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Cooperative Catalysis

Designing Efficient Catalysts for Synthesis



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Edited by René Peters

Cooperative Catalysis

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WILEY-VCH
Verlag GmbH & Co. KGaA

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Cover

The title picture was designed based on an idea commonly developed by Prof. René Peters and his (former) Ph.D. students Melanie Mechler, Carmen Schrapel, Dr. Manuel Weber and Marcel Weiss.

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Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at [<http://dnb.d-nb.de>](http://dnb.d-nb.de).

© 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Boschstr. 12, 69469 Weinheim, Germany

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Print ISBN: 978-3-527-33689-0

ePDF ISBN: 978-3-527-68105-1

ePub ISBN: 978-3-527-68104-4

Mobi ISBN: 978-3-527-68103-7

oBook ISBN: 978-3-527-68102-0

Typesetting Laserwords Private Limited, Chennai, India

Printing and Binding Markono Print Media Pte Ltd, Singapore

Printed on acid-free paper

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Preface

The field of asymmetric catalysis has witnessed an amazing progress during the last decades. Even so, technical scale applications are still largely limited to few catalytic asymmetric reaction types [1]. From a technical point of view the large majority of traditional catalytic asymmetric methodologies is not proficient enough in terms of various fundamental aspects such as catalytic activity, substrate scope, selectivity, and cost efficiency.

In order to develop asymmetric catalysts of considerably improved activity, selectivity, and general applicability, the research field of cooperative catalysis is currently intensively studied by a large number of research groups worldwide, following the seminal marks of pioneers in that field like E. J. Corey, Eric Jacobsen, Ryoji Noyori, Masakatsu Shibasaki, or Hisashi Yamamoto to mention just a few. Their research strategy has mimicked the catalytical principles used by Nature to design artificial tailor-made catalysts: like Nature's catalysts – enzymes – these artificial catalyst systems make use of the synergistic and often sophisticated interplay of two or more functional groups. By simultaneous activation of the reactants using different catalyst functional groups cooperative catalysts can decrease the energy of the transition states of the rate-limiting steps to a much greater degree compared to either functional group working independently. Cooperative catalysts can thus notably accelerate and precisely control a chemical reaction, at the same time reducing the amount of side products and accordingly the production of waste. Dual/multiple activation catalysts consequently very often accomplish higher efficiencies than conventional monofunctional catalysts in terms of reactivity, substrate scope, regio-, diastereo- or enantioselectivity and potentially also cost-efficiency. Cooperative catalysis is arguably the most promising strategy to realize high reactivity and selectivity in chemical transformations. It thus appears likely that the different strategies of cooperative catalysis will streamline organic synthesis in general and will in the future also enable a growing number of technical scale applications for catalytic asymmetric C–C, C–N and C–O bond formations. Cooperative catalysis is hence expected to significantly strengthen asymmetric catalysis as a key technology for our society.

Like mentioned, cooperative catalysis makes use of two or even more functional groups present in a catalytic system, which simultaneously work in concert to accelerate and control a chemical reaction. In the definition utilized in

most chapters of this book these activating functional groups might be part of the same bi- or multifunctional catalyst entity or of two or more separate (co)catalyst molecules. This implicates that terms like bi(multi)functional catalysis, dual (multiple) activation catalysis, contemporaneous dual catalysis, synergistic catalysis or catalyzed catalysis are all covered by the general title of this book – ‘*Cooperative Catalysis*’. Examples for cascade catalysis will thus usually (with some exceptions where suitable) not be presented, because in cascade catalysis the different activating catalyst functionalities do not collectively team up in a way that they decrease the energy of the same transition state by their simultaneous action. An exception has, e.g., been made for Chapter 11, in which the intriguing cooperation of enzymes and metal(–complexes) is described, albeit both catalysts do not activate the substrates simultaneously.

The present book is considered to provide an overview of the most intensively studied concepts of cooperative catalysis, their historical development, their mode of operation and important applications. Advantages of these concepts, and sometimes also pitfalls that need to be overcome in the future, are described and illustrated. A central but not limiting aspect of this book is asymmetric catalysis. The book is subdivided in 13 chapters – each one written by scientific experts in the corresponding field – and classified by the types of the activating principles. It needs to be mentioned though that the transition between different concepts is often floating. For example, the areas of bimetallic catalysis and Lewis acid/Brønsted base catalysis are to a certain degree related concepts and it sometimes depends on your standpoint which classification might be preferred. To avoid a large overlap, this book thus contains a chapter about bimetallic catalysis with carbophilic Lewis acids, but there is no additional chapter for azo- or oxophilic bimetallic catalysts, as the arguably most important systems are already discussed in the chapter about Lewis acid/Brønsted base catalysis. In addition, as theoretically almost every traditional catalytic activation principle may be combined with another one in a cooperative sense, a huge variability appears to be possible. For that reason the title of some chapters specifies only one of the activating principles.

Summing up the most important – often complementary – concepts of cooperative catalysis in one book is expected to support the further development of this important field by both sharpening and extending our perception. It is not very risky to predict that the future of catalysis will be cooperative! Emil Fischer described a related vision already more than 100 years ago, when he stated: *If we wish to catch up with Nature, we shall use the same methods as she does, and I can foresee a time in which physiological chemistry will not only make greater use of natural enzymes but will actually resort to creating new synthetic ones* [2].

René Peters
Universität Stuttgart, 2014

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Acknowledgments

René Peters sincerely thanks all authors of this book for their valuable contributions. Moreover, he is very grateful to Dr. Anne Brennführer of Wiley-VCH for her suggestion to edit a book about cooperative catalysis and for her excellent support during its preparation. In addition, the editor is indebted to Dr. Waltraud Wüst of Wiley-VCH for her very valued help during the whole editing process. René Peters also gratefully acknowledges the generous financial funding of his research on cooperative catalysis by the Deutsche Forschungsgemeinschaft (DFG, PE 818/3-1, PE 818/4-1, PE 818/6-1). He warmly thanks his former and present coworkers for their high commitment and enthusiasm.

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1

Lewis Acid–Brønsted Base Catalysis*Masakatsu Shibasaki and Naoya Kumagai*

1.1

Introduction

From the synthetic point of view, organic synthesis via catalytic processes offers many benefits. Catalysis frequently obviates the excessive use of the activating reagents and associated tedious purification processes, thereby offering more environmentally benign synthetic processes. Furthermore, the specific activation mode of a catalyst allows for highly chemoselective transformations that are seldom achieved by noncatalytic processes. Over the past two decades, the concept of cooperative catalysts has evolved and subsequently rapidly advanced as the most finely refined class of artificial catalysts for preparative chemistry [1]. The cooperative catalysts exhibit two catalytic functions simultaneously to achieve a dual activation mode to specific substrate(s) (Figure 1.1). The obvious advantage of this activation strategy is not only the significant enhancement of the reaction rate due to intramolecularity or a proximity effect but also the broadened scope of the applicable reactions following the synergistic activation of otherwise unreactive substrate sets.

In this chapter, cooperative catalysts that exhibit Lewis acid and Brønsted base activation modes are reviewed. While recent interest in artificial catalysts focuses on the efficient production of enantioenriched building blocks [2], herein only asymmetric Lewis acid–Brønsted base cooperative catalysts are covered. Metal-based asymmetric cooperative catalysts that display transition-metal catalysis are described in other chapters [3]. In this chapter, the focus is on the reactions promoted by the effective coupling of an *in situ* generated active nucleophile by a Brønsted base and an electrophile activated by a Lewis acid.

1.2

Lewis Acid–Brønsted Base Catalysis in Metalloenzymes

The essence of Lewis acid–Brønsted base catalysis is the manifestation of two different catalytic functions in a synergistic manner. This often occurs via two

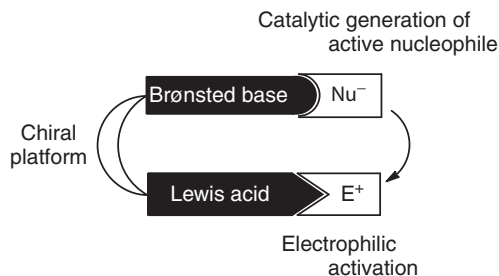


Figure 1.1 Schematic representation of the Lewis acid–Brønsted base cooperative catalysts.

different catalytic sites in near proximity – referred to as *two-center catalysis*. Two-center catalysis involving a Lewis acid and a Brønsted base is largely exploited in metalloenzyme reactions [4, 5]. A typical biological degradation reaction, such as urea hydrolysis promoted by urease, utilizes dinickel two-center cooperative catalysis (Figure 1.2) [4b, 6]. Two Ni(II) cations are located in near proximity at the active site of urease, and one Ni(II) cation is coordinated by urea to electrophilically activate the urea carbonyl. Another Ni(II) cation (Ni hydroxide) functions as a Brønsted base with the aid of the adjacent histidine side chain to produce a nucleophilically active Ni hydroxide. The synergistic activation of both the nucleophile and electrophile provides significantly accelerated hydrolysis. Urea generally does not readily undergo simple basic hydrolysis in organic synthesis, but with the cooperative catalysis of a dinickel active site the reaction rate is enhanced by a factor of 10^{14} . An artificial model of this cooperative hydrolysis has been achieved with a dicopper catalyst comprising a low molecular weight ligand and Cu(II) cations [7].

This type of Lewis acid–Brønsted base cooperative catalysis is operative also in enantioselective carbon–carbon bond-forming processes in biological contexts. Class II aldolase, a Zn-dependent metalloenzyme, illustrates this (Figure 1.3). The aldolase efficiently promotes the enantioselective aldol reaction of dihydroxyacetone phosphate (DHAP) and various aldehydes under virtually neutral conditions [8]. DHAP coordinates to a Zn(II) cation in a bidentate manner to increase the acidity of the α -proton, which is deprotonated by the adjacent glutamic acid-73 residue as a Brønsted base. This cooperation enables the catalytic generation of an active Zn-enolate, which is integrated into the following aldol addition to

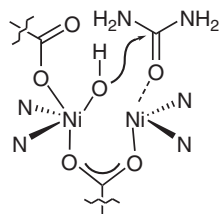


Figure 1.2 Proposed activation mode in urease.

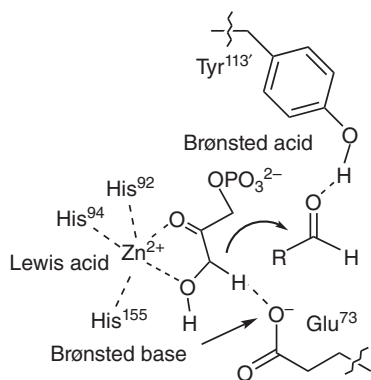


Figure 1.3 Proposed activation mode in Zn-dependent class II aldolase.

an aldehyde that is activated by the tyrosine-113 residue by hydrogen bonding. These naturally occurring macromolecular catalytic machineries have inspired chemists to mimic the cooperative activation strategy in artificial catalyst design.

Obviously, an inevitable drawback in enzymatic catalysis is its strict substrate specificity at the expense of extraordinary rate enhancement. Artificial cooperative catalysts follow a somewhat loose three-dimensional design of two catalytic functions to acquire both rate enhancement through synergistic activation and sufficient substrate generality to showcase the synthetic utility.

1.3

Hard Lewis Acid–Brønsted Base Cooperative Catalysis

1.3.1

Cooperative Catalysts Based on a 1,1'-Binaphthol Ligand Platform

1.3.1.1 Heterobimetallic Catalysts

A series of hard Lewis acid–Brønsted base cooperative heterobimetallic catalysts utilizing 1,1'-binaphthol and its derivatives as a chiral bidentate ligand were developed by Shibasaki *et al.* [9] (Figure 1.4). Depending on the nature of the central metal cation [rare earth metal (RE) or group 13 metal ($M^{(13)}$)], two general types of cooperative catalysts are generated [10]. By combining RE and alkali metals ($M^{(1)}$), heterobimetallic catalysts of the general formula RE- M_3 -tris(1,1'-binaphthoxide) (type 1) are formed. Following the initial identification of La- Li_3 -tris(1,1'-binaphthoxide) (RE = La, $M^{(1)}$ = Li, abbreviated as LLB) in the first report on the catalytic asymmetric nitroaldol reaction [10a–12] (Scheme 1.1), several heterobimetallic catalysts emerged by changing the combination of RE (Y, La, Pr, Sm, Yb) and M (Li, Na, K) to promote a wide range of catalytic asymmetric

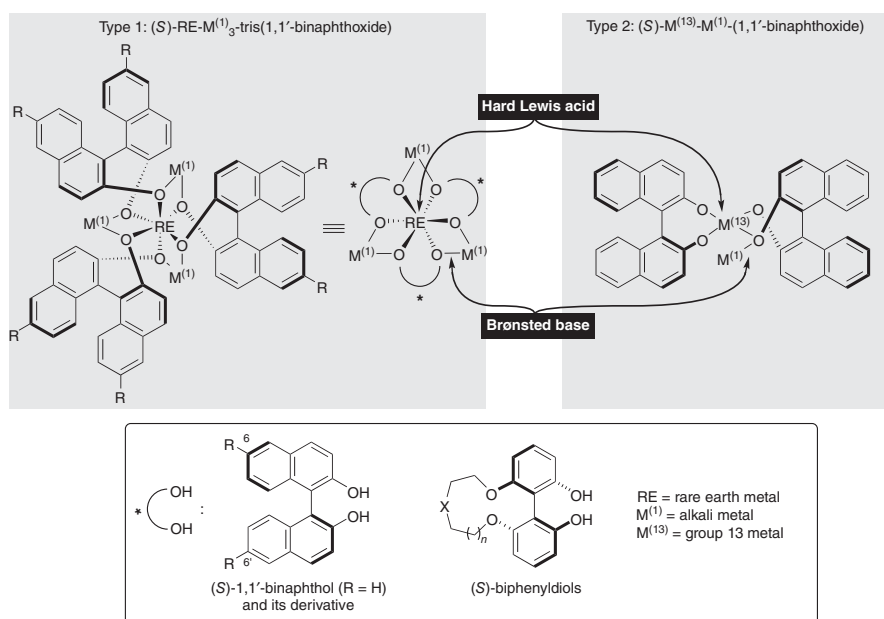
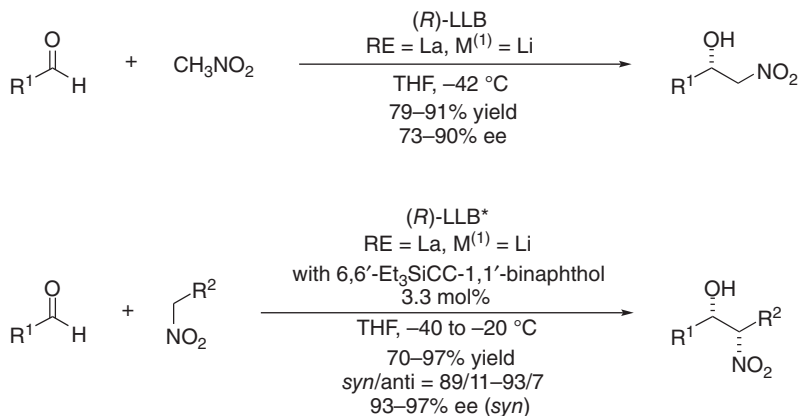


Figure 1.4 Two types of Lewis acid–Brønsted base cooperative heterobimetallic catalysts based on 1,1'-binaphthol and its derivatives as a chiral ligand platform.



Scheme 1.1 Seminal nitroaldol reaction promoted by the heterobimetallic catalyst LLB.

transformations (Figure 1.5) [13–26].¹⁾ Irrespective of the combination, a highly symmetrical architecture of RE- M_3 -tris(1,1'-binaphthoxide) is maintained (based on laser desorption/ionization time-of-flight mass spectrometry data). Some of the heterobimetallic catalysts, such as LSB (RE = La, $M^{(1)}$ = Na), PrSB (RE = Pr, $M^{(1)}$ = Na), NdSB (RE = Nd, $M^{(1)}$ = Na), and EuSB (RE = Eu, $M^{(1)}$ = Na), were unequivocally characterized by X-ray crystallographic analysis [10b, 13, 27].

Although these complexes have a chiral center at the central RE, a 1,1'-binaphthol unit existed only in the Λ configuration, presumably because of the higher thermodynamic stability. Biphenyldiols were also exploited to constitute similar catalyst architecture for some reactions. The essence of this catalytic system is the cooperative function of RE as the Lewis acid to activate electrophiles and $M^{(1)}$ -1,1'-binaphthoxide as the Brønsted base to activate pronucleophiles, allowing for the subsequent facilitated bond formation in the chiral environment. The coordination number of RE generally ranges from 6 to 12 [28]. Hence, the central RE of these complexes is not coordinatively saturated, and it is anticipated that it accepts the additional coordination of electrophiles. Coordination to the RE center of these complexes has been of interest [29], and direct evidence to prove the coordination of Lewis basic electrophiles to RE has been reported by Walsh *et al.* in a series of NMR and crystallographic studies [30]. Differences in RE- $M^{(1)}$ combinations lead to a series of complexes with slightly different metal–oxygen bond lengths, covering a broad range of catalytic asymmetric transformations (Figure 1.5). La is most frequently identified as the best RE, presumably because La has the largest ionic radius and is prone to functioning more as a Lewis acid to activate electrophiles. The exceptionally wide variety of reactions presented in Figure 1.5 is indicative that these heterobimetallic cooperative catalysts are one of the most successful classes of asymmetric catalysts known. A reaction mechanism based on Lewis acid–Lewis acid cooperative catalysis in which $M^{(1)}$

1) Although some of the reactions in Figure 1.5 were reported using *R*-configured catalyst in the original literature, the data are extrapolated for *S*-configured catalyst for clarity.

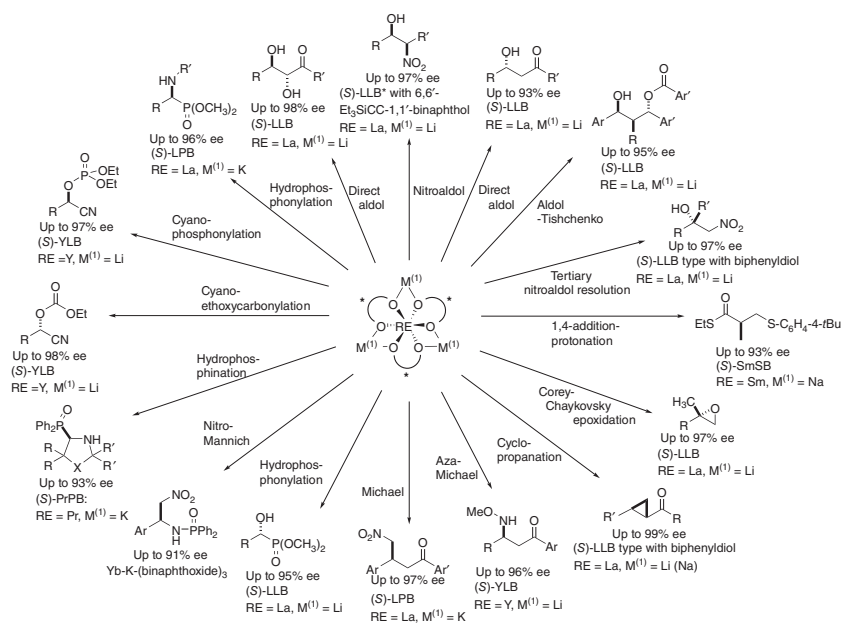
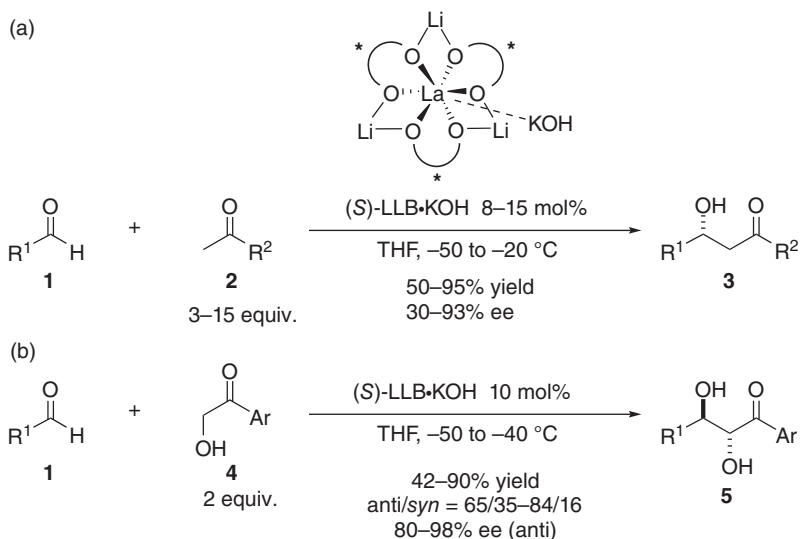


Figure 1.5 Schematic representation of the utility of $\text{RE-M}^{(1)}_3\text{-tris}(1,1'\text{-binaphthoxide})$ cooperative catalysts in catalytic asymmetric transformations.

serves as a Lewis acid has also been proposed for the aza-Michael reaction, Corey–Chaykovsky epoxidation, and cyclopropanation [21, 25].

It is worth highlighting the direct aldol reaction with LLB ($\text{RE} = \text{La}$, $\text{M}^{(1)} = \text{Li}$) because this specific reaction was the first to be demonstrated by this hetero-bimetallic cooperative catalyst and because of the sustained topic in the field of Lewis acid–Brønsted base cooperative catalysis. In 1997, Shibasaki *et al.* reported the first example of the direct aldol reaction, in which nucleophilically active enolate species were generated *in situ* and the thus-formed enolate was integrated into the following aldol addition in an enantioselective manner [20]. At that time, a commonly accepted catalytic asymmetric aldol reaction was the chiral Lewis acid-catalyzed Mukaiyama aldol reaction in which a preformed (preactivated) enol silyl ether was used as an active enolate [31]. The obvious advantage of the direct aldol strategy is the elimination of the redundant preactivation step in a separate operation, thereby offering a more operationally simple protocol without the undesired waste derived from stoichiometric amounts of reagents used for preactivation [32]. Cooperative functions of the Lewis acid and Brønsted base of LLB are crucial to electrophilically activate aldehydes **1** while generating the active enolate from ketones **2** in a catalytic manner, enabling the smooth enantioselective aldol reaction in an asymmetric environment of 1,1-binaphthyl walls [20a]. LLB modified by KOH was later found to exhibit superior catalytic activity to afford the aldol adducts **3** in moderate to high enantioselectivity (Scheme 1.2a) [20b]. In contrast to the requisite excess amount of ketones **2** to drive the reaction efficiently, the α -hydroxyketones **4** emerged as particularly suitable substrates, and high conversions were obtained with 2 equiv of **4** to afford anti products preferentially with



Scheme 1.2 (a, b) Direct catalytic asymmetric aldol reaction of unmodified ketones promoted by (S)-LLB·KOH cooperative catalyst.

high enantioselectivity (Scheme 1.2b) [20c]. These early works stimulated research into the direct aldol reaction. Today, the term “direct aldol” is widely accepted in the chemical community, and a number of achievements have been reported in both metal-based catalysis and organocatalysis [33]. The heterobimetallic catalysts of $\text{RE-M}^{(1)}_3\text{-tris}(1,1'\text{-binaphthoxide})$ architecture continue to be a topic of interest in catalysis and in the construction of metal complexes. Further explorations using Ce(III)/Ce(IV) or an actinide, for example, U(IV) , as a central metal [34, 35], and Cs or Zn as peripheral metals, have been reported [36].

Another type of heterobimetallic catalysts with the general formula $\text{M}^{(13)}\text{-M}^{(1)}\text{-bis}(1,1'\text{-binaphthoxide})$ incorporating group 13 metals (Al, Ga) has been investigated by Shibasaki *et al.* [9] (Figure 1.4, type 2 (right side)). In 1996, $\text{Al-Li-bis}(1,1'\text{-binaphthoxide})$ ($\text{M}^{(13)} = \text{Al}$, $\text{M}^{(1)} = \text{Li}$, abbreviated ALB) was designed on the basis of the concept of Lewis acid and Brønsted base catalysis, assuming that Al(III) and Li-phenoxide synergistically function as the Lewis acid and Brønsted base, respectively [37, 38]. The architecture bearing a tetra-coordinated Al(III) and pendant Li cation was unequivocally determined by X-ray crystallographic analysis. (*R*)-ALB was identified as a particularly effective catalyst for the asymmetric conjugate addition of malonates to cyclic enones, in which a cyclic enone is activated by Al and an active carbanion is generated by Li-phenoxide in close proximity (Figure 1.6). The addition of an achiral alkali metal alkoxide significantly enhanced the catalytic efficiency [11g, 39], allowing for the completion of the reaction with as little as 0.1 mol% of catalyst on a >1 kg scale [11i, 40, 41]. The use of polymeric $1,1'\text{-binaphthol}$ led to the development of immobilized ALB catalyst, which could be used iteratively [42]. The scope of $\text{M}^{(13)}\text{-M}^{(1)}\text{-bis}(1,1'\text{-binaphthoxide})$ catalyst was expanded to the analogous cooperative catalyst (*R*)-GaLB, where $\text{M}^{(13)}$ and $\text{M}^{(1)}$ are Ga and Li, respectively, promoting the ring-opening reaction of *meso*-epoxide by *tert*-butylthiol [43, 44].

1.3.1.2 Cooperative Catalysts Based on Linked-BINOL

Connecting two $1,1'\text{-binaphthol}$ units at the 3 position provides an intriguing tetraol chiral ligand referred to as *linked-BINOL* [45–47] (Figure 1.7).

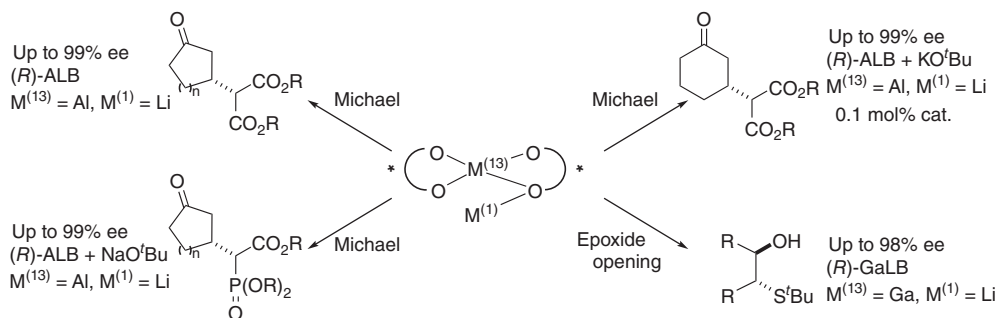


Figure 1.6 Schematic representation of the utility of $\text{M}^{(13)}\text{-M}^{(1)}\text{-(1,1'-binaphthoxide)}$ cooperative catalysts in catalytic asymmetric transformations.

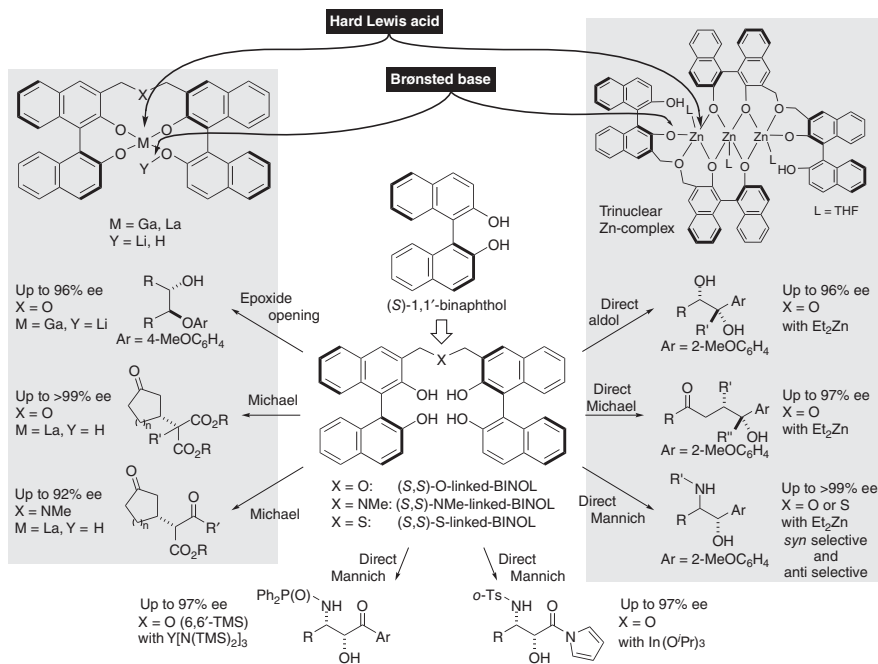
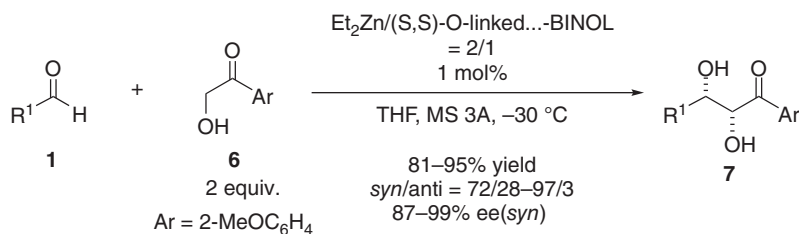


Figure 1.7 Schematic representation of the utility of linked-BINOL-based cooperative catalysts in catalytic asymmetric transformations.

Originally, this ligand was specifically designed to prevent the formation of an undesirable polymeric complex via intermolecular infinite coordination of 1,1'-binaphthols to metal cations. Indeed, complexation of (*S,S*)-O-linked-BINOL with Ga(O^{*i*}Pr)₃ and ^{*n*}BuLi afforded a monomeric Ga-Li-linked-BINOL complex, which showed higher stability than the corresponding complex GaLB prepared from the 1,1'-binaphthol complex [45a]. X-ray crystallographic analysis of Ga-Li-linked-BINOL revealed that the architecture was analogous to that of M⁽¹³⁾-M⁽¹⁾-bis(1,1'-binaphthoxide). Similar cooperative catalytic function is anticipated, as demonstrated by high catalytic performance in the asymmetric ring opening of *meso*-epoxides with *p*-methoxyphenols. The combination of O-linked-BINOL and La(O^{*i*}Pr)₃ afforded monometallic La-O-linked-BINOL, which is an air-stable and storable catalyst, effective for the asymmetric conjugate addition of malonates [48, 49]. The dual function of La(III) as a Lewis acid and La-phenoxide as a Brønsted base has been proposed [50]. The related La-NMe-linked-BINOL exhibited superior catalytic efficiency in the asymmetric conjugate addition of β-keto esters [51]. Interestingly, treatment of O-linked-BINOL with Et₂Zn afforded a trinuclear Zn complex as precatalyst. The latter emerged as particularly effective for the catalytic generation of Zn-enolate from 2'-methoxy α-hydroxyacetophenone **6**. The catalytic asymmetric aldol reaction of **6** with (*S,S*)-O-linked-BINOL/Et₂Zn catalyst afforded the *syn* adduct **7** preferentially (Scheme 1.3) [20c, 52], which is complementary to the anti-selective reaction promoted by (*S*)-LLB-KOH (Scheme 1.2b). Cold-spray ionization mass spectroscopy analysis indicated the formation of Zn-rich species containing **6**. Zn-phenoxide functions as a Brønsted base to generate Zn-enolate, while an aldehyde is electrophilically activated by a neighboring Lewis acidic Zn(II). A similar activation mode is operative in catalytic asymmetric direct conjugate addition [53] and Mannich-type reactions of **6** [54]. The combination with Y[N(TMS)₂]₃ or In(O^{*i*}Pr)₃ expanded the scope of the direct Mannich-type reaction [55, 56]. The cooperative use of nucleophilic tertiary amines in a La-O-linked-BINOL system was also explored [57].



Scheme 1.3 Direct catalytic asymmetric aldol reaction of unmodified α-hydroxy ketone **6** promoted by Et₂Zn/(*S,S*)-O-linked-BINOL cooperative catalysis.

1.3.2

Cooperative Catalysts Based on a Salen and Schiff Base Ligand Platform

Metal–salen and related metal–Schiff base complexes are commonly accepted as one of the most successful classes of organometallic entities. In this regard, these complexes have been utilized in several fields of chemistry other than asymmetric catalysis. The focus of this section is on the use of these complexes in the context of Lewis acid–Brønsted base cooperative asymmetric catalysts [58, 59]. Other applications of these complexes are beyond the scope of this section [60].

Meticulous mechanistic studies conducted by Jacobsen *et al.* revealed a second-order dependence of the reaction rate on the concentration of the catalyst in a series of mononuclear metal–salen complexes [61]. Specifically, the cooperative activation of a nucleophile (Cr–azide) and an electrophile (epoxide) is postulated in the catalytic asymmetric ring-opening reaction of epoxides with azide promoted by two molecules of monomeric $\text{Cr}(\text{N}_3)$ –salen complexes (Figure 1.8, compare with Chapter 13 in this book on cooperative catalysis in polymerization reactions). These kinetic data are in accordance with the bimolecular cooperative catalysis in an intermolecular manner [62], and the strategic linking of two metal–salen units has been systematically explored to render the cooperative catalysis intramolecularly. Systematic investigation of the position and the length of linker revealed that a dimeric $\text{Cr}(\text{N}_3)$ –salen complex **8** tethered by a pimelate diester linkage ($n=5$) at the aromatic group produced the highest catalytic efficiency, accelerating the reaction by two orders of magnitude compared with a monomeric $\text{Cr}(\text{N}_3)$ –salen catalyst (Figure 1.9) [63]. The beneficial effect of the covalently linked dimeric $\text{Al}(\text{Cl})$ –salen complexes is also observed in the catalytic asymmetric conjugate addition of *in situ* generated HCN to α,β -unsaturated imides [64], in which the second-order rate dependence on the catalyst was observed in a monomeric $\text{Al}(\text{Cl})$ –salen complex [61f, 65, 66].

Among the catalytic asymmetric reactions promoted by metal–salen complexes, the Co–salen-catalyzed hydrolytic kinetic resolution of racemic epoxides is of prime importance from a synthetic standpoint (Scheme 1.4) [61c,d,e]. From the mechanistic point of view, one $\text{Co}(\text{OAc})$ –salen complex functions as a Lewis

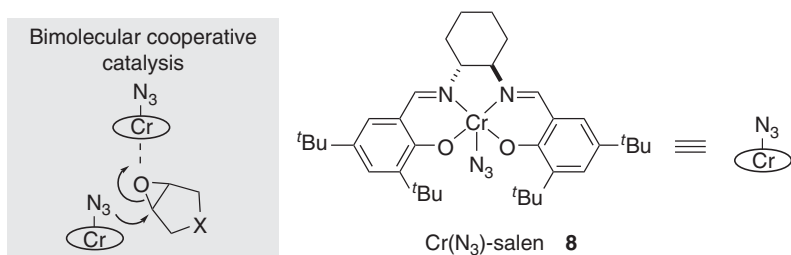
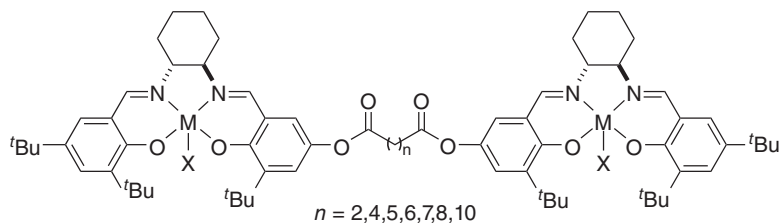


Figure 1.8 Postulated bimolecular bimetallic mechanism in ring-opening reaction of epoxides promoted by two monometallic $\text{Cr}(\text{N}_3)$ –salen complexes.



Covalently linked dimeric metal-salen complex

$M(X) = Cr(N_3)$: ring-opening reaction of epoxides by azide

$M(X) = Al(Cl)$: conjugate addition of cyanide to α,β -unsaturated imides

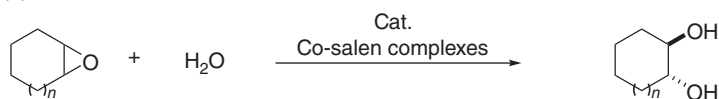
$M(X) = Co(OAc)$: kinetic resolution of terminal epoxides

Figure 1.9 Covalently linked dimeric metal-salen complexes.

(a)



(b)

**Scheme 1.4** (a) Hydrolytic kinetic resolution of terminal epoxides and (b) hydrolytic desymmetrization of *meso*-epoxides.

acid to activate epoxides and another molecule of $Co(OAc)$ -salen complex functions as a Brønsted base to nucleophilically activate H_2O (or alcohols or phenols), constituting a perfect example to elicit the power of Lewis acid–Brønsted base cooperative catalysis. Because of the broad synthetic utility of the reaction, a number of strategies have been developed to covalently or noncovalently link the monomeric Co -salen complexes to enhance the catalytic efficiency (Figure 1.10) [67]. Jacobsen *et al.* reported that the dimeric $Co(OAc)$ -salen complex **8** tethered by suberic ester ($n = 6$) outperformed the monomeric complex in the intramolecular cyclization of epoxyalcohol [68]. The same research group developed the highly active dendrimeric catalyst **9** [69] and oligomeric catalyst **10** [70] which contain multiple Co -salen units in one molecule. In particular, **10** ($X = nbs$ (3-nitrobenzenesulfonate), $Y = CH_2$, $Z = H$, $n = 1-3$) promoted the hydrolytic kinetic resolution of racemic propylene oxide with as little as 0.0004 mol% catalyst loading.

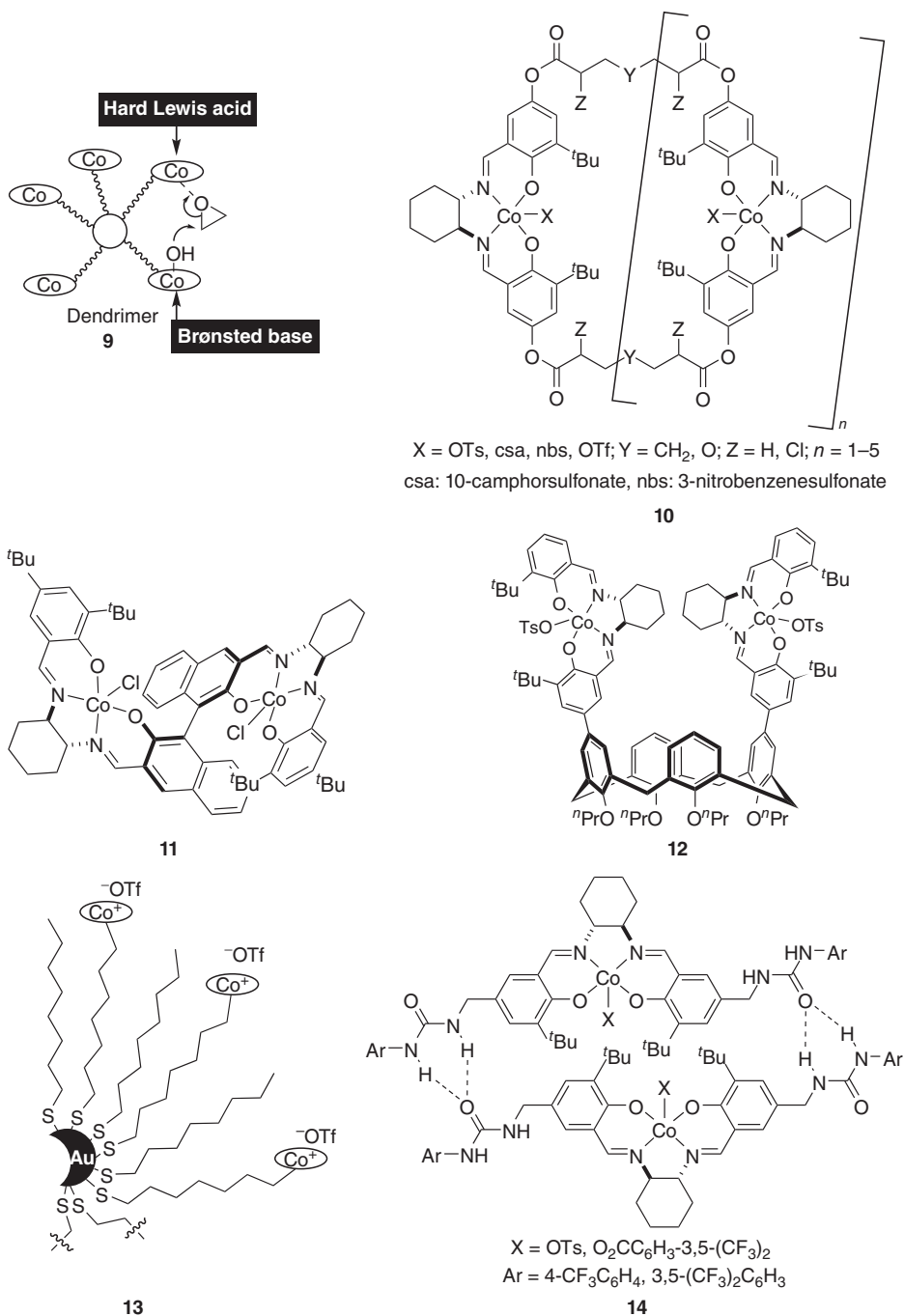
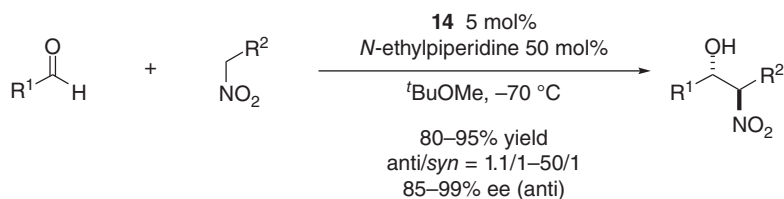


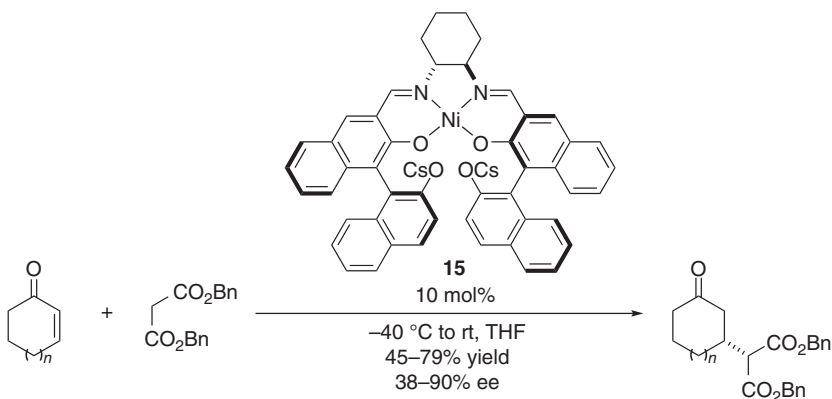
Figure 1.10 Various strategies for the construction of multimetallic Co-salen complexes.

Alcohols and phenols can be used as nucleophiles, and generally excellent yields and enantioselectivity are achieved. The beneficial effect of oligomeric catalyst **10** ($X = \text{OTf}$, $Y = \text{O}$, $Z = \text{H}$, $n = 1-4$) over the corresponding monomeric catalyst was also observed in asymmetric intramolecular ring-opening reactions of oxetanes [71]. Coates *et al.* developed a well-designed binaphthyl-embedded dimeric Co–salen catalyst **11** for the asymmetric polymerization of racemic terminal epoxides [72]. Homochiral catalyst afforded highly isotactic (99%) polyethers, and unreacted epoxides were obtained in high enantiopurity (compare with Chapter 13 in this book on cooperative catalysis in polymerization reactions). Remarkably, treatment of the racemic epoxides with the racemic catalyst allowed the polymerization to proceed in a highly isoselective manner to afford both the *S* and *R* purely isotactic polymers. Wezenberg and Kleij [73] utilized a calix[4]arene scaffold for the construction of a dimeric Co–salen complex **12**, which was applied to the hydrolytic kinetic resolution of terminal epoxides. Kinetic analysis showed an intramolecular cooperative pathway. The catalyst had greater stability than the monomeric complex, but the overall catalytic efficiency was not significantly enhanced. Noncovalent interactions also have been exploited to construct multimetallic Co–salen complexes [74]. Co–salen complexes **13** immobilized on gold colloids, developed by Belser and Jacobsen [75], enabled repetitive use in the kinetic resolution of racemic epoxides without any loss of reactivity and enantioselectivity. The cooperativity is operative in the catalyst on gold colloids, and significant rate enhancement was observed. Hong *et al.* reported an intriguing dimeric Co–salen catalyst assembled through hydrogen bonding. A monomeric Co–salen unit armed with pendant urea functionalities formed a homodimeric supramolecular complex **14** [76]. Complex **14** ($X = \text{OTs}$, $\text{Ar} = 4\text{-CF}_3\text{C}_6\text{H}_4$) exhibited significant rate enhancement in kinetic resolution of racemic epoxides with as little as 0.03 mol% catalyst loading under solvent-free conditions. The related Co–salen complex was also utilized in anti-selective catalytic asymmetric nitroaldol (Henry) reactions, in which the Lewis acid–Brønsted base cooperative function of two Co–salen units to activate both aldehydes and nitroalkane was crucial [77, 78]. With the combined use of **14** [$X = \text{O}_2\text{CC}_6\text{H}_3\text{-3,5-(CF}_3)_2$, $\text{Ar} = 3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3$] and a substoichiometric amount of *N*-ethylpiperidine, the anti-nitroaldol adduct was obtained in high enantioselectivity (Scheme 1.5).

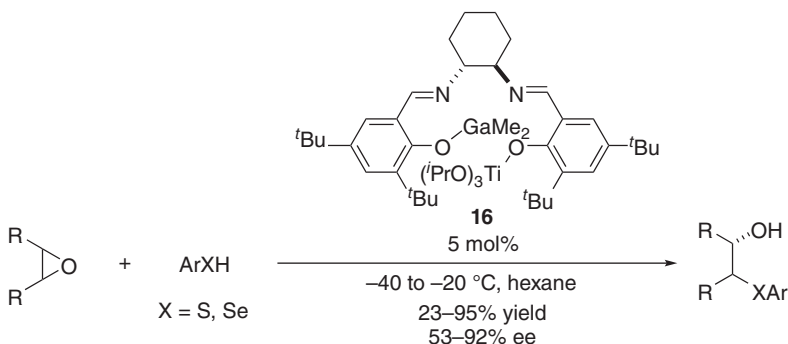


Scheme 1.5 anti-Selective catalytic asymmetric nitroaldol reaction promoted by dimeric Co–salen complex **14**.

The introduction of multiple metal cations in a Schiff base scaffold is an attractive strategy for devising a cooperative catalyst. Kozłowski *et al.* designed a dinucleating Schiff base ligand bearing two 1,1'-binaphthol units and four phenolic hydroxyl groups (Scheme 1.6) [79]. Formation of the heterobimetallic catalyst **15** comprising the Schiff base ligand Ni(II) and two Cs cations was confirmed by X-ray crystallographic analysis. It promoted the asymmetric conjugate addition of dibenzyl malonate to cyclic enones. Zhu *et al.* reported the heterobimetallic Ti–Ga–salen complex **16** prepared from the parent salen ligand, GaMe₃, and Ti(O^{*i*}Pr)₄ (Scheme 1.7) [80]. The order of metal addition (GaMe₃ first) was crucial for the heterobimetallic complex **16**, which was successfully utilized for the asymmetric ring-opening reaction of *meso*-epoxides with thiols and selenols.



Scheme 1.6 Catalytic asymmetric conjugate addition of dibenzyl malonate to cyclic enones promoted by Ni–Cs–Schiff base heterobimetallic catalyst **15**.



Scheme 1.7 Catalytic asymmetric ring-opening reaction of *meso*-epoxides with thiols and selenols promoted by Ti–Ga–salen heterobimetallic catalyst **16**.

Shibasaki and Matsunaga *et al.* developed a series of hetero- and homobimetallic cooperative catalysts utilizing a dinucleating chiral Schiff base scaffold **17**

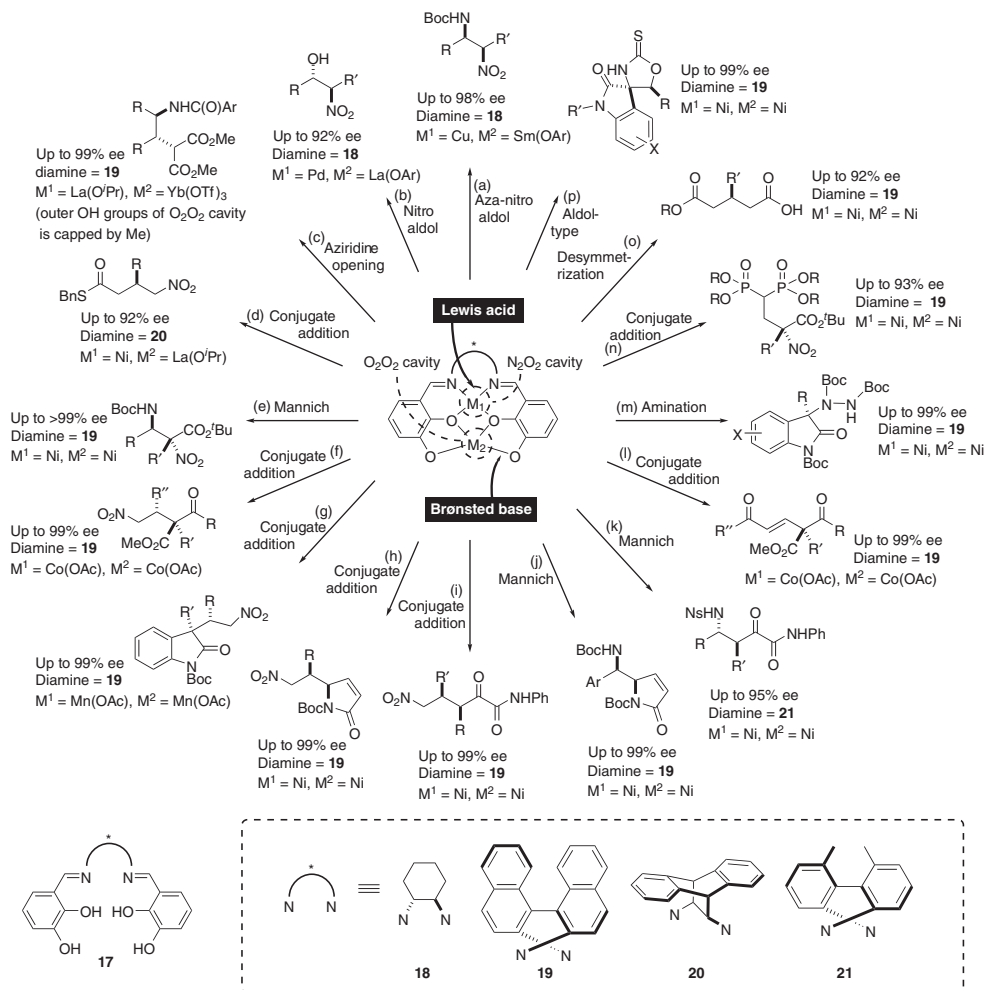


Figure 1.11 Schematic representation of the utility of bimetallic complexes of Schiff base **17** in catalytic asymmetric transformations.

(Figure 1.11) [59c, 81]. Introduction of additional phenolic hydroxyl groups on the aromatic ring of the parent salen ligand provides additional sites for metal coordination. On the basis of the coordination chemistry of this class of ligands [82], the N_2O_2 inner cavity is expected to preferentially incorporate a transition metal, and an oxophilic RE having a larger ionic radius is located in the O_2O_2 outer cavity. As a chiral diamine unit to link two coordinating aromatic groups, rigid cyclic diamines **18** and **20**, or axially chiral diamines **19** and **21**, were selected. Cu–Sm–**17** [$M^1 = \text{Cu}$, $M^2 = \text{Sm}(\text{OAr})$] initially emerged as a highly effective Lewis acid–Brønsted base cooperative catalyst in the syn-selective asymmetric aza-nitroaldol (aza-Henry) reaction, in which *N*-Boc imine and

nitroalkane were synergistically activated by Cu(II) and Sm-phenoxide, respectively (Figure 1.11a) [83]. Simple catalyst tuning by changing the incorporated metals from Cu-Sm to Pd-La permitted the use of aldehydes as electrophiles, leading to an anti-selective asymmetric nitroaldol (Henry) reaction (Figure 1.11b) [84]. Although the combination of transition metals and REs with chiral Schiff base **17** produced a variety of cooperative catalysts [85–87], the generation of uniform catalytically active species by precisely placing two different metals into two distinct cavities is not a simple task.

To further expand the utility of **17** as a platform for bimetallic catalysts, incorporation of two identical metal cations was investigated. A homodinuclear Ni_2 –**17** catalyst ($\text{M}^1 = \text{M}^2 = \text{Ni}$), prepared from **17** bearing 1,1'-binaphthyldiamine **19** as chiral diamine and 2 equiv of $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$, was a bench-stable powder and identified as a particularly useful catalyst for a wide range of asymmetric reactions, for example, Mannich reactions [88], conjugate addition reactions [89], amination [90], desymmetrization of *meso*-anhydrides [91], and aldol-type reaction of isothiocyanato oxindols (Figure 1.11e, h–j, m–p) [92]. Replacing the diamine unit from **19** to **21** proved beneficial and improved the stereoselectivity in the Mannich reaction of 1,2-dicarbonyl compounds (Figure 1.11k) [93]. The corresponding Co and Mn homobimetallic catalysts Co_2 –**17** [$\text{M}^1 = \text{M}^2 = \text{Co}(\text{OAc})$] and Mn_2 –**17** [$\text{M}^1 = \text{M}^2 = \text{Mn}(\text{OAc})$] were also readily prepared from metal acetates. They found their utility in asymmetric conjugate addition reactions [94] (Figure 1.11f, g, l). Productive interplay of Lewis acid function and Brønsted base function deployed in the designed bimetallic catalysts culminated in remarkably broad utility, and these catalytic reactions have been successfully applied to the enantioselective synthesis of natural products [95].

1.3.3

Cooperative Catalysts Based on a Ligand Platform Derived from Amino Acids

α -Amino acids are some of the most abundant homochiral materials available in nature. In 2000, Trost *et al.* developed a ProPhenol ligand platform (*S,S*)-**22** derived from L-proline, a pentadentate C_2 -symmetric ligand bearing two hydroxyl groups, one phenol, and two pyrrolidyl groups (Figure 1.12) [96]. Compound **22** can incorporate two different metal cations to synergistically offer a hard Lewis acid function and a Brønsted base function in an asymmetric environment. The utility of **22** was initially found with its dinuclear Zn complex **23** ($\text{M}^1 = \text{M}^2 = \text{Zn}$, $\text{X} = \text{Et}$, $\text{Ar}^1 = \text{Ph}$, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$) in the direct catalytic asymmetric aldol reaction of aromatic methyl ketones (Figure 1.12a), which was conveniently prepared with 2 equiv of Et_2Zn . Quantitative analysis of ethane evolution indicated that one ethyl–Zn bond remained. This dinuclear Zn complex **23** was a remarkably effective catalyst in direct asymmetric aldol reactions when using various aldol donors such as acetone [97], α -hydroxyl ketones [98], acetylenic ketones [99], or vinyl ketones (Figure 1.12b–e) [100]. Nitromethane also served as a suitable pronucleophile to enable an asymmetric nitroaldol reaction [101]. As mentioned above, the direct aldol reaction is the

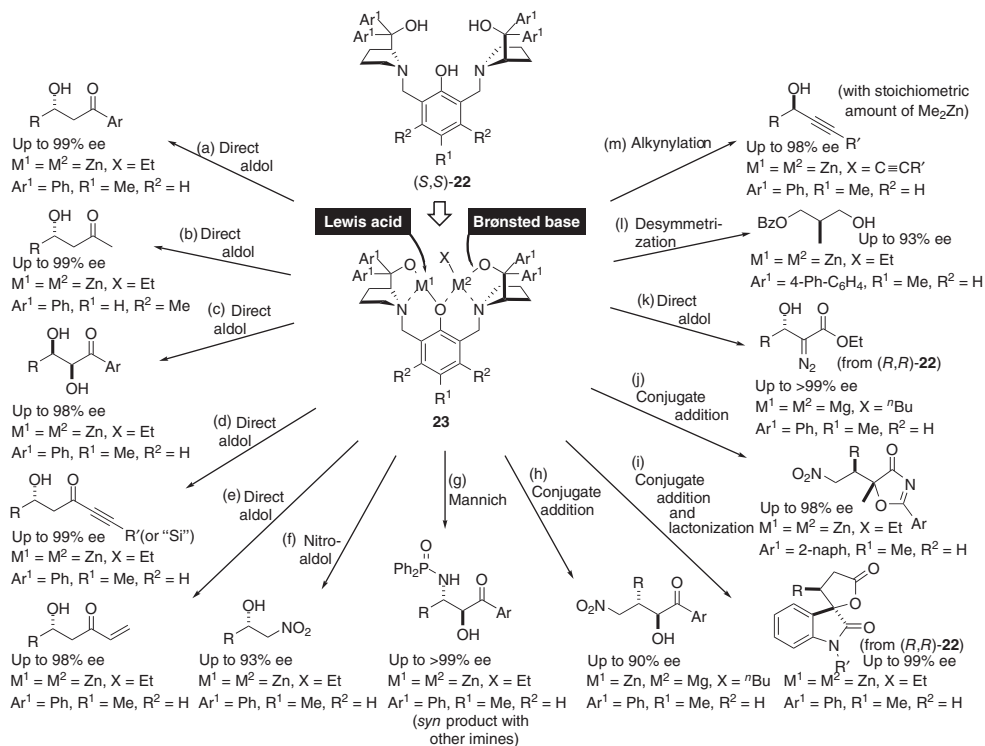
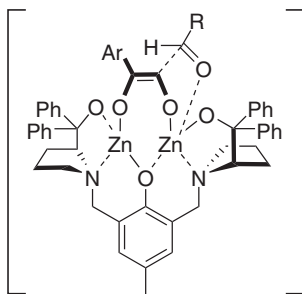
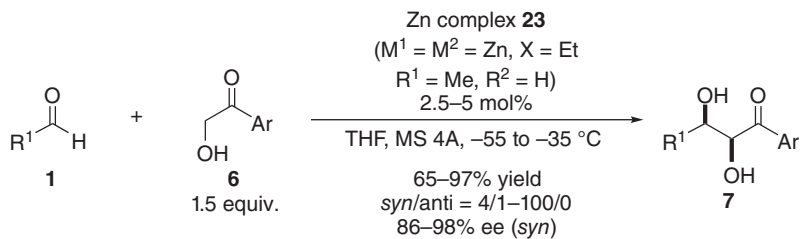
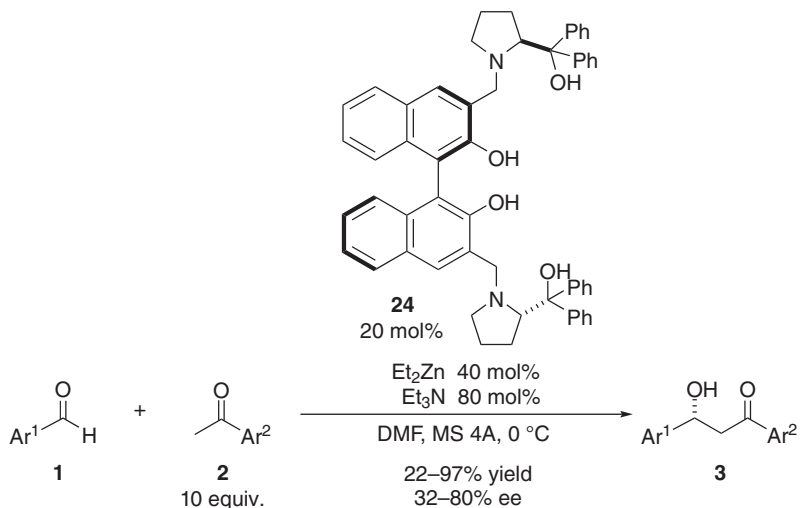


Figure 1.12 Schematic representation of the utility of bimetallic complexes of ProPhenol **22** in catalytic asymmetric transformations.

representative example in Lewis acid–Brønsted base cooperative catalysis. Zn alkoxide of **23** functioned as a Brønsted base to generate Zn-enolate, which was coupled with an aldehyde activated by another Zn cation that functioned as a Lewis acid (Scheme 1.8). A similar type of proline-incorporated chiral ligand **24** was reported by Da *et al.*, which afforded the corresponding dinuclear Zn complex to promote the direct aldol reaction, but with inferior catalytic efficiency (Scheme 1.9) [102]. The bimetallic catalytic system of complex **23** was particularly suitable for generating a nucleophilically active Zn-enolate from α -hydroxy ketones, allowing for the direct Mannich reaction [103] and the conjugate additions (Figure 1.12g–j) [104]. For the conjugate addition of α -hydroxy ketones to nitroolefins, a heterobimetallic complex **23** ($M^1 = Zn$, $M^2 = Mg$, $X = nBu$, $Ar^1 = Ph$, $R^1 = H$, $R^2 = Me$) prepared from equimolar amounts of Et_2Zn and nBu_2Mg gave the best performance. In contrast to the broad utility of dinuclear Zn complex **23** in the direct aldol reaction, the corresponding dinuclear Mg complex **23** ($M^1 = M^2 = Mg$, $X = nBu$, $Ar^1 = Ph$, $R^1 = H$, $R^2 = Me$) was the superior catalyst for the direct asymmetric aldol reaction of ethyl diazoacetate (Figure 1.12k) [105]. The diastereoselective transformation of the diazo group in the product highlights the synthetic utility. A bulkier aromatic group at the



Scheme 1.8 Direct catalytic asymmetric aldol reaction of α -hydroxy ketones **6** with dinuclear Zn complex **23**.



Scheme 1.9 Direct catalytic asymmetric aldol reaction of aromatic ketones **2** with dinuclear Zn complex prepared from ligand **24**.

tertiary alcohol of **22** was beneficial for higher yield and enantioselectivity in the catalytic asymmetric desymmetrization of *meso*-diols (Figure 1.121) [106]. Although a stoichiometric amount of Me_2Zn was required, the dinuclear Zn complex broadened the scope of its utility in asymmetric alkynylation of

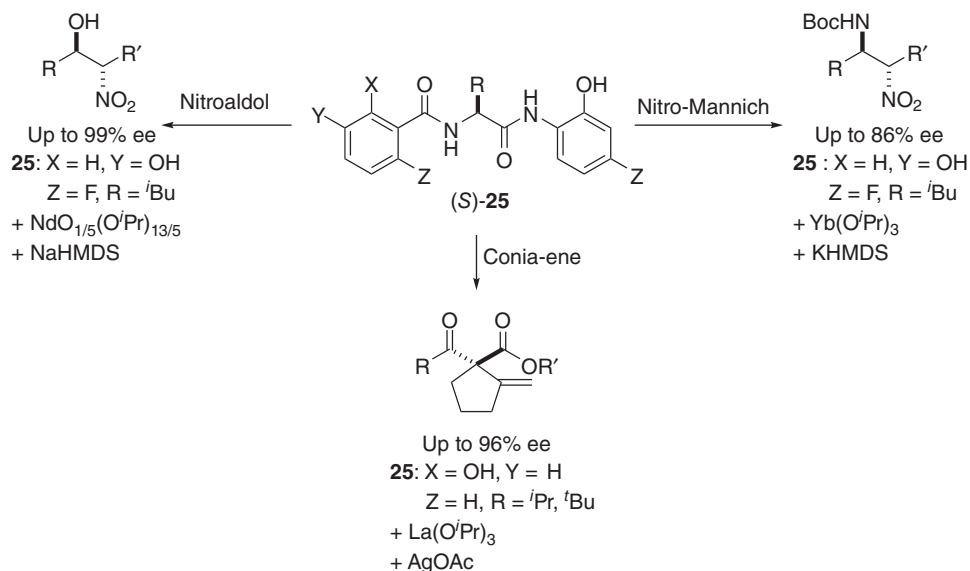
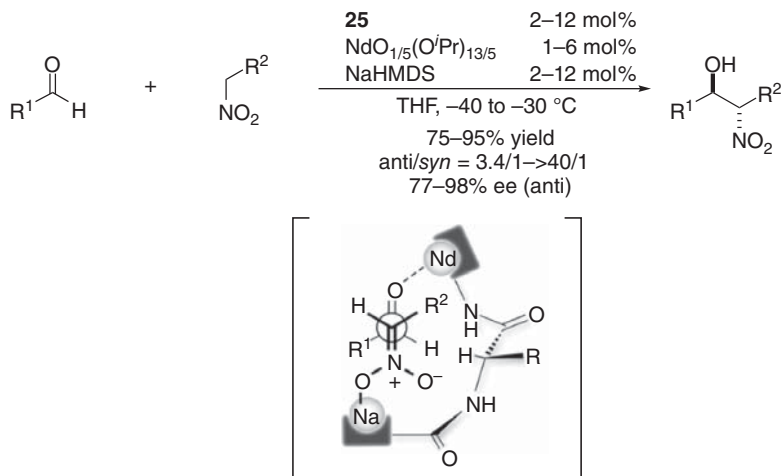


Figure 1.13 Schematic representation of the utility of the heterobimetallic catalysts derived from amide-based ligand **25** in catalytic asymmetric transformations.

aldehydes (Figure 1.12m) [107]. The synthetic utility of a variety of catalytic asymmetric carbon–carbon bond-forming reactions was demonstrated by the enantioselective synthesis of a number of natural products [108].

Shibasaki *et al.* developed a heterobimetallic catalytic system comprising an amide-based ligand **25** bearing two phenolic hydroxyl groups [109, 110], RE, and alkali metal (Figure 1.13). A Nd/Na heterobimetallic catalyst was designed on the basis of a transition state analysis for an anti-selective nitroaldol (Henry) reaction [78] in which Na-phenoxide functioned as a Brønsted base to generate nitronate, and the Nd cation functioned as a Lewis acid to electrophilically activate an aldehyde (Scheme 1.10) [111]. Intriguingly, this catalyst functioned as a heterogeneous catalyst in tetrahydrofuran (THF). It was readily prepared by mixing **25** (X = H, Y = OH, Z = F, R = *i*Bu), NdO_{1/5}(O^{*i*}Pr)_{13/5}, and NaHMDS through self-assembly. Its unique nature was exploited to produce a recyclable Nd/Na catalyst confined in a multiwalled carbon nanotube with enhanced catalytic efficiency [112]. The nitroaldol reaction offers a rapid access to enantioenriched vicinal amino alcohols, and the synthetic utility of the catalyst system culminated in the enantioselective synthesis of zanamivir (Relenza), a clinically used anti-influenza drug [113]. A similar catalytic system with Yb/K cations permits the use of *N*-Boc imines to promote the nitro-Mannich (aza-Henry) reaction [114]. The combination of La and Ag cations with amide-based ligand **25** (X = OH, Y = H, Z = H, R = *i*Pr or *t*Bu) emerged as an effective catalyst for the asymmetric Conia-ene reaction [115].



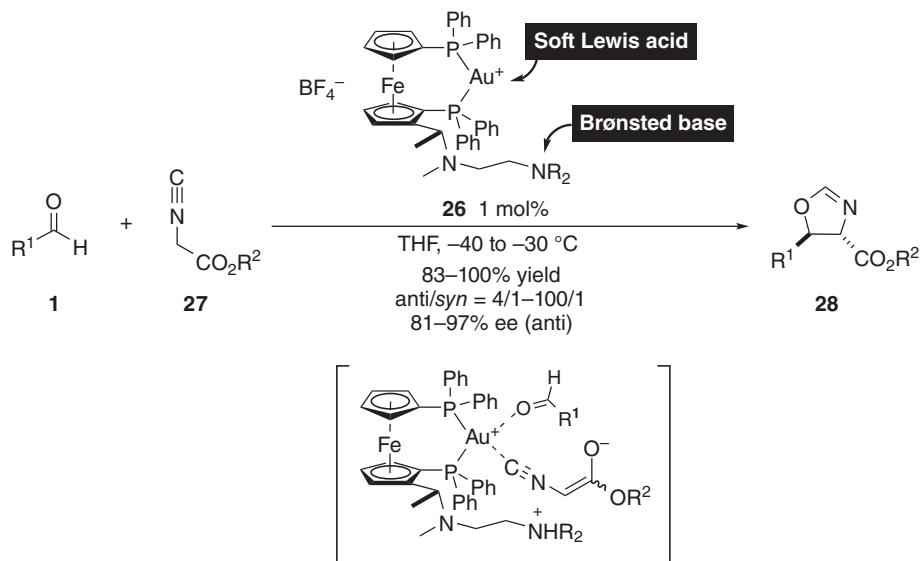
Scheme 1.10 anti-Selective catalytic asymmetric nitroaldol reaction promoted by Nd/Na heterobimetallic catalyst using amide-based ligand **25**.

1.4

Soft Lewis Acid–Brønsted Base Cooperative Catalysis

Potential pronucleophiles with high pK_a values not only mandate the use of a strong Brønsted base, which can trigger undesirable side reactions, but also retard the catalytic turnover through proton transfer, namely, the protonation of an intermediary adduct with a protonated catalyst, to regenerate the active catalyst. Therefore, an ingenious mechanistic trick to overcome the pK_a problem is required to broaden the scope of the direct catalytic asymmetric carbon–carbon bond-forming reaction. The exploitation of the specific soft–soft interaction of a soft Lewis acid catalyst and a soft Lewis basic pronucleophile is a particularly effective strategy to reinforce the chemical toolbox for direct catalytic asymmetric carbon–carbon bond-forming reactions, largely using carbon pronucleophiles with low pK_a values.

A very early example, reported in 1986 by Ito, Sawamura, and Hayashi, used a Au(I)-based soft Lewis acid–Brønsted base cooperative catalyst **26** (Scheme 1.11) [116, 117]. In the aldol reaction of isocyanoacetate **27** as pronucleophile, ferrocene-based bisphosphine catalyst **26** bearing a Au cation as a soft Lewis acid and a tertiary amine as a Brønsted base generated the nucleophilically active enolate, which was coupled with aldehyde **1** to afford the isoxazole **28**. The scope of the reaction was expanded by applying this class of catalysts to functionalized aldehydes and α -substituted isocyanoacetates with structural modification of the catalyst [118]. The thus-obtained functionalized oxazoles offered direct access to α -amino- β -hydroxy carboxylic acid derivatives. This catalytic protocol has been utilized in the enantioselective synthesis of biologically active compounds [119].



Scheme 1.11 anti-Selective catalytic asymmetric aldol reaction of isocyanoacetate **27** promoted by soft Lewis acid–Brønsted base cooperative catalyst **26**.

Shibasaki *et al.* revealed the broad utility of soft Lewis acid–Brønsted base cooperative catalysis by demonstrating a series of catalytic asymmetric transformations (Figure 1.14) [120]. The use of a soft Lewis acid is particularly advantageous to specifically activate soft Lewis basic pronucleophiles in the presence of hard electrophiles. The chemoselective coordination of soft Lewis basic pronucleophiles to a soft Lewis acid significantly enhanced the deprotonative activation of high- pK_a pronucleophiles with a mild Brønsted base. Although the deprotonative activation of nitrile-based pronucleophiles is generally difficult because of their high pK_a values, cooperative use of soft Lewis acid copper decorated with chiral bisphosphine ligand (*R,R*)-Ph-BPE and Brønsted base Li-phenoxide allowed for the smooth generation of a nucleophilically active α -cyanocarbanion. With the cooperative catalyst, direct addition of allyl cyanide proceeded efficiently with ketimines and ketones to produce tetrasubstituted stereogenic centers (Figure 1.14a, b) [121].

This catalysis is also valid for other soft Lewis basic pronucleophiles, such as thioamides **29**, leading to the direct aldol [122], Mannich [123], and conjugate additions (Figure 1.14c–e) [124]. Whereas the use of latent enolates in the carboxylic oxidation state has been a long-standing problem because of their reluctant enolization, the exploitation of soft–soft interactions enabled efficient enolization of thioamides, leading to the development of these useful reactions. In particular, the direct catalytic asymmetric aldol reaction of thioamides **29** is an intriguing example demonstrating the high chemoselectivity via soft–soft interactions. Aldehydes are inherently more prone to enolization than thioamides

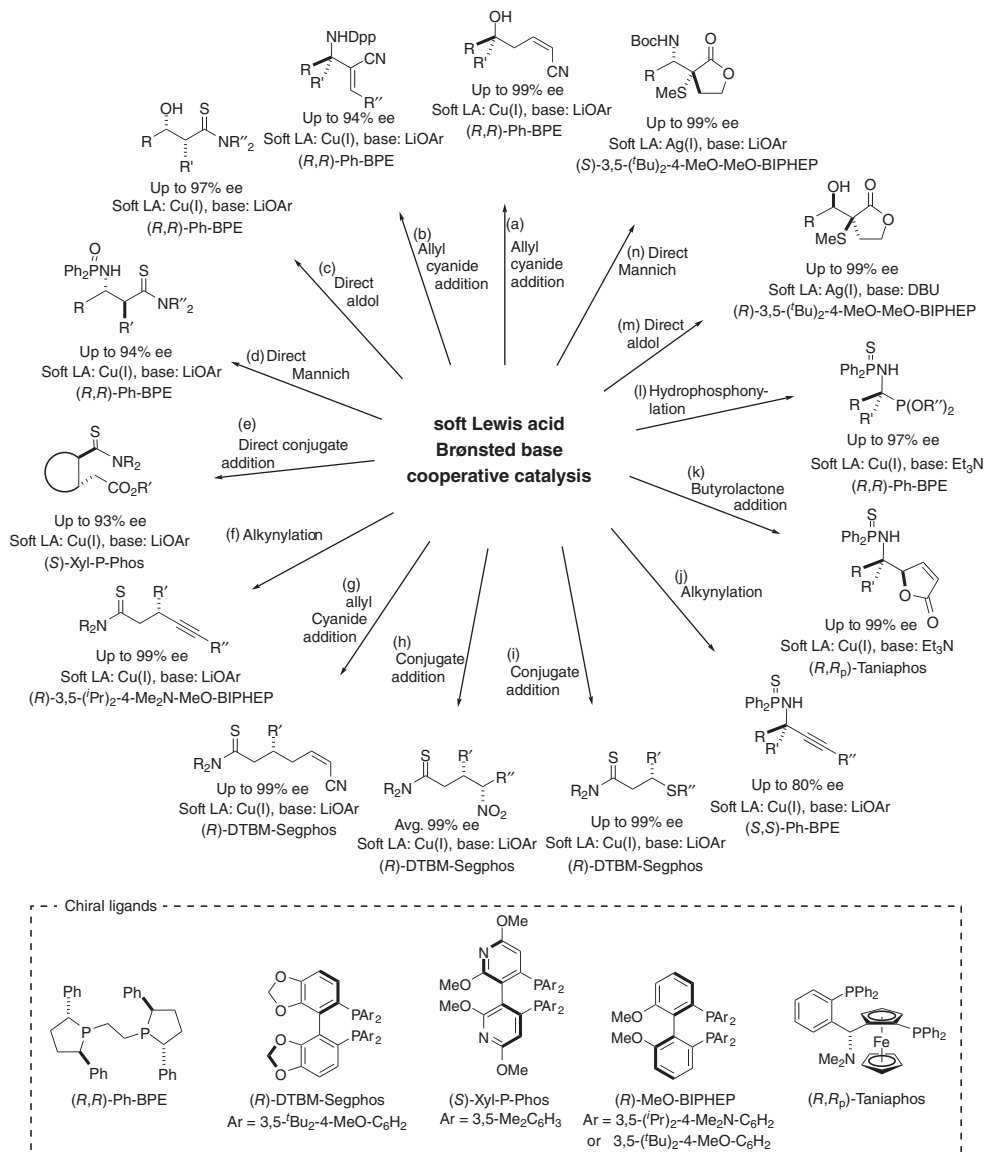
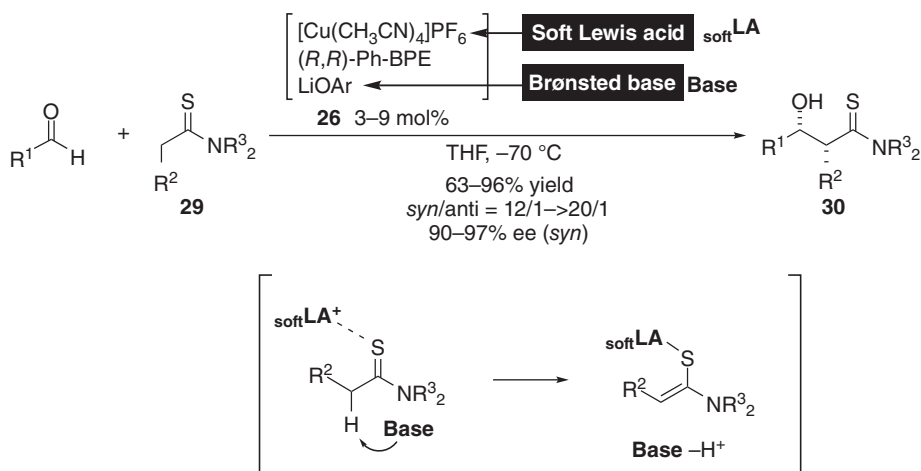


Figure 1.14 Schematic representation of the utility of the soft Lewis acid–Brønsted base cooperative catalyst in catalytic asymmetric transformations.

29, and self-condensation proceeds extensively under simple Brønsted basic conditions (Scheme 1.12). In contrast, with the soft Lewis acid–Brønsted base cooperative catalyst, chemoselective activation of thioamides **29** allowed preferential enolization of thioamides **29** to afford the desired aldol product **30** exclusively.



Scheme 1.12 Direct catalytic asymmetric aldol reaction of thioamide promoted by soft Lewis acid–Brønsted base cooperative catalyst.

The scope of this catalytic system was productively expanded to soft Lewis acidic electrophiles such as α,β -unsaturated thioamides [125–128] and *N*-thiophosphinoyl ketimines (Figure 1.14f–l) [129–131]. α,β -Unsaturated carboxylic acid derivatives and ketimines are generally poor electrophiles and are rarely used as substrates in asymmetric catalysis. The soft Lewis acid–Brønsted base cooperative catalysts has found significant potential in the promotion of the reactions of these poor electrophiles by installing soft Lewis acid functionalities, enabling the simultaneous activation of pronucleophiles and electrophiles to significantly enhance the reaction. Ag(I) as a soft Lewis acid functioned best in the chemoselective activation of α -sulfanyl lactones to facilitate the efficient enolization, promoting the direct aldol and Mannich reactions (Figure 1.14m, n) [132]. This new avenue within activation modes in asymmetric catalysis has paved the way for the enantioselective reactions of a previously neglected class of substrates. These catalysts have been applied to the enantioselective synthesis of therapeutic agents [133].

1.5

Conclusion

Over the past three decades, the arsenal of chemical tools has been substantially reinforced by the great number of asymmetric catalysts, which has allowed the efficient production of a wide variety of enantioenriched compounds. In view of the need for sustainable chemistry, including environmentally friendly chemical processes, asymmetric catalysis is a key methodology that continues to attract growing attention. An issue that requires particular attention is the overall reaction efficiency – the pursuit of atom economy of reactions to avoid the excessive

use of reagents and minimize the production of unwanted waste. The sophisticated synergism of the two concepts of asymmetric catalysis and atom economy will significantly advance synthetic chemistry, and there is no doubt that catalyst design based on the concept of cooperative catalysis will play a key role in this endeavor.

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2

Lewis Acid–Lewis Base Catalysis

Christina Moberg

2.1

Introduction

Catalytic methods are ubiquitous in organic synthesis, and therefore the design and synthesis of efficient and selective catalysts are important issues. In many cases, the desired reactivity and selectivity may not be accessible by a single catalyst, and new modes of activation may be needed in order to solve complex synthetic problems. Cooperative catalysis, whereby an electrophile and a nucleophile are simultaneously activated, can drastically improve the efficiency of chemical processes [1]. Multicatalytic systems working in concert may also lead to higher selectivity as a result of proper organization of the reacting molecules. In the design of such systems, natural catalysts frequently serve as sources of inspiration.

Simultaneous activation of electrophiles and nucleophiles by combined use of Lewis acids (electron-pair acceptors) and Lewis bases (electron-pair donors) is an attractive way to enhance chemical reactivity [2]. Lewis acids are most commonly based on main group metals such as aluminum, boron, silicon, or tin, or transition metals such as titanium, zirconium, iron, copper, or zinc, but carbocations as Lewis acids are also finding use. Lewis bases are commonly nucleophiles with N, O, S, or P donor atoms. Simultaneous activation of an electrophile and a nucleophile by the combined use of a Lewis acid and a Lewis base may lead to increased reaction rates as well as increased chemo-, regio-, and stereoselectivity.

2.2

Lewis Acid and Lewis Base Activation

2.2.1

Modes of Activation

Lewis acids are frequently used as catalysts in order to activate electrophiles. Coordination of the Lewis acid to a lone pair of electrons (Figure 2.1a, b) results in the withdrawal of electron density and thereby in the activation of the electrophile

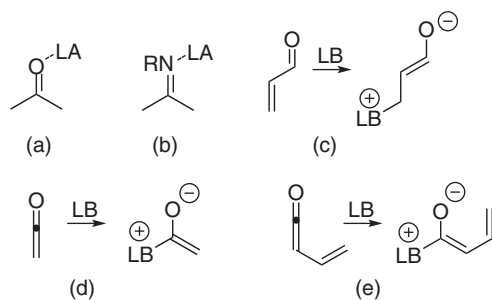


Figure 2.1 Lewis acid (a, b) and Lewis base (c–e) activation.

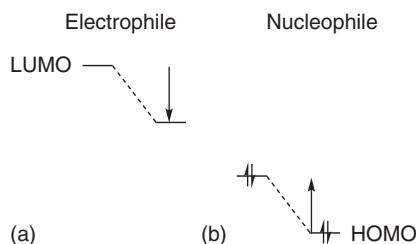
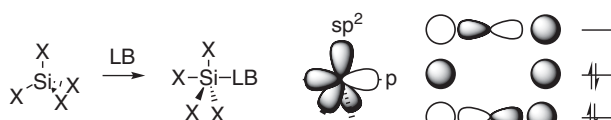
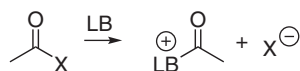
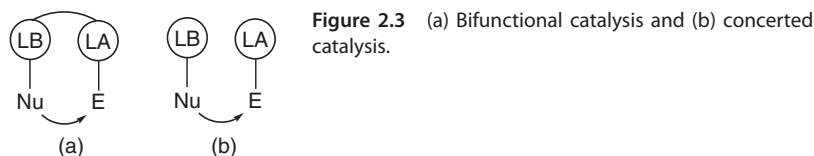


Figure 2.2 (a, b) Electrophile and nucleophile activation.

toward nucleophilic attack. Analogously, a Lewis base can be used to enhance the nucleophilicity of a reagent.¹⁾ In Lewis base catalysis, a nucleophile, such as a tertiary amine or phosphine, can add to unsaturated carbonyl derivatives to afford nucleophilic reagents, which can be employed, for example, for carbon–carbon bond formation. Common modes of activation include addition of Lewis bases to nonnucleophilic α,β -unsaturated carbonyl compounds, ketenes, and vinylketenes (Figure 2.1c–e).

The crucial effect of Lewis acids and Lewis bases on the reactivity is associated with changes in frontier orbital energies of the reaction components and consists of a lowering of the energy of the LUMO (lowest unoccupied molecular orbital) of the electrophile and an increase of the energy of the HOMO (highest occupied molecular orbital) of a nucleophile, respectively. Simultaneous activation of the nucleophile by a Lewis base serves to further increase the reactivity of the reaction system by bringing the LUMO of the electrophile and the HOMO of the nucleophile close in energy (Figure 2.2). Such dual activation can be achieved using a single catalyst containing Lewis acidic and Lewis basic centers (Figure 2.3a) or by using two separate catalysts (Figure 2.3b). According to IUPAC nomenclature, these types of catalysts are classified bifunctional and concerted catalysts, respectively. In order to obtain chiral and nonracemic products, either a chiral Lewis acid, a chiral Lewis base, or a combination of both may be used.

1) Lewis basicity is measured by relative equilibrium constants (thermodynamic) whereas nucleophilicity of a Lewis base is measured by relative rate constants of different nucleophilic reagents toward a common substrate (kinetic): the IUPAC Gold Book.



Lewis bases may also act by increasing the electrophilicity of a reagent. Addition of a Lewis base to a carboxylic acid derivative, for example, yields in addition to a reactive nucleophile an acylating agent with increased reactivity (Figure 2.4). A special mode of activation is provided by group 13 and 14 elements, which enjoy enhanced Lewis acidity on the coordination of Lewis bases [3]. Thus, silicon centers, for example, can interact with Lewis bases (Figure 2.5). The additional negative charge resides on the ligands. Contrary to intuition, the silicon center gains enhanced positive charge by binding to the Lewis base. Higher electron density in the ligand atoms results in dual activation, that is, increased electrophilicity of the central atom and increased nucleophilicity of the ligands. An orbital energy diagram illustrating the electron distribution in the three-center four-electron bond involving the silicon p orbital and the apical ligand orbitals, with all electron density in the nonbonding HOMO on the ligands, is shown in Figure 2.5.²⁾

2.2.2

Self-Quenching

A mixture of electrophile, nucleophile, Lewis acid, and Lewis base presents a challenging situation. Self-quenching is occasionally a problem: reaction of the Lewis acid with the Lewis base or with the nucleophile, or reaction of the Lewis base with the electrophile may inhibit the desired reaction (Figure 2.6). By avoiding combinations of Lewis acids and bases with high mutual affinity, that is, hard–hard and soft–soft combinations, the desired interactions may, however, be favored. Labile complexes with reversible binding of Lewis acid and Lewis base may also lead to the desired mode of activation. Another way to avoid this complication is to use bifunctional catalysts where the two catalytic functions are separated in space and therefore prevented from interacting.

2) This diagram is often incorrectly depicted in the literature, with a node in the HOMO.

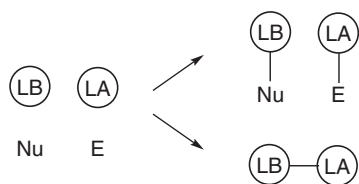
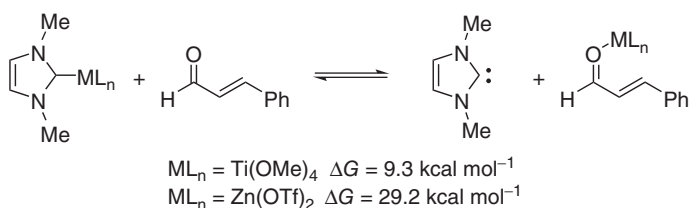


Figure 2.6 Nucleophile/electrophile activation versus self-quenching.

The problem with self-quenching was illustrated in a study where the equilibria between an *N*-heterocyclic carbene, an α,β -unsaturated aldehyde, and $\text{Ti}(\text{OMe})_4$ or $\text{Zn}(\text{OTf})_2$ were studied by DFT calculations (Scheme 2.1) [4]. Both reactions were exergonic, but only in the reaction with the zinc complex, the equilibrium was completely shifted toward the metal-carbene complex. These results provided an explanation for the observed catalytic inactivity of the carbene-Zn system (see Section 2.7.2).



Scheme 2.1 Equilibrium between Lewis acid–Lewis base and carbonyl compound [4].

During studies of β -lactam syntheses, Lectka and coworkers found that *O*-benzoylquinine (**1**) served as a Lewis basic catalyst to provide the product with excellent enantioselectivity, albeit in low yield. Attempted activation of the imine by the addition of Lewis acidic metal complexes such as $\text{Rh}(\text{PPh}_3)_3\text{OTf}$ or $\text{Cu}(\text{PPh}_3)_2\text{ClO}_4$ resulted, however, in decreased reactivity because of cocatalyst quenching (Scheme 2.2) [5].

On the other hand, harder and less azaphilic Lewis acids, such as those based on Al^{III} , Sc^{III} , Zn^{II} , and In^{III} , were found to minimize catalyst quenching. By judicious selection of catalyst components, and use of hard–soft rather than the more readily interacting soft–soft and hard–hard combinations, problems with self-quenching can thus be mastered.

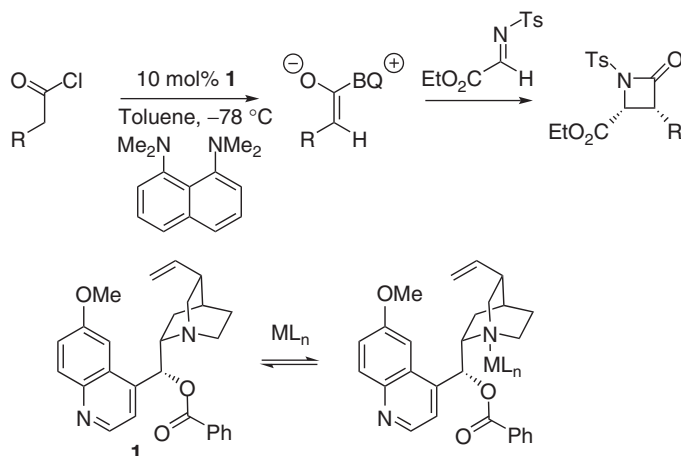
2.3

Addition to Carbonyl Compounds

2.3.1

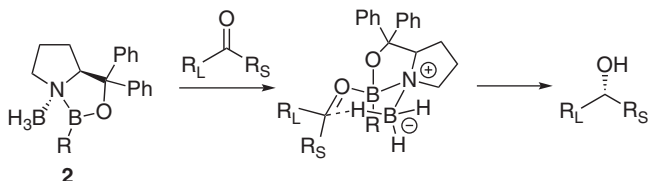
Reduction of Ketones

An early and elegant example of dual activation is the CBS reduction, developed by Corey, Bakshi, and Shibata [7] and building on earlier work by Itsuno *et al.* [6],



Scheme 2.2 Catalyst quenching [5].

where a bifunctional catalyst is used for enantioselective reduction of prochiral ketones by BH_3 (Scheme 2.3). The active catalyst, **2**, is obtained from a proline derivative, a boronic acid, and BH_3 . As a result of the preferred *cis*-junction of the five-membered rings, stereospecific coordination of BH_3 takes place to the face opposite to the substituents. The boron center incorporated in the ring acquires enhanced Lewis acidity by coordination to nitrogen (compare Figure 2.5), which leads to enhanced activation of the carbonyl group toward nucleophilic attack. The reactivity of BH_3 , which serves as the stoichiometric reducing agent, increases as a result of coordination to the Lewis basic nitrogen. A catalytic amount of reagent is sufficient, as uncomplexed BH_3 is not reactive enough to attack the carbonyl group. Both the electrophile and the nucleophile are thus activated in the reaction. Hydride transfer takes place via a six-membered transition state, where the ketone is aligned so as to minimize steric interactions, leading to excellent stereoselectivities.



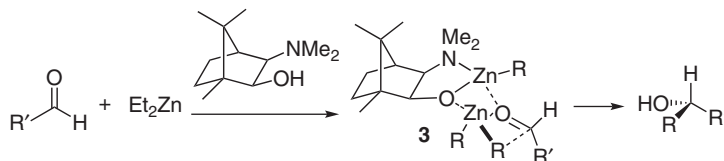
Scheme 2.3 CBS reduction of prochiral ketone [7].

2.3.2

Alkylation of Aldehydes and Ketones

Dialkylzinc additions to aldehydes, catalyzed by a variety of chiral amino alcohols, have emerged as synthetically highly versatile processes [8]. Linear dialkylzinc

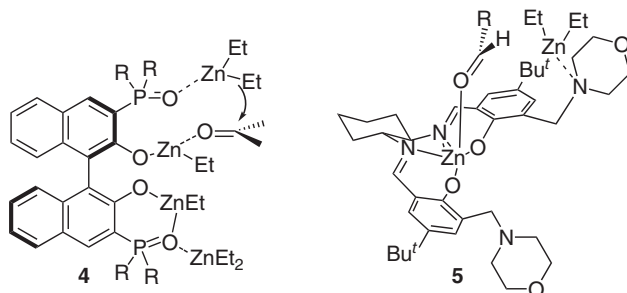
species are unreactive, but the tetrahedral compounds obtained by coordination to amino alcohols are potential alkyl nucleophiles. Noyori and coworkers introduced (–)-3-*exo*-(dimethylaminoisoborneol) (DAIB) as a particularly efficient catalyst for the reaction (Scheme 2.4) [9]. The mechanism resembles that of the CBS reduction. Increased acceptor character of the zinc atom bound to nitrogen leads to increased activation of the carbonyl group (3). The alkyl group, which is delivered by the coordinated dialkylzinc species, gains enhanced nucleophilicity by the coordination of oxygen [10]. Nonlinear effects are observed in the reactions as a result of the involvement of dimeric catalyst species acting as catalyst reservoir.



Scheme 2.4 Et_2Zn -reduction of prochiral aldehyde [9].

Ishihara and coworkers used a different type of bifunctional ligands for the same catalytic process (4) [11]. Here a phenolic oxygen serves to activate the Lewis acidic zinc atom, whereas enhanced nucleophilicity of the ethyl group results from the coordination of the phosphine oxide oxygen atom to the alkyl-delivering diethylzinc molecule.

Kozłowski and coworkers used salen complex 5, equipped with Lewis basic substituents, for alkylations of aldehydes [12], ketoesters [13], and iminoesters [14]. In the reactions with iminoesters, the Lewis acidic zinc center was replaced by titanium(IV). They found that catalysts containing amine Lewis basic sites were more efficient than those containing etheral Lewis bases. Although high yields were obtained in most cases, enantioselectivities were generally moderate. It was suggested that the carbonyl group was activated by apical coordination to the Lewis acid center, while the Lewis base activated the dialkylzinc nucleophile. The absence of a nonlinear effect in reactions with ketoesters supported the assumption of a monomeric catalyst species. In this catalyst as well as in 4, the C_2 symmetry leads to homotopic Lewis acid faces and thereby a reduction in the number of reaction paths, whereas in catalysts 2 and 3, specific coordination to one face of the catalyst has a comparable effect.



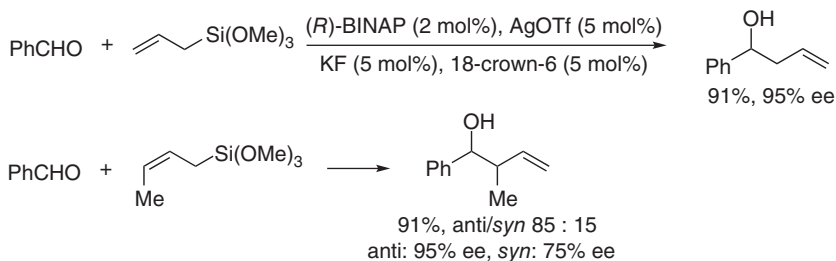
2.3.3

Allylation of Aldehydes and Ketones

2.3.3.1 Lewis Acid/Lewis Base Activation

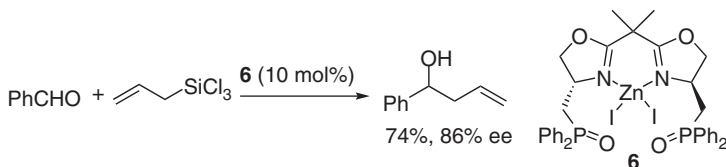
Following these first groundbreaking events, dual activation of reagents in a variety of other catalytic reactions has been investigated for various applications. Enantioselective allylations of carbonyl compounds and imines catalyzed by Lewis acids and Lewis bases using a wide range of allylmetal derivatives have been extensively explored [15].

Yamamoto and coworkers used allylsilanes for the allylation of both aromatic and aliphatic aldehydes activated by a silver 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) complex (Scheme 2.5). For the reactions to proceed, Lewis base activation of the allylsilanes was required. For this purpose potassium fluoride was used in the presence of 18-crown-6, which served to increase the solubility of the fluoride. An excess of AgOTf compared to the ligand was crucial in order to avoid the formation of competing complexes, which provided the products with lower enantioselectivities [16]. Under optimized reaction conditions, high yields and enantioselectivities were observed. (*Z*)-2-Butenyltrimethoxysilane gave mainly the γ -isomer with anti-stereochemistry. The same product mixture was obtained from a mixture of the (*Z*)- and (*E*)-isomers.



Scheme 2.5 Allylation of aldehyde [16].

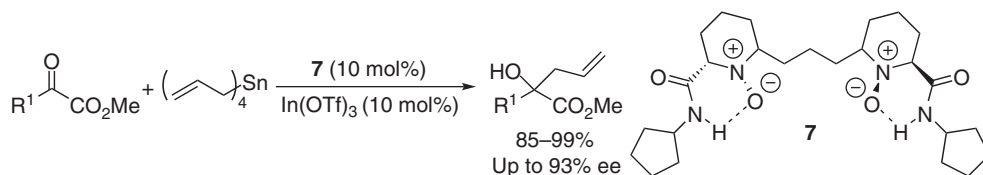
A bifunctional catalyst consisting of a bisoxazoline-zinc complex bearing phosphine oxide functions (**6**) was employed for the same purpose by Fujimoto and Yamamoto (Scheme 2.6) [17].



Scheme 2.6 Allylation of aldehyde using bifunctional catalyst [17].

Enantioselective allylations of α -ketoesters with tetraallyltin take place in the presence of In(III) and chiral *N*-oxide **7** (Scheme 2.7) [18]. While the metal

activates the ketoester via coordination to the carbonyl oxygen atoms, the *N*-oxide increases the nucleophilicity of the allyl groups by coordination to tin.



Scheme 2.7 Allylation of Ketoester by concerted catalysis [18].

2.3.3.2 Lewis Base Nucleophilic/Electrophilic Activation of Allylsilanes

As Lewis base coordination to allylsilanes, with 1 or 2 equiv. of the Lewis base (Figure 2.7), increases the Lewis acidity of the silicon center, allylations are enhanced even in the absence of an additional Lewis acid. Taking advantage of the effect of Lewis base coordination to tetrahedral silicon species, which result in higher positive charge at silicon and a more nucleophilic allyl group, Denmark has developed highly selective synthetic processes. Whereas the reactions in the presence of added Lewis acids occur via open transition states (such as Figure 2.8a, b) [19], Lewis base mediated reactions with allylsilanes are believed to occur via a cyclic transition state (Figure 2.8c), a situation that may lead to improved enantioselectivity [20].

Monodentate [21] and bidentate [22] phosphorus-based amides were successfully employed as Lewis bases in allylations by Denmark and coworkers, whereas Kočovský and coworkers used chiral pyridine *N*-oxides, such as **8**, for the same purpose and obtained high yields of highly enantioenriched products (Scheme 2.8) [23]. Crotyl derivatives reacted with high diastereo- and enantioselectivity to provide the anti-isomers as the major products.



Figure 2.7 Coordination of one and two Lewis bases.

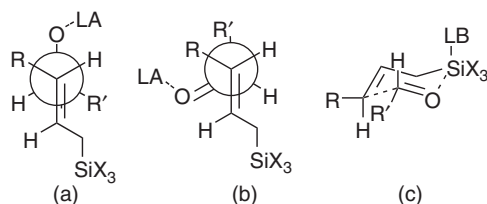
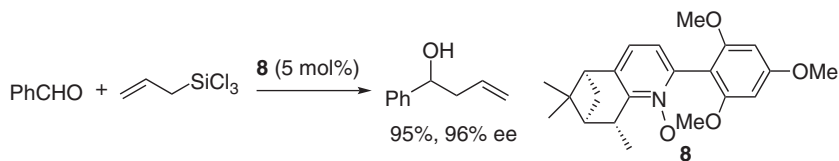


Figure 2.8 Open (a, b) and closed (c) transition states.



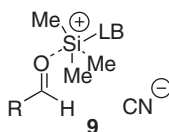
Scheme 2.8 Allylation of aldehyde using bifunctional catalyst [23].

2.3.4

Cyanation of Aldehydes, Ketones, and Imines

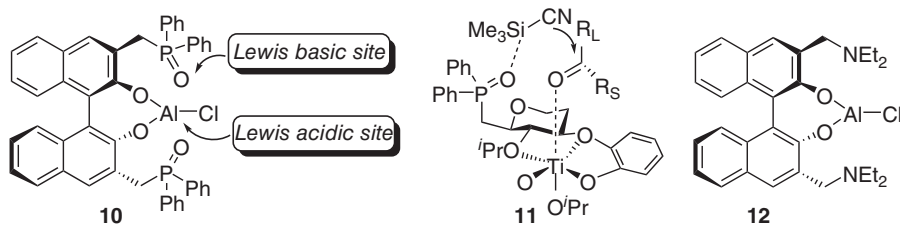
2.3.4.1 Silylcyanation

Considerable interest has been devoted to cyanations of carbonyl compounds, and a variety of catalytic systems capable of simultaneous activation of the electrophile and the nucleophile have been developed. Denmark and Chung [24] showed that the Lewis base-activated silicon center in trimethylsilyl cyanide (**9**) could serve as a Lewis acid for activation of aldehydes for silylcyanations. Use of a variety of chiral Lewis bases provided products in high yields, although with poor enantiomeric purity.



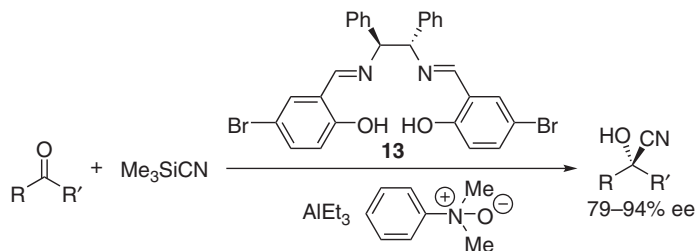
More selective catalytic systems have been obtained from Lewis acidic metal complexes and Lewis basic phosphine oxides or amines. Shibasaki and coworkers reported the first bifunctional Lewis acid–Lewis base catalyst (**10**) to provide highly enantioselective silylcyanation of aldehydes [25]. Self-quenching was avoided by a ligand design where the Lewis acid and Lewis base functions were separated in space. High yields and excellent enantioselectivities were observed for a range of aldehydes. Kinetic studies supported the suggested dual activation pathway, whereby the Lewis acidic aluminum center activates the carbonyl group for nucleophilic attack, at the same time as the nucleophile enjoys increased negative charge by coordination to the phosphine oxide. Replacement of the phosphine oxide groups by sulfoxide functions provided a catalyst for enantioselective Reissert reactions. A titanium complex containing a ligand based on D-glucose (**11**) proved to be capable of also catalyzing cyanosilylations of ketones [26].

A gadolinium complex of the same ligand was employed as catalyst for the same reaction, but afforded products with a configuration opposite that of the titanium complex **11**. The active catalyst had a metal/ligand ratio of 2:3, and the reaction was shown to follow a different mechanism. A slightly modified complex also served as a catalyst for other processes, such as Strecker reactions [27].



These early accomplishments started extensive studies resulting in a wide range of catalysts capable of simultaneous activation of carbonyl compounds and silyl cyanide. Nájera, Saá, and coworkers designed a ligand similar to **10**, but with the phosphine oxide functions replaced by amino groups (**12**) [28]. Later studies revealed, however, that this catalytic system acted as a Lewis acid–Brønsted base catalyst [29]. High selectivities were observed, in particular, for aromatic aldehydes. A ligand with the diethylamino groups replaced by piperidino functions was later used together with HMPA or triphenylphosphine oxide and molecular sieves and shown to give products with excellent enantiomeric purity also from aliphatic aldehydes [30].

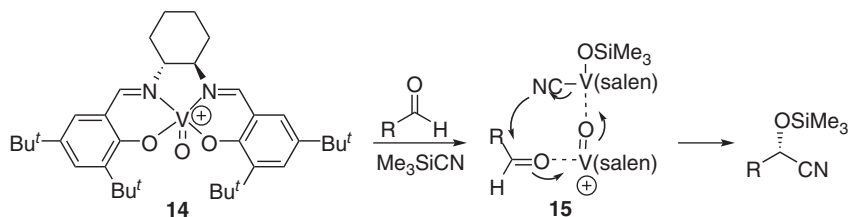
Catalytic systems where the Lewis acid and the Lewis base reside in different molecules were reported by Feng and coworkers for the cyanosilylation of ketones [31]. Several combinations of Lewis acids and *N*-oxides were tested; particularly, successful results were obtained using an aluminum complex generated from salen ligand **13** and Et_3Al (Scheme 2.9). Excellent yields and selectivities were generally observed, but aliphatic ketones gave products with somewhat lower enantiomeric excess than aromatic ketones.



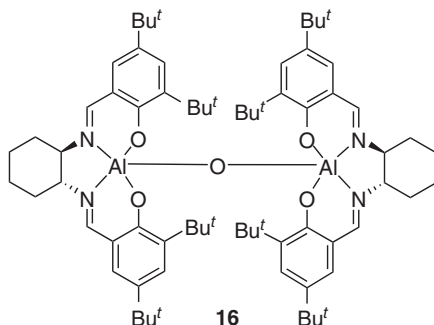
Scheme 2.9 Cyanosilylation of ketone [31].

Salen complexes with titanium, vanadium, and aluminum have also been used for silylcyanations (Scheme 2.10). Reactions using complex **14** were suggested to proceed via intermediate **15**, with simultaneous activation of the aldehyde and trimethylsilyl cyanide [32].

North and Williamson [33] used bimetallic aluminum salen complex **16** for the same reaction, but together with a phosphine oxide cocatalyst. High enantioselectivities were observed for aromatic aldehydes, whereas aliphatic aldehydes reacted with moderate selectivity.

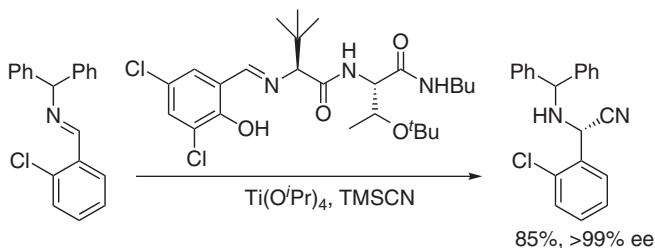


Scheme 2.10 Cyanosilylation of aldehyde [32].



Very high reaction rates were observed with a salen complex equipped with a diethylamino group. Full conversion was observed within less than 4 h with a substrate/catalyst ratio of 10 000 : 1 at room temperature [34].

A structurally different type of catalyst, consisting of a titanium(IV) complex of a Schiff base dipeptide, was developed for the Strecker reaction by Snapper, Hoveyda, and coworkers (Scheme 2.11) [35]. The Lewis acidic metal center activates the imine, while an amide function activates the nucleophile, which is HNC generated from TMSCN by the action of isopropanol. The structure and configuration of the terminal amide function proved to be crucial for the performance of the catalyst.

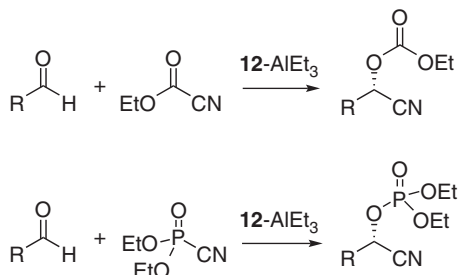


Scheme 2.11 Strecker reaction [35].

2.3.4.2 Cyanoformylation and Cyanophosphorylation

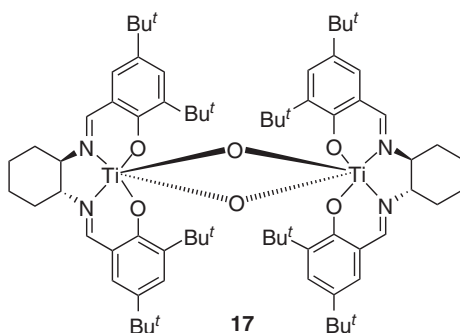
Bifunctional complex **12** could be successfully employed also for cyanoformylation [36] and cyanophosphorylation [37] of aldehydes (Scheme 2.12). Excellent

enantioselectivities were observed with a range of aldehydes. The same reaction catalyzed by an aluminum complex prepared from binol showed poor activity, which, however, increased on addition of external base (triethylamine). In the latter case the enantioselectivity was low. These observations led the authors to conclude that the original catalyst served as a bifunctional catalyst, although they did not exclude that the amino groups functioned as Brønsted catalysts.



Scheme 2.12 Cyanoformylation and cyanophosphorylation [36, 37].

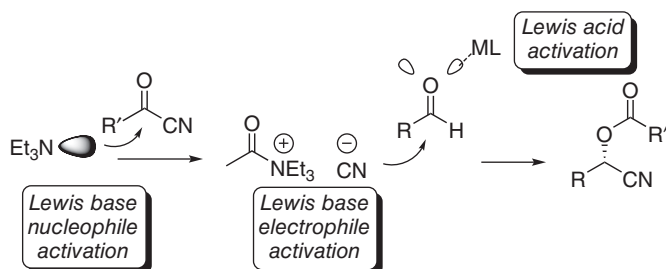
North and coworkers [38] developed and successfully used dimeric titanium salen complex **17** as a Lewis acid catalyst for the addition of cyanoformates to carbonyl compounds. By combining this catalyst with a Lewis base, such as a tertiary amine, enhanced reactivity was observed; the Lewis base was suggested to activate the nucleophile at the same time as a highly reactive formylation reagent is formed [39].



2.3.4.3 Cyanoacylation

Cyanoacylations, which lead directly to cyanohydrin esters, have been less extensively studied. A few early examples were reported where different achiral bases were used for the activation of acetyl cyanide. The first enantioselective reactions used acetyl cyanide and titanium salen dimer **17** in combination with tertiary amines [39] or aroyl cyanides together with bifunctional catalyst **12** [40]. Whereas in the latter reaction a Lewis acid–Brønsted base mechanism was suggested [41], the former process most likely occurs via Lewis acid–Lewis base activation. The

different mechanisms for the seemingly similar processes may be because of a higher tendency for cleavage of the carbon–carbon bond in the aryl derivatives, and to the different reaction conditions. In the former process, a range of ketonitriles and aromatic or aliphatic aldehydes are able to participate. The Lewis base activates the nucleophile via addition to the ketonitrile carbonyl group, which also leads to electrophilic activation of the resulting acylating agent. At the same time, the titanium center activates the electrophile (Scheme 2.13) [42].



Scheme 2.13 Acylcyanation [39].

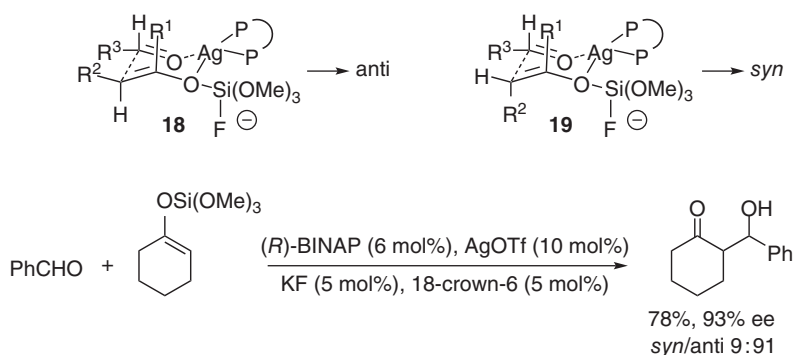
2.4

Condensation Reactions

2.4.1

Aldol Reactions

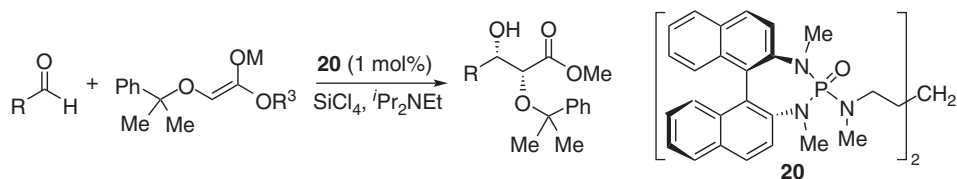
A catalyst system used for allylation of aldehydes with allylsilanes proved suitable also for Mukaiyama aldol reactions (Scheme 2.14) [16]. The diastereoselectivity, which was dependent on the geometry of the silyl enol ether, was explained by the proposed transition structures (**18** and **19**).



Scheme 2.14 Mukaiyama aldol reaction [16].

Denmark and Chung [43] were able to obtain *syn*-1,2-diols with high diastereomeric and enantiomeric purity from silyl ketene acetals and a variety

of aldehydes via glycolate aldol reactions by employing silicon tetrachloride activated by a chiral Lewis base (**20**) as catalyst (Scheme 2.15). By changing the substituents on the silyl ketene acetal, antiproducs could be obtained with high selectivity.

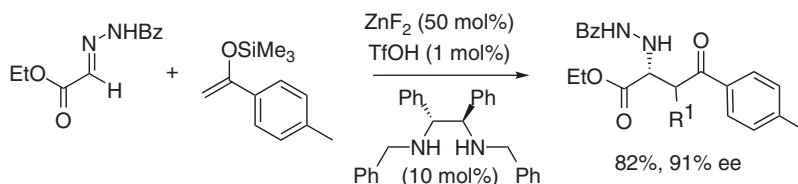


Scheme 2.15 Addition of glycolate-derived silyl ketene acetal to aldehyde [43].

2.4.2

Mannich Reactions

Kobayashi and coworkers [44] explored Mannich reactions in aqueous media and found that zinc fluoride bound to a chiral ethylene diamine analog catalyzed the enantioselective reaction of a hydrazono ester with some silyl enolates (Scheme 2.16). They believed that the reaction proceeded by Lewis acid activation of the imino function and Lewis base activation of the silicon center, the latter resulting in increased nucleophilicity of the enolate.



Scheme 2.16 Mannich reaction [44].

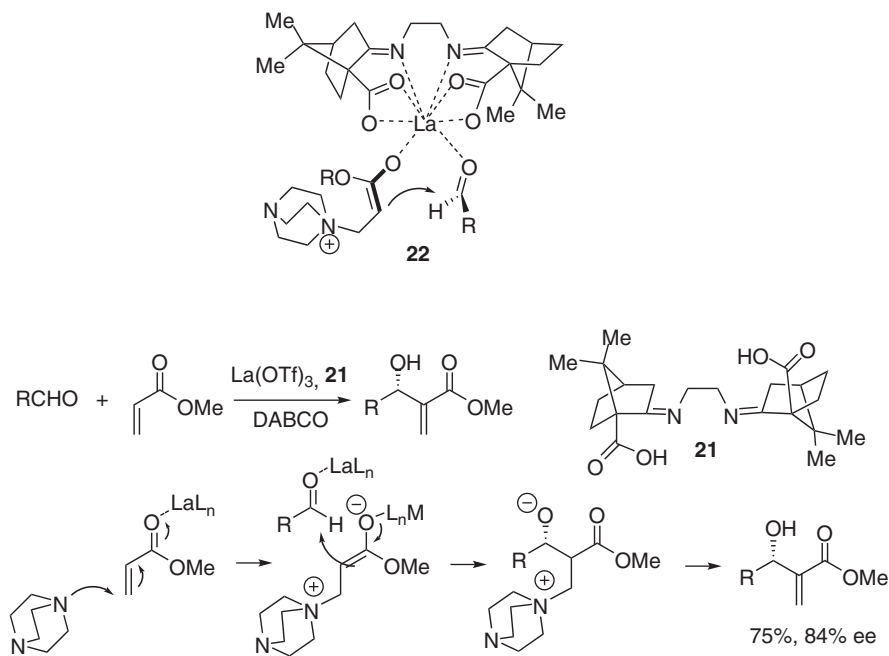
2.5

Morita–Baylis–Hillman Reactions

The Morita–Baylis–Hillman reaction, which is the coupling between an aldehyde and an α,β -unsaturated carbonyl compound or nitrile to give α -methylene- β -hydroxy carbonyl derivatives, has emerged as a synthetically highly versatile process [45]. Lewis bases, typically tertiary amines such as DABCO or tertiary phosphines, are employed as catalysts for the process. The reactions suffer from low reaction rates, and therefore Lewis bases in combination with catalyst components capable of activating the carbonyl functions, in many cases Brønsted acids or hydrogen bond donors, are used to accelerate the reactions. Examples

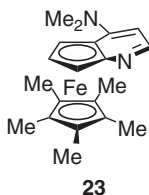
of chiral Lewis acid–Lewis base catalysis resulting in highly enantioenriched products have also been reported. The role of the Lewis acid is to activate the electrophile toward nucleophilic attack by coordination to the carbonyl group, as well as to stabilize the intermediate enolate.

Lanthanum triflate bound to ligands derived from (+)-ketopinic acid (**21**) in combination with DABCO used for the reaction of aromatic or aliphatic aldehydes with acrylates afforded products with good to high enantioselectivities (Scheme 2.17) [46]. Best results were obtained with esters derived from aromatic alcohols. Use of other lanthanides resulted in lower selectivities. The reaction was suggested to proceed via transition state **22**.

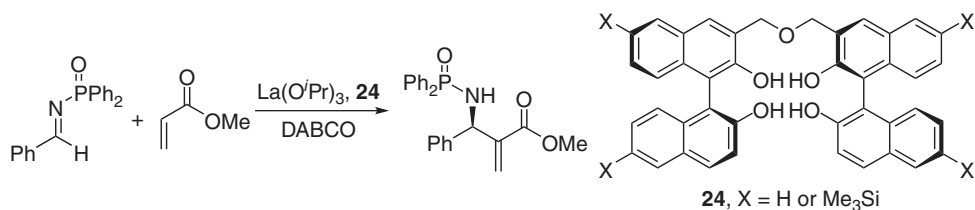


Scheme 2.17 Lewis acid–Lewis base-catalyzed Morita Baylis–Hillman reaction [46].

The opposite strategy, that is, the use of a chiral Lewis base and an achiral Lewis acid, can likewise lead to highly enantioenriched products. Thus, chiral DMAP-analog **23** was used together with MgI_2 to provide products with moderate to high enantioselectivity from 2-cyclopentenone and a variety of aldehydes [47].



A selective aza-Morita–Baylis–Hillman reaction used DABCO together with $\text{La}(\text{O-}i\text{Pr})_3$ complexes of ligands **24**, the latter serving as Lewis acids/Brønsted bases (Scheme 2.18) [48].



Scheme 2.18 Lewis acid–Lewis base-catalyzed Morita Baylis–Hillman reaction [48].

2.6

Epoxide Openings

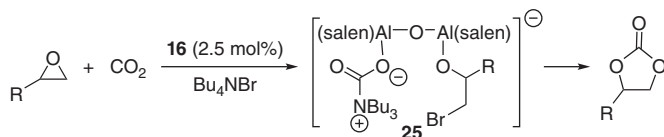
Ring-openings of epoxides by nucleophiles are usually catalyzed by Lewis acids. Simultaneous nucleophile activation has been achieved by use of bimetallic complexes (see Chapter 8) [49]. Ring-openings by carbon dioxide and carbon disulfide have been performed under dual activation conditions using a combination of Lewis acids and Lewis bases.

2.6.1

Coupling with CO_2 and CS_2

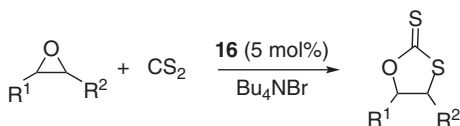
Epoxides react with CO_2 by ring-opening to form cyclic carbonates. The reactions are catalyzed by a variety of Lewis acids but usually also require the presence of a tetraalkylammonium salt or a nucleophilic amine. North and coworkers found that dimeric aluminum complex **16** in combination with tetrabutylammonium bromide serves as a highly efficient catalyst for reactions of monosubstituted epoxides under solvent-free conditions even at room temperature and atmospheric pressure (Scheme 2.19) [50]. A careful mechanistic investigation revealed that the catalytic cycle starts with the coordination of the epoxide oxygen to aluminum and ring-opening of the three-membered ring by nucleophilic attack by bromide. Simultaneous reaction of carbon dioxide with tributylamine generated *in situ* results in complex **25**, which is preorganized for final product formation; the ability of the bimetallic complex to preorganize the reactants explains the high reactivity of the catalytic system. The reaction proved to be stereospecific, but although a chiral enantiopure complex was used, no kinetic resolution was observed in reactions with racemic epoxides.

The same catalyst system can also be used for the preparation of dithiocarbamates and trithiocarbamates from carbon disulfide and epoxides (Scheme 2.20) [51]. The mechanism differs from that of the reaction with carbon dioxide:



Scheme 2.19 Ring-opening of epoxides by CO_2 [50].

tributylamine reacts with CS_2 to form a dithiocarbamate, which, because of the high nucleophilicity of sulfur, acts as a nucleophile and ring-opens the epoxide. This reaction requires heating to 50°C , probably as a result of the lack of preorganization in this case. At higher temperature, 1,3-dithiolane-2-thiones are the main products.



Scheme 2.20 Ring-opening of epoxides by CS_2 [51].

Bifunctional aluminum salen complexes with covalently attached Lewis basic phosphonium salt sites have also been prepared and successfully used for the synthesis of cyclic carbonate from epoxides and CO_2 [52].

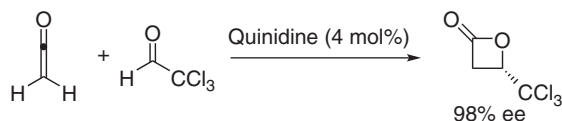
2.7

Cyclization Reactions

2.7.1

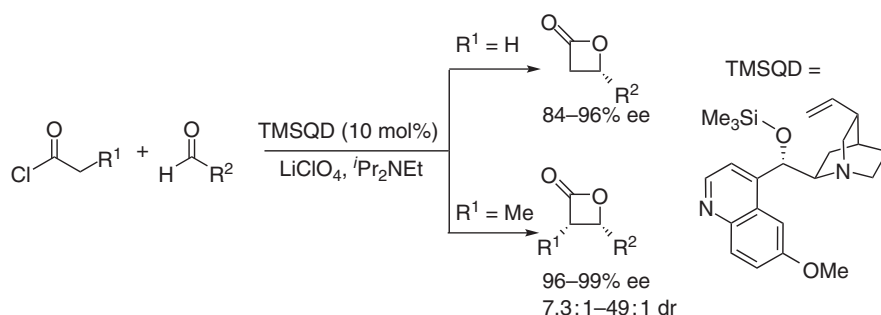
[2+2] Cycloadditions

In the 1980s, Wynberg and Staring [53] found that cinchona alkaloids catalyze [2+2]-cycloadditions of ketene and activated aldehydes, such as di- or trichloroacetaldehyde, as well as activated ketones [54] to provide lactones with high enantiomeric purity (Scheme 2.21). The role of the Lewis base is to transform the ketene to a nucleophile, as well as to transfer chirality to the product. These seminal results served as inspiration for several groups, and subsequent studies have aimed at extending the scope of this synthetically valuable process to include a wider range of aldehydes and substituted ketenes generated *in situ*. The reactions generally suffered from low yields, however, until it was discovered that high yields and excellent stereocontrol could be achieved by Lewis acid–Lewis base catalysis [55]. Recent work has resulted in several highly versatile synthetic processes. Many of the products obtained have served as versatile building blocks for biologically active compounds.



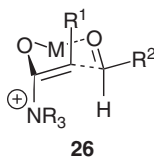
Scheme 2.21 Wynberg's seminal [2+2] cycloaddition [53].

Nelson and coworkers were able to extend the original reaction to nonactivated aldehydes by employing cinchona alkaloids in combination with a Lewis acid as catalyst (Scheme 2.22) [56]. The optimal catalyst system consisted of *O*-trimethylsilylquinine (TMSQ) or *O*-trimethylsilylquinidine (TMSQD), lithium perchlorate, and a stoichiometric amount of ethyldiisopropylamine. High yields and excellent enantio- and diastereoselectivities were observed in reactions with a wide range of aldehydes and ketene or methylketene.



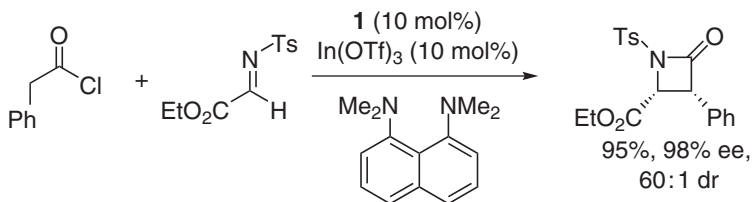
Scheme 2.22 Lewis acid–Lewis base-catalyzed [2+2] cycloaddition [56].

A mechanism with a closed Zimmerman-Traxler-type transition state (**26**), which explained the observed stereochemistry, was postulated.

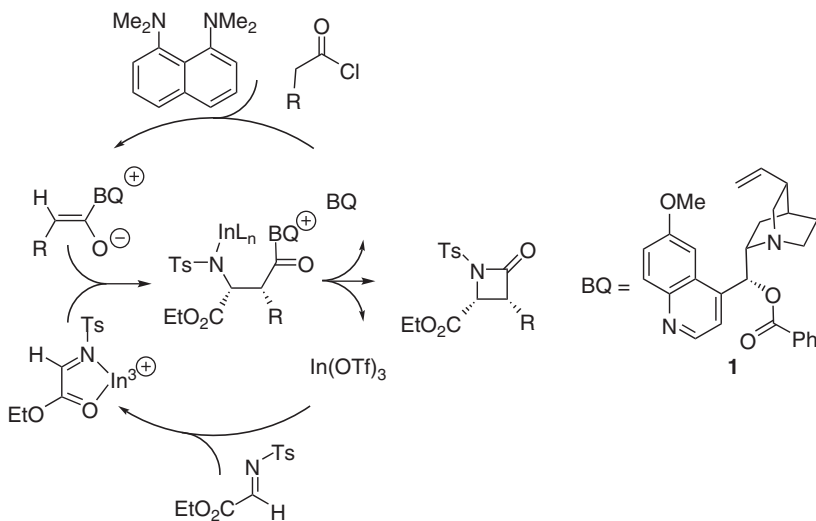


The analogous reaction with imines was studied by Lectka and coworkers and found to give β -lactams with high enantioselectivity, but in low yields. They discovered that the yields of the desired cyclized products obtained from an iminoester and acid chlorides in the presence of a catalytic amount of benzoylquinine (**1**) and a stoichiometric amine were greatly improved when performed in the presence of a Lewis acid, among which $\text{In}(\text{OTf})_3$ proved optimal (Scheme 2.23, see also Section 2.2.2) [5b]. Results from mechanistic studies, comprising kinetic and spectroscopic information, were in agreement with the mechanism shown in Scheme 2.24, where the rate-determining step is either acylation of the chiral amine or ketene formation [5b, 57]. The role of the Lewis acid is to activate

the imine for nucleophilic attack, which results in the suppression of unwanted secondary reactions and thereby increased yields: an increase from 65% to 95% was observed on addition of the Lewis acid when phenacetyl chloride was used as substrate. Under the optimized conditions, high yields and stereoselectivities were observed with a range of acid chlorides.



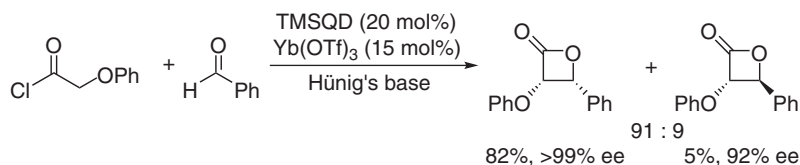
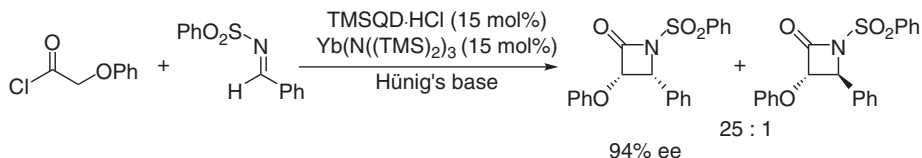
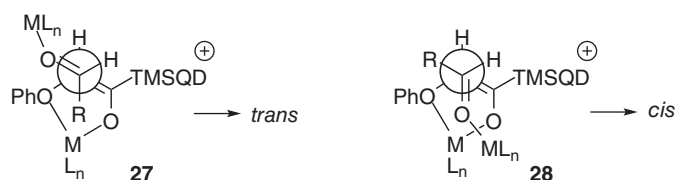
Scheme 2.23 Ketene-imine addition [5b].



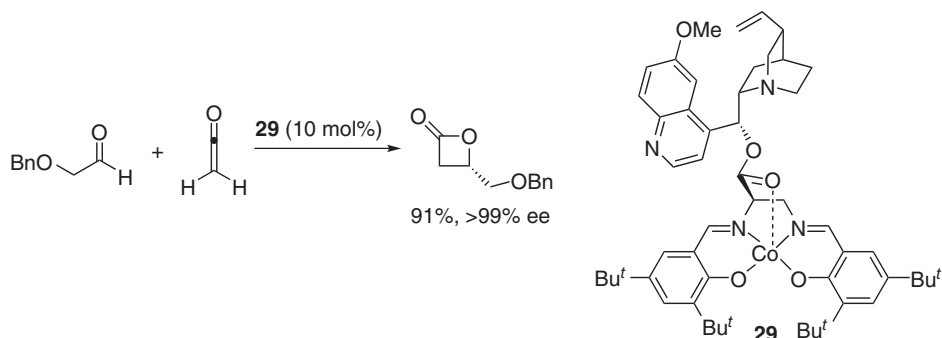
Scheme 2.24 Mechanism of keneten-imine addition [57].

Calter and coworkers [58] found that ketenes generated *in situ* from acid chlorides react with aromatic aldehydes in the presence of a stoichiometric amount of tertiary amine and a cooperative catalytic system consisting of a cinchona alkaloid and a Lewis acid to produce β -lactones with high stereoselectivity (Scheme 2.25). β -Lactams [59] were obtained by reaction of the same ketene precursors and sulfonylimines in the presence of a bifunctional catalyst system consisting of a quinine derivative and a lanthanide-based Lewis acid (Scheme 2.26). In both cases best results were obtained using ytterbium salts.

The two diastereomers of the β -lactones were assumed to originate from reactions passing through different transition states, **27** and **28**, respectively.

Scheme 2.25 Synthesis of β -lactones [58].Scheme 2.26 Synthesis of β -lactams [59].

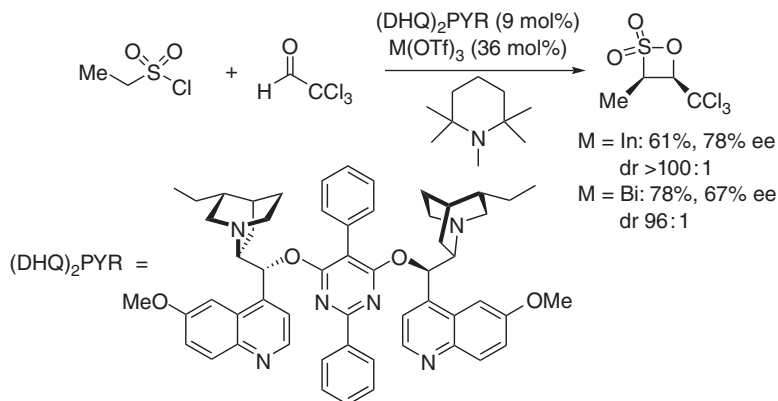
A catalyst incorporating both Lewis acid and Lewis base functions was used by Lin *et al.* [60] for a [2+2] cycloaddition. Complex **29** was prepared as a mixture of two diastereomers (*R* and *S* configurations in the salen part of the ligand) and shown to serve as an excellent catalyst for β -lactone formation from ketene and 3-benzyloxyacetaldehyde (Scheme 2.27). In contrast, use of a cobalt salen complex together with *O*-trimethylsilylquinine (TMSQ) did not provide the lactone.



