1
Lewis Acid–Brønsted Base Catalysis

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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

Cooperative Catalysis: Designing Efficient Catalysts for Synthesis, First Edition. Edited by René Peters.

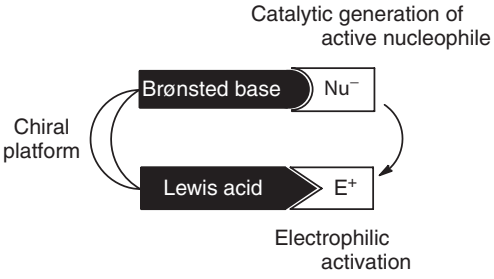


Figure 1.1 Schematic representation of the Lewis acid–Brønsted base cooperative catalysts.

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

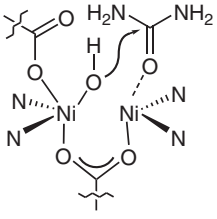


Figure 1.2 Proposed activation mode in urease.

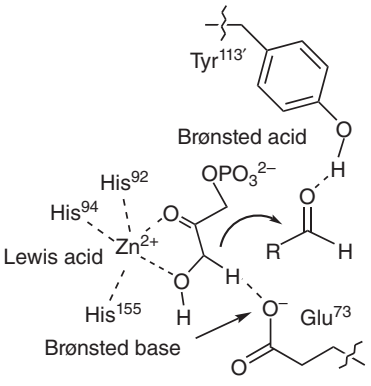


Figure 1.3 Proposed activation mode in Zn-dependent class II aldolase.

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

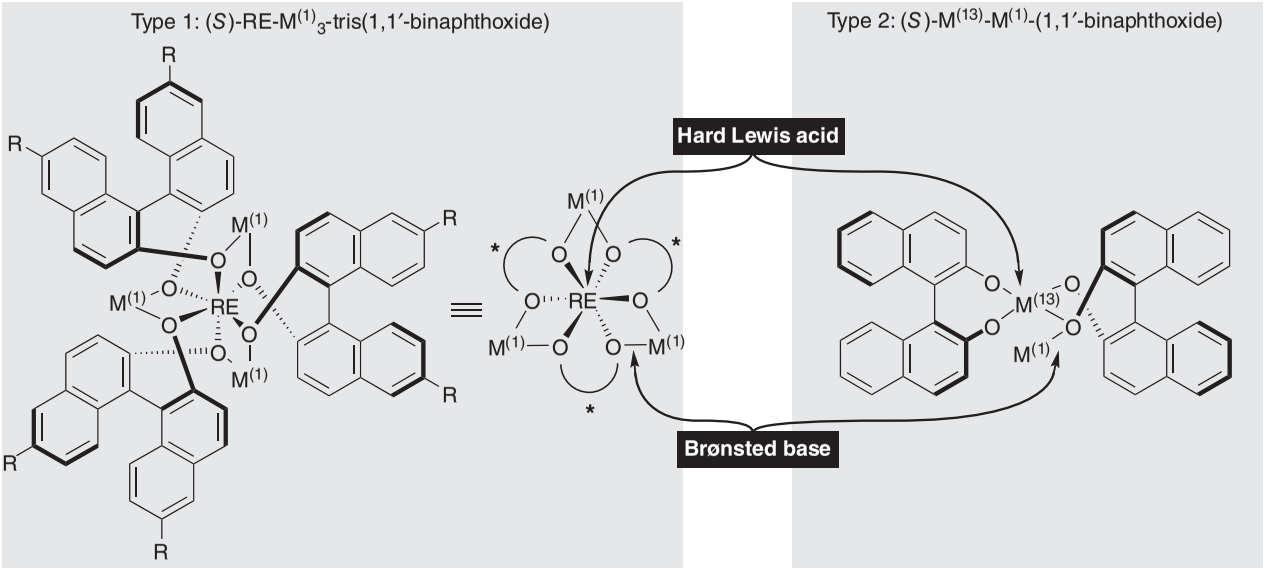
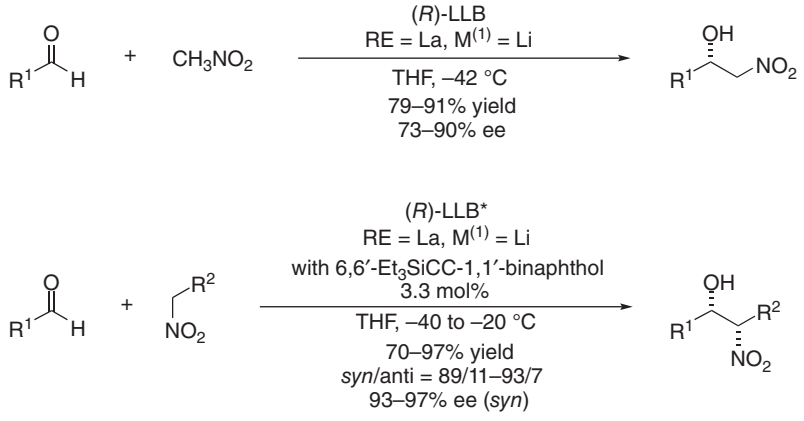


Figure 1.4 Two types of Lewis acid–Brønsted base cooperative heterobimetallic catalysts based on 1,1′-binaphthol and its derivatives as a chiral ligand platform.



Scheme 1.1 Seminal nitroaldol reaction promoted by the heterbimetallic 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.

