Topics in Organometallic Chemistry 62

Koichi Mikami *Editor*

Chiral Lewis Acids

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62
Topics in Organometallic Chemistry

Aims and Scope

The series *Topics in Organometallic Chemistry* presents critical overviews of research results in organometallic chemistry. As our understanding of organometallic structure, properties and mechanisms increases, new ways are opened for the design of organometallic compounds and reactions tailored to the needs of such diverse areas as organic synthesis, medical research, biology and materials science. Thus the scope of coverage includes a broad range of topics of pure and applied organometallic chemistry, where new breakthroughs are being achieved that are of significance to a larger scientific audience.

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Koichi Mikami
Editor

Chiral Lewis Acids

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Preface

I write this preface after the announcement of the 2017 Nobel Prize in Chemistry with the belief that within this book titled "Chiral Lewis Acid Catalyses" there are several candidates who could be considered for the distinguished title of Nobel Laureate in chemistry.

The Nobel Prize in Chemistry in the early twenty-first century was awarded to Professors Noyori and Sharpless, and Dr. Knowles for their work on "Asymmetric Catalyses" of functional group interconversion such as oxidation and hydrogenation. However, one of the most important processes in organic synthesis, namely the "Asymmetric Catalyses of Carbon-Carbon Bond Formation", has yet to be recognised by the award of the Nobel Prize.

Chiral Lewis acid catalysts work so well in the main body of carbon-carbon bond forming reactions such as the Mukaiyama aldol reaction, Friedel-Crafts reaction, Diels-Alder reaction, and Alder-ene reaction. The Lewis acid catalysts can increase the regioselectivity, stereoselectivity, and particularly enantioselectivity of these reactions in addition to accelerating the reaction rate. In this context, the principles and design concepts of Chiral Lewis Acid Catalysts are extensively covered in the chapter "The Future of Catalysis by Chiral Lewis Acids". Particularly, proof of concept in ligand design is exemplified in a showcase of peptide ligands for heterobimetallic catalyses (chapter "Chiral Bimetallic Lewis Acids"). Quite recent progress in chiral Brønsted acid catalysts (chapter "Chiral Carbophilic Gold Lewis Acid Complexes in Enantioselective Catalysis") and chiral metallic Lewis acid catalysts (chapters "Brønsted Acid/Lewis Base Hybrid Complexes", "Chiral Alkaline Earth Metal Complexes in Asymmetric Catalysis" and "Chiral Lewis Acid Rare-Earth Metal Complexes in Enantioselective Catalysis") of the conjugated bases is also discussed in this book. Gold rush in carbophilic gold Lewis acid catalysts (chapter "Brønsted Acid/Lewis Base Hybrid Complexes") is thus highlighted. Practical applications of alkaline (earth) (chapter "Chiral Alkaline Earth Metal Complexes in Asymmetric Catalysis") and lanthanide (chapter "Chiral Lewis Acid Rare-Earth Metal Complexes in

Enantioselective Catalysis") catalysts are fully covered by the specialists. Finally in the chapter "Chiral Borane-Based Lewis Acids for Metal Free Hydrogenations" the future direction of "frustrated" Lewis acid/base pair catalysts is foreseen in asymmetric catalyses.

With this in mind it is my belief that continuing progress in this field of "Chiral Lewis Acid Catalysis" will be rewarded with the Nobel Prize in Chemistry in the near future.

Tokyo, Japan Koichi Mikami

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The Future of Catalysis by Chiral Lewis Acids

Qiang Sha, Yongming Deng, and Michael P. Doyle

Abstract Even with the rapidly expanding popularity of organocatalysts for organic reactions, chiral metal-based Lewis acid catalysts continue to have a uniquely important role in asymmetric reactions. Their broad applicability to cycloaddition and condensation reactions based on close encountered associations of Lewis base reactants with these chiral Lewis acid catalysts provides architecturally confined complexes that provide high stereocontrol in their chemical reactions.

Keywords Chiral ligands · Condensation · Cycloaddition · Dipoles · Enantioselectivity · Inhibition · Transition metal complexes

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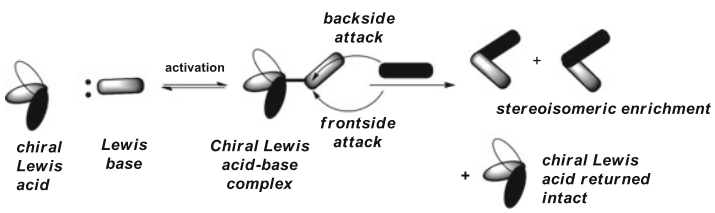
1 Introduction

A chiral Lewis acid is a coordinatively unsaturated species that is not superimposable with its mirror image. With chiral ligand-associated complexes of aluminum and boron, and more commonly of transition metals that include copper, palladium, gold, iron, rhodium, silver, titanium, and zinc, the applications of chiral Lewis acids as catalysts provide directional activation to a reactant intended to produce a stereoisomeric product (Scheme 1). The outcome is usually enantiomeric enrichment (with achiral reactants) or diastereomeric enrichment (with chiral reactants). However, although the development of effective chiral Lewis acids for asymmetric catalysis has been long standing, high stereocontrol in selected reactions has been achieved only during the past quarter century [1].

Acid catalysis is the driving force for the vast majority of organic chemical reactions, and the reactions that are most susceptible to acid catalysis are those whose rate is dependent on the polarity of the substrate(s). The acid that is selected operates as a proton donor (Brønsted acid) or an electron-pair acceptor (Lewis acid), and the specific reaction dictates what the optimum choice will be. This chapter will focus on Lewis acid catalysis to the exclusion of Brønsted acid catalysis (organocatalysis) and will overview recent directions that point to the future. The advantages of Lewis acids include their structurally well-defined ligand coordination around the central metal [2]. Lewis acid-catalyzed reactions constitute an enormity of chemical transformations, and they are well reviewed in this volume and elsewhere. This chapter is selective in its examples which are chosen to illustrate the broad spectrum of applications by chiral Lewis acid catalysis with focus on recent developments and current challenges.

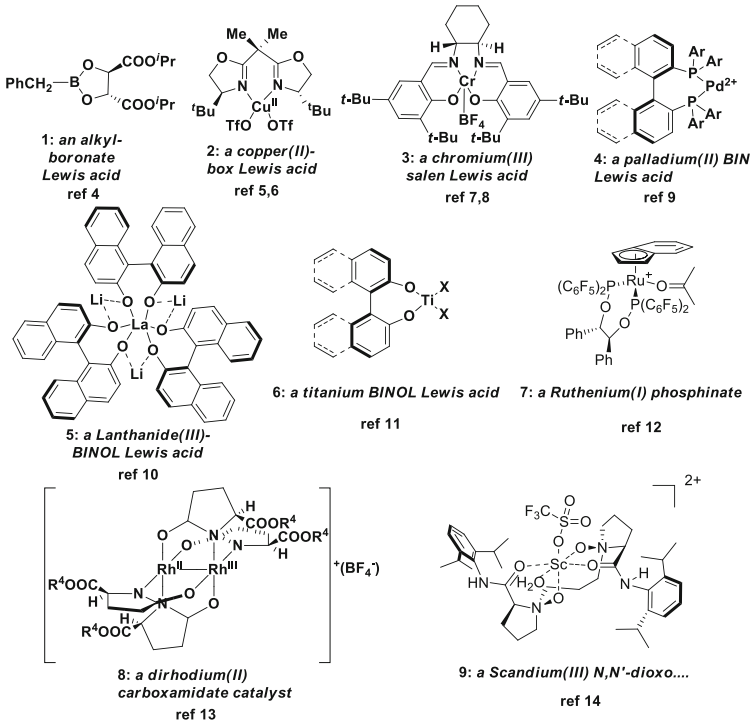


Scheme 1 Catalysis of organic reactions by chiral Lewis acids

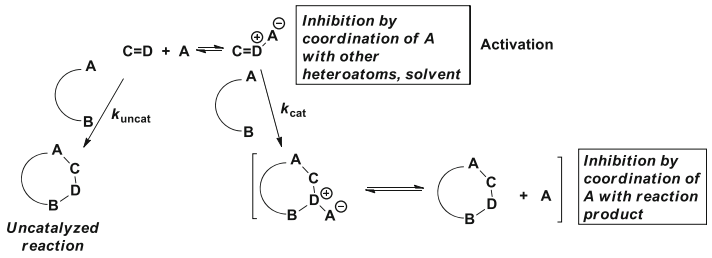
2 Metal Complexes as Chiral Lewis Acid Catalysts

The advantages of Lewis acids as catalysts are deeply embedded into the history of organic chemistry. Optimization among the possible choices of Lewis acid defines the structure–reactivity influences between reactants and catalysts that are operative, and examination of Lewis acid strength reveals which are "too strong" and which are "too weak" in efforts to find the one that is "just right". Lewis acids from second- and third-row elements that include boron and aluminum afford tetrahedral structural arrays for their Lewis acid–base complexes in catalysis, whereas transition metal complexes can exhibit structural arrays ranging from tetrahedral or square planar to octahedral [3] and provide structural rigidity by involving two or more binding sites to the coordinated ligand [4–14] (Scheme 2).

The uncatalyzed reaction is the background reaction whose relative rate determines the optimum catalytic effectiveness that can be achieved. Having a reaction whose catalytic pathway is at least two orders of magnitude faster than the uncatalyzed pathway is desirable, but to achieve this differential a large amount of catalyst is often necessary, which gives a low catalyst turnover number (TON) to the process (Scheme 3). Furthermore, since catalysis generally results from the activation of a single functional group, those substrates with multiple functional



Scheme 2 Examples of Chiral Lewis acid catalysts

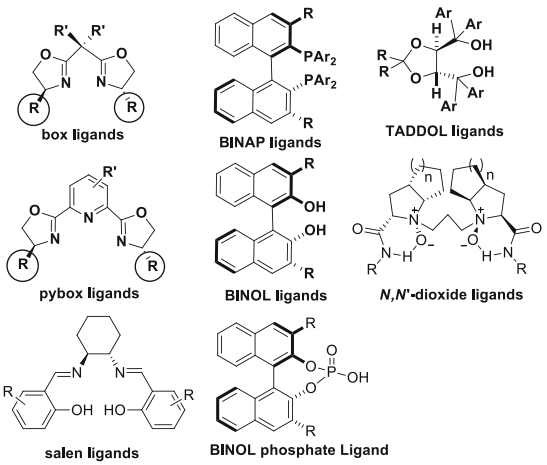


Scheme 3 Lewis acid catalysis and inhibition

groups can be rate inhibiting and, if of the same kind, lead to undesirable products. Over the years, numerous efforts have been undertaken to understand the inherent acidity of Lewis acids [15, 16] as well as to define the preferences of Lewis acids towards specific functional groups [17], and these studies have led to the development of Lewis acids that are effective catalysts in water [18], but even these efforts have left many questions unresolved. Adding a ligand to a metal complex reduces its Lewis acidity and may render the ligated metal complex inert as a catalyst in the same reaction for which the unligated Lewis acid is highly active. However, increasing the oxidation state of the metal generally increases its Lewis acidity [19]. Still, a major challenge to the application of chiral Lewis acids remains the activity of the catalyst, and there are few generalizations that guide the development of new chiral Lewis acid catalysts.

Among the chiral ligands commonly used with Lewis acids are those capable of bidentate association and have inherent C_2 symmetry (Scheme 4). Bisoxazolines (*box*) are one of the most common classes of chiral ligands used for asymmetric catalysis. They consist of two oxazoline rings connected through a linking unit that can be expanded to accommodate additional acid coordinating units (e.g., pybox) [5, 6]. These ligands are capable of bidentate (or tridentate in the case of pybox) binding to a metal. Copper(II) box forms square-planar complexes that are especially prevalent as asymmetric catalysts (e.g., **2** in Scheme 2) [20], and their advantage lies in the formation of bidentate complexes with reacting substrates which provide a rigid relationship between the sites of coordination to the metal and the chiral centers of the box ligand [21]. *BINAP* (2,2′-diphenylphosphino-1,1′-binaphthyl) is a family of chiral diphosphine ligands that are generally used with late transition metal compounds including those of nickel, palladium (e.g., **4** in Scheme 2), and ruthenium that feature two triarylphosphine moieties on a binaphthalene backbone [22]. Its hydroxyl analogue *BINOL* (1,1′-binaphthyl-2,2′-diol) is commonly found in conjunction with oxophilic Lewis acidic metals such as aluminum, titanium, zirconium, and various rare earth metals (e.g., **5** and **6** in Scheme 2) [16]. This structure can be readily elaborated by substitution at the 3,3′-positions (via lithiation) and 6,6′-positions (via the 6,6′-dibromide) to modulate steric bulk and electronic properties [23], and conversion to phosphates and phosphonates further extends their value [24]. *TADDOL* is the abbreviated name for tetraaryl-1,3-dioxolane-4,5-dimethanol in which the chirality is derived from

Scheme 4 C_2-symmetric bidentate ligands

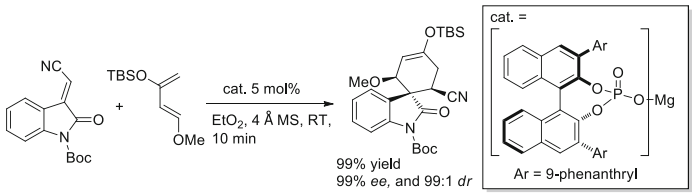


conveniently accessed tartaric acid derivatives [25]. ***N,N′***-Dioxide ligands have recently been shown to have enormous versatility as chiral ligands in asymmetric Lewis acid-catalyzed reactions [14]. Chiral *salen* ligands (e.g., **3** in Scheme 2) have had a long history of effective uses in Lewis acid-catalyzed reactions [8]. Each of these ligand structures has advantages in their influence on reactivity and selectivity in asymmetric catalysis, and the reaction outcomes provide the answer to the question of which one is most suitable for a given transformation.

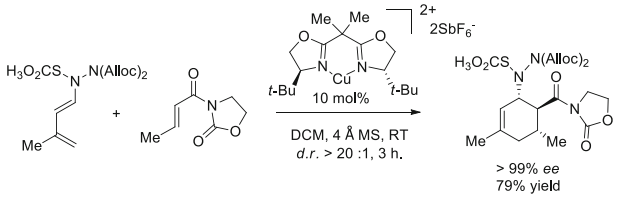
3 Cycloaddition Reactions

3.1 Diels–Alder Reactions

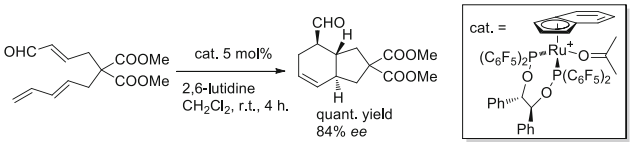
Diels–Alder reactions were among the first to be investigated with chiral Lewis acids [26–31], but it has been the hetero-Diels–Alder reactions that have commanded the most attention [24, 32–37]. With normal Diels–Alder reactions that form cyclohexene structures, activation of the dienophile by Lewis acid coordination lowers the $LUMO_{dienophile}$ energy which causes an increase in the rate of reaction, and positioning of a Lewis acid on a heteroatom near to the reacting dienophile (as in acrylates) affects stereocontrol. In these widely reviewed reactions, methods for activation of the dienophile by varying the metal (e. g., Scheme 5) [38] or using polarized substrates (e. g., Scheme 6) [39] are frequently reported; but although BINOL-type and box ligands are often employed, there is no specific ligand that can be described as optimum. Increasing the Lewis acidity of the metal, either by changing the metal or its oxidation state or by changing its counterion, influences the reaction rate and selectivity. Decreasing the Lewis basicity of the counterion, even with those considered to be inert (e. g., triflate, tetrafluoroborate), by using SbF_6^- can significantly increase the reaction rate [40].



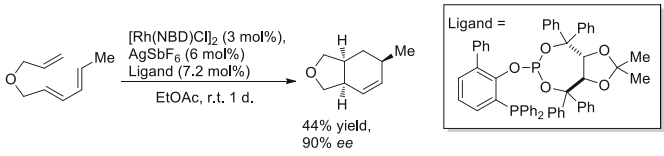
Scheme 5 An asymmetric Diels–Alder reaction catalyzed by chiral phosphate magnesium complexes [38]



Scheme 6 Catalytic asymmetric Diels–Alder reactions of 1-hydrazinodienes [39]

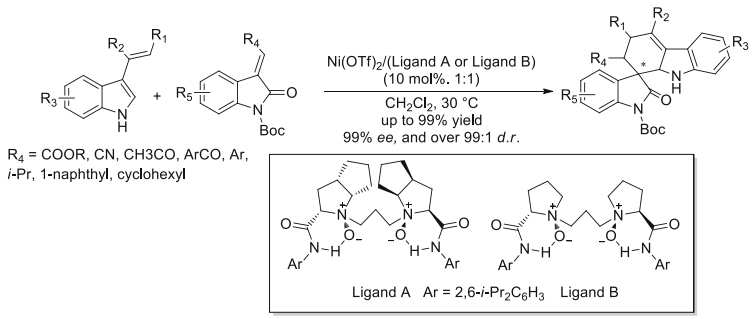


Scheme 7 Intramolecular Diels–Alder reaction using chiral ruthenium Lewis acids [12]



Scheme 8 Rhodium-catalyzed enantioselective intramolecular Diels–Alder reaction using a chiral phosphine–phosphite ligand [41]

With the successes achieved using classical ligands (Scheme 3), there is an increasing number of attempts being made to achieve high selectivity using newly developed catalysts and/or reactive substrates (e.g., Schemes 7, 8, and 9) [12, 41, 42]. Ligand exchange on the metal (e.g., of acetone in Scheme 7) forms the activated dienophile that undergoes cycloaddition, and the mechanistic details for the transformation (e.g., concerted verses stepwise) may be more complex than that from direct cycloaddition [43, 44]. Increased attention is also being given to lanthanide metals whose complexes can expand their coordination sphere and support heterobimetallic complexes [45].



Scheme 9 Chiral *N,N′*-dioxide–Ni(II) complexes catalyzed Diels–Alder reaction between 3-vinylindoles and methyleneindolinones [42]

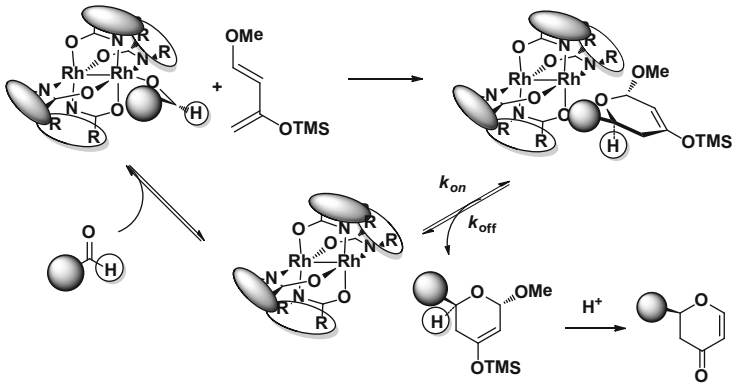
3.2 Hetero-Diels–Alder Reactions

Chiral Lewis acids find the greatest number of their applications in hetero-Diels–Alder (HDA) reactions [33, 46–49]. These transformations generate heterocyclic compounds by incorporating the heteroatom through either the dienophile (normal HDA) or through the "diene" (inverse-electron-demand HDA), and their scope is broad. Indeed, the HDA reaction is often the one first used to determine reactivity and selectivity of a new Lewis acid catalyst. The classical reaction commonly used for comparison is that between the Danishefsky diene and benzaldehydes.

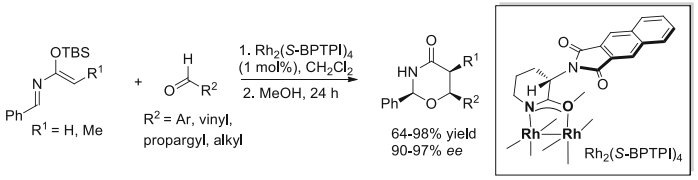
One of the limitations of chiral Lewis acids in catalysis has been the need to use relatively high catalyst loadings to maintain a dominant catalyst-directed pathway (Scheme 3), and this has been especially evident in HDA reactions where catalyst loadings of 5–10 mol% are common. An understanding of the steric factors that can lower catalyst loading and improve TON was first reported using novel chiral dirhodium(II) carboxamidates [50, 51]; these weak Lewis acids coordinate aromatic aldehydes with equilibrium constants less than 100 M^{-1} in dichloromethane with the rate of reaction inversely proportional to the equilibrium constant for association, but the product from cycloaddition does not measurably associate with the catalyst. The k_{off}/k_{on} ratio (Scheme 10) greatly influences the effective TON for these reactions, so that even 0.01 mol% of chiral dirhodium carboxamidate was demonstrated to be effective. A Ti(IV)–BINOL-type complex was shown to have an even higher TON for the same reactions [52, 53].

The applicability of chiral dirhodium(II) carboxamidates for high enantiocontrol and diastereoselectivity has been further demonstrated (Scheme 11) [54, 55]. The [*cis*-2,2] geometry of these catalysts with two adjacent nitrogens and two adjacent oxygens attached to each rhodium provides an environment for coordination that stands in contrast to the catalysts that have C_2-symmetric ligands in which the two occupied quadrants are opposite to one another, rather than adjacent.

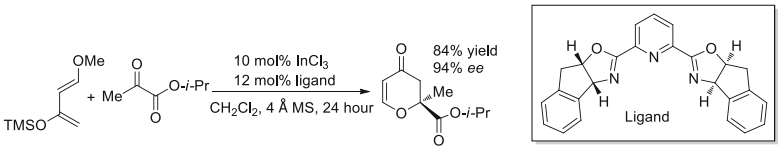
Box and pybox ligands continue to be popular ligands for asymmetric hetero-Diels–Alder reactions, and examples include reactions catalyzed by $InCl_3$ (Scheme 12) [56] as well as an enantioselective version of a thia-HDA reaction



Scheme 10 Product inhibition of Lewis acid catalysis



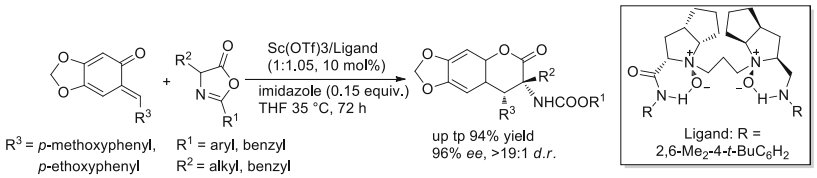
Scheme 11 Asymmetric reaction between 2-aza-3-siloxy-1,3-butadienes and aldehydes [54]



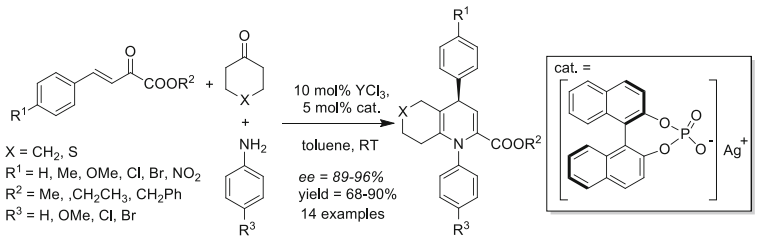
Scheme 12 Chiral In(III)–pybox complex catalyzed enantioselective hetero-Diels–Alder reaction [56]

[57]. Significant contributions have been made with the use of novel, but accessible, chiral *N*,*N*′-dioxide ligands using a wide spectrum of metal Lewis acids (Scheme 13) that provide very high stereocontrol for HDA and inverse-electron-demand HDA reactions [58–65]. An asymmetric three-component reaction that employs the rapid formation of an iminium ion intermediate, a successful variant of which is described in Scheme 14, employs a chiral BINOL–phosphate ligand of yttrium (III) [66], and the BINOL–phosphate ligands are effective for stereocontrol in other HDA reactions [67, 68]. An inverse-electron-demand HDA reaction whose complex components and very bulky chiral ligand for Zn(II) suggest the next stage of development in applications is shown in Scheme 15 [69].

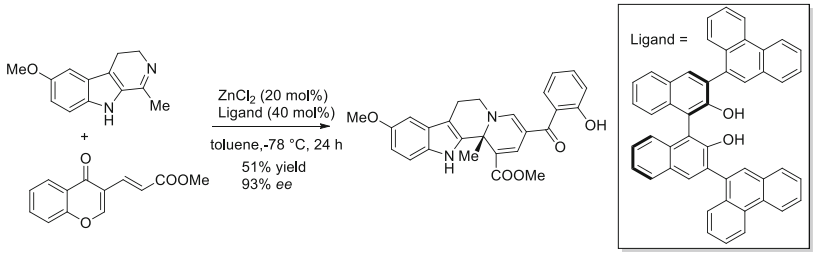
These examples suggest some of the future directions in the applications of chiral Lewis acids as catalysts. High TON and high selectivities in processes that



Scheme 13 Asymmetric inverse-electron-demand HDA reaction catalyzed by chiral *N*,*N*′-dioxide-Sc complexes [64]



Scheme 14 Enantioselective three-component inverse-electron-demand aza-Diels–Alder reaction catalyzed by chiral metal phosphate [66]



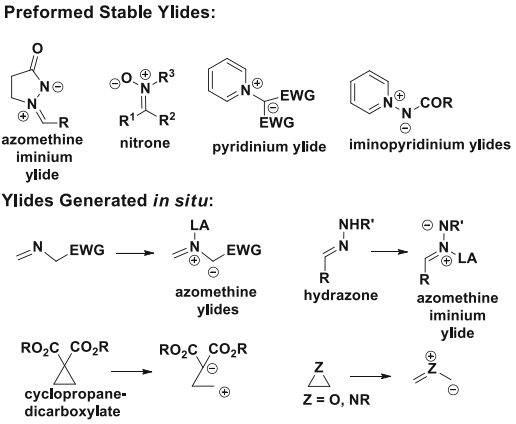
Scheme 15 Enantioselective inverse-electron-demand imino Diels–Alder catalyzed by zinc/BINOL complexes [69]

occur in high yield are established goals. Increasing reaction efficiencies by using multicomponent and domino processes is a significant growth area, and efforts to adapt green chemistry technologies continue.

3.3 Dipolar Cycloaddition Reactions

1,3-Dipolar cycloaddition reactions are efficient and effective processes for the formation of five-membered-ring heterocyclic compounds. The dipolar component is a heteroatom-based alkyl or propargyl system able to contribute 4π electrons to

Scheme 16 Common 1,3-dipoles for dipolar cycloaddition reactions

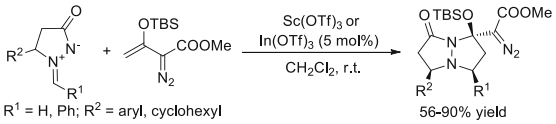


the 2π electron-contributing dipolarophile. Many of the most common 1,3-dipoles fall into the categories that are described in Scheme 16. Some are stable structures that can be synthesized and stored or are commercially available. Others are relatively unstable and must be prepared in situ. Several recent reviews have focused on these increasingly popular reactions [18, 70–72]. Theoretical analyses have given significant insights into the controlling features of 1,3-dipolar cycloaddition reactions [73].

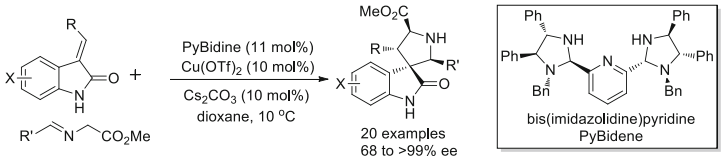
3.3.1 With Azomethine Ylides

Readily available azomethine ylides are popular 1,3-dipoles for cycloaddition reactions. Reaction occurs with preformed ylides (e. g., Scheme 17) [74] or those formed in situ by coordination with the imine nitrogen and base removal of an alpha-hydrogen (e. g., Scheme 18) [75]. Variations of base-stabilizing substituents, dipolarophile, and ligated catalyst give enormous breadth to this transformation [76–91], and enantioselectivities greater than 90% *ee* are generally achieved. Activation of the dipole occurs at nitrogen which is advantageously located between the two carbon atoms that enclose the five-membered ring formed by cycloaddition. Reactions are generally performed below room temperature, and catalyst loading is most often at or above 3 mol%.

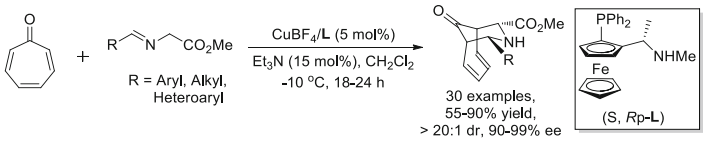
Recent efforts have extended these cycloaddition reactions to the synthesis of bicyclic compounds by using dipolarophiles having extended conjugation. The [6+3] cycloaddition reactions of 6π dipolarophiles that have included tropone [92], fulvenes [93, 94], and 2-acylcycloheptatrienes [95] exemplify the versatility of this reaction. As shown in Scheme 19, high enantioselectivity is achieved. Conceivably, [4+3] and [8+3] cycloaddition reactions can also be envisioned with cycloaddition of azomethine ylides.



Scheme 17 Diastereoselective [3+2] cycloaddition of azomethine imines with an enol diazoacetate [74]



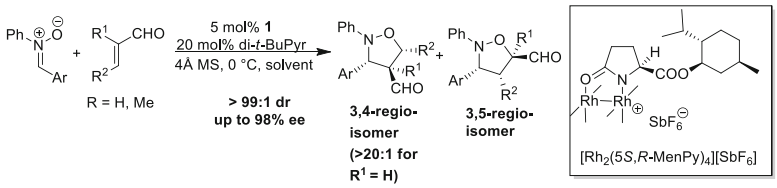
Scheme 18 Asymmetric [3+2] cycloaddition of methyleneindolinones with iminoesters [75]



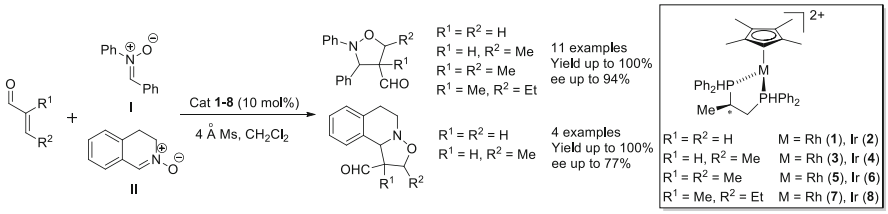
Scheme 19 Stereoselective [6+3] cycloaddition of azomethine ylides with tropone [92]

3.3.2 Nitrones and Nitrile Oxides

Formed directly by 1,3-dipolar cycloaddition of nitrones with electron-deficient alkenes, isoxazolines are synthetically advantageous precursors to β-amino acids and β-lactams, as well as γ-amino alcohols [96, 97]. Selectivity in 1,3-dipolar cycloaddition reactions of nitrones has been a challenge, not only for their regioselective access to isoxazoline cycloadducts but also for broadly applicable diastereo- and enantiocontrol. The background uncatalyzed reaction with its often-opposite influence on regio- and diastereoselectivity is only one of the factors that must be minimized. Enantioselective approaches involving transition metal catalysts have been successful with bidentate dipolarophiles such as those derived from oxazolidinones that provide two-point binding to the chiral Lewis acid [98]. However, there have been few examples of highly selective 1,3-dipolar cycloaddition reactions with α,β-unsaturated aldehydes that are monodentate dipolarophiles [8, 99–102], and those using methacrolein have shown greater selectivities than those with acrolein. A clear understanding of factors that influence reactivity and selectivity in nitrone cycloaddition reactions has been reported for reactions catalyzed by chiral dirhodium(II,III) carboxamidates (Scheme 20) [103]. Dirhodium(II, III) catalysts show preferential binding to aldehydes rather than to nitrones and thereby provide high regiocontrol. However, solvents that are weak Lewis bases like dichloromethane are catalyst inhibitors in this case, reducing regioselectivity as well as stereocontrol, and this example suggests that the potential influence of the



Scheme 20 Asymmetric formal [3+3] cycloaddition reactions of nitrones with electrophilic vinylcarbene intermediates [103]



Scheme 21 Asymmetric 1,3-dipolar cycloaddition reaction between α,β-unsaturated aldehydes and nitrones [100]

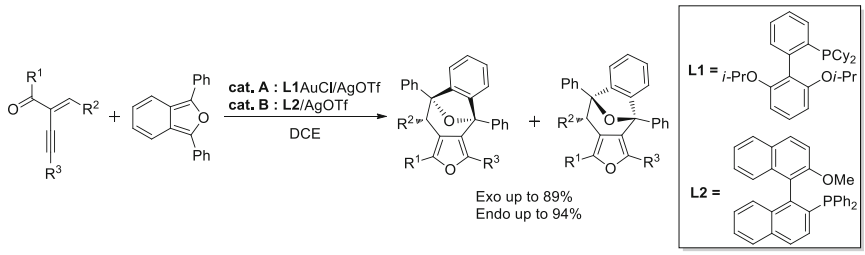
solvent on selectivity in Lewis acid-catalyzed reactions should not be overlooked. The same catalysts are also more active towards the hetero-Diels–Alder reaction, increasing the rate of reaction and its enantioselectivity.

Recent efforts have used chiral diphosphanes of rhodium and iridium for asymmetric 1,3-dipolar cycloaddition of nitrones to α,β-unsaturated aldehydes. These reactions [Scheme 21] are reported to occur quantitatively with high regioselectivity and stereocontrol [100]. The uses of chiral *N*,*N*′-dioxides for nitrone cycloaddition to alkylidene malonates [104] and to 3-arylidene-oxindoles [105] have been reported. Highly enantioselective [4+3] cycloaddition reactions of nitrones have been reported (Scheme 22) [106–110]. A major limitation that remains to the uses of nitrones in cycloaddition reactions is access to *C*-alkyl nitrones and reactivity/selectivity with those that are ketone derivatives.

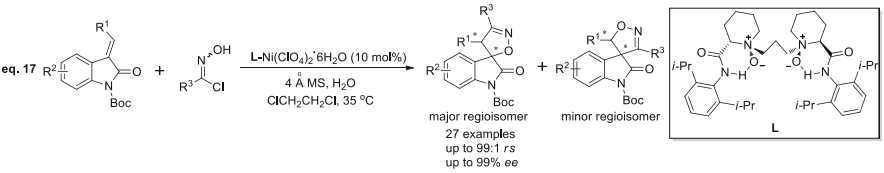
Dipolar cycloaddition reactions of nitrile oxides have received far less attention than those of nitrones [111–113]. By using a chiral *N*,*N*′-dioxide−nickel (II) complex as a catalyst, good regioselectivities and excellent enantioselectivities were obtained in the 1,3-dipolar cycloaddition reaction of nitrile oxides with 3-arylidene-oxindoles (Scheme 23) [102].

3.3.3 Diverse Dipolar Cycloaddition Reactions

With the growth in understanding of how to effect regio- and stereocontrol in dipolar cycloaddition reactions has come an expansion in their applications. Methods to form seven-membered rings through [5+2] cycloaddition using dipoles



Scheme 22 Tandem heterocyclization/formal [4+3] cycloaddition of 2-(1-alkynyl)-2-alken-1-ones and 1,3-diphenylisobenzofuran [110]

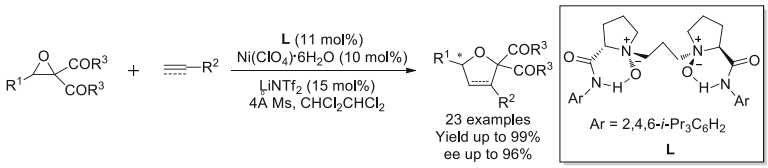


Scheme 23 Asymmetric 1,3-dipolar cycloaddition reaction of nitrile oxides with 3-arylideneoxindoles [102]

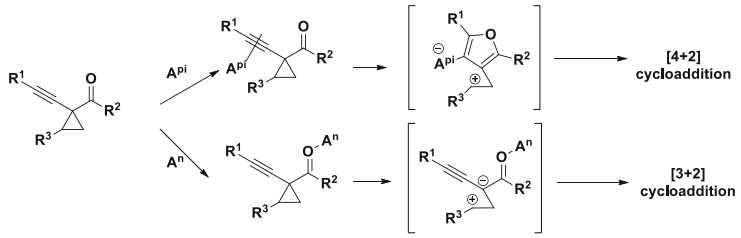
as diverse as oxidopyrylium ylides and those from vinylcyclopropanes or allylsilanes have been recently reviewed [114]. Cyclopropane-1,1-dicarboxylates [115] and epoxides from 2-vinyl-1,3-dicarbonyl substrates [116, 117] have been used to form dipolar reactants and, as suggested by Scheme 24, high enantioselectivities can be achieved [117]; in these cases carbon–carbon bond cleavage forms the reactive ylide that undergoes cycloaddition, and the Lewis acid catalyst facilitates activation by coordination with the 1,3-dicarbonyl unit. When alkynylcyclopropanes are activated to form reactive dipoles (Scheme 25), the nature of the Lewis acid – activation through the alkyne (π-Lewis acid) or through the carbonyl oxygen (*n*-Lewis acid) – defines the pathway for cycloaddition [118]. [3+2] cycloadditions of isocyanoesters occur readily, and high enantiocontrol has been realized [119, 120].

3.3.4 [2+2] Cycloaddition Reactions

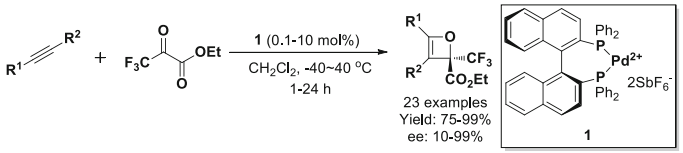
Symmetry-forbidden [2+2] cycloaddition processes have been accessed effectively and efficiently with Lewis acid catalysis when at least one of the reacting partners is polarized. Entry into β-lactam structures continues to be of major interest, and methodologies for the asymmetric syntheses of these biologically significant compounds have been reviewed [121]. The synthesis of stable oxetenes by cycloaddition of alkynes with trifluoropyruvates (Scheme 26) that occurs with exceptional enantiocontrol from reactions catalyzed by a dicationic (*S*)-BINAP-Pd catalyst is a



Scheme 24 Asymmetric [3+2] cycloaddition of alkynes with oxiranes [117]



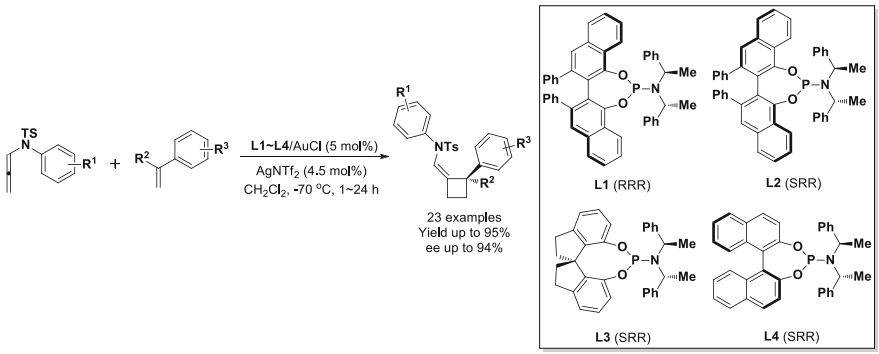
Scheme 25 [4+2] vs. [3+2] cycloaddition



Scheme 26 Asymmetric synthesis of oxetenes via [2+2] cycloaddition of alkynes with trifluoropyruvate [122]

prime example of the versatility of suitably designed chiral Lewis acids in organic synthesis [122]; catalyst loadings as low as 0.1 mol % were used.

There is increasing interest in asymmetric [2+2] cycloaddition reactions that produce cyclobutene and cyclobutane products. Highly polarized ynamide reactions with cyclic enones (the Ficini reaction), catalyzed by a chiral ruthenium(II)–PNNP catalyst, produce amidocyclobutenes in high yield with high enantiocontrol [123], and a chiral iridium catalyst has been reported to form cyclobutene products from reactions of arylacetylenes with norbornadiene derivatives [124]. Allenamide cycloadditions with alkenes that are catalyzed by gold(I) [125, 126] have added to the versatility of this methodology for the formation of cyclobutane compounds; these reactions presumably occur in a stepwise fashion involving initial activation of the allene by the gold(I) catalyst and subsequent attack by the alkene that, as shown in Scheme 27 [125], can achieve high enantiocontrol.



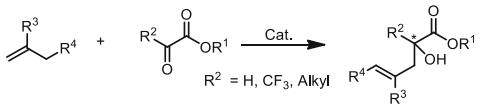
Scheme 27 Intermolecular [2+2] reaction of *N*-allenyl sulfonamides with vinyl arenes [125]

4 Carbonyl–Ene Reaction

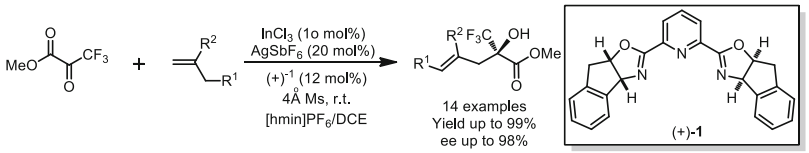
The carbonyl–ene reaction is a versatile, atom-economical process for the construction of carbon–carbon bonds to generate homoallylic alcohols that has generated considerable interest as a result of asymmetric catalysis of this transformation [127]. Lewis acid coordination with the carbonyl component (the enophile) activates the system for this pericyclic reaction, but in asymmetric reactions this activation has been mainly limited to glyoxylate, glyoxal, and pyruvate derivatives. Glyoxylates generally allow bidentate coordination to transition metal catalysts, and they provide access to functionalized chiral α-hydroxyacetates (Scheme 28). However, glyoxylate derivatives coordinate to BINOL–Ti catalysts in a monodentate fashion [128, 129]. Trifluoropyruvates are also preferred substrates; but pyruvate esters show only marginal reactivity towards alkenes, although they have good reactivity and selectivity towards silyl enol ethers.

The ene component in the carbonyl–ene reaction is a major determinant of reaction rate and selectivity. As an example, the carbonyl–ene reaction of methyl glyoxylate catalyzed by chiral BINOL–Ti complexes proceeds in high yield with excellent enantiocontrol but is restricted to reactions with 1,1-disubstituted alkenes [130]. However, the same catalytic system was rapid with silyl enol ethers [129]. Catalysis by chiral Cu(II)–box complexes has broadened the scope of the carbonyl–ene reaction to mono- and 1,2-disubstituted olefins which are less reactive alkene substrates than 1,1-disubstituted alkenes [131].

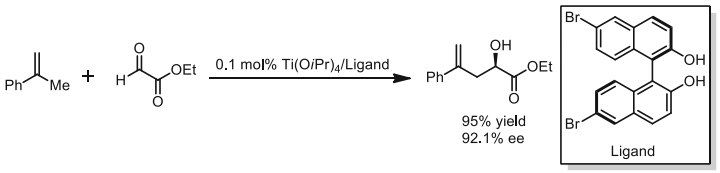
A broad spectrum of chiral Lewis acid catalysts has been used for the carbonyl–ene reaction, and recent examples show the adaptability of this transformation to recycling (Scheme 29) in an ionic liquid [132], to very low catalyst loadings (Scheme 30) in magnetic nanoreactors [133], as well as to the uses of unconventional asymmetric catalysts that include those of palladium(II) with C_2-bridged chiral diphosphine ligands [134], NCN pincer rhodium(III) catalysts [135], and chiral cationic dirhodium(II,III) [136]. An intramolecular carbonyl–ene reaction has also been shown to produce polycyclic products in high yield and stereocontrol



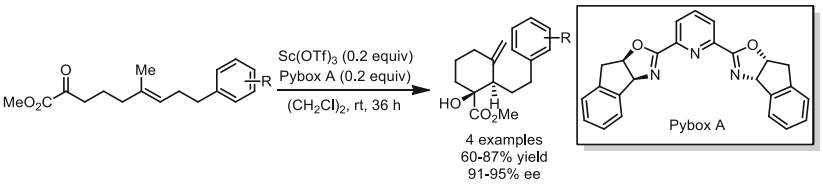
Scheme 28 The carbonyl–ene reaction [127].



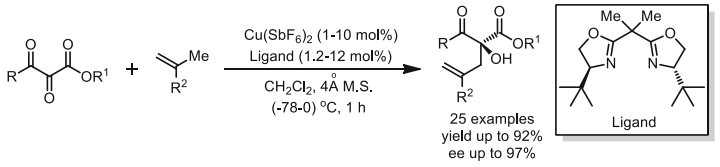
Scheme 29 Enantioselective carbonyl–ene reaction of trifluoropyruvate [132]



Scheme 30 Enantioselective carbonyl–ene reaction on BINOLate/titanium catalyst encapsulated in magnetic nanoreactors [133]



Scheme 31 Enantioselective cationic polyene cyclization of α-ketoester [137]



Scheme 32 Highly enantioselective carbonyl–ene reactions of 2,3-diketoesters [138]

that were previously formed by cationic polyene cyclization (Scheme 31), thus opening a new synthetic methodology for the stereoselective synthesis of polycyclic compounds [137].

Convenient access to α-diazo-β-ketoesters and the replacement of dinitrogen by oxygen have provided a significant expansion of the carbonyl–ene reaction through uses of 2,3-diketoesters as enophiles [138]. With chiral copper(II) box as the catalyst, high enantioselectivities are achieved under very mild conditions (Scheme 32).

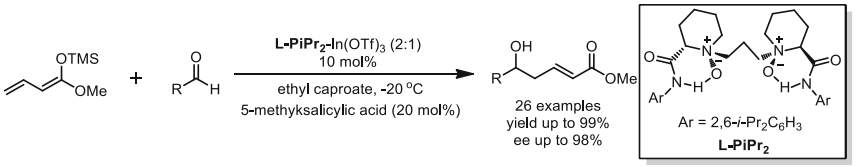
With the substituent R being a broad spectrum of structures and functional groups, the potential of these enophiles to broaden the applicability of the carbonyl–ene reaction in organic synthesis is high. Furthermore, 2,3-diketoesters should also be susceptible to other nucleophiles via asymmetric catalysis.

5 Condensation Reactions

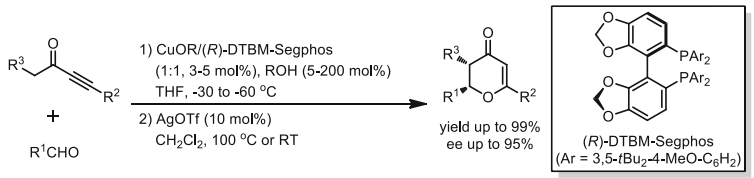
Few transformations have received as much attention in their uses of Lewis acid catalysts as have condensation reactions, and numerous reviews have been recently written that include applications to them [28, 139–147]. Because the area is so broad, the perspective of each review is generally on only one aspect (e.g., specific catalyst, ligand, reactant, and reaction) rather than being a comprehensive overview. This section also is not a comprehensive review but will focus on applications of a few chiral Lewis acids that have been used in representative transformations.

5.1 Aldol Reactions

Advances continue to be made in the development of asymmetric catalysts for aldol reactions, especially for the Mukaiyama process that involves silyl group transfer. The uses of chiral *N*,*N*′-dioxide ligands has been richly represented [148–150] and, as shown in Scheme 33, even systems having extended conjugation (vinylogous Mukaiyama aldol reactions) exhibit high reactivity and selectivity [150]. Matching the Lewis acid with the reactants is a key consideration in these processes. An amide-forming analogue has also been reported using glyoxylates [151]. Processes similar to that of Scheme 32, but with $H_2C{=}C(OR)\text{-}CH{=}C(OR)OTMS$ in place of $H_2C{=}CH\text{-}CH{=}C(OMe)OTMS$, have been successfully employed using a titanium (IV)–BINOL catalyst [152–154]. Although great advances have been made with asymmetric aldol reaction chemistry, comparative analyses of reactivity and selectivity for individual reactions are still lacking, and one seeking to use this transformation still examines reaction outcomes with selections of chiral Lewis acids to optimize the desired outcome.



Scheme 33 Chiral *N*,*N*′-dioxide–$In(OTf)_3$ complexes catalyzed vinylogous Mukaiyama aldol reaction of the silyl dienol ester with aldehydes [150]



Scheme 34 Asymmetric synthesis of dihydropyranones from ynones [155]

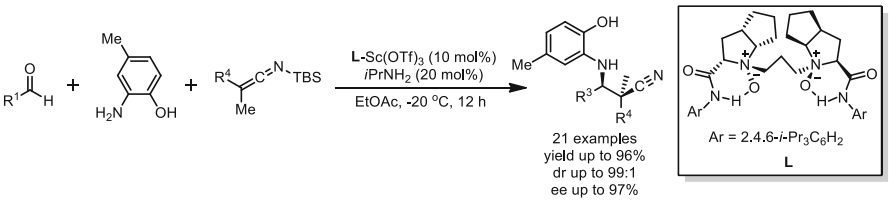
Another facet of new developments for the aldol reaction is the sequential combination of transformations to produce highly valued products with high selectivities. In one recent report [155], highly substituted dihydropyrones were produced with high enantiocontrol and moderate diastereoselectivity in sequential aldol and oxy-Michael reactions of ynones and aldehydes using a chiral copper (I) catalyst for the aldol reaction and a subsequent AgOTf catalyst for the Michael reaction (Scheme 34). The use of perfluorinated alcohols accelerates the aldol reaction, and their addition to accelerate reactions is becoming increasingly common [156].

5.2 Mannich Reactions

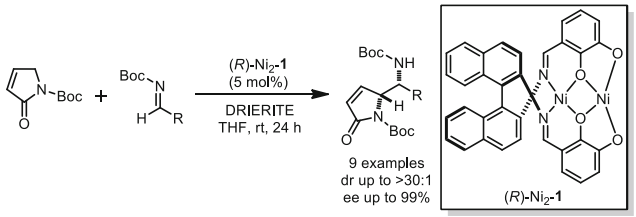
Asymmetric Mannich reactions are more challenging to Lewis acid catalysis than aldol reactions due to the basicity of the imine reactant, which is either preformed or generated in situ, and the amine product. Low catalyst loadings (10 mol%) are common, but a broad spectrum of Lewis acid catalysts are effective, especially those with *N*,*N*′-dioxide [157–159], Schiff base [160–162], and phosphine ligands [163–168]. The use of *ortho*-hydroxyaniline has been developed as an effective template for in situ imine formation that, following asymmetric condensation, can be easily removed (Scheme 35) [159]. Analogous to the asymmetric tandem aldol–Michael reactions (Scheme 34) are the asymmetric tandem vinylogous Mannich–Michael reactions of α,β-unsaturated-γ-butyrolactams with nitrovinyl compounds using a novel dinuclear nickel catalyst (Scheme 36) [161]. The variety of applications derives mainly from the reactants used and the products formed with a match in reactivity and selectivity to the chiral Lewis acid.

5.3 Michael Reactions

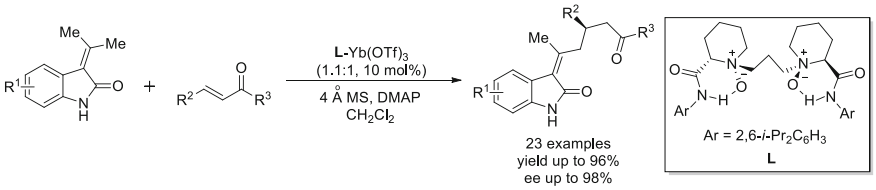
The versatility of catalytic approaches to C–C bond formation using chiral Lewis acids is also evident in conjugate addition reactions [169, 170], and several chiral catalysts have recently been highlighted. The metal triflates with chiral *N*,*N*′-dioxide ligands have shown high enantiocontrol in reactions of a wide variety



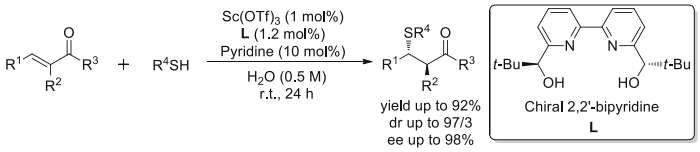
Scheme 35 Asymmetric synthesis of β-amino nitriles through a three-component Mannich reaction of silyl ketene imines [159]



Scheme 36 Asymmetric synthesis of spirooxindoles by a Mannich-type reaction of isothiocyanato oxindoles [161]

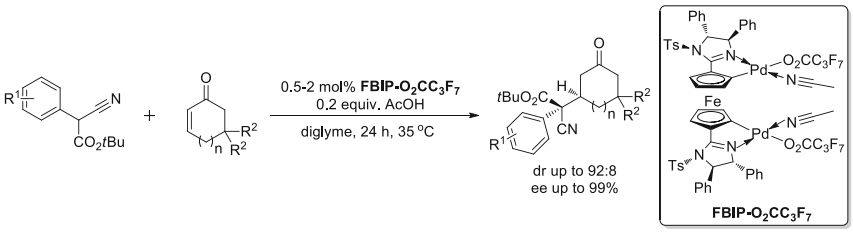


Scheme 37 Michael addition of 3-alkylidene oxindoles to chalcones [172]

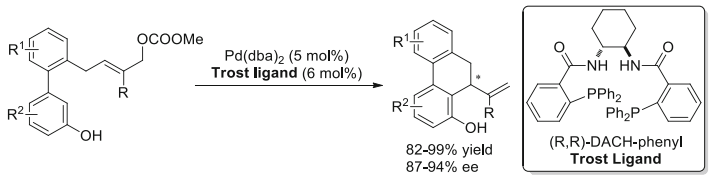


Scheme 38 Michael addition/protonation of thiols with enones [175]

of Michael acceptors [171–173], including the asymmetric vinylogous Michael addition (Scheme 37) for which regioselectivity is a common challenge. For reactions of α,β-unsaturated ketones in water, a scandium(III) triflate/chiral bipyridine complex has been advanced as offering new opportunities for asymmetric synthesis [174, 175]; these "green" reaction processes do not occur with transition metal triflates, which are inhibited by coordination with water, but they are highly effective even at low catalyst loadings with $Sc(OTf)_3$ at room temperature (Scheme 38). The challenges that remain are the applicability of the various classes



Scheme 39 Michael additions of α-cyanoacetates [177]



Scheme 40 Asymmetric intramolecular Friedel–Crafts allylic alkylation of phenols [190]

of α,β-unsaturated Michael acceptors (e.g., ketones, esters, amides, nitro compounds), with suitable Michael donors and catalyst, and adding to this array of variables the solvent presents opportunities that appear today as a multidimensional problem for which there are few guidelines.

A bis-palladacycle, $(FBIPCl)_2$, is a new chiral catalyst that has recently been introduced [176–178] as an effective catalyst (after activation by chloride abstraction with a silver salt) for Michael addition to α,β-unsaturated ketones (e.g., Scheme 39) by α-carbonyl-stabilized nucleophiles. These reactions occur with bimetallic activation and exhibit relatively low catalyst loading. Other catalytic systems have recently been reported that provide additional examples of the challenges and opportunities that exist in this area [155, 179].

5.4 Friedel–Crafts Reactions

In recent years, one of the most aggressively pursued reactions with chiral Lewis acid catalysts for asymmetric induction has been Friedel–Crafts reactions [180]. Because of their nucleophilic reactivity, indoles have been the featured substrates in the vast majority of applications, and a wide variety of chiral catalysts have been used to activate an α,β-unsaturated nitro compound [181–183], α,β-unsaturated ester [184–186], trifluoropyruvate [187, 188], or imine [189] for electrophilic substitution. Applications to phenols [190] have been more limited (Scheme 40). The continuing challenge in these reactions is to broaden applications beyond Friedel–Crafts reactions with indoles.

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Chiral Bimetallic Lewis Acids

Masakatsu Shibasaki and Naoya Kumagai

Abstract Here, we review the utility of chiral bimetallic (multimetallic) Lewis acidic complexes in catalytic asymmetric transformations. Bimetallic complexes are endowed with dual catalytic functions that synergistically activate multiple substrates and functionalities. This cooperative activation mode is particularly effective for activating low reactivity substrates in a highly stereoselective manner without the aid of stoichiometric activating reagents. The privileged bimetallic catalysts presented here highlight the importance of catalyst design in the development of widely applicable catalytic systems.

Keywords Bimetallic catalysis · Cooperative activation · Heterobimetallic · Homobimetallic · Rare earth metals

Contents

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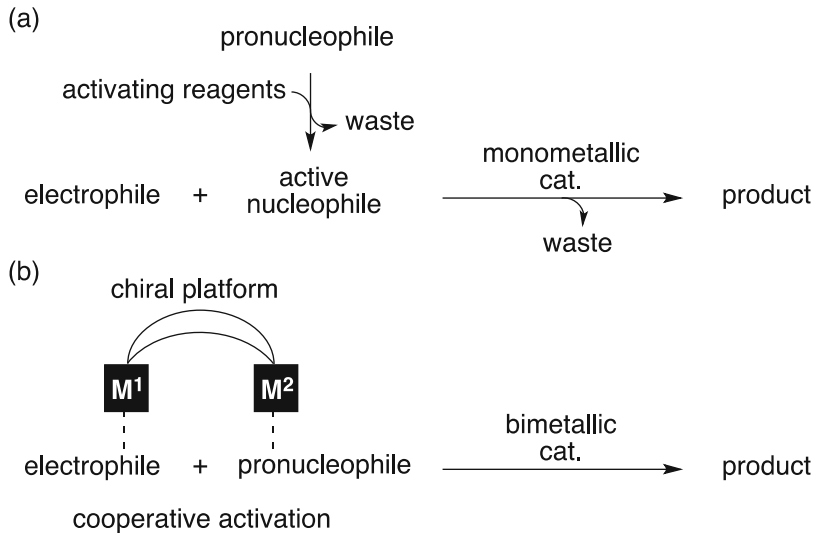
1 Introduction

Lewis acid activation is a commonly utilized methodology for promoting chemical transformations, as demonstrated by a number of examples in other chapters of this book and in prior reviews [1, 2]. Chiral decoration of Lewis acidic metals with homochiral molecular ligands renders the above transformations in an enantioselective manner, constituting a large and fruitful research area to produce enantioenriched building blocks in organic synthesis with high practical impact [3–6]. Given that most of the productive and "building" reactions are bimolecular (and sometimes trimolecular) C–C bond-forming reactions, various chiral Lewis acid catalysts bearing two (multiple) Lewis acidic catalytically active sites have been designed to cooperatively activate two (multiple) reaction substrates. Cooperative activation of two (multiple) substrates offers a new activation manifold, particularly for reactions of inherently low reactivity substrate combinations, and has gained popularity as a powerful tool in catalytic asymmetric transformations [7–15]. Transformations of low reactivity substrates commonly use stoichiometric amounts of activating reagents to prepare pre-activated substrates prior to chiral Lewis acid catalysis (Scheme 1a). In this preactivation strategy, the design principle of an asymmetric catalyst is inclined mainly to exert stereodifferentiation by fine-tuning an asymmetric environment, because promotion of the reaction is already guaranteed by preactivation of the substrates. This strategy, however, is inherently associated with the coproduction of reagent-derived waste, which is no longer acceptable with regard to sustainable chemistry. The concept of cooperative catalysis has therefore rapidly emerged to tackle this problem by replacing the use of activating reagents with multifunctional catalytic activation, similar to enzymatic catalysis (Scheme 1b). Despite the powerful catalytic performance, the substrate scope of enzymatic catalysis is too limited for application to general organic synthesis. Asymmetric cooperative catalysis is an artificial alternative to enzymatic catalysis, providing both powerful catalytic activation and broad substrate generality. Although the catalyst design must be more complicated to fulfill strong catalytic activation as well as sufficient stereodifferentiation, cooperative catalytic activation offers a more advantageous strategy to render the reaction truly catalytic without the aid of activating reagents. In this chapter, chiral bimetallic Lewis acidic catalysts exerting cooperative activation modes are reviewed. Bimetallic catalysts involving transition metal chemistry and examples of bimetallic activation via two monometallic catalyst fragments are not covered here. Reviews of a similar scope were previously published [7, 8, 13–17], and this chapter briefly summarizes



Scheme 1 (**a**) Monometallic catalysis with preactivation and (**b**) bimetallic catalysis without preactivation

prior studies, focusing mainly on highly privileged catalytic systems that are applicable to multiple reaction manifolds.

2 Bimetallic (Polymetallic) Chiral Lewis Acid Catalysts Using 1,1′-Bi-2-naphthol Derivatives as Chiral Units

2.1 Catalysts Based on 1,1′-Bi-2-naphthol and Its Derivatives

1,1′-Bi-2-naphthol has an axially chiral architecture providing two phenolic oxygens in close proximity, which allows for bidentate coordination to a range of hard Lewis acidic metals. Due to its wide availability, a plethora of monometallic Lewis acid catalysts based on 1,1′-bi-2-naphthol complexes, including numerous structural modifications, have been reported. Shibasaki et al. developed two types of higher-ordered complexes based on 1,1′-bi-2-naphthol: the first one comprises three 1,1′-bi-2-naphthols, one rare earth metal (RE), and three alkali metals ($M^{[1]}$) [7, 18–22], and the second one has two 1,1′-bi-2-naphthols tethered by a group 13 metal with a pendant alkali metal (Fig. 1). The generic chemical formula for the first type is RE-$M^{[1]}_3$-tris(1,1′-bi-2-naphthoxides), and various combinations of RE and $M^{[1]}$ produce a series of heterobimetallic asymmetric catalysts with small deviations in the O–M bond length, ionic radius, and Lewis acidity [23–26]. The initially identified heterobimetallic complex of this class was La-Li_3-tris(1,1′-bi-2-naphthoxides), abbreviated LLB (RE: La, $M^{[1]}$: Li), which exerted particular

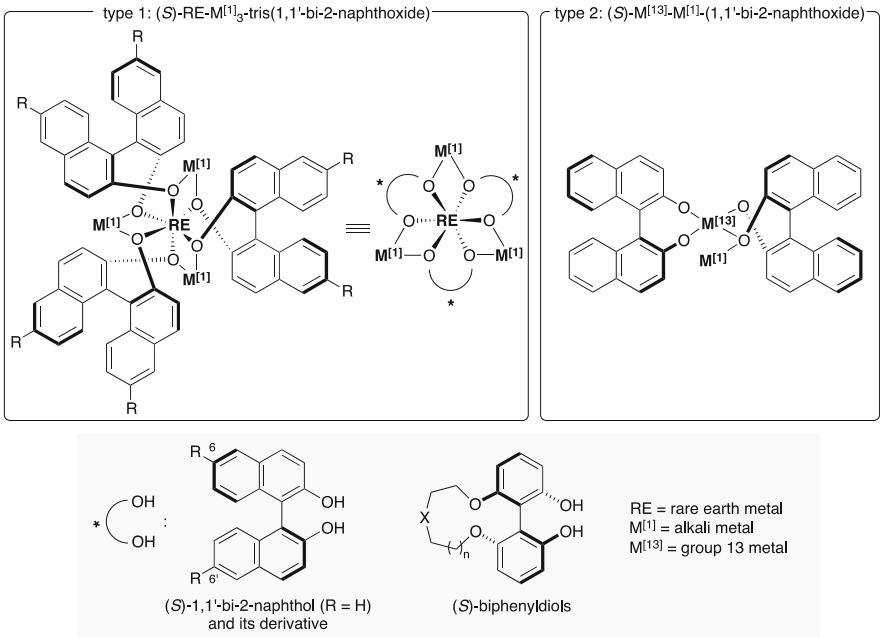
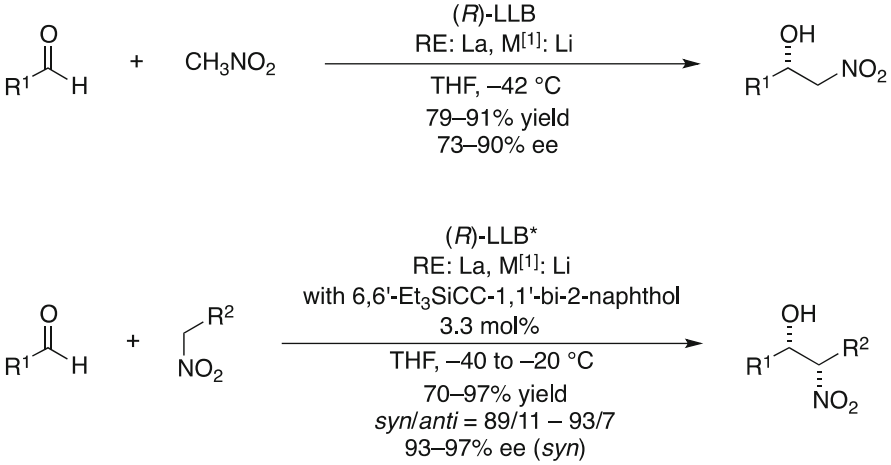


Fig. 1 Structure of heterobimetallic catalysts RE-$M^{[1]}_3$-tris(1,1′-bi-2-naphthoxides) and $M^{[13]}$-$M^{[1]}$-(1,1′-bi-2-naphthoxide)



Scheme 2 Seminal catalytic asymmetric nitroaldol reaction promoted by heterobimetallic catalyst (*R*)-LLB

catalytic performance to realize the first reported catalytic asymmetric nitroaldol reaction [23, 27–36] (Scheme 2). The flexible combination of RE and $M^{[1]}$ and facile structural modifications of the binaphthyl group are advantageous to promote

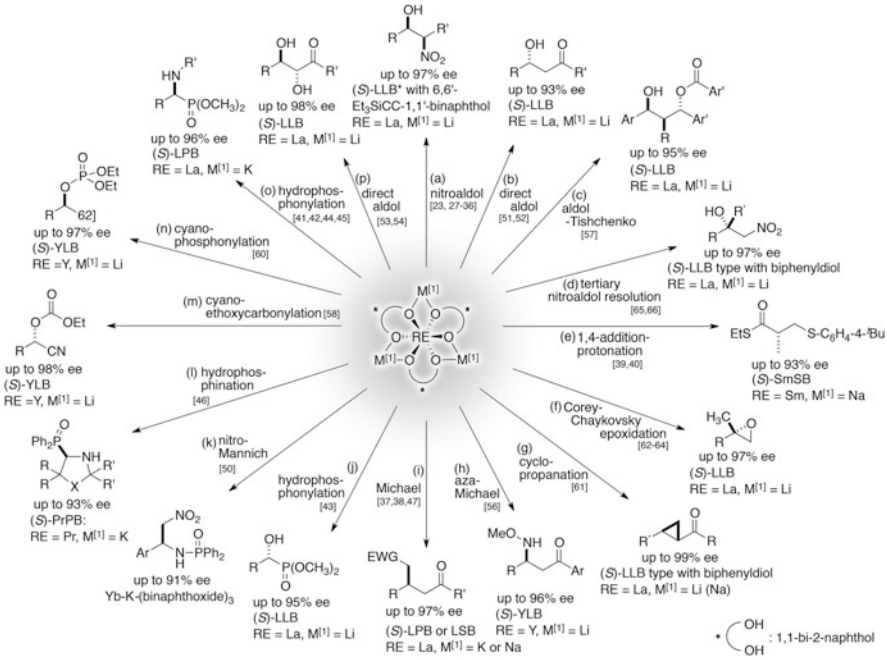


Fig. 2 Utility of heterobimetallic complexes RE-$M^{[1]}_3$-tris(1,1′-bi-2-naphthoxides) in catalytic asymmetric transformations. Although some of the reactions above were documented with an *R* catalyst in the original report, the data were extrapolated to an *S* catalyst for clarity

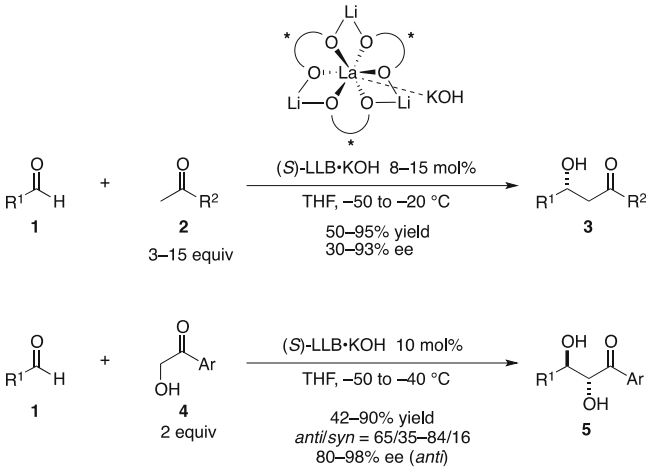
a wide range of asymmetric reactions in a highly stereoselective manner [23, 27–66] (Fig. 2). The highly symmetrical heterobimetallic structure of RE-$M^{[1]}_3$-tris(1,1′-bi-2-naphthoxides) was revealed by laser desorption/ionization time-of-flight mass spectrometry [24]. X-ray crystallographic analysis of the complexes 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) unequivocally determined the heterobimetallic structure, and other complexes are considered to have a similar architecture [37, 67, 68]. An exclusive Λ configuration was observed for the coordination mode to the central RE, presumably due to thermodynamic stability.