Scheme 2.27 Lactone formation using bifunctional catalyst [60].

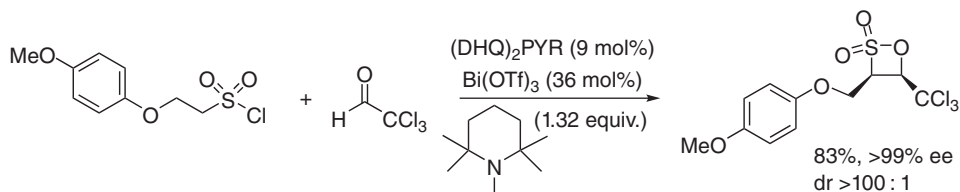
Koch and Peters [61] developed a variation of the processes where they replaced the ketenes with unstable sulfenes (Scheme 2.28). Reaction of trichloroacetaldehyde with a sulfene generated by dehydrochlorination of sulfonyl chloride in the

presence of base and various alkaloid nucleophiles gave the cyclized product in low yields and with low enantioselectivities. The different behavior of ketenes and sulfenes was rationalized considering the different hybridization of the reagents and thereby the structural differences between the reactive intermediates. However, the addition of Lewis acids, particularly $\text{In}(\text{OTf})_3$ and $\text{Bi}(\text{OTf})_3$, gave improved results.



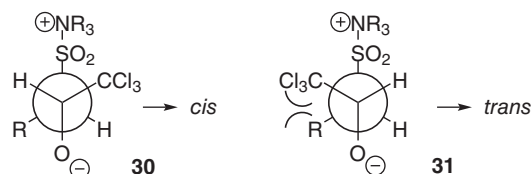
Scheme 2.28 Formation of β -sultones [61].

It was later shown that reactions performed with propanesulfonyl chloride led to improved enantioselectivities, albeit at the expense of yields; with $\text{Bi}(\text{OTf})_3$ as Lewis acid yields could be restored by the use of an excess of the aldehyde, at the same time as the enantioselectivity and diastereoselectivity were improved (Scheme 2.29) [62]. Under optimized conditions, the reaction was extended to other sulfonyl chlorides as well as to ethyl glyoxylate.

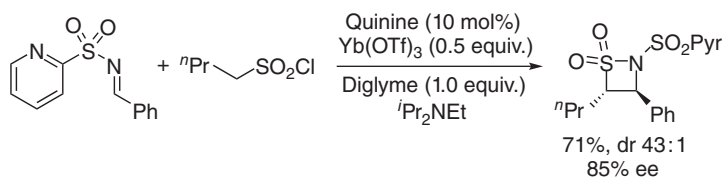


Scheme 2.29 Stereoselective β -sultone synthesis [62].

The preference for the formation of products with *cis* configuration was rationalized by assuming a transition state with an antiperiplanar (**30**) arrangement of the sulfonyl group and the developing alcoholate rather than a transition state with a sterically repulsive *gauche* interaction (**31**) of the substituents on the aldehyde and sulfonyl chloride.



β -Sultams, the nitrogen analogs of β -sultones, were obtained by formal [2+2] cycloadditions of nonnucleophilic imines and sulfonyl chlorides [63]. Whereas the reaction was limited to exceptionally electron-poor *N*-tosyl imines in the presence of Lewis bases, dual Lewis acid–Lewis base activation allowed the scope of the reaction to be extended. Thus, 2-pyridylsulfonyl imines derived from nonactivated aromatic aldehydes reacted to afford the desired sultams in high yields, with high diastereoselectivities, and with good to high enantioselectivities (Scheme 2.30). Among the Lewis acids explored, Yb(OTf)₃ provided the best results. Zwitterionic aminals were suggested to be formed as intermediates, and sulfenes were not involved in the reactions.



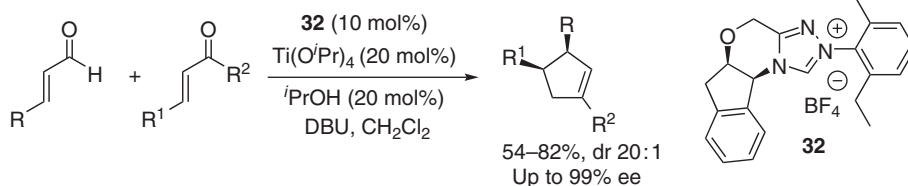
Scheme 2.30 Synthesis of β -sultams [63].

2.7.2

[3+2] Cycloadditions

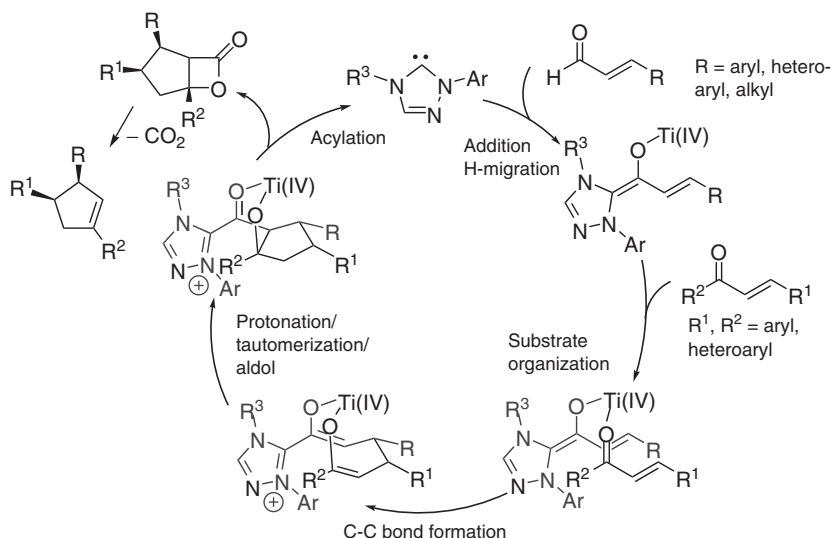
N-Heterocyclic carbenes are potent nucleophiles, which are finding use as Lewis base catalysts. The combination of a carbene and a Lewis acid catalyst is an attractive but challenging task, as *N*-heterocyclic carbenes serve as excellent ligands for transition metals. However, early transition metals bind reversibly, and by proper choice of the catalyst components, dual activation has proven possible [64]. This strategy has, for example, been successfully employed for enantio- and diastereoselective additions of enals to chalcones (annulation of homoenolates) using chiral carbene precursors, for example, **32**, and Lewis acids such as Ti(O*i*Pr)₄ (Scheme 2.31) [65]. Interestingly, the presence of Lewis acid resulted not only in enhanced enantioselectivity, but also in reversed diastereoselectivity, from *trans* to *cis*. The crucial role of the Lewis acid was also demonstrated in reactions with isatin catalyzed by a chiral carbene and LiCl, where sequestering of the lithium cation with a crown ether led to decreased stereoselectivity [66].

A mechanism, as shown in Scheme 2.32, was suggested for the reaction, and later also supported by DFT calculations [4]. The carbene reacts with the α,β -unsaturated aldehyde to generate a homoenolate, which reacts with the



Scheme 2.31 Annulation of homoenolates [65].

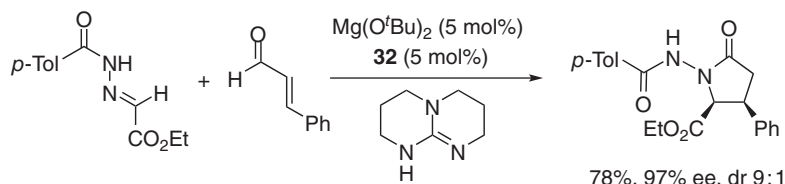
electrophilic ketone. In addition to activating the electrophile for nucleophilic attack, the Lewis acid serves to arrange the reaction components in an ordered transition state.



Scheme 2.32 Mechanism of annulation reaction [65, 66].

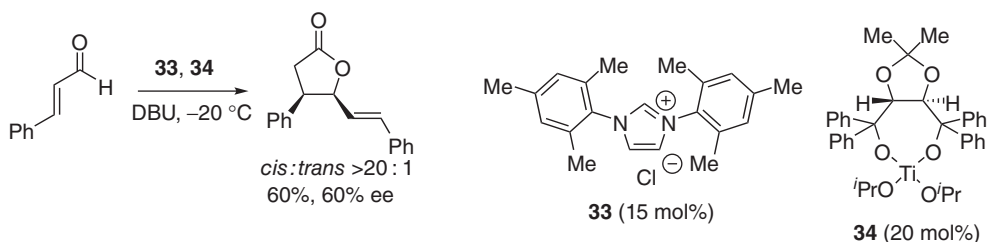
The same carbene catalyst in combination with $\text{Mg}(\text{OtBu})_2$ was also employed for the stereoselective synthesis of γ -lactams from α,β -unsaturated aldehydes and hydrazones (Scheme 2.33) [67]. Several Lewis acidic metal salts were used, but $\text{Mg}(\text{OtBu})_2$ proved to be the superior catalyst. When the reaction was run under the same conditions but without the magnesium salt, merely 31% yield and 90% ee were observed. The mechanism was assumed to proceed via the attack of the carbene on the aldehyde to produce a homoenolate, which combines with the Lewis acid-activated hydrazine.

The crucial role of the Lewis acid in bond formation was also demonstrated by the use of an achiral carbene generated from **33** and a chiral Lewis acid (**34**) in the dimerization of cinnamaldehyde (Scheme 2.34) [65]. The reaction takes place via 1,2-addition of the carbene to one aldehyde molecule followed by addition of the thus generated homoenolate to a Lewis acid-activated aldehyde. Moderate



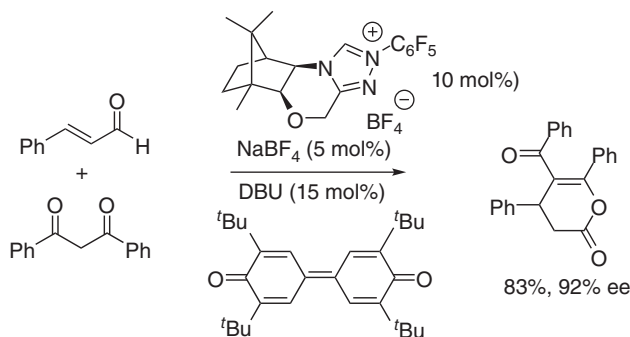
Scheme 2.33 Synthesis of γ -lactams [67].

enantioselectivities were observed, but the reaction served as an elegant proof of the concept.



Scheme 2.34 Enal dimerization using achiral carbene [65].

The presence of a Lewis acid also proved highly beneficial for the enantioselectivity in *N*-heterocyclic carbene-catalyzed Michael additions of 1,3-diketones to α,β -unsaturated aldehydes by redox-type Michael additions (Scheme 2.35) [68]. The role of the Lewis acid in this reaction was, however, unclear.



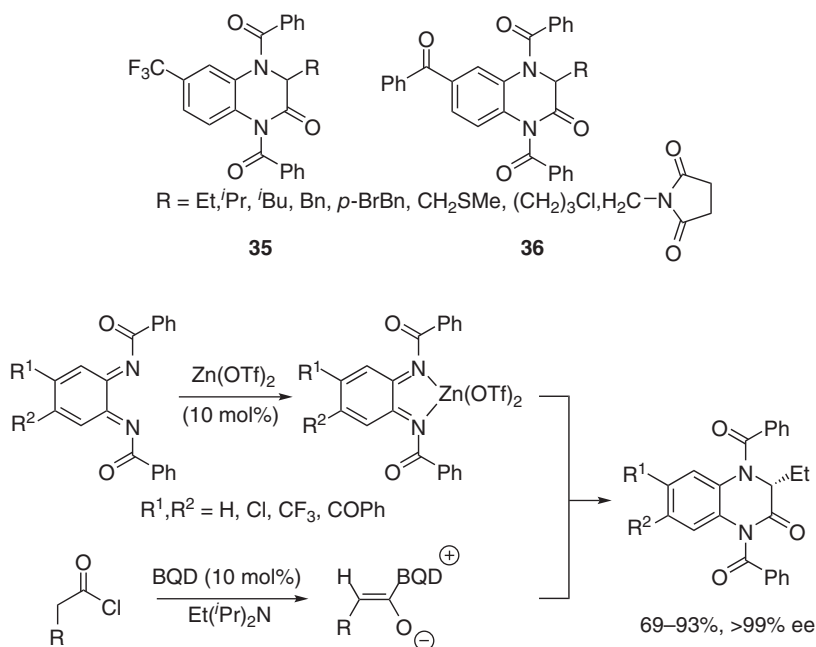
Scheme 2.35 Carbene-catalyzed Michael addition [68].

2.7.3

[4+2] Additions

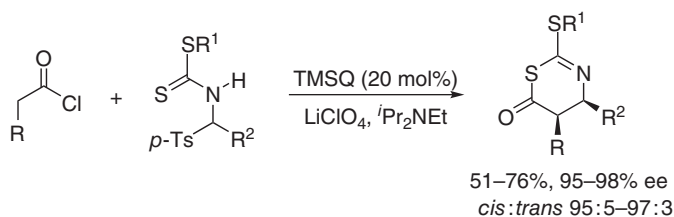
Ketene-derived enolates also serve as viable partners in inverse electron demand Diels–Alder reactions. Thus, *o*-benzoquinone diimides activated by $\text{Zn}(\text{OTf})_2$ react with acid chlorides in the presence of benzoylquinidine (BQD) and a

tertiary amine to give quinoxalinones in good to high yields as single enantiomers (Scheme 2.36) [69]. The reaction exhibits excellent regioselectivity, as shown by the formation of **35** and **36** from unsymmetrical diimides.



Scheme 2.36 Inverse electron demand Diels Alder reaction [69].

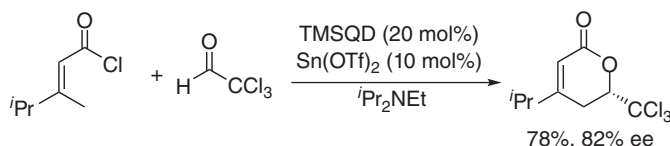
Xu and Nelson [70] were able to overcome problems with imine-enamine tautomerization in [4+2] cycloaddition reactions involving aliphatic imines by using (TMSQ) or (TMSQD) in combination with LiClO_4 as catalyst (Scheme 2.37). *N*-Thioacyl imines were found to be the most suitable electrophiles, which reacted with the enolates derived from ketenes, which were *in situ*-generated from acid chlorides.



Scheme 2.37 Cycloaddition of ketene and *N*-thioacyl imines [70].

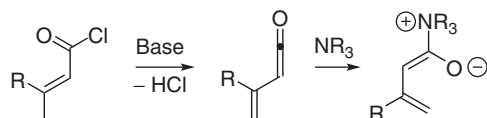
Tiseni and Peters [71] explored cycloadditions of zwitterionic ammonium dienolates with trichloromethylacetaldehyde to produce δ -lactones, which

are synthetically highly versatile building blocks (Scheme 2.38). The diene components were obtained by addition of trimethylsilylquinidine (TMSQD) to vinylketenes, generated by dehydrohalogenation of α,β -unsaturated acid chlorides. Good enantioselectivities were observed, but the yields were not acceptable as a result of incomplete conversion of the acid chloride. In the presence of metal triflates, dehydrohalogenation was facilitated, and with $\text{Sn}(\text{OTf})_2$ as Lewis acid, yields up to 80% were obtained. The Lewis acid did not seem to be involved in the cycloaddition step, as judged by the observation that the product was obtained with the same enantiomeric excess regardless of which metal triflate was used. With TMSQD as the tertiary amine, products with *S* absolute configuration were obtained.



Scheme 2.38 Lactones from unsaturated acid chloride [71].

The scope of the reaction was later extended to involve a range of aromatic and heteroaromatic aldehydes by the use of a complex formed from $\text{Er}(\text{OTf})_3$ and a norephedrine-derived ligand. Mechanistic studies confirmed that a zwitterionic dienolate was an intermediate in the reaction (Scheme 2.39), in which the Lewis acid is assumed to be involved in the formal, thus cycloaddition explaining the enhanced enantioselectivities (88–98% ee).



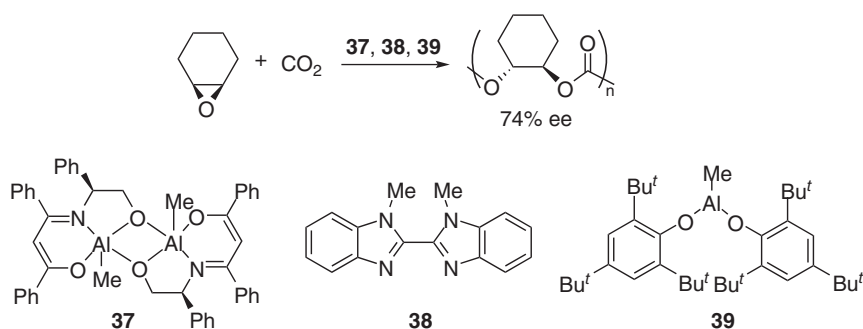
Scheme 2.39 Formation of intermediate dienolate [71].

2.8

Polymerizations

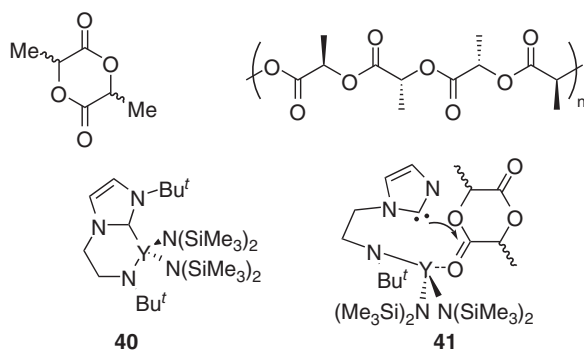
Catalysts composed of a combination of Lewis acids and Lewis bases have in recent years also been used for polymerization reactions (for more details see also Chapter 13). Alternating copolymerization of epoxides and CO_2 has been extensively explored [72]. Under suitable conditions, polymerization can be achieved without the formation of monomeric carbonates (see Section 2.6). Recent examples include the use of catalysts based on aluminum, such as **37**, in combination with nitrogen Lewis base activator **38** and epoxide activator

39 (Scheme 2.40) [73] and bifunctional chromium(III) and cobalt(III) salen complexes [74].



Scheme 2.40 Copolymerization of CO_2 and cyclohexene oxide [73].

Ring-opening polymerization of lactones and polar olefins has been demonstrated employing catalytic systems combining Al, In, and Zn Lewis acids with Lewis bases such as amines, phosphines, and carbenes [75]. In an early example, Arnold and coworkers successfully used yttrium(III) and titanium(IV) compounds tethered to *N*-heterocyclic carbenes (**40**) for polymerization of *rac*-lactide (Scheme 2.41) [76]. The mechanism was suggested to involve nucleophilic attack of the Lewis basic carbene on the Lewis acid-activated monomer (**41**).



Scheme 2.41 Ring-opening polymerization of *rac*-lactide [76].

2.9

Conclusions and Outlook

Recent years have witnessed an impressive development in the field of asymmetric catalysis. The combined use of Lewis acids and Lewis bases for simultaneous activation of electrophiles and nucleophiles has proven to be a synthetically highly

versatile concept. Such catalytic systems frequently lead not only to increased reaction rates, but also to increased selectivities as a result of organized transition states. As illustrated by the examples described in this chapter, severe problems such as incompatibility of catalyst components and catalyst quenching can be overcome by careful catalyst design. It is expected that future efforts will lead to even more efficient catalytic systems, whereby multicomponent activation and sequential reactions can be achieved.

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3

Cooperating Ligands in Catalysis

Mónica Trincado and Hansjörg Grützmacher

3.1

Introduction

A *cooperating ligand* in a metal complex can be defined as one that actively participates in the substrate activation. The chemical structure of the ligand can remain intact during the catalytic process (substrate activation via hydrogen bonding) or undergo a reversible transformation (protonation/deprotonation, reorganization of π system, or electron transfer to/from the metal). The concept of metal–ligand cooperativity requires that the metal and the ligand collaborate in a synergistic manner to facilitate a chemical process.

Relevant examples that demonstrate cooperative ligands in catalysis have been selected and are described in this chapter. These include catalytic hydrogen activation, hydrogen transfer processes, catalytic methodologies for dihydrogen formation from a proton source, and environmentally and energy-efficient oxidation methods of hydrocarbons. Outstanding examples are provided by biology, where these processes are catalyzed by a number of metalloenzymes. Significant advances in the knowledge of the structure of the active centers in metalloenzymes and mechanistic information have stimulated the design of “bioinspired” or “biomimetic” synthetic catalysts that reproduce only key components of the natural catalyst. Therefore, select metalloenzymes in which the coordination environment of the metal plays an active role in the chemical transformation are likewise briefly discussed.

3.2

Chemically Active Ligands Assisting a Metal-Localized Catalytic Reaction

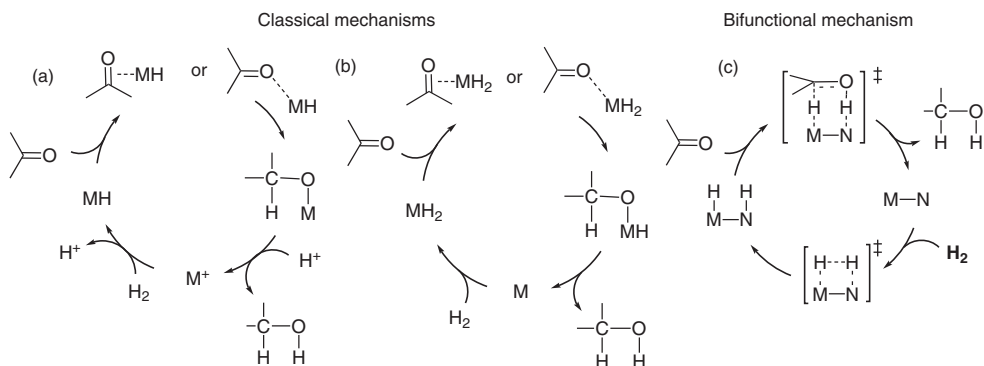
3.2.1

Cooperating Ligands with a Pendant Basic Site

Catalytic reactions promoted by a metal complex with a ligand that contains a cooperative basic site have been studied intensively in the past years [1].

3.2.1.1 Functional Sites Located in the First Coordination Sphere of a Metal Complex

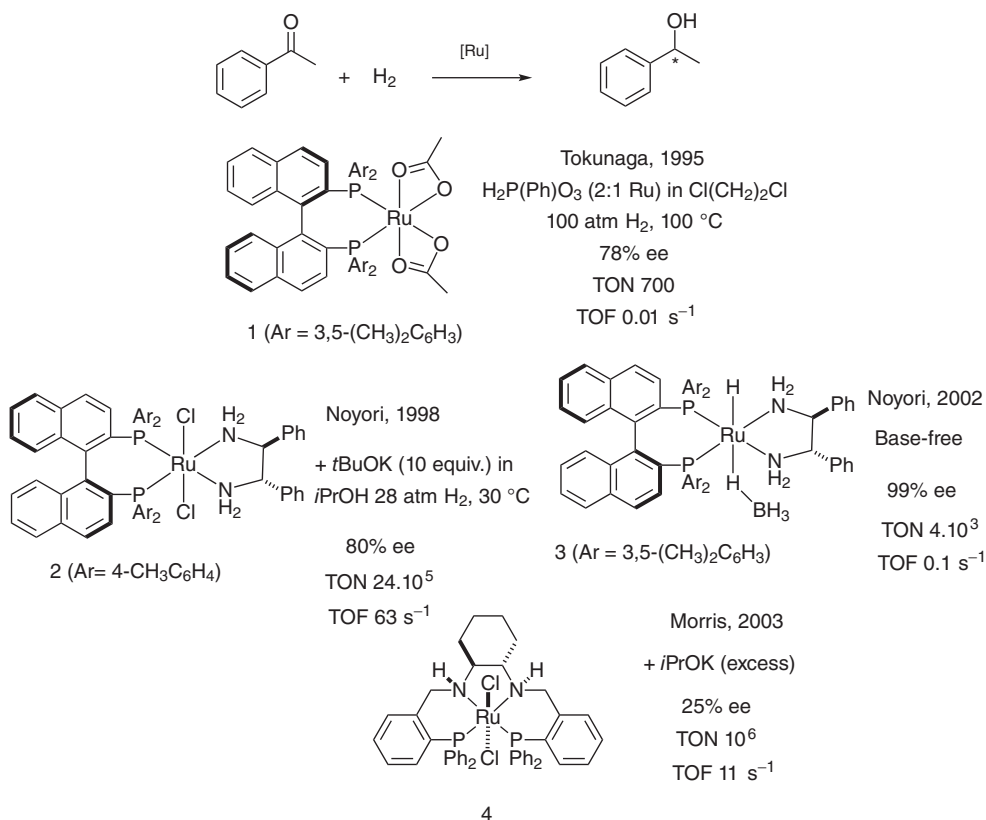
[M]-NH Catalysis When an amino group interacts with a metal center, the NH group increases significantly its acidity and becomes a $\text{H}^{\delta+}$ donor for hydrogen bonding. On the basis of this property, Noyori *et al.* discovered in the mid-1990s a new selective catalytic hydrogenation of aldehydes and ketones by using a combination of a Ru–phosphine complex fragment and an ethylenediamine ligand [2]. This is one of the most impressive examples of metal complexes in which the cooperative effect of an acidic NH function adjacent to the metal center is essential. Excellent reviews covering the diverse aspects on M–NH cooperativity have been given by Noyori and Hashiguchi [3], Bäckvall [4], Muñiz [5], Ikariya [6] and more recently, Ding *et al.* [7]. Many molecular hydrido metal complexes, often phosphane Rh species, can hydrogenate catalytically ketones via the *classical* pathways (a) or (b) in Scheme 3.1 [8]. In pathway (a), the carbonyl substrate molecule interacts in an σ or π manner with the metal hydride, followed by insertion into the M–H bond leading to a metal alkoxide intermediate. Hydrogenolysis or protonolysis of the M–O bond gives an alcohol as product. In the closely related pathway (b), an alkoxy hydrido metal complex is formed, which undergoes reductive elimination to the alcohol. In both pathways (a) and (b), the ability of an electrophilic metal center to form a π complex with the C=O group enhances the hydrogenation rate.



Scheme 3.1 Classical and nonclassical *bifunctional* mechanisms for catalytic ketone hydrogenation.

Diphosphane–Ru(II) complexes were hardly active for the hydrogenation of simple ketones and, in an early attempt, Tokunaga and Noyori achieved turnover numbers (TONs = number of product molecules per catalyst) of up to 700. Moderate enantioselectivities in the hydrogenation of acetophenone were achieved with a catalytic system containing a BINAP–Ru(II) complex (**1**) and phenyl phosphonic acid. It was proposed that the phosphonic acid activates the precatalyst by forming a hydrido Ru phosphonate which cooperatively activates the ketone substrate (Scheme 3.2) [3b]. The breakthrough came with the

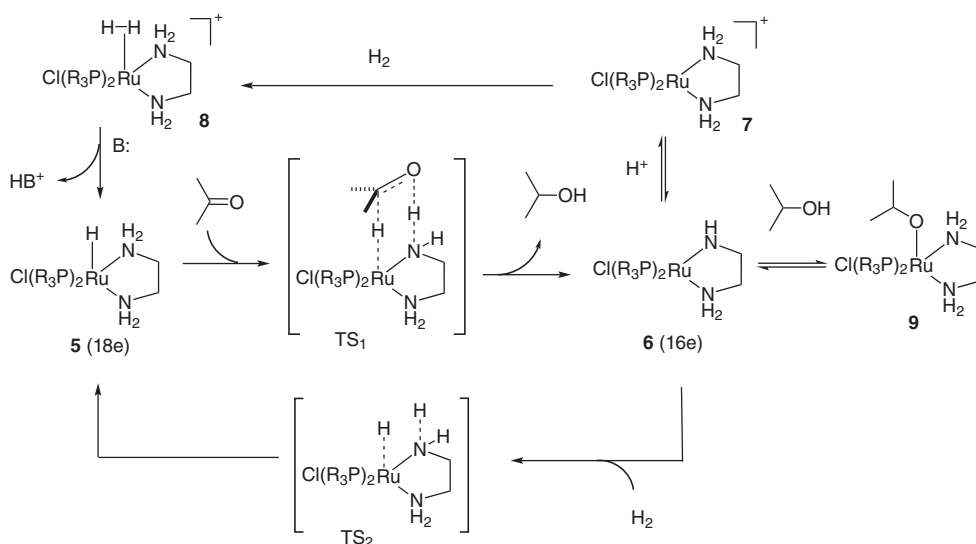
introduction of an acidic NH group directly coordinated with the Ru center. On one hand, the coordinated R_2NH group binds to the carbonyl oxygen and fixes the substrate molecule along the Ru–N bond in the second coordination sphere of the complex (Scheme 3.1c). On the other hand, it becomes deprotonated in the transfer-hydrogenation step whereby a Ru amide, $[Ru]-NR_2$, is generated. This in turn cleaves H_2 heterolytically, and the famous “bifunctional” transfer hydrogenation (TH) cycle is turned over.



Scheme 3.2 $Ru(phosphine)_2$ and $Ru(phosphine)_2$ -amine catalysts as examples for the asymmetric hydrogenation of acetophenone.

Catalytic activity of up to $TON = 24 \times 10^5$ is obtained using the complex (*S,S,S*)-**2** and base ($KOtBu$ or KOH) to generate *in situ* the Ru amide complex as active species. The stereoselectivity can be easily controlled by the electronic and steric properties of the chiral ligands [9]. For base-sensitive substrates, the hydride complex (*S,S,S*)-**3**, which does not require activation by base, gives improved selectivity under neutral conditions [10]. The Morris catalyst (*S,S*)-**4**, with a tetradentate PNNP ligand, needs activation by the addition of base but shows excellent catalytic activity, albeit with low enantioselectivity (Scheme 3.2).

For all catalysts, the outer-sphere bifunctional mechanism (c) shown in Scheme 3.1 and in detail in Scheme 3.3 is proposed. The phosphine ligands can be replaced by an arene moiety, leading to the Noyori–Ikariya Ru(II) half-sandwich complexes that are highly active in two processes: the (asymmetric) hydrogenation, and TH (transfer hydrogenation) of C=O and C=N bonds. Since its discovery, multiple modifications of this catalytic system have been performed to increase the substrate scope and selectivity. The use of these catalysts in total syntheses, in aqueous media, immobilization on solid supports, or incorporation in biomimetic and dendrimeric systems has been reported [11].

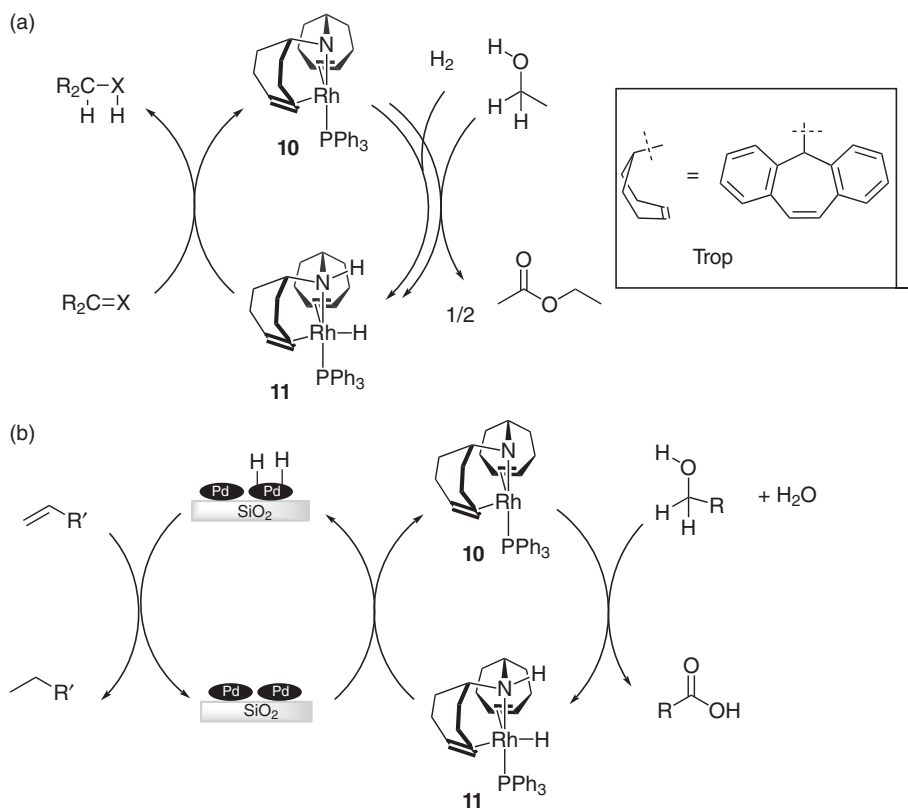


Scheme 3.3 Metal–ligand cooperativity (bifunctional mechanism) in the hydrogenation of ketones catalyzed by a diphosphine/diamine–Ru complex.

Scheme 3.3 highlights the metal–ligand cooperativity in the mechanism for the hydrogenation of ketones by amine–Ru complexes, which has been proven experimentally [12] and theoretically. Although several diastereomers are possible, the hydride and two nitrogen atoms must have a *fac* position in the octahedral structure of the 18-electron ruthenium diamino hydride **5**, which reacts with a ketone. The nucleophilic hydride ligand at the ruthenium center interacts with electrophilic carbon of the C=O group, while the NH moiety binds the oxygen center via a hydrogen bond. Through a six-membered pericyclic transition state TS₁, an alcohol molecule and the 16-electron amino amido complex [RuCl(PR₃)₂(HN∩NH₂)] **6** are obtained. Under the reaction conditions, this complex is in equilibrium with an 18-electron Ru(II) alkoxide complex [RuCl(OR)(PR₃)₂(H₂N∩NH₂)] (**9**) and a cationic 16-electron diamino complex [RuCl(PR₃)₂(H₂N∩NH₂)]⁺ (**7**). The high polarity of the H^{δ−}–Ru^{δ+}–N^{δ−}–H^{δ+} unit matches perfectly the C^{δ+}–O^{δ−} carbonyl dipole and explains the high selectivity

in the hydrogenation of polar $C=X$ bonds versus apolar $C=C$ bonds. Hydrogen activation is believed to occur via the cationic complex $[RuCl(PR_3)_2(H_2N\cap NH_2)]^+$ (7), which binds H_2 in a σ complex and reacts with base B to regenerate the hydride $[RuCl(H)(PR_3)_2(H_2N\cap NH_2)]$ (5). Alternatively, under base-free conditions, the H_2 molecule is cleaved heterolytically across the dipolar $Ru^{\delta+}-N^{\delta-}$ bond in the 16e complex 6 [13] via the transition state TS_2 [14]. Because the efficiency of the reaction is dependent on the hydrogen pressure, H_2 cleavage is considered to be the rate-limiting step, with calculated activation barriers of $33\text{--}42\text{ kJ mol}^{-1}$.

A related mechanism has been proposed for the tetracoordinated rhodium(I) amido complex $[Rh(trop_2N)(PR_3)]$ (10) with a butterfly-type structure as depicted in Scheme 3.4. The heterolytic cleavage of H_2 across the $Rh-N$ single bond and the formation of the Rh(I) amino hydride complex $[Rh(H)(trop_2NH)(PR_3)]$ (11) is exothermic ($\Delta_R H = -276.7\text{ kJ mol}^{-1}$) and occurs rapidly at -78°C . The alternative reaction mode, in which H_2 coordinates in a nonclassical way to the

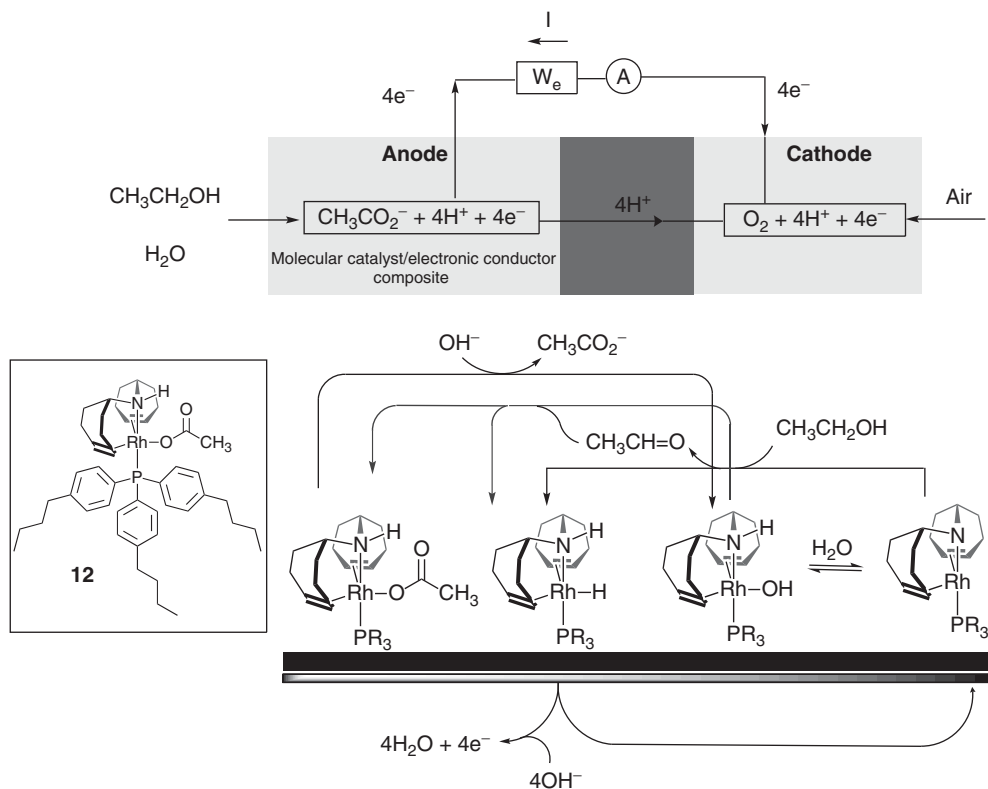


Scheme 3.4 (a) Rh–N cooperativity in hydrogenations and transfer hydrogenations using EtOH as hydrogen donor. (b) Dehydrogenative coupling of alcohols and water to carboxylic acid salts using $Pd@SiO_2$ as heterogeneous hydrogen acceptor.

metal center and subsequently adds oxidatively to give a $[\text{Rh(III)}(\text{H})_2]$ species, is thermodynamically disfavored ($\Delta_R H = 72.0 \text{ kJ mol}^{-1}$). The efficiency of the heterolytic cleavage can be explained by a favorable interaction between the highest occupied molecular orbital (HOMO) of the rhodium(I) amide, which corresponds to the antibonding combination of the lone pair at the nitrogen atom, the filled d_{xz} orbital at the metal center, and the σ^* orbital of the H_2 molecule. Reminiscent of the bifunctional mechanism (Scheme 3.3), a carbonyl substrate (or activated olefin with a polarized $\text{C}^{\delta+}=\text{C}^{\delta-}$ bond) can bind to the $\text{NH}^{\delta+}-\text{RuH}^{\delta-}$ unit of the rhodium(I)–amine complex **11**, whereby its hydrogenation occurs in the second coordination sphere. In a similar manner, an alcohol molecule interacts with the rhodium amide and transfers hydrogen from the $\text{H}^{\delta+}-\text{O}-\text{C}-\text{H}^{\delta-}$ unit to give the amino hydride complex (**11**) [15]. Furthermore, complexes **10** and **11** are excellent catalysts (TOFs up to 10^6 ; TONs $> 5 \times 10^6$) turn over frequency (TOF); in the dehydrogenative coupling (DHC) of primary alcohols to esters. Likewise, primary alcohols are coupled with water or amines in the presence of a sacrificial acceptor to the corresponding carboxylic acid derivatives according to $\text{R}-\text{CH}_2-\text{OH} + \text{HX} + 2 \text{ A} \rightarrow \text{RCO}(\text{X}) + 2 \text{ AH}_2$ with $\text{X} = \text{OH}$, NHR and $\text{A} = \text{cyclohexanone}$ or $\text{methylmethacrylate}$ [16]. These transfer DHC reactions proceed remarkably well with alcohols derived from biomass such as sugars and can be performed in aqueous media [17]. Moreover, a domino catalytic system was introduced in which the rhodium amide **10** serves as the homogeneous catalyst for the dehydrogenation of alcohols and heterogeneously suspended Pd particles serve as H_2 acceptors and as catalysts for the hydrogenation of a range of inactivated olefins (Scheme 3.4) [18].

The amine complexes $[\text{Rh}(\text{OTf})(\text{trop}_2\text{NH})(\text{PR}_3)]$ Trifluoromethanesulfonate (OTf) were used as electrocatalysts on a conducting support material in direct alcohol fuel cells (DAFCs) (Scheme 3.5) [17, 19]. In particular, the complex $[\text{Rh}(\text{trop}_2\text{NH})\{\text{P}(4\text{-}i\text{BuPh})_3\}][\text{OAc}]$ (**12**) deposited on Ketjenblack EC-600JD (Ck) worked as an excellent anode catalyst in a DAFC for the oxidation of ethanol affording up to 45% conversion and remained active in three consecutive galvanometric cycles with catalyst loading as low as 0.1 mg cm^{-2} . This example represents the highest specific activity ($10\,000 \text{ A g Rh}^{-1}$) achieved in a half-cell for ethanol electrooxidation to date. The developed organometallic fuel cells (OMFCs) delivered up to 30 mW cm^{-2} at 60°C in an active cell, which used a Fe/Co/C cathode exposed to air. Various spectroscopic methods strongly indicate that indeed the molecular Rh complexes showing metal–ligand cooperativity are the active sites in this process which converts alcohols and water selectively into carboxylic acid derivatives producing no further waste apart from electric current as a product.

A breakthrough in the asymmetric TH with complexes containing earth-abundant elements was achieved recently. The chiral iron complex **13** carrying an unsaturated amine(imine)diphosphine ligand ($\text{P}-\text{NH}-\text{N}-\text{P}$) catalyzes the asymmetric reduction of ketones and imines to alcohols and amines [20]. Under basic conditions with $i\text{PrOH}$ as the hydrogen donor, the process achieved impressive enzyme-like reaction rates of 200 s^{-1} at room temperature (at 50%

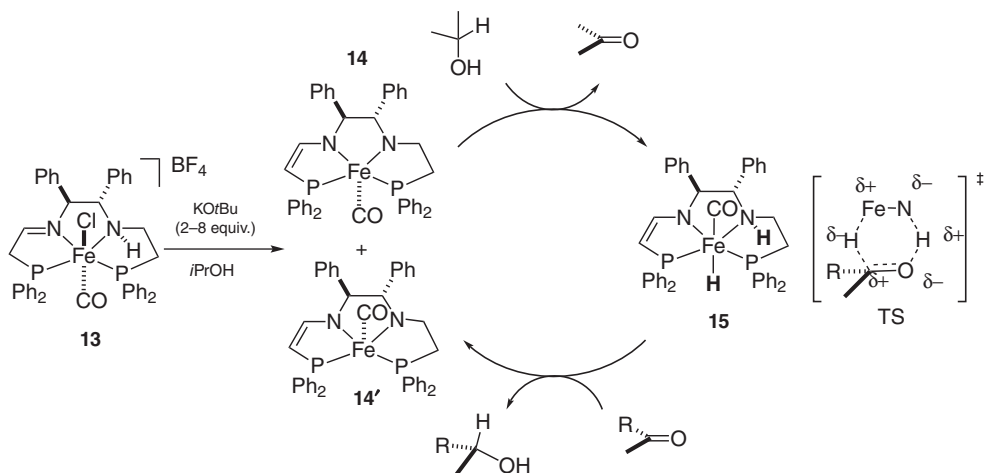


Scheme 3.5 Experimentally proven reaction steps performed by individual molecular complexes embedded in a conducting support material in the electrocatalytic oxidation of ethanol/water to acetate.

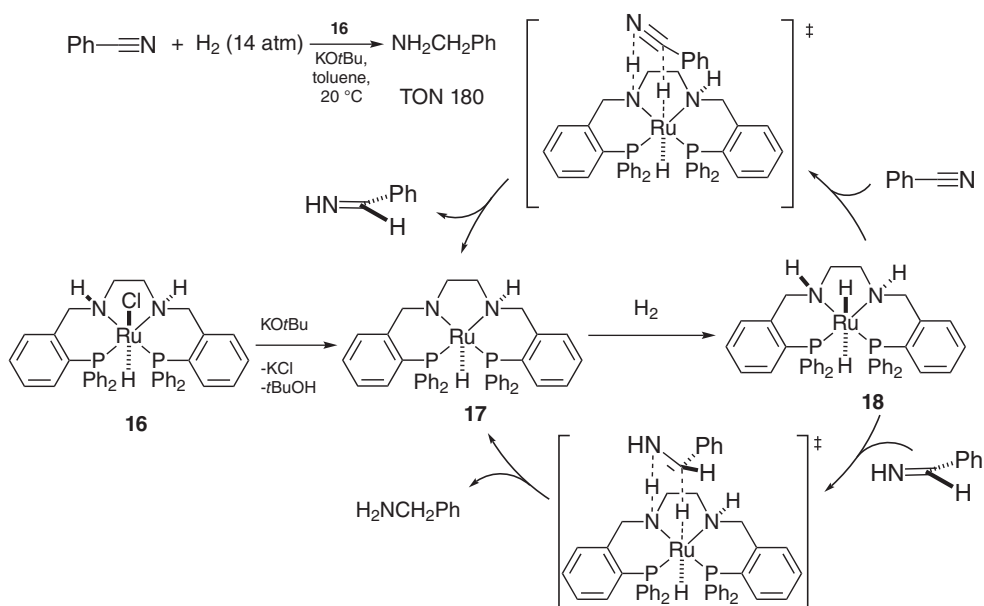
conversion), which exceeds those reported for Ru catalysts. The formation of a neutral amido-(ene-amido) iron(II) complex as well as Fe–N cooperativity is proposed in the catalytic cycle (Scheme 3.6).

With the fully saturated bis(amino)diphosphine PNNP ligand, the corresponding Ru complex **16** hydrogenates benzonitrile to benzylamine under mild conditions. Mechanistic studies support an outer-sphere pathway for the nitrile reduction. The hydrido amido Ru complex **17**, which is generated *in situ* by the reaction of the diamine complex **16** with base, splits dihydrogen heterolytically to form a bishydride complex **18**. Subsequently, the latter species transfers a hydride from the ruthenium center and a proton from the NH unit to the nitrile via a six-membered cyclic transition state (Scheme 3.7) [21].

Aliphatic pincer metal complexes and their (hetero)aromatic counterparts [22] have rapidly emerged as highly versatile catalysts for many organic reactions. Pincer ligands are generally tridentate chelate ligands that occupy a meridional (*mer*) face in an octahedron and are commonly labeled according to the donor atoms such as PNP (2,6-bis-(di-*tert*-butylphosphinomethyl)pyridine) or NNP,



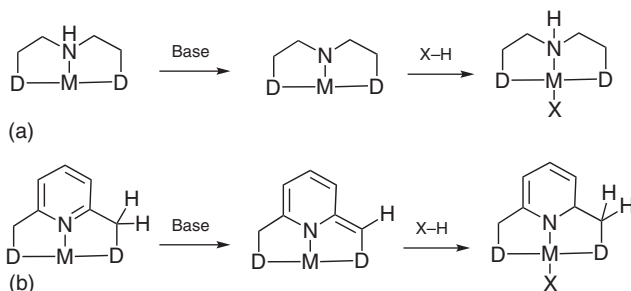
Scheme 3.6 Catalyzed asymmetric transfer hydrogenation of ketones promoted by an Fe amine(imine)diphosphine complex.



Scheme 3.7 Key steps in the Ru(PNNP)-catalyzed hydrogenation of benzonitrile to benzylamine.

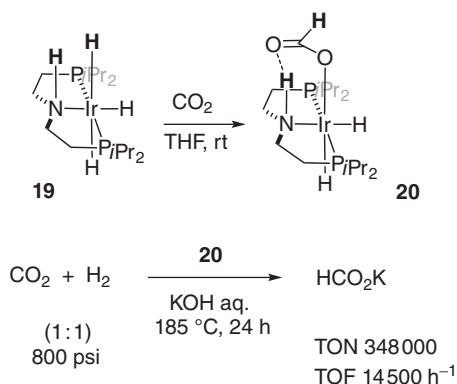
and others (see examples in the following schemes). Frequently, the ligand backbone is chemically “non-innocent” – that is, it participates in the activation of substrate bonds and is hence cooperative – which provided new approaches especially in catalytic reactions that are thought to be “green.” Again, metal amide/metal amine interconversions in aliphatic DND (D = donor atom, see

Scheme 3.8a) as well as in heteroaromatic pincer ligands (Scheme 3.8b and next section) are key steps in the cooperativity between metals and these types of ligands, which has proven to facilitate heterolytic bond cleavage reactions [23].



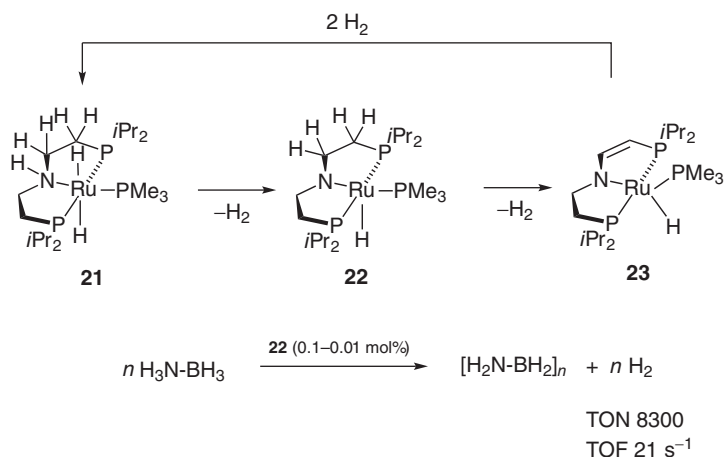
Scheme 3.8 Bifunctional activation modes with pincer metal complexes containing aliphatic (a) or heteroaromatic (b) pincer ligands (D=donor center in a phosphine, amine, carbene moiety).

The concept of metal–ligand cooperativity can be favorably used for the conversion of carbon dioxide (CO_2), a notoriously inert molecule that is rather reluctant to react directly with transition-metal complexes. Crabtree, Hazari, and others developed a simple model for predicting the feasibility of a CO_2 insertion into the Ir–H bond in pincer Ir(III) hydride complexes that is thermodynamically uphill by 11.6 kJ mol^{-1} . However, assistance by hydrogen bonding from a protic coordinated amine allows the formation of a six-membered metallacycle that provides about 30 kJ mol^{-1} of stabilization. The Ir(III)(PNP) pincer complex **20** is one of the most active water-soluble catalysts reported to date for the CO_2 hydrogenation to formate (Scheme 3.9) [24].



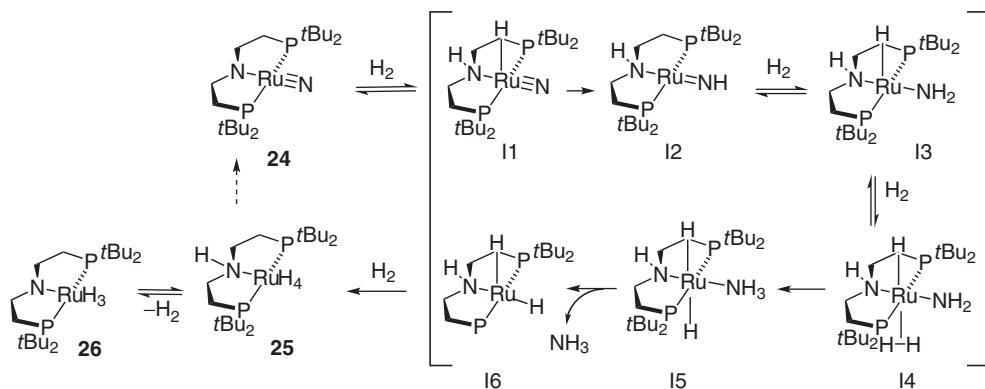
Scheme 3.9 Hydrogenation of CO_2 promoted by a Ir(III)(PNP) hydride complex showing metal–ligand cooperativity and CO_2 binding in the second coordination sphere.

Likewise, amido PNP pincer ruthenium complexes with the nitrogen center in an sp^3 valence electron configuration are capable of heterolytically cleaving H_2 . Schneider *et al.* described a bifunctional catalyst and demonstrated a new mode of ligand–metal cooperation with an unsaturated PNP pincer ligand. The amido complex **23** activates rapidly 2 equiv of H_2 across the $N^{\delta-}-Ru^{\delta+}$ and the enamidic $C=C$ bond forming the hydrido complex **21**, demonstrating the twofold cooperativity of the pincer ligand. These processes are reversible, and H_2 is released stepwise forming **22** and **23** (Scheme 3.10). The amido complex **22** was used for the partial dehydrogenation of ammonia borane, leading to the formation of an insoluble polymeric material with hydrogen release rates of up to $TOF = 21\ s^{-1}$ [25].



Scheme 3.10 Hydrogen activation by a cooperative enamide PNP-pincer metal complex and catalyzed dehydrogenation of ammonia borane (AB).

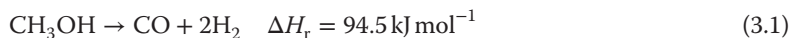
The remarkable hydrogenation of a terminal nitrido ligand to ammonia – a kind of “knightly quest” in chemistry – was successfully achieved with the help of metal–ligand cooperativity (Scheme 3.11). A ruthenium(IV) nitride complex (**24**) with a $PN(sp^3)P$ pincer ligand forms stoichiometrically ammonia (NH_3) [26]. Spectroscopic analysis and DFT calculations helped to elucidate a minimum-energy reaction pathway (MERP). In the first step, H_2 is cleaved across the Ru –amido bond because the amido group is a stronger π donor and significantly weakens the π -donating nitrido center. Subsequently, a rearrangement to an amino–imido complex (**12**) is proposed, which again activates H_2 across the $Ru=NH$ bond to give a parent amido $Ru-NH_2$ complex (**13**). This species finally activates heterolytically a third equivalent of H_2 to give the ammonia complex (**15**). The tetrahydride complex **25** was spectroscopically characterized as the final metal-containing product. Also, a small equilibrium concentration of a trihydride amido complex **26** was detected.



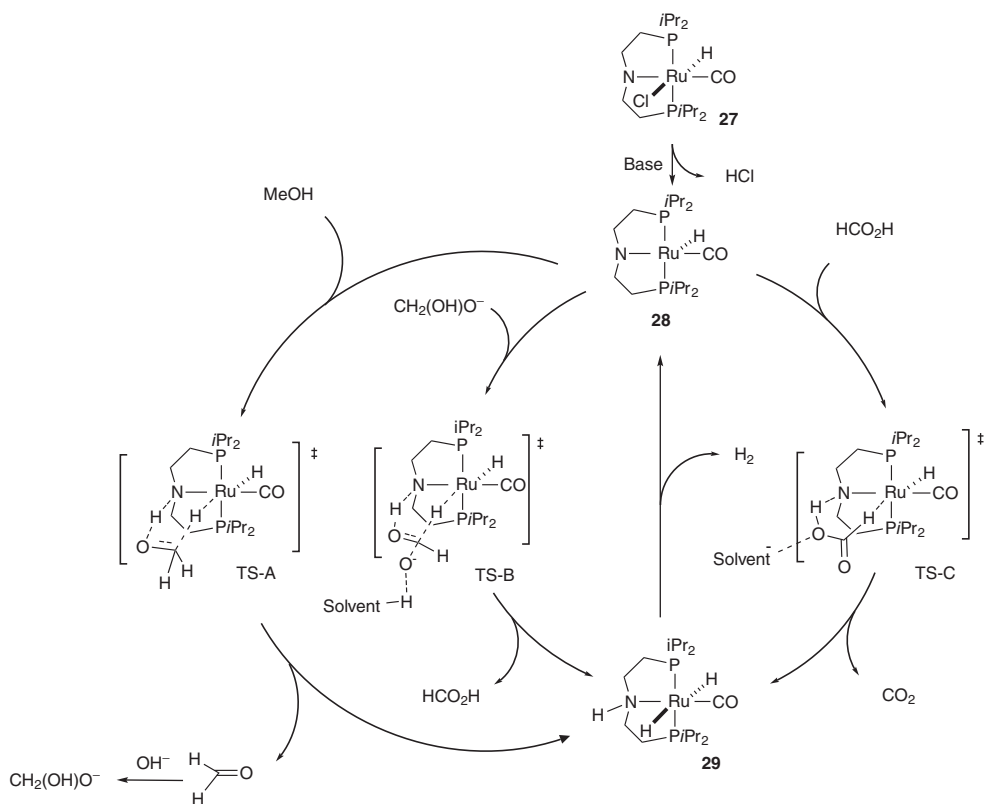
Scheme 3.11 Stoichiometric synthesis of ammonia from the metal nitrido complex **24** and H_2 .

This work beautifully exemplifies the potential of metal–ligand cooperativity (here with amido and imido ligands) in a highly challenging transformation, the synthesis of NH_3 from N_2/H_2 . Pincer ligands served once more as key components to tune the thermodynamics and kinetics of hydrogen activation. If the polyhydridic complex can be reconverted into the terminal nitride complex, a catalytic reaction for the hydrogenation of N_2 to ammonia with a single-site catalyst can be envisioned. Desirable would be the efficient use of ammonia in fuel cells according to: $2\text{NH}_3 \rightarrow \text{N}_2 + 6\text{H}^+ + 6\text{e}^-$. To date, the decomposition of ammonia is governed exclusively by heterogeneous catalysts [27]. The development of molecular catalysts with cooperative metal–ligand systems deserves further studies.

Methanol is a promising fuel because it does not interfere with the food chain, is liquid under ambient conditions, and has a high content of hydrogen (12 wt%) [28]. The development of efficient processes for releasing hydrogen from methanol or for the direct conversion in electrical energy (in a direct methanol fuel cell, DMFC) is essential. The sequential conversion of methanol to formaldehyde and its decarbonylation to carbon monoxide (Eq. 3.1) is an endothermic process (94.5 kJ mol^{-1}), which is compensated by the combustion of the hydrogen content of about 12.5 wt% H_2 . This makes the overall reaction endothermic by $\Delta E_{\text{F}} = -389.5 \text{ kJ mol}^{-1}$. However, the formation of CO is a principal problem when a metal-catalyzed process is envisioned because catalyst deactivation may occur. Instead of dehydrogenating formaldehyde ($\text{H}_2\text{C}=\text{O}$) to CO, hydration of CH_2O to give $\text{H}_2\text{C}(\text{OH})_2$ and subsequent dehydrogenation to formic acid (HCOOH) according to Eq. (3.2) is a possible solution to this problem. Formic acid is by itself an interesting hydrogen source, provided it can be efficiently decomposed by a (molecular) catalyst to CO_2 and H_2 (Eq. 3.3).

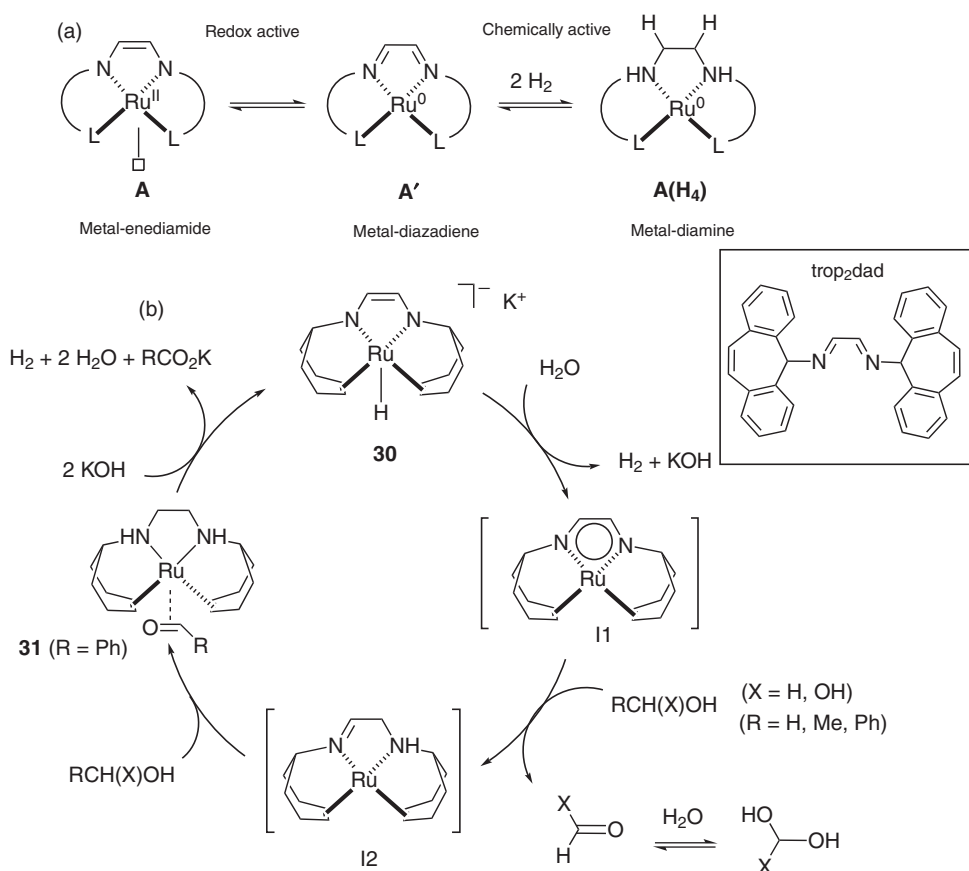


The first examples of well-defined molecular complexes as catalysts for the efficient dehydrogenation of aqueous methanol have been reported recently [29]. In both approaches, the metal center is supported by a cooperative ligand, and the reactions proceed under atmospheric pressure and temperatures below 100 °C. The catalytic cycle for methanol dehydrogenation promoted by the pincer complex $[\text{RuClH}(\text{HPNP}^{\text{iPr}})(\text{CO})]$ (**27**) (HPNP^{iPr} = bis-(2-diisopropylphosphinoethyl)amine) is shown in Scheme 3.12 [30]. Addition of base is essential to remove HCl from the precatalyst **27** and generate the bifunctional $[\text{Ru}(\text{II})\text{PNP}]$ amido complex **28** as active species. An activation of a methanol molecule is proposed through the binding of the acidic OH group to the amide function of the catalyst and the (weakly) hydridic α -CH group to the Ru center. A hydrogen molecule is transferred to and released from the complex, and formaldehyde ($\text{H}_2\text{C}=\text{O}$) is obtained as transient intermediate, which under aqueous alkaline conditions is further converted to $\text{H}_2\text{C}(\text{OH})\text{O}^-$. The aldehyde hydrate loses a second molecule of hydrogen to give formate (HCO_2^-). Finally, formate is decomposed to CO_2 and a third equivalent H_2 under regeneration of the active form of the catalyst. Alkaline conditions are necessary to ensure



Scheme 3.12 Beller's catalyst for the dehydrogenation of MeOH to CO_2 and H_2 .

Metal complexes with a 1,4-diazadiene ligand (dad) are classical examples for species possessing redox “non-innocent” ligands that can act as an electron reservoir (see Section 3.3) [33]. The catalyst $[\text{K}(\text{dme})_2][\text{Ru}(\text{H})(\text{trop}_2\text{dad})]$ dimethoxyethane (dme) (**30**) contains the redox and chemically non-innocent diolefin diazadiene ligand trop_2dad which participates actively in alcohol dehydrogenation (Scheme 3.13) [29a]. Diazadiene ligands also behave as chemically “non-innocent” ligands [34], accepting up to 2 equiv of H_2 , forming the fully hydrogenated species $\text{A}(\text{H}_4)$. This dual metal–ligand cooperativity is illustrated



Scheme 3.13 (a) A redox- and chemically active ruthenium–diazadiene complex. (b) [Ru(trdp₂dad)] as catalyst for the dehydrogenation of MeOH to CO₂ and H₂ and of higher alcohols to carboxylates.

in simplified form by the structures **A** and **A'** (Scheme 3.13) (either resonance forms or distinctive electronic states) and the fully hydrogenated complex **A(H₄)**. Although the non-innocent behavior of diimine type ligands has been extensively studied, their active participation in catalytic reactions is very rare. The tetradentate robust trop₂dad ligand contains no phosphanyl but two olefinic binding sites which also behave as non-innocent ligands. Their electronic flexibility allows for the stabilization of low-valent metal centers by metal-to-ligand back donation of electron density. Experimental data suggest that the methanol molecule is added across the Ru–N bond, leading to a methoxide complex. In this particular example, activation of the α -C–H bond in the coordinated methoxide and transfer of a hydride (H[−]) occurs to the diazadiene backbone of the trop₂dad ligand and not to the metal as in all previously discussed examples. In subsequent similar methanol activation steps, the cooperating trop₂dad ligand is fully hydrogenated to a bis(amino)ethylene ligand (trop₂dae). This process is further accompanied by a reduction of the Ru(II) center to Ru(0). Model reactions indicate that in this catalytic process, methanol is first dehydrogenated to formaldehyde: $\text{MeOH} \rightarrow \text{H}_2\text{C}=\text{O} + \text{H}_2$. To support the assumed formation of an aldehyde intermediate, a Ru(0) complex containing a side-on coordinated benzaldehyde molecule formed by hydrogen transfer from benzylalcohol was isolated and the structure fully characterized. Subsequent rapid reaction of formaldehyde with water forms di(hydroxy)methane: $\text{H}_2\text{C}=\text{O} + \text{H}_2\text{O} \rightarrow \text{H}_2\text{C}(\text{OH})_2$. This is again catalytically dehydrogenated to formic acid: $\text{H}_2\text{C}(\text{OH})_2 \rightarrow \text{HCOOH} + \text{H}_2$, which is rapidly converted to CO₂ and H₂. The complex **30** promotes the latter reaction with the highest TOF reported to date for the decomposition of pure formic acid (24 000 h^{−1}). The dehydrogenation of aqueous methanol occurs best under slightly basic conditions which are needed to promote the dehydrogenation of the isolated complex **31** to the active hydride complex **30** and to sequester the released CO₂ as carbonate.

[M]–SR Catalysis In Nature, hydrogen production is fundamentally dependent on nitrogenase and [FeFe] (see next section) or [NiFe] hydrogenase enzymes which catalyze the reversible reduction of protons and oxidation of H₂ according to $2\text{H}^+ + 2\text{e}^- \rightleftharpoons \text{H}_2$ (Figure 3.1).

Nitrogenase is a two-component system that uses a Mg(ATP) Adenosine triphosphate(ATP) complexed Fe-protein associated with a MoFe-protein that

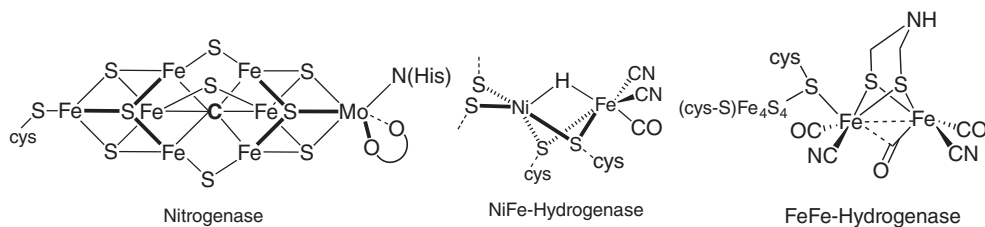
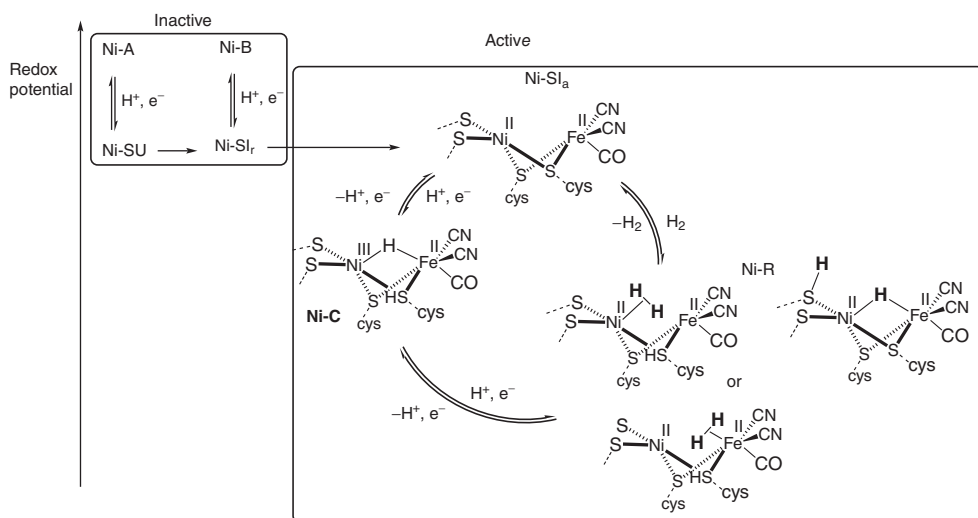


Figure 3.1 Active sites of nitrogenase and hydrogenase enzymes.

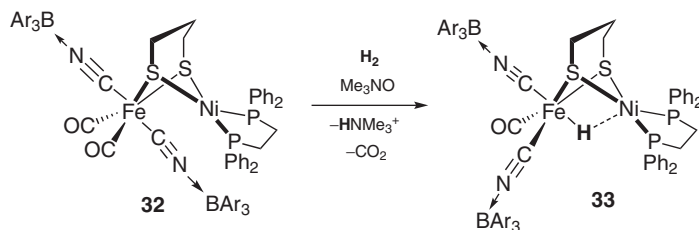
contains the $\text{Fe}_7\text{MoS}_9\text{C}$ cluster (FeMoco) as active site. Electrons stored in ferredoxins or flavodoxins at low potentials are used to reduce protons to hydrogen. These electron storage proteins, containing $[\text{Fe}_4\text{S}_4]$, $[\text{Fe}_3\text{S}_4]$, and $[\text{Fe}_2\text{S}_2]$ metal–sulfur clusters, are ubiquitous in reductase enzymes that catalyze biological reduction reactions such as nitrogen fixation, hydrogen metabolism, and deoxygenation of carbon dioxide. In the presence of N_2 , the enzyme catalyzes the production of ammonia, according to $\text{N}_2 + 8 \text{H}^+ + 8 \text{e}^- \rightleftharpoons 2 \text{NH}_3 + \text{H}_2$ [35]. The NiFe-hydrogenases are heterodimeric proteins containing a small unit consisting of two $[\text{Fe}_4\text{S}_4]$ clusters, one $[\text{Fe}_3\text{S}_4]$ cluster, a large subunit containing a dinuclear thiolate, and a hydride bridged nickel iron unit. The iron center is further coordinated to two terminal cyanides CN^- and one CO ligand [36]. Several mechanisms have been proposed for H_2 uptake by [NiFe] hydrogenases, but without reaching a definite conclusion yet [37]. The oxidized states of [NiFe] hydrogenases are catalytically inactive and are referred to as Ni-A and Ni-B (Scheme 3.14). One-electron reduction leads to EPR-silent species Ni-SU and Ni-SI_r electron paramagnetic resonance (EPR). Protonation of Ni-SI_r and dissociation of an oxygen ligand yields Ni-SI_a, which has been suggested as the redox- and chemically active species that oxidizes dihydrogen. H_2 reacts with Ni-SI_a to produce an EPR-silent form called Ni-R. Three possible structures have been proposed for the Ni-R state. The first two involve H_2 binding to nickel or iron centers. Several findings indicate H_2 binding by the Ni center: (i) the H_2 transport channel is connected to the Ni center instead of to Fe, (ii) exogenous CO, a competitor for H_2 , binds to Ni, and (iii) H_2 binds to Ni(II) center, as has recently been proved [38]. It is also possible that heterolytic cleavage of H_2 via proton



Scheme 3.14 Activation mechanism and catalytic cycle of [NiFe]-hydrogenases. The possible modes of H_2 binding (Ni-H_2) and (Fe-H_2) and heterolytic H_2 activation or oxidative addition/proton transfer are shown.

abstraction, presumably by a terminal cysteinyl ligand bound to Ni, occurs at the Ni-R stage [39]. Subsequent one-electron oxidation generates the paramagnetic Ni-C state [40]. Spectroscopic data indicate that the Ni-C state contains a bridging hydride between nickel and iron [41]. A second one-electron oxidation is followed by the release of the former hydride ligand as a proton, regenerating the Ni-SI form and thus closing the catalytic cycle. Throughout this cycle, the iron center remains in the low-spin Fe(II) configuration, a state favored by the high-field CO and CN⁻ ligands, while the nickel is the redox-active center [42].

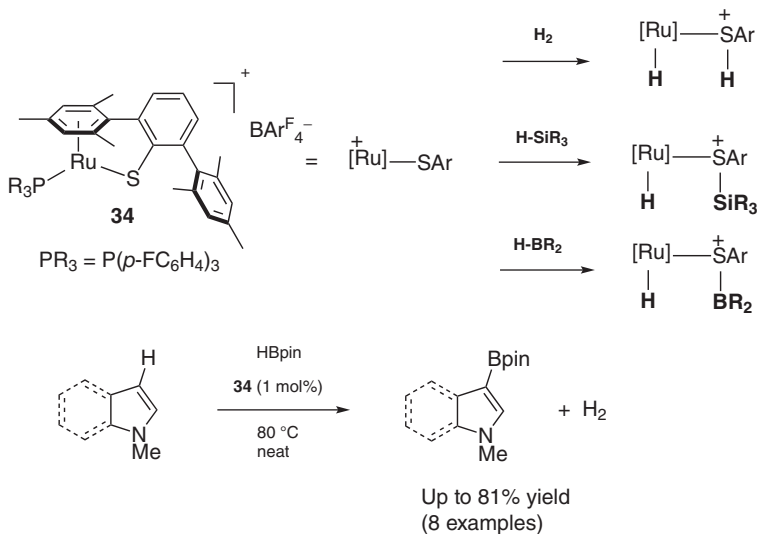
At present, none of the existent synthetic models of NiFe hydrogenase reproduces the exact coordination environment of the active site in the natural enzyme, and the reported models are not catalytically active [43]. One of the closest, the anionic complex [(dppe)Ni(μ-pdt)Fe(CO)_n(CNBAr^F₃)₂]⁻ (**32**) (dppe = 1,2-(diphenylphosphino)ethane; pdt = propanedithiolate), is however, able to activate and cleave H₂ heterolytically. This reaction is assisted by an external amine oxide which promotes decarbonylation and proton transfer to yield a bridging hydride species **33** (Scheme 3.15) [44].



Scheme 3.15 Heterolytic splitting of H₂ by [(dppe)Ni(μ-pdt)Fe(CO)_n(CNBAr^F₃)₂]⁻ (**32**)/Me₃NO.

Some complexes in which thiolate ligands serve as intramolecular proton acceptors have been reported over the past few years. For example, the Ru-S bridges in the diruthenium complex [Ru(pybuS₄)₂] (pybuS₄²⁻ = 2,6-bis(2-sulfanyl-3,5-di-*tert*-butylphenylthio)dimethylpyridine) cleave H₂ heterolytically to give the thiol hydride complex [Ru(H)(pybuS₄-H)] in which one of the bridging sulfides became protonated [45]. Other examples include the titanocene monosulfide derivatives [Cp⁺₂Ti(=S)(py)] and [Cp⁺₂Ti(η²-S₂)] reported by Bergman *et al.* [46] and the [{CpMoS_x}_y] polymers described by Rakowski DuBois *et al.* [47] which cleave H₂ heterolytically. Further recent examples reported by Rauchfuss *et al.* include the dinuclear iridium(II) μ₂-sulfido complex [Ir₂S₂(PPh₃)₄], which reacts with 2 equiv of H₂ to give the hydrido(hydrosulfide) complex [Ir₂(H)₂(μ-H)(μ-SH)(μ-S)(PPh₃)₄] [48]. A similar dimeric Rh complex reported by Bianchini, splits H₂ across the Rh-S bond [49]. While these reactions are noncatalytic, recently efficient catalytic reactions were discovered where a sulfur ligand cooperatively assists the bond activation in a substrate molecule [50]. Tatsumi, Oestreich, and Ohki reported the heterolytic cleavage of H-H, H-Si, and B-H bonds across the polar Ru-S bond of a tethered ruthenium(II)-thioether complex (Scheme 3.15).

Remarkably, a catalytic electrophilic borylation of pyrroles and indoles promoted by complex **34** was discovered, which proceeds under the evolution of H_2 (Scheme 3.16) [50b]. A Ru(II)-hydride complex containing a dative bond between a sulfido ligand and a borenium cation was proposed as the key intermediate.



Scheme 3.16 Heterolytic H_2 , Si-H, and B-H bond cleavage across a cooperative Ru-S bond in a Ru-thioether complex and catalytic electrophilic borylation of nitrogen-containing heterocycles.

3.2.1.2 Basic Functional Sites Located in the Outer Coordination Sphere

[M]-L-NH Catalysis Here, a selection of examples of “long-range” cooperation between the metal and a remote functional site of the ligand is listed. Again, Nature serves as master, and one of the most impressive examples is the active site of all [FeFe] hydrogenases, which catalyze the uptake and release of H_2 [51]. Although sharing some similarities with respect to the active site, this enzyme contains a completely different protein structure when compared to [NiFe] hydrogenases (Table 3.1). The active site consists of a Fe_2S_2 butterfly-shaped core bridged by cysteines. The Fe atoms are coordinated to CN^- and CO ligands, resulting in the so-called H cluster (Figure 3.1). The metal complex is concealed within the protein matrix, while the redox mediators (e.g., ferredoxins) are bound to the protein surface, and the [Fe-S] clusters ensure the electron transfer from ferredoxin to the polymetallic active sites. These enzymes belong to the class of the most efficient catalysts known; for example, [FeFe] hydrogenase of *Desulfovibrio desulfuricans* produces 2×10^5 l of H_2 (mol enzyme)⁻¹ s⁻¹ [52]. The combination of crystallographic and spectroscopic data allowed a rough mechanistic proposal (Scheme 3.17). The reversible oxidation of H_2 proceeds

Table 3.1 Comparison of the coordination environment in [NiFe] and [FeFe] hydrogenases and catalytic activity.

Coordination resemblance	[NiFe]	[FeFe]
Iron carbonyls	Fe ^{II} (CO)	Fe ^{I,II} (CO)
Iron cyanide	Fe ^{II} (CN)	Fe ^{I,II} (CN)
Metal-bridged thiolate	NiFe ^{II} (μ-cys-S) ₂	Fe ^{I,II} (μ-S-L-S)
Nonclassical metal-η ² -H ₂	Ni ^{II} (η ² -H ₂) or Fe ^{II} (η ² -H ₂)	Fe ^{II} (η ² -H ₂)
Cooperative basic ligands	M ^{II} (η ² -H ₂)(S-cys) → M ^{II} H(HS-cys)	Fe ^{I,II} (μ-S-L-S) + H ₂ → Fe ^{I,II} H(μ-S-LH-S)
Metal hydride and hydrogen-bonding chemistry	NiHFe	FeH, FeH...HN
Square pyramidal d ⁷ metal	(cys-S) ₂ Ni ^{III} (μ-cys-S) ₂ (μ-H)	(CO)(NC)FeI(μ-S-L-S)(μ-CO)
<i>Catalytic activities TOF^a</i>		
H ₂ oxidation	700	28 000
H ₂ production	700	6 000–9 000

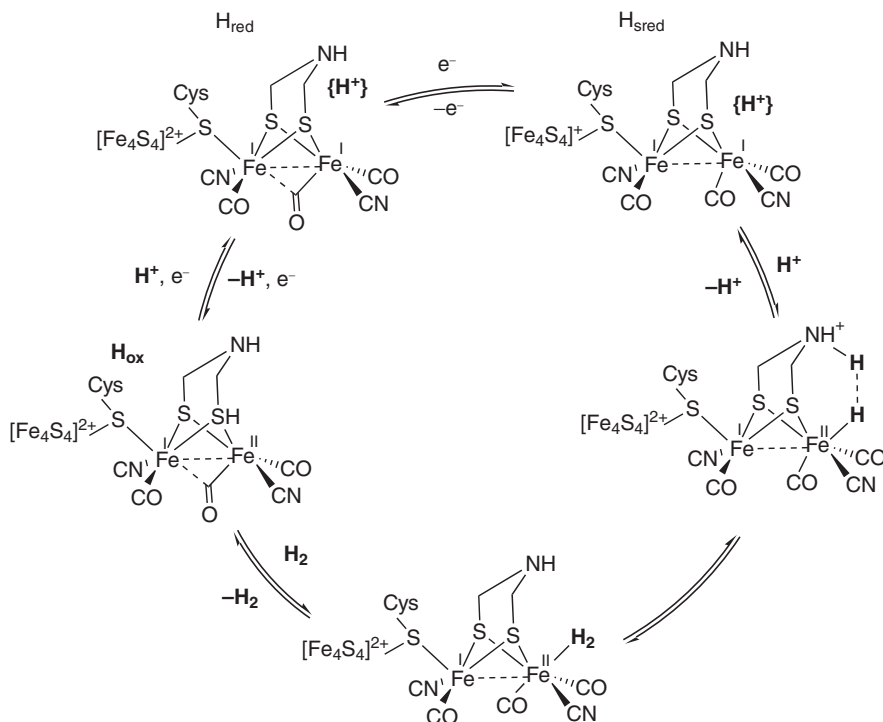
a) Rates indicated in (mol H₂)(mol enzyme)^{−1} s^{−1} (from Ref. [52b]).

Source: Adapted from R. H. Morris (Wiley-VCH) Ref. [51].

via initial binding of H₂ to the free coordination site in the H_{ox} state, followed by heterolytic cleavage assisted by the bridging amine function. In this process, an Fe(II) center is reduced to Fe(I), one electron is transferred to the [Fe₄S₄] cluster, and one proton is released, while the exact location of the second in the only recently characterized “super-reduced” paramagnetic redox state H_{sred} is not exactly known (Fe–H or NH₂). A stepwise two-electron transfer from H_{sred} accompanied by a second proton loss converts H_{sred} via H_{red} back into the H_{ox} state of the enzyme [53].

Although there are no models that match the exact coordination environment of the active site, there are hundreds of synthetic mimics reported in the past two decades [54]. Most of the recent examples investigated the influence of the bridging ligand, which has been extended to Te [55], Se [56], and Si [57] bridgeheads as a strategy to obtain a model with redox properties closer to the thermodynamic potential for H⁺ reduction. Multiple protonation sites have been proposed as proton relays: the distal Fe(I) center connected to the [Fe₄S₄] cluster in the H_{ox} state, the Fe–Fe bond, the cyanide and thiolate ligands in the first coordination sphere, or the amine function (NH). Rauchfuss *et al.* demonstrated that a pendant amine group in a dinuclear Fe complex plays a key role in the production of H₂ [58]. The biomimetic catalyst [Fe₂(adt)(CO)₂(dppv)₂] ([**35**^{NH}]) (adt = azadithiolate; dppv = *cis*-1,2-bis-(diphenylphosphino)ethylene) is 10⁴ times more active than its congener containing a propanedithiolate ligand [−S(CH₂)₃S[−]] (complex **36** in Scheme 3.18) [59].

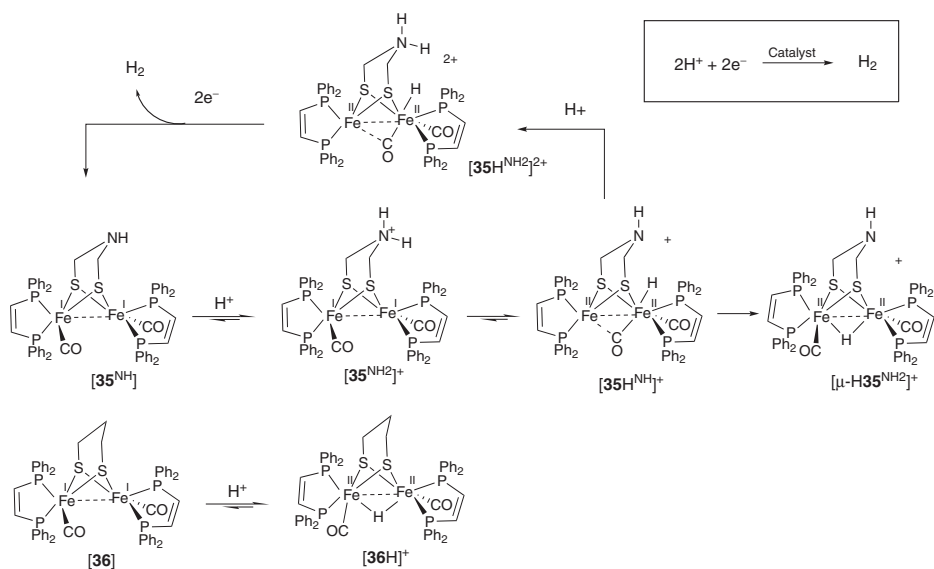
Many molecular catalysts have been reported for the production of H₂, but few for the reverse oxidation process. A “biologically inspired” electrocatalyst



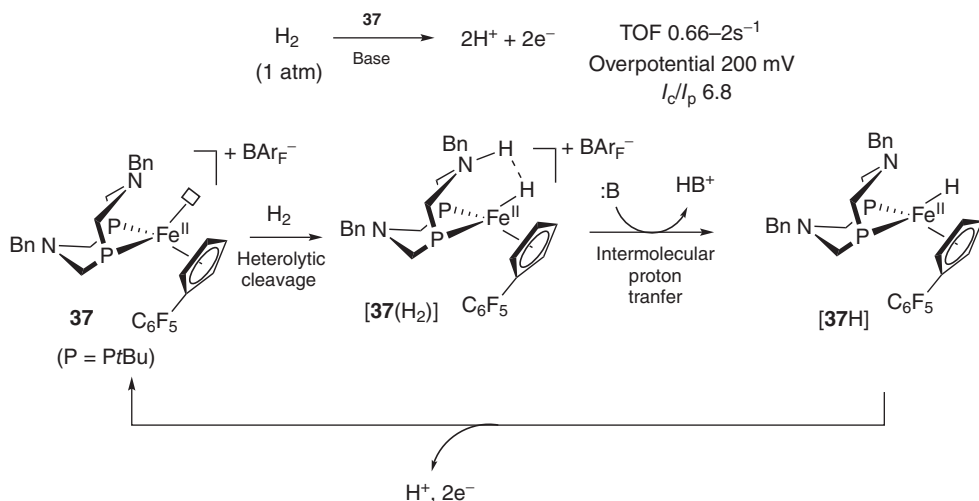
Scheme 3.17 Catalytic reversible H₂ uptake and release by [FeFe] hydrogenase. The location of H⁺ in H_{red} and H_{sred} has not been assigned.

(37), which has little in common structurally with the hydrogenase active site but contains an essential basic amine site in the second coordination sphere, operates at high rates ($0.66\text{--}2\text{ s}^{-1}$) and low overpotentials (160–220 mV) for the oxidation of H₂ (Scheme 3.19) [60].

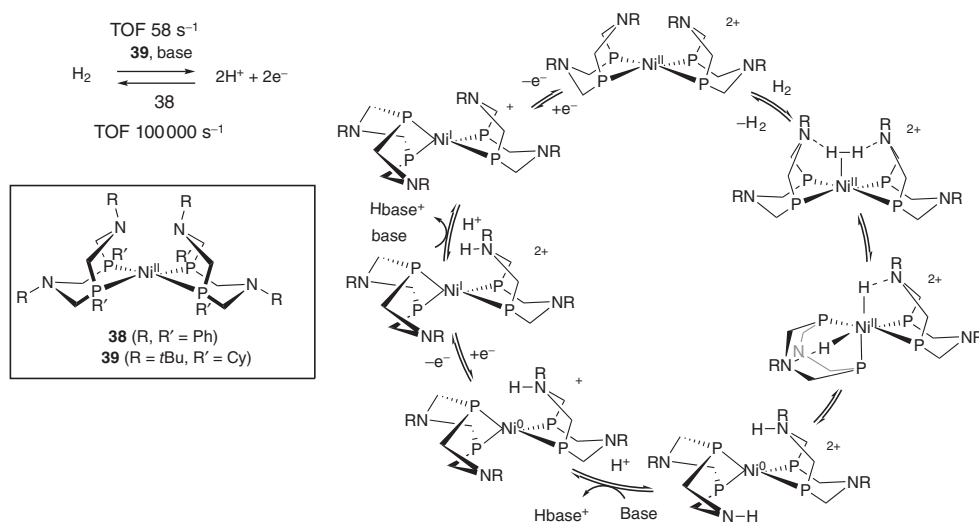
A breakthrough has been achieved with a new type of molecular catalyst based on nickel bis(diphosphine) and cobaloxyme complexes that contain proton relay ligands. The nickel complex $[\text{Ni}(\text{P}^{\text{Ph}}_2\text{N}^{\text{Ph}})_2](\text{BF}_4)_2$ **38** (**NiP₄**) ($\text{P}^{\text{Ph}}_2\text{N}^{\text{Ph}} = 1,3,6\text{-triphenyl-1-aza-3,6-diphosphacycloheptane}$) is able to promote the production of H₂ using protonated dimethylformamide $[\text{CH}(\text{OH})\text{NMe}_2]^+$ as the proton source in water with TOFs of $100\,000\text{ s}^{-1}$. However, no NiP₄ system has been reported yet that is water-soluble and does not require strong acidic conditions to achieve outstanding reaction rates [61]. The NiP₄ species is the only type of catalyst that is able to trigger both reactions: hydrogen cleavage to protons and electrons, and H₂ evolution by proton reduction [62]. The catalytic cycle is shown in Scheme 3.20. A nonclassically bound H₂ molecule is acidified by the Ni(II) center and transferred as two protons to the pendant cooperating NH groups which also assist in its binding and polarization before the cleavage. In this process, Ni(II) becomes reduced to Ni(0). In two consecutive steps, the NH functions are deprotonated



Scheme 3.18 Some biomimetic dinuclear Fe complexes with cooperative ligands containing a remote basic site as electrocatalyst for H_2 formation.



Scheme 3.19 A “bioinspired” mononuclear Fe complex as electrocatalyst for H_2 oxidation (Bn=CH₂Ph).

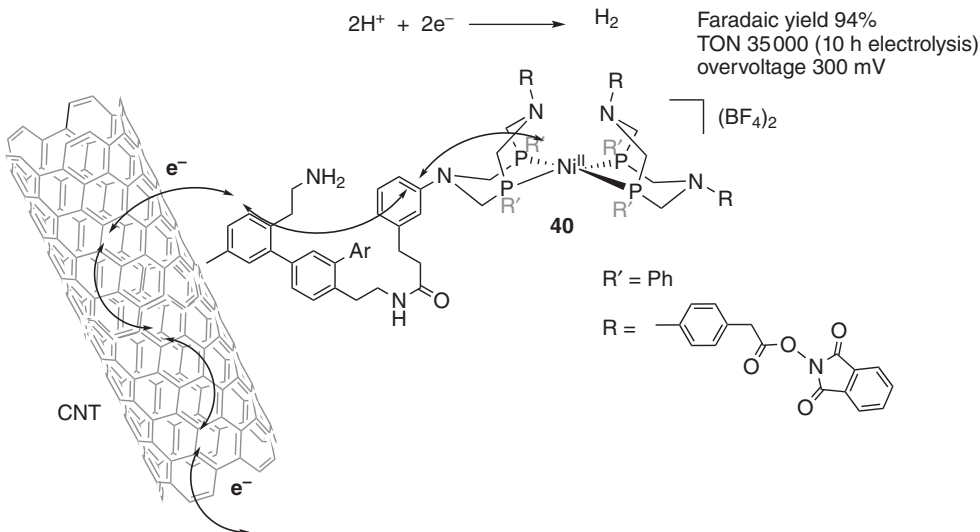


Scheme 3.20 NiP_4 complex as electrocatalyst for the formation/uptake of H_2 . In the catalytic cycle, the substituents R' at P are omitted.

by an external base, followed by the loss of an electron from the deprotonated Ni complexes, whereby the Ni(0) bis(ammonium) complex is converted via a Ni(I) (amine)(ammonium) intermediate back into the Ni(II) bis(amino) complex and the catalytic cycle turns over. This cycle can be read clockwise (as discussed)

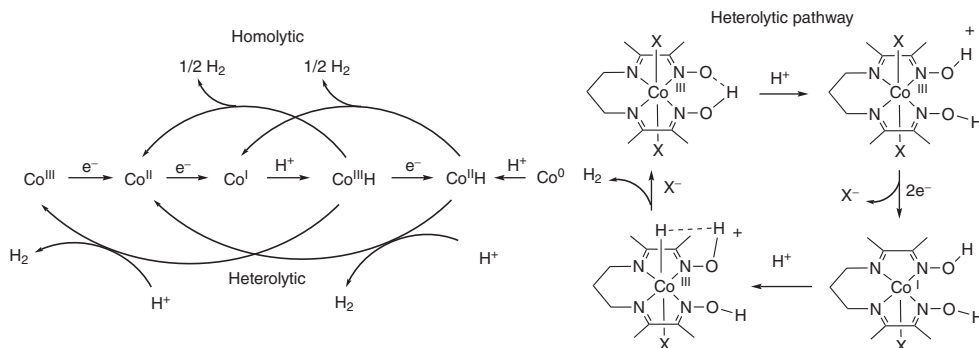
for H₂ oxidation and anticlockwise for H⁺ reduction. The conversion rate and overpotential for the generation of hydrogen are tunable by the substituents at the amine and phosphine groups [63].

Modifications of the steric and electronic properties of the amine ligands influence the proton acceptor ability of the pendant base and permit the control of the catalytic predilection for either H₂ oxidation to 2H⁺ or proton reduction to H₂. The possibility of varying the Ni complexes via the substituents R at the nitrogen centers also allowed the immobilization on carbon nanotubes (CNTs) as conducting support. This system was used as an electrode material [64]. In Scheme 3.21, the modified NiP₄ complex immobilized on the CNT surface is shown. Fast electron transfer was observed, although this device also needed strongly acidic conditions and proved to be inactive in a neutral environment.



Scheme 3.21 NiP₄-CNT composite material as electrocatalyst for the reduction of protons, leading to H₂ formation under acidic conditions.

M-L-OH Catalysis Cobaloximes are a class of catalytically active species for H₂ formation at modest overpotentials [65]. Four catalytic pathways were considered. Each begins with the reduction of a Co(II)–diglyoxime complex to generate a monovalent Co species that reacts with a proton donor to produce a hydrido–Co(III) complex. In a homolytic pathway, two Co(III) hydrides react in a bimolecular manner to form H₂. Alternatively, in a heterolytic pathway, protonation of the hydrido Co(III) hydride produces H₂ and Co(III). The Co(III) hydride may then be reduced to a Co(II) hydride, which can react via heterolytic or homolytic pathways. In the heterolytic mechanism, the role of the cooperating N–OH function as proton relay is critical (Scheme 3.22).



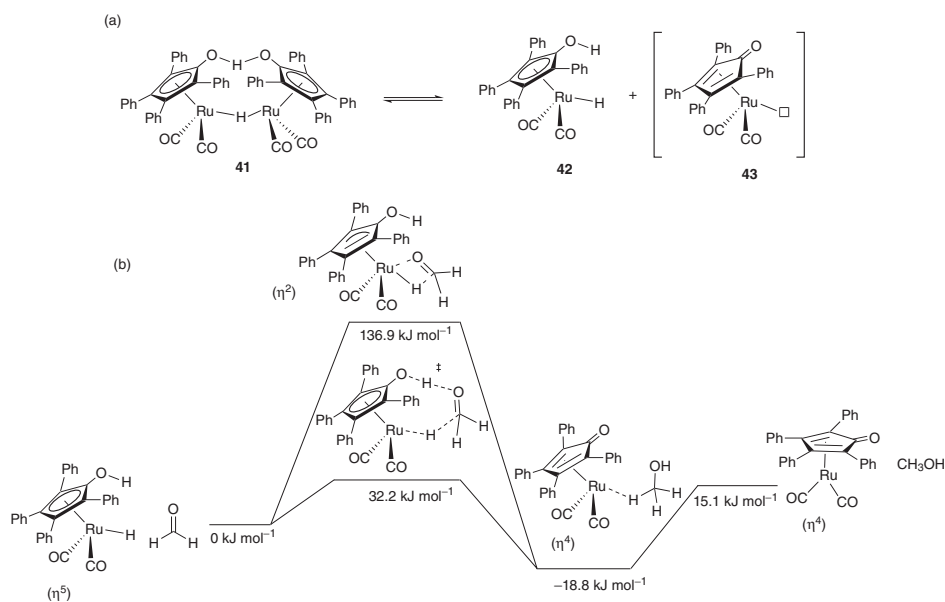
Scheme 3.22 Catalytic pathways for H_2 formation promoted by cobaloximes, highlighting the role of N–OH groups as cooperating proton relays.

3.2.2

Remote Pendant Basic Sites and Reorganization of π Systems as Driving Forces for Metal–Ligand Cooperativity

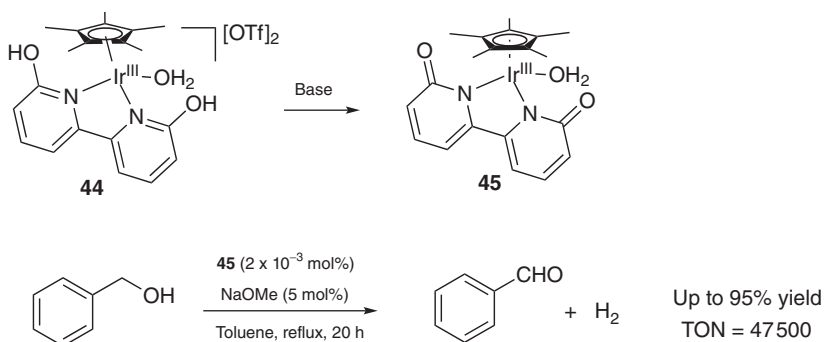
A few but instructive examples for metal–ligand cooperativity are given here in which the functional (basic) site is located in a remote position from the metal and the activation of the substrate provokes a reversible reorganization of the ligand π system. An especially enlightening example for this type of metal–ligand cooperation in catalysis is the hydroxycyclopentadienyl ligand coordinated to ruthenium. Shvo *et al.* demonstrated that the dinuclear complex **41** is an effective precatalyst for the direct oxidation of benzyl alcohol to benzyl benzoate and discovered the cooperativity of the hydroxycyclopentadienyl/cyclopentadienone ligand pair [66]. Since this pioneering work, complex **41** and derivatives have become especially useful catalysts in hydrogenations or THs of alkenes, alkynes, carbonyl, and imine compounds. Recent advances and mechanistic studies have been comprehensively reviewed [4, 67]. It has been established that the dimer is in equilibrium with monomer **42** and the η^4 -cyclopentadienone ruthenium species **43** (Scheme 3.23). The complex **42** is able to hydrogenate a hydrogen acceptor, whereas the complex **43** can dehydrogenate a hydrogen donor or activate molecular hydrogen. DFT calculations have clearly demonstrated that an outer-sphere mechanism is lower in energy by 105 kJ mol^{-1} than an inner-sphere mechanism which involves a ring-glissade for the reversible aldehyde reduction [68]. This mechanism accounts for ketones or aldehydes but does not apply to imines or amines that are likely hydrogenated in a stepwise manner. Remarkably, the Fe analog of Shvo's complex follows a similar hydrogenation mechanism which indicates that metal–ligand cooperativity may pave the way for efficient non-noble metal catalysts [69].

Yamaguchi *et al.* have developed the dicationic iridium(III) complex **44** bearing a 2,2'-bis(hydroxy)bipyridine ligand which serves as cooperative ligand in the efficient catalytic dehydrogenation of primary and secondary alcohols to aldehydes and ketones in aqueous media. The neutral iridium complex **45** with a dianionic bipyridonate ligand, obtained from **44** by double deprotonation of the hydroxyl



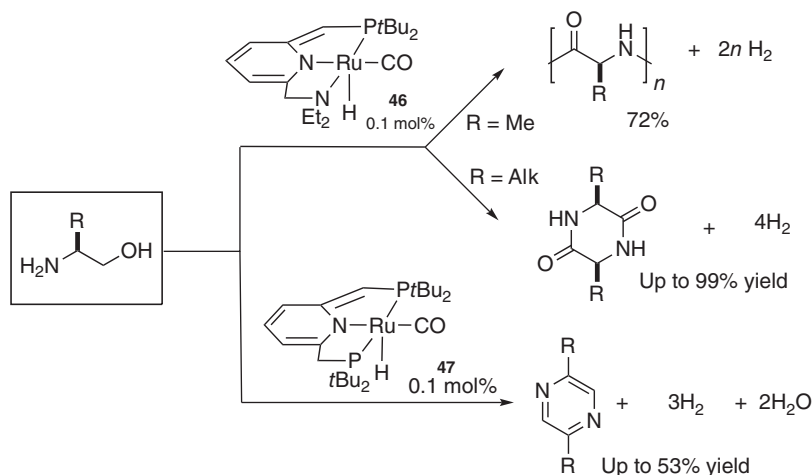
Scheme 3.23 (a) The dimer (**41**) (Shvo catalyst) in equilibrium with its active monomers (**42** and **43**). (b) Metal–ligand cooperativity in hydroxycyclopentadienyl/cyclopentadienone ruthenium complexes. DFT study of reversible formaldehyde hydrogenation.

groups, has achieved the highest efficiency for the dehydrogenation of primary alcohols to aldehydes. Benzyl alcohol afforded benzaldehyde in refluxing toluene (111 °C) and released hydrogen gas with TONs up to 47 500 (Scheme 3.24) [70]. The ligands in Ir(III) complexes **44** and **45** play a cooperative role in the substrate dehydrogenation and are responsible for the high catalytic activities attained.



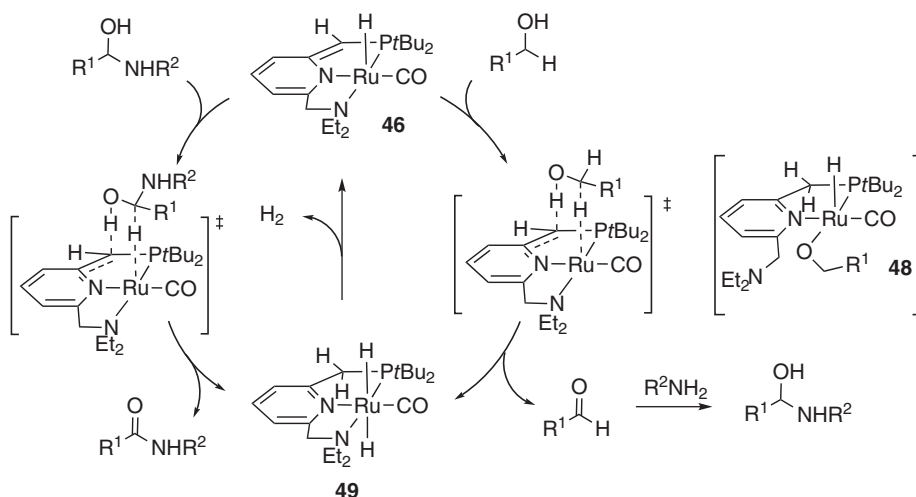
Scheme 3.24 Dehydrogenation of primary alcohols to aldehydes by Ir(III)-bipyridine ligands with cooperative sites.

Pyridine-based pincer-type ligands act as six electron donors that impose a *mer*-tridentate bonding mode. The formation of a metal–nitrogen bond and two additional donor sites in mutual trans position (amine, phosphine, or carbene) results in the formation of two annulated five-membered metallacycles, providing a rigid structure that is remarkably robust. This unique combination of bifunctional reactivity and robustness is likely responsible for the high catalytic activity in many transformations that require harsh reaction conditions. Milstein *et al.* demonstrated that PNP- and PNN (2-(di-*tert*-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine)-type ruthenium pincer complexes catalyze a range of C–O and C–N DHC processes – for example, conversion of primary alcohols into esters or primary alcohols and amines into amides – in a highly efficient and environmentally friendly manner. Hydrogen gas is the only by-product from the reaction. The catalytic properties of these complexes are attributed to the ability to activate chemical bonds by metal–ligand cooperation involving the deprotonation of the methylene arm in the ligand backbone, which causes a reversible dearomatization of the pyridine unit. This is possible because of (i) the low resonance stabilization energy of pyridine (117 kJ mol⁻¹ vs benzene 151 kJ mol⁻¹), (ii) the low pK_a of the methylene protons attached to the pyridine, and (iii) the stabilization of the dearomatized heterocycle by the acidic metal center. A certain degree of selectivity is achieved when different donor ligands are used in the side arms of the pincer ligand. For example, the DHC of amino alcohols can be directed toward the synthesis of peptides with a Ru–PNN complex (**46**), while a dehydrogenation–dehydration sequence to pyrazines occurs when a Ru–PNP complex (**47**) is used as catalyst (Scheme 3.25) [71].



Scheme 3.25 Ru-catalyzed dehydrogenative coupling of β -aminoalcohols to amides, peptides, and pyrazines.

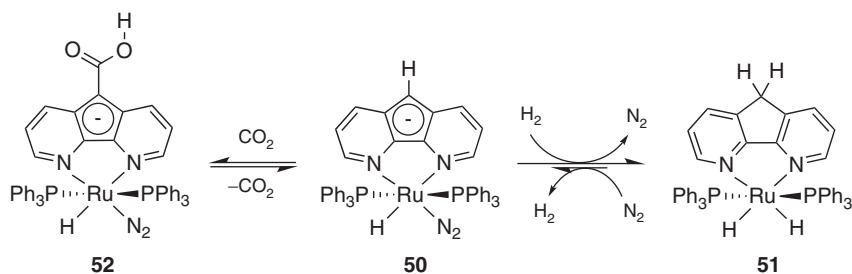
The hemilabile arm $\text{CH}_2\text{-NR}_2$ stabilizes, on one hand, the 18-electron Ru complex and generates, on the other hand, a free coordination site for binding a substrate molecule (e.g., an aldehyde, see Scheme 3.26). This concept is nicely exemplified by the dearomatized Ru-PNN complex (46), which catalyzes efficiently the dehydrogenation of equivalent amounts of alcohols and amines to amides under neutral conditions ($\text{TON} = 1000$) [72]. The reaction involves three steps: (i) dehydrogenation of the primary alcohol to an intermediate



Scheme 3.26 Mechanism proposed on the basis of DFT computations for the dehydrogenative acylation of amines with alcohols using Ru(PNN) pincer complexes as catalysts.

aldehyde; (ii) reaction with the amine to form a hemiaminal; and (iii) hemiaminal dehydrogenation to give the amide product. In an initial mechanistic proposal, after decoordination of the hemilabile NEt_2 group in complex **46**, the $\text{H}^{\delta+}-\text{O}^{\delta-}$ bond of an alcohol molecule adds across the Lewis acidic Ru center and the Lewis-basic methylene carbon between pyrazine ring and PtBu_2 group to give the alkoxide complex **48**. A β -hydrogen elimination may subsequently convert the bound alkoxide into an aldehyde, which is released to yield the dihydride complex **49**. Experiments at low temperature (-80°C) indicate that the addition of alcohols to the dearomatized Ru pincer complexes and the formation of an alkoxide complex may be reversible. When the reaction mixture was warmed to -30°C , alcohol dehydrogenation occurred and formation of the *trans*-hydride complex was observed. No free aldehyde was detected. Latest DFT calculations for the PNN–Ru complex **46** propose a direct “krypto”-(H^+ , H^-)-hydrogen transfer from the alcohol to the side arm in **46**. In this computed mechanism, no alkoxide complex such as **48** is involved and, instead of a classical β -hydrogen elimination, metal–ligand cooperativity accounts for the high reactivity. The dihydride species **49** eliminates hydrogen at a temperature $>100^\circ\text{C}$ whereby the catalytic cycle turns over [73]. The second dehydrogenation of the hemiaminal to the final product, the amide, occurs in a very similar manner. The amide prevails as a product relative to the formation of the imine, which, however, can be selectively obtained with Ru–PNP (**47**) as catalyst [74].

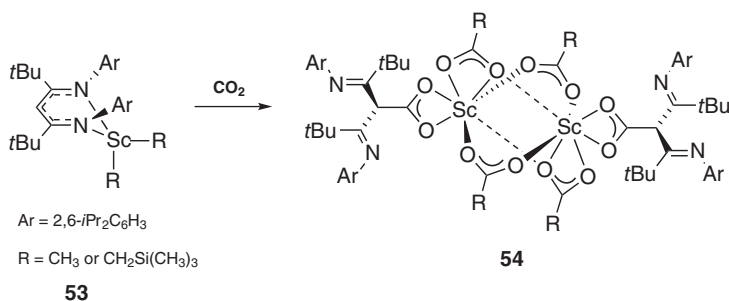
Another example of “long-range” metal–ligand cooperation by a remote basic site and reorganization of a π system was reported by Song *et al.* The zwitterionic Ru(II) diazafluorenone complex **50** splits reversibly dihydrogen between the metal center and the opposing carbon center – at a distance of about $5\text{ \AA}$ – to yield a complex where the cyclic delocalization of the whole π system of the diazafluorenone ligand is disrupted (Scheme 3.27). The reaction is reversible and H_2 is displaced from the hydride complex with N_2 . Remarkably, the complex **50** also inserts CO_2 into the C–H bond of the central five-membered ring at room temperature. The mechanism likely involves nucleophilic attack of the basic backbone carbon center to the electrophilic carbon in CO_2 followed by proton migration.



Scheme 3.27 H_2 splitting and CO_2 activation by the Ru–diazafluorenone complex **50**.

The role of the metal center is to regulate the nucleophilicity of the anionic ligand and increase the acidity of the fluorenyl proton. The reactivity of this system has been extended to analogous complexes containing Cu(NHC) (NHC = *N*-heterocyclic carbene) fragments [75].

Activation of CO₂ as thermodynamically highly stable molecule by metal–ligand cooperativity is of particular interest for CO₂ sequestration and utilization. Piers *et al.* examined the reactivity of scandium β-diiminate alkyl complexes (**53**) toward CO₂ [76]. The highly electropositive Sc(III) center and the basic non-innocent central carbon of the β-diiminate ligand are able to cooperatively activate CO₂. Addition of the CO₂ across the Sc(nacnac) ring causes the decooordination of the two imine donors β-diketiminato (nacnac). Two further molecules of CO₂ add into the Sc–alkyl bonds to form a tris(carboxylate) complex, which furthermore dimerizes to give the dinuclear complex **54** shown in Scheme 3.28. Although little is known about mechanistic details, metal–β-diiminate complexes – especially of Zn – exhibit the highest reported activities for co(polymerizations) of CO₂ and epoxides [77]. Another commendable example includes a Ru–tris(aminophosphine) complex reported by Stephan *et al.*, which can catalytically perform a ligand-based activation of CO₂ and reduction with pinacolborane [78].



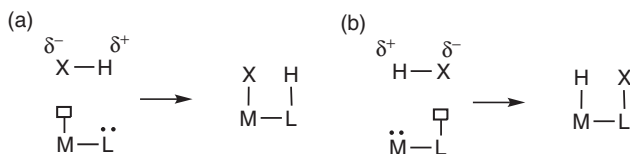
Scheme 3.28 Reactivity of scandium–β-diketiminato complexes with CO₂.

3.2.3

Metal–Ligand Cooperation with a Pendant Acid Site

A Lewis acidic functional site in the ligand scaffold can serve to stabilize lower oxidation states by direct interaction with an electron-rich metal center or to collaborate with the metal in substrate activation. Pioneering studies of Carreira, Grützmacher, and Hayashi *et al.* clearly demonstrated that olefins as electron-withdrawing π acceptors can serve as steering ligands in metal-catalyzed hydrogenations [79]. The coordination of σ-acceptor ligands (ER₃, E = B, Al, Ga, In, or ER₄, E = Si, Sn) does not only influence the geometric and electronic properties of a metal fragment [80] but also may collaborate actively with the metal center in the activation of a substrate. In Scheme 3.29, the difference in

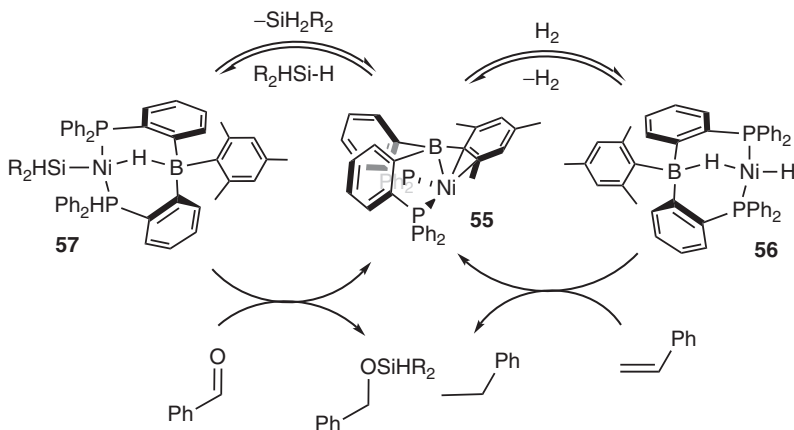
metal–ligand cooperativity with Lewis-basic ligands (a) and Lewis-acidic ligands (b) is schematically depicted. In the first case, X–H activation occurs such that an M–X bond is formed while in case (b) an M–H bond is obtained.



Scheme 3.29 Inverted polarity in the substrate activation at an M–L bond with either a basic (a) or an acidic site (b).

This concept is relatively new, and there are comparatively few examples of direct cooperativity between a ligand with an acidic functional site (Scheme 3.29a) [81]. Peters *et al.* demonstrated recently that the low-valent nickel–borane complex $[\text{MesDPB}^{\text{Ph}}]\text{Ni}$ (**55**) ($\text{MesDPB}^{\text{Ph}}$ = bis(2-(diphenylphosphino)phenyl)mesitylborane), reversibly activates H_2 to generate the nickel borohydrido-hydride species $[\text{MesDPB}^{\text{Ph}}](\mu\text{-H})\text{Ni}(\text{H})$ (**56**) with a Ni–H–B bridge. This complex catalytically hydrogenates an olefin [82]. The activation of a substrate across an M–B bond is conceptually related to activation by frustrated Lewis pairs (compare with Chapter 9) [83]. The nickel boratrane **55** also reversibly activates a Si–H bond by the cooperativity of the Ni–B unit, forming a B–H–Ni–Si species (**57**), which has been structurally characterized.

Complex **55** served as catalyst for the hydrosilylation of a variety of substituted benzaldehydes. Preliminary mechanistic studies support the assumption that the complexes **55**–**57** participate in the catalytic cycles (Scheme 3.30) [84].



Scheme 3.30 H–H and Si–H activation by nickel boratrane and catalytic hydrogenation of olefins and hydrosilylation of aldehydes.

3.3

Redox-Active Ligands Assisting Metal-Based Catalysts

The term “redox-active” refers to ligands at which redox processes occur [85] in distinction to redox “non-innocent” ligands for which the formal and spectroscopically determined oxidation state of the metal–ligand system is ambiguous [86]. In many cases, redox-active ligands change their charge by one electron and form radical species, and the discovery of radical ligands in coordination chemistry has led to their application in catalysis. Once again, Nature serves as inspiring source, and redox-active ligands are common in biological systems either as temporarily bound substrates in a catalytic reaction (O_2 , NO) or as supporting cofactor ligands (1,2-dioxolenes, dithiolenes, tyrosyl, porphyrin). This section discusses examples that highlight the importance of odd-electron ligands that are directly involved in a catalytic cycle. Two different types of redox-active metal–ligand cooperations have been established: (i) redox-active ligands that serve as electron reservoirs for a metal located chemical process, or (ii) redox and chemically active ligands that form bonds with the substrate and are the actual sites of the chemical transformation.

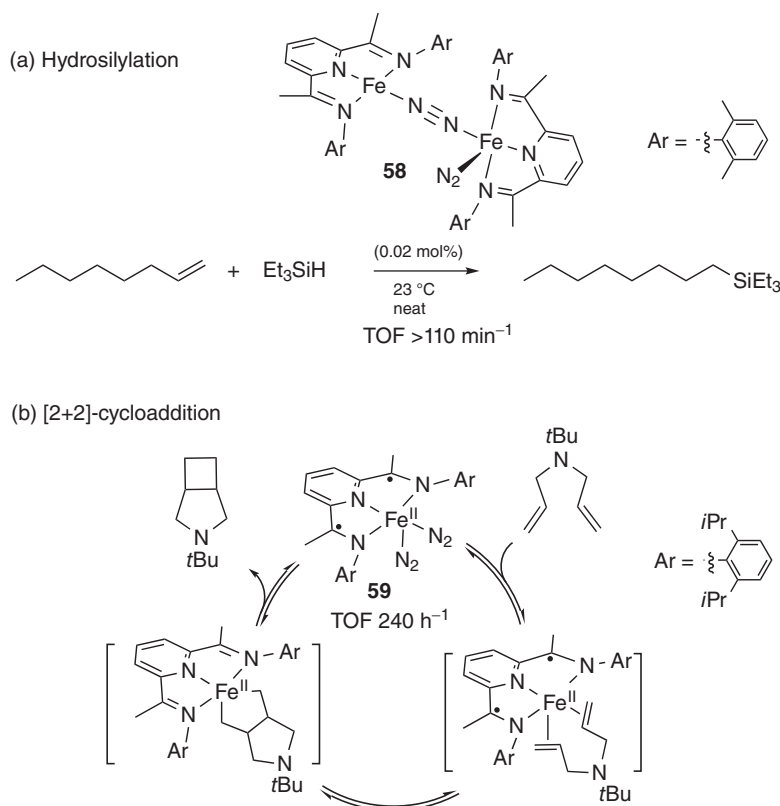
3.3.1

Redox-Active Ligands as Electron Reservoirs

Many processes homogeneously catalyzed by precious metal complexes involve two-electron oxidation state changes at the metal such as oxidative addition or reductive elimination which are crucial reaction steps in cross-couplings (Pd), oligomerization of olefins (Ti, Zr, or Cr), the Monsanto process (Rh), hydroformylations (Rh), or hydrosilylations (Pt). First-row transition metals undergo one-electron oxidation state changes, and often radical intermediates are generated, which may lead to uncontrolled or undesired reactivity.

Redox-active bis(imino)pyridine ligands can serve as electron reservoirs and therefore help to promote reaction steps that require the exchange of more than one electron. In their pioneering studies, Gibson [87] and Brookhart [88] discovered that iron and cobalt complexes of the bulky tridentate pyridinedi(imino) (pdi) ligands are efficient catalysts in ethylene polymerization. Chirik and Wieghardt emphasized recently that the combination of these redox-active pdi ligands with first-row metals may mimic precious metals in catalytic processes [85e]. For example, the zero-valent Fe complexes (**58** and **59**) are able to oxidatively insert into the C–C bond of the central four-membered ring of biphenylene to give a dibenzo-ferracyclopentane [89]. They efficiently promote the [2 + 2]-cycloaddition of dienes [90] or selective hydrosilylation of terminal alkenes [91]. The pdi ligand is able to stabilize three consecutive reduction steps from the neutral to the trianionic level. While the mono- and trianions are π radicals with one odd electron, the two electrons of the dianion $[pdi]^{2-}$ could spin-pair to form a singlet ground state (singlet diradical) or remain unpaired in a triplet ground state (see Scheme 3.31). DFT calculations support that the iron center

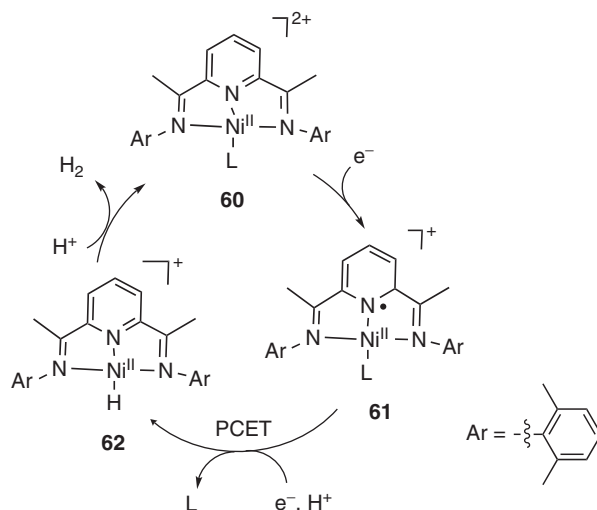
in the pyridine diimine complexes has an oxidation state of +2 with a so-called intermediate spin state. That is, the Fe(0) center in a formal Fe(0)(pdi) complex has transferred two electrons into the neutral ligand to give an Fe(II)(pdi²⁻). The oxidation state at the metal remains unaltered throughout the catalytic cycle, while the two electrons stored in the ligand are shuttled from the ligand to the substrate in the oxidative C–C coupling step and recovered from the metal during the reductive elimination in the [2 + 2] cycloaddition shown in Scheme 3.31b.



Scheme 3.31 (a) Anti-Markovnikov hydrosilylation of terminal olefins by Fe(pdi) complex **58**. (b) Intramolecular [2π + 2π] cyclization of α,ω-dienes to bicycloheptanes promoted by Fe(pdi) complex **59**.

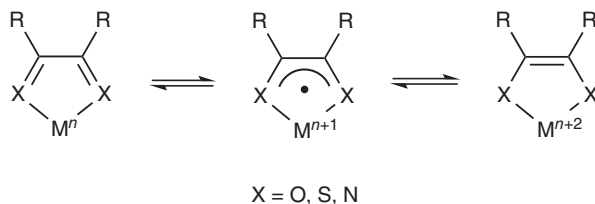
The redox-active pyridine di(imino) ligand in the nickel complex **60** allowed the electrocatalytic reduction of water [92]. Bulk electrolysis followed by a determination of the amount of H₂ indicated TOF values of 65 h⁻¹ (at -1.1 V vs NHE in 50 ml 0.1 M KCl/HCl solution at pH = 1) Normal hydrogen electrode (NHE). The computation of this process indicates that, after an initial reduction of **60** to a Ni(II)(pdi)⁻ complex **61**, a proton-coupled electron transfer (PCET) step occurs, yielding the Ni(II)hydride complex **62**. This releases H₂ after protonation

of the Ni–H bond. Note that, again, no change of the oxidation state at the Ni(II) metal occurs and the electrons are taken and expended by the redox-active ligand (Scheme 3.32).



Scheme 3.32 Electrocatalytic water reduction by a Ni–pyridinedi(arylimino) complex **60**.

The most thoroughly investigated classes of redox non-innocent ligands are those derived from the catechol/*ortho*-quinone pair with the *ortho*-semiquinone radical anion as persistent intermediate or the ene(dithiolate)/ α -dithiolene pair [93]. The relevance of these classical non-redox innocent ligands for biological processes has been recognized and extensively reviewed [94]. Although the nitrogen-containing analogous pair, ene(diamide)/ α -diimine, has not been observed yet as redox-active site in metalloenzymes, it has been used in “bioinspired” catalytic systems and behaves as a cooperative ligand (e.g., the MeOH dehydrogenation catalyzed by a Ru–enediamide complex, see Scheme 3.13). Scheme 3.33 shows a simplified equilibrium between three different “electromers” or “valence tautomers,” which may be encountered as local minima in complexes with these types of redox-active ligands. Alternatively, the given structures may represent major resonance structures that contribute to the

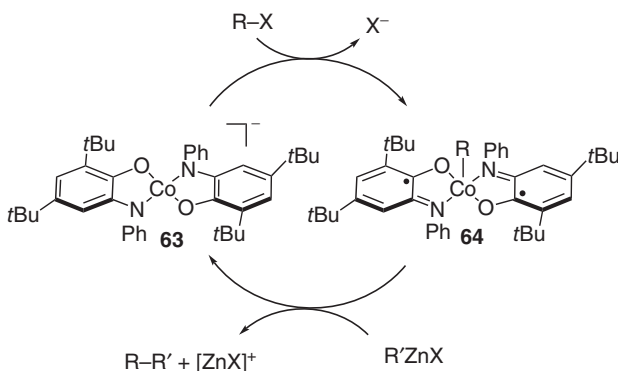


Scheme 3.33 Valence tautomerism of a coordinated noninnocent ligand at a metal center with a d valence electron count of >2 .

electronic ground state of metal complex with a redox non-innocent ligand. In this case the equilibrium arrows need to be converted to double headed resonance arrows, $\leftrightarrow$. Note also that the shift of two electrons from the metal to the ligand represents an elegant way to generate a free site in the coordination sphere with a minimal structural reorganization of the complex.

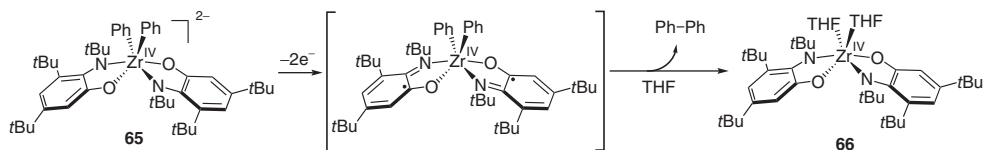
Soper *et al.* showed that an anionic Co(III) complex with two amidophenolate ligands is able to promote a Negishi-type cross-coupling under stoichiometric conditions [95]. Each of the redox-active amidophenolate ligands easily undergoes a one-electron oxidation to form a stable iminosemiquinone radical ligand. The square-planar d^6 -Co(III) bis-amidophenolate **63** complex has a triplet ground state [96] and behaves as a nucleophile displacing halide X^- from an alkylhalide $R-X$. The two electrons that are needed in this process are provided by the ligand, and a square-pyramidal Co(III) alkyl complex **64** bearing an antiferromagnetically coupled diradical ligand is obtained as product. This reaction can be compared with the established nucleophilic substitutions of d^8 -valence electron-configured noble metal complexes, and the redox activity of the ligands avoids the energetically unfavorable high oxidation states at the Co center, namely, Co(V).

The reaction of the penta-coordinated complex **64** with an organozinc reagent $R'-Zn-X$ leads to the coupling between the R^+ group of the cobalt complex **64** and the R'^- from the zinc compound. Under C–C bond formation, the starting complex **63** is generated, closing a synthetic cycle (Scheme 3.34).



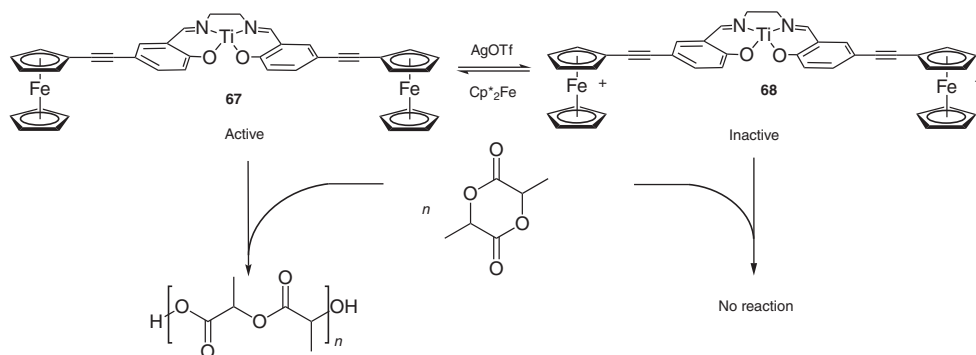
Scheme 3.34 Negishi-type C–C cross-coupling reactions with Co(III) redox-active amino/imino phenolates.

A further – at first glance surprising – example for the assistance of redox-active ligands in a C–C forming reaction is seen with the dianionic complex $[Zr^{IV}Ph_2(ap)_2]^{2-}$ (**65**). In this species, the metal center cannot be further oxidized (d^0 -Zr(IV)), and two-electron oxidation occurs in the dianionic amidophenolate ligand scaffold to give semiquinone-type radical anions. However, a “classical” reductive elimination to biphenyl is observed, which is typical for late transition metals in higher oxidation states. Cross-over experiments confirm that the C–C bond-forming step occurs at a single zirconium metal center (Scheme 3.35) [97].



Scheme 3.35 Reductive elimination from a bis(amidophenolate)Zr(IV) complex enabled by the cooperativity of redox active ligands.

The term “redox switch” refers to a ligand that can adopt different oxidation states, and each of those gives a different catalytic activity with the extreme case in which one oxidation state is catalytically active and the other inactive. This principle was pioneered in an experiment performed by Wrighton *et al.*, who showed that a Rh(I) complex containing a redox-active 1,10-diphosphino cobaltocene ligand was able to catalyze the reduction or isomerization of alkenes at different rates depending on the oxidation state of the metal – ligand set [98]. A recent application of this concept describes the ring-opening polymerization of lactones by Ti – salen complexes. These contain electronically coupled ferrocene units at the salen ligand. While the oxidized form (**68**) is almost inactive, reduction reestablished the original rate observed with the neutral catalyst (**67**) (Scheme 3.36) [99]. A possible application of this strategy could be the controlled synthesis of block copolymers by switching between the reduced and oxidized form and sequential addition of diverse type of monomers.



Scheme 3.36 Redox-controlled polymerization of lactide catalyzed by Ti – salen ferrocene complex.

Another example of a redox-active ligand was obtained with a NHC. A quinoid NHC can act as a redox-active supporting ligand for a highly active Ni catalyst in the Kumada coupling of an aryl bromide and an aryl Grignard reagent. The catalytic turnover is stopped reversibly by the addition of a one-electron reductant and reestablished with an oxidant. Although on/off redox cycling was successfully achieved, the nature of the reduced inactivated state is not known yet [100].

