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Shengming Ma *Editor*

Asymmetric Catalysis from a Chinese Perspective

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Aims and Scope

The series *Topics in Organometallic Chemistry* presents critical overviews of esearch results in organometallic chemistry. As our understanding of organometallic structures, properties and mechanisms grows, new paths 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 made that are of significance to a larger scientific audience.

The individual volumes of *Topics in Organometallic Chemistry* are thematic. Review articles are generally invited by the volume editors.

In references *Topics in Organometallic Chemistry* is abbreviated Top Organomet Chem and is cited as a journal. From volume 29 onwards this series is listed with ISI/Web of Knowledge and in coming years it will acquire an impact factor.

Preface

As we know, chirality has been well observed both in nature and in natural and artificial compounds. In 2001, three chemists (K.B. Sharpless, W.S. Knowles, and R. Noyori) were honored with Nobel prize for their contribution to the area of enantioselective epoxidation and hydrogenation. However, there are many unsolved issues in this area; thus, it is still and will continue to be a very hot and challenging topic in organic chemistry due to the importance of optically active compounds in life science and related disciplines. Although there are many original and outstanding contributions from chemists outside China, the contribution to this field from Chinese chemists had been very limited until 20 years ago. The situation has now changed dramatically. In 1995, Professors Lixin Dai (Shanghai Institute of Organic Chemistry), Xiyan Lu (Shanghai Institute of Organic Chemistry), and Guangmei Zhu (National Natural Science Foundation of China) wrote a review article in Chinese for "Hue Xue Tong Bao (Chinese Bulletin in Chemistry, 1995, issue 6, pp 15–22)" to introduce the importance and the current state of the art of chiral technology. Subsequently, the National Natural Science Foundation of China started to actively support research in this area. From 2000, the Ministry of Science and Technology also started to support research in this area via the so-called 973 programs. Due to these increasing investments from the governmental agencies, demand from industry, and the involvement of more and more organic chemists, Chinese colleagues have also been making notable achievements in this area by developing alternative effective new chiral ligands for well-established enantioselective transformations, as well as new catalytic enantioselective reactions with known or new ligands. Currently there is no monograph dealing specifically with the contribution of China to this field.

Following the proposal from Springer, I have invited the following Chinese chemists to write an account on their own contribution in this area by briefly touching on the background for the contribution from the chemists outside China: Qilin Zhou, Albert S.C. Chan, Guoqiang Lin, Meixiang Wang, Dan Yang, Liuzhu Gong, Kuiling Ding, Xuelong Hou, Yong Tang, Yonggui Zhou. At this moment, I would

like to thank them and their coworkers whose names appear in each chapter for their efforts toward this task and wish them a very fruitful future investigating the science of chirality. Of course, we acknowledge that there is still a long way to go for our Chinese organic chemists in this area. In addition, I would like to thank the involved persons from Springer for their efforts toward this project.

Shanghai, P.R. China Shengming Ma

Contents

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Chiral Spiro Catalysts

Qi-Lin Zhou and Jian-Hua Xie

Abstract Despite a number of highly efficient chiral ligands and catalysts have been developed in the past years, the searching for novel and efficient chiral ligands and catalysts is still required to satisfy the new needs of mankind for chiral compounds. This chapter describes the design and synthesis of chiral spiro ligands based on 1,1′-spirobiindane backbone and their applications in catalytic asymmetric transformations. The chiral catalysts containing these spirobiindane ligands exhibited excellent activities and enantioselectivities in a wide range of asymmetric reactions such as hydrogenations of enamines, α,β-unsaturated carboxylic acids, imines, ketones, and aldehydes, addition of organometallic reagents to α,β-unsaturated ketones, aldehydes, and imines, hydrovinylation of styrenes, reductive or alkylative coupling of dienes/alkynes and aldehydes, hydrosilylation/cyclization of 1,6-enynes, as well as X–H bond (X = O, N) insertion reactions, providing efficient and environment-benign approaches to various chiral compounds such as chiral amines and alcohols.

Keywords Asymmetric catalysis • Coupling • Cyclization • Hydrogenation • Spirobiindane

Contents

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1 Introduction

Catalytic asymmetric reaction is one of the most efficient and reliable methods for the synthesis of enantiopure compounds such as chiral pharmaceuticals, agrochemicals, flavors, fragrances, as well as advanced materials. In the past decades, tremendous efforts have been devoted to this important field and numerous highly efficient catalytic asymmetric reactions have been developed. Among them, the asymmetric reaction catalyzed by metal complexes of chiral ligands has long been the most intense, dynamic, and rapidly growing areas of research.

In the last 40 years, a huge number of efficient chiral metal catalysts bearing chiral ligands have been developed, but only a few of them could be capable of ranking the so-called "privileged chiral catalysts" [1], which mediate efficiently and enantioselectively not only one but rather a variety of seemingly unrelated reactions. Most of such catalysts are metal complexes containing relatively rigid chiral ligands in particular the ligands with C_2-symmetric skeleton. Important members of privileged chiral catalysts include BINAP [2], DuPhos [3], Bisoxazoline [4–6], and Salen derivatives [7, 8].

Recently, the highly rigid chiral ligands having a spiro backbone such as spiro[4.4]nonane and spirobiindane have emerged as a new class of efficient chiral ligands for a wide range of transition-metal-catalyzed asymmetric reactions [9, 10]. In 1997, Chan and Jiang et al. reported that the rhodium catalysts bearing a chiral spiro phosphinite ligand SpirOP (Fig. 1) are highly efficient for asymmetric hydrogenation of α-dehydroamino acid derivatives [11]. This is the first example of spiro chiral catalysts applied in asymmetric reactions. Sasai et al. reported a type of spiro bisisoxazoline ligands based on spiro[4.4]nonane

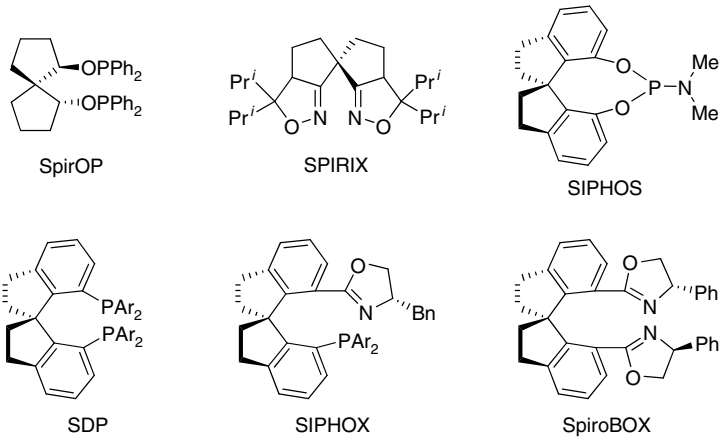


Fig. 1 Typic chiral spiro ligands

[12, 13]. These new chiral spiro dinitrogen ligands, named as SPRIX, showed excellent asymmetric induction in the palladium-catalyzed tandem Wacker-cyclization process, producing chiral bicyclic compounds. Since early this century, we have designed and synthesized a series of spiro chiral ligands bearing a spirobiindane or spirobifluorene backbone [14]. These spiro chiral ligands include monodentate phosphoramidites SIPHOS, diphosphines SDP, phosphine-oxazolines SIPHOX, as well as bisoxazolines SpiroBOX. Chiral transition metal complexes of such spiro chiral ligands exhibited excellent enantioselectivity and reactivity for a wide range of asymmetric reactions including hydrogenation, carbon–carbon bond-forming reaction, as well as carbon–heteroatom bond-forming reactions.

To date, several other research groups have involved in development of chiral spiro ligands and a variety of chiral ligands with different spiro backbones have been synthesized [9, 10]. The metal complexes of these spiro chiral ligands were also demonstrated to be efficient chiral catalysts for many asymmetric reactions.

In this chapter, we focus on the discussion of chiral spiro catalysts with 1,1′-spirobiindane backbone (including 9,9′-spirobifluorene, an analog of 1,1′-spirobiindane) developed in our laboratory and their applications in catalytic asymmetric reactions. The chiral spiro catalysts derived from spiro[4.4]nonane and other spiro molecules [9, 10] are beyond the coverage of this chapter and will not be discussed.

2 Design and Synthesis of Spirobiindane-Based Chiral Ligands

Molecules containing a spirocyclic framework are ubiquitous in nature. These molecules have a quaternary carbon atom (the spiro carbon), which joins two cyclic rings and makes them lie in perpendicular planes. This structural feature not only restricts the rotation of the two rings and gives rise to an axial chirality in spiro compounds having substituents on the rings, but also increases molecular rigidity. With these characteristics, spiro compounds, especially the C_2-symmetric spiranes, are ideal backbones for chiral ligands.

Spiro[4.4]nonane is one of the most simplest spiro molecules with high rigidity, but itself is not a chiral molecule (Fig. 2). The introduction of substituents on the rings of spiro[4.4]nonane usually generates more than one chiralities (such as a spiro[4.4] nonane-1,6-diol [15]) and increases the difficulty in the synthesis of its optically pure form. The addition of benzo groups on the skeleton of spiro[4.4]nonane gave 1,1′-spirobiindane, which has only an axial chirality. This highly rigid, C_2-symmetric, axially chiral 1,1′-spirobiindane is an excellent scaffold for the chiral ligands [14].

The 1,1′-spirobiindane-based chiral ligands (Fig. 3) including monophosphoramidites SIPHOS (**1**–**3**) [16–20], monophosphonites FuP (**4**) [21, 22], monophosphites ShiP (**5**) [23, 24], phospholane SITICP (**6**) [25, 26], diphosphines SDP (**7**) [27, 28] and SFDP (**8**) [29, 30], phosphine-oxazolines SIPHOX (**9**) [31, 32], as well as bisoxazolines SpiroBOX (**10**) [33], were synthesized from enantiomerically pure 1,1′-spirobiindane-7,7′-diol (SPINOL) or its derivatives. The racemic SPINOL can be easily synthesized by the procedure developed by Birman et al. [34], and the optically pure form of SPINOL can be obtained via an inclusion resolution with *N*-benzylcinchonidium chloride [35]. The spiro diphosphine ligands SFDP (**8**) were synthesized from enantiopure 9,9′-spirobifluorene-1,1′-diol (SBIFOL). Recamic SBIFOL was prepared from 1,2-dibromobenzene and 3-bromoanisole and the enantiopure form was obtained by an inclusion resolution with 2,3-dimethoxy-tetracyclohexyl-succinamide [36].

More than 100 chiral spiro ligands with 1,1′-spirobiindane or 9,9′-spirobifluorene backbone had been synthesized up to now, and some of them, such as SIPHOS, ShiP, and SDP, can be purchased from Aldrich or Strem chemical companies. The

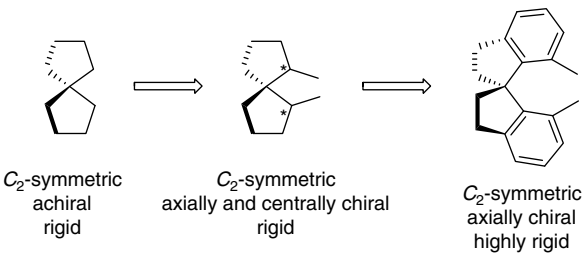
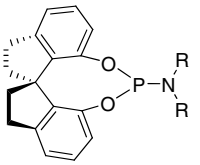
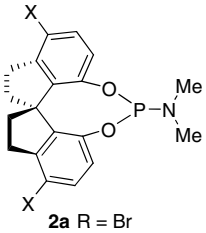


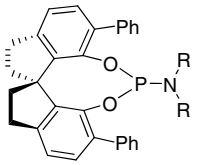
Fig. 2 The concept of spiro ligand design



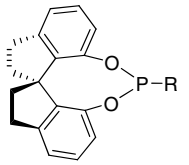
1a R = Me ((*S*)-SIPHOS)
1b R = Et
1c R = *i*-Pr
1d R = (*S*)-1-phenylethyl
1e R = (*R*)-1-phenylethyl



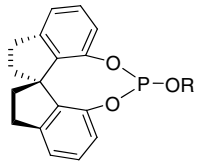
2a R = Br
2b R = C_6H_5
2c R = MeO



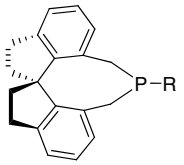
3a NR_2 = NMe_2
3b NR_2 = morpholine



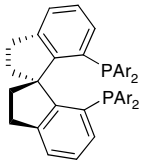
4a R = C_6H_5 ((*S*)-FuP)
4b R = 4-MeC_6H_4
4c R = 4-MeOC_6H_4
4d R = 4-ClC_6H_4
4e R = 4-FC_6H_4
4f R = Me
4g R = *i*-Pr
4h R = *t*-Bu



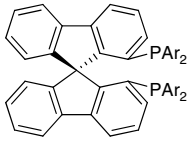
5a R = C_6H_5 ((*S*)-ShiP)
5b R = 2-MeOC_6H_4
5c R = 4-MeOC_6H_4
5d R = 2-$CF_3C_6H_4$
5e R = 4-$CF_3C_6H_4$
5f R = 1-naphthyl
5g R = 2-naphthyl



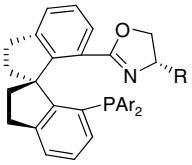
6a R = C_6H_5 ((*S*)-SITCP)
6b R = 4-MeOC_6H_4
6c R = 3,5-$(Me)_2C_6H_3$
6d R = 4-MeO-3,5-$(Me)_2C_6H_2$
6e R = 4-MeO-3,5-$(t\text{-Bu})_2C_6H_2$
6f R = *t*-Bu



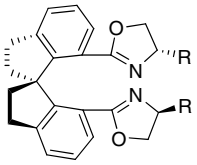
7a Ar = C_6H_5 ((*S*)-SDP)
7b Ar = 4-MeC_6H_4 ((*S*)-Tol-SDP)
7c Ar = 4-MeOC_6H_4 ((*S*)-Anl-SDP)
7d Ar = 3,5-$(Me)_2C_6H_3$ ((*S*)-Xyl-SDP)
7e Ar = 4-MeO-3,5-$(Me)_2C_6H_2$ ((*S*)-DMM-SDP)



8a Ar = C_6H_5 ((*S*)-SFDP)
8b Ar = 4-MeC_6H_4 ((*S*)-Tol-SFDP)
8c Ar = 4-MeOC_6H_4 ((*S*)-Anl-SFDP)
8d Ar = 3,5-$(Me)_2C_6H_3$ ((*S*)-Xyl-SFDP)
8e Ar = 3,4,5-$(Me)_3C_6H_2$ ((*S*)-TM-SFDP)



9a Ar = C_6H_5, R = Bn ((S_a,S)-SIPHOX)
9b Ar = C_6H_5, R = *i*-Pr
9c Ar = 3,5-$Me_2C_6H_3$, R = Bn
9d Ar = 3,5-^{t}Bu$_2C_6H_3$, R = Bn
9e Ar = 3,5-^{t}Bu$_2C_6H_3$, R = *i*-Pr
9f Ar = 3,5-^{t}Bu$_2C_6H_3$, R = H



10a R = Ph ((S_a,S,S)-SpiroBOX)
10b R = *i*-Pr
10c R = Bn
10d R = *t*-Bu
10e R = α-naphthylmethyl
10f R = β-naphthylmethyl

Fig. 3 Spiro chiral ligands based on spirobiindane and spirobifluorene

metal complexes of these chiral spiro ligands have been successfully applied in various catalytic asymmetric reactions to produce a wide range of enantiomer-enriched compounds [14].

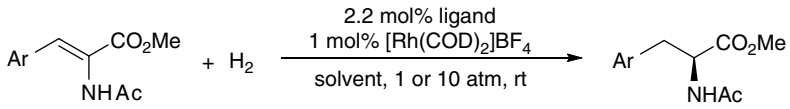
3 Asymmetric Hydrogenation

Transition metal catalyzed asymmetric hydrogenation is a highly efficient and practical way for producing optically active organic compounds. Since Knowles and Sabacky [37], and Horner et al. [38] independently reported the first example of asymmetric hydrogenation catalyzed by rhodium complexes of chiral monophosphine ligands, many excellent chiral catalysts have been successfully applied in this transformation. Notable examples include Rh-DIPAMP catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives, which has been applied in the industrial synthesis of chiral drugs L-DOPA [39]; Ir-Josiphos catalyzed asymmetric hydrogenation of imines, a practical approach to chiral herbicide Metolachlor [40]; Ru-C_3-TunePhos catalyzed asymmetric hydrogenation of ethyl 4-chloroacetoacetate, a highly efficient method for the preparation of chiral drug atorvastatin calcium (Lipitor) [41]; Ru-BINAP catalyzed asymmetric hydrogenation of ketones [42]. Chiral spiro catalysts also displayed excellent enantioselectivity and activity in asymmetric hydrogenation of olefins, imines, as well as ketones.

3.1 Asymmetric Hydrogenation of Olefins

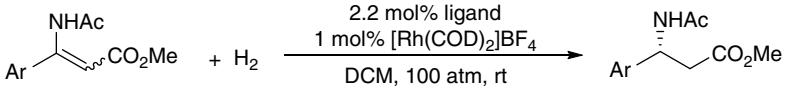
3.1.1 Asymmetric Hydrogenation of Enamines

Asymmetric hydrogenation of enamines is a convenient and economical route for the preparation of enantiopure amino acids or amines. The chiral rhodium complexes of monophosphorus ligands derived from 1,1′-spirobiindane have been demonstrated to be highly efficient catalysts for this transformation. In the asymmetric hydrogenation of α-dehydroamino acid esters, the Rh-complex of SIPHOS ligand (*S*)-**1a** gave a series of α-amino acid derivatives with excellent enantioselectivities (96–99.3% ee) under mild conditions [Scheme 1, (1)] [17, 19]. These results are better than or comparable to those obtained with diphosphine ligands and other monodentate phosphorus ligands, showing intriguing chiral inducement ability of 1,1′-spirobiindane backbone. Modification of the SIPHOS ligands on the 4,4′-positions of the spiro ring does not improve the enantioselectivity of the ligand [43]. However, the Rh-complex of spiro phosphonite FuP ligand (*S*)-**4c** with an electron-donating methoxy group at the *para*-position of the *P*-phenyl ring showed higher enantioselectivities, albeit higher hydrogen pressure is required [21].



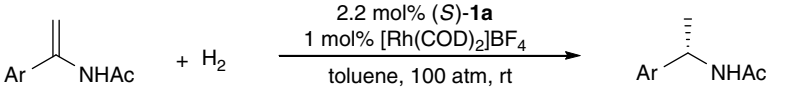
(1)

Ligand	conditions	ee [%]
(*S*)-SIPHOS ((*S*)-**1a**)	DCM,1 atm H_2	96-99.3% ee
(*S*)-**4c**	toluene,10 atm H_2	97-99% ee



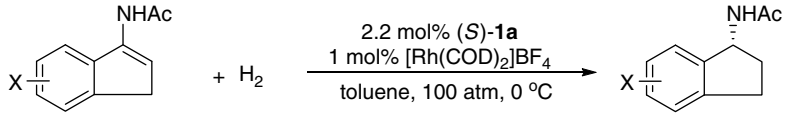
(2)

Ligand	ee [%]
(*S*)-SIPHOS ((*S*)-**1a**)	90-94% ee
(*S*)-**4c**	85-98% ee



(3)

91-99.5% ee



(4)

X	H	5-Br	6-MeO
ee [%]	94	88	95

Scheme 1 Asymmetric hydrogenation of α- or β-dehydroamino acid esters and enamides

For Rh-catalyzed asymmetric hydrogenation of β-dehydroamino acid esters, both SIPHOS ligand (*S*)-**1a** and FuP ligand (*S*)-**4c** are very efficient, providing the corresponding hydrogenation products in high enantioselectivities (90–94% ee [19] and 85–98% ee [16], respectively); however, a higher hydrogen pressure (100 atm) is need to complete the reaction [Scheme 1, (2)]. It is worth noting that both Rh-(*S*)-**1a** and Rh-(*S*)-**4c** can promote the hydrogenation of *Z*/*E* mixture of β-dehydroamino acid esters (*Z*/*E* = 98:2–50:50) with high enantioselectivities. This is of practical importance because the β-(acylamino)acrylate substrates are normally prepared as a mixture of *Z*- and *E*-isomers.

Compared with the asymmetric hydrogenation of α- or β-dehydroamino acid esters, where the chiral monophosphorus ligands have been widely used, the asymmetric hydrogenation of enamides was still dominated by chiral metal complexes ligated by diphosphine ligands such as DuPhos, BPE, and BDPAB [44]. The major

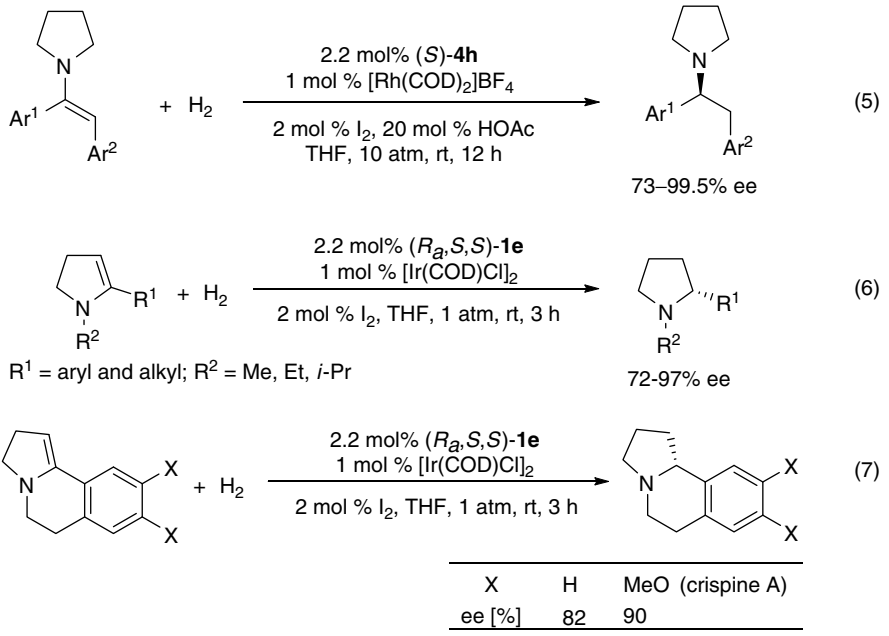
reason for this is that the simple enamides are electron-rich olefins, which are generally poor substrates for asymmetric hydrogenation. The Rh-complex of SIPHOS ligand (*S*)-**1a** is the first example of highly efficient chiral catalyst bearing monophosphorus ligand for asymmetric hydrogenation of simple enamides [Scheme 1, (3)] [16, 19]. Under mild conditions, a series of α-arylenamides were hydrogenated to the corresponding chiral α-arylethamines in high yields with excellent enantioselectivities (91–99.5% ee). These results are better than those obtained with rhodium catalysts bearing diphosphine ligands such as DuPhos and BDPAB [44].

The Rh-complex of SIPHOS ligand (*S*)-**1a** is also highly effective for the asymmetric hydrogenation of cyclic enamides, offering chiral cyclic amines, an important class of compounds in pharmaceutical synthesis, in high enantioselectivities. For example, with catalyst Rh-(*S*)-**1a**, *N*-(1,2-dehydro-1-indanyl)acetamides were hydrogenated to the corresponding cyclic amines with high enantioselectivities (88–95% ee) [Scheme 1, (4)] [19]. This reaction provides a practical method to chiral 1-aminoindanes, key intermediates for chiral drugs such as rasagiline for Parkinson's disease [45].

Asymmetric hydrogenation of *N*,*N*-dialkyl enamines is a direct method to access chiral tertiary amines, which widely exist in natural compounds and pharmaceuticals, but only a few efficient chiral catalysts have been reported for such transformation to date [46, 47]. There are two reasons for this: firstly *N*,*N*-dialkyl enamines are electron-rich olefins, which are usually reluctant to undergo catalytic hydrogenation. Secondly, the substrate has no *N*-acetyl group, which is considered to be a prerequisite for obtaining high enantioselectivity in the hydrogenation of enamides. Interestingly, the Rh-complex of FuP ligand (*S*)-**4h** with a *t*-Bu group on the *P*-atom was demonstrated to be a highly efficient catalyst for the asymmetric hydrogenation of 1-(1,2-diarylvinyl)pyrrolidines, offering the corresponding chiral tertiary amines in excellent enantioselectivities (73–99.5% ee) [Scheme 2, (5)] [22]. In this reaction, the additions of I_2 (2 mol%) and HOAc (20 mol%) are crucial for obtaining high reactivity and enantioselectivity. On the contrast, other chiral ligands including diphosphines such as BINAP, Josiphos, and monophosphorus ligands such as MonoPhos, SIPHOS are inefficient for this transformation.

For asymmetric hydrogenation of unfunctionalized cyclic enamines such as 1-alkyl-5-aryl-2,3-dihydro-1*H*-pyrroles, the Ir-complex of SIPHOS ligand (R_a,*S*,*S*)-**1e** was found to be efficient catalyst, yielding the corresponding chiral tertiary cyclic amines with excellent enantioselectivities (72–97% ee) [Scheme 2, (6)] [48]. The catalyst Ir-(R_a,*S*,*S*)-**1e** has a very high activity, it can perform the hydrogenation of cyclic enamines under ambient pressure of H_2 with 0.1 mol% of catalyst loading.

The Ir-catalyzed asymmetric hydrogenation has been successfully applied in the synthesis of chiral tricyclic amines [Scheme 2, (7)] [48]. Under the optimal conditions, 2,3,5,6-tetrahydropyrrolo[2,1-a]isoquinolines were hydrogenated by Ir-(R_a,*S*,*S*)-**1e** catalyst to afford tricyclic amines with 82 and 90% ee, respectively. This methodology provides a convenient approach to isoquinoline alkaloid crispine A [49].



Scheme 2 Asymmetric hydrogenation of unfunctionalized enamines

3.1.2 Asymmetric Hydrogenation of α,β-Unsaturated Carboxylic Acids

Enantioselective hydrogenation of α,β-unsaturated carboxylic acids by transition metal complexes is another important olefin hydrogenation reaction, which provides a straightforward access to the synthesis of chiral carboxylic acids. A number of efficient chiral catalysts, in particular Ru-catalysts ligated with chiral diphosphines such as BINAP, H_8-BINAP, and P-Phos, have showed high enantioselectivity in the hydrogenation of α,β-unsaturated carboxylic acids [44]. However, most of these chiral catalysts are strongly substrate dependent. High turnover number (TON) and high enantioselectivity were only achieved in the hydrogenation of a limited number of substrates such as α-arylacrylic acids and tiglic acids. The Ru–diacetate complexes of SFDP ligand **8** contained a 9,9′-spirobifluorene backbone were found to be highly enantioselective catalysts for the hydrogenation of a wide range of α,β-unsaturated carboxylic acids including the unsolved α-methylcinnamic acid derivatives [29, 30].

For the asymmetric hydrogenation of tiglic acid derivatives, the Ru–diacetate complex of SFDP ligand (*R*)-**8d** exhibited excellent enantioselectivities (94–97% ee) under low H_2 pressure (6 atm) [Scheme 3, (8)] [29, 30]. The catalyst loading can be reduced to 0.01 mol% (*S*/*C* = 10,000) without diminishing enantioselectivity in the hydrogenation of tiglic acid.

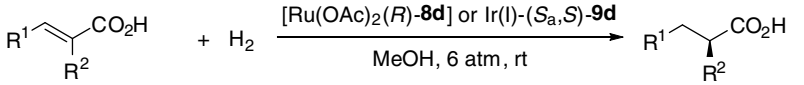
Compared with the high efficiency and excellent enantioselectivity achieved in the hydrogenation of α-arylacrylic acids and tiglic acids, the asymmetric

hydrogenation of α-substituted cinnamic acid derivatives is far from success. The Ru–diacetate complex of (*S*)-BINAP gave very low enantioselectivity (<40% ee) in the hydrogenation of α-methylcinnamic acid. By using (*S*)-H_8-BINAP, a partially hydrogenated BINAP ligand, Takaya significantly improved the enantioselectivity of the reaction to 89% ee [50–52]. The Ru–diacetate complex of SFDP ligand (*R*)-**8e** was proven to be a highly efficient catalyst for the hydrogenation of α-methylcinnamic acid derivatives [29, 30]. Under mild conditions (6 atm, *S*/*C* = 400), the catalyst $Ru(OAc)_2$-(*R*)-**8e** can hydrogenate various α-methyl cinnamic acid derivatives to 2-methyl-3-arylpropanoic acids in excellent enantioselectivities (90–97% ee) [Scheme 3, (9)]. The Ru–diacetate complex of SFDP ligand (*R*)-**8b** is also a good catalyst for the asymmetric hydrogenation of α-aryloxyl unsaturated carboxylic acids (64–95% ee) [Scheme 3, (10)] [30].

Very recently, a new type of efficient chiral spiro iridium catalysts Ir-SIPHOX was developed for asymmetric hydrogenation of α,β-unsaturated carboxylic acids. Although Matteoli et al. reported that the Ir–Phox complexes can catalyze asymmetric hydrogenation of α,β-unsaturated carboxylic acids, the catalyst demonstrates only moderate enantioselectivity (up to 81% ee) and low activity (TON 25) [53]. When the Ir-complexes of SIPHOX ligands (S_a,*S*)-**9** were introduced into this reaction, the situation was changed significantly. Extremely high enantioselectivities (up to 99.4% ee) and excellent catalytic activities (TON up to 100,000) were obtained for both α-methyl cinnamic acid and tigilic acid derivatives by using Ir-(S_a,*S*)-**9d–f** catalysts [32]. This result represents the highest level of enantiocontrol and efficiency reported to date in the asymmetric hydrogenation of α,β-unsaturated carboxylic acids.

For the asymmetric hydrogenation of α-methyl cinnamic acid derivatives, Ir-complex of ligand (S_a,*S*)-**9d** having a benzyl group on the oxazoline ring and 3,5-di-*tert*-butyl groups on the *P*-phenyl rings of the ligand gave the best results [Scheme 3, (9)]. Under mild conditions and in the presence of 0.5 eq. Et_3N, various 2-methyl-3-arylpropanoic acids were obtained in exceptionally high enantioselectivities (96–99.2% ee). While the Ir-complex of ligand (S_a,*S*)-**9e** with a *i*-Pr group on the oxazoline ring gave higher enantioselectivities in the asymmetric hydrogenation of tigilic acid derivatives [Scheme 3, (8)]. The addition of base Cs_2CO_3 (0.5 eq) accelerates the reaction rate.

This highly efficient chiral iridium catalyst has been successfully applied in the practical synthesis of enantiopure 2-[4-methoxy-3-(3-methoxypropoxy)-benzyl]-3-methylbutanoic acid, a key intermediate for the preparation of the new blood-pressure-lowering drug Aliskiren [54]. With Ir(I)-(*S*)-**9f** catalyst having no substituent on the oxazoline ring of the ligand, this chiral intermediate was produced in a quantitative yield with high enantioselectivities (*S*/*C* = 6,000, 98% ee or *S*/*C* = 10,000, 95% ee) [Scheme 3, (11)] [32]. This result was superior to those reported previously [55, 56].

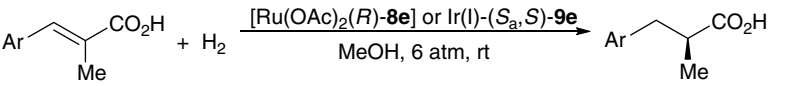


$R^1 = R^2$ = alkyl

[Ru(OAc)$_2$(*R*)-**8d**]	90-97% ee (S/C = 400)
Ir(I)-(S_a,*S*)-**9d**[a]	96-99.2% ee (S/C = 1400)

[a] 0.5 eq Cs_2CO_3 was added

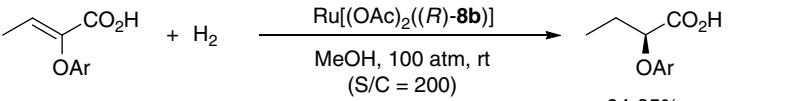
(8)



[Ru(OAc)$_2$(*R*)-**8e**]	94-98% ee (S/C = 400)
Ir(I)-(S_a,*S*)-**9e**[a]	90-99.1% ee (S/C = 400)

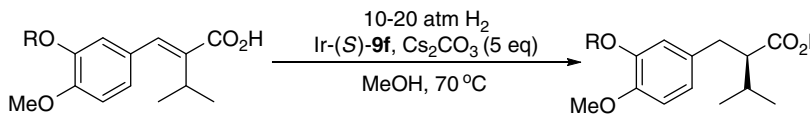
[a] 0.5 eq Et_3N was added

(9)



64-95% ee

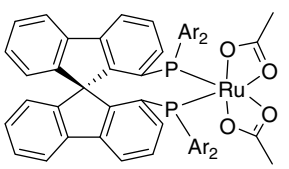
(10)



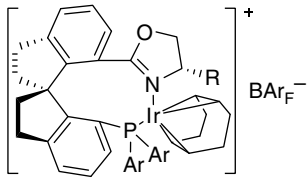
$R = (CH_2)_3OMe$

S/C = 6 000, 7 h, 100% conv., 96% yield, 98% ee
S/C = 10 000, 18 h, 97% conv., 95% yield, 95% ee

(11)



[Ru(OAc)$_2$(*R*)-**8**]

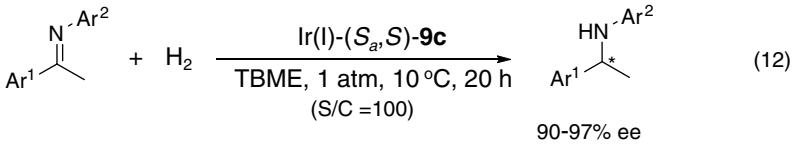


Ir(I)-(S_a,*S*)-**9**

Scheme 3 Asymmetric hydrogenation of α,β-unsaturated carboxylic acids

3.2 Asymmetric Hydrogenation of Imines

Catalytic asymmetric hydrogenation of prochiral imines represents one of the most direct and efficient approaches for the synthesis of optically pure amines. Among the catalysts developed so far, the iridium complexes of chiral phosphine-oxazoline ligands such as PHOX have showed high enantioselectivity in this transformation [57, 58]. However, the reported iridium catalysts were easily deactivated by forming inactive trimers under hydrogen atmosphere. The Ir-complexes of SIPHOX ligand (S_a,S)-**9** were found to be extraordinarily stable under hydrogen pressure and could hydrogenate imines at ambient H_2 pressure with excellent enantioselectivities [Scheme 4, (12)] [31]. With Ir-(S_a,S)-**9c** catalyst, a wide range of *N*-aryl ketimines can be hydrogenated to the corresponding chiral amines in high yields with 90–97% ee.



Scheme 4 Asymmetric hydrogenation of *N*-(1-arylethylidene)anilines

The crystal structure analysis of Ir-(S_a,S)-**9b** showed that the SIPHOX ligand (S_a,S)-**9b** constructed a crowded and efficient chiral environment around the iridium metal center (Fig. 4) [31]. In the crystal, the ligand acted as a rigid pincer, and the iridium atom was clamped in a nine-membered hetero-metal ring. The spirobiindane backbone, *P*-phenyl groups, and isopropyl group on the oxazoline ring formed a relatively crowded and rigid environment around the central metal. Such crowded structure efficiently prevents the autoaggregation of the catalyst. The ESI-MS measurement also supports the stability of the catalyst. After treatment of Ir-(S_a,S)-**9b** with 50 atm of H_2 at room temperature for 3 h, no trimeric species was detected in the ESI-MS analysis. The excellent stability of the Ir-complexes of SIPHOX ligands (S_a,S)-**9** under hydrogen interprets why they have extremely high activity in the hydrogenations of imines as well as α,β-unsaturated carboxylic acids.

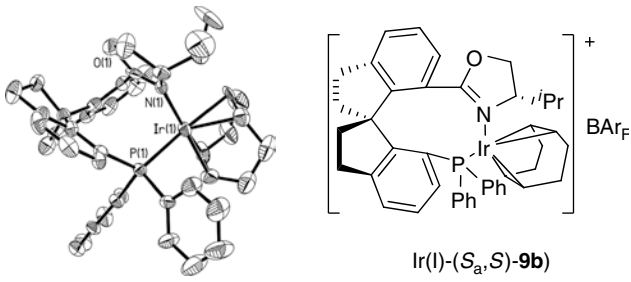


Fig. 4 The crystal structure of Ir(I)-(S_a,S)-**9b** (omitted BAr_F)

3.3 Asymmetric Hydrogenation of Carbonyl Compounds

The enantioselective hydrogenation of carbonyl compounds catalyzed by well-defined transition metal complexes is an effective tool for producing optically active alcohols. One of the best catalysts for ketone hydrogenation is the $RuCl_2$(diphosphine)(diamine) complex [42], which was initially reported by Noyori and co-workers [59]. The $RuCl_2$(SDPs)(diamine) complexes **11** (Scheme 5) were proven to be highly efficient catalysts not only for the hydrogenation of simple ketones, but also for the hydrogenation of racemic α-substituted ketones and aldehydes via dynamic kinetic resolution (DKR).

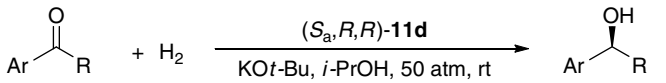
3.3.1 Asymmetric Hydrogenation of Simple Ketones

In the asymmetric hydrogenation of simple ketones, the catalyst (S_a,*R*,*R*)-**11d** with 3,5-dimethyl groups on the *P*-phenyl rings (Xyl-SDP) was demonstrated to be the best one, producing chiral secondary alcohols with excellent enantioselectivities (96–99.2% ee) [Scheme 5, (13)] [27]. The catalytic activity of catalyst (S_a,*R*,*R*)-**11d** is extremely high. For example, the catalyst loading of (S_a,*R*,*R*)-**11d** can be lowered to 0.001 mol% (*S*/*C* = 100,000) in the hydrogenation of acetophenone. Furthermore, α,β-unsaturated ketones also can be hydrogenated by the catalyst (S_a,*R*,*R*)-**11d**, affording the corresponding chiral allylic alcohols with high enantioselectivities.