The exceptionally wide scope of applicable reactions clearly demonstrates that this is one of the most successful asymmetric bimetallic catalysts (Fig. 2). La is obviously a privileged RE for this class of complexes and the optimal metal for the majority of the reactions. Biphenyldiols having similar axial chirality with different dihedral angles broadened the structural variety. The key feature of these bimetallic catalysts is bifunctional cooperative activation of pronucleophiles and electrophiles; $M^{[1]}$–O functions as a Brønsted base to activate pronucleophiles to catalytically generate active nucleophiles, while the central Lewis acidic RE functions to activate electrophiles, engaging in enantioselective bond formation in an asymmetric environment created by binaphthyl walls. The coordination number of the RE is generally high (ranging from 6 to 12) [69–73], and RE of these heterobimetallic

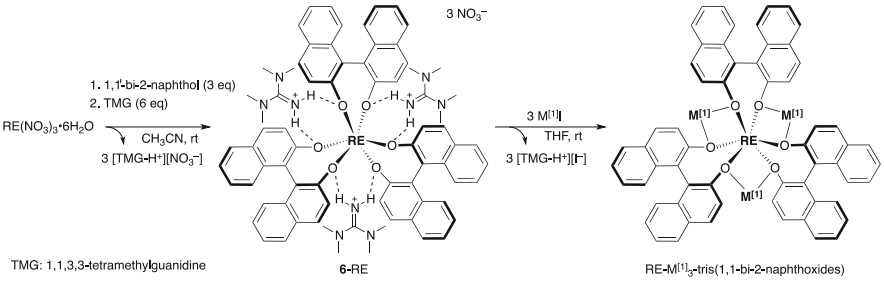
catalysts can accept further coordination of an external electrophile. The wide applicability of these heterobimetallic catalysts has led to sustained interest in their coordination chemistry [74]. Hepta- and octa-coordinated RE in the crystal structures were revealed by Walsh et al. to provide direct evidence for higher-order coordination of these heterobimetallic complexes, and the coordination of electrophiles was revealed by nuclear magnetic resonance analysis [75, 76]. Further investigations led by Walsh's group to dissect the nature of the catalysis disclosed the dynamic nature of the complex in solution [77]. ^{1}H and ^{7}Li two-dimensional exchange spectroscopy confirmed a much faster exchange of both 1,1-bi-2-naphthoxides and Li^{+} cations compared to catalytic reactions. Dissociation of one 1,1-bi-2-naphthoxide was observed upon deprotonation of a pronucleophile, and the involvement of a putative bis(1,1′-bi-2-naphthoxide) species (or oligomeric heterobimetallic species) was proposed. Several transformations, e.g., aza-Michael reaction [56], Corey-Chaykovsky cyclopropanation [61], and epoxidation [62–64], were promoted via a Lewis acid/Lewis acid mechanism, where both RE and $M^{[1]}$ were assumed to function as Lewis acids to activate electrophiles and heteroatom nucleophiles. In this Lewis acid/Lewis acid catalysis, self-exchange of the 1,1-bi-2-naphthoxides and Li^{+} cations is associative, and the reaction via tris(1,1′-bi-2-naphthoxides) is likely operative [77].

Another reaction worth highlighting is the direct catalytic asymmetric aldol reaction [51–54], which was first reported with heterobimetallic catalyst LLB in 1997 and later became a firm research area in the chemical community [78–82]. The essence of the reaction is an in situ catalytic generation of active enolate (nucleophile) that engages in subsequent enantioselective addition to the activated aldehyde (electrophile). Cooperative activation of both pronucleophiles and electrophiles was achieved by the bifunctional heterobimetallic catalyst LLB. Later, LLB with additional KOH was found to exhibit higher catalytic performance to promote the direct aldol reaction of ketone **2** or hydroxy ketones **4** to aldehydes **1**, affording the enantioenriched aldol adducts **3** and **5** without the coproduction of any waste (Scheme 3).

Walsh et al. directed further investigation into this class of heterobimetallic complexes to expand the utility of symmetrical heterobimetallic complexes [83–86]. Practical advances were made based on the development of easier preparation procedures of the heterobimetallic complex RE-$M^{[1]}{}_3$-tris(1,1′-bi-2-naphthoxides) (Scheme 4) [87]. These complexes are generally prepared from expensive and hygroscopic RE alkoxides or $RE(HMDS)_3$, which hamper the widespread use of these highly stereoselective catalysts. Starting from ~100-fold less expensive hydrates of RE nitrates, a series of bench-stable guanidino complexes **6**-RE were readily prepared as precatalysts. **6**-RE showed remarkable stability to moisture, likely due to hydrogen bonding interactions revealed by X-ray crystallographic analysis. Subsequent treatment with $M^{[1]}I$ in THF afforded the corresponding heterobimetallic catalysts RE-$M^{[1]}{}_3$-tris(1,1′-bi-2-naphthoxides) through cation exchange, which could be used directly in the presence of spectator iodide anions to exhibit similar catalytic performance.



Scheme 3 Seminal catalytic asymmetric direct aldol reaction promoted by heterobimetallic catalyst (*S*)-LLB·KOH



Scheme 4 Preparation of heterobimetallic complex RE-$M^{[1]}_3$-tris(1,1′-bi-2-naphthoxides) via bench-stable precatalysts **6**-RE

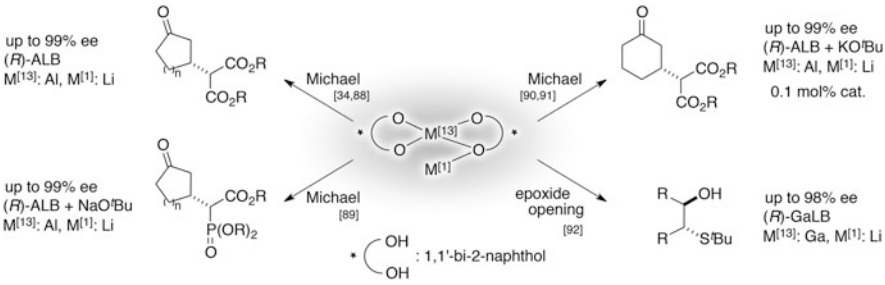


Fig. 3 Utility of heterobimetallic complexes $M^{[13]}$-$M^{[1]}$-bis(1,1′-bi-2-naphthoxides) in catalytic asymmetric transformations

Another type of 1,1′-bi-2-naphthol-based heterobimetallic complexes was reported by Shibasaki et al. utilizing group 13 metals as a central metal represented by the generic formula $M^{[13]}$-$M^{[1]}$-1,1′-bi-2-bis(naphthoxides) (Fig. 1, type 2). Al-Li-1,1′-bi-2-bis(naphthoxides) ($M^{[13]}$: Al, $M^{[1]}$: Li), abbreviated ALB, were disclosed in 1996 and are particularly useful for catalytic asymmetric Michael reactions of cyclic enones (Fig. 3) [88]. ALB was structurally characterized by X-ray crystallography and is proposed to exert a bifunctional activation mode where Al functions as a Lewis acid to activate electrophiles and Li-naphthoxide functions as a Brønsted base to activate pronucleophiles. A modified catalyst with additional KO^{t}Bu exhibited much higher catalytic performance to complete the Michael reaction with as little as 0.1 mol% of catalyst loading on a >1 kg scale [33, 89–91]. Replacing Al with Ga as $M^{[13]}$ furnished a new catalyst, abbreviated GaLB, that exhibited high catalytic performance in the asymmetric opening reaction of *meso*-epoxides with *tert*-butylthiol [92].

2.2 Catalysts Based on Linked-BINOL

Given the successful implementation of 1,1′-bi-2-naphthol (BINOL) as a privileged chiral diol ligand, a tethered analog, coined linked-BINOL, emerged as a tetraol chiral ligand to firmly construct an asymmetric environment for metal complexes [93–97]. Shibasaki et al. reported a series of catalytic asymmetric transformations utilizing linked-BINOL as a chiral platform for a Ga-Li heterobimetallic complex and Zn polymetallic complexes (Fig. 4) [13, 98, 99]. The Ga-Li-linked-BINOL complex was pursued because the undesired oligomerization/polymerization of Ga-Li-bis(1,1′-bi-2-naphthoxides) (GaLB, described above) implied low stability and inferior catalytic performance. The covalently tethered linked-BINOL was anticipated to provide a more stable complex with a similar asymmetric

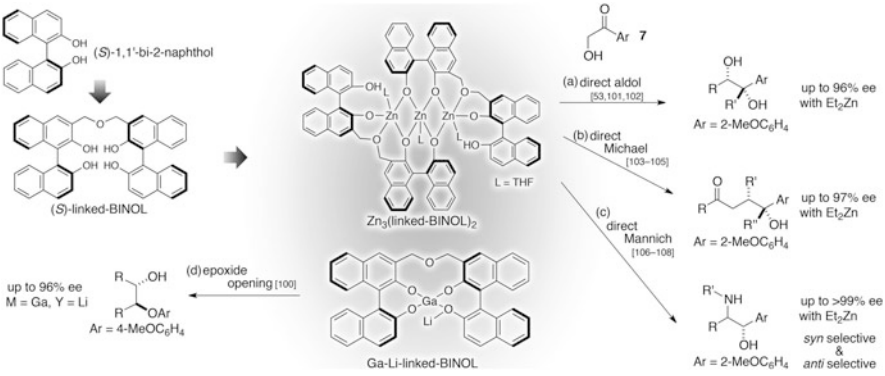


Fig. 4 Utility of heterobimetallic and Zn polymetallic complexes of linked-BINOL in catalytic asymmetric transformations

environment for enantioselectivity. Indeed, the Ga-Li-linked-BINOL complex exhibited superior stability to promote an asymmetric opening reaction of *meso*-epoxide with *p*-methoxyphenol [100]. X-ray crystallographic analysis revealed that the oxygen at the tether coordinated to Ga to stabilize the whole architecture. Although the four phenolic oxygens and an additional coordinative ether oxygen at the tether of linked-BINOL imply a strong potential to form monomeric complexes, a dimeric linked-BINOL complex Zn_3(linked-BINOL)$_2$ was formed with Et_2Zn, in which three Zn cations were captured in a linear fashion, as confirmed by ^{1}H nuclear magnetic resonance, mass spectroscopy, and X-ray crystallographic analysis [101]. The trinuclear Zn complex was found to act as a precatalyst for the direct enolization of hydroxy ketone **7**, and a higher-order polymetallic complex including **7** was observed by MS. This complex was particularly effective for catalytic generation of the nucleophilically active enolate from **7** and its prochiral face selection, leading to the development of direct catalytic asymmetric aldol [53, 101, 102], Michael-type [103–105], and Mannich-type reactions [106–108] in a highly stereoselective manner. Monometallic catalysts were also developed using this unique tetraol ligand [13, 98, 99].

3 Bimetallic Chiral Lewis Acid Catalysts Using Salen Derivatives as Chiral Units

3.1 Bimetallic and Polymetallic Complexes Based on Tethered Monometallic Salen Complexes

Salens, characterized by their diimino structure prepared by condensation of salicylaldehyde derivatives and chiral vicinal diamines, are highly successful ligand scaffolds for a range of metals in asymmetric catalysis [109–115]. The second-order rate dependence on the concentration of monomeric Cr(N_3)-salen complex in catalytic asymmetric ring-opening reactions of epoxides with azide was revealed by detailed mechanistic investigations led by Jacobsen et al. [116–123], which directed further research to the tethered salen complexes for higher catalytic activity (Fig. 5). Tethering two monomeric salen complexes renders bimetallic catalysis intramolecularly, and a series of dimeric complexes tethered with an alkyl chain was evaluated. Specifically, in epoxide opening with azide, dimeric Cr(N_3)-salen complex **8** tethered with a pimelate diester ($n = 5$) outperformed the monomeric Cr(N_3)-salen to accelerate the reaction by two orders of magnitude [124]. This dimeric strategy was valid for other reactions promoted by metal-salen complexes; dimeric Al(Cl)-salen **9** [125] and Co(OAc)-salen **10** [126] were more superior catalysts than their monomeric counterparts in catalytic asymmetric conjugate addition of HCN and hydrolytic kinetic resolution of racemic epoxides, respectively. The latter reaction in particular is of broad synthetic utility, and extensive efforts have been devoted to the identification of more active catalysts (Scheme 5, Fig. 6). Jacobsen et al. reported a dendrimeric catalyst **11** [127] and macrocyclic oligomeric catalysts

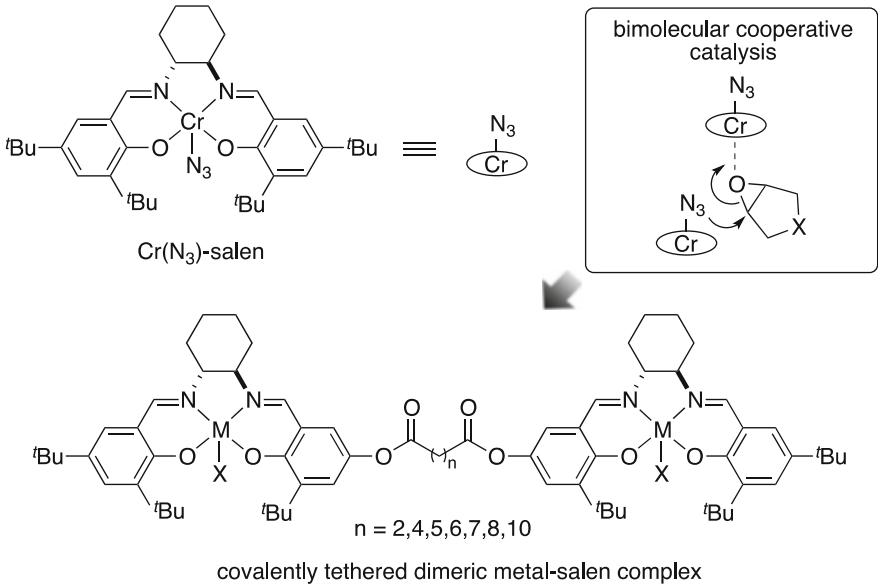
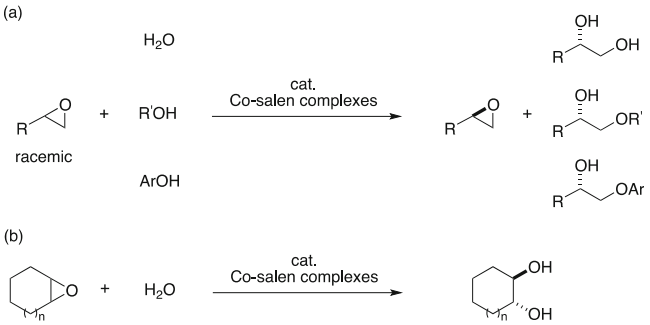


Fig. 5 Utility of covalently tethered dimeric metal-salen complexes in catalytic asymmetric transformations



Scheme 5 (**a**) Catalytic hydrolytic kinetic resolution of racemic terminal epoxides and (**b**) catalytic hydrolytic desymmetrization of *meso*-epoxides

12 [128, 129] that bear multiple Co-salen units. Catalyst **12** with X: nbs, Y: CH_2, Z: H, and n: 1–3 exhibited outstanding catalytic performance to promote hydrolytic kinetic resolution of racemic propylene oxide with 0.0004 mol% of catalyst loading. The same group also developed a recoverable Co-salen catalyst **13** in which Co-salen units were immobilized on gold colloids, allowing for their repeated use

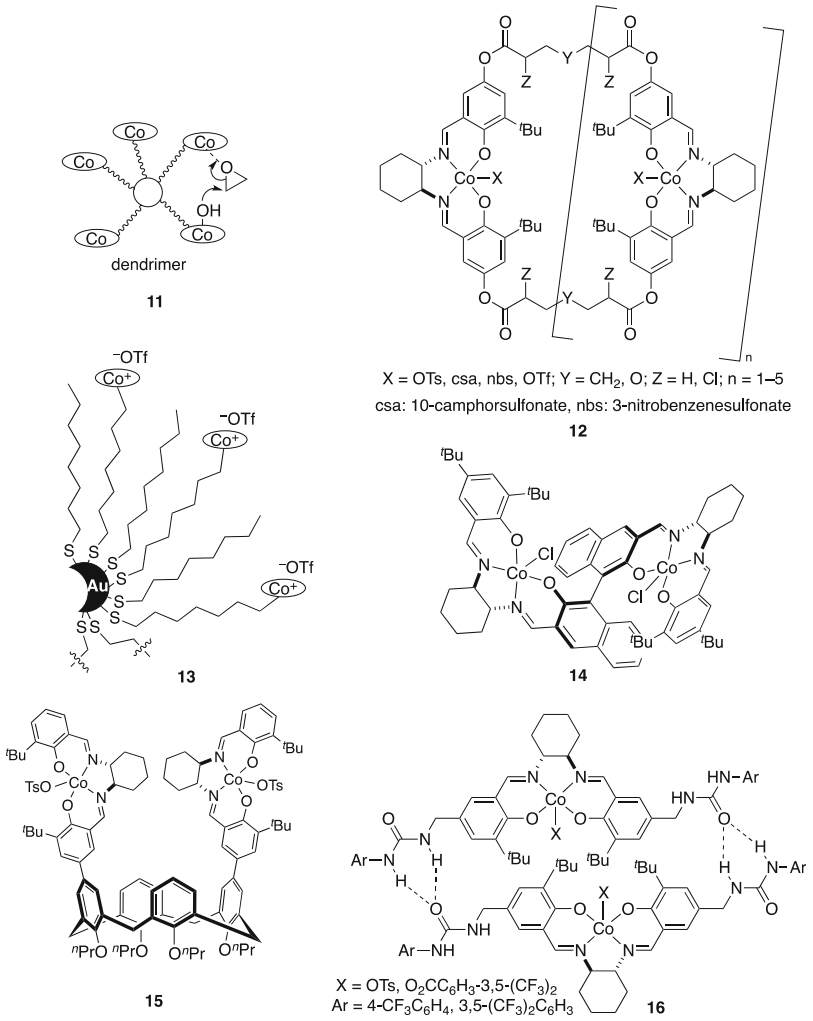


Fig. 6 A variety of tethered Co-salen complexes

without loss of stereoselectivity or catalytic efficiency [130]. As revealed by Coates et al., dimeric catalyst **14**, characterized by a central binaphthyl unit, has specific utility in asymmetric polymerization of racemic terminal epoxides, producing highly isotactic polyethers and enantioenriched unreacted epoxides [131, 132]. Wezenberg et al. utilized calix[4]arene to align two Co-salen units with a suitable spatial distance for kinetic resolution, and cooperative actions of these units were suggested by kinetic studies using the catalyst **15** [133]. Hong et al. designed noncovalently associated Co-salen complexes **16** by exploiting hydrogen bonding of urea functionalities [134]. These catalysts are effective for not only hydrolytic kinetic resolution but also nitroaldol reactions [135, 136].

3.2 *Bimetallic and Polymetallic Complexes of Monomeric Salen (Schiff Base) Ligands*

Incorporation of two different Lewis acidic metals to a salen ligand was reported by Zhu et al. [137, 138]. Although spectroscopic evidence for the structural elucidation was not documented, the proposed complex **17** bearing Ga and Ti cations promoted a catalytic asymmetric ring-opening reaction of meso-epoxide with thiols and selenols (Fig. 7). Inferior reaction outcomes were produced with monometallic Ti-salen complex and a homobimetallic Ga_2-salen complex. Introduction of additional coordinative functional groups is a logical approach for constructing well-defined multimetallic complexes based on the salen scaffolds. Kozlowski et al. introduced a dinucleating Schiff base ligand comprising a central cyclohexanediamine core and two 1,1′-bi-2-naphthol arms, tethered by an imine linkage [139–141]. Incorporation of Ni(II) and two Cs cations gave a heterobimetallic complex **18**, whose structure was unequivocally determined by X-ray crystallographic analysis. The cooperative function of **18** as a Lewis acid and Brønsted base facilitated the catalytic asymmetric Michael reaction of dibenzyl malonate to cyclic enones.

Shibasaki and Matsunaga et al. found particular utility in a Schiff base ligand **19** having two additional phenolic hydroxyl groups to construct a range of bimetallic complexes with exceptionally broad utility in asymmetric catalysis [142, 143] (Fig. 8). Extensive studies of the coordination chemistry of **19** [144–148] revealed that the N_2O_2 inner cavity prefers the incorporation of transition metals, while the larger O_2O_2 cavity is considered a suitable position for oxophilic metals with a larger ionic radius. The flexible choice of chiral diamine unit **20**–**23** and two metals for the inner and outer cavities enabled the production of a series of hetero- and homobimetallic complexes to promote a number of catalytic asymmetric transformations, illustrated in Fig. 8 [149–171]. The use of Cu(II) for the inner cavity

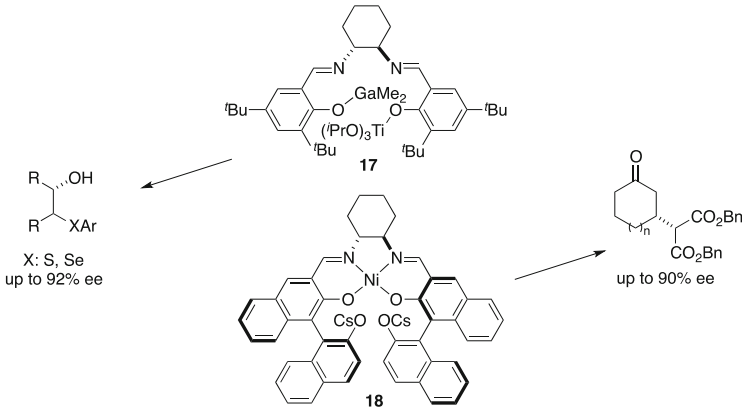


Fig. 7 Utility of heterobimetallic complexes of salen and modified salen ligands in catalytic asymmetric transformations

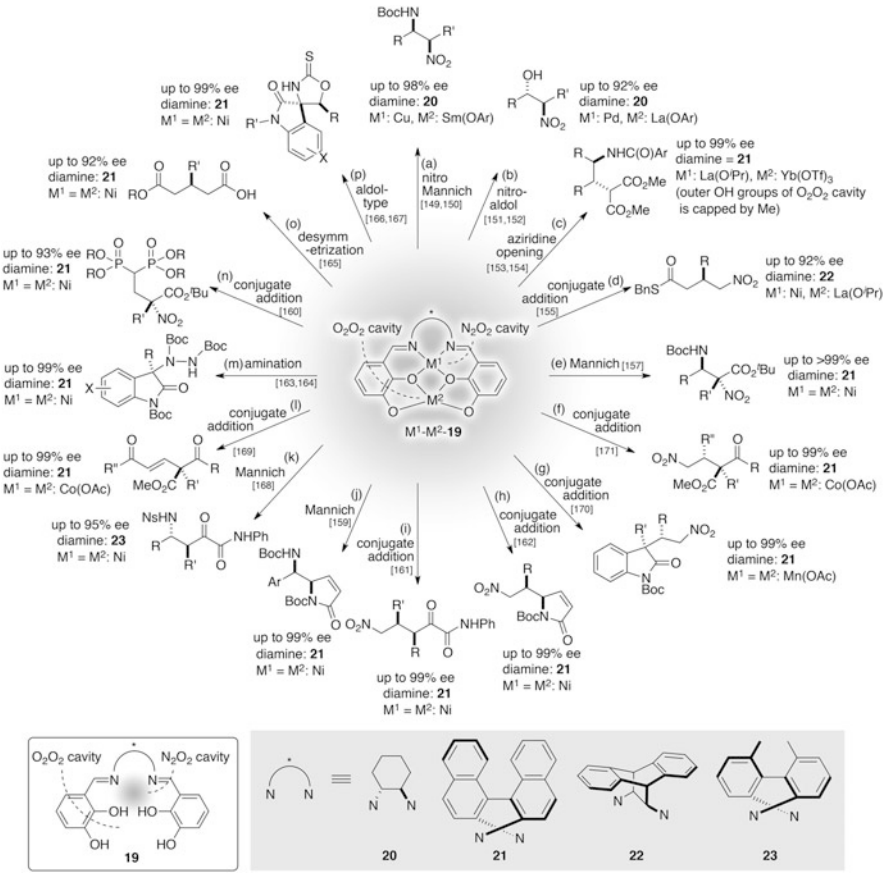


Fig. 8 Utility of hetero- and homobimetallic complexes of Schiff base **19** in catalytic asymmetric transformations

and Sm-aryloxide for the outer cavity afforded the Cu-Sm-**19** catalyst (M^1: Cu(II), M^2: Sm(OAr)) that could serve as Lewis acid/Brønsted base bifunctional catalyst for an asymmetric nitro-Mannich (aza-Henry) reaction (Fig. 8a) [149, 150]. Changing the metals from Cu-Sm to Pd-La produced a suitable catalyst for an *anti*-selective asymmetric nitroaldol reaction (Fig. 8b) [151, 152]. Construction of well-defined heterobimetallic catalysts based on scaffold **19** was not straightforward, and homobimetallic catalytic systems have been more successfully applied to asymmetric reactions (Fig. 8e, h–k,m–p). Dinickel complexes with **19** prepared from axially chiral diamine **21** or **23** exhibited broad generality. Ni_2-**19** (with diamine **21**) was readily prepared from **19** and 2 equiv. of $Ni(OAc)_2 \cdot 4H_2O$ as a bench-stable powder. Other inexpensive first-row transition metals, e.g., Co and Mn, also constitute useful catalysts [169–171]. Enantioenriched chiral building blocks produced by these bimetallic catalysts have been utilized for the enantioselective synthesis of natural products [172–174].

4 Bimetallic Chiral Lewis Acid Catalysts Using Amino Acid Derivatives and Imidazolines as Chiral Units

4.1 Bimetallic Complexes Based on Amino Acids

α-Amino acids are readily available and abundant natural homochiral materials. Trost et al. introduced a new class of multidentate ligands for bimetallic complexes, named ProPhenol **24**, in which two diarylprolinol units are linked by a phenol core (Fig. 9) [175]. ProPhenol **24** incorporates two Zn cations upon the addition of Et_2Zn, and the thus-obtained dinuclear Zn complex **25** ($M^1 = M^2$: Zn) exerts a bifunctional activation mode. A Zn cation functions as a Lewis acid to activate electrophiles and a Zn alkoxide functions as a Brønsted base to activate pronucleophiles, which is suitable for bimolecular C–C bond-forming reactions triggered by catalytic deprotonation. Indeed, homobimetallic complexes **25** demonstrate broad utility in a number of reactions in this class, as illustrated in Fig. 9. This catalyst was initially successfully implemented for the direct catalytic asymmetric aldol reaction of aromatic ketones [176] (Fig. 9a). This direct aldol reaction is among the early examples before direct aldol chemistry gained popularity in the field of organocatalysis (Scheme 6a). A similar catalyst design was reported by Da et al. using multidentate ligand **26** with a binaphthyl core and diarylprolinols with Zn cations (Scheme 6b) [177]. The lower catalytic efficiency and enantioselectivity are indicative of the importance of the distance between the two Zn cations for cooperative activation. The scope of ketones was significantly expanded, including the successful use of less tractable vinyl ketones and alkynyl ketones [178–181], and an ester surrogate α-hydroxy N-acyl pyrrole was also implemented in this direct aldol reaction [182] (Fig. 9b–e). α-Hydroxy ketones serve as suitable pronucleophiles and reactions using various electrophiles, e.g., aldehydes [179], imines [183, 184], and nitroolefins [185], proceeded smoothly (Fig. 9c, g, h). Catalytic generation and subsequent enantioselective addition of nitronates to aldehydes were also possible (Fig. 9f) [186]. In the conjugate addition to nitroolefins, heterobimetallic Mg-Zn ProPhenol complex (M^1: Mg, M^2: Zn) was identified as an optimal catalyst, which was prepared by equimolar amounts of Et_2Zn and $^nBu_2Mg$. Acidic 3-hydroxyoxindoles and 5*H*-oxazol-4-ones serve as suitable nucleophiles in conjugate additions (Fig. 9i, j) [187, 188]. Although Zn homobimetallic complexes Zn_2-**25** are generally optimal for the majority of reactions, a Mg homobimetallic complex Mg_2-**25** outperformed the Zn catalyst in an aldol reaction of diazoacetate (Fig. 9k) [189–191]. Steric factors around the tertiary alcohol of ProPhenol **24** are crucial for the desymmetrization of diols (Fig. 9l) [192]. Beyond the use of catalyst **25** for deprotonative activation of acidic pronucleophiles, this catalytic system is also effective for stereochemical control of the addition of organometallic reagents. Alkynylzinc [193–195] and alkenylzirconium [196] were utilized as nucleophiles for enantioselective addition to aldehydes and imines (Fig. 9m, n). For alkenylation, desymmetrizing two prolinol units to alter the electronic property is beneficial (Ar^1: Ph, Ar^2: 4–CF_3–C_6H_4). An extra unit (Ar^3: Ph) to bias the stereochemical course

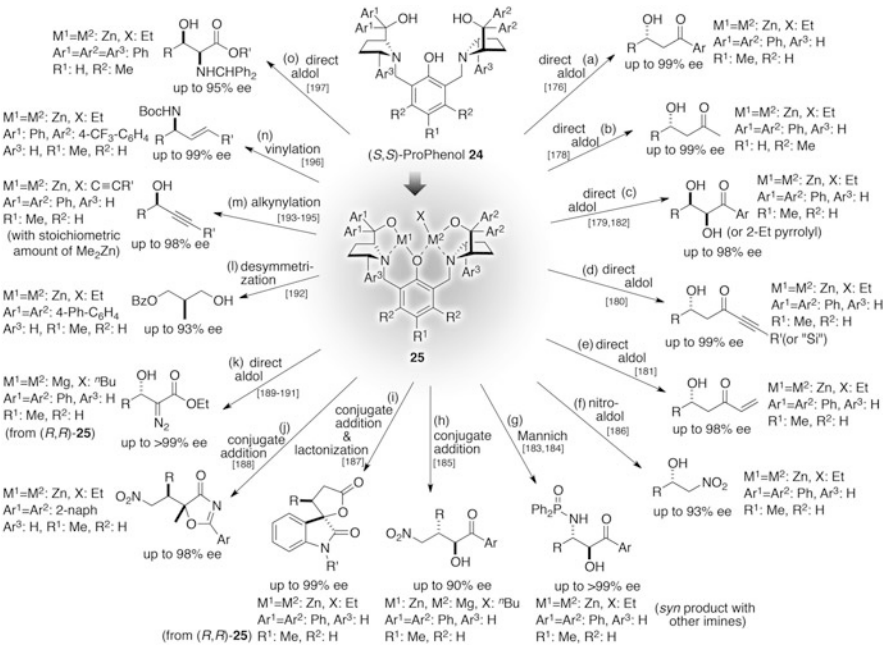
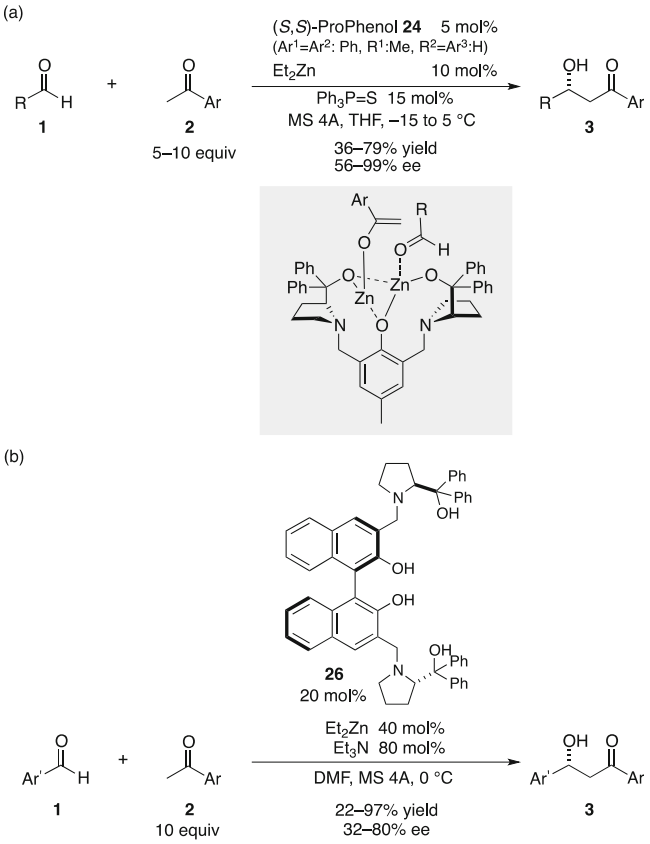


Fig. 9 Utility of hetero- and homobimetallic complexes of ProPhenol **24** in catalytic asymmetric transformations

was essential for an aldol reaction of Schiff base nucleophiles to achieve high stereoselectivity (Fig. 9o) [197]. These enantioenriched products have been applied to the enantioselective synthesis of a number of natural products [198–210].

Shibasaki and Kumagai et al. introduced an α-amino acid-derived ligand platform **27** bearing two phenolic hydroxyl groups tethered by two amide linkages (Fig. 10) [211, 212]. **27** constitutes a useful catalytic system in combination with rare earth metals to promote several catalytic asymmetric transformations. Metal coordination and hydrogen bonding synergistically function to exhibit decent stereochemical control. This amide-based ligand was also effective for constructing heterobimetallic catalysts to deploy a bifunctional activation mode. The combination of rare earth metals and alkali metals with **27** produces a heterobimetallic catalyst with particular utility for stereoselective addition of nitroalkanes to aldehydes and imines, where rare earth metals activate electrophiles as a Lewis acid and an alkali metal phenoxide moiety functions as a Brønsted base to generate nucleophilically active nitronate (Fig. 10a, b) [213–215]. A soft Lewis acid function was implemented for the La-Ag-**27** catalyst to promote a catalytic asymmetric Conia-ene reaction, in which Ag functions as a π-acid to electrophilically activate a triple bond to facilitate the intramolecular addition of an enolate derived from an α-ketoester moiety (Fig. 10c) [216]. In particular, the *anti*-selective catalytic asymmetric nitroaldol reaction is synthetically valuable for accessing enantioenriched *anti*-1,2-amino alcohols, which are frequently found in a number of biologically active compounds, culminating in enantioselective synthesis of zanamivir [217].



Scheme 6 Direct catalytic asymmetric aldol reactions of aryl methyl ketones promoted by homobimetallic catalysts (**a**) Zn_2-**24** and (**b**) Zn_2-**26**

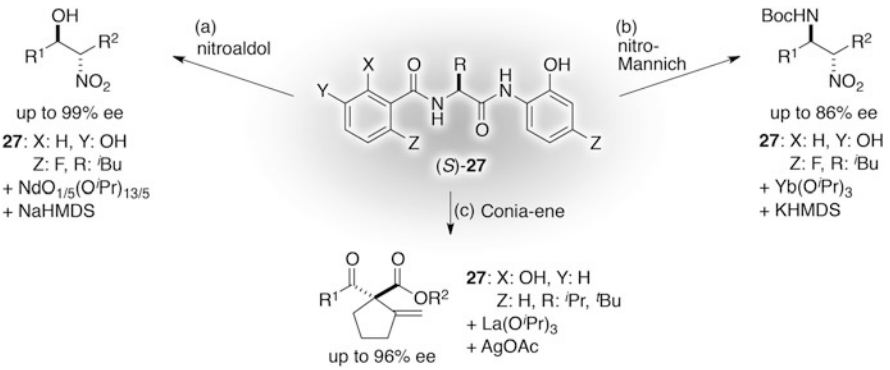
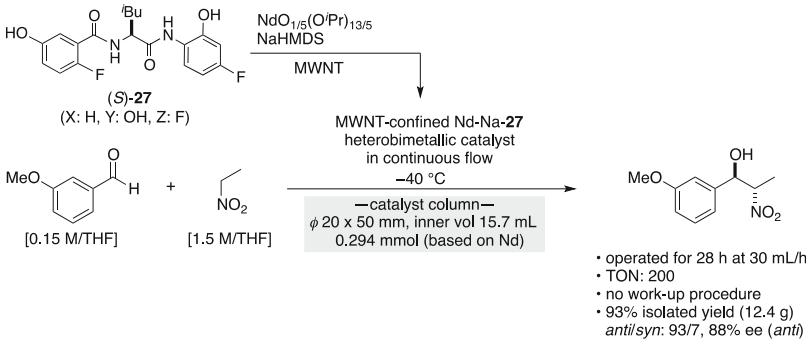


Fig. 10 Utility of heterobimetallic catalysts based on amide-based ligand **27** in catalytic asymmetric transformations



Scheme 7 *Anti*-selective catalytic asymmetric nitroaldol reaction promoted by MWNT-confined Nd-Na-**27** catalyst

Given the importance of this reaction, further efforts have been devoted to the improvement of the heterobimetallic catalyst, culminating in the discovery of a Nd–Na system. In contrast to the majority of asymmetric catalysts, this heterobimetallic catalyst functions as a heterogeneous catalyst prepared by mixing the ligand and the requisite metal salts by self-assembly. Although the stability of the self-assembled power-like catalyst is insufficient for repeated use, a readily recoverable solid phase catalyst is produced by conducting the self-assembly process in the presence of multi-walled carbon nanotubes (MWNT) (Scheme 7) [218, 219]. MWNT is chemically inert and provides nanoscale spaces for self-assembly of Nd-Na-**27** catalysts; self-assembly proceeds in the fibrous network of entangled MWNT, and the grown catalyst is trapped in the network, affording MWNT with highly dispersed catalyst clusters. This MWNT-confined catalyst outperformed the prototype catalyst presumably due to the higher surface area and was successfully implemented in a continuous-flow platform [220].

4.2 Bimetallic Complexes Based on Imidazolines

Peters et al. reported a C_2-symmetric bisimidazoline ligand embedded by a ferrocene core that provided a suitable platform for bimetallic Pd(II) complexes, named $[FBIP\text{-}Cl]_2$ **28** (ferrocene bisimidazoline bispalladacycle) (Fig. 11) [221]. The dimeric **28** is a precatalyst, and pretreatment with Ag(I) salt generates the active monomeric bimetallic Pd catalyst. The counter anion derived from the Ag(I) salt occupies the Pd(II) coordination site *trans* to the Cp ring, and its structure and electronic properties influences catalytic efficiency. The bimetallic Pd catalyst treated with AgOTs exhibited high catalytic performance in the aza-Claisen rearrangement of less reactive *Z*-configured allylic imidates (Fig. 11a) [221–223]. For bimolecular C–C bond-forming reactions, conjugate additions of α-cyanoacetates to electron-deficient olefins were investigated to exploit the

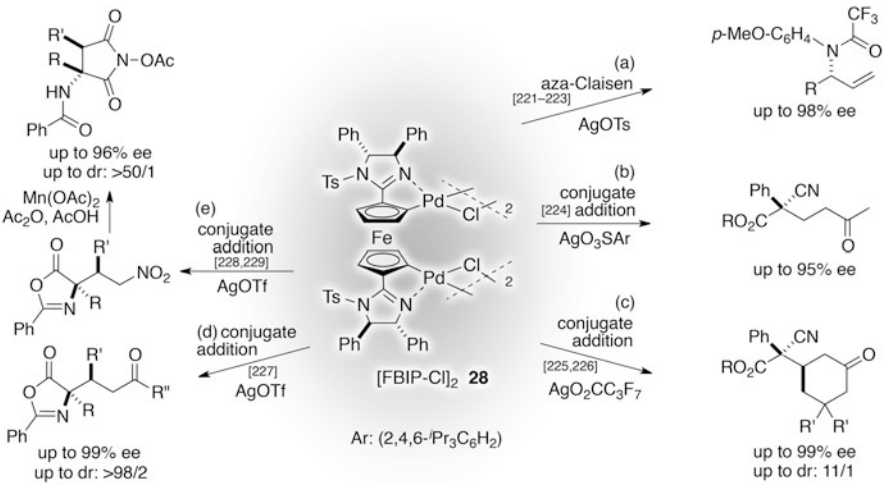


Fig. 11 Utility of bimetallic Pd catalyst [FBIP-Cl]$_2$ **28** in catalytic asymmetric transformations

preferred coordination of nitrile to Pd(II) (Fig. 11b, c) [224–226]. Kinetic studies suggested cooperative activation of pronucleophiles and electrophiles, and the reaction reached completion with as little as 0.02 mol% of catalyst loading. Azlactones are also coordinative to Pd(II) and serve as suitable pronucleophiles in this catalytic system (Fig. 11d) [227]. In situ generation of azlactones from the corresponding benzoyl α-amino acids was compatible with the catalytic conditions using enones as electrophiles, contributing to the overall synthetic utility [228]. The in situ generation of azlactones was valid for the reaction with nitroolefins as electrophiles, and subsequent treatment with $Mn(OAc)_2/Ac_2O$ afforded synthetically useful functionalized succinimide derivatives (Fig. 11e) [229]. Using the ferrocene-embedded bisimide architecture, a Pd-Pt heterobimetallic system was also developed for aza-Claisen rearrangement, and further elaboration in this bimetallic system is anticipated [230].

5 Conclusion

The demand for reliable synthetic methods to produce enantioenriched small molecules is rapidly increasing. Sustainability is an indispensable concept in modern synthetic chemistry, and cooperative catalysis is a highly promising solution to fulfill the growing demand for functionalized homochiral molecules with minimum coproduction of unwanted waste. Despite rapid advances in the field of organocatalysis, several reactions remain that can be promoted only by metal-based catalysts. New bimetallic and multimetallic asymmetric catalysts that exert cooperative activation modes must be developed in the following decades to further increase catalytic efficiency and broaden the reaction scope. Catalyst recycling and

implementation to a continuous-flow platform are underdeveloped and must be actively pursued to evolve laboratory-scale methodology into a robust synthetic technology that can be applied on an industrial scale.

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Chiral Carbophilic Gold Lewis Acid Complexes in Enantioselective Catalysis

Marcel Brill and Steven P. Nolan

Abstract Progress made over the last decade in the development of highly selective homogeneous gold catalysts for enantioselective synthesis is reviewed. Four different classes of gold complexes have been identified and their application in enantioselective catalysis discussed: (1) chiral bisphosphine digold complexes, (2) monogold complexes of chiral monodentate phosphorous ligands, (3) chiral aminocarbene gold complexes, and (4) gold complexes containing chiral phosphate counterions.

Keywords Asymmetric catalysis · Catalysis · Chiral bisphosphine · Chiral counteranion · Chiral NHC · Chiral phosphoramidite · Gold

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1 Introduction

A plethora of homogeneous gold(I)-catalyzed processes has been developed since the beginning of this century with rapid progress and adoption by the scientific community (selected recent reviews: [1–10]). In part, this can be rationalized by the vast number of interesting reactivities exhibited by gold(I) catalysts, especially with respect to the structural diversity of compounds accessible via cycloisomerization reactions [11]. Without doubt, this is partially due to the operational simplicity and stability of gold catalysts that has attracted significant interest from synthetic organic research groups over the years who have continued to push forward the boundaries of the field.

Along this line, enantioselective transformations catalyzed by chiral gold (I) complexes have made significant progress during the past 10 years, and their simplicity of handling could transform them into one of the leading transition metals used in asymmetric catalysis. Since the disclosure of an enantioselective enyne cycloisomerization reaction by Echavarren and co-workers in 2005, the improvements made within a short period of time have, again, been outstanding leading to the sudden appearance of numerous highly enantioselective protocols in 2007 (see following section), which were soon after recognized by the scientific community as quite significant as illustrated by various highlights [12, 13] and reviews [14, 15]. Recently, more specialized reviews have appeared such as a survey on the outstanding contributions from the Toste group [16] and on subclasses of the rapidly growing number of catalyst systems such as those based on chiral carbene ligands [17] or monodentate phosphorus ligands [18].

In view of these impressive developments, it is interesting to note that it had, for long, been considered especially challenging to achieve highly enantioselective processes with gold(I) catalysts due to the intrinsic structural problem originating from a preferred linear coordination. The chirality transfer from a coordinating chiral spectator ligand onto the active metal site residing 180° from the asymmetric ligand was initially believed impossible, although in 1986, Ito and Hayashi had reported a highly enantio- and diastereoselective aldol reaction between isocyano acetate and benzaldehyde catalyzed by a chiral gold(I) complex [19].

As the focus of this review is placed on asymmetric catalysis by means of chiral gold(I) complexes, other asymmetric transformations involving effective chirality transfer within a chiral substrate catalyzed by achiral gold(I) catalysts are not covered. Examples include reactions such as the Claisen rearrangement of enantiopure propargyl vinyl ethers to homoallenic alcohols [20] or the rearrangement of 1-alkynyl-2-alkenyl acetates to cyclopentenones [21].

Furthermore, a highly attractive and emerging field of research combining gold (I) Lewis acid catalysis and chiral Brønsted acid catalysis can also not be presented within the limitations of this chapter (for a recent survey on the field, see [22]). Examples will be presented in which a chiral phosphate-based Brønsted acid is used exclusively for the purpose of generating a chiral gold phosphate species from a proton-labile gold(I) source such as [(L)AuMe] (1:1 stoichiometry of acid and gold).

2 Chiral Bisphosphine Digold(I) Complexes

Nearly 20 years after Ito and Hayashi indicated the potential of gold catalysts for enantioselective transformations [19], the scientific community's interest in the field was ignited (rather than revitalized) by a report from Echavarren and co-workers [23]. The group performed a thorough study on Pt(II)- and Au(I)-catalyzed 1,6-enyne cycloisomerizations using a broad range of mono- and bidentate nitrogen- and phosphorus-based ligands. In the presence of methanol, both metal-catalyzed processes gave the corresponding alkoxycyclization products in low enantioselectivity in the presence of several chiral phosphines. However, the gold(I)-catalyzed process proceeded more readily at room temperature (Pt (II) systems: 60–80°C) and thus enabled an impressive enantioselectivity of up to 94% ee with one particular substrate using a catalyst prepared in situ from a digold complex containing an axially chiral bisphosphine [(Tol-BINAP)$(AuCl)_2$] and $AbSbF_6$ (Fig. 1). This type of precatalyst system provided an important lead structure for later developments in asymmetric gold(I)-catalyzed processes.

In the same year, Corma and co-workers reported that another bisphosphine digold system based on the well-known (*R*,*R*)-Me-DuPhos ligand (Me-DuPhos = 1,2-bis-2,5-dimethylphospholanebenzene) [24, 25] could be applied successfully in enantioselective gold(I) catalysis [26]. The neutral digold catalyst [{[(*R*,*R*)-Me-DuPhos)$(AuCl)_2$] was synthesized and used in the enantioselective hydrogenation of prochiral alkenes and imines (Fig. 2). With the

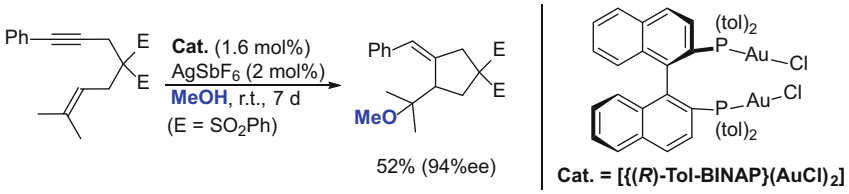
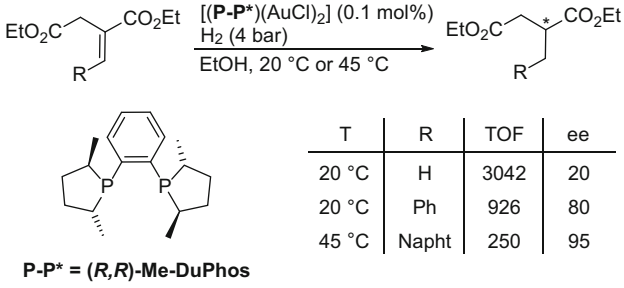


Fig. 1 Enantioselective methoxycyclization of 1,6-enynes using an axially chiral bisphosphine digold system (Echavarren and co-workers 2005 [23])



T	R	TOF	ee
20 °C	H	3042	20
20 °C	Ph	926	80
45 °C	Napht	250	95

Fig. 2 Enantioselective hydrogenation of olefins by a neutral digold complex of (*R*,*R*)-Me-DuPhos (Corma and co-workers 2005 [26])

exception of diethyl itaconate as substrate, it was found that the digold system possessed a similar activity to other third-row transition metal complexes containing the ligand in its chelated form such as [Pt{(*R*,*R*)-Me-DuPhos}Cl_2] and [(Ir(cod){(*R*,*R*)-Me-DuPhos}]PF_6. Regarding the enantioselectivity of the gold-catalyzed process, an impressive 95% ee could be obtained in ethanol as solvent for the bulkiest substrate (diethyl 2-naphthylidenesuccinate) under mild conditions (45°C, 4 bar H_2).

After these reports, chiral dinuclear bisphosphine complexes would be explored with preference as precatalysts in enantioselective gold(I) catalysis, although other concepts for successful asymmetric induction with gold catalysts such as the chiral counterion strategy already followed at the beginning of these developments (see Sect. 5). A great improvement on the Echavarren tested Tol-BINAP system was introduced by the group of Toste who were the first to explore bulky SEGPHOS derivatives containing a 3,5-substitution pattern at its P-donors aryl substituents (see Fig. 3) [27]. This substitution enabled to achieve high levels of enantioselectivity in a series of reactions for more than just a selected substrate. To date most of the successful and widely applied ligands feature an axis of chirality and include a extensive substitution pattern of the P-donors aryl groups (*meta*- and *para*-substitution) rather than one that immediately increases the steric bulk around the coordinated metal center by *ortho*-substitution (Fig. 3).

One of the most common ligands used in enantioselective gold(I)-catalysis today is DTBM-SEGPHOS (see Fig. 3), which was first employed in the asymmetric cyclopropanation of olefins using propargyl esters as gold(I)-carbene precursors [27]. On the basis of the discovered (Ph_3P)Au(I)-catalyzed process, the enantioselective reaction between propargyl pivaloates and styrene derivatives was achieved using a catalytic system of [(*R*)-DTBM-SEGPHOS$(AuCl)_2$] (2.5 mol%) and $AgSbF_6$ (5 mol%) to yield vinyl cyclopropanes with high *cis*-selectivity in up to

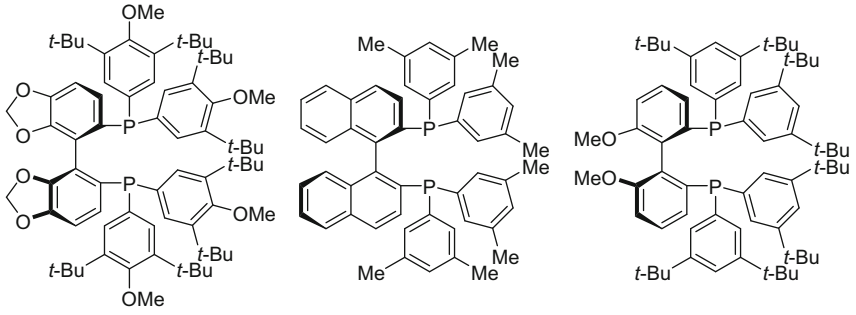
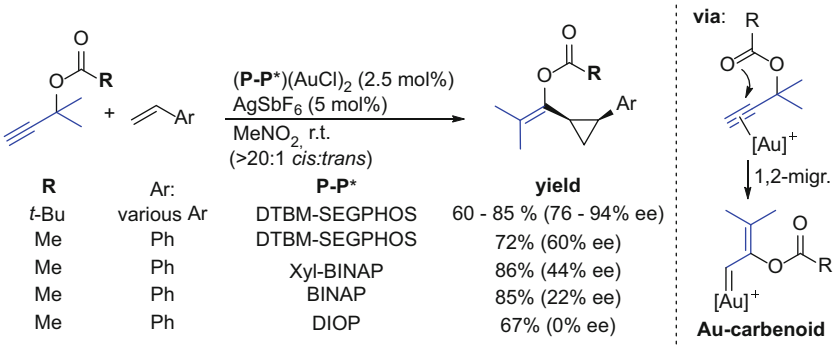


Fig. 3 Chiral bisphosphine ligands applied with high selectivities in gold(I)-catalyzed enantioselective reactions



R	Ar:	P-P*	yield
t-Bu	various Ar	DTBM-SEGPHOS	60 - 85 % (76 - 94% ee)
Me	Ph	DTBM-SEGPHOS	72% (60% ee)
Me	Ph	Xyl-BINAP	86% (44% ee)
Me	Ph	BINAP	85% (22% ee)
Me	Ph	DIOP	67% (0% ee)

Fig. 4 Au(I)-catalyzed stereoselective olefin cyclopropanation using propargyl pivaloates as carbene precursors (Toste and co-workers 2005 [27])

94% ee (Fig. 4). It was discovered that less bulky axially chiral ligands such as (*R*)-BINAP, (*R*)-Xyl-BINAP produced lower ee's with decreasing steric demands, while the well-known chiral bisphosphine DIOP, a ligand introduced at the beginning of the era of C_2-symmetic bidentate ligands (DIOP = 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) [28]), gave racemic product. It was further crucial to use pivaloates in place of acetates and benzoates in order to obtain high levels of enantioselectivity.

2.1 Cycloisomerization of Allenes

Apart from the first previously presented examples of enantioselective Au(I)-catalyzed protocols, the reaction of allenyl groups with internal nucleophiles has historically been the most important method for the construction of stereocenters with gold(I) catalysts. Due to their enhanced reactivity compared to simple alkene double bonds, they enable the direct formation of stereocenters via nucleophilic attack at a π-activated allene group. The sudden emergence of several highly enantioselective gold-catalyzed reactions in 2007 unsurprisingly involved a number of intramolecular reactions between allene functionalities and hydroxyl, amine, and other nucleophilic groups such as arene and alkene moieties. However, intermolecular reactions remain very scarce and will therefore be mentioned in the below and not in a separate section.

2.1.1 Hydroalkoxylation/Amination/Arylation/Alkenylation

Hydroalkoxylation and Hydroamination: Inspired by the promising results of the Echavarren enantioselective 1,6-enyne cyclizations, Widenhoefer and Zhang reported the first intramolecular hydroalkoxylations of γ- and δ-hydroxyallenes proceeding with good to high enantioselectivities [29]. The procedure gave

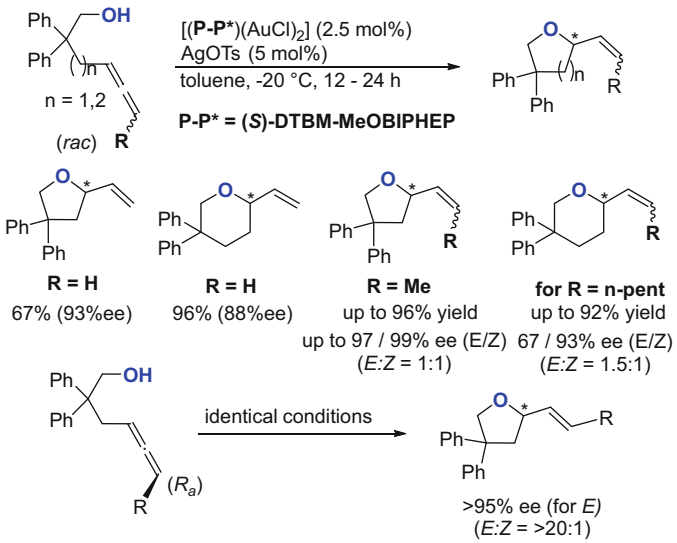


Fig. 5 Enantioselective intramolecular hydroalkoxylation of γ- and δ-hydroxyallenes (Widenhoefer and co-worker 2007 [29])

2-alkenyl tetrahydrofurans or 2-alkenyl tetrahydropyranes in high yields using a catalytic system of [((*S*)-DTBM-MeOBIPHEP)$(AuCl)_2$] (2.5 mol%) and AgOTs (5 mol%) in toluene at −20°C (Fig. 5). The reaction proceeded very rapidly at room temperature (for R = H, >10 min), albeit with slightly reduced enantioselectivity (for R = H, 94 vs 86% ee). Interestingly, it was found that axially chiral allenyl moieties bearing a terminal substituent gave the best results in terms of both yield and enantioselectivity, but with low *E*:*Z* selectivity when racemic substrates were used, thus indicating a stereospecific reaction pathway. Indeed, if an enantioenriched allene was converted under the same reaction conditions, an *E*:*Z* selectivity of >20:1 and high ee were observed. Further, the sp^3-stereocenter was confirmed to be of same configuration for both *E*:*Z* isomers, thus supporting a ligand-controlled generation of the stereocenter in a stereospecific fashion. Noteworthy, the cyclization of δ-hydroxyallenes proceeded just as efficiently, albeit with somewhat lower enantioselectivities. Substrates without geminal disubstitution in the alkyl tether produced very low ee's.

In the same year, Toste and co-workers disclosed a highly enantioselective protocol for the intramolecular hydroamination of γ-aminoallenes [30]. In accordance with Widenhoefer's study [29], the group had also discovered that a digold catalyst derived from (*R*)-Xyl-BINAP performed poorly in the related hydroalkoxylation reaction [31]. However, the investigated complex [(*R*)-Xyl-BINAP {Au(OPNB)}$_2$](OPNB = *para*-nitrobenzoate) catalyzed the analogous hydroamination reactions of γ- and δ-(*N*-tosyl)aminoallenes at room temperature in excellent enantioselectivity and good yields (Fig. 6). Interestingly, in situ generated catalysts from a 1:2 or 1:1 mixture of [{(*R*)-Xyl-BINAP}$(AuCl)_2$] and $AgBF_4$

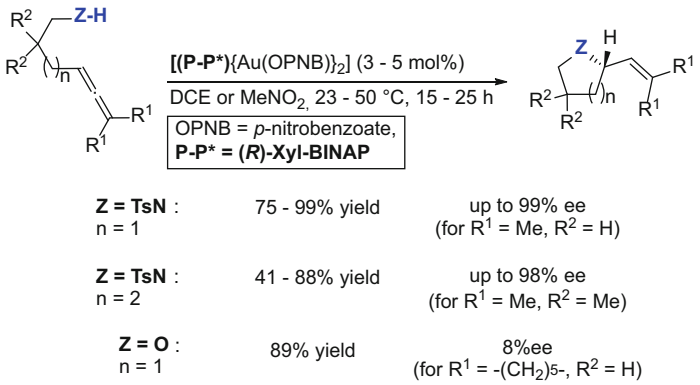


Fig. 6 Asymmetric intramolecular hydroamination [30] and hydroalkoxylation [31] of allenes (Toste and co-workers 2007)

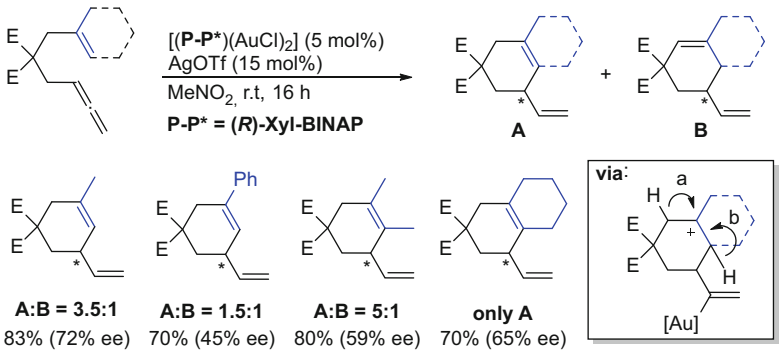


Fig. 7 Selection of enantioselective intramolecular hydroalkenylation products from 1,6-enynes (Gagné and co-workers 2007 [32]; ee of the major isomer is shown)

achieved poor selectivities of 1 or 51% ee, respectively, for the reaction of the model substrate ($R^1 = –CH_2)_5–$; $R^2 = H$). Reaction optimization further revealed that other biaryl-based bisphosphines performed generally well in this reaction, yielding the product with only slightly lower ee but with significantly lower yields. The substrate scope for this reaction was exemplified mainly by changing the substituents at the disubstituted allene terminus, which revealed tolerance of linear and cyclic alkyl chains. 6-exo-trig cyclizations as well as reactions of substrates containing substituents within the linker required a reaction temperature of 50°C in order to reach full conversion.

Hydroalkenylation: In an impressive report by Gagné and co-workers, the cycloisomerization of 1,6-eneallenes was not only achieved for the first time with selectivity towards vinylcyclohexenes, but also in promising enantioselectivities (Fig. 7) [32]. Key to this success for the 6-exo-trig cyclization process, which was catalyzed by a cationic Au(I) catalyst generated in situ from [{(*R*)-Xyl-BINAP}

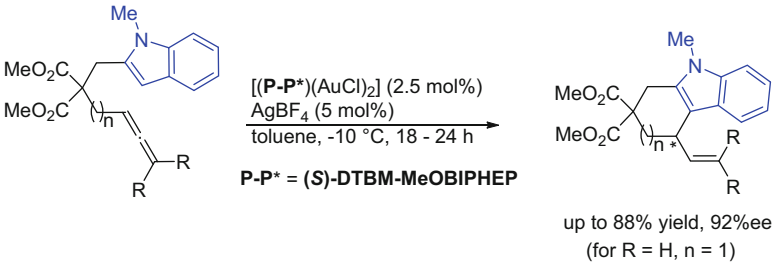


Fig. 8 Enantioselective intramolecular hydroarylation of 2-(allenyl)indoles (Widenhoefer and co-worker 2007 [37])

$(AuCl)_2$] (5 mol%) and AgOTf (15 mol%), was the presence of an additional internal substituent at the alkene moiety. These compounds had previously been reported as unreactive in eneallene cyclizations catalyzed by other transition metals (selected examples, with Rh: [33–36]). Additionally, these reactions predominantly give achiral 5-membered rings over chiral 7-membered ring structures.

The products of the new process were obtained as mixtures of two vinylcyclohexene derivatives differing only with respect to the position of the internal double bond (products **A** and **B**, Fig. 7). Initial screening of the reaction conditions revealed that while the product ratio was somewhat dependent on the solvent, it was strongly controlled by the alkene group substitution pattern. For example, a substrate containing a cyclohexenyl substituent gave only the **A** isomer due to the formation of a tetrasubstituted double bond. Whereas the use of AgOTs delivered high regioselectivity towards product **A**, a significantly enhanced enantioselectivity was obtained with AgOTf, thus revealing a strong counterion effect. Under the optimized conditions, a range of vinylcyclohexenes could be obtained from this challenging transformation with respectable enantioselectivities (up to 72% ee).

Hydroarylation: Widenhoefer and co-workers were able to achieve the enantioselective hydroarylation of 2-allenyl indoles [37] based on their protocol previously disclosed for enantioselective hydroalkoxylation (see above) [29]. A catalytic 1:2 mixture of [(*S*)-DTBM-MeOBIPHEP] and $AgBF_4$ in toluene at −10°C gave tetrahydrocarbazoles in high yields and up to 92% ee (Fig. 8).

An intermolecular variant of this reaction was studied in 2011 by Che and co-workers [38]. Several of the typical chiral bisphosphine digold systems of the type [(P-P*)$(AuCl)_2$] (2.5 mol%) in combination with AgOTf (5 mol%) in this case only afforded low enantioselectivities in the model coupling of *N*-methyl indole and 1,3-di-tolylallene to the corresponding 3-substituted indole (Fig. 9). The best catalyst, containing (*S*)-MeOBIPHEP as ligand, gave good yields and low to moderate ee's in the arylation of 1,3-diaryl-substituted allenes of substituted *N*-methyl indoles. A Hammett plot derived from the relative reaction rates of the hydroarylation of 4-X-aryl-substituted 1,3-diarylallenes with *N*-methylindole indicated a positive charge buildup at the allene and the electrophilic nature of the reactive Au^I species in the transition state. DFT calculations suggested a pathway proceeding via an outer-sphere intermolecular nucleophilic addition of free indole

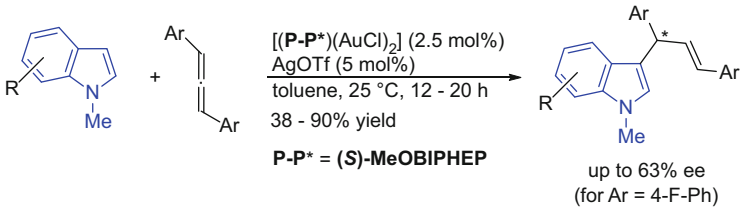


Fig. 9 Catalyzed enantioselective intermolecular hydroarylation of allenes with indoles (Che and co-workers 2011 [38])

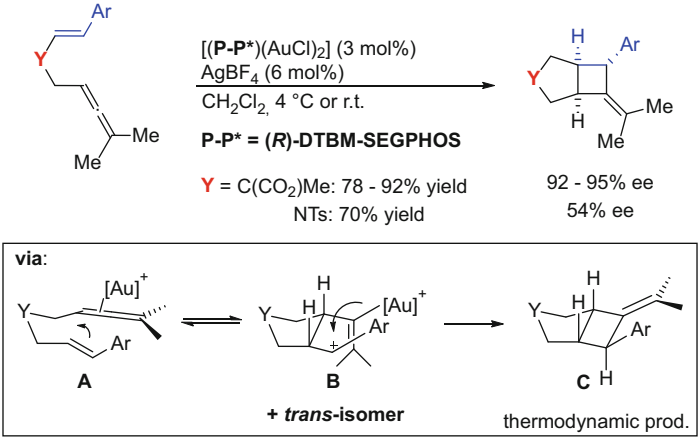


Fig. 10 Enantioselective intramolecular [2+2] cycloaddition of γ-eneallenes (Toste and co-workers [39])

to a gold–allene species rather than via the intramolecular reaction between a 3-aurated indole and a gold-activated allene species both attached to the P-donors of the bisphosphine system.