3.3.2

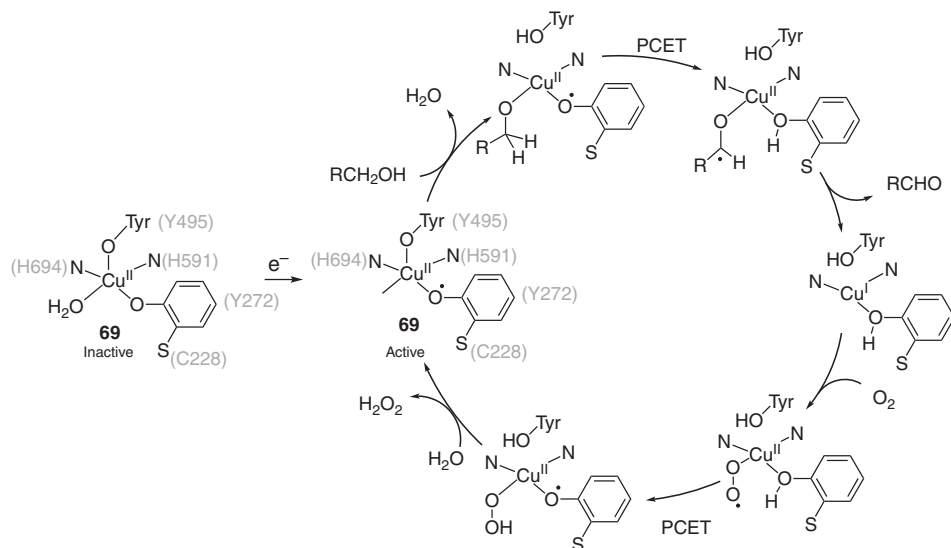
Redox-Active Ligands Participating in Direct Substrate Activation

In the previous section, a selection of examples of redox-active ligands that modify the electronic properties of the metal by acting as electron sinks and sources was presented. The chemical transformation of the substrate occurs at the metal center. In this section we discuss selected cases in which the redox-active ligand plays a direct role in substrate activation. Consequently, the ligands are redox- and chemically active. Once again, an archetypal example from Nature can be brought forward. The active site **69** of galactose oxidase (GOase), which catalyzes the oxidation of D-galactose (RCH_2OH) with molecular oxygen to hexodialdose (RCHO), contains a redox- and chemically active ligand directly bound to the copper center [101]. Under aerobic conditions, this enzyme also oxidizes highly efficiently a variety of alcohols to carbonyl compounds and H_2O_2 according to $\text{RR}'\text{CHOH} + \text{O}_2 \rightarrow \text{RR}'\text{C=O} + \text{H}_2\text{O}_2$, which may be viewed as a “transfer hydrogenation” of O_2 . The “inactive” form of GOase features an unusual tyrosinate ligand covalently linked to a cysteine (C228). In the “active” form of the enzyme, this ligand exists in a one-electron oxidized form – a tyrosyl radical – that is stabilized by a nearby tryptophan residue. In the commonly accepted mechanism, the “active” Cu(II) complex **69** is involved in the rate-determining step of the alcohol oxidation and abstracts a hydrogen center from the α -CH group, leading to a coordinated ketyl radical anion. This reduces Cu(II) intramolecularly to Cu(I), which reacts with O_2 to form a $[\text{Cu}(\text{II})\text{O}_2]^+$ superoxido species, which gives, via a proton coupled electron transfer (PCET) process, H_2O_2 and regenerates the Cu(II)–tyrosinoyl radical complex (Scheme 3.37).

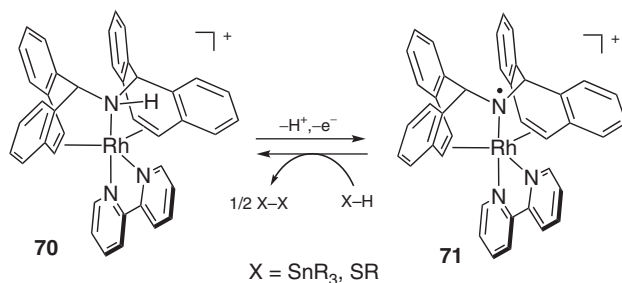
Synthetic catalysts using the same principle have been developed and applied in diverse oxidation processes [102]. For example, Wieghardt and Chaudhuri reported on a Cu(II)–thiophenol complex that catalyzes the oxidation of primary alcohols to aldehydes in the presence of air (as does GOase) and is also able to promote the formation of diols by coupling secondary alcohols [103].

Nitrogen-centered redox-active ligands, such as tryptophan radicals, also play important roles in biological transformations, although they have received less attention than their sulfur and oxygen counterparts [104]. The unambiguous isolation of metal complexes bearing open-shell nitrogen donors has been elusive for some time owing to their inherent reactivity. The first example of a stable aminyl radical transition-metal complex (**71**) was obtained by deprotonation of the diolefinamine–Rh(I) complex **70** and subsequent one-electron oxidation. DFT calculations indicated that about 54% of the total spin density is localized on the aminyl radical moiety and about 30% on the metal atom. The singly occupied molecular orbital (SOMO) is best represented by a $\text{Rh}(\text{d})\text{-N}(\text{p}) \pi^*$ interaction. Indeed, the isolated complex **71** undergoes ligand-centered radical-type reactivity with a series of hydrogen-atom donor reagents ($\text{Bu}_3\text{Sn-H}$, PhS-H , and $t\text{BuS-H}$) (Scheme 3.38).

A further example is the aminyl radical complex of copper **73** which contains nonconjugated aliphatic substituents. The precursor Cu(I) complex **72** catalyzes



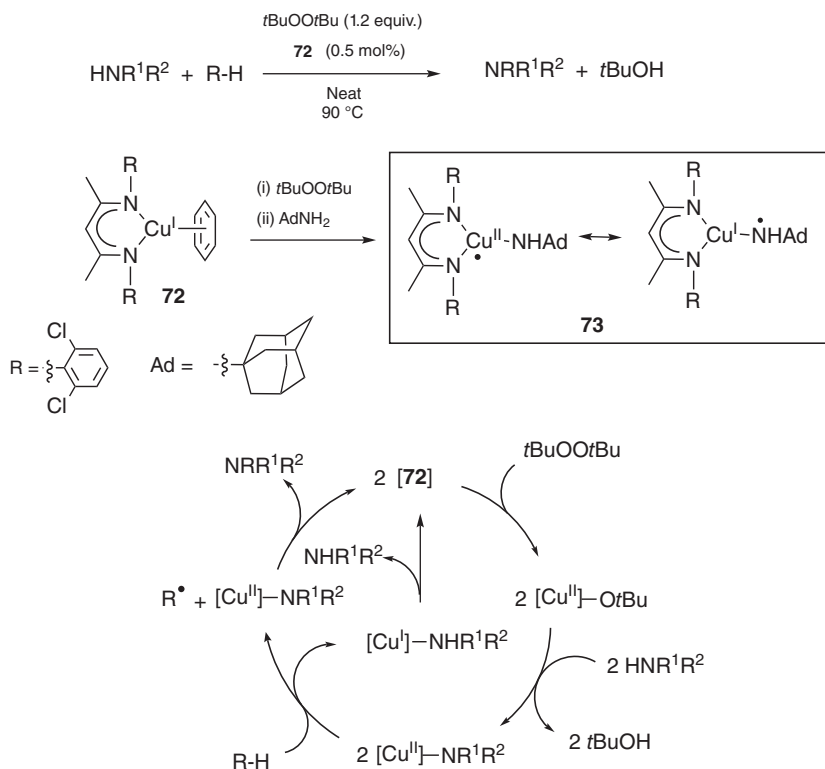
Scheme 3.37 Inactive and active form (69) of GOase showing the Cu(II)-tyrosyl radical unit (for clarity, histidine imidazolyl donor ligands are indicated by N) and the proposed mechanism for alcohol oxidation.



Scheme 3.38 Synthesis and reactivity of stable Rh(I)-aminyl radical complex.

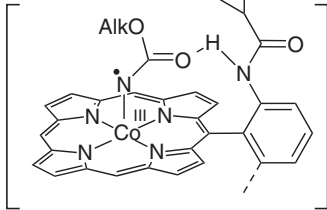
in the presence of *tert*-butyl peroxide the direct amination of sp^3 C–H bonds of a selection of unactivated primary and secondary amines [105]. Spin density calculations reveal 49% spin density on the aminyl nitrogen atom and 30% on copper in **73**, and the unpaired electron is located in a π^* molecular orbital located at Cu–N. The formation of complex **73** enables nitrene insertion reactions into the C–H bonds via the shown mechanism, which reflects the contribution of the $[Cu^I-N^{\bullet}R^1R^2]$ resonance structure to the electronic ground state of the complex with a Cu–N π interaction. Hydrogen-atom abstraction from the aliphatic substrate by the aminyl radical $[Cu^I-N^{\bullet}R^1R^2]$ leads to the formation of a Cu^I–amino complex $[Cu^I-NHR^1R^2]$ and an organic radical $R^{\bullet}$. This reacts with another equivalent of the aminyl radical complex $[Cu^I-N^{\bullet}R^1R^2]$ to form

a Cu^{I} -amino complex $[\text{Cu}^{\text{I}}-\text{NRR}^1\text{R}^2]$ from which the amine NRR^1R^2 easily dissociates (Scheme 3.39).



Scheme 3.39 Catalytic C-H amination of sp^3 C-H bonds with unactivated amines catalyzed by **72**.

Aminyl and nitrene/imido radical complexes are key intermediates in amination reactions of hydrocarbons, in olefin aziridination, and related nitrene-transfer reactions [106]. De Bruin *et al.* disclosed recently the synthesis of two $\text{Co}(\text{III})$ nitrene radical species formed in the reaction of a $\text{Co}(\text{II})$ -porphyrin complex with organic azides. The radical character of the ligands in both species was clearly demonstrated, and about 60–90% (depending on the nature of the substituent at the azide reagent, see Scheme 3.40) of the spin density in complexes **75** is localized on the nitrene N atom. The authors utilized complexes **74** as catalyst for the aziridination of styrene or amination of a sp^3 C-H bond of ethyl benzene [107]. The reaction of the cobalt(II)-porphyrin complex **74b** bearing bisamide substituents R' on the macrocyclic ligand with an azide and the corresponding catalytic amination reaction is significantly faster than with the $\text{Co}(\text{II})$ precursor **74a** with $\text{R}' = \text{Ph}$. This is likely due to stabilization of the nitrene radical complex **75b** by hydrogen bonding between the nitrene radical ligand with the NH group of the bisamide in the second coordination sphere of the complex.



for the C–H bond amination or olefin aziridination promoted by complexes **74**.

3.4

Summary

As the understanding of the underpinning mechanisms for homogeneously catalyzed reactions progressed during the past decades, concepts allowing the design of transition-metal complexes as catalysts evolved. Probably the best known is Tolman's approach to evaluate the steric and electronic effects of ligands by determining their cone angles [108]. This which has been more recently extended to a wider range of ligands such as NHCs in the form of a model in which the coverage of the surface of a sphere around a metal center is used to quantify ligand steric properties and the "percent buried volume" (% Vbur) defines the percentage of the total volume of a sphere around the metal center occupied by a ligand [109]. Related is also the so-called wide-bite-angle concept in which steric constraints built in the ligand sphere favor the population of certain intermediates that influences enormously the selectivity of a catalytic reaction [110].

Metal–ligand cooperativity is a further development that includes the lessons learnt from the above-mentioned concepts that so far focused on the impact of stereoelectronic properties of the ligands on the metal as the solely catalytically active site. A cooperating ligand directly participates in the bond activation of the substrate and undergoes reversible chemical transformations throughout the catalytic cycle. Nature uses the principles of metal–ligand cooperativity to promote a number of transformations with exceptional efficiency. Many enzymes reach activities per second which are not even matched by man-made catalytic systems per hour (specifically [FeFe] hydrogenases, which produce up to 2×10^5 l of H_2 (mol enzyme) $^{-1}$ s $^{-1}$). However, the recent advances illustrated here with select examples give hope that some long-standing challenges may be met in the future by making use of the concept of metal–ligand cooperativity. These are, above all, replacement of noble metals in catalysts by earth-abundant metals from the fourth period, such as Fe, Co, Cu, and Zn. The development of catalytic systems with these metals is a necessity for the economically and ecologically viable large-scale application in water-splitting, nitrogen fixation, and conversion reactions. Also, note that the ligands themselves need to be made out of ingredients that do not require a large investment of energy. In this respect, phosphines – ubiquitous ligands – need to be replaced by other ligands, preferably composed of C, H, and N. The production of 1 kg of phosphorus from phosphate rock requires about 46 000 kJ – an amount of energy that is hardly recovered in the catalytic process using a phosphine ligand.

The cooperativity in metal amides has been very successfully exploited in DHC reactions of, for example, alcohols and amines or water to amides and carboxylic acids. These new reactions proceed under the concomitant liberation of hydrogen. The incorporation of highly active molecular dehydrogenation and hydrogenation catalysts into electrodes has led to the discovery of OMFCs, which eventually may give fine chemicals from biomass as feedstock under almost waste-free conditions – electric current would be ideally the only by-product. It can be expected that many and better matching combinations of metals and cooperating ligands will be found in the future, which will lead to the discovery of truly efficient catalytic processes comparable to the activity of enzymes. Entirely new reactions, especially in the field of dehydrogenation reactions, which proceed under the liberation of molecular hydrogen, may be discovered. Also, new catalytic systems for cross-coupling reactions, cyclopropanations, activation of C–H bonds, and their functionalization (amination as example) will be found and developed. This is especially true for complexes with coordinated radicals as cooperating ligands, which is a research topic just in its beginnings.

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4

Cooperative Enamine-Lewis Acid Catalysis

Hong Wang and Yongming Deng

4.1

Introduction

Organocatalysis, in which a small organic molecule serves as the catalyst, has rapidly grown into the third pillar in asymmetric catalysis in slightly over a decade, along with metal catalysis and biocatalysis [1–5]. Organocatalysts are often cheap, nontoxic, and insensitive to the air and moisture, and thus are easy to handle. In addition, a large chiral pool of organocatalysts is available, making it readily manipulable to achieve high stereoselectivity in a reaction. Another major advantage offered by organocatalysis is the discovery of a number of new activation modes. Organocatalysis has extended to include enamine catalysis, iminium catalysis, Lewis base catalysis, hydrogen bonding catalysis, Brønsted acid catalysis, counterion catalysis, and heterocyclic carbene catalysis. Metal Lewis acid catalysis, on the contrary, has long been established as one of the most powerful tools in organic synthesis [6]. In particular, before the advent of organocatalysis, chiral metal catalysis had been the major player in asymmetric catalysis [7, 8]. In recent years, a new research area combining organocatalysis with metal catalysis has emerged [9–13]. This new concept aims to deliver organic transformations that cannot be achieved by organocatalysis or metal catalysis independently.

Enamine catalysis is one of the most investigated areas in organocatalysis [14–17]. A large number of new reactions have been developed based on enamine catalysis over the past decade. In enamine catalysis, a catalytic amount of a chiral aliphatic primary or secondary amine, for example, L-proline, forms an enamine with an aldehyde or ketone; the *in situ* formed enamine acts as a nucleophile reacting with an electrophile; the targeted substitution or addition reactions occur at the α -position of the carbonyl compounds (Figure 4.1). In many cases, these chiral amine catalysts act as bifunctional catalysts, because a carboxylic acid functional group, an often-modified group in organic amine catalysts, also interacts simultaneously with an electrophilic reaction partner through either hydrogen bonding or electrostatic attraction. Activation through hydrogen bonding or electrostatic attraction is relatively weak; as a result, high loadings of the amine catalysts are often required.

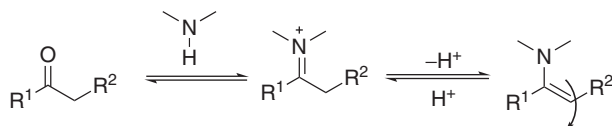


Figure 4.1 Illustration of enamine catalysis.

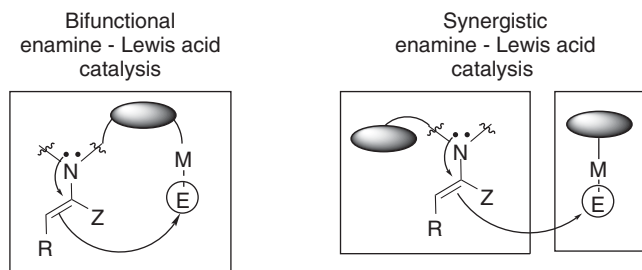


Figure 4.2 Classification of catalytic systems for the combination of enamine catalysis with Lewis acid catalysis.

In general, the combination of enamine catalysis with Lewis acid catalysis can be classified into two different types: bifunctional catalysis and synergistic catalysis (Figure 4.2) [11, 12]. In bifunctional catalysis, both the nucleophile and the electrophile are activated separately by two discrete functional groups, that is, an amine group and a Lewis acid, on the same catalyst to form a new bond. Synergistic catalysis is referred to as concurrent activation of both the nucleophile and the electrophile distinctively by the organocatalyst and the Lewis acid catalyst in two directly coupled catalytic cycles to work cooperatively to create a new single bond.

Enamine catalysis has also been cooperatively combined with hydrogen bonding catalysis, and several recent reviews have summarized this research field [18–22]. The focus of this chapter, however, will mainly lie on bifunctional and synergistic enamine-Lewis acid catalysis, including enamine-metal Lewis acid and enamine-boronic acid derivative catalysis. Several review articles on cooperative enamine-transition metal catalysis, including one from our group, have shown in the literature [23].

4.1.1

Challenge in Combining Enamine Catalysis with Lewis Acid Catalysis

Given the rich chemistry established in both areas, the merging of enamine catalysis and Lewis acid catalysis promise huge potential. However, this research area has grown rather slowly. The major challenge lies in catalyst incompatibility [24, 25]; in particular, the combination of an amine catalyst with a hard metal Lewis acid is very difficult. Chiral primary and secondary aliphatic amines are

the key amine catalysts in enamining catalysis. Aliphatic amines are hard Lewis bases; they are good ligands to a variety of metals, especially to hard metals. When an amine catalyst is mixed with a hard metal Lewis acid, the amine catalyst will coordinate to the metal irreversibly, thus to deactivate both catalysts. Overall, three strategies have been developed for the effective combination of enamine catalysis with metal Lewis acid catalysis. First, the soft–hard approach in which a hard base is employed with a soft acid or vice versa. This is a common and effective strategy to alleviate incompatibility problems. A majority of reactions developed in enamine-metal Lewis acid combined catalysis are based on the soft–hard approach. In general, in these reactions, an aliphatic amine is incorporated with a soft metal such as Pd(0), Cu(I), or Ag(I) as the cocatalytic system. Arylamines, much softer bases than aliphatic amines, have also been proved to be effective amine catalysts to promote enamine formation when combined with hard metal Lewis acids. Second, in bifunctional enamine-hard Lewis acid catalysis, bifunctional systems and chelating ligands are utilized to solve the acid-base quenching problem through competition coordination. Third, the utilization of an ammonium salt along with a harder metal Lewis acid.

Another challenge in cooperative/synergistic enamine-Lewis acid catalysis is the introduction of asymmetry to the target organic transformation. Theoretically, the enantioselectivity of the reactions can be induced either by a chiral amine catalyst, or a chiral metal catalyst using a chiral ligand, or both. However, when a chiral catalyst is incorporated, significantly decreased activity or complete inactivation of the reactions is often observed. A current approach to obtaining high enantioselectivity of a reaction is still through screening a variety of combinations of the metal, the amine, and the solvent as well as additives. Figures 4.3 and 4.4 illustrate the structure of the commonly used chiral amine catalysts and chiral ligands for transition metals. Chiral bifunctional ligands have also been developed to incorporate both enamine and Lewis acid catalysis in one entity (Figure 4.5).

4.2

Reactions Developed through Cooperative Enamine-Lewis Acid Catalysis

A number of reactions have been developed through cooperative enamine-Lewis acid catalysis. Earlier work on asymmetric reactions in this area suffered low stereoselectivity and/or low activity. In recent years, significant advances have been achieved in improving the enantioselectivity of the asymmetric reactions. A majority of these reactions are related to α -functionalization of carbonyl compounds through combining enamine catalysis with palladium catalysis. Other reactions, such as Diels-Alder reactions, Aldol reactions, multicomponent reactions, Michael reactions, and so on, have also been reported. In the following sections, the mechanism and the scope of these reactions are discussed.

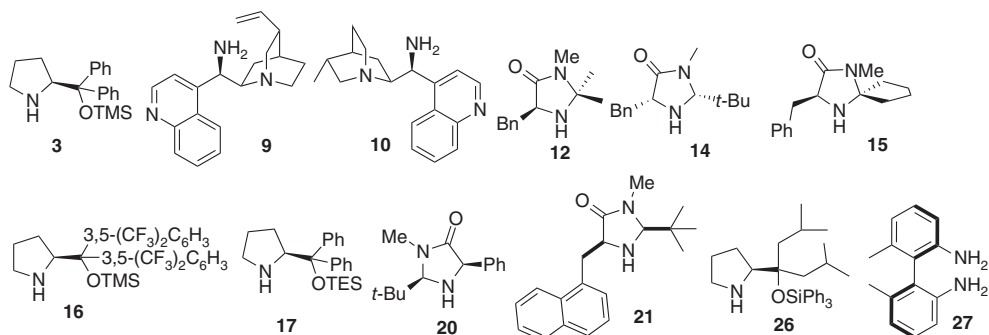


Figure 4.3 Structure of chiral amine catalysts.

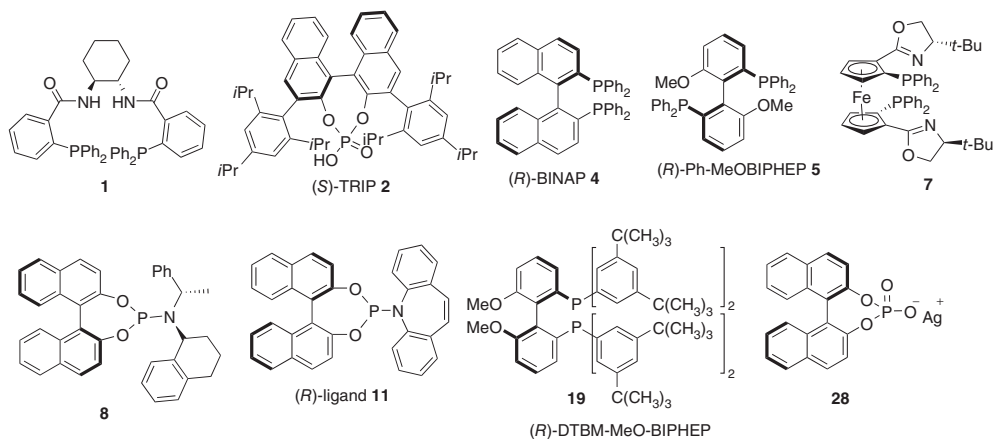


Figure 4.4 Structure of chiral ligands.

4.2.1

α -Alkylation of Carbonyl Compounds

α -Alkylation of carbonyl compounds is an important synthetic strategy to install functional groups at the α -position of carbonyl compounds. Traditionally, α -alkylation of carbonyl compounds was achieved mainly by addition of stoichiometric amounts of preactivated metal enolates to alkyl halides. Direct α -alkylation of nonstabilized aldehydes and ketones was difficult because of competing side reactions, such as aldol condensations, Cannizzaro and Tishchenko reactions, and *N*- or *O*-alkylations [26, 27]. The direct intermolecular allylation of aldehydes and ketones was not achieved until 2006 when the Córdova group described a synergistic enamine-transition metal catalysis using a Tsuji–Trost type palladium π -allyl complex as the electrophile [28]. The successful development of this

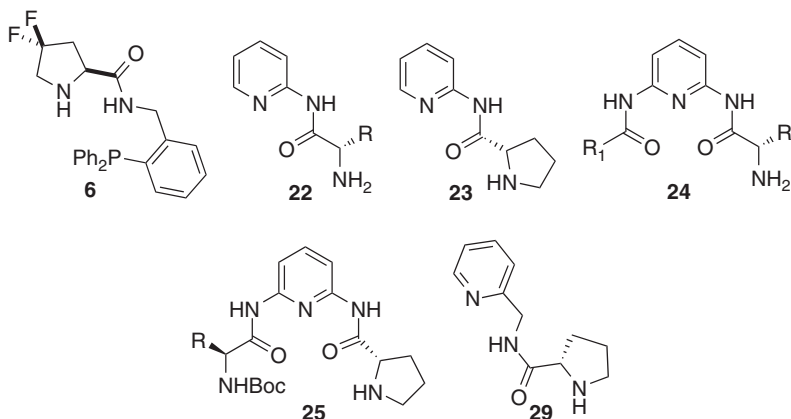


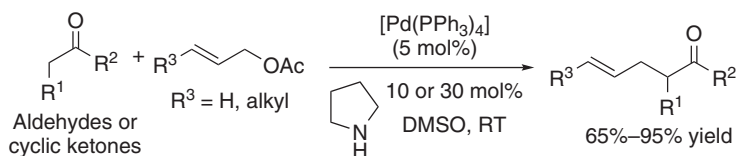
Figure 4.5 Structure of chiral bifunctional ligands.

method established a new pathway to functionalize aldehydes and ketones at the α -position.

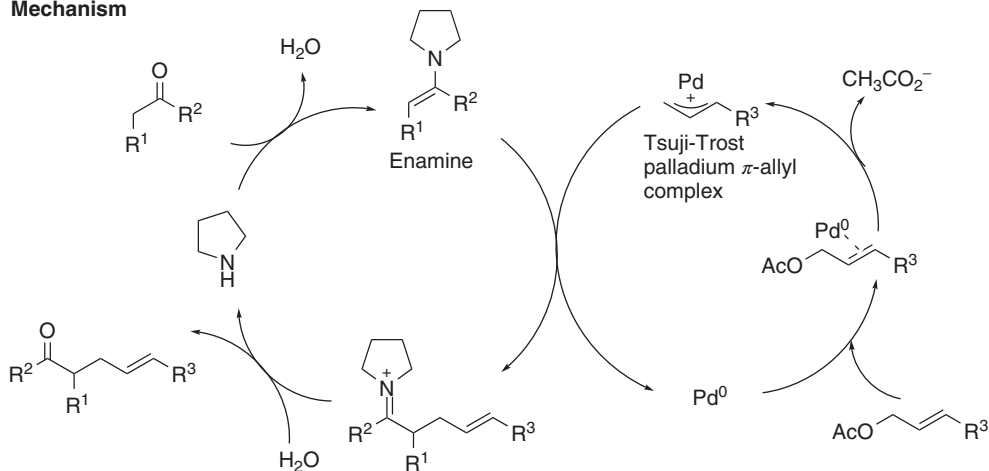
4.2.1.1 α -Allylation of Aldehydes and Ketones

α -Allylation of Aldehydes via Tsuji–Trost Type Palladium π -Allyl Complexes Palladium(0) catalyzed Tsuji–Trost allylation of a nucleophile is an attractive strategy in organic chemistry. The allylation is achieved via the *in situ* formation of an active palladium(II) π -allyl intermediate. Using this strategy, the Córdova group realized the first direct intermolecular α -allylation of aldehydes and cyclic ketones by combining enamine catalysis with Pd(0) catalysis in 2006 (Scheme 4.1) [28]. In this reaction, a catalytic amount of pyrrolidine was utilized to activate the aldehyde as an enamine intermediate, serving as the nucleophile. The allyl acetate reacted with the Pd(0) catalyst to generate a Tsuji–Trost type palladium π -allyl complex *in situ*, serving as the electrophile [29, 30]. Nucleophilic attack of the enamine intermediate to the palladium π -allyl electrophile coupled with reductive elimination led to the direct C–C bond formation at the α -position of the carbonyl compound generating an iminium intermediate, and simultaneously recovering the Pd(0) catalyst. Subsequent hydrolysis of the iminium intermediate afforded the α -allylic alkylated carbonyl compound and regenerated the secondary amine catalyst. Both aldehydes and cyclic ketones reacted smoothly with allyl acetate to produce the allylated products in high yields with high chemoselectivities, although a much higher loading (30 mol%) of pyrrolidine was required to ensure efficient allylation of ketones. It is notable that in this work an asymmetric version of this reaction was also attempted using chiral pyrrolidine derivatives. While

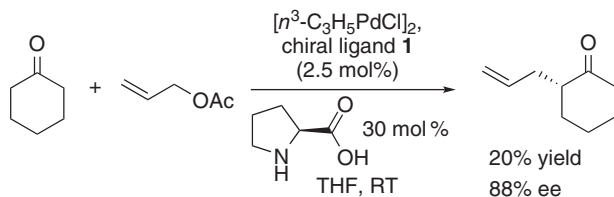
good enantioselectivity (up to 88% ee) was obtained, significantly decreased yields resulted (<25% yields) (Scheme 4.1) [28].



Mechanism



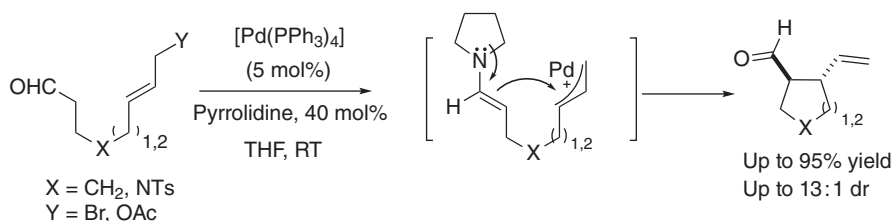
Asymmetric version



Scheme 4.1 An example of synergistic Pd/enamine catalysis: Córdova's direct α -allylic alkylation of aldehydes and cyclic ketones.

In 2007, Saicic and coworkers reported a direct intramolecular α -allylation of aldehydes to construct five and six-membered rings through cooperative enamine-Pd(0) catalysis (Scheme 4.2) [31]. The reaction was proposed to involve the addition of an enamine intermediate to a Tsuji–Trost palladium π -allyl complex *in situ* formed from allyl bromide or acetate with the Pd(0) catalyst. This intramolecular allylation was highly diastereoselective (up to 13:1 dr). Similar to Córdova's work, switching the achiral amine catalyst to a chiral amine catalyst, that is, MacMillan's catalyst, (*S*)-proline, and (*S*)-2-diphenylprolinol, caused

inactivation of the reaction. Although still effective, no enantioselectivity was obtained in the case of (*S*)-2-methoxymethyl pyrrolidine.

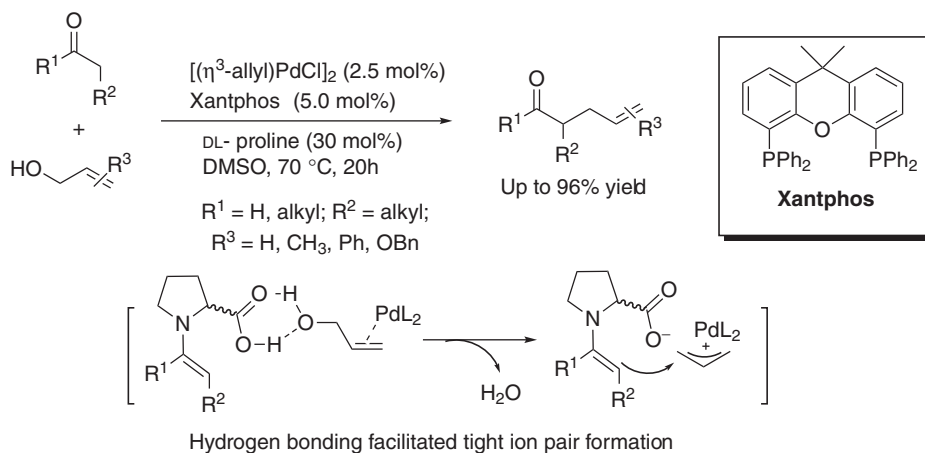
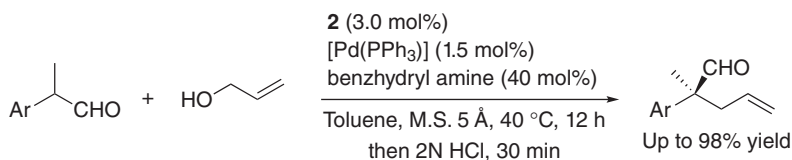


Scheme 4.2 Direct intramolecular α -allylation of aldehydes.

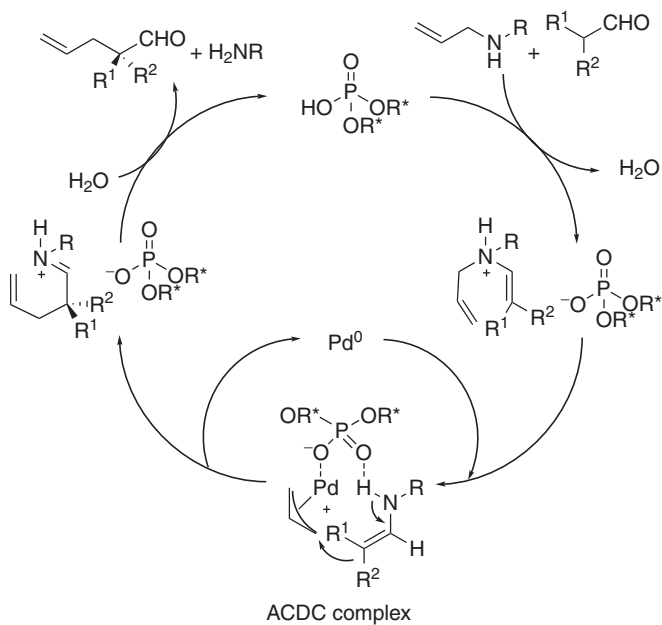
To form the electrophilic Tsuji–Trost palladium π -allyl electrophiles, it is generally required that the starting allyl compounds contain a good leaving group such as bromide and acetate at the allylic position. Direct α -allylation using allylic alcohols would avoid the conversion of the hydroxyl group into these leaving groups and would thus make this reaction more atom-economical. However, the hydroxyl group is a poor leaving group and is expected to render a much more difficult organic transformation. In 2009, Breit and coworkers reported the first α -allylation reaction of aldehydes and ketones with allylic alcohols through dual Pd/enamine catalysis (Scheme 4.3) [32]. In this reaction, a diphosphine Xantphos ligand with a large bite angle was used to obtain high activity of the catalyst. Although this reaction gave the direct intermolecular allylation products in good yields (up to 96% yield), no enantioselectivity was obtained using optically pure *L*-proline as the amine catalyst. It was suggested that the presence of a carboxylic acid group in the amine catalyst is necessary to facilitate the formation of a tight ion pair intermediate through hydrogen bonding and protonation of the hydroxyl group. The proposed tight ion pair intermediate brought the enamine nucleophile and the palladium π -allyl electrophile in close proximity and thus enabled a rapid allylation reaction.

Asymmetric Allylation of Aldehydes via Tsuji–Trost Type Palladium π -Allyl Complexes

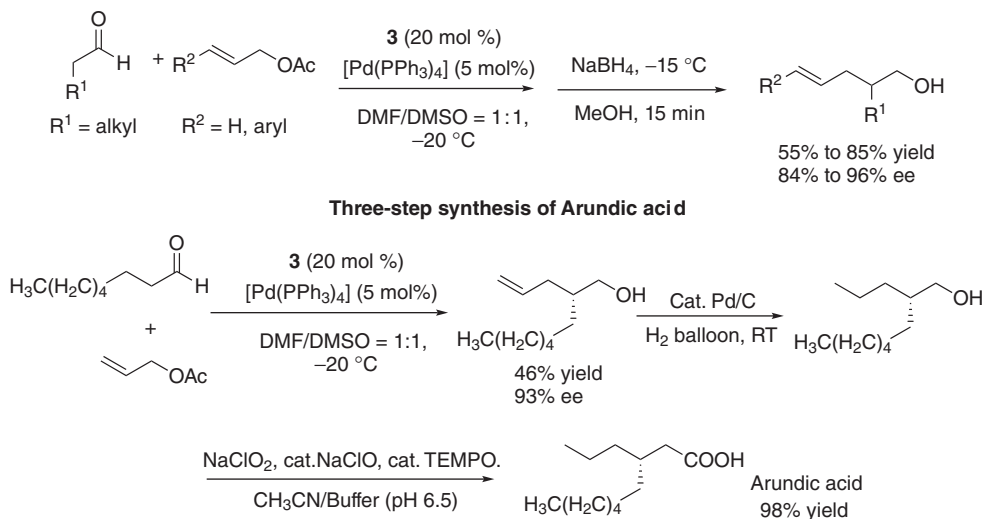
Earlier attempts for asymmetric direct intermolecular α -allylation of carbonyl compounds were not successful until 2011. Through the concerted action of three different catalytic species: $[\text{Pd}(\text{PPh}_3)_4]$, benzhydryl amine, and TRIP (**2**), asymmetric Tsuji–Trost-type α -allylation of α -branched aldehydes with allylic alcohol was achieved generating an all-carbon quaternary stereogenic center in high yields (up to 98%) and enantioselectivity (up to >99% ee) (Scheme 4.4) [33]. The high enantioselectivity of this reaction was enabled by asymmetric counteranion-directed catalysis (ACDC) [34, 35] through formation of an ACDC complex intermediate that involves all three catalysts. The preferred formation of a configurationally defined *E* enamine in the ACDC complex was also critical to ensure high enantioselectivity.

Scheme 4.3 Pd/proline-catalyzed α -allylation reaction with allylic alcohols.

Mechanism:

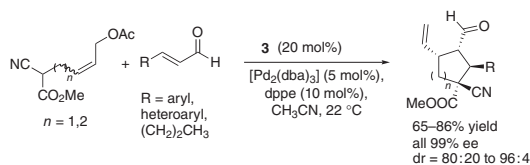
Scheme 4.4 Asymmetric α -allylation of different aldehydes.

Following their earlier work in 2006, the Córdova group disclosed an asymmetric direct intermolecular α -allylic alkylation of linear aldehydes by combining an achiral Pd(0) catalyst and Jørgensen-Hayashi chiral secondary amine catalyst (**3**) in 2012 (Scheme 4.5) [36]. High enantioselectivity (up to 96% ee) and high yields (up to 85%) for this reaction were obtained through a careful screening of the reaction conditions including a variety of combinations of solvents and the reaction temperatures. This concise cocatalytic asymmetric system was applied in the total synthesis of Arundic acid.

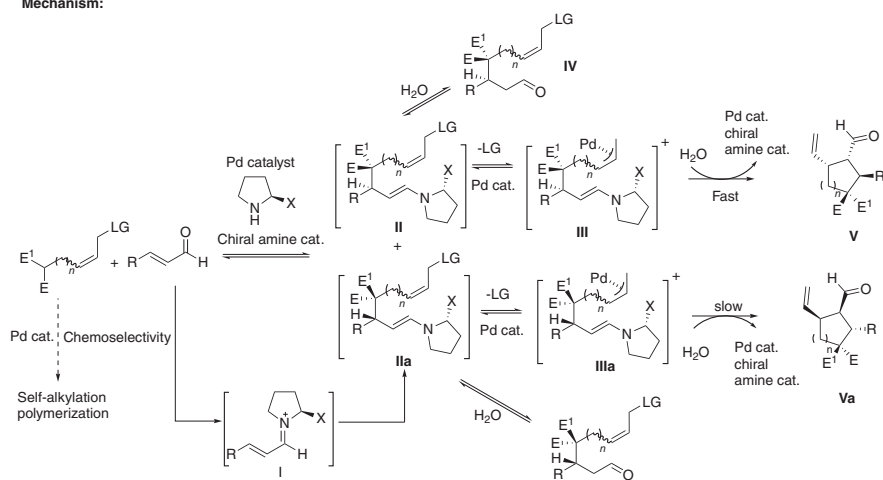


Scheme 4.5 Córdova's asymmetric direct α -allylic alkylation of aldehydes and total synthesis of arundic acid.

Using a similar approach, the Córdova group developed another asymmetric reaction involving a Michael/ α -allylation cascade very recently [37]. The asymmetry of the reaction was introduced through a chiral secondary amine catalyst (**3**) incorporating with an achiral palladium catalyst. Through careful design of the substrates and the reaction, this asymmetric dynamic kinetic organic transformation [38] afforded polysubstituted cyclopentanes and cyclohexanes bearing an all-carbon stereocenter in good yields with high chemo- and enantioselectivity (Scheme 4.6). This reaction cascade was proposed to be initiated with a reversible conjugate addition via an iminium intermediate **I**, generating the corresponding enamine intermediate **II**; enamine intermediate **II** would provide Michael adduct **IV** after hydrolysis. The overall formation of **IV** is reversible. On the other hand, oxidative addition of the Pd catalyst to intermediate **II** would afford π -allyl intermediate **III**, which can be attacked by the enamine to form polysubstituted carbocycles **V**. It is notable that four stereoisomers of **III** can be formed in this process. The chemo- and stereo outcomes of this reaction are well controlled by the dynamic kinetic process.

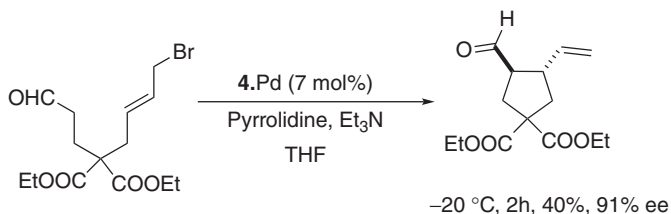


Mechanism:

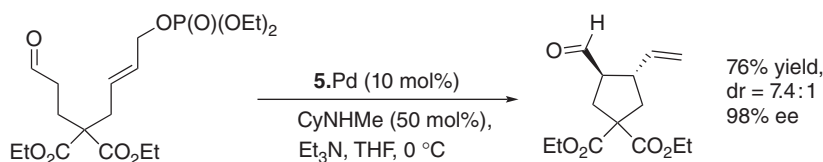


Scheme 4.6 Michael/α-allylation cascade reaction catalyzed by a palladium-chiral amine combined catalyst.

In the direct intramolecular reaction of α -allylation of aldehydes reported earlier by Saicic and coworkers, the induction of asymmetry of the reaction was not successful with chiral amine catalysts. High enantioselectivity (91% ee) was obtained when a chiral Pd(0) catalyst was employed using a chiral diphosphine ligand (*R*)-(BINAP) (**4**) at low temperature; however, only a modest yield was obtained (40%) (Scheme 4.7, Eq. 1). Later on, the same group achieved high enantioselectivity and good activity of this reaction by replacing (*R*)-(BINAP) with a structurally more hindered ligand (*R*)-(Ph-MeOBIPHEP, **5**) along with methyl cyclohexylamine serving as the amine catalyst. In addition, a phosphate group was used as the leaving group instead of the bromide group in this reaction (Scheme 4.7, Eq. 2) [39].



Eq. 1

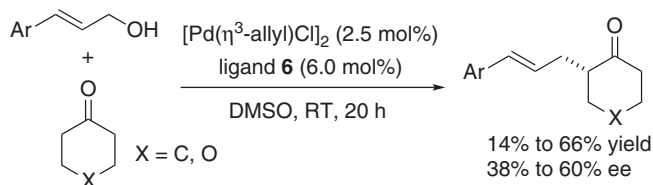


Eq. 2

Scheme 4.7 Asymmetric direct intramolecular α -allylation of aldehydes.

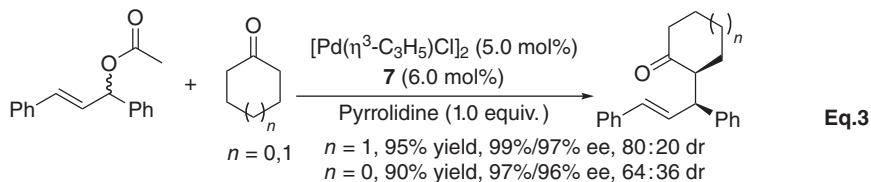
Allylation of Ketones via Tsuji–Trost Type Palladium π -Allyl Complexes While asymmetric α -allylation of aldehydes has achieved considerable success in recent years, the development of catalytic enantioselective direct α -allylation of ketones appears to be more difficult. In order to realize this difficult asymmetric transformation, the Shibasaki group [40] designed a chiral bifunctional ligand (**6**) bearing a proline unit and a phosphine unit (Scheme 4.8). This bifunctional catalyst was expected to bring the π -allyl-Pd electrophile and the enamine nucleophile in close vicinity enabling the difficult allylation of ketones to occur. However, direct asymmetric α -allylation of ketones with allylic alcohols using this bifunctional catalyst only resulted in moderate yields and enantioselectivities.

In 2011, the Zhang group demonstrated two examples of asymmetric allylation of cyclic ketones with high enantioselectivities (99 and 97% ee, respectively) through incorporation of a chiral palladium catalyst and achiral secondary amine. The enantioselectivity of the reaction was introduced via a chiral phosphorus ligand (**7**) derived from ferrocene (Scheme 4.9, Eq. 3) [41]. The drawback of this method is that a stoichiometric amount of pyrrolidine was required to ensure efficient conversion. The substrate scope of this reaction was very narrow. Using

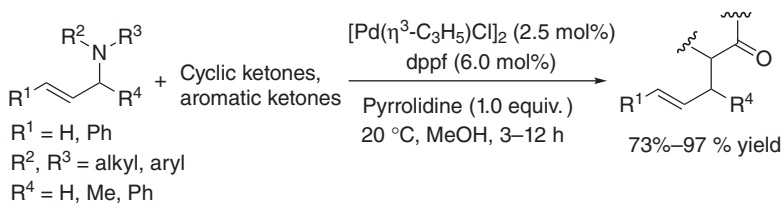


Scheme 4.8 Asymmetric allylation of ketones through bifunctional cooperative enamine-Pd catalysis.

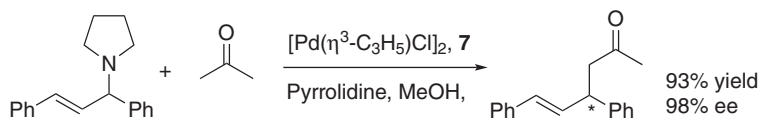
a similar approach, the same group developed another method for the allylation of ketones with allylic amines (Scheme 4.9, Eq. 4). The allylation products were obtained in high yields [42]. It is interesting that the difficult C–N bond cleavage of allylic amines was reported to be facilitated by hydrogen bond activation through the alcoholic solvent. Asymmetric version of this reaction was attempted with acetone generating the allylation products in high yields and excellent enantioselectivities (Scheme 4.9, Eq. 5).



Eq.3



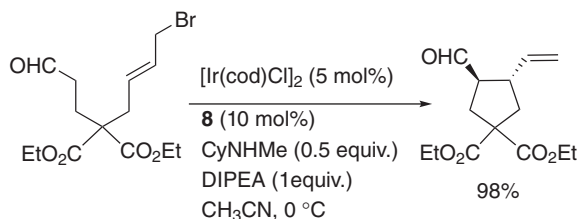
Eq.4



Eq.5

Scheme 4.9 Zhang's allylation of cyclic ketones.

Allylation of Aldehydes via Other Metal π -Allyl Complexes Other transition metals have also been used to form metal π -allyl electrophiles in direct allylation reaction of carbonyl compounds. In their effort to develop an asymmetric version of the intramolecular allylation of aldehydes, Saicic and coworkers attempted the intramolecular allylation of an aldehyde in the presence of a catalytic amount of $[\text{Ir}(\text{cod})\text{Cl}]_2$, CyNHMe, and a chiral phosphorous ligand (Scheme 4.10) [39]. Although the enantioselectivity and diastereoselectivity of this reaction were very low, the desired cyclization product was obtained in nearly quantitative yield.



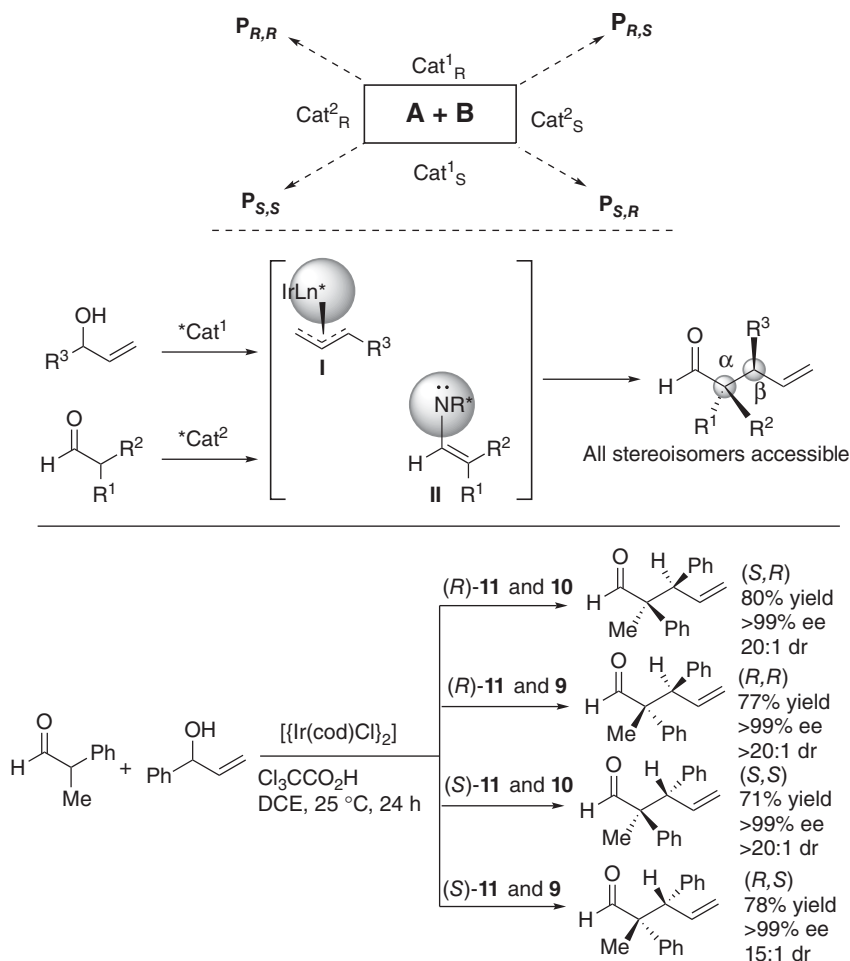
Scheme 4.10 Intramolecular allylation of aldehyde through cooperative enamine-Iridium catalysis.

On the basis of the above work a highly enantioselective α -allylation of branched aldehydes with allylic alcohols was achieved very recently by the Carreira group (Scheme 4.11) [43]. The highlight of this work is the accomplishment of stereodivergent dual catalysis. The core concept of stereodivergent dual catalysis lies in the incorporation of two distinct and highly face-selective catalytic cycles to enable access to all possible stereoisomers of the products with multiple stereocenters, which has remained a long-standing challenge in asymmetric catalysis. In this reaction, amine and Ir-catalysis were successfully coupled via chiral enamine and allyl-Ir intermediates. Through simple catalyst permutations of a chiral amino catalyst (**9**) and its (pseudo)enantiomer (**10**) with (*R*)/(*S*)-ligands (**11**), the desired γ,δ -unsaturated aldehydes bearing vicinal quaternary/tertiary stereogenic centers were obtained in moderate to good yields with excellent enantioselectivity and high diastereoselectivity.

Recently, Gold(I) has also been demonstrated to be effective in forming π -allyl electrophiles in the catalytic asymmetric intramolecular α -allylation of aldehydes with allylic alcohols (Scheme 4.12) [44]. A gold(I) complex (**13**), a chiral secondary amine (**12**), and benzoic acid were combined as the cocatalytic system. The cyclization products were obtained with high enantioselectivities, moderate to high yields, and diastereoselectivities.

Allylation and Benzylation of Aldehydes via Enamine Addition to Carbocation Intermediates The Cozzi group discovered that InBr_3 along with MacMillan's chiral amine catalyst (**14**) were effective to catalyze the asymmetric α -allylation of aldehydes with allylic alcohols (Scheme 4.13, Eq. 6) [45]. Although In(III)-salts are generally accepted as hard Lewis acids [46], the compatibility of In(III)-salts with nucleophilic aliphatic amines has been demonstrated in the literature [47–49]. In this reaction, InBr_3 activates the benzyl allylic alcohol by converting it to a stable carbocation, which subsequently reacts with an enamine intermediate formed from an aldehyde and the chiral amine catalyst to afford the desired α -alkylation products in good yields with moderate diastereoselectivities and high enantioselectivities. The stability of the carbocation was the primary driving force for this $\text{S}_{\text{N}}1$ -type reaction. In addition to the stereo control provided by the chiral amine catalyst, the steric hindrance of the carbenium ion also contributed to the stereoselectivity of the reaction. The limitation of this method lies in that an allylic alcohol that can form a relative stable carbocation is required to achieve

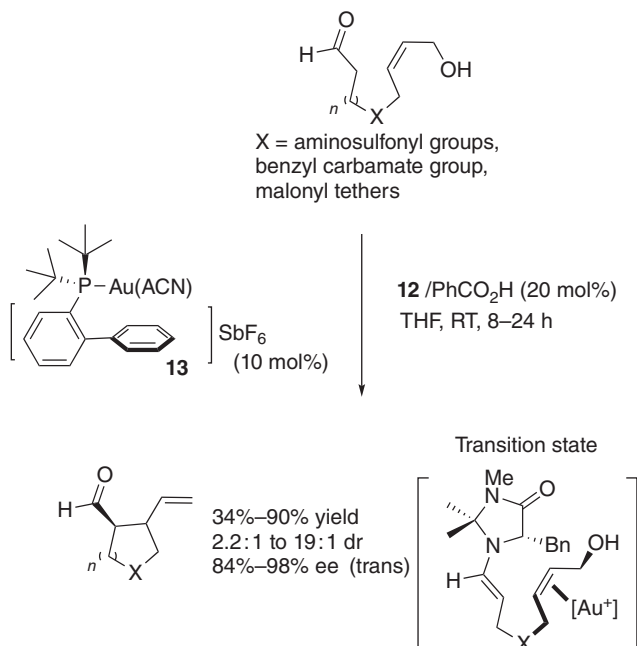
Illustration of stereodivergent dual catalysis



Scheme 4.11 Illustration of stereodivergent dual catalysis and an example of stereodivergent asymmetric α -allylation of branched aldehydes with allylic alcohols through dual catalysis.

successful alkylation. Alcohols that form carbenium ions located at -1 or above on the Mayr scale [50] were not reactive with the enamine addition.

Asymmetric benzylic and benzhydrylic α -alkylations of aldehydes with alcohols were also proved to be possible using this strategy (Scheme 4.13, Eq. 7) [51]. The alkylation products were obtained in moderate to good yields with moderate diastereoselectivities and good to excellent enantioselectivities. In these reactions, $\text{In}(\text{OTf})_3$ was used in place of InBr_3 in combination with a chiral bulky secondary amine (**12** or **15**) serving as the cooperative catalytic system. The substrate scope of the alcohol, however, was limited to benzylic and benzhydrylic alcohols carrying



Scheme 4.12 Intramolecular α -allylation of aldehydes with alcohols catalyzed by Au(I)-amine cocatalysts.

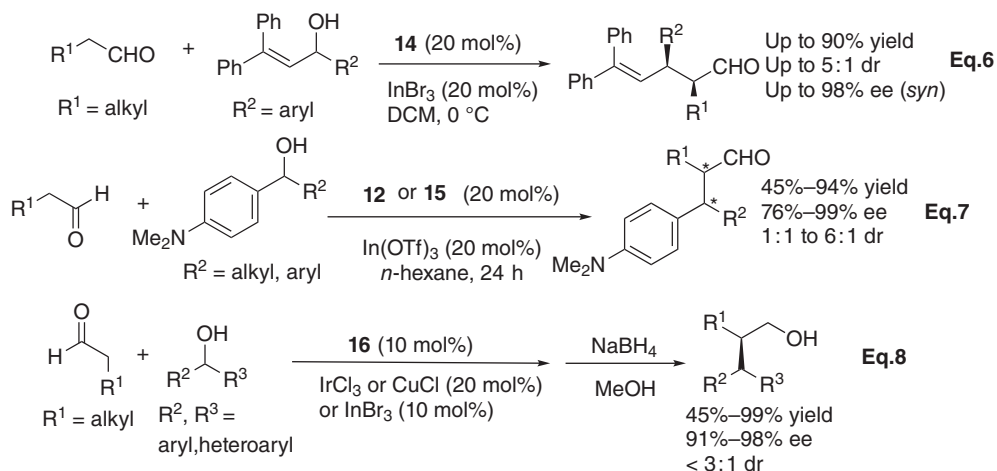
strongly electron-donating groups such as dimethylamino and methoxy groups at the *para*- or *ortho*-position of the aryl substituent.

Later on, Xiao [52] reported another intermolecular asymmetric α -benzylation of aldehydes with alcohols through cooperative metal Lewis acid-enamine catalysis via a carbocation intermediate. In this reaction, a chiral amine catalyst [diarylprolinol silyl ether (**16**)] was successfully combined with CuCl, IrCl₃, or InBr₃ to effect the α -benzylation reaction of aldehydes in good yields (up to 96%) and excellent enantioselectivities (up to 99% ee) (Scheme 4.13, Eq. 8).

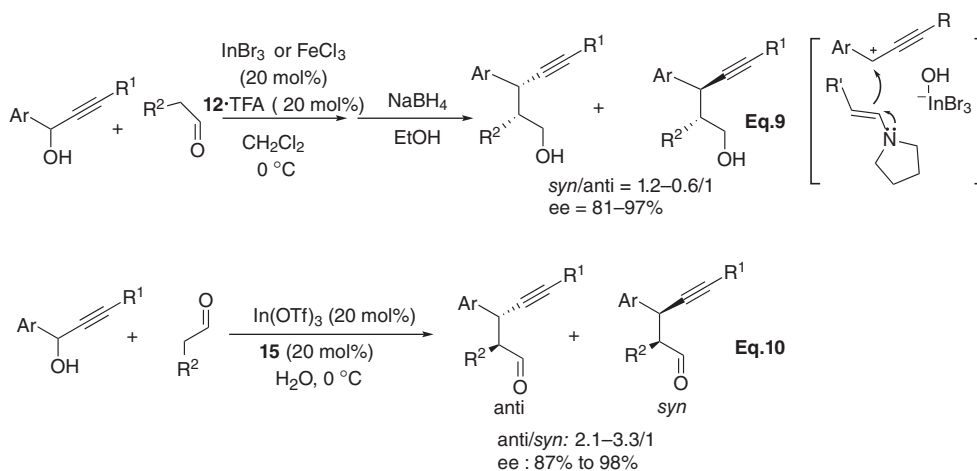
4.2.1.2 α -Propargylation of Aldehydes

Propargylation of Aldehydes via Enamine Addition to Carbocation Intermediate

Nishibayashi and coworkers reported the first asymmetric propargylation of aldehydes with a propargylic alcohol bearing an internal alkyne (Scheme 4.14, Eq. 9) [53]. In Nishibayashi's approach, the trifluoroacetate salt of MacMillan's catalyst (**12**) was combined with InBr₃ or FeCl₃ to initiate the addition of an *in situ* formed enamine to a propargylic carbocation intermediate through an S_N1 pathway, similar to Cozzi's work [45]. The alkylation products were generated with high enantioselectivities but poor diastereoselectivities. By combining In(OTf)₃ with a bulky chiral secondary amine (**15**), Cozzi and coworkers achieved the asymmetric propargylation of aldehydes with propargylic alcohols in water



Scheme 4.13 Stereoselective α -alkylation of aldehydes with allylic alcohols by combination of enamine catalysis and metal Lewis acid catalysis through a carbocation intermediate.



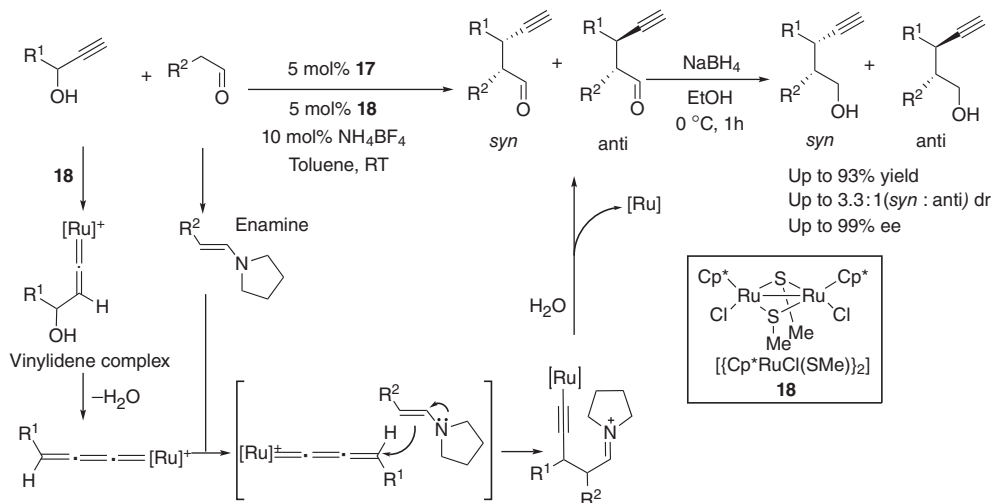
Scheme 4.14 α -Propargylation of aldehydes with propargylic alcohols through carbocation intermediates.

(Scheme 4.14, Eq. 10) [54]. In both propargylic alkylation reactions, the presence of a strong electron-donating group such as dimethylamino and methoxy groups at the *para*- or *ortho*-position of the aryl substituent is necessary in order to stabilize the carbocation intermediate generated in the reaction.

Propargylation of Aldehydes via Enamine Addition to Metal-Allenylidene Complexes

In 2010, Nishibayashi and coworkers reported a new type of enantioselective propargylic alkylation of propargylic alcohols with aldehydes through enamine addition to a metal-allenylidene complex [55]. In the presence of both a chiral

secondary amine (**17**) and a thiolate-bridged diruthenium complex (**18**), the corresponding propargylation products were obtained in excellent yields with high enantioselectivity (up to 99% ee) as a mixture of two diastereoisomers (Scheme 4.15). The cooperative action of the active ruthenium-allenylidene intermediate, which is formed by the ruthenium complex and the alcohol, and the enamine intermediate generated *in situ* from the pyrrolidine and the aldehyde is the key to lead to the success of this reaction. This method was effectively extended to a wide variety of aldehydes; however, the alcohols were limited to aromatic propargylic alcohols with terminal alkynes only.

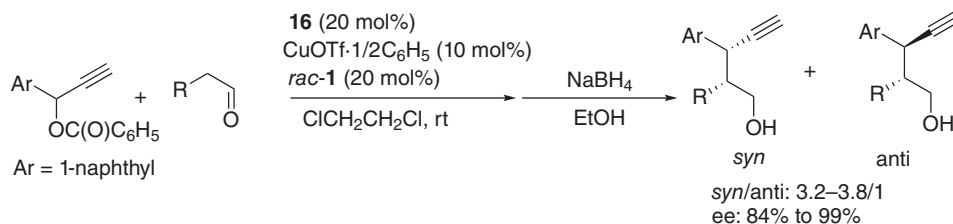


Scheme 4.15 Nishibayashi's cooperative enamine-Ru catalysis for asymmetric propargylation of aldehydes.

CuOTf has also proved to be effective in forming Cu(I) -allenylidene complex with propargyl alcohol, although the presence of an extra ligand such as BINAP is necessary to obtain higher stability of the complex [56]. Through enamine addition to a Cu(I) -allenylidene complex intermediate, the Nishibayashi group has achieved enantioselective propargylic alkylation of propargylic ester with aldehydes in the presence of CuOTf and a chiral amine (Scheme 4.16). CuOTf offers a much cheaper alternative to the diruthenium complex; however, this reaction is less active, requiring high loadings of both the amine and the metal catalysts with much narrower substrate scope, but with higher stereoselectivities.

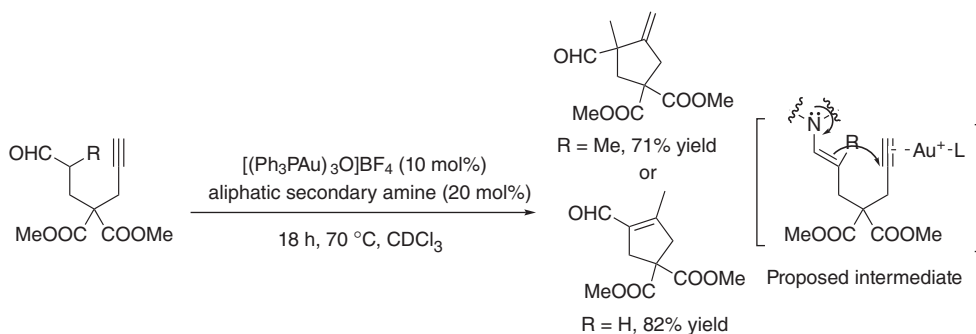
4.2.1.3 α -Alkenylation and α -Arylation of Aldehydes

α -Alkenylation of Aldehydes through Enamine Addition to Metal π -Acid Activated Carbon–Carbon Triple Bond Taking advantage of the carbophilic Lewis acidity of homogeneous gold(I) complexes [57–59], the Kirsch group developed a carbocyclization reaction of aldehydes with unactivated alkynes through



Scheme 4.16 Cooperative enamine-Cu(I) catalysis for asymmetric propargylation of aldehydes.

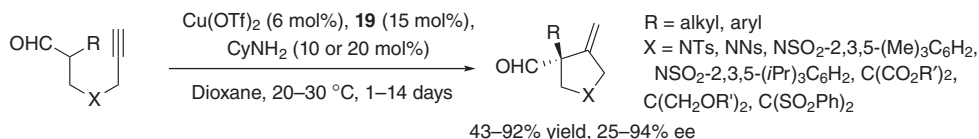
cooperative enamine catalysis-Au(I) catalysis (Scheme 4.17) [60]. An aliphatic secondary amine and a gold(I) salt were combined in the reaction to activate the aldehyde and the triple bond, respectively and simultaneously, forging a carbon–carbon bond between the α -carbon of the aldehyde and the internal sp carbon of the triple bond. 5-*exo-dig* cyclization products were obtained in good yields from secondary formyl alkynes (Scheme 4.17). When α -unbranched aldehydes were used, double bond migration was observed following the 5-*exo-dig* cyclization. Unfortunately, asymmetric version of this cyclization reaction was not attempted in this work.



Scheme 4.17 5-*exo-dig* cyclization of formyl alkyne catalyzed by combined gold(I)/amine catalysts.

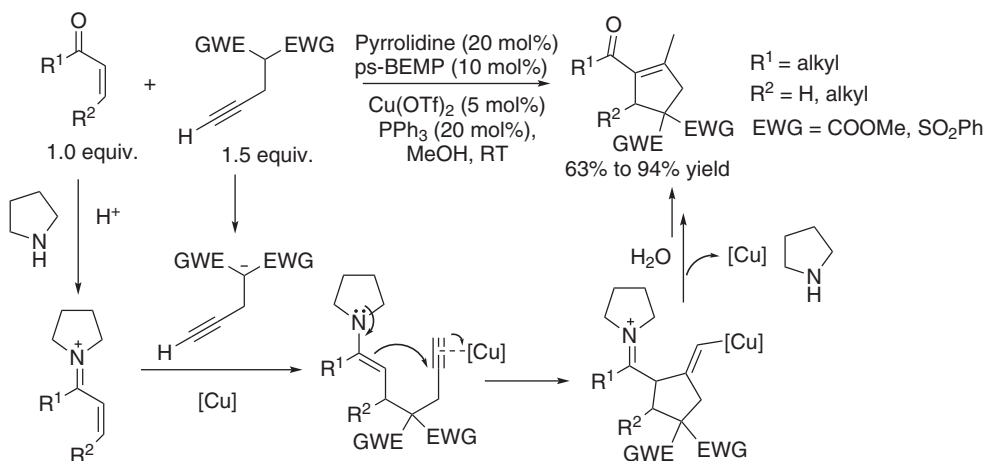
Following Kirsch's work, Michelet and Ratovelomanana-Vidal discovered that the combination of an amine catalyst with other transition metal catalysts could also effect the cyclization reaction of formyl alkynes [61–66]. The cooperative action of InCl₃ with a secondary amine provided an extended substrate scope of the carbocyclization of formyl alkynes at elevated temperature (R = methyl and phenyl) [61, 62]. Using a less bulky primary amine, for example, CyNH₂, in conjunction with InCl₃, the cyclization of sterically more bulky formyl alkynes was achieved (R = *n*-butyl, benzyl, or *i*-propyl) [62]. Replacing InCl₃ with Cu(OTf)₂ in the presence of PPh₃ together with CyNH₂ as the catalyst system decreased the reaction temperature to room temperature [63, 64]. The attempt of an asymmetric

version of this reaction was not successful until recently. Through inclusion of a chiral phosphorus ligand (**19**) in the $\text{Cu}(\text{OTf})_2/\text{CyNH}_2$ system, carbocyclization of aldehydes bearing terminal alkynes gave the corresponding cyclopentanes and pyrrolidines in moderate to good yields with moderate to excellent enantioselectivities (Scheme 4.18) [65, 66].



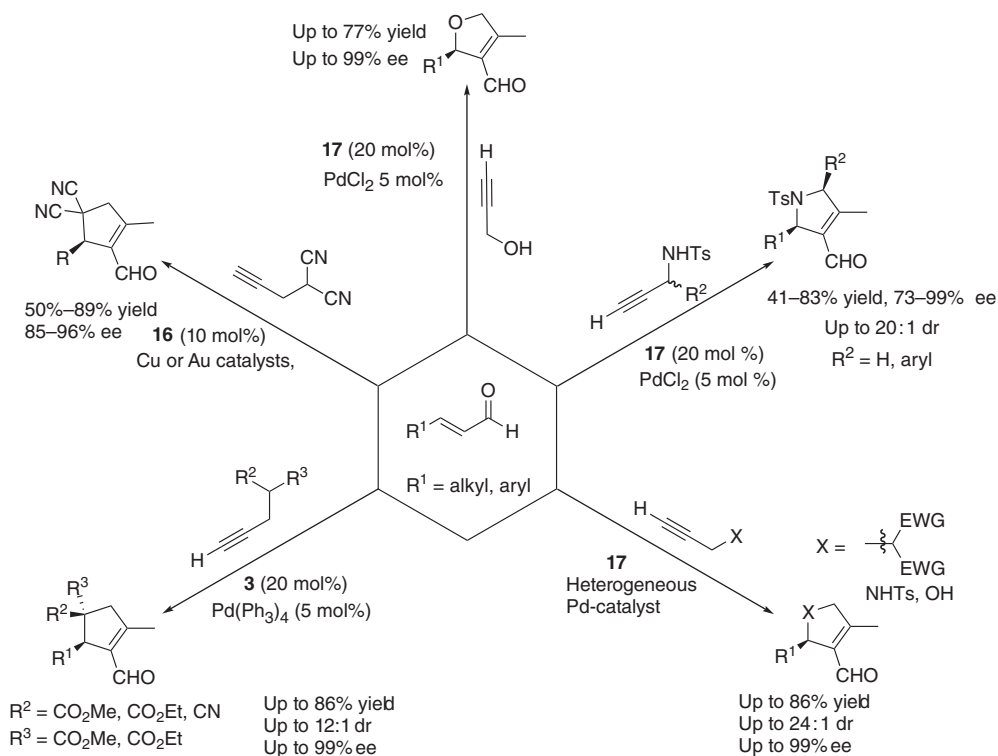
Scheme 4.18 Asymmetric carbocyclization of α -substituted formyl alkynes.

The intramolecular α -alkenylation of aldehydes provides a convenient tool to combine with sequential iminium-enamine catalysis for the design and development of efficient and atom-economical cascade reactions. Using this concept, the Dixon group developed a cascade reaction of α,β -unsaturated ketones and propargylated carbon nucleophiles for the synthesis of cyclopentene. This one-pot multistep cascade is initiated through a Michael addition to the iminium ion activated enone, forming an enamine intermediate; the enamine intermediate attacks the copper(I) activated alkyne to generate a C–C bond followed by protonolysis, hydrolysis, and isomerization to give the desired cyclopentenones in moderate to good yields under mild conditions (Scheme 4.19) [67]. This cascade reaction was catalyzed by a combined catalytic system incorporating pyrrolidine, $\text{Cu}(\text{OTf})_2$, and PPh_3 . It is believed that PPh_3 not only serves as a ligand to the copper, but also reduces $\text{Cu}(\text{II})$ to $\text{Cu}(\text{I})$, which is responsible for the alkyne activation.



Scheme 4.19 Tandem Michael addition/carbocyclization of α,β -unsaturated ketones and propargylated carbon acids.

Both the Córdoba group and the Jørgensen group achieved the asymmetric versions of this cascade annulation with some variations (Scheme 4.20). The Córdoba group used a chiral secondary amine (**3**) in combination with $\text{Pd}(\text{Ph}_3)_4$ to generate functionalized cyclopentenones in good yields, high diastereoselectivity, and enantioselectivity [67]; the Jørgensen group used a chiral secondary amine (**16**) together with $\text{Cu}(\text{OTf})_2$, CuOTf , or $\text{Au}(\text{NTf}_2)_2(\text{Ph}_3)$ as the combined catalytic system to obtain functionalized cyclopentenones with high enantioselectivity [68, 69].



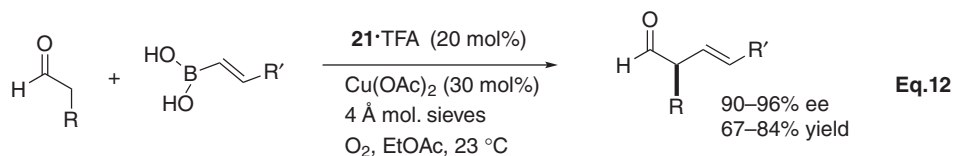
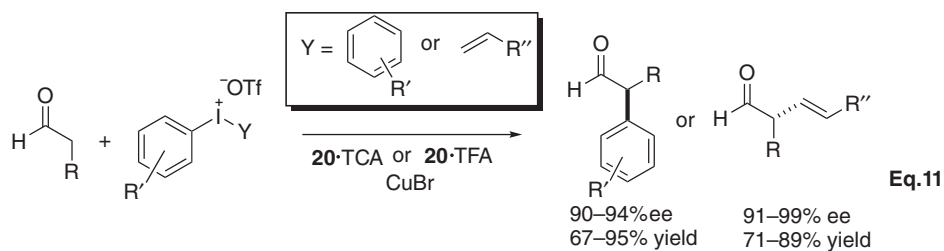
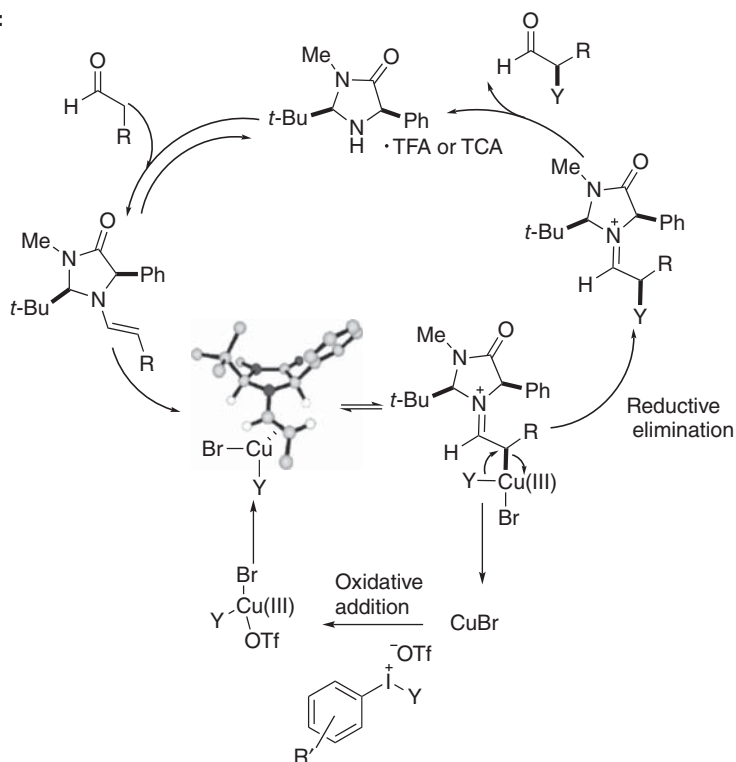
Scheme 4.20 Asymmetric cascade annulation reactions based on sequential combination of iminium catalysis with cooperative enamine/ π -acid metal catalysis.

Michael/carbocyclization cascade reactions through cooperative enamine-metal catalysis leading to the formation of heterocycles have also been reported (Scheme 4.20). Oxa-Michael/carbocyclization of enals and propargyl alcohols produced dihydrofurans [70]; aza-Michael/carbocyclization of enals and *N*-tosylpropargylamines afforded dihydropyrroles [71]. In both reactions, a chiral secondary amine (**17**) was combined with PdCl_2 as the catalytic system, and the resulting heterocycles were obtained in moderate to good yields with good enantioselectivity. A heterogeneous $\text{Pd}(0)$ catalyst along with a chiral secondary amine (**17**) also effectively catalyzed these annulation reactions in good yields with good diastereoselectivities and good to excellent enantioselectivities [72].

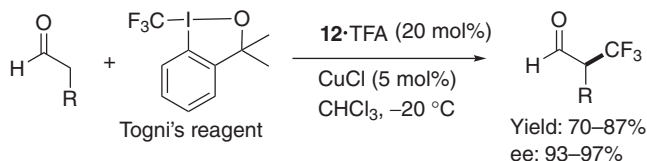
α -Arylation and α -Alkenylation of Aldehydes Through Enamine Addition to Highly Electrophilic Cu(III)-C(sp²) Species Enantioselective α -arylation and α -alkenylation of aldehydes to generate enolizable α -carbonyl benzylic/allylic stereocenters are challenging because the formed methine stereocenters readily undergo postreaction racemization and/or olefin-carbonyl conjugation [73–78]. Recently, the MacMillan group has developed two protocols for these challenging asymmetric organic transformations through synergistic combination of two discrete catalytic cycles, that is, chiral amine-enamine and Cu(I)-Cu(III) copper catalysis (Scheme 4.21, Eq. 11) [79, 80]. In both protocols, a salt of MacMillan's amine catalyst (**20**) was used to activate the aldehyde as an enamine intermediate; a catalytic amount of CuBr was incorporated to activate the iodonium salts by forming a highly electrophilic Cu(III)-C(sp²) species. The formation of this Cu(III)-C(sp²) species is initiated by oxidative addition of Cu(I) into the C–I bond of the iodonium compounds. The electron-rich enamine coordinates to this Cu(III)-C(sp²) species to form a π -Cu complex, which then undergoes bond isomerization to generate an η^1 -iminium organocopper complex intermediate followed by reductive elimination to forge a carbon-carbon bond and recover the Cu(I) catalyst. In both reactions, the corresponding α -arylated and α -alkenylated aldehydes were produced in high yields (up to 95%) and with high enantioselectivities (arylation, 90–94% ee; vinylation, 91–99% ee). The effectiveness of this arylation method has been demonstrated in a rapid synthesis of a topical analgesic [(*S*)-ketoprofen]. It is notable that the MacMillan group has extended this strategy to using aldehyde and vinyl boronic acid as the coupling partners to provide α -alkenylation products in good yields (67–84%) and high enantioselectivities (85–96% ee) (Eq. 12) [81]. In this reaction, alkenyl boronic acids were used in place of vinyl potassium trifluoroborate salts and vinyl iodonium salts in previous protocols [79, 80]. In addition, readily available and bench stable Cu(II) salts, for example, Cu(OAc)₂, was employed replacing CuBr. Boronic acids are one of the most pervasive building blocks in organic chemistry. The availability of this concise and convenient method largely extends the scope for functionalizing the α -positions of aldehydes.

4.2.1.4 α -Trifluoromethylation of Aldehydes Through Enamine Addition to Togni's Reagent

Polyfluorinated alkyl substituents are reported to enhance metabolic stability and to increase electronegativity and lipophilicity in pharmaceuticals and agrochemicals [82–84]. The first highly enantioselective α -trifluoromethylation of aldehydes was achieved by the Macmillan group using photoredox organocatalysis [85]. Recently, the Macmillan group has developed a nonphotolytic approach to the enantioselective α -trifluoromethylation of aldehydes through the merger of Lewis acid and organocatalysis using an electrophilic trifluoromethyl alkylating reagent (Togni's reagent) [86]. In this reaction, Macmillan's amine catalyst (**12**) reacts with the aldehyde to form an enamine intermediate; a metal Lewis acid, for example, CuCl, binds to Togni's reagent to facilitate the I–O bond cleavage, generating a highly electrophilic iodonium salt; nucleophilic attack of enamine on iodonium

**Mechanism:****Scheme 4.21** Asymmetric α -arylation and α -alkenylation of aldehydes.

salt enables the formation of a C–I bond via a closed-shell pathway; the resulting λ^3 -iodane species undergoes reductive elimination to forge the stereoselective formation of the C–CF₃ bond. The trifluoromethylation products were obtained in high yields (70–87%) and enantioselectivities (93–97% ee) (Scheme 4.22).



Scheme 4.22 α -Trifluoromethylation of aldehydes using Togni's reagents.

4.2.2

Asymmetric Direct Aldol Reactions

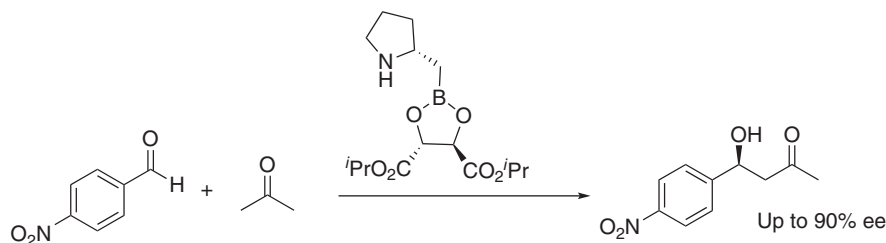
Aldol reaction is one of the most important carbon–carbon bond forming reactions in organic chemistry. Direct asymmetric cross aldol reaction was not realized until late 1990s. In particular, the advent of enamine catalysis has enabled this traditionally difficult asymmetric transformations to be achieved at ease. Asymmetric cross aldol reactions have also become a reliable model reaction to test new ideas and new designs of catalysts. Recently, cooperative enamine-Lewis acid catalysis has proven to be effective for the asymmetric cross aldol reactions.

4.2.2.1 Asymmetric Direct Aldol Reactions Catalyzed by Bifunctional Amine-Boronic Acid Catalysts

The Whiting group reported the first example of bifunctional enamine-Lewis acid catalysis in 2008 [87]. The bifunctional amine-boronic acid catalysts were constructed by installing a boronic acid or ester group on a chiral pyrrolidine moiety. These catalysts were able to catalyze the direct aldol reaction of 4-nitrobenzaldehyde and acetone (Scheme 4.23); however, the presence of the boronic acid group somehow reduced the reactivity of the pyrrolidine and resulted in low enantioselectivity of the aldol product (38% ee). On *in situ* esterification of the boronic acid, the enantioselectivity of the aldol product increased to up to 90% ee. The Lewis acidity of the boronate group is believed to play a role in assisting aldehyde activation and in the formation of transition state.

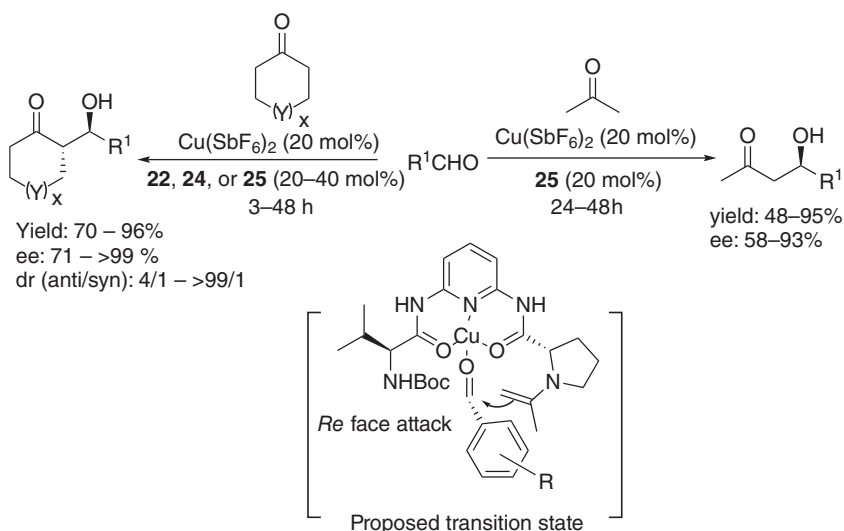
4.2.2.2 Asymmetric Direct Aldol Reactions Catalyzed by Bifunctional Amine-Metal Lewis Acid Catalysts

The Wang group designed and developed two types of bifunctional amine-metal Lewis acid catalysts to cooperatively incorporate enamine catalysis with metal Lewis acid catalysis [88–90]. In these bifunctional catalysts, the amine moiety is tethered to a bidentate ligand (**22** and **23**) and a tridentate ligand (**24** and **25**), respectively, bringing the amine group and the metal into close proximity without



Scheme 4.23 Asymmetric direct aldol reaction through bifunctional enamine-boronic acid catalysis.

interacting with each other. Both primary amines and secondary amines in these bifunctional systems proved to be efficient in forming the enamine intermediates. A number of metal salts including Zn(II), Co(II), La(III), were able to catalyze the direct cross aldol reaction of ketones and aldehydes in combining with the ligands. Cu(II) salts turned out to be the most efficient to afford the aldol products in high yields with high diastereoselectivities and enantioselectivities (Scheme 4.24). It is believed that the bifunctional nature of these catalytic systems contributes to the high stereoselectivity and exceptional activity of these aldol reactions.

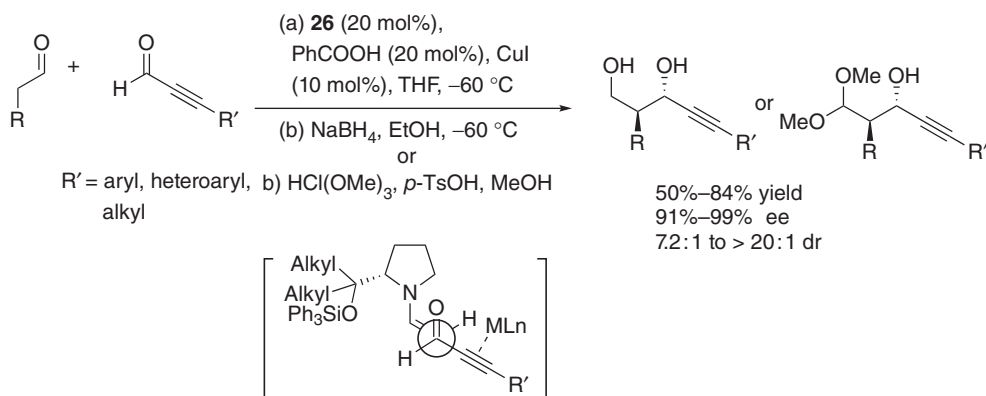


Scheme 4.24 Asymmetric direct cross aldol reaction of ketones and aldehydes catalyzed by bifunctional amine-metal Lewis acid catalysts.

4.2.2.3 Enamine Addition to Ynals Activated by Metal π -Acids

The asymmetric direct aldol reaction of aldehydes and ynals offers a valuable entry to synthetically important functionalized propargylic alcohols. The first direct organocatalytic aldol reaction of alkynyl aldehydes was reported by

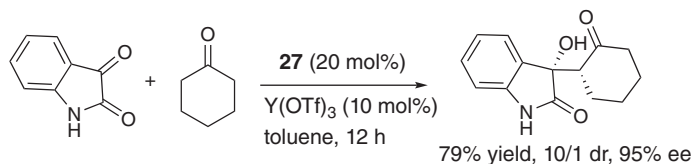
the Palomo group in 2013. This difficult, highly enantioselective reaction was catalyzed by a ternary catalyst system comprising a chiral prolinol ether (**26**), CuI, and benzoic acid (Scheme 4.25), generating propargylic alcohols in good yields, excellent diastereoselectivity [over 20/1 dr (*anti/syn*)], and enantioselectivity (up to 99% ee) [91]. In this catalytic system, the chiral prolinol ether (**26**) acts as the amine catalyst to form an enamine intermediate with the aldehyde; the metal salt activates the ynal through binding to the triple bond of the ynal. Nucleophilic addition of the enamine to the aldehyde group of the ynal affords the corresponding aldol addition product. In addition to CuI, other carbophilic metal salts, such as Ph₃PAuCl, Rh₂(OAc)₄, and AgOAc, were also suitable to promote this aldol reaction. Stereocontrol in reactions involving ynals is generally difficult. The exceptionally high diastereoselectivity of this reaction likely results from the steric inflation of the alkyne moiety as a consequence of metal–alkyne association.



Scheme 4.25 Direct asymmetric cross aldol reaction of ynals and aldehydes by cooperative prolinol ether-transition metal-Brønsted acid catalysis.

4.2.2.4 Asymmetric Direct Aldol Reactions by Cooperative Arylamine-Metal Lewis Acid Catalysis

In sharp contrast to their aliphatic counterparts, arylamines have rarely been used in enamine catalysis, likely following the general understanding of their much lower nucleophilicity as compared with aliphatic amines. In 2013, the Wang group demonstrated the feasibility of using arylamines as amine catalyst in enamine catalysis [92]. Through combining with a stronger metal Lewis acid, for example, Y(OTf)₃, a chiral arylamine (**27**) successfully catalyzed the asymmetric direct aldol reaction of cyclohexanone and isatin, affording the aldol product in 79% yield and 95% ee (Scheme 4.26). The catalytic arylamine is believed to activate the ketone by forming an enamine intermediate, and the metal serves to activate the aldol acceptor by coordinating to the isatin.



Scheme 4.26 Cooperative arylamine/metal Lewis acid catalyzed asymmetric aldol reaction of cyclohexanone and isatin.

4.2.3

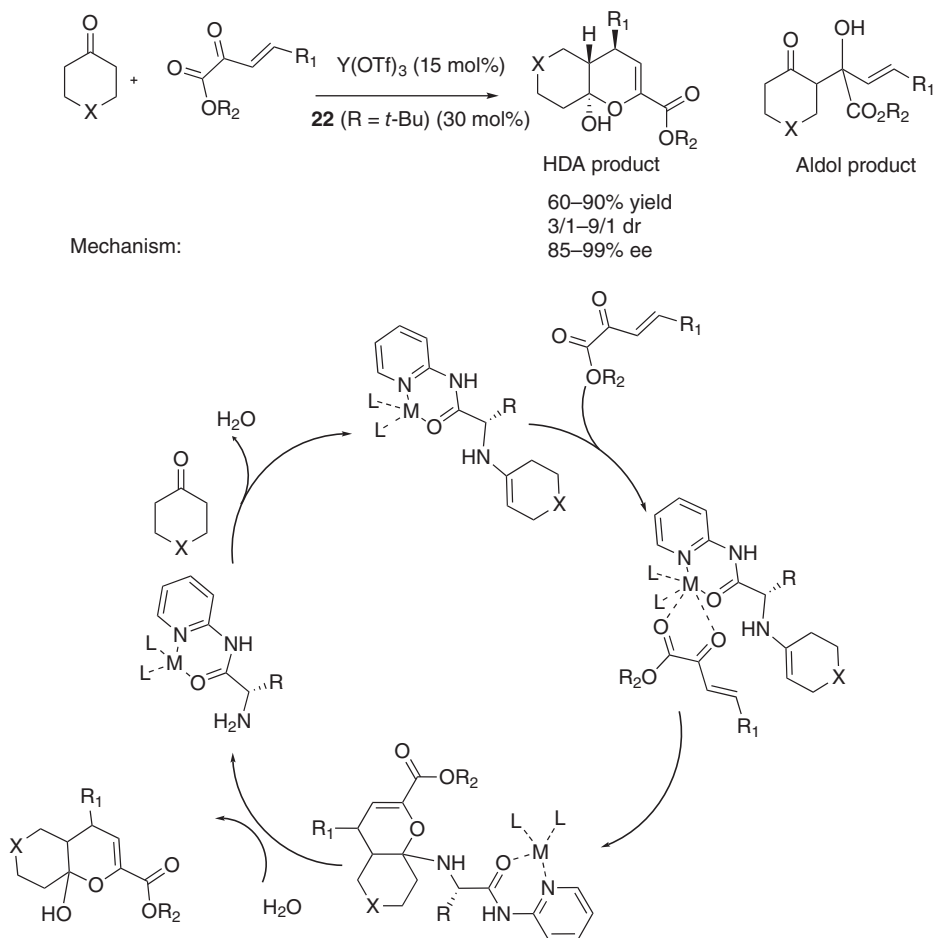
Asymmetric Hetero-Diels-Alder Reactions

4.2.3.1 Asymmetric Inverse-Electron Demand Oxa-Diels-Alder Reactions of Ketones and Activated Enones

Asymmetric inverse-electron-demand hetero-Diels-Alder (IED-HDA) reactions of electron-rich alkenes with electron-deficient α,β -unsaturated ketones (enones) offer a convenient and valuable entry to the synthesis of dihydropyran and tetrahydropyran derivatives, which constitute important structural motifs in natural products and in a variety of biologically important compounds [93–100]. Using the bifunctional amine-metal Lewis acid catalysts derived from the chelating ligands (**22** and **24**), the Wang group achieved a very difficult IED-HDA reaction of cyclic ketones and β,γ -unsaturated- α -ketoesters (Scheme 4.27) [101]. In the presence of $Y(OTf)_3$ and **22** in THF, bicyclic dihydropyrans were obtained in excellent chemo- (up to >99/1, HDA/aldol), moderate diastereoselectivities, and very good to excellent enantioselectivity (up to 99% ee). In this HDA reaction, the ketone forms an enamine intermediate with the amine function of the ligand; the enone is activated by the metal that is coordinated to the ligand; the enamine and enone (diene) are brought in close proximity by the bifunctional catalyst, enabling a highly stereoselective attack of the enamine onto the diene. This reaction is very sensitive to the metal Lewis acids and solvents. Replacing $Y(OTf)_3$ with $Cu(SbF_6)_2$, $Eu(FOD)$, or $Sc(OTf)_3$, or THF with MeOH, aldol products were resulted as the major product instead. Water was also proven to play an important role in determining the reaction pathway. Removing water from the reaction by inclusion of molecule sieves significantly slowed down the HDA reaction; on the contrary, addition of water, even with only 5 equiv., switched the reaction pathway to aldol reaction.

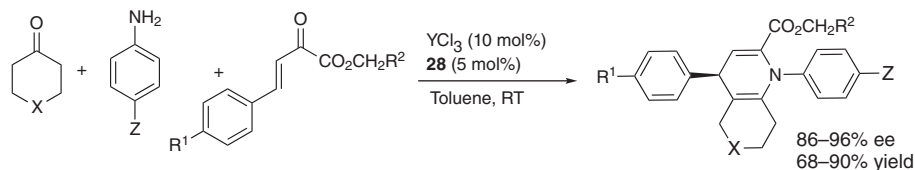
4.2.3.2 Asymmetric Three-Component Inverse-Electron-Demand Aza-Diels-Alder Reactions of Ketones and Activated Enones

The asymmetric aza-Diels-Alder reaction (ADAR) is a powerful tool to construct nitrogen-containing heterocycles. Normal electron demand ADARs based on dienamines and imine dienophiles have achieved considerable progress [102–104]. However, not much has been done for the inverse-electron-demand ADARs involving enamines as the dienophiles [105–109]. In 2008, the Chen group reported the first two-component organocatalytic asymmetric inverse-electron-demand ADAR of aldehydes and *N*-sulfonyl-1-aza-1,3-butadienes

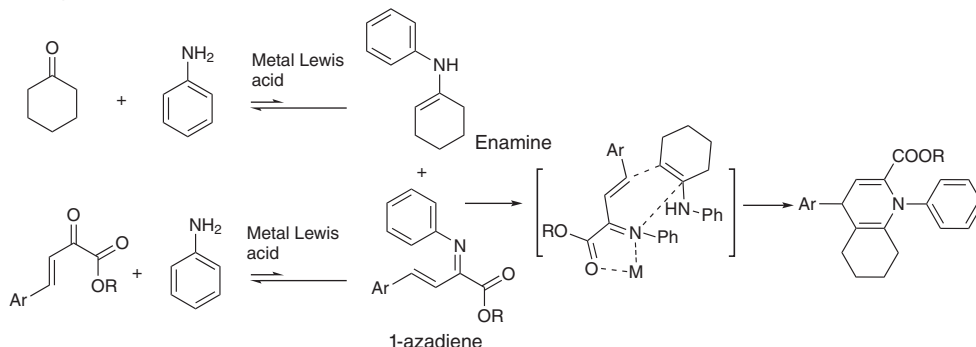


Scheme 4.27 Asymmetric inverse-electron-demand hetero-Diels-Alder reaction of cyclic ketones catalyzed by bifunctional amine/metal Lewis acid catalysts.

[105]. Very recently, a novel three-component inverse-electron-demand ADAR has been developed by the Wang group through cooperative enamine-metal Lewis acid catalysis (Scheme 4.28) [92]. In this reaction, the arylamine acts as a substrate to *in situ* form a 1-azadiene with the enone reversibly; at the same time, the arylamine also serves as the amine catalyst to form an enamine intermediate with the cyclic ketone. Enamine attack of the 1-azadiene, which is activated by the metal Lewis acid, gives the Diels-Alder products after hydrolysis followed by dehydroxylation. Aza-Diels-Alder products were obtained in high yields with excellent chemoselectivities for a variety of cyclic ketones, arylamines, and β,γ -unsaturated- α -ketoesters. High enantioselectivities were achieved for the ADAR reactions of six-membered cyclic ketones (up to 96% ee) through a chiral anion approach where YCl_3 was treated with a chiral silver phosphate (**28**).



Proposed inverse-electron-demand aza-Diels-Alder reaction:



Scheme 4.28 Asymmetric three-component inverse-electron-demand aza-Diels-Alder reaction of cyclic ketones through cooperative enamine-metal Lewis acid catalysis.

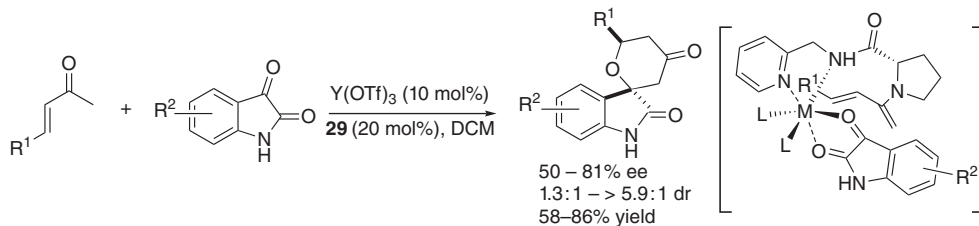
4.2.3.3 Oxa-Diels–Alder Reaction of Isatins and Acyclic α,β -Unsaturated Methyl Ketones through Cooperative Dienamine and Metal Lewis Acid Catalysis

Spirocyclic oxindoles, especially those spiro-annulated with heterocycles at the 3-position, have become an interesting synthetic targets because of their wide spectrum of biological activities [110–112]. The Wang group has developed a new method for the [4+2] cyclization reaction of but-3-*en*-2-ones and isatins affording spirooxindole tetrahydropyranones (Scheme 4.29) [113]. In the presence of a chelating ligand (**29**) and $\text{Yb}(\text{OTf})_3$, spirooxindole tetrahydropyranones were obtained in good yields and excellent chemoselectivities, but with moderate stereoselectivities and activities. This difficult organic transformation was achieved through the incorporation of bifunctional enamine-metal Lewis acid catalysis. The amine group of the ligand forms a dienamine intermediate with a but-3-*en*-2-one; the isatin is activated by $\text{Yb}(\text{OTf})_3$ through coordination; the bifunctional ligand brings the two reacting species in close proximity to ensure the [4+2] cyclization reaction.

4.2.4

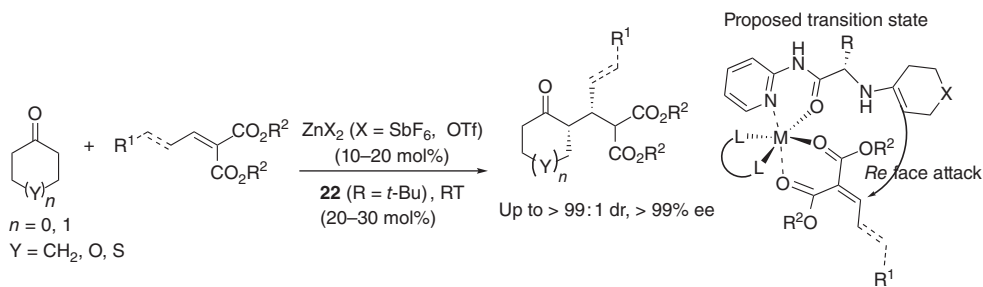
Asymmetric Michael Addition Reactions

Cooperative enamine-metal Lewis acid catalysis has also shown to be effective for asymmetric Michael addition reactions. A difficult asymmetric Michael addition of ketones to alylidene and allylidene malonates was developed by the Wang group using chiral amine-metal Lewis acid bifunctional catalysts (Scheme 4.30) [114]. When $\text{Zn}(\text{SbF}_6)_2$ was combined with ligand **22** ($\text{R} = t\text{-Bu}$), the Michael



Scheme 4.29 Oxa-Diels–Alder reaction of isatins and acyclic α,β -unsaturated methyl ketones through cooperative dienamine and metal Lewis acid catalysis.

addition products of cyclic ketones and alkylidene malonates were generated in high yields (up to 99%) and with excellent enantioselectivities (up to >99% ee) and diastereoselectivities (up to >99:1 dr). The combination of $\text{Zn}(\text{OTf})_2$ with **22** led to the Michael addition products of cyclic ketones and allylidene malonates in good yields (up to 99%), with high enantioselectivities (up to 98% ee) and moderate diastereoselectivities (up to 4/1 dr). Both five-membered and six-membered cyclic ketones including ketones containing heteroatoms were appropriate substrates for these reactions; alkylidene malonates and allylidene malonates bearing both electron-withdrawing and electron-donating groups were well accommodated in these reactions. These asymmetric Michael addition reactions feature enamine attack from the *Re* face of the malonate to generate the products with (*S,S*)-configuration.



Scheme 4.30 Asymmetric Michael addition of ketones to alkylidene malonates and allylidene malonates via enamine-metal Lewis acid bifunctional catalysis.

4.3

Conclusion

Since the realization of the first combination of enamine catalysis with transition metal catalysis in 2006 by the Córdova group, considerable progress has been made on synergistic and cooperative enamine-transition metal catalysis. Several strategies, including soft/hard combination of a Lewis acid and a Lewis base,

the utilization of a chelating ligand to construct bifunctional catalysts, as well as mixing an ammonium salt with a Lewis acid, have been developed to overcome catalyst incompatibility problems. A number of new organic transformations have been developed through cooperative/synergistic enamine-transition metal catalysis. In particular, significant advances have been achieved in asymmetric direct α -allylations and α -propargylations of aldehydes in the past several years. Even the challenging asymmetric α -arylations and α -alkenylations have been achieved with high yields and stereoselectivities. Other types of reactions such as the asymmetric direct cross aldol addition of aldehydes and ketones, the asymmetric inverse electron-demand HDA reactions of activated enones, as well as asymmetric Michael additions have also been enabled through cooperative enamine-metal Lewis acid catalysis. It can be anticipated that more exciting discoveries will come along in the near future in this emerging field.

Acknowledgment

[*Chem. Commun.*, 2014, 50, 4272–4284] – Reproduced by permission of the Royal Society of Chemistry.

<http://pubs.rsc.org/en/content/articlepdf/2014/cc/c4cc00072b>

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5

Hydrogen Bonding-Mediated Cooperative Organocatalysis by Modified Cinchona Alkaloids

Xiaojie Lu and Li Deng

5.1

Introduction

Hydrogen bonding-mediated cooperative catalysis is arguably the most prevalent mode of catalysis by enzymes [1]. Enzymes demonstrate the power of this mode of catalysis by mediating some of the most difficult reactions in astonishing rates under mild conditions [2]. Equally impressive is the range of reactions to which enzymes apply it. Yet synthetic chemists did not turn their attention to the discovery, development, and design of small molecule chiral organocatalysts based on hydrogen bonding-mediated cooperative catalysis until a decade ago [3]. The development in this area from then could be described only as “beyond anybody’s expectation” [4]. Although a wide variety of organic molecules are now known to afford enantioselective hydrogen bonding-mediated cooperative catalysis, cinchona alkaloid-derived organocatalysts constitute arguably the most widely explored and successful among them [5]. More importantly, the lessons learned by exploring modified cinchona alkaloids over the years are among the most important to this area. Because of space constrain and how wide-reaching hydrogen bonding-mediated cooperative organocatalysis by modified cinchona alkaloids has become, we are able to highlight only selective literature reports of conceptual advances in our personal opinion.

5.2

The Emergence of Highly Enantioselective Base Organocatalysis

Cinchona alkaloids constitute a family of readily available natural products [6]. As represented by quinine and quinidine in Figure 5.1, these alkaloids are highly unusual in that they exist as pseudoenantiomers. The history of cinchona alkaloids in catalytic asymmetric synthesis dated back to more than a century ago [7]. The quinuclidinyl moiety as a tertiary amine rendered cinchona alkaloids as attractive candidates for the development of chiral base or nucleophilic catalysts. In 1960, Pracejus reported *O*-acetylquinine **1** as a catalyst for the reaction of

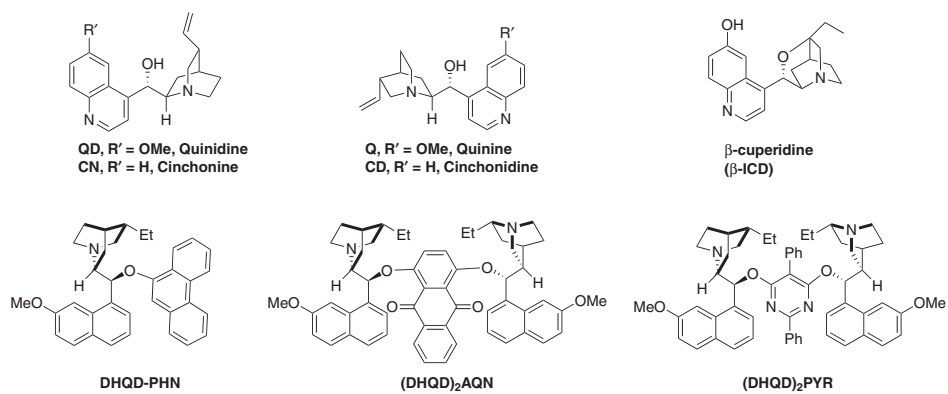
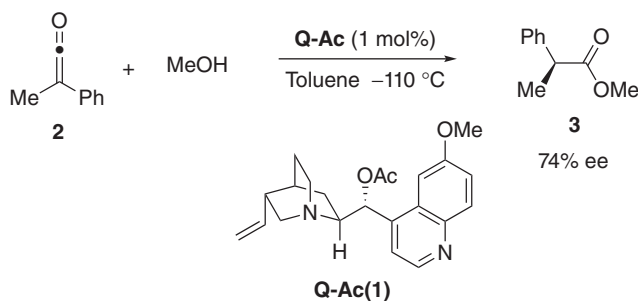


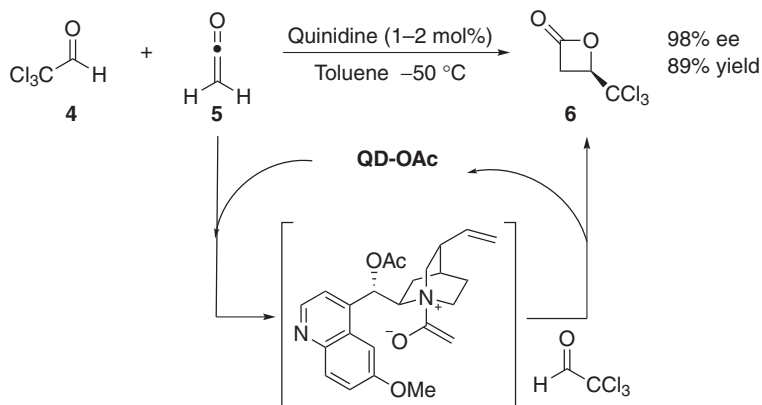
Figure 5.1 Cinchona alkaloids structures.

phenyl ketene **2** with methanol, which afforded (*S*)-methyl hydratropate **3** in 74% ee (Scheme 5.1) [8].



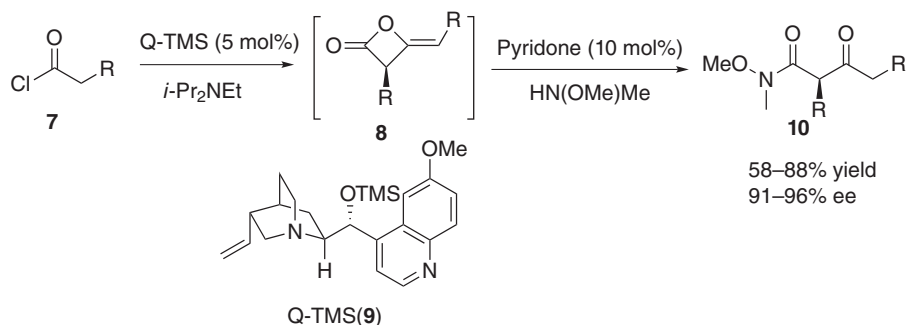
Scheme 5.1

From 1970s to 1980s, Wynberg and coworkers carried out extensive studies to explore cinchona alkaloids as chiral base/nucleophilic catalysts for a range of enantioselective 1,2- and 1,4-additions [9]. Except achieving a single case of a highly enantioselective reaction of ketene **5** and trichloroacetaldehyde **4** with the *O*-acetylquinidine (**1**) *in situ*-formed from quinidine (Scheme 5.2), these early studies showed that a range of natural and modified cinchona alkaloids were at best only moderately enantioselective [10]. A second observation from these studies was that the natural cinchona alkaloids, though not able to give useful enantioselectivity, were often found to be superior in both reactivity and enantioselectivity to modified cinchona alkaloids under investigation. In an era when the general organic synthetic community had not yet been weakened up by asymmetric catalysis, and the technical capability to determine ee of chiral products was limited, Wynberg's remarkable pioneering studies exploring cinchona alkaloids as organocatalysts did not stimulate any further interest until more than a decade passed by.

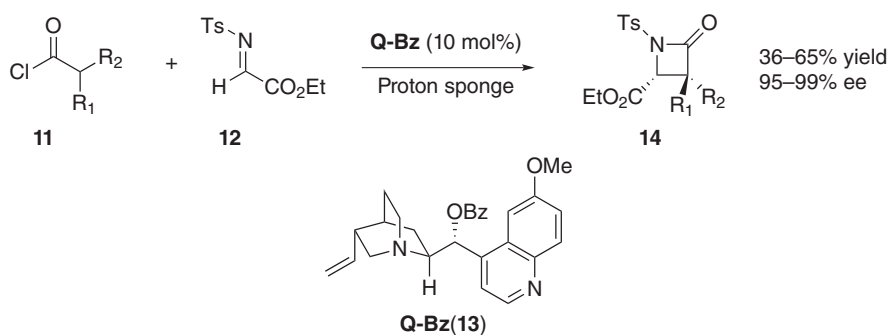


Scheme 5.2

While chiral organocatalysts were ignored, asymmetric catalysis by chiral metal complexes witnessed one breakthrough after another [11]. As a consequence, asymmetric catalysis became a major focus in synthetic organic chemistry in 1990s. Sporadic but notable reports of exploring cinchona alkaloids as chiral organocatalysts appeared in the literature from late 1990s to 2000. Calter *et al.* [12] and Lectka *et al.* [13] reported significant progress in the cinchona alkaloid-mediated additions of ketenes to aldehydes and imines, respectively. In particular, Calter reported a quite efficient asymmetric dimerization of methylketene with trimethylsilylquinine **Q-TMS 9** in 1996 (Scheme 5.3). In 2000, Lectka and coworkers reported a highly enantioselective and diastereoselective reaction of ketenes, which were generated from acid chlorides **11** and imine **12** to afford β -lactams **14** (Scheme 5.4).

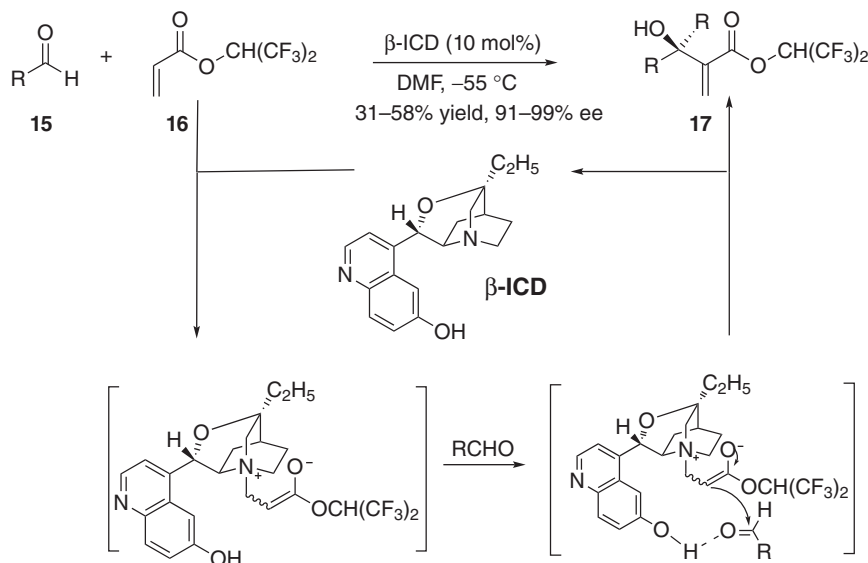


Scheme 5.3



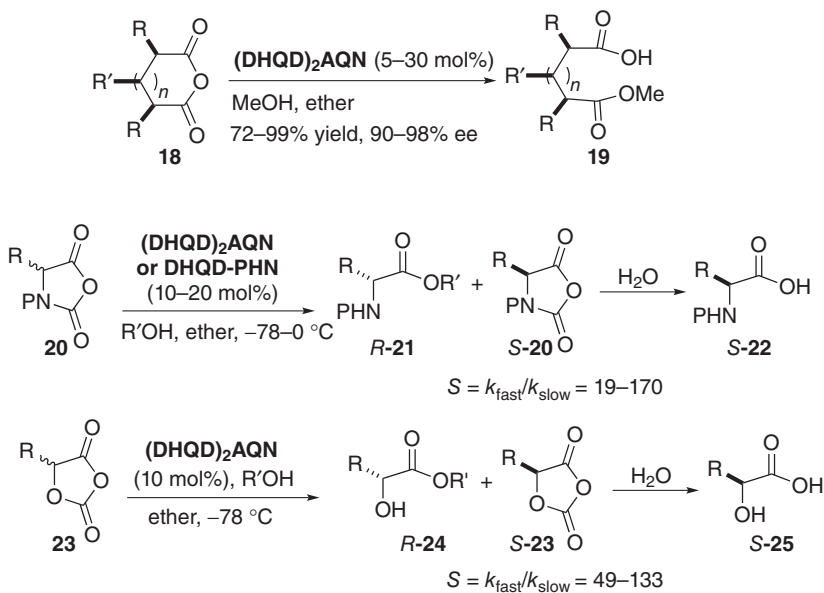
Scheme 5.4

In 1999, Hatakeyama and coworkers documented the first highly enantioselective Morita-Baylis-Hillman reaction with β -cupridine (β -ICD), a differently modified cinchona alkaloid (Scheme 5.5) [14]. These important studies began to show the potential of cinchona alkaloids as effective chiral nucleophilic catalysts, which activate the substrate via the formation of a covalent bond.



Scheme 5.5

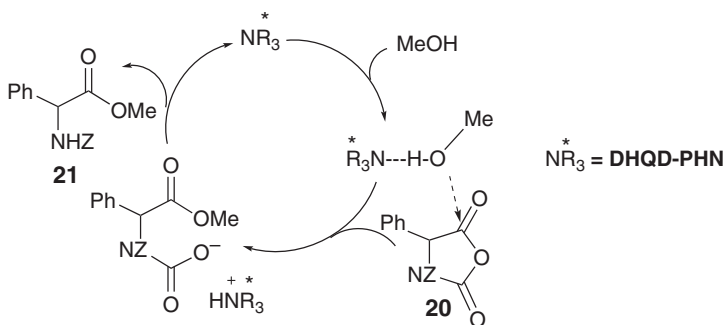
In 2000, Deng and coworkers reported that modified cinchona alkaloids such as $(\text{DHQD})_2\text{AQN}$ and DHQD-PHN catalyzed in a highly enantioselective fashion the alcoholysis of cyclic meso anhydrides **18** (Scheme 5.6) [15]. Remarkably, these modified cinchona alkaloids were widely known to the synthetic community as



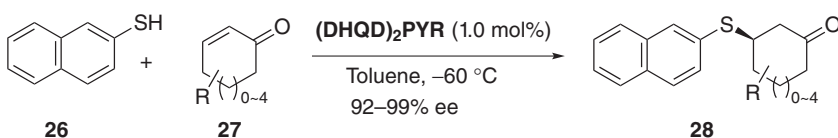
Scheme 5.6

some of the best chiral ligands for the Os-catalyzed Sharpless asymmetric dihydroxylation [16]. In fact they were already commercially available [17].

Soon the scope of this enantioselective alcoholysis was extended to the kinetic resolutions of *N*-carboxy **20** and *O*-carboxy anhydrides **23**. A profoundly important mechanistic discovery was made from a simple kinetic study on the enantioselective alcoholysis of *N*-carboxy anhydrides, which indicated that the alcoholysis with DHQD-PHN was promoted via the general base catalysis mechanism (Scheme 5.7) [18]. The salient feature of this mode of catalysis is that the hydrogen bonding interaction between the amine catalyst and nucleophile leads to the observed catalytic activity and enantioselectivity by the modified cinchona alkaloid. Thus, these cinchona alkaloid-catalyzed highly enantioselective alcoholysis provided for the first time that organocatalysts could serve as effective chiral base catalysts via hydrogen bonding-mediated activation of nucleophiles. This in turn raised the possibility of using cinchona alkaloids as general and effective base catalysts to activate nucleophiles for the development of catalytic asymmetric reactions. The key experimental result to valid this premise was to demonstrate that the general base catalysis by cinchona alkaloid could be successfully applied for the activation of nucleophiles other than an alcohol for a highly enantioselective reaction. In 2002, a modified cinchona alkaloid, (DHQD)₂PYR, was reported to be effective in the activation of aryl thiols for highly enantioselective 1,4-additions to cyclic enones (Scheme 5.8) [19].



Scheme 5.7



Scheme 5.8

These progresses recalibrated our perception on the potential of chiral base catalysis in organocatalysis [20a], just like the pioneering studies that focused on organocatalysts bearing hydrogen bond donors did on acid catalysis [20b,c]. Building on these latest developments in chiral acid and base catalysis with organic

molecules, the development of organocatalysts to afford hydrogen bonding-based cooperative catalysis, a biomimetic strategy in nature became more accessible in concept if not in reality.

5.3

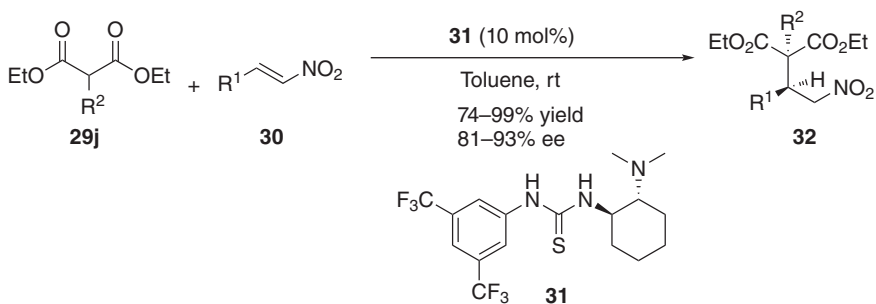
Hydrogen Bonding-Based Cooperative Catalysis by Modified Cinchona Alkaloids

5.3.1

The Emergence of Modified Cinchona Alkaloids as Bifunctional Catalysts

The major appeal of asymmetric acid–base bifunctional organocatalysis lies in their potential to afford better activity and higher selectivity than those by either acid catalysis or base catalysis alone, thereby providing a fundamentally more powerful approach for organocatalytic asymmetric synthesis. In fact, Wynberg [9] in his studies already observed that natural cinchona alkaloids, bearing a hydroxy group at the C9-position, often afforded superior activity and enantioselectivity to those afforded by modified cinchona alkaloids without the C9-OH group. However, these early attempts were unsuccessful in achieving high enantioselectivity with the natural cinchona alkaloids. Although the aforementioned progress in enantioselective base and acid organocatalysis made the hydrogen bonding-based acid–base bifunctional catalysis a more convincing topic of exploration, the realization of such cooperative catalysis remained an unmet challenge. Specifically, whether the enthalpic gain afforded by the hydrogen bonds between small molecules could meet the large entropic demand for the efficient assembly of a highly ordered ternary transition state complex with two reacting substrates and the catalyst represented an important but unanswered question in asymmetric organocatalysis. Furthermore, how general this mode of cooperative organocatalysis could be in the context of asymmetric reaction development was another open question.

In 2003, Takemoto and coworkers reported that amine–thiourea **31** catalyzed highly enantioselective conjugate additions of malonate **29j** to nitroalkenes **30**, which provided the first example of accomplishing efficient acid–base bifunctional asymmetric catalysis with an organocatalyst (Scheme 5.9) [21]. It



Scheme 5.9

is one of the most important breakthroughs in enantioselective organocatalysis. The amine-thiourea catalyst **31** featured a rigid backbone with a nonrotatable bond as the linkage between the thiourea and the tertiary amine moieties, which served as the acidic and basic catalytic centers, respectively.

Deng and coworkers reported in 2004 the use of 6'-OH cinchona alkaloids **33a** to promote highly enantioselective asymmetric conjugate additions of malonates **29a** and β -ketoesters **29b** to nitroalkenes **30** [22]. Building on their extensive studies of modified cinchona alkaloids as chiral base and nucleophilic organocatalysts, Deng and coworkers reasoned that, with a flexible linkage with two rotational bonds between the quinuclidinyl and the 6'-OH quinolinyl moieties, **33** may possess an optimal balance between conformational rigidity and flexibility for achieving highly general yet selective cooperative catalysis (Figure 5.2). From the viewpoint of minimizing the unfavorable entropic cost, the introduction of such conformational freedom should be avoided. On the other hand, this rotational linkage gives **33** the necessary conformational flexibility for it to adopt the optimal conformation for promoting the reaction between a specific pair of electrophiles and nucleophiles. Moreover, this conformational flexibility should also allow **33** to adjust its conformation to achieve optimal catalysis in response to variations in the structures of the nucleophiles and electrophiles and the stereoelectronic requirements associated with the particular reactions between the reacting substrates [22]. It should also be noted that the 9-substituent in **33** could be readily modified for catalyst tuning and optimization.

The 6'-OH cinchona alkaloids **33** afforded exceptional activity and enantioselectivity in promoting highly enantioselective conjugate additions of malonates and β -ketoesters to both β -aryl and β -alkyl nitroolefins, thereby providing the first proof that conformationally flexible cinchona alkaloid catalysts such as **33** could be effective as catalysts for asymmetric transformations (Scheme 5.10) [22].

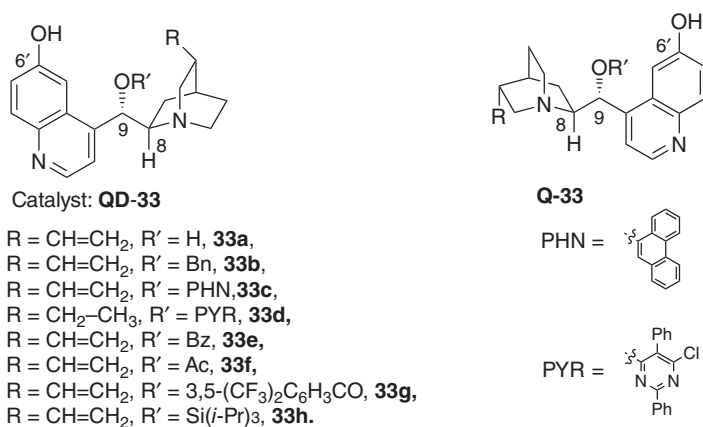
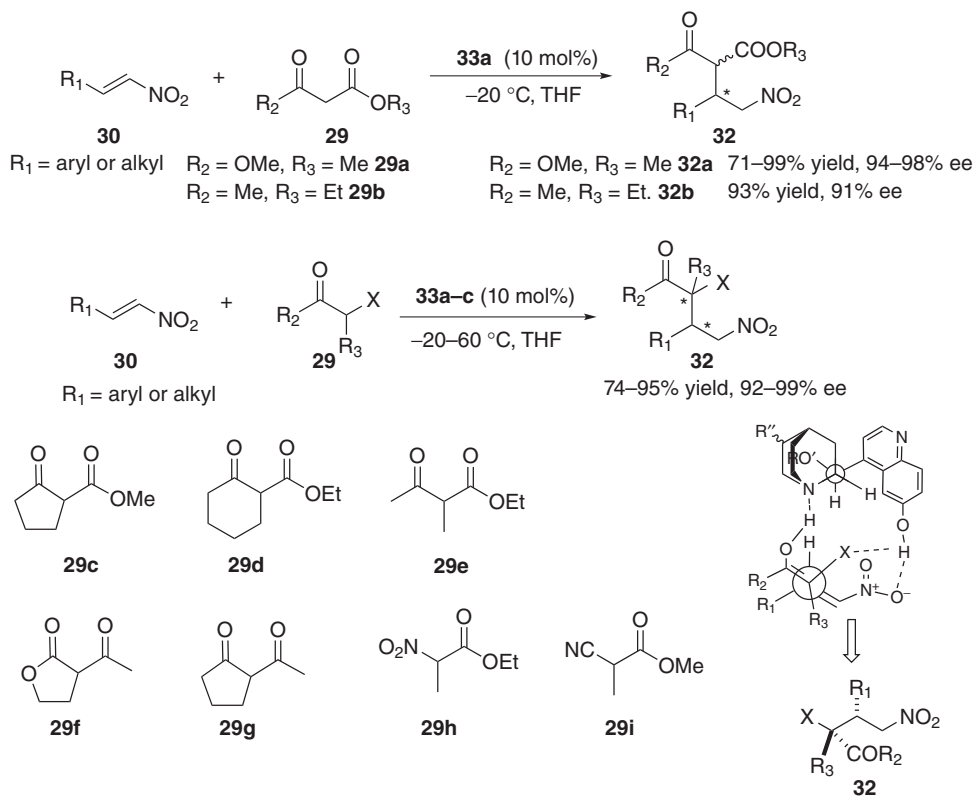


Figure 5.2 6'-OH bifunctional modified Cinchona alkaloids structures.



Scheme 5.10

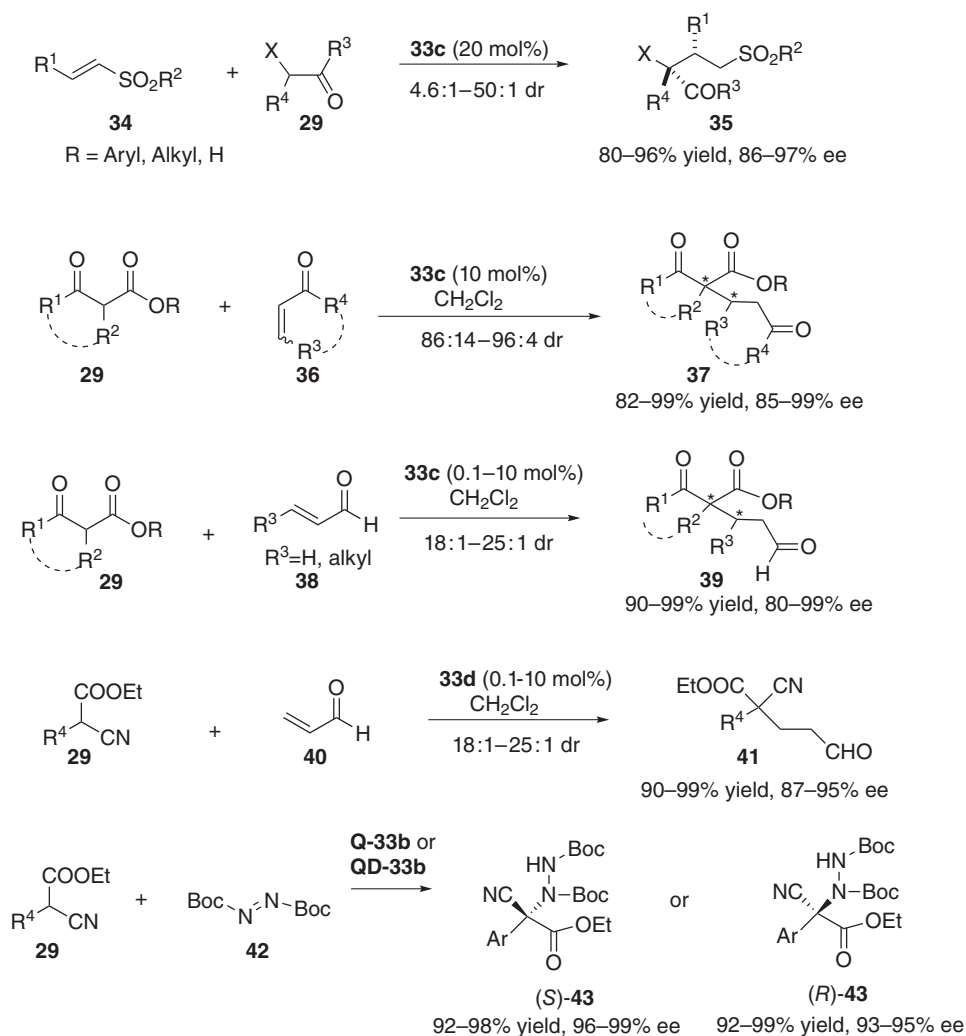
5.3.2

The Development of Modified Cinchona Alkaloids as Broadly Effective Bifunctional Catalysts

Deng and coworkers subsequently found that **33** could mediate the conjugate additions of a wide range of structurally distinctive trisubstituted carbon nucleophiles **29c**–**i** to nitroalkenes in remarkably high enantioselectivity and diastereoselectivity [23]. These results provided the first indication of **33** as not only highly selective but also broadly applicable catalysts. Deng and coworkers also carried out kinetic studies and catalyst conformational studies. These studies identified both the participants in the transition states and the active conformation of the catalyst. On the basis of these experimental results, a mechanistic model was proposed [23]. As illustrated in Scheme 5.10, the enolizable nucleophile was postulated to participate in the transition state in the enol form and was activated and oriented through hydrogen bonding interactions with both the tertiary amine and 6'-OH while the nitroalkene was activated by the 6'-OH in the catalyst **33**. Overall, a network of hydrogen bonding interactions between the reacting substrates

and the chiral catalysts are responsible for both the catalyst activity and selectivity. The configurations of the 1,4-adducts were found to be consistent with those predicted by this mechanistic model.

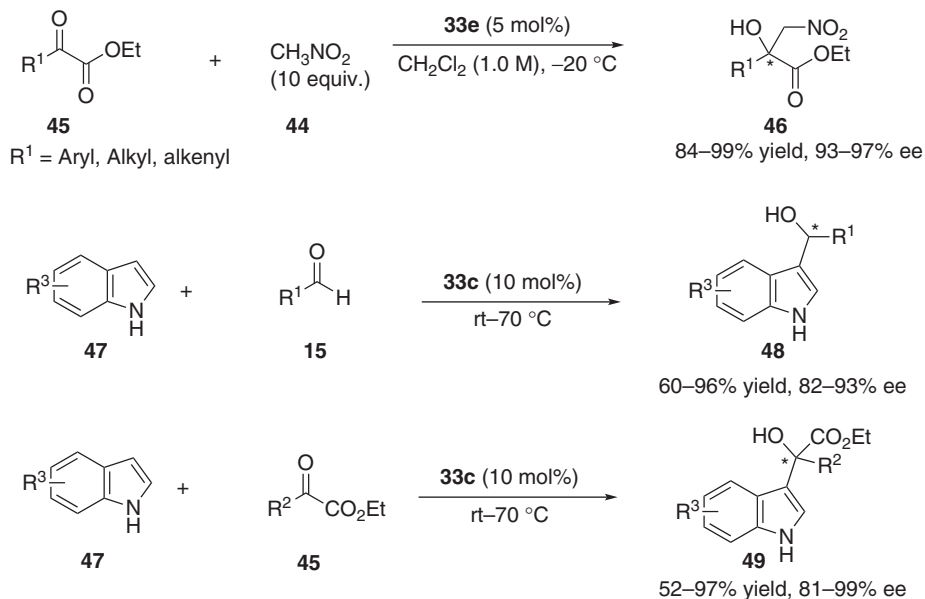
An interesting hypothesis arising from this model was that this network of hydrogen bonding might remain even when the nitro group was replaced with other organic functionalities that could serve as a hydrogen bond acceptor. According to this hypothesis, **33** could potentially afford high enantioselectivity and diastereoselectivity for conjugate reactions to Michael acceptors other than nitroalkenes **30**. This hypothesis received experimental validation from the realization of a series of highly enantioselective and diastereoselective asymmetric



Scheme 5.11

conjugate additions between a wide range of enolizable carbon nucleophiles **29** and several classes of Michael acceptors such as α,β -unsaturated sulfones **34**, enones **36**, and enals **38** (Scheme 5.11) [24–26]. Promoted by catalyst **Q-33b** and **QD-33b**, α -cyanoacetates **29** reacted with dialkyl azodicarboxylate **42**, a Michael acceptor bearing an electron-deficient N=N bond, to afford both enantiomers of the chiral amines bearing a tetrasubstituted stereocenter with high enantioselectivity [27].