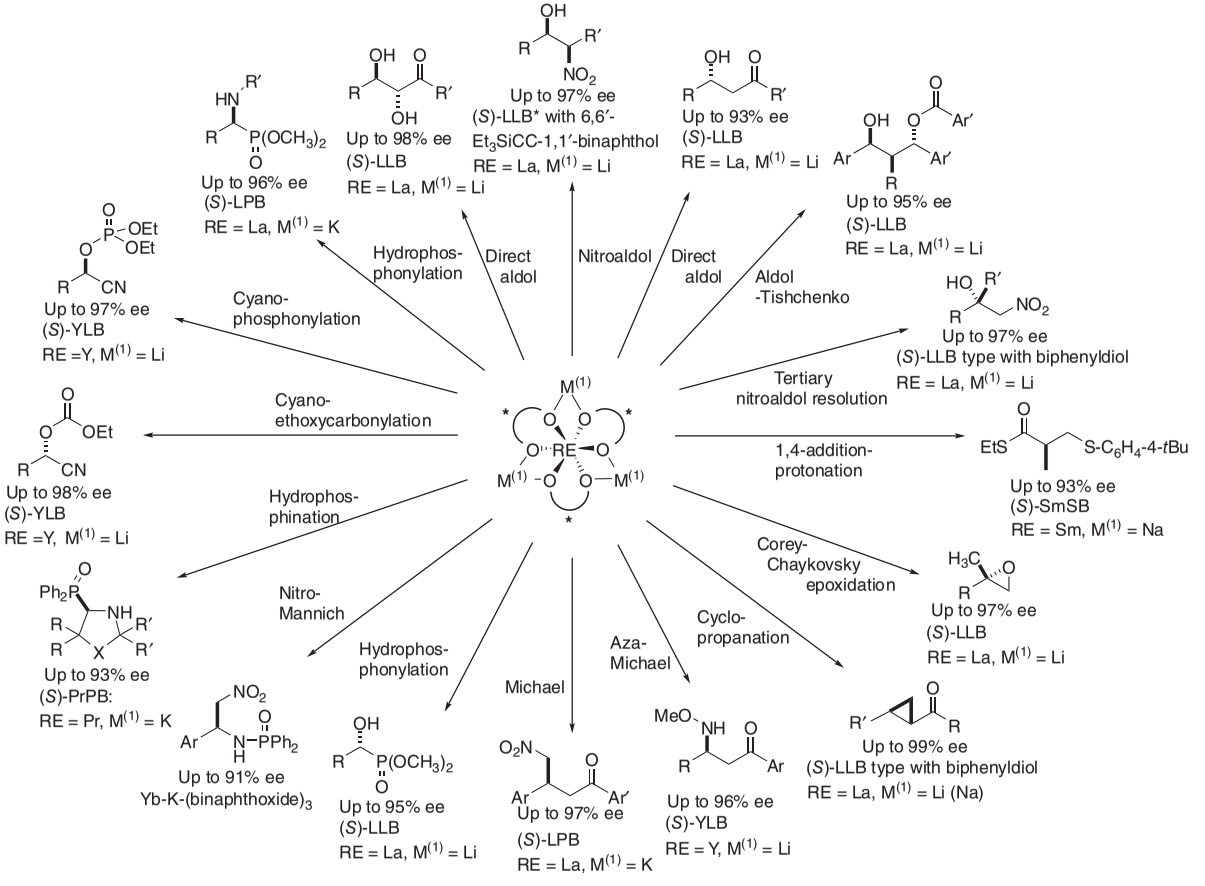
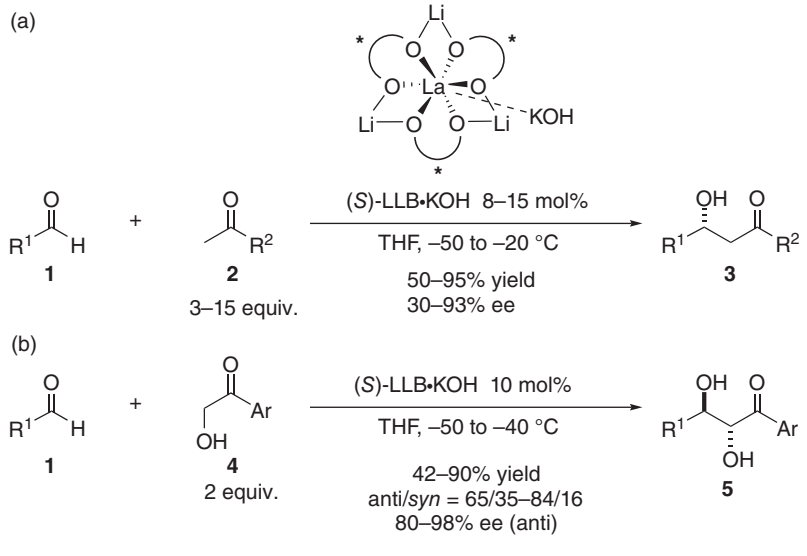


Figure 1.5 Schematic representation of the utility of RE-$M^{(1)}_3$–tris(1,1′-binaphthoxide) cooperative catalysts in catalytic asymmetric transformations.

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 (RE = La, $M^{(1)}$ = Li) because this specific reaction was the first to be demonstrated by this heterobimetallic 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 RE-$M^{(1)}_3$-tris(1,1′-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 $M^{(13)}$-$M^{(1)}$-bis(1,1′-binaphthoxide) incorporating group 13 metals (Al, Ga) has been investigated by Shibasaki *et al.* [9] (Figure 1.4, type 2 (right side)). In 1996, Al-Li-bis(1,1′-binaphthoxide) ($M^{(13)}$ = Al, $M^{(1)}$ = 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 tetracoordinated 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′-binaphthol led to the development of immobilized ALB catalyst, which could be used iteratively [42]. The scope of $M^{(13)}$-$M^{(1)}$-bis(1,1′-binaphthoxide) catalyst was expanded to the analogous cooperative catalyst (*R*)-GaLB, where $M^{(13)}$ and 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′-binaphthol units at the 3 position provides an intriguing tetraol chiral ligand referred to as *linked-BINOL* [45–47] (Figure 1.7).