2.1.2 [2 + 2]-Cycloaddition

Toste and co-workers reported that the intramolecular formal [2 + 2] cycloaddition of γ-eneallenes containing aryl-substituted *E*-configured double bonds were converted stereoselectively into *cis*-cyclobutanes by a mixture of [Au(PPh_3)Cl] and $AgBF_4$ (5 mol%) [39]. Based on these results, the enantioselective version was developed using a 1:2 mixture of [(*R*)-DTBM-SEGPHOS($AuCl)_2$] and $AgBF_4$ providing the bicyclic products in good yields and excellent enantioselectivities (Fig. 10) [39]. In contrast to the excellent selectivitities obtained by variation of the styrenyl group, the change from ageminal-dicarboxylate ester groups in the tether to an *N*-tosyl group led to a significantly lower ee (54%). A mechanistic proposal for

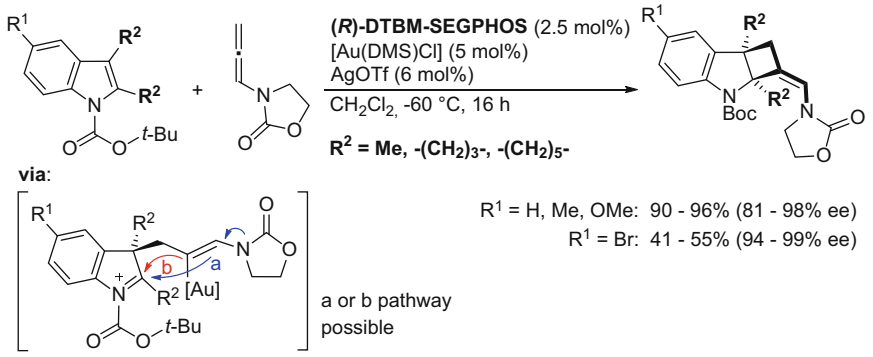


Fig. 11 Enantioselective intermolecular [2 + 2] cycloaddition of indoles and allenecarbamates (Bandini and co-workers 2015 [40])

the stereochemistry of the bicyclic ring system was presented based on an initial reversible cyclization of the gold(I)-activated allene **A** to *cis* or *trans*-cyclopentane vinyl gold species **B**. Subsequent attack of the vinyl gold on the benzylic carbocation gives the cyclobutane structure **C** with the aryl substituent in *cis*-relation to the bridgehead hydrogen atoms.

Very recently the first intermolecular approach to this reaction type was reported by Bandini and co-workers [40]. They were able to demonstrate that the dearomative [2 + 2] cycloaddition between *N*-EWG-substituted indoles (EWG = electron-withdrawing group) and allene carbamides furnishes methylenecyclobutane-fused indolines (Fig. 11) instead of the simple 3-substituted indole hydroarylation products, which are usually generated with *N*-alkyl substituted systems (see previous section 2.1.1). Again, a (*R*)-DTBM-SEGPHOS-based system proved the most efficient among a number of bidentate chiral ligands and a monodentate phosphorus amidite. Reaction optimization revealed that a low reaction temperature of −60°C was not only required to obtain high ee values, but also needed to favor the chemoselectivity of the process towards the desired cycloadduct. The optimal catalytic system was generated in situ from the ligand (2.5 mol %), [Au(DMS)Cl] (DMS = dimethylsulfide), and AgOTf in a 1:2:2 ratio and was able to efficiently generate a series of cycloadducts with two consecutive quaternary stereogenic centers in high diastereoselectivity (>20:1 dr) and excellent enantioselectivity. The scope of the reaction showed tolerance of various substituents at the aryl moiety of the indole and that the reaction is well suited for the assembly of tricyclic products in high yields (for $R^2 = -(CH_2)_n$-, $n = 3,5$).

2.1.3 Ring Expansion

Allenylcyclopropanols were shown to undergo enantioselective ring expansion to cyclobutanones bearing vinyl-substituted quaternary stereogenic centers upon treatment with the typical cationic bisphosphine digold systems derived from the

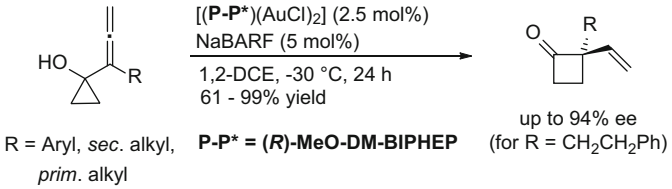


Fig. 12 Enantioselective ring expansion of allenylcyclopropanols (Toste and co-workers 2009 [41])

BIPHEP and BINAP ligand family (Fig. 12) [41]. Initial optimization of the reaction conditions in 1,2-DCE (DCE = dichloroethane) as solvent revealed an increase in enantioselectivity with lowering of temperature (−30°C) and by using a weakly coordinating counterion such as BARF (NaBARF = sodium tetrakis [3,5-bis(trifluoromethyl)phenyl]borate). Under these conditions, a range of substrates containing aryl and alkyl groups as second terminal allene substituent were transformed into the 4-membered rings in generally good enantioselectivities (84–94% ee). The effectiveness of the procedure was demonstrated on a 1.5 mmol scale (R = CH_2CH_2Ph) which required the use of only 0.5 mol% catalyst to deliver the product in high yield with only slightly reduced ee in comparison to the reaction at higher loading (89 *vs* 94% ee, respectively).

2.2 Cycloisomerization of Alkynes

2.2.1 Reactions of Enynes

1,5-Enynes: In the presence of the catalytic system [Au(PPh_3)Cl]/$AgSbF_6$ (5 mol %), o*rtho*-(alkynyl)styrenes with terminal dialkyl substitution at the alkene moiety were shown to undergo an unprecedented 5-endo-dig cycloisomerization by Sanz and co-workers [42]. In contrast to previous reports, including other transition metal-catalyzed processes (for selected examples, see [43–46]), the reaction yields indenes with a stereogenic center at C1 instead of naphthalene derivatives arising from the typical 6-endo-dig cyclization process. The enantioselective protocol of the reaction was carried out in CH_2Cl_2 at −30°C in the presence of a 1:2 mixture of [(*R*)-Xyl-MeOBIPHEP($AuCl)_2$] and AgOTs to give the products in high yields (>80%) and good enantioselectivities of up to 86% ee. In agreement with the proposed mechanism proceeding via an initial 5-endo-dig cyclization (Fig. 13), the presence of water or alcohol (30 equiv.) was able to trap the generated carbocation species **B**, to give the corresponding alkoxycyclization product. These compounds were obtained as well in high yield and up to 92% ee. Recrystallization was able to furnish ee values of greater than 98%.

1,6-Enynes: Similar to the enantioselective alkoxycyclization of 1,6-enynes reported in the Echavarren seminal publication (Fig. 1) [23], Michelet and

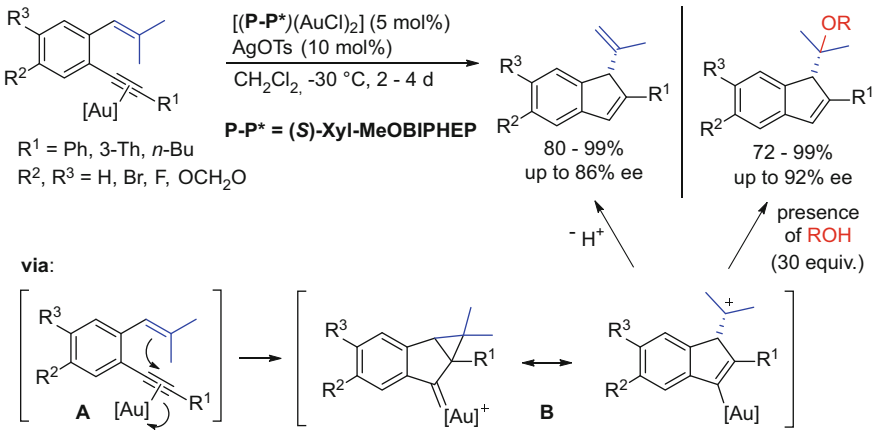


Fig. 13 Enantioselective synthesis of functionalized indenes via cycloisomerization of *ortho*-alkynyl-styrenes (Sanz and co-workers 2010 [42])

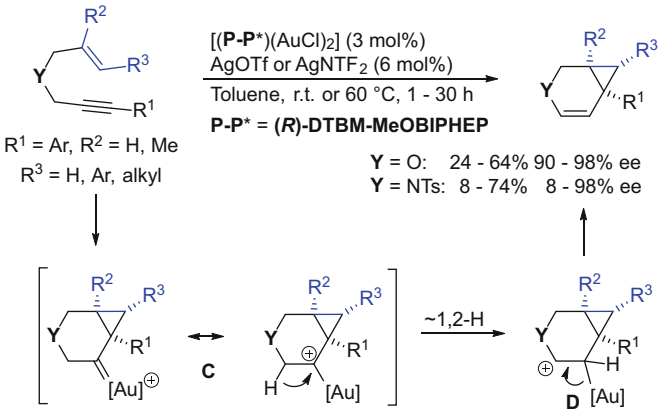


Fig. 14 Enantioselective cycloisomerization of 1,6-enynes to bicyclo[4.1.0]heptenes (Michelet and co-workers 2009 [48] and 2011 [49])

co-workers disclosed a Friedel–Crafts/cyclization sequence in 2009, based on the replacement of the external alcohol by an electron-rich arene or heteroarene system as the external nucleophile [47]. In the presence of one of the established biphenyl catalyst systems bearing a DTBM substitution, generally high yields and enantioselectivities of up to 98% could be achieved.

Based on this experience, the group developed an enantioselective synthesis of bicyclo[4,10]heptenes via cycloisomerization of heteroatom-linked 1,6-enynes catalyzed by [(*R*)-DTBM-MeOBIPHEP(AuCl)$_2$] (3 mol%) and a silver salt (AgOTf) in a 1:2 ratio (Fig. 14) [48]. These bicyclic structures are known to be formed with platinum (see, for example, [50–52]) or gold catalysts [53], specifically with heteroatom-tethered enynes as substrates (for a review on cyclopropane

formation via cycloisomerization, see [54]). Enantiomeric excesses were strongly dependent on the reaction solvent and could be slightly increased by lowering the temperature to 0°C. Thus, a range of allyl propargyl ethers with a variety of aryl substituents at the alkynyl carbon atom were cycloisomerized with perfect diastereoselectivity and generally high enantioselectivity (>90% ee), albeit in low to moderate yields (24–64%). It was found that a nitrogen-linked allyl and 3-phenylpropargyl substituted system reacted significantly slower, prompting the authors to increase the reaction temperature. Intriguingly, a higher enantiomeric excess was obtained in these cases (40 and 60°C: 98% ee) compared to the result obtained at room temperature (78% ee).

The substrate scope was later extended to a broad range of differently substituted substrates bearing up to three substituents on the alkene part in place of the previously investigated styrenyl systems (where $R^2 = H$) to even yield penta-substituted cyclopropyl systems in high enantioselectivities (Fig. 14) [49]. However, nitrogen-tethered substrates were found to give lower yields and often very low enantioselectivities (8–98% ee). The stereochemistry of the process was explained by a similar pathway proposed for Pt-catalyzed reactions [50] via the stereospecific formation of a cyclopropane gold carbenoid species **C** generated by the initial 6-endo attack of the alkene on the gold-activated triple bond. The following 1,2-hydride shift and deauration permit the formation of the internal cyclohexene double bond.

Functionalized 1,6-Enynes and Diene-ynes: Proton- or Lewis acid-catalyzed polyene cyclizations are among the synthetically most intriguing and powerful methods for the stereoselective construction of polycyclic compounds (for reviews on enzymatic polyene cyclizations, see [55, 56]). In this context, Toste and co-workers hypothesized that polycyclization reactions which are initiated by the activation of an alkyne could offer great potential as unwanted nonselective alkene activations could thereby be minimized.

The concept and the utility of chiral gold(I) complexes in the enantioselective version of these reactions was first tested in the dicyclization of a 1,6-enyne substrate featuring a β-carboxylate group at the terminal alkene position using a typical digold catalyst system [(*R*)-DTB-MeOBIPHEP$(AuCl)_2$]/$AgSbF_6$ to give the intramolecular carboxy cyclization product in good yield and high ee (86%, 92% ee) (Fig. 15) [57]. The cyclization cascade was reported to be the first of its kind proceeding by an initial alkyne activation step and enabled the use of several other internal nucleophiles for the termination step such as hydroxy, amino, and even nucleophilic arene groups (see Fig. 15). Most impressively, the protocol could be extended to non-conjugated diene-yne systems to give the corresponding tricyclization product in respectable yields (50–61%) and high ee's (88–97%) (selected example shown in Fig. 15). In all cases, single diastereomers formed in accordance with the stereochemistry defined by a Stork–Eschenmoser-type transition state for polyene cyclization [58, 59].

1,n-Enynes (n = 7, 8): Building upon their discoveries in the Au(I)-catalyzed cyclopropanation of styrenes using propargyl pivaloates as carbene equivalents (see Sect. 2, Introduction), Toste and co-workers were able to use the methodology for

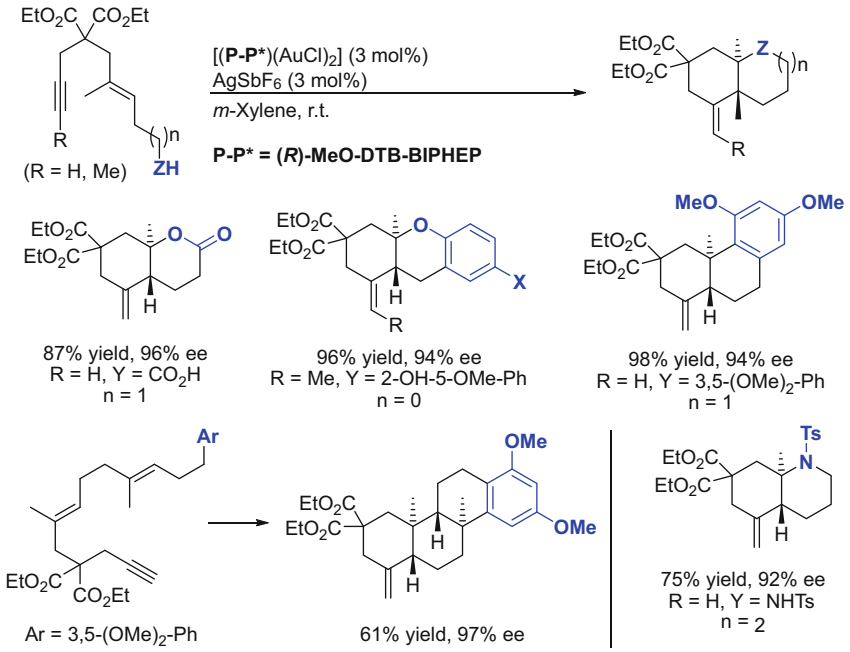


Fig. 15 Enantio- and diastereoselective di- and tricyclization of functionalized enyne systems (Toste and co-workers 2010 [57])

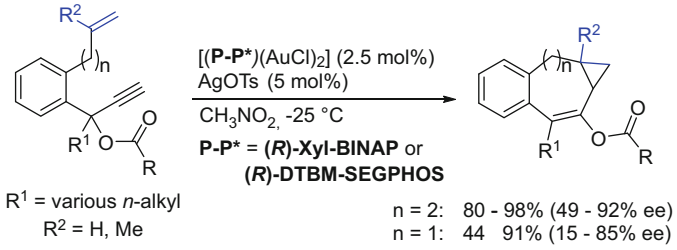


Fig. 16 Enantioselective intramolecular cyclopropanation of 1,7- and 1,8-enynes (Toste and co-workers 2009 [60])

the synthesis of medium-sized rings in the intramolecular variant of this process. Using [(*R*)-Xyl-BINAP(AuCl)$_2$]/AgSbF$_6$ (2.5 / 5 mol%) as catalyst system, 1-phenyl-propargylic acetate substrates containing allyl or homoallyl substituents attached in *ortho*-position of the phenyl ring gave cyclopropanated 7- and 8-membered rings at −25°C in MeNO$_2$ in moderate to high yields and up to 92% ee (Fig. 16). Noteworthy, the analogous reactions to give 6- or 9-membered ring structures (by shortening or lengthening the alkyl chain of the alkene tether) gave much lower yields and were thus excluded from the reaction scope. Additionally,

the 7-membered ring products were obtained in generally lower yields and enantioselectivities than cyclooctene products.

2.2.2 Hydroalkoxylation and Hydroamination

Unlike the intramolecular addition of O- and N-nucleophiles to allene moieties, the analogous alkyne reactions do not lead to the direct formation stereocenters. To overcome this limitation, the group of Uemura have been particularly active in the development of asymmetric transformations using chiral Au(I)-based desymmetrization strategies involving arylacetylene derivatives containing tethered nucleophiles in both *ortho*-positions. For the first investigated reaction, an asymmetric process was possible by rendering the nucleophilic groups enantiotopic through the coordination of a chromium tricarbonyl fragment to the arene.

Indeed, prochiral 1,3-dihydroxymethyl-2-alkynylbenzene chromium complexes were found to yield planar chiral 1*H*-isochromene chromium complexes in high enantioselectivity via intramolecular hydroalkoxylation using established digold catalysts of the type [(P-P*)$(AuCl)_2$] (10 mol%)(P-P* = axially chiral bisphosphine) and a silver salt (20 mol%) (Fig. 17) [61]. Using any of the investigated ligands of the BINAP ligand family (e.g., (*R*)-BINAP or (*R*)-Xyl-BINAP) in combination with $AgSbF_6$ as a halide abstractor led to good yields and excellent enantioselectivities in CH_2Cl_2 at room temperature. On the other hand, (*R*)-SEGPHOS led to the formation of the opposite enantiomer of the chromium complex and low selectivity (27–48% ee). In a later report, this group was able to extend the methodology to internal carbamate nucleophiles giving the corresponding 1,2-dihydroisoquinolines in somewhat reduced yields but in excellent enantioselectivity (Fig. 17) [62].

Chromium-free enantioselective cyclizations were possible by using a similar protocol for the desymmetrization of *meso*-2-alkynylbenzenediols or kinetic resolution of the corresponding D,L-diols (Fig. 18) [63]. Notably, the kinetic resolution reaction proceeded very efficiently to give the cyclized isochromenes as well as the unreacted diols after 50% conversion in high yields and enantioselectivities. In this reaction, mononuclear phosphoramidite-based catalysts, which have gained

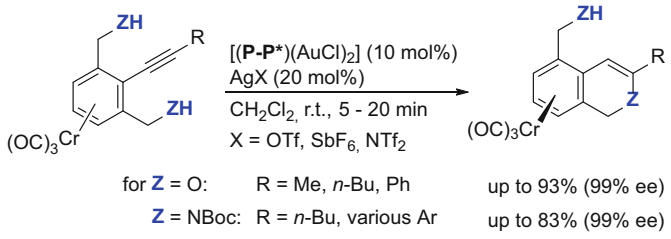


Fig. 17 Asymmetric synthesis of planar chiral arene chromium tricarbonyl complexes (Uemura and co-workers 2010 [61] and 2013 [62])

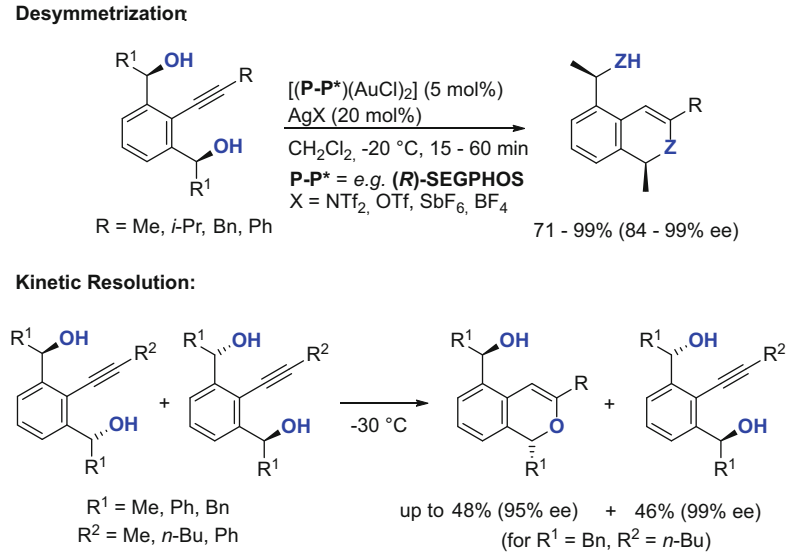


Fig. 18 Synthesis of enantioenriched 1*h*-isochromenes via desymmetrization or kinetic resolution of 2-alkynylbenzenediols (Uemura and co-workers 2010 [61] and 2015 [63])

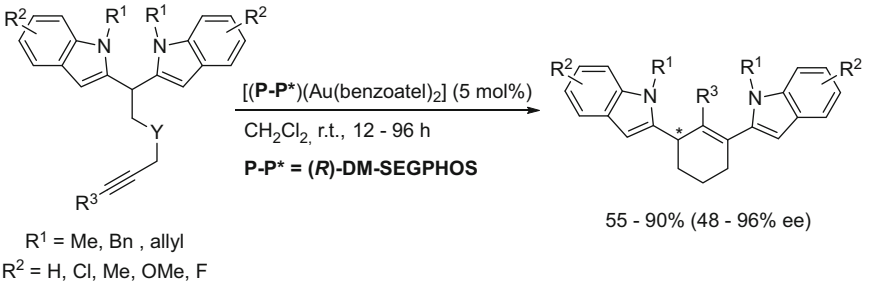


Fig. 19 Enantioselective functionalization of unreactive csp^3–h bonds through a redox–neutral domino reaction (Xu, Shi and co-workers 2013 [64])

increased attention as of late (see Sect. 3), performed with low yields and selectivity.

2.2.3 Other Cycloisomerizations

Cycloisomerization via Hydroarylation: An interesting reaction type was discovered by Xu, Shi, and co-workers that involves the cycloisomerization of 1,1-bis (indolyl)-5-alkynes to give cyclohexene bis(indole) alkaloids (Fig. 19) [64]. The formation of the product was rationalized by a mechanistic proposal consisting of initial 6-endo-dig cyclization to give a spiro alkenyl gold species followed by a

pseudo 1,5 migration of the nucleophilic indole. The intermediately formed conjugated iminium system is then attacked by the alkenyl gold nucleophile. It was discovered that isolated digold catalysts of the type [(*R*)-DM-SEGPHOS{Au(benzoate)}$_2$] (benzoate = e.g., ODTfB: 3,5-di(trifluoromethyl)benzoate, OPNB – *para*-nitrobenzoate) performed with higher yields and selectivity than catalysts prepared in situ from the corresponding gold chloride complex and a silver salt. The intramolecular hydroarylation product arising from a 7-exo-dig cyclization via nucleophilic attack of the indole C3-position to give alkylidene-azepines was identified as an operating side reaction. The desired products were generated in low to high selectivity over the azepine byproducts leading to moderate to excellent isolated yields (55–90%). Enantioselectivities ranged from low to high (48–96% ee) [65].

Cycloisomerization via Formal C–H Activation: Zhou and Zhang were able to specifically exploit the strongly carbophilic character of Au(I) Lewis acids for a redox–neutral domino reaction to generate furan-fused tetrahydroazepins in 2010 [65]. Yne-enone systems such as **A** were demonstrated to undergo a cascade reaction involving heterocyclization/1,5-hydride shift/cyclization with a catalyst system comprised of [(*R*)-Xyl-BINAP(AuCl)$_2$]/AgSbF$_6$ (5 mol%) in a 1:1 ratio (Fig. 20) [66]. On the other hand, the application of an oxophilic Lewis acid such as Sc(OTf)$_3$ does not trigger an initial cyclization of the yne-enone system, due to a lack of π-activation of the alkyne. In this case, the formation of tetrahydroquinolines via a 1,5-hydride shift/cyclization sequence was observed, proceeding possibly via an *O*-metal enolate intermediate. Impressive yields of mostly >80% and ee values ranging from 77 to 99% were obtained from this multistep reaction cascade at room temperature in CH_3CN as solvent.

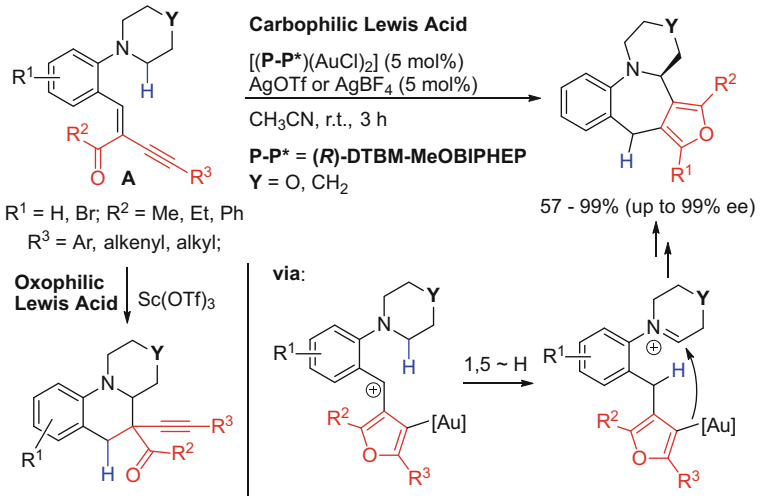


Fig. 20 Enantioselective domino reaction via a heterocyclization/1,5-hydride shift/cyclization cascade (Zhang and co-workers 2010 [65] and 2011 [66])

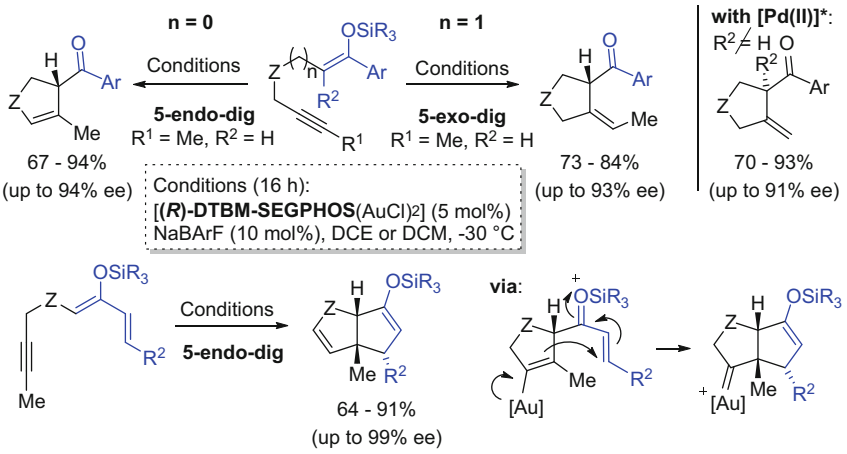


Fig. 21 Enantioselective cyclizations of silyloxyenynes (Toste and co-workers 2012 [64])

2.2.4 Other Transformations Proceeding via Cycloisomerization

Several new asymmetric cyclization strategies which are not based on previously disclosed racemic processes have been explored by Toste and co-workers. In 2012 they reported various cyclization reactions of siloxyenynes [67]. Access to highly enantioenriched chiral cyclopentenes and alkylidene cyclopentanes were achieved at −30°C in DCE via 5-endo-dig and 5-exo-dig cyclizations of 1,5- and 1,6-silyloxyenynes bearing internal alkyne functionalities (Fig. 21). As usual, the established dinuclear complexes derived from axially chiral bisphosphine derivatives showed the best results – in this case in combination with NaBARF as halide abstractor in place of the usual silver salts. Since reactions carried out in the presence of silver salts produced low conversions due to hydrolysis of the enolsilane, the formation of traces of acid from the silver salts was associated with this event.

A complementary reactivity was observed for chiral Pd(II) catalysts which preferentially achieved the enantioselective 5-exo-dig cyclization of 1,6-silyloxyenynes with a terminal alkyne group to give exomethylenecyclopentanes. However, unlike the Au(I) system, these catalysts proved unreactive towards substrates with internal alkyne groups. The use of silyloxy-1,3-dien-7-ynes as substrates led to the formation of polysubstituted bicyclo[3.3.0]octane derivatives with high diastereoselectivies and excellent enantioselectivities (up to >20:1 dr and 99% ee).

Carboalkoxylation: An interesting conversion of *ortho*-(dimethoxymethyl)-ethynylbenzenes to chiral β-alkoxyindanone derivatives was achieved by Zi and Toste using [(*R*)-DTBM-MeOBIPHEP$(AuCl)_2$]/$AgSbF_6$ (2.5 mol%) in the presence of 4 Å molecular sieves (Fig. 22) [68]. The indanone was obtained after acid workup due to hydrolysis of the carboalkoxylation product **C**. Its highly

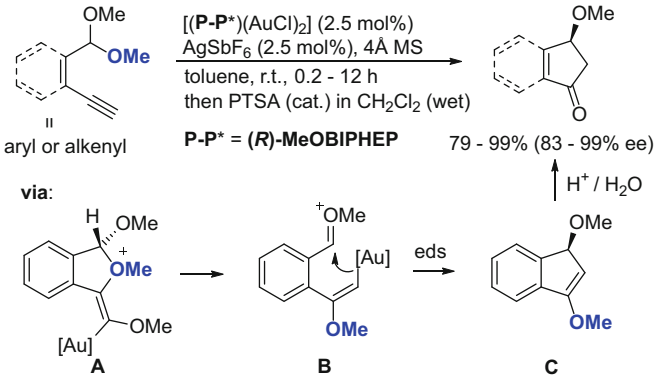


Fig. 22 Enantioselective carboalkoxylation of alkynes (Toste and co-workers 2013 [67])

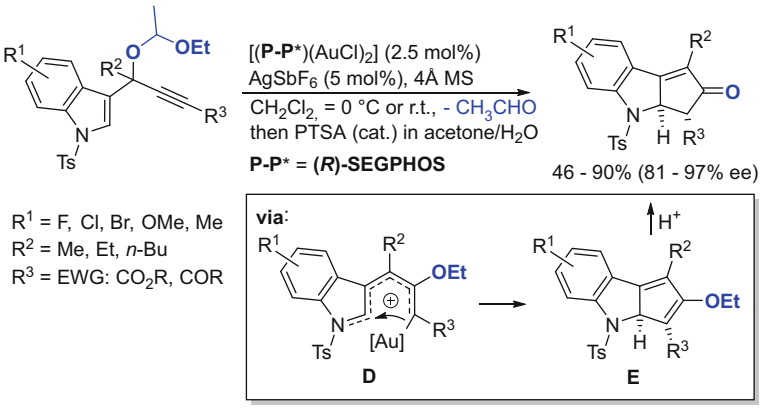


Fig. 23 Dearomative Rautenstrauch rearrangement: enantioselective access to cyclopenta[b] indoles (Toste and co-workers 2015 [68])

enantioselective formation was explained due to the generation of the planar intermediate **B** via ring opening of the short-lived species **A**. The internal attack of the vinyl gold nucleophile in **B** on the prochiral oxocarbenium group as enantiodetermining step was proposed as the origin of the induction with high levels of enantioselectivity, as this should represent a purely ligand-controlled step. Evidence for such a pathway was provided by a mechanistic study on diastereomeric mixed acetals (one OMe group is replaced by a methyl lactate group), which showed that the d.r. present in the substrate strongly changed upon conversion to the product, indicating a catalyst controlled diastereoselectivity. A range of substituted aryl acetylenes as well as a few vinyl acetylenes were shown to be efficiently converted into the corresponding chiral alkoxy carbacycles in generally high yields and good to excellent enantioselectivities (83–99% ee).

In a very similar protocol, but using a 1:2 ratio of digold complex and $AgSbF_6$, Toste and co-workers very recently achieved a highly enantioselective dearomative Rautenstrauch rearrangement (Fig. 23) [69] – historically discovered as the

Pd-catalyzed rearrangement of 1-alkynyl-2-alkenyl acetates to cyclopentenones [70]. In the new reaction, the former alkenyl group is replaced by the reactive aromatic double bond of an indenyl ring system.

Conceptionally, the work was also based on the previous carboalkoxylation study with respect to the use of a ketalin place of an acetate group used in the original rearrangement reaction. This, again, should ensure the formation of a fully planar and achiral intermediate (**D**) which then undergoes cyclization in a ligand-controlled manner. Indeed, the enantioselectivities observed for reactions involving propargylic ketals were dramatically higher (81–97%) than those of the corresponding acetate analogs. Again, the final products, indole-fused cyclopentenones, were obtained after acidic workup in moderate to high yields (46–90%).

3 Chiral Gold(I) Complexes of Monodentate P-Based Ligands

For a long time it was considered improbable to achieve efficient chiral induction with Au(I) catalysts derived from monodentate ligand structures, due to the challenging task to encapsulate a linear gold fragment within a defined chiral environment using only one binding site. However, it had also been acknowledged for some time that the well-studied chiral bisphosphine digold systems often provide higher enantioselectivities if the active cationic species is generated by the use of only one equivalent of halide abstractor (see Sect. 2) (for ligand effects in gold(I) catalysis, see [71]). Formally, the generated species could structurally resemble the cationic complex of an axially chiral monodentate phosphine in which the gold center is placed in a somewhat more defined chiral environment due to the presence of the second "AuCl-protected" phosphine moiety.

Moreover, the reason for the effectiveness of the commonly generated dicationic systems of these systems still remains unclear. Whether they act as separate chiral monogold entities rather than by cooperativity between the two metal centers (as the origin for high levels of chiral induction) has rarely been investigated. DFT calculations performed as part of a recent study on an intermolecular hydroarylation of allenes, for example, revealed an unfavorable digold pathway in the intramolecular reaction across two gold species (see Sect. 2.1.1). Based on the calculations of the intermolecular reaction pathway (only one gold-substrate species), a direct relationship between Au–Au interactions and the enantioselectivity of the process was proposed. Further hints for possible metal cooperativity were provided by Gade and co-workers in their study of mono-, di-, and trinuclear gold complexes of C_2 and C_3 symmetric chiral phospholane ligands [72]. Here, a dramatic increase of enantioselectivity was observed in the asymmetric

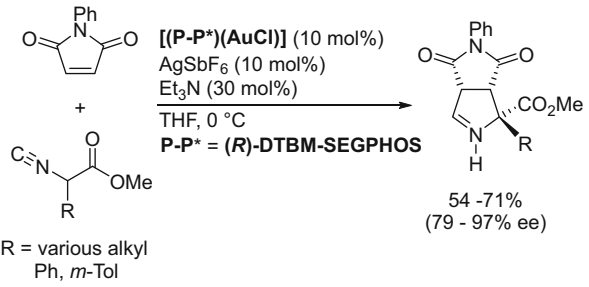


Fig. 24 Asymmetric formal [3 + 2] cycloaddition of isocyanoacetates with maleimides (Adrio, Carretero, and co-workers 2012 [73])

cyclohydroamination of *N*-protected γ-allenyl sulfonamides with an increase in nuclearity.

In a recent study by Adrio and Carretero, not only the ratio between a bisphosphine digold complex and the halide abstractor was investigated, but also the comparison between the ligands monogold and digold system [73]. The formal [3 + 2] cycloaddition between isocyanoacetates with phenylmaleimide was achieved diastereoselectively and in up to 97% ee (Fig. 24). The monogold catalytic system [(*R*)-DTBM-SEGPHOS(AuCl)]/$AgSbF_6$ (10 mol%), in the presence of NEt_3 as base (30 mol%), gave the chiral 1-substituted pyrrolines in similar yields and enantioselectivity than its corresponding digold system used at the same catalyst loading.

Due to the higher metal content of the digold complex, the mononuclear system was employed in the reaction scope, which consisted of a variety of 1-alkyl- and 1-aryl-substituted isocyanoacetates. The products were obtained in moderate yields and in high *cis*-diastereoselectivity and good to high enantioselectivities, especially in the presence of bulky 1-substituents (R = *i*-Pr, *s*-Bu, *t*-Bu, 95–97% ee). Although the nature of the active catalyst still remains speculative, the work represents yet another example supporting that monogold catalysts can indeed lead to the induction of high levels of enantioselectivity.

Despite these indications that mononuclear or even monodentate species might have already played some part in the many highly enantioselective reactions catalyzed by the bisphosphine-based systems, a true paradigm shift was observed by the introduction of chiral phosphoramidite ligands into enantioselective Au(I)-catalysis in 2009 (See following section). These ligands were able to unambiguously show that, indeed, very high levels of enantioselectivity can be induced with mononuclear complexes of monodentate ligands.

3.1 Phosphoramidite and Phosphite Ligands

Chiral phosphoramidite ligands play a pivotal role in modern asymmetric transition metal catalysis [74]. Their great structural variability, most typically achieved by

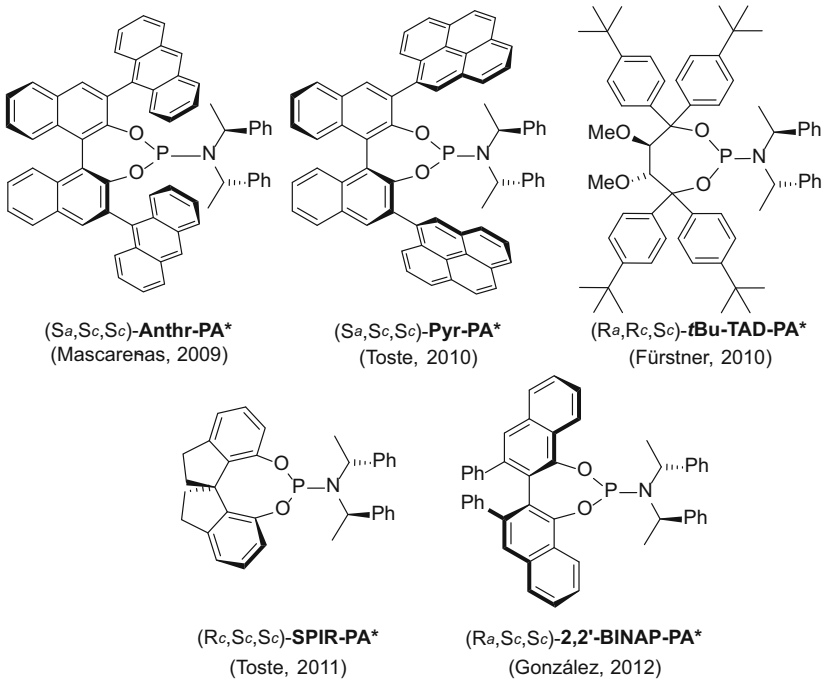


Fig. 25 Chiral monodentate phosphite and phosphoramidite ligands applied with high selectivities in gold(I)-catalyzed enantioselective reactions

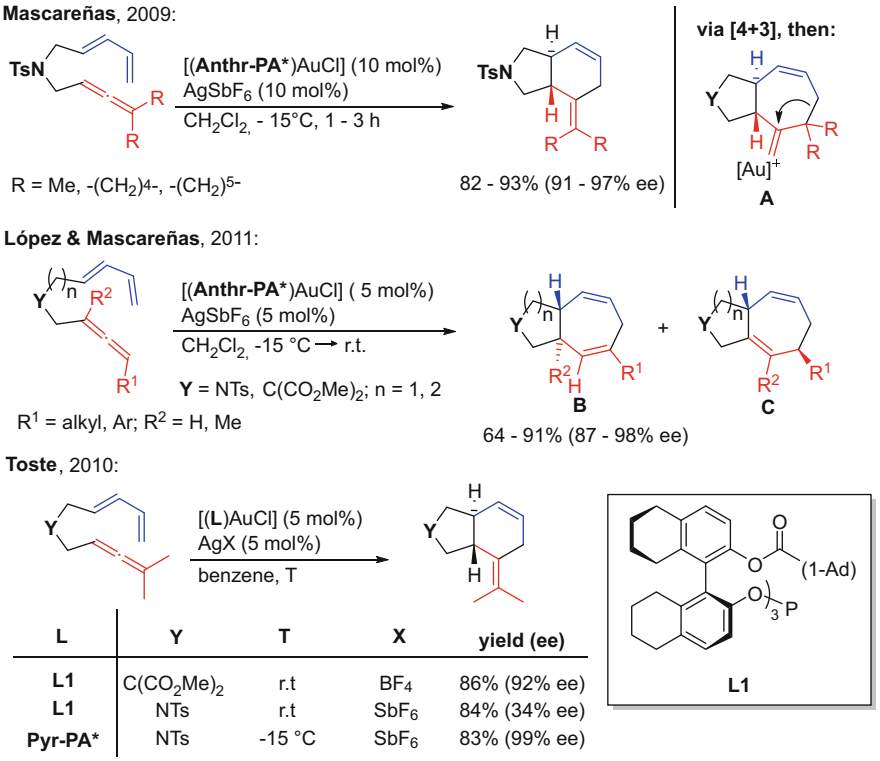
the combination of a BINOL-based diol and a chiral amine featuring two stereocenters, opens a myriad of possibilities for ligand fine-tuning [75].

The successful ligand structures for highly selective Au(I)-catalysis are typically based on more complex ligand architectures to ensure efficient encapsulation of the linear gold fragment within a chiral pocket. Thus, an extensive 3,3′-substitution pattern of the BINOL moiety is often a prerequisite for achieving high selectivities. However, some ligands of relatively simple structure have also been shown to achieve high selectivities in some instances. A selection of ligands applied in highly enantioselective transformations is given in Fig. 25.

Occasionally, some specially shaped phosphite-based systems have also been shown to be suitable for creating a defined chiral environment around the metal center, such as the helical chiral ligands introduced by Reetz [75] and first applied in enantioselective Au(I) catalysis by Toste and co-workers (see Sect. 3.1.1 [76]).

3.1.1 Intramolecular Formal [4C + 2C] and [2C + 2C] Cycloadditions

The intramolecular [4 + 2] cycloaddition of allene-dienes bearing a terminally disubstituted allene moiety proceeds favorably over the [4 + 3] cycloaddition process in the presence of cationic gold(I) complexes of electron-poor phosphite and



L	Y	T	X	yield (ee)
L1	$C(CO_2Me)_2$	r.t	BF_4	86% (92% ee)
L1	NTs	r.t	SbF_6	84% (34% ee)
Pyr-PA*	NTs	-15 °C	SbF_6	83% (99% ee)

Fig. 26 Enantioselective formal [4 + 2] and [4 + 3] intramolecular cycloadditions of allene-dienes (Mascareñas and co-workers 2009 [77] 2011 [78], Toste and co-workers 2010 [76])

phosphoramidite ligands, as demonstrated by Mascareñas and co-workers [77]. The cycloadducts were obtained with perfect diastereoselectivity in favor of the *trans*-fused bicycle. The enantioselective version of this process was achieved in a highly selective manner by the use of gold chloride complexes of chiral phosphoramidite ligands in combination with $AgSbF_6$ at −15°C in CH_2Cl_2 (Fig. 26) [77]. In contrast, an established digold catalyst derived from DTBM-SEGPHOS not only performed poorly with respect to enantioselectivity but also with low chemoselectivity, likely due to its increased electron-rich character. On the basis of DFT calculations, a cationic reaction pathway was dismissed in favor of an initial [4 + 3] cycloaddition between the diene and the gold-activated allene groups to give the cycloheptenyl gold carbene species **A** (also described as a gold stabilized carbocation; for a discussion see [79, 80]). This intermediate then undergoes ring contraction via 1,2-alkyl migration. It was later discovered that a mono-aryl substitution at the terminal allene position ensured the reaction to proceed in favor of the [4 + 3] cycloadduct as final reaction product, since a 1,2-hydride migration becomes

predominant in this case over the migration of the ring's internal bond (giving a less stabilized carbocation) (Fig. 26, middle equation) [78]. Of the two possible migrations, the bridgehead H-atom migrated less favorably. Therefore product **B** was obtained in good to complete selectivity, especially when the internal allene carbon atom contained an additional methyl substituent ($R^2 = Me$), which completely inhibited the migration of the bridgehead group.

In 2010, Toste and co-workers were able to introduce a useful modification of the phosphoramidite ligand architecture introduced by Mascareñas the year before and to apply the first chiral phosphite ligand with very high enantioselectivities in asymmetric gold catalysis [76]. Previous work by the Toste group had also revealed a strong ligand effect regarding the chemoselectivity of the formal [4 + 2] cycloaddition reaction discovering phosphites such as $P(OPh)_3$ as the most suitable ligands for this transformation [81]. Therefore, the C_3-symmetric phosphite ligand **L1** bearing three octahydro-BINOL-derived substituents was investigated in the process showing good enantioselectivities for allene-diene substrates (82–92% ee) (Fig. 12) [76]. While **L1** showed disappointing results with N-tethered allene-diene substrates, a phosphoramidite ligand containing 1-pyrenyl substituents at the 3,3′-positions of the BINOL moiety **Pyr-PA*** (see Fig. 25) showed extraordinarily high enantioselectivities. New gold chloride complexes were characterized by X-ray diffraction analysis, which revealed steric shielding of large parts of the linear gold fragment, indicating the efficient chiral encapsulation of the reactive metal center during catalysis. The group later demonstrated the effectiveness of the **Pyr-PA*** ligand platform in other reactions such as the formal [2 + 2] cycloaddition of enallenes (for comparison, see Sect. 2.1.2) [82].

Another important contribution of the year 2010 represents a nice showcase for tailor-made phosphoramidite ligand design for effective enantioselective gold (I) catalysis [83, 84]. Fürstner and co-workers discovered that chiral phosphoramidite ligands derived from TADDOL-related diols can be significantly improved in their ability for chiral induction by a simple modification: the substitution of the dimethyloxolane ligand backbone in ligand **L2** for an acyclic dimethoxy structure in **L3** leads to the axial disposition of the vicinal phenyl rings, thus creating a more closed chiral pocket around the gold center, as determined by X-ray crystal structure analysis (Fig. 27). A significant increase of enantioselectivity was observed, for example, in the formal [2 + 2] cycloaddition of eneallenes catalyzed by complexes prepared in situ from [(L)AuCl] and $AgBF_4$. An even better encapsulation of the gold center was apparently achieved by a *para-t*-Bu-substitution of the phenyl rings (**L4**), which led to a further increase in enantioselectivity to an outstanding range of 95–99% for a variety of substrates.

Other successful applications of this ligand class include [4 + 2] cycloadditions of eneallenes; intramolecular hydroamination, hydroxylation, and arylation of allenes; as well as cycloisomerizations of enynes [84], including application to natural product synthesis [85]. In contrast, intramolecular hydroamination reactions catalyzed by BINOL-based phosphoramidite gold(I) systems were discovered to proceed with lower enantioselectivities by Michon, Agbossou-Niedercorn, and co-workers [86].

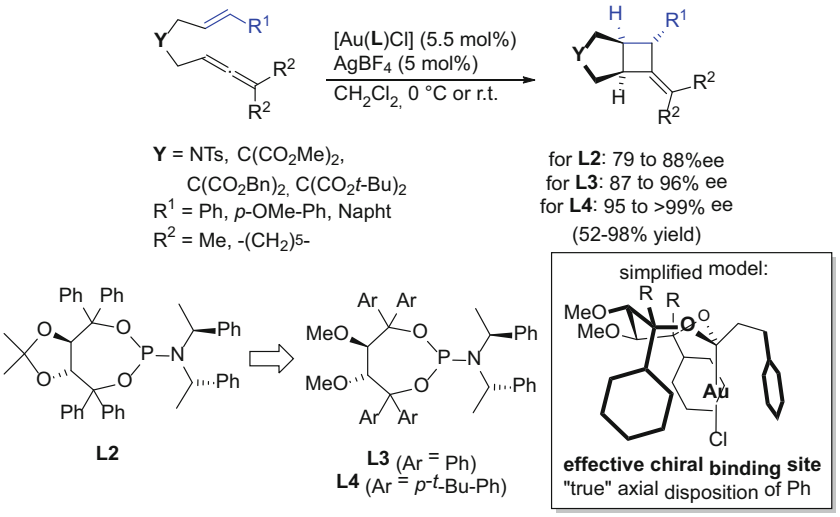


Fig. 27 Enantioselective formal [4 + 2] intramolecular cycloaddition of allene-dienes (Fürstner and co-workers 2010–2012 [83, 84])

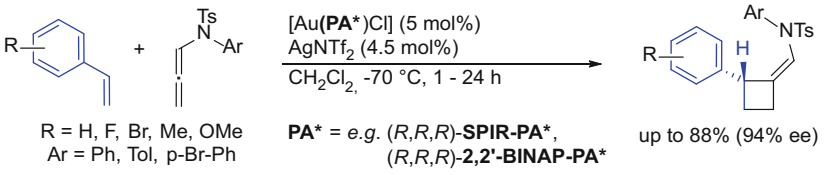


Fig. 28 Enantioselective intermolecular [2 + 2] cycloaddition of *n*-allenylsulfonamides and styrenes (González and co-workers 2012 [87])

3.1.2 Intermolecular Cycloadditions

Due to the high reactivity of allenes, the highly enantioselective intermolecular formal [2 + 2] cycloaddition of *N*-allenylsulfonamides with styrene derivatives was achieved at −70°C in high yields and in practical reaction time (1–24 h) using cationic phosphoramidite gold(I) catalysts (Fig. 28) [87]. Interestingly, the gold (I) complexes of a series of investigated ligands derived from (*R*,*R*)-bis(1-phenylethylamine) and an axially chiral diol performed with good enantioselectivities in the model coupling of allenyl-phenyl-tosyl amine and 4-methoxystyrene, even those missing substituents in the 3,3′-positions of the BINOL moiety. The reaction was compatible with electron-rich and moderately deactivated vinylarenes giving the products in moderate to high yields and up to 95% ee (for vinylarene = 2-vinylnaphtalene, not shown in Fig. 28). Notably, enantioselective access to cyclobutanes with quaternary allylic carbon centers was possible with α-methylstyrene as alkene reactant.

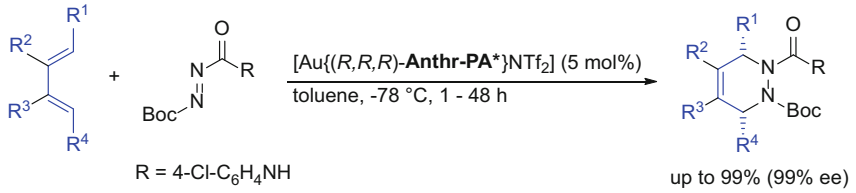


Fig. 29 An enantioselective intermolecular azo hetero-Diels–Alder reaction (Gong and co-workers 2013 [88])

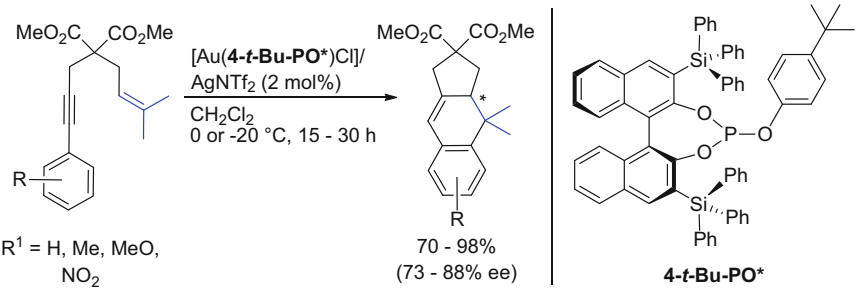


Fig. 30 Formal [4 + 2] cycloaddition reaction of aryl-substituted 1,6-enynes (Echavarren and co-workers 2013 [89])

Shortly after this seminal report on intermolecular gold(I) catalyzed cycloadditions, Gong and co-workers reported a highly regio- and enantioselective azo hetero-Diels–Alder reaction using defined or in situ generated complexes of ligand **Anthr-PA*** and some of its related congeners [88]. Several substituted butadiene systems were reacted with diazene dienophiles at −78°C with high regioselectivities, excellent yields (mostly >92%), and enantioselectivities ranging from 86 to 99% ee (Fig. 29). Impressively, the reaction could be combined with a 1,6-enyne cycloisomerization in a one-pot process. The in situ generated alkenyl cyclopentene system directly reacted with the dienophile to furnish the corresponding fused 5,6-bicycles in high yields and enantioselectivities.

3.1.3 Other Reactions

A new class of chiral phosphite ligands derived from 3,3′-bis(triphenylsilyl)-1,1′-bi-2-naphthol and an alcohol was introduced with good results in another formal [4 + 2] cycloaddition reaction by Echavarren and co-workers [89]. Using a catalytic system of [(L)AuCl]/$AgNTf_2$ (2 mol%) at −20°C in CH_2Cl_2, aryl-substituted 1,6-enynes could be converted into cyclopentane-fused tetrahydronaphthalenes via a sequence of enyne cyclization/hydroarylation with high yields and enantioselectivities of up to 88% ee (Fig. 30). Importantly, among a large series of catalysts, including the typical chiral bisphosphine digold type or mononuclear

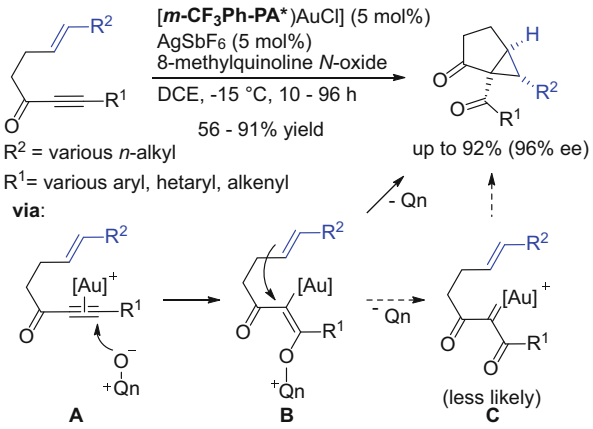


Fig. 31 Enantioselective oxidative cyclopropanation of 1,6-enynes (Zhang and co-workers 2014 [91])

systems based on common chiral phosphoramidite and phosphite ligands, a representative of the new ligand class bearing a phenol substituent showed the most promising results in the optimization reaction (substrate with R = H). Structural ligand optimization was then performed through systematic variation of the monoalkoxide substituent, which identified the 4-*t*-Bu-phenoxide derived ligand as the most selective group.

Another example for the beneficial use of phosphoramidite ligands in enantioselective Au(I) catalysis over the established digold systems (see also Sect. 3.1.1) is the oxidative cyclopropanation reaction of enynes (selected examples [90, 91]). Zhang and co-workers were able to achieve the conversion of 1,6-enynes into functionalized bicyclo[3.1.0]hexane-2-ones with a phosphoramidite catalyst in the presence of an *N*-oxide as oxidant [92] (Fig. 31). The methodology exploits the recent discovery of new reaction patterns based on the generation of α-oxo gold carbenoids from the reaction of a π-gold acetylene species with a pyridine/quinoline *N*-oxide (see, for example, [93]). By this method, three contiguous quaternary and tertiary stereogenic centers are generated with high enantioselectivity (up to 96%). Mechanistic experiments indicating the importance of the quinoline moiety for the enantiodetermining step supported that this step should take place via a β-gold vinyloxyquinolinium species **B** rather than an α-oxo gold carbenoid **C**.

3.2 Phosphine-Based Systems

The most recent approach to chiral ligand design for efficient induction of chirality at gold centers with chiral P-based ligands was introduced by Voituriez and Marinetti and co-workers who were able to develop helicenes with embedded

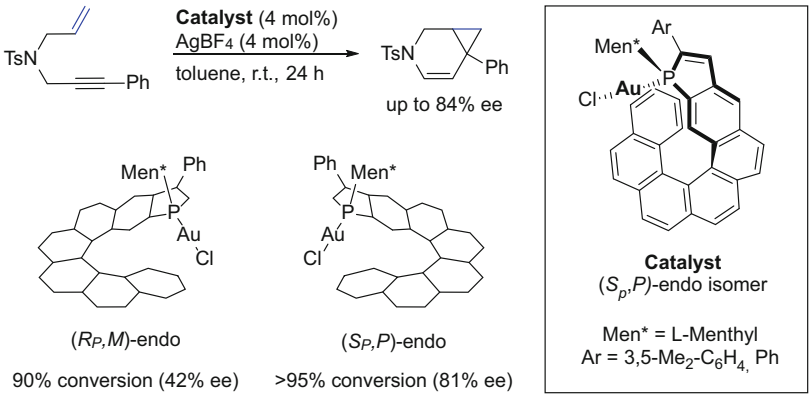


Fig. 32 New helical chiral phosphole ligands in the enantioselective gold(I)-catalyzed cycloisomerization of *N*-tethered 1,6-enynes (Voituriez, Marinetti, and co-workers 2014 [94])

phosphole units [94]. This feature contrasts with previously known helical phosphines used in catalysis (for reviews on helicenes, including catalytic applications, see [95, 96]) and enabled to achieve a good level of chiral induction in the model cycloisomerization of an *N*-tethered 1,6-enyne into a bicycle[4.1.0]heptene (Fig. 32) (see also Sect. 2.2). A series of diastereomeric gold(I) chloride complexes were synthesized and screened for their catalytic activity. It was discovered – unsurprisingly – that complexes, in which the AuCl fragment resides outside of the helical chiral vicinity (exo-isomers), not only give rise to poor enantioselectivity but also low conversion, presumably due to fast decomposition of the catalyst owing to a lack of steric stabilization of the active cationic species. In contrast, endo-isomers achieved good to high conversions, although enantioselectivities varied. There appeared to be a matched situation between the configuration of the helical chiral entity with the – in all cases – (*L*)-configured menthol substituent at the P-atom (for a representative result, see Fig. 32). An α-aryl substituent next to the phosphorus center was further found to be necessary to obtain good results, while the variation of this group only caused slight modulation in enantioselectivities.

4 Chiral Aminocarbene-Based Gold(I) Complexes

As experienced in numerous asymmetric metal-catalyzed transformations, progress in the development of highly enantioselective carbene-based protocols has been made at a much slower pace in comparison to those based on phosphines. Principally, this is due to the advantage of the latter ligand class in terms of a vast structural variety from which experimental chemists can choose from commercial sources. Furthermore, simply mimicking established phosphine-based catalysts

with carbene analogs has often proven unfruitful due to the very different steric nature of both ligand classes (for a review on concepts in chiral NHC-based catalysis, see [97]; for a general review on the field, see [98]; for a specialized review on chiral phosphorus-functionalized NHCs, see [99]). However, recent reports have shown that for enantioselective Au(I) catalysis, the established digold systems derived from axially chiral binaphthyl ligands provided an excellent lead structure for highly selective carbene-based systems – if the carbene donor moiety is chosen carefully and the chiral binaphthyl moiety is substituted appropriately [100]. Additionally, promising new ligand platforms have been discovered for the design of new highly selective monodentate chiral carbenes [101, 102].

4.1 Bidentate Systems

Similar to the results in enantioselective catalysis with bisphosphine systems (see Sect. 2), the first promising results based on carbene ligands were obtained with digold systems derived from chiral *bis*-carbene ligands.

In 2010, Iglesias, Sánchez, and co-workers used butylene-bridged *bis*-NHC ligands containing a chiral dioxolane backbone and bulky aryl *N*-substituents (Mes = mesityl or DiPP = diisopropylphenyl) in the asymmetric hydrogenation of prochiral olefins (Fig. 33) [103]. The corresponding gold chloride complexes of the new ligands showed good catalytic activity and enantioselectivities of up to 95% ee in the hydrogenation of diethyl alkylidene itaconates at 0.5 mol% catalyst loading under mild conditions (4 bar H_2, 40°C). However, bulky substituents at the alkylidene moiety were required in order to obtain satisfactory enantioselectivities of >85%. While the *N*-Mes-substituted ligand gave slightly higher enantioselectivities, it was also considerably more active than the DiPP-substituted congener, likely due to its reduced steric bulk. The *N*-Mes-substituted ligands' performance was also tested in the corresponding rhodium- and palladium-catalyzed processes using the chelated complexes of the type [Rh(*bis*NHC)(Cl)(COD)] and

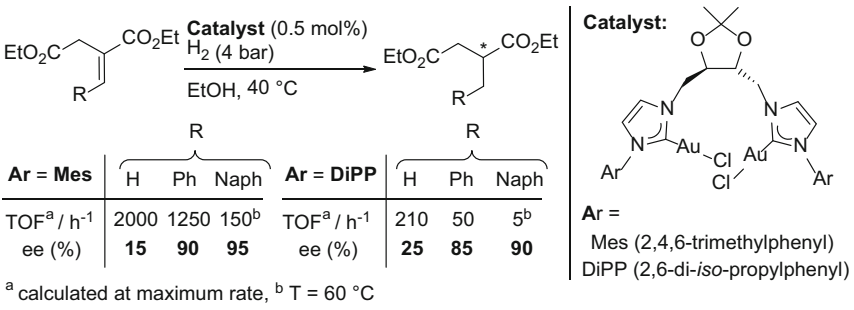


Fig. 33 Enantioselective hydrogenation of olefins with chiral bis-carbene digold complexes (Iglesias, Sánchezand, co-workers 2010 [103])

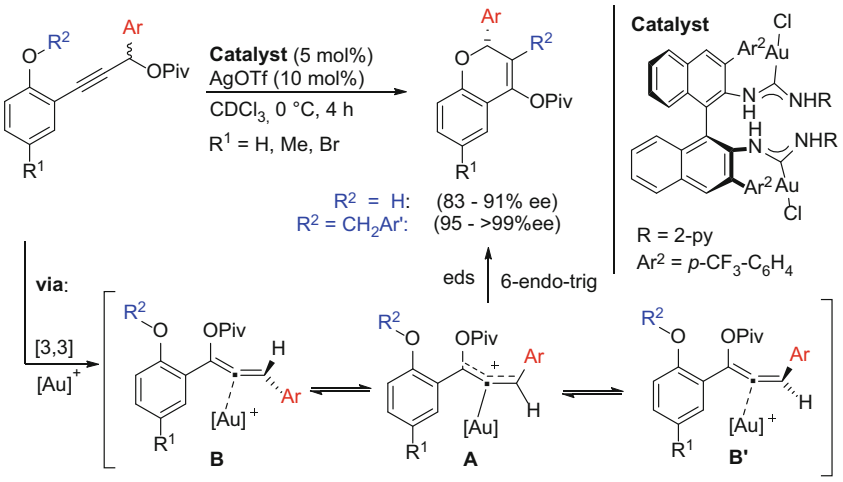


Fig. 34 Chiral (acyclic diaminocarbene)au(i)-catalyzed dynamic kinetic asymmetric transformation of propargyl esters (Toste and co-workers 2011 [100])

[Pd(*bis*NHC)Cl_2]. These showed similar trends (high ee only with bulky substrates) but, surprisingly, much lower activities than the gold-catalyzed reaction.

Toste and co-workers envisaged the necessity for the development of chiral carbene ligands derived from BINAM (BINAM = 1,1′-binaphthyl-2,2′-diamine) for an intramolecular dynamic kinetic propargylic acetate rearrangement/hydrophenoxylation process (Fig. 34) [100]. A racemic propargylic acetate was proposed to undergo the well-documented [3, 3]-sigmatropic rearrangement to a gold–allene intermediate that could be trapped by a pendant phenol nucleophile. The use of a highly electron-rich ligand such as a *bis*-carbene system would ensure the fast equilibration of the gold–allene species **B** (needed for an efficient dynamic kinetic transformation) via the planar gold allyl cation type intermediate **A**. Indeed, a highly enantioselective protocol giving 2-substituted chromenyl pivalates from racemic phenol-substituted propargyl pivalates was realized by the use of axially chiral bis(acyclic diaminocarbene)gold(I) complexes (bis(ADC) complex), while bisphosphine- and phosphoramidite-based catalysts gave moderate or poor selectivities, respectively, in agreement with a decrease in electron richness of these ligands.

However, a short mechanistic study involving the incomplete conversions of racemic and enantioenriched starting materials indicated a kinetic resolution of the starting material and a relatively slow equilibration process between **A** and **B**, which implied that the observed dynamic kinetic resolution should be due to an enantiodetermining cyclization onto **A** and/or the isomers of **B**.

In 2010, a year before this report, Espinet and co-workers prepared this type of precatalyst system by the reaction of isocyanide gold(I) complexes and chiral amines or diamines [104]. However, the ligands lacked the crucial 3,3′-substitution

at the BINAM moiety and thus only gave poor enantioselectivities in the investigated cyclopropanation and cyclohydroalkoxylation model reactions.

The Toste group, on the other hand, systematically varied the 3,3′-position of the BINAM moiety and identified a 4–CF_3–C_6H_4 group as the most efficient substituent for efficient chiral induction (83–91% ee). Intriguingly, by the use of substrates with arylmethyl phenyl ether groups in place of phenol nucleophiles, the reaction gave 2,3-disubstituted chromenyl pivalates. Presumably, a carbodemetalation of a vinyl gold species proceeds after the nucleophilic attack of the ether oxygen atom at the gold–allene group. A formal 1,3-migration of the arylmethyl group from the generated oxonium group thus generates a new C–C bond. A series of arylmethyl and hetarylmethyl groups as migrating entities resulted in the isolation of the products with outstanding enantioselectivities (95–>99%).

4.2 Monodentate Systems

Several groups have worked intensely on the development of chiral monodentate NHC ligands suitable for enantioselective gold catalysis, albeit with limited success until 2012 (for a selection of investigated systems, see Fig. 35). C_2 symmetric NHC ligands such as those derived from 1,2-diphenylethylene diamines (for successful application of these types of ligands in other transition metal-catalyzed reactions, see, for example, [108–110]) by Tomioka and co-workers [105] or a new development from Czekelius [106] derived from bis(tetrahydroisoquinoline) bearing sterically highly demanding, rigid substituents in the α-position with respect to the NHC nitrogen atom gave moderate selectivities in common benchmark reactions such as the alkoxycyclization of 1,6-enynes and the desymmetrization of 1,4-diynamides, respectively. NHC ligands bearing an axially chiral binaphthyl substituent have been tested by Shi and co-workers in the asymmetric Friedel–Crafts/cyclization reaction of 1,6-enynes providing good yields and moderate ee values [107].

A recent report by Slaughter and Handa can be considered a major breakthrough in enantioselective carbene-based gold(I)-catalysis with monodentate ligands. It was possible to demonstrate that conformationally flexible axially chiral binaphthyl

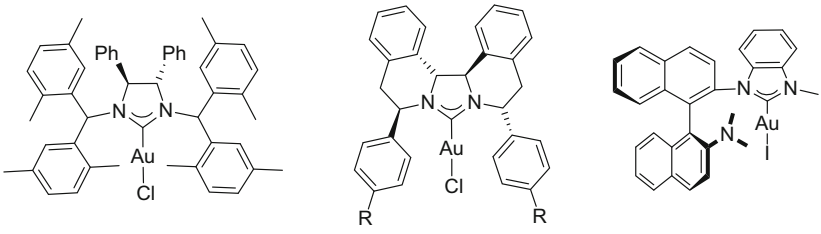


Fig. 35 Selection of chiral NHC ligands tested in asymmetric gold(i) catalysis (developments by Tomioka 2010 [105], Czekelius 2011 [106], Shi 2011 [107])

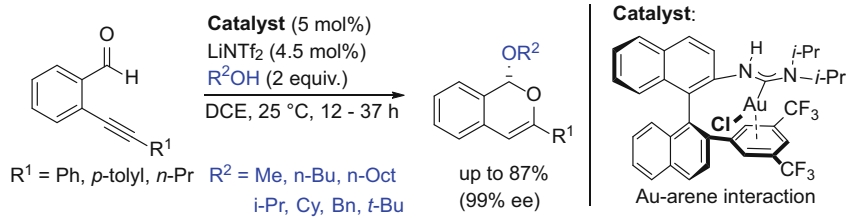


Fig. 36 Enantioselective alkynylbenzaldehyde cyclizations catalyzed by chiral gold(i) acyclic diaminocarbene complexes containing weak au–arene interactions (Slaughter and Handa 2012 [101])

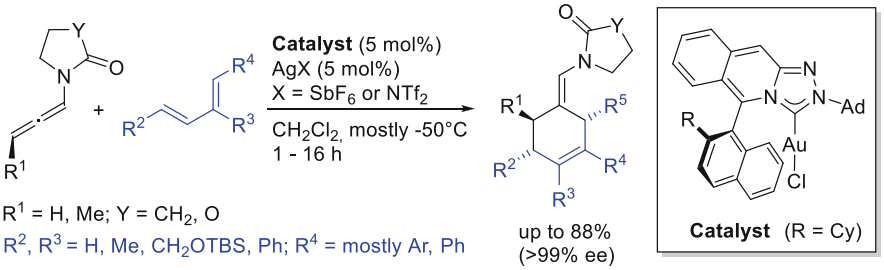


Fig. 37 Au(I)-catalyzed enantioselective intermolecular [4 + 2] cycloaddition between allenes and dienes using a novel axially chiral triazolidene ligand (Mascareñas and co-workers 2012 [102])

N-substituents can indeed induce high levels of enantioselectivity [101]. The key to success was the introduction of an electron-deficient aryl substituent (3,5–$(CF_3)_2$–C_6H_3) at the binaphthyl moieties 3′-position, which gave rise to weak gold-arene interactions, consequently leading to a more defined chiral environment around the metal center (Fig. 36). This interaction was demonstrated by X-ray crystallography and DFT calculations, and it was shown that it was absent for the analogous ligand bearing a simple phenyl substituent. Therefore, the investigated enantioselective tandem acetalization/cycloisomerization reaction of *o*-alkynylbenzaldehydes was achieved with high enantioselectivities (up to 99% ee) solely using the catalyst where gold-arene interactions were present.