In addition to the development of **33** as highly general catalysts for asymmetric 1,4-additions, the promise of **33** as a generally applicable platform for the development of asymmetric nucleophile-electrophile reactions was further advanced when **33** were found to be highly effective catalysts for several C–C bond-forming reactions other than conjugate additions. In 2005, employing catalyst **33e**, Deng and coworkers realized a highly enantioselective Henry reaction of nitromethane and pyruvate **45** (Scheme 5.12) [28]. The scope with respect to pyruvate **45** was general, including alkyl, alkenyl, and aryl substituted pyruvates. The resulting adducts **46** were demonstrated to be valuable chiral building blocks for the synthesis of chiral heterocyclic compounds such as β -lactams and aziridines bearing a tetrasubstituted carbon stereocenter.

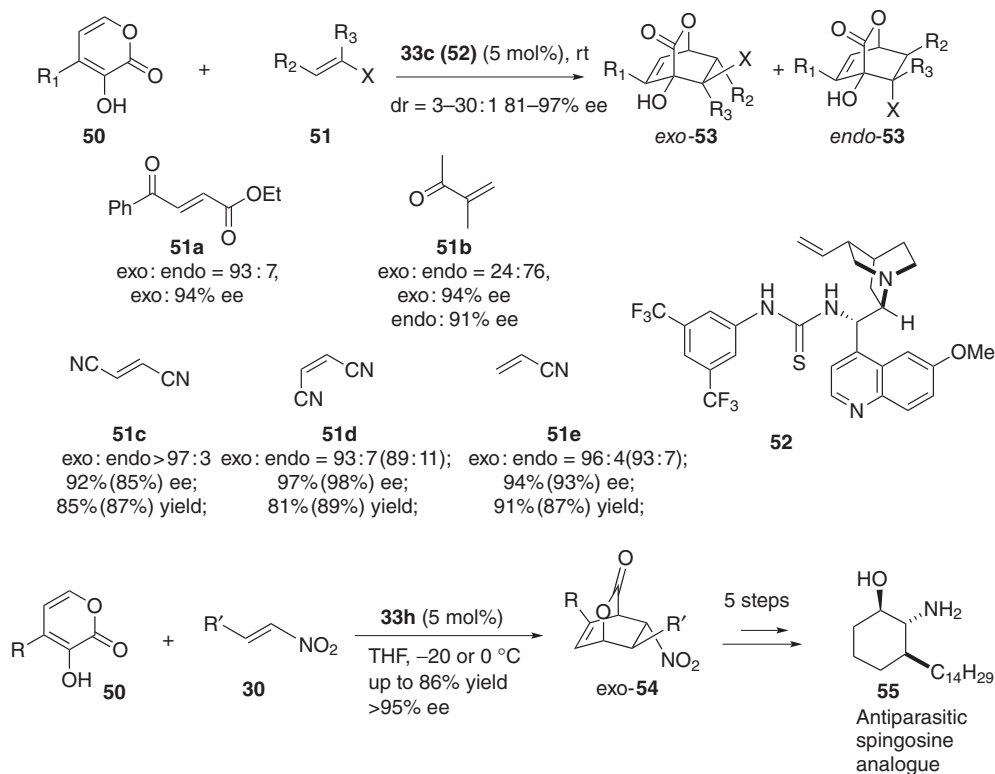


Scheme 5.12

In 2006, an enantioselective Friedel-Crafts reaction of indoles and carbonyls with **33c** was reported (Scheme 5.12) [29]. High enantioselectivity was achieved for reactions between various indoles and aryl aldehydes, glyoxalate aldehydes, aryl, and alkynyl pyruvates. The successful use of **33c** to activate indoles for an

asymmetric reaction is particularly noteworthy, as indoles are structurally distinct from the enolizable carbon nucleophiles employed in studies prior to the investigation of Friedel-Crafts reactions. Consequently, the scope of the carbon nucleophiles that could be activated by **33** for the development of asymmetric reactions was expanded significantly.

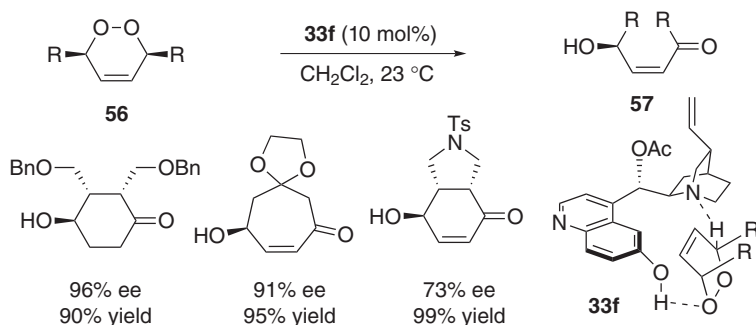
Efforts on exploring **33** to activate other structurally distinct nucleophiles bearing a hydrogen bond donor led to the development of highly enantioselective Diels-Alder reactions between 3-hydroxy-2-pyrones **50** and a range of dienophiles **51** (Scheme 5.13), which constituted the first efficient asymmetric normal electron-demand Diels-Alder reaction of 2-pyrones [30]. The development of such an asymmetric Diels-Alder reaction was a significant challenge: as the electron-deficient character of 2-pyrones renders them poor diene substrates. The **33c** was postulated to activate the 3-hydroxy-2-pyrones **50** by raising the energy of their HOMO via a hydrogen bond between **50** and the quinuclidinyl moiety, while simultaneously activating the dienophiles by lowering their LUMO via a hydrogen bonding interaction between **51** and the 6'-OH. By using a 9-thiourea cinchona alkaloid catalyst **52**, highly diastereoselective and enantioselective Diels-Alder reactions of acryl nitriles **51c–e** and pyrone **50** were



Scheme 5.13

realized. These are the first examples of a highly enantioselective Diels-Alder reaction with an α,β -unsaturated nitrile as the dienophile. Recently, Deng and coworkers extended the scope of the dienophiles to α,β -unsaturated nitroalkenes **30** employing 6'-OH cinchona alkaloid **33h** [31]. The corresponding chiral adduct **54** was transformed into the antiparasitic spingosine analog **55**.

In 2006, employing 6'-OH cinchona alkaloid catalyst **33f**, Toste and coworkers reported an asymmetric Kornblum-DeLaMare reaction to afford the optically active γ -hydroxyl-enones **57** from cyclic meso peroxides **56** [32]. According to their proposed transition state, the cyclic peroxide was activated by the 6'-OH while the basic tertiary amine deprotonated the acidic C-H (Scheme 5.14).



Scheme 5.14

These aforementioned examples of asymmetric reactions realized with 6'-OH cinchona alkaloids highlight the evolution of asymmetric cooperative catalysis in the context of discovering and developing new diastereoselectivity and enantioselectivity. In parallel, the emergence of the 6'-OH cinchona alkaloids **33** as highly efficient and general bifunctional catalysts stimulated the discovery, development, and design of acid-base bifunctional organocatalysts via modifications of natural cinchona alkaloids. The most common approach was to introduce various hydrogen bond donors as or into a substituent attached to the C9 of the cinchona alkaloids. The most important bifunctional catalysts thus invented included 9-thiourea cinchona alkaloids **52** [33], 9-sulfonamide cinchona alkaloid **54** [34], and 9-squaramide cinchona alkaloid **55** [35] (Figure 5.3).

These modified cinchona alkaloids each contributed significantly to the spectacularly rapid expansion in the utility of hydrogen bonding-based cooperative catalysis in asymmetric synthesis. Although these catalysts are first discovered when examined for their ability to promote asymmetric conjugate additions to chalcones or nitroalkenes [33], they truly shined as uniquely effective catalysts for a range of asymmetric transformations. For example, the 9-thiourea cinchona alkaloid **52** was first reported by Soös as an effective catalyst for the addition of nitromethane to chalcones (Scheme 5.15). Dixon and Deng independently found **52** to be uniquely effective for the enantioselective Mannich reactions of malonates and β -ketoesters with *N*-Boc imines [36, 37] (Scheme 5.16). A noteworthy

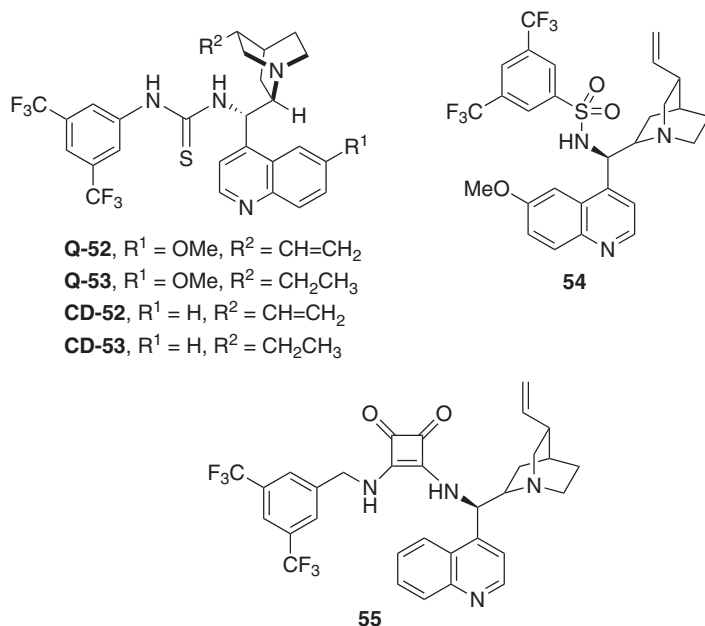
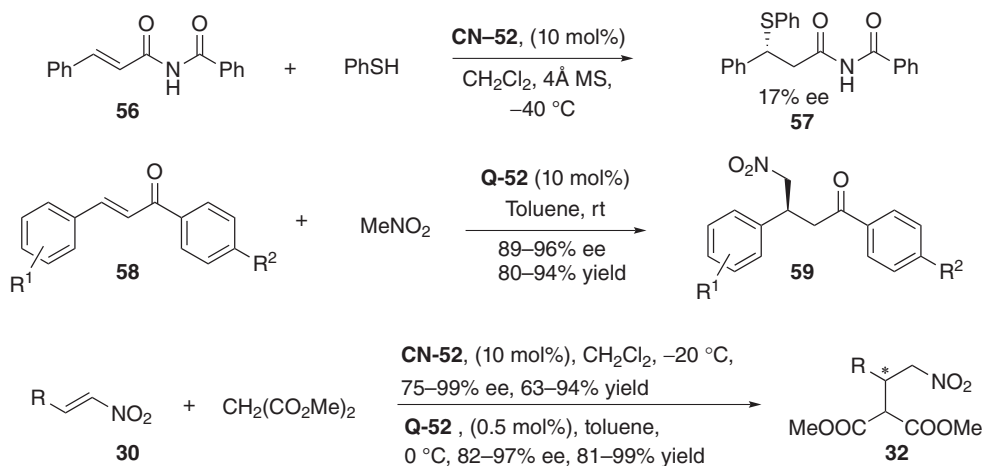
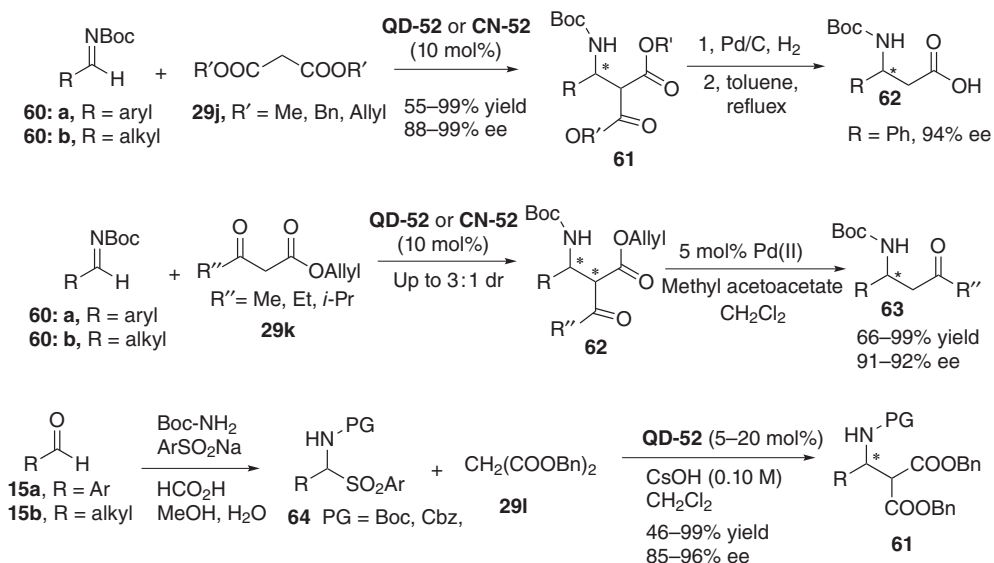


Figure 5.3 Other bifunctional modified Cinchona alkaloids structures.



Scheme 5.15

result from Deng's studies is that the highly sensitive but synthetically more important *N*-Boc alkyl imines could be tolerated by **QD-52**. The challenge to prepare the sensitive *N*-carbamate alkyl imines was circumvented by the development of a protocol to generate *in situ* the *N*-Boc or *N*-Cbz imines **60** from the corresponding stable and easily prepared α -amido sulfones **64** [38]. These early studies indicate that the 9-thiourea cinchona alkaloid **52** is a highly versatile bifunctional



Scheme 5.16

organocatalyst. It has from then on been successfully applied to the development of a great range of asymmetric reactions, thereby becoming one of the most versatile organocatalysts.

Each of the studies highlighted above, whether in catalyst discovery or in reaction development, provided enlightening experimental results that addressed legitimate concerns from boundaries set by previous state of knowledge and hence breaking new grounds over those boundaries. These studies come together to transform the concept of hydrogen bonding-based cooperative organocatalysis from a dubious idea into a conceptually accessible and practically implementable strategy in catalytic asymmetric synthesis.

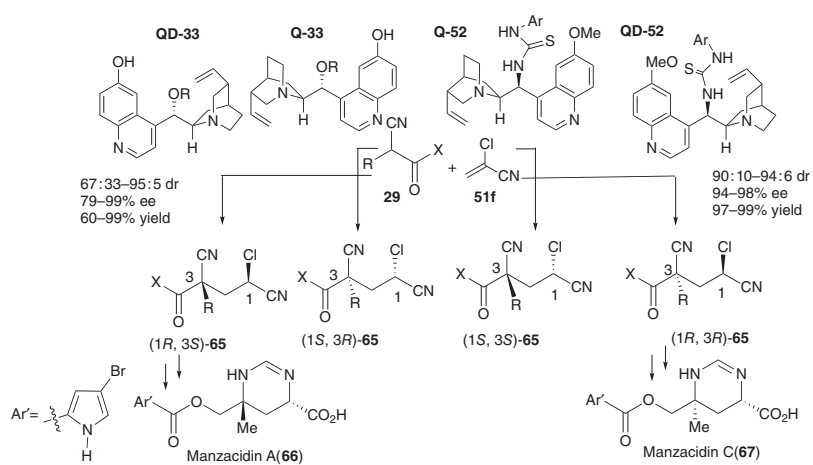
5.3.3

Multifunctional Cooperative Catalysis by Modified Cinchona Alkaloids

Hydrogen bonding-based cooperative catalysis by enzymes is also multifunctional, namely, it is applied to promote and control multiple bond-forming and/or bond-breaking steps. As illustrated in this section, such multifunctional, hydrogen bonding-based cooperative catalysis has also been successfully developed with modified cinchona alkaloids.

5.3.3.1 Asymmetric Tandem Conjugate Addition-Protonation Reactions

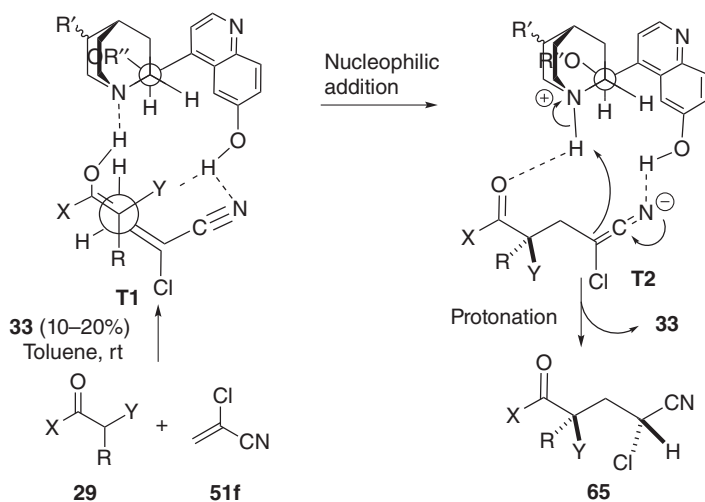
A highly stereoselective reaction cascade realized via hydrogen bonding-based, dual-functional cooperative catalysis with a cinchona alkaloid-derived bifunctional catalyst was reported in 2006 (Scheme 5.17) [39]. Deng and coworkers described that cinchona alkaloid **33** promoted highly enantioselective and



Scheme 5.17

diastereoselective reactions of trisubstituted carbon nucleophiles **29** with α -chloroacrylonitrile **51f**, which directly generated complex building blocks containing two nonadjacent tertiary-quaternary stereocenters from achiral starting materials. The quaternary stereocenter was created first in the nucleophilic addition step, and the resulting enolate was protonated to form the tertiary stereocenter. The same reaction in racemic form could be promoted by DABCO, but took place in poor diastereoselectivity.

These results indicated that the cinchona alkaloid catalyst **33** was responsible for both the enantioselectivity and the diastereoselectivity, which must result from the stereochemistry control of **33** over both the nucleophilic and the protonation steps. As illustrated in Scheme 5.18, the catalysts presumably interacted with the reacting substrates in the transition states of the nucleophilic addition and protonation steps via hydrogen bonding reactions. It is noteworthy that in these studies the capacity of bifunctional cinchona alkaloids such as **33** to serve as an efficient catalyst for asymmetric protonation reactions was revealed.

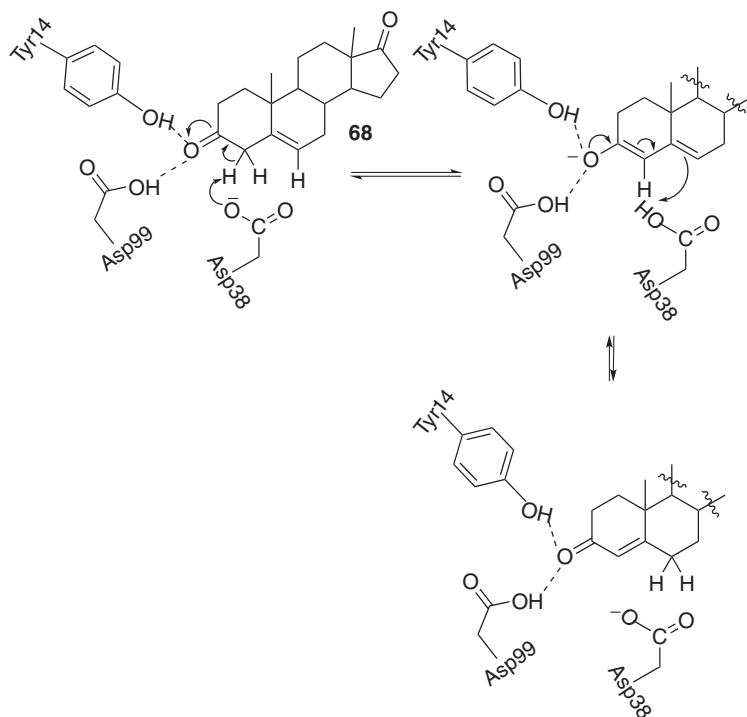


Scheme 5.18

Deng and coworkers further found that the 9-thiourea cinchona alkaloid **52** promoted the same reaction cascade with a complementary sense of diastereoselectivity (Scheme 5.17) [40]. Therefore, each of the four possible stereoisomers of the products could be prepared in a highly stereoselective fashion. On the basis of these new developed asymmetric transformations, the asymmetric synthesis of a diastereomeric pair of natural products, manzacidins A (**66**) and C (**67**), was successfully carried out through the same synthetic route.

5.3.3.2 Catalytic Asymmetric Isomerization of Olefin and Imines

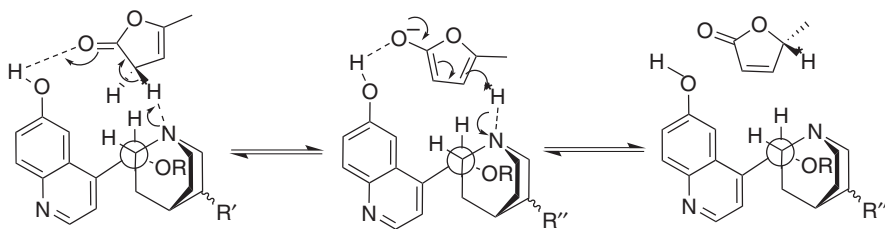
As exemplified by the Δ^5 -3-ketosteroid isomerase (KSI)-catalyzed conversion of β,γ - to α,β -unsaturated steroidal ketones (Scheme 5.19), enzyme-mediated olefin



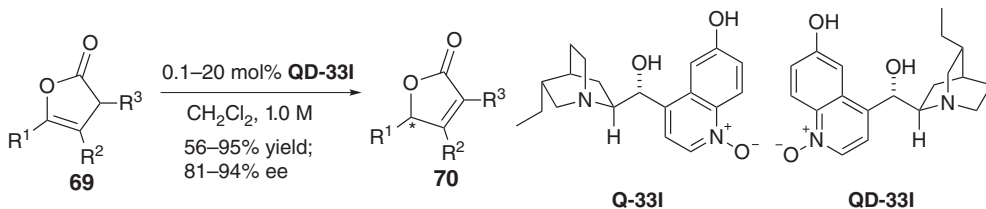
Scheme 5.19

isomerization via a proton transfer from one carbon atom to another in the same substrate molecule constitutes a common and important class of chemical reactions in biology [41]. The mechanism of this isomerization involves the deprotonation of the C4- β -proton of steroidal ketone **68** by Asp38, while Tyr14 and Asp99 serve as acidic catalytic residues by providing hydrogen bonds to the ketone group. With the oxanion engaging in hydrogen bonding interactions with Tyr14 and Asp99, the γ -carbon of the dienolate intermediate undergoes a protonation by Asp38 from the β -face.

As illustrated in Scheme 5.20, a 6'-OH cinchona alkaloid in a gauche-open conformation also has a *syn*-arrangement of acidic and basic active sites, which is similar to how Tyr14 and Asp38 are arranged in the active site of KSI. This observation in combination with the ability of 6'-OH cinchona alkaloids to serve as an acid–base bifunctional catalyst and as a chiral proton donor for asymmetric protonation led Deng and coworkers to envision the possibility of 6'-OH cinchona alkaloids as a catalyst for an enantioselective isomerization via proton transfer catalysis (Scheme 5.21). Subsequently, the 6'-OH cinchona alkaloids **33** were found to promote the isomerization of β,γ -unsaturated butenolides **69** into the corresponding chiral α,β -unsaturated butenolides **70** while the 6'-OMe failed to yield any isomerization product. Eventually, Deng and coworkers invented a novel 6'-OH catalyst **33I** to realize a highly enantioselective isomerization [42].



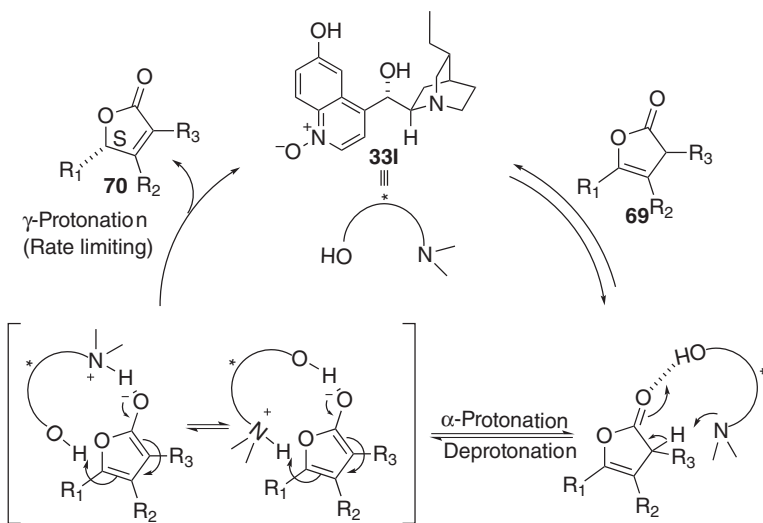
Scheme 5.20



Scheme 5.21

A broad range of mono- and disubstituted β,γ -unsaturated butenolides **69** were transformed into the corresponding chiral α,β -unsaturated butenolides **70** in high enantioselectivity and yield.

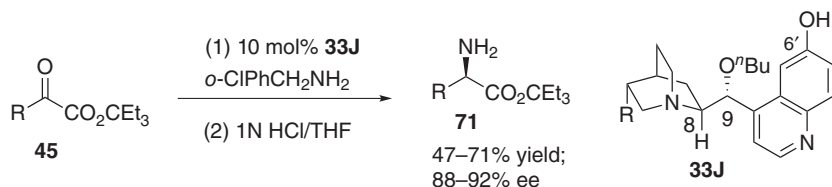
A preliminary kinetic study was carried out, which revealed that the γ -protonation step was the rate-limiting step of the isomerization reaction. A proposed catalytic cycle for this enantioselective isomerization reaction was portrayed in Scheme 5.22. The deprotonation of β,γ -butenolide **69** was facilitated via hydrogen bonding interaction between **69** with catalyst **33I**, which is followed



Scheme 5.22

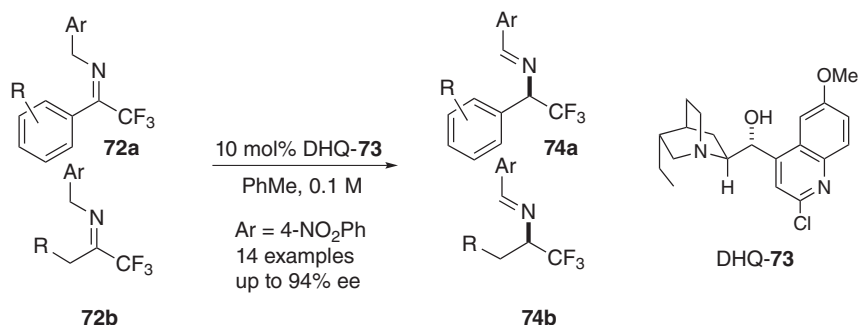
by the rate-determining γ -protonation of the diene enolate. This unprecedented biomimetic enantioselective olefin isomerization unambiguously demonstrated the power of the modified cinchona alkaloids as the multifunctional cooperative catalyst.

Shi and coworkers reported a 6'-OH cinchona alkaloid-catalyzed biomimetic transamination of imines generated *in situ* from α -keto esters and simple benzyl amines (Scheme 5.23). A variety of α -amino esters containing various functional groups can be synthesized in high enantioselectivity and moderate yield [43].



Scheme 5.23

Deng and coworkers reported a highly enantioselective catalytic isomerization of trifluoromethyl imines with a new 6'-OMe cinchona alkaloid **73** (Scheme 5.24). Not only aryl but also alkyl trifluoromethylated amines could be obtained in high enantioselectivities. Synthetically, this transformation provided a new approach toward the asymmetric synthesis of optically active trifluoromethylated amines. The efficient chiral recognition of the putative 2-azaallyl carbanion intermediate underlining the high enantioselectivity by **73** is noteworthy [44].



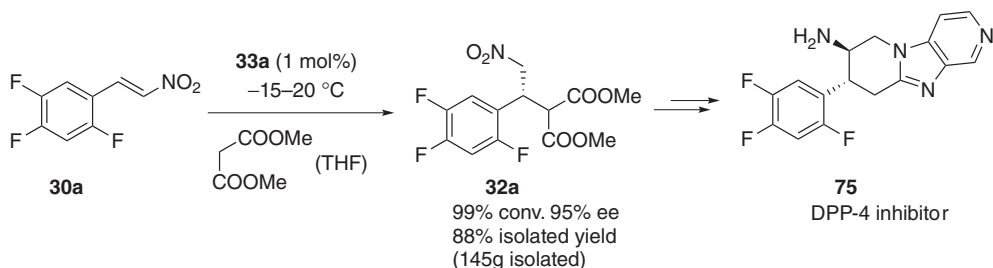
Scheme 5.24

5.3.4

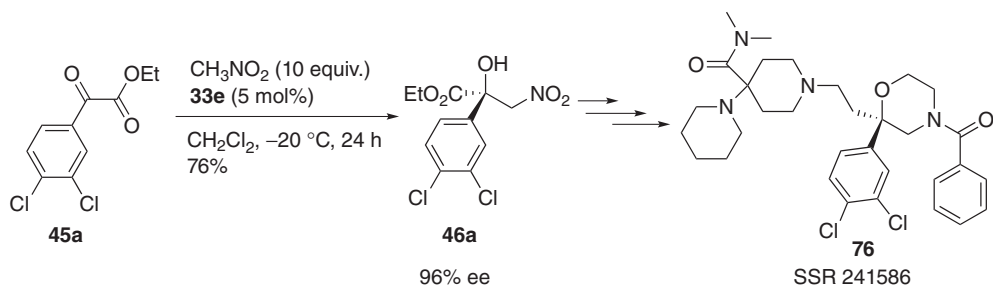
Selective Examples of Synthetic Applications

A wealth of new asymmetric transformations have been realized with modified bifunctional cinchona alkaloids. They begin to see increasing applications by synthetic chemists in both academy and industrial settings but not experts or protagonists in organocatalysis. In 2010, Xu and coworkers [45] from Merck reported

the asymmetric conjugate addition of malonates with nitroalkenes in the process development of **75**, a DPP4-inhibitor and drug candidate for treating the diabetes (Scheme 5.25). Promoted by 1.0 mol% of catalyst **33a**, the reaction of nitroalkenes **30a** with methyl malonate provided adduct **32a** in 88% isolated yield and 95% ee. The asymmetric nitro aldol reaction of nitromethane with pyruvate **45a** was successfully applied by Cossy and coworkers in the asymmetric synthesis of the drug candidate SSR 241586 (Scheme 5.26) [46].

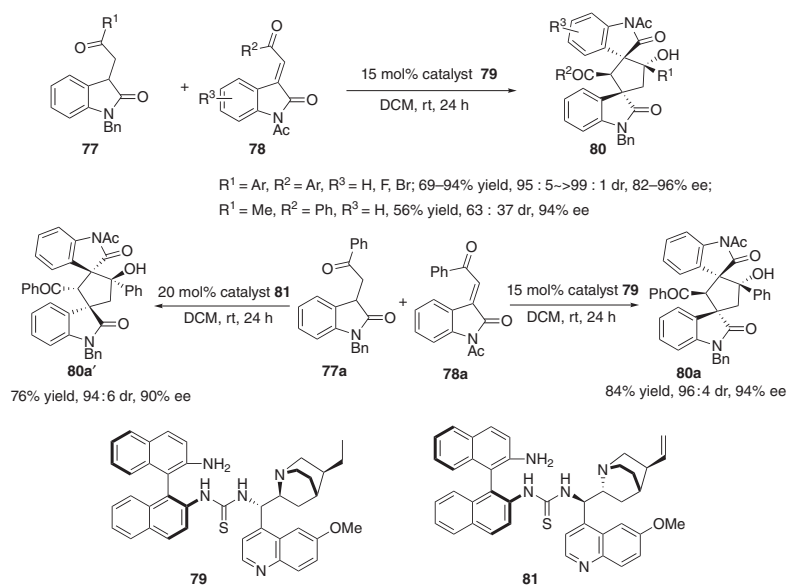


Scheme 5.25



Scheme 5.26

The development of multifunctional catalysts based on modified cinchona alkaloids has enabled powerful reaction cascades that build extraordinarily complex structures directly from prochiral starting materials. In 2011, Barbas and coworkers reported an organocatalytic asymmetric domino Michael/aldol reaction between 3-substituted oxindoles **77** and methylenoxindoles **78** to form the bispirooxindoles **80** (Scheme 5.27). Modified cinchona alkaloid **79** acted as a multifunctional catalyst to efficiently impart diastereoselectivity and enantioselectivity leading to the direct and stereoselective constructions of the four stereocenters of the chiral tricyclic products. Switching the chirality of the catalyst by employing modified cinchona alkaloid **81** as the catalyst, the opposite enantiomer of the product was obtained in similar yield and enantioselectivity, which suggested the hydrogen bonding-based cooperative catalysis plays a crucial role in the stereochemical outcome of this reaction cascade [47].



Scheme 5.27

5.4

Conclusion and Outlooks

As represented by the spectacular advancement with cinchona alkaloid-derived bifunctional organocatalysts, hydrogen bonding-based cooperative catalysis has evolved from at best an unproven idea into one of the most reliable and hence widely applied strategies in catalytic asymmetric synthesis during the past decade. The roots of this evolution originated from advances in enantioselective acid and base organocatalysis by chiral organic molecules bearing hydrogen bond donors and acceptors. The discovery of synthetically accessible, tunable, and yet powerful bifunctional catalysts, such as those based on modified cinchona alkaloids, greatly facilitated the discovery and development of new activities and selectivities, which in turn enabled the invention of numerous asymmetric transformations. While it is certain that new and enabling catalytic asymmetric reactions will continue to be developed using this now well-established strategy, some begin to ask the question of “what is left?” To answer this question one only needs to learn how primitive and limited organocatalysts still are in comparison to enzymes. Without question there is much exciting chemistry ahead.

Acknowledgments

We are grateful for the financial support from the National Institute of Health (National Institute of General Medical Sciences, R01-GM61591). We sincerely thank our colleagues Drs. Yongwei Wu, Jianping Chen, and Lin Hu for their help during the preparation of the chapter.

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6

Cooperation of Transition Metals and Chiral Brønsted Acids in Asymmetric Catalysis

Hua Wu, Yu-Ping He, and Liu-Zhu Gong

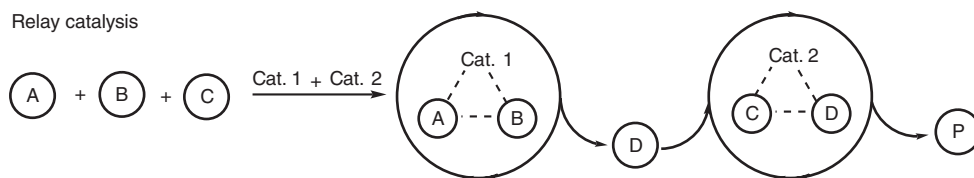
6.1

General Introduction

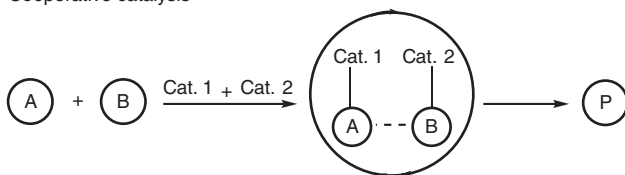
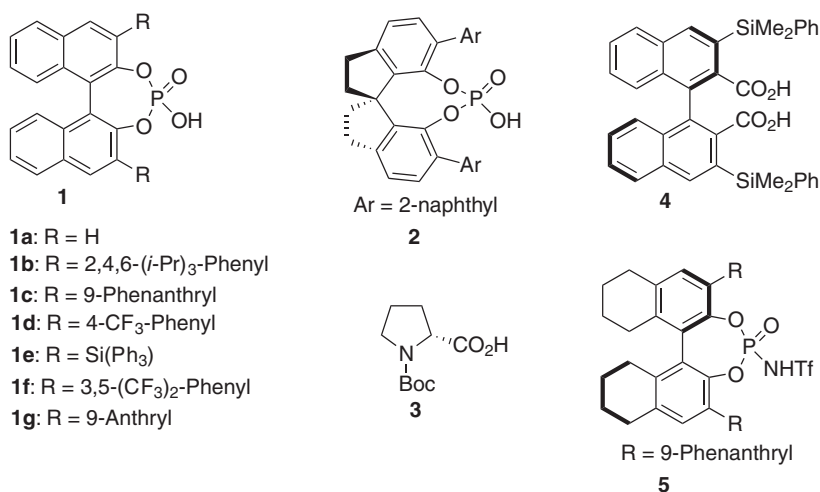
Historically, transition metal-mediated enantioselective reactions have been well established as the most efficient and powerful tools for asymmetric synthesis [1]. In the past decade, asymmetric organocatalysis has been demonstrated to be an important alternative to access chiral molecules [2]. Since the seminal reports on the combination of metal catalysis with organocatalysis in early 2001 [3, 4], the robustness of this concept in the creation of new reactions has been gradually recognized, and increasing attention has been focused on this field [5, 6]. A cooperative or relay catalysis was usually initiated by multiple catalyst systems. A relay catalytic cascade reaction describes a reaction sequence as shown in Scheme 6.1, that is, an intermediate **D** generated from a reaction of **A** with **B** under the catalysis of either metal catalyst or organocatalyst was able to be subsequently converted into the final product **P** with **C** by another independent catalyst [6]. In contrast, in the case of cooperative catalysis, a metal catalyst and an organocatalyst simultaneously operate on two substrates, respectively. Such a strategy affords extraordinarily more possibilities to realize an enantioselective transformation in comparison with a single chiral catalyst (Scheme 6.1).

Over the past decade, the combination of organocatalysts with metal-based catalysts has received increasing attention in the creation of new asymmetric reactions. Chiral Brønsted acids, in particular, chiral phosphoric acids, have been established as privileged organocatalysts since the seminal works by Akiyama and Terada [7], allowing for the accomplishment of a diverse range of unprecedented reactions [2b, 8]. More recently, the combination of Brønsted acids with transition metal complexes has emerged as a new robust strategy to create unprecedented enantioselective transformations that cannot be realized by either of the two catalysts alone. In this context, the cooperative catalysis by the combined catalyst systems of either achiral or chiral transition metal complexes with chiral Brønsted acids has been developed. As many excellent reviews have described the related advances in the metal catalysis combined with organocatalysis [5, 6], this chapter

Relay catalysis



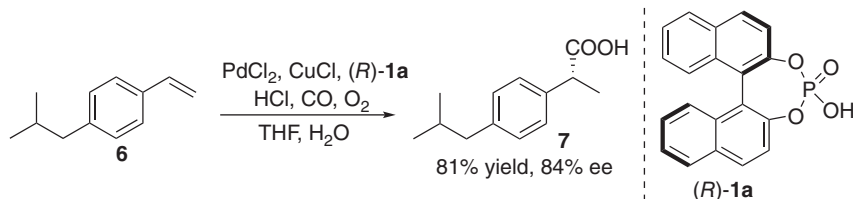
Cooperative catalysis

**Scheme 6.1** The concepts of relay catalysis and cooperative catalysis.**Figure 6.1** The Brønsted acids used in this chapter.

is strictly focused on the summarization of the asymmetric cooperative catalysis of transition metals and chiral Brønsted acids **1–5** (Figure 6.1).

6.2**Cooperative Catalysis of Palladium(II) and a Brønsted Acid**

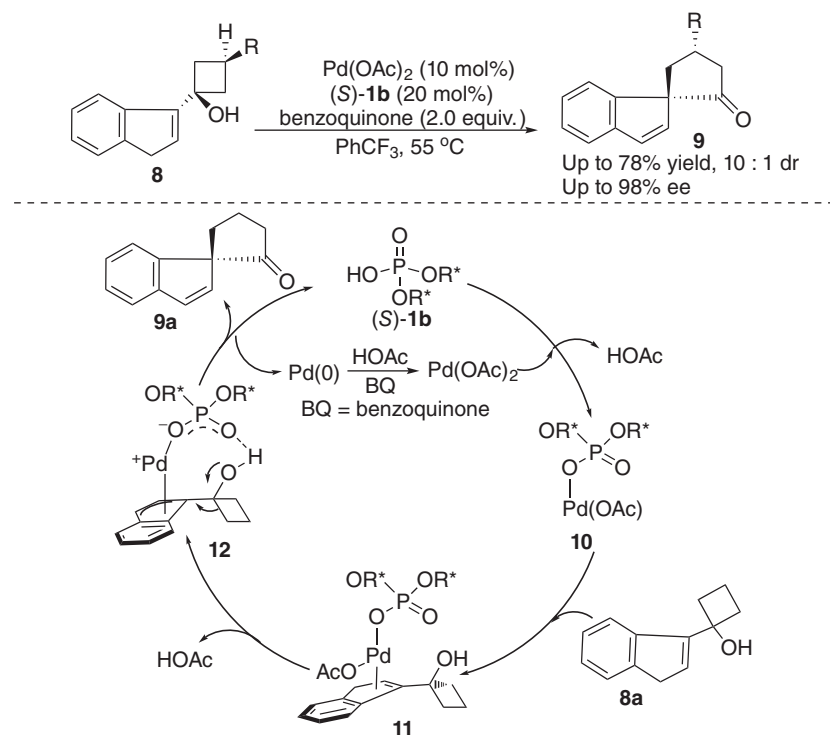
In 1990, Alper demonstrated that a palladium(II)-catalyzed enantioselective hydrocarboxylation of 4-isobutylstyrene **6** was able to give a chiral carboxylic acid **7** (commonly known as (*R*)-ibuprofen) with a high enantioselectivity of 84% ee by using the chiral BINOL-derived phosphoric acid (*R*)-**1a** as an additive [9]. The phosphoric acid was considered to behave as a ligand coordinated to a



Scheme 6.2 Asymmetric catalytic Wacker-type reaction using chiral phosphoric acids as ligand.

palladium(II) complex rather than as a cocatalyst to induce the stereoselectivity (Scheme 6.2).

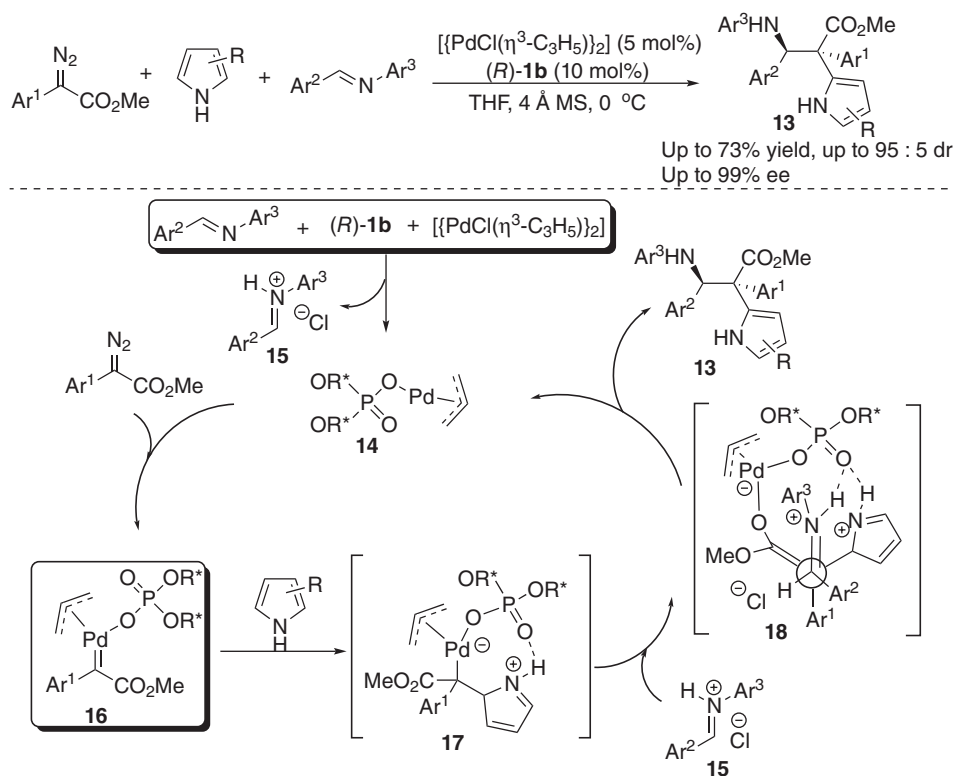
Unfortunately, no further work has been reported to describe the use of chiral Brønsted acids as additives or cocatalysts in other palladium(II)-catalyzed asymmetric transformations until recently, when Rainey and coworkers described a palladium(II)/Brønsted acid cooperatively catalyzed enantioselective allylic C–H activation for the synthesis of optically active spirocyclic rings **9** [10]. In this case, the addition of a chiral phosphoric acid (*S*)-**1b** had a dramatic effect on the catalytic activity of Pd(II) complexes. The control reactions indicated that no consumption of the starting materials **8** was observed in the absence of either



Scheme 6.3 Palladium(II)/Brønsted acid catalyzed enantioselective allylic C–H activation.

$\text{Pd}(\text{OAc})_2$ or the chiral phosphoric acid. The intermolecular kinetic isotopic effect study suggested that an active $\text{Pd}(\text{II})$ species **10** was initially generated via an exchange reaction between $\text{Pd}(\text{OAc})_2$ and the phosphoric acid additive (*S*)-**1b**, and then underwent a coordination of the substrate **8a** leading to the formation of **11**. Subsequently, a crucial π -allylpalladium intermediate **12** was formed after a C–H insertion reaction while the phosphoric anion formed a hydrogen bond with the hydroxyl group, thus cooperatively catalyzing the semipinacol ring expansion, leading to the formation of the final product **9a** (Scheme 6.3).

Hu and coworkers developed a palladium(II)/chiral phosphoric acid cooperatively catalyzed asymmetric three-component reactions of pyrroles, diazoesters, and imines [11]. As shown in Scheme 6.4, the chiral palladium phosphate complex **14** was presumably formed from an anion exchange reaction of an allyl palladium complex and phosphoric acid, together with the generation of an iminium salt **15** by the protonation of the imine. The palladium carbenoid intermediate **16** was then generated from a reaction between the aryl diazoacetate and the $\text{Pd}(\text{II})$ complex **14**. Subsequently, the nucleophilic attack of the pyrrole onto **16** resulted in the formation of the crucial zwitterionic intermediate **17**, and



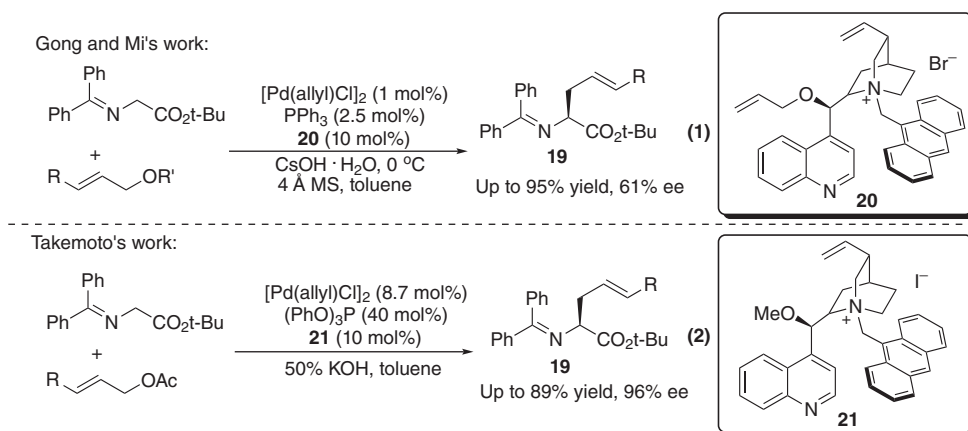
Scheme 6.4 Enantioselective palladium(II)/Brønsted acid cooperatively catalyzed three-component reactions of pyrroles, diazoesters, and imines.

a Mannich reaction proceeded with the iminium via the transition state **18** to generate the final optically active product (Scheme 6.4). A variety of chiral pyrrole derivatives **13** were formed in moderate yields with high enantioselectivities by this cooperative catalysis.

6.3

Cooperative Catalysis of Palladium(0) and a Brønsted Acid

The combination of a palladium(0) complex and chiral organocatalysts for asymmetric catalysis could date back to 2001, when two groups used palladium(0) and chiral quaternary ammonium salts, **20** and **21**, respectively, to catalyze the asymmetric allylic alkylation (AAA) reaction, affording optically active products **19** (Scheme 6.5) [3, 4].

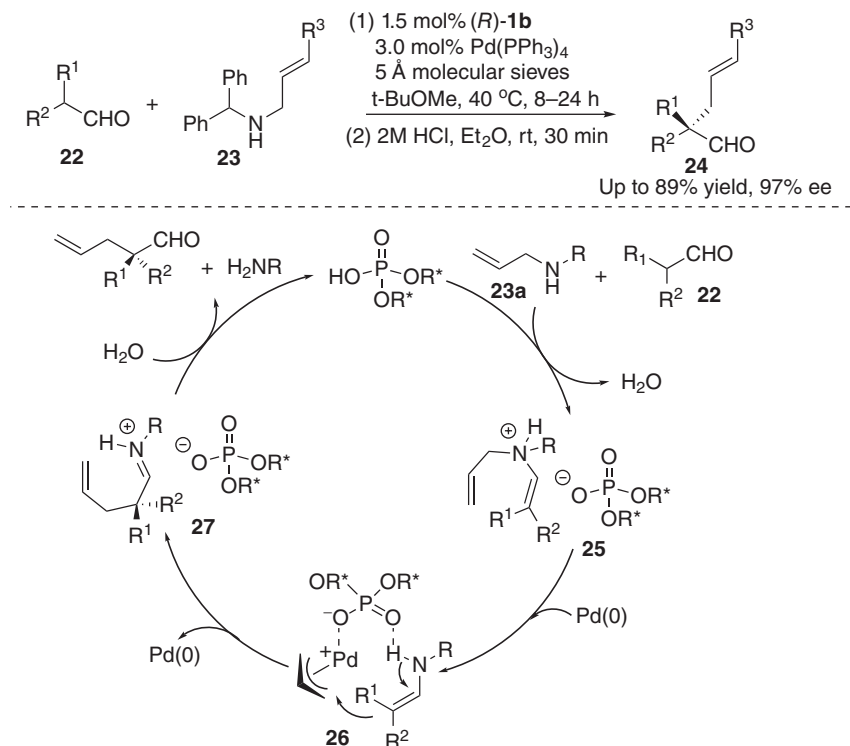


Scheme 6.5 Asymmetric catalytic allylic alkylation by the combination of *in situ* generated Pd(0) complexes and chiral phase transfer catalysts.

As a continuous study on asymmetric counteranion directed catalysis [12], List established a palladium(0)/Brønsted acid cooperatively catalyzed asymmetric α -allylation of α -branched aldehydes with secondary allyl amines [13]. The combination of Pd(PPh₃)₄ and chiral phosphoric acid (*R*)-**1b** was able to efficiently catalyze the AAA reaction of allyl amines **23** with aldehydes **22** giving rise to the corresponding optically active products **24**.

Mechanistically, the phosphoric acid initially promoted a condensation of the allylamine **23a** with aldehyde **22** to form an enammonium phosphate salt **25**, which then underwent oxidative addition with palladium(0) to give a π -allylpalladium **26** bearing an anionic chiral phosphate ligand, which forms a H-bond with the released enamine. Subsequently, the nucleophilic attack of the enamine onto the π -allyl-Pd-complex **26** in the coordination sphere of the phosphate anion occurred to result in an intermediate **27**, which after hydrolysis

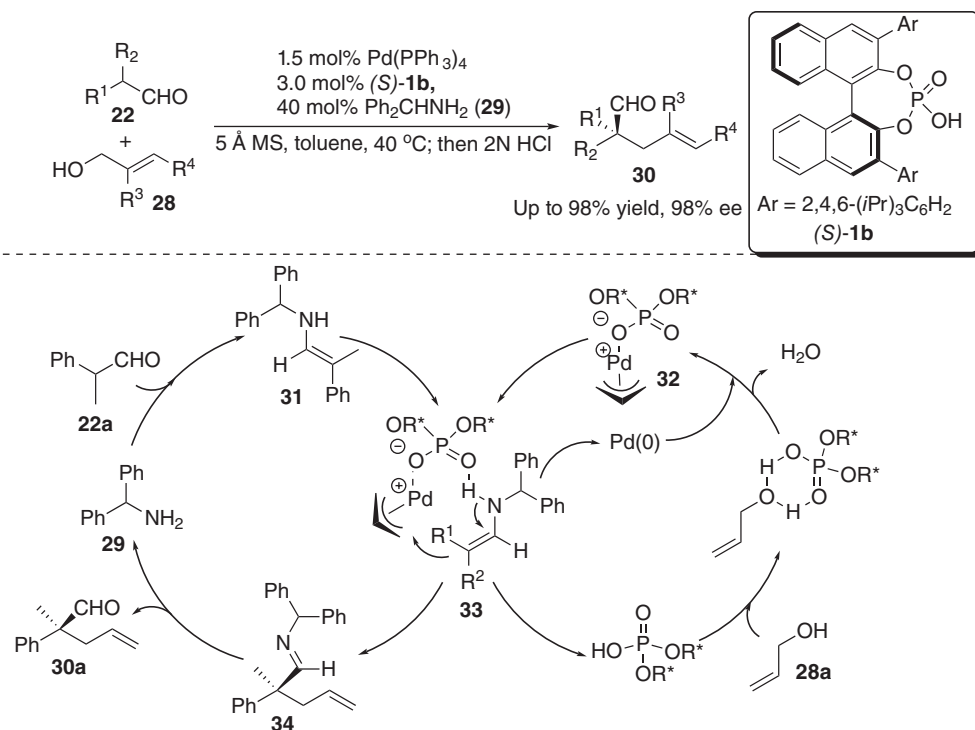
furnished the final products. The chiral phosphoric acid not only activated the allylamine to facilitate the oxidative addition of palladium(0), but also controlled the stereochemistry of the carbon–carbon forming step (Scheme 6.6).



Scheme 6.6 Highly enantioselective direct α -allylation of aldehydes catalyzed by a Pd/Brønsted acid combination.

Allylic alcohols are considered as a promising allylic component in AAA reactions because of their wide synthetic accessibility and a favorable step/waste economy. List and coworkers established a direct α -allylation of aldehydes with allylic alcohols by using palladium and benzoic acid cooperative catalysis [14]. Very recently, the same group accomplished a direct asymmetric α -allylation of aldehydes with simple allylic alcohols by using palladium(0), a chiral phosphoric acid, and an amine as a ternary catalyst system [15]. The combination of Pd(PPh₃)₄, benzhydryl amine **29**, and chiral Brønsted acid (*S*)-**1b** rendered the enantioselective coupling reaction of aldehydes **22** and allylic alcohols **28** to give the allylation products **30** in excellent yields and enantioselectivities. Mechanistically, a configurationally defined *E*-enamine **31** was initially generated from the condensation of the aldehyde **22a** and benzhydryl amine **29**. The oxidative addition of palladium(0) into the allylic alcohol **28a** activated by the chiral Brønsted acid afforded a π -allyl-Pd-phosphate **32**, which then underwent

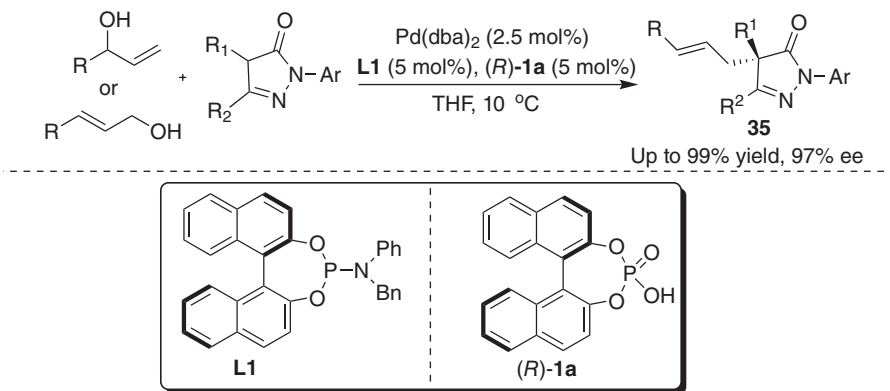
an allylation with the enamine **31** via the crucial intermediate **33** to generate imine **34**, which was then hydrolyzed to furnish the final enantioenriched product **30a** (Scheme 6.7).



Scheme 6.7 Direct asymmetric α -allylation of aldehydes with simple allylic alcohols catalyzed by three different catalysts.

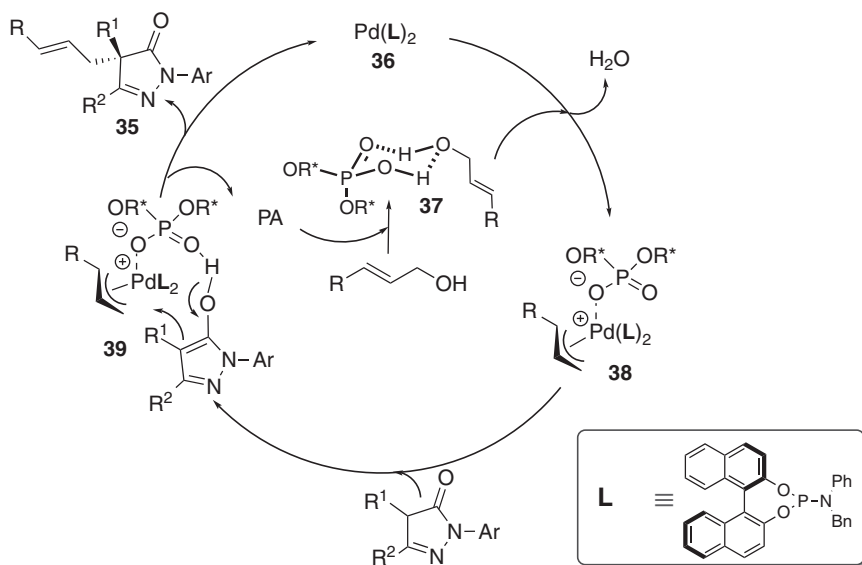
The palladium, amine, and chiral phosphoric acid combined catalyst system is basically suitable to efficiently control the stereoselectivity of the allylic alkylation of enolizable aldehydes or ketones. However, with this strategy it is principally hard to control the stereoselectivity of palladium-catalyzed allylations of the commonly used more acidic pronucleophiles.

Gong and coworkers reported that the combined use of a palladium complex of a chiral phosphoramidite ligand and a chiral phosphoric acid enables allylic alcohols to undergo a highly efficient AAA of pyrazol-5-ones, affording multiple functionalized heterocyclic products **35** in high yields and excellent enantioselectivities (Scheme 6.8) [16]. A plausible catalytic cycle was proposed on the basis of the experimental results and the HRMS analysis of the intermediates. In this reaction, the chiral palladium complex **36** first reacted with a phosphoric acid-activated allylic alcohol **37** by hydrogen bonding to generate the crucial chiral cationic π -allyl palladium(II) complex **38** bearing both chiral ligands and a chiral anion, accompanied with the generation of one molecule of water. Afterward, the



Scheme 6.8 Asymmetric allylic alkylation catalyzed by a palladium complex of a chiral phosphoramidite and a chiral phosphoric acid.

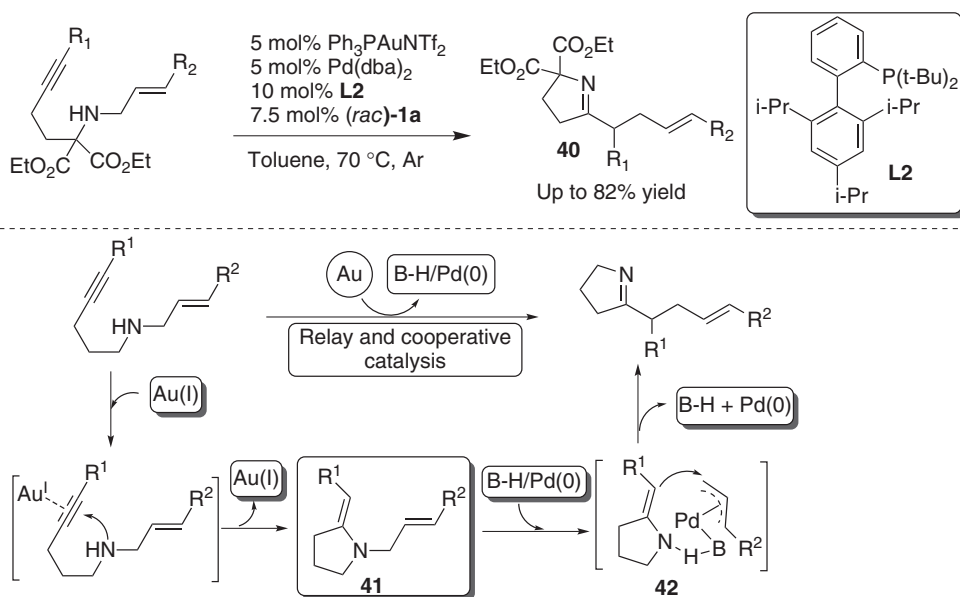
AAA reaction between **38** and the enolizable pyrazol-5-one proceeded via the key intermediate **39**, wherein the pyrazol-5-one was activated by forming a hydrogen-bond with the chiral phosphonate, to generate the corresponding optically active allylation products **35** (Scheme 6.9). In this configuration-determining step, the chiral palladium complex and the chiral phosphonate counteranion worked cooperatively to activate both substrates and to control the stereochemical outcome of



Scheme 6.9 The catalytic cycle for the allylic alkylation catalyzed by a palladium complex of a chiral phosphoramidite and a chiral phosphoric acid.

the AAA reaction, providing the final product with excellent enantioselectivity. Simultaneously the parent chiral palladium(0) complex **36** and the chiral phosphoric acid were regenerated for the next catalytic cycle.

More recently, Gong and coworkers merged relay and cooperative catalysis for the transformation of secondary amine-bridged enynes into pyrrolidine derivatives by using a gold/palladium/Brønsted acid ternary system [17]. The combination of $\text{Ph}_3\text{PAuNTf}_2$, a palladium complex of **L2**, and racemic phosphoric acid (*rac*)-**1a** enabled a cascade reaction of the amine-bridged enynes to furnish pyrrolidine derivatives **40** in high yields (up to 82%). In this reaction, the gold complex initially catalyzed an intramolecular hydroamination to give an *N*-allylic enamine intermediate **41**, which then underwent an allylic alkylation cooperatively catalyzed by the combination of palladium(0) and the Brønsted acid, as shown in **42** (Scheme 6.10).

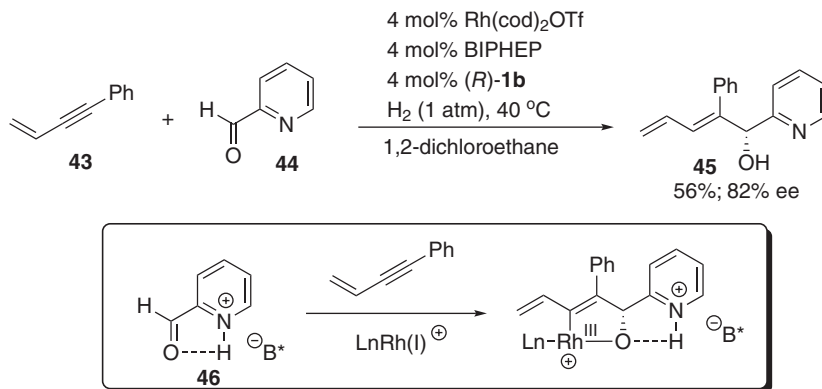


Scheme 6.10 Cascade hydroamination/allylic alkylation reaction catalyzed by a gold/palladium/Brønsted acid ternary system.

6.4

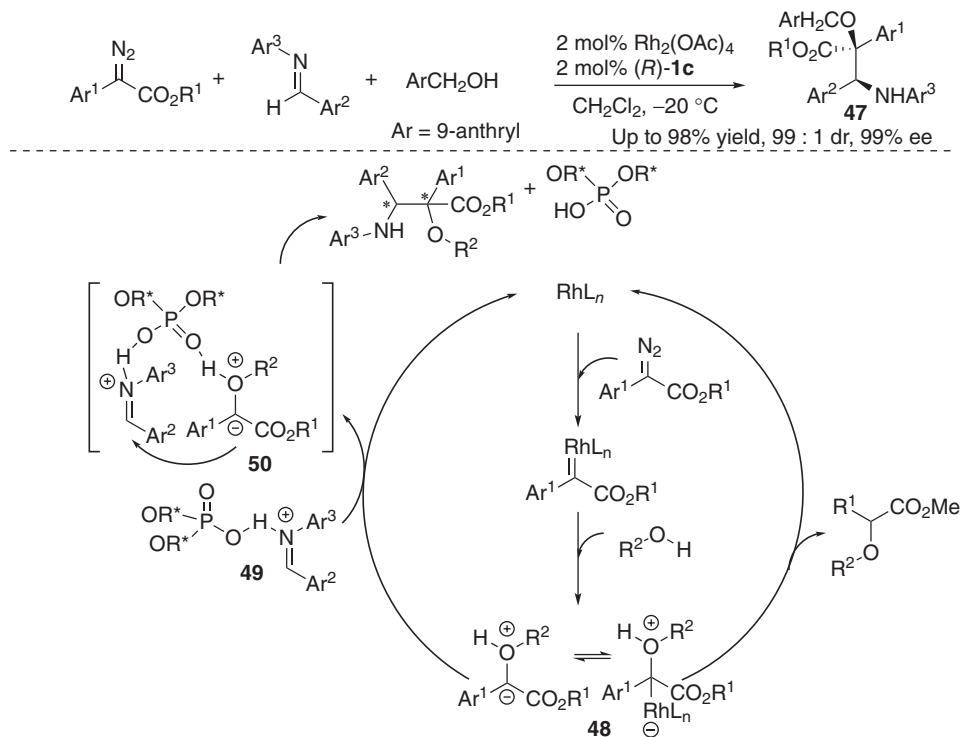
Cooperative Catalysis of a Rhodium Complex and a Brønsted Acid

In 2006, Krische reported that in the rhodium complex-catalyzed reductive coupling of 1,3-enynes **43** with picolinaldehyde **44** for the synthesis of **45**, the addition of chiral phosphoric acid (*R*)-**1b** was able to activate the aldehyde by the protonation of the pyridine moiety to result in a chiral intermediate **46** capable of controlling the stereoselectivity of the subsequent reductive vinylation reaction (Scheme 6.11) [18].

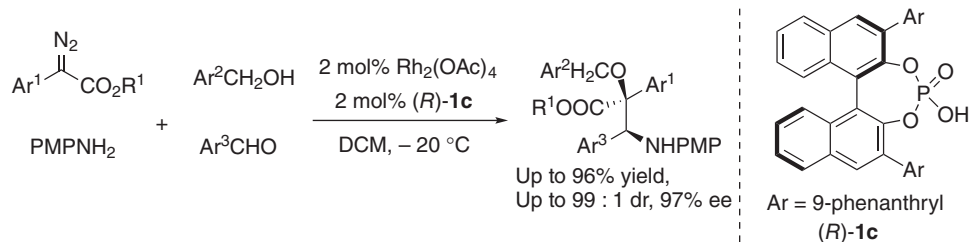


Scheme 6.11 Rhodium-catalyzed asymmetric reductive coupling.

Hu *et al.* [19] found a $\text{Rh}_2(\text{OAc})_4$ /chiral phosphoric acid binary catalyst system, which could be successfully applied to a three-component reaction of alcohols, diazo esters, and aldimines, to generate a wide range of chiral β -amino- α -hydroxy acid derivatives **47** with excellent diastereo- and enantioselectivities. In this case,

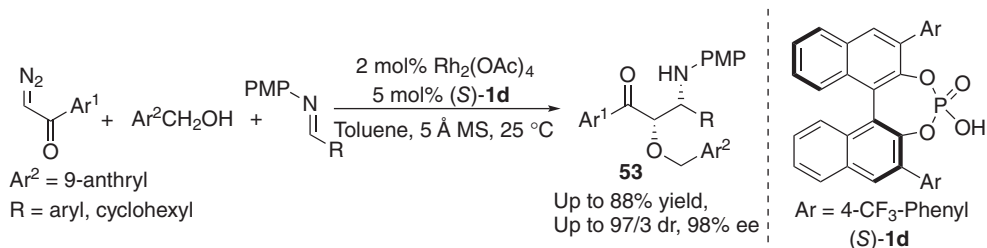


Scheme 6.12 Enantioselective three-component reaction catalyzed by a chiral phosphoric acid and a rhodium complex.

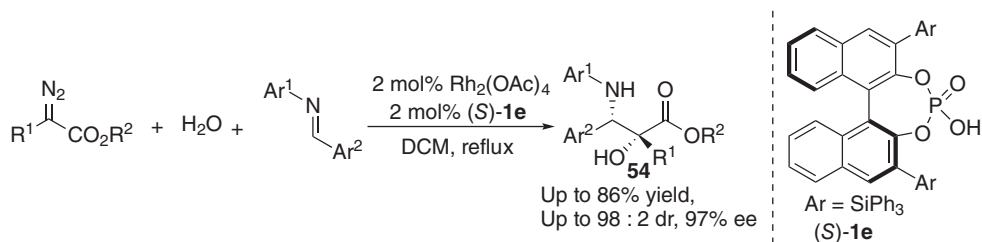


Scheme 6.14 Enantioselective four-component reactions of aryl diazoacetates with alcohols, aldehydes, and amines.

In addition to commonly used diazoacetates and alcohols, diazoketones and water could also be able to participate in Rh/Brønsted acid cooperatively catalyzed multicomponent reactions. Under the catalysis of rhodium acetate and phosphoric acid (S)-1d, the diazoacetophenone derivatives smoothly underwent a three-component reaction with alcohols and imines to furnish β-amino-α-hydroxyl ketones **53** in good yields and with excellent stereoselectivities (Scheme 6.15) [22]. The use of water to replace an alcohol as a reaction component also enabled to give rise to *syn*-β-amino-α-hydroxyesters **54** in high yields and with excellent levels of enantioselectivity (Scheme 6.16) [23].

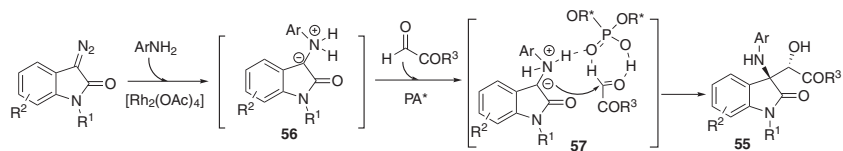
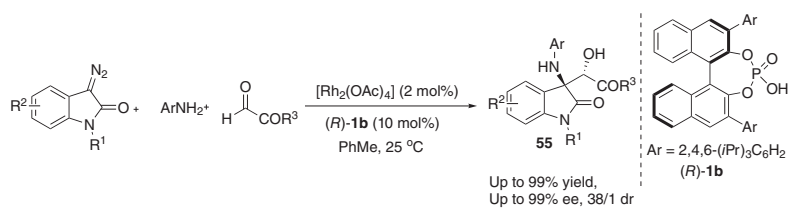


Scheme 6.15 Asymmetric catalytic reaction of diazoacetophenones with alcohols and imines catalyzed by Rh₂(OAc)₄/chiral Brønsted acid **1d**.



Scheme 6.16 Asymmetric catalytic reaction of aryl diazoacetates, water, and aldimines catalyzed by Rh₂(OAc)₄/chiral Brønsted acid **1e**.

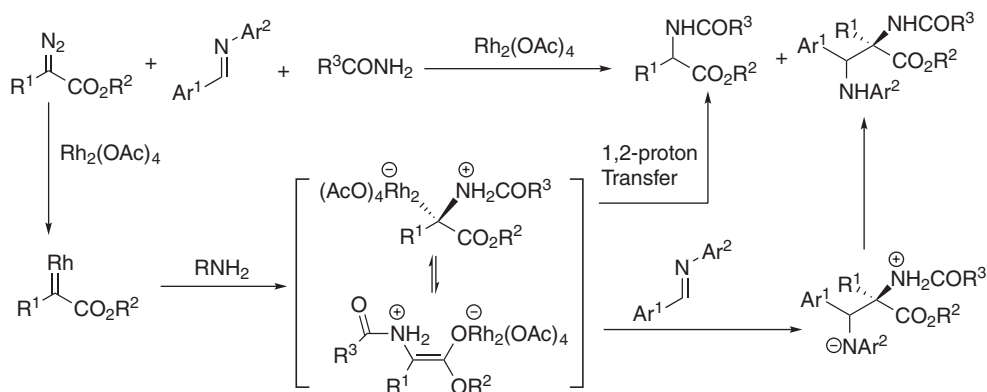
Moreover, anilines are also able to undergo N–H insertion reactions to generate ammonium ylides, which could participate in an aldol reaction with aldehydes



Scheme 6.17 Brønsted acid/rhodium(II) cooperative catalytic asymmetric three-component aldol-type reaction for the synthesis of 3-amino oxindoles.

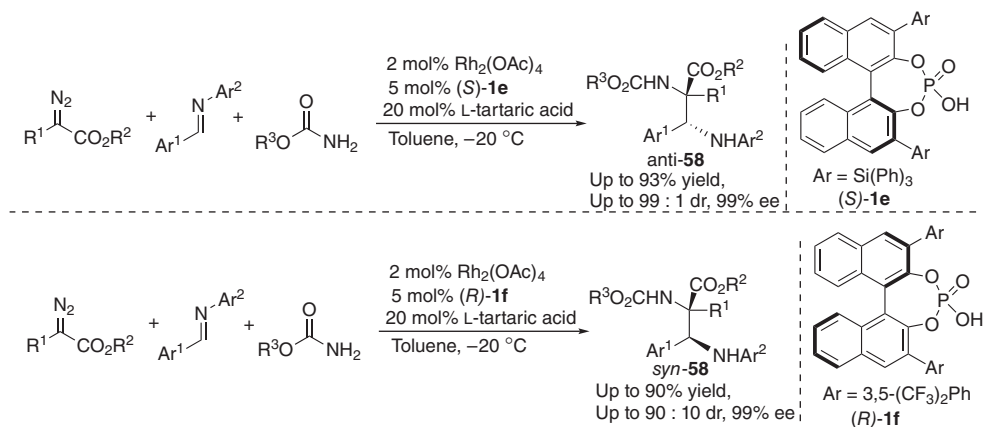
[24]. Gong *et al.* established a highly stereoselective three-component aldol-type reaction of 3-diazo oxindoles and anilines with glyoxylates by using rhodium acetate/chiral Brønsted acid cooperative catalysis [25]. The use of phosphoric acid (*R*)-**1b** as a collaborative organocatalyst tolerated a wide scope of anilines and 3-diazo oxindoles to give a collection of highly functionalized 3-amino oxindoles **55** in excellent stereoselectivities and yields (up to 99% yield, 99% ee, and 38/1 dr). The reaction basically proceeds via a rhodium-catalyzed generation of ammonium ylides **56** from 3-diazo oxindoles and anilines followed by a chiral Brønsted acid-catalyzed enantioselective aldol-type reaction with glyoxylates, as shown in **57**, to give optically active products **55**. The phosphoric acid actually activates the formyl group of glyoxylates through a hydrogen-bonding interaction and the phosphoryl oxygen functions simultaneously as a Lewis base to form an additional hydrogen bond with ammonium ylides to stabilize the transition state (Scheme 6.17).

Because of the lower electron density of the nitrogen atom, amides are relatively challenging substrates to undergo N–H insertion reactions with diazocarbonyls. Moreover, even if the desired N–H insertion reaction occurs, the resultant ylides easily undergo a 1,2-proton transfer reaction to compete with ylide-trapping reaction by other electrophiles (Scheme 6.18). Thus, highly activated electrophiles are basically required to trap the ylide and to surpass the proton transfer reaction.



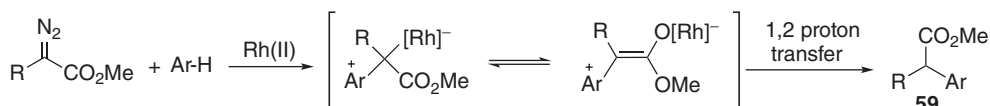
Scheme 6.18 Brønsted acid/rhodium(II) cooperative catalytic asymmetric three-component N–H insertion reaction with amides.

Hu and coworkers found that the combined catalyst system consisting of rhodium acetate, L-tartaric acid, and chiral phosphoric acids successfully allowed the highly reactive protic carbamate ammonium ylides to be trapped by imine electrophiles, rendering a three-component Mannich-type reaction of diazo compounds, carbamates, and imines to generate either *syn*- or *anti*- α -substituted α,β -diamino acid derivatives **58** with high levels of chemo-, diastereo-, and enantioselectivity (Scheme 6.19) [26].



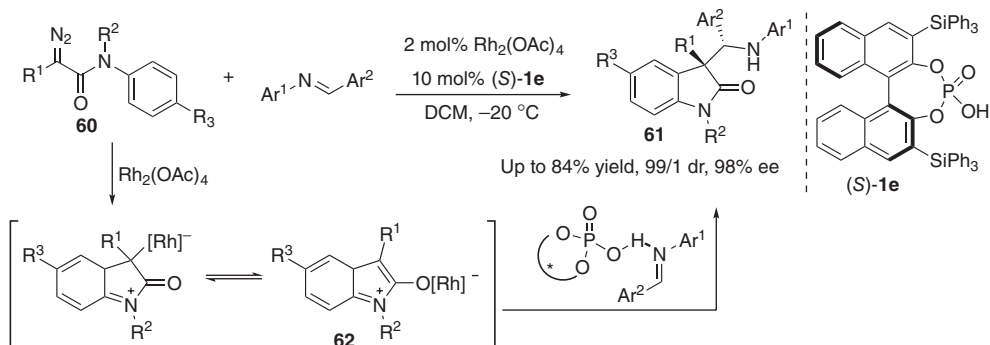
Scheme 6.19 Diastereoselectivity switchable enantioselective three-component reaction of diazo compounds, carbamates, and imines.

The rhodium carbenoids could also be attacked by electron-rich aromatic compounds to generate a zwitterionic intermediate, which then usually undergoes a rapid proton transfer to afford C–H functionalized products **59** (Scheme 6.20) [27].



Scheme 6.20 Intermolecular C–H functionalization reaction with rhodium carbenoids and aromatic compounds.

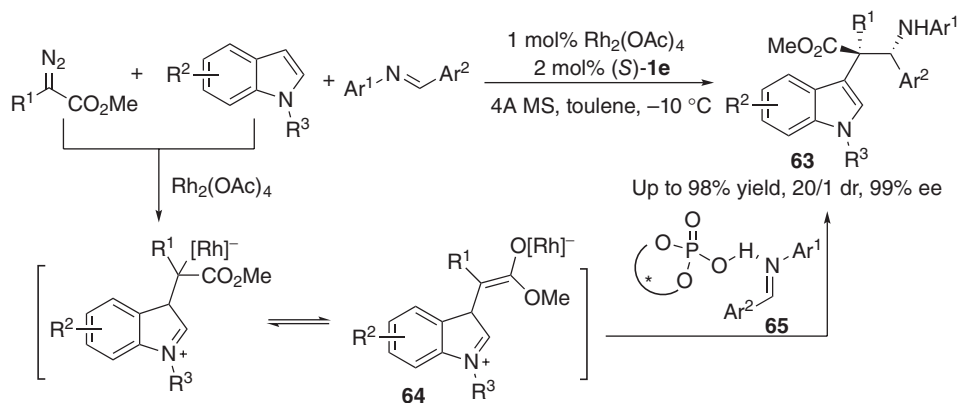
Hu and coworkers found that under the cooperative catalysis of rhodium acetate and a chiral phosphoric acid, these zwitterionic intermediates could stereoselectively be trapped by imines. For instance, the zwitterionic



Scheme 6.21 Cascade intramolecular C–H functionalization/Mannich reaction catalyzed by rhodium acetate and a chiral phosphoric acid.

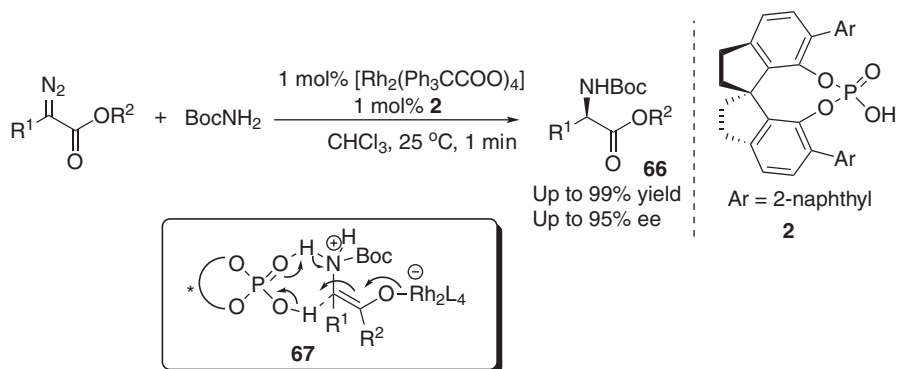
intermediates **62** generated from *N*-phenyl diazoacetamide derivatives **60** mediated by rhodium acetate smoothly underwent a Mannich-type reaction to furnish the corresponding chiral 3,3-disubstituted oxindole derivatives **61** in excellent yields and enantioselectivities (Scheme 6.21) [28].

Besides, the zwitterionic intermediates **64** formed from the reaction of a carbenoid with indole derivatives could also be trapped by a Brønsted acid-activated imine **65**. The use of chiral phosphoric acid (*S*)-**1e** allowed a three-component reaction of indole derivatives, diazoesters, and imines to efficiently access optically active indole derivatives **63** in excellent enantioselectivities (Scheme 6.22) [28].



Scheme 6.22 A three-component reaction of methyl phenyldiazoacetate, an indole, and imine.

Zhou and Zhu first expanded the rhodium/chiral Brønsted acid cooperative catalysis to asymmetric N–H insertion reactions of carbenoids [29]. They found that the use of $\text{Rh}_2(\text{Ph}_3\text{CCOO})_4$ and chiral phosphoric acid **2** as a binary



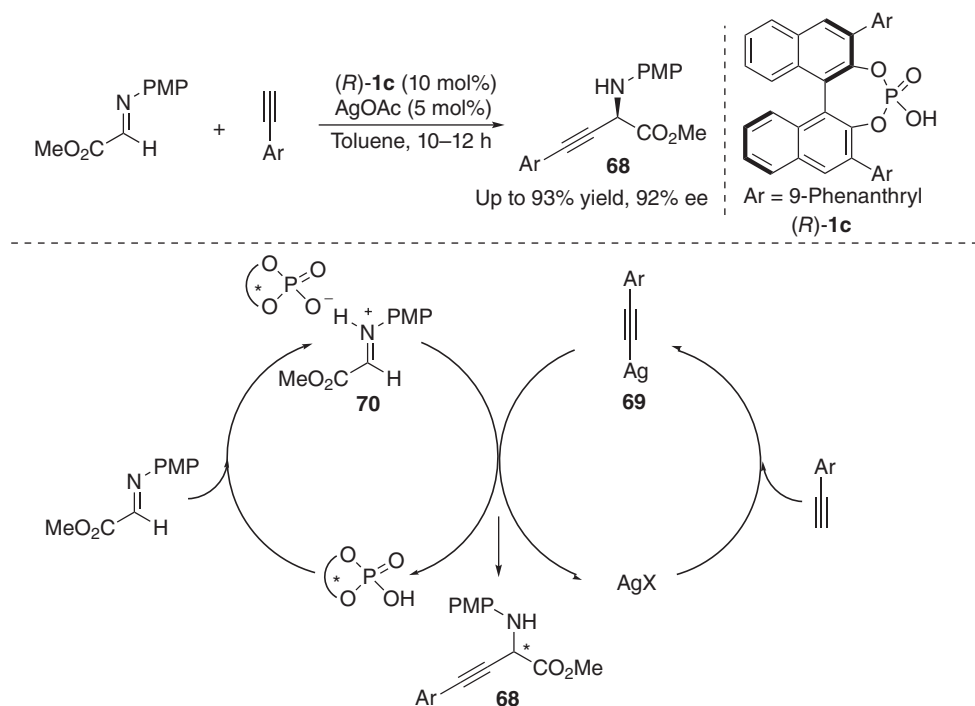
Scheme 6.23 Asymmetric N–H insertion reaction cooperatively catalyzed by rhodium and chiral spiro phosphoric acid.

catalyst allowed diazoester derivatives to undergo highly enantioselective N–H insertion reaction with *tert*-butyl carbamate. A wide range of diazoesters were tolerated to produce α -amido esters **66** in high yields (up to 99%) and excellent enantioselectivities (up to 95%). Importantly, the cooperative catalysis system had significant advantages, including a lower catalyst loading and higher yields, in comparison with chiral copper catalysts developed for a similar reaction [30]. The chiral Brønsted acid is considered to perform as a proton-transfer shuttle in this N–H insertion transformation, facilitating the stereoselective proton transfer step through a seven-membered ring transition state **67** (Scheme 6.23).

6.5

Cooperative Catalysis of a Silver Complex and a Brønsted Acid

The asymmetric catalytic alkynylation of α -imino esters represents one of the most straightforward methods to access optically active nonproteinogenic α -amino acids. In 2005, Chan and coworkers reported an enantioselective alkynylation of α -imino esters catalyzed by a chiral copper(I) complex [31]. In 2007, Rueping *et al.* [32] demonstrated that a highly enantioselective addition of terminal alkynes to imino esters could be realized by employing a binary catalyst



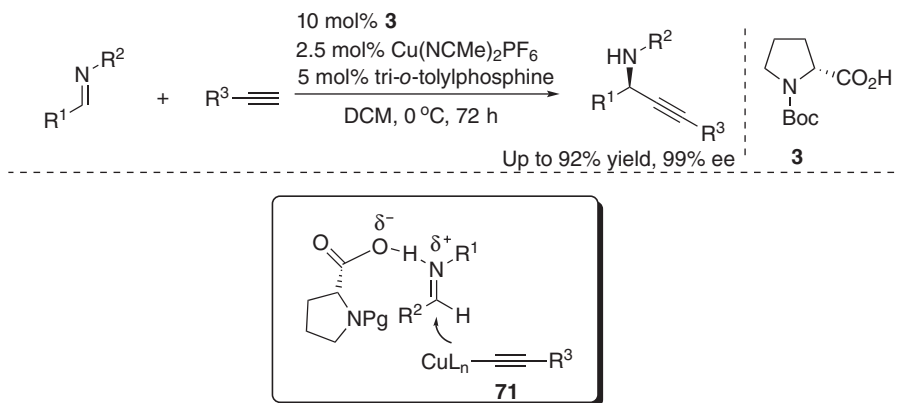
Scheme 6.24 The enantioselective alkynylation of imines through cooperative catalysis.

system of an achiral silver complex and a chiral phosphoric acid. The phosphoric acid (*R*)-**1c** turned out to be best cocatalyst and allowed a variety of β,γ -alkynyl α -amino esters **68** to be generated in high yields and with excellent enantioselectivities. In this cooperative catalysis, the achiral silver acetate activated the acetylene derivatives by the formation of alkynyl silver intermediates **69** and simultaneously the chiral phosphoric acid activated the α -imino ester by the formation of a chiral ion pair **70**, which actually controlled the stereochemical outcome of the nucleophilic addition (Scheme 6.24). Alternatively, a chiral silver phosphate complex *in situ* generated from a counterion-exchange reaction was also believed to be responsible for governing the asymmetric induction.

6.6

Cooperative Catalysis of a Copper Complex and a Brønsted Acid

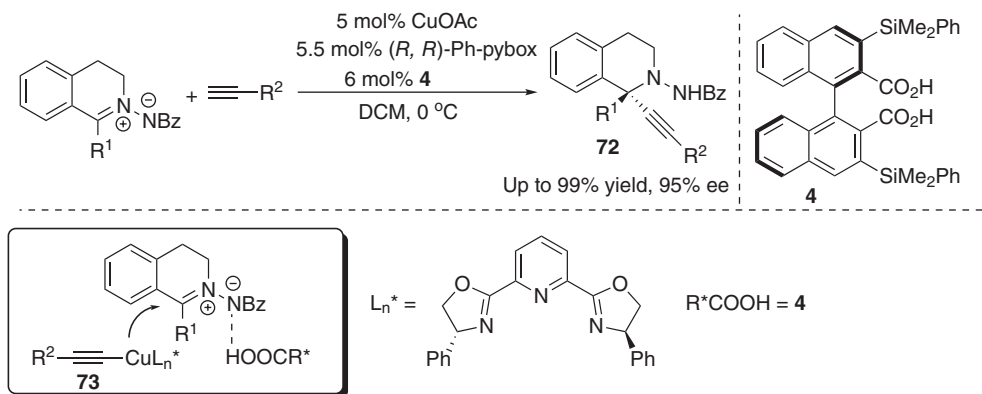
More recently, Arndtsen established an asymmetric alkynylation of imines by using copper complex/amino acid cooperative catalysis [33]. The copper(II) complex in combination with *N*-Boc proline **3** enabled the asymmetric alkynylation reaction to accommodate a wide scope of imine substrates including less reactive simple aldimines. As described in Scheme 6.25, the protected amino acid **3** was acting as a Brønsted acid to activate the imine, and the copper complex was believed to activate the alkyne by the formation of an alkynyl copper intermediate **71** (Scheme 6.25).



Scheme 6.25 Asymmetric alkynylation of imines cooperatively catalyzed by a Brønsted acid and a copper complex.

Recently, a binary catalyst system of a copper(I)/pybox complex and an axially chiral dicarboxylic acid was created by Maruoka to catalyze an alkynylation of C1-substituted *C,N*-cyclic azomethine imines for the synthesis of optically active tetrahydroisoquinolines **72**. The more acidic chiral dicarboxylic acid **4** presumably exchanged with acetic acid (*in situ* generated from the chiral copper acetate

complex of Ph-pybox and the alkyne) to protonate the azomethine imine and collaborated with the chiral cooper acetylide **73** to control the stereoselectivity (Scheme 6.26) [34].

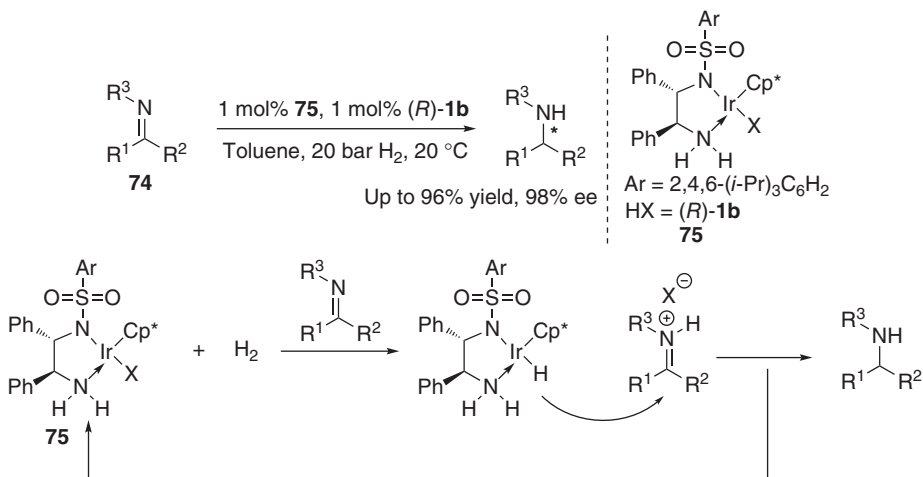


Scheme 6.26 Asymmetric alkynylation of azomethine imines catalyzed by copper(I)/pybox and an axially chiral dicarboxylic acid.

6.7

Cooperative Catalysis of an Iridium Complex and a Brønsted Acid

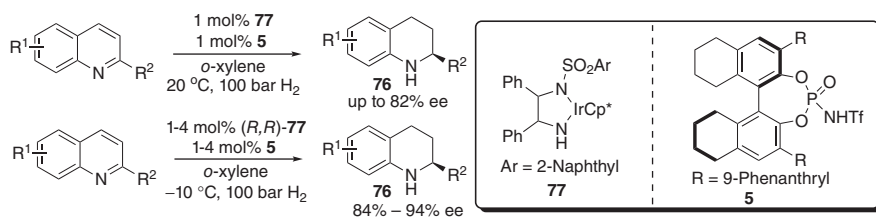
Xiao and coworkers found an obvious synergistic effect between iridium complexes and chiral phosphoric acids in the catalytic asymmetric hydrogenation of acyclic imines [35]. The combined catalyst system of iridium complex **75** and phosphoric acid (*R*)-**1b** rendered the asymmetric hydrogenation of imines **74** in a complete conversion and with excellent levels of enantioselectivity (Scheme 6.27)



Scheme 6.27 Cooperatively catalyzed asymmetric hydrogenation of acyclic imines.

[35a]. Moreover, asymmetric reductive amination of prochiral ketones was able to be realized by the combined catalysts [35b]. The chiral phosphoric acid was considered to activate the imine substrate by the formation of an iminium species and also probably participated in a reaction with the chiral iridium complex to generate a more active chiral iridium phosphate, which was actually able to induce high stereoselectivity in the hydrogenation [35].

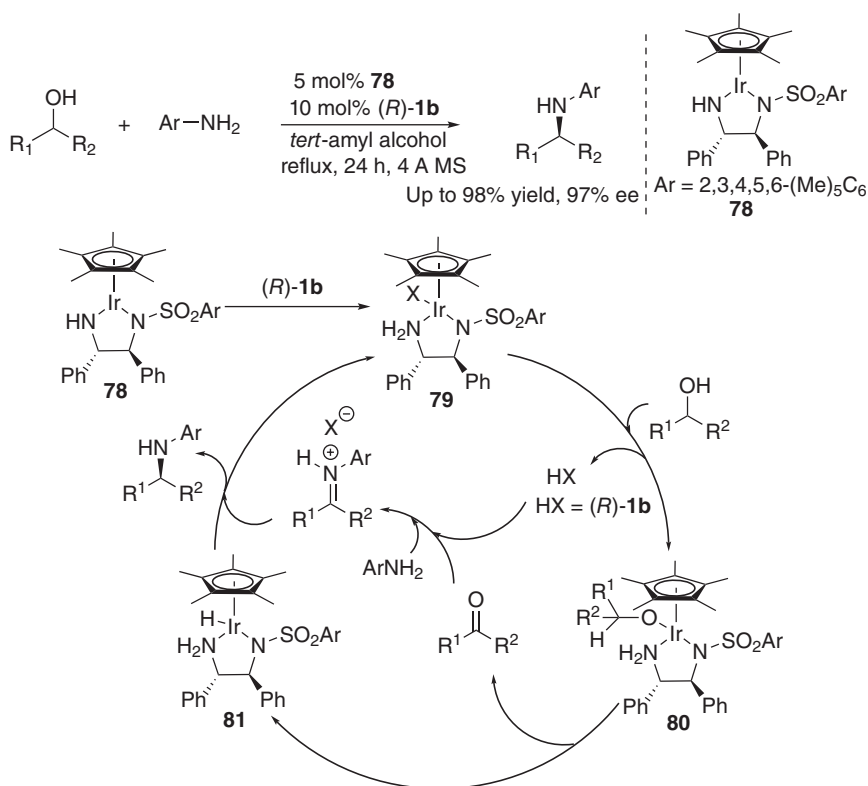
The combination of more acidic chiral *N*-triflylphosphoramides with an iridium complex for asymmetric catalysis was recently established by Rueping and Koenigs [36]. Under the assistance of chiral Brønsted acid **5**, the asymmetric hydrogenation of quinoline derivatives catalyzed by the iridium complex **77** proceeded cleanly to yield chiral tetrahydroquinolines **76** in high optical purity. More interestingly, the asymmetric reduction catalyzed by a racemic Ir-complex could be kinetically differentiated by chiral Brønsted acids. Thus, the hydrogenation catalyzed by the racemic Ir-complex in combination with the chiral Brønsted acid **5** gave enantioselectivities up to 82% ee. Detailed studies on the catalyst species suggested that **77** was protonated by the chiral Brønsted acid **5** to result in two different complexes of which the combination (*R,R*)-[Ir]-H⁺/**5**[−] was seemingly a matched species and turned out to be more catalytically active and stereoselective than the diastereomer (*S,S*)-[Ir]-H⁺/**5**[−] (Scheme 6.28).



Scheme 6.28 Enantioselective reduction of quinoline compounds catalyzed by chiral *N*-triflylphosphoramides and iridium complex **77**.

The catalytic asymmetric reduction of ketimines has been well established with many reductants. Most recently, Zhao and coworkers reported a high atom economical and enantioselective amination of alcohols by the use of the “borrowing hydrogen” methodology catalyzed by a chiral Ir complex, in combination with a chiral phosphoric acid to access optically active amines without an external reductant [37]. In this protocol, the active iridium catalyst species **79** generated from the protonation of **78** with the Brønsted acid (*R*)-**1b** presumably reacted with the secondary alcohol to generate an iridium–alkoxide complex **80**, which then underwent a β -hydride elimination to produce an iridium hydride **81**, together with a prochiral ketone. During the iridium–alkoxide complex formation the chiral Brønsted acid (*R*)-**1b** was regenerated. The released prochiral ketone then underwent condensation with the aniline catalyzed by (*R*)-**1b** to give a chiral iminium,

which was enantioselectively reduced by chiral iridium hydride **81** to produce the highly enantioenriched amine (Scheme 6.29).

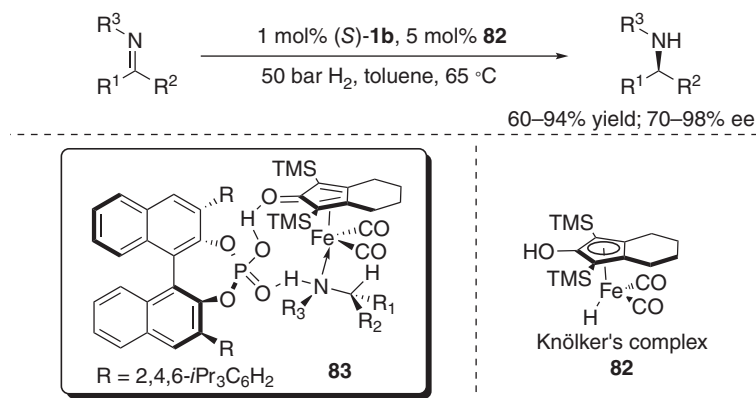


Scheme 6.29 Catalytic enantioselective amination of alcohols by the use of the “borrowing hydrogen” methodology.

6.8

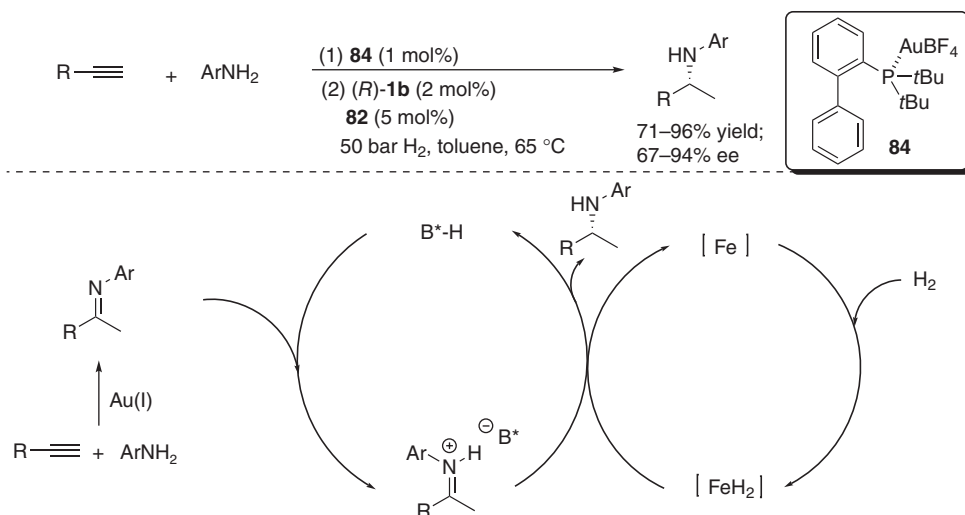
Cooperative Catalysis of an Iron Complex and a Brønsted Acid

Beller and coworkers recently developed an asymmetric catalytic hydrogenation of prochiral imines by using a combined catalyst system of an iron complex and a chiral phosphoric acid (Scheme 6.30) [38]. In this cooperative catalysis, Knölker’s achiral iron complex **82** was employed to catalytically activate hydrogen by the formation of iron hydride, which was able to efficiently reduce imines, and simultaneously the chiral phosphoric acid (*S*)-**1b** protonated the imine to form an iminium species and thereby controlled the stereochemical outcome of the nucleophilic addition, as shown in **83**. Such a cooperative catalysis essentially avoided the use of precious-metal catalysts and chiral ligands that commonly appear in classical asymmetric hydrogenations.



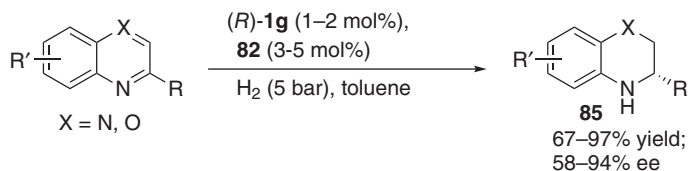
Scheme 6.30 Asymmetric catalytic reduction of imines by using an iron complex in combination with a chiral phosphoric acid.

Under the catalysis of a gold complex, aryl acetylenes were able to undergo an intermolecular hydroamination reaction with anilines to generate imines. As reported by Beller [38], the imines could be enantioselectively hydrogenated under the cooperative catalysis of Knölker's iron complex **82** and a chiral Brønsted acid. Inspired by these individual protocols, Beller and coworkers established a sequential process to directly transform the aryl acetylenes and anilines to chiral secondary amines in high yields and with excellent levels of enantioselectivity in the presence of a gold(I) complex **84**, Knölker's iron complex **82**, and a chiral Brønsted acid (*R*)-**1b** (Scheme 6.31) [39].



Scheme 6.31 Asymmetric reductive hydroamination of acetylene derivatives sequentially and cooperatively catalyzed by a gold(I) complex, Knölker's iron complex, and a chiral Brønsted acid.

More recently, Beller expanded the iron complex/chiral Brønsted acid cooperative catalysis to asymmetric catalytic reduction of quinoxalines and 2*H*-1,4-benzoxazines. In the presence of Knölker's iron complex **82** and chiral Brønsted acid (*R*)-**1g**, the asymmetric hydrogenation of quinoxalines and 2*H*-1,4-benzoxazines proceeded readily to give optically active heterocycles **85** in high yields and with excellent enantiomeric excesses (Scheme 6.32) [40].



Scheme 6.32 Asymmetric catalytic reduction of quinoxalines by an iron complex/Brønsted acid dual catalyst system.

6.9

Perspective

Asymmetric organo/metal cooperative catalysis has been undoubtedly shown to be a versatile concept that provides a new strategy to realize enantioselective transformations. A successful cooperative catalysis basically relies on both the compatibility and efficiency of metal catalysts and organocatalysts. Partially because of the robustness of chiral Brønsted acids in the asymmetric catalysis, the cooperative catalysis of transition metal complexes and chiral Brønsted acids has allowed the appearance of a diverse spectrum of enantioselective reactions that neither of the individual catalysts is able to afford. Besides the good compatibility with transition metals, the conjugate bases or corresponding counterions of chiral Brønsted acids have been excellent chiral tools to control the stereochemical outcome [41] and, therefore, can be efficiently used for cooperative catalysis. However, the capacity of the metal/chiral Brønsted acid cooperative catalysis has not been fully demonstrated yet. It can be anticipated that such cooperative catalysis will continue to play an important role in the creation of new asymmetric transformations and will be a blooming field among homogeneous catalysis.

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7

Cooperative Catalysis Involving Chiral Ion Pair Catalysts

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7.1

Introduction

Ion pairing is one of the fundamental mechanisms by which catalysts can coordinate to substrates or reaction intermediates and control the reactivity thereof. These ion-pairing catalysts may either be achiral or chiral. The potential of achiral catalysts has been impressively demonstrated for half a century now with the underlying concept of “classical” phase-transfer catalysis [1], which nowadays belongs to one of the standard techniques in academic research and on industrial scale [2]. In addition, chiral versions of such catalysts can be used to generate chiral substrate–catalyst ion pairs to facilitate highly enantioselective reactions [3]. The use of these asymmetric ion-pairing catalysts, either based on chiral cations or chiral anions, has a rich history [4–8]. It is worth noting that the majority of the research carried out in this field relies on the use of chiral cation catalysts [6], whereas the field of chiral anion-mediated ion-pairing catalysis has been less routinely described [7, 8]. One fact that should be emphasized is that an exact classification of the real activation mode is not always trivial in this field and therefore it is also a question of definition and a matter of understanding of the exact mechanism of such reactions whether a catalyst is considered to be an ion-pairing catalyst or, for example, a H-bonding activator. To illustrate the difficulties associated with respect to the classification of such reactions and the exact activation mechanism, the use of asymmetric phosphoric acid catalysts should be briefly mentioned [9]. Here, different modes of activation are possible in principle. One extreme case involves complete protonation of the substrate and formation of a chiral ion pair with the conjugated base of the catalyst. On one hand, such catalysts might also activate the substrate via H-bonding, thus illustrating that classifications concerning the exact activation mode and control in the face-differentiating step are sometimes hard to make [8]. In addition, some classification difficulties may arise when discussing reactions that proceed via the formation of an ion pair containing a chiral cation. It is without doubt that classical asymmetric phase-transfer catalysts (PTCs), such as chiral quaternary

ammonium or phosphonium salt catalysts, activate the usually anionic substrate/intermediate via the formation of a chiral ion pair. On the other hand, the activation mode of chiral *tert*-amine-based catalysts can also often be considered to proceed via the formation of a chiral ion pair between the protonated amine catalyst and the deprotonated starting material. However, these approaches are classically not considered to be phase-transfer-catalyzed ones.

Because of the complexity of this topic and to provide a focused and illustrative overview which does not overlap with the other contributions of this volume, we primarily consider and discuss here those approaches where the chiral catalyst is already used as an ionic species (chiral cation/achiral anion or achiral cation/chiral anion) and where the key ion-pair formation between the catalyst and the starting material is not achieved by ion pairing between either a protonated catalyst and an anionic intermediate or between an anionic catalyst and a protonated intermediate.

The successful use of chiral ion-pairing catalysts containing complementary activation/coordination sites dates back to the seminal reports by Wynberg's group in 1976, describing the first use of free-OH-containing cinchona alkaloid-based ammonium salt PTCs for asymmetric transformations [3]. Subsequently, the use of chiral bifunctional ammonium salt catalysts has emerged as a powerful strategy to facilitate different complex transformations [10]. In addition, a broad variety of other highly innovative cooperative approaches using either chiral cationic or anionic catalysts in combination with complementary catalytically active motives have been reported [11], as is illustrated in the following chapters. However, some words of caution are necessary concerning the use of the terminology "cooperative catalysis." Different classifications have been reported in the past [12], and we are well aware that these models do often differentiate between cooperative catalysis and, for example, bifunctional catalysis. Nevertheless, we reason that it is beneficial to provide an illustrative overview about mechanistically different strategies that describe the synergistic/cooperative combination of chiral ion-pairing catalysis with complementary activation modes, be it in the form of bifunctional single-molecule catalysts or the cooperative combination of two distinct catalysts.

7.2

Chiral Cation-Based Catalysis

The use of chiral cations as catalysts has obtained a prominent and outstanding position and has contributed significantly to the field of asymmetric catalysis [4, 5]. Compared to other strategies, this method is outstanding as it represents a generally applicable catalytic principle that allows the stereoselective activation of such important nucleophiles such as, for example, enolates, cyanides, or peroxides in a noncovalent and easy-to-handle manner. Combining this unique activation mode with other complementary activation modes (e.g., H-bonding donors to activate electrophiles) has resulted in several very powerful approaches to access chiral target skeletons where other methods fail. In general, three different strategies have

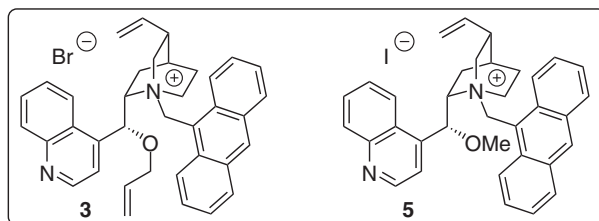
been reported in this context. On one hand, chiral cationic catalysts were successfully used in a synergistic combination with transition-metal catalysts [13]. Besides this, the development and use of bifunctional single-molecule catalysts has emerged as a powerful and promising strategy over the past years [10]. Alternatively, the use of chiral cation catalysts containing an achiral catalytically active or relevant counteranion has proven its potential in several case studies [14].

7.2.1

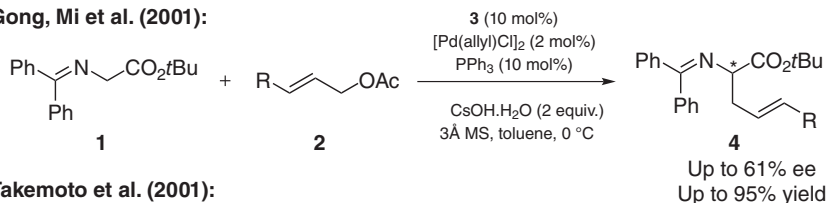
Cooperative Combination of Chiral Cation-Based Catalysts and Transition-Metal Catalysts

The cooperative use of chiral cation-based catalysts to activate prochiral nucleophiles and (a)chiral transition-metal catalysts to activate electrophiles should result in a powerful synergistic combination to facilitate a variety of challenging asymmetric reactions. Surprisingly, this seemingly powerful strategy so far has been reported only for a few applications [15, 16]. In 2001, the groups of Gong and Mi described the modestly enantioselective chiral PTC/palladium-catalyzed allylation of glycine Schiff base **1** with allylic acetates **2** (Scheme 7.1, upper reaction) [15]. The use of the cinchona alkaloid-derived chiral PTC **3** and the achiral Pd catalyst $[\text{Pd}(\text{allyl})\text{Cl}]_2/\text{PPh}_3$ in the presence of molecular sieves gave the linear allylation products **4** with enantiomeric excesses of up to 61%. Noteworthy, in this case the use of chiral phosphine ligands was not found to be beneficial, giving similar or even worse selectivities compared to the use of PPh_3 . At the same time, the Takemoto group reported a highly enantioselective protocol for the allylation of **1** with different allylic acetates **2** in the presence of a chiral PTC and an achiral Pd(0) catalyst [16]. Key to the high enantioselectivities was the choice of the achiral ligand $(\text{PhO})_3\text{P}$. The authors rationalized that this ligand favors the formation of the less reactive neutral π -allylpalladium intermediate **B** instead of a more reactive cationic complex that would lead to an increased rate of the racemic background reaction. Primary (**2**) and secondary allylic acetates (**6**) yielded preferentially the same products, namely, the linear allylation products **4**, whereas only small amounts of the branched **7** could be obtained when starting from **6** (Scheme 7.1, lower part). In these studies, also the addition of **1** to a prochiral allylic acetate in the presence of a chiral PTC and a chiral Pd catalyst was tested. However, the results were only modest in terms of diastereoselectivity and enantioselectivity [16b].

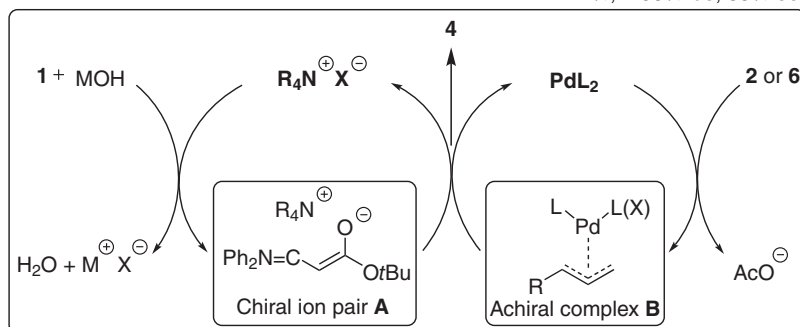
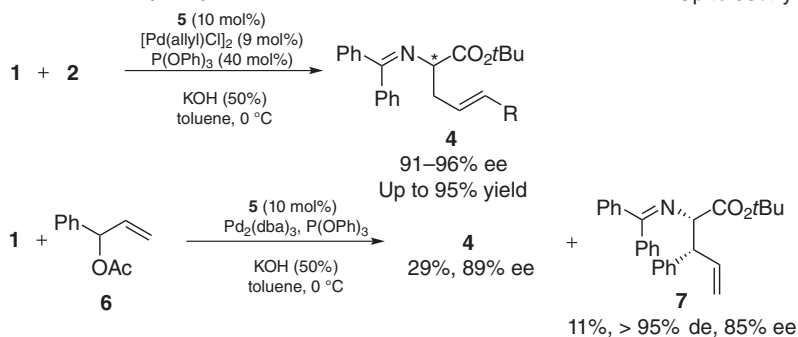
Although this early example was an illustrative proof of the feasibility of this cooperative strategy, no further advanced reports in this field have been reported. Even more interesting, the Glorius group found that cinchona-based PTCs do not succeed in classical Pd-catalyzed α -arylation reactions using arylhalide electrophiles [17], thus illustrating a major limitation of this concept. Nevertheless, we speculate that, considering the recent advances made in both fields, namely asymmetric phase-transfer catalysis and asymmetric transition-metal catalysis, it may only be a matter of time before novel powerful strategies following the synergistic use of these two complementary activation modes are introduced.



Gong, Mi et al. (2001):



Takemoto et al. (2001):



Scheme 7.1 Cooperative dual PTC/Pd catalysis for the asymmetric α -allylation of prochiral nucleophiles.

7.2.2

Bifunctional Chiral Cation-Based Catalysts

As mentioned before, the use of bifunctional free-OH-containing cinchona alkaloid PTCs dates back to the early reports in the field [3]. Surprisingly, despite these promising seminal examples, systematic investigations concerning the development and application of chiral bifunctional cation catalysts have started

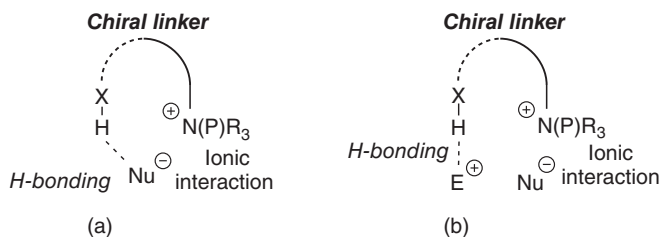


Figure 7.1 (a, b) Alternative activation modes of bifunctional cationic ion-pairing catalysts possessing H-bonding sites.

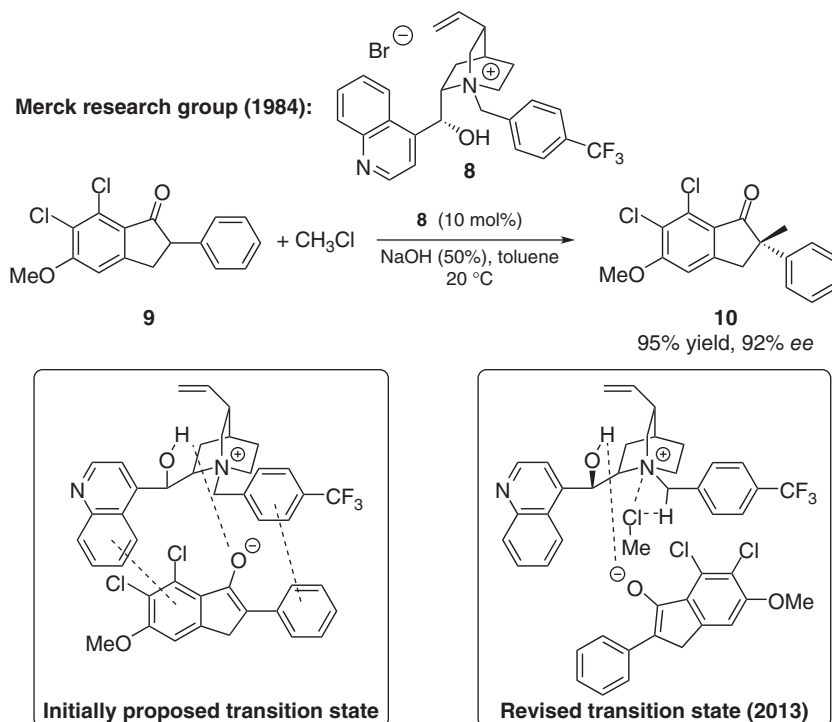
only more recently [10]. The mode of action of the second functionality (e.g., a free OH group) can either be an additional coordination of the nucleophile (see Figure 7.1a), thus achieving a better control and therefore an increased face differentiation of the nucleophile, or an activation/coordination of the electrophile, thus resulting in a highly ordered transition state (Figure 7.1b).

A variety of different strategies to incorporate additional coordination sites and access of carefully diversified bifunctional chiral cation catalysts have been reported during the past years. The breakthrough reports as well as some of the most impressive and illustrative examples are discussed in this chapter.

7.2.2.1 Free-OH-Containing Catalysts

After the seminal report of Wynberg's group describing the use of cinchona-based chiral PTCs for moderately enantioselective epoxidation reactions [3a], the first highly selective application of a chiral PTC was reported in 1984 by a group of Merck scientists (Scheme 7.2) [3c]. By using the free-OH-containing ammonium salt **8** as a catalyst, a highly enantioselective and high yielding α -methylation of phenylindanone **9** could be achieved. After careful studies and mechanistic considerations, a transition state with the quinoline ring, the C9–O bond, and the benzylic group of the catalyst lying in one plane and a coordination of the enolate via H-bonding and π – π interactions was proposed. However, very recently, a revised activation mode was proposed [18]. Following very detailed DFT calculations, it was shown that a stabilization of the pathway toward the major product enantiomer through H-bonding between the catalyst and the indanone enolate and electrostatic interaction between the ammonium group and the chloromethane takes place. This interesting result also explains the significantly better performance of CH_3Cl as the alkylating agent compared to CH_3Br and CH_3I [3c].

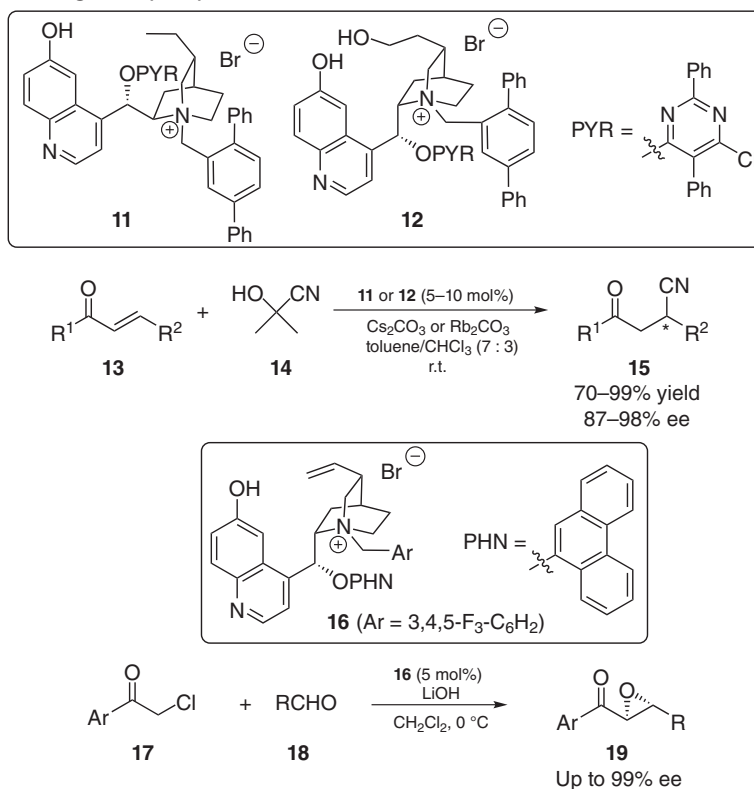
On the basis of this early breakthrough report, free-OH-containing cinchona PTCs were also the catalysts of choice in O'Donnell's pioneering studies on the synthesis of differently substituted (non)-natural amino acids [3d]. Interestingly, with respect to most of the reactions developed later in this field, O-protected (e.g., O-allylated) cinchona PTCs were found to be more powerful and selective and have therefore become the most privileged class of chiral PTCs. However, the importance of the benzylic OH group as a second coordination and activation site to facilitate a variety of otherwise not feasible or only weakly selective reactions has been increasingly recognized and reported over the past few years.



Scheme 7.2 Seminal report for the asymmetric α -alkylation of phenylindanones under asymmetric phase-transfer catalysis using a 9-OH-containing bifunctional ammonium salt PTC. Merck research group [3c], Revised transition state [18].

Some examples worthy of mention include the use of such catalysts for aza-Henry reactions as shown by Palomo *et al.* [19a] and Herrera and Bernardi [19b]. Herrera, Ricci, and others also employed these catalysts for stereoselective Strecker reactions [20], while Palomo's group demonstrated their potential for asymmetric Mannich reactions [21]. Very recently, also the first protocols for enantioselective cyclopropanation reactions proceeding via a Michael-initiated ring-closing reaction under bifunctional phase-transfer catalysis have been reported [22].

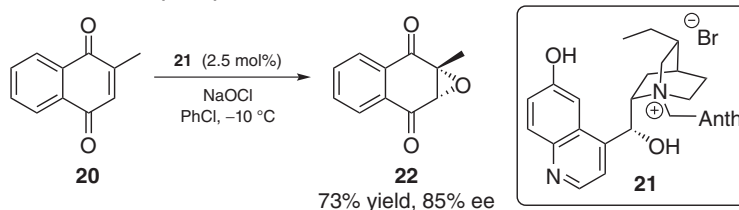
The stereoselective 1,4-addition of cyanides to Michael acceptors was a challenging task for a long time. Recently, the group of Li Deng was able to develop a highly enantioselective catalytic strategy to facilitate this important C–C bond-forming reaction (Scheme 7.3) [23a]. Very interestingly, this reaction required the use of free 6'-OH-containing catalysts with a bulky substituent in position 9. In addition, whereas the cupreidinium-derived **11** was found to be highly selective, the corresponding pseudo-enantiomeric cupreinium-based catalyst was found to give the enantiomer of **15** with significantly lower enantioselectivity only. To overcome this limitation, the introduction of an additional hydroxyl group in the former vinyl group of the cinchona skeleton was found to be beneficial (catalyst **12**). Li Deng's group also used free 6'-OH-containing

Li Deng *et al.* (2011):

Scheme 7.3 Applications of free 6'-OH-containing bifunctional cinchona ammonium salt PTCs developed by Li Deng *et al.* [23].

catalysts for the highly enantioselective Darzens reaction of α -halocarbonyl nucleophiles with carbonyl electrophiles [23b]. Noteworthy, although this is one of the most important strategies to obtain α,β -epoxy carbonyl analogs, carrying out this reaction stereoselectively is still a major challenge. Although the first reports by Arai *et al.* [24] about the use of chiral PTCs in this context date back to as early as 1998, it was only very recently that the group of Li Deng came up with the first highly enantioselective and generally applicable protocol for an asymmetric phase-transfer-catalyzed Darzens reaction (Scheme 7.3, lower part).

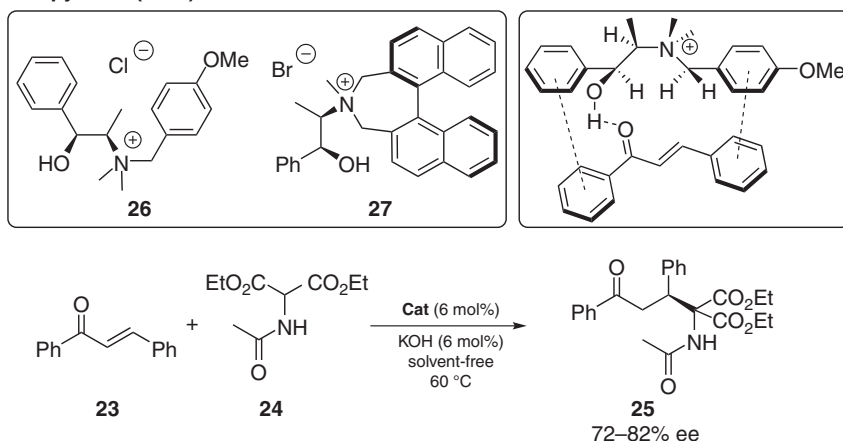
Besides cinchona-derived catalysts having either a free 9-OH or 6'-OH group, also ammonium salts possessing both free OH groups have been reported. During an exhaustive testing of different PTCs for the asymmetric epoxidation of vitamin K3 (20), the Berkessel group found catalyst **21** to be the most powerful one to obtain epoxide **22** in high enantiopurity (Scheme 7.4) [25]. Subsequent computational studies showed that the advantage of catalyst **21** was based on its ability to form an additional hydrogen bond between the 6'-OH and the oxygen of the C4-carbonyl group of the substrate, whereas ion-pair formation and hydrogen

Berkessel et al. (2007):

Scheme 7.4 Polyfunctional cinchona catalyst **21** for the asymmetric epoxidation of quinones.

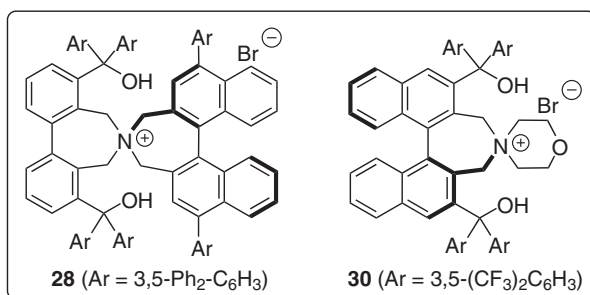
bonding between the 9-OH group and the intermediate enolate results in a structurally well-defined transition state [25].

Ephedrinium-based catalysts have been the first class of quaternary ammonium salts that have been reported to be useful in asymmetric applications [26]. Although the initial results obtained with these catalysts have been disputed [26c], this easily available chiral starting material has been reinvestigated for further applications [27] soon after the seminal reports based on cinchona alkaloids [3]. In 1989, Loupy *et al.* [27a] reported the use of ephedrinium-based catalysts for solvent-free Michael additions of malonates to chalcones, and in a more detailed follow-up study the key factors for the addition of malonate **23** to chalcone **24** have been thoroughly investigated [27b]. Among a variety of different catalysts that were tested, the bifunctional ammonium salts **26** (51% yield, 76% ee) and **27** (51% yield, 82% ee) showed the highest potential for this reaction (Scheme 7.5). It was proposed that π - π stacking between the catalyst and the electrophile, in combination with H-bonding, is a key factor to obtain high selectivities in this reaction.

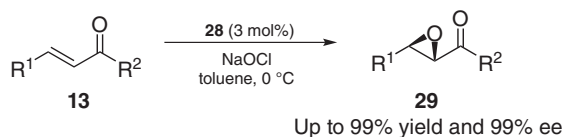
Loupy et al. (1989):

Scheme 7.5 Ephedrinium-based bifunctional catalysts for stereoselective Michael additions.

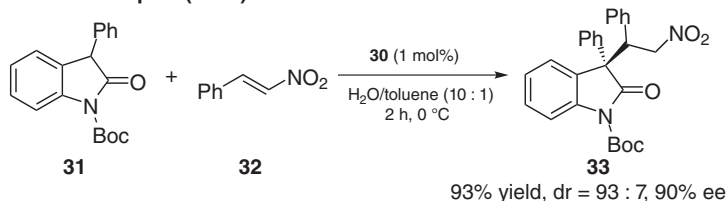
Over the years, Maruoka's binaphthyl-based ammonium salt catalysts have proven their enormous potential in numerous highly impressive applications [28]. Although initially mainly classical monofunctional quaternary ammonium salt catalysts have been employed, recent years have seen a rise in the use of free-OH-containing derivatives for a variety of extraordinarily selective transformations. Compared to cinchona alkaloids as chiral platforms for novel catalysts, Maruoka's catalyst system benefits from the modular synthesis approach, and therefore these catalysts can be systematically fine-tuned and adapted to a target reaction. In addition, both enantiomers are available in the same manner. In 2004, Maruoka *et al.* reported the ammonium salt-catalyzed epoxidation of enones **13** using NaOCl as the oxygen source (Scheme 7.6, upper reaction) [29]. In this study, the free-OH-containing spiro catalyst **28** was found to be the most powerful among the different tested ones. It turned out that the diarylmethanol group plays a fundamental role because replacing the hydroxyl groups by simple hydrogen atoms decreased the activity and enantioselectivity dramatically. Mechanistically, it was proposed that, after *in situ* ion exchange of bromide and hypochlorite, the hypochlorite ion is located in the defined chiral cavity of the catalyst, whereas the enone is bound via a hydrogen bond to the hydroxyl moiety of the catalyst, thus leading to high enantiofacial differentiation [29]. The Maruoka group



Maruoka's seminal report (2004):



First base-free report (2009):



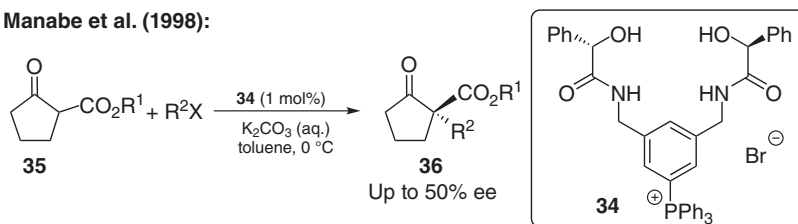
Scheme 7.6 Maruoka's bifunctional catalysts for asymmetric applications even under base-free conditions.

consequently investigated the applicability of such powerful catalysts for further, otherwise less selective, challenging transformations and discovered that they can also be successfully employed for stereoselective Michael addition reactions of malonates to chalcones [30].

In 2009, Maruoka *et al.* reported the first base-free asymmetric phase-transfer reaction in water-rich solvents using a bifunctional PTC [31]. The addition of oxindoles **31** to nitroolefines **32** in the presence of K_2CO_3 or $PhCO_2K$ as a base using catalyst **30** gave product **33** in 82% ee initially. Noteworthy, on carrying out the same reaction without any addition of base under water-rich conditions (H_2O :toluene = 10:1) even 90% ee, excellent yields, and high diastereoselectivities were obtained (Scheme 7.6, lower part). By comparing catalyst **30** with Bu_4NBr under the same reaction conditions, an important fact about these highly potential chiral ammonium salt catalysts was discovered. By using D_2O /toluene as a solvent mixture it could be shown that, in the presence of **30**, the oxindole **31** is prone to enolization, which was not the case when Bu_4NBr was used. In addition, in the absence of water no reaction took place at all, and when the hydroxyl groups were substituted by methoxy moieties the enantioselectivity diminished dramatically (6% ee) [31]. The application scope of this outstanding and mild methodology was soon after expanded toward other applications, resulting in a powerful base-free aldol reaction of nitroacetates with formaldehyde [32] and a base-free direct amination of nitroolefines [33]. Furthermore, a highly selective α -fluorination of β -keto esters under basic bifunctional phase-transfer conditions was developed [34].

