazine and oxazolines described above. They are readily prepared from aldehydes and amino alcohols. Meyers used this methodology to prepare chiral precursors for use in asymmetric synthesis. When keto-acid **299** was treated with valinol (**300**), chiral bicyclic lactam **301** was

formed.[179] Sequential alkylations with iodomethane and then 4-methoxybenzyl bromide (using *n*-butyllithium to generate the α-lithio derivative in each case, with 85% yield, 30:1 selectivity) gave **302**. Upon hydrolysis, keto acid **303** was produced in 88% yield with > 98% ee.[179] Alkylation of **301** or related analogs proceeds with excellent diastereoselectivity, and this reaction was used in Meyers' asymmetric synthesis of (+)-mesembrine.[180]



299 **300** **301** **302** **303**

It is clear that the Meyers aldehyde synthesis provides a facile route not only to a variety of aldehydes but also to esters, acids, and chiral derivatives. The disconnections available by this methodology include

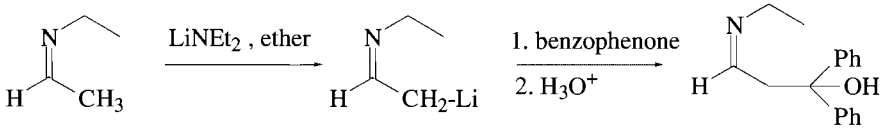


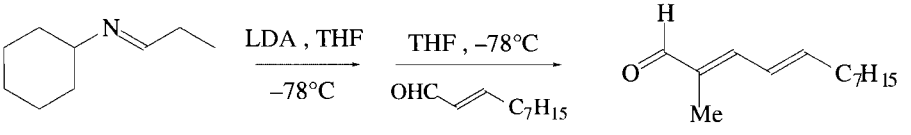
9.4.F. Imine and Hydrazone Carbanions

In Section 9.4.A, it was noted that there were problems with aldol-type reactions, especially with the directed aldol condensation. In particular, aldehydes with an α-hydrogen have great difficulty adding to ketones due to their propensity for self-condensation. The ability to use kinetic control conditions in enolate reactions of ketones and aldehydes often solves this problem. There are also several alternative approaches that involve the use of carbanions derived from imines and hydrazones and these can be very useful.[181]

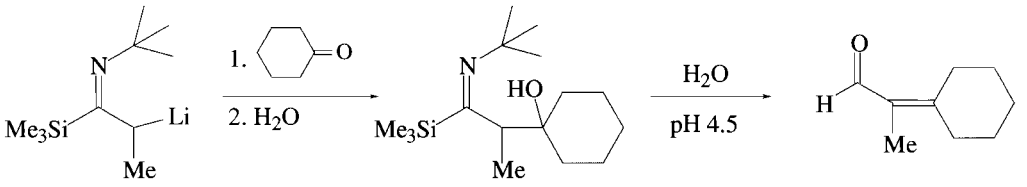
9.4.F.i. Imine Carbanions. Wittig prepared the ethylamine imine of an aldehyde such as **304** derived from acetaldehyde. He showed that **304** reacted with lithium diethylamide to give α-lithio derivative **305**. When benzophenone was added, the expected carbanion condensation reaction occurred to give a 27% yield of **306**.[182,183] With these experiments, Wittig and Stork demonstrated several important features of imine carbanions. The imine moiety functioned as a protected carbonyl (see sec. 7.3.B for protecting groups used with ketones and aldehydes) in this reaction, and it could be deprotected after the alkylation or condensation reaction to regenerate carbonyl. The imine clearly provides activation to the α-position to produce the carbanion on treatment with a suitably strong base. For Schiff bases (imines derived from aldehydes), deprotonation can occur only at the α-carbon, with no possibility of self-condensation or dimerization. The

sequence shown above was one of the first examples of an aldehyde directed aldol condensation. Snider and Liu used this app-roach in a synthesis of deoxypenostatin A. Imine **307** was treated with LDA, and then conjugated aldehyde **308** to give an 81% yield of **309** after hydrolysis.[184] This type of imine anion was also condensed with an ester to give an enamino ketone product.[185] There is a potential problem when this approach is used. When imine carbanions react with ethyl chloroformate, two products are usually formed; C-acylation as the major product and N-acylation as a minor product.[186]

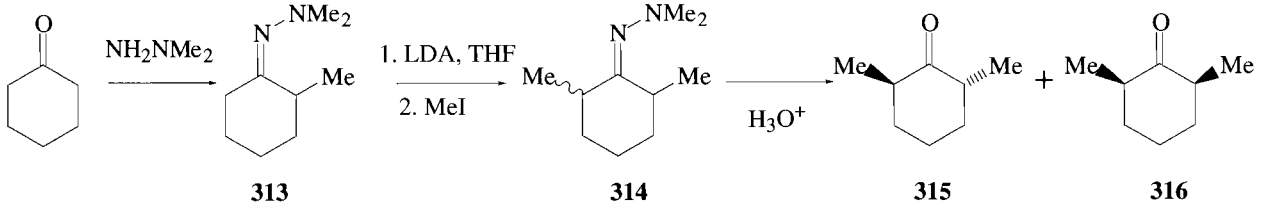




The imine-carbanion method was modified to accomplish the interesting ketone → conjugated aldehyde transformation. The α-lithioimine (**310**) reacted with cyclohexanone to give **311**. Hydrolysis at a carefully controlled pH of 4.5 led to a conjugated aldehyde **312** in 90% yield.[187]

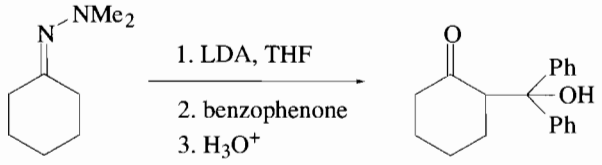


9.4.F.ii. Hydrazone Carbanions. Corey and Enders[188] introduced an alternative to Wittig's imine-carbanion methodology discussed in Section 9.4.F.i. Changing the imine to a hydrazone unit led to a more controllable and useful reaction. *N,N*-Dimethylhydrazone **313** was formed by reaction of 2-methylcyclo-hexanone and *N,N*-dimethylhydrazine . Subsequent reaction with LDA was followed by addition of methyl



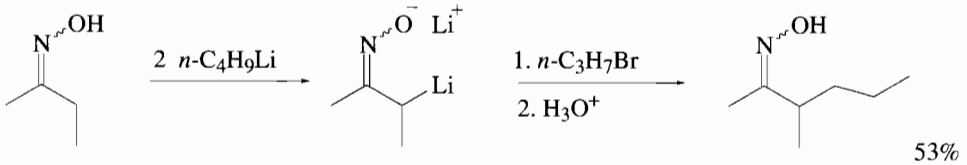
iodide to give the kinetic alkylation product, **314**.[188] Kinetic deprotonation followed by alkylation gave products in good diastereoselectivity, which is demonstrated by the fact that a 97:3 mixture of **315/316** was obtained upon hydrolysis of **314**. The hydrazone carbanion reacts like other carbanions, not only with alkyl

halides but with other electrophilic species such as carbonyl derivatives or epoxides.[189] This is illustrated by the reaction of the N,N-dimethylhydrazone derivative of cyclohexanone (**317**) with LDA, and then with benzo-phenone, to give a 90% yield of **318**.[190] Hydrazone carbanions generally show a great preference for 1,2-addition to conjugated aldehydes such as crotonaldehyde,[190] which suggests that an α-lithiohydrazone is a highly carbanionic species and that the reaction with aldehydes may be under chelation control. N-Tosyl hydrazone derivatives are readily converted to a dianion and undergo the same type of reactions..[191]



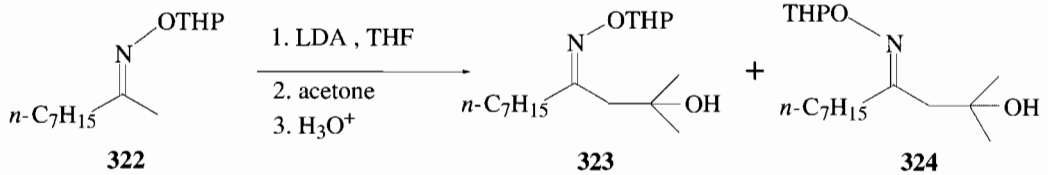
317 **318**

Oximes are a useful source of carbanions in aldol-like condensations. Jung et al. showed that oxime **319** reacted with 2 equivalents of *n*-butyllithium to give the dianion, **320**. Reaction with 1-bromopropane and treatment with water resulted in a 53% yield of **321**.[192,193] *O*-Tetrahydropyranyl oximes such as **322** can also



319 **320** **321**

be used in this sequence, and the fact that the oxygen is blocked removes the necessity for generating a dianion (dianions occasionally have solubility problems that diminish the yield of subsequent reactions). Conversion of 2-heptanone to the O-tetrahydropyranyl oxime produced a 61:39 mixture of (*E*/*Z*) isomers (**322**). Treatment with LDA followed by condensation with acetone led to a mixture of oximes (**323/323**) in 94% yield, maintaining the 61:39 (*E*/*Z*) ratio.[194] Warming **322** to –50°C (from –78°C) led to isomerization, giving exclusively the (*E*)-isomer. When the condensation of (*E*)-**322** with acetone was done at –50°C, a single product (**323**) was obtained.[194]

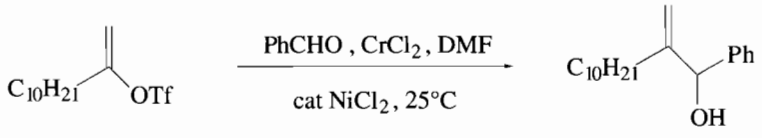


322 **323** **324**

9.4.G. Nozaki–Hiyama–Kishi Coupling

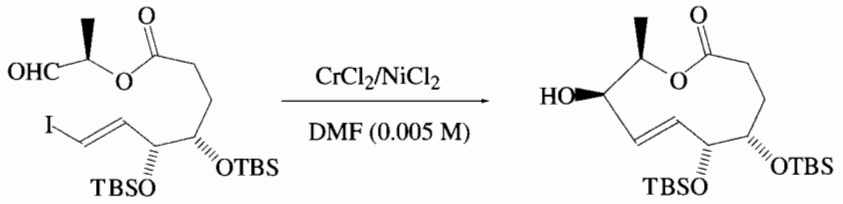
There is another acyl addition reaction that is quite useful, but it involves an organochromium intermediate. Although it is not formally an enolate anion condensation, it is related to the acyl addition reactions presented in this chapter. As originally formulated by Nozaki and co-workers, vinyl triflates such as **325** were treated

with an aldehyde and $CrCl_2$ in the presence of a nickel catalyst.[195] Initial formation of a vinyl nickel species was followed by *in situ* transmetalation to give a vinyl Cr(III) species, which added to the aldehyde. Hydrolysis gave the alcohol product. When **325** reacted with benzaldehyde, for example, an 83% yield of **326** was obtained.[195] A similar reagent was employed by Kishi and co-workers for coupling activated alkenes with aldehydes in connection with synthetic studies toward palytoxin,[196] and later work involving the synthesis of taxanes[197] expanded the reaction. Hiyama et al. had studied reactions of bromobutenes with aldehydes in the presence of Cr(II) reagents.[198] This transformation is now referred to as the **Nozaki–Hiyama–Kishi reaction**,[199] although it has also been referred to as the **Takai–Utimoto reaction**. Fürstener employed a Cr(II)—Mn(0)a redox couple to give essentially the same coupling reaction,[200] used Boeckman to prepare anti-diols with high stereoselectivity.[201]



325 **326**

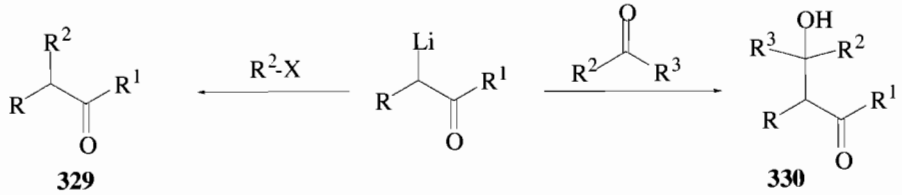
In a synthetic example using an internal Nozaki coupling, vinyl iodide **327** was treated with $CrCl_2/NiCl_2$ in very dilute DMF (0.005 M), to give the coupling product **328** in moderate yield[202] in Pilli's synthesis of aspinolide B. A similar reaction was used previously by Pilli in a synthesis of (–)-decarestrictine D.[203]



327 **328**

9.5. STEREOSELECTIVE ENOLATE REACTIONS

When a prochiral enolate reacts with an aldehyde or an unsymmetrical ketone to give a aldolate product (**329**), two new asymmetric centers are created (when R ≠ H). When the enolate reacts with an alkyl halide one new asymmetric center is created, as in **330** (when R ≠ H). There have been many advances in asymmetric enolate methodology.[204] The purpose of this section is to discuss those factors that influence diastereoselectivity and enantioselectivity in alkylation and condensation reactions of enolate anions.



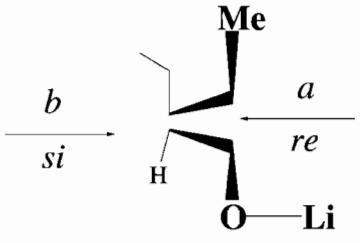
329 **330**

It is also important to note that several factors influence both the stereoselectivity of hydrogen exchange and enolate formation in base-promoted reactions. Houk, Ando and co-workers found that differing conjugative stabilization by CH p-orbital overlap does not directly influence stereoselectivity.[205] Steric effects only dominate is exceptionally crowded transition structures, but torsional strain involving vicinal bonds contributes significantly to the stereoselectivity of all cases studied.

9.5.A. Simple Diastereoselection

9.5.A.i. Alkylation. If the aldol condensation reaction that produces **330** could be controlled, one diastereomer might be formed in preference to the other, making the reaction diastereoselective. There are two essential factors that control diastereoselectivity in this reaction: the *face* from which the two reagents approach and the relative *orientation* of the two molecules.

The enolate alkylation process with simple aldehydes and ketones does not generally lend itself to enantioselective control, due to the planar nature of the enolate π system.[206] Inspection of **331** shows that the *si–re* face (face *a*) has no more steric hindrance than the *re–si* face (face *b*). When this enolate reacts with iodomethane, therefore, no facial selectivity is anticipated and the product will be racemic. In general, enolate alkylation reactions produce chiral, racemic products. The reaction can be diastereoselective, however, when substituents attached to the molecule provide facial bias. In general, enolate alkylation proceeds by approach



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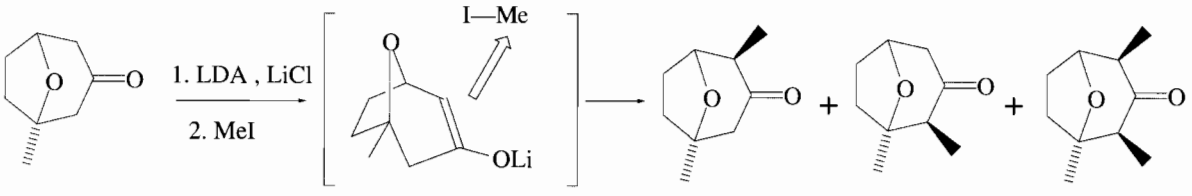
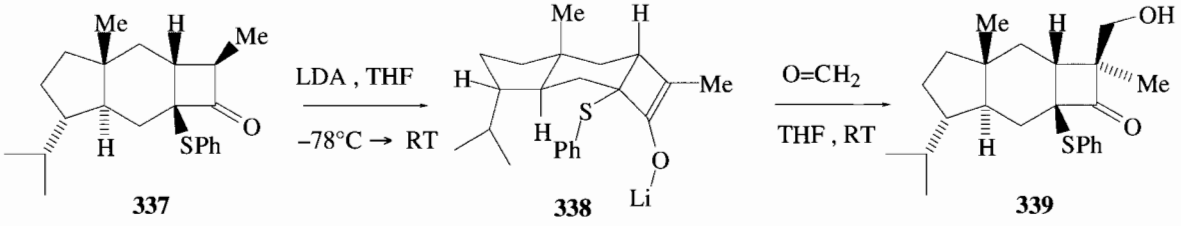


332 **333** **334** **335** **336**

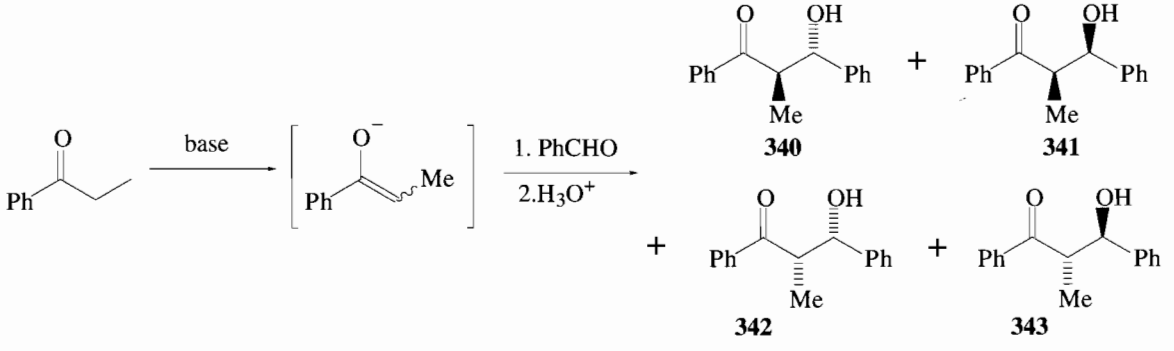
of the enolate to the halide from the less sterically hindered face of the enolate anion. It is the steric hindrance in the enolate anion, not the ketone or aldehyde precursor, that is important. In the Molander and Haas synthesis of davanone,[207] ketone **332** was treated with LDA and then with iodomethane. Three products were formed, 58% of **334**, 8% of **335**, and <2% of dialkylation product **336**. About 20% of unreacted **332** was recovered. Inspection of the enolate anion formed from **332** (see **333**) shows that the exo face of the bicyclic system is the least hindered for attack of iodomethane and accounts for the stereochemistry of the methyl group(s) in all three products The regioselectivity for **334** is attributed to formation of the enoate and

alkylation away from the bridgehead methyl group. Another example is the conversion of **337** to **339** in Paquette's synthesis of xyloside derivatives.[208] Reaction with LDA led to enolate anion **338**, and reaction with formaldehyde gave hydroxymethyl derivative **339** with reaction occurring from the less hindered exo face of the enolate anion.



337 **338** **339**

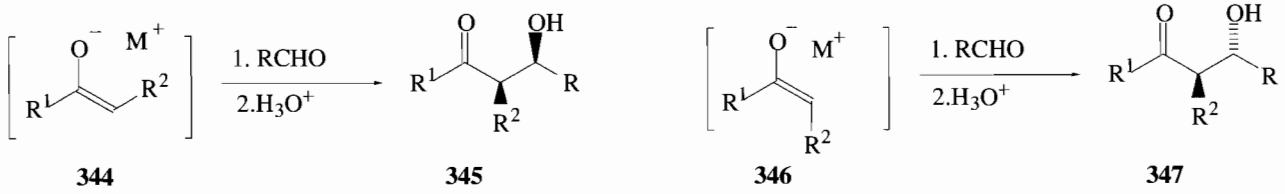
9.5.A.ii. Diastereoselection in the Aldol Condensation. In addition to the alkylation reaction, enolates react with other carbonyl compounds to give aldol or Claisen products, as discussed in previous sections. An aldol condensation with the enolate of 1-phenyl-1-propanone and benzaldehyde generates two new stereocenters and gives two racemic diastereomers (four stereoisomers). These two diastereomers are the racemic anti diastereomer (**340** and **343**) and the racemic syn diastereomer (**341** and **342**). Diastereoselectivity in this reaction is dependent on the reaction conditions and the enolate and aldehyde partners, and this section will explore the origins of that diastereoselection.



340 **341** **342** **343**

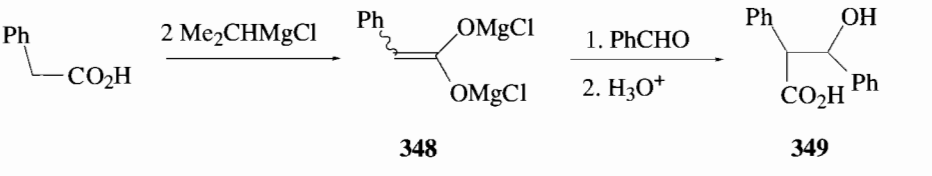
Heathcock et al. described the process that formed diastereomers in the aldol condensation, from precursors that do not contain a chiral center, as **simple diastereoselectivity**.[209,210] Naming protocols to describe the diastereomers produced in the aldol condensation include the erythro/threo nomenclature,[211,212,213,214] as well as the syn/anti nomenclature[215] was discussed in Section 1.4.B. Using this latter convention, diastereomers **340** and **343** were designated as anti and diastereomers **341** and **342** were designated as syn.

9.5.A.iii. The Zimmerman-Traxler Model. It would be useful to have a simple model that would predict the major diastereomer produced in an aldol condensation with confidence. In Section 9.2.C, the geometry of the enolate was shown to be important and, to some extent, could be controlled. In general, a (*Z*)-enolate (such as **344**) will generate a syn diastereomer such as **345**. In contrast, an (*E*) enolate such as **346** will generate the anti diastereomer (**347**). Once the geometry of the enolate has been established, a cyclic transition state model



344 **345** **346** **347**

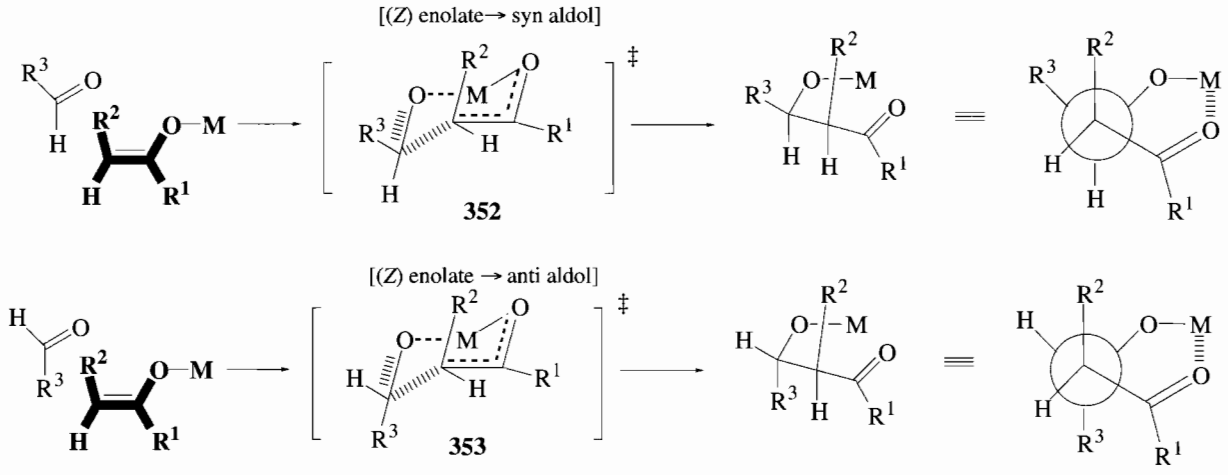
can be used to predict the diastereoselectivity stated in these examples. The most popular transition state is the closed or chelated transition state,[216] first proposed by Zimmerman and Traxler[216b] for the Ivanov condensation of phenylacetic acid and benzaldehyde. The **Ivanov condensation**[217] involves treatment of a carboxylic acid such as phenylacetic acid with excess of a Grignard reagent (such as isopropylmagnesium chloride) to give a bis(magnesium) ketene acetal (**348**)[217a] Subsequent reaction with a carbonyl compound (benzaldehyde) led to an aldol-like product (**349**). The cyclic model proposed to described the Ivanov reaction (model **350**) can be used for aldol condensations if magnesium is replaced with lithium, giving the cyclic model **351**. When **51** is used to predict stereochemistry in the aldol condensation, it is referred to as the **Zimmerman–Traxler model**.[216]



348 **349**

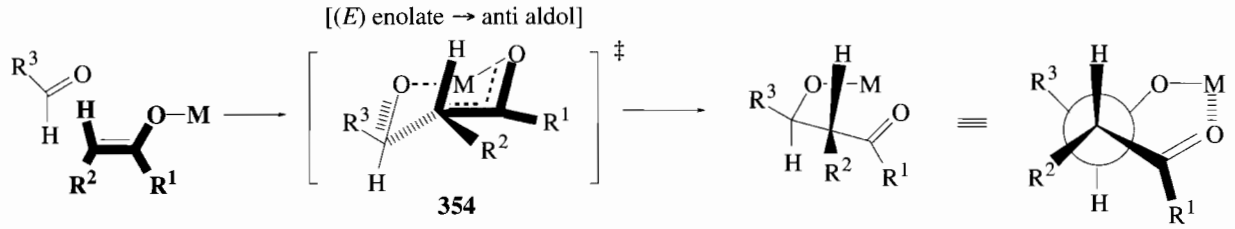
350 **351**

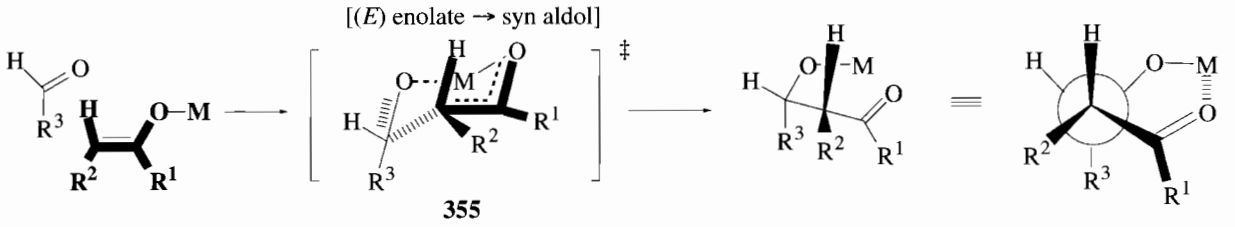
It is important to state that **there is *no* evidence that the Zimmerman–Traxler model represents the actual transition state for aldol-like reactions**. Nonetheless, this model is a useful mnemonic, extensively used and makes reasonable predictions in many cases. It is used to predict structure-selectivity relationships for lithium,



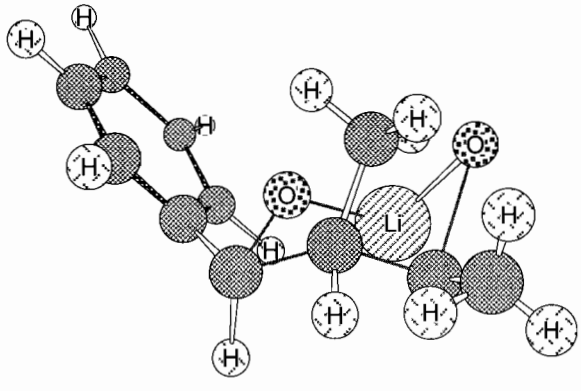
352 **353**

boron, magnesium, and zinc enolates when they react with aldehydes and ketones. There are four possible transition states, indicated by ‡, for an aldol condensation (**352**, **353**, **354**, and **355**), reflecting the different orientations of enolates with respect to the aldehyde (or ketone) as well as the (*E*/*Z*) geometry of the enolate. For simplicity, the addition is shown for approach of the aldehyde to the enolate from a single face in all cases (actually, approach from both the back face, which is shown; the front face generates enantiomers).[218]





Referring to these generalized models, when R^2 is small, the chair transition state explains the stereochemical trend. For (*Z*)-enolates, the $R^1 \leftrightarrow R^3$ interaction dominates and **352** is favored over **353** as the steric bulk increases, leading to more of the syn isomer. For (*E*) enolates, the $R^1 \leftrightarrow R^3$ interaction favors **354** over **355** and the anti aldol is the major product.



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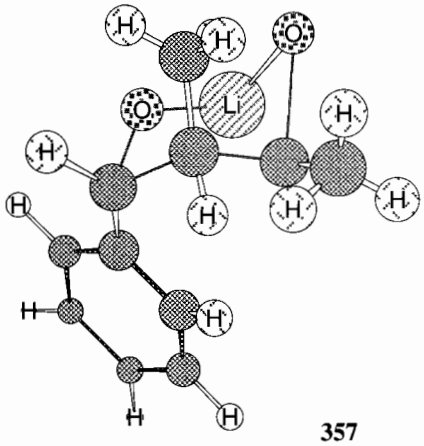
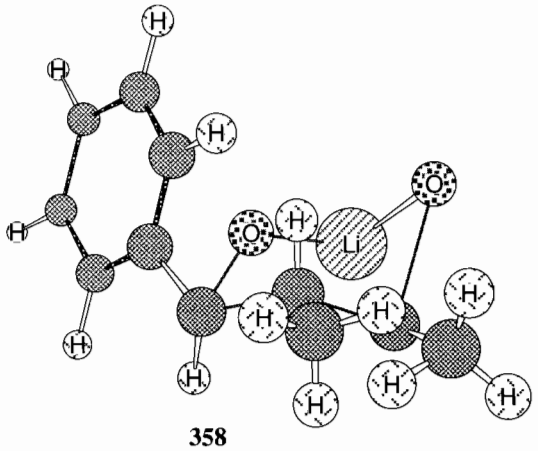
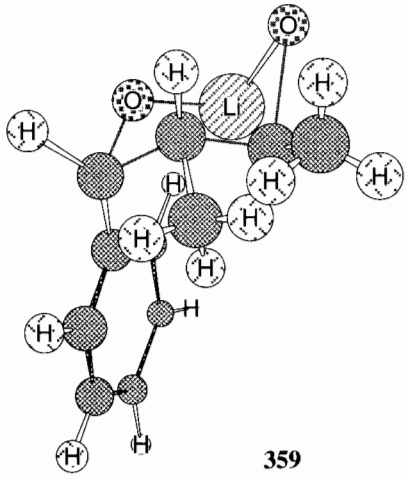


357

A 3D representation (see **356**) of transition state **352** is shown for the specific condensation of benzaldehyde (R^3 = Ph) with the (*E*)-enolate of 2-butanone (R = R^2 = Me). A similar 3D drawing (**357**) is shown for the opposite orientation (transition state **353**). These are crude representations of the transition state, but they show the pseudo-axial and pseudo-equatorial interactions of the phenyl and methyl groups for the condensation of benzaldehyde with the thermodynamic enolate of 2-butanone. Transition states **352** and **353** represent the generalized reaction with a (*Z*)-enolate with an aldehyde for two different orientations. For the

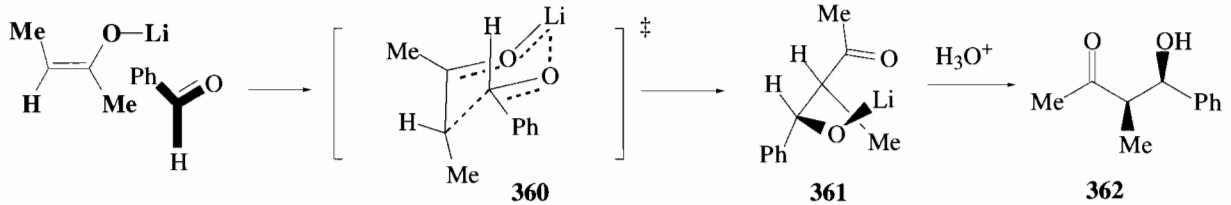


358

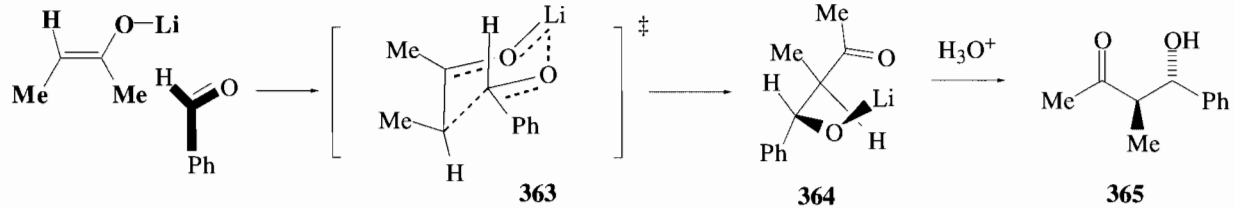


359

(*E*)-enolate, the steric interactions in **353** (see **357**) appear to be greater than those in **352** (see **356**) because the pseudo-equatorial phenyl and methyl groups are close together in **353**. In **352**, one group is pseudo-axial and the other is pseudo-equatorial, minimizing the steric interaction. Transition state **352** would therefore be



360 **361** **362**



363 **364** **365**

used to predict the major product of the reaction and the (*E*)-enolate generates the syn-diastereomer, as predicted. The 3D representation of the transition state for the reaction of benzaldehyde with the (*Z*) enolate of 2-butanone (**358** for **354** and **359** for **355**) shows the pseudo-diaxial groups in **358** to minimize the steric interactions of the groups. Conversely, the pseudo-diequatorial placement of the phenyl and methyl groups in **359** brings those groups into relatively close proximity. Transition state **354** is therefore lower in energy and will be used to predict the anti diastereoselectivity of the final product. Using the Zimmerman–Traxler model for the benzaldehyde–2-butanone system (see the 3D models), transition state **360** for this system predicts the initial aldolate product (**361**) and the final syn product, **362**. Similarly, the (*Z*) enolate uses transition state **363** to give the aldolate product (**364**) and the final anti product **365**.

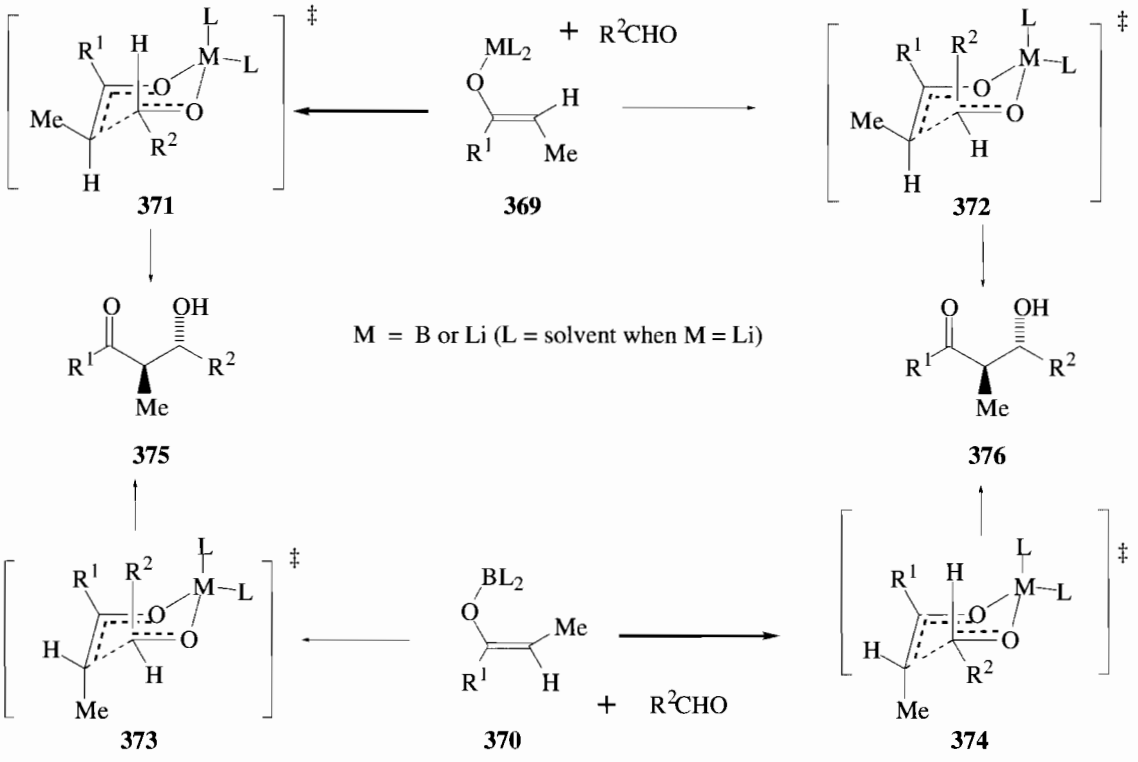
Identical conclusions can be drawn when the Zimmerman–Traxler model is applied to ester enolates. The (*Z*) enolate **366** (derived from the corresponding ester in Table 9.11)[219] reacted with various aldehydes to give a mixture of the anti **367** and the syn (**368**) product, with the anti product predominating.[219]

Table 9.11. The Syn/anti Selectivity of Ester Enolates with Benzaldehyde

R^1	R^2	R^3	367/368
Me	Me	Me	57:43
		Ph	55:45
		i-Pr	55:45
CH_2OMe	Me	Me	67:33
		i-Pr	90:10
DMP[a]	Me	Ph	88:12
		n-C_5H_{11}	86:14
		i-Pr	>98:2
		t-Bu	>98:2
	Et	*i*-Pr	>98:2

[a] DMP = 2,6-Dimethylphenyl.

A similar model has been applied to aldol condensation reactions of boron enolates.[220] The reaction of (*E*) enolate **369**, for example, can lead to either transition state **371** or **372**. Transition state **371** generates the



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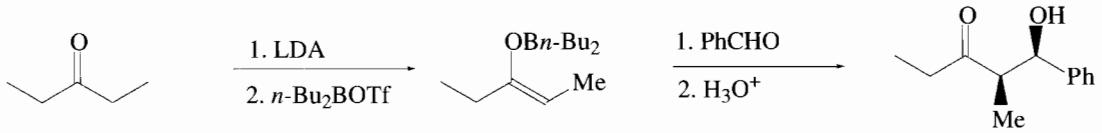
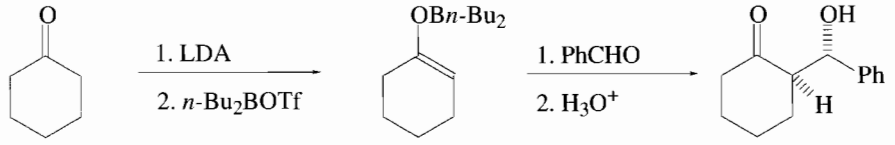
threo (anti) diastereomer, **375**. Transition state **372** leads to the erythro (syn) aldolate **376**. Likewise, (*Z*)-enolate **370** has two transition states, **373** and **374**. Transition state **373** leads to the anti- diastereomer (**375**) and **374** leads to the syn diastereomer **376**. When lithium enolates (M = Li), the reaction is highly diastereoselective if R^1 is sterically demanding (R = *tert*-butyl). When R^1 is relatively small, the diastereoselectivity is diminished. Examining boron enolates shows the B—O bond to be shorter than the O—Li bond, and this maximizes stereocontrol in a kinetic aldol process. The (*Z*)-enolate of 3-pentanone (**377**, R^1 = ethyl in **370**, L = *n*-butyl) condensed with benzaldehyde to give a >97:3 preference for the syn- diastereomer, **378**.[223] This clearly suggests transition state **374** as the lowest energy pathway. When R^1 is *tert*-butyl (**370**, L = butyl), the preference for the syn diastereomer was >97:1. For cyclohexanone enolate **379** (locked into the (*E*) geometry), the reaction with benzaldehyde gave primarily the anti diastereomer (**380**, 33:67 syn/anti).[220] A Zimmerman–Traxler-like model also is useful for predicting the diastereoselection in boron enolates as well as lithium enolates.

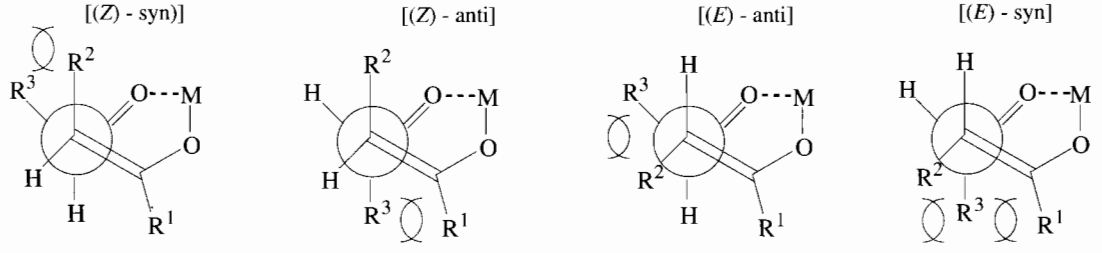


377 **378**



379 **380**

9.5.A.iv. The Evans' Model. It is known that (*Z*) enolates are more stereoselective than (*E*) enolates even when R^1 is not large. The Zimmerman–Traxler model transition states **352–355** do not account for this observation. It has been suggested that the transition states are not chair-like, but skewed, as in **381–384**.[221] In this representation (*Z*) enolate **381** leads to the syn aldol. Similarly, (*Z*) enolate **382** gives the anti aldol, (*E*) enolate **383** give the anti aldol and (*E*) enolate **384** is the precursor to the syn aldol. The major steric interactions in this model are those for $R^1 \leftrightarrow R^3$ and $R^2 \leftrightarrow R^3$. For both (*Z*) and (*E*) enolates, the $R^1 \leftrightarrow R^3$ interaction favors **381** and **383**, respectively. The $R^2 \leftrightarrow R^3$ interaction is more important for the (*E*) enolate and

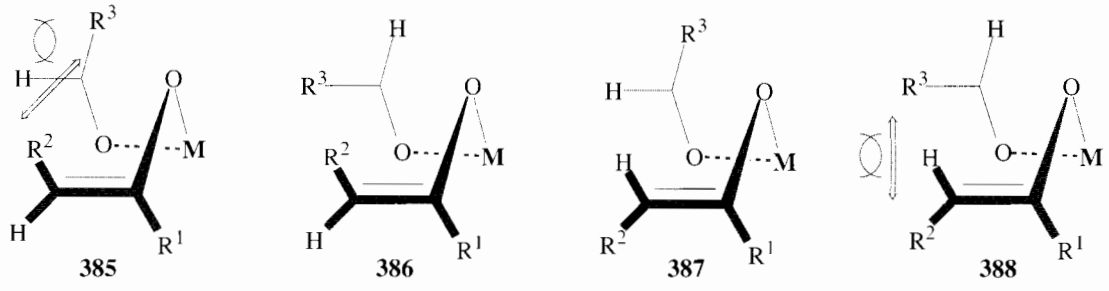


381 **382** **383** **384**

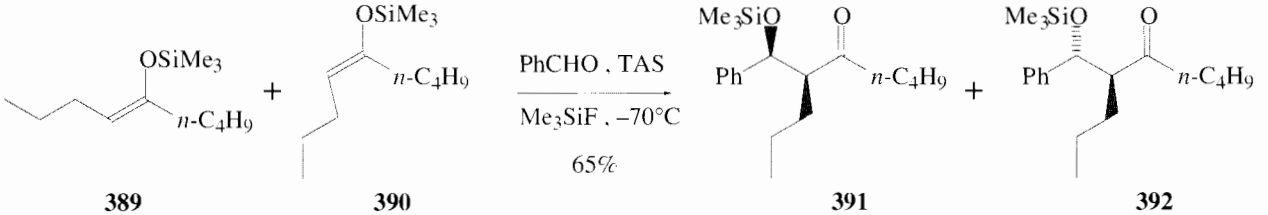
leads to **382** and **384** when R^1 is very large. The angle at which the reagents approach is obviously important for these transition states. It is assumed that the angle of attack of a nucleophile as it attacks a carbonyl is 110°

(sec. 6.6.A), the Bürgi–Dunitz trajectory (sec. 9.2.D).[46] This angle of attack brings R^2 and R^3 in **383** into close proximity and relieves the $R^1 \leftrightarrow R^3$ interaction. Similar results are observed for **382** and **384**, but to a lesser degree, which explains why (*E*) enolates show comparable $R^2 \leftrightarrow R^3$ and $R^1 \leftrightarrow R^3$ interactions unless R^1 is very large, and also accounts for the large effect of the R^2 group on the diastereoselectivity. As R^2 increases in size, transition states **381** and **383** become less important.

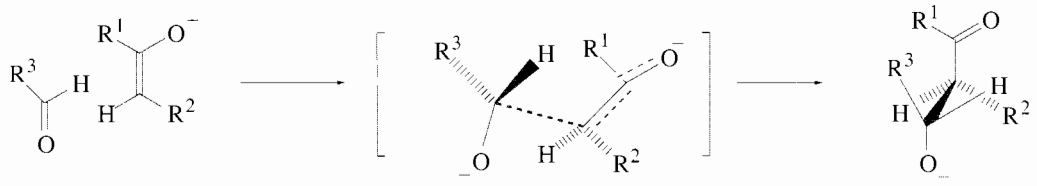
Evans et al. considered boat conformations **385–388**[222] as possible transition states, in addition to the chair conformations used in the Zimmerman–Traxler model. In these boat conformations, (*Z*) enolate **385** gives the syn aldol, (*Z*) enolate **385** gives the anti aldol, (*E*) enolate **387** gives the anti aldol, and (*E*) enolate **388** gives the syn aldol. A given (*Z*) or (*E*) enolate, therefore, has one or two chair transition states or one or two boat transition states that are energetically favorable for an aldol condensation. Only transition states **386** and **387** are considered important because of the significant $R^2 \leftrightarrow R^3$ interactions in **385** and **388**. As R^2 becomes larger, however, the (*Z*) enolate might favor **386** or the chair transition state. Boat transition states predict that increasing the steric bulk of R^2 in an (*E*) enolate will either have no effect on stereochemistry or increase selectivity for the anti aldolate. There is some evidence for a modest increase in anti selectivity with increasing the size of R^2.[223]



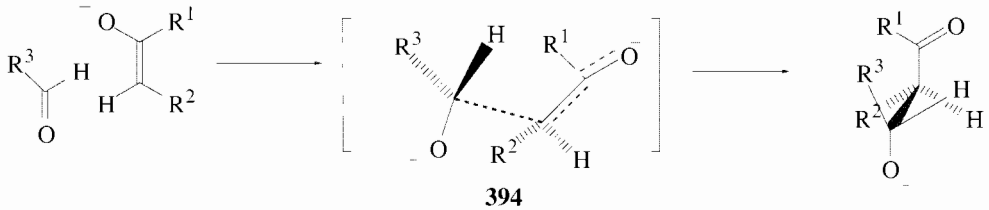
9.5.A.v. The Noyori Open-Chain Model. In the Mukaiyama reaction, the Zimmerman–Traxler and Evans' models are not satisfactory for predicting diastereoselectivity. Several open (nonchelated) transition states have been considered as useful models. The condensation reaction of carboxylic acid dianions with aldehydes indicated that anti selectivity increased with increasing dissociation of the gegenion (the cation, M^+).[224] When analyzing an aldol condensation that does not possess the bridging cation required for the Zimmerman–Traxler model, an aldehyde and enolate adapt an eclipsed orientation as they approach. Noyori reported syn selectivity for the reaction of a mixture of (*Z*)-silyl enol ether **389** and (*E*)-silyl enol ether **390** with benzaldehyde in the presence of the cationic tris-(diethylamino) sulfonium (TAS).[225] This reaction is clearly a variation of the Mukaiyama reaction, which does not usually proceed with good diastereoselectivity



389 **390** **391** **392**



393



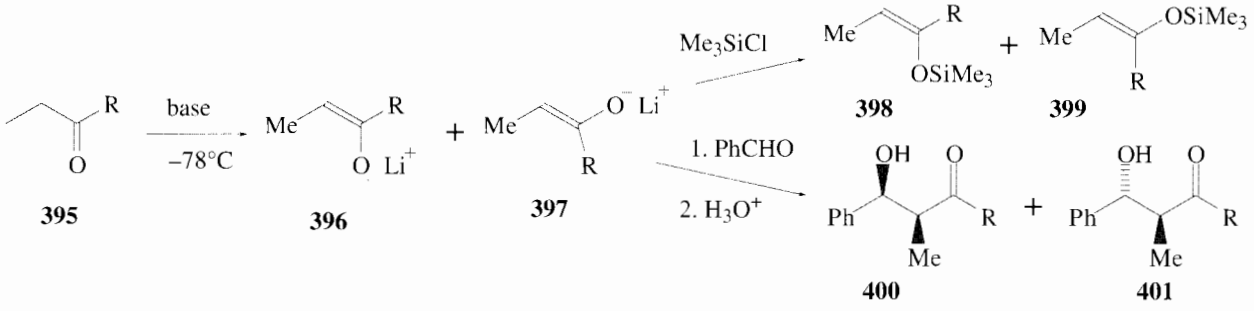
394

(sec. 9.4.C). Both the (*Z*) enolate and **390**, the (*E*) enolate, led to formation of **391**. It was clear that the 86:14 (**391/392**) preference for the syn diastereomer was operative independent of the enolate geometry.[226] These results are predicted with the open-chain model. The (*Z*) enolate will form a transition state such as **393**, which leads to the anti diastereomer. The (*E*) enolate will react via **394** to give the syn enolate. In both cases, the opposite orientation will lead to a significant $R^2 \leftrightarrow R^3$ interaction that destabilizes that transition state. This does not explain why both (*E*- and (*Z*) enolates lead to the syn-diastereomer (**391**). To explain that observation there must be some equilibration or isomerization during the course of the reaction, which will be discussed in Section 9.5.A.vi.

9.5.A.vi. Isomerization in the Aldol Condensation. With the models discussed in previous sections, it is clear that the orientation of the molecule as it approaches the enolate anion is controlled by steric effects. In simple diastereoselection processes, one observes moderate to good syn/anti selection depending on the steric demands of the enolate and carbonyl partner. Unfortunately, other processes are at work in this condensation that lead to variations in the syn/anti ratio. Heathcock showed the selectivity for a variety of lithium enolates derived from **395** with benzaldehyde (see Table 9.12).[19,227] The (*E*) and (*Z*) enolates (**397** and **396**, respectively) can be trapped with trimethylsilyl chloride to give silyl-enol ethers **399** and **398**, respectively. The observed **398/399** ratio is taken to be the ratio of (*Z*) and (*E*)-enolates originally generated from **395**. When the enolate mixture reacted with benzaldehyde, the syn aldol **400** and the anti aldol **401** were formed.[227] It is clear from Table 9.12 that the (*E*/*Z*) enolate ratio (taken to be **400/401**) is not the same as observed in the aldolate products. One explanation is that the enolate anions equilibrate under the reaction conditions. Another is isomerization during or after the aldolate forming step. A third explanation is that the enolate ratio is the same but the aldehyde adds from different faces of the enolate anion (see above).

The nature of the amide base had a substantial effect on the (*E*/*Z*) ratio of the enolate. In general, LTMP gave mainly the (*E*) enolate and LHMDS the (*Z*) enolate. As the size of R increases, the amount of (*Z*) enolate increases with LTMP and LDA, which is related to the conformation of the ketone immediately prior to deprotonation, using the Felkin–Ahn model (sec. 4.7.B). Conformation **402** is more stable than **403** for

Table 9.12. Stereoselectivity in Enolate Formation and Diastereoselectivity in the Aldol Condensation



395 **396** **397** **398** **399** **400** **401**

R	Base[a]	398/399	400/401
LiO	LDA		45:55
MeO	LDA	5:95	62:38
t-BuO	LDA	5:95	49:51
i-Pr_2N	LDA	81:19	63:37
	LTMP	52:48	68:32
H	MeLi	100:0	50:50
		0:100	65:35
Et	LDA	30:70	64:36
	LCPA	35:65	62:38
	LHDMS	66:34	77:23
	LTMP	20:80	66:34
i-Pr	LDA	60:40	82:18
	LCPA	59:41	75:25
	LHMDS	>98:2	90:10
	LTMP	32:68	58:42
t-Bu	LDA	>98:2	>98:2
	LHDMS	>98:2	>98:2
Ph	LDA	>98:2	88:12
	LCPA	>98:2	87:13
	LHMDS	>98:2	88:12
	LTMP	>98:2	83:17

[a] LDA = lithium diisopropylamide; LICA = lithium isopropylcyclohexylamide; LHMDS = lithium hexamethyldisilazide; LTMP = lithium tetramethylpiperidide

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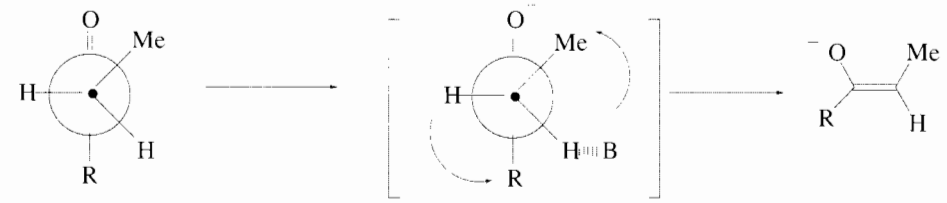
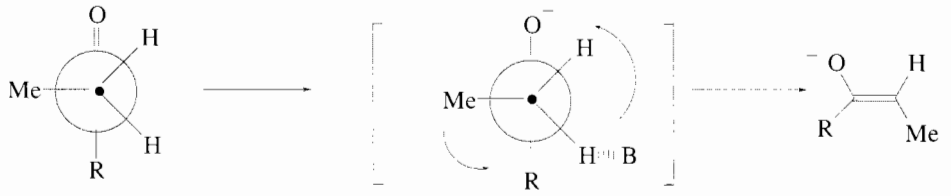
propanal by 0.8 kcal mol^{-1} (3.35 kJ mol^{-1}).[228] This difference is probably greater in ketones and esters where R is larger than H. This suggests that the (*Z*) enolate is preferred as R becomes larger, regardless of the base. The influence of influence of bases like LTMP, which give more (*E*) enolate, can be explained by a steric interaction between the approaching base (see **403**) and the methyl group in **402**. Although the interaction of the methyl group and the incoming base is minimized in **405**, the methyl↔R interaction is greater. This analysis assumes that the approach of the base and ketone is not along the axis of the C—H bond but over the face of the incipient enolate plane.[229] In reactions with benzaldehyde, (*E*) and (*Z*) enolates do not always exhibit the same degree of stereoselectivity.

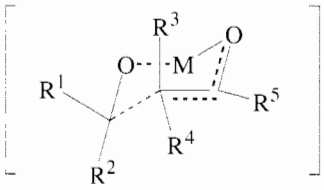


402 **403**



404 **405**

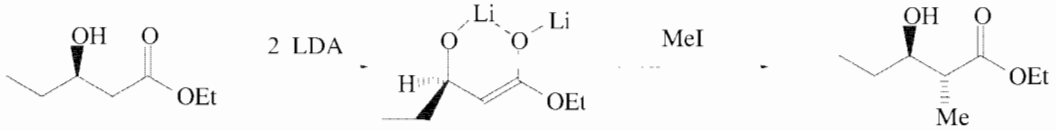
The results in Table 9.12 can be explained by the Zimmerman–Traxler-like transition state (**406**). The $R^2 \leftrightarrow R^5$ and $R^1 \leftrightarrow R^4$ interactions are very important. When R^5 is large (such as adamantyl) the (*Z*) enolate gives the syn aldol and the (*E*) enolate the anti aldol. When R^5 is small (Ph, Et), the (*Z*) enolate gives primarily the syn aldol. When R^5 = H, reactions of the (*Z*) enolate become stereorandom and lead to diastereomeric mixtures of products. When R^5 is small (Ph, Et) the (*E*) enolate usually gives a 50:50 mixture of syn and anti probably because the $R^1 \leftrightarrow R^4$ interaction balances the $R^2 \leftrightarrow R^5$ interaction. When R^5 = H or Me the (*E*) enolate is selective for the syn diastereomer.



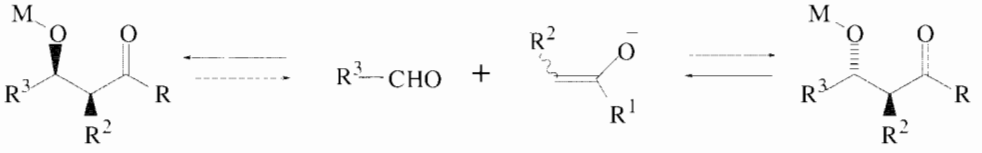
406

A complicating factor in the analysis is the observation that aldolates can undergo syn/anti equilibration by enolization or by reverse aldolization. Aldols such as **407** can be deprotonated to the dianion (**408**) and this undergoes alkylation with iodomethane to give the anti product (**409**), as shown.[230] This equilibration is clearly the basis of the aldol-transfer reaction discussed in **143** to **145** in Section 9.4.A.i. If **409** forms a new enolate, equilibration can lead to a mixture of syn and anti products. The primary mechanism for syn/anti equilibration appears to be reverse aldolization.[231] A retro-aldol will convert the syn diastereomer (**410**) into the aldehyde and enolate components, which can regenerate **410** or form the anti diastereomer **411**. Syn/anti equilibration can be much slower than reverse aldolization, as with the (*Z*) enolate of 2,2-dimethyl-3-pentanone).[227] Aldolates derived from the more basic ketone enolates are more likely to suffer reverse aldolization than aldolates derived from the less basic enolates of esters, amides, or carboxylate salts. Steric crowding in an aldolate promotes reverse aldolization. The metal is very important, and some metals form

stable chelates and generate aldolates that are resistant to reverse aldolization. Boron enolates, for example, do not undergo equilibration even at elevated temperatures. Lithium enolates equilibrate more slowly than other alkali metal enolates and potassium enolates equilibrate most rapidly.



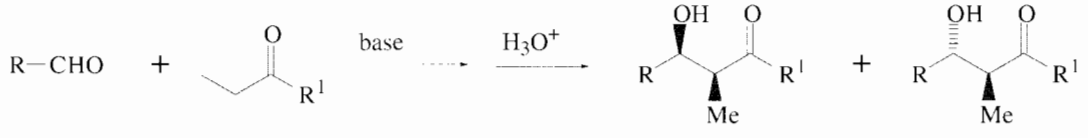
407 **408** **409**



410 **411**

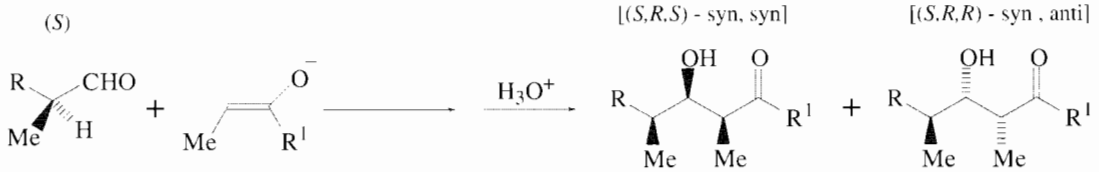
9.5.B. Selectivity with Chiral, Nonracemic Reactants

9.5.B.i. Diastereoface Selectivity[209,232] Heathcock defined three kinds of stereoselection for the aldol condensation: simple diastereoselection, diastereoface selection, and double stereodifferentiation.[209,224] Simple diastereoselection occurred when an achiral aldehyde and an achiral ketone reacted to give a mixture of syn and anti aldol products **412** and **413**, as discussed in the previous sections.



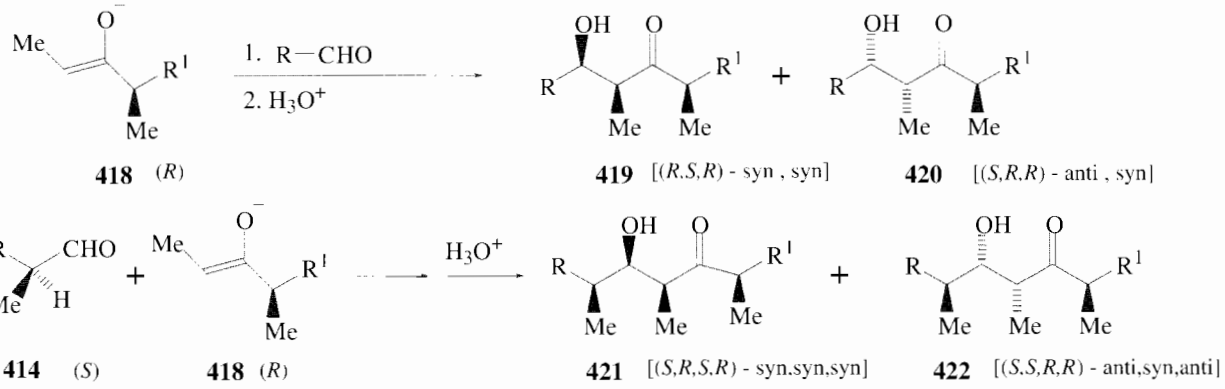
412 **413**

If either the enolate or carbonyl partner has an asymmetric center near the reactive center, this will influence both orientational and facial selectivity.[209,221] One variation is the reaction of an achiral enolate (such as **415**) with an aldehyde (or ketone) that possesses a stereogenic center (**414**). That center in **414** has an (*S*)-configuration and it is retained in the aldolate product. The syn and anti product distribution will be influenced by this chiral center, producing the (*SRS*) diastereomer (**416**) and the (*SRR*) diastereomer (**417**). A



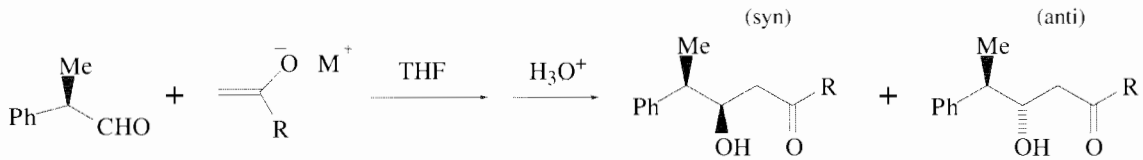
414 **415** **416** **417**

second variation involves an enolate possessing a stereogenic center (such as **418**) when it condenses with an achiral aldehyde or ketone. In **418**, the stereogenic center has an (*R*)-configuration, and reaction with the aldehyde leads to the (*RSR*) diastereomer **419** and the (*SRR*) diastereomer, **420**.



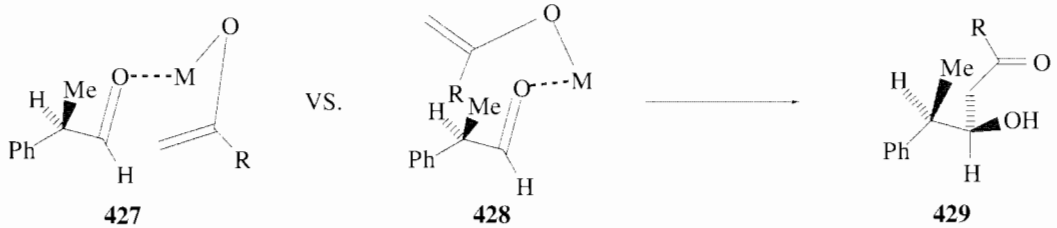
Double stereodifferentiation[233] results from the reaction of an enolate possessing a stereogenic center and an aldehyde or ketone that also has a stereogenic center, as in reaction of **414** with **418**. The (*S*) stereogenic center in **414** and the (*R*) stereogenic center in **418** do not change, and this leads to excellent enantio- and diastereoselectivity in the aldolate, producing the (*SRSR*)diastereomer (**421**) and the (*SSRR*) diastereomer (**422**). In all cases, improvement in diastereoselection arise from factors that effect the orientation of the reaction and the face from which the two reactants approach. For simple diastereoselectivity, steric factors influence the orientation of the aldehyde and enolate, leading to good syn/anti selectivity using the models previously described. When a chiral center is incorporated in the enolate or aldehyde, increased steric hindrance affects the orientation and leads to greater diastereoselectivity. The presence of the asymmetric center causes one face of the molecule to be more hindered than another. We will call this facial selectivity. As observed in Table 9.13,[234] when an aldehyde possessing a stereogenic center (such as **423**) was condensed with various enolate anions (**424**), in every case the syn-diastereomer (**425**) predominated over the anti-diastereomer (**426**).

Table 9.13. Influence of an Asymmetric Aldehyde on Facial Selectivity in the Aldol Condensation with a Metal Enolate



R	M	Temperature (°C)	425/426	Yield (%)
MeO	ZnBr	80 (PhH)	74:26	78
MeO	Li	–78	75:25	91
t-BuO	Li	–78	80:20	70
Me	Li	–78	76:24	89
Me	c-$(C_5H_9)_2B$	0	65:35	
t-Bu	Li	–78	80:20	80
Me_2N	Li	–78	78:22	67

In most cases, Crams rule (sec. 4.7.B) predicts the major isomer when the reaction partner (or partners) contain a chiral center.[235] To understand how this rule applies to orientational and facial selectivity, we must understand the transition state of the reaction (invoke the Zimmerman–Traxler model or one of the other models for predicting diastereoselectivity). The Zimmerman–Traxler model is used most often, and if it is applied to **423** and **424**, the syn selectivity can be predicted. The facial selectivity shown in **427** and **428** arises from the methyl group. In **428**, the enolate approaches from the face opposite the methyl, leading to diminished steric interactions and syn product (**429**). If the enolate approaches via **427**, the steric impedance of the methyl group destabilizes that transition state relative to **428**. In both **427** and **428**, a Cram orientation is assumed (see above) although other rotamers are possible. The appropriate rotamer for reaction therefore is that where R_L is anti to the carbonyl oxygen. Since the phenyl group is R_L, **427** and **428** are assumed to be the appropriate orientation for the aldehyde. If an aldehyde or ketone follows anti-Cram selectivity, this aldehyde orientation must be adjusted.



427 **428** **429**

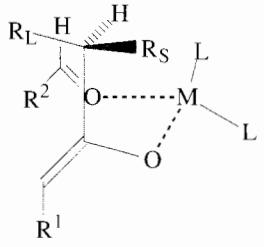
Cram selectivity (sec. 4.7.B) results from approach of the enolate over the less hindered face of the stereogenic center of the aldehyde (over the hydrogen , R_S) rather than over the larger methyl group (R_M). The phenyl group is taken to be R_L and it is anti to the carbonyl oxygen. This model assumes a reasonable steric difference between R_M and R_S (as in the Cram model), and if the steric difference between the two groups is small, there is little facial selectivity in the transition state and poor enantioselectivity in the final product.

430 **431** **432** **433**

M = Li		57	:	43
= Bu_2B	(ether)	57	:	43
	(CH_2Cl_2)	63	:	37
	(pentane)	64	:	36

Just as a stereogenic center in the carbonyl partner can induce selectivity, the presence of a stereogenic center in the enolate can also impart facial selectivity. When (*S*)-3-methyl-2-pentanone (**430**) was treated with LDA, chiral enolate **431** was formed.[236] Subsequent reaction with propanal gave the aldolates with a slight preference for the anti (*S, R*) isomer (**432**) over the syn (*S, S*) isomer (**433**). Once again, the methyl group induced a facial bias in the approach of the reagent, leading to attack on the face opposite the methyl. The

results were similar for both lithium and boron enolates. If the transition states for the boron enolates are examined (**434** and **435**),[237] the observed facial bias favors **434** rather than **435** as the least hindered transition state, *assuming an orientation of R_L in the transition state according to Cram's rule*, which leads to a preference for the (*S*,*R*) product.



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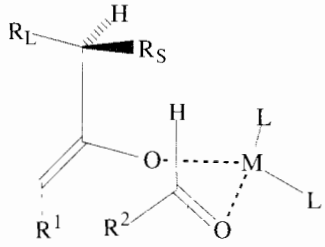
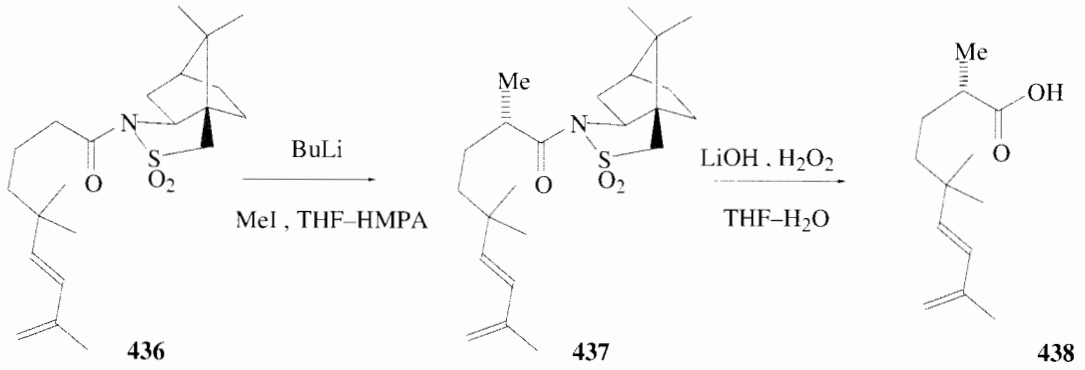
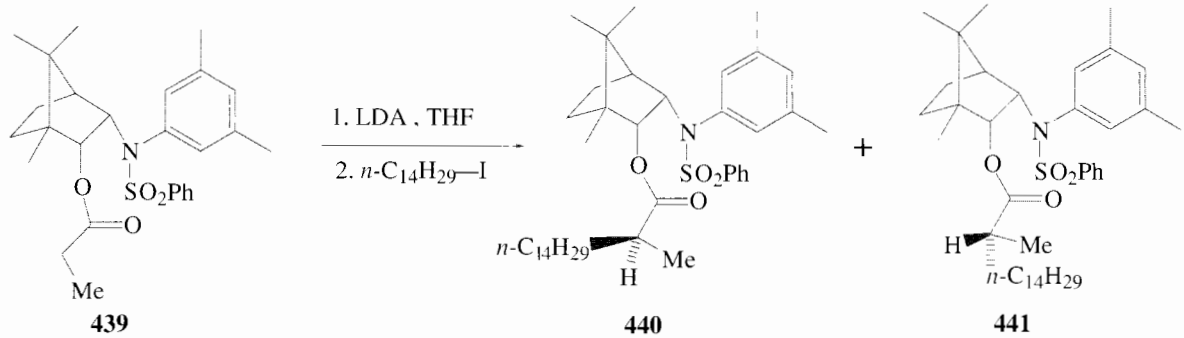


435

Diastereoface selection is observed when a chiral auxiliary is attached to either the enolates or the carbonyl substrate. A chiral auxiliary is an asymmetric group attached to an achiral substrate. The chirality of the auxiliary is transferred during a reaction (an aldol condensation) to the transition state and thereby to the final product. The auxiliary is then cleaved to give the normal aldolate product. Oppolzer et al. developed a sulfonamide alcohol auxiliary based on camphor in which an acid derivative is attached as a chiral ester[238] The auxiliary was removed by reduction of the ester group with $LiAlH_4$. A related sultam auxiliary was developed that gave good results. In Mori's synthesis of (1*S*,3*S*,7*R*)-3-methyl-α-himachalene,[239] the sex pheromone of the sand-fly *Lutzomyia longipalpis*, amide **436**, was prepared from the appropriate acid chloride and Oppolzer's sultam.[240] Treatment with butyllithium and iodomethane gave an 81% yield of **437**, and subsequent removal of the auxiliary by basic hydrolysis gave **438** in 67% yield and >99% ee.



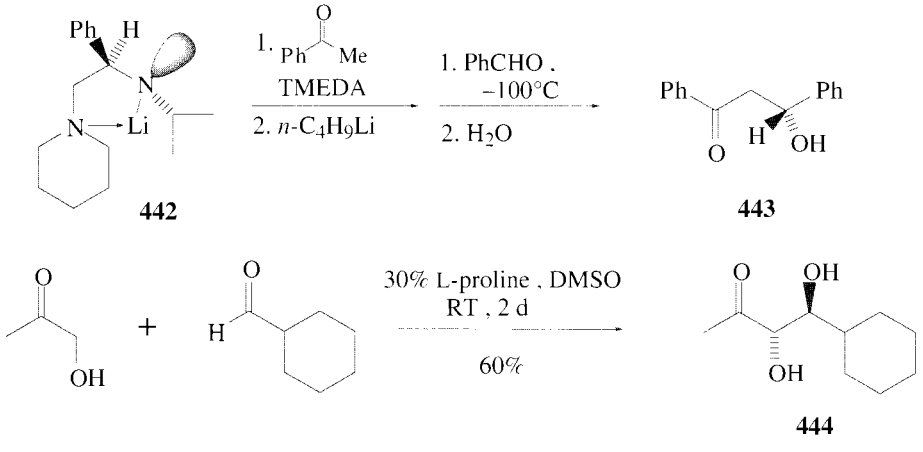
436 **437** **438**



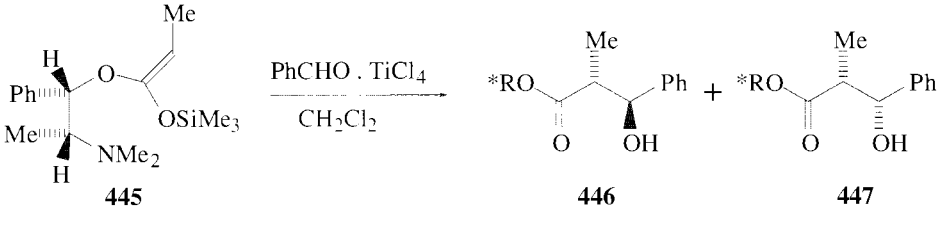
439 **440** **441**

Helmchen and co-workers achieved good asymmetric induction in the alkylation of ester enolates using the camphor based sulfonamide auxiliary in acetate **439**.[241] Alkylation of the enolate derived from **439** with iodotetradecane proceeded primarily from the less hindered face (away from the sulfonamide group, to give a 98:2 mixture of **440** and **441**. The diastereomer ratio was 98:2 favoring **440** and the yield of 74%.[241]

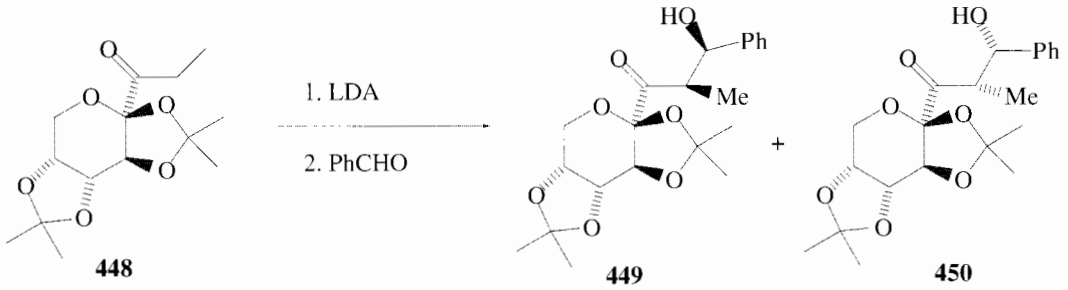
Using a chiral additive often generates a reactive species that has a transient auxiliary, is another method for inducing enantioselectivity into aldol-like reactions. This approach was used by Koga and co-workers,[242] where an achiral ketone such as acetophenone reacts with a chiral, nonracemic base (**442**), in the presence of *N,N,N′,N′*-tetramethylenediamine (TMEDA), to form an enolate that is coordinated to a chiral complex. Reaction of this complex with benzaldehyde (at –100°C) leads to asymmetric induction in the final aldolate product (**443**), which is produced in 73% yield with high enantioselectivity for the (*R*)-enantiomer.[242] List showed that the addition of 30 mol% of L-proline induced an asymmetric aldol condensation between hydroxyacetone and cyclohexanecarboxaldehyde to give **444** in 60% yield, with >20:1 regioselectivity, >20:1 diastereoselectivity, and >100:1 enantioselectivity.[243] The use of chiral Lewis bases in the aldol reaction has been reviewed,[244] as have catalytic aldol reactions in general.[245]



The presence of a chiral auxiliary can influence the stereochemistry of products formed in a Mukaiyama reaction. A stereogenic center derived from a chiral amino alcohol was incorporated in the enol ether moiety (see **445**). When this reacted with benzaldehyde and $TiCl_4$, the alcoholate products were **446** and **447** (R* = the chiral auxiliary) The diastereoselectivity in this reaction was quite good (95:5 favoring **446**) and each product was formed with high enantioselectivity.[246] It is also possible to incorporate the stereogenic center into the starting material (a **chiral template**, as discussed in sec. 10.9).[247]

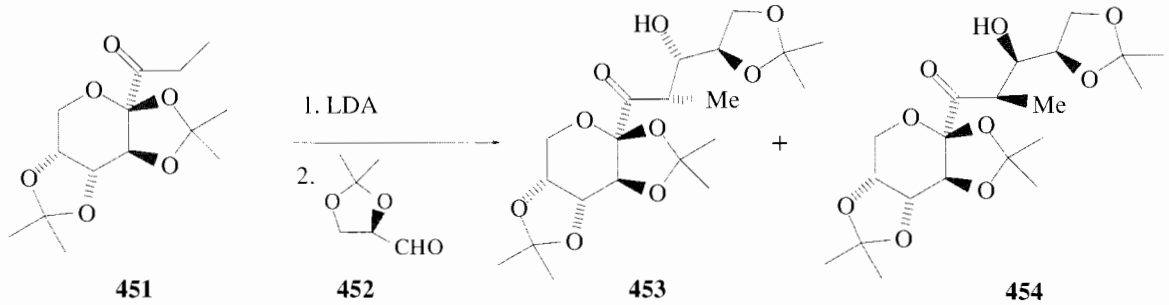


9.5.B.ii. Double Stereodifferentiation. Double stereodifferentiation employs a stereogenic center on both the enolate and the aldehyde or ketone. The presence of this chirality influences the facial and orientational

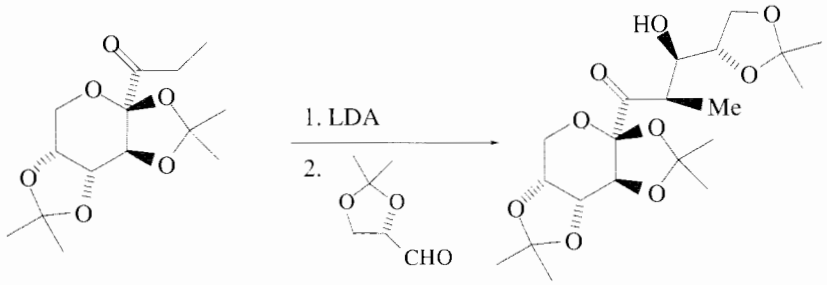


448 **449** **450**

selectivity. The two reactants may have incipient chirality whose stereogenic centers fit during the reaction (**consonant** double stereodifferentiation, matched) or that chirality can be opposed (**dissonant** double stereodifferentiation, mismatched).[223,248] This concept of matched and mismatched was introduced in the discussion of the **Sharpless asymmetric epoxidation** in section 3.4.D.i. The condensation of (*R*) aldehyde



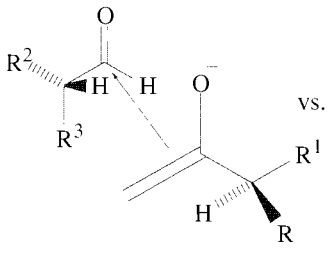
451 **452** **453** **454**



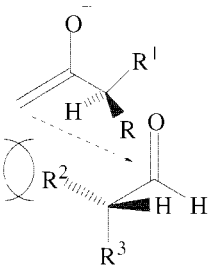
455 **456** **457**

452 or the S aldehyde **456** with enolates derived from ketone **448** illustrates this process.[248,209] The inherent selectivity for the syn isomer (**449** and **450**) is shown by the reaction of **448** with benzaldehyde. When **448** reacts with the mismatched aldehyde **452**, the selectivity is poor and this reaction pair leads to dissonance in the transition state and formation of a 62:38 mixture of **453** and **454**. Some anti diastereomers were also produced, which is quite different from the reaction of **448** with **456**, the matched aldehyde. Consonant stereodifferentiation provided excellent selectivity for a single isomer (**457**), produced in > 97% yield. The steric effects of the consonance versus the dissonance approach can be described in terms of the generalized Zimmerman–Traxler models **458** and **459**. In **458**, the R and R^2 groups are oriented away from each other

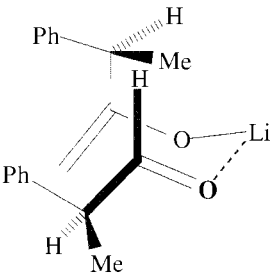
(matched), minimizing the steric interaction. In **459**, however, the R↔R^2 interaction is maximized (mismatched), destabilizing that transition state.



458 (matched , consonant)



459 (mismatched , dissonant)



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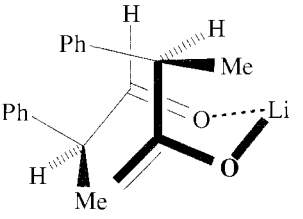
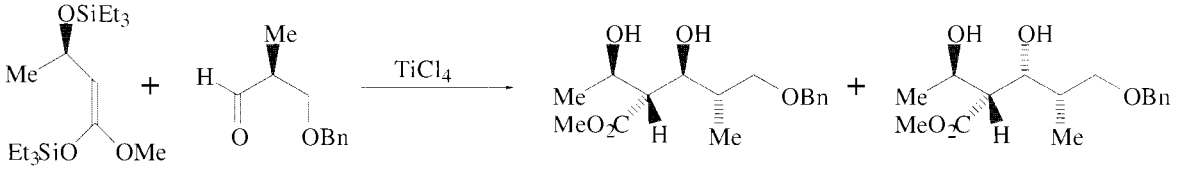


364

This selectivity is seen in a simple example involving the condensation of chiral aldehyde **460** with the chiral enolate derived from **461**. The matched transition state is **463** and the mismatched transition state is **464**. In **462** the methyl groups are oriented away from each other, which is much lower in energy than **464**. where the methyl groups interfere with each other (assuming a Cram orientation). If **462** is the preferred transition state, then the predicted product (**461**) is the anti diastereomer shown for this reaction.

460 **461** **462**

When applied to the Mukaiyama reaction, the principles of stereodifferentiation can lead to excellent diastereoselection and enantioselection. When silyl ketene acetal **465** was reacted with chiral aldehyde **466** in the presence of $TiCl_4$, a 75% yield of **467** and **468** was obtained as a 98:2 mixture, favoring **467**.[249]

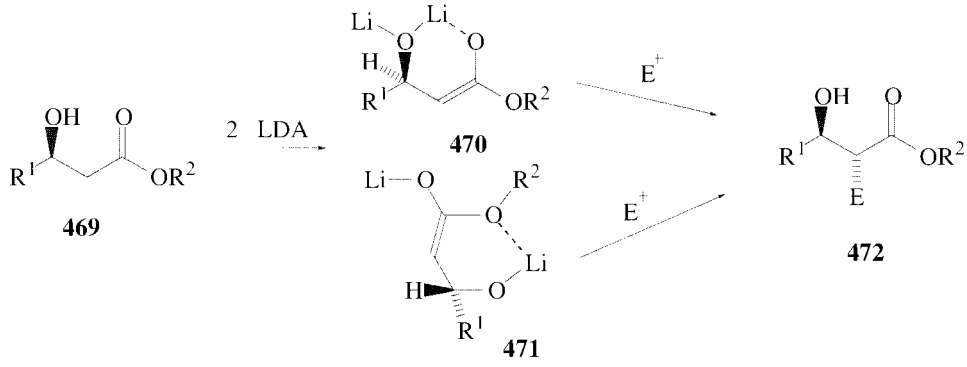


465 **466** **467** **468**

9.5.C. Chelation Control

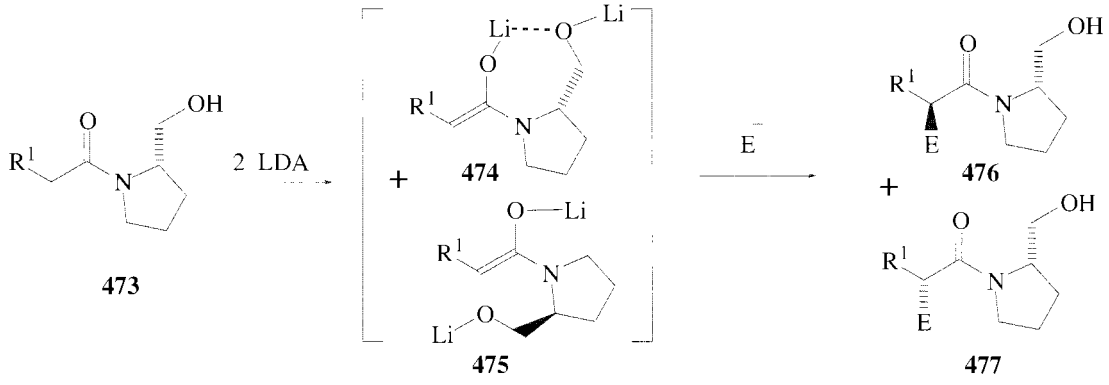
Chelating substituents influence the stereoselectivity of enolate condensation and alkylation reactions by altering the conformation of the enolate. When β-hydroxy-ester **469** was treated with 2 equivalents of LDA, the dilithio derivative was generated. This type of intermediate was seen in previous sections (see **408** and **442**) and in the dianion, lithium is chelated to both oxygens.[250,20] Reaction of the (*Z*) enolate (**470**) with an electrophile leads to its delivery from the less hindered face, giving the anti product **472**. In the (*E*)-enolate (**471**), the lithium can chelate both oxygens and delivery of the electrophile from the less hindered face (away from R^1) also gives **472**.[250,20] If the hydroxyl group is blocked (protected), the chelating effect is greatly

diminished or removed. Reaction of $OSiR_3$ derivatives of **469**, where the chelating effect is removed because there is no O—H group, with LDA/THF and an electrophile ,gave the opposite aldolate ratio and the (*E*/*Z*) ratio was > 90:10.[250,20] This particular model (structures **470** and **471**) was used by Kraus[250] to predict the stereoselectivity of an epoxidation reaction that gave glycidic esters (sec. 9.4.B.vi). The model was later applied to enolate alkylations and condensations as shown.[20]



Evans and Takacs prepared several chiral auxiliaries derived from amino alcohols such as valinol or prolinol. Prolinol amides such as **473** preferentially form the (*Z*)-enolate (**474**) over the (*E*)-enolate (**475**). Alkylation proceeds with chelation control and good diastereoselectivity (from the *si* face) to give the alkylated products **476** and **477**, favoring **476** as shown in Table 9.14.[251,20] The (*Z*) enolate (**474**) is preferred over

Table 9.14. Selectivity in the Alkylation Reaction of Prolinol Amide Enolates



R[1]	E[+]	Yield (%)	476/477
Et	MeI	98	94:6
Me	EtI	98	92:8
Me	*n*-BuI	99	94:6
Me	CH_2=$CHCH_2Br$	98	96:4
Me	$PhCH_2Br$	75	88:12
Me	*i*-BuI	84	97:3

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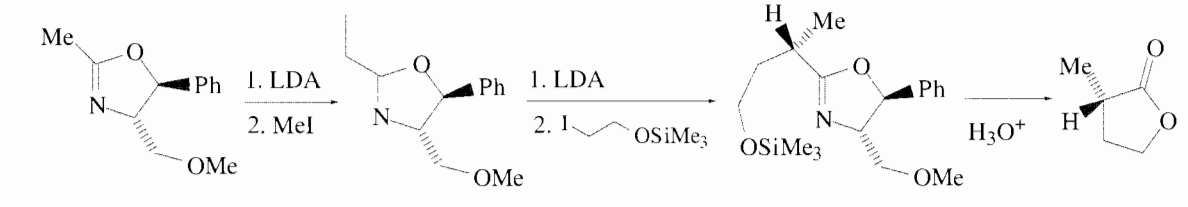
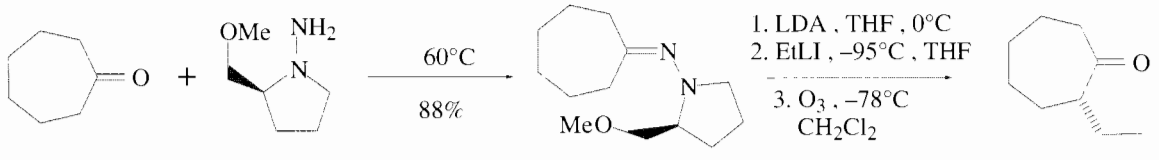
475 since **474** is chelated and **475** is not. Addition of the electrophile from the less hindered face of each enolate anion gives the observed products. Evans also prepared asymmetric carbamates that showed opposite diastereoface selectivity.[252] In both cases; small alkyl halides such as methyl iodide showed less stereoselectivity than the more sterically demanding benzyl bromide.

Diastereoselectivity is also observed in reactions of carbanions derived from imines and hydrazones, when those species contain a chiral center or a chiral auxiliary (sec. 9.4.F). Asymmetric imines can be used, and chiral oxazoline derivatives have also been prepared and used in the alkylation sequence (sec. 9.3.A). Meyers showed that chiral oxazoline **478** could be alkylated to give the ethyl derivative, **479**. A second alkylation generated the diastereomeric product **480**, and hydrolysis provided the chiral lactone (**481**) in 58% yield and with a selectivity of 70% ee for the (*R*) enantiomer.[253] As pointed out in Section 9.4.F.ii, hydrazone carbanions can be used for alkylation or condensation reactions. In a synthesis of laurencin, Holmes[254] prepared the asymmetric hydrazone **483** (prepared by Enders by reaction of cycloheptanone and the chiral hydrazine derivative called **SAMP**, **482**–*N*-amino-(2*S*)-(methoxymethyl)pyrrolidine)[255] and showed that treatment with LDA and reaction with iodomethane gave an 87% yield of the 2-ethyl derivative in >96% de. Ozonolysis cleaved the SAMP group to give (*R*)-2-ethylcycloheptane (**484**) in 69% yield. The enantiomer of **482** is also known (it is called RAMP, *N*-amino-(2*R*)-(methoxymethyl)pyrrolidine).



478 **479** **480** **481**



482 **483** **484**

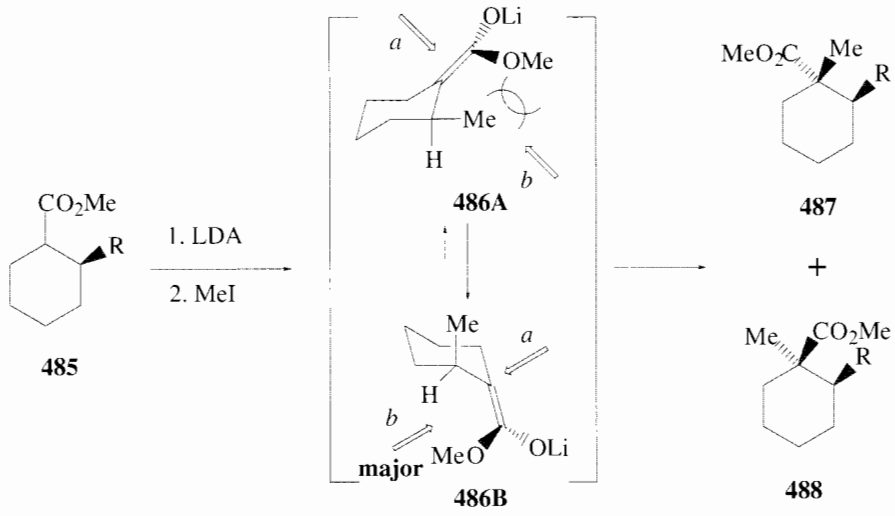
9.5.D. Diastereoselectivity in Alkylidene Enolates

Enolates derived from cyclic compounds such as cyclohexane carboxylic acid or cyclohexane carboxaldehyde generate enolates that are unique. These enolates have an exocyclic double bond that can exist as (*E*) and (*Z*) isomers. The facial and orientational bias in alkylation and condensation reactions of such enolates is influenced by the conformation of the ring it is attached to. Alkylidene cyclohexane enolates show a preference for equatorial attack, just as cyclohexanone derivatives do (sec. 4.7.C,D).

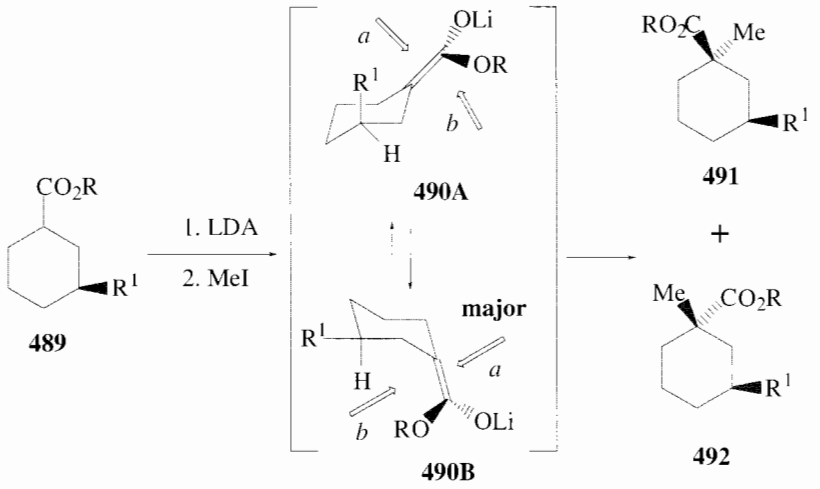
The position of a substituent on the ring also influences the selectivity. In 1,2-asymmetric systems such as **485**, treatment with LDA leads to an equilibrating mixture of enolates (**486A** and **486B**). The destabilizing Me↔OMe interaction in **486A** is alleviated in **486B** and reaction with iodomethane proceeds from the less

sterically hindered path *b* to give **487** rather than **488**.[256,19] When R in **485** was hydrogen, a 70:30 mixture of **487/488** was obtained, but when R was methyl, an 80:20 mixture was obtained, favoring **487**, which is generally opposite to results observed in the reduction of cyclohexanone derivatives (sec. 4.7.C). Another explanation for this difference is that enolates such as **486A** exist as aggregates (dimers or tetramers) that increases the blockage to path *a*.

A 1,3-disubstituted system is shown by ester **489**. Treatment with LDA generates the equilibrating enolates **490A** and **490B**, favoring **490B**. Using the acid as the enolate precursor (R = H in **489**), alkylation with iodo-

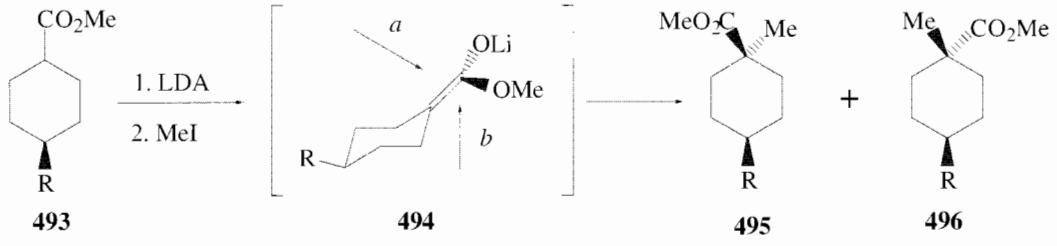


methane shows a slight preference for formation of **492** over **491** (reaction of the acid proceeded via formation of a dianion). When R^1 was methyl (R = H in **507**), however, a 52:48 mixture of **491/492** was obtained. The methyl ester of **489** (R = methyl), showed a distinct preference for **491** when R^1 was OMe (a 78:22 mixture of **491/492** was obtained). When R^1 = methyl and R = OMe), a 90:10 mixture of **491/492** was obtained.



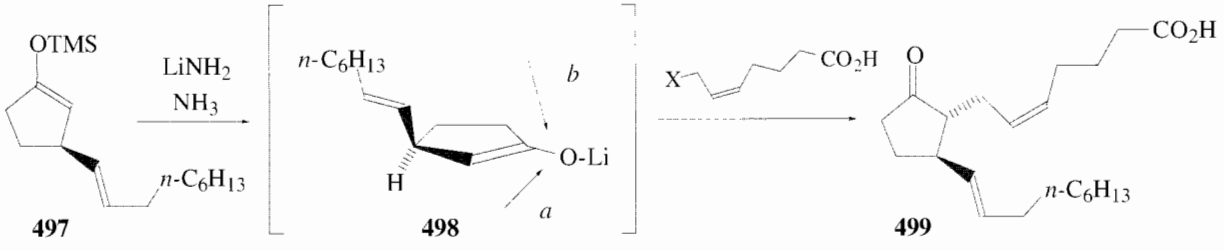
This corresponds to delivery of iodomethane from path *a* in **490B** (equatorial attack).[256b] Presumably, steric interactions with the OR group of the enolate moiety are minimal (or equal) in both conformations, making

the conformation with the equatorial R^1 group (**490B**) preferred. In the 1,4-disubstituted system (**493**), reaction with LDA generated the alkylidene enolate **494**. Alkylation with iodomethane proceeded via path *b* (interaction with the 1,3-diaxial hydrogens in **494** destabilizes attack along path *a*) to give the major product (**496**).[256b,257] An 84:16 mixture of **495**/**496** was obtained when R was either OMe or *t*-Bu. Addition of the electrophile favored equatorial alkylation (path *b* to give **495**) but a mixture of **495** and **496** was obtained.



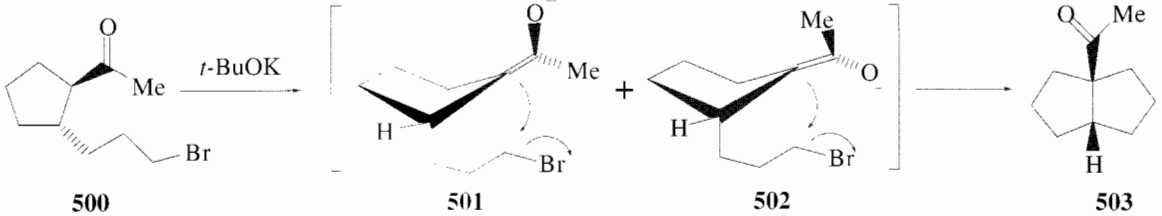
493 **494** **495** **496**

Five- and six-membered ring enolates with an endocyclic double bond also react to deliver an electrophile from the sterically less hindered face. Enolate **498** was obtained by treatment of **497** with lithium amide. Subsequent reaction with an alkyl halide led to delivery of the halide from the face opposite the alkenyl group (path *a*) and the trans product shown (**499**) was isolated in 60% yield.[258]. Approach via path *b* would have serious steric consequences, and that transition state is destabilized. Similar effects are observed with 3-alkylcyclohexanone derivatives.[259,257,258]



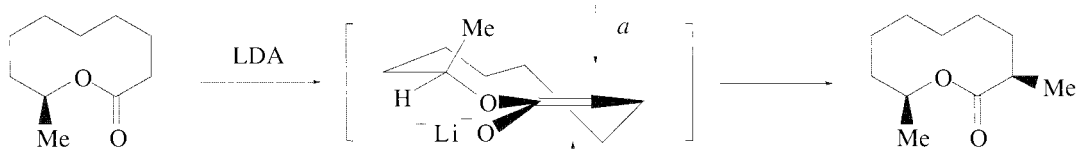
497 **498** **499**

Delivery of an electrophile to the less hindered face of an enolate also occurs in intramolecular alkylation reactions. When **500** was treated with potassium *tert*-butoxide, a mixture of (*E*) and (*Z*) enolates (**501** and **502**, respectively) was obtained. Intramolecular displacement of bromide generated a single isomer (**503**).[260] In this case, the electrophile can approach the enolate from only one face (the bottom or α face). Because of this conformational constraint, both (*E*) and (*Z*) enolates lead to the same product. In cyclopentanone and cyclohexanone enolates, an increase in the size of a facial blocking group increases selectivity. When that group was small, the selectivity decreased.



500 **501** **502** **503**

The preference for the lowest energy conformation of the enolate anion is seen in larger ring systems as well (sec. 1.5.B,C), leading to good selectivity in alkylation and condensation reactions. The methyl group provides only small steric encumbrance to approach of the electrophile in enolate **505** (derived from lactone **504** and LDA). The preferred mode of attack for this relatively stable conformation was from the top face (path *a*, pseudoequatorial attack) and gave the syn diastereomer (**506**) with >99:1 selectivity.[261]

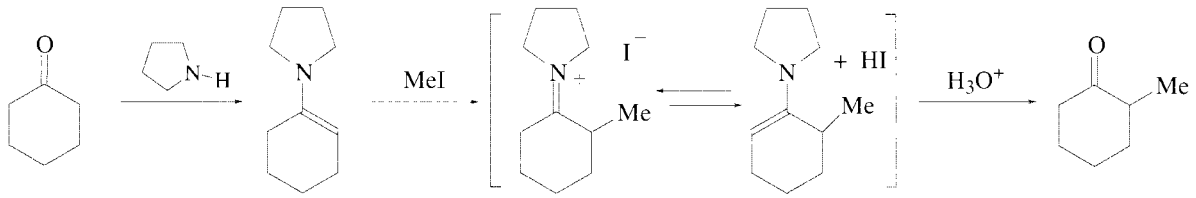


504 **505** **506**

9.6 ENAMINES

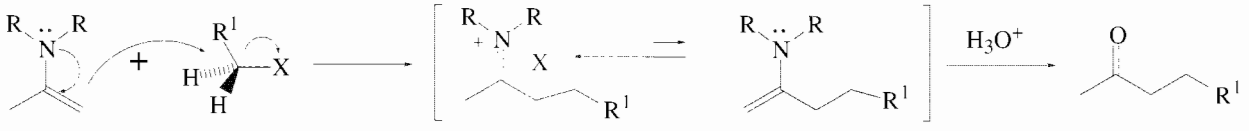
9.6.A. Preparation of Enamines

Any discussion of enolates must include an older method that is very effective in controlling the kinetic-thermodynamic product. In 1954, Stork[262] reported that cyclohexanone reacted with pyrrolidine to give the corresponding enamine (**507**),[263] a term introduced by Wittig and Blumenthal.[264] An enamine is essentially a nitrogen enolate and it can react with alkyl halides such as iodomethane to give an equilibrium mixture of the iminium salt (**508**) and the alkylated enamine (**509**).[262] Hydrolysis with aqueous acid led to loss of pyrrolidine and formation of 2-methylcyclohexanone. A more general sequence shows the behavior of a generic enamine (**510**) as a nitrogen enolate. Nucleophilic displacement of a halide by the β-carbon gives on α-alkyl iminium salt via an S_N2 process. The intermediate iminium salt (**511**) can isomerize under the reaction conditions to the less substituted enamine **512**, which is an equilibrium process and hydrolysis yields the corresponding α-alkyl carbonyl compound. Alkylation gives the best yields with reactive primary halides, since it is essentially an S_N2 reaction. This sequence is referred to as the **Stork enamine synthesis**.[262,265] Enamines are usually formed by reaction of a secondary amine with a ketone, in the presence of an acid catalyst.[266]



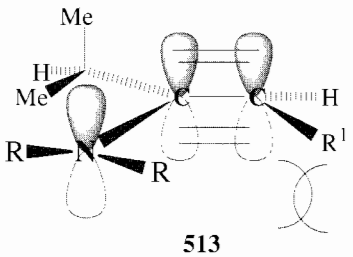
507 **508** **509**

Enamines such as **510** are bidentate nucleophiles, with both nitrogen and carbon functioning as nucleophiles.[267] Alkylation at nitrogen is a problem with reactive halides such as methyl iodide or allyl bromide and when the groups on nitrogen are small. Nucleophilicity usually parallels that of the unsubstituted amine.



510 **511** **512**

In general, the kinetic nitrogen enolate (the less substituted enamine) is formed due to reduced steric hindrance.[268] The enamine exists primarily as a planar species (**513** or **514**) in which the lone pair electrons on



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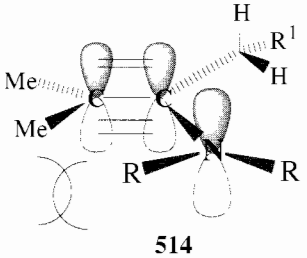
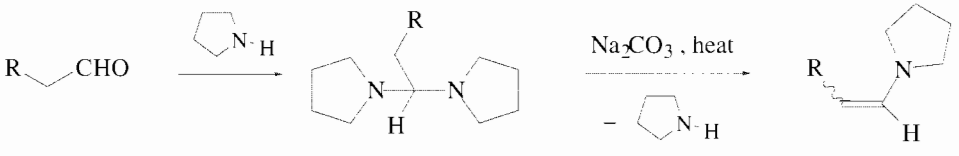


514

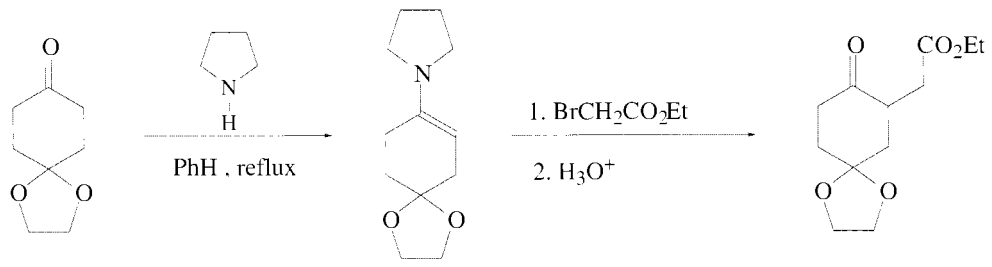
nitrogen are parallel with the π bond. If the steric interaction (R↔R[1]) in **513** is greater than the R↔Me interaction in **514**, there is a preference for that kinetic nitrogen enolate. When diethylamino or dimethylamino moieties are used, these interactions are small and a mixture of **513** and **514** is obtained. As R and R[1] increase in size, the steric encumbrance increases, favoring **514**. Pyrrolidine, piperidine, morpholine, and diethylamine are the most common amine precursors to an enamine. It is noted that when aldehydes such as **515** react with secondary amines, the reaction initially gives an iminium salt. Reaction with excess amine leads to aminal **516** rather than to the enamine. Treatment with a base such as sodium carbonate is required to induce elimination of the amine (pyrrolidine in this case) to give the enamine, **517**.[269]



515 **516** **517**

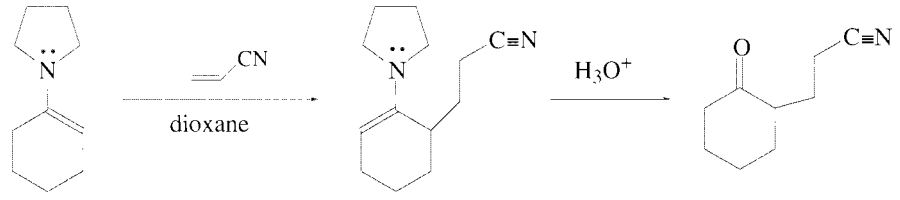
9.6.B. Reactions of Enamines

As noted above, enamines behave as nitrogen enolates in their reactions with alkyl halides, generating an iminium salt (see **511**) that can isomerize to the less substituted enamine (see **512**). Although this new enamine can react with additional halide, it is present in very small quantities in most cases. Therefore, overalkylation is not a serious side reaction. If an excess of the equivalents of halide is used, however, the second alkylation can be used to advantage. A typical enamine synthesis is taken from Carpenter's work, in which ketone **518** reacted with pyrrolidine to give **519**.[270] Reaction with ethyl bromoacetate and hydrolysis gave **520**. Enamines can react with aryl halides in addition to alkyl halides, but the aryl halide must be activated by the presence of electron-withdrawing groups since this substitution is formally a nucleophilic aromatic substitution (sec. 2.11.C).[271,268c] As noted above, pyrrolidine enamines are usually too reactive for acylation.

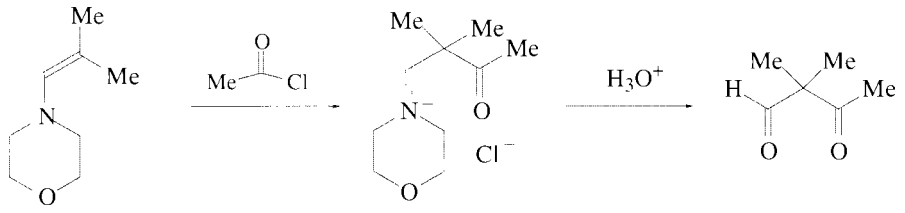


518 **519** **520**

Enamines react with α,β-unsaturated compounds almost exclusively by conjugate addition to give the corresponding substituted ester, ketone, or nitrile. Reaction of **507** with acrylonitrile, for example, gave a new enamine (**521**). Subsequent hydrolysis liberated the substitute ketone (**522**) in 80% overall yield from enamine **507**.[268a,272]



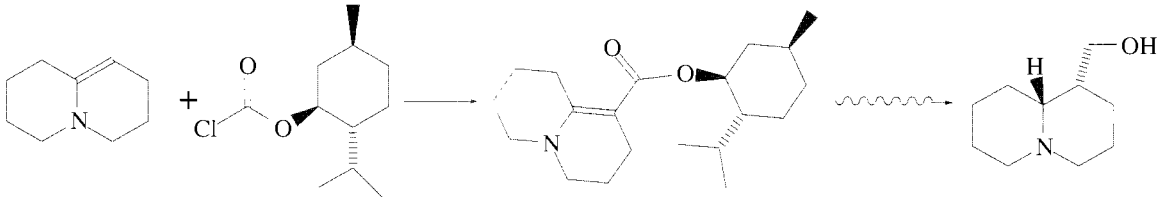
507 **521** **522**



523 **524** **525**

Enamines react very efficiently with acyl halides and the product, after hydrolysis, will be a dicarbonyl compound. The morpholine enamine of isobutryaldehyde (**523**) reacted with acetyl chloride to give keto-iminium salt **524**. Hydrolysis gave keto aldehyde **525** in 66% yield.[273] Enamines react with acid chlorides in the presence of a base to give a ketene, and this reacts via a thermal 2+2 cycloaddition to give a cyclobutanone derivative (see sec. 11.10.A). Although the potential for this being a competing reaction is real, it is usually not a significant problem in acylation reactions since the enamine is the only base in the system.[274] Morpholino enamines of cyclic ketones usually give the best yield of ketone product on reaction with acyl halides. A side reaction that is sometimes important is an aldol-like reaction between enamines and aldehydes, which are both in solution,[275] and is not a serious problem when the enamine is derived from a ketone.

Enamines have been used extensively in synthesis.[276,277] An example is the synthesis of lupinine (**529**) using the optically active chlorocarbonate **527** and octahydroquinolizine **526**.[278] The enamine product of the initial reaction (**528**) was isolated in this case and selectively reduced to lupinine (**529**).

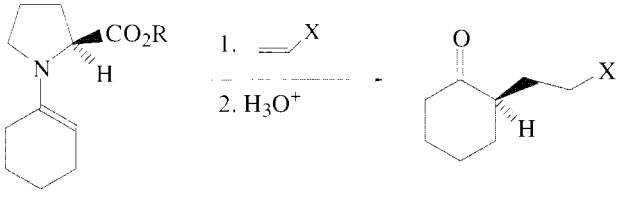


526 527 528 529

9.6.C. Asymmetric Enamine Syntheses

Asymmetric enamine derivatives are known and they generally give moderate-to-good diastereoselectivity.[279] The synthesis of lupinine (**529**) provided one example where an acid chloride substrate possessed a chiral auxiliary. An alternative approach is to prepare the enamine from a chiral amine. Yamada et al. prepared proline ester enamines such as **530**. In this case, the chiral enamine was used in a Michael addition with acrylonitrile or methyl acrylate to give **531**.[280] The yield of the ketone product was rather poor and the asymmetric induction (% ee) was modest. As shown in Table 9.15,[280] the % ee of **531** was in the range 15–59%. The chiral amine precursor to the enamine was synthesized from proline derivatives. When this chiral amine was distilled, extensive racemization occurred, and this is a major drawback to a practical use of this procedure. In addition, some racemization occurred during isolation of the enamine product (**530**). Failure to resolve these problems led to the use of crude amines and enamine products in all subsequent reactions.[281] It is possible to obtain good enantioselectivity with chiral enamines, if the chiral amine precursor is carefully chosen. Whitesell and Felman found that enamine **532** reacts with alkyl halides to give chiral ketones such as **533** with good optical yields (+ MeI = 83% ee; + *n*-PrI = 93% ee; + CH_2=$CHCH_2Br$ = 87% ee).[282]

Table 9.15. Asymmetric Conjugate Addition of Proline Ester Enamines



530 531

R	X	Reaction Conditions	% 531	% ee
Me	CN		34	
Et			36	
Me	CO_2Me		32	15
Et			38	21
t-Bu		Reflux 3 h	33	43
		40°C 3 h	22	53
		20°C 5 h	17	59

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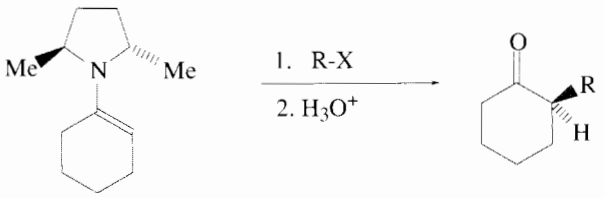


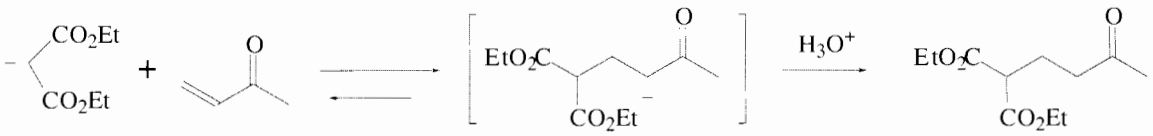
532 **533**

In general, the disconnections for enamine reactions are the same as those shown for enolates.

9.7. MICHAEL ADDITION AND RELATED REACTIONS

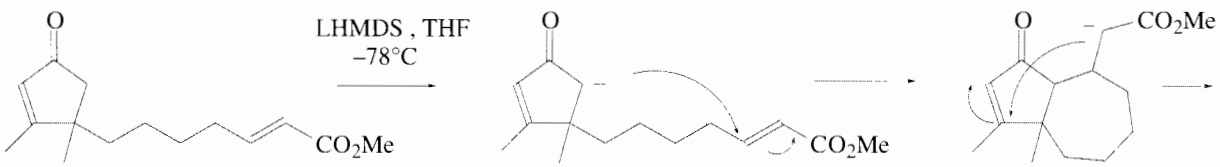
9.7.A. Michael Addition

The 1,4- (conjugate) addition[283e] of a carbon nucleophile to an α,β-unsaturated carbonyl system is well known, usually reversible, and usually referred to as **Michael addition**.[283] Enolates and carbanions are common partners in Michael additions.[284] The anion of diethyl malonate (**534**) reacts with MVK, for

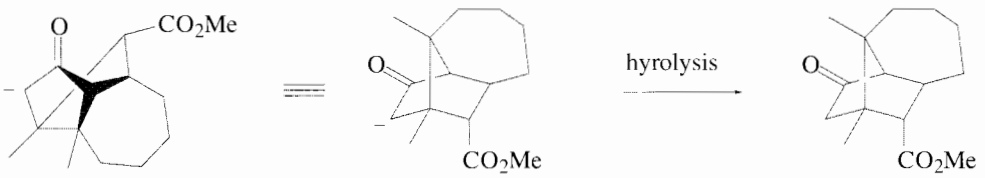


534 **535** **536**

example, to give an enolate product (**535**). When this enolate product is hydrolyzed, the final product is a keto-ester (**536**). Conjugate addition of most enolates are often reversible, and the relative stability of the enolate starting material (**534**) versus the enolate product (**535**) will determine the position of the equilibrium. The solvent is important, and alcoholic solvents usually promote the equilibrium. Many examples of



537 **538** **539**



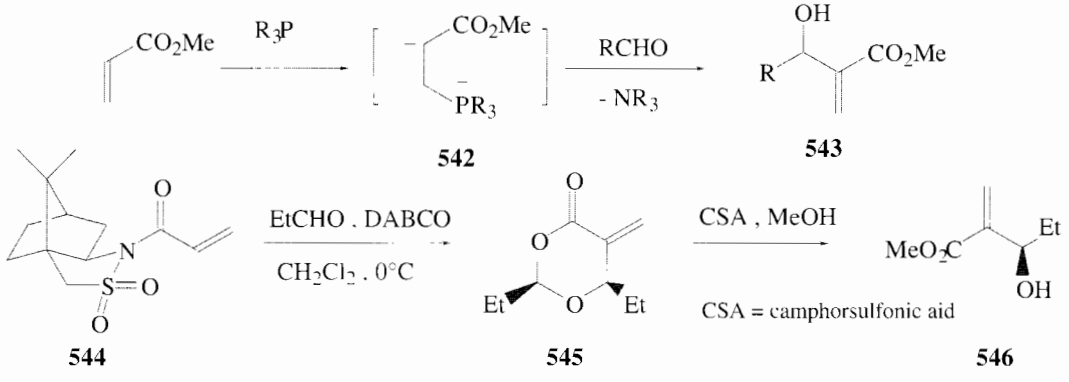
540 **541**

conjugate additions with Grignard reagents, organolithium reagents, or organocuprates were given in Chapter 8, and enolates also add to conjugated systems in a Michael fashion. Enantioselective Michael additions are well known,[285a] and a lanthanide-linked BINOL complex as been used effectively for the addition of malonate

anions to cyclohexenone.[285b] One synthetic example is taken from the Takasu et al. synthesis of culmorin,[286] in which treatment of **537** with LHDMS led to a double Michael addition to give **538** in 87% yield. Initial formation of enolate anion **538** allows a Michael addition to the conjugated ester to form a seven-membered ring in **539**. This newly formed ester enolate reacts with the conjugated ketone via a second Michael addition to give enolate anion **540**, which is drawn a second time to show the bicycloheptanone structure. Hydrolysis gave the final product **541**.

9.7.B. Baylis–Hillman Reaction

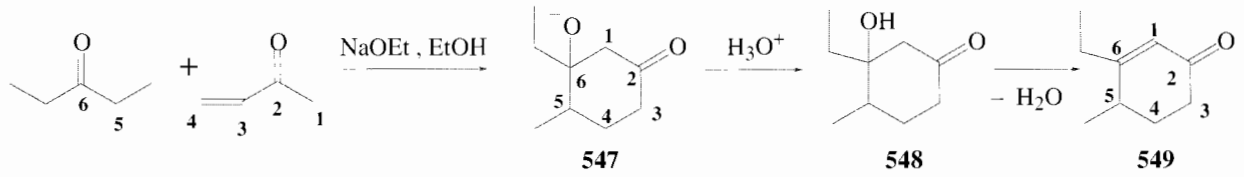
An interesting variation of Michael addition has been used to prepare highly functionalized acylate derivatives. In its fundamental form, an acrylate ester such as methyl acrylate reacts with an aldehyde in the presence of an amine or phosphine (such as tributylphosphine) catalyst. Presumably, Michael addition generates an enolate such as **542**, which condenses with the aldehydes and then loses the phosphine or amine to give the final product **543**. This transformation is known as the **Baylis–Hillman reaction**.[287] Aldol condensation, induced by the amine catalyst, can be a competing side reaction. Coupling reaction is often slow, but Leahy and co-worker found that using DABCO as the catalyst at 0°C, led to faster formation of Baylis–Hillman products, and in good yield. The reaction of methyl acrylate and isobutyraldehyde under these conditions gave a 69% yield of **543** (R = *i*-Bu) in only 8 hours.[288] At room temperature, this reaction takes about 1 week. A mixture of $TiCl_4$ and triethylamine in dichloromethane (at –78°C) generates chloromethyl derivatives and subsequent elimination induced by triethylamine or DBU gives the Baylis–Hillman product .[289] Samarium iodide (SmI_2) has also been used to mediate the Baylis-Hillman reaction.[290] Asymmetric Baylis–Hillman reactions are known as well.[291] Leahy[292] used Oppolzer's sultam[293] as an auxiliary. Amide **544** reacted with propanal under standard conditions to give an 85% yield of **545** in >99% ee.[292] Treatment of **545** with camphorsulfonic acid in methanol, in a second step, gave an 85% yield of (+)-**546**. Another camphor-based auxiliary has also been used with success.[294] A chiral acetylenic ester titanium alkoxide complex has also been used to generate chiral Baylis–Hillman products.[295]



9.7.C. Robinson Annulation[296a]

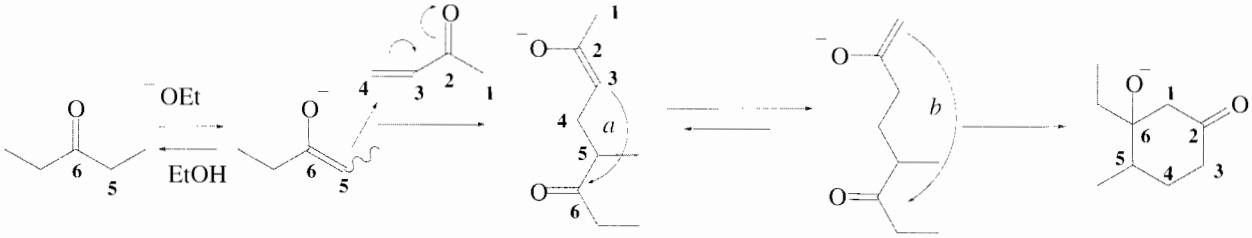
A major synthetic challenge in the 1930s through the 1950s was construction of various steroid molecules. One important route which emerged from this effort was the use of a Michael addition protocol to produce a

bicyclic ketone. This sequence soon came to be known as the **Robinson annulation**.[296,283d] The reaction can be illustrated by treatment of 3-pentanone with sodium ethoxide (equilibrating conditions) in the presence of MVK. Other bases have been used, including lanthanoid triisopropoxides, which behave as catalysts in this reaction.[297] The initial product is a cyclic alkoxy ketone (**547**), which gives alcohol **548** upon hydrolysis.



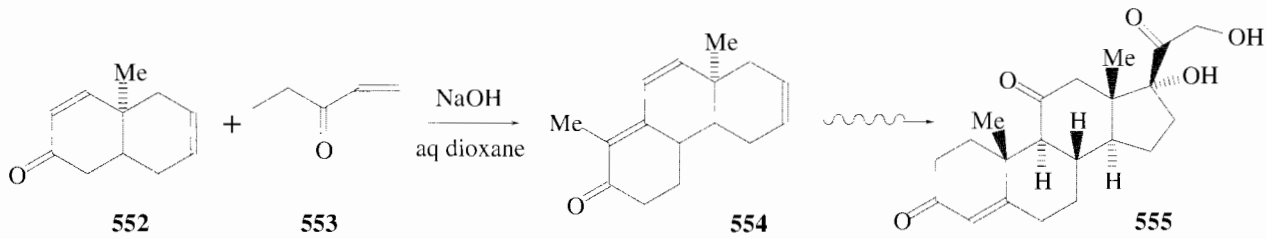
547 **548** **549**

This alcohol usually eliminates water with heating to give enone **549** as the final Robinson annulation product. The reaction conditions favor formation of a thermodynamic enolate, although this is irrelevant with 3-pentanone. Conversion of 3-pentanone to its enolate (**120**) was followed by Michael addition to MVK to give a new enolate product (**550**). This enolate could react with the carbonyl at C6 to give a four-membered ring (path *a*), but as discussed in Sections 6.6.A,B, the energy requirements for this reaction are relatively high and the process is energetically unfavorable. Under the equilibrium conditions of the reaction, a small portion of kinetic enolate **551** can be formed. An intramolecular aldol condensation at C6 is possible (path *b*) that generates a six-membered ring (**547**), and this is energetically more favorable than forming a four-membered



120 **550** **551** **547**

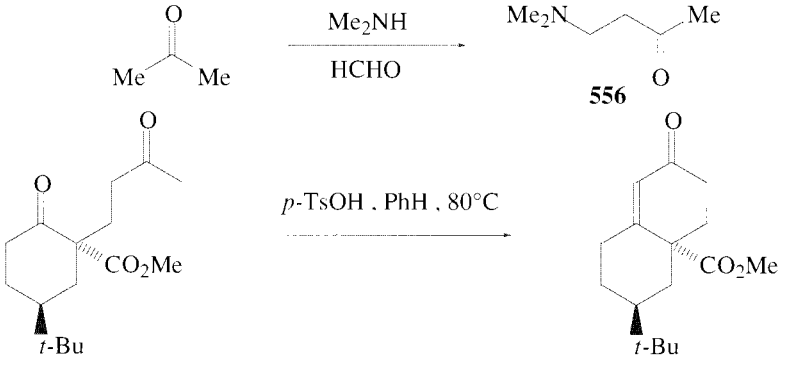
ring from **550**. When a cyclic ketone such as cyclohexanone reacts with MVK, Robinson annulation generates a bicyclic ketone.[296] This technique was used by Woodward et al. in a synthesis of cortisone (**555**).[298] A key step was the Robinson annulation of ketone **552** with ethyl vinyl ketone **553** to give **554**. There are many



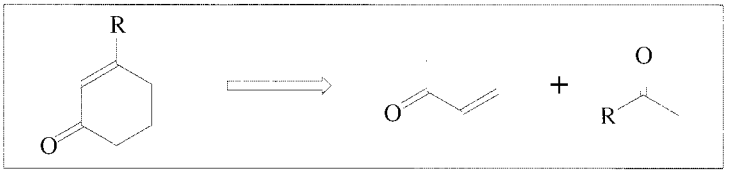
552 **553** **554** **555**

variations of the Robinson annulation that can be used to prepare synthetically useful products,[299,300] including some that use a protected conjugated ketone known as a **Mannich base** such as **556**. Under the basic conditions of the Robinson annulation, the β-amino ketone eliminates diethylamine to form the conjugated ketone *in situ*, which often avoids deleterious side reactions caused by the equilibrium condition

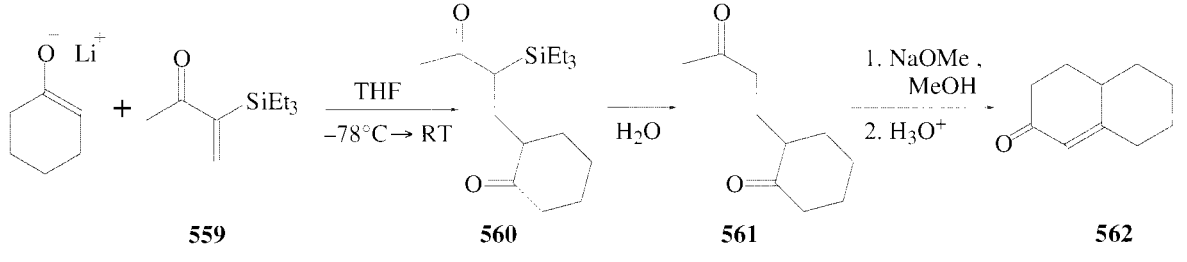
inherent to the Robinson annulation. A Mannich base is produced by a **Mannich reaction**,[301] where dimethylamine, for example, reacts with formaldehyde and acetone to give **556**.[301a,302] Acid-catalyzed Robinson annulation reactions are also known. An example is the conversion of **557** to **558** in good yield.[303]



The Robinson Annulation disconnection is



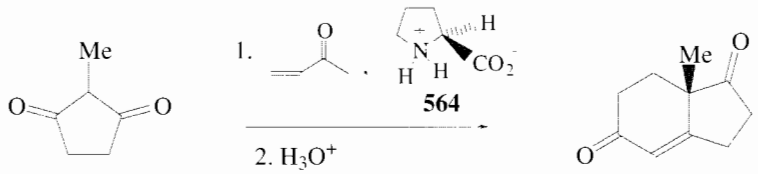
One problem with the Robinson annulation is the reversible nature of the initial Michael addition. One solution is to use a conjugated system that is particularly prone to Michael addition and forms the product, essentially irreversibly. α-Silyl vinyl ketones have been shown to be powerful Michael acceptors.[304] The lithium enolate of cyclohexanone reacted with conjugated ketone **559** to produce the Michael product, **560**.[304b] In this case, the initially formed Michael adduct was stabilized by the presence of the silyl group at the α-position, driving the reaction toward the product. Hydrolysis produced **561**, which was converted to the Robinson product (**562**) in 80% overall yield by treatment with NaOMe/MeOH under the requisite thermodynamic conditions.[304b] The need for this sequential process is justified when compared with normal treatment of cyclohexanone enolate with MVK under Robinson conditions, which gave adduct **562** in < 5% yield.



9.7.D. Selectivity in the Robinson Annulation

Many modifications of the fundamental Robinson annulation sequence have appeared over the years, one of which uses silyl derivatives such as **559**. An important modification uses chiral precursors or chiral

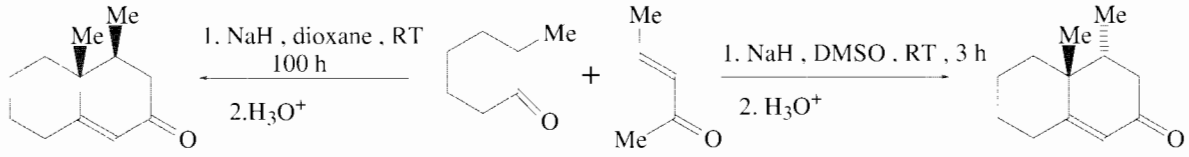
additives to give asymmetric induction in the Robinson annulation, either during the Michael addition, during the aldol cyclization or in both reactions. Excellent asymmetric induction has been obtained by using an asymmetric base such as (*S*)-(−)-proline (**564**) to generate the enolate. Hajos and Parrish obtained bicyclic ketone **565** by treating **563** with MVK and proline. The Robinson product (**565**) was isolated with an optical purity of 93.4%.[305] Proline has also been shown to act as a catalyst in an asymmetric Robinson annulation.[306] Similarly, Wynberg and Helder showed that addition of asymmetric catalysts such as *Cinchona* alkaloids gave optical yields of 5–25% ee for Michael additions of cyclohexanone derivatives,[307] but up to 71% ee in some cases.[308] Langstrom and Bergson first employed asymmetric catalysts in the Michael addition.[309] An antibody-catalyzed enantioselective Robinson annulation has also been reported.[310]



563 **565**

The stereochemistry of the Robinson annulation is influenced by the solvent.[311] The condensation of methylcyclohexanone and **566** with sodium hydride in dioxane led to >95% of **567** with syn relationship for the methyl groups. Similar reaction in DMSO, however, led to >95% of **568**, which had an anti relationship for those methyl groups. The change in stereochemistry was explained by a hydrogen transfer that is facile in the highly polar DMSO but not in dioxane.[311] In general, polar protic solvents tend to give the trans product whereas less polar aprotic solvents favor the cis product. A SmI_3 reaction has been reported that gives the Reformatsky product (see sec. 9.8.B) with high diastereoselectivity in aqueous media.[312]

The metal also plays a role. The presence of a highly covalent O—Li bond favors the trans product, but a more ionic O—Na or O—K bond, in alcoholic solvents, favors the cis.[311] The lithium species is less bulky, due to poorer solvation in the aprotic solvent. The protic solvent hydrogen bonds extensively with the ionic sodium species, leading to a large increase in the relative size of the alkoxide moiety. This bulky group influences the geometry of the intermediate and leads to an increase in the cis product.[311]



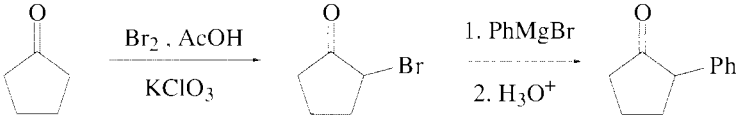
567 **566** **568**

9.8. ENOLATE REACTIONS OF α-HALO CARBONYL DERIVATIVES

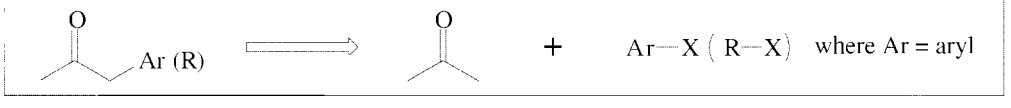
9.8.A. α-Halogenation

Several reactions formally involve enolates, but the course of the reaction is altered by the presence of reactive functionality. The **Darzens' glycidic ester synthesis** discussed in Section 9.4.B.vi is one example.

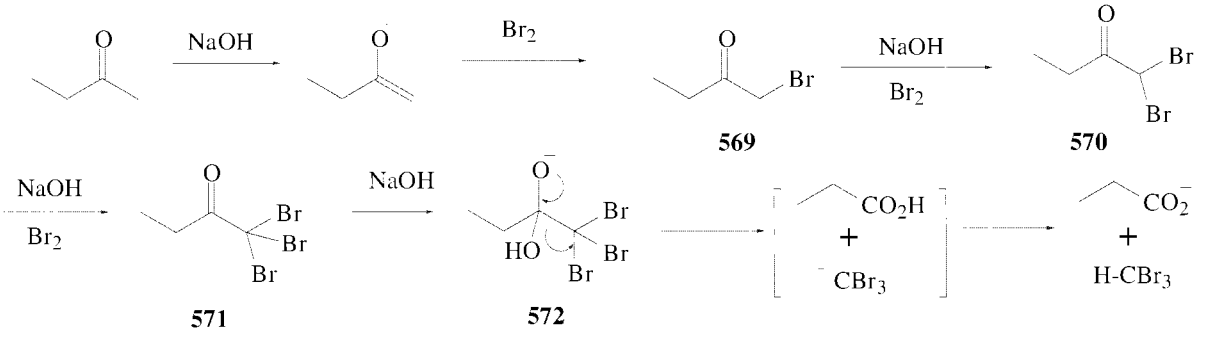
Another involves the formation of α-halogenated ketones. Treatment of a ketone with X_2 or NXS (X = Cl, Br, I) usually gives the α-halo ketone directly, as in the conversion of cyclopentanone to 2-bromocyclopentanone.[313] When there is the possibility of forming kinetic and thermodynamic products, the thermodynamic product usually predominates. In the synthesis of this α-bromoketone, $KClO_3$ oxidized the HBr byproduct back to Br_2. A serious problem in the halogenation is further reaction of the product with the halogen to give an α,α-dihalo compound. The presence of the first halogen promotes further enolization and polyhalogenation is often a serious problem. Halogenation of silyl enol ethers gives a good yield of monohaloketone.[314] Cupric (Cu^{2+}) salts such as $CuCl_2$ and $CuBr_2$ are often added to convert a ketone to α-chloro or α-bromo ketones.[315] The presence of the halogen modifies the bond polarity of the molecule so that the halogen is readily displaced by nucleophiles faster than nucleophilic addition to the carbonyl, as shown by the reaction of 2-bromocyclopentanone with phenylmagnesium bromide to give 2-phenylcyclopentanone.[316] This variation of the Grignard reaction is an excellent route to α-aryl ketones[309] (sec. 8.4.B.ii).



This leads to the interesting disconnection:



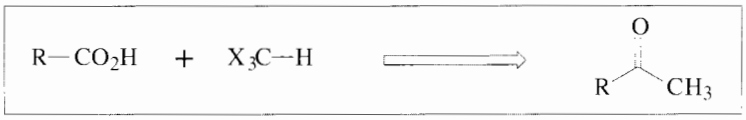
Polyhalogenation can be a severe side reaction in the formation of α-halo ketones but can be used to synthetic advantage in the **haloform reaction** (this has been called the **Lieben iodoform reaction**).[317] Reaction of 2-pentanone with sodium hydroxide gave the enolate, and in the presence of bromine the enolate displaces bromide from Br—Br to form **569**. The bromine makes the α-hydrogen more acidic and a second bromination occurs to give **570**, followed by a third bromination to give **571**. Nucleophilic acyl addition of hydroxide to all carbonyl derivatives (2-pentanone, **569** and **570**) is reversible up to this point. The Br_3C^- group in



571, however, is a sufficiently good leaving group that nucleophilic attack at the carbonyl leads to cleavage of the O=C—CBr_3 bond (via **572**) to produce butanoic acid and Br_3C^-. This carbanion rapidly deprotonates butanoic acid to produce the two final products, butanoate and a haloform (bromoform, $CHBr_3$). This

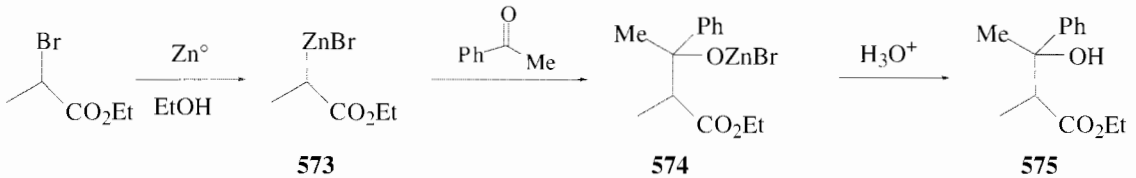
sequence is a synthetic method for oxidative cleavage of a methyl group attached to the carbonyl, complementing the known cleavage of carbonyls by Cr(VI) (sec. 3.8.C). This reaction also cleaves the H_3C—C bond of methyl carbinols [RCH(OH)Me] to give the corresponding acid and iodoform. When iodine is used rather than bromine, the cleavage of methyl ketones or methyl carbinols is referred to as the **iodoform reaction**. The iodoform reaction constitutes a classical test for the presence of a methyl ketone moiety or a methyl carbinol moiety in an unknown molecule.

The haloform disconnection is

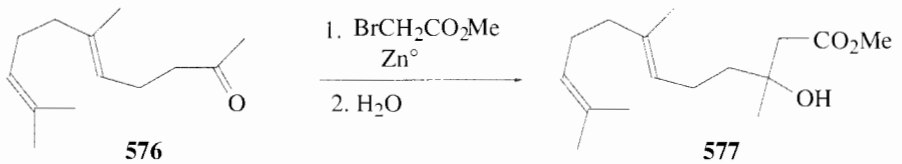


9.8.B. The Reformatsky Reaction

Another enolate-like reaction is the **Reformatsky reaction**,[318] which employs a nucleophilic organozinc intermediate, generated from an α-halo carbonyl and zinc metal. The organozinc reagent, in this case derived from ethyl 2-bromopropanoate (see **573**), attacks the carbonyl of a ketone or aldehyde (such as acetophenone) to give **574**. Hydrolysis liberates the condensation product, β-hydroxy-ester **575**. Preparation of the organo-zinc complex in the Reformatsky reaction can be a problem, and it often requires special preparation of the zinc (activated zinc). Activated zinc has been prepared by various procedures.[319] The use of ultrasound techniques produces a finely dispersed zinc that also facilitates the Reformatsky reaction.[320] As noted above, hydrolysis gives the hydroxy ester (**575**) to complete this two-carbon chain extension process. The organozinc reagent is generally less reactive than a Grignard or organolithium reagent and condensation reactions proceed well with aldehydes and ketones but are sluggish with esters. A synthetic example is Hoye's condensation of **576** and methyl bromoacetate to give a good yield of **577** in a synthesis of β-bromo-8-*epi*-caparrapi oxide.[321,322]

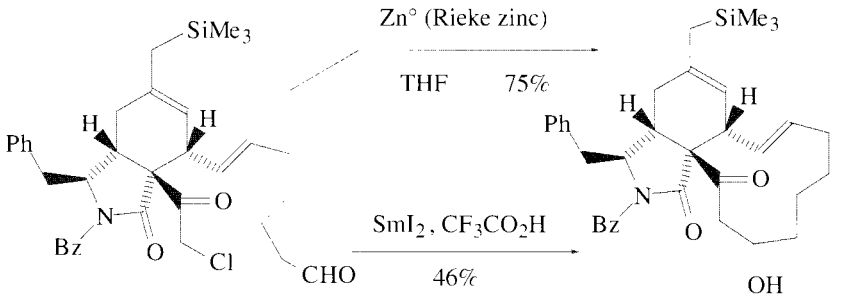


573 **574** **575**



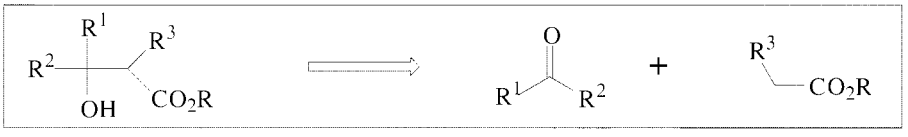
576 **577**

An intramolecular version of this reaction was used by Vedejs and Ahmad in a synthetic study of the cytochalasin ring system.[323] In this reaction, **578** was cyclized to give **579** as a 1:1 mixture of epimeric alcohols. The use of highly reactive **Rieke zinc**[324] led to a 75% yield of **579**. When samarium iodide (SmI_2) and trifluoroacetic acid were used for the cyclization,[325] a 46% yield of **579** was obtained as one diastereomeric alcohol.



578 **579**

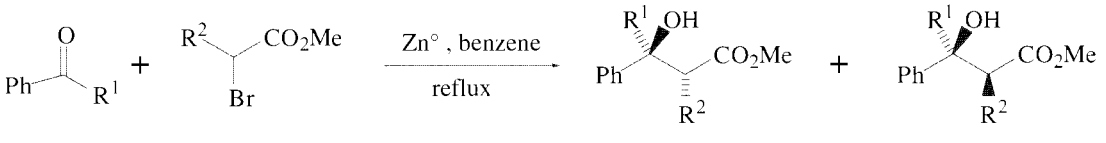
The Reformatsky disconnection is



The selectivity of the Reformatsky reaction is apparent in Table 9.16,[326,327] taken from Heathcock's work, which shows the syn/anti selectivity for the hydroxy ester products (anti product **580** and syn product **581**) resulting from reaction of α-haloesters with ketones and aldehydes.[327] Aldehydes generally show poorer selectivity than do ketones for formation of the anti product, **580**. The bromozinc aldolate products from ketones were shown to equilibrate under reaction conditions but those from aldehydes did not. Generally, increasing the size of R^2 in the α-halo-carbonyl derivative led to greater anti selectivity.

In more recent work, germanium catalysts such as $GeCl_4$ gave a highly diastereoselective Reformatsky reaction favoring the syn diastereomer.[328] Another syn selective reaction was reported using $TiCl_2$ and Cu.[329] Enantioselective Reformatsky reactions have also used chiral amino alcohols as additives.[330]

Table 9.16. syn/anti Selectivity in the Reformatsky Reaction

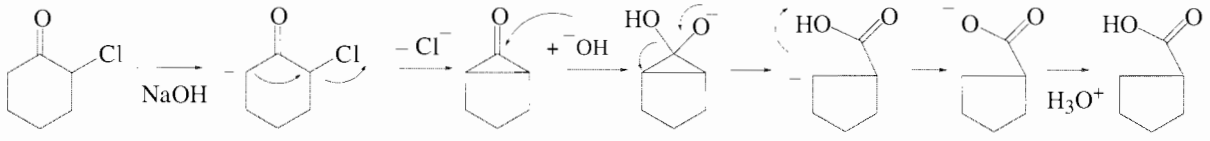


580 **581**

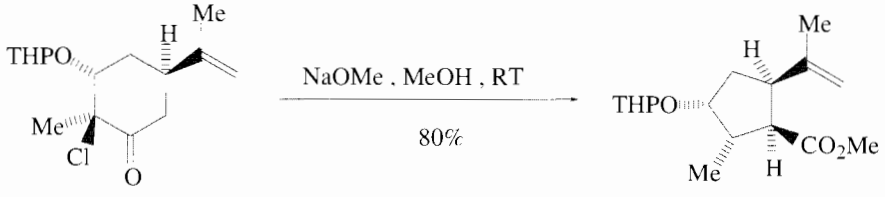
R1	R2	580/581
H	Me	37:63
H	Et	46:54
H	*i*-Pr	53:47
H	c-C_6H_{11}	50:50
H	*t*-Bu	69:31
H	Ph	76:24
Me	Me	67:33
Me	Et	70:30
Me	*i*-Pr	83:17

9.8.C. The Favorskii Rearrangement

There is a classical reaction of enolate anions derived from α-halo ketones that involves a rearrangement. In the **Favorskii rearrangement,**[331] sometimes called the **Wallach degradation**, an α-chloroketone such as 2-chlorocyclohexanone is treated with NaOH under thermodynamic conditions to form the enolate anion, **582**. Intramolecular displacement of chlorine leads to **583**, which is attacked by hydroxide to give the acyl addition product, **584**. Cleavage of the adjacent C—C bond leads to enolate **585**, which is protonated by the adjacent carboxylic acid to give carboxylate **586**. Hydrolysis gives the final product, cyclopentanecarboxylic acid. This reaction can be useful synthetically, as in Lee's synthesis of (+)-iridomyrmecin.[332] When **587** was treated with sodium methoxide in methanol at room temperature, an 80% yield of the Favorskii rearrangement product (**588**) was obtained as the methyl ester since the reaction was done in methanol.



582 **583** **584** **585** **586**



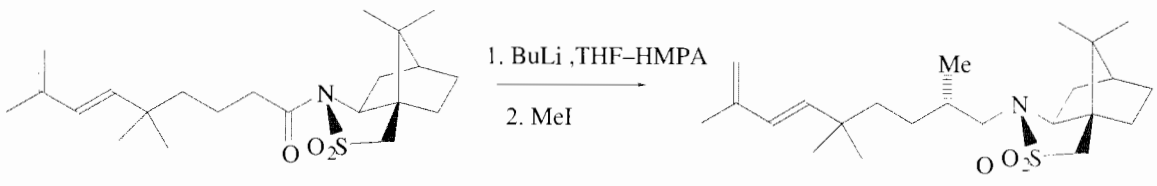
587 **588**

9.9. CONCLUSION

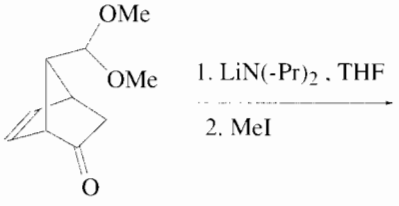
In conclusion, the reaction of enolates with alkyl halides and carbonyl compounds provides one of the most powerful and useful of all carbon–carbon bond-forming processes. Not only are a variety of synthetic products available, but the reaction can be made to proceed with excellent diastereoselectivity. In conjunction with the reactions of carbanions, nucleophilic methods constitute the largest single type of methodology for making new carbon–carbon bonds.

HOMEWORK

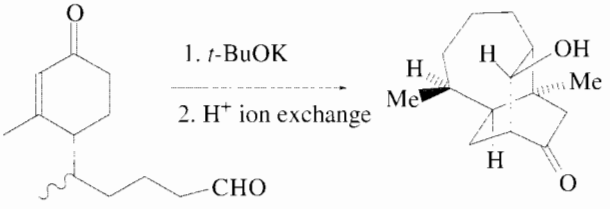
1. Explain the stereochemistry of this transformation.



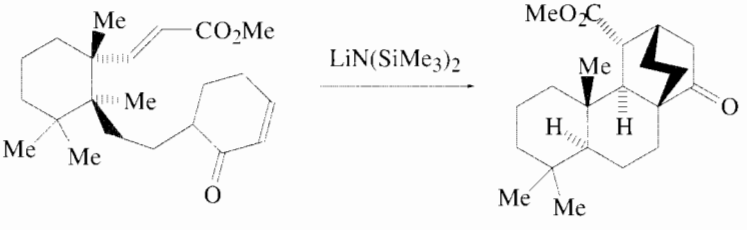
2. This reaction is regiospecific and highly stereoselective. Give the product and explain the selectively.



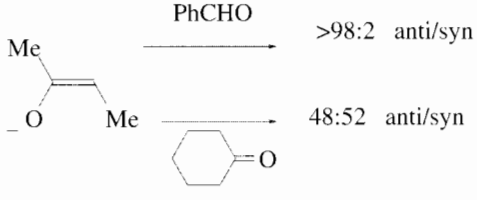
3. Give a mechanistic rationale for this process.



4. Give a mechanistic rationale for this process.



5. For the reactions shown, draw the syn and anti products. Explain why there is a difference in selectivity and why the anti product predominates with PhCHO but there is essentially a 1:1 mixture with cyclohexanone.

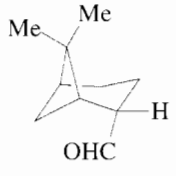


6. For the reaction of 3-pentanone and lithium diisopropylamide (-78°C, THF):

(a) Draw both (*E*) and (*Z*) enolates.

(b) Give the major product of the (*Z*) enolate when PhCHO approaches from the *re* face; from the *si* face. Show the Zimmerman–Traxler model for both approaches.

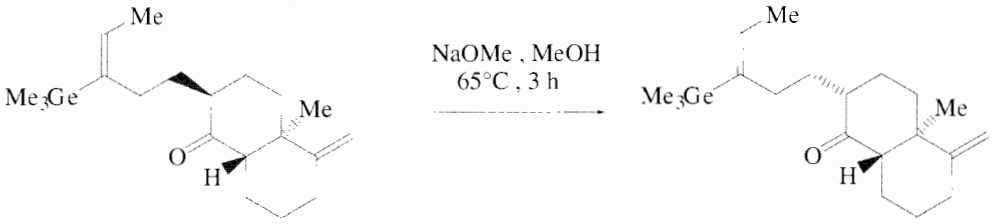
(c) Give the major product when the (*E*) enolate reacts with *A*, assuming *A* is chiral and nonracemic.



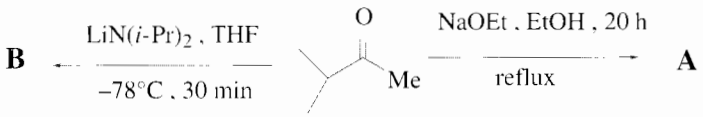
A

(d) Give the major product when the (*Z*) enolate reacts with chiral, non-racemic A.

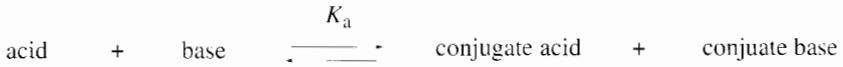
7. Explain the inversion of configuration for the alkyl side chain in this reaction.



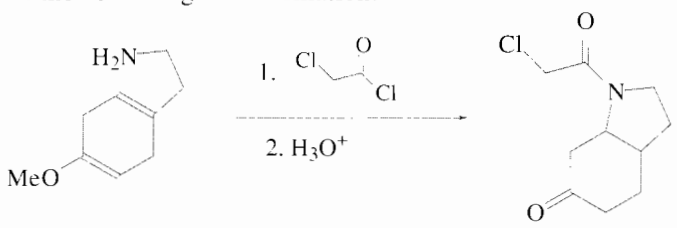
8. Enolate formation is an acid–base equilibrium process. For reactions A and B, discuss the relative acidity of all hydrogens in 3-methyl-2-butanone. Discuss the role of solvent, base, temperature and reaction time for reactions A and B.



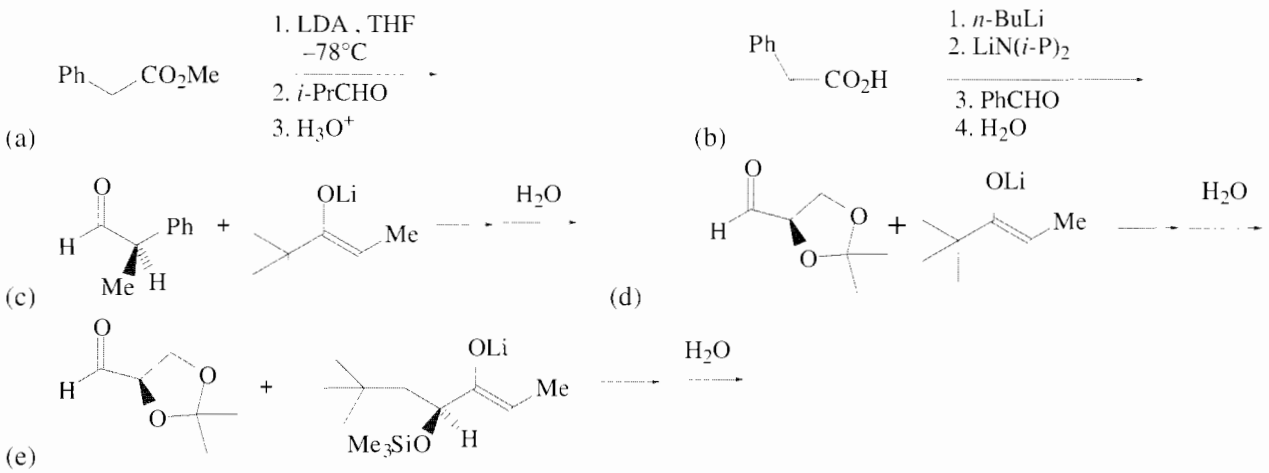
Write the acid-base equations for both A and B using the standard reaction shown.



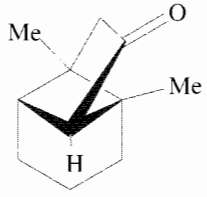
9. Explain the following transformation.



10. In each of the following reactions, predict the major diastereomer and show the Zimmerman-Traxler transition state:

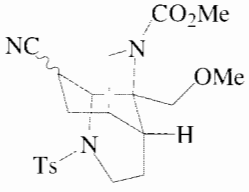


11. Give the major product and briefly explain the selectivity in the final product.



1. LDA , THF , –78°C
2. MeI
3. H_2O

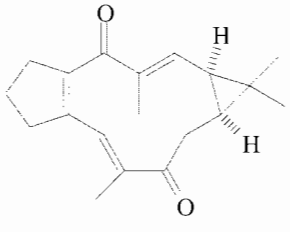
12. Predict the major product of this reaction with the correct stereochemistry, and justify your answer.



$KN(SiMe_3)_2$

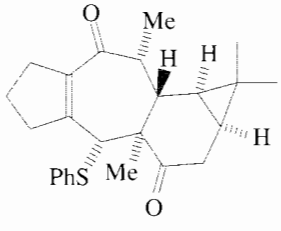
$(MeO)_2CH(CH)_9I$

13. Provide a mechanistic rationale for the following transformation.

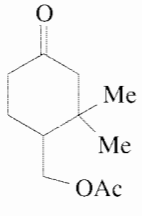


3 equiv PhSH
5 equiv K_2CO_3

MeOH , overnight



14. For each of the following, give all products. What is the strategic purpose of the first condensation with benzaldehyde? Compare and contrast routes A and B:



PhCHO

KOH , EtOH

I

p-TsCl

Pyridine

II

NaH , DME

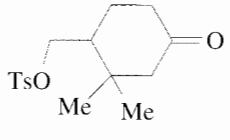
heat

III

KOH , HMPA
ethylene glycol

4-aminobutanoic acid , 195°C

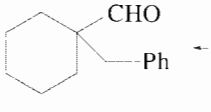
IV



NaH , DMF

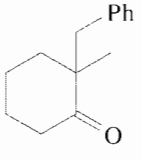
V + **VI**

15. Show a full synthetic sequence, with all intermediate products and reagents, for conversion of 1-methyl-1-cyclohexene into each of the molecules shown.

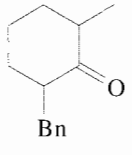


(c)

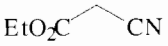
(a)



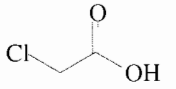
(b)



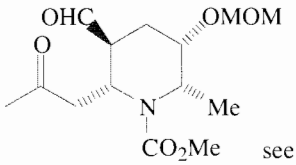
16. In each case, give the major product, with correct stereochemistry where appropriate.

(a) 

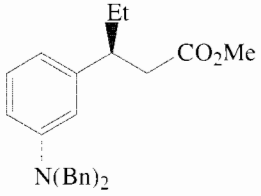
PhCHO , microwaves
P_2O_5 , piperidine
PhCl

(b) 

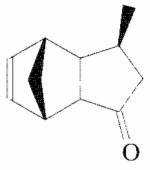
1. 2 equiv LDA , THF
2. Li , cat 4,4'-di-*tert*-butylbiphenyl
3. *t*-BuCHO
4. hydrolysis

(c) 

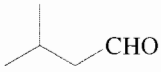
4 equiv DBU , PhH
reflux
see *J. Org. Chem.* ***1999***, *64*, 2182

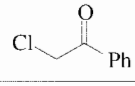
(d) 

1. LDA , THF , –78°C
2. acetyl chloride

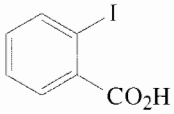
(e) 

1. NaH , dimethyl carbonate
2. NaOH , Bu_4NI , MeI

(f) 



aq LiOH , Bu_2O , 4°C
phase transfer catalyst

(g) 

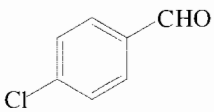
1. BH_3•SMe_2 , THF
2. MsCl, NEt_3, LiCl
3. $NaCH(CO_2Et)_2$
4. dilute H_3O^+

(h)

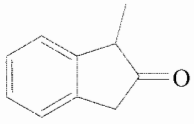
1.NaOEt , EtOH , reflux
2. H_3O^+

(i)

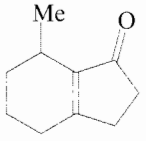
1. LDA , THF , –78°C
2. EtC≡N
3. H_3O^+

(j) 

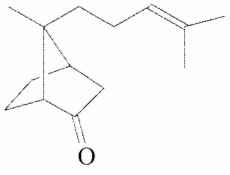
Zn , $BrCH_2CO_2Et$
Bz_2O_2 , aq THF
BF_3•OEt_2

(k) 

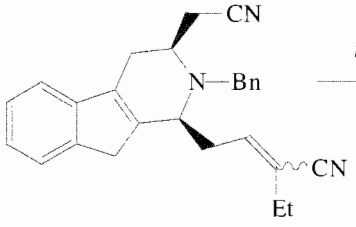
1. pyrrolidine , cat H^+
2. $PhCH_2CHO$
3. hydrolysis

(l) 

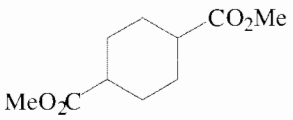
1. NaH , $(MeO)_2CO$
2. NaH , $BrCH_2CO_2Me$

(m) 

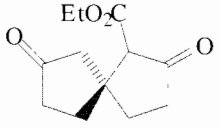
1. MCPBA
2. *t*-BuOK , *t*-BuOH

(n) 

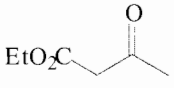
t-BuOK , THF

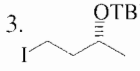
(o) 

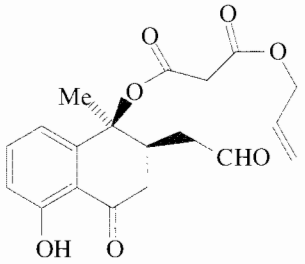
1, LDA , DMPU
2. $ClCH_2CH_2Br$
3. LDA , DMPU

(p) 

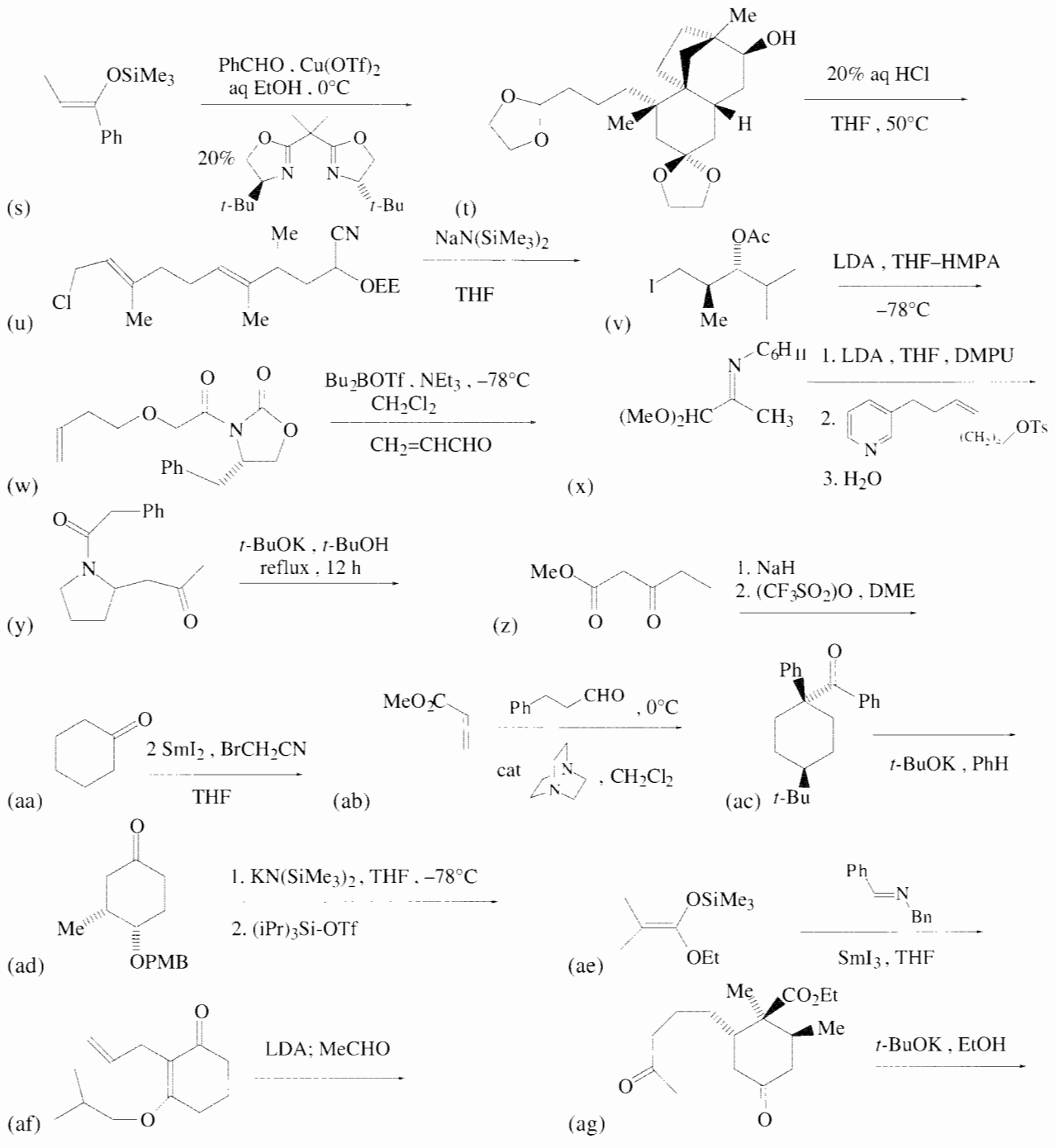
1. NaH , THF
2. MeI
3. HCl , AcOH
reflux

(q) 

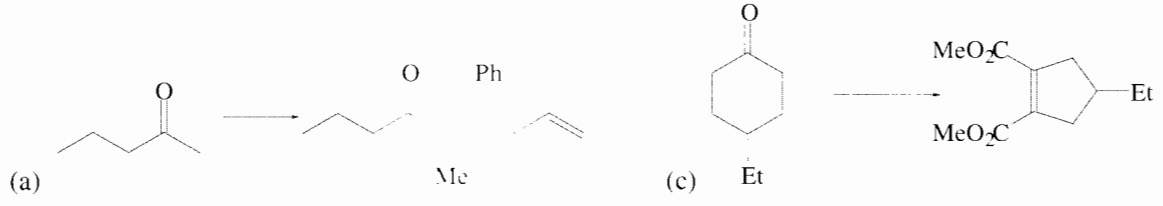
1. NaH , THF
2. BuLi , THF
3. 

(r) 

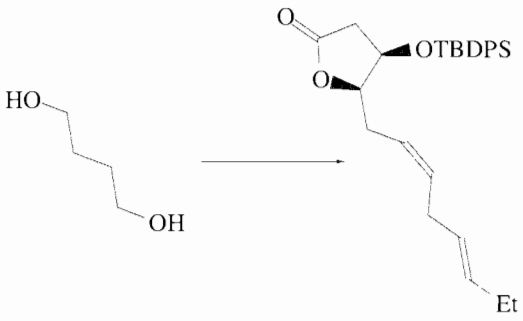
piperidine , AcOH



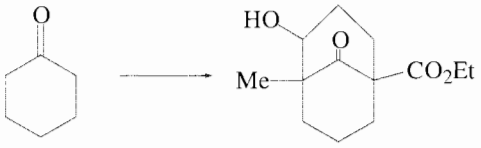
17. In each case, provide a suitable synthesis. Provide all reagents and show all intermediate products.



(b)



(d)



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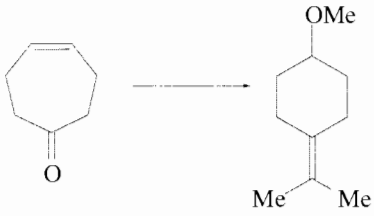

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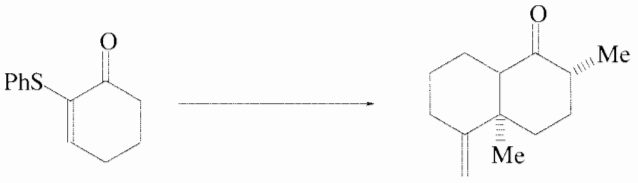
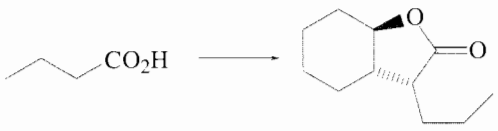
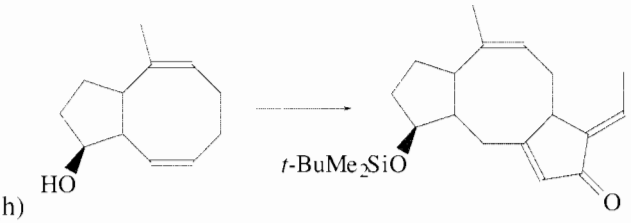


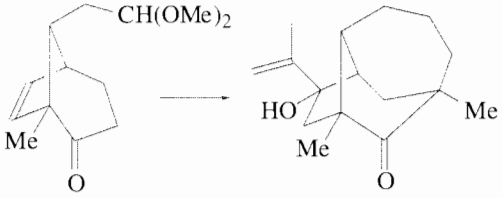
(g)



(h)



(i)



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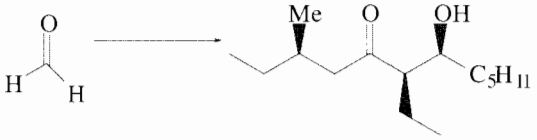
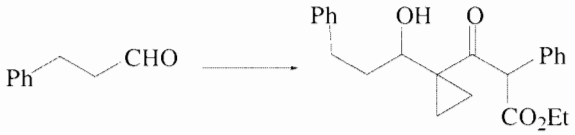
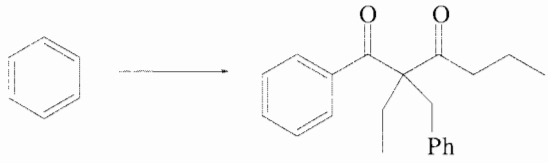


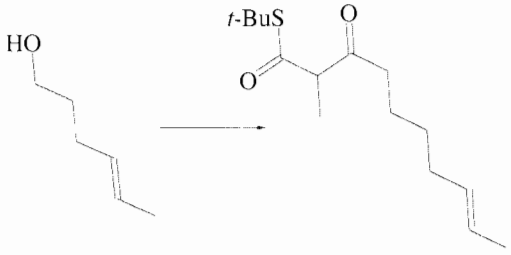
(k)



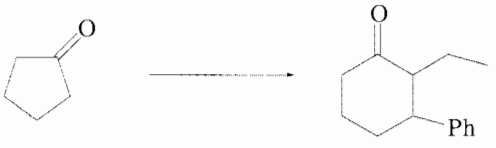
(l)



(m)



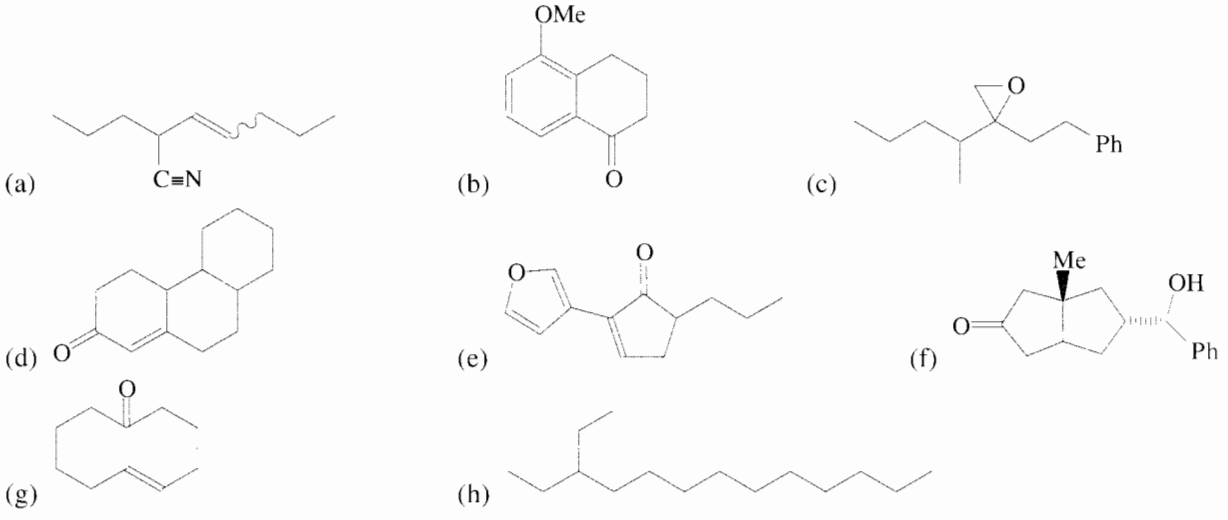
(n)



(o)

(p)

18. For each of the following, choose a commercially available starting material (give the commercial source and the price) of six carbons or less. Convert that starting material into the target shown, showing all intermediate products and all reagents. Give the commercial price of all reagents used. Show your retrosynthetic analysis:



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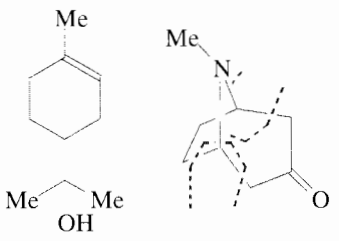
CHAPTER 10

SYNTHETIC STRATEGIES

10.1. INTRODUCTION

Throughout this book, functional group transforms for each new reaction were shown at the end of the discussion. In addition, disconnections for carbon–carbon bond–forming reactions have also been given. These transforms and disconnections form the basis of the modern approach to total synthesis. The simple strategies used for the problems in previous chapters may not work very well with complex molecules, and alternative strategies are required for their total synthesis.



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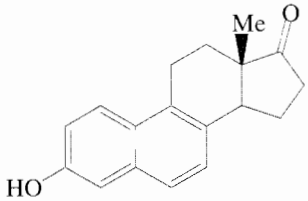

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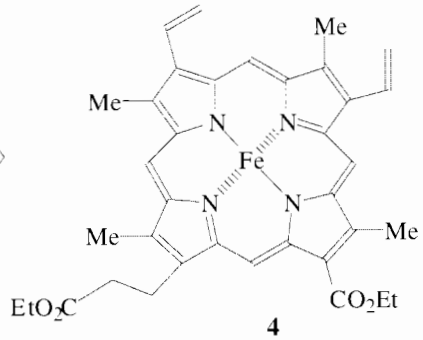

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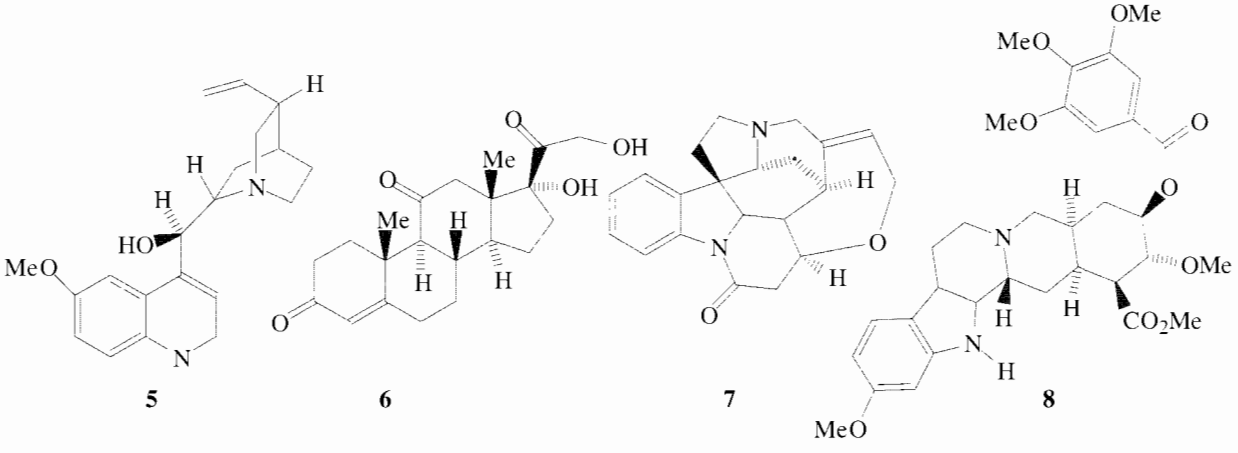
Those alternative strategies will be presented in this chapter. The logic and planning behind Corey's many syntheses spanning over 30 years were summarized in a monograph.[1a] That monograph detailed several strategic approaches to total syntheses and also presented many of Corey's syntheses, where those principles were applied. Nicolaou has also published a collection of total syntheses.[1b] Synthesis as a protocol dates to the nineteenth century, and Corey cited several examples to illustrate its history. In 1904, Perkin synthesized terpineol (**1**),[2] in part to ascertain the actual structure of this natural product. In the synthesis of tropinone (**2**) by Robinson in 1917,[3] he envisioned that an "imaginary hydrolysis of the substance (tropinone) may be resolved into succinaldehyde, methylamine, and acetone."[4b] In this analysis, he is actually disconnecting **2** into simple disconnect fragments. The synthesis of equilenin (**3**) by Bachmann et al. in 1939[4] was the first multi-step synthesis of a steroid precursor to estrone. Fischer and Kirstahler synthesized hemin (**4**),[5] and recognized that four similar pyrrole units composed the structure, requiring the synthesis of each fragment prior to assembling **4**.

With Woodward, synthesis assumed a sophistication previously unknown,[6] and targets such as quinine (**5**, with von E. Doering and co-workers),[7] cortisone (**6**),[8] strychnine (**7**),[9] and reserpine (**8**)[10] were synthesized (along with many other molecules). Over these years, the structural and stereochemical features of the targets increased in complexity. As more complex structures were targeted, the newly acquired ability to control stereochemical features and chiral centers led to greater synthetic achievements. Corey formalized the

terminology for this approach to synthesis, making it an understandable process. This approach is called **retrosynthesis**, and it allows one to dissect a molecule and arrive at relatively simple starting materials in what is now called the **disconnection (or synthon) approach.**[11] The disconnection approach is now used by most chemists when they undertake a synthetic problem but there are other strategies that can be applied to planning a synthesis. Corey included several strategies for synthesis in a computer program called LHASA (sec. 10.4.B), with the goals of assisting chemists in synthetic planning and actually suggesting syntheses for complex molecules. This approach to synthesis will be presented later in this chapter, as will other techniques for assembling a retrosynthetic plan.



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10.2. TARGET SELECTION

10.2.A. What Is the Rationale for Total Synthesis?

The choice of a target is obviously the point of departure for a synthesis. The synthesis of an organic molecule usually begins with two questions: (1) why was this molecule chosen as a target? and (2) where do I begin? The answer to (1) often lies in the needs and interests of the synthetic chemist. It may be a challenging stereochemical problem or functional group combination. A molecule may possess unique chemical or bio-logical properties.

Although these utilitarian reasons are often cited for a synthesis, the challenging problems usually encountered in a total synthesis provide many opportunities to find new reactions, processes, or strategies which may be of value to other organic chemists. Corey and Wipke stated a few of the useful applications that may be found in a retrosynthetic analysis–synthesis problem.[12] Many of these may be useful in solving problems for another target or in applications to a completely different area of organic chemistry.

"As a synthetic tree (secs. 10.3, 10.4) is developed, findings may emerge which suggest new relationships or simplifications that can lead to even more effective analysis of the original target structure. In this sense, it can be said that imbedded in each problem is a learning opportunity, which if seized can lead to extraordinarily simple or elegant situations. Learning opportunities are equally great in the subsequent stages of synthetic work which involve (i) the selection of specific chemical reactions for transforming one synthetic intermediate

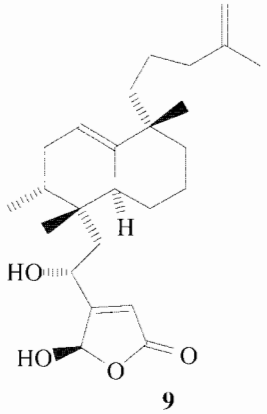
to the next in the sequence, (ii) the selection of specific reagents, (iii) the design of experiments, and (iv) experimental execution and analysis. During these stages observations, discoveries, inventions, or theorems of great importance may result." [12]

A similar fundamental basis for total synthesis was described by Deslongchamps.[13]

"Nowadays, for synthetic chemists interested in making fundamental contributions to their field of research, the choice of a given target is not which should be considered as the most important decision; the choice of a specific target is simply an excuse to put in practice a new strategy or to demonstrate the value of, either a new reaction, or a new set of reaction conditions. Also, when one chooses a very difficult target with these principles in mind, it creates a must to innovate in order to succeed. In other words, since the researcher has put himself or herself in a situation that organic chemists have not faced before, the chances of discovering something new and original are then quite high."

"The preceding suggests that what is most important is not the choice of a given target, but how the goal is going to be achieved. In other words, it is the chemistry that one discovers along the way that is the important parameter, not the fact that one succeeds in the synthesis of a given compound, natural or non-natural. Indeed, when peers eventually have to evaluate one's work, either on a short-term or even more so on a long-term basis, it is only the value of the chemistry which will count. The fact that a total synthesis is reported for the first time or that the compound has important biological properties or is of theoretical interest is of secondary importance from a chemical point of view".[13]

It is often true, however, that synthesis of a particular target is of paramount importance to an individual or organization. The criteria for that importance is always obvious to the researcher(s). To one beginning a study of organic reactions and synthesis, however, it may be of value to examine several commonly quoted criteria for synthesis. These criteria, along with Corey's and Deslongchamps' evaluations, provide a reasonable answer to question (1). The disconnection approach in its several forms will be used to address Question 2.



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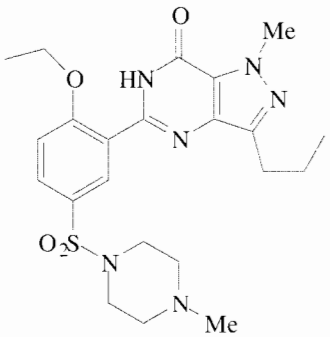

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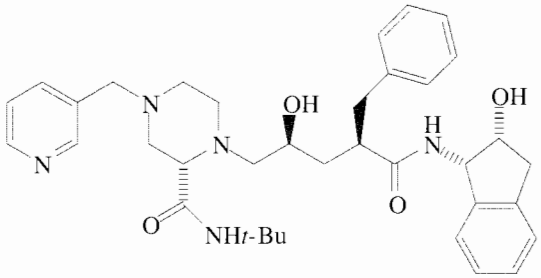
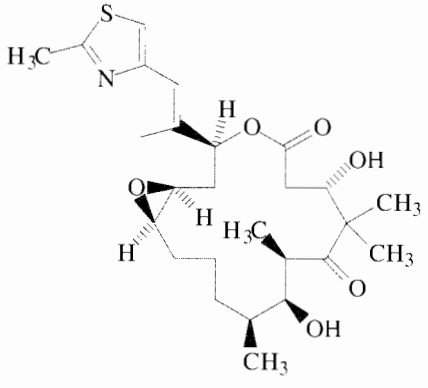


11

In addition to the eight molecules shown in the introduction, six molecules are shown as representative examples of the wide variety of organic molecules that have been synthetic targets. Dysidiolide (**9**), isolated

from the marine sponge *Dysidea etheria* de Laubenfels is a the only known natural inhibitor of a protein phosphatase called csc25A, which is involved in a signaling system for cell division, and a potential target for anticancer therapy.[14] Not all targets come from nature. Viagra (sildenafil, **10**)[15] was developed by Pfizer Inc. to treat impotence and indinavir (**11**)[16] was developed by Merck as a HIV-1 protease inhibitor. Epothilone (**12**) is a compound with the same mechanism of action as the important anticancer drug taxol, but has a less complex structure that makes it easier to prepare.[17] Pancratistatin (**13**) has been an important target for organic synthesis due to its promising anticancer activity.[18] The preparation of **14** (the common name of this compound is [4]-phenylene) helped show that the delocalized bonds of a benzene ring were effectively localized in these compounds, generating the elusive cyclohexatriene unit.[19] This discovery is causing scientists to reexamine the underlying principles of aromaticity.



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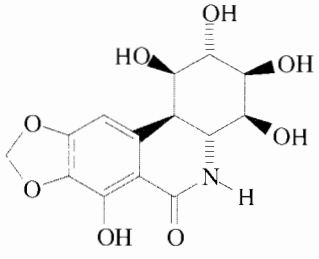

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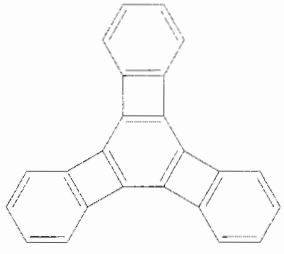

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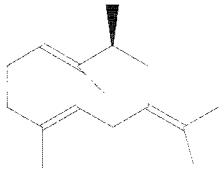
The differing structural features offer unique synthetic problems. When such syntheses are published, the step-by-step reaction sequence used to construct each molecule is reported and, occasionally, a summary of the rationale behind the synthesis. This summary sometimes provides insight into why a target was chosen, but not always. To a chemist searching for a target, inspection of previous work may not be of great value, although a close study of these syntheses will be of enormous value for understanding and devising strategies. The five criteria listed below are often cited as characteristic of important synthetic targets. These may be of value to a chemist who is being introduced to synthesis for the first time. Much of the information gained from examining these criteria may be useful for disconnecting the target. **(1) Structural verification; (2) important biological activity; (3) analog generation and studies; (4) structural or topological challenges–fundamental understanding of the nature of bonding and molecules; (5) development of new reactions or reagents.**

10.2.B. Structural Verification

An example of using synthesis for proof of structure is the sex pheromone produced by the male sand fly *Lutzomyia longipalpis*, from the Lapinha Cave region of Brazil, which was proposed as **15** based largely on mass spectrometry and on products derived from microchemical reactions.[20] "This sand fly is the principal vector of the protozoan parasite *Leishmania chagasi*, the causative agent of visceral leishmaniasis in the New

World."[20] Pickett synthesized this compound to test the proposed structure and to define the absolute stereochemistry at C9.[21] The synthetic work confirmed the structure and defined the stereocenter as (*S*).



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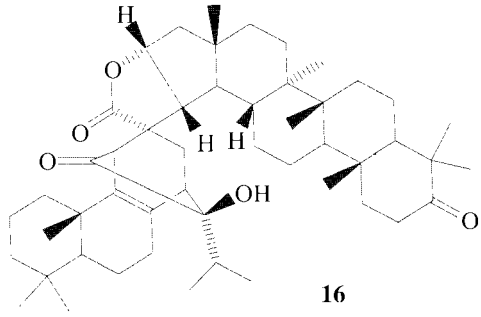

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Single crystal X-ray crystallography has become a powerful method for determining the structures of complex organic molecules.[22] The structure of a metabolite isolated from the climbing plant *Hyppocratea volubilis* L., called volubilide (**16**), was identified by means of ^{1}H and ^{13}C NMR spectroscopic studies.[23] Once the basic structure was known, Its absolute configuration was determined by X-ray analysis,[23] which is a typical application of the technique. It is reasonable to ask why a lengthy synthetic verification might be necessary for a given target when such techniques are available. In many cases, X-ray analysis is not possible due to an unsuitable crystalline form, the unavailability of single crystals, poor morphology of the molecule, or a derivative. In many cases, of course, the molecule does not form a crystalline derivative at all. As noted for volubilide, the powerful high-field NMR techniques now available often fail to give the absolute stereochemistry of all chiral centers, although the relative stereochemistry may be discerned. Chemical degradation used in conjunction with spectroscopy is also an important identification protocol but is not successful in every case. The total synthesis of all reasonable diastereomers and comparison with an authentic sample therefore remains an important method for final structure determination.

10.2.C. Biological Activity

An obvious reason for total synthesis is the importance of the target in medicine, agriculture, or other commercial and humanitarian ventures. An important or interesting molecule is usually isolated from a natural source in very small quantity, as with pancratistatin (**13**). If the molecule is subsequently shown to possess significant biological activity, additional material may be required for further testing or determination of the structure. The small quantities isolated or the difficulties and expense inherent in gathering natural specimens often prevent collection of sufficient amounts of the natural product. If the molecule is to undergo further biological screening or be used clinically, total synthesis may be the only means to obtain sufficient material.

An example of a synthesis used to verify a structure or to generate sufficient material for useful purposes is seen with one of the targets shown above, (**13**), which is an *Amaryllidaceae* isoquinoline alkaloid that was isolated by Pettit et al. from *Pancratium littorale* in 0.039% of the dry weight of the bulbs of *P. littorale*.[18a,b] It was also isolated from the bulbs of *Zephyranthese grandiflora*, but in only 0.0019% yield.[18a,b] The natural abundance of **13** reported from these plant sources clearly show that harvesting these plants is a poor source to

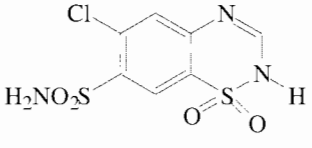
obtain quantities suitable for testing. In biological testing, pancratistatin is believed to behave similarly to narciclasine, which inhibits protein synthesis in eukaryotic cells[24] and exhibits antineoplastic activity in ovarian sarcoma and lymphatic leukemia[18c] as well as being an antimitotic.[18c] Pancratistatin is in preclinical development at the National Cancer Institute, "based on its high activity against the M5076 sarcoma system."[18d] It also exhibited good activity against the P388 leukemia.[18c] It is clear that the significant antitumor activity coupled with the small amounts of material available from natural sources prompted the many total syntheses that will be described in Section 10.7.

Note that production of a complex natural product by a multi-step synthetic route can be very expensive. To produce 1 gram of active product can require large quantities of both starting material and time. If the synthetic goal is to produce usable quantities of material at a reasonable cost, this must be factored into the retrosynthetic scheme. If one requires only milligram quantities, greater latitude in the choice of starting materials and reagents is possible.

10.2.D. Analog Studies

A target that has interesting or commercially attractive properties may exhibit deleterious side effects, or be unstable to storage and handling. Subsequent studies often show that structural modification to the basic skeleton gives a molecule with different characteristics and the new molecule becomes the synthetic target.

Chlorothiazide is 2*H*,1,2,4-benzothiadiazine-7-sulfonamide, 6-chloro-1,1-dioxide (**17**).[25] It is a diuretic also used to treat hypertension. Studies "determined that significant alterations in the pharmacological profile would follow changes in the heterocyclic ring rather than the ring bearing the sulfonamide group."[26] Structural modification led to the synthesis of chlorexolone (**18**).[27] Conversion of the heterocyclic ring in **17** to the *N*-cyclohexyl lactam moiety in **18** resulted in improved hypotensive action[28] and diuretic action, but did not increase urinary pH or urinary bicarbonate excretion relative to **17**.[29] Synthetic modification of a known structure can serve as a model and impetus for designating a synthetic target.



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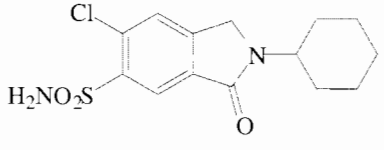

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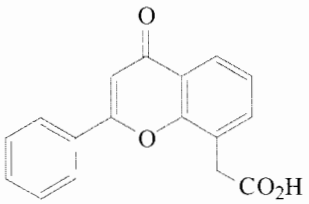
Another common rationale for preparing analogs of a given target is to study the structure–activity profile of a molecule with known biological activity. Flavone 8-acetic acid (**19**) has great potential as an antitumor agent.[30] Denny and co-workers showed that 9-oxo-9H-xanthene-4-acetic acid (**20a**) is as active as **19** against colon-38 tumors in mice and is more dose potent.[31] It was also shown that small lipophilic substituents at the 5-position (see **20b** and **20c**) enhanced dose potency.[32] A systematic study[33] of synthetic derivatives of **20** showed that many related derivatives possessed enhanced antitumor activity, which is a typical case in which a known compound was structurally modified based on structure–activity properties of a related compound. The impetus for this synthesis was therefore a search for a more potent and efficacious drug.



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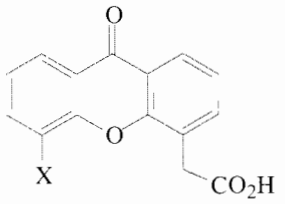
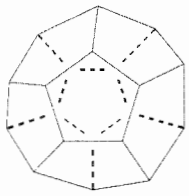


20 (a) X = H (b) X = Me (c) X = Cl



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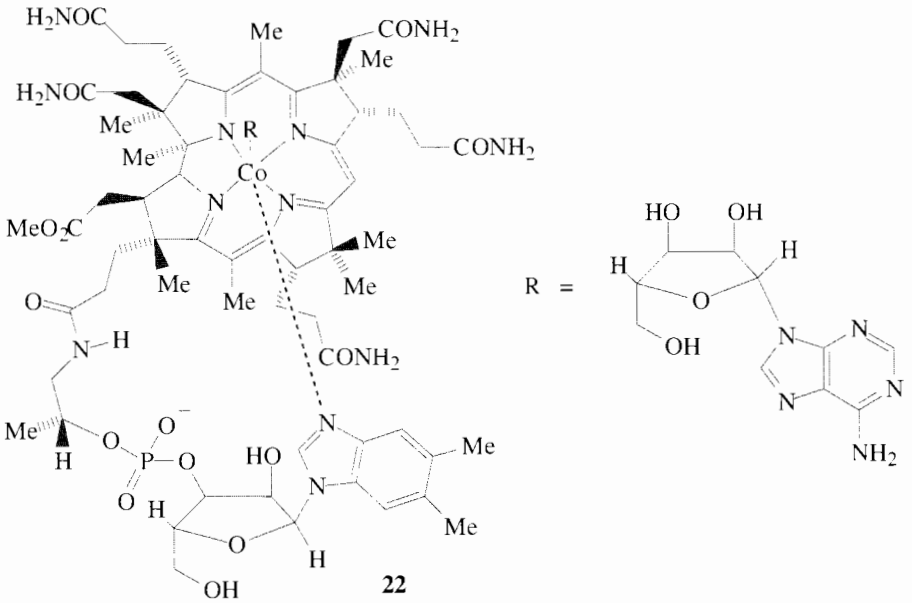
10.2.E. Topological Studies

Occasionally, a molecule presents such a structural and chemical challenge that its potential as a target is irresistible. Such a synthesis often pushes back the limits of known chemistry for making carbon–carbon bonds and gives insight into structure, bonding, or fundamental reaction properties of organic molecules.

Dodecahedrane (**21**) was synthesized by Paquette and co-workers.[34a] and the topology (shape, structural features) of **21** is essentially that of a ball. Having the form of a dodecahedron, first described as one of five regular polyhedra in 400–350 B.C. in Plato's *Timaeus*, **21** has a spherical superpolycyclopentanoid topology,[34b] which possesses the highest known point group symmetry (I_h, icosahedral).[34a] It also shows a unique encapsulation of a cavity incapable of solvation, negligible angle strain but great torsion strain,[35] 20 symmetry equivalent methine units, and an absence of structurally allied substances. Paquette was the first to synthesize this molecule and the creative and sometimes novel chemistry arising from the synthetic solution to targets such as **21** can usually be applied to other synthetic endeavors.



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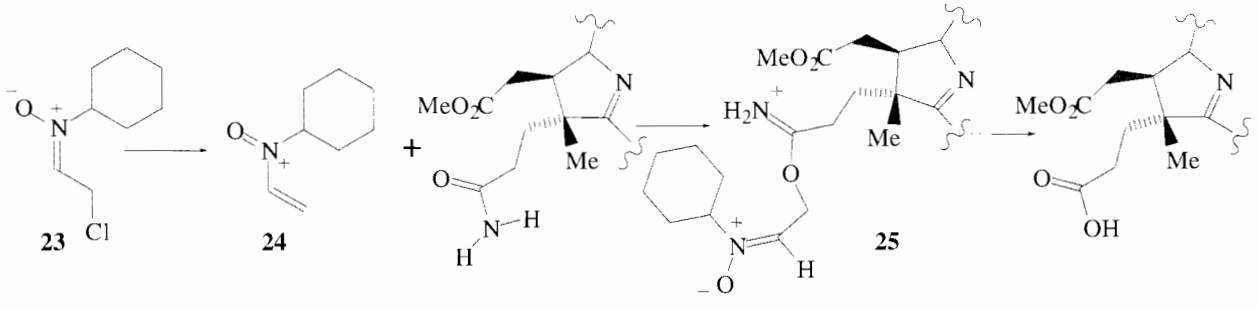
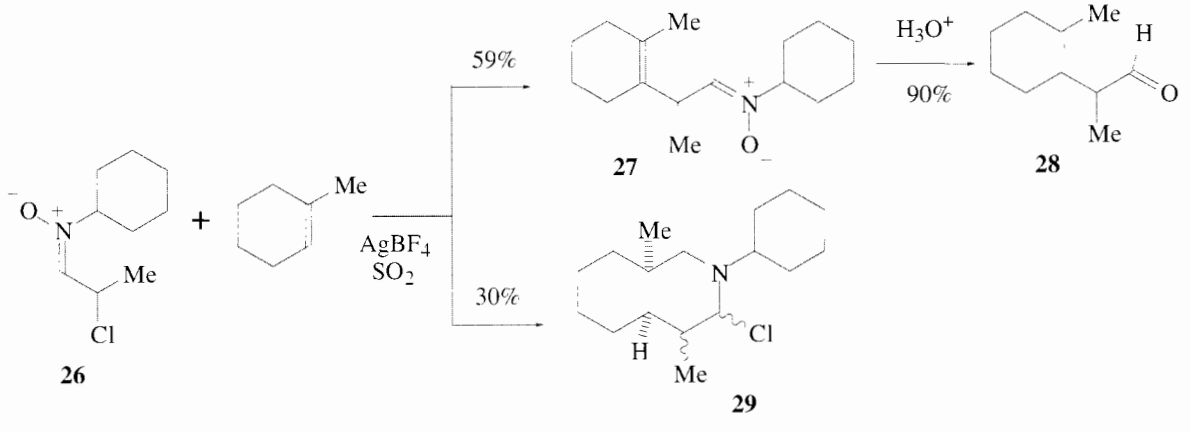
10.2.F. New Reactions and New Reagents

During a total synthesis, completion of a key transformation may be impossible via known chemical reactions. Development of new methodology or modification of existing reactions must be accomplished to give the desired transformation and complete the synthesis. Once developed, later work often shows the reagents

developed for that synthesis can be utilized for a variety of other purposes (recall Corey's and Deslongchamps' analyses). An example is the total synthesis of vitamin B-12 (**22**) reported by Woodward and Eschenmoser.[36] Late in this synthesis, a key step required hydrolysis of an amide in an intermediate possessing six ester moieties. The reagent developed for this transformation was an α-chloro-nitrone (**23**) which gave a vinyl nitronium ion (**24**) when treated with silver ion. This reagent gave the desired hydrolysis via reaction with the amide, giving **25**. Hydrolysis of **25** gave the acid and allowed the synthesis of **22** to be completed. Some years later, Eschenmoser developed a series of transformations using derivatives of the α-chloronitrone described above. The nitrone (**26**) was used as a diene partner in a Diels–Alder reaction (secs. 11.4.A, 11.7) and the resultant cycloadduct (**29**) was transformed into several synthetically useful molecules. The secondary product that competed with the cycloaddition was the addition product (**27**), which was also converted to synthetically useful products. As the addition partner is changed from alkenes to alkynes to other derivatives, the end-products include furan and alkyne derivatives.[37] In the specific example shown, cycloaddition of



methylcyclohexene and **26** gave the addition product (**27**) in 59% yield, and subsequent hydrolysis led to a 90% yield of **28**. The cycloadduct (**29**) was formed in 30% yield. This sequence illustrates how a reagent developed for one purpose can be a powerful reagent in a completely different application. Indeed, the discovery of such new reagents and transformations is commonly the result of a total synthesis.



To summarize, the criteria discussed for target selection can be useful during a search for possible molecules to synthesize. They may also offer insights into possible applications to chemical problems that may arise. In addition, an understanding of the history of a target and its utility usually provides clues to its

chemistry, isolation, and physical properties. These are essential to execution of a synthesis if not the actual retrosynthetic analysis.

10.3. RETROSYNTHESIS

When a target is chosen, there are guidelines that allow its systematic disconnection to a starting material. The roadmap of synthetic intermediates that results is called retrosynthesis. This section will describe several ways to analyze a molecule to identify key bonds for disconnection.

10.3.A. The Disconnection Approach

Once a synthetic target has been chosen, reactions must be developed that will allow the total synthesis to be accomplished. The choice of a **starting material** (the molecule, purchased or readily prepared, that is used in the first reaction of the synthetic sequence) is critical. How does one analyze a target in order to determine the best starting material? The answer to that question is the essence of total synthesis, and its answer requires:

1. A detailed analysis of the structure of the target
2. A fundamental knowledge of chemical reactions
3. A basic understanding of stereochemistry, bonding, and reactivity
4. A well-developed chemical intuition

This information is then used to **disconnect** bonds in the target, simplifying the structure along reasonable chemical reaction pathways.[1] Wipke and Howe[38] defined the important bonds that are disconnected (as approached by the computer program LHASA, sec. 10.4.B, developed by Corey for analysis of retrosynthetic pathways).[39,54]

"There are usually certain bonds in a molecule whose disconnection in the retrosynthetic direction leads to a significant simplification of the ... structure. These are termed **strategic bonds**."

If one of these bonds is to be disconnected, a reaction (or sequence of reactions) must be available that will chemically form that bond in the synthesis. Subsequent simplifications (disconnections) lead ultimately to a molecule that can be recognized as commercially available, available by simple chemical techniques, or already prepared by others. This process of structural simplification via disconnection leads to a series of molecular fragments that serve as key intermediates, and each is a synthetic target. Such intermediates allow the synthetic chemist to mentally bridge the starting material with the final target in a logical and sequential manner. This process therefore constitutes a **synthetic tree** for which chemical reactions must be provided to accomplish the planned transformations.

A synthetic tree similar to that presented by Hendrickson is shown in Figure 10.1.[40,159] The target ($\mathbf{T_0}$) is disconnected to "a logically restricted set of structures which may be converted in a single synthetic operation (a chemical step) to the synthetic target."[12] This gives the disconnection product in the first retro-reaction. The subtree represents further disconnection of one branch of the synthetic tree. After several retro-reactions, the synthetic tree will yield several starting materials from one or more of the first branches, which can then be used to construct the molecule.

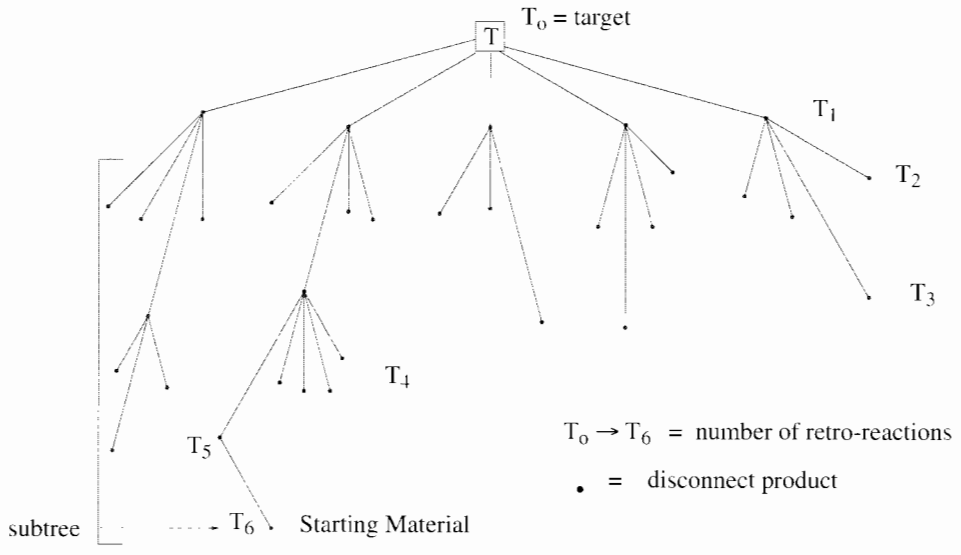


Figure 10.1. A synthesis tree.

[Reprinted with permission from Hendrickson, J.B.; Braun-Keller, E.; Toczko, A.G. *Tetrahedron (Suppl.)*, ***1981***, *37*, 359. Copyright 1981, with permission from Elsevier Science.]

The method to be presented here begins with analysis of the final target (**30**) and works *backward* toward the starting material, a process termed **retrosynthesis**.[1] Each succeeding structure has been modified and always simplified. Bonds have been disconnected and functional groups transformed until the relatively simple starting materials shown were obtained. The term **disconnection**[41,12] therefore refers to "mentally breaking bonds to give successively more simple precursor molecules, but always in a manner in which those bonds can be reformed by known or reasonable chemical reactions." This approach has been described in great detail by Warren.[41]

Disconnection of bond ***h*** leads to **31** and conversion to realistic synthetic fragments (sec. 1.2) leads to at least two possibilities, epoxide **33** and α-chloroketone (**32**). A functional group transform is required to convert **32** into **34** and **33** into **35**. If the synthetic tree is pruned to focus on **35**, a second disconnection focuses on bonds ***k***, ***l***, and ***m***. Disconnection of bond ***k*** gives the most simplification, generating **36** and 2-bromobutane (real molecules resulting from the disconnection). A new bond analysis of **36** leads to at least two disconnections. Disconnection of bond ***g*** leads to **37** and disconnection of bond ***c*** leads to two identifiable fragments: 4-bromopropanol (**38**) and the organocuprate (sec. 8.7.A) derived from 3-bromocyclopentene (see **39**). A functional group transform of **38** leads to the known starting material, 4-bromobutan-1-ol. This analysis is shown in Figure 10.2[12] and it leads to several important conclusions. First, a retrosynthesis tree can be correlated to the retrosynthetic analysis, as shown, which demands that several choices be made concerning what branch of the tree will be followed. If the route from **38**, **39** → **30** is chosen, working backward along this route provides the retrosynthetic analysis, as shown. In order to complete the synthesis, reagents for each functional group transform and carbon–carbon bond–forming reaction must be provided. *It is important to note that the retrosynthetic analysis only gives key*

transformations and not every step. The structure of the new target obtained by the first disconnection may lead to a different set of strategic bonds. This process is continued until recognizable starting materials are obtained.

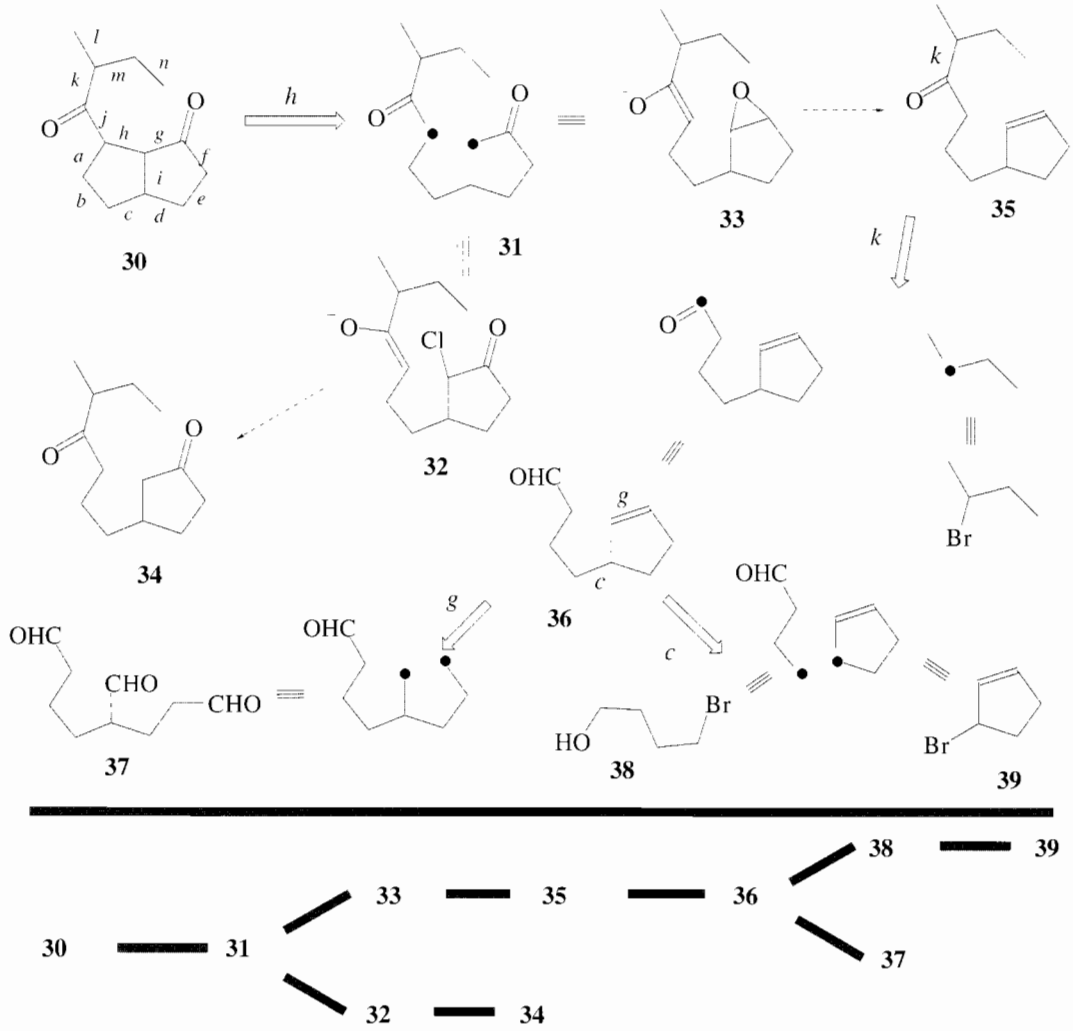


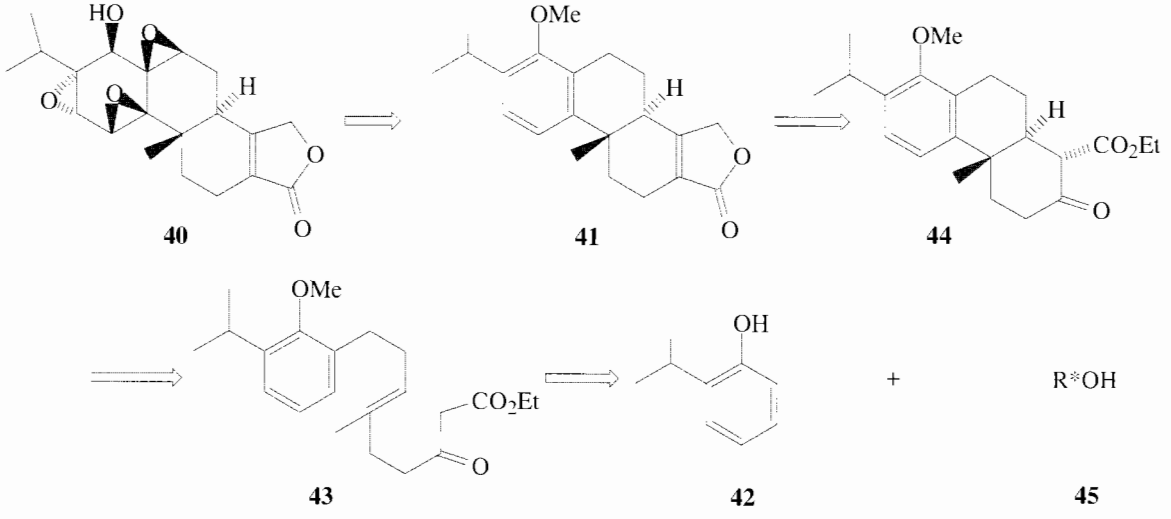
Figure 10.2. Retrosynthetic analysis of 30.

A decision must be made concerning the relative priority of simplification versus controlling the stereochemistry of the asymmetric center, which was not incorporated in the above analysis. The analysis of target **30** shows that the choice of disconnection must include the reality of re-forming the bond in the context of the remaining functionality and stereochemistry. There is not necessarily one correct answer, but rather several possibilities, each with its strengths and weaknesses.

10.3.B. The Problem of Complex Targets

The targets analyzed to this point have been structurally and stereochemically simple. When complex targets are chosen, the ability to synthetically reconnect the bond that is disconnected is not the only criterion

used for choosing that bond for disconnection. This fact is apparent in Yang's synthesis of the complex target (–)-triptolide (**40**), where the retrosynthesis shown in Scheme 10.1 was given in the paper.[42] Yang described this retrosynthesis as having four key steps. The first is triepoxide construction from the benzene precursor



Scheme 10.1. Retrosynthetic analysis of (–)-triptolide, 40.

41. The second key step is lactone formation from the carboethoxy substituted cyclohexanone unit in **44**. The third key step is construction of the tricyclic ring system by asymmetric radical cyclization of **43**, and construction of **43** from 2-isopropylphenol (**42**) using alcohol chiral auxiliaries (R*OH) was designated as the fourth key step. This disconnection scheme represents Yang's specific approach using key chemical transformations such as radical cyclization (see sec. 13.7). Clearly, other disconnections are possible, and at each stage other disconnections could lead to alternate synthetic trees.

10.3.C. Consecutive versus Convergent Syntheses

An important part of any synthetic strategy is how to proceed from starting material to product. To see the way, one can work backward linearly from the target to a starting material. Alternatively, disconnection can branch to several fragments, each with its own starting material. These fragments can be combined in a non-linear fashion to prepare the target. A synthesis based on a linear pathway is called a **consecutive synthesis**, and a synthesis based on a branching pathway is called a **convergent synthesis**. In a convergent synthesis the several pieces of a molecule are synthesized individually and the final target is sequentially assembled from the pieces, which contrasts with a consecutive synthesis, in which the target is assembled step by step from a single starting material until the final target is reached. These two approaches are illustrated in Figure 10.3,[43] which was used by Velluz et al. to describe his synthetic approach. It is apparent that the convergent synthesis will have fewer consecutive steps in the overall synthesis. In this example, if each step has a mean yield of 90%, the yield of final product after 15 steps is $(0.9)^{15} \approx 0.21$ (21%). If the largest sequence is split and divided into convergent solutions, there would be only four consecutive steps ($A_1 \rightarrow B_1 \rightarrow C_1 \rightarrow D_1 \rightarrow Z$) in a *perfectly convergent pathway*. The yield of the final product would be $(0.9)^4 \approx 0.66$ (66%). It is difficult, however, to

achieve such a perfect convergence since functional group manipulation, steric considerations, and asymmetry lead to imperfections.[43] Hendrickson's SYNGEN approach to synthesis (sec. 10.10.A) relies on a convergent synthetic strategy.

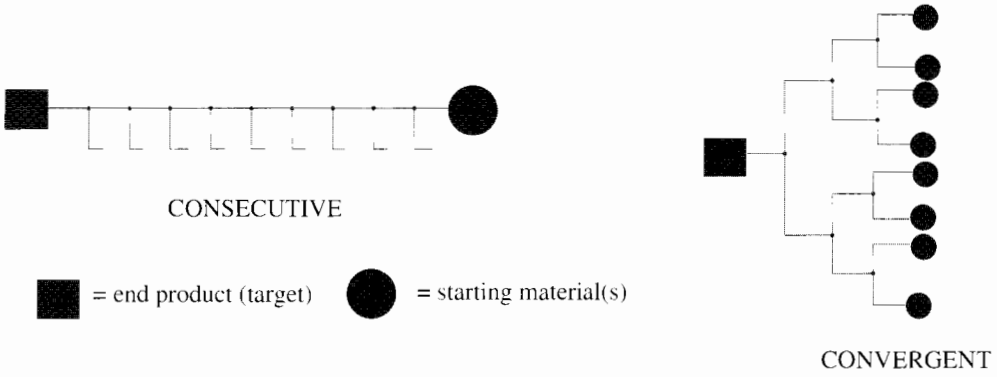


Figure 10.3. Consecutive vs. convergent syntheses.