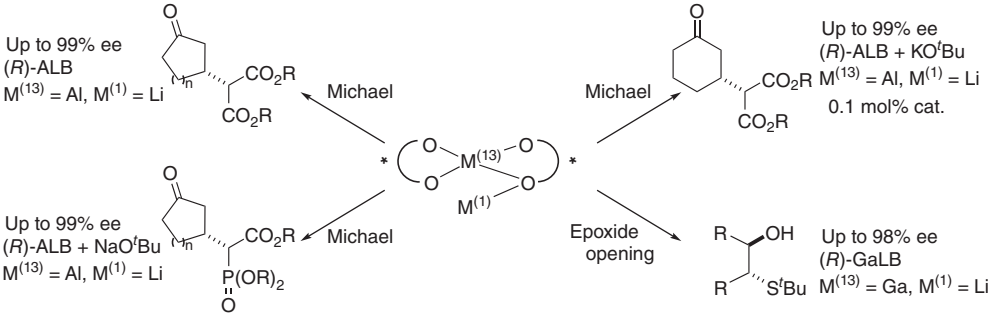


Figure 1.6 Schematic representation of the utility of $M^{(13)}$-$M^{(1)}$–(1,1′-binaphthoxide) cooperative catalysts in catalytic asymmetric transformations.

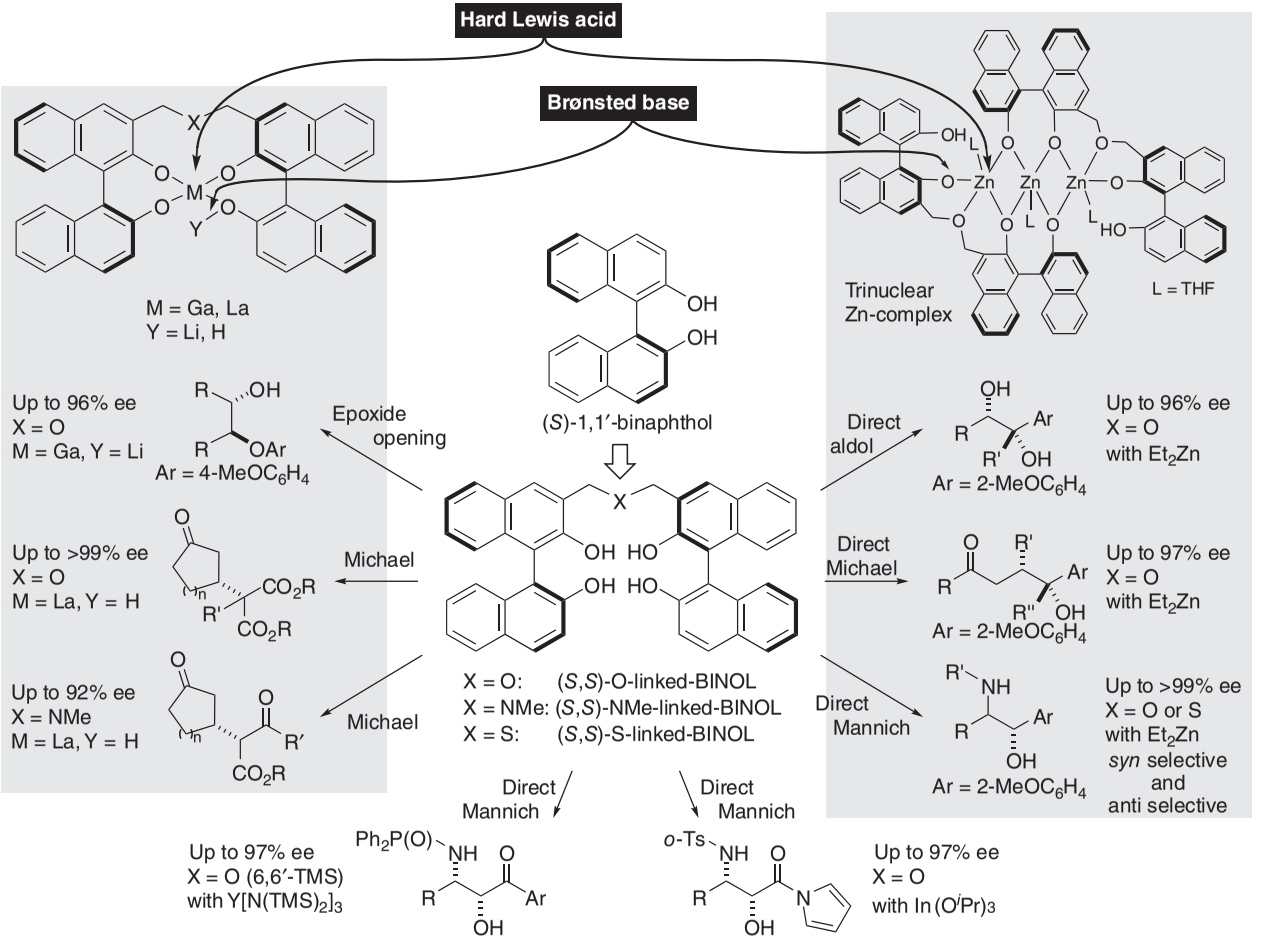
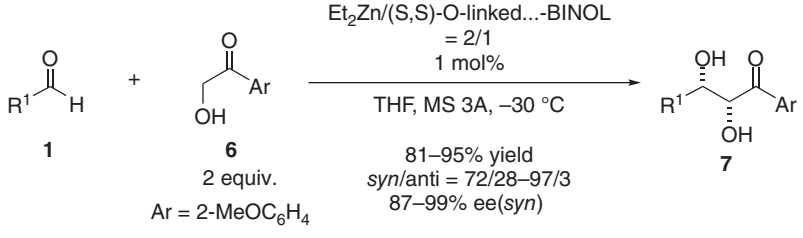


Figure 1.7 Schematic representation of the utility of linked-BINOL-based cooperative catalysts in catalytic asymmetric transformations.

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 $Ga(O^iPr)_3$ 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 $La(O^iPr)_3$ 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 Et_2Zn 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/Et_2Zn 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 $In(O^iPr)_3$ 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 Et_2Zn/(*S*,*S*)-O-linked-BINOL cooperative catalyst.