Chiral phosphonium salt catalysis has always been a little brother of ammonium salt catalysis [35]. However, over the past years, significant progress has been made in this field. In 1998, Manabe introduced the multifunctional phosphonium salt catalyst **34** based on two mandelic acid-derived moieties [36]. Despite the fact that only modest enantioselectivities could be achieved in the α -alkylation of β -ketoesters **37** (Scheme 7.7), it was an early example on the potential of such catalysts, and the importance of the bifunctional nature was clearly proven by control experiments using O-methylated catalysts that gave almost racemic products only.

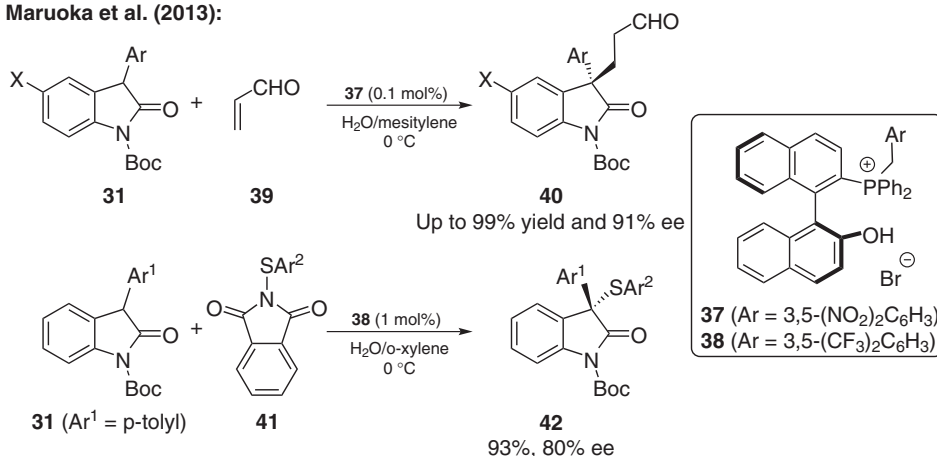
Manabe et al. (1998):



Scheme 7.7 Manabe's multifunctional phosphonium salt catalyst.

Very recently, Maruoka introduced a highly selective class of bifunctional phosphonium salt catalysts based on the privileged axially chiral binaphthyl skeleton [37]. These compounds were found to be powerful catalysts for the base-free conjugate addition of oxindoles **31** to acrolein (**39**) requiring minute amounts of the

Maruoka et al. (2013):



Scheme 7.8 Maruoka's bifunctional phosphonium salt catalysts.

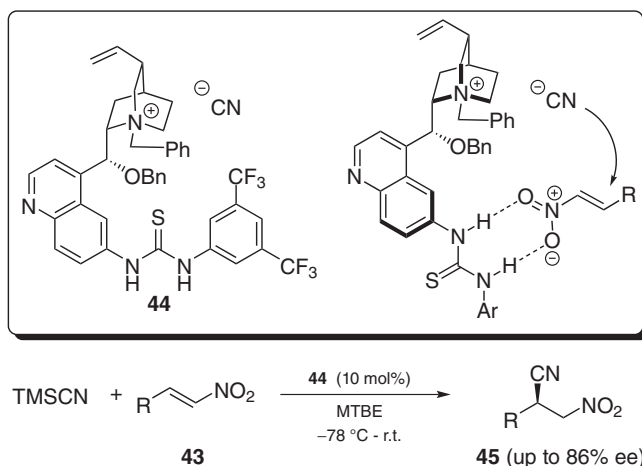
PTC only (Scheme 7.8). In addition, the asymmetric α -sulfenylation of **31** could be achieved with reasonably high enantioselectivities. Again, the beneficial effect of the free OH-group was proven by carefully chosen test reactions with, for example, O-methylated catalysts, which gave significantly reduced selectivities only.

7.2.2.2 Onium Salt Catalysts Containing Alternative H-Bonding Donors

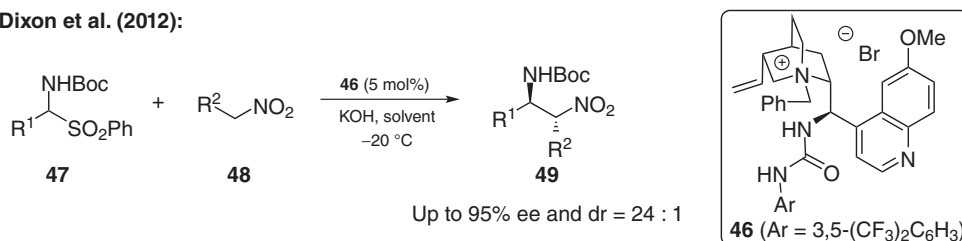
Despite the very successful use of free-OH-containing PTCs for almost three decades now, it is a surprise that so far only a few reports describing the use of other commonly used H-bonding donors in combination with chiral onium salts have been published. The successful combination of powerful H-bonding donors such as (thio-) ureas, which are known to be excellent catalysts to activate and control the reactivity of electrophiles [38], with the unique nucleophile activation potential of quaternary onium salts should result in a remarkable catalytic system. However, as illustrated in the few published reports, one of the major challenges in this approach is the synthesis of these catalysts, which explains why this strategy is still in its infancy.

In 2010, Fernandez, Lassaletta, and others reported the first synthesis and application of a thiourea-containing cinchona alkaloid-based quaternary ammonium salt catalyst [39]. During a detailed screening of different catalysts for the asymmetric cyanide addition to nitroalkenes **43**, it was found that high selectivities but low activities were obtained using bifunctional thiourea-tertiary amine catalysts and high activities but poor stereocontrol could be achieved using cinchona alkaloid-derived ammonium cyanides. Accordingly, the combination of both catalytically active motifs resulted in the unprecedented bifunctional catalyst **44**, which allowed them to obtain a broad scope of differently substituted β -cyano nitrocompounds **45** in high yields (75–98%) and with good enantioselectivities (72–86% ee) (Scheme 7.9, upper reaction) [39].

Fernandez, Lassaletta et al. (2010):



Dixon et al. (2012):



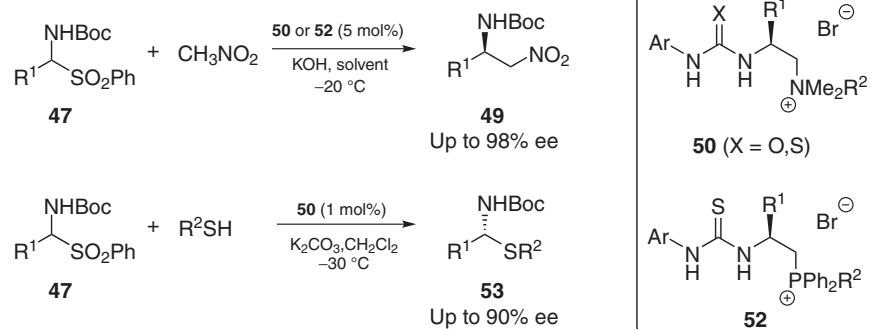
Scheme 7.9 (Thio)-urea-containing cinchona-derived ammonium salt catalysts and their application in asymmetric bifunctional catalysis.

The Dixon group recently investigated the potential of different bifunctional cinchona alkaloid-based PTCs for the enantio- and diastereoselective nitro-Mannich (aza-Henry) reaction of α -amido sulfones **47** [40]. By replacing the hydroxyl group at C9 by urea, an amide, or a sulfonamide, different catalysts were prepared and tested for the reaction of **47** with **48** (Scheme 7.9, lower reaction). Thus the urea-containing ammonium salt **46** was found to be the most powerful one, and a broad scope of differently substituted products **49** could be accessed in high yields and with good enantio- and diastereoselectivities [40]. Very recently, the Smith group has also successfully employed such urea-containing catalysts for the asymmetric synthesis of substituted indolenines via a 5-endo-dig cyclization of easily available isonitrile starting materials [41].

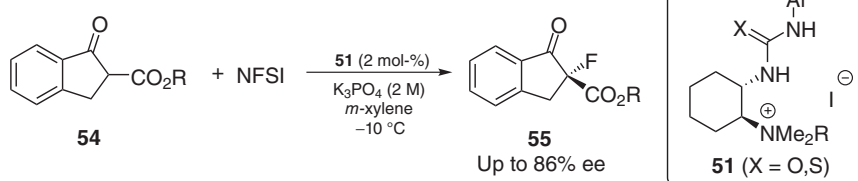
Bifunctional ammonium salt catalysts based on either α -amino acids or easily available chiral diamines (e.g., 1,2-*trans*-cyclohexanediamine) were recently introduced by Zhao's group [42] and Novacek and Waser [43]. Both catalyst classes could be synthesized in a modular approach, thus giving access to structurally diversified catalyst collections. Zhao's catalysts **50** were successfully used for highly enantioselective additions of thiols to imines and for aza-Henry reactions [42], whereas the cyclohexanediamine catalysts **51** proved to be selective

for asymmetric α -fluorination reactions (Scheme 7.10) [43]. In addition, Zhao's group also succeeded in introducing the analogous bifunctional phosphonium salt catalysts **52**, which were also found to be powerful catalysts for aza-Henry reactions [44].

Zhao et al. (2013):



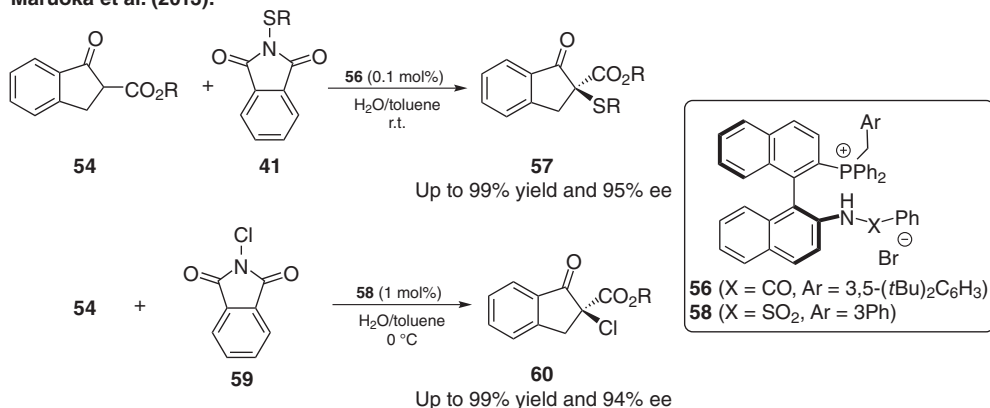
Novacek, Waser (2013):



Scheme 7.10 (Thio)-urea-containing bifunctional onium catalysts based on α -amino acids and cyclohexanediamine.

The datedness of bifunctional onium catalysis was also demonstrated by a very recent report by Maruoka's group, by introducing bifunctional phosphonium

Maruoka et al. (2013):



Scheme 7.11 Maruoka's (sulfon)-amide-containing bifunctional phosphonium salt catalysts for asymmetric α -sulfenylation and chlorination reactions.

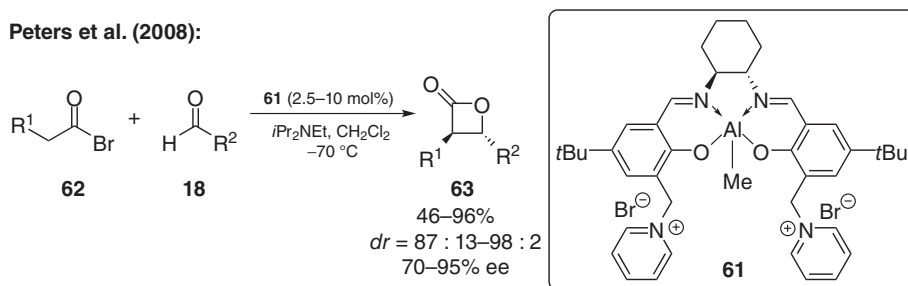
catalysts possessing a (sulfon)-amide group as the second coordination site [45]. The amide-based phosphonium salt **56** was found to be a high potential catalyst for the enantioselective α -sulfenylation of β -ketoesters **54**. Noteworthy, this catalyst gave only modest selectivities in the analogous α -chlorination reaction. However, this limitation could be overcome by using the sulfonamide-containing bifunctional phosphonium salt **58** for this reaction (Scheme 7.11) [45].

On the basis of these very recent reports by different groups, it can be said without exaggeration that the design and application of such bifunctional onium salt catalysts constitutes one of the emerging fields in asymmetric catalysis nowadays, and the introduction of novel catalyst moieties will significantly broaden the application scope of this methodology.

7.2.2.3 Lewis Acid-Containing Bifunctional Catalysts

The synergistic combination of onium salt catalysts and (transition-) metal catalysts was already discussed in a previous chapter. In 2008, Peters *et al.* presented an alternative method of dual activation by combining a Lewis acid moiety and an ammonium salt moiety in one single catalyst [46]. On targeting the syntheses of trans-configured β -lactones, the use of chiral Lewis acidic aluminum–salen complexes was investigated. Interestingly, it turned out that incorporation of two quaternary ammonium groups in positions 6 and 6' of the phenol parts resulted in catalysts that were clearly superior in terms of activity, enantioselectivity, and diastereoselectivity compared to others with alternative functional groups (e.g., tertiary amines) in these positions (Scheme 7.12). Concerning the mode of action of this catalyst system, it was proposed that the aldehyde binds with its sterically less hindered lone pair to the aluminum where the *in situ* formed E-enolate, which is generated by the addition of the catalyst counteranion to the intermediate ketene, coordinates to the pyridinium group, thus resulting in a highly ordered transition state warranting high enantio- and diastereoselectivities [46].

Peters *et al.* (2008):



Scheme 7.12 Peters' bifunctional ammonium salt/Lewis acid catalyst **61** and its use for stereoselective β -lactone formation.

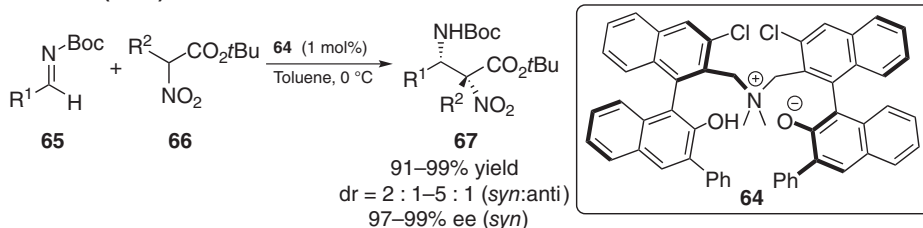
Jing *et al.* synthesized analogous Lewis acidic salen complexes containing two quaternary phosphonium groups which were found to be useful for the catalytic kinetic resolution of racemic epoxides with carbon dioxide giving chiral cyclic

carbonates in high yields and with reasonable enantioselectivities (up to 78% ee) [47, 48].

7.2.2.4 Betaines

One of the exciting novel concepts for asymmetric catalysis introduced over the past years is the use of chiral betaines. The seminal report in this field dates back to 2008 when the group of Ooi reported the use of betaine **64** as a catalyst for the highly stereoselective Mannich reaction of α -nitrocarboxylates **66** with *N*-Boc imines **65** (Scheme 7.13) [49]. The importance of the zwitterionic nature of these catalysts was clearly demonstrated because an O-protected derivative of **64** (representing a classical ion-pairing ammonium salt catalyst) gave only almost the racemic product. Later, Ooi *et al.* developed this methodology systematically by further introducing simplified catalysts and carrying out Mannich-type reactions with a variety of different starting materials [50]. The Gong group also recently contributed significantly to the field by introducing powerful bis-betaine catalysts derived from BINOL and two cinchona alkaloid moieties for the addition of azlactones to aliphatic imines [51].

Ooi *et al.* (2008):

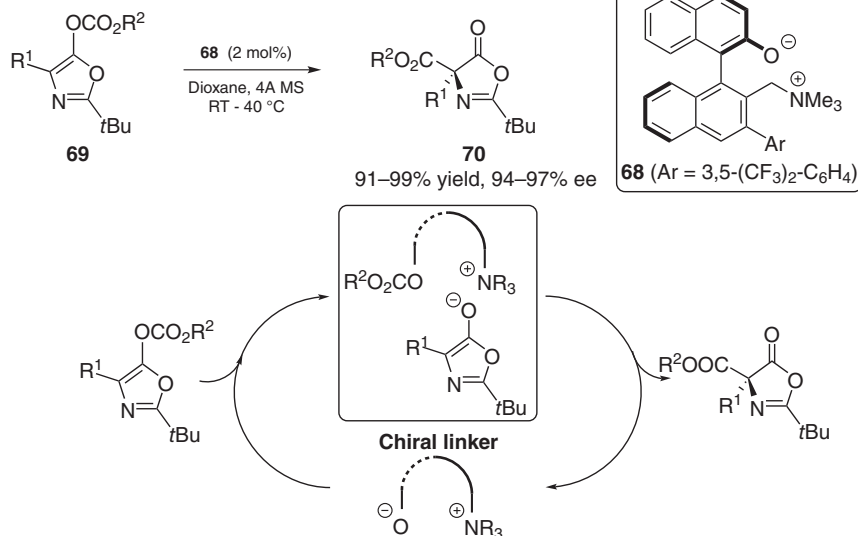


Scheme 7.13 Ooi's seminal report describing the use of chiral ammonium betaine catalysts.

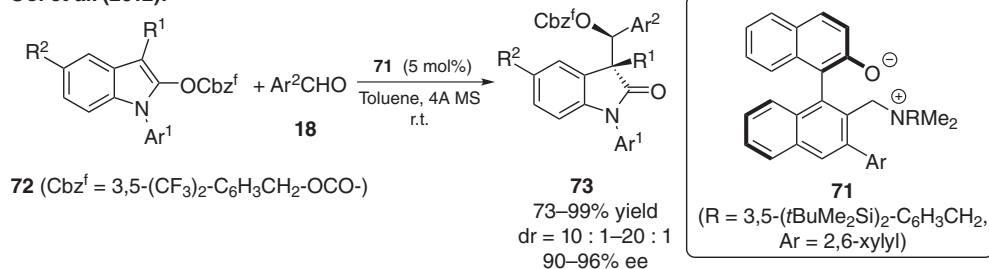
The application scope of this methodology has been further extended by successfully using the betaine **68** for a Steglich rearrangement of 5-oxazolyl carbonates **69** to furnish the chiral 4-carboxyazlactones **70** [52]. The mode of activation of the catalyst can be rationalized as shown in Scheme 7.14. The nucleophilic anionic functionality activates the enol-carbonate first, and the resulting enolate forms a sterically defined chiral ion pair with the ammonium group. An intramolecular face-selective ester transfer then results in the formation of **70** and recovery of the betaine catalyst **68**.

Very recently, the Ooi group also succeeded in using ammonium betaine catalysts for an aldol-type reaction of oxindole-derived vinylic carbonates **72** (Scheme 7.14, lower reaction) [53]. They showed that, impressively, a complete suppression of the formation of the corresponding Steglich product could be achieved (compare with the upper reaction and the mechanism shown in Scheme 7.14), and, instead, the intermolecular aldol reaction of the *in situ* formed enolate species with different carbaldehydes **18** could be achieved in high yields and with excellent (dia)stereoselectivities [53]. Finally, the unique catalytic potential of these betaines

Ooi et al. (2010):



Ooi et al. (2012):



Scheme 7.14 Chiral ammonium betaine-catalyzed Steglich rearrangement and aldol-type reaction.

was also very recently demonstrated in a highly stereoselective aza-Henry reaction employing nitroolefins as the nucleophiles [54]. On the basis of these very contemporary reports, it is without doubt that this exciting catalysis concept will allow the introduction of further highly selective methods in the near future, thus providing novel tools to facilitate reactions that are not possible with other classical strategies.

7.2.3

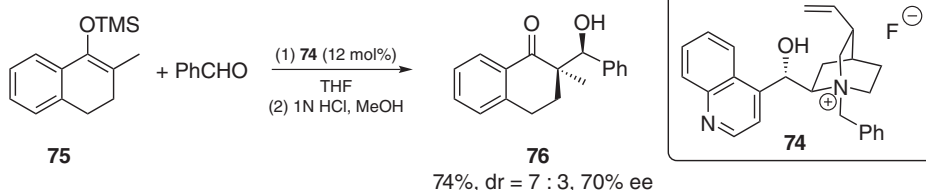
Chiral Cation-Based Catalysts Containing a Catalytically Relevant Achiral Counteranion

It was shown in the previous section that the combination of an ion-pairing moiety with a nucleophilic phenoxide in the form of a chiral betaine can result in a very versatile catalytic system. However, long before the initial reports on the catalytic

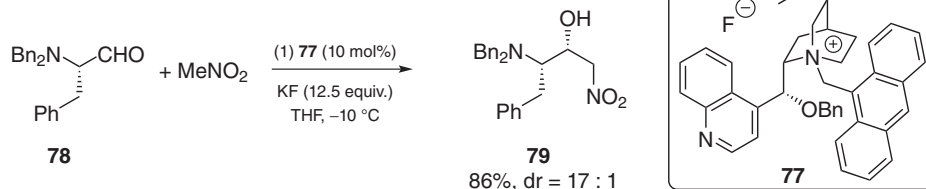
potential of chiral betaines, the use of ammonium salts containing a catalytically active (nucleophilic) achiral counteranion, such as a phenoxide or a fluoride, had been thoroughly investigated by different groups [14].

The synthetic utility of ammonium fluorides takes advantage of two characteristic key features of the anion: (i) the nucleophilic affinity of the fluoride to activate organosilicon compounds, and (ii) its basicity in aprotic solvents. The use of chiral ammonium fluorides for asymmetric transformations dates back to Wynberg's seminal reports in the 1970s describing the slightly enantioselective chiral ammonium fluoride-catalyzed Michael addition of nitromethane to chalcone [3b]. In 1993, Shioiri *et al.* reported the use of the quaternary cinchonium fluoride **74** for the asymmetric aldol reaction of enol silyl ether **75** with benzaldehyde (Scheme 7.15, upper reaction) [55]. Very shortly afterward, the moderately enantioselective trifluoromethylation of carbonyl compounds with trifluoromethyltrimethylsilane in the presence of chiral ammonium fluorides was reported [56], and, in 1999, Corey and Zhang [57] described the highly diastereoselective nitroaldol reaction of aldehyde **78** with nitromethane in the presence of catalyst **77** as a key step

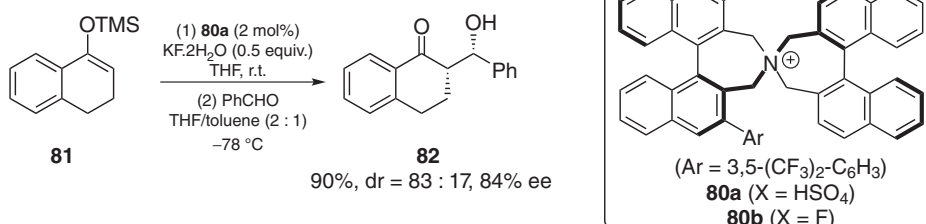
Shioiri et al. (1993):



Corey et al. (1999):



Maruoka et al. (2001):

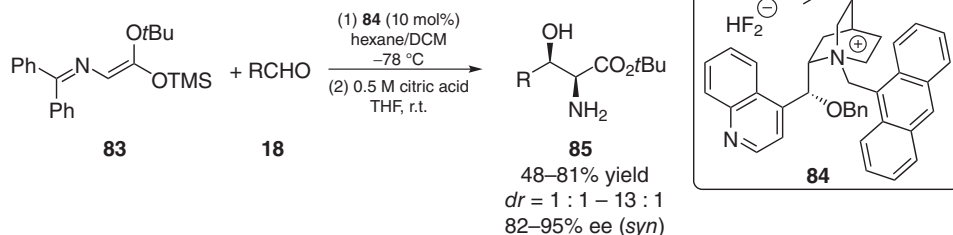


Scheme 7.15 Breakthrough reports describing the use of chiral ammonium fluorides as catalysts.

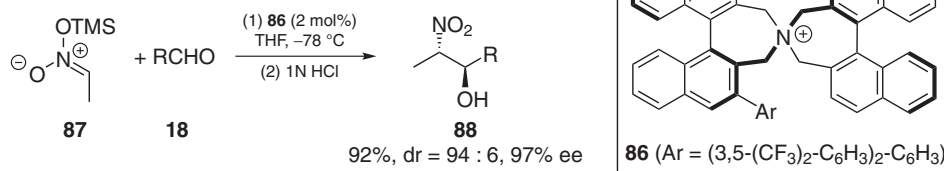
in the synthesis of the HIV protease inhibitor Amprenavir. Noteworthy, in the presence of Bu_4NF no diastereoselectivity could be obtained. The *in situ* generation of the catalytically active ammonium fluoride from suitable precursor salts was carefully investigated by Maruoka's group, and it was found that ammonium hydrogen sulfates such as **80a** can be successfully employed to obtain the corresponding ammonium fluoride **80b** on treatment with KF prior to its use as a catalyst. This operationally simple methodology allowed them to carry out the stereoselective Mukaiyama-type aldol reaction of **81** and benzaldehyde (Scheme 7.15, lower reaction) [58].

The use of ammonium fluorides sometimes faces limitations because of their hygroscopic nature and also the fact that these compounds may undergo self-decomposition reactions (e.g., Hofmann elimination) under strictly anhydrous conditions [14]. The use of more stable and easy-to-handle chiral ammonium bifluorides represents a suitable alternative to overcome these limitations. This was impressively demonstrated by Corey's group by developing a highly stereoselective Mukaiyama-type aldol reaction of the silyl enolate **83** with different carbaldehydes **18** (Scheme 7.16, upper reaction) [59]. The Maruoka group used bifluorides of their trademark catalysts to facilitate the nitroaldol reaction of silyl nitronates **87** with excellent diastereo- and enantioselectivities [60], and a similar strategy was also successfully employed for the addition of **87** to different Michael acceptors to furnish the corresponding 1,4-adducts with high selectivities [61].

Corey et al. (1999):



Maruoka et al. (2003):

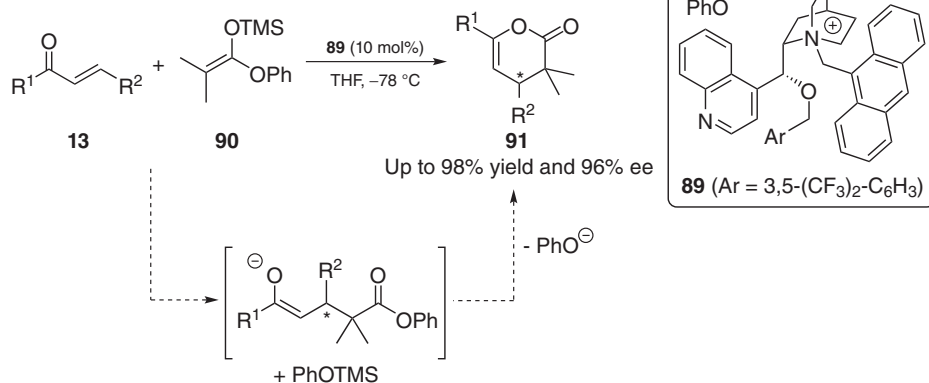


Scheme 7.16 Use of chiral ammonium bifluorides as asymmetric catalysts.

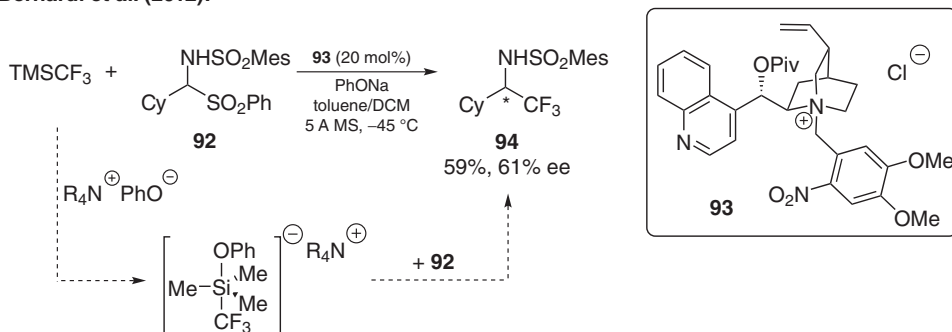
The successful application of chiral ammonium phenoxides as catalysts for the asymmetric synthesis of 3,4-dihydropyranone derivatives was reported by

Mukaiyama *et al.* in 2006 [62]. Thus, the addition of silyl enolate **90** to enones **13** in the presence of the ammonium phenoxide **89** directly furnished the target products **91** in good yields and with high selectivities. The phenoxide counteranion is supposed to initiate the catalytic cycle via addition to the silicon center, and because of the proper choice of the ester group of starting material **90**, it will be regenerated during the cyclization step again. Thus no stoichiometric amount of phenoxide is required (Scheme 7.17, upper reaction). Recently, the Bernardi group [63] reported a phase-transfer-catalyzed trifluoromethylation of imines employing TMSCF_3 as the nucleophile. Activation of this nucleophile was carried out using a stoichiometric amount of phenoxide as an achiral Lewis base in the presence of catalyst **93**. The catalytic mode of this procedure is believed to proceed via an anionic pentacoordinated silicon species with the ammonium ion as the chiral counteranion (Scheme 7.17, lower part). Noteworthy, the reaction proceeded in high yields using achiral ammonium salts, but only moderate yields

Mukaiyama et al. (2006):



Bernardi et al. (2012):



Scheme 7.17 Use of chiral ammonium salts in combination with phenoxide as a nucleophilic achiral counteranion.

and moderate enantioselectivities were obtained using chiral PTCs. Nevertheless, this report clearly illustrated the high potential of chiral ammonium salts with a nucleophilic counteranion that can participate in the catalytic cycle to activate organosilicon nucleophiles, and it might be only a matter of time before further applications of this promising concept are introduced.

7.3

Chiral Anion Based Catalysis

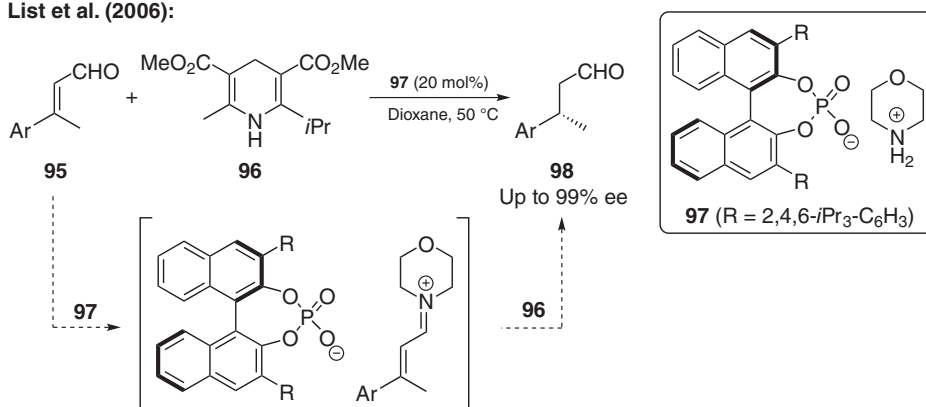
The difficulties associated with defining and classifying reactions that are catalyzed by chiral anion-based catalysts [7, 8] and with identifying the exact activation mechanism have already been described in the introductory part of this chapter, and once again the interested reader is referred to a recent very detailed discussion of this matter by Toste's group [8]. This section was written with the intention to provide a short and illustrative introduction to some of the most impressive recent cooperative catalysis strategies employing chiral anions. The examples discussed herein are supposed to be complementary to other, sometimes closely related, strategies described in this book (such as the use of chiral Brønsted acids), although some overlap may not be avoided.

7.3.1

Cooperative Organocatalytic Approaches Involving a Chiral Anion in Ion-Pairing Catalysts

One powerful synergistic strategy involves the use of achiral organocatalysts such as secondary amines in combination with asymmetric anions that form a chiral ion pair with an intermediate iminium species [64]. In 2006, List *et al.* combined the use of an achiral secondary amine such as morpholine and a chiral phosphoric acid to facilitate the highly enantioselective conjugate reduction of enals **95**, using Hantzsch ester **96** as a hydride source [64]. By using the optimized catalyst **97**, the reaction is supposed to proceed via iminium formation between **95** and morpholine first, followed by ion pairing with the BINOL-derived phosphate, thus allowing a highly effective face differentiation for the conjugate addition step (Scheme 7.18). Because of the full substitution of the iminium intermediate, this is one of those examples in which a H-bonding activation by the chiral phosphoric acid can be definitely excluded. On the basis of this groundbreaking result, the concept of asymmetric counteranion-directed catalysis (ACDC) has found widespread applications in asymmetric catalysis (either metal- or organocatalysis), and the fancy abbreviation ACDC became a catchword for a variety of mechanistically different, highly innovative stereoselective reactions [65]. For example (and fully within the context of this overview on cooperative catalysis), the List group extended this concept to the asymmetric epoxidation of enals by using the synergistic combination of an achiral *sec*-amine and a chiral phosphoric acid [66].

List et al. (2006):



Scheme 7.18 List's seminal report describing the synergistic combination of an achiral sec-amine and a chiral phosphoric acid for ion-pairing organocatalysis.

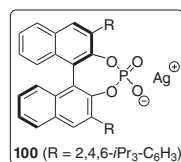
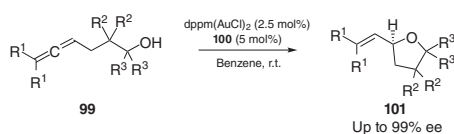
The use of chiral anions in asymmetric organocatalysis has recently been significantly extended by Toste's group, which succeeded in developing novel protocols for asymmetric anion phase-transfer catalysis by using BINOL-derived phosphates to facilitate highly enantioselective fluorocyclization [67] and α -fluorination reactions [68]. Although mechanistically not explicitly within the scope of this chapter, these are worth-mentioning examples because here the anionic PTC is supposed to form a soluble chiral ion pair with the achiral (and otherwise only sparingly soluble) fluorinating agent (Selectfluor), thus allowing for high enantioselectivities in the target reactions. Interestingly, it was proposed that here the phosphate group acts as a bifunctional motif, which not only forms the ion pair with Selectfluor but also coordinates the starting material via H-bonding, thus resulting in a high-order transition state [68].

7.3.2

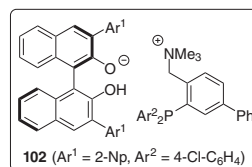
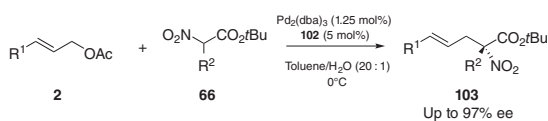
Chiral Anion Catalysis in Combination with Metal Catalysis

The use of chiral anions in combination with achiral metal catalysts is a highly investigated field, and a variety of mechanistically different strategies have been investigated in the past. As early as 1990, Alper and Hamel [69] reported the enantioselective hydrocarboxylation of styrenes using a Pd/Cu/chiral phosphoric acid catalyst system. Although no mechanistic details have been disclosed (the reaction proceeds under highly acidic conditions, and thus phosphate formation and ion pairing seems to be unlikely), this was one of the groundbreaking reports in the field of cooperative catalysis involving chiral phosphoric acids. Subsequent reports describing the combination of chiral phosphoric acids with metal catalysts proposed that the chiral phosphate acts as a metal ligand/counterion mainly [8]. For example, the Toste group developed a highly enantioselective gold-catalyzed hydroalkoxylation of allenes **99** in 2007 [70]. Here, the formation of a cationic

Toste et al. (2007):



Ooi et al. (2012):

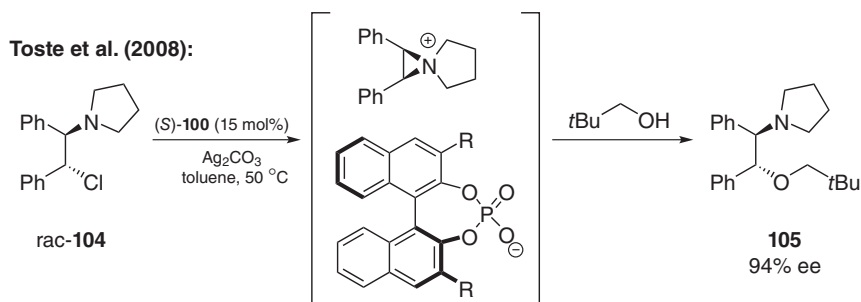


Scheme 7.19 Exemplified milestone reports in the field of asymmetric counteranion directed transition-metal catalysis.

gold species was crucial, and it was found that the use of chiral counteranions such as BINOL-based phosphates was important to obtain high enantioselectivities (Scheme 7.19, upper reaction). The beneficial use of nonpolar solvents such as benzene indicated that ion pairing plays a pivotal role to obtain high selectivities. The use of chiral anions in gold catalysis was later on extended to other highly selective transformations [71]. In addition, chiral phosphates also have been successfully used as ligands or counteranions for other achiral metal catalysts, as exemplified by the successful combination of BINOL-based phosphates and achiral Mn(III)–salen cations for asymmetric epoxidation reactions [72], their use in palladium-catalyzed Overman rearrangement reactions [73], or for the stereoselective ruthenium-catalyzed crotylation of primary alcohols [74].

Very recently, Ooi *et al.* described an exciting new strategy to achieve high enantioselectivities in Pd-catalyzed allylic alkylation reactions (Scheme 7.19, lower reaction) [75]. This concept relies on a simple achiral cationic ammonium-phosphine ligand, which is ion-paired with an easily available and straightforwardly modified chiral anion. This gives access to a very modular and flexible approach to obtain ion-paired ligands for achiral palladium sources to obtain high selectivities under operationally simple biphasic conditions.

In 2008, the Toste group published a mechanistically different approach using chiral silver phosphates such as compound **100** to catalyze the highly stereoselective ring opening of *in situ* formed meso-aziridinium or episulfonium compounds [76]. This concept resembles the use of chiral ammonium fluorides or phenoxides discussed above (Section 7.2.3), as both the achiral cation and the chiral anion play an important mechanistic role. The silver ion first facilitates aziridinium formation by abstraction of the chloride of **104**. The aziridinium intermediate then forms a chiral ion pair with the BINOL-phosphate, which then undergoes highly enantioselective ring-opening reactions with different alcohols (Scheme 7.20). The use of a stoichiometric amount of an insoluble silver source (Ag_2CO_3) allows the recovery of catalyst **100** and, because of the insolubility of Ag_2CO_3 in toluene, a racemic background reaction can be efficiently suppressed.

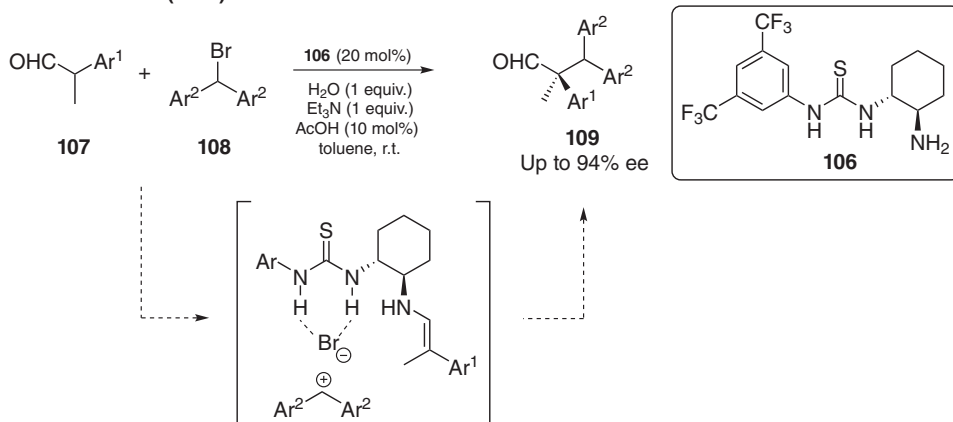
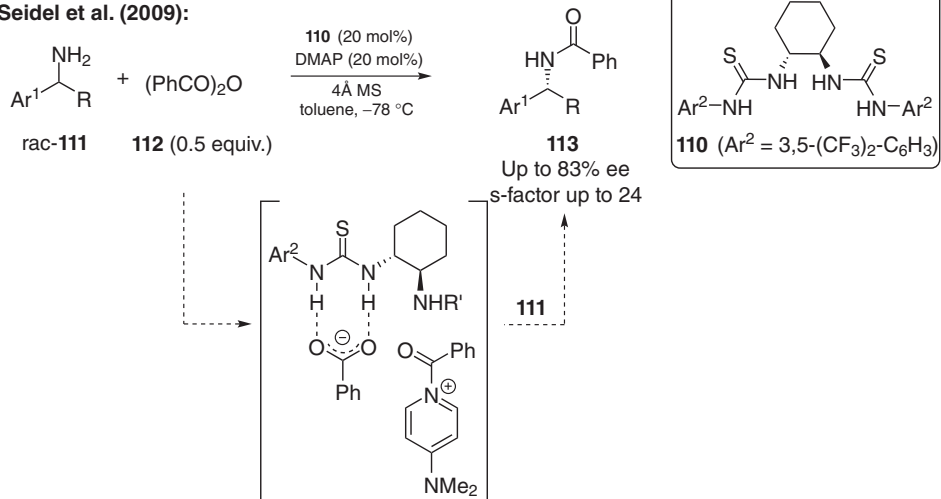


Scheme 7.20 Chiral silver phosphate-catalyzed aziridinium opening reaction.

7.3.3

Cooperative Use of H-Bonding Catalysts for Anion Binding and Complementary Activation Modes

As initially mentioned, it is not the intention of this chapter to provide a systematic discussion on the use of chiral anion-binding H-bonding catalysts in ion-pairing catalysis. However, there are some mechanistically rather unique cooperative approaches that are briefly discussed here, as these examples highlight the catalytic potential of this unique methodology very illustratively. H-bonding donors such as (thio)-ureas can serve as highly versatile anion recognition sites [77]. The Jacobsen group used H-bonding catalysts to facilitate different

Jacobsen et al. (2010):**Seidel et al. (2009):**

Scheme 7.21 Use of anion-binding thiourea catalysts in cooperative ion-pairing catalysis.

enantioselective addition reactions to *N*-acyliminium intermediates [78] and found that Pictet-Spengler type reactions of hydroxylactams could be carried out using TMSCl in the presence of a chiral thiourea catalyst. Different mechanistic scenarios can be rationalized, and it was proposed that the catalyst first promotes chloride abstraction and subsequently binds this anion, thus resulting in a chiral anionic species, which then forms an ion pair with the intermediate iminium species [78b]. On the basis of this exciting and mechanistically unique result, the Jacobsen group then developed this methodology further and employed the bifunctional thiourea-containing catalyst **106** for the stereoselective S_N1 -type α -alkylation of aldehydes **107** with stabilized carbocations generated from bromides **108** (Scheme 7.21, upper reaction) [79]. The reaction proceeded exceptionally well, giving the alkylated products **109** with high yields and excellent enantioselectivities. Mechanistic studies suggested bromide abstraction from **108** facilitated by the thiourea moiety and ion pairing between the H-bonded anion and the resulting carbocation accompanied by enamine activation of the aldehyde **107** by the primary amine functionality of the catalyst, thus resulting in a remarkable asymmetric bifunctional ion-pairing/enamine-activating catalyst system.

In 2009, the Seidel group made use of the cooperative combination of anion-binding thiourea catalysts such as compound **110** in combination with the achiral nucleophilic catalyst DMAP to achieve the kinetic resolution of primary amines **111** (Scheme 7.21, lower reaction) [80]. The postulated pathway for this reaction includes DMAP acylation on reaction with **112** and the liberation of benzoate, which is then bound by the thiourea moiety. This anionic species forms a chiral ion pair with the *N*-acylated DMAP, thus giving a chiral *N*-acylating agent for the kinetic resolution of amines **111**. The concept of this powerful methodology was also expanded to the resolution of propargylic amines [81] and the desymmetrization of *meso*-diamines [82].

7.4

Synopsis

Cooperative asymmetric ion-pairing catalysis has proven its high potential in numerous case studies over the past years. Traditionally, this field has been dominated by chiral ammonium salt catalysts, but, as illustrated in the first section of this chapter, chiral phosphonium salts have become more and more promising and powerful recently. Among the different strategies used in the field of cooperative asymmetric cation catalysis, the use of chiral bifunctional catalysts has been the most thoroughly investigated one so far, whereas the cooperative combination of cationic ion-pairing catalysts with (transition)-metal catalysts has not that routinely been used so far. However, keeping in mind the recent advances in both fields, it seems reasonable that further breakthroughs may be reported in the future. The field of asymmetric anion catalysis is closely related (and sometimes also mixed up) with the field of asymmetric Brønsted acid catalysis, and

the concept of asymmetric anion phase-transfer catalysis has only recently found more widespread use and attention in our community. Despite the definition and classification difficulties, the synergistic use of chiral anionic ion-pairing agents either in combination with organocatalysts or with transition-metal catalysts allowed the development of a variety of highly selective and synthetically useful transformations in the past. Therefore, there is no doubt that this field will attract similar attention as the field of cooperative asymmetric cation catalysis in the near future. In addition, it is fair to say that both methodologies have so far not shown their full catalytic potential yet, and therefore hold much promise for the future.

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8

Bimetallic Catalysis: Cooperation of Carbophilic Metal Centers

Marcel Weiss and René Peters

8.1

Introduction

The cooperation of two metal centers is well known for a large number of dinuclear metalloenzymes such as DNA polymerases, phosphatases, and ureases [1]. Because of the enormous efficiency of these bimetallic catalysts in Nature, the concept of synergistic cooperation of two metal centers has also been employed as an exciting design principle for artificial catalysts, mimicking the activation principle of dinuclear metalloenzymes as archetypes [2]. A growing number of research groups is nowadays developing synthetic bi- or polymetallic catalyst systems to use this synergy between two or more metal centers as a proficient way of catalyzing reactions with high activity and selectivity. This emerging field is growing very rapidly and several review articles on this topic have thus been published since 2012 [2e,f,g]. In several chapters of this book the cooperation of two metal centers plays a vital role. In particular, Chapter 1 by Shibasaki and Kumagai reports on the efficient interplay of two or more metal centers in bi- or polymetallic catalyst systems for a huge number of different catalytic asymmetric reaction types. Moreover, in Chapter 13 Rieger *et al.* demonstrate the value of bimetallic catalysts/catalysis for polymerization reactions.

In this chapter we have focused on developments, in which at least one carbophilic metal center of a bimetallic catalyst system is used for cooperative bimetallic effects. This kind of chemistry is highlighted in a separate chapter because of the constantly expanding impact of carbophilic metals in homogeneous catalysis, which might be explained by the fact that carbophilic Lewis acids allow for a large number of unique and synthetically attractive step- and atom-economic reactions that are capable of generating considerable structural complexity. At the same time a huge number of functional groups is tolerated as a result of the low oxophilicity of these metal centers [3]. For the same reason these catalysts frequently offer the advantage of high robustness against air and moisture and are thus easy to handle.

The present chapter focuses on applications in which the carbophilicity of one or two metal centers like Pd(II) or Au(I) is essential for the observed reactivity of

a bimetallic catalyst system. These are mainly reactions, where π -coordination of a carbophilic metal center serves to activate a C,C double or triple bond for the attack by a nucleophile, or where the metal center undergoes a M–C bond formation during the course of a catalytic cycle. Moreover, this chapter is largely focused on applications, for which it is known, likely or at least feasible that both metal centers of a bimetallic catalyst system cooperate by simultaneously activating the reacting substrate(s) in a C–C or C–X bond-forming elementary step. This implicates that reactions running via sequential mechanisms, for which two or more metal centers might be necessary, but do not cooperate in the same bond-forming elementary step, are only sporadically mentioned. For the same reason we also did not include a large number of applications, in which one metal center executes a structural or allosteric effect, but is not a catalytically active center. This latter type of reactions has very recently been summarized in an excellent review article by Kumagai and Shibasaki [4], to which the reader is referred.

Bimetallic catalysts can in general be classified as homo- and heterodinuclear complexes. This classification has also been chosen to subdivide the present chapter. In the first part homobimetallic complexes are discussed. In general, the synthesis of this complex type is shorter and easier as compared to related heterodinuclear complexes, because both metals might be introduced in the same step by a double metallation/coordination. Examples for homobimetallic catalysis are also described, in which two separate monometallic catalyst molecules cooperate intermolecularly.

In the second part of this chapter the use of heterobimetallic complexes is reviewed. They frequently require a larger synthetic effort for their preparation, because either two different metallation/coordination steps are necessary or two separate (monometallic) catalyst systems are required. Despite this inherent disadvantage, heterobimetallic complexes (and combinations of two different complexes) obviously offer a large potential as dual activation catalysts, as they benefit from an enhanced variability for the optimization of the cooperative effects of both metals. Complementary properties of different Lewis acid centers can thus be employed for the simultaneous activation of the reacting substrates by recognizing different functional groups. In other words, the most advantageous metals for the activation of each reactant might be selected.

8.2

Homobimetallic Catalysts

8.2.1

Cooperation of Two Palladium Centers

Most examples for the cooperation of two soft metal centers exist for bis-Pd-catalysts. This section describes first non-enantioselective, then asymmetric reaction types.

8.2.1.1 Reactions Providing Achiral or Racemic Products

As early as 1988 Robson and McKenzie showed that the hydrolysis of acetonitrile to acetamide is efficiently catalyzed by dinuclear Pd(II) complexes [5]. They proposed a mechanism in which both acetonitrile and the hydroxide nucleophile simultaneously coordinate to the different Pd centers of the homobimetallic complex, bringing both activated reactants in close spatial proximity (Figure 8.1). This mode of activation is strongly reminiscent of that of ureases (Figure 8.1, bottom), in which two Ni(II) centers cooperate. In the latter case one Ni center activates the carbonyl group of urea as an electrophile, whereas the other Ni center serves to generate the hydroxide nucleophile, which then attacks the activated electrophile intramolecularly [1].

Mechanistic studies by Robson and McKenzie support a bimetallic pathway for the bis-Pd(II)-catalysts, in which both metal centers work in concert [5]. Previous to their study the hydrolysis of acetonitrile had also been investigated in strongly basic solutions using mononuclear hydroxoplatinum(II) complexes as catalysts [6]. In this case the activated nitrile moiety is attacked by free OH^- . In contrast, the bimetallic Pd catalysts **1** and **2** are inhibited by hydroxide, and mild acidic conditions were found to be beneficial by facilitating the protonolysis step and thus the product release from the catalyst. On the contrary, strongly acidic conditions would protonate a Pd-OH species thus retarding the nucleophilic attack of the nitrile moiety. These observations seem to exclude a mechanism in which free OH^- attacks a nitrile coordinated to one Pd atom with no participation by its neighboring metal.

DuBois *et al.* [7] initially investigated monometallic palladium complexes as catalysts for the electrochemical reduction of CO_2 to CO. As it was known that cooperative effects between two metals may improve CO_2 binding [8], the authors synthesized the bimetallic Pd complex **3** to investigate its reactivity profile in the reduction of CO_2 (Figure 8.2) [9]. Indeed the bis-Pd(II) complex is a more efficient catalyst for this reaction.

During their investigations, which were published in 1995, the authors made several observations, which suggest a cooperative interaction between both metal centers. First of all, at low acid concentrations the reaction rate is first-order dependent on the acid concentration, while for the corresponding mononuclear palladium complexes a second-order dependence has been observed. This suggests a cooperative binding mechanism for the bimetallic catalyst as shown in Figure 8.2. At higher acid concentrations the rate-determining step is first-order in both CO_2 and catalyst concentration. This implies that in the rate-determining step one CO_2 molecule and one catalyst molecule are involved **4** (Figure 8.2). Finally, when compared to results of related monometallic complexes the catalytic rate of CO_2 reduction was found to be at least 3 orders of magnitude higher using the bimetallic **3**.

Following work by Sanford [10] and Yu [11], Ritter *et al.* investigated the occurrence of bimetallic Pd(III) intermediates as a mechanistic alternative to catalytic Pd(II)/Pd(IV) redox cycles in the acetoxylation of 2-phenylpyridine **5** (Figure 8.3) [12].

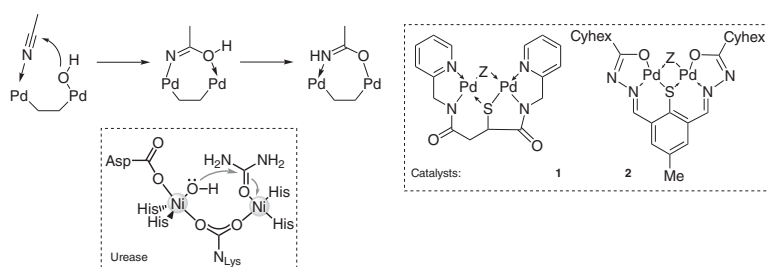


Figure 8.1 Proposed mechanism for the hydrolysis of acetonitrile catalyzed by bimetallic Pd(II) complexes (1 and 2) and comparison to the mode of activation of ureases.

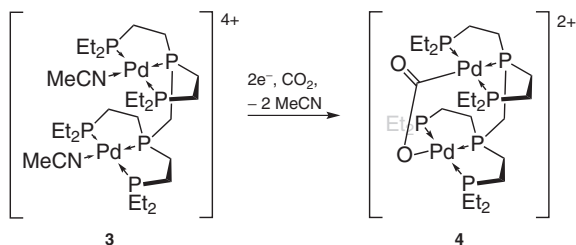


Figure 8.2 Electrochemical reduction of CO_2 to CO catalyzed by **3**.

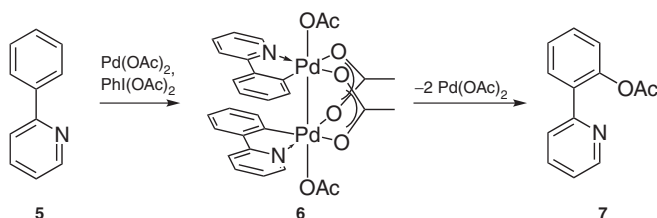


Figure 8.3 Acetoxylation of **5** via bis-Pd(III) complex **6**.

In initial stoichiometric experiments, cyclopalladation of 2-phenylpyridine **5** followed by oxidation with $\text{PhI}(\text{OAc})_2$ (performed at low temperature) produced the thermally sensitive Pd(III) complex **6** in good yields. In a catalytic cycle though it was not possible to observe this species, as it does not represent the resting state of the acetoxylation reaction. To get more mechanistic insight the authors compared the initial rates for the formation of **7** employing either $\text{Pd}(\text{OAc})_2$, a discrete monometallic Pd(IV) complex or Pd(III) species **6**. This revealed that only **6** is kinetically competent in this reaction, and it was concluded that the reaction most likely proceeds via a Pd(II)/Pd(III) cycle including a rapid bimetallic reductive elimination (Figure 8.4).

A subsequent goal was to elucidate, if the dinuclear core stays intact during a reductive elimination step and if the two Pd atoms do cooperate in that event. This was investigated in the chlorination of benzo[h]quinoline (Figure 8.5) [13].

A series of kinetic measurements determined the disappearance of complex **8** as well as the formation of reductive elimination product **9** to be of first-order dependence on **8**. Determination of the activation parameters by computational studies indicated that a bimetallic reductive elimination from **8** is energetically favorable. These results combined with crossover experiments support a scenario in which the dinuclear core stays intact during the reductive elimination step and suggest that a redox synergy between both Pd centers facilitates reductive elimination reactions [14].¹⁾

1) Ritter *et al.* were subsequently able to apply the principle of bimetallic Pd(III) catalysis to other reactions as well (see Ref. [13b]) like the α -hydroxylation of carbonyl compounds with molecular oxygen as oxidant.

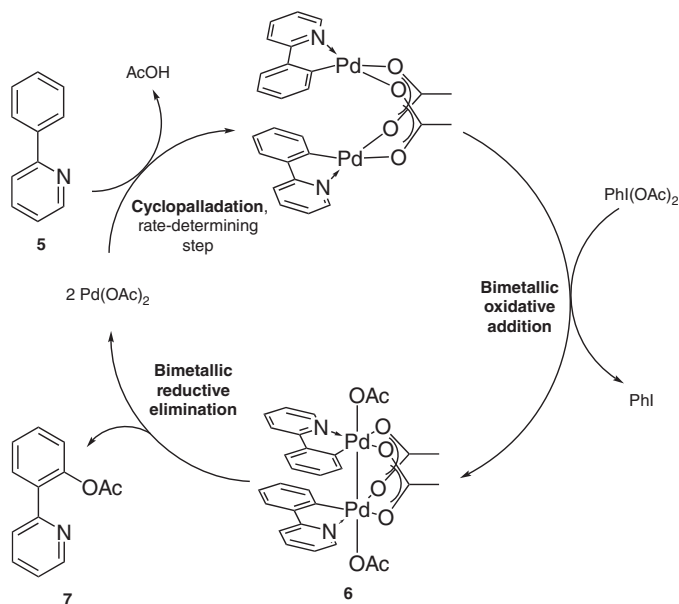


Figure 8.4 Simplified proposed catalytic cycle for the palladium catalyzed acetoxylation of **5**.

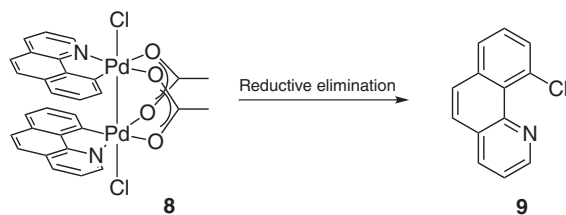


Figure 8.5 Reductive elimination from **8**.

Schoenebeck *et al.* further investigated the reductive elimination from dinuclear Pd(III) complexes like **6** and **8**. The chemoselectivity toward Ar–Cl products for the reductive elimination from the corresponding mixed Cl/OAc complexes was of particular interest to them [15]. A combination of experimental and computational studies demonstrated that the selectivity for Ar–Cl products under stoichiometric reaction conditions was consistent with an initial scrambling of mixed Cl/OAc Pd(III) dimers to the corresponding homodimers **6** and **8**. While the dichlorinated complex **8** can readily eliminate the product [13], the diacetate exhibited only minor reactivity under the investigated reaction conditions. Thus only trace amounts of Ar–OAc products are formed, explaining the high selectivity for Ar–Cl.

In 2010, the Bera group demonstrated that C–C cross-coupling reactions can also be catalyzed cooperatively by bimetallic systems [16]. They designed a dicationic dipalladium(I) complex **9** bearing two bridging *N,N,O*-ligands and

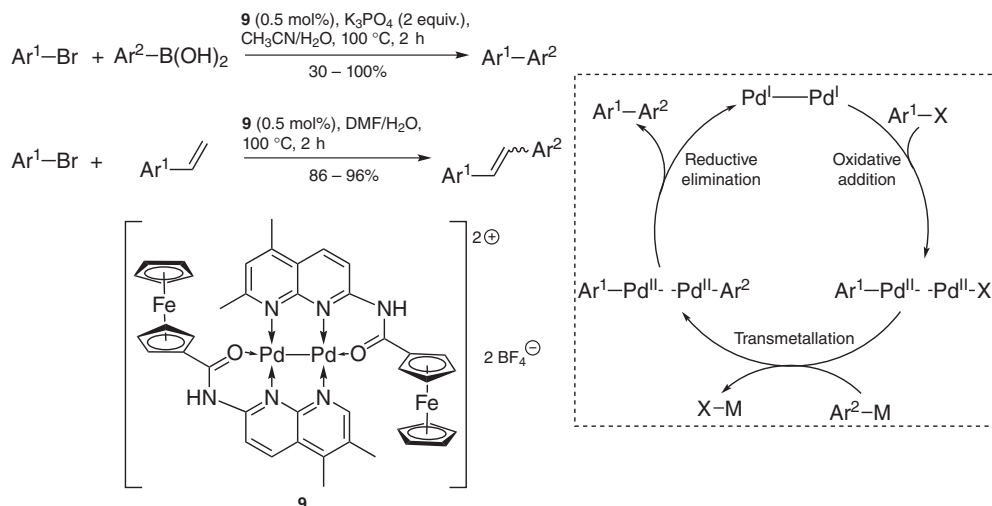


Figure 8.6 Suzuki and Heck cross-coupling reactions catalyzed by homobimetallic complex **9**.

showed its catalytic value in phosphine-free Suzuki and Heck cross-coupling reactions (Figure 8.6).

The authors proposed a bimetallic mechanism for both reactions. The initial oxidative addition occurs across the Pd–Pd single bond (Figure 8.6). Transmetalation with the arylboronic acid forms a bis-aryl-bis-Pd(II) complex, which regenerates the active catalyst by reductive elimination of the product. Further experiments including the successful use of aryl chlorides in Suzuki cross-couplings demonstrated a superior activity compared to monometallic Pd(II) complexes.

Schoenebeck *et al.* further investigated the role of dinuclear Pd(I)-complexes in cross-couplings [17]. In their case the Pd(I)-centers were bridged by halide ligands. Their results also suggested catalytic cycles involving bimetallic Pd(I) intermediates.

8.2.1.2 Enantioselective Reactions

In 2002, Henry *et al.* reported that homochiral bis-Pd(II)-catalysts are capable of efficiently catalyzing an asymmetric oxidation of terminal olefins [18]. Utilizing several chiral ligand backbones for a bis-Pd catalyst system **10** they could generate chlorohydrins in high yields and with enantiomeric excesses of up to 94% (Figure 8.7). With the exception of 1,2-diaminocyclohexane (DACH), all of the chiral bridging ligands depicted in Figure 8.7 allowed for good to high yields, and with the exception of 2,2'-methylenebis[4-benzyl-2-oxazoline] (BZOX) all ligands tested also allowed for good enantioselectivity. For high activity and enantioselectivity, the distance between both donor atoms of the ligands needed to be large enough to permit bridging between both Pd(II) atoms. Otherwise, one Pd(II) center is bound to both donor atoms of the bidentate ligand and is coordinatively

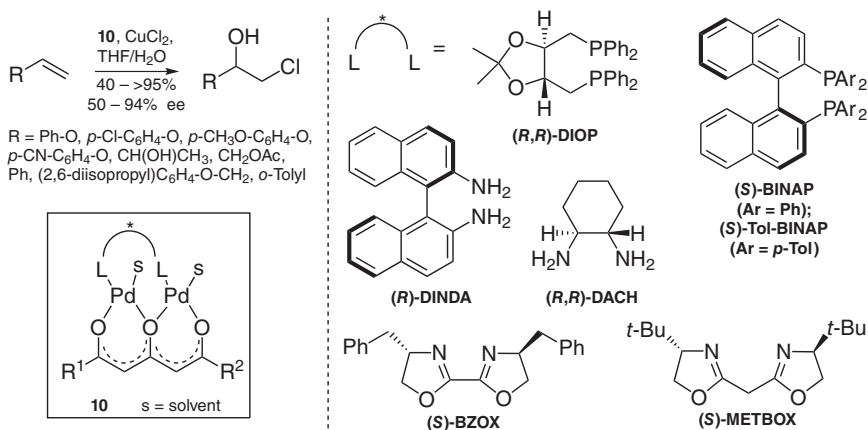


Figure 8.7 Asymmetric chlorohydrin synthesis by Henry *et al.*: substrate scope and ligands investigated.

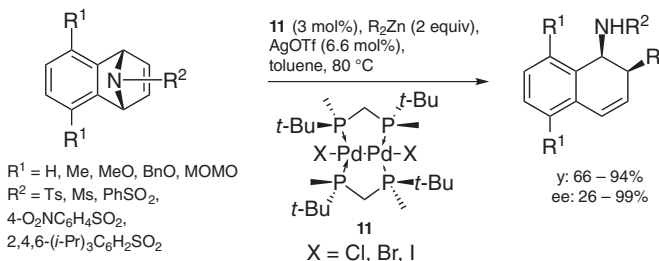


Figure 8.8 Ring-opening reaction of azabenzonorbornadiene derivatives catalyzed by **11**.

saturated and thus unreactive, while the second Pd(II) center is reactive but does not carry a chiral ligand to induce a chirality transfer. Related mononuclear complexes provided in general lower enantioselectivities [19].

In 2009, Imamoto *et al.* presented optically active dinuclear palladium(I) complexes **11** containing a Pd–Pd bond (Figure 8.8) [20]. The complex with $X = \text{Cl}$ could be prepared in a single step from the corresponding diphosphine ligand. Other halide complexes are available from the chloride complex by halogen exchange. The catalytic properties of these complexes were then investigated in the desymmetrizing ring-opening reaction of azabenzonorbornadiene derivatives with dimethylzinc.

Evidently the bis-Pd complexes were able to facilitate the ring-opening reaction and usually induce high stereoselectivities. Albeit the authors did not propose a mechanistic hypothesis for the catalytic cycle, they did compare their results with those obtained using a mononuclear palladium complex. The latter exhibited similar catalytic activity as the bimetallic one but generated the products with considerably lower selectivity. Thus it seems reasonable that the reaction proceeds via a bimetallic pathway, in which, for example, one Pd center might coordinate to the *N*-donor and the other one to the C,C double bond.

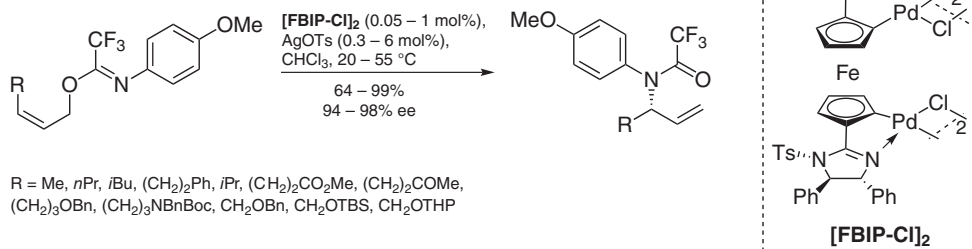


Figure 8.9 Homobimetallic palladacycle $[\text{FBIP-Cl}]_2$ as precatalyst in the aza-Claisen rearrangement of (Z)-configured allylic trifluoroacetimidates.

In 2007, Peters and Jautze reported a four-step synthesis of a C_2 -symmetric planar chiral ferrocene bisimidazoline bispalladacycle $[\text{FBIP-Cl}]_2$, featuring a direct diastereoselective biscyclopalladation as the key step. This complex was found to be the most efficient catalyst in the aza-Claisen rearrangement of (Z)-configured allylic trifluoroacetimidates (Figure 8.9) [21]. Earlier investigations with ferrocene imidazoline-based monopalladacycles [22] and other monopalladacycles [23] had shown that the corresponding (E)-configured allylic substrates are much more reactive in allylic imidate rearrangements than the (Z)-isomers. As the rearrangement is a stereospecific reaction, geometrically pure substrates are required for high enantioselectivity. Despite their lower reactivity, the (Z)-substrates are considered to be attractive starting materials, as they usually offer the advantage of being more readily available in isomerically pure form.

Prior to catalytic application, the chloro bridged dimeric $[\text{FBIP-Cl}]_2$ needs to be activated by treatment with a silver salt. This leads to monomeric complexes in which the new anionic ligand X^- selectively coordinates at the position trans to the Cp-ring in a square planar coordination sphere, whereas acetonitrile reversibly binds to the position trans to the imidazoline and is replaced by the substrate during the catalytic cycle. The mechanistic proposal includes a bimetallic bridging precoordination of both the imidate and the olefin functions, thus arranging the substrate for a nucleophilic *outer-sphere* attack on the olefin (after N-decomplexation, Figure 8.10). The substrate scope of this reaction is broad, as the tolerance for functional groups is high (Figure 8.9).

The same bispalladacycle was also reported as a precatalyst for the enantioselective Michael addition of α -cyanoacetates **12** to vinylketones **13** [24] or cyclic enones **15** (Figure 8.11) [25, 26].

Precatalyst loadings could sometimes be reduced to 0.02 mol% (200 ppm) still providing almost quantitative yields after 24 h in combination with high enantioselectivity. Spectroscopic and kinetic studies strongly support a cooperative bimetallic reaction mechanism in which both substrates are simultaneously activated resulting in an intramolecular C–C-bond formation (Figure 8.12).

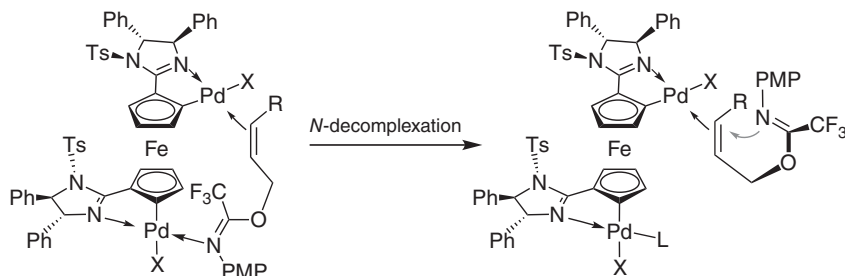
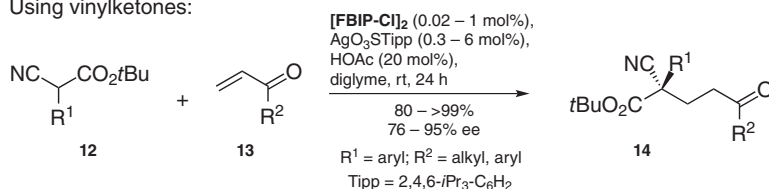


Figure 8.10 Precoordination of allylic imidate substrates and enantioselectivity-determining *outer-sphere* attack.

Using vinylketones:



Using cyclic enones:

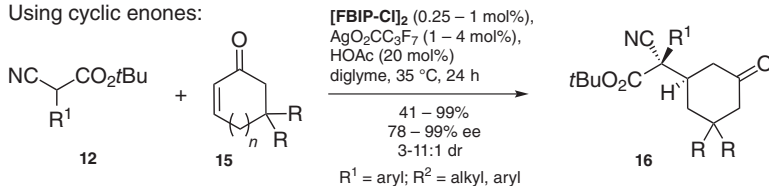


Figure 8.11 Stereoselective Michael additions catalyzed by a bispalladacycle.

The enolization of the α -cyanoacetate and thus the generation of the nucleophile is facilitated by the coordination of the nitrile to one Pd center. Simultaneously the enone is activated in **17** for a nucleophilic attack by coordinating to the other Pd atom. The 'partial rotational freedom of the Cp-Fe axis allows the catalyst to easily adopt the optimal intermetallic distance of both catalytically relevant metal centers. The latter is in general a crucial parameter regarding the efficiency of reactions catalyzed in a bimetallic mode [2a]. Thus the optimal distance of the reactive centers of the substrates can be adjusted for the stereoselective nucleophilic attack. This variability seems to be a major advantage of a metallocene backbone in a bimetallic catalyst system, as it allows the bimetallic complex to readily open and close like a pair of scissors employing just a few degrees of rotational freedom [27].

The formed σ -alkylpalladium bond in **18** then needs to be protonated by acetic acid to impede a β -H elimination, which otherwise leads to catalyst decomposition by generation of Pd(0) and the subsequent formation of Pd black. Coordination of new substrates and release of the product complete the catalytic cycle. The kinetic investigations have shown that protonolysis is a rapid step (nearly 0 order kinetic dependence on HOAc). They also revealed that the C–C bond formation

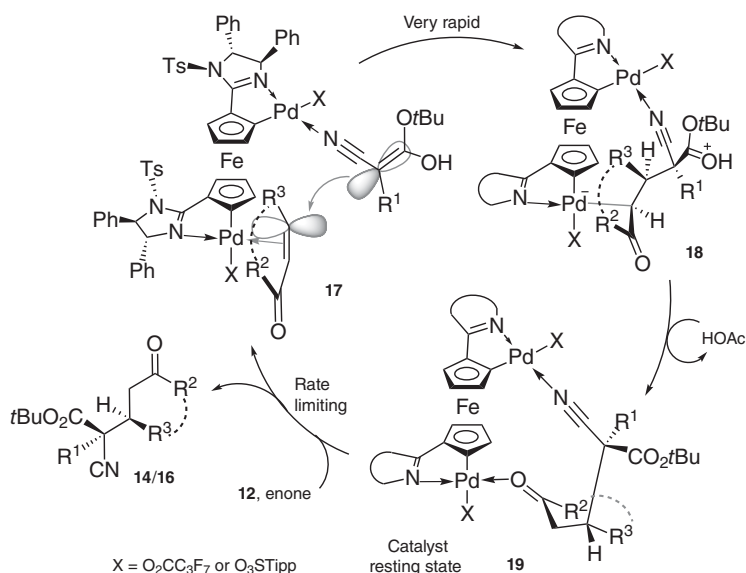


Figure 8.12 Proposed mechanism for enantioselective Michael additions catalyzed by activated [FBIP-Cl]₂.

step takes place almost instantaneously after productive substrate coordination. This unexpected and extraordinarily high reactivity for an elementary step generating a sterically demanding linkage to a quaternary stereocenter stresses the cooperativity of both metal centers. Control experiments with related planar chiral monopalladacycles provided different major stereoisomers: with vinylketone substrates, the other enantiomer was preferentially formed, while cyclic enones in general resulted in the formation of the other epimer as a major product. Moreover, using monopalladacycles the reactivity for the C–C-bond formation step is much lower. Nevertheless, despite the cooperative effect of both Pd centers using the bispalladacycle catalysts, the overall reaction rates are similar for mono- and bimetallic catalysts, as product decomplexation is rate-limiting with the bimetallic catalyst. This has been attributed to a detrimental chelate effect caused by a bridging bimetallic two-point coordination of the product. In contrast, the monometallic catalyst offers a rapid product decomplexation, but C–C bond formation is probably rate-determining.

FBIP has also been reported as a catalyst in asymmetric tandem azlactone formation-Michael addition reactions, in which the azlactone pronucleophiles are generated *in situ* from racemic *N*-benzoylated amino acids. This step-economic approach toward functionalized quaternary amino acid derivatives is possible as the bis-Pd catalyst is stable toward acetic anhydride used as a cosolvent (Figure 8.13) [28]. The optimization studies revealed that a buffer system consisting of acetic acid (used as the solvent) and sodium acetate (catalytic amounts) is necessary for high yields and enantioselectivities. On the basis of preparative, structural, and computational studies a permanent switch between

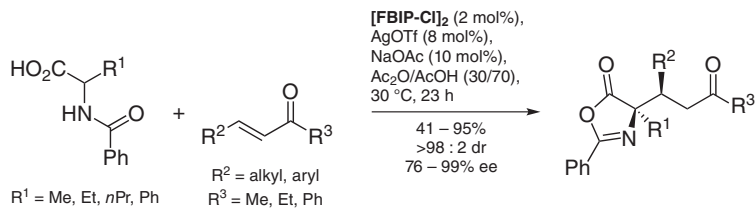


Figure 8.13 *In situ* generated azlactones as pronucleophiles in FBIP-catalyzed Michael additions.

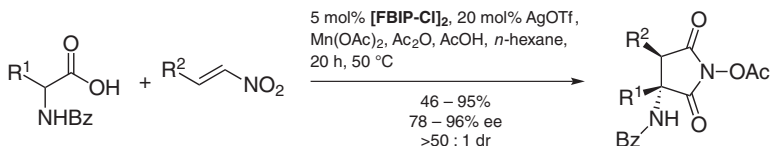


Figure 8.14 FBIP-catalyzed cascade reaction providing α -aminosuccinimides.

neutral, mono-, and dicationic catalyst species caused by acetic acid has been suggested, which could facilitate different elementary steps in the catalytic cycle [27].

In 2012, it was shown that this type of reaction can also directly start from unprotected racemic amino acids as azlactone source [29]. The most likely mechanistic hypothesis involves an *N*-coordination of the azlactone to promote an enolization and simultaneous coordination and thus activation of the Michael acceptor by the second Pd center [30]. Data obtained by control experiments with corresponding monometallic catalysts strongly suggested a bimetallic pathway for 2-Ph-azlactones, whereas the more nucleophilic 2-Me-azlactones prefer a monometallic pathway [31].

The FBIP catalyst has also been utilized to develop a regio-, diastereo-, and enantioselective cascade reaction forming biologically interesting α -alkyl- α -amino succinimides from racemic *N*-benzoylated amino acids, nitroolefins, acetic anhydride, and $\text{Mn}(\text{OAc})_2$ (Figure 8.14) [32]. The products are again generated via *in situ* formation of azlactones, which undergo an asymmetric conjugate addition to nitroolefins. The 1,4-adducts then suffer a Nef-type reaction as a key step, triggered by nitronate acylation and nucleophilic 1,2-addition of acetate. Control experiments with monopalladacycles or without any catalyst indicate that the 1,4-addition probably proceeds via a bimetallic pathway, in which one Pd triggers the azlactone enolization, whereas the second Pd center activates the nitroolefin as the Michael acceptor.

8.2.2

Cooperation of Two Gold Centers

The fascinating ability of Au(I) complexes to catalyze cycloisomerization reactions has been widely investigated [3a,b]. In 2008, Toste and coworkers published a study on the mechanism of a gold-catalyzed allenyne cycloisomerization (Figure 8.15) [33]. This formal ene type reaction could in principal proceed

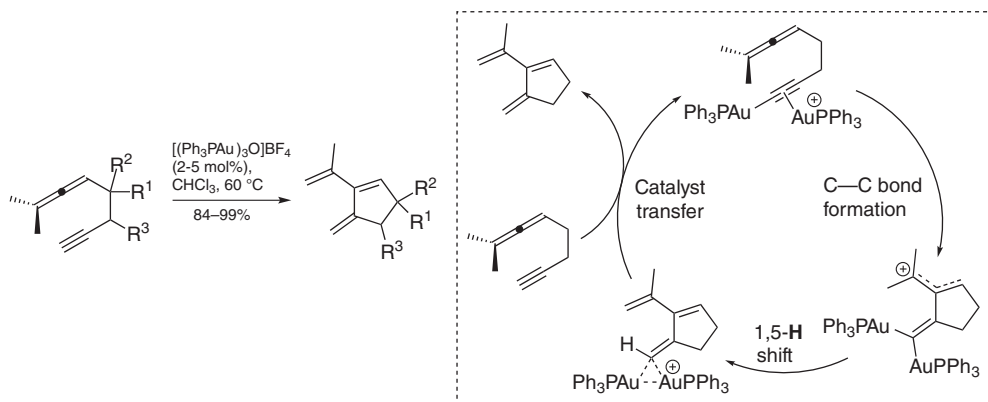


Figure 8.15 Allenyne cycloisomerization reaction catalyzed by $[(\text{Ph}_3\text{PAu})_3\text{O}]\text{BF}_4$.

via several possible mechanistic pathways involving metallacycles, vinylidene complexes, or π -complexes as intermediates. The participation of either one or two Au(I) atoms in a catalytic mechanism are both plausible.

A mechanism involving simultaneous activation by two gold atoms is more likely though, as the authors found that (i) nonterminal alkyne substrates did not undergo this reaction under catalytic conditions, (ii) in isotopic labeling experiments a H/D exchange occurred at the terminal alkyne position, and (iii) a transient phosphine-gold acetylide species could be observed under the reaction conditions. After extensive computational and experimental studies, all but one of the possible mechanistic pathways were excluded and a probable catalytic cycle could be postulated (Figure 8.15).

The phosphine-gold acetylide is initially formed by the reaction of a substrate molecule with the catalyst. Although there is only little preference for phosphine-gold(I) to coordinate to either an allene or alkyne moiety, there is a strong preference of about 22 kcal mol^{-1} for the π -coordination of phosphine-gold(I) to a Au-acetylide over an allene. π -Coordination of the second gold center to the acetylide then lowers the energy of the alkyne's LUMO thus triggering a 5-endo-dig cyclization, which generates a geminal diauraalkene and a stabilized tertiary allylic cation. After a 1,5-hydrogen shift the product can be released by protodemetalation, and the phosphine-gold is transferred to another substrate molecule to complete the catalytic cycle.

The general tendency of phosphine Au(I) precatalysts to form cationic digold acetylide complexes and their prevalence as intermediates in catalytic cycles was later confirmed by investigations of the Alvarez group [34].

Hashmi *et al.* [35] reported several *traceless dual activation catalysts* (TDACs) and showed their potential by hydroarylation/aromatization reactions as the one shown in Figure 8.16.

For that purpose they utilized σ,π -propyne acetylide complexes, which are readily prepared and air-stable crystalline solids. They are called *traceless catalysts*, as propyne serves as a volatile throw-away ligand that is released during

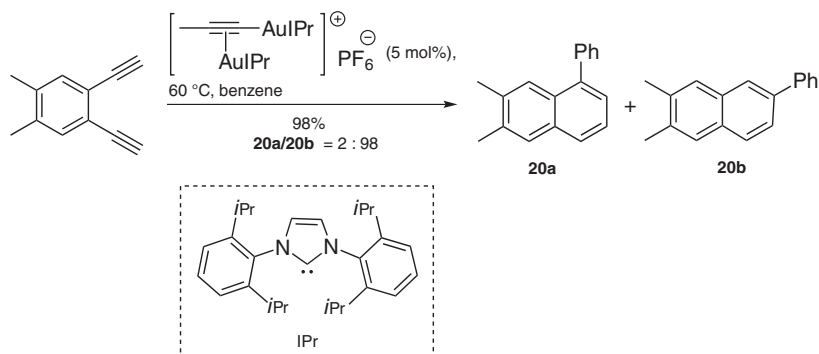


Figure 8.16 Bisgold-catalyzed hydroarylation aromatization of 1,2-diethynyl-4,5-dimethylbenzene to form naphthalenes.

ligand exchange by the substrate. The dual gold catalysis is based on the reaction of an electrophilic π -Au-complex with a nucleophilic gold acetylide moiety. Fast initiation processes and reaction rates have been achieved with these catalysts (the result shown in Figure 8.16 was obtained after 1 h). They allow for high β -selectivity with a minimum of side products. To demonstrate the general applicability of the TDACs, their potential was also examined by Hashmi *et al.* [36] in other related reactions like a dibenzopentalene synthesis (Figure 8.17, a), the intermolecular cross-dimerization of phenylacetylene (Figure 8.17, b) [37], and for alkyne/alkyne macrocyclizations (Figure 8.17, c) [38].

In general, the dual gold catalysis with TDACs allowed for lower catalyst loadings, higher reaction rates and yields, and higher selectivities as compared to more traditional single-point activation Au catalysts. Moreover the new catalysts were able to operate under milder conditions than previously reported catalyst systems.

Simultaneously, Nolan and coworkers were applying hydroxy-bridged digold complexes to the hydrophenoxylation of alkynes and were able to achieve high yields and regioselectivities in most cases (Figure 8.18) [39].

A dual activation mechanism has been postulated, in which both substrates were activated by a separate Au-complex (Figure 8.19). According to this proposal, the cationic hydroxide bridged digold complex **23a** is in equilibrium with two monometallic complexes, Lewis acid **23b** and Bronsted base **23c**. Cationic Au-complex **23b** can coordinate the alkyne **24** to form π -complex **I** while **23c** and ArOH **25** react to form phenoxide complex **II**. **I** is now attacked by **II** to form either *gem*-diaurated species **III** or σ -monoaured **IV**.

The product can then be released by protodeauration with either another substrate molecule or H_2O . This mechanistic proposal is supported by stoichiometric reactions in which among others all complexes – **23a**, **23b**, and **23c** – as well as **I** and **II** could either be isolated or at least observed. Those reactions also showed that a dual activation mechanism is necessary to ensure product formation and that a mixture of individually prepared species **I** and **II** immediately formed a product.

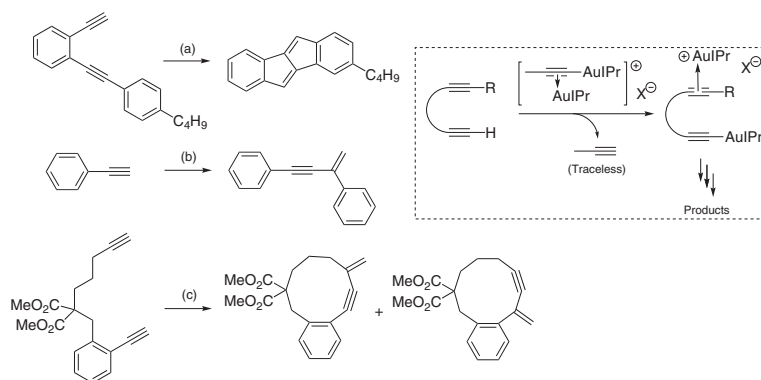


Figure 8.17 Test reactions for TDACs.

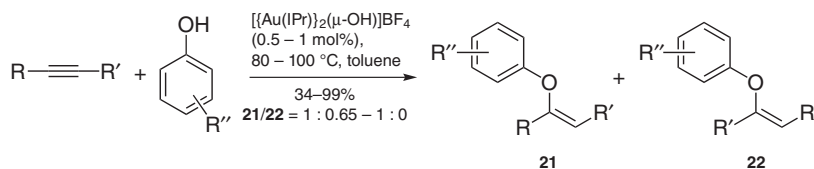


Figure 8.18 Digold-hydroxide catalyzed hydrophenoxylation of alkynes.

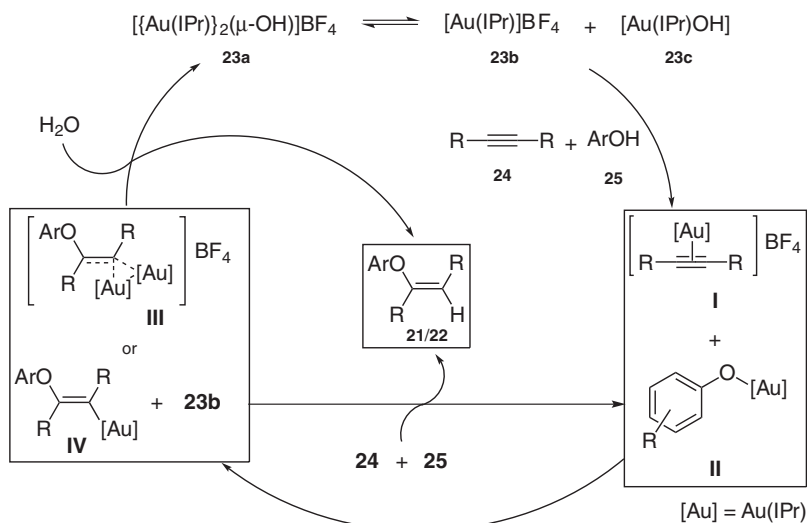


Figure 8.19 Proposed dual activation reaction mechanism.

8.2.3

Cooperation of Two Nickel Centers

The research group of Shibasaki has greatly contributed to the fascinating field of bisnickel catalysis [40]. However, as these reactions most likely involve substrate activation via coordination of heteroatoms to the metal center and are less dependent on the carbophilicity of Ni, they are not discussed in the present chapter; they have already been described in Chapter 1 by Shibasaki and Kumagai.

In the context of the present chapter fall studies by Chen *et al.*, who designed a dinuclear Ni/Ni-catalyst **26** that proved to be highly effective in the Negishi cross-coupling reaction of aryl chlorides (Figure 8.20) [41].

A broad variety of substituents was well tolerated including electron withdrawing, electron donating as well as sterically demanding groups. The bimetallic catalyst showed significantly higher activity when compared to related monometallic complexes. This is, for example, demonstrated by higher yields even with much lower catalyst loadings, thus suggesting a cooperative mechanism of the two Ni centers.

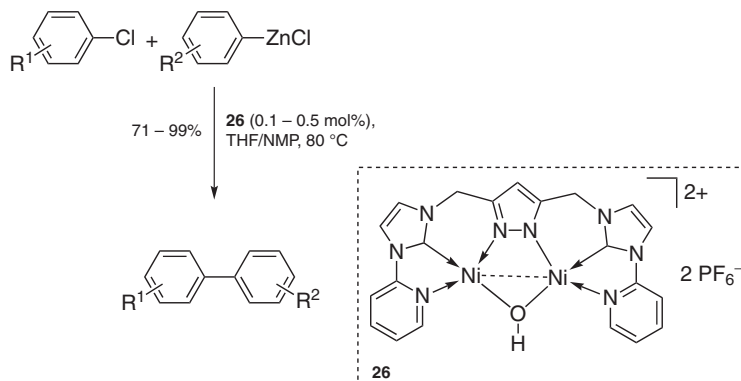


Figure 8.20 Ni-catalyzed Negishi coupling of aryl chlorides.

8.2.4

Cooperation of Two Rh or Ir Centers

In 2011, Ho *et al.* [42] developed homobimetallic dirhodium(I) and diiridium(I) complexes and investigated their catalytic value in the intramolecular dihydroalkoxylation of alkyne diols (Figure 8.21).

Comparison to monometallic catalysts revealed a significantly enhanced activity of the bimetallic systems. The dirhodium complexes seemed to be superior to their Ir counterparts for the substrate depicted in Figure 8.21. The results of these investigations led the authors to propose the key intermediates for the reaction catalyzed by bimetallic complexes. One of these transient structures is shown in Figure 8.21. In this model one metal center interacts with an OH group to preorient and activate it for a nucleophilic attack. Another possible mechanism, which cannot be ruled out, would involve a coordination of the alkyne to both metal centers.

As early as 1993 Stanley and coworkers reported a cooperative bimetallic Rh catalyst system with a chelating and bridging tetraphosphine ligand. This complex

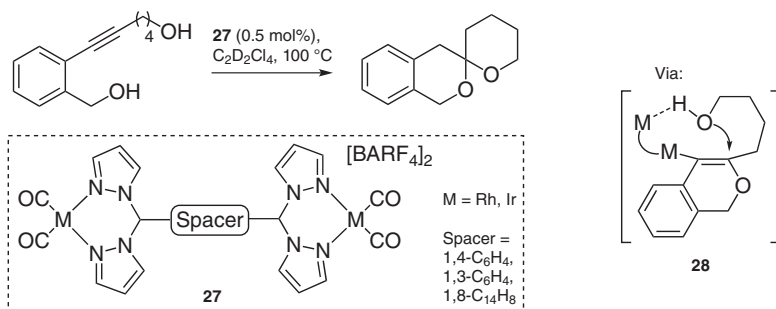


Figure 8.21 Application of Rh(I) and Ir(I) homobimetallic complexes in the intramolecular dihydroalkoxylation. **28** has been proposed as a key intermediate.

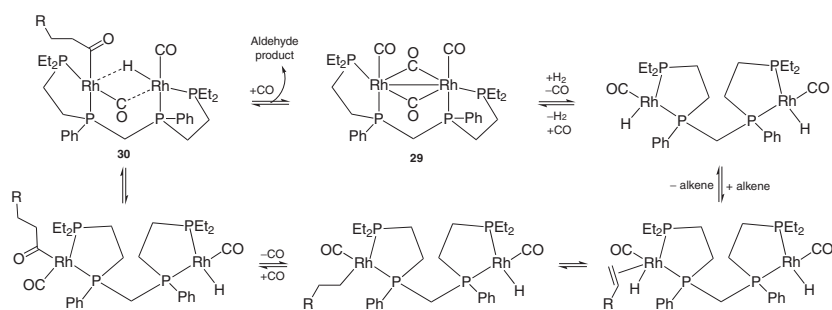


Figure 8.22 Proposed mechanism for the Rh/Rh-catalyzed hydroformylation.

catalyzed the hydroformylation of 1-hexene with high linear/branched ratios. The proposed reaction mechanism is shown in Figure 8.22 [43]. FT-IR and NMR spectroscopic investigations supported the catalyst structure as well as the proposed mechanism [44, 45].

The first step is a bimetallic addition of hydrogen to **29** followed by alkene coordination to one of the Rh centers. The coordinated olefin can then insert into the Rh–H bond. After coordination of another CO ligand, a CO insertion into the Rh–C_{alkyl} bond occurs. As both metals are in close proximity, the residual hydride is assumed to be intramolecularly transferred from the second Rh via a bridged species **30** to facilitate the reductive elimination of the aldehyde product, which completes the catalytic cycle. Monometallic model complexes, which were used in control experiments, were found to be poor catalysts supporting the cooperativity of both metal centers. Interestingly, the racemic tetraphosphine ligand resulted in considerably higher activity and regioselectivity than the corresponding meso isomer.

A related mechanism was also proposed in 2009 by the Reek group in their work on cooperative Rh-catalyzed asymmetric hydrogenation of olefins [46]. The catalyst developed by Reek *et al.* is a dinuclear neutral Rh–P–N–Rh-bridged complex. This catalyst was found to outperform other catalyst systems in the hydrogenation of sterically hindered substrates (Figure 8.23). Kinetic studies indicated that a dimeric structure remains intact during catalysis, and NMR

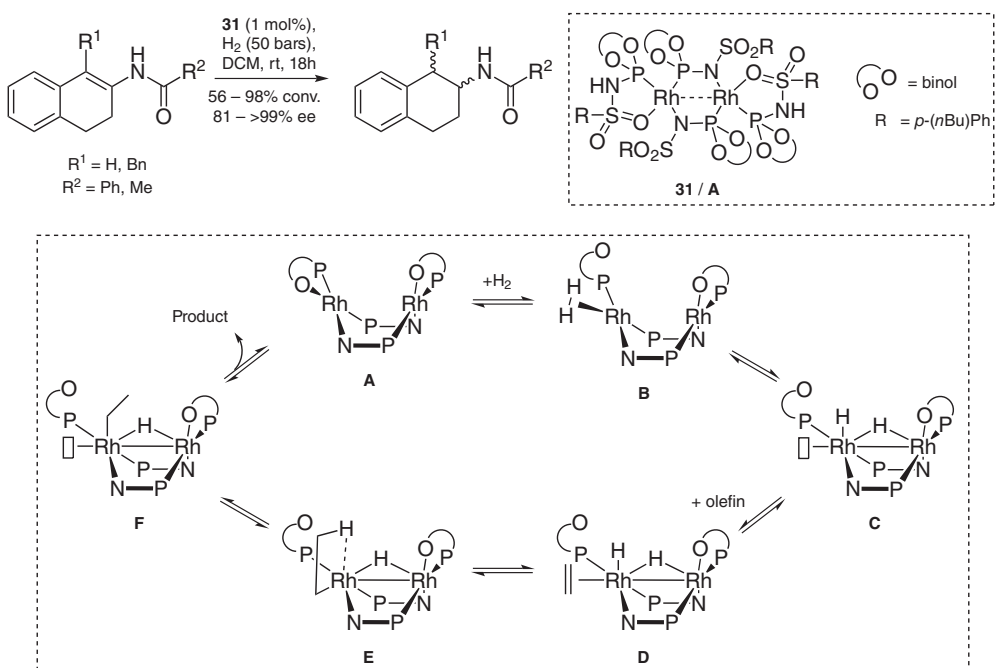


Figure 8.23 Asymmetric hydrogenation catalyzed by dinuclear Rh/Rh-complex **31**.

studies revealed that dimer **A** is the resting state of the catalytic cycle. Calculations indicate a rather short Rh–Rh distance, suggesting the possibility of a cooperation during the substrate activation (Figure 8.23).

Hydrogen is first coordinated by one of the Rh centers (**B**). Cooperative H₂-activation leads to **C**, which should be regarded as a Rh(III)/Rh(I) species as suggested by the shorter distance of the bridging hydride to the Rh center containing the terminal hydride. The sulfonamide group, which is coordinated in a hemilabile fashion, can be replaced by an olefin in **D**. After migratory insertion (**E**) the alkyl group rearranges to a position *cis* to the bridging hydride (**F**). Reductive elimination of the product regenerates the resting state **A**.

8.3

Heterobimetallic Catalysts

As mentioned in the introduction to this chapter, heterobimetallic complexes offer an enhanced variability for the cooperation of two metal centers making use of the complementary properties of the different metals employed. The most suitable metals can, in principle, be selected for the simultaneous activation of two substrate molecules or two reacting functional groups. This section is further subdivided to discuss the metal centers involved.

8.3.1

Cooperation of a Pd Center with a Different Metal Center

Heterobimetallic catalysts possessing at least one carbophilic metal center have most frequently been described for Pd/M²-systems. Various metals M² have been examined in that context, depending on the substrate, which should be activated by this center. Because of the large diversity of catalytic reactions this section is class-divided in asymmetric and nonenantioselective reactions.

8.3.1.1 Enantioselective Reactions

As early as 1982, Kumada *et al.* disclosed a new multidentate ligand system **32** and its application to the asymmetric allylic alkylation of unsymmetrical β-diketones (Figure 8.24) [47]. A major challenge of this reaction type was the configurational control of the stereocenter generated at the nucleophilic substrate, because in Pd-catalyzed allylic substitutions usually only the allyl substrate directly interacts with the metal center, whereas soft nucleophiles attack from the face remote to the Pd center. As a consequence, an efficient control of the nucleophile orientation and trajectory is a difficult task. Kumada *et al.* elegantly addressed this issue by directing the incoming nucleophile via a second metal center, in that case Na⁺. Sodium forms a chelate with the carbonyl groups of the ligand as well as with the O-atoms of the enolate substrate. By this coordination the enolate is preoriented to manage the nucleophilic attack on the π-allyl-palladium complex. Albeit the obtained

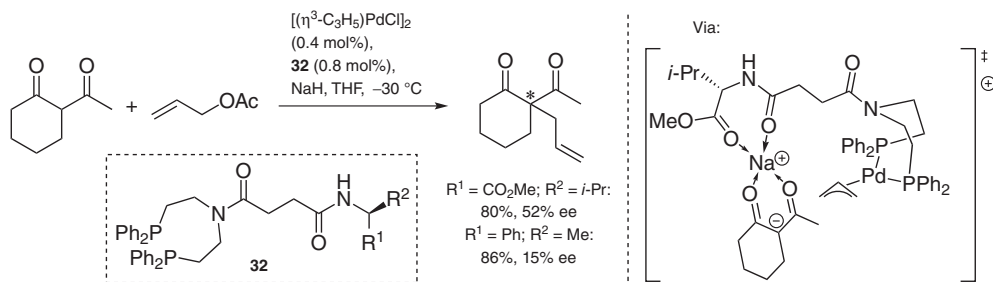


Figure 8.24 Enantioselective allylic alkylation by cooperation of a Pd and a Na center.

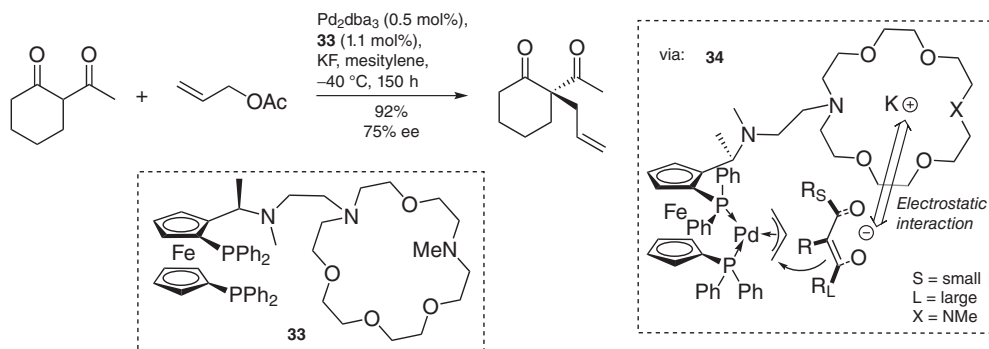


Figure 8.25 Enantioselective allylic alkylation by cooperation of a Pd and a K center.

enantioselectivity was moderate, this study established the proof of principle of this synergistic effect.

Ito *et al.* presented a more efficient cooperative Pd/K catalyst in 1992. A planar chiral ferrocenyldiphosphine **33** bearing a crown ether moiety was used as multidentate ligand in the allylic alkylation of β -diketones (Figure 8.25) [48].

The authors proposed an intermediate **34** in which the crown ether binds to a potassium cation that directs the enolate in the stereoselective attack at the π -allyl-palladium(II) moiety. It was suggested that the larger enolate substituent R_L adopts a position in which repulsive interactions with the catalyst are minimized.

In 1996, Ito *et al.* also reported a new bimetallic catalytic system for allylic substitutions consisting of two distinct Rh- and Pd-complexes, which separately activate the nucleophile and the electrophile, respectively (Figure 8.26) [49].

On the basis of the mechanistic studies by their own group and by others [50] a mechanistic proposal was postulated, which is depicted in Figure 8.27. The π -allyl-palladium(II) complex **B** is thus formed by decarboxylative oxidative addition of the allyl carbonate **35** to **A**. Meanwhile, Rh facilitates the enolization of the α -cyanoacetate **36** to form **C**. Nucleophilic attack of **C** at **B** occurs enantioselectively via transition state **E** and results in the highly enantioenriched product **37**.

In 2012, a study was reported by Peters and Weiss in which allylic *Z*-configured trifluoroacetimidates underwent enantioselective aza-Claisen

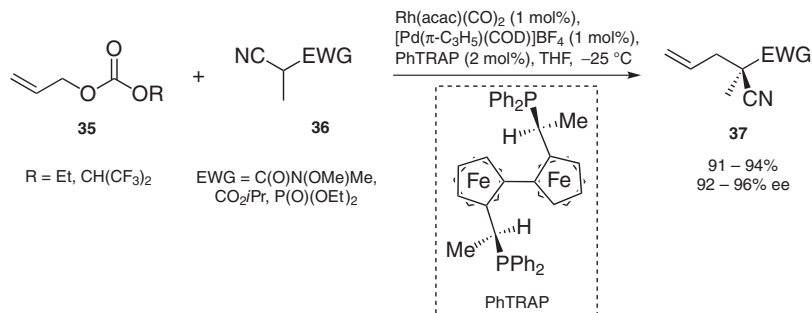


Figure 8.26 Pd/Rh-catalyzed enantioselective allylic alkylation.

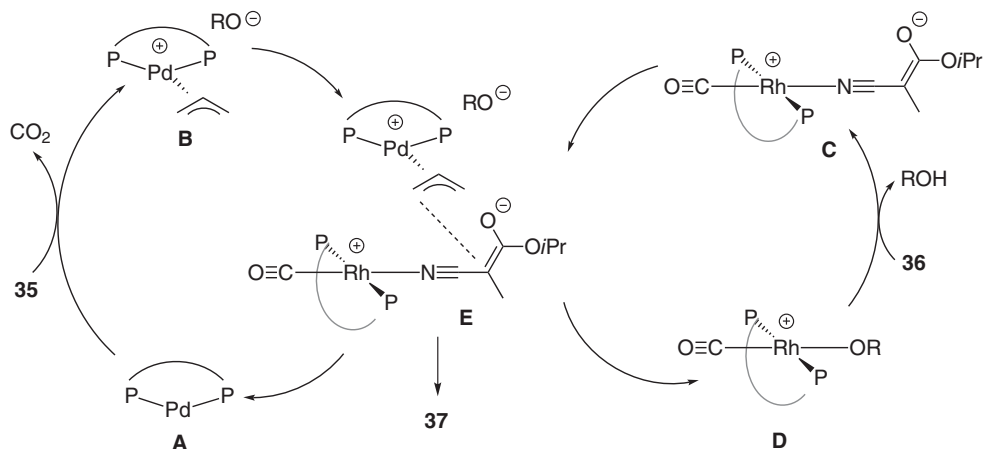


Figure 8.27 Mechanistic proposal for the Rh/Pd-catalyzed allylic substitution using α -cyanoacetate pronucleophiles.

rearrangements utilizing the heterobimetallic catalyst ferrocendiyl bisimidazoline pallada/platinacycle (FBIPP) $[\text{FBIPP-Cl}]_2$ (Figure 8.28) [51]. As described above, for this substrate type bispalladacycle $[\text{FBIP-Cl}]_2$ was previously found to be at least 1 order of magnitude more reactive than all reported monopalladacycles (Figure 8.10) [21a,b]. A comparison of the mixed pallada-/platinacycle $[\text{FBIPP-Cl}]_2$ with the closely related bispalladacycle $[\text{FBIP-Cl}]_2$ revealed that the former catalyst is less reactive at 20°C , but at a slightly elevated temperature of 55°C it is in certain cases more reactive than the homobimetallic system and in general allows for very high enantioselectivity.

The observed higher reactivity of the mixed Pd/Pt-catalyst, which might be surprising at first glance because of the low activity of other platinacycles for aza-Claisen rearrangements [51, 52], might be explained by an enhanced lifetime of a productive olefin coordination of the substrate at the Pt center because of slower ligand exchange processes at Pt. The activity difference of both catalysts at 20°C favoring the homobimetallic catalyst might reflect the traditional issues of slower

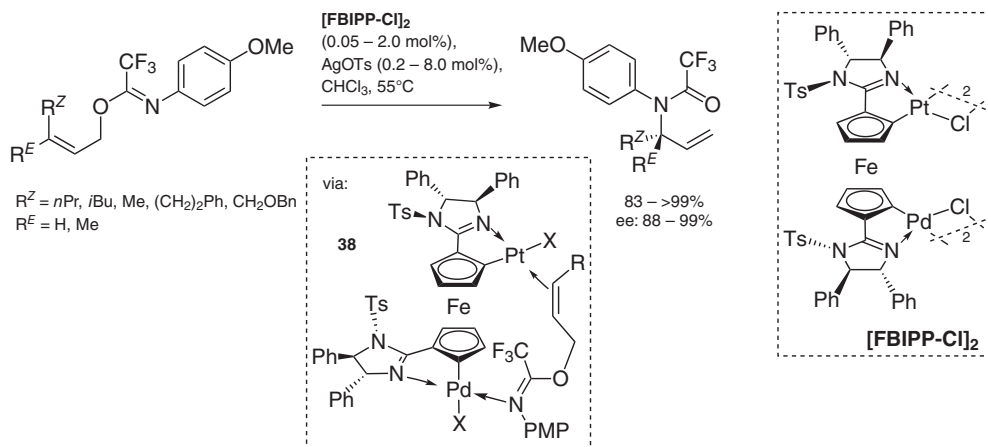


Figure 8.28 Highly enantioselective aza-Claisen rearrangement catalyzed by the heterobimetallic complex $[\text{FBIPP-Cl}]_2$.

substrate coordination/product release at Pt. These issues appear to be less relevant at 55 °C, in particular as the olefin coordination at Pt is probably accelerated by rapid precoordination of the imide N at Pd, because of a bridging chelate effect in **38**. The observed higher activity in certain cases with the heterobimetallic catalyst supports the hypothesis of an improved synergistic action of both metal centers in the case of Pd and Pt, depending on the temperature-dependent kinetic profile of each elementary step.

8.3.1.2 Nonenantioselective Reactions

In most of these reactions, a combination of Pd and a group 11 metal has been reported. A cooperation of palladium and gold was reported by the Hashmi group in 2013 [53]. They studied bimetallic catalytic systems in C,C-cross-coupling reactions. Similar to Sonogashira reactions the *in situ* generated transmetalation reagent is based on a coinage metal [54]. By the suggested heterobimetallic pathway, which is supported by theoretical and experimental investigations, the properties of both metal centers could be synergistically combined (Figure 8.29).

The gold(I) center thus activates the alkyne substrate for the attack by a nucleophile to generate a reactive vinylgold species, which undergoes a transmetalation to generate the Pd(II) complex **VII**. The latter provides the coupling product by reductive elimination simultaneously regenerating a Pd(0) species. During the transmetalation step short intermetallic Au-Pd contacts were found. Furthermore the authors were able to predict and experimentally verify the crucial nature of the counteranion X^- , as weakly or noncoordinating counterions prevented the coupling reaction, because the transmetalation step from gold(I) to palladium(II) is highly endothermic unless an additional halide source is added.

Blum *et al.* used a combination of Pd(0) and Au(I) to activate alkynes for nucleophilic metallations (Figure 8.30) [55]. Au(I) as an alkynophilic Lewis acid

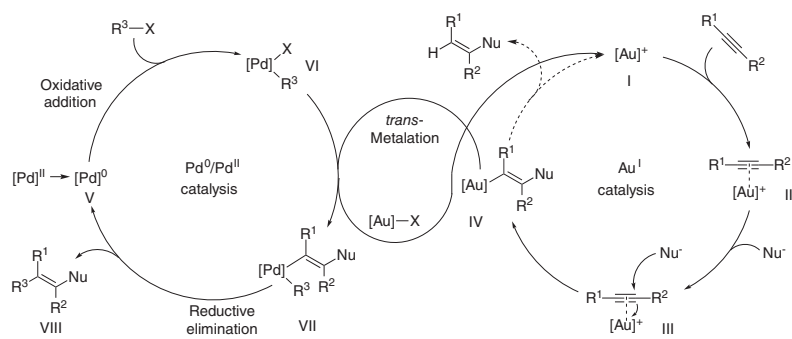


Figure 8.29 Combining gold- and palladium-catalysis in a cross-coupling.

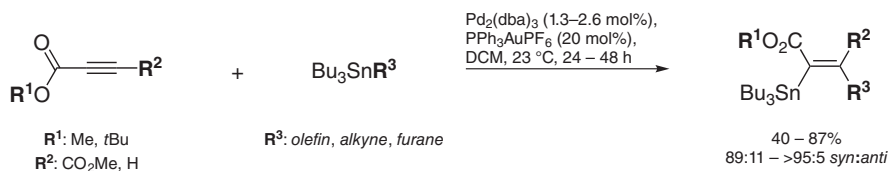


Figure 8.30 Pd(0)/Au(I)-catalyzed carbostannylation reaction.

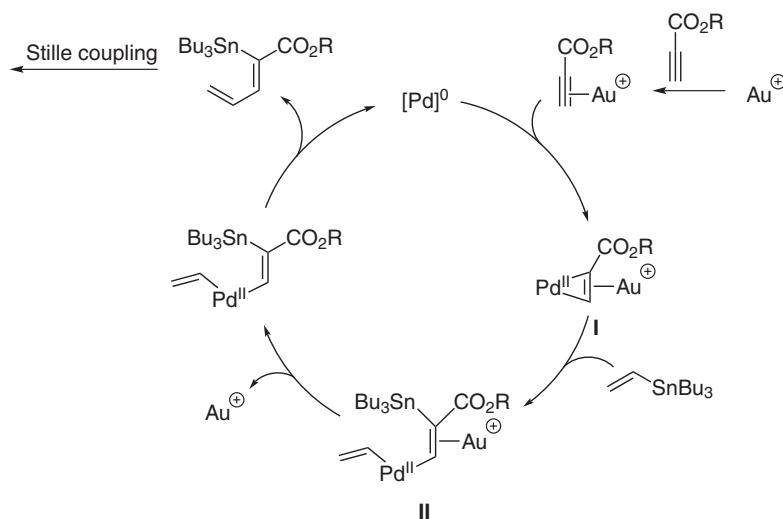


Figure 8.31 Proposed mechanism for the dual activation of an alkyne by Au(I) and Pd(0).

lowers the alkyne's LUMO, thus increasing the backbonding from Pd to the alkyne (Figure 8.31). Following the simultaneous activation of the alkyne by Pd and Au the reaction with a vinylstannane results in the formation of the α-stannylated carboxylate **II**. Dissociation of Au(I) and liberation of the vinylstannylated product by reductive elimination regenerates Pd(0). The products of this catalytic cycle might then, for example, be employed in traditional Stille cross-coupling reactions with aryl halides.

A combination of Pd(II) catalysts with different Lewis acid cocatalysts recently enabled Strambeanu and White [56] to develop an operationally simple method to distinguish between the reactive centers of ambident *O/N*-nucleophiles (**39**) in the attempt to regioselectively form either imidazolidinones (**40**) or 2-aminoxazolines (**41**) as products (Figure 8.32).

The change from Pd(OAc)₂ to a Pd(II)/bissulfoxide catalyst in combination with a change of the nature of the Lewis acid cocatalyst from hard to soft resulted in a switch of the ambidoselectivity, which could be explained by different operating mechanisms. Pd(OAc)₂ in combination with B(C₆F₅)₃ initially catalyzes an isomerization of the terminal olefin moiety to an internal (*E*)-configured double bond. Subsequent aminopalladation and β-hydride elimination lead to the

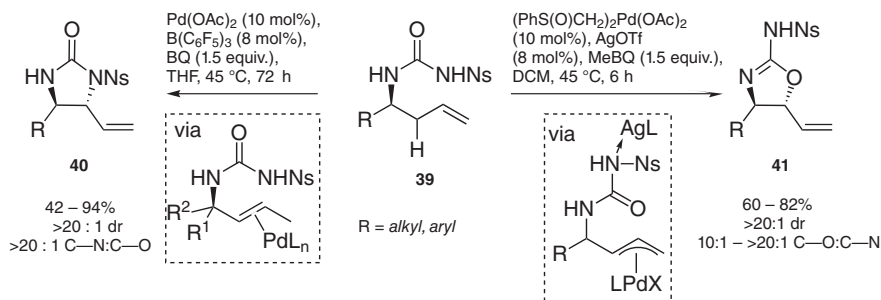


Figure 8.32 Selective synthesis of imidazolidinones (**40**) or 2-aminooxazolines (**41**) from ambident substrates.

imidazolidinone product. The isomerization of the double bond caused by Pd(II) and the necessity of the hard Lewis acid have experimentally been demonstrated. The sulfoxide ligand, on the other hand, retards an olefin isomerization, and a π -allyl-Pd complex is generated instead via an allylic C–H oxidation [57]. In addition, silver as an azaphilic Lewis acid has been suggested to inhibit the *N*-nucleophilicity by coordination to the *N*-atom thus explaining the different regioselectivity outcome.

Cooperation of palladium and silver metal centers has also been investigated recently by Ritter *et al.* in redox chemistry, which was used for the imidation of arenes. The latter do not have to be equipped with a directing group (Figure 8.33) [58]. According to the authors, the catalytic mechanism probably starts with the oxidation of Pd(II) complex **42** by *N*-fluorobenzenesulfonimide (NFBS) followed

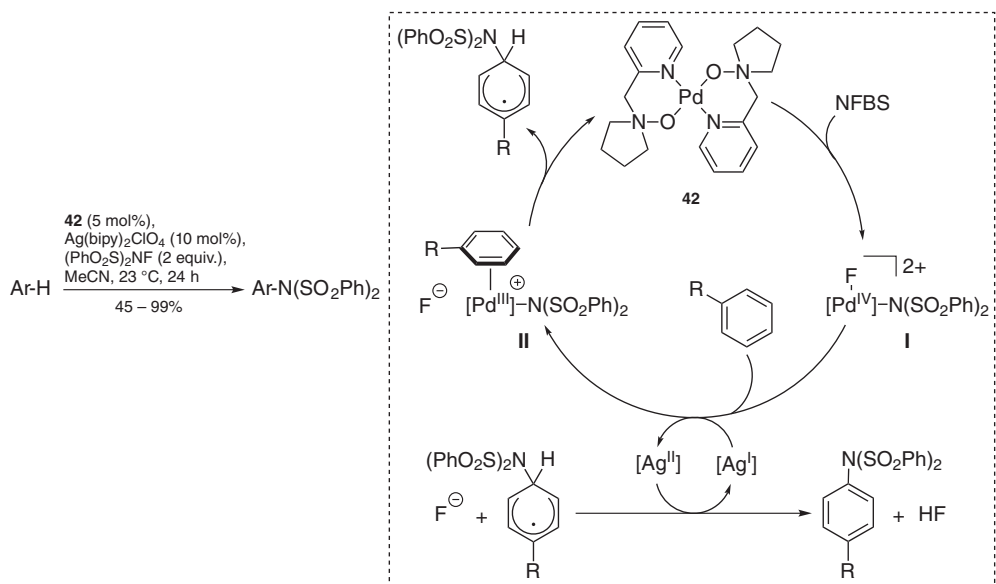
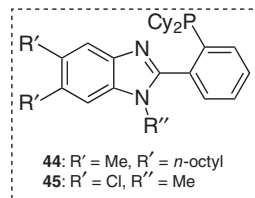
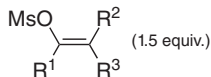
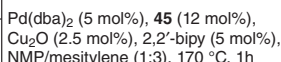
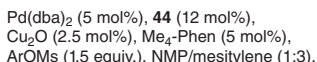


Figure 8.33 Pd/Ag-catalyzed C–H imidation and proposed mechanism.



by single-electron reduction of the formed Pd(IV) species **I** by Ag(I) and arene coordination to form the monomeric Pd(III) complex **II** plus Ag(II). C–N bond formation leads to the expulsion of the delocalized pentadienyl radical **43**. This radical intermediate is then oxidized by Ag(II) to regenerate Ag(I) and to provide the functionalized aromatic product. The proposed mechanism is supported by kinetic studies, which identified the NFBS-oxidation of the catalyst to be turnover-limiting. Furthermore, the suggested mechanism is supported by the detection of Ag(bipy)₂²⁺ by *in situ* EPR spectroscopy.

It was also possible to couple *O*-mesylated enolates, thus largely broadening the scope of accessible structures. The Cu/Pd-catalyzed cross-coupling reaction offers the advantage of high regioselectivity without the need for an additional directing group.

The authors compared the catalytic activity of the heterobimetallic complex to those of its separate components. In contrast to a separate Pd-pincer complex, a

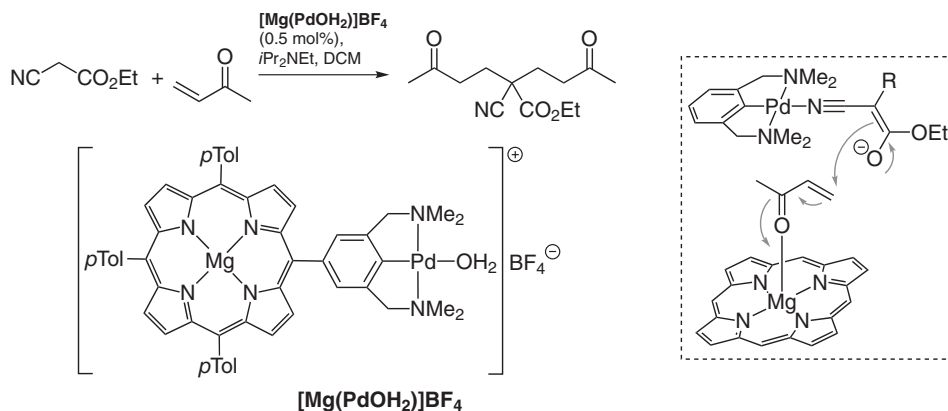


Figure 8.35 Double Michael addition catalyzed by a Mg(II)/Pd(II) heterobimetallic complex.

Mg-porphyrin complex exhibited almost no catalytic activity. Compared to the rate observed with the Pd-pincer complex, a mixture of separate Mg and Pd components could double the rate. The bimetallic complex $[\text{Mg}(\text{PdOH}_2)]\text{BF}_4$ exhibited a catalytic activity that was more than sixfold higher than that of the Pd-pincer complex. These results suggest a cooperative effect between both metals and that the increased activity of $[\text{Mg}(\text{PdOH}_2)]\text{BF}_4$ is not just because of a simple combination of both metals.

Klein Gebbink suggested a coordination of the cyano group to the Pd(II)-center to facilitate an enolization of the α -cyanoacetate. Simultaneously, the Mg(II) complex could act as an oxophilic Lewis acid to activate the enone via the coordination of the carbonyl moiety. This dual activation would explain the doubling in catalytic activity when both Pd(II) and Mg(II) complexes are present during catalysis.²⁾ However, this does not yet explain the sixfold activity increase for the bimetallic complex $[\text{Mg}(\text{PdOH}_2)]\text{BF}_4$, compared to a Pd(II)-pincer complex. Moreover, even if both substrates are simultaneously activated in this complex, the distance between the palladium-coordinated α -cyanoacetate and the magnesium-coordinated enone would be too large for an intramolecular reaction.³⁾ The authors hence came to the conclusion that an intermolecular mechanism initially occurs. They suggested that both substrates are activated as depicted in Figure 8.35. In the presence of a high excess of the substrates each catalyst molecule should contain two activated substrate species. If two of these catalyst complexes approach each other, an intermolecular Michael addition can occur. However, the addition product could remain coordinated to both catalysts and might efficiently link them afterward. Thus the next Michael additions might

2) Alternatively, the Mg-complex might also serve to generate the reactive enolate, and the palladacycle could activate the enone by the coordination of the C,C double bond.

3) Bimetallic Pd/Ni complexes based on multidentate ligands, in which a salen and two N-heterocyclic carbene moieties are merged, have also been investigated in 1,4-addition reactions, but an intramolecular cooperation is also unlikely in that case [62].

proceed on the opposite site of the complexes in a quasi-intramolecular fashion, explaining the observed rate enhancement with the bimetallic catalyst.

8.3.2

Cooperation of a Ni Center with another Metal Center

Nickel, the less expensive smaller homolog of palladium, has also been successfully investigated as a carbophilic metal center used in concert with a second metal in heterobimetallic complexes.

During their development of a practical total synthesis of the antiviral drug Tamiflu, Shibasaki *et al.* have studied a Ni-catalyzed conjugate addition of cyanide to enones [63]. In 2008, they further improved their method by employing Gd(III) as a hard Lewis acid cocatalyst, which cooperates with the soft Lewis acid Ni(0) (Figure 8.36) [64].

The substrate scope of this reaction is quite broad, including cyclic as well as linear enones. On the basis of their previous results [63] the authors proposed the mechanism shown in Figure 8.36. Enone coordination to the carbophilic Ni(0) center and additional carbonyl group coordination to the oxophilic Gd(OTf)₃ would generate an electrophilic π -allyl-nickel system, in which the nucleophilic O-atom is subsequently silylated by a silylcyanide thus liberating Gd(OTf)₃. The released cyanide then binds to nickel, and a following reductive elimination delivers the product and closes the catalytic cycle.

In 2013 Donets and Cramer [65] developed a precatalyst system comprising Ni(0), Me₃Al, and a bulky chiral diaminophosphine oxide ligand (**46**) to enantioselectively transform homoallylic formamides into γ -lactams (Figure 8.37).

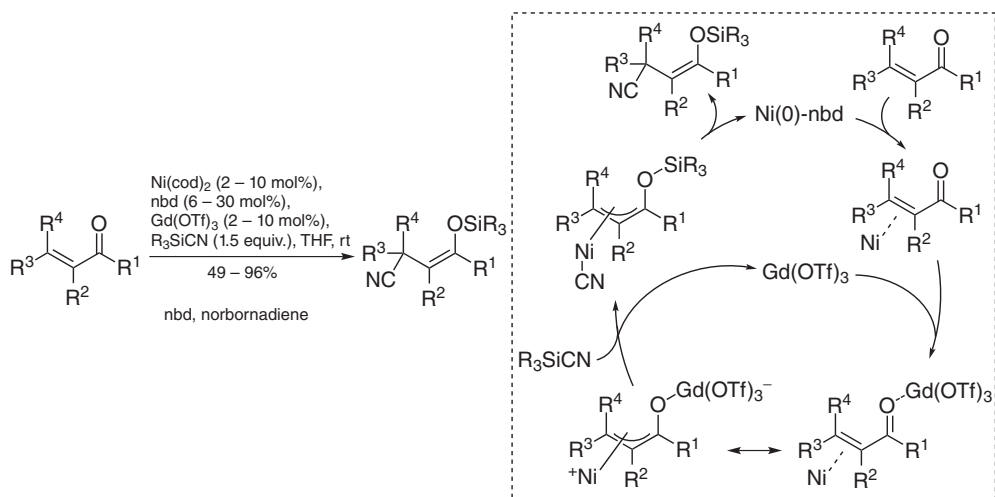


Figure 8.36 Ni(0)/Gd(III) catalyzed conjugate addition of cyanide to enones and proposed catalytic cycle.

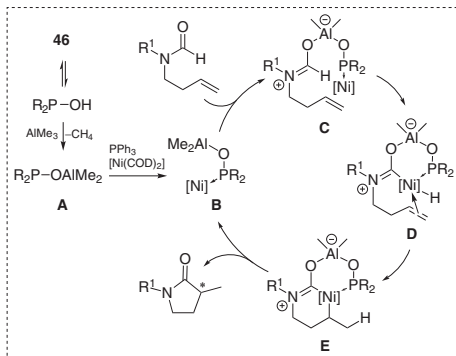
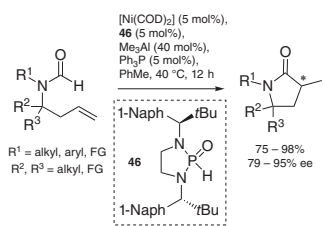


Figure 8.37 Asymmetric hydrocarbamoilation catalyzed by a heterobimetallic Ni/Al complex.

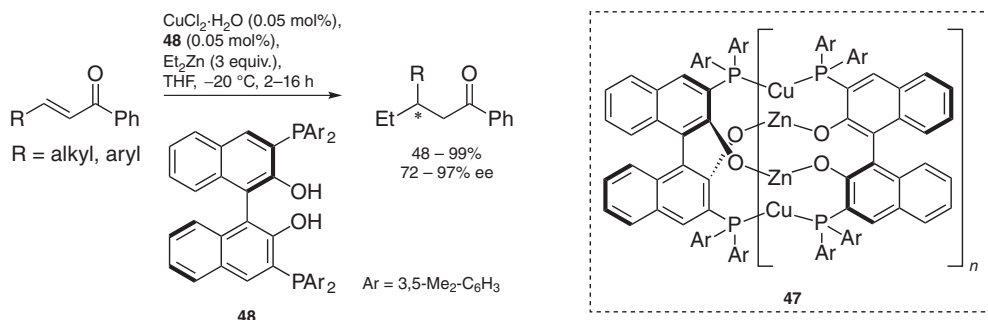


Figure 8.38 Asymmetric conjugate addition of ZnEt_2 to various enones. Structure **47** shows a possible organization of ligands and metal centers.

To determine the mechanism of the formamide C–H activation the authors also examined several other ligands, in particular with $\text{N}_2\text{P}(\text{OMe})$ and $\text{N}_2\text{P}(\text{Ph})$ functionalities instead of the $\text{N}_2\text{P}(\text{O})\text{H}$ moiety. The $\text{N}_2\text{P}(\text{OMe})$ -ligand is unable to form a covalent adduct with Me_3Al , while the $\text{N}_2\text{P}(\text{Ph})$ -ligand does not coordinate at all to Me_3Al . Both alternative ligands drastically lowered the catalytic activity. On the basis of these results the Cramer group suggested a possible mechanism (Figure 8.37). The phosphine oxide is in equilibrium with its tautomeric form, which is deprotonated by Me_3Al to form **A**. **A** displays Lewis acidic character at the Al center. Coordination of the phosphorous center of **A** to $\text{Ni}(0)$ leads to the active catalyst species **B**. The Lewis acidic Al is assumed to activate the substrate's carbonyl group (**C**). The authors proposed that this should facilitate the oxidative addition of the formamide C–H bond to the nickel(0) center, forming nickelacycle **D**. Subsequent intramolecular hydrometallation of the C,C double bond would furnish **E**, which can regenerate the bimetallic catalyst **B** by reductively eliminating the product.

8.3.3

Cooperation of a Cu or Ag Center with another Metal Center (Not Pd)

In 2010, the Shibata group reported a multinuclear complex **47** containing both copper and zinc centers, which achieved a remarkable catalytic activity in the asymmetric conjugate addition of organozinc reagents to enones (Figure 8.38) [66].

The reaction proceeded generally with high enantioselectivity. Control experiments using derivatives of ligand **48** were conducted to study the role of both metals in the catalytic addition. Use of an *O*-MOM protected ligand showed that a coordination of the organozinc reagent to ligand **48** is essential. When a ligand with only one phosphine functionality was employed, similar poor results were obtained as with the MOM protected ligands. A further control experiment in the presence of catalytic amounts of PPh_3 demonstrated that the phosphine and the BINOL moieties need to be part of the same molecule for high efficiency thus indicating the necessity of a highly organized heterobimetallic catalyst. These results

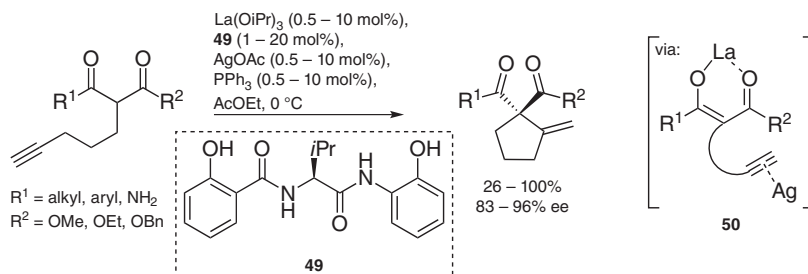


Figure 8.39 La(III)/Ag(I) catalyst system for the dual activation of substrates in the Conia-ene reaction.

prompted the authors to postulate the presence of a self-organized multimetal-centered oligomeric catalyst **47** (Figure 8.38). According to Shibata *et al.* at least four ligand molecules need to be in one catalyst molecule to account for the high yields and selectivities observed. This hypothesis was supported by mass spectroscopic studies. Albeit no signals for oligomeric complexes containing more than four ligand molecules could be detected, their formation cannot be completely ruled out.

In 2011, Shibasaki *et al.* developed a heterobimetallic catalyst system that combined the hard Lewis acid La(III) with the soft Lewis acid Ag(I). These metals were selected to develop an asymmetric catalyst for the Conia-ene reaction, because they should be able to simultaneously activate a 1,3-dicarbonyl moiety and an alkyne, respectively (Figure 8.39) [67, 68]. The valine-derived catalyst system provided the cyclic products in moderate to quantitative yields and with high enantioselectivities. Control experiments utilizing only one metal source (either La(III) or Ag(I)) did not result in any product formation, suggesting the cooperative action of both Lewis acids. NMR studies indicated that both metal complexes simultaneously associate with the substrate as depicted in the transition state **50** in Figure 8.39.

8.4

Synopsis

The use of carbophilic metal catalysts has revolutionized synthetic organic chemistry and is nowadays an indispensable tool for both the target and the diversity-oriented synthesis of complex molecules. After the seminal developments on Pd(0)-catalyzed cross-coupling reactions and Rh(I)-catalyzed hydrogenations of olefins, in the past two decades the complementary value of carbophilic Lewis acid catalysts relying on, for example, Pd(II), Au(I), or Pt(II) has moved into the focus of interest. Their unique properties have enabled synthetic chemists to add synthetic strategies to their repertoire that were previously unimaginable and often offer the advantages of excellent step- and atom-economy. With the constantly growing impact of cooperative catalysis in

general, carbophilic metals have also been investigated – particularly over the past few years – in a very diverse range of bimetallic catalyst systems. For a large number of these bimetallic catalysts, a synergy of both metal centers is very likely and has sometimes also been proven. This cooperative behavior often results in a superior catalytic performance, for example, in terms of activity and stereoselectivity and even allows for reactions that are not feasible with more traditional soft metal complexes. It is thus likely that it is only a matter of time, until these bimetallic catalysts are more frequently added to the toolbox of synthetically working chemists, to be routinely used in both academia and industry.

Acknowledgments

René Peters gratefully acknowledges the generous financial funding of his research program on cooperative catalysis by the Deutsche Forschungsgemeinschaft (DFG, PE 818/3-1, PE 818/4-1, PE 818/6-1). Marcel Weiss is grateful to the Fonds der Chemischen Industrie (FCI) and the Landesgraduiertenförderung Baden-Württemberg for Ph.D. fellowships.