3.3.2 Asymmetric Hydrogenation of Racemic α-Substituted Ketones

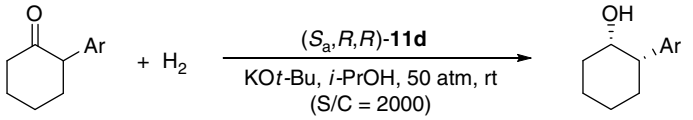
Except for the excellent performance in the asymmetric hydrogenation of simple ketones, the catalysts (S_a,*R*,*R*)-**11** also exhibited very high diastereo- and enantioselectivities in the asymmetric hydrogenation of α-substituted ketones. Generally, the addition of strong base such as a KO^{t}Bu is the prerequisite for converting $RuCl_2$(diphosphine)(diamine) complexes to active catalysts; and the α-substituted ketones can racemize rapidly under such strong basic condition. This reaction provides a possibility for achieving an asymmetric hydrogenation of racemic α-substituted ketones via DKR [60, 61]. By using (S_a,*R*,*R*)-**11d** as catalyst and KO^{t}Bu as base a series of racemic α-aryl cyclohexanones can be hydrogenated to α-aryl cyclohexanols with excellent *cis*/*trans* selectivities (>99:1) and enantioselectivities (up to 99.9% ee) [Scheme 5, (14)] [62].

Racemic cyclic α-amino ketones are another type of important substrates of asymmetric hydrogenation, but less attention has been paid to them. Noyori et al.



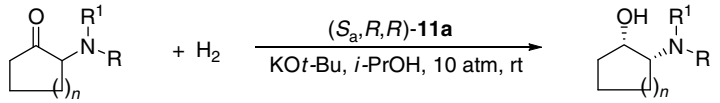
(13)

96-99% ee
TON up to 100,000



(14)

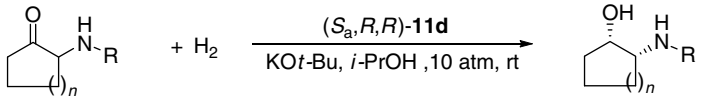
89-99.9% ee
cis/trans >99:1



(15)

R^1 = alkyl; R^2 = alkyl or aryl
n=1-3

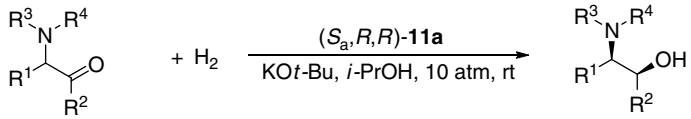
89-99.9% ee
cis/*trans* >99:1
S/C up to 30,000



(16)

R = alkyl and aryl, *n* = 1-3

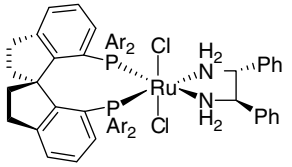
93-99.9% ee
cis/*trans* 71:29->99:1
S/C up to 10,000



(17)

R^1, R^3 = alky and aryl; R^2 = alkyl
R^4 = H and alkyl

91-99.9% ee
trans/cis 97:3->99:1
S/C up to 10,000



$RuCl_2$(SDPs)(diamine)**11**

(*Sa*,*R*,*R*)-**11a** $RuCl_2$((*S*)-SDP)((*R*,*R*)-DPEN)
(*Sa*,*R*,*R*)-**11b** $RuCl_2$((*S*)-Tol-SDP)((*R*,*R*)-DPEN)
(*Sa*,*R*,*R*)-**11c** $RuCl_2$((*S*)-An-SDP)((*R*,*R*)-DPEN)
(*Sa*,*R*,*R*)-**11d** $RuCl_2$((*S*)-Xyl-SDP)((*R*,*R*)-DPEN)
(*Sa*,*R*,*R*)-**11e** $RuCl_2$((*S*)-DMM-SDP)((*R*,*R*)-DPEN)

Scheme 5 Asymmetric hydrogenation of ketones

reported an example of asymmetric hydrogenation of racemic cyclic α-amino ketones, 2-(*tert*-butoxycarbonylamino)cyclohexanone, with catalyst $RuCl_2$[((*R*)-Xyl-BINAP)((*R*)-DaiPEN)] and obtained the desired chiral amino alcohol in 82% ee and 98% *cis*-selectivity at a ratio of substrate to catalyst (S/C) of 300 [63]. The catalyst (S_a,*R*,*R*)-**11a** was found to be the most efficient for the asymmetric hydrogenation of racemic cyclic α-amino ketones via DKR. Excellent enantioselectivities (89–99.9% ee) and cis-selectivities (cis/trans >99:1) were achieved in the hydrogenation of a wide range of racemic *N*,*N*-dialkyl or alkylarylamino cycloketones [Scheme 5, (15)] [64, 65]. The catalyst loading can be lowered to 0.0033 mol% (*S*/*C* = 30,000). In the asymmetric hydrogenation of *N*-monoalkyl/monoarylamino cycloketones, the catalyst (S_a,*R*,*R*)-**11d** is better than catalyst (S_a,*R*,*R*)-**11a** [Scheme 5, (16)].

Although excellent enantioselectivities and *cis*-selectivities have been achieved by Noyori's group and our group in the asymmetric hydrogenation of racemic α-substituted cyclic ketones, the asymmetric hydrogenation of the conformationally flexible substrates such as α-substituted acyclic aliphatic ketones is far from success. The catalyst (S_a,*R*,*R*)-**11a** was demonstrated to be highly efficient for the asymmetric hydrogenation of acyclic α-*N*,*N*-dialkyl/aryl and α-*N*-alkyl aliphatic ketones, yielding a series of chiral 1,2-amino alcohols in quantitative yields with excellent enantioselectivities (90–99.9% ee) and trans-selectivities (trans/cis 97:3 – 99:1) [66]. The catalyst loading could be as low as 0.01 mol% [Scheme 5, (17)].

A six-membered transition state model containing an additional hydrogen bonding between the amino group of the substrate and the protonic $N–H_{eq}$ of catalyst was proposed to explain significantly higher selectivities of asymmetric hydrogenation of α-amino aliphatic ketones than those obtained in the asymmetric hydrogenation of α-*N*-acylamino aliphatic ketones (Fig. 5).

These highly efficient Ru-catalyzed asymmetric hydrogenations have been successfully applied to the enantioselective synthesis of chiral drugs such as a highly selective κ-opioid agonist U-(−)-50,488 and natural piperidine alkaloid conhydrines [65].

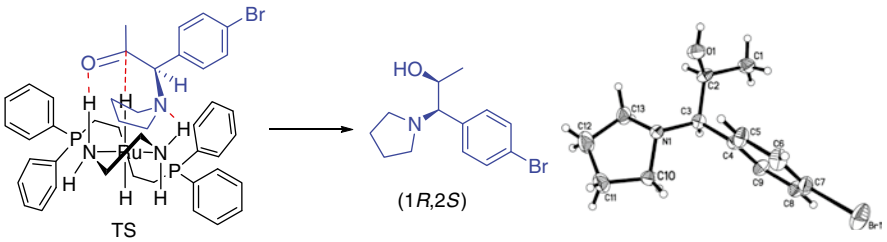
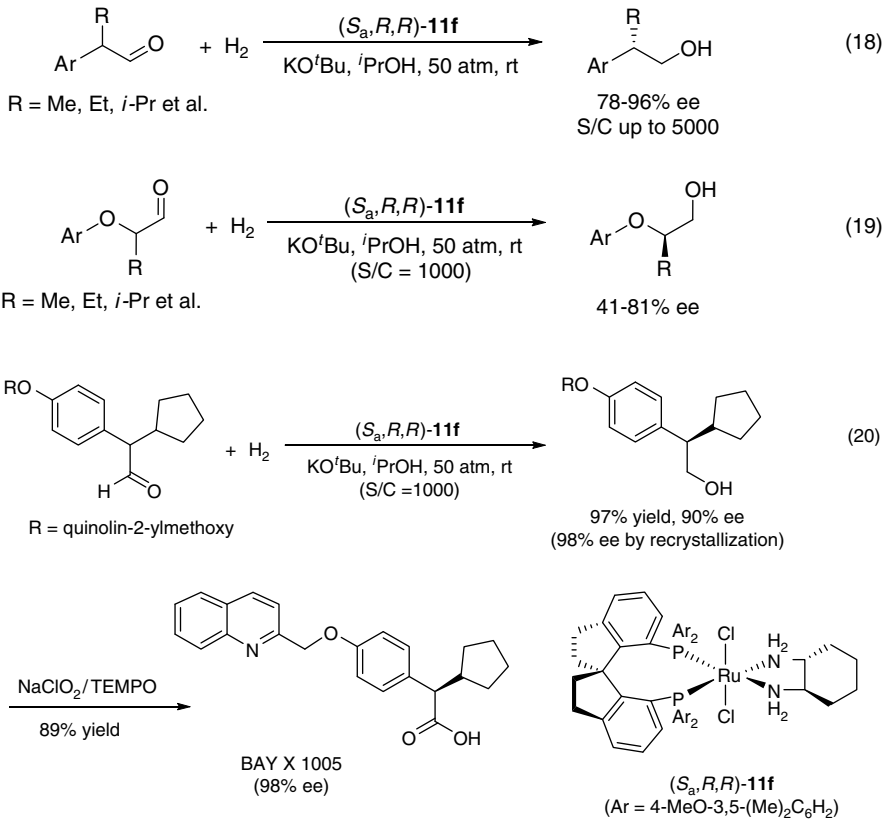


Fig. 5 Proposed model for the asymmetric hydrogenation of acyclic α-aminoketones

3.3.3 Asymmetric Hydrogenation of Racemic α-Arylaldehydes

Though exciting progress had been achieved in the asymmetric hydrogenation of ketones, no successful example of asymmetric hydrogenation of aldehydes, providing enantiopure primary alcohols, had been reported. Generally, in the hydrogenation of prochiral ketones, at least one new stereogenic center is formed; no new stereogenic center, however, is generated in the hydrogenation of aldehydes, which makes the enantiocontrol of the reaction extremely difficult. The catalyst (S_a,*R*,*R*)-**11f** having a diphosphine ligand (*S*)-DMM-SDP and a (*R*,*R*)-1,2-diaminocyclohexane was demonstrated to be very efficient for the asymmetric hydrogenation of racemic *α*-arylaldehyde via DKR, providing chiral α-substituted primary alcohols in good to excellent enantioselectivities (78–96% ee) [Scheme 6, (18)] [67]. The catalyst (S_a,*R*,*R*)-**11f** was also the choice of catalyst for asymmetric hydrogenation of racemic α-aryloxy aldehydes, offering the corresponding chiral β-aryloxy alcohols in high yields (92–98%) with moderate to good enantioselectivities (41–81% ee) [Scheme 6, (19)] [68].



Scheme 6 Asymmetric hydrogenation of aldehydes

The asymmetric hydrogenation of α-cyclopentyl quinolylmethoxyphenylacetaldehyde catalyzed by (S_a,*R*,*R*)-**11f** gave the corresponding chiral primary alcohols in 97% yield with 90% ee, providing a practical method for enantioselective synthesis of BAY × 1,005, an important leukotriene receptor antagonist and lipoxygenase inhibitor [Scheme 6, (20)] [69].

4 Asymmetric Carbon–Carbon Bond-Forming Reaction

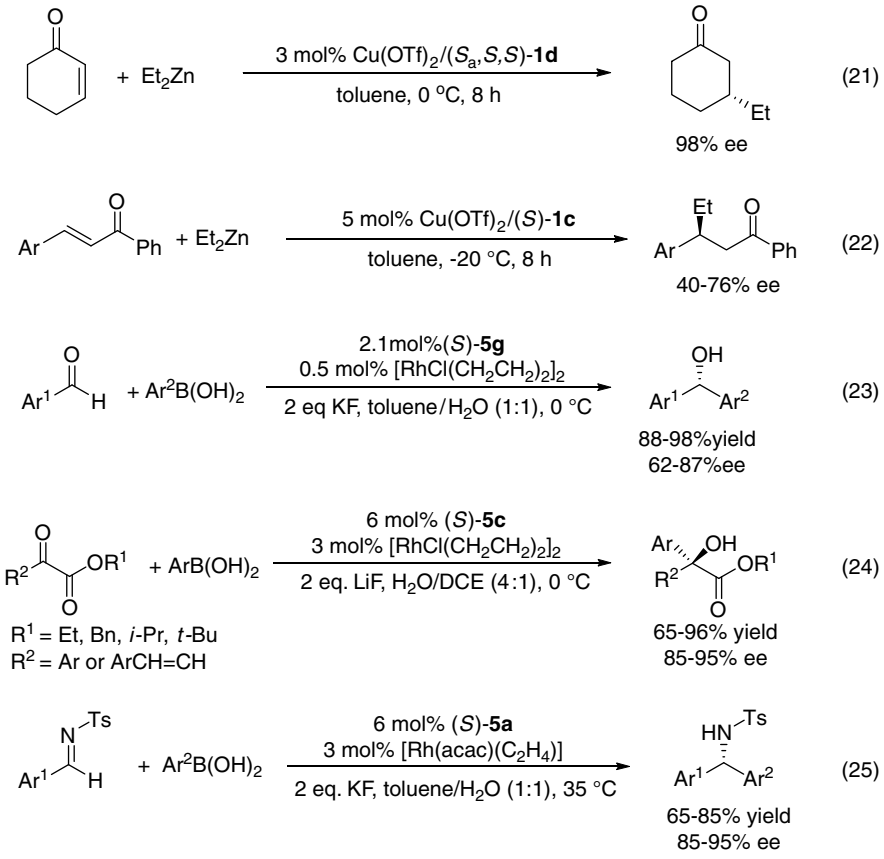
Asymmetric carbon–carbon bond formation reaction catalyzed by chiral metal complexes is one of the most essential and effective tools for the construction of chiral organic molecules. The catalysts derived from chiral spiro 1,1′-biindanyl ligands were demonstrated to be very effective in a number of such reactions, including Rh-catalyzed addition of arylboronic acids to aldehydes and *N*-tosylarylimines, Pd-catalyzed allylation of aldehydes, Cu-catalyzed ring opening reactions with Grignard reagents, as well as Ni-catalyzed hydrovinylation of vinylarenes.

4.1 Catalytic Asymmetric Addition Reactions

Among the catalytic asymmetric addition reactions leading to the formation of carbon–carbon bond, the Cu-catalyzed enantioselective 1,4-addition of organometallic reagents to α,β-unsaturated compounds has been extensively studied [70, 71]. Chiral spiro Cu-complex of SIPHOS ligand (S_a,*S*,*S*)-**1d** showed a high efficiency in the conjugate addition of diethylzinc to cyclohexen-1-one, providing the corresponding conjugate addition product in high yield (99%) and enantioselectivity (98% ee) [Scheme 7, (21)] [18]. For chalcone derivatives, Cu-complex of SIPHOS ligand (*S*)-**1c** gave a lower asymmetric induction (40–76% ee) [Scheme 7, (22)] [18].

Catalytic asymmetric 1,2-addition involves a direct addition of organometallic reagents to the carbonyl group of the substrates and yields chiral alcohol. Of which, the asymmetric addition of aryl organometallic reagents to aldehydes is a most attractive route to enantiopure diarylmethanols [72], key structural units of a number of pharmacologically active compounds [73]. The Rh-complex of ShiP ligand (*S*)-**5g** showed high enantioselectivities in asymmetric addition of arylboronic acids to arylaldehydes under mild conditions, yielding the corresponding diarylmethanols in excellent yields with up to 87% ee [Scheme 7, (23)] [24]. This result is better than that obtained by using Rh-MeO-MOP catalyst (41% ee) [74]. In the asymmetric addition of boronic acids to α-ketoesters, Rh-(*S*)-**5c** was the choice of catalyst to produce chiral tertiary α-hydroxyesters with good yields (51–96%) and high enantioselectivities (70–93% ee) [Scheme 7, (24)] [75].

Besides the outstanding performance of the asymmetric addition of arylboronic acids to carbonyl group, the rhodium complex of ShiP ligands (*S*)-**5** also exhibited high efficiency in the asymmetric addition of arylboronic acids to *N*-tosylarylimines,



Scheme 7 Asymmetric addition reactions with organometallic reagents

generating diarylmethylamines, important chiral building blocks for the synthesis of pharmaceutically active compounds. Among ShiP ligands, (*S*)-**5a** was found to be the best one, providing a series of chiral *N*-tosyl diarylmethylamines in good yields (65–85%) with excellent enantioselectivities (85–95% ee) [Scheme 7, (25)] [76].

The high enantioselectivity of Rh-(*S*)-ShiP catalysts is attributed to the effective asymmetric environment generated by two coordinating ShiP ligands around the Rh-center. From the crystal structure of [Rh(COD((*S*)-**5a**)$_2$)]BF$_4$ (Fig. 6), we can see that two phenyl groups of the ligands blocked the back side of the complex. The phenyl group of boronic acid transferred through rhodium favorably to the *Re* face of the aryl aldehydes (using aryl aldehyde as a typical example), yielding the corresponding diarylmethanols with *R* configuration, which is consistent with the result of X-ray analysis of a single crystal of the addition product.

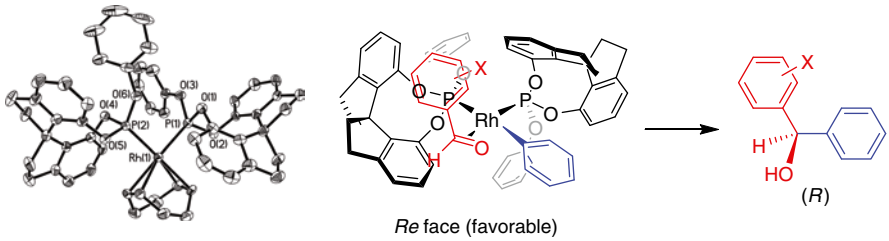


Fig. 6 Crystal structure of [Rh(COD)((*S*)-**5a**)$_2$]BF$_4$ and stereo-recognition model for addition of arylboronic acids to aldehydes

4.2 *Catalytic Asymmetric Allylation of Aldehydes with Allylic Alcohols*

Enantiopure homoallyl alcohols are important intermediates for the synthesis of many naturally occurring and pharmacologically useful molecules [77–79]. The catalytic asymmetric allylation of carbonyl compounds has become a reliable method for the preparation of chiral homoallylic alcohols [80–82]. Recently, Zanoni and co-workers developed a Pd-catalyzed asymmetric allylation of aldehyde with allyl esters by umpolung of π-allylpalladium complexes, yielding the homoallylic alcohols with up to 70% ee [83]. In the presence of Et_3B as a reducing reagent, the Pd-complex of SITCP ligand (*R*)-**6a** can promote the asymmetric allylation of aldehydes using allylic alcohols as allylation reagents, producing a series of chiral homoallylic alcohols with moderate to high enantioselectivities (58–83% ee) and excellent anti-selectivities (*anti*/*syn* 95:5–99:1) [Scheme 8, (26)] [25].

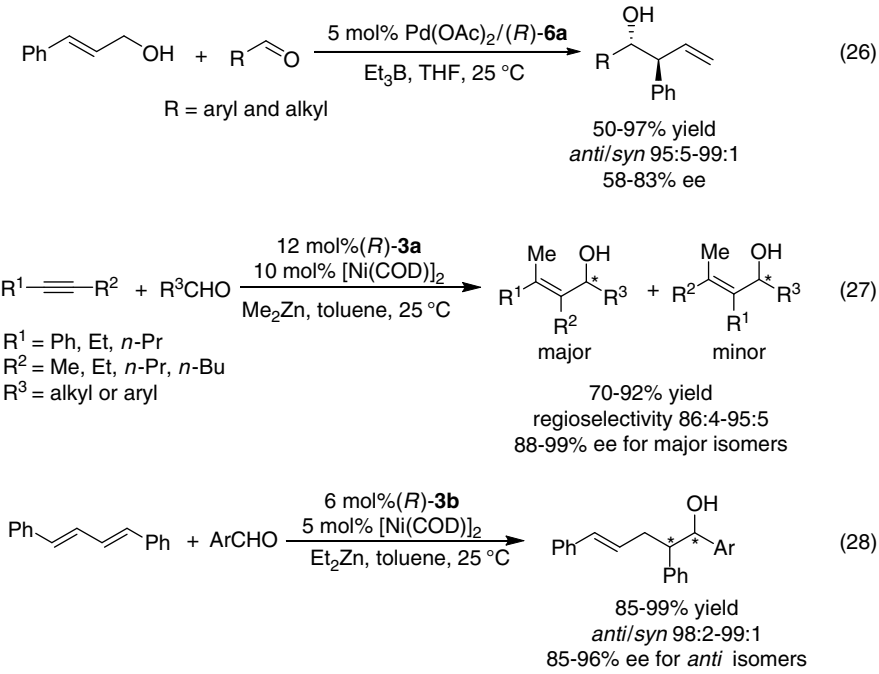
4.3 *Catalytic Asymmetric Coupling Reactions*

Ni-catalyzed coupling of carbonyl compounds and alkynes or 1,3-dienes is an efficient method for the preparation of allylic, homoallylic, and bishomoallylic alcohols [84]; however, only a few effective asymmetric versions of this transformation have been reported [85]. The 6,6′-diphenyl-modified SIPHOS ligands (*R*)-**3** showed excellent enantioselectivities and activities in Ni-catalyzed asymmetric alkylative and reductive coupling reactions.

In 1997, Montgomery and Oblinger reported the first example of Ni-catalyzed alkylative coupling reaction of alkynes with aldehydes [86]. This efficient alkylative coupling reaction involves a transfer of an alkyl group from organometallic reagents such as dimethylzinc (Me_2Zn) and the formation of two carbon–carbon bonds, and therefore is a highly efficient process for the preparation of allylic alcohols with a tetrasubstituted olefin. The Ni-complex of SIPHOS ligand (*R*)-**3a** was

found to be highly efficient chiral catalyst for this transformation [87]. With catalyst Ni-(*R*)-**3a**, the alkylative coupling reaction of aldehydes with alkynes was performed in the presence of Me_2Zn to produce a wide range of chiral allylic alcohols in high yields (70–92%) with excellent enantioselectivities (88–99% ee) and high regioselectivities (86:14–95:5) [Scheme 8, (27)]. This result represents the first example of Ni-catalyzed asymmetric alkylative coupling of aldehydes with alkynes.

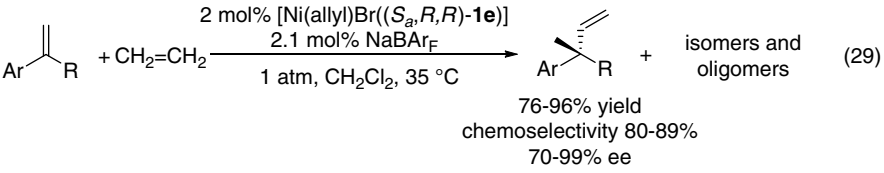
The asymmetric version of Ni-catalyzed reductive coupling of dienes with carbonyl compounds has been studied by Mori et al. in 2000 [88, 89]. By using a Ni-complex of a (2*R*,5*R*)-2,5-dimethyl-1-phenylphospholane ligand as a catalyst, Mori et al. realized intramolecular asymmetric reductive coupling reaction and obtained bishomoallylic alcohols with up to 86% ee. The Ni-complex of SIPHOS ligand (*R*)-**3b** with an N-morpholinyl group on the *P*-atom of the ligand is an extremely efficient catalyst for intermolecular asymmetric reductive coupling reaction. With this catalyst, a series of aldehydes reacted with 1,4-diphenylbuta-1,3-diene in the presence of Et_2Zn (1.2 eq), offering the corresponding chiral homoallylic alcohols in high yields with excellent enantioselectivities (up to 96% ee) and anti-selectivities (*anti*/*syn* >99:1) [Scheme 8, (28)] [20].



Scheme 8 Asymmetric alkylation, alkylative and reductive coupling of aldehydes

4.4 Catalytic Asymmetric Hydrovinylation Reactions

Nickel catalyzed asymmetric hydrovinylation of vinylarenes is an important carbon–carbon bond-forming reaction, and impressive progress has been achieved in the past decades [90, 91]. However, most of the studies focused on the hydrovinylation of vinylarenes, yielding chiral 3-arylbut-1-enes and their analogs with a chiral tertiary carbon center. Employing chiral Ni-complex of SIPHOS ligand (S_a,*R,R*)-**1e** as a catalyst, we realized the first example of highly enantioselective hydrovinylation of α-alkyl vinylarenes, generating the hydrovinylation products with a chiral all-carbon quaternary center [Scheme 9, (29)] [92]. The reaction has high yields (76–96%), excellent enantioselectivities (70–99% ee), and good chemoselectivities (80–89%).

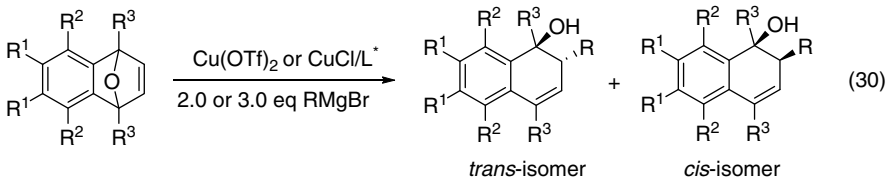


(29)

Scheme 9 Asymmetric hydrovinylation of α-alkyl vinylarenes

4.5 Catalytic Asymmetric Ring-Opening Reactions

Catalytic asymmetric ring-opening of *meso*-oxabicyclic alkenes with organometallic reagents is a powerful method to construct cyclic compounds with multiple chiral centers [93–95]. Many organometallic reagents such as dialkylzinc have been applied successfully in this reaction, and excellent stereoselectivities and enantioselectivities were achieved [94]. However, the Grignard reagent, the most readily available organometallic reagent, has been scarcely utilized in this reaction. The first example of asymmetric ring-opening with Grignard reagent was realized by using chiral Zr-complex as a catalyst, however with low yield (27%) and low enantioselectivity (48% ee) [96]. The Cu-complex of SIPHOS ligand (S_a,*S,S*)-**1d** was proven to be a efficient catalyst for asymmetric ring-opening with Grignard reagents, providing ring-opening products with good to high yields (54–90%) and moderate to good enantioselectivities [42–88% ee, Scheme 10, (30)] [97]. Further study showed that the Cu-complex of SITCP ligand (*R*)-**6e** is a more efficient catalyst. With Cu-(*R*)-**6e** as a catalyst and $NaBAr_F$ as an additive, various oxabicyclic alkenes reacted with alkylmagnesium bromide or chloride to yield the corresponding chiral ring opening products in high yields (72–93%) with excellent enantioselectivities (86–99.6% ee) and *trans*-selectivities (*trans*/*cis* >99:1) [Scheme 10, (30)] [26]. It is worth noting that the efficiency of this reaction is exceptional. For example, in the presence of 0.01 mol% catalyst Cu-(*R*)-**6e**, 1,8-dimethyl-11-oxabenzonorbornadiene



(30)

Ligand	conditions	yield [%]	*trans/cis*	ee [%][a]
(S_a,*S*,*S*)-**1d**	3 mol% $Cu(OTf)_2$ 6.3 mol% (S_a,*S*,*S*)-**1d** 2.0 eq RMgBr, toluene, -20 °C	54-90	97:3-99:1	42-88
(*R*)-**6e**	1 mol% $Cu(OTf)_2$ or CuCl 2.1 mol% (*R*)-**6e** 2.5 mol% $NaBAr_F$ 3.0 eq RMgBr, DCE, -20 °C	72-95	>99:1	86-99.6

[a] for *trans*-isomer.

Scheme 10 Asymmetric ring-opening of oxabicyclic alkenes

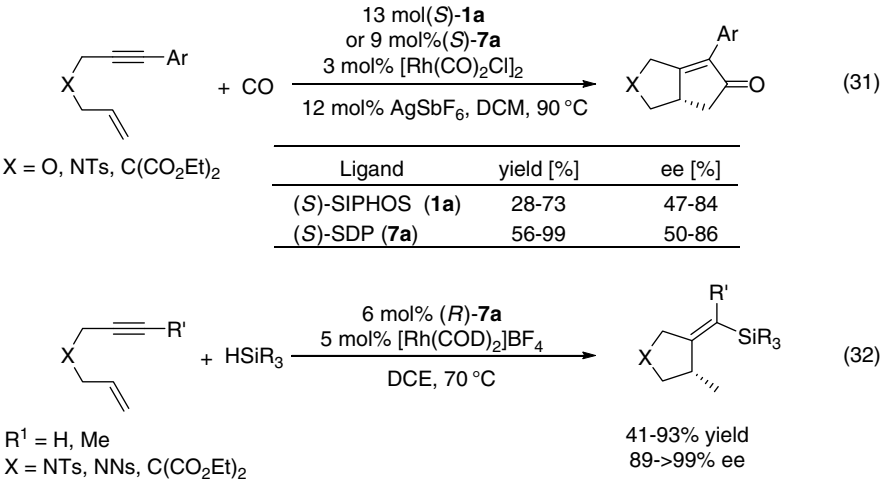
reacted with ethylmagnesium bromide in DCE at 10°C to yield the 2-ethyl-1, 4-dimethyl-1,2-dihydronaphthalen-1-ol in 90% conversion (73% yield) with 90% ee and 99:1 *trans*-selectivity. The TON of the reaction reached 9,000, which represents one of the highest TONs reported in the asymmetric carbon–carbon bond formation reaction employing Grignard reagents.

4.6 Catalytic Asymmetric Cyclization Reactions

Transition metal catalyzed cyclizations of 1,6-enynes have been emerged as the efficient and atom-economic methods for the synthesis of carbocyclic and heterocyclic compounds [98, 99]. Among them, the Pauson–Khand reaction (PKR) is one of the most powerful ones in which three carbon–carbon bonds and two five-membered rings are formed in one step. Recent progress showed that the catalytic asymmetric version of PKR can be achieved by employing chiral metal catalysts [100]. The Rh-complexes of SIPHOS ligand (*S*)-**1a** and SDP ligand (*S*)-**7a** were found to be effective catalysts for this transformation, offering a series of chiral bicyclic pentenones in moderate to high yields (28–73% and 56–99%, respectively) and enantioselectivities (47–84% ee and 50–86% ee, respectively) [Scheme 11, (31)] [101, 102].

Catalytic hydrosilylation/cyclization (silylcyclization) of 1,6-enynes is another important cyclization reaction, which was initially reported by Ojima et al. in 1992 [103].

The asymmetric version of this reaction was realized by Widenhoefer et al. by using Rh-BIPHEMP complex as a catalyst, producing silyalkylidene cyclopentanes in good to high enantioselectivities (77 – 92% ee) [104]. The Rh-complex of SDP ligand (*R*)-**7a** was found to be a superior catalyst for such cyclization reactions [Scheme 11, 32)] [105]. By using Rh-(*R*)-**7a** complex as a catalyst and trialkyl/arylsilanes ($HSiR_3$) or trialkoxysilanes ($HSi(OR)_3$) as hydrosilylating reagents, various C- or N-linked 1,6-enynes were silylcyclized to chiral silylalkylidene cyclopentane and pyrrolidine derivatives in moderate to high yields (41–93%) with excellent enantioselectivities (89–99.5% ee). However, the Rh-complexes of other chelating diphosphine ligands such as BINAP, SYNPHOS, and Me-DuPHOS gave lower enantioselectivities. These results apparently indicated that the rigid spiro backbone of SDP ligands was the key factor for achieving high enantioselectivity in the silylcyclization of 1,6-enynes.



Scheme 11 Asymmetric Pauson–Khand reaction and silylcyclization of 1,6-enynes

5 Asymmetric Carbon–Heteroatom Bond-Forming Reaction

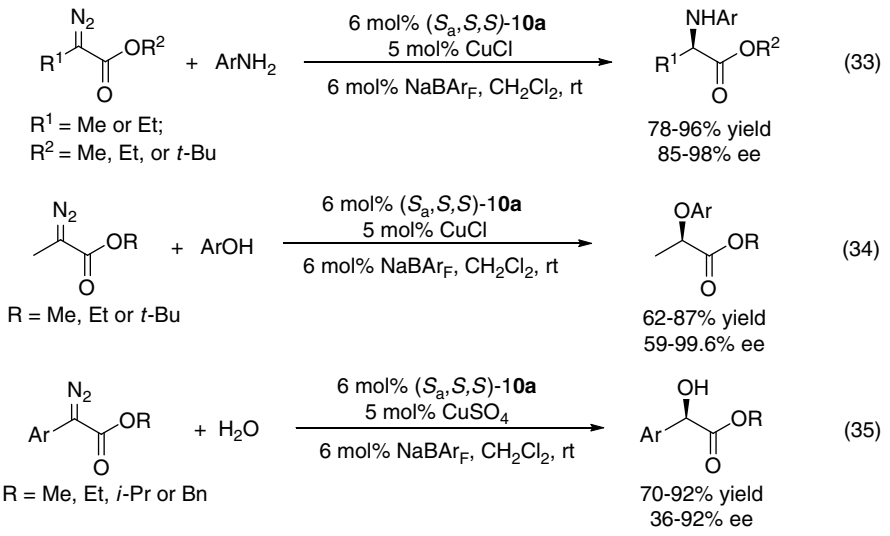
Another catalytic asymmetric reaction that received widespread attention is the enantioselective formation of carbon–heteroatom bonds. The asymmetric insertion of α-diazocarbonyl compounds, which are easily prepared from readily accessible precursors, into X–H (X = C, N, O) bonds is a very powerful transformation for preparing versatile chiral building blocks [106]. The chiral copper complexes of spiro bisoxazoline SpiroBOX ligands (S_a,*S*,*S*)-**10** showed exceptionally good enantioselectivity in the catalytic asymmetric insertion of α-diazoesters into the X–H (X = N, O) bonds of aromatic amines, phenols, or H_2O to form α-heteroatom-substituted esters.

5.1 Asymmetric Carbon–Nitrogen Bond-Forming Reaction

The N–H bond insertion of α-diazocarbonyl compound has been proven to be an efficient method for preparing α-amino ketones, α-amino esters, and nitrogen-containing heterocycles. However, only a few examples can be found in the literature about the asymmetric N–H bond insertion reaction and the obtained enantioselectivities are usually lower than 50% ee [107, 108]. The Cu-complex of SpiroBOX ligand (S_a,*S*,*S*)-**10a** was demonstrated to be a highly enantioselective chiral catalyst for the insertion of ethyl 2-diazopropionate into the N–H bond of anilines, providing α-arylamino esters in high yields (51–96%) with excellent enantioselectivities (85–98% ee) [Scheme 12, (33)] [109].

5.2 Asymmetric Carbon–Oxygen Bond-Forming Reaction

The catalytic insertion of an α-diazocarbonyl compound into an O–H bond represents a potentially attractive route to α-hydroxy derivatives. Recently, the asymmetric version of this insertion reaction has been achieved, but only the insertion of α-diazocarbonyl compounds into O–H bonds of alcohols gives high enantioselectivities. The insertion of α-diazocarbonyl compounds into O–H bond of phenols, as well as water is still a challenge [110]. By employing Cu-(S_a,*S*,*S*)-**10a** as a catalyst and $NaBAr_F$ as an additive, α-alkyl-α-diazoesters reacted with various phenols under mild conditions to yield α-aryloxyesters in good yields (62–87%) with excellent enantioselectivities (59–99.6% ee) [Scheme 12, (34)] [111]. Under similar conditions, the insertion of α-alkyl-α-diazoesters with water gave α-hydroxyesters in high yields (70–92%) and enantioselectivities (86–92% ee) [Scheme 12, (35)] [112].



Scheme 12 Asymmetric insertion of α-diazoesters into N–H and O–H bonds

6 Conclusion and Outlook

Based on the content of this chapter, it can be concluded that the chiral ligands containing a spirobiindane backbone are efficient for a wide range of catalytic asymmetric reactions, providing highly enantioselective methods for the preparation of optically active amino acids, amines, alcohols, as well as carboxylic acids. In many cases, the enantioselectivities achieved with chiral spirobiindane ligands are distinctly superior to those attained with the related chiral ligands having other backbones. These fantastic exhibitions demonstrated that the spirobiindane is a privilege scaffold for chiral ligands.

The intriguing chiral inducement of spirobiindane-based chiral ligands also causes much attention of other groups. Toste et al. applied spiro diphosphine ligand **7d** (Xyl-SDP) in Au-catalyzed cyclization of arylynylidenecyclopropanes and obtained a higher enantioselectivity against other ligands such as SegPhos and BINAP [113]. Ma et al. reported that the palladium complexes of SpiroBOX ligands **10e** and **10f** with α- or β-naphthylmethyl groups on the oxazoline rings are the best catalysts for the enantioselective cyclic allylation of 3,4-allenyl hydrazines [114] and cyclization of simple allenes with o-aminoiodobenzenes [115]. Fan and Chan et al. demonstrated that spiro phosphinite ligand SDPO is highly efficient for the Ir-catalyzed asymmetric hydrogenation of quinolines with high TON numbers and enantioselectivities [116]. Fu and Chung reported that spiro phospholane ligand **6a** (SITCP) itself can promote the enantioselective cyclization of hydroxyl-2-alkynotes to chiral oxygen-containing heterocycles with good enantioselectivities [117]. Furthermore, Kita et al. reported that chiral spiro organoiodine(III) derived from enantiopure SPINOL is an efficient chiral reagent for enantioselective oxidative dearomatization of phenols to construct chiral *ortho*-spirolactones [118]. These essential experiments further expand the application of spirobiindane-based chiral ligands/reagents in asymmetric synthesis.

Recently, a new type of spiro phosphine-oxazoline SpinPHOX ligands based on spiro[4.4]nona-1,6-diene backbone have been reported by Ding et al. [119]. The SpinPHOX ligands were successfully applied in Ir-catalyzed asymmetric hydrogenation of imines, providing chiral amines with excellent enantioselectivities (up to 98% ee). This result will encourage the development of efficient chiral ligands and catalysts with other spiro backbone.

The chiral ligands and catalysts play a crucial role in transition metal-catalyzed asymmetric reactions. The discovery of more efficient and enantioselective chiral ligands and catalysts will promote the development of highly economical, as well as environmental benign chiral technologies for the preparation of chiral compounds. Undoubtedly, the chiral spiro ligands and related catalysts offered a great potential for satisfying the requirements of mankind for chiral compounds.

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Chiral Phosphorus Ligands with Interesting Properties and Practical Applications

Fuk Loi Lam, Fuk Yee Kwong, and Albert S.C. Chan

Abstract Asymmetric transformations using a catalytic approach remain significantly important in organic synthesis, especially in the preparation of pharmaceutically interesting molecules. Indeed, chiral phosphorus ligands play an important role in this area. In this chapter, the recent development and advancement of chiral phosphines, phosphites, phosphoramides, etc. are reviewed. The potentially practical organic transformations are also described.