Even in the absence of gold-arene interactions which strongly impact the chiral environment around the metal center, axially chiral binaphthyl moieties such as *N*-substituents of aminocarbene ligands can be effectively used for steric shielding of the linear $C^{carbene}$-gold fragment. In an impressive report by Mascareñas and co-workers on the first highly enantioselective intermolecular [4 + 2] cycloaddition between allenes and dienes, a new triazolylidene ligand class was introduced which brought the axis of chirality of a binaphthyl system closer to the metal center than in previously published ligands (Fig. 37, see catalyst structure to the right) [102]. This was achieved formally by adding a naphthyl substituent to the C2 position of a naphthalene-fused heterocyclic system. Different substitution patterns at the

naphthyl groups' R-position ensured fine-tuning of the ligand. With this system in hand, a few amido-allenes were reacted with a large variety of diene systems, including 1,2-di- and 1,2,4-trisubstituted dienes. The corresponding chiral cyclohexenes were thus obtained with up to three stereocenters with moderate to high yield and excellent enantio- and diastereoselectivities using a catalyst prepared in situ from [(**L**)AuCl]/AgX (5 mol%, X = NTf_2, SbF_6) at low temperature (mostly −50°C).

5 Chiral Brønsted Acid Anion Gold(I) Complexes

During the early stages of highly enantioselective homogeneous gold catalysis, Toste and co-workers demonstrated that asymmetric gold catalysis mediated by chiral counterions (for recent reviews on the field, see [111–113]) can be used as a powerful methodology for the synthesis of enantioenriched compounds and not merely as an alternative to the chiral ligand approach. They were able to demonstrate that the established systems could also benefit from a combination with the chiral counterion strategy. A dramatic matched pairing effect between the use of a chiral ligand and a chiral BINOL-derived phosphate anion ((*R*)-TRIP, see Fig. 38) enabled to achieve the intramolecular hydrocarboxylation of a β-carboxy-allene in good enantioselectivity (82% ee) – a reaction for which both approaches individually produced poor results [31].

In the seminal publication, the chiral counterion strategy showed the best results in intramolecular hydroalkoxylation and hydroamination reactions. The combination of a dinuclear gold complex of an achiral bisphosphine ligand [(dppm)$(AuCl)_2$] (2.5 mol%, dppm = bis(diphenylphosphino)methane) with Ag-(*R*)-TRIP (5 mol%) afforded the cyclization product in excellent yield and enantioselectivity in benzene at room temperature (Fig. 38) [31]. This was in stark contrast to the

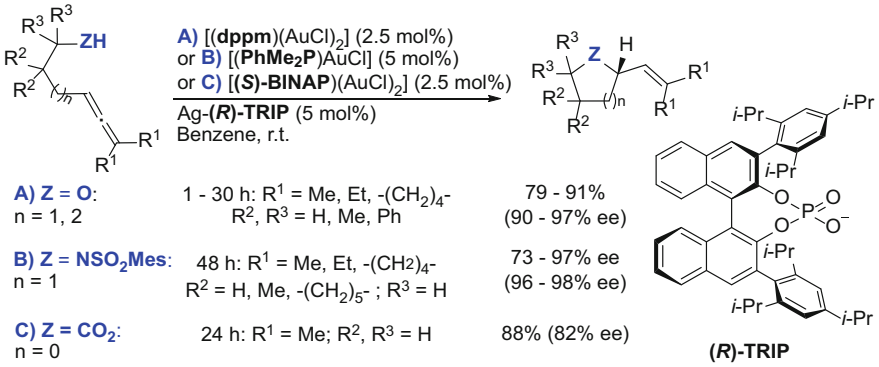


Fig. 38 Asymmetric intramolecular hydroalkoxylation of allenes using chiral Brønsted acid anions (Toste and co-workers 2007 [31])

results obtained with chiral bisphosphine catalysts such as [(*R*)-DTBM-SEGPHOS $(AuCl)_2$]/$AgBF_4$, which virtually gave racemic product. In agreement with the concept of an in situ generated chiral ion pair, the selectivity of the chiral anion-mediated process dropped dramatically in more polar solvents such as CH_3NO_2, acetone, and THF (18%, 37%, and 76% ee, respectively), due to a greater separation of counterion and cationic gold center. A series of substituted allene-alcohols were converted to chiral tetrahydrofurans and oxanes with high yields and enantioselectivities >90% ee.

The analogous hydroamination of allene-sulfonamides was performed with a monogold catalyst comprised of an equimolar mixture of [Au(Ph$(CH_3)_2$P)Cl] and (*S*)-TRIP-Ag (5 mol%) and provided the products in even higher selectivities (>96%), albeit in longer reaction times (48 h).

The scope of these reactions was later extended to the cyclizations of allenyl hydrazines and allenyl hydroxylamines [114]. Whereas the hydroaminations of hydrazines and of O-linked hydroxylamines were preferentially carried out with chiral bisphosphine digold catalysts, the hydroalkoxylation process using N-linked hydroxylamine giving 5-membered ring products (isoxazolidines) was achieved with high selectivities with the dppm digold/chiral silver phosphate system. However, the combined chiral phosphine/chiral counterion approach was required to achieve satisfactory selectivities for the hydroalkoxylation of N-linked hydroxylamines to give 6-membered ring products (oxazines).

In 2012, Czekelius and co-workers were able to exploit the chiral counterion concept in the first enantioselective desymmetrization of diynamides to give enantioenriched methylenepyrrolidines featuring a quaternary stereocenter (Fig. 39) [115]. 1,4-Diynamide substrates featuring a range of different substituents at the quaternary carbon center were converted with good to high enantioselectivities into the unsaturated heterocycles using a 1:1 mixture of [(*t*-Bu_3P)AuCl] and Ag-(*R*)-TRIP. Low reaction temperatures (−55°C) and a solvent of relatively low polarity ($CHCl_3$) were needed for a selective reaction outcome, suggesting that a close contact ion pair is formed between the cationic gold–alkyne species and the anionic chiral phosphate allowing to effectively differentiate between the alkyne groups. Notably, the typical chiral bisphosphine digold catalysts performed poorly in this type of transformation [116], which had also been shown in the desymmetrization of a dipropargyl alcohol system by Hashmi and co-workers [117].

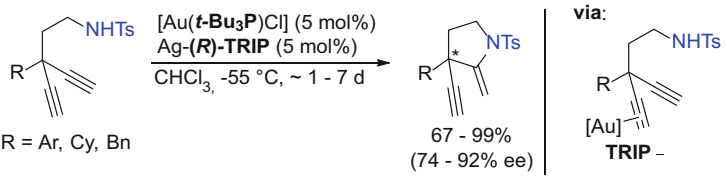


Fig. 39 Desymmetrization of diynamides (Czekelius and co-workers 2012 [115])

As Toste and co-workers had already predicted in their seminal publication [31], the additive effects of both chiral ligand and chiral counterion concepts would be a synthetically highly attractive strategy to overcome problematic substrates in enantioselective reactions. In 2013, the first gold-mediated asymmetric bromocyclization reaction involving, again, challenging β-carboxy-allenes was in need of this powerful combinatorial approach, as both individually catalyzed processes failed to give satisfactory results for this substrate class (Fig. 40) [118]. The bromocarboxylation reaction was performed in the presence of an excess of electrophilic bromine reagents such as *N*-bromolactams. The cyclization of allenes functionalized with a broad range of internal nucleophiles, including amine, hydroxylamine, carboxylic acid, hydrazine, and alcohol functionalities, was achieved using this strategy. It was discovered that an additional factor for reaction optimization was provided by the variation of the *N*-bromolactame's ring-size, which affected not only the yield, but also the enantioselectivity of the reaction. The fact that the nature of the electrophile influences enantioselectivity in the bromocarboxylation reaction, together with the result that the hydrocarboxylation reaction for a given substrate proceeds with higher enantioselectivity than the bromocyclization, suggested the bromodeauration process as a possible enantiodetermining step. Support for this proposal was provided by a recent study of Gagné and Widenhoefer that concludes that the protodeauration step in gold-catalyzed hydroalkoxylation reactions likely is enantiodetermining, while the cyclization is reversible [119].

The in situ generation of chiral phosphate gold species is not limited to the use of silver phosphate salts. Treatment of a proton-labile gold source such as [(L)AuMe] with a chiral Brønsted acid in a 1:1 ratio also delivers the desired complexes in situ. For example, a highly efficient enantioselective transfer hydrogenation of prochiral quinolines was achieved with a catalyst mixture of [Au(IMes)Me]/TRIP-H at low loading (0.01 mol%) in the presence of a Hantzsch ester as reducing agent [120]

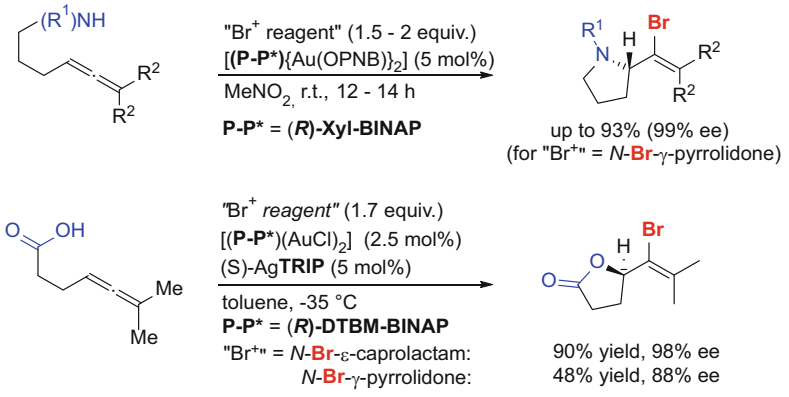


Fig. 40 Asymmetric bromocyclization of allenes (Toste and co-workers 2013 [118])

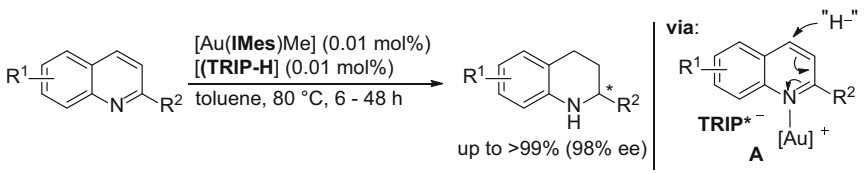


Fig. 41 Enantioselective hydrogenation of quinolines (Gong and co-workers 2012 [119])

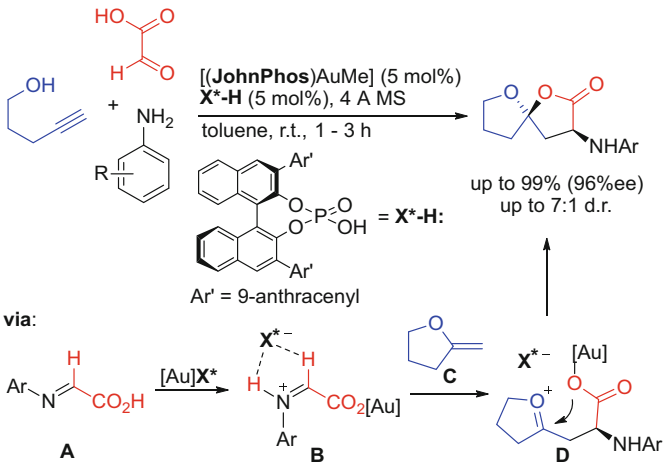


Fig. 42 Enantioselective multicomponent coupling of alkynols, anilines, and glyoxylic acid to spiroacetals (Fañanás, Rodríguez and co-workers 2013 [122])

(Fig. 41). A strong ligand effect on catalyst performance was observed indicating that the reaction proceeds via a σ-gold-activated quinoline species such as **A**, rather than a proton-activated intermediate. Moreover, the extraordinarily low catalyst loadings required for this highly enantioselective process are very unusual in light of other metal-catalyzed and chiral Brønsted acid-catalyzed procedures [121].

Fañanás, Rodríguez, and co-workers reported the first catalytic multicomponent coupling reaction for the enantioselective synthesis of spiroacetals (Fig. 42) [122]. The one-pot, three-component reaction of alkynols, anilines, and glyoxylic acid was catalyzed by a 1:1 mixture of [Au(Johnphos)Me] and a chiral BINOL-derived phosphoric acid at 5 mol% loading in toluene at room temperature. Mechanistically, it was proposed that the in situ generated chiral gold phosphate complex catalyzes the cyclohydroalkoxylation of the alkynol to give the vinyl ether **C**, which then reacts in an asymmetric formal [3 + 2] cycloaddition with the imine **A**, which as well is formed in situ from the aniline and glyoxylic acid. The double hydrogen bonded phosphate species **B** was proposed to be the key intermediate for obtaining a highly enantioselective C–C bond formation due to effective shielding of one of the iminium ions enantiotopic faces.

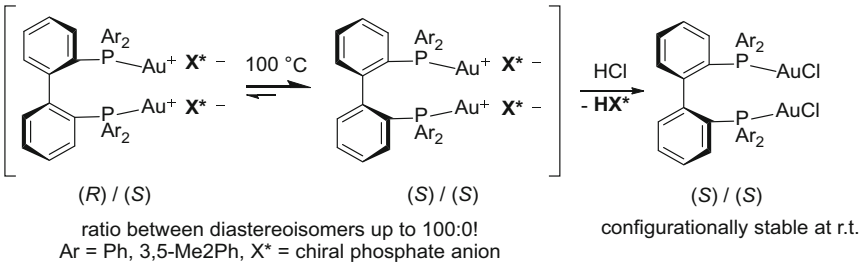


Fig. 43 Axial chirality control of BIPHEP digold complexes by chiral anions (Mikami and co-workers 2009) [124]

A related intramolecular process to generate spiroacetals from internal alkynes containing a dangling benzylic alcohol and a phenol functionality on each side of the triple bond was achieved by Brimble and co-workers [123]. The double hydroalkoxylation process proceeded in up to 74% ee using the matched pair [(*S*)-SEGPHOS(AuCl)]/Ag(*S*)-TRIP.

An important contribution to our understanding of the powerful asymmetric induction capabilities of chiral phosphate anions in gold(I) chemistry was provided by a study of Mikami and co-workers on racemic gold(I) complexes of atropisomeric BIPHEP ligands (Fig. 43) [124]. It was discovered that axial chirality can be controlled in the presence of chiral BINOL-based phosphate counterions with electron-neutral aryl groups at the 3,3′-positions of the binaphthyl backbone. Digold phosphate species generated from [BIPHEP(AuCl)$_2$] and two equivalents of silver salt were isomerized at 100°C to the thermodynamically favored (*S*)/(*S*) diastereoisomer with perfect selectivity within hours. Addition of a concentrated HCl solution furnished the starting gold chloride complex with >99% ee and quantitative yield, while the conjugate acid of the counterion was also recovered in high yield. The presence of the gold chloride fragments attached to the P-donors ensured a high energy barrier for rotation around the biphenyl axis complexes at room temperature. Thus, chirally stable complexes of atropisomeric ligands were obtained and could be tested in a benchmark intramolecular hydroamination of allene-*N*-tosylamides giving ee values of up to 91% (for Ar = 3,5-Me$_2$–C$_6$H$_4$).

Further fundamental studies on the role of chiral counterions in asymmetric Au (I) catalysis were conducted by Nguyen and co-workers in 2012 [125]. EXAFS and ^{31}P NMR spectroscopic analysis of (Ph$_3$P)Au(X*) (X* = chiral phosphate derived from BINOL) as catalyst in the intramolecular hydroalkoxylation of allenes indicated a strong Au–O bond in solution, implying that the phosphate anion remains coordinated during catalysis. However, it was concluded that this might not be generally the case, especially if a large excess of π-coordinating substrates are present.

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Brønsted Acid/Lewis Base Hybrid Complexes

Manabu Hatano and Kazuaki Ishihara

Abstract Recent progress on our Brønsted acid/Lewis base hybrid complexes in some asymmetric catalyses is reviewed. Based on the rational design of conjugated acid–base catalysts, tailor-made supramolecular catalysts can show remarkable catalytic activity and higher-ordered selectivities that cannot be realized by ready-made single-molecule catalysts. The chiral supramolecular magnesium(II) binaphtholate complexes trigger the highly enantioselective 1,4-hydrophosphinylation and 1,2-hydrophosphonylation of α,β-unsaturated carbonyl compounds, direct Mannich-type reaction, and hetero-Diels–Alder reaction. Moreover, the advanced supramolecular catalysts are prepared in situ from chiral 3,3′-disubstituted binaphthols and biphenols, arylboronic acid, and $B(C_6F_5)_3$, for promoting the anomalous *endo*-/*exo*-selective Diels–Alder reaction. The specific mechanism and deep insights into the possible key intermediates are discussed on the basis of rational design of chiral supramolecular Brønsted acid/Lewis base hybrid catalysts as artificial enzymes.

Keywords Acid–base catalyst · BINOL · Boron · Magnesium · Supramolecular catalyst

Contents

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Abbreviations

acac	Acetylacetonate
BINOL	1,1′-Bi-2-naphthol
Boc	*tert*-Butoxycarbonyl
cod	Cyclooctadiene
DABCO	1,4-Diazabicyclo[2.2.2]octane
DMF	*N*,*N*-Dimethylformamide
MS	Molecular sieves
TBHP	*tert*-Butyl hydroperoxide
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
Ts	Toluenesulfonyl

1 Introduction

A natural enzyme with an induced-fit function is a wonderful tailor-made biocatalyst, which can control both activity and multi-stereoselectivities of a specific substrate for a specific organic reaction. The huge enzymes have "key holes," which can lead only suitable substrates ("keys") into the deep active sites. On the other hand, small molecule catalysts in common organic reactions are much smaller than enzymes. Therefore, their key holes are too small and provide poor conformational flexibility. That is why we cannot expect the induced-fit function in those reactions with the use of conventional ready-made small molecule catalysts. However, these ready-made catalysts can often exhibit some excellent points depending on the kind of the desired organic reactions and substrates; they are easy to design and handle, practical, and versatile. For some previous periods, our study has focused on the rational design of conjugated acid–base catalysts (i.e., ready-made single-molecule catalysts). Recently, however, our interest turned to the rational design of tailor-made supramolecular catalysts based on conjugated acid–base units. "Supramolecule" is simply defined by Lehn for the first time as "Beyond molecular chemistry based on the covalent bond lies supramolecular chemistry based on

molecular interactions–the associations of two or more chemical entities and the intermolecular bond" [1]. Therefore, we envisioned that supramolecular catalysts, which are prepared in situ from already fine-tuned chiral conjugated acid–base units and achiral acid or base units at an appropriate molar ratio, can show unusual catalytic activity and higher-ordered selectivity that cannot be realized by single-molecule catalysts. Here we review our successive challenges of some asymmetric supramolecular catalyses by virtue of Brønsted acid/Lewis base hybrid complexes.

2 Chiral Supramolecular Magnesium(II) Binaphtholate Catalysts

2.1 General Properties of Magnesium(II) Binaphtholate Catalysts

Chiral BINOLs (1,1′-bi-2-naphthols) are some of the most versatile C_2-symmetric chiral ligands of metal complexes for both stoichiometric and catalytic asymmetric reactions (for reviews: [2, 3]). In particular, parent (*R*)- and (*S*)-BINOL and (*R*)- and (*S*)-H_8-BINOL are commercially available as both enantiomers and are inexpensive in bulk quantities (Fig. 1). For effective designs of monomeric metal species, *3,3′-disubstituted* binaphthyl skeletons in BINOL and H_8-BINOL are the most commonly accepted. In sharp contrast, chiral lithium(I) and magnesium (II) binaphtholates [4–17], which are usually prepared in situ from BuLi or Bu_2Mg and chiral *3,3′-nonsubstituted* BINOL or H_8-BINOL, are practical acid–base combination catalysts [18–22], since the ligands are the simplest and the metals are abundant, inexpensive, harmless, and environmentally benign. However, unsurprisingly, enantioselective induction with high catalytic activity is sometimes problematic, due to their oligomeric or polymeric nature. To avoid the aggregation of these complexes, not only the molar ratio of the metal ion and the BINOL ligand but also the use of highly coordinative simple additives such as water and alcohols as cocatalysts is effective. Overall, suitable disaggregated active species would be provided in situ as monomers and/or combinations of monomers (i.e., supramolecules) via self-assembly.

In this review, we focused on recent chiral supramolecular magnesium(II) binaphtholate complexes. In such catalysts, naphthoxide moieties would exhibit strong Brønsted/Lewis basicity, while Mg(II) centers would show inherent strong Lewis acidity. Also, the Lewis basic hydroxy group of BINOLs can increase the Brønsted acidity, since the Mg(II) center would be coordinated and effectively activate the hydroxy group. Due to such a diversity of the supramolecular structures of cooperative Brønsted/Lewis acid–base catalysts, conventional substituents at the 3,3′-positions in BINOL-skeleton would not be necessary.

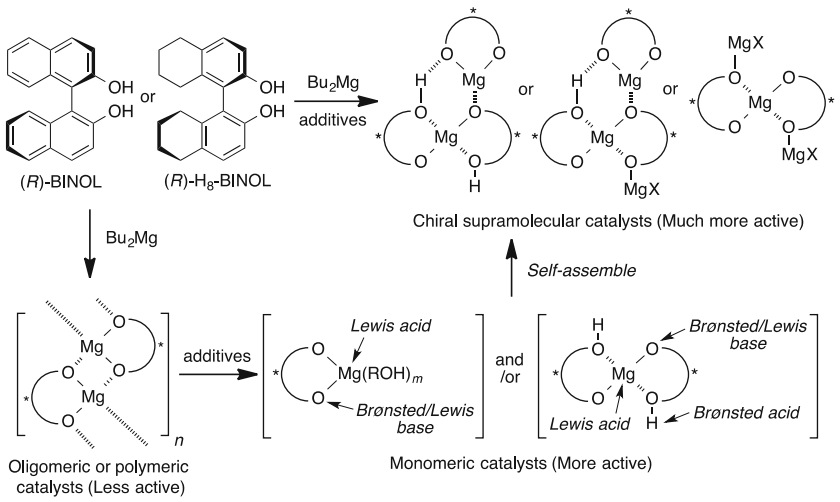
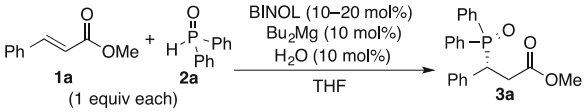


Fig. 1 In situ preparation of chiral magnesium(II) binaphtholates as cooperative Brønsted/Lewis acid–base catalysts

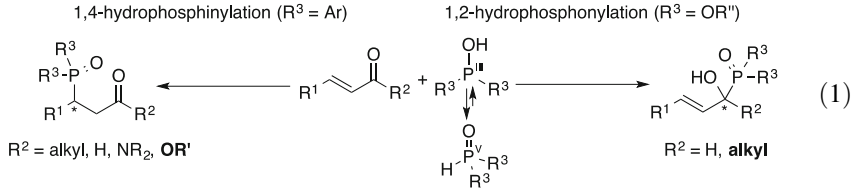
2.2 *Catalytic Enantioselective Addition of Phosphorus Nucleophiles to α,β-Unsaturated Esters and Ketones*

Chiral organophosphorus compounds show various biological activities due to their chemical properties and thus are used in many pharmaceuticals as biophosphate mimics, antibiotics, antivirals, and antitumor agents (for reviews: [23–28]). Moreover, the corresponding chiral phosphine ligands for transition metal catalysts are also important (for reviews: [29–32]). In particular, the catalytic enantioselective addition of phosphorus nucleophiles is one of the most powerful synthetic methodologies for constructing functionalized organophosphorus compounds via phosphorus–carbon (P–C) bond formation (for reviews: [33–36]) (Eq. 1). In general, reactivity and regioselectivity of hydrophosphonylation and hydrophosphinylation strongly depend on substrates, solvents, temperature, etc. However, catalytic enantioselective 1,4-addition to α,β-unsaturated esters has not been reported, despite their importance in synthesis. Moreover, catalytic enantioselective 1,2-addition to ketones has been limited in a few examples [37–39], unlike aldehydes and aldimines [40–45]. To overcome the difficulties in these undeveloped catalytic systems, catalysts must exhibit not only suitable Brønsted basicity to activate non-nucleophilic $R_2P(=O)H$ (major, valence +V) into nucleophilic R_2POH (minor, valence +III) [46, 47], but also strong Brønsted or Lewis acidity to activate less-reactive substrates such as esters and ketones.

Scheme 1 Optimization of catalysts in 1,4-hydrophosphinylation



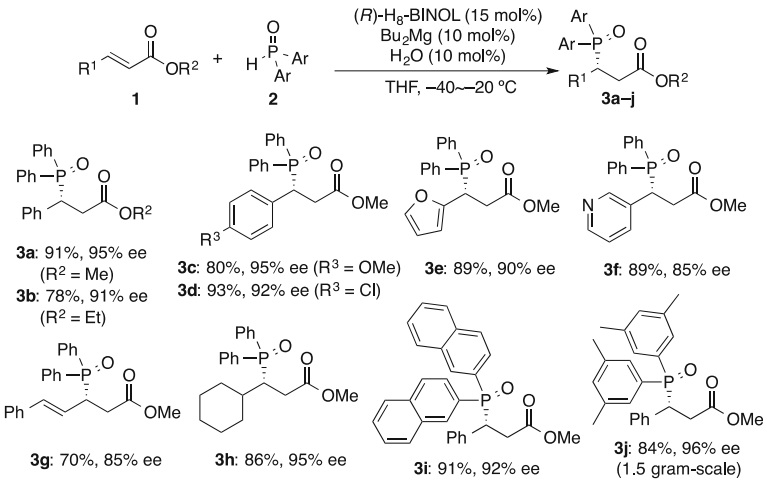
BINOL (mol%)	temperature (°C)	time (h)	yield (%)	ee (%)
(*R*)-BINOL (10)	0	22	81	80
(*R*)-BINOL (15)	0	22	76	85
(*R*)-BINOL (20)	0	22	52	82
(*R*)-H_8-BINOL (15)	–40	16	91	95
(*R*)-BINOL (15)	0	22	38	60



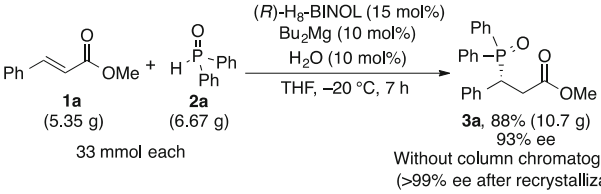
(1)

In this situation, Ishihara developed the enantioselective 1,4-hydrophosphinylation and 1,2-hydrophosphonylation of α,β-unsaturated carbonyl compounds with phosphorus nucleophiles by the use of chiral magnesium (II) binaphtholate complexes as cooperative Brønsted/Lewis acid–base catalysts [48]. At the beginning of the study, Ishihara investigated the enantioselective 1,4-hydrophosphinylation of methyl cinnamate (**1a**) with diphenylphosphine oxide (**2a**) in the presence of Bu_2Mg (10 mol%), (*R*)-BINOL (10–20 mol%), and H_2O (10 mol%) in THF at 0°C (Scheme 1). As a result, the use of 15 mol% of (*R*)-BINOL gave **3a** with better enantioselectivity than the others. This result suggests that a 2:3 ratio of Mg(II)/(*R*)-BINOL might be more effective than a 1:1 or 1:2 molar ratio (i.e., Mg(II)((*R*)-BINOLate) and Mg(II)((*R*)-BINOLate)$_2$, respectively, in Fig. 1). (*R*)-H_8-BINOL in place of (*R*)-BINOL increased the catalytic activity, and the reaction proceeded smoothly even at –40°C with high enantioselectivity (95% *ee*). Water is essential to induce the catalytic activity [6, 7, 15], since water would promote the dissociation of oligomeric magnesium(II) species into monomeric ones.

To show the synthetic potential of the present approach, >10 g-scale synthesis of **3a** was performed (Eq. 2). Since **3a** was highly crystalline, **3a** was crystallized in crude mixture by ether in 88% yield (10.7 g) with 93% *ee* without silica gel column chromatography. Furthermore, recrystallization of the powdered **3a** from chloroform gave the single crystal (>99% *ee*).



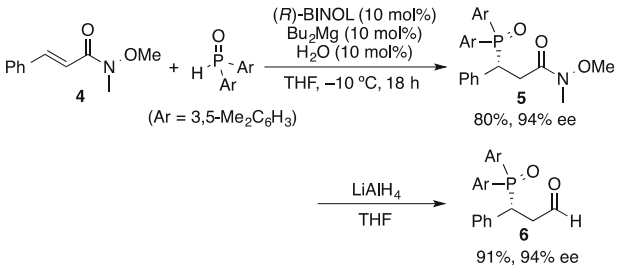
Scheme 2 1,4-Hydrophosphinylation of methyl cinnamates with diarylphosphine oxides



(2)

With the optimized reaction conditions in hand, the unprecedented 1,4-hydrophosphinylation of methyl and ethyl cinnamates with diarylphosphine oxides was examined [48] (Scheme 2). For a variety of α,β-unsaturated esters with an aryl moiety (**3a**–**d**), a heteroaryl moiety (**3e** and **3f**), a conjugated olefin (**3g**), and an alicyclic moiety (**3h**), the corresponding 1,4-adducts were exclusively obtained with 85–95% *ee*. Moreover, sterically demanding diarylphosphine oxides could be used, and the corresponding 1,4-adducts (**3i** and **3j**) were obtained with 92% *ee* and 96% *ee*, respectively, even in gram-scale synthesis.

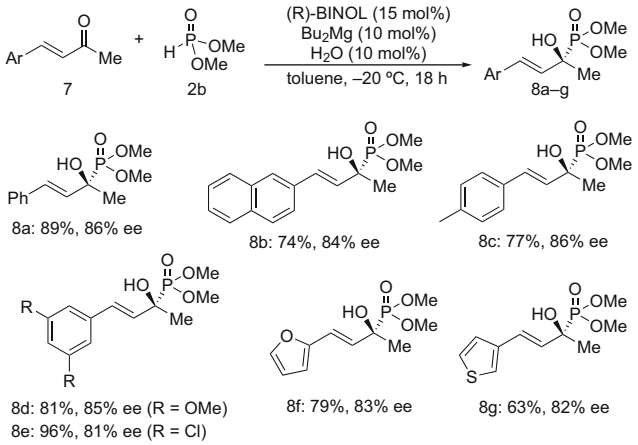
Synthetically useful Weinreb amide **4** was also applicable, and the corresponding 1,4-adduct **5** was obtained in 80% yield with 94% *ee* [48] (Eq. 3). Since compounds **4** and **5** are highly chelatable to Mg(II), the use of 10 mol% each of (*R*)-BINOL and Bu_2Mg exhibited good reactivity. A transformation of **5** to aldehyde **6**, which is usually difficult to synthesize directly by hydrophosphinylation, was readily achieved with the treatment of $LiAlH_4$ without epimerization.



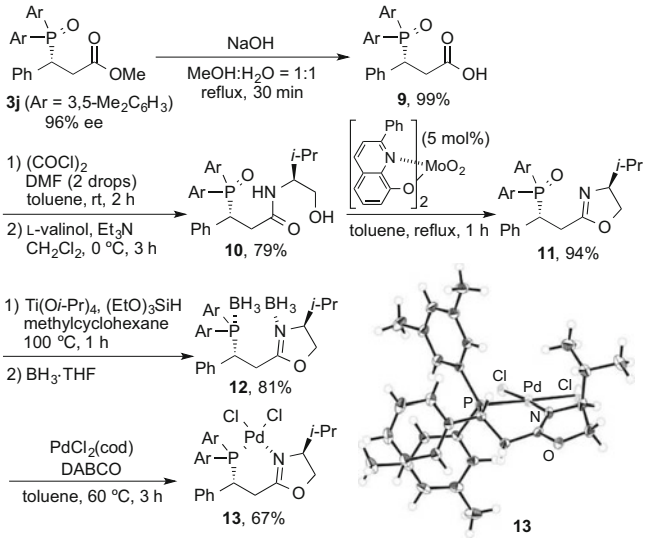
(3)

Despite the strong dependence for regioselectivity (1,2- vs. 1,4-) on substrates, solvents, and catalysts, Ishihara developed a 1,2-hydrophosphonylation of unreactive α,β-unsaturated ketones in the presence of almost the same catalyst [48] (Scheme 3). While the 1,4-hydrophosphinylation with (*R*)-H_8-BINOL/$Bu_2Mg/H_2O = 3:2:2$ (10 mol%/Mg(II)) in THF at –40°C, the use of (*R*)-BINOL/$Bu_2Mg/H_2O = 3:2:2$ (10 mol%/Mg(II)) in toluene at –20°C was effective in 1,2-hydrophosphonylation of benzalacetones (**7**) and dimethyl phosphite (**2b**). Both aromatic and heteroaromatic benzalacetones **7** were acceptable, and the corresponding novel optically active tertiary allylic alcohols (**8a–g**) were obtained with good to high enantioselectivities without the possible phospha-Brook rearrangement and/or retro-reaction [49–51]. The products were highly crystalline, and recrystallization from ethanol increased the optical purity (91~>99% *ee*) without any serious loss of yield.

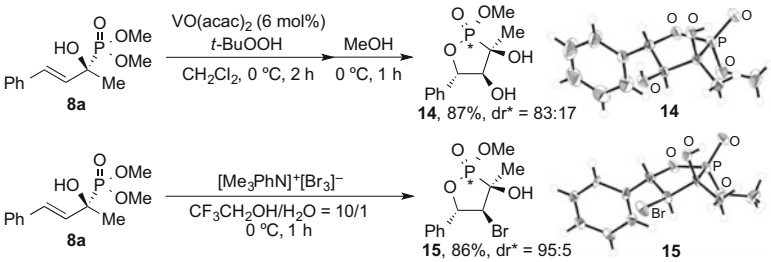
By taking advantage of the synthetic utility of esters [52], a chiral palladium(II) complex was synthesized from optically active 1,4-adduct **3j**, since chiral PN ligand is one of the most important applications of organophosphorus compounds [48] (Scheme 4). After hydrolysis and amidation with L-valinol, the oxazoline moiety was synthesized in 94% yield without epimerization when bulky bis (7-phenylquinolinolate)dioxomolybdenum(IV) complex was used as a dehydrative



Scheme 3 1,2-Hydrophosphonylation of benzalacetones with dialkyl phosphites



Scheme 4 Synthesis of a chiral palladium(II) complex with a PN ligand



Scheme 5 Synthesis of optically active cyclic oxaphospholanols

cyclization catalyst [53–55]. This method is important, since $MoO_2(acac)_2$ induced epimerization (74% de) with low reactivity (38% yield), and basic conditions using MsCl/Et_3N were much less effective (<5% yield). Eventually, the reduction of phosphine oxide, followed by treatment with BH_3·THF, resulted in diborane complex **12** in 81% yield as a stable ligand precursor. Finally, decomplexation of the BH_3-complex by DABCO and recomplexation in situ with $PdCl_2$(cod) gave the desired chiral PN ligand–Pd(II)Cl_2 complex **13** in 67% yield, which could be analyzed by X-ray diffraction. The bulkiness in the PN ligand with three sterically demanding aryl backbones could be rewarding for asymmetric transition metal catalyses.

Since the obtained 1,2-adducts are functionalized tertiary allylic alcohols, an oxidative transformation of **8a** was conducted via diastereoselective epoxidation with TBHP and $VO(acac)_2$ [48] (Scheme 5). Moreover, bromocyclization of **8a**

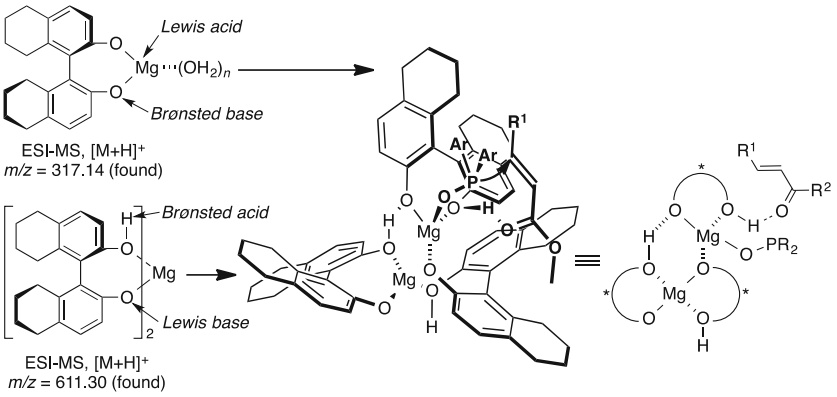


Fig. 2 ESI-MS analysis and possible transition state

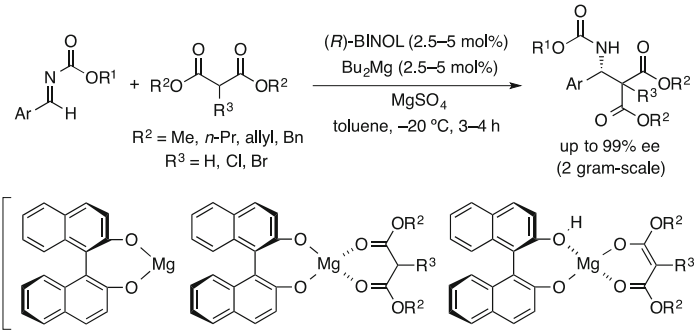
with $[PhMe_3N]^+[Br_3]^-$ gave the desired cyclized compound **15** in 86% yield with 95:5 diastereoselectivity. These novel five-membered oxaphospholanols **14** and **15** are analogues of bioactive materials with anticholinesterase properties [56, 57], and the relative configurations of the four successive stereogenic centers (C-C-C-P) were determined by X-ray diffraction analysis.

According to the established mechanistic study by Shibasaki [58], Ishihara investigated the positive nonlinear effect in 1,4-addition between **1a** and **2a** and the initial rate kinetic study, so that three (*R*)-H_8-BINOLs and two Mg(II) centers would be involved in the transition states. Moreover, ESI-MS analysis of the mixture of Bu_2Mg, (*R*)-H_8-BINOL, and H_2O (2:3:2 molar ratio) in THF showed 1:1 and 1:2 complexes of Mg(II)/(*R*)-H_8-BINOLate (Fig. 2). Overall, a correlation of cooperative 2:3 complex of Mg(II)/(*R*)-H_8-BINOLate might be strongly suggested (Shibasaki has reported the 2:3 complex of La(III)/(*R*)-BINOLate in the asymmetric Michael reaction of enones with malonates: [59]), since the 2:3 complex might be supramolecularly constructed from the directly observed 1:2 and 1:1 complexes in situ. In a possible transition state, nucleophile **2** would be activated by the highly Brønsted basic naphthoxide moiety, and then electrophile **1** or **7** would be activated by the associated Brønsted acid moiety of the naphthol. In this transition state, the absolute stereochemistry of **3** or **8** with high enantioselectivity can be rationalized due to the significant steric hindrance of the congested naphthyl moieties even if 3,3′-nonsubstituted BINOLs are used.

2.3 Catalytic Enantioselective Direct Mannich-Type Reaction

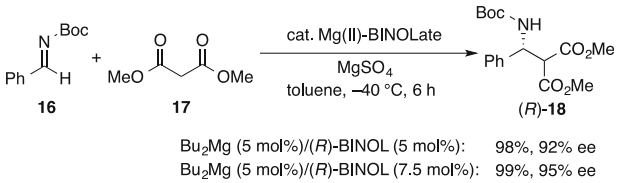
Ishihara has already developed the direct Mannich-type reaction between aldimines and dialkyl malonates [14, 15] (Eq. 4). In that report, they assumed the presence of

some disaggregated mononuclear 1:1 complexes of Mg(II)/(*R*)-BINOLate, since the catalyst was prepared in situ from 1:1 molar ratio of Bu_2Mg and (*R*)-BINOL. However, a 1:1 complex of Mg(II)/BINOLate is too simple to explain the possible asymmetric field to induce high enantioselectivities of over 90% ee. Therefore, the presence of other higher-ordered magnesium(II) complexes (e.g., di- or trinuclear magnesium(II) complexes) would not be completely ruled out.



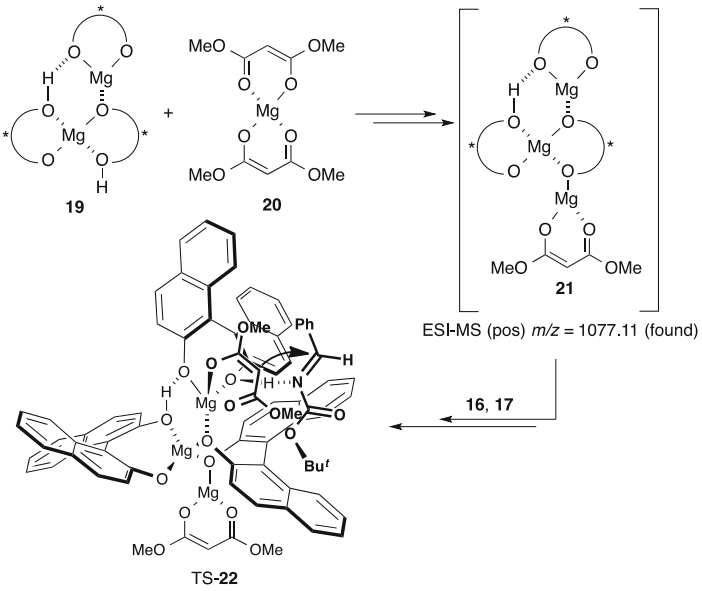
(4)

Actually, after further careful investigation of the reactions, they found that a negative nonlinear relationship was observed between (*R*)-BINOL and the products [60]. Moreover, after the further optimization of the catalysts, a 2:3 ratio of Mg(II)/(*R*)-BINOL gave better results than a 1:1 ratio of Mg(II)/(*R*)-BINOL as the original optimal catalyst (Eq. 5). Therefore, it is possible that the expected chiral supramolecular 2:3 complexes of Mg(II)/(*R*)-BINOLate (**19**) or similar supramolecular complexes might be involved in this reaction.



(5)

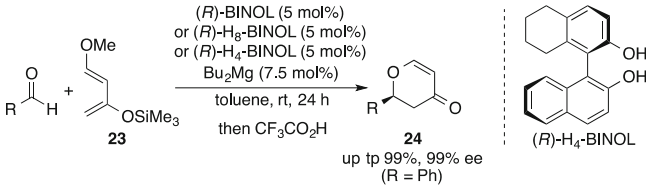
To support the assumption regarding possible supramolecules, ESI-MS analysis of a mixture of (*R*)-BINOL, Bu_2Mg, and **17** (1:1:20 molar ratio) showed a peak at $m/z = 1{,}077.11$ as the 3:3:1 complex of Mg(II)/(*R*)-BINOLate/malonate (**21**) [60] (Scheme 6). This 3:3:1 complex **21** would be based on a 2:3 complex of Mg(II)/(R)-BINOLate (**19**) and magnesium(II) dimethyl malonate (**20**). The corresponding transition state TS-**22** might explain the (*R*)-absolute stereochemistry of **18**. Nucleophile **17** would be activated by the Brønsted basic naphthoxide moiety, and then electrophile **16** would be activated by the associated Brønsted acid moiety of the naphthol. Overall, in the case of the direct Mannich-type reaction, the chiral supramolecular 3:3:1 complex of Mg(II)/(*R*)-BINOLate/malonate (**21**) would be likely rather than the originally expected 1:1 complexes of Mg(II)/(*R*)-BINOLate in Eq. (4).



Scheme 6 Possible chiral supramolecular catalyst in direct Mannich-type reaction

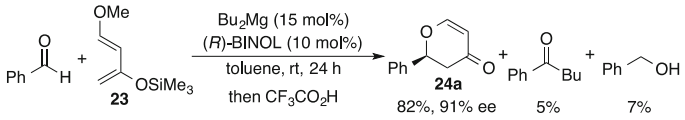
2.4 *Catalytic Enantioselective Hetero-Diels–Alder Reaction*

As another example of magnesium(II) binaphtholate-catalysis, Ding has already reported the hetero-Diels–Alder reaction of aldehydes with Danishefsky's diene (**23**) [13] (Eq. 6). Aggregation behavior of the catalysts was observed by ^{1}H NMR study and a positive nonlinear effect of the reaction. Totally, they concluded that the active site of the catalysts would be the chain ends of the zigzag-aggregated chiral magnesium(II) binaphtholates.



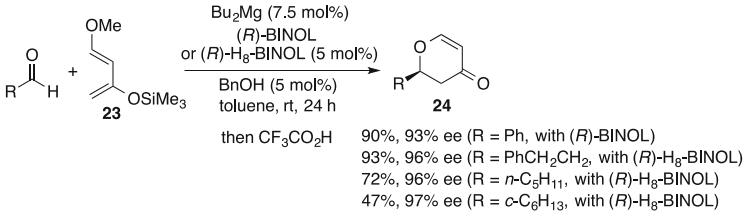
(6)

With the interest of a supramolecular approach, Ishihara examined the same reaction of benzaldehyde and **23**. However, the yield and enantioselectivity were not reproducible at the beginning. After the careful investigation, Ishihara found that valerophenone (5% yield) and benzyl alcohol (7% yield) were obtained in addition to **24a** (82% yield and 91% *ee*) [60] (Eq. 7). Valerophenone and benzyl alcohol might be generated by the Oppenauer-type oxidation of 1-phenyl-1-pentanol and benzaldehyde.



(7)

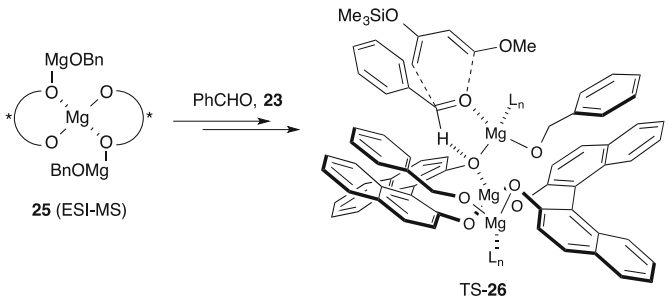
Therefore, Ishihara used benzyl alcohol in advance as an additive (10 mol%) in the reaction. As a result, the reaction proceeded smoothly, and **24a** was obtained in 90% yield with 93% *ee*, even when 5 mol% of catalysts were used [60] (Eq. 8).



(8)

This supramolecular approach (vide infra) was effective for not only benzaldehyde but also aliphatic aldehydes, which have not yet been well developed in the asymmetric hetero-Diels–Alder reaction among many research groups [61–66] (Eq. 8). For dihydrocinnamaldehyde, which is the sole aliphatic aldehyde in Ding's report (up to 80% *ee*) [13], the corresponding product was obtained in 93% yield with greatly improved enantioselectivity (96% *ee*) in the presence of benzyl alcohol. Moreover, hexanal and cyclohexanecarboxaldehyde gave the corresponding products in 16% and 17% yields, respectively, in the absence of benzyl alcohol. In sharp contrast, the corresponding products were obtained in remarkably improved yields (72% and 47%, respectively) with high enantioselectivity (96% *ee* and 97% *ee*, respectively).

The ESI-MS analysis showed a peak at $m/z = 945.32$, which should be identified as trinuclear supramolecular magnesium(II) complex **25** (vide supra) [60] (Scheme 7). Complex **25** might be based on the rigid ((*R*)-BINOLate)$_2$Mg core structure, which can ionically bind two MgOBn moieties. Although other candidates still can be considered to be active species under our reaction conditions, a plausible transition state (TS-**26**) can promote the *si*-face attack of benzaldehyde to lead to the (*S*)-product (**24a**). Probably, benzyl alcohol and/or benzyloxy moieties might keep on coordinating to the Mg(II) centers and help preventing the supramolecular catalysts from being further assembled.



Scheme 7 Possible chiral supramolecular catalyst in hetero-Diels–Alder reaction

3 Chiral Supramolecular Boron(III) Binaphtholate Catalysts

3.1 General Properties of Diels–Alder Reaction

The Diels–Alder reaction is one of the most fundamental higher-ordered stereoselective reactions that involve the formation of two carbon–carbon bonds (for reviews: [61, 67–71]). Via [4+2] cycloadditions, the efficient formation of a cyclohexane skeleton with four successive chiral carbon centers offers synthetic versatility particularly in the total synthesis of many complex natural products [61]. In fact, in several studies to date, enantioselectivity in the Diels–Alder reaction has been successfully controlled by a variety of chiral catalysts or chiral auxiliaries in substrates. On the other hand, *endo*-/*exo*-selectivity in the Diels–Alder reaction strongly depends on the substrates, based on the Woodward–Hoffmann rule and Fukui's conservation rule of orbital symmetry interactions and steric interactions between dienes and dienophiles via the formation of [4+2] pericyclic transition states under thermodynamic or photoreaction conditions [72–75] (Fig. 3).

Therefore, it is quite difficult to control not only enantioselectivity but also substrate-independent anomalous *endo*-/*exo*-selectivity, since most conventional chiral catalysts can discriminate the enantiofaces of dienophiles, but not the approach of dienes [61] (Fig. 4). In fact, many combinations of dienes with dienophiles, particularly α,β-unsaturated carbonyl compounds, allow a well-known *endo*-rule that is based on second-order orbital interactions (Fig. 4a). However, when steric interactions between dienes and dienophiles overcome the second-order orbital interactions in *endo*-transition states, less-familiar *exo*-adducts are often predominantly obtained against the *endo*-rule (Fig. 4b).

For example, in the reaction between cyclopentadiene (**27**) and acrolein (**28a**), an *endo*-preference is observed with regard to second-order orbital interactions without significant steric interactions (Eq. 9). In sharp contrast, in the reaction between **27** and methacrolein (**28b**), an *exo*-preference is observed with regard to steric interaction between the methylene moiety of **27** and the methyl moiety of **28b** (Eq. 10).

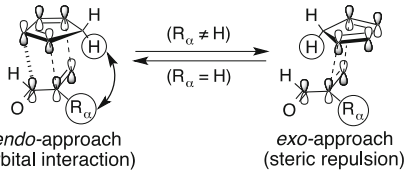


Fig. 3 Substrate-controlled *endo*-/*exo*-selectivity

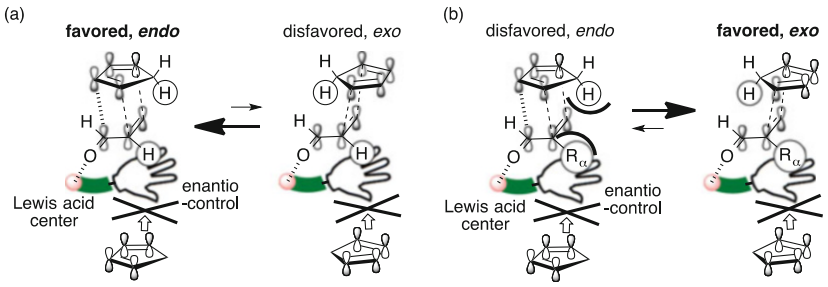
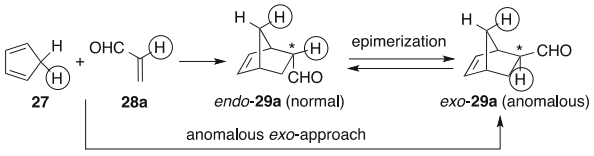


Fig. 4 Normal *endo*-/*exo*-selectivity with conventional chiral catalysts. (**a**) Normal *endo*-control by substrates ($R_\alpha = H$); (**b**) normal *exo*-control by substrates ($R_\alpha \neq H$)



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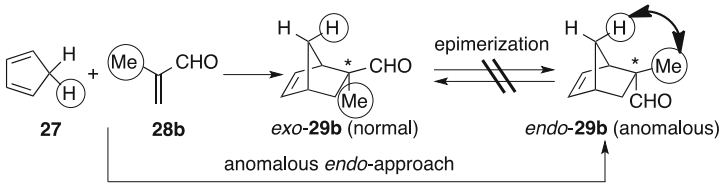


(10)

Of course, thermodynamically more stable optically active *exo*-**29a**, which has a chiral tertiary carbon center at the 2-position, can also be generated by the epimerization of *endo*-**29a** (Eq. 9), since optically active *endo*-**29a** has been synthesized using many conventional chiral catalysts. In contrast, optically active *endo*-**29b**, which has a chiral quaternary carbon center at the 2-position, cannot be generated by the epimerization of easily available *exo*-**29b** (Eq. 10).

To address the major unexplored subject in anomalous *endo*-/*exo*-control in the Diels–Alder reaction, catalysts must be able to accurately discriminate chiral transition state structures, by recognizing not only the *re*/*si*-face of dienophiles but also the *endo*-/*exo*-approach of dienes (Fig. 5). First, catalysts must be able to

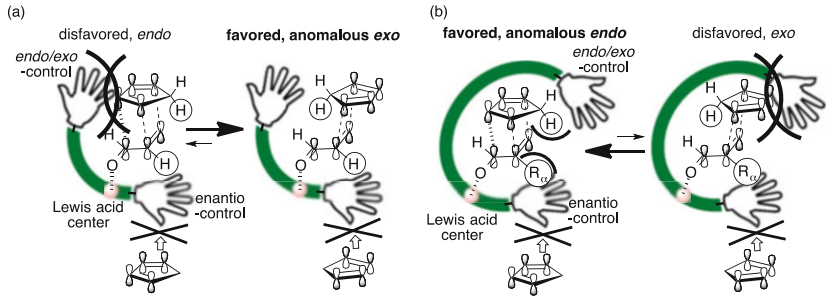


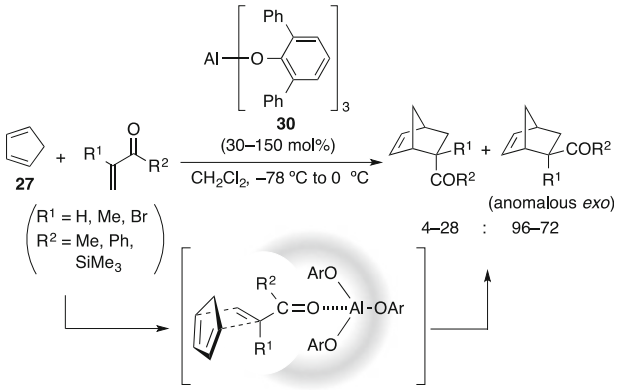
Fig. 5 Anomalous *endo*-/*exo*-selectivity with specially designed chiral catalysts. (**a**) Anomalous *exo*-control by catalyst ($R_\alpha = H$): shallow and wide cavity; (**b**) anomalous *endo*-control by catalyst ($R_\alpha \neq H$): deep and narrow cavity

discriminate the enantiofaces of dienophiles. Second, catalysts must be able to discriminate the *endo*-/*exo*-approach of dienes. Overall, the catalysts must discriminate both the diene and dienophile at the same time in transition states. For anomalous *exo*-control, the catalysts should have a shallow and wide cavity (Fig. 5a). On the other hand, for anomalous *endo*-control, the catalysts should have a deep and narrow cavity (Fig. 5b).

3.2 *Anomalous* Exo*-selective Diels–Alder Reaction with Single-Molecule Catalysts*

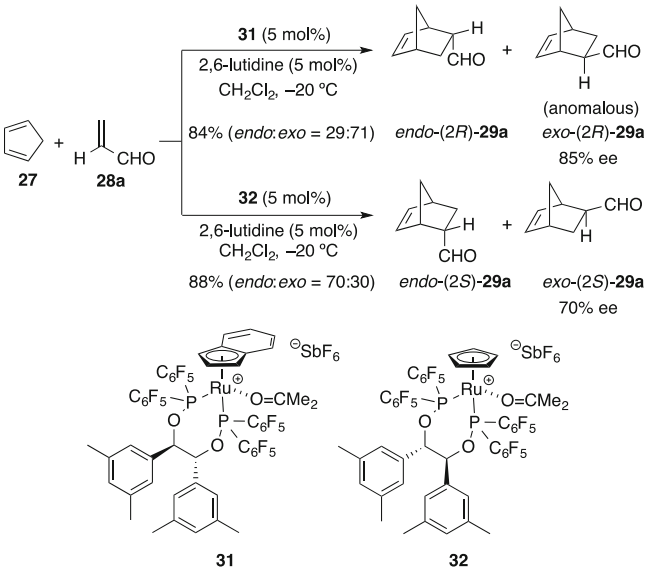
It should be a less heavy task to design promising catalysts for anomalous *exo*-control than for anomalous *endo*-control, since the external *exo*-approach can be realized when the internal *endo*-approach would be effectively prevented even with single-molecule catalysts with a relatively small structure (Fig. 5a). Thus, a deep and narrow cavity for both a diene and a dienophile is not necessary for anomalous *exo*-control.

In fact, relatively small single-molecule catalyst-induced anomalous *exo*-selective Diels–Alder reactions against the original *endo*-rule have been investigated by a few research groups. For example, Yamamoto reported a molecular recognition approach by using a bulky aluminum(III) Lewis acid catalyst, ATPH (**30**), which provides an effective small carbonyl pocket, in a non-asymmetric manner for the first time (Eq. 11) [76]. Dienophiles are effectively shielded by complexation with the bulky achiral aluminum(III) catalyst, and the external *exo*-approach can be preferred (*endo*:*exo* = up to 4:96), while secondary interactions are significantly diminished.



(11)

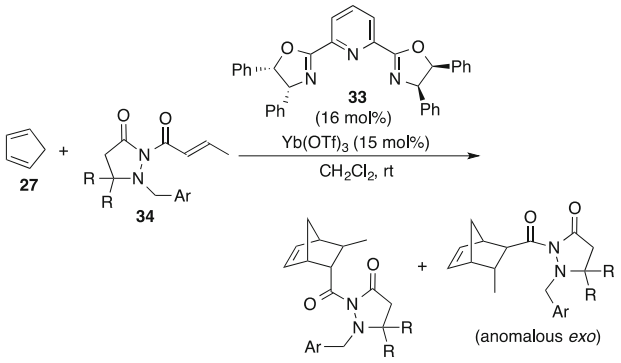
Later, Kündig developed the first anomalous *exo*-selective, catalytic enantioselective Diels–Alder reaction between **27** and **28a** that usually favors the *endo*-cycloadduct (Eq. 12) [77]. With cationic chiral indenyl ruthenium(II) catalyst (**31**), the reaction afforded anomalous *exo*-**29a** with 85% *ee* as major product with an *endo*:*exo* ratio of 29:71. Interestingly, complete inversion of *endo*-/*exo*-selectivity compared to that obtained with the cyclopentadienyl catalyst (**32**) was observed, which gave normal *endo*-**29a** as major product with an *endo*:*exo* ratio of 70:30. They concluded that the bulky indenyl arene ring would interfere with C(2)–H and C(3)–H of the approaching **27**.



(12)

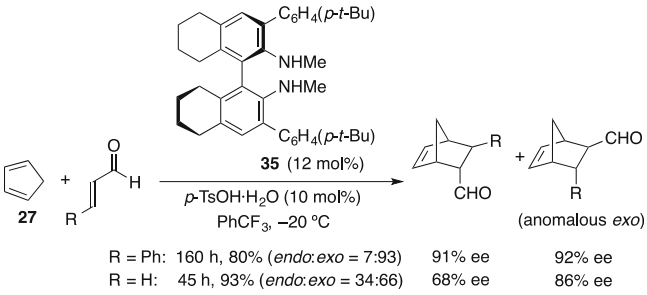
Sibi developed the chiral Pybox (**33**)–ytterbium(III)-catalyzed anomalous *exo*-selective Diels–Alder reaction with a bulky achiral pyrazolidinone auxiliary in dienophiles (**34**) (Eq. 13) [78]. In this case, sterically hindered N-1 mesitylmethyl

and C-5 ethyl substitutions in pyrazolidinone **34** were essential for realizing improved anomalous *exo*-selectivity (*endo*:*exo* = 16:84). For instance, less-hindered N-1 benzyl- and C-5 methyl-substituted substrate led to a lower *endo*:*exo* ratio of 56:44.



(13)

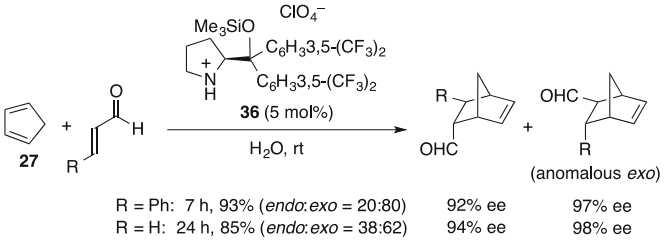
Maruoka reported the chiral diamine salt-catalyzed anomalous *exo*-selective enantioselective Diels–Alder reaction (Eq. 14) [79, 80]. The reaction of cinnamaldehyde in the presence of 12 mol% of chiral 3,3′-disubstituted *N*,*N*′-dimethyl H_8-binaphthyldiamine (**35**) and 10 mol% of *p*-TsOH·H_2O in α,α,-α-trifluorotoluene at –20°C gave the corresponding anomalous *exo*-adduct with 92% *ee* (80% yield, *endo*:*exo* = 7:93). Moreover, the reaction of acrolein (**28a**) in the presence of the same catalyst gave the anomalous *exo*-**29a** with moderate *endo*-/*exo*-selectivity (93% yield, *endo*:*exo* = 34:66, 86% *ee* for *exo*-**29a**). This is the first example of an organocatalytic anomalous *exo*-selective Diels–Alder reaction, although a prolonged reaction time was needed (40–160 h).



(14)

Hayashi reported that a chiral salt of diarylprolinol silyl ether (**36**) induced anomalous *exo*-selectivity in the enantioselective Diels–Alder reaction between **27** and α,β-unsaturated aldehydes (Eq. 15) [81]. In particular, the reaction of cinnamaldehyde in the presence of 5 mol% of catalyst **36** in water at room temperature gave the corresponding anomalous *exo*-adduct with 97% *ee* (93%

yield, *endo*:*exo* = 20:80). Moreover, the reaction of acrolein (**28a**) gave the anomalous *exo*-**29a** with moderate *endo*-/*exo*-selectivity (*endo*:*exo* = 38:62, 98% *ee* for *exo*-**29a**).



(15)

3.3 *Anomalous* Endo-*selective Diels–Alder Reaction with Chiral Supramolecular Catalysts*

In sharp contrast to previous anomalous *exo*-induced Diels–Alder reactions with α-nonsubstituted acroleins, there have been no reports on anomalous *endo*-induced catalytic enantioselective Diels–Alder reactions with α-substituted acroleins against the original *exo*-rule. In principle, for anomalous *endo*-control, a reaction intermediate should have a folding structure regardless of considerable steric repulsion between the reactants as seen in Fig. 5b. Therefore, a deep and narrow cavity in the catalyst is necessary to hold both a diene and a dienophile together throughout the transition states.

To realize this strategy, a rational design of conformationally flexible chiral supramolecular catalysts, similar to natural enzymes, might be possible. Moreover, according to Lehn's original definition of "supramolecule" [1], which includes more than two molecules with non-covalent intermolecular bonds, supramolecular catalysts might be simple extension from single-molecular catalysts.

In regard to the construction of supramolecular catalysts, non-covalent acid–base attractive interaction might be useful. In particular, Shibasaki has pioneeringly developed the acid–base combination chemistry [18], in which they often use phosphine oxides as functionalized Lewis bases [82–93]. In their early studies, for example, they developed the catalytic enantioselective cyanosilylation of aldehydes, ketones, and aldimines with the use of acid–base bifunctional catalysts **37** and **38** [82–86] (Eqs. 16, 17). In these reactions, phosphine oxides play an important role to activate trimethylsilyl cyanide or coordinate to the Lewis acid center in supramolecular fashions (Fig. 6).

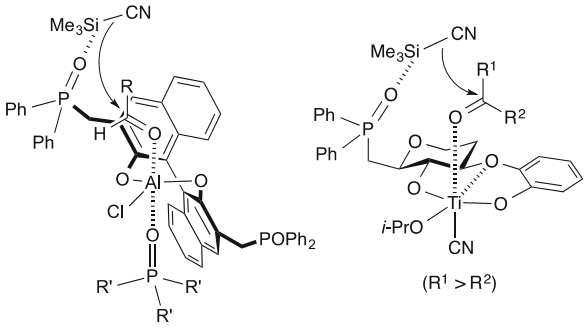
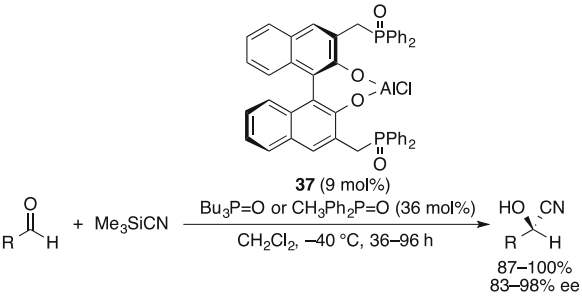


Fig. 6 Strategic phosphoryl groups as Lewis bases in asymmetric catalysis



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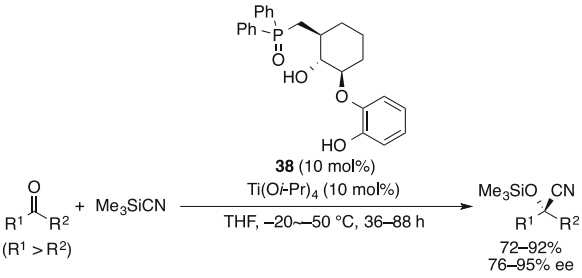
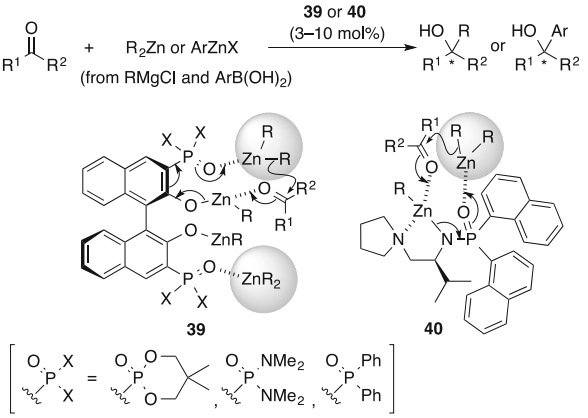


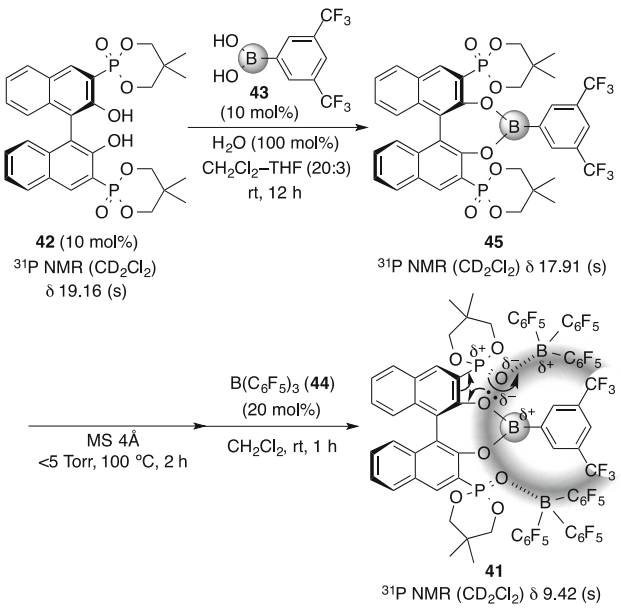
(17)

Ishihara has developed the catalytic enantioselective organozinc addition to aldehydes and ketones using acid–base conjugate Zn(II) catalysts (**39** and **40**) [94–101] (Eq. 18). In these catalysts, acid–base remote activation of both the carbonyl compound and the organozinc reagent is important. In particular, the phosphoryl moieties would have good Lewis basicity to activate the electron-deficient organozinc center. They expected that this acid–base activation system, in particular with possible bulkiness based on the C_2-symmetric chiral BINOL moiety, might be applicable to the design of novel conformationally flexible chiral supramolecular catalysts.