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9

Cooperative H₂ Activation by Borane-Derived Frustrated Lewis Pairs

Jan Paradies

9.1

Introduction

The term “frustrated Lewis pair” (FLP) was coined in 2006 by Douglas W. Stephan in the context of the observation that a borane-based strong Lewis acid and a phosphine-derived Lewis base did not form the corresponding classical Lewis adduct. Stephan reported in his seminal work the synthesis of a rigid tetrafluorophenylene bridged phosphonium fluoroborate, which was subsequently transformed into the corresponding hydridoborate by reaction with chlorodimethylsilane (Figure 9.1) [1].

On heating above 100 °C, the phosphonium borate liberated molecular hydrogen (H₂), forming the phosphinoborane. The rigidity of the linker prevented the intramolecular formation of the Lewis adduct (quenching), and the steric bulk of the phosphorous’ and boron’s substituents prevented the intermolecular quenching, leaving the individual reactivity intact. Remarkably, this molecule readily reacted with H₂ at room temperature to regenerate the phosphonium borate.

It became quickly apparent that the steric hindrance of the Lewis pair combined with high Lewis acidity and Lewis basicity was responsible for the observed reactivity with H₂. A second intramolecular example was reported by Erker. The flexible ethylidene-bridged phosphinoborane is capable of activating H₂ at room temperature and is still one of the most active FLP catalysts to date [2]. Intermolecular “frustrated” Lewis pairs together with catalytic applications have been reported [3], which laid the foundation for this field of research. From then on, the unquenched reactivity of a Lewis acid in the presence of a Lewis base was described as FLP, and inspired organic, inorganic, physical, and theoretical chemists to search for new applications [4]. This overwhelming interest of chemists is reflected by the joint publication of a two-volume compendium in “Topics in Current Chemistry” on FLPs edited by Stephan and Erker [5] describing the discovery, features, and application of this novel H₂-activation approach.

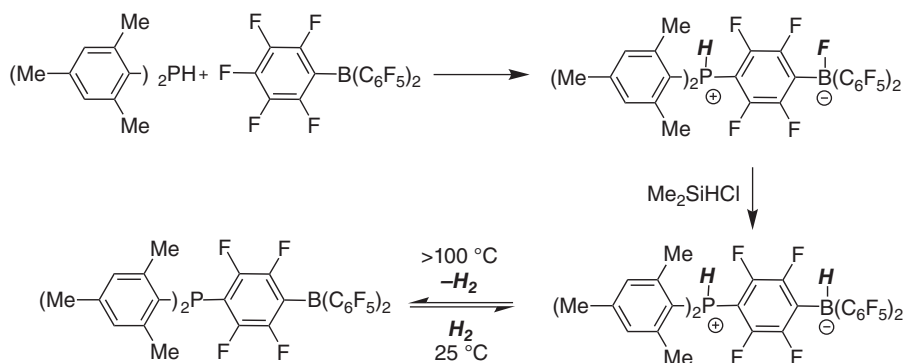


Figure 9.1 Stephan's intramolecular frustrated Lewis pair [1].

This chapter is intended to give an overview of FLP reactivity based on borane-derived Lewis acids in combination with common Lewis bases, for example, phosphines or amines. Such FLP combinations have been intensively investigated and applied in very efficient hydrogenations. Aluminum- [6], ruthenium- [7], zirconium- [8], or even carbon-based [9] Lewis acids are active in H₂ activation. However, their synthetic and catalytic scope has not yet been explored.

9.2

Mechanistic Considerations

The metal-free H₂ activation has attracted most interest because of its high relevance in chemistry. The mechanism of the metal-free H₂ activation was intensively investigated by quantum chemical methods, and just recently the first experimental investigations were communicated.

The term “frustrated Lewis pair” describes the inherent driving force of a Lewis pair to interact through the Lewis basic and Lewis acidic site to form a Lewis adduct, which is prevented by steric and/or electronic prerequisites. Such unquenched reactivity had already been observed by Brown in 1942 in his study of “Steric Strains as a Factor in the Relative Stability of Some Coordination Compounds of Boron” [10]. He observed that steric factors are primarily responsible for the presence or absence of Lewis adducts, as demonstrated by the reaction of trimethylborane with either pyridine or 2,6-lutidine (Figure 9.2).

While pyridine readily forms the Lewis adduct, the methyl groups in 2,6-lutidine prevent the formation of the corresponding Lewis adduct, thus leaving the reactive centers unquenched.

Consequently, it is reasonable to assume that an FLP features noncovalent interactions through Coulomb and dispersion forces. The formation of such an aggregate was described as an “encounter complex” [2, 11], whose highly fluctuating structure is almost impossible to be studied by experimental techniques. So far, the solid-state structure of an intermolecular FLP has not been elaborated.

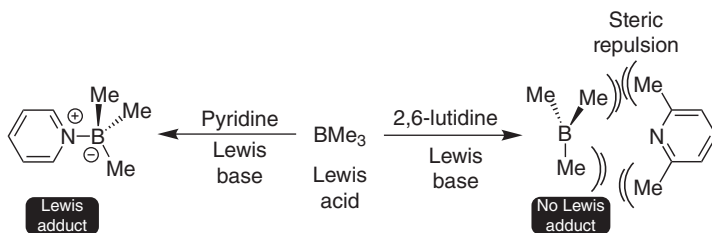


Figure 9.2 Reactivity of trimethylborane with pyridine-derived Lewis bases [10].

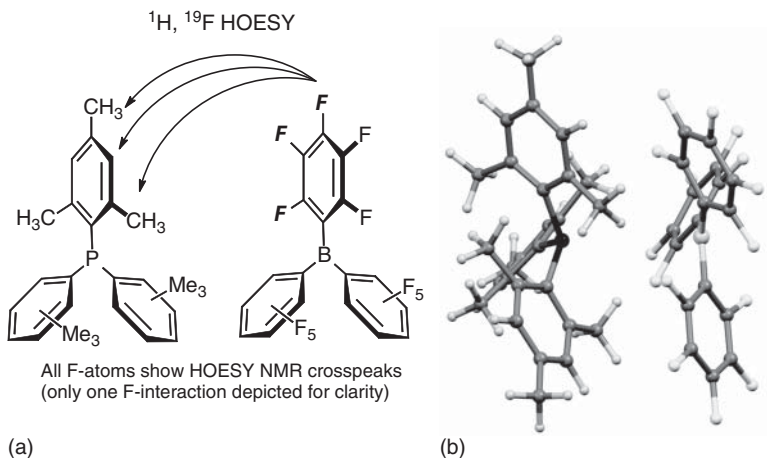


Figure 9.3 (a, b) NMR structure of $\text{PMe}_3/\text{B}(\text{C}_6\text{F}_5)_3$ determined by ^1H , ^{19}F HOESY (molecular structure representation generated with Mercury 3.1.1) [12].

However, the association of a phosphine (PMe_3) with a borane ($\text{B}(\text{C}_6\text{F}_5)_3$) was investigated by NMR (nuclear magnetic resonance) spectroscopy (Figure 9.3) [12]. ^1H , ^{19}F HOESY and diffusion NMR studies confirmed interactions between the phosphine and the borane, and the equilibrium constant was determined as $K = 0.3\text{--}0.7\text{ M}^{-1}$, which is in agreement with the fact that the formation of the encounter complex is slightly endergonic ($\Delta G^0(298\text{ K}) = +0.4 \pm 0.2\text{ kcal mol}^{-1}$).

Quantum chemical data suggests that the formation of the aggregate is responsible for the prepolarization of the hydrogen molecule [11e, 13] prior to its orbital interactions with the Lewis pair's heteroatoms [14]. The orbital interactions consist of the donation of electron density of the Lewis base to the $\sigma(\text{H}_2)^*$ orbital of H_2 , which leads to the destabilization of the H–H bond. Concomitant decrease of electron density in the $\sigma(\text{H}_2)$ orbital by interaction with the empty orbital of the Lewis acid finally leads to the heterolytic splitting of molecular hydrogen (Figure 9.4). Clearly, such mode of activation requires cooperative interaction of the Lewis pair with H_2 , in which a certain degree of Lewis acidity and Lewis basicity must be present.

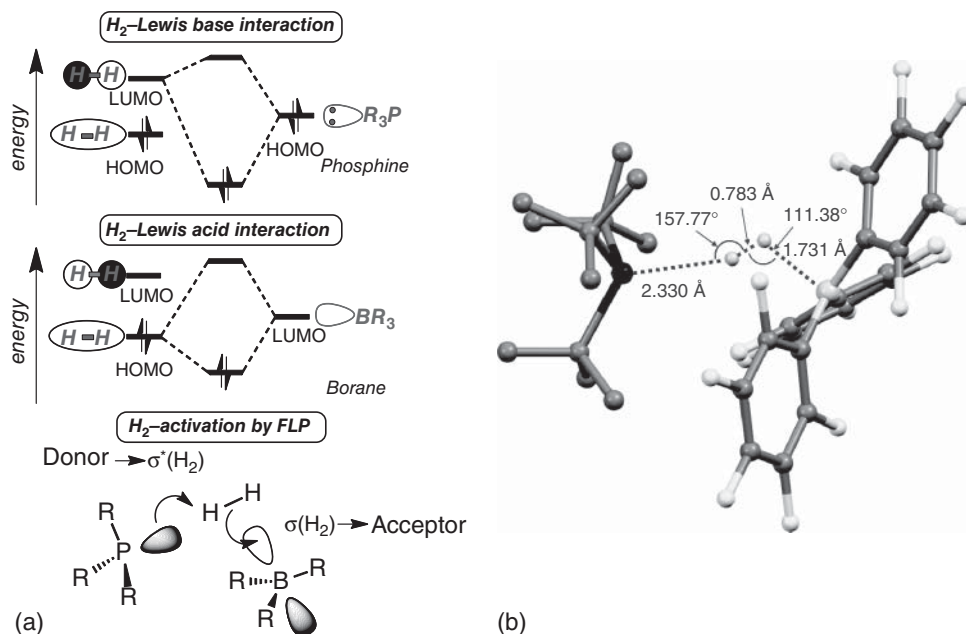


Figure 9.4 (a) Orbital interactions in the FLP-mediated H₂ activation and (b) transition state of the H₂ activation by the FLP consisting of *t*Bu₃P/B(C₆F₅)₃ [11c] (selected hydrogen atoms were omitted for clarity; molecular structure representation generated with Mercury 3.1.1).

The corresponding transition state of H₂ activation by the FLP consisting of *t*Bu₃P/B(C₆F₅)₃ is depicted in Figure 9.4b. As evidenced by the adopted geometry, severe interactions of *t*Bu₃P's lone pair with H₂ in an “end-on” (P–H–H angle 157.8°) and interactions of the empty orbital of B(C₆F₅)₃ in a “side-on” (B–H–H angle 111.4°) manner can be observed. Such a geometry can be easily adopted by Erker's intramolecular FLP Mes₂P–CH₂–CH₂–B(C₆F₅)₂ [2, 15] and is probably the reason for its unmatched reactivity in the heterolytic H₂ cleavage.

According to this model of H₂ activation, a number of Lewis bases apart from phosphines should be viable molecules for heterolytic hydrogen splitting. Indeed, a vast number of Lewis bases for such purpose have been identified, ranging from bisphosphines [16], phosphinimines [17], imines [18], amines [19], and diethyl ether [20], through carbenes [21] to carbanions [22]. The most commonly used FLPs for H₂ activation consist of an amine or phosphine as the Lewis base and B(C₆F₅)₃ as the Lewis acid.

Probably one of the most interesting aspects of FLP-catalyzed hydrogenations is the formation of the hydride donor directly from the heterolytic splitting of hydrogen. Such hydridoborates are well known for their versatility in carbonyl reductions [23], resulting in the first catalytic metal-free hydrogenation of imines with H₂ [24]. The reduction of imines requires their activation by a Lewis acid or alternatively by a Brønsted acid. The onium hydridoborate resulting from the

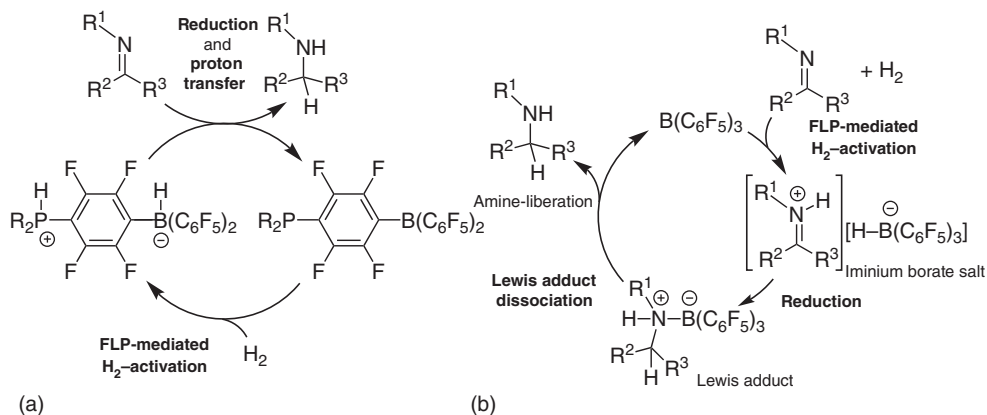


Figure 9.5 (a) Catalytic cycle for the FLP-catalyzed hydrogenation of imines [24] and (b) catalytic cycle for the phosphine-free FLP-catalyzed hydrogenation of nitrogen-containing substrates [25].

FLP-mediated H₂ activation undergoes proton transfer to the imine, liberating the Lewis base with concomitant hydride transfer, generating the amine (Figure 9.5a).

As evidenced from this catalytic cycle, the corresponding substrate should also be a viable Lewis base for H₂ activation (Figure 9.5b). Consequently, for the most FLP-catalyzed hydrogenations of aldimines, ketimines, or nitrogen-containing heterocycles, the substrate functions as the Lewis base for H₂ activation, and the addition of phosphines or other Lewis bases is not necessary [25].

9.3

General Considerations

9.3.1

Choice of Lewis Base

As discussed in the previous section, the Lewis base is responsible for retrieving the proton from the heterolytic H₂ activation. However, another significant role of the Lewis base is to transfer the proton to the substrate. Hence the pK_a of the corresponding onium species is quite relevant for the reaction rate and/or for the suppression of undesired reaction pathways. A general prerequisite is that the Lewis base does not form or only reversibly forms a Lewis adduct with the Lewis acid. This requirement can be met by the introduction of steric bulk and/or electronic modifications (Figure 9.6).

The general consensus is that only strong electron-releasing Lewis bases are capable of activating H₂ in combination with, for example, B(C₆F₅)₃. This notion is supported by the observation that for these FLP systems the H₂ activation product, the onium hydroborate, can be characterized by NMR spectroscopy or X-ray crystallography. However, it was found recently that the very weak

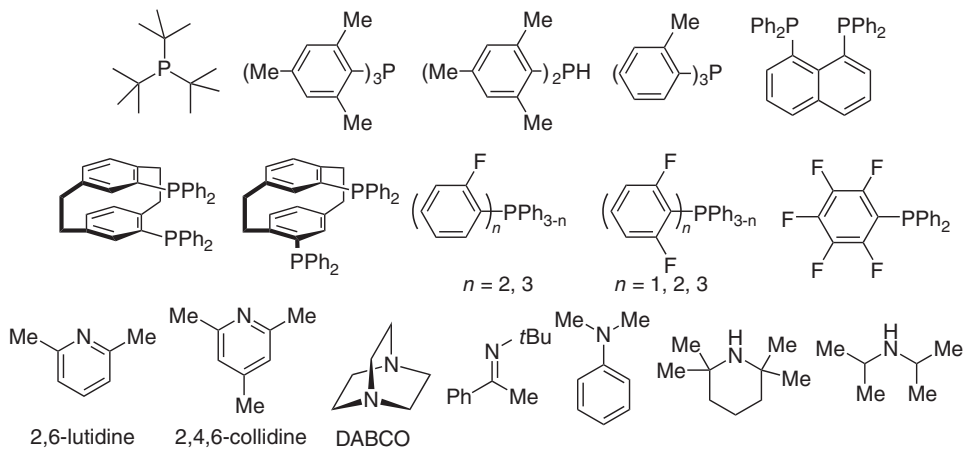


Figure 9.6 Lewis bases for the FLP-mediated H_2 activation.

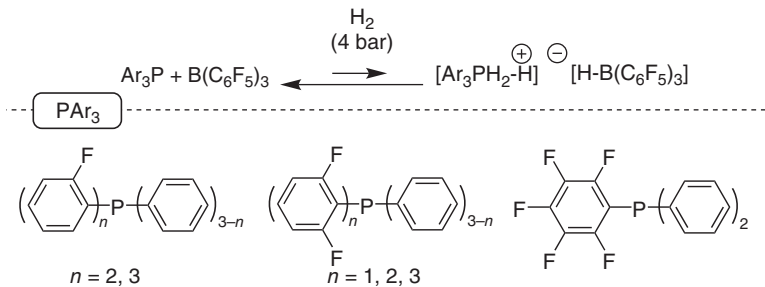


Figure 9.7 Highly reversible H₂ activation using fluorinated triphenylphosphine derivatives [26].

electron-releasing fluorinated phosphines (compare Figures 9.6 and 9.7) also activate H_2 in the presence of $\text{B}(\text{C}_6\text{F}_5)_3$ [26]. At room temperature, the H_2 activation is highly reversible, and only the coexistence of the phosphine and the borane was observed in solution (Figure 9.7).

At low temperatures (−20 to −80 °C) the corresponding phosphonium hydridoborates resulting from the H₂ activation were characterized by ¹H, ³¹P, ¹¹B, and ¹⁹F NMR spectroscopy. Consequently, the onium hydridoborate is formed transiently under hydrogenation conditions (25–120 °C), which is sufficient to perform catalytic reactions. However, the nature of the Lewis base must be adjusted to the catalytic reaction of interest. So far, a general prediction of the best Lewis base for a specific reaction could not be made.

9.3.2

Choice of Lewis Acid

The easier it is to select a suitable Lewis base from a library, the more difficult it is to synthesize new Lewis acids for FLP catalysis. The Lewis acidity determines

the strength of the $\sigma(\text{H}_2)$ orbital interaction. For borane-based FLPs, the commercially available perfluorated borane $\text{B}(\text{C}_6\text{F}_5)_3$ is the most commonly utilized. Its Lewis acidity can be determined by the Gutmann–Beckett [27] or Childs *et al.* [28] methods and was arbitrarily set to 100%. Other Lewis acids can therefore be ranked in stronger or weaker Lewis acidic boranes. A selection of Lewis acids that have been used in H_2 activation is depicted in Figure 9.8.

Although it seems appealing to use strong Lewis acids to enhance the potential for H_2 activation, one needs to take into consideration that an increased Lewis acidity will result in less nucleophilicity of the generated hydride.

The slightly reduced Lewis acidity of **B** compared to **A** (95% vs 100%) might suggest comparable reactivity. Surprisingly, this marginal difference leads to very different chemistries. Both boranes were investigated in the H_2 activation using *o*- ToI_3P as the Lewis base (Figure 9.9) [29].

The $\text{B}(\text{C}_6\text{F}_5)_3$ system split hydrogen at room temperature irreversibly. In contrast, the slightly less Lewis acidic borane $\text{B}(\text{C}_6\text{F}_4\text{H})_3$ was also capable of activating H_2 in the presence of *o*- ToI_3P but displayed reversible behavior. Hence, H_2 was removed under reduced pressure at room temperature.

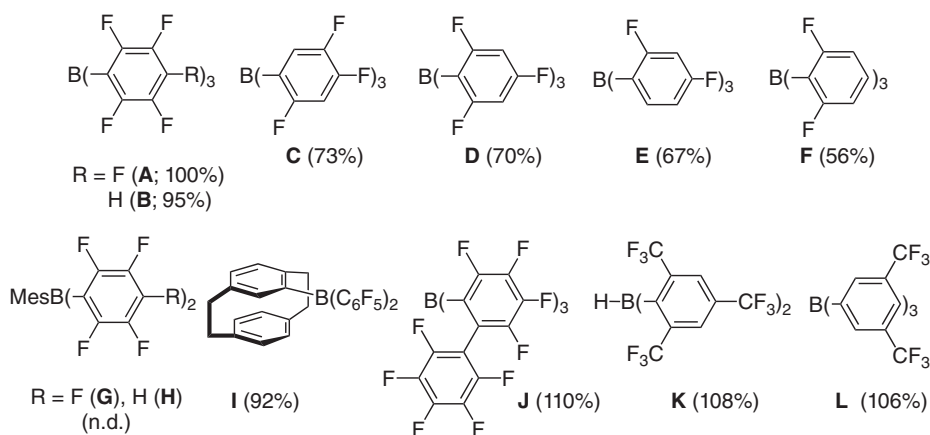


Figure 9.8 Lewis acids A–L for FLP-mediated H_2 activation (percentage in parentheses corresponds to the Lewis acidity with reference to $\text{B}(\text{C}_6\text{F}_5)_3$ (100%,

Gutmann–Beckett method)). **A** [27a]; **B** [29]; **C** [30]; **D** [30]; **E** [30]; **F** [30, 31]; **G** [32]; **H** [32]; **I** [33]; **J** [34]; **K** [35]; and **L** [36].

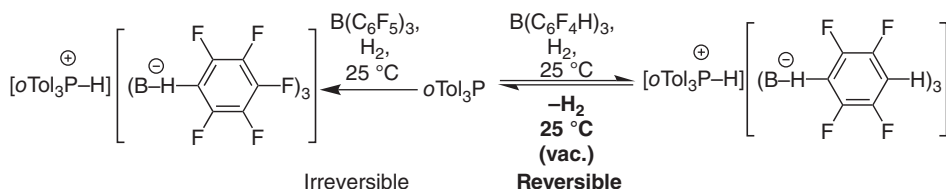


Figure 9.9 Comparison of $\text{B}(\text{C}_6\text{F}_5)_3$ and $\text{B}(\text{C}_6\text{F}_4\text{H})_3$ in H_2 activation [29].

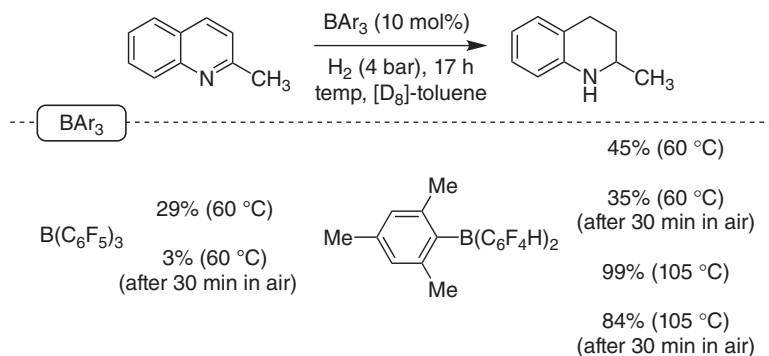


Figure 9.10 Comparative study of B(C₆F₅)₃ and MesB(C₆F₄H)₂ in the hydrogenation of 2-methyl quinoline [37a].

Steric modifications of the Lewis acid can improve the stability of the boranes toward moisture or can lead to increased functional group tolerance. According to the “size-exclusion principle” [32, 37] the two sterically encumbered boranes **G** and **H** displayed increased tolerance toward laboratory atmosphere and functional groups (Figure 9.10).

The sterically more hindered mesityl-substituted borane lost only slightly its activity in the hydrogenation after being stored for 30 min in the laboratory atmosphere. In stark contrast, the perfluorated borane was essentially inactive after being exposed to the atmosphere.

The purely electronic modification of borane-based Lewis acids can also lead to increased functional group tolerance. The weaker Lewis acids might still be involved in adduct formation with substrates bearing Lewis basic sites, but as long as this process is reversible, the amount of free Lewis acid will be available for H₂ activation. Following this idea, triarylboranes with reduced fluorine content were applied in the hydrogenation of substrates bearing strong Lewis basic sites, for example, malonates [30, 38], sulfoxides [30], or nitro groups [30, 31] (see also Section 9.8). Interestingly, the THF (tetrahydrofuran)-adduct of B(2,6-F₂-C₆H₃)₃ could even be applied as catalyst in the hydrogenation of thiophenyl- or furyl-substituted nitroolefins [31]. B(C₆F₅)₃ is irreversibly coordinated by such functional groups (furyl, nitro, small esters, etc.), and catalytic hydrogenations are out of reach.

9.3.3

Intramolecular Frustrated Lewis Pairs

The synthesis of intramolecular FLPs is much more challenging than the synthesis of intermolecular ones, because each – the Lewis base and the Lewis acid – is conveniently prepared and purified separately. Intramolecular FLPs require the installation of the Lewis acid and Lewis base in one molecular entity. Several approaches to meet this challenge have been reported. The most straightforward and most elegant strategy takes advantage of the high reactivity of Piers’ borane (HB(C₆F₅)₂)

[39] toward olefins in the sense of a hydroboration reaction. The reaction of vinyl-bis(mesityl)phosphine with $\text{HB}(\text{C}_6\text{F}_5)_2$ furnished the ethylene-bridged phosphino borane in good yield (Figure 9.11) [2, 15, 40].

The phosphino borane forms a four-membered P/B-heterocycle [11e] by a dative bond from the phosphorous to the boron atom. This intramolecular Lewis adduct is in equilibrium with its “open” form, which in turn is active in the heterolytic H_2 splitting, leading to the phosphonium hydridoborate salt.

The hydroboration can be conducted with other heterovinyl compounds, for example, cyclohexenyl phosphines or simple enamines, to generate the corresponding intramolecular FLP systems. Accordingly, the reaction of $\text{HB}(\text{C}_6\text{F}_5)_2$ with these heterosubstituted olefins furnishes novel P/B [41] and N/B systems [42] in good yields (Figure 9.12).

A second approach toward the synthesis of intramolecular FLPs uses the halide–lithium exchange of aryl bromides and subsequent treatment with bis(pentafluorophenyl)boron chloride ($(\text{C}_6\text{F}_5)_2\text{BCl}$) to introduce the Lewis acidic center. Utilizing this methodology, a selection of intramolecular FLPs was successfully accessed in good yields (Figure 9.13).

This approach can also be used for the synthesis of aniline-derived amino boranes in excellent yields (Figure 9.14) [43b, 44].

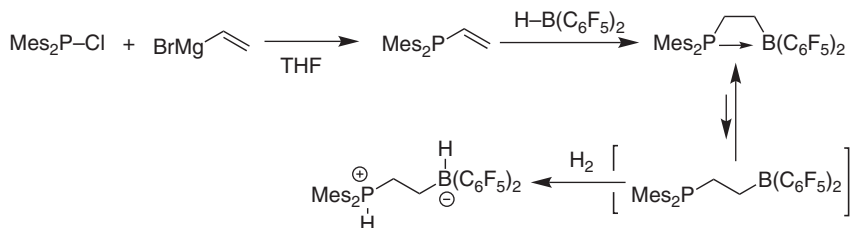


Figure 9.11 Synthesis of ethylene-bridged phosphino borane [2, 15, 40].

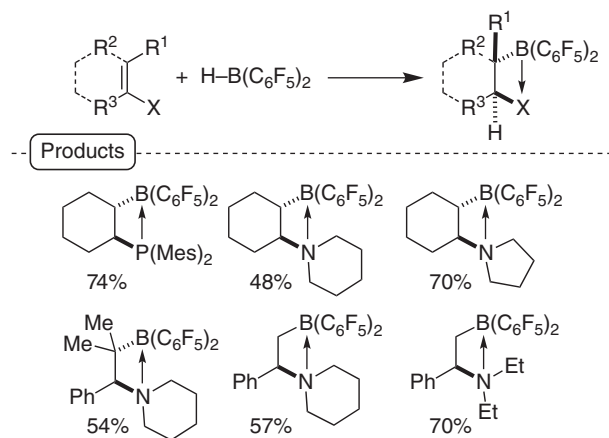


Figure 9.12 Synthesis of vicinal Lewis pairs by hydroboration [41, 42].

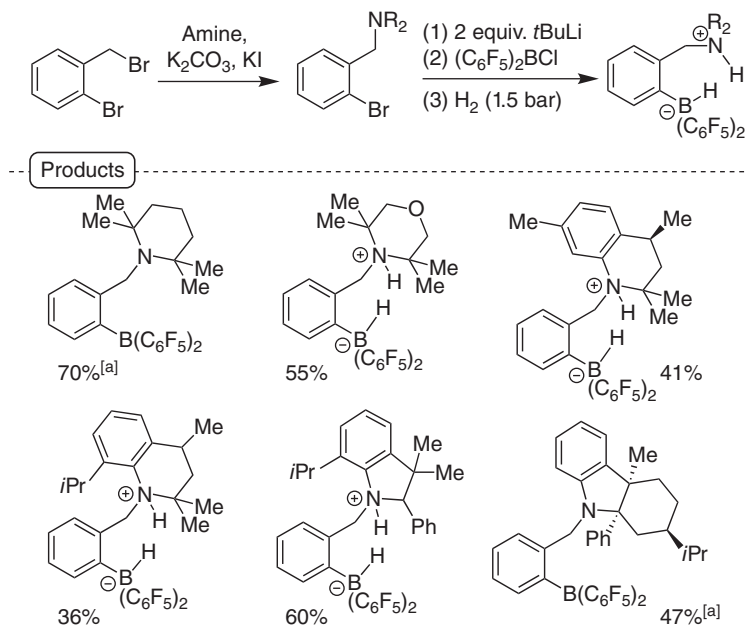


Figure 9.13 Synthesis of intramolecular FLPs bearing aryl boranes (yields correspond to the final step in the synthesis; ^aproduct isolated after second step as aminoborane) [19a, 43].

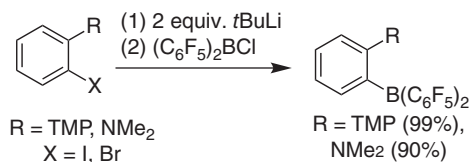


Figure 9.14 Synthesis of aniline-derived amino boranes (TMP = 2,2,6,6-tetramethylpiperidyl) [43b, 44].

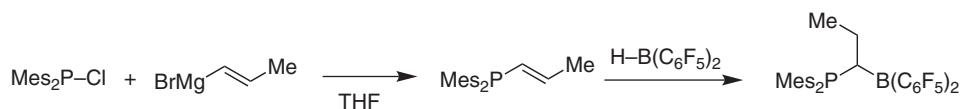


Figure 9.15 Synthesis of geminal P/B-frustrated Lewis pairs [45].

The dimethyl aniline derivative was used in the metal-free *cis*-selective hydrogenation of alkynes (see Section 9.9) [44].

Besides, vicinal geminal intramolecular FLPs also have been reported. Such structures can be efficiently accessed by the reaction of bis(mesityl)propenyl phosphine with HB(C₆F₅)₂ (Figure 9.15) [45].

The key to the synthesis by hydroboration was the introduction of an electron-donating group to the olefin to achieve the formation of the anti-Markovnikov

product. Although H_2 activation using the geminal P/B FLP has not been observed so far, it displays rich addition chemistry to alkenes, alkynes, carbonyls, and azides [46].

9.4

Hydrogenation of Imines

The hydrogenation of imines was the first application of an FLP-mediated hydrogenation using the intramolecular phosphonium borate salt as catalyst (Figure 9.16) [24].

It was noted that imines bearing bulky substituents were quickly converted to the corresponding amines in high yields. However, imines bearing more electron-withdrawing substituents, for example, sulfonyl-groups (SO_2Ph), required higher temperature and longer reaction times, which contributes to reversible adduct formation with the Lewis acid. Also, $B(C_6F_5)_3$ adducts of acetonitrile or benzonitrile were converted to the corresponding primary amines in excellent yields. As only $B(C_6F_5)_3$ -protected nitriles were viable substrates for the FLP-mediated hydrogenation, an additional Lewis base, for example, $PMes_3$, was required to achieve the H_2 activation. Besides, a number of other substrates were susceptible to the aryl-linked phosphonium borate FLP system [15, 24, 40].

The reaction was quickly extended to intermolecular FLPs using directly the corresponding imine as Lewis base for H_2 activation (Figure 9.17) [25].

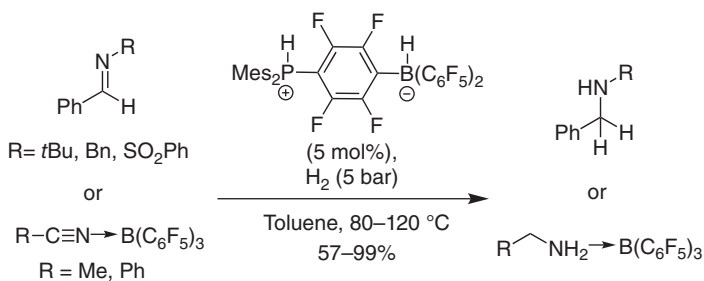


Figure 9.16 Catalytic reduction of imines [24].

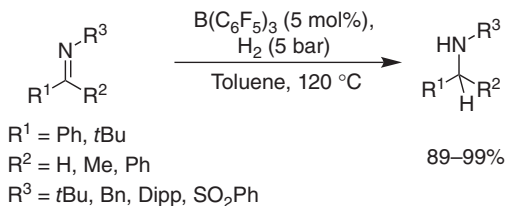


Figure 9.17 Intermolecular FLPs for the hydrogenation of imines (Dipp = 2,6-diisopropylphenyl) [25].

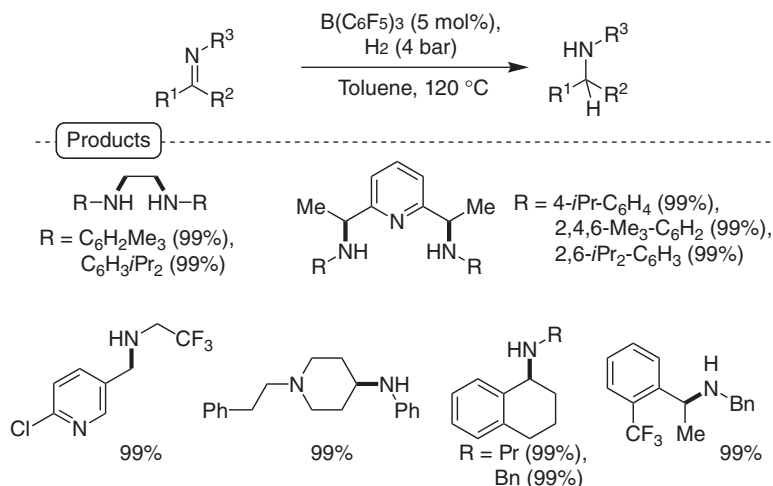


Figure 9.18 Functionalized substrates in the FLP-catalyzed hydrogenation [18].

More challenging substrates were applied in the FLP-catalyzed hydrogenation using a phosphine-free approach (Figure 9.18) [18].

The substrates including unsymmetrical ketimines were converted into the corresponding amines in high yield, while other functionalities, for example, 2-chloropyridines or CF₃ groups, remained untouched.

The reduction of unsymmetric ketimines furnishes chiral amines, and the asymmetric hydrogenation of such substrates using FLP chemistry is highly desirable. One approach is the diastereoselective hydrogenation of enantiopure substrates (Figure 9.19) [18].

For substrates bearing the chiral information in the *N*-alkyl-imino side chain, only low diastereoselectivities (11–65% de) were obtained. For substrates featuring the chiral information in the alkylidene functionality, excellent diastereoselectivities (98–99% de) were obtained combined with high yields. However, the catalytic asymmetric hydrogenation of ketimines is highly desirable and was achieved in a pioneering effort by the application of a chiral borane as Lewis acid, which was obtained by the hydroboration of a camphor-derived olefin with Piers' borane (Figure 9.20) [47].

The methyl-aryl ketimines were hydrogenated in high yield and good enantioselectivity (79–93% ee) using 5 mol% of the chiral borane. The same approach was followed for the synthesis of chiral bisboranes by the hydroboration of 1,1'-binaphthyl derivatives [48], which allowed the quick optimization of the catalyst (Figure 9.21).

The catalytically active bisborane was assembled *in situ* and provided the hydrogenation products in excellent yields (63–99%) and high enantiomeric excess (74–89% ee). Interestingly, the hydrogenation reactions could be performed at room temperature with only 20 bar of hydrogen pressure.

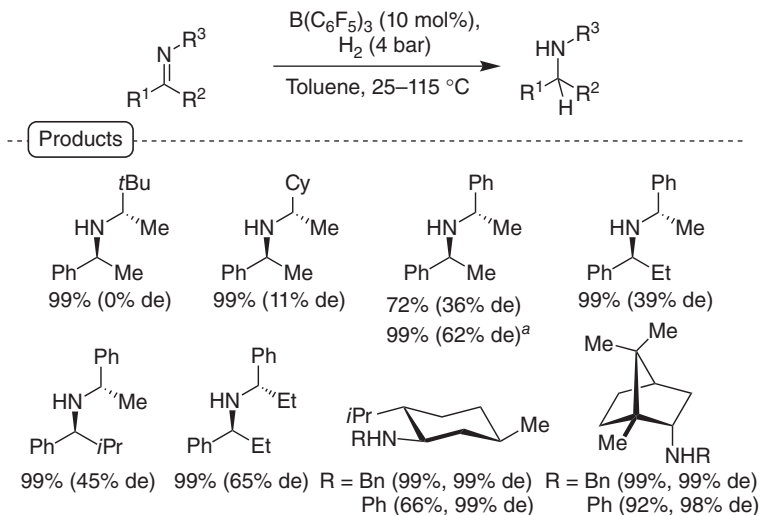


Figure 9.19 Diastereoselective hydrogenation of ketimines by FLP (^areaction performed with 115 bar H₂ pressure) [18].

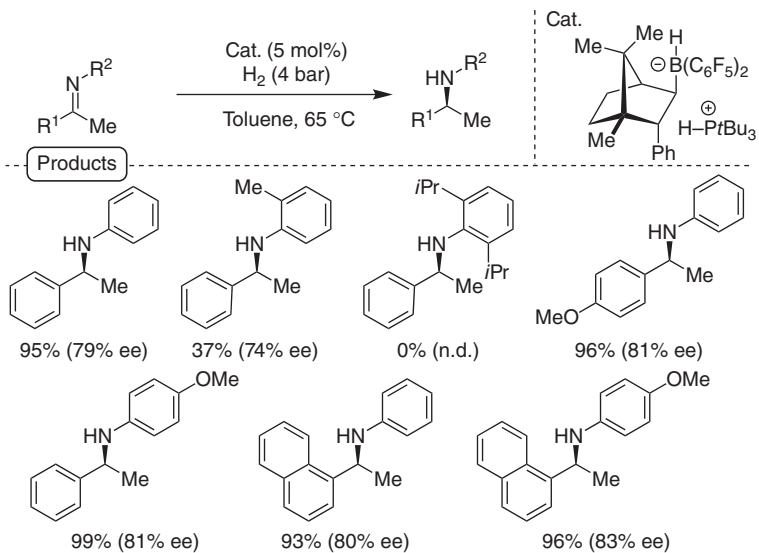


Figure 9.20 Asymmetric hydrogenation of ketimines [47a].

Chiral intramolecular FLPs were derived from readily accessible chiral indolines or quinolines and applied in the asymmetric hydrogenation of selected ketimines (Figure 9.22) [43a].

Although the *ansa*-ammonium borates allow for easy derivatization and steric modulation, only low enantioselectivity for the hydrogenation of imines was observed.

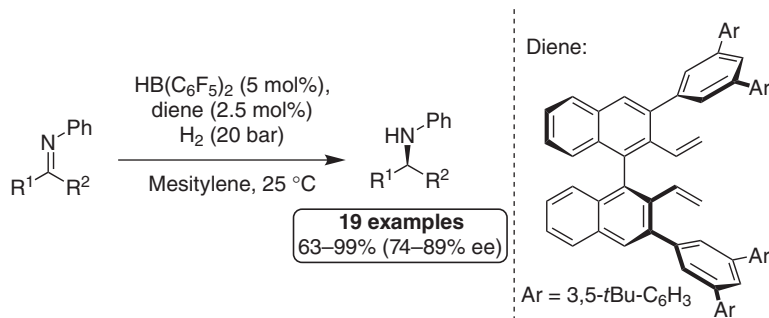


Figure 9.21 Asymmetric hydrogenation of ketimines using a chiral bisborane [48].

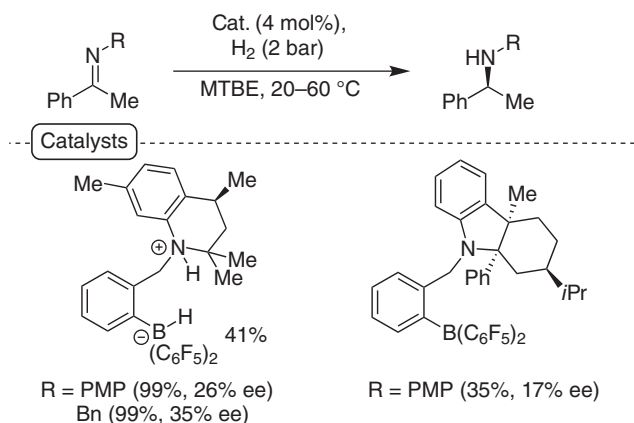


Figure 9.22 Intramolecular frustrated Lewis pairs in the asymmetric hydrogenation of ketimines [43a].

In summary, these observations show that the asymmetric hydrogenation of imines by chiral FLPs is a tremendously challenging task. The enantioselectivity is still not as high as for related Brønsted acid-catalyzed reactions and needs to be improved for potential applications. In addition, the substrate scope must be expanded. So far, only aryl-methyl ketimines have been hydrogenated with good enantioselectivity.

9.5

Hydrogenation of Enamines and Silylenol Ethers

The hydrogenation of enamines was the second reported application of an FLP-catalyzed reaction. This was achieved with Erker's intramolecular frustrated ethylene-bridged phosphino borane (Figure 9.23) [2, 15].

The catalytic hydrogenation likely proceeds via a protonation/hydride transfer to yield the saturated compounds. This mechanistic view is supported by stepwise

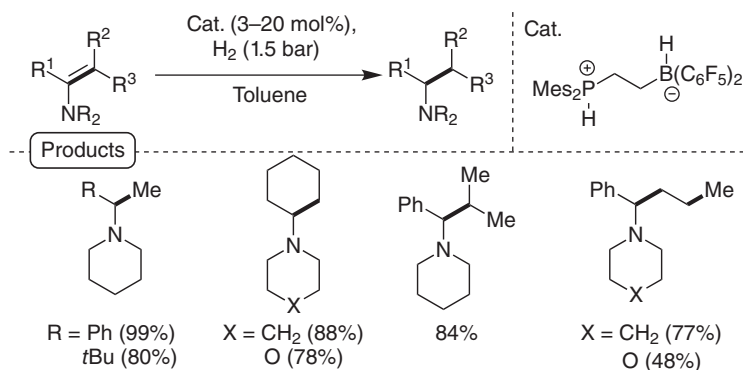


Figure 9.23 FLP-catalyzed hydrogenation of enamines [15, 49].

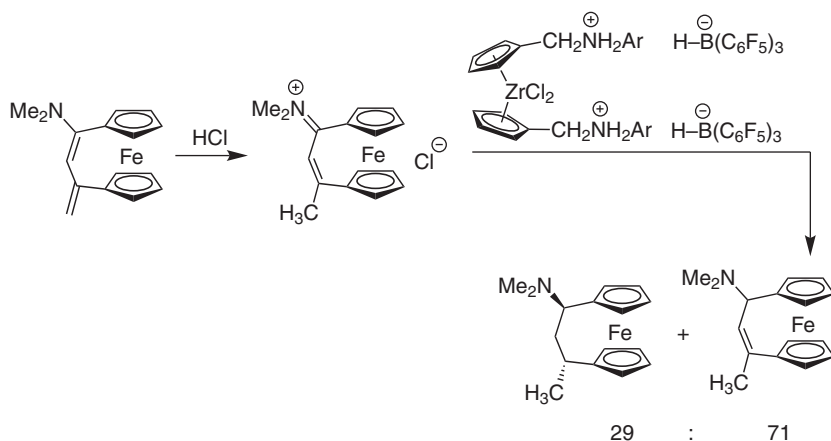


Figure 9.24 Mechanistic rationalization for the hydrogenation of enamines by proton/hydride transfer [40].

protonation/reduction sequence using a [3] ferrocenophane-derived dienamine (Figure 9.24) [40].

The dienamine was selectively protonated with hydrochloric acid at the 4-position, resulting in an electrophilic iminium species. Subsequent anion exchange with $[\text{H}-\text{B}(\text{C}_6\text{F}_5)_3]^-$ furnished the partially and fully reduced [3] ferrocenophane.

A very efficient access to vicinal B/N-based intramolecular FLPs was realized by the hydroboration of simple enamines [42]. The 1-phenylethylene-bridged ammonium borate proved to be the most reactive for the hydrogenation of enamines (Figure 9.25) [42].

Also, other intramolecular [19a, 43b] and intermolecular [32, 37b] FLPs were evaluated as catalysts for the hydrogenation of 1-piperidylcyclohexene or 1-morpholinocyclohexene.

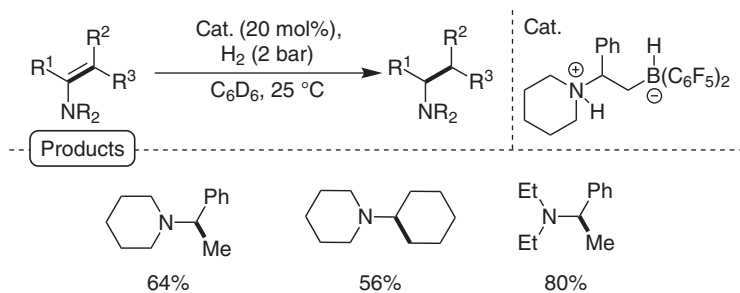


Figure 9.25 Hydrogenation with enamine-derived intramolecular FLPs [42].

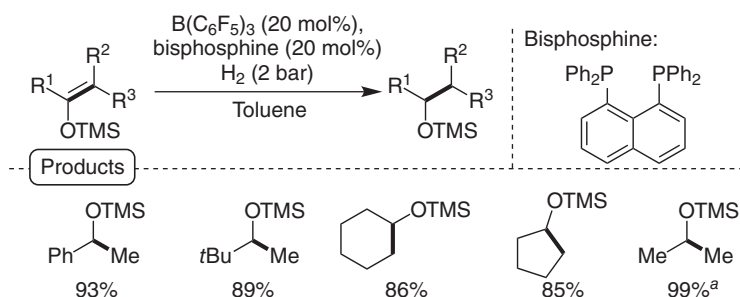


Figure 9.26 FLP-catalyzed hydrogenation of silylenol ethers (^aperformed with 60 bar H₂ pressure) [16a].

A related substance class to enamines is silylenol ethers, which accordingly undergo FLP-catalyzed hydrogenations through the proposed proton/hydride transfer mechanism. So far, only bisphosphines in combination with B(C₆F₅)₃ have been reported as viable catalysts for this transformation. The 1,8-bis(diphenylphosphino)naphthalene was capable of activating H₂ in the presence of B(C₆F₅)₃ reversibly at 60 °C [16a]. The reactivity was exploited for the catalytic hydrogenation of substituted silylenol ethers, furnishing directly silyl-protected secondary alcohols (Figure 9.26) [16a].

This reactivity was later implemented in the first FLP-catalyzed domino reaction [50]. The silylenol ether was generated *in situ* by the Lewis acid-catalyzed 1,4-hydrosilylation [51] of an enone, which was subsequently hydrogenated by a [2.2]paracyclophane bisphosphine-derived FLP (Figure 9.27) [16b, 33].

The FLP reactivity was expanded to the hydrogenation of tetrasubstituted silylenol ethers in excellent yields. Interestingly, the reduction of the double bond was highly diastereoselective, and only the formation of the *cis* diastereomers was observed.

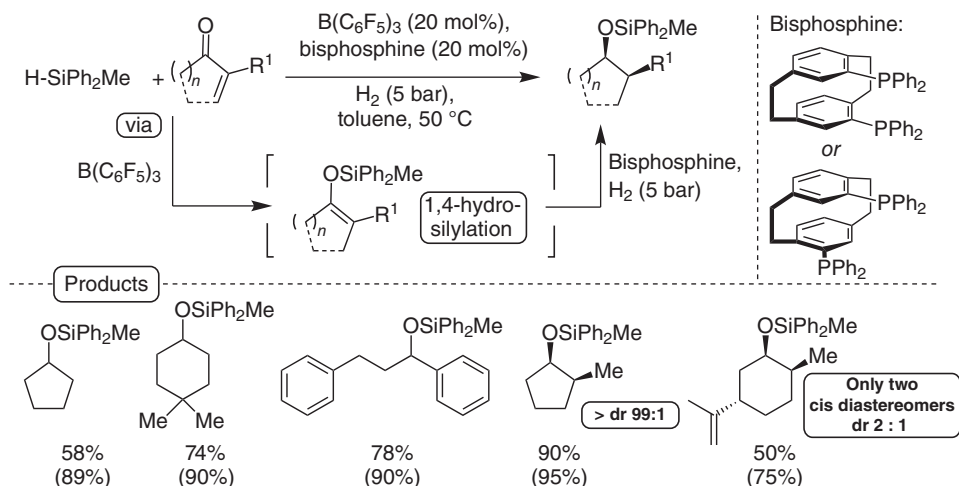


Figure 9.27 FLP-catalyzed domino hydrosilylation/hydrogenation of enones (values in parentheses correspond to yields determined by NMR spectroscopy) [16b, 33].

9.6

Hydrogenation of Heterocycles

Because of the structural relationship of imines and enamines to *N*-heterocycles, it is not surprising that such structures are also susceptible to FLP-catalyzed hydrogenations. However, some considerations must be given to the fact that *N*-heterocycles can be fairly strong Lewis bases, which might lead to Lewis acid deactivation. Consequently, most of the investigated heterocycles feature substituents in ortho position to the heteroatom to guarantee efficient shielding of the heteroatomic site.

Analogous to the phosphine-free hydrogenation of imines, the FLP-mediated hydrogenation of quinoline-derivatives requires only catalytic amounts of the Lewis acid. In the presence of 5–10 mol% $\text{B}(\text{C}_6\text{F}_5)_3$, the corresponding *N*-heterocycles were reduced to the tetrahydro-derivatives in high yields (Figure 9.28) [52].

The hydrogenation of a selection of quinolone derivatives was achieved by the use of a more sterically hindered borane, for example, $\text{MesB}(\text{C}_6\text{F}_4\text{H})_2$, which also enabled increased functional group tolerance (Figure 9.29) [37].

The corresponding tetrahydroquinolines were obtained in good to excellent yields, and, as some exquisite examples, even the hydrogenation of a styryl functionality was observed. The methodology was utilized in the efficient three-step non-enantioselective synthesis of the natural product cuspareine (Figure 9.30) [37a].

The second step comprises the FLP-catalyzed hydrogenation of the pyridine ring and the adjacent double bond, providing access to the core structure of the natural product precursor in 91% yield. Final methylation provided *rac*-cuspareine

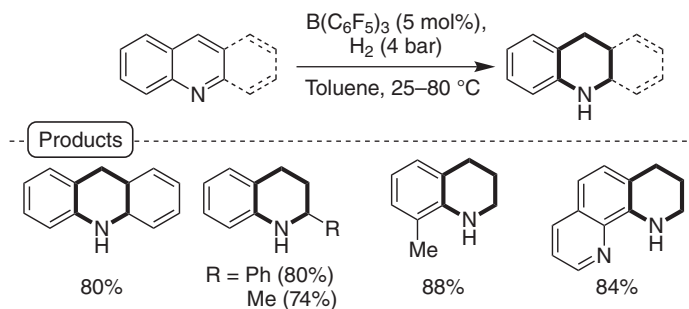


Figure 9.28 FLP-catalyzed hydrogenation of quinolone derivatives [52].

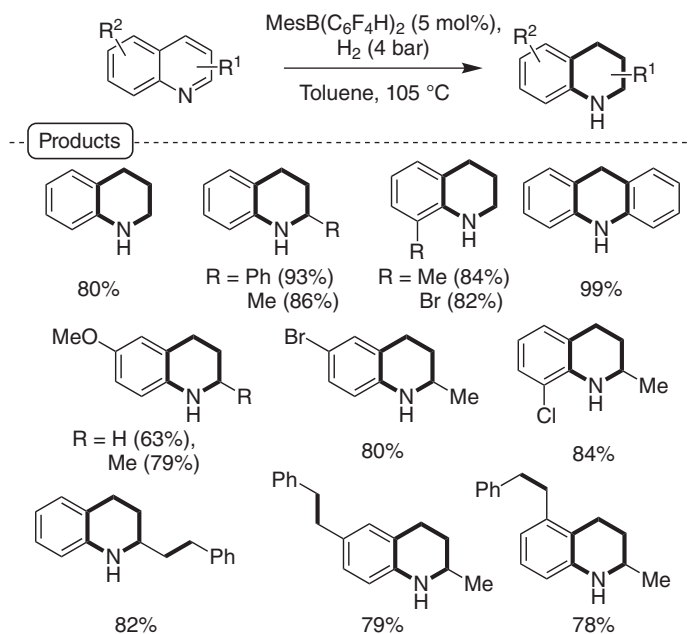


Figure 9.29 $\text{MesB}(\text{C}_6\text{F}_4\text{H})_2$ -catalyzed hydrogenation of quinolines [37a].

in an overall yield of 52%. This short reaction sequence clearly demonstrates that FLP catalysis can emerge as a synthetically useful tool in the synthesis of valuable organic compounds.

The mechanism of the FLP-catalyzed quinolone hydrogenation was investigated by quantum chemical and experimental methods. The analyses support a multi-step mechanism comprising H_2 activation by quinoline/ $\text{B}(\text{C}_6\text{F}_5)_3$ (Figure 9.31).

The resulting protonated quinoline from FLP-mediated H_2 activation is reduced by hydride addition to C2. The generated 1,2-dihydroquinoline is a strong reducing agent and converts the quinoline into 1,4-dihydroquinoline. Finally, the 1,4-dihydroquinoline is fully reduced to the corresponding tetrahydroquinoline.

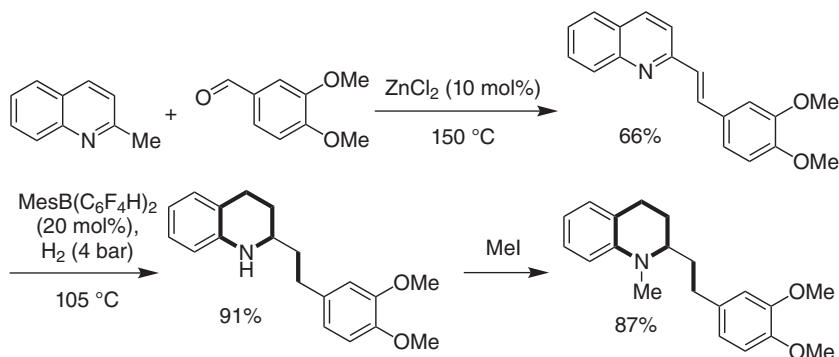


Figure 9.30 Synthesis of (*rac*)-cuspaine [37a].

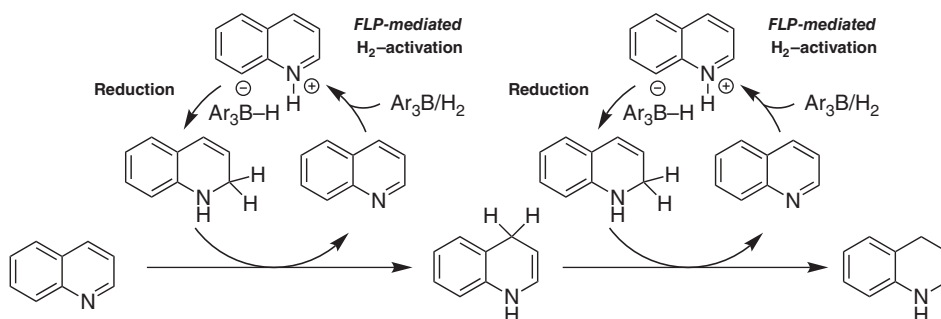


Figure 9.31 Mechanism of the FLP-catalyzed hydrogenation of quinoline [37a].

The reduction of other *N*-heterocyclic compounds was achieved using stoichiometric amounts of the Lewis acid at elevated temperatures (115 °C) [53]. Under these conditions, not only the reduction of the nitrogen-containing heterocycle but also the saturation of the annulated benzo-system in good to excellent yields was accomplished (Figure 9.32).

A catalytic process with an immense scope was developed for the highly diastereoselective hydrogenation of mono- and disubstituted pyridines using the *in situ* formation of the catalytically active, borane-derived Lewis acid. The tertiary borane $\text{C}_6\text{F}_5\text{--CH}_2\text{CH}_2\text{--B(C}_6\text{F}_5)_2$ was assembled by the hydroboration of $\text{CH}_2=\text{CH(C}_6\text{F}_5)$ with Piers' borane ($\text{HB(C}_6\text{F}_5)_2$) *in situ* and used as Lewis acid in the FLP-catalyzed hydrogenation (Figure 9.33) [54].

More than 30 pyridine derivatives were diastereoselectively hydrogenated, providing an unprecedented access to *cis*-2,6-substituted piperidines in excellent yields. The potential of the methodology was demonstrated by the strikingly simple one-step synthesis of isosolenopsin A, which displays antibacterial and anti-HIV activity (Figure 9.34) [54].

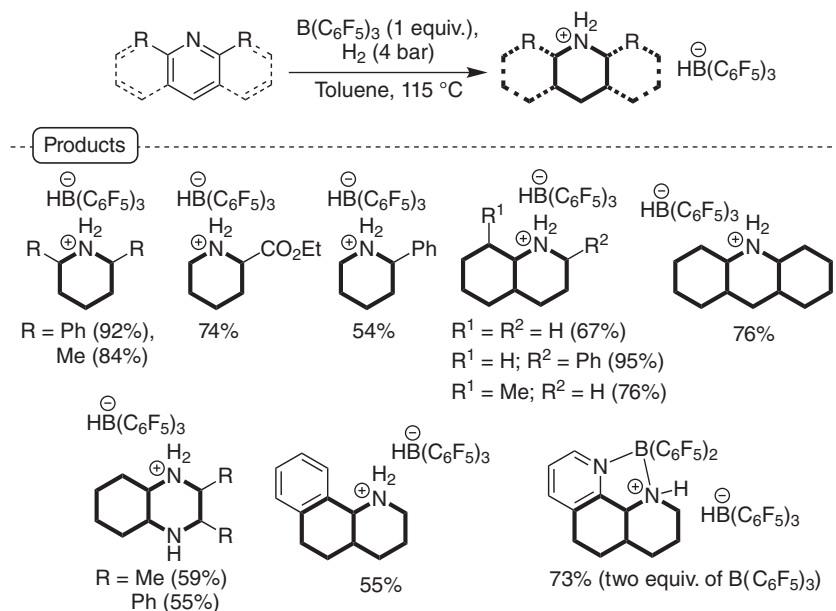


Figure 9.32 Stoichiometric reduction of pyridines, (benzo)quinolines, and quinoxalines [53].

9.7

Hydrogenation of Enones, Alkylidene Malonates, and Nitroolefins

The FLP-catalyzed hydrogenation of functionalized, especially oxygen-containing, groups is highly challenging because of the strong Lewis basic character combined with insufficient steric shielding. Consequently, catalyst inhibition is one of the most problematic issues in FLP-mediated reductions of enones, malonates, or nitroolefins.

The hydrogenation of (*S*)-carvone was achieved using a sophisticated FLP consisting of $\text{MesB}(\text{C}_6\text{F}_5)_2$ in combination with DABCO (1,4-diazabicyclo[2.2.2]octane) (Figure 9.35) [32, 37a].

Although the reaction time of 6 days strikes as quite long, the conditions are extremely mild (4 bar H_2 , 25 °C), comprising the first example of a catalytic reduction of an enone by a FLP.

Also, ynones are susceptible to FLP-catalyzed hydrogenations. Such substrates are particularly challenging, as addition reactions of the FLP to the activated triple bond or carbonyl group [46a,c] are mostly observed [55] (Figure 9.36).

The stoichiometric hydrogenation of ynones to the corresponding *cis*-enones proceeds in high yields using the phosphonium borate salts of intermolecular FLPs consisting of *t*Bu₃P and $\text{B}(\text{C}_6\text{F}_5)_3$ or *cis*-*t*BuCH=C(C_6F_5)B(C_6F_5)₂. However, with substoichiometric amounts of FLP (DABCO/*cis*-*t*BuCH=C(C_6F_5)B(C_6F_5)₂, 20 mol%), the ynone is converted in 80% yield to a mixture of *trans*-enone, *cis*-enone, and ketone in the ratio 50:1.5:1.

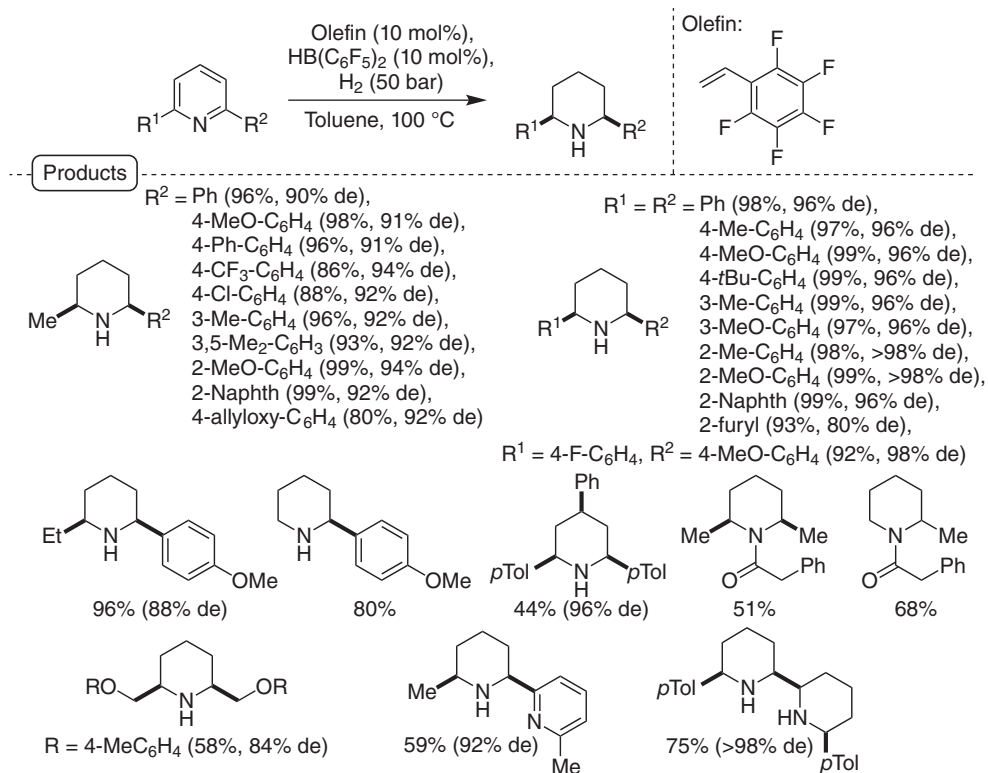


Figure 9.33 FLP-catalyzed hydrogenation of pyridines [54].

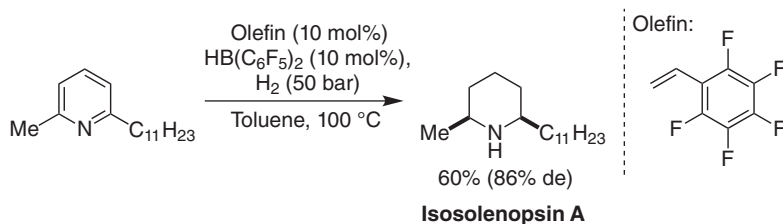


Figure 9.34 Synthesis of isosolenopsin A by FLP-catalyzed hydrogenation [54].

Electron-deficient allenes are hydrogenated in good to excellent yields to afford the corresponding substituted vinyl diethylmalonates using DABCO/B(C₆F₅)₃ (15 mol%, 60 bar H₂, 80 °C, 72 h) as catalyst (Figure 9.37) [38].

The same catalyst system was even more reactive (10 mol%, 60 bar H₂, 80 °C, 24 h) in the hydrogenation of alkylidene malonates, providing efficient access to 2-alkyl malonates in excellent yields within only 24 h (Figure 9.38) [38].

The less Lewis acidic borane B(2,4,6-F₃-C₆H₂)₃ proved to be highly active in the hydrogenation of densely functionalized, activated acrylates, sulfones, and nitroolefins [30]. The excellent functional group tolerance of the borane

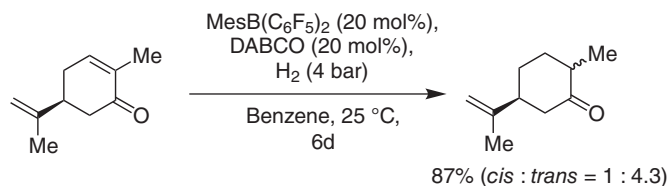


Figure 9.35 Hydrogenation of (*S*)-carvone [32, 37a].

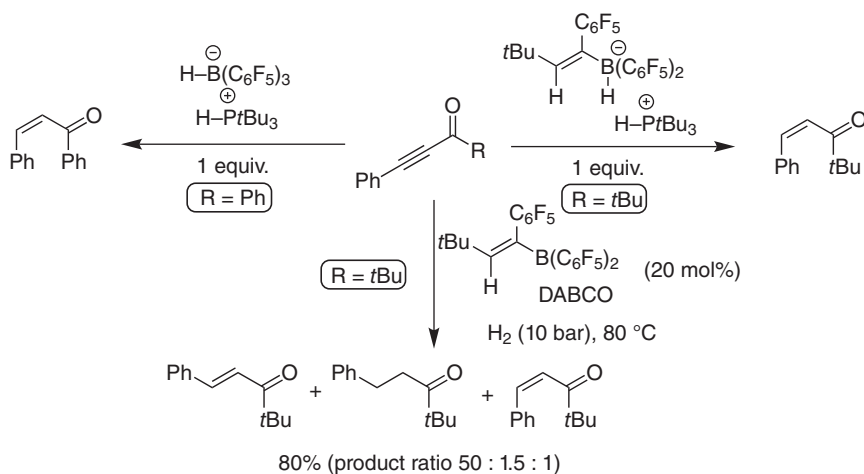


Figure 9.36 Hydrogenation of ynones [55].

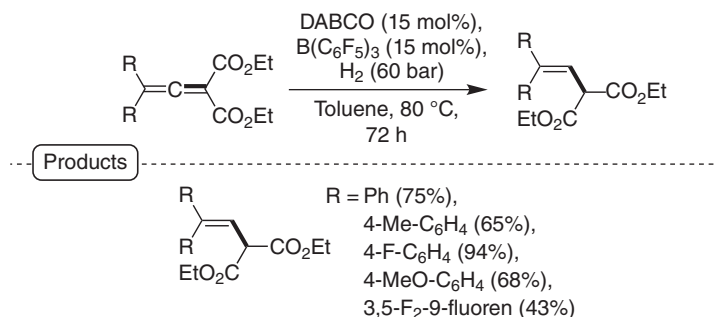


Figure 9.37 Hydrogenation of electron-deficient allenes [38].

is achieved by the reduced Lewis acidity (70% compared to $\text{B(C}_6\text{F}_5)_3$ (100%) according to Childs method) and allows mild reaction conditions (5 mol%, 10 bar H_2 , 50 °C, 24 h; Figure 9.39) [30].

A large selection of nitroolefins were hydrogenated in excellent yields under mild reaction conditions (4 bar H_2 , 40 °C, Figure 9.40) [31]. Here, the even weaker Lewis acidic $\text{B(2,6-F}_2\text{-C}_6\text{H}_3)_3$ (56% according to Childs' method) could be directly utilized as THF adduct as obtained from its synthesis.

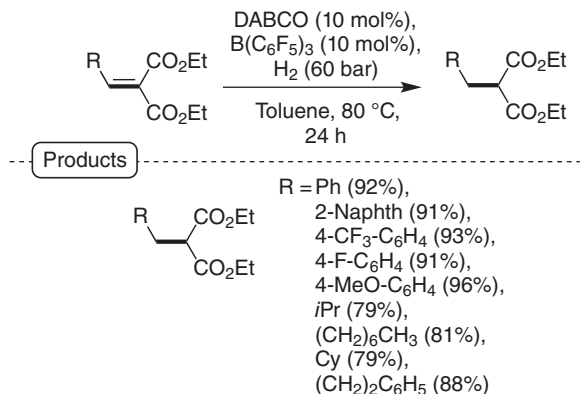


Figure 9.38 Catalytic hydrogenation of alkylidene malonates [30, 38].

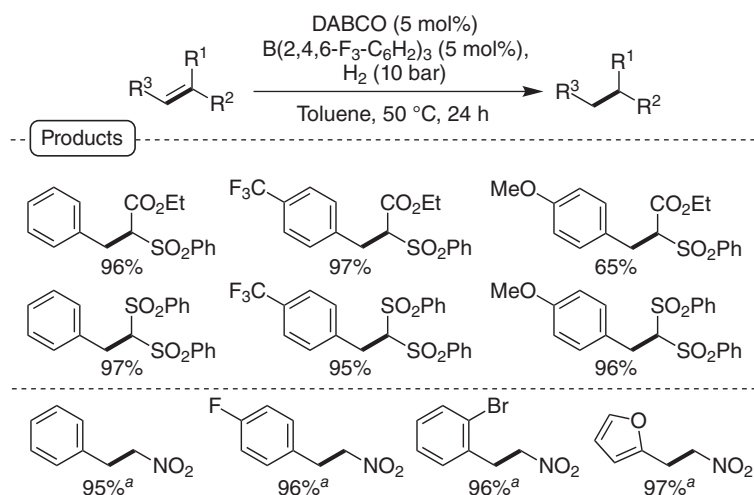


Figure 9.39 FLP-catalyzed hydrogenation of strongly activated acrylates, sulfones, and nitroolefins (^areactions were carried out with 5 bar H₂ pressure) [30].

The combination of B(2,6-F₂-C₆H₃)₃ with 2,6-lutidine as Lewis base allowed the efficient hydrogenation of a number of nitroolefins. Here, not only the nitro-functionality but also even stronger donors such as furyl or thiophenyl are well tolerated. Nitroolefins with substituents in the α-position are highly challenging substrates for metal-free Hantzsch's ester hydrogenations catalyzed by thioureas or phosphoric acid esters. However, 2-nitro-2-methyl styrene was cleanly converted to the nitro alkane in 94% yield in only 24 h. The combination of the Lewis acid B(2,6-F₂-C₆H₃)₃ with collidine was an efficient catalyst for the hydrogenation of alkylidene malonates and acrylates even at room temperature. Even the smallest α,β-unsaturated ester, methylacrylate, was hydrogenated in quantitative yield.

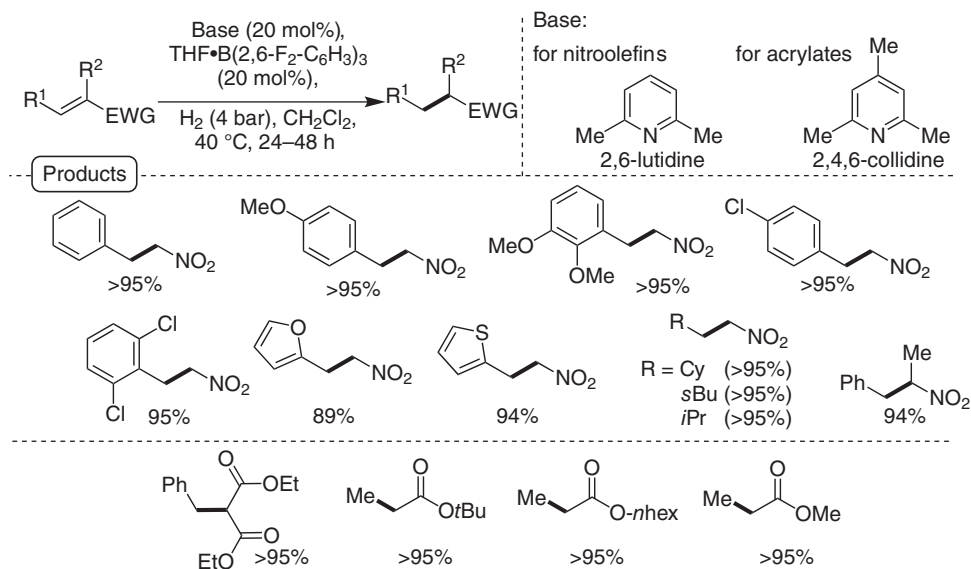


Figure 9.40 Hydrogenation of nitroolefins [31].

The combined observations support the fact that the functional group tolerance of the borane can be achieved by imposing higher steric bulk and/or by electronic modifications.

9.8

Hydrogenation of Unpolarized Olefins and Polycyclic Aromatic Hydrocarbons

One of the oldest and most important applications of the hydrogenation technology is the conversion of unsaturated hydrocarbons to alkanes or alkenes. The hydrogenation of unpolarized olefins is more challenging compared to the reduction of imines or heterocycles because of the absence of activating heteroatomic sites. The activation of double bonds can be achieved either by transition-metal coordination or by reaction with strong electrophiles, for example, hydrohalic acids. The conveyance of such a protonation/addition sequence to FLP chemistry requires the formation of a strong Brønsted-acidic onium ion together with the hydridoborate on H₂ activation. Most of the reported FLP systems derived from Lewis base (phosphine, amine, pyridine, carbene, or phosphinimide)/borane combinations have demonstrated their capability to activate H₂, but none of the resulting Brønsted acids was strong enough to protonate an olefinic double bond.

However, it was found that even weakly electron-releasing phosphines are capable of activating H₂ in combination with B(C₆F₅)₃. The process is highly reversible at room temperature, and the H₂-activation products [Ar₃P–H][H–B(C₆F₅)₃] could be detected by NMR below –60 °C. Such phosphines were used in the

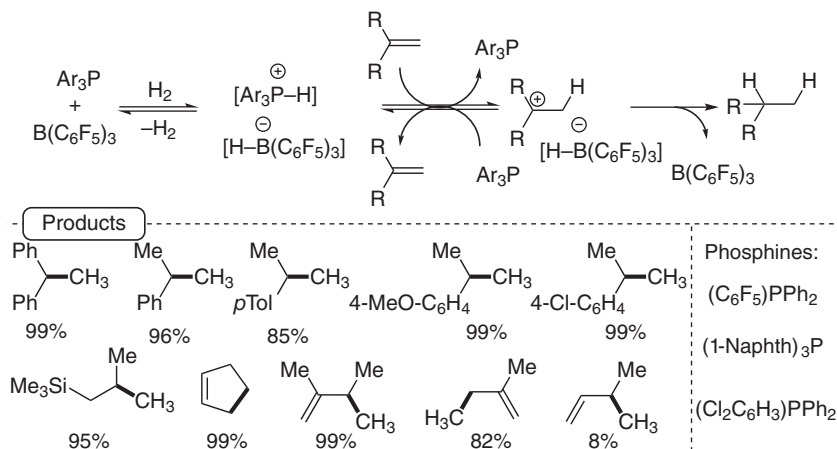


Figure 9.41 FLP-catalyzed hydrogenation of olefins [26b].

first FLP-catalyzed hydrogenation of olefins [26b]. The reaction proceeds via transient hydrogen activation by the FLP, which transfers a proton to the olefin, forming a carbocation which is then irreversibly quenched by the hydridoborate (Figure 9.41) [26b].

The hydrogenation proceeds smoothly with electron-rich olefins in excellent yield. The nature of the Lewis base influences the reaction rate and is responsible for the formation of by-products from Friedel–Crafts dimerization [26a]. Such effects are even more pronounced if less electron-releasing Lewis bases are used. Even diethyl ether can act as the Lewis base in combination with $B(C_6F_5)_3$ as hydrogenation catalyst for olefins. The presence of 2 equiv of Et_2O relative to $B(C_6F_5)_3$ was found to facilitate the H_2 cleavage and was necessary to stabilize the diethyloxonium cation through hydrogen bonding (Figure 9.42) [20].

Experimentally, the H_2 activation was verified by a H–D scrambling experiment which resulted in the catalytic isotope equilibration of H–D to a 2 : 1 : 1 statistical mixture of H–D, H_2 , and D_2 , respectively. However, the hydrogenation experiments with other olefins resulted in the formation of Friedel–Crafts dimers due to the high acidity of the diethyloxonium cation, thus underlining the importance of the Lewis base's nature in FLP-catalyzed reactions.

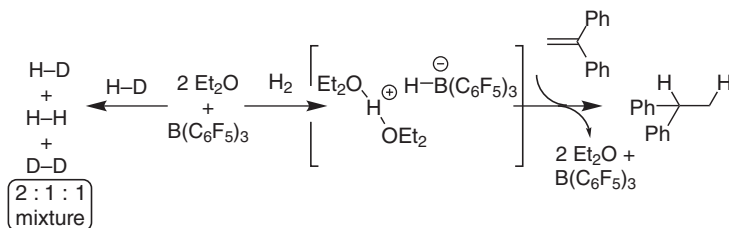


Figure 9.42 H_2 activation by $Et_2O/B(C_6F_5)_3$ [20].

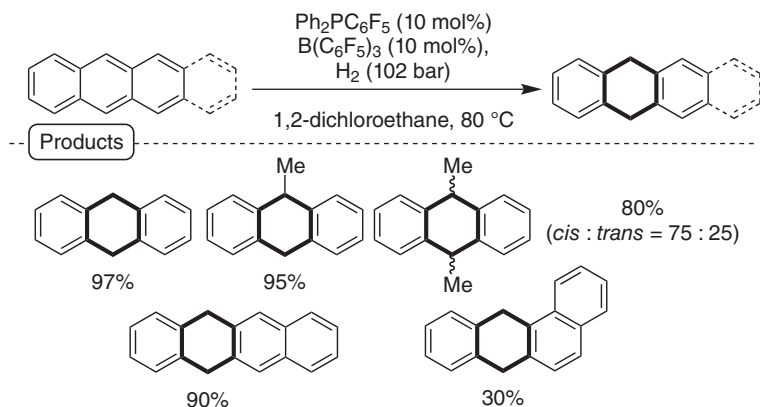


Figure 9.43 Hydrogenation of polycyclic hydrocarbons [20, 56].

Analogous to the hydrogenation of olefins, electron-rich hydrocarbons are susceptible to hydrogenation. Both the $(\text{C}_6\text{F}_5)_2\text{PPh}_2/\text{B}(\text{C}_6\text{F}_5)_3$ and the $\text{Et}_2\text{O}/\text{B}(\text{C}_6\text{F}_5)_3$ systems are active in the FLP-catalyzed hydrogenation of polycyclic aromatic hydrocarbons (Figure 9.43) [20, 56].

The reaction required elevated temperature (80 °C) and 102 atm H₂ pressure to obtain the products within a reasonable amount of time in high yields. The hydrogenation occurred selectively at the highest substituted aromatic ring, leading to isolated, and thus thermodynamically more stable, benzo or naphtha systems.

An alternative approach to the hydrogenation of olefins or alkynes takes advantage of the reactivity of hydroboranes toward olefins.

As an extension of the observation that selected olefins were hydrogenated in the presence of substoichiometric amounts of *triisobutylborane* at 235 °C and 172 bar H₂ pressure [57], Piers' borane ($\text{HB}(\text{C}_6\text{F}_5)_2$) was used in a related reaction. The drastic conditions could be optimized to comparably mild reaction conditions (6 bar H₂, 140 °C) and provided good to excellent yields for a broad selection of substrates (Figure 9.44) [58].

Particularly, higher substituted olefins, for example, methylcyclohexene or 2,3-dimethyl-but-2-ene, were hydrogenated in quantitative yields. The reaction proceeds via the initial hydroboration of the olefin to furnish the diarylalkylborane and subsequent σ -bond metathesis, liberating the saturated product with concomitant regeneration of the hydroborane catalyst.

The stereoselective *cis*-hydrogenation of alkynes was achieved by exploiting an alternative pathway to the σ -bond metathesis: protodeborylation of sp^3 or sp^2 carbon–boron bonds results in the release of the corresponding alkyl or alkene/aryl molecule. The formed FLP catalyst consists of an *ansa*-amino hydroborane, which readily undergoes hydroboration of the alkyne (Figure 9.45) [44].

The resulting vinyl borane is sufficiently Lewis acidic to form the ammonium hydridoborate by H₂ activation. The internal ammonium hydridoborate salt is perfectly set up for the final protodeborylation, releasing the *cis*-olefin under regeneration of the catalyst. The method revealed excellent substrate

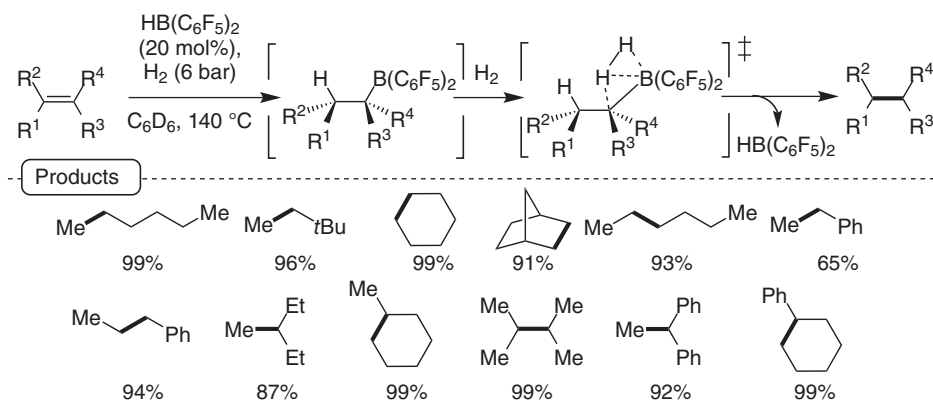
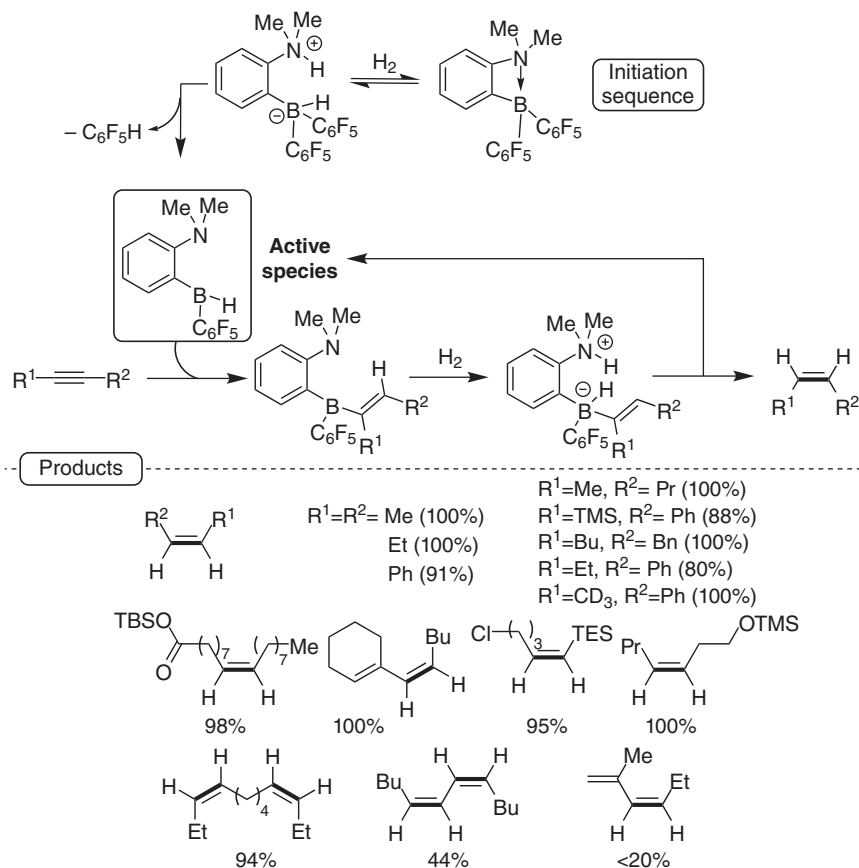
Figure 9.44 Metal-free hydrogenation of olefins involving σ -bond metathesis [58].

Figure 9.45 FLP-catalyzed diastereoselective hydrogenation of alkynes [44].

scope. A large number of alkynes were exclusively converted to *cis*-olefins. Interestingly, the overhydrogenation, a major problem in transition-metal-based hydrogenation, was not observed, and substrates bearing olefinic moieties were chemoselectively reduced. TMS (trimethylsilyl)-protected terminal alkynes and TMS-protected alcohols or esters bearing an alkyne moiety were efficiently converted to the alkenes under mild reaction conditions (2 bar, 80–120 °C), demonstrating the high preparative value for organic synthesis.

9.9

Summary

The FLP-mediated H₂ activation has undergone incredible development from a laboratory curiosity to a synthetically important method for metal-free hydrogenations. The combined interest of inorganic, organic, and physical chemists has led to this fast evolution, which is probably inspired by the strikingly simple concept. However, this concept has proved to be tremendously powerful for the synthesis of novel catalytic systems for the hydrogenation of a number of different substrates. The ever-increasing number of FLP systems allows the customization of the appropriate catalyst for the specific reaction. Exploiting this chemical space is the hydrogenation of not only polarized substrates, for example, imines, enamines, silylenol ethers, heterocycles, or anilines, but also unsaturated hydrocarbons or polycyclic aromatic hydrocarbons.

Abbreviations

2,6-lutidine:	2,6-dimethyl pyridine
2,4,6-collidine:	2,4,6-trimethyl pyridine
bar	pressure unit: 1.024 mbar, 760 Torr
Bn:	benzyl
°C:	degree Celsius
Cy:	cyclohexyl
DABCO:	1,4-diaza-bicyclo[2.2.2]octane
DCE:	1,2-dichloroethane
DCM:	dichloromethane
de	diastereomeric excess
Dipp:	2,6-diisopropylphenyl
Dr:	diastereomeric ratio
ee:	enantiomeric excess
Et:	ethyl
FLP:	frustrated Lewis pair
H ₂ :	molecular hydrogen, dihydrogen
<i>i</i> Pr:	2-methylethyl
K:	kelvin

Me:	methyl
Mes:	mesitylene, 2,4,6-trimethylphenyl
MTBE:	methyl- <i>tert</i> butyl ether
<i>n</i> Hex:	<i>n</i> -hexyl
NMR:	nuclear magnetic resonance
Ph:	phenyl
PMP:	<i>p</i> -methoxyphenyl
py	pyridine
r.t.:	room temperature
<i>s</i> Bu:	<i>sec</i> -butyl, 1-methylpropyl
TBS:	<i>tert</i> -butyldimethylsilyl
<i>t</i> Bu:	1,1-dimethylethyl
TES:	triethylsilyl
THF:	tetrahydrofuran
TMP:	2,2,6,6-tetramethylpiperidine
TMS:	trimethylsilyl
Tol:	4-methyl-phenyl

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10

Catalysis by Artificial Oligopeptides

Fabrizio Mancin, Leonard J. Prins, and Paolo Scrimin

It might appear out of place to devote a chapter on “artificial oligopeptides” in a book centered on cooperativity. However, one should remember that the quintessential catalysts, the enzymes, are based on amino acid sequences and they exploit to a substantial extent cooperativity between the various functional groups present in the lateral chains of the amino acids. Without doubt, cooperativity is at the basis of enzyme catalysis! A critical aspect required to elicit cooperativity in a protein is the presence of well-defined secondary, tertiary (and, sometimes, also quaternary) structures. In synthetic systems when a peptide sequence is too short to assume a precise conformation, this may be achieved in several alternative ways, for instance, by taking advantage of appropriate platforms or by relying on self-aggregation under proper conditions. Cooperativity in this context has many facets: (i) the functional groups may cooperate in the catalytic site; (ii) they may cooperate by preassembling the substrate with the proper orientation to face the active unit; and (iii) they may cooperate to bring in a cofactor and generate a catalytic site. What we present here is an overview of the field, far from being exhaustive, as for accomplishing this task a book would probably not be enough. Because of our interest in catalysis of hydrolysis (or transesterification) reactions most of the examples presented will consider those reactions, though not exclusively. We have reviewed the field in the past from different perspectives [1].

10.1

Cooperative Catalysis by Short Peptides

10.1.1

Unstructured Sequences

Short peptides typically lack the ability to assume a precise conformation in solution. Nevertheless, catalytically active (with hints of cooperativity) short peptides are frequently found in the literature. Here rational design and random selection may be equally successful. Accordingly, a combinatorial approach that by

definition is based on an (almost) totally random selection might be the appropriate choice. Early examples in this regard have been reported by Miller *et al.* [2c,d] who have described the synthesis of a 39-member library of 5-amino acid peptides as catalysts in converting *myo*-inositol into *D*-*myo*-inositol-1-phosphate. One of the members turned out to be an extremely efficient kinase mimic. Delivery of a phosphoryl group to exclusively one of the three hydroxyl sites of the substrate was observed with an ee > 98%. Further focusing of the library led to even more remarkable results. Although previous work by the same group (see below) using conformationally restrained short sequences in asymmetric transacylation reactions [3] led to promising results with high enantioselectivity factors (>50), the peptide discovered in the combinatorial screening performed reasonably well, even though it was not structured. More research is needed to understand the geometry of the catalyst–substrate complexes in order to propose a rationale for these results; nevertheless, it appears evident that some sort of cooperativity is in action here.

With the aim of discovering new peptide-based catalysts for alkene epoxidation from metal-binding combinatorial libraries Francis and Jacobsen [4] used a combinatorial approach similarly to what did Berkessel and Herault [5] to prepare hydrolytic metallopeptides for the cleavage of phosphates. They synthesized a 625-member library of undecapeptides. Their strategy allowed the direct on-beads screening of the library with a chromogenic model phosphate. In this way they were able to find active hits whose efficiency was also tested in homogeneous solution. Combinatorial optimization of the tripeptide Xaa-Xaa-His (where Xaa is a generic amino acid) for complexation to Ni(II) and deoxyribose-based (oxidative) cleavage of B-form DNA was also performed by Long and his coworkers [6]. The procedure these authors have employed involved the generation of two libraries (by using 18 naturally occurring amino acids and excluding Cys and Trp) in which the first and second position of the ligand were varied. The optimized metallopeptide Ni(II)-Pro-Lys-His was found to cleave DNA an order of magnitude better than Ni²⁺-Gly-Gly-His, the reference compound used as a starting point for the selection process.

Miller's group discovered [7] different oxidation catalysts capable of furnishing different isomers of epoxy farnesol and related compounds that are minor products of generic peracid-based olefin epoxidation. The approach they have used relied on split-pool combinatorial synthesis that allows for an evolutionary development of catalyst optimization [8]. Peptide A (Figure 10.1) appeared to operate via a hydroxyl-directed mechanism, analogous to the Sharpless asymmetric epoxidation and with comparable selectivity. Peptide B (Figure 10.1) provided, on the contrary, unprecedented selectivity as a catalyst for the internal olefin of farnesol with substantial site selectivity but modest enantioselectivity.

A tripeptide-derived small molecule catalyst [9] was developed by Miller's group for the dynamic kinetic resolution of racemic biaryl substrates. The reaction proceeded via an atropisomer-selective electrophilic aromatic substitution reaction using simple bromination reagents. The result was an enantioselective synthesis

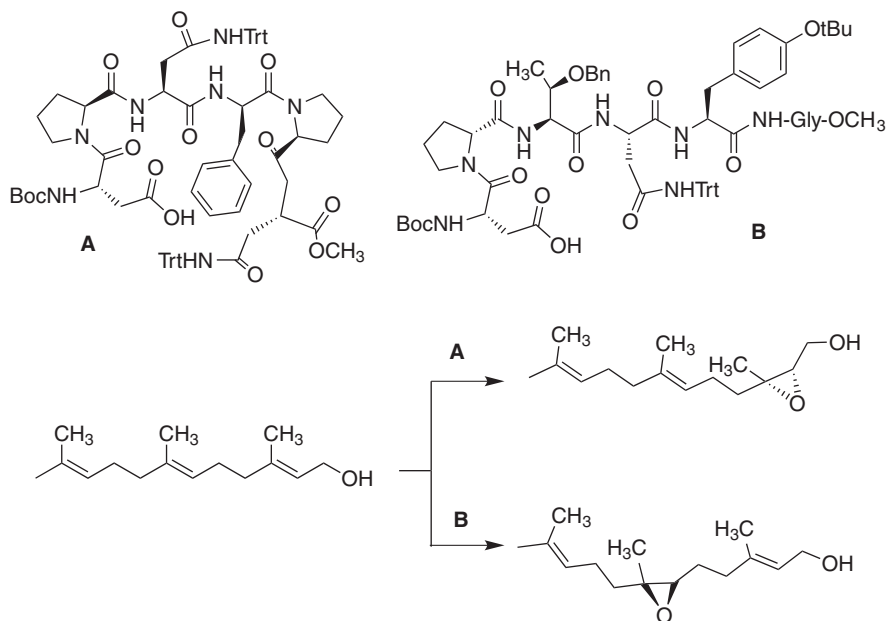


Figure 10.1 Peptides selected after combinatorial screening by Miller *et al.* [7] for the selective epoxidation of the polyene farnesol. The two peptides are very selective for two quite different double bonds. Conditions:

(A as catalyst) peptide (10 mol%), HOBT, DMAP, DIC (1 equiv.), H₂O₂ (2 equiv.), DCM, 4 °C, 7 h; (B as catalyst) peptide (10 mol%), HOBT (10 mol%), DMAP (10 mol%), 1.1 equiv. DIC, 1.5 equiv. H₂O₂, CHCl₃, –12 to –18 °C.

that delivered chiral nonracemic biaryl compounds with excellent optical purity and good isolated chemical yields.

Wennemers group is also very active in the combinatorial screening of peptide-based catalysts [10]. Although they have also prepared catalysts by rational design [11] (see below), they have reported a number of examples of combinatorial screening [12]. By preparing, screening, and evaluating a medium-size one-bead–one-compound library using the catalyst–substrate coimmobilization strategy [12a], they identified two tripeptides both showing higher activity and selectivity in catalyzing a range of aldol reactions than previously tested catalysts prepared by “rational” design. In an important paper published in 2008 [13] Wennemers has tried to clarify how important the spatial arrangement of functional groups is in the asymmetric aldol reaction catalyzed by short peptide sequences. Her conclusion was that even seemingly small structural changes, like an additional methylene group, had significant effects. The results demonstrated the difficulty in rationally designing an asymmetric peptide catalyst and highlighted the value of smart combinatorial screening methods for catalyst discovery. Generally speaking, Wennemers’ work makes for an excellent connection with the next paragraph because the presence of the Pro-Pro-Xaa sequence in most of her catalysts indicates that, if not a well-defined structure, at

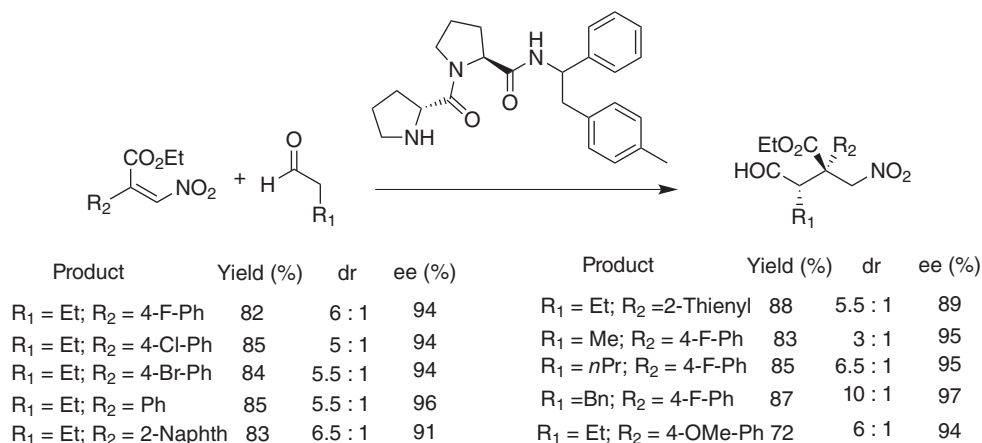


Figure 10.2 Results obtained in the conjugate addition reaction of aldehydes to β,β -disubstituted nitroolefins catalyzed by the peptide H-D-Pro-Pro-NHCH(Ph)CH₂-4-Me-C₆H₄ to afford synthetically versatile

γ -nitroaldehydes with an all-carbon quaternary stereogenic center adjacent to a tertiary stereocenter by Wennemers [14]. Yields were generally high and ee very impressive.

least a reduced conformational freedom of the catalyst is required. Her latest and most beautiful example has just been published. The group has shown [14] that the peptide H-D-Pro-Pro-NHCH(Ph)CH₂-4-Me-C₆H₄ is a powerful catalyst for the conjugate addition reaction of aldehydes to β,β -disubstituted nitroolefins in high yields and stereoselectivities. The γ -nitroaldehydes were obtained with high chemoselectivity over competing homo-aldol products and provided easy access to novel $\gamma^{2,3,3}$ -amino acids, γ -butyrolactones, and chiral pyrrolidines bearing all-carbon quaternary stereogenic centers (Figure 10.2).

The authors pointed out that their catalysts, lacking a carboxylic acid moiety, were better suited for the studied reaction compared to the peptides bearing a proton donor that had been found to be optimal for similar reactions. They suggested that steric shielding and/or interaction between the aromatic portion of the catalyst and the β,β -disubstituted nitroolefin are critical for favoring the desired conjugate addition over the competing aldol reaction. Likely here, a subtle (cooperative) interplay of interactions between the aromatic portion of the nitroolefin and that of the catalyst as well as a H-bonding with the NH bond of the peptide and the aldehyde is in action.

Racemic β -hydroxy ketones were kinetically resolved into the enantiopure isomers and (E)- α,β -unsaturated ketones using catalytic asymmetric intramolecular dehydration by Da *et al.* [15]. They prepared tetrapeptides to imitate fatty acid dehydratases to efficiently discriminate racemic β -hydroxyketones and enantioselectively catalyze the intramolecular dehydration. Mechanistically, the high discrimination of the racemic substrates and successive enantioselective dehydration were highly dependent on the cooperative catalysis of the NH₂ and COOH groups of the peptides.

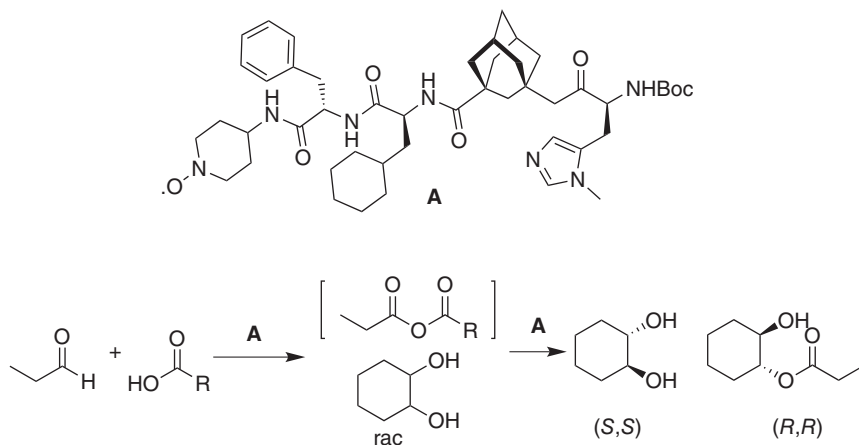


Figure 10.3 The peptide used by Schreiner's group [18] to catalyze cascade reactions. The aldehyde was oxidized by the TEMPO residue and the incipient

acid enantioselectively esterified (±)-trans-cycloalkane-1,2-diols taking advantage of the presence of the methylimidazole.

Finally, to complete the analysis, we would like to present interesting results by the Schreiner group. They have reported [16] the efficient and highly enantioselective kinetic resolution of trans-cycloalkane-1,2-diols utilizing an enantioselective Steglich reaction with a variety of carboxylic acids that form the corresponding anhydrides *in situ*. Previously, they had shown that a lipophilic peptide catalyst was effective in the desymmetrization of vicinal *meso*-diols, and that this catalyst did not hamper the subsequent one-pot oxidation of the monoacylated product [17]. This opened the interesting possibility to put both catalytic units on the same catalyst. In fact, the most exciting results, convincingly supporting cooperativity within the same peptide catalyst, were those in which they demonstrated [18] the application of a multicatalyst to both oxidize and acylate a substrate. A peptide bearing both a methylimidazole as a nucleophile and a TEMPO residue (for oxidation) was used for the kinetic resolution of *meso* alcohols followed by oxidation to the ketone [18a]. More recently, the oxidation of a broad variety of aldehydes and subsequent enantioselective esterification of the incipient acids with (±)-trans-cycloalkane-1,2-diols was demonstrated (Figure 10.3) [18b].

10.1.2

Structured Sequences

Inspired by enzyme models, Miller and coworkers started embedding nucleophiles in conformationally restricted peptide structures in order to discover catalysts for asymmetric acyl-transfer reactions [3b,c,d]. Their sequences, incorporating at least a Pro residue, appear structurally not much different from those reported by Wennemers. The reason why those of Wennemers are reported in the unstructured peptide section is connected to the fact that Miller's peptides

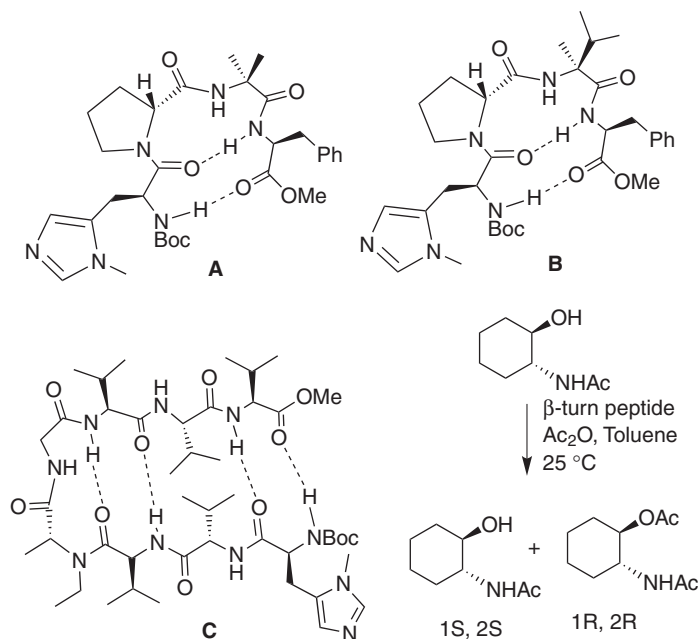


Figure 10.4 Peptides used by Miller's group for the kinetic resolution of *trans*-(±)-*N*-(2-hydroxycyclohexyl)acetamide. Here the catalytic unit was *N*-methylhistidine while enantioselectivity was provided by the secondary structure of the peptide [3].

present additional features that ensure a well-defined β -turn conformation. In Miller's peptides histidine residues served as nucleophiles for the kinetic resolution of *trans*-(±)-*N*-(2-hydroxycyclohexyl)acetamide. The enantioselectivity resulted from the secondary structure that allowed the formation of preferential interactions of one enantiomer with the peptide backbone. Control peptides lacking the secondary structure gave no selectivity at all. Importantly, a strong correlation was observed between the rigidity of the β -hairpin structure and the enantioselectivity of the catalyst [3c]. This hypothesis was confirmed by studies of related catalysts in which the β -turn inducing Aib-residue (where Aib is α -amino isobutyric acid) was replaced by other C^α -tetrasubstituted amino acids (Figure 10.4) [19].

Conformational analysis by ^1H NMR spectroscopy and FT-IR confirmed that the conformational constraint played a key role in the enantioselectivity of the catalyst. It was concluded that the changes in the selectivity factors were not because of weaker interactions, but rather due to the existence of a larger number of possible interaction modes that were not at all selective for one of the two enantiomers. As suggested by the conformational studies, the existence of such multiple interaction modes is caused by the absence of hydrogen bonds strong enough to stabilize the β -hairpin conformation thus allowing the *N*-methylimidazole to reside above or below the catalyst. In the above examples the conformationally constrained

peptide recognizes the substrate and properly places it with the optimal geometry to face the functional groups that are active in the catalytic process.

Further elaborating on their concept, Miller *et al.* have developed [20] a new strategy for the kinetic resolution of formamides and thioformamides based on their β -turn tetrapeptide catalyst. Optimization of the catalyst structure led to the identification of critical features. For instance, replacement of L-valine with L-phenylglycine enhanced selectivity, while a peptide with D-pipecolic acid in place of D-proline was less selective. This lent further support to the relevance of the secondary structure of these peptide catalysts. Moreover, modification at the N- and C-termini proved important, revealing that when the N-terminal substituent was changed from Boc to acetyl, the selectivity was enhanced. The authors speculated that the changes may be because of a more robust β -hairpin structure associated with a stronger amide-to-amide hydrogen bond.

Through a backbone modification strategy Chen and Qu [21] have prepared thioamide and sulfonamide as the isosteres of amide and introduced them in the β -hairpin secondary structure. The thioxo peptides also adopted β -hairpin conformations as did the oxopeptide. This was supported by the combined use of NMR, IR, and X-ray techniques. Thioxo tetrapeptide formed a more constrained β -hairpin conformation and therefore delivered much higher enantioselectivity in the same reaction. Moreover, the examination of the conformational changes of tetrapeptide on the protonation of the *N*-methylhistidine moiety provided evidence to explain the variation of its catalytic efficiency in the asymmetric *acyl*-transfer reaction.

Longer peptides or peptides presenting structuring amino acids may fold into well-defined secondary conformation. In these cases the possibility to elicit cooperative interactions between functional groups is highly enhanced. One of the earliest examples of a catalytically active sequence was reported by Benner *et al.* in the early 1990s [22]. The oligopeptide H₂N-Leu-Ala-Lys-Leu-Leu-Lys-Ala-Leu-Ala-Lys-Leu-Leu-Lys-Lys-CONH₂ aggregates at relatively high concentration into a four-helix bundle characterized by significant helical content. It catalyzed the decarboxylation of oxaloacetate via an imine intermediate with 3 orders of magnitude rate acceleration with respect to the uncatalyzed reaction. Cooperativity was the result of the bundle formation producing a critical decrease of the pK_a and stabilization of the anionic transition state via electrostatic interactions with the cationic lysine residues. A second early example came from the group of Baltzer. By exploiting the conformational preference of designed 42 amino acid sequences for a helix-loop-helix conformation [23], they have systematically modified specific residues in key positions of the oligopeptide in order to catalyze the hydrolysis and transesterification reactions of *p*-nitrophenyl esters [24]. Imidazole-functionalized peptides obtained by introducing several histidines in the sequence were able to provide substrate recognition and accelerations exceeding 3 orders of magnitude compared to *N*-methylimidazole. The reaction mechanism took advantage of the cooperativity of two adjacent histidines, one acting as the nucleophile and the other one as a general base. In the case of flanking His-Lys sequences the unprotonated form of the histidine attacked

the ester in the rate-determining step of the process. If several lysine residues were present, at low pH, only those that flanked the His were acylated [25, 26]. Barton and her group [27] reported the activity of Zinc-binding peptides tethered to Rhodium intercalators as catalysts for DNA hydrolytic cleavage. In these systems the intercalator provided DNA binding affinity while the metal-binding peptide contributed the reactivity. The strategy appeared to be rather general as Zn(II)-promoted DNA cleavage was observed for two rather different tethered metallopeptides. The structural feature of one of the two was such to place two imidazole units of histidines facing each other in an α -helical conformation. In this way they were directly involved in the binding of the metal ion. The other was modeled after the active site of the *Bam*HI endonuclease. Cooperativity in this system was operative at the level of binding of the metal ions in such a way that Zn(II)-catalyzed DNA cleavage could be exploited. What appeared particularly critical was the binding of the peptide to the substrate, in line with data we have obtained in our own laboratory [28].

The relatively old repertoire of catalytic peptides cannot but include the helical peptides (polyalanines and poly-leucines) reported by Julià and Colonna as catalysts for the asymmetric epoxidations of chalcones [29]. The original report required a complex triphasic system to achieve high levels of stereoselectivity. To make the reaction more appealing subsequent research has focused on developing milder reaction conditions. This led to a broader substrate scope and a better understanding of the mechanism [30]. In this regard Berkessel proposed that the reaction is governed by the N-terminus of individual and helical peptide strands (Figure 10.5) [31]. Very recently, he has shown [32], by NMR spectroscopy, that L-Leu₆, one of the shortest peptides active as a catalyst in this asymmetric epoxidation, forms a stable 3₁₀-helix in DMSO. The presence of this ordered structure lent support to the mechanistic model in which the N-terminus acts as an oxyanion hole that interacts with the β -hydroperoxyenolate intermediate of the Julià-Colonna reaction. Cooperativity between the charge and structure is hence in action.

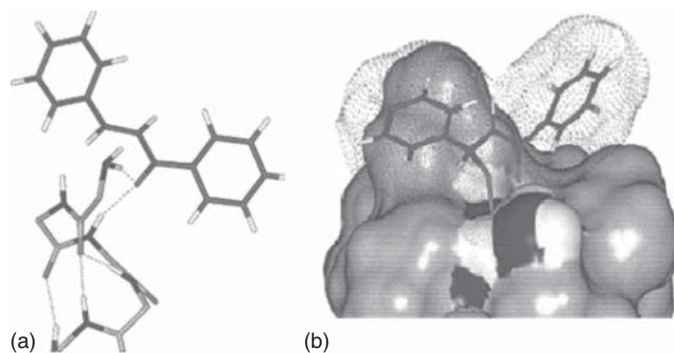


Figure 10.5 In the Julià and Colonna epoxidation of chalcones, Berkessel has proposed that the binding of the chalcone occurs at the N-terminus of a peptide α -helix (a) while

the delivery of a hydroperoxide anion to the α -carbon atom of the enone substrate occurs with face selectivity (b) [31b].

Tanaka *et al.* [33] in their search for applications of structurally well-defined peptides reported the synthesis of chiral, cyclic amino-acid-containing peptide catalysts, for achieving asymmetric epoxidation in a Julià-Colonna-like reaction. They, too, revealed the relationship between the helical structures and enantiomeric excesses and were able to enhance the peptide efficiency by taking the hydrogen bonding pattern of helices into consideration.

An interesting approach to the engineering of functional, structured peptides is the introduction of synthetic unnatural amino acids in the sequence. This may allow one to limit the conformational freedom of the oligopeptide or, alternatively, to introduce functional groups that are otherwise not available [34]. Several years ago we have synthesized the artificial amino acid ATANP [(S)-2-amino-3-[1-(1,4,7-triazacyclononane)]propanoic acid] [35] and incorporated it in a wide variety of oligopeptides. ATANP is characterized by the presence of triazacyclononane in the side chain, which forms 1 : 1 complexes with metal ions such as Cu(II) and Zn(II) with strong affinities. Subsequently, we extended the family of these amino acids with two new members incorporating, in the side arm, a 1,5,9-triazacyclododecane and 1,4,7,10-tetraazacyclododecane [36]. As mentioned above, metal ions play an essential role in the hydrolysis of DNA and RNA. Because at least two of them are required for maximum efficiency of the catalyst, in collaboration with Baltzer's group, a 42-mer peptide analogous to the one reported previously by the Swedish group (see above) was synthesized, with the difference that these new sequences incorporated up to four copies of ATANP [37]. Also, these new peptides formed helix-loop-helix motifs and bound Zn(II) ions with the triazacyclononane subunits present in the lateral arms of ATANP. Even on a partial unfolding of the structure, an acceleration of the cleavage of HPNP (2-hydroxypropyl-*p*-nitrophenyl phosphate, an RNA model substrate) was observed. Clearly, the secondary structure of the peptide ensures cooperativity between metal centers for accelerating the reaction significantly above the background.

The incorporation of ATANP in more structured peptide sequences controls even better the three-dimensional positioning of the metals and, consequently, significantly improves cooperativity required for their catalytic activity. Thus the secondary structure of a 3_{10} -helix may be used to position functional groups present in the amino acids at precise reciprocal distance. In this conformation, when placed in positions i and $i + 3$, they will face each other with a separation of about 6.2 Å, which is the pitch of the 3_{10} -helix. An example is the heptapeptide Ac-Aib-L-ATANP-(Aib)₂-L-ATANP-(Aib)₂-OMe that was shown to fold into a 3_{10} -helix in water. The dinuclear Zn(II) complex of the peptide turned out to be a good catalyst for the cleavage of both HPNP [28a] and plasmid DNA [38b]. In the latter case, cooperative action between the metal centers was demonstrated by comparison of the activity of the mononuclear versus the dinuclear complex. A mechanism was proposed requiring the formation of a DNA-peptide complex, driven by electrostatic and metal complexation interactions. A rate acceleration of about 10-million-fold over the uncatalyzed cleavage process was observed.

Ghadiri [38] and Chmielewski [39] have reported on short peptide sequences based on the coiled-coil folding motives [40, 41] that act as templates for the recognition of shorter sequences and, eventually, for their ligation. When the two short peptides each constitute complementary pairs of the templating unit, the systems represent examples of self-replicating peptides [38c,d, 39]. For instance, a 33-residue polypeptide reported by Ghadiri [38] accelerated the ligation of a 16- and 17-amino acid sequence using Kent's [42] ligation. The overall performance of the catalyst outperformed catalytic antibodies [43]. Here cooperativity occurs at the level of molecular recognition of the two fragments to be ligated and substantially reduces the entropic price to be paid for the bimolecular reaction to occur. The general limitation of the approach is the fact that it was flawed by product inhibition contrary to what is found with an antibody-based catalyst [44]. However, by destabilizing the coiled-coil structure Chmielewski was able to enhance the catalytic efficiency of the system [40] and obtained a self-replicating peptide approaching exponential growth.

The widespread use of sulfonates as synthetic building blocks and the paucity of direct, selective methods for their preparation prompted Miller's group investigation into this area [44]. They have reported the development of a methyl histidine-based tetrameric peptide that effects the desymmetrization of meso-1,3-diols through enantioselective mono(sulfonylation). The catalyst exhibited structural similarities to a previously studied catalyst found to be effective in orthogonal group transfers, but resulted in the modification of the enantiotopic alcohol. The results expanded the scope of asymmetric peptide-catalyzed group transfer reactions to include sulfur-based electrophiles. The paper is very important because it presents a synthetic catalyst behaving similarly to enzymes where a single amino acid side chain may exhibit distinct roles. For example, histidine in several histidine-dependent kinases may operate as a catalytic nucleophile while in lipases and proteases it may behave as general base. The examples reported by Miller do not demonstrate such a dramatic change in mechanism. However, the fact that they observe the reversal of enantioselectivity in two apparently similar reactions lent support to the hypothesis that different transition states for the two enantiomer determining steps were in action with their His-functionalized catalysts.

The arguably most exciting study on peptide catalysis reported by Miller's group [45] concerned three different, peptide-based catalysts that enabled site selective phosphorylation of three distinct hydroxyl groups within the complex glycopeptide antibiotic teicoplanin A2-2. Previously, the group had accomplished the synthesis of catalysts for selective thiocarbonylation [46a] and bromination [47] of vancomycin (a similar antibiotic) and bromination [47] of teicoplanin by mimicking the interaction of the antibiotic with D-Ala-D-Ala peptides through the formation of five key H-bonds. Two of the catalysts were based on a design that capitalized on a catalyst-substrate interaction mimicking the biological mechanism of action of teicoplanin. The catalysts were based on a DXaa-DXaa peptide motif known to target the teicoplanin structure in a specific manner. The third was identified through evaluation of a set of catalysts that had been developed previously. Each catalyst contained additional functionalities designed

to present a catalytic moiety (a nucleophilic alkylimidazole) at a different region of the glycopeptide structure. It is astonishing to observe that small molecule catalysts were obtained allowing control over reactions at sites that are separated by 11.6, 16.5, and nearly 17.7 Å, simply relying on the X-ray crystal structure of teicoplanin A2-2 (Figure 10.6).

Hecht and coworkers have developed a combinatorial approach toward the *de novo* design of artificial enzymes [47]. As most structures obtained from a random combination of amino acids will not be structured, focused libraries were prepared based on binary patterns of polar (P) and apolar (A) residues in which the patterns encoded secondary structure elements [48]. Libraries of proteins were generated by expressing the corresponding synthetic genes in *E. coli*. This way a 102-residue protein was obtained that folded into a four-helix bundle. Histidine units were present in the protein, and their catalytic activity in the hydrolysis of *p*-nitrophenyl acetate (PNPA) was evaluated. In comparison to 4-methylimidazole, a 100-fold rate acceleration was observed, and the bell-shaped curve of rate constant against pH indicated the involvement of two units in the catalytic cleavage.

Mayo and coworkers have reported on the development of enzyme-like proteins, called “protozymes,” using a computational design procedure [49]. Their procedure took as a starting point the catalytically inert 108-residue thioredoxin protein from *E. coli* as scaffold. By computational means, an active site scan was performed to identify favorable sites for the introduction of histidine units. In separate calculations, the high-energy state of the generated structures involved in histidine mediated hydrolysis of *p*-nitrophenylacetate was calculated. Two sequences that emerged from the computational studies were selected for experimental analysis. In the best case a 25-fold increase in activity was observed with respect to 4-methylimidazole. Although the numbers are not impressive, these studies reveal the potential of using computational methods for the design of artificial catalysts.

During the HIV-1 fusion process, the N- and C-terminal heptad repeat regions of the gp41 protein form a coiled-coil six-helical bundle (6HB) that brings the viral and target cell membranes into close proximity for fusion [50]. Liu *et al.* used [51] 6HB as the molecular model for a novel scaffold for the design of an artificial enzyme, in which the modified C34- and N36- peptides formed a unique 6HB structure through specific molecular recognition, and the position and orientation of the side chain groups on this scaffold were predictable (Figure 10.7). The histidine-modified 6HB showed enzyme-like hydrolytic activity toward PNPA through the cooperation of several inter- or intrahelical imidazole groups. As the catalytic activity of 6HB depended on the C- and N-peptide assembly, either HIV fusion inhibitors that can compete with the formation of catalytic 6HB or denaturants that could destroy the ordered structure were able to modulate its activity. Further engineering of the solvent-exposing face with Glu[−]/Lys⁺ salt bridges enhanced the helicity and the stability of 6HB. As a result, the population and stability of cooperative catalytic units increased. In addition, the Glu-Lys-stabilized 6HB had increased catalytic efficiency.

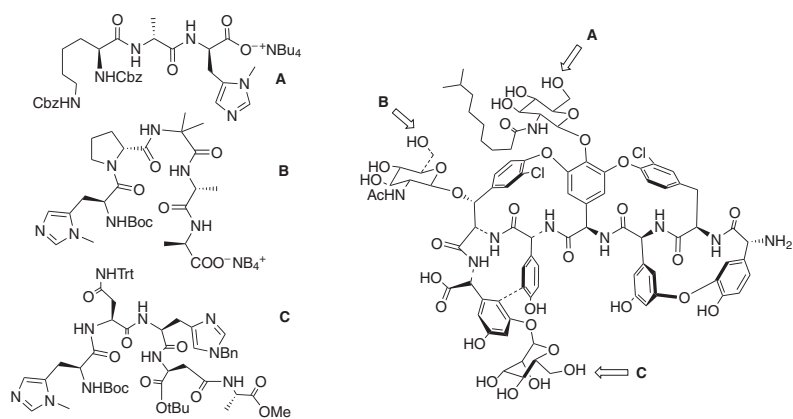


Figure 10.6 Miller's group has designed peptide catalysts based (but one) on a DXaa–DXaa pair known to target the antibiotic teicoplanin. By controlling the geometry of binding and placing the catalytic unit (a nucleophilic alkylimidazole) in the appropriate position they were able to selectively phosphorylate quite different alcohols present in teicoplanin with high selectivity [46].

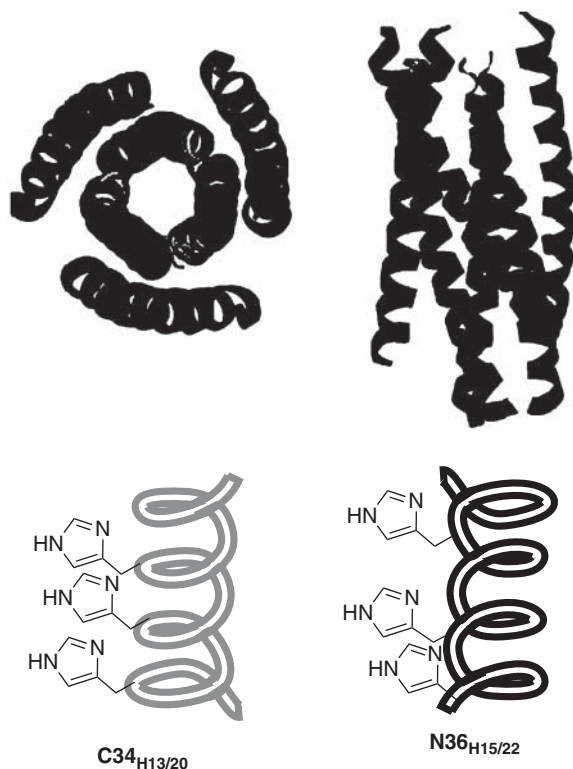


Figure 10.7 The N- (dark) and C- (gray) terminal heptad repeat regions of the gp41 protein form a coiled-coil six-helical bundle during HIV-1 fusion process (top and lateral view, left, and right at the top of the Figure). Liu *et al.* [36] prepared modified C34- and N36-peptides by inserting histidines in the 13 and 20 position (C-peptide, gray, and 15

and 22 position (N-peptide, dark) as shown on the bottom of the figure. By exploiting this self-assembling process they obtained a coiled-coil six-helical bundle that was active in the hydrolysis of *p*-nitrophenylacetate with clear evidence of cooperativity between the imidazoles.

10.2

Cooperative Catalysis by Supramolecular Systems

10.2.1

Unimolecular Receptors/Catalysts

The attachment of peptide sequences to conformationally flexible templates results in polypeptidic structures, with the separate peptide chains adopting a random orientation with respect to each other. Of special interest are those templates whose conformation can be rigidified via an external stimulus, such as pH or the presence of a metal ion, as this may also induce an organization of the peptide chains. One example of such a template is the

tetraamine tris(2-aminoethyl)amine (Tren) whose three arms are aligned on complexation of a metal ion, such as Zn(II), in the tetradentate binding pocket [36]. An artificial multinuclear metallonuclease subject to allosteric control by Zn(II) ions was described several years ago by us taking advantage of this property. A tripodal apo-peptide was synthesized by connecting three copies of the heptapeptide H-Iva-Api-Iva-ATANP-Iva-Api-Iva-NHCH₃ (where Iva is (*S*)-isovaline, Api is 4-amino-4-carboxypiperidine) to the Tren template. The oligopeptides contained C α -tetrasubstituted amino acids to induce helicity and ATANP to introduce a ligand for metal-binding (see above). The apo-peptide was able to bind up to four metal ions [Cu(II) or Zn(II)]: one in the Tren subsite and three in the triazacyclononane subunits [52]. The binding of metals to the Tren platform induced a change from an open to a closed conformation in which the three helical peptides were aligned in a parallel manner, thus creating a pseudo-cavity with the azacyclonane units pointing inward. However, this tripodal template showed a very peculiar behavior in the transphosphorylation of phosphate esters. The tetrazinc complex catalyzed the cleavage of HPNP, while the free ligand was a catalyst for the cleavage of an oligomeric RNA sequence with selectivity for pyrimidine bases. In the case of HPNP, Zn(II) was acting as a positive allosteric effector by enhancing the catalytic efficiency of the system. In the case of the polyanionic RNA substrate, Zn(II) was switching off the activity, thus behaving as a negative allosteric regulator.

Ueno and coworkers reported on a series of cyclodextrin-peptide hybrids (CD-peptides) in which three functional groups (β -CD, imidazole, and carboxylic acid) were present on the same face of an α -helical peptide [53]. In this design, the β -CD would bind *p*-nitrophenol ester substrates and place the ester group in close proximity to the imidazole and carboxylic acid functions, which would cooperatively cleave the ester moiety. The catalytic activity of the peptides was tested on both the D- and L-enantiomers of the *p*-nitrophenylester of Boc-alanine. It was observed that hydrolysis of the D-enantiomer was favored over the L-enantiomer both in terms of k_{cat} and K_{M} . Interestingly, the kinetic parameters were significantly affected by the order in which the three functional groups were positioned on the α -helix.

Dumy *et al.* [54] showed that a cationic esterase mimic having, in a controlled geometry, three distinct positive charges (via the presence of lysines) for molecular recognition and a nucleophilic/basic center (via the presence of a histidine residue), acted as a catalyst for the hydrolysis of a negatively charged fluorogenic planar, aromatic esters (Figure 10.8) [55]. The system displayed different degrees of inhibition in the presence of similar anionic molecules in water and at physiological pH. For instance, ADP strongly slowed down the formation of the fluorescent product by virtue of cooperative inhibition, hence allowing its spectroscopic or visual detection. Thus the system behaved as a sensor of ADP with good selectivity against ATP in particular. It is worth mentioning that sensors endowed of these properties are poorly represented in the literature.

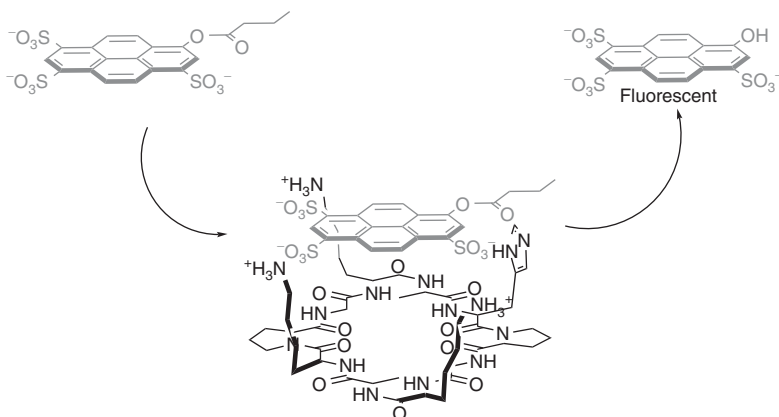


Figure 10.8 Supramolecular complex between the cyclic, cationic decapeptide designed by Dumy *et al.* acting as esterase and its anionic substrate. Anionic analytes

displace the substrate thus inhibiting the process. The system shows very good selectivity for ADP against ATP [55].

10.2.2

Molecular Aggregates

The spontaneous self-assembly of oligopeptides into a well-defined large structure is one of the most straightforward strategies to bring catalytic units in close proximity. For this purpose micellar and vesicular systems have been studied extensively since the 1970s. Surfactants functionalized with di- or tripeptides were used to rapidly generate catalytic sites on the surface of the aggregates. Frequently, these peptide sequences incorporated one histidine residue for the cleavage of esters (in cooperation with a second residue located on an adjacent surfactant) combined with additional amino acids for the creation of a chiral microenvironment. Key contributions in this area came from the groups of Moss and Sunshine [56], Ueoka *et al.* [57], and Ohkubo *et al.* [58], which have been extensively reviewed elsewhere a few years ago [59, 60].

A very elegant and related example was provided by Matile and coworkers who exploited the self-assembly of peptidic structures into synthetic pores that span lipid bilayers [61]. Small peptide units were laterally attached to rigid *p*-octiphenyl backbones that ended up forming the sidewalls of the pores. The hydrophobicity of the octiphenyl backbone and some of the amino acid residues induced incorporation of the staves into a lipid bilayer, after which β -sheet formation between peptide fragments resulted in the spontaneous formation of the pore. Synthetic catalytic pores (SCPs) were defined as pores constructed from abiotic scaffolds able to catalyze substrate conversion *during* its translocation across the same pore [62]. It was shown that a rigid-rod β -barrel pore with internal arginine-histidine dyads catalyzed the esterolysis of 8-acetoxypyrene-1,3,6-trisulfonate present inside large unilamellar vesicles composed of egg yolk phosphatidylcholine.

Stupp *et al.* have extensively reported [63] on the self-assembly of peptide amphiphiles into nanofibers driven by a hydrophobic collapse of the alkyl substituents in combination with β -sheet formation of the peptidic segment [64]. They showed that insertion of histidine residues in the peptidic segment resulted in the formation of nanofibers with a high imidazole density [65]. This resulted in a modest eightfold rate acceleration in the hydrolysis of 2,4-dinitrophenyl acetate (DNPA) with respect to free imidazole. More interestingly, a higher catalytic activity was observed for peptide amphiphiles that formed nanofibers over those that aggregated into spherical aggregates in which the components were less ordered.

Ulijn *et al.* [66] demonstrated that the combination of biocatalysis and molecular self-assembly in the presence of different salts provided access to diverse supramolecular nanostructures [67]. Specifically, they have reported that the cooperative effect of the salts on the molecular self-assembly of a Fmoc-dipeptide hydrogelator resulted in differential structuring of enzymes added to the sample. This affected the enzyme kinetics. As might be expected, supramolecular order correlated with the presence of the kosmotropic salts compared to the chaotropic salts. Interestingly, they observed an unexpected effect on the handedness of the fibrillar structure with chiral inversion observed in the final gel-phase material. The effects on the efficiency of the catalytic action could be suppressed by applying a heat/cool cycle, giving insight into the thermodynamic influence of both protein and salt on these systems and showing that the effects of catalysis, templating, and salts were cooperative. The variable molecular interactions were expressed as variable material properties, such as thermal stability and mechanical strength of the final gel-phase material. Although in the present case the peptides are not directly involved in the catalysis they provide the environment for the tuning of the catalytic process.

Kong, Wang, Yang *et al.* have developed a molecular-hydrogel system based on selenium-containing peptides with redox-controllable and reversible self-assembly and catalytic activity [68]. The reversible transformation between selenide and selenoxide was triggered by the addition of vitamin C (VC) and H_2O_2 ; the oxidized form formed clear solutions (likely micelles) contrary to the reduced one that formed gels. The sol–gel–sol cycle could be repeated at least three times. Circular dichroism spectra indicated that the oxidized compound was present in a random-coil conformation while the reduced peptides in the gel formed by VC addition adopted antiparallel β -sheet conformations. The introduction in the peptide sequence of a histidine provided catalytic properties to the peptide for the hydrolysis of an ester (Figure 10.9). The big difference in hydrolytic activity between solution and gel indicated that the catalytic activity could be switched by the redox trigger.

Finally, it is worth mentioning a work showing how appropriate enzyme fragments, on aggregation, may retain catalytic activity of the native enzyme. Rhomboid, a polytopic membrane serine protease, represents a unique class of proteases that cleave substrates within the transmembrane domain. Li *et al.* [69] have established a system that allows expression and isolation of YqgP, a rhomboid homolog

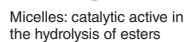


Figure 10.9 Selenium-functionalized peptides aggregate with different topologies accordingly to the oxidation state of Se. The oxidized form aggregates into micelles that are catalytically active in the hydrolysis of *p*-nitrophenyl acetate while the reduced one, forming fibers, is much less active [69].

from *Bacillus subtilis*, as a soluble protein. Intriguingly, soluble YqgP was able to specifically cleave a peptide substrate containing the transmembrane domain of Spitz, a ligand for the epidermal growth factor receptor in *Drosophila*. They have demonstrated that soluble YqgP existed as multimers, required for catalytic activity. Their results suggested also that soluble oligomers of maltose binding protein-YqgP complexes form micelle-like structures that are able to retain the active conformation of the protease for catalysis.