Keywords Asymmetric hydrogenation • Bisphosphine ligands • Enantioselectively catalytic bond-formation • Mixed-donor ligands • Transition-metal catalysts

Contents

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1 Introduction

Significant achievements have been made in chiral transition-metal complexes-catalyzed stereoselective organic transformations [1–3]. So far, most of these chiral catalysts are a combination of optically pure ligands and transition metals in various oxidation states. Often, the activity of the metal complexes can be modulated by varying the electronic properties of the ligands. With regard to stereochemical control, many structurally diverse phosphine ligands, especially the chelating C_2-symmetric atropisomeric diphosphines (e.g., BINAP, BIPHEMP and MeO-BIPHEP) prove to be highly effective for a myriad of asymmetric transformations.

Over the past two decades, enormous success has been achieved in the use of C_2-sysmmetric atropisomeric diphosphine ligands in Rh- or Ru-catalyzed asymmetric hydrogenation reactions. Irrespective to this, modification of the electronic/steric properties of these ligand systems in attempt to adjust the catalyst activity are far from trivial because of the difficulty and cumbersome procedure for structural modification of the ligand scaffold. Besides, due to the sensitivity of these chiral ligands/catalysts towards oxidation, the robustness of many of these transition metal-ligand systems, both well defined and in situ generated, has hardly been meticulously verified in solution under ambient conditions.

The catalytic properties of transition-metal complexes with chiral phosphine ligands embodying heterocyclic moieties such as pyridyl ring has been relatively unexplored even though the expansion of the scope of metal phosphine chemistry coupled with the rich chemistry of heterocycles is obvious. Here we present some recent development in the preparation of axially chiral biaryl diphosphine ligands based on heterocyclic scaffolds. Their uses in transition metal-catalyzed asymmetric synthesis will also be discussed [4]. The ligands described in this section are depicted in Fig. 1.

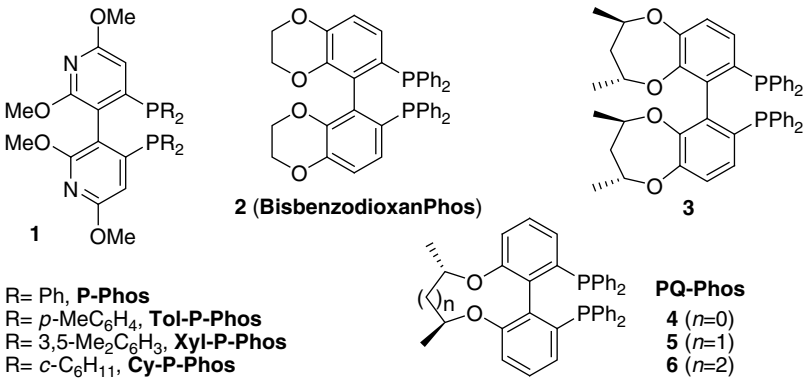


Fig. 1 Structures of diphosphine ligands containing heteroatoms

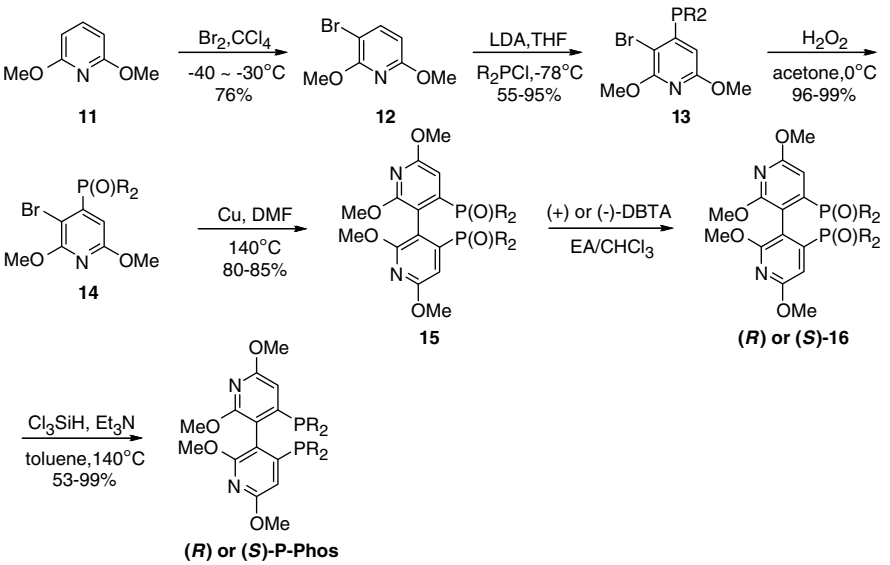
2 Development of New Chiral Diphosphine Ligands

2.1 Preparation of Bipyridyl Diphosphine Ligands

Earlier studies showed that rhodium and ruthenium complexes containing pyridylphosphine were ineffective catalysts for homogeneous hydrogenation of alkenes [5]. Competitive coordination of the unprotected pyridyl group to the metal center was thought to be the main reason for the poor catalytic activities. Having envisaged this, we embarked our research in the design and synthesis of a series of bipyridyl phosphine ligands bearing 2,2′,6,6′-tetramethoxyl groups, namely the P-Phos series, in which more hindered substituents were introduced to the *ortho* positions of the nitrogen atom. As such, steric effect should hinder access of the metal center to the pyridyl ring [6, 7]. Indeed, the Rh-P-Phos complexes were found to be effective for a variety of asymmetric hydrogenation reactions [8].

For the optimization of non-racemic diphosphines, the P-substituents represent an important structural or electronic module that can be systematically varied, and that a diverse range of chiral diphosphine ligands can be created for further examination. In this context, several P-Phos analogues: Tol-P-Phos [9], Xyl-P-Phos [10] and Cy-P-Phos [11] had been prepared by attaching different P-substituents onto the dipyridyl skeleton rather than changing the backbone itself. This modification approach is simple and straightforward for obtaining structurally distinct P-Phos analogues.

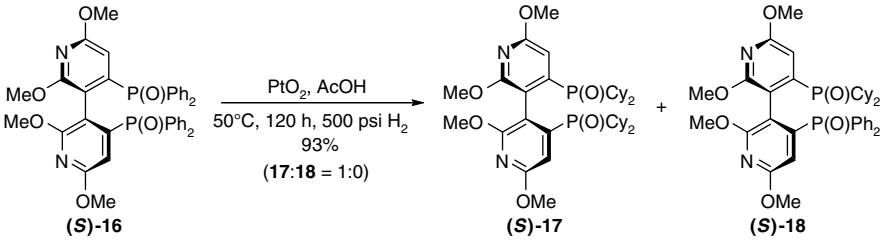
For preparation of the P-Phos ligands, the commercially available 2,6-dimethoxypyridine **11** was brominated at −40 to −30°C in CCl_4 to give compound **12**. Regioselective lithiation of **12** at *para*-position with LDA at −78°C in THF followed by treatment with chlorodiarylphosphine gave **13**. Oxidation of **13** with H_2O_2 led to the formation of the monophosphine oxide **14**. The racemic diphosphine dioxide **15** was obtained by copper-mediated Ullmann coupling of **14**, and followed by chiral resolution and subsequent reduction with trichlorosilane in the presence of triethylamine led to the target chiral ligands P-Phos (Scheme 1).



Scheme 1 Preparation of P-Phos dioxide

Racemic P-Phos dioxide **15** was resolved by fractional crystallization using enantiopure dibenzoyltartaric acid (DBTA) as resolving agent. The use of (−)-DBTA furnished the (*R*)-isomer, and (+)-DBTA provided the (*S*)-isomer of the diphosphine oxide. The absolute configuration of the corresponding enantiomer was established by single crystal X-ray diffraction studies.

With the enantiopure P-Phos oxide (*S*)-**16** in hand, the axially chiral bis(aryldicyclohexyl phosphine) dioxide [(*S*)-Cy-P-Phos oxide, (*S*)-**17**] was prepared via PtO_2-catalyzed hydrogenation [8]. Similarly, (*R*)-**17** was readily prepared from (*R*)-**16** (Scheme 2).

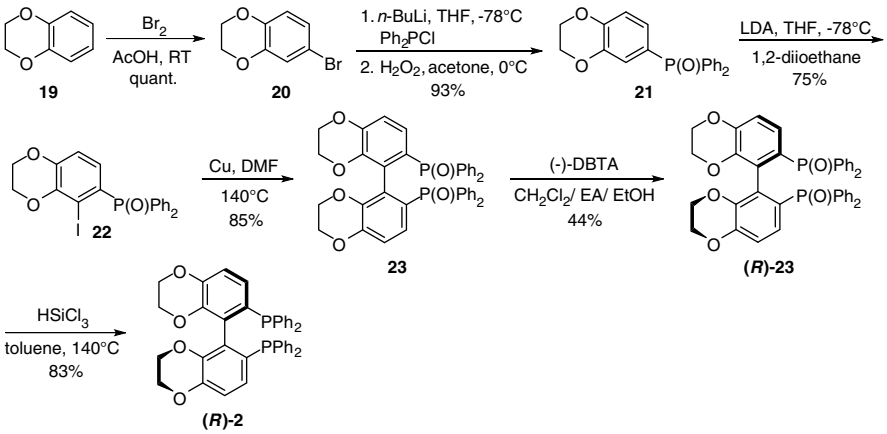


Scheme 2 Preparation of Cy-P-Phos oxide

In our initial attempt, the Pd/C system failed to catalyze the hydrogenation of (±)-**16** to the corresponding (±)-**17** using an ethanol–acetic acid mixture as solvent under 500 psi H_2 pressure at 50°C after 36 h. However, when PtO_2 was employed as catalyst, the reaction proceeded smoothly in acetic acid, and a mixture of the desired (±)-**17** along with some partially hydrogenated (±)-**18** (molar ratio as 5:1 based on ^{1}H and ^{31}P-NMR analyses) was obtained after 72 h at room temperature. The ratio of (±)-**17** and (±)-**18** was further improved to 10:1 when the reaction temperature was increased to 50°C within the same reaction time frame. Eventually, (±)-**17** was obtained exclusively by simply prolonging the reaction time to 120 h at 50°C. Thus, under identical conditions, optically pure **17** was obtained from the hydrogenation of the corresponding enantiomer of **16** [11].

2.2 Development of BisbenzodioxanPhos Ligand

Built upon the success of P-Phos and other related heteroaromatic phosphine ligands, we turned to the development of a new type of chiral ligand, BisbenzodioxanPhos [12], which was independently synthesized by Genêt et al. and was named SynPhos by these authors [13]. BisbenzodioxanPhos bears a bis-benzodioxane scaffold, a structural feature similar to that H_8-BINAP. This ligand is expected to exhibit good reactivity and selectivity in asymmetric catalytic reactions in which BINAP is uniquely useful. The dioxane moieties offer good opportunities for easy modification and tuning. Scheme 3 depicts the preparation of the chiral ligand. Bromination of a commercially available compound **19** gave the corresponding bromide **20** in almost quantitative yield. Lithiation of **20** with *n*-butyllithium in THF at −78°C, followed by the addition of chlorodiphenylphosphine and subsequent oxidation with hydrogen peroxide, produced phosphine oxide **21**. A sequence of *ortho*-lithiation/iodination with LDA via a thermodynamic-controlled process instead of the generally used iodination with diiodoethane gave product **22** in 75% isolated yield. The racemic bis(diphenylphosphine oxide) **23** was obtained in good yield (85%) via Ullmann coupling of the iodophosphine oxide **22**. The enantiomeric products **23** were resolved using either (−) or (+)-DBTA as the resolving agent. (*R*)-Phosphine oxide was obtained with (−)-DBTA as the resolving agent. The structure and the absolute configuration of (−)-DBTA.(*R*)-**23** was determined by X-ray crystallography. The chiral ligand BisbenzodioxanPhos (**2**) was obtained in over 99.9% optical purity after trichlorosilane reduction of **23** at 140°C.

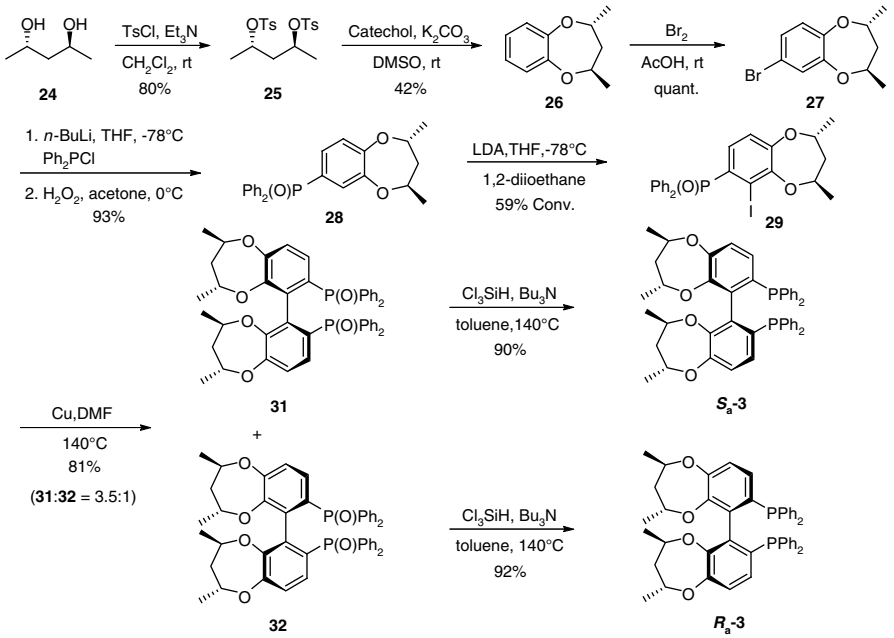


Scheme 3 Synthesis of BisbenzodioxanPhos

2.3 Diastereoselective Synthesis of Chiral Phosphine Ligands Without Resolution

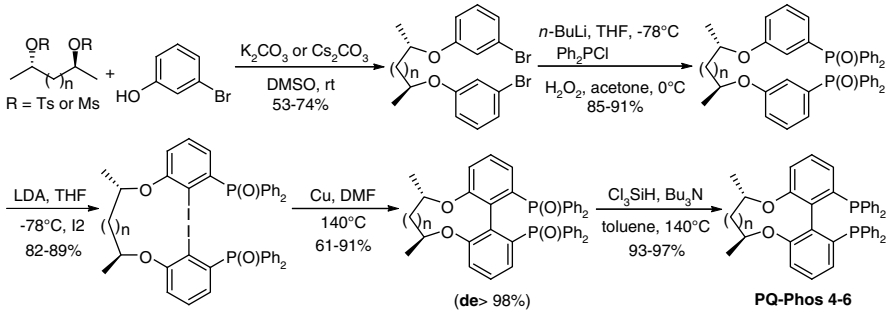
A classical method for preparing enantiomerically pure biaryl ligands involves aryl–aryl coupling followed by a resolution of the racemic atropisomers. The apparent disadvantage of the classical approach is that the maximum yield of the desired atropisomer cannot exceed 50%, and the enantiomeric purities of the ligands vary from high-to-moderate, not to mention that resolution procedures are frequently tedious. From a practical standpoint, it is desirable to develop efficient methodologies for the enantioselective synthesis of atropisomeric biaryl ligands. Various approaches, including desymmetrization of prochiral biaryls, [14] kinetic resolution of racemic substrate, [15] asymmetric catalytic coupling, [16–21] and chirality transfer from central, axial, and planar asymmetry have been reported [22–36].

Previously, most of the research focused on the syntheses of biphenols and binaphthols; however, diastereoselective syntheses of atropisomeric biaryl diphosphine oxides – the precursors of the chiral diphosphine ligands received less attention. In this regard, we pursued earlier a stereoselective intermolecular Ullmann coupling of two chiral phosphine oxides for synthesis of chiral atropisomeric diphosphine ligands. [37] As shown in Scheme 4, the reaction of catechol with (2*S*,4*S*)-pentanediol di-*p*-tosylate **25** derived from **24** gave (2*R*,4*R*)-2,4-dimethyl-3,4- dihydro-2*H*-1,5-benzodioxepine **26**. Subsequently, tandem functionalization furnished iodophosphine oxide **29**; copper-mediated Ullmann coupling gave a pair of diastereomers **31** and **32** (in a ratio of 3.5:1). With special care, both diastereomers of the chiral phosphine oxides **31**/**32** can be separated by column chromatography, and subsequent trichlorosilane reduction readily produced the target chiral ligands **3**.



Scheme 4 Diastereoselective synthesis of chiral ligand 3

To further improve the diastereoselectivity of the Ullmann coupling reaction, and to study the effects of the presence of additional chirality element as well as dihedral angle on the performance of the chiral ligands, we designed PQ-Phos type chiral ligands **4**–**6** ($n = 0$, 1, 2) (Scheme 5) [38, 39].



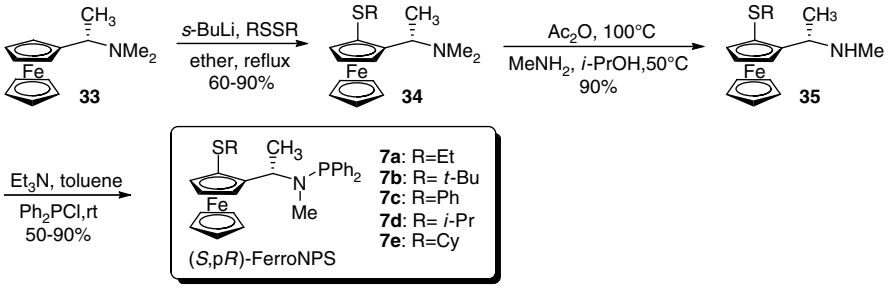
Scheme 5 Diastereoselective synthesis of PQ-Phos

Differing from chiral ligands **3** in which each aryl ring contains one chiral-inducing element, the two aryl rings in **4** were tethered by one chiral auxiliary derived from a chiral diol. The dihedral angle of the two aryl rings would be varied

by using different chiral diol, and such design was expected to have some positive effect on the stereoselectivity and reactivity of the chiral ligands. Similar to the preparation of **3**, preparation of the PQ-Phos series also started from sulfonate of optically pure chiral diols. Reaction of excess *m*-bromophenol with the chiral sulfonate produced the di(*m*-bromophenyl)ether. Subsequent conversion of the bromide to phosphine oxide, followed by Ullmann-type coupling, gave the desired chiral ligand **4**–**6** in almost complete diastereoselectivity (≥98%). Apparently, this route obviates the tedious and time-consuming resolution step. This method, in combination with the preparation of chiral ligands **4**–**6** would offer a general and practical tool for the development of previously unexplored atropdiastereomeric biaryl diphosphine ligands.

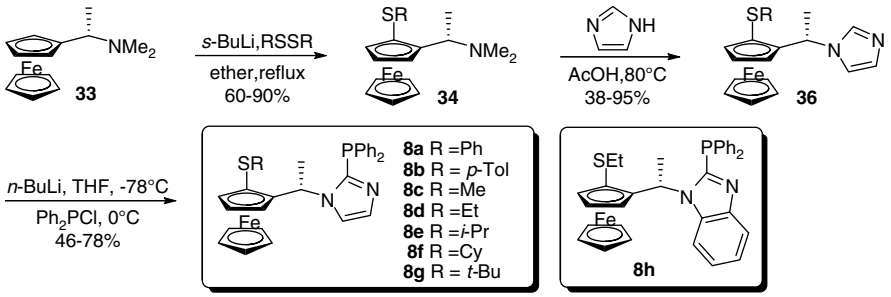
2.4 *Development of Chiral Ferrocenyl Phosphine-Sulfur Mixed-Donor Ligands*

We recently developed a convenient synthesis of Ugi amine (**33**) in an enantiomerically pure form by using Ru-(P-Phos)-catalyzed asymmetric hydrogenation of ferrocenyl methyl ketones [40] (For a large scale of production of chiral Ugi amine by asymmetric hydrogenation, see: [41]). This enantiopure Ugi amine is an important and versatile building block for further chiral ligand synthesis. In particular, a new family of P,S-type chiral ligands bearing a ferrocene scaffold with modular thioether moieties, namely (*S*,p*R*)-FerroNPS, were made (Scheme 6) [42]. The chiral intermediate aminothioether **34** was synthesized by diastereoselective *ortho*-lithiation of **33** using *s*-BuLi in Et_2O followed by quenching with disulfides (Scheme 6). Further treatment of **34** in hot acetic anhydride and aqueous methylamine solution gave ferrocenyl methylamine **35**. Phosphination of **35** using Ph_2PCl under basic conditions afforded enantiopure P,S-type ligands **7**. This route offered an easy pathway to an array of ligands with modular steric and electronic properties at both the thioether and phosphino moieties [43]. The thioether group of FerroNPS ligands in fact provided a tool for the structural modification of the ligands to achieve better results either on rate of reaction or enantioselectivity [44].



Scheme 6 Synthetic route of (S,pR)-FerroNPS chiral ligands

In 2007, we further developed a class of ferrocenyl P,S ligands **8** with imidazole or benzimidazole moiety (Scheme 7) [45]. Parts of their synthetic route are the same as FerroNPS, and aminothioether **34** which was obtained by diastereoselective *ortho*-lithiation of (*S*)-Ugi amine and tandem quenching with various disulfides. Reacting **34** with imidazole or benzimidazole in hot AcOH afforded compound **36** with retention of configuration at the central chirality. After a typical procedure of phosphination, ligands **8** were isolated in 46–78% yields.



Scheme 7 Synthetic protocol of chiral ferrocenyl ligands **8**

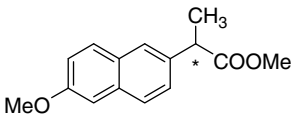
3 Application of Diphosphine Ligands in Asymmetric Catalytic Hydrogenations

Catalytic asymmetric hydrogenation is probably the simplest and yet the most powerful and economically attractive method for the production of amino acid derivatives, chiral amines, chiral alcohols, etc., which comprise a large proportion of enantiomerically pure pharmaceuticals. By utilization of various catalyst systems based on the P-Phos family of ligands, a broad scope of unsaturated substrates can be hydrogenated with high ees, which clearly shows the versatility of this new class of ligands.

3.1 Hydrogenation of C=C Bonds

3.1.1 Asymmetric Hydrogenation of Two-Substituted Propenoic Acids

Complex {(*R*)-P-Phos}Ru(acac)$_2$ was employed in the synthesis of the non-steroidal anti-inflammatory drug naproxen via the hydrogenation of 2-(6′-methoxy-2′-naphthyl) propenoic acid derivatives [8, 46]. An ee value of 95.3% was obtained at 0°C under a 1,000 psi H_2 pressure in methanol after 13–18 h. A marginal improvement (1–2%) was seen when 0.6 equiv of phosphoric acid was further added to the reaction mixture. The results compared favorably with the corresponding (*R*)-BINAP complex (94.8% ee).



Naproxen

When Ru[(*R*-**2**)Cl(*p*-cymene)]Cl was used as catalyst for the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid, the product naproxen was obtained in 91% ee. The stereoselectivity of the reaction compared favorably with that using BINAP as the chiral ligand under similar reaction conditions (89%, 1,000 psi H_2 pressure and ambient temperature) [13].

Ruthenium complexes of chiral ligand *S*a-**3** and *R*a-**3** were also tested for the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid. Results with respect to the observed enantioselectivities showed that [RuCl(*p*-cymene)-*R*a-**3**]Cl is a better catalyst than [RuCl(*p*-cymene)(*S*)-BINAP]Cl, which in turn produced better results than [RuCl(*p*-cymene)-*S*a-**3**]Cl. These findings indicated that the enantioselectivity of the hydrogenation reaction was mainly governed by the axial chirality, and the additional chiral auxiliary would influence the performance of the axially chiral ligand: better enantioselectivity was attained when the chirality of the chiral auxiliary matched the chirality of the biaryl moiety (in the case of *R*a-**3**).

Similarly, asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid with the PQ-Phos-based Ru-*S*a-**4** complex as catalyst afforded naproxen with up to 97% ee. The results indicated that introduction of an additional chiral auxiliary such as 2,3-butanediol would improve the stereoselectivity of the chiral catalyst when the chirality of the diol matched the chirality of the biaryl. Further, comparison of the results produced by ligands having different chiral auxiliaries indicated that the rigidity of the ether ring would influence the dihedral angle of the biaryl ligands, and therefore affect the stereoselectivity of the corresponding chiral catalysts.

3.1.2 Asymmetric Hydrogenation of (Z)-β-Aryl-Substituted α-(Acylamino)Acrylates

In the past three decades, Rh-catalyzed asymmetric hydrogenation of α-(acylamino) acrylic acids and their esters has been developed to be a standard procedure for the synthesis of optically active α-amino acids including bio-conjugates and building blocks for drugs and natural products, a variety of chiral ligands are suitable for this purpose. [1, 47–49] However, the corresponding chemistry mediated by ruthenium catalysts has been relatively less investigated, although ruthenium catalysts were widely applied in the enantioselective hydrogenation of other types of substrates [50].

The parent ligand P-Phos proved to be more effective than its analogues in the Ru-catalyzed low-pressure hydrogenation of (*Z*)-β-aryl-substituted α-(acylamino) acrylates in methanol, and the α-amino acid derivatives were obtained in 90–97% ee (Fig. 2) [51].

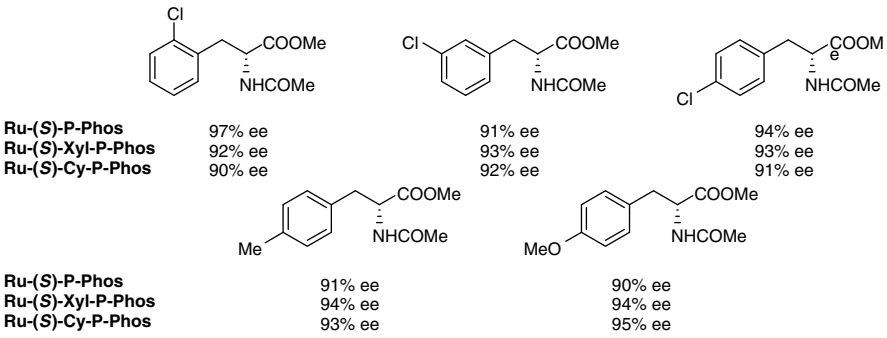


Fig. 2 Asymmetric hydrogenation of (Z)-β-aryl-α-(acylamino)acrylates by P-Phos

For the analogous hydrogenation reactions catalyzed by Rh(I) complexes of cationic P-Phos-type ligands, a sterically more encumbered catalyst was required for higher enantioselectivities. Quantitative yield of the products could be easily realized in a range of common organic solvents, while methanol was found to be the most suitable solvent. Therefore, a number of methyl (*Z*)-2-acetamidocinnamate derivatives were hydrogenated quantitatively with consistently high enantioselectivities (92–94% ee) in methanol for 18 h by using Rh-[(*R*)Xyl-P-Phos] as catalyst at 0°C under 1 atm hydrogen pressure.

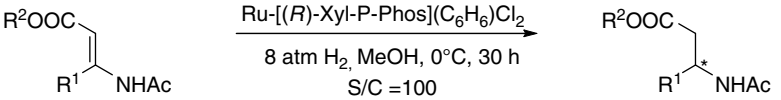
To evaluate the catalytic activities of Cy-P-Phos, this ligand was used in the Rh-catalyzed asymmetric hydrogenation of (*Z*)-β-aryl-α-(acylamino)acrylates [11]. Under the optimized conditions for the P-Phos ligand series, Cy-Phos exhibited similar enantioselectivity but substantially higher activity as compared to Xyl-P-Phos. In addition, acetone appeared to be the best solvent of choice, although the reactions could proceed smoothly in several other organic solvents.

3.1.3 Asymmetric Hydrogenation of (Z)-β-Alkyl-β-(Acylamino)Acrylates

Chiral β-amino acids have received considerable interest from researchers due to their unique structural properties, pharmacological activities, and usefulness as building blocks for the synthesis of numerous biologically active compounds such as β-lactams and β-peptides [52]. Employing chiral diphosphine-rhodium complexes (such as Rh complexes of BICP, DuPhos, MiniPhos, BDPMI, and TangPhos) as catalysts, the enantioselective hydrogenation of β-alkyl-substituted β-(acylamino) acrylates afforded good to excellent ees [48] . However, studies on the analogous ruthenium-catalyzed hydrogenation of similar substrates are comparatively limited. A few such substrates have been examined by Noyori and co-workers based on the $Ru(OCOCH_3)_2$-(BINAP) catalyst system [53] and the highest ee for the (*E*)-isomers of substrates was 96%.

In terms of both activity and enantioselectivity, Ru complexes of the P-Phos series displayed remarkably better utility in the enantioselective hydrogenation of

Table 1 Asymmetric hydrogenation of (E)-β-alkyl-β-(acylamino)acrylates



Entry	R1	R2	Conv. (%)	Ee (%)
1	Me	Et	>99	93 (*R*)
2	Me	Me	>99	92 (*R*)
3	*i*-Pr	Et	>99	98 (*R*)
4	Ph	Me	>99	98 (*R*)
5	Ph	Et	>99	98 (*R*)
6	$Ph(CH_2)_2$	Et	>99	98 (*R*)

(*E*)-β-alkyl-β-(acylamino)acrylates than the corresponding Rh complexes, irrespective of the ligand incorporated (Table 1) [54]. Interestingly, opposite enantioselection of hydrogenation by the Ru and Rh complexes of an identical chiral ligand was observed, which is in agreement with the findings by Lubell et al. [53].

When ruthenium complexes were used as the catalysts, the sterically hindered auxiliary ligand provided higher ees and faster reaction rates. The reaction was strongly solvent-dependent, and methanol was found to be the best solvent. Thus, using Ru-[(*R*)-Xyl-P-Phos] catalyst under the preferred conditions, a variety of β-amino acid derivatives were obtained in 97.9–99.7% enantiopurities. Yet, hydrogenation of the (*Z*)-isomers using the Ru-Xyl-P-Phos catalyst in methanol produced the markedly inferior enantioselectivity under otherwise identical conditions to that of the (*E*)-isomers.

The hydrogenation of (*Z*)-β-dehydroamino acids using [{(*R*)-Xyl-P-Phos}RuCl (η^6-benzene)]Cl as catalyst was not effective at all in aprotic solvents such as THF and CH_2Cl_2, and quantitative conversion was observed in MeOH with low ee. In contrast, the Rh catalyst exhibited much higher catalytic activities in THF, converting (*Z*)-β-alkyl-β-(acylamino)acrylates to the corresponding β-amino acid derivatives under 8 atm of hydrogen pressures and at ambient temperature. Nevertheless, the enantioselectivity remained moderate (68–82% ee). Again, the Rh- and Ru-complexes of the same ligands exhibited an opposite sense of asymmetric control.

The PQ-Phos type ligand *S*a-**4** in combination with a cationic Ru(II) complex was found to effect highly enantioselective hydrogenation of β-alkyl-substituted β-(acylamino)acrylates. Optimization studies revealed that methanol was the best solvent for this system. The hydrogen pressure had little influence on the enantioselectivity. Lower reaction temperature afforded higher enantioselectivity albeit with slower reaction rate. Excellent enantioselectivities were achieved in the hydrogenation of (*E*)-β-alkylsubstituted β-(acylamino)acrylates, and substrates with a bulky alkyl-substituent gave the best ee (up to 99.8%) [38].

Other ligands such as **5** or **6** also gave high ees in most of the asymmetric hydrogenation of (*E*)-β-alkylsubstituted β-(acylamino)acrylates, and no characteristic dependence of the enantioselectivity on the dihedral angles of the ligands was observed [39].

3.2 *Hydrogenation of C=O Bonds*

3.2.1 Asymmetric Hydrogenation of α-Ketoesters

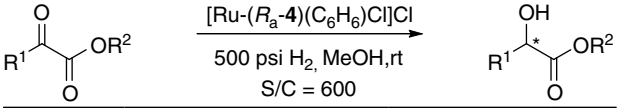
Enantioselective hydrogenation of α-ketoesters provides a direct approach to optically pure α-hydroxyesters, which are important building blocks for organic syntheses. Notwithstanding the success in the asymmetric hydrogenation of β-ketoesters, the homogeneous asymmetric hydrogenation of α-ketoesters has been substantially less developed [13, 55–64]. α-Ketoesters are known to be difficult substrates for asymmetric hydrogenation and often require delicate optimization of reaction conditions. Occasionally, acid additives may be necessary to increase both the activity and selectivity of the ruthenium catalysts for the hydrogenation of the keto group [59].

In the catalytic asymmetric hydrogenation of methyl benzoylformate, the Ru catalyst with *R*a-**4** afforded better enantioselectivity (97% ee) than that using BINAP (79% ee) as ligand [38, 39]. Other chiral ligands such as *S*a-**5** or *S*a-**6** also gave products with excellent enantiomeric excess. As expected, good results (91–92% ee) were obtained in the asymmetric hydrogenation of pyruvate. These ligands are also effective for the asymmetric hydrogenation of α-ketoesters with a bulky functional group R^1 such as *i*-Pr, Ph and $Ph(CH_2)_2$ etc. (Table 2).

3.2.2 Hydrogenation of β-Ketoesters

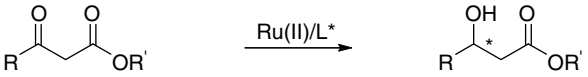
Optically pure β-hydroxy carboxylic esters are an important class of intermediates for the synthesis of bioactive or natural compounds [65, 66]. The first efficient asymmetric catalytic transformation of the β-ketoesters to β-hydroxyesters via transition metal complexes-catalyzed homogeneous hydrogenation was demonstrated by Noyori et al. utilizing BINAP/Ru(II) system [67]. Various ruthenium(II) complexes of the five-membered biheteroaromatic diphosphine series and the P-Phos family were also found to be well-suited for this transformation, providing

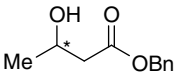
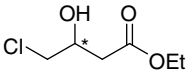
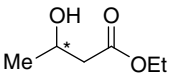
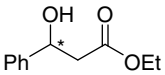
Table 2 Asymmetric hydrogenation of α-ketoesters catalyzed by Ra-4 complex



Entry	R1	R2	Conv. (%)	Ee (%)
1	Me	Et	>99	93 (*R*)
2	Me	Me	>99	92 (*R*)
3	*i*-Pr	Et	>99	98 (*R*)
4	Ph	Me	>99	98 (*R*)
5	Ph	Et	>99	98 (*R*)
6	$Ph(CH_2)_2$	Et	>99	98 (*R*)

Table 3 Asymmetric hydrogenation of β-ketoesters



	(*R*)-BINAP	(*S*)-P-Phos	(*R*)-Xyl-P-Phos	(*R*)-Tol-P-Phos	(*R*)-2
		96.6% ee	98.2% ee	96.6% ee	96.9% ee
		98.0% ee	97.9% ee	94.8% ee	97.0% ee
	99% ee	98.6% ee		97.1% ee	99.5% ee
	85% ee	95.2% ee	96.2% ee	96.2% ee	

enantioselectivities of up to 98% ee with the use of Tol-P-Phos [9]. In comparison, the asymmetric hydrogenation of 3-oxo-3-phenylpropionate employing the BINAP/Ru(II) system gave products with only 85% ee [67]. A comparison of the performance of several relevant ligands is shown in Table 3 [8–10].

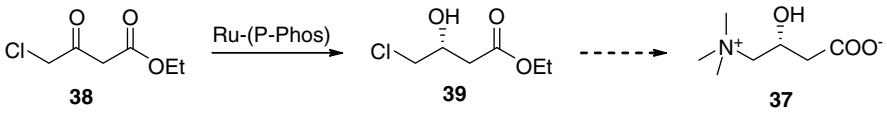
In the hydrogenation of substrates bearing a chlorine atom nearby the carbonyl group, the Ru-[(*S*)-BINAP] catalysts failed to give the desired products in satisfactory enantiopurities at room temperature. Elevated temperature (100°C) led to excellent chiral efficiency (97% ee) under 100 atm H_2 pressure [68]. Interestingly, the employment of Ru-P-Phos [8] or Tol-P-Phos [9] complexes furnished higher enantioselectivity (98% ee) under relatively milder conditions (80°C, 4–20 atm H_2).

Asymmetric hydrogenations of β-ketoesters catalyzed by the ruthenium complexes of BisbenzodioxanPhos such Ru[(*R*-**2**)$Cl_2$$(DMF)_n$] were carried out under 50 psi H_2 pressure at 80–90°C. The results revealed that the catalytic reactions are highly effective in producing alcohols of up to 99.5% ee [12].

When catalysts Ru-**3**-$Cl_2$$(DMF)_n$ were applied to the asymmetric hydrogenation of β-ketoesters, the enantioselectivities for the corresponding products were also very high and compared favorably with the Ru[(*S*)-BINAP]$Cl_2$$(DMF)_n$ system [37]. In the asymmetric hydrogenation of methyl acetoacetate, 99.8% ee was obtained when the reaction was catalyzed by the Ru-(*S*a-**4**) complex [38, 39].

Carnitine (**37**), also known as L-carnitine (*levo*-carnitine), is a quaternary ammonium compound derived from the amino acid lysine and is responsible for the transport of fatty acids from the cytosol into the mitochondria. This compound is often sold as a nutritional supplement. Traditionally, chemical synthesis of optically pure L-carnitine was carried out through resolution, and asymmetric hydrogenation of β-ketoesters would be one of the most efficient routes to this important compound. We found that asymmetric hydrogenation of 4-chloro-3-oxo-butanoate (**38**) proceeded readily in the presence of Ru-(P-Phos) complex, leading to the

corresponding 3-hydroxyl product **39** in high yield and high ee (Scheme 8). Compound **39** is the key intermediate for L-carnitine and can be easily converted to the final product via routine chemistry [69].



Scheme 8 Synthesis of optically pure carnitine

3.2.3 Asymmetric Hydrogenation of Simple Ketones

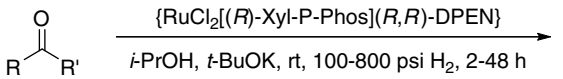
Simple secondary alcohols are important chiral intermediates, and a number of methods have been developed for the production of this type of compounds (For a review, see: [70]). However none of these methods live up to the expectations of industrial requirements because of high catalyst loading required to ensure a reasonable conversion as well as enantioselectivity of the reaction. Moreover, asymmetric hydrogenation of simple ketones was also problematic due to the lack of a contiguous ancillary coordinating group in the substrate.

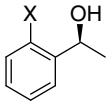
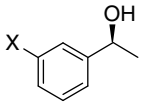
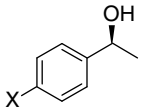
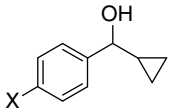
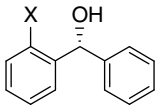
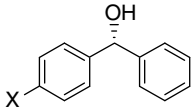
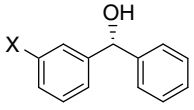
An important breakthrough was made when Noyori's group developed the BINAP-DIAPEN catalyst system [71]. Coupled with a catalytic amount of a strong base, a diverse array of unfunctionalized simple ketones were hydrogenated with a substrate-to-catalyst ratio of over two million, and yet, retaining high stereoselectivity.