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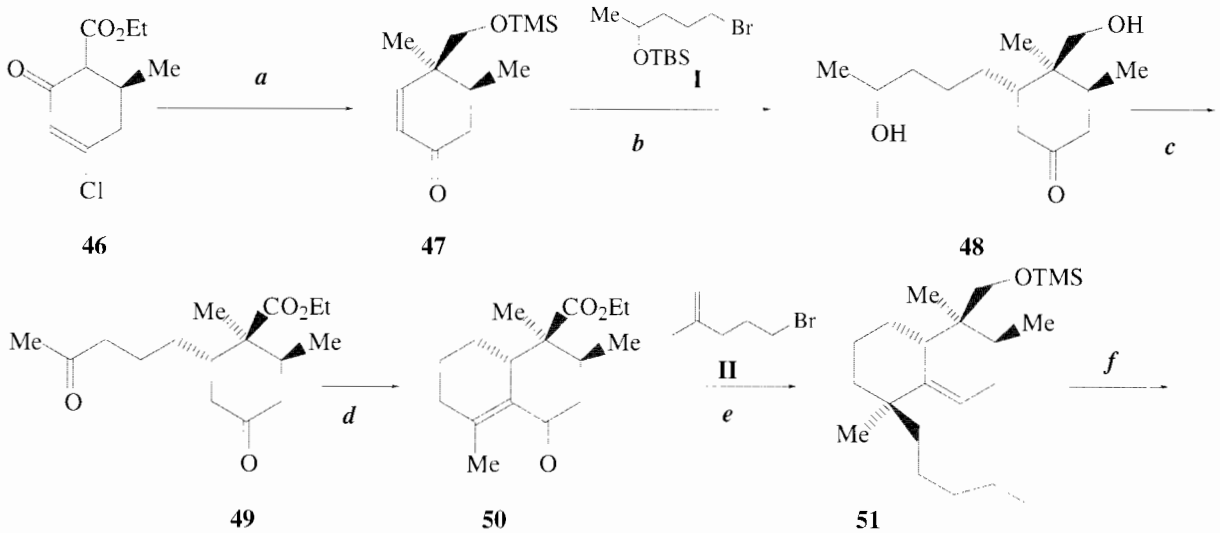
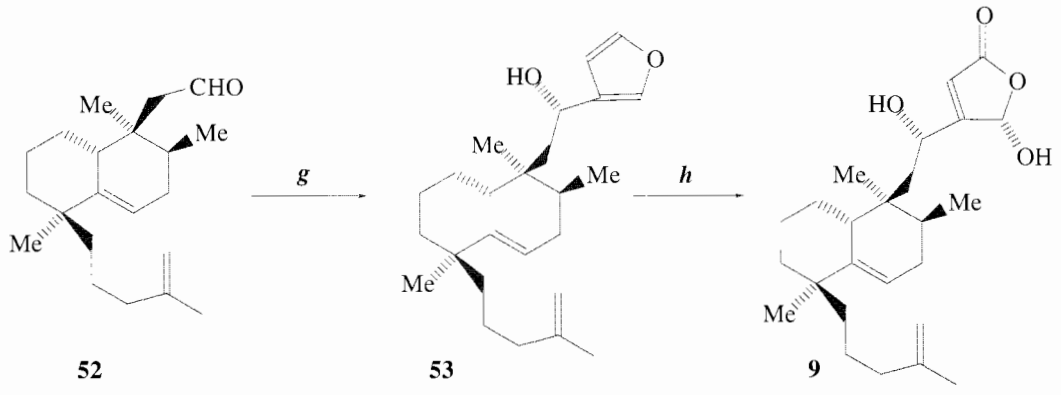
An example of a consecutive synthesis is shown in Scheme 10.2, in which Forsyth[44] converted the known keto-ester **46**[45] to dysidiolide (**9**), in 19 linear steps with an overall yield of 7%.[44] The first sequence of reactions converts **46** to the conjugated ketone **47**, which allows conversion of bromide **I** to a cyanocuprate, and conjugate addition followed by deprotection gave **48**. Manipulation of the hydroxymethyl to the ester and oxidation of the secondary alcohol to a ketone in **49** and intramolecular aldol condensation to set the second ring gave **50**. Reduction of the ester unit and protection of the resulting alcohol was followed by a second conjugate addition via a cuprate from II provides **51`**, which could be oxidized to aldehyde **52** after deprotection. Condensation with 3-lithiofuran gave **53** and manipulation of the furan unit gave the final product, **9**. Note in addition to **40**, that three large fragments are used in the synthesis, **I**, and **II**, and 3-lithiofuran. These pieces are considered to be small enough that this is a linear synthesis.

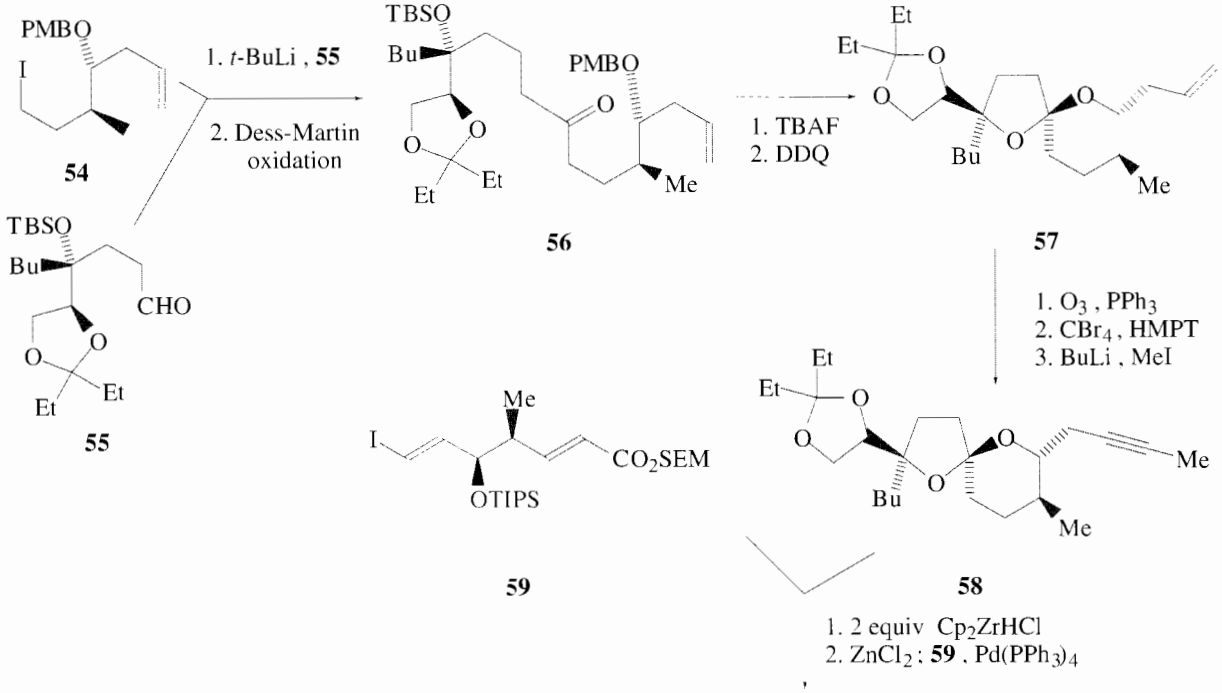


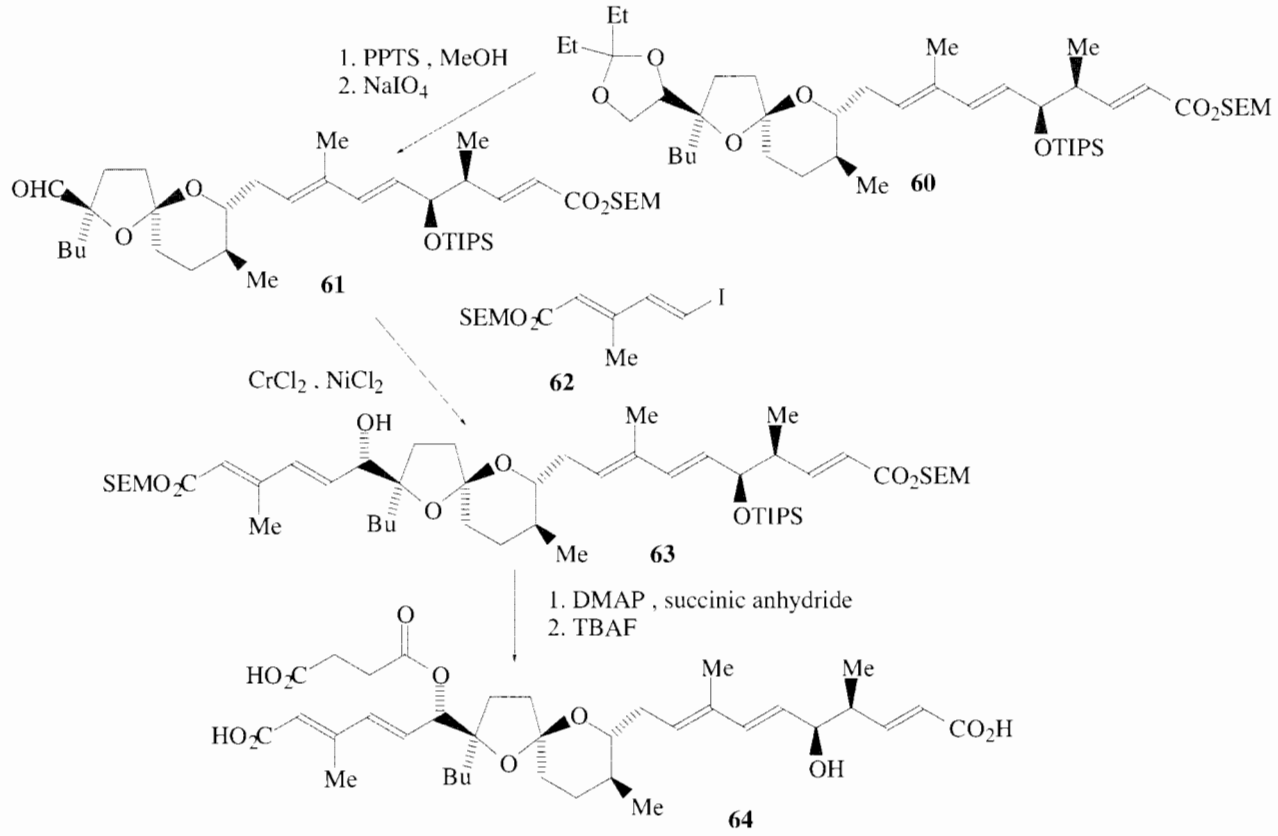


(a) i. NaH , HMPA-THF , MeI ii. NaOEt , EtOH iii. $LiAlH_4$,ether iv. TMSCl , imidazole , CH_2Cl_2
(b) i. *t*-BuLi , CuCN , **I** , ether ii. cat TsOH , MeOH–CH_2Cl_2 (c) i. CrO_3 , H_2SO_4 , aq. acetone
ii. K_2CO_3 , EtI , acetone (d) *t*-BuOK , EtOH (e) i. *t*-BuLi , CuI , **II** , PBu_3•OEt_2 , ether-THF ii. $LiAlH_4$, ether
iii. TMDSCl , DMAP , NEt_3 , CH_2Cl_2 iv. $SOCl_2$, pyridine (f) i. TBAF , THF ii. PCC , silica gel , CH_2Cl_2
iii. $MeOCH_2PPh_3Cl$, KHMDSS , THF iv. 1N HCl , dioxane (g) 3-lithiofuran , THF
(h) O_2 , Rose bengal , *i*-Pr_2NEt , W fluorescent lamp , CH_2Cl_2

Scheme 10.2. Forsyth's consecutive synthesis of dysidiolide (**9**)

A convergent synthesis of reveromycin B (**64**) is shown in Scheme 10.3, as reported by Theodorakis and co-worker.[46] Two synthetic fragments were prepared, **54** and **55**, and then coupled, giving **56** after oxidation of the initially formed alcohol. Deprotection allowed formation of spiroketal **57**, and the allylic side chain was converted to a butynyl unit in **58**. At this point, fragment **59**, prepared separately, converged into the synthesis and coupling gave **60**. The aldehyde unit was unmasked giving **61**, allowing the last synthetic fragment (**62**) to converge, giving **63**. Addition of the succinic ester unit and deprotection provided the target **64**.





Scheme 10.3. Theodorakis' convergent synthesis of reveromycin B (**64**)

Both consecutive and convergent strategies can be attractive, depending on the target and only careful consideration of each will yield the best approach for an individual target. Obviously, once it is completed a given synthesis can be continually reexamined and, in principle, improved upon. In general, a convergent strategy is expected to produce larger amounts of the target in the fewest steps if a scheme can be devised that converges at a useful point. A symmetrical convergent strategy is often the most attractive[47] (also sec. 10.10.A).

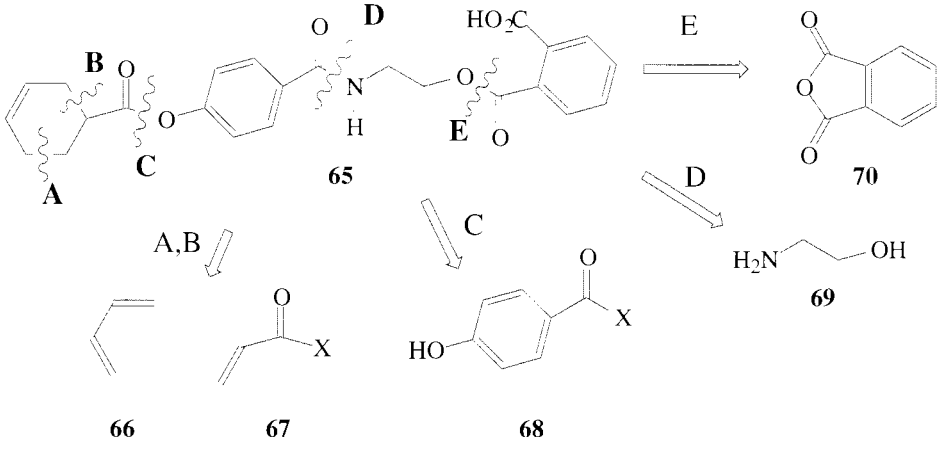
10.4. SYNTHETIC STRATEGIES

10.4.A. Defining Various Strategic Approaches

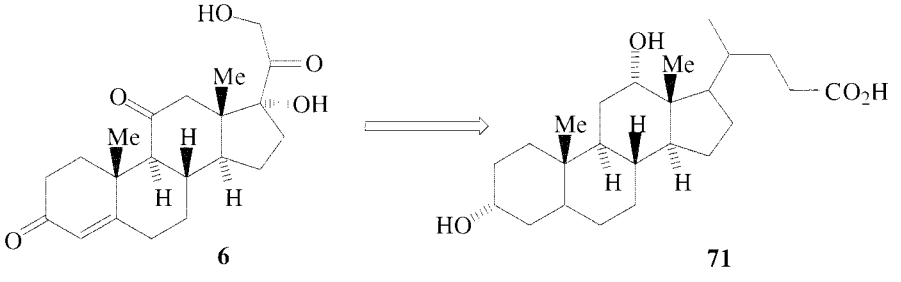
Corey and co-workers described an elegant approach to the synthesis of complex targets[1] that was incorporated in the computer program LHASA. The purpose of that program is to assist the analysis of complex synthetic targets.[12,48] This work described general approaches for constructing a synthetic tree and also described the logic used for that construction. These modifications include:[12]

1. Interconversion, removal, or introduction of functional groups.
2. Extension of the atomic chains or appendages.
3. Generation of atomic rings.
4. Rearrangement of chain or ring members.
5. Cleavage of chains or rings.

Each chemical fragment generated by the synthetic tree must possess chemical properties that are predictable and allow selective combination in only one of many possible modes.[1,12]

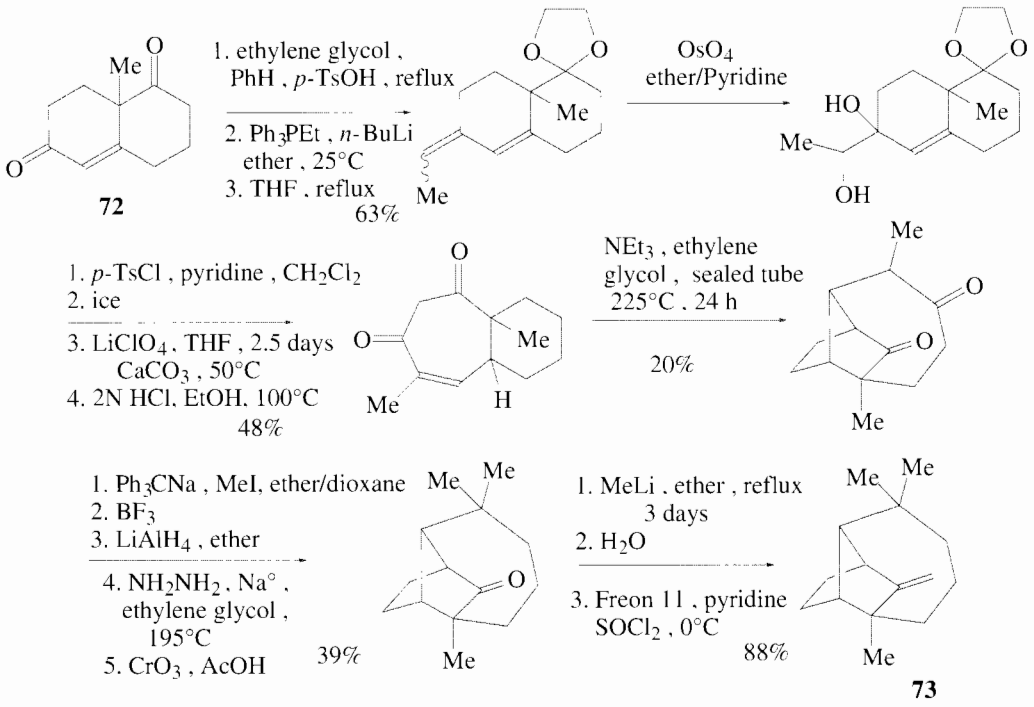


Corey and Wipke described three methodologies for synthesis: direct associative, intermediate associative, and logic centered.[12] The direct associative approach disconnects the target (such as **65**)[12] at bonds which generate a structure easily recognized by the chemist. Compound **65**, for example, gives easily recognized fragments based on well-known reactions. A retro Diels–Alder reaction gave **66** and **67**. Ester and amide hydrolyses gave **68** –**70**. This approach is limited to simple synthetic problems.



The intermediate associative approach recognizes a major subunit in the target that corresponds to a known or potentially available starting material. The choice of this starting material directs the retrosynthetic analysis along a specific pathway.[12] The scope and rigor of solutions to the problem are sometimes very limited, however.[12] Sarett's synthesis of cortisone (**6**)[49] used deoxycholic acid (**71**) as a starting material, available as an intermediate from Kendall's previous synthesis of 11-keto-etiolithocholic acid.[50] This earlier synthesis required a total of 30 steps, but Sarett's second synthesis was shorter and introduced a general method for introduction of the 17α hydroxyl group.[51]

The logic centered approach leads to a restricted set of structures that may be converted in a single step to the target. Each new structure can, in turn, be converted to a new structure. The purpose of the retrosynthetic analysis is to generate synthetic intermediates (the synthesis tree) that terminate with a number of starting materials.[48] Corey et al. outlined this approach in 1964 in his synthesis of longifolene (**73**), which is shown in Scheme 10.4.[52] This synthesis used the **Wieland–Miescher ketone** (**72**) as the starting material.[53] Analyses



Scheme 10.4. Corey's synthesis of longifolene (73).

such as this begin with a search for key structural features that may be structurally significant. These key features are[12]

1. Individual molecular chains, rings, and appendages.
2. Individual functional groups.
3. Asymmetric centers and attached groups.
4. Chemical reactivity.

The next goal is to reduce molecular complexity. This is done by meeting the following goals:[12]

1. Simplification of internal connectivity by scission of rings.
2. Reduction of molecular size by disconnection of chains or appendages.
3. Removal of functionality.
4. Modification or removal of sites of unusually high chemical reactivity of instability.
5. Simplification of stereochemistry.

There are also certain transformations that are important adjuncts to these goals but do not simplify the molecule. Examples of these transformations are:[12]

1. Functional group interchanges.
2. Introduction of functional groups.
3. Modification of functional groups to control the level of chemical reactivity.
4. Introduction of groups that permit stereochemical or positional control.
5. Internal rearrangement.

Above all, the disconnections must lead to chemical reactions that will allow construction of the target. The basic mechanistic aspects of these reactions must be well understood, since the reaction pathway is the same in the forward and reverse directions (principle of microscopic reversibility).[12] If a set of disconnections is

found to correlate with a mechanistically sound set of chemical reactions in the forward directions, those steps are taken as part of the synthetic tree. In all steps, stereochemical and topological aspects must be considered.

In an analysis of a target, the vast body of organic chemistry may lead to the generation of retrosynthetic trees that are too large to be manageable and that include numerous dead ends.[48] It is essential that simplification techniques, search strategies, screening procedures, and logical analysis be employed as the tree is constructed. If subunits of the molecule that are potential **synthons** (the disconnection products often taken as the chemical building blocks) can be found, a strong measure of control over tree branching is possible.[48,54] The retrosynthetic transform and synthetic reaction to accomplish that transform are intricately linked. Just as the power of a transform to simplify a structure is critically important, the most powerful synthetic reactions are those that reliably increase molecular complexity.[48] Transforms that decrease or increase the molecular complexity of a target are important in the retrosynthetic strategy. Bertz described the importance of molecular complexity in the context of synthetic analysis, particularly as applied to convergent syntheses,[55] a topic also addressed by Merrifield and Simmons.[55d] Bertz suggested that "topological complexity, as well as other sources of molecular complexity, be examined *in addition* to the classical considerations of synthetic efficiency when evaluating synthetic routes."[55a]

From the preceding discussions it is clear that there are many approaches for a disconnection approach that focuses upon construction of a synthesis tree. Corey et al. described five different strategies for retrosynthetic analysis:[48]

1. Transform based strategies. Identify a powerful transform for a specific target that produces a reasonable line in the synthetic tree. Two or three powerful simplifying transforms can be applied successively to the target structure. Alternatively, the same simplifying transforms can be repeatedly applied.[56]

2. Structure goal strategies. Identify a potential starting material, building block, retrosynthetic subunit, or initiating chiral element (see the chiral template approach in sec. 10.9).

3. Topological strategies. Identify one or more bonds whose disconnection can lead to major molecular simplification, that is the essence of the strategic bond approach[57] to be discussed in Section 10.5. These bonds may be in bridged or fused ring cyclic systems or appear as connectors to appendages at rings, functional groups, or stereocenters.

4. Stereochemical strategies. Heuristically derived procedures for reducing stereochemical complexity in the retrosynthetic direction, these procedures remove stereocenters and take advantage of steric screening or proximity to a functional group. The latter may allow simplification of the target by application of functional group removal transforms.[58] Corey defines heuristic as "a noun to mean heuristic principle, a 'rule-of-thumb' which may lead by a shortcut to the solution of a problem or may lead to a blind alley."[39b]

5. Functional group oriented strategies. When one or more functional groups are related to an interconnecting atom path, a simplifying transform can often be found. Interconversion, addition, or removal of functionality can pave the way for further retrosynthetic simplification. Both internal protection of functional groups and replacement of a highly reactive group by another less reactive equivalent can be useful.[59]

10.4.B. LHASA

Corey developed a computer program that uses the strategies described above in a way that emulates the most effective problem solving approaches of a synthetic chemist, with an emphasis on complex rather than routine synthetic problems. This computer program is called **LHASA** (**L**ogic and **H**euristics **A**pplied to **S**ynthetic **A**nalysis; see sec. 1.5.D). It analyzes a molecule, develops retrosynthetic schemes, and supplies appropriate chemical reactions A typical LHASA analysis is shown in Figure 10.4,[60] where a LHASA transform is shown in part (a), in this case based on the Fries rearrangement (see sec. 12.5.E). In part (b), a target molecule is shown (**Target 3**), and a retrosynthesis is provided that is based toward acetophenone. Note that a description of the projected chemistry is shown over each disconnect arrow. In part (c), a retrosynthetic tree is shown as part of the analysis of a target. In part (d), a specific retrosynthetic analysis is shown in which one unit, the hydroxymethyl group, is removed from Target 3, with the projected reaction being an organometallic transform. The data provided by Figure 10.4 is meant to illustrate the type of information that is available from the LHASA program.

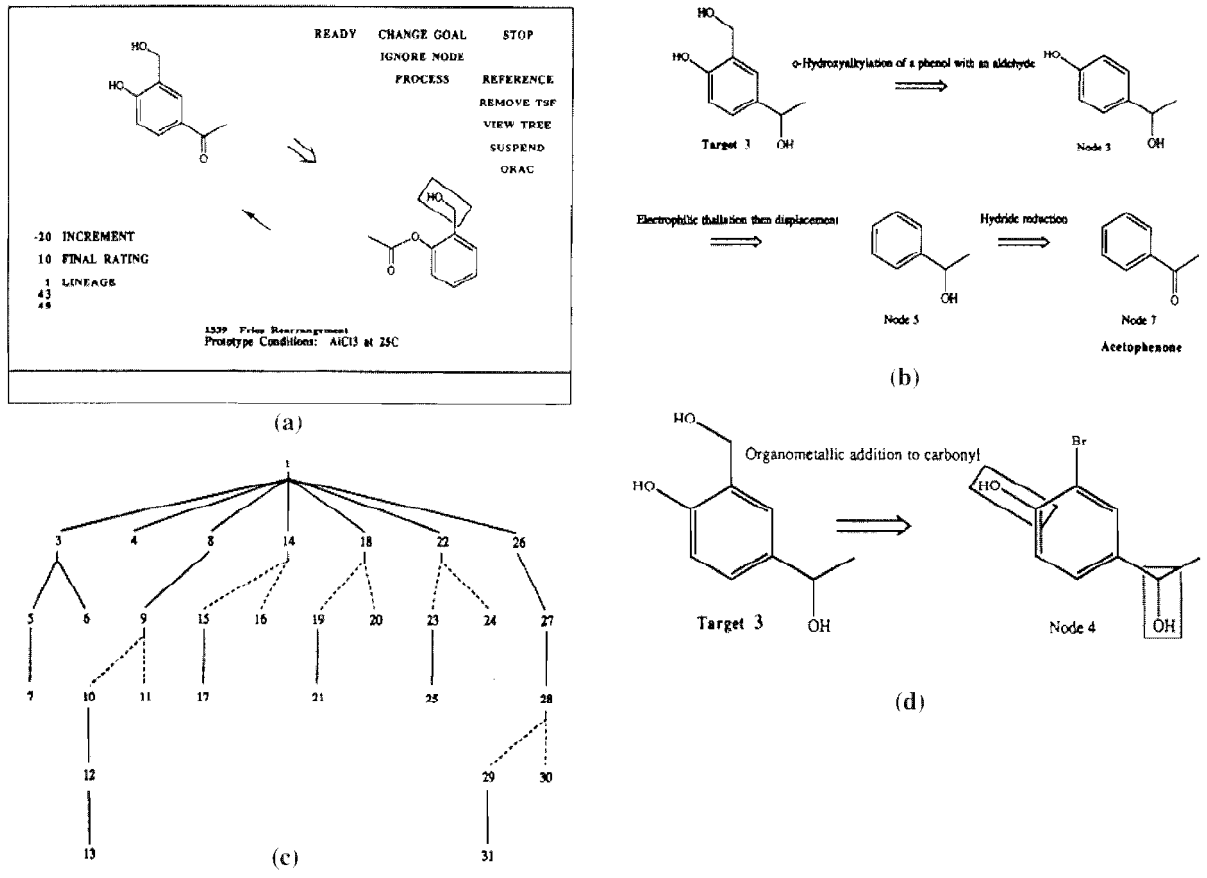


Figure 10.4. LHASA transform and retrosynthetic analysis. (a) Display of LHASA transform. (b) Retrosynthesis of **Target 3** to acetophenone. (c) Part of the tree from the retrosynthetic analysis of target. (d) Retrosynthetic removal of the hydroxymethyl group from **target 3** by a route involving an organometallic addition transform.

[Reprinted from Johnson, A.P.; Marshall, C.; Judson, P.N. *J. Chem. Inf. Comput. Sci.*, ***1992***, *32*, 411. Copyright © 1992 by the Amer. Chem. Soc.]

A useful description of this program was provided by Wipke and Howe:[38]

"One important aspect of the project has been the writing of a general purpose computer program which will aid the laboratory chemist and will employ both the basic and more complex techniques for synthetic design as elucidated by this study. The program (hereafter also called **LHASA**) is intended to propose a variety of synthetic routes to whatever molecule it is given. The responsibility for final evaluation of the merit of the routes lies with the chemist. The program is to be an adjunct to the laboratory chemist as much as any analytical tool." [38]

It is an interactive program that displays the target, allowing the chemist to select a synthetic strategy (or strategies). LHASA then suggests synthetic routes that satisfy the goals of the selected strategy.[48] The analysis generates retrosynthetic precursors and generates a synthetic tree (see Figure 10.4).[48] The chemist takes responsibility for choosing strategies and tactics and for deciding which precursors should be submitted to LHASA for further simplifications. LHASA selects the actual transforms, based on a database of known reactions. A sample retrosynthesis for aphidicolin is shown in Figure 10.5, taken from Corey's work.[61]

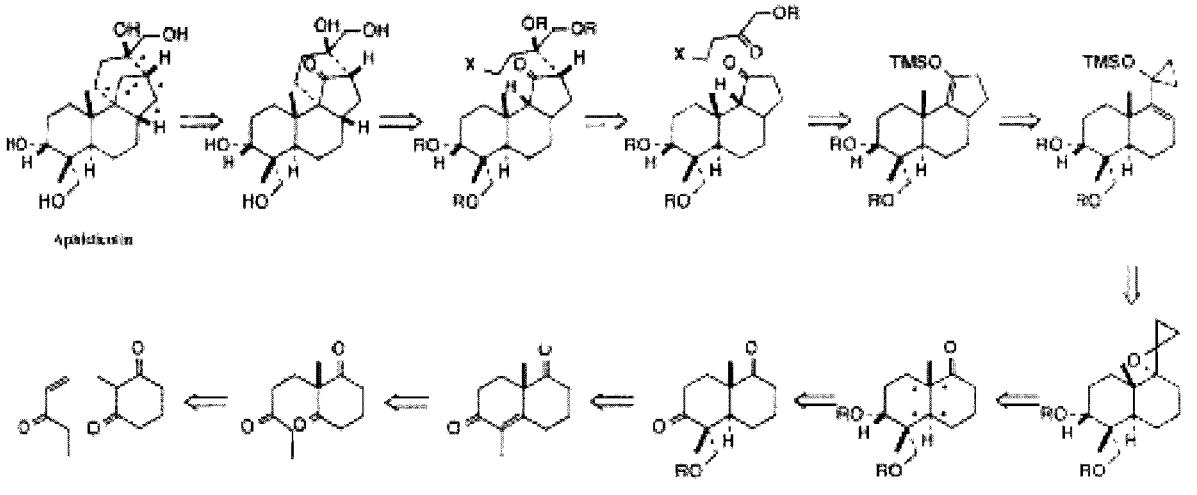


Figure 10.5. A sample retrosynthetic pathway generated by LHASA for the synthesis of aphidicolin.

[Reprinted from Corey, E.J.; Long, A.K.; Lotto, G.I.; Rubenstein, S.D. *Recl. Trav. Chim. Pays-Bas*, ***1992***, *111*, 304.]

10.5 THE STRATEGIC BOND APPROACH

Several available strategies can be applied to the specific task of breaking the first (and subsequent) bond(s) in the target. For the student beginning a study of synthesis, a more formalized approach would be useful. Corey enumerated several rules that tie together the strategies and goals of retrosynthetic analysis into a **strategic bond analysis**. These rules provide insight into the first disconnection and the complete synthetic tree. The analysis begins with an inspection of the target molecule to determine if the structure is compatible with simple solutions. Before the strategic bonds are determined, simplification may be possible if the

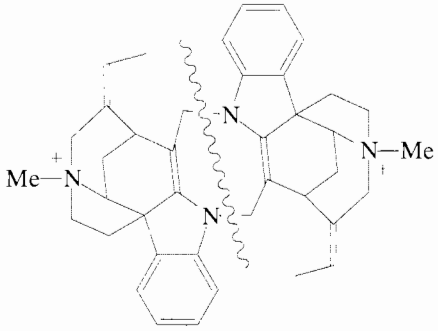
molecule possesses symmetry, is structurally similar to another molecule that has been previously synthesized, or has repeating units within the structure.

It is important to emphasize that the following rules are only guidelines. There are many examples of excellent syntheses that have violated one or more of them. They are presented as being a reasonable place to begin planning a synthesis, but by no means are they intended to discourage ideas that do not formally follow these rules. If a disconnection is reasonable and there is either known chemistry or planned chemistry to reconstitute that bond in a synthesis, proceed.

10.5.A. The Preliminary Scan

Corey's analysis begins with an inspection that will determine if there are methods by which the molecule can be simplified. Such simplification will shorten the synthesis and the retrosynthetic analysis will be biased to follow that route. There are three criteria.[62]

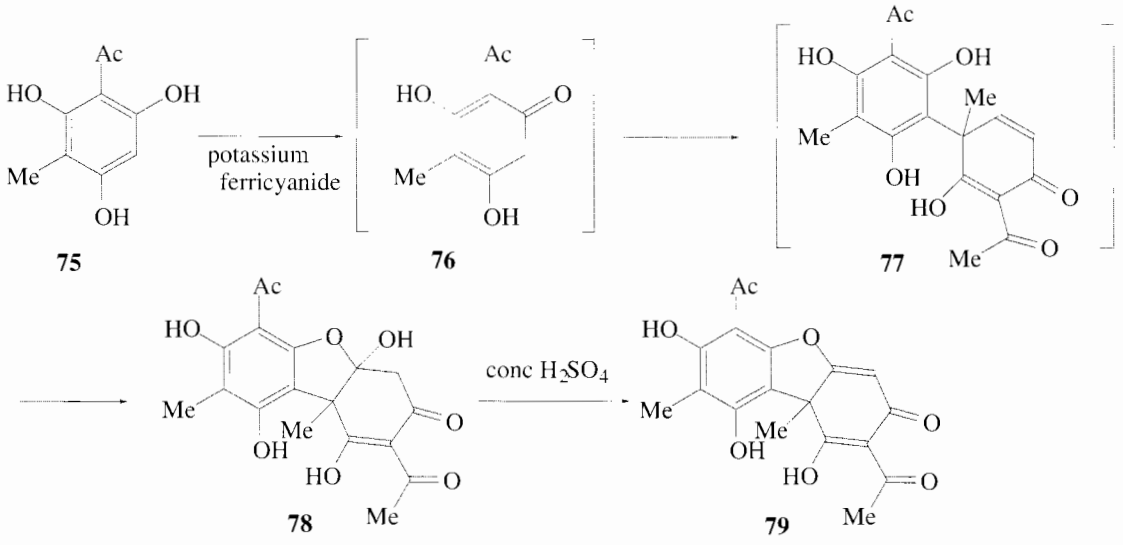
10.5.A.i. Is There Symmetry or Near Symmetry in Two Parts of the Molecule? If so, the synthesis may be simplified by synthesizing and then joining together the two or more identical pieces. A good example is the molecule C-toxiferin I (**74**),[63] which is essentially a dimer. In **74**, one-half of the molecule is



74

identical to the other and it has been shown that treatment with sulfuric acid cleaves the molecule into a single product that regenerates the dimer on treatment with hot sodium acetate.[63] Synthesis of one piece and joining the two identical pieces together greatly simplifies an overall synthesis with a built-in convergence.

The symmetry is not always obvious and the target should be carefully analyzed. Usnic acid (**79**) is an example of a molecule that possesses potential symmetry.[64] The molecule is not obviously symmetrical, but the symmetry indicated in the structure appears upon disconnection and corresponds to a retro phenolic oxidative coupling. The synthesis of usnic acid is shown in Scheme 10.5,[65] with a phenolic oxidative coupling of a single phenol derivative (**75**), which gave **77** via coupling of the initial oxidation product, **76**. The **phenolic oxidative coupling** reaction (sec. 13.8.B) is a radical process by which two phenol moieties are joined.[66] The two phenolic moieties reacted via an acid-catalyzed Michael reaction to give a dimer (**77**), which cyclized via the phenol hydroxyl group to give **78**. Treatment with concentrated sulfuric acid completed the two-step synthesis of **79**. Finding the potential symmetry greatly shortened the synthesis.

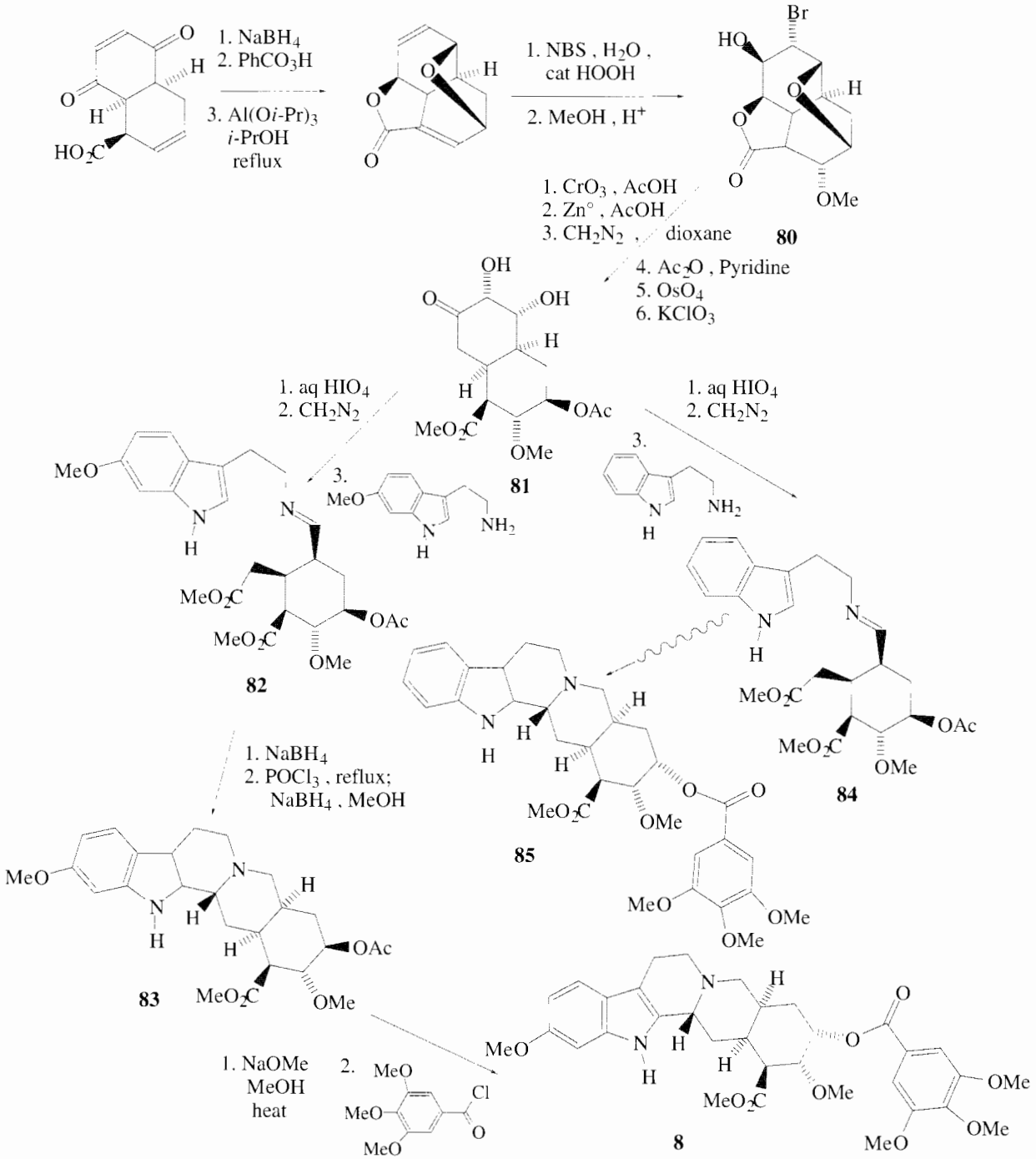


Scheme 10.5. Phenolic oxidative coupling strategy for the synthesis of usnic acid.

10.5.A.ii. Is the Problem Like One Already Solved? Woodward's synthesis of reserpine (**8**) is shown in Scheme 10.6.[8] An important intermediate in that synthesis was **80**. A natural product called deserpidine (**85**)[67] is structurally similar to **8**, but is lacking the methoxy group on the indole moiety. It closely mimics the activity of **8**[68] and a total synthesis of **77** was developed by Velluz[69] and later by Protiva.[70] Intermediate **81** from the Woodward synthesis was used as the starting material to give the alternative synthesis, also shown in Scheme 10.6.[70] Synthetic intermediate **82** (derived from **81**) was reacted with 6-methoxytryptamine (obtained with great difficulty) to give **83**.[8] Intermediate **83** was then converted to **8**. In the synthesis of **85**, the key intermediate was **84**, prepared by reaction of tryptamine with **81**. This simple modification of Woodward's synthesis obviously saved Velluz and Protiva the time and effort required to develop a new synthetic approach. This example suggests that thorough familiarization with the target, including knowledge of all previous syntheses of the target and also related compounds (i.e., thorough search of the literature) is always beneficial. One does not always want to mimic a literature approach, but when the target is structurally similar to one that is known, the use of a key intermediate or transformation sequence in designing a retrosynthesis is prudent and usually desirable. Obviously, if one has an improved method or route to a target, the retrosynthesis is biased to include this new method. It is common for a published total synthesis to be followed by several later syntheses that improve or expand upon it. Syntheses developed later are often useful for producing large quantities of the natural product, as the initial sequence may produce only small amounts (milligrams) of the target.

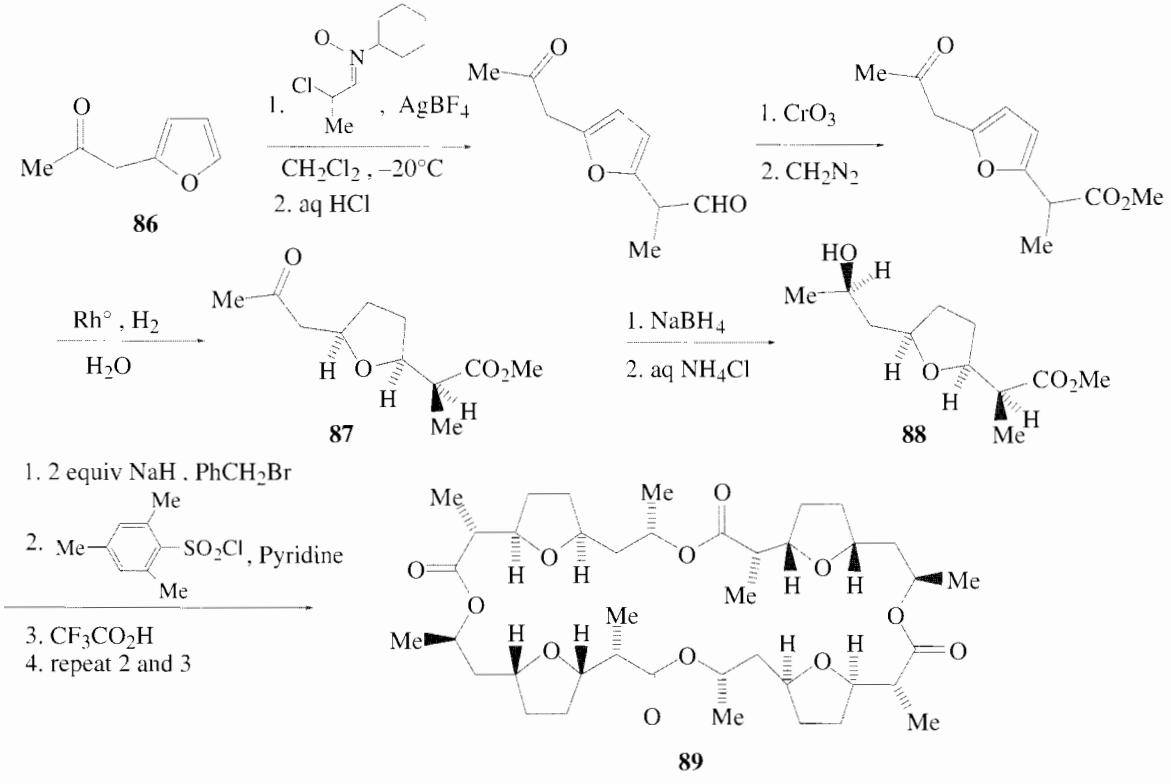
10.5.A.iii. Is the Molecule a String of Available or at Least Simple Pieces? The synthesis[71] of the macrolide antibiotic nonactin (**89**)[72] is a useful example. Nonactin consists of four units of nonactic acid (**88**), joined together in a tetrameric ring.[72] A total synthesis would be greatly simplified by preparing **88**, since the final synthesis of **89** would require only macrocyclization (formation of a large lactone ring –sec.

6.6.B),[73] for which several methods have been developed. Gerlach's synthesis of **89**, which is shown in Scheme 10.7,[71] utilized precisely this approach. The synthetic precursor of **88** was **87**, produced in several steps from furanyl derivative **86**. Note that when two remote, reactive ends of a molecule must be brought together so reaction can occur, intermolecular processes often dominate (sec. 6.6.B) and the low yield of **87** obtained by



Scheme 10.6. Syntheses of reserpine and deserpidine.

Gerlach is a result of such problems, which does not diminish the simplicity of the synthetic approach, however, which recognizes nonactin as a string of repeating fragments.



Scheme 10.7. Gerlach's synthesis of nonactin (89).

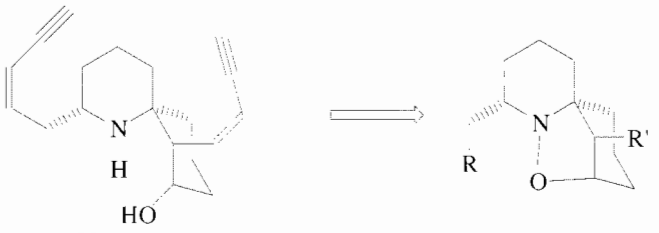
10.5.B. Criteria for Disconnection of Strategic Bonds

Once the preliminary scan is complete, the next step is to disconnect the molecule by breaking bonds that can be reconnected by known or reasonable chemical steps, to generate the synthetic tree. As discussed above, these important bonds are called strategic bonds. Bersohn has restated Corey's rules to tie together the strategies outlined in Section 10.4.[62,39] It is important to emphasize that though these rules are extremely useful, many excellent syntheses have been developed that break them. One should not be a slave to these statements but rather treat them as excellent suggestions for how to begin planning a synthesis:

1. Labile groups should be removed first.
2. Transforms should remove as much functionality as possible and should remove stereochemical centers where possible.
3. Favor transforms that generate closely related intermediates.
4. If a key process is interfered with by a certain substructure, then use a transform to remove that substructure.
5. Where possible, use transforms to build bridges between the goal atoms.
6. Convert the molecule under consideration into the product of one of the powerful reactions.
7. Disconnect appendages attached to atoms bearing certain functional groups such as OH or C=O.
8. Consider all pairs of functional groups in the molecule to ascertain whether known transforms can disconnect any of the intervening bonds.
9. In a ring system preferentially disconnect the strategic bonds.

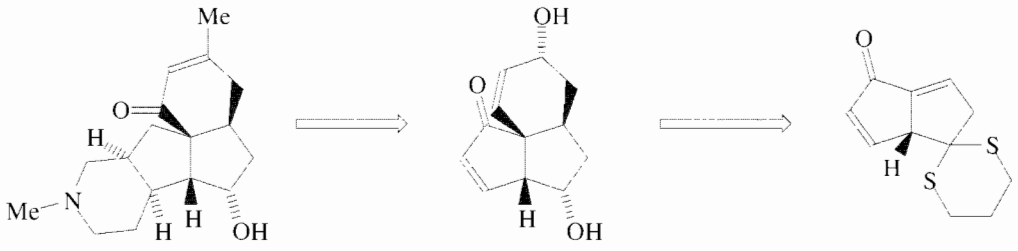
The examples that follow in Section 10.5.B.i–10.5.B.viii will illustrate an application of each of these rules.

10.5.B.i. Remove Labile Groups First. Removing a labile group is illustrated by a retrosynthetic step in Holmes' synthesis of (–)-histrionicotoxin, **90**.[74] The alcohol and conjugated ene–yne units in **90** are quite reactive,. Both units are removed in the initial disconnection and replaced with R and R' groups, which represent functionality that can be elaborated to the conjugated system. In addition, the labile amine and alcohol units are converted to the isoxazolidine unit in **91**. This disconnection allows one to focus on constructing the fundamental spirocyclic ring system, knowing that highly reactive groups will be added last.



90 **91**

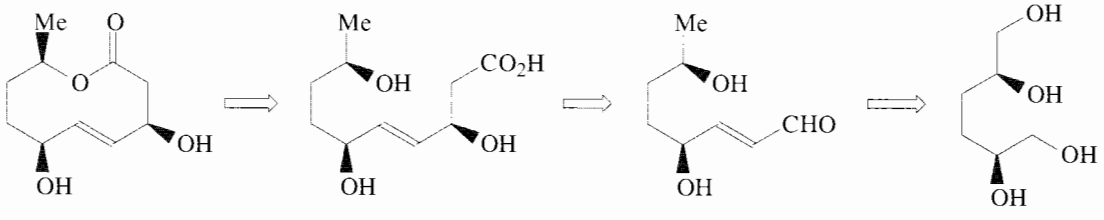
10.5.B.ii. Remove Stereochemical Centers. The vast majority of natural products and important synthetic targets are characterized by several stereogenic centers that are often contiguous. A major task of a total synthesis is the generation of these chiral centers, in a controlled and predictable manner. It is therefore important to plan all reactions, and the entire retrosynthesis, around stereoselective reactions. Chemical reactions that involve formation of bonds *at* a chiral carbon allow a measure of control over stereochemical induction. The asymmetric center and the reaction center usually have a 1,2-, 1,3-, or occasionally a 1,4-relationship. It is also possible that a remote center is held in close proximity due to a particular conformation,



92 **93** **94**

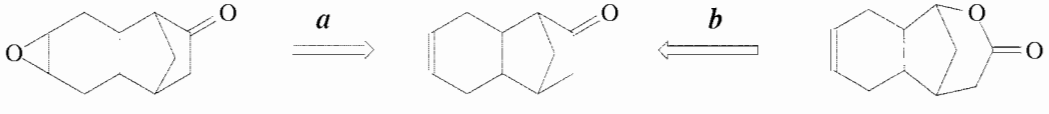
and exerts an influence on the reaction. Molecular or computer modeling is usually necessary to observe the correct influence of remote centers on a disconnection. Disconnections are, in general, made at a bond connected to the chiral center (1,2-relationship) rather than to a bond containing a pendant chiral center. In the Paquette and co-workers synthesis of magellanine (**92**),[75] disconnection of the piperidine ring removes two stereogenic centers, although the allylic alcohol center introduces another one (see **93**). The next disconnection removed the cyclohexenol ring along with two stereogenic centers, and the use of a protected carbonyl (the dithiane) effectively removes the stereogenic center at the secondary alcohol, giving **94**.

10.5.B.iii. Favor Closely Related Intermediates. It is usually preferable to simplify the target molecule in small bites (i.e., prune small branches of the synthesis tree rather than large branches). Moving too far down the synthetic tree with large disconnections will mean that several carbon–carbon bond–forming reactions or functional group exchanges are required to convert one disconnect product to another. It may be difficult to find transforms where several bonds can be formed simultaneously in the synthesis. Simplification should be done so that a minimum number of carbon–carbon bond–forming reactions and functional group exchanges are required for each disconnect product. In this way, it is easy to understand the simplification and the implications for the requisite chemical reactions., which can be illustrated by the relatively simple disconnection sequence used by Kibayashi and co-workers in a synthesis of (–)-(3*R*,6*S*,9*R*)-decarestrictine C_2, **95**.[76] The target was first converted to the seco-acid (**96**), removing the labile ester unit, and disconnection to aldehyde **97** suggests a condensation reaction to make that bond. The last disconnection leads to tetraol **98**, again suggesting a condensation reaction. In each case, one key bond is disconnected and the differences between target and disconnect product are structurally close and predictable. Generally, one disconnects only one or two bonds per disconnection, although more may be disconnected if the pieces are closely related.



95 **96** **97** **98**

10.5.B.iv. Remove Interfering Substructures. An example provided by Corey[59] is the disconnection of **99** and **101** to **100**. Path *a* is a simple epoxidation (sec. 3.4), and path *b* is a Baeyer–Villiger oxidation (sec. 3.6). A cyclic cis alkene moiety such as that in **100** shows moderate reactivity with peroxyacids, but the ketone moiety in **100** is very reactive, since it is strained. Disconnection of **101** to **100** is viable, since the synthesis will proceed without interference from the alkene moiety. Disconnection of **99** to **100**, however, requires that the interfering carbonyl be removed in any synthetic attempt. The best method for removal is to protect this ketone (sec. 7.3.B), as a ketal for example. In Figure 10.4,[60] the LHASA program generated a retrosynthetic sequence with boxes around reactive or interfering functional groups that can be protected and dashed boxes around unstable (interfering) groups that are not easily protected.

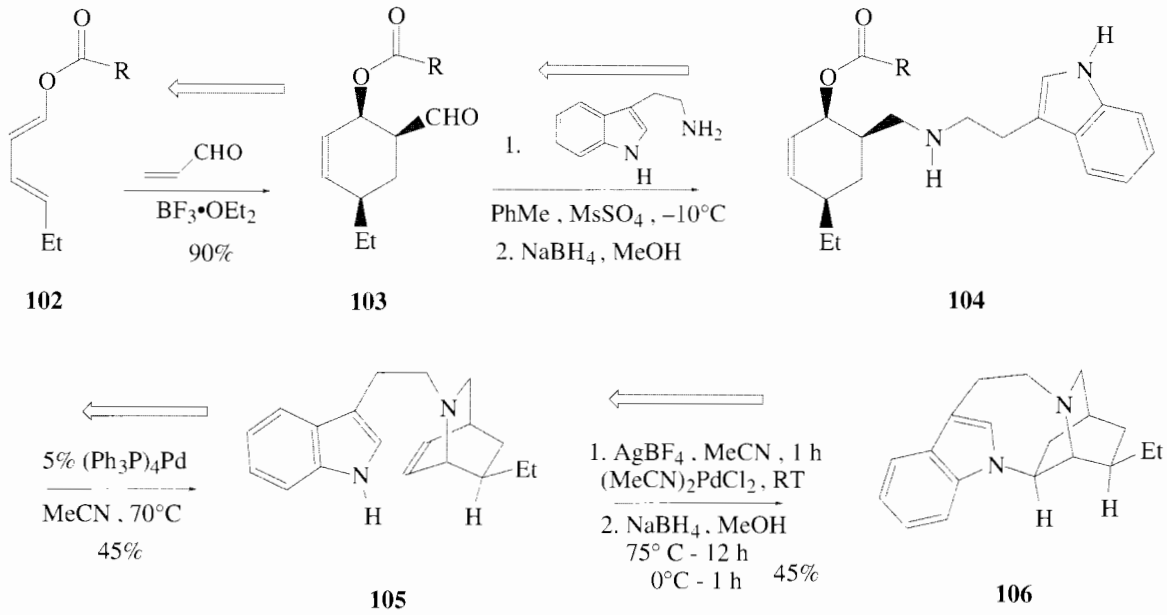


99 **100** **101**

Section 10.5.B.i suggested that labile groups should be disconnected first. Removing the reactive conjugated systems and β-amino alcohol unit in the first disconnection of (–)-histrionicotoxin illustrated this

rule. Both of these groups could interfere with reactions in a multi-step process leading to the final target. They are removed early in the synthetic tree (reconstituted late in the synthesis) to minimize any possible interference. In general, this rule refers to protection of interfering structure.

10.5.B.v. Use Transforms to Bridge Goal Atoms. If a disconnection results in cleavage of the target into separate pieces, chemical reconnection usually requires formation of one to four bonds. Two-bond disconnections are well known, although there are not many of them, and if three or four bonds must be formed, it is usually very difficult to rejoin all the bonds in one synthetic step. The Diels–Alder cycloaddition (sec. 11.4.A) is an example in which two bonds are connected. If possible, it is useful to bridge the two pieces together by formation of one of the requisite bonds in the retrosynthesis, bringing the two pieces close enough to allow subsequent formation of the other bond(s). A nice illustration of this principle is Trost's retrosynthetic analysis of ibogamine (**106**)[77] in Scheme 10.8 (⇐ represents a retrosynthetic disconnection and → represents the synthetic step). The first disconnection of the nine-membered ring gave **105** in which the two disconnected fragments are attached. The proximity of these fragments allows the usually difficult nine-membered ring to be formed in the synthesis. The bridged ring was disconnected to give **104**, in which the two fragments are still bridged. Disconnection to **103** gave a fragment (**102**) that was recognized as a precursor to the starting diene. In the actual synthesis (also in Scheme 10.8), reaction of intermediate **103** with tryptamine gave **104**, which bridged the indole and the azabicyclo[2.2.2]octane moieties, allowing formation of **105**. The organo-palladium reagent used for this coupling will be discussed in Section 12.7. Final joining of the bridged pieces gave **106**, completing the final synthesis.



102 **103** **104** **105** **106**

Scheme 10.8. Trost's synthesis of ibogamine (106).

10.5.B.vi. Convert the Molecule into the Product of One of the Powerful Reactions. Powerful reactions have been defined as those synthetic reactions that reliably increase molecular complexity.

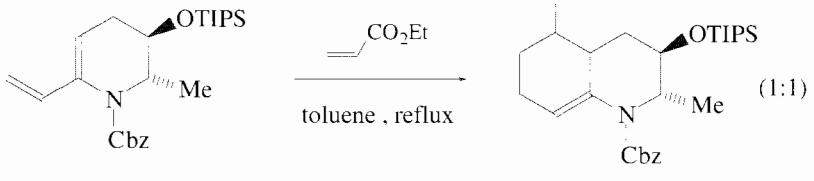
Disconnections that are based on powerful reactions will, therefore, greatly *decrease* the molecular complexity of the target, which is, of course, a major goal of a disconnection strategy. Corey listed several examples of such reactions.[48] These reactions and synthetic examples are shown in Table 10.1.[12]

The intermolecular **Diels–Alder reaction** (sec. 11.4) is shown first. Example 1 from Table 10.1 is a carbo-Diels–Alder reaction taken from the Cha and co-workers synthesis of clavepictine A.[78] Example 2 is a quinone Diels–Alder reaction reported by Mikami et al.[79] Example 3 is a hetero Diels–Alder reaction (sec. 11.7), where a Lewis acid catalyzed cyclization of an imine with a diene containing a chiral auxiliary. The initially formed cycloadduct was hydroxylated to give the corresponding ketone in good overall yield and excellent enantioselectivity. This example was take from Barluenga's synthesis of (–)-nupharamine.[80] Example 4 is a **Robinson annulation** (sec. 9.7.C) catalyzed by lanthanoid triisopropoxides.[81] Example 5 uses a **Birch reduction** (see sec. 4.9.E) in Corey's synthesis of desogestrel.[82] In this example, Birch reduction of the anisole ring was followed by hydrolysis to give the conjugated ketone in 85% yield for two steps. Example 6 is a cationic π cyclization using Speckamp's procedure[83] (sec. 12.2.C)

Table 10.1. Powerful Reactions

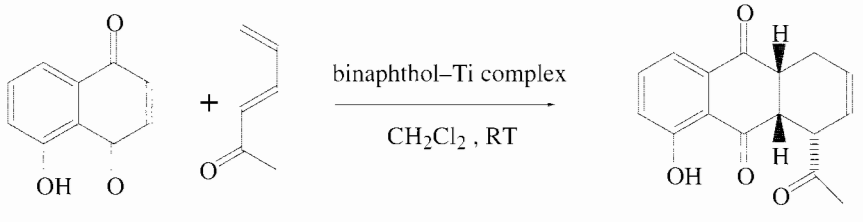
[a] The listing of reaction types 1–19 is adapted from Corey, E.J.: Wipke, W.T. *Science*, ***1969***, *166*, 178 by courtesy of Professor E.J. Corey. Copyright 1969 by the AAAS. The specific examples are duly referenced.

1. Carbocyclic Diels–Alder



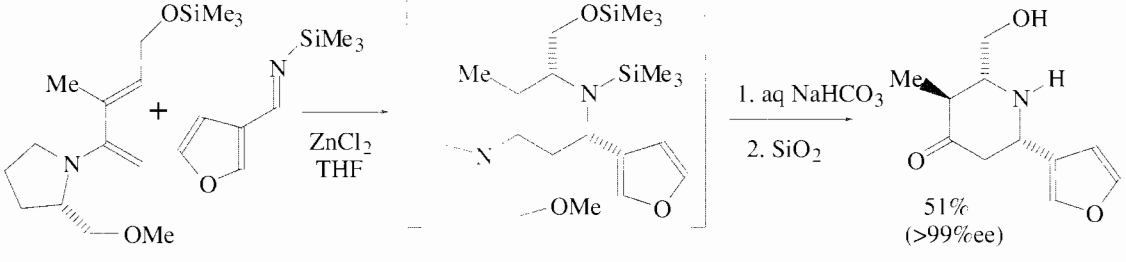
79%[78]

2. Quinone Diels–Alder



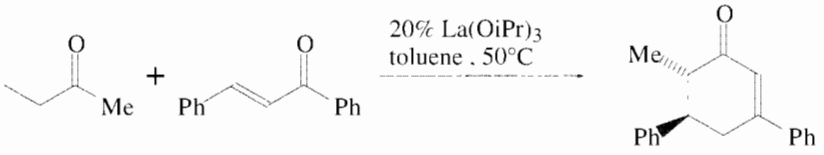
86%[79]

3. Heteroatom Diels–Alder



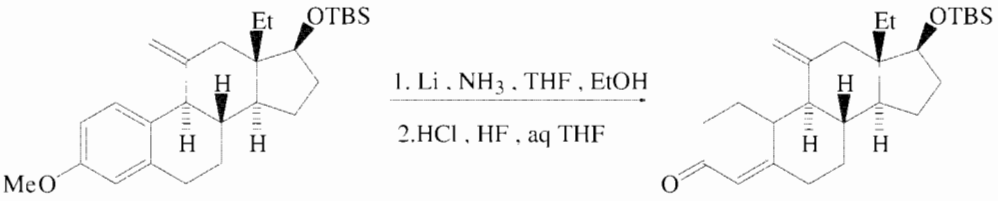
51%[80]

4. Robinson Annulation



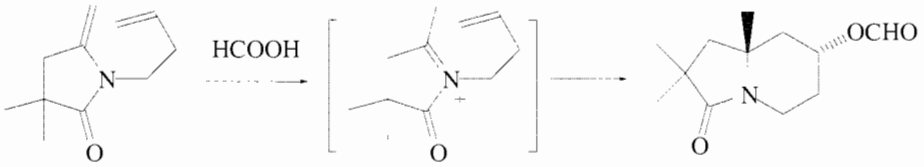
82%[81]

5. Position Selective Partial Aromatic Reduction



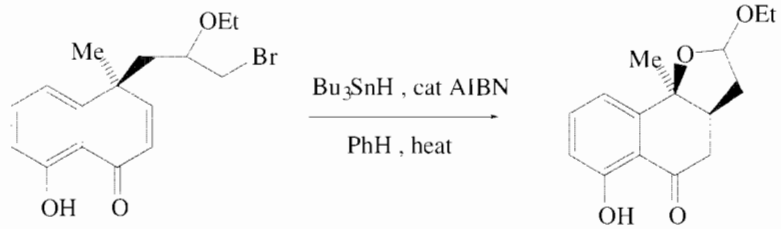
85%[82]

6. Cation π Cyclization



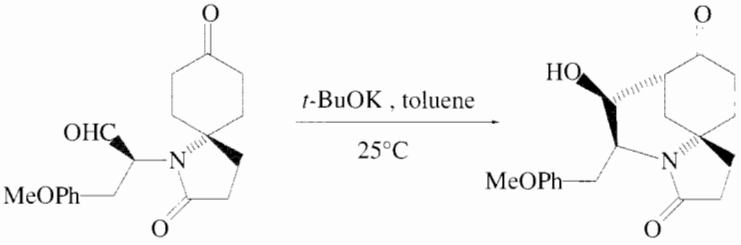
x[83]

7. Radical π Cyclization



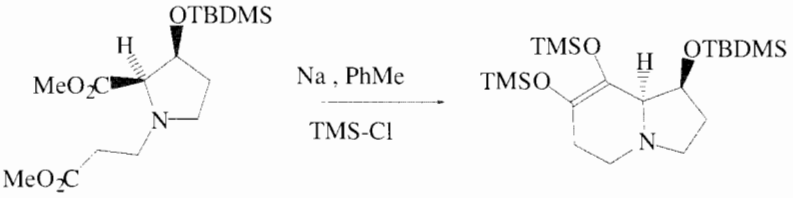
90%[85]

8. Aldol Condensation



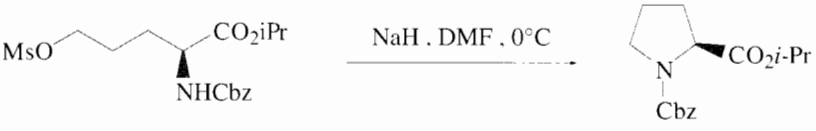
70%[86]

9. Silyl-acyloin Cyclization



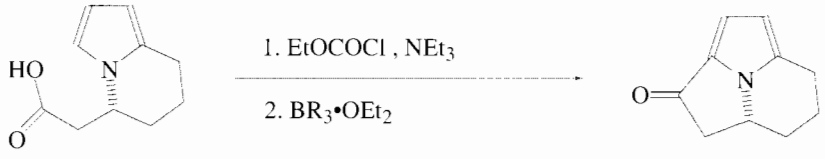
x[87]

10. Internal S_N2 Cyclization



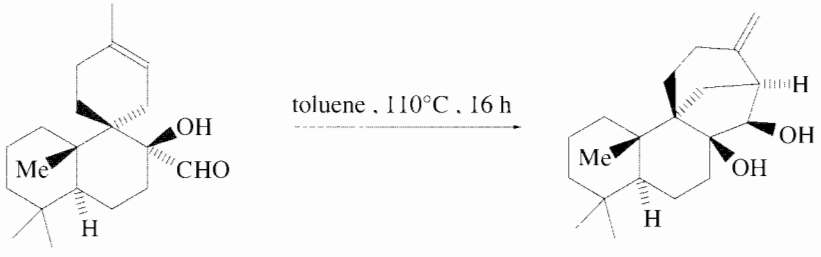
85%[88]

11. Friedel–Crafts Type Cyclization



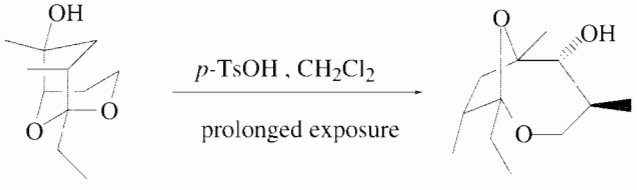
57%[89]

12. Internal Ene Reaction



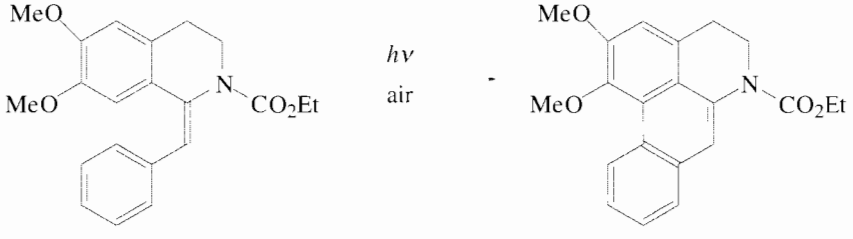
94%[90]

13. Cationic Rearrangement



-[91]

14. Photocyclization

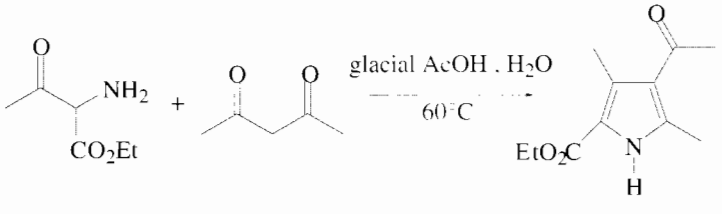


-[92]

15. Fischer Indole Synthesis

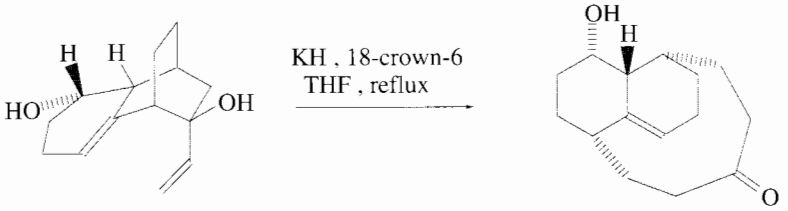
45%[94]

16. Knorr Pyrrole Synthesis



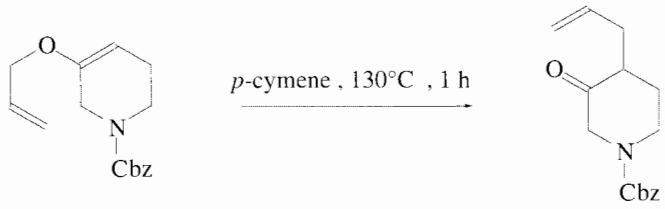
-[95]

17. [m,n]-Sigmatropic Rearrangement (anionic Oxy-Cope)



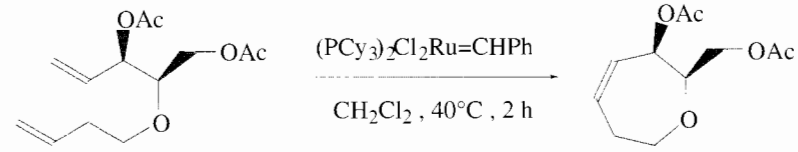
80%[96]

18. [*m,n*]-Sigmatropic Rearrangement (Claisen)



69%[97]

19. Alkene metathesis



95%[98]

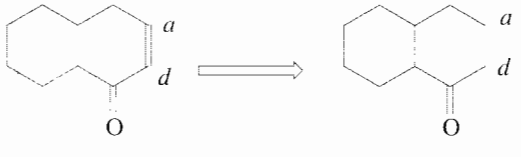
[a] Table 10.1, continued from p 862.

reported by Grubbs, which also employs a $Cp_2Ti{=}CH_2$ olefination reaction (sec. 8.8.D).[84] In Example 7 a radical π cyclization (sec. 13.7), reported by Stork et al. in a synthesis of 12a-deoxytetracycline,[85] generated the protected lactol ring in 90% yield. Example 8 is an **aldol condensation** (sec. 9.4.A) reported by Snider and Liu in a synthesis of (–)-FR901483.[86] Example 9 used the silyl-acyloin cyclization (sec. 13.8.E) to close the ring in the Sih and co-workers synthesis of castanospermine.[87] The intramolecular S_N2 displacement (sec. 2.7.A) of the primary mesylate by the nitrogen nucleophile in Example 10 was reported by Schmidt in a synthesis of hexahydropyridazine-3-carboxylic acid derivatives.[88] This transformation is not necessarily a powerful reaction, but was included because it represents those reactions that give one the ability to control relative and absolute stereochemistry because the S_N2 reaction proceeds with inversion of configuration (secs. 2.7.A, 6.2, 6.3). Example 11 shows a variation of the **Friedel–Crafts acylation reaction** (sec. 12.4.D) in which a mixed anhydride is generated, allowing a subsequent reaction with boron trifluoride etherate to give the ketone in 57% yield as part of Vallée's synthesis of (*R*)-(+)-myrmicarin 217.[89] In this particular case, the authors found that direct treatment of the acid with P_2O_5 gave only a 20% yield of the ketone. Example 12 is an internal **ene reaction** (sec. 11.13) taken from the White et al. synthesis of 2-desoxystemodinone,[90] in which the carbonyl of the aldehyde reacts with the allylic unit of the cyclohexene ring to give the final product in 94% yield. In Example 13, Martin et al. treated the spiro-ketal starting material with acid and observed the rearrangement product shown as part of a synthesis of a protected seco-acid of erythronolide A.[91] A

photocyclization (secs. 13.4, 13.7) used by Cava et al. in a synthesis of (±)-nuciferine is shown in Example 14.[92] In this case, the hexatriene-cyclohexene isomerization is reversible, allowing the cyclization to proceed in the presence of an oxidizing agent such as air.[93] A recent illustration of the **Fischer indole synthesis** (sec. 12.5.C) was reported by Bonjoch et al. in a synthesis of deethylibophyllidine,[94] shown in Example 15. In Example 16, Bullock et al. used a **Knorr pyrrole synthesis** procedure to prepare an indole used in the synthesis of coproporphyrin.[95] An illustration of the anionic **oxy-Cope rearrangement** (sec. 11.12.C.ii) is shown in Example 17 to illustrate **sigmatropic rearrangement** processes (sec. 11.12.A). This reaction was used by Hanna and co-workers in a synthesis directed towards vinigrol.[96] Example 18 is another sigmatropic rearrangement, the **Claisen rearrangement** (sec. 11.12.D), in this case used by Takeuchi et al. in a synthesis of febrifugine.[97] Finally, there has been an increased interest in the alkene metathesis reaction in recent years, illustrated by the reaction in Example 19 as part of the Crimmins and Choy synthesis of (+)-laurencin.[98] The ability to generate two alkene units in different parts of the molecule and then use them to form a ring certainly makes this reaction worthy of addition to the list of powerful reactions.

The reactions in Table 10.1 were classified as powerful due to the variety of transformations (formation of rings, molecular reorganization, generation of reactive functional groups from relatively unreactive functionality, or for functional group insertion) that were achieved all in essentially one synthetic step. Other reactions could easily be termed powerful, but these are sufficient to illustrate that if a reaction induces extensive and useful structural modifications, the synthetic tree should be biased to take advantage of that powerful chemistry.

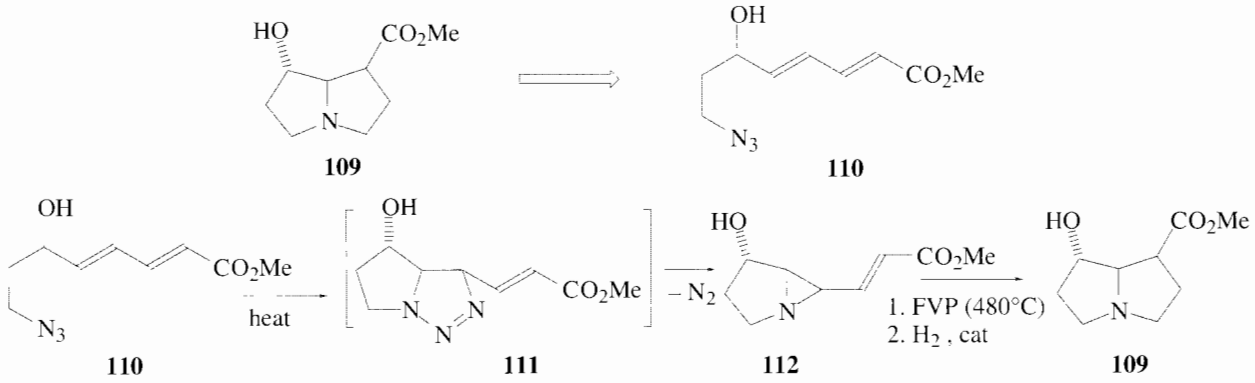
10.5.B.vii. Disconnect from Atoms Bearing Certain Functional Groups. Certain functional groups are tied together along a reaction pathway. In many cases, the functional group transforms (CH—OH → C=O and C=O → CH—OH for example) involve ionic intermediates or reactants. Ionic functional group transformations are a useful illustration of this rule. Both anionic and cationic reactions involve a (positive) or (δ+) end and a (negative) or (δ–) end. The functional groups corresponding to these reactive fragments have a special reactivity relationship which should be exploited. When a bond is disconnected, identification of each end of the disconnect product as a donor or acceptor can aid identification of possible reaction pathways to reconnect the bond (sec. 1.2). The disconnection of **107** with the appropriate donor and acceptor sites clearly suggests an **aldol condensation** (sec. 9.4.A) of **108** to generate **107**.



107 **108**

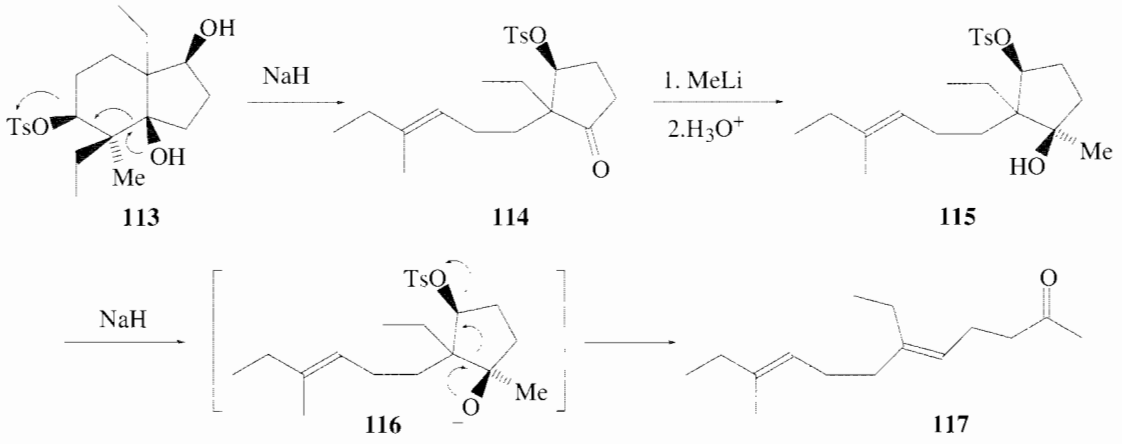
Other types of reactions often have functional groups that show a special relationship in a particular reaction. The disconnection **109** ⇒ **110** suggests a relationship between the tertiary amine in **109** and the dienyl azide moieties in **110**.[99] When **110** was heated in toluene, a [3+2]-cycloaddition occurred to give a

triazoline (**111**) (sec. 11.11.H) but this unstable molecule decomposed (with loss of nitrogen) to form vinyl aziridine **112** as a mixture of stereoisomers.[99] When **112** was heated to 480°C (using flash vacuum pyrolysis,



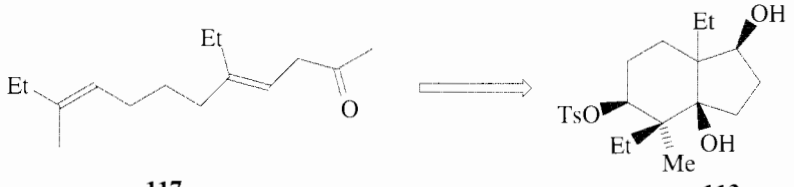
FVP), the nitrogen analog of a **vinyl cyclopropane rearrangement** (sec. 11.12.B) occurred and was followed by catalytic hydrogenation to give **109**. This reaction sequence (azide addition, vinyl cyclopropane rearrangement) led to a bicyclic amine, linking the amine in **109** with the azido diene moieties in **110**. Clearly, these groups have a special relationship that can be exploited by a combination of reactions.

10.5.B.viii. Consider Bonds Related by Known Transforms. Some functional groups are related by the reactions that transform one to the other. They may be as obvious as alcohol → ketone. There are other transformations, however, that connect or disconnect several bonds and/or functional groups at one time. The relationship is not always obvious, but its recognition and exploitation can greatly simplify a target in one disconnection.



An important and useful example is the **oxy-Cope rearrangement** (see Example 17 in Table 10.1) in which the diene structure is related to the alkene-ketone functionality in the final product. Another example is the well known 1,3 elimination reaction known as the **Grob fragmentation** (sec. 2.9.E).[100] In this case, the alkoxide and the leaving group (tosylate in **113** and **116**) are related to the carbonyl and alkenyl unit via the 1,3-elimination. Recognition of the spatial and chemical relationship available via the Grob fragmentation

allows one to plan a disconnection of **117** to **113**.[101,100] In the synthetic sequence, treatment of **113** with sodium hydride generated an alkoxide that opened the six-membered ring, with displacement of tosylate, to give **114**. A second base induced fragmentation was possible after conversion of **114** to alcohol **115**. Sodium hydride generated alkoxide **116**, and the Grob fragmentation led to **117**.[100]



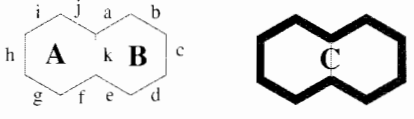
117 **113**

10.6. STRATEGIC BONDS IN RINGS

10.6.A. Carbocyclic Rings

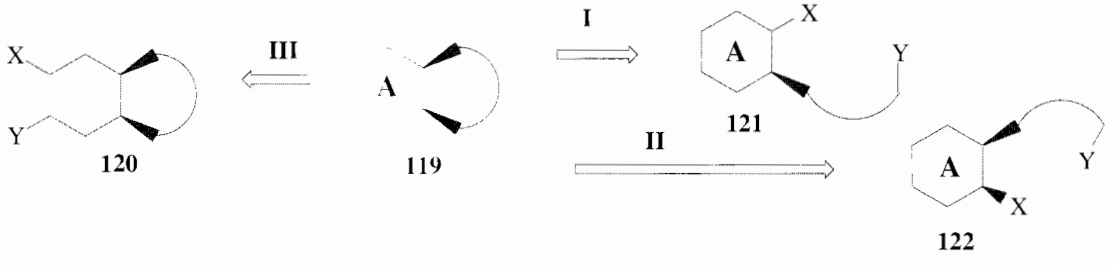
In addition to the eight criteria in Section 10.5.B, there is a ninth rule[62] that identifies strategic bonds in rings. These bonds are strategic because their disconnection gives the most simplification to a polycyclic molecule. Corey devised a set of guidelines that accommodate the special problems encountered in monocyclic and polycyclic structures.[57]

1. **Strategic bonds must be in a primary ring.** A **primary ring** is one that cannot be expressed as the envelope of two or more smaller rings bridged or fused to one another.[57,102] In general, five-, six- and seven-membered rings are easy to form, whereas other rings (especially C_8 and larger) are difficult to form by cyclization techniques (secs. 1.5.C, sec. 6.6.B). The two six-membered rings A and B in **118AB** are primary rings but the 10-membered ring C (see **118C**), which encloses A and B, is not (i.e., bond **k** is *not* strategic). It is important to note that bonds ***a-i*** are all strategic by this rule since every one is a part of a primary ring. The presence of ring C as an envelope of rings A and B does not change this.



118AB **118C**

2. **Strategic bonds must be directly attached to another ring.** The strategic bond should be exo to another ring. A ring disconnection that produces two functionalized appendages leads to a more complex overall synthesis. Three disconnections are shown for **119**. Paths I and II disconnect a bond exo to ring A, giving



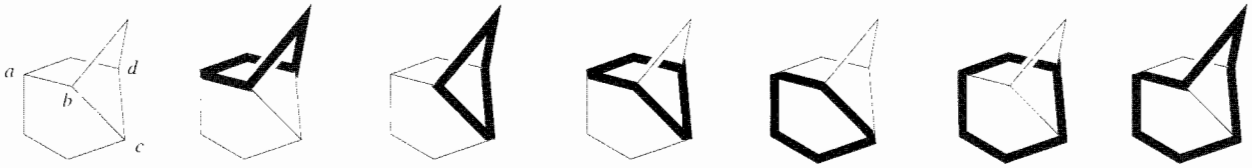
120 **119** **121** **122**

121 and **122**, respectively. Synthetically, this ring-closure is straightforward and potentially stereoselective. Disconnection III leads to **120**, which is a more difficult intermediate to prepare. Although the ring closure for III is probably facile, the disconnections in I or II lead to greater simplification and have a greater potential for stereocontrol. There are very few ring closure methods in which bonds are fused to preexisting three-membered rings and strategic bonds may not be exo to rings of that size.[57,102]

3. **Strategic bonds must be in rings with the greatest degree of bridging**. Disconnection of a bond that is highly bridged (connected to several rings) leads to greater simplification of that structure. Disconnection **A** in the highly bridged four-membered ring of **120** leads to **121** that has a bicyclo[4.4.0]decane unit, whereas disconnection **B** leads to **122**. The bicyclo[3.1.1]heptane ring system in **122** is less accessible and provides less simplification than **121**.

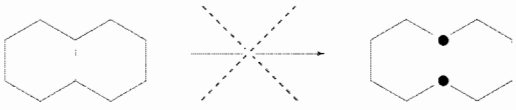
125 **123** **124**

A **maximum bridging ring** is defined as one that is bridged at the greatest number of sites. The maximum bridging ring(s) is(are) selected from the set of "synthetically significant rings that is defined as the set of all primary rings and all secondary rings less than eight membered."[57,102] Structure **126** has six synthetically



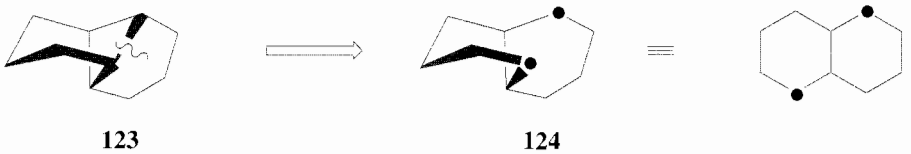
126 **A** **B** **C** **D** **E** **F**

significant rings: **A**, **B**, **C**, **D**, **E**, and **F**.[102] The highlighted rings in **A** → **D** are primary rings, but the highlighted rings in **E** and **F** are secondary. Ring structure **C** is bridged at four sites, more than any other, and is the maximal bridging ring.[57] Ring **B** contains as many bridgehead sites as **C**, but it is not a maximal bridging ring because it is bridged to other rings at only two of these sites (***b*** and ***d***). Therefore, the number of times a ring is bridged is not a valid criterion for determining maximal bridging character. Ring **E** is bridged to as many rings as ring **A** but has one less bridgehead site than **C**.



118 **127**

4. Bonds common to a pair of bridged primary rings are not strategic. Any bond common to a *pair* of bridged or fused primary rings whose envelope is eight membered or larger cannot be strategic.[57] Such a disconnection would generate a ring of more than seven members. Disconnection of the central bond in **118**



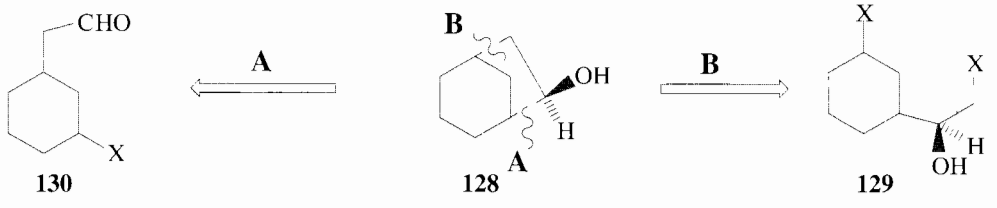
123 **124**

118 **127**

would result in a 10-membered ring compound (**127**) and rings of this size are often difficult to synthesize. For that reason, this type of disconnection should be avoided.[102] If the two fused or bridged rings are *directly* joined elsewhere by another bond (as in **123**), it *may* be strategic. As shown in **123**, disconnection of the indicated bond does not produce a 10-membered ring but two fused six-membered rings (see **124**). Similar disconnection in **115**, however, gives a 10-membered ring (**127**), as mentioned above, and is not strategic.

5. Bonds within aromatic rings are not strategic. Aromatic nuclei are common fragments in natural products but they are usually added or reduced as required. It is rare that a cyclohexene is incorporated and oxidized to the benzene derivative. Notable exceptions are quinones (sec. 3.3.A), which are commonly used as synthons and later converted to functionalized aromatic rings.[103] Incorporation of a carbocyclic ring and subsequent aromatization often requires harsh conditions and several synthetic steps. For these reasons, it is rarely useful to create an aromatic ring in a disconnection step, unless aromatization is facile and non-injurious to other functionality.

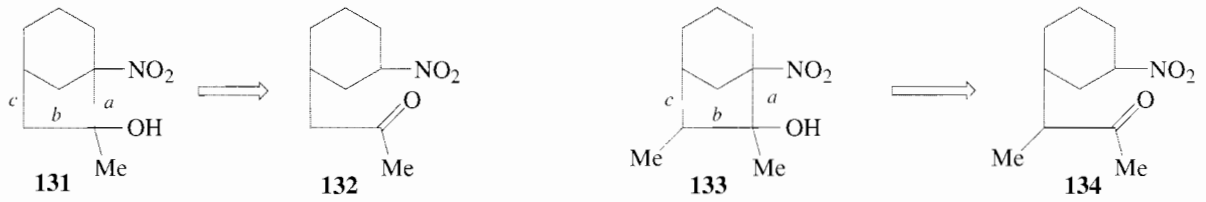
6. In a cyclic arc, cleavage of the bond should not leave stereocenters in the side chain. Reactions that join two fragments to generate a chiral center allow greater control than those reactions that join fragments containing a chiral center remote to the site of bond formation. Disconnection of bond **B** in **128** would lead to **129**, requiring the synthesis of the alcohol with a stereogenic center on the chain prior to ring closure. It is



130 **128** **129**

not clear there would be any control over the stereochemistry of that center as it is formed. The reaction resulting from disconnection of bond **A** (to **130**), however, forms the ring and generates the stereogenic center simultaneously. Disconnection of **128** to **130** will lead to a shorter synthetic sequence and is likely to proceed with reasonable stereoselectivity.

A special case arises when the bond is attached to a stereogenic center but that center is not the only one on the arc linking the two common atoms.[57] Such a bond may be strategic. In **131**, bond ***a*** is strategic, since the arc in the disconnect product (**132**) does not contain an asymmetric center. In **133**, the arc contains a stereogenic center and bond ***a*** is not strategic since that disconnection gives **134**.



These rules can be applied to a carbocyclic molecule such as **135**. An analysis based on these six rules is shown in Table 10.2.[57] Rule 1 shows that all bonds are part of a primary ring and rule 5 does not apply since there are no aromatic rings. Rule 2 shows that several bonds are exo to primary rings, indicated in **A**. The primary rings are highlighted in **B-D**. There are larger rings forming an envelope of these smaller rings, but bonds exo to those highlighted rings will take into account all possibilities. Rule 3 suggests that bonds ***i, j, l, f,*** and ***n*** are part of bridging rings. Disconnection of bond ***m*** is ruled out since the disconnection is away from the stereogenic center and does not involve an exo bond. Disconnection of bond ***k*** leads to a large ring and is ruled out. Bonds *b-d*, *f*, and *g-i* are not disconnected since it would violate Rule 6.

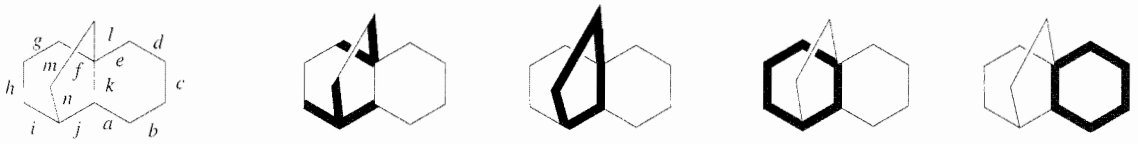


Table 10.2. Strategic Bond Analysis for Carbocyclic Compound 132

BOND \ RULE	1[a]	2[a]	3[a]	4[a]	5[a]	6[a]	Strategic
a	RA	RA		RA	X		
b	RA			RA	X		
c	RA			RA	X		
d	RA			RA	X		
e	RA	RA		RA	X	RA	
f	RA	RA	RA	RA	X	RA	YES
g	RA			RA	X		
h	RA			RA	X		
i	RA	RA	RA	RA	X	RA	YES
j	RA	RA	RA	RA	X	RA	YES
k	RA	RA		X	X	RA	
l	RA	RA	RA	RA	X	RA	YES
m	RA			RA	X		
n	RA	RA	RA	RA	X	RA	YES

[a] RA = rule applies, and X = rule is not applicable.

10.6.B. Heterocyclic Rings

The six rules discussed in Section 10.6.A are applicable to a wide variety of carbocyclic ring systems. If a bond in the ring is connected to an heteroatom, that bond can be considered strategic if it satisfies rules 2, 4, 5,

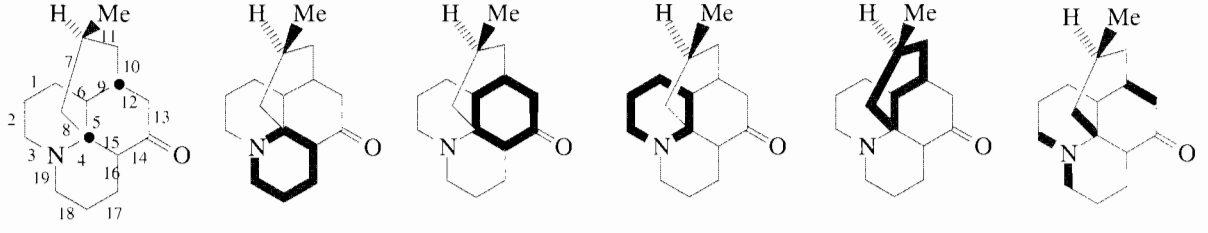
and 6. Corey generated the strategic bonds for lycopodine (**133**) in Figure 10.6 with these rules.[57] Bonds 3, 12, 14, and 19 were found to be strategic for the *first* disconnection. Thereafter, these bonds may or may not be strategic in the disconnect product, which should be reexamined to determine new strategic bonds. This process is continued as needed to generate a synthetic tree.

1. Structure of lycopodine (arbitrary bond numbering). See **136**.
2. Primary rings. There are four primary rings, highlighted in **A–D**.
3. No synthetically significant (< eight-membered) secondary rings.
4. Bridgehead atoms. There are two, marked with (•) in **136**.
5. Strategic bond determination by the carbocyclic procedure.

Disconnection of bonds ***e*** and ***a*** leads to complex ring systems relative to the other possible disconnections. The remaining disconnections are bonds ***l***, ***n***, ***f***, ***j***, and ***i***. These fragmentations show reasonable simplification of the ring system and can be reformed by reasonable synthetic routes. Rule 4 (brdigehead atoms) discounts only bond ***k*** since it would open to a 10-membered ring, which leads to bonds ***l***, ***f***, ***n***, ***j***, and ***i*** as strategic (see the highlighted bonds in **E**).

bond number (numbering from 136)

Rule 1:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Rule 2:			3	4	5	6		8	9	10		12		14	15	16			19
Rule 3:					5			8	9	10		12	13	14	15				
Rule 4:	1	2	3			6	7	8		10	11	12	13	14		16	17	18	19
Rule 5:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Rule 6:	1	2	3	4	5	6	7		9		11	12	13	14	15	16	17	18	19



136 **A** **B** **C** **D** **E**

6. Strategic bond determination: carbon–heteroatom procedure

	Bond number																		
Rule 2b:			3	4															19
Rule 4:	1	2	3			6	7	8		10	11	12	13	14		16	17	18	19
Rule 5:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Rule 6:	1	2	3	4	5	6	7		9		11	12	13	14	15	16	17	18	19

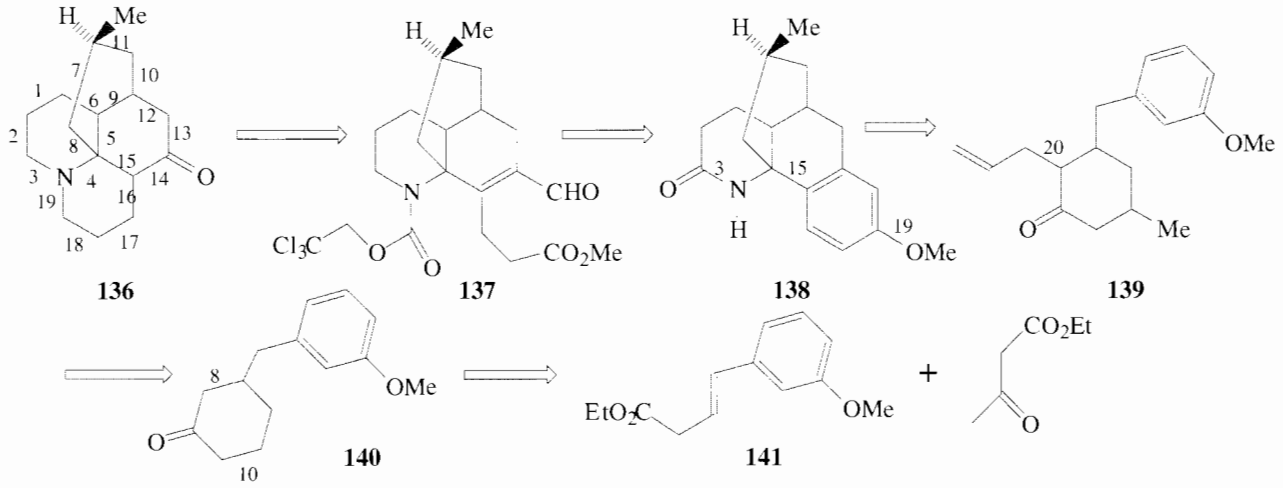
7. Strategic bonds: 3, 12, 14, 19 as shown in **E**:

Figure 10.6. Strategic bond analysis of lycopodine, 136.

[Reprinted with permission from Corey, E.J.; Howe, W.J.; Orf, H.W.; Pensak, D.A.; Petersson, G. *J. Am. Chem. Soc.*, ***1975***, *97*, 6116. Copyright © 1975 American Chemical Society.]

A retrosynthetic analysis of Stork's synthesis of lycopodine is outlined in Scheme 10.9.[104] The numbering system used in Corey's analysis (Figure 10.6) is retained, with bonds 3, 12, 14 and 19 being strategic. Bond 19

of **133** is disconnected to give **134**. It is noted that Corey's rules do not formally list manipulation of functional groups prior to disconnection of the target, but such flexibility is expected in any plan. Disconnection of **134** to **135** involves cleavage of bond 19, strategic by Corey's analysis, and the novel use of an aromatic ring as the equivalent of bonds 16–19. Further disconnection shows that bond 15 in **135** is now strategic, although it is not in **133**. This emphasizes that each disconnect product should be analyzed separately in order to make full use of the strategic bond approach and maximize one's synthetic options. Bond 3, which is strategic in **133**, is disconnected to give **136**, and disconnection of bond 20 gives **137**. The final disconnection (to **138** and ethyl 3-oxobutanoate) disconnects bonds 8 and 10. These are not strategic in **133**, but are strategic in a simple molecule such as **137**.



Scheme 10.9. Stork's synthesis of lycopodine (136).

Corey provided several additional analyses or a variety of polycyclic molecules (see Figure 10.7).[57] The strategic bonds are shown in bold lines offering several disconnections for each target. Disconnection of each strategic bond will lead to a different synthetic approach (a different branch on the synthetic tree). Indeed, disconnection of one strategic bond can generate several completely different syntheses, as will be shown in Section 10.7. Determining a few retrosynthetic schemes for these targets would be a useful exercise.

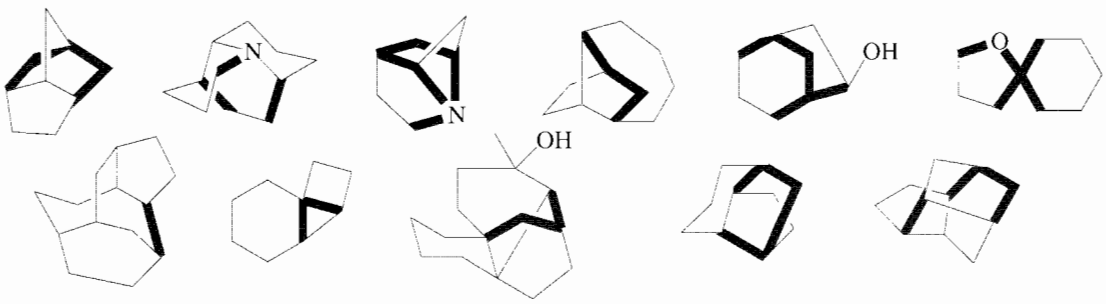


Figure 10.7. Strategic bonds in selected ring systems.

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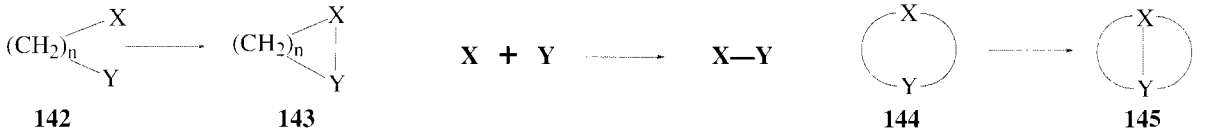
10.6.C. An Intramolecular Strategy

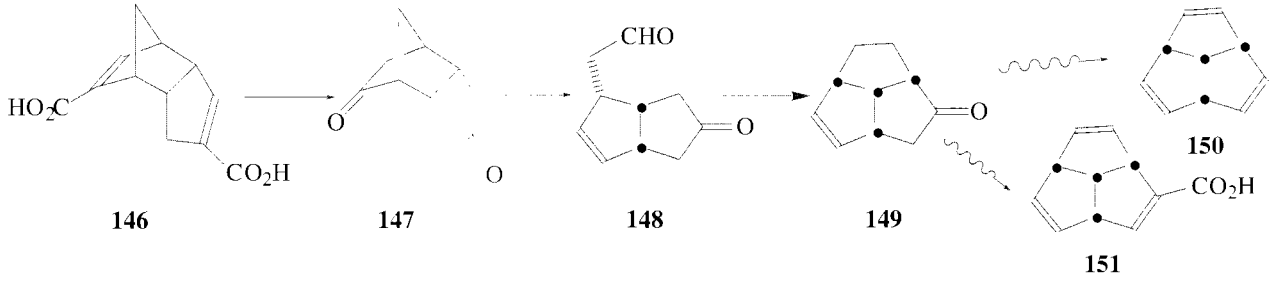
Deslongchamps developed a strategy[13] for the synthesis of dissymemetrical molecules that relies on an intramolecular approach. Such molecules are desirable since this dissymmetry imposes stereochemical restrictions, and if that structure also has a rigid conformation and the desired absolute configuration, this synthetic route is much more attractive. In other words, when two ends of a molecule react, the transition state for that reaction will assume many if not all of the conformational restriction for the ring being formed, which was discussed in Sections 1.5.B, 6.5, 6.6.B. From a strategic viewpoint, if it is possible to tie together a reaction



142 **143** **144** **145**

center and a reagent, this will limit the angles from which a reagent can approach the reaction center and has a great influence on the stereochemistry of the product.[13] This is an intramolecular process and can be illustrated by reactive species **142** where **X** and **Y** are tied together by an intervening chain of methylene units. If an intramolecular reaction occurs, the product is a ring illustrated by **143**. When this is compared to the intermolecular reaction of **X** and **Y** to give **X—Y**, it is clear there is little control in this latter process since there are no conformational restrictions. The chain length (n in **142**) must allow generation of a ring with a low barrier to its formation (3–7, n = 1–5). If the chain is made more rigid by incorporating a cis double bond or a ring, this will increase the conformational restrictions on the reaction and will favor the intramolecular process. The conversion of **142** to **143** was defined by Deslongchamps as a **Level 1 Process** (an intramolecular process having one chain),[13] which can be compared with formation of **145**, in which the reactive center and reagent in the precursor (**144**) are held together by tethering chains, which imposes a higher degree of stereochemical control and leads to **145**. This transannular reaction is defined as a **Level 2 Process** (an intramolecular process with two chains).[13] A synthetic plan based on a Level 2 process requires the use of medium and large rings. The ultimate degree of stereochemical restriction occurs when the reagent and substrate are held rigidly in space in an appropriate orientation for the desired reaction to take place,[13] which is essentially what is observed in enzymatic reactions.

Scheme 10.10 outlines Deslongchamps' synthesis of triquinacene derivatives.[105] Manipulation of Thiele's acid (**146**) gave the key product, **147**. A photochemical fragmentation gave **148**, and an intramolecular aldol

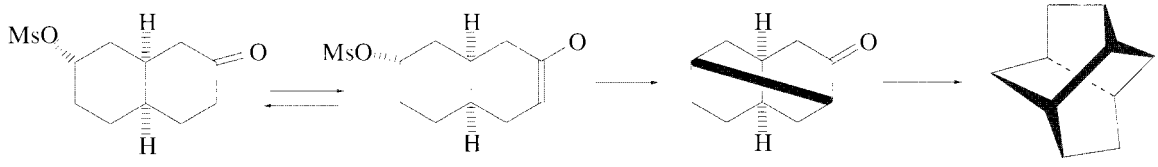


146 **147** **148** **149** **151**

Scheme 10.10. An outline of Deslongchamps' syntheses of triquinacene (150) and triquinacenecarboxylic acid (151).

(sec. 9.4.A.ii) gave **149**. With the basic skeleton formed, **149** was converted to triquinacene (**150**) and also to triquinacenecarboxylic acid (**151**). Inspection of Scheme 10.10, following the route **151** → **146**, provides a retrosynthetic analysis for the synthesis, which involved a Level 1 intramolecular aldol (**148** → **149**) and a reverse Level 1 process in the conversion of **147** → **148**.

A synthesis involving a Level 2 process is Deslongchamps' synthesis of twistane (**155**), outlined in Scheme 10.11.[106] Treatment of **152** with sodium hydride in dioxane gave **153**, and intramolecular displacement of the mesylate gave 4-twistanone, **154**. The two reacting groups are brought into proper position by the transannular nature of the cyclization.



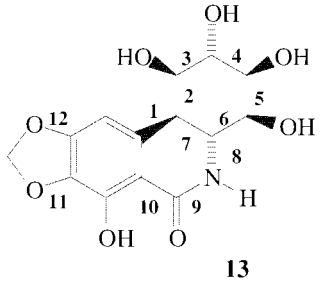
152 **153** **154** **155**

Scheme 10.11. An outline of Deslongchamps' synthesis of twistane, 155.

In a retrosynthetic analysis, the choice of Level 1 or 2 intramolecular cyclization reactions can be important in choosing a disconnection. In an interactive approach, observation of such processes, which maximize simplification in the retrosynthetic direction and allow facile bond-formation in the synthetic direction, are essential.

10.7. SELECTED SYNTHETIC STRATEGIES: PANCRATISTATIN

As mentioned in Section 10.6.C, disconnection of a single strategic bond can lead to several different synthetic schemes. The nature of this approach maximizes individuality in a given synthesis and, as shown with lycopodine (**136**), many different strategies are possible, which is shown explicitly by several syntheses of pancratistatin (**13**), first introduced in Section 10.2.A. Although **13** has important antitumor biological proper-ties,[18] the lasting importance of the syntheses to be represented here may be the new chemical reactions and general synthetic methodology that was developed. This is, of course, precisely the sentiment expressed by Deslongchamps[13] and Corey[12] as cited earlier in this chapter.



13

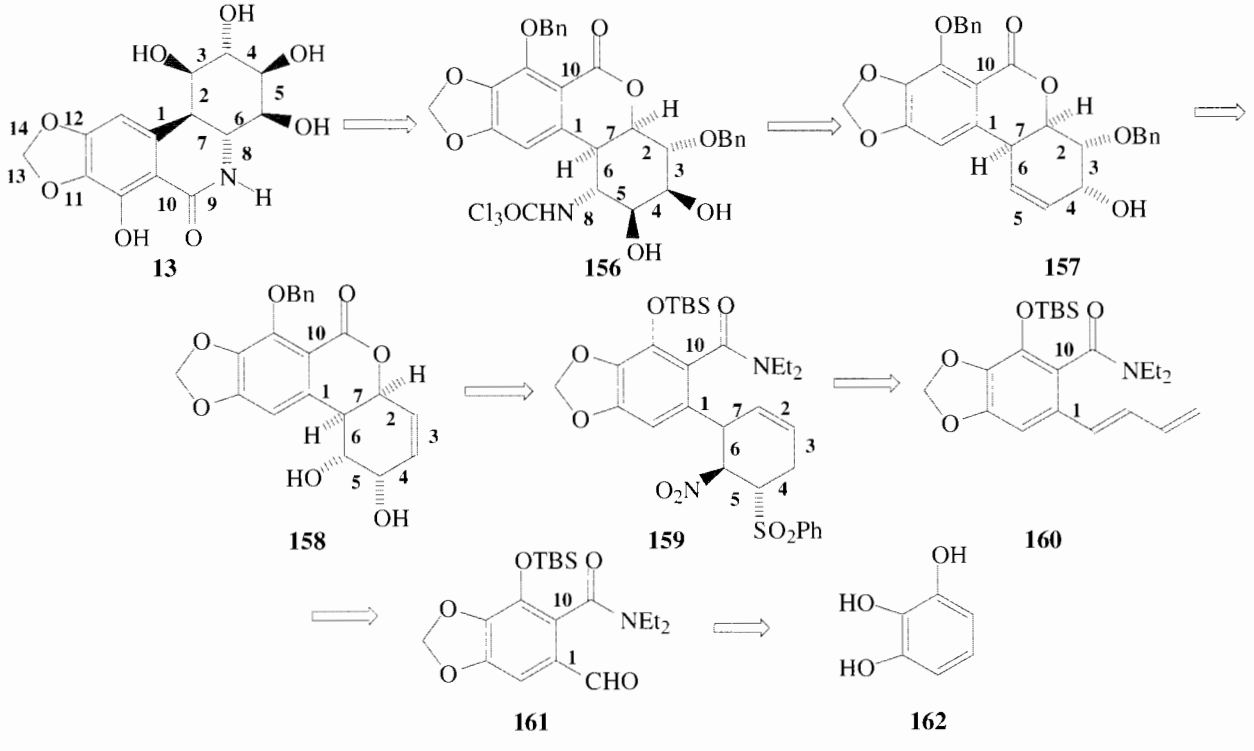
1. 1,2,3,4,5,6,8,9,10,11,12
2. 1,2,6,8,11,12 all exo
3. no bridging
4. 7 is excluded
5. aromatic ring excluded

6.1,2,6,8 are excluded

The retrosynthetic analyses for the specific approaches of Danishefsky and Lee.[107] Hudlicky and co-workers,[108] Trost and Pulley,[109] and Rigby et al.[110] are illustrated in Schemes 10.12, 10.13, 10.14 and 10.15,

respectively. In addition, Keck and co-workers synthesis of (+)-7-deoxypancratistatin (**181**)[111] is shown for a comparison of the general strategy involved. The four retrosyntheses for **13** shown in Schemes 10.12,[107] 10.13,[108] 10.14,[109] and 10.15,[110] respectively, are based on the actual published synthesis rather than a presynthesis analysis. A fifth synthesis is shown, for the closely related 7-deoxypancratistatin (**178**). A retrosynthesis for **178** is shown in Scheme 10.16.[111] An analysis of **13** via Corey's rules (sec. 10.6.A) suggests that bonds 1, 2, 6, and 8 are strategic, with the amide bond 9 considered to be labile (see sec. 10.5.B.i). Bonds 13 and 14 could also be considered labile since they are part of an acetal unit.

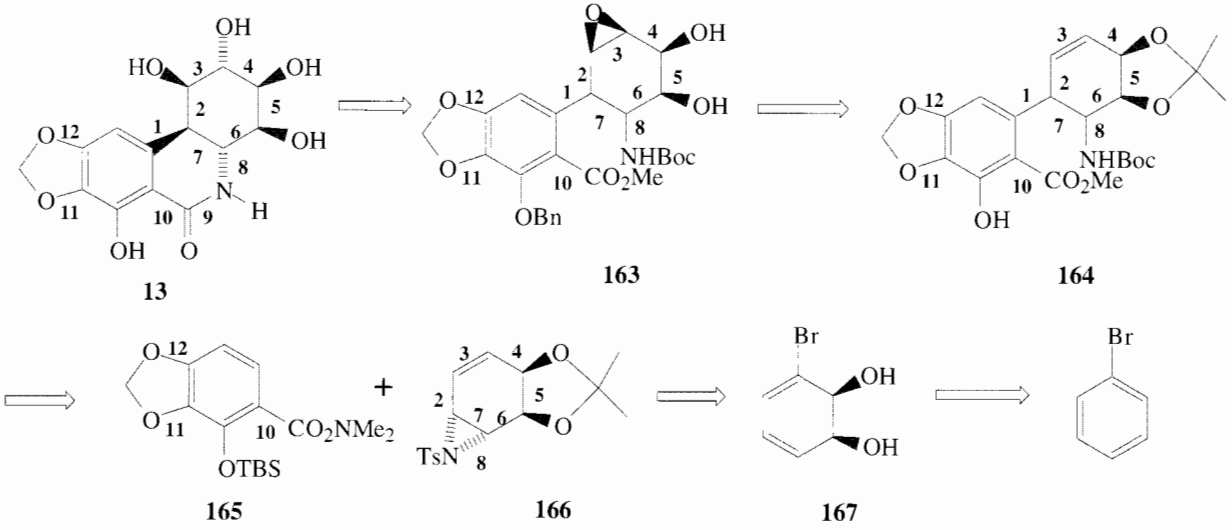
In Scheme 10.12,[107] the first disconnection of Danishefsky's actual synthesis involved cleavage of bond 9 (the amide) and converting the carboxyl unit to a lactone and the amine unit to a trichloroimidate. This disconnection also changed the trans stereochemistry found in **13** to the cis stereochemistry shown for **156**, allowing a Diels–Alder-based strategy that produced the cyclohexene ring in **157**. Disconnection to **158** mainly involved functional group manipulation that allowed the hydroxyl groups to be incorporated with the correct relative stereochemistry. This functional group manipulation was continued in the disconnection to



Scheme 10.12. Retrosynthetic analysis of Danishefsky's pancratistatin synthesis.

159, which contained the requisite cyclohexene unit that could be constructed via a Diels–Alder reaction from diene disconnect product **160** which effectively disconnects bonds 4 and 6. This diene unit was prepared from aldehyde **161** via disconnection of bond 1. Disconnection of bond 10 in **161** as well as bond 1 led to pyrogallol (**162**) as the starting material. The actual synthesis involved a total of 26 steps that produced racemic **13**. It appears that the key disconnection was bond 9, the amide unit, bonds 4 and 6 for the Diels–Alder reaction, and bonds 1 and 10 for attachment of groups to the aromatic ring.

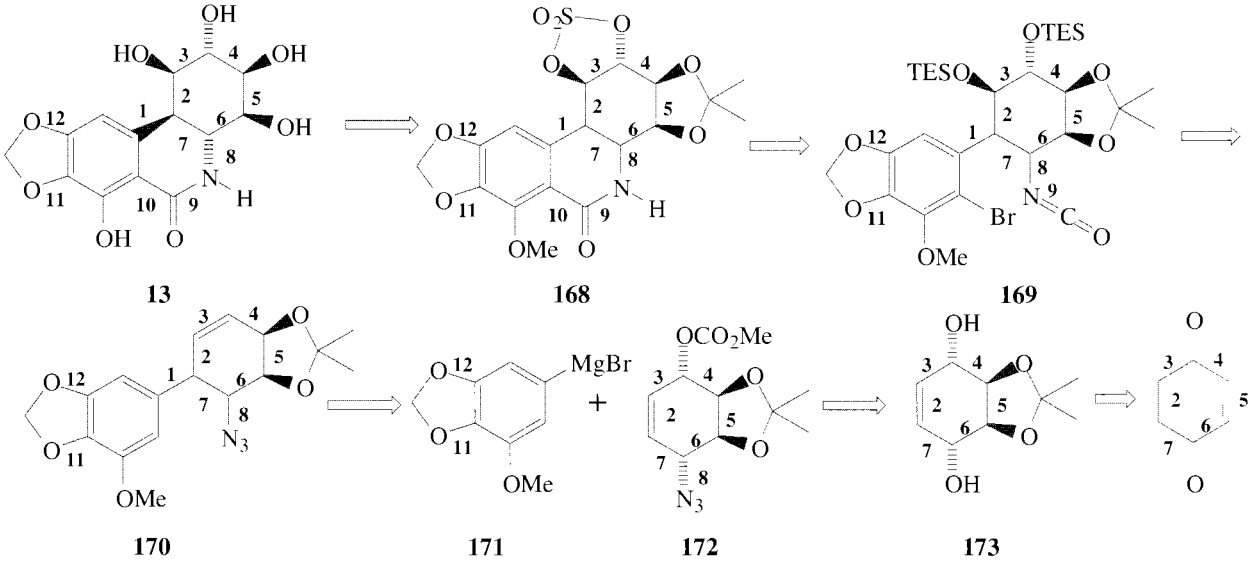
In Hudlicky's retrosynthetic analysis (Scheme 10.13),[108] bonds 9 and 1 were utilized. The amide bond (9) was again disconnected but to a N-Boc ester (**163**) rather than the lactone seen in Danishefsky's synthesis. Manipulation of the functional groups was also different, proceeding via the epoxide shown in **163**. Disconnection to **164** illustrates the manner in which the functional groups were manipulated, setting up disconnection of bond 1 to give two products, **165** and **166**. Amide **165** was prepared from commercially available materials and contains bonds 10–12. Fragment **166** contains one entire ring of **13**, and this differs significantly from Danishefsky's synthesis, where this ring was put together via a Diels–Alder reaction that required extensive manipulation (and steps) to obtain the desired functionality. In Hudlicky's approach, this ring is incorporated intact and contains functionality that allows the tetraol unit to be incorporated more efficiently. The key step is the disconnection of **164** to **165** and **166**, where the two fragments were attached by an ortho-metalation procedure described by Snieckus and co-workers (see sec. 8.5.F).[112] Fragment **166** is derived from **167**, which is commercially available, but is generated by reaction of bromobenzene with *Pseudomonas putida*, as described in sec. 3.5.D). This synthesis produced (+)-pancratistatin and required 16 steps from the commercially available diol **167**, 17 steps if **167** was prepared from bromobenzene rather than purchased.



Scheme 10.13. Retrosynthetic analysis of Hudlicky's pancratistatin synthesis.

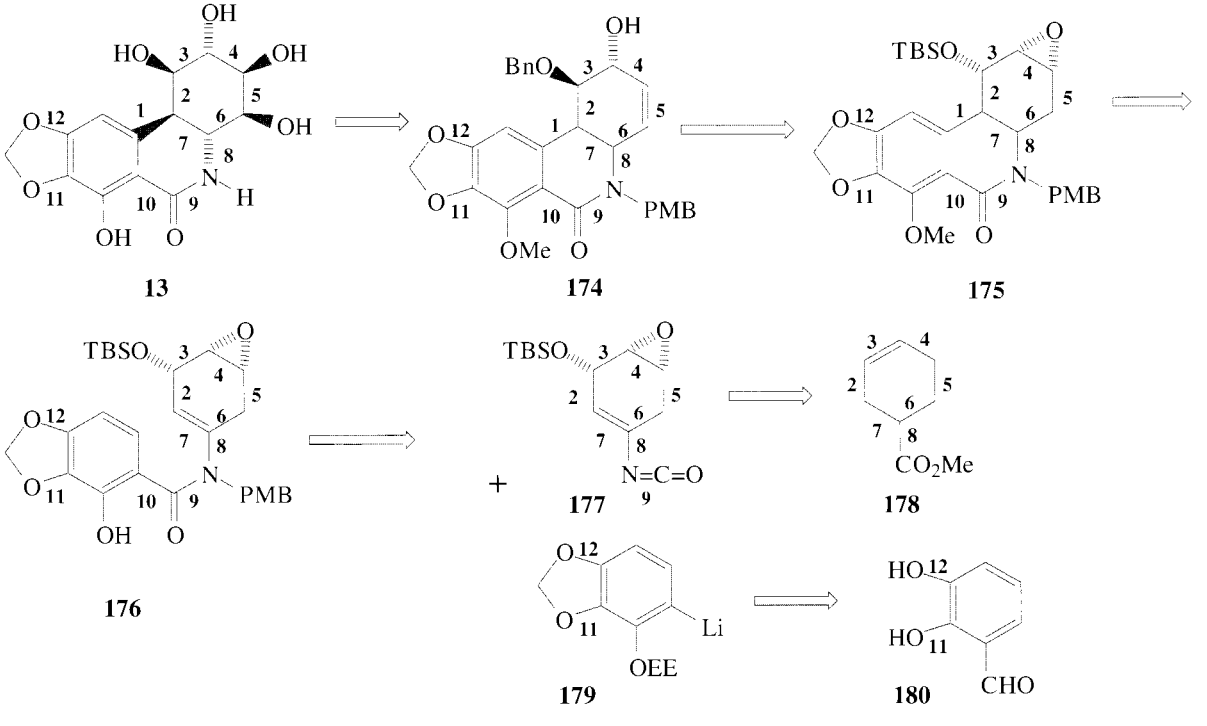
In Scheme 10.14, Trost used bonds 9 and 10, as well as 8 and 1 as outlined in Scheme 10.14.[109] The first disconnections involve functional group manipulation to set up the ring for the hydroxyl units as in **168**. The next disconnection is a key step in which bond 10 is disconnected to give **169**, rather than bond 9 in the other syntheses. This disconnection implies generation of an aryllithium from the bromide in **169** adding to the isocyanate group, generating the lactam and the requisite ring. The next disconnection to **170** gives the precursors to the isocyanate as well as the hydroxyl precursors, which sets up the next key disconnection to give two fragments, **171** and **172**. The precursor to Grignard reagent **171** was prepared using a literature procedure, and azide **172** was derived from the next disconnection to **173**, a diol readily available from

benzoquinone in five steps. If we use **173** as the starting material, this synthesis produced (+)-pancratistatin and required ≈ 16 steps. The bromide precursor to **171** was prepared separately. Since **173** was prepared from benzoquinone, that is the true starting material, and five more steps are added to bring the total to 21.



Scheme 10.14. Retrosynthetic analysis of Trost's synthesis of pancratistatin.

Rigby's synthetic plan is outlined in Scheme 10.15[110] and used bonds 1 and 10. As in the previous synthesis, the first two disconnections involve manipulation of the hydroxyl groups, first a disconnection to

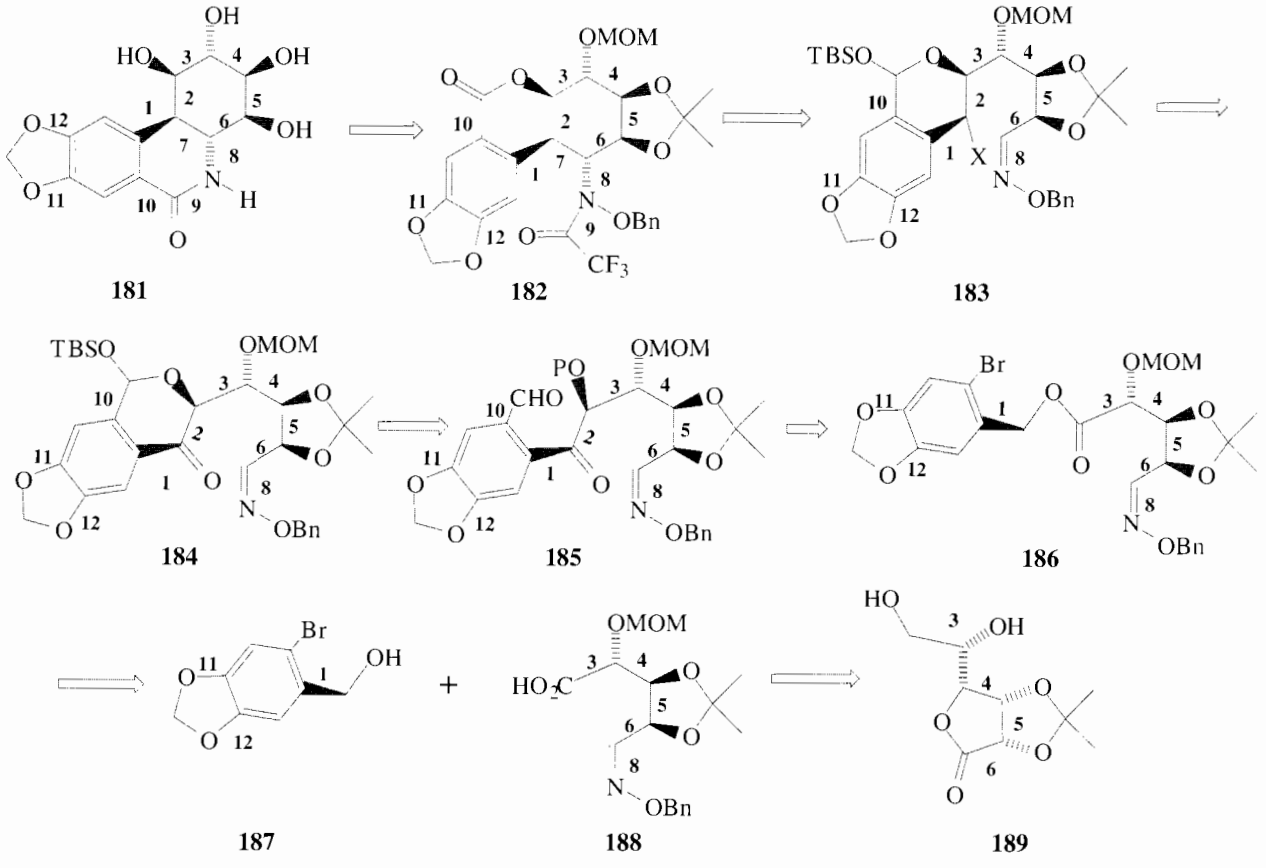


Scheme 10.15. Retrosynthetic analysis of Rigby's synthetic pancratistatin.

give **174** and then to **175**. It is noted that these represent several steps and changing the stereochemistry of the ring juncture stereochemistry, which is not shown. Disconnection of bond 1 in **175** to **176** is a key step that uses a photoaddition reaction to set that bond in the synthesis. Disconnection of bond 10 in **176** leads to two fragments, **177** and **179**. As with Trost's synthesis, bond 10 will be set via an isocyanate in **177**, this time via a Curtius rearrangement. Fragment **177** is disconnected to give **178** as one of the starting materials. The ring is used as an intact entity, with functional group manipulation to give the hydroxyl groups. Fragment **179** is derived from the commercially available 2,3-dihydroxylbenzaldehyde (**180**). The conversion of **180** to **179** required six steps. Counting the coupling of **177** to **179** as one step and using **178** as the starting material, the overall synthesis produced (+)-pancratistatin and required 24 steps. The synthesis involved an enzymatic resolution using cholesterol esterase, in the sequence that converted **178** to **177**, to prepare optically active material.

Although 7-deoxypancratistatin (**181**) is missing the phenolic OH unit relative to **13**, it is interesting to compare Keck's strategy (Scheme 10.16)[111] for the construction of the phenanthridone skeleton (see Scheme 10.15) with the other four syntheses. The initial disconnection removes bond 9 to give **182** where the lactam unit was converted to a lactone unit and the amine unit is protected similar to the strategy used by Danishefsky. Bond 9 is actually converted to a trifluoroacetyl amide unit and the last step in the synthesis is the key lactone to lactam reorganization. The next disconnection removes bond 7, which was *not* strategic using analysis by Corey's rules, to give **183**, and is a key disconnection because the six-membered ring was made in the synthesis by a radical cyclization process (see sec. 13.7). It also illustrates that bond 7 is not strategic in **13** or **181** but it *is* strategic in **182** because now it is part of a primary ring. Remember, each new disconnect product must be reexamined for strategic bonds. Disconnection of **183** to **184** essentially sets up the ring for manipulation of functional groups, as well as the functionality necessary for the radical cyclization. Disconnection to **185** is also required to set the functionality and this allows a key disconnection to **186**, which utilizes formation of an aryllithium to attack the ester carbonyl of **186** leading to the reorganized aldehyde-ketone **185** in the synthesis. Disconnection of **186** breaks the labile ester bond to give fragment **187**, which is prepared by known methods, and **188**, which contains the carbons of the tetraol ring in **181**, along with appropriate functionality. This precursor is derived from the available D-gulonolactone (**189**). This synthesis produced (+)-7-deoxypancratistatin and required 20 steps.

The syntheses in schemes 10.12–10.16 rely on disconnection of the amide bond (9), essentially a functional group inter-change although it is clearly not that simple since and either bonds 1 or 10 are also disconnected. In addition, the three key rings, the benzene ring, the lactam ring, and the tetraol ring are targeted. Although the disconnected bonds are similar, the strategies differ based on which of the three rings is key. In the syntheses of Danishefsky, Hudlicky, and Keck, the lactam ring was formed close to the end or at the end of the synthesis. In these cases, the other two functionalized rings formed atropisomers that made formation of the lactam difficult. Steps had to be added and the sequences needed to be modified to get around this problem. In Rigby's synthesis, the lactam ring was formed in the middle of the synthesis by linking the aromatic ring to the tetraol ring by an amid linkage, with formation of the lactam ring by a



Scheme 10.16. Retrosynthetic analysis of Keck's synthesis of 7-deoxypancratistatin.

photoaddition reaction. In Hudlicky and Trost's synthesis, the aromatic ring was joined to the tetraol ring, in one case by an aryl anion opening of an aziridine and in the other by a S_N2' type addition of an aryl anion to a functionalized cyclohexene derivative. The carbonyl and amine units were intact, allowing the lactam ring to be formed. In the syntheses of Danishefsky and Keck, the lactam ring was formed by a lactone-to-lactam reorganization, where the lactone unit linked the aryl ring to the tetraol ring. In Danishefsky's synthesis, the tetraol ring was generated by a Diels–Alder reaction and functional group manipulation. In the syntheses of Hudlicky, Trost, and Rigby, the tetraol ring was incorporated as an intact ring, from different precursors, requiring functional group manipulation. In Keck's synthesis, the tetraol ring was constructed by manipulating a carbohydrate precursor that contained all the requisite carbons and functionality (a chiral template driven synthesis–see sec. 10.9 for other examples of this strategy). The actual key bonds used to generate the carbon skeleton are actually very similar, but the strategies for making those bonds generated vastly different total syntheses. Which is best? All methods produce the target and all have their strengths. The most efficient route which produces the best yield of the target, is obviously one of the more important considerations but best is always relative to the needs of those asking the question. One of the most important aspects of any synthesis is how that methodology can be used in other synthetic applications and all of these routes provide useful synthetic methodology.

10.8. BIOMIMETIC APPROACH TO RETROSYNTHESIS

In previous sections, a target was analyzed and the disconnection analysis led to reactive fragments. The disconnection process was continued until a suitable starting material was found. The actual synthesis followed the disconnection sequence to construct the molecule. If there was a bias in the construction and retrosynthesis, it was usually due to the special interests of the chemist, recognition of an attractive substructure, or special knowledge of one area of organic chemistry.

There is an important alternative to the disconnection approach in which the retrosynthetic plan is biased to follow the known biosynthetic pathway for a particular target. In effect, the biosynthetic route becomes the synthetic tree, and appropriate reagents must be found to mimic the processes that nature accomplishes with enzymes. Knowledge about formation of the molecule in nature, how its functional groups interact, and which bonds are cleaved with what reagents is usually gathered during the isolation and identification process. In many cases, intermediates of the biosynthetic pathway (also called the biogenetic pathway) for the formation of a natural product are known. Targeting those intermediates to generate the synthetic tree will effectively mimic the biosynthetic pathway and is referred to as a **biomimetic** or a **biosynthetic approach**. Although many biopathways have been determined,[113] they remain unknown for many important classes of natural products. This method offers an important alternative in synthetic planning, however. A number of reviews are available that describe this approach when applied to total synthesis.[114]

10.8.A. The Johnson Polyene Cyclization

A good example of this approach is the **Johnson polyene cyclization reaction**.[114,66c] The biogenetic pathway for production of the steroid lanosterol from acetyl coenzyme A (acetyl Co-A) is shown in Figure 10.8.[115] From this scheme it is clear that squalene is the direct biogenetic precursor of squalene-2,3-epoxide

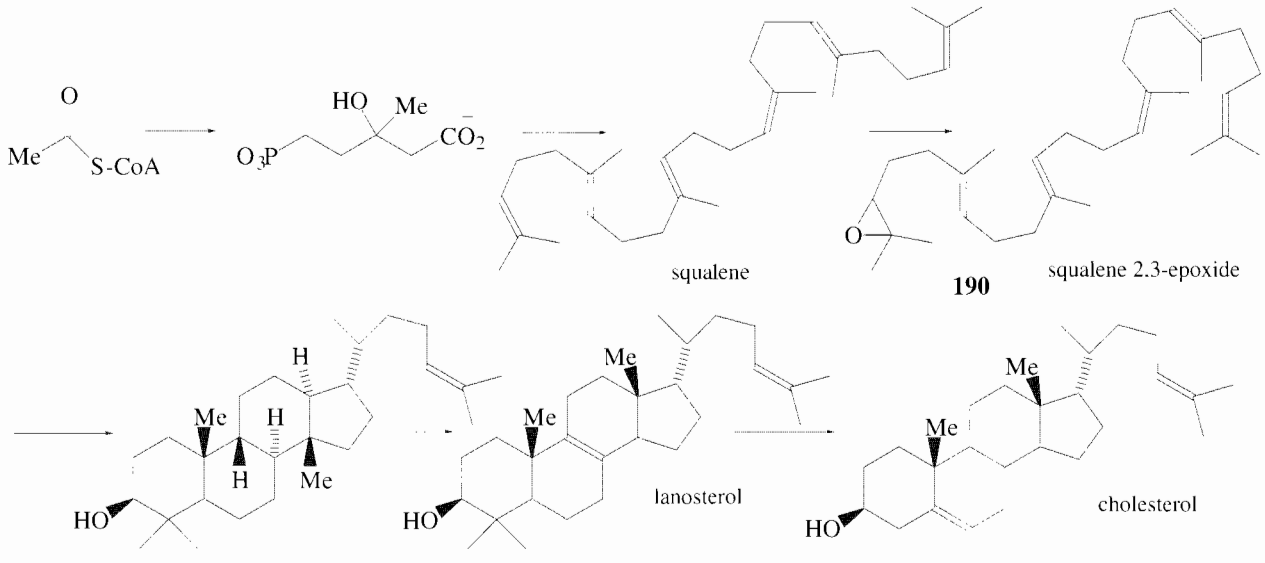
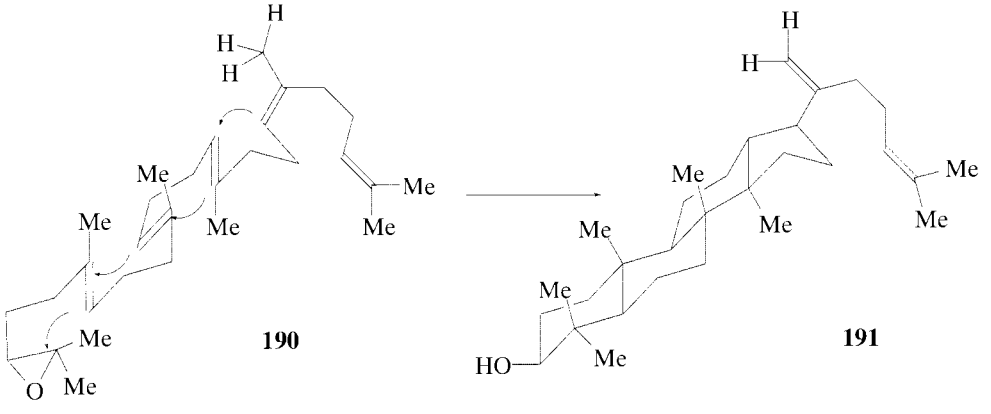
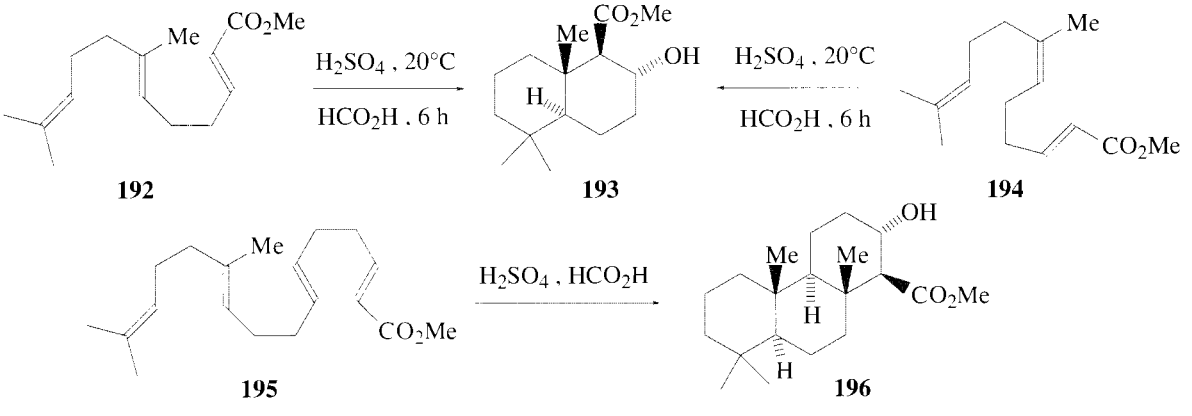


Figure 10.8. The biogenesis of cholesterol from acetyl coenzyme-A.

(**190**), which is the direct precursor to lanosterol. Lanosterol is ultimately converted to cholesterol.[115,116] Enzymes close the rings in the biological system but Johnson reasoned that treatment of a squalene-like polyene (all trans double bonds) with an appropriate acid would lead to a carbocation and the proximity of the C=C units would lead to ring formation. If this occurred in a sequential manner, several rings would be formed to build the polycyclic system via carbocation intermediates.[117] An all-chair conformation was assumed to be the preferred one[117] for this polyene system, and an all-trans geometry was required for the double bonds to be in the proper position for cyclization to the proper stereochemistry. Generation of a cation from **190** was initiated by addition of the acid catalyst to the terminal π bond. Each π bond in turn acts as a nucleophile and attacks the neighboring carbocation generated by the previous addition. Each of these ring closing reactions proceeds via a *six-center transition state*. In the final step, a five-membered ring is the only ring closure possible and the process is terminated by an E1 reaction (sec. 2.9.B) to give **191** If the



alkene precursor has an (*E*) geometry, the cyclic product should have the more stable trans-fused ring due to the thermodynamic (equilibrium) nature of the cyclization, which was confirmed when treatment of trienes **192** and **194** with acid gave the same trans-fused decalin, **193**.[118] The cis-fused decalin was not observed in either case.



When this process was extended to tetraene (**195**),[119] treatment with acid gave the expected tricyclic alcohol (**196**), but in only 5–10% yield. The remainder of the product mixture was an intractable oil. As the number

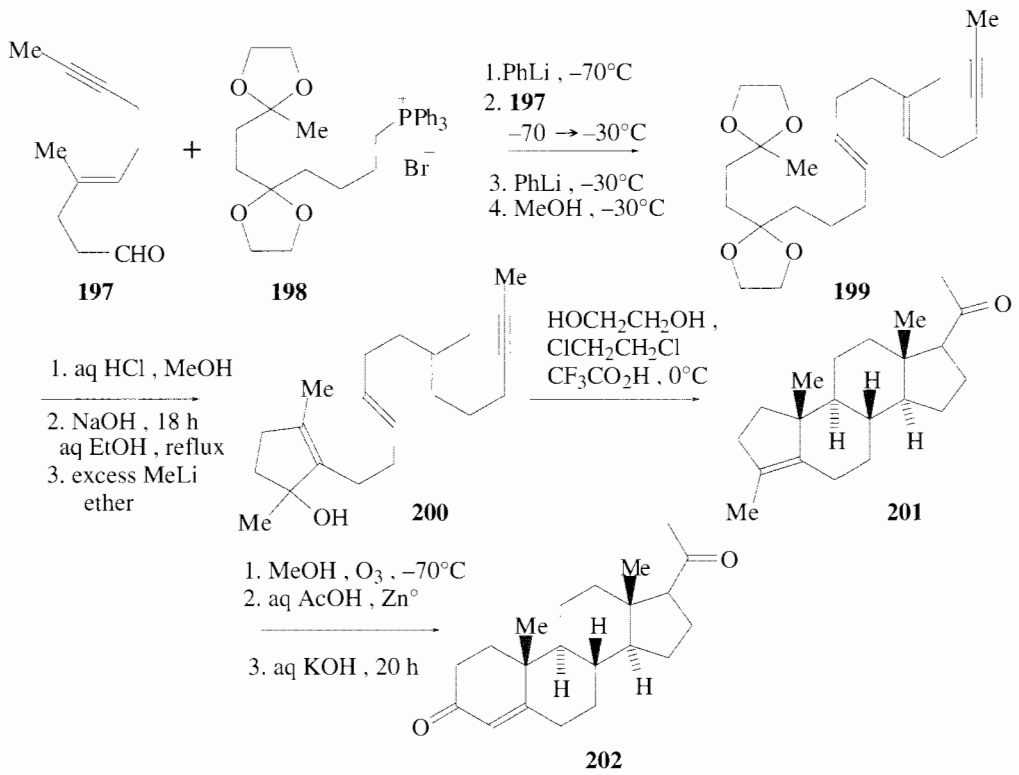
of rings being formed increased, the yield and efficiency of the polyene cyclization decreased. This problem was eventually solved by three synthetic modifications:

1. Incorporation of one pre-formed ring into the polyene system to stabilize the conformation.
2. Incorporation of a more reactive center at the terminus.
3. Use of a milder and more selective acid.

This cyclization is a Level 1 intramolecular cyclization as described by Deslongchamps (sec. 10.6.C).[13] In acyclic systems, the conformation required for cyclization may not be the low energy conformation assumed by the polyene. When the polyene is attached to a preformed ring, the conformational stability of that ring will stabilize the entire polyene system, usually in the lowest energy all chair conformation required for efficient cyclization. Cyclopentanoid derivatives were found to be very effective for this purpose.

Once the cyclization process has begun, it is important to terminate the cationic process in an efficient manner that minimizes competitive side reactions. Incorporation of an alkyne or a vinyl fluoride at the reaction terminus will give a vinyl cation or an α-fluoro cation, respectively.[120] In both cases, the highly reactive cation product will trap a nucleophile in an S_N1 process, stopping the cyclization process. Finally, acids such as hydrofluoric acid and trifluoroacetic acid were found to be the most effective catalysts for the cyclization.[114] They are strong acids, but are not oxidizing acids, and the gegenions do not induce secondary reactions during the cyclization or at the termination step.

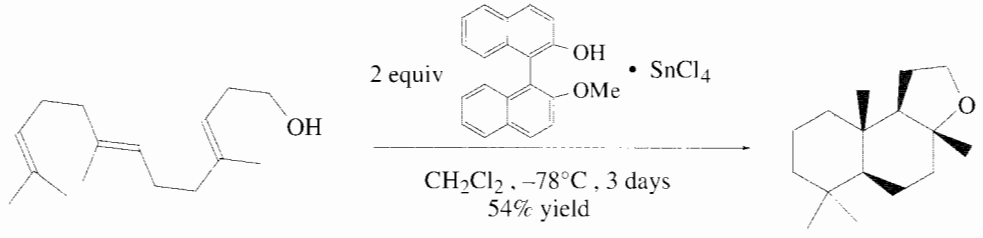
This approach is shown in the synthesis of progesterone (**202**) in Scheme 10.17.[121] A **Wittig olefination**[122] (sec. 8.8.A) coupled **197** with **198**. The improved technology developed for the cyclization led



Scheme 10.17. Johnson's synthesis of progesterone.

to a good yield of **201** from **200**. Polyene **200** was prepared by an intramolecular aldol condensation (sec. 9.4.A.ii) after hydrolysis of the dioxolane protecting groups in **199** (sec. 7.3.B.i).

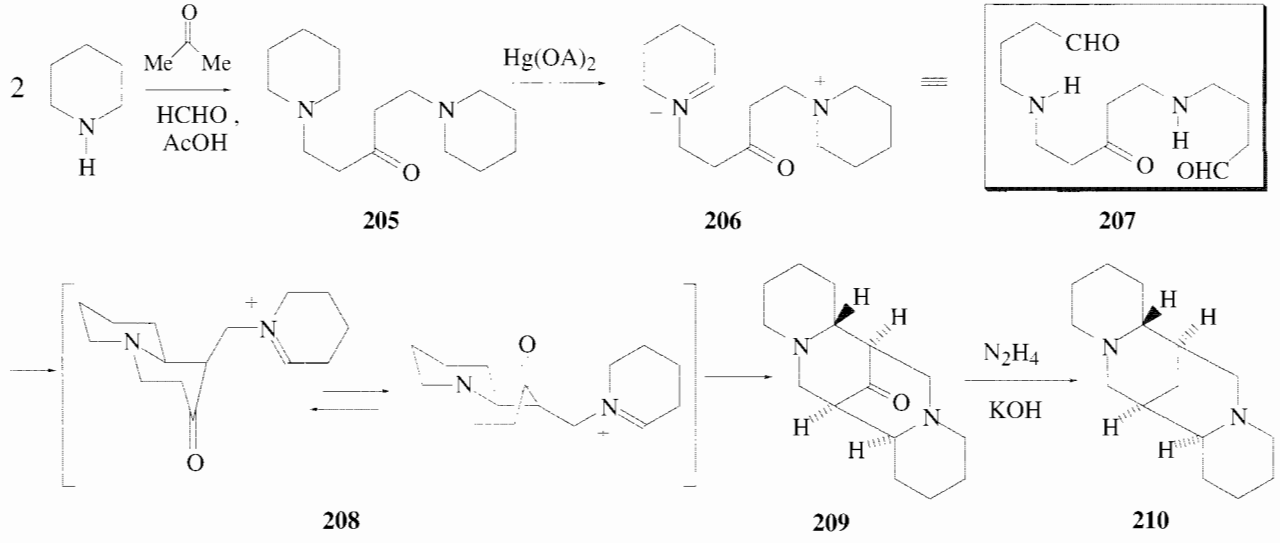
Choice of reagents and reaction conditions are critical for success in polyene cyclizations. The exact cyclization conditions are often specific to the particular target. It is also clear that to accomplish chemically what enzymes do routinely in the biopathway presents a vast array of problems, primarily in the areas of regio- and stereocontrol. Only if these problems can be overcome by suitable choice of reagents and conditions can the biogenetic route be used successfully. An enantioselective polyene cyclization has been reported, using $SnCl_4$ mixed with BINOL derivatives.[123] In one example of this transformation, (–)-ambrox (**204**), the most important commercial substituent for ambergris, used in the perfume industry, was prepared from triene **203**. Tricyclic **204** was obtained in 30% yield and only modest enantiopurity (42% ee), and three other tricyclic compounds were obtained as well (total yield of cyclized products was 54%). When the polyene was anchored to an aromatic ring, however, this approach gave good yields of polycyclic compounds with good enantioselectivity (62–87% ee).



203 **204**

10.8.B. Sparteine

van Tamelen's synthesis of sparteine (**210**), outlined in Scheme 10.18,[124] is another example that uses a known biosynthetic pathway. In this case, conversion of diaminoketoaldehyde (**207**) to 8-ketosparteine (**209**)

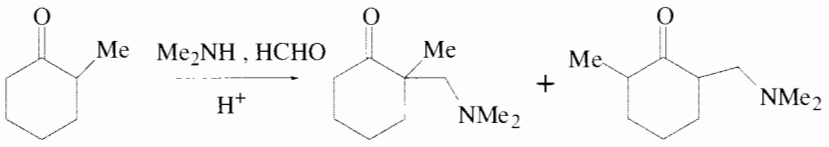


205 **206** **207**

208 **209** **210**

Scheme 10.18. van Tamelen's synthesis of sparteine (210).

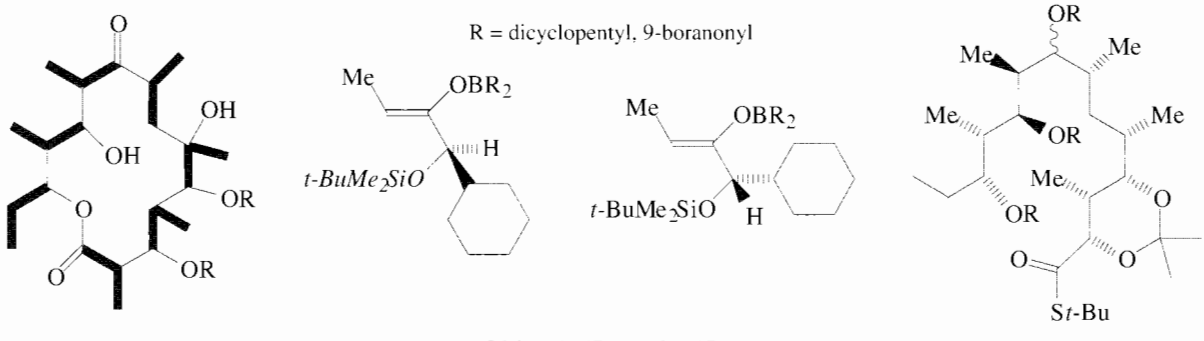
was the key biosynthetic step. van Tamelen did not use the labile and unavailable aminoaldehyde (**207**), but rather a synthetic equivalent of this compound. A **synthetic equivalent** is simply a molecule that is converted to the molecule of interest, or to a molecule that reacts identically, and is later unmasked. The chemical structure of the synthetic equivalent may be different but the final product is the same. In this example, the synthetic equivalent of **207** is the bis(iminium) ketone (**206**), generated from amino-ketone **205** by treatment with mercuric salts. van Tamelen's synthesis of sparteine (**210**) begins with piperidine. Generation of the synthetic equivalent (**206**) led to **208** and then **209** via sequential Mannich reactions. The synthesis uses a **Mannich reaction** [125] (secs. 9.7.A, 9.7.C), which usually gives the thermodynamically more stable product via addition of an intermediate enolate (or enol) to an iminium salt ($H_2C{=}NMe_2^+$), which is produced *in situ*. When 2-methylcyclohexanone was treated with dimethylamine and formaldehyde, for example, both the kinetic product (**212**) and the thermodynamic product (**211**) were formed, with **211** predominating.



211 **212**

10.8.C. Deoxyerythronolide B

The final example illustrates yet another use of the biomimetic approach. Figure 10.9 [126] shows a retrosynthetic analysis for Masamune's synthesis of deoxyerythronolide B (**213**). The biosynthetic building blocks of this and other macrolide antibiotics are known to be acetate and/or propionate units combined head-to-tail, as seen in **213**.[127] The stereocenters in **213** are clearly shown in the acyclic (seco acid) form of the macrolide **215**. The specific biopathway is not utilized but rather modified to include the basic building blocks, seven propionate units (**bold lines** in **213**).[126] Seco acid **215** was constructed by sequential aldol condensation reactions (sec. 9.4.A) of propionaldehyde units, as shown by the disconnections in Figure 10.9. Asymmetric



213 **214** (a) (*R*) (b) (*S*) **215**

induction is controlled by the chiral boron enolates derived from propionaldehyde. The diastereoface selectivity of the aldol condensation was discussed in Section 9.5.B.[128] Both (*R*) and (*S*) boron propionaldehyde enolates (**214a** and **214b**) were prepared and used extensively as the fundamental biomimetic

building block. Sequential aldol condensations generate the erythronolide skeleton, with the correct stereochemistry predominating in each aldol product. The targeted macrolide[126] is generated from the acyclic seco acid thioester (**215**) via treatment with copper triflate and Hünig's base (diisopropylethyl amine). This and other techniques for macrolactonization[129] were discussed in Section 6.6.B.

The synthetic examples in this section show that a biosynthetic pathway can be used to generate a synthetic tree, which can be of great utility and simplifies the task of growing the synthesis tree. If the biosynthesis is unknown one can turn to other processes for guidance.

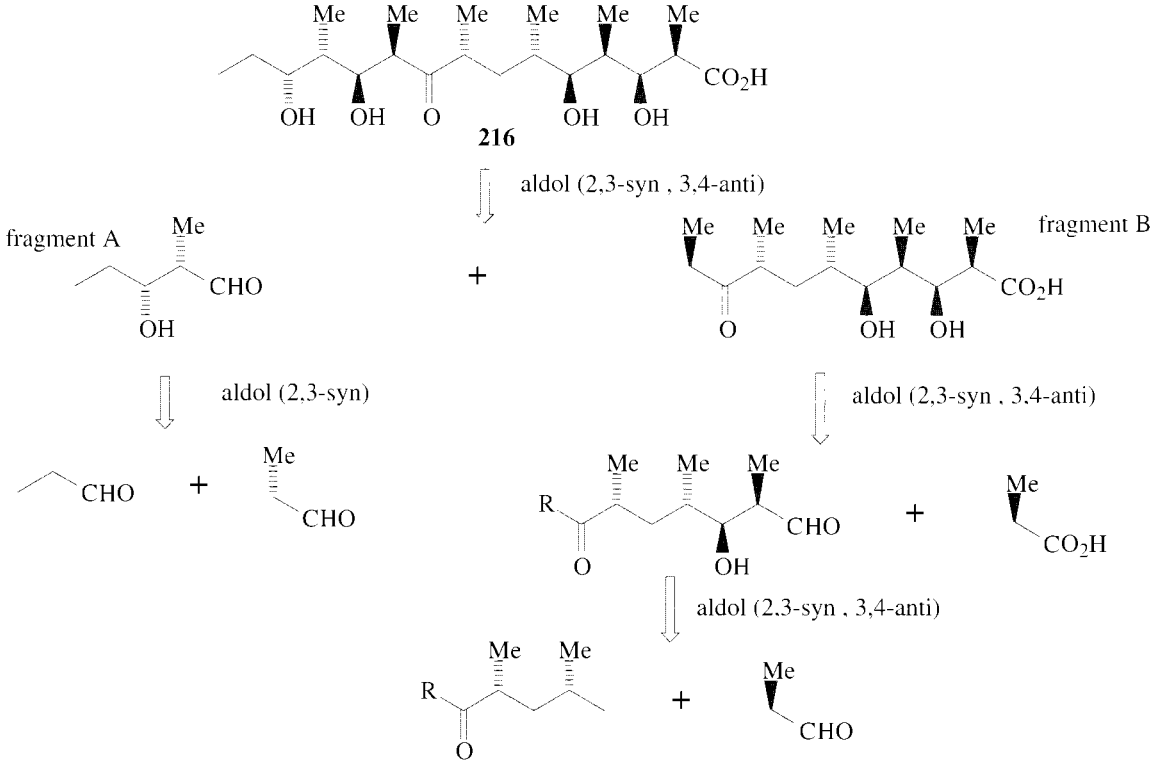


Figure 10.9. Retrosynthetic analysis of the seco acid of deoxyerythronolide B.

10.9. THE CHIRAL TEMPLATE APPROACH

In previous sections, a target was disconnected to give a suitable starting material, usually without prior knowledge of the identity of that compound, which is the *synthon approach*.[1] An alternative strategy generates strategic bond disconnections by "locating segments containing a number of chiral centers".[130] The fragments containing these stereogenic centers are part of a structure (a **chiron**, which is a **chir**al synth**on**), that will be a fragment of, or related to, a naturally occurring and/or readily available chiral material.[131] Such synthons are now commonly referred to as chiral templates. A chiral template will be chosen by examining the structure of a target for symmetry, chirality, and functionality. This information is then *decoded* and transposed onto a carbon framework of a suitable synthetic precursor (the chiron or template), which has been called the **chiron approach**, but is more commonly referred to as the **chiral template approach**. The chiron

is obtained from chiral starting materials (chiral templates) by systematic functionalization.[131a] This process is illustrated in Figure 10.10,[131a] where a target (**217**) is disconnected to a key chiron (**218**). The chiron is prepared from one of several chiral templates. Hanessian et al. analyzed a chiron-based synthesis in Figure 10.11,[131a] which shows many

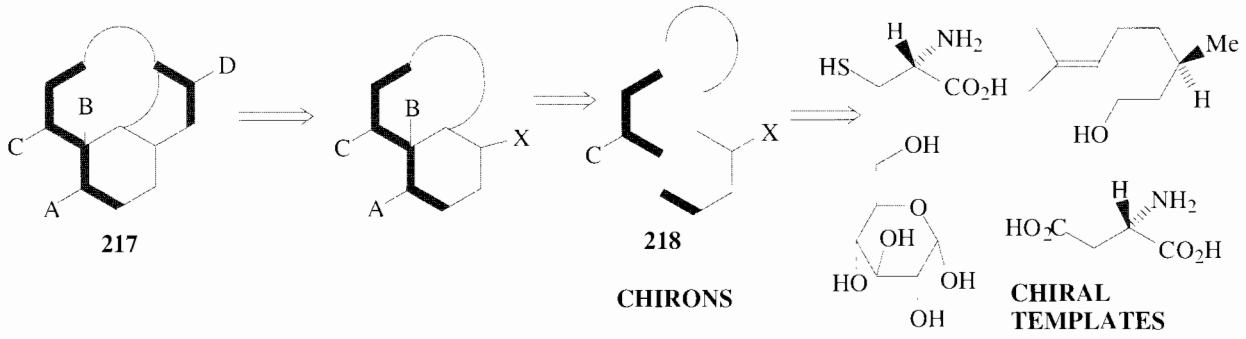


Figure 10.10. Model for total synthesis using the *chiron approach*.

[Reprinted from Hanessian, S.; Franco, J.; Larouche, B. *Pure. Appl. Chem.*, ***1990***, *62*, 1887. Copyright ***1990*** IUPAC.]

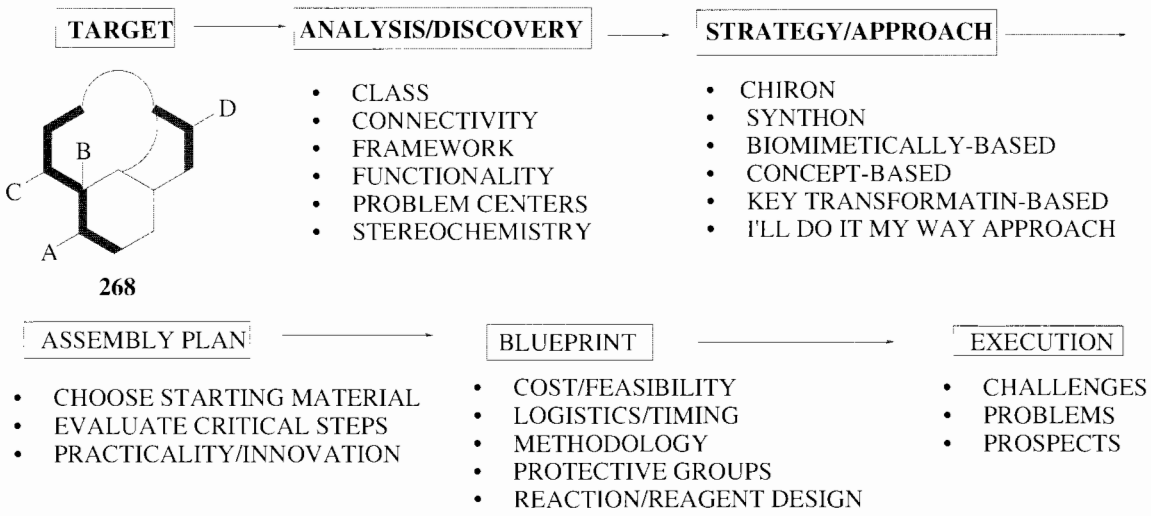


Figure 10.11. Anatomy of a synthesis using the *chiron approach*.

[Reprinted from Hanessian, S.; Franco, J.; Larouche, B. *Pure. Appl. Chem.*, ***1990***, *62*, 1887. Copyright ***1990*** IUPAC.]

of the elements found in Corey's various strategies. Hannessian also shows the fundamental difference between Corey's synthon approach and the chiron approach. In Figure 10.12[131a] the synthon approach was applied to a target, which was disconnected to a diene and a carbene.[131a] The chiron disconnection led to a chiron (**220**), which is available from a suitable chiral template (**219**).[131a] The synthon approach can be correlated with "the type of functionality present in the target molecule and the chemical feasibility or precedent that dictates the strategy. The chiron approach to synthesis involves disconnection of strategic bonds in a target molecule with minimum perturbation of stereogenic centers. A maximum overlap of functionality, as well as stereochemical and carbon framework relationships between target (or substructure) and the chiron is ideally sought. It is the

type of substructure and its possible chiral progenitor that dictate the strategy and chemistry to be carried out.[132]

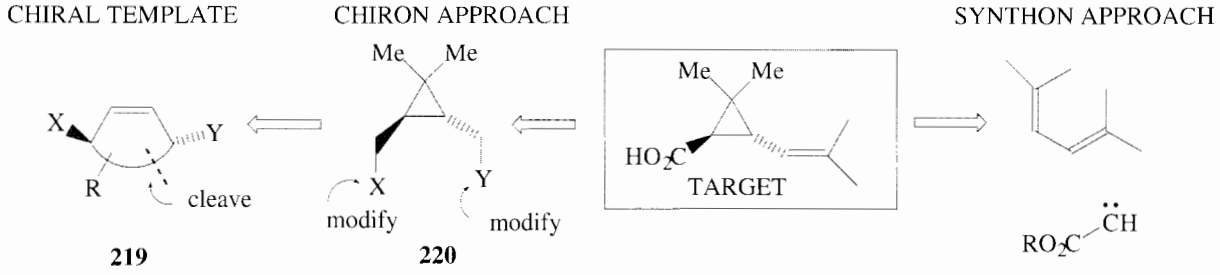


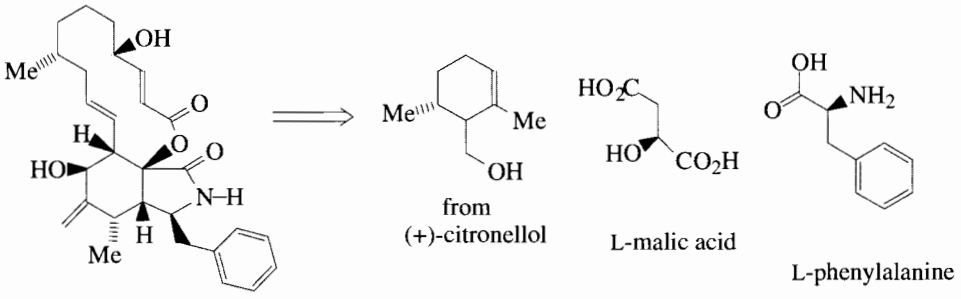
Figure 10.12. A comparison of the *synthon approach* and the *chiron approach.*

[Reprinted from Hanessian, S.; Franco, J.; Larouche, B. *Pure. Appl. Chem.*, ***1990***, *62*, 1887. Copyright ***1990*** IUPAC.]

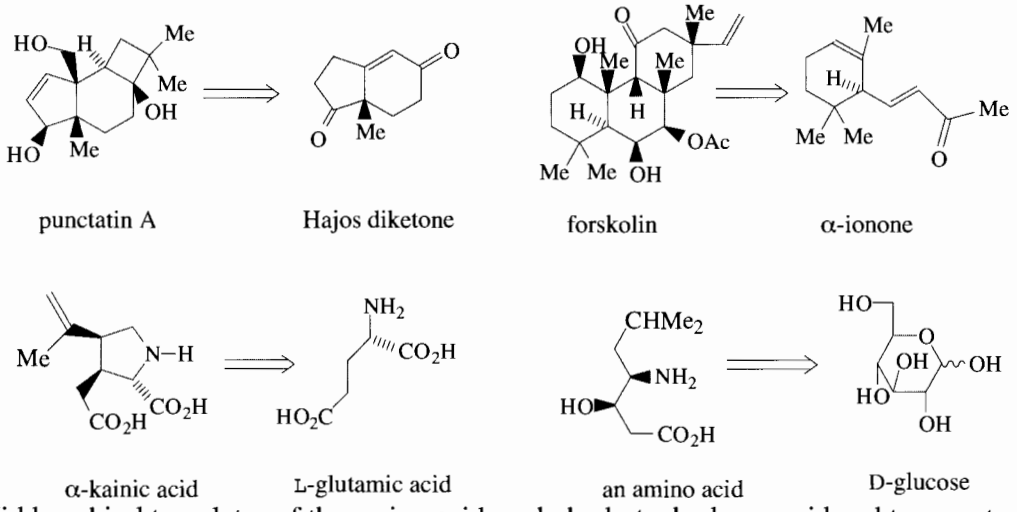
The distinguishing feature of the chiral template approach is recognition of the structural elements of a particular compound within the target structure. The retrosynthetic scheme is then biased so that the selected molecule will be the starting material. This leads to a single branch of the synthesis tree rather than analysis of several branches. There may be several chiral templates for a given chiron, however, leading to flexibility in the choice of which branch is chosen. This approach is analogous to Corey's starting material based strategy previously discussed in Section 10.4.[48] If the recognized starting material is readily available as a single enantiomer (see Figure 10.13),[131a] the chirality of this compound can be transferred to the final target without a resolution step, which is clearly of great value and the main driving force for exploitation of this technique. Carbohydrates, amino acids, and terpenes are a few of the many classes of organic compounds that provide readily available chiral molecules, usually from natural sources. This supply of starting materials is often called the **chiral pool**. A few of these chiral starting materials are shown in Figure 10.13[131a] where they were used for the synthesis of naturally occurring molecules. It is important to note that the chiral template can be well hidden, as shown in Figures 10.13 and 10.14.[131a] (*S*)-Carvone was the chiral template for a disconnection analysis of eucannabinolide (**221**) and (+)-camphor was the chiral template for pheromone **222**.[131a] Some searching is required to discover the 'hiding place' of these chiral templates in the target (see Figure 10.14).

In general, Hanessian discusses three types of asymmetric induction that appears in synthesis, and is pertinent to all syntheses, not only those to which the chiron approach will be applied (see Figure 10.15).[131a] The first type of asymmetric induction is auxiliary dependent (a chiral auxiliary is attached to an achiral substrate, used to transfer asymmetry during the reaction and later removed). The internal (resident chirality) dependent form of asymmetric induction relies on a chiral center being part of the reactant. The external type of asymmetric induction makes use of a chiral reagent or a chiral catalyst. Auxiliaries were used in Chapter 9 for asymmetric aldol condensations (sec. 9.5) and internal asymmetric induction was a key element of Cram's rule as applied to reductions (sec. 4.7.B) and Grignard addition to carbonyl derivatives (sec. 8.4.F.ii), as well as stereodifferentiation reactions related to the **aldol condensation** (see sec. 9.5.B). Both chiral reagents and chiral catalysts were used in asymmetric reductions (sec. 4.7.A), asymmetric Grignard reagents (sec. 8.4.F), and organocuprate reactions (sec. 8.7.A.vii).

Apparent chiral temples in cytochalasin B



Partially hidden chiral templates in punctatin A, α-kainic acid, forskolin and an amino acid from pepstatin



Hidden chiral templates of the amino acid, carbohydrate, hydroxy acid and terpene types

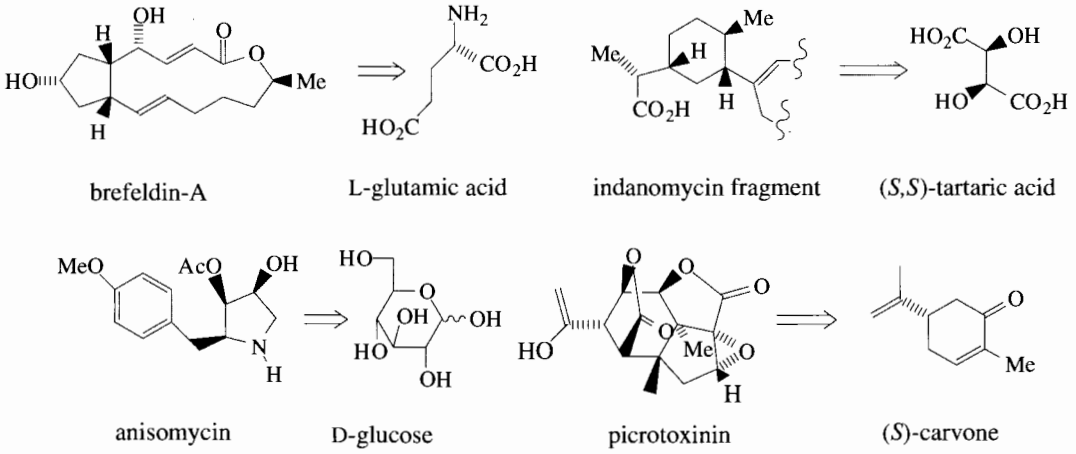


Figure 10.13. Hidden chiral templates.

[Reprinted from Hanessian, S.; Franco, J.; Larouche, B. *Pure. Appl. Chem.*, ***1990***, *62*, 1887. Copyright ***1990*** IUPAC.]

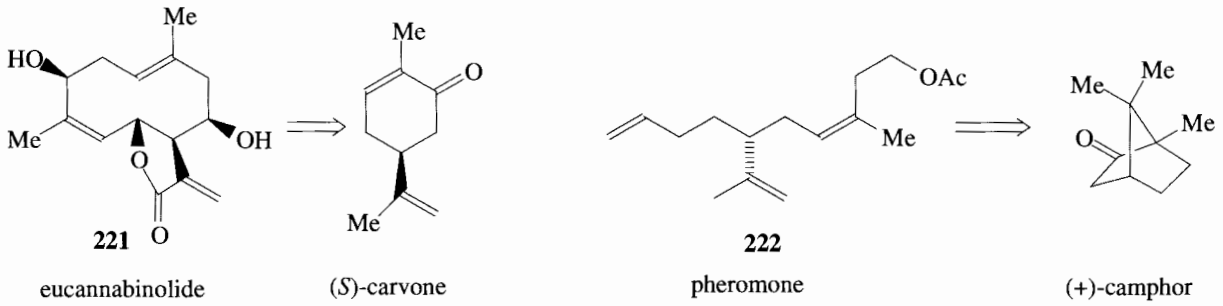


Figure 10.14. Very hidden chiral templates.

[Reprinted from Hanessian, S.; Franco, J.; Larouche, B. *Pure. Appl. Chem.*, ***1990***, *62*, 1887. Copyright ***1990*** IUPAC.]

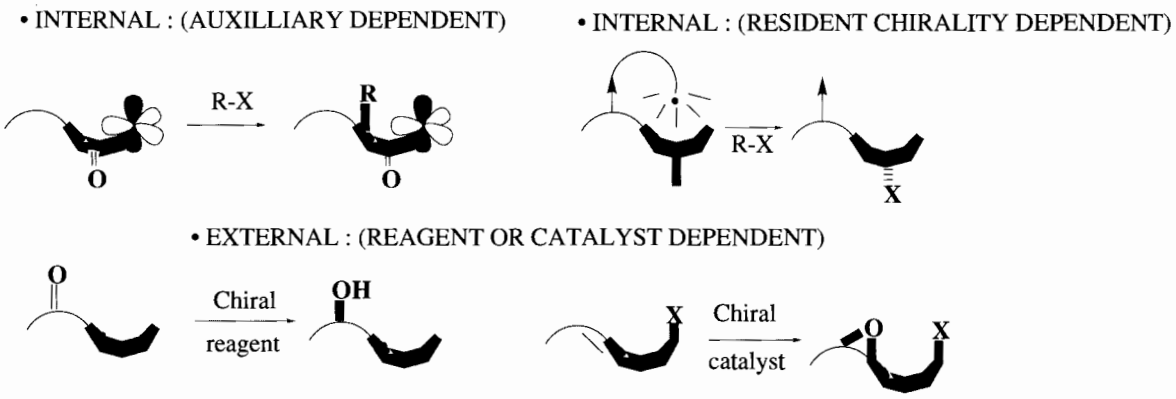


Figure 10.15. Types of asymmetric induction.

[Reprinted from Hanessian, S.; Franco, J.; Larouche, B. *Pure. Appl. Chem.*, ***1990***, *62*, 1887. Copyright ***1990*** IUPAC.]

Carbohydrates are particularly useful chiral templates.[133] The pyranose or furanose form of a sugar can be opened to give a chiral acyclic fragment. Functional groups can be systematically replaced with others, with a high degree of stereocontrol. In Figure 10.16[134] an analysis of erythronolide A (**223**) reveals two carbohydrate chirons (**224** and **225**). Various synthetic manipulations of the sugar moiety are also shown, eventually leading to a recognizable sugar (D-glucose), protected as the O-methyl derivative.

Fraser-Reid has suggested that the two most valuable advantages offered by carbohydrate derivatives for organic synthesis are (1) highly stereoselective reactions resulting from conformational bias and (2) ready proof of molecular stereochemistry.[135] Synthetic targets derived from sugars with two to four contiguous chiral centers can be constructed from simple pyranose rings. Higher carbon sugars (with greater than four chiral centers) offer formidable challenges.[136,137] Many macrolides, or segments thereof, may be regarded as higher carbohydrate sugars,[138] but challenges arise in stereoselectivity and availability in known configurations. Fraser-Reid outlined a concept he terms **pyranoside homologation** to fill this need.[139,140] An excellent description of this approach using carbohydrates and many other chiral starting materials was given in a monograph by Hanessian.[130] This monograph is strongly recommended to provide a detailed explanation of this approach. In this section, the approach can only be outlined in the context of beginning the construction of a synthetic tree.

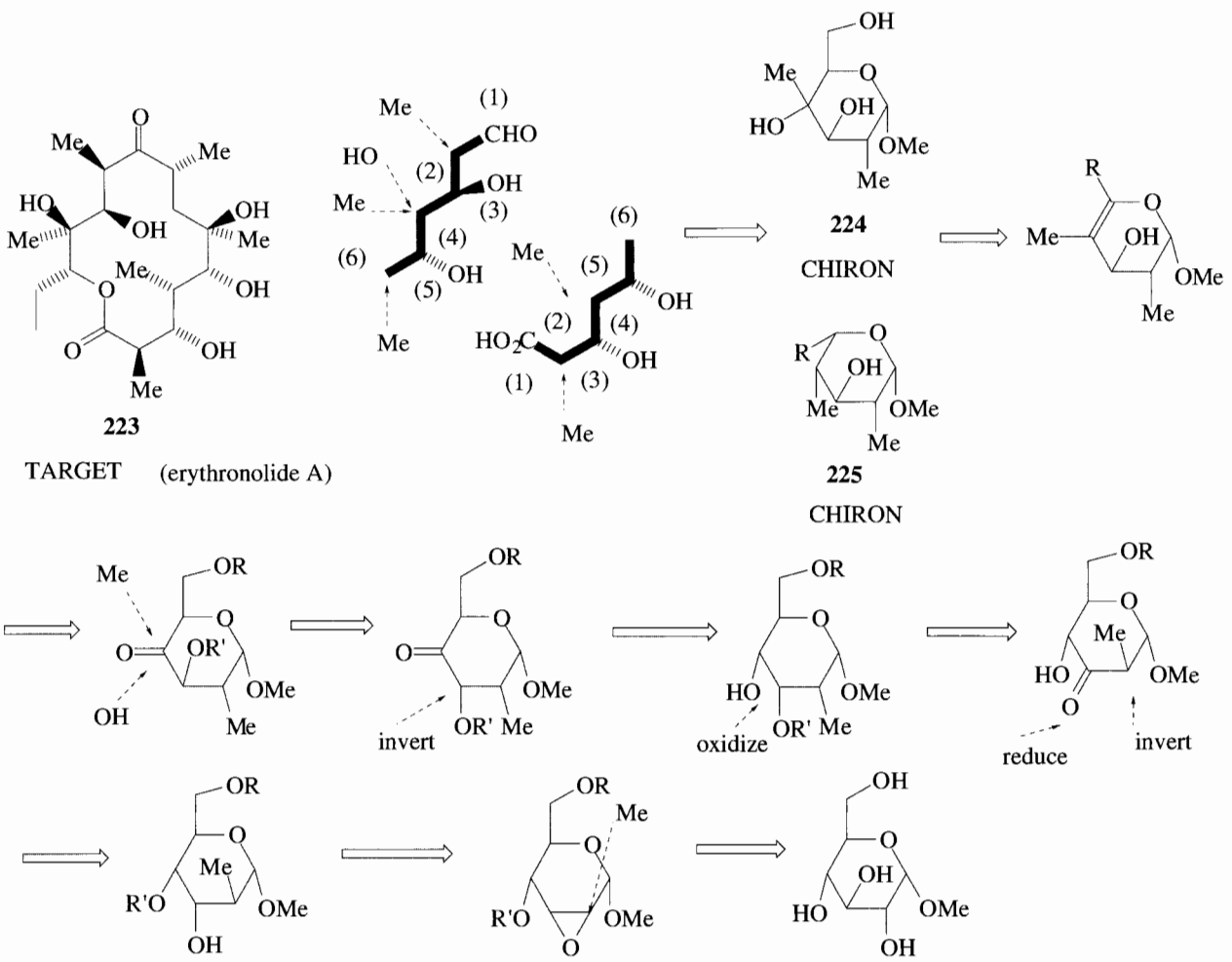
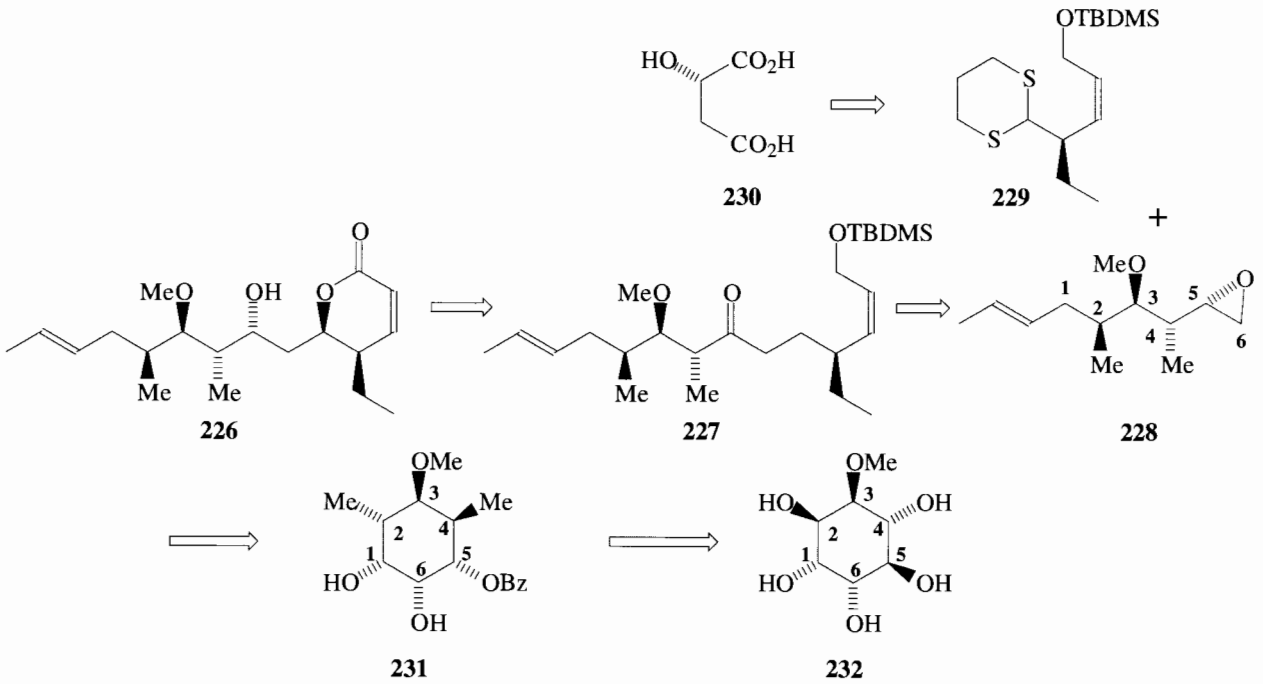


Figure 10.16. Chiron analysis of erythronolide A (223).

[Reprinted from Hanessian, S., *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon Press, ***1983***, pp. 34 by courtesy of Professor Stephen Hannesian. Copyright 1983, with permission from Elsevier Science]

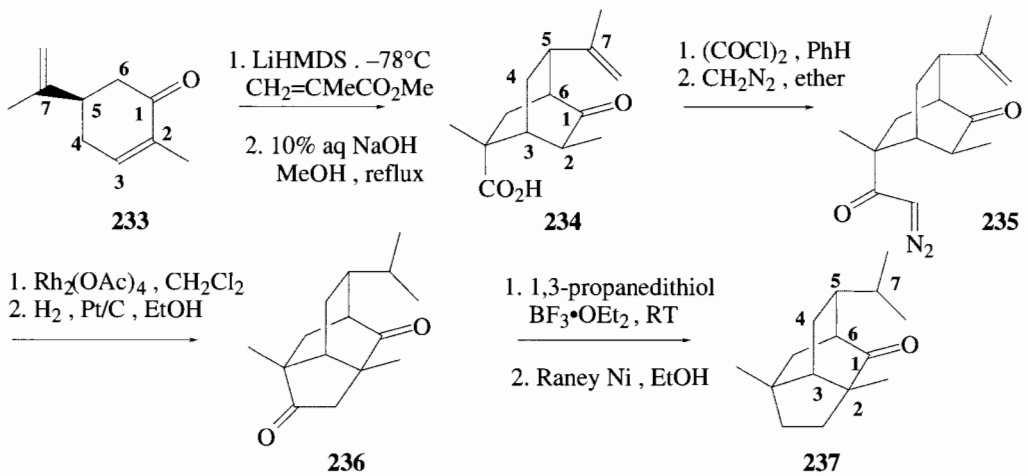
The retrosynthesis of pironetin (**226**) in Scheme 10.19[141] clearly shows how the disconnection roadmap has been biased toward L-quebrachitol, (**232**), an optically active cyclitol obtained in large quantify from the serum of the rubber tree. This retrosynthetic scheme is taken from Chida's synthesis of **226**. Disconnection of the lactone ring to **227** and functional group manipulation of one alcohol was required for the next key disconnection to **228** and **229**. In the synthesis, this reaction set the carbon skeleton and the elements of the lactone ring. Note that **229** is derived from L-malic acid (**230**), so two chiral templates are used in this synthesis. Disconnection of **228** leads to the functionalized cyclohexane derivative **231**, and from here the template **232** can be seen, including which functional groups must be manipulated and which stereochemistry must be changed. The carbon atoms in **228, 231, and 232** are numbered so the needed transformations can be followed more easily. In the actual synthesis, significant functional group modification was required to use the chiral cyclitol and synthesize the final target, which is both the major advantage and the major disadvantage of the method. It is a disadvantage in that the chiron approach does not necessarily lead to shorter syntheses,

since the synthetic tree is pruned to give a single option. Persistence in this one approach may cost the synthesis several extra steps in functional group transformations. It may also lead to difficult carbon–carbon bond-forming reactions. There is usually sufficient pliability in the synthetic tree, however, that a reasonable pathway can be found to a useful chiral template. The advantage is that the asymmetry in the starting materials leads to increased enantioselectivity in all reactions, which usually means that no resolution steps are necessary.



Scheme 10.19. Chiral template-based retrosynthesis of pironetin (226).

Any of the wide variety of chiral molecules available from nature or other sources can, in principle, be used in a synthesis. Scheme 10.20[142] shows Srikrishna's synthesis of (–)-neopupukean-10-one (**237**) from the chiral template (*R*)-carvone (**233**). Formation of the enolate anion at C6 and 1,4-addition to the conjugated



Scheme 10.20. Srikrishna's synthesis of (–)-neopupukean-10-one (237).

ester, followed by a second conjugate addition of the resulting anion to the conjugated ketone at C3 leads to **234** after saponification of the ester. Formation of the acid chloride and reaction with diazomethane gave diazo-ketone **235**, and rhodium catalyzed insertion (see sec. 13.9.C.iii) closed the five-membered ring, and hydrogenation of the alkene unit gave **236**. Conversion of the less hindered ketone to the dithiolane and reductive cleavage with Raney nickel gave the target **237**. The carbon atoms in the template (**233**) are numbered in **234** and in **237** for convenience.

Hanessian has developed a computer program that will execute retrosynthetic plans based on the chiron approach, called the **Chiron program.**[143] Hanessian synthesized (+)-meroquinene based on the analysis shown in Figure 10.17,[143c] where the computer generated four chiral templates, along with notations as to how they must be modified for conversion to a requisite chiron. In the total synthesis, tetraacetyl glucose was chosen as the chiral template starting material, readily available from D-glucose.[144] In a chiral template approach, not all of the chiral centers must be used. It is possible to use only one or two without changing the target, while other chiral centers are generated by highly diastereoselective and/or enantioselective reactions of the chiral template.

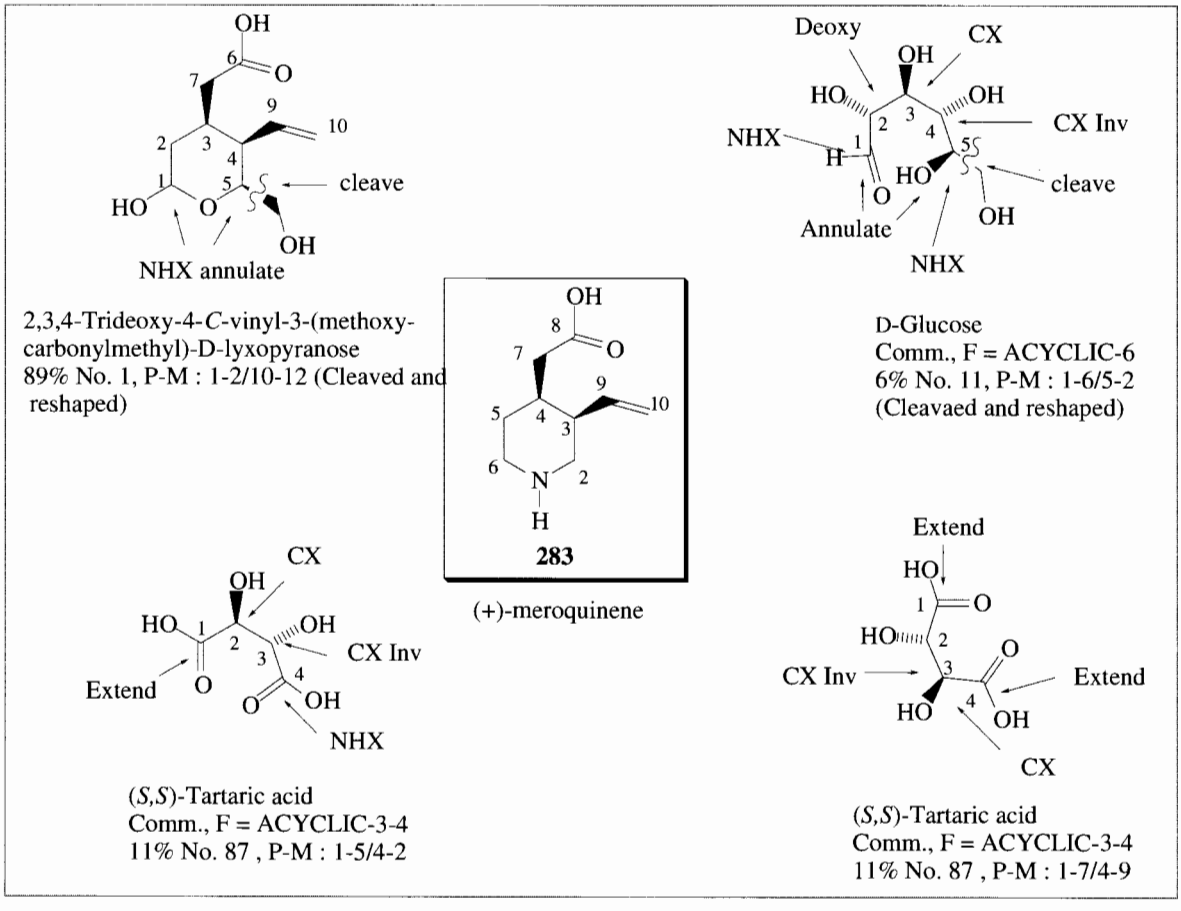


Figure 10.17. Chiron analysis of meroquinene.

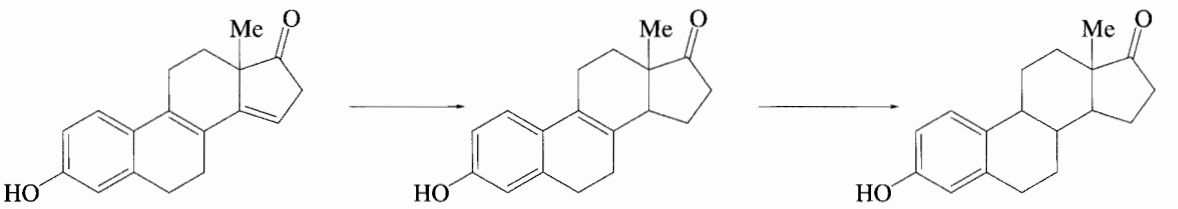
[Reprinted with permission from Hanessian, S.; Faucher, A.-M.; Léger, S. *Tetrahedron*, ***1990***, *46*, 231, Copyright 1990, with permission from Elsevier Science.]

10.10. COMPUTER GENERATED STRATEGIES

In Section 10.4.B a computer based method for generating retrosyntheses was presented called LHASA, and Section 10.9 mentioned the computer program Chiron. There are now other computer methods generically known as computer-assisted organic synthesis. This section will present two such approaches, the SYNGEN approach of Hendrickson, and the MARSEIL-SOS approach of Barone. Other, so-called second generation programs, are also available[145] but this section will use the two mentioned programs to introduce the fundamental approach.

10.10.A. Hendrickson's SYNGEN Approach

The strategic bond approach often leads to consecutive type syntheses, although disconnection of two or more strategic bonds can easily generate convergent pieces. The strategic bond approach generates intermediates on the synthetic tree in an interactive manner that leaves selection to the chemist.[146] The interactive-decision making aspects of the strategic bond approach maximizes opportunities to create new methodology and strategy. If the aim, as stated by Deslongchamps,[13] is to develop new methodology and chemistry as a lasting achievement, then this is an attractive approach. If direct synthesis of a specific target by the most efficient route is more important, rather than one that develops new methodology, then alternative strategy may be desirable. The interactive approach tends to focus on the first levels of the synthetic tree and does not allow the chemist to see which retrosynthetic start leads to early discovery of starting materials and so the shortest pathway.[146]



238 **239** **240**

Hendrickson pointed out that the stepwise backward protocol described in the previous sections suffers from several problems:[147]

1. The procedure creates too many intermediates to manage and most must be deleted without knowing if they will lead to more efficient syntheses.
2. There is no method for predicting yield.
3. The procedure requires an extensive data base of transforms and reactions.
4. The focus of a transform is on the functional groups and those reactions that will completely remove a functional group are not discernible by this method. Estrone (**240**), for example, is easily obtained from **238** via stepwise reduction. Initial reduction of **238** gives **239**, which is then converted to **240**.[148,149] This sequence is not likely to be derived from LHASA or the strategic bond approach since there are no functional groups that could be correlated with the pertinent transforms.

In a complex synthetic tree (see Figure 10.18),[146] which pathway is the best? As stated by Hendrickson, "selection, not generation, is the central problem."[147] The tree must be first simplified and then subdivided.

Let us assume there is a retrosynthesis to a given target with five levels (five disconnect products). A single disconnection may generate 30 reactions that can synthesize the target. If each of the disconnect targets is

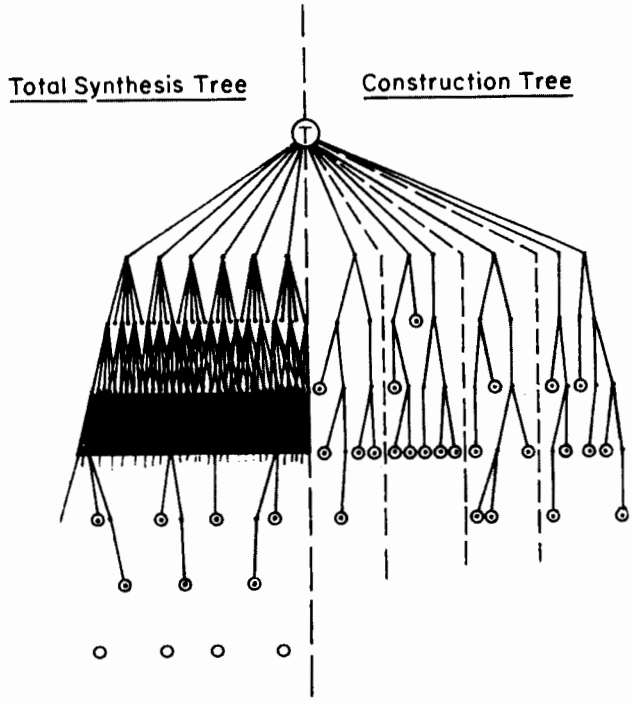


Figure 10.18. The synthesis tree.

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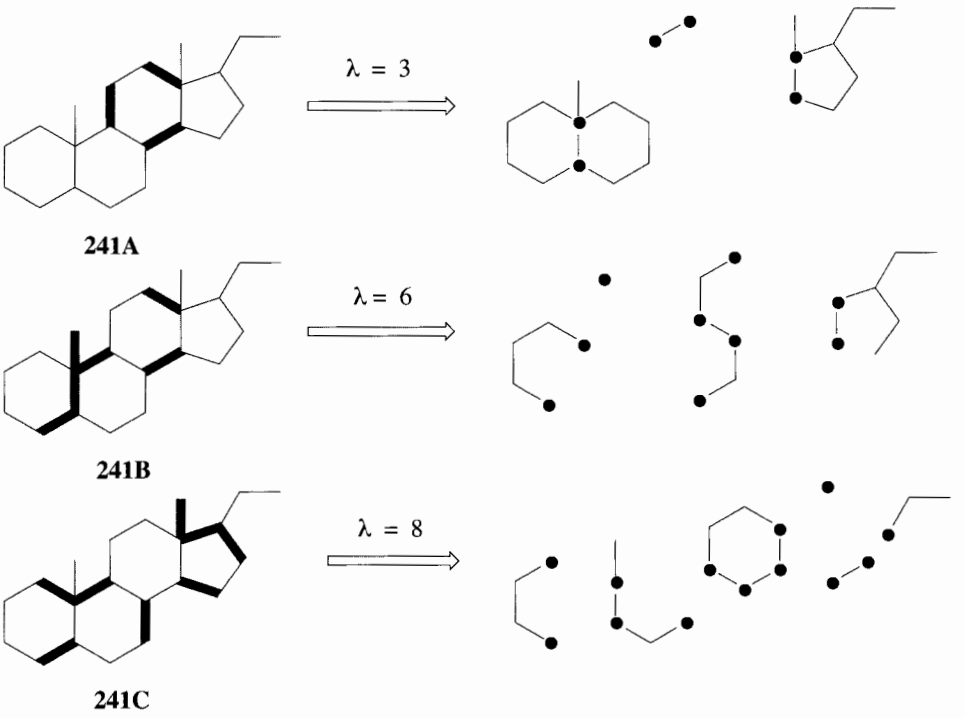
approximately this complex, then the second disconnection will also generate ≈ 30 reactions. If the synthesis is taken to five levels in the synthesis tree, each with the same 30 reaction complexity, there are 30^5 (24.3 million) routes.[147] If the reaction sequence has 25 steps, an already unmanageable problem becomes worse. If the number of synthetic routes at each disconnection stage were only three, a 25 step synthesis would have 25^3 (15,625) possibilities, still rather unmanageable. Hendrickson conceived of four methods to simplify the synthesis tree:[150]

1. Systematize structures and reactions into digital form for a computer.
2. Simplify the tree by "condensing trivial disconnections into familial generalizations".
3. Subdivide the tree into independent subtrees that have no reactions in common, and analyze each subtree separately.
4. Select the optimal pathways.

The process begins with a search for key reactions, the construction reactions (carbon–carbon bond–forming reactions) that will assemble the target skeleton from the skeletons of the starting materials. Initial consideration affords only a major simplification of the total synthesis tree to generate a construction tree. The construction tree contains only the key constructions that assemble the target skeleton from starting skeletons.[146] Each full synthetic sequence is a separate construction plan,[150] separated by the dashed lines in

Figure 10.18. Each such plan is an independent smaller tree that may be examined separately for its detailed chemistry.[146] The consideration can be systematized by breaking the target into smaller fragments. The simplest gross definition of a particular synthesis is the **bondset**–the set of all bonds constructed in a synthesis (γ in number).[151] The concept of bondset is illustrated by three different disconnection schemes[151] for the same steroid: **241A** ($\gamma = 3$),[152] **241B** ($\gamma = 6$),[153] and **241C** ($\gamma = 8$).[154]



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Such a bondset, once defined, implies a multistep sequence passing through the tree from starting material to target, seeing both at once.[151] The bondset is a skeletal conception and immediately defines the skeleton of the starting material as well as the sites on each synthon at which construction is to occur (heavy dots), that is, the construction sites.[151] Each bondset defines an independent subtree of synthetic sequences, all of which construct only that particular set of γ bonds in the target. In general, there are 8! ordered bondsets for a given molecule, although relatively few are efficient. Hendrickson's analysis indicated that the typical total synthesis constructs 25–33% of all skeletal bonds in the target using starting skeletal fragments averaging about three-to-four carbons. That is, for every three or four bonds that are made in a synthesis, only one skeletal bond is made. Synthons actually used are predominantly acyclic unbranched skeletons of four carbons or less, or aromatic derivatives. The average size of starting materials can be defined as n_0/k for an overall average of 4.0 carbons. The bondset size as a proportion of the total bonds is therefore $\gamma/b_0 \approx 0.24$ (the construction ratio).

Hendrickson used two different syntheses of estrone (**240**) to illustrate this approach and Figure 10.19[151] shows the bondsets, construction plans, and weights (see below) for both. Velluz's convergent retrosynthetic strategy is shown in Figure 10.20.[43,155] Hendrickson compared this with the closely related syntheses of

Torgov and co-worker [148] and Smith et al.[149] With Hendrickson's bondset analysis, the 18 carbons of **240** should give an average of six pieces, each of three or more carbons. If a molecule is composed of 15–25 carbons and the construction ratio of ≈ 0.21, a synthesis should require 4–7 constructions.[151] For this example, there are nine bond constructions ($\gamma = 9$). A skeleton of n atoms and r rings has $n_o + r_o - 1$ bonds and $b_o = n_o + r_o - 1$. If there are k pieces then $\gamma = k + r_o - r - 1$. The following definitions apply: $\boldsymbol{b_o}$ = number of C—C single (σ) bonds in the target; $\boldsymbol{n_o}$ = number of carbons in the target; $\boldsymbol{r_o}$ = number of carbocyclic rings in the target; $\boldsymbol{r}$ = number of carbocyclic rings in the starting material; $\boldsymbol{k}$ = number of synthons; γ = number of bonds constructed (bondsets).

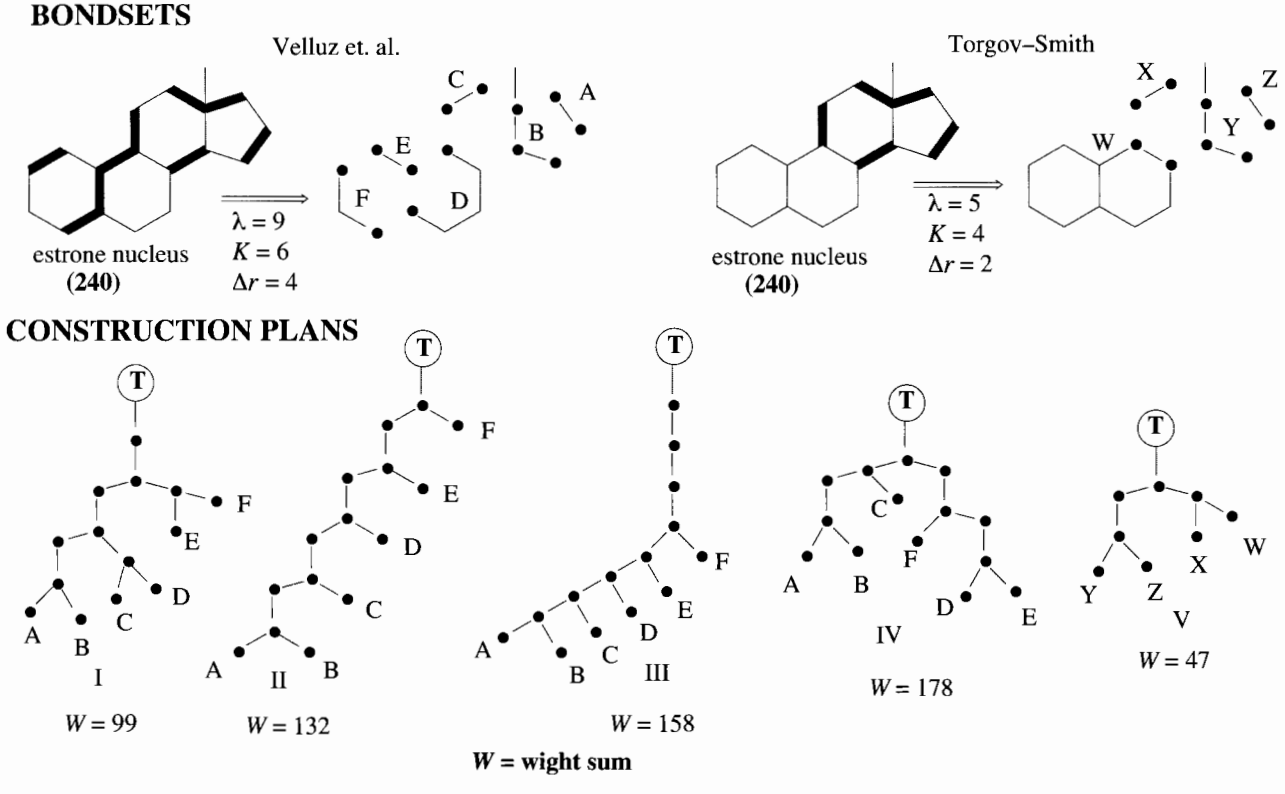

Figure 10.19. Bondsets and construction plans for estrone (240)

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For Velluz's synthesis, $b_o = 21$, $n_o = 18$, $r_o = 4$, $r = 0$ and $k = 6$. Therefore, $b_o = 18 + 4 - 1 = 21$ and

$$\gamma = 6 + 4 - 0 - 1 = 9.$$

Convergent syntheses disconnect the target into at least two pieces, each of which is further disconnected, which usually leads to a more efficient strategy, as with the Torgov–Smith approach. Rather than proceeding retrosynthetically, one step at a time, the convergent disconnection goes down many levels into the tree, closer to the starting materials to be used. After restricting the disconnection to the convergent type to maximize simplification, the next step is to examine the various functional groups and reactions necessary for the construction sequences. The number of steps should be kept to a minimum. In the estrone synthesis, there are 24

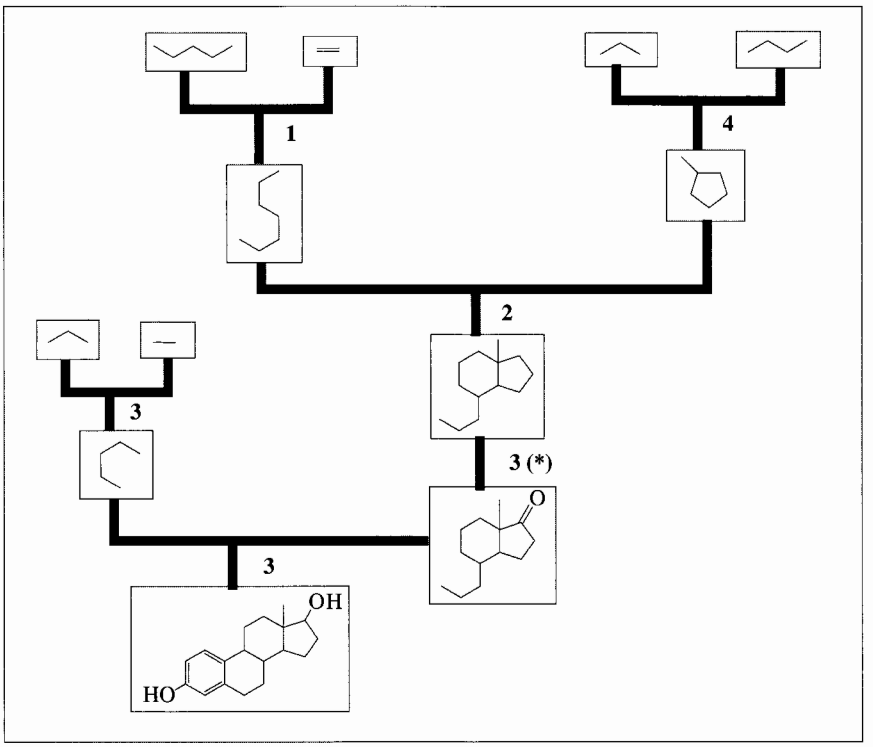


Figure 10.20. A convergent retrosynthetic analysis of Velluz's estrone synthesis. Total synthesis of estradiol, schematic. The figures between the individual stages indicate the numbers of reaction steps. (*) denotes optical resolution at that step.

[Reproduced with permission from Velluz, L.; Valls, J.; Mathieu, J. *Angew. Chem. Int. Ed. Engl.*, ***1967***, *6*, 778. Copyright 1967 VCH Weinheim.]

bonds. If these are to be made from one-carbon pieces (the bondset = 1), there are 24! (= 6 x 10^{23} different pathways for assembly). The convergent strategy will increase the number of bondsets and decrease the number of convergent routes that can be applied.[147] If the bondset is increased to five members ($\gamma = 5$), there are 20,349 ways to cut estrone, but there are $\gamma!$ routes (2.5 million ordered bondsets), which is an enormous number, but better than 6 x 10^{23}.

Hendrickson devised a weighting scheme for each construction tree based on the weights of the several starting materials for each level of the synthesis tree.[146,150] The fundamental idea is to calculate the overall weight of starting materials that will be required to generate a gram of the target. Since these molecular weights are unknown at the time the synthetic fragments are assembled, the number of skeletal carbons in each piece (η_i) and the weight sum (W) gives a measure of the efficiency of the reaction. The reciprocal of the average yield for each step is X, and the number of steps each fragment (i) passes through is l (the level of the starting material in the synthetic tree is i). The quantity W is then given by the expression[147]

$$W = \left(\Sigma \eta_i \right) \left(X^{li} \right)$$

Hendrickson provided a table of X^{li} values that are correlated to the number of steps (l, see Figure 10.21).[147] Table 10.3[147] reproduces Hendrickson's table, but the yield has been inserted, remembering that X is the *reciprocal* of the yield. The value of W assumes ***no*** refunctionalization in the synthesis.

Table 10.3. Values of X^a and the Yield for Syntheses of Steps *l*

l (No. steps)	X^l Approximate	X^l Actual	Yield (%)
1	1.25	1.25	80
2	1.5	1.56	64.1
3	2	1.95	51.3
4	2.5	2.44	41.0
5	3	3.05	32.8
6	4	3.81	26.2
7	5	4.77	21.0
8	6	5.96	16.8
9	7.5	7.45	13.4
10	9.5	9.31	10.7
11	11.5	11.64	8.6
12	14.5	14.55	6.9
13	18	18.19	5.5
14	23	22.7	4.4
15	28	28.4	3.5

[a] $X = \frac{1}{\%\ \text{Yield}}$

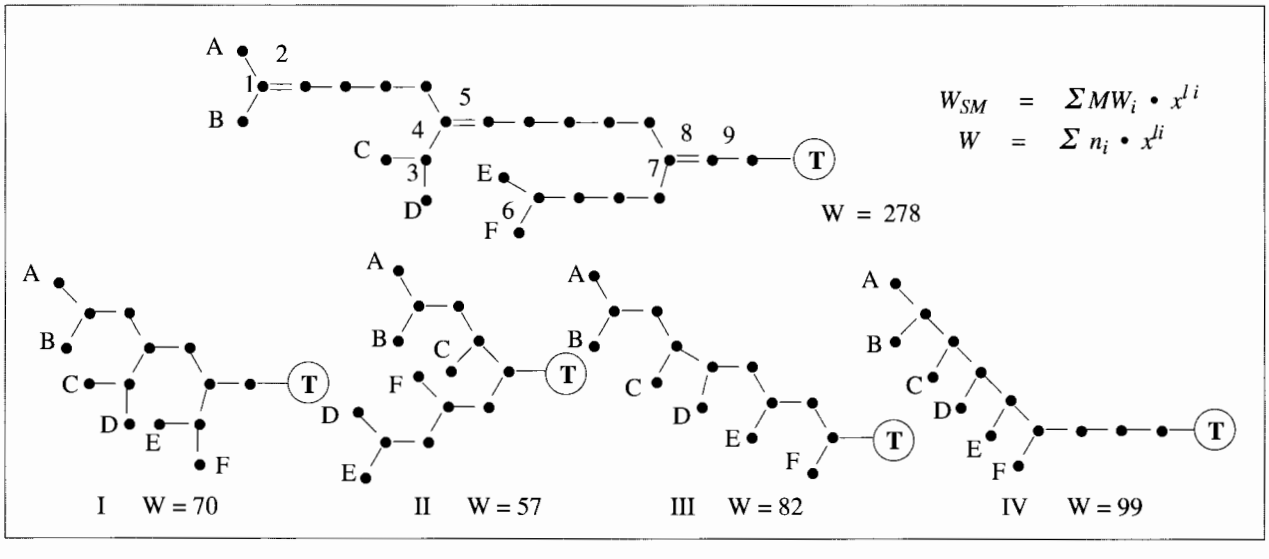
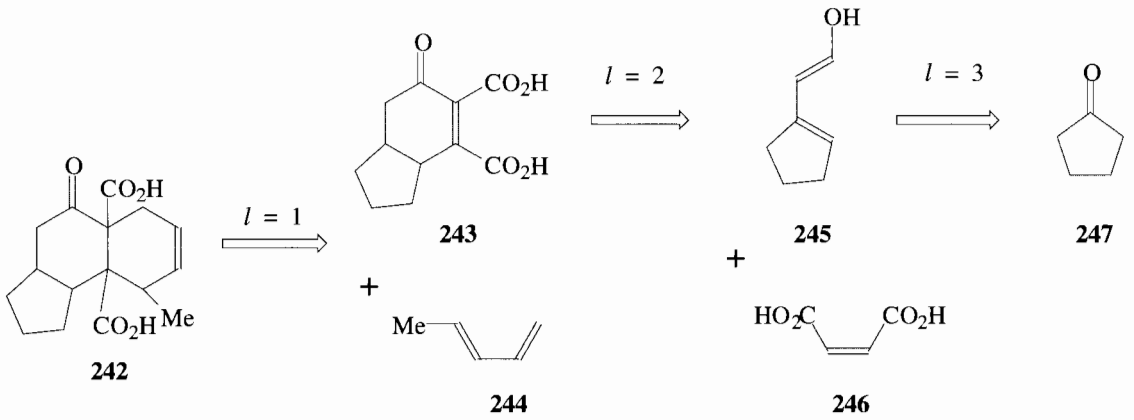


Figure 10.21. Weighting scheme for synthetic tree analyses.

A simple analysis of **242** shows a three-level synthetic tree. The first disconnection ($l = 1$) to **243** (η = number of carbons = 11) and **244** ($\eta = 5$) requires a Diels–Alder disconnection (sec. 11.4.A). The level 2 disconnection to **245** ($\eta = 7$) and **246** ($\eta = 4$) is also a Diels–Alder disconnection. The final disconnection (level 3) generates cyclopentanone (**247**, $\eta = 5$) suggesting a condensation reaction with an organometallic. For this example, the weighted average (W) is given by the following calculation:

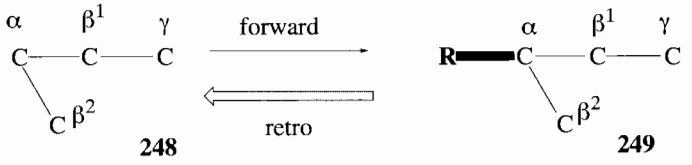
$$W = \eta_{\mathbf{243}} \cdot X^1 + \eta_{\mathbf{244}} \cdot X^1 + \eta_{\mathbf{245}} \cdot X^2 + \eta_{\mathbf{246}} \cdot X^2 + \eta_{\mathbf{247}} \cdot X^3$$

$$W = (11)(1.25) + (5)(1.25) + (7)(1.5) + (4)(1.5) + (5)(2) \quad \text{so,} \quad W = 46.5$$



The weighted averages shown in Figures 10.21 and 10.19 were calculated in this manner. In Figure 10.21, synthesis tree II is taken to be the most efficient (lowest *W*) and represents the *fully convergent* synthesis.

An ideal synthesis in the context of this method requires only sequential construction reactions, with no refunctionalization needed to repair functional groups between constructions.[146] This ideal synthesis was assumed in the weighting scheme discussed above, although it is very difficult to attain as a practical matter. Hendrickson's approach was to develop a numerical description of functionality.[156] The structures become a list of simple numbers, ordered by the numbering of the skeletal carbons. A reaction is expressed by its net structural change, the arithmetic change in the functionality from substrate to product or vice versa.[146] The reaction is then represented by a number list for the pertinent carbons that generate the substituent functionality when add to the product list (or vice versa).[157] Hendrickson chose to use half-reactions in the actual analysis,[146] and a construction reaction may be seen as two linked half-reactions on each side of the bond–formed.[158,159] Each partial synthon undergoes a half-reaction and each construction half-reaction is characterized by the net structural change relating substrate and product for that particular synthon.[146] The skeletal format for construction of a half-reaction is shown by the relationship of a substrate (**248**) and a product (**249**). Functionality appears on these carbons and changes from substrate to product in a manner characteristic of a given half-reaction.[147b] A numerical system was developed to describe structures,[156,158] based on four kinds of attachments to any carbon: to hydrogen (H); a σ bond (R); a π bond (Π); and a carbon–heteroatom bond (*Z*). The functionality is then $\pi + z$ for a given skeleton of known σ bonds and $\underline{h}$ derived by difference. Functionality is, therefore, expressed by z and π.



These concepts were developed into the computer program **SYNGEN**[147] (**SYN**thesis **GEN**eration).[160] As with Corey's LHASA program, inspection of the main principles of the program can offer useful information for a synthesis. It is emphasized that this section has only touched the surface of Hendrickson's detailed and comprehensive analysis. Once understood, any target can be analyzed in detail to provide a synthetic tree.

The purpose of this discussion is to give general concepts that may be applied without a computer analysis or dependence on any one approach. With this in mind, SYNGEN has two parts. The first is a skeletal dissection of the target and the second is generation of functionality necessary to assemble the synthesis. There are several general rules for design of an optimal synthesis, as described by Hendrickson:[147]

1. Minimize refunctionalization.
2. Refunctionalize early.
3. Minimize constructions (γ), which implies the use of large structural pieces of several constructions in a single step (sec. 10.5.B.vi for powerful reactions).
4. Join large pieces last to minimize their large weight loss.
5. Fully convergent routes are preferred.
6. Cyclize early. The structure weight will be minimized if cyclizations are carried out early.
7. Chiral resolution should come early. Since resolution discards > 50% of the material, the rationale is obvious.

There are nine characteristics of the SYNGEN approach.[160]

1. It is an executive program not interactive with the chemist.
2. It assesses all possible routes within clearly defined constraints.
3. It uses digital expressions for molecules and reactions.
4. It dissects the initial skeleton for efficient assembly.
5. It draws on a pool of several thousand available starting materials .
6. It attempts to weight each route to economize the number of steps.
7. It limits the analysis primarily to construction reactions.
8. It generates reactions from mechanistic logic.
9. It does not predict yields.