10.3

Cooperative Catalysis by Nanosystems

10.3.1

Dendrimer-Based Catalysts

Most of the work on catalytic, peptide-based dendrimers comes from the laboratory of Reymond and Darbrea [70, 71]. The first catalytic peptide dendrimers were reported by the group for the hydrolytic cleavage of esters [72–74]. In these examples the dendrimers were prepared by disulfide dimerization of second-generation dendritic peptides containing all possible combinations of the catalytic triad of the serine proteases (aspartic acid, histidine, and serine) resulting in 21 dimeric dendrimers. Screening with a fluorogenic substrate showed that peptide dendrimers having eight histidine groups at the surface were catalytically active and displayed enzyme-like Michaelis-Menten kinetics with substrate binding and rate acceleration. Modification of the amino acid composition led to the conclusion that catalysis most likely originated from the cooperative action of two imidazoles, whereas the serine residues did not appear to play a significant role [72]. This led to the preparation of a second series of dendrimers of different generation in which histidine units were repeated in each generation [75]. The catalytic activity was studied using a pyrene trisulfonate ester as a substrate. A systematic study of the dendritic effect in peptide dendrimer catalysis revealed that the catalytic rate constant k_{cat} and substrate binding constant $1/K_{\text{M}}$ both increased with increasing generation number. The dendrimers showed rate accelerations up to $k_{\text{cat}}/k_{\text{uncat}} = 20\,000$ and K_{M} values around 0.1 mM. The reactivity of histidine side chains within the dendrimer was increased up to 4500-fold when compared to 4-methylimidazole. A bell-shaped pH-rate profile around pH 5.5 in the dendrimer-catalyzed reactions confirmed that catalytic activity resulted from the cooperative action of two histidines (nucleophilic and a general base contribution to catalysis).

With the aim of extending the scope of peptide dendrimers and to apply a combinatorial approach they were also prepared by solid-phase peptide synthesis [72, 76]. Generally, peptide dendrimers with one to three amino acids between branches could be prepared with up to 38 amino acids (MW $\sim$ 5000 Da). Larger peptide dendrimers (MW $\sim$ 30 000) could be obtained by a multivalent chloroacetyl cysteine (ClAc) ligation. One limitation of their combinatorial

libraries was that the dendrimer topology was fixed and only the nature and number of the amino acids within the branches could be varied systematically [77]. To probe the effect of both sequence and topology on catalysis, the Reymond group has prepared a small 96-membered combinatorial library on cellulose (SPOT synthesis) [78]. In this method the solid support is a cellulose sheet, and compounds are identified by their position on the sheet rather than by bead decoding. The library contained linear undecapeptides and up to the third generation peptide dendrimers with up to 54 amino acids. Kinetic studies of oligohistidine peptides with one to 15 residues showed that these peptides were catalytically quite active but reached a plateau of relative proficiency per histidine residue for the heptamer. Further oligomerization did not significantly increase catalytic proficiency per histidine up to 15 residues. Worth of note is the fact they observed that a branched peptide dendrimer also carrying 15 histidines remained 1 order of magnitude more active than the linear counterpart, highlighting that the dendritic topology was particularly well suited for catalysis. Prins has elegantly evidenced the source of catalysis in these (and similar) systems [79]. His claim has been that it is not necessary to ascribe the positive dendritic effect to, for instance, changes in the catalytic site, increased substrate binding constant, or changes in the microenvironment. Rather, it appears that the efficient catalytic behavior of dendritic catalysts is mainly determined by two factors: the number of catalytic sites occupied by substrate molecules under saturation conditions and the efficiency of the multivalent system to generate catalytic sites in which multiple catalytic units act cooperatively on the substrate.

Structural studies of the peptide dendrimers by CD, FT-IR, NMR, and molecular dynamics revealed molten globule states containing up to 50% of α -helix [80]. Apart from the catalytic activity, strong ligands for *Pseudomonas aeruginosa* lectins (LecA and LecB) able to inhibit biofilm formation were obtained with glycopeptide dendrimers [81]. Efficient ligands for cobalamin, cytotoxic colchicine conjugates, and antimicrobial peptide dendrimers were also developed showing the versatility of dendritic peptides [82]. Complementing the multivalency, the amino acid composition of the dendrimers strongly influenced the catalytic or biological activity obtained demonstrating the importance of the “apple tree” configuration for protein-like function in peptide dendrimers (Figure 10.10).

The most recent development on peptide dendrimers led Reymond's group to the synthesis of bipyridine-based system [83] to mimic peroxidase activity (Figure 10.11). The dendrimer was obtained by double thioether bond formation between 5,5'-bis(bromo-methyl)-2,2'-bipyridine and 2 equiv. of peptide dendrimer N1 (Ac-Glu-Ser)8(Dap-Glu-Ala)4(Dap-Amb-Tyr)2Dap-Cys-Asp-NH2 (where Dap = branching 2,3-diaminopropanoic acid and Amb = 4-aminomethylbenzoic acid). At pH 4.0 BP1 bound Fe(II) to form the expected tris-coordinated complex $[\text{FeII}(\text{BP1})_3]$ ($K_f = 2.1 \times 10^{15} \text{ M}^{-3}$). At pH 6.5 a monocoordinated complex $[\text{Fe}^{\text{II}}(\text{BP1})]$ was formed instead ($K_f = 2.1 \times 10^5 \text{ M}^{-1}$) following electrostatic repulsion between the polyanionic dendrimer branches, as confirmed by the behavior of three analogs where glutamates were partially or completely replaced by neutral glutamines or positive lysines. $\text{Fe}^{\text{II}}(\text{BP1})$ catalyzed the oxidation of

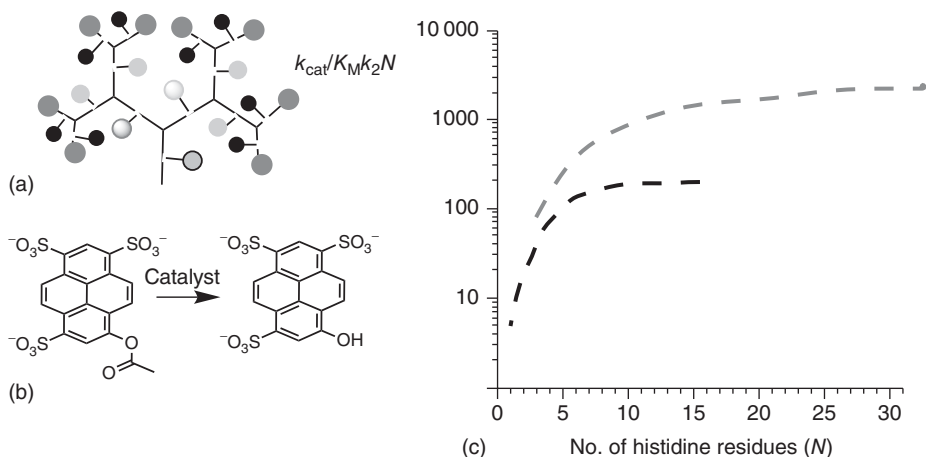


Figure 10.10 (a) The concept of the “apple tree” branched dendrimer. (b) Ester substrate used to compare the esterolytic activity of dendrimer-like peptides and linear peptides. (c) Trend of the activity of linear (dark) and

dendritic (gray) peptides as a function of the number of His residues (N) in the sequence. The dendrimeric structures outperform the linear one at least by an order of magnitude [71].

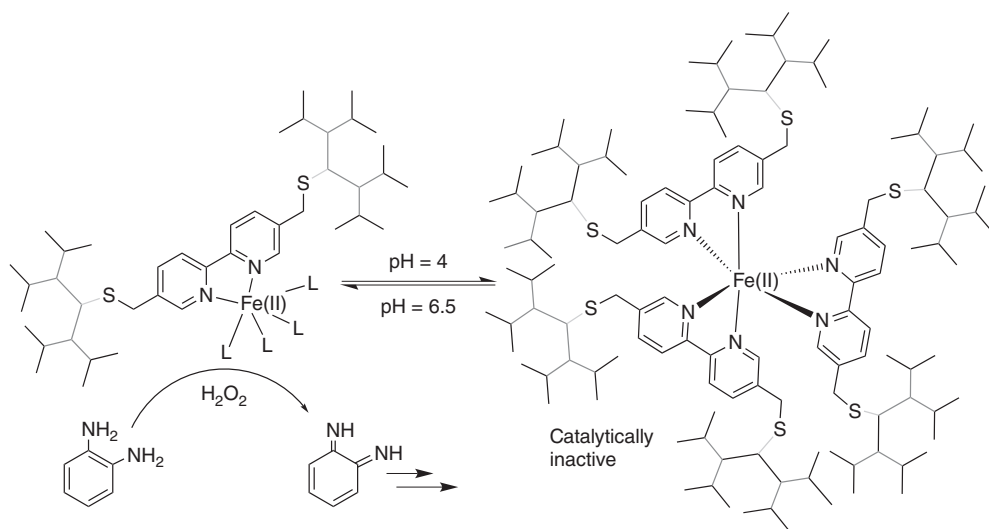


Figure 10.11 Monomeric and trimeric Fe(II) complexes were formed by bipyridine functionalized in the 5,5' position with dendrimers. According to the pH the monomeric

complex is converted into the trimeric one. The monomeric one catalyzed the oxidation by H_2O_2 of o -phenylenediamine with enzyme-like kinetics [84].

o-phenylenediamine with H_2O_2 with enzyme-like kinetics ($k_{\text{cat}}/k_{\text{uncat}} = 90\,000$) and multiple turnover, while Fe^{2+} or $[\text{Fe}(\text{bipy})_3]^{2+}$ were inactive. The labile coordination positions allowing coordination to H_2O_2 and to the substrate were likely responsible for the enhanced peroxidase activity of the metallopeptide dendrimer.

10.3.2

Nanoparticle-Based Catalysts

Clusters of gold atoms of nanometer size covered by a monolayer of organic molecules constitute examples of self-assembled nanosystems [84]. Typically, individual molecules are anchored on the gold surface via a thiol that ensures a strong (about 20 kcal/mol) interaction with the metal. This means that these thiols are kinetically inert toward dissociation at least on the time scale of most catalyzed reactions. Thus, although the monolayer covering a gold nanoparticle may be regarded as very similar to a surfactant aggregate (either a micelle or vesicle), the rate of the exchange of the monomers makes for a huge difference between the two classes of systems. Furthermore, thiols anchored on the surface of a cluster of gold atoms, present a unidirectional orientation of these molecules, which means that the self-assembly process contains an element of topological control. It is not surprising that peptides also have been anchored on the surface of these clusters of gold atoms. Their properties may be such to control even the chirality on the gold cluster surface [85].

Hydrolytic reactions have been used as typical benchmarks for studying cooperativity between different functional groups confined on the surface of the monolayer covering a cluster of gold atoms [86]. Contrary to molecular recognition where the single units play mostly repetitive, identical roles in recognition processes, in catalysis they are complementary to each other (acid/base, acid/nucleophile, for instance). This adds complexity to the system and to its design. This is not much different from what happens with the peptide dendrimers shown above. An early attempt to obtain cooperative catalysts for the cleavage of a carboxylate ester was performed by incorporating an imidazole in the thiols forming the monolayer [87]. This is not a peptide but it is reported here for its relevance as the first example of cooperativity in this kind of system. The nanoparticles consisted of a mixed monolayer of dodecanethiol and an *N*-methylimidazole-terminated thiol. The catalytic activity of the Au MPCs was tested on the substrate DNPA. Packing of the imidazole units on the Au-nanoparticle surface induces a modest 30-fold rate acceleration with respect to the monomer. However, the bell-shaped dependence of k_2 with a maximum in the proximity of the $\text{p}K_{\text{a}}$ of the imidazole, supported cooperativity between two methylimidazoles in the DNPA cleavage (general acid/base or nucleophilic catalysis). The kinetic behavior was very similar to that reported by Baltzer *et al.* who studied four-helix bundle-forming peptides bearing multiple imidazole subunits [24a] or that found by Reymond with His-functionalized peptide dendrimers [76]. The simple conclusion from these studies is that by confining the catalytic units in an environment like that provided by the monolayer covering the gold

nanocluster, it was possible to elicit cooperativity between them. This is probably because of their reduced mobility.

Dipeptides designed to induce cooperativity between carboxylates and imidazoles by using histidine and a carboxylate either from a terminal amino acid or from aspartic acid were used for passivation of the gold cluster. Nanoparticles functionalized with these peptides not only gave positive proof of cooperativity [88], but showed that within the monolayer, hydrolytic mechanisms not available for similar monomeric systems became operative. The complementary role of a carboxylate and an imidazolium ion was demonstrated by studying the hydrolysis at low pH. The thiol used for the passivation contained a HisPhe-OH terminal sequence and was used in conjunction with a tris-ethyleneglycol methyl ether (TEG)-containing thiol, which made the system water-soluble. At all pH values the Au-nanoparticle catalyst was far better than the monomeric catalyst (not bound to the gold surface). The most striking difference was, however, that the monomeric catalyst behaved as a system in which the catalytically relevant nucleophile (pK_a 6.6) was the imidazole while the nanoparticle showed a more complex profile. A first nucleophilic species was generated at low pH (pK_a 4.2, carboxylic acid) then the curve flattened up to pH 7 where a second nucleophile was generated (pK_a 8.1, imidazolium). Mechanistically, this has been interpreted by the involvement of a carboxylate anion in the cleavage that acts as a general base deprotonating a water molecule and of a protonated imidazole acting as a general acid. The absence of this mechanism in the monomeric system clearly indicated that this behavior resulted from cooperativity because of the confinement of the dipeptide on the monolayer covering the nanoparticle.

A dodecapeptide was used for passivation of a 2 nm gold cluster by us in collaboration with the group of Baltzer [89]. The results we obtained in the hydrolysis of DNBP further supported the occurrence of such a cooperative process in these systems in the presence of the appropriate functional groups. The dodecapeptide presented a combination of a His, two Arg, and a Lys residues potentially allowing nucleophilic, general-acid, and/or general base catalysis, but also stabilization of the negatively charged transition state that arises along the pathway of ester hydrolysis. The results of the rate versus pH studies, compared with those of the monomeric *S*-acetylated peptide, showed that, at low pH values, cooperativity between carboxylate and protonated imidazole was in action in the nanoparticle-based catalyst. This produced an additional 10-fold gain in activity, amounting to a 3000-fold rate acceleration over that exerted by the simple dipeptide of the previous example. At higher pH values, the activity of the peptide–nanoparticle increased significantly with respect to the previous dipeptide-functionalized nanoparticle reaching an extra 40-fold rate acceleration, as a consequence of the presence of an additional nucleophile (the phenoxide of tyrosine) with an apparent pK_a of 9.9 (Figure 10.12). Very interestingly, we showed that, when the imidazole was the nucleophile, the concentration of a lipophilic substrate was able to regulate the activity of the system by shifting the rate-determining step from imidazole acylation to the hydrolysis of this intermediate. This was attributed to dehydration of the monolayer. Thus the

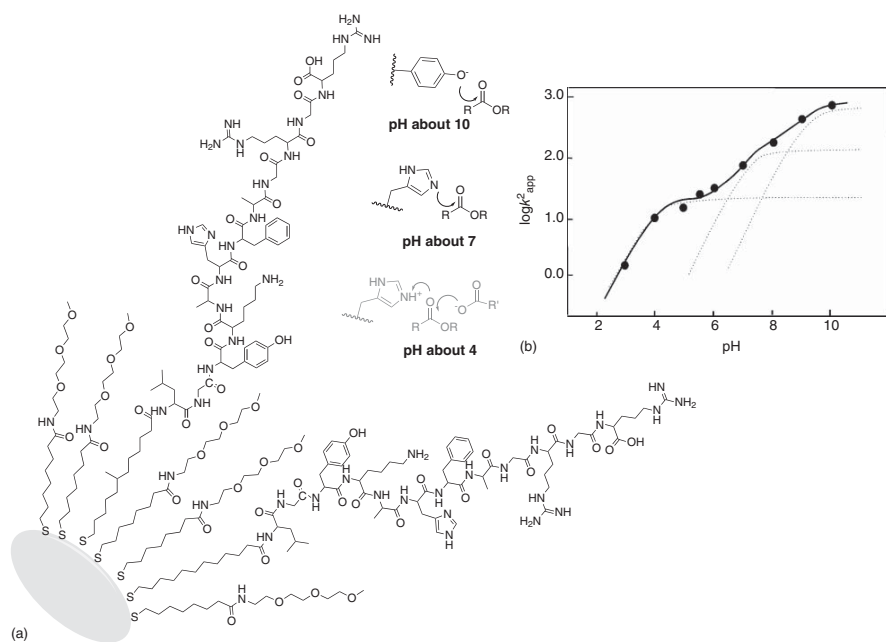


Figure 10.12 Fragment of an Au nanoparticle passivated with an esterolytically active dodecapeptide (a) and the pH profile observed in the hydrolysis of the active substrate 2,4-dinitrophenylacetate and the mechanisms suggested at the different pH (b). The mechanism highlighted in grey is absent in the monomeric catalyst [89].

concentration of the substrate regulated the activity of the nanoparticle-based catalyst.

An interesting alternative to the use of monolayers composed of different thiols bearing diverse functional groups to engineer new catalytic sites, which was conceived by Prins *et al.* by binding molecules bearing appropriate functional groups on the surface of a “universal” nanoparticle via noncovalent interactions. Prins and his coworkers used cationic nanoparticles and bound, by a self-assembling process, small catalytic peptides on their surface [90, 91]. These peptides contained a negatively charged patch of Asp-residues to ensure strong binding through multivalent, electrostatic interactions, a fluorescent Trp-residue to detect binding, and one or more His-residues for catalytic cleavage of esters (Figure 10.13). When bound to the surface, the peptides accelerated the cleavage of the *p*-nitrophenylester of *N*-Cbz-protected phenylalanine by more than 2 orders of magnitude. A thorough analysis of the system showed that colocalization of substrate and catalyst on the multivalent surface was the main reason for observing catalytic activity at micromolar concentrations in water. The catalysis was further enhanced by the local pH at the surface that was 0.7 units higher than the pH of the bulk solvent, caused by the cationic ammonium groups. The pH tuning by the charge of the surface is very similar to what is observed with cationic micelles or vesicles. The higher local pH increased the concentration of unprotonated imidazole, which acted as the nucleophile during catalysis. These results indicated that it is possible to create complex catalytic systems through

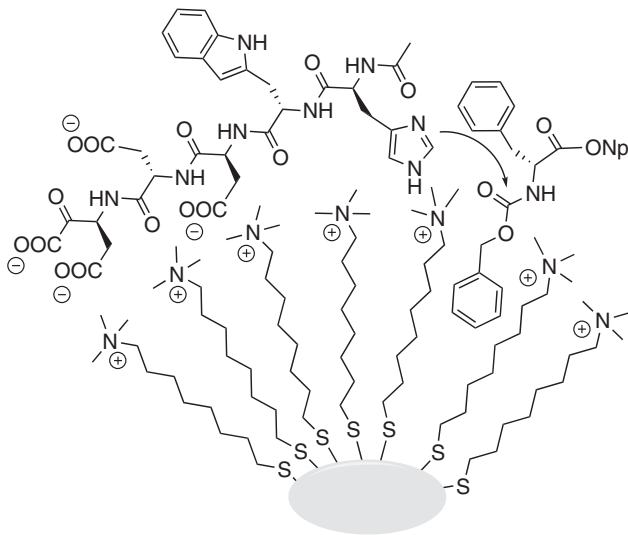


Figure 10.13 A histidine-bearing, anionic peptide bound to the surface of a gold nanoparticle passivated with cationic thiols was reported as a powerful catalysts for the cleavage of an active ester substrate.

The monolayer of the nanoparticle acted as a template for bringing the catalytic peptide and the ester in close proximity for the hydrolytic reaction to occur [91].

the self-assembly of small peptide sequences and gold nanoparticles, without the need for the preparation of (hetero)monolayers.

Earlier Rotello and Chmielewski had reported a system where functionalized gold particles (Au MPC) promoted the association and ligation of peptide fragments [92]. The complementary electrostatic interactions between the peptide and the Au MPCs were presumably the major cause for templation and subsequent ligation. The study highlighted the utility of nanoparticle surfaces for mediating supramolecular coupling reactions that can be extended toward other relatively large scaffolds that require appropriate positioning of the reactive centers. The authors speculated that their system could resemble a model (although rather simplified) for prebiotic conditions in which small charged inorganic particles could have assisted the polymerization of early biopolymers.

Indirectly related to the previous examples is a mesostructured silica/organic composite reported by Aida *et al.* in which the organic component is an amphiphilic short peptide. The system is reported here although it is constituted by a rod-like micelle whose surface is stabilized by mesoporous silica. Accordingly, it resembles more a nanoparticle than a micellar aggregate from the morphological point of view. The authors claimed that this was a way to stabilize a micellar aggregate in a nonaqueous solvent. The mesostructured composite was found to be able to catalyze the acetalization of cyclohexanone, whereas no reaction took place with unfunctionalized mesoporous silica [93]. In sharp contrast, hydrolytic removal of the C16 alkyl tail of the immobilized peptide resulted in the complete disappearance of the catalytic activity, which suggested the importance of a hydrophobic inner domain for the admission of cyclohexanone. Interestingly, an unsupported peptide amphiphile, under identical conditions to those reported above, was inefficient for acetalization regardless of the absence or presence of mesoporous silica. In sharp contrast with the above results reported by Prins, the growth of mesoporous silica on the surface of the peptide aggregate through electrostatic interactions was also catalytically inactive. Aida's group observations indicated the importance of covalent immobilization of the peptidic amphiphile for catalysis.

Phosphate ester cleavage is much more challenging than the hydrolysis of a carboxylate ester. In biological system this is typically achieved by exploiting the presence of metal ions like Zn(II) or Mg(II) in the catalytic site of the enzyme. These metal ions work in a concerted manner and, accordingly, catalysis of the hydrolysis of these esters is an excellent test for the presence of cooperativity between two (or more) metal centers. An early example addressing phosphate cleavage with Au MPCs was reported by us by using a thiol bearing a triazacyclononane-functionalized amino acid [35] grafted on a gold cluster in a 1:1 mixture with dodecanethiol [94]. Again this was not a peptide but just a simple amino acid. The impressive results obtained, however, highlighted the possibility to obtain highly efficient catalysts for these demanding substrates using nanosystems. Peptide-based catalysts have not been reported yet, but likely they will come soon.

Moving away from catalysis of hydrolytic (or transacylation) reactions it is worth mentioning a number of reports on peptide-stabilized nanoparticles for

quite different applications. Peptides have been used by several laboratories for the preparation of nanostructures [95]. For instance, Wennemers' group used them for the preparation of Ag nanoparticles [96]. We provide here a few examples of these peptide-stabilized nanoparticles with catalytic activity. The TSNAVHPTLRHL peptide was isolated in Knecht's group using a phage display technique with an affinity for palladium [97]. Using this sequence, palladium particles, which have a diameter of approximately 1.9 nm, were prepared that were active for Stille coupling reactions in water, at room temperature, with palladium loadings of ≥ 0.005 mol% [95]. Modeling of the peptide–nanoparticle interactions suggested that the histidine residues at positions 6 and 11 were most likely responsible for the binding as they form a kinked structure that exposes the palladium surface [95]. Knecht *et al.* have shown [98] that by selectively replacing the histidine residues with alanine, the catalytic activity could be modulated to affect the reactivity while maintaining the particle size. Their results were a step forward in understanding the activity of these peptide-stabilized nanoparticles. By demonstrating that the activity of these nanocatalysts could be modulated by the peptide sequence they provided hints for the rational design of peptides for the production of the nanoparticles [99].

By using the Lauryl-VVAGHH-C(O)NH₂ peptide amphiphile, nanofibers were prepared by Guler *et al.* [100] to be used as templates for the formation of one-dimensional Pd nanostructures. The peptide-based Pd nanoparticles turned out to be an efficient catalyst for the Suzuki cross-coupling reactions in water at room temperature with yields of about 99% (but for a single case where the yield was 85%). It was shown that not only it could be easily prepared but also reused in successive reactions without significant loss in activity and structural integrity.

10.4

Conclusions

We hope to have provided to the reader the flavor of research in the field of catalytic peptides. This is just the tip of the iceberg and those intrigued by some of the results here presented may dig into the literature for a more complete overview of the field. We would be happy if we were able to induce curiosity and, perhaps, ideas for new research. Peptides are unique molecules. Because of their relationship with proteins and other biomolecules their synthesis has been optimized and is amenable to a combinatorial approach. Furthermore, the repertoire of functional groups present in their side chains and the possibility to expand it with unnatural derivatives renders the possible combinations unmatched by any other catalyst. Their structural features are also well known and principles for their control are well established. In a recent review on asymmetric catalysis with peptides Helma Wennemers [101] concluded by saying: "Peptides are ideally suited to accommodate the requirements of different substrate combinations and can be expected to prove valuable as asymmetric catalysts for more and more synthetically useful transformations within the next decade." Extending the concept to catalysis in general we cannot but agree with her.

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101. Wennemers, H. (2011) *Chem. Commun.*, **47**, 12036–12041.

11

Metals and Metal Complexes in Cooperative Catalysis with Enzymes within Organic-Synthetic One-Pot Processes

Harald Gröger

11.1

Introduction

Today although organic chemistry and catalysis are considered to be closely connected to each other, thus representing the so-called “two sides of a medal,” this has not been the case for a long time in the history of chemistry [1]. The achievements by Ostwald in the field of physical chemistry, for example, kinetics, led to his definition of catalysis that certainly was one of the early milestones in this field. Although from the first half of the past century on catalysis was widely applied in the emerging petrochemical industry, typically, organic chemists were less involved in the development of such heterogeneously catalyzed processes running under vapor phase conditions at higher temperature. In parallel, organic chemistry has its roots in the synthetic achievements accomplished already in the nineteenth century based on starting materials from coal tar with many applications in the field of dyes. In the last decades of the twentieth century, the disciplines “classic organic chemistry” and “catalysis” merged more and more, and the application of catalysis in organic chemistry is recognized as one of the most attractive approaches when focusing on the development of novel synthesis today. The importance of catalysis for the chemical industry is underlined by the impressive percentage of more than 85% of chemical processes, which run in the presence of catalysts [2].

Although we do not know how decades from now on our way to conduct organic synthesis will look like, the parallel developments of “catalysis” and “organic synthesis” with a fruitful merger at a later stage might have some analogy to what we can observe today and expect for the future for the fields of “metal catalysis” and “enzyme catalysis.” Metal catalysis has made a tremendous jump from early developments to groundbreaking technologies utilized for the industrial production of bulk chemicals as well as highly complex pharmaceuticals [3]. On the side of homogeneous catalysis the impressive developments on hydrogenation, hydroformylation, and Wacker oxidation (for bulk chemicals) as well as the numerous catalytic (asymmetric) metal-catalyzed technologies (for the synthesis of chiral building blocks) shall be mentioned at this stage

as representative examples. In recent years (since 2000) metal catalysis has been awarded a range of, for example, Nobel prizes (hydrogenation, oxidation, metathesis, cross-coupling reaction), thus underlining its high efficiency, applicability, and importance in organic synthesis. In parallel, also enzyme catalysis found an important place in organic synthesis and emerged as a highly efficient and broadly applicable synthetic tool, making tremendous contributions in particular to the field of synthesis of specialty chemicals, fine chemicals, and pharmaceuticals [4]. A further major advantage of enzyme catalysis can be seen in its potential to establish sustainable production methods for chemicals even on a large scale.

Although in parallel highly efficient and economically as well as ecologically attractive process technologies have been developed by means of metal and enzyme catalysis, their synergistic use is still rare. Among others, the following two reasons might play a major role. First, the scientific interest of combining in general modern catalytic transformations arose to a large extent only recently (although some earlier examples are known as well). Besides being an academically exciting subject, one further currently driving force to establish multistep one-pot processes has been the increasing industrial demand for strategies to develop sustainable production technologies by combining several reactions steps without intermediate isolations. Second, historically, the development of processes by means of metal catalysts and enzymes as catalysts, respectively, have been for a long time considered as two “different worlds.” Lack of teaching in both research areas within one chemistry degree program as well as the difficulty to find access to enzyme catalysts for organic chemists without linked microbiology infrastructure might represent some of the reasons. A further explanation often given is the inhibition of enzymes by metals: although this is certainly true for some combinations, it has to be studied case by case and (as it is shown below) there is a surprising huge potential for combining metal complexes with enzymes with decreased, negligible, or no enzyme inhibition and deactivation.

Thus, the design of one-pot processes is a highly timely topic as is the combination of metal catalysis with enzyme catalysis. Notably, in the past decades several efficient proofs of concepts have been demonstrated that underline the tremendous potential of such combinations in one-pot transformations. An interesting overview about the variety of metals that already turned out to be feasible for their combination with enzymes in the young discipline of chemoenzymatic one-pot syntheses is given in the periodic system of the elements in Scheme 11.1, in which all such “enzyme-compatible” metals are highlighted in gray color. As can be seen therein there is a wide range of “enzyme-compatible metals,” in particular, among the so-called heavy metals, which already have been proven to be suitable for a combination with biotransformations within organic one-pot syntheses.

Moreover, process strategies have been developed to overcome hurdles such as inhibition and deactivation of, for example, the enzyme by metals or reagents. The achieved better understanding about the “do’s and don’ts” when combining

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
I A	II A	III B	IV B	V B	VI B	VII B	VIII B	VIII B	VIII B	I B	II B	III A	IV A	V A	VI A	VII A	VIII A
H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	J	Xe
Cs	Ba	*	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	**	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn	Uut	Fl	Uup	Lv	Uus	Uuo

Scheme 11.1 Periodic system of the elements with indicated “enzyme-compatible” metals. (*: elements 57-71: lanthanide series (not shown in detail); **: elements 89-103: actinide series (not shown in detail))

metal and enzyme catalysis also serves as an excellent current starting point for future developments in this exciting field. As for the processes developed up to now, synthetic one-pot processes in which metal catalysis and biocatalysis run in cooperative fashion can be clustered into three major types of combinations, which are as follows:

- 1) metal-catalyzed *in situ*-preparation of an enzyme’s reagent (cofactor) required for the biotransformation, in particular enzyme-catalyzed redox reaction under consumption of the cofactors NAD(P)H and NAD(P)⁺, respectively, and *in situ*-regeneration of this either oxidized or reduced cofactor by means of a metal-catalyzed reaction;
- 2) racemization of a substrate with a metal catalyst combined with a stereoselective transformation of the substrate catalyzed by an enzyme toward dynamic kinetic resolutions;
- 3) consecutive chemoenzymatic cascade processes in which formed intermediates are directly converted into the corresponding products (e.g., a reversible initial metal-catalyzed transformation and a subsequent irreversible enzymatic transformation).

Examples of such combinations of metal and enzyme catalysis running in a cooperative fashion are given in the following sections (thus complementing earlier and more recent reviews [5–9] about chemoenzymatic one-pot syntheses or specific aspects thereof).

11.2

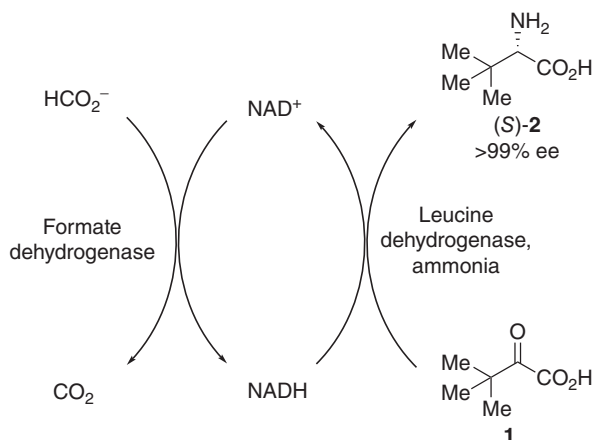
Metal-Catalyzed *In situ*-Preparation of an Enzyme's Reagent (Cofactor) Required for the Biotransformation

11.2.1

Overview About the Concept of *In situ*-Cofactor Recycling in Enzymatic Redox Processes

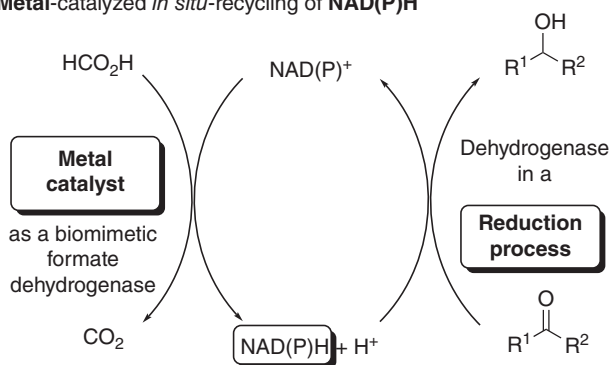
Cooperative catalysis can consist of an *in situ*-recycling and thus delivery of a “reagent” for the enzyme by means of a metal-catalyzed reaction. In this case, the “reagent” typically represents a cofactor required for an enzymatic redox process. In today's organic synthesis based on the use of biocatalysts, redox enzymes play a prominent role with a broad range of even industrial examples reported up to now for both (enantioselective) reductions as well as oxidation reactions. When considering oxidoreductases (enzyme class E. C. 1) as a catalyst, however, one often has to solve the task of *in situ*-regeneration of the cofactor consumed by the enzyme in the desired redox step. In contrast to chemocatalytic redox reactions with economically attractive reducing or oxidizing agents (such as, e.g., hydrogen or peroxides), cofactors such as NAD(P)H and NAD(P)⁺ are highly expensive chemicals, thus excluding their use in stoichiometric amount as synthetically attractive option. Thus, the consumed cofactor is recycled *in situ* by means of an additional reaction, which at the same time converts a cheap and economically attractive chemical that serves as the stoichiometric reducing or oxidizing agent. Typically, this second process is conducted by an enzyme as well, and a range of enzymatic cofactor regenerations methods have been developed (which have been reviewed [10, 11] extensively elsewhere). A representative example for such a process done on industrial scale with *in situ*-cofactor regeneration with enzymes in “free” form is the synthesis of L-*tert*-leucine, (*S*)-**2**, utilizing a leucine dehydrogenase and a formate dehydrogenase in combination with ammonium formate as stoichiometric nitrogen (ammonia) donor and reducing agent (formate; Scheme 11.2). The cofactor is regenerated *in situ*, and formate as a stoichiometric reducing agent is oxidized toward carbon dioxide, thus shifting the reaction irreversibly toward the desired amino acid product direction.

It is noteworthy, however, that for the *in situ*-cofactor recycling in general also a metal catalyst can be utilized, which then cooperatively acts with the enzyme in a tandem-like one-pot fashion. The simultaneous action of metal and enzyme catalysts in the field of redox chemistry with *in situ*-cofactor regeneration is based on two types of metal applications, which are graphically summarized in Scheme 11.3 exemplified for the *in situ*-recycling of the cofactors NAD(P)H and NAD(P)⁺ in enzymatic reduction and oxidation reactions, respectively, catalyzed by means of dehydrogenases. According to Scheme 11.3, Part (A), the metal component acts as a catalyst for the *in situ*-reduction of NAD(P)⁺ under formation of NAD(P)H (as the required cofactor form for dehydrogenase-catalyzed reductions), oxidizing at the same time formate under formation of carbon dioxide. Alternatively, as a second option (according to Scheme 11.3, Part (B)), a metal complex can act as a

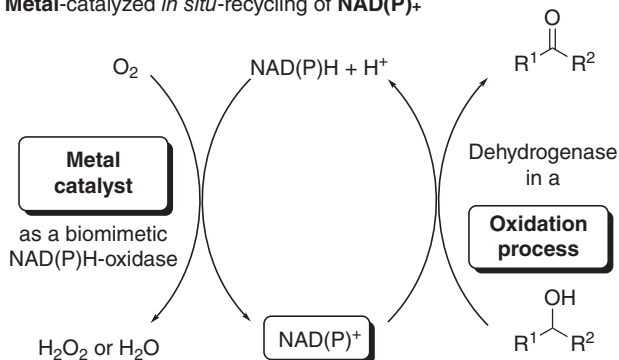


Scheme 11.2 The concept of an enzymatic *in situ*-recycling applied in industrial L-tert-leucine synthesis.

(a): Metal-catalyzed *in situ*-recycling of NAD(P)H



(b): Metal-catalyzed *in situ*-recycling of NAD(P)+



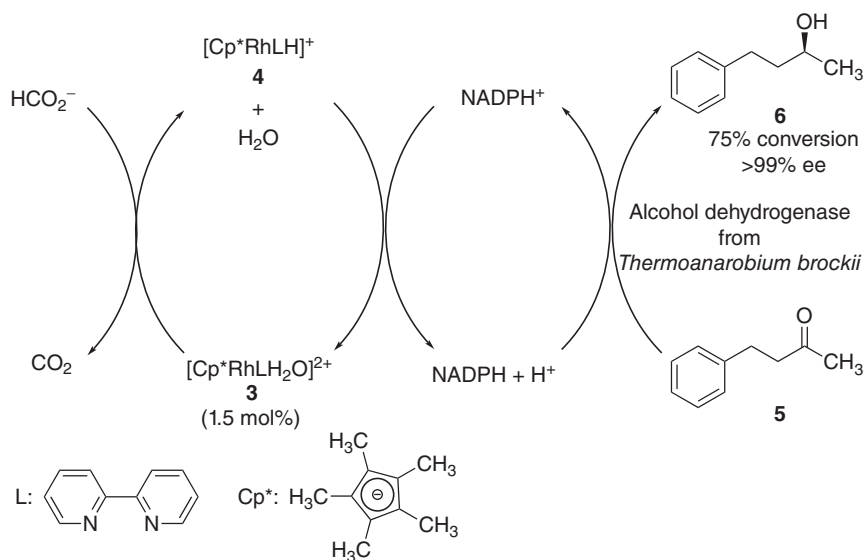
Scheme 11.3 Concepts for an *in situ*-cofactor regeneration based on the use of metal complexes.

catalyst for the *in situ*-oxidation of NAD(P)H under formation of NAD(P)⁺ (as the required cofactor form for dehydrogenase-catalyzed oxidations), reducing at the same time molecular oxygen under formation of either hydrogen peroxide or (ideally directly) water. The prerequisite in terms of an economically attractive process, namely, that the cosubstrates (used as oxidizing or reducing agent) represent cheap, ideally nontoxic, and readily available bulky chemicals of a low molecular weight is fulfilled in both cases (with formate and molecular oxygen, respectively).

11.2.2

Metal-Catalyzed *In situ*-Recycling of Reduced Cofactors NAD(P)H for Enzymatic Reduction Reactions

The approach according to Scheme 11.3, Part (A), has been reported by the Steckhan group utilizing such a formate-based and metal-catalyzed *in situ* cofactor-regeneration in the enantioselective reduction of a ketone in the presence of an alcohol dehydrogenase (Scheme 11.4) [12]. The rhodium complex turned out to be highly compatible with a range of (*R*)- and (*S*)-alcohol dehydrogenases and enabled an efficient enantioselective enzymatic reduction of 4-phenylbutan-2-one, **5**, with excellent enantioselectivities of up to >99% ee. The metal-catalyzed *in situ*-cofactor recycling proceeds even at low catalyst loading of typically 1.5 mol% of the rhodium-complex **3**. Notably, a high robustness of this chemoenzymatic process concept has also been demonstrated by Schmid *et al.* in gram scale applications for the reduction of 3-methylcyclohexanone and 2-decalone, respectively [13]. Turnover numbers up to 28.000 with respect to



Scheme 11.4 Cooperative catalysis of a rhodium-complex for *in situ*-recycling of NADPH with an alcohol dehydrogenase for asymmetric ketone reduction.

the alcohol dehydrogenase from *Thermus* sp. and up to 233 with respect to the rhodium-complex **3** were achieved.

Furthermore, this metal-catalyzed *in situ*-cofactor recycling can be used in combination with monooxygenase-catalyzed reactions as demonstrated by Schmid and Steckhan *et al.* [14]. It is noteworthy that besides the “formate-driven” approach the reduction of the Rh catalyst can be conducted also electrochemically as an alternative method. Both methods were studied in this monooxygenase-catalyzed biotransformation, which enabled a comparative study of these two methods for *in situ*-recycling of NADH. As a metal component the rhodium-complex $[\text{CpRh}(\text{bpy})\text{Cl}]\text{Cl}$ ($\text{Cp}=\text{C}_5\text{Me}_5$; bpy: 2,2'-bipyridine) was used, which notably showed a high stability and activity over a broad range of pH and temperature. In addition, an excellent review on the use of this type of Rh complexes for efficient and nonenzymatic regeneration of nicotinamide and flavin coenzymes has been reported by Schmid *et al.* [15].

A mechanistic insight into the reduction process of cofactors by such types of Rh complexes was given by the Fish group when studying structure–activity relationships, kinetics, and mechanistic aspects in the regioselective reduction of NAD models in the presence of this rhodium catalyst [16]. A further interesting extension is the metal-catalyzed *in situ*-regeneration of nicotinamide coenzymes by means of the use of molecular hydrogen [17].

11.2.3

Metal-Catalyzed *In situ*-Recycling of Oxidized Cofactors NAD(P)^+ for Enzymatic Oxidation Reactions

For the enzyme-coupled *in situ*-regeneration of the oxidized cofactor form NAD(P)^+ , typically NAD(P)H -oxidases are used as enzyme component, which convert molecular oxygen as oxidizing agent into either water or hydrogen peroxide [10, 18–20]. Coupling of such an *in situ*-cofactor recycling with dehydrogenase-catalyzed oxidations was done for, for example, resolution of *rac-tert*-leucine through oxidation of the L-enantiomer with an L-*tert*-leucine dehydrogenase, thus leaving the D-*tert*-leucine untouched as remaining substrate and desired product [18].

However, *in situ*-cofactor recycling can also be achieved by means of metal complexes instead of enzymatic methodologies. A pioneer work in this field reported by Steckhan and coworkers represents the application of a rhodium-*ortho*-quinone-type complex, which acts as a “biomimetic NADH-oxidase” by converting molecular oxygen – as the oxidizing agent in stoichiometric amount – into hydrogen peroxide, thus reconverts NAD(P)H into NAD(P)^+ required for the enzymatic oxidation reaction [21]. Resulting oxidative applications in the presence of alcohol dehydrogenase comprise in particular desymmetrization of *meso*-compounds, thus enabling asymmetric processes running with high enantioselectivities. Notably, the role of the rhodium metal in this complex is more of a “spectator character” as the catalytically relevant functional group is the *ortho*-quinone moiety (by accepting two electrons). The

hydrogen peroxide formed as a by-product can be easily cleaved by the addition of some amount of catalase, thus transforming hydrogen peroxide into water and molecular oxygen. Also, the rhodium-complex used for the reduction successfully can be applied alternatively [13]. In addition, for the oxidative direction of the cofactor regeneration, electrochemical methods have been developed as well [22].

Addressing the challenge to provide enzyme-compatible metal complexes, which form water instead of hydrogen peroxide as a by-product in the *in situ*-recycling of NAD(P)^+ from NAD(P)H with molecular oxygen, Gröger *et al.* identified the highly water-soluble iron complex Fe(III)TSPP as a suitable component for this purpose [23, 24]. On the basis of this iron complex used as a “biomimetic NAD(P)H -oxidase,” several synthetic oxidation processes under consumption of the cofactor NAD(P)^+ and its *in situ*-recycling were developed. One of the examples is the combination of this cofactor recycling with the iron complex **9** with a glucose dehydrogenase-catalyzed oxidation of carbohydrates under formation of the corresponding lactones, which then spontaneously undergo hydrolytic ring-opening toward the acids. A representative example is shown in Scheme 11.5, Part (A) with the biocatalytic oxidation of D-glucose (**7**) with >95% conversion via *in situ*-cofactor recycling of NAD^+ by means of FeTSPP with a catalytic loading of 2 mol%. This cooperative interaction of the iron complex **9** with a dehydrogenase has also been demonstrated in an alcohol dehydrogenase-catalyzed oxidation process of cyclooctanol as a representative for a hydrophobic substrate, and >95% conversion was obtained for the resulting cyclooctanone. Furthermore, this *in situ*-cofactor recycling with the FeTSPP complex has been combined with an L-glutamate dehydrogenase in a process transforming in water the readily available and cheap sodium L-glutamate into the desired α -ketoglutarate, which represents an industrially required α -keto acid (Scheme 11.5, Part (B)) [24]. For example, by means of an L-glutamate dehydrogenase from *Clostridium difficile* and a catalyst loading of 7 mol% of iron complex **9**, an overall conversion of >99% and a conversion of 88% related to the formation of α -ketoglutarate was observed when operating at a substrate concentration of 15 mM.

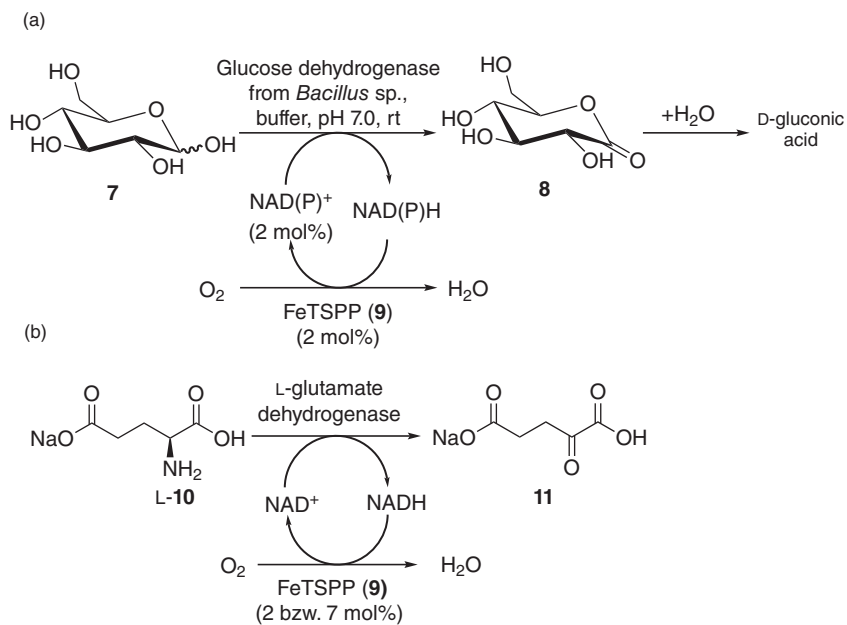
11.3

Combination of a Metal-Catalyzed Racemization of a Substrate with a Stereoselective Biotransformation Toward a Dynamic Kinetic Resolution

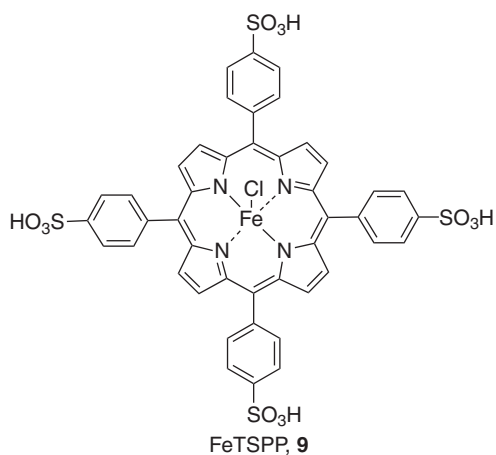
11.3.1

Dynamic Kinetic Resolution Based on Metal-Catalyzed Racemization of the Substrate in Combination with Enzymatic Resolution in Aqueous Media

Although studied to a less intensive extent compared to analogous processes in organic media (which are described in the Section 11.3.2), dynamic kinetic resolutions under combination of a metal catalyst and a hydrolase running in aqueous

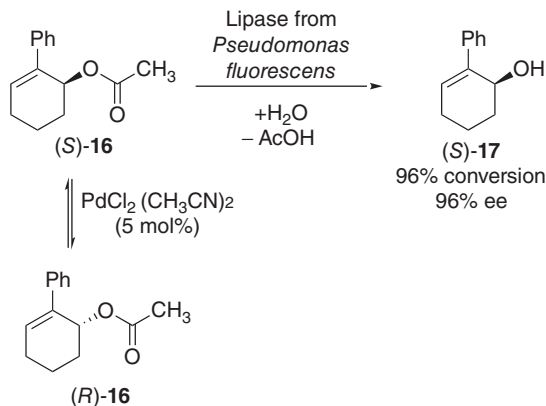


Iron catalyst structure



Scheme 11.5 Cooperative catalysis using FeTSPP in combination with dehydrogenases for oxidation processes.

reaction medium have been reported as well. A palladium-catalyzed racemization of *O*-acylated allylic alcohols in combination with a hydrolase-catalyzed enantioselective hydrolysis of the ester was developed by Allen and Williams [25], leading to the formation of allylic alcohols. For example, when using a lipase from *Pseudomonas fluorescens* and a palladium(II) salt a conversion of 96% and an enantioselectivity of 96% ee was found for the formation of alcohol (*S*)-**17** (Scheme 11.6). Besides limitations in terms of enantioselectivities in some cases, a further challenge consists of improvement of the long reaction times.



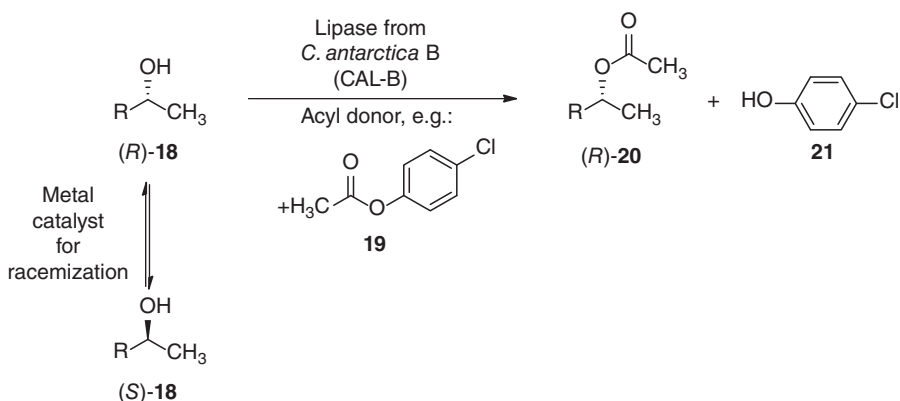
Scheme 11.6 Dynamic kinetic resolution of allylic alcohols in water based on the use of a palladium catalyst for racemization and a hydrolase for enantioselective hydrolysis.

11.3.2

Dynamic Kinetic Resolution Based on Metal-Catalyzed Racemization of the Substrate in Combination with Enzymatic Resolution in Organic Media

On first glance it might look surprising that such types of dynamic kinetic resolution concepts under combination of metal and enzyme catalysis have been developed based on the use of organic reaction media. This is because of the specific properties of, in particular, lipases that work efficiently under organic reaction conditions and even require such an organic phase for achieving high activities. On the contrary, organic reaction media enables the use of “typical” metal catalysts, thus opening a perspective toward a broad range of interesting combinations of metal and enzyme catalysts toward dynamic kinetic resolutions. So far this has been realized in particular for dynamic kinetic resolutions of alcohols and amines [6, 7]. Typically the concept of such resolutions is based on an acylation of alcohols and amines catalyzed by lipases. These steps then led enantioselectively to chiral esters and amides, respectively, which are less prone toward redox racemization in contrast to their corresponding substrates (alcohols, amines). The racemization of the utilized substrate (alcohols, amines) catalyzed by the metal complex is carried out via an *in situ*-reversible oxidation and reduction. The basic principle of this

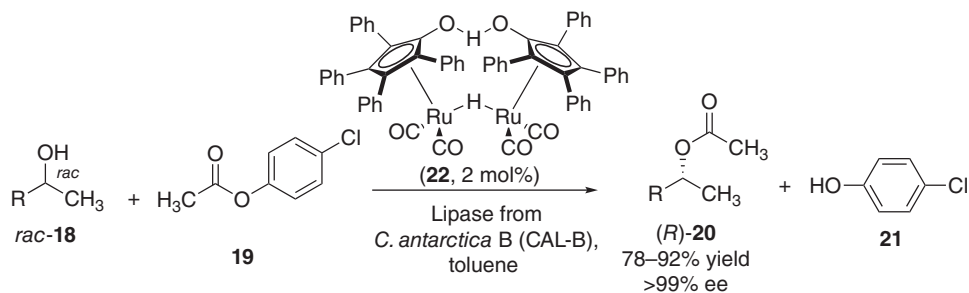
process is shown in Scheme 11.7, exemplified for the dynamic kinetic resolution of racemic secondary alcohols.



Scheme 11.7 Concept of the chemoenzymatic dynamic kinetic resolution with metal catalysts and a lipase exemplified for the synthesis of chiral esters starting from racemic secondary alcohols.

In the first report in the field of such a chemoenzymatic dynamic kinetic resolution of secondary alcohols Williams and Harris *et al.* described a screening of a range of metal complexes based on iridium, aluminum, or ruthenium toward their suitability to racemize (S)-1-phenylethanol, and based on these findings a proof of concept for the combination of such a metal-catalyzed racemization with an enzymatic enantioselective acylation of 1-phenylethanol was developed [26]. However, for this process some additives were required and also conversion was somewhat limited. The first broadly applicable process also running in organic media and showing a high practicability was disclosed by the Bäckvall group [27, 28]. In this chemoenzymatic one-pot process the ruthenium complex **22** (as a redox (pre-)catalyst for racemization of the alcohol substrate) and the lipase (as a catalyst for enantioselective acylation of one of the alcohol enantiomers) act cooperatively as catalysts, thus leading to the desired ester products with both high conversion and enantioselectivity (Scheme 11.8). Notably, the dynamic kinetic resolution proceeds at a (for biotransformations unusual) high temperature of 70 °C, and by means of *p*-chlorophenyl acetate as acylating reagent the desired esters (R)-**20** were obtained in high yields of 78–92% and with excellent enantioselectivities of >99% ee.

Process improvements, which were made by Kim and Park *et al.* [29, 30] as well as Bäckvall *et al.* [31], enabled analogous dynamic kinetic resolutions running at decreased reaction temperature when utilizing modified types of ruthenium catalysts suitable for racemization of alcohols even at room temperature. Notably, both high conversions as well as enantioselectivities were obtained under these smooth reaction conditions.

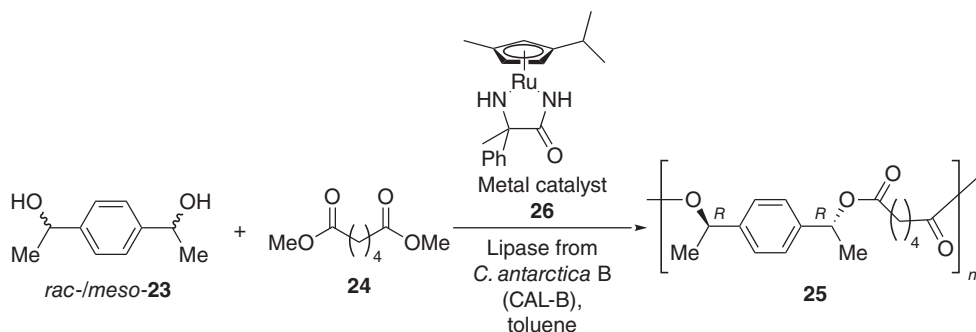


Scheme 11.8 Dynamic kinetic resolution of secondary alcohols running in the presence of metal catalyst **22** and a lipase from *C. antarctica* B.

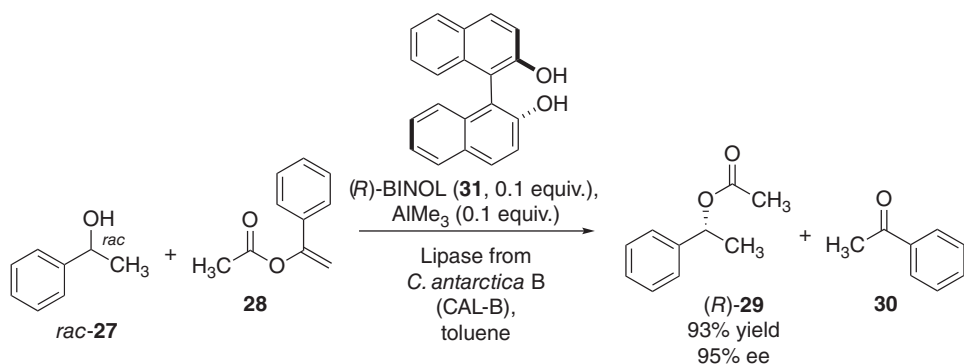
Two further aspects of this technology are noteworthy: first, this technology already made it toward a technically feasible process for industrial purpose. This has been demonstrated by the chemical company DSM utilizing simplified ruthenium or iridium catalysts, respectively, for racemization. In the resulting dynamic kinetic resolution in the presence of a lipase from *Candida antarctica* B, phenylethan-1-ol was transformed into the ester with up to 99% yield and >99% ee [6, 32]. Second, this combination of metal-catalyzed racemization and lipase-catalyzed enantioselective acylation shows an impressive substrate scope [6, 7]. For example, among many other types of suitable racemic alcohols substrates are substituted 1-arylethan-1-ols, 1-heteroarylethan-1-ols, secondary alcohols with two “bulky” substituents, allylic alcohols, and β -halohydrins [33–36].

A further exciting extension of this dynamic kinetic resolution concept toward the synthesis of enantiomerically pure polymers when starting from readily available mixtures of racemic and *meso*-diols (which are easily accessible through reduction of diketones) was shown by DSM researchers [37, 38]. Permanent *in situ*-epimerization of the diol catalyzed through the metal complex in combination with simultaneous lipase-catalyzed acylation of one specific alcohol moiety [bearing the preferred absolute (*R*)-configuration] with a diester **24** as an acylation agent then led to the desired chiral polyester **25** with high enantioselectivity and molecular weights in the range of multithousand grams per mol of polymer (Scheme 11.9).

Besides ruthenium catalysts (or heavy metal complexes in general) it is noteworthy that aluminum complexes also turned out to be suitable for racemization of alcohols under conditions feasible to be combined with lipase-catalyzed acylations toward dynamic kinetic resolutions. Berkessel *et al.* [39] demonstrated successfully such a process for a range of secondary alcohols utilizing preferably an aluminum catalyst, which was prepared from trimethyl aluminum and 2,2'-binaphthol in racemic form or enantiomerically pure (*R*)-form. The corresponding esters are formed with both high conversion and enantioselectivity by means of the lipase from *C. antarctica* B as a catalyst as demonstrated, for example, for the synthesis of the ester (*R*)-**29** in 93% yield and with 95% ee (Scheme 11.10).



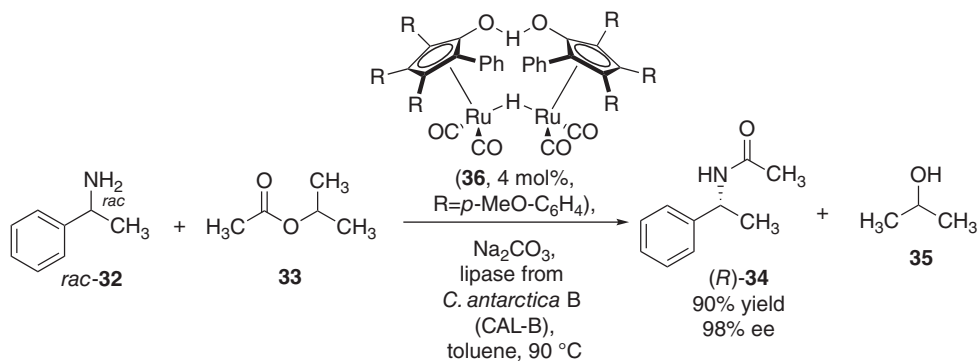
Scheme 11.9 Cooperative catalysis for chiral polyester synthesis using a ruthenium metal complex and a lipase as catalyst components.



Scheme 11.10 Chemoenzymatic dynamic kinetic resolution of secondary alcohols by means of an aluminum complex as a metal component for racemization.

Besides for secondary alcohols, analogous chemoenzymatic dynamic kinetic resolution processes were developed for secondary amines as racemic substrates. In an early work by Reetz and Schimossek [40], Pd/C was used as a catalyst for racemization leading to the corresponding amides in good yield and with high enantioselectivity. For example, when starting from racemic phenylethyl-1-amine as a substrate, the resulting amide was obtained in 64% yield and with 99% ee, however, at a prolonged reaction time of 8 days. A broadly applicable dynamic kinetic resolution process for amines with shorter reaction time was developed by Bäckvall and Paetzold by means of a ruthenium catalyst operating at a high reaction temperature of 90 °C in combination with a lipase from *C. antarctica B* [41]. A representative example is the synthesis of amide (*R*)-**34** in 90% yield and with 98% ee at a catalyst loading of 4 mol% of the ruthenium catalyst **36** and a reaction time of 3 days (Scheme 11.11).

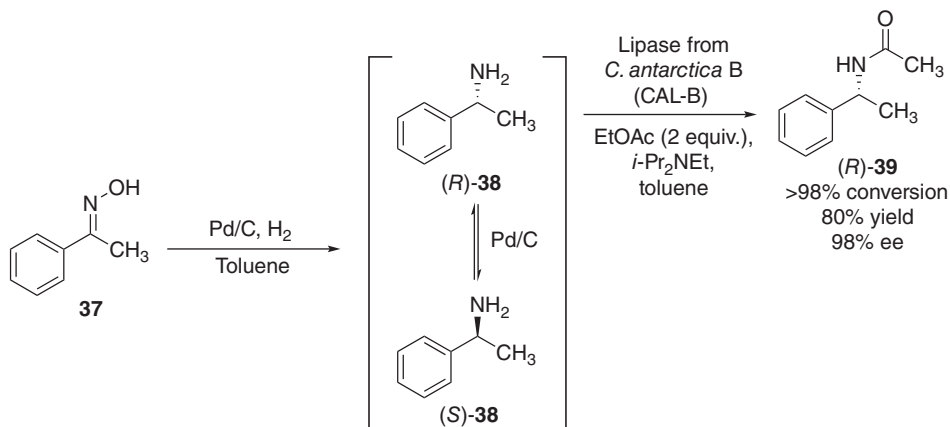
Furthermore, a range of heterogeneous heavy metal catalysts turned out to represent suitable racemization catalysts showing also a high compatibility with the



Scheme 11.11 Dynamic kinetic resolution of an amine through combination of a ruthenium catalyst and a lipase.

lipase catalyst for dynamic kinetic resolutions of amines, leading to both high conversion and enantioselectivities. Such a process based on the use of heterogeneous palladium catalysts on alkaline earth metal salt supports for racemization was reported by Jacobs *et al.* [42], and Kim *et al.* [43] utilized a palladium nanocatalyst in this type of dynamic kinetic resolution.

An interesting extension of this process type under integration of substrate synthesis was developed by Kim *et al.*: in the first step, a ketoxime (which is readily accessible through condensation of a ketone with hydroxylamine) is reduced to the racemic amine, followed by a subsequent chemoenzymatic dynamic kinetic resolution process (Scheme 11.12) [44]. As a metal component heterogeneous Pd/C is used for both hydrogenation and racemization. In such a multistep one-pot process the ketones, e.g., **37**, were transformed into amides, e.g., (R)-**39** with conversions of >98% in all cases and with up to 99% ee.



Scheme 11.12 Enantioselective chemoenzymatic multistep one-pot transformation of ketoximes into amides with integrated dynamic kinetic resolution.

11.4

Combinations of Metal Catalysis and Biocatalysis Toward “Consecutive” One-Pot Processes without Intermediate Isolation

11.4.1

Introduction of the Concepts of “Consecutive” One-Pot Processes without Intermediate Isolation

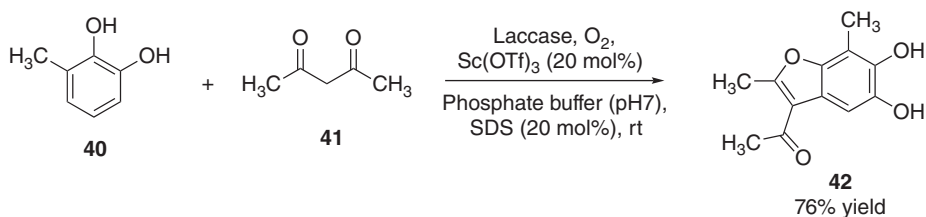
As a consecutive one-pot process one can define the combination of a substrate synthesis by a method other than racemization, in particular racemization, with a subsequent second transformation. Typically, such initial reaction steps involve carbon–carbon bond formations or redox processes. In general, one can consider different options of consecutive processes and there is no general rule (and in contrast more case-by-case dependent) as to which of the concepts are most suitable because all of these options have their strengths and weaknesses. In the following paragraphs, a very brief and preliminary overview is given: (i) Tandem-like processes in which both catalysts, here metal catalyst and enzyme, act at the same time. As a consequence the intermediate is directly converted into the desired product without accumulation. This process is in particular interesting when, for example, labile and rather unstable substrates are formed or when equilibrium issues require a second step for shifting the equilibrium toward the desired product formation. (ii) One-pot processes that complete the initial reaction prior to catalyst addition for the second step. This strategy is in particular advantageous in cases when the catalyst for the second reaction can also convert the substrate of the first step or is inhibited by a reagent consumed in the first step. In the following examples, the cooperative effects of metal and enzyme catalysts according to both types of consecutive one-pot processes are given.

11.4.2

“Consecutive” One-Pot Processes Running in a Tandem-Mode

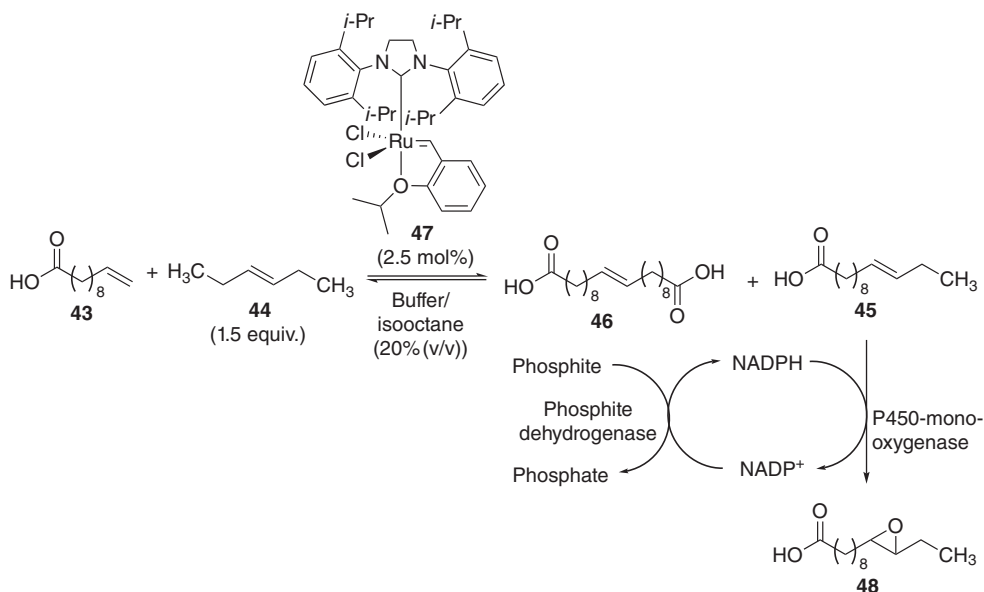
To start with the one-pot processes conducted in a tandem-mode, a combination of a laccase-catalyzed oxidation with a subsequent Michael addition catalyzed by the hard Lewis acid scandium triflate was reported by Ragauskas and coworkers [45]. This process was applied for the synthesis of benzofuran derivatives, for example, **42**. In the first step of this tandem process a substituted catechol is converted initially into an *o*-quinone derivative by means of the enzyme catalyst. Then, subsequent Michael addition with diketone **41** and an intramolecular oxo-Michael addition gives regioselectively one isomer of the benzofuran derivatives (Scheme 11.13).

The combination of an olefin metathesis and a biotransformation toward a tandem process was reported by Zhao and Hartwig *et al.* for the synthesis of epoxy-functionalized fatty acids [46]. In detail, the metathesis reaction as a reversible transformation is conducted by means of a ruthenium catalyst, and a P450-monooxygenase serves as a catalyst for the irreversible epoxidation, thus



Scheme 11.13 Combination of a laccase-based oxidation and a scandium triflate-catalyzed Michael addition in a one-pot process running in tandem-mode.

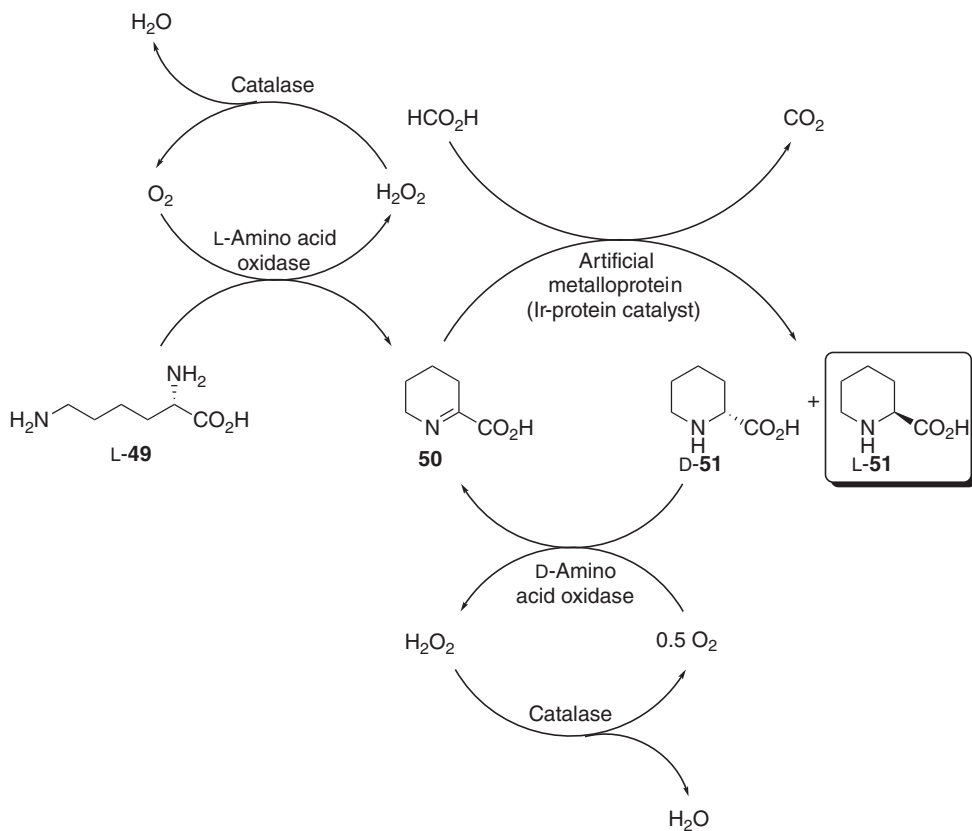
shifting also the metathesis reaction in the desired direction. For example, when starting with the unsaturated fatty acid **43** the desired epoxy fatty acid product **48** was obtained in 27% yield (Scheme 11.14), which is 1.5-fold higher compared with the hypothetical yield of 18% (which was calculated from the two reaction steps when conducted as individual reactions in separated fashion) resulting from a stepwise process with the two reactions carried out in a separated fashion and isolation of the metathesis intermediates.



Scheme 11.14 Combination of a metathesis reaction and an enzymatic epoxidation in a tandem-type one-pot process.

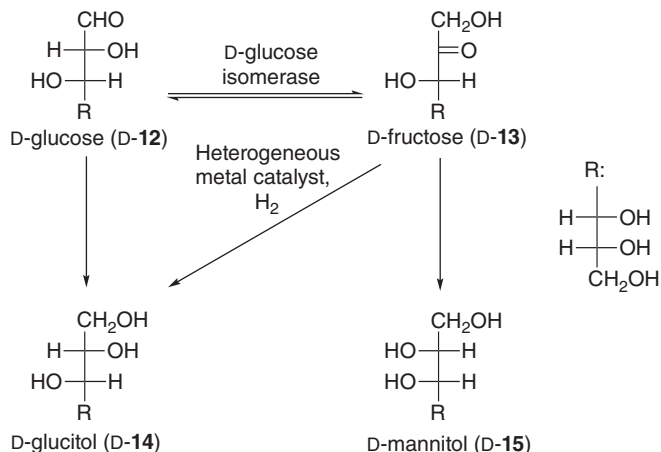
Furthermore, several tandem-type processes based on the cooperative use of an “artificial metalloprotein” as a metal catalyst in combination with oxidoreductase-type enzymes were developed by Hollmann, Turner, and Ward *et al.*, in which the metalloprotein component serves as an artificial transfer hydrogenase [47]. A very successful example is the application of this concept toward a

multistep one-pot transformation of readily available L-lysine into L-pipecolic acid, L-**51** (Scheme 11.15). First, Δ^1 -piperidine-carboxylic acid, **50**, is synthesized from L-lysine through enzymatic oxidation and spontaneous ring-formation via condensation. Next, reduction of the imine moiety in **50** by means of the artificial iridium-protein-complex gives a mixture of D- and L-enantiomers of pipecolic acid, **51**. Subsequently, a deracemization-type process takes place: an enantioselective oxidation of the enantiomeric mixture of **51** with a D-amino acid oxidase enantioselectively consumes only the D-amino acid under formation of prochiral **50**, whereas the L-enantiomer of **51** remains unchanged, leading to L-**51** with high enantioselectivity. As a further enzyme catalase is needed to decompose the formed hydrogen peroxide.



Scheme 11.15 Combination of an iridium-protein-complex as “artificial metalloprotein” with redox enzymes toward a multistep one-pot process for the synthesis of L-pipecolic acid.

Although not representing a “consecutive” reaction process according to the definition given above in Section 11.4.1, a related tandem process consisting of an enzymatic isomerization and a metal-catalyzed hydrogenation of the isomers is



Scheme 11.16 Combination of heterogeneous metal-catalyzed hydrogenation and enzymatic isomerization for L-mannitol synthesis.

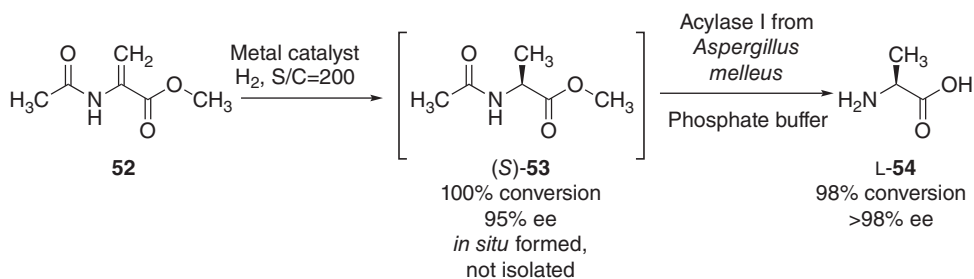
described in the following. The concept of combining these reactions with each other has been successfully addressed in their pioneer work by van Bakkum *et al.*, which was reported early in 1980 (Scheme 11.16) [48]. It should be added at this stage that this process not only demonstrates an early and very successful proof of concept for the high compatibility of (heterogeneous) metal catalysts with biocatalysts, but also represents the first example for the combination of a chemocatalyst with a biocatalyst toward a synthetic chemoenzymatic multistep one-pot process. The hydrogenation by means of metal catalysts belongs to one of the most important organic transformations and also represents a process technology of high industrial importance. At the same time, representatives of E. C. 5, so-called isomerases, are suitable to interconvert different types of isomers into each other. In order to develop an efficient process for the sugar substitute D-mannitol starting from the readily available D-glucose as a substrate, in the initial step, an enzyme-catalyzed isomerization of D-glucose into D-fructose is carried out by means of a D-glucose isomerase. Subsequently, a hydrogenation step by means of a heterogeneous platinum catalyst is conducted *in situ* with a preference for the desired hydrogenation of D-fructose compared with the hydrogenation of D-glucose. For example, in the presence of an immobilized isomerase as biocatalyst and Pt/C (5%) as heterogeneous metal catalyst such a combination of isomerization and hydrogenation (running at 20 atm of molecular hydrogen) then gives a product mixture consisting of 46% of D-mannitol, 46% of D-glucitol, 3% of D-fructose, and 5% of the remaining substrate D-glucose. In addition, a detailed screening work of the impact of both types of catalysts, namely, the immobilized D-glucose isomerase and heterogeneous metal catalyst, has been carried out. Therein it was found by Stewart and Ruddlesden that a ruthenium-loaded zeolite can also serve as a suitable catalyst in combination with a D-glucose isomerase, leading to D-mannitol in

a 29% yield [49]. Furthermore, an improved process was reported by van Bekkum *et al.*, which is based on the use of a heterogeneous copper-on-silica catalyst for the hydrogenation step in combination with a D-glucose isomerase immobilized on silica, which then led to the formation of D-mannitol in high yields of 62–66% [50]. As substrate components, both a 1 : 1 mixture of D-glucose and D-fructose as well as D-glucose alone have been utilized successfully.

11.4.3

“Consecutive” One-Pot Processes with Completion of the Initial Reaction Prior to Catalyst Addition for the Second Step

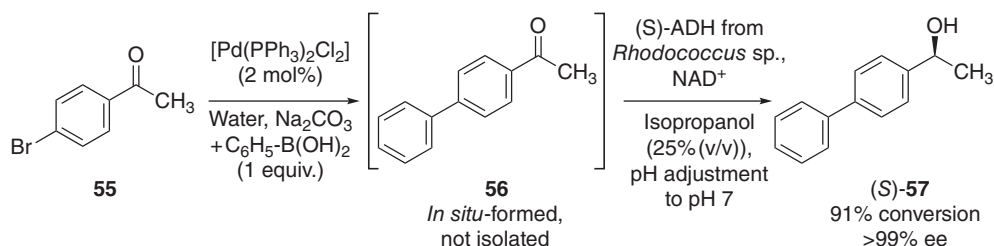
The combination of a metal-catalyzed hydrogenation and a subsequent aminoacylase-catalyzed hydrolysis, thus representing at the same time the first example of a combination of a metal-catalyzed substrate synthesis with a biotransformation conducted in a “consecutive” two-step one-pot fashion, was developed by Hanefeld, Maschmeyer, Sheldon *et al.* for enantioselective L-amino acid synthesis [51]. The initial step consists of an enantioselective hydrogenation of methyl *N*-acetyl amino acrylate **52** in the presence of a heterogeneous rhodium-diphosphane-catalyst under formation of *N*-acetyl alanine, (*S*)-**53**, with 100% conversion and 95% ee (Scheme 11.17). After separation of the immobilized metal catalyst an L-aminoacylase-catalyzed enantioselective hydrolysis then furnishes the desired amino acid L-alanine, L-**54**, with 98% conversion and with >98% ee.



Scheme 11.17 Combination of a metal-catalyzed hydrogenation and an aminoacylase-catalyzed hydrolysis toward a one-pot process for L-alanine.

A further important field of metal-catalyzed applications are carbon–carbon bond formations, and a broad range of such processes has been successfully developed. One of the “key metals” in this area is palladium. Accordingly, there has also been an interest in combining successful palladium-catalyzed reactions with biotransformations toward one-pot processes. The combination of the Suzuki reaction as a representative example for a palladium-catalyzed cross-coupling reaction with an enantioselective alcohol dehydrogenase-catalyzed ketone reduction in a one-pot process running in aqueous medium has been jointly developed by Gröger and Hummel *et al.* for the synthesis of biaryl-substituted

secondary alcohols (Scheme 11.18) [52]. In the first step, the Suzuki reaction gives a biaryl-substituted ketone an intermediate, which is then enantioselectively reduced by means of the biocatalyst. In order to achieve compatibility of the reaction mixture resulting from Suzuki cross-coupling with the biotransformation, the enzyme-critical component boronic acid had to be consumed prior to the addition of the alcohol dehydrogenase. For example, the biaryl alcohol (*S*)-**57** was formed in 91% yield and with >99% ee when starting from *p*-bromoacetophenone **55**. An extension of this two-step one-pot concept toward the synthesis of chiral C2-symmetric diols as monomers for chiral polymer synthesis has also been reported by Gröger and Hummel *et al.* [53].

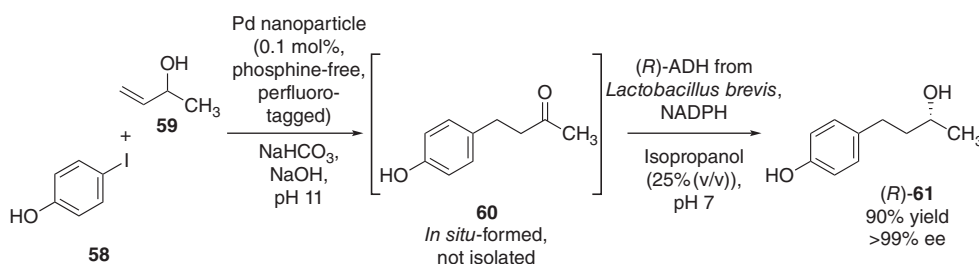


Scheme 11.18 Combination of palladium-catalyzed Suzuki reaction and biocatalytic ketone reduction in a one-pot process running in aqueous medium.

On the basis of this type one-pot process, several successful extensions and improvements have been reported by various groups. Cacchi *et al.* utilized water-soluble palladium nanoparticles, which were stabilized within the protein cavity of a thermostable DNA binding protein, thus leading to a phosphane-free palladium catalyst being a very efficient catalyst for the Suzuki reaction as well as compatible with the subsequent enzymatic ketone reduction within a one-pot process. In their one-pot syntheses Cacchi *et al.* obtained the desired biaryl alcohols in up to 91% yield and with >99% ee [54]. Furthermore, Schmitzer and Kroutil *et al.* reported process conditions suitable for efficient recycling of the catalyst components [55]. In this process the Suzuki cross-coupling reaction runs in an ionic liquid phase, whereas the subsequent enzymatic ketone reduction proceeds in a biphasic system consisting of the ionic liquid phase and buffer. Both phases can be recycled, and the ionic liquids phase as well as the aqueous phase were successfully reused up to four reaction cycles, thus obtaining the biaryl alcohol product in 94–98% yield and with >99% ee. An analogous chemoenzymatic one-pot process running at decreased reaction temperature was established by Gröger, Schatz, and Hummel *et al.* [56]. Utilizing a water-soluble palladium-phosphane complex at room temperature as metal catalyst furnished the biaryl-substituted products in good yields, thus demonstrating a high compatibility of this palladium complex with the enzymatic reaction.

The Heck reaction as a further palladium-catalyzed cross-coupling reaction was also combined with an enzymatic ketone reduction toward a two-step one-pot process. As a first methodology, Cacchi *et al.* carried out a Heck reaction of an

aryliodide with butanone in organic media and used the crude product obtained after the removal of the volatile components for a subsequent biocatalytic reduction [57]. It was demonstrated that the alcohol dehydrogenase is compatible with this crude product, thus enabling formation of the resulting allylic alcohols in up to 85% yields and with excellent >99% ee for all examples. Furthermore, a combination of a Heck reaction running in aqueous media has been combined with an enzymatic reduction toward a one-pot process by Cacchi *et al.* [58]. As a catalyst for the Heck reaction a phosphine-free perfluoro-tagged palladium nanoparticle turned out to be very suitable for the Heck reaction as well as in terms of compatibility with the enzymatic reduction, thus forming the allylic alcohol products in yields of up to 92% and with excellent >99% ee in all cases. A representative example of this two-step one-pot process is the synthesis of (*R*)-(-)-rhododendrol, (*R*)-**61**, in 90% yield, and with excellent >99% ee (Scheme 11.19).



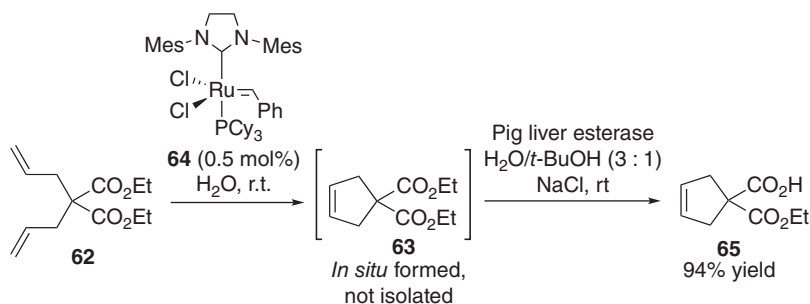
Scheme 11.19 Synthesis of (*R*)-(-)-rhododendrol through combination of a Heck reaction with an enzymatic reduction in a one-pot process in aqueous medium.

Furthermore, also an asymmetric metal-catalyzed carbon–carbon bond formation, namely, an aldol reaction, has been successfully combined with a biotransformation, namely, an enzymatic reduction. After Gröger, Hummel, and Berkessel *et al.* demonstrated that an organocatalytic asymmetric aldol reaction of acetone with an aldehyde can be combined with a biocatalytic reduction of the *in situ*-formed aldol adduct [59, 60], thus forming 1,3-diols with high diastereo- and enantioselectivity in a one-pot process, Aoki *et al.* reported an analogous one-pot synthesis of 1,3-diols based on the use of a metal-catalyzed aldol reaction [61]. As a metal catalyst, phenylalanine-derived Zn(II) complexes were used, and the resulting 1,3-diols were obtained with, for example, 88% yield and 99% ee.

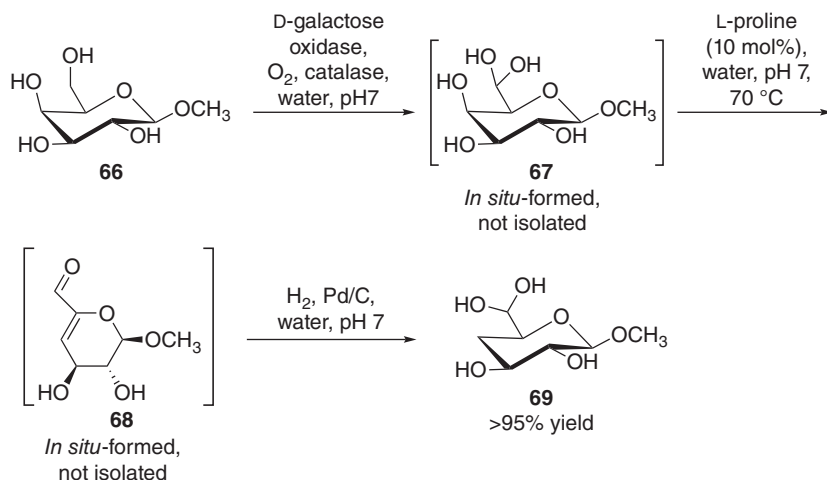
In addition, with the Wacker oxidation a further palladium-catalyzed reaction was combined with an enzymatic reduction, thus enabling a one-pot transformation converting styrene enantioselectively into 1-phenylethan-1-ol [62]. Thus, although the process concept follows a different sequence, this process corresponds to a “formal” addition of water to styrene. The initial steps consists of a Wacker oxidation transforming styrene into acetophenone, followed by an enantioselective enzymatic reduction under formation of 1-phenylethanol. An additive such as thiourea and 1,1'-bipyridine turned out to be needed for an efficient biotransformation step (thus presumably complexing metal complexes

formed in the first step, which turned out to have a negative impact on the biotransformation step).

A catalytically important metal apart from palladium, which was also successfully combined with biotransformations in consecutive reaction sequences, are ruthenium-based metathesis catalysts. The first example in this field has been reported by Gröger and Schatz *et al.*, who combined a ring-closure metathesis of diethyl 2,2-diallylmalonate, **62**, with a selective hydrolysis using pig liver esterase (Scheme 11.20) [63]. In such a one-pot process the desired monoester **65** was obtained in high yield of 94%, thus indicating a high compatibility of the metathesis catalyst with the biotransformation. The high tolerance of the ruthenium catalyst for the enzyme component was also demonstrated when conducting biotransformations in the absence and presence of the metathesis catalyst: in these experiments similar reaction courses have been observed.



Scheme 11.20 Combination of a metathesis reaction with enzymatic hydrolysis in a one-pot process.



Scheme 11.21 Combination of catalysts from all three disciplines – metal catalysis, organocatalysis, and enzyme catalysis.

A concept of consecutive reaction sequences toward integration of all three catalytic disciplines – metal catalysis, organocatalysis, and biocatalysis – has been demonstrated by Kieboom and Schoevaart in their synthesis of methyl 4-deoxy-6-aldehydo- β -D-xylo-hexapyranoside (**69**, Scheme 11.21) [64]. In the initial step a galactose oxidase catalyzes the oxidation of the D-galactoside derivative **66** with molecular oxygen. Subsequent organocatalytic dehydration with proline gives the enal **68**, which is then transformed in a metal-catalyzed hydrogenation with Pd/C as a metal catalyst under formation of the desired product **69** as the single product with >95% yield.

11.5

Summary and Outlook

In conclusion, combination of metal catalysis and enzyme catalysis turned out to be suitable for numerous different chemocatalytic as well as biocatalytic reactions, which enabled the development of proof of concepts for a broad variety of chemoenzymatic one-pot processes. Notably, a range of metal catalysts turned out to be compatible with enzymes as a prerequisite for establishing such one-pot processes. The developed one-pot processes based on cooperative metal and enzyme catalysis can be clustered into three major types of combinations, which are (i) metal-catalyzed *in situ*-regeneration of cofactors required for enzyme-catalyzed redox reactions under consumption of the cofactors NAD(P)H or NAD(P)⁺, (ii) racemization of a substrate with a metal catalyst combined with an enantioselective transformation of the substrate catalyzed by an enzyme toward dynamic kinetic resolutions, and (iii) consecutive one-pot processes in which formed intermediates were directly converted into the corresponding products (e.g., a reversible initial metal-catalyzed transformation and a subsequent irreversible enzymatic transformation).

Representing a young and emerging research field, among current challenges, is the extension of the range of chemoenzymatic one-pot processes, thus enabling the use of many other metal complexes as catalyst components running in a cooperative mode with enzymes. In addition, further process development addressing in particular issues such as space-time-yield and downstream-processing of reaction mixtures resulting from one-pot processes are further tasks as well as the development of tailor-made compartmentation strategies for immobilized metal and enzyme catalysts in cases when their direct synergistic use is not possible.

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12

Cooperative Catalysis on Solid Surfaces versus Soluble Molecules

Michael M. Nigra and Alexander Katz

12.1

Introduction

Cooperative catalysis relies on a delicate degree of control of molecular connectivity and environment at an active site, beyond that of just bulk composition, and benefits greatly from an understanding of how catalyst geometry and structural features impact catalysis, in order to achieve catalytic cooperativity. Because no synthetic catalyst active sites are as refined from the perspective of structure and geometry as those of enzymes in terms of catalyst design, Nature's catalysts serve as beacons of what is possible on beholding control of catalyst active-site structure at the penultimate level of intricate resolution. From the perspective of materials science, the synthesis-by-design of catalysts on surfaces that function according to cooperative mechanisms benefits the general grand challenge of assembling active-site structures on solids with ever more information density, which is required for enabling cooperativity [1, 2].

Yet when comparing molecular (homogeneous) and surface (heterogeneous) approaches to cooperative catalysts, there has always remained a considerable knowledge gap between these two areas, which is often colloquially referred to as the *homogeneous–heterogeneous gap* in catalysis. This gap requires filling in order to understand what molecular-scale features make synthetic surfaces unique from cooperative soluble molecular analogs with similar function, from a catalytic perspective, and at times advantageous in catalysis over these soluble molecular active-site counterparts, beyond the simple concepts of filtration and ease of catalyst recovery. This understanding of cooperative mechanisms of molecular catalysis on surfaces remains at the state of the art of the field. Specifically, a holy grail is the design of the organic–inorganic interface in solid catalysts so as to mimic, in a crude but general way, approaches used by biological catalysts for achieving cooperativity. This is invaluable for enabling the design of evermore intricate active and selective catalysts in the future – as required by emerging applications [3].

Here, in this chapter, we discuss approaches for understanding enhanced cooperative catalysts on a solid platform, and contrast and compare these with

pertinent soluble molecule cooperative catalysts, which form a bridge between the two areas and emphasize synthesis of organic–inorganic interfaces with greater information density at the active site. Such sites are required for performing multiple functions, such as either controlling the relative strength of binding or the selectivity of a catalyst active site, while still retaining a high degree of activity and enabling a greater degree of tunability of the active site. We describe seminal examples of systems where catalytic structure–function relationships have been elucidated on the molecular level, starting with the ubiquitous concept of acid–base bifunctional catalysis, in which an acid and a base group form a cooperative pair, and discuss the control of binding and reactivity in model organic–inorganic catalysts. By drawing parallels and distinctions between homogeneous and heterogeneous catalysts, when appropriate, this treatment emphasizes that catalysis on surfaces spans the fields of both materials design and molecular catalysis, often using one to advance the other, and vice versa, in a synergistic fashion. The examples also highlight the power of controlling environment around an active site in organic–inorganic materials, and specifically the role that the surface plays in this system versus soluble molecule or enzymatic systems, in terms of decreasing the required precision of organization in order to achieve cooperative catalysis.

12.2

Tuning Cooperativity of Acid–Base Bifunctional Groups by Varying the Distance Between Them in a Soluble-Molecule Platform

Cooperativity between an acid and a base functional group is commonly invoked in enzymatic systems and forms the basis for the ubiquitous push–pull catalysis. The precise geometric placement of the acid and base moieties relative to each other is key to enabling acid–base bifunctional catalysis, as shown in Figure 12.1 for the case of a catalytic antibody, and, as shown by data below, allows for unprecedented high activity and selectivity that cannot be achieved with acid or base groups alone, under very mild conditions.

The original work of Hine *et al.* [5] explores the degree to which it is possible to replicate this high level of bifunctional cooperativity in soluble molecular systems, and highlights the difficulties of doing so when acid–base bifunctional geometric requirements at the transition state for a particular reaction may be unknown. Using the formation of imines from acetone as a model probe reaction that benefits from acid–base cooperativity, Hine *et al.*'s data in Figure 12.2 illustrate an increase in the rate when using a general base molecule, shown as black circles in Figure 12.2, as the primary ammonium pK_a increases, following higher amine nucleophilicity. Such an observation is consistent with the general concept of linear free-energy relations when using a base group on the molecule alone to promote the condensation. On the other hand, for the bifunctional molecule consisting of both acid and base sites, for which data are represented as open squares in Figure 12.2, as the primary ammonium pK_a decreases, the rate

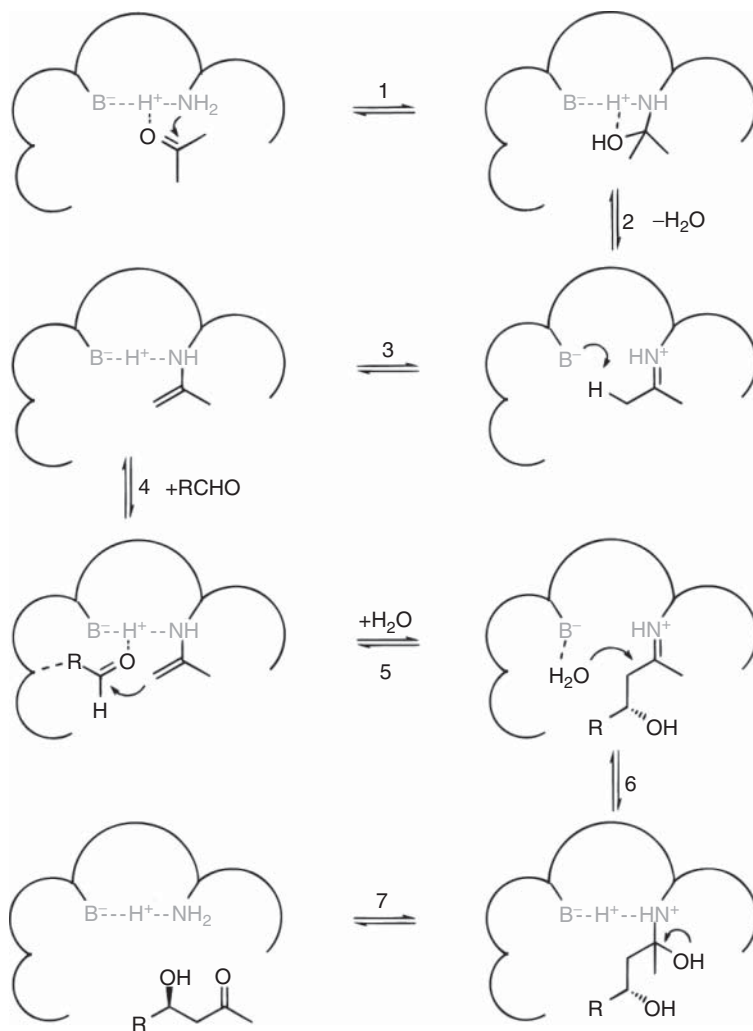


Figure 12.1 Illustration of cooperative catalysis involving an acid and base functional group for the aldol condensation reaction. One can observe the pulling of electron density from the carbonyl oxygen, while polarizing the carbonyl carbon for nucleophilic

attack from base, as shown in the upper left-most panel. Alternatively, one can observe similar acid–base cooperativity involving the enamine as the nucleophile two panels lower. (Adapted from Ref. [4].)

increases approximately 100-fold compared to that for the general base molecule. Also, in contrast to the general-base data in Figure 12.2, for the acid–base bifunctional molecules the rate significantly decreases as the primary ammonium pK_a increases, indicative of a completely different reaction mechanism for the bifunctional catalysts. This different mechanism relies sensitively on the organization of the acid–base pair, which controls the catalytic cooperativity within this

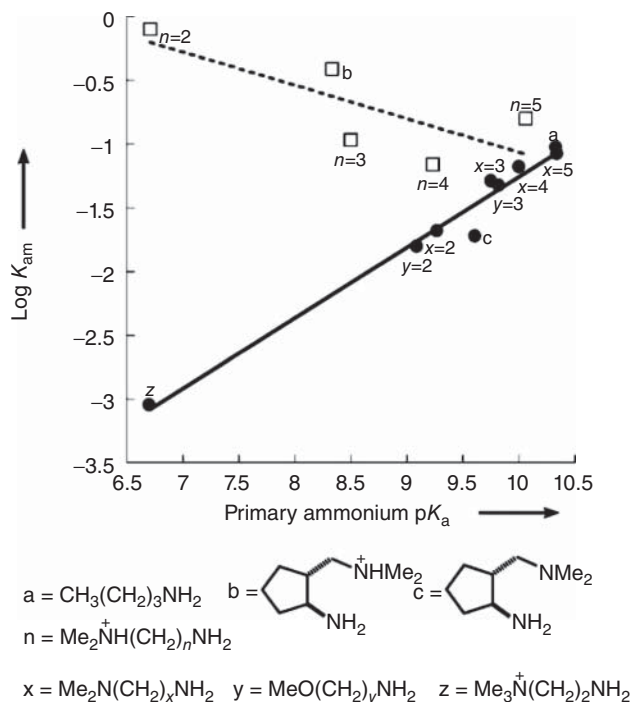


Figure 12.2 Linear free-energy relationships of the logarithm of the rate constant for formation of imines from acetone and various primary amines (k_{am}) versus amine $\text{p}K_{\text{a}}$. (From [2] Copyright © 2006 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Reprinted by permission of Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.)

pair, and this sensitivity can be directly observed by systematically varying the length of the alkyl chain between the acidic $\text{Me}_2\text{N}^+\text{H}$ group and the basic NH_2 group in the $\text{Me}_2\text{N}^+\text{H}(\text{CH}_2)_n\text{NH}_2$ bifunctional molecule. As n increases from 2 to 4, the primary ammonium $\text{p}K_{\text{a}}$ increases, which can be elucidated on the basis of neighboring electrostatic effects; however, the rate of imine formation for the bifunctional catalysts decreases by over an order of magnitude, overriding the effect of increasing primary amine nucleophilicity (solid line in Figure 12.2 for the general base molecules) [5].

It can be hypothesized that the differences in catalytic activity between the bifunctional molecules with alkyl spacers of different lengths between the acidic and basic moieties can be explained by the ability of the catalyst to form hydrogen bonds and stabilize the transition state of the imine formation reaction shown in Figure 12.3, rather than a mechanism that involves basicity alone. Presumably, the likelihood of forming the cyclic transition state as well as the corresponding ring strain associated with the "R" group controls the kinetic barrier for the acetone–amine condensation reactions in Figure 12.3. This is completely orthogonal to the situation of a monofunctional amine reactant, for which the linearity of the solid line in Figure 12.2 demonstrates that only the ability to

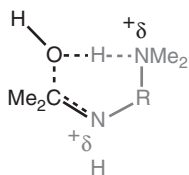


Figure 12.3 Proposed acid–base bifunctional transition state for a reaction consisting of condensation of acetone with primary amine substituent, comprising both pushing of electron density from primary amine and pulling from acidic ammonium cation. (Adapted from Ref. [5].)

“push” electron density via amine nucleophilicity rather than the ability to “push and pull” at the same time as in the bifunctional molecules is what is crucial.

The seminal work of Koshland ties well the extreme sensitivity of optimally positioning two disparate functional groups on a soluble molecular scaffold back to enzymes. Figure 12.4 shows data for the lactonization of a molecule labeled as **I**. This molecule exhibits a rate of lactonization that is 1 660-fold higher relative to intermolecular esterification of acetic acid and ethanol, even when corrected for proximity effects, conformational isomers, and torsional strain. Yet, when the alcohol OH functional group of **I** in Figure 12.4 is changed to a thiol SH, the corresponding rate of intramolecular thiolactonization is reduced 25 000-fold relative to the observed rate of lactonization for **I**. This reduction cannot be explained on the basis of proximity, conformational isomers, or torsional strain, and forms the basis for the concept of orbital steering and Koshland’s induced-fit mechanism of cooperative enzyme catalysis. As shown in Figure 12.4, the thiol analog has a slight mismatch between the lone pairs on sulfur and those on the oxygen, which the corresponding five-membered ring in compound **I** does not. It

(a) Uncorrected rates:

Observed rates*

Uncorrected relative rates

7.23

6630

(b) Corrected rates:

Correction factors:

Corrected rates

Corrected relative rates

Torsional strain: 4.4X

Conformational isomers: 3X

9.95×10^1

1660

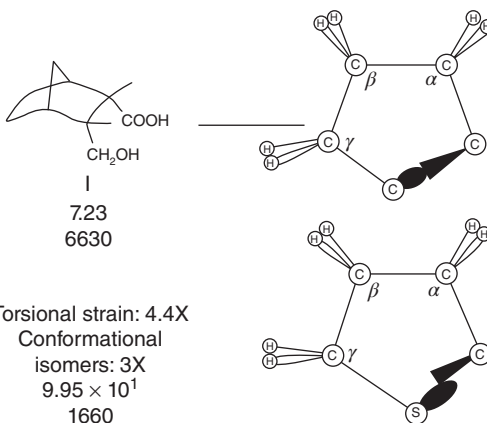


Figure 12.4 Corrected (b) and uncorrected (a) rates of condensation between alcohol and carboxylic acid functionality, to make a lactone in compound **I**. Rates in (b) are relative to the rate of condensation between ethanol and acetic acid. Right panel: diagram showing orbital alignment in compound **I** (top), which promotes the condensation reaction, and lack of such alignment in the

thiol analog of compound **I** (bottom), which results in 25 000-fold decreased rates of lactonization. Though electron orbitals are represented as diffuse clouds, the sensitive dependence of the structure on the rate suggests that the precise fine structure within the cloud determines reactivity. (Reprinted from [6] with permission from the authors.)

is exactly this geometric alignment of orbitals in compound **I** that is hypothesized to account for its greater relative rate of condensation between the alcohol and carboxylic acid functional group. Thus this poignant example from the work of Koshland clearly demonstrates that it is not only proximity but also geometric orientation of two reacting functional groups on a molecule that need to be just right in order for optimum cooperativity between two different functional groups to occur during reaction [6].

In later work, Hine and Flachskam [7] used poly(ethyleneimine) polymers (PEI) as bifunctional catalysts. As the average molecular weight of the PEI polymer increased, the reaction rate of isobutyraldehyde-2-*d* de-deuteration increased. It is hypothesized that the increased rate for the larger molecular weight polymer catalyst comes from this polymer's ability to access a wider range of separation distances between the bifunctional moieties, compared to the lower molecular weight analog [7].

12.3

Acid–Base Bifunctional Catalysts on Two-Dimensional Surfaces: Organic–Inorganic Materials

The following section addresses the question of whether the catalyst design principle of providing an array of geometric possibilities for pairing two cooperative catalytic functional groups can be applied to catalysis on two-dimensional surfaces, where the surface in principle provides a vast array of possibilities for pairing two surface functional groups, related to the role of the one-dimensional polymers in the example above from Hine *et al.* but now presumably enhanced by greater local density of surface-active sites and the additional dimension for pairing that is available on a two-dimensional (or three-dimensional in the case of a microporous material) surface rather than a one-dimensional strand. Such an enhanced

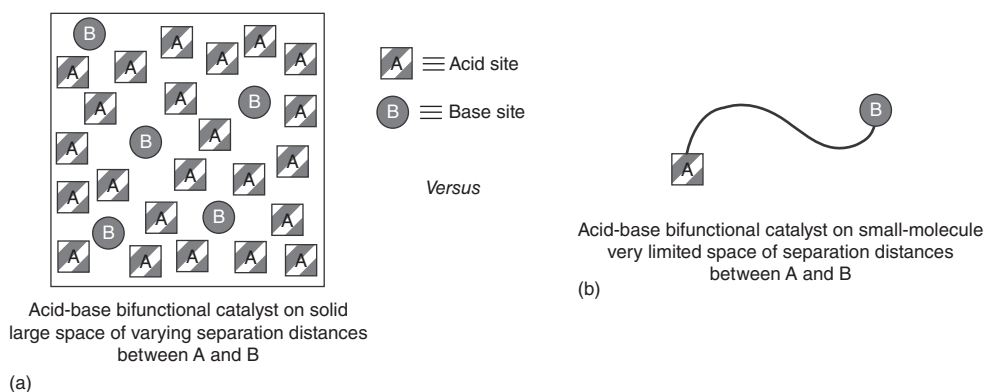


Figure 12.5 Schematic representation for the organization of a base site (B) within an acid-site (A) environment, within the context of a two-dimensional surface (a) as well as a small-molecule (b) platform.

ability to achieve cooperativity between two functional groups as enabled by the solid surface is schematically represented in Figure 12.5 for the case of tethered functionalities on silica. This ability fundamentally reduces to a solid catalyst being able to provide a much higher local density of active sites B within an environment of A-type sites, some of which may be at the correct required distance of separation for cooperativity, than what is possible with a one-dimensional platform, which is usually the category of small-molecule cooperative catalysts.

Referring further to Figure 12.5, Katz *et al.* demonstrated [8] the catalytic effect of cooperativity between an active site B with an environment A on a solid surface, using tethered primary-amine base active sites (B), in which the environment (A) around the active site was controlled by the composition of capping groups (or native silanols) on the silica surface. This approach enabled comparative catalytic studies that dissected the role of dielectric constant and acid–base cooperativity on aldol-related catalysis involving C–C bond-forming reactions. It exemplified the native inorganic-oxide surface as a source of mildly acidic OH-defect sites (i.e., silanols on silica surface), each of which is at a differing distance away from a particular active site (B). This diverse space of silanol distances crucially removes the constraint of atomically precise geometric positioning of functional groups as a requirement for cooperativity, which is present in soluble and enzymatic catalysis.

The effects of controlling the acidity and dielectric environment in the outer sphere environment of a catalyst's active site were first investigated in carbamate thermolysis using materials synthesized using silica imprinting techniques. These materials are shown in Figure 12.6.

Acidity has by far the largest effect on the thermolysis rate, as shown by data in Table 12.1 (these data can equivalently be converted to activation energies using Redhead analysis – demonstrating lowest activation energy for carbamate thermolysis in **II**) [8]. The polar and acidic material **II** exhibits carbamate thermolysis at the lowest temperature as compared to both the aprotic surface environments of materials **III** and **IV** in Figure 12.6. When comparing these latter two materials, the slightly lower carbamate thermolysis temperature for material **IV** versus **III** is a reflection of the higher local dielectric constant of the environment of the polar nitrile-containing catalyst, which is able to more effectively stabilize the charge of the transition state in this reaction.

Katz *et al.* used salicylaldehyde binding (chemisorption) as a reporter of the cooperative local environment surrounding the base active site (B) for materials shown in Figure 12.6, by monitoring the materials after binding using diffuse-reflectance UV–vis spectroscopy. This technique measures the contribution of the zwitterionic iminium tautomer, which is selectively formed on reaction with amines in the polar-acidic catalyst **1**, relative to the neutral phenolic form of the bound salicylaldehyde, which is formed with the aprotic environments in catalysts **2** and **3**. This result unequivocally demonstrates control of selectivity via the surrounding surface as a cooperative environment. It demonstrates acid–base cooperativity, with the environment consisting of acidic silanols in the outer sphere environment of **II** that hydrogen-bond to the phenolate oxygen and thereby stabilize the zwitterion of bound salicylaldehyde in Figure 12.7. The slight red shift

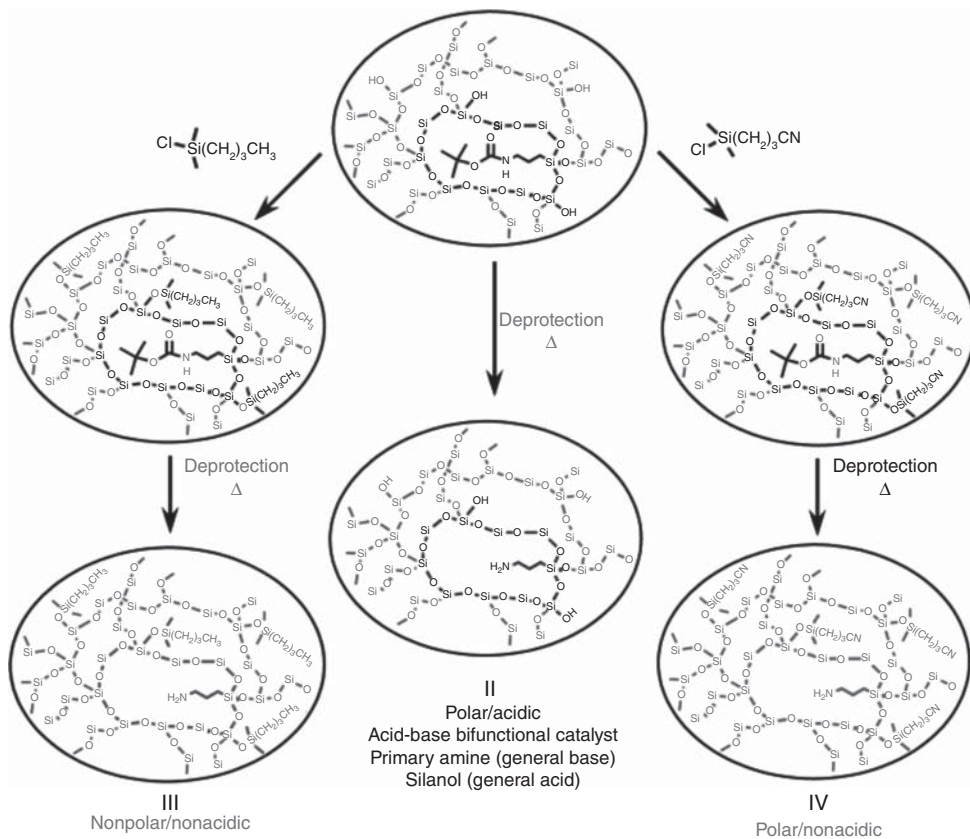


Figure 12.6 Imprinted silica materials used by Katz *et al.* to show the effect of acidic silanols and dielectric constant of the environment in thermolysis and catalysis. (Figure adapted from Ref. [8].)

Table 12.1 Kinetics of immobilized carbamate deprotection via thermolysis [8].

Material	Temperature at maximum rate of thermolysis (°C)
II	198
III	251
IV	244

Source: Table adapted from Ref. [8].

in the position of the neutral phenolic band between **IV** and **III** (i.e., red-shifted band for **III**) in Figure 12.7 is consistent with a higher local dielectric constant for cyano-containing **IV** relative to **III** (because the excited state for the zwitterionic species is less polar than the ground state).

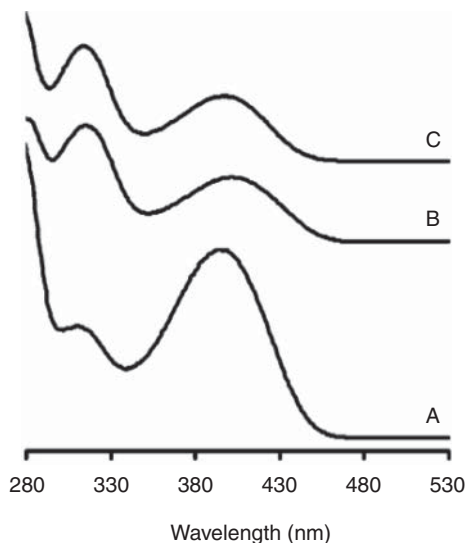


Figure 12.7 Solid-state diffuse reflectance UV–vis spectra in Kubelka–Munk units of salicylaldehyde bound to tethered amine sites in various environments as defined by (A) polar/acidic catalyst **II**, (B) nonpolar/nonacidic catalyst **III**, and (C) polar/nonacidic catalyst **IV** after reaction with salicylaldehyde to form a solvochromatic indicator. The bound probe in **II** shows a zwitterionic band at approximately

400 nm because of the acidic silanol environment. The bound salicylaldehyde within the nonacidic environments of **III** and **IV** exhibits the phenolic band as the predominant one, at around 315 nm, with the more polar environment of **IV** resulting in a blue shift in the position of this band relative to **III**. (Reprinted with permission from [8]. Copyright 2006 American Chemical Society.)

Further examples of the catalytic behavior of materials **II**, **III**, and **IV** illustrate the effect of the environment around a site in a solid catalyst. Using **II**, **III**, and **IV** in the Henry (nitroaldol) reaction, it is observed that the reaction proceeds via two different pathways depending on the outer-sphere environment: one is through imine formation, and the other is through an ion-pair mechanism. In the acidic environment of material **II**, cooperativity between acidic silanols and the primary amine shuttles catalysis through an iminium cation intermediate, which synthesizes a highly electrophilic azomethine carbon atom that is a much more potent electrophile (and one invoked within the mechanism of enzymes) than the carbonyl carbon. This leads to selective formation of the α,β -unsaturated product under kinetics that are zero order in aldehyde reactant, which is consistent with the aldehyde binding being quasi-equilibrated under acid–base bifunctional catalysis conditions. In contrast, in catalyst **IV**, the reaction proceeds through an ion-pair mechanism involving an aldolate anion that is derived by deprotonating the acidic methylene compound directly, which attacks the carbonyl carbon as electrophile, and, subsequently, the rate of β -nitroalcohol formation is approximately 50 times greater than on **III**, following the ability of **IV** to better stabilize the formation of ion pairs and separate charge. Similar observations were also

observed in the Knoevenagel condensation reaction of 3-nitrobenzaldehyde and malononitrile, where the acidic silanol-primary amine cooperativity in **II** exhibited the highest rates and proceeded through an imine mechanism as with the Henry reaction. Material **IV** was also observed to have a faster rate than **III** by a factor of 3 because of dielectric effects described earlier. In another reaction, consisting of the general base-catalyzed Michael addition of malononitrile to β -nitrostyrene, the effect of the higher dielectric environment of the polar catalyst **IV** led to a sevenfold increase in rate relative to the nonpolar outer sphere environment of catalyst **III**. The polar environment is more favorable to the ion-pair formation and separation of charge necessary for the transition state of this reaction.

The examples above are not the first ones where either acid–base bifunctional or other type of surface cooperativity has been invoked in solid catalysts [9, 10]. For example, pioneering work by Tanabe *et al.* has demonstrated that a bifunctional zirconium oxide catalyst can have its basic sites poisoned by carbon dioxide and lose its catalytic activity for the isomerization of 1-butene. However, at the same time, the acidic sites of zirconium oxide were poisoned by *n*-butylamine and led to a decrease in activity of the dehydration of *sec*-butanol [11]. The examples of Katz *et al.* described above are the first to spectroscopically characterize the signature intermediate of acid–base bifunctional catalysis (iminium tautomer formed selectively on binding salicylaldehyde on such a catalyst), and crucially dissect the effect of dielectric constant from acid–base cooperativity in catalysis on solids. In all cases, the surface acts as a microsolvation environment surrounding the tethered amine base site to enforce several cooperative interactions at varying distances between native acidic silanol groups (or capping substituents on the silica surface).

In stark contrast, no evidence for acid–base bifunctional cooperativity could be achieved in molecules consisting of calixarenes containing both acid site and pendant amine as substituents [8]. Binding of salicylaldehyde to these calixarene amines synthesized products whose tautomerism was controlled entirely by the solvent and where the nearby nest of three phenolic OH groups did not alter the zwitterion-neutral phenolic tautomer equilibrium, despite the ability of this nest to fully protonate the amine, as fully characterized by single-crystal X-ray diffraction. Yet, when a similar calixarene was anchored to the surface of silica and salicylaldehyde was condensed to this amine, the zwitterionic product was observed exclusively [12]. This result means that the calixarene amine has cooperativity only after anchoring to the surface of silica – but not when acid groups are exposed on the adjacent substituents on the calixarene. This result demonstrates that silanols can be proficient at achieving cooperativity with tethered amines on silica, whereas the three phenolic OH groups of the calixarene are unable to do so, despite having pK_a values similar to those of silanols on silica [8].

Zeidan and Davis [13] elegantly probed the effect of functionalizing silica with moieties that are more acidic than the native silanols described above, which they demonstrated to function cooperatively in catalysis as an environment (A in Figure 12.5) surrounding surface-tethered amine sites (B in Figure 12.5) on silica. Three different silica-tethered acid groups (site A in Figure 12.5) were investigated within this context, and these consisted of sulfonic, phosphonic,

and carboxylic acid sites, with pK_a values of approximately -2 , 3 , and 5 (for reference, the average pK_a of a native silica silanol is approximately 7), respectively. Zeidan and Davis [13] used these acid–base bifunctional catalysts for the aldol condensation between *p*-nitrobenzaldehyde and acetone. Though these functionalities completely neutralized one another and resulted in catalytically inactive salts in solution, when both the acid and base were immobilized on the silica surface (of silica SBA-15), the conversions were 62%, 78%, and 99%, for the sulfonic, phosphoric, and carboxylic acid groups, respectively, after 20 h, as

Table 12.2 Catalytic data for bifunctional catalysis of an aldol condensation with acids of varying strength paired with primary amines on silica.

Reaction scheme: *p*-nitrobenzaldehyde + acetone $\xrightarrow[50\text{ }^\circ\text{C}]{\text{Catalyst}}$ A + B

Entry	Catalyst (10 mol%)	% A	% B	Total conversion
1		45	17	62
2		62	16	78
3		75	24	99
4		0	0	0
5		0	0	0
6		8	8	16
7		25	8	33

Source: Reprinted from [13], Copyright 2007, with permission from Elsevier.

summarized in Table 12.2. This type of activity trend favoring weaker acids to act cooperatively with amines as bifunctional catalysts has been observed in other systems as well [14]. Control experiments demonstrate significantly reduced catalysis by materials functionalized with amines, acids, or a physical mixture of these monofunctional materials (Table 12.2) [13]. Other relevant examples of an active site (B) functioning cooperatively within an environment (A) on the surface of a solid catalyst are summarized in review articles [2, 15, 16] and include phenalkyl phenyl ether pyrolysis [17, 18], which is relevant for lignin depolymerization, as well as depolymerization of polysaccharides via hydrolysis, which is discussed further below.

The examples above clearly highlight the ability of a surface to function as an array of acid sites that facilitates cooperativity in catalysis with a surface-tethered base site, in a manner that is difficult to accomplish with a soluble molecular scaffold. This enables versatile acid–base bifunctional catalysis on surfaces that spans many reactions, all of which have different distance requirements, when using the same catalyst. The comparisons with soluble homogeneous catalysts above demonstrate that such versatility is difficult to achieve, in general, when using a soluble molecular catalyst. One of the notable exceptions to the last statement is a class of soluble molecular catalysts that still achieves a high local density of acid site (A in Figure 12.5) as an environment surrounding an active site (B in Figure 12.5). Such examples may consist of hydrolysis catalysts based on a cyclodextrin system studied by Rao *et al.* [19] and an ascorbic acid system by Shaskus and Haake [20], both consisting of a nucleophile active site (B in Figure 12.5) surrounded by multiple OH groups (environment of A in Figure 12.5). In both of these last two examples, catalytic cooperativity may be enforced by the same approach of having a high local density of OH groups in the vicinity of the nucleophilic center, as in Figure 12.5a, representing the solid surface. In the following section, we describe in detail other soluble molecular systems, relating to kinetic resolution of racemic epoxides, which also achieve a similar construct enforcing a preferred environment at a high local density surrounding a catalyst active site in order to achieve catalytic cooperativity.

12.4

Cooperative Catalysis on Surfaces versus Soluble Molecular Platforms for Kinetic Resolution of Racemic Epoxides

Kinetic resolution of epoxides is a powerful method for resolving racemic epoxides, and, when using water as nucleophile in hydrolytic kinetic resolution (HKR), for synthesizing chiral diols or alcohols in quantitative yields, high enantioselectivity, and mild reaction conditions [21]. These reactions are catalyzed by chiral metal-salen complexes as originally proposed by Jacobsen and coworkers. From the perspective of cooperativity, two metal-salen complexes cooperate within the mechanism: one is thought to activate the epoxide as a Lewis acid, while the other binds the nucleophile (hydroxide in HKR). Such bimetallic cooperativity between

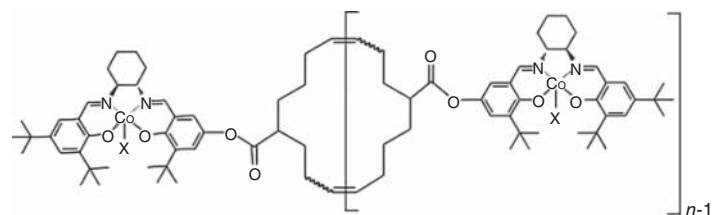
two salen complexes is consistent with the observed second-order kinetics for HKR when using metal-salen catalysts, as well as full characterization of the bound nucleophile when using trimethylsilylazide and phenol [22].

Jacobsen originally demonstrated that the cooperativity between two Co-salen complexes and the corresponding rate of HKR could be accelerated greatly by synthesizing catalysts consisting of a dimeric metal-salen complex [23]. Similar to the trends in the work of Hine *et al.* described above, Jacobsen's data in this area demonstrate how the sensitivity of cooperativity depends on the separation distance and geometry of the two groups involved [23].

With hydroxide derived from water as the nucleophile, Jacobsen *et al.* also investigated how cooperativity between two sites can be enhanced by increasing local density of Co(III)-salen complexes in soluble molecular structures. Jacobsen compared HKR catalysts consisting of monomeric and cyclic lactone oligomeric complexes [24]. In this case, the oligomer consists of a mixture of ring sizes corresponding to 2–5 Co(III)-salen complexes within the cycle. The rate and enantioselectivity of HKR are greatly improved (more than the order of magnitude effect on rate) when using the oligomerized catalyst, because this catalyst facilitates two Co centers to approach one another in a more facile manner than what is possible with monomer, presumably because of both the intrinsic flexibility of the macrocyclic lactone ring and the higher local Co density within the oligomerized complex. Using related effects, Jacobsen *et al.* also increased HKR rates with a dendrimer platform for organizing Co-salen complexes [25].

Weck *et al.* systematically investigated the effect of local number density of Co(III)-salen complexes pendant on a macrocycle on the catalytic activity of the HKR catalyst, as shown in Figure 12.8, for catalysts consisting of monomer, dimer, trimer, tetramer, and larger macrocycle mixtures of tetramer to hexamer and pentamer to decamer. At the same catalyst loading (0.01 mol%), the dimeric species exhibited barely detectable catalytic activity. A sharp monotonic enhancement of the catalytic activity was observed on increasing the macrocycle ring size and the corresponding number of Co(III)-salen oligomers within the ring. Indeed, the larger isolated cyclic Co(III)-salen oligomers demonstrate an exceptional increase in reactivity, enantioselectivity, and reaction scope, making them the most active and selective Co(III)-salen HKR catalysts that have been reported to date.

The ability to enforce a cooperative bimetallic mechanism for HKR catalysis in this system increases monotonically as the size of the macrocycle increases. Qualitatively, as the macrocycle size increases in this system, the organization for enforcing cooperativity changes from one dimensional (corresponding to Figure 12.5b) to two dimensional (corresponding to Figure 12.5a), with a corresponding increase in HKR catalytic activity and enantioselectivity. Molecular dynamics modeling studies indicate that the dimer lacks the required flexibility to allow adjacent Co(III)-salen groups to form a bimetallic complex – as required in the HKR catalysis scheme of Figure 12.5. Indeed, the dimer, regardless of the cis or trans distribution, never formed a complex between the two Co-salen sites during modeling. These modeling studies further demonstrate that the larger cyclic structures more efficiently enforce cooperativity, by bringing two or more



Monomer ($n = 2$); dimer ($n = 3$); trimer ($n = 4$); tetramer ($n = 4$); pentamer ($n = 5$); hexamer ($n = 6$); heptamer ($n = 7$); octamer ($n = 8$); nonamer ($n = 9$); decamer ($n = 10$)

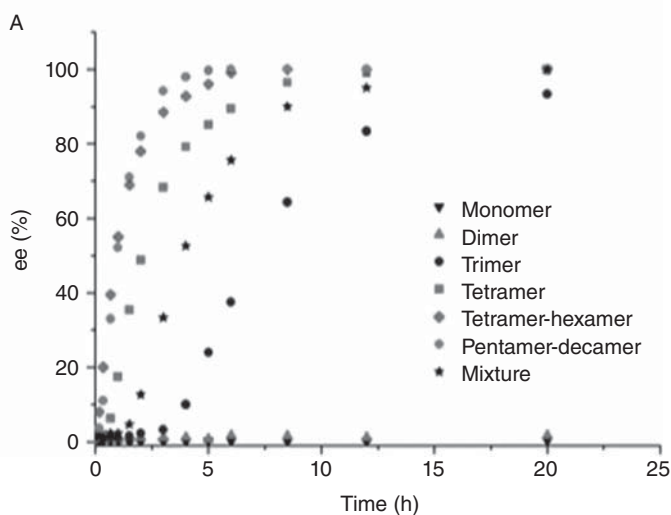
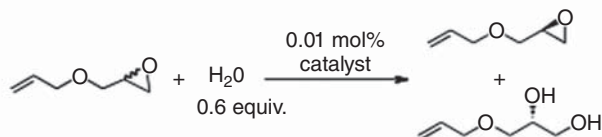


Figure 12.8 Macrocyclic Co(III)-salen HKR catalyst (top) and HKR catalysis data for systematically increasing macrocyclic ring sizes corresponding to monomer, dimer,

trimer, tetramer, as well as large-cycle cuts of tetramer-hexamer and pentamer-decamer. (Reproduced from Ref. [26] with permission of The Royal Society of Chemistry.)

functional moieties in close proximity, because of both their intrinsic flexibility as well as high local density of Co-salen sites.

The benefit of increasing the local density of Co(III)-salen complexes according to the construct of cooperativity shown in Figure 12.5a on HKR catalyst rate is also evident in the results of Jacobsen and Annis, who tethered Co(III)-salen complexes on the two-dimensional surface of silica at various dilute coverages (corresponding to more than 6.7 nm^2 per tethered Co(III)-salen complex) [27]. Results of styrene-oxide and epichlorohydrin HKR catalysis experiments when

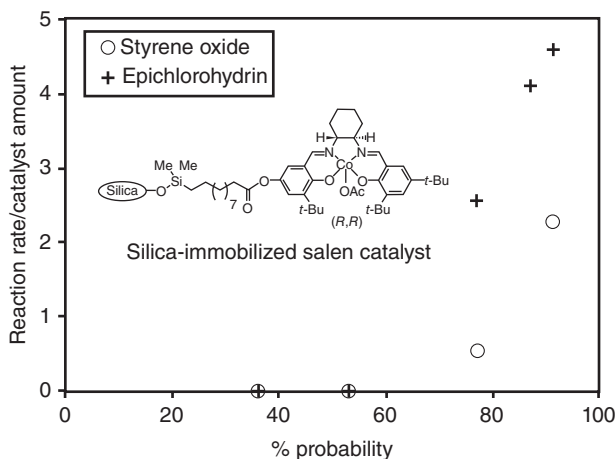


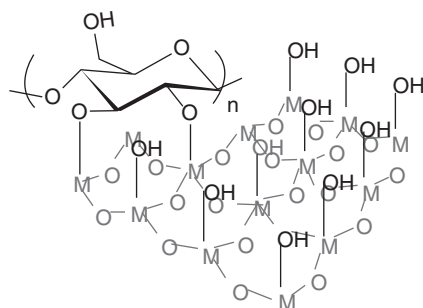
Figure 12.9 HKR rate of styrene oxide and epichlorohydrin versus probability that silica-tethered Co(III)-salen complexes interact on the surface. (Reprinted (adapted) with permission from [27]. Copyright 1999 American Chemical Society.)

using these organic–inorganic silica-based catalysts are shown in Figure 12.9. These data clearly demonstrate that the silica surface of these tethered catalysts enforces cooperativity between sites, and this cooperativity leads to direct rate increases when the probability of any two sites on the surface coming into contact increases, at higher surface coverages. This data essentially support the mechanism of surface-assisted bifunctional cooperativity shown in Figure 12.5a. In contrast to the system of Katz *et al.* described above, the surface concentration of tethered sites in the Jacobsen *et al.* materials are significantly less (nearly an order of magnitude lower than the surface concentration of capping groups that promote cooperativity in the Katz *et al.* system). This higher surface concentration of (A)-type sites of Figure 12.5 in the Katz *et al.* system promotes catalytic cooperativity with active sites (site B in Figure 12.5).

12.5

Depolymerization of Biomass Polymers via Cooperative Catalysis on Surfaces

Now focusing on the topic of cooperativity as promoted by anchored sites on a surface, we discuss another example of the versatility of acid sites on a surface functioning as an array that promotes catalysis. This example is relevant to cellulose (the most abundant form of biomass on earth) depolymerization, which has been identified as a crucial cost-controlling step in the processing of biomass to fuels and chemicals [28]. Examples from both enzymatic and intramolecular catalysis literature show that a weak acid (carboxylic acid) hydrogen-bond donor to the glycosidic oxygen activates the glycosidic bond for hydrolysis [29, 30]. Such a weak-acid polysaccharide hydrolysis catalyst could be useful from the perspective of operating under mild conditions where selectivity as well as lack of leaching in



Continuum of surface acidity

Figure 12.10 Demonstration of the different distances and acidities of M–OH groups on a metal oxide surface accessible for glycosidic bond hydrolysis.

the presence of metal salts can be high, which are prevalent in biomass. However, the sensitivity of placement of this weak-acid hydrogen-bond donor on the rate of hydrolysis catalysis is demonstrated by the following data from a model system of Capon: moving the hydrogen-bond donor from ortho to para position on the same aromatic ring results in a 13 000-fold decrease in the rate of catalysis [29]. Such a rate decrease is reminiscent of the high degree of sensitivity observed by Koshland and Hine in intramolecular catalysis systems described above.