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 Cr(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 Cr(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 Cr(N_3)–salen catalyst (Figure 1.9) [63]. The beneficial effect of the covalently linked dimeric Al(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 Al(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 Co(OAc)–salen complex functions as a Lewis

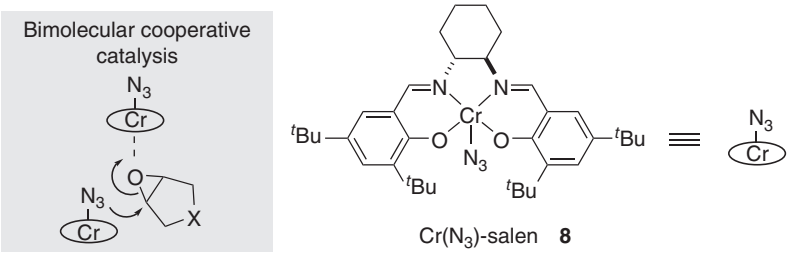
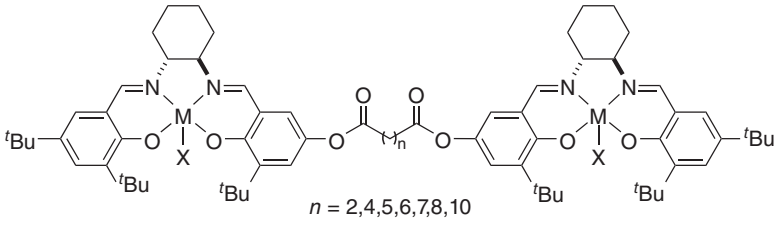


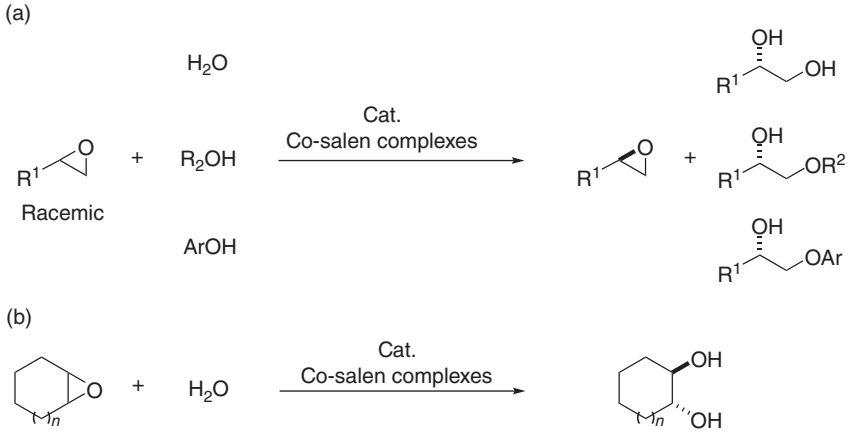
Figure 1.8 Postulated bimolecular bimetallic mechanism in ring-opening reaction of epoxides promoted by two monometallic Cr(N_3)–salen complexes.



Covalently linked dimeric metal-salen complex

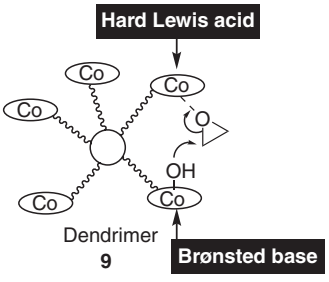
M(X) = $Cr(N_3)$: ring-opening reaction of epoxides by azide
M(X) = Al(Cl) : conjugate addition of cyanide to α,β-unsaturated imides
M(X) = Co(OAc): kinetic resolution of terminal epoxides

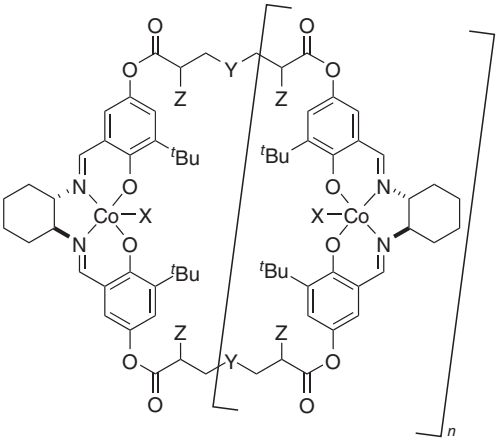
Figure 1.9 Covalently linked dimeric metal–salen complexes.



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.





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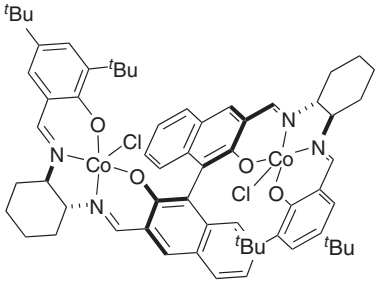

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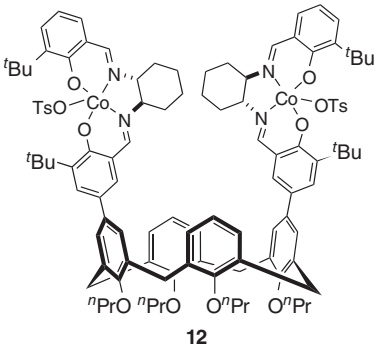

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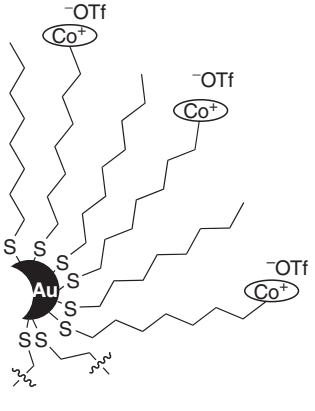