When Xyl-P-Phos was used, a much cheaper diamine (*trans*-1,2-diphenylethylene diamine, DPEN) was sufficient to attain high degree of enantio-induction without using the exotic DAIPEN diamine. Excellent ees have been obtained for the hydrogenation of a variety of aryl-substituted acetophenones, heteroaryl methyl ketones and aryl cyclopropyl ketones with up to >99% ee at *S*/*C* ratio of 100,000. As for unsymmetrical benzophenones, the position of the substituent has an enormous effect on enantioselectivity. *Ortho*-substituent on the benzene ring usually provides steric bias for excellent stereocontrol. However, *meta*- or *para*-groups are too distant to exert significant stereodiscrimination, and the products with only low to moderate ees were obtained. In addition, a profound electronic effect was observed for the hydrogenation of *para*-R-C_6H_4-COPh. When R was a methyl group, product with 3.9% ee was obtained while this methyl group was fully fluorinated (R = CF_3), the ee value rose up to 77.2% (Table 4) [40].

Most of the well-known chiral ferrocenyl ligands with 1,2-disustituted functionalities are originally derived from chiral Ugi amine (Fig. 3). However, the laborious procedure for accessing an optically pure Ugi amine by resolution is expensive. In this regard, our group developed a convenient method for the synthesis of the versatile Ugi amine and its derivatives via the asymmetric hydrogenation of ferrocenyl ketones [41] in which up to 150 g-scaled prochiral ketones were successfully transformed to the corresponding enantio-enriched ferrocenyl

Table 4 Ru-catalyzecd asymmetric hydrogenation of ketones



	X	S/C	Ee (%)
	H	100,000	99.1
	Me	4,000	97.7
	OMe	4,000	93.3
	Br	10,000	>99.9
	Me	12,000	97.7
	OMe	4,000	98.8
	Br	4,000	99.5
	Me	20,000	98.8
	OMe	20,000	98.7
	Br	50,000	>99.9
	CF3	12,000	97.7
	H	5,000	97.6
	OMe	1,000	96.1
	F	2,000	92.0
	Cl	5,000	92.3
	Me	2,000	95.9
	F	2,000	97.6
	Cl	10,000	97.4
	Me	2,000	3.9
	Cl	2,000	47.3
	CF3	2,000	77.2
	Me	2,000	43.2

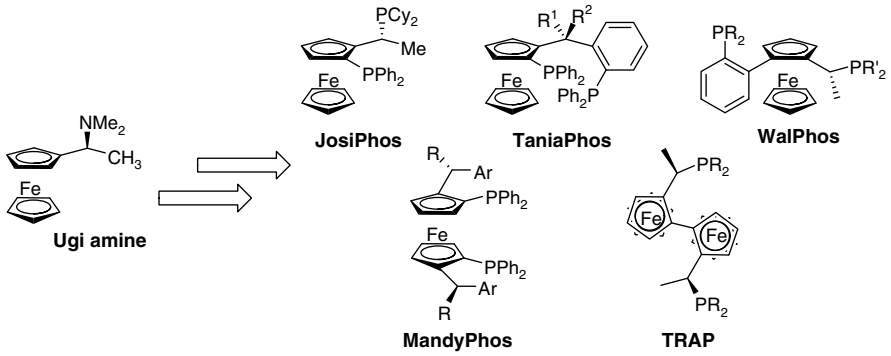
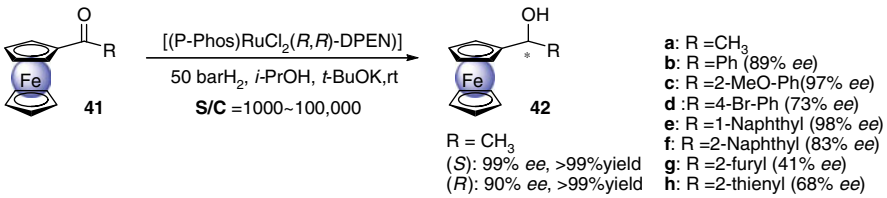
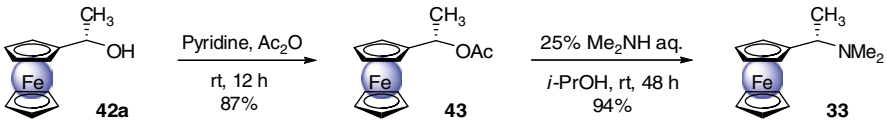


Fig. 3 Various ferrocenyl chiral ligands derived from the chiral Ugi amine

precursors in an enantioselective catalytic manner (Scheme 9). The precursors can be further converted into the optically pure Ugi amine in (*S*)- or (*R*)-configuration by a simple transformation (Scheme 10) [72, 73].



Scheme 9 Asymmetric hydrogenation of prochiral ferrocenyl ketones



Scheme 10 Transformation of ferrocenylethanol to Ugi amine

3.2.4 Asymmetric Hydrogenation of Enol Acetates

Asymmetric hydrogenation of enol acetates is an attractive alternative to the direct hydrogenation of unfunctionalized ketones. In addition to a π-donating olefin group, this type of substrate supplies a secondary donor group for chelation, which is helpful for obtaining high enantioselectivities in hydrogenation. Most of the studies on this reaction focused on using Rh-phosphines as catalysts. The use of the Ru-phosphine system in this reaction is limited in the literature [74, 75]. In our study of the asymmetric hydrogenation of enol acetates, it was found that asymmetric hydrogenation using *R*a-**3** as chiral ligand produced the corresponding product with enantioselectivity similar to those obtained using the Ru-TunaPhos system. In the hydrogenation of relatively electron-rich substrates such as 1-(4-methoxyphenyl)-1-(acetyloxy)ethylene and 1-phenyl-1-(acetyloxy) ethylene, no reaction was observed with Ru-TunaPhos as catalyst [75]. Yet, the Ru-**3** catalyzed reaction still brought about effective formation of the desired products in high ees (up to 94.9%).

3.2.5 Asymmetric Catalytic Hydrosilylation of Simple Ketones

The development of asymmetric hydrosilylation of prochiral ketones as a desirable alternative to asymmetric hydrogenation could be highly rewarding due to the mild reaction conditions employed and the technical simplicity. However, the high cost of the catalysts and the rather low substrate-to-catalyst ratio ($S/C = 50–500$) rendered previous hydrosilylation work not competitive with hydrogenation [76, 77].

By using the Buchwald's protocol for conjugate reduction [78, 79], Lipshutz and co-workers disclosed a highly active $Cu^{I}Cl$/diphosphine (e.g., 3,5-xyl-MeO-BIPHEP or DTBM-SegPhos)/*t*-BuONa/polymethylhydrosiloxane (PMHS) system for the enantioselective hydrosilylations of both aryl alkyl and heteroaromatic ketones even at a substrate-to-ligand ratio (*S*/*L*) of over 100,000 [80–82]. Recently, they also described a robust $Cu(OAc)_2 \cdot H_2O$/DTBM-SegPhos/PMHS hydrosilylation system (CuH in a bottle) [83, 84], which offered a new opportunity for asymmetric hydrosilylation in conjunction to practical applications.

At the time that we initiated our investigation in this area, we noted an air-accelerated and base-free CuF_2/BINAP/$PhSiH_3$ system demonstrated by Riant et al. which catalyzed the hydrosilylation of some aryl alkyl ketones in moderate to good ees at lower *S*/*L* ratios of 100–200 under ambient conditions [85]. Although the mechanism of this air-accelerated system remained elusive at that stage, it appeared that air played a key role in the formation of the active catalyst precursor in the catalytic cycle, and the much less air-sensitive diphosphine ligands would therefore be very crucial to the generation of the active catalyst systems. We then conjectured that our P-Phos-type ligands embracing unique air stability might be especially suited for this important reaction.

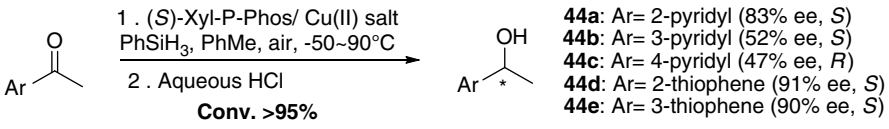
Indeed, the dipyridylphosphine/CuF_2/$PhSiH_3$ system served as an effective system rendering competitive levels of enantioselectivities of up to 97% ee for the hydrosilylation of *para*-substituted acetophenones [86]. Moreover, the excellent practical viability of this catalyst system was evident by its remarkably high activities (*S*/*L* ratio up to 100,000) and very mild reaction conditions such as normal atmosphere, moderately low temperatures (ambient temperature to −20°C) and compatibility with traces of moisture.

Polymethylhydrosiloxane (PMHS) is an attractive reducing reagent for environmentally benign reductive processes since it is inexpensive, nontoxic, and stable to air and moisture [87]. In light of this, the efficiency of the present catalyst system using PMHS as the hydride source has been examined. The sense of enantioselective induction appeared to be independent of silane regardless of using either P-Phos or Xyl-P-Phos, but PMHS was less reactive than $PhSiH_3$. For instance, when the hydrosilylation of acetophenone was carried out with 1 mol% CuF_2 and 0.05 mol% (*S*)-Xyl-P-Phos with 1.2 equiv of $PhSiH_3$ at room temperature under air atmosphere, complete conversion was observed in 10 min with 76.7% ee, whereas, in the case of PMHS, 76.8% conversion was achieved within 25 min with 75.3% ee under otherwise identical conditions.

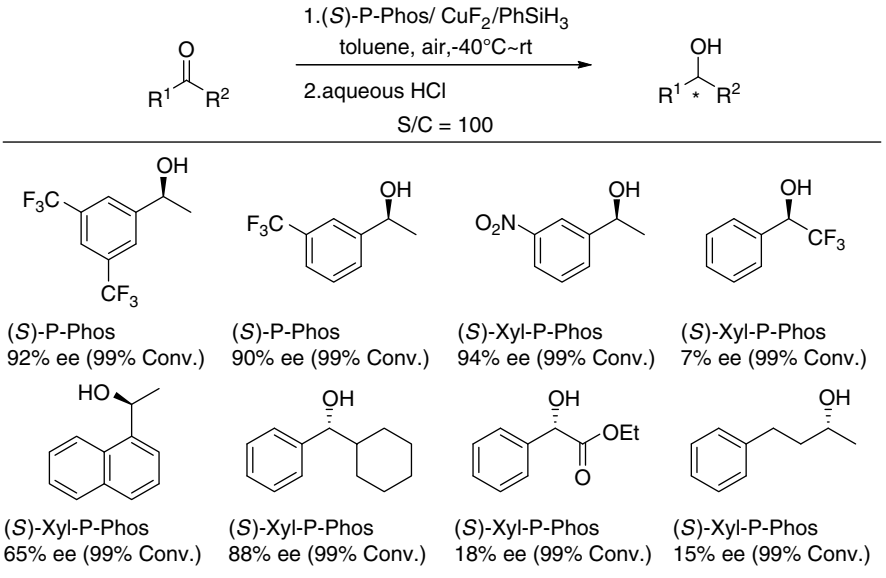
In addition, the enantioselective hydrosilylation of unsymmetrical diaryl ketones to benzhydrol had remained a formidable challenge, and the highest enantioselectivity reported in the literature prior to our study was around 20% ee [88]. In this regard, the P-Phos catalyst system was found to be surprisingly effective in the stereoselective hydrosilylation of *ortho*-substituted benzophenones with good to excellent ees (up to 98%) [86]. As expected, because of the lack of steric bias, *meta*- and *para*-substituted benzophenones were converted to the corresponding alcohols in low to moderate ees.

Optically active alcoholic compounds with heterocyclic moieties serve as useful building blocks for a vast array of physiologically active target products [89, 90]. The

asymmetric hydrosilylation of heteroaromatic ketones to these alcohols represents a harsh challenge for chemists [91]. Lipshutz et. al. found that the heteroaromatic ketones were converted to the corresponding alcohols in good-to-excellent enantiopurities by using a SegPhos-ligated CuH catalytic system [82]. Recently, we have successfully established an asymmetric hydrosilylation system, (*S*)-P-Phos/Cu(II)salt/$PhSiH_3$, in the effective reduction of heteroaromatic and several other type of ketonic substrates [92]. In this study, hydrosilylation of three pyridyl ketones (**44a-c**) was performed by (*S*)-P-Phos/ or (*S*)-Xyl-P-Phos/CuF_2 in air at various temperatures, and remarkable temperature effects on the asymmetric induction of the pyridyl ketones were observed. The combination of (*S*)-Xyl-P-Phos/ $Cu(OAc)_2 \cdot H_2O$, an air- and moisture-stable catalyst system, quantitatively provided the desirable product in 91% ee (**44d**) and 90% ee (**44e**), respectively (Scheme 11). To the best of our knowledge, this is the first highly effective copper-catalyzed enantioselective hydrosilylation of acetyl thiophene-type substrates. The catalyst system of CuF_2/(*S*)-P-Phos/$PhSiH_3$ was employed to transform several ketonic substrates to crucial chiral intermediates of physiologically active targets depicted in Scheme 12. This catalytic system features widespread substrate scope, high air stability, fast rate of reaction, good-to-excellent enantioselectivity, and mild reaction conditions and thus affords a practical protocol to access optically enriched alcohols.



Scheme 11 Cu-catalyzed asymmetric hydrosilylation of acetyl pyridines and thiophenes

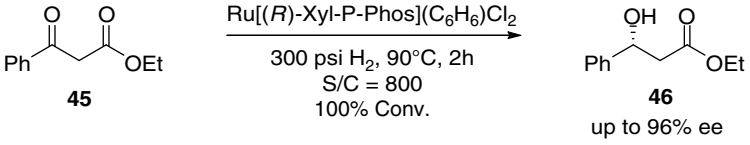


Scheme 12 Cu-catalyzed asymmetric hydrosilylation of several ketonic substrates

3.2.6 Activity and Air Stability of the Ru-(P-Phos) Catalyst System

The hydrogenation of 3-oxo-3-phenyl propionate leads to a useful pharmaceutical intermediate, (*S*)-3-hydroxy-3-phenyl propionate [93]. In the presence of Ru[(*R*)-Xyl-P-Phos]-$(C_6H_6)Cl_2$, the reaction with a substrate-to-catalyst molar ratio (*S*/*C*) of 800 was completed in 2 h, giving the desired product in up to 96.2% ee [10]. Even with a substrate-to-catalyst ratio as high as 7,500, the hydrogenation can be conveniently conducted on a 30 g substrate scale leading to 98% conversion within 15 h with the retention of high enantioselectivity (93.2% ee).

Further, the Ru complexes of the P-Phos family of ligands have been found to be highly air stable. When experimental procedures prior to the charging of hydrogen were performed in air and solvents without pre-degassing and drying, or even when the catalyst solution was exposed to air for 10 h before its application, both the catalyst activity and enantioselectivity for the hydrogenation of **45** remained unchanged (Scheme 13, 100% conversion, 95.5–96.1% ee for product **46**) from the air-purged system (96.2% ee) [10], while the ee obtained from using Ru[(*R*)-BINAP]$(C_6H_6)Cl_2$ as catalyst precursor, in a side-by-side comparison study, sharply dropped from 92.0 to 66.6%.



Scheme 13 Ru-catalyzed asymmetric hydrogenation of β-ketoester

3.3 Asymmetric Hydrogenation of C=N Bonds

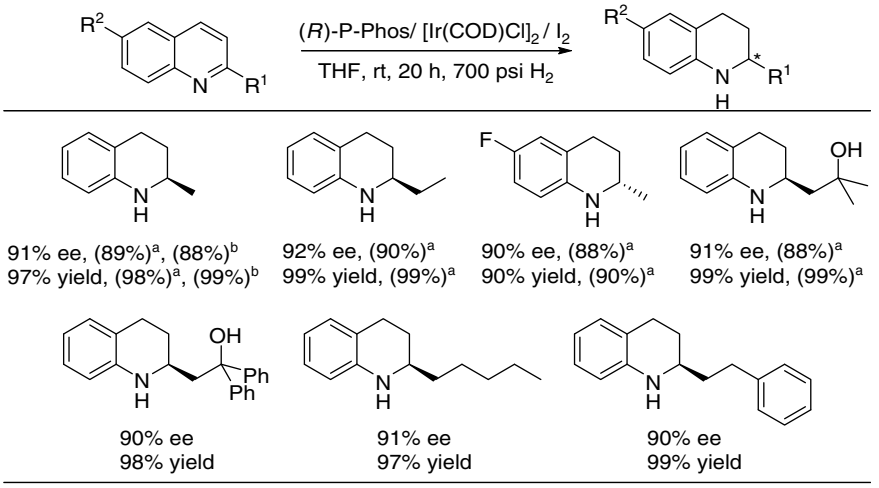
The asymmetric hydrogenation of C=N bonds is an appealing protocol for the synthesis of chiral amines. The enantioselective hydrogenation of quinolines, and other *N*-heteroaromatic compounds can provide enantiomerically pure tetrahydroquinoxalines and heterocycloalkanes of great biological interest [94, 95].

The catalytic asymmetric hydrogenation of easily accessible and less expensive quinoline derivatives is doubtlessly the most direct and convenient access toward enantiomerically enriched tetrahydroquinoline derivatives, which are significant synthetic intermediates for biologically active compounds [96]. Reports on this methodology are rather scarce. Zhou and co-workers recently discovered that iridium complexes bearing MeO-BIPHEP or ferrocenyloxazoline-derived P/N-ligand performed effectively for this conversion into optically active tetrahydroquinolines containing a chiral carbon at the 2-position [97–99].

Iridium complex generated in situ from $[Ir(COD)Cl]_2$ and P-Phos in combination with 0.1 equiv of I_2 in THF served as a highly efficient catalyst system for the hydrogenation of this class of challenging substrates at room temperature (Scheme 14) [100], furnishing hydrogenation products in 90–92% ee. Meanwhile,

we found that the Ir-(P-Phos) catalyst was particularly robust and air-stable. No deterioration was detected according to the ^{31}P NMR spectrum of the catalyst solution even after two weeks in air. The reactivity and enantioselectivity for the hydrogenation of 2-methylquinoline were virtually retained even though the catalyst solution had been exposed to air for 24 h before use. In contrast, sharp diminutions both in conversion (from 99 to 21%) and in ee (from 94 to 28%) occurred if Ir-(MeO-BIPHEP) was used under the same conditions.

Given the high efficiency and the air stability of the Ir-(P-Phos) catalyst system, we further explored the recyclability of this catalyst using 2-methylquinoline as a model substrate. By using a two-phase reaction medium involving a 1:1 mixture of hexane and poly(ethylene glycol)dimethyl ether (DMPEG), complete conversion and high enantioselectivity were essentially maintained (89% ee vs. 91% ee in THF). Most importantly, the product was conveniently separated by simple decantation of the hexane layer. Upon extraction of the product residue with hexane, the DMPEG phase encompassing the Ir-(P-Phos) catalyst could be reused. In a catalyst reusability study, we observed essentially no loss of the ee after eight times of recycle (Scheme 14).



Molar ratio of substrate: Ir: L*: I_2=100: 0.5: 1.1: 10. [a]The mixture of DMPEG/hexane mixture was used as solvent instead of THF. [b]The catalyst was recycled 8 times.

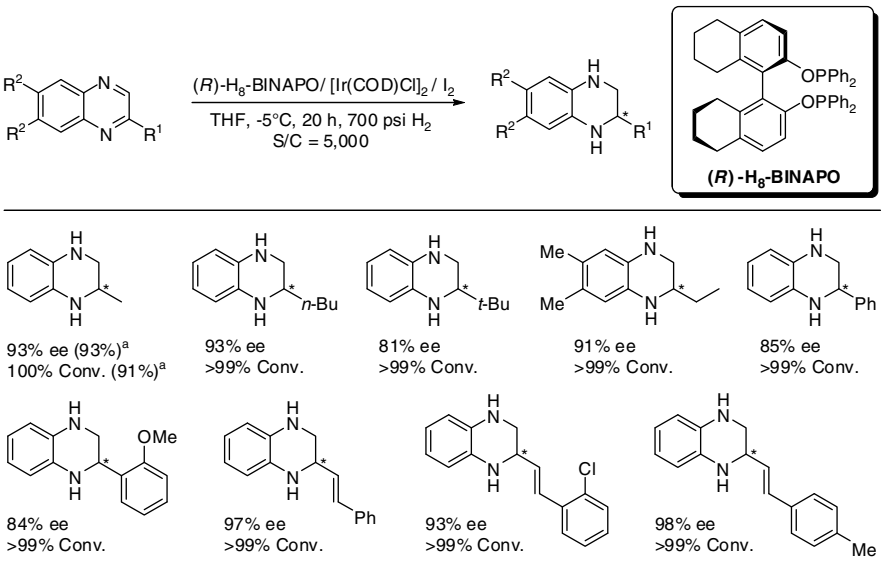
Scheme 14 Asymmetric hydrogenation of quinolines

Iridium complexes containing PQ-Phos type ligands **4**–**6** are also effective in the asymmetric hydrogenation of *N*-hetereoaromatic compounds. The reaction was strongly solvent dependent. Toluene was found to be the solvent of choice for the reaction of quinoline. For example, the best enantioselectivity (92% ee) was

obtained for the hydrogenation of 2,6-dimethylquinoline in toluene. Nevertheless, for the hydrogenation of 2-methylquinoxaline and 2,3,3-trimethylindolenine, THF and CH_2Cl_2 appeared to be the better choices of solvents.

The enantioselectivities of these reactions are highly sensitive to the dihedral angles of the chiral ligands used. For example, with *R*a-**4** ligand (dihedral angle = −66.5°), the catalytic hydrogenation of 6-methoxy-2-methylquinoline gave 6-methoxy-2-methyl-1,2,3,4-tetrahydro-quinoline in 93% yield and 77% ee. Likewise, 91% yield and 84% ee were obtained for the analogous reaction with *S*a-**6** as ligand (dihedral angle = 88.8°). The best result (89% ee) was attained with ligand *S*a-**5** [with dihedral angle = 80.0°, which is close to that of MeO-BIPHEP (83.2°)]. A more pronounced dihedral angle effect was observed for the hydrogenation of 2-methylquinoxaline and 2,3,3-trimethylindolenine [39].

The 1,2,3,4-tetrahydroquinoxaline ring is an important structural unit in many bioactive compounds [101–106], and the most convenient and straightforward protocol to its enantio-enriched form is achieved by asymmetric hydrogenation of quinoxalines. However, the enantioselective hydrogenation of substituted quinoxalines derivatives has been less extensively studied and successful cases are limited [39, 107–111]. Recently, we have developed a highly efficient Ir-(H_8-BINAPO)-catalyzed asymmetric hydrogenation of quinoxalines with high *S*/*C* ratio (up to 20,000) to access the optically pure tetrahydroquinoxalines derivatives in excellent ee (up to 98%) depicted in Scheme 15 [112]. Initially, Ir/(*R*)-H_8-BINAPO (*S*/*C* = 100) enantiomerically hydrogenated 2-methylquinoxalines to give the desired product in 89% ee with complete conversion at ambient temperature; while



[a]The S/C ratio was set to 20,000.

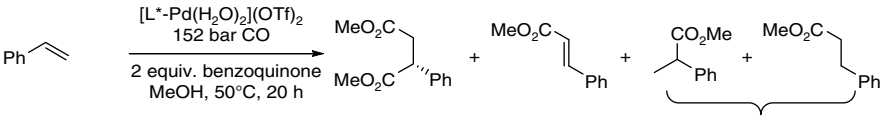
Scheme 15 Asymmetric hydrogenation of quinoxalines catalyzed by H_8-BINAPO

under identical reaction conditions, Ir/BINAP and Ir/MeO-BIPHEP only provided the hydrogenation product in 18 and 59% ee, respectively. With optimization of reaction parameters, the enantioselectivity of the Ir/(*R*)-H_8-BINAPO system was improved to 93% ee at −5°C. This ee value represented the highest enantioselectivity attained so far in the catalytic asymmetric hydrogenation of 2-methylquinoxaline. Remarkably, when the *S*/*C* ratio was increased to 20,000, 2-methylquinoxaline was hydrogenated in 1 h to give the desired product without any loss of enantioselectivity. The 28% conversion indicated a TON of 18,140 and a TOF 5,620 h^{-1}. Notably, this TOF value was the highest reported so far in the asymmetric hydrogenation of heteroaromatic compounds. Under the same reaction conditions, various two-substituted quinoxalines were tested and generally afforded the corresponding desired products in high ees (up to 98%).

4 Asymmetric Catalytic C–C Bond Formation

4.1 Bis-Alkoxycarbonylation of Styrene

Pd(II)-catalyzed asymmetric bis-alkoxycarbonylation of styrene for the synthesis of optically active butanedioic acid derivatives with high chemoselective and/or enantioselective control represents a significant challenge [113]. With the use of 0.8 mol% of catalyst and 2 equiv of benzoquinone as oxidant, the reaction was carried out in methanol under 152 bar CO pressure with 56–67% conversion. The best chemoselectivity of 79% and enantioselectivity of 84% for the desired product dimethyl-2-phenylsuccinate (DMPS) were achieved in the presence of P-Phos with a catalyst loading of 1.6 mol% (Scheme 16) [114].



	S/C		DMPS	MC	MP
(*R*)-P-Phos	125	67% Conv.	71% (83%ee)	20%	2.7%
(*R*)-P-Phos	63	67% Conv.	79% (84%ee)	18%	1.5%
(*R*)-Tol-P-Phos	125	58% Conv.	52% (82%ee)	24%	4.4%
(*R*)-Xyl-P-Phos	125	56% Conv.	42% (82%ee)	28%	1.7%

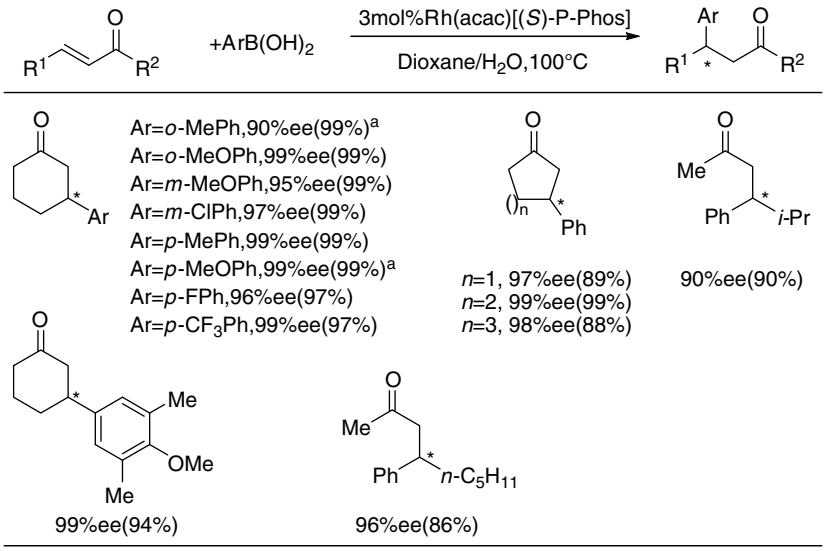
Scheme 16 Pd(P-Phos) complex-catalyzed asymmetric bis-alkoxycarbonylation of styrene

4.2 1,4-Conjugate Addition to α, β-Unsaturated Ketones

Enantioselective construction of quaternary carbon stereocenters is an important objective in organic chemistry (For reviews, see: [115], [116–118], and asymmetric

1,4-conjugate addition of carbon nucleophiles to α,β-unsaturated compounds is a useful method for it. Successful examples include copper-catalyzed asymmetric 1,4-conjugate addition of dialkylzinc reagents [119–121] and trialkylaluminum reagents [122, 123], and rhodium complex-catalyzed 1,4-addition of alkenylboronic acids to α,β-unsaturated pyridyl sulfones [124].

Since Hayashi et al. reported the asymmetric 1,4-addition of organoboronic acids to α,β-unsaturated ketones mediated by Rh(I)-BINAP catalyst [125], impressive progress has been made in reactions involving a variety of other electron-deficient olefins [126]. [Rh(acac)(P-Phos)] complex, generated in situ from equimolar amounts of Rh(acac)(CH_2=CH_2)$_2$ and P-Phos in dioxane/H_2O (10/1) at 100°C, has also been found to be well suited for this transformation [127]. In the presence of excess of arylboronic acids (1.4–5.0 equiv), a vast selection of aryl groups with either electron-donating or electron-withdrawing substituents on the *ortho*-, *meta*- or *para*-position have been readily incorporated onto the β-position of several kinds of cyclic and acyclic enones with exceptionally good yields and ees (up to 99%) in most cases, which are either comparable to or better than the relevant Rh-BINAP system (Scheme 17).



Note: The yield was given in brackets. [a]Ratio of dioxane/water was changed to 20:1

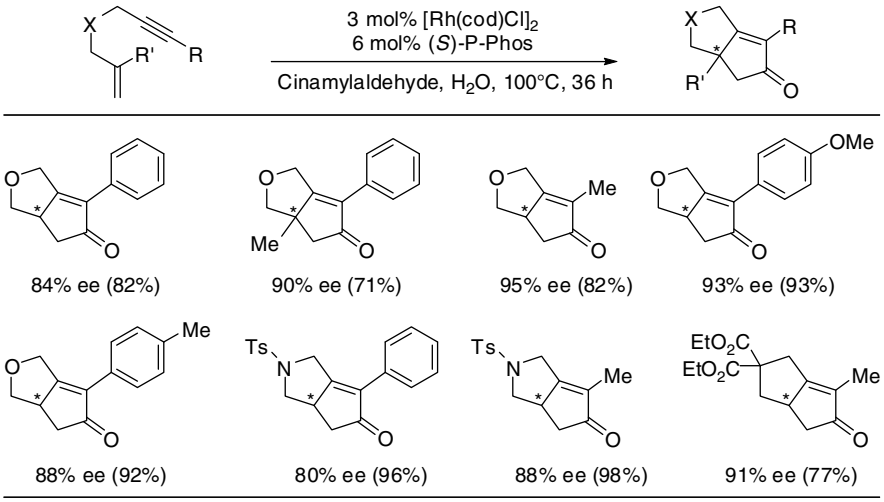
Scheme 17 Enantioselective addition of arylboronic acids to α,β-unsaturated ketones

4.3 Asymmetric Pauson–Khand-Type Reaction (PKR)

Asymmetric transition metal-catalyzed/mediated [2+2+1] carbonylative cycloaddition of an alkene and an alkyne (asymmetric Pauson–Khand-type reaction) offers

an excellent opportunity for the preparation of various optically active cyclopentenones [128]. No catalytic asymmetric aqueous PKR systems had been developed prior to our study. Recently, we found that P-Phos is highly effective in a rhodium-catalyzed PKR using aldehydes as nontoxic "carbon monoxide" source and water as the only solvent without a surfactant. This protocol allowed the handling of both the catalyst and the reactants under air without special precautions [129].

The higher concentration of reactants in conventional organic solvents proved to offer higher rates in the reaction. This finding prompted us to use water as the sole solvent, which was expected to increase the effective concentration of the reactants based on the aqueous micellar concept [130] and thereby to accelerate the reaction. Indeed, water turned out to be much more conducive than organic solvents to higher reactivity and ees (Scheme 18, R = Ph, R′ = H), and P-Phos displayed far superior efficacy to the other screened chiral ligands we screened. Aldehydes as CO surrogates also appeared influential in determining both optical and chemical outcomes, and cinnamylaldehyde gave the best results among the aldehydes examined. Additionally, these attractive aqueous conditions were also well-adapted to a broad collection of oxygen-, nitrogen-, and carbon-tethered enynes providing excellent isolated yields in most cases and an ee range of 74–95% (Scheme 18).



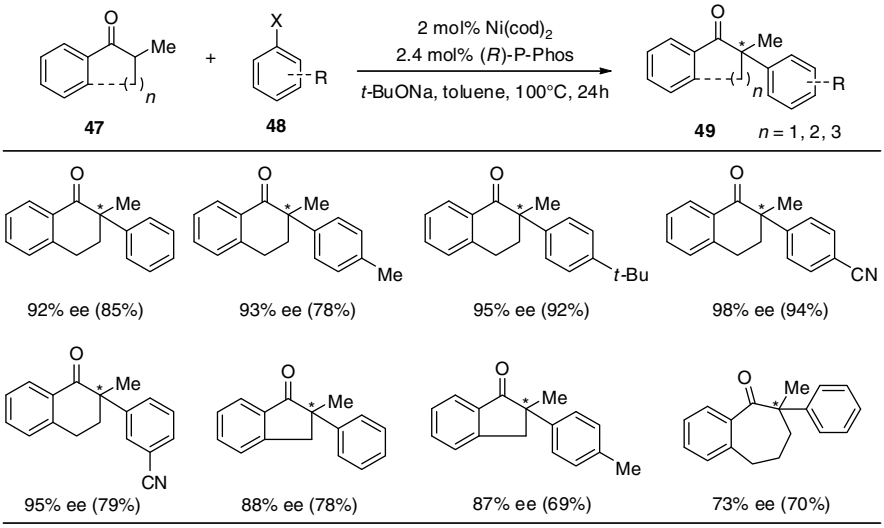
Note: The isolated yield was given in brackets.

Scheme 18 Rh(P-Phos)-catalyzed asymmetric Pauson–Khand reaction

Diphosphane ligand (*S*)-**2** (BisbenzodioxanPhos) was also highly effective in the co-operative processes of aldehyde decarbonylation and cascade enantioselective Pauson–Khand-type reactions. Various 1,6-enynes were transformed to the corresponding bicyclic cyclopentenones in good yields and enantiomeric excesses (up to 96% ee). The attractive feature of this new Rh-catalyzed homogeneous dual catalysis system is that the reaction can be performed in alcoholic solution [131].

4.4 Nickel-Catalyzed Asymmetric α-Arylation of Ketone Enolates

Optically active α-aryl carbonyl moieties are important structural features of many naturally occurring products, pharmaceuticals, synthetically useful intermediates and precursors to emissive polymers [132–134]. The asymmetric arylation of enolates is an attractive means to prepare optically active carbonyl compounds. Buchwald et al. achieved the asymmetric α-arylation of ketone enolates in good yield and enantioselectivity by using Pd complex of BINAP [135] or dialkylphosphinobinaphthyl ligands [136]. Studies revealed that the atropisomeric dipyridyldiphosphine P-Phos served as an effective ligand for the asymmetric α-arylation of ketone enolates, and the corresponding all-carbon quaternary stereogenic center was generated in high enantioselectivity (Scheme 19) [137].



Note: The yield was given in brackets.

Scheme 19 Ni-catalyzed asymmetric α-arylation of ketone enolates

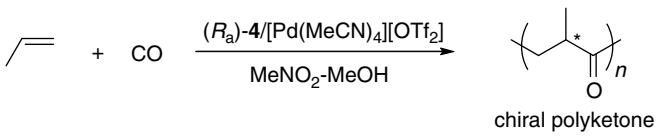
In a prototypical reaction, 2-methyl-1-tetralone (**47**, $n=2$) was treated with bromobenzene (**48**, X = Br) in the presence of 2 mol% $Ni(COD)_2$ and 2.4 mol% (*R*)-P-Phos. The α-phenylated product **49** was obtained in 88% isolated yield and 90% ee with NaHMDS as base. Further study indicated that toluene in combination with sodium *tert*-butoxide formed a superior reaction system. Weaker inorganic bases such as K_3PO_4 resulted in lower productivity even with prolonged reaction time. The yield and enantioselectivity decreased in THF at 60°C. Addition of $ZnBr_2$ led to poor reactivity and enantioselectivity. Adding LiOAc increased the product yield slightly, albeit with a compromised ee value.

Various aryl bromides **48** were examined under these preliminarily optimized conditions using **47** as substrate. The *meta*- and *para*-substituted aryl bromides

gave good yields and moderate-to-excellent enantioselectivities. However, poor reactivity was observed with 2-bromoanisole. Excellent enantioselectivity (98% ee) was attained for the reaction with 4-bromobenzonitrile. Iodobenzene was also an effective reactant under these reaction conditions at 70°C, furnishing the coupling product in 97% yield and 92% ee. Notably, unactivated aryl chloride was found, for the first time, to react with **47** in Ni-catalyzed reaction conditions to give the coupling product in 91% yield.

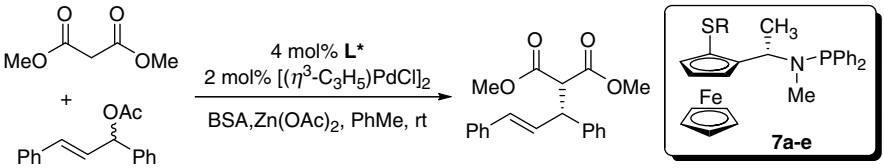
4.5 Asymmetric Alternating Co-Polymerization of Propene and Carbon Monoxide

The alternating copolymerization of propene with carbon monoxide catalyzed by chiral diphosphine ligand modified cationic palladium(II) complexes is a useful tool to generate a variety of polyketones with main-chain chirality. It is known that chiral polyketones exhibit unique chemical and physical properties. Their beneficial features include biodegradable nature which makes them attractive and environmentally friendly materials. Additionally, they are valuable as piezo-, pyro-, and ferroelectric, nonlinear optical materials, chromatographic supports and excellent starting materials for further functionalization [138–148]. Though cationic palladium(II) complexes bearing chiral C_2-symmetric bidentate ligands were successfully employed for this type of copolymerization, only a few examples of highly regio- and stereo-selective propene/CO copolymerization were documented [149–151]. Recently, we have reported a highly efficient chiral-bridged biphenyl diphosphine ligand (*R*a-**4**) modified cationic Pd(II) catalyst system for the synthesis of optically active polyketone via stereoselective alternating copolymerization of propene and carbon monoxide (Scheme 20) [152]. The screening results showed that $[Pd(MeCN)_4][OTf]_2$ was an excellent catalyst precursor in a mixed solvent of $MeNO_2$–MeOH for the copolymerization, and the catalytic activity was found to be up to 221 g polymer/(g Pd·h). In addition, a chiral polyketone with high molecular weight ($Mn = 2.9 \times 10^4$), narrow polydispersity (Mw/Mn = 1.4), and high stereoregularity (which was supported by molar optical rotation = +37°) was afforded under optimized reaction conditions. To the best of our knowledge, the catalytic activity and this molecular weight were the highest among Pd-catalyzed propene/CO alternating copolymerization using artropisomeric biphenyl diphosphine as ligands, including chiral BINAP and BIPHEP.