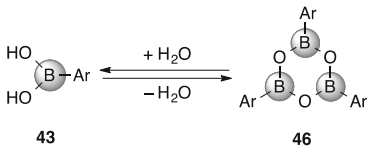
(18)

In such a situation, Ishihara developed a new type of conformationally flexible, highly active, chiral supramolecular catalyst based on well-designed single-molecule components [102, 103]. A chiral supramolecular catalyst (**41**) was readily prepared in situ from three components, including 10 mol% of chiral (*R*)-3,3′-bis(5,5-dimethyl-2-oxido-1,3,2-dioxaphosphorinan-2-yl)-BINOL (**42**), 10 mol% of 3,5-bis(trifluoromethyl)phenylboronic acid (**43**), and 20 mol% of tris(pentafluorophenyl)borane (**44**) [102] (Scheme 8). Since the arylboronic acid **43** is usually allowed at hydrolysis equilibrium with the triarylboroxin **46** (Eq. 19), the addition of a small amount of water is necessary to provide the boron BINOLate inter-



Scheme 8 Preparation of a chiral supramolecular catalyst

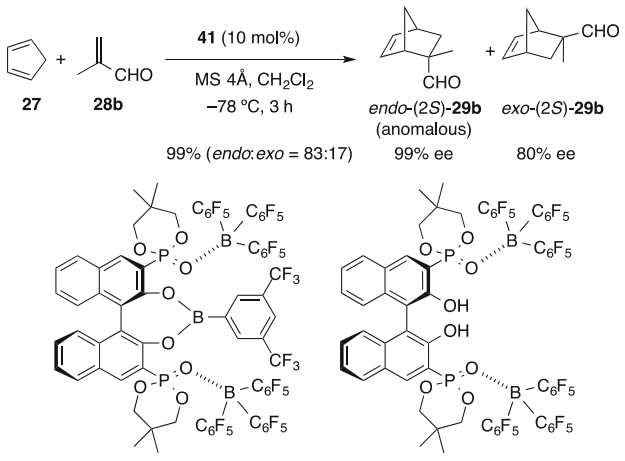
mediate **45** [104]. On the other hand, highly coordinative water molecules must be removed by MS 5 Å before the subsequent supramolecular formation of non-covalent bonds between **44** and **45**. Preliminary investigations by ^{31}P NMR analysis in CD_2Cl_2 showed a corresponding peak shift of two C_2-symmetric phosphoryl moieties: 19.16 ppm for **42**, 17.91 ppm for **45**, and 9.42 ppm for **41**.



(19)

For the design of conformationally flexible supramolecule **41**, intermolecular acid–base coordination bonds in the two P=O···B(C_6F_5)$_3$ are critical [105]. Compound **44** would act as a bulky functional group to make a chiral, narrow, and deep cavity around the Lewis acidic boron center. Moreover, the strong electron-recipient ability of Lewis acid **44** would increase the Lewis acidity of the central boron through conjugate bonds (Scheme 8), which would take advantage of Lewis acid-assisted chiral Lewis acid (LLA) catalysts [106, 107].

In the presence of chiral supramolecular catalyst **41** (10 mol%), the Diels–Alder reaction between **27** and **28b** was conducted in dichloromethane at –78°C for 3 h [102] (Scheme 9). As a result, anomalous *endo*-(2*S*)-**29b** was obtained as a major product (99% yield, *endo*:*exo* = 83:17) with excellent enantioselectivity (99% *ee*). In sharp contrast, **42** and incomplete complexes **45** (i.e., [**42**+**43**]) and **47** (i.e., [**42**+**44**]) showed almost no catalytic activity (0–2% yield). Moreover, **43** and **44** gave



cf.
42 (10 mol%): 0%
43 (10 mol%): >99% (*endo*:*exo* = 6:94)
44 (10 mol%): 93% (*endo*:*exo* = 12:88)
45 (10 mol%): 2%
47 (20 mol%): 0%

Scheme 9 Anomalous *endo*-selective enantioselective Diels–Alder reaction between **27** and **28b**

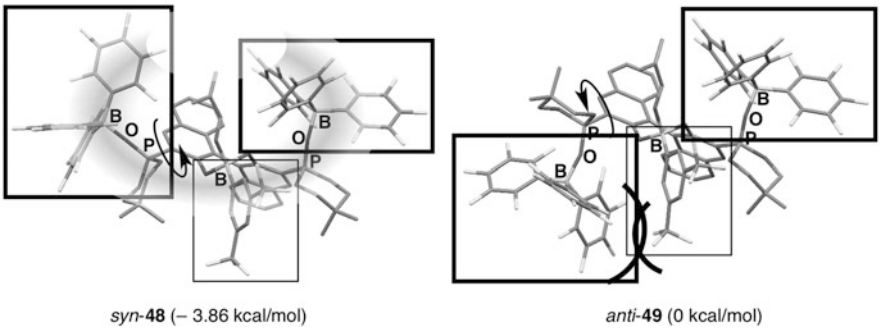


Fig. 7 Theoretical calculations using Gaussian03 (B3LYP/6-31G*)

the normal *exo*-**29b** as a major product (*endo*:*exo* = 6–12:94–88). For catalyst **27**, the phosphoryl moieties of **42** would coordinate to **44**, and thus **44** as a Lewis acid would be deactivated. For catalyst **45**, the corresponding boron(III) BINOLate would not be reactive, since it lacks conjugated activation by Lewis acid **44**. Therefore, the catalytic activity of **41** decreased even in the absence of either **43** or **44**.

To date, there has been no solid evidence for the possible geometry of the supramolecular catalyst. However, as a working model to explain the anomalous stereoselectivity, a chiral, narrow, and deep cavity is assumed due to the six bulky C_6F_5 moieties. In this regard, theoretical calculations for a **28b**–**41** complex with the B3LYP/6-31G* method supported that the two non-covalent P=O···B(C_6F_5)$_3$ moieties have a *syn*-conformation (**48**) on one hand and an *anti*-conformation (**49**) on the other hand [102] (Fig. 7). Remarkably, *syn*-**48** is more stable than *anti*-**49** by 3.86 kcal/mol. In *anti*-**49**, significant steric repulsion would be observed among the C_6F_5 moieties and the central 3,5-$(CF_3)_2C_6H_3B$ moiety. Therefore, *syn*-**48** is more favored.

In *syn*-**48**, the formyl moiety of **28b** with a favored *s*-trans geometry was doubly coordinated with the B-O(Naph) moiety at the C(=O)H and C(=O)H parts (Fig. 7). Among the possible transition states, a *si*-face attack would be disfavored due to enantio-face control by a C_6F_5 group. In a possible transition state (TS)-**50**, an *endo*-approach inside the cavity via a *re*-face attack would be relevant, while an *exo*-approach via a *re*-face attack (TS-**51**) would be unlikely because of the bulkiness of another C_6F_5 group [102] (Fig. 8).

To demonstrate other anomalous *endo*-selective Diels–Alder reactions, the reactions between **27** and α-haloacroleins, which usually provided *exo*-adducts as major products (Scheme 10), were examined [102]. Electron-deficient α-haloacroleins are extremely reactive, and thus their enantioselective Diels–Alder reactions have been especially limited. Moreover, the reports were on substrate-dependent *exo*-selective reactions. Corey reported pioneering *exo*-selective examples with both α-bromoacrolein (**28c**) [108] and α-chloroacrolein (**28d**) [109, 110], and other research groups later came to report *exo*-selective and enantioselective catalysis with **28c**. However, there have been no catalytic asymmetric examples of the Diels–Alder reactions of α-fluoroacrolein (**28e**).

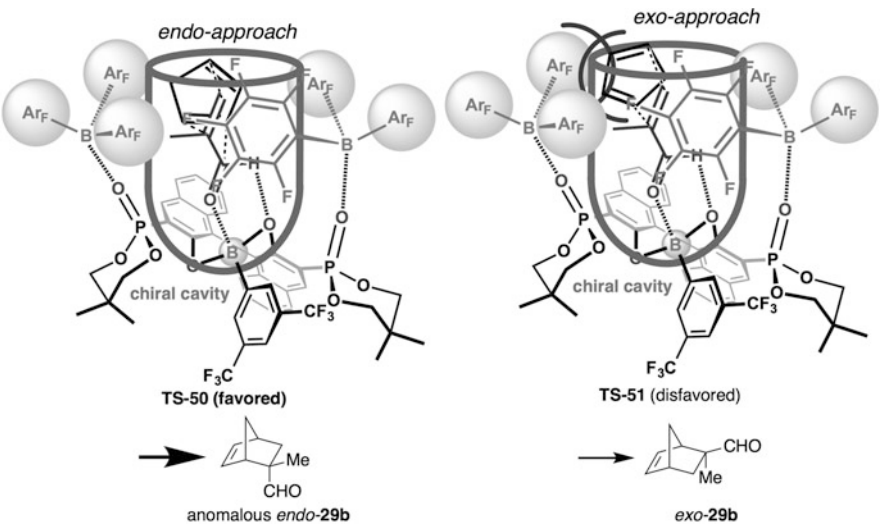
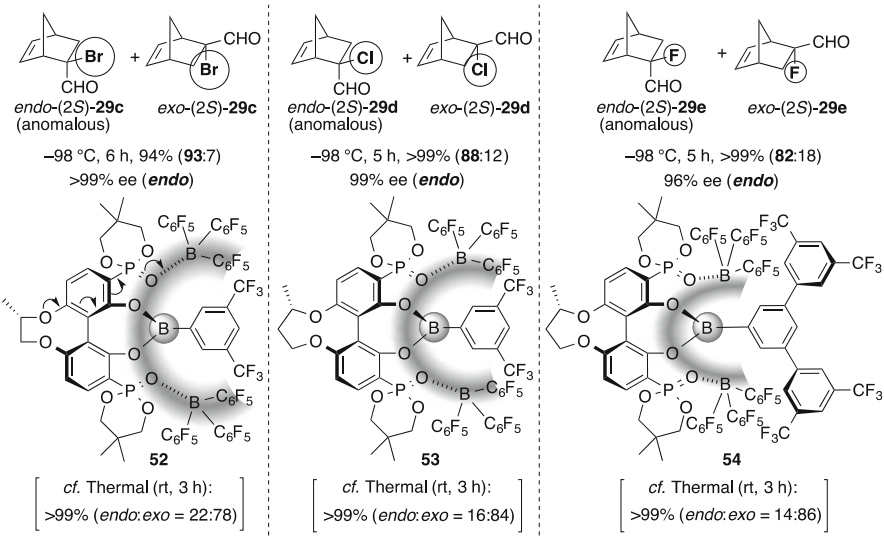


Fig. 8 Possible transition states for anomalous *endo*-selectivity



Scheme 10 Anomalous *endo*-selective enantioselective Diels–Alder reaction of α-haloacroleins

In the reaction between **27** and **28c** in dichloromethane at –98°C for 6 h, supramolecular catalyst **41** was ineffective, and *exo*-**29c** was obtained as a major product with low enantioselectivity (>99% yield, *endo*:*exo* = 16:84, 10–11% *ee*). However, after optimization of the chiral biaryl skeleton, another supramolecular catalyst **52** with chiral biphenol in place of chiral binaphthol **42** was extremely

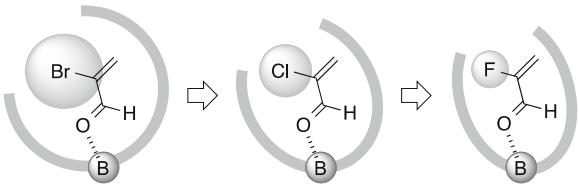
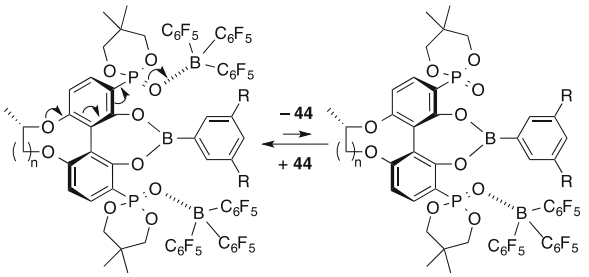


Fig. 9 Tuning the size of a suitable cavity for each substrate

effective, and the anomalous *endo*-selectivity was dramatically improved (94% yield, *endo*:*exo* = 93:7) with excellent enantioselectivity for *endo*-(2*R*)-**29c** (>99% *ee*). Furthermore, in the reaction between **27** and **28d** in dichloromethane at –98°C for 5 h in the presence of hydroquinone (10 mol%) as a polymerization inhibitor, after another fine-tuning for the chiral biaryl skeleton, supramolecular catalyst **53** provided anomalous *endo*-selectivity, and *endo*-(2*R*)-**29d** was obtained as a major product (>99% yield, *endo*:*exo* = 88:12) with excellent enantioselectivity (>99% *ee*). Finally, unprecedented α-fluoroacrolein (**28e**) was examined. Under thermodynamic conditions without catalysts, *exo*-product **29e** was obtained predominantly (>99% yield, *endo*:*exo* = 14:86). On the other hand, anomalous *endo*-(2*R*)-**28e** was obtained as a major product (>99% yield, *endo*:*exo* = 82:18) with high enantioselectivity (96% *ee*) when bulky **54**, which was derived from 3,5-bis[3,5-bis (trifluoromethyl)phenyl]phenylboronic acid, was used.

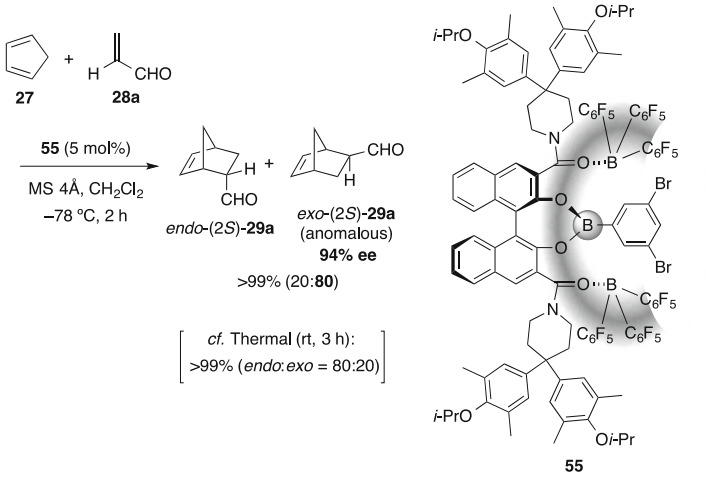
Overall, as with an enzymatic methodology, fine-tuning of the conformationally flexible supramolecular catalysts for each α-haloacrolein was essential for establishing anomalous *endo*-selectivity as well as excellent enantioselectivity. As the halogen in α-haloacrolein becomes smaller, larger components at the central aryl boron moiety and the biphenyl moiety were effective. The more bulkiness may directly or indirectly create a smaller cavity that could suitably recognize a smaller substrate (Fig. 9).

The reason why the anomalous *endo*-selectivity of **29c** was significantly improved when biphenyl catalyst **52** was used in place of binaphthyl catalyst **41** is not yet completely solved. As a possible explanation, there might be a slight difference in the dihedral angle of the binaphthyl or biphenyl skeleton. As another possible explanation, the electron-donating ability of the 6,6′-ether moieties in **52**–**54** (i.e., –$OCH(CH_3)CH_2O$– or –$OCH(CH_3)CH_2CH_2O$–), through a resonance effect in the conjugate system, might induce a stronger intermolecular acid–base coordination of non-covalent P=O···$B(C_6F_5)_3$ (Scheme 11). This stabilization of the supramolecular catalysts might reduce the adventitious dissociation of achiral **44**. Consequently, normal Diels–Alder reactions with extremely low enantioselectivity by incomplete supramolecular catalysts and/or **44** would be prevented when reactive **28c**–**e** were used in place of much less-reactive **28b**.



52–54

Scheme 11 A resonance effect in chiral biphenol catalysts



Scheme 12 Anomalous *exo*-selective enantioselective Diels–Alder reaction between **27** and **28a**

3.4 Anomalous Exo-selective Diels–Alder Reaction with a Chiral Supramolecular Catalyst

The reaction with acrolein (**28a**) in place of α-haloacroleins was examined [102] (Scheme 12). Generally, the reaction of **27** with **28a** was *endo*-selective under substrate control (e.g., *endo*:*exo* = 80:20 under thermal conditions). For anomalous *exo*-control, another supramolecular catalyst with amido moieties in place of phosphoryl moieties was developed. Supramolecular catalyst **55** (5 mol%) was thus prepared in situ from chiral 3,3′-(dicarbamoyl)binaphthol, (3,5-dibromophenyl)boronic acid, and **44**. As a result, **55** was highly effective for the anomalous *exo*-selective Diels–Alder reaction of **28a** with high enantioselectivities (94% *ee* for *exo*-(2*S*)-**29a**, *endo*:*exo* = 20:80).

Similar to the case of supramolecule **41** with phosphoryl moieties, a possible transition state (TS-**56**) for supramolecular **55** with amide moieties is shown in Fig. 10 [102]. Unlike the pseudo-tetrahedral phosphorus structure, the amide has a

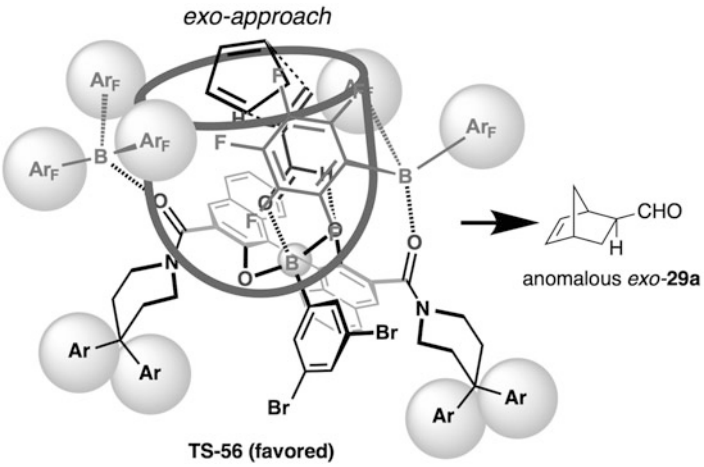
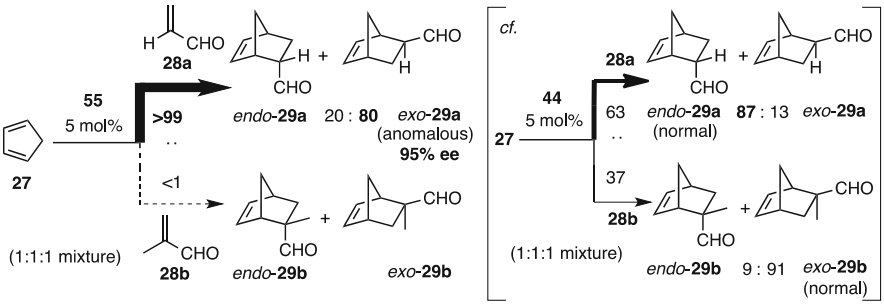


Fig. 10 Possible transition states for anomalous *exo*-selectivity

less-hindered planar structure, and the non-covalent amide–$B(C_6F_5)_3$ moiety may turn outside the **27**–**28a**–**55** complex in the transition states. Therefore, a shallow and wide cavity would be provided, and this would promote the anomalous *exo*-approach without significant steric repulsion via TS-**56**.

3.5 Molecular Recognition by the Chiral Supramolecular Catalyst

To further investigate the function of conformationally flexible supramolecular catalysts, a molecular recognition under substrate-competitive Diels–Alder reaction conditions was performed. For a 1:1:1 equimolar mixture of **27**, **28a**, and **28b**, *exo*-inducing supramolecular catalyst **55** (5 mol%) promoted the reaction of **28a** exclusively (**28a**:**28b** = >99:<1), and anomalous *exo*-(2*S*)-**29a** was obtained as a major product (*endo*:*exo*-**29a** = 20:80, 95% *ee* for *exo*-(2*S*)-**29a**) [102] (Scheme 13). In sharp contrast, achiral Lewis acid catalyst **44** (10 mol%) gave a mixture of *endo*-**29a** and *exo*-**29b** as major products with low substrate selectivity (**28a**:**28b** = 63:37) and normal *endo*-/*exo*-selectivity (*endo*:*exo*-**29a** = 87:13, *endo*:*exo*-**29b** = 9:91). This result suggests that the supramolecular catalyst may have some induced-fit functions to adapt to a specific substrate.



Scheme 13 Molecular recognition under substrate-competitive reaction conditions

4 Conclusion

Here we discussed key issues based on our supramolecular Brønsted acid/Lewis base hybrid catalysts. In one section, we reviewed the highly enantioselective 1,4-hydrophosphinylation and 1,2-hydrophosphonylation of α,β-unsaturated carbonyl compounds, which were catalyzed by simple chiral aggregated magnesium (II) binaphtholate aqua complexes as cooperative Brønsted acid/Lewis base hybrid catalysts in situ. Insights into the mechanistic details showed that 2:3 supramolecular complexes of Mg(II)/(*R*)-BINOLate were involved as the active species. This finding encouraged us to investigate the two precedent reactions, such as the direct Mannich-type reaction and the hetero-Diels–Alder reaction. As a result, the detailed mechanistic studies strongly suggested that chiral di- and trinuclear supramolecular magnesium(II) complexes should play key roles as the active catalytic species in these reactions. Such a practical methodology with a fundamental acid–base aggregation, which is induced by diversity of simple, inexpensive, and harmless magnesium(II) binaphtholate catalysts, can open up further efficient asymmetric catalyses in the future. In the other section, we reviewed more artificial enzymatic supramolecular catalysts, which were readily prepared in situ from chiral 3,3′-disubstituted binaphthols and biphenols, arylboronic acid, and $B(C_6F_5)_3$. The evolution from "ready-made" single-molecule catalysts to "tailor-made" supramolecular catalysts based on conjugated acid–base units could offer not only high enantioselectivity but also anomalous *endo*-/*exo*-selectivities in the Diels–Alder reaction. Conformationally flexible chiral cavity like "key holes" in enzymes with an induced-fit function was provided in "tailor-made" chiral supramolecular catalysts for each substrate. This unique methodology might be hardly achieved by conventional "ready-made" single-molecule catalysts. Totally, the full properties of chiral supramolecular catalysts to realize substrate-independent regio- and/or stereoselectivity in organic synthesis have just taken off, and these ongoing studies shown here might be the tip of iceberg. Therefore, trial and error approach will be necessary to overcome unprecedented difficulties, and the supramolecular Brønsted acid/Lewis base hybrid catalysts will contribute the further increasing progress in the near future.

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Chiral Alkaline Earth Metal Complexes in Asymmetric Catalysis

Yasuhiro Yamashita, Tetsu Tsubogo, and Shū Kobayashi

Abstract Alkaline earth metal catalysis for asymmetric reactions is a hot topic from the viewpoint of green sustainable chemistry. The stable alkaline earth metals, calcium (Ca), strontium (Sr), and barium (Ba) are abundant in the Earth's crust, and their strong Brønsted basicity and mild Lewis acidity are useful for construction of alkaline earth metal complexes as chiral catalysts. In this chapter, the development of chiral alkaline earth metal catalysts for catalytic asymmetric reactions is described. The chiral alkaline earth metal complexes are categorized into three types of complexes, types I–III, by coordination modes, and those complexes successfully promoted many types of reactions in acid–base catalysis with high enantioselectivities.

Keywords Alkaline earth metal · Asymmetric reaction · Barium · Calcium · Flow synthesis · Heterogeneous catalysis · Homogeneous catalysis · Polymer-supported catalyst · Strontium

Contents

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1 Introduction

The development of new methodologies for catalytic asymmetric reactions is a mainstream in the asymmetric synthesis of optically active compounds. Among these compounds, chiral metal catalysts have become the most important, and the use of these systems has enabled high enantioselectivities to be achieved in many asymmetric reactions [1, 2]. However, to reduce the damage on the environment, the use of less toxic and less harmful metals is now strongly preferred in synthetic processes, and much effort has been made to develop environmental-friendly metal catalysts from the viewpoint of green sustainable chemistry [3–6]. The stable alkaline earth Group II metals, calcium (Ca), strontium (Sr), and barium (Ba), are abundant in the Earth's crust [7–9]; however, it has been a long time since much attention has been paid to these metals for application in asymmetric reactions as catalysts, presumably because of the less distinctive characteristic nature of group I and group III metals, especially with respect to the acidic or basic characters of these compounds. For example, Group I metal phenoxides (lithium, sodium, and potassium phenoxides) are known to be Brønsted basic species, whereas group III metal phenoxides (scandium, yttrium, and lanthanide phenoxides) are known to be Lewis acidic species, although the stable valences of the ions are different. Among them, alkaline earth metals have been considered to possess amphoteric acid/base characteristics. However, recently, these characteristics have been reappraised with a view of developing cooperative acid/base catalysts. Their low but significant Lewis acidity and strong Brønsted basicity turned out to be attractive for the design of highly reactive metal acid/base catalysts. Moreover, as mentioned above, the ubiquitous existence of such metals on Earth makes them economically valuable, and their lower levels of toxicity are promising for their use in industrial processes. Therefore, the development of chiral catalysts using group II alkaline earth metals is one of the hottest topics in catalytic asymmetric synthesis [10–16]. In this chapter, we focus on recent progress in the development of chiral alkaline earth metal complexes for catalytic asymmetric reactions.

2 Types of Alkaline Earth Metal Complexes

For the preparation of chiral alkaline earth metal complexes, characteristic chemical properties of alkaline earth metals are utilized effectively. In this respect, notable chemical properties of alkaline earth metals are (1) their divalent stable oxidation state, (2) the high coordination numbers to the metal center derived from their large ion size, and (3) the mild but significant Lewis acidity that enables them to accept coordinative ligands. Furthermore, their complexes can show strong Brønsted basicity. These features come from the position of the elements on the periodic table. Asymmetric environments around the alkaline earth metals can be

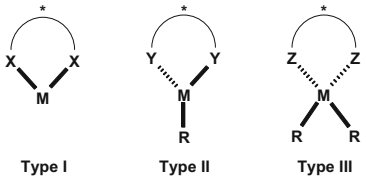


Fig. 1 Categories of chiral alkaline earth metal complexes

prepared based on these properties. Historically, chiral modification of alkaline earth metals has been considered very difficult because of their large ion size and high coordination numbers; however, recent progress in this area has revealed that it is possible by careful design of the chiral metal complexes.

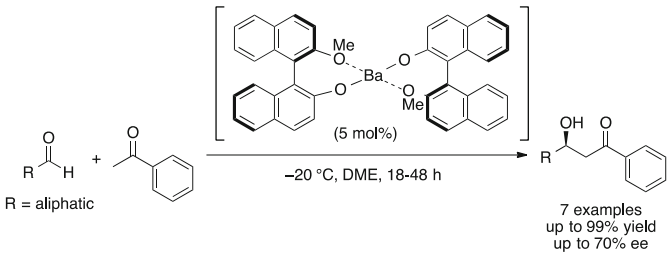
Chiral alkaline earth metal complexes that have been reported can be classified into three types (Fig. 1) [16]. The first type of complex (type I) is constructed through only covalent bonds between the metal and the ligand. In this system, the asymmetric environment has only been prepared with anionic chiral ligand(s). Therefore, the metal is tightly connected to the ligand, which means that strict control of the asymmetric environment is possible. In this type of complex, however, fine control of the basicity of the catalyst is difficult because the ligand itself works as a Brønsted base. The second type of complex is constructed by both covalent and coordinative bonds to a ligand (type II). When a chiral ligand is bound to a metal by a combination of one covalent bond and other coordinative bonds in more than a bidentate fashion, strict control of the asymmetric environment is possible. In the complexes, the remaining counter anion is still free; therefore, the Brønsted basicity of the complex can be controlled by changing the free counteranion. The third type of complex is constructed by using a coordinative ligand through only coordinative bonds (type III). In type III complexes, there is no covalent bond between the metal and a chiral ligand with which to prepare an asymmetric environment; it has also been considered difficult because the Lewis acidity of alkaline earth metals was not so significant. However, recently, it has been revealed that the Lewis acidity of alkaline earth metals is sufficient to form a complex with a coordinative ligand even when Brønsted basic alkaline earth metal complexes are employed. The advantage of this type of complex is significant. We can choose several kinds of alkaline earth metal salts; not only Brønsted basic salts but also neutral and Lewis acidic salts and many well-known coordinative chiral ligands are available. Furthermore, type III alkaline earth metal complexes prepared as neutral salts are expected to be more robust under ambient conditions compared with type I and II alkaline earth metal catalysts, which are sometimes air and moisture sensitive. These features are promising for the preparation of solid-supported chiral alkaline earth metal catalysts. In the following sections, chiral alkaline earth metal complexes are classified into the three types and introduced briefly with an explanation of their characteristics.

3 Type I Chiral Alkaline Earth Metal Complexes for Asymmetric Reactions

At the dawn of the development of chiral alkaline earth metal complexes, chiral modification of alkaline earth metals was performed by using bidentate-type chiral ligands bearing relatively acidic hydrogen atoms to form type I chiral alkaline earth metal complexes. In this type of complex, the formation of a relatively rigid asymmetric environment is possible. The most commonly employed chiral backbones of such complexes are 1,1′-bi-2-naphthol (BINOL) and 1,1′-bi-2-phenol derivatives. In these catalysts, relatively strong Brønsted basicities were observed. On the other hand, recently, modification of alkaline earth metals has also been conducted by using two equivalents of chiral phosphoric acids. In these cases, the steric bulk of the phosphoric acids can lead to the formation of a highly asymmetric environment around the metal centers. Furthermore, the enhanced Lewis acidity of the alkaline earth metal can be used to control the coordination of substrates, although their Brønsted basic nature is sometimes not significant.

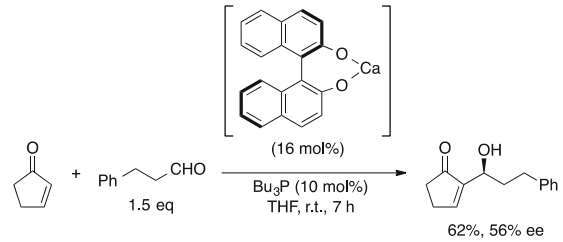
3.1 Chiral Alcohol, Phenol, and Amide-Based Complexes

BINOL derivatives are one of the most frequently employed chiral units in many types of chiral catalysts. The ability of these compounds to coordinate in a bidentate fashion can lead to very promising asymmetric environments around the metal center. Yamada and Shibasaki reported a chiral barium catalyst prepared from two equivalents of BINOL monomethyl ether and barium alkoxide, which promoted catalytic asymmetric direct-type cross aldol reactions of ketones to aldehydes in high yields with good enantioselectivities [17]. In the structure of this complex, it was assumed that two BINOL moieties coordinated to the barium center in a bidentate fashion even after deprotonation of the ketone prenucleophile (Scheme 1).

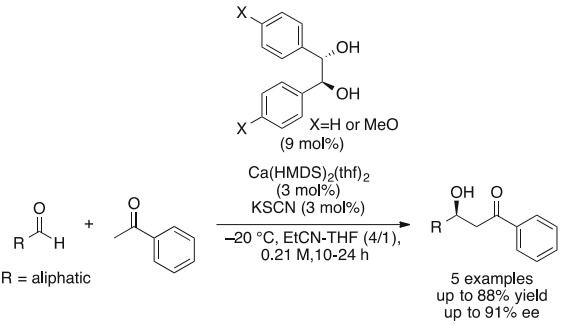


Scheme 1 Asymmetric aldol reactions catalyzed by chiral barium–BINOLate

Scheme 2 Asymmetric Morita–Baylis–Hillman reaction catalyzed by a chiral calcium–BINOLate with Bu_3P



Scheme 3 Asymmetric aldol reactions catalyzed by chiral calcium alkoxide

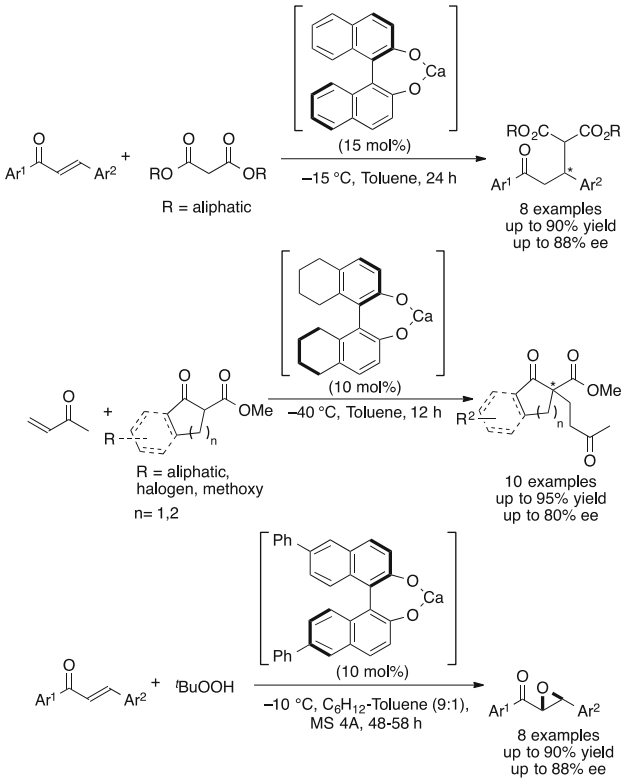


Yamada and Ikegami reported that a chiral calcium catalyst prepared from $Ca(O^iPr)_2$ and (*R*)-BINOL with tributylphosphine could promote the asymmetric Morita–Baylis–Hillman reaction [18]. The reaction of cyclopentenone with 3-phenylpropanal proceeded in the presence of the calcium complex to afford the desired adduct in 62% yield with 56% ee. In this reaction, the calcium complex worked as an effective Lewis acid catalyst (Scheme 2).

Noyori and Shibasaki et al. developed a chiral calcium–diolate complex prepared from $Ca(HMDS)_2(thf)_2$ and a chiral diol, which was effective in asymmetric direct-type aldol reactions [19]. The enantioselectivity was improved significantly by using potassium thiocyanate (KSCN) as an additive (73–89% ee). Cold-spray ionization mass spectrometry (CSI-MS) analysis suggested the formation of a highly aggregated chiral calcium complex. It was assumed that a ketone enolate was formed kinetically in the presence of the chiral calcium complex (Scheme 3).

Kumaraswamy et al. also prepared chiral calcium complexes from calcium chloride and a potassium salt of BINOL derivatives and applied them to asymmetric Michael reactions of malonates [20] or β-ketoesters [21] to α,β-unsaturated carbonyl compounds and to asymmetric epoxidation reactions [22, 23] of chalcone derivatives with ^{t}BuOOH. The desired reactions proceeded in good to high yields with moderate to good enantioselectivities. Those calcium catalysts worked as both Lewis acid and Brønsted base species (Scheme 4).

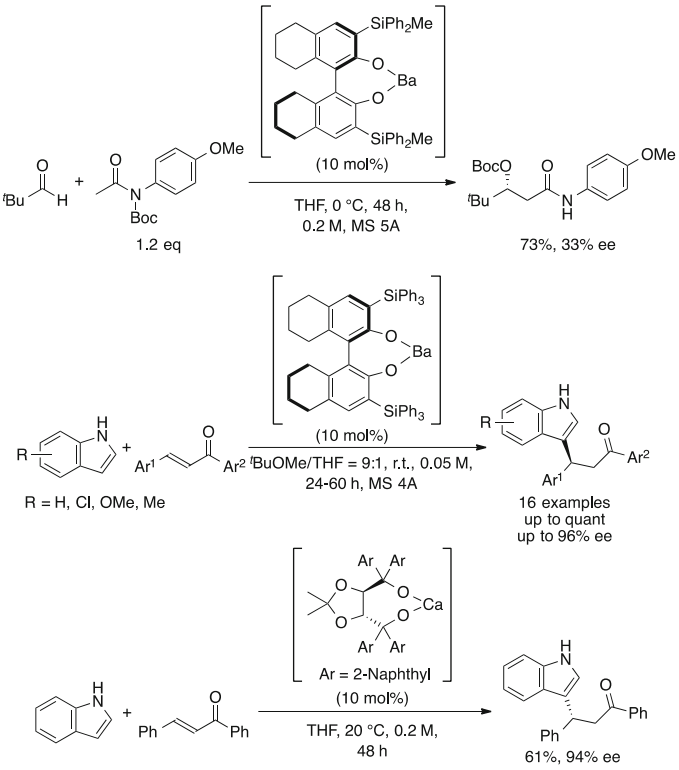
Saito and Kobayashi reported that a chiral barium complex prepared from a 3,3′-disilyl-substituted BINOL derivative was effective in a catalytic asymmetric



Scheme 4 Asymmetric reactions catalyzed by chiral calcium–BINOLates

direct-type aldol reaction [24]. It was found that the reaction gave the desired adduct in good yield with moderate enantioselectivity. They also found that a similar chiral barium complex prepared from $Ba(HMDS)_2$ and H_8-3,3′-$(SiPh_3)_2$-BINOL could work well in asymmetric Friedel–Crafts-type alkylation reactions [25] of indole derivatives with chalcone derivatives and that the desired adducts were obtained with high enantioselectivities. In this reaction, it was assumed that the most acidic proton of the indole was deprotonated to form a chiral barium-indole species. In this system, the use of $Ba(HMDS)_2$ gave better results than the use of barium alkoxide because of the more basic nature of the former, which led to a more active catalyst. Similarly, they also reported that a chiral calcium complex prepared from $Ca(HMDS)_2$ and the chiral Taddol ligand could promote the asymmetric Friedel–Crafts-type alkylation reaction [25] with high enantioselectivity. $Ca(HMDS)_2$ could also form a more active calcium complex than $Ca(O^iPr)_2$ with the chiral diol (Scheme 5).

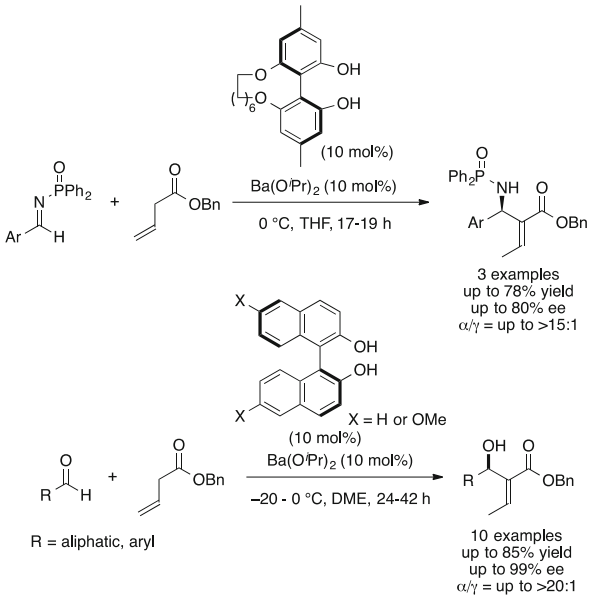
Shibasaki et al. developed chiral barium catalysts that were prepared from barium alkoxide and a BINOL and a chiral biphenol derivative, which were



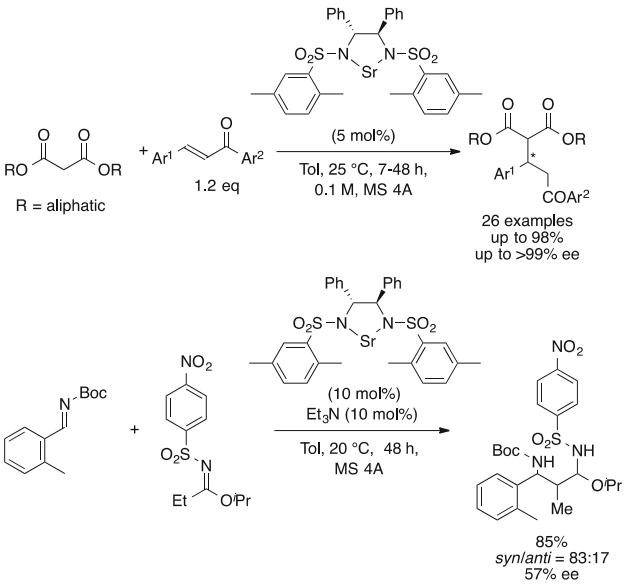
Scheme 5 Asymmetric reactions catalyzed by chiral barium–H_8–BINOLates and a calcium–TADDOLate

successfully applied to asymmetric Mannich reactions [26] of β,γ-unsaturated esters. In this reaction, the initially formed Mannich adducts isomerized to afford aza-Morita–Baylis–Hillman-type products in moderate to good yields with good enantioselectivities. They also reported that a barium–BINOL catalyst system could be used in asymmetric aldol-type reactions [27] of β,γ-unsaturated esters. The desired Morita–Baylis–Hillman-type products were similarly obtained in good yields with high enantioselectivities after isomerization (Scheme 6).

Kobayashi et al. reported the first chiral strontium catalyst prepared from chiral bissulfonamide derived from 1,2-diphenylethylenediamine and strontium alkoxide for asymmetric 1,4-addition reactions [28] of malonates with chalcones. The desired products were obtained in high yields with high enantioselectivities. It was revealed that the chiral strontium complex contained two covalent bonds between strontium and the ligand in a bidentate fashion. The use of $Sr(HMDS)_2$ instead of $Sr(O^iPr)_2$ led to the formation of a more active catalyst [29]. Furthermore, the authors revealed that the chiral strontium catalyst could promote asymmetric

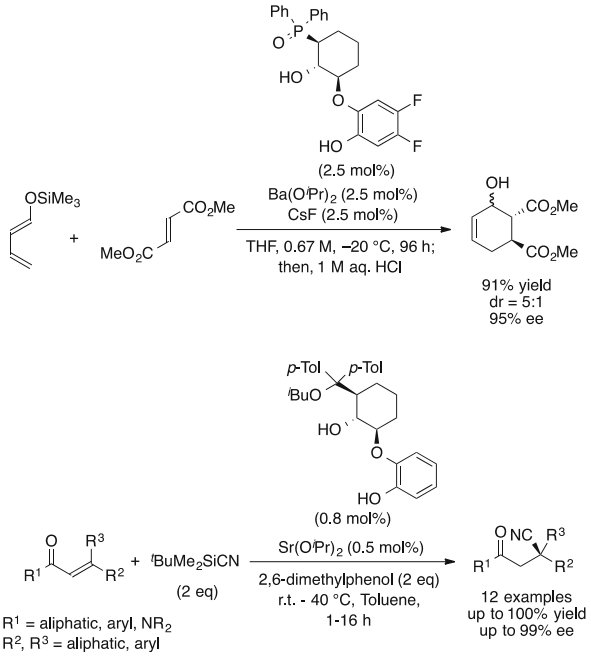


Scheme 6 Asymmetric reactions catalyzed by chiral barium biphenolate and BINOLates



Scheme 7 Asymmetric reactions catalyzed by a chiral strontium bissulfonamide

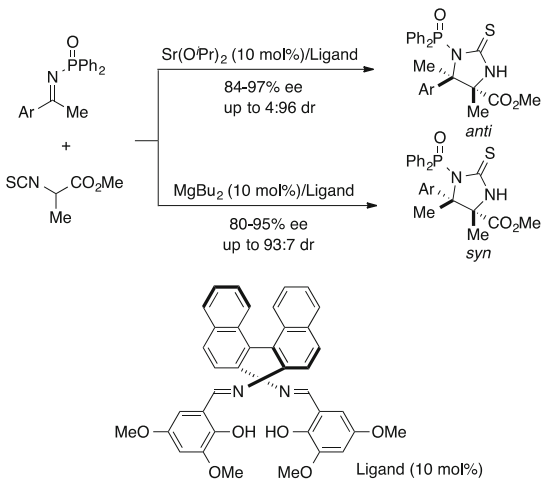
Mannich reactions [30, 31] of sulfonylimidates with imines. The desired products were also obtained in good yields with moderate to good stereoselectivities in the presence of additional tertiary amine (Scheme 7).



Scheme 8 Asymmetric reactions catalyzed by chiral strontium and barium alkoxides

Shibasaki et al. also found that a chiral barium complex prepared from barium alkoxide and a chiral diol bearing a phosphine oxide moiety could be used to catalyze the asymmetric Diels–Alder-type reaction of siloxydiene with fumarate, which afforded a precursor for the synthesis of optically active Tamiflu® [32]. Transmetalation from silicon to barium occurred through activation by F^- to form achiral barium-activated diene, which reacted with fumarate to form the optically active cyclohexene derivative with high enantioselectivity. They also developed a chiral strontium complex prepared from a similar chiral diol bearing an ether moiety, which could be used to promote asymmetric cyanation reactions [33] of β,β-disubstituted α,β-unsaturated carbonyl compounds to form chiral quaternary carbon stereocenters with high enantioselectivities. Previously, the authors applied Gd catalyst systems in this reaction, but the degree of enantioselectivity was not sufficient. After screening several metals, they finally found that the strontium complex worked well to afford the desired products with high enantioselectivities (Scheme 8).

Shibasaki et al. further reported that monometallic salen catalysts containing strontium or magnesium could be effective for asymmetric Mannich-type reactions [34] of α-isothiocyanate esters with ketoimines. Whereas *anti* products were obtained by using the strontium complex, *syn* products were obtained by using the magnesium complex. The diastereo- and enantioselectivities of the reactions were high in both cases. Switching of the diastereoselectivity might be caused by



Scheme 9 Asymmetric reactions catalyzed by chiral strontium and magnesium salen

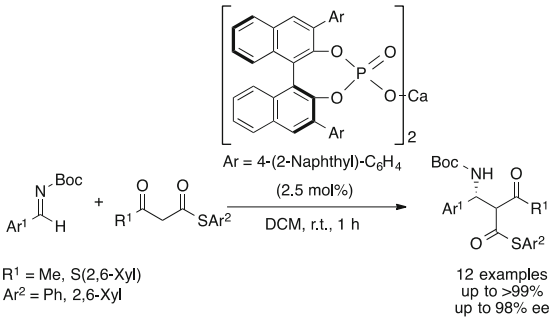
the difference in the dihedral angles of the binaphthyl unit in the metal complexes (Scheme 9).

3.2 *Chiral Phosphoric Acid-Based Complexes*

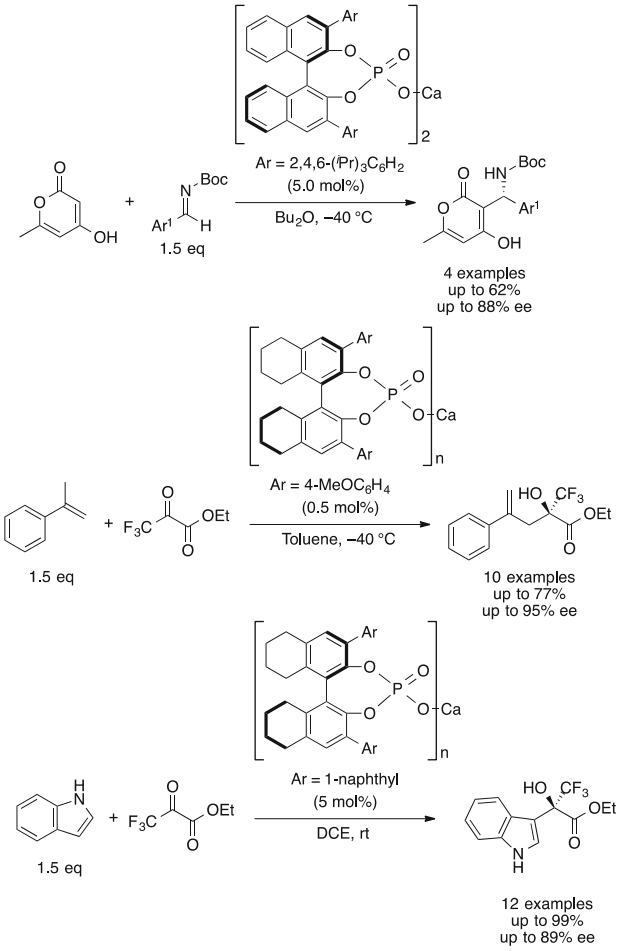
Ishihara et al. found that a chiral calcium phosphate that was prepared from calcium alkoxide and a phosphoric acid bearing chiral BINOL backbone was a good catalyst for asymmetric Mannich reactions of 1,3-dicarbonyl compounds with *N*-Boc-imines [35, 36]. Mass spectrometric and ^{31}P NMR spectroscopic analyses revealed that the catalyst existed in an oligomeric structure in the absence of substrates, but the actual catalyst formed as a monomeric species containing two equivalents of the ligand to the metal center when the reaction proceeded. Since this discovery, several groups successfully applied these catalysts to other asymmetric reactions, such as amination, benzoyloxylation, chlorination, and the Michael reaction (Scheme 10).

Rueping et al. applied a BINOL phosphoric acid calcium salt to catalytic asymmetric Mannich reactions [37] of cyclic 1,3-diketones to form *N*-Boc-amines. They investigated pyrone and 1,3-cyclohexadione as the carbonyl donors, and the Mannich products were obtained with high enantioselectivities. The authors also used a similar BINOL phosphoric acid calcium salt in catalytic asymmetric carbonyl-ene reactions and in Friedel–Crafts reactions of indole derivatives for the synthesis of quaternary hydroxyesters [38] (Scheme 11).

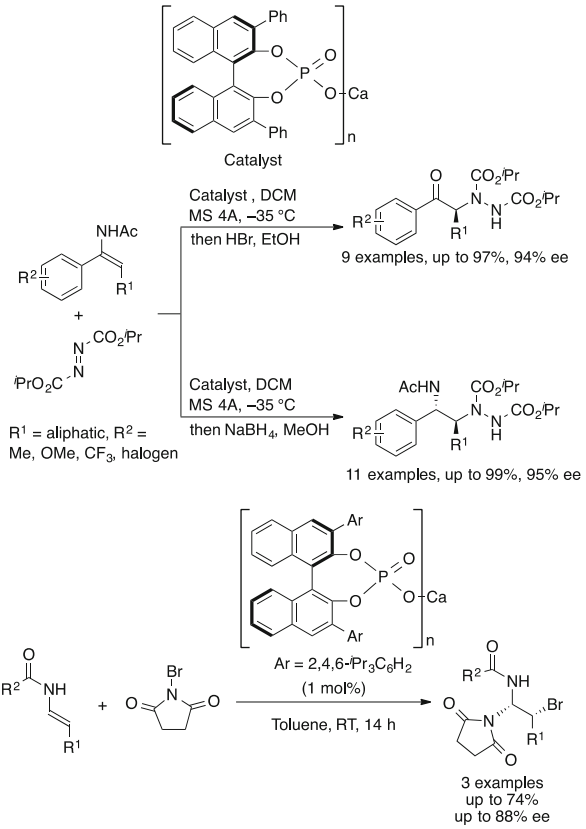
Masson and Zhu et al. applied a calcium phosphate catalyst to asymmetric amination reactions [39, 40] of enamides with an azodicarboxylate. The products



Scheme 10 Asymmetric Mannich-type reactions catalyzed by a chiral calcium phosphate



Scheme 11 Asymmetric reactions catalyzed by chiral calcium phosphates

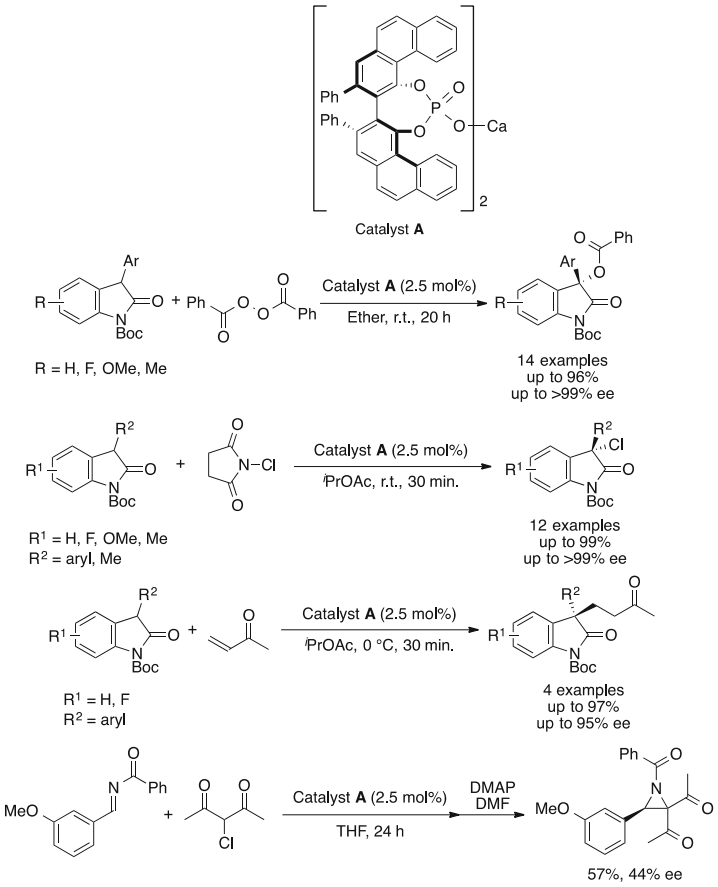


Scheme 12 Asymmetric amination reactions catalyzed by chiral calcium phosphates

obtained were isolated after conversion into 2-hydrazinoketones and 1,2-diamines by hydrolysis or diastereoselective reduction, and the enantioselectivities of these reactions were very high. Masson et al. also reported that a similar catalyst promoted the asymmetric bromination [41] of enecarbamates using NBS (Scheme 12).

Antilla et al. reported on chiral calcium VAPOL phosphate-catalyzed asymmetric reactions. Benzoyloxylations [42], chlorinations [42], and Michael reactions [43] of 3-substituted oxindoles proceeded in high yields with excellent enantioselectivities. In this system, calcium complexed by two chiral phosphates is also assumed to be an active catalyst. It was also found that catalytic asymmetric aziridine formation reactions [44] proceeded with moderate enantioselectivity (Scheme 13).

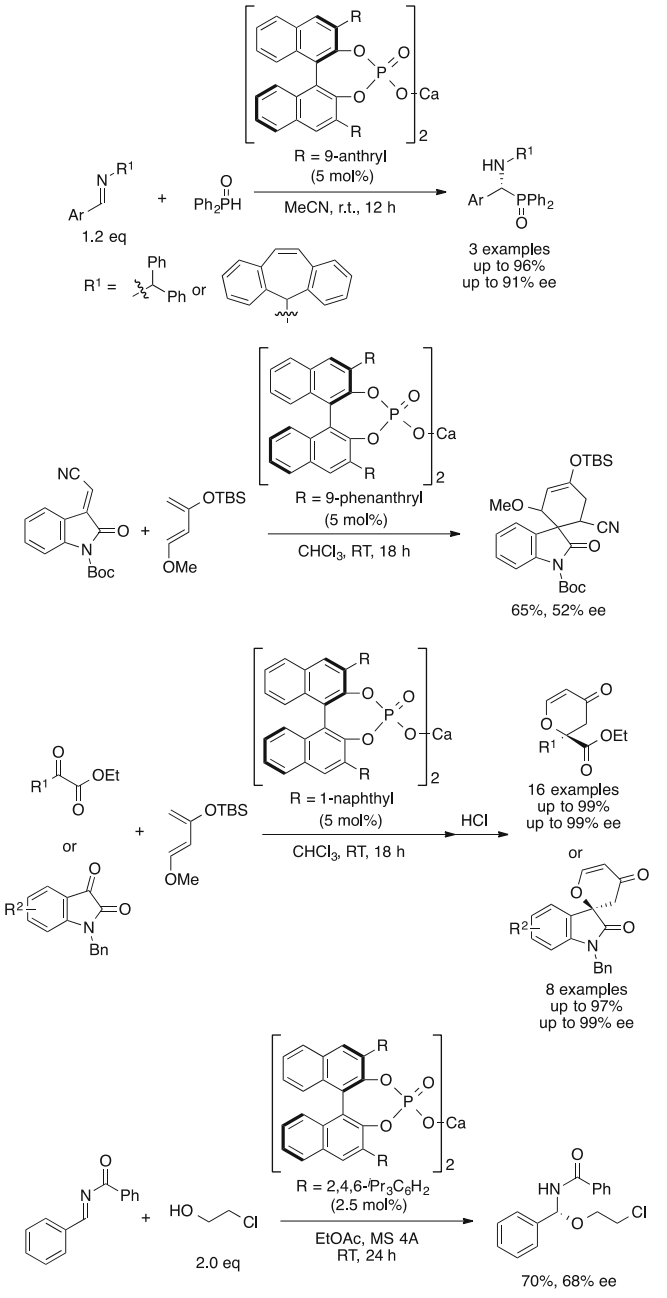
Antilla et al. further reported the possible use of chiral calcium BINOL phosphate catalysts in other asymmetric reactions. Catalytic asymmetric phosphination



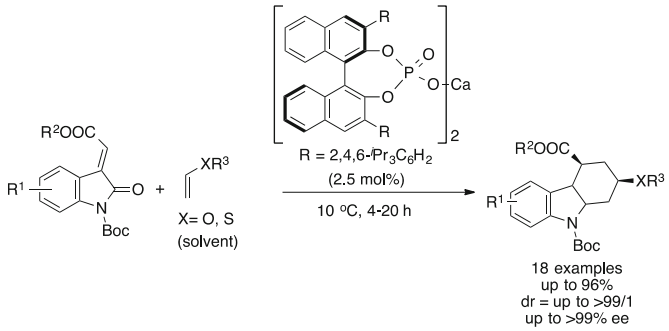
Scheme 13 Asymmetric reactions catalyzed by a chiral calcium VAPOL phosphate

reactions [45], catalytic asymmetric Diels–Alder reaction [46], and hetero-Diels–Alder reactions [47] were found to be promoted by a chiral calcium phosphate catalyst, and moderate to high enantioselectivities were observed. The calcium phosphate catalyst was also applied to asymmetric *N*,*O*-acetal forming reactions [48] (Scheme 14).

Zhu and Cheng et al. reported chiral calcium phosphate-catalyzed asymmetric oxo-hetero-Diels–Alder reactions [49] of heterodienes with vinyl ethers. In this reaction, Lewis acidic activation of the heterodiene might be important in promoting the desired reaction (Scheme 15).



Scheme 14 Other asymmetric reactions catalyzed by chiral calcium phosphates



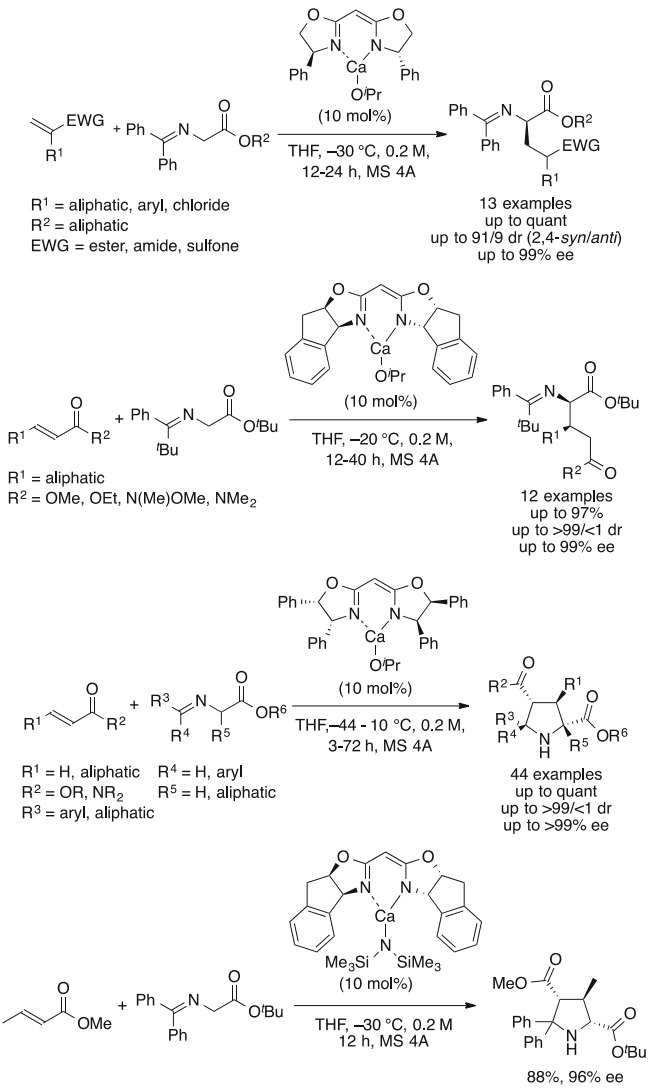
Scheme 15 Asymmetric *oxo*-hetero-Diels–Alder reactions catalyzed by chiral calcium phosphates

4 Type II Chiral Alkaline Earth Metal Complexes for Asymmetric Reactions

Highly enantioselective type II alkaline earth metal catalysts were first reported by Kobayashi et al.; these were prepared from calcium alkoxides or amide with chiral bisoxazoline (Box) ligands bearing methylene moieties with an acidic hydrogen atom. During the preparation of the catalyst, the acidic hydrogen atom on the tether part is deprotonated by an alkoxide or an amide to form an anionic bidentate Box ligand, which makes a rigid complex with the alkaline earth metal to form an effective asymmetric environment. Furthermore, the mild Lewis acidity of alkaline earth metals can assist the coordination of the ligand. In these structures, one alkoxide or amide group remains and functions as a strong Brønsted base. Therefore, by changing the remaining counteranion, the overall Brønsted basicity of the chiral complexes can be controlled. They applied these catalysts to asymmetric 1,4-addition reactions and [3 + 2] cycloaddition reactions [50–52] of Schiff bases of α-aminoester with α,β-unsaturated carbonyl compounds, and the desired products were obtained in high yields with high chemo- and enantioselectivities (Scheme 16).

Harder et al. investigated asymmetric hydroamination and hydrosilylation reactions by using chiral calcium amide catalysts prepared from $Ca(HMDS)_2(thf)_2$ and a chiral diimine or Box-type ligand [53]. In both reactions, the yields were high, but the enantioselectivities were low. In a ^1H NMR study, it was revealed that a Schlenk equilibrium between 1:1 complexes ($[Ca(Ligand)(HMDS)]_2$) and 1:2 complexes ($Ca(Ligand)_2 + Ca(HMDS)_2(thf)_2$) existed in solutions of these complexes. The low enantioselectivities might be caused by reactions mediated by the ligand-free calcium amide species formed in the equilibrium (Scheme 17).

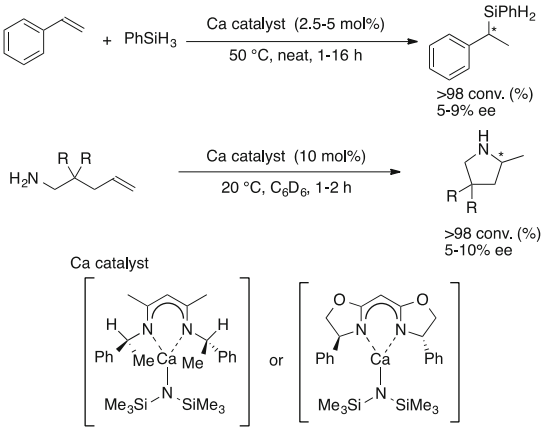
Kobayashi et al. also developed a chiral calcium chloride catalyst system by using calcium chloride, a similar Box-type ligand, and an external base [54]. Calcium chloride is an attractive metal salt that is commonly used in daily life as



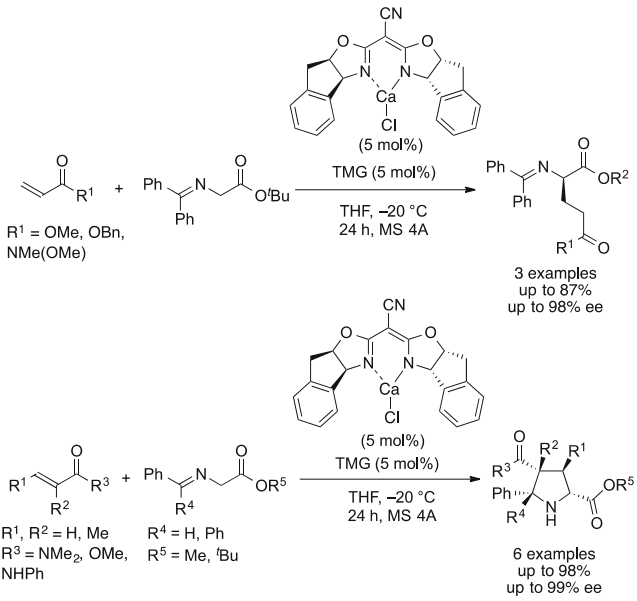
Scheme 16 Asymmetric 1,4-addition and [3 + 2] cycloaddition reactions catalyzed by Box–calcium complexes

a desiccant and food additive and in deicing, medicine, freezing point depression, and chemical procedures for drying chemicals under vacuum. It is also inexpensive, air stable, and less toxic compared with other metal salts. Therefore, the use of this salt in organic synthesis as a catalyst is highly desirable.

For the preparation of the chiral calcium chloride catalyst, the introduction of a cyano group on the methylene tether to enhance the acidity of the hydrogen on the tether part was effective, and 1,1,3,3-tetramethylguanidine (TMG) was used as a



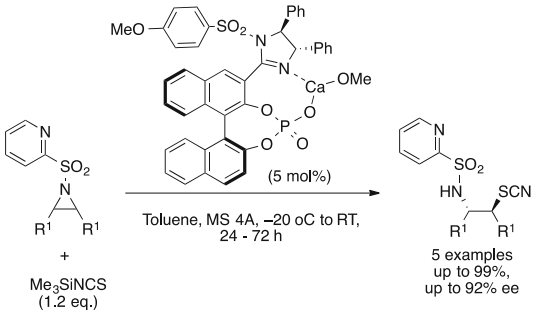
Scheme 17 Asymmetric hydroamination reactions catalyzed by chiral calcium amide complexes



Scheme 18 Asymmetric 1,4-addition and [3 + 2] cycloaddition reactions catalyzed by a CN-Box–calcium chloride

good external base. The catalyst system was found to work well in asymmetric 1,4-addition and [3 + 2] cycloaddition reactions (Scheme 18).