Hendrickson summarized seven reductive criteria for the basic protocol of the approach.[158]

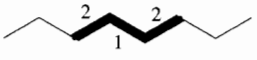
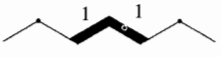
1. Select from the target structure prime bonds for construction.
   (a) Functionality criteria: pairwise consideration of functionalities and their relative positions on the skeleton.
   (b) Skeletal (and stereochemical) criteria.
2. Combine these bonds into bondsets, adequate to dissect reasonable synthon skeletons but minimal in γ.
3. From each bondset isolate the synthon skeletons dissected, noting the pattern of construction sites on each.
4. For each synthon skeleton, locate in the general sequence list corresponding to its pattern of construction sites the sequences applicable to the skeletal (σ) levels of those sites. This defines for each synthon a set of all self-consistent sequences of half-reactions, their particular starting materials and their consequent product functionalities.
5. Eliminate, for each synthon, undesirable sequences:
   (a) Sequences unsuitable for the synthon skeleton (at sites other than construction sites), which must bear functionality, $f = 4 - \sigma$.
   (b) Unavailable starting materials.
   (c) Unacceptable product functionality for the target structure.
   (d) Exclusion of certain functionalities in rings (e.g., triple bonds) and certain reactions (cf. Grignard) for cyclizations.
   (e) other criteria, such as implicit refunctionalization or regiospecificity in sequences.
6. Select a prime synthon, with the most construction sites, and match successive constructions serially with the other synthons as dictated by the bondset, accepting only matching half-reactions of opposite polarity, to create full synthetic routes.
7. Eliminate matchings in which subsequent constructions on one synthon are not compatible with existing functionality on any other synthon already linked to it.

Hendrickson provided details for several of these criteria, which are instructive to a chemist beginning the disconnection process.

1a: A particular skeletal bond is identified, defined by the functional group (or pair of groups)

examined.[151] These may be summarized (Table 10.4)[151] as a function of the position of the functionalized sites on the target skeleton. Some bonds will have a higher priority if the target functionality is exactly correct for certain constructions or if more constructions are available to yield the particular sites of functionality.[161] A more detailed table of construction bond data is available.[161]

Table 10.4. Construction of Bonds Dictated by Product Functionality

Molecular Form[a]	Common Examples[b]
Single Functionality	1. Grignard addition; activated anion alkylation 2. Enolate alkylation; Grignard + epoxide 3. Alkylcuprate conjugate addition
Functional Group Pairs Functionality span =	
2	1. Activated anion addition or acylation 2. Acetylene alkylation 3. Allylic anion alkylation
3	1. Claisen condensation; Aldol reaction 2. Allylic activated anion alkylation
4 	1. Enolate or acetylene anion + epoxide 2. Activated anion conjugate addition
5 	1. Michael addition; Claisen rearrangement

[a] Heavy bonds indicate those marked for construction.

[b] Activated anion = heteroatom stabilized carbanion, as Wittig reagent, nitroalkyl anion, dithiane anion, cyanide ion, and so on; addition = carbonyl and relate additions.

1b: Certain considerations of the skeleton define particular bonds to be considered for construction. (i) The first is the presence of the skeleton in available starting materials of recognizable large skeletal units such as aromatic rings or monoterpenes for sesquiterpene synthesis. (ii) The second is division into two or three similar sized skeletons for convergent synthesis efficiency (*divide* each *target into two disconnect fragments at each retrosynthetic step*). Two or three synthons of similar size may be separately constructed in parallel, then linked. Bonds at or near the center of the skeleton can be used to disconnect the skeleton into separate component synthons. (iii) Choose bond pairs for annelation. (iv) Inspect for the presence of several like groups that could be introduced simultaneously. (v) Inspect for the presence of skeletal features with limited synthetic choices: quaternary or tertiary centers and small (three- and four-membered) rings. (vi) Consider strategic ring disconnections in polycyclic skeletons. (vii) Consider stereochemical features.

Hendrickson restated this principle[151] in a manner that can be used for planning the first disconnection.

"Fully convergent bondsets of any target skeleton are readily created by dissection of the target into two pieces, then cutting each of these in two again. When all the pieces so obtained also corresponds to skeletons of available starting materials, this creates an ordered bondset for a potential synthesis using those starting materials."

2. In the bondsets γ, which is the number of construction reactions in the synthetic sequence, should be minimized to make the synthesis more economical (shorter).

3. It is possible to define the pattern of construction sites on any synthon as to their relative placement or location and the order in which they undergo construction half-reactions.[151] The synthon skeletons are marked as construction sites on which is placed the appropriate functionality for actually constructing half-reactions in a self-consistent sequence. The numerical codification for individual half-reactions[161] defines a reactive strand of up to three functionalized carbons out from the construction site. Except for a terminal (primary) construction site ($\sigma = 1$), there is a question as to which strand of carbons from the site bears the activating functionality. Secondary construction sites ($\sigma = 2$) have two choices and tertiary ($\sigma = 3$) have three. For a synthesis with three steps having secondary sites to undergo construction ($\alpha\beta\gamma$), there are $2^3 = 8$ ways to lay on the skeleton the reactive strand of functionality needed to initiate the construction.[151] Hendrickson has provided an extensive table of sequence lists for use in this procedure.[162]

4. The process is illustrated in Figure 10.22[146] for testrone (**204**). The skeletal fragmentations lead to bicyclo[4.4.0]decane (F), the two-carbon fragment (E), and the cyclopentane fragment (D). The appropriate functionalization is also shown in which vinyl chloride (J) is the synthetic equivalent of (E), ketone (K) is the equivalent of F, and 2-methyl-1,3-cyclopentanedione (H) substitutes for (D).

5–7: These are self-explanatory.

Hendrickson's methods can be learned, and the principles applied, without a computer. However, the novice does not have the extensive background of reactions or a mental pool of reasonable starting materials and so, without a computer, may not be able to take full advantage of this methodology. The main lesson from this section will point a beginner toward a search for convergent disconnections and the use of an approach that breaks the molecule into two fragments at each disconnection level. Some rationale must be provided as to which two fragments are the best. Unless Hendrickson's complete approach (and the SYNGEN program) is used, the answer still lies with the chemist, who is gazing at the top of the synthesis tree rather than at the bottom.

10.10.B. Barone's MARSEIL/SOS System

Barone developed a disconnection approach that relies on a microcomputer and the program **MARSEIL/SOS** (**S**imulated **O**rganic **S**ynthesis).[163] It aims to be a usable electronic lab notebook for organic synthesis. The fundamental basis of this program is[163] "about 350 reactions which constitute about 33% of March and Smith,"[164] and it follows a retrosynthetic approach.[165] The structural features of the target are determined in two parts. (1) Rings and standard features such as nucleophilic centers, electron-withdrawing groups, and so on are determined using classical organic chemistry; (2) A file of substructures is available that are matched with the target. In a general sense, both parts are excellent advice to the chemist beginning a disconnection. Attempting to correlate known substructures and reactive fragments can point to which fragmentation makes the most chemical sense.

The actual search for a particular transform is accomplished by looking for a characteristic substructure, evaluating that substructure, and providing reactions to build it as a precursor. A major drawback to the program is the lack of attention to stereochemistry in the target or disconnect products. In one example

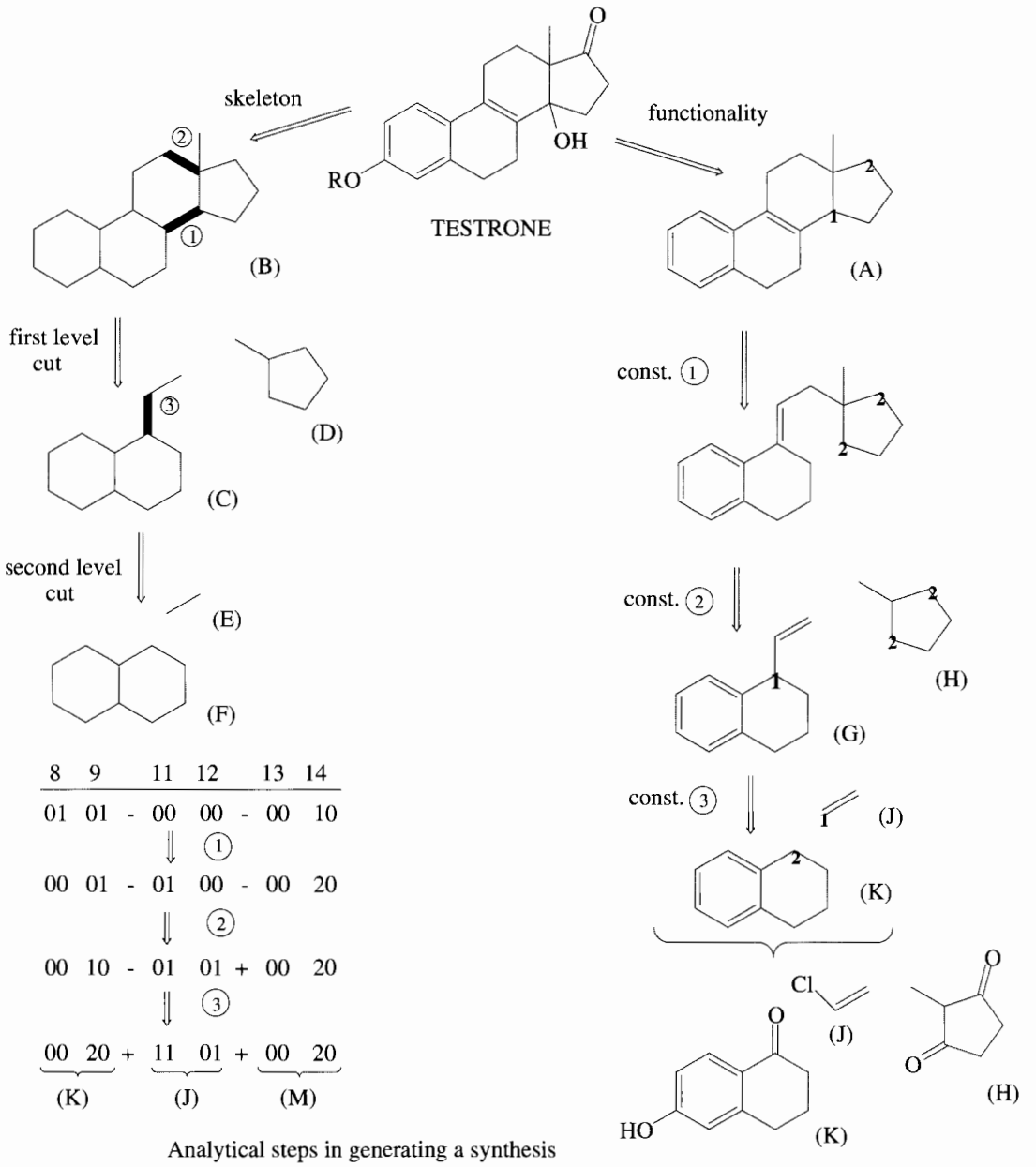


Figure 10.22. A SYNGEN-generated retrosynthesis for testrone.

[Reprinted with permission from Hendrickson, J.B. *Accounts Chem. Res.*, ***1986***, *19*, 274. Copyright © 1986 American Chemical Society.]

t(Figure 10.23),[166] this program generated several synthesis pathways for (±)-ar-turmerone (**250**).[167] It was pointed out that the students who used this program must choose the more reasonable path, "after discussion with the instructor."[166] The instructor chose path 6 (Figure 10.24), and it is clear that this program relies on he chemical intuition and knowledge of reactions of an experienced chemist. In this case, the novice will not be able to reasonably choose the best approach. Barone used a retrosynthetic approach to define the logic of Marseil/SOS, and this was contained in another program, **REKEST** (**RE**search for the **KE**y **ST**ep).[168] The

fundamental logic for disconnection is based on a library of stylized reactions, shown in Figure 10.24.[168] Each reaction is a pattern that allows deletion or addition of one or several bonds in the target. The labels A, B, C, and D are any atoms and the disconnections generally involve deletion of one or two bonds. An analysis

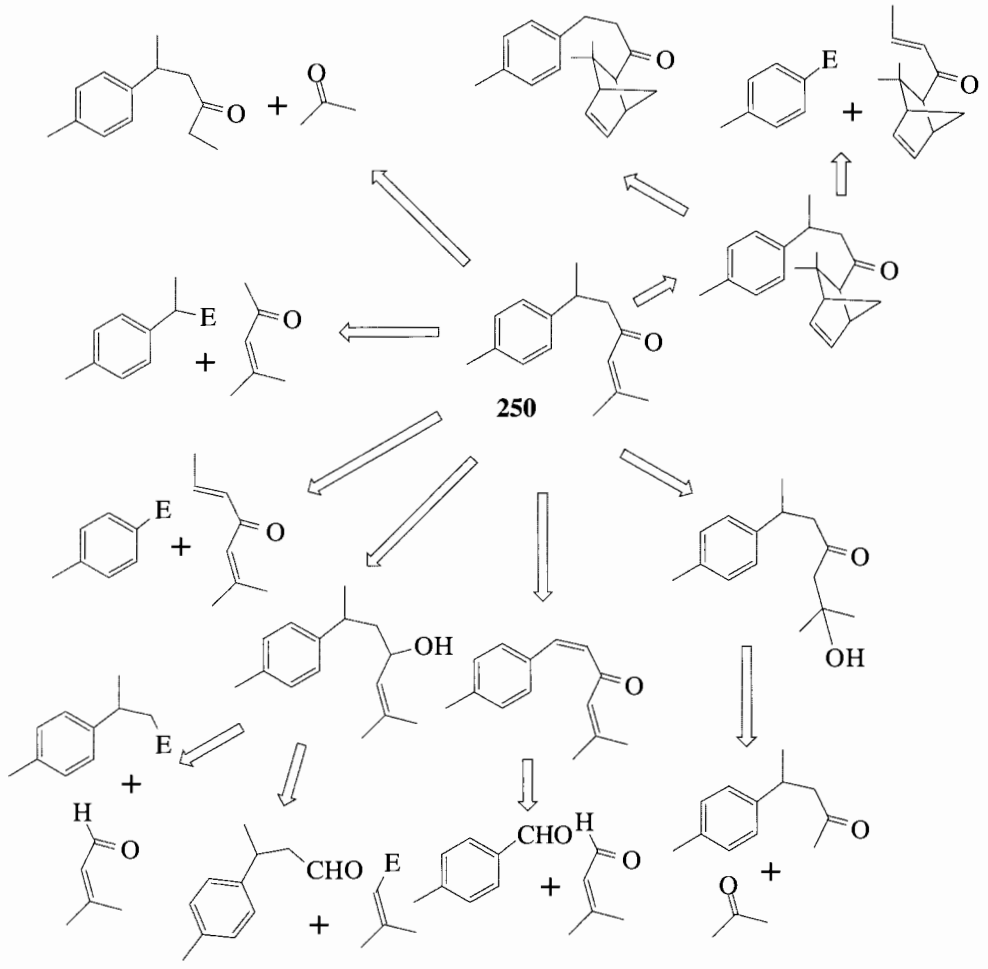


Figure 10.23. MARSEIL-SOS generated retrosynthetic scheme for turmerone.

[Reprinted with permission from Bertrand, M.P.; Monti, H.; Barone, R. *J. Chem. Educ.*, ***1986***, *63*, 624. Copyright © 1986 American Chemical Society.]

for **251** is shown in Figure 10.24.[168] Once the choice of reaction has been made, appropriate atoms for A, B, C, and D are determined within the boundaries of atoms that are compatible with real chemical reactions. Clearly, this general approach is of value because the chemist can examine a target for disconnections that follow the reactions in Figure 10.24, which leads to better decisions as to which disconnections should be made.

In these approaches, the bonds chosen for disconnection maximize simplification of the target. Bonds are chosen that can easily be re-formed. A pool of known starting materials and chemical reactions is essential. Once the disconnection process begins, the chemical experience and interest of the chemist will usually determine which pathway is best suited for their purpose.

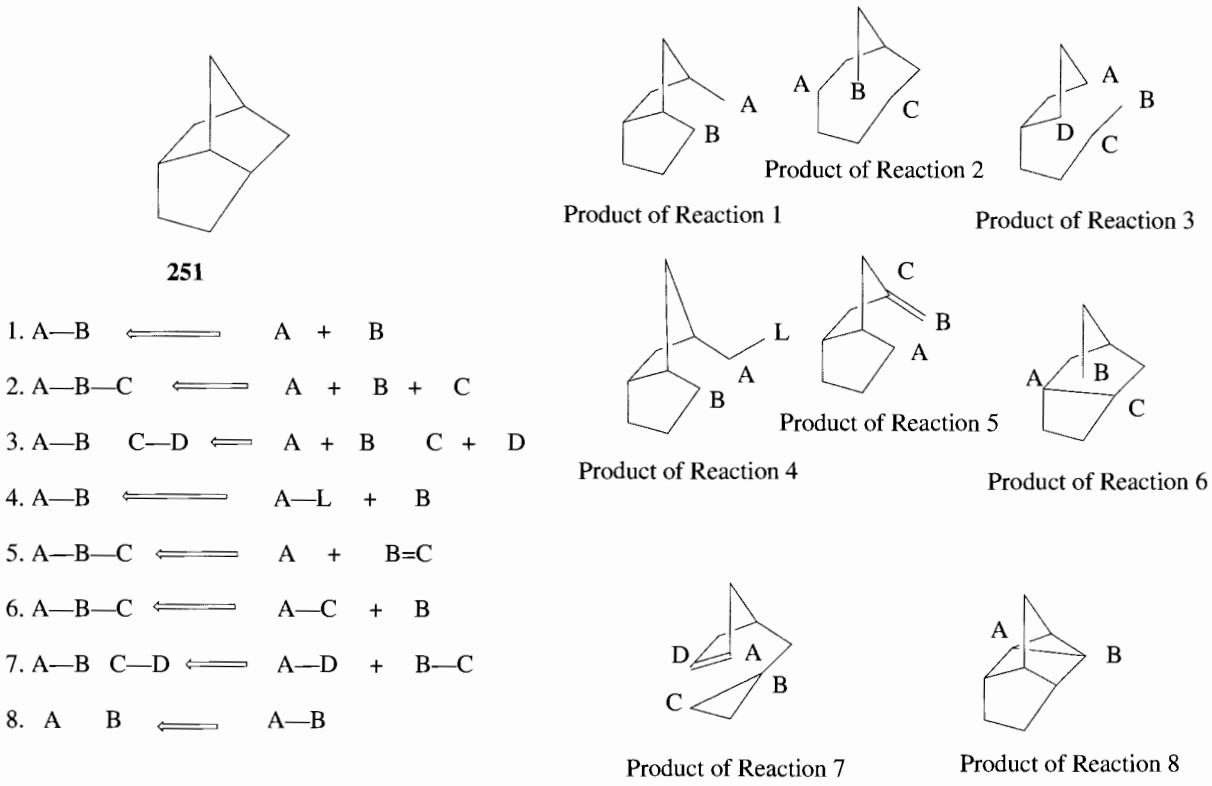


Figure 10.24. Reaction types for REKEST and MARSEIL/SOS.

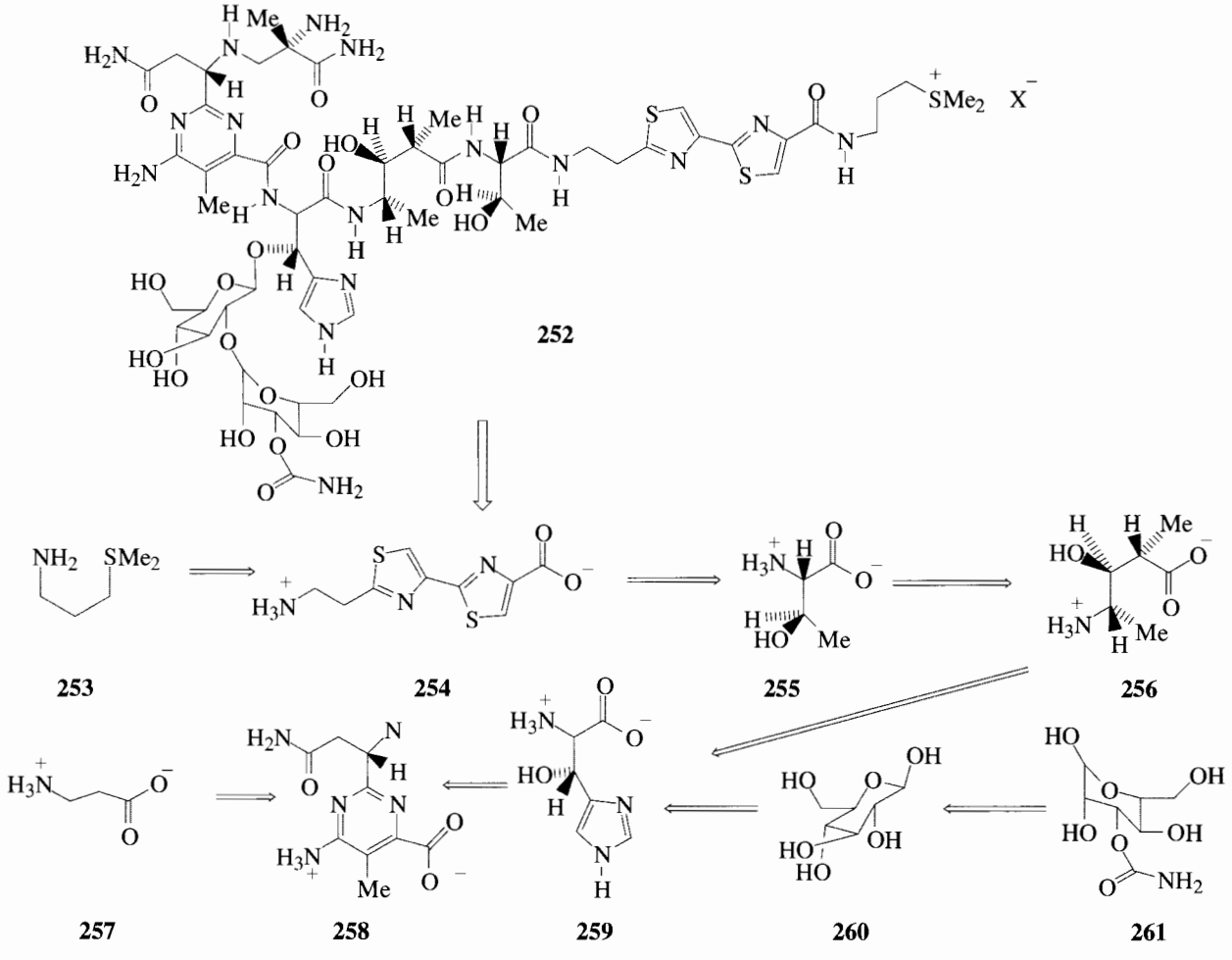
10.11. DEGRADATION TECHNIQUES AS A TOOL FOR RETROSYNTHESIS

10.11.A. Chemical Degradation

Structural information about complex molecules is often obtained by degrading a target into simple and identifiable pieces. Hydrolysis, thermolysis, photolysis, and treatment with chemical reagents are common methods for degrading a molecule. The points at which the molecule breaks apart are correlated with the known reactions by which these bonds can be re-formed. Analysis of all degradation products can then be used to construct a complete or partial synthetic tree or it can point to a key reaction that a synthesis can be built around.

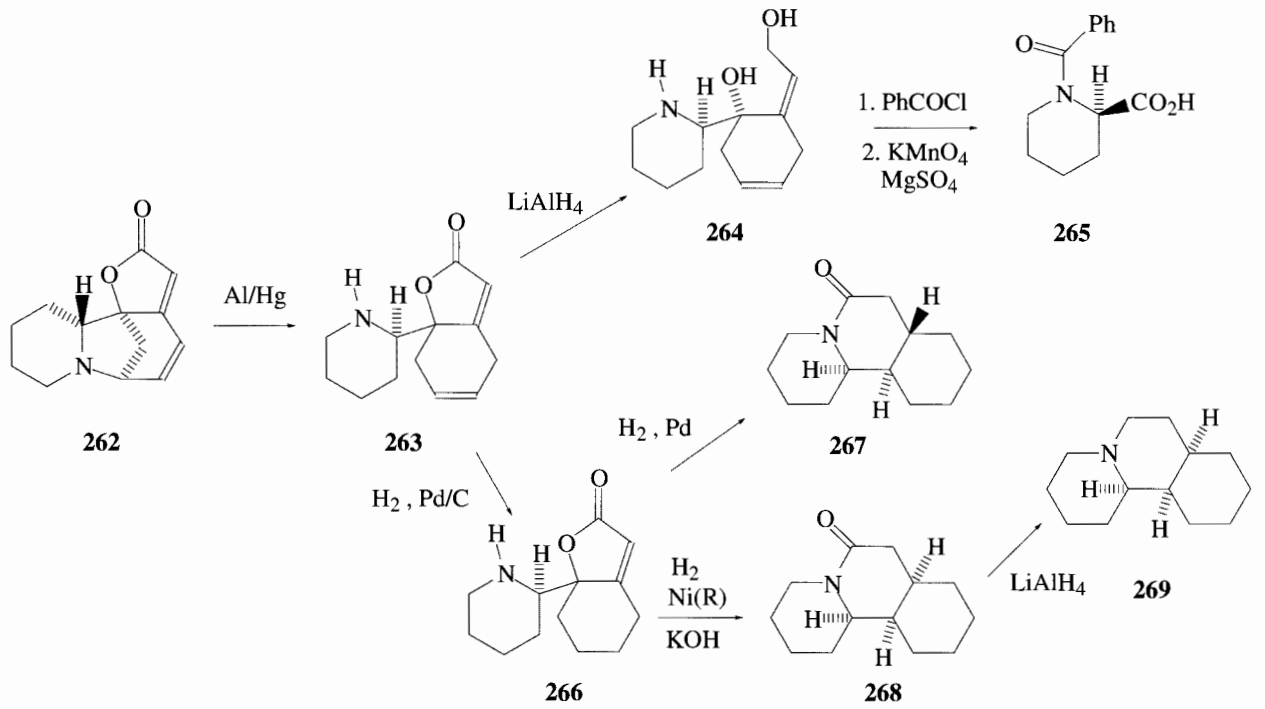
A superb example of this approach is the total synthesis of bleomycin A_2 (**252**) reported by Hecht. Bleomycin was isolated by Umezawa and co-workers[169] and shown to be a potent anticancer agent.[169] While determining the structure, it was shown that hydrolyses and other chemical manipulations of **252** gave nine identifiable fragments: (a) aminopropyldimethyl sulfonium (**253**); (b) 2-aminoethyl-2',4-bithiazole-4'-carboxylic acid (**254**); (c) L-threonine (**255**); (d) (2*R*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylpentanoic acid (**256**); (e) L-*erythro*-β-hydroxyhistidine (**258**); (f) β-amino-β-(4-amino-6-carboxy-5-methylpyrimidin-2-yl)propionic acid (**259**); (g) a rearrangement product, L-β-aminoalanine (**257**); (h) gulose (**260**); and, (j) carbamoyl mannose (**261**).

Hecht's synthetic approach was to first synthesize each of the individual pieces. The total synthesis required connection of the nine molecules to give bleomycin.[170] The disconnected pieces are shown in Scheme 10.21[170] and the plan to synthesize bleomycin from these pieces constitutes an outline of the synthetic tree. Hecht's synthesis of bleomycin A_2 is also an excellent example of a convergent synthesis (sec. 10.3.C). Boger synthesized bleomycin using a different strategy.[171]

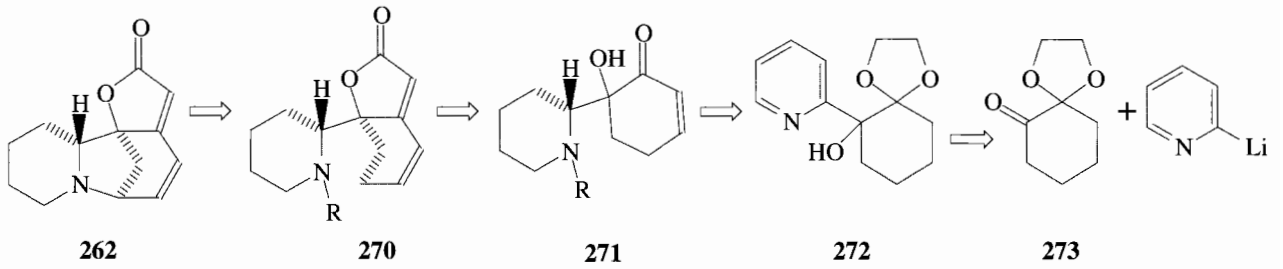


Scheme 10.21. Retrosynthetic analysis of Hecht's bleomycin A_2 synthesis.

Chemical degradations other than hydrolysis can fragment a molecule and generate a synthetic tree, as with the degradation of securinine (**262**) in Scheme 10.22.[172] Reductive cleavage of the C—N bond yielded **263**. The alkene unit was reduced by catalytic hydrogenation to **266** but the lactone unit could also be reduced with $LiAlH_4$ to give **264**. Allylic alcohol (**264**) was oxidatively degraded to **265** with permanganate. Reduction of **266** liberated **267**. Hydrogenation in the presence of base, however, gave **268**. Reduction of the lactam carbonyl in **268** with $LiAlH_4$ gave **269**. With this degradation scheme in mind, a retrosynthesis is shown in Scheme 10.23,[173] based on Horii's total synthesis. Note the similarity of **270** to **263** and **266**, and also the relationship of **271** to **264**. Disconnection product **272** yielded the two starting materials, the monoethyl-eneketal of 1,2-cyclohexanedione (**273**) and 2-lithiopyridine.



Scheme 10.22. Chemical degradation of securinine (262).



Scheme 10.23. Retrosynthetic analysis of Horii's securinine synthesis.

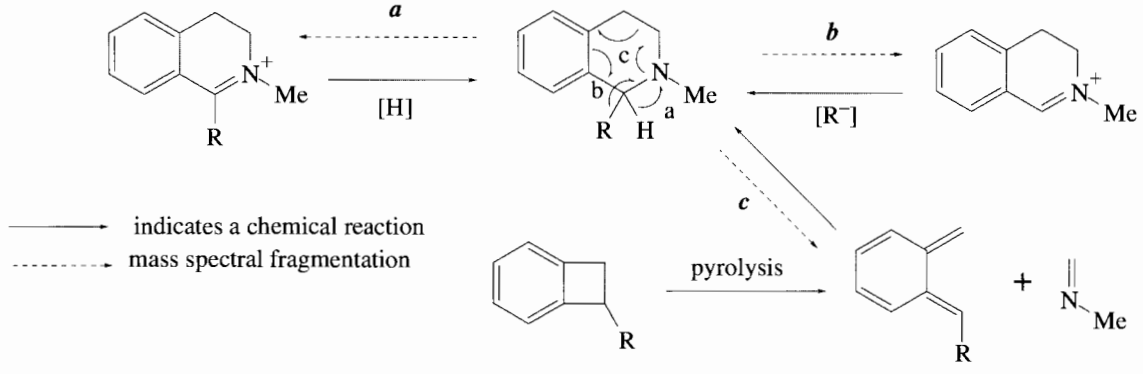
10.11.B. Retro-Mass Spectral Degradation

A target may resist hydrolysis or chemical degradation, or the degradation products may not yield useful information. It is also common that insufficient material exists for proper analysis. In these cases, an alternative degradation technique is available that uses the ionizing electron beam of a mass spectrometer. The ionization pathways available from electron impact in the mass spectrum are bond fission processes that occur by known and predictable pathways. Indeed, each pathway usually follows analogous chemical reaction pathways *in a retro-synthetic manner*. It therefore follows that an examination of mass spectral ionization patterns can give clues for suitable disconnections and a synthetic tree.

This basic premise was outlined by Kametani and Fukumoto[174] and used for the synthesis of a number of important alkaloids. As mentioned, the key feature of the analysis is the fact that many chemical reactions appear as their retro analog in the mass spectrum. These retro reactions are disconnections that can be translated directly to a synthetic tree. Some examples of retroreactions that have been identified in the mass

spectrum are (1) retro-Diels–Alder (sec. 11.5.B),[175] (2) a retro-1,3-dipolar addition (sec. 11.11),[176] (3) a retro Wagner-Meerwein (sec. 12.2.B),[177,178] and (4) a retro-Ritter reaction.[179] It is noted that the **Ritter reaction**[180] couples and alkene and a nitrile to give an amide.

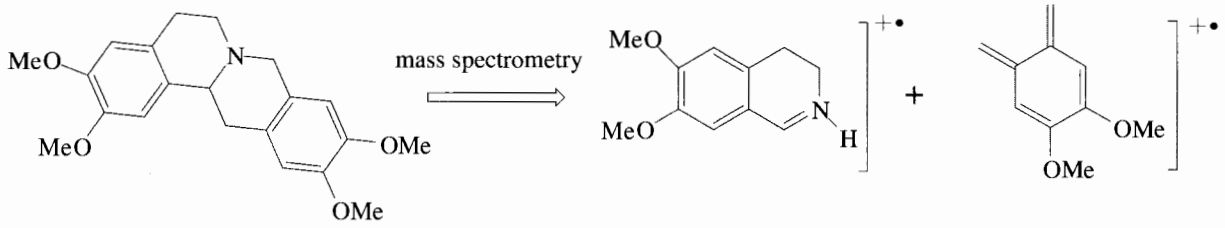
In many cases, fragmentations corresponding to the retroreaction of a powerful reaction (sec. 10.5.B.vi) can be identified and used retrosynthetically. Retro-mass spectral analysis has been applied to total synthesis by Kametani. The mass spectra of tetrahydroisoquinoline alkaloids show fragmentations by the three major pathways shown in Scheme 10.24.[174] Kametani observed that path *c* (a retro Diels–Alder reaction) was the major fragmentation pathway (sec. 11.5.B).[174] Xylopinene (**274**) gave this specific fragmentation (to **275** and



Scheme 10.24. Kametani's mass spectral analysis of tetrahydroisoquinoline alkaloids.

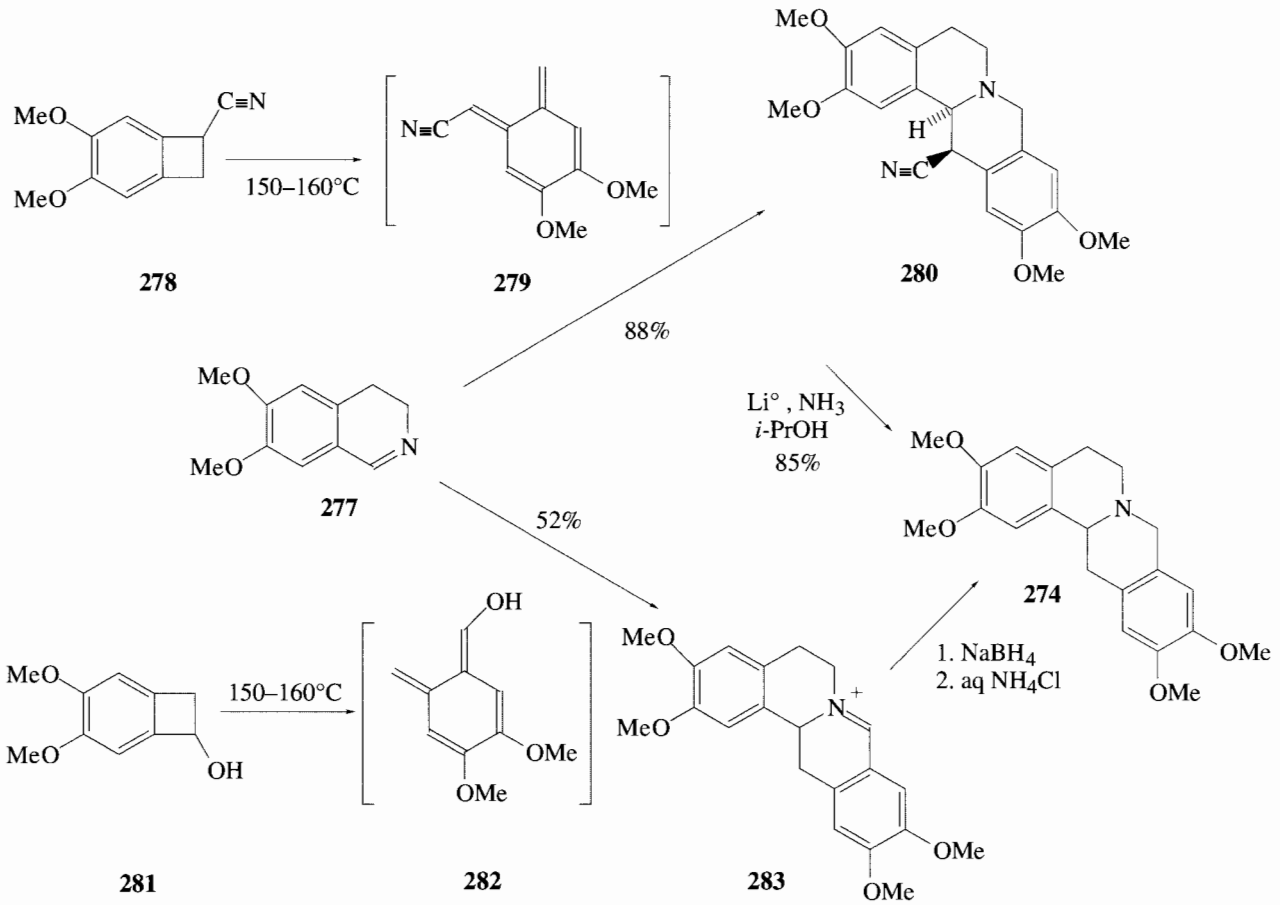
[Reprinted with permission from Kametani, T.; Fukumoto, K. *Accts. Chem. Res.*, ***1976***, *9*, 319. Copyright © 1976 American Chemical Society.]

276),[181] and Scheme 10.25[174] shows the resulting total syntheses reported by Kametani, based on the Diels–Alder reaction suggested by path *c* in Scheme 10.24 and the observed fragmentation pattern. Two related synthetic routes involve thermal conversion of benzocyclobutane derivatives to a diene (sec. 11.10.F) that reacts with the dihydroisoquinoline starting material (**277**). In one case, heating cyano derivative **278** gave a transient diene (**279**) that reacted with **277** to give the Diels–Alder adduct **280**.[182] In the second case, alcohol **281** was heated to generate **282**, which reacted with **277** to give **283**.[183] Reduction of either **280** or **283** gave **274** in good yield. The carbocyclic analog of this reaction had been used previously in synth-esis,[184,185] and Oppolzer had previously used the amido analog of this condensation reaction for alkaloid synthesis (sec. 11.10.F).[186] Its use by Kametani in this case, however, was the direct result of construction of a synthesis tree from the mass spectrum.



274 **275** **276**

The availability of mass spectrometers clearly makes this an attractive tool for retrosynthetic analysis. The major drawback is that structural identification of the mass spectral fragment is a necessity, which is often unknown and its determination can require fragmentation studies on isotopically labeled compounds. Modern mass spectrometry makes *mass spectrometry of mass spectrometry* fragments fairly easy, and with the high-resolution mass spectrometers capable of identifying the mass of individual fragments, identification of key fragments is usually possible. This analytical technique brings retro-mass spectral analysis into the fold of modern methods for determining a retrosynthesis tree. If the structure of a fragment is not easily determined, however, this approach will be of little value for constructing a synthetic tree. If the fragment is known, retro-mass spectral analysis can be a useful tool.



Scheme 10.25. Synthesis of xylopinene (274) based on retro-mass spectral analysis.

10.12. COMBINATORIAL CHEMISTRY

Combinatorial chemistry is a term used to describe various microscale methods of solid-state synthesis and testing. It involves the synthesis of large numbers of compounds (called libraries) by doing reactions in a manner that produces large combinations of products, usually as mixtures.[187] This approach has been called *irrational drug design* since it usually involves making a large vat of all possible chemical combinations of several reactants. Compare this with parallel synthesis, where the same reactions are repeated separately to

produce many individual but related products. In other words, a parallel synthesis means that a compound library is constructed by synthesizing many compounds in parallel, keeping each compound in a separate reaction vessel. When the final compounds are kept separate in this manner, their identity is easily discerned. The pin-method of combinatorial synthesis described below is one such parallel synthesis method. Libraries of compounds can also be generated by pooling strategies, and the teabag method described below illustrates this type of approach. The methods of combinatorial synthesis will be described below, but there are several strategies for efficient synthesis of a target, illustrated by the cartoons in Figure 10.25.[187c] The first strategy (A) is one where doubly functionalized monomer units are linked in peptide synthesis and other oligomer synthesis. In strategy B, the synthesis begins with a template that is already equipped with several functional groups. Different building blocks are attached through these groups in a series of separate steps or in one pot. In strategy C, the reactions introduce new functionality in the product. As each new functional group is added, that product becomes the template for the next reaction. Combinatorial syntheses can be performed both in solution and on a solid support.

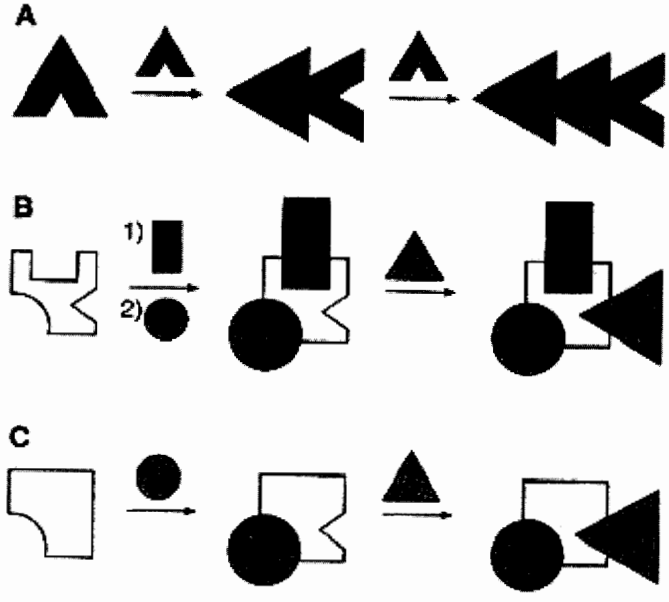
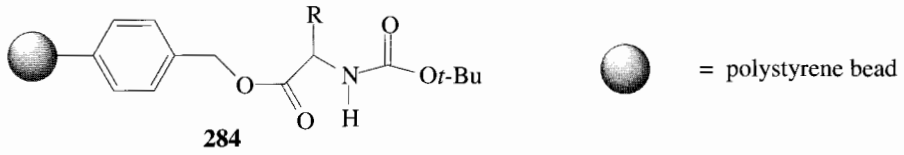


Figure 10.25. Strategies in combinatorial synthesis.

[Reprinted with permission from Balkenhol, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.*, ***1996***, *35*, 2289.]

In 1963 Merrifield introduced solid-state synthesis for the synthesis of peptides.[188] This technique involves chemical functionalization of a polystyrene bead that reacts with the carboxylic acid portion of a N-protected amino acid to give a polymer-bound amino ester such as **284**. When **284** is treated with a reagent to deprotect the amine, it can react with another N-protected amino acid, activated at the carbonyl, to give a dipeptide. This procedure can be repeated to generate the desired polypeptide, and when the target has been attained a reagent is added to cleave the polypeptide from the bead (usually by hydrolysis). This solid-state synthesis can be applied to other types of chemical transformations.[189]



284

We can take the fundamental idea of the Merrifield solid-state synthesis, but use several beads where each one is loaded with a different amino acid (V, I, S, etc.)[190] We can generate a "pool" of peptides. If this mixture of beads were treated with three activated amino acids (V, I, S), a total of nine products would be generated, each one attached to a bead, as shown in Figure 10.26. This approach can be expanded to generate large numbers of peptides. If the bead containing V were made to react with 20 different amino acids, a mixture of 20 dipeptides would be generated. If each of these 20 dipeptides were to react with 20 different amino acids, 20 x 20 or 400 tripeptides would be generated as a mixture. If this 400 member tripeptide library were to react with 20 amino acids, a mixture of 20 x 20 x 20, or 8000 tetrapeptides, would be generated. If we continued this process, 20^4 (160,000) pentapeptides, 20^5 (3,200,00) hexapeptides, 20^6 (1,280,000,000) heptapeptides, and 20^7 (25,600,000,000) octapeptides would be generated–a huge library of compounds all mixed together.[191] It is easy to imagine variations that would build other libraries. A mixture of the three amino acids shown in Figure 10.26, for example, could be mixed with 20 amino acids and this would generate 60 dipeptides. This library of dipeptides could be reacted with 20 amino acids to generate 60^{20} different tetrapeptides (3.656×10^{35}) compounds, which would be a library from a library.

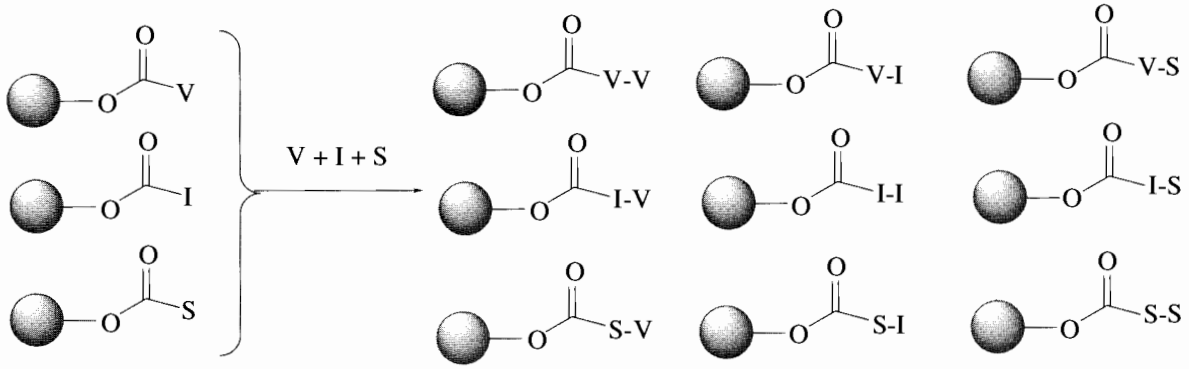
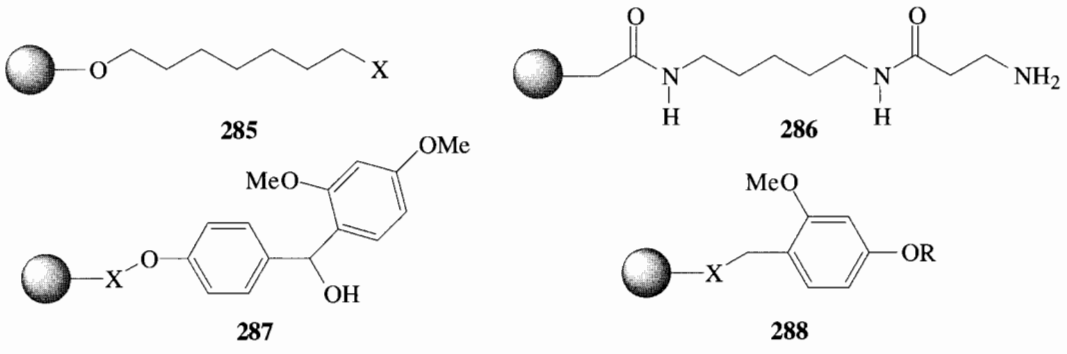


Figure 10.26. Generation of a nine-component dipeptide library.

Early in the development of combinatorial chemistry it was discovered that attempting to do chemical reactions close to the polymer bead caused problems, both in chemical reactivity and in releasing the final product from the bead. An important variation added a *spacer* between the bead and the functional group used for chemistry. Hydrocarbon chains connected to the ether linkage (as in **285**) diamide groups, and polyamide chains such as **286** are commonly used. The group must usually be attached to the bead by an acid-labile unit, or one that is susceptible to enzymatic cleavage. Two common, and highly acid-labile anchors are the aryl derivatives 4-(2',4'-dimethoxyphenylhydroxylmethyl)phenoxy (**287**) or 2-methoxy-4-alkoxybenzyl (**288**).[192]



A reasonable question is how is the combinatorial technique done experimentally? Two methods will be presented here to illustrate the fundamental techniques. Houghten described a teabag method[193] that could prepare as many as 150 different peptides with a yield of up to 50 mg.[194] A polypropylene bag (see Figure 10.27)[194] is charged with ≈ 100 mg of a polymeric support (usually polystyrene-1% divinylbenzene). Each bag contains a label and is immersed in a polyethylene bottle containing piperidine/DMF. A computer automated device adds amino acids and the peptide is generated within each teabag. Treatment of the bags with a deprotection reagent and subsequent washing liberates the peptides.

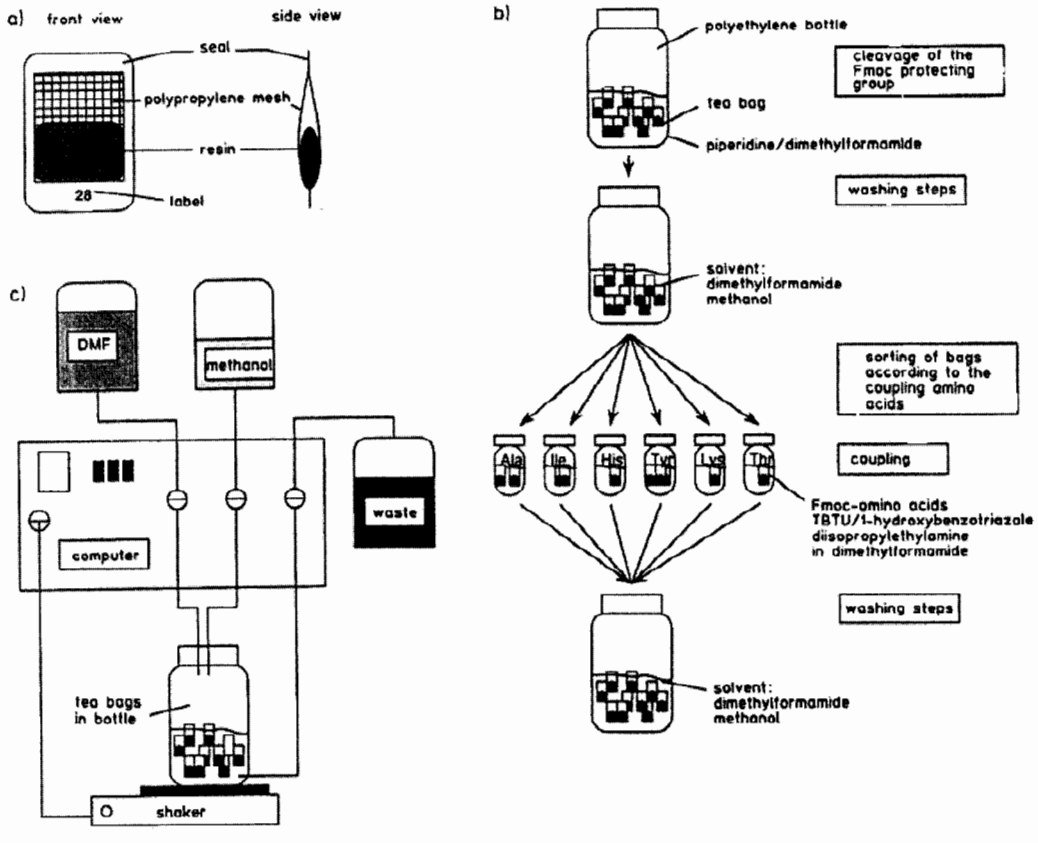


Figure 10.27. The teabag approach to combinatorial peptide synthesis.

[Reprinted with permission from Jung, G.; Beck-Sickinger, A.G. *Angew. Chem., Int. Ed. Engl.*, **1992**, *31*, 367.]

A second technique that accomplishes peptide synthesis on polyethylene rods was developed by Geyson et al.[195] A typical array of rods (called pins) consists of 96 pins (typically 4 mm in diameter and 40 mm in length)[194] arranged in 8 rows of 12 rods (see Figure 10.28b). The pins fit into the wells of plates (see Figure 10.28)[194] that were developed for the enzyme-linked immunosorbent assay (ELISA). The polyethylene rods are functionalized with acrylic acid and N$^{\beta}$-Fmoc-β-alanyl-1,6-diaminohexane is attached as a spacer (see Figure 10.28a). The idea is to attached an amino acid to each of the pins, and place the solution containing the reactants into the wells. The pins are dipped into the wells and allowed to react. To deprotect the terminal

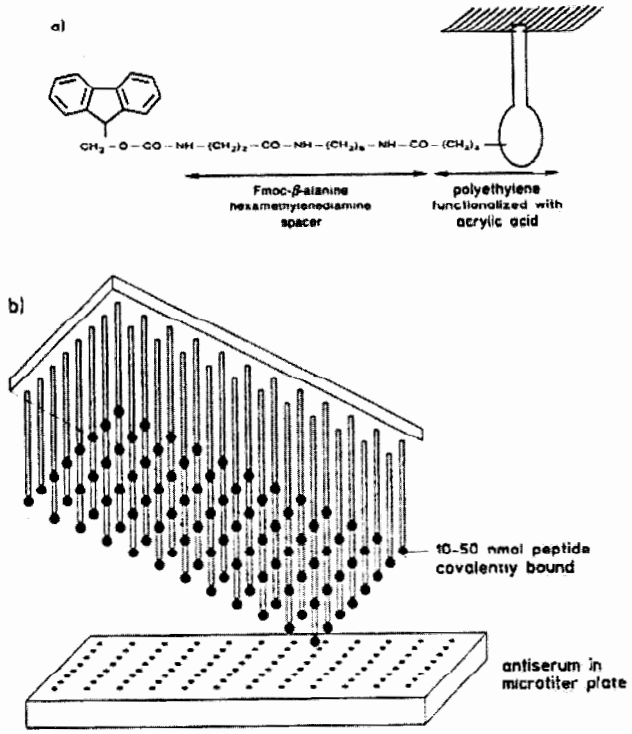


Figure 10.28. The pin approach to combinatorial peptide synthesis.

[Reprinted with permission from Jung, G.; Beck-Sickinger, A.G. *Angew. Chem., Int. Ed. Engl.*, ***1992***, *31*, 367.]

position, deprotection reagent is added to a new plate of wells, and the pins are dipped into that. Since the "polyethylene rods cannot swell or shrink, and adsorbed molecules can only be removed with difficulty, thorough washing after each reaction step of the synthesis cycle is of utmost importance".[194] Recent work has shown that soft but mechanically strong polymer rods derived from styrene–divinylbenzene copolymers prepared by adjusting the reaction conditions, could be cut into disks with good swelling characteristic in various solvents, and that resist osmotic shock.[196] Such disks are an alternative support for solid phases synthesis.

One problem that must be addressed is chemical reactivity. If a bead reacts with many different reactants (n coupling partners), there will be n products, which is also a problem in solution combinatorial synthesis. Indi-vidual substances can be obtained by fast parallel syntheses, that is, n substances are synthesized in n reaction vessels.[187c] Since it is reasonable that some reactants will react faster and in higher yields than others,

there may be different *amounts* of the *n* products. In other words, some coupling reactions occur at faster rates than others. This problem of different reaction rates can be avoided by the so-called *split method.*[197,205] As shown in Figure 10.29,[187d] the solid support is divided into three equal parts in this case, and each of these is treated with a component A. The resulting products are mixed and divided again, giving three mixtures in which the resin-linked components (A^1, A^2, A^3) are present in equimolar amounts. When these are treated with new reagents (B^1, B^2, B^3), nine defined products are produced. Since there is only one reactant in solution in each reaction vessel at any one time, all reactions proceed to completion despite possible differences in kinetics.[187c] Repetition of the cycle of division, reaction, and mixing gives large compound libraries in which all compounds are present in equimolar amounts. Ley and co-workers developed an approach for the rapid automated optimization of polymer supported reagents in synthesis using an optimized set of reaction conditions with an array of 80 compounds.[198]

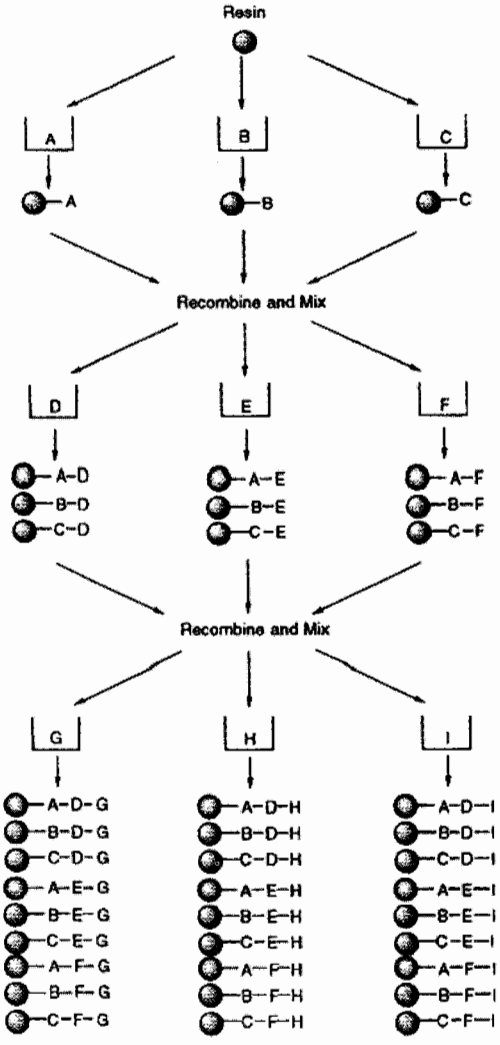


Figure 10.29. Split synthesis method.

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An important component of the split method is *deconvolution*. The library formed by these methods will be a mixture, and when the mixture must be tested in solution, structure determination can be very difficult. An example of deconvolution is shown in Figure 10.30[187c] for a molecule with four variable substituents (A–D). If there are five different possibilities for each substituent, the total library consists of $5^4 = 625$ compounds.[187c] In the first deconvolution, 25 sublibraries are synthesized, each containing 25 compounds where the substituents A and B are defined. Using a predetermined measure of activity (which compounds are being targeted), the most active sublibrary contains the optimal combination of substituents A and B, A^2B^1 in Figure 10.30. Based on this, five further sublibraries in the form $A^2B^1C^nC^{1-5}$ are prepared,[187c] each containing five

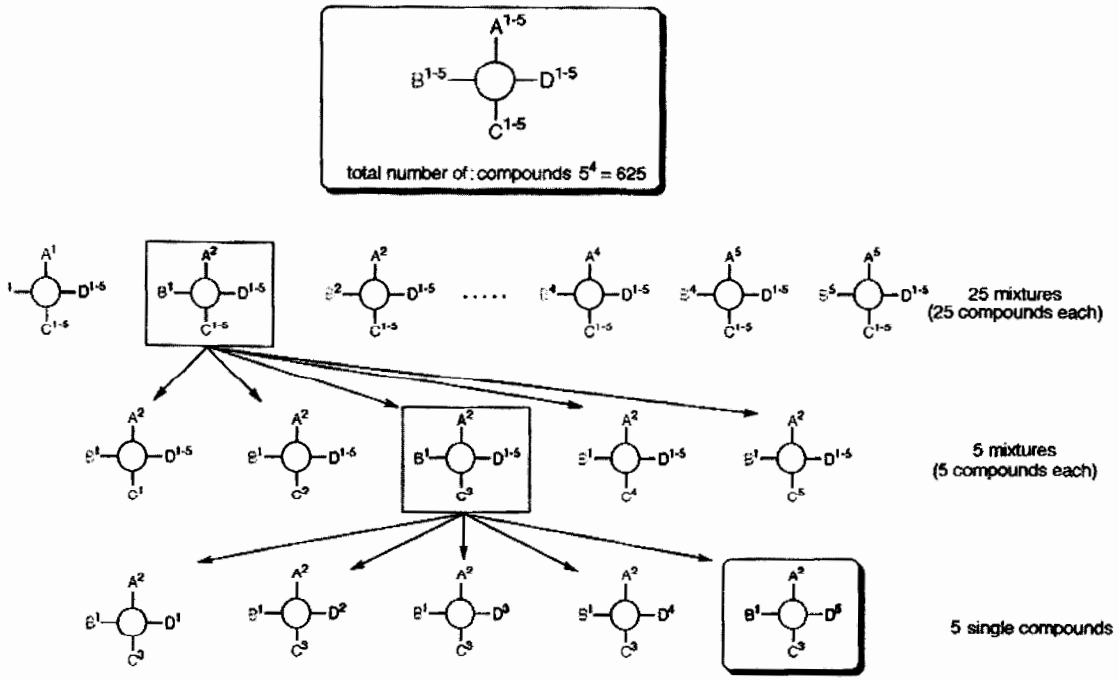


Figure 10.30. Identification of the most active library component by deconvolution.

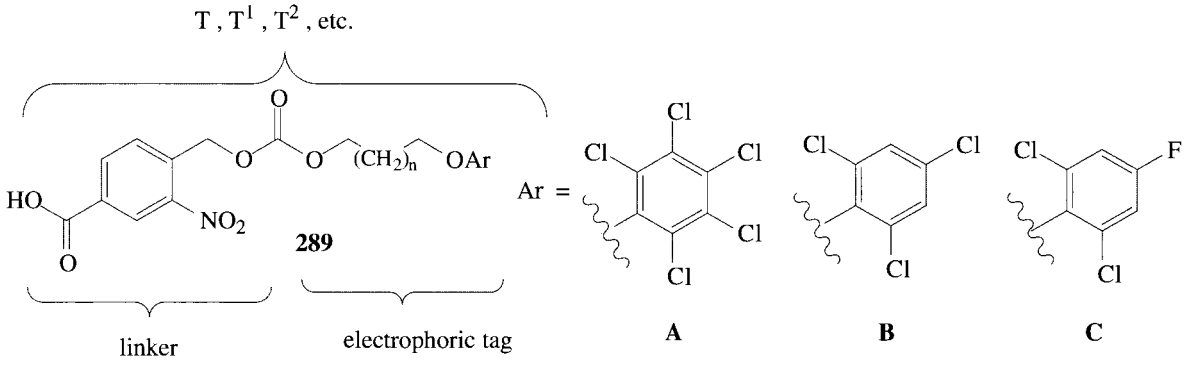
[Reprinted with permission from Balkenhol, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.*, ***1996***, *35*, 2289.]

components in which C is now defined. The optimal residue D is determined in the last step by synthesis of the five individual compounds in the form $A^2B^1C^3D^n$, and in Figure 10.30, the most active compound was $A^2B^1C^3D^5$.[187c] To get around the need for a new synthesis of another sublibrary for each assay of the total library, Hand et al. used a procedure called recursive deconvolution.[199] In this method, an aliquot is held back after each cycle of the split synthesis. From active mixtures, similarly in one or more steps, the single active compound is identified.[187c] No new split syntheses are involved since only the intermediates retained during the first split synthesis need to be elaborated further.[187c]

A reasonable question to ask is how each product of a massive library can be identified as a unique entity, and isolated? There are several techniques by which this can be accomplished. All products can be detached from the beads and isolated as a mixture. This mixture can be analyzed using high performance liquid

chromatography (HPLC) and gas chromatography (GC) techniques, particularly when combined with mass spectrometry (HPLC/mass spectrometry and GC/mass spectrometry). In principle, each component can be separated an identified.[193,200]

It would be useful to known to which bead each product was attached. A solution to this problem is the use of a molecular tag, work pioneered by Brenner and Lerner in 1992[201] and by Nielsen.[202,191] The idea is to give a binary chemical tag for each reagent. In the work of Still and co-workers work, a constant segment of a library is attached to a polymeric bead using standard solid-phase methods.[203] A tag for the first reagent is attached and then the amino acid is attached. After processing, a second tag is attached, followed by the second amino acid in the sequence. Still's coding strategy used haloaromatic tags such as **289**.[203,187d] When attached as an amide, the chain length (n) can be varied along with the haloaryl ether unit to crate a binary synthesis code. The reagents can be designated in binary as 001 (reagent 1), 010 (regent 2), 011 (reagent 3),-to-111 (reagent 7). If reagent 3 were used in the first step and reagent 1 in the second and reagent 6 in the third, the description would be 001 011 011.[203] In **289**, nine different haloaryl units could be attached to create nine tags, T^1–T^9 and each could be linked to one reagent. Therefore, aryl halide A might be 001 (T^1), B 002 (T^2), and C 011 (T^6) and so on. Two possibilities are pentachlorophenyl and 2,4,6-trichlorophenyl. Using different haloaromatic units results in a large number of unique tags. As the peptide chain grows, each tag gives the exact sequence of that chain. Any attached tag can be detached by UV irradiation in this case, and decoded by electron capture GC. Still related the tagging molecules to the binary bits of the synthesis code by arranging them (T^1–T^9) in order of their GC elution order where T^1 is retained the longest on the GC column used and designates the rightmost bit of the binary synthesis code.[203] In this way, the tags are easily identified and the product can be identified.

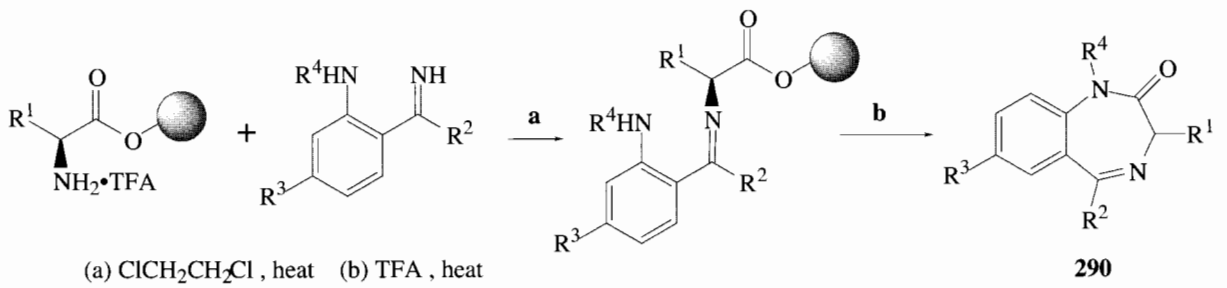


An interesting solution is to color code the beads and the vessel in which the reaction is done.[204] If there were eight subunits, for example, each one could be partitioned into different containers with different color caps. If each subunit were attached to a different color bead, one bead of each color could be added to each color-coded vessel. When the next subunit is attached, the compounds formed can be sorted individually by cap and by color. This process can be contained as each new subunit is attached. Another color-coded approach can be used to identify products that are susceptible to a particular chemical reaction. The approach is to couple the acceptor molecule to an enzyme such as alkaline phosphatase or to a fluorescent, and then add

these in soluble form to generate the peptide-bead library.[205] Those beads that contain compounds active for this analysis will be stained and are usually visible to the naked eye or under a low-power microscope. The stained beads can then be removed for analysis. In one reported study, a monoclonal antibody active against β-endorphin was of interest because it had a high affinity for the epitope sequence UCCFL[204] and six reactive beads were obtained from 2 million screened beads from a pentapeptide library.

A powerful method to identify individual components of a combinatorial library known as encoded combinatorial chemistry. Brenner and Lerner[201] designed a method where each chemical sequence is labeled with a so-called genetic tag (nucleotide sequences), and each tag is constructed by chemical synthesis. A monomeric chemical unit is attached to a polymeric structure and this is followed by addition of an oligonucleotide sequence. The sequence of that oligonucleotide constitutes a tag. Active products from the library are selected by binding to a receptor. After the chemical entity is bound to a target, the genetic tag can be amplified by replication and utilized for enrichment of the bound molecules by serial hybridization to a subset of the library.[201] The nature of the chemical structure bound to the receptor is decoded by sequencing the nucleotide tag.[201] Another encoding technique is illustrated by synthesizing a peptide and a nucleotide chain in an alternating, bidirectional manner.[191] Sequencing the nucleotide chain, therefore, determines the sequence of the peptide chain.

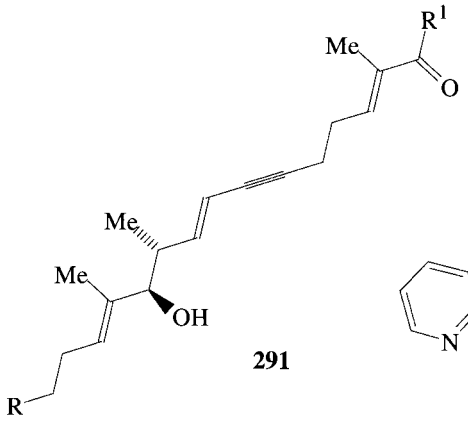
This chapter concerns synthesis. How is combinatorial chemistry pertinent to this discussion? Many small molecules can be synthesized using combinatorial techniques and evaluated for biological activity. One example is the synthesis of substituted benzodiazepines, such as **290**, shown in Scheme 10.26.[206] This approach has become very important in the pharmaceutical industry for drug discovery.[207]



Scheme 10.26. Combinatorial synthesis of benzodiazepines.

A number of combinatorial-based syntheses have been reported. Andrus et al. prepared a solution-phase indexed combinatorial library of nonnatural polyenes such as **291** for multidrug resistance reversal.[208] This library was formed by modification of R and R^1. Ellman and co-workers reported a combinatorial library of synthetic receptors targeting vancomycin-resistant bacteria,[209] and Paterson et al. prepared polyketide-type libraries by iterative asymmetric aldol reactions on solid support.[210] Rieser et al. used combinatorial liquid-phase synthesis to prepare [1,4]-oxazepine-7-ones by the Baylis–Hillman reaction (see sec. 9.7.B).[211] Schreiber and co-workers reported the synthesis and evaluation of a library of polycyclic small molecules for use in chemical genetic assays.[212] Bauer et al. reported a library of N-substituted 2-pyrazoline compounds

such as **292**, by parallel solution-phase synthesis, for screening as therapeutic agents as antibacterials, antivirals, and anti-inflammatory compounds.[213] Libraries of trisaccharides have been prepared by combinatorial methods.[214] Highly substituted thiophene derivatives such as **293** were reported by Han et al. as novel phosphodiesterase-4 (PDE-4) inhibitors[215] and Ley et al. reported the solution phase synthesis of functionalized bicyclo[2.2.2]octanes.[216]



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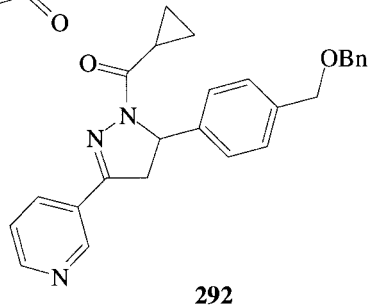

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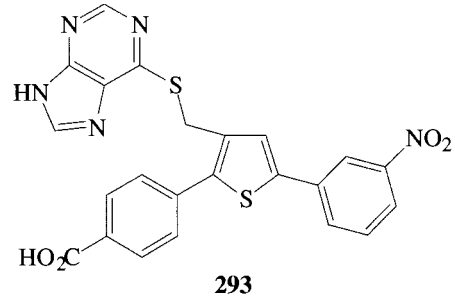


293

10.13. CONCLUSION

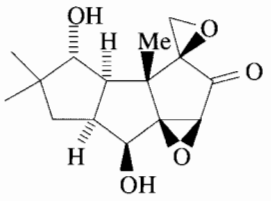
This chapter has tried to summarize general approaches to the total synthesis of complex molecules. These techniques can just as easily be applied to simple molecules and to short synthetic sequences. One must remember that the concepts of conformational control, regio- and stereochemical control, and steric considerations (discussed in all previous chapters) must be an integral part of the planning at each step of a synthesis. These concepts should be applied to every disconnection. If they are not, one may complete the synthesis but find that all possible stereoisomers and regioisomers have been produced and that the wrong isomer is usually the major product. In short, the multistep synthesis will be a nightmare, as well as a disaster. Planning is essential.

The key steps of a synthesis usually involve formation of carbon–carbon bonds. In Chapters 8 and 9, nucleophilic methods involving the disconnect product C^d were discussed in detail. In the chapters that follow, methods of forming carbon–carbon bonds by pericyclic reactions (disconnect products that arise from breaking more than one bond), and by reactions that have cationic intermediates (C^a disconnect products) or radical intermediates ($C^\bullet$ disconnect products–carbenes are included in this chapter) will be presented. In each chapter, additional examples of synthetic strategy using those particular reactions will be presented.

HOMEWORK

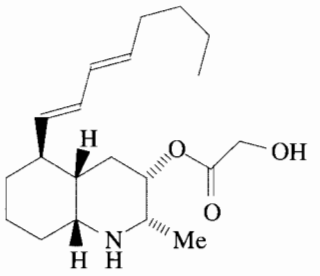
1. For each of the following literature syntheses. (1) Determine the total number of steps and the percentage yield for each of the carbon–carbon bond–forming steps. (2) Identify all powerful reactions–justify each choice in the context of that synthesis. (3) Determine the number and percentage yield for all protection–deprotection steps (if any). (iv) Discuss why each protecting group was chosen for that particular application.

(a)



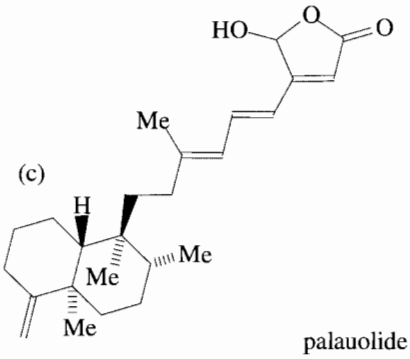
(–)-coriolin
see *J. Org. Chem.*, ***1999***, *64*, 2648

(b)



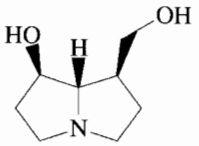
lepadin A
see *J. Org. Chem.*, ***1999***, *64*, 2182

(c)



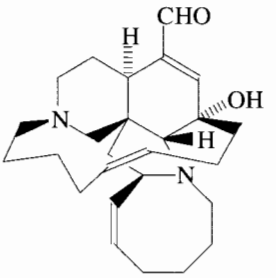
palauolide
see *Can. J. Chem.*, ***1994***, *72*, 146

(d)



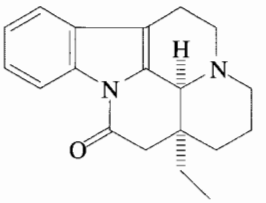
(–)-hastanecine
see *Synthesis*, ***1993***, 615

(e)



ircinal A
see *J. Am. Chem. Soc.*, ***1999***, *121*, ***866***

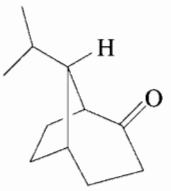
(f)



eburnamonine
see *J. Org. Chem.*, ***1999***, *64*, 7586

2. For each of the following: (i) Determine the strategic bonds. (ii) Give two different retrosyntheses based on two different first disconnections. (iii) Show all donor and acceptor sites in each disconnect fragment. (iv) Give a synthesis for each molecule based on <u>one</u> of your strategic bonds. Choose a starting material that is commercially available with at most five carbons. (Give the cost per gram of that starting material.)

(a)



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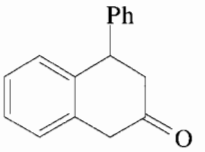

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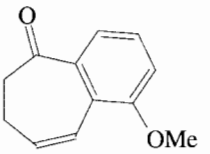

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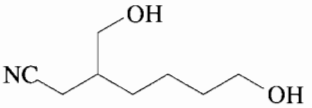

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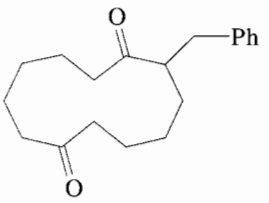

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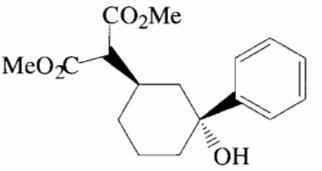
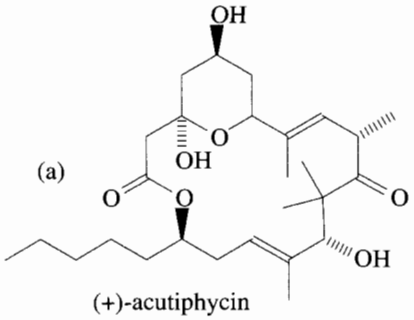


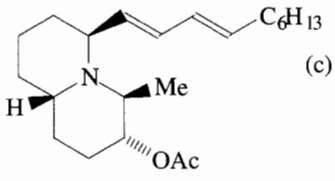
3. For each of the following: (i) Determine the strategic bonds. (ii) Devise a retrosynthetic scheme based on a consecutive strategy. (iii) Devise a retrosynthetic scheme based on a convergent strategy. (iv) Show a total synthesis based on <u>both</u> (ii) and (iii).

(a)



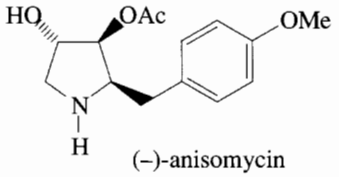
(+)-acutiphycin

(b)



clavepictine A

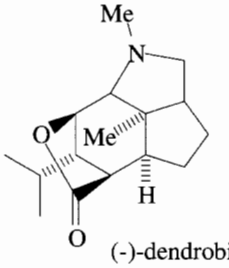
(c)



(–)-anisomycin

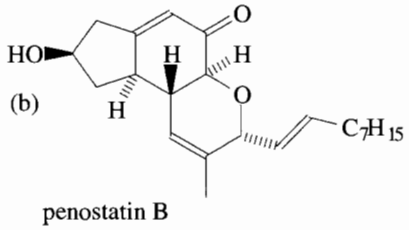
4. For each of the following, show a reasonable retrosynthetic analysis that gives a starting material with a reasonable cost (current chemical catalog). Show the complete synthesis. Assume an average yield of 75% for each step. What is the overall percentage yield for your synthesis? How many grams of your starting material do you need in order to synthesize 1 gram of the target?

(a)



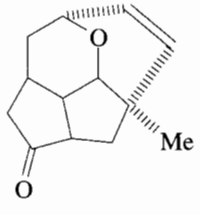
(-)-dendrobine

(b)



penostatin B

(c)



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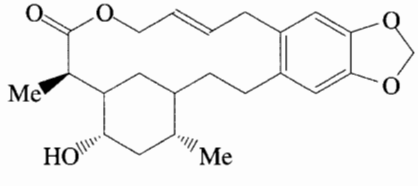

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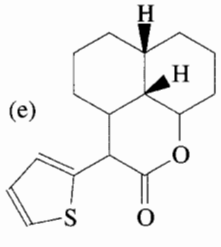

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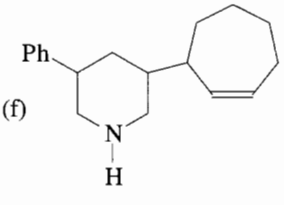

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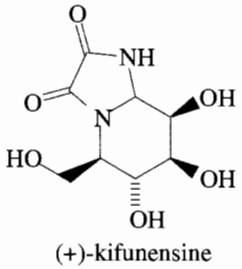
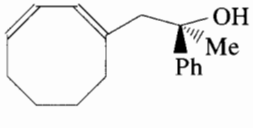
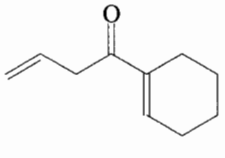


(+)-kifunensine

(h)

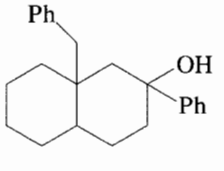


(i)



5. Synthesize each of the following from starting materials of at most six carbons (cite chemical catalog and price per gram):

(a)



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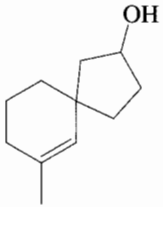

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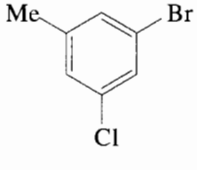

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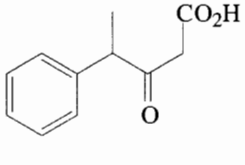
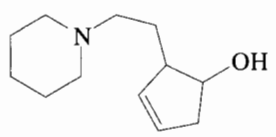
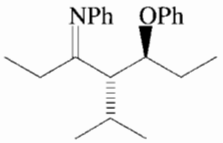
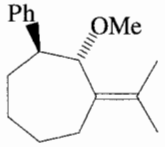
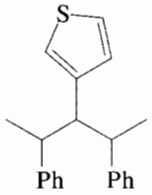


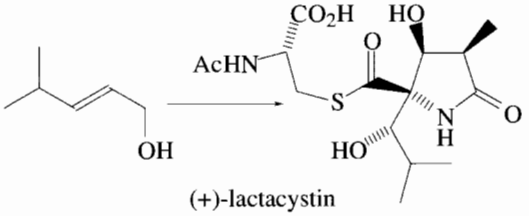
(e) 

(f) 

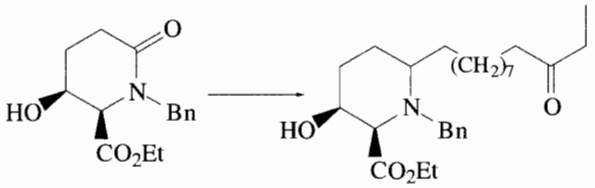
(g) 

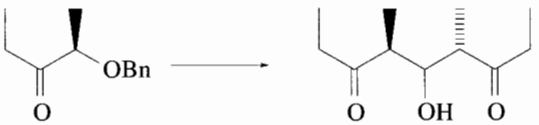
(h) 

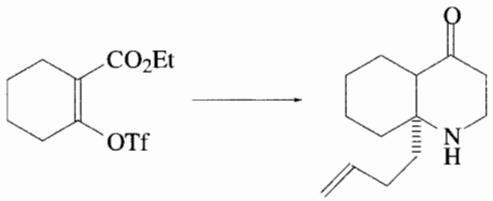
6. For each of the following show a synthesis of the designated starting material to the indicated target. Show all reagents and intermediate products.

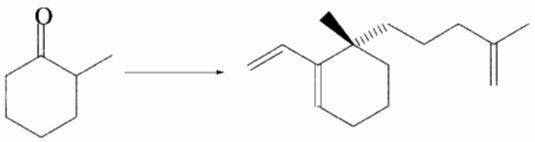
(a) 

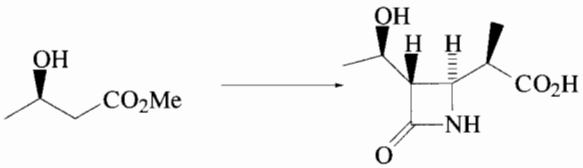
(+)-lactacystin

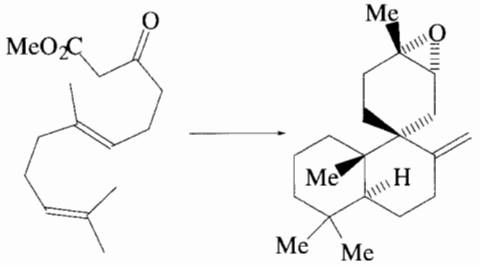
(b) 

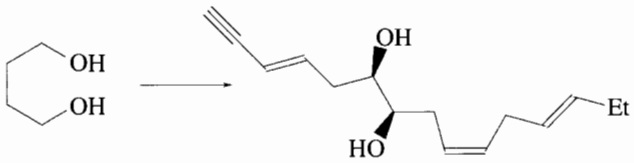
(c) 

(d) 

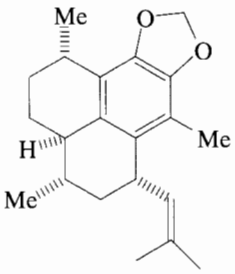
(e) 

(f) 

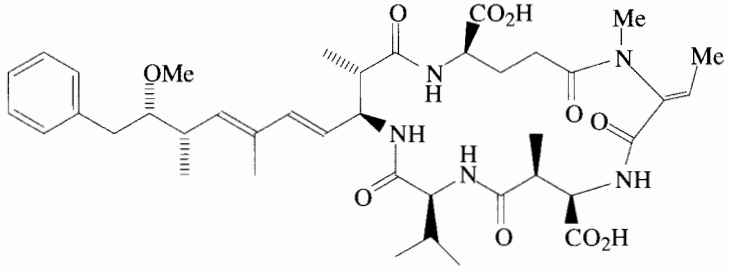
(g) 

(h) 

7. Suggest a complete synthesis of the molecule shown (helioporin E) from any starting material of no more than six carbons. Show your retrosynthetic analysis, all intermediate products and all reagents.



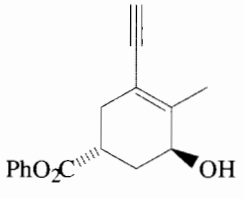
8. Suggest a complete synthesis of the molecule shown (motuporin) from any reasonable starting material. Show your retrosynthetic analysis, all intermediate products and all reagents.



9. Plumet has published a synthesis of (+)-7-deoxypancratistatin, starting with furan as a starting material (see *Org. Lett.*, ***2000***, *2*, 3683). Draw the retrosynthesis from this paper and compare and contrast it with those syntheses given in Section 10.7. Pay particular attention to strategic bonds and to strategy.

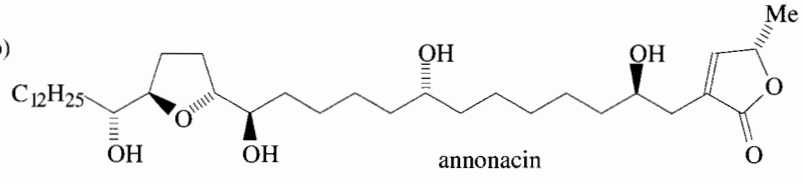
10. Construct a retrosynthetic tree based on the given template as a starting material.

(a)



from (*R*)-carvone

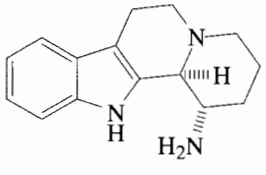
(b)



annonacin

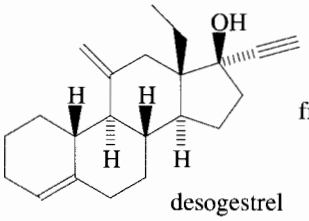
from L-ascorbic acid

(c)



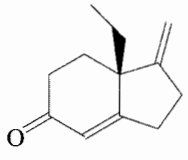
from L-glutamic acid

(d)



desogestrel

from

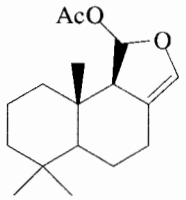


11. In a review article (*Synthesis,* ***1998***, 1559), Chanon presents 8 different syntheses of silphinene and 18 different syntheses of hirsutene. Based on your definitions of efficiency, cost of starting materials, control of stereochemistry, and so on., compare and contrast these syntheses and draw a conclusion as to which you believe to be the best for each target.

12. In 1992, Sir John Cornforth presented a lecture entitled *The Trouble with Synthesis* (see *Aust. J. Chem.,* ***1993***, *46*, 157). Read the article and consider the points made in the context of this chapter, particularly the quoted comments by Corey and Deslongchamps early in the chapter. Also see *Aldrichimica Acta,* ***1994***, *27*, 71.

13. Each reference discusses a proposed biosynthetic pathway for the molecule shown. Construct a retrosynthetic tree based on that pathway and then show the total synthesis.

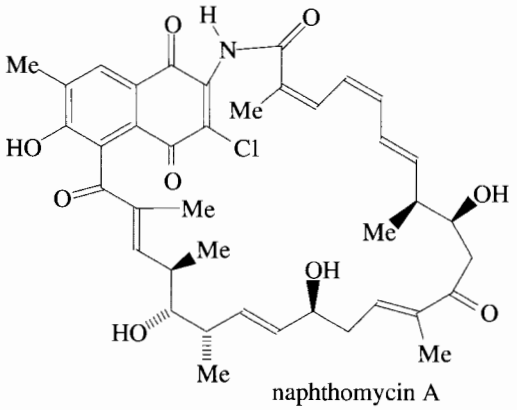
(a)



drimane ester

see *Tetrahedron Lett.*, ***2000***, *41*, 2429

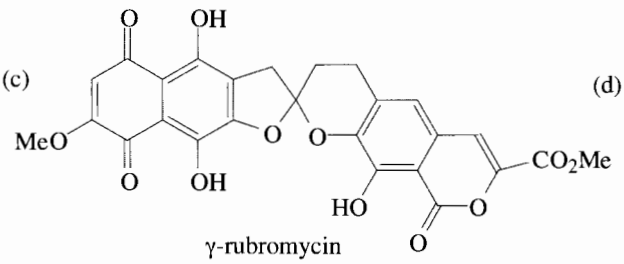
(b)



naphthomycin A

see *Can. J. Chem.*, ***1994***, *72*, 182

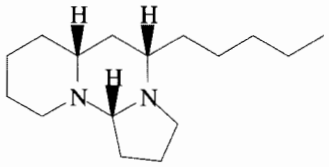
(c)



γ-rubromycin

see *Eur. J. Org. Chem.*, ***2000***, 729

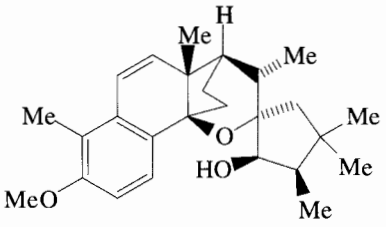
(d)



tetraponerine-8

see *Can. J. Chem.*, ***1994***, *72*, 105

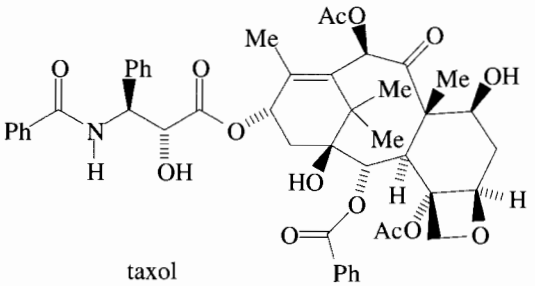
(e)



blazeispirol A

see *Tetrahedron Lett.*, ***2000***, *41*, 6101

(f)



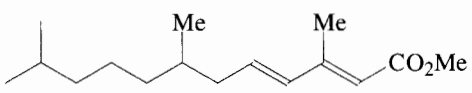
taxol

see *J. Org. Chem.*, ***2000***, *65*, 7865

14. Each of the following references give mass spectral fragmentation information for the molecule shown. Construct a retrosynthetic tree based on this information and then give the total synthesis.

[Reference 1. *Natural Products Chemistry, Vol. 2*, Nakanishi, K.; Goto, T.; Itô, S.; Natori, S; Nozoe, S. (Eds.), Academic Press, New York, ***1974***. Reference 2. *Structure Elucidation of Natural Products by Mass Spectrometry*, Vol. 1, Budzikiewicz, H.; Djerassi, C.; Williams, D.H., Holden-Day, San Francisco, ***1964***.]

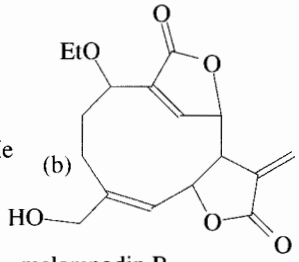
(a)



Juvinile hormone

Org. Mass Spectrom., ***1976***, *11*, 1120

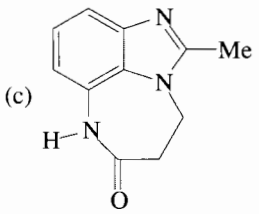
(b)



melampodin B

Org. Mass Spectrom., ***1978***, *13*, 325

(c)

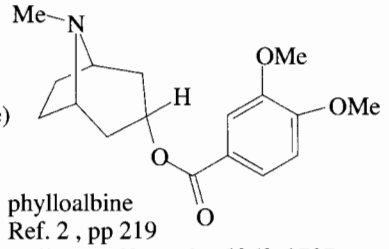


Org. Mass Spectrom., ***1978***, *13*, 141

(d) ciguatoxin congener CTX3C ($C_{60}H_{86}O_{19}$)

see *J. Am. Chem.Soc.*, ***2000***, *122*, 4988

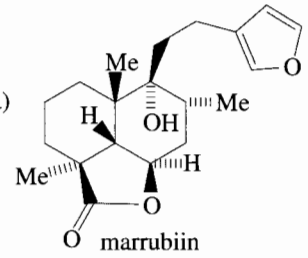
(e)



phylloalbine
Ref. 2 , pp 219
Bull. Soc. Chim. Fr., ***1963***, 2787
Tetrahedron, ***1964***, *20*, 585

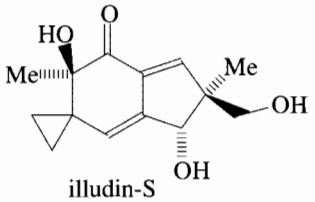
15. Each reference describes a chemical degradation of that structure. Construct a retrosynthetic tree based on that degradation scheme and then show the total synthesis.
[Reference 1 is the same as in question 11. Reference 2. *Natural Products Chemistry, Vol. 1*, Nakanishi, K.; Goto, T.; Itô, S.; Natori, S; Nozoe, S. (Eds.), Academic Press, New York, ***1974***. Reference 3. *Natural Products Chemistry, Vol. 2*, Nakanishi, K.; Goto, T.; Itô, S.; Natori, S; Nozoe, S. (Eds.), Academic Press, New York, ***1974***.]

(a)



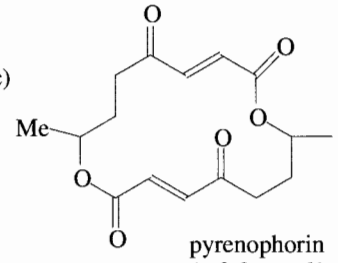
marrubiin
Ref. 1, pp 203–205

(b)



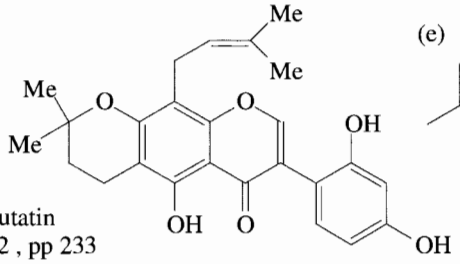
illudin-S
Ref. 1 , pp 90–91

(c)



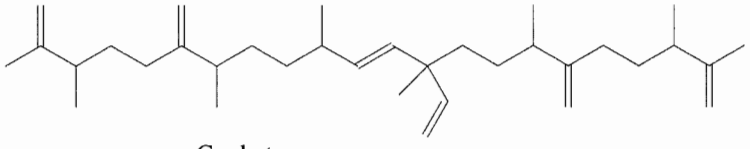
pyrenophorin
Ref. 2 , pp 68–69

(d)



auricutatin
Ref. 2 , pp 233

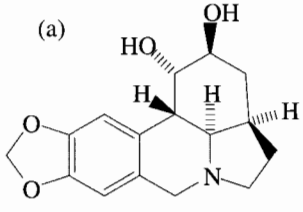
(e)



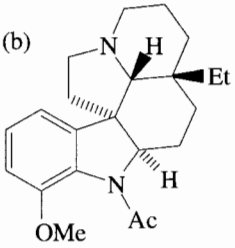
C_{34}-botryococcene
see *J. Org. Chem.*, ***1992***, *57*, 4991

16. For each of the following, use a convergent strategy to devise a synthetic scheme. Show the total synthesis based on that scheme.

(a)

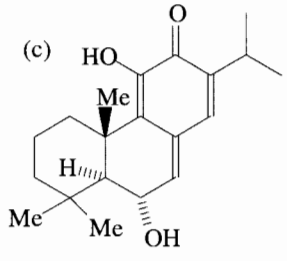


(b)



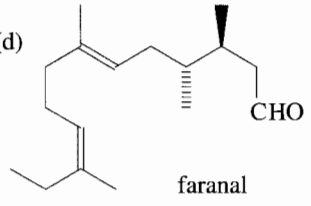
aspidospermine

(c)



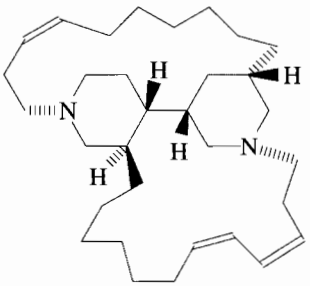
taxodone

(d)

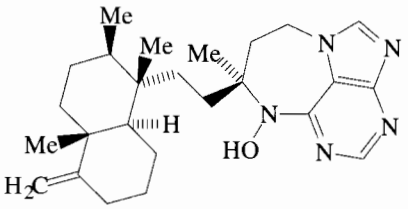


faranal

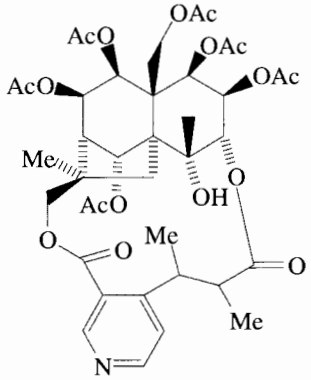
18. Devise a synthesis for the following molecules showing all chemical steps and reagents. The literature reference given with each molecule refers to its isolation and structure determination, not its synthesis.



haliclonacyclamine E
J. Nat. Prod., ***2000***, *63*, 1098



asmarine A
J. Nat. Prod., ***2000***, *63*, 299



wilfordinine A
J. Nat. Prod., ***2000***, *63*, 357

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1 (a) Corey, E.J.; Cheng, X.–M. *The Logic of Chemical Synthesis*, Wiley, New York, ***1989***; (b) Nicolaou, K.C.; Sorenson, E.J. *Classics in Total Synthesis*, ***1996***, VCH, Weinheim.

2 Perkin, Jr., W.H. *J. Chem. Soc.*, ***1904***, *85*, 654.

3 (a) Robinson, R. *J. Chem. Soc.*, ***1917***, *111*, 762; (b) Fleming, I. *Selected Organic Syntheses*, Wiley, London, ***1973***, p 18.

4 Bachmann, W.E.; Cole, W.; Wilds, A.L. *J. Am. Chem. Soc.*, ***1939***, *61*, 974.

5 (a) Fischer, H.; Kirstahler, A. *Annalen*, ***1928***, *466*, 178; (b) Fischer, H.; Zeile, K. *Ibid.,*, ***1929***, *468*, 98.

6 Woodward, R.B. in *Perspectives in Organic Chemistry*, Todd, A.R. (Ed., Interscience, New York, ***1956***, pp 159–184.

7 Woodward, R.B.; Doering, W.E. *J. Am. Chem. Soc.*, ***1945***, *67*, 860.

8 (a) Woodward, R.B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W.M. *J. Am. Chem. Soc.*, ***1952***, *74*, 4223; (b) Woodward, R.B.; Sondheimer, F.; Taub, D. *Ibid.*, ***1951***, *73*, 4057, 3547.

9 Woodward, R.B.; Cava, M.P.; Ollis, W.D.; Hunger, A.; Daeniker, H.U.; Schenker, K. *Tetrahedron*, ***1963***, *19*, 247.

10 Woodward, R.B.; Bader, F.E.; Bickel, H.; Frey, A.J.; Kierstead, R.W. *Tetrahedron*, ***1958***, *2*, *1*.

11 Reference 1, pp 81–91.

12 Corey, E.J.; Wipke, W.T. *Science*, ***1969***, *166*, 178.

13 Deslongchamps, P. *Aldrichimica Acta*, ***1984***, *17*, 59.

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15 (a) Bell, A.S.; Brown, D.T.; Nicholas, K. *Eur. Pat. Appl. EP 463 756* [*Chem. Abstr.*, ***1992***, *116*:P255626q]. For biological activity, see (b) Boolell, M.; Gepi-Attee, S.; Gingell, J.C.; Allen, M.J. *Br. J. Urol*, ***1996***, *78*, 257; (c) Terrett, N.K.; Bell, A.S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.*, ***1996***, *6*, 1819.

16 (a) Vacca, J.P.; Holloway, M.K.; Dorsey, B.D.; Hungate, R.W.; Guare, J.P. Eur. Pat. Appl. 541,168 [*Chem. Abstr. 120*: 54552w ***1994***]; (b) Vacca, J.P.; Dorsey, B.D.; Guare, J.P.; Holloway, M.K.; Hungate, R.W.; Levin, R.B. US Patent 5,413,999 [*Chem. Abstr. 123*: 47889v ***1995***]; (c) Dorsey, B.D.; Levin, R.B.; McDaniel, S.L.; Vacca, J.P.; Guare, J.P.; Darke, P.L.; Zugay, J.; Emini, E.A.; Schleif, W.A.; Quintero, J.C.; Lin, J.H.; Chen, I.-W.; Holloway, M.K.; Fitzgerald, P.M.D.; Axel, M.G.; Ostovic, D.; Anderson, P.S.; Huff, J.R. *J. Med. Chem.*, ***1994***, *37*, 3443; (d) Askin, D.; Eng, K.K.; Rossen, K.; Purick, R.M.; Wells, K.M.; Volante, R.P.; Reider, P.J. *Tetrahedron Lett.*, ***1994***, *35*, 673; (e) Maligres, P.E.; Upadhyay, V.; Rossen, K.; Cianciosi, S.J.; Purick, R.M.; Eng, K.K.; Reamer, R.A.; Askin, D.; Volante, R.P.; Reider, P.J. *Tetrahedron Lett.*, ***1995***, *36*, 2195; (f) Vacca, J.P.; Dorsey, B.D.; Schleif, W.A.; Levin, R.B.; McDaniel, S.L.; Darke, P.L.; Zugay, J.; Quintero, J.C.; Blahy, O.M.; Roth, E.; Sardana, V.V.; Schlabach, A.J.; Graham, P.I.; Condra, J.H.; Gotlib, L.; Holloway, M.K.; Lin, J.; Chen, I.-W.; Vastag, K.; Ostovic, D.; Anderson, P.S.; Emini, E.A.; Huff, J.R. *Proc. Natl. Acad. Sci.*, ***1994***, *91*, 4096.

17 For a synthesis, see (a) Meng, D.; Bertinato, P.; Balog, A.; Su, D.–S.; Kamenecka, T.; Sorensen, E.J.; Danishefsky, S.J. *J. Am. Chem. Soc*, ***1997***, *119*, 10073. For isolation and characterization, see (b) Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiotics*, ***1996***, *49*, 560; (c) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg,

D.; Gerth, K.; Reichenbach, H. *Angew. Chem. Int. Ed. Engl.*, ***1996***, *35*, 1567. For biological activity, see Bollag, D.M.; McQueney, P.A.; Zhu, J.; Hensens, O. Koupal, L.; Liesch, J. Goetz, M.; Lazarides, E.; Woods, C.M. *Cancer Res.*, ***1995***, *55*, 2325.

18 (a) Pettit, G.R.; Gaddamidi, V.; Cragg, G.M. *J. Nat. Prod.*, ***1984***, *47*, 1018; (b) Pettit, G.R.; Gaddamidi, V.; Cragg, G.M.; Herald, D.L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun.*, ***1984***, 1693; (c) Pettit, G.R.; Gaddamidi, V.; Herald, D.L.; Singh, S.B.; Cragg, G.M.; Schmidt, J.M.; Boettner, F.E.; Williams, M.; Sagawa, Y. *J. Nat. Prod.*, ***1986***, *49*, 995 (d) *Antitumor Alkaloids*, Suffness, M.; Cordell, G.A. *The Alkaloids, Vol. XXV*, Academic Press, Orlando, FL, **1985**, pp 198–212, 338–340 (see p 207)

19 The chemical name of **14** is bis–benzo[3,4]cyclobuta[1,2–a:1',2'–c]biphenylene. See (a) Diercks, R.; Vollhardt, K.P.C. *J. Am. Chem. Soc.*, ***1986***, *108*, 3150; (b) Vollhardt, K.P.C.; Mohler, D.L. *Adv. Strain Org. Chem.*, ***1996***, *5*, 121; (c) Schulman, J.M.; Disch, R.L. *J. Phys. Chem. A*, ***1997***, *101*, 5596.

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CHAPTER 11

PERICYCLIC CARBON–CARBON BOND FORMING REACTIONS: MULTIPLE BOND DISCONNECTIONS

11.1. INTRODUCTION

Reactions involving ionic or highly polarized compounds comprise the majority of organic reactions, as seen in other chapters. Chapters 8 and 9 discussed methods for making carbon bonds via nucleophilic carbon species. Chapter 12 will discuss carbon–carbon bond formation with reagents involving electrophilic carbon and chapter 13 will discuss making carbon–carbon bonds via radical and related processes. The reactions in these chapters involve one-carbon disconnections for the most part. Some reactions involve two-bond disconnections, and they often lead to disconnect products that are readily assembled by known reactions. In addition, great simplification can accompany such disconnections, making them very attractive. Many of these reactions generate carbon–carbon bonds by electronic reorganization of molecules rather than via ionic or radical species in what are generically called **pericyclic reactions**. The **Diels–Alder reaction**, the **Claisen rearrangement**, the **Cope rearrangement** and the **ene reaction** fall into this category. Without question, the synthetic utility of these reactions ranks them among the highest in importance. This chapter will focus on methods that use pericyclic reactions and it will present a brief overview of the mechanistic basis for each reaction. As in previous chapters, however, the emphasis will be on the synthetic utility of each reaction.

11.2. FRONTIER MOLECULAR ORBITAL THEORY

11.2.A. Frontier Orbitals

This chapter deals with molecules containing π bonds: alkenes, dienes, carbonyls, imines, nitriles, and so on. In a typical alkene, bonding is described in terms of the σ- and π-orbitals. Electronic interactions are represented by the molecular orbitals, which also involve σ-orbitals (sp^2 hybridized for alkenes, **1**) and π-orbitals (**2**). These orbitals take on a directional character [represented by (+ or dark) and (– or light)] when they are in close proximity to another atom, orbital, or polarized species, as is the case in a covalent bond. There are, therefore, two possibilities when two sp^2 hybridized orbitals come together. Orbitals of the same sign can be directed toward each other, as in **3**, or orbitals of opposite sign can be directed toward each other, as in **4**. In **3**, the electron density between the two nuclei is maximized (electronic attraction for the positive nucleus) but in **4** it is minimized. Since a strong covalent bond (mutual sharing of electron density between nuclei) is associated with significant electron density between the nuclei, **3** represents a **bonding** interaction and **4** can be viewed as an **antibonding** interaction. These terms have meaning only when considering the outermost orbital containing electrons, the valence electrons (valence orbitals).

1 2

Similar arguments can be made for the overlap of p-orbitals that constitutes a π bond. In **5**, the overlap of orbitals with the same sign represents the maximum bonding interaction for the π-bond of ethylene (a bonding molecular orbital), and **6** represents an antibonding molecular orbital. As with a σ-bond, the net energy of the bonding interaction in a π bond is lower than that of the antibonding interaction, as shown in Figure 11.1, and it is more stable. The energy of each molecular orbital can be measured, and this energy difference (ΔE) will vary with substituents on the alkene, which has important implications for the reactivity of these compounds, and this concept will be discussed below.

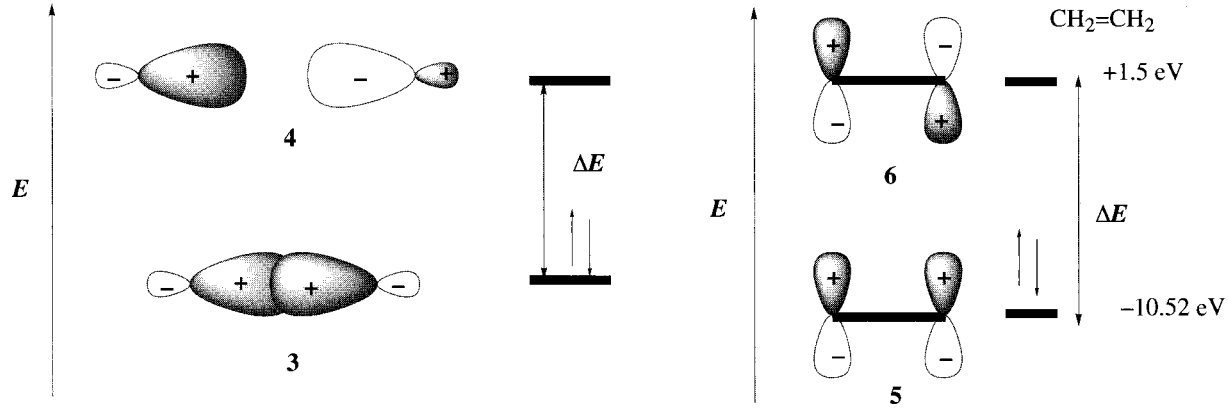


Figure 11.1. Bonding and antibonding σ- and π-orbitals.

The π-orbitals are the key to understanding pericyclic reactions and we will focus on the π bond of alkenes and dienes in this section. The difference in energy between the two π molecular orbitals (**5** and **6**) can be represented in terms of their relative energies as shown in Figure 11.1, taken from Houk's work.[1] The lowest energy orbital containing the bonding electrons is called the **highest occupied molecular orbital**, the **HOMO**. Experimentally, the energy of the HOMO is the **negative** of the **ionization potential** (**IP**) of the molecule.[2] In terms of chemical reactivity, the HOMO is the orbital that donates electrons, and the IP is a reasonable measure of its energy. The higher energy orbital does not contain electrons, but is the next available energy level if electrons are available. The energy that describes accepting electrons is the **electron affinity** (**EA**) and this orbital is called the **lowest unoccupied molecular orbital**, the **LUMO**. Experimentally, the energy of the LUMO is taken to be the **negative** of the EA of the alkene.[1,2] *In a simplistic reaction model, the LUMO would be expected to accept electrons from the HOMO of another π bond.* The difference in energy between the HOMO and LUMO (ΔE) is determined by the difference of the IP (–10.52 eV for ethene[2] where 1 eV = **electron volt** = 23.06 kcal mol^{-1} = 96.53 kJ mol^{-1}) and the EA is +1.5 eV (for a Δ*E* of 12.02 eV = 277.2 kcal mol^{-1} = 1160.4 kJ mol^{-1}).

The reactive HOMO and LUMO of ethene (or of any other molecule) are referred to as **frontier molecular orbitals** (**FMO**), after the pioneering work of Fukui.[3] Analyzing several different types of reactions with FMO

theory, the HOMO was believed to deliver electrons to the LUMO of a reactive center that could accept the charge (as mentioned above). The FMO theory has now been shown to be "a first approximation to a perturbation treatment of chemical reactivity".[4] Perturbation theory,[5] as first described by Coulson and Longuet-Higgins,[6] treats the molecular orbital of two interacting components as a perturbation of the product of their individual orbitals.[7] *The theory fails to explain large perturbations and does not predict the transition state, but gives "an estimation of the slope of an early part of the path along the reaction coordinate leading to the transition state".*[7] This theory usually allows one to identify the higher and the lower energy transition state, and this information is useful for predicting reactivity. The transition state energies can be described as reactant-like (early transition state) or product-like (late transition state). The well-known **Hammond postulate** states "that transition states for exothermic reactions are reactant-like, and for endothermic reactions are product-like".[8] Frontier orbital effects are therefore particularly important in exothermic reactions.[9]

Analysis of a reaction by frontier orbital theory has additional benefits, particularly for predicting reactivity and stereochemistry. Woodward and Hoffman[10] pointed out "that electrocyclic reactions followed the stereochemistry dictated by the symmetry, or nodal properties of the HOMO of the polyene".[11] This concept of orbital symmetry will be important for discussions of all pericyclic reactions. Of particular importance is the difference in energy between the HOMO one π system and the LUMO of a second π-system, because this will be used to predict reactivity in pericyclic reactions (see below).

11.2.B. HOMO, LUMO Energies and Orbital Coefficients

Figure 11.1 showed the molecular orbitals for ethylene, and these are labeled **7** and **8** in Figure 11.2. In this figure, the magnitude of each orbital is shown, called the **orbital coefficient**. The + and – signs correlate with the + (dark) or – (light) symmetry of the orbital,[2] which is somewhat arbitrary, but useful for examining the directionality of two reactive orbitals. When two π systems differ in their substitution pattern, there will be differences in the magnitude of orbital densities (larger or smaller orbitals). Predictions concerning reactivity must, therefore, indicate the magnitude of electron density in each orbital.

The orbital coefficients in the HOMO of a symmetrical molecule such as ethene are identical in magnitude and sign. The LUMO coefficients are equal in magnitude but opposite in sign, also a result of this symmetry, and this leads to no node in **7** and one node in **8** (a **node** is a *point of zero electron density* relative to the orbital lobes). The importance of orbital coefficients will be discussed in Section 11.4.C. Low energy orbitals are associated with a minimal number of nodes and higher energy orbitals with increasing numbers of nodes. If we change the structure of ethene by replacing a hydrogen atom with an electron-withdrawing group, as is the case for methyl acrylate, electron density is distorted away from the π bond of the alkene, toward the carbonyl. This will influence the energies of the HOMO and LUMO as well as the magnitude of the orbital coefficients. The energy of the HOMO of methyl acrylate is –10.72 eV and the LUMO energy is 0 eV,[12] lower than the frontier orbitals of ethene (see Figure 11.2), which is shown in Figure 11.2[2] by the dashed line, marking the energy of the LUMO of ethene as the reference point. The LUMO energy is affected to a greater extent than the HOMO energy. As seen in Figure 11.2, the electron–withdrawing group diminishes the size

(orbital coefficient) of the orbitals closest (*proximal*) to the δ+ carbonyl carbon, leaving the most distant (*distal*) orbital with the largest coefficient.

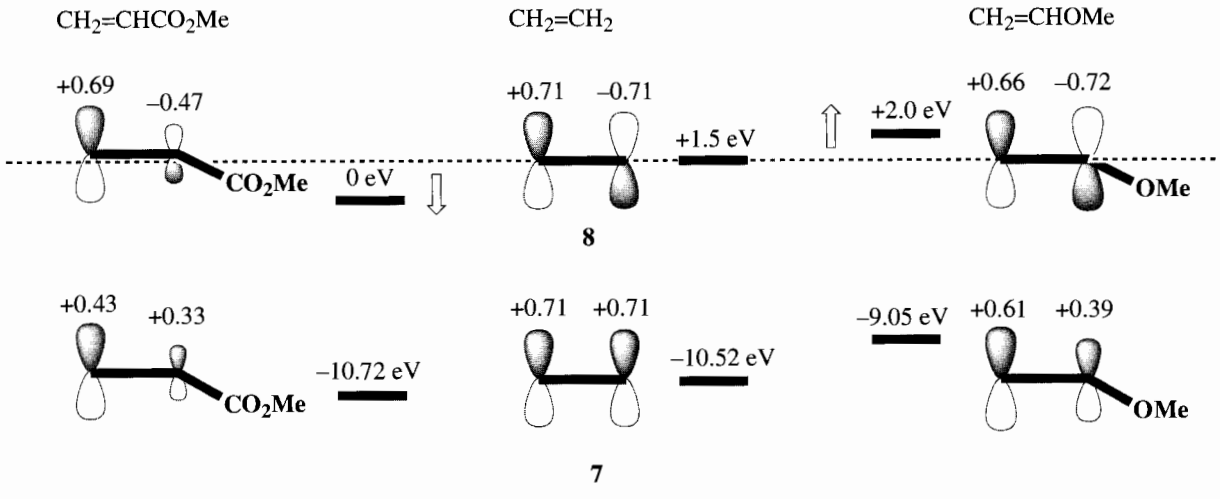
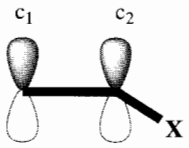


Figure 11.2. Changes in alkene HOMO and LUMO energies upon introduction of substituents.

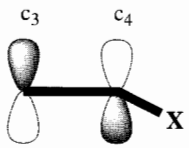
The opposite effect is expected when a hydrogen of ethene is replaced with an electron releasing group such as OMe, as is the case with methyl vinyl ether (see Figure 11.2). As seen in Figure 11.2, the oxygen atom releases electrons toward the π bond, raising the energy of the orbitals relative to ethene (to –9.05 eV for the HOMO and +2.0 eV for the LUMO).[2] Also seen in Figure 11.2,[2] the HOMO coefficients of the carbon proximal to the methoxy are diminished (0.39 vs. 0.61), whereas the orbital density of the distal carbon is increased. In the LUMO, however, the orbital on the proximal carbon is slightly larger than that on the distal carbon. In general, the HOMO coefficients for methyl vinyl ether are typical of other electron-releasing substituents but the LUMO coefficients are often closer to each other in magnitude. Table 11.1 shows the HOMO and LUMO energies for several common alkenes, along with the HOMO and LUMO coefficients, where available. Note that the coefficients for substituted alkenes are often *smaller* than those in the parent, ethene.

The data in Table 11.1 came from a variety of sources, including calculations and experimentally determined ionization potential and EA data. These numbers vary with the experimental method and the sophistication level of the calculation. They should be viewed as useful first estimates when comparing ΔE's using values from two different sources (and/or methods). Caution should be exercised. The purpose of this table is to use the HOMO–LUMO energies to predict chemical reactivity (*vide infra*, sec. 11.4.B). The orbital coefficients will be used to predict regioselectivity (*vide infr*a, sec. 11.4.C.ii). When two or more electron-withdrawing groups are present (tetracyanoethylene, benzoquinone, maleic anhydride, etc.) greater lowering of the HOMO is apparent and the LUMO energy may fall below 0 eV. Ethyne is generally higher in energy than ethene, but electron-releasing and -withdrawing substituents have a similar effect (note –11.4 eV for acetylene vs. –11.5 eV for dimethyl acetylene dicarboxylate, pointing to the problems of using different methods to determine the ionization potential).

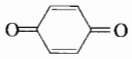
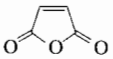
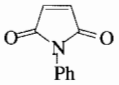
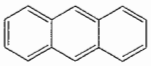
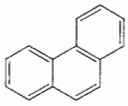
Table 11.1 HOMO and LUMO Energies and Orbital Coefficients of Common Alkenes



HOMO



LUMO

Alkene	HOMO (eV)	c_1	c_2	LUMO (eV)	c_3	c_4
$CH_2{=}CH_2$[a]	–10.52	0.71	0.71	+1.5	0.71	–0.71
$CH_2{=}CHCl$[a]	–10.15	0.44	0.30	+0.5	0.67	–0.54
$CH_2{=}CHMe$[a]	–9.88	0.67	0.56	+1.8[a,b]	0.67	–0.65
MeCH=CHMe	–9.13[c]			+2.22[d]		
$EtCH{=}CH_2$	–9.63[e]			+2.01[e]		
	–8.94[f,g]			+2.1[g]		
$CH_2{=}CHOMe$[a]	–9.05;–8.93[c]	0.61	0.39	+2.0	0.66	–0.72
$CH_2{=}CHSMe$[a]	–8.45	0.34	0.17	+1.0	0.63	–0.48
$CH_2{=}CHNMe_2$[a]	–9.0	0.50	0.20	+2.5	0.62	–0.69
$CH_2{=}CHCO_2Me$	–10.72	0.43	0.33	0	0.69	–0.47
$CH_2{=}CHCN$	–10.92	0.60	0.49	0	0.66	–0.54
$CH_2{=}CHNO_2$[a]	–11.4	0.62	0.60	+0.7	0.54	–0.32
$CH_2{=}CHPh$	–8.48	0.49	0.32	+0.8	0.48	–0.33
$CH_2{=}CHCHO$	–10.89[b]	0.58[a]	0.48[a]	+0.60[b]	0.404[b]	–0.581[b]
$CH_2{=}CHCHO/BF_3$[b]	–12.49			+0.43	0.253	–0.529
$CH_2{=}CHCO_2H$[b]	–10.93			+2.91	0.461	–0.631
	–10.29[h]			–1.91[i]		
	–11.95[h]			–0.57[j]		
$(N{\equiv}C)_2C{=}C(C{\equiv}N)_2$	–11.8[k]			–1.80[l];–2.03[m]		
$HC{\equiv}CH$	–11.4[g]			+2.6[g]		
$MeC{\equiv}CMe$	–9.9[c]			+3.43[n]		
	–10.64[o]			–0.49[i]		
$MeO_2C{-}C{\equiv}C{-}CO_2Me$	–11.5[p]			–0.60[f]		
	–7.55			–0.56		
	–8.1[c,q]			–0.31[q]		
	–9.34[c,q]			–0.64[q]		
$HC{\equiv}C{-}C{\equiv}N$[r]	–11.81	0.56	0.43	0	0.57	–0.41
$CH_2{=}C(C{\equiv}N)_2$[r]	–11.38	0.61	0.45	–1.54	0.66	–0.49
	–10.16[s]					

$CH_2=C=CH_2$[t]	–10.14	–0.47	–0.56;.20[u]	+2.4	0.64	–0.62;–0.09[u]
$CH_2=C=CMe_2$[t]	–9.67	–0.66	–0.63;.09[u]	+0.78	0.65	–0.66;–0.07[u]
$CH_2=C=CHOMe$[t]	–9.33	–0.53	–0.63;.12[u]	+1.01	0.67	–0.63;–0.10[u]
$CH_2=C=CHC{\equiv}N$[t]	–10.45	–0.63	–0.55;.22[u]	–0.01	0.54	–0.65;–0.05[u]
$CH_2=C=CHCO_2Me$[t]	–10.62	–0.67	–0.53;.23[u]	–0.07	0.48	–0.63;–0.04[u]
$CH_2=C=O$[v]	–12.55;–12.7[x]	–0.73	–0.27;.61[w]	2.55	0.22	0.57;.75[w]
$MeCH=C=O$[v]	–11.52;–8.95[y]	–0.67	–0.33;.55[w]	x	–0.51	0.71;–0.32[w]
$PhCH=C=O$[v]	–10.61;–10.56[x]	–0.53	–0.30;.43[w]	x	–0.16	0.45;–0.23[w]
$Me_2C=C=O$	–8.45[y]					
$ClCH=C=O$	–9.24[y]					
$Cl_2C=C=O$	–9.15[y]					
$N{\equiv}CCH=C=O$	–10.07[y]					

[a] All data From Ref. 12 unless otherwise noted. [b] From Ref. 13. [c] From Ref. 14. [d] From Ref. 15. [e] From Ref. 16. [f] From Ref. 17. [g] From Ref. 18. [h] From Ref. 19. [i] From Ref. 20. [j] From Ref. 21. [k] From Ref. 22. [l] From Ref. 23. [m] From Ref. 24. [n] From Ref. 25. [o] From Ref. 26. [p] From Ref. 27. [q] From Ref. 28. [r] all data From Ref. 29. [s] From Ref. 30. [t] all data From Ref. 31. [u] third coefficient (C1 for $\mathbf{C}R_2$; C2 for =**C**=; C3 for $\mathbf{C}H_2$=); .[v] all data From Ref. 32 unless otherwise noted. [w] third coefficient (C1 for **R**CH; C2 for =C=; C_3 for =O). [x] From Ref. 33. [y] From Ref. 34

Data are also shown for allene and ketene derivatives, which react similarly to alkenes in pericyclic reactions. The HOMO and LUMO energies are generally lower than those of ethene and the orbital coefficients of interest are those at C2 and C3 in the LUMO of allenes and C1 and C2 in ketenes. As will be seen in Sections 11.4.B and 11.11, the LUMO energies and coefficients are important for predicting reactivity and selectivity in several types of pericyclic reactions.

As seen above, a conjugating substituent (C=O or C≡N, Ph) lowers the energy of both the HOMO and the LUMO and its presence also perturbs the orbital coefficients. Table 11.1 shows an entry for styrene in which the HOMO is higher in energy but the LUMO is lower (relative to ethene), as seen in Figure 11.3.[35] The orbital coefficients are smaller closest to the phenyl and are also significantly smaller in magnitude. These effects appear in dienes where the conjugating substituent is another ethene moiety (1,3-butadiene, for example). In Figure 11.3, the HOMO energy is –9.03 eV (with coefficients of 0.57 and 0.41). The LUMO energy is lowered to +1.0 eV with coefficients of 0.56 and –0.42, relative to ethene,[35] which is a net electron-withdrawing effect, but the influence of the HOMO and LUMO is similar to the effects noted for styrene.

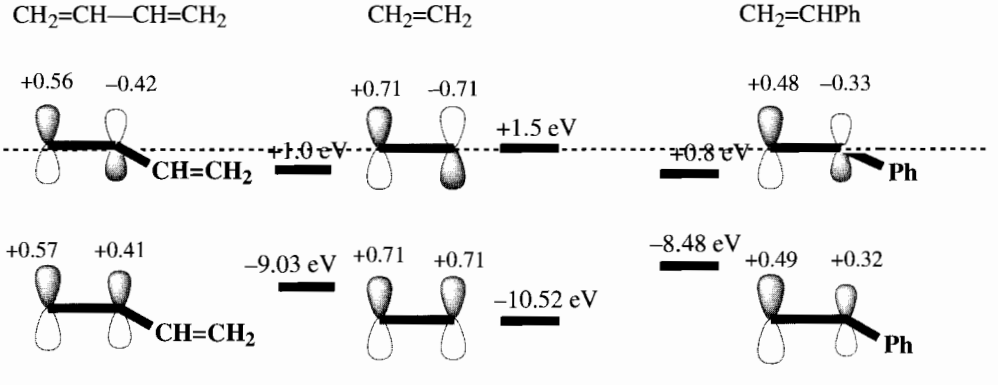


Figure 11.3. Influence of a conjugating substituent on alkene HOMO and LUMO energies.

In Figure 11.3, 1,3-butadiene is treated as a substituted alkene, which is a contrivance since the conjugated π system shows significant interaction, reflected in the HOMO and LUMO energies. Although the HOMO–LUMO coefficients for all four atoms of the conjugated system must be considered, only those at the termini will interact with the alkene in a Diels–Alder reaction. 1,3-Butadiene is symmetrical, and the coefficients reflect not only the equal distribution of electron density in the orbitals (see Figure 11.3), but also the electron withdrawing effect invoked in Figure 11.3. The largest concentration of electron density occurs at the terminal carbons, and these are expected to be the major sites of reactivity. In butadiene, there are four π orbitals and four π electrons, there are four molecular orbitals as shown. The HOMO and LUMO energy levels in Figure 11.4[35] are only two of four frontier orbitals. The lowest energy orbital has no node, the HOMO has one node, the LUMO has two nodes and the highest energy orbitals has three nodes. In this diagram, the two lowest energy orbitals contain electrons, with the HOMO being the higher of the two. The HOMO will be more

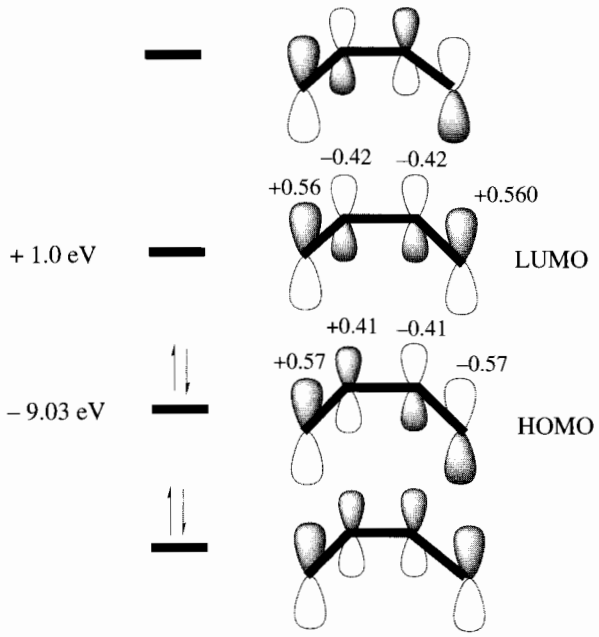


Figure 11.4. Orbital diagram for 1,3-butadiene.

important for reactions than the other orbitals, since it contains electrons that can be donated. Similarly, the LUMO is the lowest energy of the unfilled orbitals and is more important for reactions since it will preferentially accept electrons. In all cases involving dienes, attention will be focused entirely on the HOMO and LUMO.

When substituents are attached to a diene, effects on the frontier orbitals are similar to those observed with alkenes. Electron withdrawing groups decrease the energy of the HOMO and LUMO relative to butadiene and electron releasing groups increase the HOMO and LUMO energies. There is a new problem of regiochemistry, however, since the substituent can be attached to C1 or C2 of the diene. The Z group is a generic electron-withdrawing group, and the X group is a generic electron-releasing group, as used by Fleming[36] and Houk.[37] The energies for the HOMO and LUMO are mostly taken from the work of Houk.[37] As expected, the electron

withdrawing groups lower the HOMO and the LUMO (see Figure 11.5).[37] The C1 substituent lowers the energy more than a C2 substituent and the orbital coefficients are larger on the orbitals distal to the Z group for C1 substituents, although they are larger on the proximal carbon for C2 substituents. The orbital on the carbon distal to the X group is smallest for C1 substituents and largest for C2 substituents in the LUMO. In the HOMO, the orbital on the carbon distal to the Z group attached to C1 is largest for the HOMO and smallest for the LUMO (see **9**), which is reversed when the Z group is attached to C2 (see **10** in Figure 11.6) and largest for C2 substituents in the LUMO. Typical substituted dienes are presented in Table 11.2, along with the HOMO and LUMO values and the available coefficients.

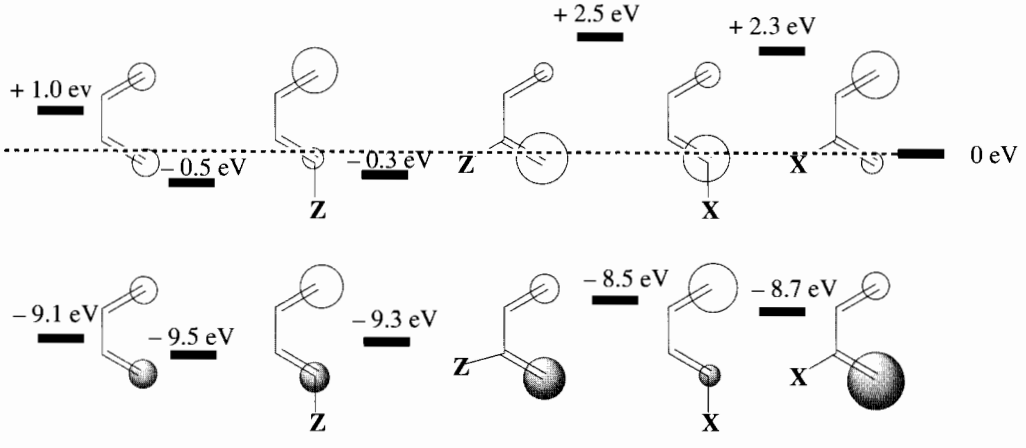
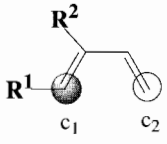
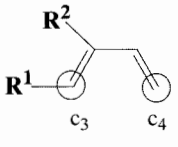


Figure 11.5. Relative HOMO and LUMO energies of electron-rich and -poor dienes.

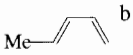
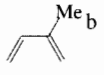
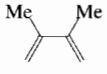
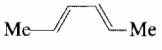
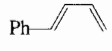
Table 11.2 HOMO, LUMO Energies and Orbital Coefficients for Substituted Dienes

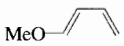
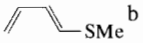
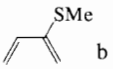
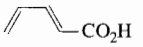
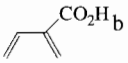
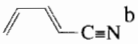
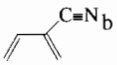


HOMO



LUMO

Diene	HOMO[a]	c_1	c_2	LUMO	c_3	c_4
	–9.07;–8.85[b]	0.57	–0.57	+1.0;3.38[b]	0.56	0.56
	–9.78[a];–8.54	0.314	0.315	+3.51	0.629[c]	0.617[c]
	–9.04[a];–8.72	0.340	0.296	+3.38	0.56[d]	0.55[d]
	–8.76[a]			2.18[e]		
	–8.39[a]					
	–8.16[a]	0.408[f]	0.416[f]			
	–8.77[a]	0.572[g]	0.335[g]			

	–8.21[a];–8.24[b]	0.235[b]	0.313[b]	+3.77[b]	0.644[c]	0.609[c]
	–8.62[a]	0.352[b]	0.103[b]	+3.60[b]		
	–7.94	0.240	0.256	+3.25		
	–8.37	0.399	0.201	+3.25		
	–9.41[b]	0.483[f]	0.460[f]	+1.99[b]		
	–9.24	0.279	0.326	+2.39		
	–9.45			+1.86		
	–9.58	0.595[g]	0.490[g]	+2.12		
	–8.97[h]			+0.75[i]		
	–8.2[j,k]			+0.73[k];+0.80[j,l]		
	–8.2[h,m]			+2.38[l,n]		
	–8.8[h,m]			+1.76[l,n]		
	–8.9[h,m]			+1.17[l,n]		

[a] taken from Ref. 38 unless otherwise noted. [b] taken from Ref. 13 unless otherwise noted. [c] from Ref. 39. [d] from Ref. 29. [e] from Ref. 40. [f] from Ref. 41. [g] from Ref. 42. [h] from Ref. 14. [i] from Ref. 17. [j] from Refs. 15,43. [k] from Ref. 44. [l] from Ref. 45. [m] from Ref. 46. [n] from Ref. 47

As with the energy levels and coefficients presented in Table 11.1, the values in Table 11.2 vary with the experimental method used to obtain them and with the sophistication level of the calculation. Two HOMO and LUMO values are given for butadiene to illustrate this. It is clear, however, that the electron-releasing and -withdrawing effects are as predicted. Cyclopentadiene is interesting in that it shows significant lowering of the LUMO, as does cyclohexadiene relative to butadiene and especially relative to the acyclic 2,4-pentadiene. Introduction of an electron-releasing heteroatom in the ring (furan, thiophene, and pyrrole) leads to a LUMO of lower energy relative to methoxy or methylthiobutadiene, but the LUMOs are higher in energy than cyclopentadiene. The HOMO energies (as well as the c_1 and c_2 orbital coefficients) will prove useful for analyzing Diels–Alder and [3+2]-cycloaddition reactions.

11.3. ALLOWED AND FORBIDDEN REACTIONS

Most of the reactions involving multiple π bonds can be classified by the number of π-electrons in each reaction partner. A single π bond (2 π electrons) can interact with another single π bond of an alkene or a

diene (2 more π electrons). The reaction of two alkenes (see Figure 11.6) is therefore classified as a **2 π + 2 π** reaction. When a diene with four π electrons reacts with an alkene having two π electrons (Figure 11.6) there are a total of 6 π electrons and this is a **4 π + 2 π** reaction. Reaction of an allyl anion with an alkene (Figure 11.6) is classified as a **3 π + 2 π** reaction, and is a simple example of a so-called dipolar addition discussed in Section 11.11. Woodward and Hoffman[10b,48] correlated each reaction type with the symmetry of their frontier orbitals, allowing predictions to be made concerning their reactivity. They classified reactions as **allowed** or **forbidden**. In an allowed reaction, a four-center transition state is stabilized more than a two-center transition state; in a forbidden reaction, vice versa. For reaction of a diene and an alkene (see Figure 11.6), the four-center transition state is represented by **9** and the two-center transition state by **10**.[49] This problem can

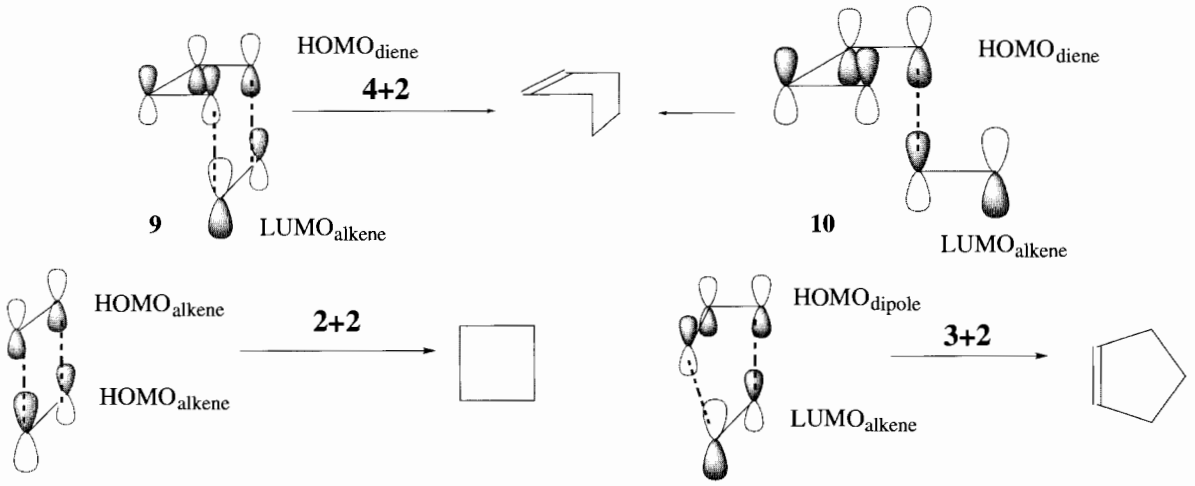
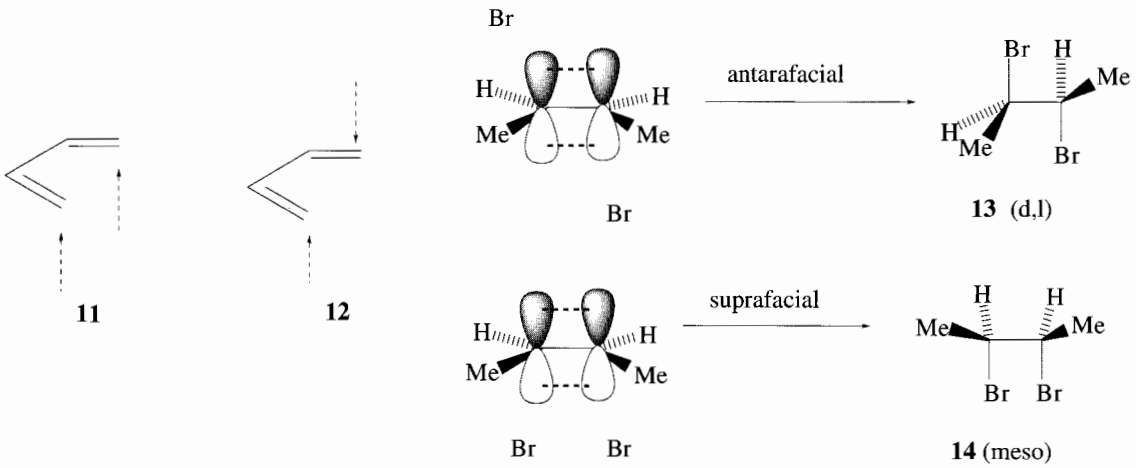


Figure 11.6. Common pericyclic [*m*+*n*] reactions.

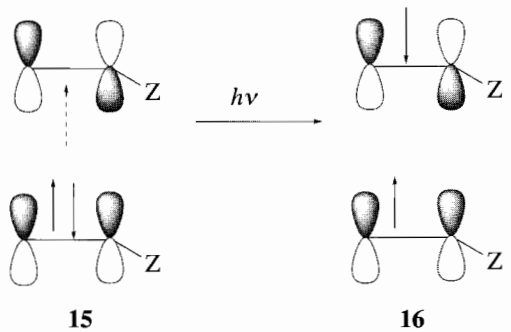
be further defined in terms of the number of π electrons in the polyene. One system contains **4 n + 2 n** π systems (*n* = the number of π-electrons). An example is the 4 π-electrons in 1,3-butadiene reacting with the 2 π electrons of an alkene. The HOMO of the diene contains terminal atoms with orbitals of opposing symmetry (HOMO$_{diene}$ in **9**) and the orbital coefficients have opposite signs,[50] which contrasts with a 4n π electron system (n = 0, 1, 2, 3, ..., with 0, 4, 8, 12, ..., π electrons, such as the 2 π-electrons of one alkene reacting with the 2 π electrons of a carbonyl π bond). The HOMO contains orbitals of the same symmetry and sign in symmetrical alkenes but the LUMO contains orbitals of opposing symmetry and sign (see LUMO$_{alkene}$ in **9**). The symmetry of the alkene LUMO is the same as that found in the HOMO of the diene. In a reaction, maximum stability in the transition state is observed when the terminal carbons of the HOMO$_{diene}$ interact with the termini of the LUMO$_{alkene}$. These orbitals have the same symmetry and such interactions are allowed. If the orbitals have the opposite symmetry (and sign) the interaction is forbidden.[51]

Woodward and Hoffman described addition modes based on the facial approach of the reactive termini as **suprafacial** and **antarafacial**.[52] "A suprafacial process is one in which bonds made or broken lie on the same face of the system undergoing reaction", as in **11**.[52] An antarafacial process has the "newly formed or broken bonds on opposite sides of the reaction system," as in **12**.[52] Woodward and Hoffman then described several

specific π interactions and classified them as **symmetry allowed** or **symmetry forbidden** (the so-called **Woodward–Hoffman rules**). Each π process could then be assigned an ***s*** or an ***a*** (**suprafacial** or **antarafacial**) to describe the facial approach of the reactive termini. Lehr and Marchand use addition of bromine to



cis-2-butene to illustrate these modes of addition.[53] Antarafacial addition leads to the *d,l*-dibromide (**13**), whereas a suprafacial addition would give the meso-dibromide (**14**). These modes of addition for electrocyclic reactions will be further illustrated in later discussions.



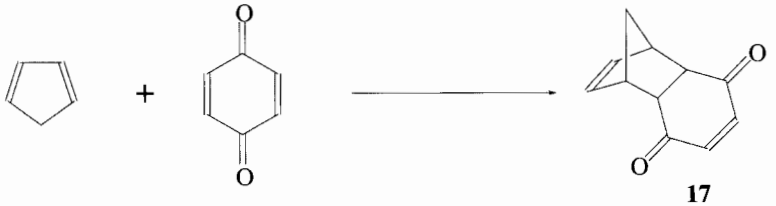
Finally, it is imperative that we categorize the energy source used to effect the reaction either heat (a thermal reaction) or light (a photochemical reaction–sec. 11.10.B for a brief introduction to photochemistry). The lowest energy arrangement of electrons (shown in **15** for an alkene) is referred to as the **ground state**. If this orbital is used for reaction, the HOMO will react with an orbital of like symmetry, but does not require promotion of an electron to the LUMO. This type of reaction only requires heating, since absorption of a photon of light will promote an electron to the antibonding orbital (convert **15** → **16**). If the alkene reacts photochemically, a singly occupied molecular orbital (a SOMO) is formed, represented by **16**, and it is the reactive orbital. Under thermal conditions, the ground state HOMO will dominate. If, however, the HOMO cannot react, heating will not affect the desired reaction and it will occur only under photochemical conditions where an electron is promoted to the higher energy SOMO. It is, therefore, possible to characterize reactions as thermally allowed or forbidden and as photochemically allowed or forbidden.

With these tools in hand, the **Woodward–Hoffman rules** of cycloaddition can be presented. Two π systems of ***m*** π electrons and ***n*** π electrons, 4 *q* and 4 *q*+2 systems (*q* = 0, 1, 2, 3, 4, 5, ...) can be classified as thermally and photochemically allowed or forbidden, as presented in Table 11.3.[54] "For suprafacial interactions, the thermally allowed reactions involve one 4 *q* + 2 molecule and one 4 *q* molecule"[10] [an alkene (*q* = 1 for 4*q*)

Table 11.3. Rules for [*m*+*n*] Cycloadditions

[*m*+*n*]	Allowed (ground state, thermal) Forbidden (excited state, *h*ν)	Allowed (excited state, *h*ν) Forbidden (ground state, thermal)
4 *q*	$m_s + n_a$	$m_s + n_s$
	$m_a + n_s$	$m_a + n_a$
4 *q* + 2	$m_s + n_s$	$m_s + n_a$
	$m_a + n_a$	$m_a + n_s$

and butadiene (*q* = 1 for 4 *q* + 2)]. "This gives a total of (4 *q*+2) π-electrons and the reaction is allowed. Forbidden reactions involve two 4 *q* or two 4 *q*+2 systems for a total of 4 *n* π electrons".[10] In the following section, the three major types of cycloaddition reactions shown in Figure 11.6 will be examined. In Figure 11.6, the [4+2]-cycloaddition (4 *n* + 2 *n*) is thermally allowed, the [2+2]-cycloaddition is photochemically allowed and the [3+2]-cycloaddition is thermally allowed (although it is a 3 *n* + 2 *n* reaction).



17

11.4. [4 + 2]-CYCLOADDITIONS

11.4.A. The Diels–Alder Reaction

In 1906, Albrecht reported a thermal reaction between cyclopentadiene and *p*-benzoquinone that gave a dimeric complex, later identified to be the [4+2]-cycloadduct, **17**.[55] In 1928, Diels and Alder reported this reaction along with those of several dienes and alkenes, including maleic anhydride and acrolein, and characterized the products.[56,59] From these initial reactions, countless variations have been reported, and this has become one of the most important methods for constructing molecules in all of organic chemistry. This thermal reaction of a diene and an alkene (or other two π-electron system, generically known as a **dienophile**) is now called the **Diels–Alder reaction**.[57] Diels and Alder were awarded the Nobel Prize for this reaction in 1950. The reaction is explained in terms of molecular orbital theory and is recognized as a [4 *n* + 2 *n*]-cycloaddition reaction. In Section 11.3, a [4+2]-reaction was shown to be thermally allowed, and Figure 11.7 shows that the HOMO of butadiene has the same symmetry as the LUMO of ethene. The reaction proceeds thermally by donation of electrons from the $HOMO_{diene}$ to the $LUMO_{alkene}$. Orbitals of the same symmetry

(see **9**) react with transfer of electrons in a six-center transition state (**18**) to form two σ bonds and a new π bond in the cyclohexene product (**19**), as shown in Figure 11.8. The diene is shown in a cisoid conformation (sec. 1.5.A) because that is the one in which the terminal orbitals bear the proper symmetry for reaction with

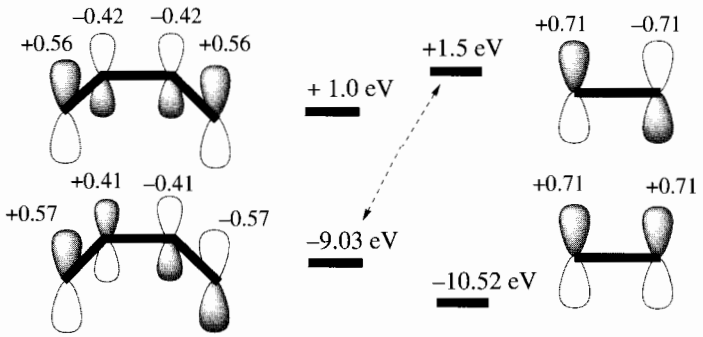


Figure 11.7. $HOMO_{butadiene}$–$LUMO_{ethene}$ interactions that control the Diels–Alder cyclization.

the alkene, and come within bonding distance of the LUMO orbital of the alkene. Acyclic dienes are in a dynamic equilibrium consisting of both cisoid (**20c**) and transoid (**20t**) conformations, but the lower energy transoid conformation is the major one. The equilibrium mixture can be used because as the cisoid conformation reacts with the alkene, the equilibrium is shifted to give more cisoid as the reaction proceeds. If a diene

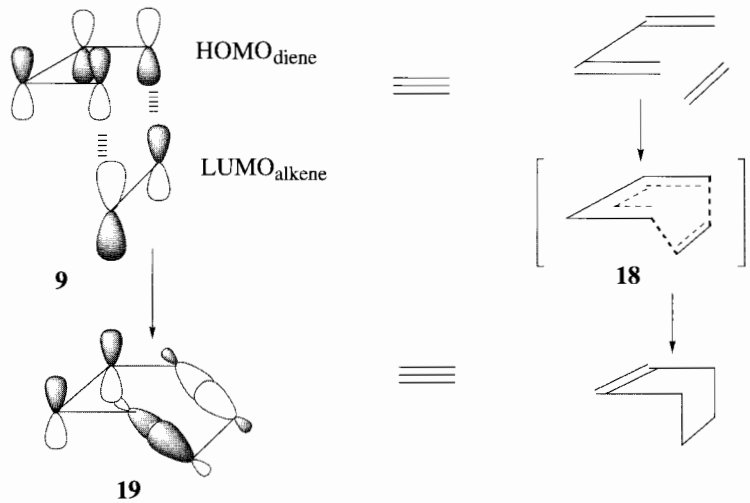
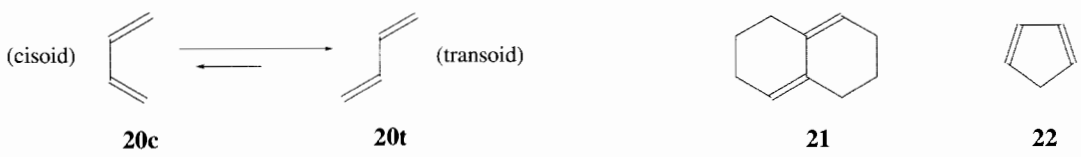
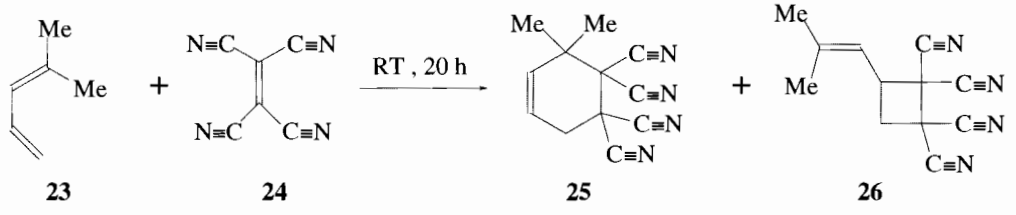


Figure 11.8. The Diels–Alder reaction of butadiene and ethene.

is locked into a transoid geometry, as in **21**, the Diels–Alder reaction does not occur. If the diene is locked into the cisoid form, as in cyclopentadiene (**22**), the reaction is expected to proceed faster. It is important to point out that this simple analysis ignores the steric interaction between diene and dienophile.



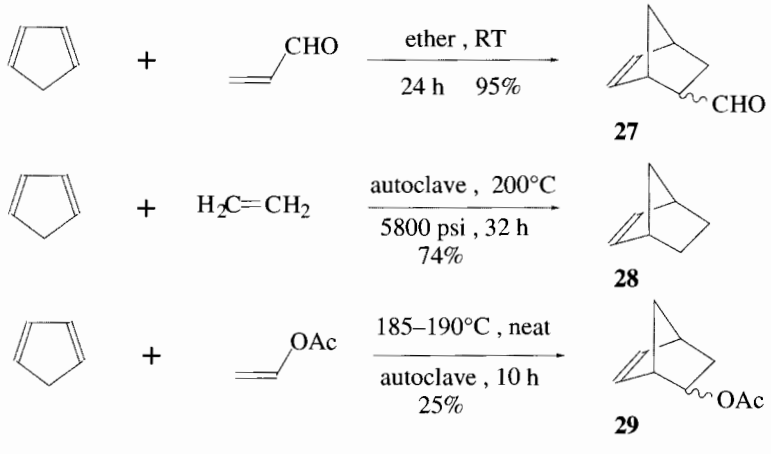
Substituents on the diene can increase the energy barrier to the cisoid form and retard the Diels–Alder reaction. Attempts to react 2-methyl-2,4-pentadiene (**23**) with maleic anhydride at ambient temperature gave no reaction. The more reactive alkene tetracyanoethylene (TCNE, **24**) gave 11% of **25** in 20 h, but the major product was the [2+2]-cycloaddition product (**26**) in 69%.[58] This poor reactivity was attributed to the energy barrier for **23** to assume a cisoid conformation.



23 **24** **25** **26**

11.4.B. Reactivity in the Diels–Alder Reaction

Diels–Alder reactions of cyclopentadiene with different alkenes proceed at different rates. Cyclopentadiene reacts with acrolein in ether at room temperature (24 h) to give a 95% yield of **27**.[59] This contrasts with the reaction of cyclopentadiene and ethene in ether to give a 74% yield of norbornene (**28**), but required heating to 200°C in an autoclave at 5800 psi pressure or 32 h. The presence of an electron releasing group on the alkene causes the reaction to proceed with greater difficulty. Vinyl acetate reacted with cyclopentadiene at 190°C in an autoclave (10 h, neat) to give only 25% of **29**.



Generally, simple alkenes and electron-rich alkenes (bearing an electron-releasing group) will react with butadiene or cyclopentadiene only under very vigorous conditions. Molecular orbital theory explains these results by comparing the relative energy levels of the HOMO and LUMOs. If we use butadiene as an example (shown in Figure 11.9), the $HOMO_{diene}$–$LUMO_{alkene}$ energy difference (ΔE) is 9.07 eV (209.15 kcal mol^{-1}, 875.5 kJ mol^{-1}) for a reaction between butadiene and ethyl acrylate. The ΔE for ethene-butadiene is 10.57 eV (243.74 kcal mol^{-1}, 1020.3 kJ mol^{-1}) and 11.07 eV (255.27 kcal mol^{-1}, 1068.6 kJ mol^{-1}) for methyl vinyl ether–butadiene. The smaller ΔE for ethyl acrylate is associated with a faster reaction.[60] These energy effects are correlated with the energy expression [Equation (11.1)][61] derived by Klopman[62] and Salem[63] from

perturbation theory. Fleming noted that the energy separation term of the HOMO and LUMO (E_r-E_s) is in the denominator of the equation, and a larger energy gap will slow the overall reaction.[61] The equation is

$$\Delta E = -\Sigma (q_a+q_b)\,\beta_{ab}S_{ab} + \sum_{k<l} \frac{Q_k Q_l}{e R_{kl}} + \sum_{r}^{occ}\sum_{s}^{unocc} - \sum_{s}^{occ}\sum_{r}^{unocc} \frac{2(\Sigma_{ab} c_{ra} c_{sb} \beta_{ab})^2}{E_r - E_s} \qquad 11.1$$

where q_a and q_b are electron populations of atomic orbitals ***a*** and ***b***; β and S are the resonance and overlap integrals, respectively; the energy of the bonding orbital is

$$E_r = \frac{\alpha_1 + \beta}{1 + S} \qquad 11.2$$

and the energy of the antibonding orbital is

$$E_s = \frac{\alpha_2 - \beta}{1 - S} \qquad 11.3$$

The first term in Equation 11.1 is the Coulomb integral,[63b] and Q_k and Q_l are the total charges on atoms **k** and **l**; e is the local dielectric constant; R_{kl} is the distance between atoms **k** and **l**; C_{ra} is the coefficient of atomic orbitals (***a***) in molecular orbital (***r***), where ***r*** refers to the molecular orbitals on one molecule and ***s*** refers to those on the other; and E_r and E_s are the energies of the molecular orbitals.

A comparison of ΔE for the $HOMO_{diene}$ and $LUMO_{alkene}$ of electron rich dienes and electron poor dienes upon reaction with ethyl acrylate (see Figure 11.9) shows that ΔE is smaller for electron rich dienes. For

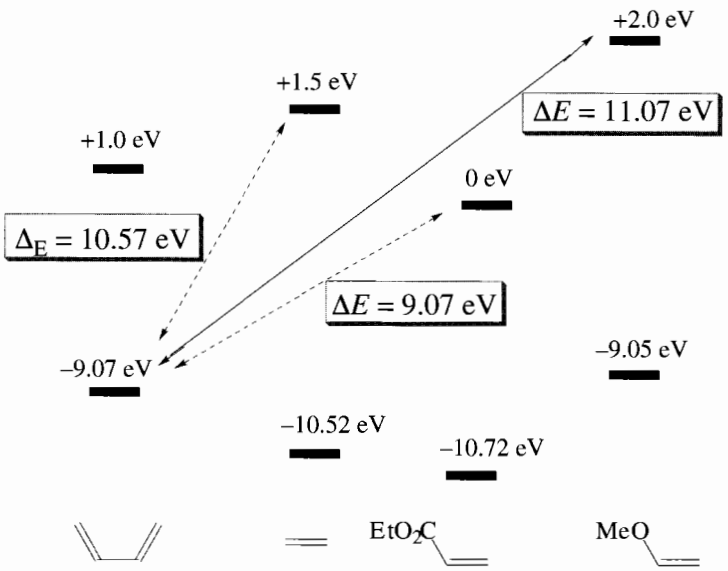
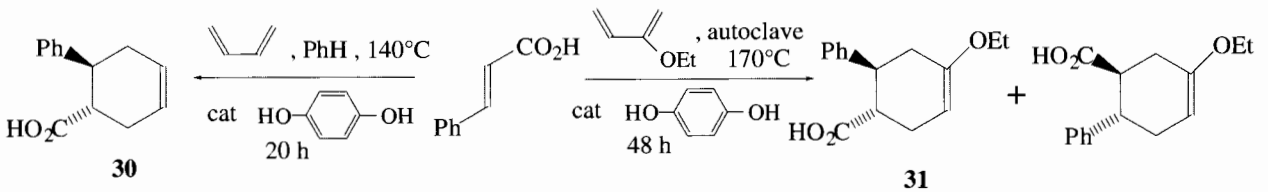


Figure 11.9. $HOMO_{diene}$–$LUMO_{alkene}$ interactions of butadiene and representative alkenes

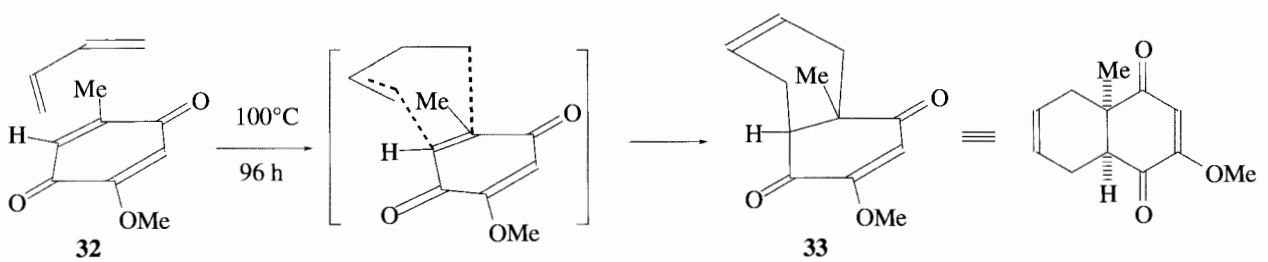
example, 1-ethoxy-butadiene reacts faster than ethyl 1,3-pentadienoate. A similar trend is observed with ethene and methyl vinyl ether, but the overall trend that the diene reacts faster with the electron poorer alkene is retained, as observed in the reaction of 1,3-butadiene with *trans*-cinnamic acid to give **30**, which required

heating to 140°C for 20 h.[64] Similar reaction with 2-ethoxy-1,3-butadiene gave a mixture of two cycloadducts after heating to 170°C for 48 h in an autoclave, but **31** was the major product.[65] The reaction of maleic anhydride and tetracyanoethylene showed similar reactivity.[66]

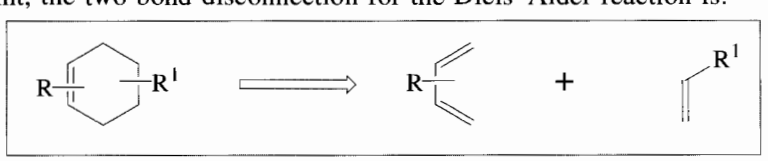
Electron-releasing or -withdrawing substituents have a significant effect on the reactivity of the diene. Comparing the reaction of cyclopentadiene and acrolein to give **27** with cyclopentadiene and vinyl acetate to give **29** illustrates this point. Substituent effects on the HOMO of the diene will increase or decrease the $HOMO_{diene}$–$LUMO_{alkene}$ interaction (ΔE). Electron-withdrawing groups will lower the HOMO of the diene and electron-releasing groups will raise the LUMO of the diene.



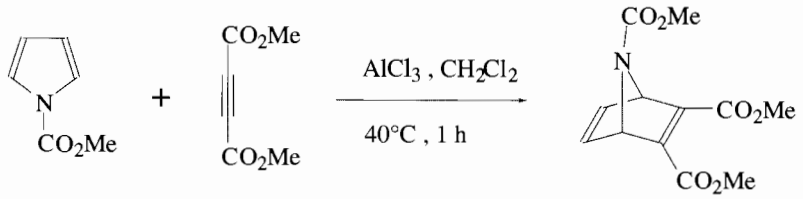
The conclusions drawn from these analyses show that the $HOMO_{diene}$–$LUMO_{alkene}$ ΔE correctly predicts the *relative* reactivity of a given diene with a variety of alkenes, or of an alkene with a variety of dienes. As seen above, cyclopentadiene reacted faster with ethyl acrylate and slowest with methyl vinyl ether. The HOMO of cyclopentadiene is –9.87 eV (Table 11.2), the LUMO of methyl acrylate is 0 eV, and the LUMO of methyl vinyl ether is +2.0 eV (Table 11.1). The ΔE for methyl acrylate and cyclopentadiene is 9.87 eV, but the ΔE for methyl vinyl ether and cyclopentadiene is 11.87 eV. Methyl acrylate is expected to react faster. In general, alkenes with electron-withdrawing substituents react faster than alkenes with electron releasing substituents. A synthetic example is Woodward's synthesis of reserpine, which began with the Diels–Alder reaction of benzoquinone **32** and 1,3-butadiene to give **33** in 86%.[67] Reaction occurred preferentially at the double bond bearing the methyl group rather than at the more electron-rich vinyl ether. The $HOMO_{diene}$–$LUMO_{alkene}$ ΔE for the



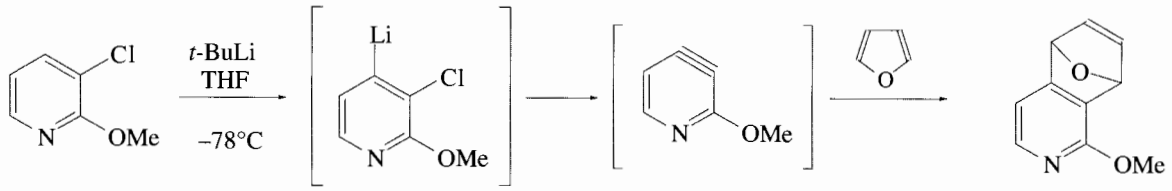
methoxy side is larger than that for the methyl side, and butadiene reacts preferentially with the methyl side rather than the methoxy side. The Diels–Alder reaction forms two bonds in a single reaction and from a retrosynthetic standpoint, the two-bond disconnection for the Diels–Alder reaction is:



To conclude this section, it is important to note that alkenes are not the only hydrocarbon dienophiles that are useful partners in the Diels–Alder reaction. Alkynes and even benzyne are quite useful. As a structure proof of an intermediate in Pandey's synthesis of epiboxidine,[68] the methyl carbamate of pyrrole (**34**) reacted with dimethyl-2-butynoate (**35**),in the presence of aluminum chloride (see sec. 11.6.A for a discussion of Lewis acid catalysis) to give a 90% yield of azanorbornadiene (**36**). A benzyne derivative of pyridine was



34 **35** **36**



37 **38** **39** **40**

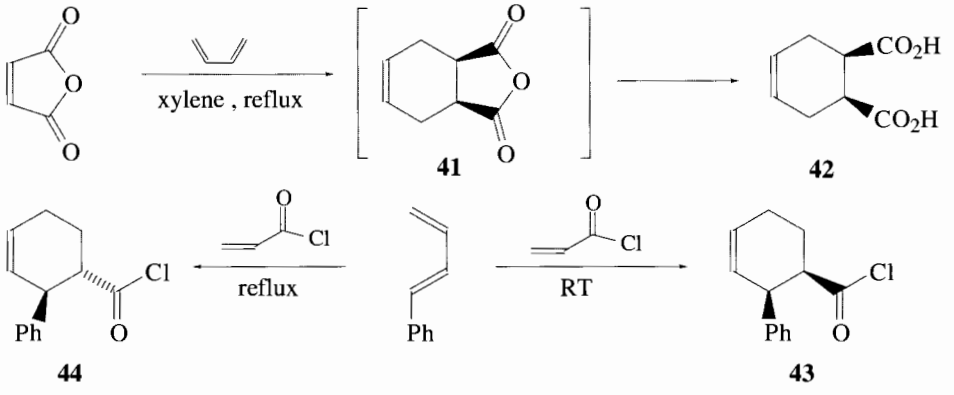
shown to undergo Diels–Alder reactions.[69] When 3-chloro-2-methoxypyridine (**37**) was treated with *tert*-butyllithium in THF at –78°C and then with furan, for example, cycloadduct **40** was obtained in 74% yield. The reaction is believed to proceed by aryl lithiation to give **38**, which loses LiCl to give the benzyne, **39**, which traps furan in a Diels–Alder reaction to give **40**.

11.4.C. Selectivity in the Diels–Alder Reaction

The Diels–Alder reaction is one of the powerful reactions referred to by Corey in his LHASA program for synthesis (sec. 10.4.B). One of the powerful features of the Diels–Alder reaction is the stereochemical selectivity inherent to the cycloaddition and many examples exist in the total synthesis of natural products.[70]

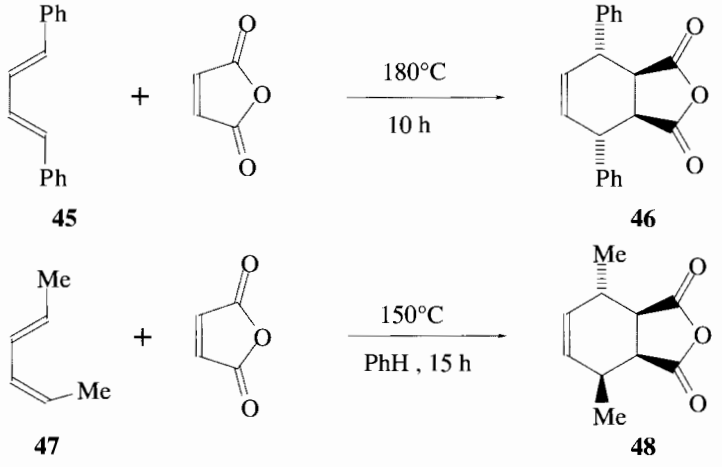
11.4.C.i. Cis–Trans Selectivity. In the reaction of **32**, the cycloadduct (**33**) showed a cis relationship at the ring juncture. The methyl and the hydrogen at the bridgeheads were derived from the respective alkene and it is clear that the relative stereochemistry of these groups in the alkene reactant was retained in the Diels–Alder cycloadduct (**33**). As seen in the transition state for that reaction, as butadiene approached the alkene, the hydrogen and the methyl are pushed away and there is no isomerization during the course of the reaction. The product (**33**) reflected this stereochemistry, with the methyl and hydrogen cis to each other. In general, reactions requiring relatively low reaction temperatures and fast reaction times show little epimerization (cis → trans). Maleic anhydride reacts with butadiene in refluxing xylene to give the cis cycloadduct (**41**), which was opened under the reaction conditions to the cis-diacid (**42**).[71] The cis configuration of the alkene reaction partner (maleic anhydride) is locked by the cyclic nature of the anhydride and this is retained in the product. When the stereochemistry is not locked, it can be controlled in some cases. When 1-phenyl-1,3-butadiene

reacted with acryloyl chloride, for example, the cis adduct (**43**) was formed, but at refluxing temperatures, a mixture of **43** and **44** was formed, with **44** predominating.[72] This example illustrates that epimerization to a more stable product is possible when the product contains an α-hydrogen that is subject to enolization.



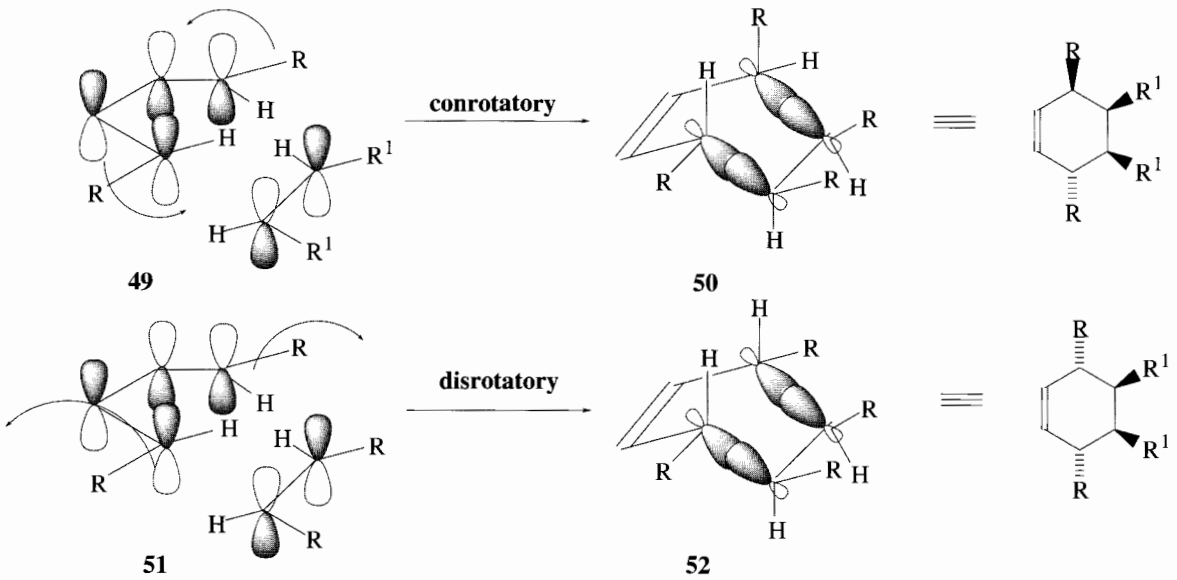
In the excellent monograph by Desimoni et al.,[73] four rules are listed for Diels–Alder reactions, taken from Sauer's work[74] and based on molecular orbital arguments.

1. Electron-withdrawing substituents (Z) on dienophiles and electron releasing substituents (X) on dienes increase the rate of reaction. The reverse substituent effects (inverse electron demand) likewise increase the rate.
2. The diene and dienophile configurations are retained in the adduct (the **cis principle**).
3. The endo transition state is favored over the exo transition state (the **endo rule**).
4. The Z-substituted dienophiles react with 1-substituted butadienes (in normal electron demand Diels–Alder reactions) to give 3,4-disubstituted cyclohexenes, independent of the nature of diene substituents (the **ortho effect**).



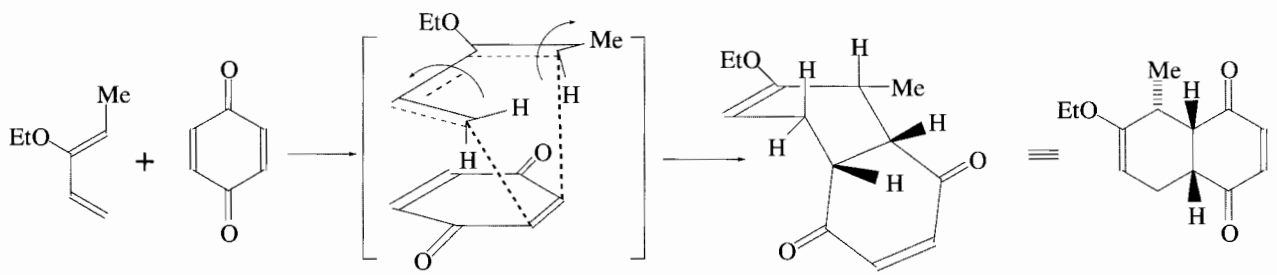
The effects of electron-withdrawing and -releasing substituents on a diene (Rule 1) was previously discussed and the configuration of alkenes (dienophile, Rule 2) was shown to give retention of stereochemistry in the cycloadduct. This latter rule is also illustrated for dienes by the reaction of trans-,trans-dienes such as **45** with maleic anhydride to give **46**.[75,76] With a wide range of substrates, the cis substituents in dienes retain their cis relationship in the cycloadduct. Similarly, cis/trans- butadienes such as **47** react with maleic anhydride to give **48**, with the trans geometry in the cycloadduct.[77,78]

In order for the stereochemistry of the diene substituents to be maintained in **46** and **48**, the relative motions of these substituents during ring formation must be as shown in **51**. The outer substituents on the diene move toward each other, and the inner substituents move away from each other producing **52**. Such motion is described as **conrotatory** (orbital motion in the same direction; **51** → **52**). Alternatively, the motion is opposite to conrotatory, where the outer substituents move in opposite directions as indicated in **49**. This motion is termed **disrotatory** (orbital motion in opposite directions, **49** → **50**). It is clear from previous



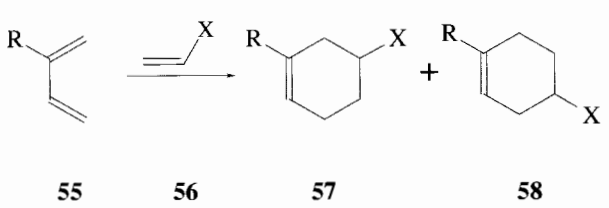
49 50 51 52

examples that the Diels–Alder reaction proceeded with a disrotatory motion in those cases, leading to predictable stereochemistry in the cycloaddition. The Merck cortisone synthesis, performed by Sarett et al.[79] began with reaction of **53** and benzoquinone to give **54**. The cis stereochemistry at the ring juncture is predictable by examination of transition state shown. Disrotatory motion of the methyl and hydrogen led to the all cis stereochemistry for the hydrogens in **54**.

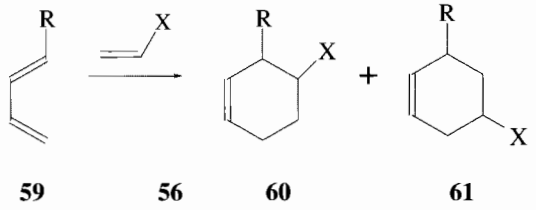


53 54

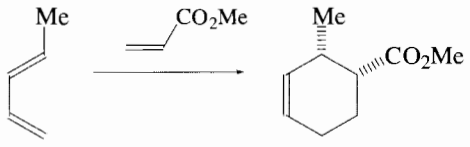
11.4.C.ii. Regioselectivity of Cycloaddition Reactions. It is apparent from several of the preceding examples that with certain substituent patterns on the diene and/or alkene, more than one regioisomeric cycloadduct is possible. When the 2-substituted diene **55** reacts with alkene **56**, two orientations for the X group are possible relative to R: the meta orientation in **57** and the para orientation in **58**. Dienes with substituents at C1,



55 56 57 58



59 56 60 61



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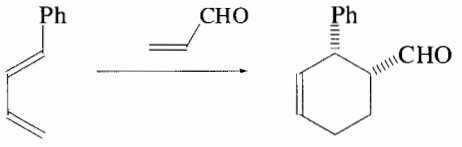

63

such as **59**, react with **56** to give a mixture of the ortho product (**60**) and the meta product (**61**). Despite the possibility of a mixture of regioisomers, the Diels–Alder reaction is highly regioselective in most cases. The reaction of 1,3-pentadiene and methyl acrylate, for example, gave 68% of the ortho adduct, **62**.[80] Similarly, 1-phenyl-1,3-butadiene reacted with acrolein to give **63** in 64% yield.[65] The cis geometry in **62** and **63** corresponds to the endo product in both cases. The selectivity of the 1-alkyl butadienes for the ortho regioisomer is usually between 4:1 and 10:1, as seen in Table 11.4.[81] In this reaction, diene **59** reacted with electron-deficient alkenes (**64**) to produce a mixture of the ortho cycloadduct (**65**) and the meta cycloadduct (**66**).

Table 11.4. Regioselectivity of 1-Alkyl-1,3-butadienes with Electron Deficient Alkenes

59 64 65 66

R	Z	65/66
Me	CHO	8:1
Me	C≡N	10:1
Me	CO_2Me	6.8:1
i-Pr	CO_2Me	5:1
n-Bu	CO_2Me	5.1:1
t-Bu	CO_2Me	4.1:1

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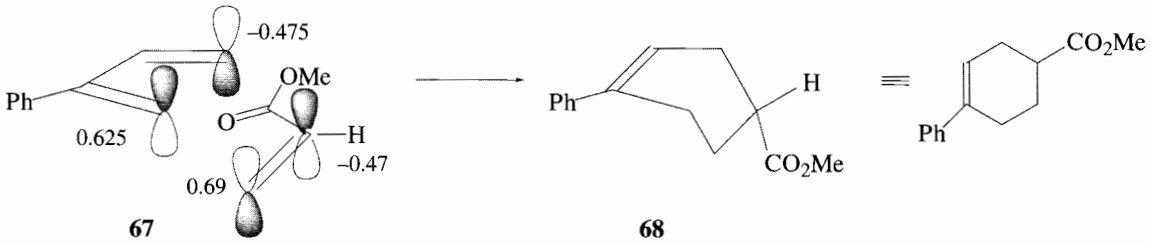
The propensity for ortho, meta, or para selectivity will vary with the diene (electron-releasing or -withdrawing substituents) and the alkene (electron-releasing or -withdrawing substituents). Fleming

assembled an excellent table that predicts regioselectivity for the generalized reagents alkene CH_2=CH—R, CH_2=CH—Z and CH_2=CH—X (where R = an alkyl group, Z = an electron-withdrawing group, and X = an electron-releasing group) using frontier orbital considerations.[82]



Selectivity is predicted by examination of the orbital coefficients of the HOMO and LUMO for both diene and alkene. The transition state for a typical reaction is shown for the reaction of methyl acrylate and 2-phenyl-1,3-butadiene (see **67**), where the orbitals with largest coefficients ($HOMO_{diene}$-$LUMO_{alkene}$) combine (the absolute value of the orbital coefficient is used, |–0.625| ↔ |0.69| and |–0.475| ↔ |–0.471|) to predict the cycloadduct produced in the greatest amount (the para product, **68**). Just as the $HOMO_{\mathbf{67}}$–$LUMO_{alkene}$ ΔE is [0 – (–8.77) = 8.77], and it predicts the relative reactivity of these reactants. The magnitude of the orbital coefficients in each partner is important for predicting selectivity. In this case, the orbital coefficients are 0.065 and 0.004, respectively, and there is selectivity for the para product. Similarly, the orbital coefficients for 1-methoxy-1,3-butadiene and acrolein correctly predict the major product is the ortho adduct. For simple cases, the orbital coefficients can be estimated by a simple Hückel molecular orbital calculation[83] (a very low level calculation but one that gives a first approximation that is useful for estimating *relative* differences).

This discussion allows an explanation of the **ortho effect** presented earlier, in connection with the Diels–Alder reaction. When a C=X or a C≡X unit (where X is a heteroatom) reacts with a 1-substituted diene, the ortho product is generally preferred. Ortho selectivity is explained by the size of the orbital coefficients. When coefficient size is combined with secondary orbital interactions (sec. 11.4.C),[41,37,84] as indicated in the transition state shown in Figure 11.10, the carbonyl orbital is responsible for a secondary interaction that stabilizes the ortho transition state. If the meta transition state is involved, then orbital symmetry dictates an exo mode and there is no possibility of secondary orbital interactions. Secondary orbital interactions such as this are possible only in an endo transition state. It should be noted that the application of secondary orbital interactions to this problem has been questioned.[85]

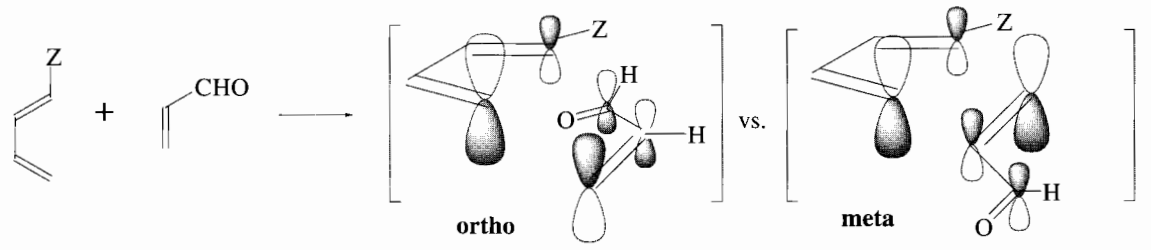
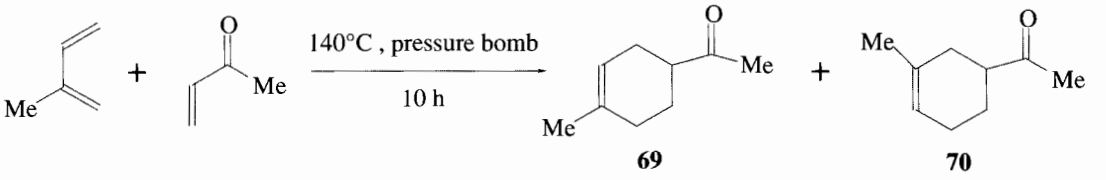


Figure 11.10. Frontier orbital control of regiochemistry for electron-rich dienes and acrolein.

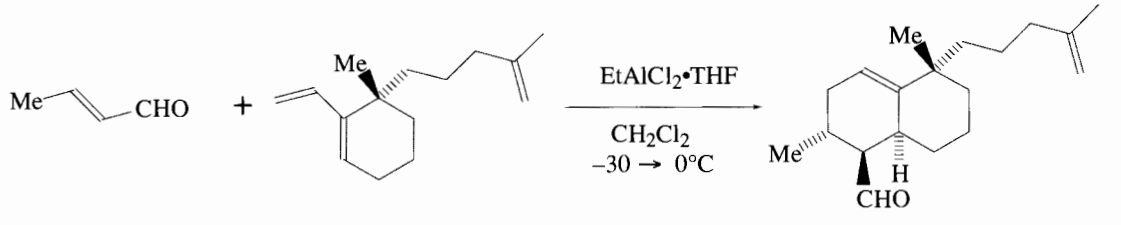
The ability to predict the regioselectivity of Diels–Alder reactions is a cornerstone of their use in synthesis. Methyl vinyl ketone, for example, reacted with 2-methyl-1,3-butadiene to give a 3:1 mixture of **69** and **70**. Gutsche et al. used the para product (**69**) to synthesize α-bisabalol.[86] They also reported that using stannic chloride as a catalyst (sec. 11.6.A) increased the ratio of **69/70** to 93:7.[86]



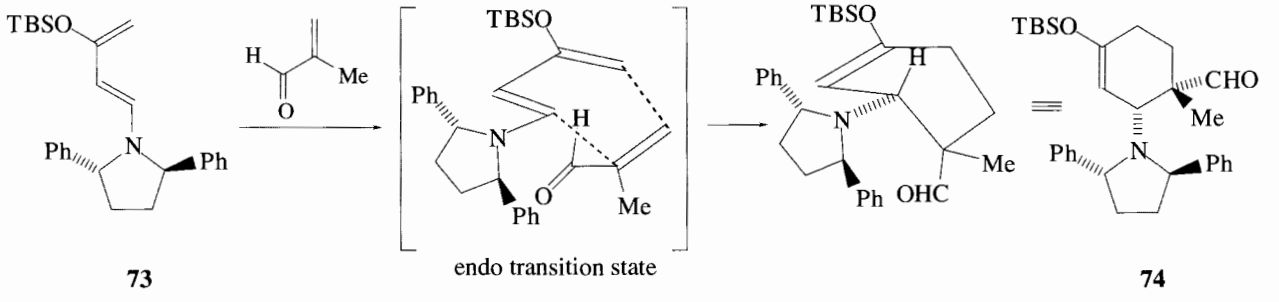
69 **70**

The diene and/or the alkene components can be part of a very complex structure. An example is the reaction of (*E*)-butenal with **71** to give an 83% yield of **72** in Shirai's synthesis of dysidiolide.[87] Note the regioselectivity and stereoselectivity of the reaction. Note also that it is catalyzed by a Lewis acid which, as mentioned, will be discussed in Section 11.6.A.

Hehre et al. proposed an alternative method to predict the regioselectivity of Diels–Alder reactions. The FMO approach does not predict "that a phenyl substituent is a significantly better regiodirector than methyl".[13,88] Hehre suggests using the average hydride potentials for the carbons of substituted ethylenes,[13] and the electrostatic (proton) potentials for the carbons of substituted dienes.[13] Correlating the largest coefficients of each reactive pair of molecules can accurately predict the regioselectivity of the resulting cycloadduct.



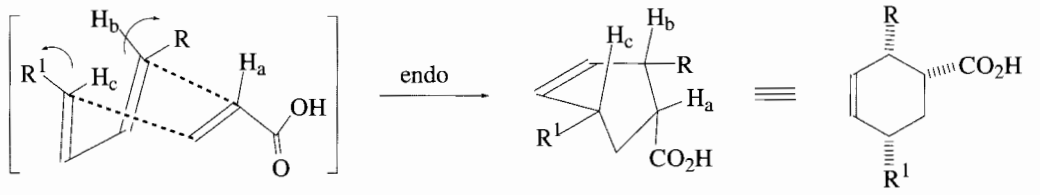
71 **72**



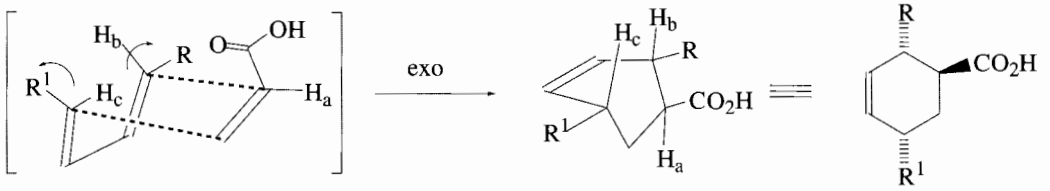
73 endo transition state **74**

11.4.C.iii. Endo Selectivity. In the reaction that generated **54**, the observed stereochemistry demanded that the benzoquinone be under the diene at the time of reaction (see that transition state in sec. 11.4.C.i), which is the normal reaction of dienophiles bearing a substituent with a π-bond and is called an **endo mode** of addition (the group of interest is under or down, relative to the diene, rather than out or up). This endo addition is seen

again in the reaction of diene **73** with methacrolein to give **74**, via the endo transition state shown, taken from Rawal's synthesis of (–)-α-elemene.[89] In this case, the disrotatory motion of the pyrrolidine unit places it down in the transition state. The carbonyl moiety is endo in the transition state, leading to the observed cis geometry (CHO and pyrrolidino in **74**). This endo orientation is seen again in the transition state for a reaction of acrylic acid with a generic diene (**75**) and it contrasts with the exo orientation in **77**, which gives the opposite relative stereochemistry for the ring substituents (trans- in **78** vs. cis- in **77**). In many reports of Diels–Alder reactions spanning many years, the endo orientation is preferred, usually in a ratio of 2→4:1, which is the basis of rule 3 listed previously, the so-called **endo rule** or **Alder endo rule**.[90] Martin and Hill give an excellent definition of the rule as follows: "Endo addition involves the tendency for dienophile substituents to be so oriented in the favored transition state that they lie directly above the residual unsaturation of the diene.... The transition state that is best stabilized by spatial orbital overlap and simultaneously least destabilized by unfavorable steric repulsion has the lowest free energy of all possible transition states, and consequently predominates in the kinetically determined product".[75]



75 **76**

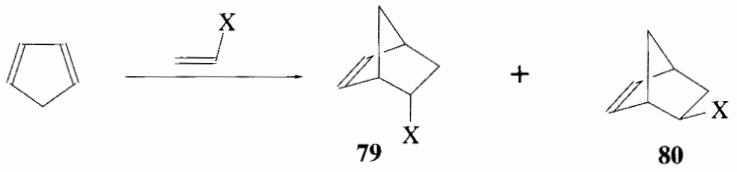


77 **78**

An endo *t*ransition state is best observed in reactions with cyclic dienes such as cyclopentadiene where the exo, endo orientation is easily detected in the cycloadduct. Cyclopentadiene, for example, reacts to give an endo product (X group is under the ring in **79**) and an exo product (X group is up as in **80**). As shown in Table 11.5,[91] the endo product (**79**) is favored over the exo product (**80**) in every case. Both electron-rich and -poor alkenes exhibit endo selectivity upon reaction with cyclopentadiene (see Table 11.5).

The **Alder endo rule** is explained by FMO theory, invoking **secondary orbital interactions**, as mentioned in Section 11.4.C.[92] A comparison of the endo transition state (**81**) with the exo transition state (**82**) for the reaction of cyclopentadiene and acrolein shows the orbitals of the carbonyl are properly aligned in **81** and of the correct symmetry for stabilization by the orbitals of the $HOMO_{diene}$. This interaction is absent in the exo transition state (**82**). This secondary orbital interaction stabilizes **81** and lowers the energy of that transition state relative to **82**. Maleic anhydride reacts with cyclopentadiene, for example, to give only the endo product,[93] and in like manner *cis*-methacrylic acid reacts to give a 90:10 mixture of endo/exo cycloadducts.[94]

Table 11.5. endo/exo Selectivity in Diels–Alder Reactions of Cyclopentadiene



79 **80**

X	79/80
CO_2H	75:25
CO_2Me	76:24
$CONH_2$	10:1
CHO	Only **79**
C≡N	60:40
CH_2OH	80:20
CH_2Br	Only **79**
CH_2NH_2	Only **79**
$CH_2C{\equiv}N$	Only **79**
CH_2CO_2H	Only **79**
NO_2	Mostly **79**
OAc	81:19
OCHO	Only **79**
Br	Mostly **79**

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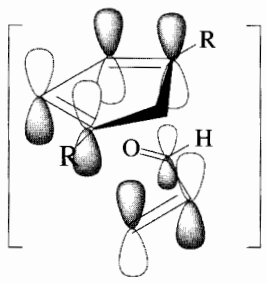

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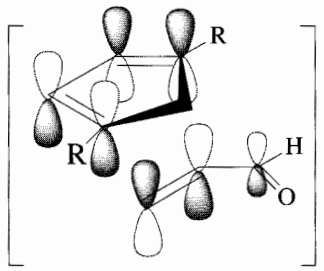

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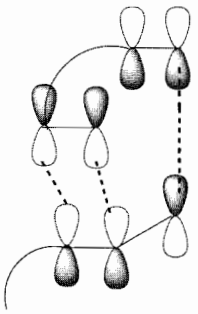

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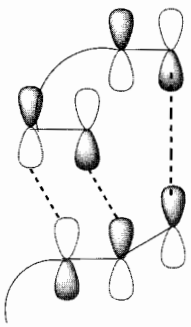

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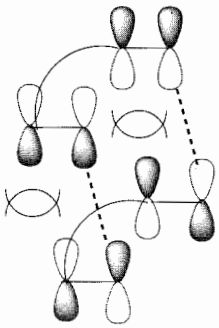


85

Examination of such interactions is important for the understanding of regioselectivity in Diels–Alder reactions. Houk formulated a general approach for secondary orbital interactions.[95]

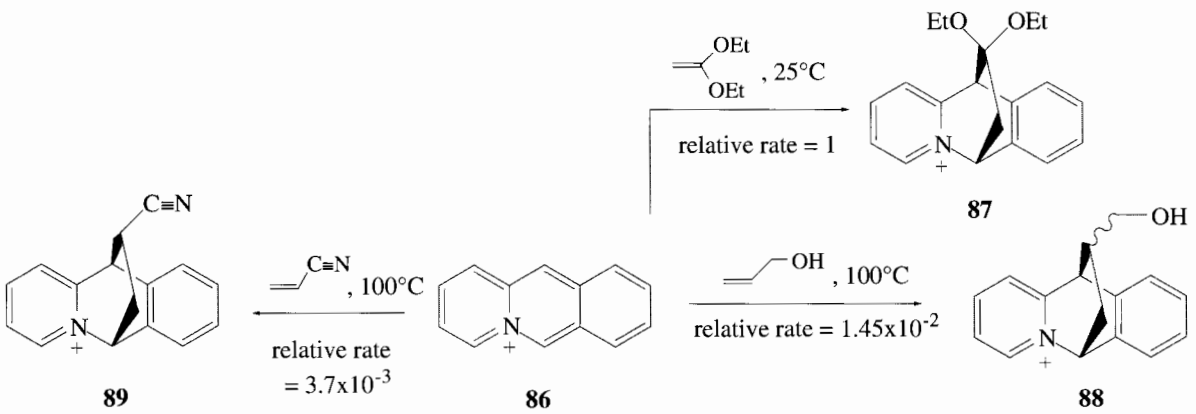
1. For all allowed cycloadditions involving the reaction of a 4n electron polyene with an alkene with extended conjugation, the endo transition state can be stabilized by secondary orbital interaction (see **83** and **84**)
2. For the allowed 4n + 4m+2 cycloaddition of two polyenes, where m ≠ 0, the endo transition state will be destabilized (see **84**).[96]

11.5. INVERSE ELECTRON DEMAND AND THE RETRO DIELS–ALDER

There are two important variations for the Diels–Alder reaction and both are synthetically useful. In one, the HOMO–LUMO interactions that drive the reaction change due to heteroatoms and/or substituents on the diene and/or alkene units. In such cases, the reaction is driven by the $LUMO_{diene}$–$HOMO_{alkene}$ interaction rather than the $HOMO_{diene}$–$LUMO_{alkene}$ interaction. In the second variation, the reversible nature of the Diels–Alder reaction is exploited. Cycloadducts are produced that can be manipulated and then a retro-Diels–Alder reaction generates a new diene or alkene. Both of these reactions will be examined in this section.

11.5.A. Inverse Electron Demand Diels–Alder Reactions

The $LUMO_{diene}$–$HOMO_{alkene}$ interaction for butadiene and methyl vinyl ether is lower than the comparable $HOMO_{diene}$–$LUMO_{alkene}$ interaction in dienes bearing an electron-withdrawing group. In many cases, but not all, this leads to the **inverse electron demand** reaction mentioned above. Fleming uses the example of azonia salt **86**,[97] which reacted with diethyl ketene acetal to give **87**. Similar reaction with allyl alcohol gave **88**, and acrylonitrile gave **89**.[97a] In all cases, the reaction proceeded to 75% completion, and it is clear from the relative rates of reactions provided with each transformation that the electron-rich alkenes reacted faster. The concept of inverse electron demand applies to a Diels–Alder reaction that is controlled by the LUMO of the diene and the HOMO of the alkene, which usually means that an electron-rich alkene reacts faster than an electron-poor alkene, the opposite of what is normally observed (see above).



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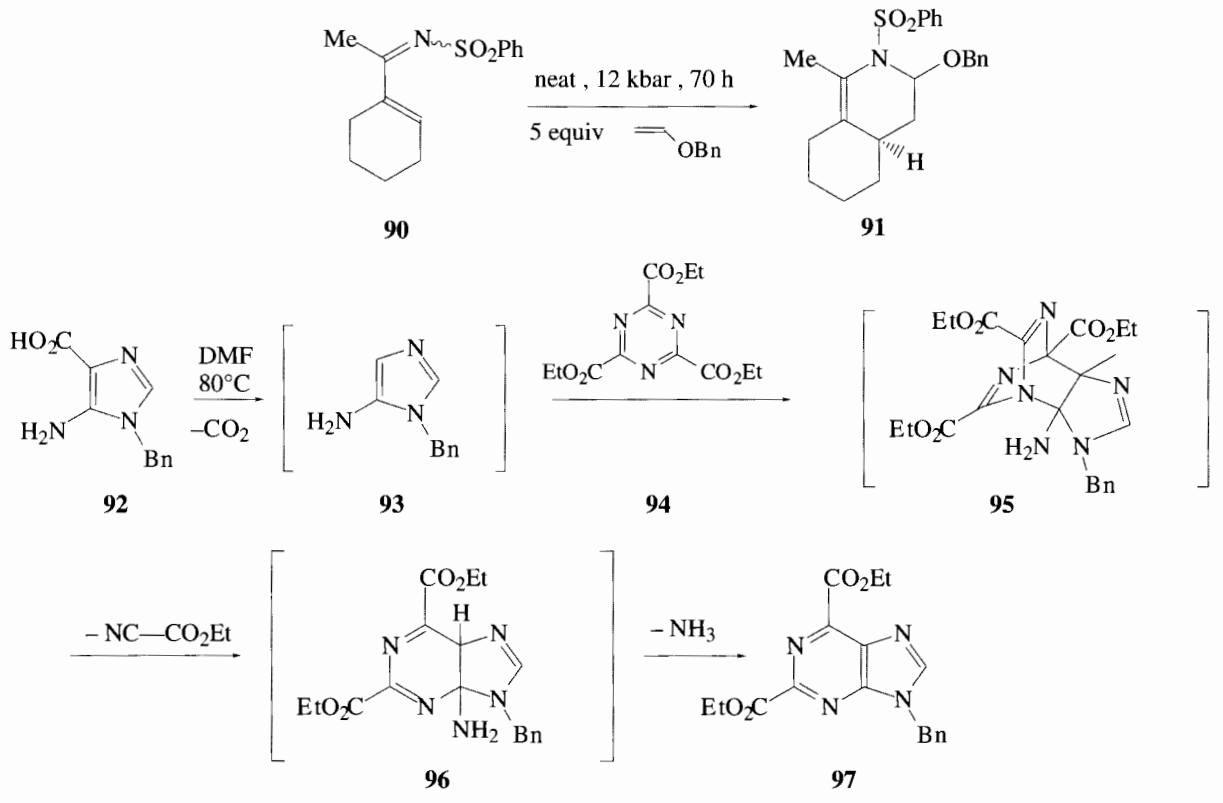
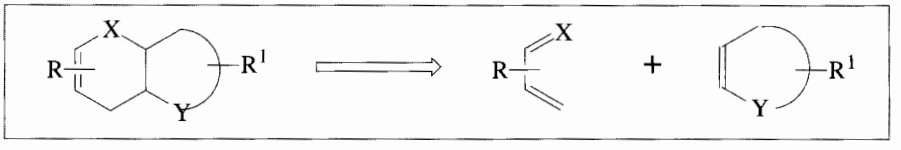
In another example, Boger prepared 1-azadiene **90** (azadienes are discussed in sec. 11.7.C.v) and showed that the LUMO of the diene controlled the subsequent Diels–Alder reaction. Reaction of **90** with butyl vinyl ether (n-BuOCH=CH_2) gave a 74% yield of **91** (>20:1 endo/exo).[98] This reaction was sluggish and high



pressure (sec. 11.6.C) was required to force the reaction to product with a reasonable reaction time and in good yield. It is apparent from these few examples that the structural features of most reverse electron demand Diels–Alder reactions involve heteroatoms or another unique feature. They are less prevalent than the normal electron demand Diels–Alder reactions discussed elsewhere in this chapter. A synthetic example is taken from Dang's synthesis of purine nucleosides,[99] in which 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (**94**), a useful diene used by Boger for the synthesis of pyrimidines,[100] reacted with 5-amino-1-benzyl-4-imidazolecarboxylic acid (**92**) to give **97** in 83% yield. Decarboxylation of **92** occurred during the reaction to give the reactive species **93** prior to the Diels–Alder reaction, which gave cycloadduct **95**.[99] This compound was not isolated, but rather decarboxylated to give **96**, and this compound lost ammonia to give the observed product. Imidazole **93** is so reactive, that this reaction occurs at the relatively mild conditions shown, which is somewhat unusual for inverse-electron demand Diels–Alder reactions.

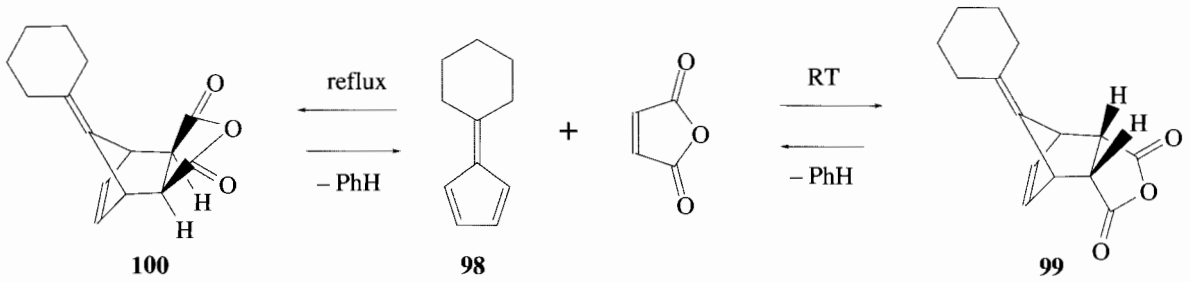
A typical inverse electron demand disconnection is:



11.5.B. Retro Diels–Alder Reaction

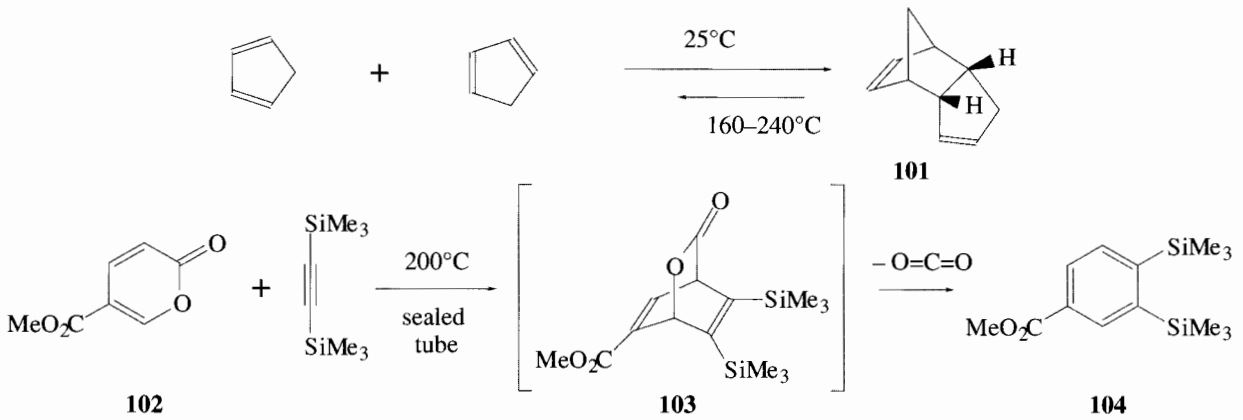
The Diels–Alder reaction is reversible under certain circumstances.[101] This reversibility can be exploited synthetically with the correct choice of diene, dienophile and reaction conditions because the equilibrium

usually favors the thermodynamically more stable cycloadduct, which is the major product. Woodward showed that maleic anhydride reacted with **98** at ambient temperatures to give **99** the endo product (see below).[102] When heated to 50°C for 10 min., however, **100** was formed with only 20.5% of **99**, and this dropped to 3.1% upon heating at 50°C for 60 min,[102] which is consistent with a reversible reaction pathway,. favoring the more stable exo product.[102] This reverse reaction (cycloadduct → diene + dienophile) is called a **retro Diels–Alder reaction**.[103]



100 **98** **99**

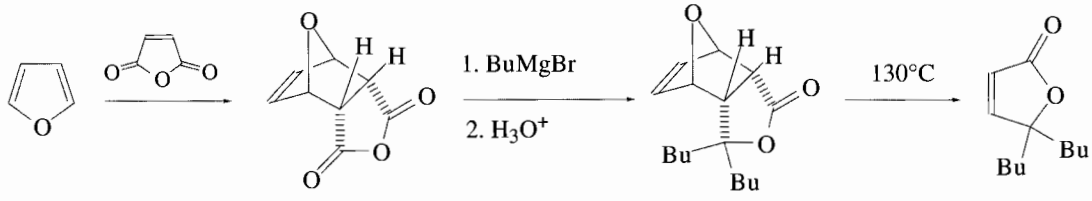
A classical example of a retro Diels–Alder reaction is the self condensation of cyclopentadiene (**22**) to give the cyclopentadienyl dimer **101**. This reaction occurs quickly at temperatures > 25°C, but is slow at low temperatures such as –78°C. Many Diels–Alder reactions involving cyclopentadiene are done at low temperatures with Lewis acid catalysts (sec. 11.6.A) to suppress cyclopentadiene dimerization. When heated to 160–240°C, **101** undergoes a retro-Diels–Alder reaction to generate 2 equivalents of monomeric cyclopentadiene.[104]



101 **102** **103** **104**

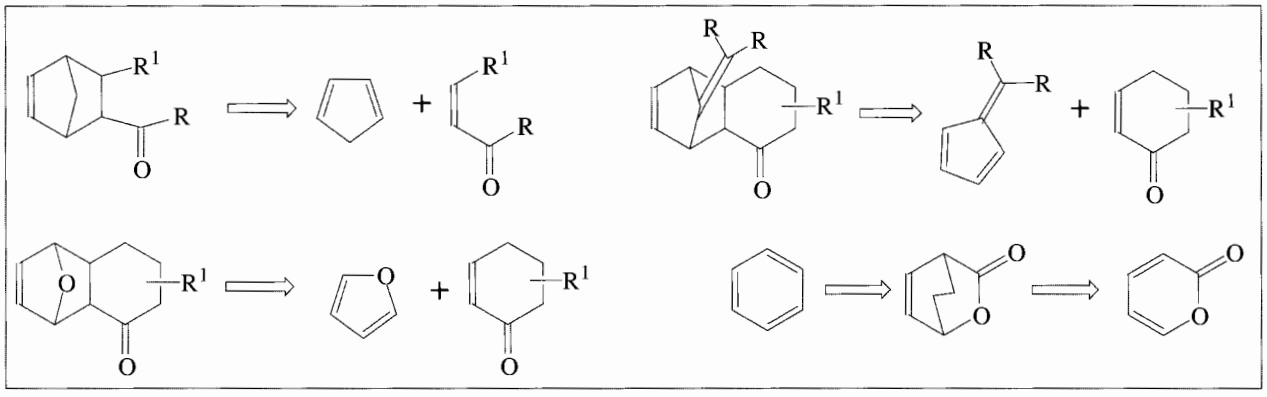
Most of the synthetic applications of retro-Diels–Alder reactions involve cyclopentadiene or furan derivatives, but there are other dienes that have appropriate functionality for this process. One example is illustrated by heating pyrone **102** in a sealed tube at 200°C with bis(trimethylsilyl)acetylene to give **103**, after initial formation of cycloadduct **104** and loss of carbon dioxide via a retro-Diels–Alder reaction.[105] The retro-Diels–Alder usually requires higher temperatures than the Diels–Alder reaction, and the normal Diels-Alder product can be obtained without competition from the retro reaction. When the retro Diels-Alder reaction is desired, flash vacuum pyrolysis is a common technique used in synthesis.[106] Retro-Diels–Alder reactions can also be catalyzed by Lewis acids (sec. 11.6.A).[107] An example that uses furan as a retro-Diels–Alder synthon is taken from work by Cannone et al., who used the retro-reaction as a synthetic route to 4-substituted

butenolides.[108] Initial reaction of furan and maleic anhydride gave **100**, and subsequent reaction with butylmagnesium bromide gave **101** (sec. 8.4.C.ii). Heating **101** to 130°C liberated furan and the butenolide (**102**) i



105 **106** **107**

in quantitative yield. A variety of interesting and useful products are available by using the Diels–Alder reaction to insert functionality and the retro-Diels–Alder to transform that product into another. The retro-Diels–Alder reaction therefore leads to several interesting disconnections, including

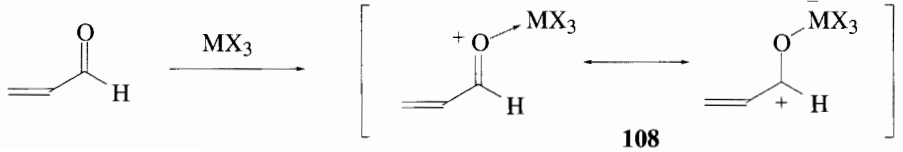


11.6. RATE ENHANCEMENT IN DIELS–ALDER REACTIONS

In many instances, Diels–Alder reactions give poor yields and/or require excessively harsh reaction conditions and long reaction times. There are several fairly straightforward techniques that increase the rate and, in some cases, the selectivity of Diels–Alder reactions. The three most important methods are catalysis by Lewis acids, rate enhancement in aqueous media and the use of high pressure (usually greater than 5 kbar). These three methods will be the focus of this section.

11.6.A. Catalysis by Lewis Acids

Lewis acids are, in general, excellent catalysts for the Diels–Alder reaction.[109] Their catalytic activity lies in the ability of the Lewis acid to complex a heteroatom component of the diene or dienophile (usually the dienophile). Complexation with acrolein, for example, generates an ionic intermediate such as **108**,[110] and



108

this zwitterion influences the course of the Diels–Alder reaction.[111] Formation of **108** lowers the net energy of both the HOMO and the LUMO relative to the uncomplexed dienophile.[112] Protonated acrolein is used to mimic **108** and the energy lowering of these frontier molecular orbitals is significant, as seen in Figure 11.11.[113] In the reaction of acrolein with cyclopentadiene, ΔE for the $HOMO_{diene}$–$LUMO_{alkene}$ is lowered from 8.57 eV for the acrolein reaction to 1.57 eV for the protonated acrolein reaction. It is known that latter the reaction proceeds faster and at a lower temperature. In Table 11.1, the HOMO and LUMO energies for acrolein were reported as –10.89 and +0.6 eV, respectively. The analogous energies for the acrolein-boron trifluoride complex were –12.49 and +0.43 eV. Using these values in a reaction with cyclopentadiene, the ΔE ($HOMO_{diene}$–$LUMO_{alkene}$) for reaction with cyclopentadiene is lowered from 11.17 for acrolein to 9.0 eV, for the complex, which predicts acceleration of the Diels–Alder reaction. When the Lewis acid lowers the HOMO and LUMO energies, the activation energy of the reaction is diminished since the denominator in Equation (11.1) is lowered.

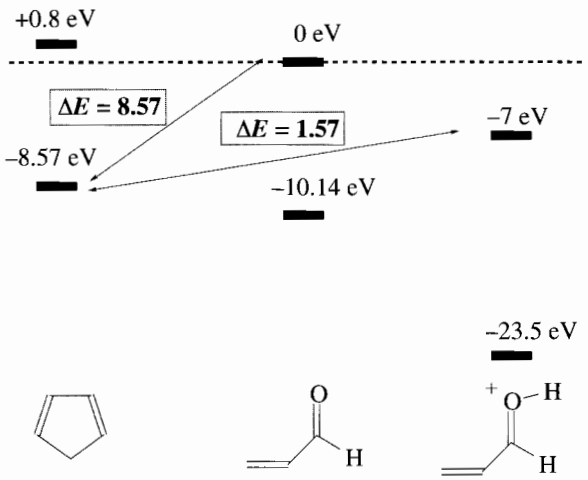
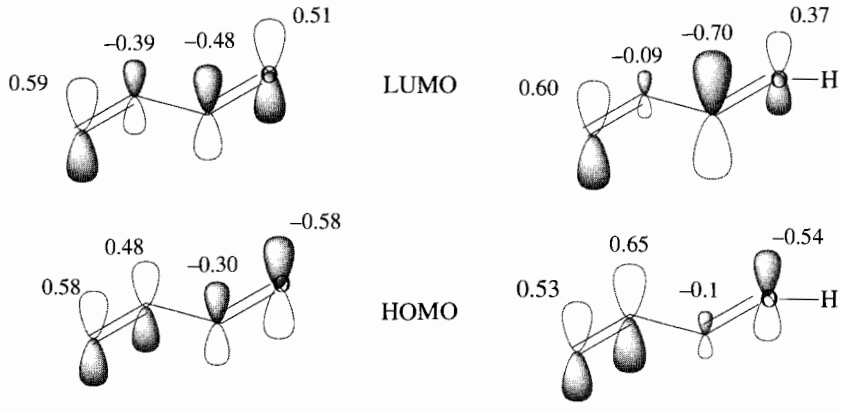


Figure 11.11. The HOMO–LUMO diagram for protonated acrolein. [Reprinted with permission from Fleming, I. Frontier Molecular Orbitals and Organic Chemical Reactions, Wiley, London, *1976*, pp. 163. Copyright © *1976* by John Wiley and Sons, Inc.]

The orbital coefficients are influenced by the extent of coordination with the Lewis acid.[110] All orbital coefficients of acrolein (**109**) are affected (see the protonated form **110**) but those of the alkene moieties are changed less than those of the carbonyl, bringing about rather large effects in the HOMO (0.48 → 0.65) and in the LUMO (–0.39 → –0.09). The carbonyl carbon is most affected, as expected.[110,113] In the reaction of acrolein with 2-phenylbutadiene, the para product (**111**) is preferred in the uncatalyzed reaction. The difference in orbital coefficients is much greater in the catalyzed reaction and this leads to a greater preference for the para product in the catalyzed reaction, due to more efficient overlap of the larger coefficients. Therefore, a common benefit of Lewis acid catalysis is greater regioselectivity in the cycloadduct.[114] In general, the Lewis acid decreases the reaction time and increases product yield and selectivity. Reaction with cyclopentadiene derivatives generally show increased endo selectivity when done in the presence of aluminum chloride.[115] Aluminum chloride increases the endo/exo ratio to favor the endo-product and the anti/syn ratio to favor the



109 **110**

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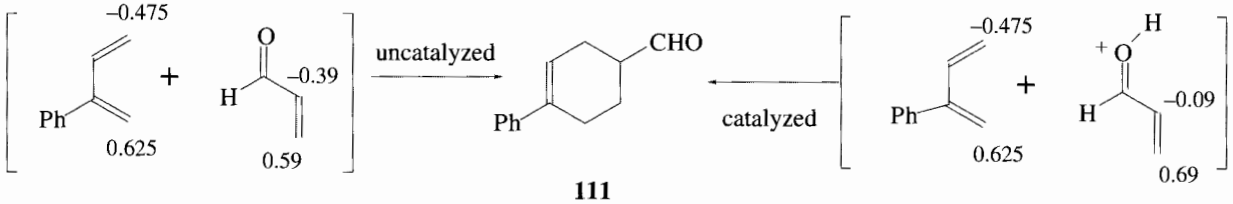
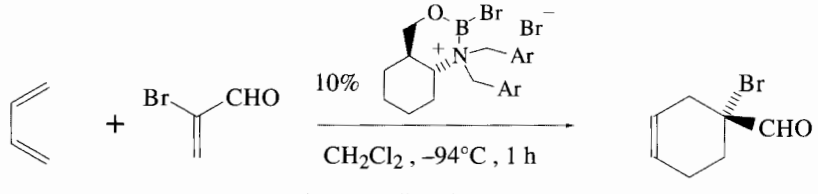
anti product. The syn/exo product was not formed in reportable amounts, presumably due to the severe steric interaction between the anti-chlorine and an exo-carbomethoxy. Stronger Lewis acids ($AlCl_3$ > $TiCl_4$ > BF_3–see sec. 2.3) have a greater effect on this reaction. Increased selectivity and rate of reaction are also observed with acyclic dienes. Additional examples of Lewis acid catalysis will be presented throughout this chapter. There is also a report that amidinium ions catalyze the Diels–Alder reaction.[116]



111

There are many synthetic applications of Lewis acid catalyzed Diels–Alder reactions. The conversion of **71** to **72** in Section 11.4.C.ii is one example. Another example is the reaction of 1,3-butadiene with 2-bromoacrolein, catalyzed by the chiral oxaborinane Lewis acid shown to give a 99% yield of **112** with 94% ee. Asymmetric Diels–Alder reactions will be explored further in Section 11.9.