Gazit and Katz [31–33] posited that this extreme dependence of weak-acid group positioning on hydrolysis catalysis rate could be alleviated using a solid surface, via the construct in Figure 12.5, in which the surface provides an array of possible interactions with the substrate. These investigators synthesized a new class of materials in order to demonstrate the correlation between glycosidic bond hydrolysis catalysis and surface –OH group density on alumina and silica supports. This work bridges the gaps between the enzymatic, intramolecular, and solid phase catalysts that all utilize weak Brönsted acid sites for cellulose hydrolysis.

Gazit and Katz demonstrated the first example of the OH-defect sites during catalysis in water [33]. The OH-defect sites on the surface of the metal oxide provide a continuum of different distances and acidities, as shown in Figure 12.10, which are accessible to the grafted glucan. On the basis of a procedure for grafting glucans on inorganic-oxide surfaces described previously by Gazit *et al.* [32, 33], grafted glucans on both silica and alumina surfaces were synthesized in order to elucidate the OH-defect site during hydrolysis catalysis on the rate of catalysis. A ninefold increase in the hydrolysis rate per glucan was observed when comparing alumina and the fastest silica material, as shown in Figure 12.11 and Table 12.3. Part of the difference in hydrolysis rates can be explained by the difference in available grafting sites on alumina (14.2 OH nm^{-2}) versus silica (4.6 OH nm^{-2}), which reveals an approximately threefold difference in the number of grafted sites on alumina versus silica where the glucan is grafted to the metal oxide surface. The same authors showed that the hydrolysis rate scales linearly with the glucan grafted site density for all silica-based materials in Figure 12.11 [31]. This implies that the active site around which hydrolysis occurs is the site where grafting of the

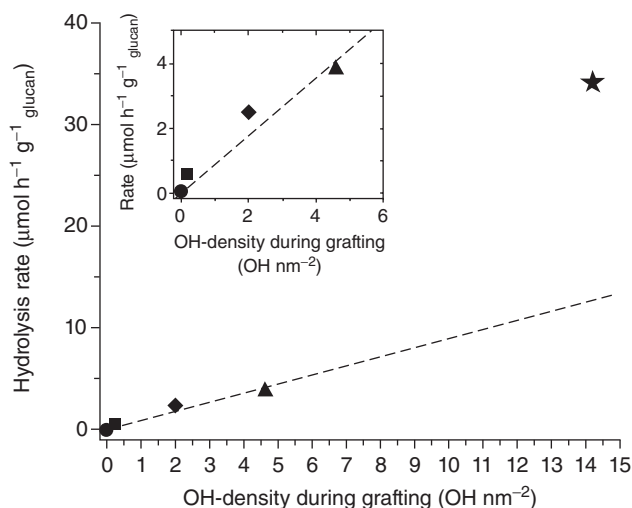


Figure 12.11 Rate of grafted β -glu strand hydrolysis increases with density of OH-defect sites during β -glu grafting. Hydrolysis reaction conducted at 95 °C and pH 4 aqueous solution: (●) amorphous cellulose, SGEXL (■), SGL (◆), SGH (▲), and AGL (★). Rates

for hydrolysis at 95 °C (corresponding to oil bath temperature of 105 °C) corresponding to amorphous cellulose, SGEXL, and SGL. (Reprinted (adapted) with permission from [31]. Copyright 2013 American Chemical Society.)

Table 12.3 Material properties and initial rates of reaction Ref. [31].

Sample	Available OH-defect sites during grafting (OH nm ⁻²)	Initial hydrolysis rate at 95 °C (μmol h ⁻¹ g ⁻¹ glucan)
Glucan-grafted alumina (AGL)	14.2	34.1 ± 2
High-density grafted silica (SGH)	4.6	3.8 ± 0.2
Low-density grafted silica (SGL)	2.0	2.5 ± 0.2
Extra-low-density grafted silica (SGEXL)	0.2	0.6 ± 0.2

Source: Reprinted (adapted) with permission from [31]. Copyright 2013 American Chemical Society.

glucan occurs to the surface (where the grafted glucan loop is constrained most to interact with the surface OH-defect sites). The other factor of 3 in the nine-fold difference in rates between the alumina and silica materials comes from the density of OH groups, which are present during hydrolysis catalysis on the underlying silica or alumina. Alumina has a OH-defect site density of approximately 17 OH/nm² while for silica it is approximately 5 OH/nm². This difference in the underlying OH-defect site density accounts for the second factor of 3 difference

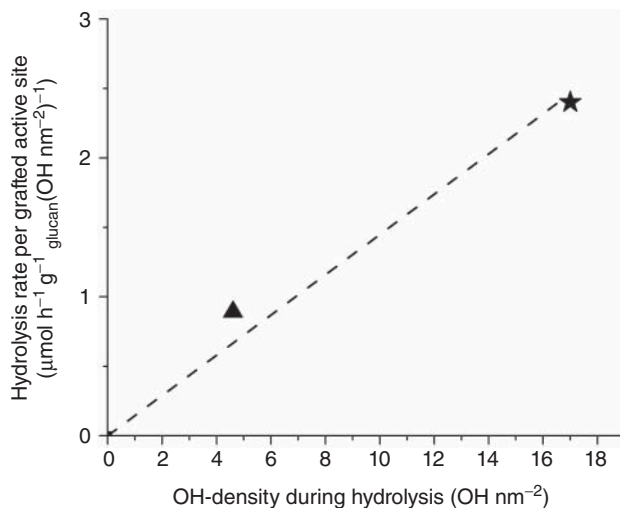


Figure 12.12 Rate of grafted β -glu strand hydrolysis normalized to grafted active-site surface density as a function of OH-defect site density during reaction. Reaction conducted at 95 °C and pH 4 aqueous solution: (▲) grafted β -glu strands on silica (representing grafted β -glu on silica materials SGEXL, SGL, and SGH using equation of

linear regression trend line in Figure 12.1) and grafted β -glu strands on alumina as represented by material AGL (★). Dashed line represents best-fit linear regression trend-line. (Reprinted (adapted) with permission from [31]. Copyright 2013 American Chemical Society.)

in the hydrolysis rates between the two materials. The role of the underlying OH groups is to act as weak acidic hydrogen-bond donors that activate the glucan, similar to the role of the carboxylic acid as hydrogen-bond donors in the enzymatic and intramolecular catalysis cases described above. The higher concentration of OH defects on alumina versus silica leads to a greater probability of interaction between the glycosidic oxygens and the OH-defect sites and thus a faster hydrolysis rate. The observed linear relationship between the OH groups present during hydrolysis and the hydrolysis reaction rate is shown in Figure 12.12 for both silica and alumina materials. This means that the probability of hydrogen bonding between the glucan and underlying surface controls the hydrolysis rates. Such a conclusion is further supported by the lower measured activation energies on alumina versus silica (70 kJ mol^{-1} for alumina versus 87 kJ mol^{-1} for silica) [31]. In the Gazit *et al.* system, the higher surface concentration of OH-defect sites as (A)-type sites (referring to Figure 12.5 in this context) promotes catalytic cooperativity with glycosidic oxygen active sites in the vicinity of the surface (site B in Figure 12.5). The difference in qualitative features between Figure 12.12 (which is linear) and Figure 12.9 (which has a plateau near zero rate followed by a linearly increasing region) is due to the much lower surface concentration of A-type sites in the Jacobsen system relative to the Gazit *et al.* system. This results in a region of no cooperativity at lower surface concentrations in Figure 12.9, which the results

in Figure 12.12 do not access as a result of the much higher surface concentration of A-type sites (Figure 12.12 only probes the highest surface concentrations of Figure 12.9 regime).

The theme of a weak-acid surface site catalyzing biomass hydrolysis shown above can be extended to a system that exhibits catalytic turnover, using unfunctionalized mesoporous carbon materials, which have demonstrated catalytic activity for cellulose hydrolysis [34–36]. The weak-acid sites in this catalyst consist of carboxylic acid or phenolic $-OH$ species. This result is all the more surprising because an inorganic oxide, such as alumina, with a similar amount of $-OH$ sites exhibits very little catalytic activity [31].

To provide some insight into a mechanism of hydrolysis on weak-acid-functionalized mesoporous carbon materials, Chung *et al.* [37] first investigated the adsorption of long-chain glucans on MCN (mesoporous carbon nanoparticle) materials. It was observed that the MCN adsorbs 30% glucan by mass with preferential adsorption of longer chain glucans (more than 40 glucose repeat units were demonstrated to adsorb) as compared to carbon nanopowders which adsorb less than 1% by mass of glucan but have higher external surface area [37]. This difference in adsorption capacities requires the internal surface area to be the location of adsorption rather than the external surface. Such adsorption must result in a highly constrained environment inside of the MCN pores, which leads to highly strained adsorbed glucan strands. This phenomenon has an analog in the field of polymers where the force needed to confine a polymer between two parallel plates increases exponentially as the polymer's radius of gyration approaches the distance between the two parallel plates [38, 39]. The glucans used in the study by Chung *et al.* have a calculated radius of gyration that is larger than the radius of the pores in the MCN material. Looking further into a possible mechanism for catalysis, these highly strained adsorbed glucan strands are now constrained to interact with the array of $-OH$ groups present on the MCN surface. Hydrolysis, by breaking the bonds present in the glucan, relieves some of that strain within the glucan chain. This hydrolytic activity was also observed in systems with grafted glucans on silica and alumina, where polymer strands were constrained to interact with the surface because of their grafting, and the grafted glucans were in turn placed in an environment of close proximity (high effective concentration) of weak-acid $-OH$ groups that activated the glucans for hydrolysis [31].

A very recent example of weak-acid sites on mesoporous carbon catalyzing hydrolysis with proven turnover was demonstrated by Chung *et al.* [40] with the hydrolysis of xylans to xylose at pH values similar to the source hemicellulose extract with no external acid solution added to the mixture. Prior work had studied the conversion of xylan to xylose, where typically a low pH (below 1.8) was required and typical xylose yields were below 50% because of sequential degradation reactions [41]. Sulfonated MCN as well as untreated MCN were tested; these experiments were also carried out in the presence of buffer to negate the effect that strong acid sites following the sulfonic acid treatment may have on the catalysis. Careful experiments were completed to illustrate that the weak acid sites present on MCN were responsible for the hydrolytic activity. Xylose

yields of 74% xylose were observed with these weak-acid catalysts at a buffered pH of 3.9 – conditions in which strong-acid sulfonic acid sites on the surface are ineffective as catalysts because of their leaching and neutralization by buffer [40].

12.6

Conclusions

This chapter highlighted systems where functional organic–inorganic interfaces on surfaces are used to understand, control, and enhance catalysis. The first portion of the article highlighted the role of the surface as a macroscopic ligand that enforces cooperativity in a bifunctional catalyst. Such cooperativity is difficult to achieve when using a small-molecule, soluble molecular catalyst active site, though it has been demonstrated in areas such as HKRs. This is applied to depolymerize glucans derived from cellulose via hydrolysis under unusually mild conditions of pH, in the first demonstration of OH-defect site catalysis in water on an inorganic-oxide surface. The results of this model system have a direct bearing on the development of current catalysts consisting of unfunctionalized carbon with OH-defect sites for cellulose depolymerization, when coupled with our recent demonstration of long-chain glucan binding and demonstration of catalytic activity to carbon mesopores. These results quantitatively elucidate essential features of weak Brønsted acid catalysts for cellulose depolymerization, such as unfunctionalized mesoporous carbon consisting of aromatic/aliphatic OH-defect sites. These features are (i) adsorption of the β -Glu strand within a highly constrained environment which favors hydrogen bonding with OH-defect sites on the surface, and (ii) an increasing probability of the aforementioned hydrogen bonding, which activates glycosidic bonding for hydrolysis via the high local density of OH-defect site donors during hydrolysis catalysis. The future of cooperative catalysis as enforced by surfaces appears promising and is expected to yield an ever-expanding toolkit for molecular control of active sites on surfaces, as well as practical applications of such sites that combine the best of conventional homogeneous and heterogeneous systems.

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13

Cooperative Catalysis in Polymerization Reactions

Malte Winnacker, Sergei Vagin, and Bernhard Rieger

13.1

Introduction

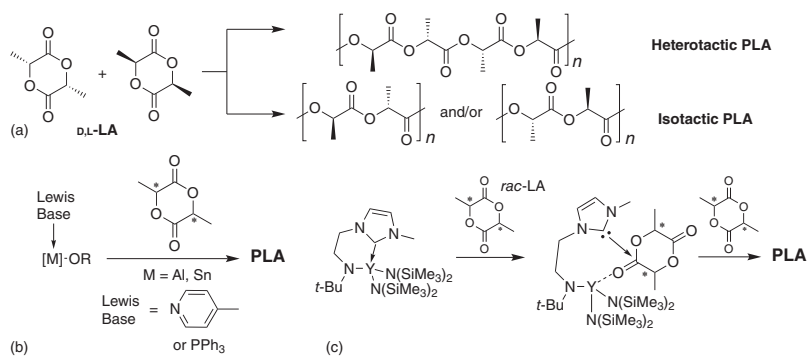
The term “cooperative catalysis” implies that two (or more) catalytic compounds or active centers simultaneously interact with one (or more) substrate(s) to have an effect on the catalyzed reaction. This is a wide definition, and – especially for polymerization reactions – it is sometimes hard to make an exact distinction between a cooperative effect of a dual system, where two factors (e.g., two metal centers instead of one) influence each other altering the reaction results, or a cooperative effect where the factors – which can also be of completely different nature – cannot work individually and where only their combination makes the polymerization reaction to occur.

In nature, the interplay of the amino acid residues within the active centers or of the subunits of polymerase enzymes can also be considered as cooperative catalysis [1]. This is enough material for an independent chapter and is not addressed here. In general, many synthetic studies have been described where cooperative effects in polymerization reactions appear in different manners, and within the scope of this chapter it is nearly impossible to refer to all the excellent work that has been done in this wide field. For instance, many bimetallic organo-group-4 “constrained geometry” catalysts and bisborane and bisborate cocatalysts have been investigated for cooperative effects of the catalytic centers on olefin polymerization and copolymerization processes, with partially significant nuclearity effects versus mononuclear controls [2]. We discuss here some select examples where innovative cooperative catalytic systems produce important polymer scaffolds that have had high impact in the past few years. Thus, we focus on the polymerization of cyclic esters (lactide, caprolactone) of vinyl monomers (methyl methacrylate (MMA) and derivatives) and of CO₂ with epoxides.

13.2

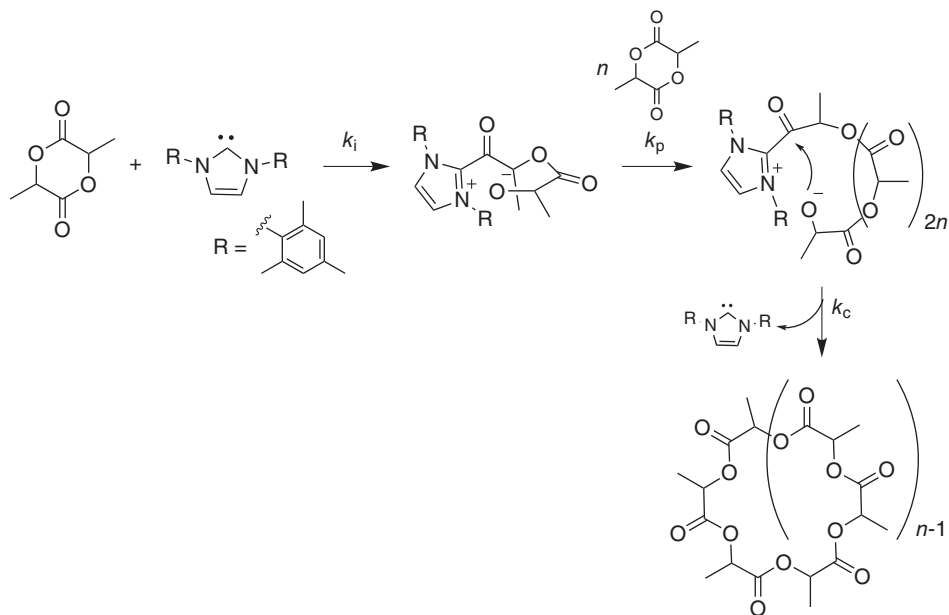
Cooperative Effects for the Polymerization of Lactide and Other Cyclic Esters

The combination of organic catalysis and metal catalysis has established itself as a powerful concept in organic synthesis (see Chapter 2 of this book) [3], and its application for polymer synthesis has now started to develop. Here, a metal complex and an organic compound promote a chemical transformation cooperatively, which cannot occur with one of these components alone. For instance, the polymerization of lactones can be promoted by a catalytic systems combining an Al, In, or Zn Lewis acid with organic bases such as amines, phosphines, or *N*-heterocyclic carbenes (NHC) [4]. These dual approaches can provide high activity, excellent control, and good stereoselectivity of the polymerization reactions. For this, pioneering work was performed by Hedrick in 2001, who described the first organocatalytic living ring-opening polymerization (ROP) for the polymerization of lactide to polylactide (PLA) by using dimethylaminopyridine (DMAP) as the catalyst and EtOH or PhCH₂OH as the initiator [5]. PLA, a bio-based and biodegradable polyester that can be obtained by the polymerization of the cyclic ester lactide, is suitable for a variety of applications such as packaging, sutures for controlled dissolution, or matrixes for tissue engineering [6]. The exact properties of this polymer can be tuned in a wide range by influencing the tacticity (Scheme 13.1a). Thus, controlled and stereoselective ROPs of D,L-lactide have become an important task, and have been investigated with different approaches. After some strategies focused on discrete metal complexes that rely on steric or chiral effects of ligands to influence the stereochemical selectivity [7], the focus turned more on dual catalytic systems. For instance, the impact of Lewis base additives on the Al- and Sn-promoted ROP of lactide was described in the early 1990s by Dubois *et al.* [8] In these studies, the polymerization rate was strongly increased by the addition of 4-picoline to Al(Oi-Pr)₃ without changing the properties of the PLA in terms of molecular weight and molecular weight distribution. Furthermore, the addition of triphenylphosphine (PPh₃) to SnOct₂ accelerated the polymerization and resulted in PLA of higher molecular weight (50–100%) and narrower molecular weight distribution (polydispersity index $PDI = M_w/M_n = 1.5–1.6$ instead of 2, where M_w is the weight-average and M_n is the number-average molecular weight of the polymer). From these examples it was concluded that the monomer insertion is facilitated by a polarization of the metal–alkoxide bond that is induced by a coordination of the Lewis base – which acts as a ligand – to the metal (Scheme 13.1b). Similarly, a bifunctional activation of *rac*-lactide by a yttrium complex that featured a labile *N*-heterocyclic carbene was described by Arnold *et al.* [9] (Scheme 13.1c). The polymerization mechanism was proposed to involve the monomer activation by the metal center (Lewis acid) and an attack of the NHC fragment as the nucleophile, producing highly regular heterotactic poly(*rac*-lactide). A related mechanism for the ROP of *rac*-lactide was also defined with similar magnesium and zinc complexes [10].



Scheme 13.1 (a) D,L-Lactide and its polymers heterotactic and isotactic PLA. (b) Concept of adding a Lewis base to the Al- and Sn-promoted coordination/insertion of lactide [8]. (c) Activation of *rac*-lactide with a yttrium complex containing a labilized NHC [9].

A related concept is zwitterionic polymerization, which have been described in different contexts [11] and which can mostly also be considered to rely on cooperative effects. Such a zwitterionic polymerization of lactide has been described by Waymouth *et al.* [12]. In their study, an *N*-heterocyclic carbene was used for the kinetically controlled polymerization of lactide to different cyclic polyesters of defined molecular weight up to 26 kDa and narrow molecular weight distributions (PDIs 1.16–1.27). A mechanism was proposed where lactide is opened by the carbene and the resulting charged chain ends direct the next monomer to its position. In the end, the circle is closed by a transesterification and the release of the carbene catalyst (Scheme 13.2).



Scheme 13.2 Mechanism for a NHC-mediated lactide polymerization resulting in cyclic polyesters [12].

The MALDI (matrix-assisted laser desorption/ionization) spectrum of a sample showed cyclic PLAs complexed by sodium and potassium (Figure 13.1a). Signals for cyclic polymers were separated by 72 mass units, which corresponded to the mass of half a lactide unit and indicated that both odd- and even-numbered rings have been formed. The cyclic structures of these polyesters were also confirmed by gel-permeation chromatography (GPC). PLA obtained in the absence of alcohol eluted later than those of the same molecular weight synthesized with the alcohol initiator. The fact that ring polymers have smaller hydrodynamic volumes than their linear analogs was considered to be indicative of cyclic structures in this case (Figure 13.1b) [12]. The ROP of lactide for the synthesis of cyclic PLA has

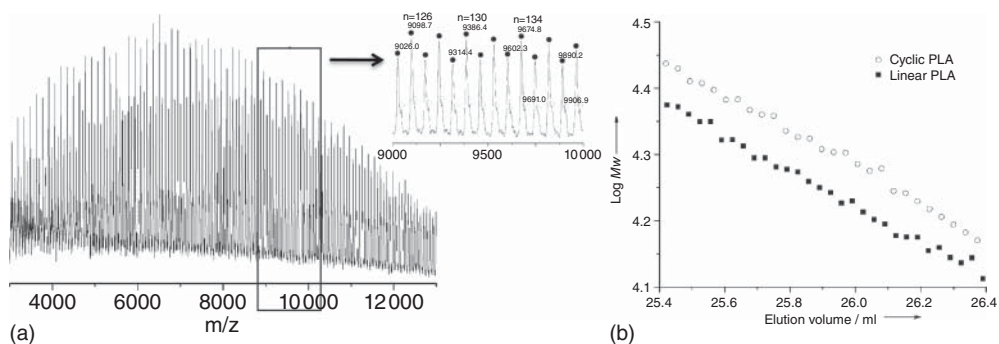
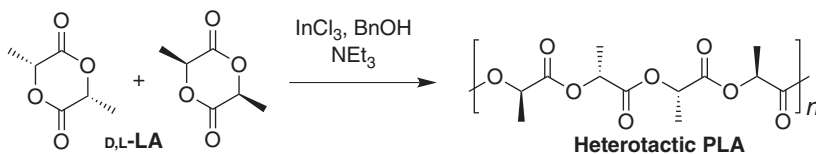


Figure 13.1 (a) MALDI-TOF spectrum of cyclic polylactide and (b) plot of logarithm of molecular weight versus elution volume. (Adapted with permission Ref. [12].)

also been described with $\text{Zn}(\text{C}_6\text{F}_5)_2$ -based Lewis pairs as the catalysts [13]. A similar zwitterionic polymerization with heterocyclic carbenes for the generation of cyclic poly(carbosiloxane)s is also known [14].

The combination of Lewis acids and amines for the polymerization of lactide and other cyclic esters was described by Hillmyer and Tolman [15], who used a catalytic system that was generated with the three components InCl_3 , NEt_3 , and BnOH (Scheme 13.3). All components were necessary for the polymerization reaction to occur, which was shown by experiments in the absence of one of these compounds per entry, where no polymerization occurred. An experiment with a 1.0 M LA solution (100 equiv) with BnOH (1 equiv), InCl_3 (1 equiv), and NEt_3 (2 equiv) at 25 °C showed 96% conversion after 2.5 h as well as a PDI of 1.09 and a number-average molecular weight (M_n) of 23.8 kg mol⁻¹. Kinetic measurements showed a first-order dependence on D,L-LA concentration ($k_{\text{obs}} = 2.7 \times 10^{-4} \text{ s}^{-1}$ ($t_{1/2} = 43 \text{ min}$), $[\text{BnOH}]_0 = 9.8 \text{ mM}$, and $[\text{InCl}_3]_0 = 9.1 \text{ mM}$). Replacing InCl_3 with group-13 chlorides AlCl_3 and GaCl_3 gave no D,L-LA polymerization. NMR experiments showed a highly heterotactic microstructure of the PLA. M_n was examined as a function of monomer equivalents in order to establish a basis for the quantitative control of the molecular weight. Here it was demonstrated that BnOH may be used in excess to InCl_3 without any negative impact on the quantitative control of M_n . In contrast to this, an excess of InCl_3 hampered the polymerization and broadened the molecular weight distributions. Interestingly, the polymerization of *meso*-LA at different temperatures resulted in atactic PLA. Thus it was suggested that more than one stereocenter influence the stereocontrol. These



Scheme 13.3 Polymerization of lactide with an InCl_3 -based cooperative system [15].

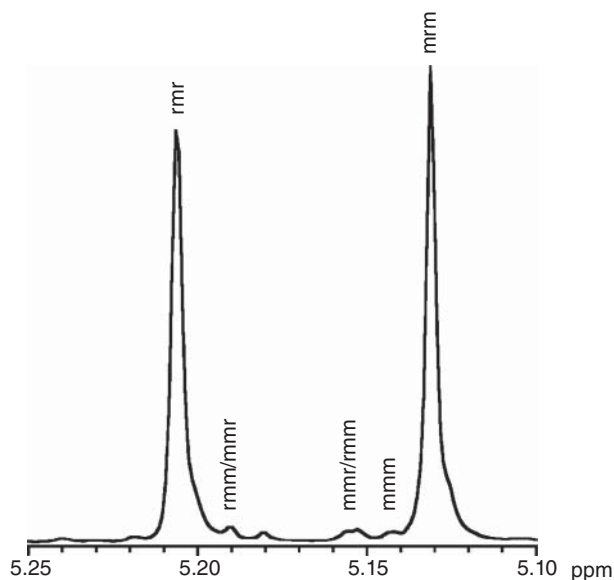


Figure 13.2 Homuncular decoupled ^1H -NMR spectrum of the methine region of heterotactic PLA prepared by the InCl_3 -based system at 0°C . (Reproduced with permission Ref. [15].)

stereocenters can be inside the incoming monomer and/or the polymer chain. Another conclusion is that the catalyst prepared *in situ* contains an LA component, which has an influence on the catalyst stereochemistry and stereoselectivity. Depending on the exact conditions, the resulting PLA in this study had a molecular weight of $M_n = 11\,000 - 159\,000\text{ g mol}^{-1}$ and M_w/M_n ratios between 1.06 and 1.62. Figure 13.2 shows the ^1H -NMR spectrum of the methine region of the prepared heterotactic PLA [15].

In a subsequent study, intensive investigations were performed to elucidate the mechanism and structure of this catalytic In-based system [16]. A well-controlled polymerization was confirmed by the determination of a linear relationship between the average molecular weight (M_n) and the monomer-to-alcohol concentration ratio as well as the monomer conversion. Kinetic studies showed a first-order process in terms of $[\text{InCl}_3]_0$ and zero-order process in terms of both $[\text{BnOH}]_0$ and $[\text{NEt}_3]_0$. The D,L-LA conversion rate was found to be also dependent on the nature of the indium salt and the lactide stereoisomer. A model system was developed that consisted of 3-diethylamino-1-propanol (deapH) as a substitute for NEt_3 and BnOH (see later). A reaction of deapH with InCl_3 resulted in the formation of $[\text{InCl}_3(\text{deapH})(\text{H}_2\text{O})]_2$ or – depending on the conditions – a water-free version of this complex. This and an evaluation of the reaction kinetics suggested that the reactive species for the $\text{InCl}_3/\text{BnOH}/\text{NEt}_3$ system is of the type $[\text{InCl}_{(3-n)}(\text{OBn})_n]_m$ and thus similar to the model system $[\text{InCl}_3(\text{deapH})(\text{H}_2\text{O})]_2$.

A mechanism was proposed that explained the observed stereocontrol in D,L-LA polymerization.

For this, polymerization experiments were performed by adding BnOH and NEt₃ to InX₃ (X = Cl, Br, I) in a D,L-LA solution (1 M in CH₂Cl₂). For evaluation of the degree of molecular weight control, M_n was determined by size-exclusion chromatography (SEC) and plotted versus the converted monomer to initial alcohol concentration ratio $([D,L-LA]_0 - [D,L-LA]_t)/[BnOH]_0$; Figure 13.3a) and versus the percent monomer conversion at fixed initial monomer to alcohol ratio $([D,L-LA]_0/[BnOH]_0 = 400$; Figure 13.3b). An excellent molecular weight control could be confirmed by the linear relationships in these plots in combination with the low PDI values (<1.1). Polymerization of D,L-lactide did not occur in the absence of BnOH, InX₃, or NEt₃, which indicates that all three components form the catalytic species. Replacing NEt₃ with other bases (NBu₃, NHBu₂, 1,8-bis(dimethylamino)naphthalene (proton sponge)) produced polymers with similar stereocontrol and weight, indicating that the amine acts rather as a base than as a part of the catalytically active species. A MALDI experiment of a sample of the oligomers ($[D,L-LA]_0/[BnOH]_0 = 46$) showed different oligomers until m/z of approximately 4800. Using every peak in the spectrum for calculation gave an average degree of polymerization (DP) of 17.6 (Figure 13.3c). The tacticity of the polymers was determined by analyzing the methine proton resonances in homonuclear decoupled ¹H-NMR spectra (see also above).

Attempts to obtain crystals of a coordination complex from solutions of InCl₃, BnOH, and NEt₃ failed; however, with the help of the model system deapH instead of BnOH and NEt₃ (see above), it was possible to obtain crystals over a period of 2 months. According to X-ray diffraction and NMR data (pulsed gradient spin-echo, PGSE), the complex formed a dimeric structure with alkoxide bridges (Scheme 13.4a). The amine acts as a base and helps to form the dianionic dinuclear complex. A mechanism was postulated where this complex enables the lactide polymerization to occur by a coordination/insertion mechanism (Scheme 13.4b) [16].

The capability of the InCl₃/NEt₃/BnOH system has also been applied for the polymerization of ε-caprolactone (CL) and substituted derivatives [16]. For instance, polycaprolactone (PCL) with $M_n = 32.0 \text{ kg mol}^{-1}$ and a PDI of 1.16 was obtained from the reaction of ε-caprolactone (100 equiv) with InCl₃ (1 equiv), BnOH (1 equiv), and NEt₃ (2 equiv) in CH₂Cl₂ ($[CL]_0 \approx 0.84 \text{ M}$). The reaction reached 99% conversion after 24 h and was shown to be slower than the polymerization of D,L-LA, which proceeded to 96% conversion in 2.5 h under similar conditions. In kinetic studies, a good control of the PCL molecular weight could be confirmed at $[InCl_3]_0/[BnOH]_0 = 1$, but only over a narrow range of the monomer/alcohol ratios. The system was then used for the substituted derivatives 6-methyl-ε-caprolactone (**1**), 4-methyl-ε-caprolactone (**2**), and (–)-menthide (**3**, Table 13.1). As expected, the different structures of the monomers required different conditions for effective polymerization. The conditions used were (i) $[M]_0 \approx 0.7\text{--}0.9 \text{ M}$, CH₂Cl₂, 25 °C; (ii) $[M]_0 \approx 0.7\text{--}0.9 \text{ M}$, CH₂Cl₂, 60 °C; and (iii)

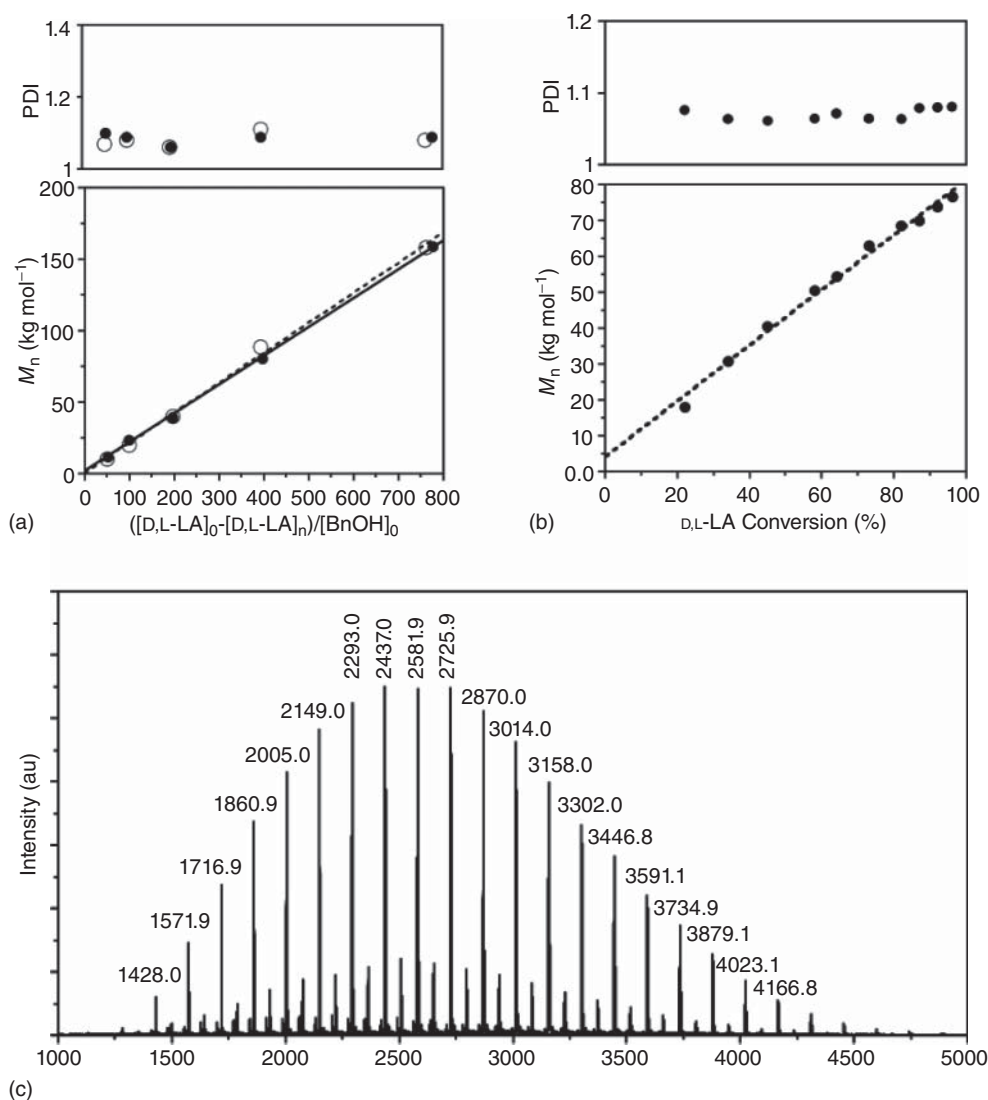
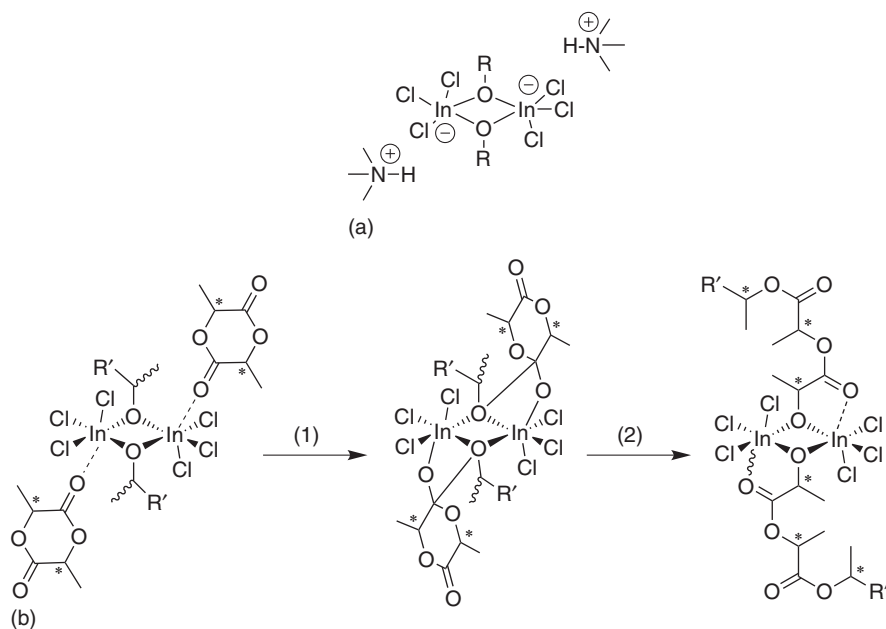


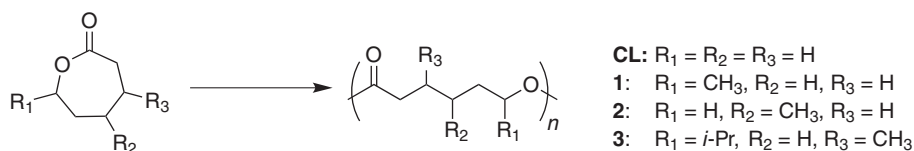
Figure 13.3 (a) Plot of M_n and PDI versus $([D,L-LA]_0 - [D,L-LA]_t) / [BnOH]_0$ using $InCl_3$ (●) and $InBr_3$ (○). Linear fits are shown as solid and dashed lines, respectively. Conditions: $[BnOH]_0 / [InX_3] \approx 1$, $[D,L-LA]_0 \approx 0.8-1$ M, CH_2Cl_2 , 25 °C, M_n determined by SEC relative to polystyrene. (b) Plot of M_n (●) and PDI versus D,L-LA conversion for the synthesis of heterotactic PLA using the $InCl_3/BnOH/NEt_3$ system. Conditions:

$[D,L-LA]_0 = 0.84$ M, $[D,L-LA]_0 / [BnOH]_0 = 400$, $NEt_3/BnOH/InCl_3 = 2:1:1$, 25 °C, CH_2Cl_2 . (c) MALDI-TOF spectrum of PLA from a polymerization of D,L-LA by the $InCl_3/BnOH/NEt_3$ system quenched at 42% monomer conversion. Conditions: $[D,L-LA]_0 = 0.84$ M, $[D,L-LA]_0 / [BnOH]_0 = 46$, $NEt_3/BnOH/InCl_3 = 2:1:1$, 25 °C, CH_2Cl_2 . (Reproduced with permission Ref. [16].)



Scheme 13.4 (a) Structure of the dinuclear In complex and (b) coordination/insertion mechanism according to and adapted from Ref. [16].

Table 13.1 Polymerization of seven-membered lactones.



Entry ^{b)}	Monomer (M)	$[M]_0/[BnOH]_0$	$T(^{\circ}C)$	$t(h)$	%Conv ^{a)}	$M_n^{c)}$ ($kg\ mol^{-1}$)	PDI ^{c)}
1 ^{d)}	1	93	60	24	87	19.9	1.05
2 ^{e)}	1	115	60	24	99	20.2	1.30
3 ^{d)}	2	100	25	24	97	19.6	1.20
4 ^{d)}	2	106	60	24	95	20.0	1.62
5 ^{e)}	2	99	60	24	99	21.8	1.78
6 ^{e)}	3	102	65	25	99	22.9	1.13

a) Determined by ^1H NMR spectroscopy.

b) $NEt_3/BnOH/InCl_3 = 2 : 1 : 1$.

c) Determined by SEC (relative to polystyrene in $CHCl_3$).

d) $[M]_0 \approx 0.7\text{--}0.9\ M$.

e) $[M]_0 \approx 4\ M$.

Source: Adapted with permission Ref. [16].

$[M]_0 \approx 4 \text{ M}$, CH_2Cl_2 , 60°C . Monomer **3** required a higher monomer concentration and a higher temperature, which may be due to steric effects resulting from the alkyl groups at positions 6 and 3 (for details see Table 13.1).

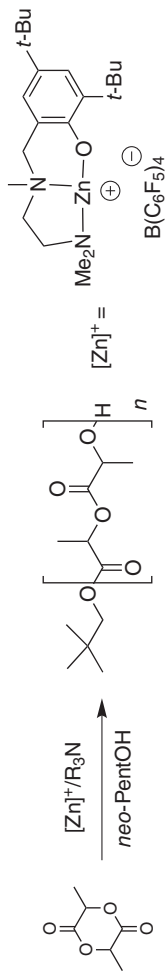
Further similar examples for multiple site catalysts for cyclic ester polymerizations can be found in the corresponding literature [17]. Another study described a dual metallic/organic system with the cationic complex $[\{\text{NNO}\}\text{Zn}]^+[\text{B}(\text{C}_6\text{F}_5)_4]^-$ (NNO is a tridentate diamino-phenolate ligand) in combination with 1,2,2,6,6-pentamethylpiperidine (PMP) for the ROP of *rac*-lactide with neopentanol (neo-PentOH) as the initiator (Table 13.2) [18]. The polymerization resulted in PLA of controlled molecular weight (M_n up to 22 000 g/mol) and low molecular weight distributions ($1.2 < M_w/M_n < 1.4$) in up to 98% yield. Again, a bifunctional mechanism was confirmed by control experiments with only the zinc complex or PMP, where no polymerization occurred (24 h, 50°C). Table 13.2 shows an overview of the experiments performed in this study.

In these experiments, the lactide is assumed to be activated by the zinc complex while the initiating/propagating PentOH, which attacks the lactide, is activated by the amine via hydrogen bonding (Scheme 13.5).

The *in situ* formation of a metal-alkoxide species was excluded in this case, in contrast to the $\text{InCl}_3/\text{NET}_3$ system developed by Hillmyer and Tolman (see above). A clear relation was shown between the basicity of the amine and the speed of the polymerization [PMP ($\text{p}K_a = 11.2$) > collidine ($\text{p}K_a = 7.5$) > PhNMe_2 ($\text{p}K_a = 5.1$)]. Increasing the amount of the alcohol with respect to the catalytic Zn^+ /amine system gave the possibility to perform lactide ROP with catalytic amounts of metal, which was shown by studies with an excess of alcohol. Interestingly, the basic amine does not induce racemization of the chiral monomer, and no epimerization takes place, resulting in isotactic PLA when L-lactide is polymerized [18].

ROPs of lactide have also been performed by cooperative thiourea/amine and bis-sulfonamide/amine associations through cooperative hydrogen-bonding catalysis [19]. For instance, bis-sulfonamide $m\text{-C}_6\text{H}_4(\text{SO}_2\text{NHPh})_2$ promotes the ROP of lactide with *N,N*-DMAP (Scheme 13.6a) to result in PLAs of molecular weights up to 17 700 g/mol and good molecular weight distributions ($M_w/M_n < 1.11$), obtained in a living manner [19a]. According to the authors, the bifunctional mechanism comprises activation of the monomer and the alcohol, as also shown for the thiourea derivatives with amines (Scheme 13.6b) [19b,c]. The ROP of lactide, β -butyrolactone, and substituted trimethylene carbonate has also been described with fluorinated bis-alcohols as dual hydrogen-bond donors in combination with sparteine [19d]. For the bis-sulfonamides, a cooperative dual hydrogen bonding of lactide to both the (SO_2NHAr) moieties has been shown by modulation of the sulfonamide compound. In this case, a multicenter activation was proposed for the ROP of lactide triggered by this bifunctional system, based on experimental and theoretical studies. The carbonyl group of the monomer is activated by hydrogen bonding, while the amine group of the catalyst promotes the nucleophilic attack of the alcohol (Scheme 13.6b). The combination of the thiourea and the amine shows high selectivity for polymerization over unwanted transesterification, and a high functional group tolerance was shown.

Table 13.2 Polymerization of lactide with the cationic complex $[(\text{NNO})\text{Zn}]^+ [\text{B}(\text{C}_6\text{F}_5)_4]^-$ ^{a)}



Entry	$[\text{LA}]_0 : [\text{neo-PentOH}]_0 : [\text{Zn}]^{+1}_0 : [\text{amine}]_0$	Amine	Solvent	Temperature (°C)	Time (h)	Conversion ^{b)} (%)	$M_{n,\text{theo}}^{\text{c)}$ (g mol ⁻¹)	$M_{n,\text{NMR}}^{\text{d)}$ (g mol ⁻¹)	$M_{n,\text{SEC}}^{\text{d)}$ (g mol ⁻¹)	M_w/M_n
1	100 : 1 : 1 : 0	—	Tol	50	24	0	—	—	—	—
2	100 : 1 : 0 : 1	PMP	Tol	50	24	0	—	—	—	—
3	100 : 1 : 0.5 : 0.5	PMP	Tol	50	3	98	14 200	14 500	11 700	1.34
4	100 : 1 : 0.2 : 0.2	PMP	Tol	50	3	95	13 768	14 500	12 600	1.32
5	100 : 1 : 0.5 : 0.5	PMP	THF	50	24	94	13 600	12 500	8700	1.70
6	100 : 1 : 0.5 : 0.5	PMP	DCM	25	3	92	13 336	13 900	12 700	1.34
7	100 : 1 : 0.5 : 0.5	Et ₃ N	DCM	25	8	90	12 904	13 900	13 100	1.33
8	100 : 1 : 0.5 : 0.5	Collidine	DCM	25	168	56	8152	8000	—	—
9	100 : 1 : 0.5 : 0.5	PhNMe ₂	DCM	25	144	3	—	—	—	—
10	50 : 1 : 0.2 : 0.2	PMP	DCM	25	3	96	7000	7300	7100	1.22
11	70 : 1 : 0.2 : 0.5	PMP	DCM	25	2.1	98	9965	10 200	10 300	1.21
12	50 : 1 : 0.5 : 0.5	PMP	DCM	25	2.5	97	7072	6300	6800	1.22
13	100 : 2 : 0.5 : 0.5	PMP	DCM	25	5	87	6496	6100	5700	1.17
14	100 : 4 : 0.5 : 0.5	PMP	DCM	25	5	95	3688	4400	4300	1.30
15	100 : 6 : 0.5 : 0.5	PMP	DCM	25	5.5	90	2488	3100	3000	1.30

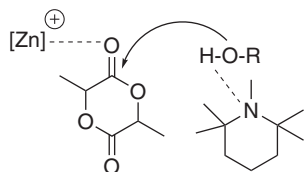
a) *neo*-PentOH, *neo*-pentanol; PMP, 1,2,2,6,6-pentamethylpiperidine.

b) Monomer conversion was determined by ¹H NMR.

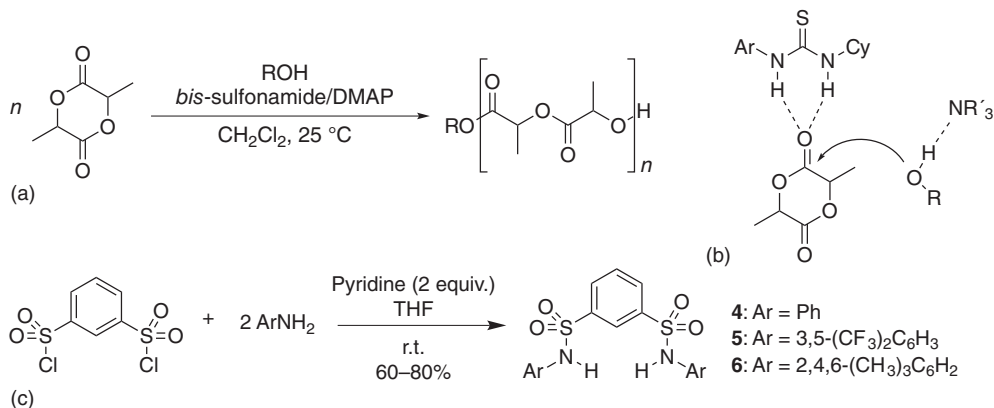
c) Calculated from $[\text{LA}]_0/[\text{neo-PentOH}]_0 \times \text{LA conversion} \times M_{\text{LA}} + M_{\text{neo-PentOH}}$ with $M_{\text{LA}} = 144 \text{ g mol}^{-1}$ and $M_{\text{neo-PentOH}} = 88 \text{ g mol}^{-1}$.

d) Determined by SEC using a viscometer or a RI detector versus PS standards.

Source: Reproduced with permission Ref. [18].



Scheme 13.5 Bifunctional activation of lactide by the cationic Zn complex and of the attacking alcohol by an amine base [18].



Scheme 13.6 (a) Lactide polymerization by cooperative dual hydrogen-bonding catalysis with bis-sulfonamides. (b) Proposed dual mechanism. (c) Synthesis of bis-sulfonamides **4–6** [19].

Bis-sulfonamides **4–6** were synthesized from 1,3-benzenedisulfonyl chloride and the corresponding aniline compounds (Scheme 13.6c). The catalytic activity of **4–6** was then evaluated toward the ROP of lactide using *n*-pentan-1-ol as the initiator and DMAP (in control experiments, no polymerization took place without DMAP). The lactide monomer conversion after 5 h was 97% for sulfonamide **4**, 76% for **5**, 68% for **6**, and 37% when only DMAP was used [19a].

Different modes of action of the bis-sulfonamides for the lactide activation have been proposed, which can be found in the corresponding literature [19]. A SEC experiment confirmed the living character of this polymerization: PLA with $M_n = 6200 \text{ g mol}^{-1}$ and $M_w/M_n = 1.07$ was first synthesized by polymerization of 30 equiv lactide with *n*-pentan-1-ol/sulfonamide **4**/DMAP 1/10/10 (Figure 13.4a, (i)). Then, addition of further 30 equiv lactide restarted the polymerization, resulting in the formation of PLA of $M_n = 11\,900 \text{ g mol}^{-1}$ and $M_w/M_n = 1.07$ (Figure 13.4a, (ii)). For a better understanding of the mode of action of compound **4**, the related sulfonamides **7–11** were synthesized (Figure 13.4b) and compared to each other in terms of the ROP of 10 equiv of lactide (in combination with DMAP). The initiator/sulfonamide/DMAP ratio was 1:1:1 for the bis-sulfonamides and 1:2:1 for the mono-sulfonamides in order to keep the ratio between the hydrogen-bond donor entities and the cooperative partners

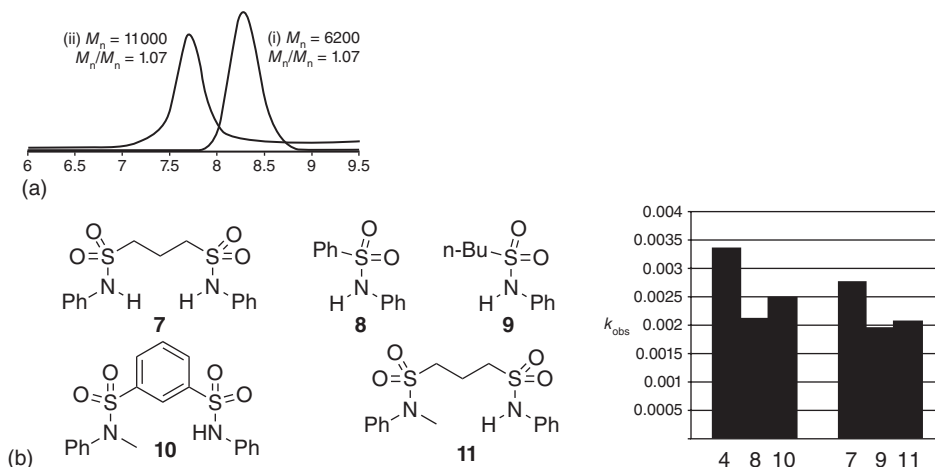


Figure 13.4 (a) SEC experiment described in the text and (b) bis-sulfonamides described in the text and their activities. (Adapted with permission Ref. [19].)

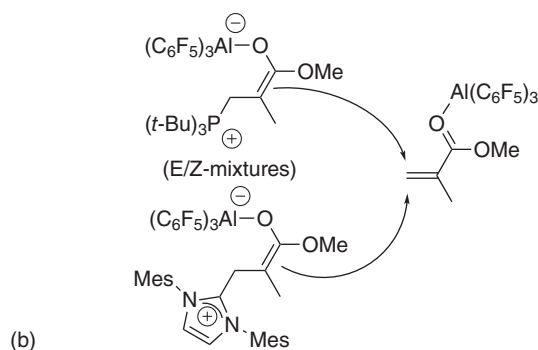
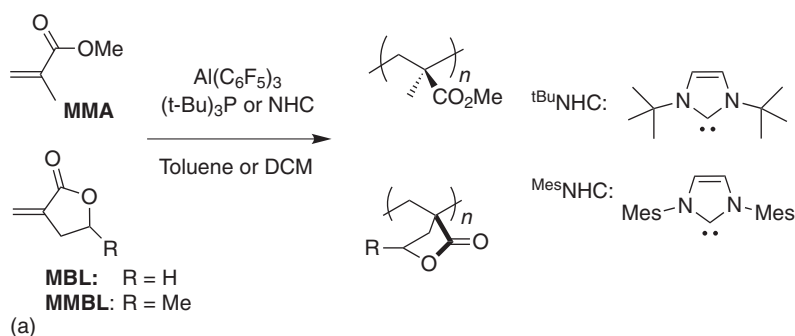
constant. The activity of **4** was significantly higher than that of **8**, in agreement with the proposed cooperative mode of the dual hydrogen-bond activation of the monomer by the bis-compound. The monomethylated bis-sulfonamide **10** showed moderate activity, which was still higher than the activity of **8**. This fact can probably be explained by the electron-withdrawing manner of the (SO_2NMePh) group attendant in **10**. A similar behavior was observed when comparing the activity of compound **7** with that of mono-sulfonamide **9** and *N*-methylated bis-sulfonamide **11**. Interestingly, the activity of **4** is remarkably higher than that of **7**. The higher fixity of the phenylene linker in comparison to the trimethylene linker seems to foster the dual cooperative hydrogen bonding by the two sulfonamide moieties (Figure 13.4b) [19].

13.3

Polymerization Reactions of Vinyl Monomers with Frustrated Lewis Pairs

Cooperative catalytic effects are very evident in the zwitterionic polymerization of polar vinyl monomers, which has been investigated with many catalysts. There are classical anionic and cationic mechanisms that are based on metals [20], and single-site group-4 metal and lanthanide complexes catalyze the polymerization of methyl acrylates by means of a coordination-addition mechanism [21]. In this context, cooperative effects of Lewis acid/base pairs have been described for the polymerization of acrylic monomers. For example, the polymerizations of methyl methacrylate (MMA), γ -methyl- α -methylene- γ -butyrolactone (γ -MMBL), and α -methylene- γ -butyrolactone (γ -MBL) were efficiently catalyzed by a combination of alane $\text{Al}(\text{C}_6\text{F}_5)_3$ with sterically encumbered phosphines or *N*-heterocyclic carbenes (see also Chapter 9 of this book) [22]. With this procedure, polymers

with a molecular weight up to $600\,000\text{ g mol}^{-1}$ and narrow molecular weight distributions ($1.3 < M_w/M_n < 1.7$) have been synthesized. Interestingly, no polymerization occurred when only the Al-based Lewis acid or the Lewis base was applied. Furthermore, the activity of the dual system depends remarkably on the order of addition of these components. When $\text{Al}(\text{C}_6\text{F}_5)_3$ and $(t\text{-Bu})_3\text{P}$ were mixed prior to addition of MMA, no polymerization was observed. In contrast, when $\text{Al}(\text{C}_6\text{F}_5)_3$ was mixed with MMA prior to addition of $(t\text{-Bu})_3\text{P}$, a fast polymerization occurred. These Lewis pair polymerizations were further investigated by performing stoichiometric reactions in order to get insight into the mechanism. In this example, on cooperative activation of the monomer MMA, 1 : 1 : 1 adducts of zwitterionic phosphonium and imidazolium enol aluminates were obtained (Scheme 13.7), which were characterized and suggested to be the active species. Kinetic and computational studies confirmed that initiation and propagation occurred via a bimetallic mechanism (see Chapters 1 and 8 of this book), which involved the nucleophilic attack of a zwitterion on another monomer which was activated on coordination to $\text{Al}(\text{C}_6\text{F}_5)_3$.



Scheme 13.7 (a) Polymerization of vinyl monomers by frustrated Lewis pairs and (b) proposed cooperative mechanism [22].

A variety of Lewis acid/Lewis base pairs have been tested for the polymerization of MMA and γ -MMBL. The best results among the evaluated Al-based

Table 13.3 Selected results of polymerization by base/ $\text{Al}(\text{C}_6\text{F}_5)_3$ pairs.^{a)}

Run	Monomer	Solvent	Acid (adduct)	Base (1 equiv)	[acid]/[base]	t (min)	Conversion (%) (yield (%)) ^{b)}	TOF (h ⁻¹)	$M_n \times 10^4$ (g mol ⁻¹)	MWD (M_w/M_n)	rr (%)	mr (%)	mm (%)
1	MMA	Toluene	Al·MMA	(<i>t</i> Bu) ₃ P	1:1	60	100	800	28.3	1.42	75.5	23.1	1.4
2	MMA	Toluene	Al·MMA	(<i>t</i> Bu) ₃ P	2:1	4	100	12 000	39.7	1.52	73.5	25.0	1.5
3	MMA	Toluene	Al·MMA	(<i>t</i> Bu) ₃ P	2:1	7	100	6840	31.5	1.72	73.6	24.7	1.7
4	MMA	CH ₂ Cl ₂	Al·TOL	(<i>t</i> Bu) ₃ P	1:1	60	100	800	38.0	1.41	75.8	22.6	1.6
5	MMA	CH ₂ Cl ₂	Al·MMA	(<i>t</i> Bu) ₃ P	2:1	4	100	12 000	36.9	1.47	75.0	23.0	2.0
6	MMA	Toluene	Al·MMA	Mes ₃ P	2:1	1440	0	0	—	—	—	—	—
7	MMA	CH ₂ Cl ₂	Al·MMA	Mes ₃ P	2:1	1440	0	0	—	—	—	—	—
8	MMA	Toluene	Al·MMA	Ph ₃ P	2:1	1	100	48 000	38.8; 13.3	1.04; 1.05	73.0	25.4	1.6
9	MMA	Toluene	Al·MMA	MesNHC	2:1	1	100	48 000	2.66	1.77	72.7	25.7	1.6
10	MMA	Toluene	Al·MMA	<i>t</i> BuNHC	2:1	15	100	3200	52.5	1.43	75.1	23.3	1.6
11	MMA	CH ₂ Cl ₂	Al·MMA	<i>t</i> BuNHC	2:1	15	100	3200	60.0	1.34	74.3	24.3	1.6
12	MBL	CH ₂ Cl ₂	Al·TOL	(<i>t</i> Bu) ₃ P	2:1	60	(90.5)	7660	4.48	2.18	n.d	n.d	n.d
13	MBL	CH ₂ Cl ₂	Al·TOL	<i>t</i> BuNHC	2:1	60	(85.5)	704	16.3 ^{c)}	1.28	n.d	n.d	n.d
14	MBL	CH ₂ Cl ₂	Al·TOL	Ph ₃ P	2:1	60	(32.7)	262	20.3; 1.53	2.99; 1.33	n.d	n.d	n.d
15	MMBL	CH ₂ Cl ₂	Al·TOL	(<i>t</i> Bu) ₃ P	2:1	10	100	4800	19.2	2.28	29.4	47.0	23.6
16	MMBL	CH ₂ Cl ₂	Al·TOL	<i>t</i> BuNHC	2:1	1	100	48 000	13.9	1.15	33.8	46.9	19.3
17	MMBL	CH ₂ Cl ₂	Al·TOL	MesNHC	2:1	1	100	48 000	6.28	1.42	n.d	n.d	n.d
18	MMBL	CH ₂ Cl ₂	Al·TOL	Ph ₃ P	2:1	1	100	48 000	13.9; 5.01	1.03; 1.04	n.d	n.d	n.d

a) Reaction conditions: 800 equiv of monomer relative to base; 10 ml total solution volume [solvent toluene (TOL) or dichloromethane + monomer] and room temperature (about 25 °C).

b) Conversions and yields of the isolated polymer determined by using gravimetric methods.

c) The GPC trace shows a small (about 4%) low-MW tail peak.
 n.d = not determined, conversion = % monomer conversions measured by ¹H NMR spectroscopy, and rr, mr, mm = polymer methyl triads, measured by ¹H (PMMA) or ¹³C NMR (poly-MMBL) spectroscopy, M_n determined by GPC relative to PMMA standards.
 Source: Reproduced with permission Ref. [22].

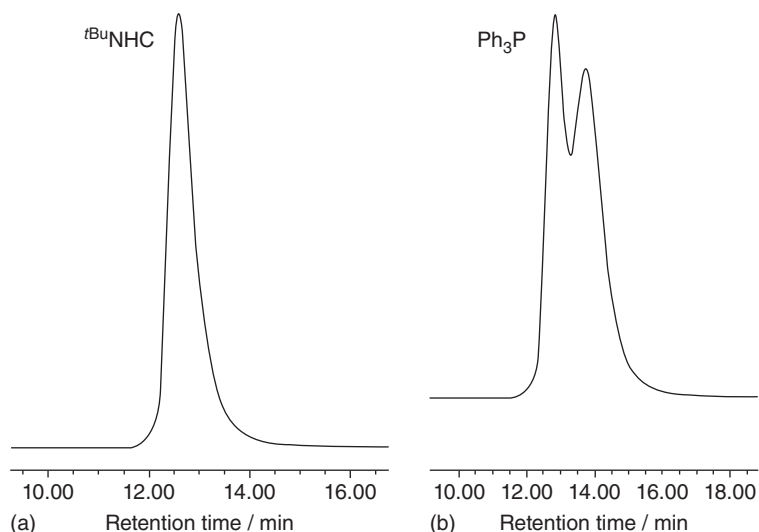


Figure 13.5 Gel-permeation chromatography (GPC) traces of poly-MMBL synthesized by $t\text{BuNHC}$ (a, run 16) and by Ph_3P (b, run 18). (Reproduced with permission Ref. [22].)

Lewis acids were observed with $\text{Al}(\text{C}_6\text{F}_5)_3$, while no polymerization occurred with boron- or silicon-based Lewis acids. Table 13.3 shows an overview of the performed experiments according to Ref. [22]. When the alane/monomer adduct $\text{MMA} \cdot \text{Al}(\text{C}_6\text{F}_5)_3$ was pretreated with the phosphine (rt, toluene), for 10 min, followed by addition of MMA (800 equiv), fast polymerization took place which consumed all monomer within 60 min resulting in high molecular weight (MW) polymer with $M_n = 2.83 \times 10^5$ Da and a molecular weight distribution of $M_w/M_n = 1.42$ (Table 13.3, run 1). This polymerization was more rapid with an $[\text{Al}]/[\text{base}]$ ratio of 2:1, where all MMA was transformed into polymer within only 4 min ($M_n = 3.97 \times 10^5$ Da, $\text{PDI} = 1.52$, rr-triad^1 content = 73.5%; run 2), resulting in a turnover frequency (TOF) of $1.2 \times 10^4 \text{ h}^{-1}$. Further experiments showed, for example, that generating $\text{MMA} \cdot \text{Al}(\text{C}_6\text{F}_5)_3$ *in situ* followed by addition of the Lewis base led also to a highly active polymerization system (run 3) and that replacing nonpolar toluene by the more polar dichloromethane did not considerably affect the polymerization activity (run 4 and 5). The $\text{Ph}_3\text{P}/\text{Al}(\text{C}_6\text{F}_5)_3$ pair exhibits exceptional activity, while the polymer produced by this pair has a bimodal PDI (~41% higher MW fraction, ~59% lower MW fraction, run 8). Furthermore, the $^{\text{Mes}}\text{NHC}$ carbene is very active for polymerization of MMA, consuming all 800 equiv of the monomer in less than 1 min and resulting in a high TOF value $>4.8 \times 10^4 \text{ h}^{-1}$ (run 9) [22].

The polymerization of MBL by $(t\text{Bu})_3\text{P}/\text{Al}(\text{C}_6\text{F}_5)_3$ in CH_2Cl_2 achieved a polymer yield >90% in 1 h (run 12). Again, the use of Ph_3P as the base resulted in the formation of bimodal polymer products (~32% high MW fraction and ~68% low MW

1) Polymer tacticity descriptor, showing the degree of syndio-tacticity.

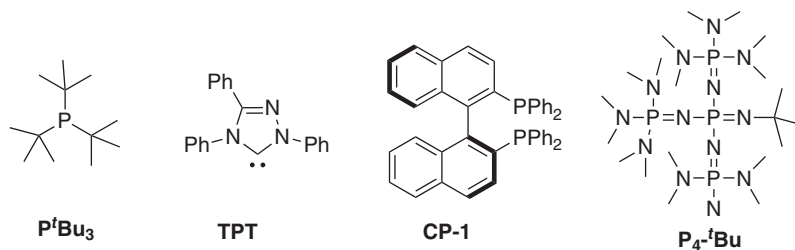


Figure 13.6 Selected bases (phosphines, carbene, and phosphazene derivatives) tested for the polymerization of vinyl monomers in combination with Lewis acids [23].

fraction; run 14). This performance could also be confirmed in the polymerization of MMBL (run 18) and by the corresponding GPC trace, where two clear peaks could be seen in the case of Ph_3P in comparison to $t\text{BuNHC}$ (Figure 13.5) [22].

A variety of further Lewis acid/Lewis base combinations (with phosphines, chiral chelating diphosphines, *N*-heterocyclic carbenes, and phosphazene superbases) have been tested, and the $\text{P}_4\text{-}t\text{Bu}/\text{Al}(\text{C}_6\text{F}_5)_3$ pair exhibited the highest activity with a TOF of $9.6 \times 10^4 \text{ h}^{-1}$ toward MMA at room temperature (rt) (Figure 13.6) [23]. The resulting polymers prepared at rt were typically atactic or syndio-rich, but highly syndiotactic poly(methyl methacrylate) (PMMA) could be produced at -78°C [23].

Figure 13.7 shows exemplarily the X-ray structure of the intermediate $t\text{Bu}_3\text{P-CH}_2\text{C}(\text{Me})=\text{C}(\text{OMe})\text{O-Al}(\text{C}_6\text{F}_5)_3$ (a) as well as plots of monomer conversion (%) versus reaction time (min) of the polymerization of MMA in toluene at rt by the $\text{Al}(\text{C}_6\text{F}_5)_3/\text{P}'\text{Bu}_3$ pair with two different procedures and Lewis acid catalyst

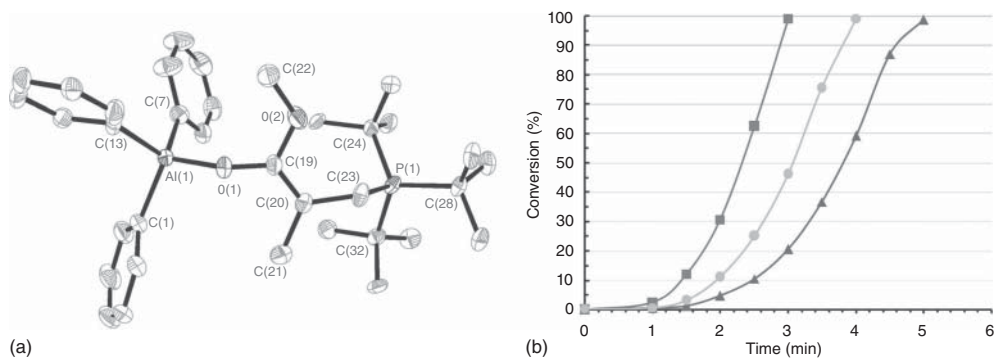


Figure 13.7 (a) X-ray structure of $t\text{Bu}_3\text{P-CH}_2\text{C}(\text{Me})=\text{C}(\text{OMe})\text{O-Al}(\text{C}_6\text{F}_5)_3$ (fluorine atoms are omitted for clarity) and (b) plots of monomer conversion (in %) versus reaction time (min) for MMA polymerization (toluene, rt) by the $\text{Al}(\text{C}_6\text{F}_5)_3/t\text{Bu}_3\text{P}$ pair with different procedures and conditions (see text). Line ▲: procedure A, $[\text{MMA}]/[\text{Lewis acid}]/[\text{Lewis$

$\text{base}] = 800/2/1$; $[\text{MMA}]_0 = 0.935 \text{ M}$, $[\text{MMA} \cdot \text{Al}(\text{C}_6\text{F}_5)_3] = 2.34 \text{ mM}$, $[t\text{Bu}_3\text{P}] = 1.17 \text{ mM}$. Line ■: procedure B, $[\text{MMA}]/[\text{Lewis acid}]/[\text{Lewis base}] = 800/2/1$. Line ●: procedure B, $[\text{MMA}]/[\text{Lewis acid}]/[\text{Lewis base}] = 800/1.8/1$. (Reproduced with permission Ref. [23].)

concentrations (b). In procedure A, $\text{MMA} \cdot \text{Al}(\text{C}_6\text{F}_5)_3$ (2 equiv) was dissolved in MMA (800 equiv) in toluene, and P^tBu_3 (1 equiv) was added in toluene to start the polymerization. Obviously, after an initial slow induction period (about 2 min), the MMA conversion occurred, and increased almost linearly with reaction time until completion of the reaction, which showed a zero-order dependence on $[\text{MMA}]$ (Figure 13.7, $\blacktriangle$ line). In procedure B, $\text{MMA} \cdot \text{Al}(\text{C}_6\text{F}_5)_3$ (1 equiv) was first premixed with P^tBu_3 (1 equiv) in toluene for 10 min (for the formation of the zwitterionic species), which was followed by the addition of another equivalent $\text{MMA} \cdot \text{Al}(\text{C}_6\text{F}_5)_3$ and 800 equiv of MMA. The resulting polymerization was remarkably faster (by 55%); now, after a much shorter induction period (1 min), the kinetic plot showed a linear increase of the MMA conversion with time (Figure 13.7, $\blacksquare$ line). Furthermore, a remarkable effect of the Lewis acid concentration on the polymerization rate has been demonstrated: for instance, using procedure B while reducing the total amount of the alane from 2 to 1.8 equiv resulted in a slowdown of the polymerization by 23% ($\bullet$ line). Accordingly, increasing the amount of the alane to 2.5 equiv accelerated the polymerization by approximately 50%. These experiments confirmed that this polymerization reaction is effectively catalyzed by Lewis acid, which is in agreement with the proposed bimolecular mechanism, where the activated monomer is propagated [23].

Figure 13.8a shows the NMR spectra (^1H , ^{19}F , ^{31}P) of the zwitterionic phosphonium enolaluminate $t\text{Bu}_3\text{P}-\text{CH}_2\text{C}(\text{Me})=\text{C}(\text{OMe})\text{O}-\text{Al}(\text{C}_6\text{F}_5)_3$ as two isomers (*E/Z*) in 7:3 ratio, which can easily be seen from the signal intensity. Correspondingly, replacing MMA with the cyclic compound MBL, where the *s-cis*-conformation is fixed, in the reaction with the $\text{P}^t\text{Bu}_3/\text{Al}(\text{C}_6\text{F}_5)_3$ pair results in an accordant zwitterionic phosphonium enol aluminate as one single isomer, which could also be confirmed by NMR (Figure 13.8b).

In addition to these vinyl monomer polymerizations, Lewis pair polymerization for the ROP of lactones was performed with the described adducts. These polymerizations worked but were found to have only moderate activity and quite poor control; for instance, the ROP of ϵ -caprolactone occurred with 58% conversion after 20 h (rt) and an M_w/M_n ratio of 2.76 [23].

13.4

Zinc-Based Cooperative Catalysis of Epoxide/ CO_2 Copolymerization

One of the most investigated polymerization reactions, for which cooperative effects in the catalyst system play a crucial role, is perhaps the copolymerization of epoxides with CO_2 . The reaction was originally discovered by Inoue in 1969 [24], who applied $\text{Et}_2\text{Zn}/\text{water}$ co-reactants for the *in situ* generation of a heterogeneous zinc hydroxide/oxide-based catalyst capable of copolymerizing propylene oxide (PO) and CO_2 toward poly(propylene carbonate) (PPC) (Scheme 13.8).

Inoue's structurally unidentified catalyst system became the starting point for the rich chemistry of epoxide/ CO_2 copolymerization both with respect to the

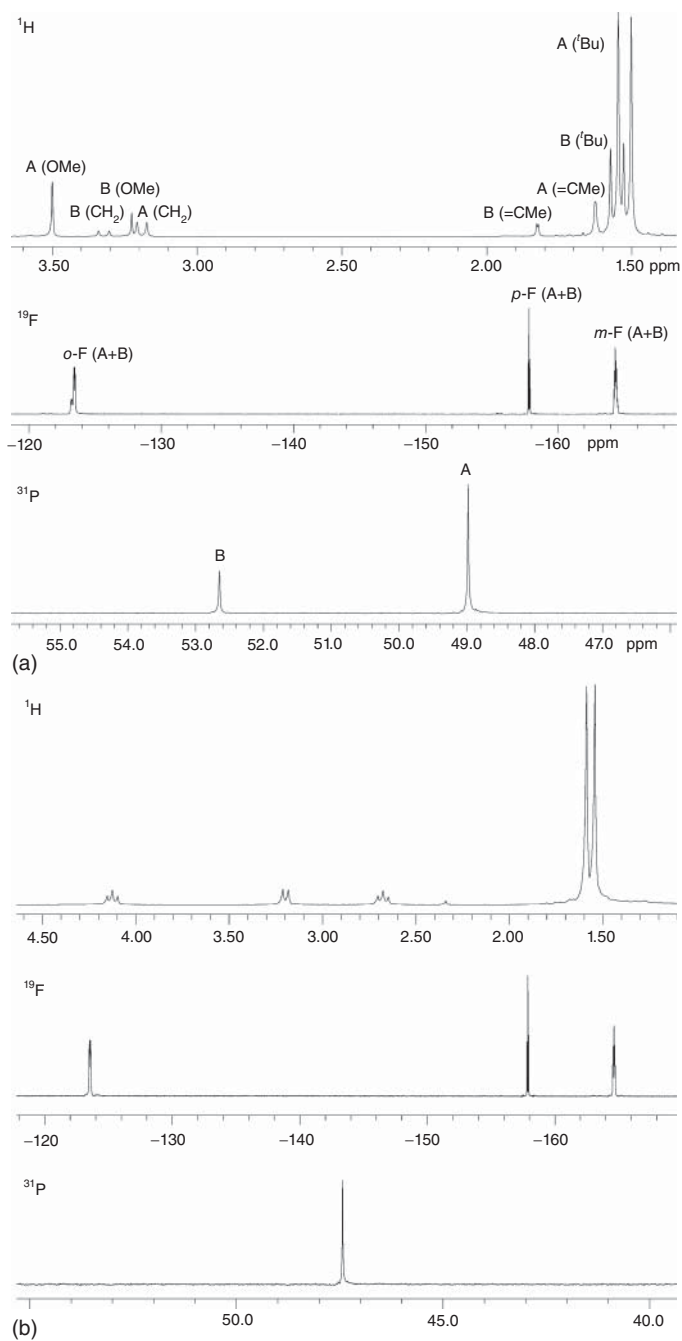
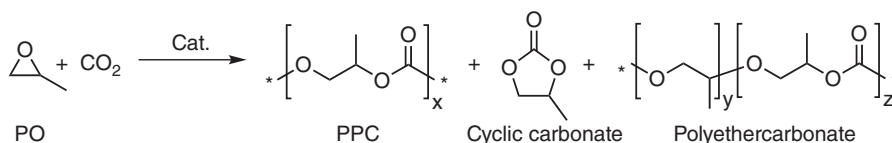


Figure 13.8 NMR spectra of the zwitterionic phosphonium enolaluminate ${}^t\text{Bu}_3\text{P-CH}_2\text{C(Me)=C(OMe)O-Al(C}_6\text{F}_5)_3$ (a) and of corresponding MBL adduct (b) [23].



Scheme 13.8 Catalytic copolymerization of propylene oxide and CO_2 : besides pure poly(propylene carbonate) (PPC), ether-linkage-rich polycarbonates and cyclic propylene carbonate are possible products.

number of applied epoxide substrates and the diversity of the corresponding catalytic systems described in the literature [25].

Among them, zinc dicarboxylates such as glutarate (GA) received great attention and became industrially relevant heterogeneous catalysts for PO/ CO_2 copolymerization [26]. Although this compound class is known for a relatively long time in its copolymerization applications, little was recognized on the mechanism of the reaction, and most of the works were dealing with the improvement of these systems by modification of synthetic procedures and activation protocols. However, some mechanistic considerations have been reported for the heterogeneous systems derived from ZnEt_2 and water or dihydric (polyhydric) phenols [27]. These studies revealed that the simultaneous presence of $-\text{O}-\text{Zn}-\text{ethyl}$ and $-\text{O}-\text{Zn}-\text{OH}$ ($-\text{O}-\text{Zn}-\text{O}-$) entities was essential for the PO/ CO_2 copolymerization. In addition, a strong effect of the phenols' substitution pattern on the activity of the resulting catalysts has been observed [28].

Recently, a systematic comparative study of the activity and structural peculiarities in a series of zinc dicarboxylates (succinate SA, GA, adipate AA, and pimelate PA) allowed shedding light on the mechanistic aspects of the PO/ CO_2 copolymerization in the presence of these catalysts [26d]. Besides the importance of certain initiating groups at the surface of these heterogeneous systems, the mutual arrangement of zinc centers in the crystal lattice appeared to have a great impact on the catalysts' activity and selectivity. That is, in ZnGA, ZnAA, and ZnPA possessing comparable activity, the structural motif in the crystallographic *hkl* plane (100) remains entirely the same, with four Zn atoms in a well-defined spatial conformation and a Zn–Zn distance of 4.6–4.8 Å. Ball-milling of these materials results in the formation of new surface-located Zn–Zn couples with this particular interatomic distance, thus improving the copolymerization activity. This is, however, not the case for ZnSA, a lowest homolog of the series with a noticeably poorer catalytic performance.

The findings strongly suggested the occurrence of a bimetallic mechanism (see also Chapters 1 and 2 of this book), which implies a transition state where the growing polymer chain at one metal center interacts with the activated monomer at another metal center (Figure 13.9). According to such a mechanism, the number of accessible active sites and a proper metal–metal distance between the cooperatively working metal centers at the surface of the heterogeneous catalyst are essential for efficient copolymerization.

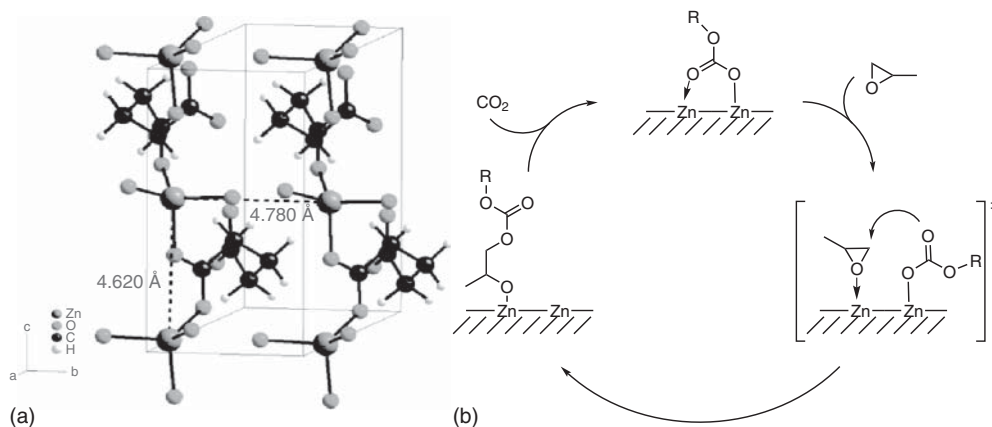


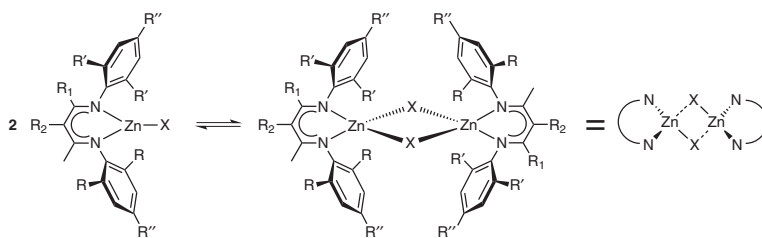
Figure 13.9 Fragment of the structure of ZnGA showing the copolymerization relevant arrangement of the zinc atoms at the crystal surface (a) and the schematic bimetallic

mechanism of epoxide/CO₂ copolymerization on ZnGA (b). (Adapted with permission from Ref. [26d]. Copyright 2011 American Chemical Society.)

These conclusions are in good agreement with previous experimental and theoretical studies on homogeneous catalysts such as complexes of Schiff bases, porphyrins, and so on. Because of the – in most cases – defined molecular structure of homogeneous catalysts, elucidation of the mechanistic features of catalytic epoxide/CO₂ copolymerization in relation to the electronic and steric properties at the active catalyst centers is to a certain extent facilitated. This is especially true for the theoretical modeling of catalytic processes, where the nonuniform nature of active centers in heterogeneous systems would require exceedingly complex calculations to get reliable results. Even for the calculations on defined molecular catalysts, certain simplifications are often applied to reduce the computation time.

Clear experimental evidence with respect to a cooperative catalysis of epoxide/CO₂ copolymerization on homogeneous complexes was obtained, to our knowledge, for the first time for the zinc β-diiminate coordination compounds (Scheme 13.9) [29].

Comprehensive structural analysis of these catalysts in solid state and in solution was complemented by the measurements of kinetics of CHO/CO₂ copolymerization (CHO = cyclohexene oxide) providing the reaction order on the catalyst [29d]. The complexes exhibited a pronounced tendency to dimerize via μ-bridging anionic ligands such as alkoxides, carboxylates, and carbonates, however, with the extent depending on the substitution pattern of the β-diiminate ligand. Moreover, the catalytic activity of these systems correlates well with their dimerization ability passing through a maximum, which corresponds to the optimal steric properties of the ligand. Excessive steric crowding dampens the dimerization, which is reflected in poorer copolymerization performance. On the contrary, insufficient bulkiness of the substituents at the β-diiminate ligand



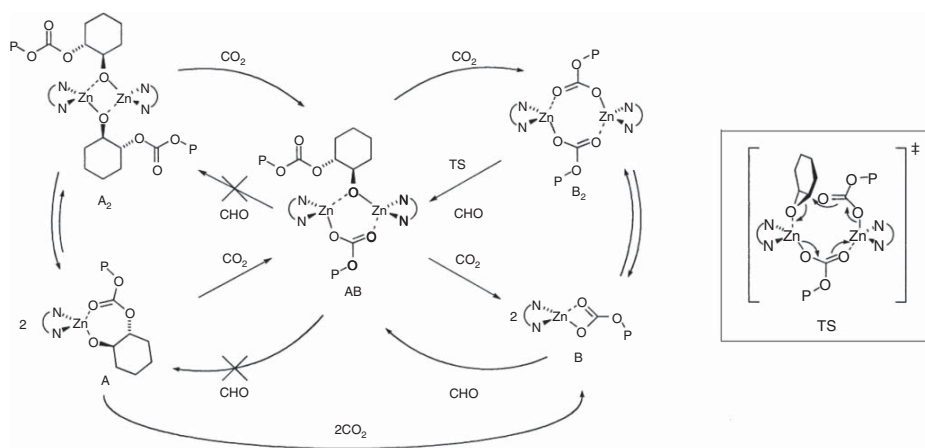
Scheme 13.9 Zinc β-diiminate complexes in their monomeric and dimeric state. X is an alkoxide, carboxylate, or carbonate; R, R', and R'' are aliphatic substituents of varying bulkiness.

causes the formation of too tightly bound dimers, which, again, are not reactive enough. Mixing the two border-case complexes (too high and too low bulkiness) together gives a more active catalytic system. Further, mimicking the catalytic copolymerization process by synthesizing various putative intermediate complexes permitted the verification of the rate-limiting step, which is the enchainment of CHO. In the course of CHO/CO₂ copolymerization experiments, catalyst reaction orders ranging from 1.0 to 1.8 have been observed. These values were a function of temperature and the ligand substitution motif. All these observations are in good agreement with a cooperative bimetallic mechanism of the epoxide enchainment (step B₂→AB in Scheme 13.10).

These findings have stimulated further research on Zn-based homogeneous catalysts for epoxide/CO₂ copolymerization with the idea to better exploit the cooperative action of two metal centers. For example, dinuclear zinc complexes of anilido–aldimine ligands with open and closed structure (Figure 13.10) have been prepared with the argumentation that these species will not undergo dissociation on high dilution in contrast to the Zn-β-diiminate systems (see the equilibrium in Scheme 13.9), thus maintaining their activity and allowing the synthesis of copolymers with higher molecular weights [30].

Indeed, although the activity of the complexes with an open structure in the copolymerization of CHO and CO₂ was dependent on the substitution pattern, in general it was comparable with that of the Zn-β-diiminates at high concentrations of catalysts (~1 : 1000 catalyst/epoxide ratios). As expected, the anilido–aldimine complexes were still active at 1 : 16 800 catalyst/epoxide ratio, yielding the copolymers with an average molecular weight M_n of up to 284 kg mol⁻¹. Interestingly, the closed anilido–aldimine structures were negligibly active, which was referred to initiation problems. That is, the methylsulfinato groups bridging the two Zn centers in the macrocyclic ligands are too tightly bound because of the optimal coordinative arrangement, as found from single-crystal X-ray analysis. Further improvement of the catalytic activity of anilido–aldimine complexes with the open structure was achieved by tuning both electronic and steric properties, with the highest TOF observed for a fluorinated derivative with R = Me, R' = *i*-Pr (Figure 13.10) [31]. However, in contrast to Zn-β-diiminates [29c], increase of the Zn Lewis acidity by introduction of these electron acceptor substituents in anilido–aldimine complexes does not render them active for PO/CO₂ copolymerization.

In the search for a cooperative action of two Zn centers, covalently bridged β-diiminate-based dinuclear complexes shown in Figure 13.11 have been prepared, structurally characterized, and tested for CHO/CO₂ copolymerization. A bimodal polymer molecular weight obtained with catalyst **12** gave hints that both cooperative bimetallic and monometallic mechanisms of copolymerization were operating [32]. However, the achieved TOFs were fairly low (<10 h⁻¹), a drawback that was attributed to the steric bulk of the catalyst, although the question of suitable mutual arrangement of Zn centers should not be excluded from the consideration as well. In this respect, *meta*-phenylene bridged catalyst **13** appeared to be significantly more active than its *para*-phenylene bridged analog



Scheme 13.10 Mechanism of CHO/CO₂ copolymerization in the presence of Zn-β-diiminates and the rate-determining transition state introduced by Coates *et al.* (Reproduced with permission from Ref. [29d]. Copyright 2003 American Chemical Society.)

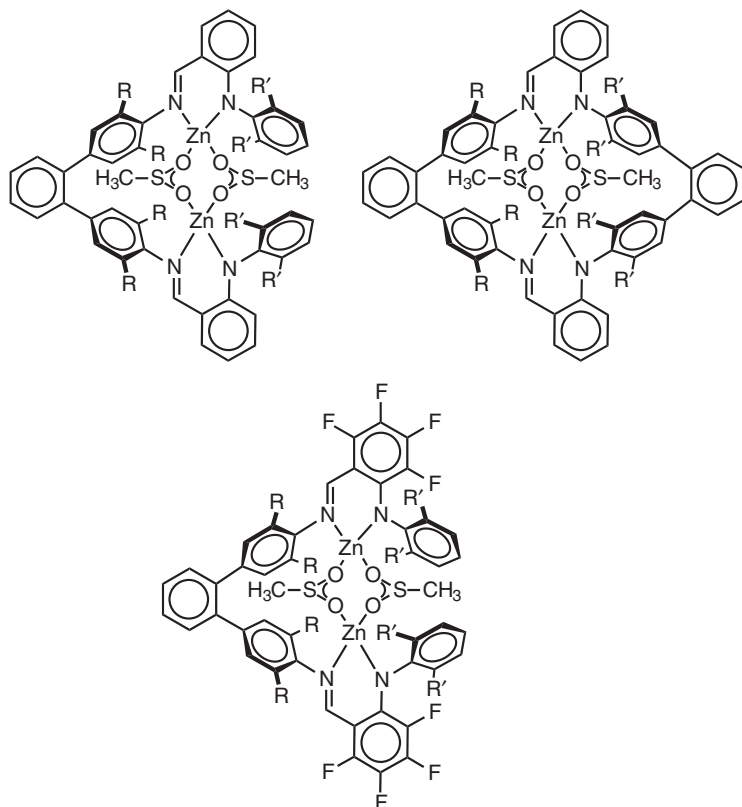


Figure 13.10 Open, closed, and fluorinated Zn anilido–aldimine complexes for CHO/CO₂ copolymerization; R, R' = Me, Et, *i*-Pr [30, 31].

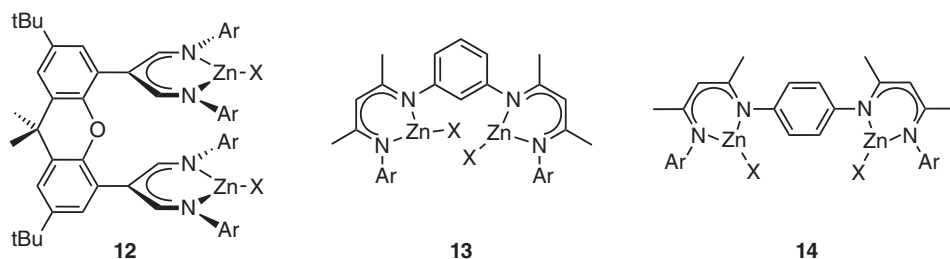
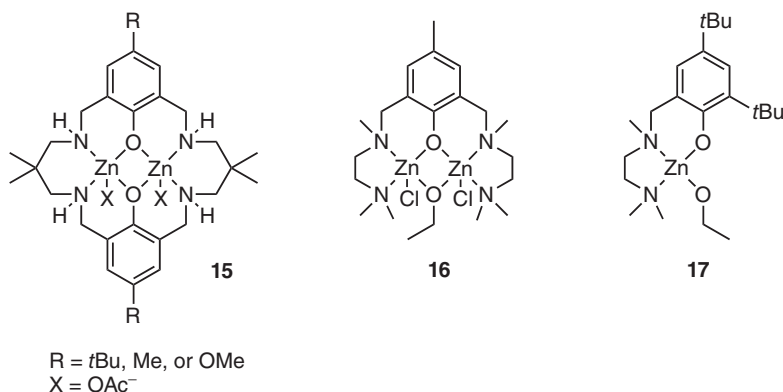


Figure 13.11 Acyclic dinuclear Zn complexes based on bridged β -diiminates.

14 or the complex **12** [33]. In addition, initiation of CHO/CO₂ copolymerization by CO₂ insertion into Zn–Et bonds has been observed with these complexes, which is known to be very slow in case of mononuclear Zn- β -diiminates. This fact was ascribed to the bimetallic nature of this initiation reaction as well, thus again emphasizing the importance of cooperative interactions in the catalysis by Zn- β -diimine complexes.

Another example of a dinuclear catalyst, for which a synergistic effect of two Zn centers was established in the epoxide/ CO_2 copolymerization, is based on the “reduced Robson’s type” macrocyclic ligand and is represented in Scheme 13.11. The advantages of the dinuclearity and macrocyclic structure of the dizinc diacetate complexes **15** for the activity in CHO/CO_2 copolymerization were shown by comparison with the opened dinuclear (**16**) and mononuclear (**17**) analogs, which did not promote the copolymerization [25c].

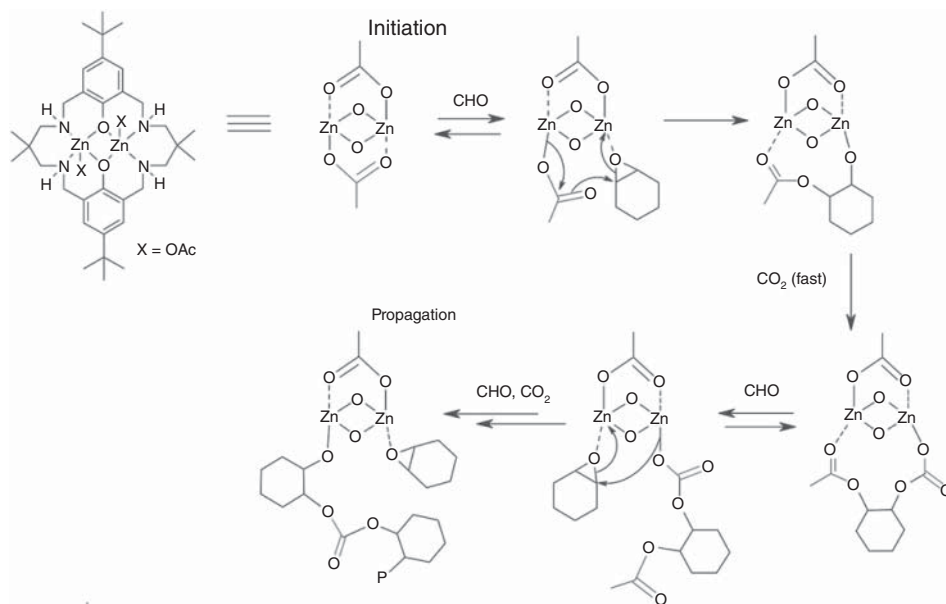


Scheme 13.11

In contrast, complexes **15** were active already at 1 bar CO_2 pressure, reaching a TOF of 13 h^{-1} at 100°C (TOF values are calculated per metal center) [34]. Moreover, substitution of zinc by cobalt in these structures results in an increase of the activity up to a TOF of 250 h^{-1} at 1 bar and 1700 h^{-1} at 10 bar CO_2 pressure [35].²⁾ In the case of Zn complexes, a zero order of reaction was found for CO_2 by measuring the reaction kinetics [36]. However, the direct determination of the reaction order for CO_2 using the cobalt complexes could not be performed [37], whereas an indication for a first-order reaction in CHO and catalyst was obtained for complexes with both metal types. In total, the results allowed the suggestion that a bimetallic mechanism is operating according to Scheme 13.12 (shown for the case of Zn complex **15**), which closely resembles the one introduced by Coates (see above).

According to the mechanistic proposal, one side of the macrocyclic complex with a bridging acetate group is not active as a propagating site. This acetate group plays a role in completing the octahedral coordination at both metal centers and

2) At this point, it has to be mentioned that the TOF values reported in the literature do not necessarily represent the actual activity of the catalyst, as they are most often calculated as a simple ratio of the turnover number (TON) to the total reaction time. Therefore, it appears that the same catalyst can exhibit extremely different TOFs if these values were determined for different reaction durations, which can be misleading. This derives from a commonly nonlinear dependence of conversion on time due to the occurrence of an initiation period, nonzero order of reaction for the monomer, and viscosity effects in course of polymerization besides the catalyst deactivation and other side reactions.



Scheme 13.12 Suggested CHO/CO₂ copolymerization mechanism with complexes **15**. (Adapted with permission from Ref. [36]. Copyright 2011 American Chemical Society.)

maintaining the neutral charge balance throughout the whole reaction. It was also supposed that the axial positions of the macrocyclic ligand might have different steric accessibilities under the reaction conditions.

All in all, the coordinative flexibility of the ligand, the balance of its steric and electronic properties with Lewis acidity of the metal, and the proximity of the two metal centers allowing for the cooperative action are the essential prerequisites for the high activity to be reached in the copolymerization of CO₂ and epoxides with Zn-based catalysts. These conditions appear to be particularly well realized in complex **18** shown in Figure 13.12.

In the copolymerization of CHO and CO₂, the spatial arrangement of the two Zn centers in **18** as well as the flexibility of the cyclic ligand framework appeared to be optimal for the rate-determining step to be shifted from epoxide ring opening to CO₂ insertion at low CO₂ pressure [38]. That is, in contrast to all the previously reported Zn systems, the experimentally determined reaction orders for CO₂ and CHO are 1 and 0, respectively, in the pressure range of 5–25 bar. Above 25 bar of CO₂, there is an inversion of these reaction orders: zero order for CO₂ and first order for CHO were observed in the pressure range of 25–45 bar. At 100 °C and 40 bar CO₂ pressure, a TOF as high as 9130 h⁻¹ was documented for the complex **18**. This TOF value was calculated as a ratio of TON to the reaction time of 26 min, during which a nearly complete conversion of CHO was achieved. Taking into account the first order of the reaction for CHO under such conditions, the maximum activity of the complex achieved in this experiment in terms of TOF

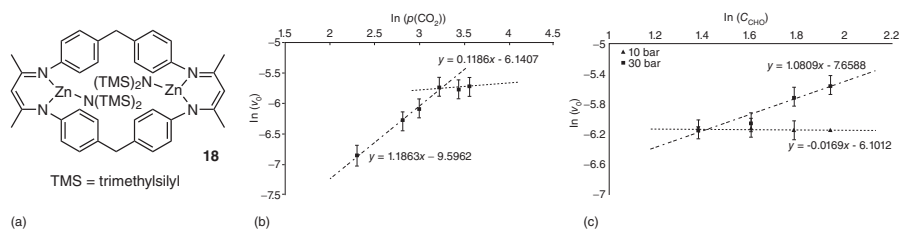
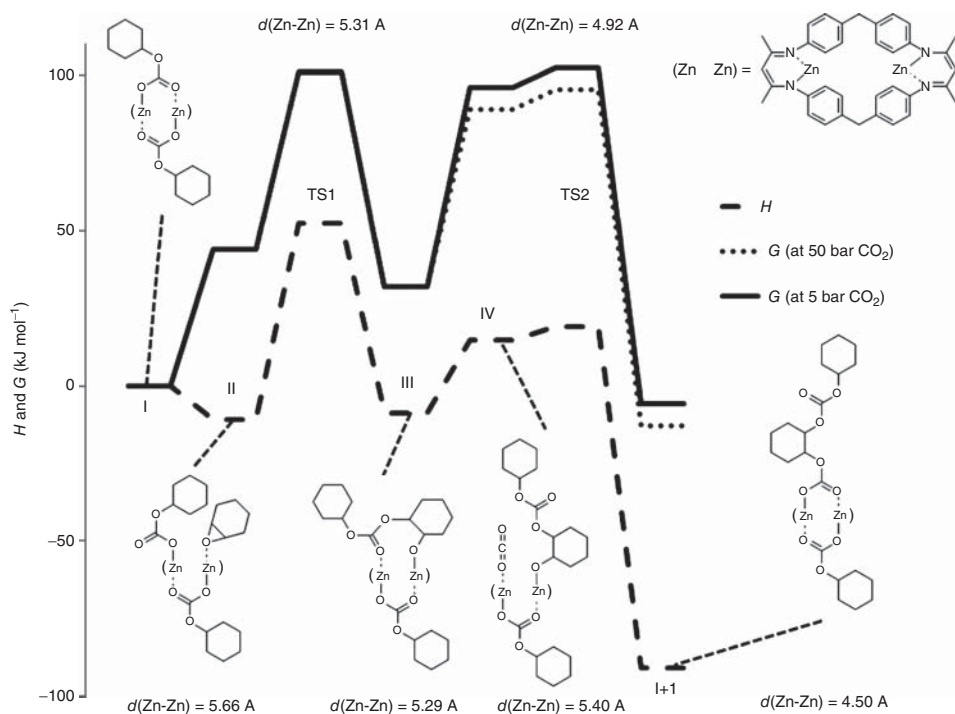


Figure 13.12 Highly active cyclic binuclear Zn complex for CHO/CO₂ copolymerization (a) and the graphs showing the reaction order on CO₂ (b), and CHO (c). (Adapted with permission Ref. [38].)

(e.g., in the beginning of the polymerization) undoubtedly exceeds the reported value.

These experimental findings were well supported by theoretical calculations based on a bimetallic intramolecular chain propagation mechanism [38]. Indeed, taking into account enthalpic and entropic components of the activation energy for each elementary step, the transition states for the epoxide enchainment (TS1) and for the CO₂ enchainment (TS2) were calculated to lie energetically very close. Moreover, the energy of the TS for CO₂ insertion was found to depend on the CO₂ pressure, being slightly lower than the TS1 at 50 bar and slightly higher than TS1 at 5 bar CO₂ pressure. As a consequence, this computation predicts a change of the rate-determining step with varied pressure (Scheme 13.13).



Scheme 13.13 Adapted with permission Ref. [38].

The same calculations have supported the conformational flexibility of the binuclear system **18**. That is, the Zn–Zn distances computed for various intermediates and transition states of the catalytic cycle span the range 4.50–5.66 Å, whereas the Zn–Zn distance calculated for the bis[bis(trimethylsilyl)amido] precursor complex equals 7.77 Å, which is close to the value of 7.70 Å experimentally found from a crystallographic study (S. Kissling and B. Rieger, manuscript in preparation). Thus, the superior activity of the complex is, most probably, connected with the

accessibility of various Zn–Zn distances within this flexible ligand frame, allowing every transition state to adopt an optimal structure, thus avoiding additional barriers from catalyst rigidity.

Interestingly, **18** does not copolymerize PO and CO₂, similar to the majority of other dinuclear Zn complexes. This fact is remarkable and remains the subject of intense investigations.

13.5

Cooperative Mechanism of Epoxide/CO₂ Copolymerization by Salen-Type Complexes

One of the earliest DFT-based detailed descriptions of PO/CO₂ copolymerization has been performed for the process in the presence of chromium(III) and aluminum(III) salphen complexes, where various pathways and elementary steps of this complex reaction have been considered [39]. Among the probable chain propagation routes involving the attack of the carbonato chain end as a nucleophile onto the epoxide, an intermolecular bimetallic step was suggested. Thus, the reaction path involving two metal complexes – one acting as Lewis acid to activate a molecule of epoxide via coordination, and another bearing a coordinated nucleophilic chain end capable of attacking the PO – was found to be energetically the most favorable, comprising the elements of cooperative catalysis. The experimental approval of this finding long appeared to be difficult to realize because of the overall complexity of the occurring parallel and consecutive reactions and equilibria, including the induction period, simultaneous formation of several products, influence of CO₂ concentration, solvents, and poisoning effects of the products in some cases, and so on. In this respect, the appropriate catalyst design became the approach to show the importance of bimetallic steps in PO/CO₂ copolymerization in the presence of trivalent metal complexes of salen-type ligands. Hence, synthesis of dinuclear catalysts via bridging the salen or salphen entities by flexible tethers and comparison of their catalytic properties with the mononuclear analogs were performed (Figure 13.13) [40].

Both for chromium(III)salphens and for cobalt(III)salens, the effect of complex dimerization was prominent, resulting in an enhancement of the PO/CO₂ copolymerization rate specifically at low concentrations of the catalysts. This has been explained in terms of increased/constant local concentration of metal centers in dinuclear complexes favorable for a bimetallic reaction step, which is definitely limiting in case of the mononuclear counterpart at high dilution. Such behavior has been previously described and studied in detail by Jacobsen for the ring-opening reaction of epoxides, where he could prove the occurrence of the cooperative catalysis also by the investigation of the kinetics [41]. Similarly, in case of PO/CO₂ copolymerization by salen-type complexes, intense exploration of the reaction kinetics has been performed. In contrast to the batch autoclave copolymerization experiments, the most reliable data have been obtained by *in situ* IR monitoring over the entire course of the reaction with specifically designed equipment [42]. Nevertheless, because of the extremely complex network of the

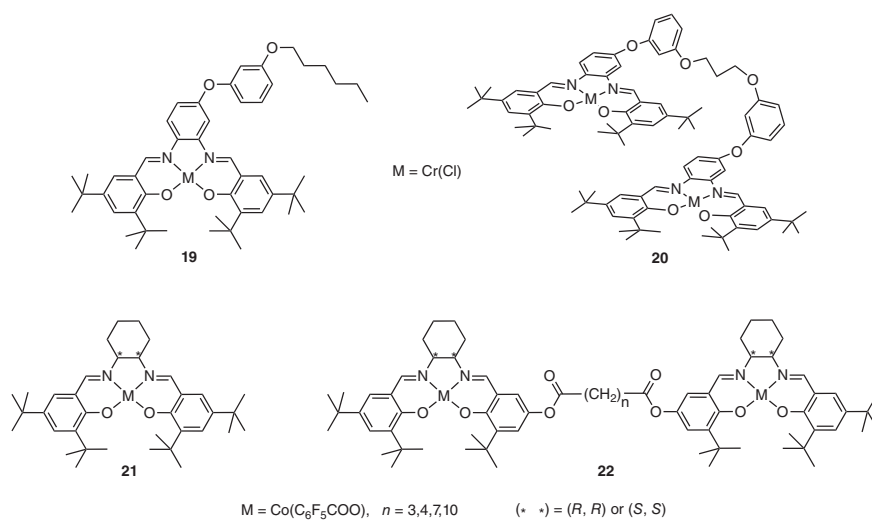
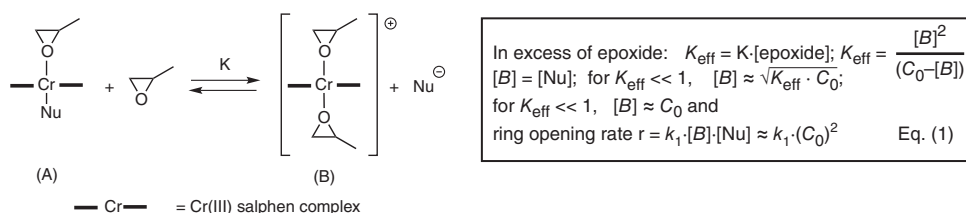


Figure 13.13 Mononuclear and flexibly bridged dinuclear salphen (a) and salen (b) complexes.

elementary steps including various coordination/dissociation equilibria [39], the interpretation of the results appears to be not straightforward. For example, the chromium(III)-salphen complex **19** alone exhibits the reaction order of about 1.7, which was considered as an indication for the occurrence of bimetallic steps in the catalysis [43]. On the contrary, analysis of the hypothetical equilibrium in Scheme 13.14 demonstrates the ambiguity of the catalyst reaction order interpretation. That is, if $K \ll 1$, the major species is the hexacoordinated Nu complex (A), and the second order in catalyst for the ring-opening reaction can be observed only if species (A) reacts with another species (A), which implies a bimetallic ring-opening event for the coordinated epoxide. Conversely, if $K \gg 1$, the major species are cationic complex (B) and free nucleophile, meaning that the polymer chain propagation would occur mainly by their interaction toward epoxide ring opening. This means a participation of only one metal center, but it still gives a second order in catalyst concentration according to the Eq. (1):



Scheme 13.14 Hypothetical equilibrium and its influence on the observed reaction order in the catalyst loading.

Interestingly, for very small $K_{\text{eff}} (\ll 1)$ on assuming that species (B) and Nu^- are responsible for the PO enchainment, Eq. (1) would give a first order in catalyst loading, whereas the order of 1.5 will be observed if Nu^- is interacting with species (A).

In this respect, the analysis of the microstructure of the resulting polymer is important. Catalyst **19** yields an ether-rich PPC (Scheme 13.8), which would be evident for the comparable rates of epoxide enchainment by the alkoxide and by the carbonate chain ends. This is probably the consequence of the close rates for the alkoxide attack onto PO and on CO_2 , which, again, may explain the observed fractional catalyst reaction order. The amount of ether linkages in PPC obtained with the dinuclear catalyst **20** was notably higher than in case of the mononuclear analog **19**, whereas the measured reaction order on the catalyst was clearly lower for the dinuclear one. Taking into account the faster polymer formation with the dinuclear catalyst, probably by an intramolecular reaction, it all points to the realization of epoxide enchainment according to Jacobsen's bimetallic mechanism [41].

Stereostructure of polymers prepared with chiral catalysts can also give indications for the type of polymerization mechanism. A very good example for this is the copolymerization of *rac*-PO and CO_2 in the presence of either (*R,R*)-(salen)CoX ((*R,R*)-**21**) or (*R,R*)/(*S,S*)-(salen)CoX (racemic mixture of **21**) alone or

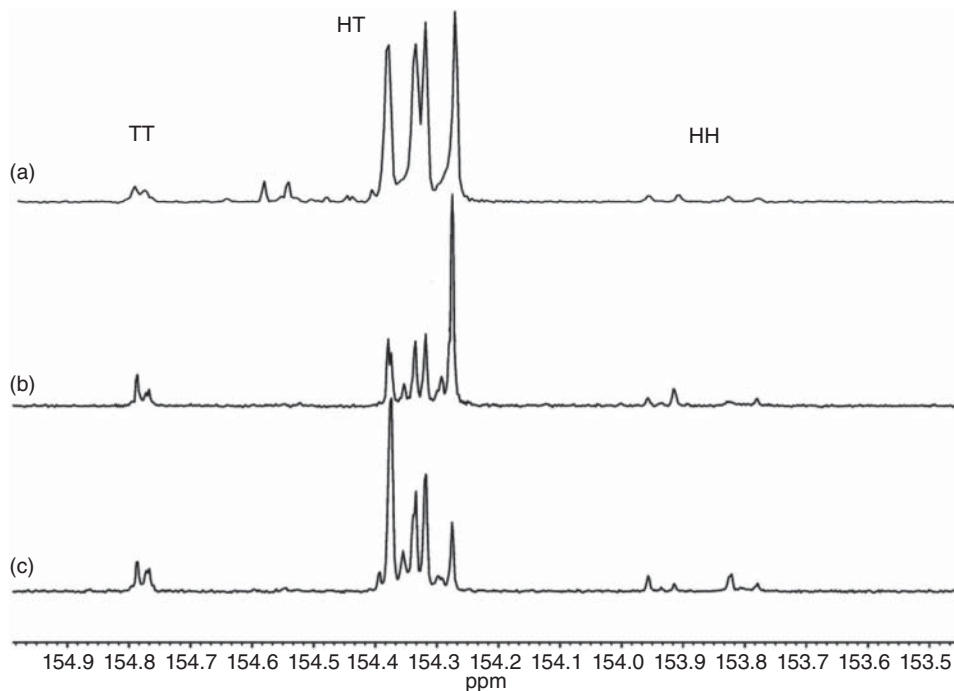


Figure 13.14 ¹³C NMR spectra in the carbonyl region of atactic (a), iso-enriched (b), and syndio-enriched (c) regioregular (high head-to-tail (HT) content)

predominantly alternating poly(propylene carbonate). (Adapted with permission from Ref. [44a]. Copyright 2012 American Chemical Society.)

in a mixture with PPNCl (bis-(triphenylphosphorylidene)ammonium chloride) as cocatalyst, respectively [40b, 44]. Whereas (*R,R*)-**21** alone or with PPNCl affords isotactic-enriched PPC because of the stereoselective coordination of (*S*)-PO by the complex, (*R,R*)/(*S,S*) catalyst mixture alone gives syndiotactic-enriched PPC and nearly atactic PPC in the presence of PPNCl (Figure 13.14). The following proposition describes well the above observations: In the absence of PPNCl, the bimetallic PO enchainment takes place, whereas in the presence of PPNCl the coordinated epoxide is being ring-opened via an attack of a noncoordinated anionic carbonato chain end of the growing polymer, which therefore occurs noticeably faster (see below). Because of the fairly remote location of the chiral center from the nucleophilic center in this chain end, it can attack both (*S*)-PO coordinated at the (*R,R*) catalyst and (*R*)-PO at the (*S,S*) catalyst with nearly the same probability, giving the atactic microstructure of PPC. Without the PPNCl, the dissociation of carbonato chain end is retarded, and the ring opening of the coordinated epoxide proceeds via an attack of the carbonato chain end bound to another metal center. For steric reasons, this bimetallic step appears to be faster for the (*R,R*)/(*S,S*) pair (also in the dinuclear species **22**) [40b],

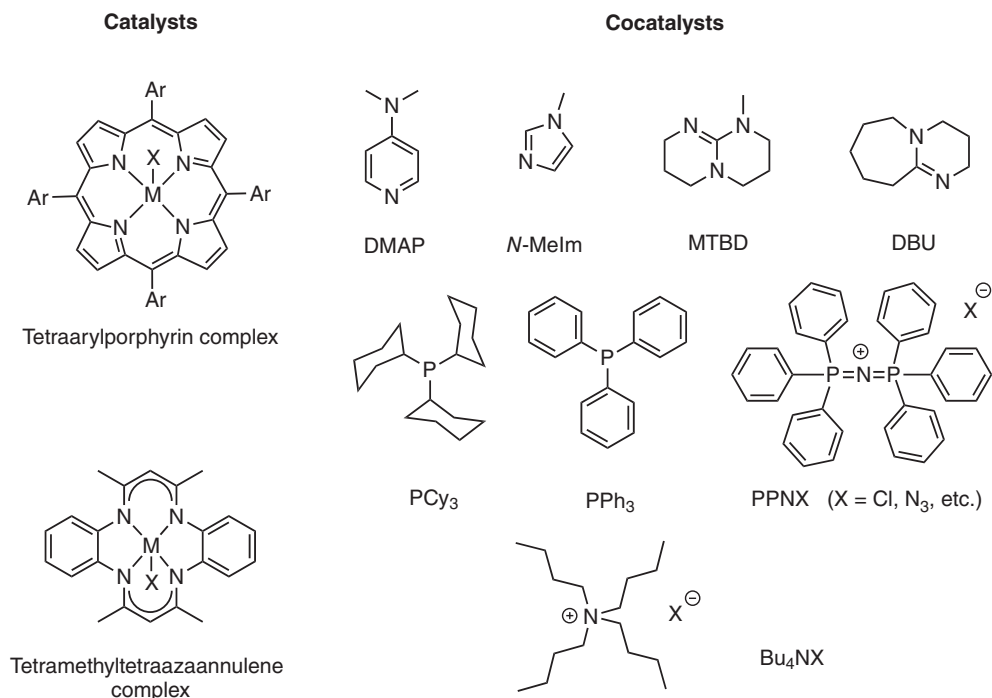
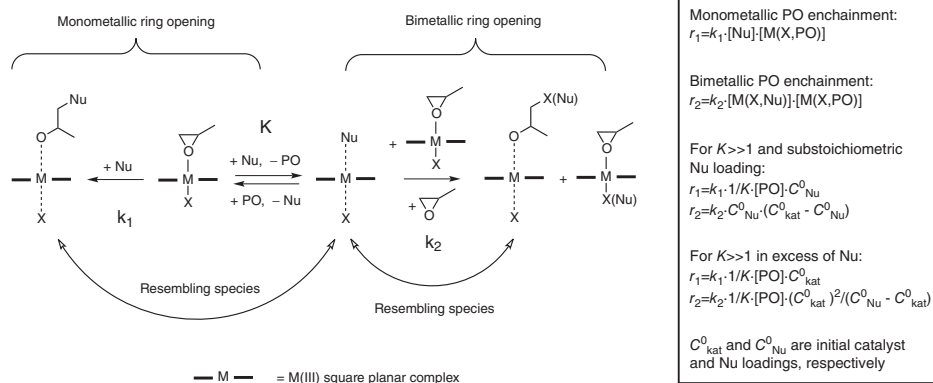


Figure 13.15 Examples of catalysts and cocatalysts for epoxide/CO₂ copolymerization.

giving predominantly the syndio-enriched copolymer. Similar effects have been observed also for CHO/CO₂ copolymerization with (salen)CoX catalysts [45].

Utilization of cocatalysts is an especially important point in homogeneous epoxide/CO₂ copolymerization catalysis by trivalent metal complexes with ligands such as salens, porphyrins, and other square-planar dianionic compounds. Indeed, most of these coordination compounds alone appear insufficiently active for the copolymerization of, for example, PO and CO₂, and the addition of external nucleophiles (Nu) such as *N*-heterocycles, phosphines, quaternary ammonium halides, and so on (Figure 13.15) is necessary to render the system catalytically sthenic (cooperative effect of catalyst and cocatalyst) [46].

This necessity is dictated by the properties of the metal complexes employed. For example, depending on the Lewis acidity of the coordinated metal in complex M(X,PO) (Scheme 13.15), one can expect the nucleophilicity of the coordinated anion X to be sufficiently reduced, thus prohibiting the bimetallic ring opening of coordinated epoxide (the epoxide must be activated by coordination because of the fact that commonly applied nucleophiles alone are barely active in the ring opening of PO under moderate conditions). In this respect, the external nucleophile as cocatalyst can be involved both in the initiation of a polymer chain and PO enchainment by directly attacking the coordinated epoxide in complex M(X,PO) and in the labilization of the coordinated nucleophile X by the formation of a complex M(X,Nu) according to the equilibrium in Scheme 13.15.



Scheme 13.15 Consideration of ideal mono- and binuclear epoxide ring-opening events, accounting for a coordination equilibrium.

The formation of $M(X,Nu)$ species including hexacoordinated anionic complexes has been proven by IR studies in solution (e.g., when Nu is an azide anion) as well as by isolation and single-crystal X-ray analysis [47]. In this respect, it is interesting to mathematically examine the equations in Scheme 13.15 taking into account the equilibrium step:

For the bimetallic PO enchainment step, an equilibrium strongly shifted toward $M(X,Nu)$ species would give a maximum reaction rate for the substoichiometric amount of added Nu (0.5 equiv to catalyst loading). A zero reaction order in epoxide is expected for such conditions. Excess of Nu would prohibit the epoxide enchainment for the bimetallic mechanism by lowering the concentration of $M(X,PO)$ species at practically constant $M(X,Nu)$ concentration, and the first order in PO should be observed. For the mononuclear enchainment, the reaction rate is proportional to the Nu loading at substoichiometric ratios to catalyst and may be mathematically predicted not to depend on Nu concentration in excess of Nu for high values of the equilibrium constant. First order in PO should be observed for the mononuclear reaction step both with sub- and superstoichiometric Nu amounts.

These theoretical considerations agree well with the experimental observations on CHO/CO₂ copolymerization [26e, 46c, 48]. Indeed, increase in the added amount of neutral cocatalysts such as *N*-methylimidazole (*N*-MeIm),

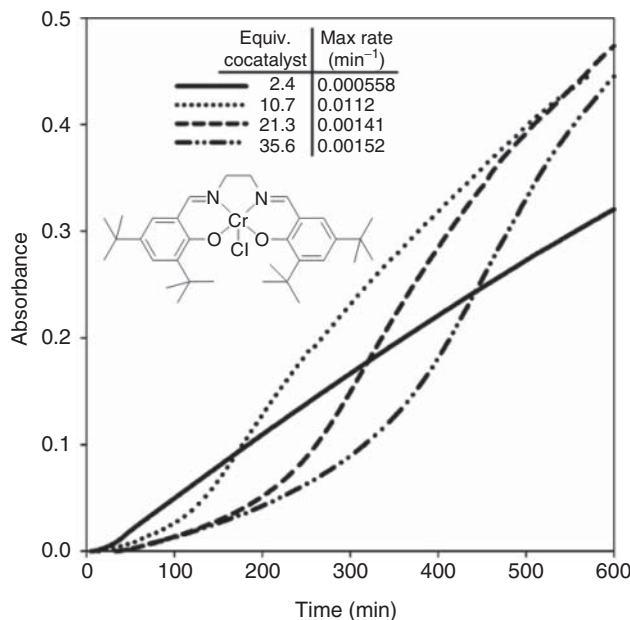


Figure 13.16 IR traces for copolymerization of 2-(3,4-epoxycyclohexyl)-trimethoxysilane with CO₂ in presence of Cr(III)-salen catalyst showing the rate of polymer formation

with different amounts of *N*-Melm cocatalyst. (Adapted with permission from Ref. [48b]. Copyright 2004 American Chemical Society.)

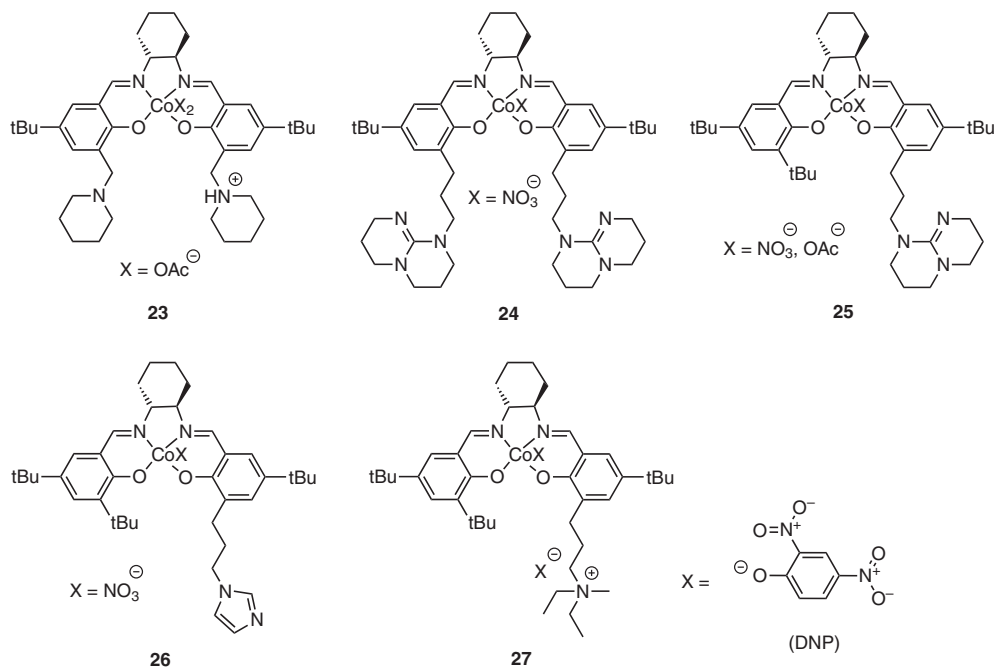
N,N-DMAP, and other amine or phosphines retards the initiation of copolymerization with Cr(III)-salen complexes, while the reaction rate after the initiation increases with the added cocatalyst only until a certain limited value (Figure 13.16), suggesting a slow initiation step with these particular cocatalysts, followed by a monometallic propagation.

During the initiation period, the polymer chains can be started by a labilized X group trans to Nu as well as by a cocatalyst itself, leading to zwitterionic polymer chains in case of neutral Nu (the presence of Nu in the macromolecules was unambiguously verified by mass spectrometric studies) [48]. At the end of initiation, one should expect only alkoxy and carbonato chain ends playing the role of nucleophiles. If this is so, at this point the copolymerization rate should become independent of the nature of the applied cocatalyst. Studies on various anionic initiators, however, do not entirely support this, although the observed differences in catalyst activity in relation to the anionic nucleophile nature are not as extreme and may arise from the incomplete initiation over the total copolymerization time or some side reactions [48, 49]. It is worth remarking that the highest TOFs have been achieved with the strongest anionic nucleophiles, and the lack of an obvious initiation period was noticed in this case. Two equivalents of anionic nucleophile per cationic chromium center in these particular catalytic systems gave a maximum copolymerization rate for 2-(3,4-epoxycyclohexyl)-trimethoxysilane and CO₂, with no change in the rate above this ratio. Besides the nature of the anion, properties of the cationic counterions of the cocatalysts have also been observed to influence the copolymerization efficiency, probably due to their different ability to dissociate from the anion, so that their role in the reaction cannot be neglected.

It has to be mentioned that CHO/CO₂ copolymerization is ideally suited for the mechanistic studies, taking into account the usually excellent product selectivity toward polymer, as the formation of the corresponding cyclic carbonate by-product is kinetically disfavored. In this respect, in case of PO/CO₂ copolymerization the proper cocatalyst/catalyst ratio appears crucial, as it easily inverts the copolymerization into cyclic carbonate production, especially at increased temperatures [46a, 50]. This phenomenon is attributed to the facile backbiting of the coordinatively unstabilized anionic PPC chain ends [39].

In general, the investigations on metal-salen-, salphen-, and porphyrin-based catalytic systems and the applied epoxides do not easily allow for a universal mechanistic description of the CO₂ copolymerization catalysis. However, efforts made in the elucidation of copolymerization peculiarities, especially in the presence of cocatalysts, have opened another strategy for the design of highly active epoxide/CO₂ coupling promoters. That is, the development of bifunctional systems comprising the catalytically active center and the cocatalyst in one molecule has been started. Such systems have shown impressive cooperative effects both in terms of selectivity and activity, for example, for PO/CO₂ copolymerization, maintaining their superior catalytic performance even at very high dilution. For example, Co(salen) complex **23** bearing piperidine and piperidinium groups anchored to the ligand framework appeared to be highly selective for the PO/CO₂

polymer formation even at the elevated temperature [51]. This selectivity was explained in terms of easy protonation of the anionic copolymer chain end on its dissociation from the metal center, thus preventing the backbiting toward cyclic propylene carbonate. Further examples of tethered Co(salen) cocatalyst systems are presented in Scheme 13.16.

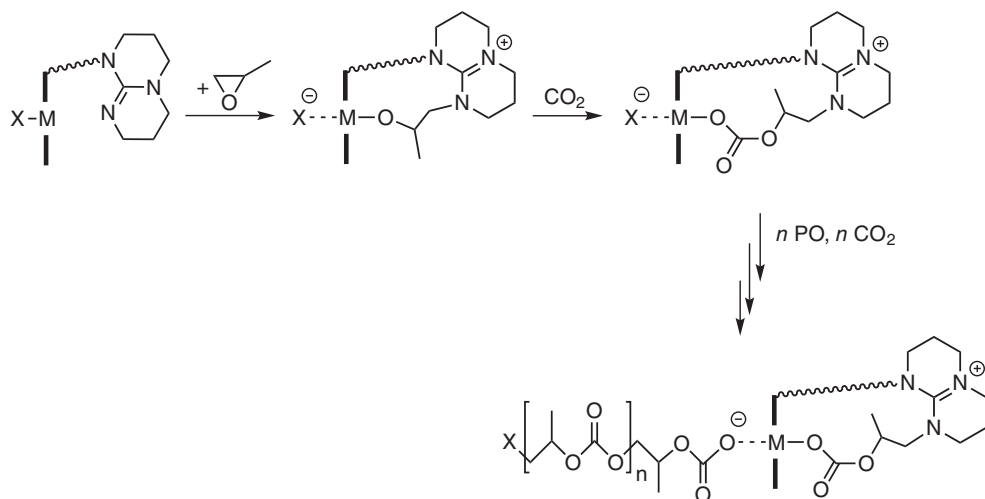


Scheme 13.16

Among them, the 1,5,7-triazabicyclo-[4.4.0]-dec-5-ene (TBD)-functionalized complex **25** with a 1,3-propylene tether reveals especially high activity ($\text{TOF} \approx 11\,000\text{ h}^{-1}$) and selectivity (97%) toward polymer in PO/ CO_2 coupling at a temperature as high as 100°C and a ratio to PO of 1:10 000 [52]. Remarkably, the corresponding methylene-tethered analog of **25** is noticeably less active, showing the importance of the linker flexibility and proper spatial separation of the cocatalyst functionality from the metal center. Furthermore, complexes with two TBD moieties (**24**) or with one anchored imidazole entity (**26**) are also relatively inactive, presumably due to the steric hindrance and blockage of Co active sites by too tight coordination of the pendant groups.

The particular activity and selectivity of complex **25** was explained by a reversible intramolecular coordination of a carbonato group initiated by a TBD moiety to the Co(III) center as shown in Scheme 13.17.

According to the proposed mechanism, which is supported experimentally, the anchored TBD moiety ring-opens one epoxide molecule followed by CO_2 insertion. The thus-formed carbonato group stabilizes the Co(III) center against



Scheme 13.17 PO/ CO_2 copolymerization with **25** (—M— denotes the Co(salen) framework).

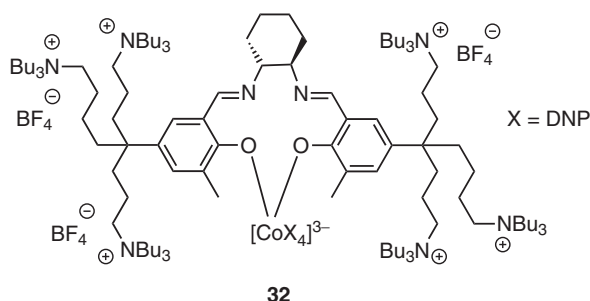
reduction to Co(II), a common deactivation pathway of the Co(III) catalysts [53], and facilitates the dissociation of the trans ligand, promoting the subsequent polymer chain propagation at the trans coordination site. On the contrary, full dissociation of the trans anionic group from the cationic complex probably does not take place, and this binary catalytic system can be rather described as a contact ion pair under the reaction conditions (see also Chapter 7 of this book and Ref. [54] for comparison with small-molecule catalytic synthesis). This would well explain both the improved catalytic activity of the system (increase in local concentration of the Lewis-acidic center and nucleophile) and its selectivity toward copolymer. Indeed, many of the copolymerization catalysts produce cyclic carbonate via polycarbonate depolymerization according to the backbiting mechanism, whereby a fully dissociated anionic polycarbonate chain end is especially prone to that [39]. Stabilization of such chain end by a positive charge of the complex can be assumed to slow down the backbiting to a certain extent. Furthermore, increased copolymerization rate would simultaneously improve the ratio of produced copolymer and cyclic carbonate. These principles are most probably realized in Co(salen) systems bearing pendant moieties of quaternary ammonium salts such as **27–29** (see Schemes 13.16 and 13.18) [52, 55]. Indeed, in contrast to the two-component systems based on neutral XCo(salen) complexes, species **27–29** remain catalytically active and highly selective for copolymer formation at extremely high dilution, for example, in a ratio to the epoxide of up to 1:150 000. The highest TOF of $26\,000\text{ h}^{-1}$ in PO/ CO_2 copolymerization was reported for the complex **29** ($\text{R} = \text{Me}$) at 20 bar CO_2 , 80°C , and 1:50 000 catalyst/epoxide ratio [55].

Another explanation of a superior activity of the complexes **29** was proposed on the basis of their NMR studies in solution, which indicated the presence of several species. On one hand, Co(salen) complexes can exist in their isomeric form with



Scheme 13.18

phenolic O atoms coordinated in the *cis* configuration, such as in **31**, and such form could be expected to copolymerize PO and CO₂ more efficiently than the isomer with a square-planar configuration of the salen ligand [56]. The presence of pendant quaternary ammonium groups in combination with *trans*-cyclohexene backbone was thought to favor the *cis* configuration. However, recent synthesis of numerous analogs of **31** that easily adopt the *cis* configuration has disproved this hypothesis, as most of such complexes appeared to be inactive for PO/CO₂ copolymerization [57]. On the other hand, structures resembling complexes **30** in which the central Co ion is not coordinated by imine groups of salen ligand but rather by the DNP nucleophilic anions (DNP = 2,4-dinitrophenolate) were also proposed to coexist in solutions [58]. Remarkably, the IR and NMR spectra suggested that such structures are realized with salen framework bearing methyl substituents at the phenolic entities, but not with the *tert*-butyl substituents, which are less active in PO/CO₂ copolymerization by a factor of 20. Two of the anionic X groups at the Co center in **30** were found to be fluxional, thus allowing for epoxide coordination and chain propagation by the attack of an anionic nucleophile from the outer coordination sphere of Co onto the coordinated PO. Other structural variations in the salen backbone and in the coordination sphere of Co (e.g., by utilizing DNP-H-DNP conjugates as ligands) widely influence the activity of these bifunctional systems, with the complex **32** (Scheme 13.19) being unexpectedly completely inactive. In general, the cooperative effects and, therefore, the catalytic efficiency of bifunctional derivatives seem to be controlled by an intricate combination of steric, electronic, and electrostatic factors, influencing their coordinative dynamics and solution behavior.



Scheme 13.19

13.6 Summary

The considered examples show that proper combinations of Lewis-acidic metal centers or other Lewis acids with nucleophiles and organic bases can successfully effect ROP of lactones, the zwitterionic polymerization of vinyl monomers such as, for example, acrylates, as well as the copolymerization of CO₂ and epoxides. The two components can be varied over a wide range as well as combined

in a single molecule, and new dual systems are being continuously developed for improved performance in terms of activity, polymerization control, and so on. The scope of monomers capable of polymerization via cooperative mechanisms is thought to be broadly extendable, and the work in this direction is certainly worthy of attention [4]. Cooperatively acting dual systems can combine the advantages of organic and metallic catalysis to come to new strategies of synthesizing innovative materials and copolymer scaffolds. These can be achieved, for instance, by means of higher tolerance of such catalytic systems to functional groups or their particular selectivity in copolymerization.

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