Nakamura et al. reported that a calcium BINOL-based chiral imidazoline–phosphonate complex could be used to promote asymmetric aziridine ring-opening



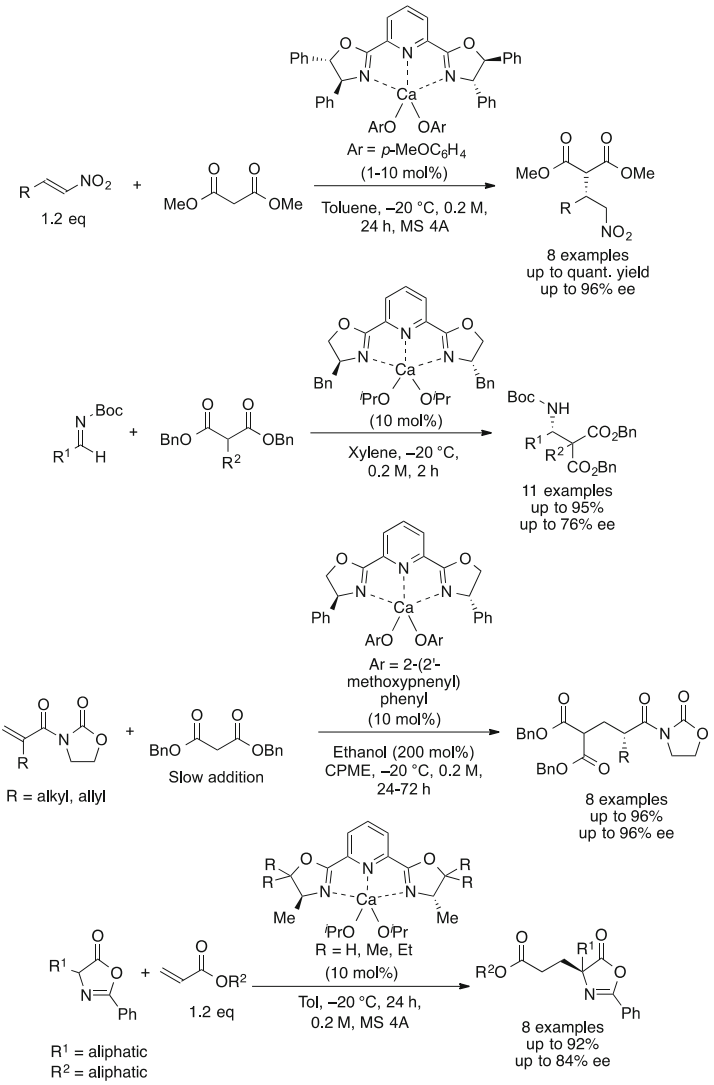
Scheme 19 Asymmetric aziridine ring-opening reactions with Me_3SiNCS catalyzed by a calcium BINOL-based chiral imidazoline–phosphonate complex

reactions with Me_3SiNCS [55]. In these reactions, the calcium complex activated the 2-pyridylsulfonyl group of the aziridines to enhance their electrophilicity, and the methoxide moiety might not work as a base. The desired reactions proceeded with good to high enantioselectivities. The phosphonate part enhanced the Lewis acidity of the calcium to accelerate the reaction (Scheme 19).

5 Type III Alkaline Earth Metal Complexes for Asymmetric Reactions

After investigating type II catalysts, Kobayashi et al. revealed that calcium metal had more significant Lewis acidity than previously considered, which suggested that construction of an asymmetric environment by a chiral ligand through only coordinative bonds was possible. Thus far, only pyridine bisoxazoline (Pybox)–calcium complexes have been reported, but these catalysts showed new possibilities in chiral alkaline earth metal catalysis.

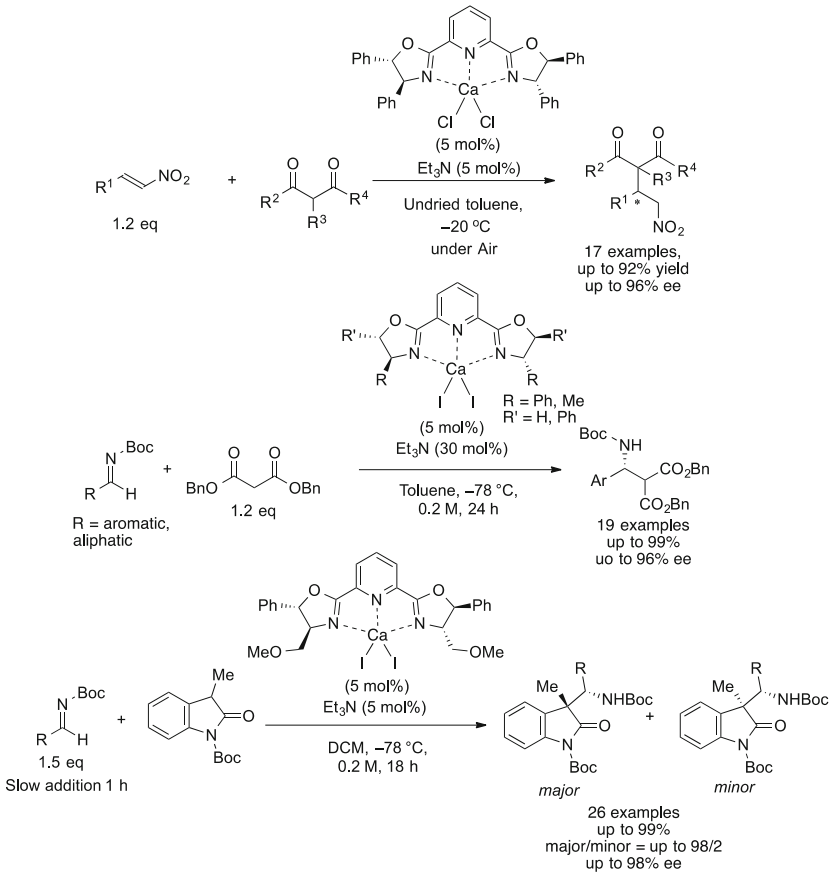
Kobayashi et al. reported that type III chiral calcium complexes, prepared from a chiral Pybox and calcium aryloxide, could work in catalytic asymmetric 1,4-addition reactions [56] of malonates with nitroalkenes, and the desired products were obtained in high yields with excellent enantioselectivities. The catalyst loading could be decreased to 1 mol%. This was the first example of a type III chiral calcium catalyst. They also reported catalytic asymmetric Mannich-type reactions [57] of malonates with *N*-Boc-protected imines and catalytic addition of malonates to acrylate derivatives accompanying highly enantioselective protonation [58], and catalytic asymmetric Michael reactions [59] of azlactone by using the related chiral calcium aryloxide or alkoxide catalyst systems. However, in some cases, free calcium aryloxide or alkoxide without Pybox might promote the desired reaction leading to a decrease in the enantioselectivity. This was caused by imperfect complex formation between the calcium and the ligand because of insufficient



Scheme 20 Asymmetric reactions catalyzed by Pybox–calcium alkoxides

Lewis acidity of the calcium center, even when the acceleration of the reaction by a ligand occurred effectively (Scheme 20).

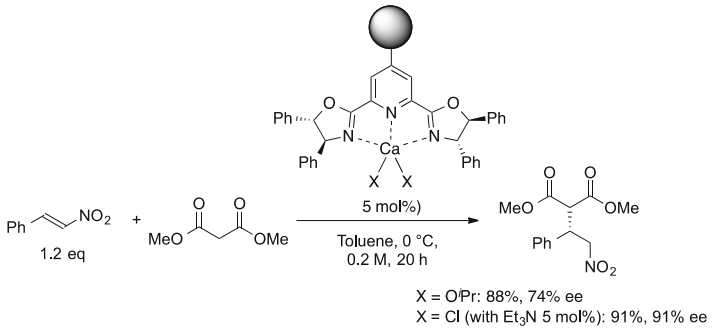
Similar to the type II alkaline earth metal complexes, Kobayashi et al. also reported that a chiral Pybox–calcium chloride complex worked as a good chiral Lewis acid and that the catalytic asymmetric 1,4-addition reactions [60] of



Scheme 21 Asymmetric reactions catalyzed by Pybox–calcium halides

malonates with nitroalkenes proceeded in good yields with high enantioselectivities in the presence of triethylamine as an additional amine base. Other chiral Pybox–calcium halide complexes have also been developed. The introduction of iodide instead of chloride was found to enhance the activities of the catalyst, and the chiral Pybox–calcium iodide complex could promote catalytic asymmetric Mannich reactions [61, 62]. Not only aromatic but also aliphatic Boc imines reacted with malonate or oxindole derivatives, and the reactions proceeded in high yields with high enantioselectivities (Scheme 21).

Interest in the development of chiral heterogeneous catalysts for asymmetric catalysis has recently become more intense because recovery and reuse of expensive chiral catalysts should be possible through their immobilization on an insoluble

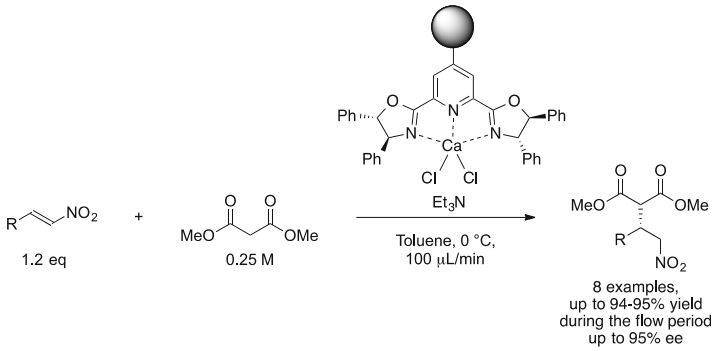


Scheme 22 An asymmetric reaction catalyzed by PS-Pybox–calcium

solid support. Moreover, the application of such catalysts in flow reaction systems can provide a powerful method to supply optically active compounds continuously with high performance [63]. However, immobilization of chiral catalysts is often problematic because it can lead to 1) a decrease in the enantioselectivity of the reaction upon immobilization, 2) a decrease in catalyst activity upon use over longer periods of time, and 3) leaching of precious metal catalysts, which is a serious issue that can lead to contamination of the product by toxic material. Therefore, highly active, highly enantioselective, and very stable and robust chiral catalysts are required.

To address this issue, Kobayashi et al. investigated the immobilization of chiral calcium catalysts [60, 64]. The Pybox–calcium chloride complex (type III) was immobilized on a polystyrene-based polymer through a tether between the ligand and the styrene units to form polymer-supported (PS) Pybox–calcium catalysts for the asymmetric 1,4-addition reaction of malonate with nitroalkene. Although PS-Pybox–calcium alkoxide complex was prepared and employed in the reaction, its stability to air (moisture) was not good, and lower enantioselectivity was obtained. This result suggested that calcium alkoxide was relatively unstable and that it hydrolyzed to form calcium hydroxide during the reaction. On the other hand, it was found that PS-Pybox–calcium chloride catalyst was a stable catalyst even after the immobilization, and the desired 1,4-addition reaction of a malonate with a nitroalkene proceeded ever under air to afford the desired product with high enantioselectivity. As mentioned before, calcium chloride is ubiquitous, less toxic, less harmful, and a more economical metal salt, and, consequently, it is one of the most attractive metal compounds in asymmetric metal catalysis (Scheme 22).

Kobayashi et al. then employed this chiral PS-Pybox–calcium chloride catalyst for the asymmetric 1,4-addition reaction of malonate with nitroalkene under continuous-flow conditions [64]. The PS-chiral calcium catalyst was packed inside a



Scheme 23 Asymmetric 1,4-addition reactions catalyzed by PS-Pybox–calcium chloride under continuous-flow conditions

high-pressure column, and the substrates and triethylamine were flowed through it. Collection and analysis of the product that eluted from the column exit showed that the reaction proceeded very well and that the desired product was obtained in high yield with excellent enantioselectivity. In this system, the 1,4-adduct was obtained continuously for at least 204 h and the total TON of the catalyst reached 228; after this period, the catalyst remained active. This catalyst system was also successfully applied to other substrates. This is the first successful example of an asymmetric 1,4-addition reaction of malonates that uses a continuous-flow system (Scheme 23).

Kobayashi et al. employed the PS-calcium catalyst in the key step of a multistep flow synthesis of optically active rolipram [65], which is an anti-inflammatory drug and one of the family of γ-amino butyric acid (GABA) derivatives. Although drugs are normally synthesized by using a batch system, the use of a flow system for multistep synthesis has many advantages, particularly in terms of productivity, heat and mixing efficiency, safety, and reproducibility. Currently, a number of synthesis methods are beginning to shift from a batch system to a flow system [66]. The multistep flow synthesis of optically active rolipram was achieved by combining chiral and achiral heterogeneous catalysts. By using the flow reactor, all eight reactions proceeded very well, and (*R*)-rolipram was obtained in high yield with excellent enantioselectivity. In these systems, by changing the PS-chiral calcium catalyst to the other enantiomer of the ligand, (*S*)-rolipram was obtained in the same yield and with the same enantioselectivity. This is the first example of the synthesis of an optically active drug under continuous-flow conditions by using only heterogeneous catalysts (Fig. 2).

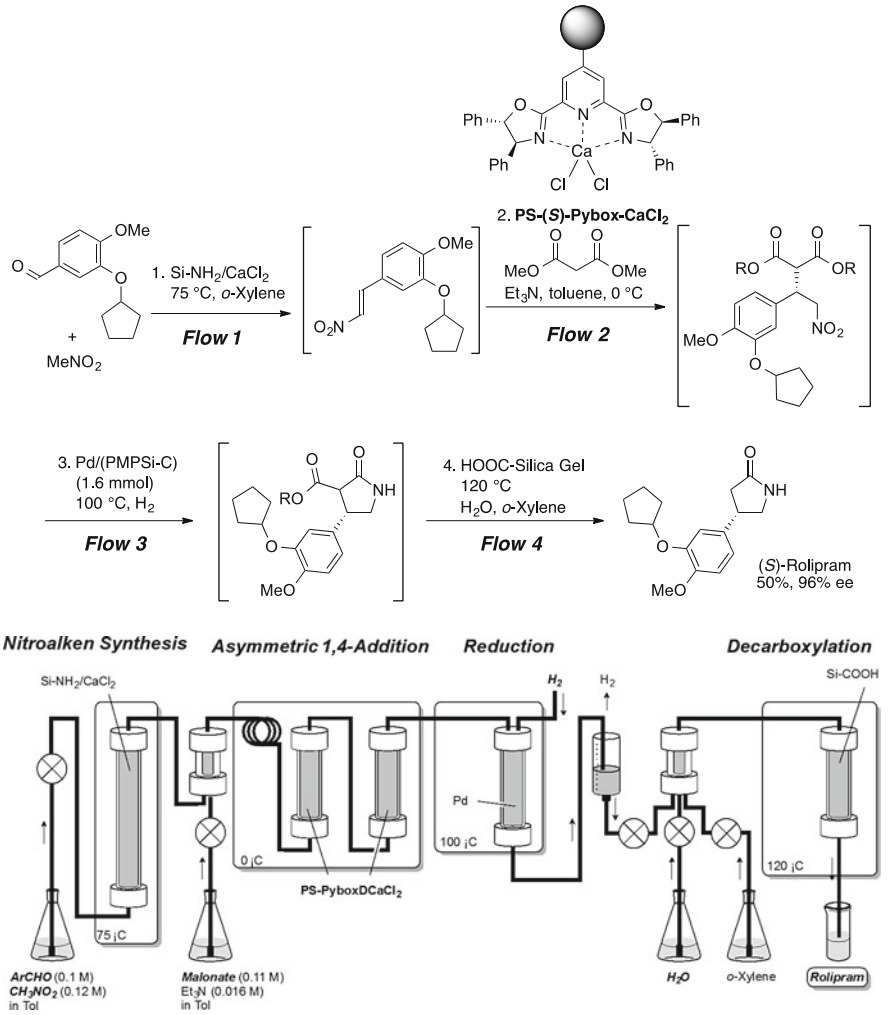


Fig. 2 Flow synthesis of chiral rolipram

6 Summary and Outlook

In this chapter, recent progress in the development of chiral alkaline earth metal catalysts was described for each type of complex. Previously, alkaline earth metal compounds were not often employed in fine organic synthesis because of their amphiphilic acid/base characters. However, their recent reassessment has revealed new possibilities for their use as catalysts. In catalytic asymmetric synthesis, whereas many kinds of chiral metal catalysts have been developed, the use of chiral alkaline earth metal catalysts remains limited; however, their ubiquitous, relatively

safe, and economical characteristics make these elements attractive for the development of useful chiral catalysts in the future. Further studies may lead to these metals becoming a major player on the stage of asymmetric catalysis.

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Chiral Lewis Acid Rare-Earth Metal Complexes in Enantioselective Catalysis

Xiaoming Feng, Zhen Wang, and Xiaohua Liu

Abstract The progress made over the past two decades in asymmetric catalysis, focusing on chiral Lewis acid complexes of rare-earth metal, is reviewed. The applications of several different catalytic systems of chiral Lewis acid complexes in various asymmetric reactions have been discussed: (1) asymmetric aldol reaction, (2) asymmetric Mannich reaction, (3) asymmetric Michael reaction, (4) asymmetric Friedel-Crafts reaction, (5) asymmetric homologation of carbonyl compounds with α-diazoesters, (6) asymmetric ene-type reaction, (7) asymmetric cycloaddition reaction, (8) asymmetric ring-opening reaction, and (9) asymmetric miscellaneous reaction.

Keywords Asymmetric catalysis • Chiral bipyridine alcohol • Chiral bis (oxazolinyl)pyridine • Chiral ligand • Chiral *N,N′*-dioxide • Lewis acid • Rare-earth metal

Contents

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1 Introduction

Chiral Lewis acid rare-earth metal (RE) complexes constitute an integral part of modern organic synthesis. The rare-earth elements comprising the group of three metals Sc, Y, and La and the inner transition metals Ce-Lu provide new structural and reactivity patterns, emerging in structure-activity relationships unprecedented in main group and *d*-transition metal complexes. In contrast to extensively studied *p*-block or *d*-block metal elements in asymmetric catalysis, the application of chiral rare-earth metal complex was scarce until europium complex $Eu(hfc)_3$ was first introduced as a Lewis acid in hetero-Diels-Alder reaction by Danishefsky group in 1983, although only moderate enantioselectivities (up to 58% ee) were obtained [1]. And then, the use of rare-earth metal complexes combining appropriate chiral ligands as new catalysts in the catalytic asymmetric transformations became intense interest due to their intrinsic electronic properties, low toxicity, and availability as well. RE(III) is the most stable oxidation state, and the high electropositive character of lanthanide metals is comparable to that of the alkali and alkaline earth metals. According to HSAB terminology of Pearson, rare-earth metal cations are regarded as hard acids, which cause the strong complexation of hard ligands. In general, rare-earth metal complexes exhibit high coordination numbers of 6 or up to 12, which are highly advantageous for assembling various chiral ligands around the metal ions to create an integrated chiral space. The interaction of oxophilic and azaphilic metal center with substrate molecules leads to the efficient control of chemo-, regio-, and stereoselectivities in chiral rare-earth metal complex-catalyzed transformations. During the past two decades, many chiral ligands, including bidentate BINOL derivatives with O-donors, tetradentate *N,N′*-dioxides with O-donors, tridentate pybox with N-donors, and tetradentate bipyridine-alcohol with N,O-donors, etc., have been commonly and efficiently used to form the chiral rare-earth metal complexes for a wide range of reactions. Among this "17-element series," Sc(III), Yb(III), Y(III), Eu(III), La(III), Nd(III), Gd(III), Ho(III), Dy(III), and Pr(III) have been found to be the used metal cations involving Lewis acid-promoted asymmetric reactions, and the other seven remain unexplored. Sc(III) as by far the smallest RE(III) cation that is located in a "pole position" reveals its superiority in many catalytic applications than the others.

The rare-earth metal salts with triflate as the counterion are found to be frequently used as one of the strongest Lewis acids due to the electron-withdrawing nature of trifluoromethanesulfonyl group, which are especially stable and recoverable. Since the first report of water-compatible Lewis acids of $Yb(OTf)_3$ in 1991 [2], many rare-earth metal triflate-promoted reactions could be available not only in organic solvents but also in aqueous media, leading to really environmentally friendly reaction systems.

In this chapter, the major achievements of rare-earth metal complex-catalyzed asymmetric reactions are highlighted. The asymmetric reactions promoted by bimetallic Lewis acids involving rare-earth metal elements are not included in this chapter. The examples are overviewed according to the reaction type, including aldol reaction, Mannich reaction, Michael reaction, Friedel-Crafts reaction, homologation of carbonyl compounds with α-diazoesters, ene-type reaction, cycloaddition reaction, and miscellaneous reaction. For more or other examples of chiral rare-earth metal catalysis, see the reviews and references cited therein [3–18]. The general asymmetric catalytic models are introduced for some selected examples.

2 Asymmetric Aldol Reaction

Catalytic asymmetric aldol reactions such as Mukaiyama aldol reaction, direct aldol reaction, and nitroaldol reaction (Henry reaction) provide access to important building blocks for the synthesis of biologically active compounds and nature products. Several examples of chiral rare-earth metal complex-catalyzed asymmetric aldol reactions have been examined either in organic solvent or in water.

The *syn*-selective Mukaiyama aldol reaction was reported by the Evans group [19]. Chiral Lewis acid complexes [Sc(pyridyl-bis(oxazolinyl)]Cl_2SbF_6 **1**, formed in situ by treatment of the $ScCl_3$-pybox complex and $AgSbF_6$, were found to be effective catalyst to perform highly diastereo- and enantioselective addition of thiosilylketene acetals to ethyl glyoxylate. A range of substituted (*Z*)-thiosilylketene acetals was employed in the presence of 10 mol% of **1a** at −78°C to give malate derivatives with high *syn* diastereoselectivity (92:8–95:5 dr) and enantioselectivity (90–99% ee). The screening of counterion of the catalyst showed that [Sc(*S*,*S*)-Ph-pybox]Cl_2SbF_6 **1a** was effective, whereas [Sc(*S*,*S*)-Ph-pybox)]$(OTf)_3$ complex gave unsatisfactory results. As for the enantioselective glyoxylate aldol process with enolsilane nucleophiles derived from a variety of aryl ketones, [Sc(*S*,*S*)-*t*Bu-pybox]Cl_2SbF_6 complex **1b** was selected as an efficient catalyst to generate the α-hydroxy-γ-keto esters with 91–98% ee and 80–96% yield (Fig. 1). In the latter process, the addition of 2.0 equiv. of chlorotrimethylsilane was essential to facilitate the catalyst turnovers. Interestingly, the stereocenters rising from ethyl glyoxylate in the two cases governing catalyst **1a** and **1b** showed opposite facial selectivity. The explanation might be the reversal of binding preference of ethyl glyoxylate binding to the Sc(III) center of **1a** and **1b** which creates different steric environment due to the ligand architecture (Fig. 1) [19, 20]. In addition, the complexes of $Sc(OTf)_3$ or $Lu(OTf)_3$ cooperating with chiral pybox ligand were also found to be efficient catalysts for the enantioselective Mukaiyama aldol of pyruvates with 1-phenyl-1-trimethylsilyloxyethene [21].

One unique characteristic of rare-earth metal triflates is that they are tolerable in water. An intermolecular variant of asymmetric Mukaiyama aldol reaction that is compatible with aqueous media was studied in 2003 by Kobayashi using chiral bis-pyridino-18-crown-6 **2**/$Pr(OTf)_3$ complex (Fig. 2) [22]. The strategy was based

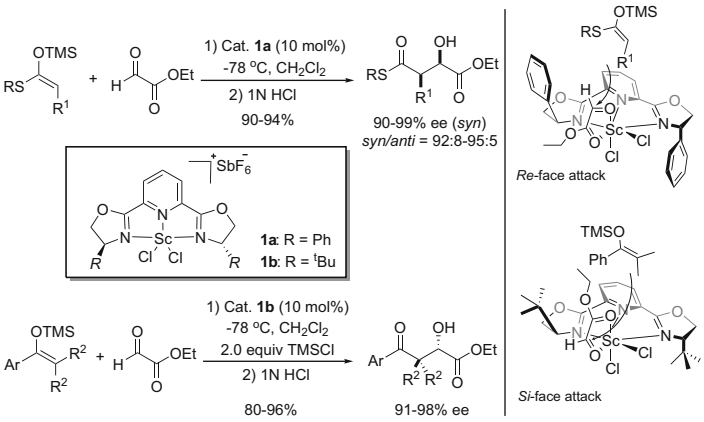

Fig. 1 Sc(III)-pybox complex-catalyzed asymmetric Mukaiyama aldol reactions [19, 20]

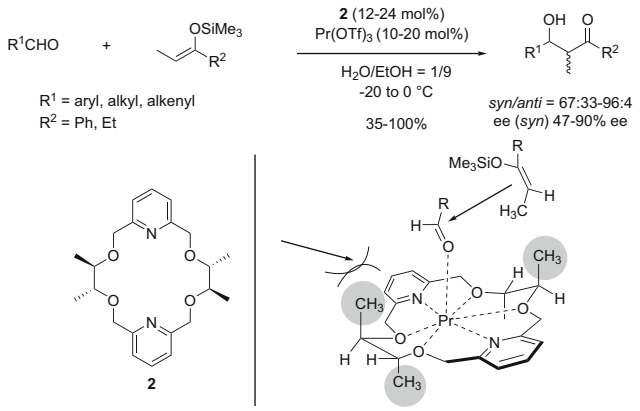

Fig. 2 $Pr(OTf)_3$ and the crown ether complex-catalyzed asymmetric Mukaiyama aldol reactions [22]

on the size-fitting effects of macrocyclic ligands, for the X-ray structures of RE $(NO_3)_3$-crown ether complexes showed that they had similar structures regardless of the cations and the crown ethers. The diastereo- and enantioselectivities of the reactions were obviously affected by slight changing in the ionic diameters of the metal cations. While the larger cations such as La(III), Ce(III), Pr(III), and Nd(III) gave higher diastereo- and enantioselectivities, the smaller cations such as Dy(III), Y(III), Ho(III), Yb(III), and Sc(III) led to lower selectivities. The substituents at the 4-position of the pyridine rings of the chiral crown ether ligand did not affect the selectivities of the aldol products but affected the binding ability of the crown ether with rare-earth cations, which was related to the reaction rates of the asymmetric reaction with $Pr(OTf)_3$-crown ether complex catalysis. The proposed transition

state as shown in Fig. 2 was rationalized to explain the asymmetric induction. The aldehyde coordinated to scandium(III) with the *Si*-face being shielded by the methyl substituent of the 1igand, allowing nucleophilic attack of silyl enol ethers from the *Re*-face. The catalytic system can tolerate a wide range of aldehydes and silyl enol ether substrates to provide the aldol products in good yields (35–100%) and stereoselectivities (67:33–96:4 *syn*/*anti* and 47–90% ee) in a mixture of water/EtOH. When silyl enol ether derived from a thioester was employed, the addition of 2,6-di-*tert*-butylpyridine suppressed hydrolysis of the substrate to significantly improve the yield of the aldol product.

In 2010, Allen and co-workers disclosed a C_2-symmetric ligand **3** in combination with rare-earth metal triflate for asymmetric Mukaiyama aldol reactions in aqueous/alcohol media (Fig. 3) [23]. The catalytic system provided a range of β-hydroxy carbonyl products from aliphatic and aromatic substrates with high diastereo- and enantioselectivities (*sny*/*anti* = 32:1–1:49, 84–97% ee). A transition state model was proposed to explain the absolute configuration of the favored enantiomer in the reaction. The benzaldehyde coordinates to the Eu(III) metal center at the top position, and then the silyl enol ether can prefer to attack from the *Re*-face of benzaldehyde as the opposite face is shielded by an ester substituent of **3**. Further investigation of the effect of lanthanide ions also showed the importance of size-fitting effects of macrocyclic ligands [24].

Formaldehyde is considered as one of the most important C1 electrophiles in organic synthesis. The development of asymmetric aldol reaction of formaldehyde with useful nucleophiles is of special importance. The Kobayashi group achieved the enantioselective hydroxymethylation of silicon enolates with aqueous formaldehyde. A chiral catalyst from Bolm's chiral bipyridine ligand **4** and $Sc(OTf)_3$ in H_2O/DMF at −20°C gave optically active α-hydroxymethylated carbonyl compounds with 24–90% yields and 60–94% ee (Fig. 4) [25]. X-ray analysis of **4**-$ScBr_3$ complex showed the ligand acting as N,O-donors coordinating to Sc(III) center in a tetradentate manner to adopt a pentagonal bipyramidal structure, which might be a key for obtaining high enantioselectivity. This new catalytic system was also

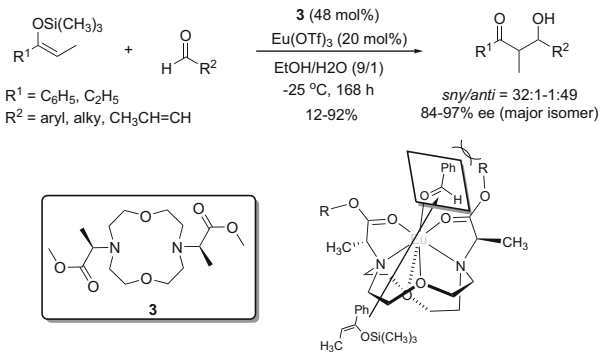

Fig. 3 Chiral europium complex-catalyzed asymmetric Mukaiyama aldol reactions [23]

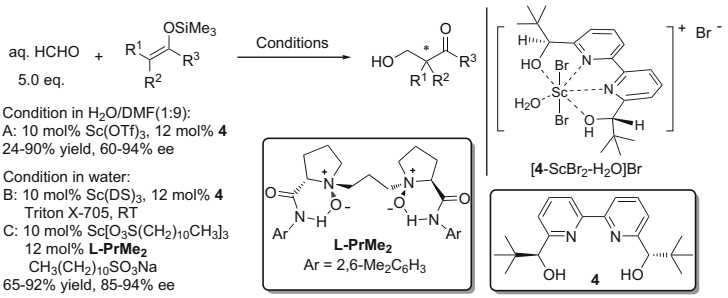

Fig. 4 Chiral Sc(III) complex-catalyzed asymmetric hydroxymethylation reaction [25, 26]

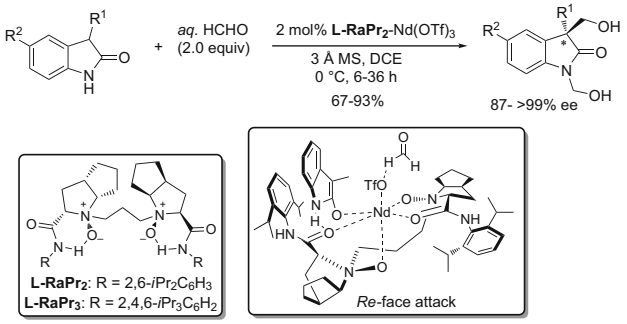

Fig. 5 Chiral Nd(III) complex-catalyzed asymmetric hydroxymethylation reaction [27]

extended to various catalytic asymmetric reactions in aqueous media, including Friedel-Crafts reaction and Michael reaction.

Later, Kobayashi and co-workers updated the asymmetric hydroxymethylation reaction of hydrophobic silicon enolate completely in water (Fig. 4) [26, 165, 166]. Two catalytic systems were proven effective. One is the use of $Sc(DS)_3$ and chiral bipyridine ligand **4** in the presence of Triton X-705, and the other is the combination of $Sc[O_3S(CH_2)_{10}CH_3]_3$ and Feng' *N,N′*-dioxide ligand **L-PrMe$_2$** in the presence of $CH_3(CH_2)_{10}SO_3Na$. These two procedures require none of organic cosolvents, affording hydroxymethylated adducts in 65–92% yields and 90–96% ee.

Feng's group utilized their chiral *N,N′*-dioxide ligand rare-earth metal complex catalysts in hydroxymethylation reaction of *N*-unprotected 3-substituted-2-oxindoles (Fig. 5) [27]. An unexpected tandem C- and N-addition process between oxindoles and formalin underwent well in the presence of *N,N′*-dioxide-RE$(OTf)_3$ complex catalyst. Evaluation of the effect of RE cations indicated that metal ions with smaller ionic radii and stronger Lewis acidity, such as Sc(III), Yb(III), and Lu(III), generally resulted in lower enantioselectivity in this case. With **L-RaPr$_2$**-Nd$(OTf)_3$ catalyst, a variety of 1,3-bis(hydroxymethyl)-2-oxindoles were obtained in up to 97% yield with >99% ee under mild conditions. It was found that the catalytic system could tolerate

30 equiv. of water. Moreover, the $Nd(OTf)_3$ and *N,N′*-dioxide could be recovered and reused without loss in catalytic activity and enantioselectivity. A possible catalytic model was given based on the NMR spectra analysis and the general coordination manner of *N,N′*-dioxide-metal complexes [10, 15]. *N,N′*-dioxide behaves as a tetradentate ligand, both oxygens of *N*-oxide and carbonyl oxygens coordinated to oxophilic RE(III) center to form good chiral pocket. The α-position of 3-substituted-2-oxindole was deprotonated to form chiral neodymium enolate, and then the reaction was carried out through C-addition and N-addition sequentially.

The combination of *N,N′*-dioxide with strongly oxophilic rare-earth metal salts exhibited advantages in a variety of enantioselective transformations that could be showcased in several sections. Chiral *N,N′*-dioxide-$Sc(OTf)_3$ complexes could catalyze enantioselective direct catalytic aldol-type reaction of 3-substituted-2-oxindoles with glyoxal derivatives and ethyl trifluoropyruvate (Fig. 6) [28]. The reaction underwent via a ligand-accelerated process, as neither $Sc(OTf)_3$ nor *N,N′*-dioxide could initiate the reaction alone. The enantioselective process was carried out in CH_2Cl_2 at 0 or 35°C in the presence of $Sc(OTf)_3$ complex of *N,N′*-dioxide **L-PiPr$_2$** derived from *L*-pipecolic acid and 2,6-diisopropylbenzenamine, giving 3-(α-hydroxy-β-carbonyl) oxindoles with quaternary stereocenters in good yields and excellent enantioselectivities. In this aldol reaction, a (+)-NLE was observed implying a consequence of the formation of oligomeric species. Additionally, the same scandium catalyst could also successfully be employed in the enantioselective aldol reaction of α-keto esters using α-diazoacetate to generate tertiary alcohols with the reservation of the diazo group [29].

The rare-earth metal complexes of chiral pybox were successfully applied in the addition of TMS-CN to aldehydes to afford chiral cyanohydrins [30–32]. In 1999, Aspinall and co-workers reported that the chiral complex $Yb(pybox)Cl_3$ could efficiently catalyze the cyanosilylation of benzaldehyde with 89% ee (Fig. 7) [30]. The optimum ratio of pybox **5**:$LnCl_3$ was found to be 2:1. And it was found that the enantioselectivities were affected by both the reaction solvents and ionic

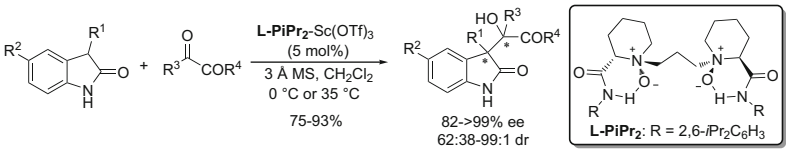

Fig. 6 Chiral Sc(III)-*N,N′*-dioxide complex-catalyzed asymmetric aldol reaction of 3-substitued-2-oxindoles [28]

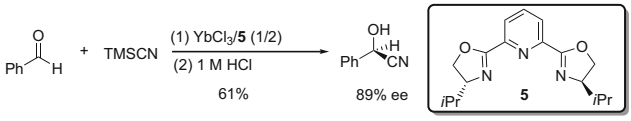

Fig. 7 Chiral Yb(III)-pybox-catalyzed asymmetric addition of TMS-CN to aldehydes [30]

radii of rare-earth metals. Of the Ln metal salts examined, $YbCl_3$ with the smallest ionic radius showed the best enantioselectivity. Next, Moberg extended this reaction by using the complex of polymer-supported pybox ligand and $Yb(OTf)_3$. The enantioselectivity is little inferior to the nonsupported system (80% vs 89% ee) [32].

A rare-earth metal complex-catalyzed enantioselective decarboxylative aldol reaction of β-ketoacids has been developed by Wang and co-workers (Fig. 8) [33, 34]. In the presence of indapybox **6**-$Yb(OTf)_3$ complex, a range of substituted isatins as well as β-ketoacids were shown to be efficiently converted into the corresponding chiral 3-hydroxy oxindoles in generally high yields and good to excellent enantioselectivities (77–99% ee, Fig. 8, Eq. 1) [33]. However, *N*-benzyl protecting group of isatins was required in order to obtain satisfactory enantioselectivities. Neither with more sterically hindered protecting groups such as triphenylmethyl nor without any protecting group, isatins could provide the desired 3-hydroxy oxindoles in a similar yield but much lower enantioselectivity. Notably, pybox **7**-$Sc(OTf)_3$-catalyzed decarboxylative aldol reactions between β-ketoacids and α-keto esters proceeded very efficiently to give the chiral α-hydroxy esters in high yields and moderate enantioselectivities (Fig. 8, Eq. 2) [34].

Since the first report of asymmetric catalytic nitroaldol reaction by rare-earth metal complexes [35], Shibasaki and co-workers continued to develop the asymmetric multimetallic catalysts that exhibit both Lewis acidity and Brønsted basicity [4, 8–18]. In particular, heterobimetallic rare-earth-alkali metal-BINOL (REMB, Fig. 9) complexes that contain a rare-earth metal, three alkali metals, and three 1,1′-bi-2-naphthols (BINOLs) offered a versatile framework for asymmetric catalysis. The property of the catalyst can be tuned dramatically according to the choice of combinations of alkali metal and rare-earth metal, to realize a variety of asymmetric transformations. An independent chapter discovered the application of heterobimetallic rare-earth-alkali metal catalysts, and herein it was omitted (see chapter Bimetallic Lewis Acids).

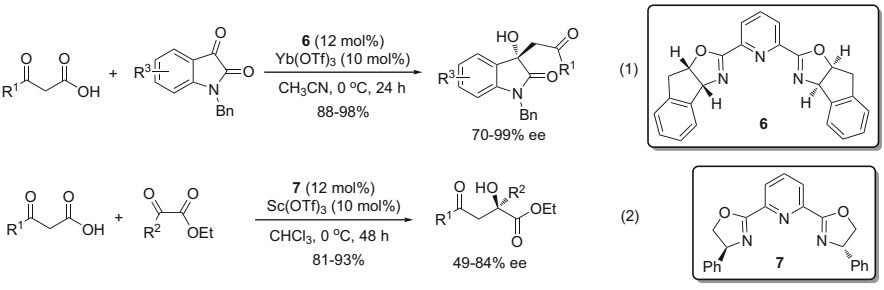

Fig. 8 Chiral rare-earth metal-pybox complex-catalyzed asymmetric decarboxylative aldol reactions [33, 34]

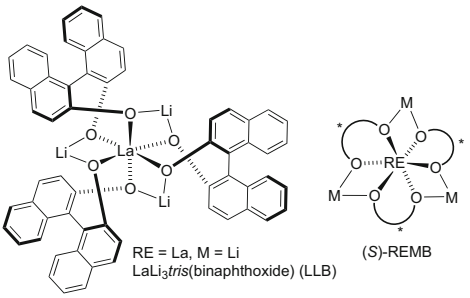

Fig. 9 Chiral heterobimetallic rare-earth-alkali metal-BINOL catalysts

3 Asymmetric Mannich Reaction

The catalytic asymmetric Mannich reaction is one of the most powerful methods to obtain optically amino compounds. Since the first report of chiral BINOL-derived Zr(IV) complex-catalyzed Mannich reaction of aldimines with silyl enolates by Kobayashi's group [36], a couple of efficient catalytic systems have been developed. As for chiral rare-earth metal complex catalysis, Feng and co-workers reported that one-pot, three-component Mannich-type reaction of 2-aminophenol, aldehydes, and ketene silyl acetal was converted enantioselectively into optically active β-amino esters by a 1:2 mixture of $Sc(OTf)_3$ and *N*,*N*′-dioxide **L-RaPr$_2$** (Fig. 10, Eq. 1) [38]. The corresponding β-amino esters were obtained in moderate to good yields (55–82%) and excellent enantioselectivities (82–98% ee) under mild conditions. The same chiral *N*,*N*′-dioxide **L-RaPr$_2$**-$Sc(OTf)_3$ complex was also successfully employed in asymmetric three-component vinylogous Mannich reaction of 2-aminophenol, aldehydes, and acyclic silyl dienol esters (Fig. 10, Eq. 2) [37]. The reaction tolerated a wide range of aldehydes to give active δ-amino α,β-unsaturated esters in good yields (90–99%), enantioselectivities (80–>99% ee), and complete regioselectivities. Furthermore, maintained reactivity and enatioselectivity were found when the reaction was carried out at 10 mmol scale under air-tolerant conditions.

In a very similar protocol, but using a 1:1 ratio of $Sc(OTf)_3$ and *N*,*N*′-dioxide **L-RaPr$_3$**, Feng and co-workers achieved a highly enantioselective addition of silyl ketene imines to imines in a three-component one-pot fashion (Fig. 10, Eq. 3) [39]. The use of 20 mol% of *i*$PrNH_2$ as the additive made a dramatic improvement in both enantio- and diastereoselectivity. The explanation for this might be the basis to facilitate the deprotonation of aldimines formed in situ, which benefits the later coordination to the Sc(III) center in a bidentate manner. A variety of linear β-amino nitriles with tertiary and quaternary stereogenic carbon centers were obtained in excellent yield (65–95%) and stereoselectivity (80:20–99:1 dr and 77–97% ee). The catalyst was also applied to the three-component Kabachnik-Fields reaction of aromatic aldehydes, 2-aminophenol and diphenyl phosphate, producing α-amino phosphonates with 80–87% ee within 1 h (Fig. 10, Eq. 4) [40].

Very recently, Feng and co-workers reported an asymmetric imine amidation of 2*H*–azirines with oxindoles using *N*,*N*′-dioxide **L-RaPr$_2$**-$Sc(OTf)_3$ complex

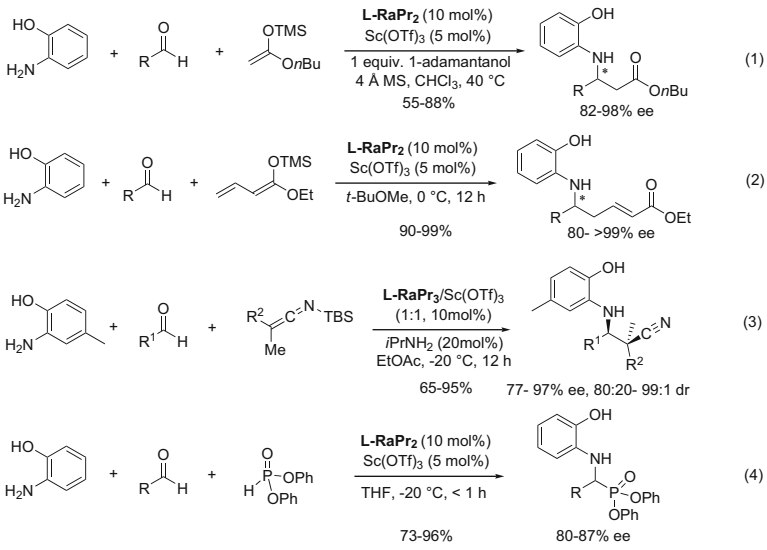

Fig. 10 Chiral Sc(OTf)$_3$-*N*,*N*′-dioxide complex-catalyzed asymmetric three-component Mannich-type reaction of aldimines [36–40]

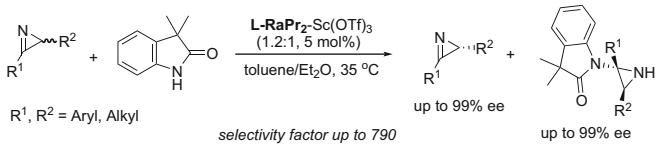

Fig. 11 Chiral Sc(OTf)$_3$-*N*,*N*′-dioxide complex-catalyzed asymmetric imine amidation [41]

(Fig. 11) [41]. The kinetic resolution of 2*H*–azirines was realized through an enantioselective nucleophilic addition of N1 of oxindole in the reaction over C3, providing the enantioenriched 2*H*–azirine derivatives and aziridines with protecting group free at the same time (selectivity factor up to 790). Regardless of the electronic nature on the 4-position of the phenyl ring (R^1, R^2), 2*H*–azirines could be smoothly converted into the corresponding aziridines in good yields and excellent enantioselectivities (up to 99% ee). Meanwhile, the unreacted 2*H*–azirines were recovered in 43–52% yields with 94–99% ee.

Taking advantage of the high coordination number of rare-earth metal, Shibasaki and co-workers realized a highly ordered transition state upon the complexation with simple amide ligand **8** to construct a suitable asymmetric environment. The combination of chiral amide **8** with Sc(O*i*Pr)$_3$ in ratio 2:1 was emerged as the ideal catalyst for the Mannich reaction of α-cyanoketone with *N*-Boc imine (Fig. 12) [42]. The *N*-Boc imine, α-cyanoketone, chiral amide **8**, and Sc(O*i*Pr)$_3$ were employed as a dynamic conglomerate of substrate/ligand/metal mixture to generate a defined transition state assembly. In the presence of 2–5 mol% of the

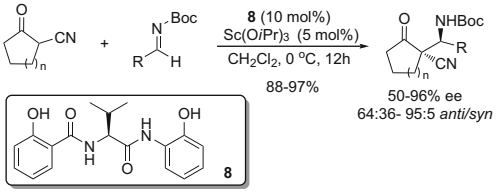

Fig. 12 Asymmetric Mannich-type reaction of α-cyanoketone to imines [42]

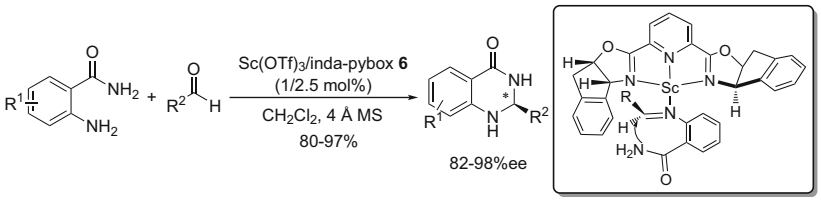

Fig. 13 Chiral $Sc(OTf)_3$-inda-pybox complex-catalyzed asymmetric intramolecular imine amidation [43]

catalyst, a range of aromatic imines and cyclic cyanoketones was found to be suitable substrates at 0°C to furnish the Mannich products with all-carbon quaternary and trisubstituted stereocenters in good yield (80–97%) and selectivities (*anti*/*syn* 75:25–95:5, 77–96% ee). The stereoselectivity could not be affected by noncoordinative substituents on the aromatic ring of imines, while the stereoselectivity diminished in the reaction with imines bearing coordinative substituents.

2,3-Dihydroquinazolinone containing a cyclic aminal chiral center was a class of important pharmacologically active heterocycles. Rare-earth metal complexes could efficiently promote the intramolecular amidation of imines for the asymmetric synthesis of 2,3-dihydroquinazolinones [43, 167, 168], which was initially reported by Kesavan and co-workers (Fig. 13) [43]. The complex prepared in situ from $Sc(OTf)_3$ and inda-pybox **6** was employed to efficiently promote the reaction between 2-aminobenzamide and aldehyde in the presence of 4 Å MS, providing remarkable catalytic activation of 2-amino-*N*-phenylbenzamide to afford the corresponding 2,3-dihydroquinazolinone in 80–97% yields with 82–98% ee. In addition, aliphatic aldehydes were also found to be suit substrates.

A combined catalyst of lanthanum aryloxide-pybox ***ent*-5** and lithium aryloxide was found to efficiently catalyze the direct asymmetric Mannich-type reaction of trichloromethyl ketone as a propionate equivalent donor (Fig. 14) [44]. In the presence of 2.5–10 mol% catalyst, various aryl, heteroaryl, alkenyl, and alkyl *N*-2-thiophenesulfonyl imines reacted smoothly to afford *syn*-Mannich adducts in up to >99% yield, 8:1–>30:1 *syn*/*anti*, and 92–98% ee. The Mannich products could be converted into ester and other useful building blocks. It was noted that the tris(aryloxide) species [La(*i*Pr–pybox)$(OAr)_3$] was considered as catalytically active species.

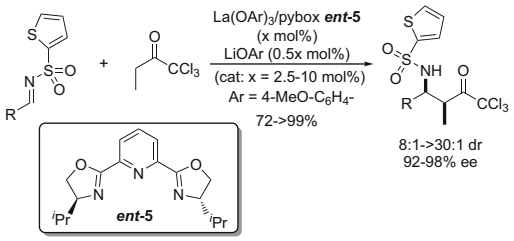

Fig. 14 Chiral lanthanum aryloxide/pybox-catalyzed asymmetric Mannich-type reactions [44]

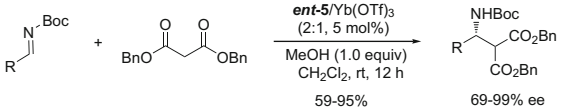

Fig. 15 Chiral $Yb(OTf)_3$-pybox complex-catalyzed asymmetric Mannich reaction of dibenzyl malonate with *N*-Boc aldimines [45]

Chiral $Yb(OTf)_3$-pybox ***ent-5*** complex could catalyze enantioselective Mannich reaction of dibenzyl malonate and *N*-Boc aldimines, affording β-amino carbonyl products (Fig. 15) [45]. The addition of one equivalent of MeOH as protic additive was a key to dramatically enhance the enantioselectivity. A variety of aryl aldimines including heteroaryl *N*-Boc aldimines were investigated, and the corresponding β-amino carbonyl products were obtained in good yields (59–95%) with excellent enantioselectivities (69–99% ee). Neither the electronic property nor the positions of the substitution at the aromatic ring had obvious influence on the enantioselectivity.

4 Asymmetric Michael Reactions

Asymmetric Michael reactions are important carbon-carbon and carbon-heteroatom bond formation reactions. Early in 2001, the Nakajima group extended *N*-oxide-mediated reactions into catalytic asymmetric Michael addition of β-keto esters with α,β-unsaturated carbonyl compounds. They found the complex of axially chiral biquinoline *N*,*N*′-dioxide **9** with $Sc(OTf)_3$ is efficient (Fig. 16) [46, 47]. The corresponding Michael products were obtained in high yields (73–98%) with good enantioselectivities (38–84% ee).

Kobayashi and co-workers developed a highly enantioselective conjugate addition of β-keto esters and α,β-unsaturated ketones using a chiral $Sc(OTf)_3$-bipyridine **4** complex (Fig. 17) [48]. It was found that the key to attain high enantioselectivities was a lower concentration of the reaction mixture. In most cases, the desired Michael reaction adducts could give out in good to high yields (54–98% yield)

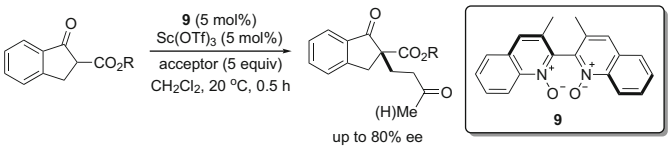

Fig. 16 Chiral *N,N′*-dioxide-Sc(III) complex-catalyzed asymmetric Michael reaction of β-keto esters [46, 47]

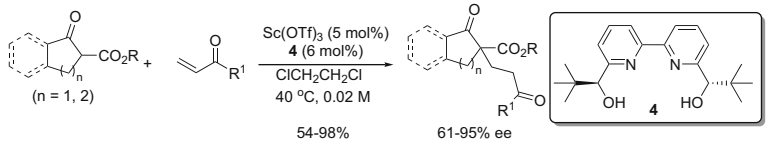

Fig. 17 Chiral bipyridine-Sc(OTf)$_3$ complex-catalyzed asymmetric Michael reaction [48]

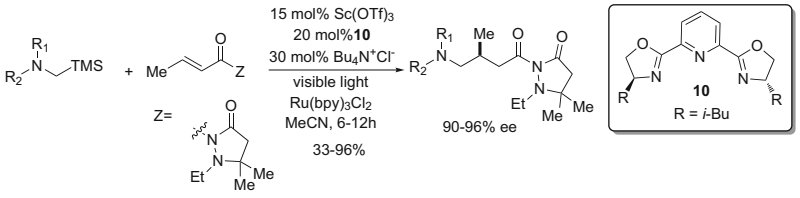

Fig. 18 Asymmetric Michael reaction of α-amino radicals via cooperative photoredox and Lewis acid catalysis [49]

with excellent enantioselectivities (61–95% ee). A pentagonal bipyramidal structure was formed from the coordination of nitrogens of pyridine and the hydroxy groups, and the efficient chiral induction occurs after the generation of scandium enolate intermediate from β-keto esters.

A highly enantioselective addition of photogenerated α-amino radicals to Michael acceptors has been realized by combination of transition metal photoredox catalysis and chiral Lewis acid catalysis (Fig. 18) [49]. In the presence of Ru(bpy)$_3$Cl$_2$ and Sc(OTf)$_3$-pybox **10** complex, the reaction between α-silylamines and Michael acceptor underwent smoothly under the irradiation with a 23 W fluorescent light bulb. The desired adducts were obtained in good yield (up to 96%) with excellent ee values (up to 96% ee). Most importantly, this process developed by Yoon and co-workers showed the ability of chiral Lewis acid catalysts to control the reactivity and enantioselectivity of these photogenerated nucleophilic intermediates.

Feng and co-workers reported an efficient asymmetric Michael addition of malonic esters to enynes (Fig. 19) [50]. The combination of *N,N′*-dioxide **L-PiEt$_2$Me**, Sc(OTf)$_3$, and *n*Bu$_3$N was evaluated as an efficient catalyst system for the reaction to provide a range of trisubstituted 1,2-allenyl ketones containing contiguous axial and carbon center in high yields (up to 99%) with excellent *ee* values (97–99%) and

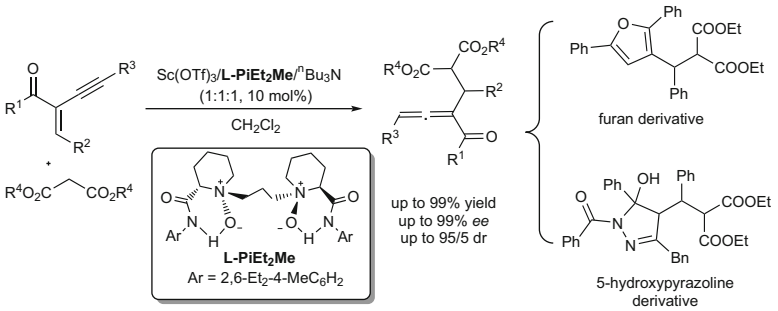

Fig. 19 Chiral *N*,*N*′-dioxide-Sc(III) complex-catalyzed asymmetric Michael addition of enynes [50]

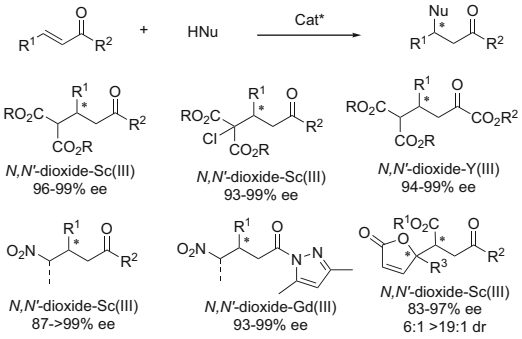

Fig. 20 Chiral *N*,*N*′-dioxide-RE(III) complex-catalyzed asymmetric Michael reactions [51–56]

good diastereoselectivity (up to 95/5 dr). Moreover, the products could be easily transformed into 5-hydroxypyrazoline derivatives and chiral furan, both of which are important skeletons of many pharmacologically and biologically active compounds.

The chiral *N*,*N*′-dioxide-rare-earth metal complex catalysts enabled highly efficient Michael additions to α,β-unsaturated carbonyl compounds with a range of Michael donors, such as malonic esters, nitroalkanes, and γ-unsaturated butenolides (Fig. 20) [51–56]. All of the desired adducts were obtained in good to excellent yield (up to 99%) with excellent ee values (up to >99% ee). In addition, the *N*,*N*′-dioxide-Gd(III)-catalyzed products from nitroalkanes and α,β-unsaturated pyrazolamides could be easily transformed into γ-nitroesters as key intermediates for the preparation of pregabalin, paroxetine, and baclofen [56].

A reversal of enantioselectivity was observed in *N*,*N*′-dioxide-RE(III) complex-catalyzed asymmetric Michael addition of 4-substituted pyrazolones to 4-oxo-4-arylbutenoates (Fig. 21) [57]. Using the same ligand by changing the metal center [Sc(III) or Ln(III)] and reaction solvent, both enantiomers of a range of 4-substitituted-5-pyrazolone derivatives were obtained in good to excellent enantioselectivities and

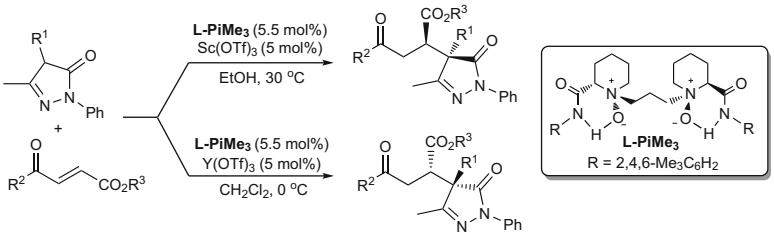

Fig. 21 Chiral *N*,*N*′-dioxide-RE(III) complex-catalyzed Michael addition of pyrazolin-5-ones [57]

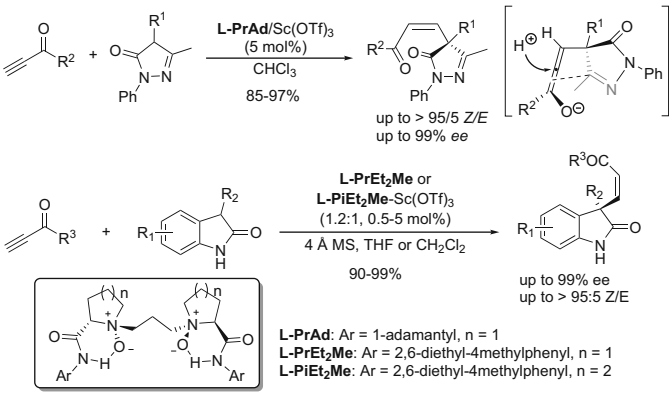

Fig. 22 Chiral *N*,*N*′-dioxide-Sc(III) complex-catalyzed *Z*-selective asymmetric conjugate addition of alkynyl carbonyl compounds [58, 59]

diastereoselectivities. The size of metal cations as well as coordination number might be crucial to the coordination of the reactants which led to the reversal of enantioselectivity.

The $Sc(OTf)_3$-*N*,*N*′-dioxide complexes were successfully employed in highly *Z*-selective asymmetric conjugate addition of 3-substituted oxindoles and pyrazol-5-ones to alkynyl carbonyl compounds (Fig. 22) [58, 59]. The thermodynamically unstable *Z*-olefin products were obtained in excellent yields and enantioselectivities and good geometric control. One possible intermediate as showed in Fig. 22 was proposed to rationalize the sense of geometric induction. The protonation process occurs from the suitable side of dienolate; and the other side was shielded by the pyrazoline ring due to the interaction between electron-enriched π-orbital of dienolate and electron-deficient carbon atom at the 3-position of the pyrazoline ring, affording the thermodynamically unstable *Z* isomer.

Furthermore, *N*,*N*′-dioxide **L-RaPr$_3$**-$Sc(OTf)_3$ complex catalyzed highly enantioselective Michael addition/desymmetrization reaction of *N*-(2-*t*-butylphenyl) with 3-substituted oxindoles, affording the chiral succinimides with both elements – atom chirality and axial chirality (up to 99% ee, >19:1 dr) (Fig. 23, Eq. 1) [60]. In the presence of $Sc(OTf)_3$-*N*,*N*′-dioxide **L-RaPr$_2$** complex, a series of 3,3-disubstituted

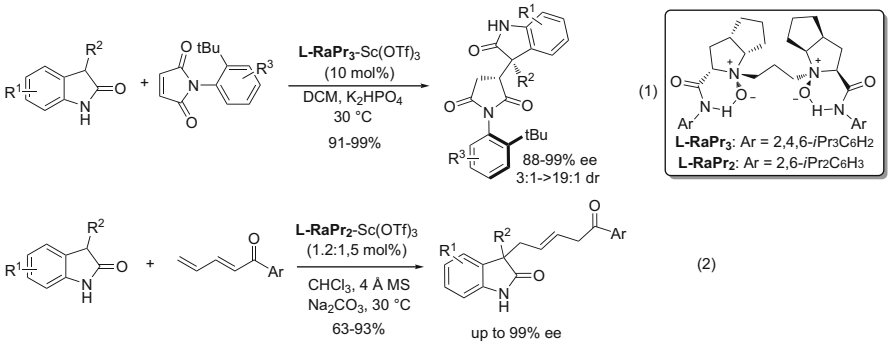

Fig. 23 Chiral *N,N′*-dioxide-Sc(III) complex-catalyzed asymmetric conjugate addition with unprotected 3-substituted-2-oxindoles [60, 61]

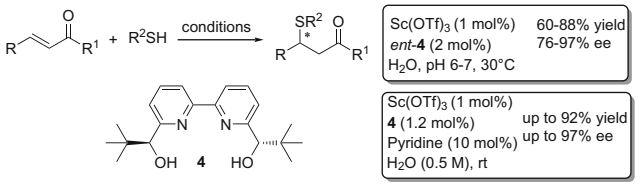

Fig. 24 Chiral bipyridine-Sc(III) complex-catalyzed asymmetric sulfa-Michael reaction [62–64]

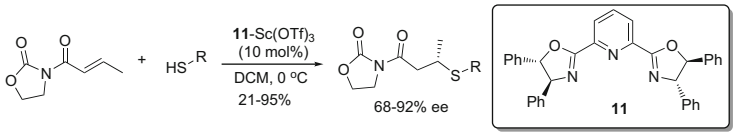

Fig. 25 Chiral diphenyl-pybox-Sc(III) complex-catalyzed asymmetric sulfa-Michael reaction with thiols [65]

oxindole derivatives could also be obtained in excellent yields and enantioselectivities via 1,6-addition with 3-substituted oxindoles (Fig. 23, Eq. 2) [61].

The Michael addition of thiols to α,β-unsaturated ketones promoted by chiral $Sc(OTf)_3$-bipyridine **4** complex has been realized independently by Vaccaro's and Kobayashi's groups (Fig. 24) [62–64]. The corresponding products, β-keto sulfides derived from aliphatic thiols, were obtained in satisfactory yields and high stereoselectivity. It was noteworthy that the reaction medium of the protocol is water. Moreover, both of the aqueous medium and the catalyst could be recovered and reused without any loss in enantioselectivity.

Koskinen and co-workers presented an improved method for the synthesis of (4*S*,5*S*)-diphenyl-pybox ligand **11** and applied it to participate in $Sc(OTf)_3$-promoted asymmetric conjugate addition reactions between various thiols and 3-crotonyl-2-oxazolidinone (Fig. 25) [65]. The reaction afforded the corresponding adducts in good yields and up to 92% ee.

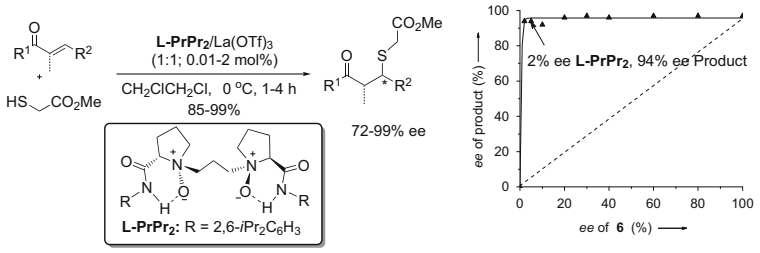

Fig. 26 Chiral *N*,*N*′-dioxide-La(III) complex-catalyzed asymmetric Michael reaction with thioglycolate [66]

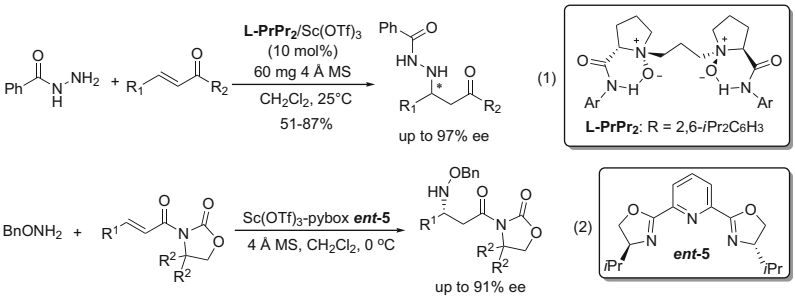

Fig. 27 Asymmetric aza-Michael reaction [67, 68]

A highly efficient asymmetric conjugate addition of chalcone derivatives with thioglycolate has been achieved in the presence of only 1 mol% of La(OTf)$_3$-*N*,*N*′-dioxide **L-PrPr$_2$** complex (Fig. 26) [66]. This method represents a rare example of the highly efficient synthesis of the chiral sulfur compounds (up to 99% ee). Meanwhile, when using a 0.01 mol% catalyst loading (on 4.165 g scale), excellent enantioselectivity (93% ee) was maintained. Additionally, a strong positive nonlinear effect was observed in this catalyst system. Using the catalyst prepared from only 2% ee of ligand **L-PrPr$_2$**, 94% ee still could be obtained.

The asymmetric conjugate addition of amine to α,β-unsaturated carbonyl compounds was realized in the presence of the Sc(OTf)$_3$-*N*,*N*′-dioxide **L-PrPr$_2$** complex (Fig. 27, Eq. 1) or Sc(OTf)$_3$/pybox ***ent*-5** complex (Fig. 27, Eq. 2), respectively [67, 68]. Both of the two catalytic systems could give the corresponding β-amino carbonyl compounds in good yields with high enantioselectivities. The screening of other rare-earth metal RE(OTf)$_3$ complex with neither *N*,*N*′-dioxide nor *i*Pr-pybox ligand led to poor enantioselectivity.

5 Asymmetric Friedel-Crafts Reaction

The Friedel-Crafts alkylation of *N*-alkyl-substituted indole with different β-alkyl substituted unsaturated acyl phosphonates was reported by the Evans group, while chiral complex of pybox **6**-Sc(OTf)$_3$ was utilized as the catalyst (Fig. 28) [69, 70].

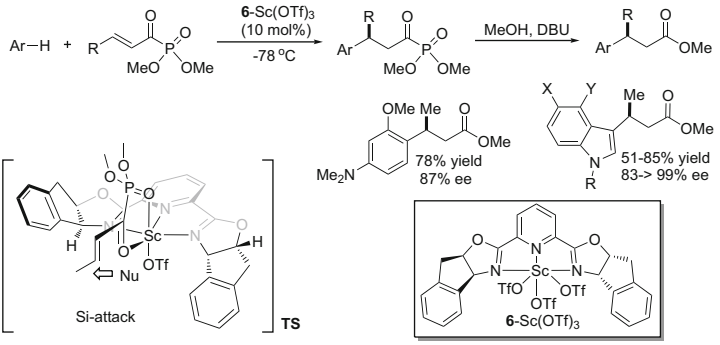

Fig. 28 Chiral pybox **6**-Sc(OTf)$_3$ complex-catalyzed asymmetric indole Friedel-Crafts alkylations with α,β-unsaturated acyl phosphonates [69, 70]

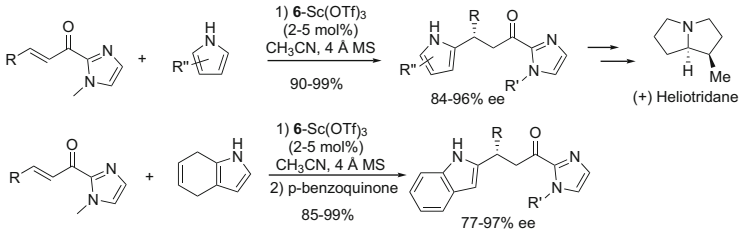

Fig. 29 Chiral pybox **6**-Sc(OTf)$_3$ complex-catalyzed asymmetric Friedel-Crafts alkylations of α,β-unsaturated 2-acyl imidazoles [71, 72]

Under mild condition, a series of β-alkyl-substituted unsaturated acyl phosphonates were tolerated well with up to 99% ee. Indole derivatives with either electron-withdrawing or electron-donating substituents at C5 were competent substrates, while a 4-Cl substituent lowered conversion with high enantioselectivity. It is noteworthy that electron-rich 3-dimethylaminoanisole was also an effective nucleophile for this transformation, and the desired intermediates could be further transformed into esters or amides with good results. On the other hand, a transition state was proposed to rationalize the observed sense of stereoinduction. The oxygen of phosphonate coordinates in the more accessible apical position, and carbonyl oxygen orients toward the ligand plane, leading nucleophilic attack on the *Si*-face to form the corresponding *S*-product.