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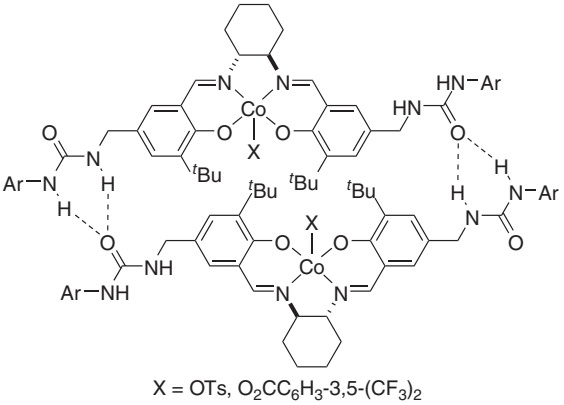

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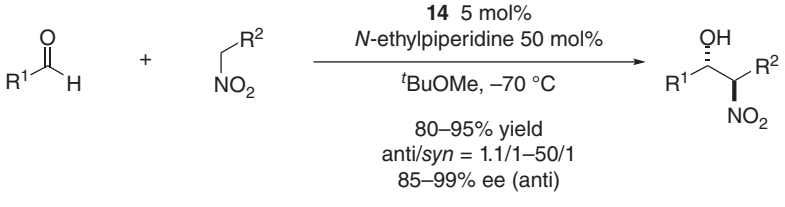
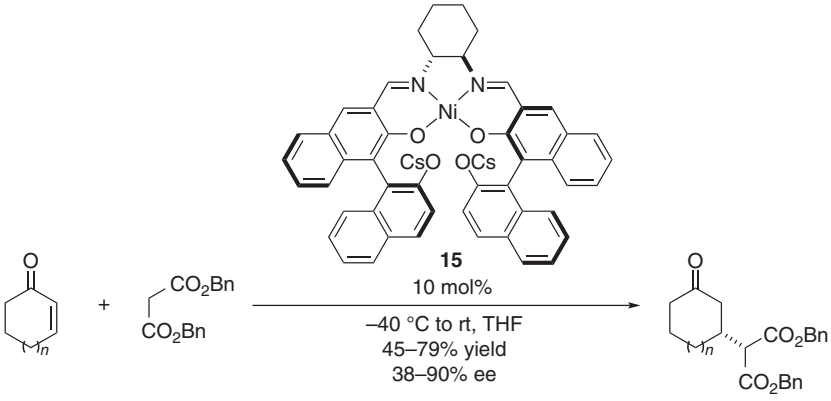
Figure 1.10 Various strategies for the construction of multimetallic Co–salen complexes.

Alcohols and phenols can be used as nucleophiles, and generally excellent yields and enantioselectivity are achieved. The beneficial effect of oligomeric catalyst **10** (X = OTf, Y = O, Z = 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 = OTs, Ar = 4-$CF_3C_6H_4$) 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 = $O_2CC_6H_3$-3,5-$(CF_3)_2$, Ar = 3,5-$(CF_3)_2C_6H_3$] and a substoichiometric amount of *N*-ethylpiperidine, the anti-nitroaldol adduct was obtained in high enantioselectivity (Scheme 1.5).

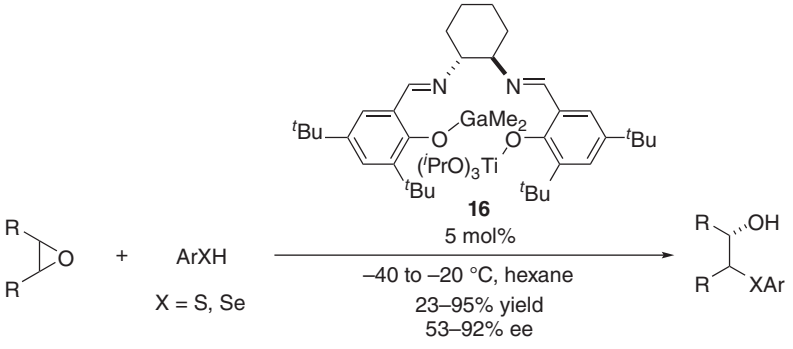


Scheme 1.5 anti-Selective catalytic asymmetric nitroaldol reaction promoted by dimeric Co–salen complex **14**.

The introduction of multiple metal cations in a Schiff base scaffold is an attractive strategy for devising a cooperative catalyst. Kozlowski *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, $GaMe_3$, and $Ti(O^iPr)_4$ (Scheme 1.7) [80]. The order of metal addition ($GaMe_3$ 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**