Scheme 20 Asymmetric alternating copolymerization of propene and CO catalyzed by Pd/(Ra-4) catalyst

Table 5 Effect of thioether moiety on catalyst activity and enantioselectivity

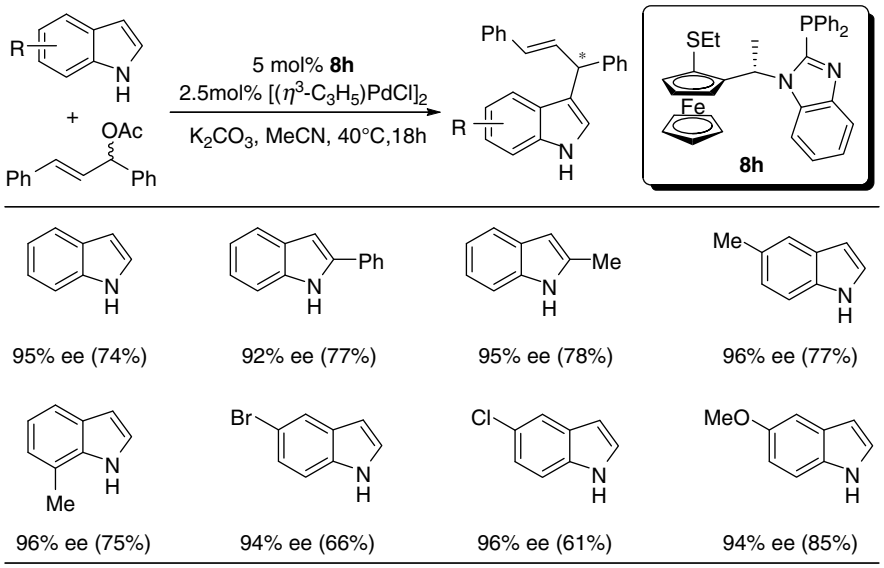


L*	R	*t* (min)	Yield (%)	ee (%)
7a	Et	45	97	91.8 (*R*)
7b	*t*-Bu	90	94	92.7 (*R*)
7c	Ph	120	94	93.5 (*R*)
7d	*i*-Pr	45	94	96.6 (*R*)
7e	Cy	45	96	95.7 (*R*)

5 Application of FerroNPS Catalysts in Asymmetric Allylic Substitutions

5.1 Asymmetric Catalytic C–C Bond Formation

The effectiveness of the FerroNPS family was examined under the optimized reaction conditions for allylic alkylation. The results from Table 5 showed that all of the N-P/S ligands were effective with high to excellent enantioselectivity.



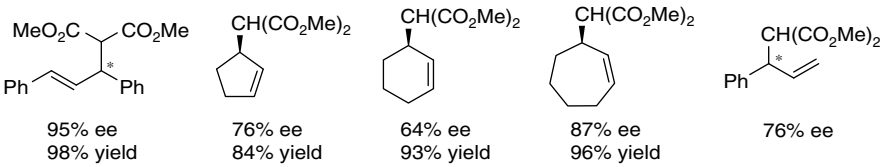
Note: The yield was given in brackets.

Scheme 21 Pd-catalyzed indole allylation using P,S-type ligands 8h

Although the effect on the size of the thioether group was found to be not dominant for the stereochemical outcome, relatively sluggish catalyst activity was found in using ligands containing sterically hindered R groups such as *tert*-butyl and phenyl group. For both enantioselectivity and reactivity, **7d** was found to be the best ligand.

This class of ferrocene-based P/S-type ligands was initially adopted in Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with indoles (Scheme 21). Through systematic evaluation of the ligand library and optimization studies, **8h** was found to be the best ligand for the Pd-catalyzed asymmetric indole alkylation with up to 96% *ee* [45].

In addition, ligand **8h** was further applied in the Pd-catalyzed asymmetric allylic alkylation of various allylic acetates with different nucleophiles and produced the alkylated products in modest to high enantioselectivities with high yields (Scheme 22) [153].



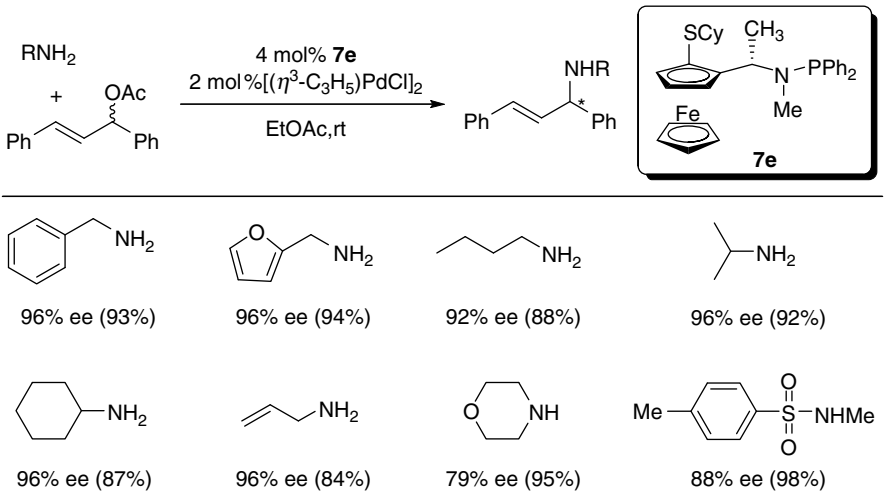
Scheme 22 Various alkylated products afforded from their corresponding substrates

5.2 Asymmetric Catalytic C–N Bond Formation

FerroNPS ligands were also applied to allylic amination and were found to exhibit excellent enantioselectivity (Scheme 23). Ligand **7e** which possessed a cyclohexyl-thioether group was found to be the ligand of choice. Under the optimized reaction conditions, heteroarmatic, primary and secondary amines were compatible in the palladium-catalyzed allylic amination system. In general, the corresponding amine products were obtained in excellent enantiopurities and high yields, except in the cases of morpholine, pyrrolidine, piperidine, and *para*-toluenesulfonamide. Interestingly, by adding BSA as an additional base, the case of sulfonamide gave the desired product in high enantioselectivity and excellent chemical yield.

5.3 Asymmetric Catalytic C–O Bond Formation

The enantioselective transition-metal-catalyzed allylic substitution [1–3, 154, 155] has been one of the most powerful tools for the generation of carbon–carbon and carbon–heteroatom bonds with various nucleophiles. The development of the synthesis of chiral compounds containing carbon–carbon or carbon–nitrogen bonds



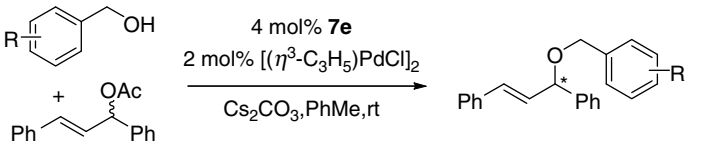
Note: The yield was given in brackets.

Scheme 23 Pd-catalyzed asymmetric allylic amination

from racemic allylic electrophiles has been well documented. However, the enantioselective allylic substitution of oxygen nucleophiles has only been sporadically studied. Enantioselective iridium-catalyzed allylic substitutions with a broad range of phenols (relatively soft nucleophiles) have been reported previously [156–160]. The reaction furnished good enantioselectivity by using monodentate phosphoramidites ligands. Apart from the iridium system, asymmetric palladium-catalyzed C–O bond formation between phenols and various allylic substrates to give ethereal products has also been studied [161, 162] (For Pd-catalyzed enantioselective etherification with limited scope of O-nucleophiles, see: [163]), [164–169]. In 2002, Kim and Lee [170] demonstrated that palladium-catalyzed etherification of allylic acetates with aliphatic alcohols afforded achiral ethers by using zinc alkoxides generated from diethyl zinc and an alcohol. These investigators claimed that zinc alkoxide-based nucleophile was critical for promoting the etherification and that might have resulted from a "softening" of the alkoxide anion by Zn(II) center [171, 172]. We explored the etherification under mild reaction conditions with good stereocontrol [173]. The fine-tunable ferrocenyl phosphinamidite-thioether ligands, (*S*,p*R*)-FerroNPS was used for this investigation. The ligand efficiency, which was studied by using ligand **7** with a thioether containing ethyl, *tert*-butyl, phenyl, and isopropyl group, showed somewhat lower enantioselectivities compared to the cyclohexyl analogue **7e** which afforded 91.6% *ee* and 98% isolated yield.

We further tested the effectiveness of the Pd-**7e** catalyst system. A diverse array of substituted benzyl alcohols were examined (Table 6). It was notable that an intriguing relationship between the enantioselectivity of the product and the electronic property of the substituted benzyl alcohols was found. A higher value of *ee* was observed when the benzyl alcohol containing an electron-rich *para*-substituent

Table 6 The non-conjugate electronic effect on product enantioselectivites



R	Hammett constant (σp)	Yield (%)	ee (%)
H	0	98	91.6 (*S*)
p-OCH3	–0.27	94	94.5
p-CH3	–0.17	94	93.4
p-F	0.06	95	89.6
p-Cl	0.23	92	88.8
p-CF3	0.54	93	77.4

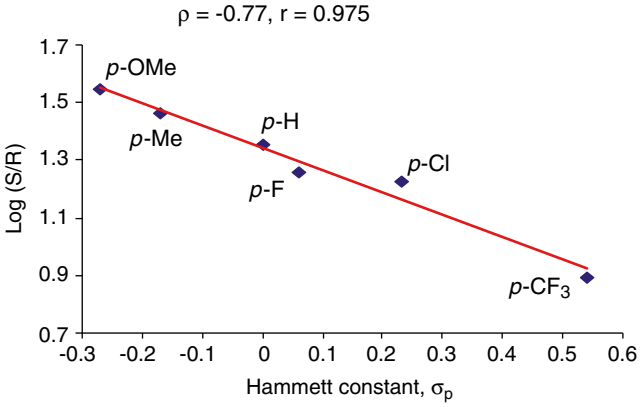
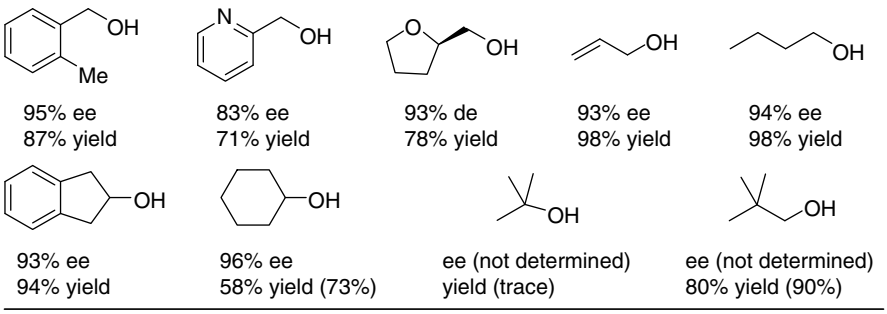


Fig. 4 Hammett Plot for the Pd-catalyzed asymmetric allyic etherification with 7e (ee range: 77–95%)

(such as OMe, Me etc.), while the selectivity gradually diminished as the substituent became more electron-deficient. The aromatic electronic effect was represented by a Hammett relationship (For a review of Hammett study, see: [174], [175], which showed a linear-free energy relationship between enantioselectivity and the electronic character of the substituent (Fig. 4) [129] (For recent references on aromatic electronic effects in asymmetric catalysis, see: [176]), [177–181]. This electronic effect on enantioselectivity was reported to be significant in this non-conjugated system, which has not been reported before.

The substrate scope of this etherification was further extended (up to 21 examples). Various substrates, such as primary, secondary, tertiary, and aromatic alcohols were compatible in the Pd-**7e**-catalyzed system (Scheme 24). The Pd-**7e** catalyst system was found to be also compatible with heterocycles. The reaction of the problematic substrate 2-pyridinemethanol, whereas the nitrogen atom of which might coordinate competitively to the metal center of the catalyst, proceeded smoothly to give the corresponding ether, although the reaction time had to be extended to 21 hours.



Note: The conversion was given in brackets.

Scheme 24 Examples of alcohol substrates examined in the asymmetric allylic etherification

Primary aliphatic alcohols, such as allyl alcohol and *n*-butanol underwent the reaction to provide the desired etheral product in excellent yield with high enantioselectivity. The use of the secondary alcohol 2-indanol led to the desired product in good yield with 93% *ee*, whereas only moderate conversion was observed with the less strained cyclohexanol under the same reaction conditions albeit it gave a better *ee* value of 96%. *tert*-Butanol was found to be an inferior substrate in this transformation and such a result may be obtained from a highly steric congestion from the *tert*-butyl functional group. So as for an acquisition of proof, *neo*-pentyl alcohol was used under the identical conditions and the reaction provided the desired product with almost complete conversion (90% conversion attained).

6 Summary

The modular ligands with phosphorus donor atom have an extraordinary broad performance profile, are useful for a variety of synthetic applications, and have been successfully proven in enantioselective hydrogenation of prochiral ketones and acrylic acid derivatives, 1,4-addition of arylboronic acids to enones, bisalkoxycarbonylation, and other C–C bond formation reactions. The newly developed catalysts sometimes showed better reactivity or stereoselectivity comparing to the state-of-the-art BINAP and MeO-BIPHEP, probably due to the wide range of electronic properties exhibited by these diphosphine ligands. Particularly noteworthy is that the ruthenium(II) complexes of the P-Phos series are air-stable compounds that can be handled in air and can be used with a low catalyst loading. Further, with the inherently beneficial feature of the additional chiral auxiliary, axially chiral biaryl diphosphine ligands could be easily prepared without carrying out the tedious and time-consuming resolution. This strategy significantly simplified the preparation of chiral ligands and would make it possible to produce chiral ligands on a large scale.

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Advances in Biocatalysis: Enzymatic Reactions and Their Applications

Jiang Pan, Hui-Lei Yu, Jian-He Xu, and Guo-Qiang Lin

Abstract Biocatalysis is widely studied as an alternative to conventional chemical methods in chiral synthesis due to its high selectivity and the reaction ability under mild conditions. Various types of enzymes with high stereoselectivity have been screened from nature for the purpose of preparing important chiral synthons. In this chapter, some enzymatic reactions, including enantioselective bioresolution and asymmetric biotransformation, catalyzed by hydrolases, oxidoreductases and lyases, as well as their applications to chiral synthesis are overviewed, and some special enzymatic reaction modes, such as enantioconvergent reaction, dynamic kinetic resolution, and deracemization, are described.

Keywords Asymmetric biotransformation • Biocatalysts • Chiral synthesis • Kinetic resolution

Contents

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Abbreviation

ADH	Alcohol dehydrogenase
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Conv.	Conversion
DEAE	Diethylaminoethyl
DGG	Didodecyl *N*-D-glucono-L-glutamate
ee	Enantiomeric excess
E-factor	Kilogram waste per kilogram product
EH	Epoxide hydrolase
E-value	Enantiomeric ratio
GlcNAc	*N*-acetyl-D-glucosamine
GPE	Glycidyl phenyl ether
HCN	Hydrogen cyanide
HIV	Human immunodeficiency virus
Hnl	Hydroxynitrile lyase
m	Meta
ManNAc	*N*-acetyl-D-mannosamine
NADH	β-1,4-nicotinamide adenindinucleotide
NADPH	β-1,4-nicotinamide adenindinucleotide phosphate
Neu5Ac	*N*-acetyl-D-neuraminic acid
NMR	Nuclear magnetic resonance
o	Ortho
p	Para
PCR	Polymerase chain reaction
rac	Racemic
S/*C*	Substrate/catalyst
sec	Second
t-PeOH	*tert*-Pentanol
TsCl	*p*-toluenesulfonyl chloride

1 Introduction

Chirality has become increasingly common in pharmaceuticals, as well as in fine chemical industry. As reported, in 2006, as much as 80% of small-molecule drugs approved by FDA are chiral and 75% are single enantiomers [1], many of them contain an average of two chiral centers [2]. According to the regulatory requirements for chiral drugs, an enantiomeric purity of 99.5% is necessary [2].

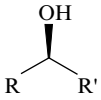
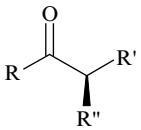
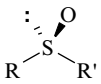
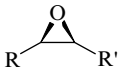
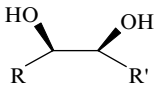
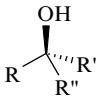
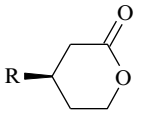
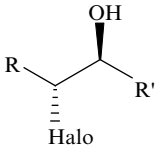
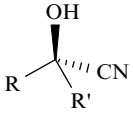
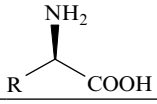
Though efficient chemical approaches, such as asymmetric hydrogenation [3], isomerization [4], and epoxidation [5], have been well developed for the synthesis of enantiopure compounds, the universality of these methods is limited. Classical resolution of a racemate with chiral auxiliary is often used by chemists for manufacturing of optically active compounds, however, these methods suffer from low efficiency, large waste, and more importantly, the optical purity of product is often not always satisfied.

By taking the advantages in several scenes, biocatalysis is a robust competitor and a good alternative to chemical process for the production of enantiopure compounds due to the exquisite stereo- and regioselectivity of enzymes under mild reaction conditions, such as aqueous medium, at physiological pH, and ambient temperature. Activation or protection and deprotection steps of functional groups are usually not required for biotransformations. And more interestingly, complex chemical synthesis process involving the product with multiple chiral centers may be resolved by a simple and elegant bioconversion process [6–8]. The reduced number of process steps makes biocatalysis more environmentally and economically attractive with less waste, i.e., reducing the *E*-factor [6].

Classical kinetic resolution of racemates is frequently used for the preparation of enantiopure compounds. In order to overcome the limitation of 50% yield in classical bioresolution, dynamic kinetic resolution processes based on in situ enzymatic or transition metal-catalyzed substrate racemization were developed [9–11]. Compared with enantiomeric resolution, asymmetric biotransformations are more attractive because enantiopure compounds can be obtained in 100% theoretical yield with excellent atom efficiency. Examples of the biocatalytic asymmetric synthesis reactions are listed in Table 1. Among them, asymmetric carbonyl reduction by dehydrogenase, stereoselective hydroxylation by monooxygenase, and asymmetric hydroxynitrilation by hydroxynitrile lyase have become the topics of common interests.

Industrial productions have high demands on biocatalysis and biotransformation [12]. Poor stability of enzyme, low solubility of hydrophobic substrate in aqueous phase, and low regeneration efficiency of cofactor are the limitation of bioprocess application in industry. Development in biotechnology, such as immobilization of biocatalyst (enzymes or whole cells), introduction of two-phase reaction system, use of whole cells as biocatalysts, and regeneration of cofactor by enzyme-coupled systems, significantly improved the efficiency (cost, yield, and productivity) of biocatalysis. Another important limitation of biocatalysis is the availability of biocatalysts with excellent properties. With the breakthrough of the development in

Table 1 Biocatalyzed asymmetric synthesis

Substrate	Enantiopure compound	Enzyme	Reaction type
Ketone		Dehydrogenase	Reduction
Enoate		Enoate reductase	Enoate reduction
Sulfide		Monooxygenase	Sulfoxidation
Alkene		Monooxygenase Haloperoxidase	Epoxidation
Olefin or aromatic ring		Dioxygenase	Dioxygenation
Alkane or benzyl		Monooxygenase	Hydroxylation
Ketone		Monooxygenase	Baeyer–Villiger oxidation
Alkene		Haloperoxidase	Halohydrin formation
Ketone, aldehyde		Hydroxynitrile lyase	Hydroxynitrilation
α-Keto acid		Transaminase	Transamination

biotechnology, for example, in molecular biology, analytics, bioinformatics, and gene synthesis, an increasing spectrum of biocatalysts is readily available for industrial application by directed screening and evolution [13].

With the access to the broader spectrum and stable biocatalysts, more and more conventional chemical processes (first generation) in pharmaceutical manufacture have been replaced by second-generation processes of biocatalysis with substantial impacts

to the pharmaceutical industry [14]. In this chapter, some commonly used biocatalytic reactions for chiral preparation, including hydrolytic reaction, acyl and glycosyl transfer reaction, asymmetric reduction/oxidation reaction, and asymmetric formation of C–C bonds, are introduced and exemplified with the research achievements developed by our laboratories and other research groups in China. Some of the bioprocesses described herein have been successfully applied on pilot or even an industrial scale.

2 Hydrolytic Reactions

In industrial biotransformation, hydrolytic reactions occupied prominent positions for production of optically active amines, alcohols, and carboxylic acids [15]. Compared with other reactions, hydrolytic reactions need no cofactor, the reaction systems are relatively simple, which make the hydrolytic reaction process easy to be scaled up. Lipase/esterase, epoxide hydrolase, nitrilase, and glycosidase are the often used enzymes in biohydrolytic reactions.

2.1 Kinetic Resolution of Chiral Esters Using Esterase/Lipase

Many highly active and enantioselective lipases have been developed as commercially available biocatalysts. Instead, compared with the large quantity of readily available lipases, the number of esterases is relatively small. Some of the commercial lipases and esterase are listed in Table 2.

Both lipase and esterase can catalyze the hydrolytic resolution of chiral esters, which have been widely used for the preparation of bulk chemicals such as unnatural amino acids [16], fine chemicals, and especially pharmaceuticals such as enantiopure esters, alcohols, or acids [17]. In the following text, some examples of lipases/esterases catalyzed bioresolution of chiral esters are introduced.

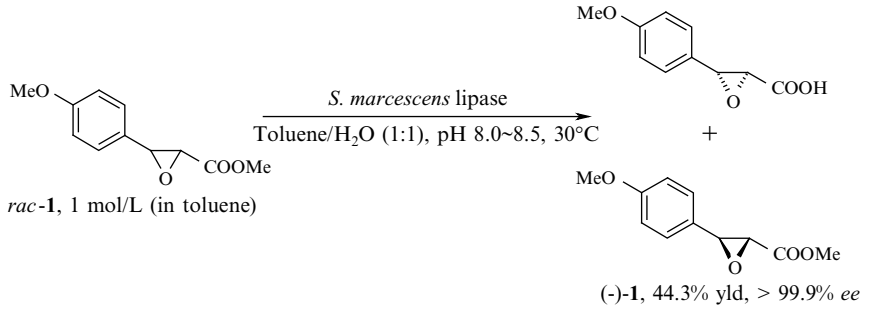
2.1.1 Preparation of Enantiopure Chiral Esters

Enzymatic resolution of *trans*-3-(4′-methoxyphenyl) glycidic acid methyl ester (*rac*-**1**) is a key step in the chemo-enzymatic synthesis of diltiazem hydrochloride, an coronary vasodilator developed by Tanabe Seiyaku Co. Ltd. After introducing a lipase-catalyzed hydrolytic resolution, the desired enantiomer (2*R*, 3*S*)-(−)-**1** with two chiral centers was obtained in one step and the whole synthetic process of diltiazem was curtailed from nine steps to five steps [7]. In one of authors' group, a strain of lipase-producing bacterium, *Serratia marcescens* ECU1010, was isolated [18–20] and the extracellular lipase secreted was employed for enzymatic preparation of (−)-**1** with an optical purity of >99% enantiomeric excess

Table 2 Some commercially available lipases/esterases

Name	Source	Supplier	Name	Source	Supplier
PLE (esterase)	Pig liver	Sigma–Aldrich Co.	Lipase PS "Amano" SD	*Burkholderia cepacia*	Amano Enzyme Inc.
PPL	Porcine pancreas	Sigma–Aldrich Co.	Lipase PS "Amano" IM (Immobilized)	*Burkholderia cepacia*	Amano Enzyme Inc.
CRL	*Candida rugosa*	Sigma–Aldrich Co.	Lipase AS "Amano"	*Aspergillus niger*	Amano Enzyme Inc.
MJL	*Mucor javanicus*	Sigma–Aldrich Co.	Lipase AYS "Amano"	*Candida rugosa*	Amano Enzyme Inc.
MML	*Mucor miehei*	Sigma–Aldrich Co.	Lipase AK "Amano"	*Pseudomonas fluorescens*	Amano Enzyme Inc.
RAL	*Rhizopus arrhizus*	Sigma–Aldrich Co.	CALB	*Candida antarctica*	Novozymes
RML	*Rhizomucor miehei*	Sigma–Aldrich Co.	Novozym 435 (Immobilized)	*Candida antarctica*	Novozymes
PFL	*Pseudomonas fluorescens*	Sigma–Aldrich Co.	Novozym TL 100 L	*Thermomyces lanuginosus*	Novozymes
Lipase OF	*Candida rugosa*	Meito Sangyo Co., Ltd	Novozym TL IM (Immobilized)	*Thermomyces lanuginosus*	Novozymes

(*ee*) in a yield of 37.2% [21] (Scheme 1). The lipase has been purified to homogeneity [22] and heterologously expressed in *Escherichia coli* (*E. coli*) afterwards [23].



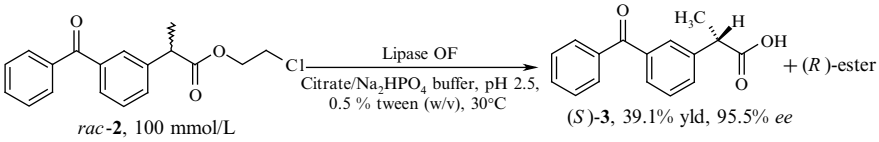
Scheme 1 Stereoselective hydrolysis of *rac*-**1** by a lipase from *Serratia marcescens* ECU1010

Several methods have been investigated for the immobilization of lipase from *S. marcescens* ECU1010 to improve the enzyme stability [18, 21, 24, 25]. Using the chitosan immobilized lipase as biocatalyst, the operational mode of enzymatic resolution of *rac*-**1** was compared in a 2-L stirred tank reactor, and batch reaction was found to be the most suitable mode, affording enantiopure (−)-**1** in 44.3% overall yield and >99.9% *ee* [24]. A pilot test in a stirred tank reactor of 1 m^3 has also been fulfilled, giving as the similar results as on lab-scale.

2.1.2 Preparation of Enantiopure Chiral Acids

α-Arylpropionic acids, such as naproxen, ibuprofen, ketoprofen, flurbiprofen, and suprofen are a class of *anti*-inflammatory drugs. The *anti*-inflammation activities of these drugs are relied on the (*S*)-isomers, so the separation of (*S*)-α-arylpropionic acids has been the focus. Enzymatic hydrolysis of racemic esters is now a standard method for preparation of (*S*)-α-arylpropionic acids.

Lipase catalyzed hydrolytic resolution of ketoprofen esters was usually employed for the preparation of (*S*)-ketoprofen [(S)-**3**], as shown in Scheme 2. Some isolated microorganisms [26–29] and commercial lipases [30, 31] were applied for the enantioselective hydrolysis of racemic ketoprofen esters. A commercial enzyme, Lipase OF produced by *Candida rugosa*, was found to be a good biocatalyst for the kinetic resolution of 2-chloroethyl ketoprofen (*rac*-**2**).



Scheme 2 Lipase catalyzed enantioselective hydrolysis of ketoprofen esters

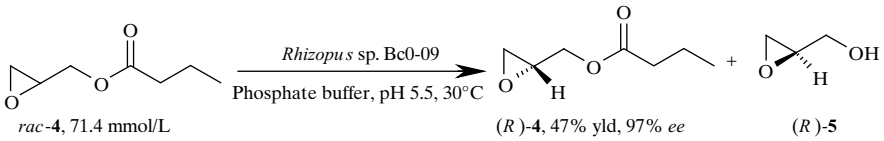
Since ketoprofen ester is water-insoluble substrate, dispersion turned out to be a critical factor affecting the reaction conversion. It was found that addition of surfactants efficiently improved the substrate dispersion, and on the other hand, it also enhanced the lipase activity [30]. With the addition of Tween-80 (2%, w/v) or nonyl phenol polyethyleneoxy ether (3%, w/v), the activity of the crude lipase was greatly increased up to 13 and 15 times, respectively. Interestingly, the addition of surfactant also improved the enantioselectivity of the enzyme. The enantiomeric ratio (*E* value) was greatly enhanced from 8 to 100 for the purified lipase in the presence of 2% (w/v) Tween-80 [30].

The pH value of the reaction medium was found to be another important factor affecting both the activity and the enantioselectivity of Lipase OF [32]. The enzyme showed the optimal hydrolysis activity at pH 4.0, while the enantioselectivities were increased sharply with the decrease of the medium pH from 4.0 to 2.2. Based on spectroscopic studies [33], the enhancement of the lipase activity and enantioselectivity at the lower pH could be attributed to the changes of the flexible and sensitive conformation of the lipase induced by tuning the biocatalyst microenvironment. By combination of the low pH and addition of Tween-80, enantiomer-enriched (*S*)-**3** could be obtained with 95.5% *ee* and 39.1% yield from *rac*-**2** (100 mM) at pH 2.5 in the presence of 0.5% (w/v) Tween-80 [34]. After terminating the reaction, pH of the reaction mixture was adjusted to ca. 10.0 and then centrifuged to remove the unreacted (*R*)-2-chloroethyl ketoprofen. The supernatant containing the salt of (*S*)-**3** was acidified to pH 2.0 to give a precipitate of (*S*)-**3** [30]. The resulting product was further purified by recrystallization.

The crude preparation of Lipase OF contains several isoenzymes, which could be separated by column chromatography on a cation ion resin (Sephadex C-50) and eluted by citrate–phosphate buffers of pH 3.3, 4.7, and 6.8. The active fractions eluted were designated as L1, L2, L3, respectively [30]. Active fractions L2 and L3 have higher enantioselectivities as compared with the component L1. Considering that the lipase has high enantioselectivity at low pH, the partial purification of the crude enzyme was integrated with the enzyme immobilization by simply adsorbing the lipases onto Sephadex C-50 at pH 3.5 [35]. Thank to the selective removal of the unfavorable lipase isoenzyme L1, the tightly fixed enzyme components on the resin displayed significantly improved enantioselectivity, and (*S*)-**3** was obtained with >94% *ee* at 22.3% conversion in the presence of 0.5 g/L Tween-80 at pH 3.5. The operational stability of the immobilized biocatalyst was examined in a packed column and air-bubbled column reactors. As a result, the air-bubbled column was an ideal bioreactor, which was operated smoothly for at least 350 h, retaining nearly 50% activity of the immobilized lipase in the end.

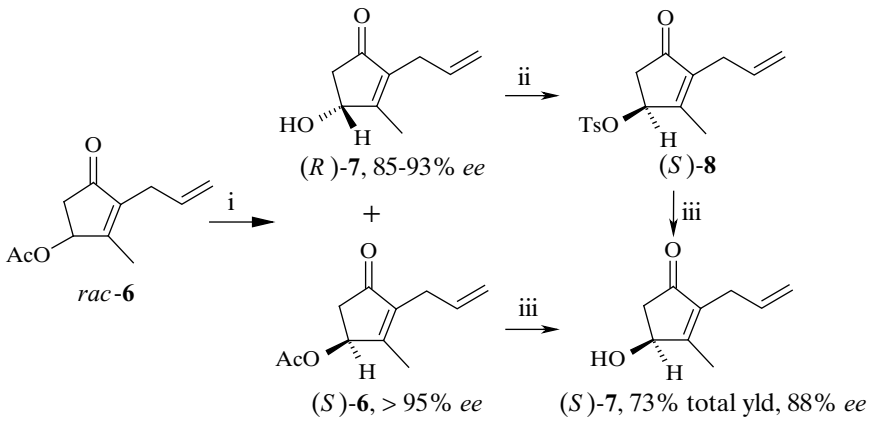
2.1.3 Preparation of Enantiopure Chiral Alcohols

Enantiopure glycidols (**5**) are key intermediates for the preparation of many β-blocker drugs. Enzymatic hydrolysis of glycidyl butyrate (*rac*-**4**) was an efficient process for the production of enantiopure **5** [36], which has been developed by Andeno-DSM on a multi-ton scale [37]. Xu has isolated the strain, *Rhizopus* sp. Bc0-09 [38] which resolved *rac*-**4** effectively. The extracellular lipase preferred to catalyze the hydrolysis of (*S*)-**4**, as shown in Scheme 3. Under the optimal reaction conditions of pH 5.5 at 30°C, the *ee* of residual (*R*)-**4** could reach 97% at a conversion of 53%, with an *E* value of 57. *S. marcescens* lipase was also able to catalyze the hydrolytic resolution of *rac*-**4** with an *E* value of more than 100, therefore, the enantioselectivity is complementary to that of *Rhizopus* sp. lipase [22].



Scheme 3 Bioresolution of *rac*-**4** by a lipase from *Rhizopus* sp. Bc0-09

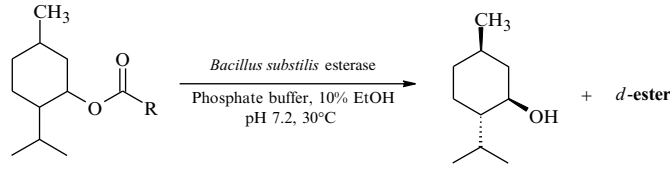
(*S*)-4-Hydroxy-3-methyl-2-(2-propenyl)-2-cyclopent-2-enone [(*S*)-**7**] is secondary alcohol moiety of a widely employed synthetic pyrethroid insecticide (*S*)-prallethrin. The insecticidal activity of (*S*)-prallethrin is several times higher than the (*R*)-antipode [39]. An esterase-producing bacterium, *Acinetobacter* sp. CGMCC 0789, was isolated and employed for the enantioselective hydrolysis of (*R*)-**6** (Scheme 4). The highly enantioselective (*R*)-ester hydrolase was partially purified [40], and a low concentration of isopropanol was found to be helpful for improving the esterase activity and enantioselectivity [41]. The whole cells were entrapped in calcium alginate beads and used repeatedly for the catalytic resolution of *rac*-**6**. In the presence of 10% (v/v) isopropanol [41], the *ee* of (*R*)-**7** was kept in the range of 85–93% and that of the unreacted (*S*)-**6** was higher than 95% at nearly 50% conversion after 24 h of biotransformation. The stability of the immobilized cells was very high, without any significant loss of activity observed after ten batches of recycling use. The hydrolytic product (*R*)-**7** could be converted to (*S*)-**8** by reacting with *p*-toluenesulfonyl chloride (TsCl) and the combined mixture of (*S*)-**6** and (*S*)-**8** was hydrolyzed to give (*S*)-**7** of 88% *ee* with a total yield of 73% (unpublished data).



i) Whole cells of *Acinetobacter* sp. CGMCC0789, Tris-HCl buffer (pH 8.0), with 10% of *i*-PrOH, 30ºC;
ii) TsCl; iii) K_2CO_3/MeOH

Scheme 4 Chemo-enzymatic preparation of (*S*)-**7** by whole cells of *Acinetobacter* sp. CGMCC0789

Table 3 Enzymatic preparation of *l*-**11** using *Bacillus subtilis* esterase



d,l-**9 (a-e)**, 100 mmol/L

l-**10**

R	Conv. (%)	ee_p (%)	*E*
CH_2Cl	97	5.1	NA
CH_3	49	97.7	> 200
$(CH_2)_2CH_3$	41	92.0	47
Ph	32	78.1	11
$(CH_2)_2COOH$	1	>99.0	NA

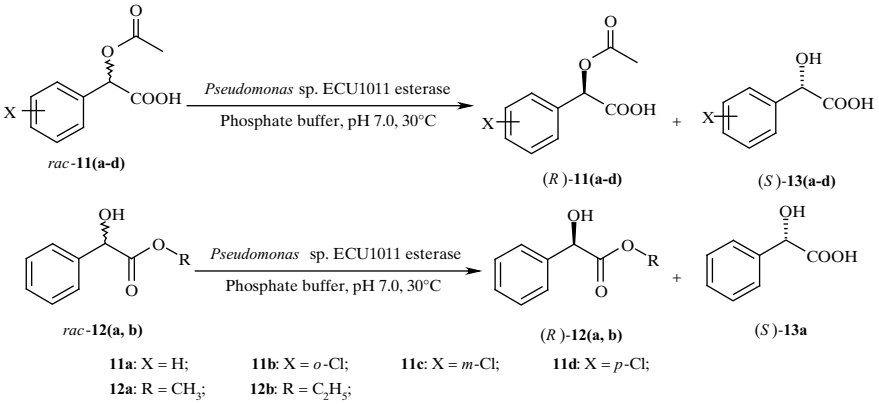
NA not available

- Synthesis of *l*-menthol (**10**) by asymmetric isomerization of allylic amines using cationic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl-Rh (BINAP-Rh) complex as catalyst has been exploited by Noyori et al. [4]. Using this technology, more than 1,000 tons of *l*-**10** was produced annually from myrcene by Takasago International Co. [3]. Enzymatic resolution of *dl*-menthol esters was another approach for the preparation of *l*-**10**. *Bacillus subtilis* ECU0554, isolated from soil samples through enrichment culture, produced a high-substrate-concentration tolerable esterase which exhibited high hydrolytic activity and moderate to excellent enantioselectivity towards *l*-**9** (Table 3) [42]. When

dl-**9b** was used as substrate, the esterase showed the highest enantioselectivity, affording *l*-**10** of 98% *ee* at 49% conversion ($E > 200$). The substrate concentration was able to enhance to as high as 500 mM [42].

2.1.4 Preparation of Enantiopure Hydroxy Acids

Mandelic acid (**13a**) is the simplest α-aryl hydroxyl acid. Enantiopure mandelic acid and its derivatives (**13b–13d**) can be prepared by enzymatic hydrolysis of the corresponding esters such as *rac*-**11** or **12** as illustrated in Scheme 5.



Scheme 5 Enzymatic resolution of mandelates

A microorganism, *Pseudomonas* sp. ECU1011, isolated from soils exhibited the ability of enantioselective deacylation of **11a–11d** with high enantioselectivity [43], as shown in Table 4. Whole cells of *Pseudomonas* sp. ECU1011 was also found to catalyze the enantioselective hydrolysis of mandelic esters **12a** and **12b**, though with much lower enantioselectivities.

Table 4 Enzymatic resolution of mandelates by esterase from *Pseudomonas* sp.