In 2005, the author utilized the same catalyst to accelerate the Friedel-Crafts reactions of α,β-unsaturated 2-acyl imidazoles with electron-rich heterocycles (Fig. 29) [71, 72]. The reaction exhibits good enantioselectivities over a broad range of nucleophiles such as indole, 2-methoxyfuran, pyrrole, and dihydroindole. Substituents on the indole had great influence on the enantioselectivity, while alkyl and aryl substitution on the β-position of enones were well tolerated (43–99% yield, 65–98% ee). Dihydroindole was also employed as the nucleophile with 2-position accessing to the α,β-unsaturated 2-acyl imidazoles. In addition, 2-methoxyfuran

and pyrrole were competent substrates under this transformation with good yields and excellent enantioselectivities. Besides, an intramolecular indole alkylation has been investigated in 99% yield with 97% ee. The products could be easily transformed into synthetically useful amides, esters, carboxylic acids, ketones, and aldehydes.

Electrophiles of the asymmetric Friedel-Crafts reactions were also enlarged to methyl (*E*)-2-oxo-4-aryl-3-butenoates (Fig. 30) [73]. Using a chiral pybox **12**-$Sc(OTf)_3$ complex, a number of substituted 4-(indol-3-yl)-2-oxo-4-arylbutyric acid methyl esters were efficiently formed in excellent yields and enantioselectivities (up to 99% yield, 99% ee) regardless of the electronic character of the substituent and its location on the indole ring, albeit with the exclusion of C2-position. According to the absolute configuration of the products and the Sc(III) complex, an octahedral reactive intermediate was rationalized to elucidate the stereoinduction. As shown in Fig. 30, the ketonic carbonyl group of butenoate coordinates to Sc(III) ion in the equatorial position and the ester carbonyl group and triflate ion in axial positions. The indole attacks from sterically less demanding *Re*-face to form the *R*-product.

Feng and co-workers disclosed the highly enantioselective Friedel-Crafts alkylation reactions of indoles and pyrrole with chalcone derivatives catalyzed by chiral *N*,*N*′-dioxide-$Sc(OTf)_3$ complexes (Fig. 31) [77]. Ligand *N*,*N*′-dioxide **L-RaMAn** derived from *L*-pipecolic acid and 9-anthracenylmethylamine was efficient for the alkylation of a range of indoles with electron donation or withdrawing groups with various α,β-unsaturated ketones. Good to excellent yields and high enantioselectivities were obtained, regardless of the electronic nature or positions of the substituents on the phenyl ring (43–99% yield, 83–92% ee). Besides, they extended the current catalytic system to other electrophiles (including ethyl glyoxylate, alkylidene malonates, aldimines, and 4-oxo-4-arylbutenoates) and nucleophiles, such as pyrrole and sesamol [74–78]. It was worth mentioning that good to excellent yields and enantioselectivities were obtained for all this reaction partners only by adjusting subunits of chiral *N*,*N*′-dioxides.

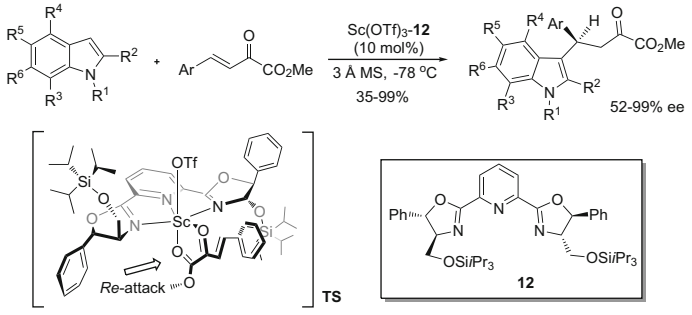

Fig. 30 Chiral pybox-$Sc(OTf)_3$ complex-catalyzed asymmetric Friedel-Crafts alkylation of indoles with methyl (*E*)-2-oxo-4-aryl-3-butenoates [73]

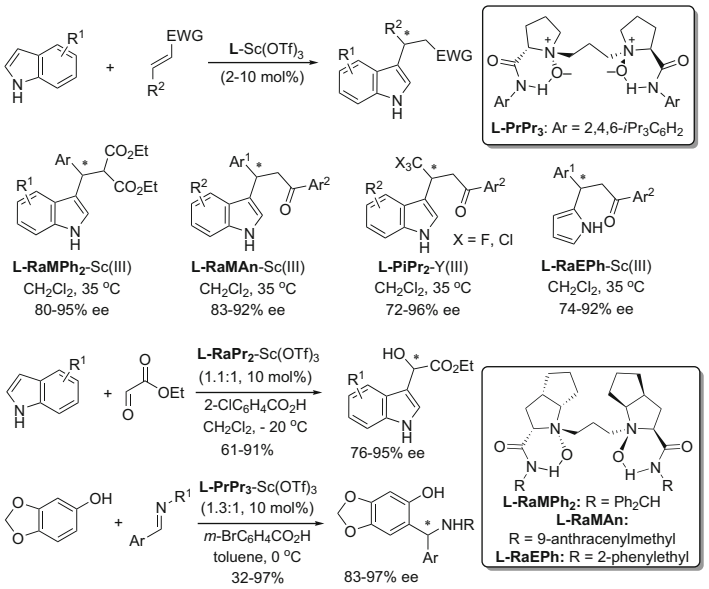

Fig. 31 Chiral *N*,*N*′-dioxide-Sc(III) complex-catalyzed asymmetric Friedel-Crafts alkylation [74–78]

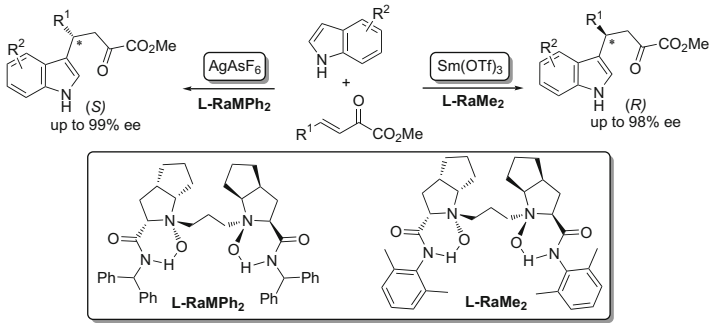

Fig. 32 $AgAsF_6/Sm(OTf)_3$ promoted reversal of enantioselectivity for the asymmetric Friedel-Crafts alkylations of indoles [79]

By the electrophiles mentioned above, *N*,*N*′-dioxide-metal complex-promoted Friedel-Crafts alkylation of β,γ-unsaturated α-keto esters was also developed from which a reversed enantioselectivity was observed (Fig. 32) [79]. *N*,*N*′-dioxides **L-RaMPh$_2$** and **L-RaMe$_2$** were derived from the same chiral source but different amines. However, the corresponding metal complexes **L-RaMPh$_2$**/$AgAsF_6$ and **L-RaMe$_2$**/$Sm(OTf)_3$ delivered opposite facial selectivity, giving both enantiomers of various indole esters in good to excellent yields and enantioselectivities. It should be noted that *N*,*N*′-dioxides **L-RaMe$_2$-**$Sm(OTf)_3$ catalyst allowed the performance of the reaction at the catalyst loading lower to 0.01 mol% of complex without considerable loss in reactivity and enantioselectivity.

6 Asymmetric Homologation of Carbonyl Compounds with α-Diazoesters

The catalytic enantioselective diazoalkane-carbonyl homologation reaction with cyclic ketone substrates to access nonracemic 2-aryl cycloalkanones was reported by the Kingsbury group (Fig. 33) [80, 81]. Asymmetric aryldiazomethyl insertion giving ring-extending products was accomplished via chiral Sc(III) catalysts with simple bis- and tris(oxazoline) ligands. A range of medium ring 2-aryl ketones were prepared in one step in up to 96% ee and 99% yield, regardless of different cyclic ketones and substituents on different position on the phenyl ring except for cyclopentanone substrate. As shown in Fig. 33, a transition state was assumed to illustrate the asymmetric introduction. The nucleophile of the diazoalkane accesses to cycloalkanone ring with the aryl group directed away from the chiral pocket established by the trisox ligand, followed by the concerted 1,2-rearrangement and loss of dinitrogen to form the enantioenriched 2-aryl cycloalkanone.

The Roskamp reaction could be extended to an asymmetric version which delivered chiral α-alkyl-β-keto esters. The breakthrough has been made by Feng and co-workers in 2010 (Fig. 34) [82]. The reaction is difficult in controlling the chemoselectivity because the diazonium intermediate can undergo three rearrangement pathways (Fig. 34). Furthermore, high enantioselectivity for α-alkyl-β-keto ester could be achieved only if the racemization via enolization was avoided. In the presence 0.05 mol% of **L-RaPr$_2$**-Sc(OTf)$_3$ complex, the first catalytic enantioselective Roskamp reaction of α-alkyl-α-diazoesters with various aromatic aldehydes has been realized to provide chiral α-alkyl-β-keto esters in excellent yields and enantioselectivities. Additionally, the flash filtration as the isolation procedure was necessary to prevent racemization of the products.

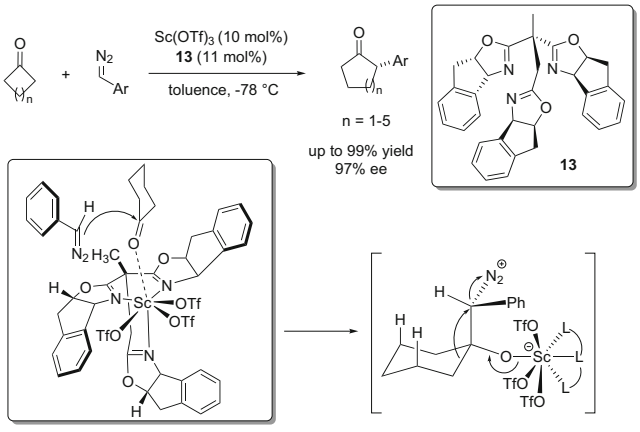

Fig. 33 Chiral tris(oxazoline)-Sc(OTf)$_3$ complex-catalyzed asymmetric diazoalkane-carbonyl homologation [80, 81]

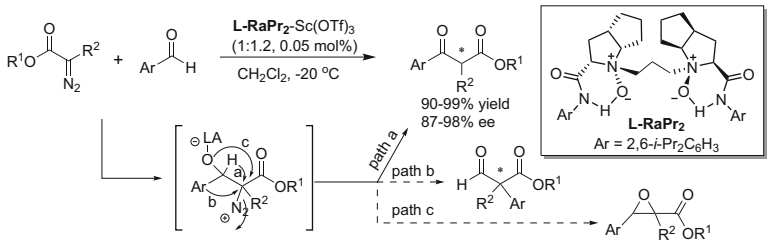

Fig. 34 Chiral *N*,*N*′-dioxide-Sc(III) complex-catalyzed asymmetric Roskamp-Feng reaction [82]

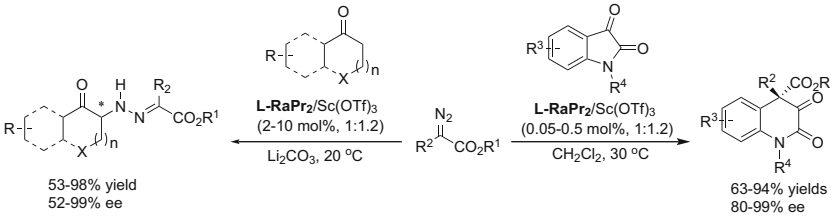

Fig. 35 Chiral *N*,*N*′-dioxide-Sc(III) complex-catalyzed asymmetric homologation and hydrazonation [83, 84]

Later, when Feng's group attempted to extend the current catalytic system to the reaction of simple ketones, interestingly, an unexpected C–N bond formation rather than homologation reaction was found (Fig. 35) [83]. The primary theoretical calculations indicated that the carbonyl group of the α-dizoester combined with the strong Lewis acid $Sc(OTf)_3$ increased the electrophilicity at N atom, thus promoted the unexpected process. With the same chiral catalyst of *N*,*N*′-dioxide **L-RaPr$_2$**-$Sc(OTf)_3$, a wide range of α-diazoesters and ketones underwent the reaction smoothly, providing the chiral nitrogen-containing products in excellent yields (up to 98%) and enantioselectivities (up to 99% ee). Nevertheless, when isatins were subjected into the reaction with α-dizoester, the carbonyl group accepted the electrophilic addition of α-diazoester, and various ring expansion products of functionalized 2-quinolone derivatives were obtained. Excellent yields (up to 94%) and excellent enantioselectivities (up to 99% ee) were given in the presence of 0.05–0.5 mol% of *N*,*N*′-dioxide **L-RaPr$_2$**-$Sc(OTf)_3$ [84].

The catalytic asymmetric homologation of diazoesters with α-keto esters led to a carbon-chain extension reaction (Fig. 36) [85]. After preliminary screening of conditions, the chiral *N*,*N*′-dioxide **L-PrPr$_2$**-$Y(OTf)_3$ complex proved to be an efficient catalyst. A number of aryl- and alkyl-substituted α-keto esters as well as substituted diazoesters underwent the reaction smoothly, providing the corresponding 1,2-aryl/alkyl-shift products with all-carbon quaternary centers in moderate to good yields (up to 81%) and excellent enantioselectivities (up to 95% ee).

When ketone and diazoester functional groups were designed into one substrate, an intramolecular homologation occurred to afford cyclic α-aryl/alkyl β-keto esters

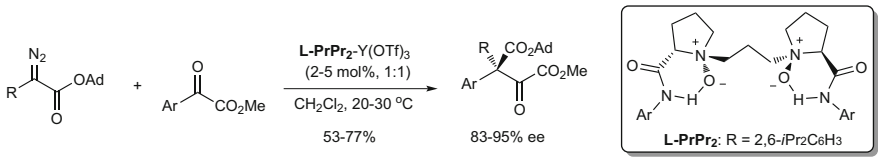

Fig. 36 Chiral *N,N′*-dioxide-Y(III) complex-catalyzed asymmetric homologation of acyclic ketones [85]

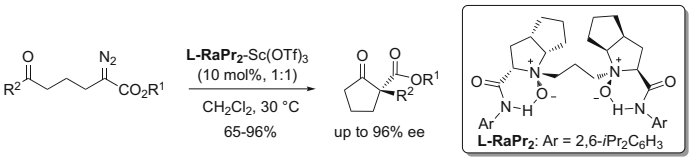

Fig. 37 Chiral *N,N′*-dioxide-Sc(III) complex-catalyzed asymmetric intramolecular homologation [86]

(Fig. 37) [86]. Aromatic ketones could tolerate the reaction well, and aliphatic ketones resulted in reduced enantioselectivity and steric-hindrance dependence. By-products including tetrasubstituted epoxide and cyclobutene derivative generated from oxygen and 1,2-alkyl migration processes, respectively, were detected from a gram-scale synthesis. In addition, the length of the carbon-chain tethering the α-diazoester affected the migration preference, resulting in varied major product.

7 Asymmetric Ene-Type Reaction

The carbonyl-ene reaction is a powerful and atom-economic C–C bond-forming reaction. Qian and co-workers initially reported chiral 6,6′-dibromo-substituted binaphthol-Yb(III) complex-catalyzed carbonyl-ene reaction of methyl glyoxylate with α-methylstyrene to give α-hydroxy ester with 38% ee [87]. Later, chiral bis (oxazoline)-rare-earth metal catalysts were employed to this reaction. The pybox **7**-$Yb(OTf)_3$ was found to be the best catalyst, promoting the glyoxylate-ene reactions with a range of 1,1-disubstituted alkenes to afford good yields and up to 54% ee (Fig. 38) [88]. In the proposed transition model, the coordination of the pybox **7**-Yb $(OTf)_3$ with dicarbonyl groups of glyoxylate benefited a distorted trigonal bipyramidal Yb(III) complex in which the ene compound attacked the formyl group from less hindered *Re*-face which resulted in *R* configuration.

In 2005, the Evans group achieved a highly enantioselective carbonyl-ene reaction of *N*-phenyl glyoxamide, using pybox-$Sc(OTf)_3$ and inda-pybox-$Sc(OTf)_3$ complexes as the optimal catalysts (Fig. 39) [89, 90]. In the presence of pybox **6**-$Sc(OTf)_3$ complex, good yields (73–99%) and excellent enantioselectivities (92–94% ee) were obtained using 1,1′-disubstituted olefins. When nonsymmetrical 1,1′-disubstituted

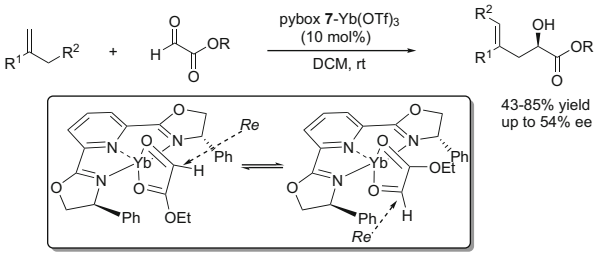

Fig. 38 Chiral pybox **7**-Yb(III) complex-catalyzed asymmetric glyoxylate-ene reaction [88]

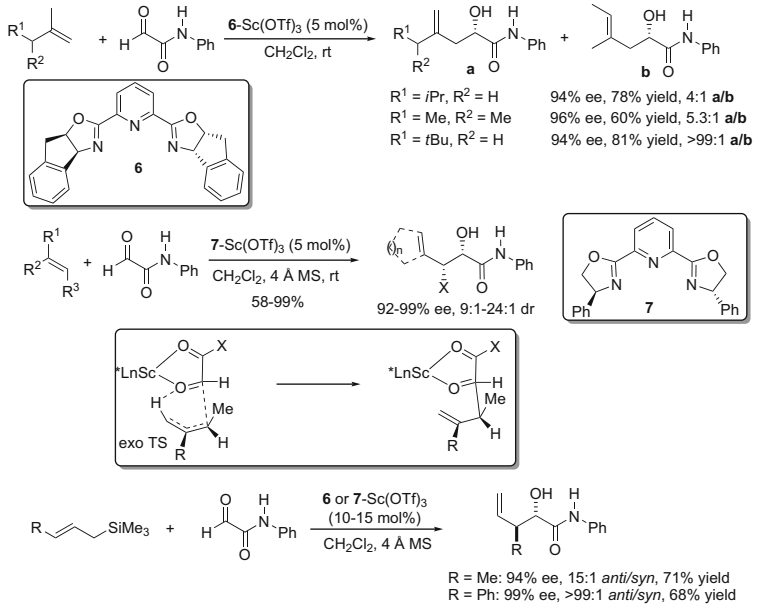

Fig. 39 Chiral pybox-Sc(III) complex-catalyzed asymmetric ene reaction [89, 90]

olefins were employed, terminal olefin products were preferentially formed, and the discrimination was based on the steric hindrance. In addition, pybox **7**-Sc(OTf)$_3$ complex was found to catalyze ene reaction of trisubstituted olefinic substrates with better result, affording the coupling products with good *syn* selectivities (9:1–24:1 dr) and enantioselectivities (94–99% ee). The controlled result of 3-methylpent-2-ene olefin and its geometric isomer indicated that the major products of ene reactions produced in both cases corresponded to the proton transfer from the β-cis substituent through an exo-transition state. As related work, the reaction between acyclic allylsilanes and *N*-phenyl glyoxamide was efficiently catalyzed by Ph-pybox **7**-Sc(OTf)$_3$ complex, affording the "ene-type" products with *anti* selectivities in good yields (68–71%) and excellent selectivities (15:1–99:1 *anti*/*syn*, 94–99% ee).

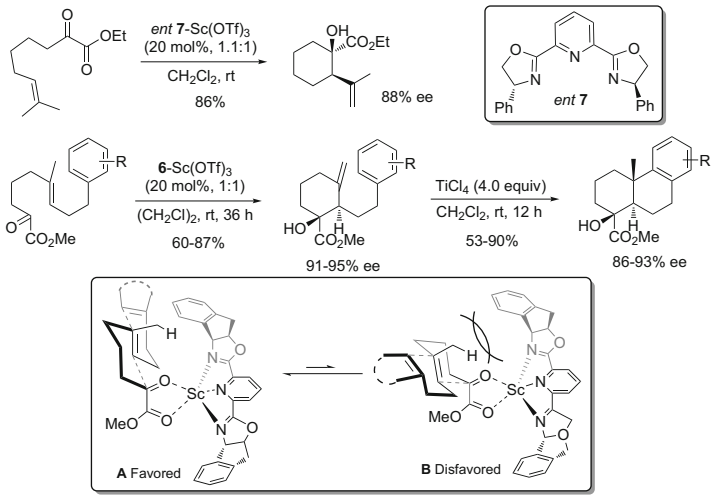

Fig. 40 Chiral pybox-Sc(III) complex-catalyzed asymmetric intramolecular carbonyl-ene reaction [91, 92]

Yang and co-workers developed chiral *ent* pybox **7**-Sc(OTf)$_3$ and box-Cu(OTf)$_2$ complexes as efficient promoters for the enantioselective intramolecular carbonyl-ene reactions of unsaturated α-keto esters (Fig. 40) [91]. Active monocyclic *cis*-1-hydroxy-2-alkyl ester was obtained with 86% yield and 88% ee, using chiral *ent* pybox **7**-Sc(OTf)$_3$. Loh and co-workers achieved a highly efficient catalytic enantioselective cationic polyene cyclization and catalytic enantioselective intramolecular carbonyl-ene reaction. The cyclization products which are the chiral fragments of natural products and pharmaceuticals could be obtained in good yield and high enantioselectivity [92]. The transition state to rationalize the origin of enantioselectivity was shown in Fig. 40, containing a catalyst-substrate-binding complex via chelation of carbonyl oxygen of the α-keto esters moiety to pybox **6**-Sc(OTf)$_3$. Carbonyl-ene reaction benefited the shift of conformational equilibrium from transition state B toward transition state A to minimize the steric repulsion between the alkyl chain of substrate and the phenyl moiety of the catalyst, affording high selectivity.

8 Asymmetric Cycloaddition Reaction

Asymmetric cycloaddition reactions including [4 + 2], [3 + 2], [2 + 2], and others constitute important methodology to access optical active cyclic compounds. The first chiral rare-earth metal complex catalysis in cycloaddition was reported in 1983 until Danishefsky and co-workers developed an asymmetric hetero-Diels-Alder reaction between Danishefsky's diene and benzaldehyde using a [Eu(hfc)$_3$] complex **14** (Fig. 41, Eq. 1) [1].

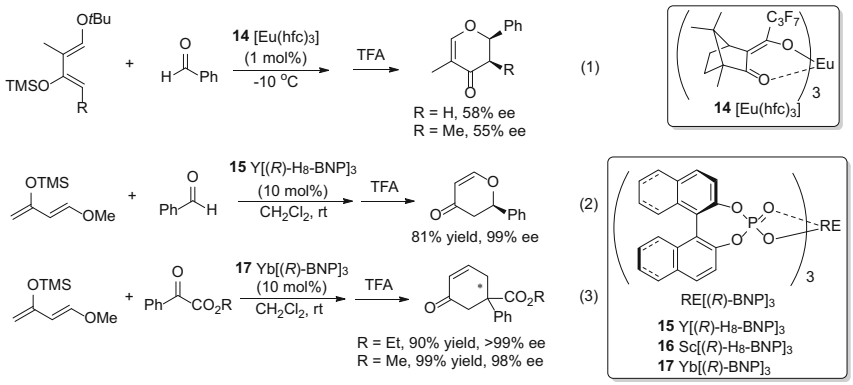

Fig. 41 Asymmetric hetero-Diels-Alder reaction [1, 93]

Fig. 42 Chiral *N*,*N*′-dioxide-Sc(III) complex-catalyzed asymmetric aza-Diels-Alder reaction with Danishefsky-type diene [94]

The rare-earth metal phosphates were used to catalyze hetero-Diels-Alder reaction of carbonyl compounds and Danishefsky's diene under the homogeneous conditions (Fig. 41, Eqs. 2–3) [93]. The Y[(*R*)-H_8-BNP]$_3$ complex **15** could promote the reaction of aromatic aldehydes to afford a little higher enantioselectivity than Sc[(*R*)-H_8-BNP]$_3$ **16** catalysis (Fig. 41, Eq. 2). Nevertheless, the catalyst Sc[(*R*)-H_8-BNP]$_3$ **16** could be recovered and reused with high reactivity and slightly decreased enantioselectivity. For phenylglyoxylate substrates, the corresponding cycloadducts could be obtained in high yields with excellent enantioselectivities (up to 99% ee) in the presence of Yb[(*R*)-BNP]$_3$ complex **17** (Fig. 41, Eq. 3).

The *N*,*N*′-dioxides **L-PrPr$_2$** ligand in combination with Sc(OTf)$_3$ was employed in the asymmetric aza-Diels-Alder reaction of aldimines derived from aldehydes and 2-aminophenol with Danishefsky-type diene (Fig. 42) [94]. The complex showed good activity and enantioselectivity in the presence of 4-aminobenzenesulfonic acid as an additive, affording various 2,5-disubstituted dihydropyrimidinones in 46–92% yield and 71–90% ee. Moreover, *N*,*N*′-dioxides **L-PiPr$_2$**-Yb(OTf)$_3$ complex has been identified useful for enantioselective aza-Diels-Alder reaction of aldimines with Brassard's diene [95]. A number of α,β-unsaturated δ-lactam derivatives were obtained in moderate yields with good enantioselectivities (up to 81% ee) under mild conditions. On the basis of the isolated reaction intermediates, this cycloaddition reaction proceeded through a stepwise Mannich cyclization pathway.

An important contribution from the Kobayashi group in 1996 represents the first asymmetric catalytic inverse electron-demand aza-Diels-Alder (IEDDA) reaction of *N*-arylimines with electron-rich alkenes for the synthesis of tetrahydroquinoline derivatives (Fig. 43, Eq. 1) [96]. The chiral Lewis acid prepared from $Yb(OTf)_3$, (*R*)-BINOL, and DBU was found efficient to catalyze a range of imines and dienophiles in the presence of an additive (2,6-di-*t*-butylpyridine or 2,6-diphenylpyridine), providing the corresponding products in good yield with up to 91% ee. The three-component IEDDA reaction was successfully carried out for unstable imine derived from cyclohexanecarboxaldehyde and 2-hydroxyaniline.

The Feng group explored chiral *N*,*N*′-dioxide **L-RaPr$_2$**-$Sc(OTf)_3$ catalyst to the asymmetric three-component IEDDA reaction of 2-hydroxyanilines, aldehydes, and cyclopentadiene (Fig. 43, Eq. 2) [97]. In the presence of 0.5–5 mol% of the chiral complex, a variety of ring-fused tetrahydroquinolines with three contiguous stereocenters were generated in 62–99% yields and excellent diastereo- and enantioselectivities (90:10–99:1 dr, 90–99% ee, respectively). Furthermore, the same catalyst could also be applied into the Povarov reaction with α-alkyl styrenes as the dienophiles (Fig. 43, Eq. 3), affording a wide range of tetrahydroquinolines containing a quaternary stereocenter at the C4 position with excellent diastereo- and enantioselectivities (up to >99:1 dr and 92 to >99% ee) [98].

Asymmetric Diels-Alder reactions of cyclopentadiene and acyl-1,3-oxazolidin-2-ones were well developed by different chiral scandium(III) complexes employing a variety of chiral ligands. The combination of $Sc(OTf)_3$, (*R*)-BINOL, and 1,2,6-trimethylpiperidine formed the catalyst **18** which promoted the reaction with 86–99% yields, 78:22–90:10 endo/exo and 74–97% ee (endo) selectivity (Fig. 44) [99]. The employed 1,2,6-trimethylpiperidine was crucial to the enantioselectivity.

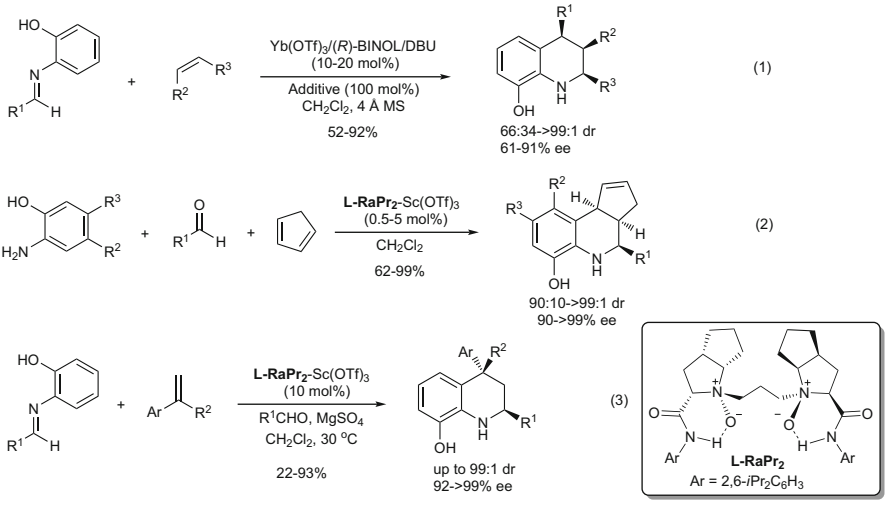

Fig. 43 Asymmetric inverse electron-demand aza-Diels-Alder reaction [96–98]

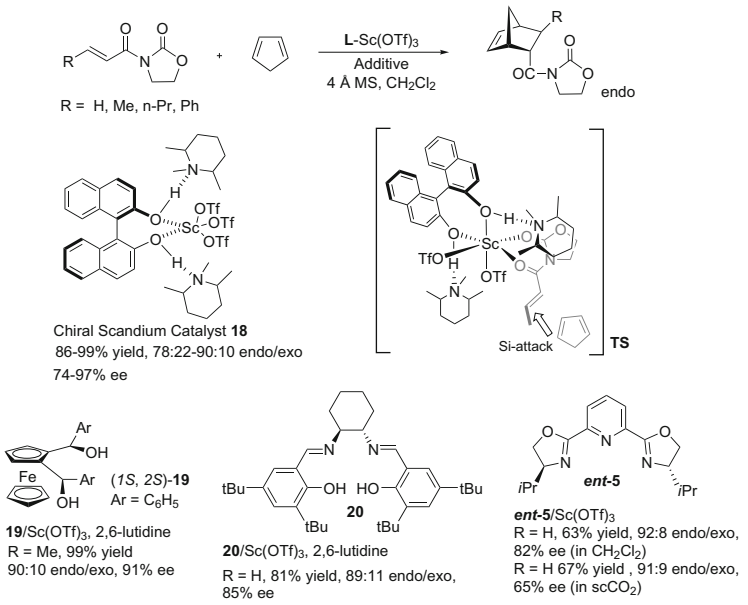

Fig. 44 Sc(III) complex-catalyzed asymmetric Diels-Alder reaction [99–103]

The unique structure of catalyst as shown in Fig. 44 indicated that the axial chirality of (*R*)-BINOL was postulated to be transferred to amine part through the interaction between the nitrogen of amine and the phenolic hydrogen of (*R*)-BINOL. The stereoinduction of the reaction was rationalized by assuming an octahedral intermediate, in which *Re*-face of the dienophile was shielded by amine and the diene approached the dienophile from the free *Si*-face to afford the Diels-Alder products with (2*R*,3*R*)-configuration in high enantioselectivity.

Other chiral catalysts were used for the same Diels-Alder reaction (Fig. 44) including $Sc(OTf)_3$/FERRODIOL complex **19** [100], $Sc(OTf)_3$/(*S*,*S*)-salen complex **20** with 2,6-lutidine as the additive [102], and $Sc(OTf)_3$-pybox ***ent*-5** complex as well [101, 103]. It should be noticed that in the last case, both organic solvent dichloromethane and less toxic supercritical carbon dioxide ($scCO_2$) were employed as solvent, although the enantioselectivity decreased in sc-CO_2 (from 82% ee to 65% ee).

For the pybox ligand in rare-earth complex catalyst, several groups investigated the electronic and steric effect of the ligand in Diels-Alder reactions between cyclopentadiene and acyl-1,3-oxazolidin-2-ones. The pybox ligand **21** with electron-withdrawing chloride and sterically bulky *t*Bu substituent in 4′-positions (Fig. 45) in coordination with $Sc(OTf)_3$ could increase the enantioselectivity in comparison with pybox **5** [104]. The effect of substituent on 5′-position of pybox and ionic radius of the metal cations was thoroughly investigated [105–107]. Using the complex of pybox

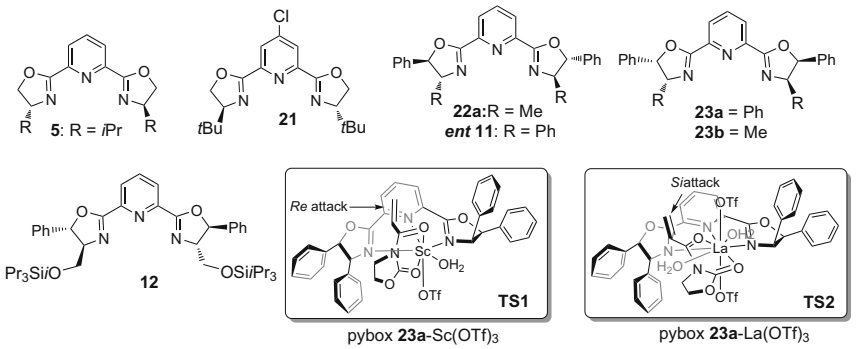

Fig. 45 The electronic and steric effect of pybox ligand and transition states for asymmetric Diels-Alder reaction of acyl-1,3-oxazolidin-2-ones [104–107]

22a–$Sc(OTf)_3$ or ***ent*-11**-$La(OTf)_3$ that ligands contained a phenyl group in 5′-positions of oxazoline rings, the enantioselectivity of Diels–Alder products could be increased up to 97% ee and 96% ee, respectively. The incorporation of the phenyl substituent in 5′-positions could lead to the reverse of enantioselectivity. The catalysts prepared from $Sc(OTf)_3$ with pybox **5** or pybox **23b** gave (*R*)-adducts as preferred enantiomers, while pybox **22a**–$Sc(OTf)_3$ afforded the reversed (*S*)-adduct. In addition, the sense of enantioselectivity was greatly influenced by the size of metal cations. In the case of RE-pybox **23a** catalysts, the Sc(III)-based one produced (*S*)-adduct as the preferred enantiomer, while La(III)-based one gave the reversed (*R*)-adduct. The information of X-ray structures of Sc(III) and La(III) complexes as well as the proposed transition states may interpret the phenomenon of metal-switched enantioselectivity. As shown in Fig. 45, the Sc(III) complex occurred a pentagonal-bipyramidal coordination that the two phenyl groups of the ligand **23a** shielded the *Re*-face, giving major (*S*)-adduct (**TS1**). While La(III) has higher coordination number of nine, two phenyl groups induced shielding of the *Si*-face to provide the major (*R*)-adduct (**TS2**).

Later, Desimoni and co-workers developed pybox ligand **12** for three types of cycloaddition reactions of 3-acryloyl- and 3-crotonyloxazolidinones as the 2π-components, including Diels-Alder reaction with cyclopentadiene, 1,3-dipolar cycloaddition with diphenyl nitrone, and Mukaiyama-Michael reaction with 2-trimethylsilyloxyfuran [108]. Excellent enantioselectivities were observed in these reactions, and the opposite enantiomers could be obtained by changing the metal cations.

As related work, Desimoni and co-workers developed Diels-Alder reaction of methyl (*E*)-2-oxo-4-aryl-3-butenoates and cyclopentadiene using pybox-rare-earth metal complexes [109–111]. The catalysts were inefficient in the control of regioselectivity with typically 1:2 Diels-Alder/hetero-Diels-Alder adducts but resulted in excellent enantioselectivities for both products with $Sc(OTf)_3$-based catalysts (>99% ee). The scandium catalyst also could promote the hetero-Diels-Alder reaction of (*E*)-2-oxo-4-aryl-3-buteneoates with 1-trialkylsiloxy-1-cyclohexenes

to afford the cycloadducts in good yield with excellent enantioselectivity and moderate diastereoselectivity [111].

Evans successfully applied the pybox **7**-Sm(OTf)$_3$, pybox **7**-Gd(OTf)$_3$, and pybox *ent* **22a**–Sm(OTf)$_3$ complexes to the asymmetric quinone Diels-Alder reactions. Three quinones and five dienes reacted smoothly to afford *endo*-products in excellent yields and enantioselectivities (Fig. 46) [112]. A linear effect was observed between enantioselectivities of the ligand and ee of the product in the pybox **7**-Sm(OTf)$_3$ catalytic system, thus suggesting that the monomeric species was the active catalytic intermediate.

Feng and co-workers reported *N*,*N*′-dioxide **L-RaMe$_2$Bu**-Sc(III) complex-catalyzed asymmetric inverse electron-demand hetero-Diels-Alder reaction of *o*-quinone methides with azlactones (Fig. 47) [113]. Organic base such as imidazole as the additive could not only increase the yield but also promote the enantioselectivity. Under the optical reaction conditions, various azlactones were employed to give the corresponding functionalized 3,4-dihydrocoumarins bearing nitrogen atom substituents in good yield and enantioselectivity. The operando IR experiments clearly demonstrated that the amount of the product increased with the consumption of *o*-quinone methides and azlactone; none of signal related to the Michael-addition product was detected. Furthermore, under the standard reaction conditions, Michael-addition product could not transfer to 3,4-dihydrocoumarin product in the control experiment. These experiments indicate the reaction undergoes a concerted pathway.

The asymmetric Diels-Alder reactions between 3-[1-(silyloxy)vinyl]-indole and *N*-acyloxazolidinones were developed by Nishida and co-workers (Fig. 48). A chiral holmium catalyst in situ generated from Ho(NTf$_2$)$_3$ and chiral bis-thiourea ligand **24** in the presence of DBU proved efficient [114]. In addition, *N*,*N*′-dioxide

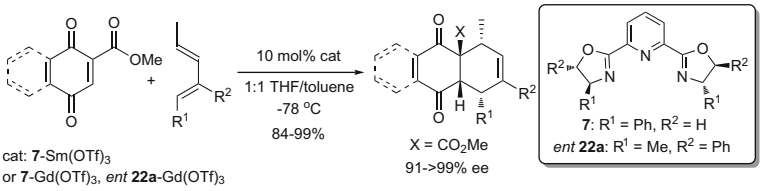

Fig. 46 Asymmetric rare-earth complex-catalyzed quinone Diels-Alder reactions [112]

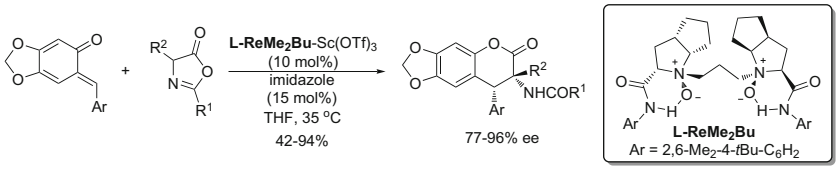

Fig. 47 Asymmetric hetero-Diels-Alder reaction of *o*-quinone methides with azlactones [113]

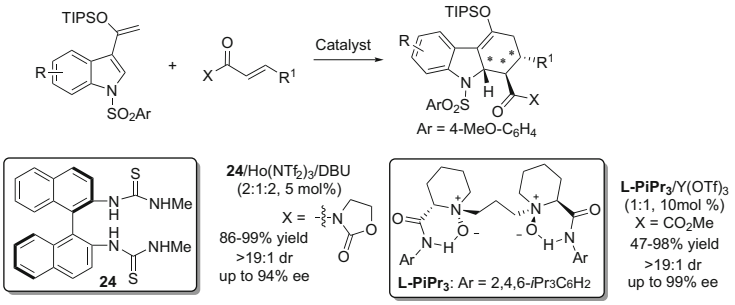

Fig. 48 Asymmetric Diels-Alder reactions of 3-[1-(silyloxy)vinyl]indole [114, 115]

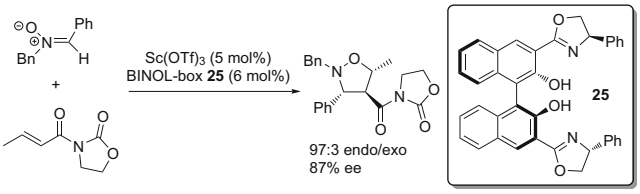

Fig. 49 Asymmetric 1,3-dipolar cycloaddition of nitrone [116]

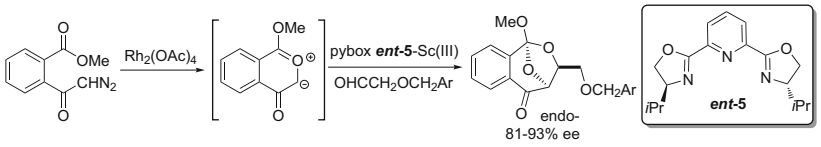

Fig. 50 Asymmetric tandem carbonyl ylide formation-cycloaddition sequence [117]

L-PiPr$_3$-Y(OTf)$_3$ complex was employed as an efficient promoter for Diels-Alder reactions of 3-[1-(silyloxy)vinyl]indole with β,γ-unsaturated α-keto esters [115].

The enantioselective 1,3-dipolar cycloaddition of nitrones to alkenes afforded *endo*-isoxazolidines with good selectivity (97:3 endo/exo, 87% ee) in the presence of chiral BINOL-box **25**-Sc(OTf)$_3$ complex catalyst (Fig. 49) [116]. The use of other lanthanide triflates led the enantioselectivities to be diminished largely.

The carbonyl ylide formed from diazo precursors with Rh(II) catalysis, could be underwent enantioselective 1,3-dipolar cycloadditions to provide epoxy-bridged tetrahydropyran skeleton (Fig. 50). Suga and co-workers utilized dual-activation methodology involving an achiral Rh(II) catalysis followed by a chiral Lewis acid catalyst-catalyzed asymmetric 1,3-dipolar cycloaddition. In the case of benzyloxyacetaldehyde derivatives, the pybox ***ent*-5**-Sc(III) complex efficiently promoted the reaction to yield the *endo* adducts (67:33–91:9 endo/exo) with high enantioselectivity (81–93% ee). Next, the dual activation of tandem carbonyl ylide

formation-cycloaddition sequence was extended to either normal electron-demand cycloadditions of electron-deficient dipolarophiles, such as β-keto esters and 2-alkenoyl-3-oxazolidinones [117–120] or inverse electron-demand cycloadditions of electron-donating dipolarophiles, such as vinyl ethers and *N*-methylindoles [121–123].

Feng and co-workers developed an efficient *N*,*N*′-dioxide **L-PiPr$_2$**-Gd(III) complex for the highly diastereo- and enantioselective [3 + 2] cycloaddition of aldehydes with aryl oxiranyl diketones. The reaction proceeds via selective C–C bond cleavage of oxiranes to form carbonyl ylide, followed by a chiral Lewis acid *N*,*N*′-dioxide **L-PiPr$_2$**-Gd(III) complex-catalyzed asymmetric 1,3-dipolar cycloaddition (Fig. 51) [124]. The addition of 15 mol% of $LiNTf_2$ dramatically increased the yield from 18 to 92% with 90% ee. Under the optical reaction conditions, a variety of chiral 1,3-dioxolanes were obtained in excellent yields (92–99%) with high selectivities (77–91% ee, >95:5 dr, respectively). With a similar protocol, but using *N*,*N*′-dioxide **L-RaPr$_2$**-Nd(III) complex, the [3 + 2] annulation of donor-acceptor aziridines with aldehydes was realized in the presence of $LiNTf_2$, affording various chiral *cis*-1,3-oxazolidines in 38–98% yields with 72–95% ee. The process was promoted to be a relay catalysis that $LiNTf_2$ promotes the formation of azomethine ylide intermediates, and then chiral *N*,*N*′-dioxide **L-RaPr$_2$**-Nd(III) complex accelerates the asymmetric 1,3-dipolar cycloaddition [125]. In addition, the pybox **6**-$Sc(OTf)_3$-catalyzed [3 + 2] annulation of aziridines and alkyne could give highly substituted 3-pyrroline in 80% yield with 70% ee [126].

As an important contribution, Evans and co-workers reported the first example of asymmetric [3 + 2] annulation and addition reaction involving allenylsilanes using a pybox **7**-$Sc(OTf)_3$ complex (Fig. 52, Eq. 1) [127]. When allenylsilanes bearing a steric bulky *tert*-butyldiphenylsilyl group was used, an enantioselective [3 + 2] cycloaddition occurred with ethyl glyoxylate as the 2π-component. The corresponding dihydrofurans were obtained in moderate to good yields (32–91%) with high levels of enantioselectivities (85–94% ee). If trimethylsilylallenes reacted with ethyl glyoxylate catalyzed by the same catalyst, the optically propargylic alcohols were provided through the addition reaction (Fig. 52, Eq. 2).

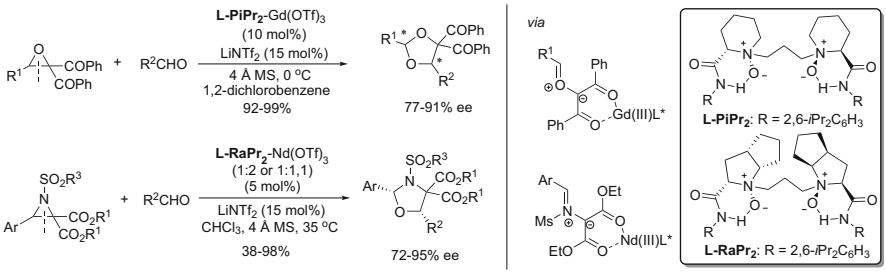

Fig. 51 Asymmetric [3 + 2] cycloaddition of aromatic aldehydes with oxiranes and aziridines [124, 125]

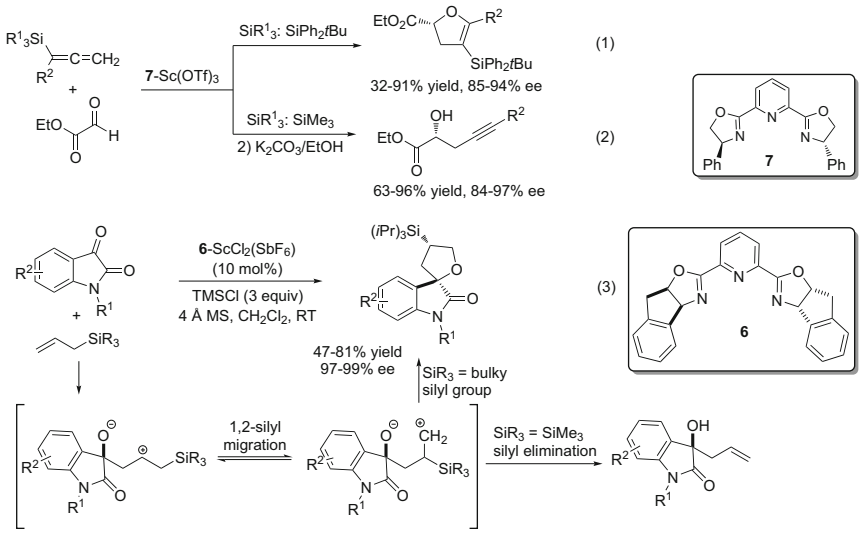

Fig. 52 Asymmetric annulation with allenylsilanes and allylsilanes [127–129]

The combination of pybox **6**, $ScCl_3$, $NaSbF_6$, and TMSCl performed an efficient promoter for the enantioselective [3 + 2] annulation reaction of allylsilanes and isatins (Fig. 52, Eq. 3) [128]. The optical active 3′-silyl-spirooxindoles were obtained in good yields (47–81%) and excellent enantioselectivities (97–99% ee). The bulky silyl group is employed to avoid silyl elimination pathway after Lewis acid-catalyzed addition of allylsilane to a C = X π electrophile. In addition, TMSCl was crucial to enhance the reaction rate. Taking the advantage of easy oxidizability of benzhydryl silyl group, the Si-C oxidation with TBAF and hydrogen peroxide conditions took place to afford the corresponding hydroxy-spirooxindoles in high yields. In another case, the complex pybox **6**/$ScCl_3$/NaBArF was used for [3 + 2] carboannulation reactions of allylsilane with 2π substrates including alkylidene oxindole, coumarin, or malonate, thus allowing excellent control of both the diastereo- and enantioselectivities in spirocyclopentane core structure formation (up to 99:1 dr and 99% ee) [129].

Highly diastereo- and enantioselective [2 + 2]-cycloaddition of ketenes and isatins was realized by chiral *N*,*N*′-dioxide **L-RaPr$_2$**-Sc(OTf)$_3$ catalyst (Fig. 53, Eq. 1) [130]. In the presence of 0.2–2 mol% of the chiral Lewis acid, a wide range of arylalkylketenes and isatins was employed to give optically active β-lactones with vicinal chiral centers in 77–99% yields and excellent enantioselectivities (88–99% ee), as well as exclusively high diastereoselectivities. The Lewis acid *N*,*N*′-dioxide-Y(OTf)$_3$ was also found useful for the [4 + 2]-cycloaddition of disubstituted ketenes and β,γ-unsaturated α-keto esters (Fig. 53, Eq. 2), providing chiral δ-lactones with excellent selectivities (94–99% ee) [130].

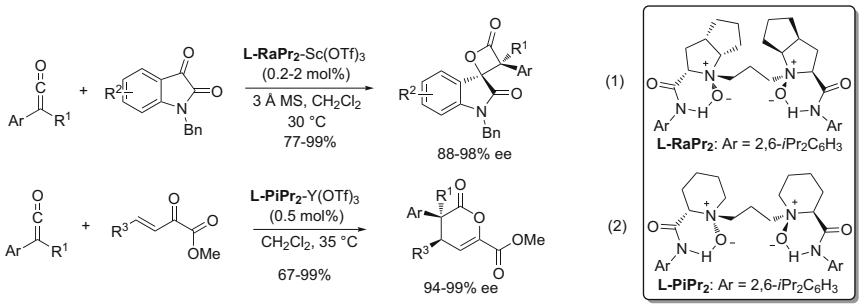

Fig. 53 Asymmetric [2 + 2] and [4 + 2] cycloaddition with disubstituted ketenes [130]

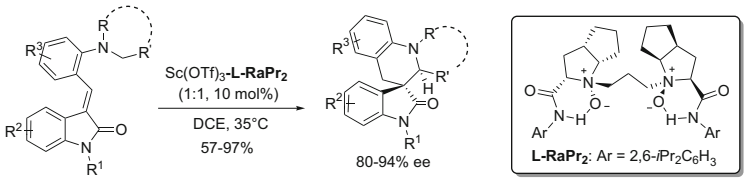

Fig. 54 Asymmetric 1,5-hydride shift/ring-closing reactions [131]

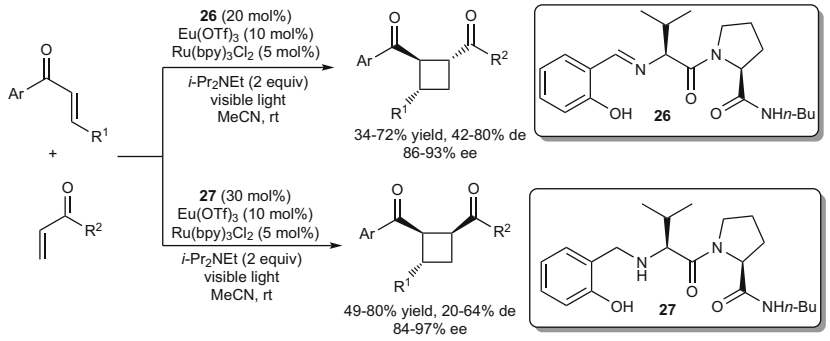

Fig. 55 Asymmetric [2 + 2] photocycloadditions of α,β-unsaturated ketones [132]

The highly diastereo- and enantioselective 1,5-hydride shift/ring-closing cascade has been developed by Feng and co-workers (Fig. 54) [131]. The complex of chiral *N*,*N*′-dioxide **L-RaPr$_2$** and Sc(OTf)$_3$ promoted the reaction well, affording the optically active spirooxindole tetrahydroquinoline derivatives bearing quaternary stereogenic centers in good yields (57–97%) and excellent diastereoselectivities (>20:1 dr) and enantioselectivities (80–94% ee).

Yoon and co-workers have developed dual-catalyst systems to promote the asymmetric [2 + 2] photocycloadditions of α,β-unsaturated ketones with visible light (Fig. 55) [132]. The key step of this cycloaddition was realized by Ru(bpy)$_3$Cl$_2$ as

a visible light-absorbing photocatalyst for the one-electron reduction of Lewis acid Eu(III)-activated aryl enone in the presence of *i*-Pr_2NEt. The selectivity was controlled by chiral Lewis acid catalyst that generated in situ by the treatment of chiral Schiff base ligand **26** with $Eu(OTf)_3$. Under the optical reaction conditions, various aryl enones and alkyl enones reacted smoothly at room temperature in acetonitrile, affording the corresponding chiral cyclobutanes in 34–72% yield with 42–80% diastereoselectivity and 86–93% enantioselectivities. Interestingly, the use of chiral secondary amine ligand **27** from reduction of **26** instead, resulted in complementary diastereoselectivity (20–64% ee) with excellent enantioselectivity (84–97% ee).

9 Asymmetric Ring-Opening Reaction

The asymmetric ring-opening reaction of *meso*-epoxides is one of the most efficient methods to provide chiral 1,2-difunctional compounds. Jacobsen and co-workers developed an asymmetric ring opening of *meso*-epoxides with TMSCN using pybox-$YbCl_3$ complexes (Fig. 56) [133]. The corresponding β-trimethylsilyloxy nitrile ring-opened products were obtained in good yield (72–90%) and high enantioselectivity (83–92% ee). In addition, the kinetic experiments showed a second-order kinetic dependence on catalyst concentration and a first-order dependence on epoxide concentration, indicating the reaction proceeded under a possible bimetallic pathway with simultaneous activation of epoxide and cyanide.

Schneider and co-workers used bipyridine *ent* **4**-$Sc(OTf)_3$ complex for asymmetric ring-opening reaction of *meso*-epoxides with alcohol amines and phenylselenol to afford the corresponding ring-opening products in generally good yields with moderate to high levels of enantioselectivities (44–98% ee) (Fig. 57) [134, 136–138]. Kobayashi and co-workers realized the ring-opening reactions of *meso*-epoxides in water, using chiral bipyridine **4** complex of Sc(III) salt-bearing dodecyl sulfate counterions. It was found that just 1 mol% of catalyst loading was sufficient for the aminolysis of epoxides with high enantioselectivities (60–96% ee; Fig. 57) [135]. Similarly, asymmetric ring-opening reactions with aromatic amines, indoles, and thiols also performed well in water [135, 139].

Ring opening of *meso*-epoxides and racemic epoxides with different nucleophiles was also achieved with *N*,*N*′-dioxide-rare-earth complexes by several groups. The Feng group used *N*,*N*′-dioxide **L-Ra*m*Me$_2$**-$Sc(OTf)_3$ complex to catalyze the enantioselective addition of pyrazole derivatives to *meso*-epoxides, and excellent

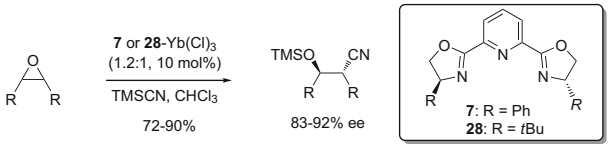

Fig. 56 Asymmetric ring-opening reaction with TMSCN [133]

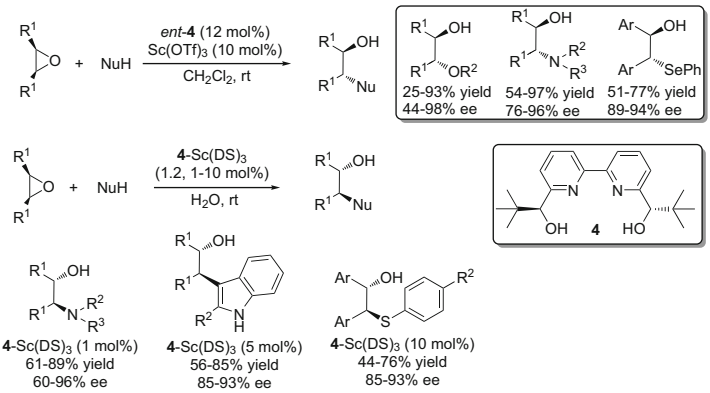

Fig. 57 Asymmetric ring opening of *meso*-epoxides [134–139]

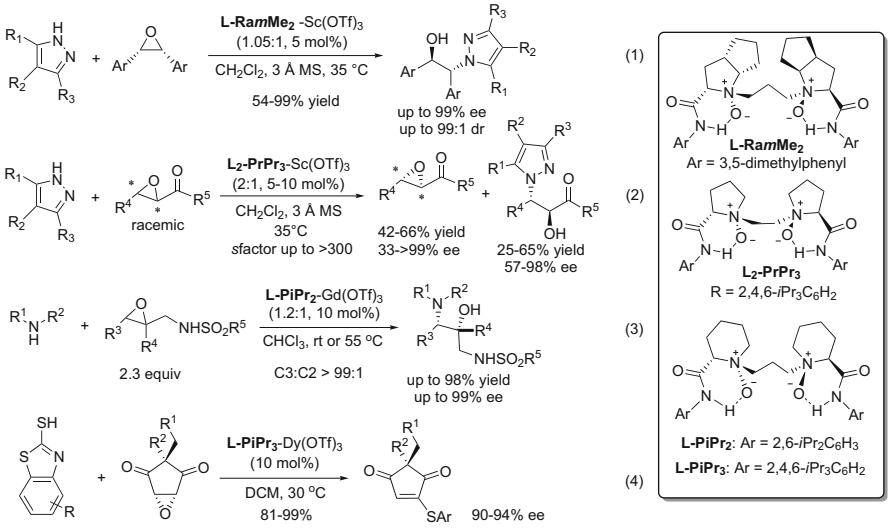

Fig. 58 Asymmetric *N,N′*-dioxide-RE(III) complex-catalyzed ring-opening with heteronucleophile [140–143]

diastereoselectivities and enantioselectivities (up to 99:1 dr and 99% ee) were given (Fig. 58, Eq. 1) [140]. The catalyst also enabled to distinguish *cis*- and *trans*-stilbene oxides via the preference ring opening of *cis*-epoxides. This group next realized an efficient kinetic resolution of racemic 2,3-epoxy 3-aryl ketones, using a complex of *N,N′*-dioxide **L_2-PrPr$_3$** and Sc(OTf)$_3$ in 2:1 ratio (Fig. 58, Eq. 2) [143]. The optically active β-pyrazole-substituted alcohols and unreacted epoxides were obtained for a broad substrate generality, and the excellent selectivity factors were observed up to >300. An enantioselective aminolysis of aromatic *trans*-2,3-epoxy sulfonamides was reported by Yamamoto's group by the use of chiral Gd

$(OTf)_3$ complex of *N*,*N*′-dioxide (Fig. 58, Eq. 3) [141]. The kinetic resolution of this ring-opening reaction proceeded selectively at the C-3 position (C3:C2 > 99:1) under the directing effect of the sulfonamide group, affording a range of 3-amino-3-phenylpropan-2-olamines in high enantioselectivities (up to 99% ee). Later, desymmetrization of *meso*-epoxides with 2-mercaptobenzothiazoles was accomplished by the Wang group, which provided chiral cyclopentene derivatives with an all-carbon quaternary stereogenic center (Fig. 58, Eq. 4) [142]. The reaction efficiently proceeded with a thiolysis/elimination sequence in the presence of *N*,*N*′-dioxide **L-PiPr$_3$**-Dy$(OTf)_3$ complex in good yield (81–99%) with excellent enantioselectivities (90–94% ee).

The racemic cyclopropyl diketones employed in the asymmetric ring-opening reaction was first realized by Feng and co-workers (Fig. 59) [144]. The mixture of *N*,*N*′-dioxide **L-PiPr$_3$**, $Sc(OTf)_3$, and LiCl was found efficient for the ring-opening reaction of cyclopropyl ketones using thiols, alcohols, and carboxylic acids as the heteroatom nucleophiles, affording the corresponding sulfides, ethers, and esters in up to 99% yield and 95% ee. When primary alanine was used to react with cyclopropyl diketones, a ring-opening/cyclization process accomplished to afford variety of chiral 2,3-dihydropyrroles in good yield and high enantioselectivity [145]. Furthermore, if benzene-1,2-diamine was subjected into the catalyst prepared from **L-PiPr$_3$** and $ScCl_3$, the cyclopropyl diketones underwent asymmetric ring-opening/cyclization/retro-Mannich process, affording the benzimidazoles bearing chiral side chains under mild reaction conditions in excellent enantioselectivities (up to 97% ee) [146]. In these cases, the reactions were initiated predominately through a kinetic resolution of racemic cyclopropyl diketones, and then one enantiomer followed the ring-opening reaction.

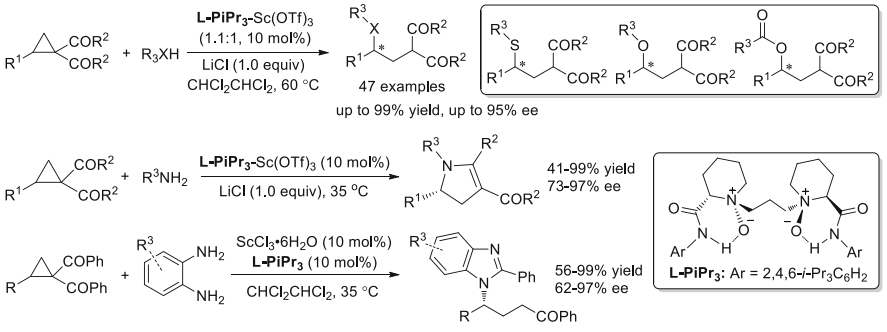

Fig. 59 Chiral *N*,*N*′-dioxide-Sc(III) complex-catalyzed asymmetric ring opening of cyclopropyl ketones [144–146]

10 Asymmetric Miscellaneous Reaction

Evans' group developed an asymmetric carbonyl addition of vinylsilane nucleophiles (Fig. 60) [147]. The catalyst prepared from pybox **22a** and $Sc(OTf)_3$ was found to efficiently catalyze the reaction between aryl- or alkyl-substituted trimethylvinylsilanes and glyoxamide to give chiral allylic alcohol derivatives. The geometry of vinylsilane retained in the products, and the reactions resulted in moderate to good yields (45–99%) and excellent enantioselectivities (97–99% ee).

Feng and co-workers extended the *N*,*N*′-dioxide-RE(III) complex catalytic systems to various reactions. The diastereo- and enantioselective bromoamination of chalcones was developed by the employment of *N*,*N*′-dioxide-$Sc(OTf)_3$ catalyst (Fig. 61) [148]. Only just 0.05 mol% of the chiral complex loading was sufficient for bromoamination with a range of chalcones to afford the corresponding α-bromo-β-amino ketone derivatives in excellent yields (up to 99%), diastereoselectivities (up to 99:1 dr), and enantioselectivities (up to 99% ee). The similar catalytic protocol was successfully extended to asymmetric chloroamination reaction and iodoamination as well by employing $TsNCl_2$ and NIS as halo-reagents, respectively [148, 149].

The enantioselective α-functionalizations of 3-substituted oxindoles constitute important access to a series of optically active 3,3-disubstituted oxindole derivatives which related to natural products and biologically active compounds. The chiral rare-earth metal complex-catalysis was found as a new asymmetric catalytic strategy for α-arylation of *N*-unprotected 3-substituted oxindoles, using diaryliodonium salts (Fig. 62) [151]. Taking the advance of Lewis acid scandium cation with strong oxygen affinity, cationic hypervalent iodine preferred to attack the C3 atom of Sc(III)-based enolate of 3-substituted oxindoles to form C-linked

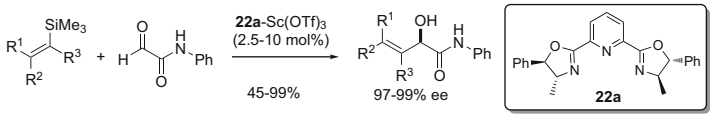

Fig. 60 Chiral pybox-Sc(III) complex-catalyzed asymmetric carbonyl addition of vinylsilane nucleophiles [147]

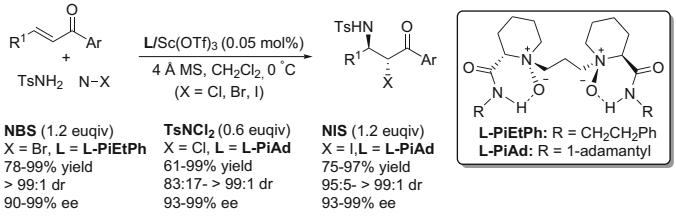

Fig. 61 Chiral *N*,*N*′-dioxide-Sc(III) complex-catalyzed asymmetric haloamination reaction [148–150]

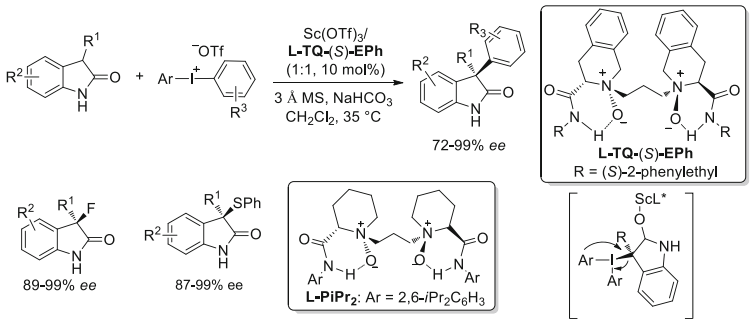

Fig. 62 Chiral *N*,*N*′-dioxide-Sc(OTf)$_3$ complex-catalyzed asymmetric α-functionalizations of 3-substituted oxindoles [151–153]

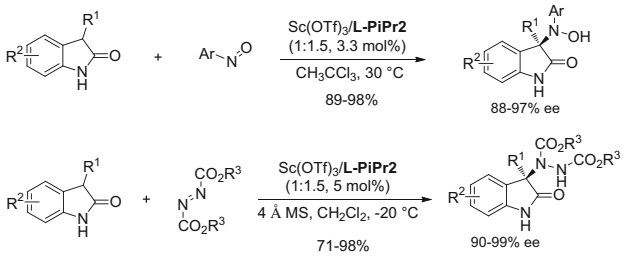

Fig. 63 Chiral *N*,*N*′-dioxide-Sc(OTf)$_3$ complex-catalyzed asymmetric additions of 3-substituted oxindoles [154, 155]

intermediate enantiotopically, followed by [1, 2] rearrangement to give 3,3-disubstituted oxindoles. Other asymmetric α-functionations of *N*-unprotected 3-substituted 2-oxindoles, including α-fluorination and α-sulfenylation with *N*-(phenylthio)phthalimide and NFSI as electrophilic reagent were also tolerable with *N*,*N*′-dioxide **L-PiPr$_2$**-Sc(OTf)$_3$ complex and Na_2CO_3 or K_2CO_3 as additives [152, 153]. Using 3-substituted-2-oxindoles or 4-substituted pyrazolones as the nucleophiles, highly *N*-selective additions of nitrosoarenes or azodicarboxylate were accomplishe to give 3-amino-2-oxindole and 4-amino-5-pyrazolone derivatives in high efficiency (Fig. 63) [154, 155, 169].

The asymmetric dearomatization of 2-naphthols with azodicarboxylates has been developed by Luan's and Feng's groups, respectively [156, 157], using Sc(OTf)$_3$ complexes of chiral pybox and *N*,*N*′-dioxide **L-PrAd**.