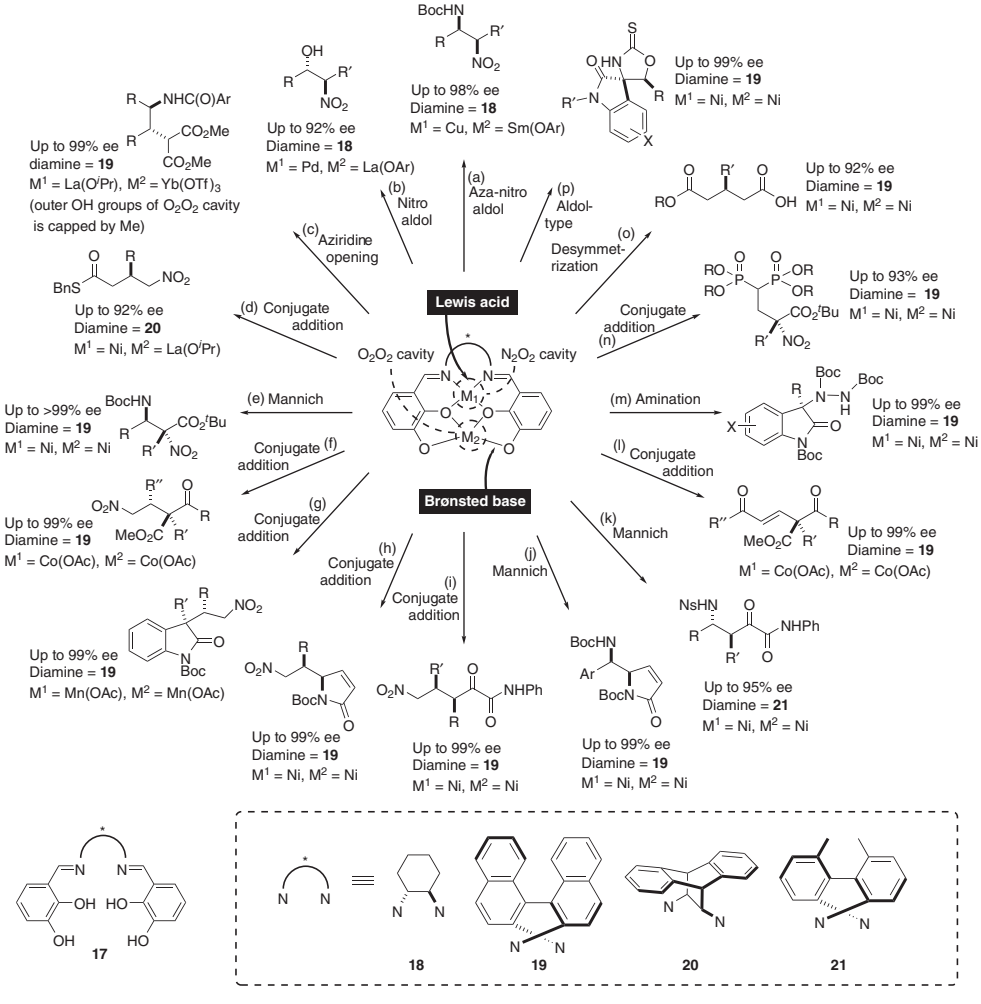


Figure 1.11 Schematic representation of the utility of bimetallic complexes of Schiff base **17** in catalytic asymmetric transformations.

(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** [$M^1 = Cu$, $M^2 = Sm(OAr)$] 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 ($M^1 = M^2 = Ni$), prepared from **17** bearing 1,1′-binaphthyldiamine **19** as chiral diamine and 2 equiv of $Ni(OAc)_2 \cdot 4H_2O$, 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** [$M^1 = M^2 = Co(OAc)$] and Mn_2–**17** [$M^1 = M^2 = Mn(OAc)$] 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** ($M^1 = M^2 = Zn$, X = Et, Ar^1 = Ph, R^1 = Me, R^2 = 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

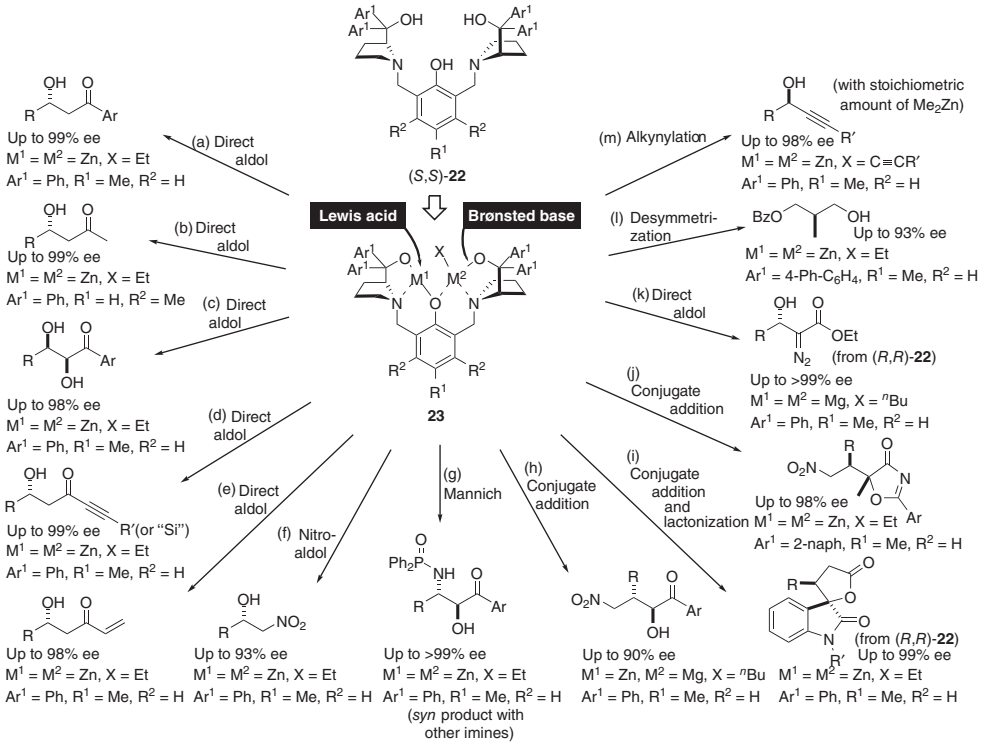
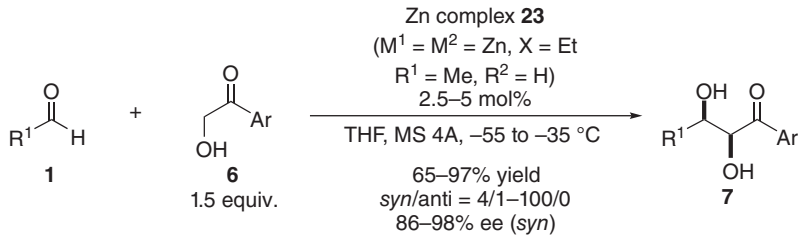
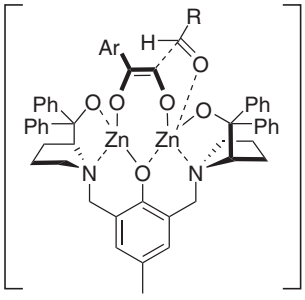