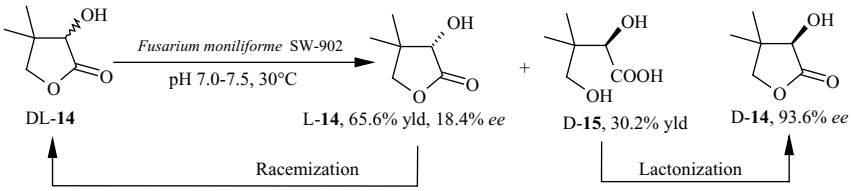
Substrates	Conv. (%)	ee_p (%)	Substrates	Conv. (%)	ee_p (%)
11a	45.5	98.1	**11d**	50.7	96.8
11b	44.2	97.2	**12a**	42.2	23.0
11c	40.2	97.1	**12b**	39.6	56.2

2.2 Bioresolution of Lactones with Lactonase

Lactonase, which catalyzes the asymmetric hydrolysis of chiral lactone compounds to optically enriched hydroxyl acids, belong to the esterase family. Enzymatic resolution of DL-pantolactone (**14**) for the production of D-**14**, a chiral intermediate for

the synthesis of cosmetic additive provitamin B5 (D-Panthenol) and feed additive (D-calcium pantothenate), is perhaps the most important application of lactonase in fine chemical industry.

Many species of fungi, including *Fusarium*, *Gibberella*, *Gliocladium*, *Aspergillus*, *Cylindrocarpon,* and *Volutella*, catalyze the preferential hydrolysis of D-**14**, giving D-pantoic acid (D-**15**) with high enantiopurity [44]. The resultant D-**15** was easily separated from the unhydrolyzed L-**14** by organic solvent extraction and converted to D-**14** by heating under acidic condition (Scheme 6). The novel process for D-**14** synthesis, involving the enzymatic resolution of DL-**14** by *Fusarium* lactonase, has been in practical use since 1999 [45]. Currently, about 30% of D-calcium pantothenate in the world market is produced through this chemo-enzymatic process.

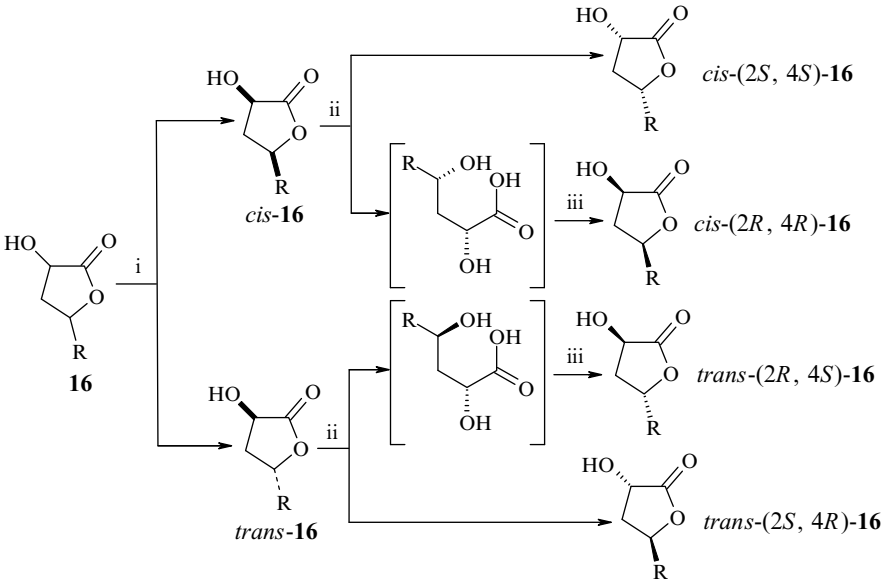


Scheme 6 Production of D-**14** by enantioselective hydrolysis with lactonase

Sun et al. obtained a highly productive D-pantonohydrolase producing strain, *Fusarium moniliforme* SW-902, by isolation and mutation. The whole cells of *F. moniliforme* were immobilized by entrapment in κ-carrageenan [46] or by direct cross-linking with glutaraldehyde [47, 48]. The cross-linked cells were repeatedly employed for as many as 110 successive times in 10% (w/v) DL-**14**, keeping the conversion around 30%. Moreover, this D-lactonohydrolase was cloned and expressed in *Saccharomyces cerevisiae* [49]. Directed evolution of the D-pantonohydrolase was attempted through error-prone polymerase chain reaction (PCR) combined with DNA shuffling, resulting in a mutant with high stability and a tenfold increase of specific activity [50].

One of the authors also succeeded in the isolation of a highly active strain producing *levo*-lactonase (*Fusarium proliferatum* ECU2002) from soil fungus, which was capable of hydrolyzing various chiral lactones to optically enriched hydroxyl acids [51, 52]. The *levo*-lactonase of *F. proliferatum* ECU2002 preferentially hydrolyzes the *levo*-enantiomer of **14** and some butyrolactone derivatives, affording *dextro*-hydroxy acids with high enantiopurities (94.8–98.2% *ee*) and acceptable conversions (38.2–44.2%) [51]. The crude lactonase was easily immobilized with glutaraldehyde and used in the repeated batch resolution of DL-**14** at a concentration of 35% (w/v), producing D-**15** in 94–97% *ee* at >30% conversion. The half life of the immobilized enzyme reached 20 runs [51].

The *levo*-lactonase gene of *F. proliferatum* ECU2002 has been cloned and expressed in *E. coli* [53] for biocatalytic resolution of industrially important chiral lactones, such as 4-substituted 2-hydroxy-4-butyrolactones (**16**). Enantiopure isomers were obtained by combination of diastereoisomers separation by column chromatography and enzymatic resolution, as shown in Scheme 7 [54].



R = Et, thienyl, Ph, *o*-F-C_6H_4, *p*-MeO-C_6H_4, *m*-Br-C_6H_4
i) separation by column chromatography; ii) whole cells of recombinant *E. coli* with *levo*-lactonase; iii) heating at pH 1.0-2.0.

Scheme 7 Chemo-enzymatic production of four stereoisomers of **16**

2.3 *Preparation of Enantiopure Epoxides with Epoxide Hydrolase*

Due to their ability to react with various nucleophiles, enantiopure epoxides are valuable intermediates for the synthesis of many chiral pharmaceuticals, such as β-blockers, *anti*-obesity and *anti*-HIV drugs. Many chemical methods have been developed to prepare enantiopure epoxides. Among them, Sharpless epoxidation method gave the epoxides with excellent optical purities and predictable configurations, however, the substrates were limited to allylic alcohols [5]. Jacobsen epoxidation method gave high stereoselectivities for nonfunctionalized *cis*-alkenes [55, 56], but the results in most cases were not satisfactory enough toward *trans*- and terminal olefins. As an alternative, epoxide hydrolase (EH, EC 3.3.2.3) catalyzed stereoselective hydrolysis of racemic epoxides attracts much attention for the preparation of enantiopure epoxides.

2.3.1 Kinetic Resolution of Racemic Epoxides

According to the differences of property, position, and amount of the substituted group, epoxides can be divided into four types: (a) monosubstituted epoxides, (b) styrene oxide-type epoxides, (c) 2,2-disubstituted epoxides, and (d) 2,3-disubstituted and trisubstituted epoxides. Epoxide hydrolases can catalyze the enantioselective hydrolysis of various types of epoxides under environmentally gentle conditions to furnish the enantio-riched corresponding vicinal *trans*-diols by addition of H_2O through SN_2 mode and leave the remaining epoxides with high enantiopurities [57, 58]. The enantiopure vicinal diols are also versatile chiral synthesis blocks, employed as their corresponding cyclic sulfate or sulfite esters [59].

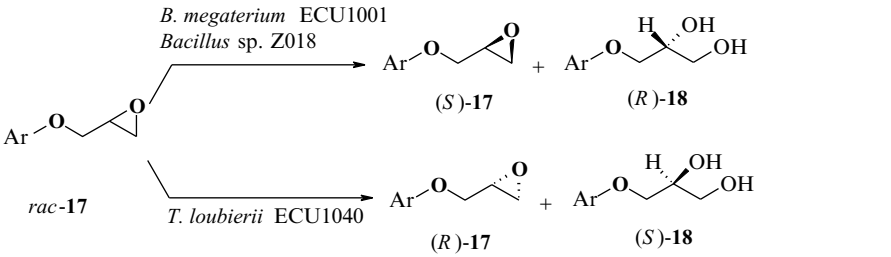
Bioresolution of Glycidyl Aryl Ethers

Glycidyl aryl ether derivatives belong to the type of monosubstituted epoxides. Some strains, *Bacillus megaterium* ECU1001 [60, 61], *Trichosporon loubierii* ECU1040 [62], and *Bacillus* sp. Z018 [63] were isolated from soils by enrichment culture using *rac*- or (*R*)-glycidyl phenyl ether (GPE) as the sole carbon and energy sources. Addition of *rac*- or (*R*)-GPE enzymatic hydrolysis substrates was found to enhance significantly the production of epoxide hydrolases in these microorganisms [62, 63]. The epoxide hydrolases of these strains showed complementary enantioselectivity toward *rac*-**17**. Epoxide hydrolases from *B. megaterium* ECU1001 [60, 61, 63, 64] and *Bacillus* sp. Z018 [63] preferred to catalyze the hydrolysis of (*R*)-epoxides firstly, while epoxide hydrolase from *T. loubierii* ECU1040 favored to (*S*)-epoxides [65, 66] (Table 5).

The stability of EHs is usually poor. Activity of the whole cells of *T. loubierii* ECU1040 was completely lost in only 24 h. The enantiopurities of the residual epoxides was found to be severely affected by the ratio of cells to substrates during the whole-cells catalyzed resolution of GPE, and high optical purities of the remaining epoxides were obtained only at relatively high cell/substrate ratios [66].

Many epoxides are poorly soluble in water and the high reactivity of the epoxy bond makes epoxides easy to be hydrolyzed spontaneously in neat aqueous environment. Cosolvent or emulsifier, such as Tween-80, thus improves the substrate solubility or dispersion in water [64], and organic–aqueous biphasic systems are also often used for hydrolytic resolution of insoluble epoxides to increase the substrate concentration, and in the meantime, to suppress the spontaneous hydrolysis of epoxides, resulting in the enhancement of enantioselectivity. By using isooctane as the organic solvent, 600 mM of *rac*-GPE (90.1 g/L, in isooctane phase) was hydrolyzed by the whole cells of *B. megaterium* ECU1001 with an *E* value of 94.0, affording (*S*)-GPE in 100% *ee* at 44.5% yield [67, 68], which was much better results than the reaction in aqueous mono-phase system [60]. The enantioselectivity was significantly affected by the alternation of phase ratios, with a ratio of 1:5 (oil in water) as the best.

Table 5 Epoxide hydrolases catalyzed asymmetric hydrolysis of *rac*-**17a–17h**

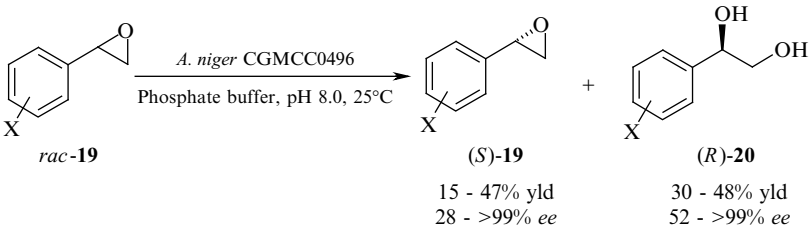


Strains	Substrates	Epoxides		Diols		Ref.
		Yield (%)	ee (%)	Yield (%)	ee (%)	
B. megaterium ECU1001	Ph	25.6	99.5	40	73.3	[60]
Bacillus sp. Z018	Ph	–	–	45.8	96.3	[63]
	o-NO_2-Ph	41.0	97.2	41.8	74.0	[65]
	m-NO_2-Ph	28.2	67.2	29.4	90.4	[65]
	p-NO_2-Ph	33.1	58.7	34.2	85.7	[65]
T. loubierii ECU1040	Ph	35	>99	35	60	[66]
	o-Me-Ph	40	>99	54	72	[66]
	m-Me-Ph	32	95	46	71	[66]
	p-Me-Ph	45	88	51	72	[66]
	1-Naphthyl	26	97	36	59	[66]

Bioresolution of Styrene Oxide-Type Epoxides

Styrene oxide-type epoxides possess a benzylic carbon atom, where the formation of carbonium ion can be stabilized by the resonance of the adjacent aromatic ring, thus the nucleophilic attack at benzylic position is electronically favored though with steric-hindrance. Mixed regioselective hydrolysis routes are common for this type of substrates. That is, the attack can happen at the both carbon atoms of the oxirane ring and the ratio is dependent on the properties of the enzyme employed. Generally, epoxide hydrolases from some fungi, such as *Beauveria sulfurescens*, *Beauveria densa,* and *Syncephalastrum racemosum*, catalyze the addition of water at the more substituted benzylic position preferentially, while EHs from the species of *Aspergillus* and *Corynebacterium* catalyze the addition of oxygen atom at the less substituted carbon atom.

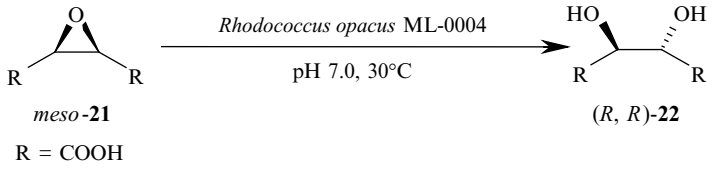
Aspergillus niger species CGMCC 0496 [69, 70] and SQ6 [71, 72] were screened for the enantioselective biohydrolysis of styrene oxide derivatives. These two strains are all (*R*)-stereospecific. The epoxide hydrolase from *A. niger* SQ6 has been cloned by inverse-PCR and expressed in *E. coli* as a fusion protein containing a poly-histidine tag [72]. Epoxide hydrolases from *A. niger* CGMCC 0496 exhibited moderate to excellent enantioselectivities toward styrene oxides *rac*-**19** (Scheme 8) [69, 70]. The hydrolysis product (*R*)-diols were transformed to the corresponding (*R*)-epoxides by chemical methods [69].



Scheme 8 *A. niger* catalyzed asymmetric hydrolysis of styrene oxide-type epoxides

2.3.2 Desymmetrization of Meso-Epoxides

Biocatalytic production of chiral diol derivatives via desymmetrization of *meso*-epoxides is an attractive route, which can simultaneously "construct" two contiguous stereogenic centers theoretically in 100% yield [73], as illustrated in Scheme 9. Zheng et al. [74] isolated and identified a strain of *Rhodococcus opacus* ML-0004. This epoxide hydrolase can catalyze the stereoselective hydrolysis of meso-racemic *cis*-epoxysuccinic acid (R=COOH, in *meso*-**21**), producing only L-(+)-tartaric acid. Then, the gene was cloned, sequenced, and expressed in *E. coli*. This epoxide hydrolase showed high stereospecificity and activity for L-(+)-tartaric acid, and the V_{max} was calculated to be 2.24 mM/min/mg enzyme.



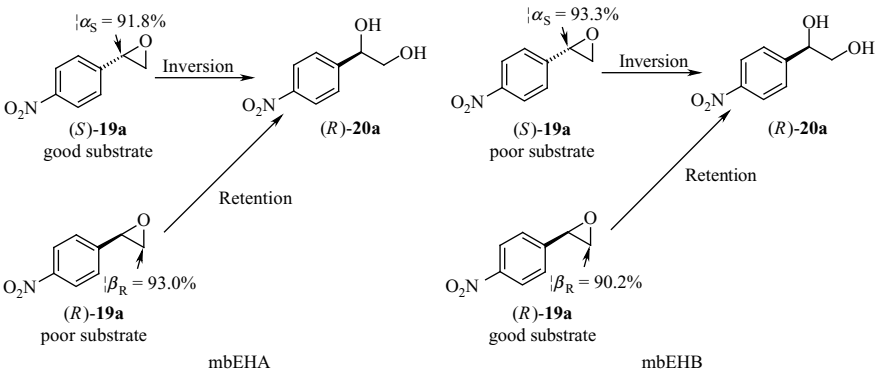
Scheme 9 Desymmetrization of *meso*-**21** catalyzed by epoxide hydrolase

2.3.3 Enantioconvergent Hydrolysis of Epoxides

During the hydrolysis process of esters catalyzed by lipases or esterases, the configuration of the chiral centers is remained. But for the epoxide hydrolase catalyzed hydrolysis of epoxides, it is not always the case. It has been known that epoxide hydrolase catalyzed hydrolysis of epoxides follows SN_2 type, so if the enzymatic attack happens at the substituted oxirane carbon atom, the configuration of the chiral carbon would be inverted, while keeping the configuration of the unattacked carbon atom unchanged.

Two epoxide hydrolases (mbEHA and mbEHB) were isolated from the crude powder of mung bean (*Phaseolus radiatus L.*) [75, 76], which catalyze the stereoselective hydrolysis of **19a** with complementary enantioselectivities. That is, (*S*)-**19a**

was a good substrate for mbEHA, while mbEHB preferred (*R*)-**19a**, as shown in Scheme 10. For mbEHA, (*S*)-**19a** was attacked at the benzylic carbon position (C_α) with a regioselectivity coefficient α_S=91.8%, affording (*R*)-**20a** via inversion of configuration, while for the poor substrate (*R*)-**19a**, the terminal carbon (C_β) was mainly attacked with a regioselectivity coefficient β_R=93.0%, thus (*R*)-**20a** was produced again with configuration retention. In this case, enantio-riched product (*R*)-**20a** was obtained from *rac*-**19a** with 100% conversion, which overcomes the limitation of maximal 50% yield in the case of conventional kinetic resolution and is referred to as enantioconvergent hydrolysis. Obviously, such a biocatalytic process is very attractive and has drawn much attention [77]. mbEHB showed similar regioselectivity toward (*R*)- and (*S*)-**19a**, as shown in Scheme 10. When the crude powder of mung bean was used as biocatalyst, (*R*)-**20a** with 82.4% *ee* was obtained when *rac*-**19a** was hydrolyzed completely. The optical purity of (*R*)-**20a** could be improved up to 99% *ee* via once recrystallization, with a total yield of 68.7%.

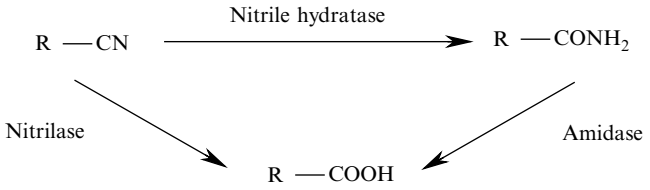


Scheme 10 Mechanism for mung bean epoxide hydrolases-catalyzed enantioconvergent biohydrolysis of *rac*-**19a**

2.4 Hydrolysis or Hydration of Nitriles with Nitrilase or Nitrile Hydratase

Nitriles are important raw materials for the synthesis of acids, amides, and other derivatives. Chiral nitriles are important building blocks for the manufacturing of pharmaceuticals, fine chemicals, and food additives. Chemical hydrolysis of nitriles requires strong acid or base at high temperatures. On the contrast, biotransformation of nitriles into the corresponding carboxamides or carboxylic acids proceeds with excellent selectivities under very mild conditions. Two types of enzyme systems are involved in the enzymatic hydrolysis of nitriles [78]. One system involves a two-step reaction: the nitrile is hydrated at first to amide by nitrile hydratase and then the amide is further hydrolyzed to carboxylic acid and ammonia by an amidase.

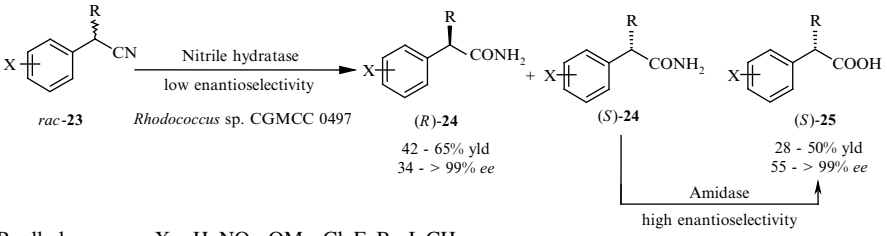
The other system involves the direct conversion of a nitrile to the corresponding carboxylic acid with the release of ammonia by a nitrilase (Scheme 11).



Scheme 11 Enzymatic conversion of nitriles

2.4.1 Conversion of α-Alkyl Substituted Phenylacetonitriles

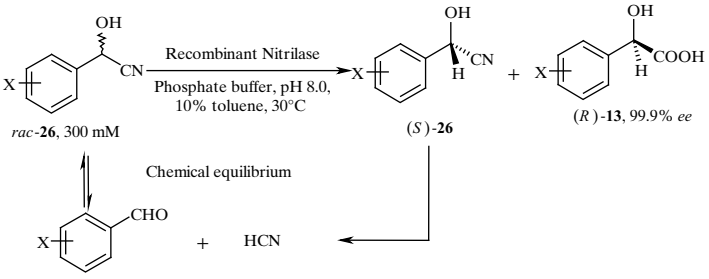
Many nitrile hydratase/amidase containing microorganisms catalyze the conversion of α-substituted phenylacetonitriles and phenylacetamides, including *Rhodococcus* sp. AJ270 [79, 80] and *Rhodococcus* sp. CGMCC 0497 [81]. Nitrile hydratases of these microorganisms showed high catalytic activity but relatively low (*R*)-selectivity against α-aryl propionitriles **23** while the amidases exhibited high (*S*)-enantioselectivity toward α-aryl propionamides [79, 81]. The amides **24** formed by a nitrile hydratase was further resolved by an amidase, affording the corresponding (*R*)-amides ((*R*)-**24**) and (*S*)-carboxylic acids ((*S*)-**25**) with high optical purities, as shown in Scheme 12. The selectivity of the hydrolysis reactions was sensitive to the position of the substitute groups: high enantioselectivity was obtained with substitute groups (X) at *meta*- or *para*-positions, whereas only moderate enantioselectivities were obtained when the substituting group was located at the *ortho*-position [81]. By this mean, enantiopure (*S*)-naproxen was prepared from racemic 2-(1′-naphthyl)propionitrile and 2-(1′-naphthyl)propionamide with high yields [81].



Scheme 12 Enantioselective bioconversion of α-alkyl phenylacetonitriles by *Rhodococcus* sp. CGMCC 0497

2.4.2 Conversion of α-Hydroxy Nitriles

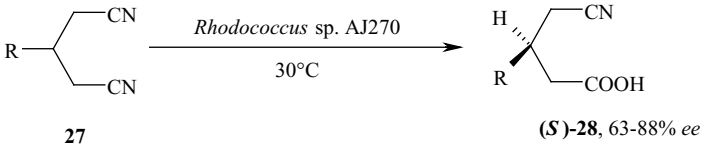
As mentioned earlier, enantiopure **13** can be obtained by lipases/esterases catalyzed hydrolysis of the corresponding esters. On the other hand, **13** can also be prepared by enantioselective hydrolysis of cyanohydrins *rac*-**26**. Due to reversible conversion of **26** to hydrogen cyanide (HCN) and the corresponding prochiral aldehyde under a high-pH environment, production of enantiopure **13** by deracemization of *rac*-**26** could be easily achieved in nitrilase catalyzed dynamic kinetic hydrolysis resolution, as shown in Scheme 13, which is much attractive with 100% theoretical yield [82]. Whole cells of *Alcaligenes* sp. ECU0401 can catalyze the deracemization of mandelonitrile (X=H, in *rac*-**26**), affording enantiopure (*R*)-**13a** (X=H) [83]. The nitrilase of *Alcaligenes* sp. ECU0401 has been cloned and overexpressed in *E. coli*, resulting in a recombinant transformant with as 160 folds higher specific activity as compared with the wild-type strain. By using the recombinant strain as biocatalyst, as high as 300 mM *rac*-26 could be completely transformed to enantiopure (*R*)-**13** in a toluene-aqueous biphasic system (unpublished data).



Scheme 13 Deracemization of *rac*-**26** for the production of (*R*)-**13** mediated by nitrilase

2.4.3 Stereoselective Conversion of Dinitriles

Whole cells of *Rhodococcus erythropolis* AJ 270 catalyze the desymmetrization of prochiral 3-alkyl- and 3-arylglutaronitriles **27** to afford *S*-(+)-3-alkyl/aryl-4-cyanobutyric acids **28** with moderate enantioselectivities [84, 85] (Scheme 14). Interestingly, addition of acetone or β-cyclodextrin into the reaction mixture elevated the enantioselectivities significantly [84]. From the hydrolysis product (*S*)-**28a**, optically active amino acid (*R*)-(−)-4-amino-3-phenylbutyric acid and lactone (*R*)-(−)-4-phenyltetrahydropyran-2-one were obtained by further chemical conversion [84].



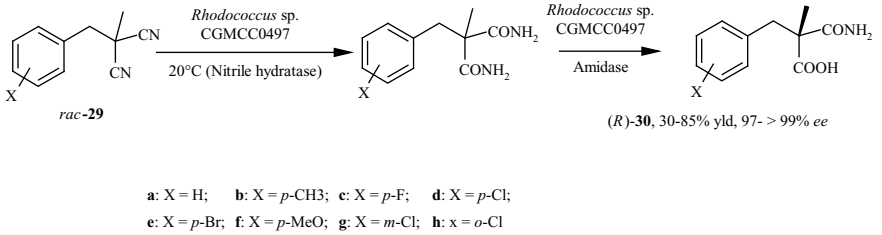
27

a: R = Ph; b: R = 4-F-Ph; c: R = 4-Cl-Ph; d: R = 4-CH_3-Ph;

(*S*)-28, 63-88% *ee*

Scheme 14 Desymmetrization of 3-substituted glutaronitrile compounds

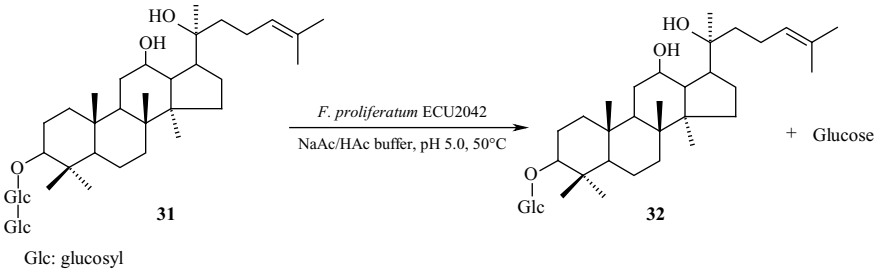
Moreover, highly enantioselective hydrolysis of α, α-disubstituted malononitriles **29** by the strain *Rhodococcus* sp. CGMCC 0497 expressing both nitrile hydratase and amidase activity to give (*R*)-**30** were reported, as shown in Scheme 15 [86]. The yields of the enantiopure products were remarkably improved at a lower reaction temperature of 20°C as compared with that at 30°C. (*R*)-**30** can be further converted to valuable α-alkylated amino acids.



Scheme 15 Biocatalyzed desymmetrization of prochiral malononitriles

2.5 Hydrolysis of Glycoside by Glycosidase

Many natural glycosides with steroids or triterpenes as aglycons are physiologically active compounds. Sugar chains of the saponins were found to be closely related to the biological activity of the saponins, so modification of saponins sugar chain may markedly change the biological activity of the saponins. A fungus strain, *F. proliferatum* ECU2042, was isolated with an intention to enzymatically hydrolyze a ginsenoside Rg_3 (**31**) to produce a more potent antitumor agent Rh_2 (**32**) (Scheme 16) [87]. The β-glucosidase purified from *F. proliferatum* ECU2042 catalyzes the hydrolysis of 3-C, β-(1→2)-glucoside of **31**, but not β-D-glucosidic bond of **32** [88]. This enzyme also exhibited significant activity towards various alkyl glucosides, aryl glucosides, and several natural glycosides [88]. Addition of some biocompatible nonionic surfactants was proved to promote the hydrolysis conversion of **31** [89].



Scheme 16 Enzymatic hydrolysis of ginsenside Rg3 to Rh2

3 Carbonyl Reduction Reactions

Biocatalyzed asymmetric reduction of carbonyl compounds is perhaps one of the most important, fundamental, and practical reactions for the preparation of optically active chiral alcohols, which are versatile chiral synthons for the synthesis of industrially important chemicals, such as pharmaceuticals, flavors, agrochemicals, vitamins, antibiotics, and pheromones [16].

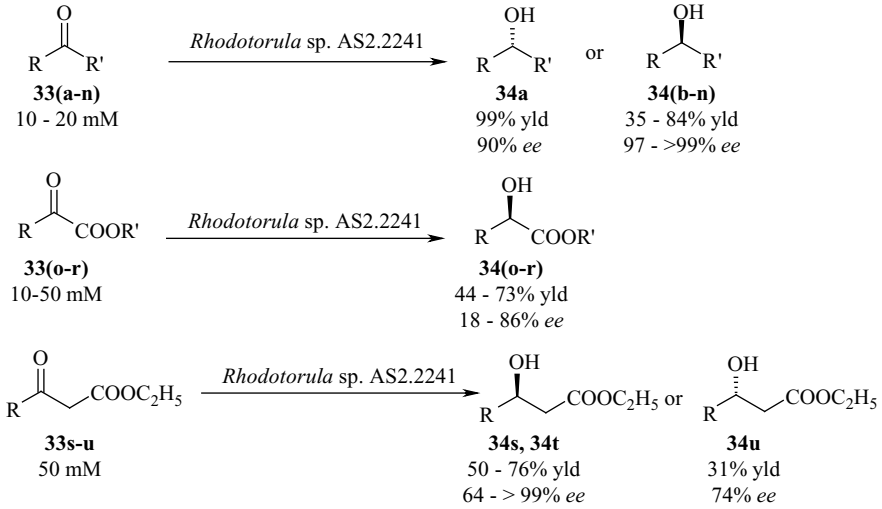
Compared with the lipase/esterase catalyzed kinetic resolution of alcohols, dehydrogenase catalyzed ketones reduction has the advantage that enantiopure *sec*-alcohols can be directly obtained from prochiral ketones possibly in 100% yield, although bioreduction also has a disadvantage that the presence of the cofactors in reduced state, including β-1,4-nicotinamide adenindinucleotide (NADH) or β-1,4-nicotinamide adenindinucleotide phosphate (NADPH), is absolutely needed. Prices of these cofactors are too high to be used stoichiometrically, so whole cells with the full cofactor in situ regeneration systems are often used for efficient bioreduction processes.

3.1 Asymmetric Reduction of Prochiral Ketones

3.1.1 Prelog Conversion

Alcohol dehydrogenases (ADHs) exist widely in nature, thus reductases with high activity and enantioselectivity can be obtained by rational high throughput screening from the nature [90]. Baker's yeast (*S. cerevisiae*) is the most famous biocatalyst frequently used in reduction of aldehydes and ketones due to its easy availability and cheap price. *S. cerevisiae* ADH showed moderate to high enantioselectivities toward various carbonyl compounds, ranging from simple aliphatic ketones to complex functionalized carbonyl compounds, such as cyclic or aromatic ketones and β-ketoesters, thus enabling organic chemists to use the whole cells of *S. cerevisiae* as a good bioreduction catalyst for preparing chiral hydroxyl compounds [91, 92].

A newly isolated red yeast, *Rhodotorula* sp. AS2.2241 [93], exhibited high activities and excellent enantioselectivities (>97% *ee*) for acetyltrimethylsilane **33a** [94], aromatic ketones **33b–33l** (except **33g**) [95], and acetylpyridines **33m–33o** [95], however with moderate enantioselectivities for α-keto esters **33p–33s** and β-keto esters **33u–33v** except for **33t** [95] (Scheme 17).



a-g: R' = CH_3; a: R = $Si(CH_3)_3$; b: R = Ph; c: R = *p*-NO_2-Ph; d: R =*p*-Br-Ph; e: R = *p*-Cl-Ph; f: R = *p*-MeO-Ph;

g-j: R = Ph; g: R' = CH_2Br; h: R' = CH_2Cl; i: R' = C_2H_5; j: R' = C_2H_4Cl;

k: R' = *p*-NO_2-Ph, R' = CH_2Br

l-n: R' = CH_3; l: R = 2-pyridyl; m: R = 3-pyridyl; n: R = 4-pyridyl,

o-r: R = Ph; o:R' = CH_3; p: R' = $CH(CH_3)_2$; q: R' = $C(CH_3)_3$; r: R = *m*-Me-Ph, R' = C_2H_5

s: R = Ph; t: R = CH_2Cl; u: R = CH_3

Scheme 17 Asymmetric reduction of various ketones by *Rhodotorula* sp. AS2.2241

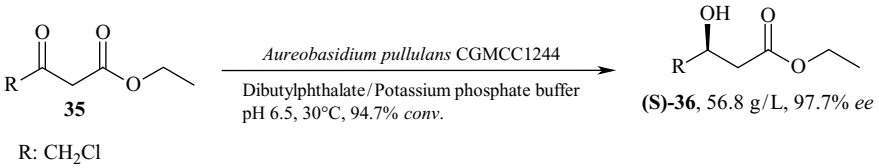
Aromatic ketones were found to be toxic to microorganisms, and the resultant corresponding alcohols could inhibit the dehydrogenase severely, thus limiting the bioreduction of substrate occurring at a high concentration. Many approaches have been explored to address this problem, including screening of novel strains with high substrate tolerance, employing solid–liquid biphasic system, or other reaction systems to reduce the substrate/product concentration in aqueous environment. By changing screening strategies, increasing substrate concentration in screening medium and using medium supplemented with small amount of yeast extract to improve the viability of microbes, a bacterial strain *Bacillus* sp. ECU0013 was isolated with excellent enantioselectivities and very high substrate tolerance against aryl ketones. As high as 200 mM of **33h** could be transformed with moderate conversion [96]. Addition of adsorption resins into reaction medium is efficient to weaken substrate/product inhibition. By employing hydrophobic resins in the *Rhodotorula* sp. cells catalyzed reduction of **33b**, conversion of the ketone was increased from 54 to 91% as compared with the control without hydrophobic resin, and the death rate of cells was decreased from 99 to 10% when the substrate concentration was 100 mM [97]. The resin could be reused after desorption of product by ethanol. In addition, a cloud-point system was demonstrated to be an

effective biotransformation medium for **33b** reduction by resting cells of *S. cerevisiae* [98]. The maximum inhibitory concentration of **33b** was enhanced to >1.0% (v/v) in cloud point system as compared with that of 0.8% (v/v) for the control.

Recently, a new resource of biocatalyst for asymmetric reduction of aromatic ketones was discovered from a common plant seed, adzuki bean [99]. By using crude meal of adzuki bean as the biocatalyst, various aromatic ketones (**33b**–**33c**, **33f**, **33g**, **33i**, **33l**–**33n**, *m*-MeO- acetophenone and 2-acetylthiophene) at relatively high concentrations (e.g., 100 mM) were efficiently reduced with excellent stereoselectivities (>98% *ee*).

A new dehydrogenase catalyzing the dehydrogenation of mannitol and regenerating NADPH from $NADP^+$ was discovered from the cell-free extract of *Rhodotorula* sp. AS2.2241 [100]. By using the cell-free extract as biocatalyst and mannitol as cosubstrate, **33l** was efficiently reduced with a catalytic amount of NADPH, giving (*S*)-**34l** in >99% *ee*, with a total turnover number (TTN) of 4,220 for NADPH recycling. In addition, it was confirmed that NADPH is also the reducing cofactor of adzuki bean reductase and can be regenerated by the endogenous cofactor regeneration system using glucose as an auxiliary substrate [99].

Bioreduction is a useful method for the preparation of enantiopure **36**. Sun et al. [101] utilized whole cells of a fungus strain, *Aureobasidium pullulans* CGMCC1244, for highly stereoselective reduction of ethyl 4-chloro-3-oxobutanoate (R=CH_2Cl, in **35**) to ethyl (*S*)-4-chloro-3-hydroxybutanoate (R=CH_2Cl, in **36**) in a biphasic system composed of potassium phosphate buffer and dibutylphthalate. After optimization of reaction conditions, the maximum concentration of (*S*)-**36** (R=CH_2Cl) in the organic phase reached 56.8 g/L, with an optical purity of 97.7% *ee* (Scheme 18).



Scheme 18 Biocatalyzed stereoselective reduction of **35**

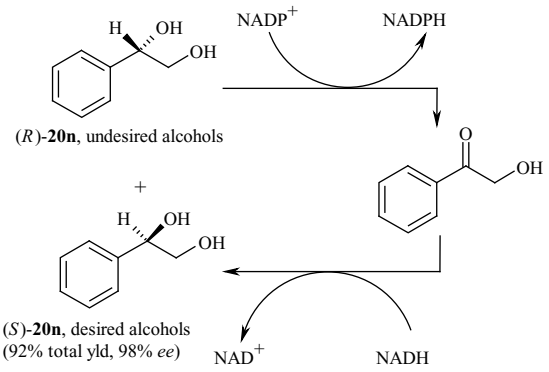
3.1.2 Anti-Prelog Reduction

So far, the enzyme catalyzing the *anti*-Prelog reduction of ketones has been rarely reported. Li et al. isolated an *anti*-Prelog reductive fungus, *Geotrichum* sp. 38, from a large number of cultures [102]. Aryl α-halomethyl ketones [103], aryl α-hydroxymethyl ketones [103, 104], and aryl α-acetoxy ketones [104] with different substituents on the aromatic ring, except the chloro and nitro groups on the *ortho*-position, were reduced by whole cells of *Geotrichum* sp. 38 with *anti*-Prelog mode, giving aryl halohydrins, 1,2-diol, and monoacetates with *S*-configuration and with moderate to excellent enantioselectivities.

3.2 Deracemization of sec-Alcohols

Biocatalyzed deracemization of alcohols has drawn much attention as attractive optically pure single enantiomers can be obtained from relatively cheap racemic alcohols through such a transformation process. The undesired enantiomer is oxidized stereoselectively to an intermediate ketone with the assistance of oxidative cofactor while the desired enantiomer is produced by asymmetric reduction from the intermediate ketone. One of the examples was the deracemization of **20n** using whole cells of *Candida parapsilosis* CCTCC M203011. In this case, the undesired (*R*)-**20n** was oxidized with $NADP^+$ as the cofactor and in the meantime enantiopure (*S*)-**20n** was produced with an optical purity of 98% *ee* and 92% total yield using NADH as the cofactor [105], as elucidated in Scheme 19.

Scheme 19 Sketch map of enzymatic deracemization of *sec*-alcohols



4 Biooxidation Reactions

4.1 Asymmetric Oxygenation

Enzyme catalyzed asymmetric oxygenation reactions include benzylic/allylic hydroxylation, epoxidation, Baeyer–Villiger oxidation, and heteroatom oxidation. Several types of enzymes involve the biocatalytic asymmetric oxidation, including monooxygenases, dioxygenases, and chloroperoxidases.