Ar = 3,5-dimethylphenyl

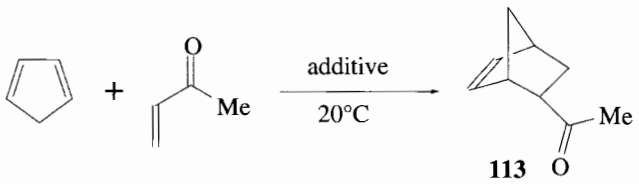
112

11.6.B. Rate Enhancement in Aqueous Media

For a long time, solvent polarity was believed to have no effect on the course of a Diels–Alder reaction. Berson, however, showed a clear relationship between the endo/exo product ratio and solvent polarity in the

Diels–Alder reaction of cyclopentadiene and acrylates.[117] The first indication that water accelerated a reaction was in a patent by Hopff and Rautenstrauch in 1939,[118] who reported that yields in the Diels–Alder reaction were enhanced in aqueous detergent solutions. In 1980, Breslow showed there was a hydrophobic acceleration for an intermolecular Diels–Alder reaction in which cyclopentadiene reacted with methyl vinyl ketone to give **113**.[119] When non–polar compounds are suspended in water their relative insolubility causes them to associate, diminishing the water–hydrocarbon interfacial area (a **hydrophobic effect**). This association is greater in water than in methanol and brings the reactive partners into close proximity, increasing the rate of reaction. Any additive that increases the hydrophobic effect will increase the rate, as shown in Table 11.6[119] for the preparation of **113**. Lithium chloride (LiCl) increases the hydrophobic effect by salting-out nonpolar material. Guanidinium chloride, however, decreases hydrophobic interactions. β-Cyclodextrin (cycloheptaamylose) possesses a hydrophobic cavity and if the reactive intermediates can fit within this cavity there is a significant rate enhancement. The smaller α-cyclodextrin cannot accommodate the reactive species, and the rate is significantly diminished.

Table 11.6. Hydrophobic Effects in the Diels–Alder Reaction of Cyclopentadiene and Methyl Vinyl Ketone in Aqueous Media



113

Solvent	Additive	$k_2 \times 10^5$ $M^{-1}s^{-1}$
Isooctane		5.94
Methanol		75.5
Water		4,410
	LiCl	10,800
	$(NH_2)_3C^+Cl^-$	4,300
	β-Cyclodextrin	10,900
	α-Cyclodextrin	2,610

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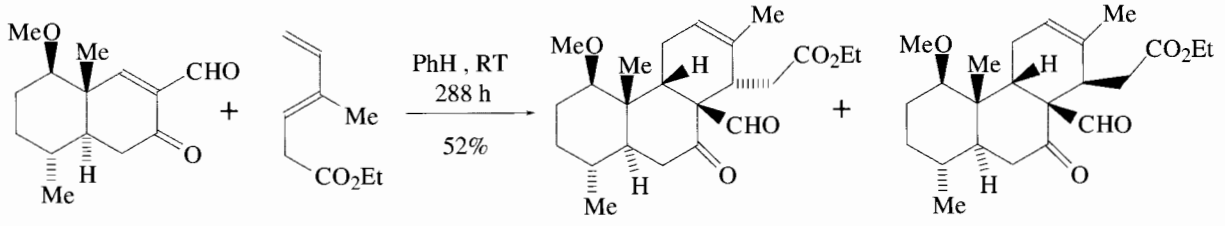
There are many examples of Diels–Alder reactions that exploit this rate enhancement effect. Grieco's interest in quassinoids led him to react **114** and **115** in benzene at ambient temperature, and this gave a 1:1.18 mixture of **116** and **117** in 52%, but required a reaction time of 288 h.[120] When the same reaction was done in water, an 82% yield was obtained (1.3:1 **116/117**) after 168 h. Diels–Alder cyclization with the free acid rather than the ester, in water, gave an 85% yield (1.5:1 **116/117**) in 17 h. Similar reaction in 1:1 aqueous methanol gave a quantitative yield after 97 h (1:1.25 **116/117**). When the sodium salt of the acid was used, a quantitative

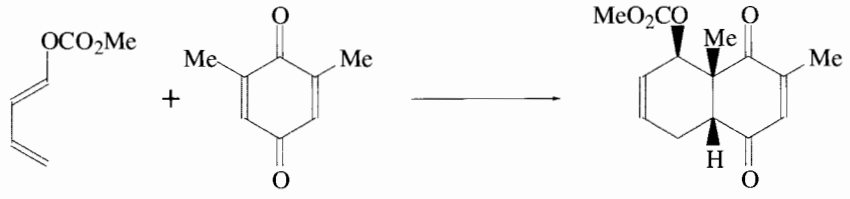


114 **115** **116** **117**

yield was obtained in 5 h (3:1 **116/117**).[120] In all cases, the reactions were carried out at room temperature with a fivefold excess of diene over dienophile. Breslow et al. showed that addition of guanidinium perchlorate to a Diels–Alder reaction slowed the reaction, which was taken as evidence that the special ability of water to enhance the rate of the Diels–Alder reaction was due to a hydrophobic effect.[121]

An aqueous environment creates a medium where the "reactants orient themselves within a micelle, thereby increasing their effective molarity and, consequently, the rate."[122] Liotta, however, points out that reaction of 2,6-dimethylbenzoquinone (**119**) and diene carbonate **118** showed no rate enhancement in water relative to the same reaction in benzene. The carbonate was essentially insoluble in water and rate enhancement requires at least partial solubility of the diene and/or dienophile in the aqueous medium. Liotta showed that other solvents enhance molecular aggregation while maintaining the solubility of the reactants. Ethylene glycol, for example, showed a large rate enhancement for the reaction of **118** and **119** to give **120**. The influence of several solvents, along with their relative dielectric constants and relative rates (reaction in benzene is taken as the standard), is shown in Table 11.7.[122] Liotta explains this effect by comparing **121** and **122** in Figure 11.12,[122]

Table 11.7 Rate Enhancement of Solvents of Varying Dielectric Constant on the Diels–Alder Reaction of 118 and 119



118 **119** **120**

Solvent	Dielectric Constant	Relative Rate
C_6D_6	2.3	1.0
$CD_3C{\equiv}N$	36.2	1.8
$CD_3S(=O)CD_3$	46.6	3.1
CD_3OD	32.6	4.1
D_2O	78.0	No reaction
$HOCH_2CH_2OH$	37.7	26.1

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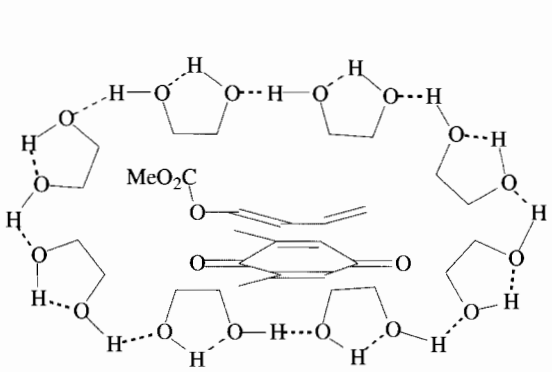
where the π-stacked arrangement in the micelle (**121**) assumes a smaller volume and is probably preferred. The larger micelle volumes in the end-on arrangement (**122**) will disrupt hydrogen bonding and be higher in energy. The smaller volume of **121** will retain the maximum hydrogen bonding and minimize disruption.[122]



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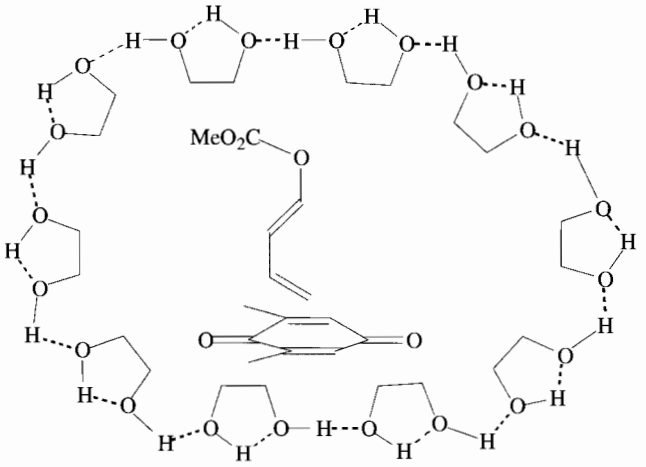

117

Figure 11.12. π Stacked versus end-on arrangement in the micelle of aqueous Diels–Alder reactions.

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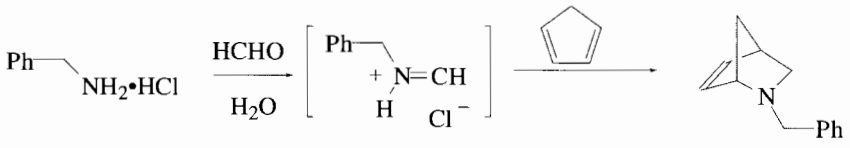
]

Grieco and co-workers also showed that iminium salts such as **123**, formed by reaction of an amine and formaldehyde (sec. 4.4) reacted with cyclopentadiene in aqueous media to give a near-quantitative yield of the Diels–Alder adduct.[123] An internal Diels–Alder reaction was also possible (sec. 11.8). Treatment of an aqueous solution of **124** with formaldehyde at 50°C gave a 98% yield of indolizidine **125**.[123]



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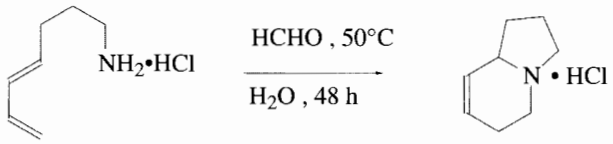


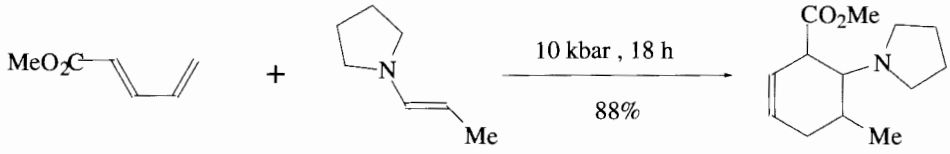
124 **125**

The use of highly polar media such as water clearly assists the Diels–Alder reaction, and similar rate enhancement has been observed in other reactions. Grieco et al. showed that 5.0 M lithium perchlorate in diethyl ether is an effective medium for these reactions.[124] There is a problem, however, because weak acids in highly polar media such as this become strong acids, and protonation of dienes in intramolecular reactions can lead to diene isomerization that is competitive with cycloaddition.[125] Grieco and Kaufman found that for such

reactions, water is the polar medium of choice.[125] Recently, Augé found that lithium trifluoromethanesulfonate in ether or acetonitrile is a useful substitute for lithium perchlorate in cycloaddition reactions.[126]

11.6.C. Rate Enhancement under High–Pressure Conditions

The rate of Diels–Alder reactions can be increased by the application of high pressure. An early example by Dauben and Kozikowski demonstrated that methyl 1-pentadienoate reacted with **126** to give **127** in 88% yield.[127] Applications of high-pressure techniques to organic synthesis are enumerated in an excellent review by Matsumoto[128] as well as in his monograph.[129] The second part of this review[129] deals with high-pressure pericyclic reactions, including Diels–Alder reactions.



126 **127**

The thermodynamic properties of solutions are well known, and the rate of a reaction can be expressed in terms of the activation volume, $\Delta V^{\ddagger}$

$$\frac{\delta \ln k}{\delta p} = \frac{\Delta V^{\ddagger}}{RT} \qquad 11.4$$

"The activation volume is the difference in partial molal volume between the transition state and the initial state. From a synthetic point of view this could be approximated by the molar volume."[128] If the volume of activation is negative, Equation (11.4) suggests that the rate of the reaction will be accelerated by increasing pressure. As the pressure increases, the value of $\Delta V^{\ddagger}$ decreases and the system does not strictly obey equation (11.4) > 10 kbar (1 bar = 0.986924 atm. = 1.1019716 kg cm^{-2}). Considerable information has been collected concerning $\Delta V^{\ddagger}$, principally from work by le Noble.[130] If the transition state of a reaction involves bond formation, concentration of charge, or ionization, a negative volume of activation often results. Cleavage of a bond, dispersal of charge, or neutralization of the transition state and diffusion control lead to a positive volume of activation. Matsumoto summarizes the reactions for which rate enhancement is expected at high pressure.[128]

1. Reactions in which the molecularity number (number of molecules) decreases when starting materials are converted to products: cycloadditions, condensations.
2. Reactions that proceed via cyclic transition states: Claisen and Cope rearrangements (sec. 11.12.D and 11.11.C, respectively).
3. Reactions that take place through dipolar transition states: **Menschutkin reaction** (of tertiary amines with alkyl halides to produce quaternary ammonium halides)[131], electrophilic aromatic substitution.
4. Reactions with steric hindrance.

Table 11.8[128] shows the variation of rate constants with pressure. Many high-pressure reactions are done neat, but if a solvent is used, the influence of pressure on that solvent is important. The melting point generally increases at elevated pressures, and this influences the viscosity of the medium (the viscosity of liquids

increases approximately two times per kilobar increase in pressure). Controlling the rate of diffusion of reactants in the medium is also important, leading to another influence of high pressure on reactivity.[128,132] In most reactions, pressure is applied (5–20 kbar) at room temperature and then the temperature is increased until reaction takes place. The temperature is lowered and the pressure is reduced to isolate the products.

Table 11.8. Variations of Rate Constants with Pressure

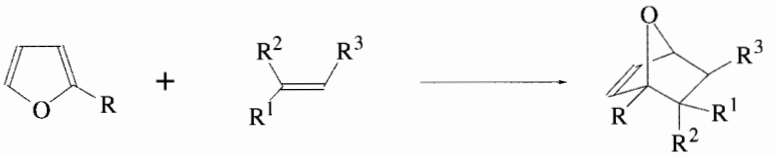
$\Delta V^{\ddagger}$	Temperature	k_p/k_1[a] ($\Delta GG^{\ddagger}$ (kJ mol^{-1}))					
(cm^{3}mol^{-1})	(°C)	5 kbar	10 kbar	15 kbar	20 kbar	30 kbar	50 kbar
–10	25	7.5	57	430	3200	1.810^5	$7.5x10^8$
	50	6.4	41	270	1700	$7.1x10^4$	$1.5x10^8$
	100	5.0	25	130	630	$1.6x10^4$	$1.2x10^7$
		(–5)	(–10)	(–15)	(–20)	(–30)	(–50)
–20	25	57	3200	$1.8x10^5$	$1.0x10^7$	$3.3x10^{10}$	$5.6x10^{17}$
	50	41	1700	$7.1x10^4$	$2.9x10^6$	$5.0x10^9$	$2.4x10^{16}$
	100	25	630	$1.6x10^4$	$4.0x10^5$	$2.5x10^8$	$1.5x10^{14}$
		(–10)	(–20)	(–30)	(–40)	(–60)	(–100)
–30	25	430	$1.8x10^5$	$7.7x10^7$	$3.3x10^{10}$	$6.0x10^{15}$	$4.2x10^{26}$
	50	270	$7.1x10^4$	$1.9x10^7$	$5.0x10^9$	$3.6x10^{14}$	$3.7x10^{24}$
	100	130	$1.6x10^4$	$2.0x10^6$	$2.5x10^8$	$4.0x10^{12}$	$1.9x10^{21}$
		(–15)	(–30)	(–45)	(–60)	(–90)	(–150)

[a] k_p = rate constant under high pressure, k_1 = rate constant at atmospheric pressure.

[Reprinted from Matsumoto, K; Sera, A.; Uchida, T. *Synthesis, **1985***, pp. 1. Copyright 1985 by Georg Thieme Verlag.]

Diels–Alder reactions with furans can be very problematic due to the thermal sensitivity of the cycloadduct and their tendency for cycloreversion, which is due to the strain inherent to the 7-oxabicycloheptane cycloadduct (**128**) as well as the aromatic character of the furan. As shown in Table 11.9,[128] high pressure significantly increases the yield of Diels–Alder adduct with furan derivatives. 2-Methylfuran is more reactive than furan but substituents on the alkene (dienophile) lower the

Table 11.9. Diels–Alder Adducts of Furan Derivatives and Mono-Activated Dienophiles



128

R	R^1	R^2	R^3	Reaction conditions[a]	% 128
H	CN	H	H	Neat, 0.001 kbar.RT.5 weeks	39
				Neat, Cu(I), 0.001 kbar, RT, 9 days	48
				Neat, ZnI_2, 0.001 kbar, 40°C, 2 days	100

				CH_2Cl_2, 15 kbar, RT, 4 h	55
H	CO_2Me	H	H	Neat, 0.001 kbar, 40°C, 1 month	18
				Neat, 0.001 kbar, RT, 2-3 months	50
				Neat, Cu(I), 0.001 kbar, RT, 14 days	33
				Neat, ZnI_2, 0.001 kbar, 40°C, 2 days	55
				CH_2Cl_2, 15 kbar, RT, 4 h	62
H	CHO	H	H	CH_2Cl_2, 15 kbar, RT, 4 h	53
H	CO_2Me	H	H	CH_2Cl_2, 15 kbar, RT, 4 h	48
H	CO_2Me	H	Me	Neat, Cu(I), 0.001 kbar, RT	0
				CH_2Cl_2, 15 kbar, RT, 14 h	6
H	CHO	H	Me	CH_2Cl_2, 15 kbar, RT, 8 h	24
H	CO_2Me	H	Me	CH_2Cl_2, 15 kbar, RT, 8 h	20
H	CO_2Me	Me	H	CH_2Cl_2, 13.5 kbar, RT, 8 h	8
H	CHO	Me	H	CH_2Cl_2, 13.5 kbar, RT, 8 h	7
Me	CN	H	H	CH_2Cl_2, 13.5 kbar, 37.2°C, 24 h	100
Me	CO_2Me	H	H	CH_2Cl_2, 13.5 kbar, 37.2°C, 24 h	100
Me	CHO	H	H	CH_2Cl_2, 13.5 kbar, 37.2°C, 23 h	100
Me	CO_2Me	H	Me	CH_2Cl_2, 13.5 kbar, 37.2°C, 23.5 h	43
Me	CHO	H	Me	CH_2Cl_2, 13.5 kbar, 37.2°C, 25 h	>50

[a] High pressure is underlined.

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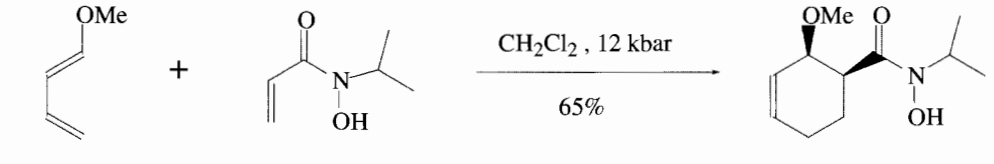
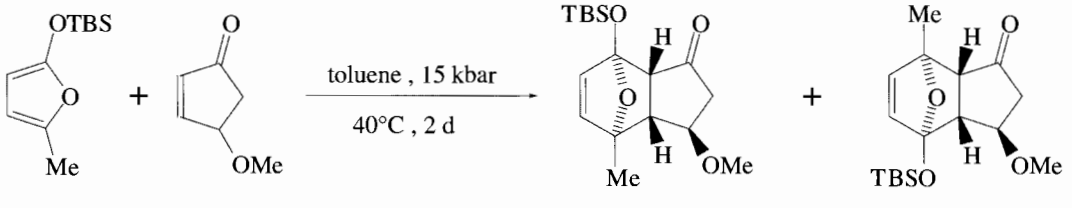
yield of the cycloadduct, even under high pressure. In all other cases, however, it is clear that reaction at 15.0 or 13.5 kbar, in dichloromethane as a solvent, leads to fast reactions and yields approaching those obtained with Lewis acid catalysts and long reaction times. One synthetic example is Weinreb's reaction of 1-methoxy-1,3-butadiene with conjugated amide **129** in dichloromethane at 12 kbar, giving a 65% yield of **130** in a synthesis of peduncularine.[133]



129 **130**

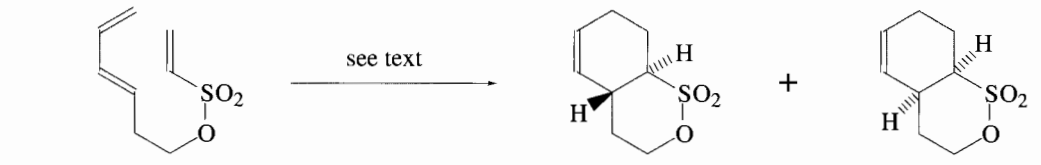


131 **132** **133**

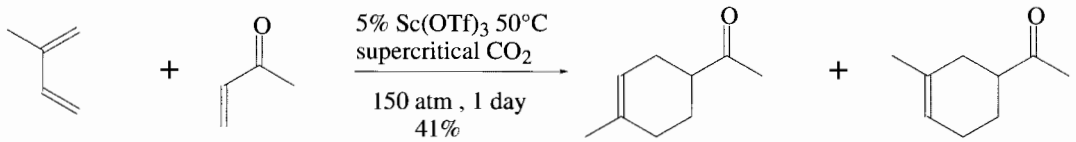
Furan also reacts with benzoquinone (at 20 kbar) to give a 14% yield of the endo adduct and a 15% yield of the exo adduct, along with 71% of unreacted benzoquinone.[134] Better results are obtained with functionalized furans such as **131**, which reacted with 4-methyl-2-cyclopentenone at 15 kbar to give a 1:2 mixture of **132/133** in 95% yield (2 days) in Ghosez's synthesis of polyfunctionalized cis-hydrindanones.[135]

Cycloaddition with 2-pyrones usually requires high temperatures and the products often lose carbon dioxide in a retro-Diels–Alder reaction.[136] Pyridones also react at high pressure to give the cycloadduct,[137] although heating at atmospheric pressure usually gives no reaction at all.[137] A variety of relatively unreactive dienes and/or dienophiles give enhanced yield of cycloadducts under pressure. Naphthalene reacted with maleic anhydride at 9.5 kbar and 100°C.[138] Acetaldehyde reacted with 1-methoxybutadiene (sealed tube, 160–180°C, 6 h) to give only 2% of the dihydropyran cycloadduct.[139] When the reaction was done neat, at 14 kbar and 80°C for 6 h, 50% of pyran was obtained[139] and reaction in ether at 20 kbar (65°C, 5 h)[140] gave 62% of pyran. Dienamines reacted with conjugated esters at 13.9 kbar to give 70% of an enamine cycloadduct.[141,127]

It has been shown that intermolecular Diels–Alder reactions have a large negative volume of activation (≈ –25 to –45 cm^3 mol^{-1})[142] and a large negative volume of reaction. The activation volume for intramolecular Diels–Alder reactions was measured as –25 cm^3 mol^{-1}.[143] Intramolecular Diels–Alder reactions do not always respond to high pressure, although the effects on the intermolecular Diels–Alder can be dramatic.[127,141] There are exceptions, however, and high pressure has been applied to intramolecular Diels–Alder reactions.[144] In one example, **134** could be cyclized to give a 1:1 mixture of **135/136** in refluxing toluene at ambient pressure.[145] In order to suppress side reactions, a small amount of the radical scavenger BHT (2,6-di-*tert*-butyl-4-phenylphenol) was used. When this reaction was done at 13 kbar, in dichloromethane at room temperature, an 88% yield of a 1:2.3 mixture of **135/136** was obtained, without the need for added BHT. It is noted that attempts to cyclize **134** using several Lewis acids were not successful. Intramolecular Diels–Alder reactions will be discussed in Section 11.8.



134 **135** **136**



137 **138**

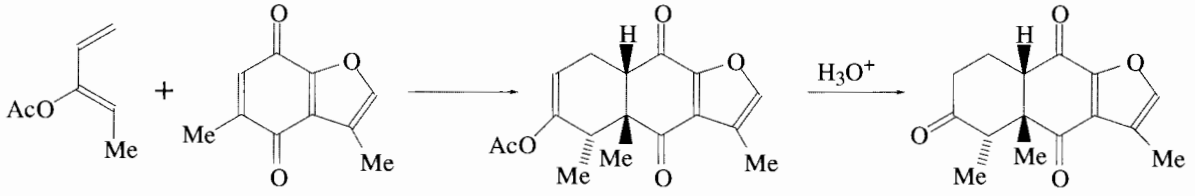
A variation in this technique has recently been reported, although not necessarily using the high pressures described above. Diels–Alder reactions can be done under pressure in supercritical carbon dioxide., although the synthetic application may be limited by slow reaction rates.[146] Addition of a Lewis acid appears to overcome this problem, as in Kobayashi's use of scandium triflate in the reaction of methyl vinyl ketone with 2-methyl-1,3-butadiene to give a 93:7 mixture of **137/138**.[147a] Rayner and co-workers had previously reported the use of scandium triflate in supercritical CO_2,[147b] and observed that the maximum selectivity was obtained at a density of 1.12 g mL^{-1}.

11.7. HETEROATOM DIELS–ALDER REACTIONS

The Diels–Alder reaction is quite remarkable in its scope. One of the more attractive features is the ability to incorporate heteroatoms into either the diene, or the alkene unit, generating heterocyclic compounds. This section will examine several of the more useful variations.

11.7.A. Heteroatom Substituents

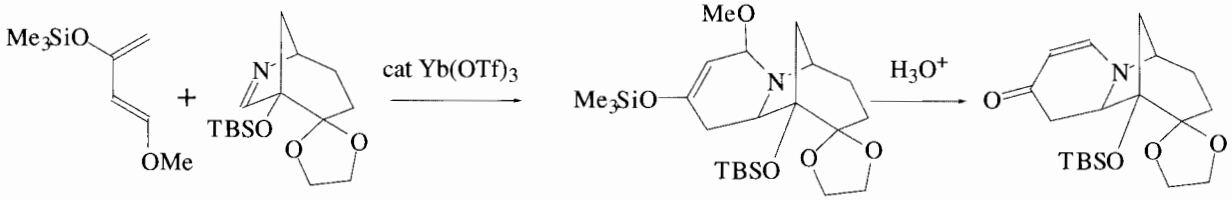
In previous sections, several examples were shown using alkoxydienes or alkoxyalkenes. Acyloxy dienes are very useful in organic synthesis. One example is Bohlmann's synthesis of liglularone, which used acetoxydiene **139** in a reaction with quinone **140** to give **141**.[148] An attractive feature of dienes that contain a vinyl



139 **140** **141** **142**

ether or vinyl ester moiety is the facile hydrolysis of the cycloadduct (the vinyl ester unit in **141**) to give a ketone (**142**). This reaction is analogous to the hydrolysis of the vinyl ether products observed with the Birch reduction (sec. 4.9.E).

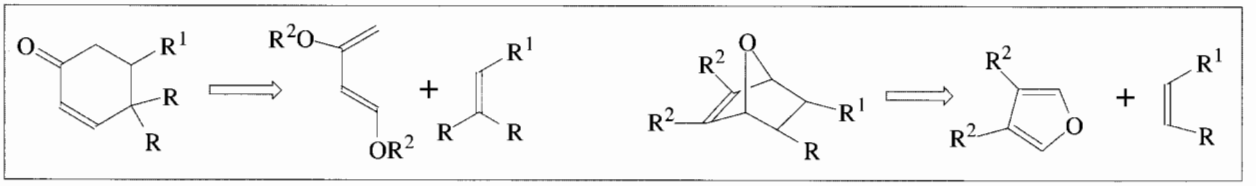
Danishefsky used a variety of silyloxybutadienes in Diels–Alder reactions[149] in place of alkoxy and acetoxy derivatives. Treatment of these cycloadduct siloxy derivatives with fluoride (sec. 7.3.A.i) will unmask an enol moiety, which tautomerizes to the carbonyl under very mild conditions. Silyloxy dienes have become very popular for this type of reaction. In Weinreb's synthesis of phyllanthine,[150] imine **144** reacted with diene **143**[151] in the presence of $Yb(OTf)_3$ to give **145**. Hydrolysis converted this functionality to the conjugated ketone **146** in 84% overall yield. The previous development of **143** as a reagent was due to several unsuccess-



143 **144** **145** **146**

ful attempts to prepare large quantities of 1,3-diethoxy-1,3-butadiene.[151c] The preparation of the silyl enol ether was significantly easier than the preparation of the corresponding enol ether.[152] Diene **143** is commercially available and has come to be called **Danishefsky's diene**. This diene or analogs have been very useful for a variety of natural product syntheses.[151a] Many structural variations are possible for the alkoxybutadiene partner in the Diels–Alder reaction. Chiral heterosubstituted 1,3-butadienes are now common in [4+2]-cycloaddition reactions.[153]

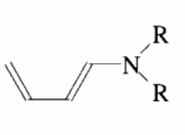
It is clear from these examples that oxygenated dienes are convenient and useful precursors to cyclohexenones and 7-oxabicycloheptane derivatives. Typical disconnections for oxygenated dienes are



11.7.B. Amino and Amido Dienes

Azadienes (amino or amido dienes) constitute another important class of hetero-substituted dienes. There are three major types, amino dienes such as **147**, amido dienes such as **148**, and carbamoyl dienes such as **149**. Both 1- and 2-substituted aminodienes are possible and function as diene partners in Diels–Alder reactions.

Enamines have been used as dienophiles in several previous examples. There are a few examples of Diels–Alder reactions with 1-(dialkylamino)-1,3-butadienes. [154] It is noted that a density functional study of the Diels–Alder reaction of 1,2-diaza-1,3-butadiene with alkenes showed the transition state to be concerted but



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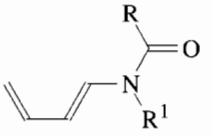

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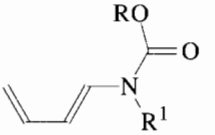
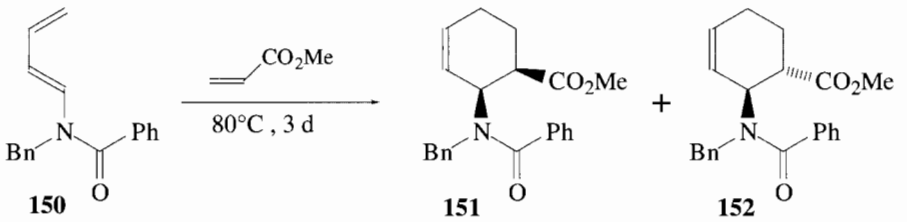


149

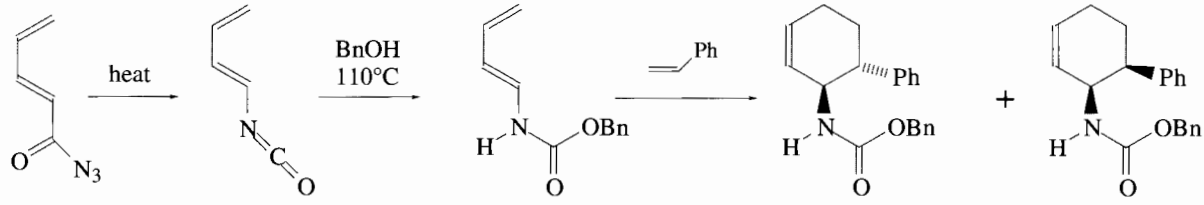
asynchronous.[155] The allylic amine cycloadducts of this reaction show a propensity for elimination, and this has led to the use of dienyl amides (**148**) and carbamates (**149**), whose cycloadducts are significantly more stable and easier to isolate.[156] The conversion of **73** to **74** in Section 11.4.C.iii used a diene of this type (see above). In another example, Oppolzer et al. showed that **150** reacted with methyl acrylate to give 73% of **151** and 18% of **152**.[157] The endo- (cis-) selectivity is apparent in this example and is general for this class of dienes. Amido dienes such as **151** are prepared by reaction of crotonaldehyde with an amine, a base, and an acid chloride.[158] Similarly, Overman prepared dienyl carbamate **153** via a **Curtius rearrangement**[159] (a



150 **151** **152**

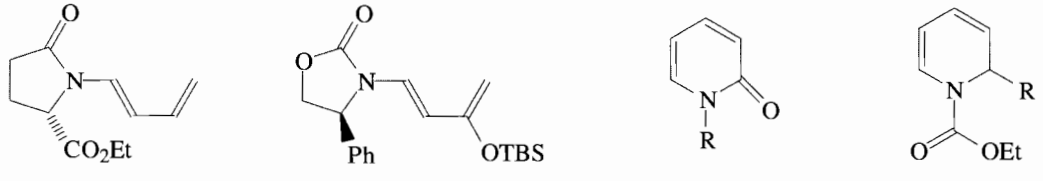
thermal rearrangement of a diazoketone to an isocyanate; dienyl azido ketone **153** → **154**). Heating with benzyl alcohol gave carbamate **155**.[160] Overman and co-workers also found thermolysis of trichloroacetimidic esters of propargyl alcohols generated trichloromethyl dienyl carbamates.[161,162] Dienyl carbamate reacted with styrene to give a quantitative yield of a mixture of **156** and **157** in a 93:7 ratio.[163] 1-Amino-3-siloxy-1,3-butadienes also react with unactivated aldehydes under very mild conditions, at room temperature and in the absence of Lewis acids.[164] Dienyl lactams such as **158** have also been prepared and shown to

undergo Diels–Alder reactions.[165] The same ortho and endo selectivity that was observed with dienyl amides was observed when N-(1,3-butadienyl)-2-pyrrolidinone reacted with ethyl acrylate and other alkenes.[165c] When chiral lactam **158** reacted with ethyl acrylate, the cycloadduct was formed with excellent enantioselectivity.[165d] Rawal prepared **159** and showed that Diels–Alder reactions proceed in good yield and with moderate-to-excellent stereoselectivity.[166]



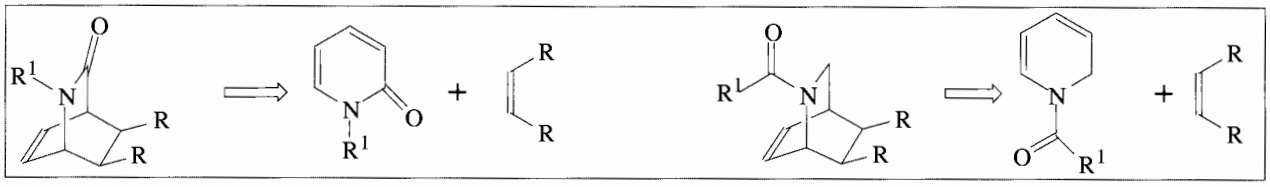
153 **154** **155** **156** **157**

There are two other classes of dienyl lactams that have been used synthetically, *N*-alkyl-2-pyridones (**160**) and *N*-acyl-1,2-dihydropyridines (**161**). Pyridones tend to be relatively unreactive, requiring high temperatures and often giving low yields of the cycloadduct.[167] *N*-Acyl pyrrole derivatives also function as diene partners in the Diels–Alder reaction.[168]



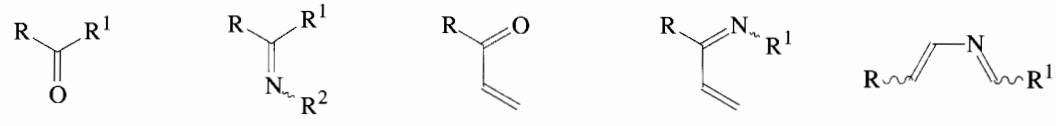
158 **159** **160** **161**

Nitrogen containing dienes lead to useful synthetic disconnections such as



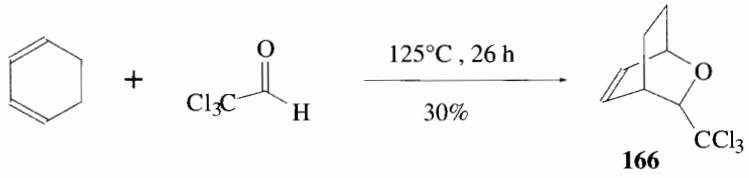
11.7.C. Heteroatom Dienes and Heteroatom Alkene Dienophiles

Heteroatoms can be incorporated into the π framework of either the alkene partner or the diene partner of Diels–Alder reactions. This section will focus on two structural types that function as dienophiles: ketones or aldehydes, and imines (**162**), as well as three types that function as dienes: conjugated carbonyls (**163**), 1-azadienes (**164**), and 2-azadienes (**165**). The use of heteroatom dienes and alkenes in organic synthesis was thoroughly reviewed in the monograph of Boger and Weinreb[169] and that of Fringuelli and Taticchi.[170]



(R,R^1 = alkyl, H) **162** **163** **164** **165**

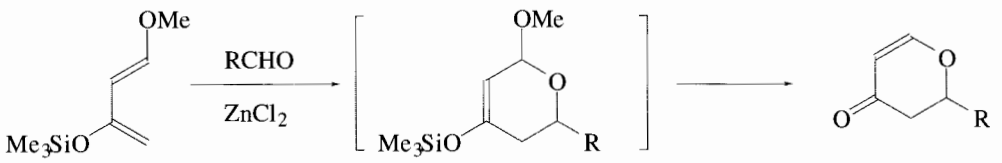
11.7.C.i. Aldehydes and Ketones. Although simple aldehydes and ketones do not react very well in uncatalyzed reactions, electron-deficient aldehydes and ketones are good partners. Chloral, for example, reacts with cyclohexadiene to give **166**.[171] Glyoxalates (RO_2CCHO) also add to dienes.[172] The carbonyl moiety of electron deficient ketones also functions as a dienophile.[173a] Other ketone dienophiles require elevated temperatures and or high pressure in order to obtain good reactivity.[173]



166

As mentioned, relatively simple aliphatic and aromatic aldehydes are unreactive except with very reactive dienes, and the reaction usually requires Lewis acid catalysis.[174] Danishefsky and co-workers showed that γ-pyrones such as **168** could be formed by reaction of aldehydes with Danishefsky's diene (**143**), catalyzed by zinc chloride.[175] The initial cycloadduct (**167**, see Table 11.10)[175] was hydrolyzed to pyrone **168**.

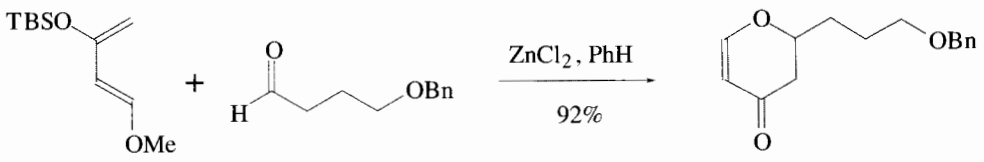
Table 11.10. Pyrone Formation by Reaction of Danishefsky's Diene with Aldehydes



143 **167** **168**

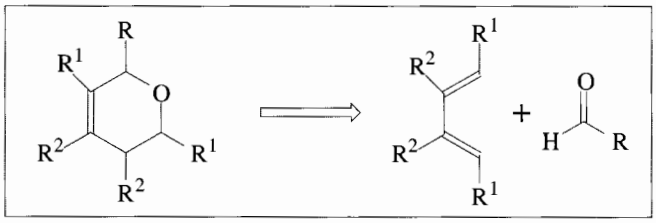
R	% 168
H	55
Ph	65
Me	17
Et	48
i-Pr	43
$CH{=}CH_2$	50
(*E*)—CH=CHPh	25
CH_2OBn	87
CH_2SPh	70
CH_2NHCbz	80

[Reprinted with permission from Danishefsky, S.; Kerwin Jr., J.F.; Kobayashi, S. *J. Am. Chem. Soc.*, ***1982***, *104*, 358. Copyright © 1982 American Chemical Society.]

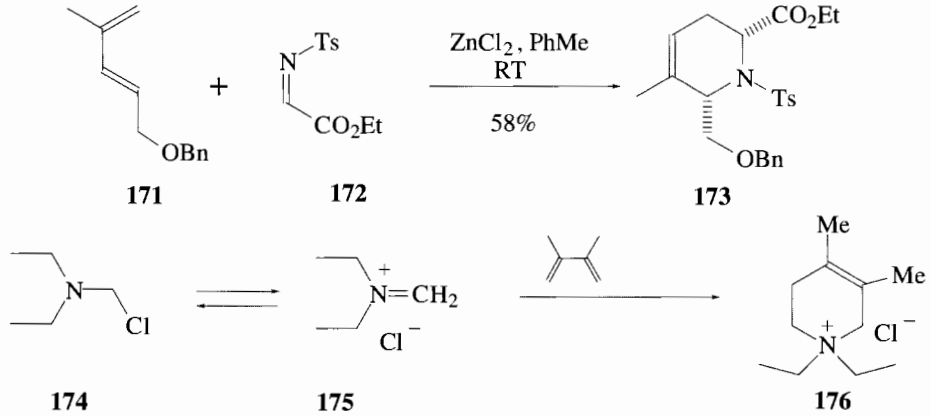


169 **170**

In Rainier's synthesis of the hemibrevetoxin B ring system,[176] diene **169**, which is obviously related to Danishefsky's diene, reacted with *O*-benzyl 4-hydroxybenzaldehyde, in the presence of zinc chloride, to give **170** in 92% yield. Pyrones and pyrans are particularly useful for the preparation of acyclic precursors to macrocyclic antibiotics. The stereochemistry of the highly oxygenated acyclic fragment can be controlled by exploiting the selectivity inherent in the cyclic pyran (sec. 6.5).[177,178] The disconnection for this reaction is



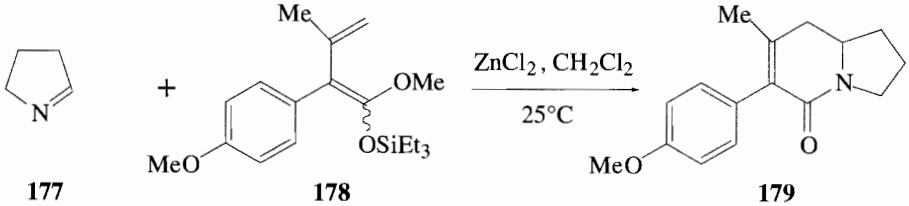
11.7.C.ii. Imines. Imines are used less often as dienophiles, but there are examples. Iminium salts are also known dienophiles. Simple imines are usually generated *in situ*, although more useful imines can be stabilized by the presence of electron-withdrawing groups on the nitrogen. N-Tosyl imines such as **172**, for example,



171 **172** **173**

174 **175** **176**

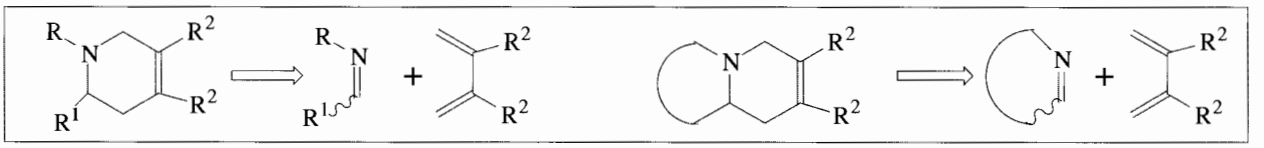
can be isolated. When reacted with diene **171**, a 58% yield of tetrahydropyridine (**173**) was obtained as part of Weinreb's synthesis of cylindrospermopsin.[179] N-Acyl imines react similarly via the corresponding iminium salt. Bis(carbamates) are precursors to iminium salts that undergo Diels–Alder reactions.[180] Böhme generated iminium salt **175** from chloromethylamine **174**, and subsequent reaction with 2,3-dimethylbutadiene gave **176**



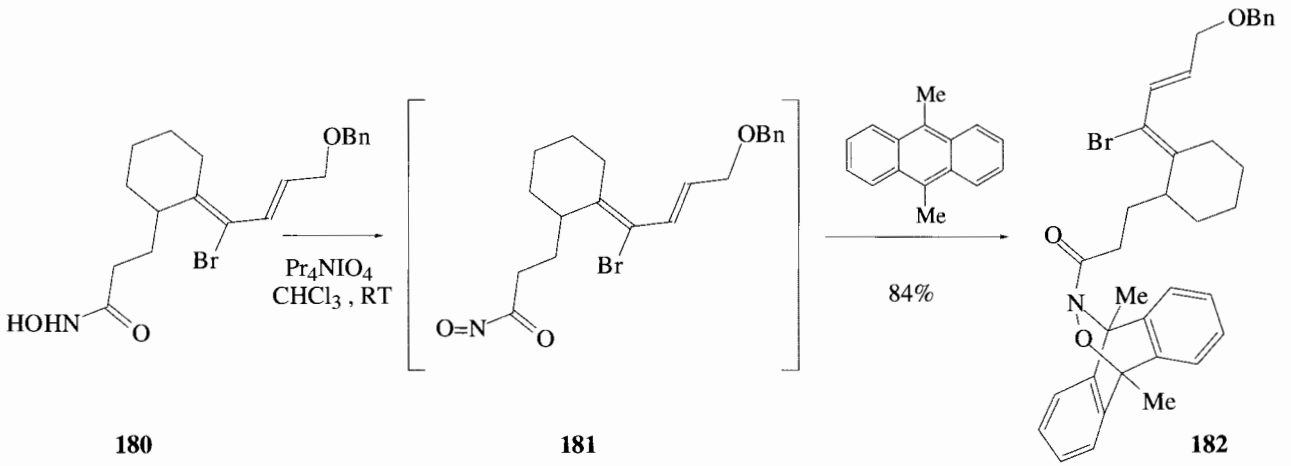
177 **178** **179**

in 69% yield.[181] Grieco's previously cited preparation and Diels–Alder reaction of iminium salt **118** and the one derived from amine **120** in aqueous media are related to this type of cycloaddition (sec. 11.6.B). Formation of nitrogen-containing cycloadducts via Diels–Alder reactions is an attractive route for the synthesis of

alkaloids. Even simple imines can function as dienophiles. Danishefsky and Vogel reacted pyrroline (**17**) with siloxydiene **178** to give **179** in a synthesis of ipalbidine.[182] A large variety of stable imines are easily prepared, making this technique valuable for the preparation of nitrogen-containing cyclic and polycyclic molecules. Catalytic asymmetric hetero-Diels–Alder reactions using imines are known.[183] Two important disconnections for this type of Diels–Alder reactions are

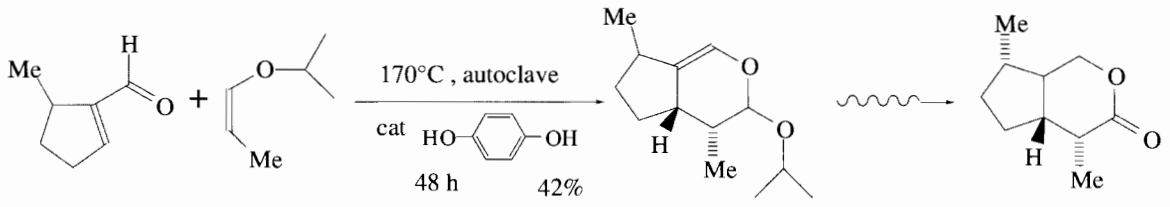


11.7.C.iii. Nitroso-Type Compounds. Nitroso compounds (R—N=O) show reactivity as dienophiles in Diels–Alder reactions, giving heterocyclic rings. In Kibayashi's synthesis of fasicularin,[184a] for example, hydroxamic acid **180** was treated with tetrapropylammonium periodate in the presence of 9,10-dimethylanthracene to give transient acylnitroso compound **181**, and the resultant Diels Alder product **182** was formed in 84% yield. In this particular example, the Diels-Alder adduct essentially "protected" the acyl nitroso unit, which was used in a subsequent reaction.



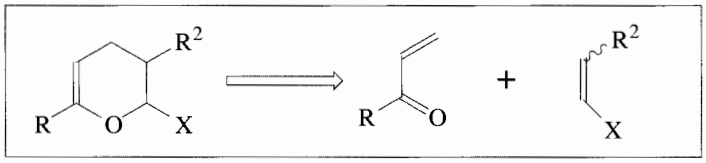
180 **181** **182**

11.7.C.iv. Conjugated Aldehydes and Ketones. Conjugated aldehydes and ketones function as dienes, in addition to their better known capabilities as dienophiles, as observed by Sherlin et al.[185] Methyl vinyl ketone reacted with acrolein, for example, but this gave only 15% of a pyran cycloadduct in Mundy's synthesis of brevicomin.[186] However, pyran formation by this reaction is well known,[187] and 2-substituted 3,4-dihydropyrans are the major products in almost all cases, which is obviously related to the reaction of aldehydes with dienes, but provides pyran products with regiochemical differences relative to those prepared in sec. 11.7.C.i. Both Lewis acid catalysis and high-pressure techniques facilitate the cycloaddition. Electron deficient alkenes can also react as dienophiles with conjugated carbonyl derivatives,[188] but electron rich alkenes (such as methyl vinyl ether) also react. An example is the reaction of **183** with **184** to give 42% of **185** in Korte's synthesis of *dl,iso*-iridomyrmecin (**186**).[189] Boger and Weinreb provide many additional reactions of this type of cycloaddition.[190]

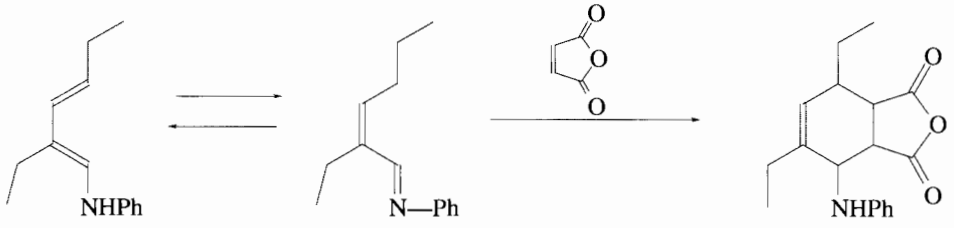


183 **184** **185** **186**

The disconnection for this Diels–Alder reaction is

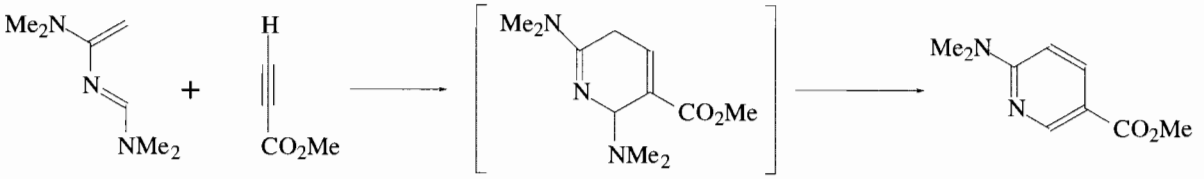


11.7.C.v. Azadienes. Azadienes such as **163** and **164** are useful diene partners that can be used for the preparation of many heterocycles and alkaloids.[191] The utility of 1-azadienes in the Diels–Alder reaction is limited by the fact that isomerization occurs to give a conjugated imine, probably via a proton transfer. An example is the equilibration of **187** and **188**. Addition of maleic anhydride to this mixture gave the Diels–Alder adduct derived from aminobutadiene (**187**), and the cycloadduct **189**.[192] Even when isomerization is prevented, the aminobutadiene is relatively unreactive and the yields can be poor. An important side reaction is a competitive [2+2]-cycloaddition (sec. 11.10.A), which often leads to poor yields of the [4+2]-cycloadduct.[193,194] Incorporation of tertiary alkyl substituents are also used to stabilize the 1-azadiene.

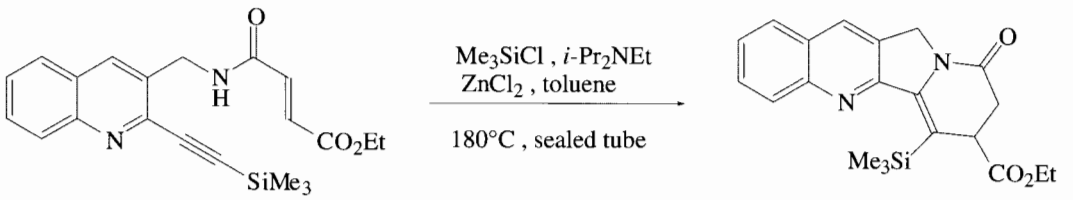


187 **188** **189**

2-Azadienes such as **190** were prepared by Ghosez and then reacted with conjugated alkynes [such as the methyl propiolate (**191**)] to give cycloadducts such as **192**, which is an interesting choice of aza-diene because facile loss of dimethylamine led to aromatization and pyridine derivative **193**.[195] The usual azadiene–aminobutadiene rearrangement is impossible in **190** and the dimethylamino moieties further stabilize the azadiene structure. Ghosez also used 2-azadienes that were stabilized by the presence of silyloxy groups.[195] 2-Azadienes give a normal Diels–Alder reaction with classical dienophiles. Once again, Boger and Weinreb discuss many examples of 1- and 2-azadienes in Diels–Alder reactions.[196] An interesting variation was used in the Toyota et al. synthesis of mappicine,[197] in which **194** was treated with $ZnCl_2$, chlorotrimethylsilane, and Hünigs base. Initial formation of the OTMS imine allowed the intramolecular Diels–Alder reaction with the alkyne unit to give a 76% yield of **195**.

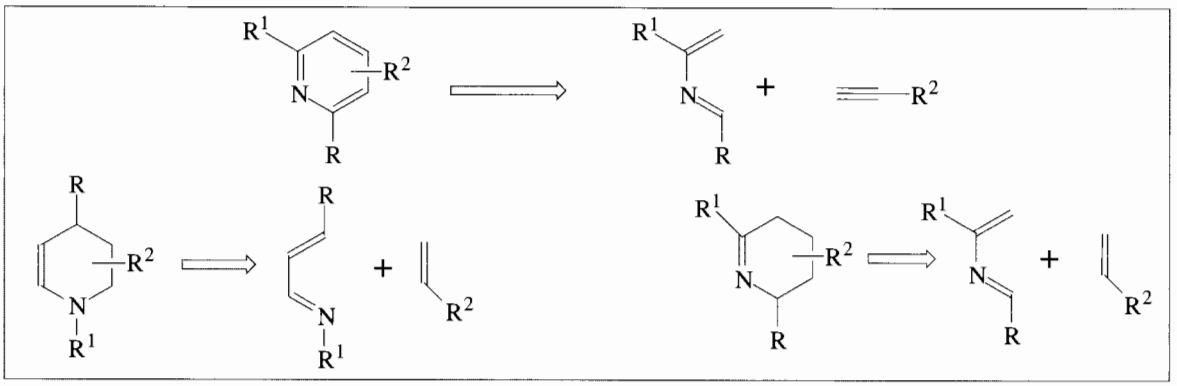


190 **191** **192** **193**



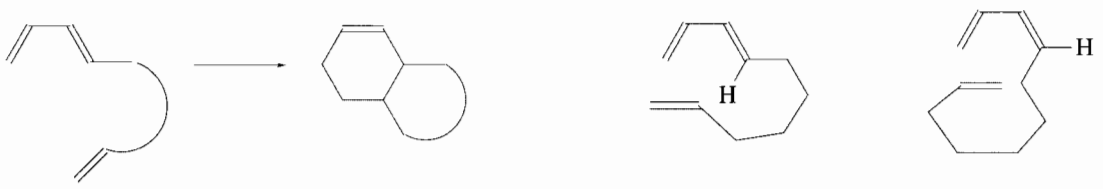
194 **195**

The synthetic utility of azadienes Diels–Alder reactions lies in the synthesis of heterocycles and alkaloids. Three disconnections related to this section are



11.8. INTRAMOLECULAR DIELS–ALDER REACTIONS

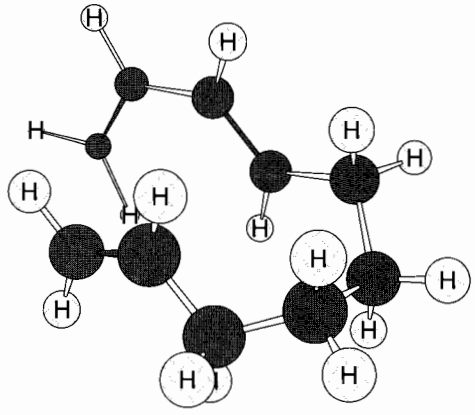
If the diene and alkene are connected by an intervening chain of atoms, the Diels–Alder reaction can occur intramolecularly, illustrated by the conversion of **196** to **197**. This reaction has become one of the most powerful



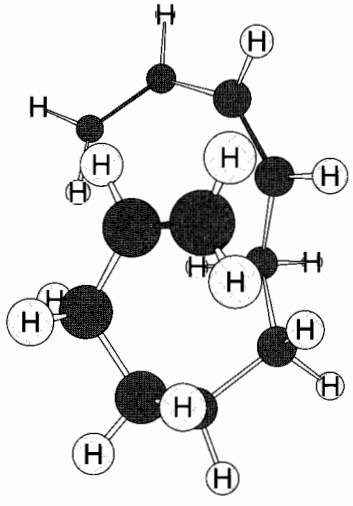
196 **197** **198A** **199A**

synthetic methods (sec. 10.5.B.vi) for constructing cyclic compounds with high regio- and stereoselectivity.[198] There is much interest in intramolecular Diels–Alder reactions and many reviews, including those by Carlson in 1974,[199] Oppolzer in 1977,[200] Brieger and Bennett in 1980,[201] Fallis in 1984,[202] and Smith in 1990.[156]

Virtually all of the intermolecular reactions shown in previous sections have intramolecular analogs. Close approach of the diene and alkene is sometimes inhibited by the atoms that link the two (the **tether**). The geometry of the diene and alkene (*E*) or (*Z*) also plays a role, which can be illustrated by comparing the intramolecular Diels–Alder reactions of **198A** and **199A**. trans-Diene **198A** readily attains the proper geometry for reaction (see 3D-drawing **198B**) with the methylene groups in the tether assuming a relatively normal conformation for a small ring. The cis-diene **199A**, however, requires significant distortion of the methylene groups in the tether to attain the proper orientation of diene and alkene for the cycloaddition (see **199B**).

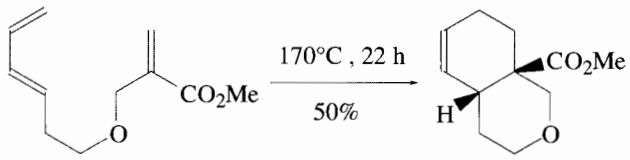


198B

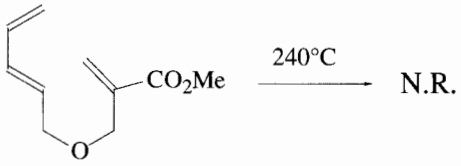


199B

The ***length*** of the tether is very important.[203,204] Boeckman showed that Diels–Alder cyclization of **200** gave 50% of a 70:30 mixture (βH/αH = cis/trans) of **201.**[205] Attempted cyclization of **202**, which has fewer carbons in the tether, gave no cyclized product. This latter example shows a preference for the transoid conformation and has a higher energy of activation for interconversion of the two rotamers than does **200**.[205,206a]



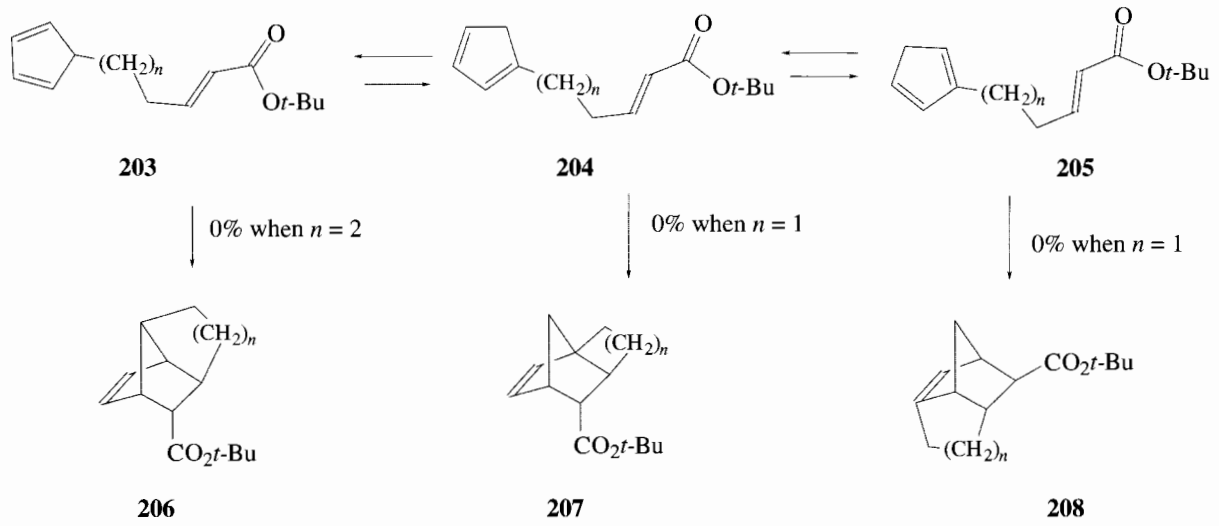
200 **201**



202

The influence of the tether length is particularly striking in the substituted cyclopentadienes examined by Stille and Grubbs.[207] Each cyclopentadiene derivative is in equilibrium with three isomers, the 1-substituted, 2-substituted, and 3-substituted cyclopentadienes. A two-carbon tether (n = 1), as in **203** → **205**, gave 53% of **206** when heated in benzene.[207] The 2-substituted derivative (**204**) and 3-substituted derivative (**207**) gave no cycloadduct (**207** and **208**, respectively, where n = 1), presumably due to the difficulty in forming the four-membered ring in **207** and attaining the proper geometry for the bridgehead π bond in **208** (see **Bredt's rule** in sec. 6.6.A). The endo-transition state required to generate **206** is relatively easy to achieve. Adding one

carbon to the tether (**203**, n = 2), however, and heating led to a 6.4:1 mixture of **207** and **208** (n = 2).[207] The cyclization of **203** → **206** (n = 2) was *not* observed. The 2-substituted derivative gave the highest yield of cyclized product when n = 2.[207] Adding a total of four carbons to the tether gave results similar to when n = 2 in **203–205**.[207] These examples clearly show that the length and nature of the tether is important and inspection of all possible transition states is essential for predicting the cycloadducts arising from intramolecular Diels–Alder reactions.



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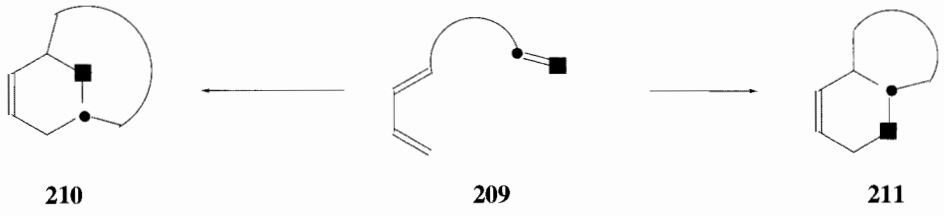
In addition to the problems concerning reactivity and the nature of the tether, at least two different regioisomers are possible for internal Diels–Alder reactions (**210** and **211** from **209**), depending on the orientation of the alkene as it approaches the diene. If the tether is short, only **211** is possible, but with longer tethers **210** can be a side product or even the major product. An example taken from Thomas' studies on the synthesis of cytochalasin is an intramolecular Diels–Alder reaction of **212** that gave a 27:5% mixture of **213** and **214**.[208]



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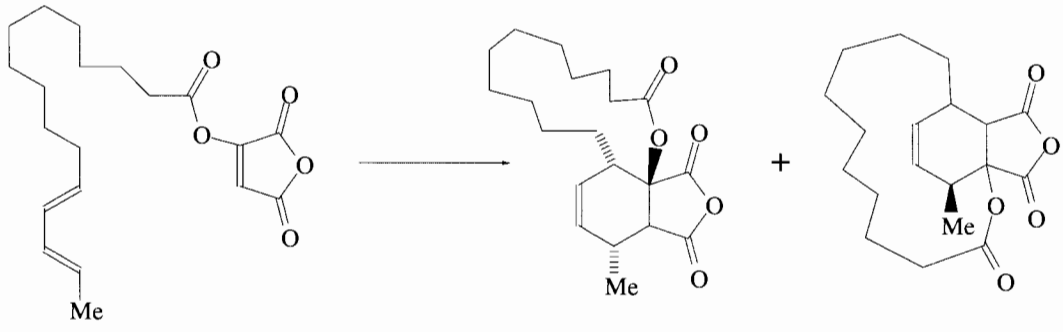
In general, (*E*)-dienes do not give products such as **204** although (*Z*)-dienes do. As the reactive termini approach, the alkene arm can assume an exo or an endo mode. The exo transition state leads to the trans-product and the endo transition state leads to the cis product. The final outcome depends on the conformational energies of the reactive species (sec. 1.5.D).[201] In general, the exo transition state is preferred.



212 **213** **214**

The cis/trans ratio is influenced not only by the length of the tether, as mentioned previously, but also by the reaction conditions and catalyst, if any. Houk compared the cyclization of several trienes (**215**) to give **216** under both thermal and catalytic conditions and with a variety of tether lengths. This study is shown in Table 11.11.[209] The acyclic analog (methyl vinyl ketone and 2,4-pentadiene) is also shown for comparison,

Table 11.11. cis–trans Selectivity in Internal Diels–Alder Reactions of Trienyl Ketones

215 **216**

n	Conditions	% 216	cis/trans (H_a)
1	180°C, 1.5 h	51	87:13
	0.02M Me_2AlCl_3, PhH, RT[a]	0	
2	22°C, 4 h	100	95:5
	120°C, 22 h		10:90[226]
	110 h	78	Only cis[210]
3	155°C, 5 h	90	62:38
	A	88	only cis
4	140°C, 68 h	53	64:36
	A	69	Only cis
5	155°C, 96 h	14–19	46:54
	A	23–37	90:10
6	155°C, 200 h	0	
	A	6–30	80:20
7	155°C, 100 h	0	
	A	11–24	86:14
0[b]	140°C, 252 h		
	Sealed tube	54	78:22
	A	25	95:5

[a] Defined as reaction condition **A**. [b] 2,4-Pentadiene + methyl vinyl ketone.

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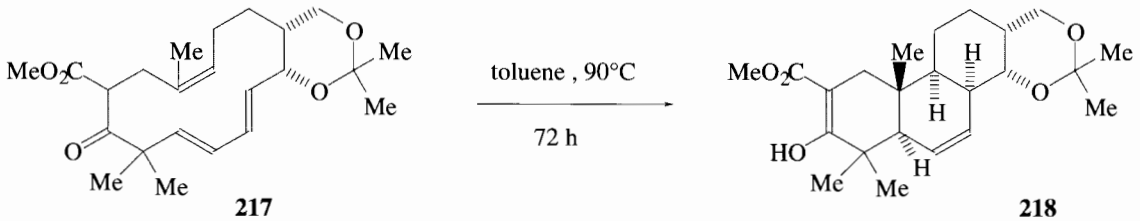
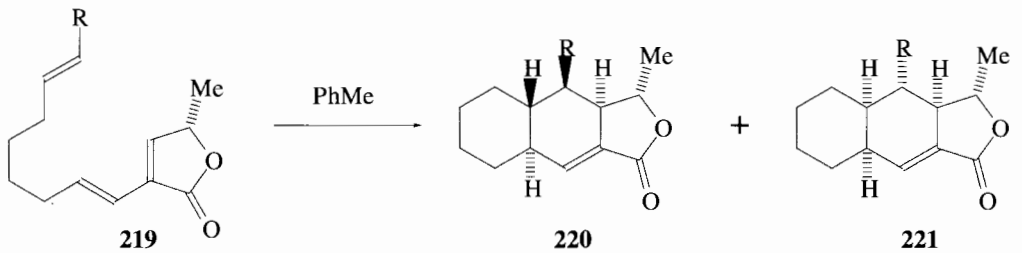
giving primarily the cis product. The cis adduct is generally preferred in all cases except when $n = 5$ (to form a nine-membered ring). Gras initially reported that when $n = 2$ the trans product was preferred[211] (this was later corrected), but Houk found that the cis product was preferred. Catalyzed and uncatalyzed reactions gave similar stereochemical preferences but the catalyzed reaction was more highly selective, as expected. When n = 4–7, the yields of products were dramatically decreased, reflecting the difficulty in generating the transition state for an eight- to eleven-membered ring in **216** (secs. 1.5.B,C, 6.6.B). It appears that internal cyclization is most efficient for forming five to seven-membered rings and the cis ring juncture is generally preferred. There are many applications of the intramolecular Diels–Alder reaction to natural product synthesis. Using a transannular Diels–Alder strategy, for example, Deslongchamps converted **217** to **218** in 83% yield as part of a synthesis of cassaine.[212]



217 **218**

Even when a single substrate is used, the ratio of diastereomeric products can vary with reaction conditions. In Hart, Kozikowski and co-workers synthesis of (+)-himbeline and (+)-himbacine,[213] **219** was cyclized to a mixture of **220** and **221** using the conditions in Table 11.12. At higher temperatures, the reaction favored **221** but with an acid promoter at lower temperatures, **220** was favored. When the ester group in **219** was changed to the reduced form (a TBS protected alcohol), heating to 110°C gave a 1:1 mixture whereas the acid promoted lower temperature reaction gave a 20:1 mixture favoring **220**.

Table 11.12. Intramolecular Cycloaddition of Selected Trienes[213]



219 **220** **221**

R	Conditions	%	220/221
CO_2Et	200°C (3 h)	77	1:4
CO_2Et	110°C (1 day)	58	1:1
CO_2Et	SiO_2–Et_2AlCl	31	3:1
CH_2OTBS	110°C (16 h)	30	1:1
CH_2OTBS	SiO_2–Et_2AlCl	75	20:1

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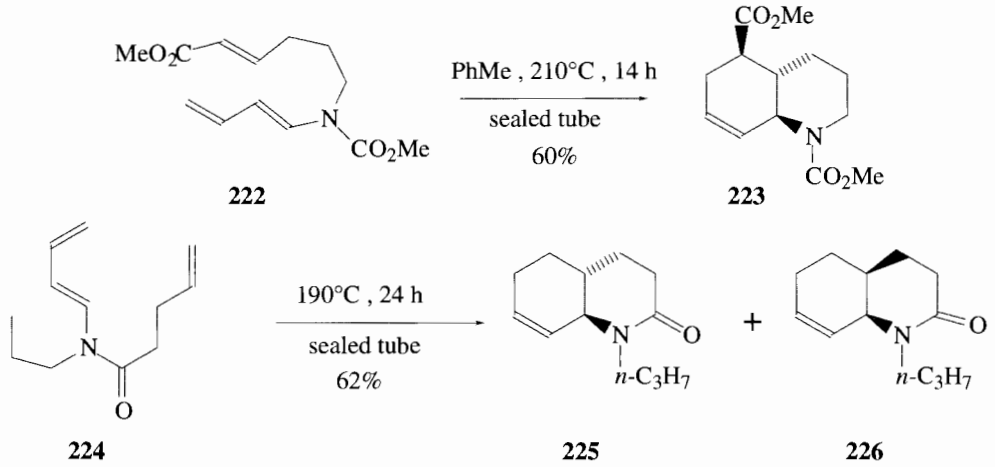
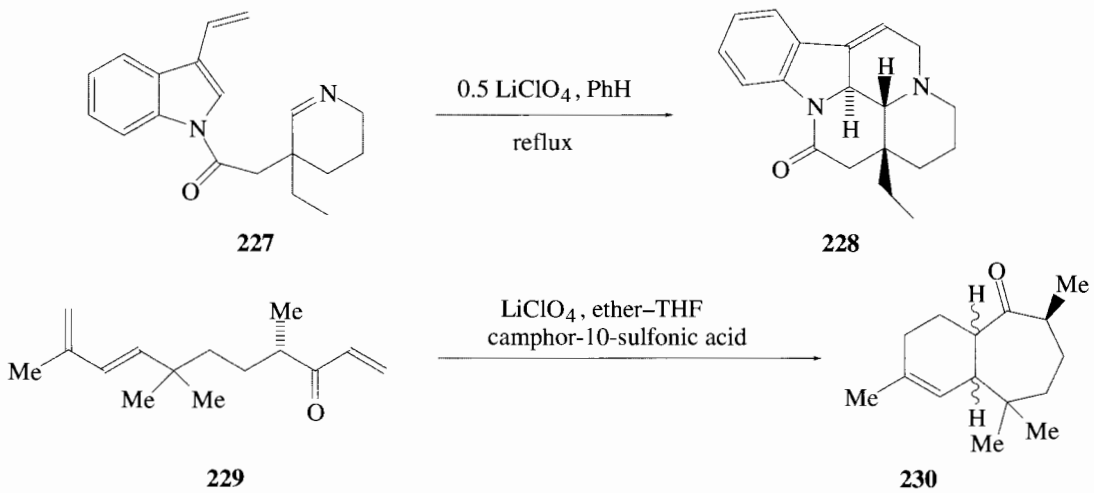
In the cyclization of dienyl amides, Oppolzer noted a difference in regiochemistry between dienes having the carbonyl *external to the ring being formed* (**222** → **223**)[214,215] and dienes having the carbonyl *in the ring being formed* (**224** → **225** + **226**),[214a] which was rationalized by a preference for the transition state that maximized overlap of the amide π-orbitals and the diene π-orbitals. This secondary orbital interaction is analogous to the endo effect noted in sec. 11.4.C).



222 **223** **224** **225** **226**

There are many synthetic examples involving intramolecular Diels–Alder reactions. In the Grieco and Kaufman synthesis of eburnamonine,[216] indole derivative **227** was treated with 0.5 equivalents of $LiClO_4$ in refluxing benzene, and an 81% yield of **228** was obtained. Interestingly, simply heating **227** on Florisil in

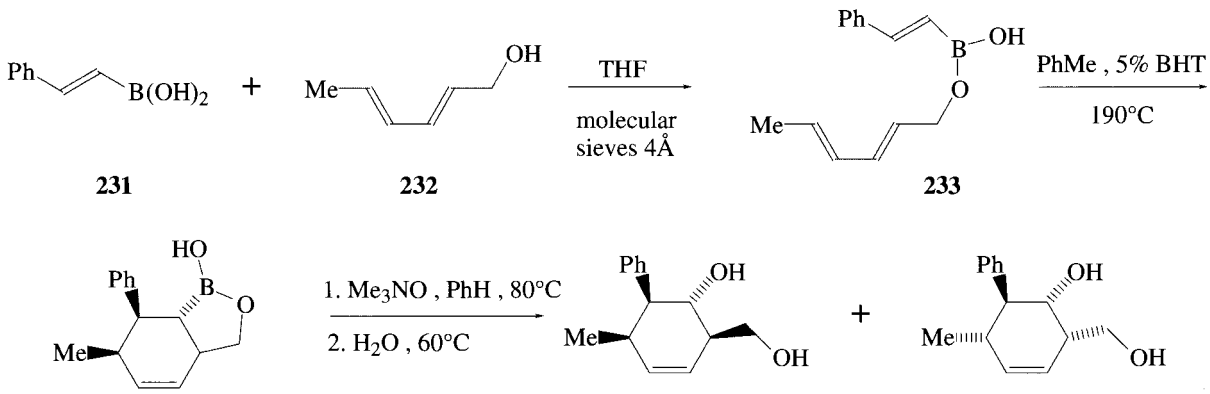


227 **228** **229** **230**

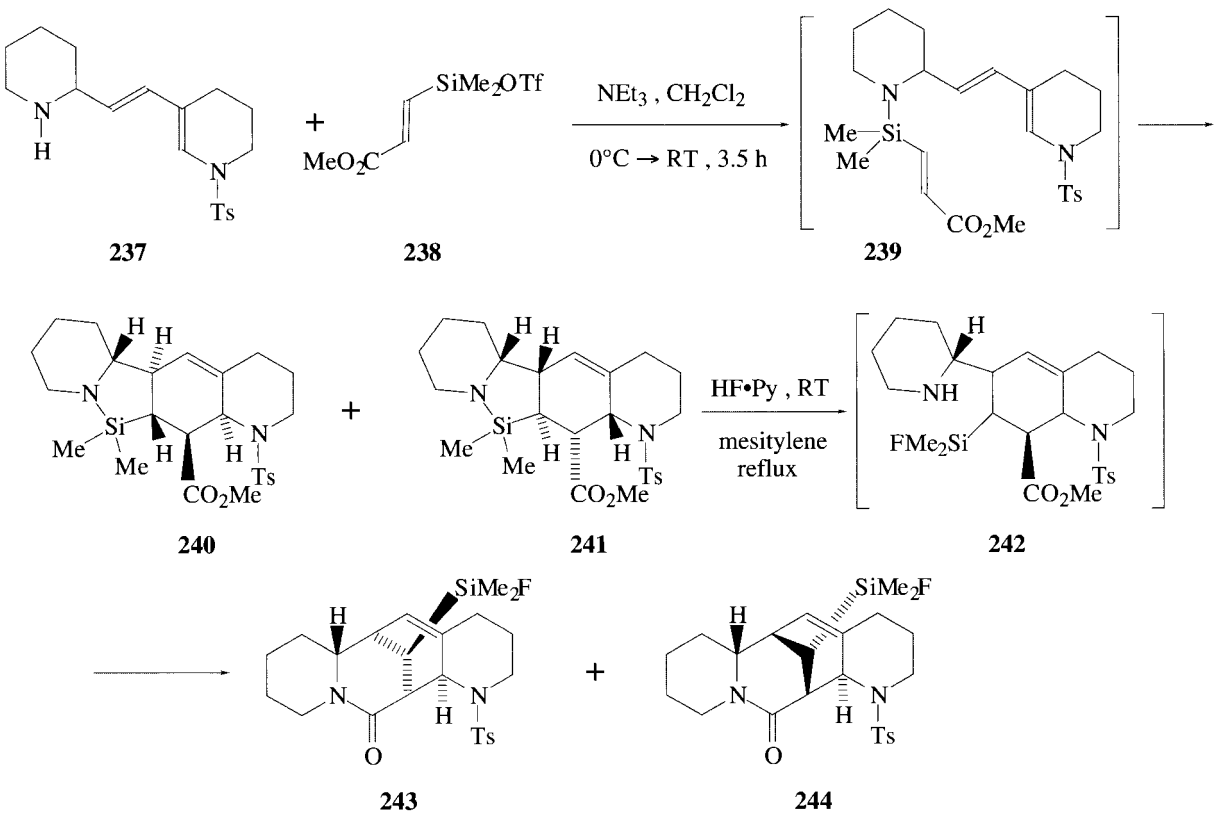
ethyl acetate at 50°C led to an 82% yield of **228**. In Mori's synthesis of (1*S*,3*S*,7*R*)-3-methyl-α-himachalene,[217] treating **229** with $LiClO_4$ with (+)-camphor-10-sulfonic acid, in an ether-THF mixture, gave **230** as a 55:45 mixture of cis/trans isomers (ring juncture hydrogen hydrogens).

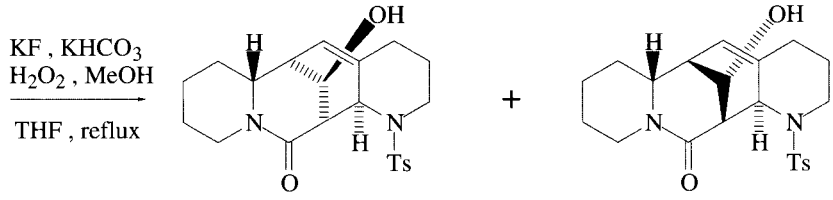
In recent years, the concept of tethered intramolecular reactions has become popular. The basis of this concept is that the diene and alkene units are linked together by a species that allows an intramolecular Diels–Alder but can be chemically removed later. In the work of Batey et al.,[218] reaction of boronic acid (**231**) with

sorbic alcohol (**232**) gave **233**, and heating in a sealed tube at 190°C, in the presence of the radical inhibitor BHT (2,6-di-*tert*-butyl-4-phneylpheonol), gave the cycloadduct **234**. Oxidation with trimethylamine-*N*-oxide and hydrolysis gave a 90:10 mixture of **235/236** in 84% yield. The boronic ester linkage in **233** acted as a tether to allow the regio- and stereoselectivity possible with an intramolecular process. Treatment with the amine oxide and hydrolysis removed the tether to give the cycloadducts.



Silane tethers are also quite useful. In Overman's synthesis of (+)-aloperine,[219] reaction of **237** with vinylsilane (**238**) gave **239**, where the dimethylsilane unit acted as a tether for the amido-diene and the methyl



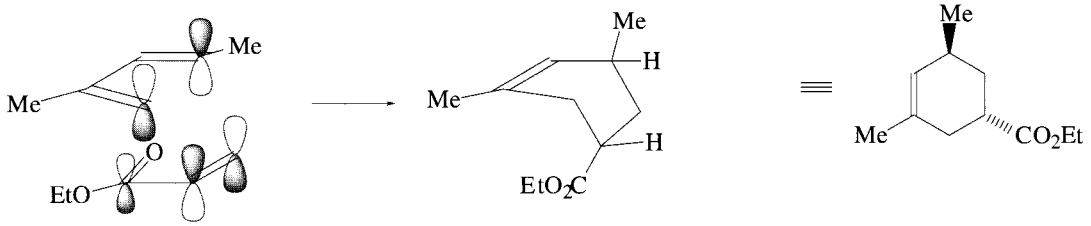


245 **246**

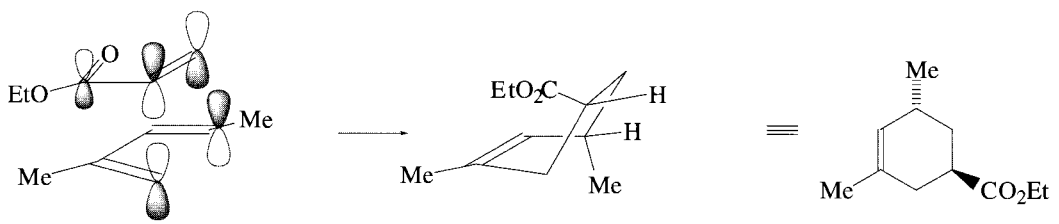
acrylate units. Under these reaction conditions, cyclization occurred to give a 5:1 mixture of **240/241**. When the silane was removed by treatment with HF–pyridine, the free amine was liberated (see **242**), and this cyclized with the ester to give a mixture of lactams **243** and **244**. This mixture was not isolated but rather treated with KF and H_2O_2 to give alcohol **245** in 63% yield and **246** in 13% yield.[219] This latter transformation is an example of the Tamao–Fleming oxidation introduced in section 3.8.C.

11.9. ASYMMETRIC DIELS–ALDER REACTIONS

The diastereoselectivity inherent to the Diels–Alder reaction can be seen in most of the examples in preceding reactions. The reaction is not, however, enantioselective since there is no facial control for intermolecular reactions (some facial control is available for intramolecular reactions). The ortho rule, the endo rule (secondary orbital interactions), and steric interactions provide some orientational control but facial control is also required for enantioselectivity. When ethyl acrylate reacts with 2-methyl-1,3-pentadiene, it can approach from the bottom as in **247A** or from the top as in **247B**. Clearly, the two products (**248A** and **248B**) are mirror images and enantiomers. This lack of facial selectivity leads to racemic mixtures in all Diels–Alder cyclizations discussed to this point.



247A **248A**



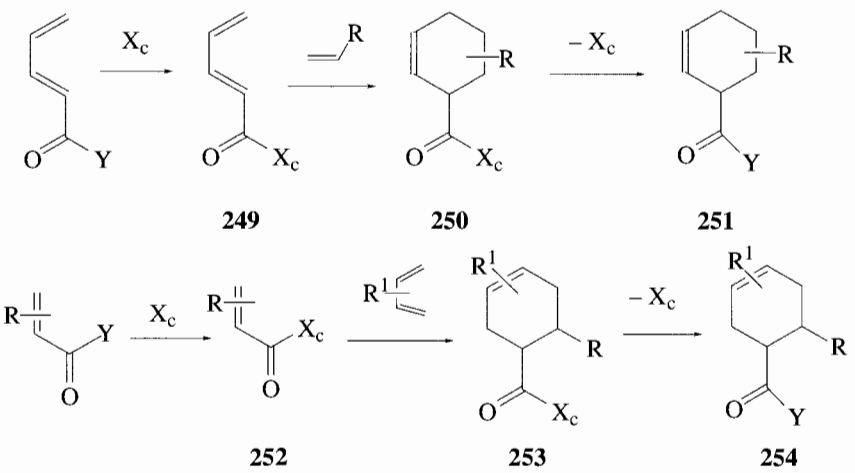
247B **248B**

As in Chapters(1–5, and 8–9, the key to enantioselectivity is providing both facial and orientational control in the transition state of the reaction. The orientational control (regioselection and endo selectivity) for the

diene and alkene is provided by orbital interactions, including secondary orbital effects. Facial selectivity, as in previous chapters, will be provided by the presence of stereogenic centers in the molecule. The diene can be constructed from a chiral precursor (a **chiral template**–sec. 10.9), or a chiral auxiliary (X_c) can be attached to the diene or alkene. A third approach is related to using a chiral auxiliary in that a chiral material (usually a chiral catalyst) is added to the reaction, usually providing a transient chiral auxiliary (sec. 4.7.A).

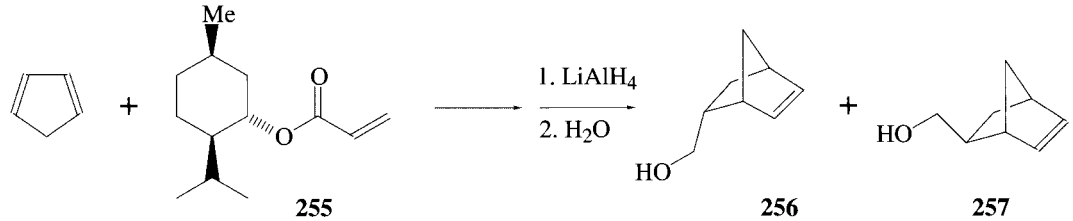
11.9.A. Chiral Auxiliaries

A chiral auxiliary is a chiral molecule, usually derived from a naturally occurring one, which is attached to the reaction substrate (in high yield and under mild conditions) and provides facial selectivity (and hopefully orientation control as well) in a reaction.[220] After the reaction of interest, the auxiliary must be removed (in high yield and under mild conditions) to regenerate the original functional group. The chiral auxiliary is attached to either an achiral diene (as in **249**) or an achiral dienophile (as in **252**) to generate a chiral molecule. Diels–Alder reaction with **249** generated **250** as a mixture of diastereomers, each in high enantiomeric purity (% ee, sec. 1.4.F). The auxiliary is then removed to give the chiral target **251**. A similar sequence with **252** generated **253**, and removal of X_c gave **254**. The auxiliary provides facial selectivity in the Diels–Alder reaction, transferring that chirality to the cycloadduct. Diels–Alder reactions of both **249** and **252** *may* proceed with excellent enantioselectivity but with only moderate-to-good diastereoselectivity. This problem of diastereoselectivity and enantioselectivity must be addressed in all asymmetric reactions and has been seen in reductions (Chap. 4) as well as nucleophilic carbon bond forming reactions (Chap. 8) and especially in enolate reactions (Chap. 9).



One of the most common auxiliaries is menthyl, where an acrylic acid derivative is attached to menthol to form a menthyl ester, **255**. Morrison and Mosher[221] showed that asymmetric induction is possible with **255** when it reacts with cyclopentadiene to give diastereomers **256** and **257**,[222] as shown in Table 11.13.[221] In the absence of a Lewis acid, however, the % ee is rather poor. Similarly, (–)-dimenthyl fumarate (**258**) reacted with butadiene to give **259** and **260**, after reduction of the ester products with lithium aluminum hydride. Hydride reduction of esters (sec. 4.2.B) is a common method for removing ester auxiliaries. The work of

Table 11.13. Selectivity in the Diels–Alder Reaction of Cyclopentadiene and Menthyl Acrylate



255 256 257

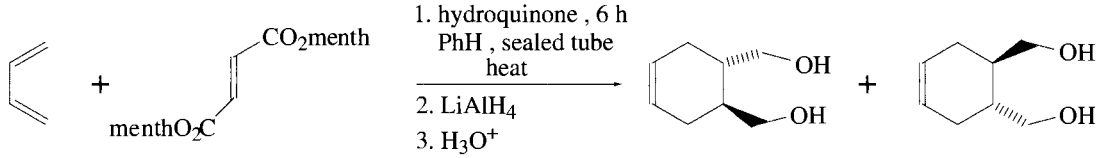
Catalyst	Solvent	Temperature (°C)	256 (% ee)	257 (% ee)
None	CH_2Cl_2	0	+ (9)	
None		35	+ (7)	+ (3.1)
$AlCl_3$•OEt_2		0	+ (49)	– (36)
		–70	+ (67)	
BF_3•OEt_2		0	+ (74)	– (43)
		–20	+ (82-85)	
$SnCl_4$	PhMe	48	+ (41)	
None	Neat	160	- (6)	

[Reprinted by courtesy of Professor James D. Morrison from Morrison, J.D.; Mosher, H.S. *Asymmetric Organic Reactions,* American Chemical Society, Washington, DC ***1976***, pp. 256.]

Walborsky et al.[223] is shown in Table 11.14[224] and is one of the first examples of asymmetric induction in a Diels–Alder reaction.

Asymmetric induction can sometimes be improved by using an auxiliary that is attached to either the dienophile or the diene. In Rawal's synthesis of (–)-α-elemene a chiral pyrrolidine unit attached to the diene

Table 11.14. Selectivity in the Diels–Alder Reaction of (–)-Dimenthyl Fumarate and 1,3-Butadiene



258 259 260

Catalyst	Solvent	Temperature (°C)	259 (% ee)	
$TiCl_4$	PhMe/CH_2Cl_2	25	43% (*SS*) (+)	64%
	PhMe	25	78% (*SS*) (+)	
$SnCl_4$	PhMe		75% (*SS*) (+)	64%
$AlCl_3$	CH_2Cl_2	–70	72% (*SS*) (+)	
	PhMe	50	27% (*SS*) (+)	57%
None	Hydroquinone			
	PhH, sealed tube	25	5.8%	80%
None		65	1.1% (*RR*) (–)	

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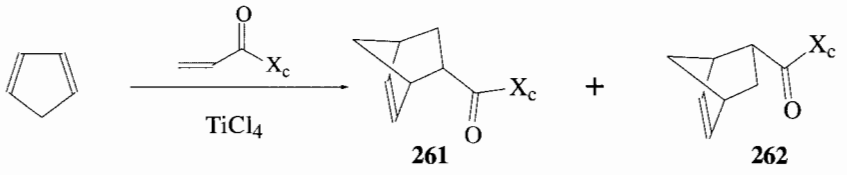
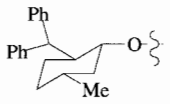
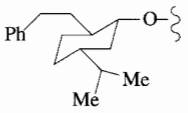
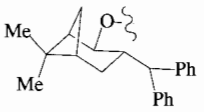
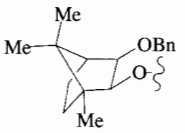
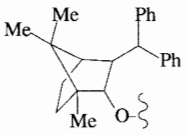
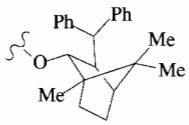
unit of **73** and served as a chiral auxiliary (see sec. 11.4.C.iii). In that synthesis, the Diels–Alder adduct was **74**, but the auxiliary was removed by elimination to an alkene unit later in the synthesis.[89] In general, menthol type auxiliaries provide only moderate selectivity.[225]

In Oppolzer's review,[226] several chiral auxiliaries related to menthol and other chiral alcohols were presented, giving the diastereomeric endo adducts **261** and **262**, as shown in Table 11.15.[227] In all cases, the chiral

Table 11.15. Enantioselectivity in the Diels–Alder reaction of Cyclopentadiene with Conjugated Esters Derived from Chiral Alcohols



X_c	% ee	X_c	% ee
	88% (*R*)		63% (*R*)
	85% (*R*)		88% (*S*)
	81.5% (*R*)		82.7% (*S*)

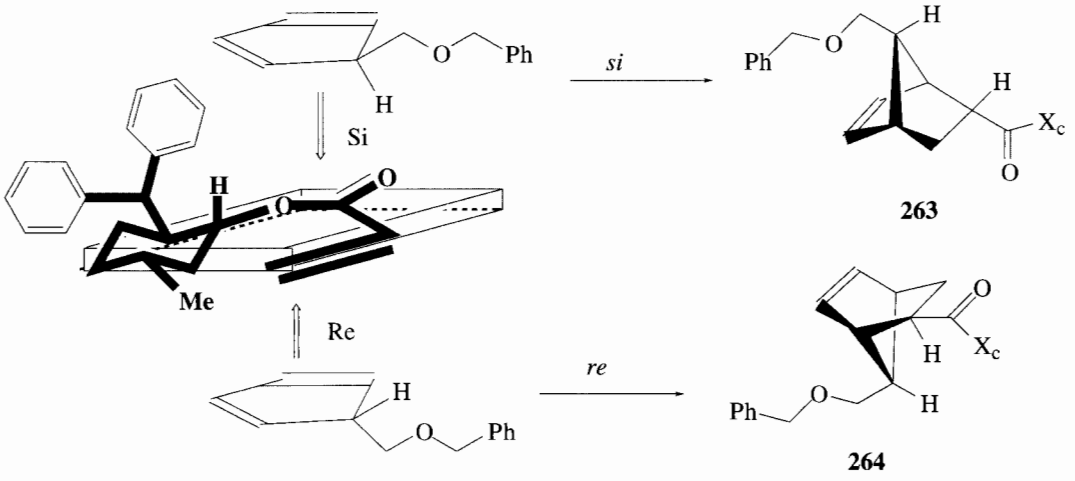
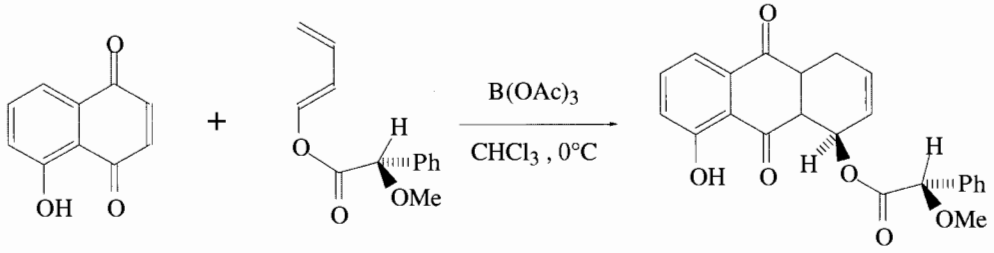


Figure 11.13. Facial selectivity of chiral acrylates in the Diels–Alder reaction. [Reproduced with permission from Oppolzer, W. *Angew. Chem. Int. Ed., Engl.*, ***1984***, *23*, 876. Copyright © 1984 VCH Weinheim.]

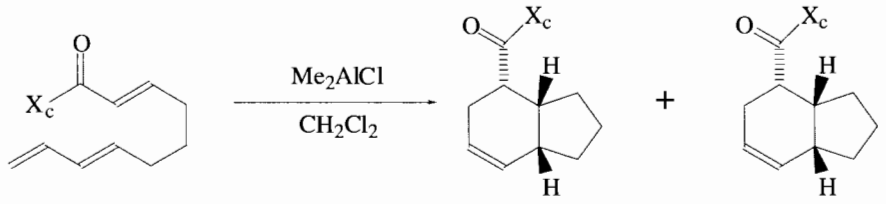
ester in Table 11.15 provided good-to-excellent selectivity. Oppolzer discussed the source of this selectivity by invoking Figure 11.13[227] (from 5-benzyloxymethyl cyclopentadiene) in which the chiral auxiliary provided facial selectivity, leading to attack from either the *re* face or the *si* face. Figure 11.13 provides an illustration of the source of facial selectivity for other chiral auxiliaries. There, the *si* face is less hindered and **263** [the (*R*) cycloadduct] is preferred to **264**, consistent with the results in Table 11.15. The poor-to-moderate asymmetric induction with menthol and related auxiliaries contrasts with Trost's use of **266** with napthoquinone **265**, which gave 98% of **267** with >97% ee.[228]



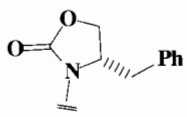
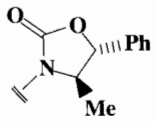
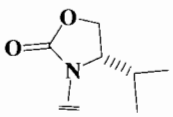
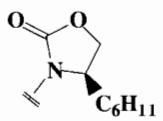
265 **266** **267**

Evans exploited this concept of chelation in the transition state with the development of a new generation of chiral auxiliaries based on conversion of amino alcohols to oxazolidinone derivatives. As shown in Table 11.16,[229] conversion of these auxiliaries (to give the corresponding conjugated amide **268**) gave excellent selectivity in the intramolecular Diels–Alder reaction, which generated mixtures of **269** and **270**. Coordination with the Lewis acid catalyst generates a complex in which facial selectivity is enhanced relative to the

Table 11.16. Evans' Oxazolidinone Auxiliaries in an Intramolecular Diels–Alder Reaction



268 **269** **270**

X_c	**263/264**	Yield (%)	X_c	**269/270**	Yield (%)
	95:5	73		15:85	70
	83:17	60		3:97	65

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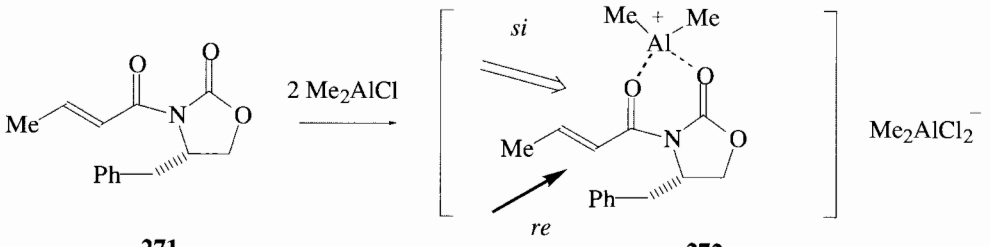
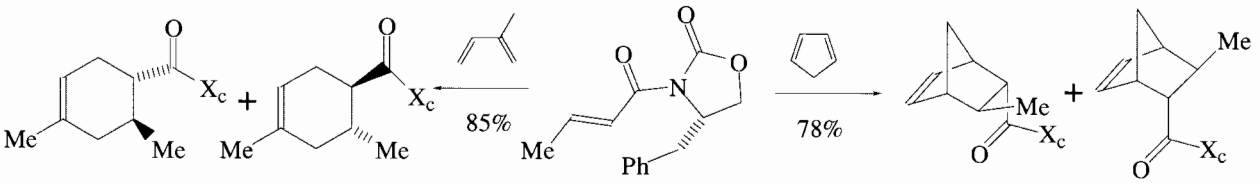


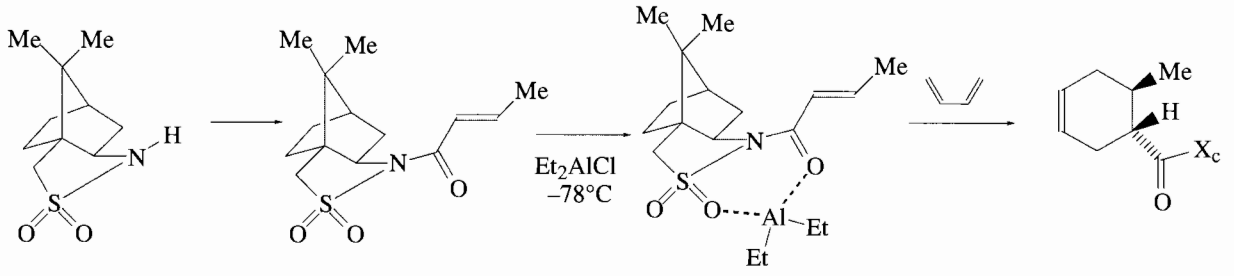
271 **272**

uncomplexed species. When dimethylaluminum chloride is used as a Lewis acid catalyst with **271**, for example, chelated intermediate **272** is formed. This provides orientational control for the dienophile and the chiral nature of the auxiliary provides the requisite facial control, with approach of the diene from the less sterically hindered face. Good selectivity is observed with the intermolecular Diels–Alder reaction of **271** with 2-methyl-1,3-butadiene to give **273** and **274** (95:5 in 85%) and also the conversion of **271** to **275** and **276** (>100:1 endo/exo and 95:5 in 78%) upon reaction with cyclopentadiene.[230]



273 **274** **271** **275** **276**

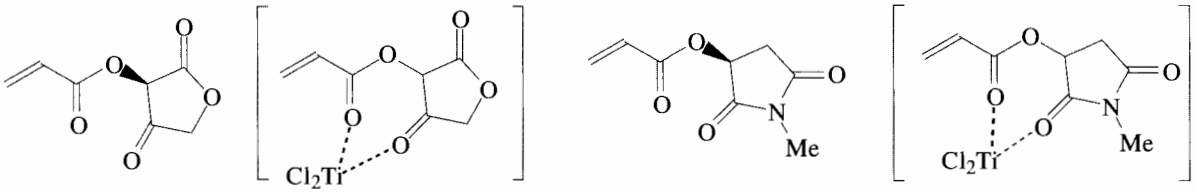
Oppolzer et al. developed useful auxiliaries based on a camphor precursor,[231] and one of the best was a sultam (**277**). When this sultam was converted to an acrylamide (**278**) and reacted with butadiene, cycloadduct **280** was produced (85% yield, 95 % ee).[232] Selectivity in this Diels–Alder reaction is due to chelation of the amide oxygen and the sulfonyl group, as shown in **279**. Oppolzer and co-workers applied this methodology to a chiral synthesis of the aglycone of loganin.[233]



277 **278** **279** **280**

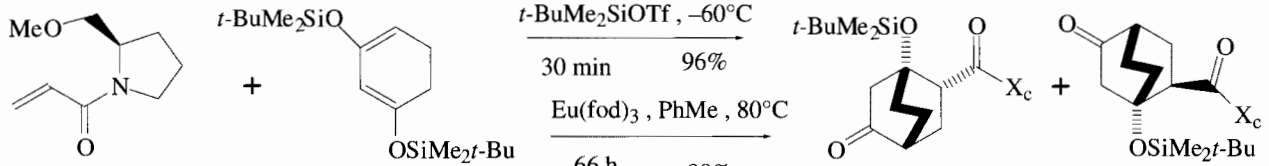
A variety of other auxiliaries have been developed that gave excellent asymmetric induction in the Diels–Alder reaction. Helmchen and Schmierer also developed an auxiliary based on camphor that is quite useful.[234] In addition, Helmchen prepared the lactone auxiliary **281** and the imide auxiliary **283** and showed they give opposite enantioface selectivity in the Diels–Alder reaction.[235] In the presence of a Lewis acid such as $TiCl_4$, differences in coordination site led to a different chiral face in the transition state of the

cycloaddition, and opposite stereochemistry. Lactone **281** led to **282** and imide **283** led to **284**. The auxiliary based on **281** was used by Helmchen in a synthesis of cyclosarkomycin.[236]



281 **282** **283** **284**

Ghosez and co-workers showed that changing the catalyst in Diels–Alder reactions using a chiral auxiliary can influence selectivity. When **285** reacted with diene **286**, in the presence of a silyl triflate catalyst, an 88:12 mixture of **287/288** was obtained in 96%.[237] Changing the catalyst to europium [Eu(fod)$_3$], however, gave



285 **286** **287** **288**

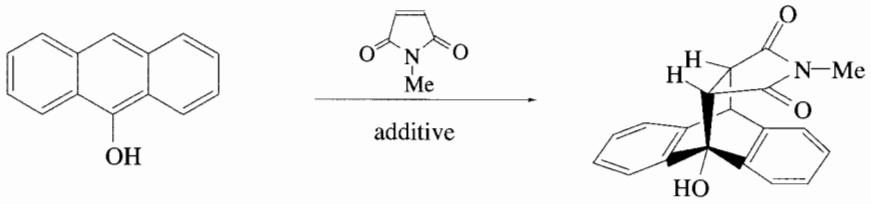
98% of **288** (0:100 **287/288**). A variety of auxiliaries have been developed that can be very effective in catalyzing Diels–Alder reactions with high asymmetric induction. It is clear that the best results are obtained when the substrate–auxiliary complex can chelate to the catalyst. The only major drawback with these auxiliaries is that they can sometimes be difficult to remove (vigorous aqueous acid or base or treatment with $LiAlH_4$ may be required). They are also restricted to esters, amides (or carbamates), ethers, or amine functionalized dienes and alkenes. Dienes and dienophiles without heteroatom substituents are not amenable to these auxiliaries, and other methodology must be developed for asymmetric induction.

11.9.B. Chiral Additives and Chiral Catalysts

Clearly related to chiral auxiliaries are chiral additives, which usually form transient auxiliaries to provide the requisite facial selectivity. In Section 11.6.A, we saw that a chiral Lewis acid was used to catalyze formation of **107**. In Section 4.7.A, we saw that naturally occurring chiral amines were added to reducing agents to achieve asymmetric induction. Protected proline and abrine esters and related compounds have been used as chiral catalysts.[238] These amines can also be used in Diels–Alder reactions, with variable results. One example is the reaction of **289** with *N*-methylmaleimide to give **290**. As shown in Table 11.17,[239] various amine additives gave poor-to-good asymmetric induction in the cycloadduct. In this particular example, quinidine proved the most effective additive. Presumably, the chiral amine coordinates with **289** via hydrogen-bonding (or a dipole-dipole interaction) to provide diastereoselection via formation of a transient auxiliary, which then reacts with *N*-methylmaleimide.

A different and more useful approach is to prepare a chiral catalyst that will provide facial selectivity when it coordinates to the substrate (usually the dienophile) to form a chiral transition state containing the transient

Table 11.17. Asymmetric Induction in the Diels–Alder Reaction on Addition of Naturally Occurring Chiral Amines.



289 **290**

Chiral Additive	Temperature (°C)	% 290	% ee
Quinine	0	96	32
Quinidine	–50	93	61
Cinchonine	25	84	16
Cinchonidine	25	98	27
(*S*)-Prolinol	–20	100	43
(1*R*,2*S*)-*N*-Methylephedrine	–20	86	17

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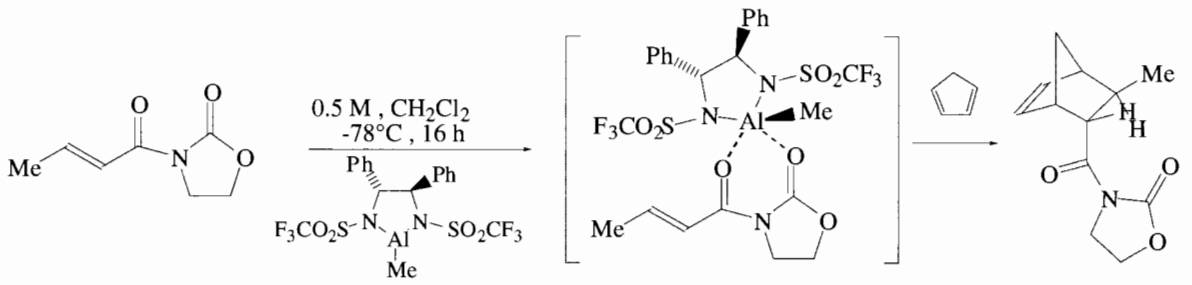
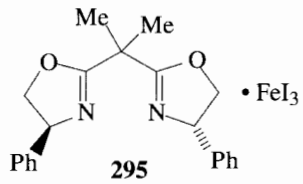
auxiliary. Menthoxyl and bornyloxyaluminum catalysts were used by Roush,[225] providing an example in which traditional chiral materials are attached to aluminum chloride. Significantly more effective catalysts have been developed based on the coordination of chiral molecules (usually bis-amines or diols) with aluminum or titanium reagents. Corey et al. prepared chiral catalyst **292** and used it in a reaction of cyclopentadiene with **291** to give an 88% yield of **294** with 94% ee (in a ratio of 96:4 endo/exo).[240] The source of the selectivity arises from the transient complex **293**.



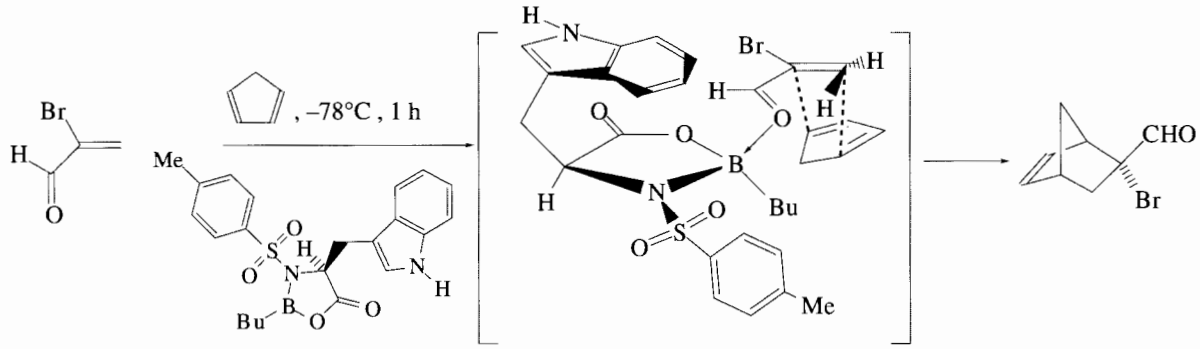
291 **292** **293** **294**

Corey developed other catalysts for enantioselective Diels–Alder reactions. One is a C_2-symmetric chiral bis-(oxazoline)-Fe(III) complex (**295**).[241] Other similar copper-coordinated catalysts have been developed and give good-to-excellent enantioselectivity in Diels–Alder reactions.[242] The **295**•$FeCl_2I$ catalyst gave excellent enantioselectivity (93:7 in reactions of analogs of **291** with cyclopentadiene with 99:1 endo/exo-selectivity) at -50°C in dichloromethane (15, 10 mol% of the catalyst).[241] The FeI_3 complex that is shown and the $FeCl_3$ complex gave slightly poorer selectivity than the $FeCl_2I$ complex. Another catalyst was designed to

exploit intramolecular interactions for a highly enantioselective Diels–Alder reaction.[243] The (*S*)-tryptophan derived oxazoborolidine (**296**) catalyzed the reaction of 2-bromoacrolein and cyclopentadiene to give (2*R*)-2-bromobicyclo[2.2.1]hept-5-ene (**298**). A chiral complex (**297**) forms to "mediate the cyclization in which the π-basic indole and the π-acidic dienophile can assume a parallel orientation at the ideal separation (3 Å) for donor–acceptor interaction."[243]

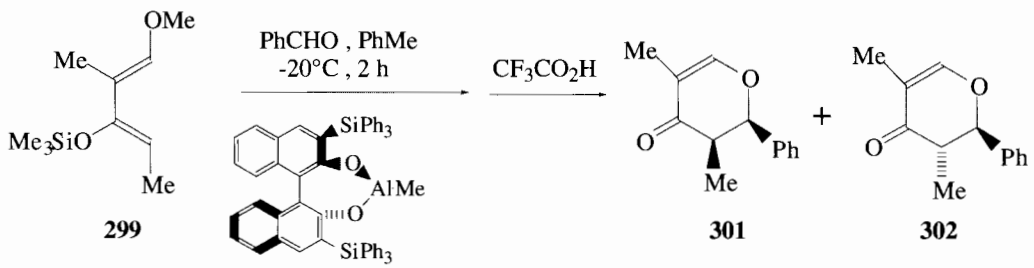


295



296 **297** **298**

Yamamoto reported an asymmetric hetero-Diels–Alder reaction that was catalyzed by a chiral organoaluminum reagent (**300**).[244] When diene **299** reacted with benzaldehyde in the presence of 10 mol% of **300**, a mixture of *cis*-dihydropyrone (**301**) and *trans*-dihydropyrone (**302**) was obtained in 77 and 7% yield, respectively. The optical activity of(**301** was 95% ee, and that of **302** was 53% ee.[244] In the complex that mediates this reaction, the diene approaches benzaldehyde with an endo alignment that minimizes steric repulsion between the incoming diene and the front triphenylsilyl moiety.



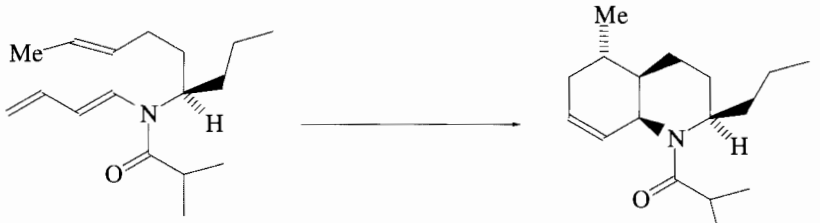
299 **300** **301** **302**

Narasaka et al. developed a titanium catalyst generated by complexation with chiral diols.[245] The dienophile must contain functionality that will coordinate with the metal catalyst to form a chiral complex, and these catalysts are less effective with dienes and dienophiles that do not contain heteroatoms. A related titanium–BINOL complex has been used to catalyze Diels–Alder reactions.[246] Kelly prepared a transient

boron catalyst, prepared *in situ* with borane and a chiral diol.[247] It is clear that chiral additives, particularly chiral catalysts, can be effective. The asymmetric induction is usually good to excellent with properly designed dienophiles. Effective chiral catalysts continue to be reported and will undoubtedly be a major force in chiral synthesis involving Diels–Alder reactions.

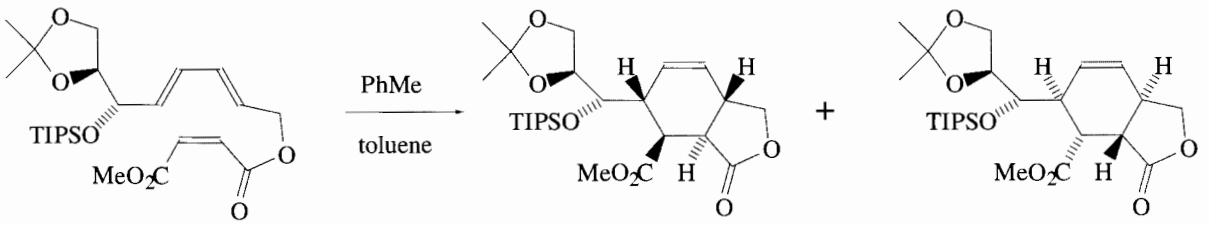
11.9.C. Diels–Alder Chiral Templates

The last approach to chiral synthesis begins with a chiral precursor whose components will be integrated into the final product, which is the **chiral template approach** (sec. 10.9). The examples of asymmetric syntheses involving Diels–Alder **templates** are as varied as the targets. One typical example is by Oppolzer, who reported an asymmetric synthesis of pumiliotoxin C via Diels–Alder cyclization of **303**, prepared from (*R*)-norvaline, to give **304**.[248]



303 **304**

Carbohydrates are efficient chiral templates and have been used in the Diels–Alder reaction. Sherburn used L-ascorbic acid as a template to synthesize **305**.[249] Heating this compound in refluxing toluene led to a 96:4 mixture of **306** and **307** (68% yield). The chirality inherent in the carbohydrate precursor provides the needed facial selectivity that is transferred to the cycloadduct product. The use of chiral templates for preparing Diels–Alder precursors will undoubtedly increase in importance. As the need for enantiomerically pure material increases, the chiral template approach coupled with the power of the Diels–Alder reaction will be an effective combination.

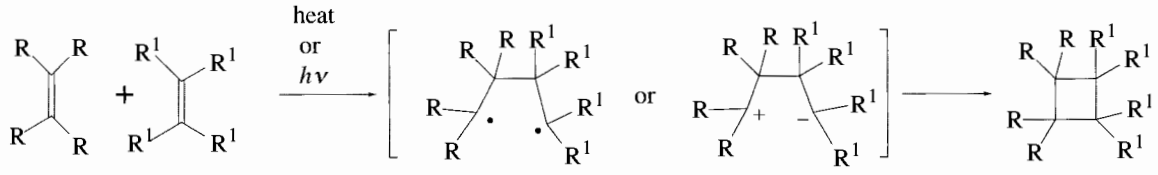


305 **306** **307**

11.10. [2+2]-CYCLOADDITION REACTIONS

The Diels–Alder reaction occupies a prominent place in organic synthesis, as we have seen, but there are other pericyclic reactions that are also quite useful. One of them is the [2+2]-cycloaddition that occurs between two alkenes or between an alkene and a carbonyl or imine.[250] Cyclobutanes and oxetanes are

available from this reaction and β-lactams and β-lactones have been prepared. This section will focus on both thermal and photochemical [2+2]-cycloaddition reactions.



308 **309** **310**

11.10.A. Thermal [2+2]-Cycloadditions

As seen in Section 11.3, thermal [2+2]-cycloaddition reactions that form cyclobutane derivatives such as **310** are symmetry forbidden, but photochemically allowed.[251,10a] There are, however, several examples of

311 **312**

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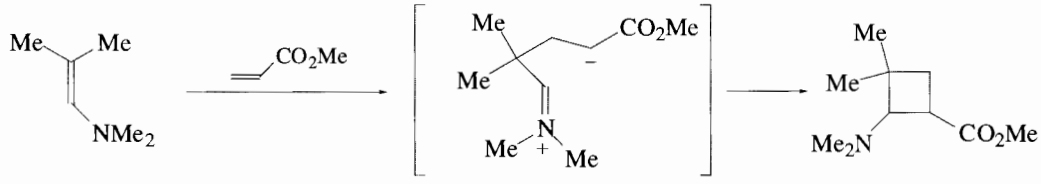
thermal [2+2]-cycloadditions, probably occurring by a radical or dipolar intermediate (**308** or **309**, respectively), or by HOMO–HOMO (**311**) or LUMO–LUMO (**312**) interactions.[252] Reaction of dimethylaminoisobutene (**313**) with methyl acrylate, for example, gives cyclobutane **315** by what is believed to be a zwitterionic intermediate (**314**).[253] As seen in the reaction of **313**, enamines are excellent partners and alkynes also react with ketenes to form cyclobutene derivatives.[254] Ionic intermediates need not be invoked in all cases, since some reactions proceed via diradical intermediates. The HOMO of **313** and LUMO of methyl acrylate can be used to predict the regiochemistry in **315**.[255] In general, the presence of an electron-withdrawing group on the ketene, such as a chlorine, an alkoxy group, an aryl group, or a vinyl group, greatly enhances the rate of the [2+2]-cycloaddition reaction with alkenes, particularly intramolecular cycloadditions.[256] It is also known that cis alkenes are more reactive than trans alkenes in reactions with ketenes.[257] Cycloaddition reactions with cis alkenes are stereospecific, but some loss of stereochemistry is observed in reactions with trans alkenes.[255,256,37]



313 **314** **315**

Ketenes ($R_2C{=}C{=}O$) react at the C=C unit via thermal [2+2]-cycloaddition reactions to give cyclobutanone derivatives. Ketenes are highly electrophilic due to a low-lying LUMO (π^* C=O), and the HOMO is relatively

high in energy (see Table 11.1). Ketene, for example, has a HOMO of –12.55 eV and a LUMO of +2.55 eV. These values and the orbital coefficients are shown in Figure 11.14[32,258] (also see Table 11.1). Polarization of the C=C unit in ketene (the combination of electrophilic and nucleophilic character) is responsible for the facile [2+2]-cycloaddition reactions. As mentioned above, the presence of an electron-withdrawing group enhances the rate of the [2+2]-cycloaddition reaction. Inspection of Table 11.1 shows that the HOMO for ketene is –12.55 eV but the HOMO for PhCH=C=O is -10.61 eV, that for ClCH=C=O is –9.24 eV and that for

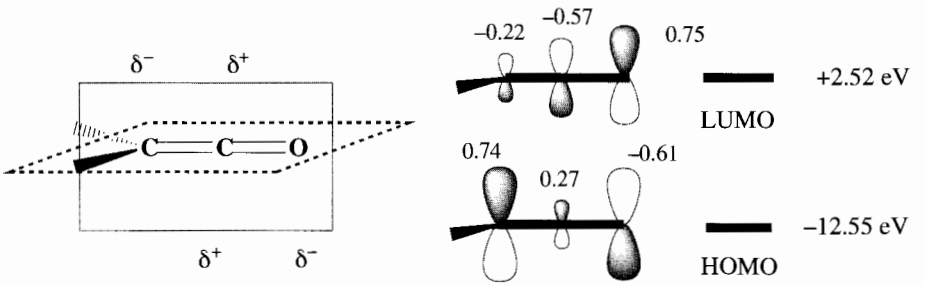
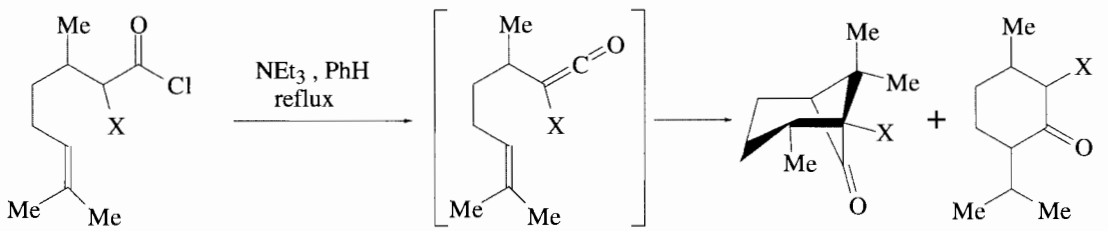


Figure 11.14. Orbital diagram for ketene.

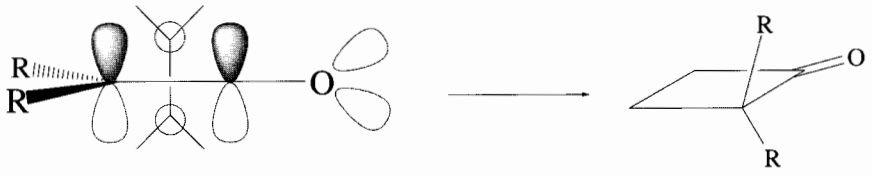
Cl_2C=C=O is –9.15 eV. Clearly, the presence of these groups raises the energy of the HOMO and would be expected to increase the rate of a cycloaddition driven by the LUMO of an alkene. This has been noted in many intermolecular reactions of ketenes and alkenes.[259] This rate enhancement is apparent in the attempted intramolecular cyclization (see below) of **316** (X = H), which failed. When the α-chloro analog (**316**, X = Cl) was prepared, however, treatment with triethylamine led to **317**, which cyclized to give a 55% yield of the [2+2]-cycloadduct (**318**), along with 19% of the ene adduct (**319**–see sec. 11.13) where X = Cl.



316 **317** **318** **319**

In a typical reaction, dimethylketene (**320**) and ethene were heated to give cyclobutanone **321** in a reaction controlled by the $HOMO_{alkene}$–$LUMO_{ketene}$ interaction.[260] Inspection of the orbital picture for this reaction (see **322**) shows that [2+2]-cycloadditions are allowed when one component is suprafacial and the other is antarafacial. In **322**, the HOMO of the alkene is of the correct symmetry to interact with the low-lying LUMO of the ketene.[261a] Reaction of an alkene and a ketene (see **322**) yields a cyclobutanone (**323**).[262] Ketenes such as **320** are readily generated by reaction of an acid chloride with an amine[262] or by treatment with Zn—Cu in the case of α-chloro acid chlorides. Since acids and acid chlorides are readily available, ketenes are convenient partners for reaction with both alkenes and dienes.[263] In Greene's synthesis of (–)-anisomycin,[264] the acid chloride of trichloroacetic acid was treated with Zn-Cu to give dichloroketene (**324**), which reacted with **325** to give dichlorocyclobutanone **326**.

320 **321**



322 **323**

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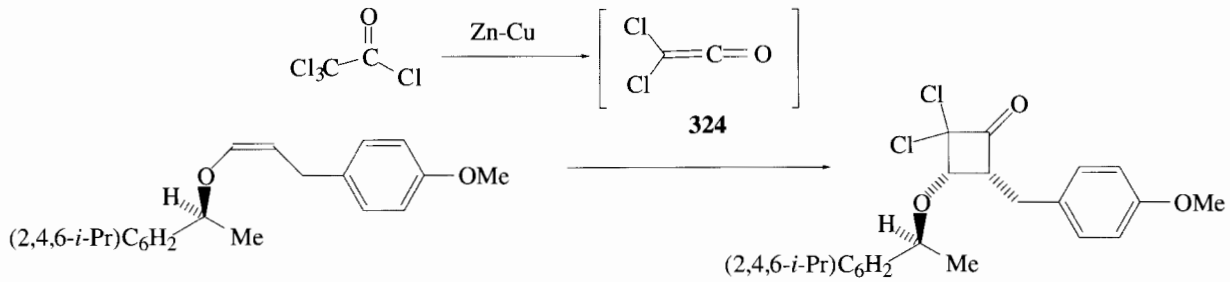
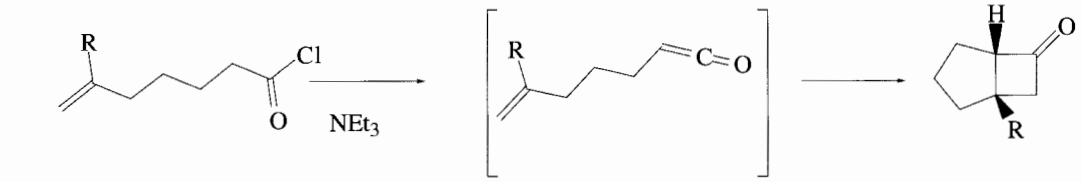
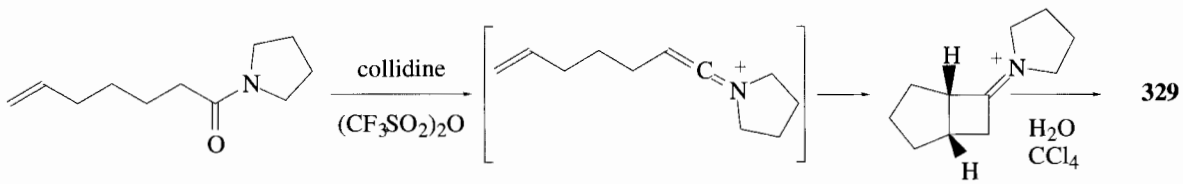


324 **325** **326**

The intramolecular version of this reaction is usually more efficient than the intermolecular version. When **327** (R = Me) was treated with triethylamine (0.2% solution of acid chloride in refluxing dichloromethane), ketene **328** (R = Me) was formed and the intramolecular [2+2]-cycloaddition gave 80% of **329**.[265] Ghosez reported, however, that reaction of **327** (R = H) under the same conditions gave only 3% of **329** (R = H). As



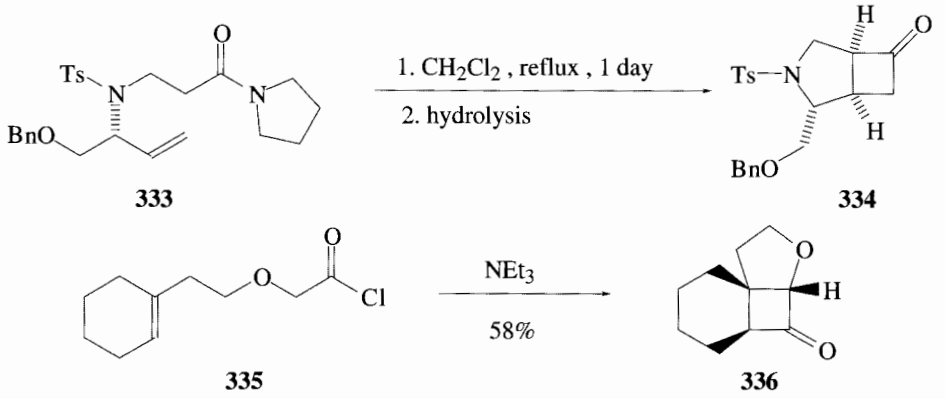
327 **328** **329**



330 **331** **332**

with many unactivated ketones (see above), **327** (R = H) showed poor reactivity. In order to enhance the reactivity of such molecules, Ghosez and co-workers developed a ketene iminium salt[266] cyclization procedure in which pyrrolidine amide **330** was treated with triflic anhydride [$(CF_3SO_2)_2O$] and collidine to generate the

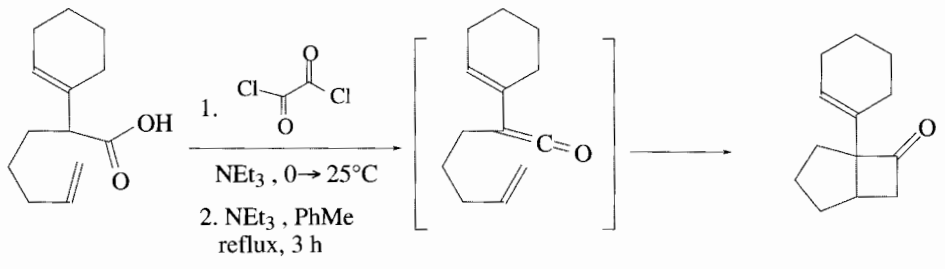
ketene iminium salt (**331**). Subsequent internal [2+2]-cycloaddition gave **332** (75% after hydrolysis of the iminium salt product, **329**). Ghosez showed that ketene iminium salts were more electrophilic than ketenes and did not dimerize.[267] Another example of this approach is the conversion of **333** to **334** in ≈ 65% yield,.[268] There are many examples of internal [2+2]-cycloaddition reactions of ketenes, primarily from the work of



333 **334**

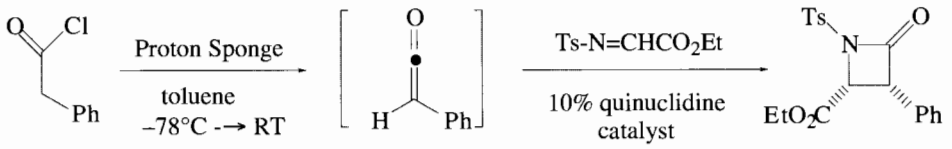
335 **336**

Ghosez and co-workers,[265] Snider et al. (as in the conversion of **335** to **336**),[269] and Brady and Giang.[270] In both Snider's and Brady's examples, the α-alkoxy substituent was present, leading to a more facile cycloaddition. As mentioned above, vinyl ketenes also react very well in the cycloaddition. For intramolecular [2+2]-cycloadditions involving vinyl ketenes, Snider defined three different reaction types: Type I (a side chain is attached to the ketene carbon),[271] Type II (a side chain is attached α- to the ketene carbon),[272] and Type III (a side chain is attached β- to the ketene carbon).[269a] An example of a Type I cyclization is the conversion of acid **337** to the ketene (**338**) and cyclization to **339** in 97% yield.[273] With vinyl ketenes, [1,5]-sigmatropic hydrogen shifts are sometimes a problem[273] (sec. 11.12.A). Snider used a Type III cyclization of this type in a synthesis of isocomene.[274] Funk et al. synthesized clovene using this methodology,[275] and Ernst and co-workers showed this method was effective for the synthesis of triquinane derivatives.[276] In another extension of this methodology, Halcomb and co-worker reported an intramolecular ketene–allene cycloaddition.[277]



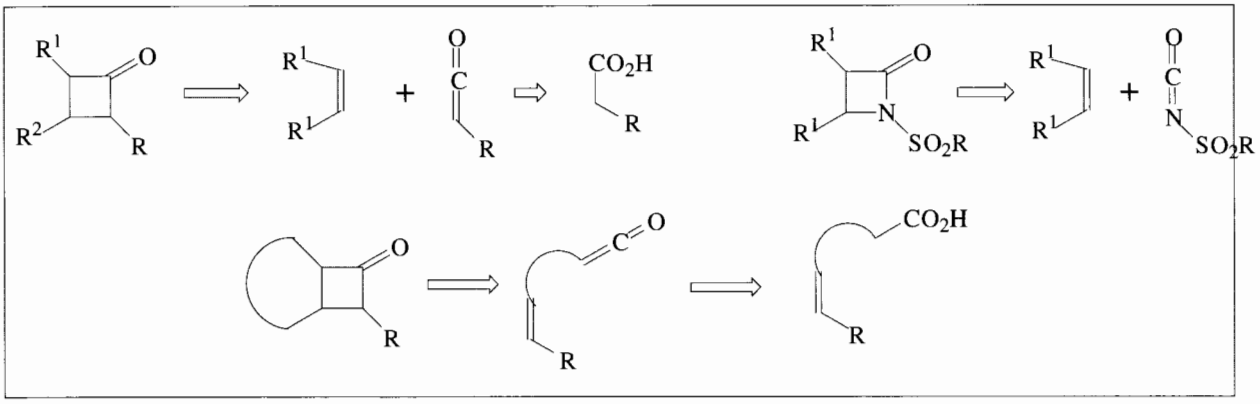
337 **338** **339**

Ketenes react with imines via [2+2]-cycloaddition to produce β-lactams.[278] An example is the reaction of the acid chloride of phenylacetic acid with Proton Sponge™ to give ketene **340**, which reacted with the tosyl imine shown and a quinuclidine catalyst to give a 65% yield of β-lactam **341**, in 96% ee.[279] *N*-Substituted isocyanates also undergo thermal [2+2]-cycloaddition reactions with alkenes, generating β-lactams.[280]

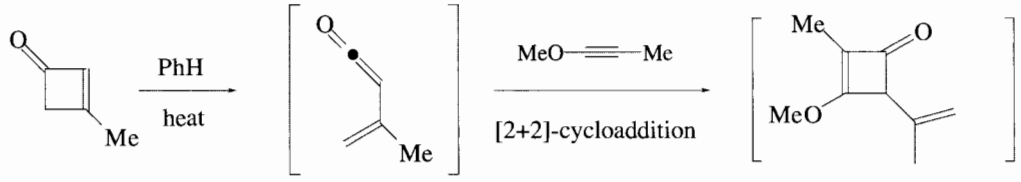


340 **341**

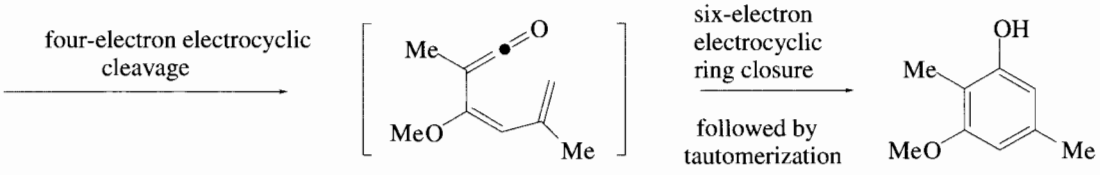
Thermal [2+2]-cycloadditions lead to the following disconnections:



The intramolecular ketene–alkene cycloaddition has also been used to prepare highly substituted phenols. As originally formulated, a cyclobutenone such as **342** was converted to a phenol derivative (**346**). When **342** was heated in benzene, ketene **343** was formed. When done in the presence of an alkyne,[281] an *in situ* [2+2]-cycloaddition led to a new cyclobutenone (**344**) but under the reaction conditions, a four-electron electrocyclic cleavage reaction occurred to give **345**. This compound also reacted, via a six-electron electrocyclic

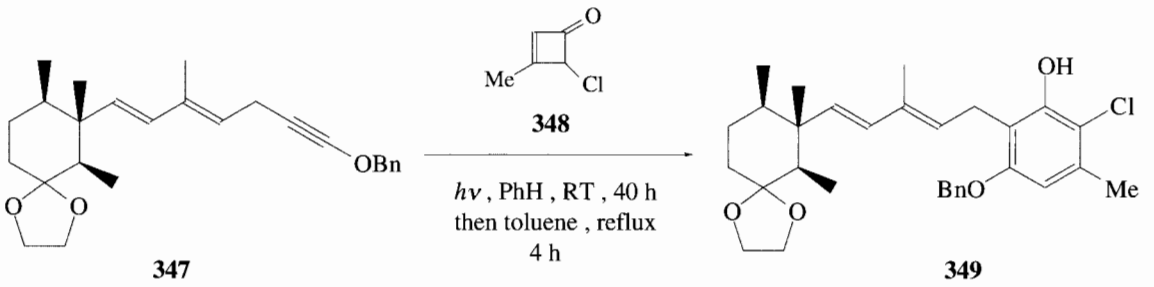


342 **343** **344**



345 **346**

ring closure to form a six-membered ring, and tautomerization gave the aromatic final product, phenol **346**. This sequence is now known as the **Danheiser annulation**. In a synthetic application, alkyne **347** was photolyzed with **348** and then treated in toluene to give **349** in 65% yield, in Danheiser's synthesis of (–)-ascochlorin.[282] Resorcinols have been prepared by this method.[283] Liebeskind reported a related method for the synthesis of highly substituted quinones.[284]



11.10.B. General Principles of Photochemistry

It is known that a normal [2+2]-cycloaddition of two alkene moieties does not occur readily under thermal reaction conditions. In one sense, therefore, the thermal [2+2]-cycloaddition reactions noted in Section 11.10.A can be considered highly useful special cases. In contrast to the thermal reaction, photochemically induced cycloaddition occurs with great ease. In the photochemical [2+2]-cycloaddition, an electron is promoted from the populated HOMO of the alkene to the unpopulated LUMO, generating an excited state. Fleming's generic orbital pictures[285] can be used in a simple illustration of this process. The HOMO and LUMO for C-substituted alkenes and for electron-deficient alkenes is shown in Figure 11.15.[285] The $HOMO_{alkene}$–$LUMO_{alkene}$ interaction is symmetry forbidden. When an electron is promoted to the LUMO via absorption of a photon of light, however, the $LUMO^*_{alkene}$–$LUMO_{alkene}$ interaction is now symmetry allowed (where * represents the excited state). The higher energy **singly occupied molecular orbital** (a **SOMO**) is of the correct symmetry to interact with the HOMO of another alkene.

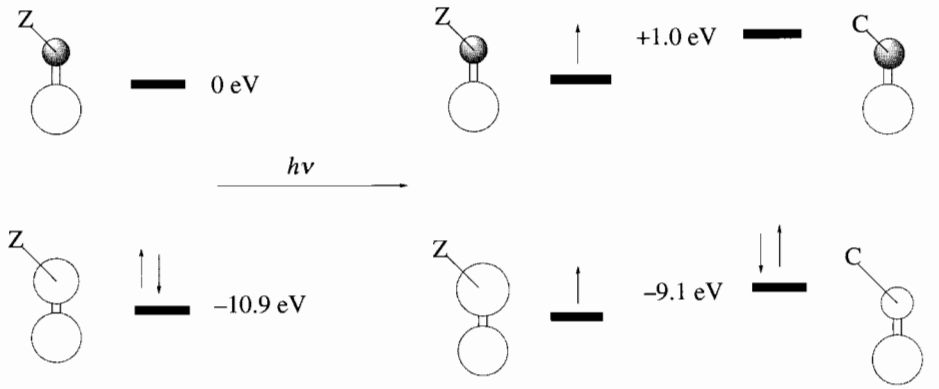


Figure 11.15. Photochemically induced electron promotion in cycloaddition reactions of alkenes. [Reprinted with permission from Fleming, I. *Frontier Molecular Orbitals and Organic Chemical Reactions*, Wiley, London, ***1976***, pp. 128. Copyright © ***1976*** by John Wiley and Sons, Inc.]

Before discussing photochemical reactions, however, we will introduce some general principles of photochemistry. Photochemistry is "concerned with the chemical change that may be brought about by the absorption of light".[286] Chemical change is not a requirement, however, since **fluorescence** (light emitted from a species that has absorbed radiation) and **chemiluminescence** (light emitted as a product of a chemical reaction) can occur.[286] A molecule can absorb a photon of light and the photoactivated species can undergo [2+2]-cycloaddition or a variety of other reactions (sec. 13.4).

Just as energy is applied to a molecule by heating, application of light can increase the energy of a molecule according to

$$E = h\nu \quad \text{where} \quad \nu = \frac{c}{\lambda} \qquad 11.5$$

The factor h is Planck's constant (6.63×10^{-34} J sec), c is the speed of light (3×10^8 m sec^{-1}), ν is its frequency in sec^{-1}, and λ is the wavelength of the light in nm, which is inversely proportional to frequency. As E is usually expressed in kcal mol^{-1}, the molecular value of E calculated from Eqn 11.5 must be multiplied by Avogadro's number, $N = 6.02 \times 10^{23}$ mol^{-1}. This gives, including conversion factors, $E = 2.86 \times 10^4/\lambda_{nm}$ kcal mol^{-1}. An energy of 1 kcal mol^{-1} corresponds to a wavelength (λ) of 2.86×10^5 Å, and in general:[287]

$$1 \text{ kcal mol}^{-1} = \frac{2.86 \times 10^5 \text{ kcal mol}^{-1}}{\lambda \text{ [Å]}} \quad \text{and} \quad \lambda = 2.86 \times 10^5 \text{ Å} \qquad 11.6$$

This wavelength corresponds to a wavenumber (ν) given by

$$\nu = \frac{c}{\lambda} = \frac{10^8 \text{ Å cm}^{-1}}{2.86 \times 10^5 \text{ Å}} = 353 \text{ cm}^{-1}, \quad \text{also} = 1 \text{ kcal mol}^{-1} \qquad 11.7$$

Therefore, 1 kcal mol^{-1} = 2.86×10^5 Å = 353 cm^{-1}, which is in the infrared (IR) region of the electromagnetic spectrum. An energy of 10 kcal mol^{-1} corresponds to 3530 cm^{-1}, also in the IR. Light of wavelength 2000 Å is at the lower end of the UV region (see Figure 11.16) and corresponds to 143 kcal mol^{-1}. Light in the UV and visible region can excite molecules to higher electronic states. Wavelengths in the UV are usually expressed in nanometers (1 nm = 1 mμ = 1×10^{-7} cm), and the UV region is 200–400 nm.

Violet Red

UV	Near UV	Vis.	IR			
10	200	400	800	2860	28600	ν (mμ = nm)
2860	143	71.5	35.75	10	1	E (kcal mol^{-1})
11972	598.6	299.3	149.7	41.86	4.186	E (KJ mol^{-1})
100	2000	4000	8000	2.86×10^4	2.86×10^5	λ (Å)
1000×10^3	50×10^3	25×10^3	12.5×10^3	3530	353	ν (cm^{-1})

Figure 11.16. Electromagnetic spectrum.

How does one know what wavelength of light to use for a particular molecule? Each functional group absorbs light according to its individual structure. If that absorption is in the UV or the IR, a UV spectrum or an IR spectrum can be obtained to determine the maximum wavelength of light absorbed. Ultraviolet light is probably used most often, and the wavelength of maximum absorption (λ_{max}) is a good guide as to which wavelength of light should be chosen for irradiation. Table 11.18[288] shows the energy of absorption in the UV (λ_{max}) for several common types of organic molecules, along with the energy in kilocalories per mole and kilojoules per mole.

Table 11.18. Absorption Maxima for Representative Molecules and Functional Groups

Molecule	Transition	λ_{max} (nm)	E (kcal mol^{-1})	(kJ mol^{-1})
C_4H_9-I	$n \rightarrow \sigma^*$	224	127.7	534.6
CH_2=CH_2	$\pi \rightarrow \pi^*$	165	173.3	725.4
HC≡CH	$\pi \rightarrow \pi^*$	173	165.3	691.9
Acetone	$\pi \rightarrow \pi^*$	150	190.7	798.3
	$n \rightarrow \sigma^*$	188	152.1	636.7
	$n \rightarrow \pi^*$	279	102.5	429.1
CH_2=CHCH=CH_2	$\pi \rightarrow \pi^*$	217	131.8	551.7
CH_2=CHCHO	$\pi \rightarrow \pi^*$	210	136.2	570.1
	$n \rightarrow \pi^*$	315	90.8	380.1
Benzene	$\pi \rightarrow \pi^*$	180	158.9	665.2
		200	143.0	598.6
		255	112.2	469.7

Functional Group	λ_{max} (nm)	E (kcal mol^{-1})	(kJ mol^{-1})
RCH=CHR	165	173.3	725.4
	193	148.2	620.4
RC≡CR	173	165.3	691.9
R(C=O)—R'	188	152.1	636.7
	279	102.5	429.1
RCHO	290	98.6	412.7
RCOOH	<208	<137.5	>575.6
—C≡N	<160	<178.8	>748.5
—N=N—	347	82.4	344.9
R_2C=N—	190	150.5	630.0

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From this table it is apparent that organic molecules absorb energy in the region of ≈ 80-200 kcal mol^{-1}, easily accessible by exposure of the molecule to a UV light source. Some molecules can react with far less amounts of energy, undergoing photochemical transformations on exposure to visible light or even IR light.

The wavelength of light absorption and corresponding energy for several common functional groups is also shown in Table 11.19,[289] along with the bond dissociation energies of that functional group. This table illustrates that the wavelength of light used for irradiation closely matches the amount of energy necessary to rupture a given bond (bond dissociation energy). In this section, the main focus will be on using alkenes and carbonyls in [2+2]-photocycloaddition reactions. These generally absorb in the 200–300 nm range (140–90 kcal mol^{-1}, 586-377 kJ mol^{-1}). Many light sources will generate light in this region, usually as a broad band of wavelengths, although it is easy to obtain a light source where one or two wavelengths predominate. A low-pressure sodium lamp, for example, generates light of primarily 589 nm (48.6 kcal mol^{-1}, 203.3 kJ mol^{-1}). Mercury lamps usually generate light at ≈ 253.7 nm (112.7 kcal mol^{-1}, 471.9 kJ mol^{-1}). A low pressure mercury lamp tends to give only this wavelength whereas a high-pressure mercury lamp gives several other intense lines as well.[290] If a molecule is irradiated with a light source generating several intense wavelengths of

Table 11.19. Bond Dissociation Energies and Spectral Regions for Irradiation

Bond	E[a] (kcal mol^{-1})	(kJ mol^{-1})	Wavelength (nm)	Spectral Region	E (kcal mol^{-1})	(kJ mol^{-1})
C=O	145	607.0	200	UV-C	140	586.0
O—H	118	494.0	250		110	460.5
C=C	102	427.0	250		110	460.5
C—H	94	393.5	300	UV-B	90	376.7
S—H	87	364.2	350	UV-A	80	334.9
C—O	69	288.8	400	Visible, violet	70	293.0
S—S	63	263.7	400		70.0	293.0
C—C	58	242.8	450	Visible, blue	62	259.5
			500	Visible, green	54	226.0
			550	Visible, yellow	50	209.0
			600	Visible, red	48	200.9
			650	Visible, red	44	184.2
			1000	IR	29	121.4

[a] Bond dissociation energy.

light, other functional groups in a molecule can absorb the light and react, including the photoproduct. A convenient method for limiting the wavelength of light (and thereby the energy of irradiation) is to filter out higher energy wavelengths (and lower energy if necessary). A filter is inserted between the light source and the reactants. Sometimes this is simply the reaction vessel, made out of Pyrex glass or quartz glass. More often, the filter material is attached to the light source. Table 11.20[291,292] shows several common filter materials and the approximate range where they transmit light.

Table 11.20. Photochemical Filters and Their Effective Transmittance Range.

Filter	Range (nm)[a]	Range (kcal mol^{-1})	(kJ mol^{-1})	E_{max} (nm, kcal mol^{-1})	(kJ mol^{-1})[a]
Quartz crystal[b]	>200	143	598.6	>230, 124.3	520.3
Vycor[b]	>200	143	598.6	≈280, 102.1	427.4
Pyrex[b]	>280	102.1	427.4	≈360, 79.4	332.4
Lead glass[b]	>290	98.6	412.4	≈380, 75.2	314.8
Window glass[c]	>310	92.3	386.4	≈350, 81.7	342.0
Schott UV-R–310[c]	275–310	104–92.3	435.3–386.4	310, 92.3	386.4
Schott UV-R–280[c]	240–320	119.2–89.4	499.0–374.2	280, 102.1	427.4
Schott UV-R–250[c]	225–300	127.1–95.3	532.0–398.9	250, 114.4	478.9
Suprasil[c]	>160	178.8	748.2	180, 158.9	665.2
Corning 5850[c]	280→450	102.1–63.6	427.4–266.2	≈360, 79.4	332.4
Corning 5970[c]	310→420	92.3–68.1	386.4–285.1	≈360, 79.4	332.4

[a] Estimated at 50% transmittance from an absorption curve. [b] Reference 292. [c] Reference 291.

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When a molecule absorbs a photon of light, an electron is promoted from the bonding molecular orbital to an anti-bonding molecular orbital ($n \rightarrow \sigma^*$, $n \rightarrow \pi^*$, or $\pi \rightarrow \pi^*$) generating a SOMO. This energy transition is illustrated by Figure 11.17.[293]

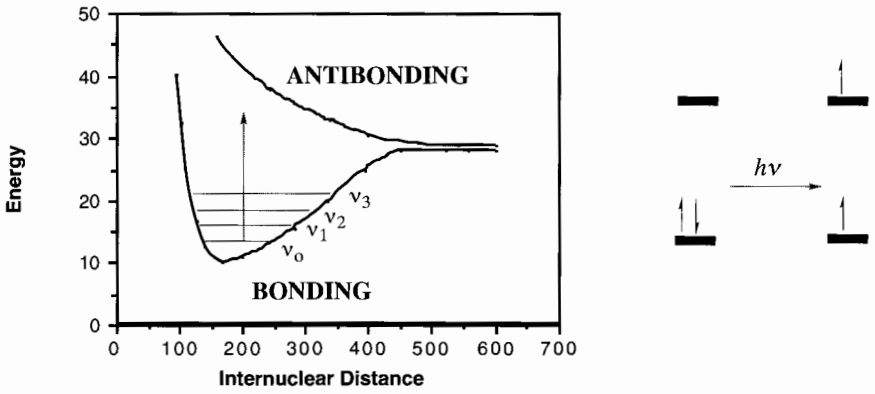


Figure 11.17. Energy transition in an electronically excited molecule. [C.H. Depuy/O.L. Chapman, MOLECULAR REACTIONS AND PHOTOCHEMISTRY, ©1972, pp. 6. Reprinted by permission of Prentice Hall, Englewood Cliffs, New Jersey.]

There are several ways a molecule can dissipate excess energy from an excited state. These are shown in a Jablonski diagram (Figure 11.18).[294] When the excess energy is lost by emission of light (**radiative deactivation**), the process is termed **fluorescence** (occurs with spin conservation) or **phosphorescence** (occurs with spin inversion). If the deactivation is nonradiative, the transition can occur between two states of the same spin (**internal conversion**) or with inversion of spin (**intersystem crossing**). The excess energy is liberated as heat in both cases. Deactivation must occur in such a way that there is no motion of the atoms during the electronic transition (the **Franck–Condon principle**). The transition can occur when the geometries of the excited and ground state are similar as an absorption (solid curves in Figure 11.19)[294] or an emission (dashed curves in Figure 11.19).[294]

In Figure 11.19, (I) is the 0→0 transition, which is the most intense for emission and absorption (most probable transition). In Figure 11.19, (II) is a case where the excited and ground states have different geometries, and the most intense transitions are 0→2' and 0'→2 (the 0→0 transition is indicated as a point of reference for case II). In both cases, the absorption and emission spectra are approximately mirror images. Therefore, it is possible to estimate the energy difference (ΔE) between the excited and ground states.

The excited state can also interact with another molecule in a bimolecular process[295] via energy transfer

$$A^* + B \longrightarrow B^* + A \qquad 11.8$$

or via exciplex formation

$$A^* + B \longrightarrow A^* : B \qquad 11.9$$

Energy transfer occurs when ΔE_{A^*A} is > ΔE_{BB^*}. In this case, an excited molecule in a triplet state can transfer

energy to the other molecule which is in the singlet state:

$$^3B_1 + {}^1A_o \longrightarrow {}^1B_2 + {}^3A_1 \qquad 11.10$$

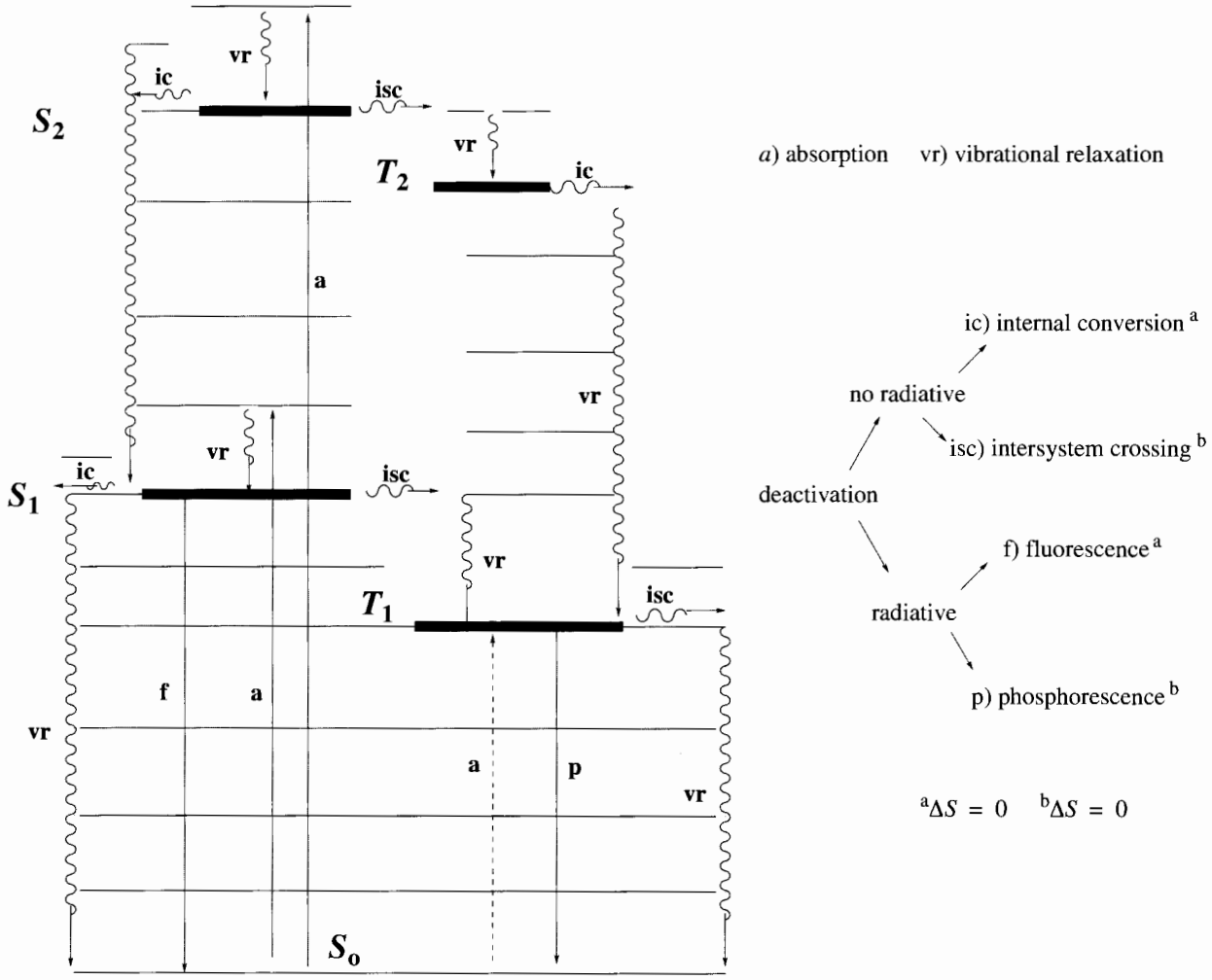


Figure 11.18. Jablonski diagram.

This process is important if the rate constant of intersystem crossing $k_{si \rightarrow tr}$ for a given molecule is small or if direct irradiation of these molecules is inconvenient. It is the foundation of a sensitized reaction.

In many cases, photon absorption is not facile and a sensitizer (S*) is added to facilitate electron transfer between two molecules,[296] as shown for the conversion of D-Y to D• and A-X to A•.[297] In these reactions,

$$S^* + D{-}Y \longrightarrow \dot{S}^- + D\bullet + Y^+$$

$$S^* + A{-}X \longrightarrow \dot{S}^+ + A\bullet + X^-$$

D-Y is an electron-rich species that generates the **sensitizer** (a molecule that donates an electron to S). Reductive fragmentation (S donates an electron to A—X) allows fragmentation of the electron poor (acceptor)

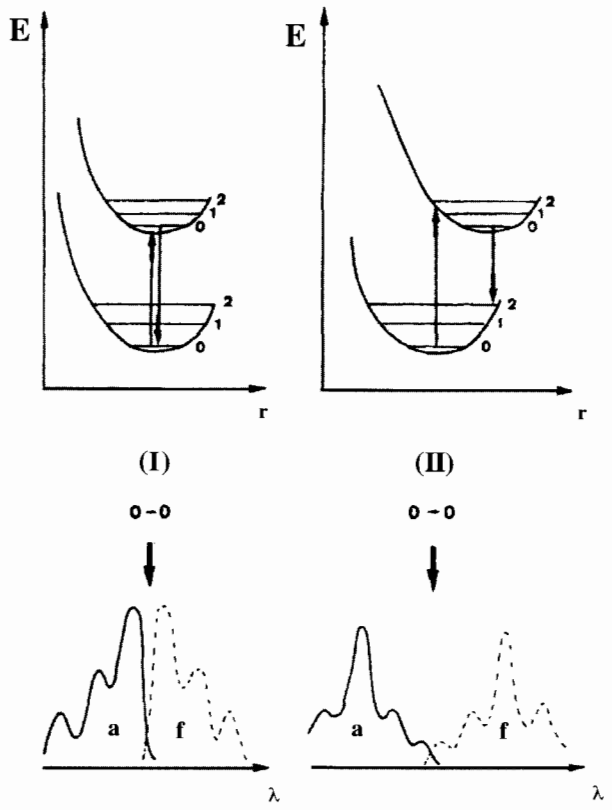


Figure 11.19. Correlation between absorption (a) and emission (fluorescence, f) spectrum.

species. As seen in Figure 11.20,[298] the use of a sensitizer involves transfer of excitation energy from an electronically excited molecule (the sensitizer) to the ground state of another molecule, usually providing a

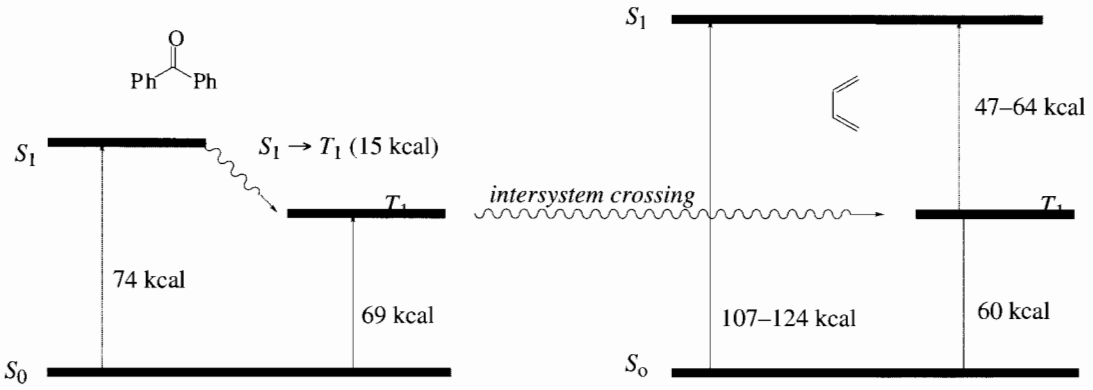
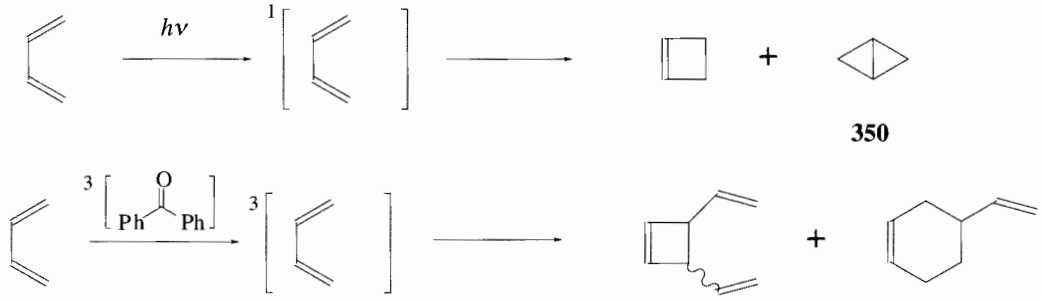


Figure 11.20. Singlet to triplet intersystem crossing for sensitized reactions. [C.H. Depuy/O.L. Chapman, MOLECULAR REACTIONS AND PHOTOCHEMISTRY, ©1972, pp. 36. Reprinted by permission of Prentice Hall, Englewood Cliffs, New Jersey.]

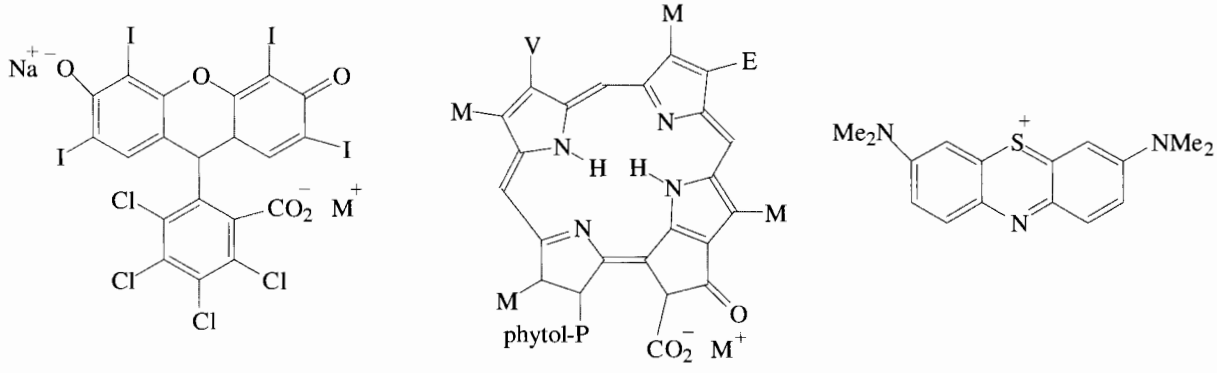
triplet excited state. Singlet excitation energy can be transferred but the lifetime of single excited states is remarkably short (10^{-8} vs. $>10^{-6}$ s for triplets).[298] Triplet energy transfer requires that the triplet energy of

the donor be higher than that of the acceptor molecule by 3 kcal mol^{-1} (12.6 kJ mol^{-1}) or more. Benzophenone is a common triplet sensitizer. The electron transfer occurs by intersystem crossing ($S_1 \rightarrow T_1$, where S is the singlet and T is the triplet), which is spin forbidden. Nonetheless, it occurs with great efficiency in molecules such as benzophenone. These processes are illustrated in Figure 11.20.[298] In the photoinduced electrocyclization reaction of 1,3-butadiene, cyclobutene and bicyclobutane (**350**) are produced, via the singlet diene. Photolysis in the presence of triplet excited benzophenone gave the dimers (**351** and **352**) via the triplet diene.[299] Irradiation at 366 nm (78.1 kcal mol^{-1}, 327.1 kJ mol^{-1}) of a mixture of butadiene and benzophenone led to exclusive absorption by benzophenone. The triplet energy of benzophenone (69 kcal mol^{-1}, 288.8 kJ mol^{-1}) is transferred with 100% efficiency via intersystem crossing ($S_1 \rightarrow T_1$) due to this small energy gap.[300] Triplet butadiene is ≈ 60 kcal mol^{-1} (251.2 kJ mol^{-1}) above the ground state, and the 69 kcal mol^{-1} (288.8 kJ mol^{-1})of benzophenone is more than adequate for diffusion controlled energy transfer to butadiene, as shown on the Jablonski diagram in Figure 11.20.[298] Since the $S_0 \rightarrow S_1$ energy gap of benzophenone is lower than the $S_0 \rightarrow S_1$ transition for butadiene, transfer between singlet benzophenone and singlet butadiene does not occur.[298]



350 **351** **352**

[C.H. Depuy/O.L. Chapman, MOLECULAR REACTIONS AND PHOTOCHEMISTRY, ©1972, pp. 37. Reprinted by permission of Prentice Hall, Englewood Cliffs, New Jersey.]



353 **354** **355**

Benzophenone is one of many commonly used sensitizers. Others include acetophenone and naphthalene. More exotic sensitizers are known and used but rose bengal (**353**), chlorophyll a (**354**), and methylene blue (**355**) are readily available and commonly used.

In photochemical reactions, it is important to measure the efficiency of the photolysis, which is done by the parameter known as **quantum yield** (or **quantum efficiency**), defined as the number of molecules reacted or formed per light quanta absorbed.[301] The quantum yield for formation of a product (Φ_{form}) is

$$\Phi_{form} = \frac{\text{No. of molecules of product formed}}{\text{No. of quanta absorbed}} \qquad 11.11$$

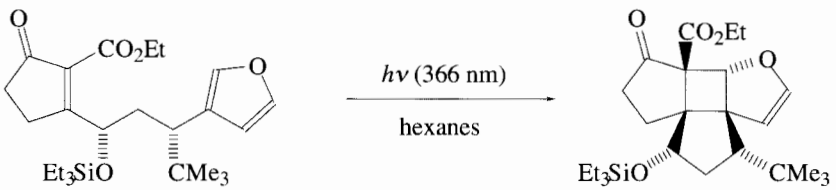
It can also be expressed in terms of the number of molecules of starting material (SM) which disappear per quantum of light (Φ_{dis}):[302]

$$\Phi_{dis} = \frac{\text{No. of molecules of SM destroyed}}{\text{No. of quanta absorbed}} \qquad 11.12$$

For photochemical reactions that give a single product, $\Phi_{form} = \Phi_{dis}$. If several products are formed, however, $\Phi_{dis} = \sum \Phi_{form}$. If a reaction does *not* go through a chain mechanism, Φ will have a value between 0 and 1. Free radical chain mechanisms have quantum yields as high as several thousand,[292] which reflects the photochemical initiation step leading to a radical chain carrier molecule or molecules.

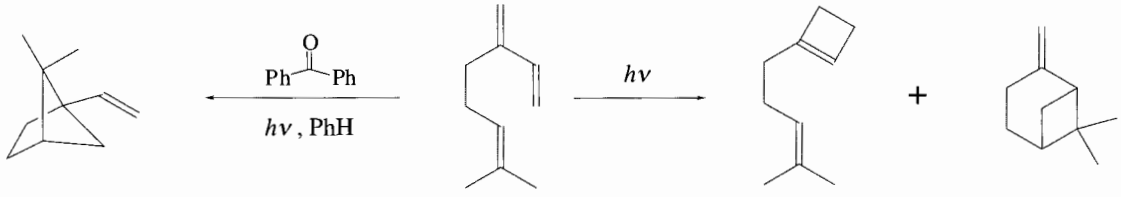
11.10.C. Photochemical [2+2]-Cycloadditions

[2+2]-Photocycloaddition reactions are quite useful in synthesis, and variations include the cycloaddition of alkenes, alkynes, and conjugated carbonyl compounds with other alkenes, alkynes or conjugated systems.[303] In general, photolysis of enones uses light with wavelengths > 3000Å (300 nm, 95.3 kcal mol^{-1}, 399.1 kJ mol^{-1}), corresponding to the n→π* transition.[304] This transition is usually obtained by photolysis in a Pyrex container, which is opaque to light < 300 nm. The n → π* transition for acrolein occurs at 315 nm (90.8 kcal mol^{-1} = 380.1 kJ mol^{-1}; the λ_{max} for acrolein).[305] Ethene, however, has a strong π→π* transition at ≈ 165 nm. Irradiation of alkene must use higher energy (165 nm, 173.3 kcal mol^{-1} = 725.4 kJ mol^{-1}) to populate the LUMO. In the case of the conjugated ester–furan units in **356**, irradiation at 366 nm led to a quantitative yield of **357** as part of Crimmins' synthesis of ginkgolide B.[306]



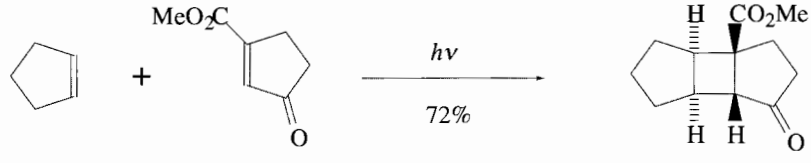
356 **357**

This type of photocyclization was studied by Hammond and co-worker, who showed that myrcene (**358**) cyclized to **359** in the presence of a benzophenone sensitizer.[307] Direct (unsensitized) photocyclization of **358** gave primarily **360** with a small amount of β-pinene (**361**).[308] Photolysis in the presence of the benzophenone sensitizer leads to a triplet diradical intermediate, whereas the direct photolysis generated an excited diene that does not cross to the triplet manifold (see above) prior to cyclization.



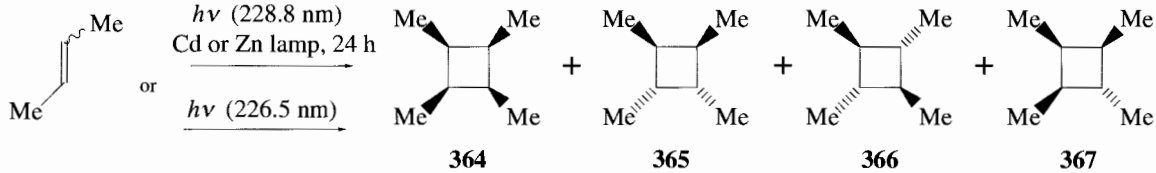
359 **358** **360** **361**

There are many examples of photochemical [2+2]-cycloadditions involving enones and alkenes. A typical example is taken from Lange's synthesis of terpenoids in which conjugated ketone **362** was photolyzed in the presence of cyclopentene to give a 72% yield of **363**.[309] Note that the two hydrogen atoms on the cyclopentene are cis to each other in **362** as are the hydrogen and CO_2Me unit. Williams and Callahan used this reaction in a synthesis of shyobunone[310] and Wender and Lechleiter synthesized 10-epijuneol by a similar route.[311] It should be noted that the selectivity for **363** is due to the fact that both of the alkene reactants are cycloalkenes. A cyclohexen-one derivative reacting with 1- or 2-butene will give a mixture of diastereomers.



362 **363**

It is apparent from these examples that the cycloaddition is highly stereoselective. The relative stereochemistry between the CO_2Me group derived from **362** and the hydrogen atom from cyclopentene (i.e., from the different alkenes) was anti, however (see **363**). Formation of this product corresponds to a suprafacial addition for both alkene fragments.[312] Free rotation around the original carbon–carbon double bond can take place in the excited state of the molecule, would not be seen in the formation of **363** since both reactants are cyclic. When 2-butene is photocyclized, however, four tetramethylcyclobutane isomers are formed (**364**–**367**).[312] Similar results are observed when unsymmetrical alkenes are photocyclized. Reaction of pure *cis*-2-butene gave only **364** and **365** with complete retention of configuration. Similarly, pure *trans*-2-butene gave only **366** and **367**. In general, reaction of an alkene and a conjugated carbonyl derivative gives a derivative such as **368**, and coupling of two nonconjugated alkenes gives **369**. Despite the selectivity shown in



364 **365** **366** **367**

the reaction of 2-butene, the relative proportions of cis and trans cycloadduct may depend on the reaction conditions. Eaton showed that irradiation of cyclopentene gave a mixture of **370** (the head-to-head dimer) and **371** (the head-to-tail dimer).[304,313] Both the molarity of cyclopentene and the solvent were varied (see

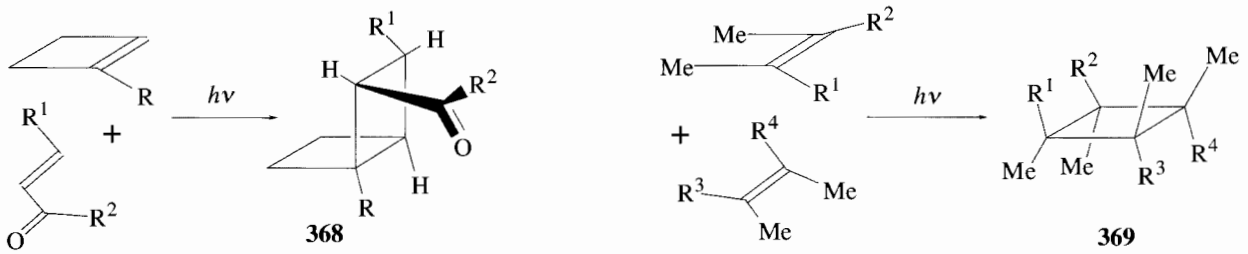
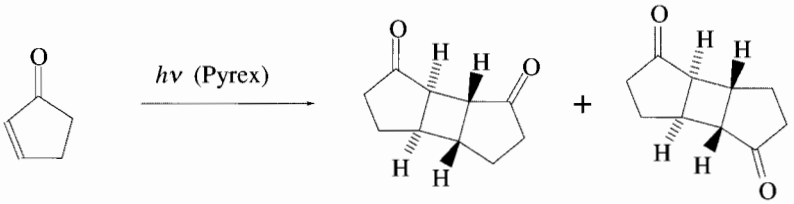


Table 11.21).[313] The trans cycloadduct was the major product in all cases but the selectivity of the cycloaddition varied with reaction conditions, generally favoring **371**. The ratio of dimers was independent of the method of triplet generation, also independent of the concentration of the sensitizer and quencher and was unaffected by the presence of excess reactant. The solvent had an effect, and the concentration effect was more pronounced in nonpolar solvents. The regiochemistry of the cycloaddition is controlled by the orbital coefficients.[314] Interaction of the largest coefficients predicts the regiochemistry. The chemoselectivity can also be predicted by frontier orbital considerations.

Table 11.21. Influence of Solvent and Concentration on the Photocyclization of Cyclopentenone



370 **371**

Solvent	Molarity	370/371
Neat	12.4	43:57
PhH	10.0	41:59
	5.0	35:65
	2.0	27:73
	1.1	23:77
	0.093	15:85
PhH/cyclopentanone	1.0	27:73
t-BuOH	1.0	24:76
EtOAc	1.0	30:70
Dimethyl 1,4-cyclohexanedicarboxylate	1.0	33:67
MeOH	10.5	41:59
	1.0	41:59
	0.1	39:61

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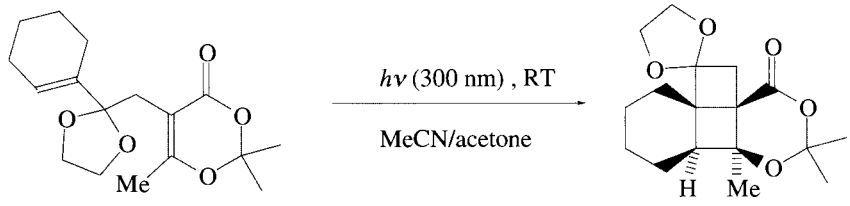
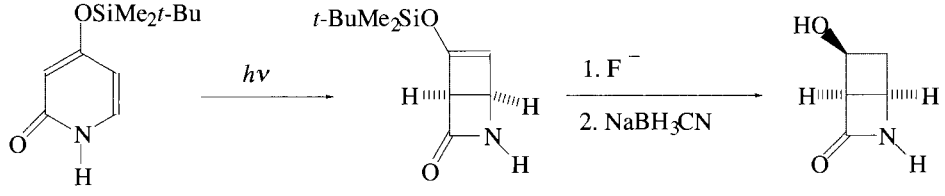
Intramolecular alkene cycloadditions are also important, not only for generation of quaternary centers but also for construction of highly bridged molecules. We saw an example of this in the photocyclization of **356**

to **357**. Photocycloaddition **372** at 300 nm gave a 95% yield of **373**, as part of Hiemstra's synthetic studies toward solanoeclepin A.[315] It is clear that very complex ring systems can be constructed with high efficiency via [2+2]-photocycloaddition reactions.



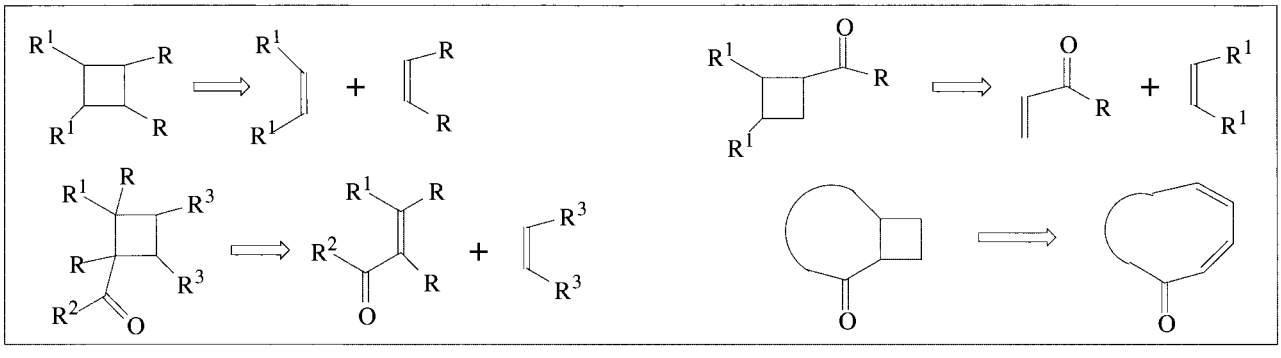
372 **373**

Electrocyclic ring closure can occur in diene systems. Even small rings can undergo internal electrocyclic ring closure. Photolysis of 2-pyridone **374**, for example, gave **375**. Unmasking the enol with fluoride gave the carbonyl, and reduction with cyanoborohydride (sec. 4.5.D) gave **376**,[316] an interesting and useful β-lactam.



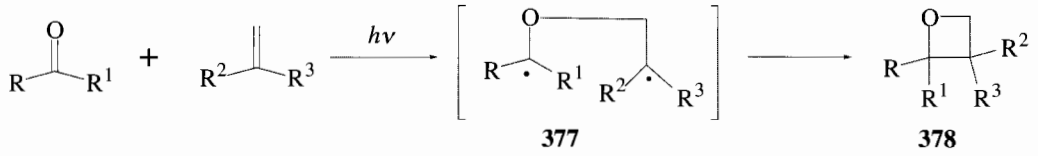
374 **375** **376**

[2+2]-photocycloaddition and electrocyclic reactions of alkenes allow the following disconnections:



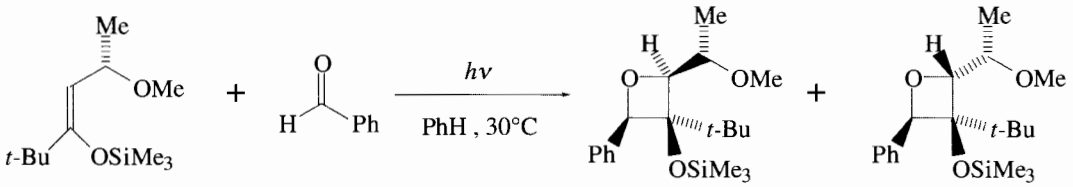
11.10.D. The Paternò–Büchi Reaction

[2+2]-Photocyclization is not limited to two alkene partners, and one important reaction involves cycloaddition of a carbonyl and an alkene. This reaction was discovered by Paternò and Chieffi in 1909[317] and expanded by Büchi et al.;[318] thus it is called the **Paternò–Büchi reaction**.[319] The product is an oxetane (**378**) and the reaction is believed to proceed via a diradical intermediate (**377**). The regioselectivity of the reaction can be explained by molecular orbital considerations, however. Electron-rich carbonyls of both aldehydes or ketones can be used. The alkene moiety is usually electron rich but this is not a requirement.

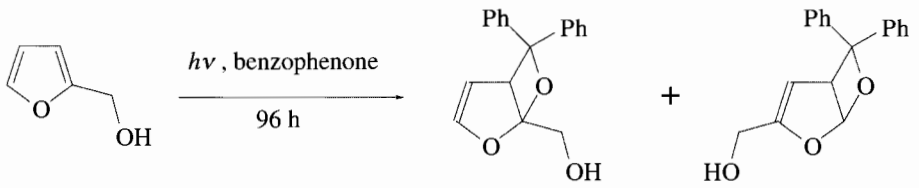


377 **378**

An interesting case is Bach's example is which silyl enol ether **379** was photolyzed in the presence benzaldehyde to give a 91:9 mixture of oxetanes **380/381**.[320] Irradiation of aldehydes such as this often uses light at 290 nm (98.6 kcal mol^{-1}; 412.8 kJ mol^{-1}), generally corresponding to the n→π* transition of the carbonyl. Lower energy irradiation can also be used, however, such as laser irradiation in the visible region (445–515 nm, 64.3–55.5 kcal mol^{-1}, 269.2–232.3 kJ mol^{-1}).[321]



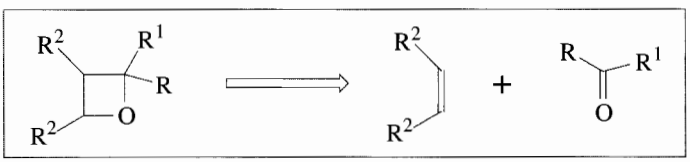
379 **380** **381**



382 **383** **384**

This reaction can be done in the presence of a rather wide range of functionality. It has been used with aromatic compounds such as 2-furylmethanol derivatives, as in the reaction of **382** with benzophenone to give a 65% yield of **383** along with a 20% yield of **384**.[322] The photocycloaddition product of the Paternò–Büchi reaction with these substrates is an acetal or a ketal, and it can be hydrolyzed to produce acyl derivatives or other functionality. This synthetic route is attractive since achiral fragments generate cycloadducts with several contiguous chiral centers whose relative stereochemistry can usually be predicted with great accuracy.

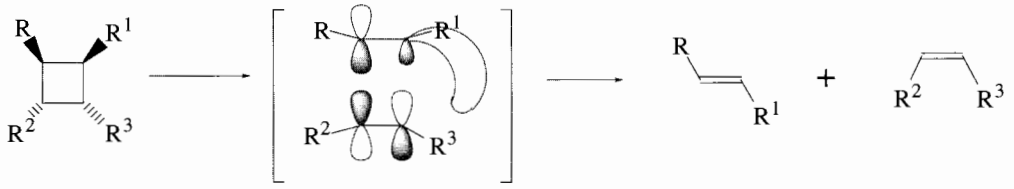
The Paternò–Büchi disconnection is



11.10.E. [2+2]-Cycloreversion Reactions

The reverse of the [2+2]-cycloaddition is a thermally allowed σ2s + σ2a cycloreversion.[323] Conversion of **385** to alkenes **387** and **388** illustrates this process. Note that the geometry of one alkene precursor is retained (suprafacial ring opening) but the other is reversed (antarafacial ring opening represented by **370**).[324] The thermal process requires interaction of a HOMO and a LUMO, which must proceed via the antarafacial inter-

action in **386**. This reaction actually expands the synthetic utility of the [2+2]-photocycloaddition. An example is the photochemical [2+2]-cycloaddition to form **389**, which is followed by thermal ring opening with cleavage of either cyclobutane moiety (**path *a*** or **path *b***). **Path *a*** leads to a 10-membered ring diene (**390**), and path *b*



385 **386** **387** **388**

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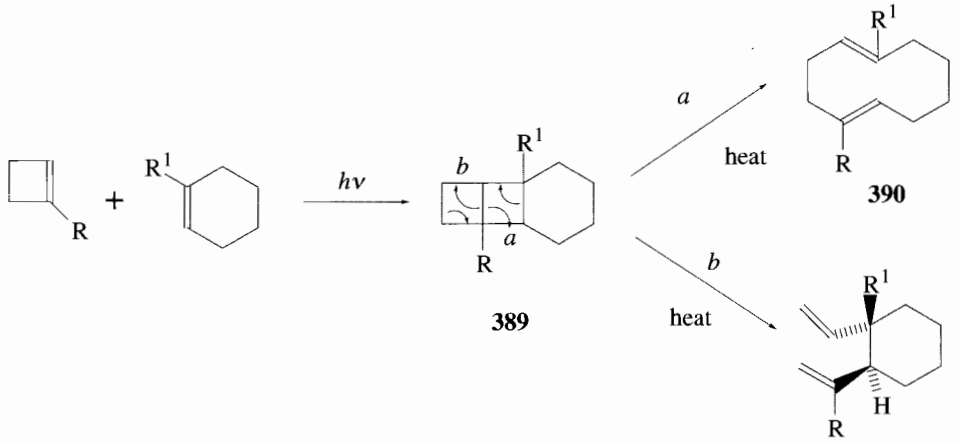
to the monocyclic diene (**391**).[325] The pathway taken by the reaction appears to depend on the substituents. Cycloaddition of ketone **392** with methylcyclobutene generates derivatives such as **393**, with alkyl substituents at the bridgehead positions. Upon heating, cycloadducts of this type open to give **394** (shyobunone), which is



389 **390** **391**

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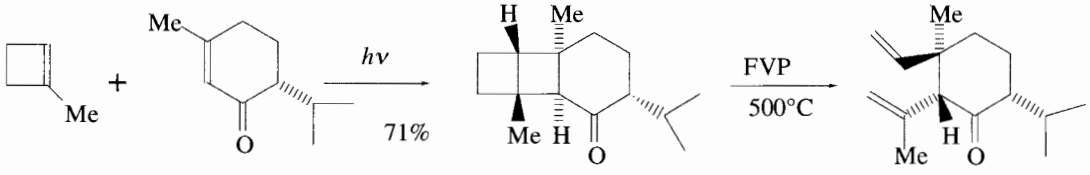
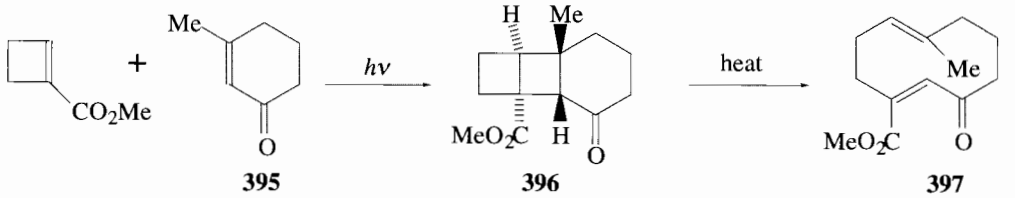
an example of an elemane sesquiterpene. This particular example gave only a 5% yield of **394**,[326,221] which contrasts with **396**, formed from methyl cyclobutene-carboxylate and cyclohexenone **395**. Cycloadduct **396** contains an ester moiety and upon heating it opened to give the germacradiene sesquiterpene isabelin, **397**, in the synthesis reported by Wender and Lechleiter.[327]

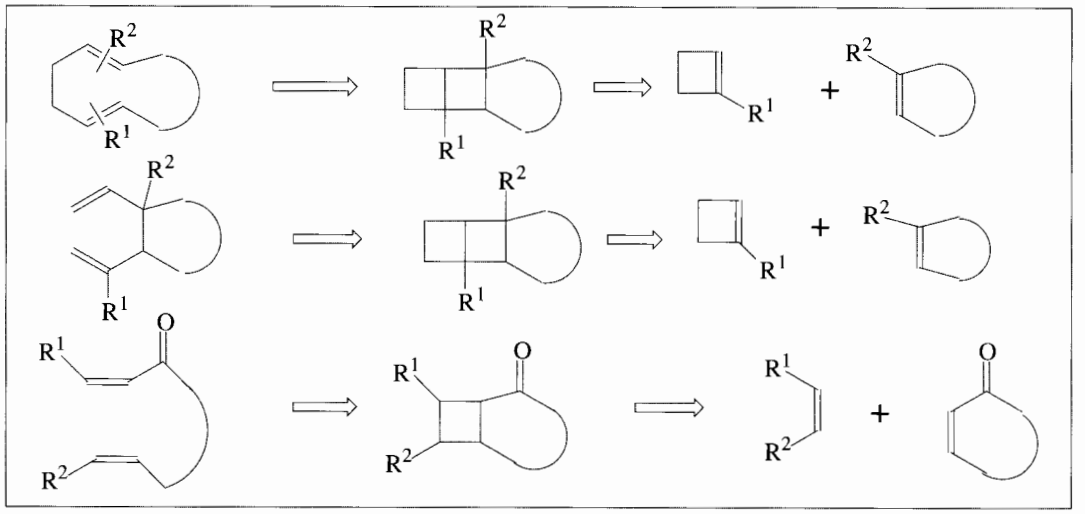


392 **393** **394**



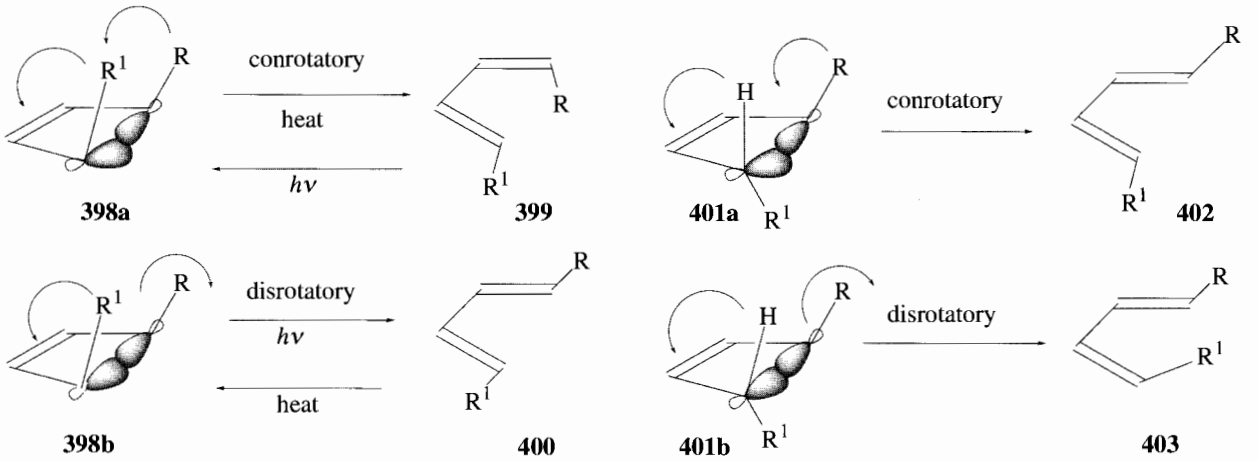
395 **396** **397**

Typical cycloreversion disconnections are



11.10.F. Cyclobutene Ring Opening

Thermal and photochemical ring opening reactions of cyclobutenes (**398** and **401**) are related to both [4+2]-cycloadditions and [2+2]-cycloreversions. Although both (*E,E*) and (*E,Z*) dienes are possible by opening a cyclobutene ring, cis disubstituted cyclobutenes (**398a**) give only the (*E,Z*) diene (**399**) thermally and only the (*E,E*) diene (**400**) photochemically. The trans disubstituted cyclobutene (**401a**) gives **402** thermally and **403**

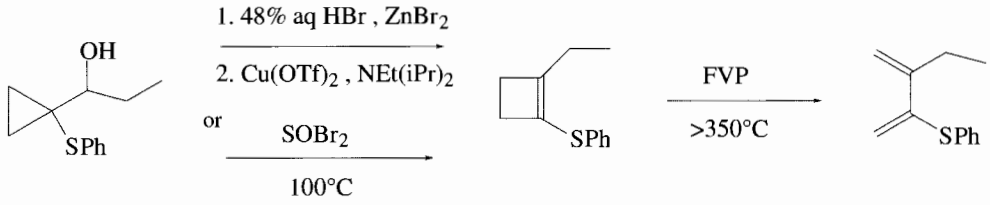


398a **399** **401a** **402**

398b **400** **401b** **403**

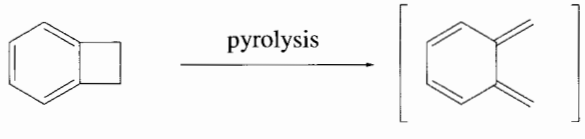
photochemically.[328] Opening of **398** can proceed via a conrotatory process (**398a**) to give **399** or a disrotatory process (**398b**) to give **400**. Experimental results suggest that the thermal process is conrotatory and the

photochemical process is disrotatory. Similarly, thermal conrotatory ring opening of **401a** leads to **402** and photochemical, disrotatory ring opening (**401b**) leads to **403**.[329] A synthetic example is the pyrolysis of cyclobutene **405** to give substituted butadiene derivative **406**. Cyclobutene derivatives can be prepared by several routes, In this example, cyclobutene **405** was prepared from cyclopropylcarbinyl alcohol **404** by treatment with thionyl bromide at 100°C[330] or by treatment with aqueous $HBr/ZnBr_2$ followed by heating with copper triflate and Hünig's base.[331] Heating **405** [with thionyl bromide at 100°C[330] or via FVP][331] opened the ring to the S-phenylthiobutadiene derivative (**406**).

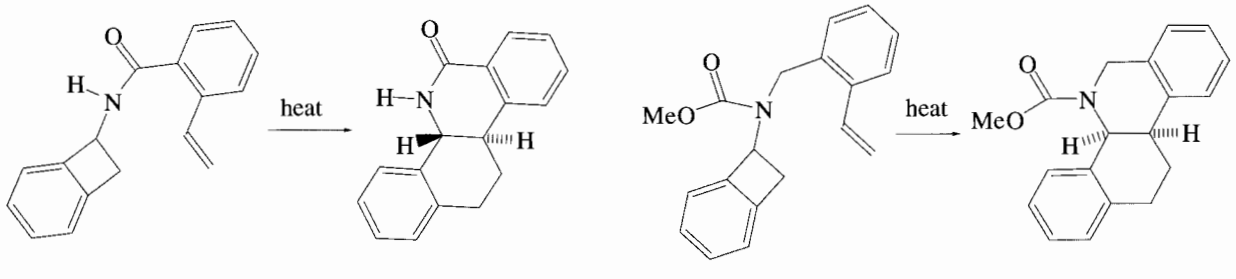


404 **405** **406**

A related reaction has been applied to several natural product syntheses, primarily in work reported by Oppolzer[332] and Kametani Nemoto.[333] In these cases benzocyclobutene derivatives (**407**) open upon heating to form a transient diene (**408**) that is highly reactive in Diels–Alder reactions because formation of the cycloadduct regenerates the aromatic ring. This method is powerful for constructing polycyclic ring systems, and the use of amide cyclobutane derivatives leads to heterocyclic alkaloids. The structure of the ring bearing the hetero-atom is dependent on the type of amide (as seen previously in sec. 11.7). Heating **409**, for example, gave the trans-adduct **410** in 90% yield, but **411** gave the cis-adduct **412** in 78% yield.[334] Amide **409** has the carbonyl within the ring being formed and **411** has the carbonyl external to the ring being formed. This methodology was used in Oppolzer's synthesis of chelidonine.[334a] The presence of a nitrogen



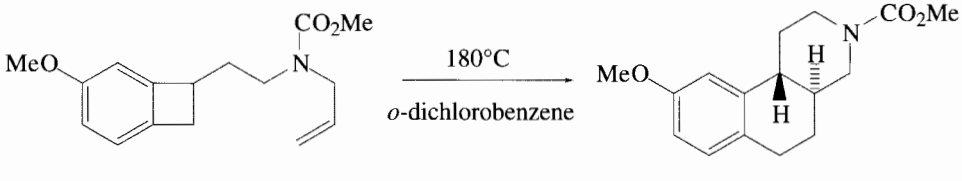
407 **408**



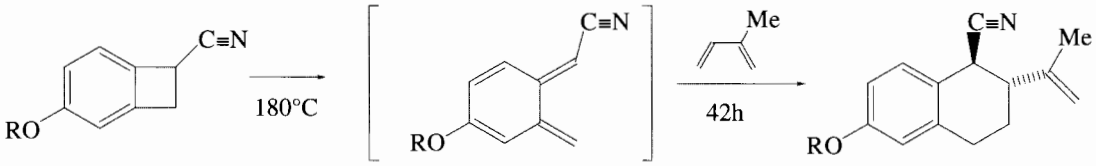
409 **410** **411** **412**

atom attached to the cyclobutane unit is not required for the reaction, and other alkaloids can be produced when the nitrogen atom is moved away from the cyclobutane unit. Heating **413**, for example, gave a 62% yield of **414**.[335] Other substituents are compatible with this reaction. Kametani, for example, synthesized

alnusenone and friedelin via ring opening of cyanobenzocyclobutene (**415**) to give the transient species **416**. When **416** is generated in the presence of isoprene, Diels–Alder cycloadduct **417** was formed in 42% yield (also see sec. 10.11.B).[336] This intermediate was chemically modified to allow a second ring opening, and a subsequent internal Diels–Alder completed the syntheses.

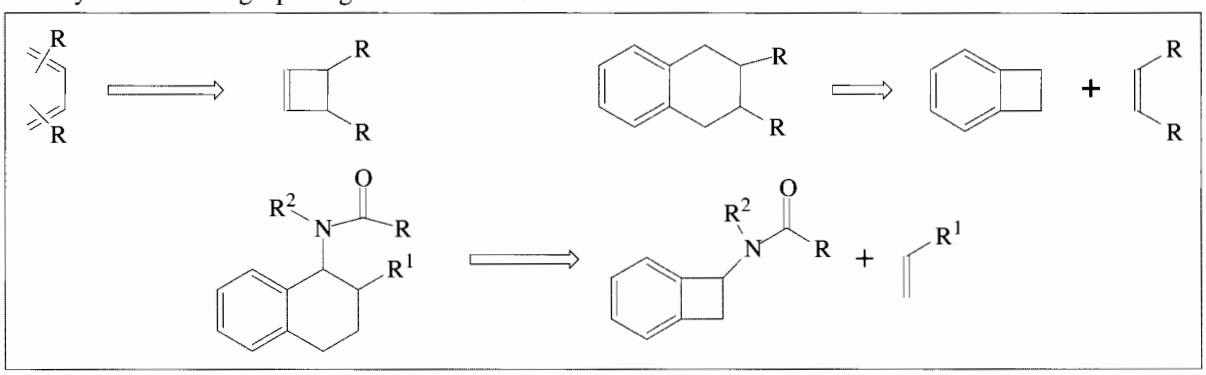


413 **414**



415 **416** **417**

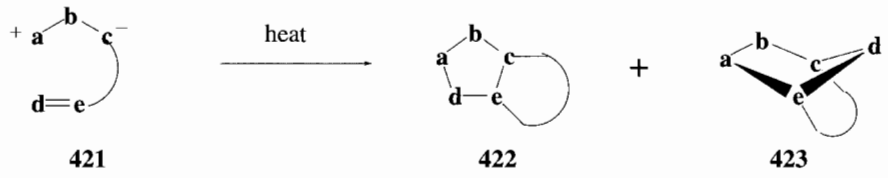
The cyclobutene ring opening disconnections are



11.11 [3+2]-CYCLOADDITION REACTIONS

We have seen both [4+2]- and [2+2]-cycloaddition reactions in previous sections. There is another class of cycloaddition reactions that involve a molecule containing a π bond (an alkene, alkyne, etc.–see **419**) with a highly polarized and usually ionic compound that is called a 1,3-dipole. 1,3-Dipoles usually take the form of **418**. When these two react, a five-membered ring is generated. Depending on the nature of a–e, carbocyclic or heterocyclic rings can be formed, and a variety of substituents can be incorporated on the ring.[337] This section will explore this class of reactions.

418 **419** **420**



11.11.A. Dipoles and Dipolarophiles

Cycloaddition reactions that involves dipolar species such as **418** (called **1,3-dipoles**) reacting with π-bonds [called **dipolarophiles** (**419**)] to give five-membered rings (**420**) are often called 1,3-dipolar cycloaddition but the formal name is [3+2]-cycloaddition reactions. A 1,3-dipole usually contains heteroatoms, and it usually contains four π-electrons, distributed over three atoms. The dipolarophile is usually an alkene or alkyne derivative. Huisgen showed that the rate of bimolecular reactions is not greatly influenced by the dielectric constant of the solvent and proceeds with high stereo- and regioselectivity.[338,339] The reaction is believed to proceed by a concerted, thermal cyclization.[340] It is noted that Firestone has proposed a two step diradical mechanism.[341] Cossío, Schleyer and co-workers studied these cycloaddition reactions computationally and found that the transition structures associated with concerted supra–supra processes are in-plane aromatic, but aromaticity does not determine regiochemistry.[342] Electrostatic interactions and solvent effects can modify the regiochemical and stereochemical outcome.[342] In a computational study of the 1,3-dipolar cycloaddition of nitrone to alkenes, Di Valentin et al. found that the concerted path (Huisgen's mechanism) should overwhelm the stepwise diradical mechanism proposed by Firestone.[343]

Both intermolecular cycloadditions (**418** → **420**) and intramolecular reactions (**421** → **422**) are possible. An isomeric bridged cycloadduct (**423**) can be produced in this latter reaction if the tether is long enough. Padwa reviewed the internal [3+2]-cycloaddition reaction,[344] as did Oppolzer.[345]

This type of dipolar addition reaction was introduced in chapter 3 in connection with ozonolysis (sec. 3.7.B), as well as permanganate (sec. 3.5.A),[346] and osmium (sec. 3.5.B) oxidation of alkenes. Ozone is a classical example of a dipolar molecule (see canonical forms of **424** $^{+}O—O—O^{-}$ and $^{-}O—O—O^{+}$). Fleming showed that the HOMO/LUMO orbitals of ozone interact with those of ethene (as shown in Figure 11.21).[347]

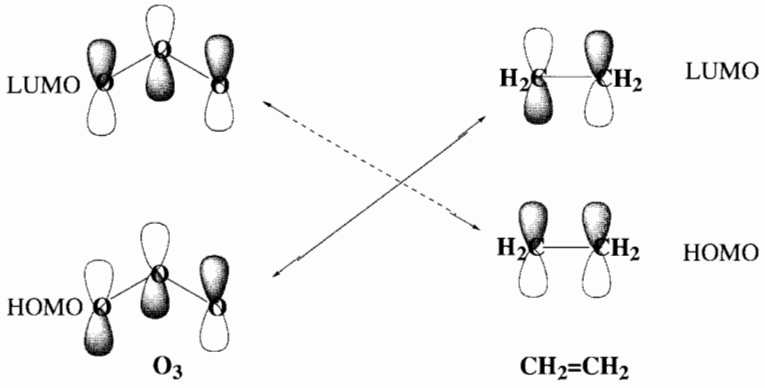
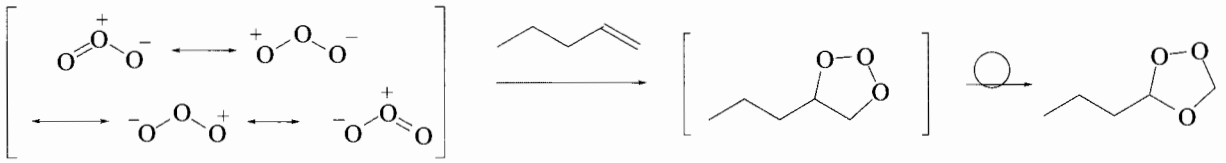


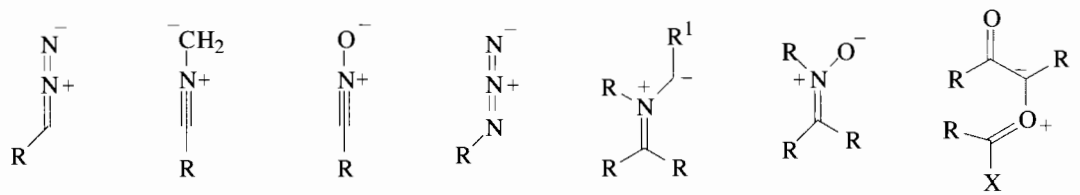
Figure 11.21. Frontier orbital interactions of ozone and ethene. [Reprinted with permission from Fleming, I. *Frontier Molecular Orbitals and Organic Chemical Reactions*, Wiley, London, ***1976***, pp. 93. Copyright © ***1976*** by John Wiley and Sons, Inc.]

Interaction of the HOMO of ozone with the LUMO of the alkene, and of the LUMO of ozone with the HOMO of the alkene are symmetry allowed. Just as with [4+2]-cycloaddition, the energy difference of these orbitals will control the facility of the reaction. In general, the low-energy interaction is the one between $HOMO_{dipole}$ and $LUMO_{alkene}$.



424 **425** **426**

As discussed in Section 3.7.B, ozone adds to an alkene to generate a 1,2,3-trioxolane. Addition of ozone to 1-pentene, for example, generated **425**. Rearrangement of this initially formed cycloadduct is facile, even at temperatures as low as –78°C, and results in cleavage of the carbon–carbon bond in **425**, with formation of a 1,2,4-trioxolane (**426**). This product is usually called an ozonide and can be either oxidized or reduced to give the carbonyl compounds characteristic of the oxidative or reductive cleavage reactions.



427 **428** **429** **430** **431** **432** **433**

There are many types of 1,3-dipoles in addition to ozone (see Table 11.22).[348] A few synthetically useful examples are diazoalkanes (**427**, secs. 13.9.B.ii, 13.9.C), nitrile ylids (**428**), nitrile oxides (**429**), azides (**430**),

Table 11.22 HOMO and LUMO Energies and Orbital Coefficients of Common 1,3-Dipoles

R^1—X—Y—Z

HOMO c_1 c_2

LUMO c_3 c_4

Dipole	X—Y—Z	HOMO	c_1	c_2	LUMO	c_3	c_4
Ozone	$^+O—O—O^-$	–13.5			–2.2		
Nitrile ylid	$HC{\equiv}N^+—CH_2^-$	–7.7	1.07	1.50	0.9	0.69	0.64
Nitrile oxide	$HC{\equiv}N^+—O^-$	–11.00	0.81	1.24	-0.5	1.18	0.17
Diazoalkanes	$H_2C{=}N^+{=}N^-$	–9.0	1.57	0.85	1.8	0.66	0.56
Azides	$HN{=}N^+{=}N^-$	–11.5	1.56	0.72	0.1	0.37	0.76
Azomethine ylids	$H_2C{=}NH^+—CH_2^-$	–6.9	1.28	1.28	1.4	0.73	0.73
Nitrones	$H_2C{=}NH^+—O^-$	-9.7	1.11	1.06	-0.5	0.98	0.32

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azomethine ylids (**431**), nitrones (**432**), and carbonyl ylids (**433**). The HOMO–LUMO values for these dipolar compounds and their orbital coefficients at the terminal atoms as shown in Table 11.22,[348] taken largely from Houk's work but also from work by Bastide and Henri-Rouseau.[349] When the energies and orbital coefficients of the alkene LUMO (from Table 11.1) are used with Table 11.22, reactivity and regioselectivity can be predicted.

11.11.B. Nitrile Ylids

These principles can be illustrated by reaction of nitrile ylid **434** [350] with ethene, methyl acrylate, and methyl vinyl ether in Figure 11.22[350] (all HOMO and LUMO values and coefficients are from Table 11.1). The ΔE values from Figure 11.22 suggest that nitrile ylids should react fastest with electron-deficient alkenes

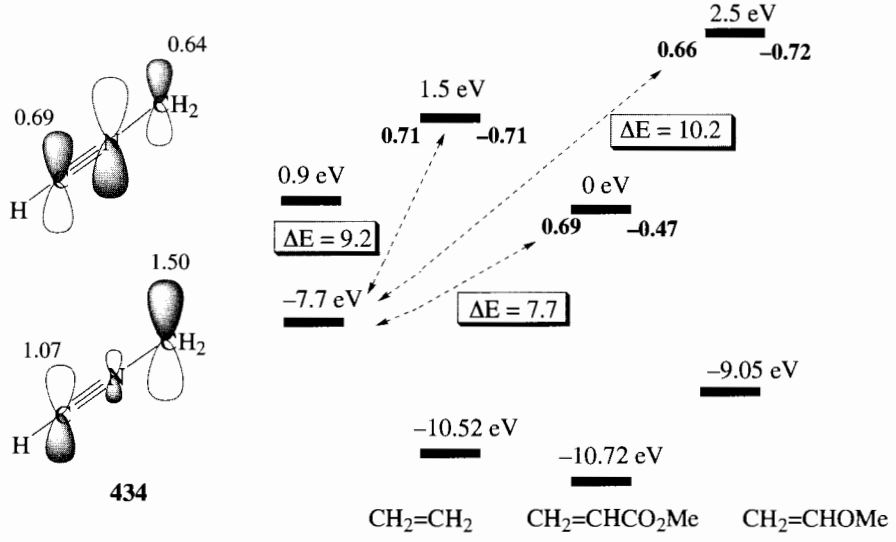
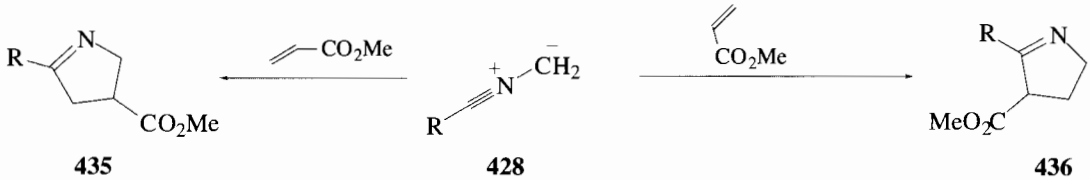
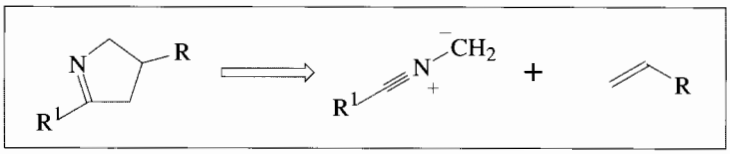


Figure 11.22. The HOMO–LUMO interactions of nitrile ylid with alkenes.

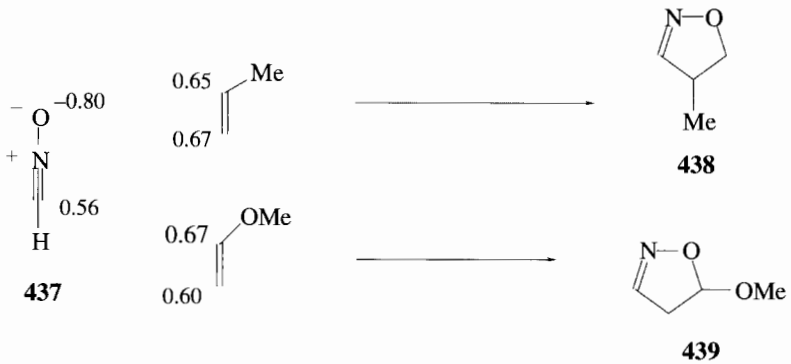
and slowest with electron-rich alkenes, similar to the normal electron demand found in Diels–Alder reactions. If so, there are two possible regioisomers for reaction of **428** with methyl acrylate, **435** and **436**. The orbital coefficients (see **434** and Table 11.1) suggest that **436** is the preferred product. Estimation of the values from Table 11.22 (for H—C≡N^+—CH_2^-) and the observation that Ph—C≡N^+—CH_2^- has a HOMO of –6.4 eV and a LUMO of +0.6 eV[351] shows that these values are sensitive to structural modification. It is therefore risky to give general predictions of either reactivity or regioselectivity and each case should be considered individually. Electron deficient alkenes have the lowest ΔE for all of the dipoles shown in Table 11.22 and should react fastest. The inverse electron demand ΔE is lower for reaction of ozone, azides, and nitrile oxides and suggests fastest reactions with electron-rich alkenes.