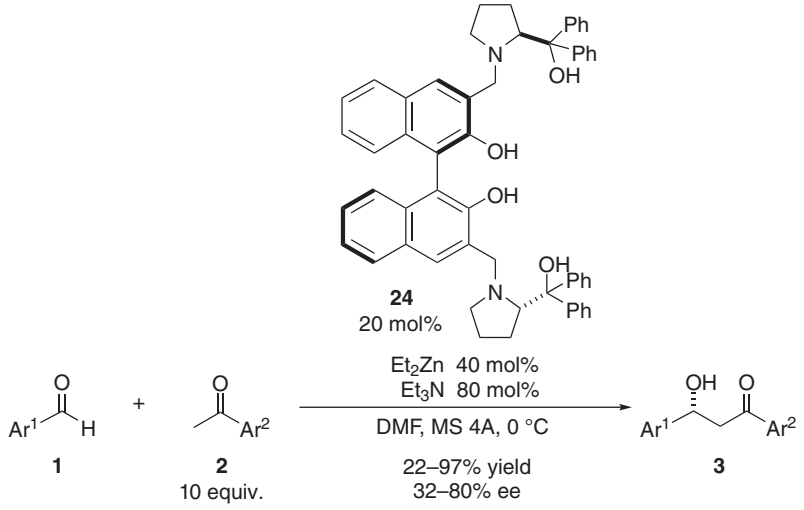
Figure 1.12 Schematic representation of the utility of bimetallic complexes of ProPhenol **22** in catalytic asymmetric transformations.

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** ($M^1 = Zn$, $M^2 = Mg$, $X = {}^n Bu$, $Ar^1 = Ph$, $R^1 = H$, $R^2 = Me$) prepared from equimolar amounts of Et_2Zn and ${}^n Bu_2Mg$ 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** ($M^1 = M^2 = Mg$, $X = {}^n Bu$, $Ar^1 = Ph$, $R^1 = H$, $R^2 = Me$) 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 1.12l) [106]. Although a stoichiometric amount of Me_2Zn was required, the dinuclear Zn complex broadened the scope of its utility in asymmetric alkynylation of

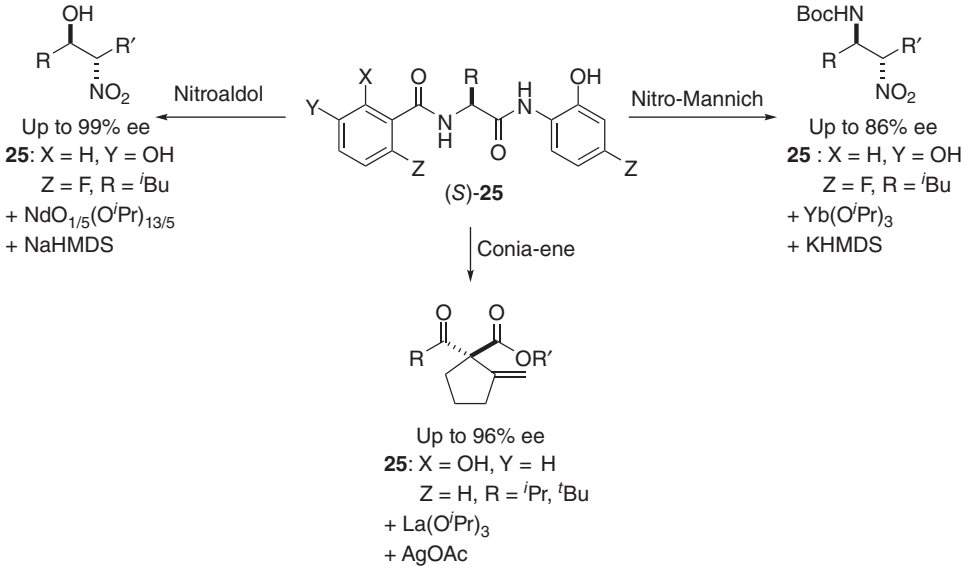
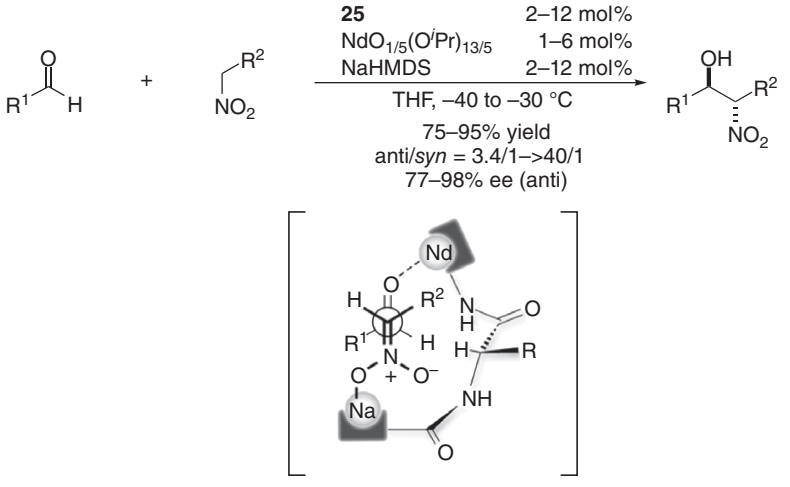


Figure 1.13 Schematic representation of the utility of the heterobimetallic catalysts derived from amide-based ligand **25** in catalytic asymmetric transformations.

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].