Oxygenases are enzymes that introduce one or two oxygen atoms of molecular oxygen into an organic molecule. Monooxygenase catalyzes the addition of a single oxygen atom from molecular oxygen into a substrate molecule while the other oxygen atom is reduced to water by a reduced cofactor NADH or NADPH. Monooxygenases are the most versatile oxidative enzymes and become increasingly attractive for organic synthesis because they can catalyze various asymmetric oxidation of a wide range of organic substances under mild conditions [106]. By using whole cells of *Rhizopus* sp. as oxygenation biocatalysts, llα-hydroxyprogesterone was obtained through oxygenation of steroids at carbon-11 in one simple step with

high conversion and excellent enantioselectivities and regioselectivities [8], while by conventional chemical techniques, the same conversion needs more than ten steps with subsequent protection and deprotection. This invention advanced the development of steroids industry. Whole cells systems are often employed in monooxygenase-catalyzed reactions because most monooxygenases are membrane associated, not very stable and sensitive to the oxygen spray, and more importantly, a reduced cofactor (e.g., NADPH) is needed [107].

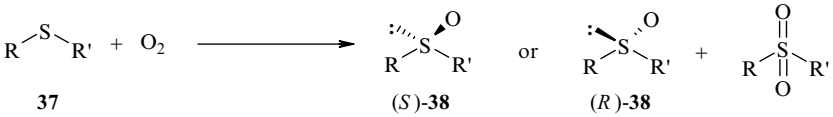
Recently, a novel sulfide oxidation bacterium, *Rhodococcus* sp. ECU0066, was isolated from soil samples. It catalyzed the asymmetric oxidation of **37a**–**37e** with high activities and good enantioselectivities, to afford (*S*)-sulfoxide with >90% *ee* (Table 6), indicating a good potential for practical application in asymmetric synthesis of chiral sulfoxides. Investigations showed that the resting cells catalyze the sulfoxidation of **37a** to (*S*)-**38a** with only moderate enantioselectivity, but the undesired (*R*)-**38a** formed in minority could be further oxidized by the same cells to achiral sulfone, thus resulting in a significantly improved optical purity (99% *ee*) for the product (*S*)-**38a**. A monooxygenase have been cloned from *Rhodococcus* sp. ECU0066, which showed significant sulfoxidation activity towards **37**, giving (*S*)-sulfoxides with moderate to excellent stereoselectivities [108].

4.2 Biocatalytic Oxidative Resolution

Biocatalytic oxidative resolution is an alternative method for preparation of optically active *sec*-alcohols, especially when the corresponding *rac*-alcohols are readily available. This method is particularly attractive when coupled with a selective carbonyl reduction reaction, thus an efficient deracemization of *sec*-alcohol is established, as described in Sect. 2.

As a type of *sec*-alcohols, optically active **13** can also be obtained by biooxidative resolution of *rac*-**13**, in addition to enzymatic hydrolysis of mandelates and mandelonitriles. Wide screening was preformed for isolation of microorganisms

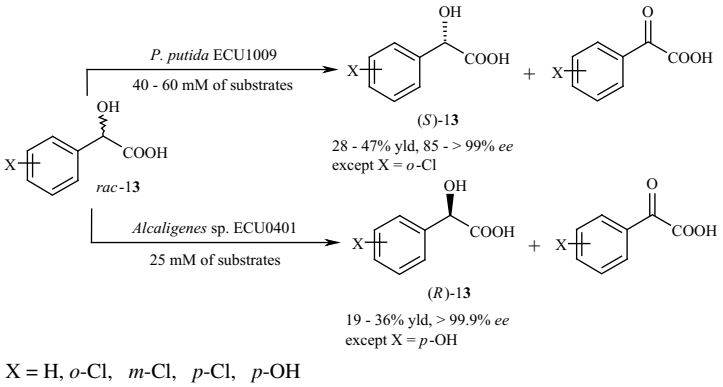
Table 6 Enantioselective oxidation of prochiral sulfides **37**



37 (*S*)-**38** (*R*)-**38**

	R	R′	Yield (%)	*Ee* (%)
a	Ph	Me	44.2	99.0 (*S*)
b	*p*-CH_3-Ph	Me	85.7	97.3 (*S*)
c	*p*-F-Ph	Me	69.6	91.7 (*S*)
d	*p*-Cl-Ph	Me	60.0	98.8 (*S*)
e	2-Thiazolyl	Me	13.7	71.3 (*S*)
f	*p*-MeO-Ph	Me	61.2	38.2 (*R*)
g	Ph	Et	81.8	17.4 (*S*)

catalyzing the enantioselective degradation of one enantiomer of *rac*-**13**. Two strains, *Pseudomonas putida* ECU1009 [109] and *Alcaligenes* sp. ECU0401 [110] were found to degrade **13a**–**13e** with complementary enantioselectivities. The former degrades (*R*)-**13** preferentially, while the later prefers (*S*)-**13**. Using the resting cells as biocatalyst, optically pure **13** was thus prepared by asymmetric degradation of *rac*-**13** with high yields, as shown in Scheme 20.



Scheme 20 Biocatalytic oxidation for preparation of optically pure **13**

Furthermore, since the microorganisms could metabolize and utilize the mandelate, a fed-batch culture was performed using *rac*-**13a** as the carbon source [110, 111]. Using this strategy, enantiopure (*S*)-**13a** and (*R*)-**13a** were prepared, respectively, with 41% yield by *P. putida* ECU1009 [111] and 32.8% yield by *Alcaligenes* sp. ECU0401 [110], based on 30 g/L of *rac*-**13a**.

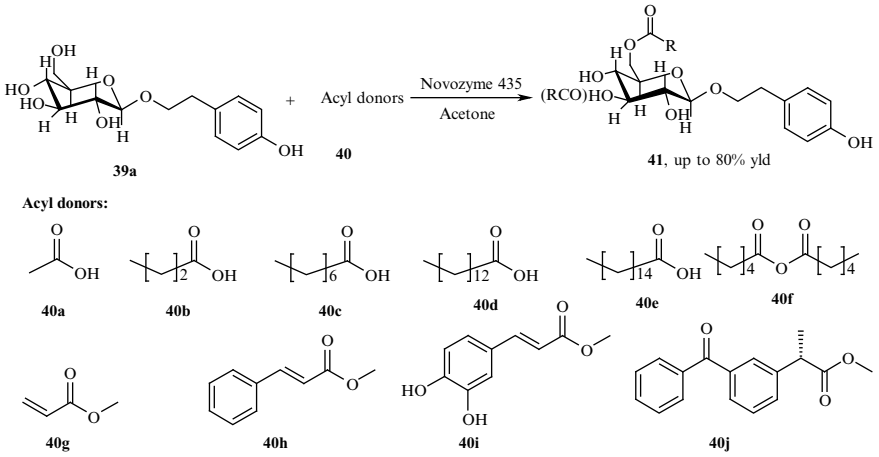
5 Acyl-Transfer Reactions Using Esterase/Lipase

Hydrolysis of esters catalyzed by lipase or esterase is reversible. In dry organic solvent, lipase/esterase can also catalyze the enantioselective esterification of chiral alcohols or acids. Water is formed during the esterification, which will significantly retard the reaction rate and enantioselectivity, so enzyme-catalyzed direct esterification of acids and alcohols was rarely reported. Instead, transesterification reaction was usually used to avoid the formation of water.

5.1 Esterification

Salidroside (**39a**), a natural glycoside, was derived into sugar esters **41** using commercial lipase as biocatalyst, as shown in Scheme 21 [112]. The yield of the synthesis of acetyl salidroside reached 80% in the presence of 3 Å molecular sieves in anhydrous *t*-PeOH system. Two products were observed when a short-chain

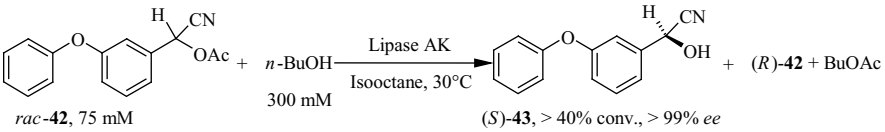
carboxyl acid **40a**–**40d** was adopted as the acyl donors. While for long chain aliphatic acid **40e**–**40g**, only a single product could be obtained. No product was detected when free aromatic acids were used. However, the situation changed completely, giving rise to single product, when their corresponding methyl esters **40h**–**40j** were supplied as acyl donors. Based on these results, a combinatorial catalysis approach was performed for the construction of glycoconjugates array by **using** glycosidase and lipase in nonaqueous media. This array was started from glucose, with three aryl alcohols as the aglycon moiety of glycosides and five acids or esters as acyl donors for combinatorial acylation of glycosides, affording a three-dimensional array containing about 30 members with diverse structures [113].



Scheme 21 Enzymatic synthesis of novel salidroside esters

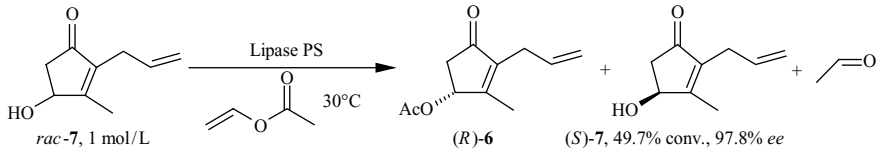
5.2 Transesterification Resolution

Synthesis of (*S*)-α-cyano-3-phenoxybenzyl alcohol (**43**) was successfully achieved by lipase-catalyzed alcoholysis of *rac*-**42** in an organic medium, as shown in Scheme 22 [114]. A commercially available *Pseudomonas fluorescens* lipase, Lipase AK (Amano), showed excellent enantioselectivity ($ee_p > 99\%$, $E = 568$) and high alcoholysis activity (1.88 μmol/min/mg enzyme) towards (*S*)-ester. The water effect was suppressed by the presence of anhydrous sodium sulfate. Effect of solvents on the conversion was then investigated. It was shown that hydrophobic organic solvents, such as isooctane, were favored for this reaction, while polar solvents deactivated the lipase. Chain length of aliphatic alcohols (C_2–C_5) has little effect on the initial rate of alcoholysis. *n*-Butanol was selected as hydroxyl donor and the optimal concentration was 200–500 mM. A celite-adsorbed preparation of Lipase AK was used repeatedly for the alcoholysis resolution. After eight batches of reaction, no significant loss of enzyme activity was observed.



Scheme 22 Preparation of (*S*)-**43** by lipase-catalyzed enantioselective alcoholysis

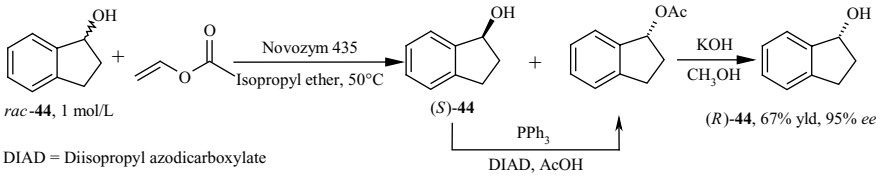
Another commercial lipase, lipase PS, from *Burkholderia cepacia*, was coated by didodecyl *N*-D-glucono-L-glutamate (DGG) [115] and stearic acid [116], or adsorbed on microcrystal salt and celite [116], and afterwards used in the preparation of optically pure (*S*)-**7** in a solvent free system. Vinyl acetate was acted as both acyl donor and reaction solvent, with a merit that the acyl transfer product, vinyl alcohol, can be spontaneously transformed to acetaldehyde by molecular rearrangement, which makes transesterification irreversible. As low as 1.0 g/L of stearic acid-modified lipase PS was enough for the acylation of as high as 1 mol/L of *rac*-**7**, affording (*S*)-**7** with 97.8% *ee* at 49.7% conversion in 25 h (Scheme 23).



Scheme 23 Enantioselective transesterification of *rac*-**8** with vinyl acetate by lipase PS

5.3 Chemo-Enzymatic Deracemization

Ou et al. investigated the esterification of *rac*-**34b** and *rac*-**44** by a commercial lipase, *Candida antarctica* lipase (Novozym 435) [117]. Vinyl acetate was selected as the acyl donor and diisopropyl ether as the reaction medium. An efficient bioresolution system was established, affording ca. 49.5–50.2% conversion for both the two alcohols, with >99% *ee* for the unreacted (*S*)-alcohols in repeated batch reactions. The volumetric productivities reached 529 and 198 g/L/d, respectively. Based on the enzymatic resolution of alcohols, in situ Mitsunobu inversion of the unreacted



Scheme 24 Preparation of (*R*)-indanol by chemoenzymatic deracemization

(*S*)-alcohols was performed. Preparation of (*R*)-**44** by chemoenzymatic deracemization was shown in Scheme 24. Finally, (*R*)-**44** and (*R*)-**34b** were obtained in 95% and 97% *ee*, and in 67% and 71% totally isolated yields, respectively.

6 Glycosyl-Transfer Reactions

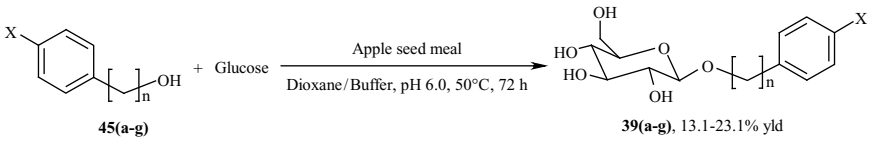
Chemical method for glycoside synthesis such as Koenigs–Knorr method requires multisteps of protection and deprotection. Enzymatic synthesis is attractive as they might allow the regio- and stereospecific synthesis of a target structure without extra tedious protection and deprotection steps.

6.1 Glycosidase-Catalyzed Reverse Hydrolysis

As the glycosidase-catalyzed hydrolysis reaction of glycoside is reversible, the thermodynamic procedure of direct reversal of glycoside hydrolysis is usually carried out in medium with low water activity. High concentration of free monosaccharide and alcohol are used as substrates to shift the reaction equilibrium from glycoside hydrolysis to glycosylation. If the alcohols are in liquid state at the reaction temperature (e.g., 50°C) and have no strong denaturing or inhibiting effect on the enzyme, then a solvent-free system can be adopted. Otherwise, use of a water-miscible organic solvent is necessary. The water-miscible organic such as dimethyl formamide, dimethylsulfoxide, dioxane, pyridine, and *tert*-butanol solvents may be chosen for this purpose [118].

Plant seeds are good glycosidase sources [119]. Almond β-D-glucosidase was used in glycosylation of *p*-nitrobenzyl alcohol with D-glucose through reverse hydrolysis in a monophasic aqueous–organic medium, producing *p*-nitrobenzyl β-D-glucopyranoside [120]. Dioxane was an appropriate organic solvent for this synthetic procedure. The ratio of dioxane to water has significant effect on the stability and activity of almond β-D-glucosidase. The stability of glucosidase was raised but the stability was declined when the dioxane content was increased from 50 to 90% (v/v). Under the optimal reaction conditions, i.e., 90% dioxane (v/v) + 10% buffer (Na_2HPO_4–KH_2PO_4, 70 mM, pH 6.0) with an alcohol-to-glucose molar ratio of 9:1, *p*-nitrobenzyl β-D-glucopyranoside was produced in a yield of 13.3%. According to investigation, the low yield was caused by the thermodynamic equilibrium.

Crude meal of apple seed is another source of good glycosidase catalyst for glycoside synthesis, and the active β-glycosidase components have been purified and characterized [121]. A facile method was reported for enzymatic glycosylation of tyrosol (**45a**) and four-substituted benzyl alcohols (**45b–g**) with glucose using crude meal of apple seed as catalyst in a monophasic aqueous-dioxane medium [122]. The corresponding β-D-glucosides **39a–39g** were synthesized in 13.1–23.1% yields (Scheme 25).

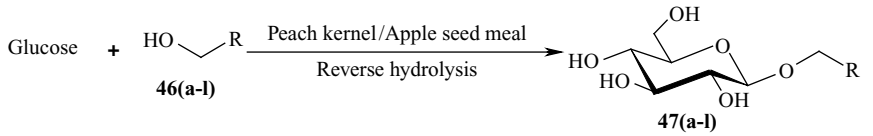


45(a-g) **39(a-g)**, 13.1-23.1% yld

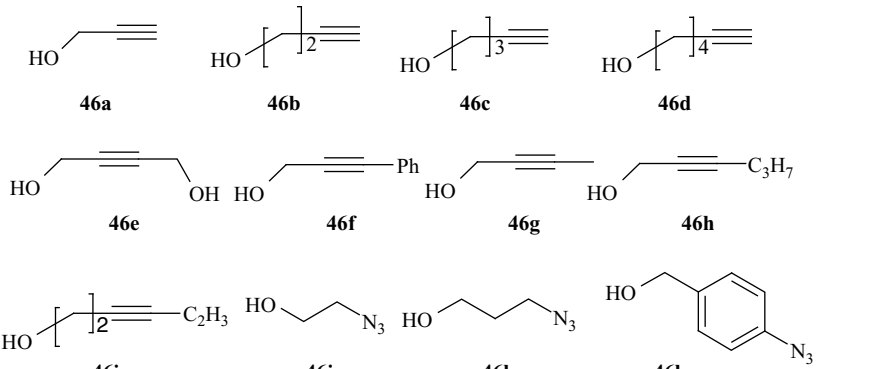
a: n = 2, X = OH; **b**: n = 1, X = H; **c**: n = 1, X = OCH_3;
d: n = 1, X = CH_3; **e**: n = 1, X = NO_2; **f**: n = 1, X = F; **g**: n = 1, X = Cl;

Scheme 25 Synthesis of β-D-glucopyranosides by reverse hydrolysis

Table 7 Glycosylation of alkynyl alcohols and azide-containing alcohols



46(a-l) **47(a-l)**



46a **46b** **46c** **46d**

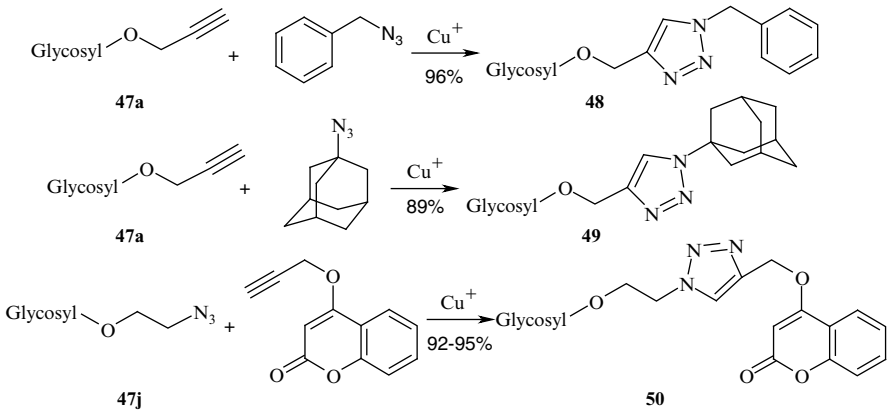
46e **46f** **46g** **46h**

46i **46j** **46k** **46l**

Substrates	Yield (%)	Substrates	Yield (%)	Substrates	Yield (%)
46a	32–35	**46e**	27–31	**46i**	15–16
46b	30–31	**46f**	12	**46j**	39–45
46c	17–18	**46g**	5–12	**46k**	51–53
46d	15–16	**46h**	9–14	**46l**	N.R.

In order to improve the usage of the raw material and simplify the product extraction, selective adsorption of glycoside was developed so that the unreacted substrate (aglycon) could be recycled for use, and the adsorbed glycoside was then eluted by appropriate solvent and refined. Alumina was successfully used for salidroside adsorption [123]. An efficient system for synthesis of **39a** was established, which was composed of a batch stirred tank reactor and an alumina adsorption column. The productivity of **39a** reached ca. 1.9 g/L/d.

Recently, glycosidation of alkynyl alcohols **46a**–**46i** and azide-containing alcohols **46j**–**46l** was carried out (Table 7), followed by a click reaction, affording various types of triazole glycosides (Scheme 26) [124]. Some alkynl glycosides, such



Scheme 26 Synthesis of triazole glycosides by click reactions

as **47d** and **47f**, and triazole containing glucoside **50** were found to have antifungal activities.

6.2 Glycosidase-Catalyzed Transglycosylation Reaction

Glycosidase catalyzed transglycosylation reaction is an efficient alternative for glycoside synthesis. In transglycosylation reaction, an activated glycosyl is linked onto a glycosyl acceptor catalyzed by an appropriate glycosidase through an enzyme–glycosyl intermediate, which is trapped by nucleophile glycosyl acceptor other than water to yield a new glycoside. Since the new glycoside formed during the reaction is also a substrate for the enzyme in hydrolysis, a successful transglycosylation reaction depends on the following crucial points: the rate of transglycosylation must be faster than that of glycoside hydrolysis and the hydrolysis rate of product must be slower than that of the glycosyl donor. The activated glycosyl donor usually possesses an aglycon moiety with good leaving property but poor nucleophilicity, such as fluoro, azido, (hetero)aryl, vinyl, or allyl group. Although an activated glycoside was required for transglycosylation reaction, the reaction is kinetically controlled and usually gives higher glycoside yields as compared with reverse hydrolysis.

Lin et al. found that galactosidase from *Aspergillus oryzae* catalyzed transglycosidation of galactosyl from galactose onto alcohols **46a**–**46l**, giving corresponding alkynyl and azide containing β-galactosides with acceptable yields. Followed by click reactions, triazole containing galactosides were obtained and two of them (compound **51** and **52**, Fig. 1) possess antifungal activities [124].

Hu et al. [125, 126] discovered a β-D-glycosidase of broad specificity from viscera of *Achatina fulica* (China white jade snail), which could efficiently catalyze the transfer of β-D-fucosyl, β-D-glucosyl, or β-D-galactosyl moiety from the corresponding *p*-nitrophenyl-β-D-glycosides and some disaccharides to various glycosyl acceptors,

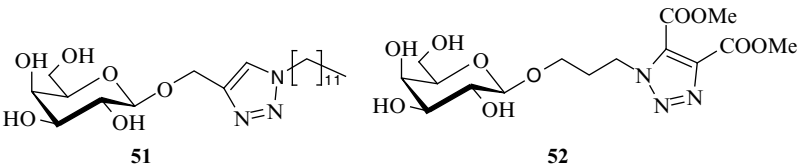
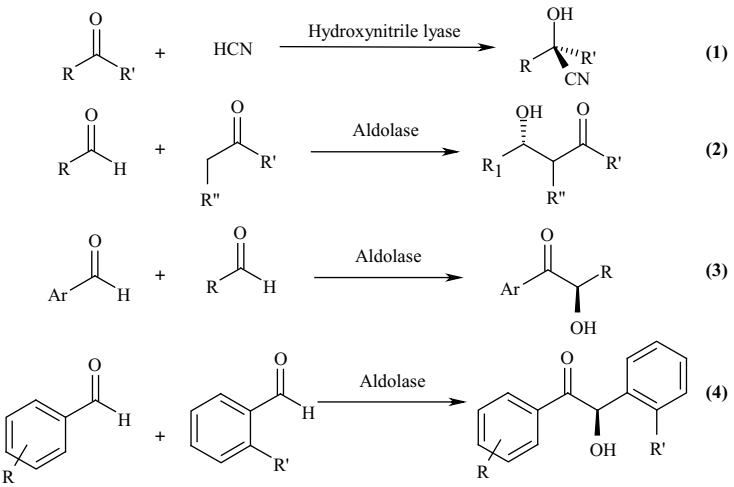


Fig. 1 Triazole containing β-galactosides with antifungal activities

such as alkyl alcohols [125] and monosaccharides [126]. By using *p*-nitrophenyl-β-D-fucopyranoside as the glycosyl donor and glucose or xylose as the acceptor, the product yields reached 88 and 93%, respectively. The product of glucosyl transfer was isolated and identified as β-fucosyl-1,6-glucose by an NMR analysis [126].

7 Formation of C–C Bonds

Lyases catalyze reversibly stereoselective addition of nucleophilic donor onto prochiral electrophilic acceptors with double bonds. Some lyase-catalyzed reactions, such as cyanohydrins formation by hydroxynitrile lyases (reaction 1), aldol reactions (reaction 2), acyloin reactions (reaction 3), and benzoin reactions (reaction 4), catalyzed by aldolases have attracted much attention in organic synthesis due to the ability of forming new C–C bonds with chiral stereocenters, as presented in Scheme 27.



Scheme 27 Some lyases-catalyzed reactions

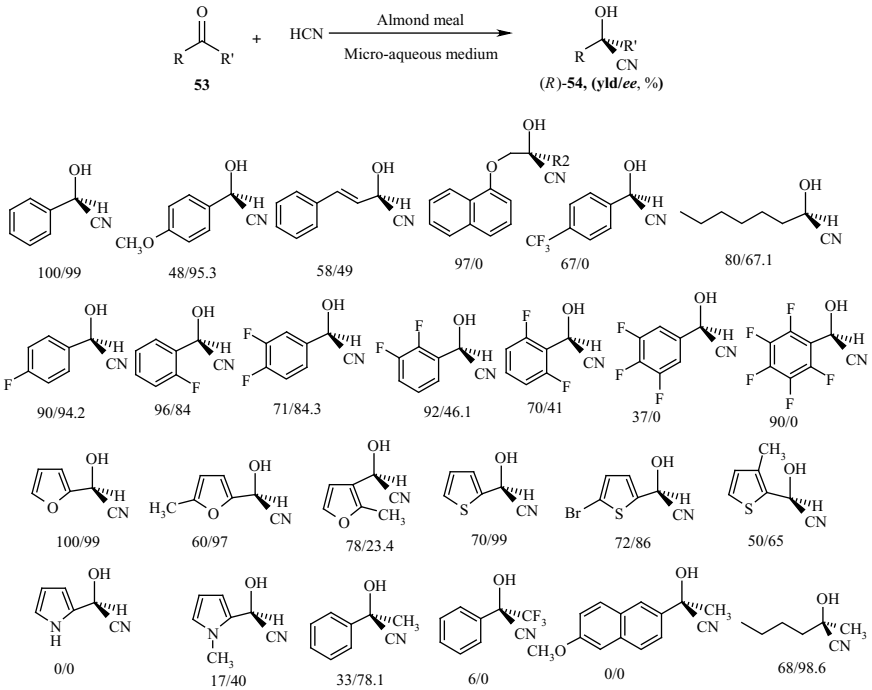
In as early as 1920, fermenting yeast was used to catalyze the stereoselective acyloin condensation of benzaldehyde and endogenous acetaldehyde to form (*R*)-1-hydroxy-1-phenylpropanone for the production of (–)-ephedrine. Even today, most synthetic ephedrine derivatives are produced by this method, which shows the

efficiency of this process [16]. Therefore, it is not surprising that these reactions have been increasingly used in fine chemical industry.

7.1 Preparation of Cyanohydrins Using Hydroxynitrile Lyase

Hydroxynitrile lyases (Hnls) are important biocatalysts for the synthesis of optically pure cyanohydrins, which are important precursors or building blocks for a wide range of high value-added fine chemicals [127]. Hnls occur widely in microorganisms and plants, and it was found that Hnls from plants prefer to form (*R*)-cyanohydrins while microbial Hnls are often (*S*)-selective [128]. Fruit seeds meals, including that of almond (*Prunus armeniaca L.*), peach (*Prunus persica L.*), and Loquat (*Eriobotrya L.*) kernels, are good sources of (*R*)-oxynitrilase [129].

Hnl-catalyzed formation of cyanohydrins is usually competed with nonenzymatic cyanohydrin reaction to some extent. In order to inhibit and avoid the nonenzymatic addition, a microaqueous system was established using isopropyl ether as the organic solvent for the enzymatic synthesis of (*R*)-cyanohydrins [130]. Various aliphatic and aromatic aldehydes, fluoro-substituted benzaldehydes, furanyl carboxaldehydes, thien-2-yl carboxaldehydes, pyrrolyl carboxaldehydes, as well as aryl and alkyl ketones were accepted as carbonyl substrates (Scheme 28), affording enantio-riched (*R*)-**54** [129–132].



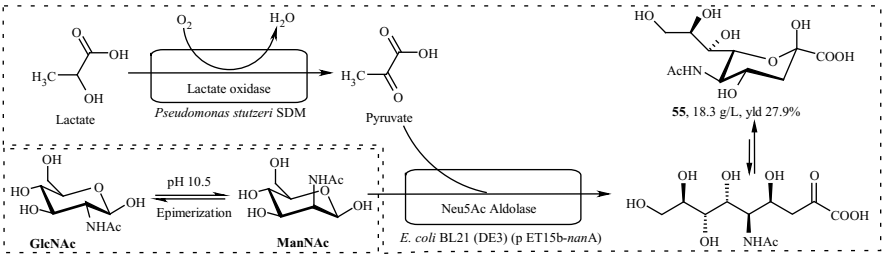
Scheme 28 Enantioselective synthesis of cyanohydrins from various aldehydes and ketones

A high throughput continuous process was developed for the synthesis of chiral cyanohydrins [133]. Pretreated almond meal (or other solid raw enzyme sources) was loaded into a tube-like reactor, substrate in solution and the solution of HCN were mixed and supplied to the column continuously; the elution containing the (*R*)-cyanohydrin with high enantiopurity was collected. The efficiency of the column bioreactor was very high. The ratios of substrates benzaldehyde and furanyl-2-carboxaldehyde to pure (*R*)-oxynitrilase (S/C) were estimated as 66.7 mol/g and 40 mol/g, respectively, and the time-space productivities were calculated as 3,630 and 1,176 g/L/d, respectively. The resultant cyanohydrins were sufficiently pure and could be used as intermediates for further reaction directly without purification.

7.2 Aldolase Catalyzed Synthesis of Sugar Derivatives

Aldolase catalyzed aldol, acyloin, and benzoin reactions are important C–C bond-formation reactions and act as key steps in asymmetric synthesis of complex chiral molecules [134], Aldolases are also widely used in bioorganic chemistry for asymmetric synthesis of rare sugars and sugar-derived compounds such as iminocyclitols, statins, epothilones, and sialic acids. The application of aldolases for asymmetric aldol reactions in chemoenzymatic synthesis has been reviewed in-depth over the past years [135], mostly from the viewpoint of bioorganic chemists.

Xu et al. [136] efficiently synthesized *N*-acetyl-D-neuraminic acid (Neu5Ac, **55**) by using lactate and a mixture of *N*-acetyl-D-glucosamine (GlcNAc) and *N*-acetyl-D-mannosamine (ManNAc) as substrates (Scheme 29). The biotransformation had two steps: production of pyruvate from lactate catalyzed by the whole cells of *Pseudomonas stutzeri* expressing lactate oxidase, and the addition of pyruvate onto ManNAc utilizing the recombinant *E. coli* cells containing the Neu5Ac aldolase. After 20 h of reaction, 18.3 g/L of **55** was obtained. Since lactate is much cheaper than pyruvate, the biosynthetic process of **55** catalyzed by combination of two kinds of cells efficiently reduced the cost and can be compared favorably with natural product extraction and/or chemical synthesis processes.



Scheme 29 A procedure for the production of **55** from GlcNAc/ManNAc and lactate

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Enantioselective Biotransformations of Nitriles

Mei-Xiang Wang

Abstract Enantioselective biotransformations of nitriles using nitrile hydrolyzing microbial whole cell catalysts are a powerful method for the synthesis of highly enantioenriched carboxylic acids and amide derivatives. In this article, progress of *Rhodococcus erythropolis* AJ270-catalyzed enantioselective biotransformations of nitriles including various functionalized nitriles, α- and β-amino nitriles and β-hydroxy nitriles, cyclopropane-, oxirane-, aziridine- and azetidine-containing carbonitriles is summarized. Applications of enantioselective biotransformations of these nitriles in the synthesis of natural and bioactive products are also discussed.

Keywords Amidase • Amide biotransformation • Carboxylic acid • Nitrile biotransformation • Nitrile hydratase

Contents

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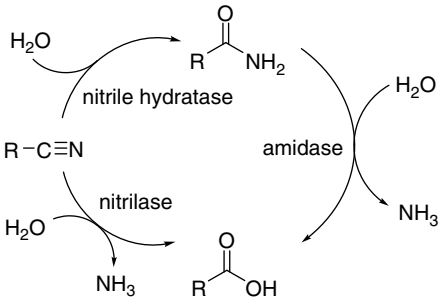
1 Introduction

Nitriles are useful intermediates in organic synthesis because they are easily available and, more importantly, they can be readily transformed into diverse functional organic compounds [1]. The simplest transformations of nitriles are the hydration and the hydrolysis reactions, and they are used extensively to produce carboxamides and carboxylic acids, respectively. However, chemical hydration and hydrolysis generally require harsh conditions such as using a strong acid or base under heating. They suffer from low reaction efficiency and poor selectivity. Chemical transformations of nitriles also generate a large amount of waste.

In *Nature*, nitriles are degraded by various biological systems [2]. Nitrile biotransformations have been revealed to proceed through two distinct pathways (Scheme 1) (For an overview, see: [3]). Catalyzed by nitrilase, nitriles are converted directly into the corresponding carboxylic acids, while in the presence of nitrile hydratase, nitriles are hydrated to give amides, which undergo further hydrolysis with the aid of amidase to afford carboxylic acids. Till now, a large number of nitrile-hydrolyzing microorganisms have been reported [4], and microbial hydrolysis of nitriles has been utilized in industry and in academia to synthesize amide and carboxylic acid products [5–7]. In comparison with the conventional chemical hydration and hydrolysis of nitriles, the salient advantages of nitrile biotransformations include high catalytic efficiency, excellent chemo-, regio- and enantio-selectivities, and very mild reaction conditions. Most noticeably, nitrile biotransformations have been shown to display intriguing and high enantioselectivity that enables the synthesis of enantiopure carboxylic acids and amides, synthetically valuable organonitrogen compounds, which are not readily available from chemical synthesis [5–7].

Rhodococcus erythropolis AJ270 is a microorganism isolated from a soil sample by Colby and his coworkers in the mid-1990s [8, 9]. The biochemical and genetic studies have indicated that it contains both nitrile hydratase and amidase [9, 10]. The high-resolution X-ray molecular structure of the nitrile hydratase shows it is an iron-containing enzyme [11]. The mechanism of nitrile hydration involves activation of cyano group by a water molecule that is bonded to iron of the enzyme. Our early



Scheme 1 Nitrile biodegradation pathways

studies showed that *Rh. erythropolis* AJ270 is a stable and powerful microbial whole cell catalyst able to transform a large number of aliphatic and aromatic nitriles [12, 13] and dinitriles [14, 15]. In recent years, we have been systematically investigating the enantioselective biotransformations of nitriles and amides using *Rh. erythropolis* AJ270 biocatalyst. We have demonstrated that these biotransformations are a very useful synthetic method for the preparation of highly enantiopure carboxylic acids and their amide derivatives [6, 7]. In this chapter, I will summarize our recent progress in this area.

2 Biotransformations of Functionalized Nitriles

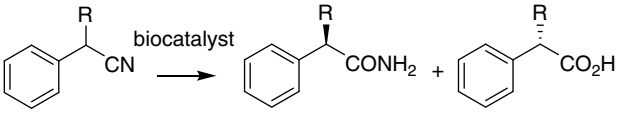
To explore synthetic potentials of enantioselective nitrile biotransformations and also to have a deep insight into the biocatalytic mechanisms, a number of racemic and functionalized nitriles have been examined [16–19]. In general, *Rh. erythropolis* AJ270 catalyzed biotransformations of (±)-**1** proceed efficiently under very mild conditions to afford enantioenriched amide (*R*)-**2** and acid (*S*)-**3** products with high enantiomeric ratio (*E*) [20, 21]. Results summarized in Table 1 indicate that the overall biotransformation rate is determined predominantly by the steric effect of the substituent R. Increase of the bulkiness of the substituent such as from methyl [(±)**1a**] to ethyl [(±)-**1b**], isopropyl [(±)-**1c**] and *n*-propyl [(±)-**1d**] leads to the decrease of biotransformations (entries 1–4, Table 1) [16, 17]. Noticeably, however, the unsaturated carbon–carbon bond, especially the allyl group [(±)-**1e**] facilitates the reactions (entry 5, Table 1) [18, 19]. Studies [14–17] also reveal that the nitrile hydratase shows good catalytic activity against all substrates except racemic 2-phenylpentanenitrile (±)-**1d**, the enantioselectivity, however, appears very low. This has been exemplified by very low enantiomeric excess (ee) values obtained for both nitrile and amide products from the nitrile hydratase-catalyzed kinetic resolution of nitriles (±)-**1**. The overall excellent enantioselectivity of nitrile biotransformations shown in Table 1 originates from the amidase. This is also evidenced by the amidase-catalyzed kinetic resolution of racemic amides (±)-**2**, which affords high yields of amide and acid products with high ee values. It is concluded that the nitrile hydratase is an active enzyme but with none or low enantioselectivity, while the amidase is highly enantioselective and very sensitive to the steric effect of the substrates [16–19].

The release of steric crowdedness of the substrates (±)-**1** by inserting one methylene between benzene ring and α-chiral center leads to dramatic increase of reaction efficiency [19]. In comparison with (±)-**1** (Table 1), for example, racemic α-substituted β-phenylpropanenitriles (±)-**4a–d** undergo much fast biotransformations to produce enantioenriched amides **5a–d** and acids **6a–d** in very good yields (entries 1–6, Table 2). The biocatalytic reactions of all functionalized substrates (±)-**4a–d** give good to excellent enantioselectivity with enantiomeric ratio (*E*) being in the range of 32 to >200. For allenyl- and vinyl-substituted nitriles, biotransformations proceed even efficiently at 20°C to give the corresponding amide and acid

products with improved enantioselectivity (entries 4 and 6, Table 2). Very intriguingly, when the unsaturated bond including allyl, propargyl, and allenyl is reduced to propyl, the racemic nitrile (±)-**4e** undergoes sluggish hydrolysis to form amide (R)-**5e** and acid (S)-**6e** with only moderate ee values (entry 7, Table 2).