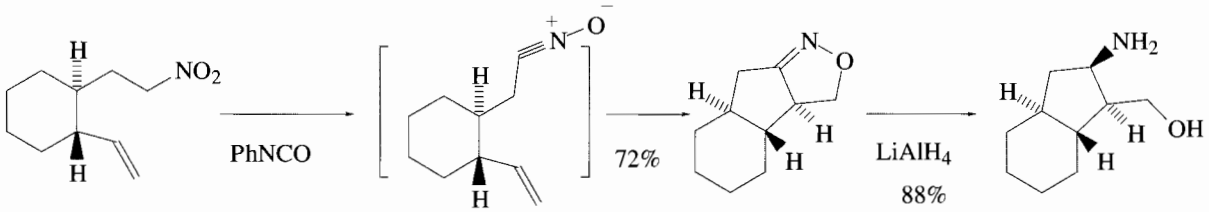
The typical nitrile ylid disconnection is



11.11.C. Nitrile Oxides



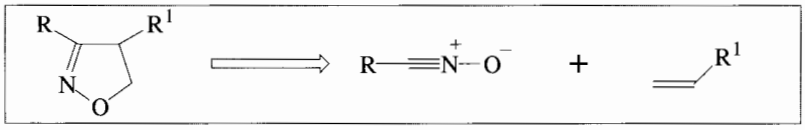
The FMO theory predicts that nitrile oxides should react faster with electron-rich alkenes (vinyl ethers, enamines, or simple alkenes). The orbital coefficients suggest (see Tables 11.1 and 11.22) that propene reacts with **437** ($HOMO_{dipole}$-$LUMO_{dipolarophile}$) to give **438**. The regiochemistry of the product depends on the substrate,. Substituents on the alkene are usually adjacent to the oxygen in the product. Products in which an alkyl substituent is adjacent to a carbon that bears an electron-releasing groups(such as methyl vinyl ether to give **439**) or an electron withdrawing group are usually preferred. A typical intermolecular cycloaddition of a nitrile oxide is shown in Bhattacharjya's synthetic studies toward papuamine, in which nitro compound **440** was treated with PhNCO in benzene to give nitrile oxide **441**, which cyclized to give a 72% yield of **442**.[352] In this synthesis, $LiAlH_4$ reduction of the isoxazoline gave amino alcohol **443**. Two procedures appear routinely



440 **441** **442** **443**

when one attempts to prepare a nitrile oxide. These two methods are (1) treatment of a hydroxamic acid with base and (2) oxidation of substituted oximes.[353] Nitrolic acids [$R(NO_2)C{=}NOH$] also give nitrile oxides upon heating.[354] Relatively complex applications of this reaction are possible, as illustrated by the sequential dipolar additions of nitrile oxides in Stevens' synthesis of corphins, and another method for the preparation of nitrile oxides is illustrated in this synthesis (from nitro compounds and isocyanates).[355,356] A [3+2]-cycloaddition reaction of nitrile oxide has been reported that was catalyzed by antibodies.[357]

The nitrile oxide disconnection is



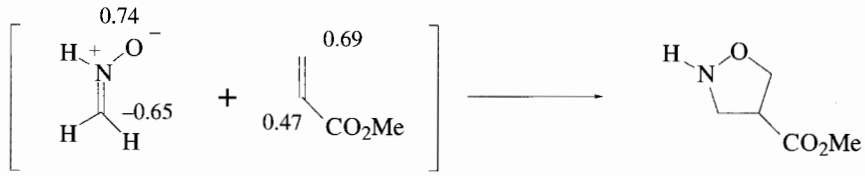
11.11.D. Nitrones

Nitrones (**444**) are potent dipoles in cycloaddition reactions.[358] Cycloaddition of an alkene to a nitrone produces an isoxazolidine (**445**) and internal cycloaddition gives a fused-ring isoxazolidine (**446** → **447**). Nitrones are commonly prepared *in situ* via oxidation of an *N*-alkenyl hydroxylamine or condensation of an

444 **445**

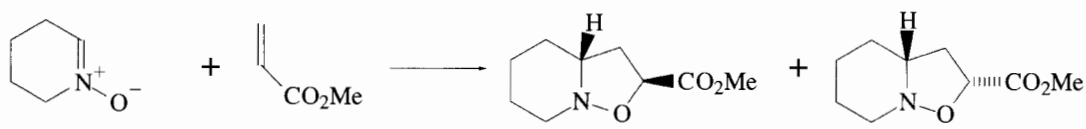
446 **447**

aldehyde with *N*-methyl hydroxylamine or any secondary hydroxylamine.[344] The $HOMO_{nitrone}$–$LUMO_{alkene}$ ΔE also suggests that nitrones react best with electron-deficient alkenes (such as methyl acrylate) The HOMO coefficients for **448** (Table 11.22) and the LUMO coefficients of methyl acrylate (Table 11.1)

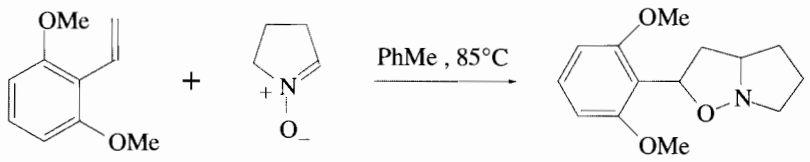


448 **449**

suggests that the electron-withdrawing substituent is aligned with the C terminus of the dipole, giving **449** as the preferred regiochemistry. When a simple nitrone reacts with a simple alkene such as propene (see Table 11.1), the same regiochemical outcome is predicted . The very small difference in the magnitudes of the orbitals, however, suggests poor regioselectivity. Good regioselectivity is observed when electron-withdrawing groups are present in the alkene, as in the reaction of nitrone **450** and methyl acrylate to give an 82% yield of **451**, along with 18% of **452**.[359,360a,338b] A synthetic example of this reaction involved nitrone **455**, which

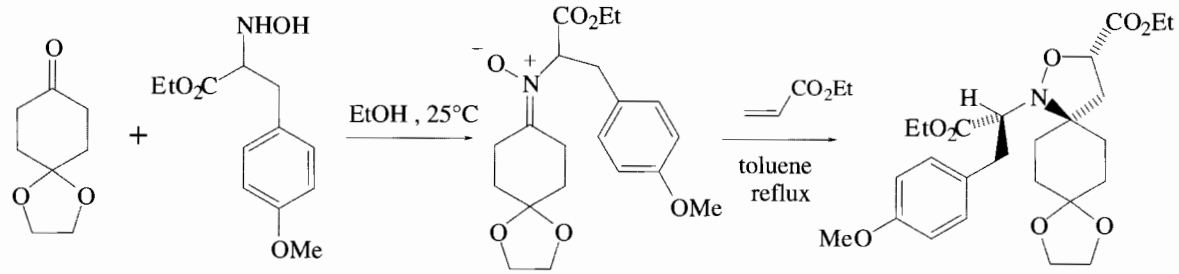


450 **451** **452**



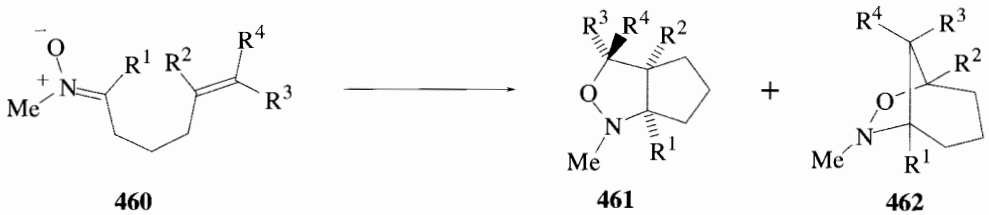
453 **454** **455**

reacted with styrene derivative **453** to give **455**, with predictable regiochemistry. This isoxazolidinone was converted to elaeocarpine by Tufariello.[359,360a] Alkyl dipolarophiles with a tendency for strong secondary orbital interactions give significant amounts of the endo product.[360] Racemization can occur in the cycloadduct after it is formed in some cases.[361]



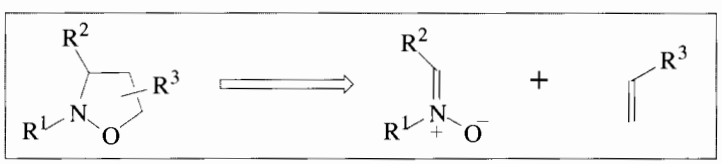
456 **457** **458** **459**

Nitrones can be prepared by reaction of an aldehyde or ketone and a *N*-alkylhydroxylamine, as in the reaction of ketone **456** with hydroxylamine **457** to give nitrone **458**. Treatment with ethyl acrylate resulted in a 9:1 mixture of isoxazolidine (**459**) as well as a diastereomer, in 74% yield, as part of the Snider and Lin synthesis of (–)-FR901483.[362] An alternative preparation of nitrones is via reduction of a nitro-ketone with zinc, which gave the nitrone, *in situ*.[363] Intramolecular cycloadditions are possible with nitrones. Cyclization of **460** gave primarily **461**. If C2 of the alkene and the α-position of the nitrone were hindered, however, the bridged product (**462**) was produced in significant amounts.[364] Two recent reports have shown that enantioselective nitrone cycloadditions are possible, using chiral imidazolidinones[365a] or chiral aluminum BINOL complexes.[365b] A recent review outlines some of this work.[366]



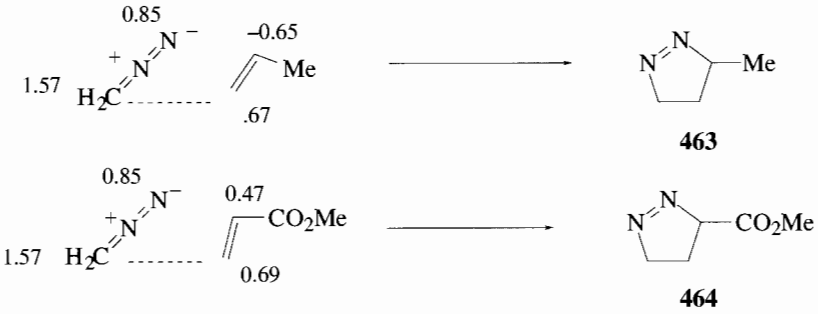
460 **461** **462**

The nitrone disconnection is



11.11.E. Diazoalkanes

Diazoalkanes are common 1,3-dipoles that are used in organic synthesis (see sec. 13.9.C for other reactions of diazoalkanes). In a simple example, diazomethane reacts with alkenes such as propene or methyl acrylate to form pyrazolines **463** and **464**. Orbital coefficients indicate the regiochemical preference of both electron-releasing and -withdrawing substituents on reaction with diazomethane is toward the N portion of the dipole. In general, diazoalkanes react fastest with electron-deficient alkenes, with **463** or **464** as the major regioisomer. A synthetic example is the [3+2]-cycloaddition of vinyl diazoalkane **465** with the terminal alkene moiety of (1,3,5*Z*)-octatriene, to give pyrazoline **466** in 55% yield.[367] Photolysis (sec. 11.10.B) of the pyrazoline led to extrusion of molecular nitrogen (N_2) via a nonsynchronous cleavage of the C—N bond.[368] This reaction is



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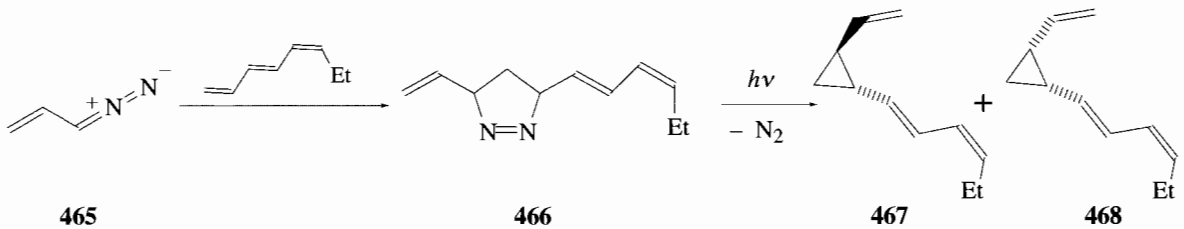
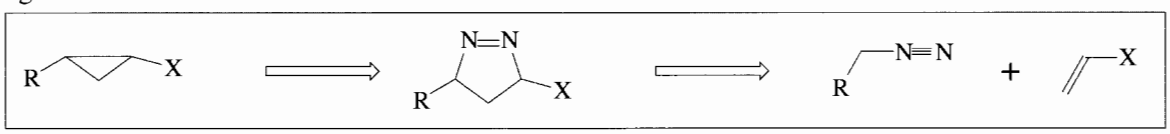
thought to proceed via discreet diradical intermediates[369] that close to form a cyclopropane ring.[370] Therefore, photolysis of **466** gave a mixture of **467** and **468** that was converted to dictyopterene B. Cyclopropane **468** was isolated and then converted to ectocarpene via a Cope rearrangement (sec. 11.12.C). The synthetic utility of pyrazoline usually arises from the ability to extrude nitrogen from the molecule under relatively mild conditions. The reaction is amenable to intramolecular [3+2]-cycloadditions.[371]



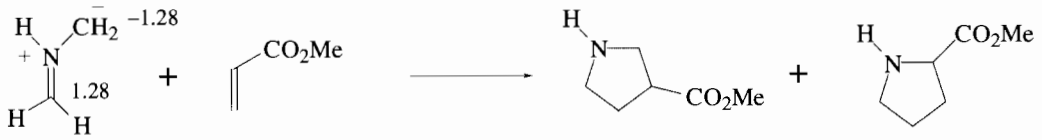
A general diazoalkane disconnection is



11.11.F. Azomethine Ylids

Azomethine ylids are useful dipoles in the synthesis of pyrroline-containing compounds. Table 11.22 indicated electron-deficient alkenes and simple alkenes react fastest (in that order), but the orbital coefficients

predict near symmetrical orbital density with simple azomethine ylids (see **469**) and little regioselectivity in the cyclic imine products. Reaction of **469** with methyl acrylate is therefore expected to give a mixture of pyrrolidines **470** and **471** and reaction with propene would also lead to a mixture of regioisomers. An alkyl group attached to the imino carbon leads to several reactive possibilities, including **472a** and its resonance contributor

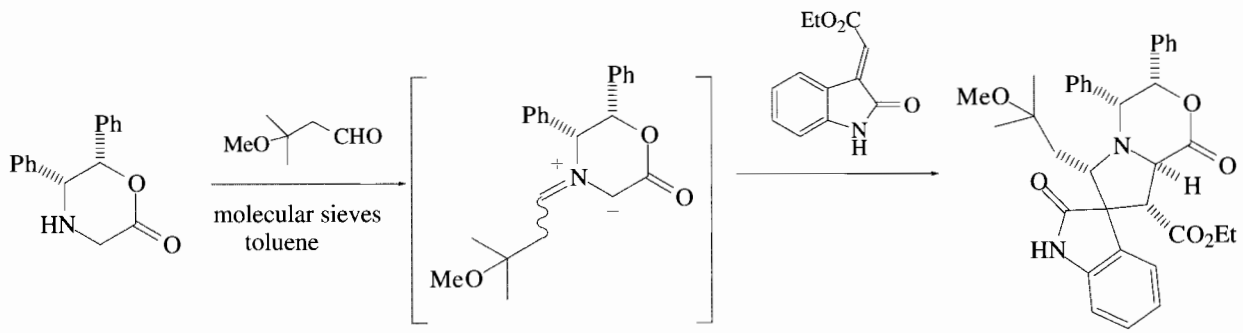


469 **470** **471**

472b. The presence of the electron-releasing alkyl group will change the orbital coefficient, leading to some regioselectivity in the cycloaddition. The relative stability of the iminium salt moiety ($C{=}NR_2^+$) will also play a role. Resonance contributor **455a** is favored over **455b** and is expected to dominate the cycloaddition.

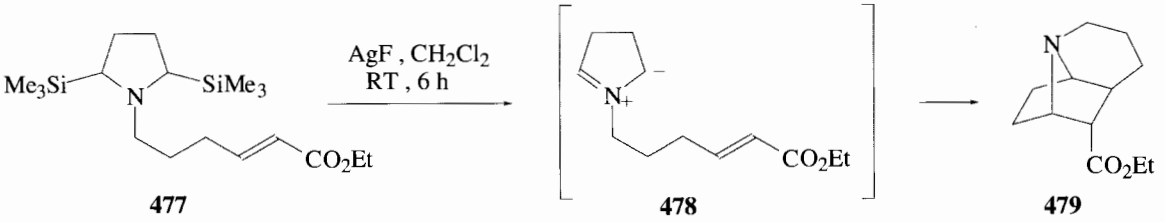
472a **472b**

Due to the presence of these resonance forms in azomethine ylids, reaction with alkenes often leads to mixtures of regioisomeric cycloadducts. Resonance stabilizing substituents are usually employed to enhance the regioselectivity. Intramolecular reactions usually favor only one mode of addition. An example of an intermolecular reaction is taken from Williams' synthesis of spirotryprostatin B,[372] in which 5,6-diphenylmorpholin-2-one (**473**) reacted with the aldehyde shown to give a mixture of (*E*)- and (*Z*)-azomethine ylids (**474**). This product was generated *in situ* with oxindole **475**, and [3+2]-cycloaddition product **476** was obtained in 82% yield.



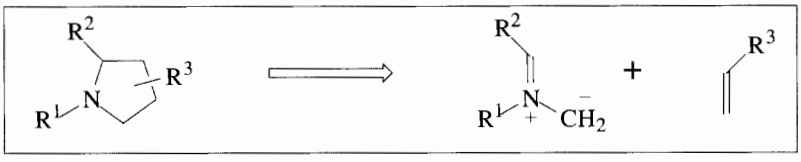
473 **474** **475** **476**

Intramolecular versions of the reaction are not only possible but are quite useful. One illustration is Pandey's treatment of bis(trimethylsilylamine) **477** with AgF to generate azomethine ylid **478**.[373] In the presence of the conjugated ester unit, cycloaddition gave a 61% yield of the azatricyclo product **479**.



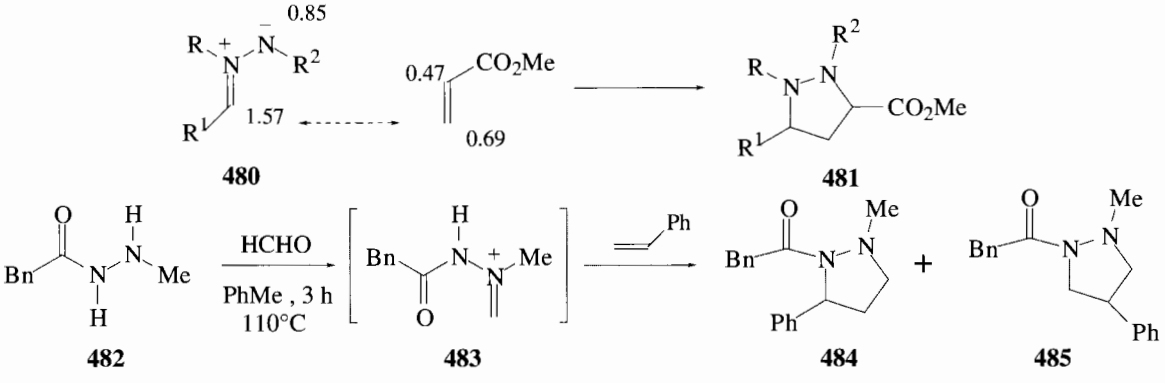
477 **478** **479**

The azomethine ylid disconnection is



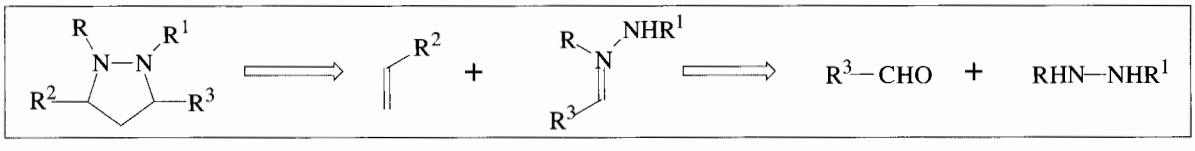
11.11.G. Azomethine Imines

Another important class of [3+2]-dipolar additions uses azomethine imines (**480**) in reactions with alkenes to give tetrahydropyrazines (pyrazolizidines) such as **481**. In this example, reaction with methyl acrylate is expected to give the regioisomer with the carbomethoxy group adjacent to the nitrogen. A similar regiochemical preference is predicted upon reaction with simple alkenes such as propene. Azomethine imines are usually generated from substituted hydrazone derivatives, which are prepared by reaction of the corresponding aldehydes with substituted hydrazine derivatives. Reaction of **482** and formaldehyde, for example, gave **483**. Once formed, the cycloaddition reaction with styrene gave 98% of **484** with only a trace of **485**.[374] This finding is consistent with the regiochemistry predicted by orbital coefficient considerations in **480**.



480 **481** **482** **483** **484** **485**

The azomethine imine disconnection is

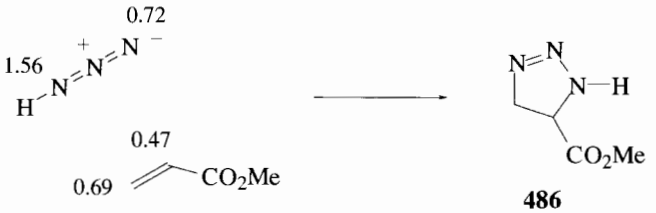


11.11.H. Alkyl Azides

Another class of organic molecules that undergo [3+2]-cycloaddition reactions are the alkyl azides, which have the structure R—N_3 (R—N^-—$^+$N≡N). In Table 11.22, hydrazoic acid (HN_3) was shown to have a

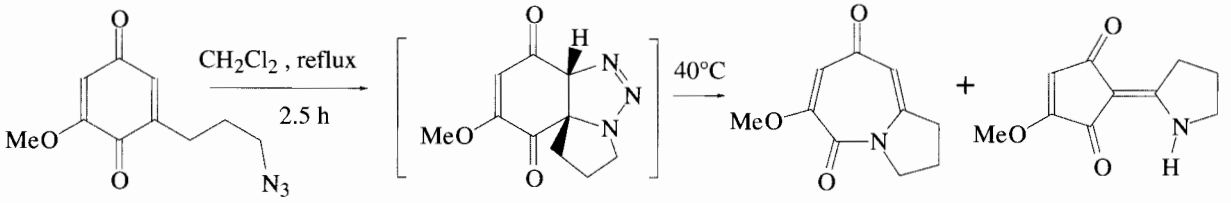
HOMO of –11.5 eV, with orbital coefficients of 1.56 and 0.72. In a reaction with methyl acrylate, the [3+2]-cycloadduct is the triazoline (**486**), based on correlation of the largest orbital coefficients.

The first report of the reaction of an azide with an alkene was by Wolff in 1912,[375] and its scope and stereochemistry were later examined by Alder and Stein.[376] This [3+2]-cycloaddition reaction is believed to



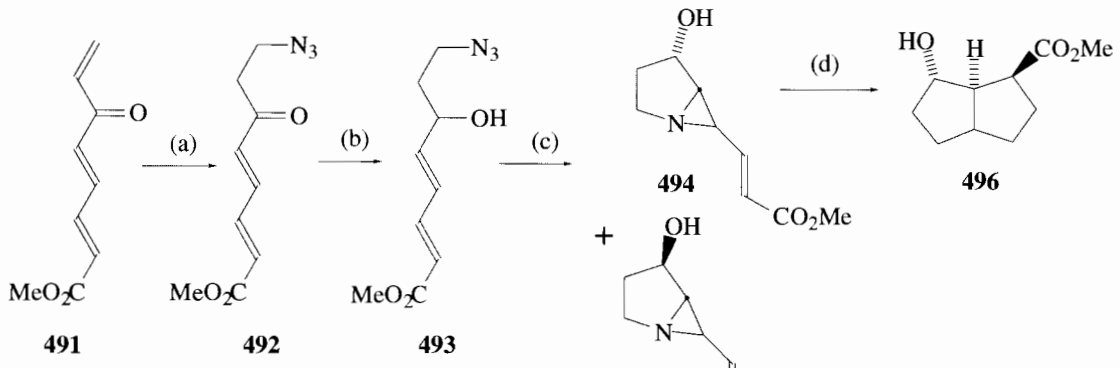
486

be concerted,[377] and it gives a triazoline product such as **486**. This heterocycle usually decomposes thermally to give pyrrolidine derivatives,[378] and photochemically to give aziridines.[379,380] An example of the thermal process is the internal cyclization of azide **487** to give the triazoline (**488**), which decomposes to give a ≈ 50%



487 **488** **489** **490**

yield of **489**.[381] At the 40°C reaction temperature, the initially formed **488** loses nitrogen (N_2) to give a 1:1 mixture of **489** and **490**. Photochemical decomposition is also possible.[350a] The aziridine product can also be formed under thermal conditions but it does not appear to be an intermediate in the pathway that forms the five-membered ring derivatives.[382]



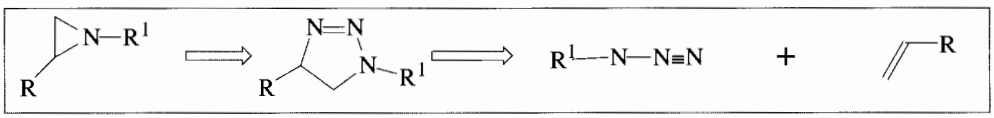
491 **492** **493** **494** **495** **496**

(a) NaN_3 , aq AcOH , RT. (b) $NaBH_4$, $CeCl_3$, MeOH , 0°C.
(c) PhMe , reflux. (d) 1. FVP (480°C) 2. H_2 , 5% Pd–C , MeOH.

An interesting application of this process to synthesis is Hudlicky's preparation of several pyrrolizidine alkaloids via treatment of conjugated ketone **491** with sodium azide (NaN_3) to give keto-azide **492** in 88% yield.[383] Addition of the azide to the diene apparently generates a triazoline, which was not isolated but

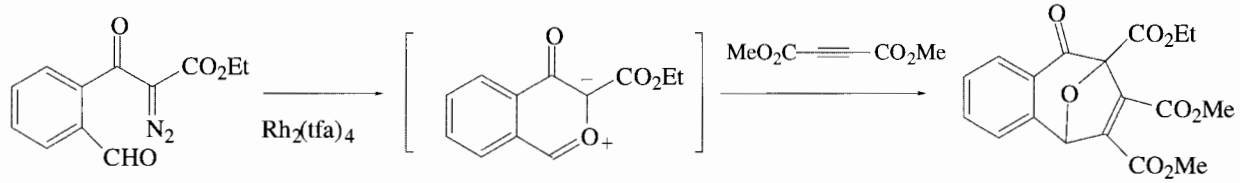
'decomposed to a transient vinyl aziridine.[384] Reduction of the carbonyl unit in **475** to give alcohol **493** (in 64% yield) used cerium borohydride ($NaBH_4/CeCl_3$–sec. 4.4.B). Subsequent heating in toluene gave **494** and **495** in ≈ 50% yield (as a 64:36 mixture) via cycloaddition followed by extrusion of nitrogen (N≡N).[383] Hudlicky combined this reaction with a nitrogen analog of the vinyl cyclopropane rearrangement (to be discussed in sec. 11.12.B). Flash vacuum pyrolysis of **494** induced the rearrangement to give pyrrolizidine **496** in 43% yield (after hydrogenation of the initially formed unstable enamine). The extent of nitrogen extrusion to form an aziridine ring depended on the reaction conditions.[385] Alkyl azides of the type shown in these examples can be generated by reaction of a suitable derivative with tosyl azide[386] or mesyl azide.[387]

The alkyl azide disconnection is:



11.11.I. Carbonyl Ylids

The final class of dipoles discussed here are the carbonyl ylids. Padwa et al. generated these reactive intermediates from a rhodium (II)-catalyzed reaction with 1-diazopentanediones.[388] A synthetic example of this reaction is taken from Padwa's synthesis of ribasine,[389] where diazo compound **497** was treated with $Rh_2(tfa)_4$ [tfa = trifluoroacetic acid ligand] to give carbonyl ylid **498**. In the presence of dimethylacetylene dicarboxylate (DMAD), cycloadduct **499** was isolated in 82% yield. Interestingly, formation of the carbonyl ylid and cycloaddition was very dependent on the rhodium catalyst used, and when $Rh_2(OAc)_4$ was used, **482** was not produced.

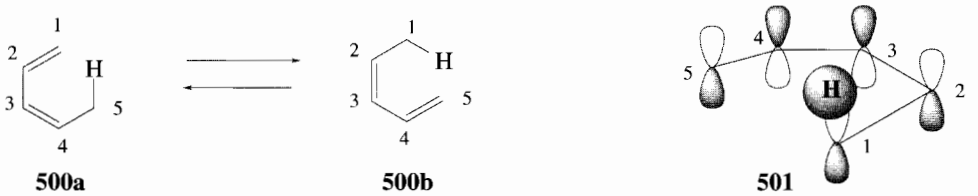


497 **498** **499**

11.12. SIGMATROPIC REARRANGEMENTS

11.12.A. [*m*, *n*]-Sigmatropic Shifts

Fleming defines a sigmatropic rearrangement as a "reaction in which a σ bond (a substituent) moves across a conjugated system to a new site", as in the transfer of hydrogen across the face of **500a** to generate **500b** (which in this simple case is identical to **500a**)[390] The nomenclature used for this process is a [m,n]-sigmatropic shift, where an atom or group migrates from position *m* to position *n*. For **500**, the hydrogen atom at bond 1 migrates to bond 5, and this is a [1,5]-sigmatropic shift. The π framework facilitates the hydrogen transfer and it can be represented by the orbital diagram in **501**. The conversion of **502** to **503** is another example of this migration, which occurs in allylic 1,3-dienes and is suprafacial ("the σ bond is made and broken on the same side of the conjugated system").[391,390] This example also shows the process to be



500a **500b** **501**

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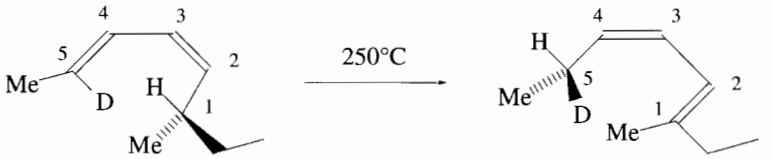
thermal, often requiring high reaction temperatures. This reaction is explained by the HOMO of the σ-bond interacting with the LUMO of the diene (see **501**), with migration of hydrogen across the π face. Since the hydrogen moves from C1 to C5, the process is called a [1,5]-sigmatropic rearrangement. A synthetic example of this rearrangement is seen by heating allene **504** to 100°C, which led to formation of **505** in 59% yield.[392] This transformation was essential to Okamura's synthesis of 9,11-dehydrovitamin D_3 analogs.



502 **503**

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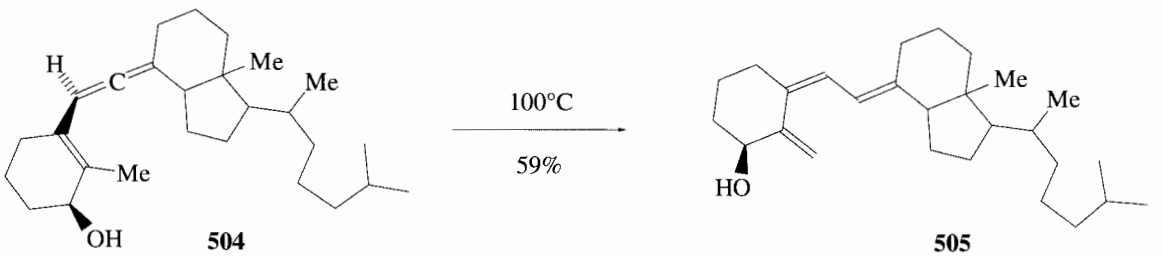
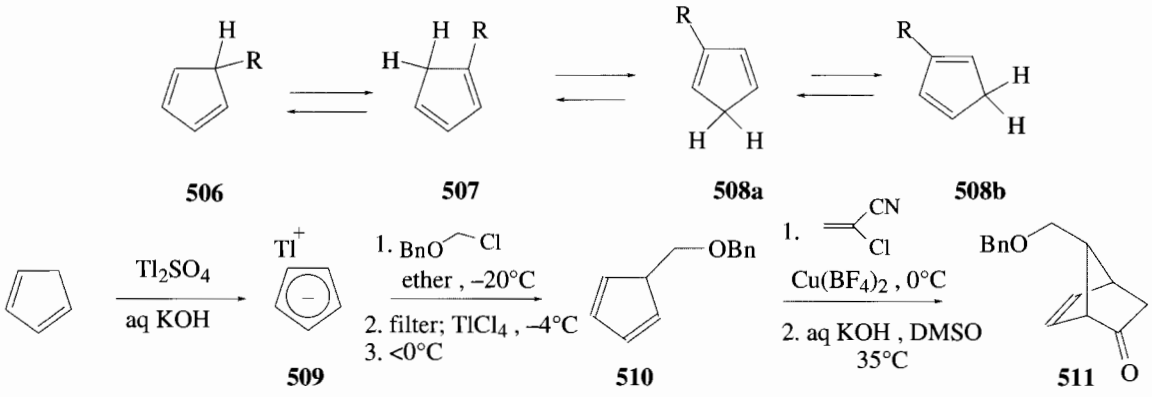
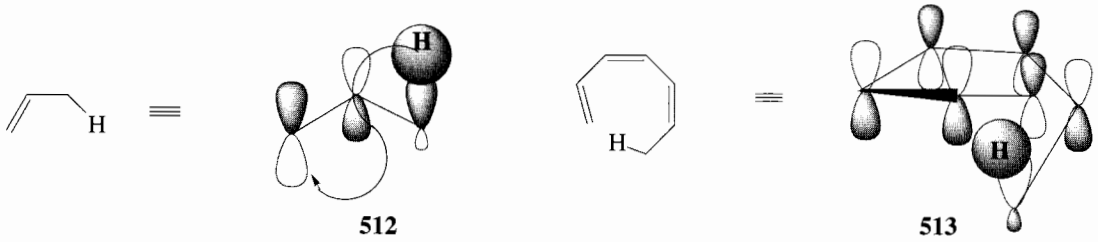


504 **505**

Sigmatropic shifts do not always require high temperatures; the [1,5]-sigmatropic rearrangement of substituted cyclopentadienes (**506**) occurs readily at room temperature,[393] which will generate three different species (**506–508**). Note that the rearrangement produces two forms of **508** (**a** and **b**) that are identical in this simple case. With substituent cyclopentadienes, they may be different isomers. The presence of several isomeric compounds leads to regiochemical control problems in Diels–Alder reactions of substituted cyclopentadienes as discussed in Section 11.8[394] (see **203**).[207] Those rearrangements can now be defined as a series of [1,5]-sigmatropic hydrogen shifts. It is possible to trap the 5-substituted cyclopentadiene, however, as in the Diels–Alder reaction of **510** to give **511** in 55% yield.[395] Diene **510** was prepared via alkylation of the thallous salt of cyclopentadienyl anion (**509**). Note that the isolation technique for **510** avoided heating above 0°C (in order to suppress the [1,5]-sigmatropic rearrangement). The Diels–Alder reaction that produced **511** used a Lewis acid to catalyze the reaction, allowing the temperature to be maintained below 0°C.[395]



Sigmatropic rearrangements can occur in other π systems. In an allylic system (**512**), hydrogen migration requires an antarafacial shift for a [1,3]-sigmatropic rearrangement and the reaction is rare.[396] With longer conjugated systems such as triene **513**, [1,7]-sigmatropic rearrangement is thermally allowed, although it is an antarafacial shift.[397] The carbon backbone is sufficiently long that it can twist, which allows antarafacial



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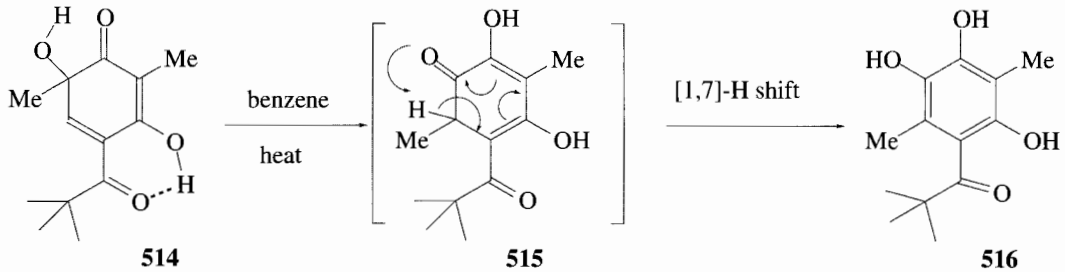
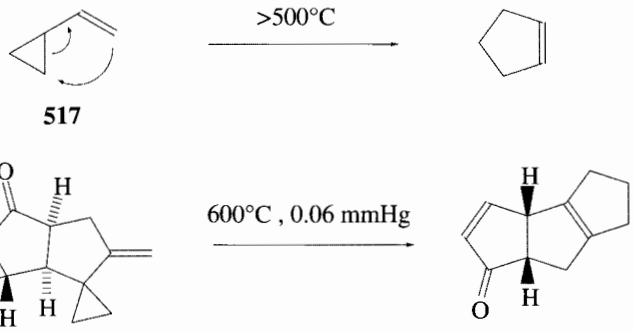
delivery of the C1 hydrogen to C7, as illustrated in **513**. This rearrangement can be difficult, and rarely occurs in cyclic trienes. There are exceptions, however, as in quinol **514** where heating in benzene led to **515**, and a [1,7]-H shift gave trihydroxybenzene **516**, as part of Nicolaou's synthesis of bisorbicillinoids.[398] In systems such as **496**, heating > 150°C leads to a [1,5]-sigmatropic shift.[399]



11.12.B. Vinylcyclopropane Rearrangements

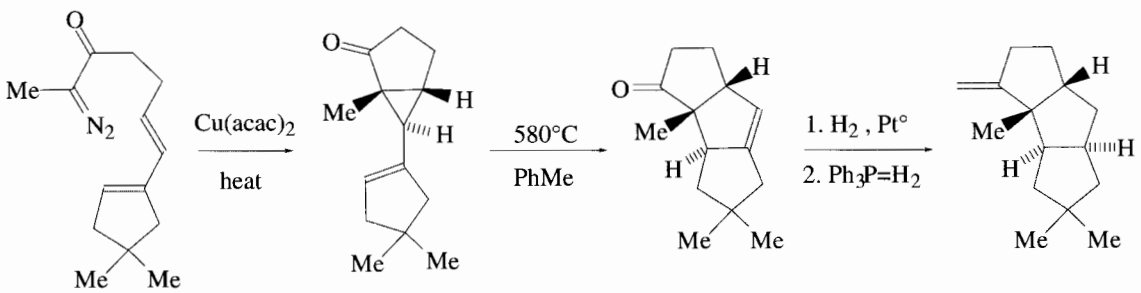
An interesting application of this chemistry involves cyclopropylcarbinyl systems that generate cyclopentenes via a [1,3]-alkyl sigmatropic rearrangement.[400] The prototype examples involves heating a vinyl-

cyclopropane such as **517** to high temperatures (usually >500°C), and rearrangement leads to a cyclopentene as shown. Both concerted[401] and diradical[402] pathways have been proposed for this reaction. An alternative proposal suggests a continuous diradical transition state.[403] The reaction has been used in synthesis. An example is Trost's synthesis of 11-hydroxyjasionone,[404] where **518** was heated to 600°C at 0.06 mmHg (FVP) to give a 97% yield of **519**.



517 **518** **519**

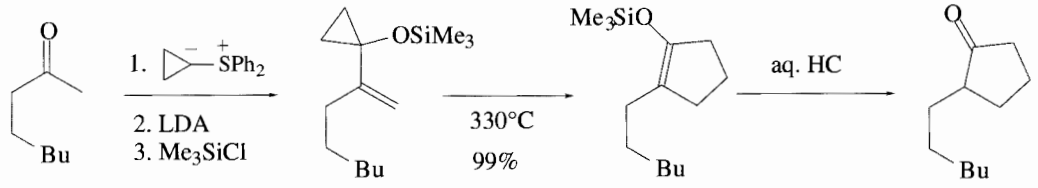
A useful source of vinylcyclopropane derivatives is the cyclopropanation reaction that occurs when diazoalkanes are decomposed to form a carbene-type intermediate, in the presence of a diene (sec. 13.9.C.i). Heating diazoketone **520** in the presence of a cupric salt generates a carbene, which adds to one C=C unit of the diene moiety to give the bicyclo[3.1.0]hexanone derivative **521**. Heating to 580°C induced the vinylcyclopropane rearrangement, which gave a cyclopentene ring in **522**. Hudlicky et al. converted **522** to hirsutene (**523**) in two steps.[405] Additional examples of cyclopropanation of alkenes with diazoalkane derivatives will be discussed in sections 13.9.B.ii and 13.9.C. This vinylcyclopropane rearrangement is general in its scope and very useful in organic synthesis.[406] There is a distinct preference for the trans isomer, as is seen in the conversion of **520** to **521**, where one cyclopropyl hydrogen and the methyl have a trans-relationship.[407]



520 **521** **522** **523**

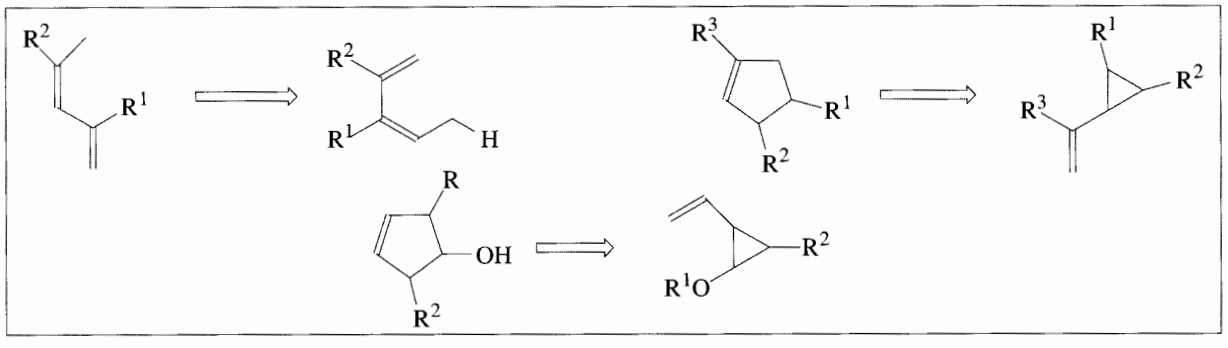
The vinylcyclopropane rearrangement is an important part of Trost's **seco-alkylation** sequence (see sec. 8.8.B.ii). In this protocol, trimethylsilyloxyvinylcyclopropanes such as **524** are generated by reaction with diphenylcyclopropyl sulfide and subsequent reaction with lithium diisopropyl amide (LDA), to open the oxaspiro-pentane) and trapping the resulting alkoxide anion with chlorotrimethylsilane. Thermal

rearrangement of the vinylcyclopropane[408bc] gave the five-membered ring enol silylether (**525**), which gave ketone **526** when subjected to hydrolysis.[408a]



524 **525** **526**

The sigmatropic hydrogen shift and vinylcyclopropane disconnections are

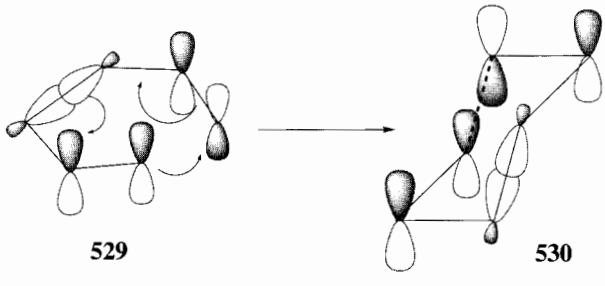


11.12.C. The Cope Rearrangement

11.12.C.i. The Normal Cope Rearrangement. Sigmatropic rearrangements are not confined to hydrogen shifts occurring within a π framework. Thermolysis of *1,5-dienes* results in a six π-electron reorganization, a

527 **528**

[3,3]-sigmatropic rearrangement, illustrated by the interconversion of **527** and **528**. This reaction is known as the **Cope rearrangement**[409] and both the reactivity and the selectivity of this reaction can be explained by



529 **530**

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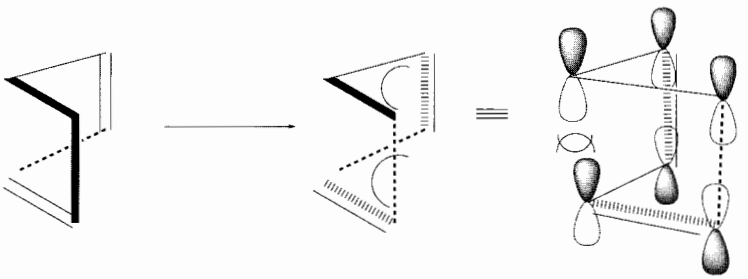
frontier molecular orbital theory. In practical terms, a 1,5-diene is converted to another 1,5-diene.[410] As seen in **529**, the orbitals of interest are at the termini (C1 and C6), which approach each other most favorably if the molecule twists into a chair-like conformation (**530**), which has important implications both for reactivity and stereochemistry. Mechanistic work also suggests that the transition state for the Cope rearrangement is predominantly aromatic in nature.[411] If the 1,5-diene cannot attain a chair conformation, the Cope rearrangement is a relatively slow reaction (this means that higher reaction temperatures are required). A boat transition state is also possible (**531**) but there is a destabilizing orbital interaction making it energetically more difficult to attain. Cope rearrangement can occur by a boat transition state, however, if the chair transition state is inaccessible. It has been determined that the chair transition state is preferred to the boat transition state by ≈ 5.7 kcal mol^{-1} (23.8 kJ mol^{-1}).[412]



531

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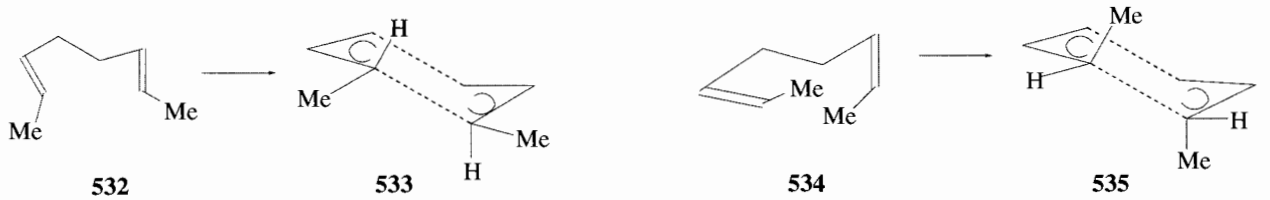
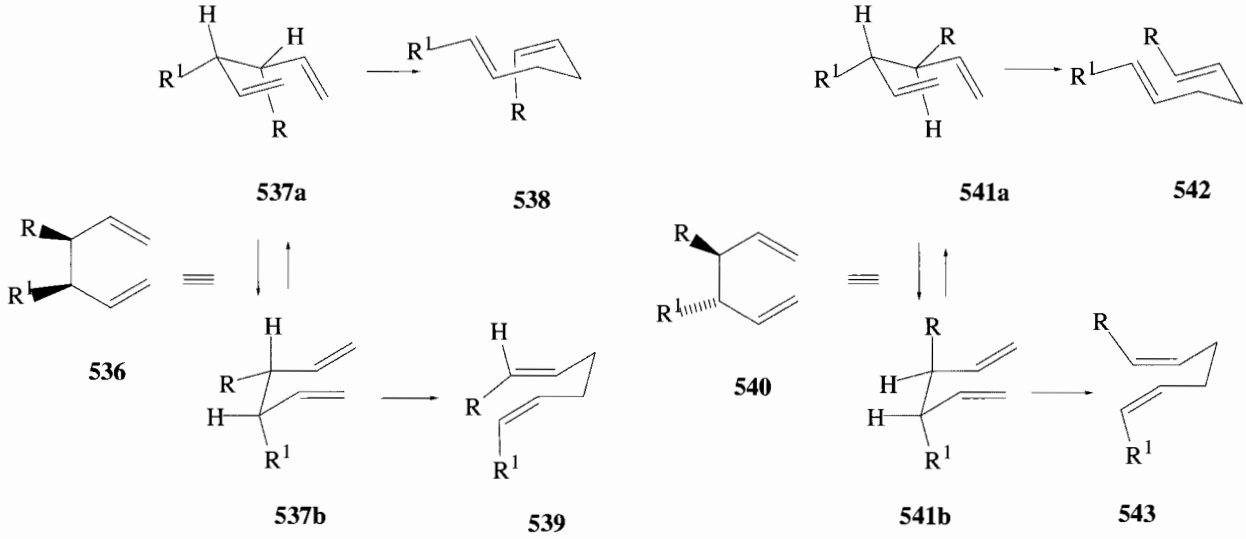
There is a significant difference in rate between (*E*)- and (*Z*)-alkenes in the Cope rearrangement. It is known that (*E,E*)-diene **532** rearranges faster than (*Z,Z*)-diene **534**. The (*E,E*)-diene is more stable than the (*E,Z*)-diene by ≈ 2 kcal mol^{-1} (8.37 kJ mol^{-1}), due to the pseudo-1,3-diaxial methyl–hydrogen interactions in transition state **535**. These interactions are absent in transition state **533**, which has two pseudo-equatorial



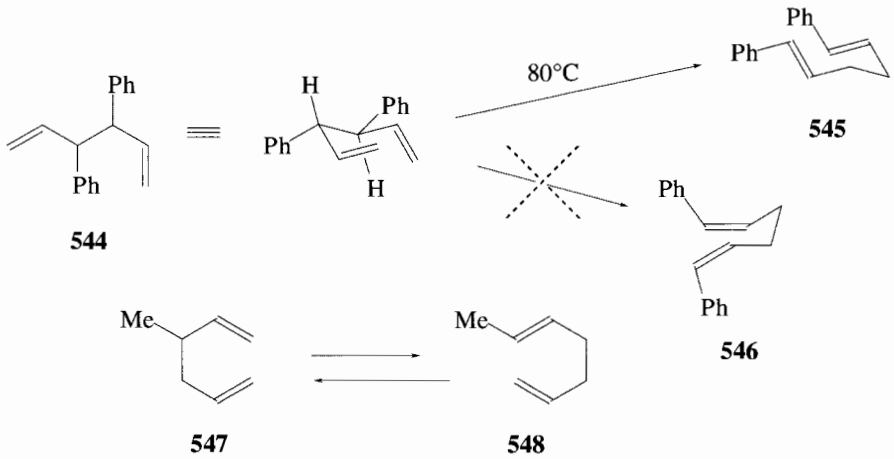
532 **533** **534** **535**

methyl groups.[412] In general, (*EE*)-dienes are expected to react faster than (*E,Z*)- or (*Z,Z*)-dienes. As the steric bulk of the substituents on the diene increase, more vigorous reaction conditions (higher temperatures) are required. These results can be generalized by examining syn-3,4-disubstituted hexadienes such as **536**.[412] Two chair-like transition states (**537a** and **537b**) are in equilibrium, and each has a pseudo-equatorial and a pseudo-axial group, leading to similar energies for each conformation. Cope rearrangement of **537a** gave **538**, the (*E,Z*)-diene, but **537b** also gave the (*E,Z*)-isomer (**539**). trans-3,4-Disubstituted hexadiene (**540**), however, generated **541a** (with two pseudo-equatorial groups) and **541b** (with two pseudo-axial groups).[412] Since the 1,3-diaxial interaction (R-R) in **541b** will be greater than the analogous interaction (H—H) in **541a**,

541a will be lower in energy. Conformation **541a** leads to the (*E,E*)-isomer **542** and **541b** leads to the (*Z,Z*)-isomer **543**. Since **541a** is the lowest energy transition state, the (*E,E*)-diene should predominate. These predictions are borne out with the reaction of meso-2,3-dimethyl-1,5-hexadiene (**536**, R = Me), which gave 99.7% of **538** (R = Me) and 0.3% of **539** (R = Me) at 225°C for 6 h. The (*dl*)-isomer (**540**, R = Me) gave 90% of **542**, 10% of the cis-,cis-diene product and <1% of **543** (R = Me).[412] von E. Doering and Roth[412] determined that the reaction gave a >300:1 preference for products derived from the chair transition state over



the boat transition state, leading to the energy preference of 5.7 kcal mol^{-1} (23.9 kJ mol^{-1}) for products derived from the chair transition state, mentioned previously. The influence of the pseudo equatorial versus the pseudo axial groups can be seen in the Cope rearrangement of **544**, also drawn as the pseudo-diequatorial rotamer. Hexadiene **544** gave only the (*E,E*)-diene (**545**) rather than **546** when heated to 80°C for 8 h. The diaxial rotamer would lead to the unobserved (*Z,Z*)-isomer (**546**).[413] The obvious implication is a marked conformational preference for the pseudo-diequatorial rotamer (see alternative rendering of **544**). This compares with the 3-phenyl-4-methyl derivative, which gave a 90% yield of the (*E,E*) diene and 10% of the (*Z,Z*)-diene.[413]



3,4-Disubstituted dienes (such as **544**) undergo Cope rearrangement more easily (at lower temperatures) than the corresponding 1,6-disubstituted dienes (see **432**). Substituents at the C2 and C5 positions, however, have little effect. These observations can best be explained by identifying the Cope rearrangement as an equilibration process (as seen in **537a** ⇄ **537b**). Under the thermal conditions of the reaction, the thermodynamically most stable diene will accumulate. Heating 3-methyl-1,5-hexadiene (**547**), for example, gave ≈60:40 mixture of **547** and **548**.[414] In this case, the energy difference between **547** and **548** is rather small, and **547** is only slightly favored, leading to the mixture. The Cope rearrangement is, therefore, most efficient when the product diene of the equilibrium is significantly more stable than the starting diene.

Introducing strain into the molecule lowers the activation barrier for the [3,3]-sigmatropic shift, as does introduction of an oxygen atom. The relative rate of each reaction is inversely proportional to the highest activation barrier:[415] 33.5 kcal mol^{-1} (140.2 kJ mol^{-1}) for **549**,[416] 23.1 kcal mol^{-1} (96.7 kJ mol^{-1}) for **550**,[417] 19.4 kcal mol^{-1} (81.2 kJ mol^{-1}) for **551**,[418] and 18.2 kcal mol^{-1} (76.2 kJ mol^{-1}) for **552**.[419]

549 **550** **551** **552**

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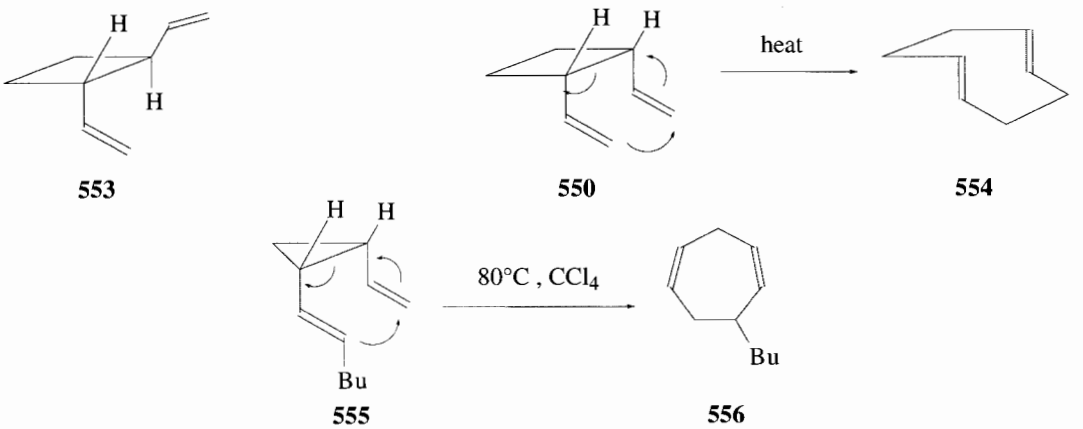
When both strain and stereochemical bias are present in the diene, remarkable rate accelerations can be observed. The activation energy for **550** ($\Delta E \approx$ 23.1 kcal mol^{-1}, 96.7 kJ mol^{-1}) is lower than that for the trans isomer, **553** (ΔE = 34.0 kcal mol^{-1}, 142.3 kJ mol^{-1}).[417] Diene **553** cannot assume either a chair or a boat conformation without distortion of the molecule, making the Cope rearrangement slow. It is possible to distort the cyclobutane ring to generate a chair conformation, but such a structure will be higher in energy. The cis compound can readily assume both a chair and a boat conformation and will undergo the Cope rearrangement



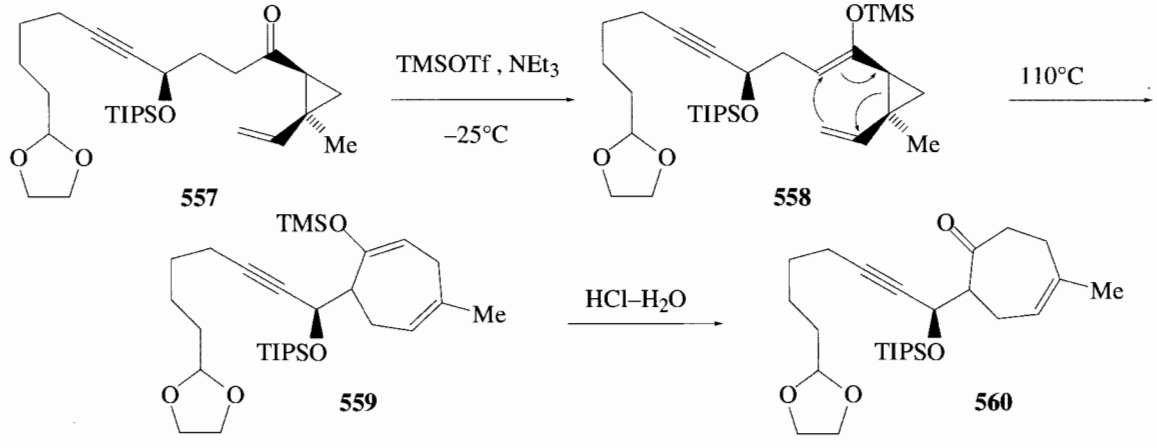
553 **550** **554**

555 **556**

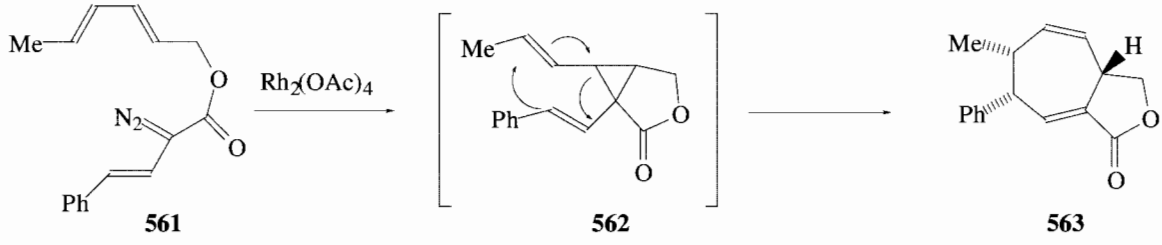
with relative ease. The strain imparted by a cyclobutane ring is seen in the 3,4 bond of the diene (see **550**), but this strain is diminished in the Cope rearrangement product (**554**), which is an eight-membered ring with some

inherent strain (sec. 1.5.B), but not enough to preclude opening the four-membered ring. Dictyopterene C (**556**) was prepared via Cope rearrangement of the cis-diene, **555**.[420] The strain of the cyclopropane ring accelerated the reaction, which required heating to only 80°C. Significant differences in energy between product and starting material can make the process effectively irreversible.

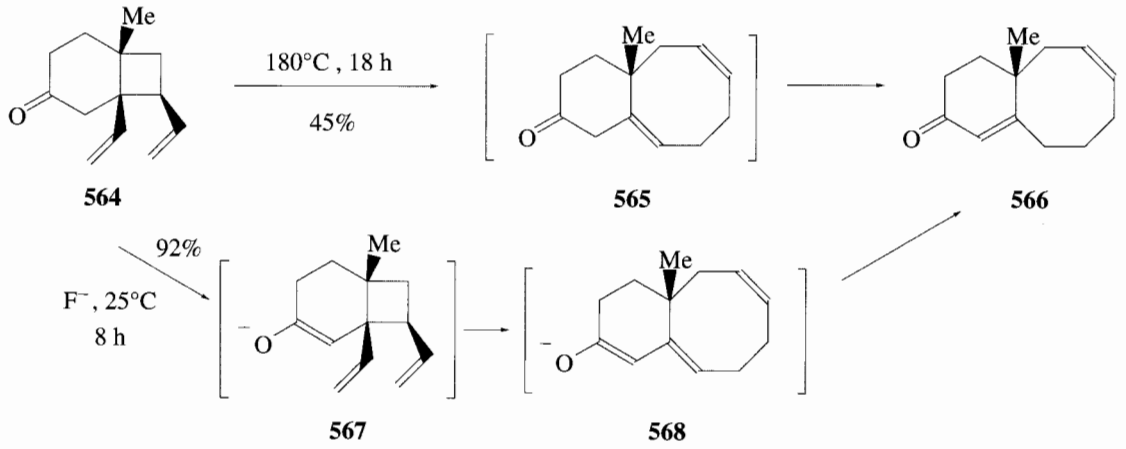
There are many synthetic applications involving the Cope rearrangement and they usually involve interesting structural changes. A typical example begins with conversion of the ketone unit in **557** to the silyl enol ether **558** in Overman's synthesis of scopadulcic acid A.[421] Heating **558** to 110°C lead to the Cope rearrangement product (**559**), and subsequent treatment with aqueous HCl gives ketone **560** in 76% overall yield.



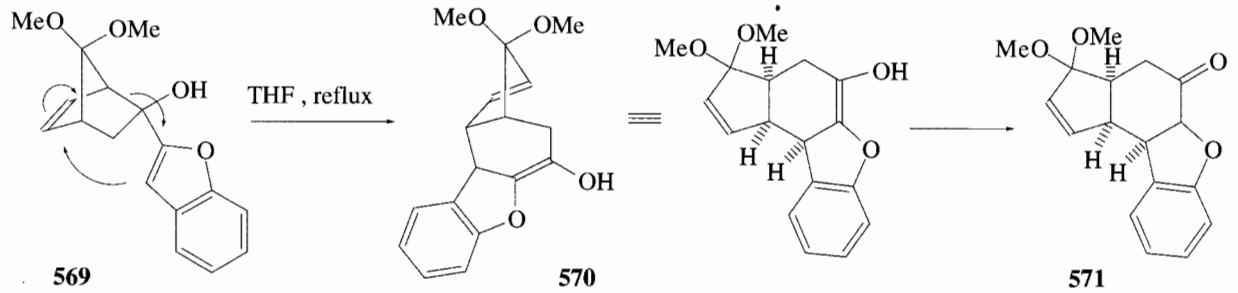
The Cope rearrangement is also effective when used in conjunction with other reactions. Davies used a cyclopropyl-accelerated Cope rearrangement in conjunction with a rhodium-catalyzed diazoalkane cyclopropanation (sec. 13.9.C.iii). Treatment of **561** with rhodium acetate [$Rh_2(OAc)_4$] gave **562**, which gave the Cope rearrangement under the reaction conditions (the rate of rearrangement was accelerated by the cyclopropane ring) to give **563** in 76% yield.[422] The rearrangement of **562** could also be viewed as a vinylogous vinyl cyclopropane rearrangement but the Cope mechanistic view is probably best, which is an effective synthesis of seven-membered ring compounds.



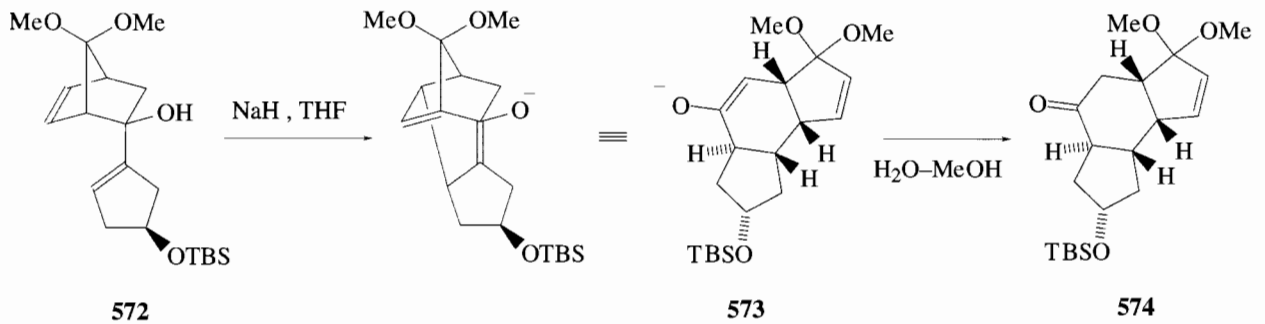
Majetich and Hull also showed that the presence of an enolate moiety in conjunction with the diene can facilitate the Cope rearrangement. This variation was called an **enolate accelerated Cope rearrangement**.[423] When **564** was heated to 180°C, **566** was formed in 45% yield via bond migration from the initial Cope product, **565**. When **564** was treated with fluoride, however, enolate **567** was formed and Cope rearrangement to **568** occurred at 25°C (92% yield). Hydrolysis gave **566**.



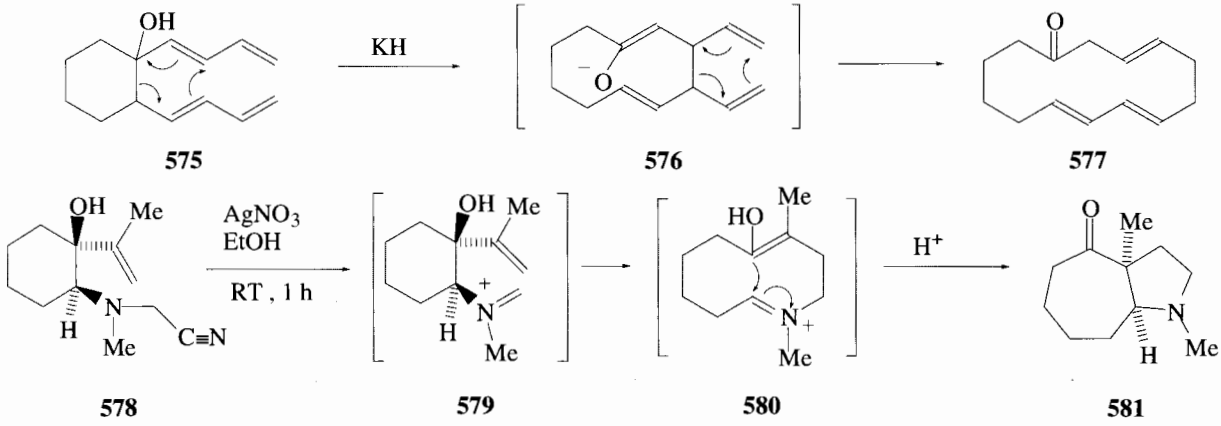
11.12.C.ii. oxy-Cope Rearrangement. Problems caused by the equilibrium inherent to the Cope rearrangement can be circumvented by the presence of an oxygen group on C3 or C4 of the diene (**552**), as mentioned above.[424] Rearrangement of **569**, for example, required heating to only 65°C (refluxing THF) to give the Cope product, which in this case is an enol (**570**). The enol tautomerized to the ketone (**571**),[425] and Jung used it in a synthesis of coronafacic acid. When the OH unit is at C3 of the diene, the enol product is subject to keto–enol tautomerism and this shifts the equilibrium toward the final ketone product. This facilitates the overall transformation. Conversion of the allylic alcohol to the potassium alkoxide enhances the rate



of rearrangement by a factor of up to 10^{10}–10^{17}. A major factor in the rate enhancement observed for hydroxy and alkoxy dienes is the irreversibility of the reaction, assisted by formation of an enol (or enolate under basic conditions–*vide infra*), which favors the ketone form and inhibits the reverse Cope rearrangement. This alcohol variant of the Cope rearrangement is called the **oxy-Cope rearrangement**.

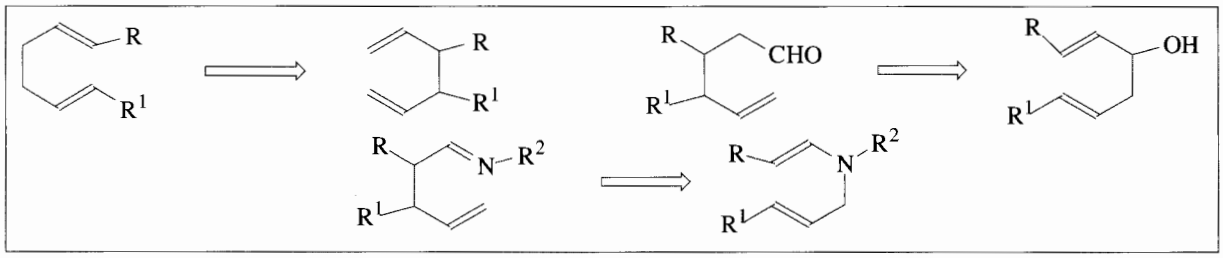


The reaction can be accelerated even more by converting the alcohol unit to an alkoxide, in what is called the **anionic oxy-Cope rearrangement**. This rearrangement generates an enolate anion directly, and hydrolysis gives the ketone or aldehyde. An example is take from Paquette's synthesis of spinosyn A,[426] where **572** was treated with NaH to give the alkoxide, which rearranged to **573**. Subsequent hydrolysis led to **574** in 90% yield. It has also been observed that a sulfur substituent, in addition to the alcohol unit, leads to an even greater rate acceleration.[427] An interesting application of this reaction is **Wender's macroexpansion reaction**, in which an initial anionic oxy-Cope rearrangement of **575** generated **576**, in which the allylic groups are properly positioned for a second Cope rearrangement, giving **577**.[428] Since this work was published, it has been argued that **576** is not an intermediate and that a [5,5]-sigmatropic rearrangement leads directly to **577**.[428c] Other bases can be used to generate the requisite alkoxide, including phosphazene bases.[429]



11.12.C.iii. The aza-Cope Rearrangement. It is well established that the presence of an oxygen atom adjacent to the π bond accelerates the Cope rearrangement. Overman and co-workers[430] also reported that nitrogen, usually as an iminium salt fragment in the diene, can induce an **aza-Cope rearrangement**.[431] When cyanomethylamine (**578**) was treated with silver nitrate ($AgNO_3$) an iminium salt (**579**) was formed that gave the aza-Cope rearrangement to **580** under the reaction conditions. The enol moiety in **580** attacked the iminium carbon as shown to give **581** as the final product, in 78% yield.[430] Overman applied this methodology to the synthesis of 6a-*epi*-pretazettine.[432] This reaction can also be viewed as an aza-Claisen rearrangement (sec. 11.12.D.iii). A recent report showed that a 3-azo-Cope rearrangement occurred using Zn^{2+}-Montmorillonite clay catalysis, with microwave irradiation.[433]

The Cope disconnections are



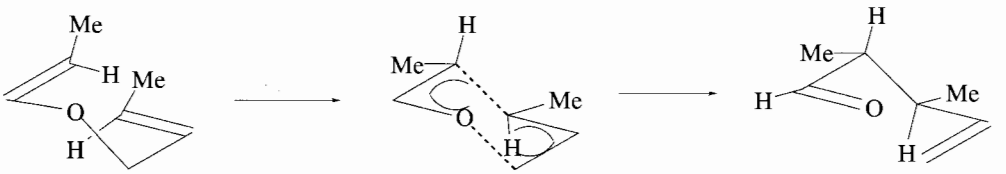
11.12.D. The Claisen Rearrangement

[3,3]-Sigmatropic rearrangements are possible when heteroatoms are part of the chain linking the alkene moieties. Overman's aza-Cope rearrangement of **579** was an illustration. When that heteroatom is an oxygen, as in allyl vinyl ether **582**, the [3,3]-sigmatropic rearrangement to **583** is called the **Claisen rearrangement**.[434,409b] Claisen rearrangements are thermal reactions[435] usually done with substrates in solution, but a microwave-assisted reaction has been done on solid phase.[436]

11.12.D.i. Allyl–Vinyl Ether Rearrangements. This reaction predated the Cope rearrangement and is obviously very similar. An alkenyl carbonyl product is obtained just as in the oxy-Cope rearrangement, but the carbonyl is generated directly rather than via initial enol formation. As with the Cope rearrangement, the

582 **583** **584**

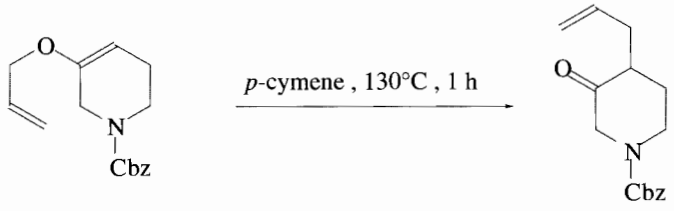
Claisen rearrangement proceeds via a chair-like transition state (**584**), which was reported to be favored over the boat by 2.5–3.0 kcal mol^{-1} (10.5–12.6 kJ mol^{-1}).[437] In different work, Houk and co-workers estimated that the chair transition state for this reaction is more stable than the boat transition state by ≈ 6.6 kcal mol^{-1} (27.6 kJ mol^{-1}).[438] The synthetic applications of the Claisen rearrangement were reviewed by Ziegler and the stereoselectivity that characterizes this reaction is apparent in those applications.[439] A generic Claisen rearrangement is illustrated by heating an allyl vinyl ether such as **585**, which rearranges to **586** via chair



585 **586** **587**

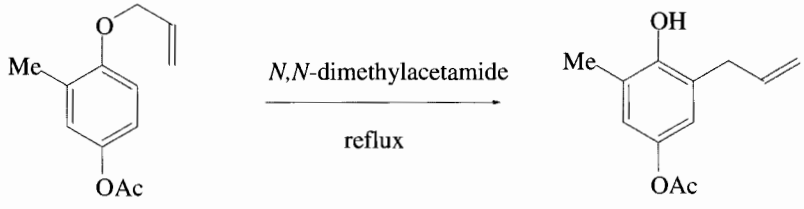
transition state **587**. The two methyl groups are equatorial in the transition state, as a result of the (*E,E*)-geometry in **585**.[439,437] The (*E,Z*)- and (*Z,Z*)-derivatives will rearrange more slowly since one or both of the methyl groups will be axial in the transition state (**586**). When a substituent is present at C4 (see **582**), the substituent prefers the equatorial position in the transition state. The selectivity is ≈ 99% when an alkyl group is present rather than a hydrogen (greater selectivity is observed when the substituents are —OR or —NR_2).[439,440,449] The energy requirements and stereochemical arguments are virtually identical with those discussed for the Cope rearrangement. A synthetic example is taken from Takeuchi's synthesis of

febrifugine,[441] in which **588** was heated to 130°C in *p*-cymene to give a 69% yield of **589**. The allyl vinyl ether is a precursor to molecules containing both an aldehyde (or ketone) and an alkene.



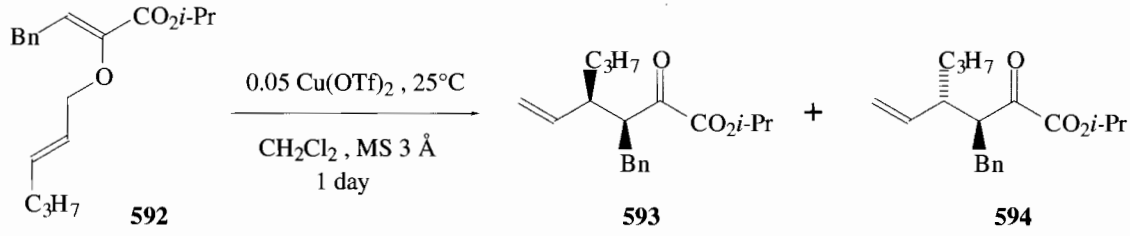
588 **589**

The Claisen rearrangement is not restricted to aliphatic derivatives. It can also occur with aryl allyl ethers such as **590**, which gave **591** in 74% yield as part of Díez's synthesis of an analog of usneoidol E.[442] These rearrangements are often sluggish, and a Lewis acid catalyst such as $TiCl_4$ is sometime required.[443] A catalyst is not always necessary for the Claisen rearrangement to occur.[444]



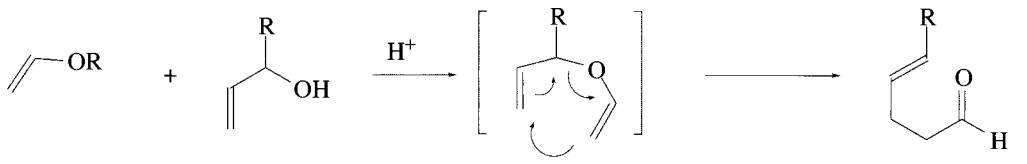
590 **591**

The Claisen rearrangement can be catalyzed by Lewis acids, often with improved stereoselectivity. Acyclic allyl vinyl ethers give a Claisen rearrangement upon treatment with a catalytic amount of Pd(II).[445] A Ho(fod) catalyst has been used as well.[446] An example of this type of reaction is the conversion of **592** to a 22:71 mixture of **593 and 594** in 99% yield.[447]



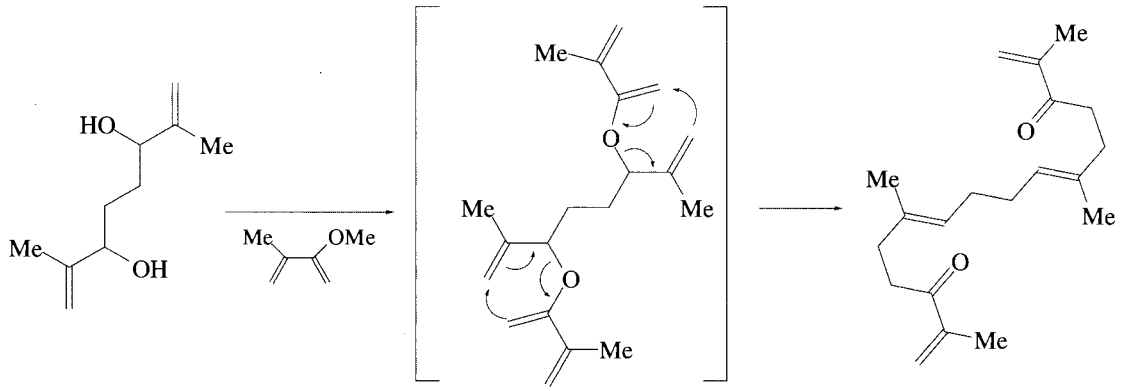
592 **593** **594**

11.12.D.ii. Variants of the Claisen Rearrangement. Many methods are used to prepare the allyl vinyl ether precursors required for the Claisen rearrangement. Many of these preparations have led to rather specialized variations, usually named after the scientist(s) who developed them. One method used for the preparation of allyl vinyl ethers (**595**) is the acid catalyzed reaction of vinyl ethers and allyl alcohols. Ether **595** is not isolated since a Claisen rearrangement occurs under the reaction conditions to give **596**, which has been termed the **Marbet–Saucy variant** of the Claisen rearrangement (**Marbet–Saucy reaction**).[448] An example is the treatment of **597** with 3-methoxyisoprene to generate **598** as a reactive intermediate. Subsequent Claisen rearrangement gave **599** in Faulkner's synthesis of squalene.[449]



595 596

A similar variant of the Claisen rearrangement reacts allyl alcohols such as **600** with β-bromoselenides (**601**) to give **602**. Oxidation to the transient selenoxide (**603**) and *in situ* syn-elimination (sec. 2.9.C.vi) gave **604**. This ether possessed the proper functionality for Claisen rearrangement to the final product, ester **605**.[450] Petrzilka used a variation of this method for the synthesis of phoracantholide J.[451]



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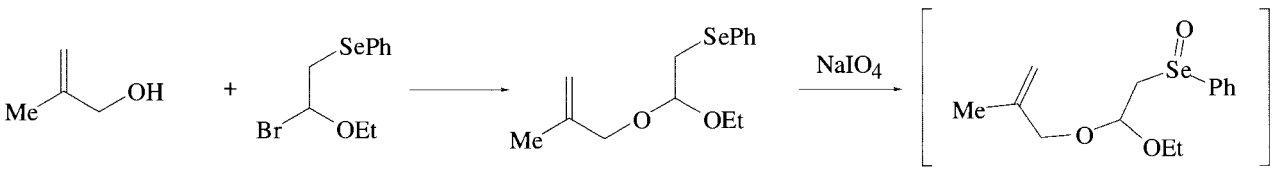
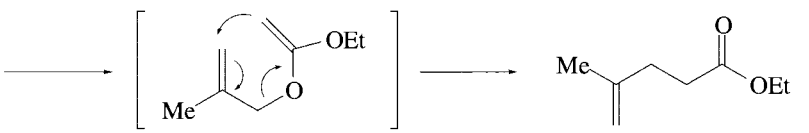


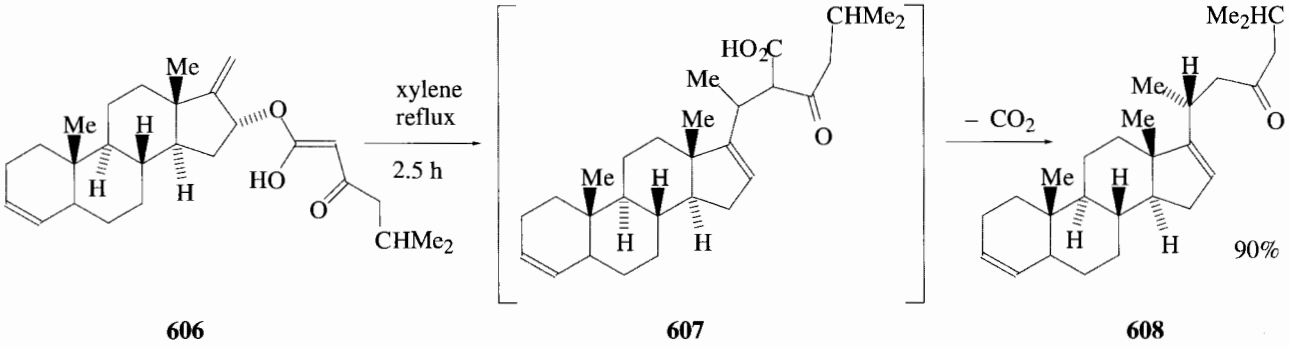
600 601 602 603



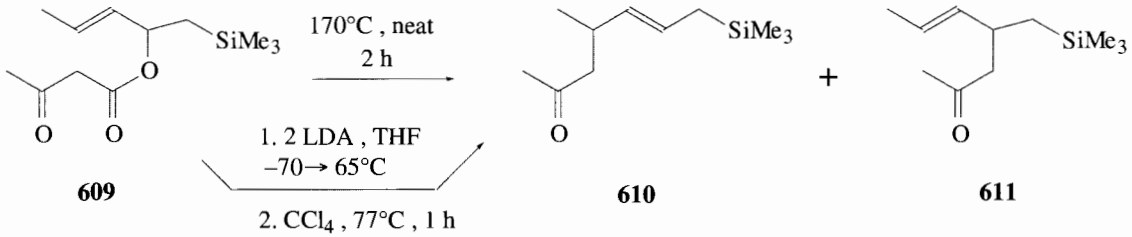
604 605

Carrol prepared the allyl ester of β-keto acids, which exist largely as the enol (as in **606**). These compounds give a Claisen rearrangement to a β-keto acid (**607**)[452] in what is usually called the **Carrol variant** or the **Carrol reaction**,[453] although it has also been called the **Kimel–Cope rearrangement**.[454] Decarboxylation is facile at this reaction temperature and in the example given, **607** lost CO_2 to give **608** in Tanabe's synthesis of cholesterol.[452] Wilson introduced a variation of the Carrol reaction that is very useful due to the mild conditions under which the rearrangement occurs.[455] Dianions of allylic acetoacetates rearrange at room temperature or in refluxing THF. When **609** was heated to 170°C for 2 h (neat), 50% of a mixture (67:33) of **610** and **611** was obtained. When **609** was treated with 2 equivalents of LDA (sec. 9.2.B

and 9.4.B.vii), however, the enolate dianion rearranged in refluxing THF and subsequent decarboxylation in refluxing carbon tetrachloride led to an 84% yield of **610** with no **611**.[455]

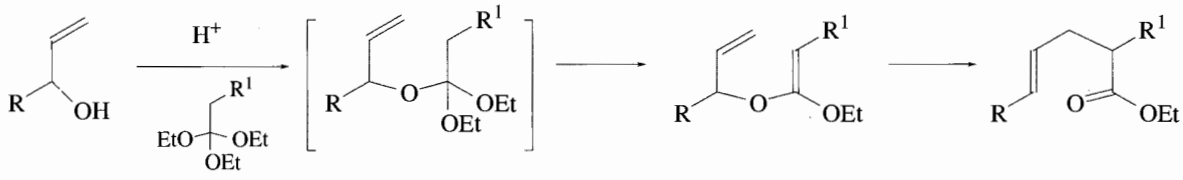


606 **607** **608**

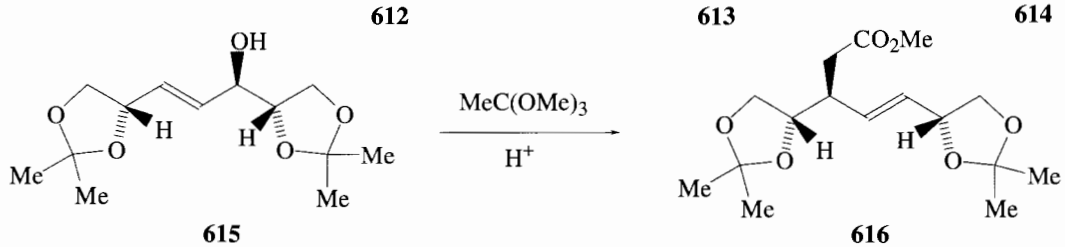


609 **610** **611**

Another variation of the Claisen rearrangement involves ketene acetals, which are generated by reaction of allylic alcohols with ortho esters [$R^1CH_2C(OEt)_3$] under acidic conditions. The resulting product (**612**) eliminates ethanol to give **613**, and this product undergoes a Claisen rearrangement to give ester **614**. This



612 **613** **614**

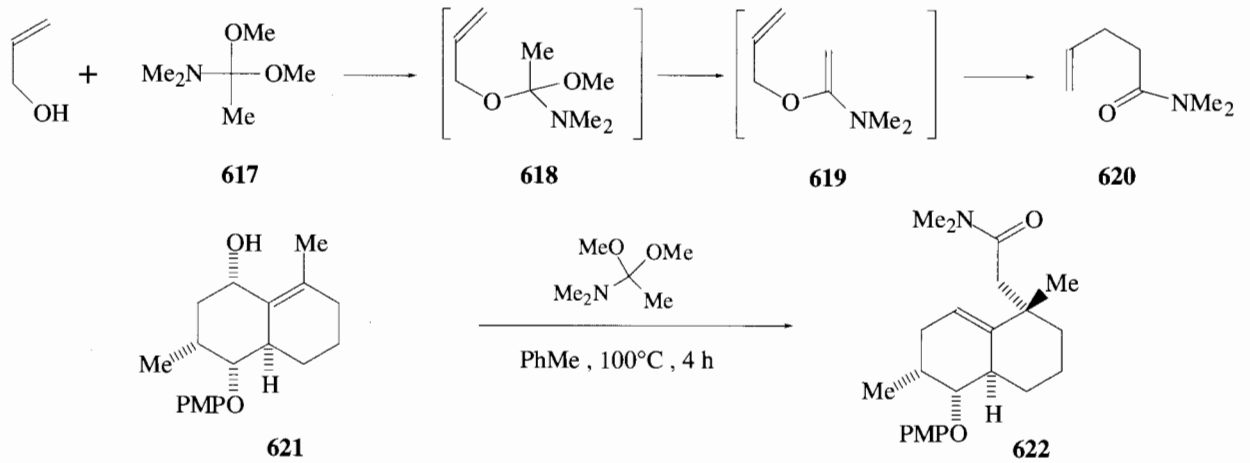


615 **616**

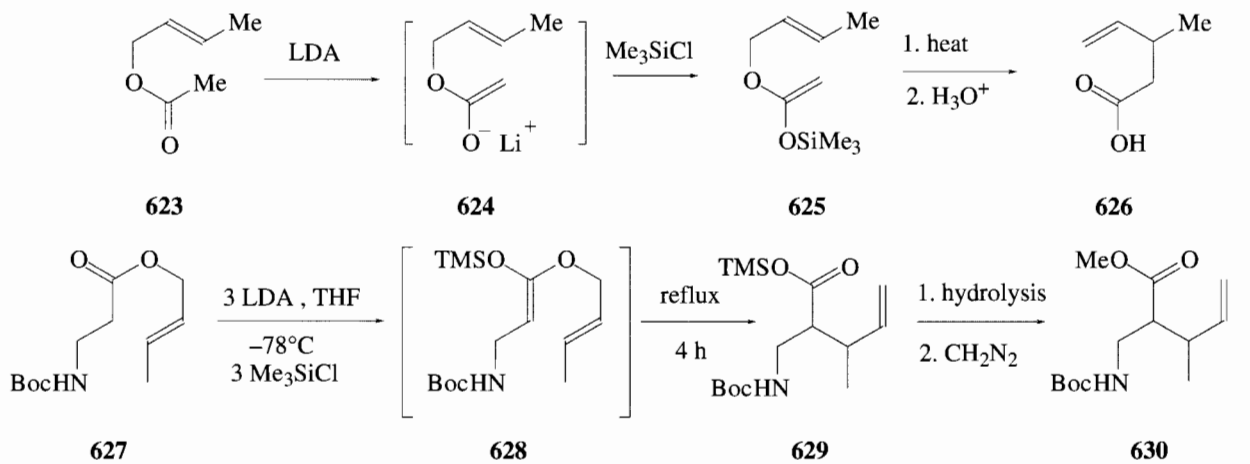
sequence is known as the **Johnson–ester variant**[456] of the Claisen rearrangement. It is also known as the ortho ester Claisen rearrangement.[457] An asymmetric version of this variant was used in Stork's chiral synthesis of prostaglandin $F_{2\alpha}$, where allylic alcohol **615** reacted with trimethyl orthoacetate to give **616** in 80% yield.[458]

A related variation was reported by Eschenmoser, who showed that heating an allylic alcohol with *N,N*-dimethylacetamide dimethyl acetal (**617**) gave **618**. This intermediate eliminated methanol to give **619**, and

subsequent Claisen rearrangement generated amide **620**, which is known as the **Eschenmoser variant** or the **Eschenmoser–Claisen rearrangement**.[459] Corey's synthesis of thromboxane B_2 utilized this methodology.[460] Another synthetic example is the conversion of **621** to **622**, in 93% yield, in Piers' synthesis of dysidiolide.[461]



Esters can be converted to the corresponding enolate via treatment with base. Arnold and Hoffman observed that esters rearrange upon treatment with base.[462] When that enolate was trapped as the *O*-trialkylsilyl ether, a 1,5-diene was generated that gave a Claisen rearrangement under milder conditions. The solvent has a great influence on the selectivity of the reaction, and THF is commonly used.[463] The enolate Claisen rearrangement occurs at ambient temperatures, whereas most Claisen rearrangements require temperatures of 120-200°C.[464] The enolate accelerated Claisen rearrangement is obviously similar to the enolate accelerated Cope rearrangement described by Majetich in sec. 11.12.C.[433] If hexamethylphosphoramide (HMPA) is added, then the lithium ion (Li^+) is solvated, lithium coordination with oxygen is poor and the syn-isomer predominates. If THF is used, then the O↔Li coordination is strong and the anti-isomer is the major product.

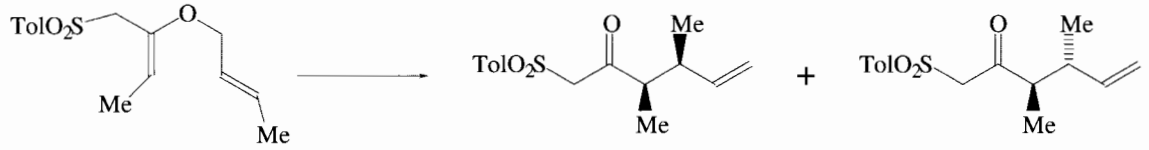


As we saw in section 9.4.B,C, the reaction of an ester such as **623** with LDA, under kinetic control conditions, and subsequent reaction of the enolate anion (**624**) with chlorotrimethylsilane gives the silyl enol

ether **625**. Compounds such as **625** were prepared by Ireland and Mueller, who found that subsequent Claisen rearrangement followed by hydrolysis of the initially formed silyl ester gave the acid (**626**) in what has come to be known as the **Ireland variant** or the **Ireland–Claisen rearrangement**.[465] Knight and co-workers used this variant in a synthesis of (α-allyl-β-amino acids.[466] When ester **627** as treated with 3 equivalents of LDA and then chlorotrimethylsilane, **628** was obtained, and after refluxing for 4 h, the Claisen rearrangement product was silyl ester **629**. Hydrolysis followed by esterification with diazomethane gave a 71% overall yield of protected amino ester **630**.

It is possible to enhance the rate of a Claisen rearrangement, especially in the enolate Claisen reaction. Denmark et al. showed that other carbanionic centers accelerate the Claisen rearrangement (as in Table 11.23).[467] Generation of the anion of sulfone **631** (sec. 8.6.A) with various bases led to acceleration of the reaction relative to the thermal reaction of **631** and also influenced the syn/anti ratio (**632/633**). In general, a donor group at the allyl position accelerates the rate and the presence of an amino stabilizing group increases the rate even more.

Table 11.23. Acceleration of the Claisen Rearrangement by Sulfoxide Stabilized Anions



631 **632** **633**

Base	Solvent	Temp., °C	Time, h	632/633	Yield (%)
2.2 equiv KH	DMSO	100	4	96:4	97
	DMSO	20	4	93:7	79
	THF	20	4	89:11	78
	HMPA	20	2	64:36	83
2.2 equiv NaH	DMSO	20	4	98:2	85
	DMSO	50	0.25	98:2	93
1.0 equiv $NaN(TMS)_2$	DMSO	20	5	78:22	29
2.5 equiv BuLi	DMSO	20	4	89:11	87
2.2 equiv KH 4.2 equiv LiCl	DMSO	20	4	97:3	73

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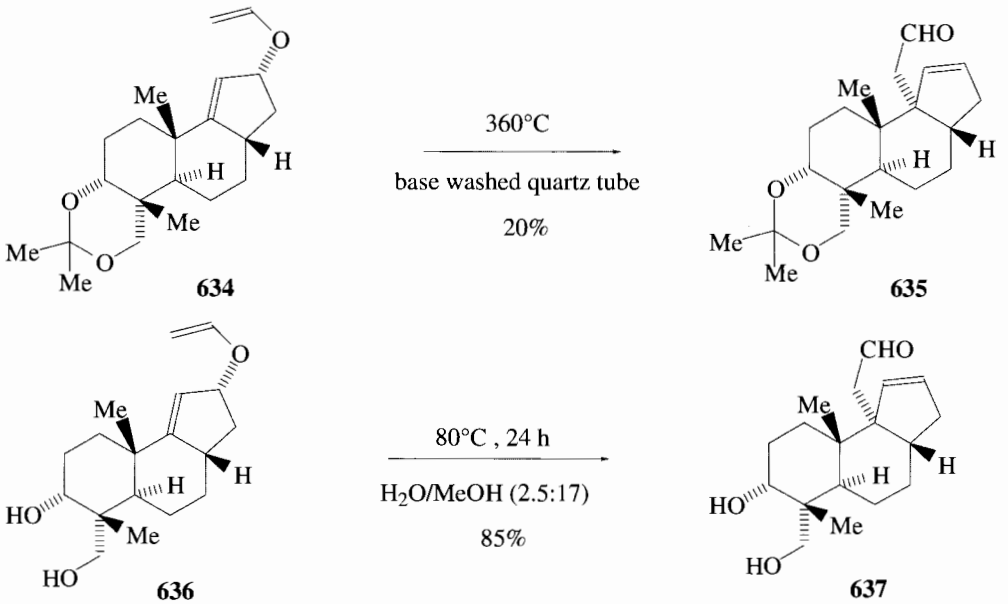
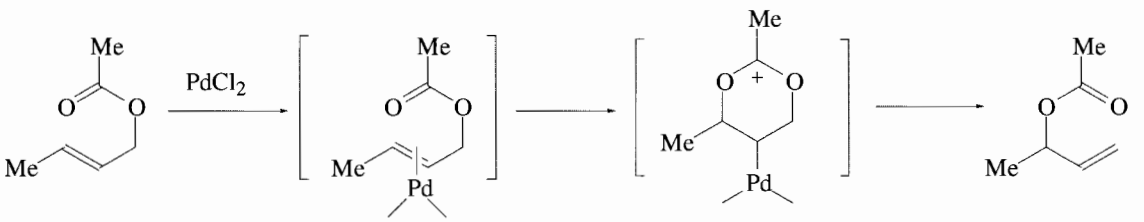
Performing the reaction in aqueous solvents accelerates the Claisen rearrangement in many cases, just as observed with the Diels–Alder reaction (sec. 11.6.B). McMurry et al. showed that heating **634** to 360°C gave only a 20% yield of **635** in a synthesis of aphidicolin.[468] The difficulty lay in the sensitivity of the product to the reaction conditions and the steric hindrance that hindered formation of the correct chair transition state. When Grieco heated the water soluble diol **636** to 80°C, an 85% yield of **637** was obtained,[469] which

dramatically demonstrates the rate enhancement possible in aqueous solvents. As with Diels–Alder reactions, solubility of the Claisen precursor in the aqueous medium is required.

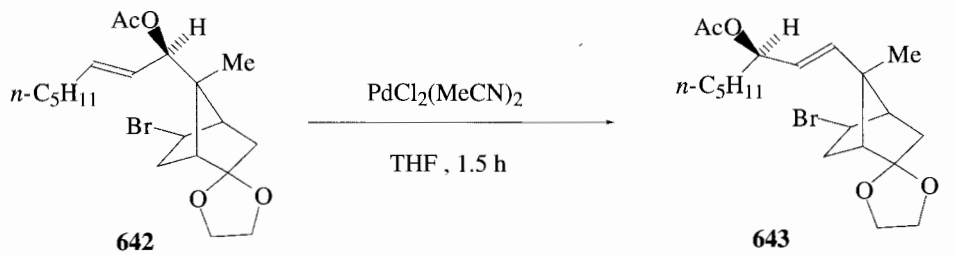


634 635 636 637

Many transition metals catalyze the Claisen rearrangement, as with the use of titanium tetrachloride ($TiCl_4$).[443] Palladium chloride ($PdCl_2$) is known to catalyze the rearrangement of allyl ethers in a reaction that looks very much like a Claisen transition state. Treatment of **638** with $PdCl_2$, for example, initially generated the π-palladium complex (**639**), which was attacked by the carbonyl oxygen to give **640**, and ring opening



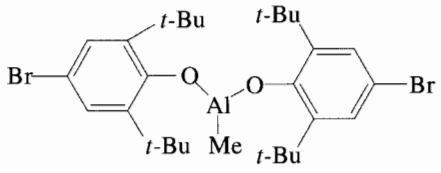
638 639 640 641



642 643

gave the rearrangement product **641**.[470,471] It is important to note, however, that this reaction proceeds in a step-wise manner via a π-allyl palladium intermediate and not via a concerted [3,3]-sigmatropic rearrangement (sec. 12.6 for a discussion of palladium-catalyzed reactions) and one must exercise care in categorizing reaction types. It is included here only because of the similarity in products obtained by this process and is

not meant to imply that it proceeds by an identical mechanism to the Claisen rearrangement. Grieco used a similar palladium catalyzed Claisen rearrangement to convert **642** to **643** (93%) in a synthesis of 15-epi-12-methyl prostaglandin $F_{2\alpha}$.[472] Aluminum reagents can also catalyzes the Claisen rearrangement. Yamamoto and co-workers showed that **644** or **645** catalyze the Claisen rearrangement, with opposite stereochemistry.[473]



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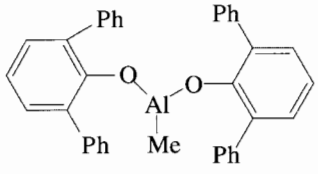
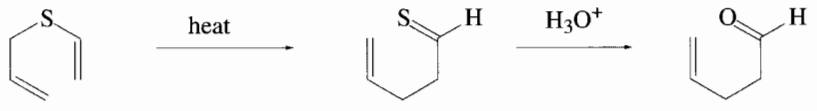
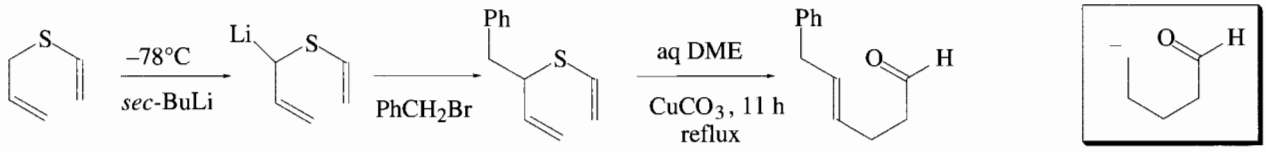


645

11.12.D.iii. thio-Claisen and aza-Claisen Rearrangements. Heteroatoms other than oxygen can be used in a Claisen rearrangement. The two most common are sulfur and nitrogen (giving thio-Claisen and aza-Claisen rearrangements, respectively). Heating allyl vinyl sulfides (**646**) leads to a [3,3]-rearrangement that gives thioaldehyde (**647**), which generates an aldehyde (**648**) upon hydrolysis.[474] This variant is known as the **thio-Claisen rearrangement**,[475] and there are a number of synthetic examples.[476]

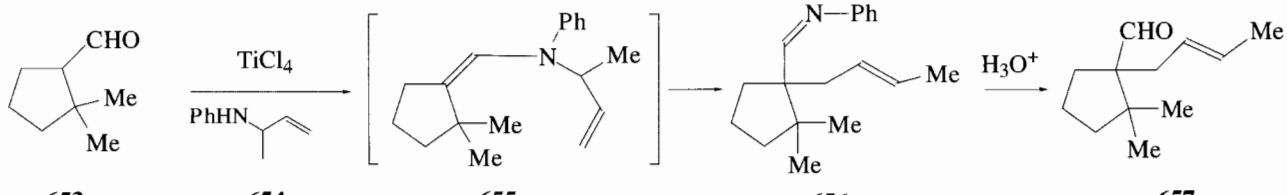


646 **647** **648**



646 **649** **650** **651** **652**

The thio-Claisen rearrangement was the basis of an **umpolung** reagent discussed in Section 8.6.B.vi. Treatment of **646** with *sec*-butyllithium gave the α-lithio sulfide (**649**), and condensation with benzyl bromide gave the alkylated sulfide, **650**. Heating led to a thio-Claisen rearrangement and hydrolysis gave aldehyde **651** in 62% overall yield.[477] This sequence was correlated with umpolung equivalent **652**.[477]

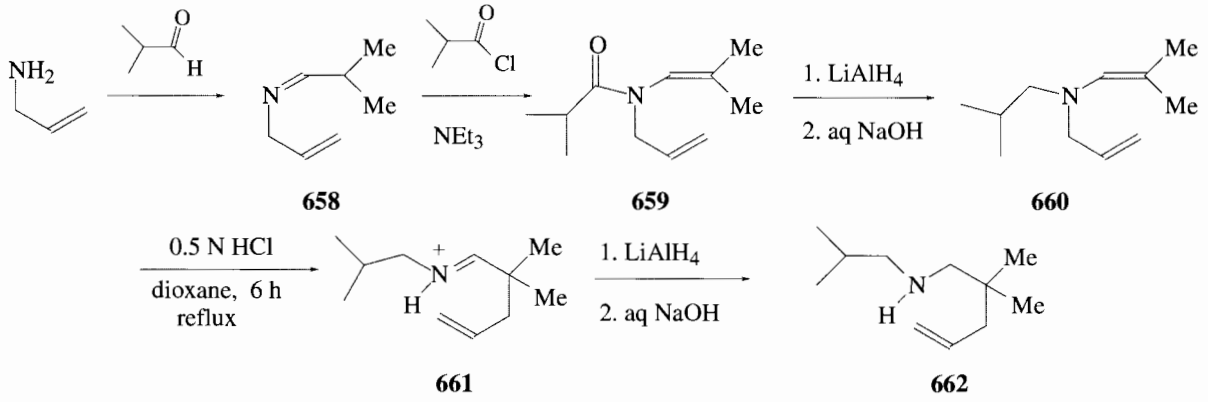


653 **654** **655** **656** **657**

Nitrogen compounds have also been used in **aza-Claisen rearrangement** reactions (also see the aza-Cope rearrangement in sec. 11.12.C.iii).[453,478] In the generic reaction, heating N-allylic enamines leads to an imine, which could be hydrolyzed to an aldehyde[479] or converted to another nitrogen-containing moiety.

The aza-Claisen rearrangement can be catalyzed by Lewis acids such as titanium tetrachloride ($TiCl_4$). When aldehyde **653** reacted with 3-(*N*-phenyl)-1-butene (**654**) in the presence of $TiCl_4$, the initially formed enamine (**655**) rearranged to **656** and was hydrolyzed to aldehyde **657** in 61% overall yield.[480]

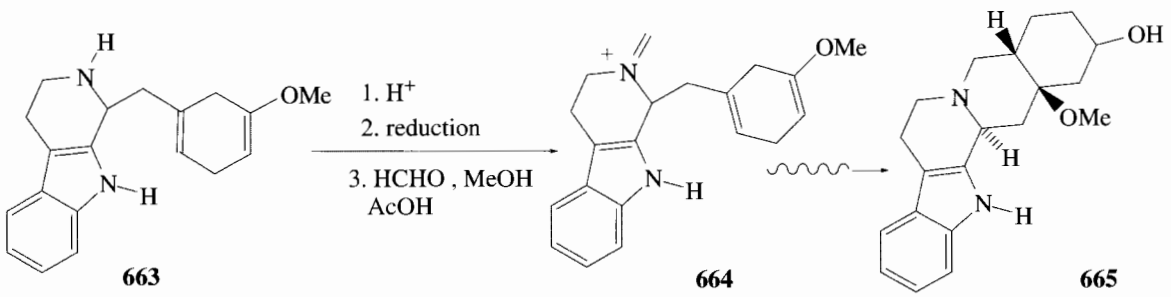
Stille and co-worker developed an attractive route to aza-Claisen precursors. Allylamine reacted with 2-methylpropanal (isobutyraldehyde), for example, to give allylimine **658**.[481] When **this** reacted with 2-methylpropanoyl chloride, N-acyl derivative **659** was produced (94% overall yield from allylamine) and reduction with $LiAlH_4$ give a 98% yield of the tertiary amine, **660**. Stille found that conversion of the amine to the ammonium salt by treatment with HCl led to clean conversion to **661** in 82% yield via a [3,3]-sigmatropic rearrangement (an aza-Claisen rearrangement). Reduction of the iminium salt led to an 81% yield of **662** from **661**. Stille and co-workers also found that Lewis acids as well as HCl react with the allyl enamine precursor to facilitate the aza-Claisen rearrangement.[482]



658 **659** **660**

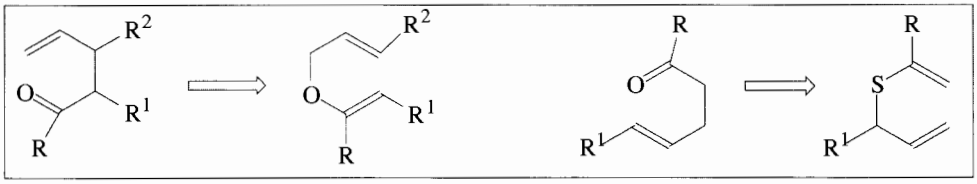
661 **662**

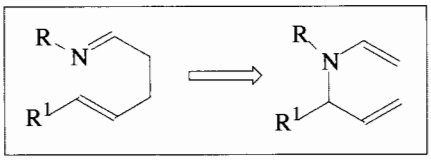
Other types of iminium salts can be used this reaction. β-Carboline **663** was reduced and converted to iminium salt **664** by treatment with formaldehyde (secs. 4.4.B, 4.10.D). The aza-Claisen rearrangement (sometimes called an **2-azonia rearrangement** in this system) was used by Winterfeldt and co-workers to generate **665** (15β-methoxyyohimban-17-ol) in 96% yield.[483]



663 **664** **665**

The Claisen rearrangement disconnections are





11.13. THE ENE REACTION

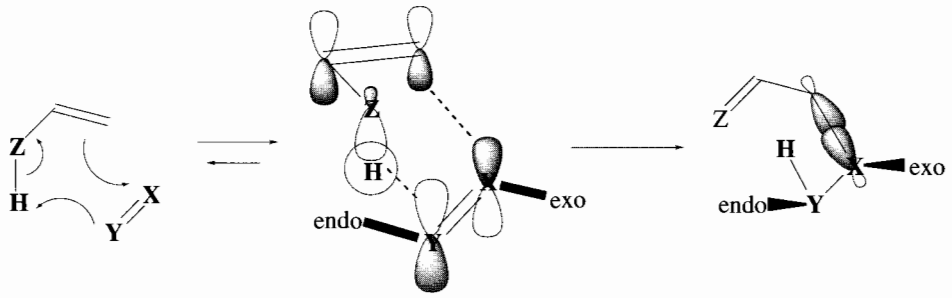
The Diels–Alder reaction is a thermal cycloaddition involving 1,3-dienes and alkenes, and [3+2]-cycloaddition reactions involve a π bond and a 1,3-dipole. The Cope, oxy-Cope, and Claisen rearrangements are thermal, intramolecular reactions of 1,5-dienes. [2+2]-Cycloadditions usually involve reaction between two alkenes, or certainly two π bonds. A reaction that is different from any seen so far occurs with certain alkenes and allylic systems. In its fundamental form, it is "the indirect substituting of a compound with a double bond

666

(**enophile**) to an alkene that has an allylic hydrogen (the **ene**)"[484] to give a new, substituted alkene. This transformation is called the **ene reaction**.[485] Although several related examples of this reaction were reported early in this century,[456] it was not until the work of Alder in 1943[486] that the ene reaction was recognized as a synthetically useful tool. Because of his work, this transformation is often referred to as the **Alder ene reaction**.

11.13.A. Enes and Enophiles

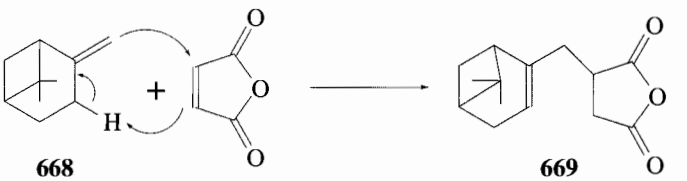
The ene reaction involves an alkene fragment (the ene) that removes a hydrogen from an allylic fragment, with formation of a new carbon bond, as in **666**.[487,226] As with the other reactions in this chapter, reactivity and stereochemistry in the ene reaction can be explained by frontier orbital theory. The reaction proceeds via interaction of the HOMO of the alkene (ene) and the LUMO of the allylic partner (enophile), illustrated by **667** in Figure 11.23.[488] The intermolecular reaction usually requires very high temperatures (typically 250-



667

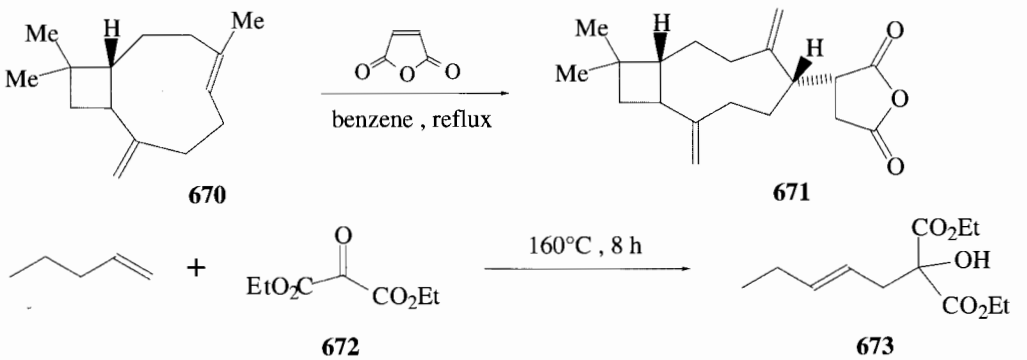
Figure 11.23. Generalized transition state for the Alder ene reaction. [Reproduced with permission from Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed., Engl., 1978, 17*, 476. Copyright 1978 VCH Weinheim.]

600°C). 2-Methylpropene reacts with acetylene to give a 40% yield of 2-methyl-1,4-pentadiene but the reaction requires a large excess of isobutylene under 170 atmospheres.[489] The fact that the reaction is concerted (rather than involving a cationic intermediate) can be illustrated by the ene reaction of β-pinene (**668**) and maleic anhydride to give **669**, without skeletal rearrangement of the pinene ring.[490] In general,



668 **669**

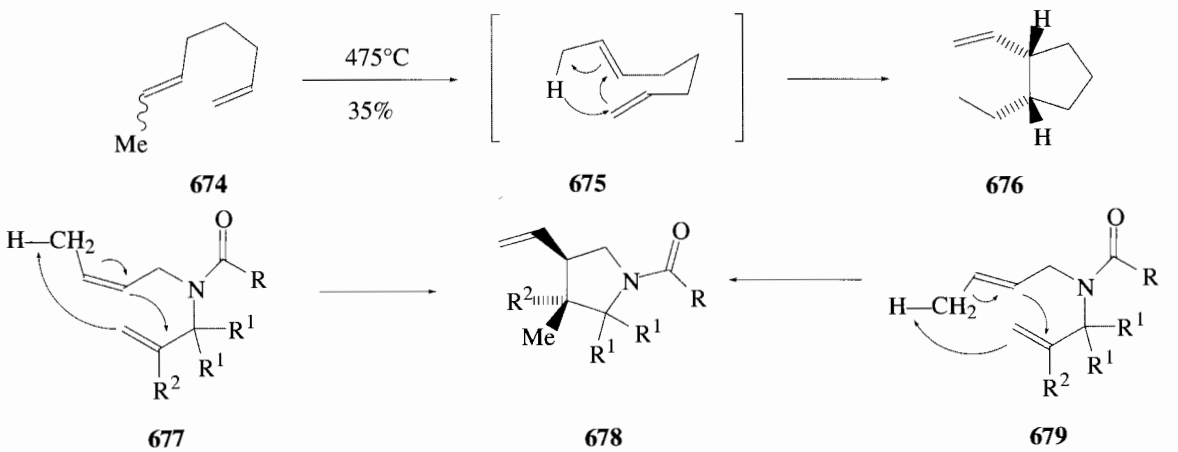
allylic alkenes react faster than allylic alkynes in the ene reaction.[484] The vigorous conditions for the previously cited reaction of acetylene is an example. If the alkene contains a strained double bond, the ene reaction is accelerated (lower reaction temperatures). Caryophyllene (**670**), for example, contains a strained trans-double bond and undergoes an ene reaction with maleic anhydride under very mild conditions (refluxing benzene) to give **671**, but the yield is only 19%.[491]



670 **671**

672 **673**

Carbonyl compounds can be as enophiles in the ene reaction and the best results are obtained when the enophilic carbonyl is conjugated to another carbonyl moiety. Diethyl mesoxalate (**672**), for example, reacts with 1-pentene to give **673**.[492]

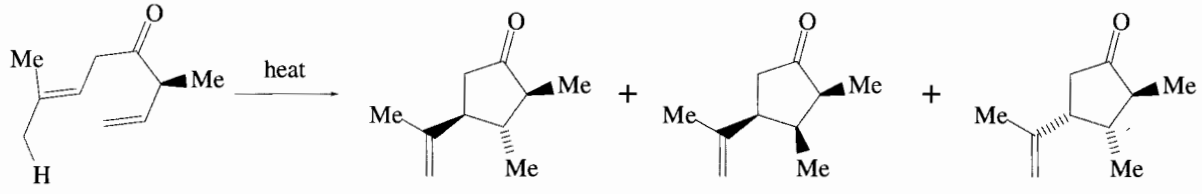


674 **675** **676**

677 **678** **679**

Intramolecular ene reactions are popular in synthesis and have been studied in great detail.[493,345] The most common ene precursors are 1,6- and 1,7-dienes, with 1,6-dienes the more reactive and more useful. The product of the ene reaction of a 1,6-diene is a five-membered ring derivative. A cis–trans mixture of 1,6-octadiene (**674**) cyclized at 457°C, via a transition state that is believed to resemble **675**, to give exclusively cis-isomer **676** in 35% yield.[494] Internal ene reactions typically give a mixture of diastereomers.[495]

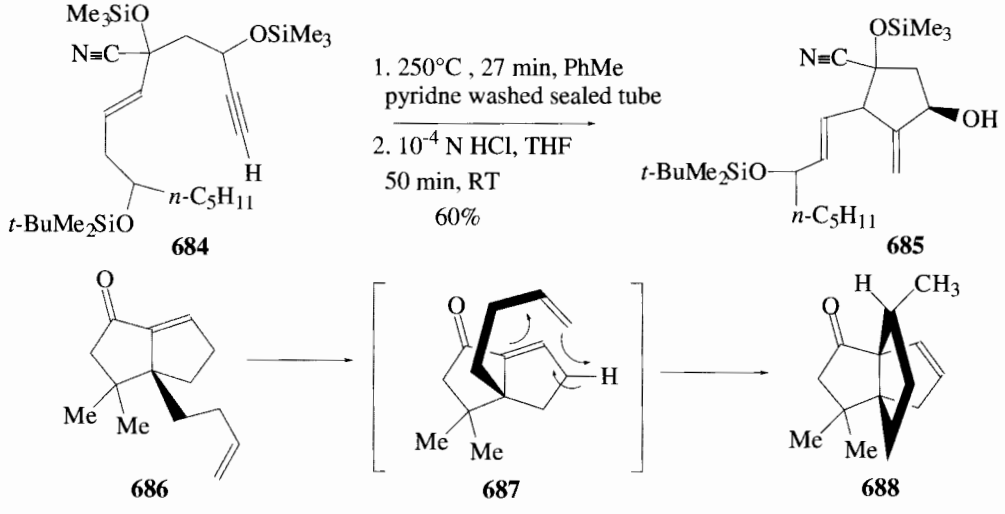
Oppolzer et al. described the stereochemistry for cis- and trans-enophiles when reacting in the ene reaction. If amide **677** containing a cis- alkene unit and amide **679** containing a trans-alkene unit react via an ene reaction, the same product (**678**) is formed.[496] The product distribution and stereochemistry depend on the temperature used for the reaction. Cyclization of **680** at 450°C, for example, gave a mixture of **681**, **682** and



680 **681** **682** **683**

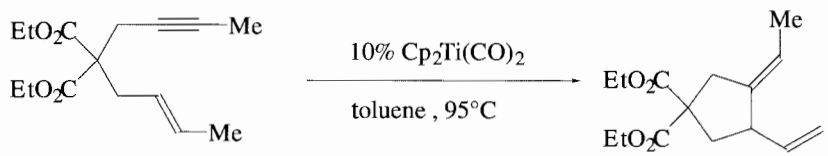
450°C	(9	:	25	:	41)
290°C	(2	:	7	:	40)

683 (9:25:41). Ene reaction of **680** at 290°C gave the same products, but in a ratio of 2:7:40.[497] Good selectivity is possible in the ene reaction, as in the conversion of **684** to **685** in 60% yield at 250°C, in Stork's explorations toward the synthesis of prostaglandins.[498] In this case, the silyl group on the secondary hydroxyl was selectively removed by treatment with dilute HCl in THF (sec. 7.3.A.i). This selectivity may be due to increased steric hindrance at that position or to a rate-determining oxygen protonation step, or both.[498]



Oppolzer used an ene reaction to convert **686** to **688**, via an endo-transition state (see **687**) in a synthesis of modhephene, with good selectivity.[499] The conformational constraints imposed by the molecular structure of the ene led to high selectivity in the rearrangement products. Conjugated alkynes are also enophiles.[500]

Lewis acid are effective catalysts for the ene reaction in many ene–ene or ene–yne reactions, although they are most effective with carbonyl ene reactions (see below). Buchwald and co-workers, for example, reported a titanocene-catalyzed intramolecular ene reaction in which ene-yne **689** was treated with $Cp_2Ti(CO)_2$ in hot toluene to give a 97% yield of ene product **690**.[501]



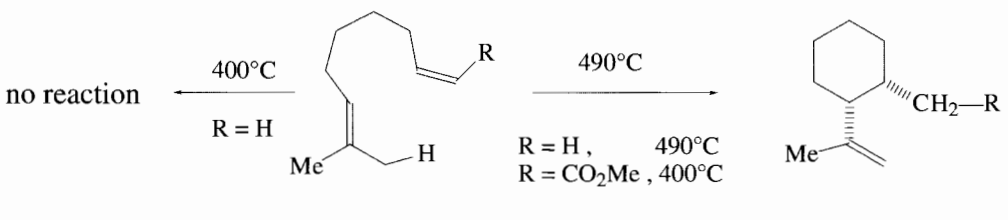
689 **690**

11.13.B. Ene Reactions of 1,7-Dienes

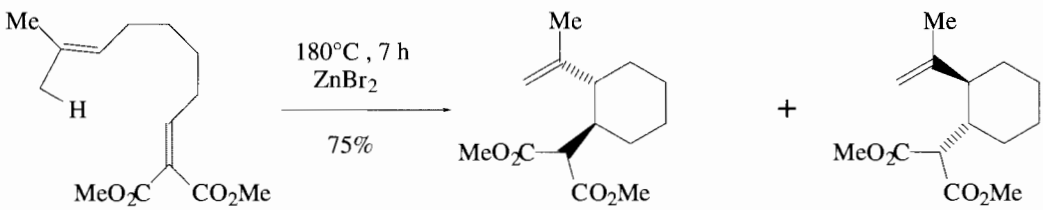
Ene reactions of 1,7-dienes are less common. Both six-membered ring products (such as **691** via path *a*) and eight-membered ring products (such as **692** via path *b*) are possible.[484] The first ene reaction with a 1,7-diene was probably reported by Hunstman et al..[502] Six-membered rings are usually preferred to eight-

691 **692**

membered rings, but ene reactions of 1,7-dienes require higher reaction temperatures. Heating 8-methyl-1,7-nonadiene (**693**, R = H) to 440°C, for example, gave no reaction, although a good yield of **694** was obtained at



693 **694**



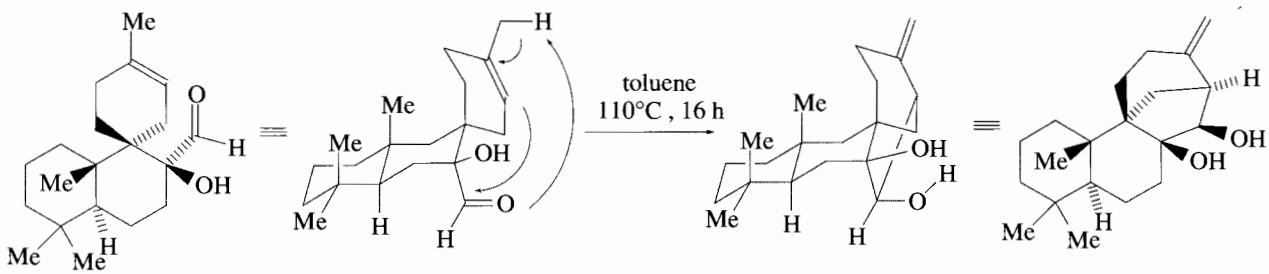
695 **696** **697**

490°C.[498] The presence of a carbomethoxy group led to a more facile ene reaction in which **693** (R = CO_2Me) was converted to **694** in ≈ 25% yield, but still required a temperature of 400°C.[502] The presence of

an electron-withdrawing group increases the rate of the ene reaction by lowering the LUMO energy. Lewis acids greatly enhance the rate of ene reactions involving 1,7-dienes.[503] When **695** was treated with zinc bromide ($ZnBr_2$), for example, the ene reaction occurred at room temperature to give an 88% yield of desmethyl **696/697** (>99:1 favoring **696**).[503a,504]

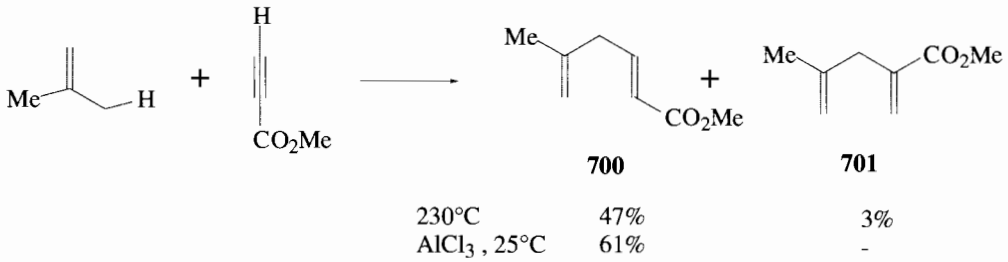
11.13.C. Carbonyl and Imino Ene Reactions

When a carbonyl moiety is the ene component of a 1,6- or 1,7-diene system, the ene reaction is more favorable. Heating **698** to 110°C, for example, led to a 94% yield of **699** in White's synthesis of 2-desoxystemodinone.[505] In **845**, the π-bond of the aldehyde carbonyl and the π bond of the cyclohexene unit constitutes a 1,6-diene, which is more easily seen in the conformational drawing. The reaction occurred at a very reasonable temperature, in good yield, and with excellent stereoselectivity due to the rigid nature of the tricyclic system.

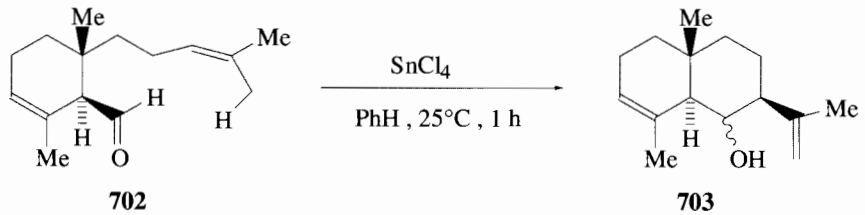


698 **699**

As with other reactions in this chapter, the carbonyl ene reaction is catalyzed by Lewis acids.[506] When isobutylene reacts with methyl propiolate at 220°C, a mixture of 47% of **700** and 3% of **701** was obtained. Reaction in the presence of aluminum chloride ($AlCl_3$), however, allowed reaction at 25°C and gave 61% of **700**.[507] Coordination of the Lewis acid and enophile apparently lowers the LUMO, accelerating the reaction due to the



	700	**701**
230°C	47%	3%
$AlCl_3$, 25°C	61%	-



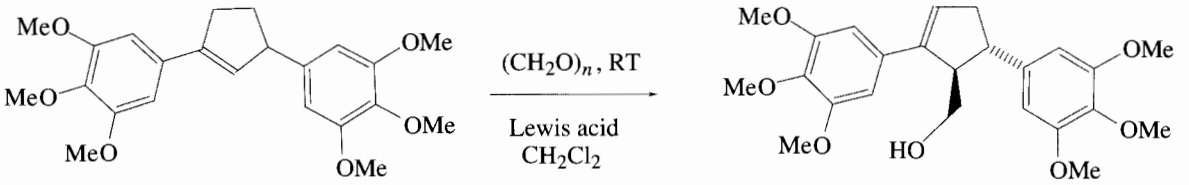
702 **703**

diminished ΔE, just as in the Diels–Alder reaction. Ene reactions are also possible with aldehydes, where the C=O unit functions as the ene. An example is the tin chloride ($SnCl_4$) catalyzed ene reaction of **702** to **703**, as

a 1:1 mixture of diastereomeric alcohols. The α-isomeric alcohol was isolated in 18% yield, and it was used in the Schwartz et al. synthesis of juneol.[508] Alkenyl ketones also undergo an ene reaction under these conditions.[509] Dimethylaluminum chloride (Me_2AlCl) and diethylaluminum chloride (Et_2AlCl) are excellent catalysts for the carbonyl ene reaction and are often the catalyst of choice.

The reaction is very dependent on the catalyst. The reaction of **704** with formaldehyde gave **705**, but only diethylaluminum chloride (Et_2AlCl) gave good yields (see Table 11.24).[510] The selectivity in the reaction is due to the more favorable interaction of the aluminum and aryl moieties in **706**. In the alternative **707**, the

Table 11.24. Dependence of the Ene Reaction of 704 and Formaldehyde on the Lewis Acid Catalyst



704 **705**

Lewis Acid	% 705
$ZnCl_2$	0
Me_3Al	0
$AlCl_3$	11
$EtAlCl_2$	23
Et_2AlCl	61

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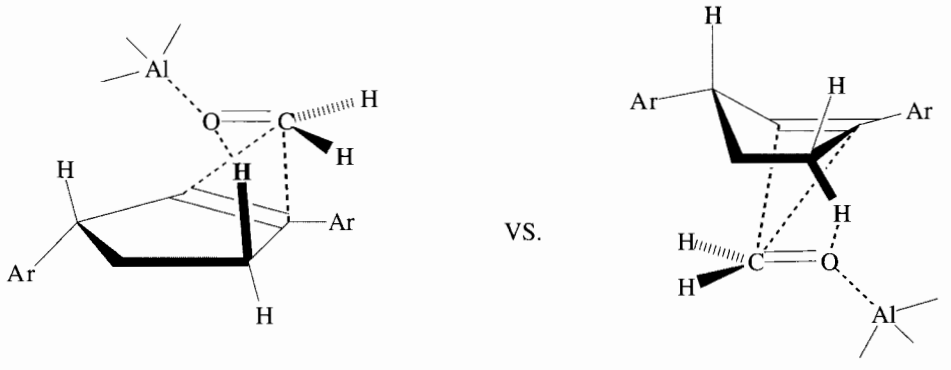

706 **707**

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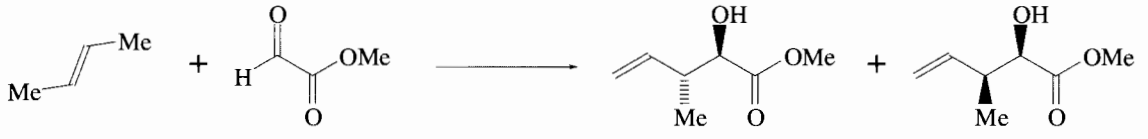
groups on aluminum interact to a greater extent with the aryl group, making this transition state higher in energy and less favorable. Good selectivity was also observed in the reaction of *trans*-2-butene with **708**.

Anti–selectivity (to give **709**) was observed when tin chloride ($SnCl_4$) catalyzed the reaction with either *cis*- or *trans*-2-butene, but syn selectivity (to **710**) was observed when alkyl aluminum catalysts were used (see Table 11.25).[511]

Table 11.25. cis–trans Selectivity in the Reaction of 2-Butene with Methyl Glyoxalate (708), as a Function of the Lewis Acid



708 **709** **710**

Alkene	Catalyst	Yield (%)	709/710
trans-2-Butene	$SnCl_4$	100	18:62
cis-2-Butene	$SnCl_4$	100	28:72
trans-2-Butene	Me_2AlCl	5	82:18
	Me_2AlOTf	29	79:21
	$MeAl(OTf)_2$	1	65:35

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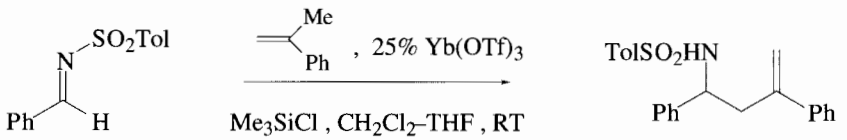
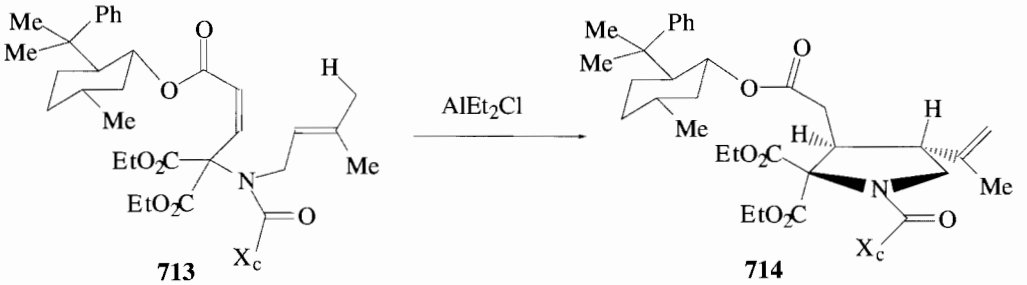
Imino–ene reactions are known.[512] In one report, lanthanum derivatives catalyze the reaction. When imine **711** reacted with α-methyl styrene in the presence of $Yb(OTf)_3$, for example, a 90% yield of the ene product (**712**) was obtained when chlorotrimethylsilane was used as an additive.[513] Catalytic, enantioselective imino–ene reactions of α-imino esters have also been reported.[514]



711 **712**

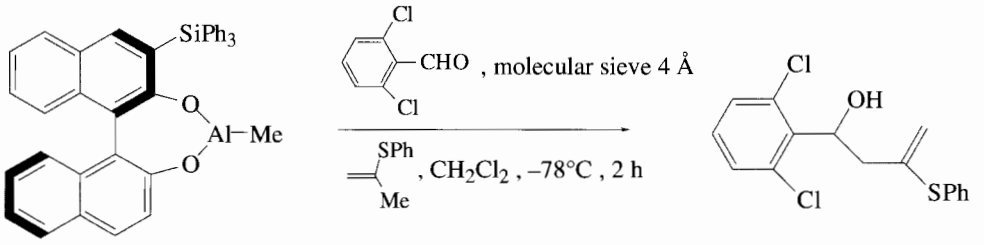
11.13.D. Chiral Ene Reactions

The fundamental principles of asymmetric synthesis employed throughout also apply to ene reactions. Chiral additives, chiral auxiliaries, and the preparation of chirons all lead to good enantioselectivity when applied to the ene reactions. Most chiral ene reactions seem to involve addition of a chiral catalyst or the use of a chiral auxiliary. Oppolzer et al. utilized a chiral auxiliary in **713** to prepare **714** (90 % de) in a synthesis of (+)-α-allokainic acid.[515] Yamamoto used the chiral aluminum catalyst **715** for the intermolecular ene reaction of 1,6-dichlorobenzaldehyde and 2-phenylthio-1-propene to give **716** in 96% yield (65 % ee).[516] These catalysts are similar to those used in Section 11.9.B. A similar titanium catalyst (**717**) was used to couple methylenecyclohexane and methyl glyoxalate, giving 89% of **718** (98 % ee). The titanium catalyst

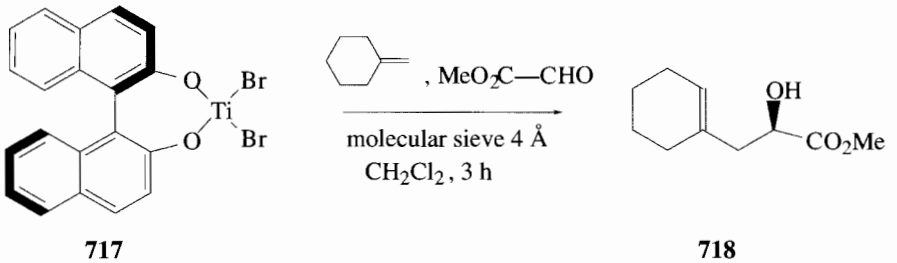


713 714

was prepared *in situ* by reaction of (*R*)-binaphthyl and bis(diisopropoxytitanium) dibromide [$(iPrO)_2TiBr_2$].[517] These few examples are sufficient to illustrate that chiral induction is possible in the ene reaction, using the same techniques that were successful in other pericyclic reactions.



715 716



717 718

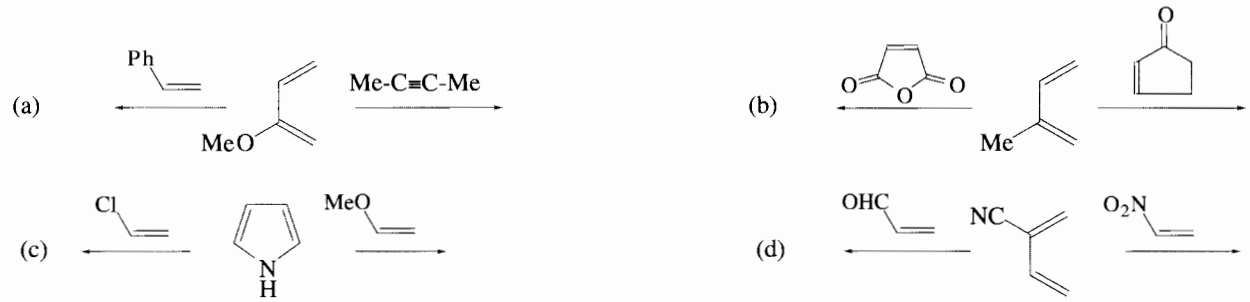
11.14. CONCLUSION

It is clear from the preceding sections that a wide range of cyclic and polycyclic molecules can be prepared by pericyclic reactions. In addition, stereocontrolled syntheses of acyclic molecules is possible via initial cycloaddition, followed by cleavage of the ring. The power of these reactions lies in the ability to make carbon bonds with high regioselectivity and stereoselectivity. If the proper chiron or chiral auxiliary is used, high enantioselectivity can be obtained as well. Few synthetic methods allow access to such a large number of natural products, with compatibility with such a large number of functional groups. In succeeding chapters, methods for generating carbon bonds via electrophilic or radical intermediates will be presented. For power and versatility, however, few reaction types will rival the reactions found in this chapter.

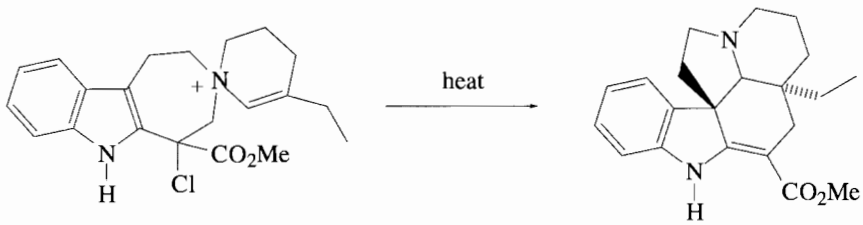
HOMEWORK

1. Using the tables in this chapter (where possible), particularly Tables 11.1 and 11.2, evaluate the relative rate of reaction for each of the following. For the *faster* reaction, predict the structure, and where data is available

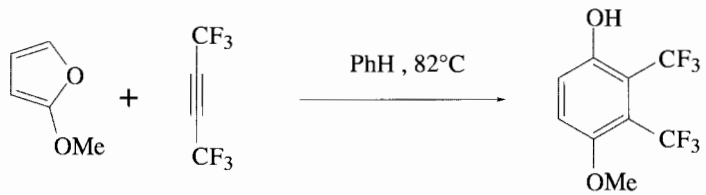
predict the regiochemistry and stereochemistry of the major product(s).



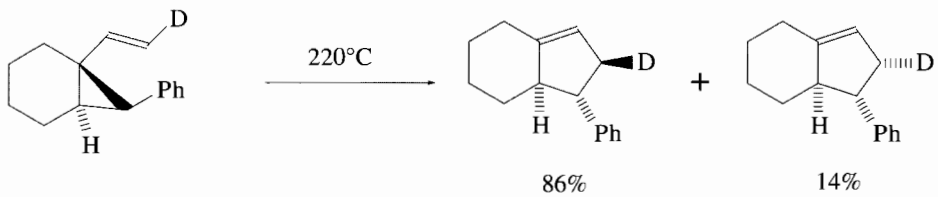
2. Give a mechanistic explanation for the following transformation:



3. Give a mechanistic rationale for this transformation that accounts for formation of the indicated product.

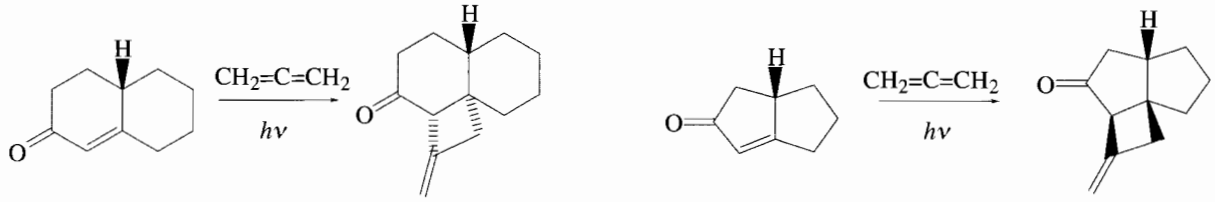


4. Give a mechanistic rationale for the transformation that accounts for one product being formed preferentially and also accounts for the stereochemistry of both products.



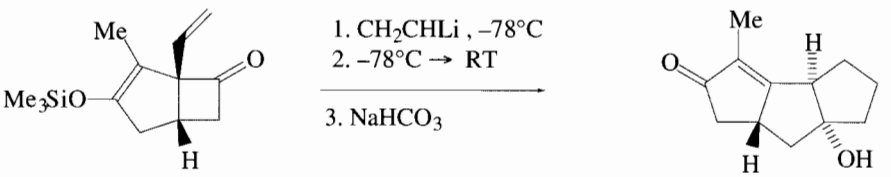
86% 14%

5. Explain the different stereochemical outcomes of these reactions:

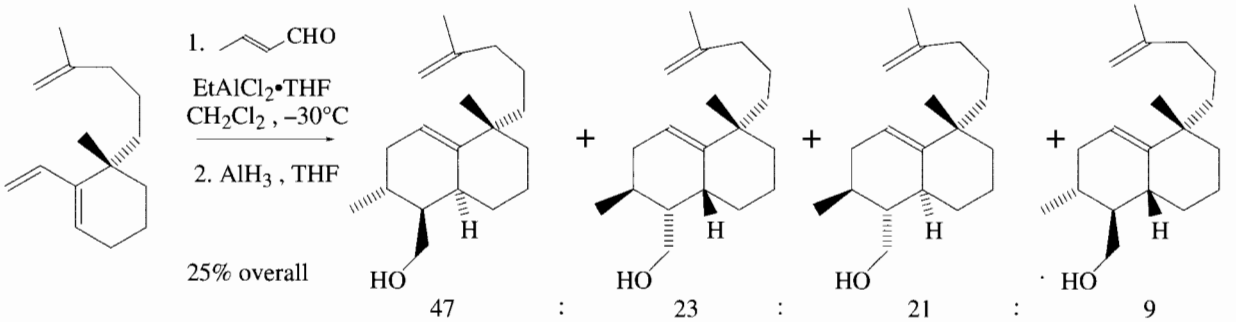


6. Explain the following transformation:

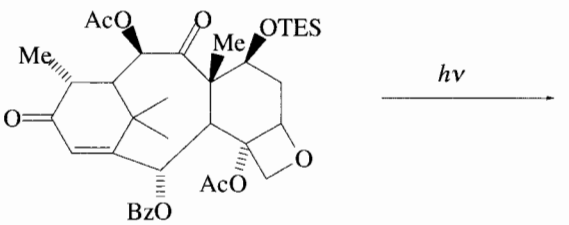
7. Explain the following transformation:



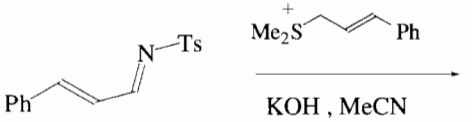
8. Rationalize the stereochemistry and relative ratios of the four products.



9. Give the product for this reaction, and rationalize its formation.

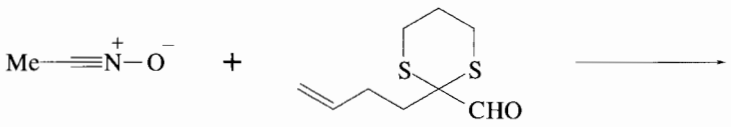


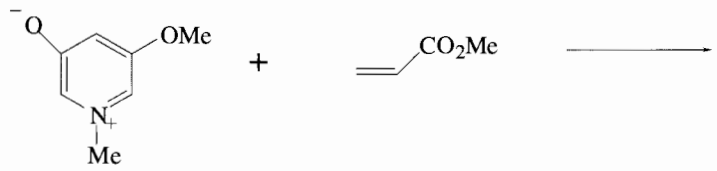
10. Reaction of N-tosylimines and allylic sulfonium salts under basic conditions leads to aziridines in this particular work. When the imine shown was treated with the sulfonium salt given in the reaction, a mixture of aziridine and a dihydroazepine were formed. Draw both products and explain formation of the dihydroazepine.



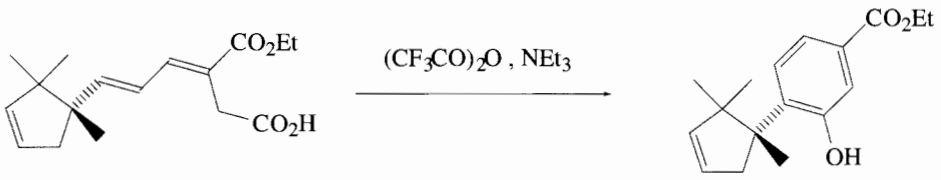
11. Use the tables in this chapter (where possible) to estimate the correct regiochemistry for the products in the following reactions.

(a)

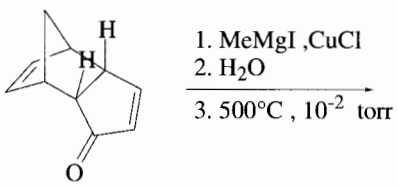
(b) 

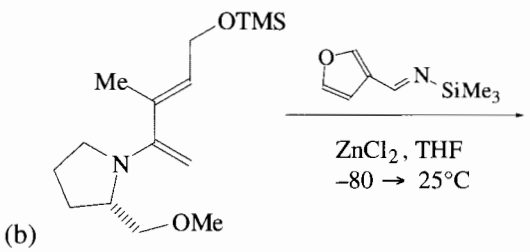
(c) 

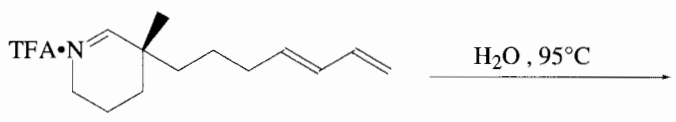
12. Explain the following transformation:

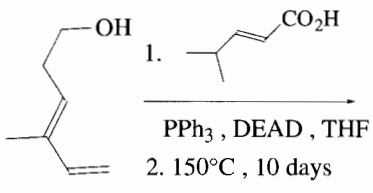


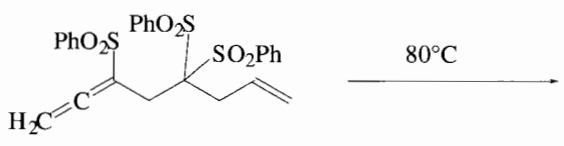
13. For each of the following reactions give the major product, with correct regiochemistry and stereochemistry:

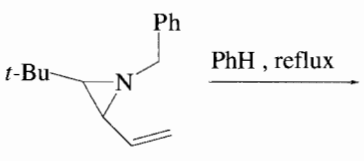
(a) 

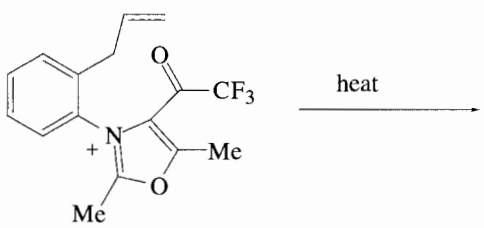
(b) 

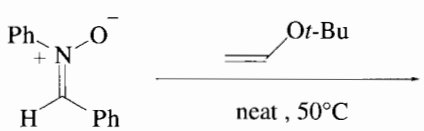
(c) 

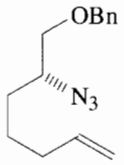
(d) 

(e) 

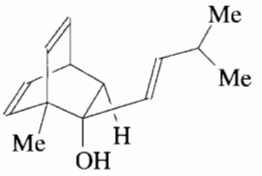
(f) 

(g) 

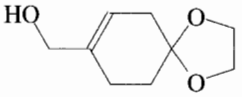
(h) 

(i) 

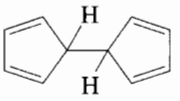
o-dichlorobenzene, 165°C

(j) 

300°C, 1 h

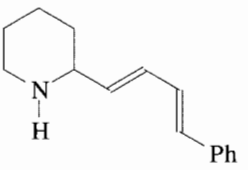
(k) 

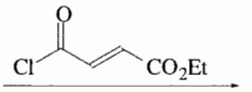
5% $EtCO_2H/EtC(OEt)_3$, 140°C, 3 h

(l) 

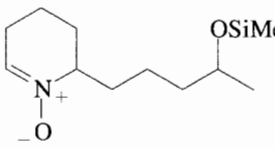
H—≡—CO_2Me

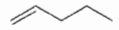
(m)
EtO_2C—C(=O)—CO_2Et, catalyst-$Cu(OTf)_2$, CH_2Cl_2

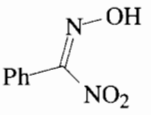
(n) 

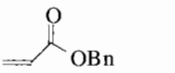


Pyridine, CH_2Cl_2, 0°C, 2 h

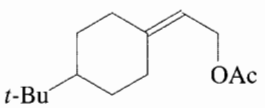
(o) 


48°C, 135 h

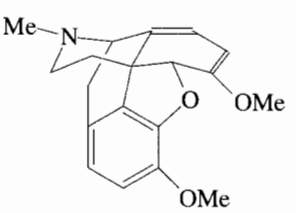
(p) 

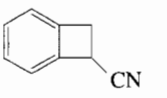


THF, reflux

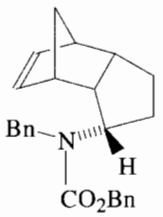
(q) 

p-benzoquinone, *hν*, PhH

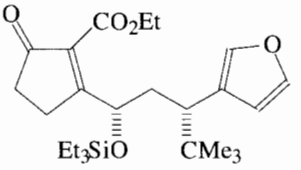
(r) 



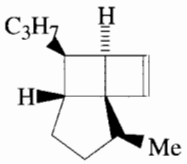
PhBr, reflux

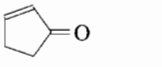
(s) 

PhOPh, reflux

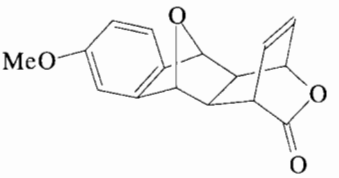
(t) 

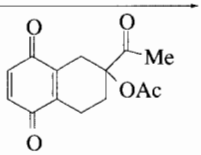
hν (366 nm), hexanes

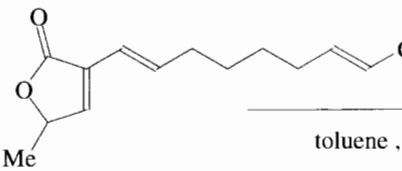
(u) 



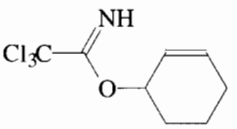
hν (Pyrex), pentane, 12 h, 5–10°C

(v) 

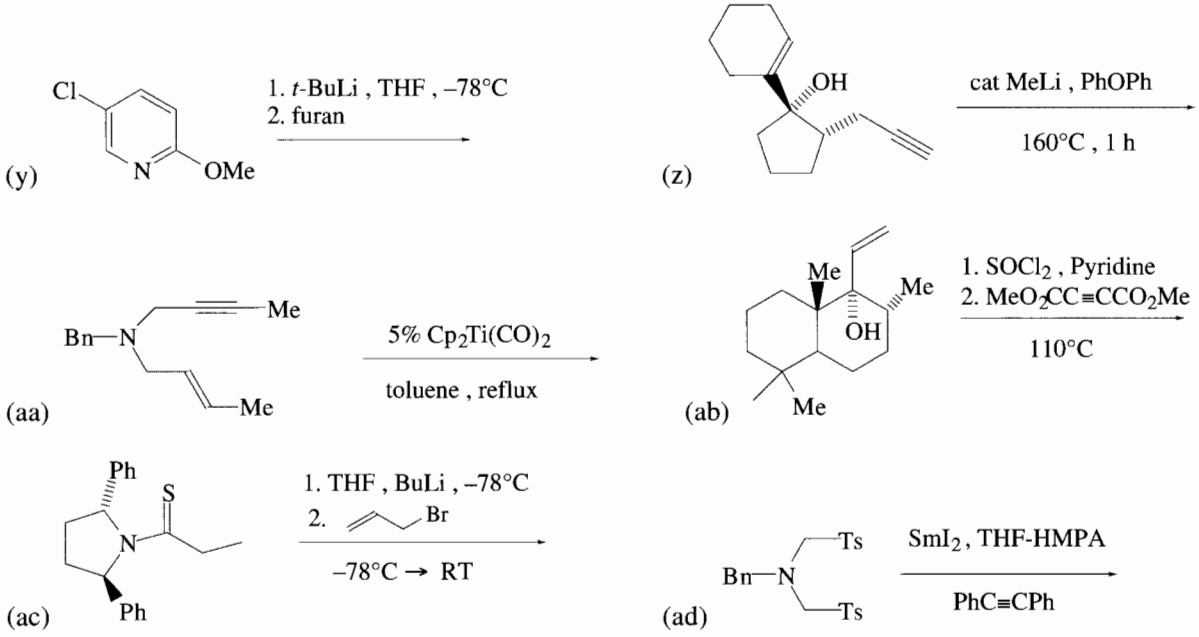
140°C


(w) 

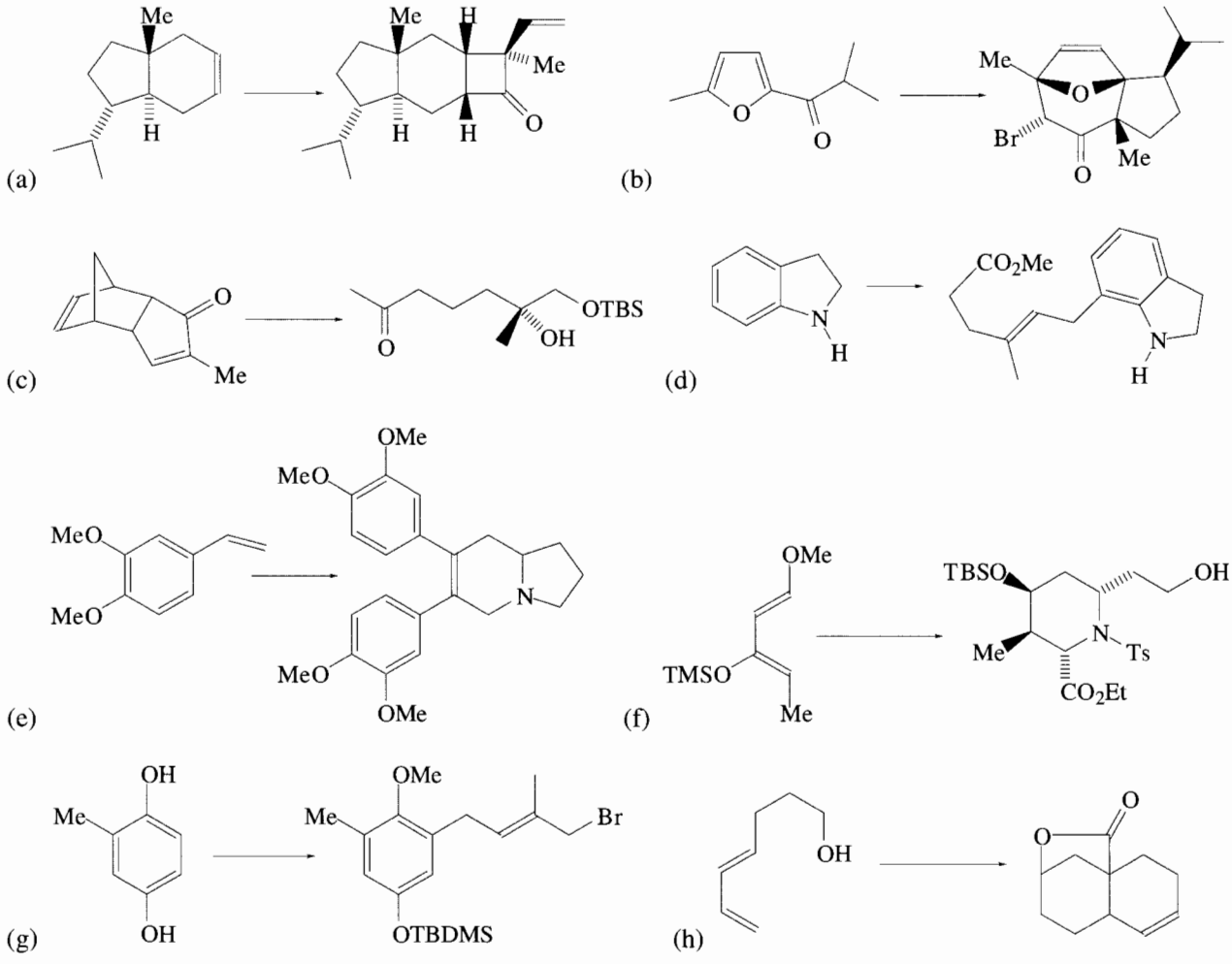
toluene, 170°C

(x) 

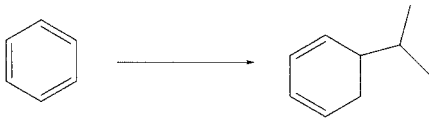
heat



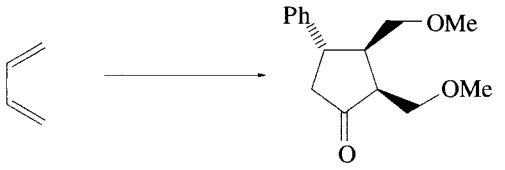
14. In each case, provide a suitable synthesis. Show all intermediate products and all reagents.



(i)

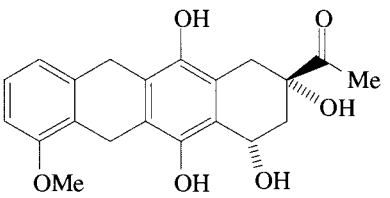


(j)

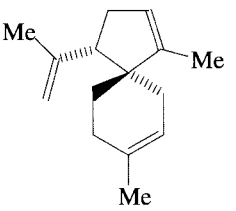


15. In each case, devise a retrosynthetic strategy that will lead to a suitable starting material that costs < $1.00 per g (cite the price and your commercial source). Show the complete synthesis, with all intermediate products and all reagents.

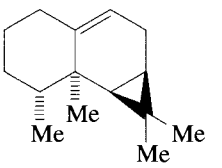
(a)



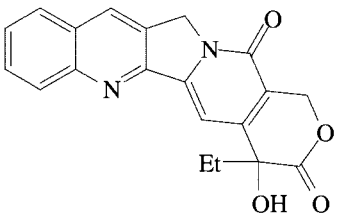
(b)



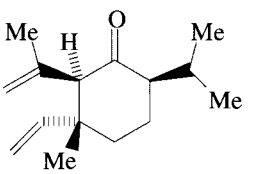
(c)



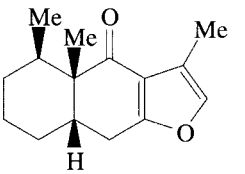
(d)



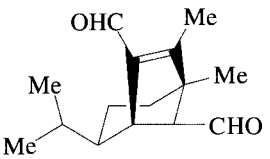
(e)



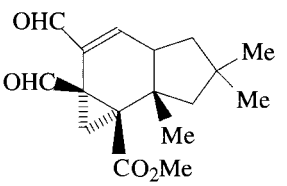
(f)



(g)



(h)



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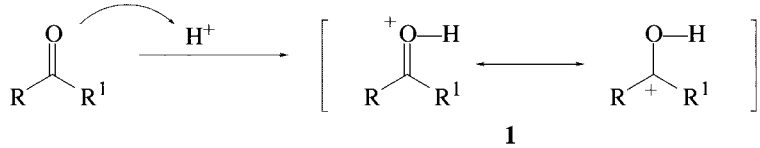
CHAPTER 12

C^a DISCONNECT PRODUCTS: ELECTROPHILIC CARBON–CARBON BOND–FORMING REACTIONS

12.1. INTRODUCTION

Chapters 8, 9, and 11 introduced many reactions for making carbon–carbon bonds. Molecules possessing a polarized electrophilic carbon (δ^+) were common in previous chapters, as with the reaction of an alkyl halide or a carbonyl compound reacting with nucleophiles and organometallics in Chapter 8, or with nucleophilic enolates in Chapter 9. In Section 1.2, disconnection of carbon–carbon bonds generated C^d and C^a fragments and Chapters 8 and 9 focused on C^d fragments. This chapter will focus on reagents and reactions that effectively generate equivalents for a C^a fragment, including $C^{\delta+}$, carbocations, and metal-stabilized cation reagents. Chapter 2 briefly discussed the structure and nature of carbocations in the context of S_N1 reactions (sec. 2.7.B). It was clear the nucleophilic partners that reacted with a carbocation were limited to alkenes, alkynes, aromatic rings or compounds containing heteroatoms such as oxygen, sulfur, halogen, or nitrogen. Reactions of carbocations with these species will also be discussed in this chapter, with an emphasis on their synthetic utility. Since many organometallic reagents (particularly organopalladium and organonickel reagents) generate species that react with nucleophiles, they can be categorized as a C^a equivalent and in many cases react as stabilized cationic species. Therefore, many organometallic reactions are included in this chapter.



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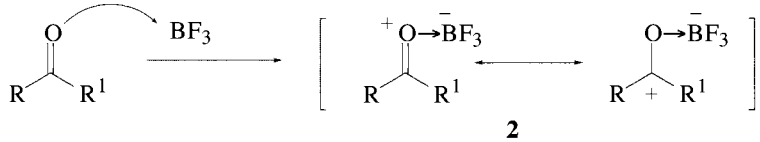


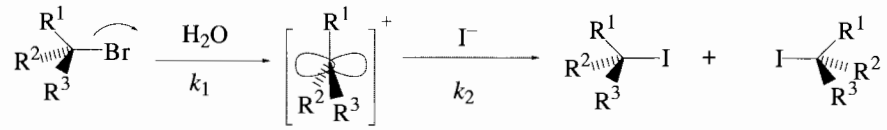
2

In Chapter 2, the conditions used to generate a free carbocation were usually incompatible with the presence of a nucleophilic organometallic reagent, a carbanion, or an enolate anion. The propensity of cations to rearrange was also discussed in Chapter 2, but it is known that rearrangement can often be suppressed by stabilizing the cationic carbon with a heteroatom substituent (an oxygen or mercury atom–secs. 2.7.B, 2.10.B). If a carbocation were sufficiently stable, it might react with traditional nucleophiles such as enolates, providing an interesting entry to the formation of carbon–carbon bonds. Reagents that provide this type of stabilization will be discussed. This chapter will begin with a discussion of free carbocations and, specifically, exploitation of their molecular rearrangements to generate carbon–carbon bonds and different structures.

12.2. CARBOCATIONS

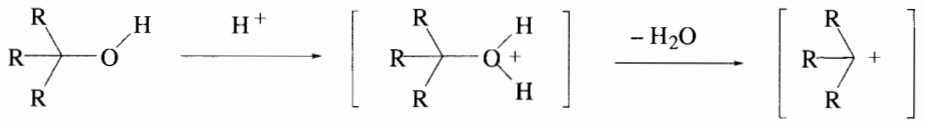
12.2.A. Cation Stability

A carbocation is an sp^2 hybridized carbon bearing three substituents with an empty p orbital perpendicular to the plane of the other atoms (see **3**), which has been termed a **carbenium ion** by Olah.[1] It is a transient inter-mediate and reacts with reagents that can provide a pair of electrons to form a new bond to the electrophilic carbon. Formation of this cation is usually the slowest step (the rate determining step) in a



3

mechanistic sequence because subsequent reactions with a nucleophilic species are very fast. The classical S_N1 reaction of *tert*-butyl bromide and aqueous potassium iodide (KI) to give *tert*-butyl iodide is an example where the slowest step is k_1, ionization of the bromide to the cation **3** (sec. 2.7.B). The second reaction, trapping the cation, is the fastest step (k_2) regardless of the method used to generate the cation. There are many different methods for generating carbocations in addition to the classical ionization shown. Addition of an acidic reagent (HX) to an alkene or alkyne generates a carbocation intermediate (sec. 2.10.A). Treatment of a secondary or tertiary alcohol with an acid catalyst gives an onium salt (**4**), which loses water (a good leaving group) to give the cation.



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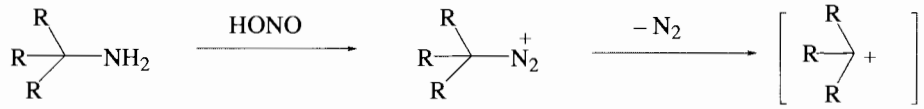
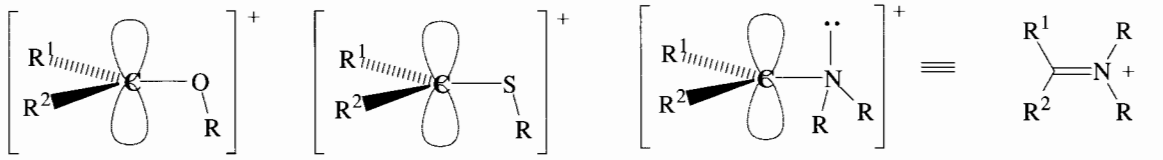


5

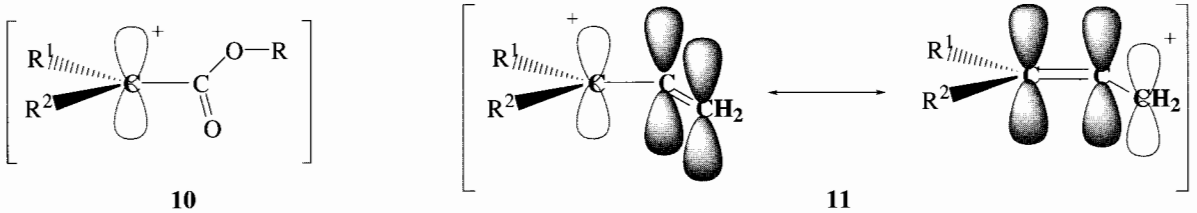
In this process, 3° alcohols react faster than 2° alcohols. Heterolytic bond cleavage of a halide or sulfonate ester (C-X, X = Br, Cl, I, OMs, OTs, etc.) in aqueous solvents (usually with heating) generates tertiary cations easily, secondary alcohols with difficulty, and primary cations with extreme difficulty. Reaction of aldehydes and ketones with an acid catalyst gives the oxygen-stabilized cation (see **1** and **4**). Reaction of amines with nitrous acid (HNO_2) initially gives a diazonium salt (**5**, also see sec. 13.9.B) but alkyl diazonium salts readily decompose to cations.[2]

There are two properties of cations that must be considered *before* considering their reaction with a nucleophilic species: regioselectivity in formation of the cation and migration of substituents (rearrangement). The first is easily dealt with. In general, the more stable cation is formed. Since **3** is essentially a carbon with an empty p orbital, electrons from the adjacent bonds will be attracted to that positive center (inductive effect),

diminishing the net charge and stabilizing the cationic center. When R^1, R^2, and R^3 in **3** are alkyl groups, the carbon atoms of the alkyl substituents release electrons to the positive center, and this effect increases with increasing numbers of alkyl groups leading to greater stability. A tertiary cation ($R^1 = R^2 = R^3$ = alkyl in **3**) will, therefore, be more stable than a secondary cation ($R^1 = R^2$ = alkyl, R^3 = H), which is more stable than a primary cation ($R^1 = R^2$ = H, R^3 = alkyl). The least stable cation in this alkyl series will be the methyl cation ($R^1 = R^2 = R^3$ = H in **3**). The energy difference between 1°, 2° and 3° cations is ≈ 11–15 kcal mol^{-1} (46.1–62.8 kJ mol^{-1}): ΔE 2°↔3° = 11–15 kcal mol^{-1} and ΔE 2°↔1° = 11-15 kcal mol^{-1} with 3° > 2° and 2° > 1°.[3] Given a choice of generating a secondary or a tertiary cation, the tertiary will be formed with high selectivity. Other electron releasing substituents (those with a negative or δ– charge, i.e., high electron density) also stabilize the charge. Both oxygen stabilized cations (see **4** and **6**) and sulfur stabilized cations (see **7**) are well

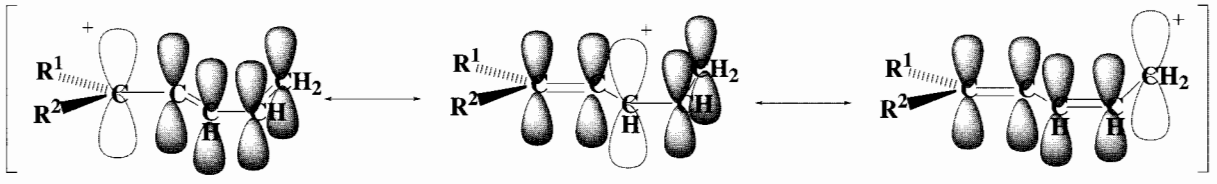


6 **7** **8** **9**

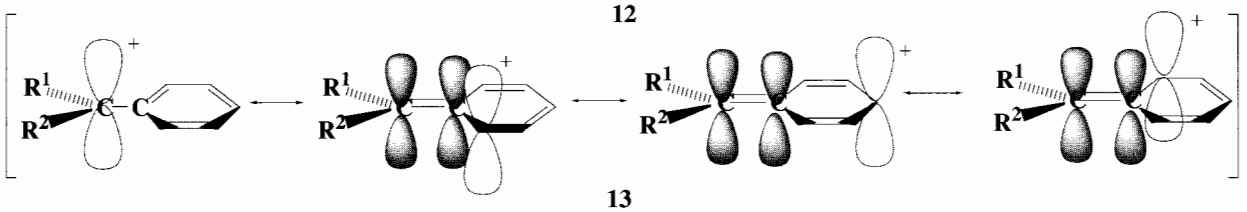


10 **11**

known. Stabilization of a cation by an adjacent nitrogen (see representation **8**) is very efficient and the actual structure has a π bond between the carbon and nitrogen to give an iminium salt (**9**) as a stable, isolable product. Although oxygen-and sulfur-stabilized cations are well-known intermediates, nitrogen-stabilized cations are actually iminium salts, which are discreet and well-characterized species (with the structure **9**). In terms of their reactivity, it is useful to consider iminium salts as amino cations (represented as **8**), since they react with nucleophiles at the electrophilic carbon, *but this is not the actual structure.*



12



13

The stabilization produced by heteroatoms contrasts sharply with cationic centers bearing an electron withdrawing group (see **10**), where the positive and δ+ centers repel, destabilizing the cation. It should be difficult to form this type of cation. On the other hand, if a π system (not bearing a δ+ center) is conjugated to the cationic center, the electron deficiency (the positive charge) will be dispersed via resonance, diminishing the net charge of the initially formed cationic carbon, stabilizing it. An allylic cation (**11**), for example, disperses the charge over three atoms. If the cationic center is conjugated to a diene (as in **12**) the charge is dispersed over five atoms, and in benzylic cations (**13**) the charge is dispersed over seven atoms. By this simplistic view, the benzylic cation (**13**) should be more stable than **12**, which is more stable than **11**.

The relative order of cation stability can be related to the ionization potential of the cation, which can be experimentally determined by electron bombardment in a mass spectrometer. As shown in Table 12.1,[4] the ionization potential and relative energies (determined by mass spectrometry) show the relative order of cation stability to be tertiary > secondary > primary > methyl, as expected. In Table 12.1, the lower energy ionization (7.42 eV vs. 8.64 eV for *tert*-butyl vs. *n*-butyl) represents the more stable cation. Similarly, Table 12.2[5] shows mass spectral data (ionization potential) for a variety of cations, but also shows the energy of cations

Table 12.1. Ionization Potentials and Relative Cation Stability Produced by Electron Bombardment

$$R\bullet + e^- \longrightarrow R^+ + 2\,e^-$$

R	IP (eV)	Relative Energy (kcal mol^{-1})	(kJ mol^{-1})
n-Propyl	8.69	29.2	122.2
sec-Propyl	7.90	11.1	46.5
n-Butyl	8.64	28.1	117.6
Isobutyl	8.35	21.4	89.6
sec-Butyl	7.93	11.7	49.0
tert-Butyl	7.42	0	

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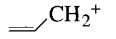
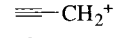
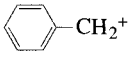
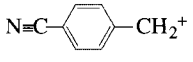
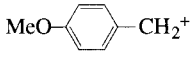
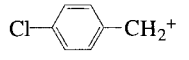
calculated for a chemical ionization pathway ($\Delta H^{\ddagger}_{calc}$). Since the two energy values are not related, they cannot be correlated. The mass spectral data obviously exclude solvent effects, which can have a profound influence on the relative stability of the cation. Table 12.2, however, shows that for alkyl cations, tertiary > secondary > primary. Similarly, the primary benzyl cation is less stable than the *tert*-butyl cation but more stable than the secondary isopropyl cation. Electron-releasing groups on the aromatic ring make the benzylic cation more stable and electron withdrawing groups make it less stable, due to the usual inductive effects (sec. 2.2). The $\Delta H^{\ddagger}_{calc}$ data suggest that the primary allyl cation is less stable than a primary alkyl cation but more stable than methyl. Generally, however, the allylic cation is taken to be only slightly less stable than the benzylic cation. The propargyl cation is significantly less stable than the allylic cation. Interestingly, secondary cations derived

Table 12.2. Ionization Potential and $\Delta H^{\ddagger}_{calc}$ for Cations

R• + e⁻ ⟶ R⁺ + 2 e⁻

R	IP (kcal mol^{-1})	IP (kJ mol^{-1})	$\Delta H^{\ddagger}_{calc}$ (kcal mol^{-1})	$\Delta H^{\ddagger}_{calc}$ (kJ mol^{-1})
Me	950	3979.6	1080	4524.1
Et	835	3497.8	943	3950.2
n-Pr	835	3497.8	912	3820.4
n-Bu	835	3497.8	885	3707.3
i-Pr	760	3183.6	810	3393.1
t-Bu	715	2995.1	730	3058.0
t-pentyl	685	2869.5	678	2840.1
Neopentyl	805	3372.2	815	3414.0
			1000	4189.0
			890	3728.2
			815	3414.0
			782	3275.8
			955	4000.5
			1105	4628.9
			920	3853.9
	748	3133.4		
	806	3376.3		
	660	2764.7		
	766	3208.8		

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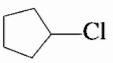
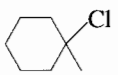
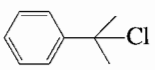
from cyclic molecules are influenced by the size of the ring, with a stability order C6 > C5 > C4 > C3, and the cyclopentyl cation is about equal in energy to the isopropyl cation.

The relative order of 2°, 3°, and benzylic cations is also shown in Table 12.3,[6] based on a hydrolysis reaction for which ΔH_{rxn} was measured. In this table, cyclic 2° and 3° alkyl cations are more stable than their acyclic counterparts. Tertiary benzylic cations are more stable than the tertiary alkyl cations. An important conclusion apparent in Table 12.3 is that the order 3° > 2° > 1° applies to all cations and 3° benzylic > 2° benzylic > 1° benzylic. It is not surprising that a 3° benzylic cation is more stable than a 3° alkyl cation since the former is resonance stabilized. The 3° alkyl cation is more stable than the 1° benzylic cation, however.

3° benzylic > 2° benzylic > 3° alkyl > 1° benzylic ≈ 1° allylic ≈ 2° alkyl > 1° alkyl > methyl

The relative rates of solvolysis for several secondary, tertiary and benzylic chloroalkanes represented by **14** are shown in Table 12.4.[7] The general stability of the cation (**15**, benzylic > tertiary > secondary) is reflected

Table 12.3. Relative Stability of Alkyl and Benzylic Cations Formed by Hydrolysis of Alkyl Chlorides

Halide	ΔH_{rxn} , kcal mol^{-1})	(kJ mol^{-1})
	–15.3	–64.0
	–15.9	–66.6
	–17.3	–72.4
	–24.8	–103.8
	–27.1	–113.4
	–26.9	–112.6
	–27.1	–113.4
	–27.9	–116.8
	–30.3	–126.8
Ph_3C—Cl	–38.0	–159.0
Ph_2CH—Cl	–27.9	–116.8

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in these rate data (the more stable cations are formed fastest, leading to a faster reaction, since this is the rate determining step). The presence of a second phenyl group led to greater conjugation, greater stability and a significantly higher rate (19,000 for Ph_2CMeCl vs. 1.57 x 10^{-6} for Me_2CHCl).

The stability provided by an adjacent oxygen atom is apparent in the solvolysis data for a primary alkyl chloride, which are shown in Table 12.5.[7] Stabilization by the oxygen (in $EtOCH_2Cl$) is a significant contributor to the huge increase in the rate of solvolysis for this primary cation over that for a simple primary cation derived from 1-chlorobutane). The electron-withdrawing effect at the α-carbon in $EtOCH_2CH_2Cl$ further destabilizes the cation and lowers the rate. When a cyclopropyl group is conjugated to a cation, that cation is also significantly more stable.[8] The cyclopropane bonds have a relatively high degree of **s character** (sec. 2.2) and provides stabilization to a cationic center only when conjugated to that center.

As briefly discussed in Section 2.7.B.i, cations are planar, and S_N1 type reactions are expected to proceed with racemization since there is little or no facial selectivity in the simple cases. Retention or partial retention and even inversion can occur "if the structure contains a configuration-holding group, a nucleophilic group which can interact with the carbonium centre".[9] If a tight ion pair is generated, the S_N1 reaction will show

Table 12.4 Relative Rate of Solvolysis of Substituted Chloroalkanes[10]

14 **15**

R^1	R^2	Rate
H	Me	1.57×10^{-6}
Me	Me	0.086
Ph	Me	394
H	Ph	0.216
Me	Ph	394
Ph	Ph	19,900

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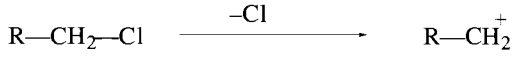
some memory of the departing group since it is in close proximity, and partial inversion can occur, which will clearly be solvent dependent. Table 12.6[11] shows the percentage-inversion for a series of secondary halides in solvolysis reactions, under a variety of solvolysis conditions. These results indicate that addition of silver ion increases the inversion, presumably via coordination with the halide, which will not generate a free cation and the departing bromide is close to the cationic center at the time of the substitution.

Table 12.5. Acceleration Effects of Oxygen Substituents on Solvolysis Rates

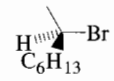
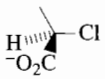


R	Relative Rate
EtO	109
C_3H_7	1
$EtOCH_2$	0.2

[Reprinted with permission from Streitwieser Jr., A. *Solvolytic Displacement Reactions*, McGraw-Hill, New York, ***1962***, pp. 102-103. Copyright 1962, McGraw-Hill.]

As a practical matter, reactions of carbocations do not necessarily proceed with complete inversion or retention, but many proceed with partial inversion. It is reasonable, however, to assume that racemization or partial racemization will be the stereochemical outcome of cationic reactions, unless there is experimental evidence or literature precedent to support inversion or retention.

Table 12.6. % Inversion in S_N1 Type Solvolysis Reactions

Alkyl Halide	Solvent	Inversion (%)
	60% aq EtOH	83
	60% aq EtOH + Ag^+	97
	80% aq acetone	60
	H_2O	58
	aq acetone	51
	H_2O	0
	H_2O + Ag^+	61

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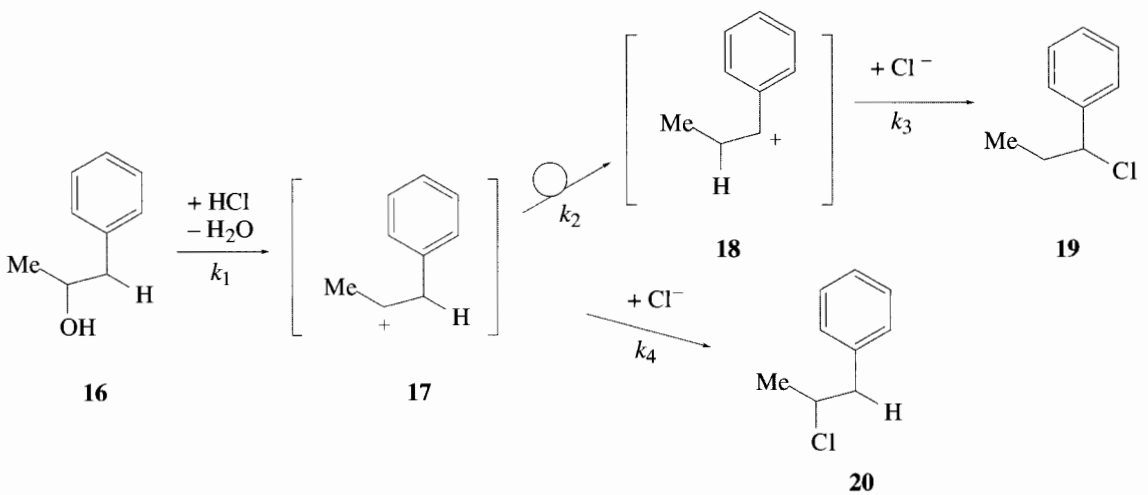
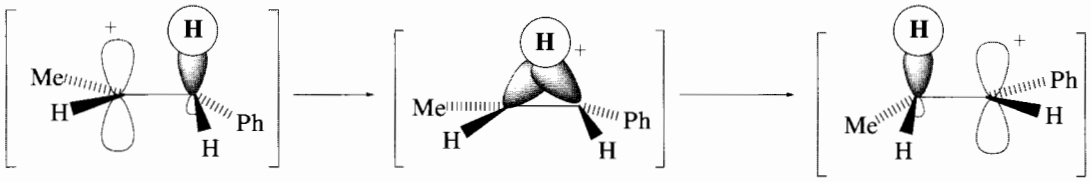
2.B. Cationic Rearrangements

A second property of carbocations that influences their synthetic utility is their propensity to rearrange to a more stable cation. When alcohol **16** is treated with HCl, two products are possible, the direct S_N1 product (**23**; sec. 2.7.B.ii) that results from trapping the initially formed cation (**17**) with chloride ion (rate constant = k_4) and the rearranged product (**19**). Rearrangement via a 1,2-hydride shift can occur (rate constant = k_2) because benzylic cation **18** is more stable than the initially formed **17**, and subsequent trapping with chloride ion (rate



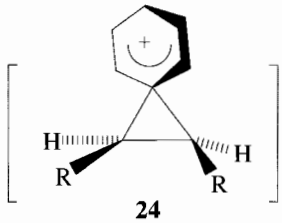
constant = k_3) gives **19**. In the limiting cases, if $k_2 >> k_4$, only **19** will be observed, whereas only **20** will be observed if $k_4 >> k_2$. In both cases, the initial ionization step (rate constant = k_1) is the slowest (rate-determining) step, and $k_3 \approx k_4$. If the two cations are close in energy, then $k_2 \approx k_4$ and a mixture of products will result or only a modest amount of rearrangement will occur. In many cases, the rearrangement (k_2) proceeds faster than the S_N1 type reaction (k_4) and the rearranged product predominates. If the cation and nucleophile are particularly reactive, however, k_4 may be much faster than k_2. A simplifying *assumption* is that $k_2 > k_4$ in most cases. This is, of course, not always true but it provides a good working model for these types of reactions.

This type of rearrangement is understood in terms of an electron deficient p orbital (the positive center) gaining electron density from an adjacent σ bond. When the σ-bond (C—H) adjacent to the p-orbital is parallel (as in **21**) the σ and p orbitals can overlap and electron density (i.e. the bond) migrates toward the



21 **22** **23**

positive center. The transition state for this process is usually represented as a bridged electrophilic species, **22**. In this transition state, the hydrogen atom is transported as the electrons in the bond move, leading to a 1,2-shift of the hydrogen atom to the adjacent carbon, giving **23**. This rearrangement occurs when the reaction (**21** → **23**) is exothermic and if the bond bearing the migrating group can become parallel with the p orbital of the cationic center. In this case, the more stable benzylic cation is favored over the secondary cation and the 1,2-hydrogen shift is an exothermic reaction. In general, secondary → tertiary, primary → secondary, and primary → tertiary rearrangements are exothermic reactions, and the rearrangement is facile.



24

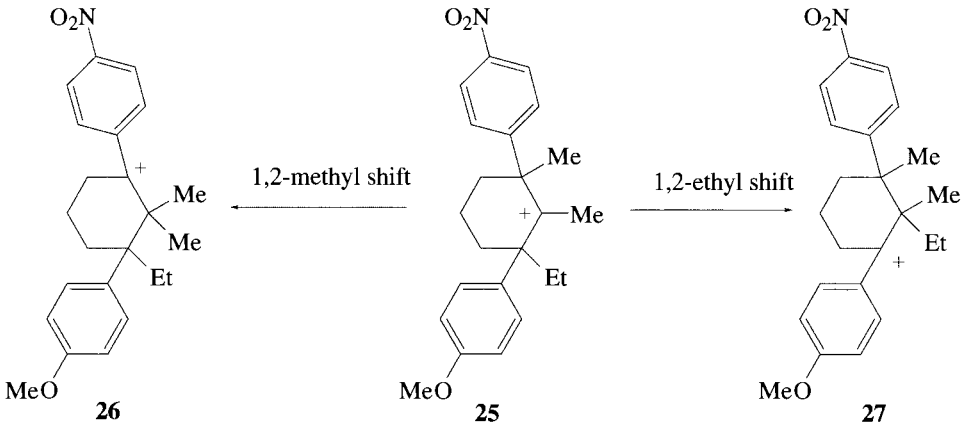
Why did the hydrogen group in **21** migrate and not the phenyl? First, migration of the phenyl would lead to a significantly less stable primary cation and the reaction would be endothermic. Second, migration of the larger phenyl group may require more energy than the smaller hydrogen,. It should be noted, however, that the phenyl group can migrate and a relatively low-energy phenonium ion (such as **24**) has been invoked in many aryl migrations.[12] In a transition state such as **22**, considerable positive charge can be present, and charge dispersal (as in **24**) can facilitate the rearrangement.

In the absence of special electronic effects, alkyl groups show a clear dependence on the size of the migrating group. In general, smaller groups migrate before larger ones:

H	>	Me	>	$CHMe_2$	>	CMe_3

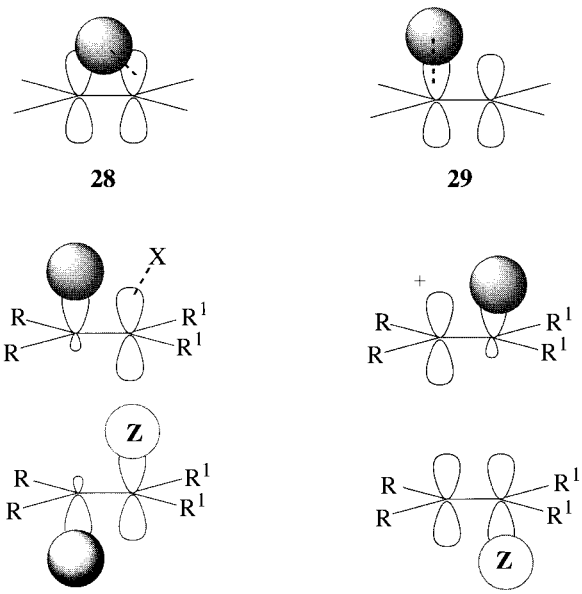
It is difficult to give an absolute scale for migratory aptitude, however, since migratory aptitude is inevitably linked to the stability of the cation being formed. An example is cation **25**, where the larger ethyl group can migrate preferentially (to give **27**) rather than the smaller methyl group to give **26**. The *p*-methoxyphenyl group will stabilize cation **27** to a greater extent than the *p*-nitrophenyl group stabilizes **26**. The electron

releasing methoxy diminishes the net charge, but the electron-withdrawing nitro group destabilizes the cationic center in **26**. In other words, the larger ethyl group can migrate rather than the smaller methyl, due to formation of a more stable cation. The criteria for determining which group migrates must involve both the stability of the cation being formed (relative to that initially available) and the size of the migrating group. If the rearrangement for either hydrogen or methyl, for example, will generate a cation of similar stability, the relative size of the migrating group is usually the determining factor and the hydrogen will migrate preferentially.



26 **25** **27**

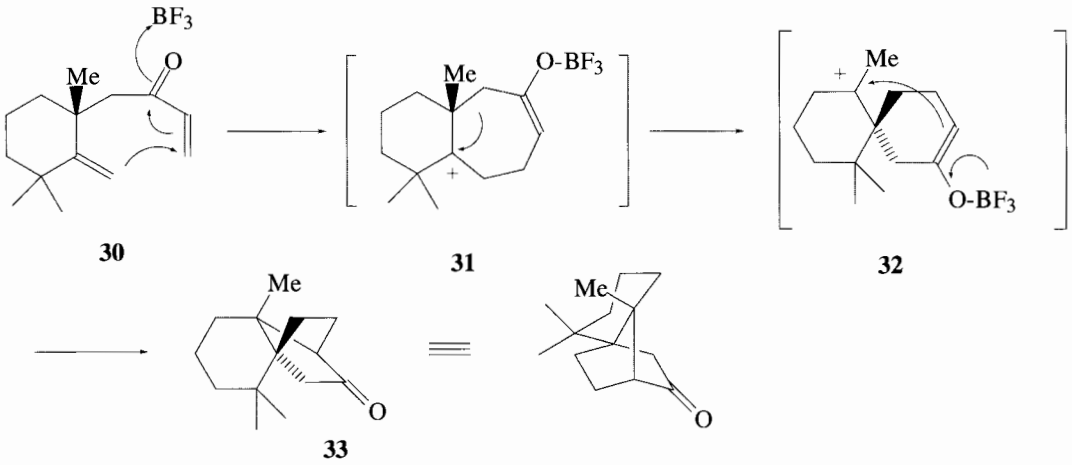
If an atom or group is present that can *assist* migration in some way, that migration is usually faster, which is another example of neighboring-group participation, noted in several previous chapters.[13] The term σ-**participation** has been used to describe the through-space interaction (sec. 2.2) of an empty p orbital with the electrons in a neighboring bond (see **28** and **29**).[14] The term σ **conjugation** (usually the same as **hyperconjugation**) "implies sideways interaction of orbitals, as in Figure 12.1".[15] Such neighboring-group effects can both accelerate the rate of rearrangement and stabilize the cation.



28 **29**

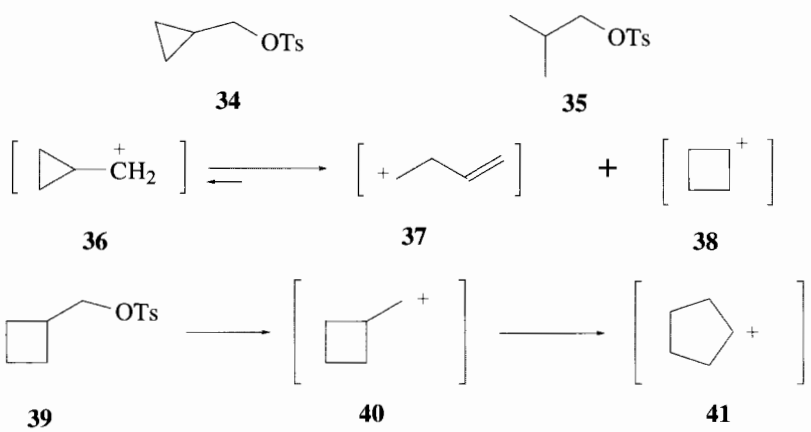
Figure 12.1. σ Conjugation in 1,2-bond migrations.

Cationic rearrangements can be highly selective. In the Srikrishna et al. synthesis of 6-epijunicedranol, the authors also synthesized normylataylanone (**33**)[16] when conjugated ketone **30** was treated with boron trifluoride•etherate. Coordination of the carbonyl and Michael-type addition of the exocyclic alkene unit gave tertiary cation **31**. Despite the fact that this is a tertiary cation, it rearranged via a 1,2-alkyl shift to give spirocycle **32**. The migration occurred on the face opposite the methyl group, and the enolate unit in **32** attacked the tertiary cation from that same face to give the stereochemistry shown in **33**. Ketone **33** was obtained in 60% yield.



30 **31** **32** **33**

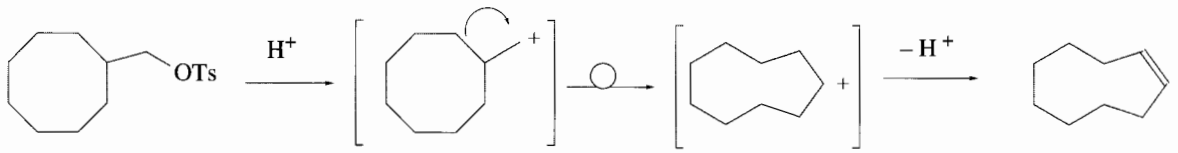
Cyclopropylcarbinyl systems (where the cationic carbon is connected directly to a cyclopropyl ring) are subject to ring-expanding cationic rearrangements. In Section 12.2.A, it was noted that the cyclopropyl group imparts special stability to an adjacent cationic, but cyclopropylcarbinyl cations such as **36** easily open via participation of the strained cyclopropyl bonds, forming a homoallylic cation (**37**).[17] Participation of the cyclopropane ring is apparent in the solvolysis of cyclopropylcarbinyl tosylate (**34**), which occurs 10^6 times faster than solvolysis of the tosylate of 2-methyl-1-propanol (**35**).[18] A cyclobutyl cation (**38**) can also form under these conditions via a ring-expansion reaction (see below). Cyclobutane provides some stabilization to a cation in cyclobutylcarbinyl cations such as **39**, formed by solvolysis of the tosylate (**40**). In this case, the major product is the cyclopentyl cation (**41**), formed by ring expansion.



34 **35** **36** **37** **38**

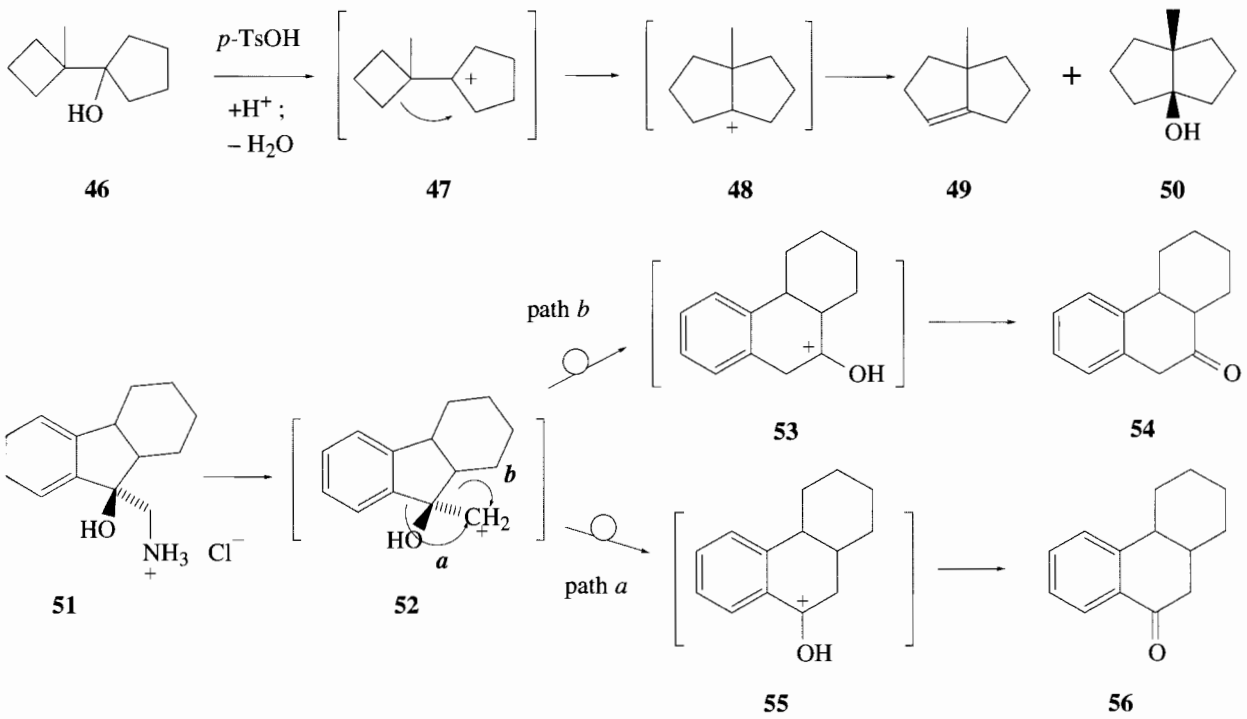
39 **40** **41**

Cationic rearrangement can be used in other ring expansion reactions, such as the formation of **45** when **42** was treated with acid, albeit in only 9% yield.[19] Solvolysis of the tosyl group in **42** produced the very unstable primary cation **43**. Rearrangement led to ring expansion and the more stable secondary cation **44**, which lost a proton to give the alkene product (**45**). The overall result was expansion of the eight-membered ring to a nine-membered ring. If bond migration leads to a medium size ring (8–13), the high energy inherent in these rings may inhibit the bond migration to form a larger ring (sec. 6.6.B), leading to poor yields.



42 **43** **44** **45**

The poor yield of **45** is interesting since a secondary cation is much more stable than a primary cation. In this case, ring expansion generates a nine-membered ring with higher energy than the eight-membered ring precursor. Treatment of an amine with nitrous acid (HONO) generates an unstable diazonium salt, which decomposes to a transient primary cation. The initially formed cation rearranged to the larger ring cation in what is now known as the **Demjanov rearrangement**.[20] In the initially reported reaction, water was present, which trapped the ring-expanded cation as the alcohol.[21,2ac] It is possible to generate the cation under milder



46 **47** **48** **49** **50**

53 **54**

51 **52**

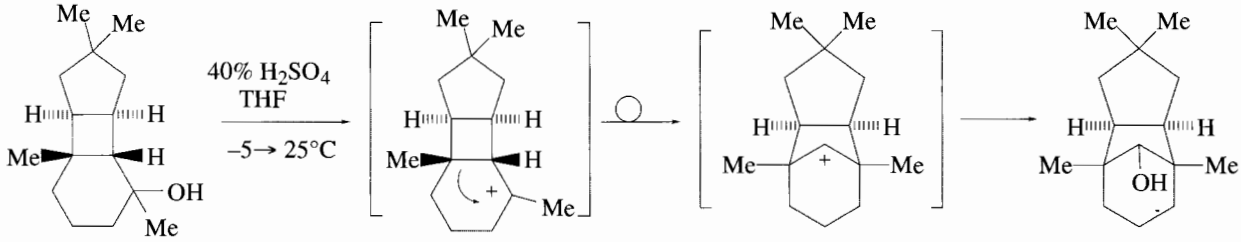
55 **56**

and more controlled conditions. An example is found in Fitjer's synthesis of laurene,[22] where alcohol **46** was treated with *p*-toluenesulfonic acid in benzene and the initially formed cation (**47**) had the positive charge adjacent to a strained four-membered ring. Opening the strained four-membered ring to the lower energy

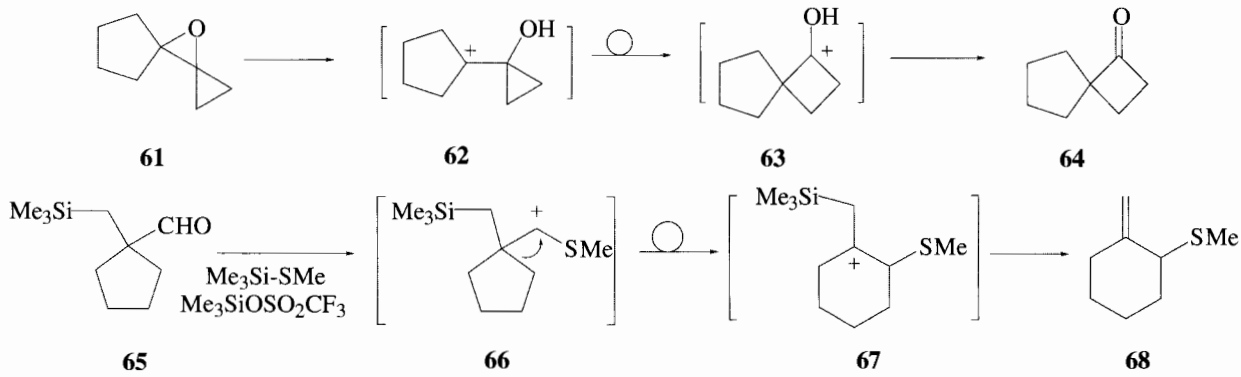
five-membered ring product occurred by a 1,2-alkyl shift to give **48**. Under the reaction conditions, elimination occurred to give a 90% yield of **49**, although ≈ 10% of **50** was also observed. It is noted that the stereochemistry of the groups adjacent to the cation can have a significant effect on the migratory aptitude of the groups adjacent to the cationic center.[23]

A relatively simple variation of this reaction is the **Tiffeneau–Demjanov ring expansion**,[24,20c] involving treatment of amino alcohols with nitrous acid to produce ring-expanded ketones. The conversion of **51** to a mixture of isomeric ketones in 81% yield is an example.[25] This example illustrates a common problem in ring-expansion reactions in particular and in rearrangements in general, that of regioselectivity. Treatment of **51** with nitrous acid produced cation **52**. Two ring expansion pathways are possible, paths *a* and *b*. The major pathway is path *a*, first giving ring expansion to cation **53** and then a 55% yield of **54**. This pathway also produced 0.7% of the trans ketone. Path *b* led to **55**, which produced 25.6% of ketone **56**.

This ring-expansion process is quite useful when applied to polycyclic systems. Corey treated **57** with 40% sulfuric acid and isolated the rearranged alcohol, α-caryophyllene alcohol (**60**).[26] The initially formed cyclobutylcarbinyl cation (**58**) rearranged to the cyclopentyl cation (**59**), which was trapped by water to give **60**.



Trost and co-workers used this type of rearrangement to generate oxaspiropentane derivatives that were converted to cyclo-butane derivatives.[27,28] In section 8.8.B.ii, oxaspiropentanes such as **61** were prepared by the reaction of ketones and sulfur stabilized cyclopropyl ylids. Treatment of **61** with aqueous tetrafluoroboric acid (HBF_4) gave cation **62**, which rearranged to **63**. Loss of a proton gave the final product, ketone **64**.[28,27]

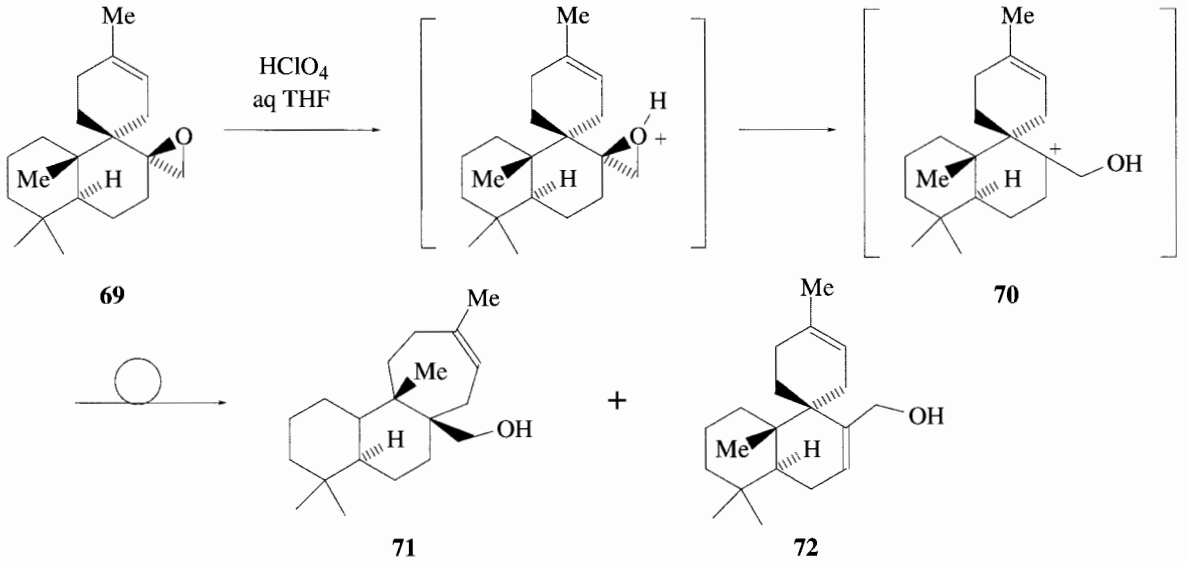


Another variation of this ring expansion used sulfur stabilized cations. When aldehyde **65** was treated with trimethylsilyl methyl sulfide and trimethylsilyl triflate, cation **66** was formed and rearranged to the more stable tertiary cation **67**. Elimination of the silyl group gave a 59% yield of the *exo*-methylene derivative (**68**).[29]

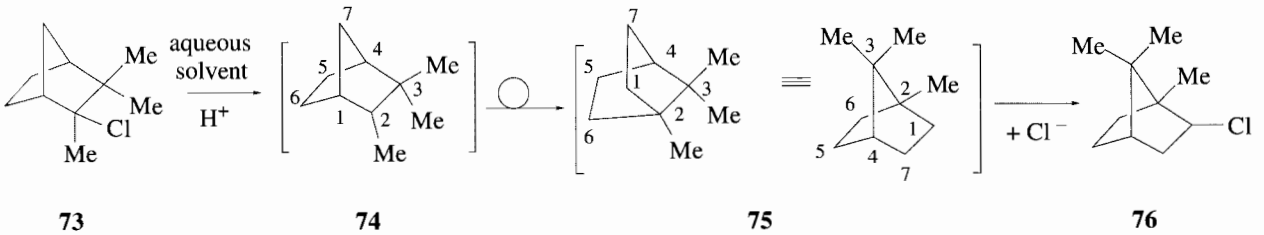
The driving force of this reaction is probably formation of the β-silyl cation in **67**. A recent variation treated α-hydroxydithianes with red HgO and HBF_4, leading to good yields of ring-expanded 1,2-diketones.[30]

Epoxides react with protonic or Lewis acids to generate cations, and once formed they are also subject to rearrangement. In White's synthesis of 2-desoxystemodinone,[31] attempts to convert **69** to an aldehyde via an acid-catalyzed rearrangement failed. Upon treatment with perchloric acid in aqueous THF, a 39% yield of the rearranged product **71** was obtained, along with 17% of an elimination product (**72**). The epoxide unit reacted with acid to generate the protonated epoxide, which opened to give tertiary cation **70**. A subsequent 1,2-alkyl shift followed by a 1,2-methyl shift and then elimination gave **71**. Elimination directly from **70** gave **72**.

A specialized cation rearrangement first observed with bornyl systems is the acid catalyzed rearrangement of camphene hydrochloride (**73**) to isobornyl chloride (**76**).[32] The reaction, which proceeds by a 1,2-alkyl shift called the **Wagner–Meerwein rearrangement**, initially generates bornyl cation **74**, but rearrangement to

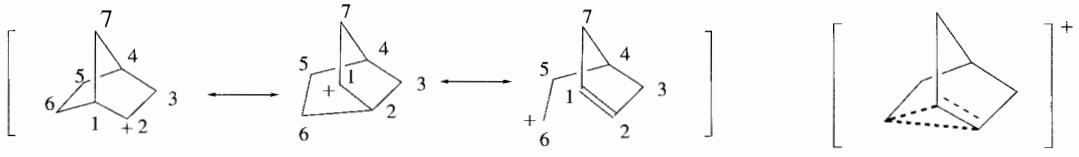


75 occurs prior to trapping the chloride. The term Wagner–Meerwein is often applied to the acid-catalyzed rearrangement of [*m.n.o*]-bicyclo and [*m.n.o*]-tricyclo species, although it applies formally to bicyclo-[2.2.1]heptane derivatives.

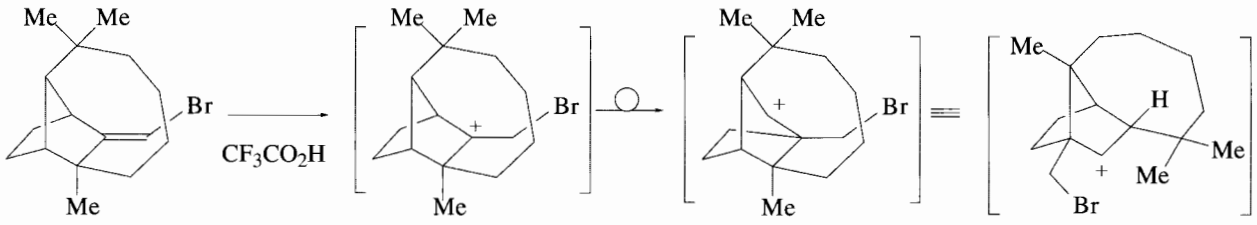


This reaction has been the center of a controversy concerning the structure of norbornyl cations such as **74** and **75**.[14c] Norbornyl cations have been described in terms of the resonance structures shown in **77**, or as the nonclassical ion **78**.[33] This view was questioned, primarily by Brown,[14c] who did not believe that the evidence proved the existence of a bridged intermediate.[34] Brown suggested that the facile rearrangements are explain-

ed by a series of fast 1,3-Wagner–Meerwein shifts.[35] The dispute continues in some quarters.[36] There is considerable evidence, however, that the norbornyl cation rearranges with considerable σ-participation,[37] and there is strong NMR evidence for the nonclassical ion in super acids at low temperatures.[38] Olah is more forceful, stating that "it can be concluded that the original views of Winstein[39] on the nonclassical nature of the norbornyl cation, based on kinetic and stereochemical reactivity, have been fully substantiated by direct spectroscopic studies of the long-lived ion".[40]



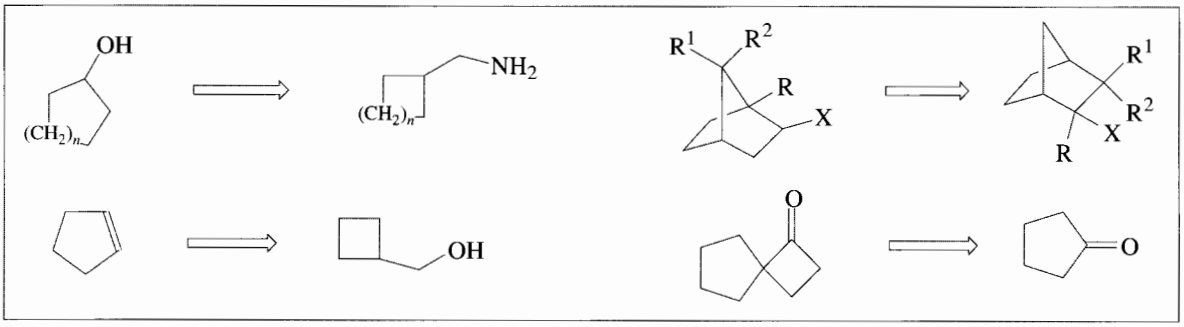
77 **78**



79 **80** **81**

The mechanistic controversies have not diminished the synthetically interesting transformations possible with controlled cation rearrangements.[41] Mehta and Kapoor exploited the Wagner–Meerwein shift to synthesize himachalene via treatment of **79** with trifluoroacetic acid at 35°C, initially forming the norbornyl cation **80**.[42] This cation gave the usual norbornyl cation rearrangement[38] to **81**, which was trapped by trifluoroacetate to give the final product

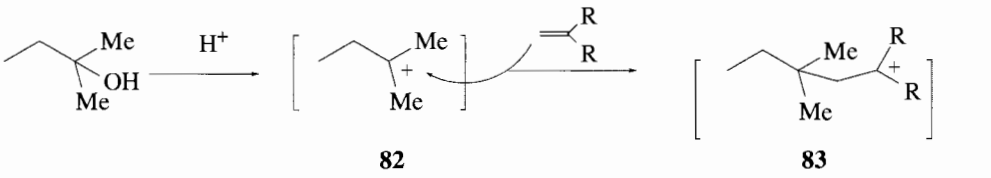
Although they are difficult to generalize, several interesting disconnections are possible utilizing cationic rearrangements. Some general examples are



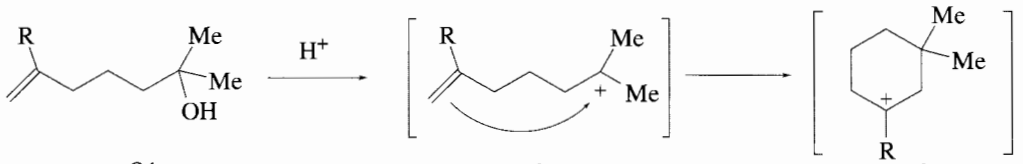
12.2.C. Carbocation Reactions with Alkene Nucleophiles

Alkenes can donate the two electrons from the π bond to a carbocation, forming a new bond to one carbon of the C=C. Forming this new bond leaves behind a cation at the other carbon. Both intermolecular (as in the formation of **83**) and intramolecular (as in the formation of **86**) versions are known. The intermolecular pro-

cess is often plagued by cationic polymerization and/or competitive elimination reactions (E1, sec. 2.9.B), depending of the solvent and relative basicity of the counterion (sec. 2.6). The intramolecular reaction is subject to competing inter- and intramolecular reactions (sec. 6.6.B) but is generally less prone to polymerization. Elimination remains a problem, however. In an intermolecular example, 2-methyl-2-butanol is treated with acid, leading to protonation of the oxygen atom. Loss of water from this oxonium salt leads to tertiary cation **82**. In the presence of a second molecule (the alkene), the cationic center is attacked by the π bond in an intermolecular reaction to form a new cation (**83**). This cation can be contrasted with alcohol **84**, which gives



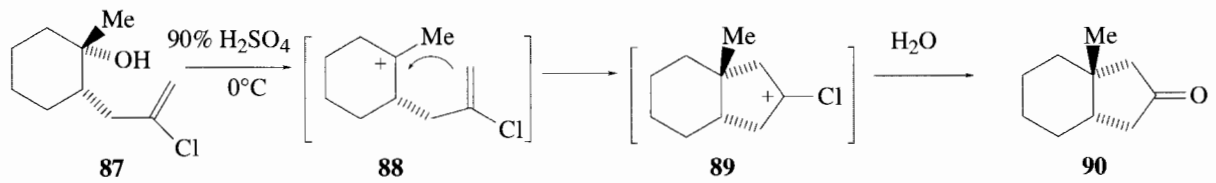
82 **83**



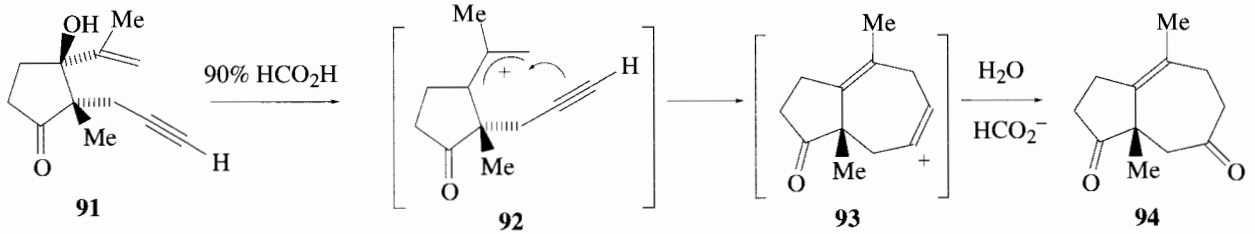
84 **85** **86**

cation **85** when treated with acid, and is easily attacked intramolecularly by the alkene moiety on the other side of the same molecule, producing cation **86**. Formation of **86** is a 6-endo-trig type reaction (see Baldwin's rules, sec. 6.6.A), which can compete with the 5-exo-trig reaction resulting from attack of the cationic center by the other carbon of the alkene moiety. That cyclization process would generate a less stable primary cation, and the more stable **86** is favored. Since polymerization and formation of competing cations is diminished in intramolecular cases, they are most commonly used in synthesis. The remainder of this section will therefore focus on cationic cyclizations and controlled rearrangements.