Taking advantage of the strong Lewis acidity and stability properties of *N*,*N*′-dioxide-Sc(OTf)$_3$, Feng and co-workers successfully achieved both asymmetric 1,2-reduction of enones with potassium borohydride solution and epoxidation of α,β-unsaturated carbonyl compounds with H_2O_2 (Fig. 64) [158, 159]. The catalyst could also accelerate enantioselective Baeyer-Villiger oxidations of achiral or racemic cyclic ketones (Fig. 65) [160, 161]. Ranges of optically active ε-lactones and γ-lactones were obtained from prochiral cyclohexanones and cyclobutanones, respectively, with excellent yields and enantioselectivities (Fig. 65, Eq. 1).

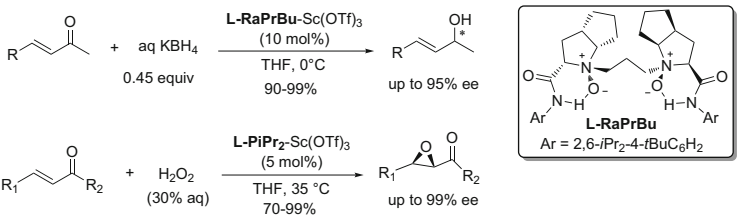

Fig. 64 Asymmetric reduction and oxidation reaction [158, 159]

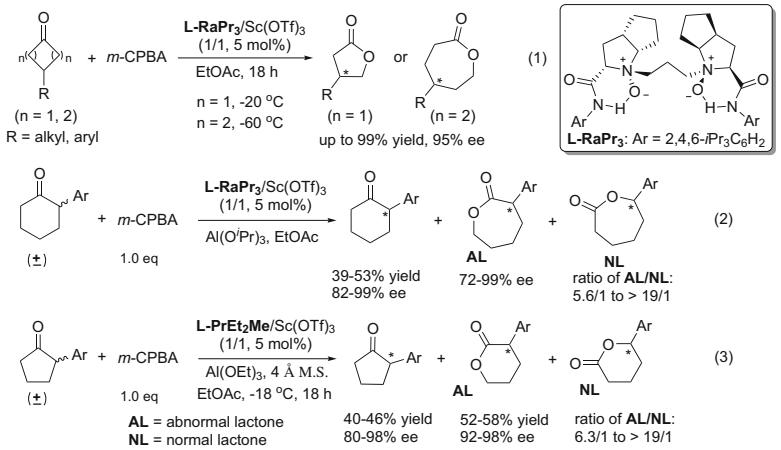

Fig. 65 Asymmetric Baeyer-Villiger oxidation reactions [160, 161]

Meanwhile, the kinetic resolution of racemic 2-substituted cyclopentanones and 2-arylcyclohexanones was also realized via highly regio- and enantioselective oxidation process. Both the lactone products and the unreacted ketones were obtained with high levels of enantioselectivities. It should be noted that an abnormal regioselectivity was observed with 2-arylcyclohexanone substrates, and normal migration products were given with 2-arylcyclopentanones (Fig. 65, Eqs. 2 and 3).

As a classic electrocyclization, acid-mediated Nazarov reaction represented a challenge for a long period due to low reactivity and special difficulty in stereo control. Trauner and co-workers established that pybox **6**-Sc(OTf)$_3$ complex could efficiently catalyze the asymmetric Nazarov cyclization of 2-alkoxy-1,4-pentadien-3-ones, involving an asymmetric protonation as the key step to generate chiral cyclopentenones in moderate to high yield (65–94%) and enantioselectivity (Figs. 66, 72–97% ee) [162, 163]. Shindo and co-workers utilized pybox *ent* **7**-Sc(OTf)$_3$ complex for enantioselective Nazarov reaction interrupted through a nucleophilic attack of an alcohol on the α-position of the keto function, which afforded range of chiral cyclopentenones bearing quaternary centers from monodentate coordinated divinyl ketone substrates in up to 71% yield and 91% ee [164].

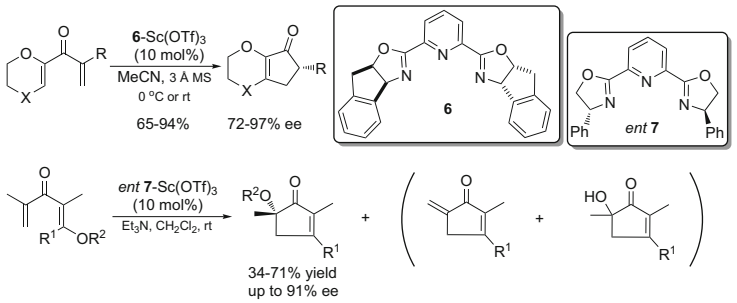

Fig. 66 Chiral pybox-Sc(III) complex-catalyzed asymmetric Nazarov reaction [162–164]

11 Conclusion

The Lewis acid rare-earth metal complexes have unique reactivity, stability, and safety properties which are fundamental to most of their applications in asymmetric synthesis. Rare-earth metal salts, especially with triflate as the counterion, are regarded as hard acids, which have complexation with ligands involving O- or N-donors. The substrates that are activated by rare-earth metal centers are carbonyl groups or imines via monodentate or bidentate coordination manner. Several reactions could be available not only in organic solvents but also in aqueous media, leading to really environmentally friendly reaction systems. For further development of asymmetric Lewis acid rare-earth metal complex catalysis, the promise of highly efficient, environmentally friendly, and recyclable use of chiral rare-earth metal complexes in "green chemistry" has not yet been fulfilled, and the development of effective chiral ligands is still in high demand.

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Chiral Borane-Based Lewis Acids for Metal Free Hydrogenations

Jan Paradies

Abstract The unquenched reactivity of strong Lewis acids in the presence of Lewis bases in solution, the so-called frustrated Lewis pairs (FLP), has led to the discovery of the metal-free activations, whereas the FLP-mediated hydrogen activation is the most prominent. So far, the metal-free hydrogenation is the most studied application of FLP chemistry and highly efficient methodologies for a number of unsaturated substrates have been developed. This chapter starts with a brief introduction to frustrated Lewis pair chemistry. The second part focuses on the synthetic challenges of chiral borane-derived Lewis acids for asymmetric transformations. The last part gives a state-of-the-art summary of asymmetric transformations using chiral FLPs.

Keywords Aldimine • Amine • Asymmetric hydrogenation • Borane • Enamine • Frustrated Lewis pair • Heterocycle • Hydrogen • Hydrogenation • Ketimine • Lewis acid • Lewis base • Metal-free • Phosphine • Pyridine • Quinoline • Silyl enol ether • Small molecule activation

Contents

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Abbreviations

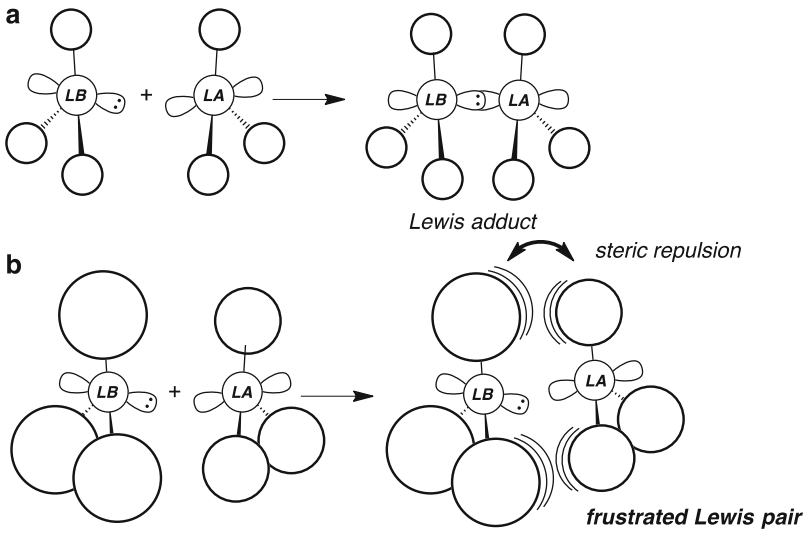
°C	Degree Celsius
bar	Pressure unit, 1.013 mbar, 760 Torr
Bn	Benzyl
DCM	Dichloromethane
de	Diastereomeric excess
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
FLP	Frustrated Lewis pair
H_2	Molecular hydrogen, dihydrogen
*i*Pr	2-Methylethyl
K	Kelvin
Me	Methyl
Mes	Mesitylene, 2,4,6-trimethylphenyl
MTBE	Methyl-*tert*butyl ether
NMR	Nuclear magnetic resonance
Ph	Phenyl
PMP	4-Methoxyphenyl
r.t.	Room temperature
*s*Bu	*sec*Butyl, 1-methylpropyl
*t*Bu	1,1-Dimethylethyl
THF	Tetrahydrofurane
TMP	2,2,6,6-Tetramethylpiperidine
Tol	4-Methyl-phenyl

1 Introduction

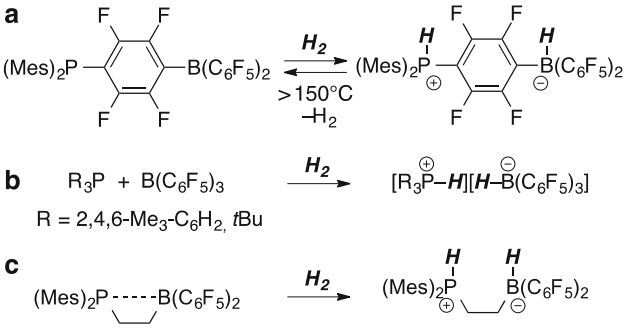
The reaction of a Brønsted acid and a Brønsted base is commonly accepted as a neutralization. An equivalent reactivity for the reaction of an electron-pair acceptor (a Lewis acid) with an electron-pair donor (a Lewis base) was established by Gilbert N. Lewis which ultimately leads to the formation of a Lewis acid-base adduct (Scheme 1a).

An interesting situation occurs when steric demands of peripheral groups of the Lewis acid and/or the Lewis base preclude the neutralization (Scheme 1b).

This phenomenon of unquenched reactivity in Lewis pairs remained largely unexplored [1–3] until 2006 when Douglas W. Stephan demonstrated in his seminal work that the exposure of a non-quenching Lewis pair is capable of splitting molecular dihydrogen (H_2) (Scheme 2a, b) [4, 5, 7]. Such reactions are usually considered as typical transition-metal based chemistry territory. Later, Douglas Stephan coined this concept “frustrated Lewis pairs” (FLP) [8] which provided a guideline for synthetic chemists.



Scheme 1 (**a**) Small substituents allow the formation of the stable Lewis adduct; (**b**) steric bulk prevents the formation of the Lewis adduct and the individual reactivity is retained



Scheme 2 (**a**) First metal-free activation of H_2 with a FLP [4]; (**b**) intermolecular FLP in the H_2-activation [5]; (**c**) metal-free activation of H_2 by an intramolecular FLP [6]

The third FLP reported by Gerhard Erker (Scheme 2c) is highly active in the H_2-activation and proved to be a general hydrogenation catalyst for a large number of substrates. Besides the fact that this is one of the most active catalysts, its synthesis through hydroboration established the synthetic access to chiral boranes or intramolecular FLPs (see the following section).

The overwhelming interest of synthetic organic and inorganic chemists and theoreticians in this new evolving field of research led to the fast development of a large number of FLPs based on boron, aluminum [9–11], silicon [12, 13], phosphorus [14], and even carbon Lewis acids [15, 16]. These developments have been thoroughly reviewed and the reader is referred to these references [17–25].

2 Currently Accepted Mechanism of the Hydrogen Activation by FLPs

The metal-free H_2-activation attracted most of the interest [8, 19–21, 24–26] due to its high relevance in chemistry. The mechanism and thermodynamics of the metal-free H_2-activation was intensively investigated by quantum chemical methods [27–33] and just recently the first experimental investigations were communicated [34–39]. The relevance of steric bulk is not to underestimate. Despite detailed mechanistic studies are not at hand, the peripheral substituents are not only required to inhibit the Lewis adduct formation, but more importantly for the prepolarization of hydrogen [32, 33] prior to its orbital interactions with the Lewis pair's heteroatoms [29]. Therefore the presence of non-covalent interactions through Coulomb and dispersion forces seems to have significant impact on the FLP's reactivity. The formation of dispersion-bound aggregates was termed "Encounter Complex" [6, 27, 28, 30, 31, 33, 40, 41], whose highly fluctuating structure is practically impossible to study by experimental techniques. The solid state structure of an *intermolecular* FLP has not been elaborated so far. However, the association of a phosphine ($PMes_3$) with a borane ($B(C_6F_5)_3$) was investigated by NMR spectroscopy [42]. NMR studies established interactions between the phosphine and the borane, and the equilibrium constant was determined to $K = 0.3–0.7\ M^{-1}$ which is in agreement that the formation of the encounter complex is slightly endergonic (ΔG^0 (298 K) = +0.4 ± 0.2 kcal/mol).

The activation of molecular hydrogen by FLPs can be described through the donation of electron density of the Lewis base into the $\sigma(H_2)^*$ orbital of H_2, which in turn leads to destabilization of the $\sigma(H_2)$ bond. This bond is further weakened through the concomitant reduction of electron-density by "side-on" coordination of Lewis acid, which ultimately leads to the heterolytic splitting of molecular hydrogen (Fig. 1) [27]. Such mode of activation may be compared with the Dewar-Chatt-Duncanson model [43] for the activation of H–E bonds (E = carbon, chalcogenes, silanes) by transition metals and clearly requires cooperative interaction of the Lewis pair with H_2, in which a certain degree of Lewis-acidity and Lewis-basicity must be present.

According to this model of the H_2-activation any Lewis base should be in principle reactive in the FLP-mediated heterolytic hydrogen-splitting. Indeed a steadily increasing number of Lewis bases for such purpose have been identified ranging from bisphosphines [44, 45], phosphinimines [46], imines [47], amines [48, 49], diethyl ether [50] over carbenes [51–57] to carbanions [58]. Commonly applied FLPs for H_2-activation consist of an amine or phosphine as Lewis base and $B(C_6F_5)_3$ as Lewis acid. Probably one of the most interesting aspects of FLP-catalyzed hydrogenations is the formation of the hydride-donors directly from the heterolytic splitting of hydrogen, which in turn are very well established as reagents for carbonyl reductions [59, 60]. The reduction of imines requires their activation by a Lewis acid or alternatively by a Brønsted acid. The onium hydridoborate resulting from the FLP-mediated H_2-activation undergoes proton transfer to the imine and liberates the Lewis base with concomitant hydride transfer (Scheme 3a).

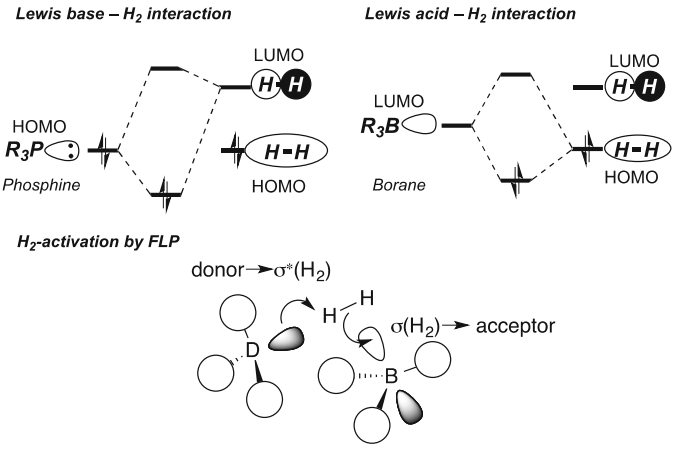


Fig. 1 Orbital interactions for the FLP-mediated H_2-activation

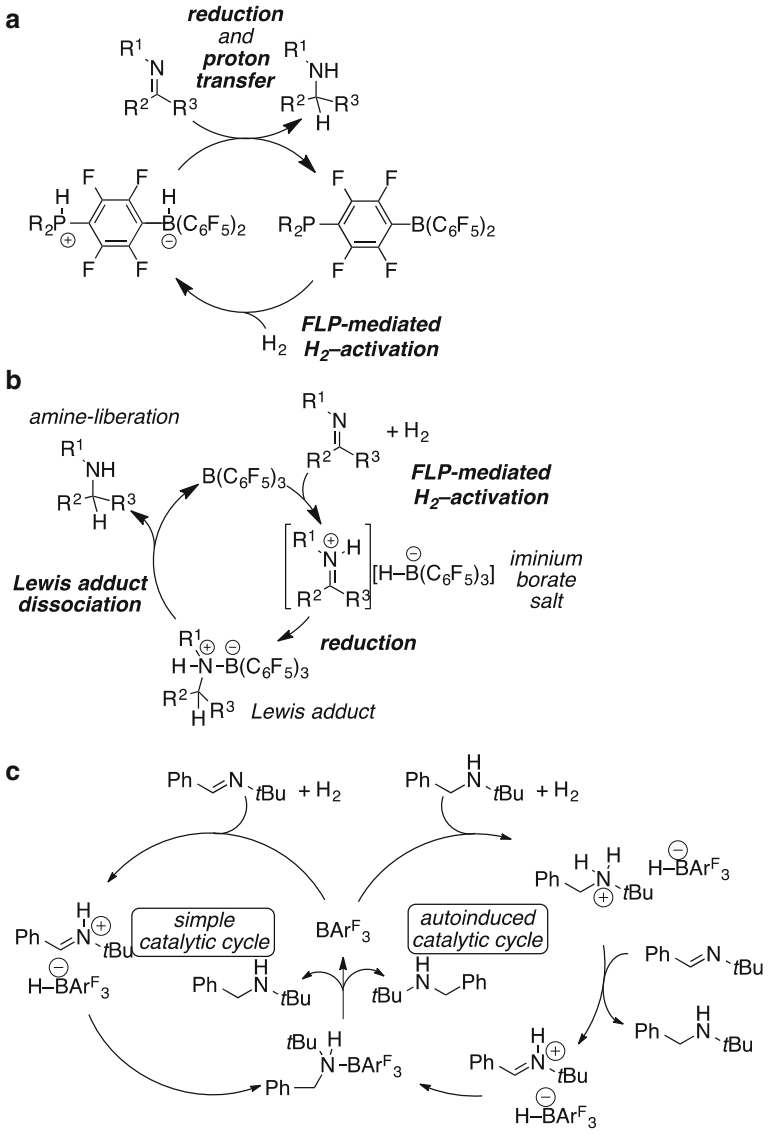
When imines or nitrogen-containing heterocycles are investigated the corresponding substrate (Scheme 3b) and even the product (Scheme 3c) can act as Lewis base in the H_2-activation. Consequently for the most FLP-catalyzed hydrogenations of aldimines, ketimines, or nitrogen-containing heterocycles the substrate functions as Lewis base for the H_2-activation and the addition of phosphines or other Lewis bases is not necessary [61].

In the event that the resulting hydrogenation product is a much stronger Lewis base the reaction proceeds through an autoinduced catalytic mechanism, in which the reaction rate increases during the reaction [37, 38]. This mechanistic rational is the basis for the design of new FLP-catalyzed hydrogenations and clearly explains the importance of chiral borane-derived Lewis acids in FLP-catalyzed hydrogenations. Attempts were made, in which chiral bisphosphines were applied as Lewis bases to induce stereoselective hydrogenation, but only 25% ee were obtained at best [47]. On the other hand, chiral hydride donors have been successfully applied with a variety of unsaturated compounds, which will be in the focus of the following sections.

3 Synthesis of Borane-Derived Chiral Lewis Acids

The synthesis of Lewis acids for FLP applications is often limited by the requirement of very high electrophilicity. Consequently, suitable boranes for FLP-activations are sensitive to moisture and air. This clearly limits the synthetic methodologies available for the synthesis of chiral borane-derived Lewis acids. Currently there are two synthetic strategies to access chiral boranes for FLP-catalysis (Scheme 4).

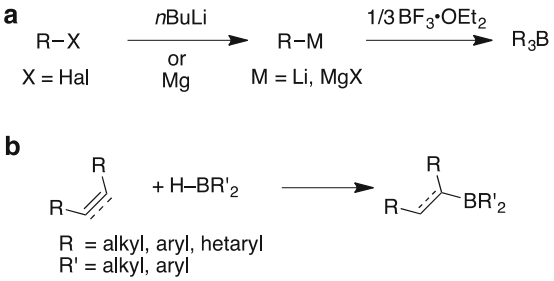
The first strategy (a) covers the reaction of an organometallic reagent with an appropriate boron halide or ester electrophile. Diverse boranes are accessible



Scheme 3 (**a**) Catalytic cycle for the FLP-catalyzed reduction of imines [7]; (**b**) catalytic cycle for the phosphine-free FLP-catalyzed reduction of nitrogen-containing substrates [61]; (**c**) auto-induced catalytic cycle

according to this synthetic route, keeping in mind that these reactions often suffer from overreaction furnishing the corresponding borates.

The second strategy comprises the hydroboration of alkenes or alkynes (Scheme 4b). Although this reaction appears as most straightforward and atom economic, one has to pay careful attention to the reversibility of the reaction. This particular feature has to be



Scheme 4 General strategies for the synthesis of highly electrophilic boranes for FLP-applications

considered when it comes to highly electrophilic hydroboranes, e.g., the ubiquitously applied Piers' borane ($HB(C_6F_5)_2$, **1**) at high temperatures. Whereas the hydroboration is (so far) the most successful/straightforward approach for the synthesis of chiral boranes the reaction of chiral organometallic reagents with chloro boranes offers access to diverse and often to more stable scaffolds, since the structural or stereochemical setup does not allow the retrohydroboration.

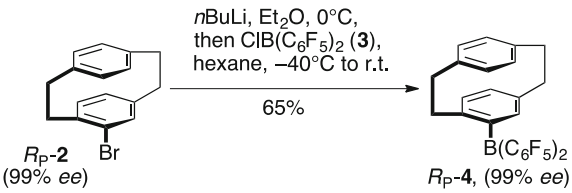
3.1 Chiral Borane Synthesis by Organometallic Reagents

Although the organometallic approach has been extensively used in the synthesis of achiral boranes [62, 63] the corresponding synthesis of enantiopure boranes is far less described. The reaction of the enantiomerically pure planar-chiral 4-bromo [2.2]paracyclophane (**2**) with *n*butyllithium and subsequent treatment with chloro bis(pentafluorophenyl)borane (**3**) provided the planar chiral borane **4** in good yields (Scheme 5) [64].

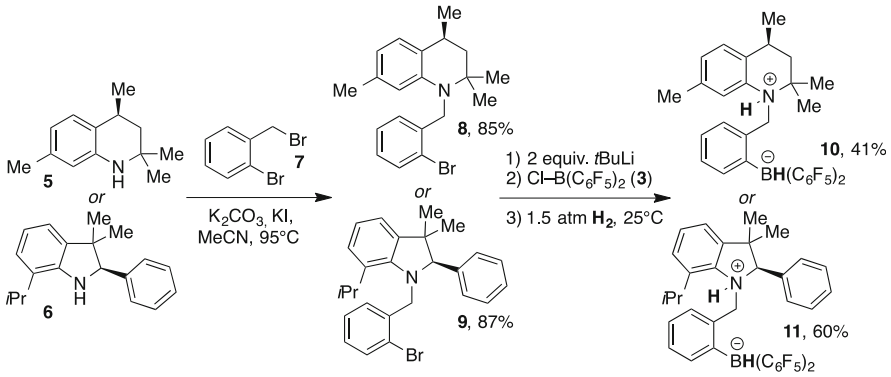
Timo Repo accomplished the synthesis of intramolecular FLPs using organolithium reagents [65–67]. The intramolecular FLPs were synthesized from chiral tetrahydroquinoline **5** or indoline **6** by the reaction with *ortho*-bromo benzyl bromide (**7**, Scheme 6).

Treatment of the *N*-benzylic substituted heterocycles **8** and **9** with *tert*butyllithium followed by chloro bis(pentafluorophenyl)borane (**3**) and direct exposure to hydrogen atmosphere afforded the chiral ammonium hydroborates **10** and **11** in moderate to good yields. However, it turned out that generally the 2-position of the quinolone and indoline ring is not innocent and underwent epimerization. Blocking of this position by a phenyl-group resulted in configurationally stable FLPs, but unfortunately low enantioselectivities were observed in hydrogenations of imines [65].

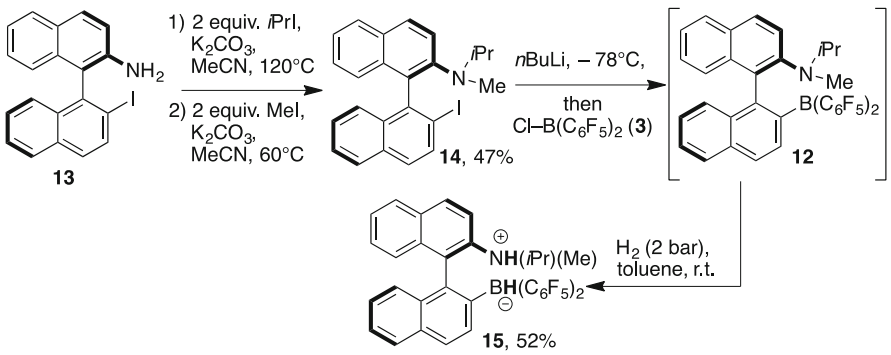
However, the synthesis of a related intramolecular N/B FLP based on the 1,1′-bis (naphthyl) scaffold (**12**) resulted in a configurationally stable and highly selective catalyst for imine hydrogenation [67]. The synthesis commenced with the two step alkylation of (*R*)-2-iodo-2′-amino-1,1′-bis(naphthyl) (**13**) with *iso*propyl iodide and methyl iodide to yield the tertiary amine **14** (Scheme 7).



Scheme 5 Synthesis of (R_p)-4-(bis(pentafluorophenyl)boryl)-[2.2]paracyclophane (**4**) [64]



Scheme 6 Synthesis of enantiomerically pure intramolecular FLPs [65]



Scheme 7 Synthesis of enantiopure (*R*)-1,1′-bis(naphthyl)-derived intramolecular N/B FLP **12** [67]

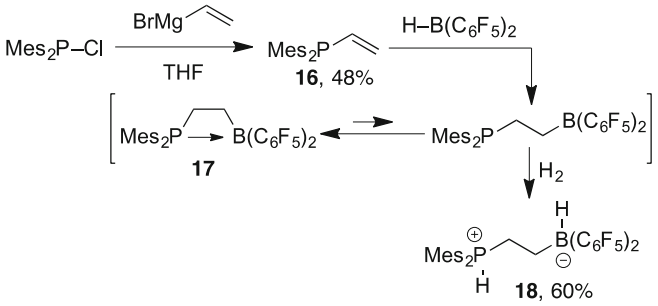
Finally, the amino borane **12** was obtained by lithiation and subsequent reaction with chloro bis(pentafluorophenyl)borane (**3**) and was isolated as the corresponding ammonium hydroborate **15** after heterolytic splitting of H_2.

3.2 Chiral Borane Synthesis by Hydroboration

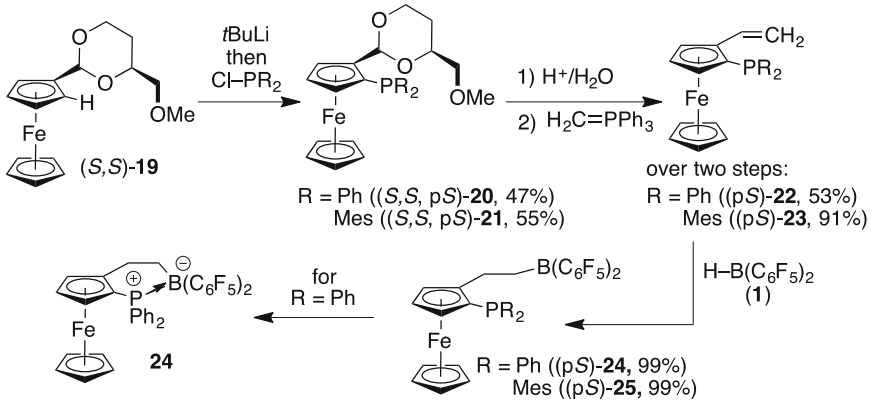
One of the most useful and at the same time one of the earliest tools for the synthesis of a borane as FLP-component is the hydroboration of an alkene by Piers' borane $HB(C_6F_5)_2$ (**1**) [68, 69]. Gerhard Erker used this reagent for the synthesis of an ethylene-bridged intramolecular FLP. The reaction of vinyl-bis(mesityl)phosphine (**16**) with $HB(C_6F_5)_2$ furnished the ethylene-bridged phosphino borane (**17**) in good yield (Scheme 8) [6, 70, 71].

The phosphino borane forms the four membered P/B-heterocycle **17** [33] by a dative bond from the phosphorus to the boron atom. This intramolecular Lewis adduct **17** is in equilibrium with its "open" form, which in turn is active in the heterolytic H_2-splitting leading to the phosphonium hydridoborate salt **18**.

The hydroboration of phosphinoalkenes was utilized to synthesize planar-chiral ferrocene-derived intramolecular P/B FLPs [72]. The synthesis of these FLPs commenced with the diastereoselective deprotonation of the enantiomerically pure acetal **19** as described earlier by Kagan [73] and Stepnicka (Scheme 9) [74, 75].



Scheme 8 Synthesis of an intramolecular FLP [6]



Scheme 9 Enantiopure P/B-derived intramolecular FLPs [72]

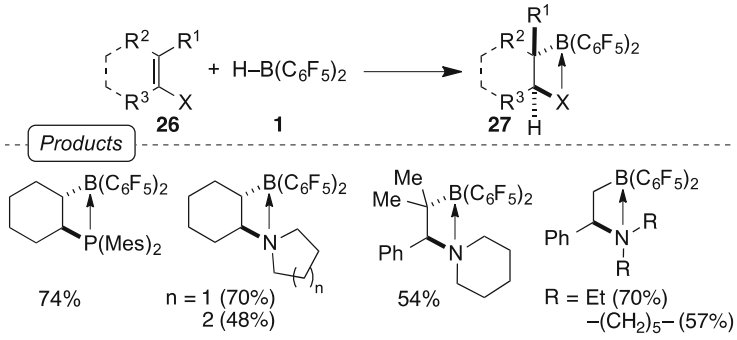
The metallated species reacted with the corresponding chlorophosphine to furnish the phosphine-acetals **20** and **21** in high diastereomeric excess. Hydrolysis and Wittig-olefination provided the enantiomerically pure phosphinyl(vinyl)ferrocenes **22** and **23** in high yields. Finally, clean hydroboration of both (vinyl)ferrocenes was observed; however the diphenylphosphino-derivative **24** existed in the "closed," unreactive form and the dimesitylphosphino-derivative **25** was obtained as the reactive FLP.

Accordingly, the hydroboration can be performed with other heterovinyl compounds, e.g., employing cyclohexenyl phosphines or enamines to produce the corresponding intramolecular FLP-systems. The reaction of $HB(C_6F_5)_2$ (**1**) with these heterosubstituted olefins **26** furnished the novel but racemic P/B [76] and N/B-systems **27** [77] in good yields (Scheme 10).

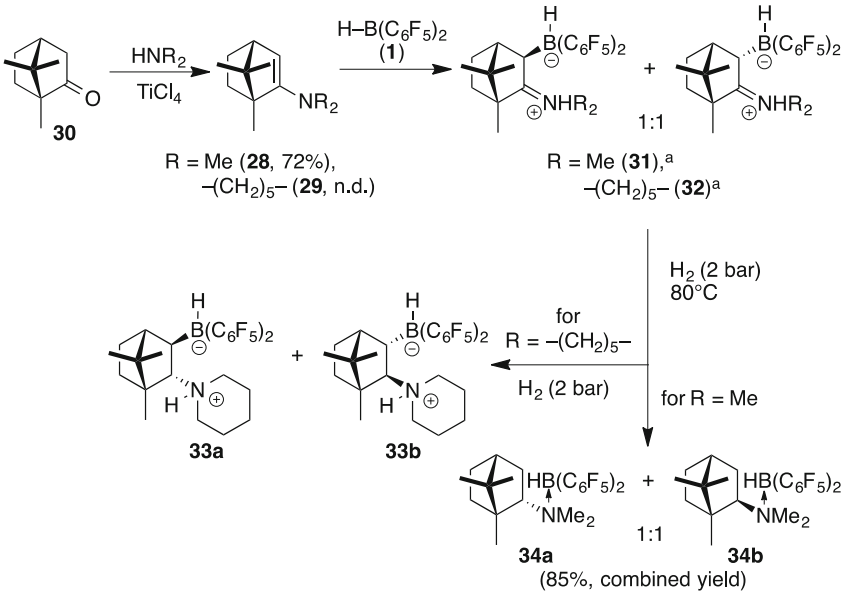
However, the synthesis of enantiopure intramolecular FLPs should be readily achievable by reacting enantiopure enamines with Piers' borane. Accordingly the reaction of Piers' borane (**1**) with the (1*R*)-camphor-derived enamines **28** and **29** was investigated (Scheme 11).

The enantiopure enamines R = Me (**28**) and $-(CH_2)_5-$ (**29**) were synthesized by condensation of (1*R*)-camphor (**30**) with the corresponding secondary amines. Surprisingly, the reaction of the enamines **28** and **29** with borane **1** gave the corresponding zwitterionic imminium-borohydrides **31** and **32** in quantitative conversion as a 1:1 mixture of the corresponding *endo* and *exo* diastereomers. The two imminium-borohydrides **31** and **32** reacted quite differently upon exposure to H_2 (Scheme 11). While the piperidine derivative **32** initiated the H_2-activation after imminium-reduction (**32** → **33**) the dimethylamine derivate **31** gave the *N*,*N*-dimethylbornyl- and -isobornylamines as Lewis adduct (**31** → **34**) with $HB(C_6F_5)_3$, which arose from reduction and subsequent retro-hydroboration.

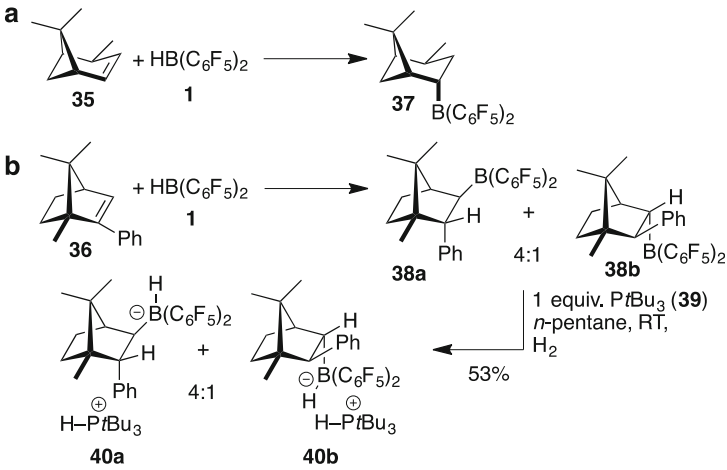
The synthesis of chiral boranes for intermolecular FLPs through hydroboration appears to be less challenging compared to intramolecular FLPs. The first examples of chiral boranes for the asymmetric hydrogenation by an FLP were synthesized by Klankermayer [79, 80]. The reaction of terpene-derivatives **35** and **36** with **1** provided access to the corresponding boranes **37** and **38** (Scheme 12).



Scheme 10 Synthesis of vicinal Lewis pairs by hydroboration [76, 77]



Scheme 11 Synthesis of enantiopure N/B FLP-systems through hydroboration of enamines ([a]products not isolated) [78]



Scheme 12 Borane synthesis by hydroboration of monoterpenes [79, 80]

The hydroboration of the pinene-derivative **35** occurred diastereoselectively while the camphor-derivative **38** was furnished as a mixture of 1:4 ratio. These two diastereomers **38a** and **38b** were separated by the reaction with P*t*Bu$_3$ (**39**) and pressurization with hydrogen. The corresponding phosphonium hydridoborates **40a** and **40b** were separated by crystallization. While **40a** proved less enantioselective

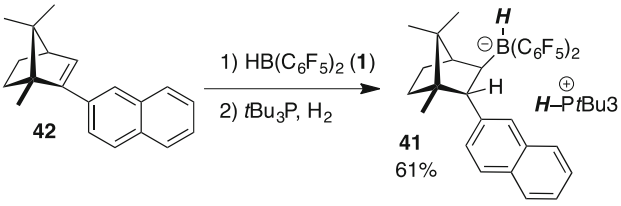
in the hydrogenation of ketimines, **40b** is one of most enantioselective boranes for the FLP-catalyzed hydrogenation of ketimines (see below). The camphor-structural motif was further exploited for the synthesis of a borane featuring increased steric bulk (Scheme 13).

This borane **41** was synthesized according to the hydroboration strategy as shown in Scheme 12b; however the 2-naphthyl substituent in **42** induced the selective formation of only one diastereomer, which is isostructural to the highly selective borane **40b**. This borane was active in the hydrosilylation of ketimines and provided the products in high yields and enantioselectivities of 81–87% ee (see below) [81].

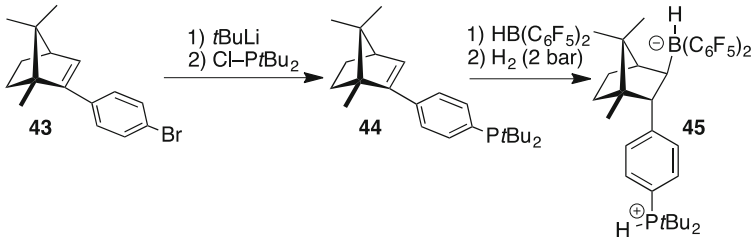
The same scaffold has been used for the synthesis of intramolecular FLPs (Scheme 14) [82].

The corresponding bromo-derivative **43** was lithiated and reacted with chlorobis (*tert*butyl) phosphine to give the phosphine **44**. Subsequent hydroboration and exposure to hydrogen atmosphere provided the diastereomerically pure intramolecular FLP **45** as stable hydroborate salt.

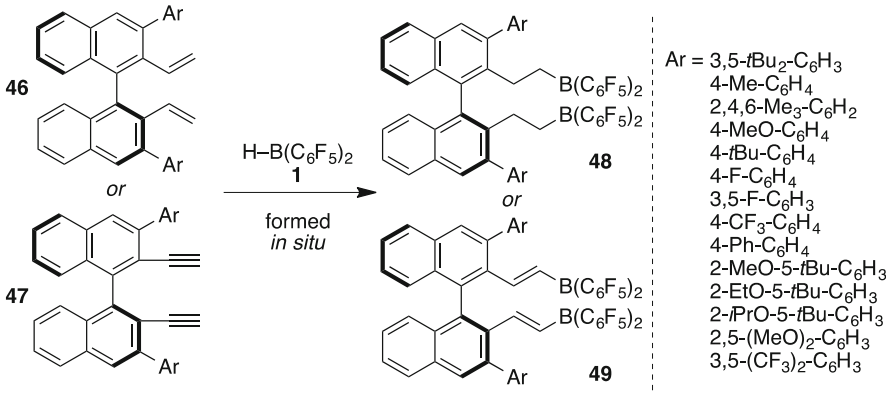
By far the most enantioselective chiral boranes for FLP-catalyzed hydrogenations and hydrosilylations have been developed by Haifeng Du. He extended the hydroboration strategy to the double hydroboration of atropisomeric bis(olefins) and bis(alkynes) based on the axially chiral 1,1′-bisnaphthyl scaffold [83–93]. This scaffold is well known from chiral bi- and monodentate phosphines and chiral Brønsted acids, e.g., phosphoric esters. The modification of the 3,3′-positions of the 1,1′-bisnaphthyl scaffold is essential to obtain high enantioselectivities in Brønsted- and FLP-catalyzed reactions. Accordingly, the hydroboration of the 2,2′-bis(olefins) **46** or alkynes **47** bearing high steric bulk in 3,3′-position afforded highly



Scheme 13 Synthesis of diastereomerically pure 2-naphthyl-derivative **41** [81]



Scheme 14 Synthesis of a camphor-derived intramolecular FLP [82]



Scheme 15 Synthesis of bis(boranes) **48** and **49**

enantioselective boranes **48** and **49** for FLP-catalyzed hydrogenations [83, 85, 87, 89–93] and hydrosilylations (Scheme 15) [86, 88].

Although the 1,1′-bis(naphthyls) **46** and **47** require some synthetic effort, the FLP-catalyzed reactions are pleasingly simple from a preparative point of view. The assembly of the boranes **48** and **49** occurred in the reaction mixture (or prior to the addition of the reactants) by simple treatment of easily accessible Piers' borane **1** with the appropriate diene **46** or diyne **47**. Therefore the isolation, storage, and handling of the moisture sensitive organoboranes are eliminated advancing the FLP-catalyzed hydrogenation to a ready-to-use methodology.

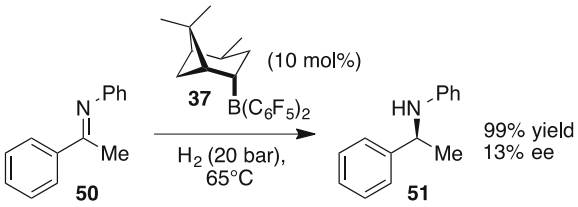
4 Application of Chiral Boranes in the FLP-Catalyzed Asymmetric Hydrogenation

The first asymmetric hydrogenation by an FLP was achieved by Jürgen Klankermayer using the terpene-derived boranes **37** and **40**. Initial hydrogenation experiments with the prochiral imine **50** and **37** as catalyst resulted in quantitative conversion but the product **51** was only obtained in 13% ee (Scheme 16) [79].

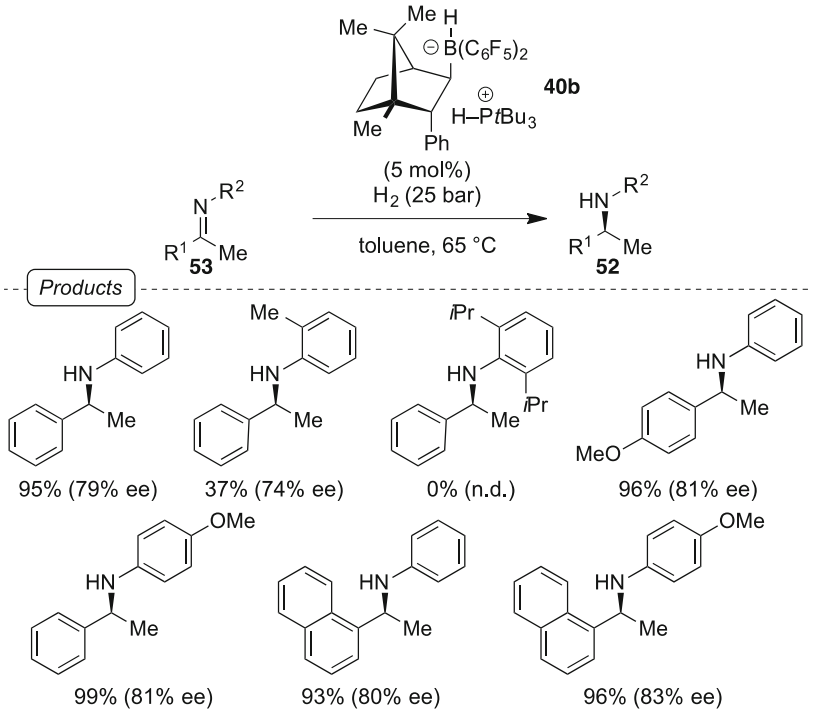
These studies clearly provide evidence for the feasibility to induce stereoselective hydride transfer by the application of a chirale borane. Nevertheless, it took further 2 years until reactions with higher enantioselectivity could be realized. The same group synthesized the camphor-derived enantiopure borane **40b**, which provided the hydrogenation products **52** of the ketimines **53** in almost quantitative yields with enantioselectivities of up to 83% (Scheme 17) [80].

Modification of **40b** to the related chiral intramolecular FLP **45** provided also an active catalyst in the asymmetric hydrogenation of the methyl-aryl ketimines **52** (Scheme 18) [82].

Although the stereoselectivity of the hydrogenation is slightly diminished compared to the initial system **40b**, the intramolecular FLP **45** has the significant



Scheme 16 First asymmetric FLP-catalyzed hydrogenation [79]

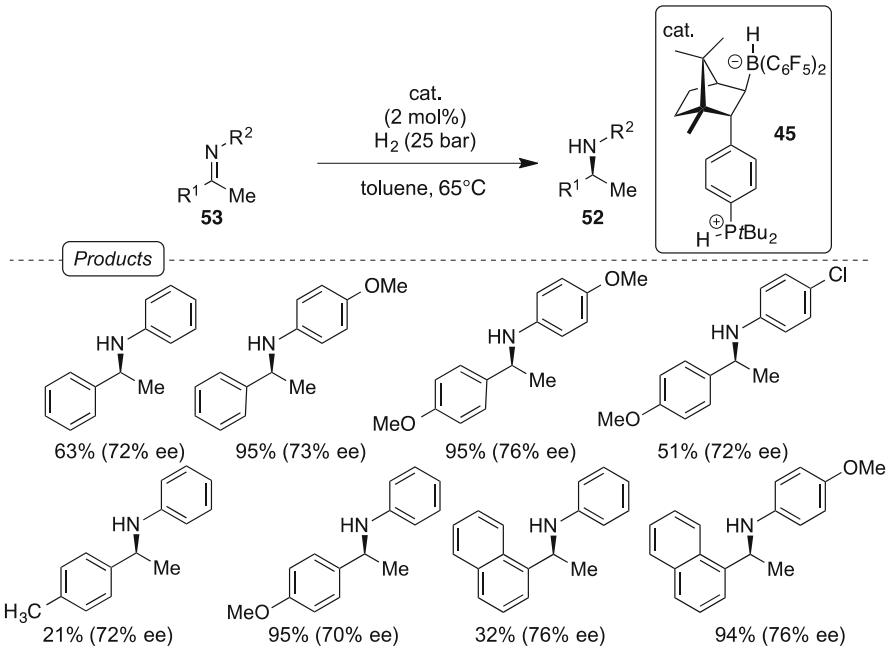


Scheme 17 Asymmetric hydrogenation of ketimines (**53**) by a camphor-derived borane [80]

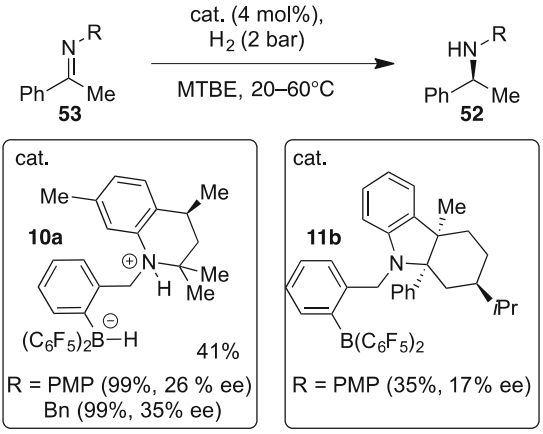
advantage. It can be easily recovered from the reaction mixture by simple precipitation with pentane in air. The solid catalyst was recycled five times without loss of enantioselectivity but with slight decrease of activity (>99–70% conversion).

Chiral *intramolecular* FLPs were derived from readily accessible chiral indolines or quinolines and applied in the asymmetric hydrogenation of selected ketimines (Scheme 19) [65].

Despite straightforward derivatization of the *ansa*-ammonium borates to modulate the steric properties only low enantioinduction in the hydrogenation of imines was observed. The intramolecular FLP based on the *ansa*-aminoborane **12** was



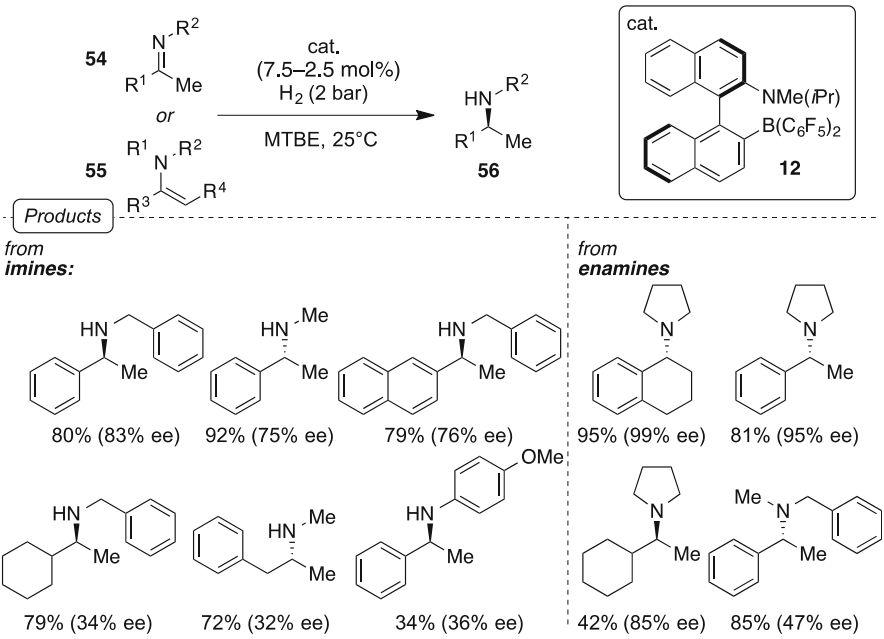
Scheme 18 Asymmetric hydrogenation by the easily recyclable chiral intramolecular FLP **45** [82]



Scheme 19 Intramolecular FLPs in the asymmetric hydrogenation of ketimines [65]

more enantioselective in the asymmetric hydrogenation of imines **54** and enamines **55** (Scheme 20) [67].

The enantioselective hydrogenation of ketimine-derived substrates displayed high dependency on the *N*- as well as on the imine's substituent leading to moderate



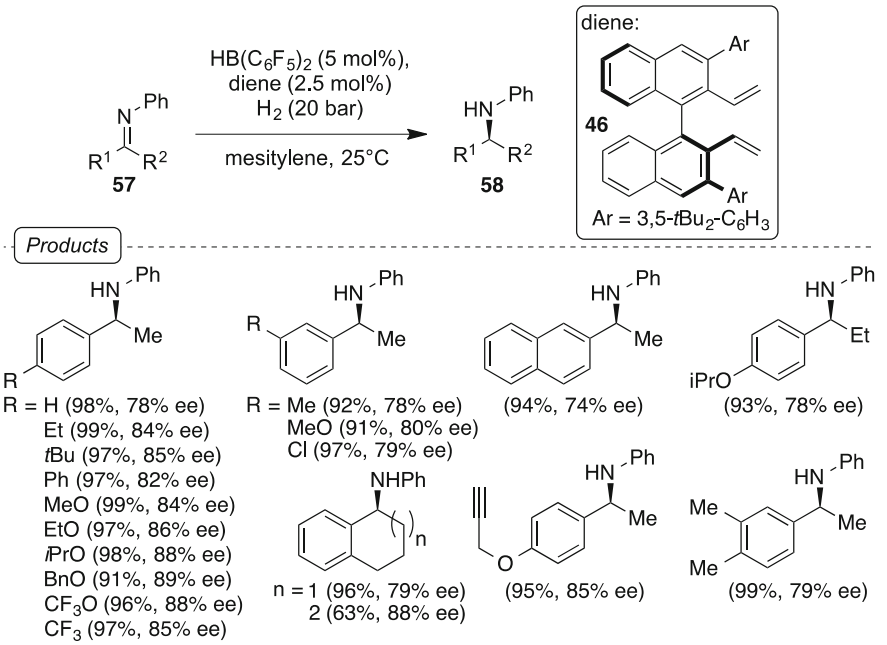
Scheme 20 Asymmetric hydrogenation by the *ansa*-aminoborane **12** [67]

to high enantioselectivity (32% ee up to 83% ee). However, the enamines proved as more suitable substrates for the FLP-catalyzed hydrogenation, so that quantitative yields and moderate to excellent enantioselectivities were achieved under mild conditions applying 2 bar hydrogen pressure.

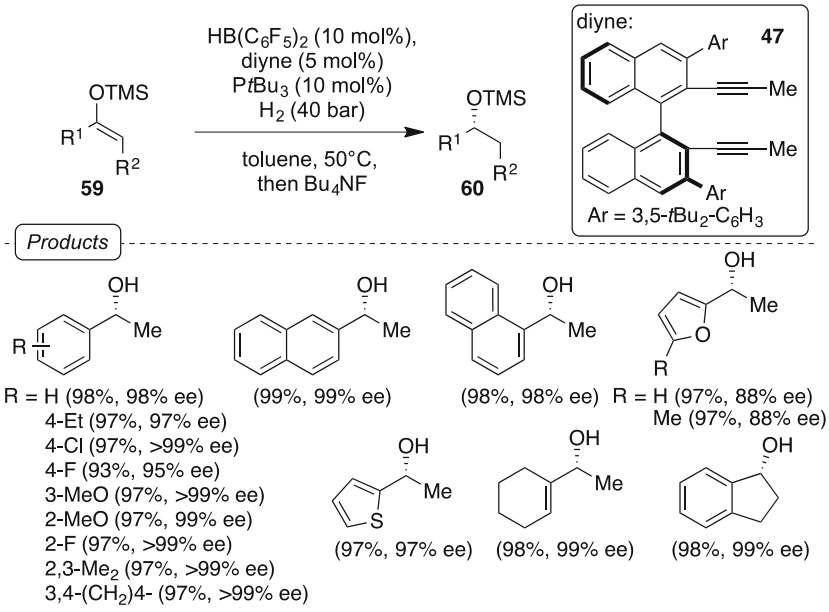
The chiral bis(boranes) derived from 2,2′-di(vinyl)-1,1′-bis(naphthyl) **48** were comparably efficient and as enantioselective in the hydrogenation of imines **57** as the camphor-derived systems. However, the substrate scope has been more intensely studied (Scheme 21). The catalytically active bisborane **46** was assembled in situ and provided the hydrogenation products **58** 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.

The borane **48**, which was generated in situ from **46**, tolerated functional groups, e.g., ethers, halides, and even propargyl ethers and the products were obtained in excellent yields and enantioselectivity of 74–89% ee. Silyl enol ethers are susceptible to FLP-catalyzed hydrogenation [44, 45]. Here, the catalyst **48** derived from the diene **46** was remarkably efficient and stereoselective in the enantioselective hydrogenation of silyl enol ethers (Scheme 22) [87].

The secondary alcohols **60** were obtained in excellent yields and in most cases enantiopure after TBAF (tetrabutylammonium fluoride) deprotection. The chiral diyne-derived bis(alkenylborane) **49** was also highly efficient in the hydrogenation



Scheme 21 Asymmetric hydrogenation of ketimines by in situ formed chiral bis(boranes) [85]



Scheme 22 Enantioselective hydrogenation of silyl enol ethers [87]

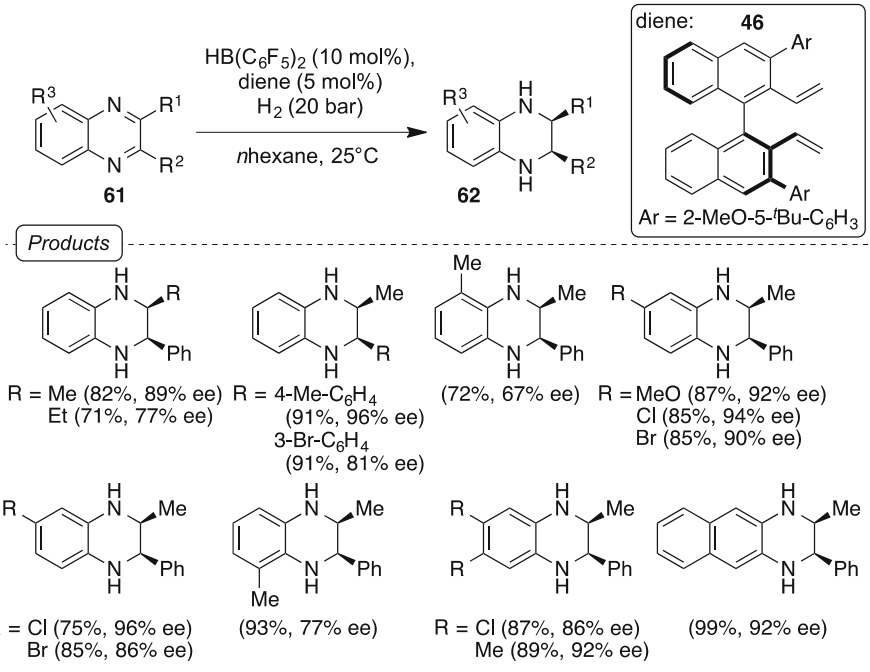
of silyl enol ethers and provided the products in comparable yield and enantioselectivity [89].

The broad scope of the 1,1′-bis(naphthyl)-derived catalysts was demonstrated by the enantioselective hydrogenation of nitrogen-containing heterocycles using the diene **46**. 2,3-Disubstituted quinoxalines **61** were very efficiently hydrogenated under mild conditions (20 bar H_2 at room temperature) and provided the tetrahydroquinoxalines **62** with high to excellent enantioselectivities (67–96% ee, Scheme 23) [83].

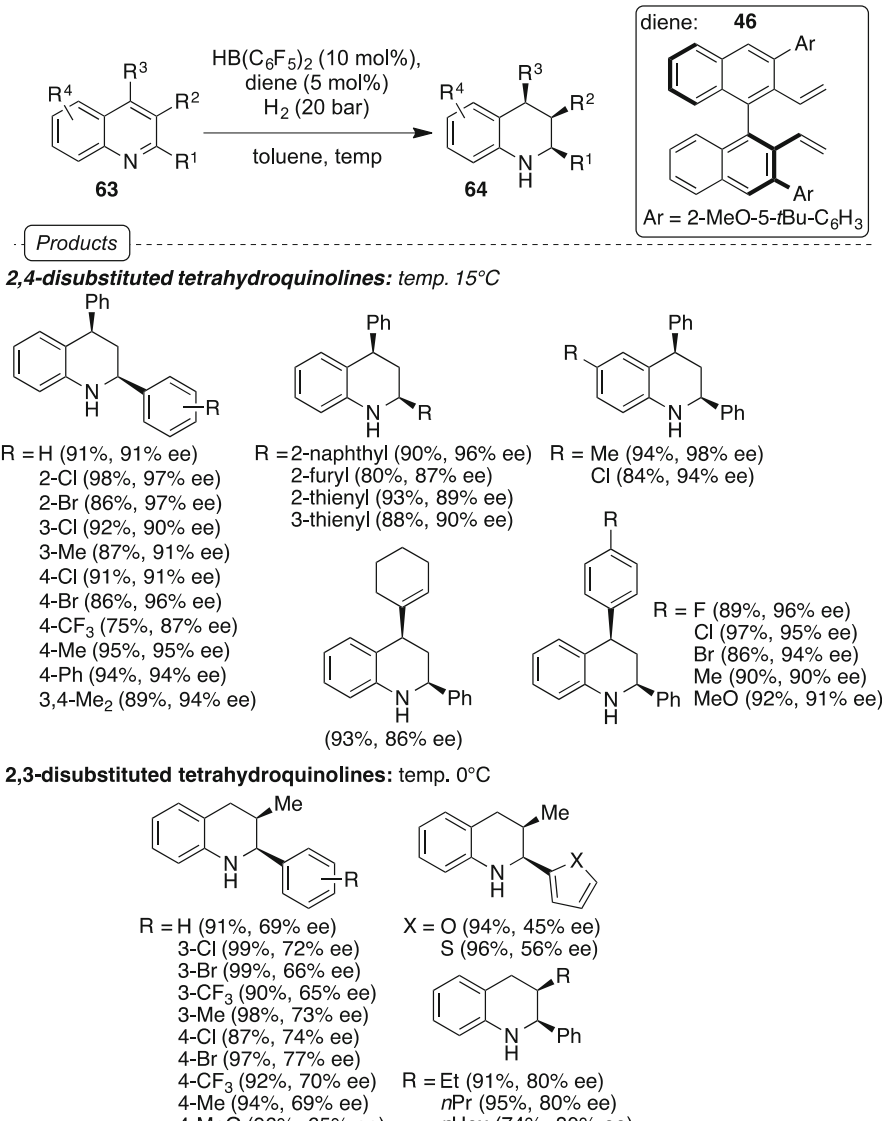
The hydrogenation proceeded highly diastereoselective and exclusively the cis-terahydroquinoxalines were obtained. Slight modifications of the catalysts system to the 2-*i*PrO-5-*t*Bu-C_6H_3-modified **46** allowed the stereoselective hydrogenation of di- and trisubstituted quinolines **63** [90, 91].

However, the stereoselective hydrogenation of 2,3-disubstituted quinolines turned out to be more challenging compared to the corresponding 2,4-disubstituted quinolines (Scheme 24) [90].

For both substrate classes the hydrogenation provided highly *cis*-selective (94:4–>99:1) the efficient access to the tetrahydroquinolines **64** while the enantioselectivity of the reduction was generally higher (86–98% ee) for the 2,4-substituted quinolines (Scheme 24a). The stereoselective hydrogenation of the corresponding 2,3-disubstituted quinolines was realized at reduced temperatures of 0°C (Scheme 24). Surprisingly, the enantioselectivity dropped from 87 or 89% ee



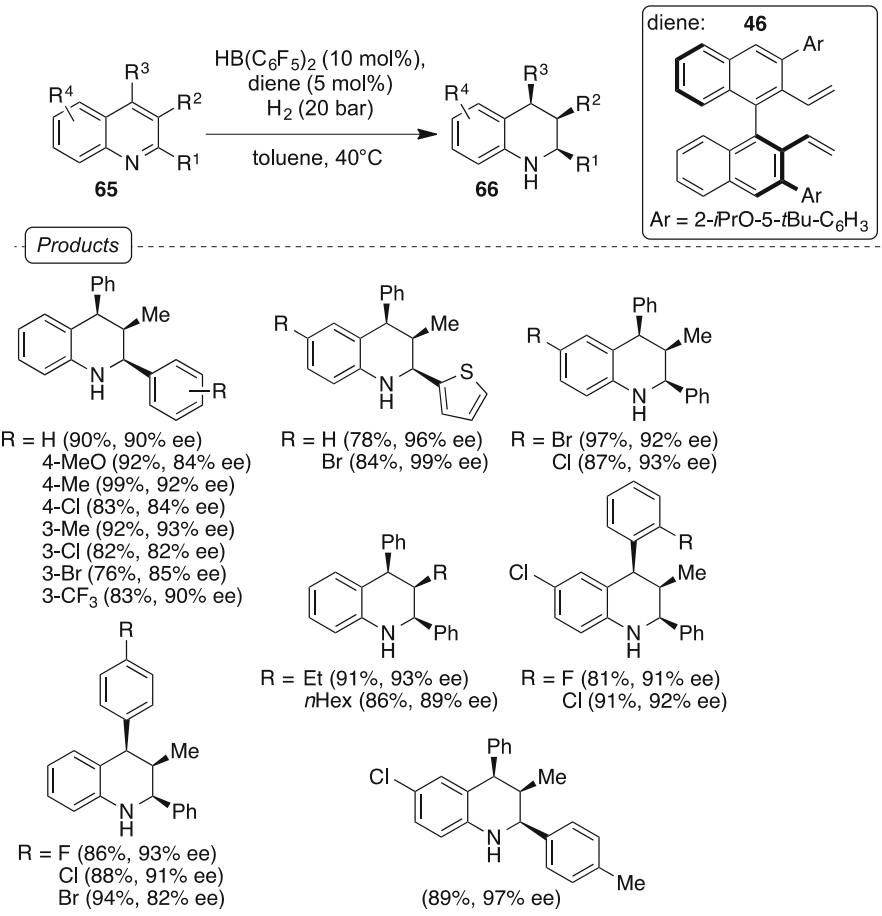
Scheme 23 FLP-catalyzed enantioselective hydrogenation of quinoxalines [83]



Scheme 24 FLP-catalyzed enantioselective hydrogenation of disubstituted quinolines [90]

to 45 or 56% ee respectively, when the 4-substituent was translocated to the 3-position. Also the FLP-catalyzed hydrogenation of 2,3,4-trisusbstitued quinolines was realized employing the 2-O*i*Pr-5-*t*Bu-C_6H_3-derivative of **46** (Scheme 25) [91].

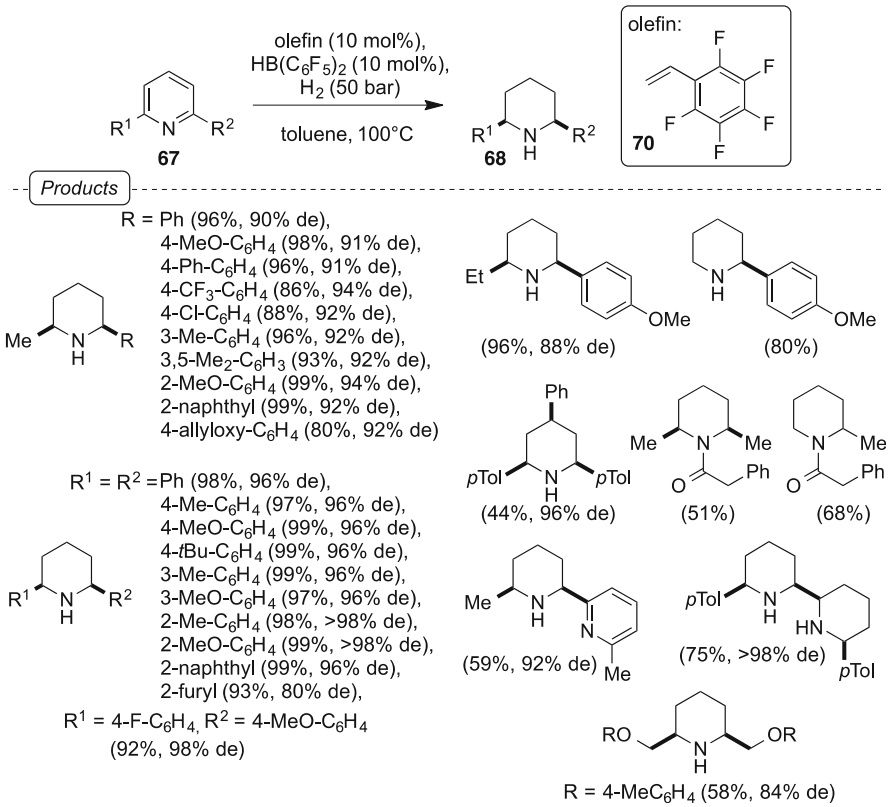
The all-*cis* configured tetrahydroquinolines **66** were obtained at slightly elevated reaction temperature (40°C) in high to excellent yields and excellent enantiomeric excess of 82–99% ee.



Scheme 25 Cis-selective and enantioselective metal-free hydrogenation of 2,3,4-trisubstituted quinolines [91]

Though not an enantioselective catalytic process but a highly diastereoselective process with an immense scope was developed for the hydrogenation of mono- and di-substituted pyridines **67** to yield the corresponding piperidines **68** using the in situ formation of the catalytically active borane-derived Lewis acid. The tertiary borane C_6F_5–CH_2CH_2–$B(C_6F_5)_2$ **69** was assembled by the hydroboration of $CH_2 = CH(C_6F_5)$ (**70**) with Piers' borane ($HB(C_6F_5)_2$ (**1**)) in situ and used as Lewis acid in the FLP-catalyzed hydrogenation (Scheme 26) [84].

More than 30 pyridine derivatives were diastereoselectively hydrogenated providing an unprecedented access to *cis*-2,6-substituted piperidines in excellent yields.



Scheme 26 FLP-catalyzed hydrogenation of pyridines [84]

5 Summary

The FLP-mediated H_2-activation underwent an incredible development from a laboratory curiosity to a synthetically important method for metal-free hydrogenations. The joined interest of inorganic, organic, and physical chemists led to this fast evolution, which is probably inspired by the strikingly simple concept. However this concept proved as tremendously powerful for the synthesis of novel catalytic systems for metal-free asymmetric hydrogenations of imines, enamines, silyl enol ethers, and heterocycles.

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