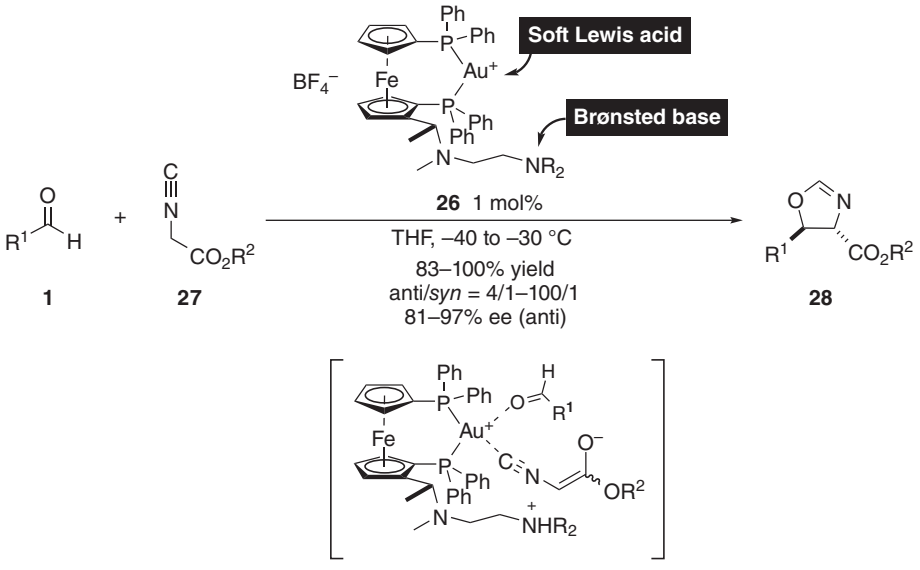


Scheme 1.10 anti-Selective catalytic asymmetric nitroaldol reaction promoted by Nd/Na heterobimetallic catalyst using amide-based ligand **25**.

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

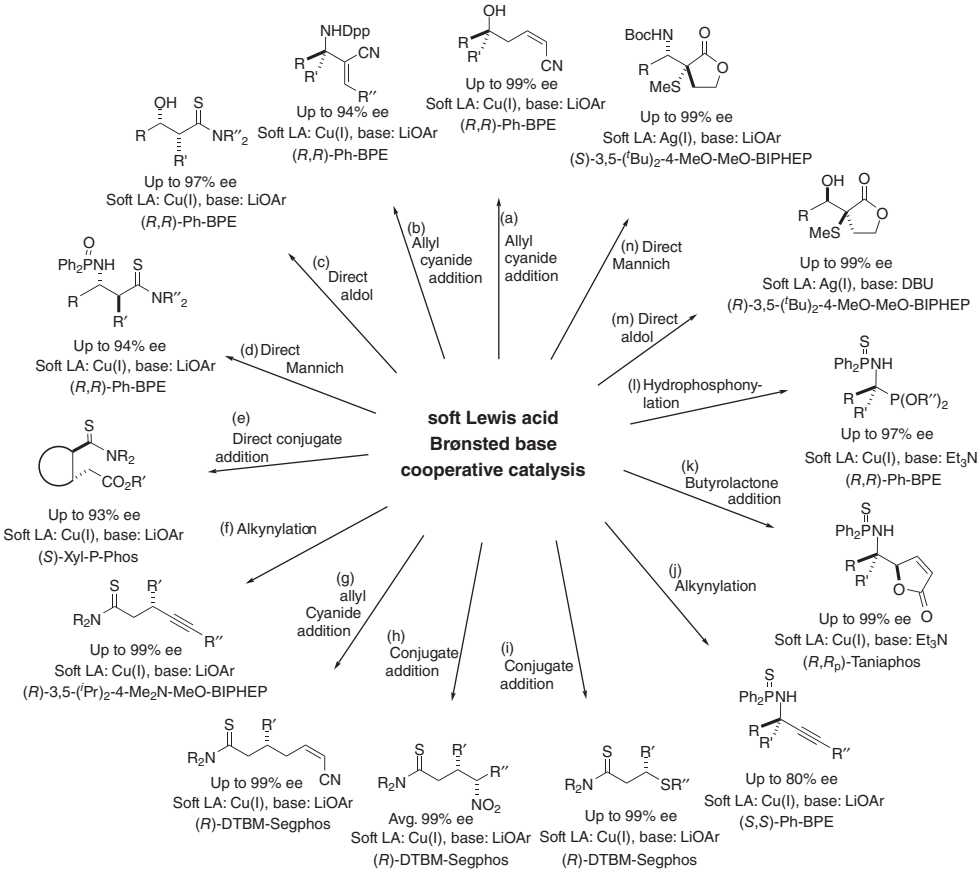
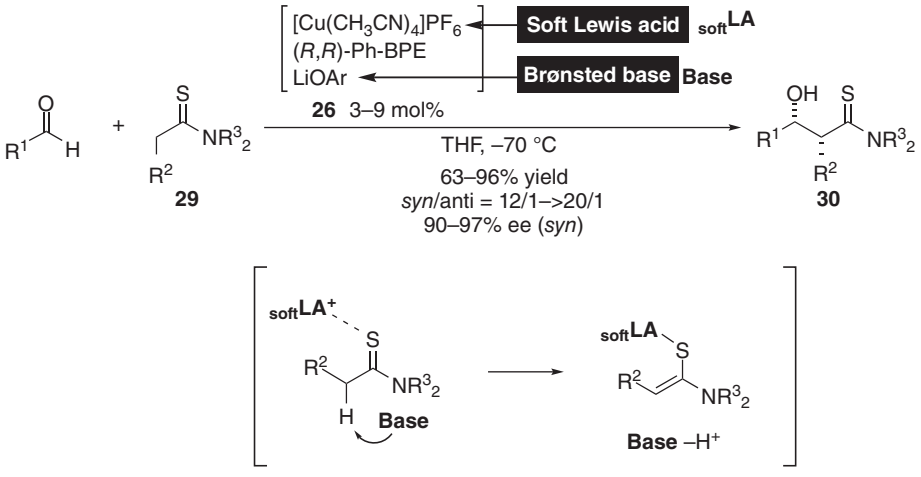


Figure 1.14 Schematic representation of the utility of the soft Lewis acid–Brønsted base cooperative catalyst in catalytic asymmetric transformations.

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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