Alcohols are common precursors to cations, which then react with an alkene unit elsewhere in the molecule. Tertiary alcohol **87** served as a cationic precursor, and reaction with 90% sulfuric acid gave **88**. The cation was trapped intramolecularly by the alkene to give tertiary cation **89**. Reaction with water (an S_N1 process) led to an enol, via elimination of HCl, which gave ketone **90** in 15% yield.[43]



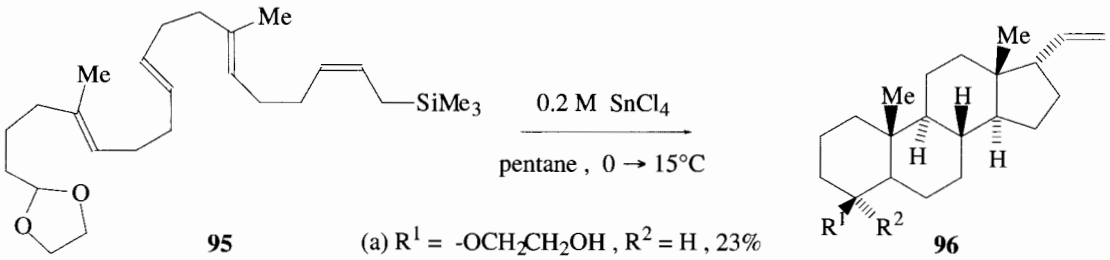
87 **88** **89** **90**



91 **92** **93** **94**

Alkynes are useful partners in cationic cyclization reactions. Initial reaction of the allylic alcohol moiety in **91** with formic acid gave allyl cation **92**. Subsequent attack by the alkyne moiety across the molecule generated vinyl cation **93**. This cation trapped formate anion to generate a formate enol ester (C=C—OCHO). Hydrolysis liberated the final ketone product **94**, which Lansbury converted to damsinic acid.[44]

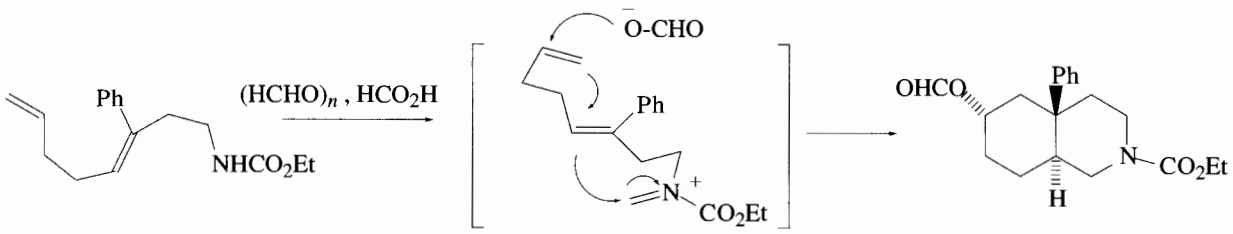
A spectacular example of cationic cyclization is the **Johnson polyene cyclization**, described in Section 10.8.A.[45] Polyenes such as squalene are expected to assume a steroid-like conformation in the lowest energy form (sec. 1.5.E), based on the biogenetic preparation of cholesterol from squalene.[46] In practice, treatment of polyenes with acid led to a very low yield of tri- or tetracyclic products, giving instead significant amounts of polymeric material. Diligent work over many years prevailed, however, and Johnson solved the many problems (as described in sec. 10.8.A) to make this reaction an excellent and efficient synthetic route to di-, tri-, and tetracyclic molecules. One of the later examples of polyene cyclization uses an allyl silane to quench the cyclization process.[47] A Lewis acid was used to initiate the reaction via reaction with the acetal. Treatment of



95 (a) R^1 = -OCH_2CH_2OH , R^2 = H , 23%
(b) R^1 = H , R^2 = -OCH_2CH_2OH , 11%

96

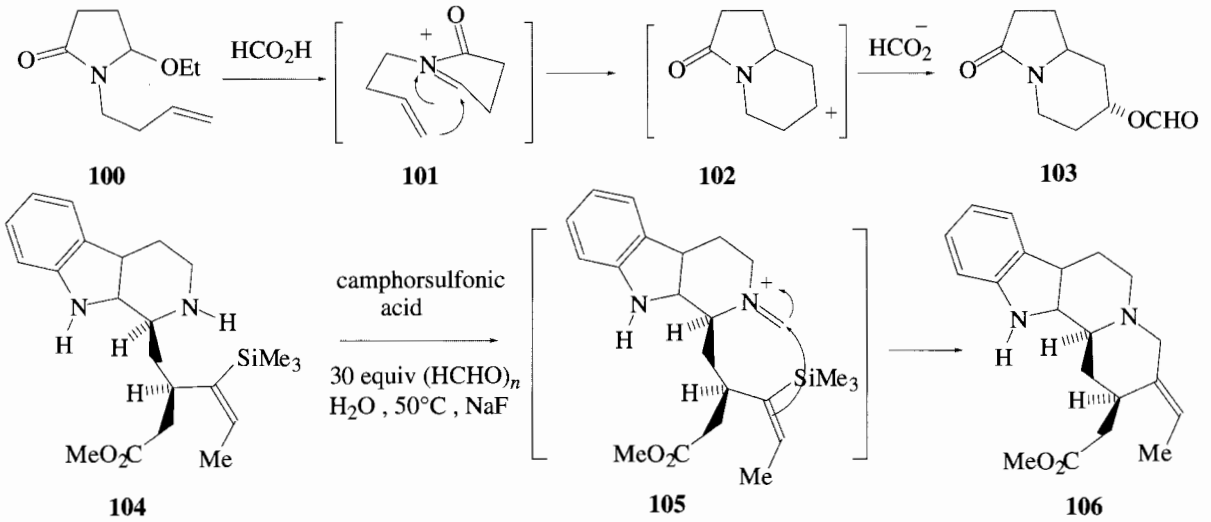
95 with tin tetrachloride ($SnCl_4$) gave 23% of tetracyclic **96a** (2:3 α:β 17-vinyl) and 11% of **96b** (1:1 α:β 17-vinyl). In this case, the Lewis acid partially cleaved the ketal protecting group (sec. 7.3.B.i) during the cation initiation process. The cyclization generated the stereochemical centers at the ring junctures with high selectivity, but provided little stereocontrol for the final reaction, which gave a mixture of 17α- and 17β-vinyl groups. Better results were obtained by use of a cyclopentenyl moiety to conformationally anchor the cationic cyclization process and of an alkyne to terminate that process (with a vinyl cation that was converted to a ketone).[48] A Brønsted–Lowry acid (trifluoroacetic acid, TFA) reacted with the allylic alcohol moiety to initiate the cationic cyclization.



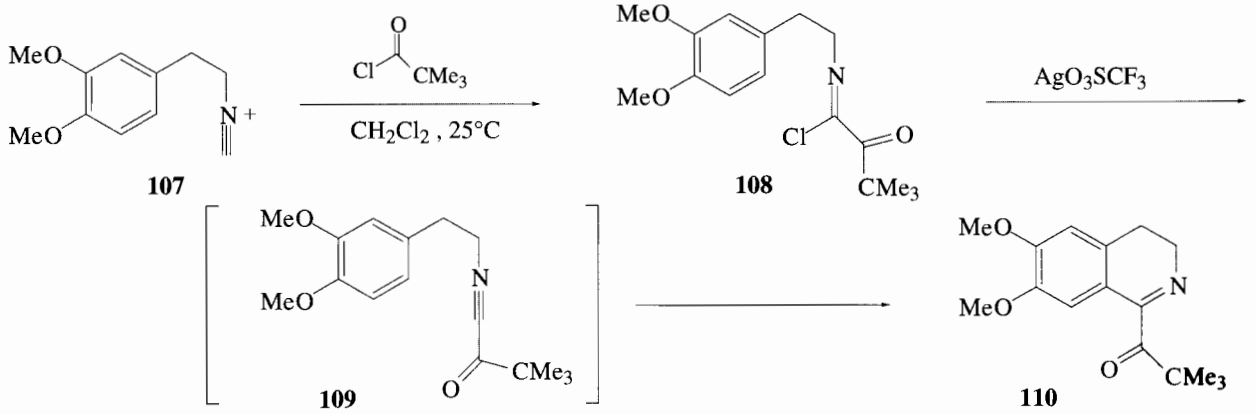
97 **98** **99**

This reaction can also be utilized when there are heteroatom substituents. Reaction of amide-diene **97** with paraformaldehyde and formic acid generated iminium salt **98**. Cationic cyclization (formate is the nucleophilic trapping agent) generated the perhydroisoquinoline **99**.[49] A related cyclization procedure that involves

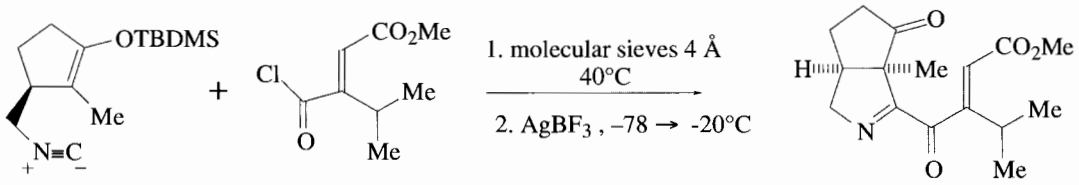
N-acyl iminium intermediates was developed by Speckamp, and Hiemstra,[50] and has been used for the preparation of alkaloids.[51] In this reaction an *N*-alkenyl, ω-hydroxy (or alkoxy) lactam such as **100** is treated with formic acid, generating the acyl iminium salt **101**. Subsequent alkene cyclization led to **102** and trapping with formate (an S_N1 reaction) gave the final indolizidine product **103**.[52] The ethoxy lactam (**100**) required for generating the iminium salt was formed via selective reduction of an imide precursor (sec. 4.4.A). The reaction appears to be under kinetic control and proceeds via a chair-like transition state (**101**), where the incoming nucleophile (HCO_2^-) and the carbon being attacked are antiperiplanar. Speckamp and co-worker applied this method to the synthesis of mesembrine.[53] Overman used a variation of this reaction to a synthesis of geissoschizine.[54] Initial reaction of **104** with paraformaldehyde and camphorsulfonic acid generated iminium salt **105** *in situ*. The vinyl silane moiety facilitates addition of the alkene to the iminium salt via reaction with sodium fluoride (sec. 7.3.A.i). The alkylidene product (**106**) was produced in 80% yield as a 9.1:1 mixture of (*Z*/*E*) isomers, which is very similar to the **Pictet–Spengler isoquinoline synthesis** described in Section 12.5.B.



A similar cyclization procedure uses *C*-acylnitrilium ions for the synthesis of heterocyclic compounds.[55] A typical example treated isonitrile **107** with trimethylacetyl chloride to give **108**.[56] Subsequent treatment with AgO_3SCF_3 (silver trifluoromethanesulfonate) gave an intermediate *C*-acylnitrilium ion (**109**), which cyclized

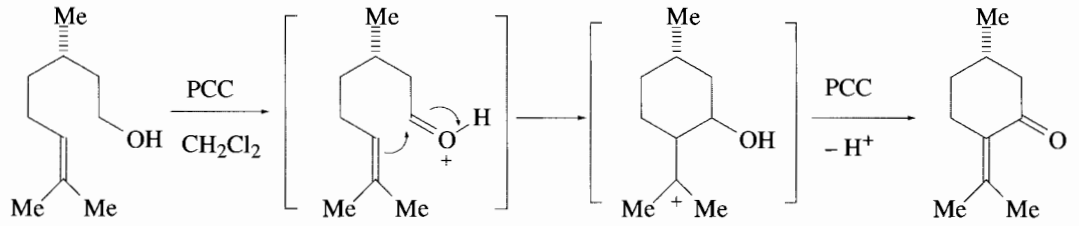


to give dihydroisoquinoline derivative **110** in 82% yield. Livinghouse and co-workers used this strategy to synthesize dendrobine,[57] where a key step was the coupling of **111** with **112**, in the presence of molecular sieves, and subsequent treatment with silver tetrafluoroborate gave an 88% yield of **113**. Stevens had previously reported a mercury(II) nitrate-mediated Ritter coupling that involved formation of an organomercury compound.[58] Addition to an isonitrile gave an iminium salt that could be reduced. Although this method did not involve an acylnitrilium ion, it is related to this chemistry.



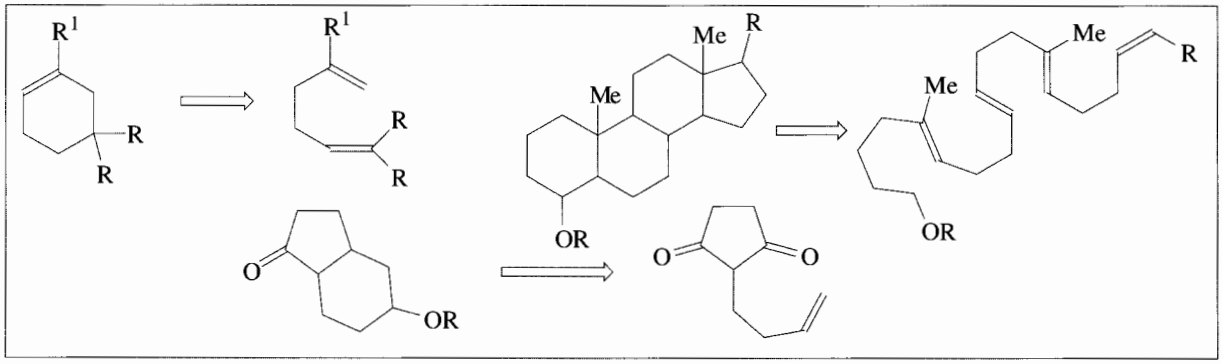
111 **112** **113**

The cationic precursors for making carbon–carbon bonds are not limited to alkenes. Ketones and aldehydes are protonated under various conditions to form an oxo-stabilized cation ($^{+}$C-OH), which is then attacked by an alkene to form a new carbon–carbon bond. In section 3.2.B.ii, it was shown that oxidation of acid-sensitive alcohols with PCC could be accompanied by a secondary reactions. The oxidation of citronellol (**114**) with PCC not only gave the expected aldehyde, but the aldehyde oxygen was protonated to give **115**.[59] Once formed, this oxo cation is attacked by the adjacent π-bond of the alkene to form cation **116**. Elimination to an alkene (E1–sec. 2.9.B) and oxidation to the ketone under the reaction conditions leads to the final product, isopulegone (**117**).



114 **115** **116** **117**

A variety of disconnections are possible utilizing intramolecular cationic reactions. A few of the more useful are

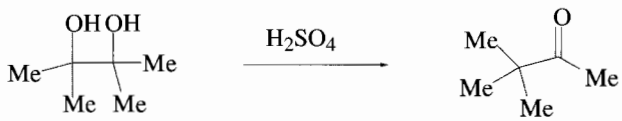


12.3. SELECTIVE CATION REARRANGEMENTS

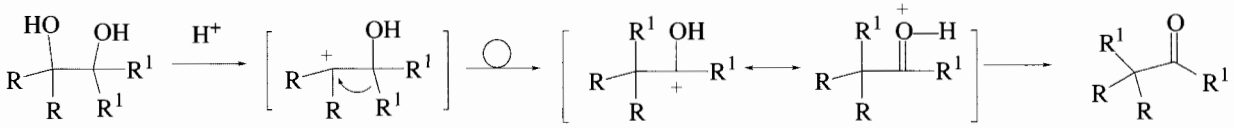
There are many variations of the synthetically useful and highly selective cation rearrangements discussed in section 12.2. There are many classical named reactions that rely on cationic rearrangements to form specific products. Variations in functional groups and the reaction conditions used to generate the cation lead to chemoselective transformations and, very often, highly stereoselective rearrangements. Mundy's monograph is an excellent source that presents many examples of these named reactions.[60] The intent of this section is not to simply present named reactions, but to focus attention on the variety of reaction types and on synthetic applications.

12.3.A. The Pinacol Rearrangement

Perhaps the quintessential cationic rearrangement reaction used for synthesis is the **Pinacol rearrangement**.[61] Fittig was the first to discover that treatment of 2,3-dimethyl-2,3-butanediol (**118**) with sulfuric acid

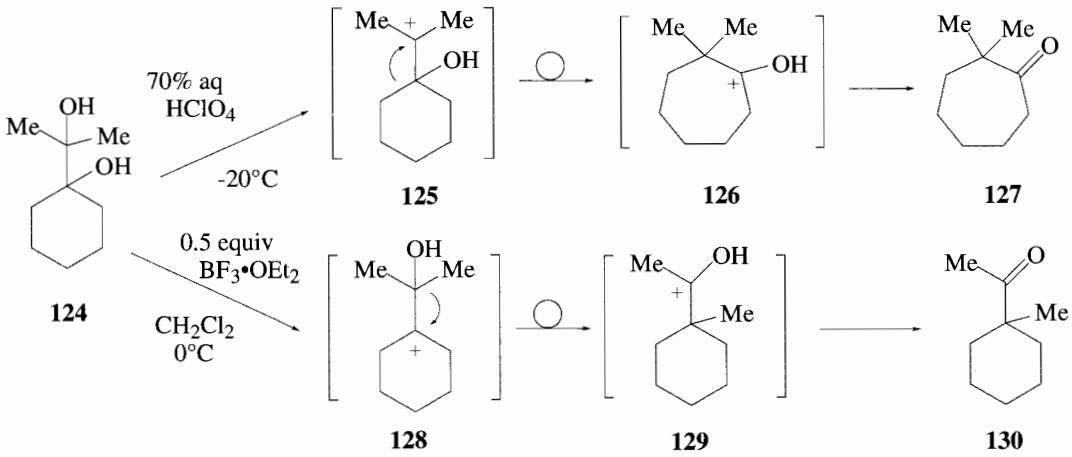


118 **119**



120 **121** **122** **123**

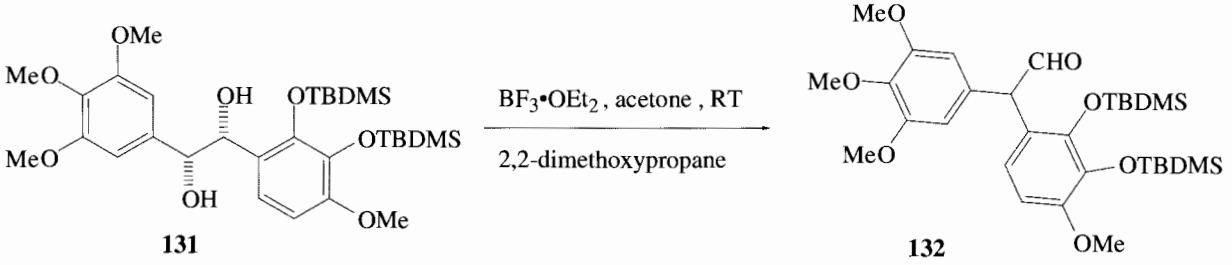
generates 3,3-dimethyl-2-butanone (pinacolone, **119**).[62,61a] This transformation gave rise to the name of the reaction and was shown to be applicable to the acid catalyzed rearrangement of most 1,2-diols. The reaction



124 **125** **126** **127** **128** **129** **130**

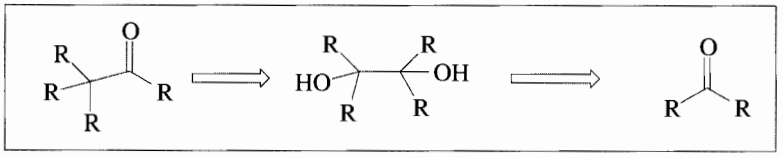
can be generalized to show that 1,2-diols (**120**) are converted first to a β-hydroxy carbocation (**121**). Rearrangement to the more stable **122** (an oxygen-stabilized cation rather than a tertiary alkyl cation, sec. 12.2.A) is

followed by loss of a proton to give **123**.[63] Rearrangement of pinacol (2.3-dimethyl-2,3-butanediol, for which the reaction is named) to pinacolone (3,3-dimethyl-2-butanone) is the classical example, but the reaction can be done with a variety of 1,2-diols (cyclic and acyclic), utilizing both protonic and Lewis acid initiators. When Lewis acids are used rather than protonic acids, differences in the reaction pathway are often observed. Treatment of **124** with aqueous perchloric acid gave 81% of **127** but reaction with boron trifluoride in dichloromethane gave 88% of **130**.[64] In aqueous media, tertiary cation **125** was formed from **124**, leading to ring expansion to cycloheptyl cation **126**. Loss of a proton gave ketone **127**. Reaction with boron trifluoride in aprotic media, however, proceeded by coordination with the cyclohexanol moiety and this led to cation **128**. A subsequent 1,2-methyl shift (to **129**) rather than ring expansion and loss of a proton gave **130**. The cation that is formed can be influenced by rather subtle factors, however. Incorporation of a double bond in the



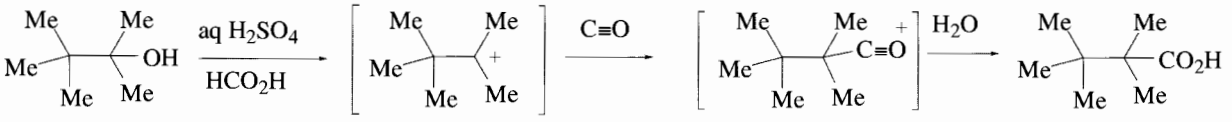
131 **132**

cyclohexane ring of **124**, for example, led to ring expansion with no products such as **130**.[65] This reaction is useful for synthesis. An example is the conversion of **131** to **132**, taken from Pettit's synthesis of hydroxyphenstatin.[66] Pinacol–type rearrangements are useful for the preparation of spirocyclic ketones, when cyclic diol precursors are used. There are many examples where spirocyclic compounds are formed by this type of rearrangement.[67,68] Pinacol-like rearrangements are possible from precursors other than diols, especially oxiranes[69] and allylic alcohols.[70] The disconnection for these reactions is



12.3.B. Koch–Haaf Carbonylation[71]

When an alcohol is heated in strong acid with carbon monoxide (CO), the initially generated cation rearranges and traps carbon monoxide to give a tertiary carboxylic acid in what is known as the **Koch–Haaf**



133 **134** **135** **136**

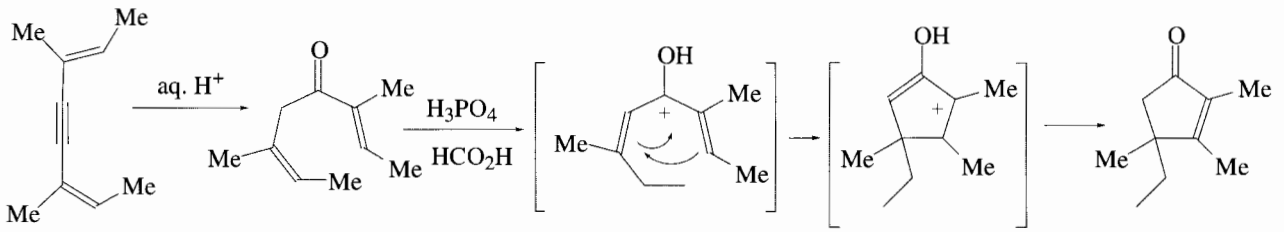
carbonylation. Reaction of **133** with aqueous sulfuric acid initially gave cation **134**. In the presence of carbon monoxide (generated *in situ* from formic acid and sulfuric acid), acylium ion **135** was formed and

reaction with water gave the carboxylic acid (**136**) in 90% yield. Similar treatment of alkenes with these reagents also gave carboxylic acids, but the yields were usually poorer. In most cases, using a sulfuric–formic acid mixture to generate carbon monoxide is more efficient than bubbling in carbon monoxide gas. Lactones are formed when diols are treated with carbon monoxide and acid.[72]

The Koch–Haaf disconnection is

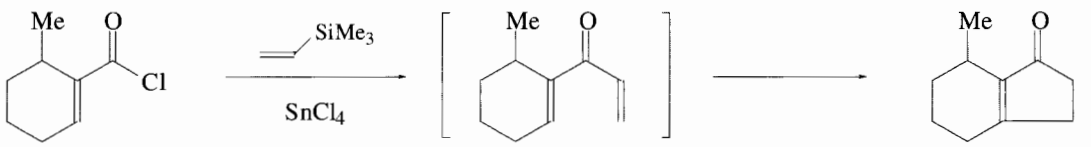
2.3.C. Nazarov Cyclization[73]

Reaction of a divinyl alkyne such as **137** with aqueous acid generates a conjugated ketone (**138**), via hydration of an intermediate vinyl cation. Subsequent treatment with a mixture of phosphoric and formic acids leads to a new, oxygen-stabilized carbocation (**139**), which reacts with the adjacent alkene (a cyclization reaction) to form **140**. Elimination led to the conjugated ketone (**141**).[73b] This cationic ring-closing reaction



137 **138** **139** **140** **141**

is called the **Nazarov cyclization**.[73,74] The bis-conjugated ketones required for this reaction are rather specialized, but several methods are available for their preparation. Most involve coupling a vinyl carbanion equivalent with a conjugated carbonyl. The strongly acidic conditions used for preparing **141** are not required for the cyclization. For more sensitive systems, Lewis acids can be used. When acid chloride **142** was treated with a vinyl silane and $SnCl_4$, dienone **143** was formed *in situ*, but it cyclized to give a 70% yield of **144** as part of Zwanenburg's synthesis of sorgolactone.[75] Marino and Linderman had previously showed that tin chloride ($SnCl_4$) or iodotrimethylsilane could be used in a Nazarov cyclization.[76]

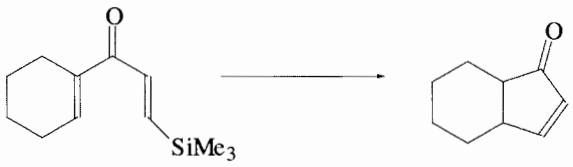


142 **143** **144**

The cyclization can be accomplished under even milder conditions by incorporating a stabilizing group on the alkene. Both silane and stannane derivatives have been prepared. Denmark and Jones later studied the Nazarov cyclization of vinyl silanes with several Lewis acids (see Table 12.7).[77] Cyclization of **145** gave **146** but both the temperature and the nature of the Lewis acid had a significant effect on the reaction.[77] Ferric

chloride ($FeCl_3$) gave the best yield of the Nazarov product (**146**). Vinyl silane cyclization can proceed with modest diastereoselectivity.[78] West showed that a normal Nazarov Lewis acid catalyzed cyclization in the presence of a triethylsilane led hydrogenation and formation of a reduced product. When **147** was treated with BF_3•OEt_2 and 2 equivalents of triethylsilane and then with 1N HCl in a second step, for example, a 71% yield of **148** was obtained, along with 14% of **149**.[79]

Table 12.7. Influence of Lewis acids on the Nazarov Cyclization of Vinyl Silanes



145 **146**

Lewis Acid	Temperature (°C)	% 146
$AlCl_3$	–30→25	30
$SnCl_4$	–30→25	30
$TiCl_4$	–78	0
BF_3•OEt_2	–30→25	23
$ZnCl_2$	25	N.R.
$FeCl_3$	–30→25	84

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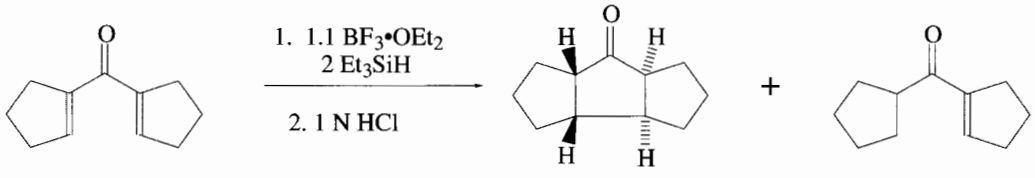
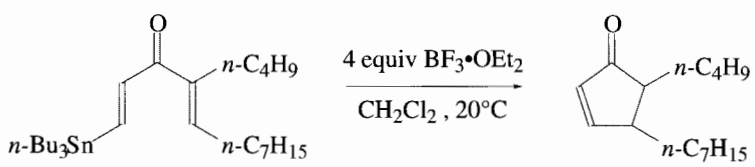


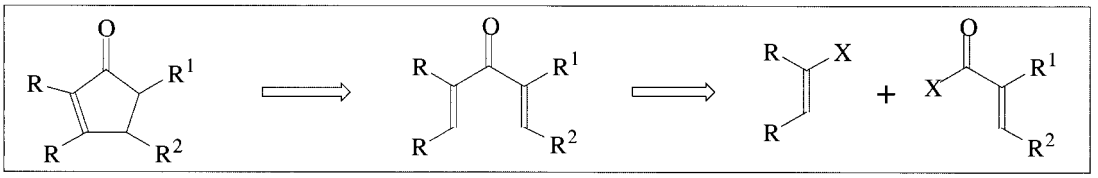
147 **148** **149**

Vinyl stannanes are excellent Nazarov precursors. Johnson and co-worker showed that vinyl stannanes such as **150** generate cyclopentenone derivatives such as **151** via Nazarov cyclization.[80] Cyclization showed only modest selectivity for forming the trans isomer (1.7:1 trans/cis) in **151** (formed in 87% yield). When the butyl group in **150** was replaced with a hydrogen, the yields were generally < 50%.[80]



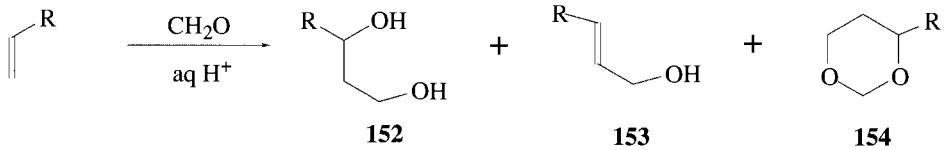
150 **151**

The Nazarov disconnection is

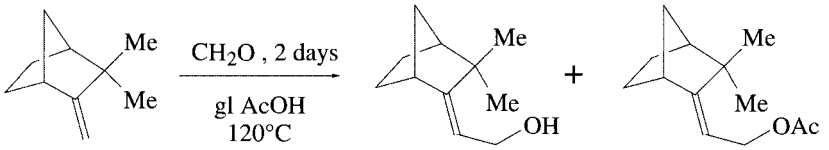


12.3.D. The Prins Reaction[81]

Formaldehyde can be coupled to an alkene in the presence of an acid to give a diol (**152**) or a 1,3-dioxane derivative (**154**) in what is known as the **Prins reaction**.[81] Allylic alcohols such as **153** can also be produced in this reaction. Camphene (**155**) reacted with formaldehyde and acid to give a 1:1 mixture of allylic alcohol **156** and the acetate **157**, in 94% yield.[82] Scandium triflate has been used to prepare tetrahydropyran-4-ol derivatives from aldehydes and homoallylic alcohols via a Prins-type cyclization.[83]

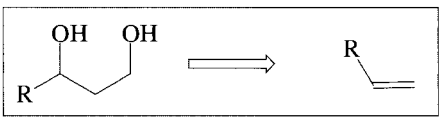


152 **153** **154**



155 **156** **157**

The Prins disconnection is



The examples in this section demonstrate that stable cations can be generated and trapped with alkenes, alcohols or carbonyl derivatives. The resulting reaction products contain new carbon–carbon bonds, often produced with controllable and predictable stereo- and regiochemistry.

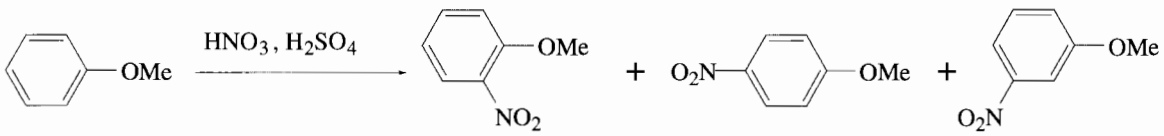
12.4. FRIEDEL–CRAFTS REACTIONS

This section will expand the theme of reactions between a carbocation and a nucleophilic species such as an alkene or an alcohol. In this section, however, the carbocation will be attacked by an aromatic ring to form a Wheland-type intermediate, which leads to a substituted aromatic system. These are the Friedel–Crafts reactions and they are among the most important reactions in organic chemistry.

12.4.A. Electrophilic Aromatic Substitution

In chapter 2, we saw that benzene reacts with electrophilic reagents such as the bromonium ion [Br^+, generated by the reaction of bromine (Br_2) and aluminum bromide ($AlBr_3$)] to give a resonance stabilized

cation called a **Wheland intermediate**. This intermediate is for the well-known electrophilic aromatic substitution reaction (sec. 2.11).[84] Loss of a proton, with concomitant aromatization, completes the substitution to give bromobenzene. In a similar manner, chlorine and aluminum chloride (Cl_2 + $AlCl_3$) react with benzene to give chlorobenzene,. Fuming sulfuric acid [H_2SO_4 + sulfur trioxide (SO_3)] gives benzenesulfonic acid and a mixture of nitric acid and sulfuric acid (HNO_3 + H_2SO_4) gives nitrobenzene.[84] The presence of electron-releasing groups (alkyl, oxygen, nitrogen, sulfur, aryl–all contain high electron density and/or a (–) or δ- charge adjacent to the aromatic ring) leads to ortho- and para-substituted derivatives. These groups are known as **activating substituents** because they increase the rate of substitution relative to benzene. The rate of nitration of anisole was 9.7 x 10^6 times faster than nitration of benzene. In general, electron-releasing groups increase the rate of substitution.[84] Activating substituents on a benzene ring usually lead to formation of the ortho/para products and are called ortho/para directors. Reaction of anisole with nitric/sulfuric acids, for example, gives 44% of the ortho product (2-nitroanisole), 56% of the para product (4-nitroanisole), and < 1% of the meta product, 3-nitroanisole.[85] As discussed in Section 2.11, the cationic intermediates produced with aromatic molecules containing an electron-releasing group place a positive charge adjacent to a (–) or δ– center (an electron releasing alkyl group) to stabilize the charge when ortho–para substitution occurs. Meta substitution cannot generate an intermediate where the charge is adjacent to the stabilizing substituent.

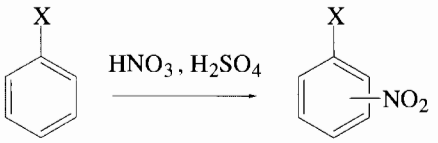


Electron-withdrawing groups [NO_2, C=O, SO_2R, SO_3R, NR_4^+–all have a (+) or δ+ charge adjacent to the aromatic ring] have the opposite effect to activating substituents. They slow the rate of reaction relative to benzene (they are called **deactivating groups**) and are meta directors. The cationic intermediate resulting from an aromatic substitution reaction places the positive charge adjacent to a (+) or δ+ center with ortho–para substitution, destabilizing that intermediate and retarding the reaction. Meta substitution does not generate a cation with the charge adjacent to nitrogen and although it is not particularly stabilized, it is not strongly destabilized. Meta substitution, therefore, predominates, although the intermediate for the reaction has the positive charge and the electron withdrawing substituents close together, slowing the rate of the reaction relative to benzene. Selectivity for the meta product is usually very good. Nitration of nitrobenzene with a mixture of nitric and sulfuric acid gave, for example, 1,3-dinitrobenzene in 94% yield with only 6% of the ortho product, and < 1% of the para product.[84] The ortho/para or meta selectivity is illustrated in Table 12.8,[86,84] which shows the relative of ortho, meta, and para products observed in the nitration of aromatic derivatives.

12.4.B. Friedel–Crafts Alkylation

12.4.B.i. Alkyl Cations and Regioselectivity. This chapter deals with generating carbocations that can be used to form carbon–carbon bonds. Just as alkenes react with cations to form cationic intermediates, the π bonds of aromatic rings also react with cations (sec. 12.4.A) to form a cationic intermediate identical to that found in electrophilic aromatic substitution (namely, **158**). Just as in bromination, chlorination, nitration, and

Table 12.8. Regiochemical Preferences for Nitration of Aromatic Substrates



	Nitration		
X	% ortho	% meta	% para
OMe	44	<1	56
NHAc	20	<1	80
Ph	69	<1	31
Me	59	4	37
F	9	<1	91
Cl	30	1	69
Br	37	1	62
CO_2H	22	76	2
NO_2	6	94	<1
NMe_3^+	<1	89	11

[Leon M. Stock, AROMATIC SUBSTITUTION REACTIONS, ©1968, p. 44. Reprinted by permission of Prentice Hall, Englewood Cliffs, New Jersey.]

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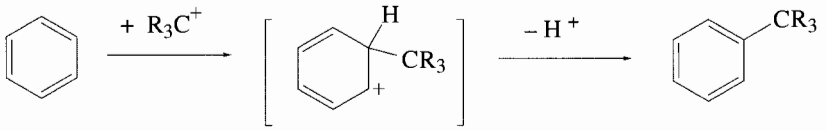
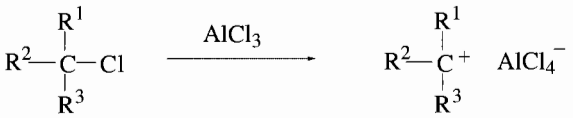
so on, loss of a proton leads to aromatization, completing the substitution reaction to form the new carbon bond in **159**. Electrophilic aromatic substitution with alkyl carbocations is called **Friedel–Crafts alkylation**.[87] It was reported by Friedel and Crafts in 1877.[88] The carbocation precursor can be an alkene, an alcohol, or an alkyl halide.



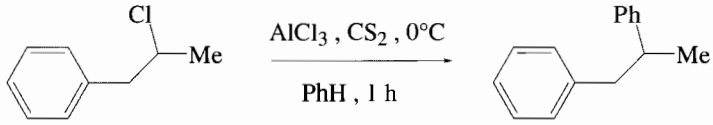
158 **159**



160

Alkyl halides react with Lewis acids to form tertiary, secondary, or primary carbocations. The tertiary cation (**160**, R^1=R^2=R^3= alkyl) is sufficiently stable that good yields of alkylated products are obtained upon reaction with benzene. Formation of the primary cation (**160**, R^1=R^2=H, R^3= alkyl) is energetically more difficult and is, of course, subject to rearrangement; primary alkyl derivatives are rarely observed under these conditions. Secondary cations (**160**, R^1=H, R^2=R^3= alkyl) are readily formed but are also subject to rearrangement. The extent of rearrangement is dependent on the reaction conditions and the nature of the

cation. Reaction of benzene and 1-phenyl-2-chloropropane (**161**), for example, gave 60% of **162**,[89] with little rearrangement to the benzylic cation, which suggests that the initially formed cation can be trapped very rapidly, probably due to the solvent (carbon disulfide, CS_2), which minimizes solvent separation of the ions.

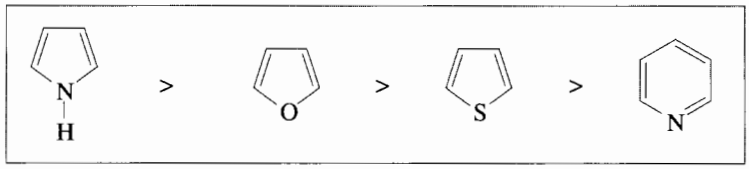


161 **162**

Alkyl fluorides are the most reactive of the alkyl halides. Boron trichloride (BCl_3), boron trifluoride (BF_3), boron triiodide (BI_3), and boron tribromide (BBr_3) all catalyze the reaction of alkyl fluorides and benzene, although they are ineffective catalysts for the analogous reaction of alkyl chlorides and alkyl bromides.[90] In a reaction with mixed halides, the C—F bond reacts faster than the C—Cl, C—Br or C—I bond.[91] This is consistent with the observed order of reactivity for alkyl halides with aluminum chloride ($AlCl_3$):

$$R—F > R—Cl > R—Br > R—I^{92}$$

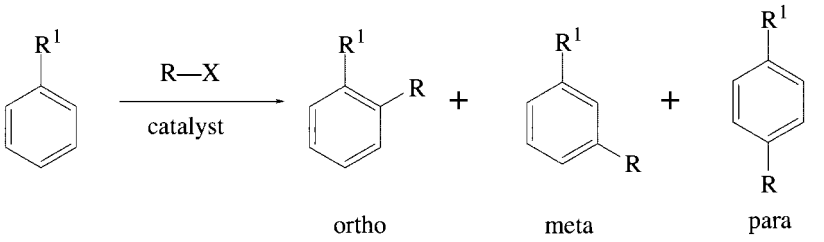
As expected, electron-rich aromatic rings such as phenols and aryl ethers react very well. Heterocyclic aromatic derivatives also react with pyrrole the most reactive and pyridine being rather unreactive, giving a relative order of reactivity:[93]



As with other electrophilic aromatic substitution reactions, anisole, toluene, and aromatic derivatives bearing an electron releasing group react faster than benzene in Friedel–Crafts reactions, giving primarily ortho- and para substituted products. Electron-withdrawing substituents (such as NO_2 in nitrobenzene and C=O in aryl ketones) slow the reaction. Indeed, Friedel–Crafts alkylation is very difficult with deactivated aromatic nuclei. The product distribution varies with the halide, the catalyst, the solvent, and the aromatic substrate. As shown in Table 12.9,[94] ortho-substituted products are generally preferred except with highly hindered alkyl halides such as *tert*-butyl. This preference for the ortho product has been called the **ortho effect**: Additional stabilization of cation intermediates occurs when an electron-releasing group can stabilize the intermediate generated by ortho-substitution relative to the intermediate formed for para substitution.[94] This increase in ortho substitution is usually explained by the linear coordination effect of oxygen with the incoming reagent. In this particular case, an O-alkyl product can be formed, followed by an O→C migration where migration to the ortho carbon is faster than migration to the para carbon.[95] It is apparent from Table 12.9 that the ortho effect is more pronounced when the aromatic ring contains the stronger electron-releasing methoxy group (in anisole) when compared to the methyl group in toluene. Increasing the ability of the activating group to release electrons also led to significantly lower amounts of meta product. Unless strongly activating groups drive the reaction to essentially one product, separation of the isomeric arenes is a problem in the reaction.

Even when strongly activating groups are present on the aromatic nucleus, however, mixtures of products are usually obtained and the problem of separating isomers persists.

Table 12.9. The ortho Effect and ortho–para Substitution in Friedel–Crafts Reactions of Anisole and Toluene



R^1	RX	Catalyst	Solvent	Time (min)	Temperature (°C)	%ortho	%meta	%para
OMe	MeF	BF_3	Anisole	30	25	75	<1	25
			$MeNO_2$	15	25	55	<1	45
Me			Anisole	30	25	54	18	28
OMe	MeCl	$AlCl_3$	$MeNO_2$	5	25	68	2	30
Me				52	17	31		
OMe	MeBr		$MeNO_2$	30	25	67	2	31
Me				54	17	29		
OMe	MeI		$MeNO_2$	60	25	67	<1	32
Me				57	12	31		

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Very active catalysts such as aluminum chloride often lead to significant amounts of meta products, even when the aromatic ring contains activating substituents,[90a,b,91] which is due to the thermodynamic nature of the reaction with aluminum chloride and the thermodynamic preference for the meta product. Excess catalyst and high reaction temperatures also favor more meta product. The use of BF_3, sulfuric acid, ferric chloride ($FeCl_3$) and zinc chloride ($ZnCl_2$), in lower concentrations and at lower temperatures, gives primarily the expected ortho–para products.[96]

Since the reaction proceeds via a cation, chiral alkyl halides are expected to give racemic arene products, which is, however, dependent on the Lewis acid and the reaction conditions. As shown in Table 12.10,[97] Suga et al. found some asymmetric induction during the aromatic substitution, if the reaction temperature was maintained below 0°C and the reaction time was kept to a minimum. Reaction of (*S*)-2-chlorobutane and benzene gave **163** with up to 24% ee (*R*) and short contact times at low temperature. Some asymmetric induction was observed when mild Lewis acids were used, even at ambient temperatures. The use of strong Lewis acids, higher temperatures, and longer contact times, however, led to the expected racemization. Presumably, at lower temperatures the C—Cl-M^+X^- species is generated as a tight ion pair where some asymmetric character is retained in the transition state of the reaction.

The typical Friedel–Crafts alkylation disconnection is

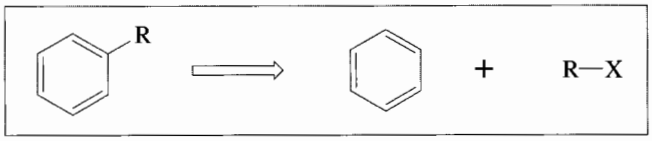
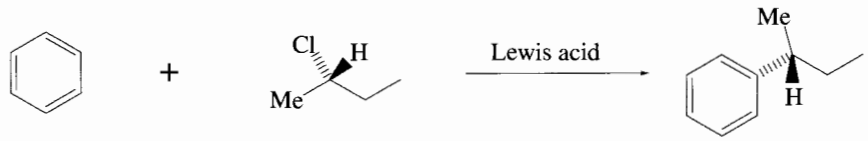


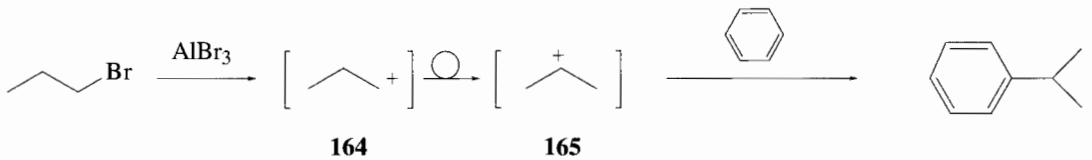
Table 12.10. Asymmetric Induction in the Friedel Crafts Reaction of (*S*)-2-Chlorobutane



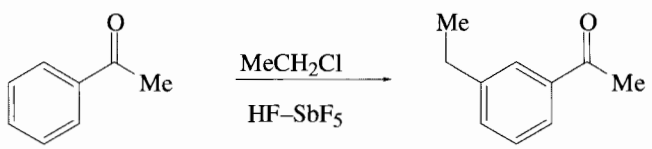
163

Lewis Acid	Temperature (°C)	Time (min)	% 163	% ee (R)
$AlCl_3$	–30	0.8	100	24
	–30	1.6	100	14
	–30	2	100	12
	–10	20	100	0
$FeCl_3$	0	4	70	24
$AlCl_3$•$MeNO_2$	30	15	30	13
$AlBr_3$	–30	1	100	0

12.4.B.ii. Isomerization. There are several problems associated with Friedel–Crafts alkylation. The first occurs when primary and secondary halides are used, because the cations formed from these substrates are subject to rearrangement. Reaction of benzene with 1-bromopropane and aluminum bromide ($AlBr_3$), for



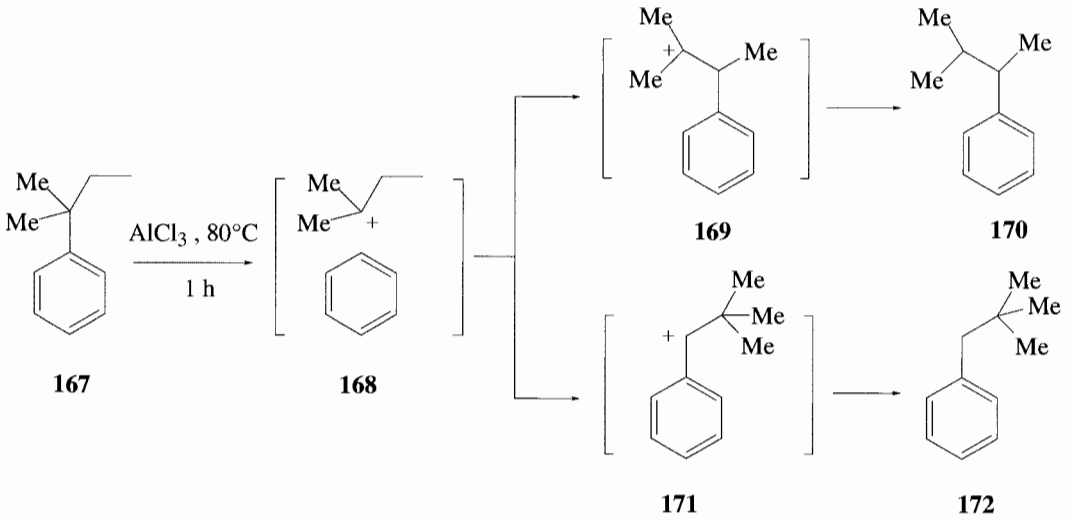
164 **165**



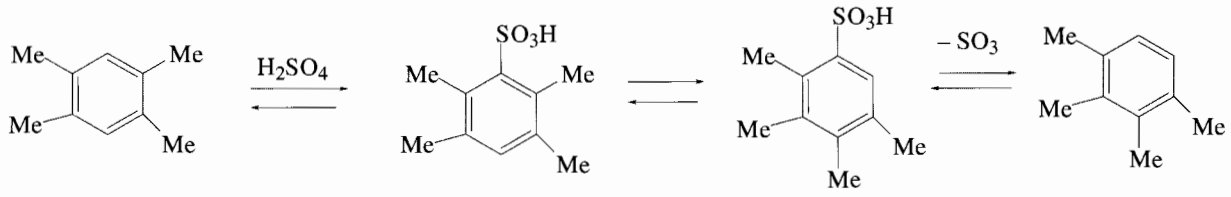
166

example, gives the primary cation (**164**) but this rearranges to the more stable secondary cation (**165**), which reacts with benzene to give the final product, isopropylbenzene (cumene).[98] For this reason, preparation of primary arenes (alkyl benzenes) is very difficult via Friedel–Crafts alkylation, which contrasts with the preparation of tertiary arenes (such as *tert*-butylbenzene), which is straightforward since the tertiary cations are easily formed and usually do not rearrange. Isomerization is minimized when an electron-withdrawing group is on

the benzene ring since the deactivated ring is less prone to further reaction. Acetophenone, for example, reacts with chloroethane (this reaction is sluggish and required using HF/SbF_5 as a catalyst) to give 3-ethylacetophenone (**166**) in 78% yield.[99]

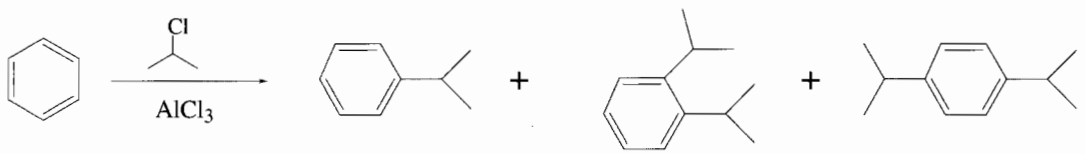

Me
Me
AlCl3 , 80°C
1 h
Me
Me
+
Me
Me
+
Me
Me
Me

When an aromatic ring contains several alkyl groups or complex alkyl groups, treatment with strong acids can lead to isomerization at relatively low temperatures (<100°C for methyl, room temperature for ethyl, and –80°C for isopropyl and *tert*-butyl).[104] With weaker catalysts, higher temperatures are required. In an example involving simple groups, sulfonation of durene (**174**) led to **177**, presumably via initial sulfonation to **175**, rearrangement to **176**, and loss of sulfur trioxide (SO_3) to give **177**.[105] This transformation has come to be known as the **Jacobsen rearrangement**.[106,105b]



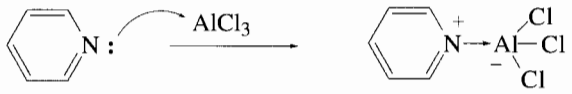
174 **175** **176** **177**

A second problem in Friedel–Crafts alkylation reactions arises from the fact that alkyl substituents are weakly electron releasing (and therefore activating), making the arene product more reactive than the benzene starting material. Alkylation of the arene leads to disubstituted products, which are often contaminants or, occasionally, the major product in Friedel–Crafts alkylations. If benzene, for example, reacts with 2-chloropropane, the initial product is isopropylbenzene. Since isopropylbenzene is more reactive than benzene, it reacts with the carbocation intermediate in competition with benzene, leading to both *o*-diisopropylbenzene (**178**) and *p*-diisopropylbenzene (**179**) as secondary products. The steric hindrance inherent to formation of **178** leads to a large proportion of the para product. Using a large excess of benzene can suppress this overalkylation, or **polyalkylation** reaction.[107,88b] It is noted, however, that Francis reported alkyl groups on benzene have only a small effect on the rate of Friedel–Crafts alkylation.[108] Francis showed that "alkylation occurred in a heterogeneous reaction system, specifically in the catalyst layer and that the reason for polysubstitution is the preferential extraction of the early reaction product by this catalyst layer".[109] Using a solvent to solubilize both hydrocarbon and catalyst minimized polyalkylation, as does efficient (high speed) stirring and higher temperatures (which solubilizes the aluminum chloride).[101]



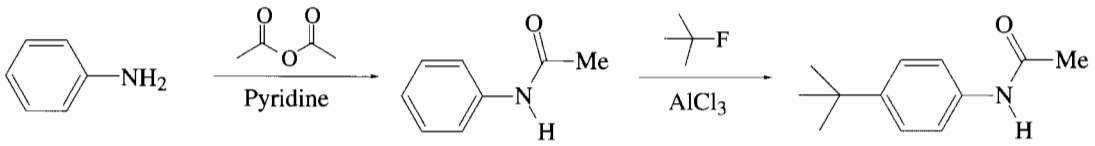
178 **179**

A third problem arises when a basic atom is present, as in pyrrole, pyridine, and aniline derivatives. Lewis acids react with the basic nitrogen to give the complex (**180**–sec. 2.3), where the nitrogen has a positive charge. The electron-releasing nitrogen group has been converted to an electron-withdrawing ammonium salt, deactivating the aromatic ring to substitution. The reaction also removes the catalyst from the reaction and the cation cannot be generated unless a large excess of Lewis acid is used.



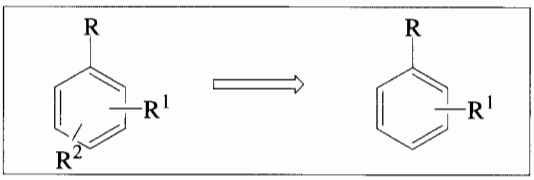
180

In the case of nitrogen-containing aromatic derivatives, the basic nitrogen atom can be protected (sec. 7.3). Conversion to an amide (such as *N*-acetylaniline –called acetanilide, from aniline) withdraws electron density that diminishes the basicity of the amino group, allowing the Friedel Crafts reaction to give **181**.



181

Friedel–Crafts isomerization disconnections are



12.4.B.iii. Influence of the Catalyst. Several different types of aromatic reactions are catalyzed by Lewis acids, including alkylation, polymerization, isomerization, acylation, and halogenation. The dependence of these reactions on various Lewis acids is shown in Table 12.11.[110] This table shows a few common Lewis acids and the type of reaction(s) for which each is best suited. The relative strength of Lewis acids was discussed in Section 2.3. Olah gives a comprehensive list of Lewis acid catalysts, and includes several typical synthetic applications.[110] Metal alkyl catalysts are also effective catalysts, but the aromatic substrate is usually converted to a mono-, di-, or trialkyl derivative. Both metal halides and their alkyl derivatives are effective Friedel–Crafts catalysts, as shown in Table 12.11,[111] as are common inorganic and organic acids.[112] Triflate derivatives are trifluorosulfonate ester (—SO_2CF_3, **OTf**) can be prepared with various metal counterions. Triflates are very effective catalyst in Friedel Crafts reactions. Some of the more common catalysts are $B(OTf)_3$, $Al(OTf)_3$, and $Ga(OTf)_3$.[113]

It is clear that many Lewis acids and protonic acids can be used to catalyze various Friedel–Crafts reactions. The choice of halide, alkene, or alcohol substrate will largely determine which catalyst is used, although, as seen in Table 12.11, the type of reaction that is of interest is also dependent on the choice of catalyst. The following sections provide several examples to illustrate common catalysts used in various reactions, as well as the synthetic utility of the reaction.

12.4.C. Friedel–Crafts Reactions from Alkene and Alcohol Substrates

Friedel–Crafts reactions can occur between an aromatic substrate and an alkene or alkyne upon treatment with acids, via reaction of the aromatic ring with the cation formed from the alkene or alkyne. The cationic

Table 12.11. Selected Friedel–Crafts Catalysts and Reactions That are Catalyzed

Catalyst	Reactions[a]	Catalyst	Reactions[a]	Catalyst	Reactions
$AlBr_3$	General	PBr_3	al,deal	$TiCl_3Et$	al
$AlCl_3$	General	PCl_3	al,deal	$ZnEt_2$	al
AlF_3	Poly, iso	PF_3	al,deal	$Al_2Br_3Et_3$	General
AlI_3	General	$SiBr_4$	ac	HBF_4	al,poly
AsF_6	Poly,al, ac, nitr	$SiCl_4$	ac	HBr	Poly
BBr_3	al,ac,poly	SiF_4	ac,al,nit	HCl	al,poly
BCl_3	al,ac,poly,con	$SnCl_2$	ac,poly	HF	al,ac,poly
BF_3	general	$SnCl_4$	ac,al,halo,poly	HI	ac
BI_3	al,ac	$TiCl_3$	ac,al,poly	$HClO_4$	ac,al,poly
$CaCl_2$	al	$TiCl_4$	General	$BF_3{\cdot}H_2O$	al
$CaBr_2$	ac	$ZnBr_2$	ac,al,halo	H_2SO_4	General
$CdCl_2$	Poly	$ZnCl_2$	General	H_3PO_4	ac,al
$CeCl_3$	acetal formation	ZnI_2	al,ac,poly	PPA[a]	ac,cycl,rearr
$CoCl_2$	for,al,dehydr	$Al_2X_2R_n$	al	$ClCH_2CO_2H$	ac,poly
$CuBr_2$	Halo,iso	$AlEt_2Br$	al	$(ClCH_2CO)_2O$	ac
$CuCl_2$	iso	$AlEt_3$	al,poly	Cl_3CO_2H	chlor,poly
$FeBr_3$	al,ac,halo,poly,for	$AlMe_3$	al	CF_3CO_2H	ac,chlor,iso
$FeCl_3$	General	$Al(t\text{-}Bu)_3$	al	$(CF_3CO)_2O$	ac,al,poly,cycl
$HgBr_2$	ac,halo,poly	$Al(iBu)_3$	al,poly	RSO_3H	al,poly
$HgCl_2$	ac,al,iso,poly	BR_3	al	$PhSO_3H$	al,poly
$MgBr_2$	al,ac,halo	MgR_2	al,poly	$TolSO_3H$	al,poly
$MgCl_2$	al,iso	$TiCl_3Me$	al		

[a] PPA = polyphosphoric acid ; **al** = alkylation; **ac** = acylation; **chlor** = chlorination; **iso** = isomerization; **halo** = halogenation; **cycl** = cyclization; **poly** = polymerization; **for** = formylation; **dehydr** = dehydration; **nitr** = nitration; **general** = active in most Friedel–Crafts reactions; **deal** = dealkylation; **rearr** = rearrangement.

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intermediate can also react with the alkene or alkyne starting material, leading to cationic polymerization as a competitive side reaction. The usual problems of polyalkylation and rearrangement associated with aromatic substitution persist. Toluene reacts with propene to give isopropylbenzene in 52%,[114] but 20% of diisopropylbenzene, 3% of trisubstituted products, and 1.3% of tetrasubstituted products were formed when 0.75 equivalents of propene were used. As shown in Table 12.12,[114] reaction of toluene and ethene gives a wide array of products. The nature of those products is completely dependent on the relative amount of ethene.

Hydrogen fluoride (HF) is often used as a catalyst for alkenes, since there is less tar (fewer decomposition and polymeric by–products) and the volatile catalyst is easily removed.[115] Both ferric chloride ($FeCl_3$) and BF_3 are common catalysts for alkene-aromatic coupling. Typical alkyne catalysts are aluminum chloride, gallium trichloride ($GaCl_3$), BF_3, and sulfuric acid.[116] Reaction of a mixture of xylenes with a trace amount of BF_3 in liquid HF gave the thermodynamic mixture: 18% ortho, 60% meta, and 22% para; but treatment with excess BF_3 gave virtually 100% *m*-xylene.[108,107b,117]

Friedel–Crafts reactions with alkenes are synthetically attractive but, as with alkyl halides, are most useful when stable cations are formed and when done intramolecularly. An internal Friedel–Crafts cyclization with

Table 12.12. Polyalkylation Products from the Reaction of Toluene and Ethene

Equiv ethene	PhH	PhEt	di-Et	tri-Et	tetra-Et	penta-Et	hexa-Et
0.20	87.9	10.9	1.24				
0.50	80.8	15.5	2.14	0.67	0.15	0.06	0.67
0.56	80.5	15.2	1.67	0.71	-	-	1.91
1.14	31.6	35.2	21.1	4	2.4	2.8	2.82
1.68	35.4	23.4	13.6	6.3	4.2	3.6	13.4
3.66	0.2	1.1	10.6	56.2	11.6	1.5	18.7
5.24	-	-	-	7.00	18.8	2.4	7.8
5.74	-	-	-	-	8.5	0.9	90.6

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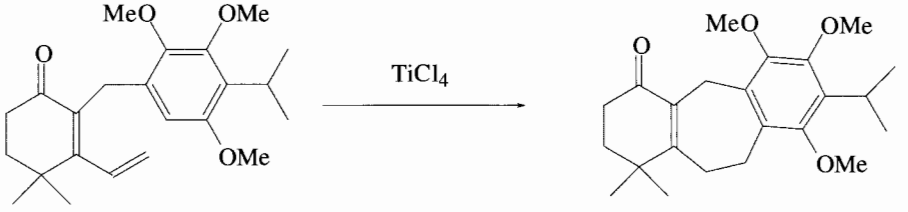
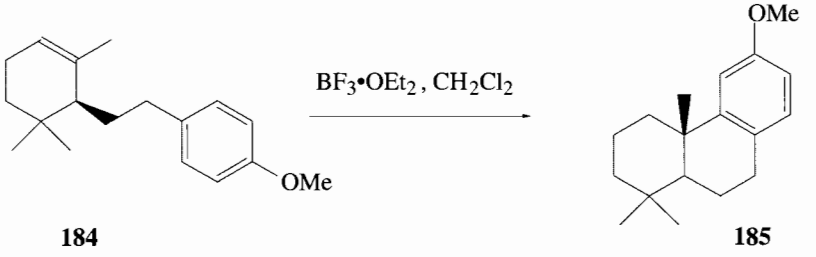
alkenes forms the basis of many natural product syntheses. Majetich and Zhang treated **182** with $TiCl_4$ in a synthesis of perovskone,[118] and obtained a 95% yield of **183**. In this case, a primary cation led to the final product, due to stabilization by extended conjugation with the carbonyl unit. Pan and co-workers used an



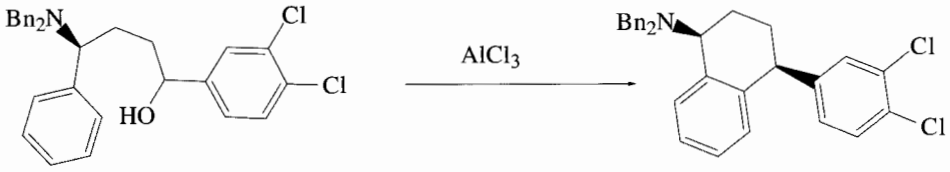
182 **183**



184 **185**

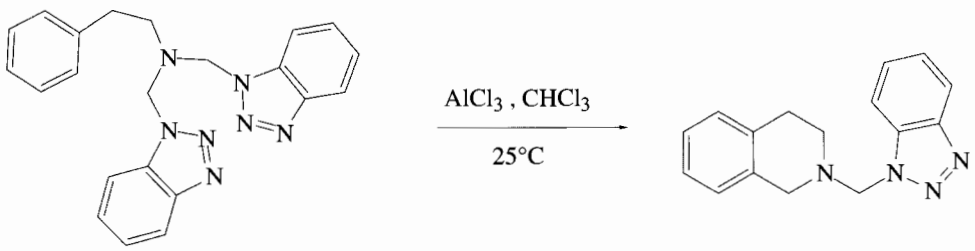
alkene precursor in a synthesis of (–)-6,7-dehydroferruginyl methyl ether.[119] When **184** was treated with BF_3•OEt_2 in dichloromethane, the alkene was converted to a carbocation and intramolecular Friedel–Crafts alkylation led to an 85% yield of **185**.

Cations can be formed from alcohols, and they add to aromatic rings in the usual manner. Sulfuric acid is a common catalyst for alcohols, forming an alkyl sulfate that then reacts with the aromatic substrate.[120] Alcohols are more reactive than halides, although large quantities of the Lewis acid are usually required for Friedel–Crafts reactions.[121] Alcohols form a complex with aluminum chlorides [$R(H)O{\rightarrow}AlCl_3$], and a complicating side reaction is loss of HCl and formation of an alkyl chloride.[122] A full equivalent of the Lewis acid



186 **187**

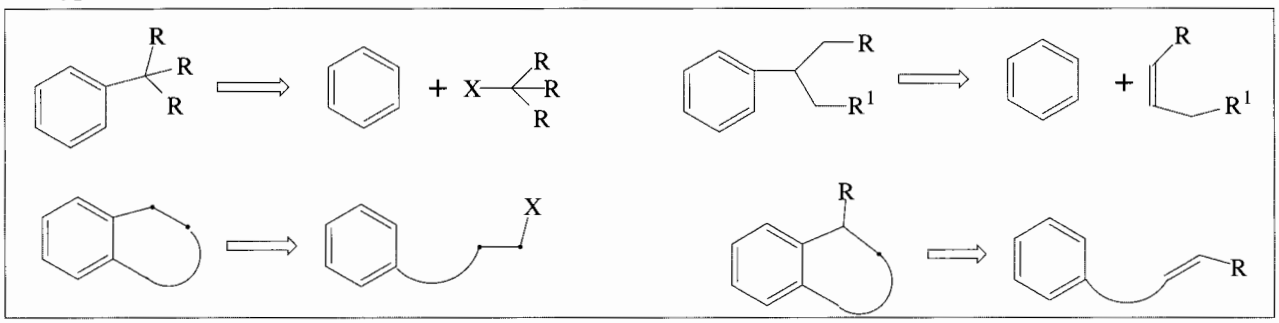
is required to form the complex. In a synthesis of cis-(+)-sertraline, Chandrasekhar and Reddy[123] treated alcohol **186** with aluminum chloride, and obtained a 78% yield of **187**.



188 **189**

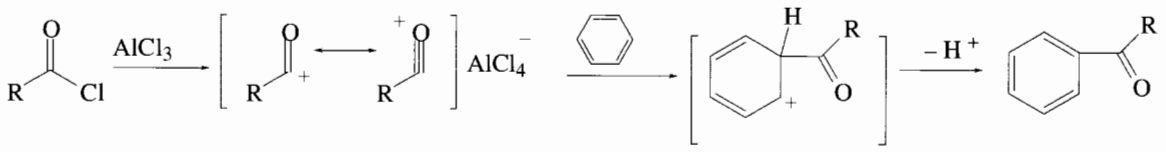
Other cation precursors can be used in these reactions. Locher and Peerzada used a benzotriazole unit in a synthesis of tetrahydroisoquinolines.[124] In this reaction, **188** was converted to **189** in 87% yield under very mild conditions.

Typical Friedel–Crafts disconnections involving alcohol and alkene precursors are



12.4.D. Friedel–Crafts Acylation

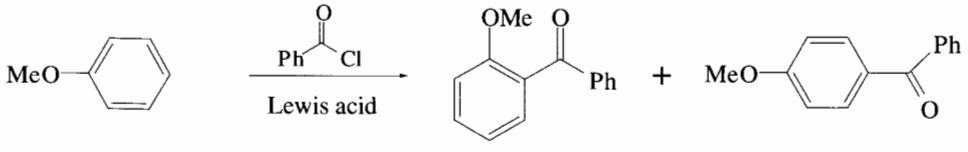
When a Lewis acid reacts with an acyl halide or an anhydride, a resonance stabilized acylium ion (**190**) is produced. This can be attacked by the π bond of a benzene ring to produce **191**, in the usual electrophilic aromatic substitution reaction, and loss of a proton and aromatization gives an aryl ketone (**192**. This reaction[125] is known as **Friedel–Crafts acylation**.[89,88a] The carbonyl group in the ketone product is polarized δ+ and is attached directly to the aromatic ring. The ketone product is deactivated relative to the starting material (benzene) and further reaction to give a polyacylated derivative is not a major problem since **190** is less reactive than benzene. Acylium ions (**190**) are resonance stabilized, as shown, and are not subject to skeletal rearrangement prior to reaction with the aromatic ring. Isomerization of the ketone product is also not a problem.



190 **191** **192**

Acylium ions can be produced from acyl bromides and iodides, but acid chlorides are so readily available (and usually more stable) that they are the most common precursor. Table 12.13[126] shows the influence of

Table 12.13. ortho/para Selectivity as a Function of Lewis Acid in Friedel–Crafts Acylation



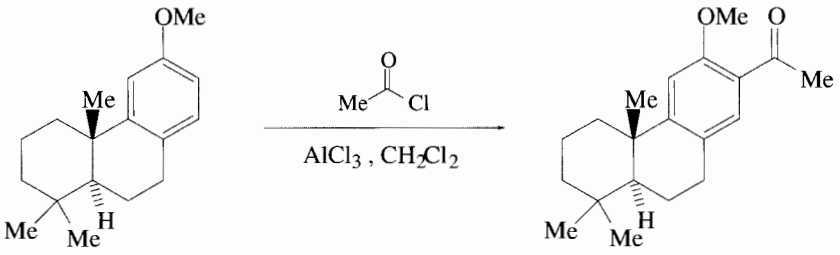
193 **194**

Catalyst	% 193 + 194
$ZnCl_2$	93
$SnCl_4$	90
$FeCl_3$	83
$MoCl_5$	80
$NbCl_5$	54
$AlCl_3$	52
$TaCl_5$	52
$BiCl_3$	49
WCl_6	47
$SbCl_5$	43
$ZrCl_4$	39
$TiCl_4$	35
$TiCl_2$	32
VCl_3	10

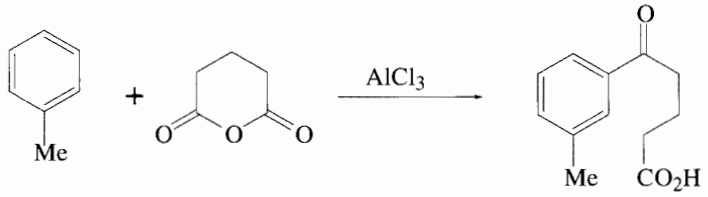
various catalysts on the reaction of benzoyl chloride and anisole. The para product (**194**) predominates over the ortho product (**193**) by ≈ 31:1.[126] A simple example of Friedel–Crafts acylation is the reaction of **195** with acetyl chloride and $AlCl_3$ to give **196** in 67% as part of the Tada et al. synthesis of (+)-ferruginol.[127] Note that the aluminum chloride also deprotected the OMe unit (see sec. 7.3.A.i) to give the phenol.

Other derivatives from carboxylic acids can be used as substrates in Friedel–Crafts acylation reactions, including anhydrides and esters. Toluene reacted with glutaric anhydride in the presence of aluminum chloride to give **197**, which was used in the Vig et al. synthesis of curcumene ether.[128] Lactones are also effective substrates in this cyclization, generating ketones.[129]

Intramolecular Friedel–Crafts acylations are among the most valuable synthetic reactions known for synthesizing polycyclic aromatic compounds. The length of the tether directly influences the site of attack on the aromatic nucleus, and the aromatic nucleus can be benzene or a heteroaromatic compound such as pyrrole,

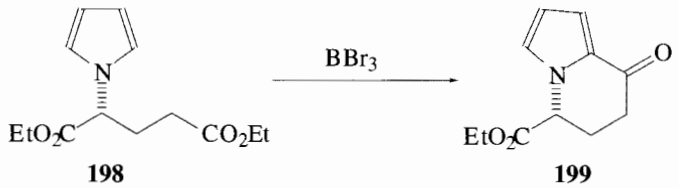


195 **196**

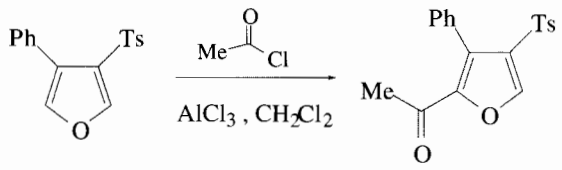


197

furan, or thiophene. This relationship to tether length can be illustrated by the reaction of pyrrole-diester **198** with BBr_3, which led to ketone **199** in Vallée's synthesis of *(R)*-(+)-myrmicarin 217.[130] In intermolecular reactions, pyrroles usually give the α-acyl derivative with the soft acylium electrophile (sec. 2.4) for Friedel–Crafts acylation reactions. Using hard electrophiles such as trimethylsilyl triflate (Me_3SiOTf), however, led to the β-derivative.[131] When pyrrole was treated with acetic anhydride (at 150-200°C), a mixture of 2-acetylpyrrole and 2,5-diacetylpyrrole was formed by reaction with the soft acylium ion.[132] Acylation of an N-silyl pyrrole led predominantly (an 83:17 mixture in 46% yield) to the β isomer rather than the α isomer, when reacted with either anhydrides or acyl chlorides.[133] The bulky $SiMe_3$ group presumably blocks the C2 position. The tosylate directed acylation of furan **200** to **201** is another example using a heterocycle. The tosyl group sterically blocks the C2- position and directs the acyl group toward the C2' position, as shown.[133] The tosyl group can be removed later by various reduction methods (secs. 4.2.C.vii, 4.8.E, 4.9.D).



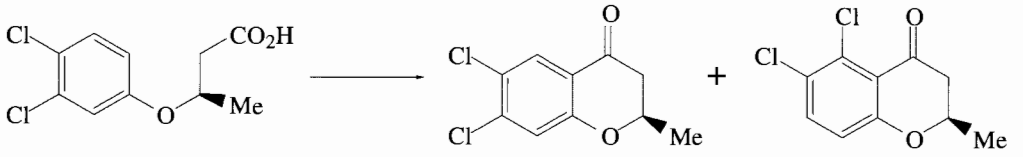
198 **199**



200 **201**

For benzene derivatives, both ortho positions are subject to acylation if they do not have substituents. As shown in Table 12.14,[134] Friedel–Crafts acylation of **202** gave a mixture of coumarins **203** and **204**. Sulfuric acid gave a mixture favoring **204**, whereas a mixture of phosphorus pentabromide and aluminum chloride

Table 12.14. Regioselectivity in a Friedel–Crafts Synthesis of Coumarins



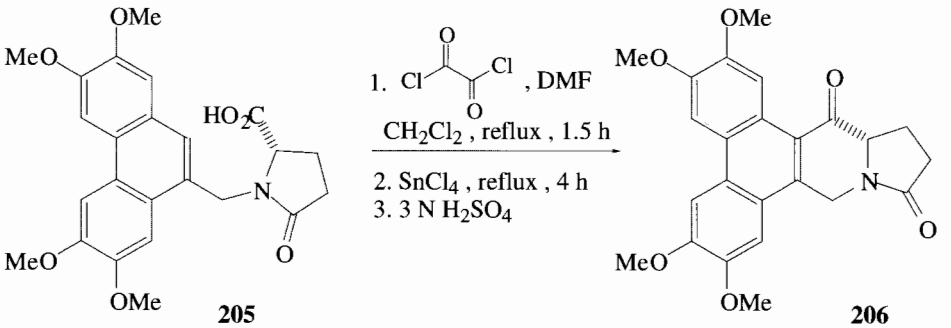
202 **203** **204**

Reagent	Yield (%)	203:204
H_2SO_4	65	35:65
$MeSO_3H/P_2O_5$	70	50:50
$PCl_5/AlCl_3$	90	85:15
$PBr_5/AlCl_3$	87	95:5

[Reprinted with permission from Dr. Frank Urban, Pfizer Central Research, Groton, CT.]

($PBr_5/AlCl_3$) was highly regioselective for the formation of **203**. It is clear that the ortho selectivity depends upon the catalyst used as well as upon the nature of the substrate.

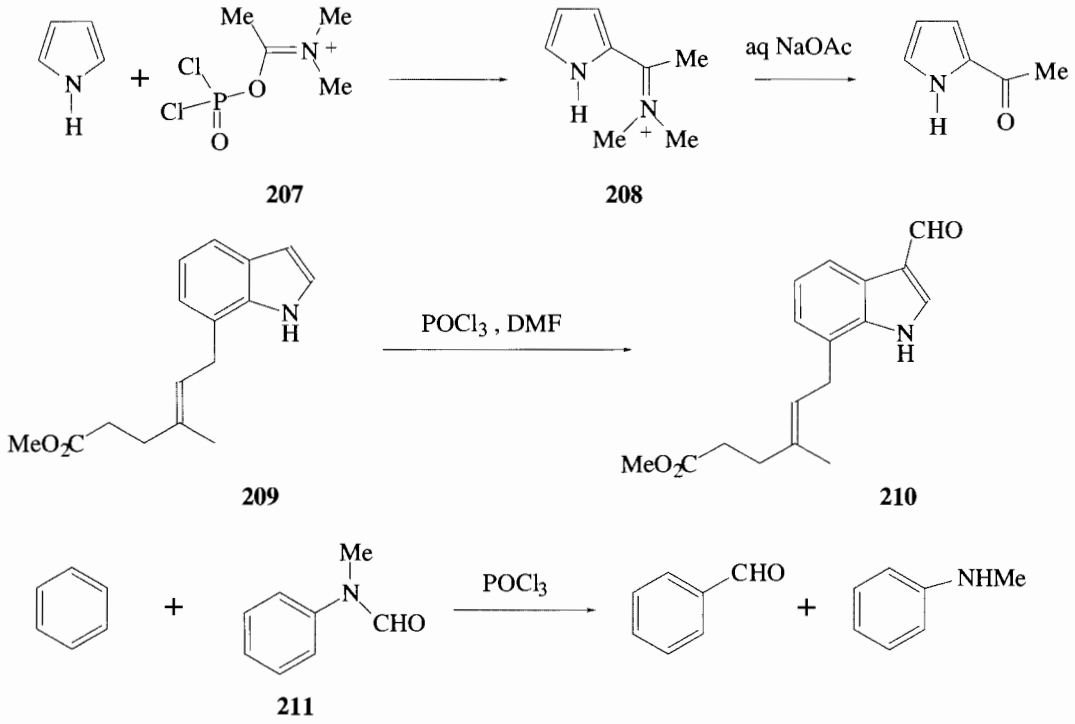
Mild Lewis acids can also be used to effect Friedel–Crafts cyclization, which is particularly important with synthetic targets bearing other functional groups. An example is the cyclization of **205** (after initial conversion to the acid chloride with oxalyl chloride) to give a 94% yield of **206** in the Rapoport and co-workers synthesis of tylophorine.[135]



205 **206**

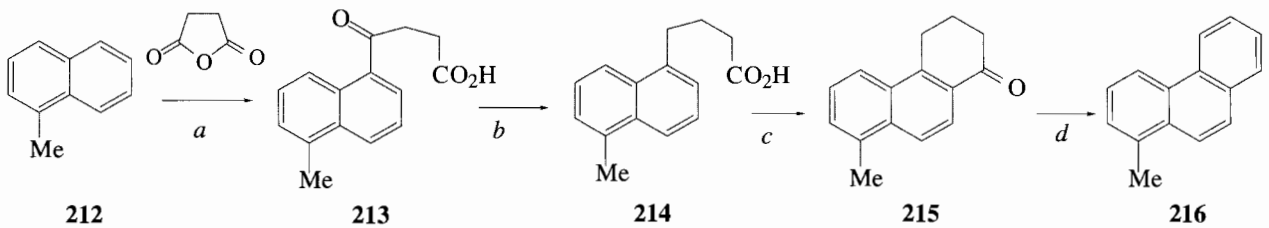
Another acylation procedure uses iminium salts rather than acyl halides. The **Vilsmeier–Haack** reaction[136] is a well-known process illustrated by reaction of pyrrole with the $POCl_3$ complex of *N,N*-dimethylacetamide (**207**, which can decompose to a chloroiminium salt). The acylation reaction gave **208**, which was converted to 2-acetylpyrrole by hydrolysis with aqueous sodium acetate.[137] A synthetic example is taken from Lai's synthesis of indole analogs of mycophenolic acid,[138] in which **209** reacted with $POCl_3$ and DMF to give a 77% yield of the aldehyde **210**.

A variation of the Vilsmeier–Haack reaction uses a formamide such as **211** with benzene (or another aromatic compound) to give the aromatic aldehyde (benzaldehyde) and the amine precursor to the formamide (*N*-methylaniline in this case).[136a] A solvent-free Vilsmeier reaction has been reported using microwave irradiation on silica gel.[139]



12.4.E. Synthesis of Polycyclic Aromatics That Do Not Contain Nitrogen

A classical reaction that takes excellent advantage of the power inherent to Friedel–Crafts techniques is the **Haworth phenanthrene synthesis**,[140] which uses anhydride precursors. It is a simple Friedel–Crafts reaction applied in a stepwise manner to prepare polynuclear aromatic derivatives. When 1-methylnaphthalene (**212**) was heated with succinic anhydride in the presence of $AlCl_3$, keto acid **213** was formed. Reduction of the ketone (via **Clemmensen reduction**-sec. 4.9.G or via **Wolff–Kishner reduction**, sec. 4.10.A) gave **214**, and a second Friedel–Crafts cyclization in the presence of sulfuric acid led to the tricyclic ketone, **215**. Reduction of the carbonyl and aromatization (here by heating with selenium) led to phenanthrene **216**. It is interesting to observe that using a more vigorous catalyst (sulfuric acid) allowed direct cyclization of the acid rather than requiring the use of the acid chloride. If benzene were used as a starting material in this sequence, naphthalene derivatives would be formed.

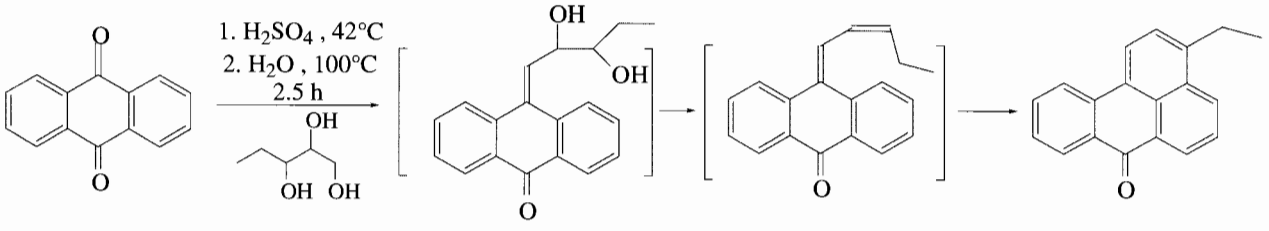


212 **213** **214** **215** **216**

(*a*) $AlCl_3$, $PhNO_2$, 0°C (*b*) Zn°/HCl (*c*) H_2SO_4 (*d*) i. Zn°/HCl ii. Se, heat.

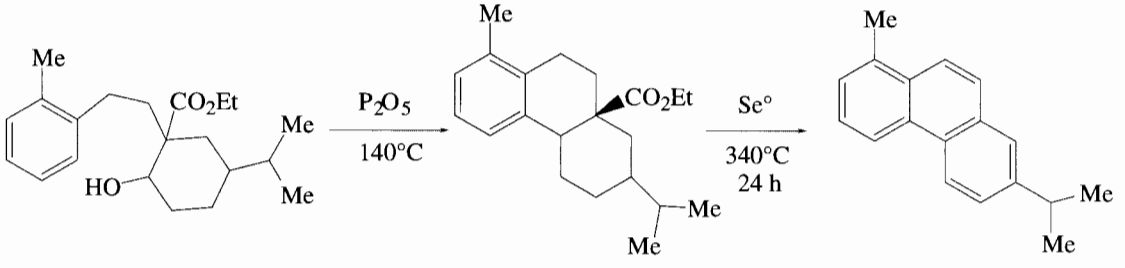
Another useful sequence that produces polynuclear aromatic compounds is the **Bally–Scholl synthesis**.[141] This variation involves addition of a glycerol derivative (a 1,2,3-propanetriol) to an aromatic ring, usually an

anthraquinone moiety. An example is the reaction of anthraquinone (**217**) with 1,2,3-pentanetriol (**218**, also called α-ethylglycerol) to form an alkenyl diol, **219**. Elimination to diene **220** was followed by ring closure under the acidic conditions to give **221** (1-ethylmesobenzanthrone) in ≈ 5% yield.[142] Poor yields with such multistep processes are common under the strongly acidic conditions used. In many other types of reactions, milder conditions involving milder Lewis acids and structural changes in the substrate led to enhanced yields. In some cases, poor yields such as that observed for **221** are acceptable due to the relatively straightforward manner in which the product is produced and the lack of alternative synthetic routes.



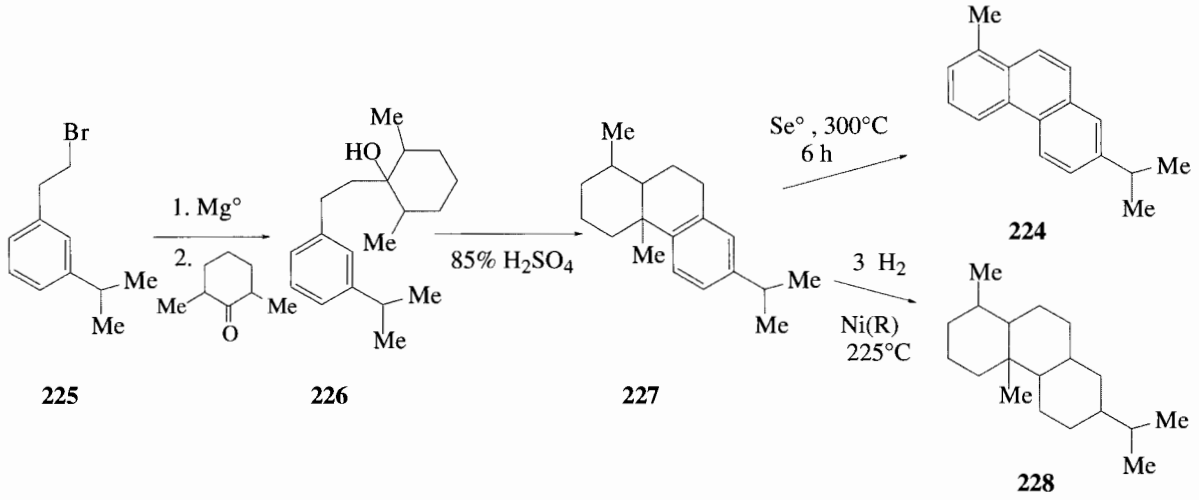
217 **218** **219** **220** **221**

Another Friedel–Crafts route to phenanthrenes is the **Bardhan–Sengupta phenanthrene synthesis**.[143] When phenethylcyclohexanol **222** was cyclized with phosphorus pentoxide at 140°C, the product was **223**.[143] Aromatization was accomplished by heating with selenium to give the phenanthrene derivative **224** (1-methyl-7-isopropylphenanthrene, otherwise known as retene).[143] An improvement in the reaction used hydrogen fluoride (HF) to induce cyclization.[144]

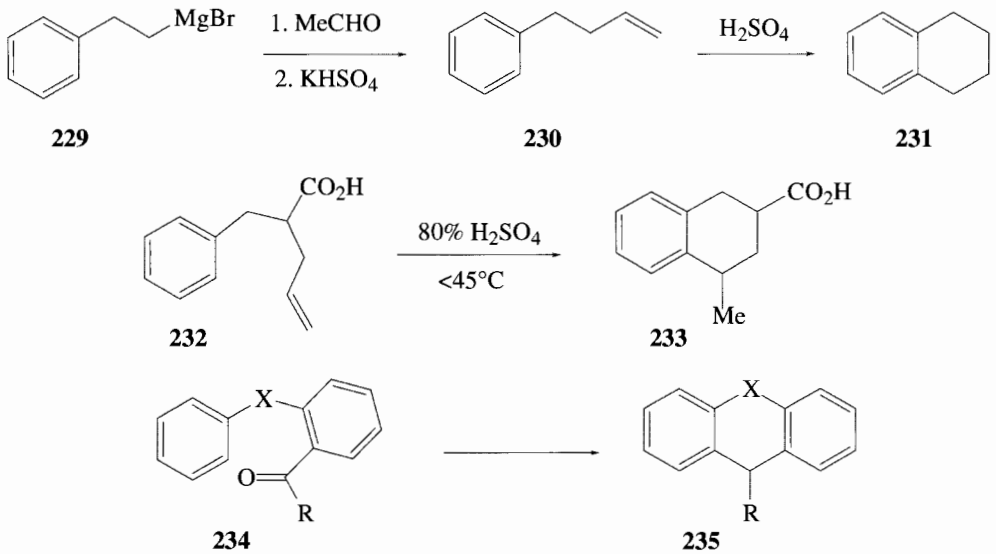


222 **223** **224**

Both phenanthrenes and hydronapthalenes are available by the **Bogert–Cook synthesis**.[145,143] When the Grignard reagent derived from **225** reacted with 2,5-dimethylcyclohexanone, alcohol **226** was produced in 43% yield. Treatment with 85% sulfuric acid effected dehydration of the alcohol to a cyclohexene derivative, which closed on the aromatic ring to give **227** in 81% yield. Dehydrogenation with selenium at 300°C gave retene (**224**), whereas hydrogenation with Raney nickel (sec. 4.8.F) gave abietane (**228**) in 39% yield.[146] Larger polycyclic rings can be produced by using 1-bromonaphthalene derivatives as a starting material.[145b] An alkene unit can also be used to generate a cation and cyclize to form a polycyclic aromatic compound. When **229** reacted with acetaldehyde, **230** was produced and this was cyclized by treatment with sulfuric acid to give hydronapthalene (**231**). This modification does not incorporate the additional ring of the cyclic ketones used in the Bogert–Cook reaction; it is sometimes called the **Bogert synthesis**.

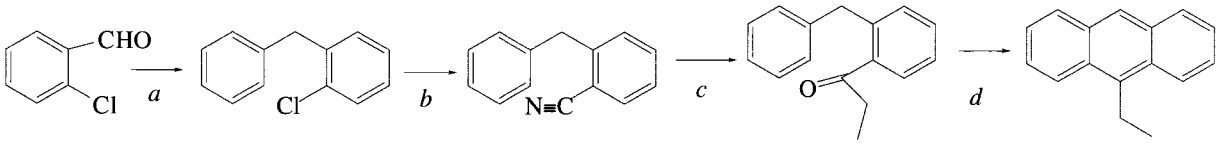


A related modification also involves alkenes and is called the **Darzens tetralin synthesis.**[147] In this process, the alkenyl group is used directly as the cation precursor. An example is **232**, which was treated with concentrated sulfuric acid followed by gentle heating to give the tetralin (tetrahydronaphthalene, **233**)[148] The only difference between this and the Bogert synthesis is the method by which the alkenyl arene is formed. Tetralin formation from an alkenylbenzene derivative is most often referred to as the Darzens tetralin synthesis rather than the Bogert synthesis.



The **Bradsher reaction**[149] is a synthetic route that converts aryl ketones (**234**) to polycyclic hydrocarbons such as **235**. This reaction can also be applied to heterocyclic derivatives of **234** (X = O, S, Se). A common route to ketones such as **234** is shown for the preparation of **240**. Two of the aryl groups are incorporated by a Grignard reaction of aldehyde **236** with phenylmagnesium bromide, producing **237** in 81% yield. Subsequent treatment with cuprous cyanide (also see sec. 2.11.E) leads to nitrile **238**, and reaction with ethylmagnesium bromide gives the ketone precursor (**239**). Subsequent reaction with HBr (reflux for four

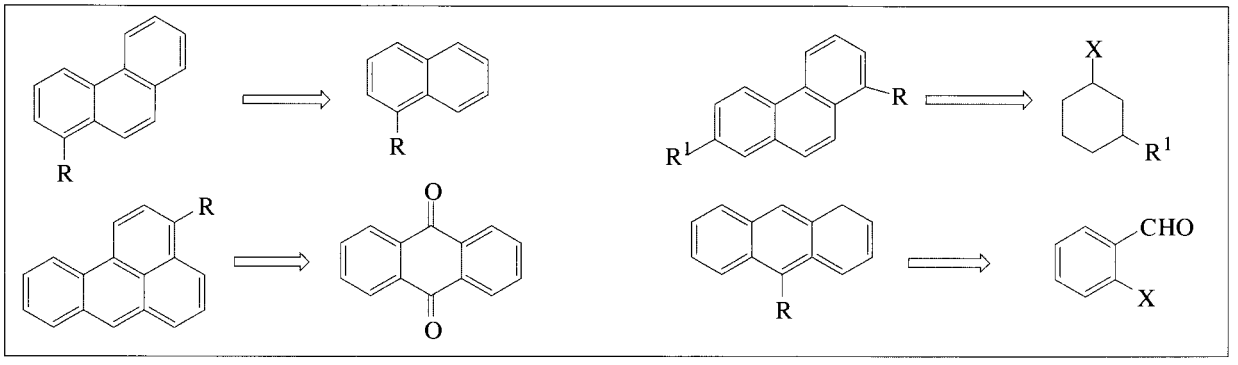
days) generated ethyl anthracene (**240**) in 69%.[149] The lesson of the alkene reactions given in this section is that Friedel–Crafts cyclizations are sensitive to minor changes in substrate and reaction conditions.



236 **237** **238** **239** **240**

(*a*) i. PhMgBr ii. I_2 , P , AcOH , reflux , 29 h (*b*) CuCN , 250°C , 23 h
(*c*) i. EtMgBr , PhH , reflux, 20 h ii. H_3O^+ (*d*) 30% HBr , AcOH , 4 d

The disconnections found in this section are



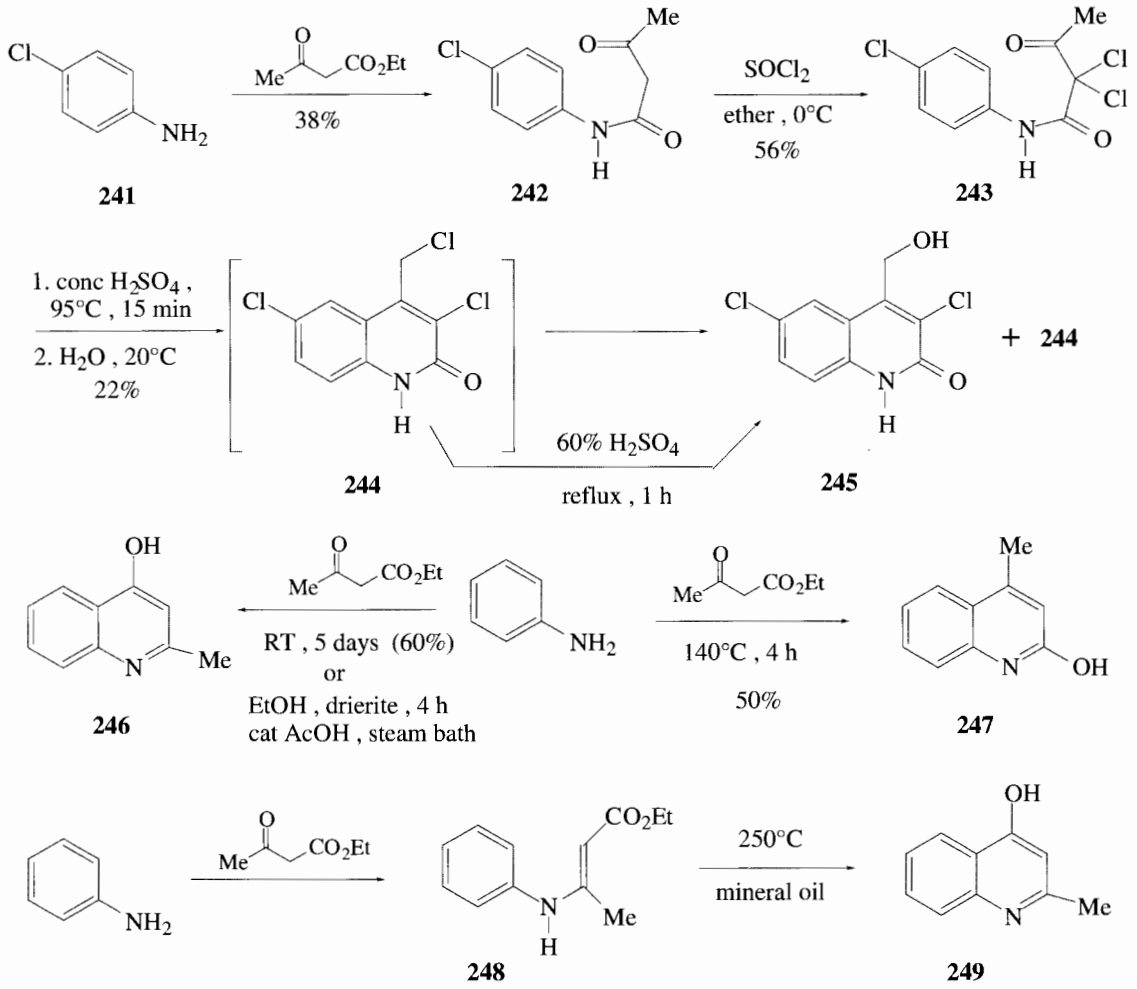
12.5. Friedel–Crafts Reactions: Formation of Heteroatom-Containing Derivatives

Friedel–Crafts alkylation and acylation reactions are quite versatile. They form the basis of several named reactions that have been used to synthesize heteroatom-containing compounds such as quinolines, isoquinolines, indoles, and many others. This section will examine several more common transformations that will show the scope and utility of these processes. It will also introduce a modest amount of heterocyclic chemistry into our synthetic discussion.

12.5.A. Synthesis of Quinoline Derivatives

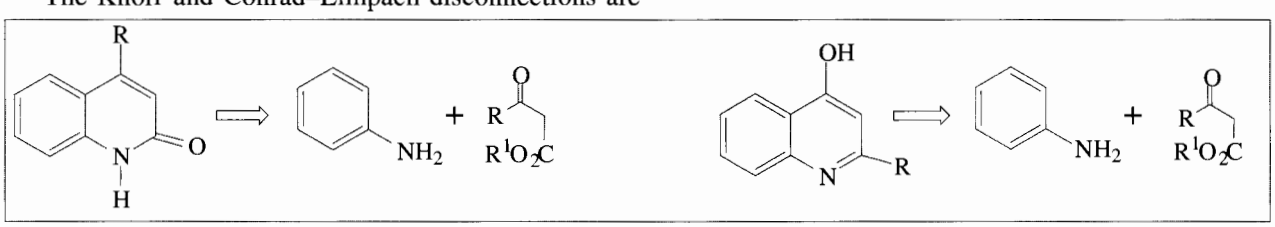
The quinoline unit is an essential feature of many natural products and there are a large number of reactions that prepare quinolines. One of the older, yet still useful methods, is the **Knorr quinoline synthesis**.[150] This reaction couples an aromatic amine (usually aniline or a derivative) with a β-keto ester. Heating 4-chloroaniline (**241**) and ethyl acetoacetate to 130°C gave aryl amide **242** in 38% yield. Subsequent treatment with sulfuryl chloride led to a 56% yield of **243** . Heating with sulfuric acid (95°C) led to Friedel–Crafts cyclization with formation of the chloromethyl derivative **244**, which reacts further to give α-hydroxymethylquinoline (**245**) in 79% yield (along with 22% of **244**).[151] In another example, heating aniline and ethyl acetoacetate to 140°C gave 50% of **247**. However, if aniline and ethyl acetoacetate were reacted at room temperature for 5 days (or for 3 days with a catalytic amount of HCl), 60% of the isomeric hydroxyquinoline

246 was isolated. A 70% yield of **246** was also obtained when aniline was treated with ethyl acetoacetate in ethanol with a catalytic amount of acetic acid in the presence of Drierite®.

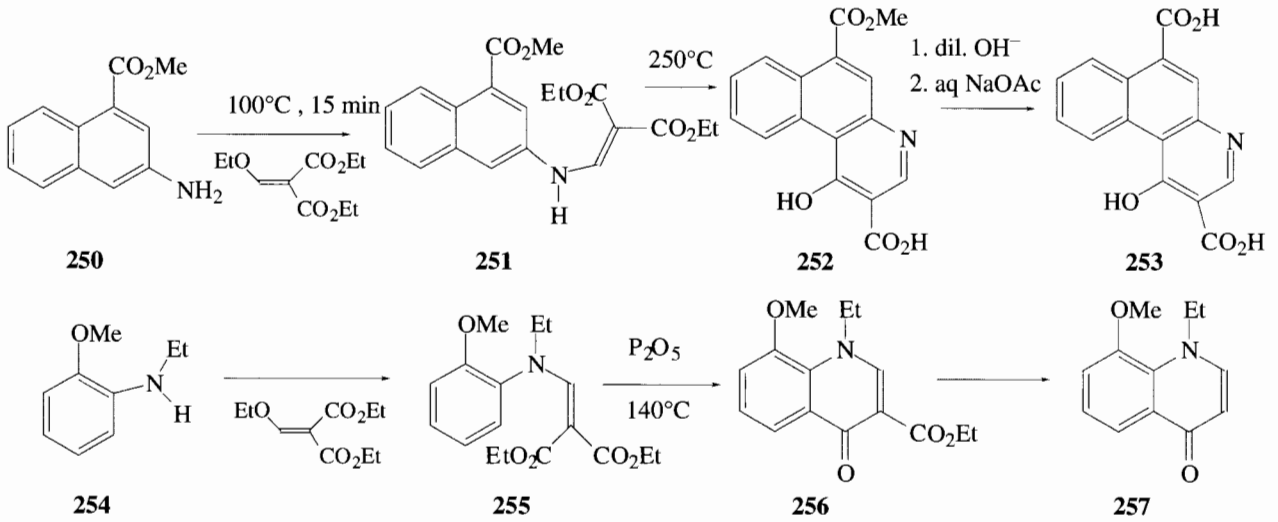


The lower temperature variation of this reaction initially forms an imine or an enamine. Friedel Crafts cyclization gives the 4-hydroxyquinoline in what is called the **Conrad–Limpach reaction**.[152] This reaction generally gives the opposite regioisomeric product to that obtained by the Knorr quinoline synthesis. The initially formed product is usually the enamine (as in the formation of **248** from aniline and ethyl acetoacetate).[153] Under acidic conditions the iminium salt is formed and cyclized with the aromatic ring. A more efficient method simply heated **248** to 250°C in mineral oil, giving a 90% yield of **249**. A variety of other functional groups can be tolerated in the molecule when this procedure is used.

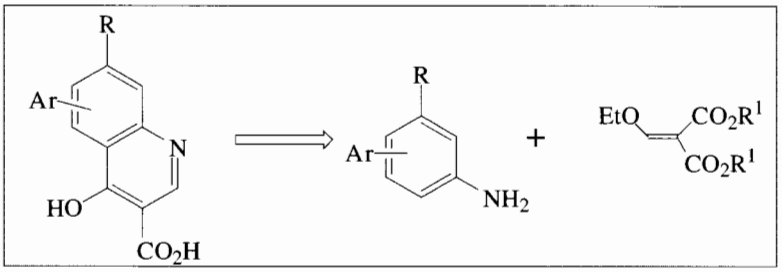
The Knorr and Conrad–Limpach disconnections are



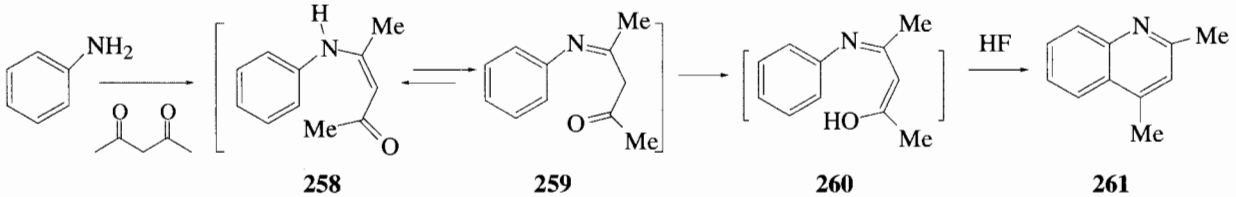
Related to this is the **Gould–Jacobs reaction**,[154] which reacts an aromatic amine such as **250** with ethoxyalkylidene malonate [EtOCH=C(CO_2Et)$_2$] to generate an enamino ester (**251**). Heating to 250°C induced cyclization to give 4-hydroxyquinoline ester **252** in 83% yield.[154] Saponification gave 4-hydroxy-5,6-benzoquinidine-3,7-dicarboxylic acid, **253**.[155] This sequence can be used with many aromatic substrates, but when secondary amines are used as precursors the reaction takes a slightly different course. 2-Methoxy-*N*-ethylaniline (**254**) was converted to **255** (80%) in the same manner. Subsequent cyclization in the presence of P_2O_5 required only 140°C to give an 85% yield of **256**.[154a] The presence of a tertiary amine moiety in this product prevented aromatization and decarboxylation led to **257** in 41% yield.



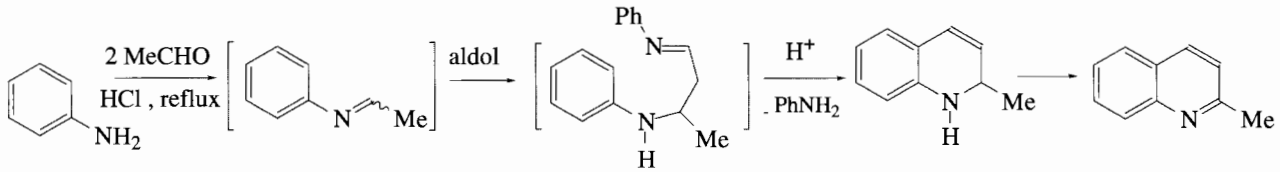
The Gould–Jacobs disconnection is



If a β-diketone is used rather than a β-keto ester, the result is a 4-alkylquinoline in what is known as the **Combes quinoline synthesis**.[156] Reaction of aniline with acetyl acetonate (2,5-pentanedione), for example, generated enamine **258**, which is in equilibrium with the imine (**259**). Enolization to **260** in the presence of HF was followed by cyclization to give the quinoline (**261**) in 96% yield.[157,156a]

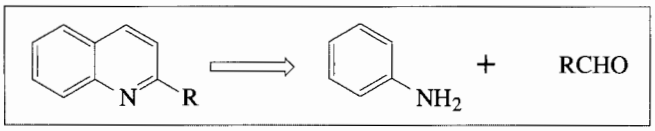


Reaction of a primary aromatic amine (such as aniline) with a carbonyl compound such as acetaldehyde, in the presence of acid, also generates a 2-alkylquinoline in the **Doebner–Miller reaction**.[158] Reaction of aniline with acetaldehyde gave **262**, but a subsequent aldol condensation with the imine derived from acetaldehyde (sec. 9.4.F.i) led to **263**.[159] Friedel–Crafts cyclization was followed by loss of aniline to give **264**, and aromatization gave 2-methylquinoline (**265**).

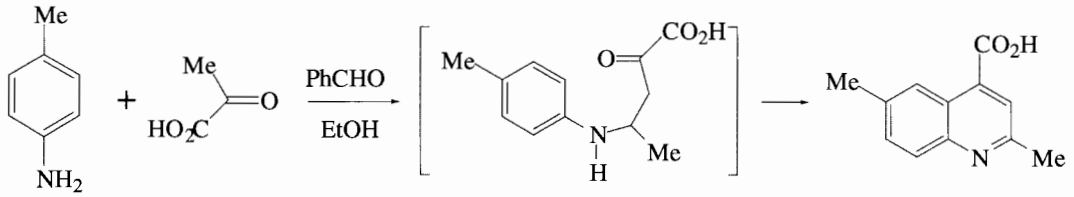


262 **263** **264** **265**

The Combes and Doebner-Miller disconnection is

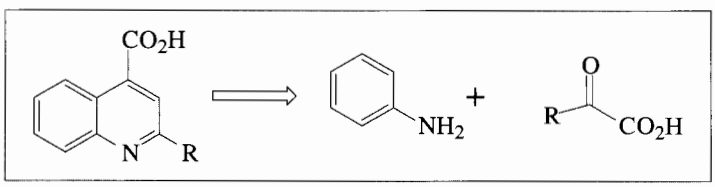


Similarly, the **Doebner reaction**[160,156b] condenses aromatic amines and aldehydes and pyruvic acid derivatives. Reaction of *p*-toluidine with pyruvic acid (**266**) gave the aminopyruvic acid (**267**) *in situ* and subsequent cyclization and air oxidation under Friedel–Crafts conditions generated the 4-carboalkoxyquinoline (**268**).[161] Presumably, the reaction proceeds via initial imine formation (via reaction with benzaldehyde) followed by condensation with pyruvate (in its enol form).[151] Similar cyclization occurs with imines and pyruvate derivatives.[162]

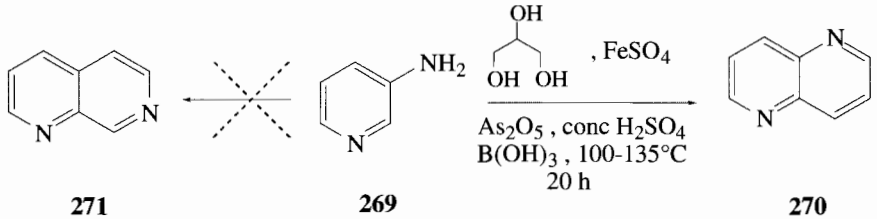


266 **267** **268**

The Doebner disconnection is



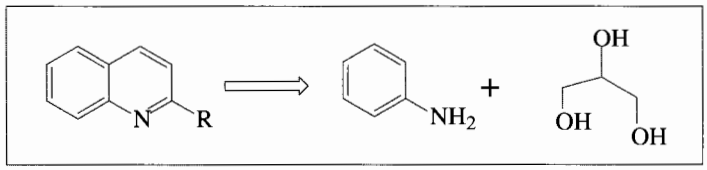
The **Skraup reaction**[163] presents another variation in which an aniline derivative reacts with glycerol, in the presence of acid, to generate a quinoline derivative. Rapoport reacted 3-aminopyridine (**269**) with glycerol to produce **270** (1,5-naphthyridine) in 31% yield.[164] It is important to note that none of the isomeric 1,7-naph-



271 **269** **270**

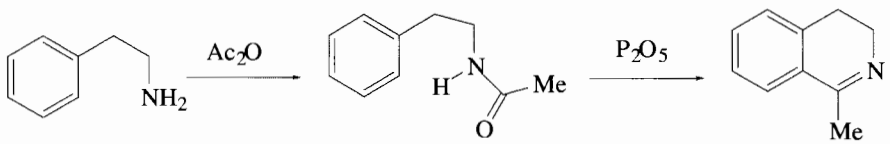
thyridine (**271**) was produced in this reaction. Attack at the carbon adjacent to both nitrogens seems to be the preferred regioselectivity with aminopyridines. The reaction is regioselective[165] rather than regiospecific, however, since Rapoport reported ≈ 4% of 3-methyl-1,5-naphthyridine and 3-ethyl-1,5-naphthyridine. This is obviously related to the **Bally–Scholl synthesis** introduced in sec. 12.4.E.

The Skraup disconnection is:

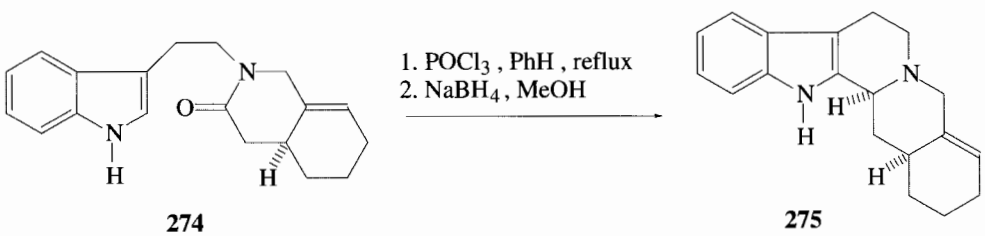


12.5.B. Synthesis of Isoquinoline Derivatives

Isoquinolines are as important as quinolines in the chemistry of natural products and there are also many syntheses of these compounds. One of the most important Friedel–Crafts routes is the **Bischler–Napieralski reaction.**[166] This process is the reaction of an N-acyl amine such as **272** with a reagent such as PPA or P_2O_5 to give an dehydroisoquinoline derivative (**273**). Wender and Smith used this reaction to convert **274** to **275** in 86% yield as part of a synthesis of yohimban alkaloids.[167] Shea and co-worker used a similar reaction to synthesize alloyohimbane.[168]

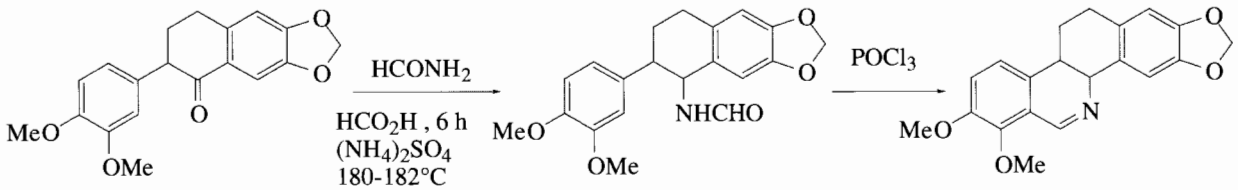


272 **273**



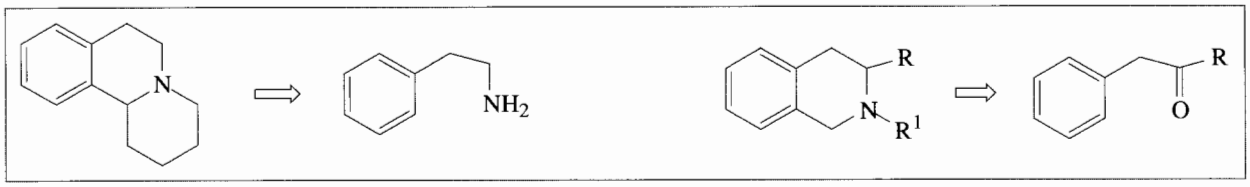
274 **275**

A useful variation first converts the amino group to a formamide derivative, usually by treatment of a ketone (such as **276**) with formamide and formic acid. Treatment of **276** with these reagents led to formamide **277**. When this was treated with $POCl_3$, cyclization occurred via the N-acyl group to give the isoquinoline, **278**, in 66% yield. Zee-Cheng and Cheng used this sequence in a synthesis of nitidine.[169]

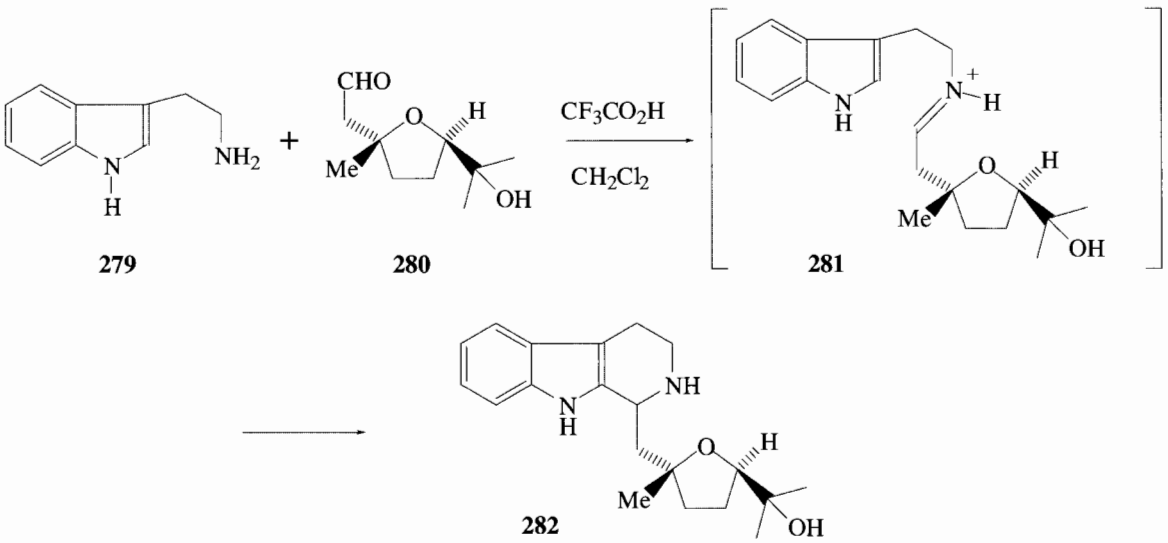


276 **277** **278**

Bischler–Napieralski disconnections are



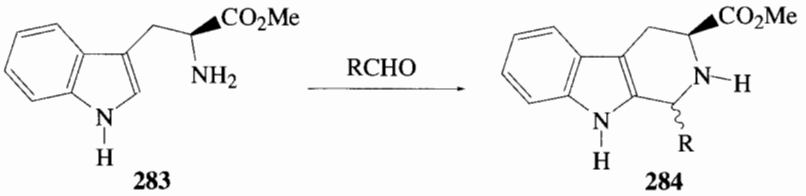
Another classical approach is the **Pictet–Spengler isoquinoline synthesis.**[170,166c] This variation generates an iminium salt from an amine and an aldehyde (a Schiff base), which cyclizes with an aromatic ring to complete the reaction.[171] A synthetic example is taken from Liang's synthesis of chrysotricine.[172] The reaction of amine **279** with aldehyde **280**, in the presence of trifluoroacetic acid, initially gave an iminium salt (**281**). Subsequent Friedel–Crafts cyclization of the iminium salt gave the isoquinoline product (**282** in 70% yield). The amino groups of amino acid derivatives also serve as excellent partners in this reaction.[173]



279 **280** **281** **282**

When the aromatic ring has substituents, cis or trans imines can be formed. As shown in Table 12.15, the carbomethoxy substituent of tryptophan methyl ester (**283**) shows a preference for the cis isomer (**284**) in dichloromethane and a very slight preference for the trans isomer in refluxing benzene.[174,173] This difference in selectivity is probably a thermal effect rather than a solvent effect, and higher selectivity is observed at lower temperatures. It was also shown that lower reaction temperatures led to retention of optical activity, whereas racemization occurred at higher reaction temperatures.

Table 12.15. Influence of Temperature on the Pictet–Spengler Reaction of 283



283 **284**

R	Solvent	Temperature (°C)	cis/trans	% 284
Ph	CH_2Cl_2	0	82:18	74
	PhH	reflux	37:63	76
C_6H_{11}	CH_2Cl_2	0	71:29	71
	PhH	reflux	59:41	85
$MeCH_2CH_2$	CH_2Cl_2	0	80:20	72
	PhH	reflux	47:53	88
Me_2CHCH_2	CH_2Cl_2	0	83:17	82
	PhH	reflux	43:57	76

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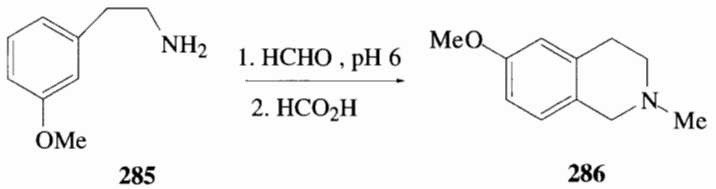
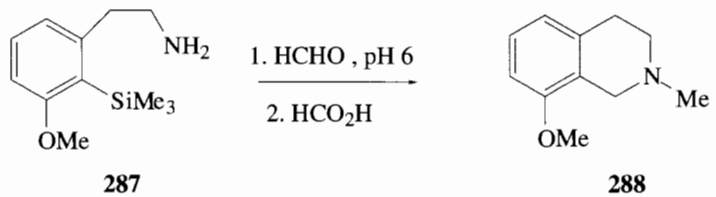
The regioselectivity of the reaction can be controlled by modifying groups on the aromatic ring. A normal Pictet–Spengler reaction with formaldehyde converted **285** to **286** in 22% yield. The silyl directed reaction, however, converted **287** to **288** in 72% yield.[175]

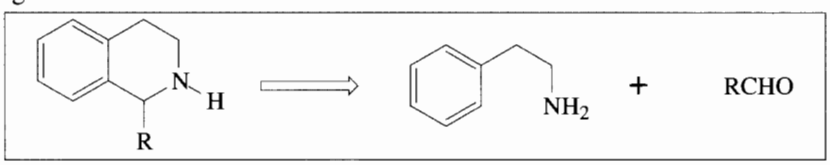


285 **286**

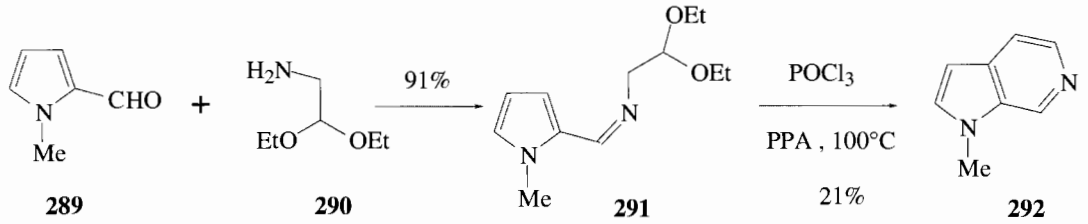


287 **288**

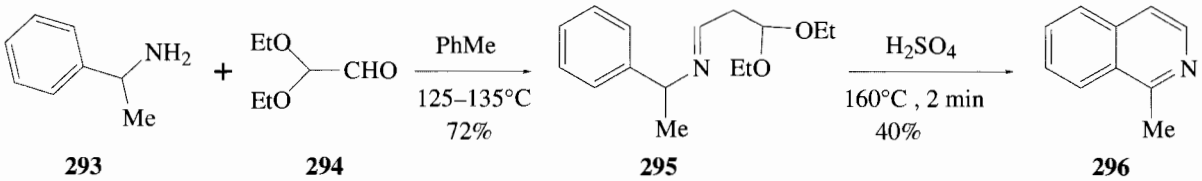
The Pictet–Spengler disconnection is



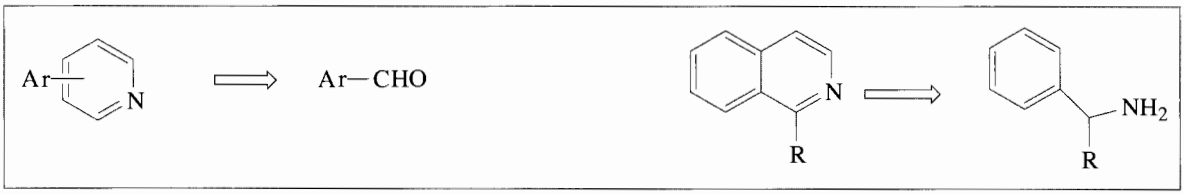
Another method for the synthesis of isoquinoline derivatives is the **Pomeranz–Fritsch reaction**.[176] Simple aniline derivatives can be used but this is very useful for acid sensitive substrates such as thiophene and pyrrole



derivatives. In those cases, it is an excellent alternative to the Pictet–Spengler reaction. An example of an acid sensitive substrate is **289**, which reacted with glycinal diethyl acetal (**290**) to generate Schiff base **291** in 91% yield. Subsequent treatment with PPA gave a 21% yield of pyrrolo-[1,2*a*]-pyrazine (**292**).[177] When the reactive partners are reversed to react an amine (such as α-methylbenzylamine, **293**) and a glyoxal semiacetal (**294**), a different Schiff base is formed (**295**). Treatment with acid led directly to isoquinoline **296**.[178] The yield of **296** was only 15% by the Pomeranz–Fritsch method but 40% with this variation, which is known as the **Schlittler–Müller modification**.[178]

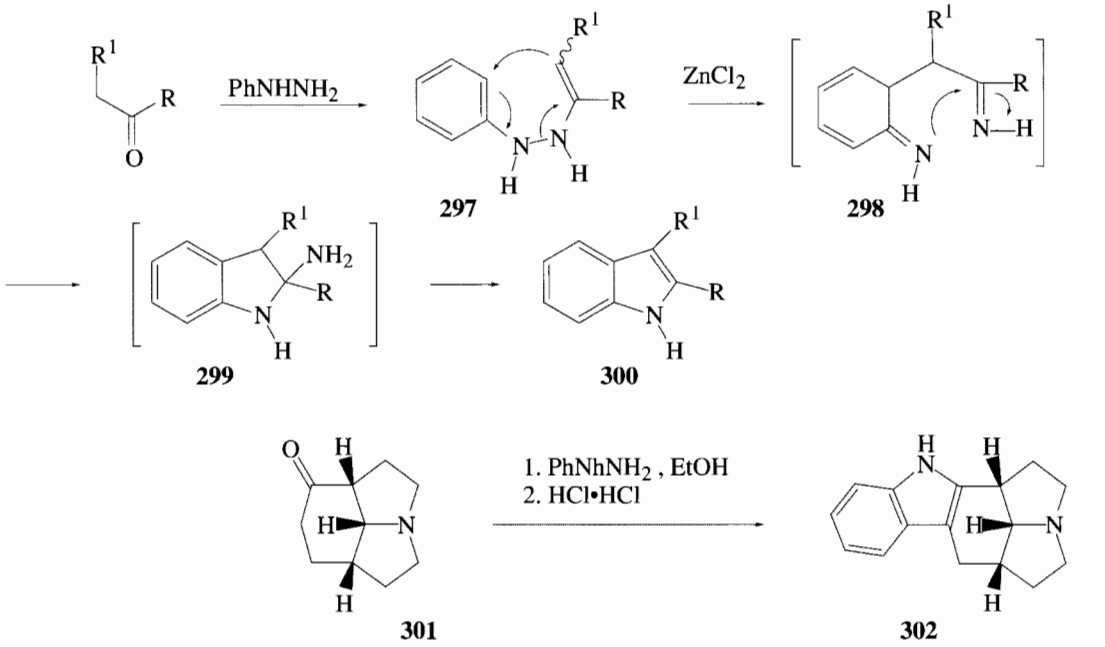


The Pomeranz–Fritsch and Schlittler–Müller disconnections are



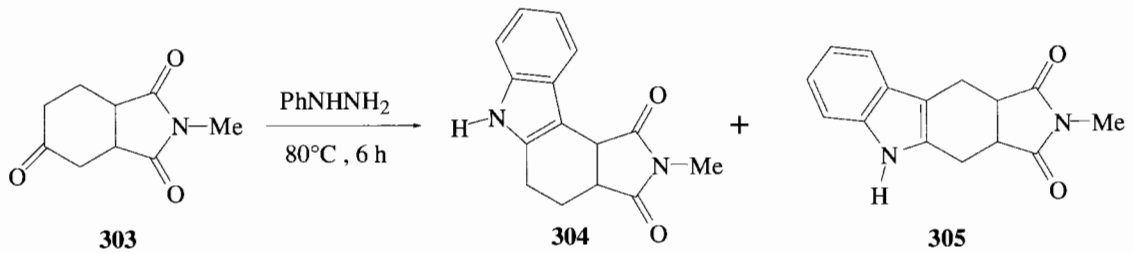
12.5.C. The Fischer Indole Synthesis[179,181]

The indole nucleus (see **300**) is a component of many natural products and medicinal compounds.[180] In 1883, Fischer reported a straightforward synthesis of indoles that is today considered a powerful reaction in Corey's **LHASA** program (sec. 10.4.B). It remains one of the best methods for the preparation of indoles. It begins with conversion of an aldehyde or ketone to a phenylhydrazone **297** (by treatment with phenylhydrazine). Subsequent treatment with a Lewis acid (zinc chloride is generally preferred) induces a reaction cascade that results in indole **300**. The mechanism of this transformation involves formation of a hydrazone that reacts via an N-amino enamine form (**297**), in what is probably an electrocyclic process that is analogous to a Claisen rearrangement (sec. 11.12.D), followed by attack of the aromatic ring to give bis(imine) **298**.[181] Attack of the imine nitrogen generates amino compound **299** via hydrogen transfer and aromatization. Loss of the ammonium species completes the synthesis of the indole ring (**300**). An application of the Fischer indole reaction is taken from Bonjoch's synthesis of deethylibophyllidine.[182] In this synthesis, ketone **301** was treated with phenylhydrazine and then with ethanolic HCl to give a 40% yield of the indole product (**302**).

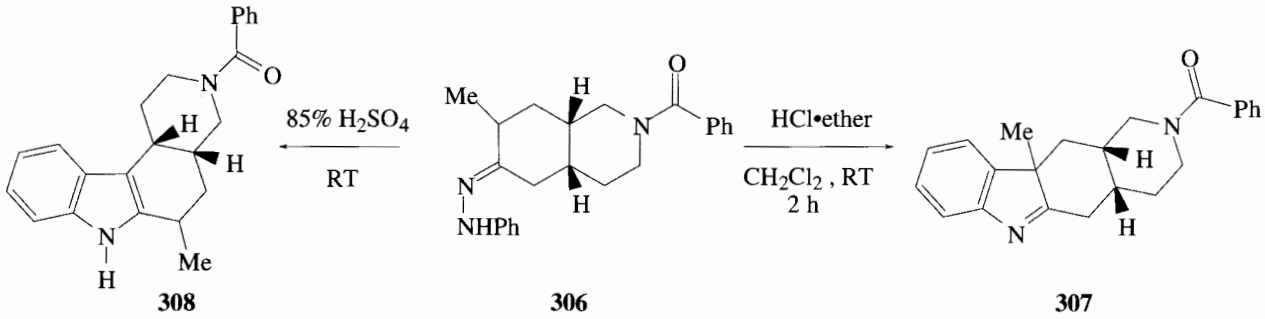


The cyclization proceeds with reasonable regioselectivity. In ketone **303** there are two α-carbons, and two different enamine structures can be formed, as well as two bis(imine) intermediates.[183] The final indole products were **304** and **305**. Table 12.16[183] shows the changes in selectivity for this mixture of products in a Fischer indole syntheses under various conditions. As the concentration of acid catalyst increases, the yield decreases but the regioselectivity is about the same, (2:1 **304/305**).[183,184] There is remarkably little change in this ratio until the acid concentration exceeds 45%. The stereochemical course of the reaction also depends on the stereochemistry of the hydrazone substrate. In another example, hydrazone **306** (with a cis ring juncture) was treated with ethereal HCl in dichloromethane at room temperature, a 61% yield of **307** was obtained.[185] Reaction of **306** with 85% sulfuric acid gave a 42% yield of the isomeric **308** and the course of the reaction

Table 12.16. Regioselectivity in the Fischer Indole Synthesis as a Function of Acid Concentration

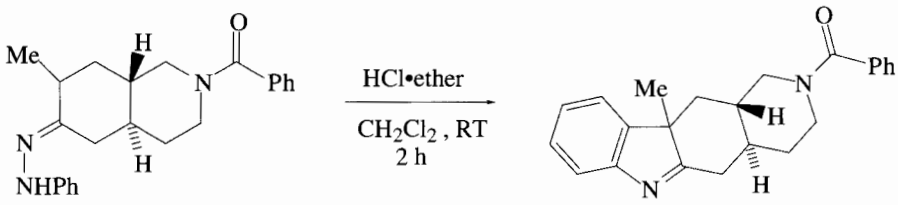


Acid	Concentration (%)	%304	% 305
H_2SO_4/MeOH	7	45	21
H_2SO_4/MeOH	15	45	22
H_2SO_4/MeOH	30	45	24
H_2SO_4/MeOH	45	36	18
H_2SO_4/MeOH	60	15	6

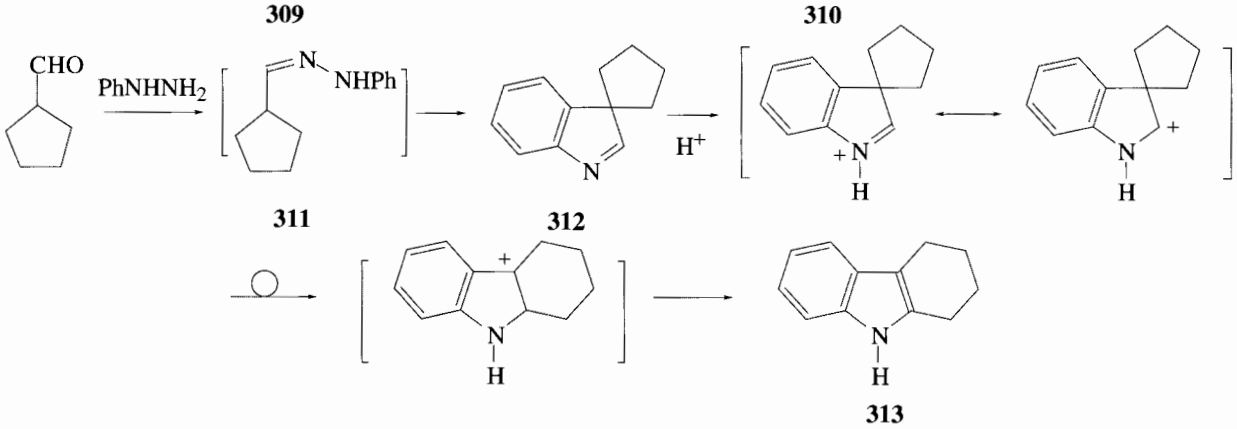


308 **306** **307**

was highly dependent on the acid strength of the medium. When the trans derivative (**309**) was treated with ethereal HCl under the same conditions, 38% of a single product (**310**) was isolated. Treatment with 85% sulfuric acid gave no cyclization and only unreacted starting material. Treatment with more concentrated acid led to decomposition of the starting material but no cyclization.



309 **310**

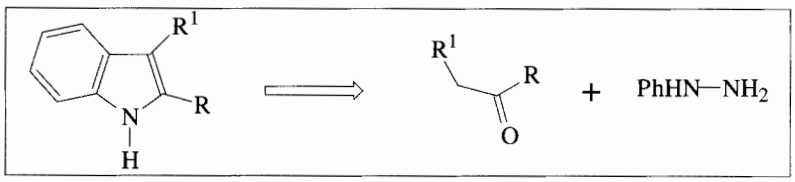


311 **312**

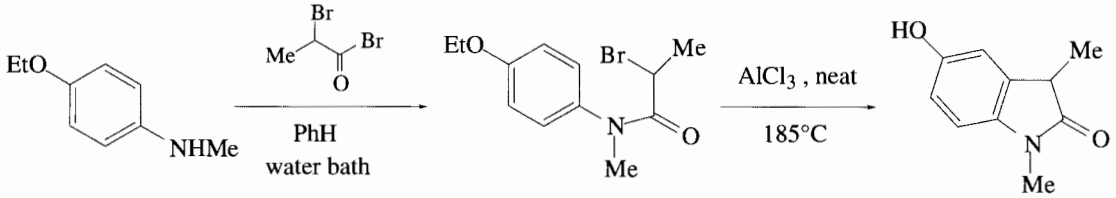
313

The initially formed imine product may be subject to rearrangement under the strongly acidic reaction conditions. Treatment of the phenylhydrazone of cyclopentane carboxaldehyde (**311**) with acetic acid, for example, led to a 90% yield of **313** via the acid catalyzed rearrangement of imine **312**.[186] Cyclopentane carboxaldehyde derivatives gave only fused ring indoles, but larger ring carboxaldehydes led to spiro derivatives or mixtures of fused-ring and spirocyclic products.[186]

The Fisher indole disconnection is

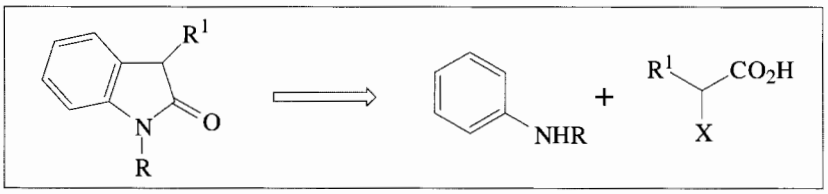


A related synthesis produces indolones by a different Friedel–Crafts route. The **Stollé synthesis**[187] reacts with a secondary aryl amine such as diphenylamine with an α-chloro acid chloride or an α-bromo acid bromide to give an α-bromoamide (such as **315**) or an α-chloroamide. An early version of the reaction used oxalyl chloride, but a more typical example is the reaction of 2-bromopropanoyl bromide with **314** to give **315**. Friedel–Crafts cyclization (with $AlCl_3$) led to the indolone **316**.[188]



314 **315** **316**

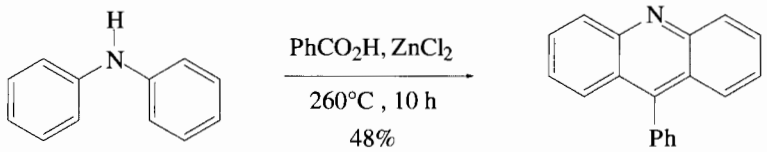
The Stollé disconnection is



12.5.D. Synthesis of Acridines, Carbazoles, and Phenanthridines

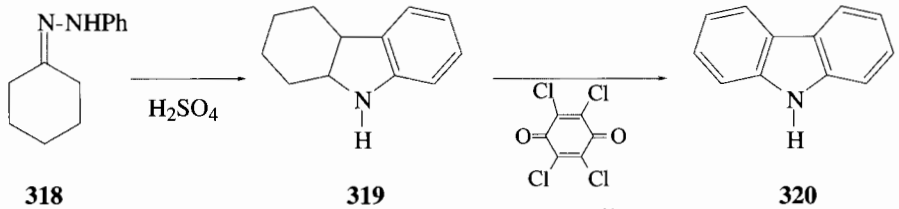
Acridines are an important structural feature of many natural products and medicinally important compounds. They can be produced in a straightforward manner by a Friedel–Crafts reaction, the **Bernthsen acridine synthesis**,[189] which couples diaryl amines (such as diphenylamine) with a carboxylic acid (such as benzoic acid) in the presence of a Lewis acid (zinc chloride, $ZnCl_2$, is a typical reagent). Heating to 260°C (10 h) gave a 48% yield of acridine **317**.[189b]

Carbazole derivatives (carbazole itself is **320**) are also an important structural feature of many alkaloids. The **Borsche–Drechel cyclization**[190] is a Friedel–Crafts route to these compounds, which is related to the Fischer indole synthesis discussed in Section 12.5.C. This sequence begins with phenylhydrazone derivatives



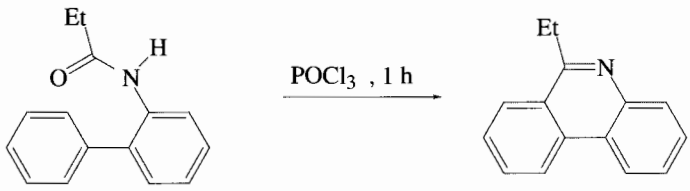
317

of ketones such as that derived from cyclohexanone (**318**), and they are cyclized with sulfuric acid to give **319** in good yield. Aromatization with lead oxide (Pb_3O_4) gave **320** in low yield. The use of glacial acetic acid gave cleaner products in the dehydrogenation,[191] but using tetrachlorobenzoquinone, also known as chloranil, led to the best yield of aromatic product.[192]



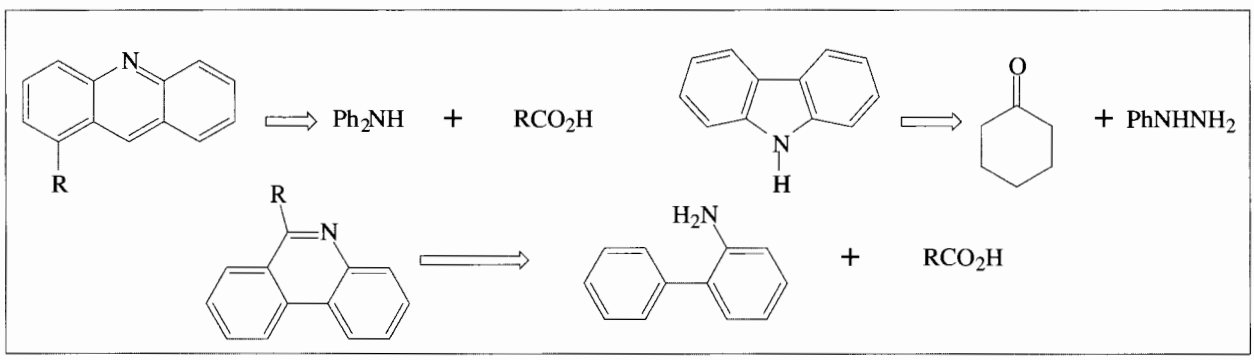
318 **319** (chloranil) **320**

Phenanthridines can be prepared by modification of the Friedel–Crafts reaction. The **Pictet–Hubert reaction**[193] reacts an acyl *o*-aminobiphenyl (**321**) in the presence of zinc chloride at 300°C[194] or with $POCl_3$ in refluxing nitrobenzene,[195] to give the Friedel–Crafts cyclization product **322**, a phenanthridine. Zinc chloride required long heating and wasteful purification, and gave poor results with reactive substrates. Both the use of $POCl_3$ and the use of a high-boiling solvent improved the yields of phenanthridine products.



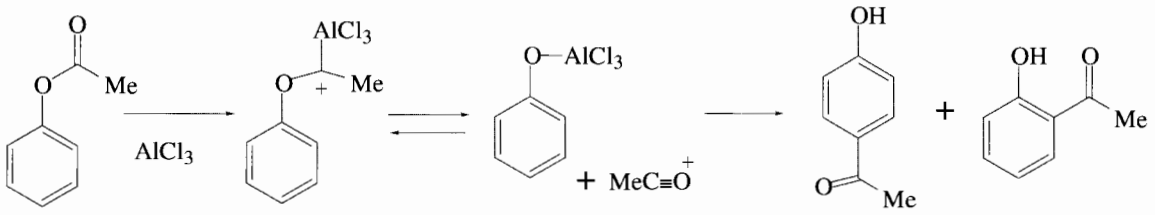
321 **322**

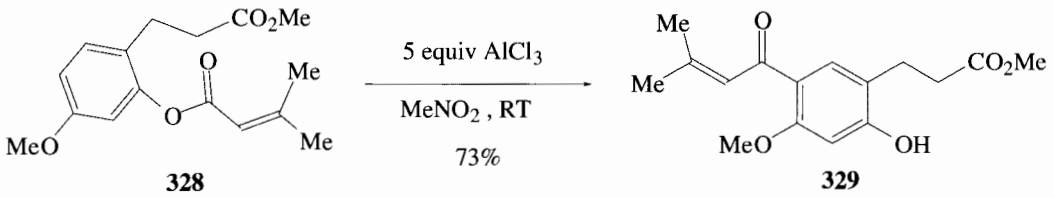
The disconnections discussed in this section are



12.5.E. Synthesis of Oxygenated Aromatic Derivatives

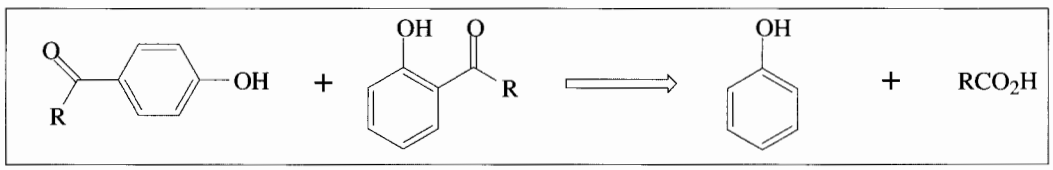
The **Bradsher reaction** (see **236** in sec. 12.5.A, where X = O) is an example of a reaction that can generate aromatic derivatives containing an oxygen atom in the polycyclic framework. There are other routes to these compounds. There are also many phenol derivatives, where the oxygen atom is appended to the aromatic ring, as well as polycyclic aromatics that contain a phenolic unit. An interesting route to such compounds exploits the propensity of aryls to rearrange under Friedel–Crafts conditions. When a phenolic ester (such as phenyl acetate, **323**) is heated with a Lewis acid such as $AlCl_3$, a rearrangement occurs, generating an ortho ketone (**327**) and a para ketone (**326**) in what is known as the **Fries rearrangement**.[196] The reaction generates an acylium ion (**324**) and cleavage generates an aluminum alkoxide (**325**). Friedel–Crafts acylation generates both ortho and para products.



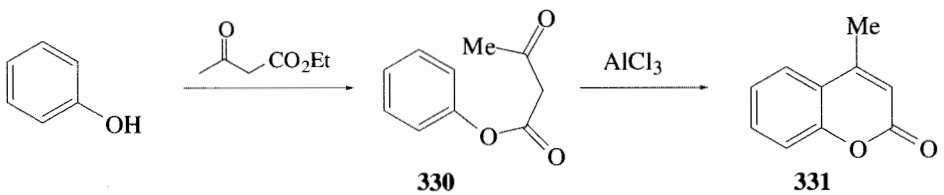


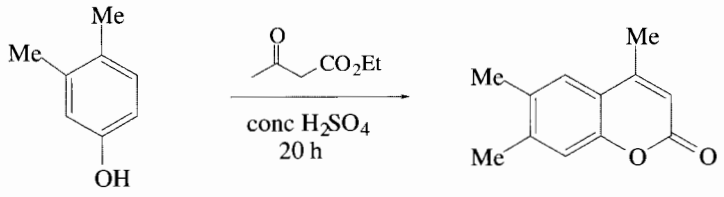
Although this reaction is probably used most often to prepare acetate derivatives,[197] Harwood and co-workers used the Fries rearrangement to convert **328** to **329** in 73% yield, and this was a precursor for the coumarin natural product, geijerin.[198] The regiochemical preference for the para product (para to the hydroxyl group in **354**) is due to the steric effects, which hinder reaction at the only available ortho position.[199] When electron-withdrawing groups are on the aromatic ring, the reaction does not work well. A thia-Fries rearrangement of aryl sulfonate esters such as phenyl *p*-toluenesulfonate has been reported.[200] Irradiation of this tosylate with microwaves on silica gel, for 10 min, gave an 87% yield of *o*- and *p*-toluenesulfonyl phenol (80:20). There is also a **photo Fries rearrangement**, which proceeds via radical intermediates formed by the initial photolysis (sec. 11.10.B, for a brief overview of photochemical theory). The ketone is formed from the bis(acyl) derivative under photolytic conditions.[201]

The Fries rearrangement disconnection is



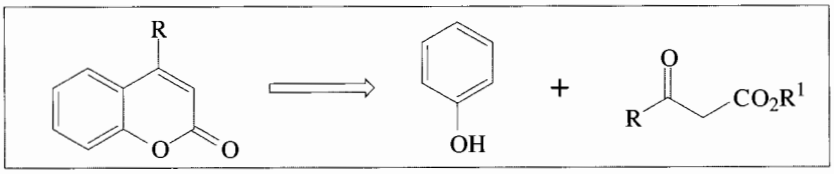
Coumarin derivatives (see **333**) can be formed via Friedel–Crafts techniques. The **Pechmann condensation**[202] begins by esterification of a phenol with a β-keto-ester (a transesterification reaction) to give **330**. Subsequent cyclization with $AlCl_3$ generates coumarin **331**. Isolation of the esters such as **330** is not always necessary. Reaction of 3,4-dimethylphenol (**331**) with ethyl acetoacetate and sulfuric acid gave 4,6,7-trimethyl coumarin (**332**), directly.[203] The reaction is facilitated by the presence of hydroxyl (OH), dimethylamino (NMe_2) and alkyl groups (R) meta to the hydroxyl of the phenol.[204,205]





332 **333**

The Pechmann disconnection is:

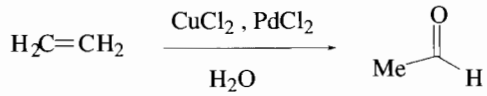


12.6. π-ALLYL PALLADIUM COMPLEXES

Palladium salts react with allylic hydrocarbons and with functionalized allylic derivatives to produce π-allyl complexes. These complexes can react with nucleophilic species, including enolate anions, to produce new carbon–carbon bonds.[206] In these reactions, π-allyl palladium complexes function as C^a equivalents; thus they are included in this chapter.

12.6.A. The Wacker Process

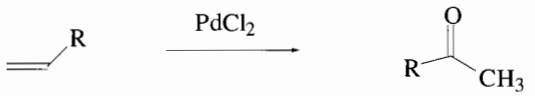
The first process to be discussed is a traditional one that probably does not occur via a π-complex. Nonetheless, it sets the stage for the organopalladium chemistry to be discussed in this section. The **Wacker process** (or the **Wacker oxidation**) is used in industry to convert ethylene to acetaldehyde using soluble palladium catalysts.[207] In this reaction, ethylene reacts with cupric chloride ($CuCl_2$) and palladium chloride ($PdCl_2$) to



give acetaldehyde. Other alkenes can be oxidized to carbonyls as well, as in the conversion of **334** to **335** (see Table 12.17).[208] Both aldehydes and ketones can be formed in moderate to excellent yields. It is also interesting to note that conjugated dienes such as 1,3-butadiene give conjugated aldehydes under these conditions. Cyclic alkenes give the expected cyclic ketones and vinyl and allylic halides are also converted to the corresponding carbonyl compound.[209,210] Wacker oxidation has been reported using molecular oxygen. A catalytic amount of palladium(II) acetate, pyridine, and oxygen, for example, converted dodec-1-ene to 2-dodecanone in up to 70% yield.[211] Similarly, cyclopentene was oxidized to cyclopentanone under an oxygen atmosphere using palladium acetate and molybdovanadophosphate on activated carbon.[212]

The Wacker oxidation can be used with more complex substrates than those shown. Indeed, it can be used in synthesis. An example is taken from Yokokawa's synthesis of (–)-hennoxazole A,[213] in which the terminal

Table 12.17. Palladium Catalyzed Conversion of Alkenes to Carbonyl Compounds



334 335

R	Temperature (°C)	Time (min)	%
H	20	5	85
Me	20	5	90
Et	20	10	80
n-Pr	20	10	81
n-Bu	20	20	75
C_5H_{11}	50	30	65
C_6H_{13}	50	30	42
C_7H_{15}	70	45	35
C_8H_{17}	70	60	34

Alkene/diene	Temperature (°C)	Time (min)	%	product
CH_2=CHCH=CH_2	80	30	34	3-Buten-2-one
MeCH=CHCH=CH_2	20	15	91	2-Pentenal
Cyclopentene	30	30	61	Cyclopentanone
Cyclohexene	30	30	65	Cyclohexanone
Vinyl bromide	10	15	98	Acrolein
1-Bromo-1-pentene	50	15	61	2-Pentanone
1-Bromo-2-phenylethene	40	20	60	Acetophenone
Allyl chloride	50	30	65	Methyl glyoxal
Allyl bromide	50	30	80	Methyl glyoxal

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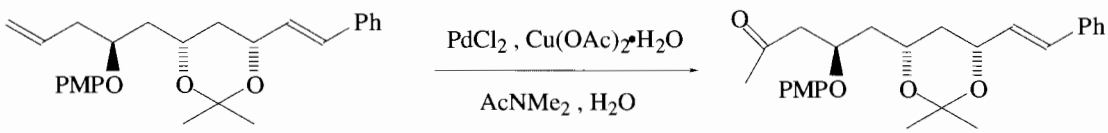
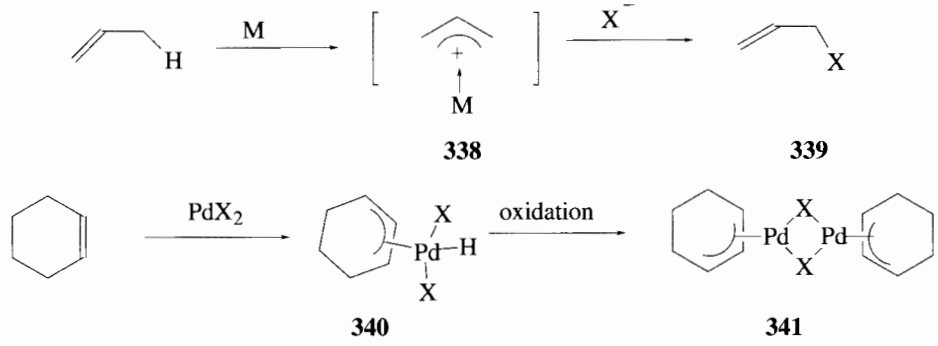
alkene unit in **336** was converted to a methyl ketone in **337**, in 77% yield. The OPMB unit is a *p*-methoxybenzoyl ester. A Wacker oxidation was also used in Bonjoch's synthesis of nakamurol-A.[214]



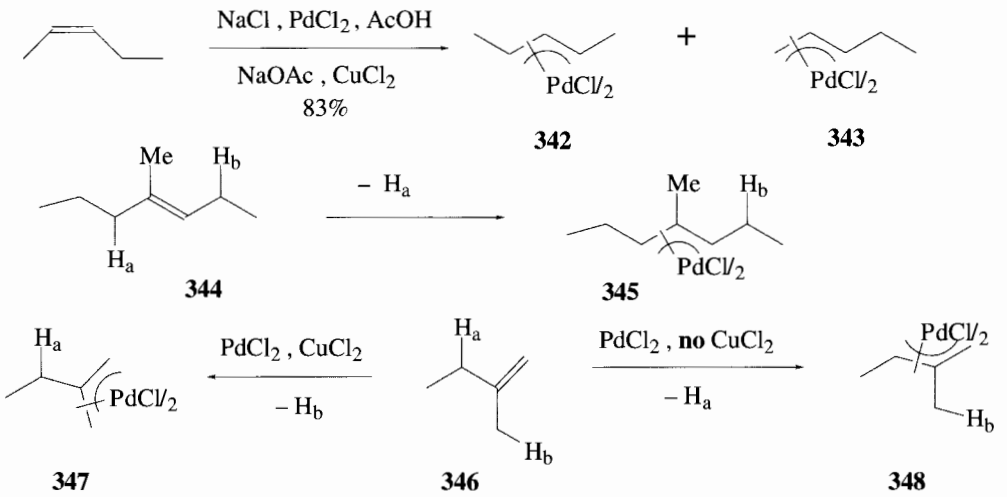
336 337

12.6.B. Formation of π-Allyl Palladium Complexes

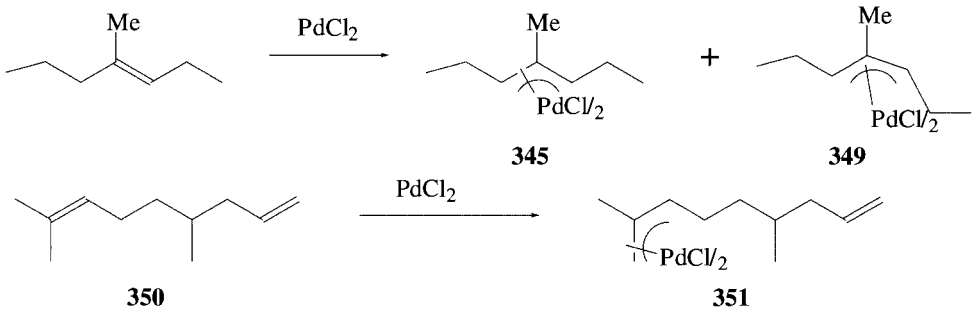
Throughout this chapter, stabilized cations have been used for a variety of transformations. The Wacker process involved alkenes but when the alkene has an allylic position, a new type of organometallic can be formed with palladium reagents. 1-Propene, for example, reacts to give a π-allyl metal complex such as **338**, stabilized by back-donation from the metal atom. Substitution reaction of this π-allyl complex with a suitable nucleophile will generate the allylic species, **339**, where X is the nucleophile. Early work by Hüttel and Christ[215] and also Volger[216] established that π-allyl complexes could be prepared, but often in very poor



yield.[215c] This low yield was probably due to preferential formation and attempted oxidation of a hydropalladium species such as **340** (derived from cyclohexene), which readily decomposed. It was later discovered that oxidation of **340** converts it to the more stable halo-bridged dimer (**341**).[217] This observation allowed π-allyl palladium complexes to be examined for their synthetic utility. Trost reacted allylic compounds with disodium tetrachloropalladate (Na_2PdCl_4), in the presence of sodium acetate (NaOAc) and acetic acid (AcOH), and found that halogen dimers were formed. The alkene was used in excess, and a ratio of 2:1 alkene/Pd was optimal. A variety of alkenes can be converted to their palladium complex using Trost's conditions, including (*Z*)-2-pentene, which generated an 87:13 mixture of **342/343** in 83% yield.[217]

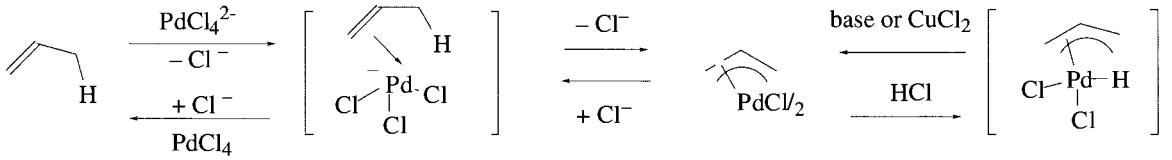


The reaction follows a Markovnikov orientation (see secs. 2.10.A, 6.2.A, 6.3.A), with the removed hydrogen being allylic to the most substituted end (as in the removal of H_a in the conversion **344** → **345**). Addition of cupric chloride ($CuCl_2$) influences the ratio of the Markovnikov-like to the anti-Markovnikov-like product.[217] Palladation of 2-methyl-2-butene without $CuCl_2$ preferentially removed H_a to give **348** (71% **348** + 29% **347**). Addition of $CuCl_2$, however, led to removal of H_b to give 74% of **347** and 26% of **348**.[218] The general order for removal of allylic protons appears to be $CH_3 > CH_2 >> CH$.[217] Conformational effects can alter this order or reactivity, however. The syn-complex usually predominates, as in the reaction of 4-methyl-3-heptene to give **345**. Both (*E*)- and (*Z*)-isomers of the alkene led to the syn-isomer **345**, without a trace of the anti-isomer (**349**).



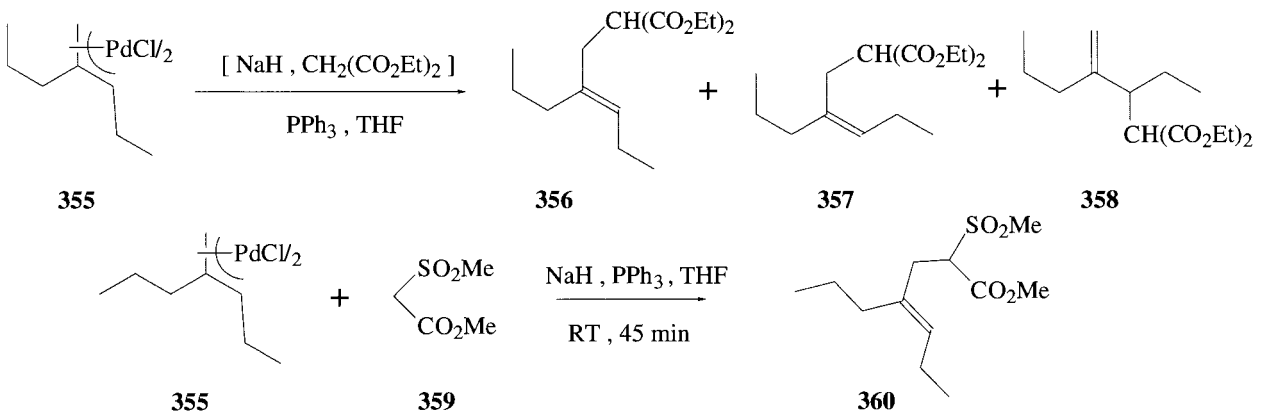
More highly substituted alkenes react faster (trisubstituted > disubstituted > monosubstituted),[218] as illustrated by the reaction of 4,8-dimethylnona-1,7-diene (**350**) to give **351**. Allylic systems conjugated to a carbonyl react slower than unconjugated alkenes. Conjugated alkenes do react if there is no competition.[217,219]

Trost proposed the following mechanism to explain formation of π-allyl complexes from alkenes.[271,216] Initial reaction with $PdCl_4$ generates a π-alkene complex (**352**), which is in equilibrium with the π-allyl palladium hydride complex **353**. The presence of a base (such as an amine or a phosphine) or $CuCl_2$ led to removal of the hydrogen from Pd—H to give the π-allyl palladium dimer **354**. The $CuCl_2$ oxidative procedure is more efficient than addition of a base.



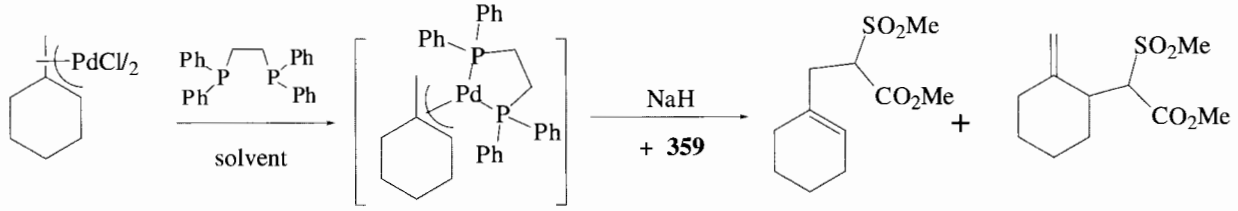
12.6.C. Reactions of π-Allyl Palladium Complexes

Initial reactions with π-allyl palladium complexes involved treatment of this stabilized cation with nucleophiles. Trost found that **355** reacted with diethyl sodiomalonate in the presence of triphenylphosphine (PPh_3). The phosphine acted as a basic ligand and coordinated with the palladium. The major product from reaction with sodium malonate was **356**, formed in 68% yield.[220] This reaction completes the initially set goal (in



sec. 12.1) of forming a new carbon bond by reacting a stable cation with a carbon nucleophile. The distribution of products shows a preference for attack at the less substituted carbon [the ratio (**356**+**357**)/**358** was ≈ 8:1, and the ratio **356**/**357** was 1.6:1]. When **355** reacted with methyl methanesulfonyl sodioacetate (**359**), only one product was observed (**360**), in 80% yield.[220] The extent of attack at the less substituted carbon was dependent on the nature and amount of the added phosphine ligand, as shown in Table 12.18.[220]

Table 12.18. Dependence of Regioselectivity on Ligands in Alkylation of Di-μ-chlorobis(1,2-tetramethylene-π-allyl)dipalladium (II) with Methyl methanesulfonyl Sodioacetate



361 **364** **362** **363**

Ligand	Solvent	Yield (%)	%362	%363
Triphenylphosphine	DMSO	75	62	38
	THF	81	89	11
Tributylphosphine	DMSO	100	100	
	THF	57	90	10
1,2-Bis(diphenylphosphino)ethane (dppe)	DMSO	64	76	24
	THF	100	75	25
1,3-Bis(diphenylphosphino)propane (dppp)	DMSO	100	75	25
	THF	72	78	22
Diphenyl-*o*-tolylphosphine	DMSO	66	54	46
	THF	53	87	13
Tri-*o*-tolylphosphine (TOT)	DMSO	90	18	82
	DMSO	79	12	88
	THF	0		
Tri-*o*-anisylphosphine	DMSO	80	70	30
Tri-*o*-trifluoromethylphosphine	DMSO	79	49	51
Hexamethylphosphorus triamide (HMPT)	DMSO	58	100	
	THF	90	100	
Trimethylphosphite	DMSO	91	87	13
	THF	88	91	9
Triphenylphosphite	DMSO	86	93	7
	THF	69	91	9
N,N,N',N'-Tetramethylethylenediamine (TMEDA)	DMSO	12	66	34
	THF	17	100	
Triphenylarsine	DMSO	4	62	38
	THF	86	100	
None	DMSO	0		
	THF	0		
	HMPA	0		

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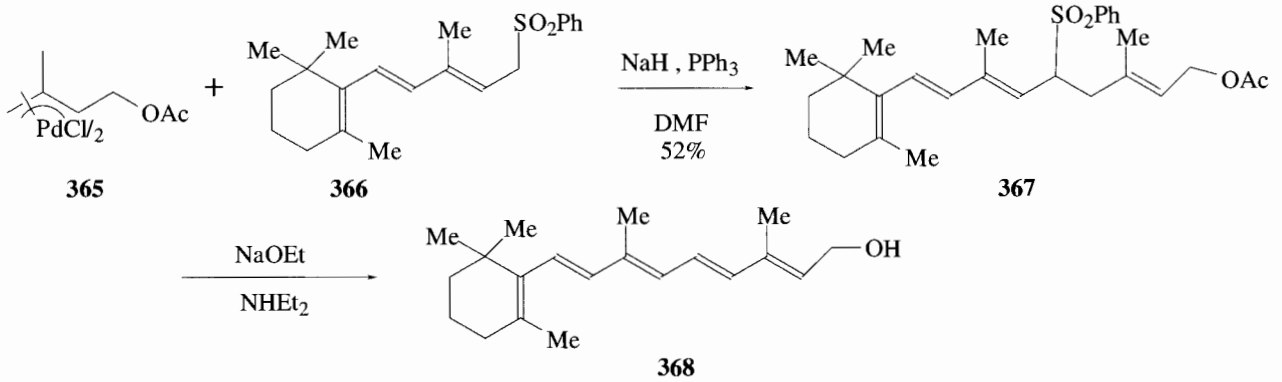
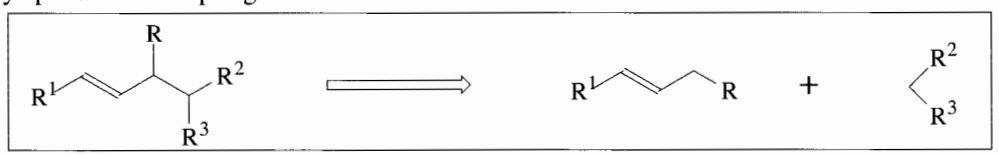
Many common ligands are shown there. It is seen that **361** was converted to the π-allyl complex with various ligands and reacted with methyl methanesulfonyl sodioacetate (**359**) to form a mixture of **362** and **363**. A variety of carbanion nucleophiles can be reacted with π-allylpalladium complexes.[221]

If TOT was used in place of HMPT, the regioselectivity was reversed,[221] as seen in Table 12.18. Although the coordinating ligand is critically important, there does not seem to be a strong solvent effect on the stereochemistry of the reaction. Addition of bis(phosphine) ligands, such as dppe, generates a complex such as **364** rather than the dimeric palladium chloride structure observed previously. Reaction of **361** with **359** in the presence of dppe gave a 4:1 mixture of **362** and **363**. This methodology has many applications in synthesis. One example is Marchand's reaction of **365** and the allylic sulfone anion (from **366**) gave a 52% yield of **367**. Elimination of the sulfone moiety generated vitamin A alcohol **368**.[222]



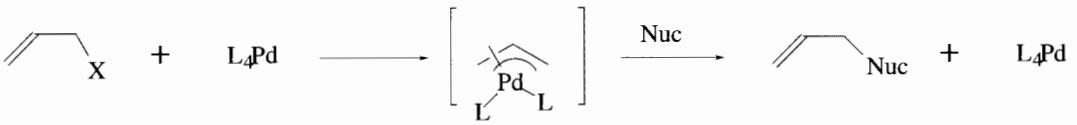
365 **366** **367** **368**

The π-allyl palladium coupling disconnections are



12.6.D. Catalytic π-Allyl Palladium Reactions

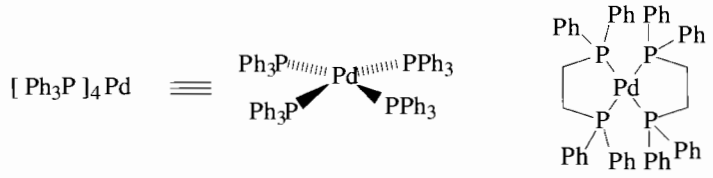
The entire allyl palladium alkylation process discussed in Sections 12.6.A and 12.6.B can be made catalytic in palladium. The basis for this catalytic activity involves the use of an allylic substituted species (**339**, allylic acetate, allylic chloride, etc.) rather than an allylic hydrocarbon. A *tetrakis*-palladium(0) complex (L_4Pd) reacts with the allylic substrate to form a π-allyl palladium complex (**369**). Substitution with a nucleophile generates **370** with liberation of palladium species L_4Pd, which is recycled to react with additional **339**.[223]



339 **369** **370**

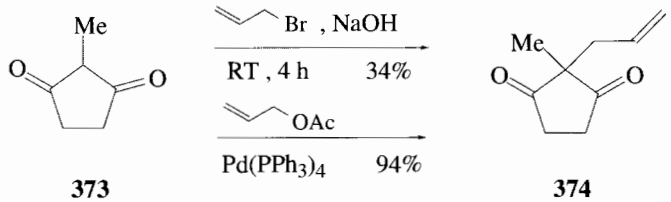
Two of the common Pd(0) catalysts are the commercially available *tetrakis*-(triphenylphosphino) palladium (**371**) and bis-[1,2-bis-(diphenylphosphino)ethane] palladium (**372**). They can be prepared by reduction of

palladium acetate [$Pd(OAc)_2$] in the presence of triphenylphosphine or bis-1,2-diphenylphosphinoethane.[223c,d] The use of these ligands was important to the reactions discussed in with Table 12.18.



371 **372**

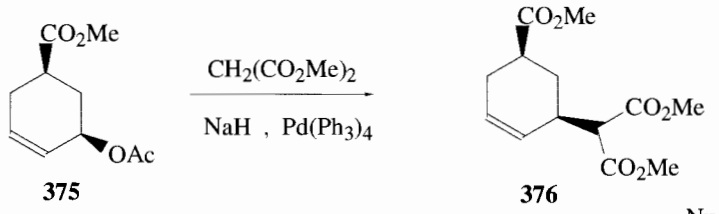
12.6.D.i. Reactions with Nucleophiles. Previously, a π-allylic palladium complex was generated by reaction of palladium reagents with allylic hydrocarbons prior to reaction with nucleophiles. In the catalytic version of this reaction, an allylic halide or an allylic acetate is used with a palladium(0) reagent. Why use a palladium complex when enolate alkylation is a well-known process (sec. 9.3.A)? A typical enolate coupling reaction is the conversion of 2-methylcyclopentane-1,3-dione (**373**) to the enolate anion by reaction with NaOH, allowing reaction with allyl bromide. Under these conditions only 34% of **374** was obtained. When allyl acetate was used in place of allyl bromide in this reaction and *tetrakis*(triphenylphosphino)palladium was used as a catalyst, a 94% yield of **374** was obtained.[224] In this reaction, formation of the π-allyl palladium complex facilitated coupling with the nucleophilic enolate derived from **373**, which exhibited poor reactivity in the normal enolate alkylation sequence.



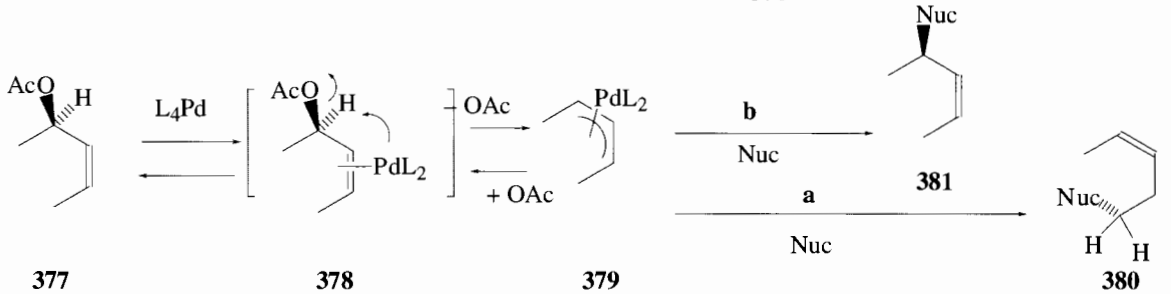
373 **374**

As alluded to above, this version of the π-allyl palladium reaction uses an allylic acetate or chloride. The use of the acetate is more common because acetate is a much weaker nucleophile than chloride. When it involves a substrate where diastereomeric products can result, the stereochemistry of the nucleophilic displacement is an important issue. Palladium assisted alkylation proceeds with net retention of configuration of the acetate or chloride, as seen in the conversion of **375** to **376**.[223e,f]

Trost proposed the following mechanism to account for these catalytic transformations. Reaction of the palladium catalyst with **377** generates π-alkene palladium complex **378**. Palladium removes the allylic hydrogen, with expulsion of the acetate moiety to generate the π-allyl palladium complex (**379**). Attack of a nucleophile at C_a leads to **380**, with expulsion of the PdL_2 species, whereas attack at C_b leads to **381**. Palladium coordinates on the face of the alkene *distal* to the acetate (distant from the acetate: C_a rather than C_b). Palladium displaces acetate with inversion (**378** → **379**). When the nucleophile displaces the palladium, a second inversion occurs at C_a or C_b, whichever is less sterically hindered, to give a net retention of configuration for the conversion **377** → **380** and/or **381**.

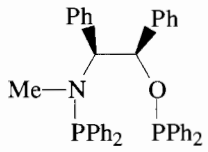


375 376

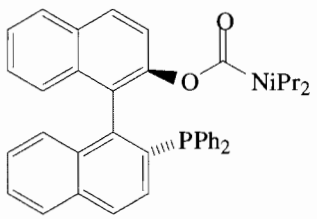


377 378 379 380

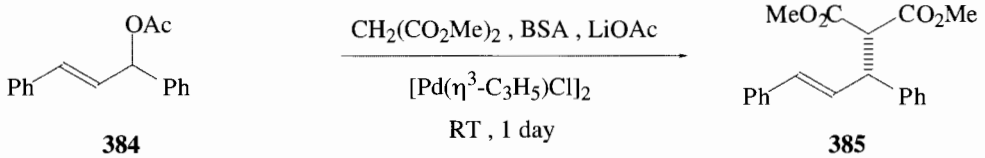
When chiral ligands are used with the palladium catalyst, good enantioselectivity can be achieved in the alkylation reaction. Two ligands that have been used are the bis(phosphine) complex derived from chlorodiphenylphosphine and optically active amino alcohols, such as **382**.[225] Phosphino-ester ligands such as **383** derived from 2'-binaphthyl have also been used.[226] The enantioselectivity can be quite good, as when allylic acetate **384** reacted with diethyl malonate, in the presence of **383** and *N,O*-bis(trimethylsilyl)acetamide (BSA) and LiOAc as additives, to give an 89% yield of **385**, with 99% ee.[226] The identical reaction with **384**, but using **382** as a ligand, gave a 93% yield of **385**, but in 56% ee.[225]



382

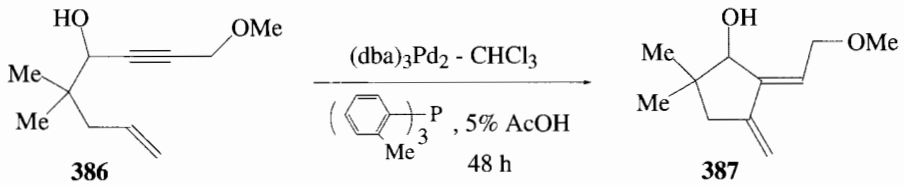


383

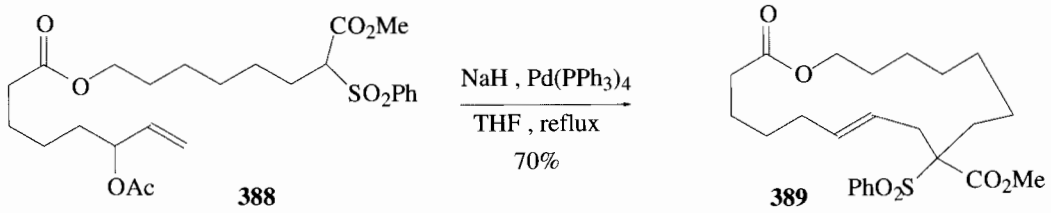


384 385

12.6.D.ii. Palladium Mediated Cyclization Reactions. It is possible to use organopalladium chemistry for cyclization reactions. Treatment of **386** with the palladium catalyst ([dba]$_3$Pd$_2$, where dba = dibenzylidene acetone) led to cyclization that generated a five-membered ring (**387**) in 78% yield.[227]

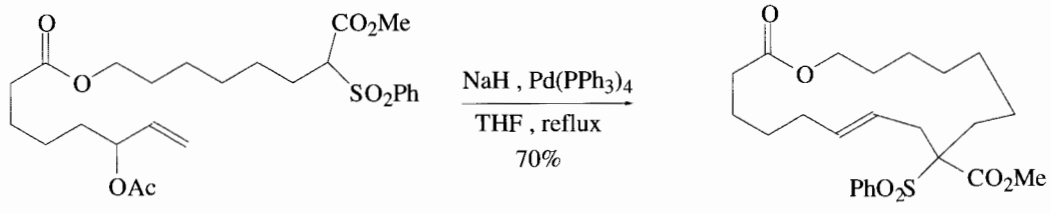


386 387



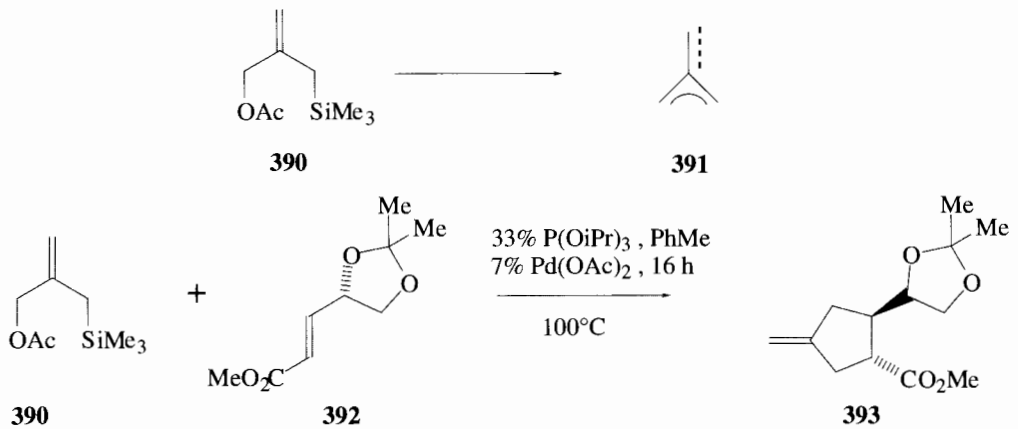
388 389

Since the π-allyl species is bound to palladium, there is a template effect in the π-allyl palladium reactions that can be exploited to form large rings (sec. 6.6.B).[228] Ester **388** was converted to **389** in 70% yield by this procedure, but the yields have been poor in some cases.[228]



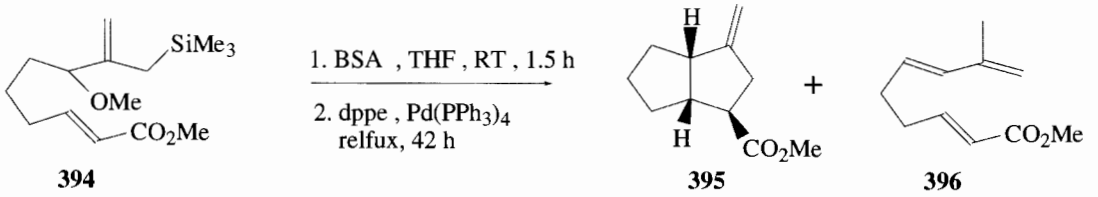
388 389

12.6.D.iii. Trimethylenemethane Equivalents. Palladium catalysts can be used to convert trimethylsilyl acetate **390** to a trimethylene methane (TMM, **391**) equivalent. Reaction with alkenes via [3+2]-cycloaddition (sec. 11.11) generates cyclopentanes (this process constitutes a **quinane annulation** reaction).[229] In this reaction, the trimethylsilyl unit is a carbanion equivalent and acetate is a carbocation equivalent. In one example, Trost reacted **390** and **392** with palladium acetate and triisopropyl phosphite [P(O*i*-Pr)$_3$] to generate **393** in



390 392 393

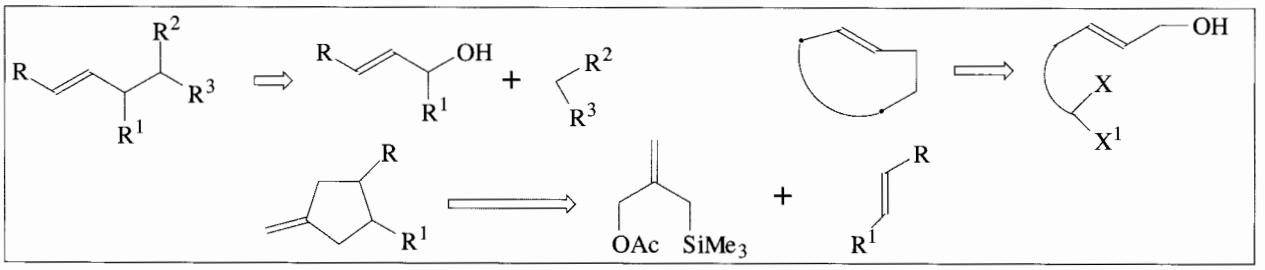
87% yield.[230] The reaction is characterized by retention of the geometry of the dipolarophile in the cycloadduct and proceeds with high diastereoselectivity and good regioselectivity. Trost used **393** in a synthesis of brefeldin-A.[230] This reaction can also be applied to the formation of larger rings if a diene is used as the dipolarophile.[231] Trost later showed that *Z*-alkenes show greater selectivity in this cyclization process.[232] Reagents related to **390** react with aldehydes as well as alkenes to produce THF derivatives.[233] Alkynes also react with TMM equivalents to form methylenecyclopentene derivatives.[234]



394 **395** **396**

When TMM equivalents are tethered to alkenes, intramolecular cyclization generates bicyclic methylenecyclopentane derivatives. Cyclization of **394**, for example, led to a 51% yield of **395** along with 18% of the uncyclized triene, **396**.[235] The cyclization reaction proceeded with excellent diastereoselectivity, as shown. Trost has also examined the attachment of chiral auxiliaries to the alkene partner to give asymmetric induction in reactions with TMM equivalents.[231]

The disconnections for catalytic allyl palladium reactions are essentially the same as for the uncatalyzed version. A few representative examples are

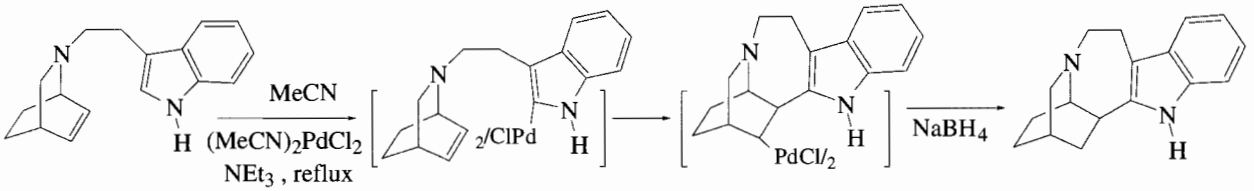


12.7. Palladium Coupling Reactions

As organometallic chemistry in general, and organopalladium chemistry in particular, have become more popular, many new reactions have been developed. Several of these are so useful that they have joined the list of named reactions. This section will explore several of these named reactions that involve palladium catalysts.

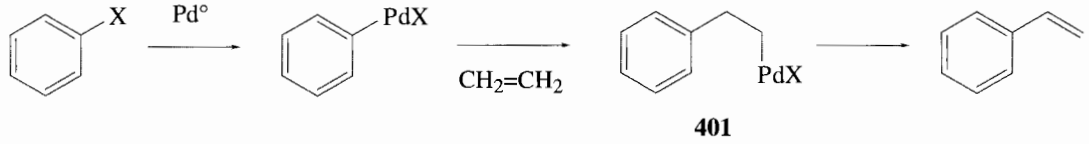
12.7.A. The Heck Reaction

There are several variations of the organopalladium reaction, some involving alkenyl palladium and others σ-palladium complexes. One variation generates the palladium species from a heterocyclic alkene. Trost used bis(acetonitrile) palladium chloride to convert **397** to desethylibogamine (**400**) by this method.[236] Initial reaction of the palladium with the enamine moiety of **397** generated **398**, and cyclization with the allylic amine moiety gave **399**. Sodium borohydride was required to reduce the initially formed palladium chloride species to **400**. Organopalladium species are commonly used in coupling reactions of alkenes, alkynes, and aryls.[237]

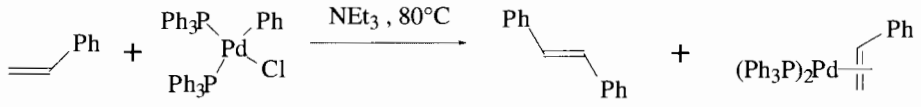


397 **398** **399** **400**

The aryl palladium complexes that are formed via oxidative coupling of aryl halides with palladium(0) can undergo the **Heck reaction**.[238,239] The Heck reaction is the coupling of aryl halides or aryl sulfonate esters with alkenes.[240] The reaction proceeds with formation of a palladium species such as **401**, with elimination of palladium to give arylated alkene derivatives.[241] Aryl halides differ greatly in their reactivity, ArI being the most reactive, followed by aryl bromides. In general, aryl chlorides are very unreactive in the Heck

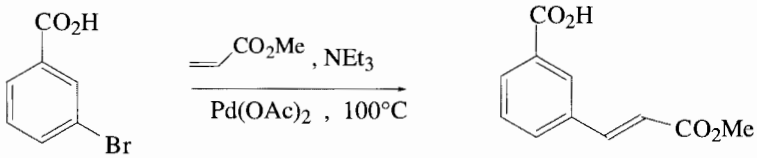


401



402 **403**

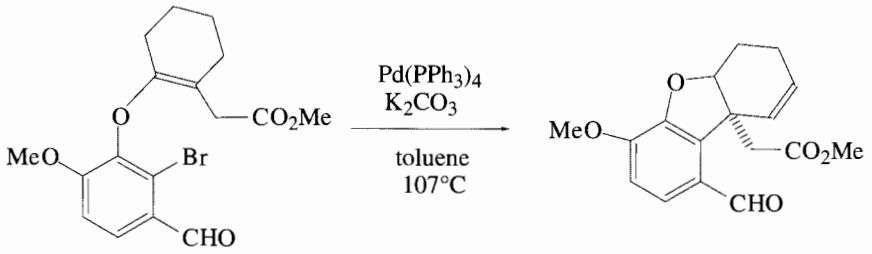
reaction unless the chlorine is attached to a heteroaromatic ring. Aryl triflates have become popular partners in this reaction. This coupling occurs with many alkenes and aryl derivatives. Styrene reacted with phenylbis(triphenylphosphino)palladium chloride (**402**), in the presence of triethylamine, to give *trans*-stilbene, with loss of the palladium complex **403**.[242] The palladium reagent (**402**) was generated *in situ* by reaction of palladium acetate [$Pd(OAc)_2$] and triphenylphosphine, in the presence of an aryl halide such as iodobenzene.



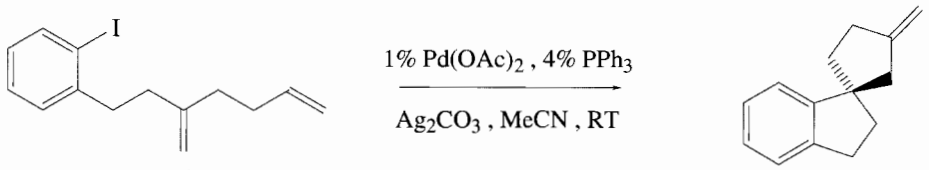
404

The stereochemistry of the reaction product is explained by syn addition of the organopalladium followed by syn elimination of palladium hydride.[242] The use of chiral ligands allows asymmetric induction in some Heck reactions.[243] Conjugate addition is usually preferred when the alkene contains an electron-withdrawing group. Without such a group, addition occurs at the less sterically substituted carbon.[242] 3-Bromobenzoic acid, for example, reacted with ethyl acrylate under these conditions to give **404** in 67% yield.[242] 2-Iodoanisole was coupled to cyclopentene at the allylic position under similar conditions.[244] New catalysts have been developed, however, that allow Heck coupling with deactivated aryl chlorides.[245] Beller showed that chlorobenzene reacted with styrene, for example, to give *trans*-stilbene in 63% yield in the presence of K_2CO_3 and a palladium catalyst having a di(1-adamantyl)-*n*-butylphosphine ligand.[245]

An intramolecular version of this reaction is known.[246,247] An example of this variation is taken from Fels' synthesis of the galanthamine ring system,[248] where treatment of **405** with $Pd(PPh_3)_4$ in hot toluene gave a 66% yield of **406**. A very interesting example is the palladium-catalyzed polyene cyclization of dienyl aryl iodides, reported by Overman and co-workers.[249] In a typical example, **407** was treated with 1 mol% of $Pd(OAc)_2$, 4% PPh_3, and 1 equivalent of Ag_2CO_3 in acetonitrile and gave an 86% yield of spirocycle **408**.

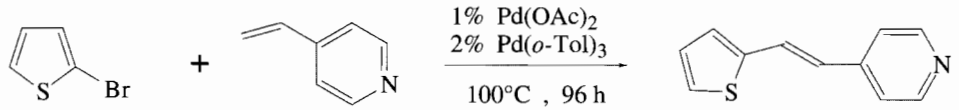


405 **406**

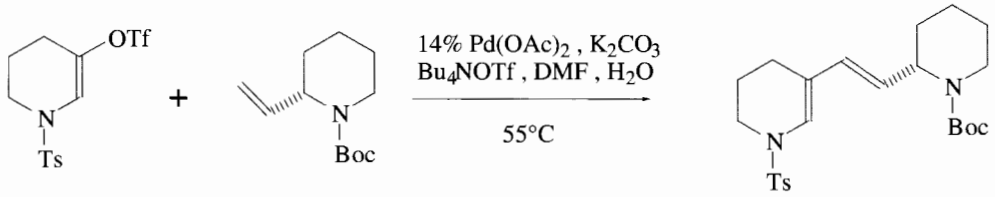


407 **408**

Heterocyclic halides and alkenes can be coupled by the Heck reaction. For example, 2-bromothiophene (**409**) and 4-vinylpyridine (**410**) reacted to a give 57% yield of **411**.[250] The Heck reaction can also be applied to vinyl halides,[251] and vinyl triflates. Pure cis or trans alkenes can isomerize to a mixture of cis and trans products.[251] In some cases, however, the selectivity is good, as can be seen in Overman's synthesis of (+)-aloperine.[252] In this work, vinyl triflate **412** reacted with **413** to give an 83% yield of the coupled product **414**, with high selectivity for the (*E*)- alkene unit of the diene. Although the enantiopurity of **414** was 97% ee, deprotection of the Boc group with trifluoroacetic acid led to racemization of the resultant diene.[252] This was remedied by using other reagents to deprotect the nitrogen.



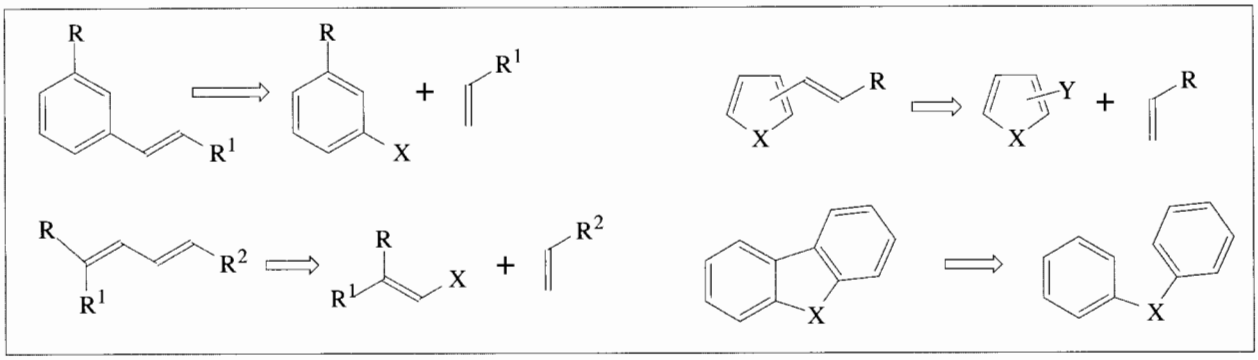
409 **410** **411**



412 **413** **414**

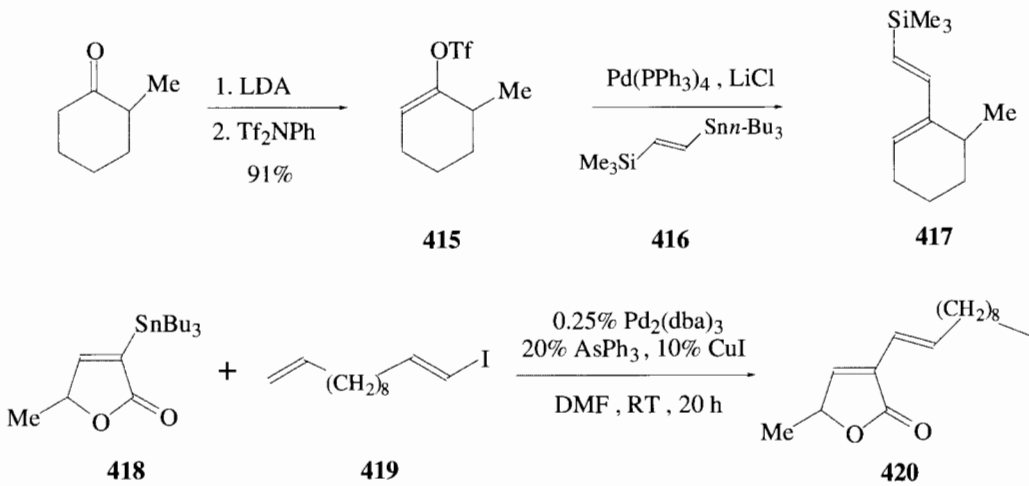
There are several variations that involve heteroatom substituents, including biaryl ethers, amines, and ketones, which can be coupled to alkenes using palladium acetate.[253] Silyloxyalkenes (silyl enol ethers) can also be coupled to another alkene upon treatment with palladium acetate, to form conjugated ketones.[254] The solvent can be changed if the reactive partners are changed. Aryldiazonium salts can be coupled to alkenes with palladium acetate in aqueous media.[255a] Carbohydrate-based vinyl bromides have been coupled to methyl acrylate using $Pd(dba)_2$ in aqueous DMF.[256] Alkynes have been coupled to pyrrole using Heck-like conditions.[257]

The Heck and related disconnections are

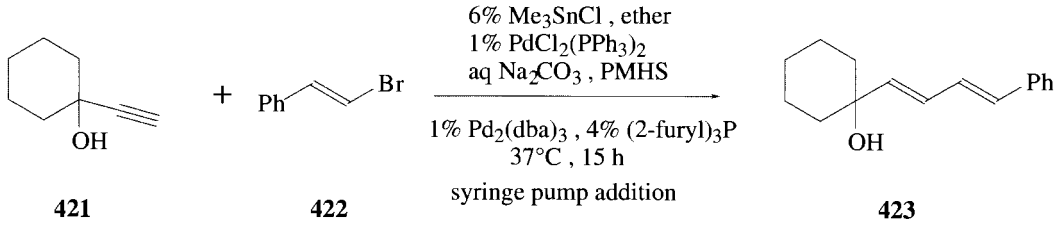


12.7.B. Stille Coupling

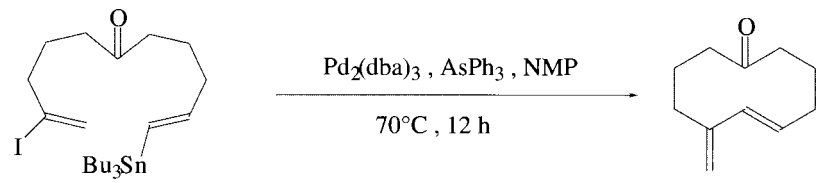
Stille showed that vinyl triflates (C=C-OSO_2CF_3) readily react with vinyltin derivatives to generate dienes, in what is known as the **Stille coupling**.[258,259] One way to prepare the requisite vinyl triflate (see **415**) is illustrated by trapping the enolate of 2-methylcyclohexanone (sec. 9.2, 9.3.B) with *N*-phenyl triflimide.[260] When **415** was treated with the vinyltin compound **416** in the presence of a Pd(0) reagent, diene **417** was formed quantitatively as a 95:5 (*E,E*)/(*E,Z*) mixture.[260] Putting together two different alkene units in this way has been referred to as Stille cross-coupling. In Sweeney's synthesis of (+)-hamabiwalactone B, (**420**),[261] tributyltin lactone **418** was coupled to vinyl iodide **419**, giving a 46% yield of **420**.



The Stille coupling has been shown to be catalytic in tin.[262,263] Reaction of alkyne **421** with vinyl bromide **422**, in the presence of a palladium catalyst and 6% Me_3SnCl, for example, gave a 90% yield of **423**, which required syringe pump addition of the vinyl bromide over 15 h to the rather complex reaction medium, but the yields were quite good. A method has been developed that allows the coupling with aryl chlorides.[264] There has been increasing interest in intramolecular Stille reactions in organic synthesis.[265] A specific example is taken from Hodgson's synthesis of (–)-periplanone B,[266] in which cyclodecenone **424** was prepared in 96% yield by Stille coupling of **425**.

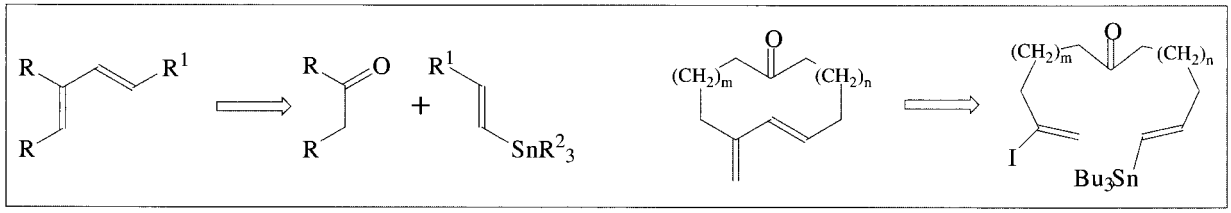


421 **422** **423**



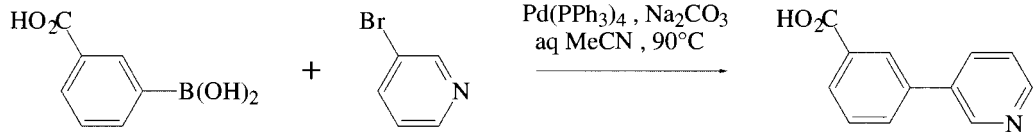
424 **425**

The Stille coupling disconnections are



12.7.C. Suzuki Coupling

This reaction involves organoboronic acids [$RB(OH)_2$] and could be included in chapter 5 with organoborane chemistry. The chemistry is sufficiently different from that presented in Chapter 5, and involves organopalladium catalysts so it is presented with the Heck reaction and Stille coupling. This assumption is reasonable since it may be a synthetic alternative to those reactions.[267]

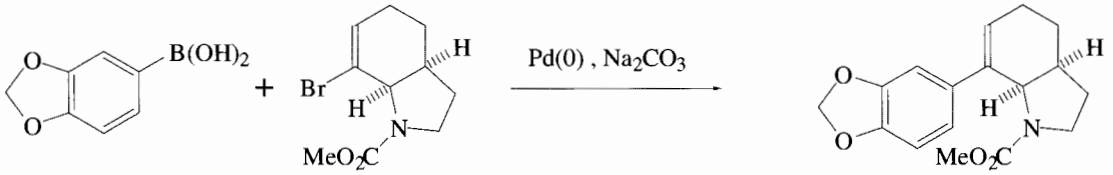


426 **427**

Suzuki and co-workers found that aryl triflates react with arylboronic acids [$ArB(OH)_2$],[268] in the presence of a palladium catalyst, to give biaryls in a reaction that is now known as **Suzuki coupling**.[269] Even hindered boronic acids give good yields of the coupled product.[270] Organoboranes, react with aryl triflates under these conditions as well.[271] In a simple example, boronic acid **426** reacted with 3-bromopyridine in the presence of $Pd(PPh_3)_4$ to give a 90% yield of the biaryl **427**.[272]

The reaction is not restricted to forming biaryls. Aryl boronic acids can also react with vinyl halides and vinyl triflates in the presence of palladium (0). Thallium (I) ethoxide is known to promote Suzuki cross coupling reactions for vinyl or arylboronic acids with vinyl and aryl halide partners.[273] A synthetic example is

taken from Banwell's synthesis of γ-lycorane,[274] in which **428** reacted with the vinyl bromide unit in **429** to give an 87% yield of coupling product (**430**).

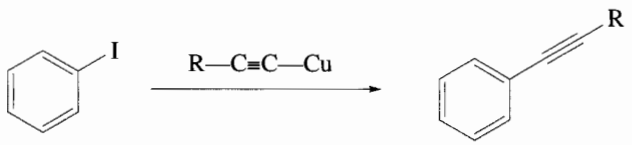


428 **429** **430**

Other catalysts have been used to effect Suzuki coupling reactions. A mixture of $Pd_2(dba)_3$ and tri-*tert*-butylphosphine has proven to be very effective.[275] Nickel on charcoal,[276] rhodium catalysts,[277] and silver oxide mediated palladium catalysts[278] have also been used. The latter catalyst was effective for the preparation of 4-substituted 2(*5H*)-furanones.[279]

12.7.D. Sonogashira and Stephens–Castro Coupling

Under certain conditions, alkynes can be coupled to aryl halides.[280] When aryl halides react with copper acetylides to give 1-aryl alkynes such as **431**, the reaction is known as **Stephens–Castro coupling.**[281] Both aliphatic and aromatic substituents can be attached to the alkyne unit, and a variety of aryl iodides has been used. A palladium–catalyzed variation is also known in which an aryl halide reacts with a terminal alkyne to give derivatives such as **434**. In this variation, called the **Sonogashira coupling**,[282] the reaction is catalyzed by



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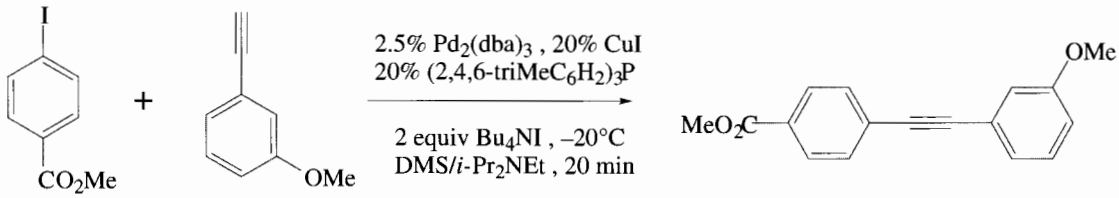


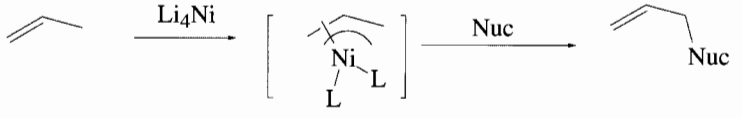
432 **433** **434**

a palladium–copper complex at or near ambient temperatures. Several reaction variations have brought renewed attention to the coupling. The reaction of aryl iodide **432** and alkyne **433**, for example, gave a quantitative yield of **434** but used the complicated catalyst mixture of 2.5% of $Pd_2(dba)_3$, 20% CuI and 20% of the addition tri(2,4,6-trimethylphenyl)phosphine, at –20°C.[283] A combination of $Pd(PhCN)_2Cl_2$ and $(t\text{-Bu})_3P$ has been shown to be very effective for Sonogashira coupling at room temperature,[284] and the reaction has been done without solvent, on alumina, using microwave irradiation.[285]

12.8. π-ALLYL NICKEL COMPLEXES

Nickel can stabilize allylic cations in a manner similar to palladium.[286] Indeed, the use of organonickel complexes for generating carbon–carbon bonds[287] is synthetically older than the analogous organopalladium chemistry. Nickel chloride ($NiCl_2$) is the nickel analog of $PdCl_2$ and reacts similarly to form zero-valent complexes [Ni(0)], which are the reactive species in π-allyl nickel complexes such as **435**. The most common Ni(0) complex is nickel tetracarbonyl [$Ni(CO)_4$], but this is a volatile, *extremely toxic* and dangerous material.

Nickel tetracarbonyl should be used with great caution and only in a specially ventilated hood.



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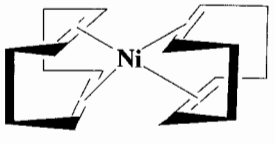

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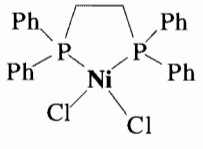

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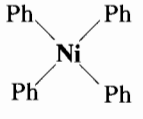
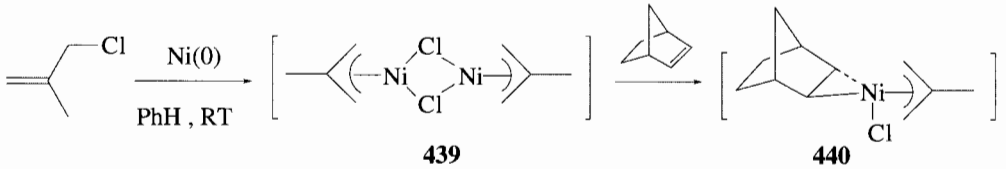
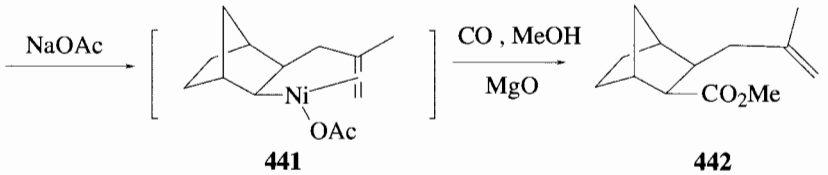


438

Tetrakis(triphenoxyphosphino)nickel is also a useful organonickel reagent. Widely used Ni(0) complexes are the *bis*-complex of nickel and cyclooctadiene (cod), which has the structure **436** [$Ni(cod)_2$], bis(diphenylphosphinoethane)nickel chloride (**437**), and tetraphenylnickel (**438**).



439 **440**

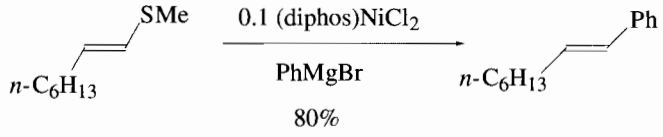


441 **442**

A typical reaction involving nickel(0) treats an allylic halide such as 3-chloro-2-methyl-1-propene with $Ni(CO)_4$ to form **439**,[288] a nickel dimer analogous to the palladium chloride dimer discussed in the previous section. This complex reacts with an alkene to form a new complex (**440**), and subsequent reaction with a variety of electrophilic reagents removes nickel. In this example, the chlorine was converted to an acetate ligand (in **441**) and reacted with methanolic carbon monoxide to give the ester (**442**).[288]

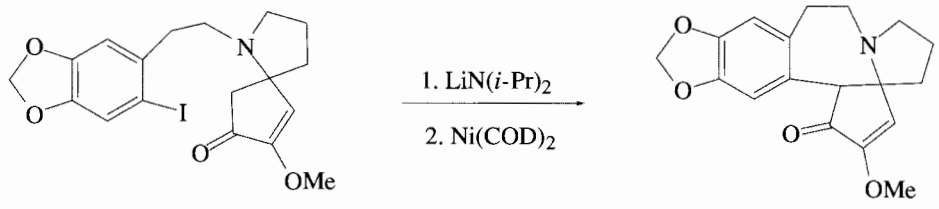
π-Nickel complexes facilitate the coupling of vinyl ethers and vinyl sulfides with Grignard reagents. Wenkert showed that **443** was converted to **444** in 80% yield (as a 4:1 trans/cis mixture) by reaction with

phenylmagnesium bromide and bis-(diphenylphosphinoethane)nickel chloride.[289] Zero-valent nickel can also catalyze the coupling of aryl halides and alkenes.[290,289a,b]



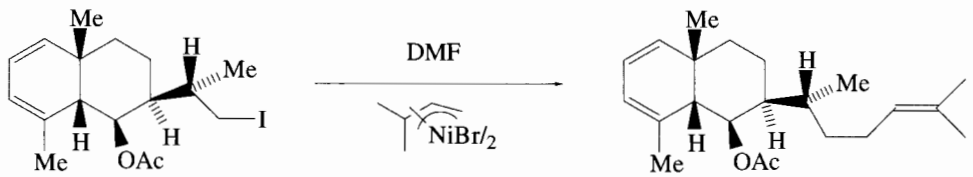
443 **444**

A nickel-catalyzed ene cyclization (sec. 11.13) has been reported that uses $Ni(cod)_2$. The reaction proceeds by initial formation of a π-allylnickel complex, which facilitates the intramolecular ene reaction with an allylic amine unit.[291] π-Allylnickel complexes can be used in coupling reactions with both aryl and alkyl halides. Enolate anions react with nickel(0) reagents to form a complex that subsequently couples to aryl iodides. Semmelhack's final step in the synthesis of cephalotaxinone (**446**) treated **445** with $Ni(cod)_2$ to



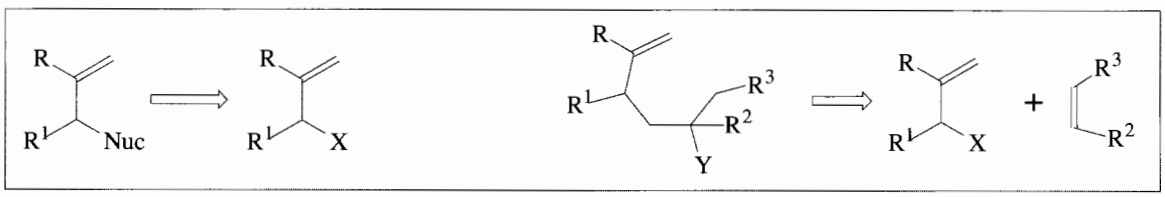
445 **446**

produce it in 94% yield.[292] Nickel coupling reaction with halides is not limited to aryl halides. Alkyl halides also react, as seen in Marshall's coupling of **447** with the π-allyl nickel dimer **448** to give dictyolene **449**.[293]



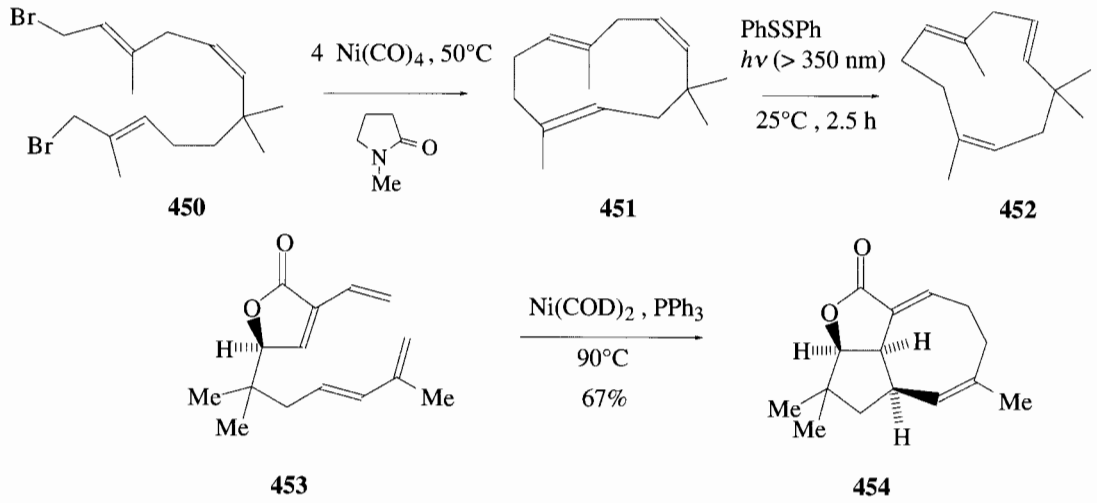
447 **448** **449**

The nickel(0) coupling disconnections are:

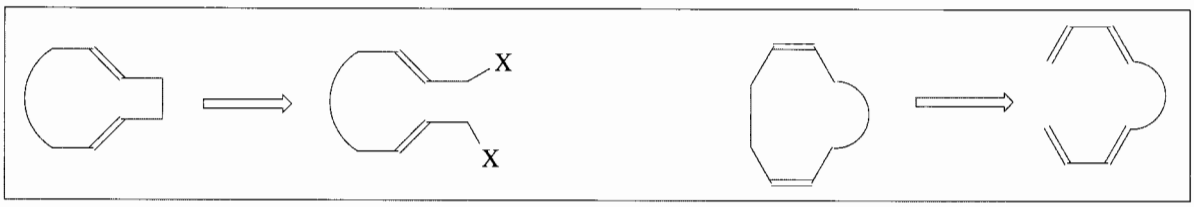


Zero-valent nickel is especially effective for the cyclization of *bis*(allyl) bromides.[294,295] Corey used this technique to cyclize **450** to **451**. Subsequent photolysis in the presence of diphenyl disulfide (PhSSPh) gave humulene, **452**.[294] Wender et al. reported a novel [4+4]-cycloaddition reaction in which two diene moieties are coupled with a nickel(0) catalyst to form eight-membered rings. In Wender's synthesis of asteriscanolide,

453 was converted to **454** in 67% yield using the nickel cyclooctadiene catalyst (**436**). This technique gave < 5% of the [4+2]-cycloaddition product. In this particular case, attempts to use a palladium-catalyzed reaction gave poor yields, presumably due to instability of the vinyl iodide intermediates.[296]



The nickel catalyzed cyclization disconnections are



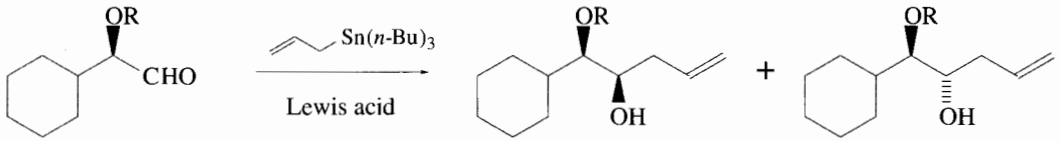
12.9. ALLYLIC TIN, ALKYLTITANIUM, AND ALLYLIC SILANE COMPLEXES

Other metal derivatives can be used for coupling. Among the more popular reagents are allyl- or alkyl-metallic compounds of tin and titanium. Allylsilanes can also be used if a Lewis acid is added.

12.9.A. Allyltin Reagents

In Section 12.7.B, the **Stille coupling** reaction reacted a vinyl tin compound with a vinyl triflate, in the presence of palladium(0).[258] Tetravalent tin complexes add to aldehydes and ketones, in the presence of a Lewis acid. Allyltin complexes are, by far, the most widely used of these compounds.[297] A typical example is taken from the work of Keck, in which a chiral aldehyde (**455**) was treated with allyltributyltin, in the presence of various Lewis acids.[298] As shown in Table 12.19,[298] a mixture of syn (**456**) and anti (**457**) products was obtained. The ratio of **456/457** was dependent on the structure of the R group in **455**, the solvent and the Lewis acid.[298] The anti product (**457**) was obtained by using the *tert*-butyldimethylsilyloxy derivative (sec. 7.3.A.i) of **455** with 2 equivalents of boron trifluoride in dichloromethane. The syn product is obtained preferentially when the benzyloxy derivative of **455** is used with titanium tetrachloride in dichloromethane.[298]

Table 12.19. Condensation of Allyltributyl Stannane with Chiral Aldehydes (453)



455 **456** **457**

R	Lewis Acid	Solvent	(Temperature (°C)	456/457
CH_2Ph	BF_3•OEt_2	CH_2Cl_2	–78	39:61
	$MgBr_2$	Et_2O		94:6
		THF		20:80
		CH_2Cl_2	–23	>250:1
	$MgCl_2$	Et_2O		No reaction
		THF		22:78
		CH_2Cl_2		No reaction
	$Mg(ClO_4)_2$	Et_2O		69:31
	$ZnBr_2$	THF	67°	27:73
		CH_2Cl_2		77:23
		PhMe		41:59
	ZnI_2	Et_2O		35:64
		CH_2Cl_2		97:3
	$TiCl_4$	CH_2Cl_2	–78°	>250:1
$SiMe_2t$-Bu	$TiCl_4$	CH_2Cl_2	–78°	36:64
	$MgBr_2$	CH_2Cl_2		21:79
	ZnI_2	CH_2Cl_2		53:47
	BF_3•OEt_2	CH_2Cl_2	–78°	9:91
	BF_3•OEt_2 (2 equiv)	CH_2Cl_2	–78°	5:95

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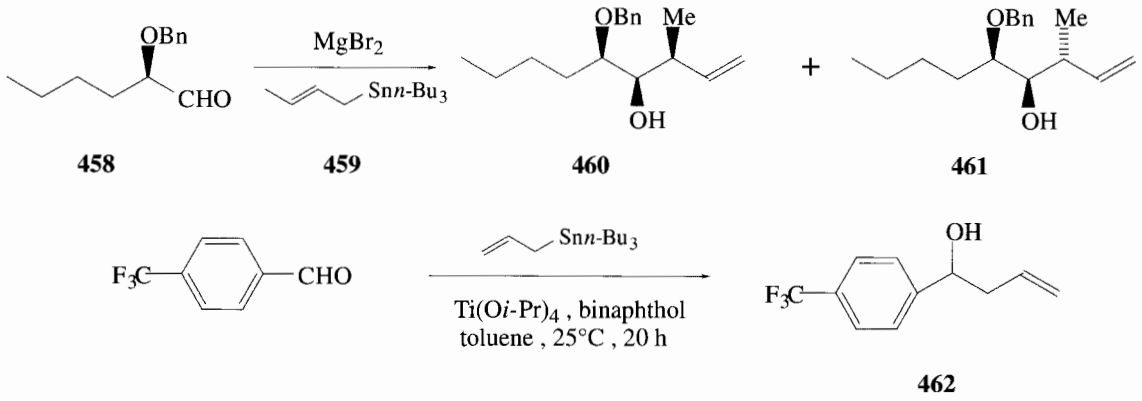
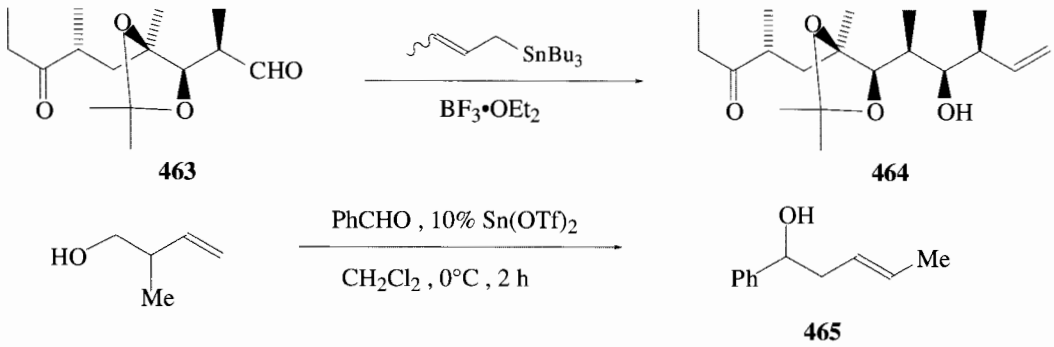
Allyltin coupling is highly diastereoselective with crotyltin derivatives as well as with allyltin compounds. Keck and Boden showed that the reaction proceeded under chelation control and that when **458** was coupled with crotyl tributyl stannane (**459**) in the presence of magnesium bromide ($MgBr_2$), a 90.8% yield of **460** was obtained, along with 9.2% of **461**.[299] As the size of the group attached to the α-carbon of the aldehyde increased, the diastereofacial selectivity increased for the syn diastereomer relative to allyltin compounds. In the example cited, the chelation product exceeded the product predicted by the Felkin–Ahn model (sec. 4.7.B), being formed in a ratio of >200:1. In general, the Felkin–Ahn model (predicting the syn diastereomer) gave the greatest success when BF_3 was used as a catalyst in the presence of diphenyl-*tert*-butylsilyloxy aldehydes.[300] Chelation control with silyloxy derivatives did not contribute significantly to any condensation product,[299a] although $MgBr_2$ gave 91:9 diastereofacial selectivity and 89:11 syn selectivity.[300a] Enantioselective addition of allyltributytin to aldehydes is also possible, using Ti(O*i*-Pr)$_4$ and binaphthol. A chiral complex is formed, and 4-trifluoromethylbenzaldehyde reacted to give a 94% yield of **462**, in 97% ee.[301]

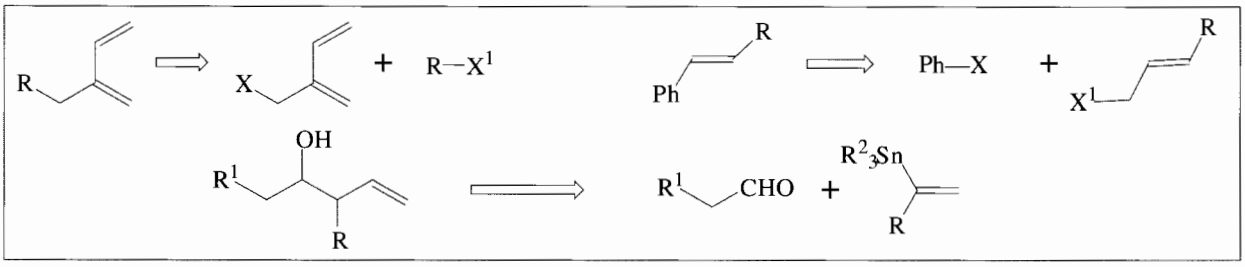


Martin used a tin-coupling reaction in a synthesis of erythronolide A.[302] Keto-aldehyde **463** reacted with the crotyltin compound shown, in the presence of BF_3 to give a 66% yield of the syn-diastereomer (**464**), along with 16% of the anti-diastereomer.

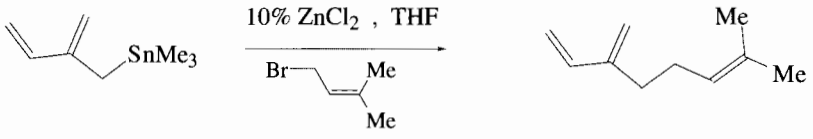


A relative of this reaction can also be used to prepare homoallylic alcohols. When benzaldehyde reacted with 2-methylbut-3-en-1-ol, a 78% yield of **465** was obtained as a 49/1 (*E*/*Z*) mixture.[303] Tin-catalyzed addition of the alcohol substrate to the aldehyde followed by a [3,3]-sigmatropic rearrangement led to the products. Clearly, this is not the same reaction, but it is useful to compare it with the other reactions.

The allyltin disconnections are



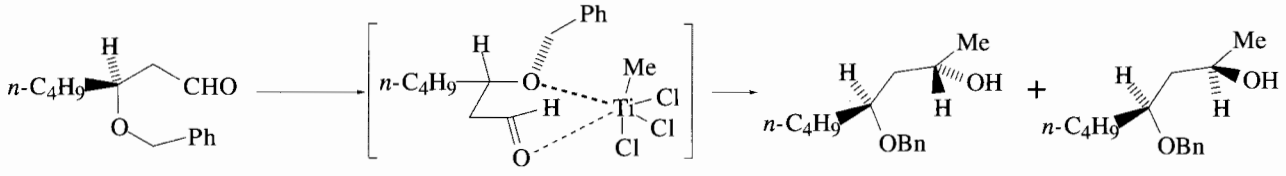
Other allyl metal complexes can be used to generate carbon bonds, including allyl zinc complexes. Stille showed that 3-methyl-1-bromo-2-butene reacted with zinc chloride ($ZnCl_2$) to generate the π-allyl zinc species. Coupling required the use of an organotin species such as α-trimethyltin isoprene (**466**). Reaction in refluxing THF led to a 94% yield of myrcene (**467**).[303]



466 **467**

12.9.B. Alkyltitanium and Allylsilane Reagents

A related coupling reaction is the condensation of aldehydes with alkyl trichlorotitanium compounds ($RTiCl_3$). When methyltrichlorotitanium ($MeTiCl_3$) was coupled with aldehyde **468** in dichloromethane at –78°C, a 91:9 mixture of **470/471** was formed via the chelated complex **469**.[304] Sakurai and co-worker had previously noted the coupling of allylsilanes to aldehydes in the presence of $TiCl_4$.[305]

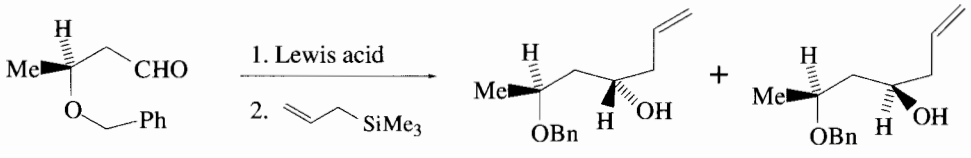


468 **469** **470** **471**

Another variation of this reaction couples an aldehyde with an allylsilane (rather than an allyltitanium species), in the presence of a Lewis acid. Reetz et al. used $TiCl_4$, $SnCl_4$, BF_3, and $AlCl_3$ in the reaction of **472** and trimethylallylsilane to produce **473** and **474** with good diastereoselectivity, as shown in Table 12.20.[306]

Heathcock and co-worker examined a similar coupling with chiral aldehydes, but the stereogenic center was the α-carbon (as in **475**) rather than the β-carbon (as in Reetz's **472**). Aldehyde **475** gave **476** and **477** upon reaction with allyltrimethylsilane.[307] Using tin tetrachloride ($SnCl_4$) as a catalyst provided better syn selectivity in the products (**476** and **477**) than did BF_3 or $TiCl_4$ ($TiCl_4$ did not catalyze this coupling reaction).[307] As with the allyltin complexes, these results are explained by chelation control.

Table 12.20. Reaction of 472 with Allyltrimethylsilane and Various Lewis Acids



472 **473** **474**

Lewis acid	Reaction Temperature (°C)	Solvent	Time (h)	473/474
$TiCl_4$	–78°	CH_2Cl_2	2	95:5
$SnCl_4$	–78°	CH_2Cl_2	2	95:5
BF_3•OEt_2	–78°	CH_2Cl_2	2	85:15
		THF	2	NR
2 BF_3 (gas)	–78°	CH_2Cl_2	2	91:9

$AlCl_3$[b]	–78°	CH_2Cl_2	2	NR
	+22°	CH_2Cl_2	2	a
$AlCl_3$[c]	–78°	CH_2Cl_2	2	89:11
$ZnCl_2$[b]	–78°	CH_2Cl_2	2	NR
	+22°	CH_2Cl_2	2	NR
$SbCl_5$	–78°	CH_2Cl_2	2	a
	–100°	CH_2Cl_2	0.25	a
	+22°	CH_2Cl_2	2	NR

[a] Extensive decomposition. [b] Significant insolubility. [c] Complexed for 2 h prior to addition of substrate.

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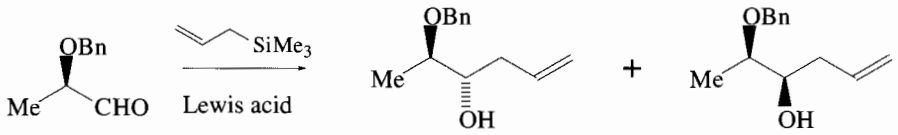
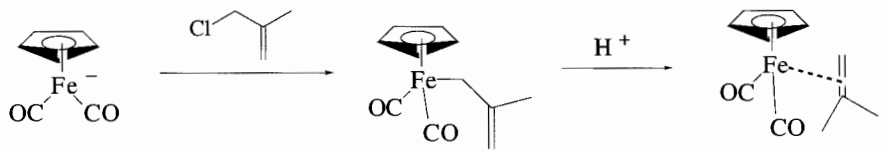


475 **476** **477**

12.10. ELECTROPHILIC IRON COMPLEXES

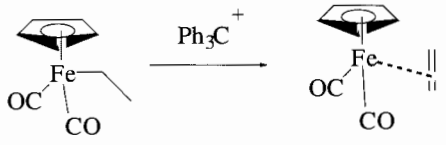
12.10.A. Alkene and Diene Iron Complexes

In iron reactions where the reagent was equivalent to C^d, described in Section 8.9.A, the iron moiety was used as an auxiliary. Iron can also stabilize cations, which then react with nucleophiles to generate new carbon–carbon bonds.[308] These cations are formed as iron–alkene complexes, usually by reaction of cyclopentadienyl dicarbonyl ferrate anion (**478**) with an allylic halide such as 3-chloro-2-methyl-1-propene. The



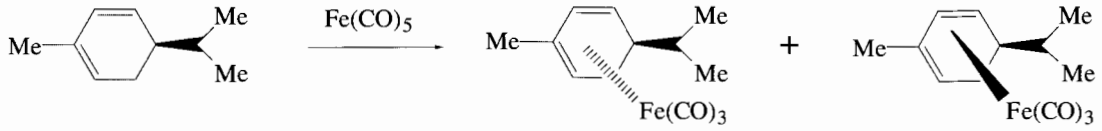
478 **479** **480**

initial product is the σ-iron adduct (**479**). Subsequent reaction with an acid generates the π-iron complex **480**, where the double bond acting as a two-π-electron donor.[309] An alternative preparation treats an alkyl cyclopentadienyl dicarbonyl ferrate (**Fp**) complex (such as **481**) with trityl cation (Ph_3C^+) to form **482**.[310] Diene complexes can also be formed by reaction iron pentacarbonyl [$Fe(CO)_5$].[311] The presence and nature of the



481 **482**

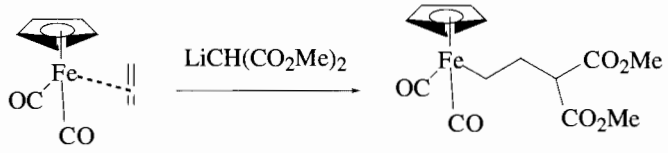
substituents on the diene will influence the regiochemical outcome of the complex, as does the method of preparation. Treatment of **483** with iron pentacarbonyl under thermal conditions, for example, gave a 4:1 mixture of **484** and **485**, with greater selectivity for reaction at the unhindered face. Photolysis, however, led to a 1:1 mixture of **484** and **485**.[312] Treatment of an unconjugated dienes with iron pentacarbonyl led to conjugated dienyl complexes, which were converted to the isomeric π complexes with trityl cation.[313]



483 **484** **485**

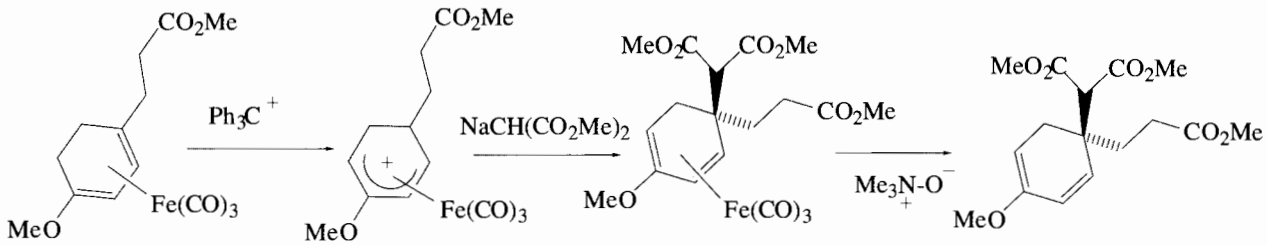
12.10.B. Reactions of Iron Complexes with Nucleophiles

Alkyl iron complexes behave as electrophiles in the presence of nucleophiles. Rosenblum and co-worker showed, for example, that the ethene complex of cyclopentadienyl dicarbonyl iron (abbreviated as **Fp**), Fp–ethene (**482**), reacted with dimethyl lithiomalonate to give **486**.[314] Conjugated iron complexes can also be prepared.[313]



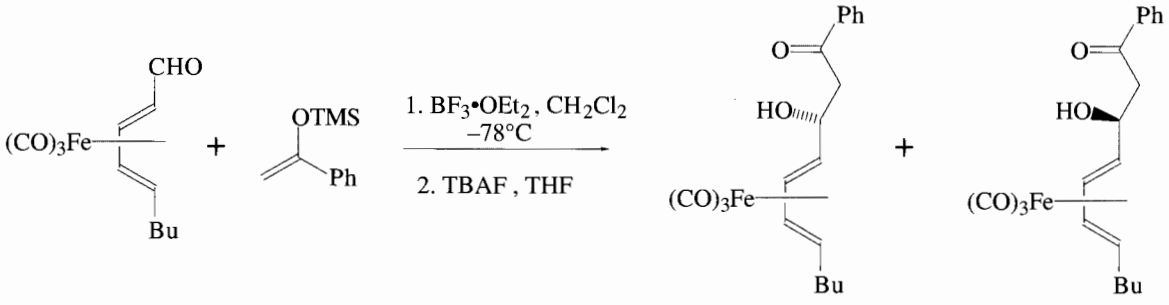
482 **486**

These Fp–alkene complexes react with a variety of other nucleophiles,[315] including water, alcohols, amines,[316] phosphines, and thiols as well as carbon nucleophiles (enamines, organocuprates, enolates),[317,318] and dialkyl cadmium reagents.[319] Diene complexes such as **487** were converted to the corresponding cationic complexes (**488**), for example, and reaction with malonate gave **489**. The iron complex was removed with trimethylamine N-oxide (Me_3N-O) to give **490**.[320]

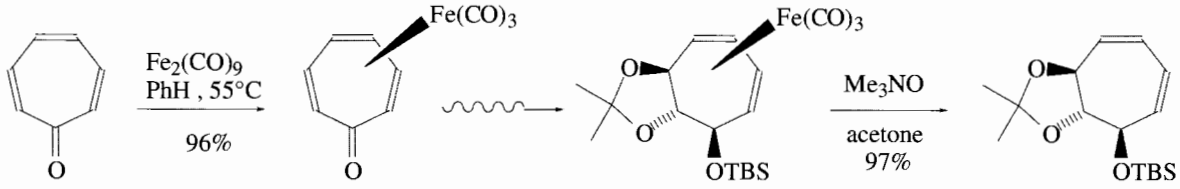


487 **488** **489** **490**

It is interesting that iron carbonyl can be used as a protecting group for dienes. Iron diene complex **491**, for example, reacted with **492** in a Mukaiyama aldol reaction (sec. 9.4.C), giving an 81% yield of **493** and **494** in an 84:16 ratio.[321] In a synthesis of heptitol derivatives,[322] Pearson protected tropone as the iron tricarbonyl derivative (**495**), and prepared **496** using a multistep sequence before deprotecting the diene to give **497**.

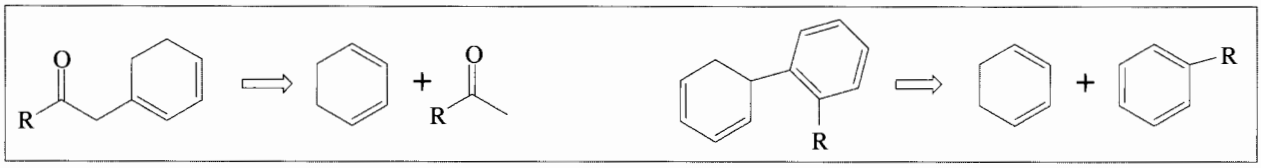


491 **492** **493** **494**



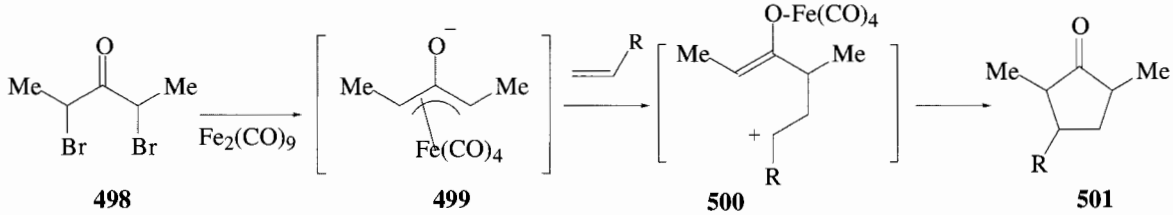
495 **496** **497**

The disconnections for this section are



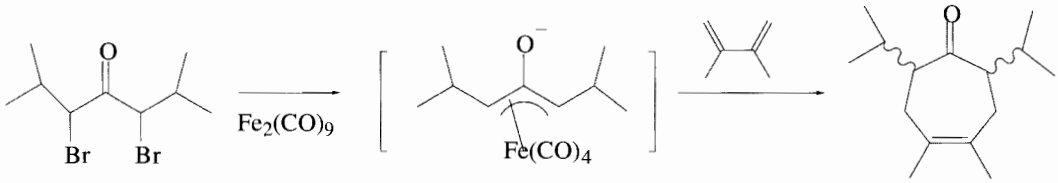
12.10.C. Noyori Annulation

Another synthetically useful carbon bond–forming reaction involves reaction of diiron nonacarbonyl with halo-carbonyl compounds. Noyori found that α,α'-dibromoketones (**498**) react with diiron nonacarbonyl [$Fe_2(CO)_9$] to give an iron stabilized alkoxy zwitterion (**499**). The intermediate π-allyl iron species reacts with alkenes in a stepwise manner (initially producing **500**) to give cyclic ketones such as **501**,[323] and the product is equivalent to the product of a [3+2]-cycloaddition with an alkene (sec. 11.11). This cyclization method is now known as **Noyori annulation**. This reaction is related to the Nazarov cyclization previously discussed in Section 12.3.C. Enamines can react with **498**, but the initially formed enamino ketone product eliminates the amino group to form cyclopentanone derivatives.[324] Intermediates such as **499** may actually exist as cations bound to a metal rather than as the alkoxide-iron structures shown.[323b-d] It is also noted that Zn/$B(OEt)_3$ is also an effective reagent and is a less toxic and less expensive alternative to $Fe_2(CO)_9$.[323e]



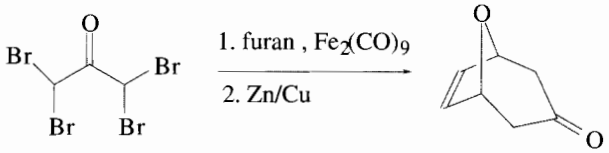
498 **499** **500** **501**

Dienes react to give cycloheptenones, as in the reaction sequence initiated by the reaction of **502** with $Fe_2(CO)_9$ to give **503**. In the presence of 2,3-dimethyl-1,3-butadiene generates the cycloheptenone derivative (**504**) in 55% yield.[325] This variation of the reaction is the formal equivalent of a [4+3]-cycloaddition. Both



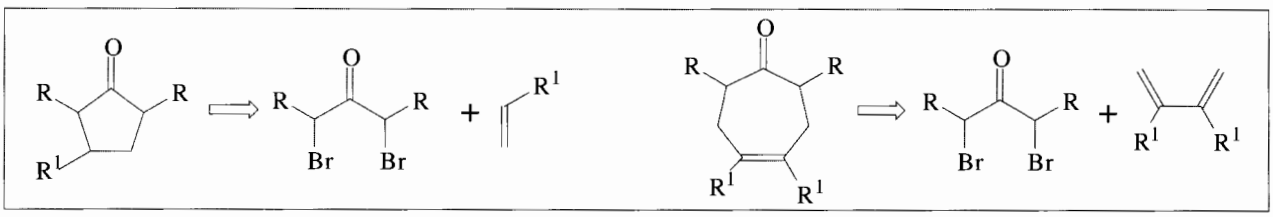
502 **503** **504**

furan and pyrrole can be used as the diene component.[324] Furan is a useful partner in this annulation, reacting with **505** to produce **506** in a synthesis of showdomycin.[326] Cycloadduct **506** was isolated after reduction of the bromide moieties with Zn/Cu (sec. 4.9.G) in the initially formed adduct. A similar strategy was used for a synthesis of nezukone.[327] N-Boc-pyrroles have also been cyclized to give 8-azabicyclo[3.2.1]octan-3-one derivatives using diethyl zinc to initial the Noyori annulation.[328]



505 **506**

The Noyori annulation disconnections are



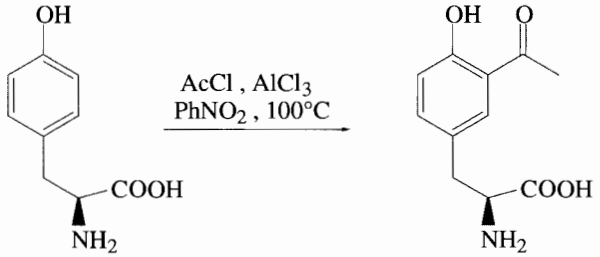
12.11. CONCLUSION

This chapter has shown that chemical equivalents for C^a include cations and organometallic reagents. Although formal carbocations are usually subject to racemization and rearrangement, they can be stabilized in a variety of ways and react with carbon nucleophiles ranging from alkenes and alkynes, to aromatic compounds, to Grignard reagents, and enolate anions. Even free cations can be used synthetically if the coupling is done intramolecularly and/or if a tertiary or oxygen stabilized cation is generated. The Friedel–Crafts family are classical reactions that are among the most powerful and useful of all organic reactions for constructing carbon–carbon bonds when aromatic nuclei are involved. The more recent contributions of metal stabilized cations, including π-allylpalladium, π-allylnickel, π-allyliron and other organometallic reagents allow nucleophiles such as Grignard reagents and enolate anions to be coupled with those C^a species.

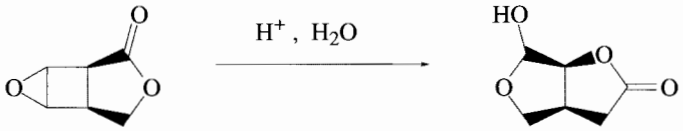
In Chapter 13, methods for generating carbon–carbon bonds via radical intermediates and carbenes will be discussed, completing the collection of chapters for generating carbon–carbon bonds in organic synthesis.

HOMEWORK

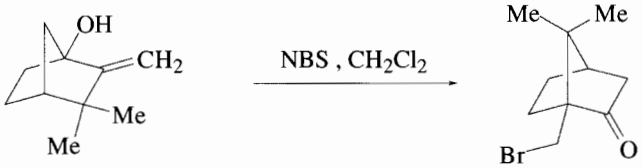
1. Friedel–Crafts alkylation is not a useful synthetic method for the synthesis of primary arenes such as 1-phenylhexane. Explain why not.
2. Briefly explain the regioselectivity for this reaction.



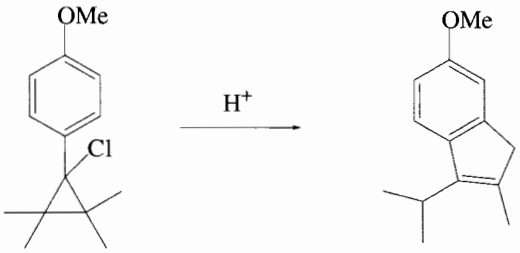
3. Provide a mechanistic rationale for the following transformation:



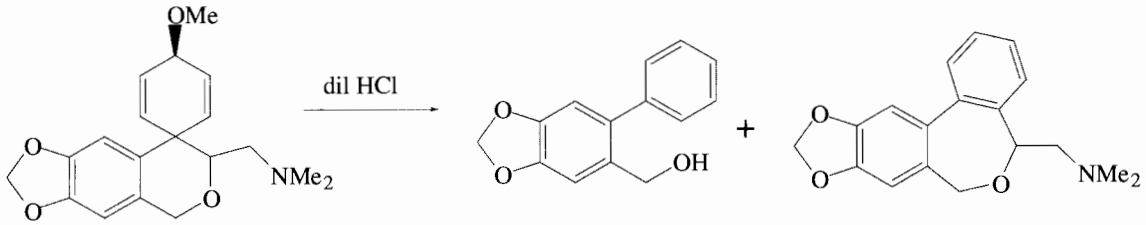
4. Offer a mechanistic rationale for the following transformation:



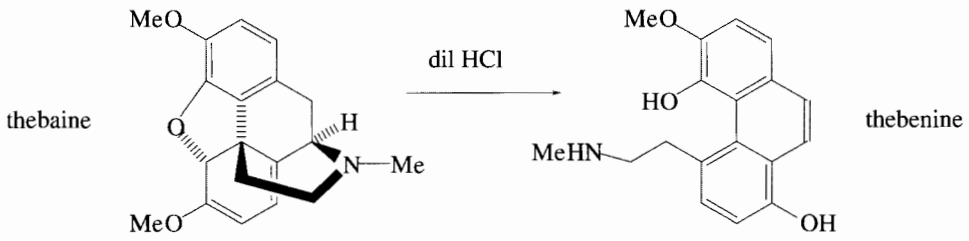
5. Give a mechanistic rationale for the following transformation:



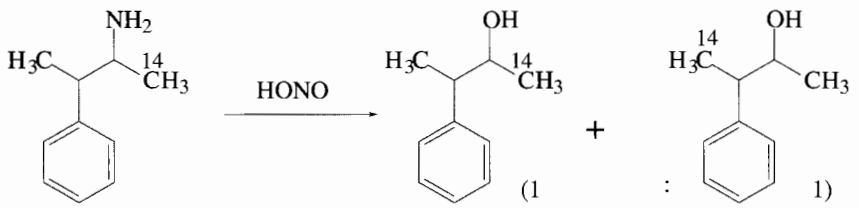
6. Give a mechanistic rationale for this transformation:



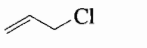
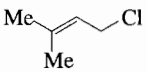
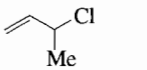
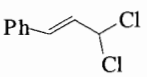
7. Give the complete mechanism for the following transformation:

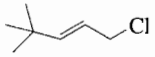
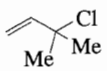


8. What are the mechanistic implications of the following experiment? Of what possible value is this experiment to synthesis if the R—NH_2 → R—OH transformation is planned?

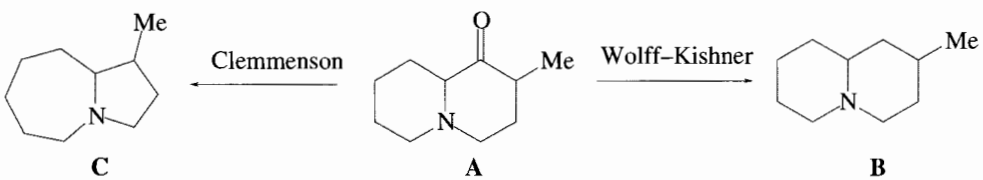


9. Explain the following rate data for a solvolysis reaction:

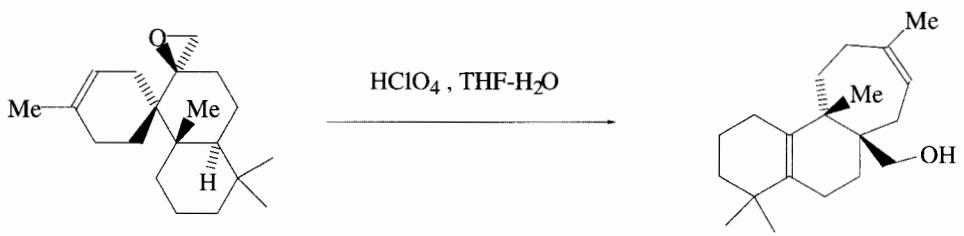
Halide	Rel Rate
	1.0
	1.5×10^7
	5.7×10^3
	2.2×10^8

Halide	Rel Rate
	2.3×10^3
	65.4
	8.7×10^7

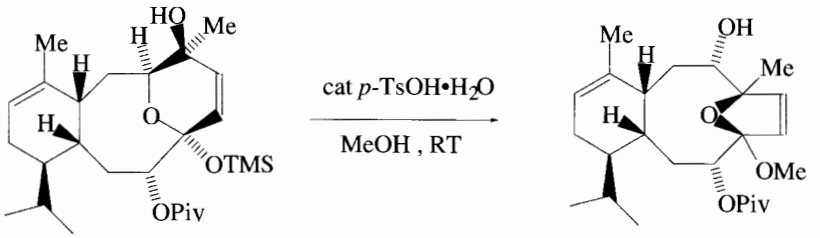
10. Explain the fact that Wolff–Kishner reduction of A gave B but Clemmenson reduction of A gave C.



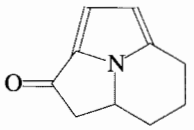
11. Give a mechanistic rationale for the following transformation:



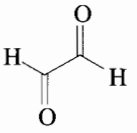
12. Provide a mechanism for the following transformation:



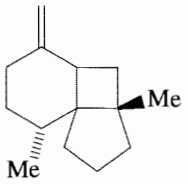
13. For each of the following, give the major product. Show the correct stereochemistry where appropriate.

(a) 

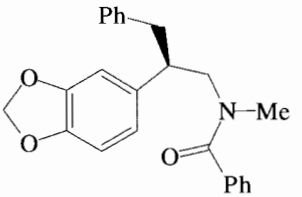
$AcCl$, $AlCl_3$

(b) 

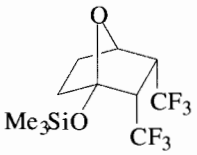
1. Sn , allyl bromide, aq THF , ultrasound
2. $NaIO_4$

(c) 

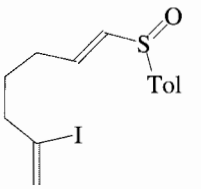
TsOH , PhH
reflux

(d) 

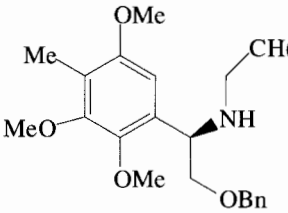
1. $POCl_3$, toluene , heat
2. $NaBH_4$, MeOH , 0°C

(e) 

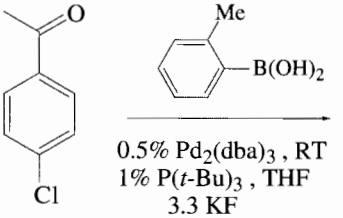
0.2% HCl
THF/H_2O

(f) 

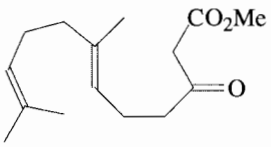
$Pd(OAc)_2$, PPh_3
Ag_2CO_3 , MeCN

(g) 

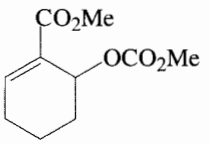
1. 12N HCl-THF
2. NaOH

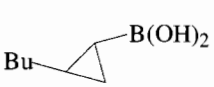
(h) 

0.5% $Pd_2(dba)_3$, RT
1% P(*t*-Bu)$_3$, THF
3.3 KF
phthalimide
$[\eta^3\text{-}C_3H_5PdCl]_2$
NEt_3 , CH_2Cl_2

(i) 

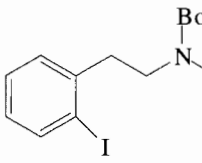
$SnCl_4$
$CH_2Cl_2\text{-}H_2O$

(j) 

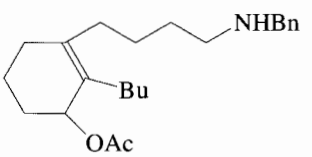
(k) 

$PhCOCl$, Ag_2O , 80°C
cat $PdCl_2(dppf)$, K_2CO_3

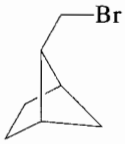
(l) $PhC{\equiv}CH$
$PhBr$, 3% $Pd(PhCN)_2Cl_2$
6% P(*t*-Bu)$_3$, 2% CuI
1.2 *i*-Pr_2NH , dioxane , RT

(m) 

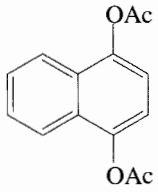
10% $Pd(OAc)_2$
$NaHCO_3$, Bu_4NCl

(n) 

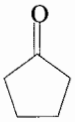
$Pd(PPh_3)_4$
MeCN , heat

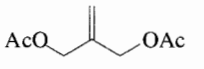
(o) 

$AlBr_3$

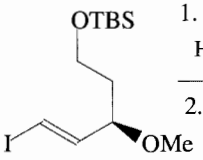
(p) 

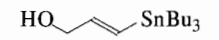
BF_3•OAc

(q) 

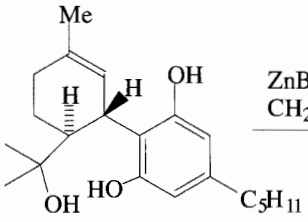


cat $Pd(OAc)_2/PPh_3$

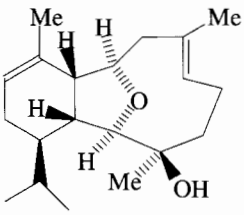
(r) 

1. $Pd(MeCN)_2Cl_2$


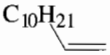
2. Swern oxidation

(s) 

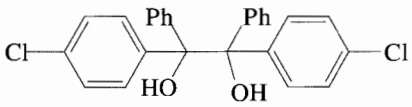
$ZnBr_2$, $MgSO_4$
CH_2Cl_2 , 20°C

(t) 

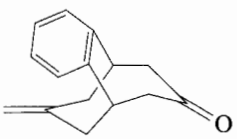
BF_3•OEt_2
ether , 0°C

(u) 

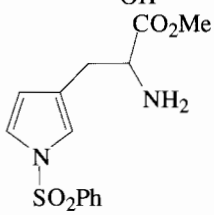
5% $Pd(OAc)_2$, O_2
20% pyridinie , *i*-PrOH
60°C , 6 h

(v) 

CF_3SO_3H

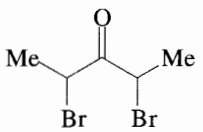
(w) 

aq H_2SO_4

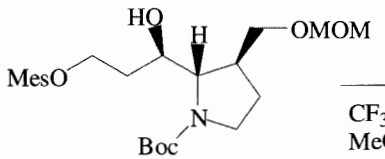
(x) 

aq HCHO
CF_3CO_2H
CH_2Cl_2

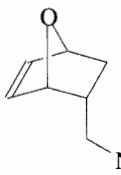
see *J. Org. Chem.*, ***1998***, *63*, 2731

(y) 

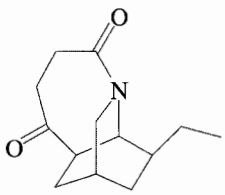
1. $Fe_2(CO)_9$, PhH
reflux
2. CH_2=CHCN

(z) 

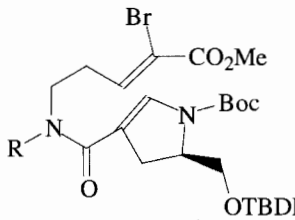
CF_3CO_2H
MeOH , RT

(aa) 

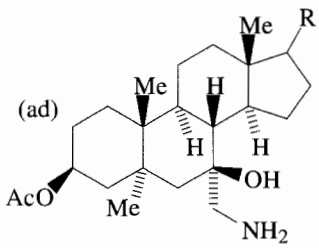
$NaNO_2$, 0.25M H_2SO_4

(ab) 

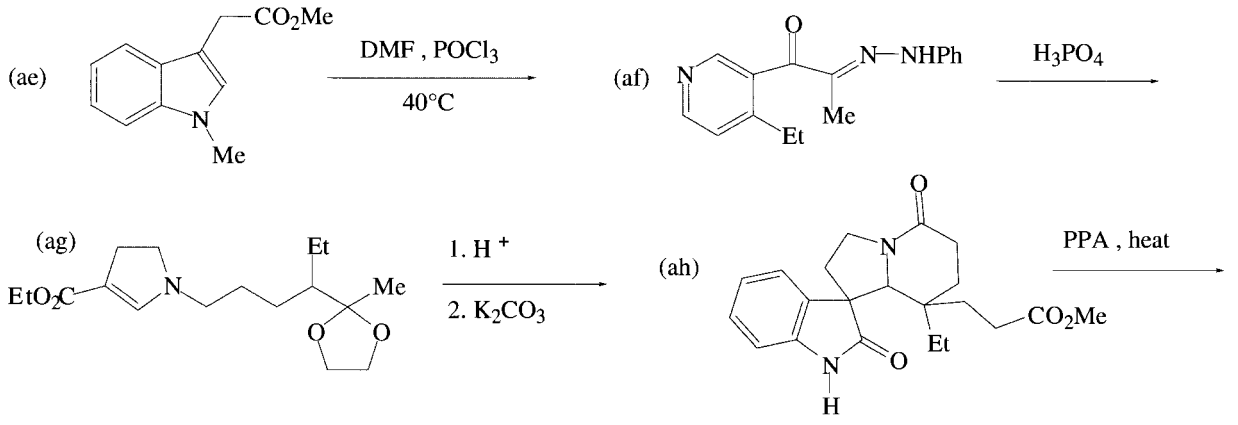
1. $PhNHNH_2$, AcOH
2. BF_3•OEt_2 , 80°C

(ac) 

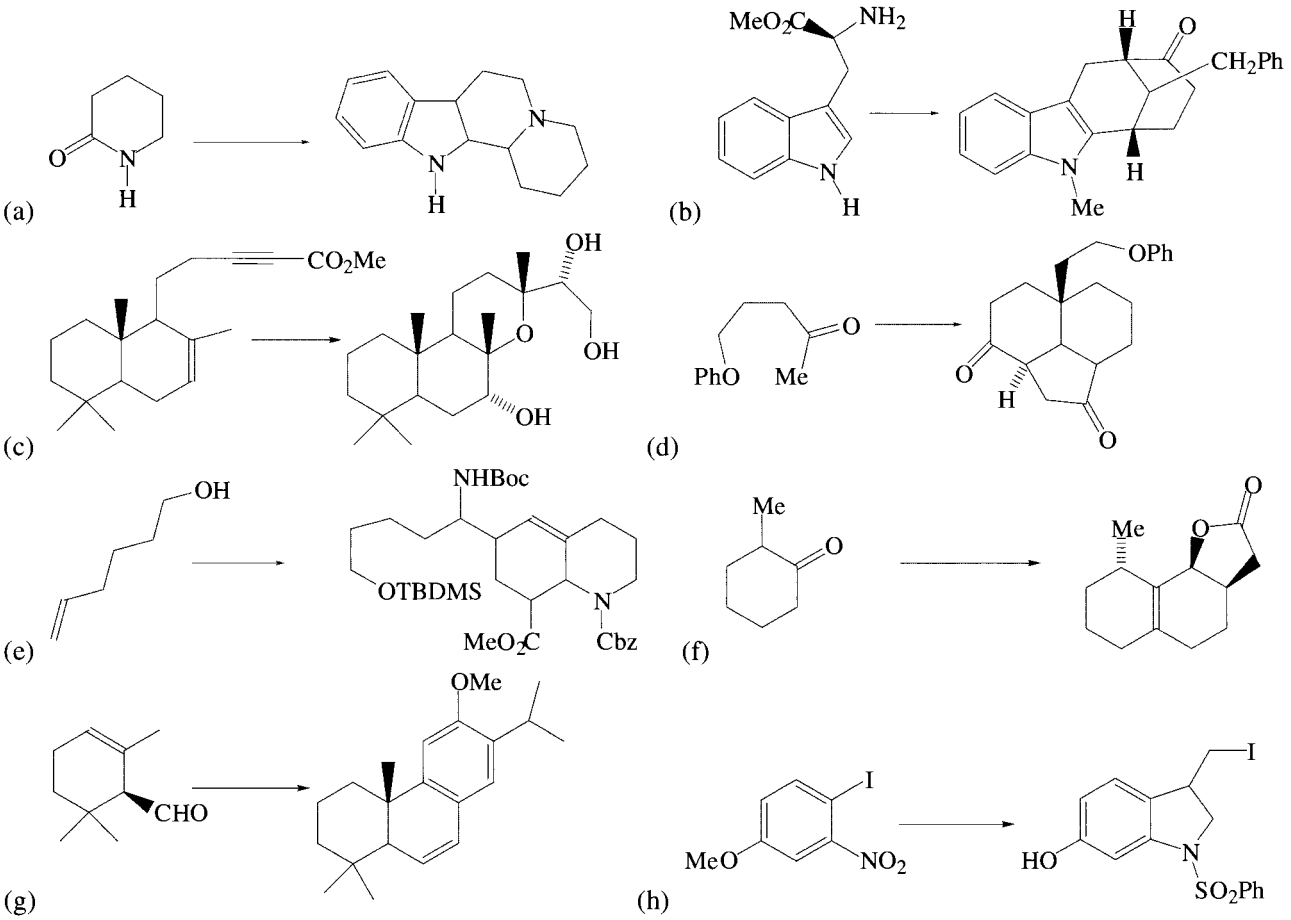
$Pd(PPh_3)_4$
toluene , heat

(ad) 

$NaNO_2$, AcOH



14. In each case give a complete synthesis of the target from the designated starting material. Show all intermediate products and give all reagents.



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1 Olah, G.A. *J. Am. Chem. Soc.*, ***1972***, *94*, 808.

2 (a) Collins, C.J. *Acc. Chem. Res.*, ***1971***, *4*, 315; (b) Friedman, L. in *Carbonium Ions, Vol. II*, Olah, G.A.; Schleyer, P.v.R. (Eds.), Wiley, New York, ***1970***, p 655; (c) Kirmse, W. *Angew. Chem. Int. Ed., Engl.*, ***1976***, *15*, 251.

3 (a) Lossing, F.D.; Semeluk, G.P. *Can. J. Chem.*, ***1970***, *48*, 955; (b) Radom, L.; Pople, J.A.; Schleyer, P.v.R. *J. Am. Chem.Soc.*, ***1972***, *94*, 5935; (c) Arnett, E.M.; Petro, C. *Ibid.*, ***1978***, *100*, 5408.

4 Deno, N.C. in *Progress in Physical Organic Chemistry, Vol. 2*, Cohen, S.G.; Streitwieser Jr., A.; Taft, R.W. (Eds.), Interscience, New York, ***1964***, p 135.
5 Isaacs, N.S. *Reactive Intermediates in Organic Chemistry*, Wiley, London/New York, ***1974***, p 151.
6 Arnett, E.M.; Hofelich, T.C. *J. Am. Chem. Soc.*, ***1983***, *105*, 2889.
7 (a) Reference 7, see p 391; (b) Streitweiser Jr., A. *Solvolytic Displacement Reactions*, McGraw–Hill, New York, ***1962***, pp 102–103.
8 (a) Hart, H.; Law, P.A. J. *Am. Chem. Soc.*, ***1962***, *84*, 2462; (b) Hart, H.; Sandri, J.M. *Ibid.*, ***1959***, *81*, 320.
9 Reference 5, pp 118–119.
10 (a) Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry, 3rd Ed.*, Harper and Row, New York, ***1987***, p 385; (b) Brown, H.C.; Rei, M. *J. Am. Chem. Soc.*, ***1964***, *86*, 5008.
11 Reference 5, p 119.
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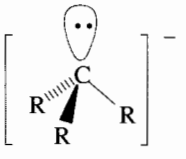
CHAPTER 13

CARBON RADICAL DISCONNECT PRODUCTS: FORMATION OF CARBON–CARBON BONDS VIA RADICALS AND CARBENES

Carbanion reagents, electrophilic reagents, and molecules that undergo pericyclic reactions are important for the formation of carbon–carbon bonds. Radical intermediates (molecules that possess a single electron in a reactive orbital) are also very important. When a C—C bond is disconnected, ionic disconnect products C^a or C^d may occasionally lead to synthetic equivalents that are either impractical or have side reactions that are intolerable. A useful alternative disconnect product, in many cases, is a radical that can be represented as $C^{\bullet}$. Radical reactions have become an important and largely controllable synthetic tool in recent years and should be considered as an important part of synthetic planning. Carbenes are also important for forming carbon–carbon bonds and they are sufficiently related to radicals that they are included in this chapter. This chapter will discuss methods for preparing radicals and carbenes as well as their applications to synthesis.

13.1. INTRODUCTION

A carbon radical is a trivalent species containing a single electron in a p orbital. A carbanion is viewed as a tetrahedral species containing a pair of electrons in an orbital (**1**). We have viewed a carbocation (carbenium ion) as an sp^2 hybridized, trigonal planar carbon with an empty p orbital (**2**). A radical, which contains one electron in an orbital, can be tetrahedral, planar, or 'in between', with properties of both a carbanion and a carbocation. As shown in **3**, a reasonable 'in between' structure is a flattened tetrahedron (the actual structure of radicals will be discussed below). In terms of its reactivity, radical **3** could be considered electron rich or electron poor. In most of its reactions, the electron-deficient characterization is the most useful for predicting products.



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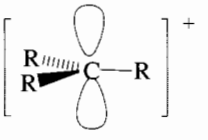

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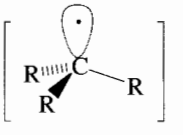
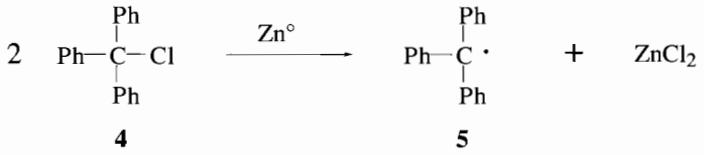


3

Gomberg was the first to characterize a free radical when, in 1900, he generated triphenylmethyl radical **5** by reacting chlorotriphenylmethane (**4**) with zinc metal.[1] Triphenylmethyl radical **5** is unusual in that it is quite stable and its formation is probably the first experimental verification of a free radical. Frankland, however, may have been the first to generate transient methyl and ethyl radicals in the reaction of iodomethane and iodoethane with zinc, in 1849.[2] In the last 30 years, attention has been focused on radicals, their reactivity, and their applications to organic synthesis. Excellent monographs by Davies and Parrott,[3] Lazár et al.,[4] Hay,[5]

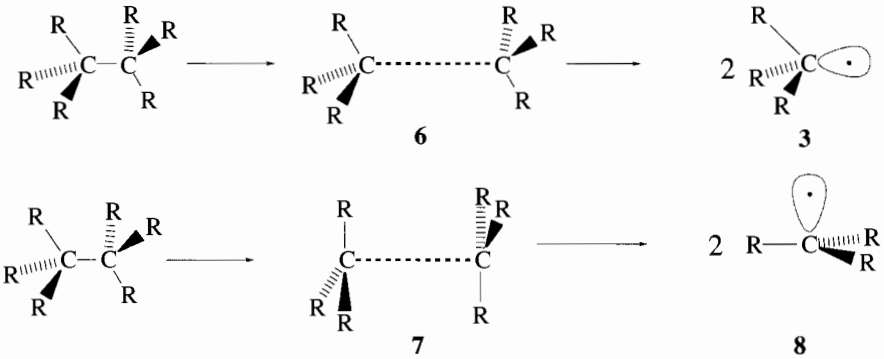
Giese,[6] and Kochi[7] describe radical chemistry in great detail, as well as the many applications to synthesis. A review by Curran[8] places an emphasis on synthetic applications.



4 5

13.2. STRUCTURE OF RADICALS

As mentioned in the introduction, there are several possible structures for a radical. The two most common are pyramidal (see **3**) and planar (see **8**). Formation of pyramidal radical **3** "involves a transition state differing from the original molecules only in the length of the central bond", represented by **6**.[9] Dissociation to a



planar radical (**8**) is also possible, but requires a transition state like **7**, where both parts of the molecule must be flattened.[9] Generally, transition state **7** is favored over **6** (this latter transition state represents an "instantaneous bond dissociation"). Dissociation of the molecule in the transition state prior to cleavage appears to be lower in energy, which is graphically presented in Figure 13.1.[10] For **path 1b**, the C—C bond is changing

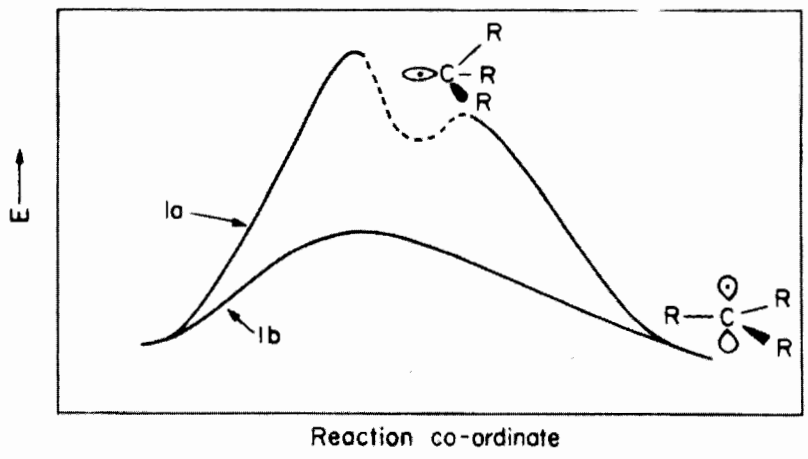


Figure 13.1 Energy diagram for dissociation to planar and pyramidal radicals.

from C^{sp3}—C^{sp3} to C^{p}—C^{p}, which is facile. Formation of the C—R bond is bond strengthening, and energy is released as the radical changes from a pyramidal structure to the planar arrangement. **Path 1a** is the instantaneous bond dissociation and does not possess as much stabilizing energy. It is important to note that if flattening in **7** is hindered by large steric interactions, then E_{act} increases and in those cases **3** may be the intermediate.

The methyl radical ($H_3C\bullet$) is a good example to begin a discussion of the properties and structure of free radicals. Structure **3** (R = H) represents the ground state of the radical, which has been experimentally determined to be planar, or nearly so.[11] The inversion energy for the methyl radical has been estimated to be only 4.2 kcal mol^{-1} (17.6 kJ mol^{-1}).[12] As the temperature increases, the pyramidal model (**8**, R = H) explains the ^{1}H and ^{13}C NMR as well as the electron spin resonance (ESR) spectra.[13] Three factors control the configuration of a radical: "(a) the energy of the unpaired electrons, (b) the energies of the bond in the radical and (c) the H—H interaction,[14] which is illustrated by a **Walsh diagram**[15], shown in Figure 13.2 for the methyl radical".[14] The total energy for inversion supports a double barrier for inversion between the two pyramidal forms, proceeding through the planar form (see the total energy curve in Figure 13.2). The energy of the most stable configuration of the methyl radical was calculated to be ≈ 5 kcal mol^{-1} (20.9 kJ mol^{-1})[14] and the energy of the pyramidal methyl was calculated to be ≈ 10 kcal mol^{-1} (41.9 kJ mol^{-1}) higher than the ground state.[14,16]

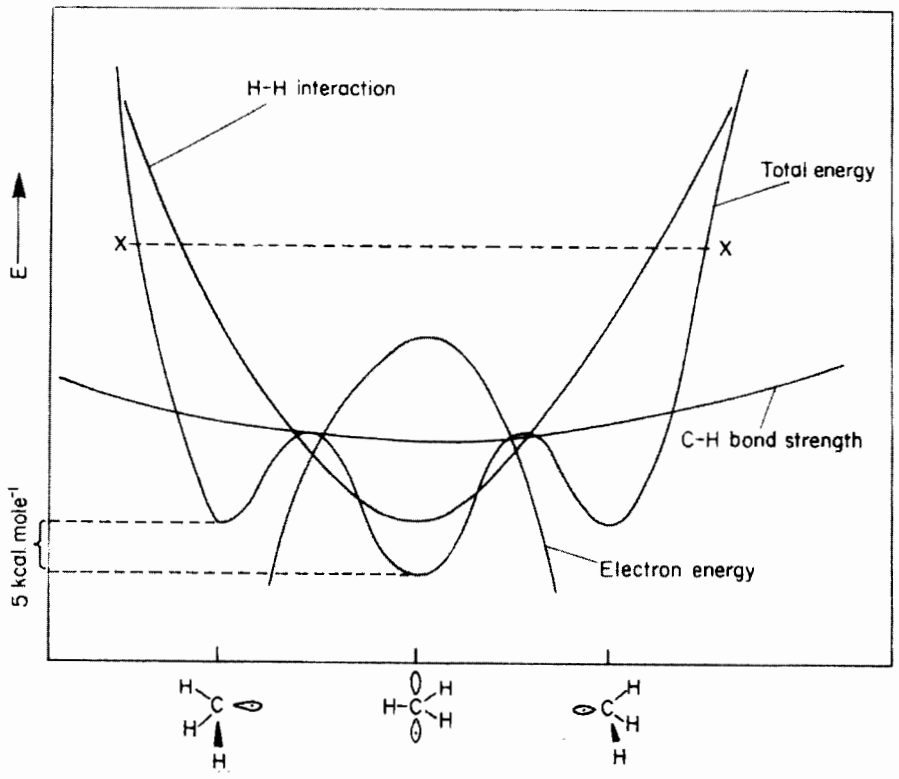
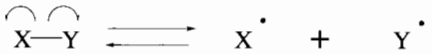


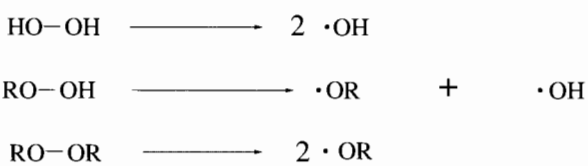
Figure 13.2. Walsh diagram for inversion of pyramidal methyl radical

13.3. FORMATION OF RADICALS BY THERMOLYSIS

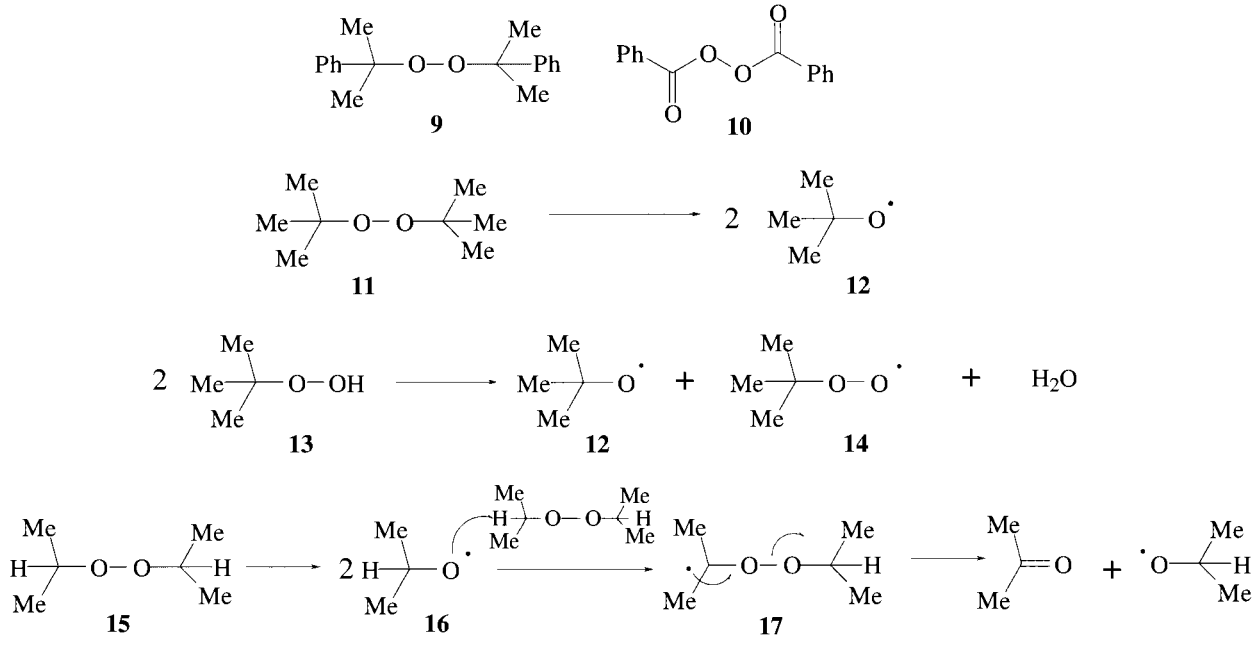
Radicals can be formed in several ways, but all involve **homolytic cleavage** (one electron is transferred to each adjacent atom from the bond), as depicted by X—Y, leaving two radical products. The equilibrium constant for this homolytic cleavage process depends on both the relative bond strength of X—Y and also on the relative stabilities of X• and Y•. Increasing the temperature of the reaction will generally shift the equilibrium toward a higher concentration of free radicals.[17] This equilibrium makes it convenient to



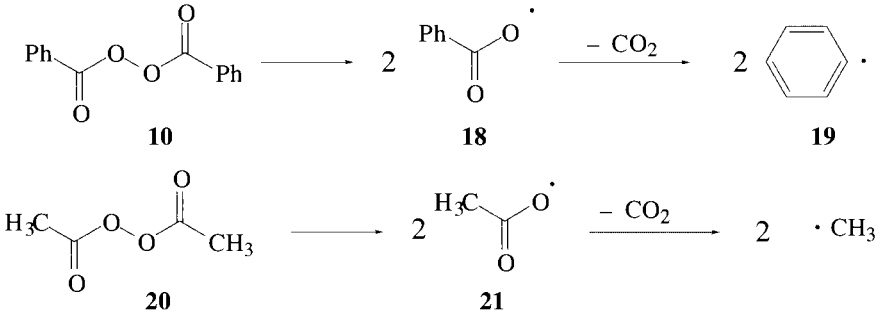
correlate homolytic cleavage with bond dissociation energy. Lazár[18] published a table of bond energies, in ascending order of bond strength[17,19] that correspond to the instantaneous bond dissociation energies (*D*). In principle, lower bond dissociation energies should correlate with an increased propensity for homolytic cleavage. Dissociation of C—C (357 kcal mol^{-1}; 1429.3 kJ mol^{-1})[18], C—O (351 kcal mol^{-1}; 1467.2 kJ mol^{-1}),[18] H—O (464 kcal mol^{-1}; 1939.5 kJ mol^{-1}),[18] and C—halogen bonds (230 kcal mol^{-1} for C-I to 334 kcal mol^{-1} for C—Cl; 961.4 kJ mol^{-1} to 1396.1 kJ mol^{-1})[18] all require high reaction temperatures for homolytic cleavage. Alkali metals (K—K, Na—Na, Li—Li), however, with bond dissociation energies of 55, 69, and 103 kcal mol^{-1}, respectively (229.9, 188.4, and 430.5 kJ mol^{-1}),[18] undergo homolytic cleavage under very mild reaction conditions. The potent electron-transfer capabilities of these metals for dissolving metal reductions was discussed in Section 4.9. Particularly weak bonds that are expected to give homolytic cleavage are the peroxide bond (O—O, 140 kcal mol^{-1})[18] and those of the halogens., which is reflected in the chemical methods used to generate organic radicals, which usually begin with thermolysis of peroxides (H_2O_2, ROOR, etc.), diazo compounds (RN_2), or halogens.



Peroxides are potentially dangerous compounds because many of them can detonate upon exposure to heat or light, and under conditions where there is friction or shock. Peroxides are known to oxidize alkenes to oxiranes (especially in the presence of transition metals, see sec. 3.4.B), but if heated they decompose to hydroxy radicals (HO•) or alkoxy radicals (RO•). Lazár et al. published a table of approximate decomposition temperatures for several common peroxides.[20] Hydrogen peroxide requires a rather high temperature of 380°C for a decomposition half-life of 1 h,[20] and it is not very soluble in organic solvents. Peroxide **9**, however, decomposes at such a low temperature (–16°C)[20] that controlling the reaction will be difficult in most instances. Benzoyl peroxide (**10**) cleaves at ≈ 95°C,[20] a temperature that is compatible with many organic reactions, allowing some control of the reaction, and is reasonably soluble in organic solvents. Di-*tert*-butyl peroxide (**11**) decomposes at ≈ 150°C[20] to produce **12**. It is a useful radical initiator, but the higher temperature

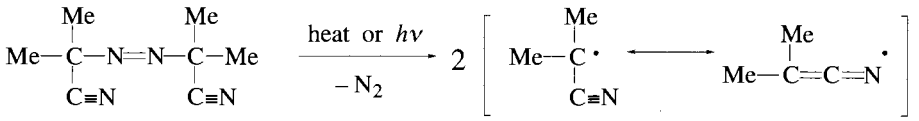


required for decomposition occasionally causes problems. *tert*-Butyl hydroperoxide (**13**) is another useful peroxide that decomposes to give **12**, **14**, and water. The presence of an α-hydrogen, as in diisopropyl peroxide (**15**), increases the facility of additional decomposition reactions. Initial homolytic cleavage gives the expected **16**, but this reacts with **15** to remove the α-hydrogen, generating **17** and 2-propanol. The carbon



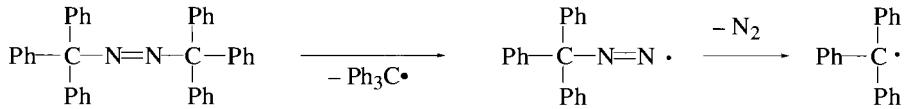
radical (**17**) fragments to acetone and **16**.[21] Acyl peroxides such as **10** react to give acyl radicals (**21**) that decarboxylate under thermal conditions to give an aryl radical (such as **19**) or an alkyl radical from an alkyl acyl precursor [$(RCO_2)_2$]. Benzoyl peroxide (**10**) is a commonly used peroxide for inducing radical reactions. Decarboxylation of primary alkyl acyl peroxides such as acetyl peroxide (**20**) is very facile, leading to **21** and the methyl radical, $\bullet CH_3$.[21] Aryl acyl radicals decarboxylate more slowly. When a peroxide decomposes, the oxygen radical remains in a "cage" for ≈ 10^{-11} s before diffusing away. It can recombine (dimerize) or react with other molecules (see below).

Azo compounds, characterized by a —N=N— bond, are free radical precursors that liberate stable nitrogen gas (N≡N) upon decomposition. One of the best known azo compounds used in organic reactions is *azo-bis*-isobutyronitrile (AIBN, **22**), which decomposes much faster than dibenzoyl peroxide to give nitrogen and the



22 23

cyano stabilized radical, **23**.[22] Just as with carbanion and carbocation intermediates, the presence of a conjugating π bond will delocalize the single electron of the radical via resonance, increasing the stability of that intermediate. Homolytic dissociation of symmetrical diazo compounds may be stepwise,[23] as in the decomposition of **24** to **25** and triphenylmethyl radical (**26**). Azo radical **25** loses nitrogen to form **26**.[24] The temperature of decomposition for diazo compounds is dependent on the groups attached to the α-carbon.[25] AIBN, for example, undergoes homolytic cleavage at ≈ 67°C,[25] whereas MeN=NMe decomposes at about 275°C and azobis-2,2-dimethylethane ($Me_3CN{=}NCMe_3$) decomposes at 172°C.[25] The stability imparted by the electron-withdrawing cyano group leads to greater stability of the radical and more facile decomposition.



24 25 26

13.4. PHOTOCHEMICAL FORMATION OF RADICALS

The general principles of photochemistry were introduced in section 11.10.B. A molecule can absorb a photon of light, and the resultant photoactivated species can, in the context of this chapter, undergo homolytic cleavage to form radicals. As discussed in Chapter 11, the energy required for bond cleavage can be provided by IR, visible or UV light. An energy of 10 kcal mol^{-1} (41.86 kJ mol^{-1}) corresponds to 3530 cm^{-1}, which is in the IR. Light of wavelength 2000 Å corresponds to 143 kcal mol^{-1} (212.5 kJ mol^{-1}), and is at the lower end of the ultraviolet (UV) region. Light in the UV or visible region can excite molecules to higher electronic states. Wavelengths in the UV are usually expressed in nanometers (1 nm = 1 mμ = 1 x 10^{-7} cm) and a wavelength of 200–400 nm is used most often for inducing photolysis in the UV region[26] for common functional groups (sec. 11.10.B).

If a molecule were irradiated with a light source generating several intense wavelengths of light, it is possible for several different functional groups to absorb the light and react, including the photoproduct we are trying to synthesize. A convenient method for limiting the wavelength of light (and thereby the energy of irradiation) is to filter out higher energy wavelengths (and lower energy if necessary). The filter is imposed between the light source and the reactants. Sometimes this is simply the reaction vessel, made out of Pyrex or quartz glass.[27,28] More often, the filter material is attached to the light source.[27,28]

When a molecule absorbs a photon of light, an electron is promoted from the bonding to an antibonding molecular orbital (n → σ*, n → π*, or π → π*), generating a singly occupied molecular orbital (a **SOMO**),

which is pertinent to radical reactions (sec. 11.10.B).[29] If the excited state is expressed as AB*, there are several pathways available for dissipation of this energy, as shown by Wayne in Figure 13.3.[30] The pathway which is pertinent to radical formation of radicals is dissociation of AB* to A• and B•:

$$AB \xrightarrow{h\nu} [AB]^* \longrightarrow A\bullet + B\bullet$$

Photochemical homolysis of the carbon–carbon bond of alkanes is difficult. The carbon–carbon bond of ethane has a bond strength of 83 kcal mol^{-1} (347.4 kJ mol^{-1}) and it fragments to methyl radicals ($\bullet CH_3$) only at temperatures approaching 600°C. Absorption of a photon of light is also difficult since alkanes absorb only

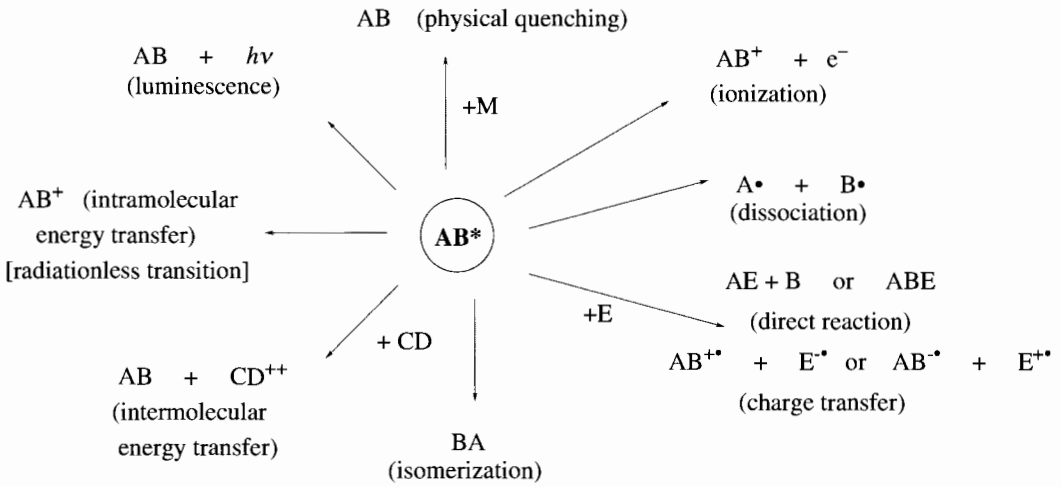
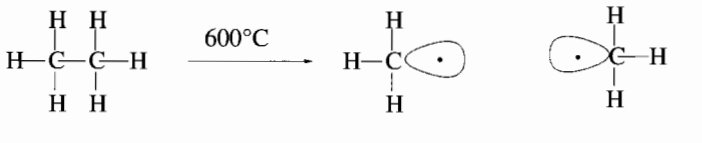


Figure 13.3. Routes available for loss of electronic excitation.

in the "vacuum" UV (methane absorbs at 144 nm, 198.6 kcal mol^{-1}, 831.4 kJ mol^{-1}).[31] Loss of molecular hydrogen (H_2) usually accompanies conversion of an alkane (**27**) to the alkyl radical (**28**).[32] If a long alkyl chain is present, loss of H• can occur at many points, leading to a large number of different radicals.

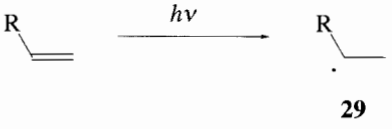


27 **28**

Alkenes show a $\pi \rightarrow \pi^*$ absorption for the π bond at ≈ 180 nm (158.9 kcal mol^{-1}, 665.1 kJ mol^{-1}).[32] Conjugated alkenes show a shift in absorption toward the visible spectrum (lower energy). Both isomerization (of ethene to ethyne) and fragmentation are observed.[32] As the size of the alkyl portion of 1-alkenes increases, the yield of alkenyl radicals decreases.[33] Photolysis of a terminal alkene generates the radical (**29**) in a typical photolysis reaction.

Carbonyl compounds show a symmetry forbidden $n \rightarrow \pi^*$ transition at ≈ 290 nm (98.6 kcal mol^{-1}, 412.8 kJ mol^{-1}) for aliphatic aldehydes and at ≈ 280 nm (102.1 kcal mol^{-1}, 427.6 kJ mol^{-1}) for ketones. Conju-

gation to an aromatic substrate (as in benzophenone) shifts the absorption to longer wavelength (≈ 340 nm, 84.1 kcal mol^{-1}, 52.1 kJ mol^{-1}). Acid derivatives absorb at a shorter wavelength [<250 nm (114.4 kcal mol^{-1}, 478.9 kJ mol^{-1}) for acids, anhydrides, and so on, and <260 nm (110 kcal mol^{-1}, 460.5 kJ mol^{-1}) for



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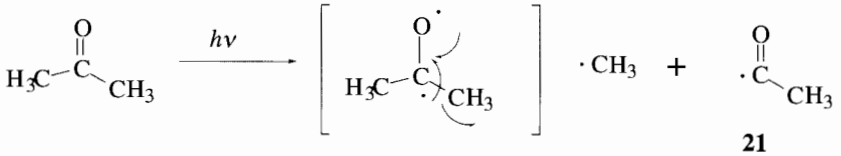

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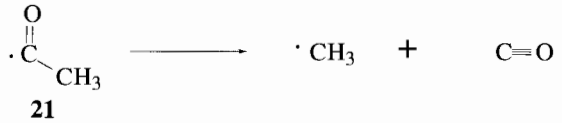
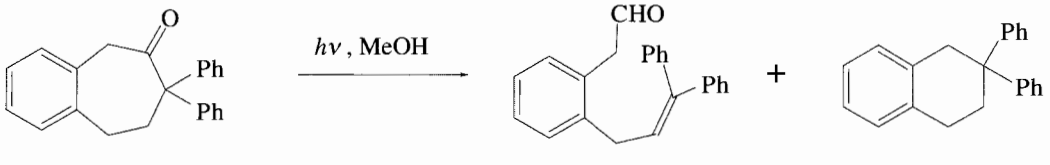
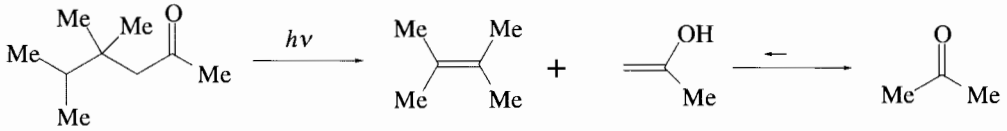


amides].[34] The allowed transitions ($\pi \rightarrow \pi^*$ and $n \rightarrow \sigma^*$) absorb at shorter wavelengths [≈ 180 and 160 nm (158.9 and 178.8 kcal mol^{-1}, 665.2 and 748.5 kJ mol^{-1})] for aldehydes.[34]

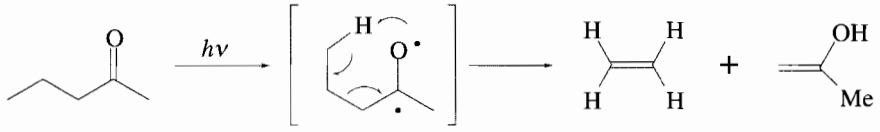


30 **31** **32**



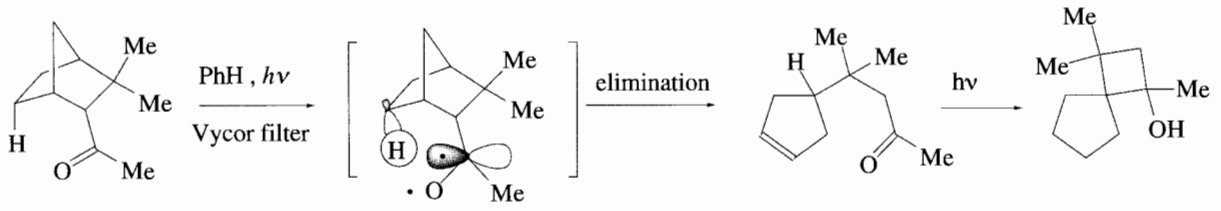
33 **34**

There are two main dissociative fragmentations for carbonyls upon photolysis, **Norrish type I** and **Norrish type II** fragmentations.[35] Norrish type I cleavage involves loss of carbon monoxide (CO) and generation of an alkyl radical. For acetone, absorption of a photon leads to cleavage to the methyl radical and the acyl radical (**21**). Subsequent fragmentation of **21** leads to another equivalent of methyl radical with concomitant loss of CO. In a more complex example, irradiation of ketone **30** led to a 47% yield of **31** and 40% of **32** via Norrish type I cleavage.[36] The Norrish type II process is an intramolecular fission of the bond α–β to the carbonyl (as in the fragmentation of **33** to 2,3-dimethyl-2-butene and enol **34**). The enol tautomerizes to a



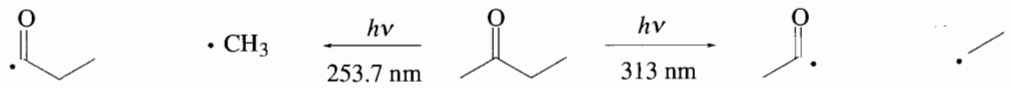
35 **34**

carbonyl compound, here acetone. Similarly, photolysis of 2-pentanone undergoes cleavage to ethene and **34** likely via a six-center transition state such as **35**.[37] This reaction is analogous to a **McLafferty rearrangement**, which is observed in the mass spectrum of ketones such as this.[38] The formation of product **31** from **30** illustrates this process and that Norrish I and II processes can complete. A synthetic example of a Norrish–type II cleavage is the photolysis of **36** to the radical (**37**), which loses hydrogen to form **38** prior to ring closure to the alcohol **39**.[39]



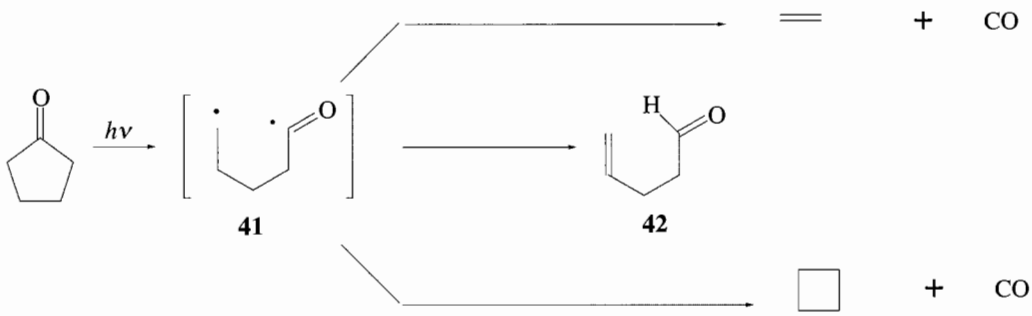
36 **37** **38** **39**

The Norrish type I process is considered to be the mechanism by which radicals are formed. The regiochemical outcome of Norrish type I cleavage depends on the wavelength of light employed. For example, photolysis of 2-butanone at 313 nm (91.4 kcal mol^{-1}, 382.5 kJ mol^{-1}) gave a 40:1 mixture of **40** and ethyl radical (CH_3CH_2•). Irradiation at 253.7 nm (112.7 kcal mol^{-1}, 471.9 kJ mol^{-1}), however, gave a 2.4:1 mixture of methyl radical and acyl radical **21**.[40]



40 **21**

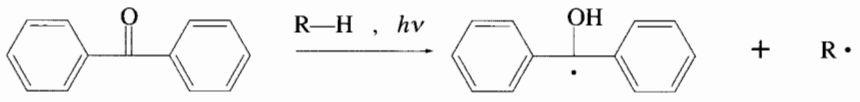
Aldehydes show an elimination reaction (loss of carbon monoxide, CO), that is not possible with ketones. Butanal, for example, photodissociates to propane and carbon monoxide. Cyclic ketones dissociate to a diradical (**41** from cyclopentanone), which then reacts in any of several ways including elimination to ethene or **42** and coupling to cyclobutane. Formation of cyclobutane and ethene is accompanied by expulsion of CO prior



41 **42**

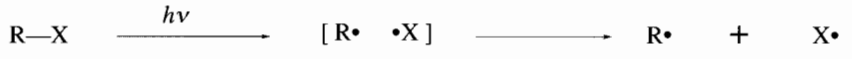
to formation of the alkene or the cyclic alkane.[37] The Norrish reactions can occur with the reaction of an alkane and an aromatic ketone such as benzophenone[41] to give a radical such as **43** and R•.[39,42] Benzophenone acts as a sensitizer in this reaction. As discussed in Section 11.10.B, a **sensitizer** (S*) is added

to facilitate electron transfer between two molecules.[43] The use of a sensitizer involves transfer of excitation energy from an electronically excited molecule (the sensitizer) to the ground state of another molecule, usually providing a triplet excited state.[44,29,30]



43

Bimolecular halogens and alkyl halides also serve as a source of radicals. Gaseous molecular iodine (I_2) gave the radical (I•) upon photolysis at ≈ 500 nm (57.2 kcal mol^{-1}, 239.4 kJ mol^{-1}).[45] Other halogens behave similarly, although they absorb at shorter wavelength. Alkyl halides cleave into alkyl radicals and halogen radicals upon absorption of light, presumably via a diradical cage species represented by **44**.[46] Alkyl iodides appear to generate intermediates with significant ionic character, whereas alkyl bromide intermediates show much more radical character.



44

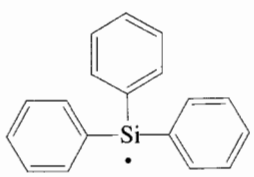
As discussed in Section 11.10.B, the efficiency of the photolysis is measured by the **quantum yield** (or **quantum efficiency**): the number of reacted or formed molecules per absorbed light quantum.[47] Quantum yield is measured for formation of a product (Φ_{form}) as just defined. It can also be defined in terms of the number of molecules of starting material (SM), which disappear per quantum of light (Φ_{dis}):[48]

$$\Phi_{form} = \frac{\text{No. of molecules of product formed}}{\text{No. of quanta absorbed}} \qquad 13.1$$

$$\Phi_{dis} = \frac{\text{No. of molecules of SM destroyed}}{\text{No. of quanta absorbed}} \qquad 13.2$$

13.5. REACTIONS OF FREE RADICALS

Davies and Parrott[49] discuss several types of reactions available to radicals once they have been generated. General aspects of radical chemistry has also been discussed.[50] This section will focus on the reaction types that are pertinent to synthetic applications or must be considered as competing processes in synthetic applications.



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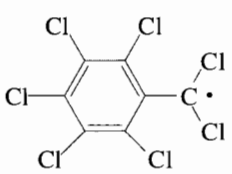

46

The reactivity of free radicals is linked to their stability. Reactivity is a function of spin density of the atom and the type of orbital occupied by the unpaired electrons. Increasing the number of atoms in a radical generally decreases reactivity, making monoatomic radicals such as Li• and F• very reactive. Conjugation decreases the spin density and therefore the reactivity. The resultant delocalization does not necessarily, however, lead to a very stable radical.[51] Steric effects play a significant role in radical reactivity. "If the bulkiness of the surrounding substituents exceeds ≈ 12-fold that of the central atom containing a radical site", the radical is unreactive and fails to react at all in many cases.[51] Triphenylsilyl radical (**45**), for example, is very reactive but perchlorobenzyl radical (**46**) is not.

The reactivity of radicals can be explained by molecular orbital theory, in a manner similar to that used for Diels-Alder reactions (secs. 11.2–11.4). Lázar et al. lists four rules that define an allowed reaction of a radical:[52]

1. The HOMO and LUMO of the reactant are decisive for the reaction course. At the mutual approach of reactants, there occurs the stabilization interaction between HOMO and LUMO. This interaction may be understood as a partial flow of electrons from the filled molecular orbitals to the empty ones.
2. The frontier orbitals should be of a proper symmetry to achieve the most efficient overlap. Only molecular orbitals of the same symmetry can be mixed.
3. The energy difference between HOMO and LUMO should be low (6-eV maximum). Presuming that point (2) is not fulfilled for some reason, the role of the frontier orbitals may be shifted to other orbitals of proper symmetry having the required energy difference.
4. If both orbitals are bonding, the HOMO should correspond to decaying bonds and LUMO to forming bonds. The opposite is true for an antibonding orbital.

A **SOMO**, defined above and in Section 11.10.B, can react with either a HOMO or a LUMO of another molecule, as shown in Figure 13.4.[53] The SOMO–LUMO interaction (as in Figure 13.4) occurs with nucleophilic radicals (high energy SOMO) that react best with molecules possessing a low energy LUMO

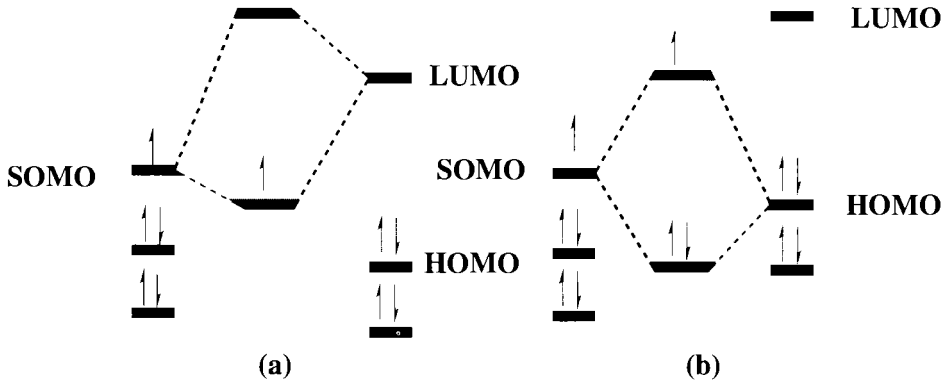

Figure 13.4. The interaction of a SOMO of a radical with the frontier orbitals of a molecule: (a) SOMO-LUMO interaction, (b) SOMO-HOMO interaction.[53]

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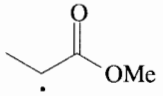
(electron-deficient alkenes –sec. 11.2, Table 11.1). Conversely, the SOMO–HOMO interaction dominates with electrophilic radicals (low-energy SOMO), which react best with molecules possessing a high-energy HOMO (electron rich alkenes). Radical **47** has unpaired electrons closer to the carbonyl and is expected to have a low-

energy SOMO, making it an electrophilic radical. Radical **48** possesses a radical center closer to the oxygen, has a high energy SOMO, and is a nucleophilic radical. Radical **47** is expected to react best with electron-rich alkenes such as vinyl ethers, and **48** with electron deficient alkenes such as acrylates. The SOMO energy is taken to be the ionization potential (IP, see sec. 11.2) of the radical. Table 13.1[54] shows the SOMO energies



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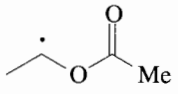
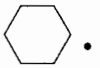
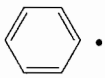


48

for several free radicals. In Section 11.2, Table 11.1, the LUMO and HOMO energies of a variety of alkenes were listed. The LUMO of methyl acrylate is 0 eV and the HOMO is –10.72 eV. The LUMO of methyl vinyl ether is +2.0 eV and the HOMO is –9.05 eV. Comparison of the SOMO energy of methyl radical ($H_3C\bullet$ in Table 13.1, –9.8 eV) and the acetate radical ($HO_2CCH_2\bullet$ in Table 13.1, –10.9 eV) shows that both reactions are $SOMO_{radical}$–$HOMO_{alkene}$ controlled. The methyl radical will react somewhat faster with methyl vinyl

Table 13.1. The SOMO Energies (IP) for Common Radical Types

Radical R•	SOMO Energy (eV)
$Me_3C\bullet$	–6.9
	–7.8
C_5H_{11}—CH(Me)•	–7.8
$Et_3Si\bullet$	–7.0
$Me_3Si\bullet$	–7.0
$C_{10}H_{23}$—$CH_2\bullet$	–8.7
	–9.2
$H_3C\bullet$	–9.8
H•	–13.6
t-Bu—O•	–12.0
t-Bu—O—O•	–11.5
HO_2C—$CH_2\bullet$	–10.9
Cl•	–13.0
Br•	–11.8
$Cl_3C\bullet$	-8.8

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ether than with methyl acrylate, but acetate radical will react significantly faster with methyl acrylate. In general, the reactant with the lower energy SOMO will react faster than the radical with the higher energy SOMO. The greater the $SOMO_{radical}$–$HOMO_{alkene}$ (or $SOMO_{radical}$–$LUMO_{alkene}$) energy difference, the faster the reaction (see Figure 13.5).

There are several major reaction types available to radicals: coupling, addition, substitution, fragmentation, rearrangement, and oxidation. The frontier molecular orbital treatment shown here for addition to alkenes can, with modification, be used to predict reactivity in virtually all radical reactions, if the molecular orbitals for the reactive species are known. The following sections will describe the various radical reaction types.

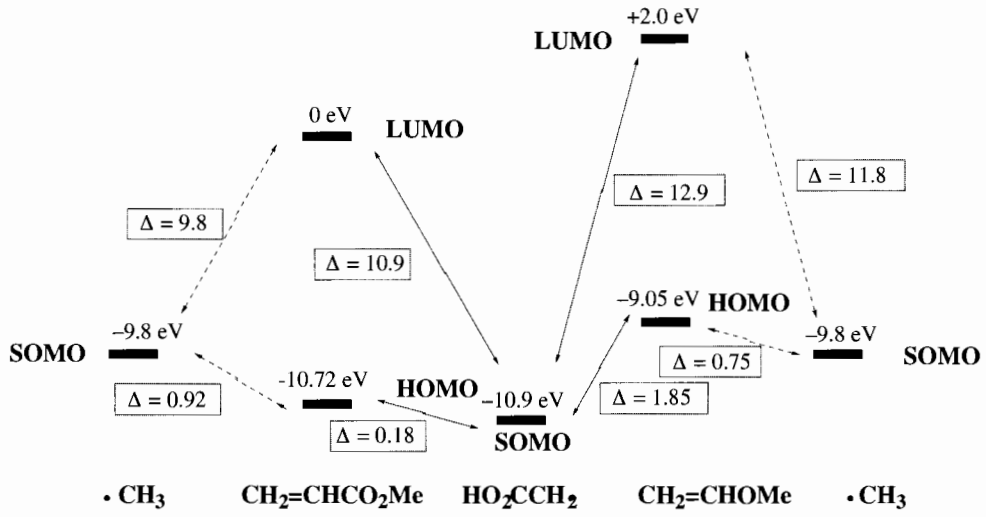


Figure 13.5. The SOMO–HOMO interactions for methyl and acetate radicals with methyl acrylate and methyl vinyl ether.

13.5.A. Coupling

Two radicals can combine to form a new carbon bond, as in the coupling of two ethyl radicals (CH_3CH_2•) to give butane. When one of the radical moieties possesses a β-hydrogen (or a β-leaving group), disproportionation can occur to form an alkene and an alkane. Ethyl radicals, for example, react to give ethane and ethene by disproportionation. Disproportionation often competes with coupling, but its competitiveness

$$CH_2{=}CH_2 \quad + \quad CH_3CH_3 \longleftarrow CH_3CH_2\bullet \quad + \quad \bullet CH_2CH_3 \longrightarrow CH_3CH_2{-}CH_2CH_3$$

depends on the method used to generate the radical. Resonance stabilized radicals are less prone to disproportionation reactions. Methyl and benzyl radicals have no β-carbon and do not undergo disproportionation. In a solvent, a radical is more likely to encounter a solvent molecule or a substrate rather than disproportionate, although coupling is sometimes competitive.

49 **50**

5 **5** **51**

If the radical is particularly stable (such as diphenylmethyl radical, **49**), coupling with a second radical molecule (to give **50**) is preferred to disproportionation, which is not always the case, as shown by triphenylmethyl radical (**5**), which possesses significant steric encumbrance at the radical carbon such that attack at a phenyl ring is preferred (to give **51** rather than Ph_3CCPh_3).[55]

13.5.B. Addition Reactions

Radical addition to π bonds (see above) generates a new alkyl radical species (**52**), which can undergo coupling, disproportionation, or other reactions. Since **52** is generated in the presence of the alkene in this particular reaction, a chain reaction is possible in which the newly formed radical adds to unreacted alkene to generate another radical. An example is the radical polymerization of an alkene, as shown in Figure 13.6 (cationic polymerization tends to be more efficient in many cases and may be accomplished under milder

conditions). An **initiation step** generates the radical, which in this case involves fragmentation of an alkyl peroxide to give RO•. This radical adds to the alkene to give a new reactive species (**53**). Addition of a second molecule of alkene generates **54**, and sequential addition to *n* molecules of alkenes generates **55**. These are

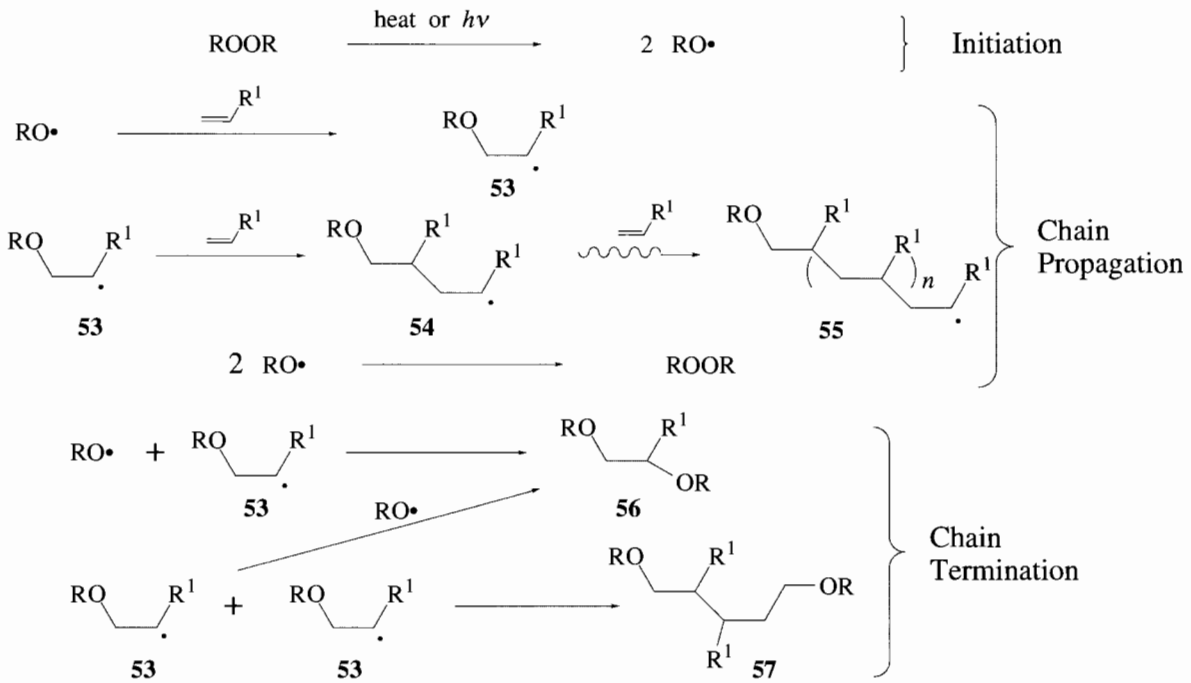
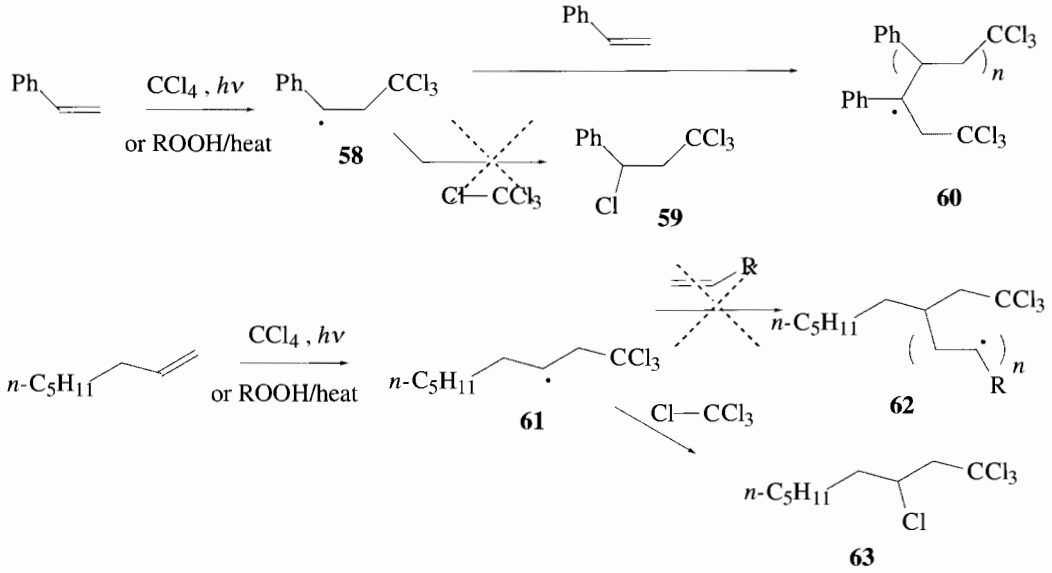


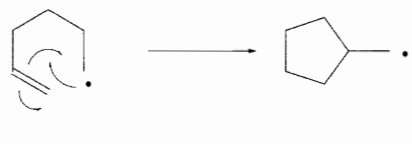
Figure 13.6. Chain radical addition reactions.

called **chain propagation** steps, in which each new step generates a reactive radical intermediate. If the radicals undergo coupling (several examples are shown, including formation of ROOR and **56**, as well as coupling to

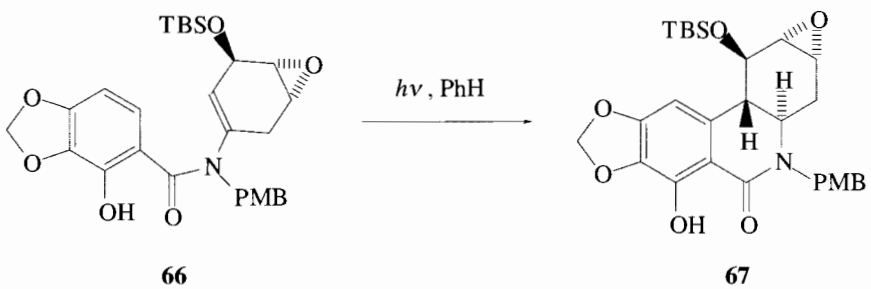
give **57**) the chain process stops, since no radical is available to continue the process. This coupling is called a **chain termination** step. A new initiation step must occur to initiate the chain process again. If a compound is added that will readily transfer a hydrogen atom, or another atom, to the radical, this can stop the chain process in a controlled manner. Such a compound is called a hydrogen-transfer agent or a radical quenching agent. Tributyltin hydride is an excellent hydrogen transfer agent in such reactions (see secs. 13.5.D, 4.9.H).



If the product radicals are stable, and/or if the stoichiometry of the reagents is controlled, a single product can be obtained in high yield. An example is the free radical addition of carbon tetrachloride (CCl_4) to styrene, which gives the benzylic radical **67** as an intermediate. Subsequent addition of **58** to styrene gives **60**. Since addition of the benzyl radical to styrene (to produce another benzylic radical) is faster than chlorination with a chlorine atom from carbon tetrachloride (which would give **59**), polystyrene is the final product.[56] When 1-octene reacted with CCl_4, however, the alkyl radical (**61**) was produced, and coupling with a chlorine atom to give **63** was favored over addition to 1-octene (to give **62**, which was not observed). In fact, this reaction gave an 85% yield of **63**.[57]



64 **65**

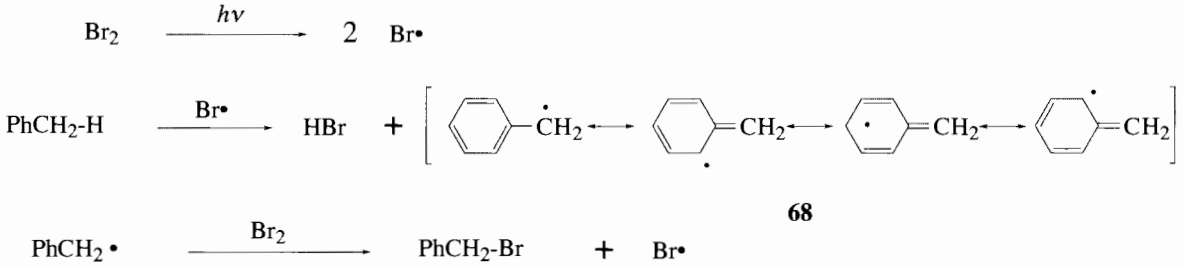


66 **67**

If a radical is generated in a substrate that also has a π bond in the molecule, intramolecular cyclization can occur (as in **64** → **65**). The highly reactive radical center is positioned to react with the π bond of the alkene, as shown, and the product (**65**) can be trapped to give the final product. Radical cyclization reactions will be discussed in Section 13.7. A synthetic example is taken from Rigby's synthesis of (+)-pancratistatin,[58] in which photolysis of **66** generated an aryl radical that added to the alkene unit intramolecularly to give a 50% yield of **67**. For a brief discussion of this and other pancratistatin syntheses, see Section 10.7.

13.5.C. Substitution Reactions

A classical radical substitution reaction is that of bromine with a hydrocarbon such as toluene. Initiation of the reaction by photolytic cleavage of bromine gives bromine radicals ($Br_2 + h\nu \rightarrow 2\ Br\bullet$). Bromine can also be converted to Br• by adding a peroxide or another radical initiator. Bromine radical abstracts a hydrogen

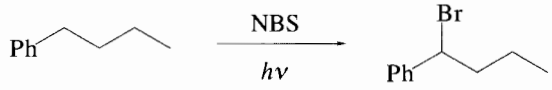


atom from the α-carbon of toluene to give a resonance delocalized benzylic radical (**68**) and HBr. The benzylic radical abstracts a bromine atom from diatomic bromine to give benzyl bromide and Br•, the radical carrier in a chain propagation step.[59] This reaction can be applied to simple alkanes, if a relatively stable tertiary radical can be produced. The relative order of hydrogen abstraction has been shown to be[60]

$$CH_3{-}H < CH_3CH_2{-}H < CH_3CH_2CH_2{-}H < Me_2CHCH_2{-}H < Me_2CH{-}H < Me_3C{-}H$$

There is a great preference for forming tertiary radicals upon reaction of a hydrocarbon with bromine (via hydrogen atom abstraction by Br•). The relative rates for hydrogen atom abstraction by a bromine radical are 1 for primary hydrogen, 82 for secondary hydrogen and 1640 for a tertiary hydrogen, which means that a tertiary hydrogen will be abstracted to form the corresponding radical 1640 times faster than that for a primary hydrogen. When the radical reacts with more bromine to give the alkyl bromide, this selectivity leads to good yield of the tertiary bromide, with smaller or trace amounts of isomeric bromides. This selectivity is not shared with the analogous chlorination reaction, however. For chlorination reactions, the relative rate of hydrogen atom abstraction is 1 for primary, 3.9 for secondary, and only 5.2 for tertiary, which means that a tertiary hydrogen atom is removed only 5.2 times faster than a primary, so there is much less selectivity. In fact, a chlorine radical abstracts all hydrogen atoms in the molecule, and the resulting radicals react to give close to a statistical distribution of the corresponding isomeric chloride products. The difference in selectivity between chloride and bromide radicals can be explained by molecular orbital theory. A tertiary hydrogen (as in 2-methylpropane, HOMO = –10.4 eV)[61] is selectively removed by a bromine radical (SOMO = –11.8 eV, ΔE = 1.4 eV) but removal of this hydrogen by a chlorine radical (SOMO = –13.0 eV, ΔE = 3.4 eV) is less

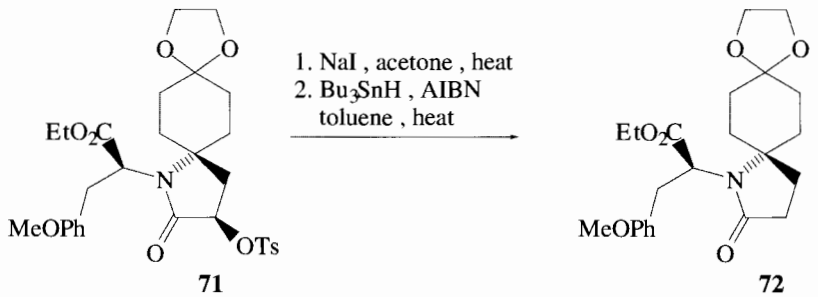
selective than with secondary and primary hydrogens. In other words, the difference in energy for removal of a tertiary versus a secondary hydrogen is greater in reactions with bromine radicals than with chlorine radicals. The bromine reactions are therefore more selective for removal of tertiary hydrogens. Free radical substitution reactions have been discussed in great detail by Ingold and Roberts.[62] It is important to note that free radical substitution of hydrogen by bromine is accomplished with *N*-bromosuccinimide (NBS), and that by chlorine with *N*-chlorosuccinimide (NCS) if the alkane substrate contains an allylic or benzylic hydrogen (sec. 2.8.B). An example is the conversion of 1-phenylbutane (**69**) to 1-bromo-1-phenylbutane (**70**).



69 **70**

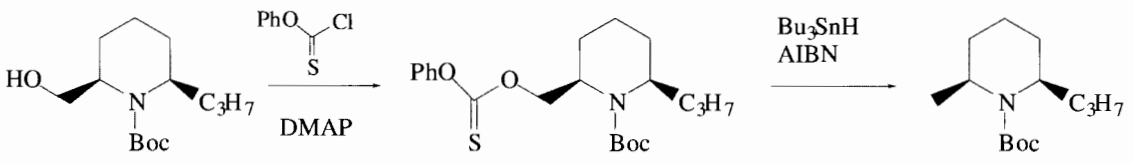
13.5.D. Reduction

When a radical is generated in the presence of a hydrogen transfer agent, it is possible to reduce various functional groups. Since an X group is replaced with H, this is a form of the substitution reaction described in Section 13.5.C, but it is separated into a different section because of it synthetic importance. The best example may be the one presented in Section 4.9.H in which an alkyl halide is reduced by treatment with tributyltin hydride, illustrated here by the Finkelstein reaction of tosylate **71** and subsequent reduction of the resultant iodide to give a 96% yield of **72**, in an example taken from Snider's synthesis of (–)-FR901483.[63] The AIBN (**22**) is the radical initiator, converting the alkyl iodide to the radical. The intermediate radical reacts with Bu_3SnH via hydrogen transfer to give **72** and $Bu_3Sn•$, which reacts with the iodine radical to form the other product, Bu_3SnI, which is a very effective method for the controlled reduction of halides.



71 **72**

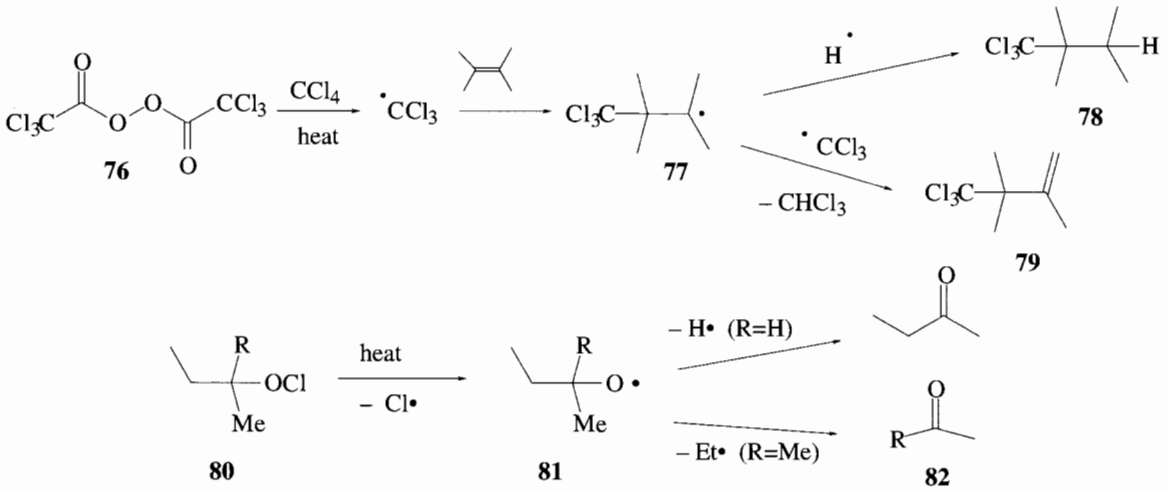
A very useful radical-based reaction has been developed that can be applied to alcohols. As seen in chapter 4, conversion of an alcohol such as **73** to a thionocarbonate (**74**), followed by treatment with tributyltin hydride under radical conditions, gives cleavage to the C—O bond to give, in this case, **75**.[64] This example is take from Beak's synthesis of (–)-dihydropinidine, and is an example of a transformation called the **Barton deoxygenation** or the **Barton–McCombie reaction**.[65]



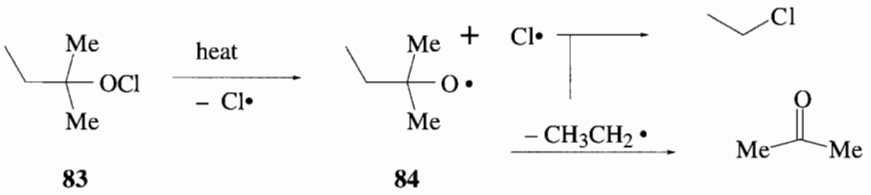
73 **74** **75**

13.5.E. Fragmentation

A radical can fragment to form a new radical and a neutral molecule. Typically, the neutral molecule is an alkene, making the process a simple elimination.[66] Addition of trichloromethyl radical ($Cl_3C\bullet$), generated by thermolysis of the acyl peroxide **76** to 2,3-dimethyl-2-butene, gave **77**. Abstraction of a hydrogen atom by $\bullet CCl_3$ gave trichloromethane and **79**.[67] Transfer of a hydrogen atom to **77** (from solvent, the alkane, or a hydrogen atom), however, led to **78**. Both processes occurred in this reaction and are typical of radical additions. Alkoxy radicals such as **81** (formed by thermal loss of a chlorine atom from hypochlorite **80**) often lose a hydrogen atom (to give 2-butanone when R = H) or an alkyl radical (to give **82** when R = Me) via

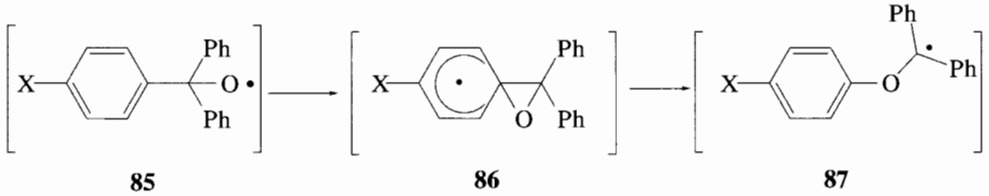


cleavage of the bond β to the radical center.[68] Thermolysis of hypochlorite **83**, for example, gave acetone and chloroethane via coupling of the intermediate ethyl radical with alkoxy radical **84**.[69] Hypochlorites are excellent sources of alkoxy radicals and can be used to initiate other radical reactions.

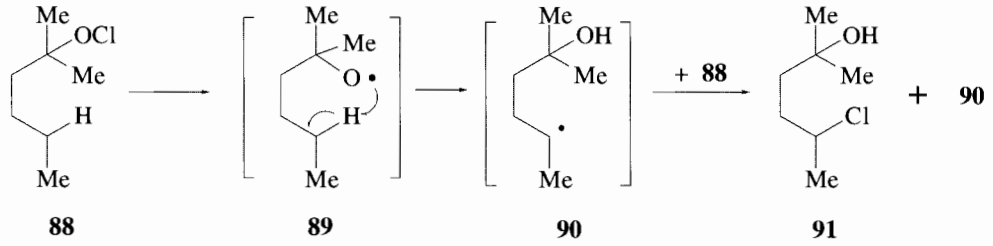


13.5.F. Rearrangement and Hydrogen Abstraction

There are a few rearrangement processes of free radicals.[70,56] When chlorine, phenyl, acetoxy, and acyl groups are in the β-position with respect to the radical center, 1,2-shifts have been observed. An example is the rearrangement of **85** to **87** via **86**.[71]

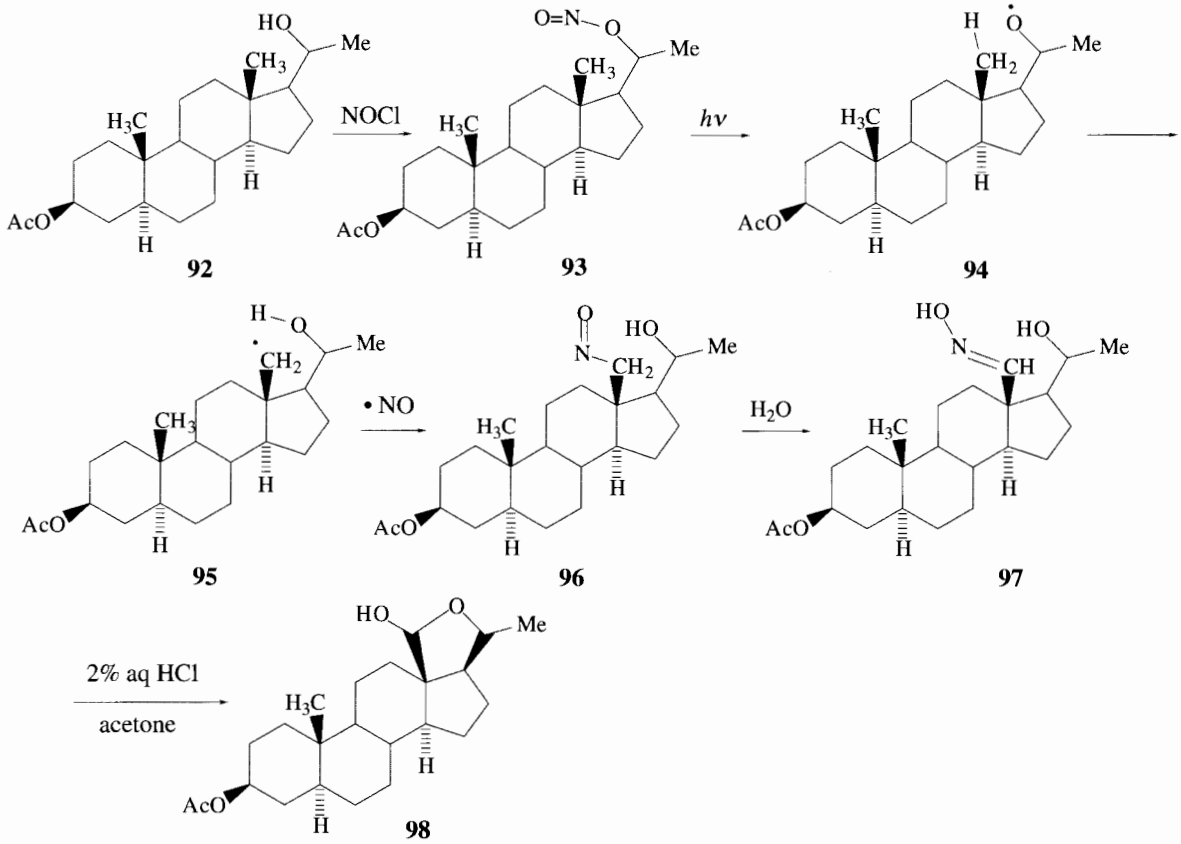


Skeletal reorganization occurs in radical intermediates, primarily via hydrogen atom shifts observed that are probably hydrogen abstraction reactions. An example is the **Barton reaction**,[72] in which an alkoxy radical



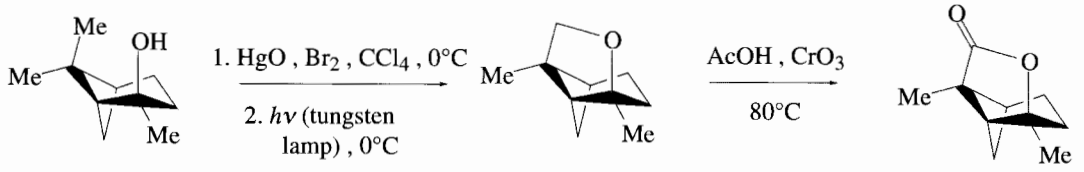
88 **89** **90** **91**

(**89**) abstracts a hydrogen atom via a six-center transition state to give **90**. In this example, radical **89** was generated from the hypochlorite (**88**). Radical **89** removed the hydrogen atom as shown to give **90**, **which** abstracted a chlorine atom from **88** to give **91** and regenerate **90**.[73] In a synthetic example, Barton converted 3β-acetoxy-5α-pregnan-20β-ol (**92**) to the nitrite derivative (**93**) via reaction with nitrosyl chloride (NOCl).[60a] Photochemical cleavage (mercury lamp and a Pyrex filter) of **93** generated alkoxy radical **94**,



92 **93** **94** **95** **96** **97** **98**

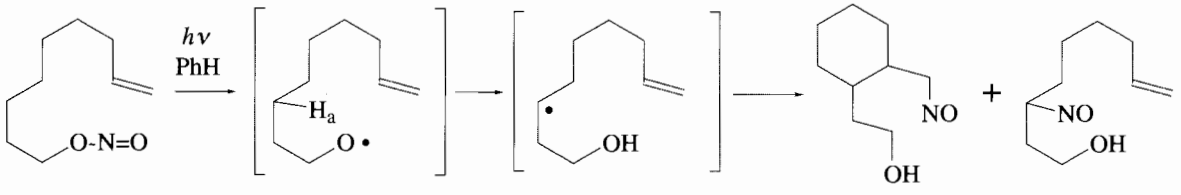
which abstracted the hydrogen atom from the neighboring methyl, properly positioned for reaction via a six-center transition state by virtue of the rigid steroidal structure. The newly formed radical (**95**) was trapped by the nitrosyl radical to give **96** and treatment with water gave the oxime (**97**) in 34% yield. Hydrolysis with dilute acid gave lactol **98**. The net result of this transformation is an oxidation (—CH_3 → —CHO; sec. 3.8).



99 **100** **101**

The reaction is not restricted to steroids, but simply requires that the hydrogen being abstracted be positioned close enough to react with the alkoxy radical. Reaction of alcohol **99** with bromine and mercuric bromide gave the corresponding hypobromite (—OH → —OBr). Subsequent photolysis gave a 43% yield of **100**.[74a,b] Oxidation with chromium trioxide in acetic acid gave the lactone (**101**), which was used by Magnus in a synthesis of grandisol.[74d] Gibson and Erman used similar intermediates and methodology for the synthesis of cis-bergamotenes.[74c]

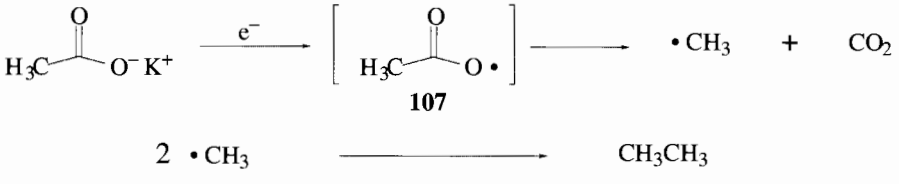
Note that there are potential side reactions. Once the oxygen radical is generated, the hydrogen can be abstracted via a four-center transition state if the six-center transition state is not readily accessible. A Barton-like reaction involved photolysis of **102** to give the oxygen radical, **103**.[75] Removal of H_a in **103** via a five-center transition state (•O—C—C—C—H) gave the corresponding carbon radical (**104**), which gave two products via either cyclization in the presence of the alkene and trapping by NO (to give **105**, 25% yield) or by direct trapping with NO to give **106** (14% yield).



102 **103** **104** **105** **106**

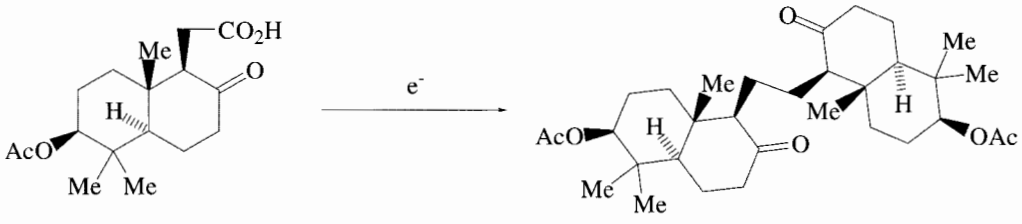
13.6. INTERMOLECULAR RADICAL REACTIONS

In 1849, Kolbe found that electrolysis of potassium acetate generated carbon dioxide (CO_2) and ethane,, presumably via an acetoxy radical (**107**).[76] The methyl radical (•CH_3) generated from potassium acetate coupled to give ethane. The reaction works very well with long, straight chain alkanoic acids. This reaction is



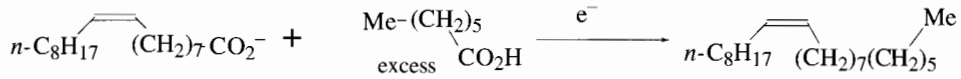
107

known as the **Kolbe electrolytic synthesis**[76,77] and it was used to convert hexadecanoic acid to *n*-triacontane (*n*-$C_{30}H_{62}$) in 88% yield.[78] Rigid, rod-shaped hydrocarbons based on oligo-bicyclo[2.2.2]octane derivatives have been prepared using Kolbe electrosynthesis.[79] Much larger and more complex molecules can be synthesized by this method. Stork used the Kolbe electrosynthesis use to dimerize **108** to **109** (in 40% yield) in a



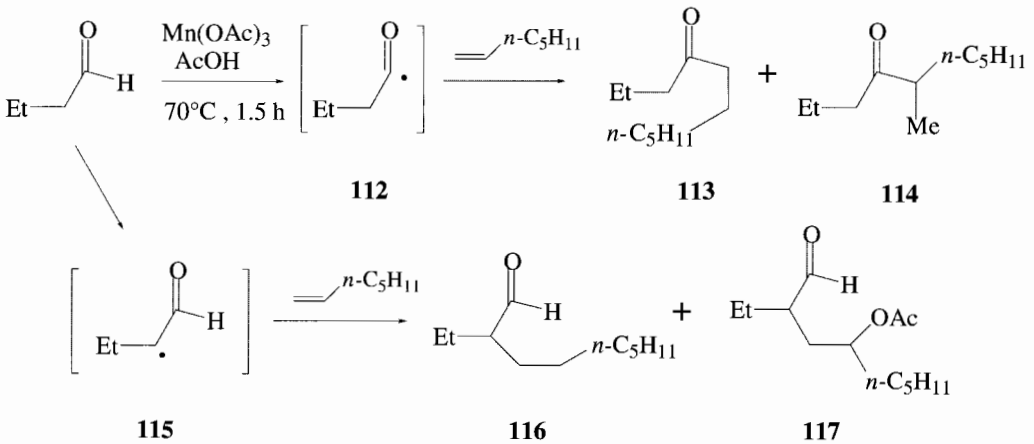
108 **109**

synthesis of α-onocerin.[80] As illustrated by the synthesis of **109**, the reaction is very efficient when two identical acids are coupled together. The Kolbe synthesis of two different acids (RCOOH + R'COOH) generally leads to a mixture of products arising from statistical coupling (R—R, R—R', R'—R'). Using an excess of one acid can lead to the desired mixed-coupling product (R—R'), as in the reaction of **110** with an excess of heptanoic acid to give **111** in 80% yield.[81] There are several variations of this reaction.[81]



110 **111**

Aldehydes can also be a source of radicals via reaction with transition metal salts such as Mn(III) acetate. Aldehyde-based radical addition to alkenes generates ketones such as **113** in good yield.[82] An acyl radical is initially generated via reaction with the transition metal [Mn(III) and Fe(II) are the most common].[83] Reaction of butanal and 1-heptene, in the presence of manganese acetate [$Mn(OAc)_3$], began with addition of the acyl radical (**112**) to both carbons of the π bond, giving regioisomers **113** (48% yield) and **114** (3% yield), as well as a 27% yield of **116** and a 22% yield of **117**. Removal of the hydrogen atom α to the carbonyl led to **115**, and addition to the alkene gave **116**.[84] This reaction also occurs with ketones, but usually requires catalysis (with di-*tert*-butyl peroxide, for example).[85] A simple application is seen in the coupling reaction of cyclopentanone with 1-decene to give 2-decylcyclopentanone in 71% yield.[85b]

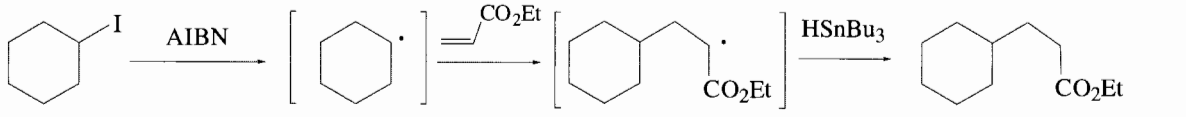


112 **113** **114**

115 **116** **117**

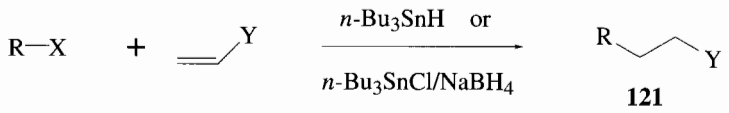
Giese's describes many synthetic applications of radical coupling with alkenes.[6,86] Reactions with simple alkenes are not very efficient, but reactions with alkenes bearing an electron-withdrawing group are usually

quite facile. Perhaps the most common method for generating the radicals that react with alkenes is heating an alkyl halide with AIBN (or via photolysis) in the presence of tri-*n*-butyltin hydride (*n*-Bu_3Sn—H). In a typical reaction, AIBN (**22**) is thermally decomposed (refluxing benzene) and reacts with iodocyclohexane to give **118**. This radical reacts with ethyl acrylate to give **119**. Tributylin hydride is an efficient intermolecular hydrogen donor, reacting with **119** to form the product (**120**) and generate a chain-carrying radical Bu_3Sn•, which can react with additional halide to produce **118**. Table 13.2[87] shows the radical coupling of alkyl halides and alkenes (to give **121**) under both photochemical and thermal (with AIBN) conditions. Giese used this technique to couple **122** with methyl methacrylate, giving **123** in 70% yield. Removal of the benzylidene acetal group (sec. 7.3.B.i) by hydrogenation and subsequent lactonization gave malyngolide (**124**).[88]



118 **119** **120**

Table 13.2. Intermolecular Radical Coupling of Alkyl Halides and Alkenes



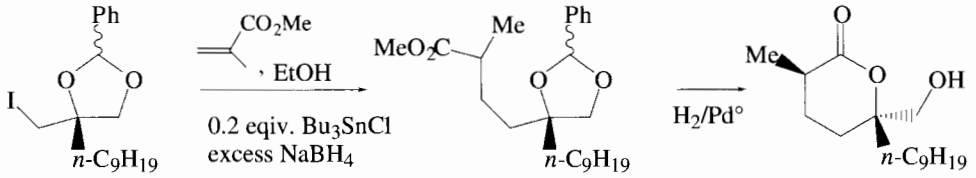
121

Alkyl Halide	Alkene	% 121	
		hν	Δ (AIBN)
n-$C_6H_{13}I$	CH_2=CHCN	80	
c-$C_6H_{11}I$		95	
t-C_4H_9Br		87	98
n-$C_6H_{13}Br$			68
c-$C_6H_{11}Br$			80
t-C_4H_9Br		62	
c-$C_6H_{11}I$	Methyl vinyl ketone	85	
	Acrolein		90
	Ethyl acrylate	85	
	Styrene	83	
	1,1-Dichloroethene	87	
	(*E*)-Dicyanoethene		72
	(*E*)-1-Cyano-1-propene	86	

[Reprinted with permission from Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–carbon Bonds*, Pergamon Press, Oxford, ***1986***, p. 58, Copyright 1986, with permission from Elsevier Science.]

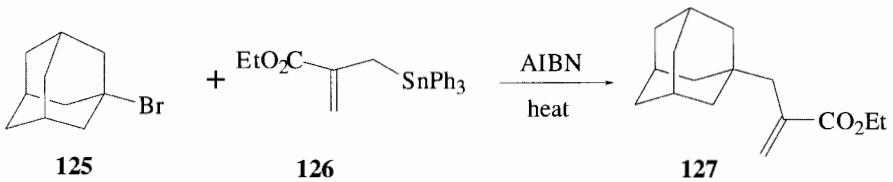
A problem with radical coupling in the presence of a hydrogen donating species such as tin hydride is competing hydrogen transfer to directly reduce the alkyl halide (—CH_2I → —CH_2H) as described in Section 13.5.D. If the initially formed radical is long lived, and/or if the radical coupling reaction is slow, that radical can be reduced by hydrogen abstraction from the tin hydride, which can be the major reaction in many cases,

but ≈ 20–25% yields are typical. α-Halo esters add to alkenes to form either lactones or substituted ester derivatives.[89,90]



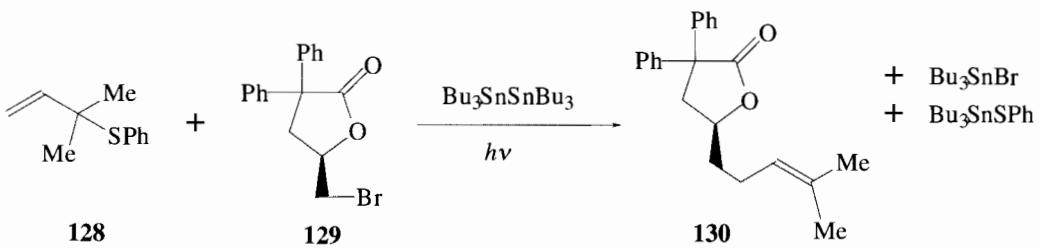
122 **123** **124**

An alternative route has been used for radical coupling, involving alkyl halides and allyl tin derivatives (such as allyltributyltin, n-$Bu_3SnCH_2CH{=}CH_2$).[91,94] Allyltin compounds used in this context were introduced by Migata[92] and Peryne,[93] but Keck contributed significantly to their synthetic development.[94,91] Allyl tin compounds react with alkyl halides to give the corresponding coupling product (see sec. 12.9.A). An electron-withdrawing substituent at C2 of the allyl stannane increased the reactivity, illustrated by the coupling of bromoadamantane (**125**) and **126** to give **127** in 70% yield.[95] Usually, it is not possible to use allyl stannanes bearing substituents at C1 or C3,[96] but there are exceptions.[97] When the C3 position is substituted, addi-

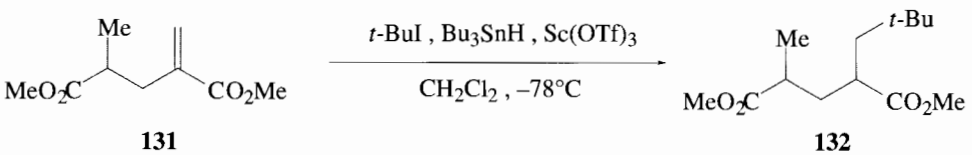


125 **126** **127**

tion of the radical is slow. When C1 is substituted, the stannane is subject to rearrangement, which can be competitive with addition.[98] This latter problem has been solved, at least for prenylation, by the use of an allyl sulfide precursor such as **128**. Keck showed that **128** reacted with **129** in the presence of tributyltin dimer ($Bu_3Sn—SnBu_3$) to give **130** in 76% yield.[99] The radical initiating reaction is generation of $Bu_3Sn•$ by



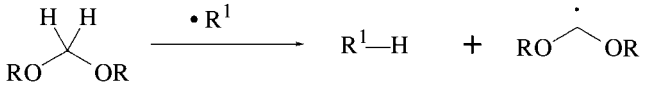
128 **129** **130**



131 **132**

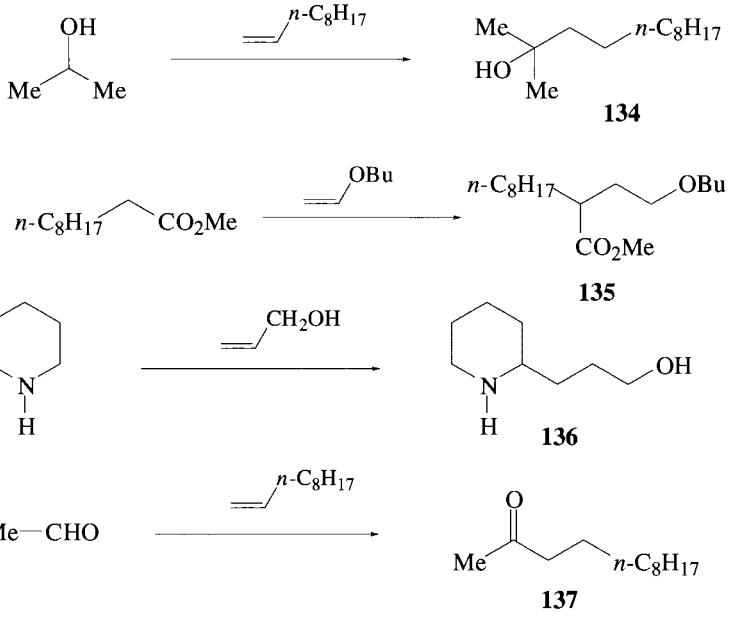
photolysis of tributyltin dimer. Under certain conditions, good diastereoselectivity can be achieved in radical addition reactions. When **131** was treated with *tert*-butyl iodide, Bu_3SnH, and $Sc(OTf)_3$, for example, a 58% yield of **132** was obtained as a 1:99 anti/syn mixture.[100]

When heteroatom containing substrates react with peroxides, or other radical initiators, hydrogen atom transfer can occur, as in the transfer of hydrogen from an acetal to the radical, generating the alkane and the α-alkoxy radical, **133**. The presence of the heteroatom α to the carbon bearing the radical center leads to enhanced stability. Such radicals add to alkenes, usually with anti-Markovnikov orientation, as in the radical

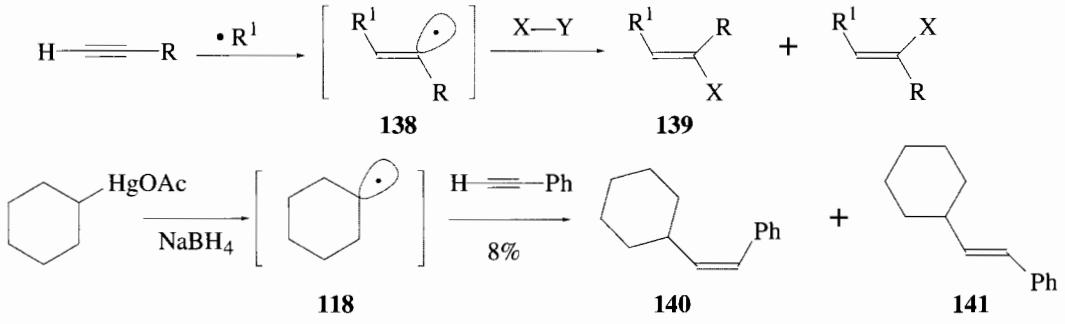


133

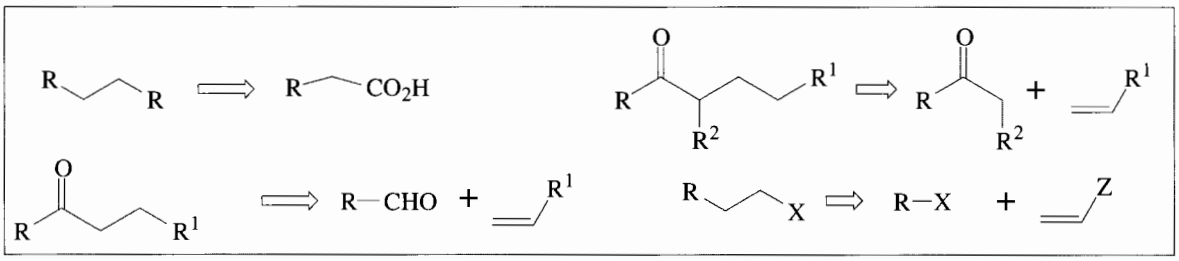
induced addition of HBr to alkenes (sec. 2.10.A). The reaction usually involves slow addition of a large excess (5–10 equivalents) of the heteroatom containing substrate. Peroxides and peroxyesters are the usual radical initiators. The hydrogen atom transfer reaction is often very slow, and an excess of the hydrogen atom donor (the heteroatom substrate) and higher reaction temperatures are essential.[101] Curran showed several general examples of this type of reaction involving alcohols (to give **134**), esters (to give **135**), amines (to give **136**), and aldehydes (to give **137**).[102]



Alkynes are generally less reactive than alkenes in radical coupling reactions since the LUMO of the alkyne is energetically higher than the LUMO of an alkene (sec. 11.2.A, Table 11.1). Formation of the requisite SOMO is therefore more difficult.[103] The intermediate vinyl radical (**138**) undergoes coupling to give a mixture of cis and trans isomers, as shown, generally favoring the cis compound (**139**), which results from trans-attack, but is important only when R is rather bulky. An example is formation of **118** from cyclohexyl mercuric acetate. Addition to 1-phenylethyne gave a 70:30 mixture of **140/141** in 8% yield.[103] Addition to methyl propiolate showed better reactivity but poorer selectivity.[103] As the size of R increases, syn approach of the hydrogen donor is increasingly hindered.[103] Nonradical nucleophiles usually react faster with alkynes than with alkenes, however.[104]



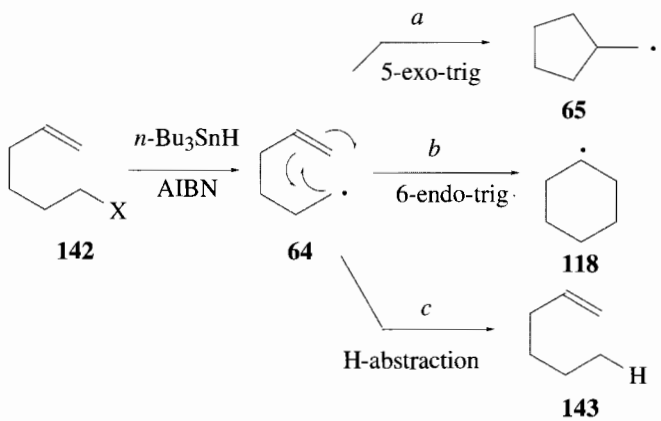
The disconnections that are pertinent to intermolecular radical coupling reactions include



13.7. INTRAMOLECULAR RADICAL REACTIONS (RADICAL CYCLIZATION)

13.7.A. Carbocyclic Ring Systems

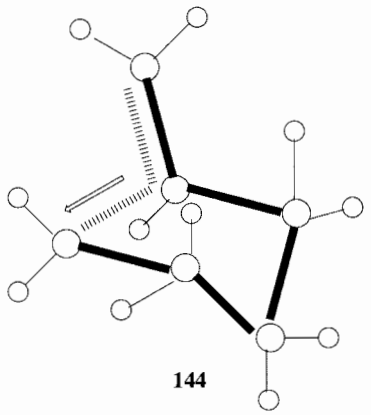
Curran's review[8] discusses many examples of radical reactions that produce rings.[105] The fundamentals of the reaction can be illustrated by the AIBN induced reaction of tributyltin hydride and **142** (X = I or Br), which generates radical **64**. Once formed, at least three different pathways are possible under these conditions.[106] The first is **path *a***, a favored 5-exo-trig-cyclization to give **65**. **Path *b*** is a favored 6-endo-trig-cyclization to give **118**. These descriptors are based on **Baldwin's rules** (sec. 6.6.A). The last pathway is the usual hydrogen-transfer process where tin hydride reacts with **64** to give **143** (**path *c***), as discussed in Section 13.5.D. In general, the 5-exo-trig-pathway is lower in energy than **path *b*** and faster than **path *c***, leading to **65**



as the major product, which is subject to steric effects or electronic effects that arise from interaction of substituents on the alkenyl moiety. At high concentrations (> 5 M) hydrogen transfer to give **143** usually

predominates so most successful radical cyclization reactions are done at low concentrations (< 0.05 M).[8] In cases where path *c* is faster than path *a* or *b*, photolysis in the presence of *n*-Bu3Sn—Sn-*n*-Bu3 (a halogen transfer agent such as iodomethane is usually added) will usually give cyclized products such as **65** rather than **141** (see below). The commercially available dilauroyl peroxide has also been used to induce radical cyclization with alkyl iodides, and constitutes a tin-free procedure for radical iodine atom transfer reactions.[107]

Formation of the five-membered ring via a 5-exo-trig reaction is a kinetic process. Given a choice between a larger and a smaller ring, radical cyclization generally gives the smaller ring. The reason for the 5-exo-trig preference is a better SOMO–LUMO overlap (≈ 109° angle of attack) than is possible in the 6-endo-trig transition state.[108] Beckwith calculated the transition state strain energies for radical cyclization of ω-alkenyl radicals, as shown in Table 13.3.[109] The ΔE_S for the exo transition state is lower in energy than the corresponding endo transition state, except for octenyl radical and 2-methyl-1-hexenyl radical. The former reflects the difficulty in forming eight-membered rings, and the latter reflects the increase in steric strain due to the presence of methyl group. Beckwith used **144** as the model for exo-trig ring closure and **145** as the model for endo-trig ring closure.[109]



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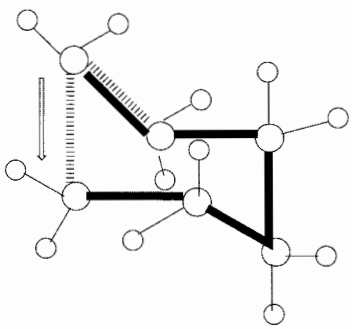

145

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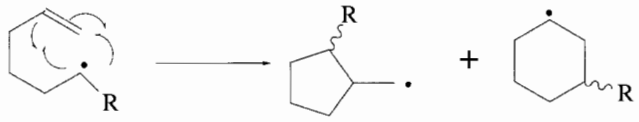
This preference is seen for the cyclization reaction of **146**, where the five-membered ring radical product (**147**) predominated with a variety of substituents R rather than the cyclohexyl radical (**148**).[110] When R is hydrogen or an alkyl group, the ratio of **147/148** is >95:5. That ratio is 93:7 when R is CO_2R^1, and ≈ 75:25 when R is COR or COPh.[110] The radical cyclization products **150–152** illustrate another potential problem

Table 13.3. Transition Structure Strain Energies (kcal mol^{-1})

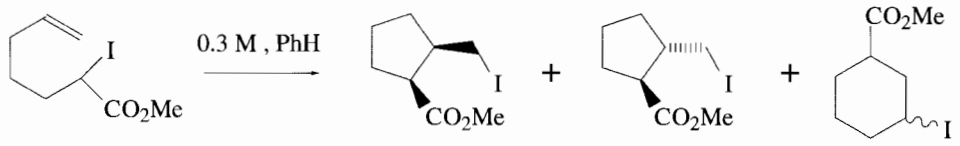
Structure	E_S(ground)	ΔE_S (exo)	ΔE_S (endo)	E_{act} (exo)	E_{act} (endo)
CH_2=CH(CH_2)$_3CH_2$•	2.9	7.5	10.3	6.8	8.5
CH_2=CH(CH_2)$_4CH_2$•	3.5	9.2	10.5	7.9	8.8
CH_2=CH(CH_2)$_5CH_2$•	4.2	15.8	15.3	9.6	
CH_2=CMe(CH_2)$_3CH_2$•	3.4	9.7	9.5	8.5	7.9
HC≡C(CH_2)$_3CH_2$•	2.3	7.5	14.7	8.3	

with this reaction, formation of cis or trans isomers. As seen in Table 13.4,[110] iodoalkene **149** gives essentially a 1:1 mixture of cis (**150**) and trans (**151**) products under a variety of conditions, with the 6-endo-trig product (**152**) as a minor constituent, These results illustrate that in the absence of special controlling factors (steric, electronic, neighboring group effects, etc.) the cyclization proceeds with poor cis–trans selectivity.



146 **147** **148**

Table 13.4. cis–trans Selectivity in the Radical Cyclization of 149



149 **150** **151** **152**

Conditions	Yield (%)	150/151/152
10% Bu_3SnH, AIBN, 5 h	48	48:45:7
10% AIBN, 24 h	78	49:43:8
$Me_3SnSnMe_3$, heat, 16 h	83	53:40:7
$Bu_3SnSnBu_3$, *hν*, 24 h	42	50:40:10

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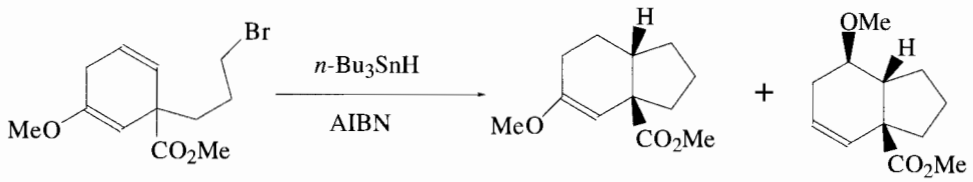
In the formation of polycyclic systems the cyclization process can lead to more than one regioisomer or stereoisomer. As noted in Table 13.4, the ratio of (*E*) and (*Z*) isomers is often ≈ 1:1. In most cyclizations, cis-ring fusion predominates when the final product is a bicyclo[3.3.0]- or bicyclo[4.3.0]- system but formation

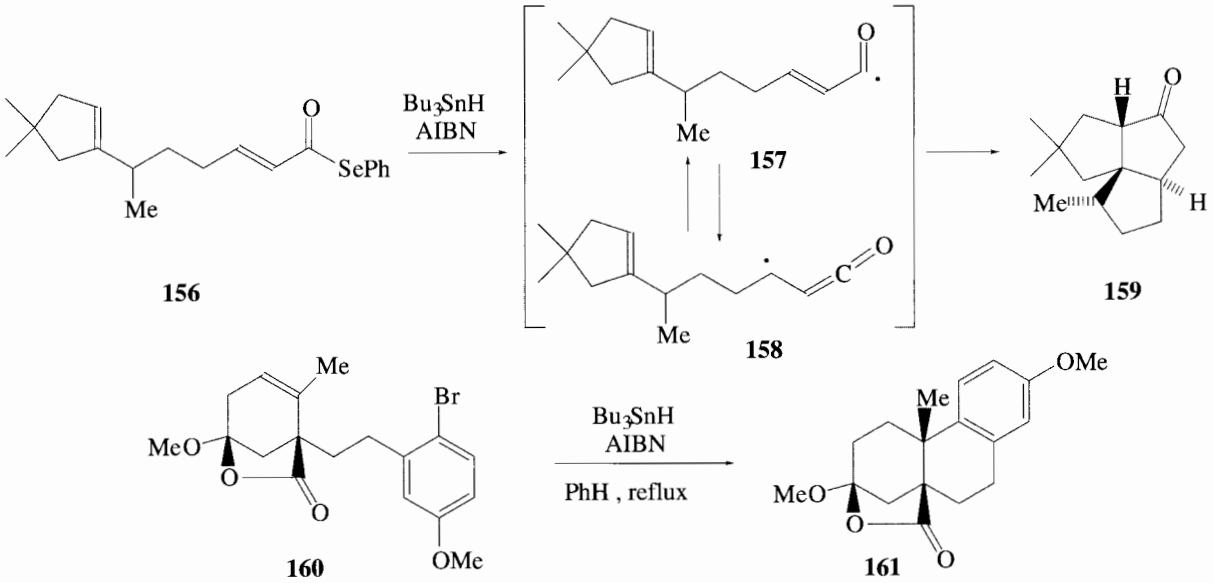


153 **154** **155**

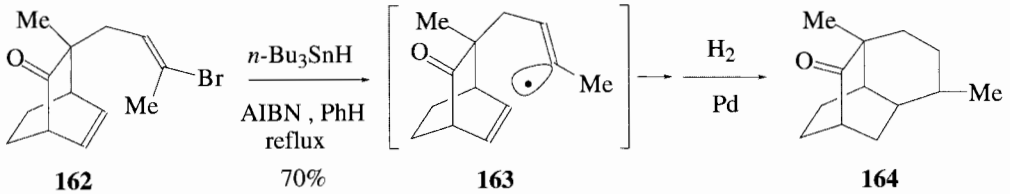
of a bicyclo[5.3.0]- system usually leads to significant amounts of trans-fused products.[111] In the cyclization of **153**, not only are mixture of (*E*) and (*Z*) isomers possible, there are two different alkene moieties that lead to different regioisomeric products. Abstraction of the bromide in **153** with $Bu_3Sn•$ generates a radical that cyclizes and is then quenched with tin hydride via hydrogen transfer to give a 1:1 mixture of **154/155** in 89% yield (there are diastereomers resulting from the presence of OMe and the ratio of α/β-methoxyl isomers in

155 was 3:1).[112] All products are cis fused. The reaction was controlled by frontier molecular orbitals (SOMO-LUMO, sec. 13.4) rather than stabilities of radical intermediates.

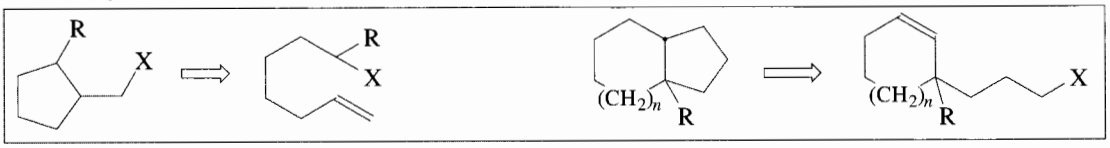
There are many synthetic examples that use radical cyclization as a key step, and the radical precursor is not limited to iodides or bromides. In Pattenden's synthesis of pentalenene,[113] conjugated selenyl ester **156** was treated with Bu_3SnH and AIBN to give a 45% yield of tricyclic ketone **159**. Loss of PhSe generated the acyl radical **157**, which exists in equilibrium with the ketene radical **156**. Radical cyclization via the latter intermediate leads to **159**. Cyclization via aryl radicals is also possible. In Schultz's synthesis of hexahydrophenanthren-2-one derivatives,[114] aryl bromide **160** was cyclized to **161** in 78% yield under standard conditions. Radical cascade reactions have become quite popular for the synthesis of polycyclic ring systems. In these reaction, polyenes are subjected to radical cyclization, generating tricyclic or even tetracyclic ring systems.[115] Chiral auxiliaries have been used effectively in radical cyclization reactions.[116]

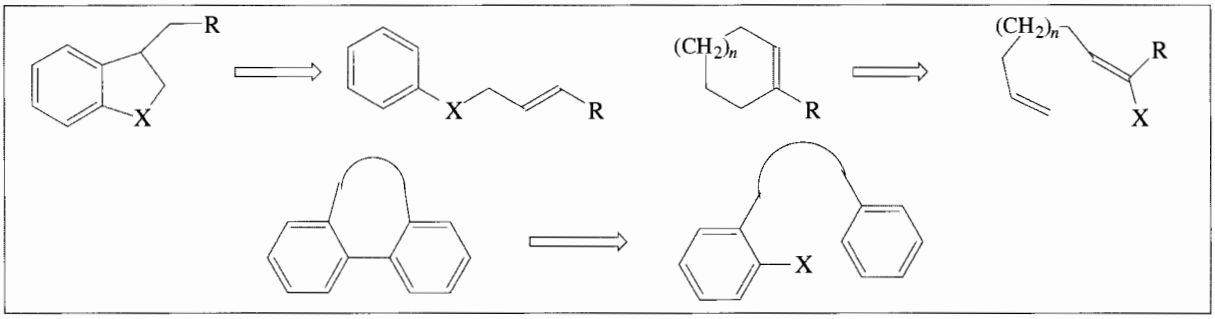


Vinyl radicals are useful in radical coupling and addition reactions.[117] Stork used the cyclization of vinyl radical **163** (derived from vinyl bromide **162**) to complete a synthesis of norseychellanone (**164**).[118] The cyclization step proceeded in 70% yield.



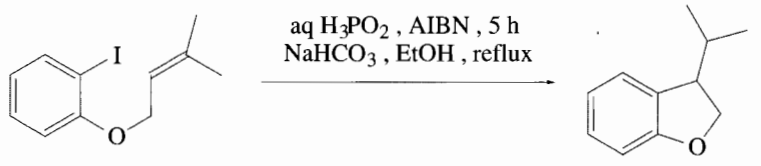
The radical cyclization disconnections are



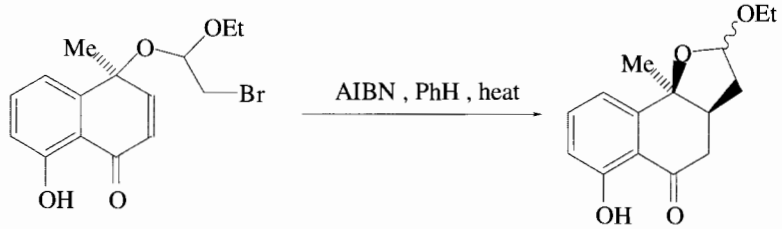


13.7.B. Heteroatom Ring Systems

Although the examples shown for the most part use AIBN and tributyltin hydride in refluxing benzene, other solvents can be used. For instance, radical cyclization of **165** in aqueous ethanol using a combination of phosphoric acid and a base led to **166** in 83% yield.[119] In this example, it is clear that heteroatoms can be part of the chain that links the radical precursor and the alkene. Stork introduced a modification that produces protected lactones via radical cyclization. In a synthesis of 12a-deoxytetracycline, Stork converted **167** to **168** under standard conditions, in 90% yield.[120]

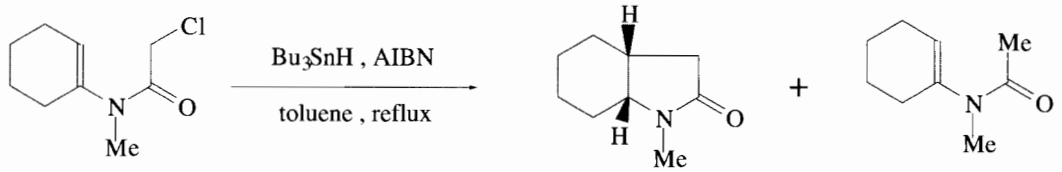


165 **166**



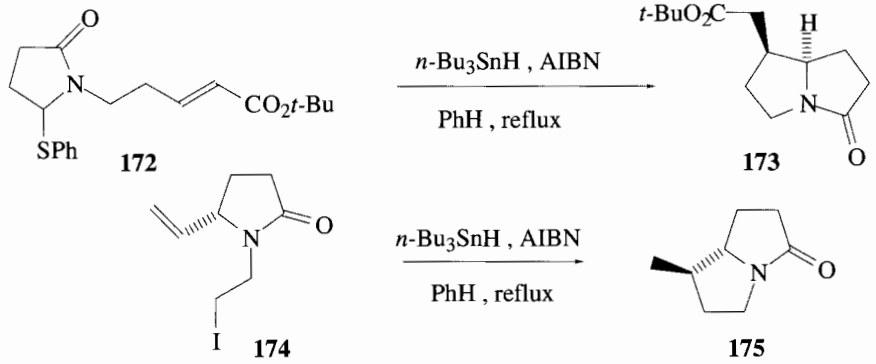
167 **168**

Heterocyclic rings can be prepared by simply incorporating a heteroatom into the chain, as in the cyclization of **165** to **166** or **167** to **168**. When enamide systems such as **169** are used, 5-exo-trig cyclization is possible (see sec. 6.6.A), but the success of the cyclization depends on the leaving group. When **169** was subjected to standard cyclization conditions, a 63% yield of **170** was obtained, along with 8% of **171**.[121] When the iodo derivative was used, however, 0% of **170** was obtained but a 5% yield of **171** was isolated.

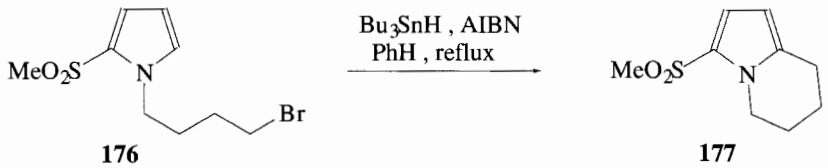


169 **170** **171**

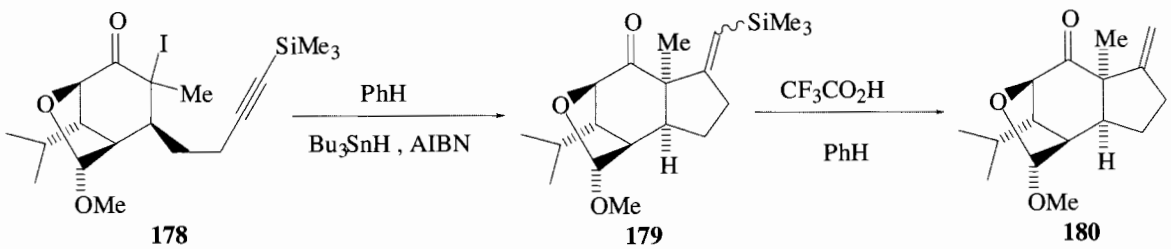
Both phenylthio (—SPh) and phenylseleno (—SePh) groups can be used as leaving groups for radical cyclization (see above). In these cases, sulfur or selenium atom transfer leads to formation of the radical. Hart and Tsai used this technique to cyclize **172** in a synthesis of isoretronecanol.[122c] The cyclization provided primarily racemic diastereomer **173**. Smith, however, used a chiral template approach and prepared alkenyl iodide **174** from the chiral precursor pyroglutamate. Radical cyclization gave pyrrolizidinone **175** in a synthesis of pseudoheliotridane, with high asymmetric induction.[123] Knapp et al. also used pyroglutamate derivatives for asymmetric radical cyclizations.[124]



Other heterocycles can be used in radical cyclizations. [125] Treatment of pyrrole derivative **176** with AIBN and tributyltin hydride gave a 60% yield of **177**. The sulfonyl group on the pyrrole ring was required for good yields of cyclized product.[126]

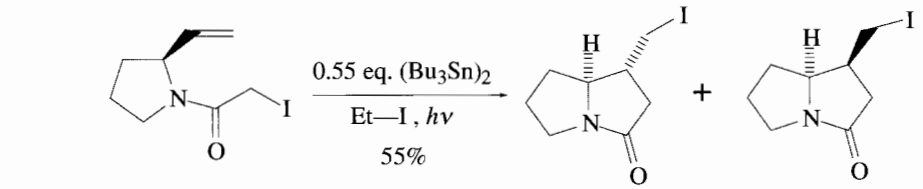


Alkynes are common precursors to *exo*-methylene compounds, as in Sha's synthesis of (–)-dendrobine.[127] The iodide in **178** was removed to form a radical, which added to the alkyne to form a five-membered ring with an exo-methylene unit in **179** [69% yield, (*E*/*Z*) = 1:9]. The trimethylsilyl group is important to sterically inhibit a 6-endo-dig reaction that can complete with the 5-exo-dig process. The silyl group was removed by treating **179** with trifluoroacetic acid in benzene, giving **180** in 84% yield.

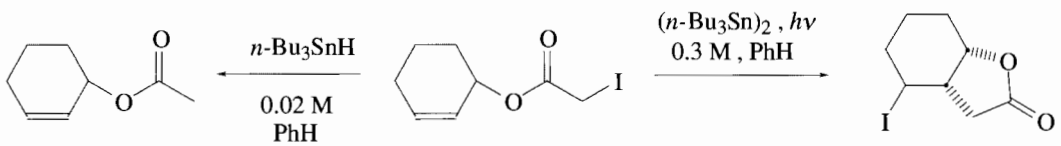


Radical cyclization with high diastereoselectivity and high asymmetric induction is possible when chiral precursors are used (as with **174** → **175** from pyroglutamate). Livinghouse and co-worker reported a chiral

synthesis of (–)-trachelanthamidine via cyclization of **181**, prepared from prolinal. He obtained a 30:1 mixture of **182** and **183** in 55% yield.[128] In this reaction, initiation with AIBN in the presence of tri-*n*-butyltin hydride led to significant amounts of the hydrogen transfer product (2-ethenyl-*N*-acetyl-2-pyrrolidinone). Hydrogen transfer is a common problem, and it was solved in this work by changing the method by which the radical is generated. Radical cyclization in the presence of tributyltin dimer ($Bu_3SnSnBu_3$) gave the desired products (as shown), but required photochemical initiation with a sunlamp.

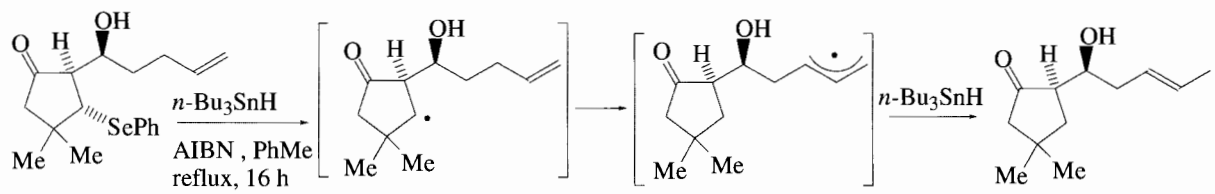


181 **182** **183**



185 **184** **186**

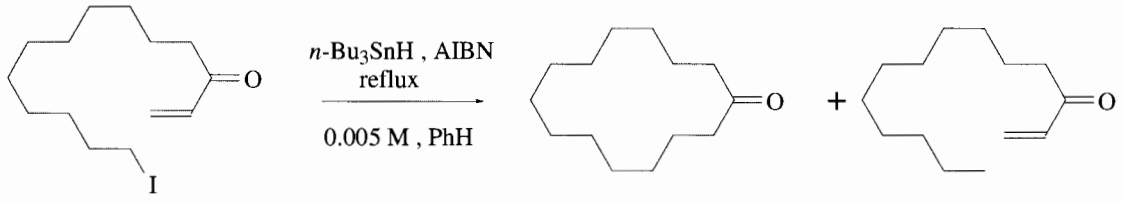
The use of dibutyltin dimer under photochemical methods is an atom-transfer method, and is most useful when the cyclization step is slow (see above). In those cases, hydrogen atom transfer to give reduced products usually dominates. Photolysis of the tin dimer generates the radical intermediate without a hydrogen atom transfer agent present (other than the substrate and the solvent). Another example illustrating the utility of this reagent in cyclization reactions is Curran's attempt to cyclize **184**, which gave only **185** on treatment with tin hydride/AIBN and no **186**. Cyclization with dibutyltin dimer and photochemical induction gave a radical intermediate that was quenched by reaction with the iodine radical byproduct to give **186**.[129] The iodine could be reduced by reaction with tin hydride.[129]



187 **188** **189** **190**

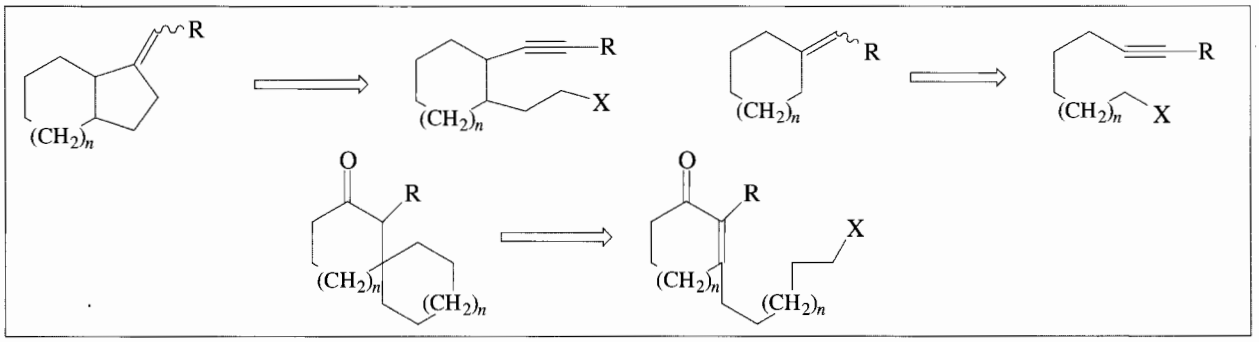
In radical cyclizations that involve formation of a six-membered ring, allylic hydrogen abstraction can be the preferred reaction. Attempted cyclization of **187** gave only **190** via hydrogen abstraction (from **188** to **189**), and no cyclization was observed.[130] A six-center transition state is possible in **188** for removal of the allylic hydrogen, and this process is faster than the 6-exo-trig transition state required for ring formation. The methyl groups in **188** presumably prevent close approach of the requisite hydrogen to the radical center. If an activating group is attached to the alkene receptor, formation of the six-membered ring is accelerated relative to hydrogen transfer.

Conjugate additions of this type are very facile in radical reactions. Many internal cyclizations of this type have been reported.[131] Relatively large rings can be prepared by this technique, as illustrated by the cyclization of **191** to **192** and **193** (63 and 22% yields, respectively).[132] The cyclization process is faster than the hydrogen transfer under high dilution conditions. The two remote reactive fragments of the long chain must be in close proximity for the cyclization.



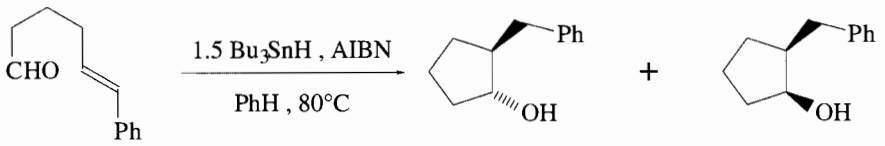
191 **192** **193**

The alkenyl and alkynyl radical disconnections are



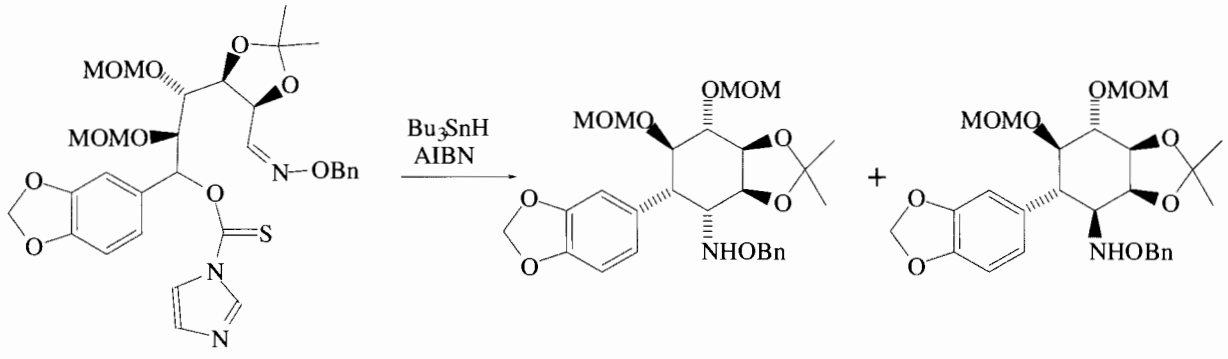
13.7.C. Cyclization to C=X and Cyclization of Heteroatom Radicals

Radical cyclization is not limited to addition to alkenes and alkynes. Carbonyls and imines can also be radical receptors. Enholm showed that when **194** was treated with AIBN and tributyltin hydride, the major product was a mixture of alcohols **195** and **196.**[133] Fu showed that this could be made catalytic in tributyltin hydride. When **194** was treated with 0.1 Bu_3SnH, 0.5 $PhSiH_3$, 2 equivalents of EtOH and AIBN, an 85% yield was obtained as a 1.1:1 **195/196** mixture.[134]

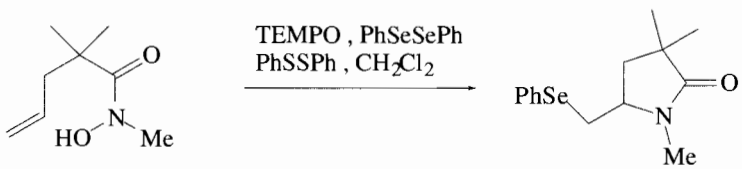


194 **195** **196**

In Keck's synthesis of 7-deoxypancratistatin, radical precursor **197** was cyclized to the oximine ether unit under radical conditions to give a 3:1 mixture of **198** and **199** in 90% yield.[135] Another very interesting variation was reported by Weinreb involving generation, cyclization, and trapping of amidyl radicals.[136] When hydroxamic acid **200** was cyclized with TEMPO in the presence of diphenyl diselenide, lactam **201** was obtained in 64% yield.

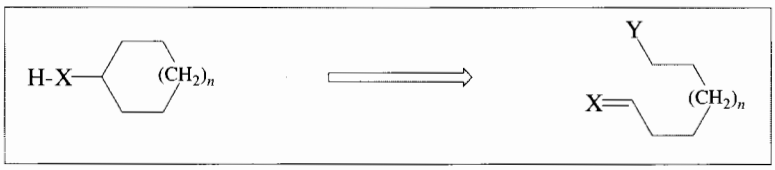


197 **198** **199**

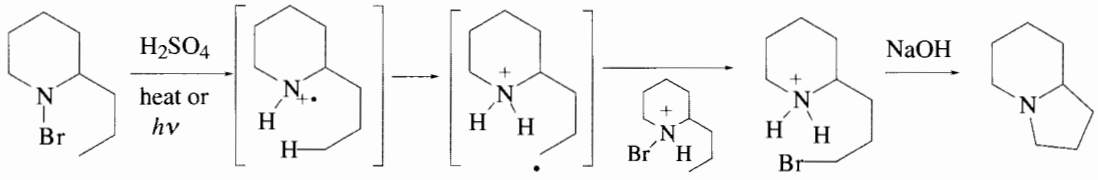


200 **201**

The C=X radical cyclization disconnection is



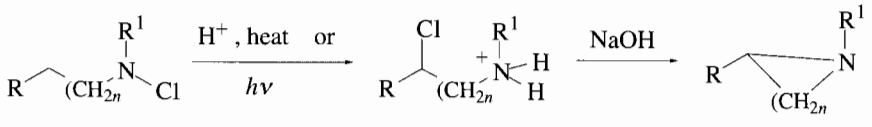
A classical named reaction provides another example of a hydrogen atom transfer reaction that produces a heterocyclic compound. When *N*-halo-amines[137] such as **202** are treated with concentrated sulfuric acid, the amino radical cation **203** is produced. Hydrogen atom transfer via a six-center transition state generates the



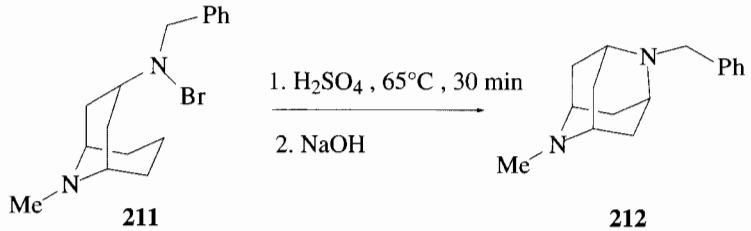
202 **203** **204** **205** **206** **207**

ammonium radical (**204**), which reacts with the protonated form of **202** (ammonium salt **205**) to give **206**. When **206** is neutralized, the amine displaces the primary halide to give a hexahydroindolizine (an indolizidine, **207**).[138] The conversion of N-haloamines to cyclic amines is called the **Hofmann–Löffler–Freytag reaction**.[139] In its original form, the reaction generated pyrrolidine derivatives and other cyclic amines, as in the conversion of **208** to **209**. When treated with base, the free amine was generated and subsequent nucleophilic displacement of chloride (cyclization) led to **210** as the final product. This reaction can be initiated photochemically[140] or thermally (in the presence of acid), as in the conversion of **211** to **212** in 84% yield.[141] The high temperatures required for this conversion sometimes leads to poor stereoselectivity. One

solution to this problem is to use a mixture of cuprous chloride and cupric chloride (CuCl—$CuCl_2$) in acidic media to effect cyclization.[142]

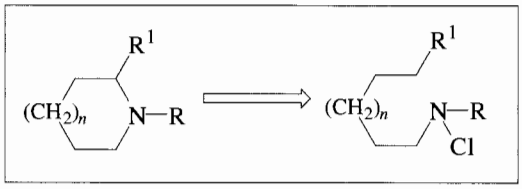


208 **209** **210**



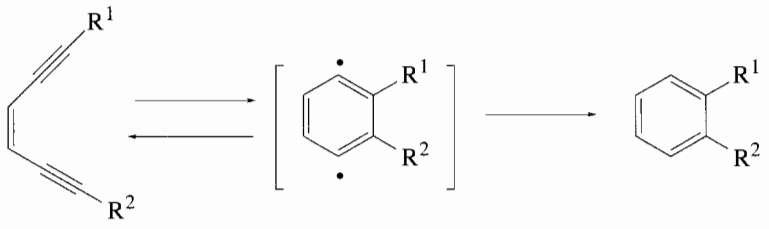
211 **212**

The Hofmann–Löffler–Freytag disconnection is



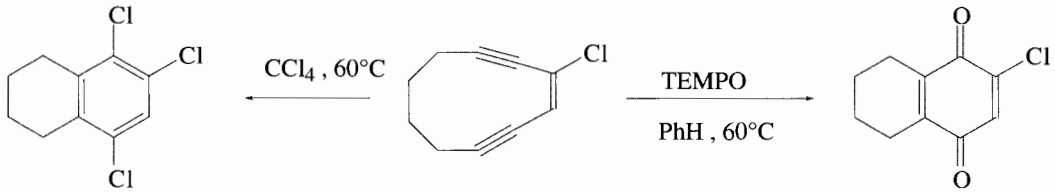
13.7.D. Bergman Cyclization

Ene–diynes undergo a cycloaromatization reaction that is formally a thermally allowed electrocyclic reaction. In principle, it belongs in Chapter 11, but it is known that the reaction proceeds by a diradical. For that reason and since a ring is formed, it is placed in this section, although it is not formally a radical cyclization. In a generic example, ene–diyne **213** cyclizes to give diradical **214**, which loses two hydrogen atoms via aromatization to give the benzene ring in **215**. This conversion of an ene–diyne to a benzene derivative is called the **Bergman cyclization**.[143] The activation barrier for this process can be greatly influenced by electronic substituent effects.[144] A metal-accelerated Bergman cycloaromatization has been reported, using an arene complex, [(η^5-C_5Me_5)Ru(η^6-3,4-benzocyclodec-3-ene-1,5-diyne][OTf].[145] This reaction has taken on great importance with the discovery that the biological action of several anticancer antibiotics [calicheamicin, dynemicin, esperamicin, and kedarcidin] is linked to Bergman cyclization of an ene–diyne core structure accompanying cleavage of double-stranded DNA[146]



213 **214** **215**

From a purely synthetic viewpoint, the radicals generated by the Bergman cyclization have been used to initiate further cyclization, including the preparation of aromatic compounds. In one example, Jones and Plourde prepared a series of chlorinated ene–diynes and used the Bergman cyclization to convert them to chlorinated aromatic compounds.[147] Heating **216**, for example, gave a 40% yield of **217**. Interestingly, heating **216** with tetramethylpiperidinyloxy free radical (TEMPO) led to a 30% yield of the chlorinated benzoquinone **218**. The additional chorine atoms in **217** are attributed to atom transfer chemistry from carbon tetrachloride to the diradical intermediate.



216 **217** **218**

13.8. METAL–INDUCED RADICAL REACTIONS

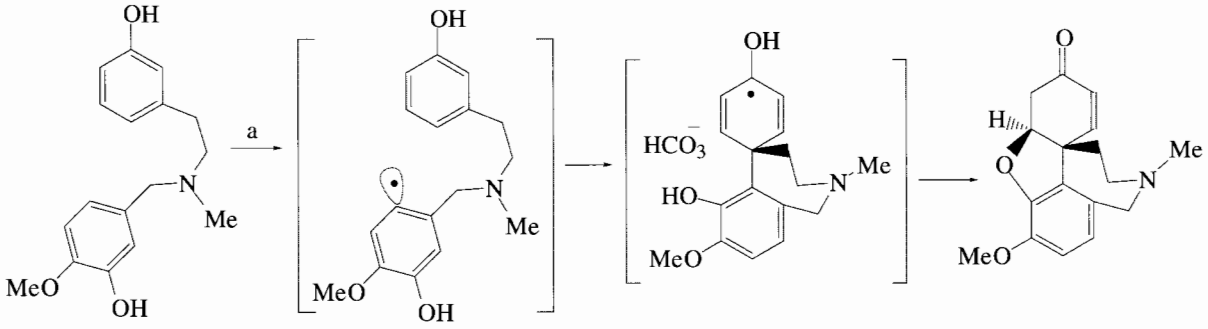
13.8.A. General Principles

This type of reaction can take at least two forms: (1) electron transfer of a metal to a peroxide, leading to reactive free radicals and (2) direct electron transfer from a metal to an alkene, carbonyl, or aromatic substrate. An example of the first type of reaction is oxidation with **Fenton's reagent** (sec. 3.3.A)[148] which initiates oxidation of aryls to phenols, although the yields are usually only 5–20%. In this reaction, ferrous ion (Fe^{2+}) is oxidized to ferric ion (Fe^{3+}) by hydrogen peroxide, which gives hydroxide and hydroxyl radicals (HO•),[148] which initiates a chain process, which can be terminated by reaction of HO• with Fe^{2+}. Oxidation of benzene with Fenton's reagent gave only a small amount of phenol, but large amounts of biphenyl, arising from coupling of the aryl radicals. Another metal system is Ti^{3+}—H_2O_2 (at pH 2), which generates HO• and HOO• radicals.[149] Transition metals such as titanium, cobalt, and manganese are often used in conjunction with hydroperoxides, and decompose under these conditions to alkoxy radicals (RO•) and alkyl peroxyls (ROO•).[148a,150] In all cases, reaction with the metal generates a radical, which then reacts with the carbon fragment to induce the desired radical reaction. The latter metal–peroxide reaction was discussed previously in Section 3.4.B in connection with the transition metal–peroxide oxidation of alkenes to oxiranes.[151]

13.8.B. Phenolic Oxidative Coupling

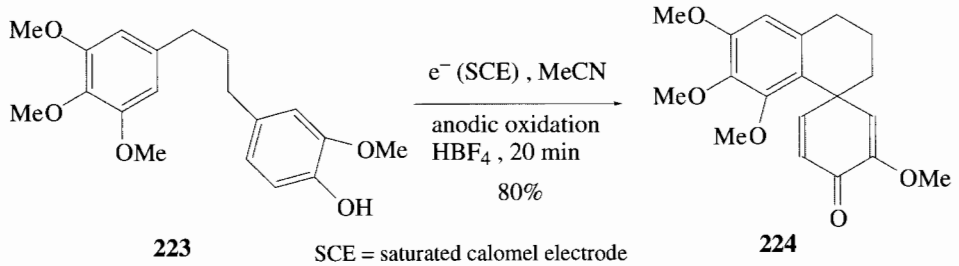
A classical oxidation reaction that involves radicals is the **phenolic oxidative coupling**,[152] which is introduced in Section 10.5.A.i. In this reaction, electron transfer from a metal salt to a bis(phenol) leads to intramolecular coupling and a quinone product. The early yields were poor. For example, Barton reacted **219** with potassium ferricyanide [$K_3(Fe(CN)_6$] and the product was aryl radical **220**. This radical reacted with the second phenolic ring in an intramolecular process that gave **221**. Loss of a hydrogen led to the quinone narwedine (**222**) in a synthesis of galanthamine.[153] The yield of **222**, however, was only 1.4% under optimal

conditions. Kametani et al. improved the yield of the oxidation only slightly by using an amide derivative of **219**, but the cyclization proceeded in 5% yield in his synthesis of galanthamine.[154] A similar oxidation procedure was used by Gervay et al. to generate erythrinadienone in 35% yield,[155] which constituted a great



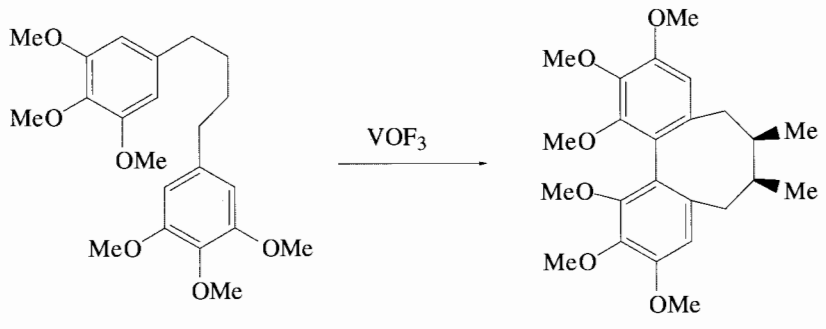
(a) $K_3[Fe(CN)_6]$, $NaHCO_3$

improvement in the yield. It remained relatively low, however, due to the shortness of the tether between the two aryl moieties, or from the steric hindrance provided by the hydroxyl and alkoxyl groups.[156] Other oxidative methods can be used, including anodic oxidation under electrolysis conditions. In simple systems, good yields can be obtained, as in the anodic oxidation of tetramethoxy derivative **223** to give **224** in 80% yield, where **224** was a key intermediate in Tobinaga's synthesis of colchicine.[156] In another variation, Stevenson and co-workers used VOF_3 to convert **225** to deoxyschizandrin (**226**) in 54% yield.[157] Phenyliodine (III)bis(trifluoroacetate) has also been used to effect phenolic oxidative coupling.[158] It is noted that the success of phenolic oxidative coupling is dependent on the nature of the substituents on the aromatic rings, as well as the length of the tether.[159]



223 **224**

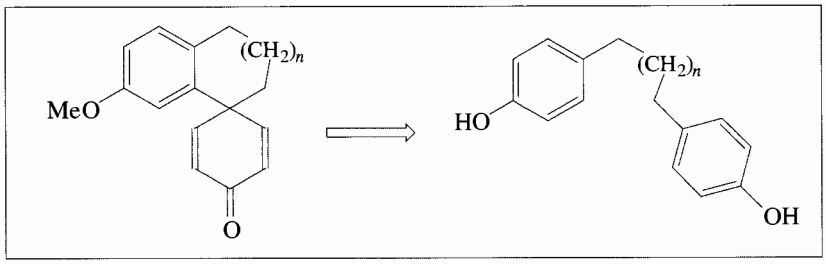
SCE = saturated calomel electrode



225 **226**

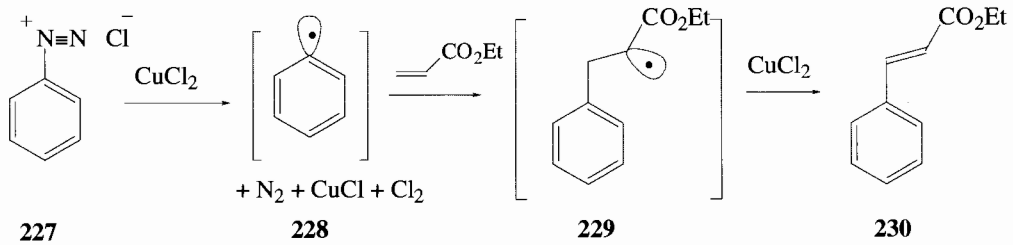
It is important to note that many phenolic coupling reactions may proceed via radical cation intermediates and/or phenoxonium ions, especially when the coupling is induced by electrochemical methods. In such cases, it is not always clear that the mechanism involves a radical–radical coupling reaction.

The phenolic oxidative coupling disconnection is

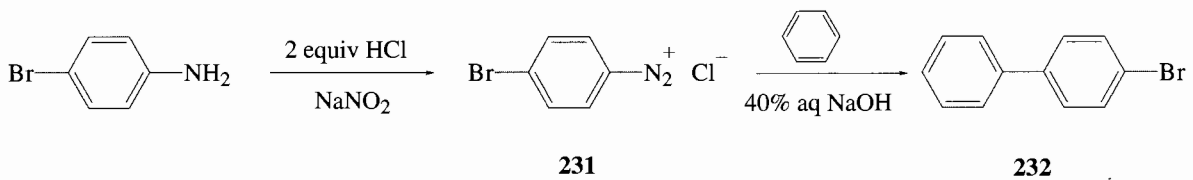


13.8.C. Copper–Catalyzed Coupling Reactions

Another metal–catalyzed radical reaction is the **Meerwein arylation.**[160] This reaction combines an aryl diazonium salt (such as phenyldiazonium chloride, **227**) with an electron-deficient alkene (containing an electron-withdrawing group such as carboethoxy in ethyl acrylate) to give the arene derivative (**230**). Cupric chloride ($CuCl_2$) was used to catalyze this coupling. Under these conditions, $CuCl_2$ induces loss of nitrogen



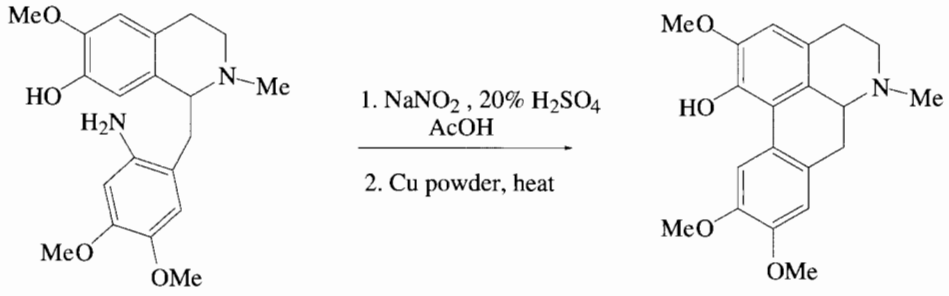
(N_2) from **227** to give the aryl radical (**228**), and formation of this radical is followed by addition to the alkene to give **229**. Subsequent reaction of this reactive intermediate with $CuCl_2$ generates the alkene (**230**) via loss of HCl, also generating CuCl. Titanium trichloride ($TiCl_3$) has also been used to initiate 1,4 addition to conjugated carbonyl derivatives.[161] It is noted that palladium salts are also used to induce similar aryl couplings. An example is the Heck reaction in Section 12.7.A.



There are many variations, and a wide range of aromatic diazonium salts can be used. One method for generating the diazonium salt is treatment of an aromatic amine with nitrous acid (HONO via reaction of HNO_3/HCl or $NaNO_2$/2 HCl).[162] These diazonium salts can be coupled to other aromatic compounds in the presence of base in what is commonly called the **Gomberg–Bachmann reaction.**[163] Treatment of 4-bromoaniline with nitrous acid, for example, gave the diazonium salt (**231**) which reacted with benzene to give the

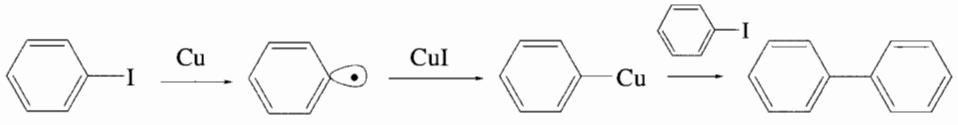
biphenyl derivative (**232**) in 46% yield.[164] The aromatic amine precursors are usually obtained by hydrogenation of nitrobenzene derivatives (secs. 4.8.D, 4.8.F).[165]

A related process that involves diazonium salts is the **Pschorr reaction**,[166] which also couples aryl diazonium compounds to other aromatic rings. This diazonium salt coupling can be done under acidic conditions, but addition of copper powder usually promotes the radical process. Aryl amines generate aryl diazonium salts upon treatment with nitrous acid.[167] An example is the reaction of **233** to give an aryl diazonium salt, which cyclized in the presence of copper to give thaliporphine (**234**) in 43% yield. Kupchan called this transformation an improved Pschorr reaction.[168]



233 **234**

The **Ullmann reaction**,[169,170] is very similar in that aryl halides are coupled to form biaryls (such as biphenyl) by heating with copper. Once again, the copper generates an aryl radical (in this case **19**), which reacts with Cu^+ to form an arylcopper(I) species (**235**). Subsequent reaction of the aryl copper with iodobenzene leads to a coupling reaction that gives biphenyl, which is actually an organocuprate coupling reaction, discussed in Section 8.7.A.ii, but is placed here to highlight the radical intermediate.



19 **235**

The reactivity of the aryl halide is dependent on the halide: I > Br > Cl.[170] An electronegative group in the ortho position activates the reaction. Nitro groups on the aromatic ring are activating in this type of coupling: ortho > para > meta.[171] 2-Iodonitrobenzene, for example, is very reactive but the 3-iodo and 4-iodo derivatives are about as reactive as iodobenzene. Even functionalized aryls such as ferrocene can be coupled using copper salts.[172] The preparation of several biaryls from aryl halides via Ullmann coupling is shown in Table 13.5.[170] For unsymmetrical coupling (two different aryl halides) the best yields are observed when one aryl halide is very reactive and the other is relatively unreactive. Reactive aryl halides have electronegative groups, such as nitro or carbomethoxy, ortho to the halogen. The use of bromides and chlorides maximize unsymmetrical coupling while iodo compounds generally give the symmetrical coupling product (Ar—Ar rather than Ar—Ar').[173] Unreactive halides lack an electronegative group in the ortho position and are usually

iodo derivatives. When unsymmetrical coupling is attempted with two unreactive aryls, three biaryls are usually produced in approximately equal amounts.[170] Ultrasound was shown to be very effective for the synthesis of diaryl ethers via the Ullmann reaction.[174] This reaction is similar to the Ni(0) coupling reactions discussed in Section 12.8.[175,176]

Table 13.5. Ullmann Coupling of Aryl Halides

$$Ar{-}X + Ar'{-}X' \xrightarrow{Cu \text{ or } Cu(I),\ PhH} Ar{-}Ar'$$

Ar	X	Ar'	X'	Conditions	% Ar—Ar'
Ph	I	Ph	I	Reflux	78
o-Me—Ph	Cl	*o*-Me—Ph	Cl	245°C	71
	I		I	60°C	99
2,4-diMe—Ph	I	2,4-di-Me—Ph	I	150°C	45
4-*i*-Pr—Ph	I	4-*i*-Pr-Ph	I	270°C	79
3,4-di-OMe—Ph	I	3,4-di-OMe—Ph	I	235°C	77
3-Ph—Ph	I	3-Ph—Ph	I	260°C	83
2-Me—Ph	I	2,4-di-NO_2—Ph	Br	175°C	55
4-OMe—Ph	Br	2-NO_2—Ph	Cl	195°C	20
2-CO_2Me—Ph	I	3-Me—Ph	I	260°C	13
Ph	I	2-NO_2—Ph	Br	200°C	60
2-Ph—Ph	I	Ph	I	Reflux	40

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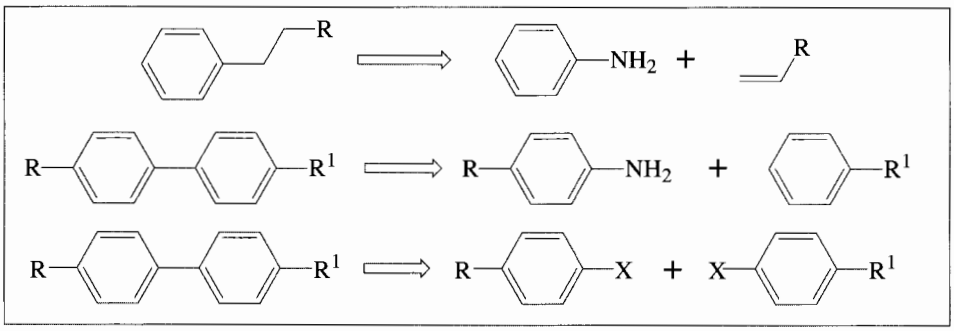
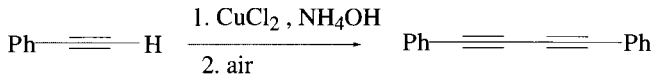
The disconnections for copper promoted coupling are



Alkynes can be coupled under a variety of conditions,[177] including reactions that involve alkynyl copper derivatives. There are two classical alkyne coupling reactions. The first is the **Glaser reaction**[178] in which an alkyne such as phenylacetylene reacts with basic cupric chloride ($CuCl_2$) to give a diyne (**236**) in 90% yield upon oxidation with air. The second is the **Cadiot–Chodkiewicz coupling**[179] in which a bromoalkyne (such as **238**) reacts with a terminal alkyne (3-ethoxy-1-propyne, **237**) in the presence of cupric chloride and an amine to give the diyne (a 90% yield of **239**).[179a] Glaser type coupling of alkynes can be accomplished with other copper derivatives and bases other than hydroxide. The mixture of cupric acetate and pyridine was an effective reagent for this coupling.[180] Intramolecular coupling reactions are known.[181] It is also possible to

couple alkynyl copper derivatives with aryl halides [182,183] or other aromatic substrates.[184] This methodology can also be applied in an Ullmann–type reaction, analogous to that described for aryl halides where a vinyl iodide is coupled in the presence of copper.[185] Alkynylsilanes can also be coupled using Cu(I) salts.[186]



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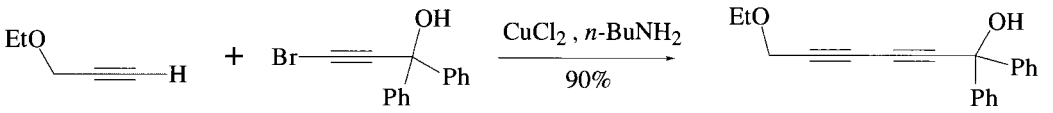
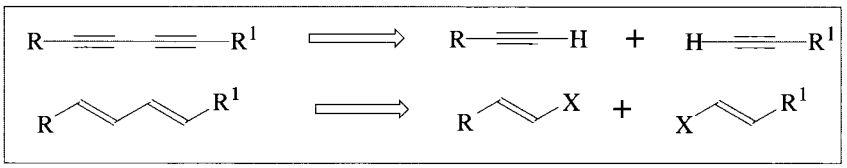


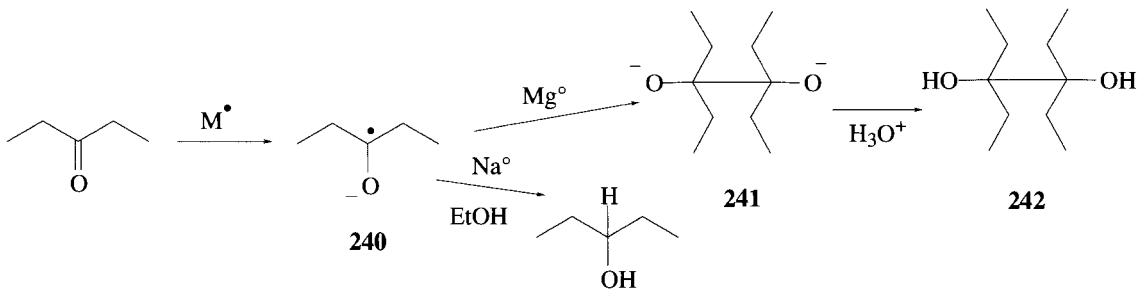
237 **238** **239**

The disconnections for copper promoted coupling of alkynes and alkenes are



13.8.D. Pinacol Coupling

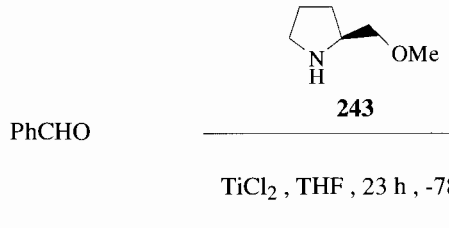
Perhaps the classical metal transfer reaction is the **pinacol reaction** or **pinacol coupling**,[187] in which alkali metals react with a ketone such as 3-pentanone to produce a radical anion (ketyl **240**) via electron transfer (secs. 4.9.A, 4.9.B).[188] Other reagents have been developed that also give pinacol coupling,[189] including samarium iodide,[190] titanium(IV) iodide,[191] and $TiCl_4$–Bu_4NI.[192] In another study, lanthanide metals were shown to be quite effective for promoting pinacol coupling, in the presence of chlorotrimethylsilane.[193] If a monovalent metal such as sodium or potassium is used in the presence of an alcohol (ethanol is the most



240 **241** **242**

common), the carbonyl is reduced to the alcohol (3-pentanone → 3-pentanol, for example, sec. 4.9.B). If a bivalent metal such as magnesium is used, however, the ketyl (the radical anion) is stabilized to a greater extent and reduction is slow. In such a case, the ketyl behaves more like a radical, leading to the coupling product (**241**). Hydrolysis leads to the diol **242**.[187,197] This reaction with ketones or aldehydes is a preferred method for the synthesis of 1,2-diols.[197,194] An asymmetric pinacol coupling of aromatic aldehydes was reported by Enders, using $TiCl_2$ and an enantiopure amine or hydrazine reagent.[195] When benzaldehyde was treated with

$TiCl_2$ and chiral amine **243**, for example, a 31% yield of **244** was obtained, as an 81:19 mixture of dl/meso diastereomers, and the *dl*-diastereomer was obtained in 65% ee (*S,S*).[194] When the reaction time was increased to 48 h, the yield improved to near quantitative, but the diastereomeric ratio was 56:44 dl/meso, and the enantioselectivity was only 37% ee.



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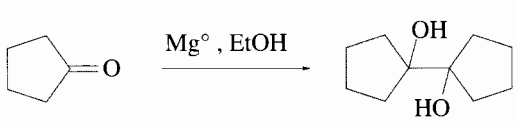

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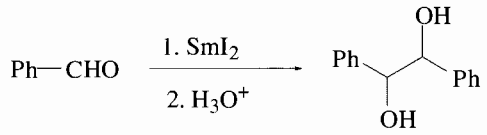
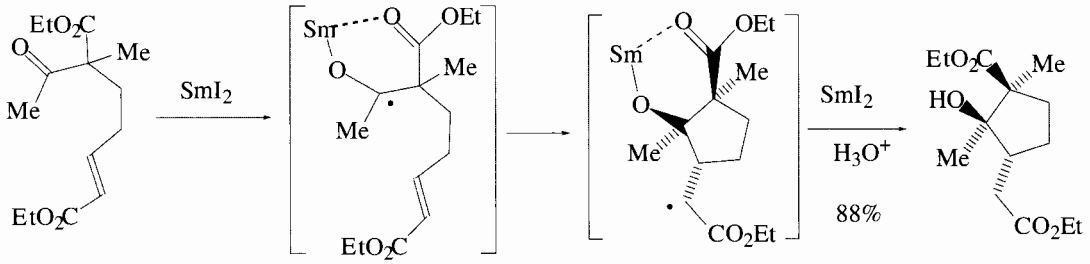


244

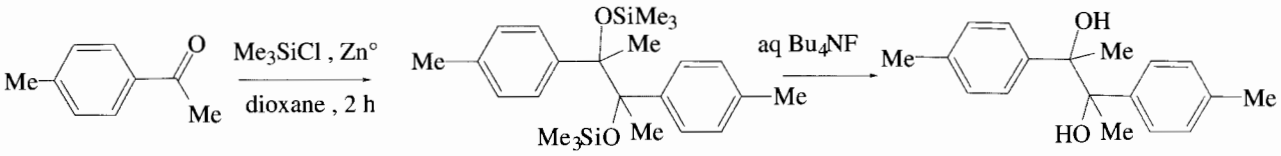
The preferred method for reductive coupling uses a mixture of magnesium and magnesium iodide (Mg + MgI_2), although magnesium amalgam (Mg/Hg) can also be used.[196] A classical example is reductive condensation of cyclopentanone to the 1,2-glycol **245**.[187] 2,3-Dimethyl-2,3-butanediol (also known as pinacol) is formed by pinacol reduction of acetone and gives the reaction its name.[187,194,197] Many other reductants can be used for this condensation reaction in addition to magnesium or sodium. Samarium iodide (SmI_2) was used for the coupling of benzaldehyde to **244** in 95% yield. Another lanthanide, ytterbium (Yb), has been used as the free metal for the reduction of ketones, but extensive coupling was observed. The extent of coupling depended on the ratio of ytterbium to ketone.[198] A related ketyl coupling reaction is Molander's conversion of **246** to the samarium stabilized ketyl (**247**). Conjugate radical addition to the acrylate moiety gave **248**, and hydrolysis led to an 88% yield of **249** (200:1 diastereoselectivity).[199]



246 **247** **248** **249**

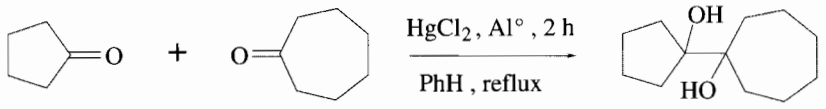
The pinacol coupling reaction can be applied to most ketones and aldehydes when two identical molecules are being coupled. An improvement in the reaction involves trapping the initial coupling product as the bis(trimethylsilyl) derivative. Coupling of 4'-methylacetophenone (**250**) with zinc in the presence of chlorotrimethylsilane gave 76% of the bis-*O*-silylether, **251**.[200] Treatment with tetrabutylammonium fluoride removed

the silyl protecting group (sec. 7.3.A.i) to give the pinacol product **252**. Coupling of two different ketones is also possible, but several different products can be formed in relative proportions close to those expected



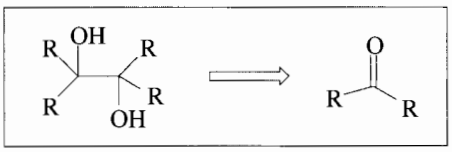
250 **251** **252**

from statistical coupling. In some cases, one product predominates but the yields can be low. When cyclopentanone was coupled to cycloheptanone in the presence of aluminum and mercuric chloride ($HgCl_2$), for example, only 23% of the cross-coupled diol (**253**) was formed.[201]

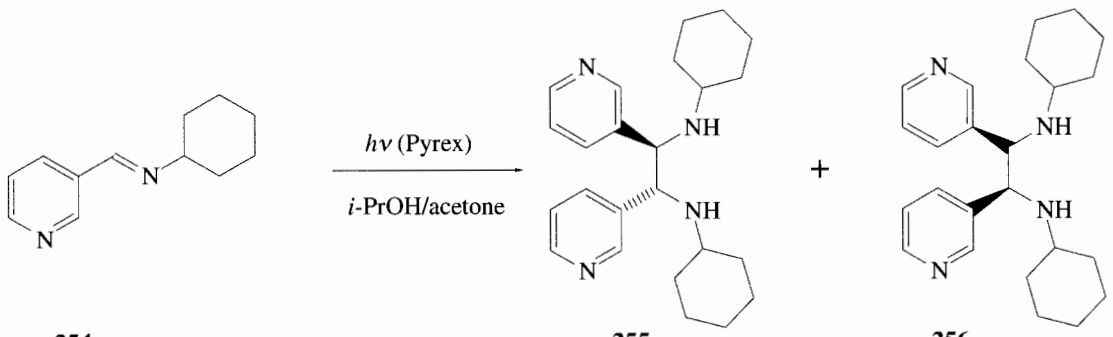


253

The pinacol disconnection is:



A related coupling reaction has been reported using imines. Photoreductive coupling of aldimines leads to the synthesis of C_2-symmetrical diamines. An example is the photocoupling of aldimines **254** to a 52:48 mixture of **255/256** in 85% yield.[202]

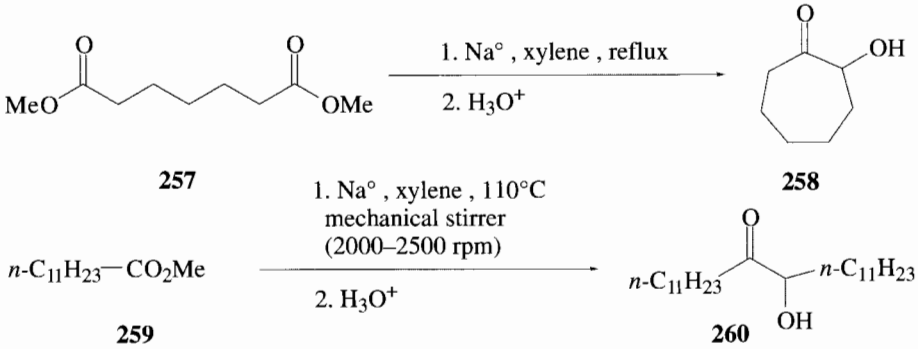


254 **255** **256**

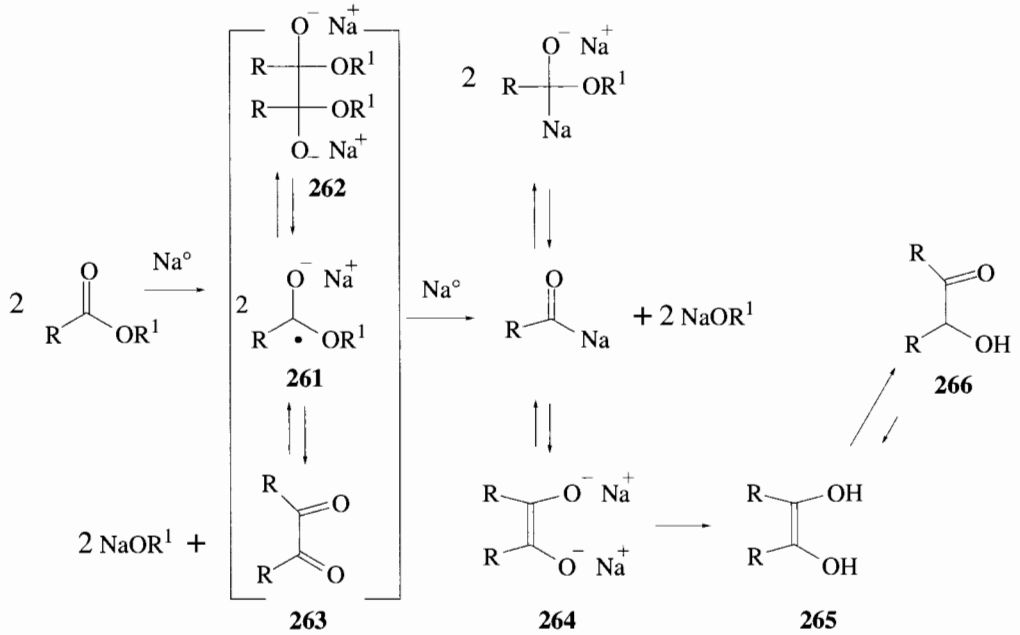
13.8.E. The Acyloin Condensation

A variation of the pinacol reaction has been applied to esters for the preparation of hydroxyketones (**acyloins**). A simple example is the reaction of **257** with sodium metal (Na°) in refluxing xylene, which gave a good yield of 2-hydroxycycloheptanone (**258**) after hydrolysis.[203] The condensation of an α,ω-diester to an

α-hydroxy ketone,[204] the **acyloin condensation**,[205,203] was first reported by Bouveault in 1905.[206] The reaction works well with relatively high molecular weight esters in an intermolecular reaction. Methyl laurate (**259**), for example, was treated with Na° (in xylene at 110°C) to give a 90% yield of lauroin (**260**).[207] The reaction conditions shown are typical, where high dilution techniques (sec. 6.6.B) were not required but effective stirring (high speed stirrer at 2000–2500 rpm) was necessary. The reaction proceeds[208] via initial transfer of an electron to form a ketyl (**261**), which is in equilibrium with the coupling product (**262**) and the



diketone (**263**). Transfer of a second electron to this mixture leads to **264**, and protonation generates a dihydroxy intermediate (**265**), which gives acyloin **266**. Radical coupling of the ketyl intermediate is most efficient when the ketyl is bound to or closely associated with the surface of the metal. The high-speed stirrer generates a fine "sodium sand", which maximizes the surface area for effective electron transfer and radical coupling of the ketyl. Under these conditions, both intermolecular coupling and intramolecular cyclization reactions are possible. The preparation of **261** is one example of an intermolecular acyloin condensation.



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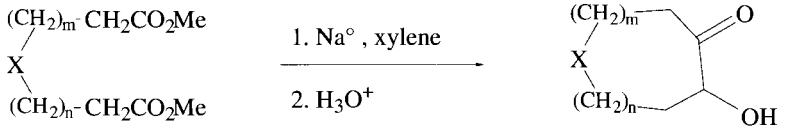
The intramolecular cyclization of α,ω-diesters to form cyclic acyloins appears to be the most efficient version of this reaction. This reaction does not require high dilution, and because of the template effect arising from reaction on the surface of sodium, good yields can be obtained even with medium sized rings. As shown in Table 13.6, the yields of acyloin (**268**) from simple diesters[203a] or diesters containing heteroatoms or aromatic 'spacers'[203b] are quite good, even when *n*+*m* in **267** is large. Introduction of double and triple bonds is also possible if the ring size of the final product is large.[203b] Amino and aryl functionality can be also incorporated (as in the paracyclophanes).[203b] For simple diesters, the yield was reasonable for medium and large ring compounds. Alkenyl derivatives gave good yields if the ring size was nine or greater, where the large ring size can accommodate flattening of the molecule due to the presence of the double bond (see sec. 1.5.D). cis-Alkene derivatives could be formed with even small rings but an eight-membered ring or larger was usually necessary for a trans-alkene. Even larger rings are required for derivatives containing an alkyne moiety. The two examples in Table 13.6 suggest that only 12-membered rings and larger can be formed if **267** contains an alkynyl group. The presence of an amino group is compatible with good yields for a variety of ring sizes, although the substituent on nitrogen plays a role. As expected, the paracyclophanes are more rigid and require even larger rings for good yields (15–18 membered).[209] The 20-membered ring (*m*=*n*=6), however, gave no acyloin under these conditions.

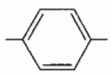
A modification of the acyloin condensation adds chlorotrimethylsilane, which traps the alkoxide intermediate. This has become the standard version of the acyloin condensation. Rühlmann and co-worker showed that ethyl butanoate reacted with excess sodium to generate the expected bis(alkoxide), **269**. Addition of chlorotri-methylsilane led to a 92% yield of the bis(trimethylsilyl)derivative, **270**,[210] and hydrolysis with 1N HCl in THF gave 96% of the acyloin (**271**). This modification serves two purposes. First, trapping the enolate

Table 13.6. Intramolecular Acyloin Condensations of 267



267 **268**

X	m	n	Ring Size	% 268
CH_2	2	1	8	47[c]
	2	2	9	9[b]
	2	3	10	45[b]
	3	4	12	76[ab]
	4	4[a]	13	72[c]
	4	5[a]	14	79[b]
	5	5[a]	15	77[b]
	5	6[a]	16	84[b]
	6	6[a]	17	85[b]

	6	7[a]	18	96[b]
	7	8[a]	20	96[b]
	13	14[a]	34	20[c]
MeCH	2	2	9	60[c]
C≡C	3	3	12	73[c]
	3	4	11	0[c]
cis-CH=CH	2	2	10	80[c]
trans-CH=CH	2	2	10	51[c]
Ph—N	1	1	7	10[c]
Me—N	2	2	9	75[c]
Et—N	2	2	9	73[c]
Ph—N	2	2	9	3[c]
C_6H_{11}—N	2	2	9	50[c]
p-Me-Ph—N	2	2	9	38[c]
Me—N	3	3	11	64[c]
Et—N	3	3	11	85[c]
	6	6	20	0[c]
	5	5	18	70[c]
	4	4	16	76[c]
	3	4	15	36[c]
	2	5	15	0[c]
	1	6	15	75[c]

[a] diethyl ester. [b] Ref. 203a. [c] Ref. 203b.

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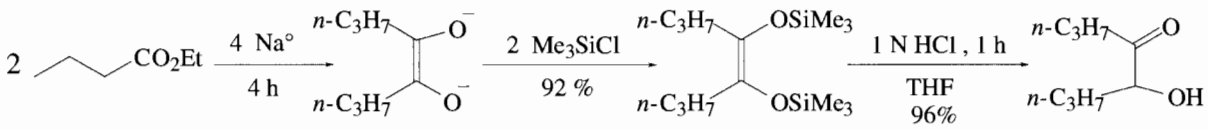
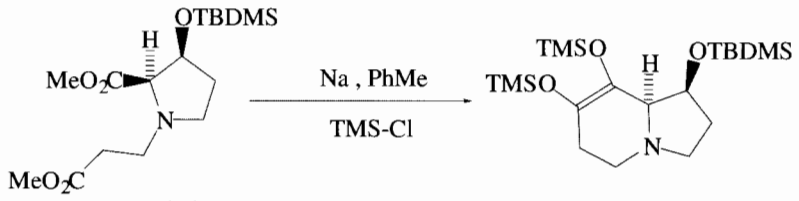
product allows its isolation and minimizes side reactions. Second, the O—TMS group protects the acyloin (see sec. 7.3.A.i), allowing further manipulation prior to unmasking the relatively sensitive α-hydroxyketone moiety. In those cases where there are no enolizable hydrogens in the O—TMS derivative, for example, treatment with bromine generates a 1,2-diketone.[211] When enolizable hydrogens are present, however, the normal acyloin product is observed.



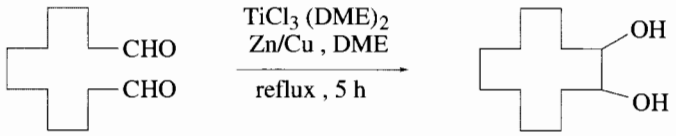
269 **270** **271**

A synthetic example is taken from Sih's synthesis of castanospermine,[212] in which diester **272** derived from hydroxy-proline was refluxed with sodium metal and chlorotrimethylsilane in toluene. This reaction led to formation of **273**, which could be isolated, and converted to the corresponding acyloin by mild acid hydrolysis.



272 **273**

McMurry and Rico generated an acyloin-like reaction using a titanium trichloride ($TiCl_3$)–zinc–copper couple. α,ω-Dialdehydes are coupled with this reagent to give 1,2-diols.[213] This procedure generates mixtures of cis and trans diols with the cis predominating for smaller rings and the trans predominating for larger rings.[213] Cyclization of 1,6-hexanedial [OHC—$(CH_2)_4$—CHO] under these conditions gave only *cis*-1,2-cyclohexanediol in 85% yield but cyclization of **274** gave a 25:75 cis/trans mixture of **275** in 75% yield.[213] As with the acyloin condensation, good yields are realized even with medium size (8–13 membered) rings.

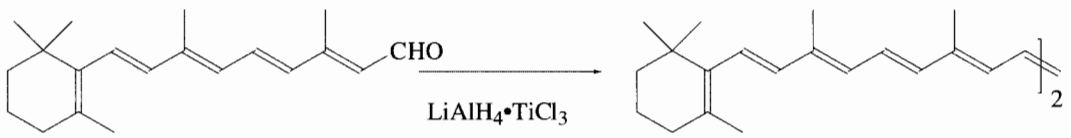


274 **275**

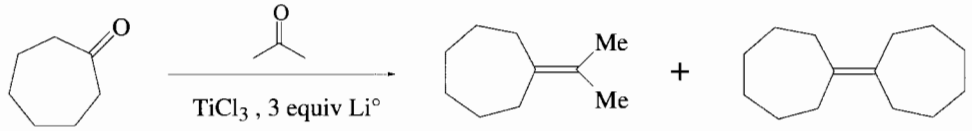
The acyloin disconnections are

13.8.F. McMurry Olefination

A useful relative of the acyloin condensation is the **McMurry olefination reaction**.[214] In this reaction, ketones or aldehydes are treated with Ti(0) ($TiCl_3$ + $LiAlH_4$; $TiCl_3$ + K; $TiCl_3$ + Li)[215] to give alkenes.[216] Reductive coupling is possible with a wide variety of ketones and aldehydes.[214,217] Retinal (**276**), for example, was coupled with this reagent to give β-carotene (**277**) in 85% yield.[217]



276 **277**



278 **279**

The $TiCl_3/K$ mixture is the most commonly used reagent, and a variety of carbonyl compounds can be coupled to give the corresponding alkene.[214,217] Decanal was coupled with $TiCl_3$ and K to give a 60% yield of the C_{20} alkene (10-icosene).[217] Cross-coupling is also possible as illustrated by the treatment of a mixture of cycloheptanone and acetone with $TiCl_3/Li$ to give a 50% yield of **278** along with 26% of **279**.[217]

The mechanistic studies of this coupling suggest it occurs "in a heterogeneous process on the surface of an active titanium particle", as outlined in Figure 13.7.[215] The byproduct is titanium dioxide (TiO_2) and electron transfer to the carbonyl generates the dianion (**280**), presumably via a ketyl-like intermediate. It has been suggested that the metallopinacol is not the only precursor, and that carbenoid intermediates and/or nucleophilic intermediates can be important.[218] In the commonly accepted mechanism, the initially formed dianion binds to the titanium particle as shown, and sequential homolytic cleavage (via **281**) liberates the alkene and titanium dioxide. McMurry's experiments discredited alternative mechanisms such as formation of a discrete cyclic (or acyclic) titanium dialkoxy species.[214] This reagent also led to elimination of 1,2-diols to alkenes, as in the conversion of *trans*-1,2-cycloheptanediol to cycloheptene in 55%.[219,214]

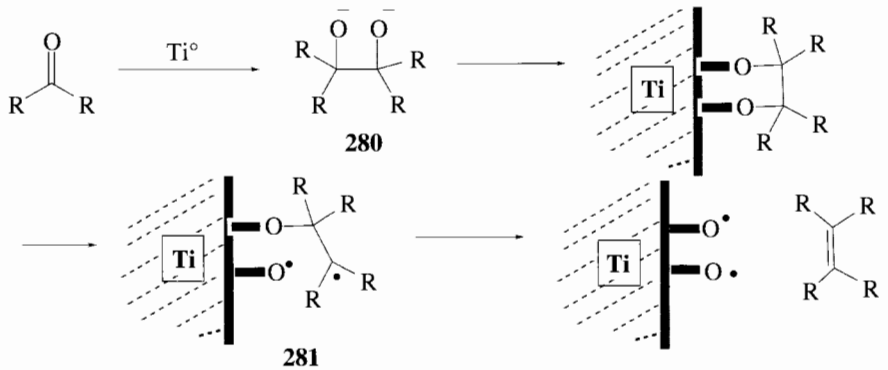
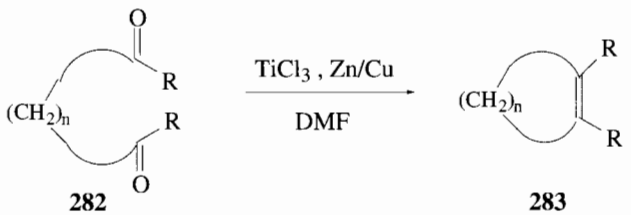


Figure 13.7. Mechanism of the McMurry coupling reaction. [Reprinted with permission from McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.*, ***1978***, *43*, 3255. Copyright © 1978 American Chemical Society.]

This reaction can be done intramolecularly, but Zn–Cu/$TiCl_3$ is the more common catalyst, although Zn and $TiCl_4$ are also used (see Table 13.7).[215] The final product of the intramolecular reaction is a cyclic

Table 13.7. Intramolecular McMurry Coupling of Diketones and Dialdehydes (282)

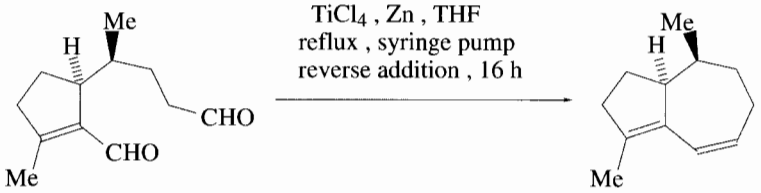


n	R	R^1	% 283
2	Ph	Ph	87
3	Ph	Me	70

4	Me	C_7H_{15}	79
6	Am	Am	67
7	Am	Am	68
8	Bu	Bu	76
9	Bu	Bu	76
10	H	H	76
10	Pr	Pr	71
11	H	H	52
12	H	H	71
12	Et	Et	75
13	H	Ph	80
14	H	H	85
20	Me	Me	83

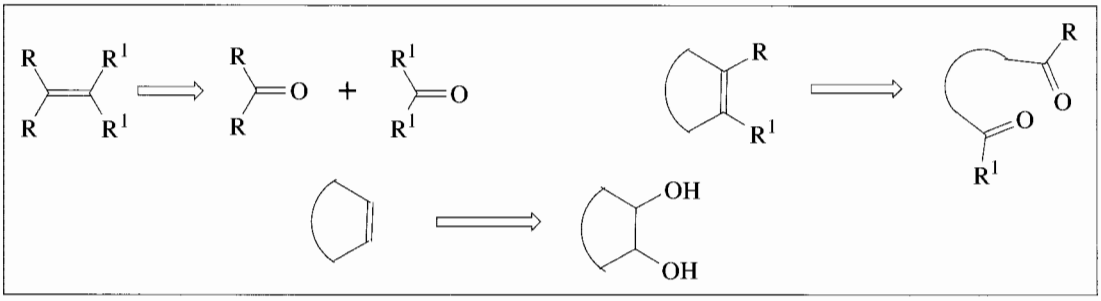
[Reprinted with permission from McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. *J. Org. Chem.*, ***1978***, *43*, 3255. Copyright © 1978 American Chemical Society.]

alkene. Since the reaction proceeds via a titanium bound ketyl species, the two reactive ends are in close proximity, allowing efficient coupling of even medium and large rings, analogous to the acyloin condensation.[220] Table 13.7[215] shows the power of this reaction for the preparation of medium- and large-ring alkenes (**283**) from both diketones and dialdehydes (**282**). In a synthetic example, Lee converted dialdehyde **284** to (–)-clavukerin A (**285**) in 85% yield using McMurry coupling.[221] The McMurry coupling of esters leads to enol ethers.



284 **285**

The disconnections for McMurry coupling are



13.9. CARBENES AND CARBENOIDS

There is another class of molecules called carbenes that in many ways can be considered to be *radical-like* . They are important in several synthetic methods and are growing in importance, especially the intramolecular

versions. The remaining sections of this chapter will discuss the preparation and reactions of carbenes and related compounds.

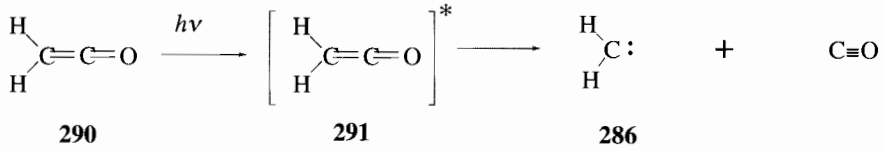
13.9.A. Definition of a Carbene

A carbene is a divalent carbon species linked to two adjacent groups by covalent bonds,[222] possessing two nonbonded electrons and six valence electrons (as in **286**).[223] The two nonbonded electrons can have anti-parallel spins in a single orbital (see **287**, a **singlet carbene**) or parallel spins in different orbitals (see **288**, a **triplet carbene**). Generally, carbenes (**289**) are expected to be in the singlet state from most precursors, although "intersystem crossing to the triplet (sec. 11.10.B) may or may not occur before the individual carbene reacts with a suitable precursor".[224] "Singlet carbenes are electron deficient species comparable to carbocations," but "they possess a nonbonding pair of electrons comparable to that of carbanions."[223] If an adjacent group on the carbene withdraws electrons, the carbene will have electrophilic character. If that group supplies electrons, the carbene will have nucleophilic character. "Triplet carbenes may be considered as diradicals, although the interaction of two unpaired electrons in orbitals on the same carbon atom gives rise to some peculiarities."[224] "The term carbenoid has been suggested" by Closs and Moss "for the description of intermediates which exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species".[225]

286 **287** **288** **289**

13.9.B. Preparation of Carbenes

There are many methods for the preparation of carbenes. A simple approach is to photolyze ketenes (**290**) at 270–370 nm (100.5–76.5 kcal mol^{-1}, 438.8–320.2 kJ mol^{-1}) in the presence of oxygen.[226] Irradiation of **290** at 270 nm gave carbon monoxide (CO, with a quantum yield = 2) and the yield of ethene was independent of the pressure of oxygen. At 370 nm, the quantum yield of CO varies with the pressure of applied oxygen and also with the temperature. The presence of additional oxygen diminishes the yield of ethene by $\approx \frac{2}{3}$.[226] The reaction proceeds via formation of excited ketene (**291**), which fragments to methylene (**286**) and CO. The reactive carbene reacts with additional ketene to give ethene and CO. It is noted that a possible intermediate to **291** is an excited cyclopropanone species.[227] Photolysis of alkyl and aryl ketenes generates alkyl and aryl carbenes. Methylketene and dimethylketene led to methylcarbene[228] and dimethylcarbene,[229] respectively, upon irradiation. The quantum yields were close to unity at 270 nm.[230] Methylcarbene coupled with itself to form an activated ethene, which gave both ethene and ethyne.[228] 2-Butene was also formed by reaction with methyl-carbene and the starting ketene. Similarly, photolysis of dimethylketene led to cyclopropanone (via dimethylcarbene and the ketene), which lost CO under the photolytic conditions to give 2,3-dimethyl-2-butene.[229]



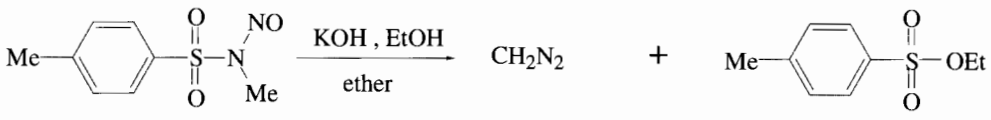
290 **291** **286**

286 **290**

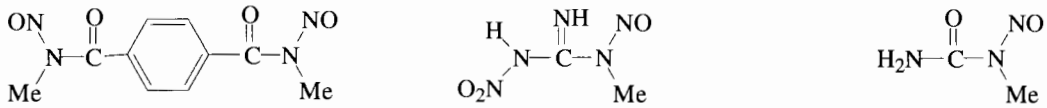
13.9.B.i. Diazomethane. Important precursors for the preparation of carbenes and related molecules are diazoalkanes. Although diazomethane is not used in carbene preparations, it has other synthetic applications There are four convenient preparations of diazomethane, which is a highly reactive gas.

Since diazomethane can detonate on contact with ground glass, its preparation requires the use of specialized glassware. Diazomethane is also toxic.

All preparative methods for diazomethane (CH_2N_2) involve N-nitroso compounds. Treatment of the commercially available *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®, **292**) with hydroxide liberates diazo-

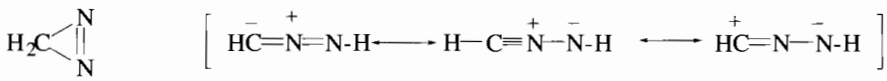


292 **293**



294 **295** **296**

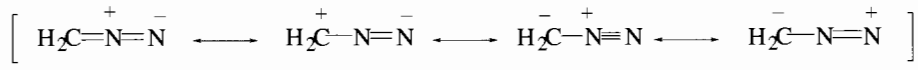
methane and **293**.[231] Similar treatment of *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide (**294**),[232] *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG, **295**),[233] or *N*-Methylnitrosourea (**296**)[234] give diazomethane. It is noted that *MNNG is allergenic and is potentially mutagenic*. These reagents and synthetic uses of diazomethane are outlined in an excellent review by Hopps.[235] It is noted that at least two other structural isomers of diazomethane are known, diazirine (**297**)[236] and isodiazomethane (**298**).[237]



297 **298**

13.9.B.ii. Diazoalkanes. One of the most convenient and useful sources of reactive carbenes are diazoalkanes. Diazoalkanes (RN_2) have been known and used synthetically for over 50 years.[238] The simplest diazoalkane is diazomethane, represented by several resonance hybrid structures (**299**), which are zwitterionic,

although it can also be written as a nitrene. The preparation and reactions of other alkyl diazoalkanes are described in a review by Cowell.[238b,239] Hydrazones (such as that from acetophenone, **300**) are convenient sources of carbenes via their reaction with *p*-toluenesulfonyl azide (**301**) in THF to give the corresponding diazoalkane (**302**) along with *p*-toluenesulfonamide.[240]



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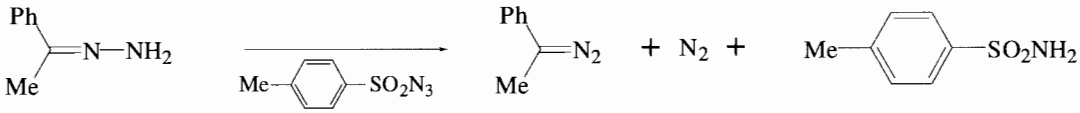
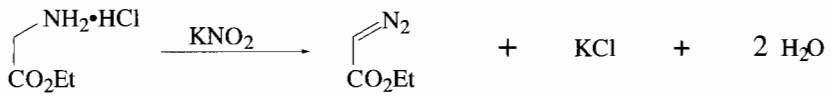


300 **301** **302**

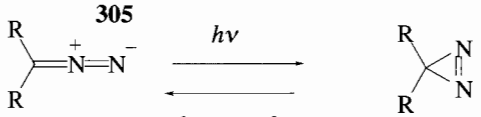
In some cases, amines can be converted to diazo compounds by treatment with potassium nitrite or nitrous acid. The first aliphatic diazo compound known was ethyl diazoacetate (**304**), prepared by Curtius in 1883.[241] Treatment of ethyl glycinate hydrochloride (**303**) with potassium nitrite (KNO_2) gave **304**. This technique is most useful when an electron withdrawing group is adjacent to the amino group.



303 **304**

Photolysis of diazo compounds (**305**) generates nitrogen and the carbene **289**. Photolysis of diazomethane (**311**, R = H), for example, generates methylene (H_2C:).[242] Benzophenone is often added as a sensitizer for the photolysis of diazomethane. Under these conditions, triplet methylene is formed via intersystem crossing ($S_1 \rightarrow T_1$)[243] (sec. 11.10.B). Energy transfer from triplet benzophenone to triplet diazomethane followed, and triplet diazomethane decomposed to triplet methylene.[244] A similar thermal reaction gives the carbene and the usual carbene reactions.[245]

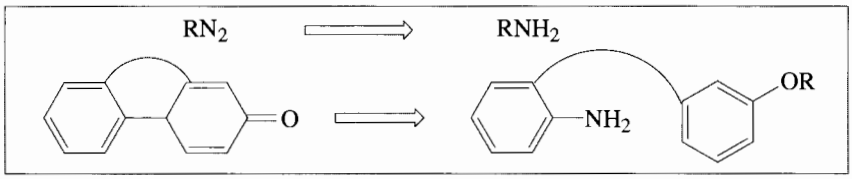
305 **289**



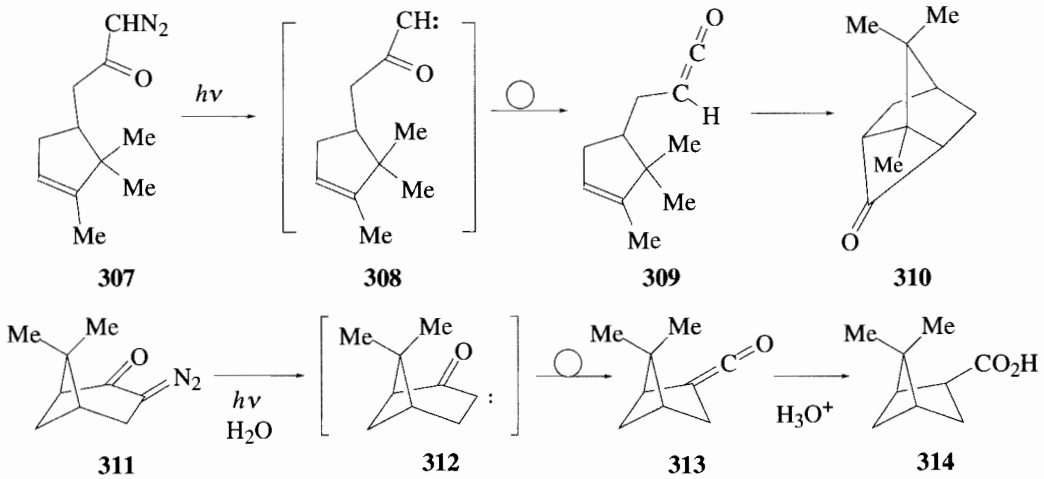
305 **306**

Diazoalkanes (**305**) can undergo valence isomerization to diazirines (**306**) upon photolysis, but reversal to the diazoalkane occurs both photochemically and thermally.[246,236cd] Diazirines can be photolyzed back to the diazoalkane or directly to the carbene.[247]

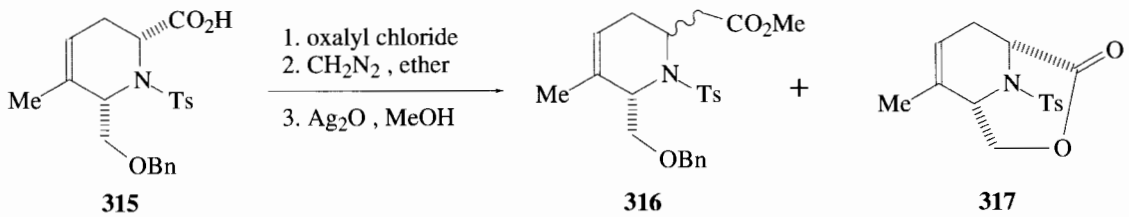
The diazoalkane disconnections are



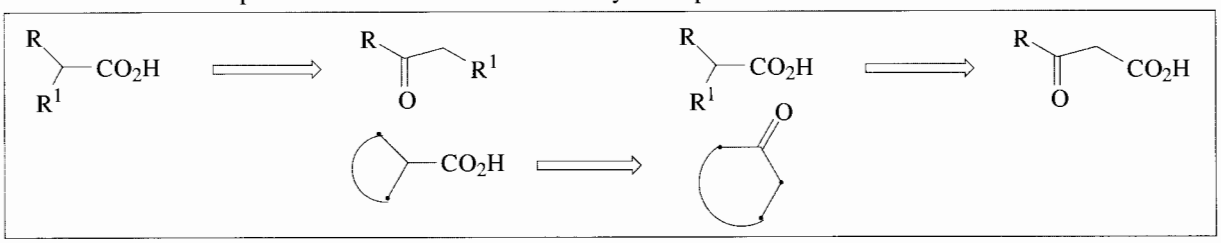
13.9.B.iii. α-Diazocarbonyl Compounds. Another reaction that generates carbenes is a rearrangement of α-diazocarbonyl compounds (called the **Wolff rearrangement**),[248] in which a diazocarbonyl compound (**307**) loses nitrogen (N_2) to give an acyl carbene (**308**). This reaction occurs under both thermal and photochemical conditions, and the resulting carbene rearranges to a ketene (**309**) (completing the Wolff rearrangement of diazoketone to ketene). In this case, the Wolff rearrangement to ketene **309** was followed by an internal [2+2]-cycloaddition (secs. 11.10.A, 11.10.C) to give **310** in 79% yield[249] but hydrolysis of a ketene will generate an acid (or an ester in the presence of an alcohol).[250] Meinwald and Gassman used this rearrangement to "shrink" bicyclic systems. Irradiation of **311** in water gave a 68% yield of **312** via initial formation of a carbene (see **313**) and rearrangement to the ketene, **314**.[251] Hydrolysis gave the carboxylic acid.



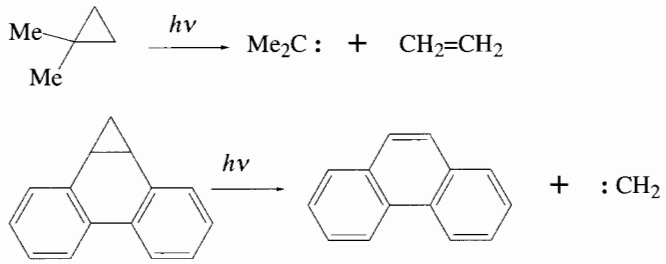
Diazoketones such as **307** can be formed from acid chlorides by reaction with diazomethane. Subsequent treatment with aqueous Ag_2O leads to the Wolff rearrangement and formation of a carboxylic acid of one carbon more than the starting acid chloride. This sequence is known as the **Arndt–Eistert synthesis**.[252] A synthetic example using this is taken from Weinreb's studies toward the synthesis of cylindrospermopsin,[253] in which **315** was treated with (1) oxalyl chloride, (2) CH_2N_2 and (3) Ag_2O , MeOH to give a mixture of products: 22% of **316** and 39% of **317**.



The disconnections pertinent to these α-diazocarbonyl compounds are



13.9.B.iv. Photolysis of Cyclopropanes. Photolysis of cyclopropanes generates carbenes via elimination of an alkene.[254] Photolysis of 1,1-dimethylcyclopropane in the gas phase, for example, gave dimethylmethylene (Me_2C:) and ethene.[255] Similarly, irradiation of 9,10-dihydro-9,10-methanophenanthrene (**318**) gave carbene and phenanthrene.[256] Oxiranes can be photolyzed to carbenes as well.[257]



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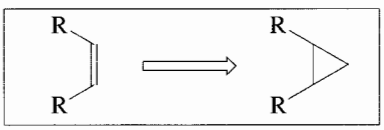
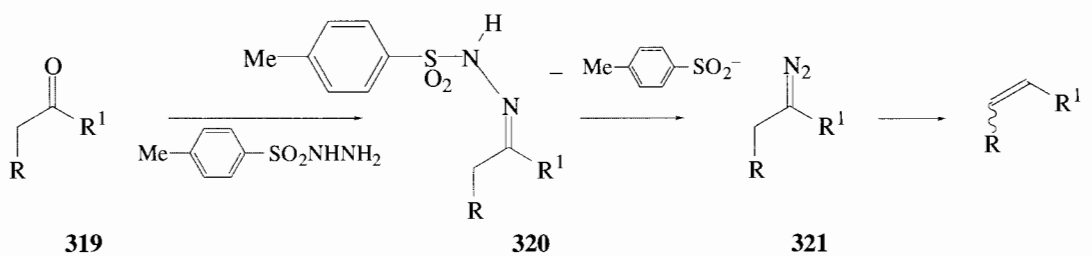
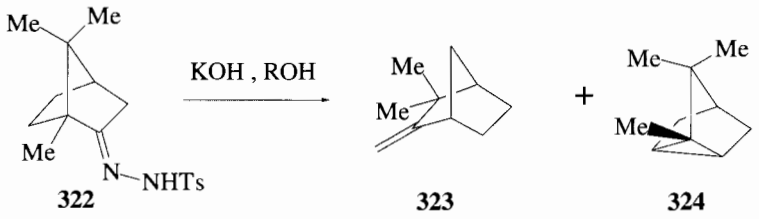
The cyclopropane–alkene disconnection is



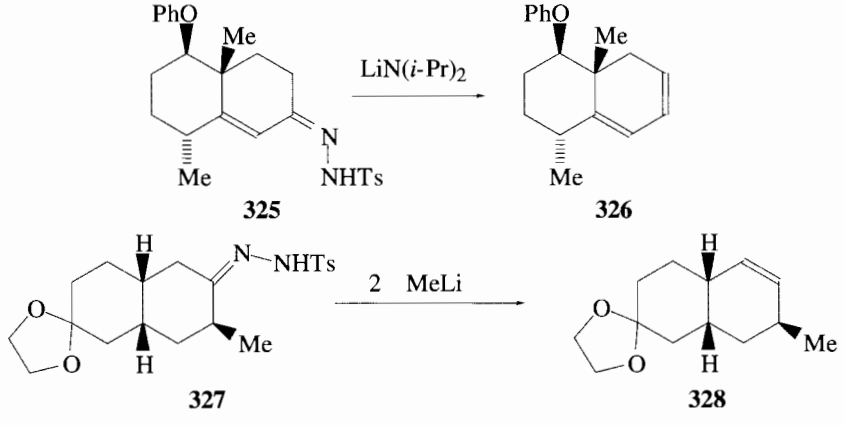
13.9.B.v. The Bamford–Stevens Reaction. Aldehydes and ketones such as **319** can be converted to a tosylhydrazone (**320**) via reaction with tosylhydrazine. Subsequent treatment with base followed by heating results in the loss of *p*-toluenesulfinate to give the corresponding diazo compound (**321**). This diazo compound generates a carbene by loss of nitrogen and forms an alkene. The carbene nature of this intermediate was detected by examination of camphor tosylhydrazone (**322**),[258] which on heating with hydroxide give a mix-ture of camphene (**323**) and tricyclene (**324**).[259] When the reaction was done in acidic alcohols such as ethylene glycol, camphene was the main product (via rearrangement). In aprotic solvents, the carbene insertion product (**324**) was observed (sec. 13.9.C.iii).



319 **320** **321**

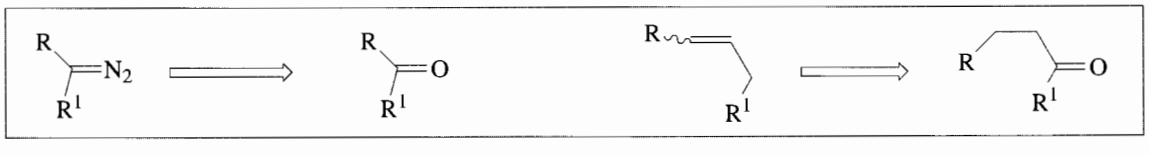


The formation of alkenes from tosyl hydrazones when they are treated with base is called the **Bamford–Stevens reaction**.[260,259a] Although this is *not* a carbene mechanism, but involves extrusion of nitrogen via a carbanion, it is included here for comparison with the reactions just cited. Grieco et al. used this method to convert **325** to diene **326** (>98% yield) in a synthesis of (±)-ivangulin.[261] When an organolithium is used as the base, the alkene-forming reaction is sometimes called the **Shapiro reaction**.[262,264b] Two equivalents of organolithium are required, and the reaction generates the *less substituted* alkene (as in the conversion of **327** to **328**).[263] The Bamford–Stevens reaction generates the *more substituted* alkene.



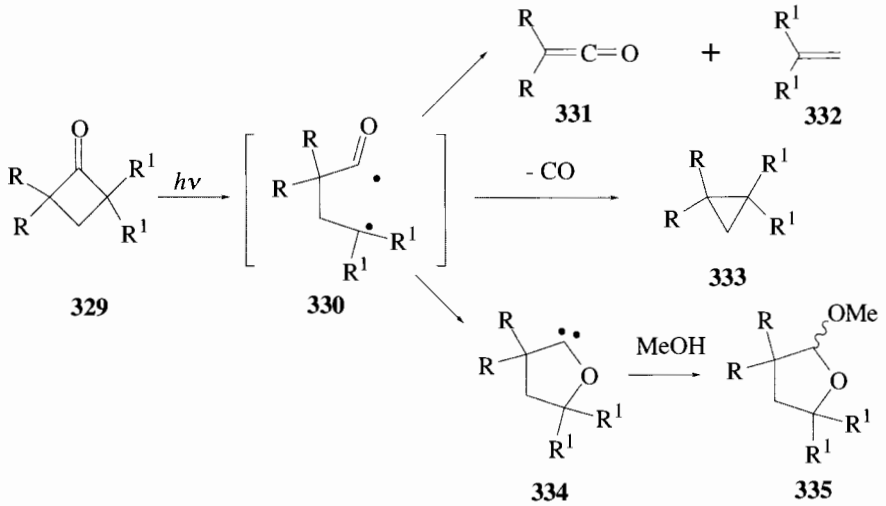
The relative amount of base has a significant effect on the product distribution. When the tosyl hydrazone of pinacolone was treated with > 1.8 equivalents of *n*-butyllithium, 3,3-dimethyl-1-butene was formed. When only 1 equivalent of *n*-butyllithium was used, however, a 57% yield of 3,3-dimethyl-1-butene, 40% of 1,1,2-trimethylcyclopropane, and 3% of the rearranged alkene (2,3-dimethyl-1-butene) were isolated.[264] The type of base employed is also important. The product distribution from the hydrazone of cyclopentanone, for example, gave a mixture of cyclopentene/(*E*)-2-pentene/(*Z*)-2-pentene.[265] When sodium methoxide was used, a 2:84:14 mixture of these products was obtained whereas sodium hydride led to a 83:14:3 mixture and sodium amide a 60:35:3 mixture.[265]

The Bamford–Stevens disconnection is

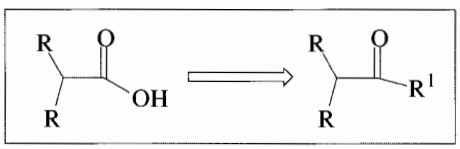


13.9.B.vi. Photolysis of Carbonyls. Under certain conditions, carbonyl compounds can be photolyzed to diradicals, and these can rearrange to carbenes.[266] Photolysis of cyclobutanone **329**, for example, generated

diradical **330**, and in one pathway it eliminated an alkene unit (**332**), thereby generating ketene **331**. In an alternative pathway, it decarbonylated to form cyclopropane **333**. Yet another pathway involved ring expansion to give carbene **334**, which reacted with methanol to give **335**.[267] When R = R^1 = H, 48% of **331** and **332** was observed, with 8% of **335** and a trace of **333**.[267a] When R = R^1 = Me, however, 68% of **335** was obtained, with 13% of **331** + **332** and 11% of **333**.[267a]



The carbonyl disconnection is:

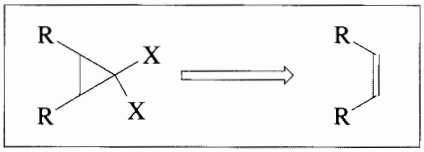


13.9.B.vii. Halocarbenes. Polyhalomethanes can be converted to halocarbenes via photolysis, thermolysis, or treatment with base. When cyclohexene was treated with a mixture of chloromethane and phenylsodium,, methylene (:CH_2) was formed, and it added to the alkene gave norcarane (**336**), but in only 3.2% yield.[268] Obviously, chloromethane is not the best source of carbenes. Polyhalomethanes give much better results, and the most common method for generating halocarbenes is treatment of dihalomethanes and trihalomethanes with sodium metal or with another base.[269]

Chloroform is a particularly useful carbene precursor. Reaction of chloroform with hydroxide begins with an acid–base reaction to generate the anion ($Cl_3C:^-$) and water. Loss of chloride ion generates dichlorocarbene (Cl_2C:). This type of carbene was first suggested by Geuther in 1862.[270] Potassium *tert*-butoxide is the base most commonly used to generate dichlorocarbene, after its initial introduction by von E. Doering and

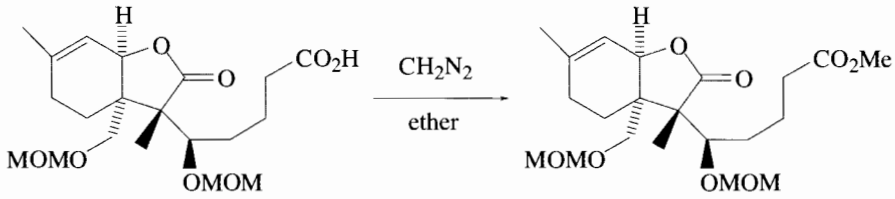
Hoffmann.[271] A typical reaction is that of cyclohexene and chloroform with potassium *tert*-butoxide to give **337**. In general, reaction with alkenes give dichlorocyclopropanes [dibromocyclopropanes with bromoform ($CHBr_3$) and diiodocyclopropanes with iodoform (CHI_3)]. Tri-*n*-butyltin hydride (Bu_3SnH) can be used to reduce the product dihalide to a monohalide (sec. 4.9.H).

Typical halocarbene disconnections are



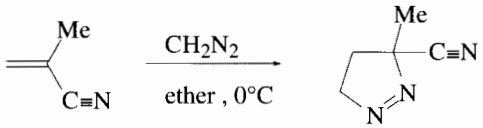
13.9.C. Reactions of Diazomethane

As with other diazoalkanes, diazomethane reacts with alkenes to form cyclopropane derivatives (sec. 13.9.C.i).[272] Reaction with aromatic derivatives leads to ring expansion to cycloheptatriene derivatives.[273] Both of these reactions (addition to an alkene or arene insertion) involve generation of an intermediate carbene and addition to a π bond; they will be discussed below. Many of the reactions of diazomethane tend to be ionic in nature and are, therefore, set aside from the other diazoalkane chemistry in this section. One of the commonest uses of diazomethane itself is esterification of small quantities of acids, especially acids that are precious for one reason or another. The reaction is quantitative and gives good yields of a single product, as in Tadano's conversion of **338** to the methyl ester of **339**[274] in a synthesis of (–)-verrucarol.



338 **339**

Diazoalkanes undergo [3+2]-cycloadditions in the presence of alkenes to give pyrazolines, as discussed in Section 11.11.E. Diazomethane reacts with α-methylacrylonitrile, for example, to give pyrazoline **340** in 76%



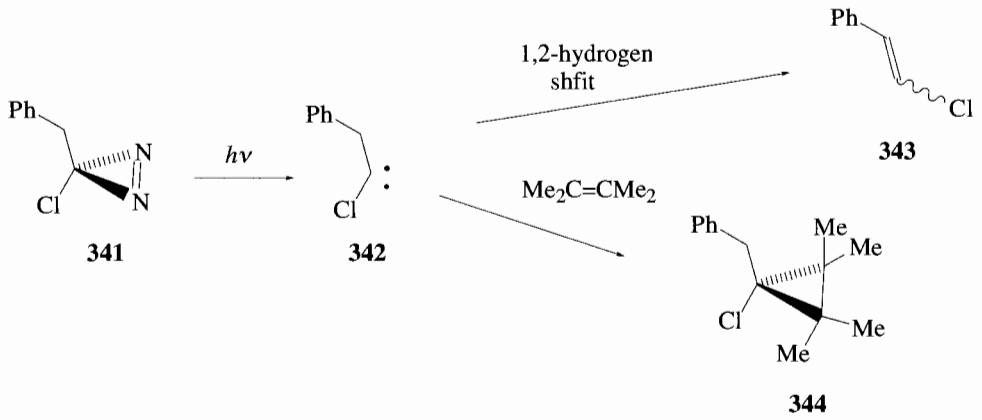
340

yield.[275] In another ionic reaction, diazomethane reacts with aldehydes to give methyl ketones, as in the conversion of benzaldehyde to acetophenone (97% yield),[276] which is a useful reaction for extending carbon chains. Diazomethane also reacts with cyclic ketones to give ring-expanded ketones, along with epoxides as minor products. This method was used to prepare cycloheptanone from cyclohexanone in 65% yield by reaction with diazomethane, along with 15% of oxaspirooctane.[277,231a]

Some of these specialized diazoalkane disconnections are

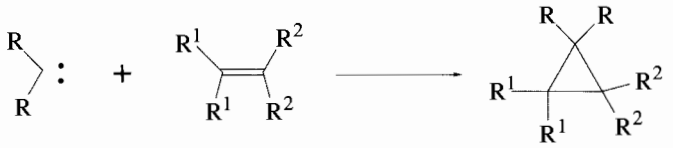
13.9.D. Carbene Reactions of Diazoalkanes

Carbenes are relatively easy to generate and they have several synthetic uses. Diazoalkanes are converted to carbene and react with electron deficient alkenes in the presence of copper derivatives such as $Cu(acac)_2$, although $Rh_2(OAc)_4$ was found to be a better catalyst in some cases.[278] Metal carbenes are also very important in synthesis.[279] Carbenes can undergo 1,2-hydrogen shifts to generate alkene products. When diazine **341** was photolyzed (355 nm, 103.7 kcal mol^{-1}, 433.9 kJ mol^{-1}), chlorocarbene **342** was formed. In the presence of 2,3-dimethyl-2-butene, a 73% yield of the cyclopropane product (**351**) was produced[280] (see below). In addition to **343**, alkene **344** was formed by a 1,2-hydrogen shift during the course of the reaction and was competitive with the addition. The energy barrier for this rearrangement was calculated to be about 6.4 ± 2 kcal mol^{-1} (26.79 ± 8.37 kJ mol^{-1}) and proceeded at a rate of 4.9-6.7 x 10^7 s^{-1}.[280a] Although the addition reaction is usually faster, the 1,2-shift should be considered an important side reaction in many carbene reactions.



13.9.D.i. Addition to Alkenes. Perhaps the most common reaction of carbenes is their addition to alkenes to generate cyclopropanes,[281] as shown in the formation of **344** above. A generalized example is the preparation of **346** from carbene **289** and alkene **345**.[282] The carbenes can be generated by any of the methods discussed in Section 13.9. The addition is usually exothermic (a typical value is 91 kcal mol^{-1}, 380.9 kJ mol^{-1}) with an activation energy of ≈ 64 kcal mol^{-1} (267.9 kJ mol^{-1}).[283] Reaction of *cis*- and *trans*-2-butene with diazomethane (under photolytic conditions) showed that the yield of cyclopropanes increased with increasing pressure. Insertion into allylic and vinyl bonds was competitive in many cases. The reaction is stereoselective for retention of the geometry of the starting alkene when diazomethane is used.[284] For other methylene precursors, *trans*-1,2-dimethylcyclopropane is favored for both *cis*- and *trans*-2-butene.[284] The ratio of cis to trans isomers is, however, dependent upon the wavelength of light used and on the additive. The reaction was

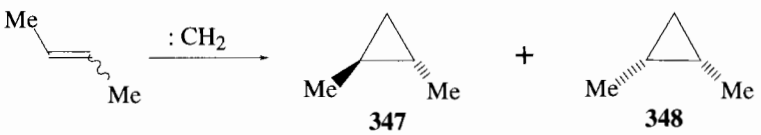
more stereoselective at higher pressures and when long wavelengths of light were used.[285] Molecular oxygen appears to be the best additive, and irradiation at 313 nm (91.4 kcal mol^{-1}, 382.6 kJ mol^{-1}) is optimal for methylene generation from ketenes. The yield of cyclopropanes was 87% at 366 nm (78.1 kcal mol^{-1} = 326.9 kJ mol^{-1}), but only 29% at 313 nm.[284c] Oxygen scavenges triplet methylene, which gives diminished stereoselectivity relative to singlet methylene, although isomerization of the active intermediates is also a factor.[286]



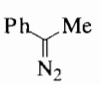
289 **345** **346**

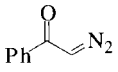
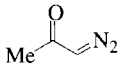
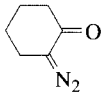
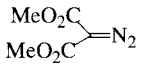
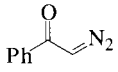
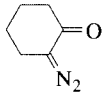
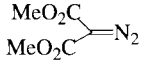
When the reaction occurs in the liquid phase, which is more common, the reaction is stereoselective unless the carbene "has a readily accessible triplet state".[287] Photolysis of diazomethane in the presence of *cis*-2-butene, for example, gave *cis*-1,2-dimethylcyclopropane (**348**) with complete retention of configuration.[288] Other diazoalkanes led to a mixture of **347** and **348**. When triplet methylene was produced (by photolysis of diazomethane) in a large excess of perfluoropropane ($CF_3CF_2CF_3$), a decrease in stereoselectivity was observed.[284d] Reaction of triplet methylene with a cis alkene (**349**) proceeds by a two-step mechanism. The initially generated diradical (**350**) is in rotational equilibrium with **351**. Both of these triplet diradicals are slowly converted to singlet diradical **353** and **353**, which close to give the cis-cyclopropane **354** and the trans-cyclopropane **355**.[288,289] Singlet carbenes are produced from singlet diradicals and close with high selectivity. Bond rotation in the triplet diradical is faster than $T_1 \rightarrow S_1$ conversion or ring closure. Ring closure of the singlet radical is faster than bond rotation (an equilibrium between **352** and **353** and unfavorable relative to conver-sion to **354** or **355**). Table 13.8[290,244] summarizes the reaction of various diazo compounds (and the carb-enes therefrom) with 2-butene. There was a decrease in stereoselectivity for the sensitized reaction in compari-son with direct photolysis. The rate of carbene addition also varies with the type of alkene, as shown in Table 13.9.[291]

Table 13.8. cis-trans Selectivity of 2-Butene with Various Diazo Compounds



347 **348**

Alkene	Diazo Compound	hν	347/348
cis	CH_2N_2	Direct	0:100
		Sensitized	34:66
		Direct	4:96

		Sensitized	15:85
		Direct	50:50
		Sensitized	55:45
		Sensitized	56:44
		Sensitized	86:14
		Sensitized	90:10
trans		Direct	73:27
		Sensitized	74:26
		Sensitized	86:14
		Direct	90:10
		Sensitized	86:14

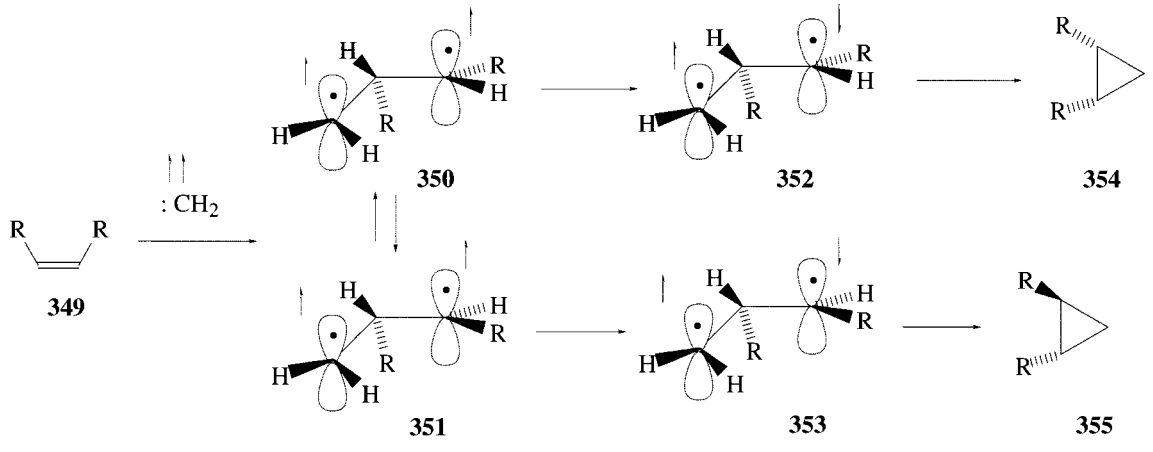


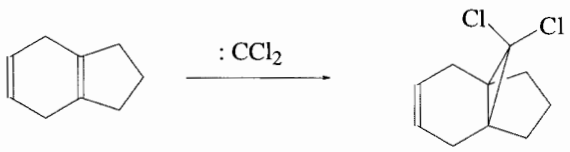
Table 13.9. Rate of Carbene Addition as a Function of Both Alkene and Carbene

Alkene	Carbene Generation: (Relative Rate)						
	A	B	C	D	E	F	G
	0.89	0.66	0.56	0.90	0.011	0.045	
	0.79		1.10		0.15		0.25

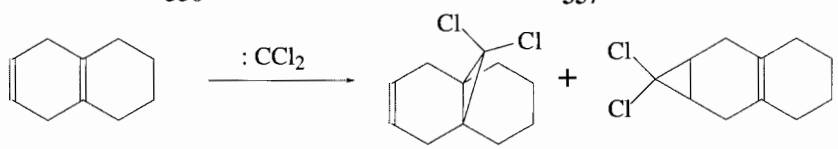
	0.78		1.01		0.23		0.53
		1.00		1.00	0.13	0.27	
	1.0		1.0		1.0	1.0	1.0
	1.17	3.32	1.9	1.62	2.8	2.0	2.5
	1.13	3.46		1.6	6.5	1.85	4.4

A. CH_2=C=O, 260 nm. B. CH_2N_2, Cu(II.) C. $PhCHN_2/h\nu$. D. EtO_2C-$CHN_2/CuSO_4$. E. $CHCl_3/KOt$-Bu.
F. $CHBr_3/KOt$-Bu. G. , $h\nu$.

In addition reactions, where more than one alkene moiety is present in a molecule, there is the potential for formation of isomers via addition to one or both of the double bonds. In general, carbenes add to the more



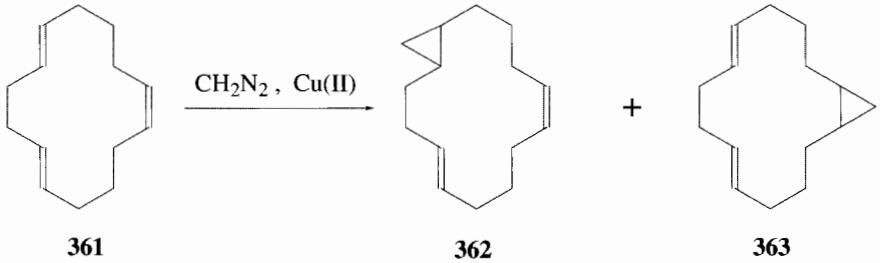
356 **357**



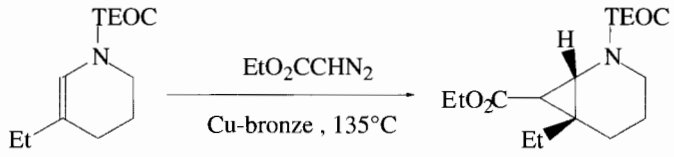
358 **359** **360**

electron-rich alkene. Reaction of **356** with dichlorocarbene (Cl_2C:) gave only **357**, but **358** gave an 80% yield of **359** with 20% of **360**.[292] There also seems to be a preference for trans double bonds, as seen in the reaction of methylene with *cis,trans,trans*-1,5,9-cyclodecatriene (**361**), which gave a 97:3 mixture of **362/363**.[293] It is noted that the trans double bond may be more sterically accessible, and this can account for the stereochemical preference. Similar reaction with dichlorocarbene and also with the Simmons–Smith reagent (sec. 13.9.D) showed the same preference for reaction with the (*E*)-alkene (this preference ranged from 2:1 to 9:1).

A wide range of cyclopropane derivatives can be prepared by this carbene addition to alkenes.[294] There is a general preference for the less congested exo product in reactions with cyclic alkenes. Initial addition of the



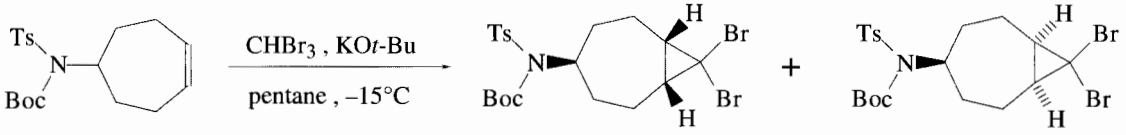
361 **362** **363**



364 **365**

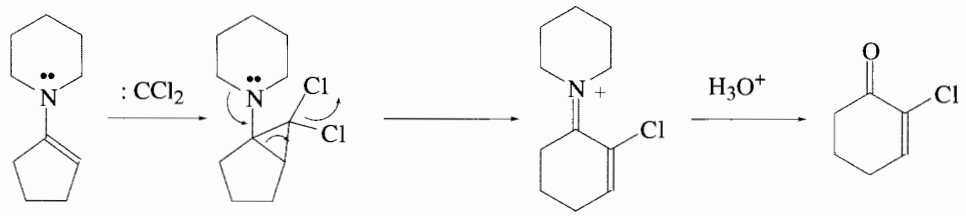
carbene can be accompanied by rearrangement of the product, as discussed in the previous section (see above).[295] In many cases, however, the cyclopropanation proceeds without rearrangement. Diazoalkanes add to alkenes give cyclopropane derivatives. An example is the reaction of ethyl diazoacetate with **364** to give **365** (in 65% yield as a 1.1:1 mixture of exo- and endo- cyclopropanes).[296] Note that TEOC = 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonyl. This example was taken from Grieco's synthesis of eburnamonine.

Carbenes generated the more traditional way react similarly. In Trost's synthesis of (–)-anatoxin,[297] the alkene unit in **366** reacted with dibromocarbene, generated from bromoform and base, to give an 85% yield of **367** and **368** as a 3.5:1 mixture of exo and endo isomers.



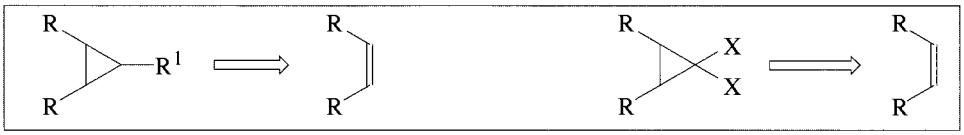
366 **367** **368**

Carbenes react with enamines in the normal way, as seen in the reaction of **364** to give **365**. However, in some cases the reaction is accompanied by a ring expansion that generates ketones via rearrangement of the initially formed aminocyclopropane. The cyclopropane product can be very stable and is usually isolated as the major product. Dichlorocarbene reacted with 1-piperidinocyclopentene (**369**) (derived from piperidine and cyclopentanone–sec. 9.6.A) to give **370**. Loss of chloride ion generated the conjugated iminium chloride (**371**), and hydrolysis gave **372**.[298]

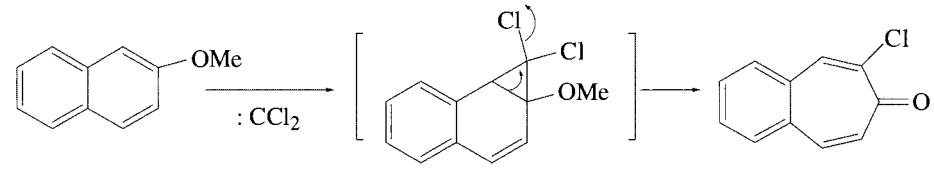


369 **370** **371** **372**

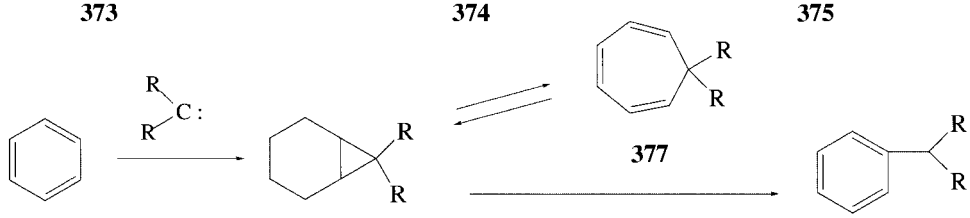
The disconnections available from carbene additions are



13.9.D.ii. Addition to Aromatic Derivatives. Aromatic compounds also react with carbenes, but ring expansion usually follows the initial cyclopropanation. In a typical example, 2-methoxynaphthalene (**373**) reacted with dichlorocarbene to give **374**, and subsequent ring expansion gave **375**,[299] which is a general reaction of enol ethers, which give either unsaturated acetals or unsaturated carbonyls.[300]



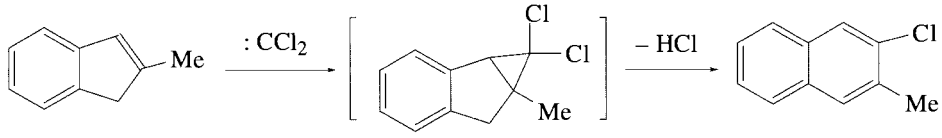
373 **374** **375**



376 **377** **378**

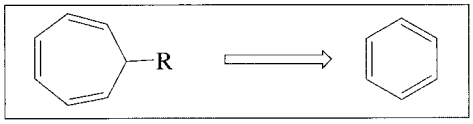
Rearrangement or ring opening of the cyclopropane adducts derived from aromatic compounds are possible, depending on the carbene. Addition of carbene to benzene gave norcarane **376** (R = H) and cycloheptatriene (**377**, R = H) in equilibrium. With functionalized norcarane products , ring opening usually occurs to give the substituted benzene, **378** (R = R^1= CN, for example). Product **377** is favored when **376** is generated by reaction of benzene with diazomethane or ester carbenes such as **:**$CHCO_2R$.[301] Photolysis of diazomethane in benzene, for example, gave a 4.8:1 mixture of cycloheptatriene and toluene.[302]

Other compounds react similarly. Methyl indene (**379**), for example, reacted with dichlorocarbene to give **380**. Subsequent rearrangement was accompanied by loss of HCl to give the naphthalene derivative **381**.[303] The course of the reaction is dictated by the inherent stability of the final product.[304]

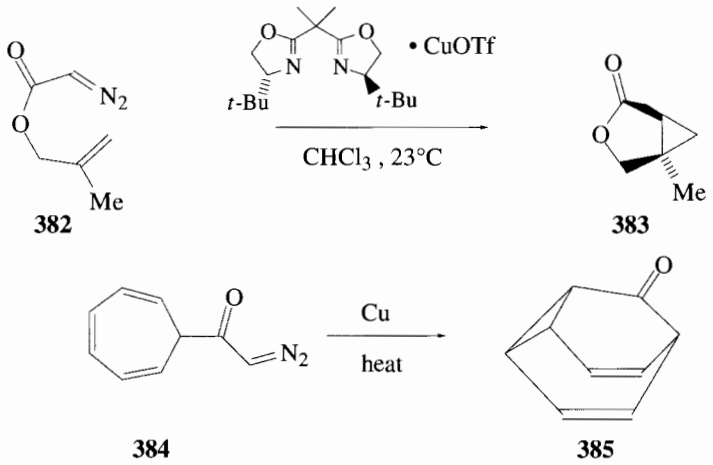


379 **380** **381**

The carbene ring expansion disconnection is



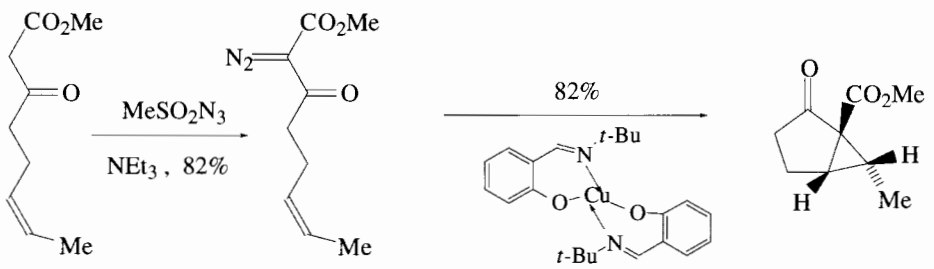
13.9.D.iii. Cyclization Reactions of α-Diazo Ketones. An attractive application of cyclopropanation is intramolecular trapping of carbenes to form bicyclic compounds with a three-membered ring appended to another ring. When diazoalkanes are treated with transition metals in the presence of an alkene, particularly



382 383 384 385

copper or rhodium derivatives, cyclopropanation occurs although the reactive intermediate may not be a free carbene. With rhodium compounds, in particular, C=Rh is the reactive species rather than a free carbene. When diazoester **382** was heated with cupric triflate, bicyclic ester **383** was obtained (in 62% yield and an initial enantiopurity of 88% ee) in Overman's synthesis of scopadulcic acid.[305] The addition of the chiral ligand led to the high asymmetric induction during the cyclopropanation reaction. Heating with cupric sulfate or copper metal[306] can also be used to initiate this cyclization, as in von E. Doering's synthesis of barbaralone (**385**) by heating **384** with copper.[307]

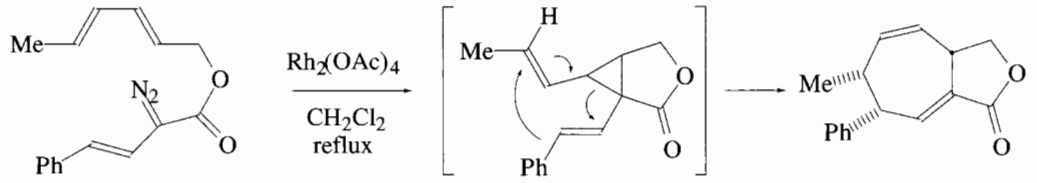
This carbene insertion reaction has been used in a variety of syntheses, and is especially attractive when coupled with other synthetic techniques. Taber et al. used carbene cyclopropanation in several synthetic endeavors. In one example, the diazoketone was treated with bis-*N*-*tert*-butylsalicylaldiminato copper(II) [Cu(TBS)$_2$, **388**] to induce the carbene cyclopropanation reaction. The diazoketone was prepared by treating **386** with mesyl azide to give **387** in 82% yield, which was followed by treatment with the Cu(TBS)$_2$ reagent to produce **389** in 80% yield in Taber and co-workers synthesis of (+)-isoneonepatelactone.[308]



386 387 388 389

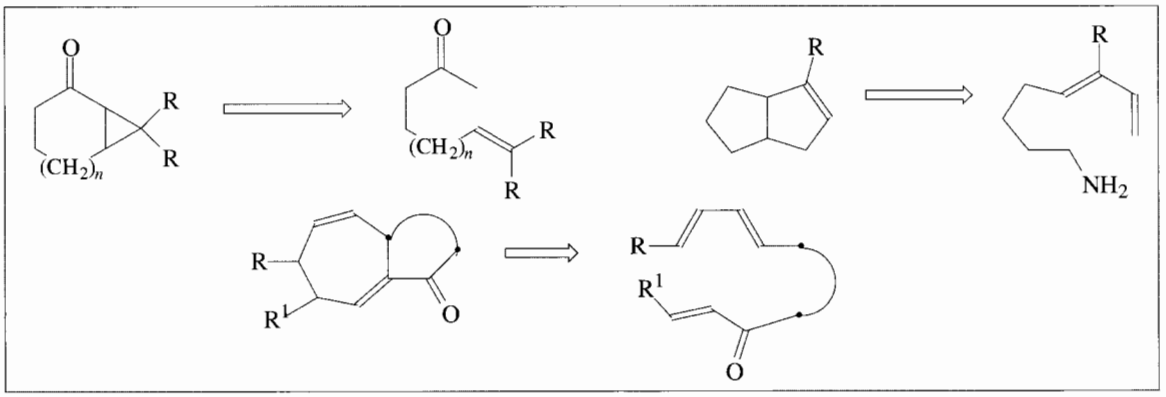
As mentioned, rhodium-catalyzed cyclopropanation reaction of diazoketones is quite useful. As we saw in Section 11.12.C, Davies used a carbene insertion reaction in tandem with a Cope rearrangement to prepare

392. The sequence began with the rhodium-catalyzed reaction of diazoketone **390** to give the cyclopropyldiene **391**. This new diene was properly aligned to undergo a **Cope rearrangement**, accelerated by the proximal cyclopropane moiety (sec. 11.12.C), to generate the seven membered ring in **392** (76% yield).[309]

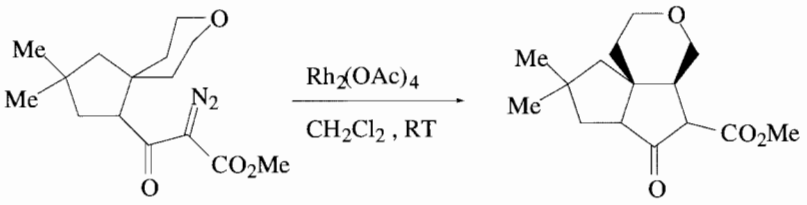


390 **391** **392**

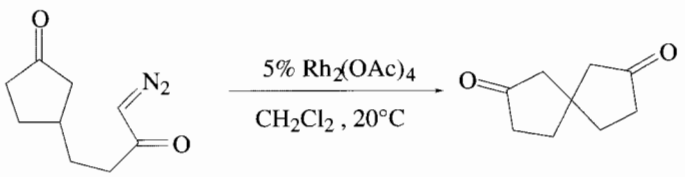
The intramolecular carbene addition disconnections are



Taber and co-workers also showed that diazocarbonyls undergo C—H insertion reactions in the presence of rhodium acetate [$Rh_2(OAc)_4$].[310b,311] Taber and Schuchardt used this method for the conversion of **393** to **394** (91% yield) in a synthesis of (±)-pentalenolactone E methyl ester.[312] α-Cuparenone was also synthesized by this method.[313] Undheim used this approach for the synthesis of β-oxaspirane systems.[314] When **395** was treated with a catalytic amount of rhodium tetraacetate, for example, spiro diketone **396** was obtained in 43% yield.

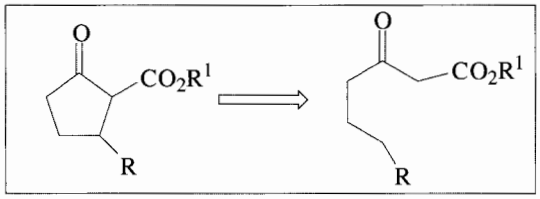


393 **394**

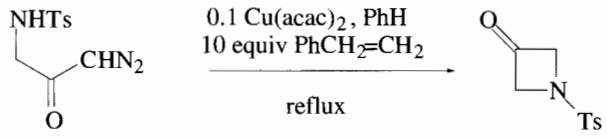


395 **396**

The carbene C—H insertion disconnection is



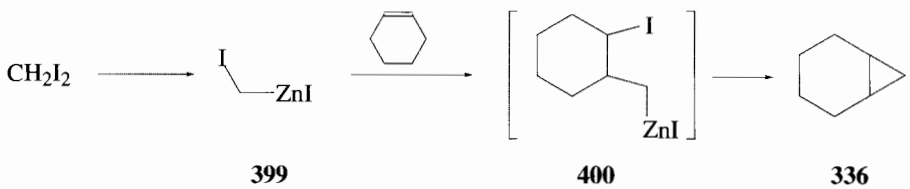
There is another interesting variation of this reaction that involves intramolecular N—H insertion of α-diazo-carbonyls. When diazoketone **397** was treated with cupric bis(acetylacetonate), for example, a 74% yield of azetidinone (**398**) was obtained.[315] It was shown that competitive intramolecular C—H insertion by the carbenoid was not a problem, illustrated by the presence of 10 equivalents of styrene in the reaction. The styrene actually seemed to enhance the N—H insertion reaction.



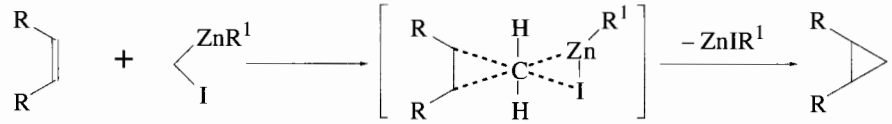
397 **398**

13.9.E. Carbenoids

The rhodium chemistry just presented actually involves C=Rh species rather than a free carbene. In this section, we will look at a general class of compounds called carbenoids. A carbenoid is a reactive intermediate that reacts similarly to a carbene but does not actually involve formation of a carbene. The most commonly used carbenoid is generated by reaction of diiodomethane and a Zn/Cu couple; this reaction, when it adds to alkenes, is called the **Simmons–Smith reaction**.[316] A simple example is the conversion of cyclohexene to bicyclo[4.1.0]heptane (norcarane, **336**). Initial reaction of diiodomethane with zinc gave an iodozinc compound (**399**–see sec. 9.8.B for a brief discussion of organozinc compounds), which added to the alkene to give **400**. Loss of zinc iodide (ZnI_2) gave the cyclopropane derivative (**343** in this case).[317] A one-step

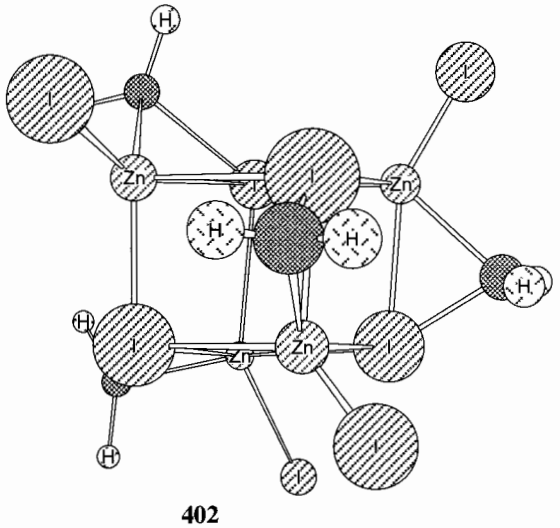


399 **400** **336**



401

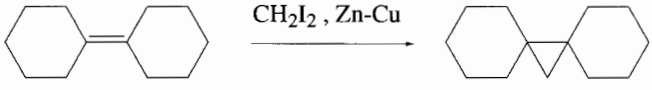
mechanism has also been proposed that involves **401**[316a,318] and generates the cyclopropane derivative. The actual structure of the iodomethylene zinc intermediate is probably best represented as **402**,[319] which is based, in part, on the structure of known organozinc compounds.[320]



402

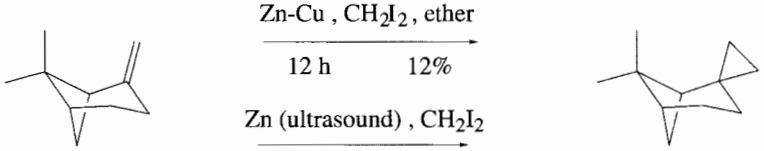
[Reprinted with permission from Simmons, H.E.; Cairns, T.L.; Vladuchick, S.A.; Hoiness, C.M. *Org. React.*, ***1973***, *20*, 1. Copyright © ***1973*** by John Wiley and Sons, Inc.]

As with carbenes, more highly substituted alkenes react somewhat faster than less substituted alkenes.[318d] Even highly substituted alkenes such as **403** gave an 87% yield of the Simmons–Smith product (**404**).[321] It is known that 1-substituted cyclic alkenes react faster than unsubstituted alkenes.[322] 1-Methylcyclohexene (relative rate 21.4) and methylenecyclohexane (relative rate 3.84) both react faster than cyclohexene (relative rate 1.0). 1,2-Dimethylcyclohexene, however, reacts slightly slower, with relative rate of 0.94. Cyclohexene (relative rate 1.0) reacts slower than cyclopentene (relative rate 1.60) or norbornene (relative rate 1.70).[322] In addition, 1-methylcyclopentene (relative rate 5.14) reacts faster than cyclopentene (relative rate 1.60).[322]



403 **404**

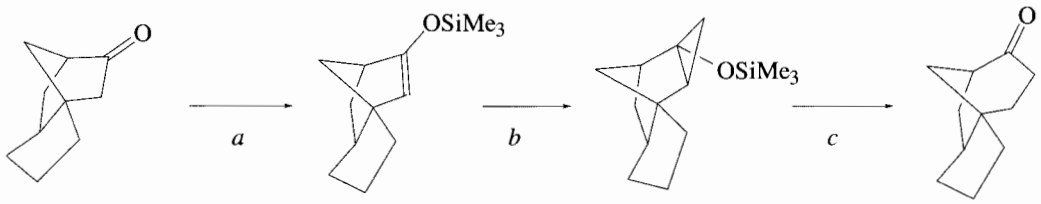
Preparation of the zinc is critical to good yields in the Simmons–Smith reaction. Both Zn–Cu and Zn–Ag couples have been used, with both iodine and lithium.[323] The zinc must be activated or the yield of cyclopropane product would be very poor. A useful development is the use of ultrasound to activate the zinc. Treatment of (–)-α-pinene (**405**) with the usual Simmons–Smith reagent gave only 12% of **406**.[324] When the zinc was activated by ultrasound, however, a 67% yield of **406** was obtained.[325]



405 **406**

Electron-rich alkenes such as vinyl ethers and silyl enol ethers usually react faster than other alkenes. Cyclopropanation of a silyl enol ether was used for a ring-expansion reaction beginning with ketone **407**,

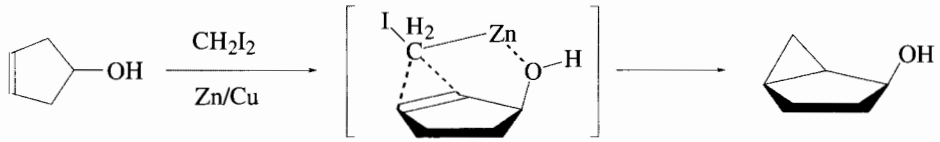
which was converted to the *O*-trimethylsilyl enol (**408**) in 95% yield.[326] (sec. 9.2, 9.3.B). Subsequent Simmons-Smith cyclopropanation gave a 65% yield of **409**, and basic hydrolysis opened the ring to produce ketone **410** in 88% yield.



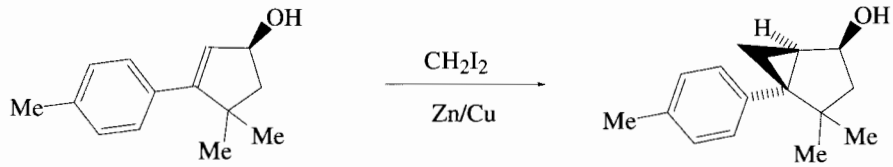
407 **408** **409** **410**

(*a*) LiN(*i*-Pr)$_2$, THF ; Me$_3$SiCl , –78°C (*b*) CH_2I_2 , Zn–Ag , ether , reflux (*c*) aq NaOH , MeOH , 0°C

There is a pronounced neighboring-group effect when a hydrogen-bonding oxygen is present as a substituent. The oxygen will "coordinate with the reagent, increasing the rate and control the stereochemistry of the addition."[327,322a,b] Reaction of **411**, for example, gave **413** via coordination of the oxygen in **412**. In a synthetic example, Casares and Maldonado used this neighboring group effect to convert **414** to **415** in a synthesis of β-cuparenone.[328]

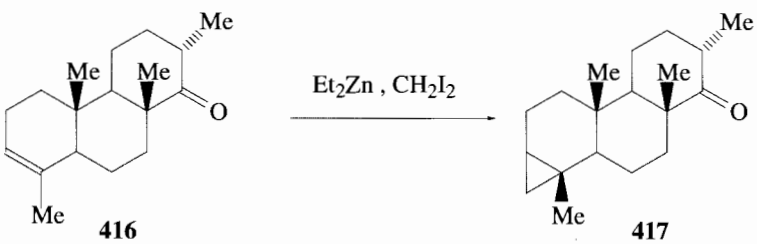


411 **412** **413**



414 **415**

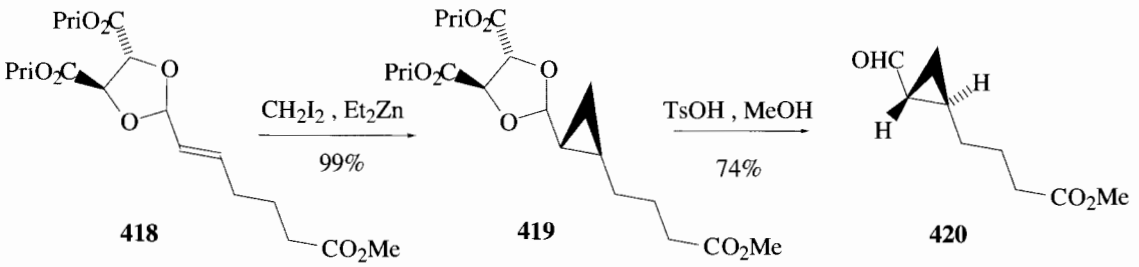
An alternative preparative method avoids the use of the Zn/Cu couple, using diethyl zinc instead. An example is taken from Abad's synthetic studies directed at spongiane.[329] In this work, tricyclic alkene **416** was treated with diethylzinc and diiodomethane to give a 97% yield of **417**.



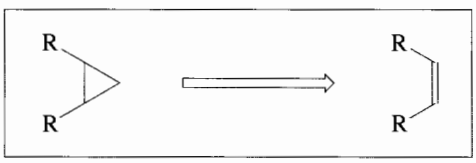
416 **417**

Asymmetric induction is possible in the Simmons–Smith reaction if a suitable auxiliary is used, or if the chirality is built in via a chiral template precursor (sec. 10.9). When **418** was prepared from diethyl tartrate,

subsequent treatment with diethyl zinc gave a 99% yield of **419**.[330] Subsequent hydrolysis gave **420** (90% ee), which allowed Yamamoto to complete an asymmetric synthesis of 5,6-methanoleukotriene A_4. This example also illustrates another zinc reagent that can be used for the Simmons–Smith reaction, diethyl zinc (Et_2Zn).[331] Imai et al. has also reported a chiral boronic acid auxiliary that leads to good enantioselectivity in the Simmons–Smith reaction.[332] The ability to produce the highly useful cyclopropane derivatives in an asymmetric manner greatly enhances the utility of an already classical reaction.

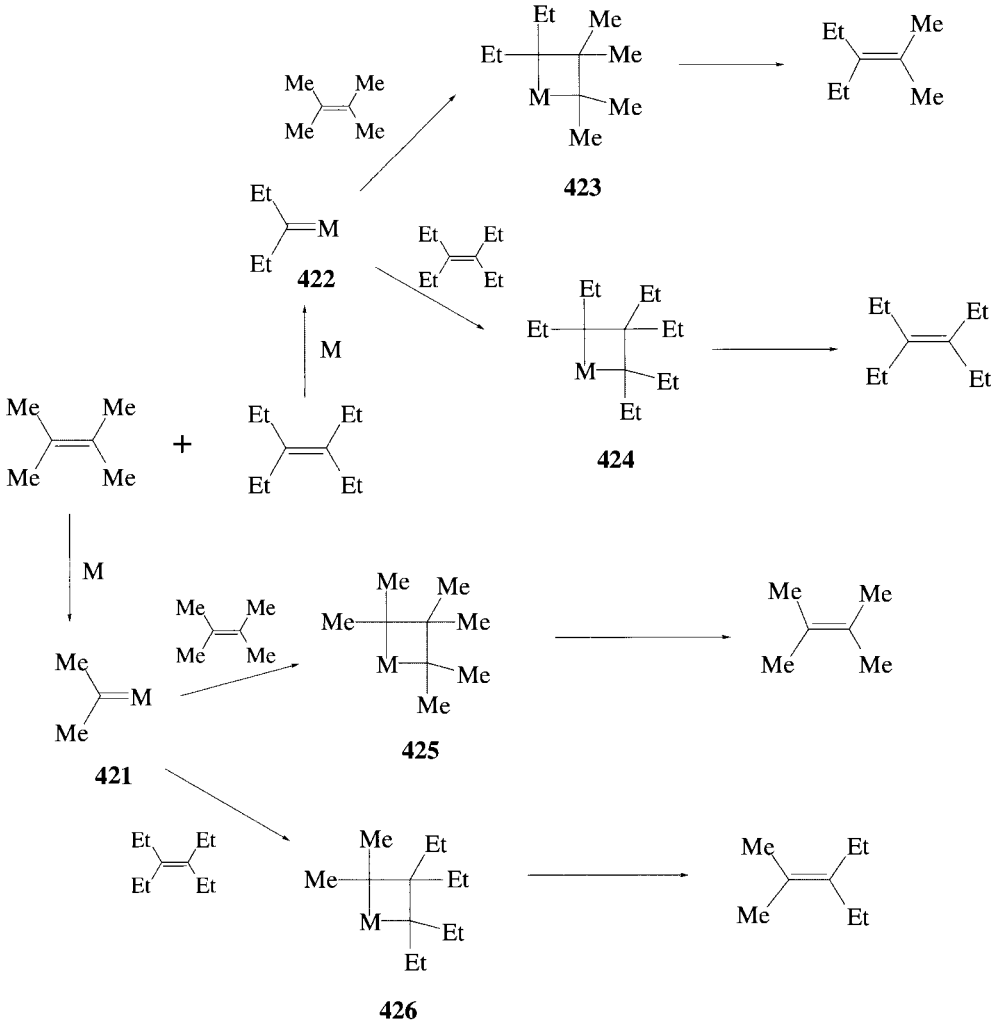


The Simmons–Smith disconnection is



13.10. Metathesis Reactions

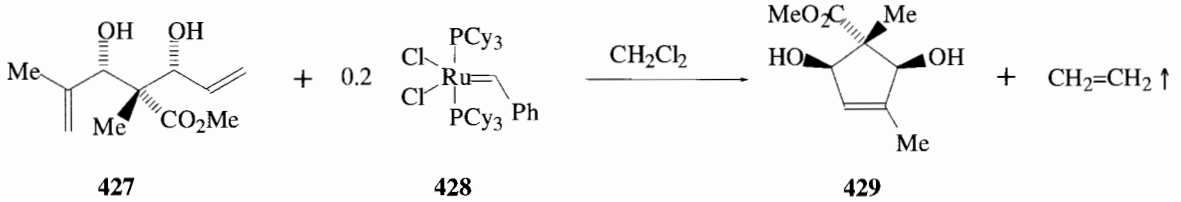
In the presence of transition metal catalysts, two alkenes such as 2,3-dimethyl-2-butene and 2,3-diethyl-3-hexene react to form the original alkenes along with 3-ethyl-2-methyl-2-pentene. This reaction is an example of **metathesis** or **alkene metathesis**[333] and an alkene is produced from an alkene or diene precursor.[334] As implied in the reaction shown, a mixture of alkenes can be formed but the reaction can be controlled in many cases, as will be seen below. The mechanism of this reaction is probably a chain mechanism that involves initial formation of a metal-carbene complex.[335] The metal-carbene reacts with each alkene to form a four-membered ring containing a metal (**423** and **424** from **422**; **425** and **426** from **421**).[336] Decomposition of the four-membered ring generates the two possible alkenes (2,3-dimethyl-2-butene and 3-ethyl-2-methyl-2-pentene from **426**, for example) and regenerates a metal carbene complex. The net result is formation of a new alkene. A single unsymmetrical alkene gives a mixture of itself and two other alkenes, and a mixture of two alkenes gives different alkenes but the number depends on the symmetry of the reactants. The reaction can be done intermolecularly between two alkenes, or intramolecularly using dienes. Both intermolecular or intramolecular reactions of dienes are known.[337] Simple alkenes usually give a statistical mixture of products.[338] but thermodynamic stability can influence the relative proportion of products. The equilibrium can be shifted if one of the products is volatile, such as ethylene. Terminal and internal alkenes have been used and the facility of reaction changes with branching according to the order $CH_2{=} > RCH_2CH{=} > R_2CHCH{=} > R_2C{=}$.[339]



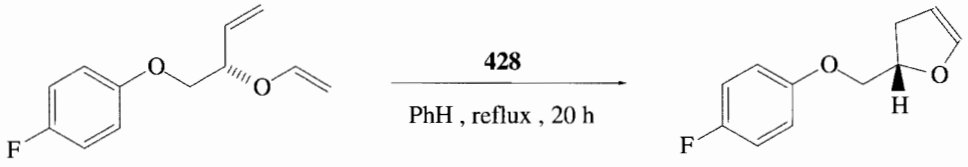
Metathesis reactions have been known for many years and can be carried out using both homogeneous[340] and heterogeneous[341] catalysts. Although other catalysts have been used,[342] ruthenium complexes[343] have been the most common. With the development of the Grubbs catalyst (**428**) the reaction has taken on increased synthetic utility. The Grubbs catalyst is also stable to Lewis acidic conditions.[344] Catalysts have been developed that allow the reaction to take place in aqueous and alcohol solution[345] and polymer-bound catalysts have been used.[346]

Without question, intramolecular metathesis reactions dominate synthetic applications and alkenes containing a $=CH_2$ unit are commonly used so that one product is ethylene, which escapes from the reaction medium and drives the equilibrium toward the desired cyclized product. A representative example is taken from the Ōmura, Smith et al. synthesis of (+)-madindoline A,[347] in which diene **427** was treated with 0.2 equivalents of the Grubbs catalyst (**428**), to give a 69% yield of the cyclized product **429**, along with ethylene.

With some of the early catalysts, alkenes containing functional groups[348] did not work very well. The Grubbs catalyst, however, is compatible with many functional groups, WCl_6—$SnMe_4$ can be used,[349] and heteroatoms can be incorporated in the ring being formed. In Gurjar's synthesis of the antiasthmatic

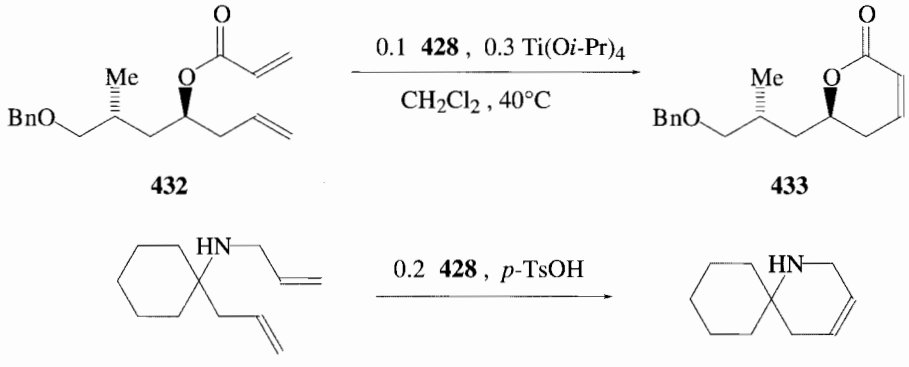


427 **428** **429**



430 **431**

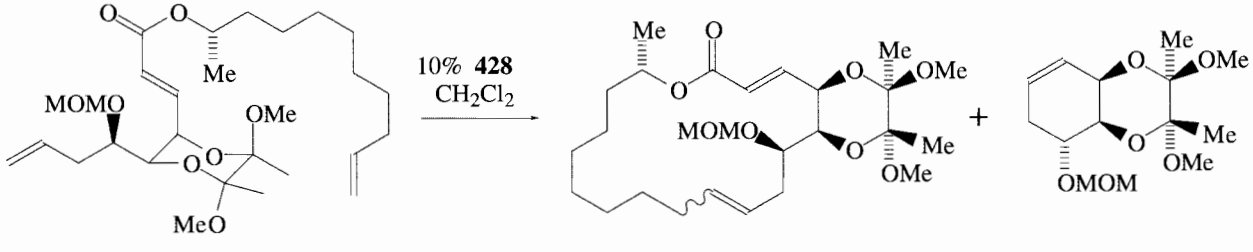
compound CMI-977,[350] for example, treatment of **430** with **428** gave a 52% yield of **431**. In the Ghosh and Wang synthesis of the C2–C16 segment of laulimalide, metathesis was used to form the lactone ring in **433** from **432**.[351] Nitrogen-containing compounds have also been prepared.[352] An example is taken from Wright's approach to the synthesis of halichlorine,[353] where N-allyl amines such as **434** were converted to spirocycle **435** in 76% yield.



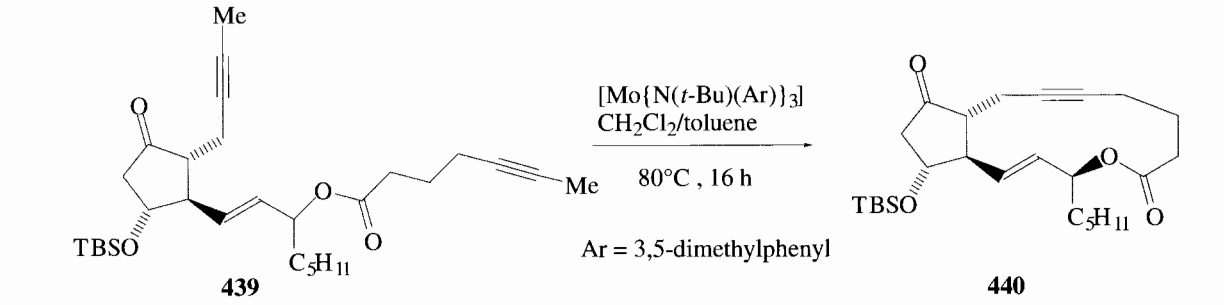
432 **433**

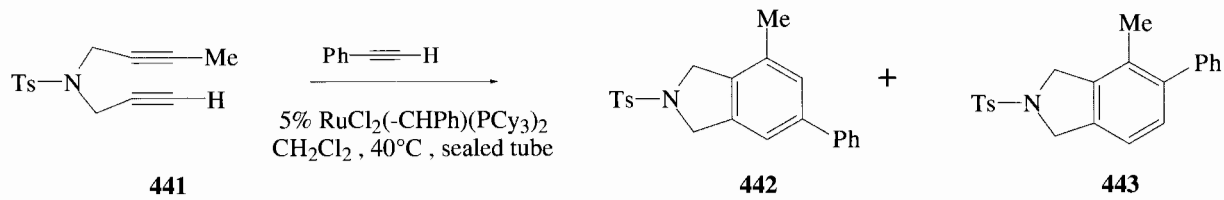
434 **435**

One of the more attractive features of this methodology is the ability to form macrocyclic compounds. In Ley's synthesis of (+)-aspicilin,[354] **436** was treated with 10% of the Grubbs catalyst to give a 73% yield of **437** as a 1.5:1 mixture of (*Z*/*E*) isomers, along with 26% of a byproduct (**438**) formed by metathesis across the double bond of the conjugated ester. With other ruthenium catalysts, the metathesis reaction can proceed with good stereoselectivity.[355]



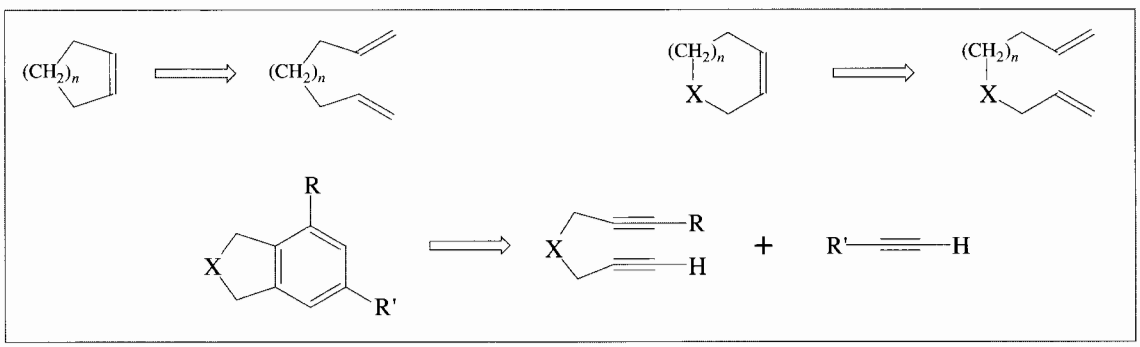
436 **437** **438**





Metathesis with alkynes is also quite useful in synthesis,[356] particularly for internal alkynes[357] although terminal alkynes are not good partners in this reaction.[358] Internal metathesis reactions with alkynes are known,[359] including the conversion of **439** to **440** (in 73% yield) in Fürstner's synthesis of prostaglandin E_2-1,15-lactone.[360] Note the use of a molybdenum metathesis catalyst for this reaction. Diynes also react with alkynes in an intermolecular reaction to form aromatic rings. An example is the conversion of **441** to a 6:1 mixture of **442/443**, in 82% yield.[361a] A similar, palladium-catalyzed cycloaromatization is also known.[362]

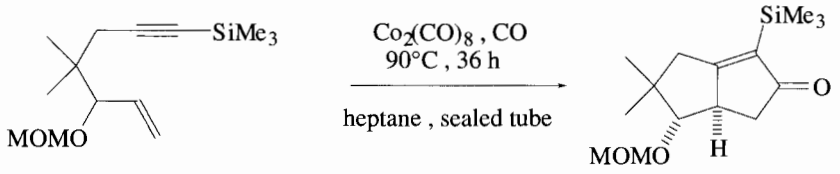
The metathesis disconnections are



13.11. Pauson–Khand Reaction

An interesting cyclization reaction was reported that involved the reaction of dienes, diynes, or ene–ynes with transition metals to form cyclopentenone derivatives in the presence of carbon monoxide.[363] In a simple example, ene–yne **444** was heated with dicobalt octacarbonyl and CO to give a 68% yield of **445**.[364] This transformation has become an important synthetic tool known as the **Pauson–Khand reaction**.[365] The mechanism probably involves insertion of the alkene (or alkyne) into the transition metal bond, which is why it is presented in this section. Formally, it is a [2+2+1]-cycloaddition, but the accepted mechanism is the one proposed by Magnus,[364] and shown in Figure 13.8.[366] It has been stated that further study is required to

firmly establish the mechanism[366] although Krafft's work supports it.[367] Other metal complexes have been used,[368] and the addition of primary amines enhances the rate of the reaction.[369]



444 **445**

This reaction has found its way into organic synthesis[366] and is attractive because of its generality and selectivity. In Brummond's synthesis of hydroxymethylacylfulvene,[370] for example, a Pauson–Khand reaction of the allene–alkyne **446** gave a 69% yield of **447**. In this case, molybdenum hexacarbonyl was used. In Takano's synthesis of dendrobine, **448** was treated with dicobalt octacarbonyl and then NMO to give an 89%

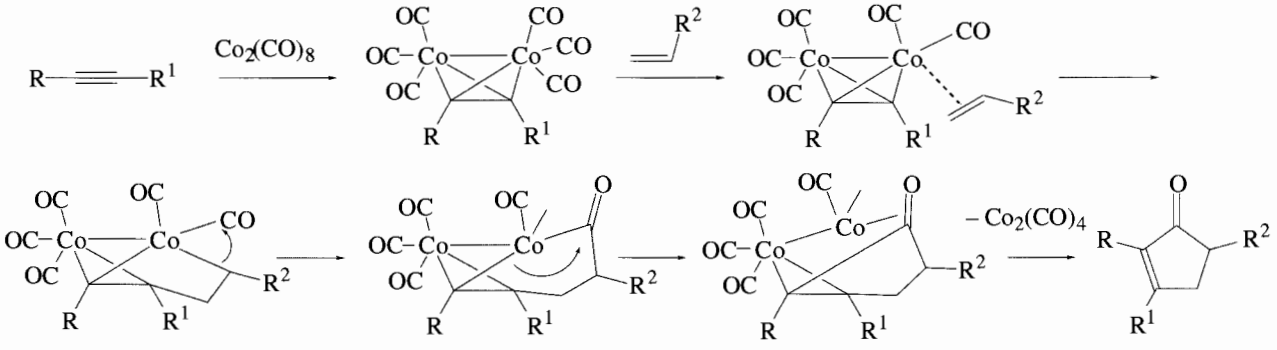
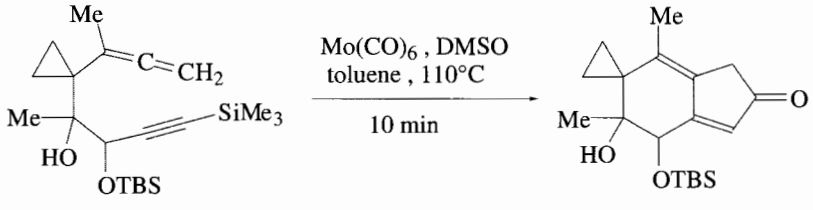
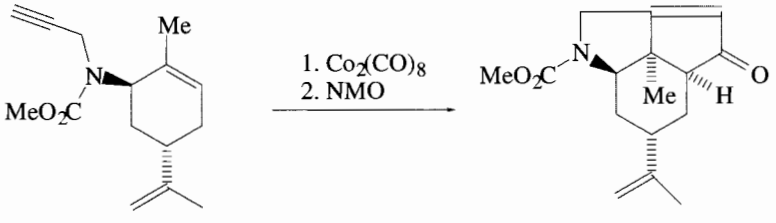


Figure 13.8. Magnus mechanism for the Pauson–Khand reaction. [Reprinted with the permission from Magnus, P.; Principe, L.M. *Tetrahedron Lett., 1985, 26,* 4851, Copyright 1985, with permission from Elsevier Science.]

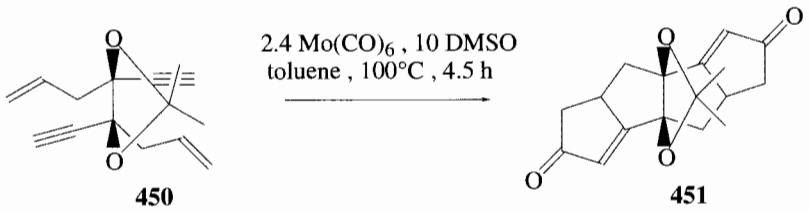


446 **447**



448 **449**

yield of the tricyclic compound **449**.[371] Very sophisticated ring systems can be produced by this technique. An example is Cook's synthesis of [5.5.5.5]-tetracyclic systems (pentalenes) in which **450** was treated with $Mo(CO)_6$ to give an 89% yield of **451**.[372]

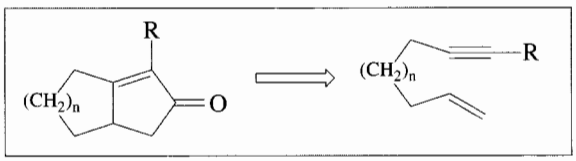


450 **451**

Although this reaction usually requires stoichiometric amounts of the metal carbonyl, Kraft has shown that substoichiometric amounts can be used.[373] In her work, 35–50% of $Co_2(CO)_8$ was used under a nitrogen atmosphere, in dimethoxyethane with 3 equivalents of cyclohexylamine. Kraft and Boñaga also developed dodecacarbonyltetracobalt as a viable catalyst.[374] The use of amines to promote the reaction was mentioned above. Molecular sieves have also been used to promote the Pauson–Khand reaction,[375] and high intensity ultrasound is also effective.[376] Polymer-supported promoters of this reaction are also known.[377]

Enantioselective versions of the Pauson–Khand reaction have been reported.[378] Brucine-*N*-oxide promotes an asymmetric Pauson–Khand reaction, for example.[379] An enantiospecific variation has been reported by using a menthol chiral auxiliary and by replacing one of the cobalt centers with an isoelectronic molybdenum fragment.[380] Chiral phosphine derivatives have also proven to be effective.[381]

The Pauson-Khand disconnection is



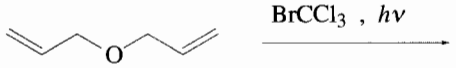
13.12. CONCLUSION

This chapter has shown the great control and selectivity of modern radical reactions, especially intramolecular radical coupling reactions. Carbenes, especially those derived from diazoalkenes, have also played a prominent role in organic synthesis. The chemical reactions illustrated in this chapter are excellent additions to the list of nucleophilic, pericyclic, and electrophilic reactions presented previously. This chapter concludes the methodology for generating carbon–carbon bonds. With the functional group reactions in the first part of the book, all the tools for pursuing a synthesis are at hand.

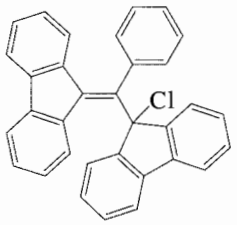
The last chapter will present several actual syntheses done by students, not their teachers. Examination of these syntheses will show common mistakes made by beginning synthetic chemists. They will also show some of the correct approaches to presenting a synthesis.

HOMEWORK

1. Predict the major product of the following reaction and briefly discuss why it is formed and other possible products are not (or are minor products).



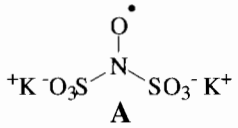
2. Treatment of this molecule with mercury produced a radical. This radical product literally sat on the shelf for 25 years before the work was published. Give the structure of the radical and discuss its stability.



Hg

J. Am. Chem. Soc., ***1957***, *79*, 4439

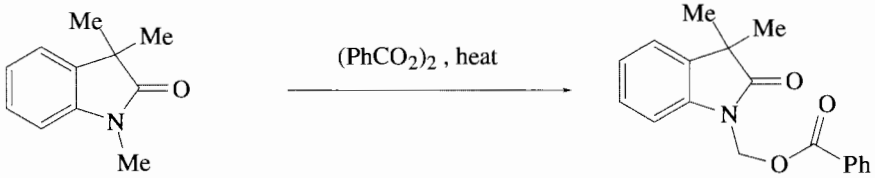
3. The structure of Fremy's salt is given. It is a rather stable free radical. Discuss the stability of this salt and also discuss its synthetic utility.



A

Chem. Ind., ***1953***, 244
Ann. Chim. Phys., ***1845***, *15*, 459

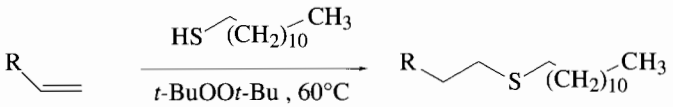
4. Give a mechanistic rationale for the following transformation.



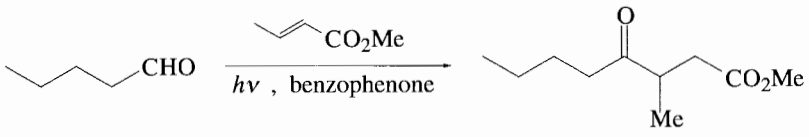
5. Explain the following results.

6. Explain the following rate data for the reaction shown.

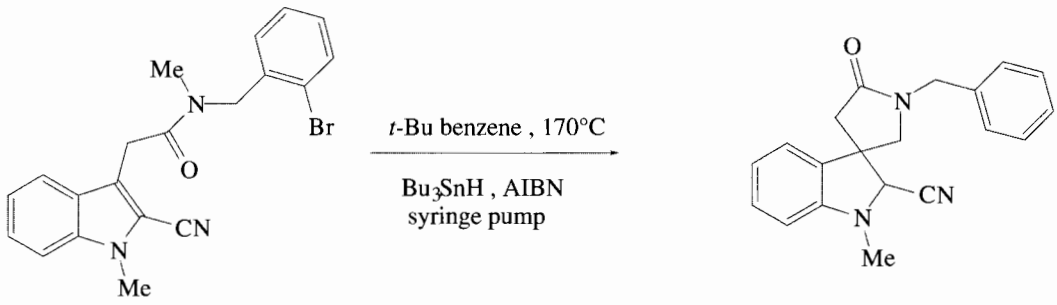
R (relative rate): Ph- (17.0); *n*-BuO- (3.9); MeO_2C- (2.0); *n*-C_6H_{13}- (1.0); $ClCH_2$- (0.7).



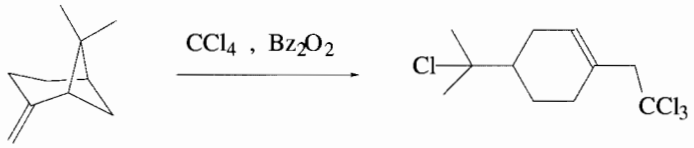
7. Why is benzophenone added to the following reaction? Give a mechanistic rationale for this transformation.



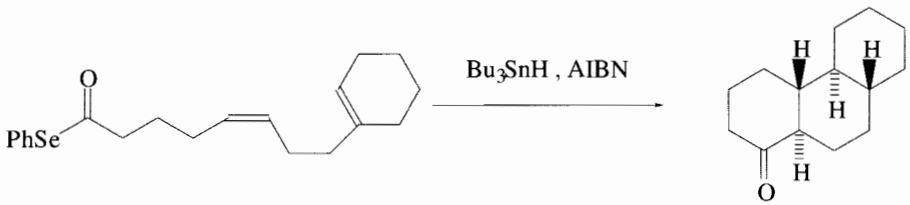
8. Give the mechanism for this transformation.



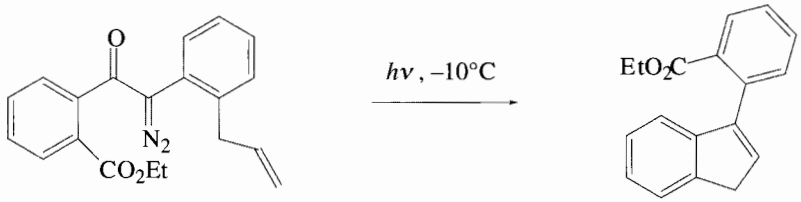
9. Explain the formation of the indicated product from β-pinene and carbon tetrachloride.



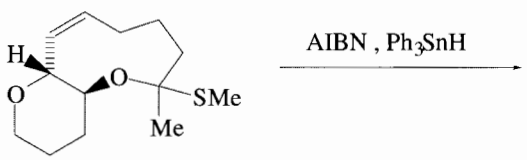
10. Explain the following transformation:



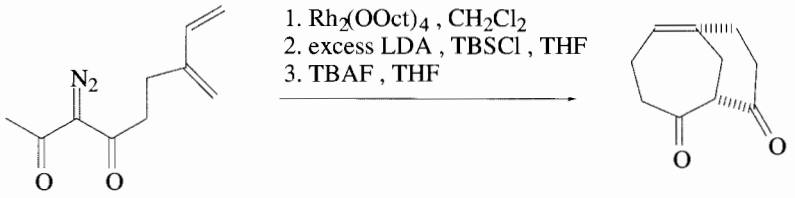
11. Explain the following transformation:



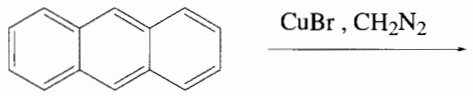
12. Two major cyclized products are produced in this reaction. Draw their structures and discuss the mechanism of their formation.



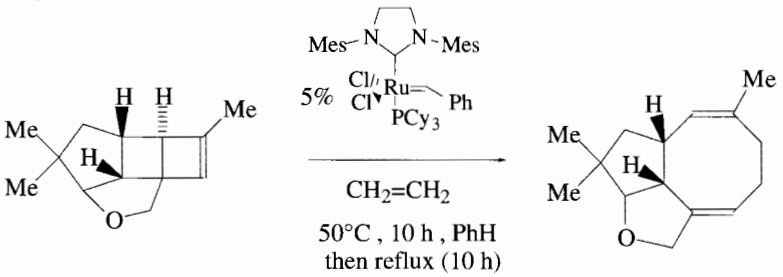
13. Explain the following transformation:



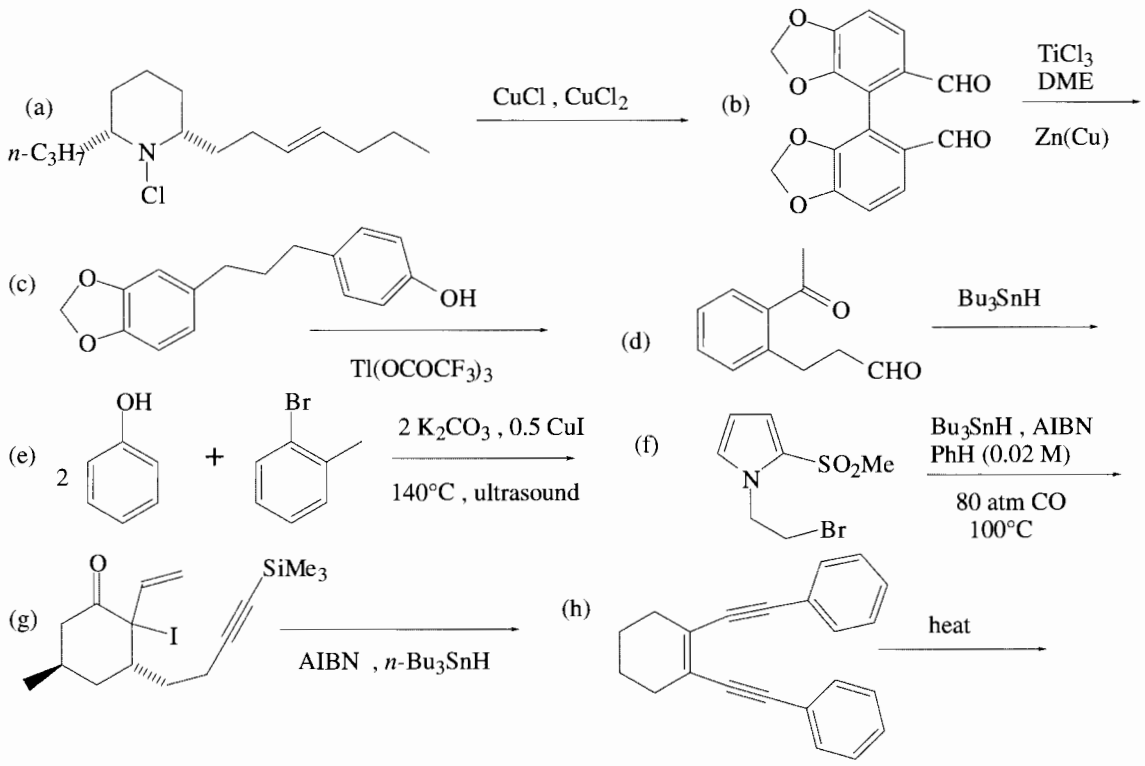
14. Three products are formed in this reaction, two minor and one major. Show all three products and indicate which one is the major product. Explain your choice.

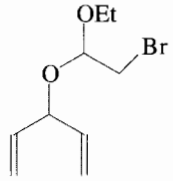


15. Explain the following transformation.



16. In each case show the major product. Indicate stereochemistry where appropriate.

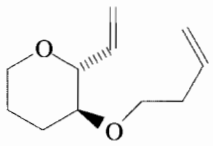


(i) 

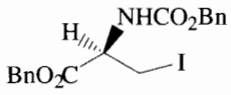
Bu_3SnH , AIBN
PhH , 80°C

(j) 2

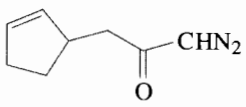
CuCl , DMF
60°C

(k) 

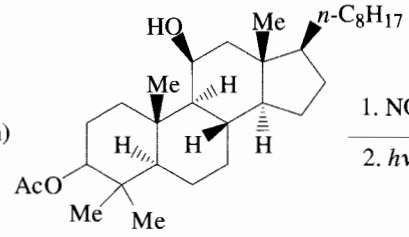
cat
$Cl_2Ru(PCy_3)_2$=CHPh
CH_2Cl_2

(l) 

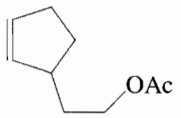
AIBN , n-Bu_3SnH
CH_2=$CHCO_2H$

(m) 

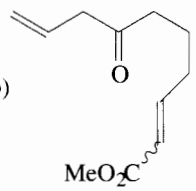
$CuSO_4$

(n) 

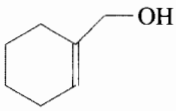
1. NOCl
2. $h\nu$, PhMe

(o) 

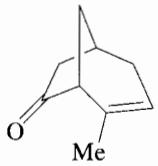
$CHBr_3$, NaOH

(p) 

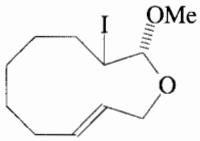
Bu_3SnH , AIBN
PhH , 80°C

(q) 

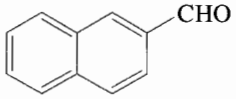
1. Zn , CuCl
2. CH_2I_2 , ether

(r) 

$h\nu$, acetone

(s) 

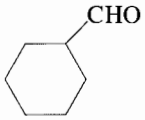
Bu_3SnH , BEt_3

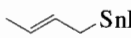
(t) 

$TiCl_4$
Bu_4NI

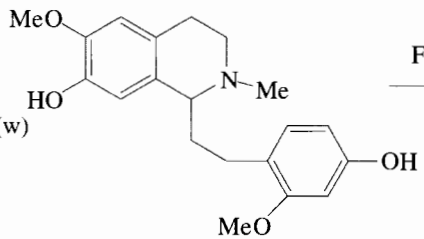
(u)

e^- , MeOH

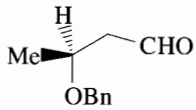
(v) 

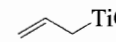
2 

BF_3•OEt_2

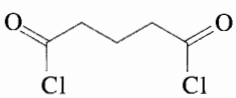
(w) 

$FeCl_3$, H_2O

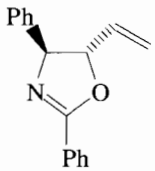
(x) 



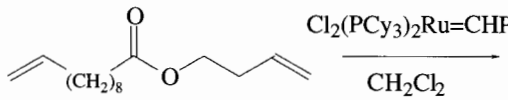
THF

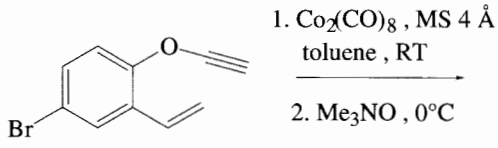
(y) 

1. excess CH_2N_2 , ether
2. 5% $Rh_2(OAc)_4$
CH_2Cl_2 , 20°C

(z) 

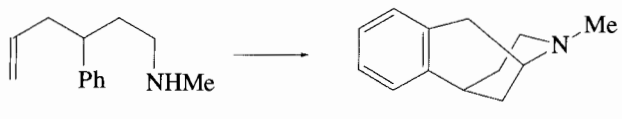
1. $RuCl_3$, $NaIO_4$
$NaHCO_3$, aq MeCN
2. CH_2N_2 , ether

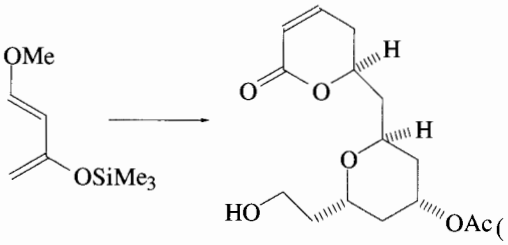
(aa) 

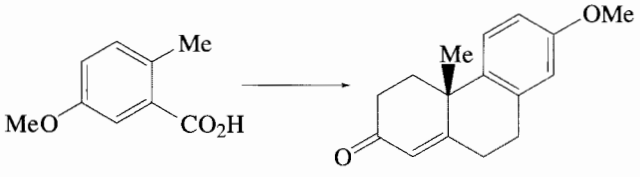
(ab) 

17. In each case provide a suitable synthesis from the designated starting material. Show all intermediate products and all reagents.

(a)

(b) 

(c) 

(d) 

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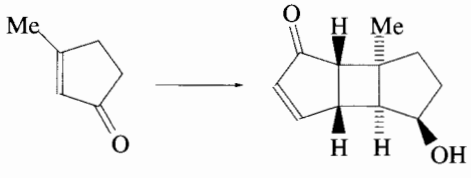
(f) 

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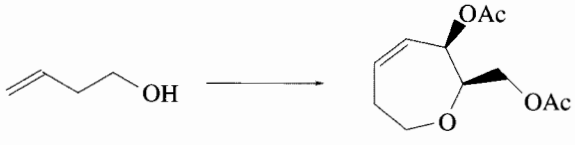
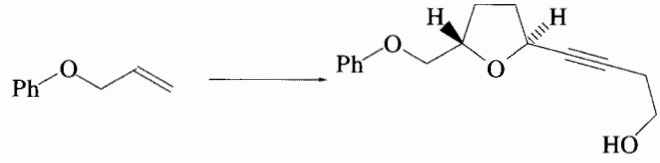
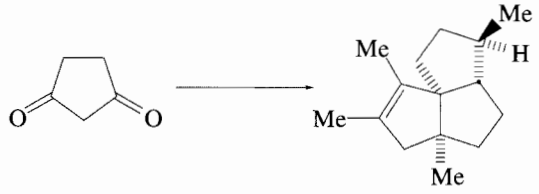
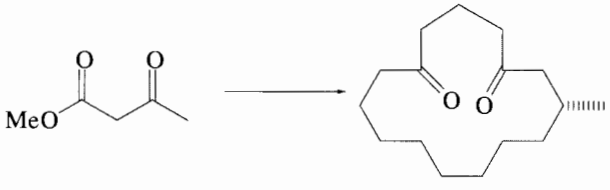
(h) 

(i) 

(j) 

(k) 

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CHAPTER 14

STUDENT SYNTHESES: THE FIRST SYNTHETIC PROBLEM

14.1. INTRODUCTION

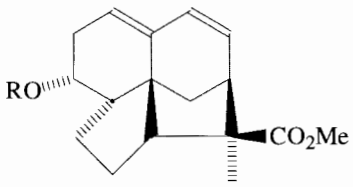
It is one thing to learn all the reactions and processes described in this book. It is another to apply them to a complex molecule. A total synthesis first demands a review and understanding of the various disconnections and retrosynthesis strategies. Once a strategy is chosen, functional group exchange reactions and carbon bond forming reactions must be reviewed, in order to choose those reactions best suited to a particular strategy. Those reactions pertinent to the problem are then studied, forcing a thorough literature search (in the library or using one of the various literature searching techniques available for computers). Every step forces a complete review of chemical principles, stereochemical and conformational relationships in order to justify the use of each reagent that is not obvious. This collection of steps must then be examined for continuity, and the continuum of functional groups must all be compatible. In other words, groups introduced in the first synthetic step must not react with any succeeding steps. If they do, protection of those groups or redesign of the strategy is required. This discussion clearly suggests that a total synthesis focuses attention on organic chemistry in a way few, if any, other area of organic chemistry is able to do. For these reasons, a synthesis and reactions course often includes a proposal by the student for the synthesis of a natural product.

In most of the papers where a total synthesis is presented, the strategy and rationale for the synthesis is given. Most of the paper is devoted to explaining how and why the reactions worked, the stereochemical and conformational importance of various steps and, in some cases, a detailed explanation of things that did not work well in the initial planning. If a detailed study of published syntheses is of interest, and it should be to anyone proposing to synthesize a molecule, there is an excellent series that will provide information about how and why a synthesis was done. Lindberg's excellent series "Strategies and Tactics in Organic Synthesis", Volumes 1–3 [QD 262.s85] (1984, 1989, and 1991), Academic Press, San Diego is *strongly* suggested for anyone who is using this book in a synthesis course.

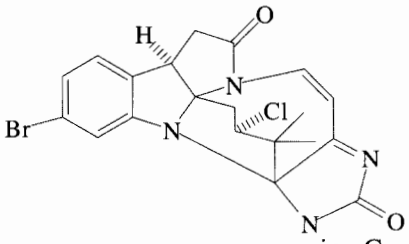
The course that spawned this book also asked the students for such a synthesis proposal. There are many formats for the write-up, including those used by the National Institutes of Health (NIH) and the National Science Foundation (NSF). Each have somewhat different formats and page requirements. It is convenient to write a synthesis proposal following one of these formats, although any arbitrary format is acceptable.

This chapter is intended to show the first synthesis submitted by students who have had a course based on the material in this book. Scanning the literature will provide many examples of finished and polished total syntheses. Many have been used as source material to illustrate various reactions and those literature citations will lead to a broader explanation of that particular synthesis. The work behind such publications, however, is sometimes lost in the highly focused final paper. Various attempts to solve problems are sometimes, but not

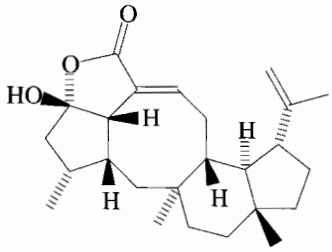
always, fully discussed. A study of known syntheses is very useful and provides a basis for the thoughts and strategies of the investigator (refer to Linderg's work–*vide supra*). As a teaching tool for the beginner, however, many points are glossed over or are not obvious. The next three sections will discuss proposals submitted by beginners that targeted isocedrene esters (sec. 14.2), securamine C (sec. 14.3) and variecolol (sec. 14.4). The first proposal illustrates the impact of using hand-drawn structures. Clearly, the proliferation of computers and drawing software makes this presentation less likely. However, it is useful to compare it with proposals using computer generated schemes and figures. The first proposal was prepared using a typewriter rather than using a word processor. Once again, it is useful to compare it with the last two proposals.



an isocedrene ester



securamine C



variecolol

The intent of this chapter is not to simply criticize a first-time proposal, but rather to show common mistakes that creep into that first proposal. In each section there will be three parts. The first part is the proposal by the student, as submitted. The second part is a list of all reaction types proposed by the student, and the third is the instructor's critique. The comments in the critique are often aimed at specific chemical problems related to that target and will serve as only a brief review of some chemistry. Others, however, are more general and will hopefully illustrate things to avoid while planning a synthesis. The proposals are reproduced exactly as submitted to show the importance that a presentation can make to the visual and conceptual interpretation of the proposal.

There are many ways for the reader to approach this chapter. The reader could construct a synthetic proposal of their own before reading further. The reader could act as the reviewer and construct their own critique. Of course, one could simply read my comments about each proposal. It is my belief that an active role in reviewing each proposal will be far superior to a passive role. Compare my criticisms with your own. Agree or disagree! That is the first step to a good proposal.

14.2. TOTAL SYNTHESIS OF ISOCEDRENE ESTERS

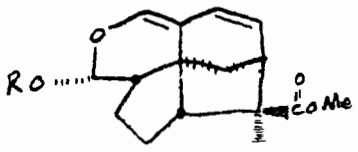
This proposal will not work as written. There are simply too many problems and, although the strategy may be workable, a viable route was not presented. Some of the errors are silly, such as proposing an S_N2 reaction at a tertiary center. The lesson from such errors is to pay sufficient attention to the details of each reaction and not allow the strategy to blind you to problems. In this proposal, key reactions are glossed over or presented with little or no discussion. There is virtually no discussion of regiochemistry and stereochemistry. The final evaluation determined that there were too many serious problems for this to be successful.

It is noted that this proposal was reviewed and its author had 10 days to rebut the critique before the grade was assigned. In this case the author presented an entirely new strategy and received an excellent grade. This first proposal is presented to show how serious problems can creep into what appears to be a sound strategy that has been applied to other systems.

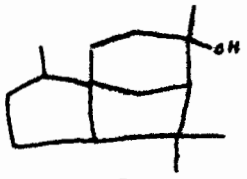
14.2.A. The Proposal

A. Introduction

Recently, a paper appeared which reported the isolation of two new sesquiterpene esters I (R = isovaleryl, 2-methylbutryl) from Trisis Parodoxa. These two compounds as well as two other sesquiterpene lactones reported,extend further the list of natural isocedrene derivatives.[1]



I



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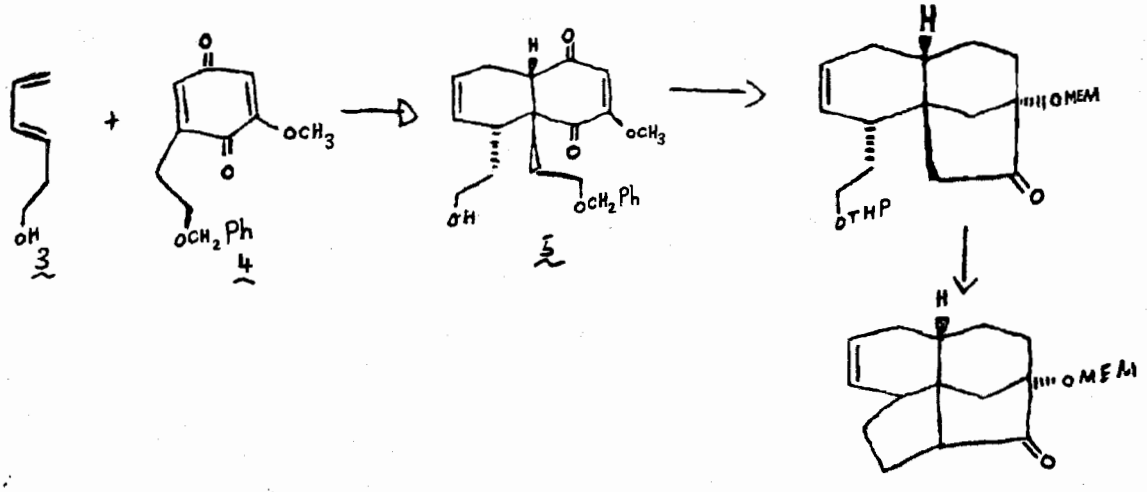
The isocedrenes are considered to be analogs of the tricyclic sesquiterpene cedrol (2) which has been synthesized by G. Stork.[2] Cedrene and its derivatives, most notably the 9 and 10- oxy derivatives have found applications in the cosmetics field as additives to perfumes, and in other fields as plant growth stimulators.[3]

SCHEME I

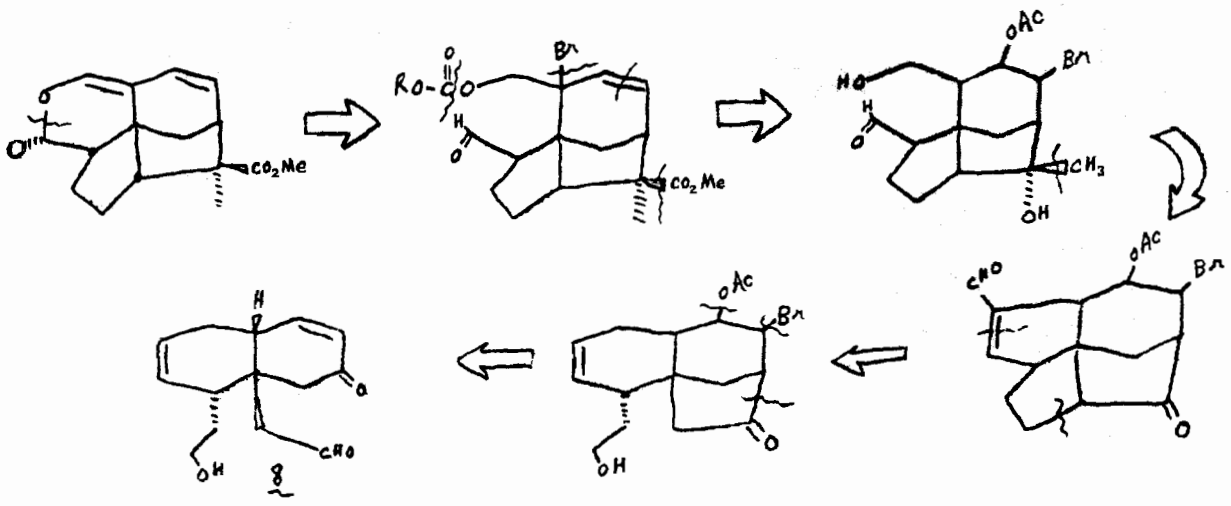


This proposal descrbes the first stereospecific synthesis of the isovaeryl-isocedrene ester (1).[4] The synthesis is based on a key intermediate in Cory's total synthesis of Gibberillic acid.[5] The key intermediate (5) allows us to generate two of the six chiral centers strereospecifically.[6] This Gibberillic acid intermediate which is generated by a Diels- Alder reaction[26] has the appropriate geometry which allows us to generate two of the remaining four chiral centers also in a stereospecific manner. Scheme 1 shows some key intermediates in the synthesis of four of the stereospecific centers.

The disconnections in Scheme II are based on the key intermediate mentioned above and lead to synthon

8. Synthon 8 is clearly preceeded by (5) which is a Diels- Alder Adduct as shown in Scheme I. This Diels - Alder reaction is clearly the most important reaction in the synthesis as it paves the way for the stereoselective generation of at least four of the six chiral centers.

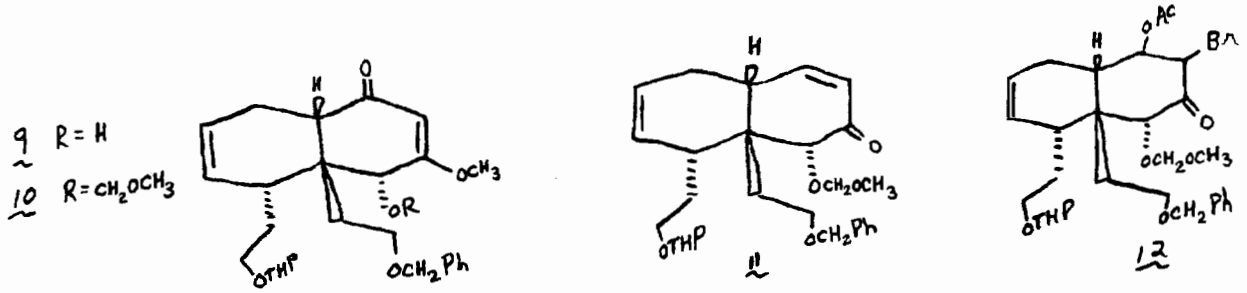
SCHEME II



B. METHODS

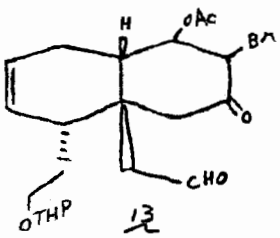
As we have mentioned, a reasonable precursor for synthon 8 is the Diels - Alder Adduct 5. Reaction of the Quinone 4 with trans- 3,5 hexadien-1 - ol 3 occurs upon heating in benzene solution at reflux for about 30 hours.to afford a single crystalline adduct 5. Reaction of 5 with dihydropyran in methylene chloride will give the THP ether. Reduction of the THP ether with sodium borohydride in absolute ethanol gives the hydroxy enone 9. Convertion of the hydroxy enone 9 to the alpha- methoxymethyl-epoxy ketone 10 can be accomplished by reaction with N,N - diisopropylethylamine and chloromethyl methyl ether in methylene chloride at reflux. Reduction of the keto group in 10 with lithium aluminum hydride in ether, followed by isolation and immediate mesylation of the resulting alcohol, followed by slow addition of saturated potassium bicarbonate to effect solvolysis and finally chromatography of the product on silica gel gives 11.[7]

Here we are faced with the task of protecting the enone double bond,so that it can be regenerated at the end of our synthesis. This is accomplished by selective hydrogenation of the enone double bond with hydrogen and five percent rhodium - on - carbon catalyst at room temperature in THF.[8] This redcued double bond is then masked as the phenyl selenide by reaction with lithium diisopropylamide and the di- henylselenide.[9] The



isolated double bond is then protected with the iron dicarbonyl cyclopentadienyl complex,[10] and the enone double bond is regenerated using hydrogen peroxide in THF and a trace of acetic acid. The enone double

bond is then protected against oxidative or reductive conditions using the acetyl hyprobromate reagent.[11]The isolated double bond can then be regenerated using hydrogen and a catalyst.We now have compound 12.



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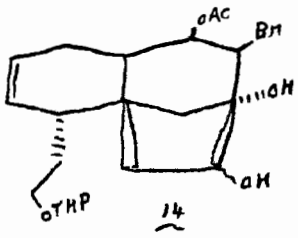

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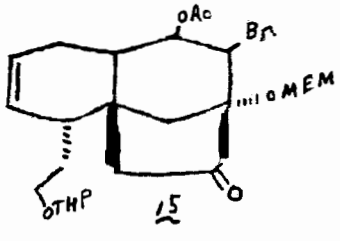

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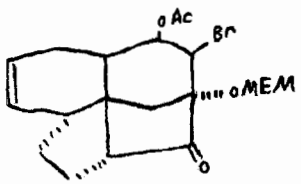
Oxidation of 12 with excess Collins Reagent in methylene chloride yields the sensitive keto aldehyde 13. A pinacol cyclization of the keto aldehyde 13 to the tricyclic intermediate 14 is accomplisehd by reaction with finely powdered metallic Titanium inTHF.[12, 13] Oxidation to the ketol without appreciable glycol cleavage can be readily accomplished via an oxysulfonium intermediate.[14, 15] The ketol can then be converted to the MEM ether derivative by treatment with MEM chloride and diisopropylethylamine in methylene chloride at reflux to give the MEM ether derivative 15.[16]



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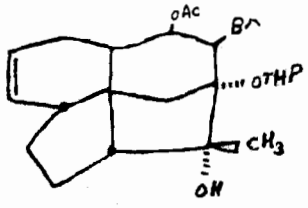

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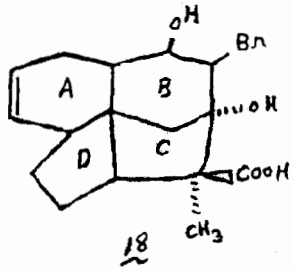

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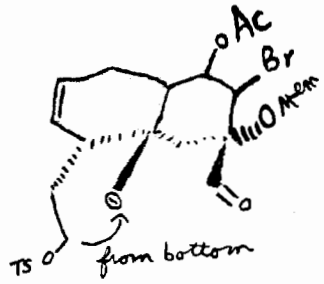
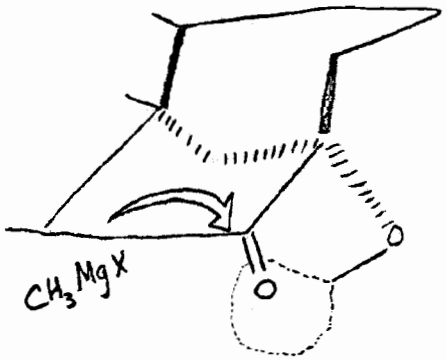
Addition of MEM will also generate two diastereomers, so that chromatographic separation will allow us to generate the intermediate with the same stereochemistry as the ester isolated from Trixis Parodoxa.

Next, the THP protecting group is removed using aqueous acid, p - toluenesulfonic acid and ethanol,[17] and the alcohol is then reacted with p- toluenesulfonyl chloride in pyridine to give the Tosylate. The Tosylate is then cyclizedwith sodium hydride in dimethylformamide to give the tetracyclic ketone 16. Models indicate that attack will predominately occur from the bottom, since attack from the top will generate e severely strained ring system. A very good yield of the stereospecific product should then be anticipated.

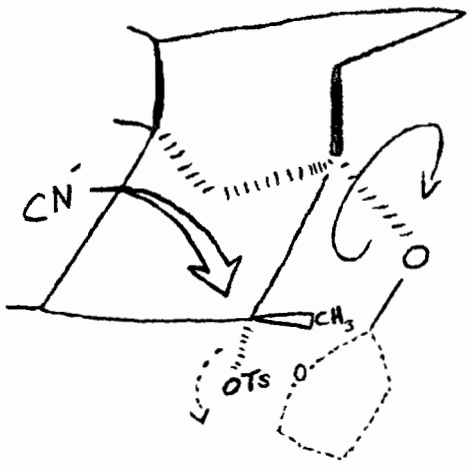


The next step is the proper functionalization of the carbonyl carbon.the ktone is methylated using methyl grignard reagent followed by aqueous acid workup to give the alcohol 17.But in hopes to increase the steroeoselectivity of the reaction, the MEM ether is first removed using zinc bromide in methylene chloride,[18]

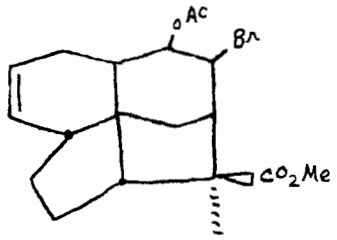
and a tetrahydrofuranyl group is added using dihydrofuran with copper chloride and phenyl,tert - butyl ester. Here, we would expect the THF ether to prevent bottom attack. As opposed to the MEM ether which is long enough to easily block both sites of attack, the THF ether resides mostly underneath the carbonyl.group. therefore, models would indicate a predominant amount of topside attack.



Next, the alcohol is tosylated as in a previous step, and potassium cyanide is added followed by acid hydrolysis to give the carboxylic acid 18. Again, the THF ether along with S_N2 like conditions should give the preferred stereospecific isomer as the major product. the reason again being that topside attack should occur. After removal of the THF ether with aqueous acid, para - toluenesulfonic acid and ethanol, the diastereomers can again be separated to give the optically pure product.Refluxing of the product with sodium methoxide in methanol gives the methoxy ester in very good yield. Since the alcohol now seves no useful purpose, we may remove it by forming the tosylate, from tosyl chlride and pyridine, and reducing with sodium borohydride. We now have compound 19.



Treatment of a solution of 19 in acetone - water with N- methyl morpholine N- oxide and Osmium tetroxide[19] will give the single cis diol which can be cleaved by reaction with lead tetraacetate in benzene to give the sensitive dialdehyde 20. Treatment of 20 with benzylammonium trifluoroacetate in benzene and refluxing will give the alpha,beta unsaturated aldehyde 21.



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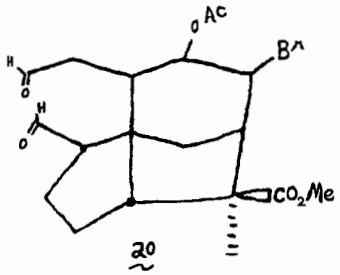

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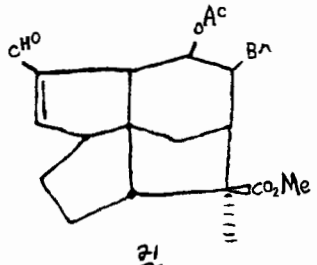

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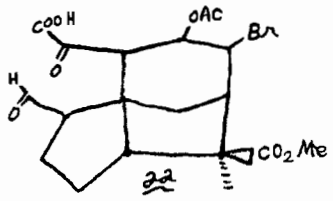
Oxidation of the aldheyde with chromate and pyridine, followed by ozonolysis with ozone and workup with zinc and acetic acid gives the alpha keto acid 22.[20]Decarboxylation with lead tetraacetate gives the alcohol aldehyde 23.[21]



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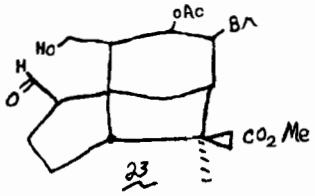

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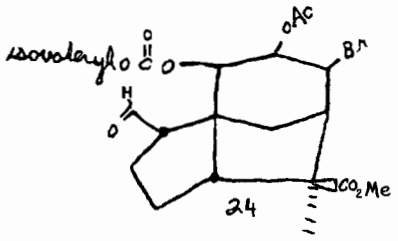

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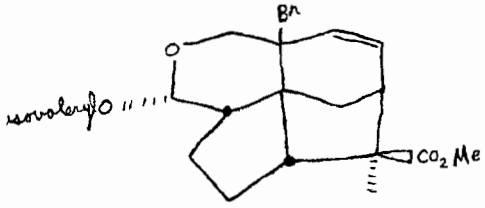
Reaction of this compound with phosgene gives the alkylchlorocarbonate which when reacted with isoveleric acid should yield the mixed anhydride.[22]The mixed anhydride under heat can then react by a [3.2.1] bicylcic mechanism to give the acetal product.[23] The bromoacetate protecting group can then be removed with a zinc - copper couple.[24] Allylic bromination with NBS[25]followed by dehydrohalogenation with potassium hydroxide and methanol gives the sesquiterpene ester 1. Chromatographic separation of the product will give the optically active product.

Although there is precedent in the literature for the preparation of mixed anhydrides and their possible thermal rearrangement to acetals,[22,23]extensive studies on model systems would be required to determine if the particular reaction we are proposing would indeed occur. From an academic point of view, these studies would indeed be quite interesting. Admittedly, it is doubtful that this would have general practical application in organic synthesis, especially because to date, no biological activities of the isocedrene ester 1 has been reproted in the literature. But looking ahead, this method may prove to be a practical means of making this class of compounds.



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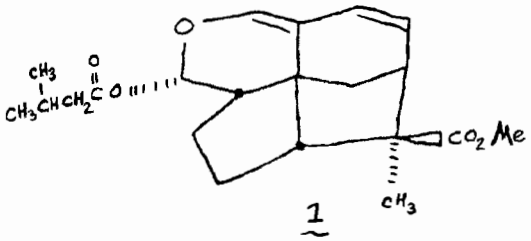

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6. The structure and stereochemistry of the adduct was anticiapted to be that expressed by 5 on the basis of much precedent in the literatauare, and this expectation is fully confirmed by the data. J.A.C.S. 100 8031(1978)
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J.A.C.S. 86 2942(1964) 90 747(1968)
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14.2.B. The Critique

Several reactions were proposed in this synthesis. They are listed below, along with the chapter and section where each is discussed in this book.

1. Diels-Alder Reaction (sec. 11.4).
2. Alcohol protection and deprotection as a tetrahydropyranyl ether (sec. 7.3.A.i).
3. Reduction of ketones with sodium borohydride (sec. 4.4.A).
4. Alcohol protection and deprotection as a MEM ether (sec. 7.3.A.i).
5. Reduction of ketones with lithium aluminum hydride (sec. 4.2.B).

6. Conversion of an alcohol to its methanesulfonate ester (sec. 7.3.A.ii).
7. Alcohol protection and deprotection as a benzyl ether (sec. 7.3.A.i).
8. Catalytic hydrogenation of alkenes (sec. 4.8.B).
9. α-Phenyl selenide formation via a ketone enolate (sec. 9.3.C).
10. Syn elimination of selenoxides (sec. 2.9.C.vi).
11. Protection of an alkene as an iron complex (not covered in chap. 7).
12. Bromoacetate formation via alkenes and acetyl hypobromite (sec. 2.10.C).
13. Collins oxidation of alcohols (sec. 3.2.B.i).
14. Pinacol coupling (sec. 13.8.D).
15. McMurry coupling (sec. 13.8.F).
16. Swern oxidation of alcohols to carbonyls (sec. 3.2.C.i).
17. Grignard reaction with carbonyls (sec. 8.4.C).
18. S_N2 reaction of cyanide and a tosylate (sec. 2.7.A and sec. 8.2).
19. Acid hydrolysis of nitriles to carboxylic acids (sec. 8.2).
20. Reduction of tosylates (hydrogenolysis). (sec. 4.2.C.vii, 4.8.E and 4.9.D).
21. 1,2-Diol formation by reaction of alkenes with osmium tetroxide (sec. 3.5.B).
22. Oxidative cleavage of 1,2-diols with lead tetraacetate (sec. 3.7.C.i).
23. An intramolecular aldol condensation (sec. 9.4.A.ii).
24. Oxidative cleavage of alkenes via ozonolysis (sec. 3.7.B).
25. Decarboxylation (sec. 2.9.D).
26. Chlorination of alcohols with phosgene (sec. 2.8.A).
27. Allylic bromination with NBS (sec. 2.8.B).
28. E2 elimination (sec. 2.9.A).

Critique of the Proposal (Numbers refer to points highlighted in the proposal)

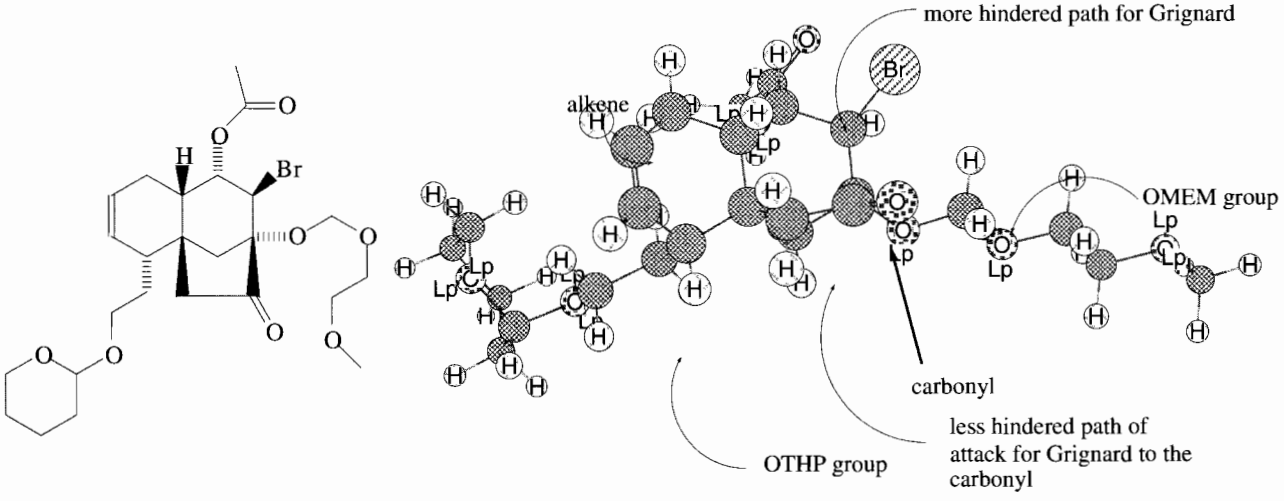
GENERAL: There are numerous typographical errors in the manuscript

1. The author refers to 9 and 10 oxy derivatives. The structures must be numbered or it is impossible to follow the sequence.
2. As submitted this line was of too poor a quality to be read. This is cosmetic but it detracts from the overall proposal and more care should be placed on the appearance of the proposal.
3. The statement "of the stereospecific centers" is vague. It is not clear which molecule this refers to. In addition, stereospecific refers to a reaction type. Does the author mean a stereogenic or a chiral site?
4. This implies all chiral centers are created at the time of the Diels-Alder reaction, but some are formed prior to the Diels-Alder and some after. It is important to specify the 'timing' of the reactions and their sequence. If chiral centers are created from prochiral substrates, control of the geometry of diene and alkene is important. If chiral centers are incorporated into the diene and alkene, an asymmetric synthesis is required, possibly using a chiral starting material.
5. This sentence is too long and, most importantly, contains too many synthetic steps without explanation. For example, the mesylation step was clearly intended to facilitate elimination and allow formation of the conjugated ketone. This is not clearly spelled out, in the text or in the reaction diagram. One should not assume a multi-step pathway is obvious.
6. The poorer reactivity suggested for nonconjugated double bonds should have a literature citation to support the claim.
7. This transformation requires kinetic enolate conditions. They should be specified.
8. This sequence raises several questions that are not addressed. What is the structure of this iron complex? Does this complex also react with the π-bond of the carbonyl? Halogens are known to cleave C-Fe bonds. Will the acetyl hypobromate (structure?) reagent or the use of aqueous acetic acid cleave the iron complex? The author should preempt such questions and diffuse them. Even if the answer to these questions will not adversely effect the synthesis, a brief comment indicates that potentially important side reactions were considered.
9. Both the carbonyl and the bromine α-to the carbonyl are subject to reduction under these conditions. The choice of catalyst and reaction conditions are important and should be specified, preferably with a leading reference.

GENERAL COMMENTS

For structures **9** → **12**, no mention is made of diastereomer formation and diastereoselectivity in the reactions. In compound ***12*** three chiral centers have been created, assuming the three centers in structure ***5*** have previously been attended to. This is non-trivial since there is the potential for a mixture of several different compounds. The diastereoselection of the reactions and some prediction of the stereochemical outcome of each reaction is important and must be discussed.

10. The O-benzyl protection group must be removed prior to the oxidation, which was done without comment. The usual conditions involve catalytic hydrogenation but then comment 9 (above) is important with regard to the bromine and the carbonyl.
11. This is called a McMurry coupling - use the correct name. Elimination of the bromide could result in an alkene as a competitive side reaction.
12. This oxidation is referred to as a Swern Oxidation - the correct name should be used if there is a need to use a name for a reaction. DMSO could react with the bromo acetate moiety and this should be demonstrated, or discounted.
13. Diisopropylamine could induce an E2 reaction with the bromide.
14. Finally, at this late point in the proposal, mention is made of diastereomer formation. The reaction forming the MEM ether does not generate diastereomers, they were present prior to this reaction. How effective will the chromatographic separation be? How many compounds may be present at this point and what is the predicted major product? This point, as in the general comment above, must be treated much earlier in the synthesis.
15. The argument for selectivity in the enolate displacement is probably correct but the structure shown does <u>not</u> indicate this. The enolate anion could, in principle, react with the bromine or the acetate, if they are properly oriented. This depends of the conformational preferences of the molecules. Some attempt to show the three dimensional representation of the molecule must be made in order to address these points.
16. The conformational drawing does not clearly show that attack will follow the author's predictions. This simple model suggests selectivity but it does not accurately reflect the real conformation, and its results are suspect. If the ketone is treated as part of a 'norbornyl-like' system, 'exo' attack is from the 'bottom' and should be preferred, which is opposite to that predicted by the author. Both the 2D representation and the 3D drawing are shown with these comments. These drawings suggest that attack by the Grignard should be from the 'bottom' of the molecule (as it is drawn). This emphasizes that it is important to draw the molecule in the correct conformational representation.



17. Can zinc bromide react with the bromine?
18. Is copper chloride cuprous or cupric?
19. The same comments as those in statement 16 (above) apply here. The stereochemistry must be demonstrated by an accurate conformational drawing. It would also be useful to draw the structure that contains the O-THF group since great emphasis is placed on its steric bulk.

20. This is another reaction that is absolutely incorrect. The S_N2 reaction of cyanide will not occur at the tertiary center.
21. Two comments apply here. The first one concerns the reaction forming the methyl ether. How does this work? How does one obtain a methyl ether by reacting basic sodium methoxide and the alcohol? The second comment is general in nature. It is known (see your reference 8) that the bromoacetate reacts with base to generate an epoxide, which is never mentioned in the proposal although basic conditions are used in several steps. Presumably, the bromoacetate will be sensitive to acidic conditions also, which is a poor for 'protecting' the double bond and is incompatible with many of the subsequent reactions. This should be completely redone.
22. Sodium borohydride is usually ineffective for removing tosylate. Sodium cyanoborohydride, lithium aluminum hydride or possibly lithium borohydride (or $NaBH_4$ + metal salts) are better choices to accomplish this transformation. This is a poor choice and should be reconsidered unless a specific reference can be found for this exact transformation.
23. Although the diol is meant to be oxidatively cleaved, its stereochemistry is important. Whether the diol moiety is 'up' or 'down' will have an influence on its ability to bind the oxidizing agent used to effect cleavage, due to increased or decreased steric hindrance. Some comment should be made concerning the stereochemistry of the diol and the facility of the oxidative cleavage.
24. Why was benzylammonium trifluoroacetate chosen to induce the Aldol cyclization reaction? This appears to be an unusual reagent and deserves comment. The bromoacetate moiety remains a problems since it might react with the enolate anion generated during the Aldol condensation.
25. What is the reagent 'chromate and pyridine'? Is this a Collin's oxidation or does it use PCC or PDC? Specify.
26. Ozonolysis with ozone is redundant.
27. How does treatment with lead tetraacetate give the alcohol aldehyde in structure ***23***? Was a step omitted or is this a special transformation obtained from the literature? It is not obvious.
28. Does the reference to 'this compound' refer to structure ***23***?
29. This is a carbonate, not an anhydride. Is transesterification a problem for the methyl ester and the acetate group? In other words, what is the mechanism of this transformation?
30. What is a 3.2.1 bicyclic mechanism? How is this transformation accomplished - what reagents, what is the mechanism? This is not obvious and demands discussion and/or specific examples from the literature.
31. There are two tertiary allylic sites. There is no reason to suspect regioselectivity for one of them. Therefore, one expects a mixture of isomeric bromides which will probably be difficult to separate. Is the acetal moiety stable to these reaction conditions?
32. How facile is an E2 elimination of a β-bromoether to the vinyl ether? Does the same reactivity apply to a β-bromoacetal?
33. Specify what model studies are proposed, why they are necessary, what one expects to learn from them and how this will be applied to the 'real' system. The structures, preparation and proposed reactions for all model structures must be included.
34. Why will these studies be 'quite interesting'?
35. There are several format errors in the references. In reference 1, do not use et al. The appropriate contraction for *Journal of the American Chemical Society* is *J. Am. Chem. Soc.*, not J.A.C.S, as in reference 2. Reference 3 should refer to the primary reference as well as the abstract and should show all authors. All authors should be shown for all references. Reference 7 uses ibid incorrectly. That reference should simply be cited as Reference 6 in the body of the text.

14.3. TOTAL SYNTHESIS OF SECURAMINE C

14.3.A. The Proposal

This synthesis is reasonable, but there are some problems with the presentation. In several places there is the potential for side reactions that have not been addressed. In one or two places, the proposed reaction maybe difficult. In general, however, the proposal has a good literature basis.

Introduction

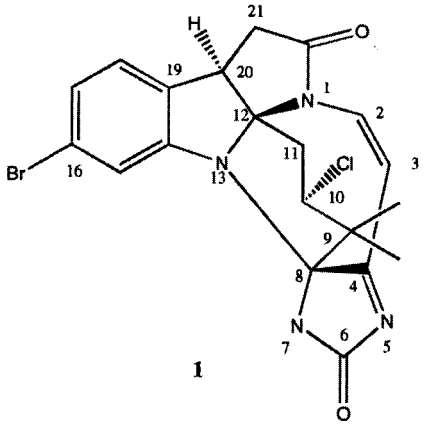


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Figure 1
Structure of Securamine C

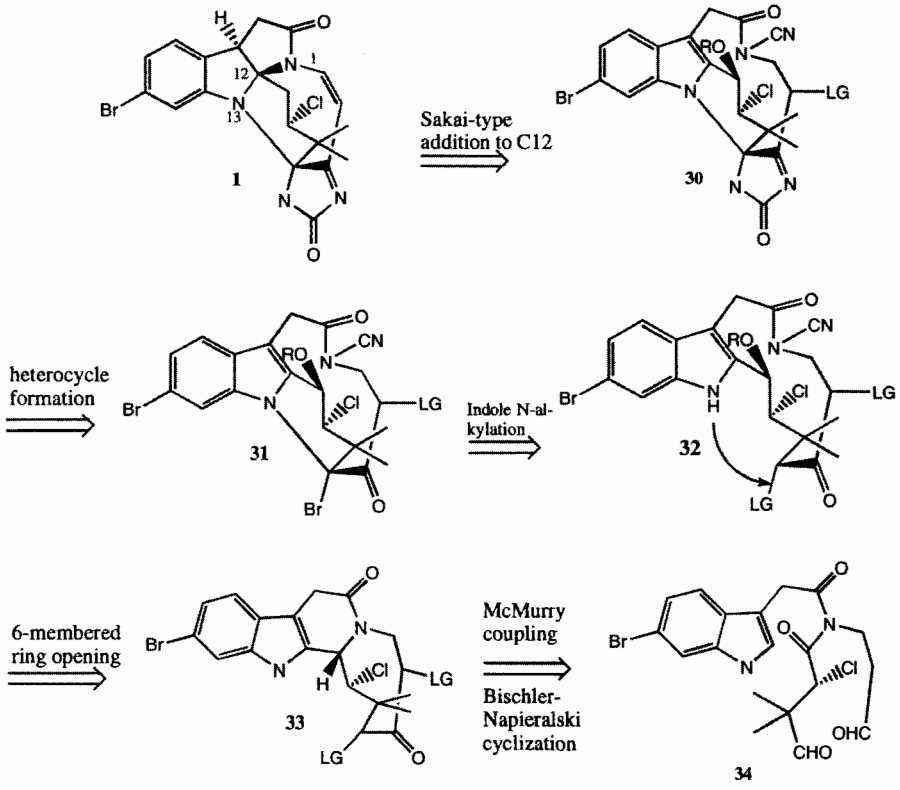
Retrosynthetic Analysis

Securamine C from the marine bryozoan *Securiflustra Securifrons* farnily has recently been isolated and characterized by researchers at the University of Copenhagen[1]. This interesting hexacyclic structure is an indole-imidazole alkaloid from a family of alkaloids that has yielded important biological activity[2]. This proposal outllines a total synthesis of **1**.

Our approach to the synthesis of **1** is shown in **Scheme 1**. The crucial N_1-C_{12} bond making reaction is based on a serendipitous discovery of a Japanese group working on the related Picraline alkaloid system[3]. Using an intermediate closely related to **32**, they were hoping to form a bond between C_8(bearing the leaving group) and C_{20}(the 3-position of the indole); instead the bond was formed between the indole nitrogen and C_8. The formation of this new six-membered ring resulted in an isopleiocarpamine-type skeleton similar to **31**. From there, under acetic acid/ammonium acetate conditions, C_{20} was protonated then N_1 attacked the resulting iminium function at C_{12}(the 2-position of the indole) to give the unusual skeletal structure analogous to **1**.

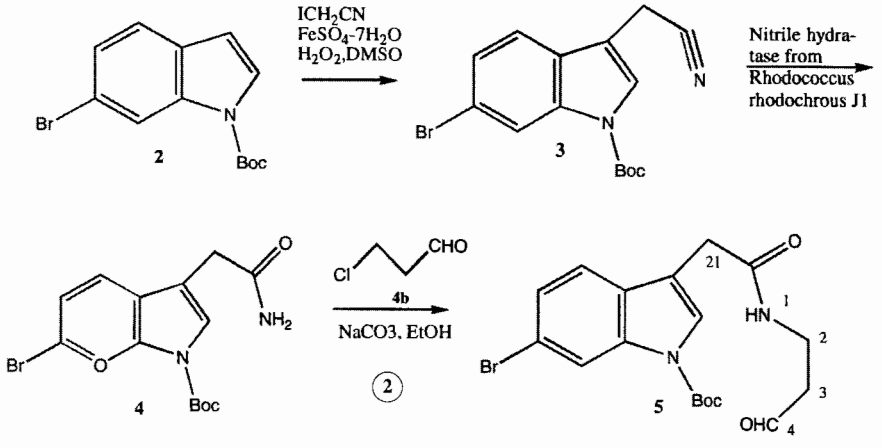
① **32** in turn can be made by opening of the yohimbane-type ring structure pictured in **33** with the use of cyanogen bromide.[3] The C-D rings of yohimbane-type alkaloids are usually constructed by way of a Bischler-Napieralski reaction of an amide intermediate such as **34**.[4] Not shown but critically important in the transformation from **34** to **33** is the construction of the 8-membered ring. It is envisioned that this difficult task can be accomplished using a radical McMurry coupling[5]. **34** can be made by subsequent alkylation and acylation of N_1 on a tryptamine-type of precursor.

The synthesis begins with the known 6-bromoindole **2**,[6] which has recently been made in high yield from the 6-aminoindole using a Sandmeyer reaction (Scheme 2). After protection of the indole nitrogen as the Boc derivative,[7] the electron rich three position of the indole moity can be alkylated with an alkyl halide using iron sulfate with hydrogen peroxide in DMSO to give **3**.[8] The nitrile can then be hydrolyzed enzymatically to the



Scheme 1

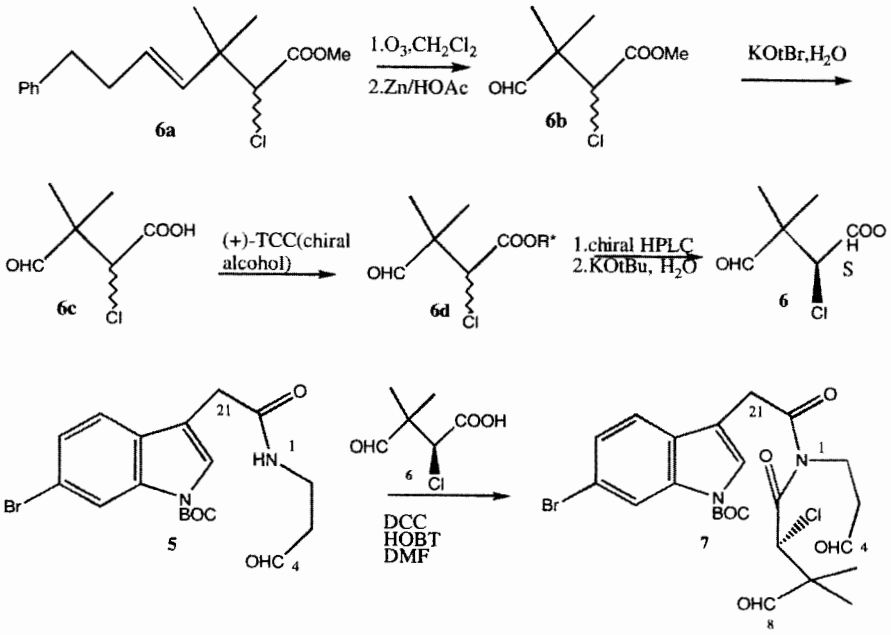
Retrosynthetic Analysis



Scheme 2

Construction of the C_{21}-C_4 Side Chain

Synthetic Proposal



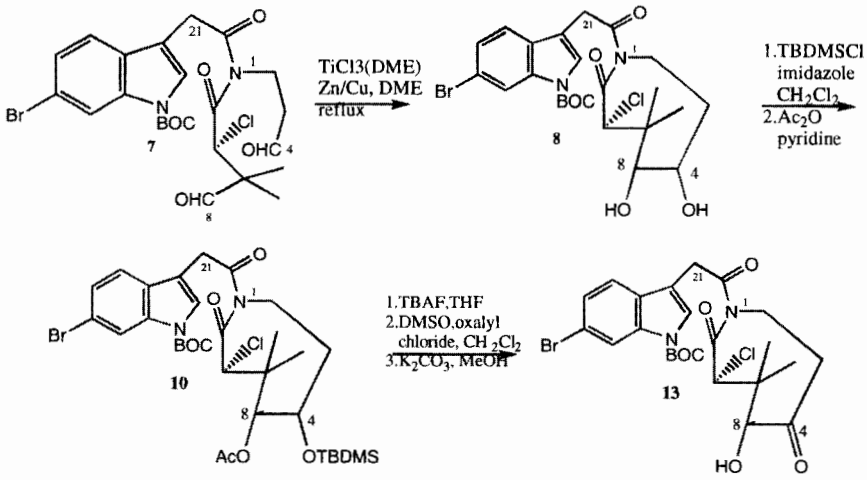
Scheme 3

Synthesis and attachment of the C_8 - C_{11} Side Chain

acetamide using the nitrile hydratase taken from the *Rhodococcus rhodochrous J1* organism.[9] Intermediate **4b** can then be alkylated with the commercially available propionaldehyde **4b** in EtOH with sodium carbonate as base[10] to give **5**. (2) This alkylation attaches C_2-C_4.

From our retrosynthetic scheme we now need to attach C_8-C_{11} to N_1 in order to set up the construction of the medium sized ring *via* McMurry coupling. This C_8-C_{11} fragment (intermediate **6**, **Scheme 3**) can be attached using a dicyclohexylcarbodiirnide (DCC) coupling of the carboxylic acid of **6** to N_1 in the presence of hydroxybenzotriazole in DMF as the solvent.[10,11] The synthesis of fragment **6** begins with known **6a**.[12] This interesting compound can undergo ozonolysis (3) with a reductive workup to give aldehyde **6b,**[13,14] which can be hydrolyzed with potassium t-butoxide and water to give the carboxylic acid **6c**.[15] Resolution of racemic **6c** will follow the protocol of Daniel Comins; the procedure calls for esterification with a chiral alcohol (5) to produce a pair of diastereomers which can be separated with a chiral HPLC column.[16] The particular chiral alcohol to be used here is *(+)-trans-2-(alpha-cumyl)*cyclohexanol((+)-TCC). (4) The desired diastereomer will then be hydrolyzed to the carboxylic acid **6** using the *t*-butoxide/water conditions mentioned above. This hydrolysis would also regenerate the expensive chiral alcohol.

Dialdehyde was prepared with a view towards making the 8-membered ring which includes N_1 to C_4 and C_8 to C_{11}. These medium sized rings are notoriously difficult to make because of the transannular strain generated. The one called for here would be particularly difficult since the dimethyl group at C_9 would add an even greater dimension of steric hindrance. The method of choice to accomplish this task would be the use of a radical coupling, which has been successfully employed in the formation of a key 8-membered ring in the



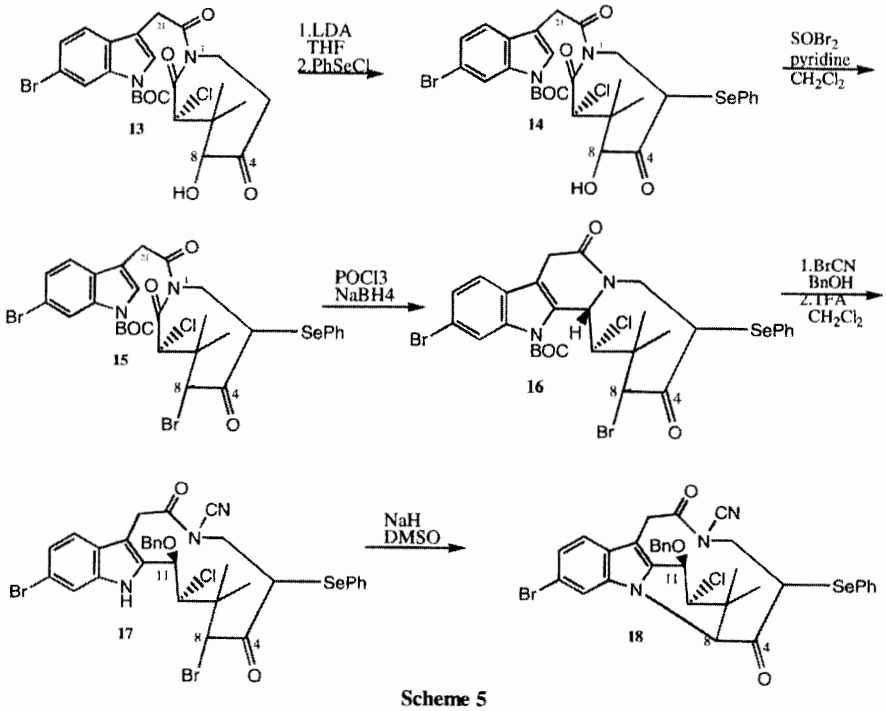
Scheme 4

Synthesis of hydroxy-keto 8-membered ring

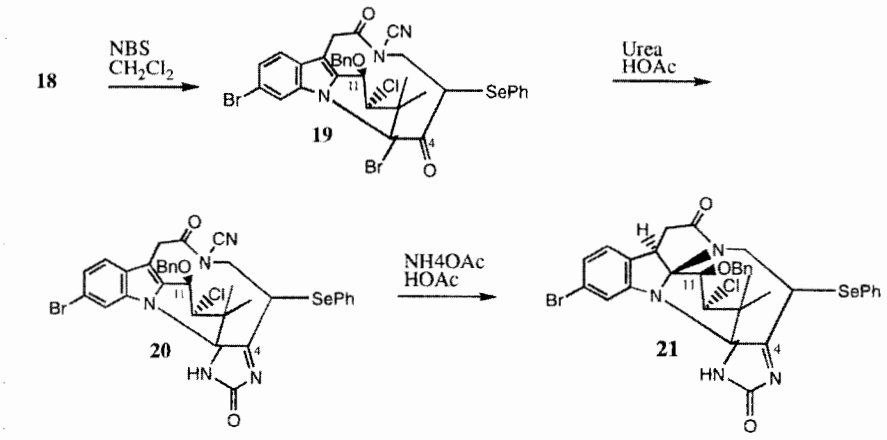
important taxol structure.[17] Radical cyclizations are less susceptible to the steric effects which cause other methods to fail.[5] For the present synthesis, **7** can be cyclized using a titanium induced reductive coupling of the two carbonyl units in the presence of a zinc-copper couple (6) using dimethoxyethane as solvent. The zinc-copper mixture is generated by adding zinc dust to a solution of copper sulfate in deoxygenated water.[5]

Once the C_4,C_8 diol is in hand, (7) the two hydroxy bearing carbons need to be differentially oxidized. The same C_9 methyl groups that would make the ring closure difficult could become an asset in differentiating C_8 from C_4. In particular, it may well be possible to oxidize the C_4 hydroxy group to the ketone and give **13** directly from **8**, without the need for the protection/deprotection method shown in **Scheme 4**. The Swern oxidation,[18] for example, uses the bulky base TEA; this could lead to selective oxidation of C_4, since C_8 should be sterically less accessible. Failing that, the method shown in **Scheme 4** could be employed. C_4 would be protected with a silyl group.[19] Then the C_8 hydroxyl could be acetylated with acetic anhydride and pyridine.[20] Deprotection at C_4 with fluoride, followed by oxidation[18] to the ketone with Swern conditions(oxalyl chloride and DMSO in methyene chloride followed by the addition of TEA), and finally deprotection of the acetate with potassium carbonate in methanol would give intermediate **13**.

The final target securamine contains a dou le bond between C_2 and C_3. We would like to introduce that double bond after th important Sakai-type addition of N_1 to C_{12} since an sp^2 center at C_1 may adversely affedt that ring closure. The strategy employed here is to introduce a functional group at C_3 which can be easily transformed into the C_2-C_3 double bond at a later stage. For this reason, **13** (9) will be converted to the selenide *via* addition of phenyl selenium chloride to the enolate generated at C_3 with LDA,[21] to give 14. (10) The selenide will be oxidized later and will eliminate thermally at mild temperature to give the olefin.



Scheme 5



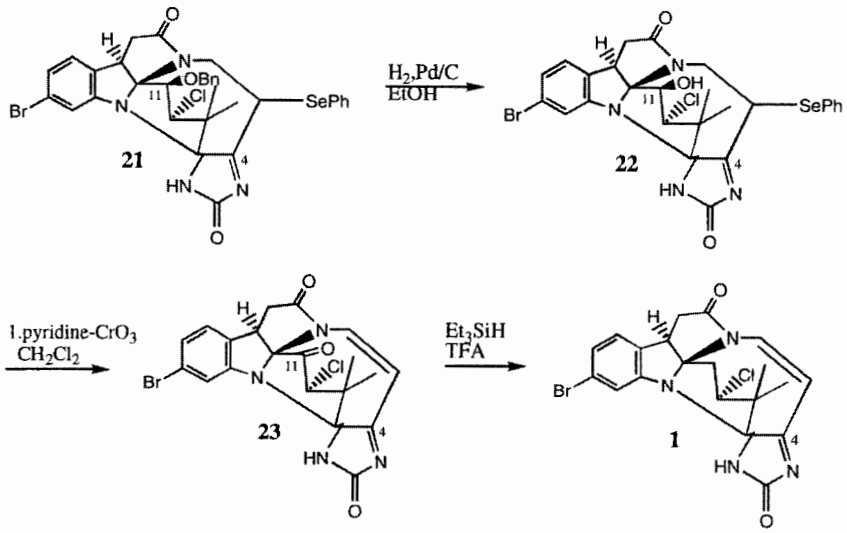
Scheme 6

Sakai Cyclization and Imidazolinone Formation

The hydroxy group at C_8 needs to be converted to a leaving group for eventual bond formation with the indole nitrogen. This can be done by conversion to the bromide **15** (11) with thionyl bromide and pyridine in methylene chloride at ambient temperature[22]. The leaving group could just as easily have been tosylate by converting the hydroxyl group with tosyl chloride and base in methylene chloride.

The closure of the new 6-membered lactam ring to give **16** from **15** is based on extensive literature precedent from synthetic work in the yohimbane-type indole alkaloids.[23] The mechanism of this Bischler-Napieralski reaction involves conversion of the amide function to an imidoyl chloride, (12) (13) which makes C_{11} electrophilic enough to add to the two position of the indole.[24]

In preparation for the important N_{13}(indole N)-C_8 bond forming reaction(**17** to **18**), the newly formed 6-membered ring of **16** must now be reopened with cyanogen bromide to give, after deprotection of the Boc group, intermediate **17**. (14) The stereochemistry at C_{11} is critical because if the OR(in this case OBn) group is *alpha*(behind the plane of the page) then you will not get Sakai-type addition of N_1 to C_{12} but rather N_1 will simply add back into C_{11} to form the 6-membered ring again. With the OBn group at C_{11} *beta,* as would be expected from the literature precedent, intermediate **17** is now poised for the immediate N_3-C_8 bond formation and subsequent Sakai ring closure.[3] In the original paper the cyanogen bromide reaction was done in MeOH which gave an OMe group at C_{11}. In the current target, C_{11} needs to ultimately become a methylene group. Towards that end, the cyanogen brotnide reaction would be done in benzyl alcohol to give the benzyl ether at C_{11} , which can be removed(hydrogenolysis) and reduced(triethyl silane reduction of the ketone) more easily than the methyl ether.



Scheme 7

Reduction at C11 to Complete Securamine C

(15) When **17** is subjected to sodium hydride in DSMO to generate the indole anion, the isopleiocarpamine-type skeleton **18** should be formed by the formation of the new sixmembered ring.[3] In our case there is the danger that N_{13} could displace the C10 chlorine to give a new four-membered ring; modeling studies would need to be done to evaluate that possibility.

The target molecule contains an imidazolinone off of the C_4, C_8 positions. This heterocycle can be formed by adding a molecule of urea to an alpha-bromoketone. (16) (17) (18) Accordingly, intermediate **18** would be brominated with a radical process using Nbromosuccinimide in methylene chloride,[25] then urea (19) would be added under acetic acid conditions to give the new heterocycle.[26] Ammonium acetate in acetic acid would then complete the hexacyclic intermediate **21**.[3] (23)

What is left to complete the synthesis of Securamine C is essentiallythe (24) reduction of C_{11} to a methylene.

Removal of the benzyl ether can be done by hydrogenolysis using palladium on carbon in ethanol.[27] Literature precedent shows that the oxidation of the resulting alcohol to the ketone using the Collins reagent(pyridine-chromium trioxide in methylene chloride)(24) (20) would also oxidize the C_3 selenide to the selenoxide which would immediately eliminate under the reaction conditions.[28] Reduction of the C_{11} ketone with triethyl silane would complete the synthesis of **1**.(21)

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14.3.B. The Critique

The reaction types used in this proposal are as follows.

1. Bischler–Napieralski reaction (sec. 12.5.B).
2. McMurry coupling (sec. 13.8.F).
3. Sandmeyer reaction (sec. 2.11).
4. DCC coupling (not discussed in this book).
5. Ozonolysis (sec. 3.7.B).
6. Radical cyclization (sec. 13.7).
7. Birch reduction (sec. 4.9.E).
8. Swern oxidation (sec. 3.2.C.i).
9. Sakai coupling (not discussed in this book).
10. Selenoxide elimination (sec. 2.9.C.vi).
11. Alcohol to bromide with thionyl bromide (sec. 2.8.A).
12. N-Boc protection (sec. 7.3.C.iii).
13. NBS allylic bromination (sec. 2.8.B).
14. Alcohol protection - benzyl ether (sec. 7.3.A.i).
15. Silane reduction of ketones (sec. 4.10.C).

The number of each critique appears in the body of the proposal.

The critique of this proposal is

1. Do not begin a sentence with a number
2. For the conversion of **4** to **5**, the CHO group may not be compatible with this reaction? Does it have to be protected?
3. In the conversion of **6a** to **6b**, there may be a problem because zinc and acetic acid can reduce halides . There is a question as to whether or not the Cl will be reduced.
4. How will TCC be used? It would be appropriate to give some reaction conditions.
5. In the conversion of **5** to **7** there maybe a problem putting the second C=O on the amide. This can be difficult. The chloro-acid is rather hindered and there is a question whether this will have an effect on the reaction with DCC.
6. In the conversion to **8** the Cl adjacent to the carbonyl may be reduced?
7. What is the stereochemistry of the diol?
8. Since one secondary alcohol is adjacent to a gem-dimethyl unit, it might be possible to selectively oxidize the less hindered OH to the acyloin (compound **13**) without all those steps?
9. In the conversion of **13** to **14**, the OH group probably requires protection.
10. Once the enolate is formed, is displacement of the chlorine across the ring possible?
11. In the conversion of **14** to **15**, does thionyl bromide react with seleno ethers?
12. In the conversion of **15** to **16**, this is actually 2 steps over the arrow, not one as shown
13. Will the chlorine survive this step?
14. In the conversion of **16** to **17** - is seems unlikely that the SePh unit, the Cl unit, the Br unit will survive without some secondary reactions, particularly when TFA is being used.
15. In the conversion of **17** to **18** - **17** NaH may form the enolate at the O=C—C—SePh carbon. Although it may be less favored, it formation of a three-membered ring possible (see Favorskii rearrangement)? Can the enolate anion displace the Cl across the ring?
16. In the conversion of **18** to **19** bromine radicals are generated. Will the presence of the chlorine pose a problem?
17. Under these conditions, SePh can be lost to form a radical. Will this cause any problems?
18. It is also possible to brominate at the C bearing the SePh unit. To form the targeted bond requires displacement of bromide from a neopentyl carbon, which is very difficult
19. In the conversion of **19** to **20**, the new bond generating the heterocycle occurs at a qua ternary carbon. Can this occur as planned?
20. The Collins oxidation is applied to a hindered substrate. Will this cause problems?
21. In the conversion of **23** to **1** - will Cl survive treatment with silane and TFA?
22. In the references, do not use et al - cite all authors for each paper.
23. For the transformation of **18** to **1**, there is minimal discussion. This section should be expanded.

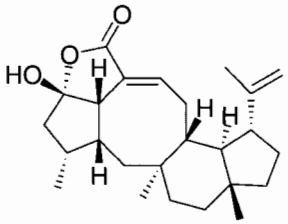
24. Note the typographical error.

14.4. TOTAL SYNTHESIS OF VARIECOLOL

This proposal is reasonable considering it is a difficult target. The main problems have to do with stereochemistry of proposed products and, in some cases, choice of reagents. There is at least one reaction, the last one, that is questionable, but in general it is a reasonable approach.

14.4.A. The Proposal

I. Introduction



1

Variecolol (**1**), a new sesterterpene was recently isolated from the mycellium of *Emericella purpurea.*[1] Presently, a study of variecolol's ability as an agent for preventing and treating hypertension, cardiovascular and cerebrovascular diseases and renal disease is taking place.[2] However, variecolol can only be obtained by extraction from the mycellium of *Emericella purpurea.* This is due to the fact of variecoloactone's highly functionalized complex fused ring structure making its total synthesis rather difficult. Herein is described a synthetic strategy to obtain the basic ring structure of variecolactone which can be applied to other natural products with a similar ring structure.[1]

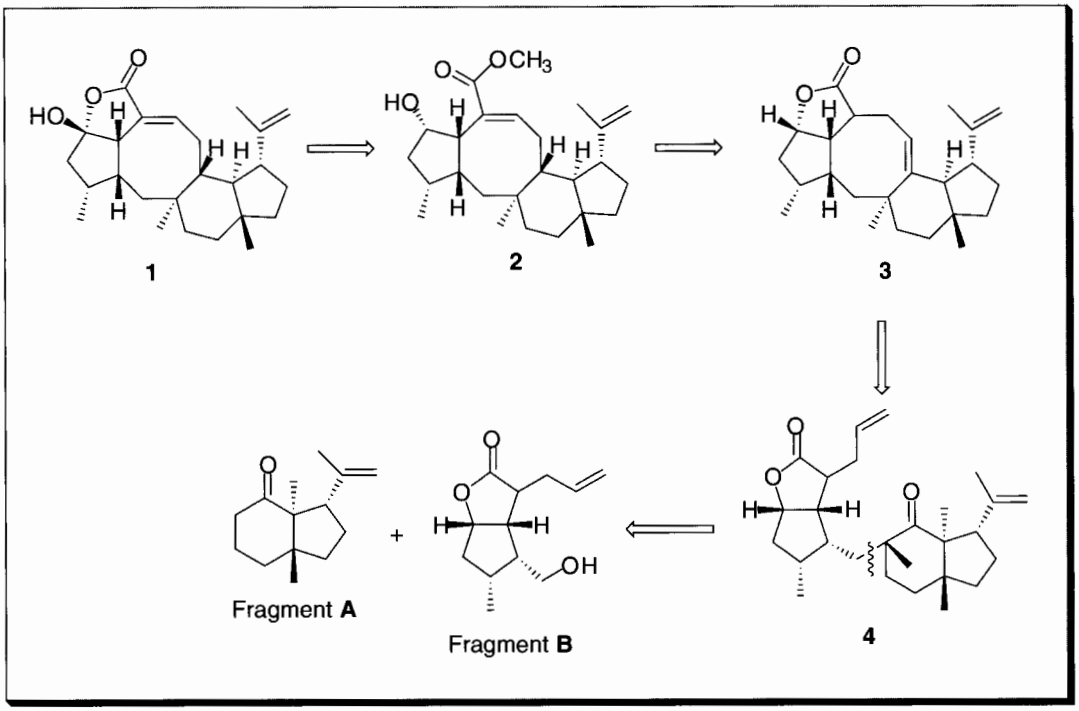
II. Retrosynthetic Analysis

The key features of the synthesis of variecolol are outlined retrosynthetically in Scheme 1. Working one step back from (**1**) gives the _-hydroxy-carboxylic acid (**2**). Manipulation of the double bond contained within the eight membered ring gives (**3**) followed by a ring closing metathesis reaction utilizing Grubb's catalyst leads to (**4**). Cleavage of the indicated bond leads to Fragments **A** and **B** which can be synthesized using slightly modified literature procedures.

III. Synthesis of Variecolol

A. **Synthesis of Fragment A**

The complete synthesis of the known[3] Fragment A will follow literature procedures and is outlined in Scheme 2. Bromoacetal (**5**) can be prepared following the procedure by Buchi and West.[4] Condensation of acrolein with ethylene glycol in the presence of anhydrous hydrogen bromide affords the bromoacetal (**5**) in good yield. The bromoacetal (**5**) is then converted to the corresponding grignard[5] (**6**) by treatment with magnesium in tetrahydrofuran at room temperature. Treatment of (**6**) with a mixture of the α,β-unsaturated

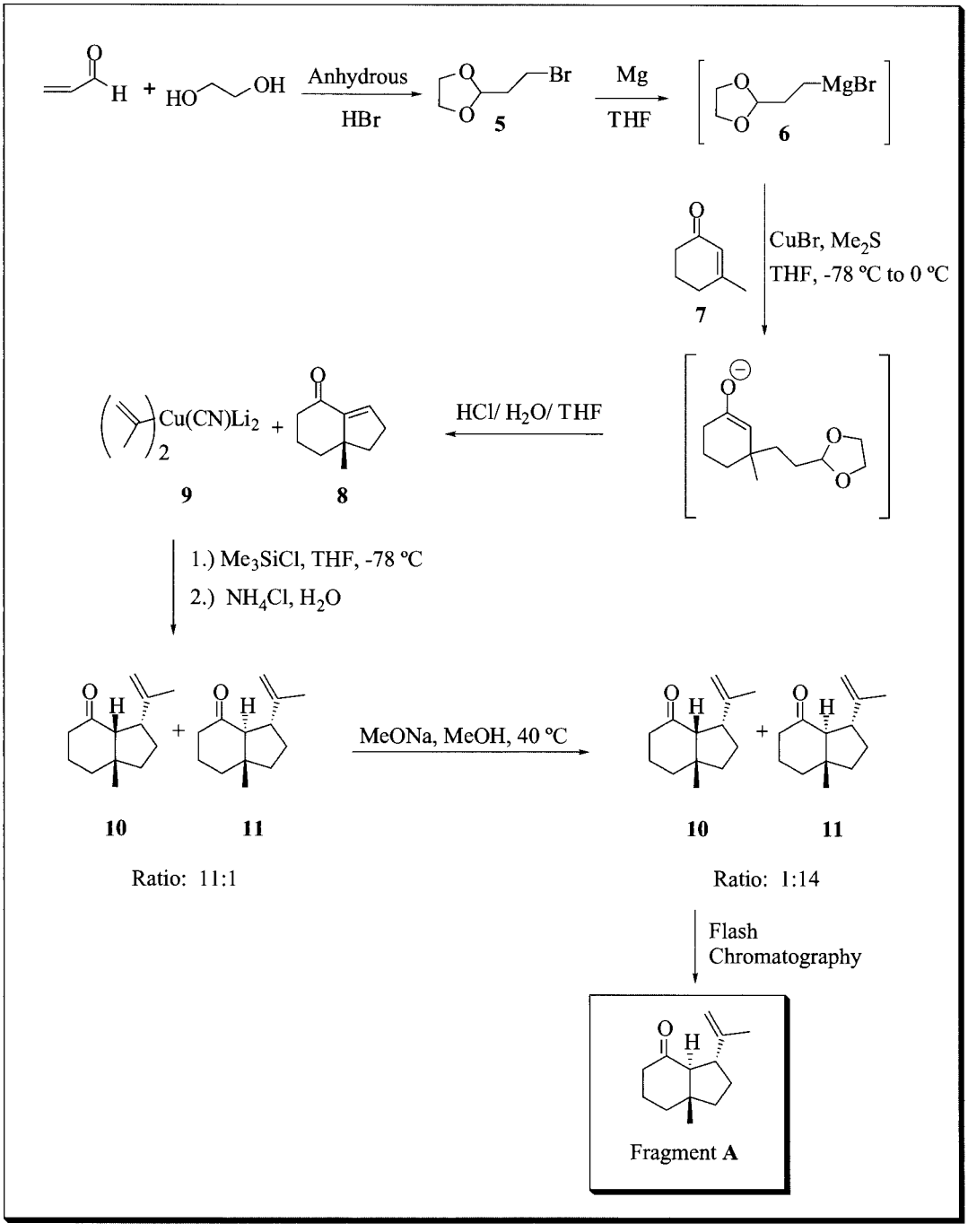


Scheme 1: Retrosynthetic Analysis of Variecolol (**1**).

ketone (**7**), cuprous bromide and dimethyl sulfide in tetrahydrofuran yields the 1,4-addition product (**8**) after aqueous acidic workup in moderate yield. Treatment of (**8**) with the previously prepared[6] lithium dialkyl cyano cuperate (**9**) adds stereoselectively in a Michael fashion to provide a mixture of (**10**) and (**11**) in a ratio of approximately 11:1 and in excellent yield, however, the major isomer is not the desired one. This problem can be circumvented using the methodology described by Piers[7] and Oballa and the conformational studies of 4-hydrindanones done by Dana[8] and co workers. The results of the work done by Dana and co workers suggest that (**11**) would be the thermodynamically more stable isomer and the rationale is logical: isomer (**11**) has the trans ring juncture and less gauche interactions when compared to (**10**) which has the cis juncture. Thus, isomer (**11**) can be obtained preferentially by treating the 11:1 mixture with sodium methoxide in methanol at 40 °C causing epimerization at the α-carbon and hence approximately yielding a 1:14 mixture of (**10**) and (**11**). Separation of the two epimers by flash chromatography gives pure (**11**) in modest yield. In summary, a literature precedent for the synthesis of Fragment **A** will be used and is quite convenient, setting the absolute configurations in three of the nine stereogenic centers in Variecolactone

B. Synthesis of Fragment B

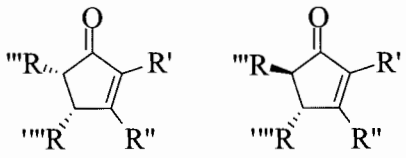
The synthesis of fragment **B** will be done according to Scheme 3. The known hexacarbonyldicobalt complexed alkyne (**12**) will be prepared according to the work done by Krafft and co workers.[9] First, 3-butyn-1-ol (**13**) will be converted to its *tert*-butyldimethylsilyl (TBS) ether by treating a mixture of (**13**) with TBS-Cl in triethylamine and DMAP. Treatment of the protected alkynol with *sec*-butyl lithium in THF followed by low temperature quench with ethyl chloroformate yields the alkynoate (**14**). The alkynoate is then complexed with dicobaltoctacarbonyl in petroleum ether to yield (**12**) in excellent yield.



Scheme 2: Synthesis of Fragment **A**

Production of the tetrasubstituted cyclopentenone (**15a, 15b**)) involves condensing the protected vinyl ether (**16**) with (**12**) via a Pauson-Khand reaction.[10,11] ① Studies on the Pauson-Khand reaction[10,11] have shown that upon condensing an unsymmetrical alkene with an unsymmetrical alkyne in the presence of a cobalt carbonyl compound give rise to mixtures of diastereomers (Fig 1) with the bulkier substituents of the alkene and alkyne being α to the carbonyl of the cyclopentenone. However, the stereochemistry α to the

carbonyl is unimportant as it will be lost in later steps. ④ The stereochemistry at the β position is important, and in both products gives the correct absolute configuration, thus, no separation is necessary.



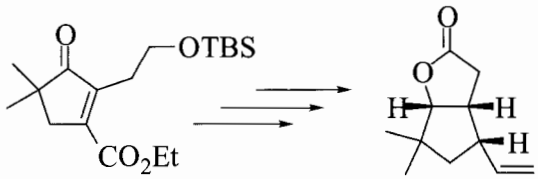
Major Minor

R' > R"
R''' > R'''' in steric bulk

Fig 1

The next step involves selectively deprotecting the trimethylsilyl ether to produce (**17**) by a method described by Bunce and Hertzler.[12] Their method involves treating TMS ethers with sulfonic acid type exchange resins which will remove the TMS group and not the TBS group.[13]

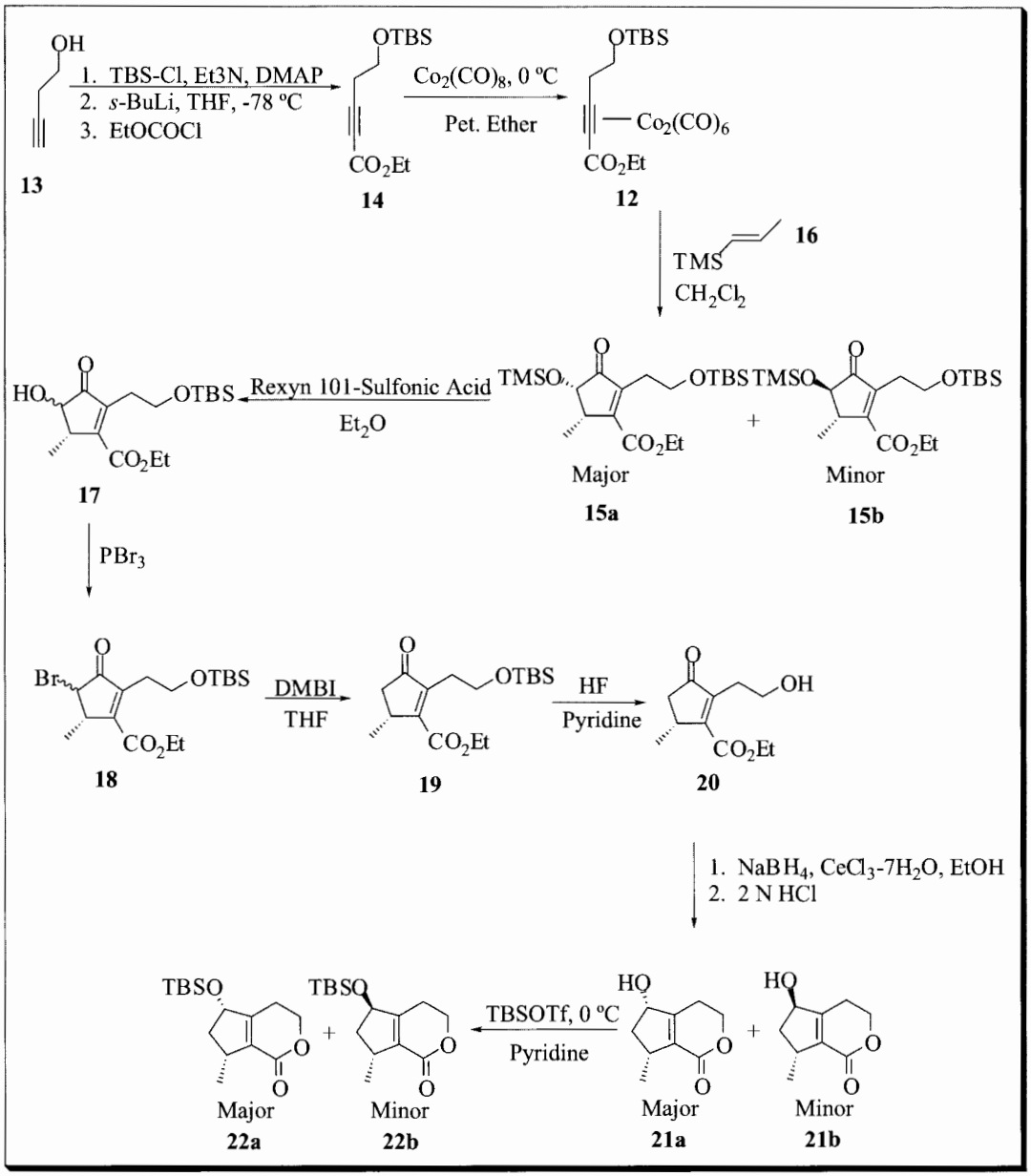
The two preceding steps serve to eliminate the hydroxyl group of (**16**) by first converting the alcohol to a bromine and then replacing the bromine with a hydrogen. The bromo analog will be made using a method described by Sacks and Aston[14] for converting α-hydroxyketones to α-bromoketones. Thus, treatment of (**17**) with phosphorus tribromide yields the α-bromoketone (**18**). Subsequent removal of the bromine and replacement with hydrogen to produce (**19**) will follow work done by Chikashita and Itoh.[15] Their work involves using 1,3-dimethyl-2-phenylbenzimidazoline (DMBI) ② as the reducing agent and is believed to go through a radical reaction mechanism. Through their studies, DMBI was shown not to react with other functioanlities contained within the α-bromoketones such as esters, α,-systems, and ethers making this methodology attractive for this synthesis.



25 **26**

Removal of the TBS protecting group to produce (**20**), cyclization (**21a, 21b**), protection (**22a, 22b**), hydrogenation (**23a, 23b**), and rearrangement (**24a, 24b**) will follow the procedure done by Krafft and coworkers.[9] The structure (**25**) they did this series of transformations on to produce (**26**) is very similar to (**20**) and we believe it to work without incident. ㉒

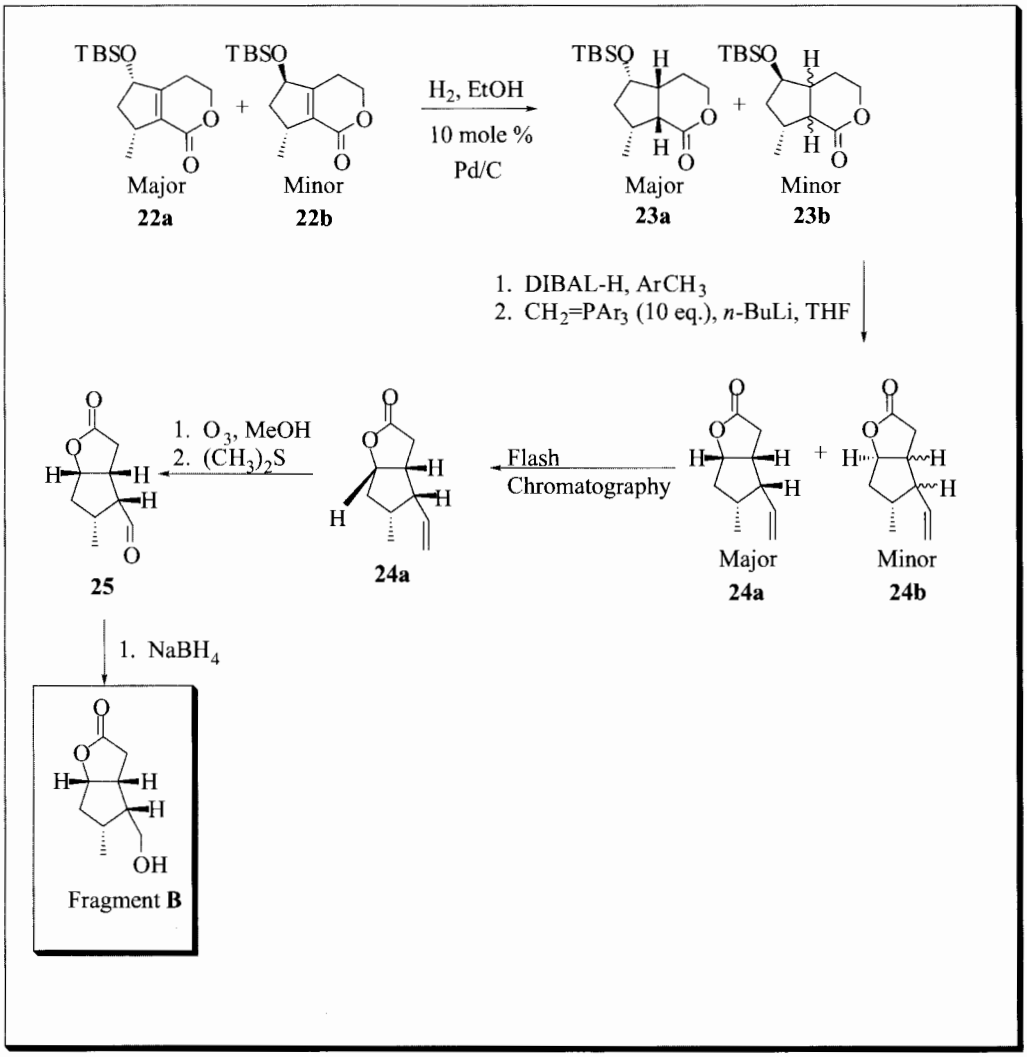
Thus treating a pyridine/acetonitrile solution of (**19**) with hydrofluorous acid will lead ⑥ to (**20**) in excellent yield. Subsequent cyclization to (**21a, 21b**) ⑦ by treating (**20**) first with an ethanolic solution of sodium borohydride and cerium (III) heptahydrate, and second a two normal solution of hydrochloric acid.



Scheme 3: Synthesis of Fragment **B**

This reaction is predicted to be highly diasteroselective. Because of the methyl's orientation, hydride transfer will occur preferentially on the opposite face of the methyl. Protecting the alcohol again with the TBS group using TBS-triflate in pyridine produces (**22a, 22b**). Hydrogenation of this mixture is also predicted to be highly diastereoselective. With the bulky TBS group present, hydrogen should add across the double bond on the opposite face thus producing a mixture of (**23a, 23b**).[5][8] The three step rearrangement process to form (**24a, 24b**) is as follows. Upon reducing the lactone moiety in the mixture from the previous step with diisobutyl aluminum hydride in toluene, gives a lactol which is then treated with ten equivalents of methyltriphenylphosphonium bromide and *n*-butyl lithium in THF to give the corresponding alkene. The

large excess of ylide is required to avoid epimerization of the stereocenter adjacent to the aldehyde prior to the Wittig olefination. Oxidation of the primary alcohol using Jone's Reagent[9] to the carboxylic acid, followed by refluxing in two normal hydrochloric acid will yield, by and Sn2 reaction, (**24a, 24b**). ⑨ Separation of the mixture of diastereomers by flash chromatography is predicted to yield pure (**24a**) in moderate yield. Ozonolysis of (**24a**) to produce (**25**) will follow the pioneering work done by Pappas and co workers.[16] A mixture of (**24a**) in methanol is treated with ozonized oxygen followed by reductive workup with dimethyl sulfide to produce (**25**). The attractive methodology developed by Pappas and co workers has shown that carbonyl moieties present in olefinic compounds do not interfere with the oxidation by ozone. Reduction of the aldehyde moiety of (**25**) with sodium borohydride[17] to produce the corresponding alcohol is a well known reaction in which the lactone group is known to be left unmolested by the reducing agent, will complete the synthesis of Fragment **B**.

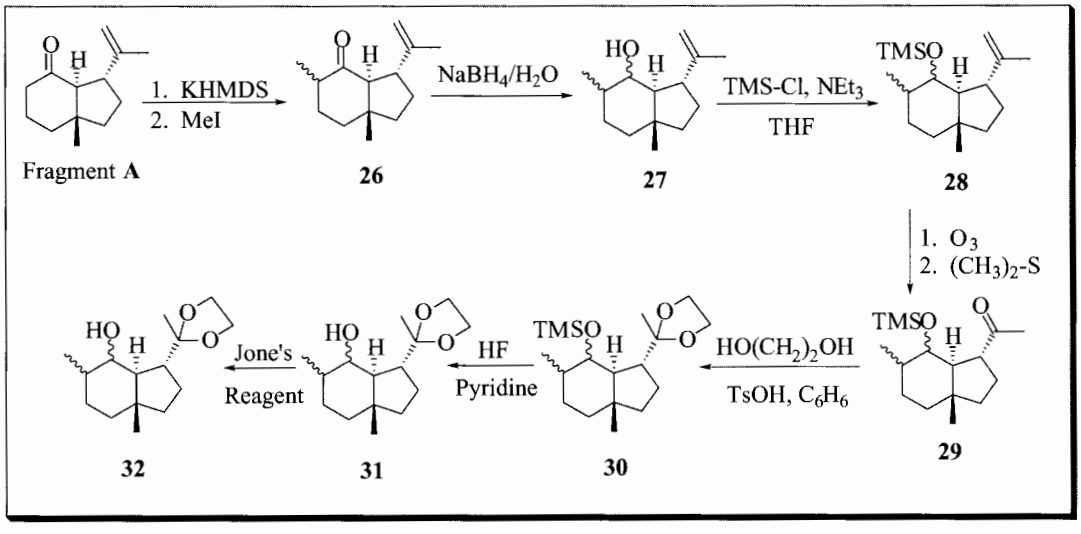


Scheme 3: Synthesis of Fragment **B** (continued)

C. Modification of Fragment A Before Condensation with Modified

Fragment B

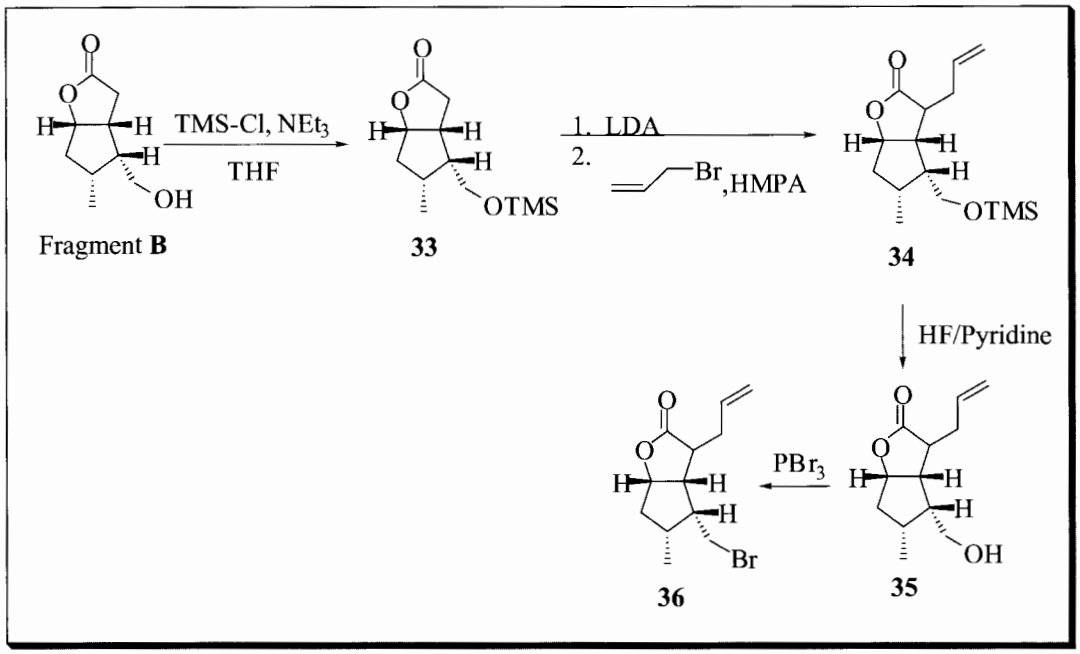
The modifications of Fragment **A** which are required before it's condensation with Fragment **B** are outlined in Scheme 4. Conversion of Fragment **A** to (**26**) will follow a procedure described by Bailey and Khanolkhar.[18] Their work ⑩ describes a procedure using potassium hexamethyldisilizane as a non-nucleophilic base to produce an enolate and subsequently substituting a methyl group α to the carbonyl of a phenyl ketone. Although the hydrogens at each α position of Fragment **A** are available for abstraction, it is predicted that the kinetic hydrogen will be removed due to the steric bulk of the base employed. Thus, treatment of Fragment **A** with KHMDS followed by methyl iodide will yield (**26**). Reduction of (**26**) with sodium borohydride[17] in THF leads to the corresponding alcohol mixture (**27**). ⑪. Protection of this alcohol mixture with TMS-Cl[19] to (**28**) prepares the fragment for subsequent ozonolysis[16] to produce the ketone (**29**). Protection of this ketone with ethylene glycol[20] to make (**30**) followed by deprotection[9,17] (**31**) ⑫ and reoxidation[9,17] ⑬ (**32**) prepares Fragment **A** to be condensed with the modified Fragment **B**. The above list of modifications indirectly protects the double bond of the isopropenyl group of Fragment **A** in order to conduct a ring closing metathesis utilizing Grubb's catalyst in later steps.



Scheme 4

D. Modification of Fragment B before Condensation with Modified Fragment A

The modifications of Fragment **B** which are required before it's condensation with Fragment **A** are outlined in Scheme 5. Fragment **B** will be converted to its TMS protected form (**33**) by the method cited above.[19] Allylation of (**33**) to (**34**) ⑭ will follow a procedure described by Walton and Reid[21] in their work of allylating γ-butyrolactone. Thus, treating (**33**) with LDA in hexane followed by HMPA and allyl bromide will produce (**34**). Deprotection[9] of (**34**) to recover the alcohol moiety (**35**) followed by displacement with phosphorus tribromide[17] to produce (**36**) prepares Fragment **B** to be condensed with the modified Fragment **A**.

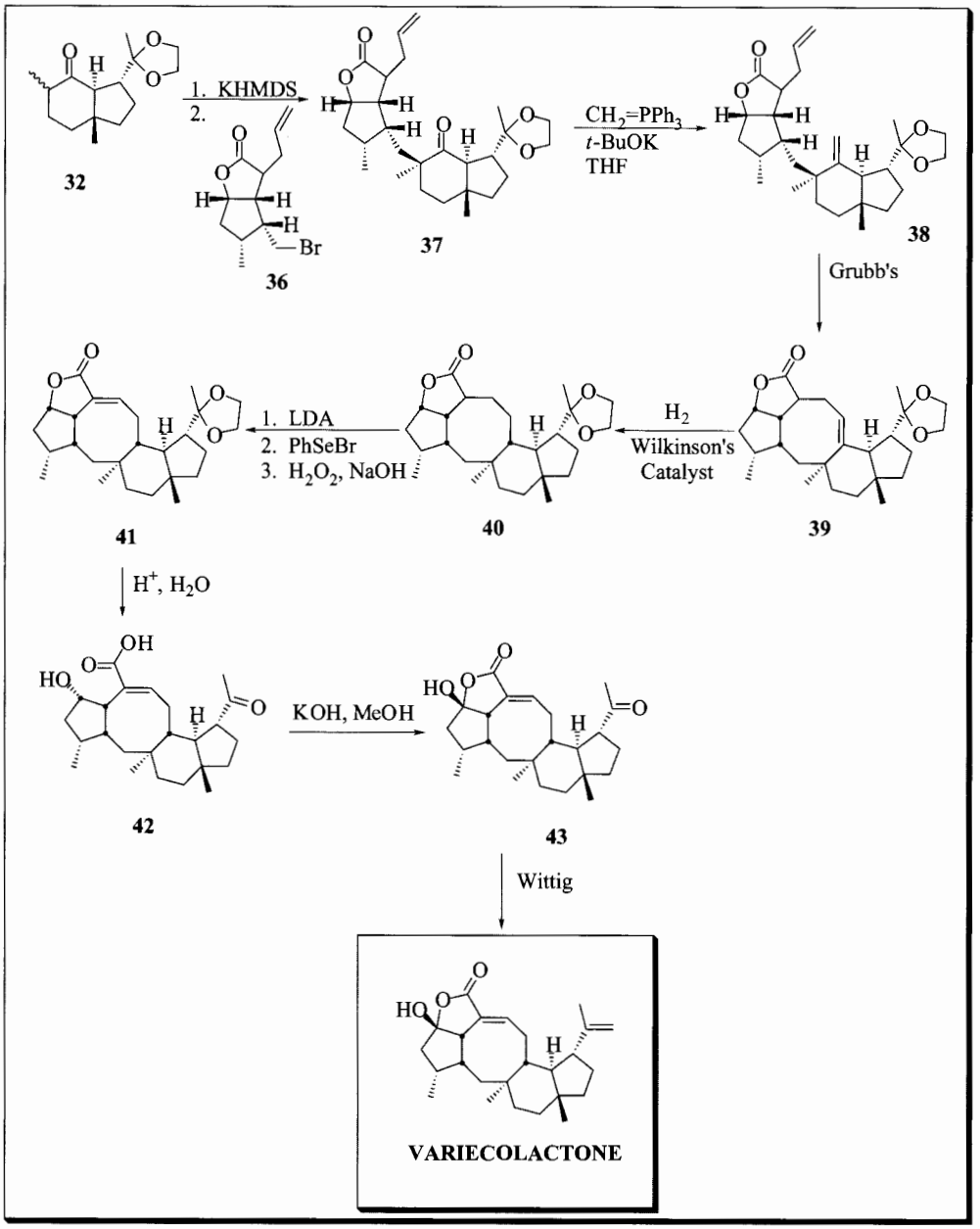


Scheme **5**

E. **Completion of the Synthesis of Variecolactone**

The completion of the synthesis of variecolactone is outlined in Scheme 6. First, treatment of (**32**) with KHMDS[18] is predicted to remove the _-hydrogen adjacent to the methyl group due to the fact of the nature of the bulky base employed and the steric hinderance of the 1,3-dioxalane group adjacent to the other α-hydrogen. Once the enolate has formed it is predicted that the incoming electrophile will preferentially come in on the same face as the angular methyl ⑮ thus producing (**37**). If this prediction turns out to be wrong, the problem can be alleviated by first condensing Fragment **A** with (**36**) followed by methylation. Subsequent Wittig olefination[22] ⑰ of (**37**) to produce (**38**) under basic conditions will not molest the ketal or ester moiety. Cyclization of (**38**) using Grubb's catalyst will follow a procedure done by Prasad and Hoppe.[23] In their work, several 8-membered rings were synthesized containing ester and cyclic ether linkages using Grubb's catalyst. It is believed that their methodology can be applied in converting (**38**) to (**39**). The stereochemical outcome ⑯ concerning the hydrogen α to the ester is unimportant as it will be transformed to a double bond in a later step. Hydrogenation of (**39**) to (**40**) using Wilkison's catalyst[24] is predcited to occur on the same face as the angular methyl due to the bulky 1,3-dioxalane group present α to the prochiral center. Hydrogenation with Wilkinson's catalyst has also been show not to interfere with ester functionalities.

Incorporation of the double bond to produce (**41**) will follow work done by Bella and Pirgo[25] as well as Fallis and co workers.[26] Their work involves incorporating a double bond into saturated γ-lactones containing a ketal group using phenyl selenium bromide followed by hydrogen peroxide and sodium hydroxide to execute a syn elimination to produce the double bond in conjugation with ester carbonyl. It is predicted that when (**41**) is enolized with LDA, the phenyl selenium bromide will preferentially approach from the bottom face due to the three angular hydrogens present α and β to the enolized carbon. Once treated with peroxide a



Scheme 6

and sodium hydroxide, the only hydrogen which can be abstracted is from the bottom face thus producing (**41**). Treatment of (**41**) with aqueous acid[17] will serve two purposes, to hydrolyze the ester [18] and ketal moiety to produce(**42**). The next step will follow work done by Dutler and co workers in their work involving steroids. One key step of their synthesis was converting a α-hydroxy carboxylic acid to a α-hydroxy lactone by using a dilute solution of potassium hydroxide in methanol. It was also noted that the stereochemistry of the hydroxyl group was observed to invert upon completion of this transformation as well as the ketone moiety being left unmolested. It is predicted that this methodology will work on our system to produce (**43**) [19] with one possible problem and that is the stereochemistry of the hydroxyl group. If it turns out to be the wrong

stereochemistry , Mitsunobu[28] conditions can be utilized to invert the hydroxyl group before the cyclization. Another Wittig olefination[22] reaction on (**43**) shall complete the synthesis of Variecolactone.

Summary

In conclusion, a methodology has been presented to synthesize Variecolactone. More generally, a synthesis has been proposed to attain the complex fused ring structure of variecolactone which could be applied to other products with this similar structure.

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14.5.B. The Critique

The reactions used in this proposal are as follows:

1. Grignard reactions (sec. 8.4).
2. Magnesium cuprate conjugate additions (sec. 8.4.D).
3. Higher order cuprates, conjugate additions (sec. 8.7.B).
4. Pauson-Khand reaction (sec. 13.11).
5. Alcohol protection - trimethylsilyl ether (ec. 7.3.A.i).
6. DMBI reduction (not covered in this book).
7. Luche reduction (sec. 4.4.B).
8. Dibal reduction of lactones (sec. 4.6.C).
9. Wittig olefination (sec. 8.8.A).
10. Ozonolysis (sec. 3.7.B).
11. Sodium borohydride reduction of aldehydes (sec. 4.4.A).
12. Enolate alkylation of ketones (sec. 9.3).
13. Ketone protection - dioxolane (sec. 7.3.B.i).
14. Jones oxidation (sec. 3.2.A.iii).
15. Enolate alkylation of lactones (sec. 9.3).
16. Conversion of alcohol to bromide with PBr_3 (sec. 2.8.A).
17. Olefin metathesis (sec. 13.9.E).
18. Selenoxide elimination (sec. 2.9.C.vi).

The Critique

The number for each critique appears in the body of the proposal.

1. There is a discussion about the stereochemistry of the Pauson–Khand, saying it give the correct stereochemistry. Is this speculation, or based on the two references in a similar or identical system? This needs to be specific.
2. Is DMBI compatible with conjugated ketones also?
3. Note typographical error.
4. For the cyclization step–it is not clear why the reaction is diastereoselective n this system, or what the selectivity will be. Use models to explain.
5. Why is this hydrogenation diastereoselective? Is it subject to equilibration or isomerization?
6. In the conversion of **19** to **20**, will the use of HF cause problems with the ester?
7. In the cyclization, use models and discussion to show that **21a** is the major product.
8. Prove the stereochemistry of **23a** and discuss the selectivity.
9. Is there a step missing in the conversion of **23** to **24?**
10. While it is OK to cite a recent reference, this transformation was reported much earlier and the original reference should be cited –see House's book, for example.
11. Although the stereochemistry of **27** is not important for the final product, it is important for isolation and handling and there should be a comment.
12. Is the dioxolane unit stable to treatment with HF?
13. The conditions used with Jone's reagent include strong acid, which might cause problems if the contact time is long. There are many other oxidizing agents where this is not potentially a problem. Is one of them better?
14. What is the stereochemistry of the allylic unit in **34**?
15. The statement concerning stereochemistry of **37** requires proof - use models?
16. Prove the stereochemistry of **39** to **40** using models?
17. Compound **37** contains a sterically hindered carbonyl. The Wittig reaction can be slow in such systems and/or give poor yields. Is this a problem here?
18. This compound is a lactone, not an ester. When the lactone is treated with aqueous acid, it can open. However, the equilibrium of most five-membered ring lactones lies towards the lactone. Why should this behave differently, and can the equilibrium be manipulated to obtain the target?
19. It is not at all obvious that the transformation of **42** to **43** will work. It may have precedent, but there should be more discussion of this reaction, particularly regarding the stereochemistry of the system and the relative distance of the two reactive centers.
20. Why are the letters included with the references?
21. Reference 9. Krafft is misspelled.
22. This scheme indicates the sequence will follow the work of Krafft and that it is similar. More detail should be provided as to the similarities and particularly differences between the proposed work and the literature work. Specifically, the differences must be highlighted since they are a potential source of problems.

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