The effect of an unsaturated carbon–carbon bond on the biocatalytic efficiency and enantioselectivity is also observed in the biotransformations of racemic 3-arylpent-4-enenitriles (±)-**7**, the substrates bearing a chiral center at the β-position to hydrolytic reaction group [22]. The efficient reactions afford highly enantiopure amides (*S*)-**8** and acids (*R*)-**9** in very good yields (entries 1–8, Table 3). The biotransformations can be easily scaled up, and amide (*S*)-**8a** and

Table 1 Biotransformations of α-substituted phenylacetonitriles[a]

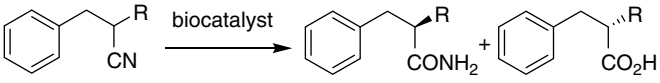


(±)-**1** (*R*)-**2** (*S*)-**3**

Entry	**1**	R	Time (h)	**2** (%)	ee (%)	**3** (%)	ee (%)	*E*
1	**1a**	Me	10	42	>99.5	48	90	99
2	**1b**	Et	96	34	96	40	>99.5	>200
3	**1c**	i-Pr	120	47	>99.5	46	>99.5	>200
4	**1d**	*n*-Pr	168	Trace	–	2	>99.5	–
5	**1e**	Allyl	75	48	>99.5	49	95.5	>200
6	**1f**	Propargyl	144	49	98.6	51	94.8	>200

[a] The biocatalytic reaction was performed by incubating substrate with *Rhodococcus erythropolis* AJ270 cells (2 g wet weight) in potassium phosphate buffer (0.1 M, pH 7.0, 50 mL) at 30°C. The yield is isolated yield and the ee value is determined by chiral HPLC analysis. *E* is calculated following a literature method [21]

Table 2 Biotransformations of α-substituted β-phenylpropanenitriles[a]



(±)-**4** (*R*)- or (*S*)-**5** (*S*)- or (*R*)-**6**

Entry	**4**	R	Time (h)	**5** (%)	ee (%)	**6** (%)	ee (%)	*E*
1	**4a**	Allyl	5.5	49	95.4	47	>99.5	>200
2	**4b**	Propargyl	14.5	48	>99.5	50	94.5	>200
3	**4c**	Allenyl	2.5	42	98.5	54	82.3	52
4	**4c**[b]	Allenyl	4	48	>99.5	46	92.5	144
5	**4d**	Vinyl	0.58	48	90.0	51	83.1	32
6	**4d**[b]	Vinyl	1	50	87.0	46	90.9	60
7	**4e**	*n*-Pr	96	47	66.5	47	52.8	6.3

[a] See footnote of Table 1

[b] Reaction was carried out at 20°C

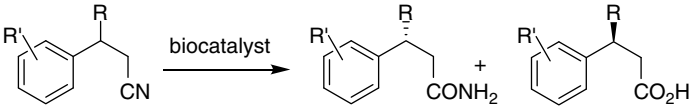
acid (*R*)-**9a** were prepared on a multigram scale (entry 2, Table 3). When vinyl substituent is replaced by ethyl group, the biocatalytic reaction of (±)-**7h** under same reaction conditions proceeds very slowly with diminished enantioselectivity (entry 9, Table 3) [22].

The studies show that the nitrile hydratase catalyzes virtually nonenantioselective nitrile hydration reaction equally efficient against all nitrile substrates (±)-**4** and (±)-**7**, regardless of the presence or absence of a carbon–carbon unsaturated bond. The amidase-catalyzed hydrolysis of amides is influenced strongly by the structures of the amide substrates. In other words, it is the amidase that discriminate the different substituent on the amide structure, giving varied reaction rate and enantioselectivity [22].

The results compiled in Tables 1–3 indicate clearly that an unsaturated carbon–carbon bond such as vinyl, acetylenyl, and allenyl in the substrates facilitates the biocatalytic reactions. It is also beneficial for achieving high enantioselectivity of biocatalysis. Even with a vinyl group moving from α- to β-position, high efficiency and excellent enantioselectivity are obtained. It is proposed that the amidase in *Rh. erythropolis* AJ270 may contain a binding domain specific to the unsaturated carbon–carbon bond of the amide substrate. It is most likely that the binding to the unsaturated carbon–carbon bond functionality further strengthens the interaction and the recognition of the amidase with the amide substrate, leading to the significant acceleration of the reaction rate and the remarkable enhancement of the enantioselectivity [19, 22].

The highly efficient and enantioselective biocatalytic hydrolysis of functionalized nitriles and amides offers great opportunity for the straightforward generation of useful enantiomeric pure carboxylic acid and amide products. Coupled with

Table 3 Biotransformations of β-substituted β-phenylpropanenitriles[a]



(±)-**7a-g** (R = vinyl)
(±)-**7h** (R = Et)

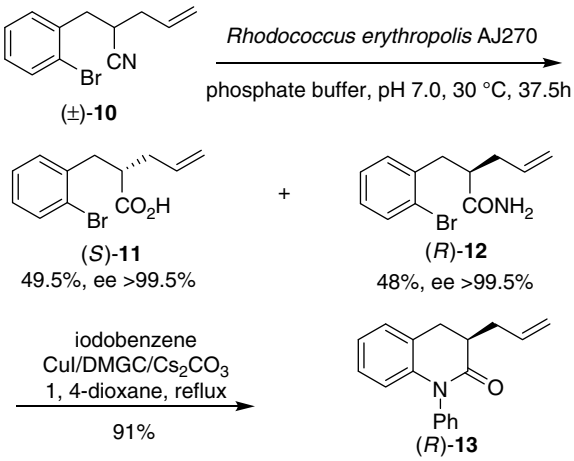
(*S*)- or (*R*)-**8**

(*R*)- or (*S*)-**9**

Entry	**7**	R′	Time (h)	**8** (%)	ee (%)	**9** (%)	ee (%)	*E*
1	**7a**	H	6.5	50	90.5	46	94.6	124
2	**7a**[b]	H	24.3	45	>99.5	49	92.5	144
3	**7b**	4-OMe	9.0	49	>99.5	50	90.0	99
4	**7c**	4-Me	10.5	49	94.9	50	95.0	145
5	**7d**	4-F	4.75	50.5	94.5	48	90.0	70
6	**7e**	4-Cl	5.5	49	97.4	50	91.0	89
7	**7f**	3-Cl	8.5	47	93.2	49	94.2	110
8	**7g**	2-Cl	3.5	51	78.9	44	92.9	66
9	**7h**	H	26	48	85.8	47	82.2	27

[a]See footnote of Table 1
[b]Nitrile (13 mmol) was used

simple chemical transformations, both antipodes of enantiomeric pure carboxylic acids and amides are readily available. The resulting enantiopure functionalized carboxylic acids and amide derivatives listed in Tables 1–3 have been employed as useful intermediates in the synthesis of chiral amino acids and various chiral heterocycles [18, 19, 22]. Scheme 2 shows a chemoenzymatic synthesis of (*R*)-3-allyl-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one (*R*)-**13** [19], an important intermediate for the synthesis of various 3-alkyl-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one derivatives, which are potent and selective norepinephrine reuptake inhibitors [23]. Starting with the enantioselective biotransformations of racemic 2-(2-bromobenzyl) pent-4-enenitrile (±)-**10**, (*R*)-2-(2-bromobenzyl)pent-4-enamide (*R*)-**12** has been obtained in an almost quantitative yield with ee of >99.5%. Catalyzed by the CuI/*N,N*-dimethylglycine (DMGC) catalyst, intra- and intermolecular *N*-arylation reactions of (*R*)-**12** in the presence of iodobenzene are effected in a one-pot reaction fashion to produce, without racemization, (*R*)-3-allyl-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one (*R*)-**13** in 91% yield [19].



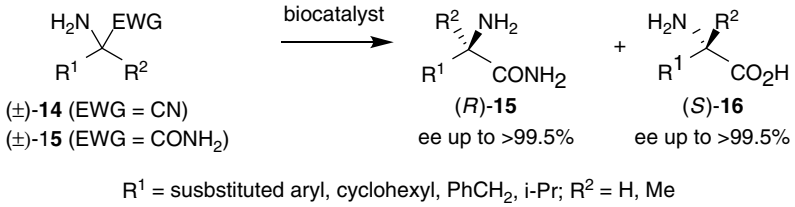
Scheme 2 Chemoenzymatic synthesis of (*R*)-3-allyl-1-phenyl-3,4-dihydro-1*H*-quinolin-2-one

3 Biotransformations of Amino and Hydroxy Nitrile Derivatives

The *Rh. erythropolis* AJ270 whole cell catalyst efficiently transforms racemic α-amino nitriles into amino amides and amino acids with excellent enantiocontrol. Although the nitrile hydratase catalyzes nitrile hydration reactions of racemic α-amino nitriles nonenantioselectively, the amidase exhibits good to excellent enantioselectivity in its catalyzed amide hydrolysis reactions. The biotransformations have been used to synthesize many nonproteinogenic and nonnaturally occurring

α-amino acids [24–26]. For example, highly enantiopure aryl and alkyl glycines and alanines (*S*)-**16** and their amide derivatives (*R*)-**15** are obtained in good efficiency from biotransformations of either α-amino nitriles (±)-**14** or α-amino amides (±)-**15** (Scheme 3). The microbial whole cell catalyst is also able to kinetically resolve racemic α-methylamino amides to yield optically active α-methylamino amides and acids [26].

In contrast to the successful enantioselective nitrile biotransformations for the preparation of α-amino acids and other chiral carboxylic acids and amide derivatives that bear an α-stereocenter (*vide supra*), biotransformations of substrates having a chiral center remote from the cyano or the amido functional group have been reported to proceed with, in most cases, disappointingly low enantioselectivity. Biotransformations of the Baylis–Hillman nitriles [27] and its one carbon homologated nitriles [28], for example, give only moderate enantioselectivity. With the exception of β-vinyl-β-phenylpropanenitrile [22] as we discussed in the previous section (Table 3), β-phenylbutyronitrile [22, 29], β- [30], γ- or δ-hydroxylated

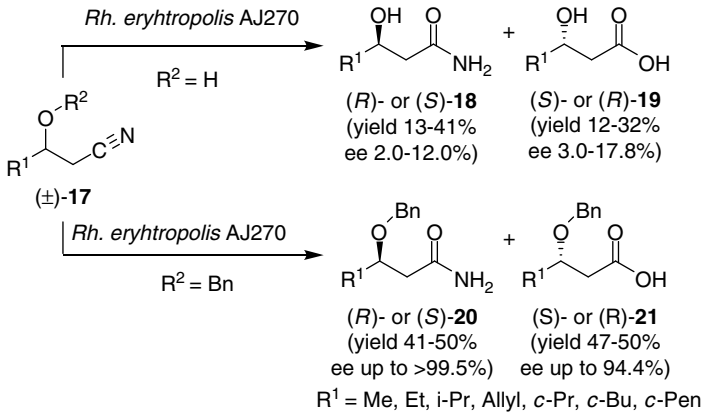


Scheme 3 Biotransformations of racemic α-amino nitriles and α-amino amides for the preparation of enantiopure α-amino acids

nitriles [31] yield no or extremely low enantiocontrol. *Rh. erythropolis* AJ270-catalyzed hydrolysis of racemic β-hydroxy nitriles (±)-**17** (R^1 = alkyl, R^2 = H) also shows poor enantioselectivity (Scheme 4). Because of the high polarity and further degradation of β-hydroxy acids, the chemical yields of the products **18** and **19** are also very low (Scheme 4) [32].

It is generally believed indeed that the movement of a stereocenter from the reactive site (α-position to functional group) to a remote place results in the decrease of enantioselectivity in catalytic asymmetric reactions. However, this notion is not always true in biocatalytic reactions since the enzyme may contain a chiral recognition pocket or domain, which is away from the active site. The careful design of the substrates might therefore achieve high enantioselectivity.

To circumvent the problem of low enantioselectivity of biotransformations of racemic β-hydroxy nitriles (±)-**17** (R^1 = alkyl, R^2 = H), a very simple and powerful protection/docking strategy is developed based on the hypothesis that chiral recognition site of the nitrile hydratase or amidase might locate in some distance to the catalytic center [32, 33]. It is found that the introduction of benzyl group on hydroxyl group increases dramatically the enantioselectivity of biotransformation. The ee values of the resulting β-benzyloxy amides **20** and acids **21** are up to



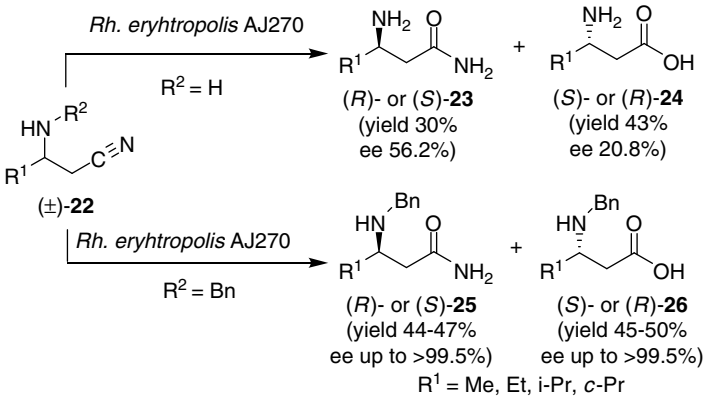
Scheme 4 Protection/docking strategy to improve the enantioselectivity of biotransformations of β-hydroxy nitriles

>99.5% and 99.4%, respectively, compared to the biotransformations of β-hydroxy nitriles (±)-**17** that give products **18** and **19** with ee values below 20% (Scheme 4). The excellent enantioselectivity is attributable most probably to the enhanced chiral recognition between the amidase and the *O*-protected β-hydroxy amides, as the nitrile hydratase shows very low enantioselectivity against *O*-benzyloxy nitriles. In addition, introduction of an *O*-benzyl group also leads to high chemical yields of the products, because the increased hydrophobicity enables their recovery from aqueous reaction media. Moreover, the presence of the benzyl protection group facilitates the detection and the monitoring of the reaction process because of its UV activity [32, 33].

The protection/docking protocol using benzyl group is also found very effective in the biotransformation of β-amino nitriles. For example, the *Rh. erythropolis* AJ270-catalyzed hydrolysis of racemic nitrile (±)-**22** (R^1 = Me, R^2 = H) gives low enantioselectivity (Scheme 5). The same reaction of N-benzylated analogs (±)-**22** (R^1 = alkyl, R^2 = Bn) affords high yields of amides (*R*)-**25** and acids (*S*)-**26** with ee up to >99.5%. As useful chiral building blocks, the benzyl protected β-hydroxy and β-amino acids and their amide derivatives can be applied directed in organic synthesis or they undergo convenient catalytic hydrogenolysis to yield debenzylated acids and amide products [33].

4 Biotransformations of Nitriles Bearing a Small (Hetero) Cyclic Unit

Chiral cyclopropane structures [34] are prevalent in natural products and synthetic pharmaceuticals and agrochemicals. Biotransformations of nitriles provide a valuable approach to enantioenriched cyclopropane carboxylic acids and their amide



Scheme 5 Enantioselective biotransformations of racemic β-amino and β-benzylamino nitriles

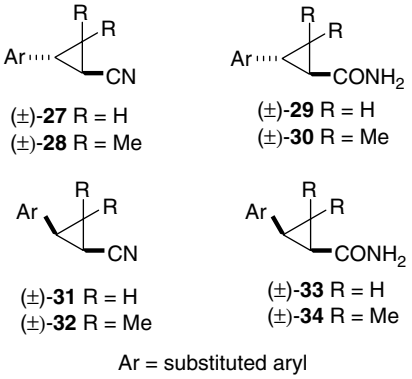


Fig. 1 Structures of racemic cyclopropanecarbonitriles and carboxamides used in biotransformations

derivatives. Furthermore, diverse racemic cyclopropane carbonitrile and carboxamide substrates can serve as molecular probes to investigate the catalytic features of the nitrile hydratase and the amidase [35–38].

A large number of *trans*-configured racemic aryl-substituted cyclopropanecarbonitriles (±)-**27** [35, 37] and (±)-**28** [38] as well as their amides (±)-**29** and (±)-**30**, *cis*-configured aryl-substituted cyclopropanecarbonitriles (±)-**31** [36, 37] and (±)-**32** [38] as well as their amides (±)-**33** and (±)-**34** (Fig. 1) have been used as substrates to examine *Rh. erythropolis* AJ270-catalyzed reactions. In terms of reaction velocity, it is found that *trans*-configured nitriles (±)-**27** and amides (±)-**29** are much better substrates than their *cis*-configured analogs (±)-**31** and (±)-**33** [37]. Increase of steric bulkiness of the substrates by the introduction of a pair of geminal methyl groups leads to decreased reaction rate of (±)-**28** and (±)-**30** [38]. The *cis*-configured nitriles (±)-**32**, for example, are not accepted at all by the biocatalyst studied [38]. While the electronic nature of a substituent on benzene ring does not impose decisive

influence on the reaction speed, the substitution pattern plays an important role on the efficiency of hydrolysis. For instance, while the substitution at the para position of the benzene ring has a negligible effect on the biotransformations of *trans*-configured substrates [35, 37, 38], it does have a detrimental effect on the reactions of *cis*-configured analogs [36, 37]. The amidase shows good enantioselectivity against both *trans*-amides (1*R*,3*R*)-**30** [38] and *cis*-amides (1*S*,2*R*)-**33** [36], but moderate enantiocontrol for *trans*-amides (1*S*, 2*S*)-**29** [35]. Interestingly, the nitrile hydratase, an enzyme regarded for long time as nonenantioselective, also shows some degrees of enantiocontrol. For example, the ee values of recovered (1*S*, 2*S*)-*trans*-2,2-dimethyl-3-phenylcyclopropanenitrile **28** (Ar=Ph) [38] and (1*S*, 2*R*)-*cis*-2-phenylcyclopropanenitrile **31** (Ar=Ph) [36, 37] from the reactions are around 99%. The observed biotransformation results are explained by the steric effect of the substrates as the *trans*-configured substrates are roughly linear in shape, whereas the *cis*-isomers adopt a heavily folded conformation [38–40].

On the basis of biocatalytic efficiency and enantioselectivity, it is proposed that a readily reachable reactive site is embedded within the spacious pocket of the nitrile hydratase [38–40]. It is therefore able to accept a wide range of substrates but with none or low enantioselectivity. Only when the nitrile substrates are sterically bulky or crowded does the nitrile hydratase show low activity with enantioselection. Excitingly, the proposal for the action of the nitrile hydratase has been proved by the high-resolution X-ray molecular structure [11]. As the enzyme structure reveals, there is indeed a large spacious pocket on the top of iron-containing active site. It can allow both antipodes of racemic nitriles entering into the pocket without effective enantiodiscrimination. On the contrary, the amidase probably comprises a relatively deep-buried and size-limited enantioselective active site. It is sensitive toward the structure of substrates and usually exhibits high enantioselectivity [38–40].

Correlation of the reaction profile with the structure of the substrates, especially with the configurations and the nature of the substituents and their substitution pattern lead to the proposal of a predictive mode in terms of reaction efficiency and enantioselectivity (Fig. 2) [38–40]. For racemic *trans*-configured cyclopropane-containing substrates, the higher reaction rate with lower enantioselectivity is expected when both substituents R^1 and R^2 are small, whereas large substituents R^1 and R^2 generally lead to very slow reaction but with high enantioselection. Good match of substituents R^1 and R^2 results in the excellent enantiocontrol with satisfactory reaction velocity. Only the substituent of R^1 is smaller than phenyl, do the hydrolyses of *cis*-3-substituted 3,3-dimethylcyclopropanecarbo-nitriles and amides proceed at an appreciable rate with excellent enantioselectivity.

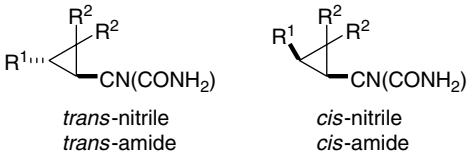
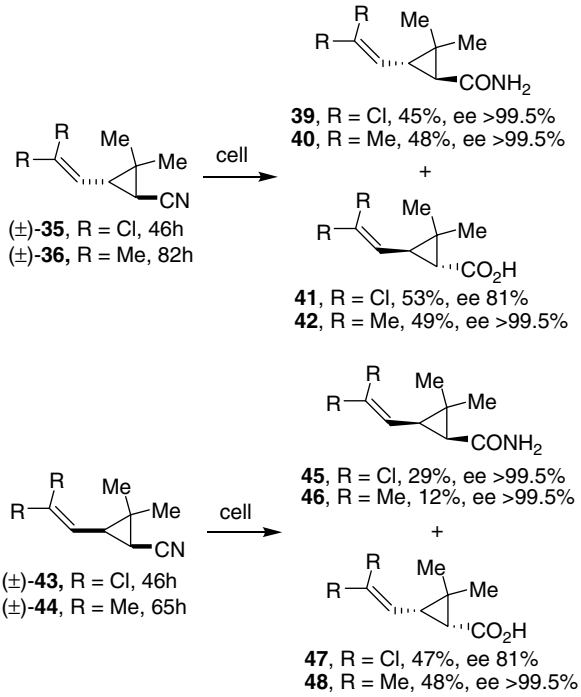


Fig. 2 Structures used for the prediction of biotransformations in terms of efficiency and enantioselectivity

To our delight, biocatalytic reactions of other cyclopropane-containing substrates [38–41] including chrysanthemic nitriles [38] and geminally dihalogenated cyclopropanecarbonitriles and amides [39, 40] have been found to follow the prediction mode very well. Illustrated in Scheme 6 are the biotransformations of *trans*- and *cis*-configured chrysanthemic nitriles [38]. Being slightly smaller than phenyl group, 2,2-dichlorovinyl substituted nitrile (±)-**35** undergoes efficient biotransformations to produce amide (1*S*, 3*R*)-**39** and acid (1*R*, 3*S*)-**41** in good yields with high ee values. Increase of steric bulkiness of the substituent from chloro to methyl results in a slower reaction of (±)-**36**, and enantiopure amide (1*S*, 3*S*)-**40** and acid (1*R*,3*R*)-**42** products are obtained in an almost quantitative yield. For the *cis*-configured substrates (±)-**43** and (±)-**44**, slow conversion of nitriles was observed, and highly enantiopure amide products (1*S*,3*S*)-**45** and (1*S*,3*R*)-**46** were obtained in low yields.

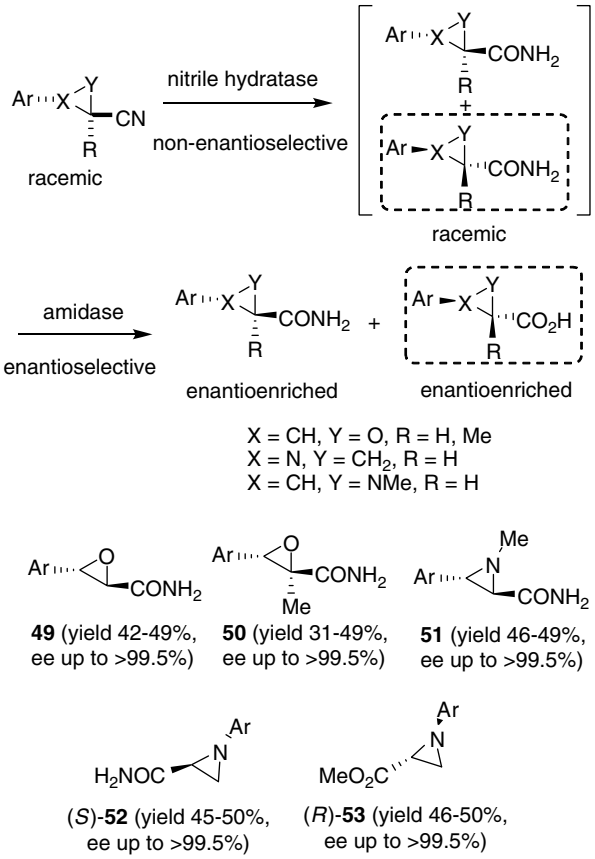
Our recent works have demonstrated that the prediction model can be extended to three-membered heterocyclic nitriles and amides [42–45]. Racemic oxirane- and aziridine-carbonitriles and -carboxamides all follow the prediction when they are interacted with *Rh. erythropolis* AJ270. As depicted in Scheme 7, all *trans*-configured racemic 3-aryloxirane-2-carbonitriles [42], 1-arylaziridine-2-carbonitrile [43], 3-aryl-1-methylaziridine-2-carbonitriles [44] and their amides undergo



Scheme 6 Enantioselective biotransformations of *trans*-and *cis*-configured racemic chrysanthemic nitriles

efficient biotransformations to afford highly enantiopure products in excellent yields. 3-Aryl-2-methyloxirane-2-carbonitriles [45], the substrates bearing a quaternary carbon center, are equally hydrolyzed under biocatalytic conditions. It should be pointed out that with the exception of biotransformations of racemic 1-arylaziridine-2-carbonitriles which give both amides (*S*)-**52** and acids (isolated as methyl ester (*R*)-**53**) [43], reactions of all substrates do not allow the isolation of acid products because they undergo spontaneous decomposition under reaction conditions [42, 44, 45].

It is interesting to address that the amidase involved in *Rh. erythropolis* AJ270 is able to recognize all three-membered ring-containing carboxamides with a *trans*-aryl substituent in the same steric sense. In other words, irrespective of the nature of the three-membered ring, all racemic amides are kinetically resolved into the optically active amides and acids by the amidase following the same chiral selection mode (Scheme 7) [41, 43–45]. This fits well with the hypothesis



Scheme 7 Enantioselective biotransformations of racemic oxiranecarbonitriles and aziridinecarbonitriles

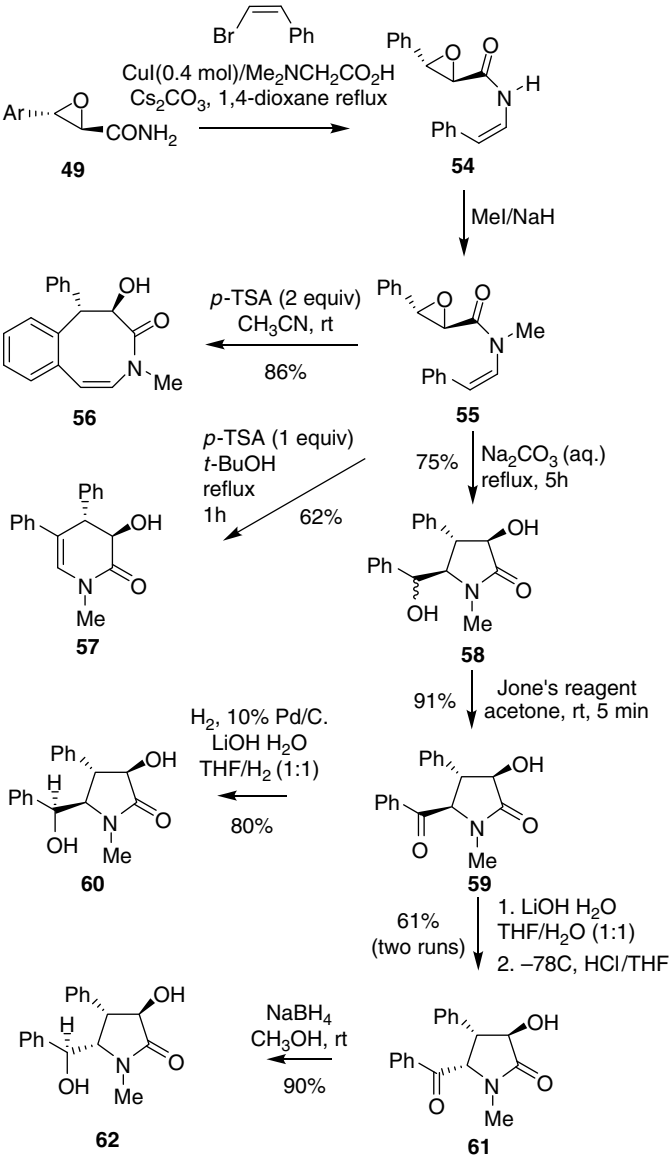
that the amidase might comprise a deeply buried and highly steric-demanding active site [38].

The highly enantiopure oxirane- and aziridine-containing carboxamides and esters listed in Scheme 7 are not readily available from conventional chemical synthesis. They are unique and valuable intermediates in organic synthesis. The ring opening reactions of three-membered heterocycles obtained, for example, provide efficient routes to unusual hydroxyl acids, amino acids and diamino acids [42–45]. Using enantiopure oxirane-containing carboxamide (2*R*,3*S*)-**49** as the key starting material, we have very recently accomplished the biomimetic synthesis of clausena alkaloids [46–48].

Rutaceae Clausena *lansium* (Lour.) Skeels is a fruit tree widely distributed in southern China. In folk medicine, its leaves and fruits are used to treat asthma, influenza, gastrointestinal disorders, viral hepatitis, and dermatological diseases. Due to the pioneering work of Huang and her co-workers in the mid to late 1980s [49], a number of clausena alkaloids including clausenamide **62**, neoclausenamide **60** (a diastereoisomer of clausenamide), homoclausenamide **57** and ζ-clausenamide **56** were isolated from the hot-water extract of the leaves (Scheme 8). Clausena alkaloids have been shown to possess efficacious liver-protecting and antiamnesia effects. In 1996, *N*-methyl-*N*-[(*Z*)-styryl]-3-phenyloxirane-2-carboxamide, SB-204900 **55**, was isolated from a hexane extract of Clausena *lansium* leaves (Scheme 8) [50].

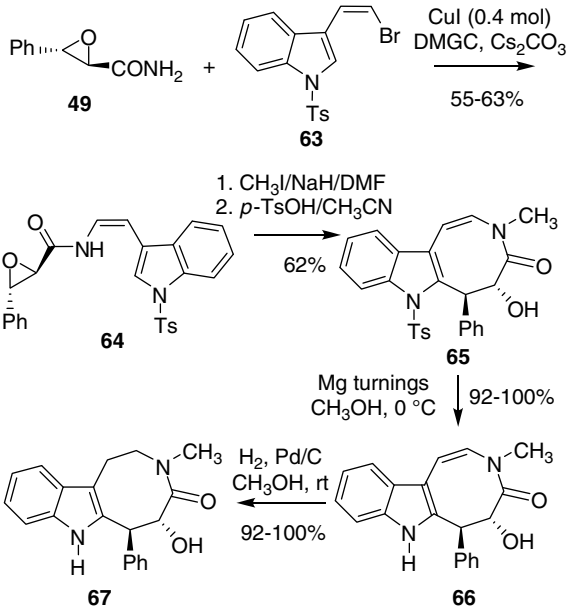
Despite important pharmacological activity and interesting molecular structures, the synthesis of clausena alkaloids has remained largely unexplored [46–48]. Having had enantiopure oxirane-containing carboxamide (2*R*,3*S*)-**49**, (2*R*,3*S*)-SB204900 was synthesized from the CuI-catalyzed cross coupling reaction with *Z*-styryl bromide followed by the exclusive N-methylation with the aid of sodium hydride [46]. Remarkably, (2*R*,3*S*)-SB204900 is found to undergo different intramolecular cyclization reactions under varied conditions to furnish eight-membered ζ-clausenamide (5*R*,6*S*)-**56**, six-membered homoclausenamide (3*R*,4*S*)-**57** and five-membered neoclausenamide and its six-epimer [46, 47]. Selective oxidation of a mixture of neoclausenamide and its epimer forms ketone **59**. Enolization of the ketone in the presence of LiOH and the subsequent protonation under kinetic conditions at −78°C leads to the epimerization of **59** into **61**. Reduction of ketone **61** using $NaBH_4$ furnishes clausenamide **62** in good yield (Scheme 8) [48]. Enantiopure oxiranecarboxamide (2*R*,3*S*)-**49** has also been employed successfully in the synthesis of (5*R*,6*S*)-balasubramide **67** [46, 48], an indole-fused eight-membered lactam-containing alkaloid isolated from Clausena *indica* [51], which grows in the central montane rainforests in Sri Lanka (Scheme 9).

In addition to nitriles and amides bearing a three-membered ring such as cyclopropane, oxirane, and aziridine, four-membered heterocyclic nitriles and amides are also excellent substrates to *Rhodococcu*s erythropolis AJ270 biocatalyst. Very recently, we [52] have shown that a number of racemic 1-arylmethylazetidine-2-carbonitriles (±)-**68** ($R^1 = R^2 = H$), and their amide substrates (±)-**69** ($R^1 = R^2 = H$) undergo efficient and enantioselective biotransformations to afford the

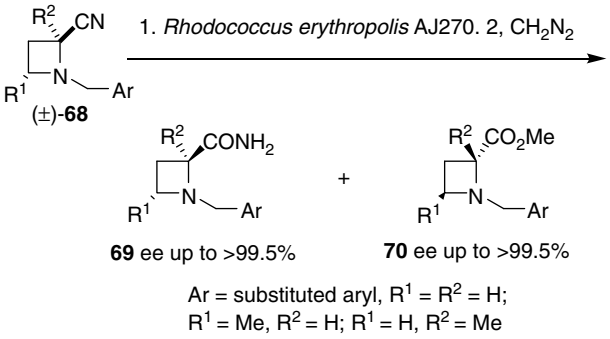


Scheme 8 Application of oxiranecarboxamide in the synthesis of clausena alkaloids

Scheme 9 Synthesis of balasubramide from oxiranecarboxamide



corresponding azetidine-2-carboxylic acids (*R*)-**70** and their amide derivatives (*S*)-**69** in excellent yields with ee up to >99.5% (Scheme 10). Disubstituted substrates, racemic *trans*-1-benzyl-4-methylazetidine-2-carbonitrile (±)-**68** (R^1 = Me, R^2 = H) and its amide (±)-**69** (R^1 Me, = R^2 = H), quaternary carbon-bearing 1-benzyl-2-methylazetidine-2-carbonitrile (±)-**68** (R^1 = H, R^2 = Me) and its amide (±)-**69** (R^1 = H, R^2 = Me) are transformed under the same conditions to produce highly enantioenriched amide and acid products in good yields. The impressive enantioselectivity of overall nitrile biotransformations stems from the combination of the low enantioselective nitrile hydratase and the high (*R*)-enantioselective amidase



Scheme 10 Enantioselective biotransformations of racemic azetidine-2-nitriles

involved in *Rhodococcus erythropolis* AJ270 whole cell catalyst. The resulting azetidine-2-carboxylic acid derivatives are interesting intermediates, and their ring opening reactions by nucleophiles such as azide, cyanide, and phenoxide give rise to the formation of functionalized γ-amino carboxylic acid derivatives [52].

5 Outlook

Owning to the easy preparation of virtually all kinds of nitrile substrates, availability of nitrile-hydrolyzing biocatalysts and very mild reaction conditions, efficient and enantioselective nitrile biotransformations provide a powerful method for the synthesis of highly enantioenriched carboxylic acids and amide derivatives that are not readily accessible from conventional chemical synthesis. It is expected that nitrile biotransformations will be more frequently applied in the generation of chiral building blocks that are key intermediates in the synthesis of natural and bioactive compounds. The elucidation of the structure of the amidase and the understanding of mechanism of the amidase are also expected in the years to come.

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Asymmetric Epoxidation Catalyzed by Chiral Ketones

Man Kin Wong, Yiu Chung Yip, and Dan Yang

Abstract Chiral ketones have been developed as efficient catalysts for asymmetric alkene epoxidation in the past decades. The development of different classes of chiral ketones for asymmetric epoxidation of unfunctionalized alkenes will be discussed. In addition, studies on diastereoselective epoxidation are also covered.

Keywords Asymmetric epoxidation • Chiral ketones • Dioxiranes • Epoxides

Contents

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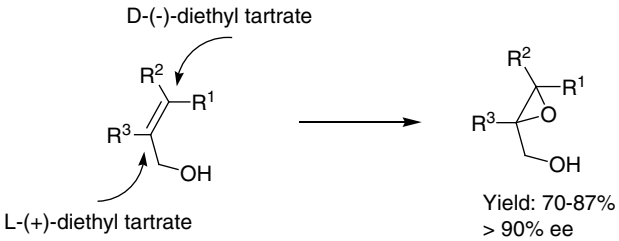
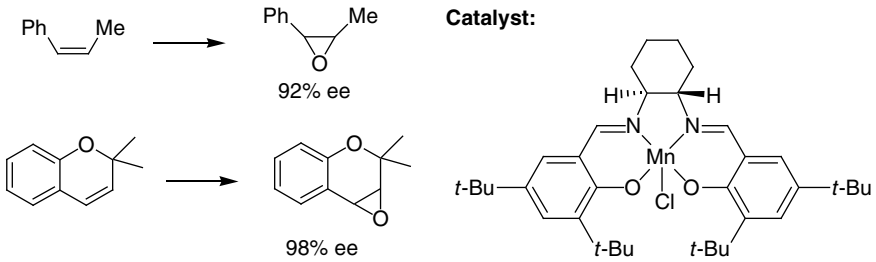
1 Introduction

Epoxides are recognized as an important class of functionality, which plays crucial roles in both chemistry and biology. In the realm of chemistry, epoxides are widely employed as key synthetic intermediates in organic synthesis. Within biological contexts, many natural products such as triptolide, epothilone A and B, and cryptophycin A contain epoxides as the principal structural moieties that are responsible for their biological activities. Not surprisingly, the development of effective epoxidation method has received considerable attention over the decades.



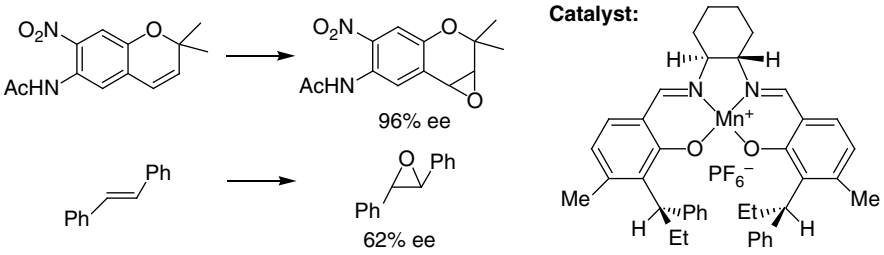
Scheme 1 Sharpless epoxidaton

Sharpless epoxidation [1] is the first general method for catalytic asymmetric epoxidation of allylic alcohols, but this is not effective for epoxidation of unfunctionalized olefins (Scheme 1). Later, Jacobsen and co-workers [2, 3] reported the use of chiral Mn(salen) complexes for catalytic asymmetric epoxidation of unfunctionalized olefins to produce *cis*-epoxides (1991) and *trans*-epoxides from *cis*-olefins (1994) in the presence of cinchona alkaloid-derived salts (Scheme 2).



Scheme 2 Chiral Mn(salen) complex for asymmetric epoxidation

Apart from that, Katsuki and co-workers [4] developed optically active salen complexes containing stereogenic centers not only at C1″ and C2″ but also at C8 and C8′ carbons (Scheme 3).



Scheme 3 Chiral Mn(salen) complex for asymmetric epoxidation

The feasibility of employing chiral dioxiranes in asymmetric epoxidation of unfunctionalized olefin was first demonstrated by Curci and co-workers [5] (Fig. 1). High yield was obtained but enantioselectivity was low (up to 20% ee). Therefore, we set out to design and synthesize efficient ketone catalysts that can achieve high enantioselectivity.

Dioxiranes contain a three-membered cyclic peroxide structure, as shown in (Fig. 2). Dioxiranes can perform epoxidation under neutral reaction conditions. They are highly reactive toward both electron-rich and electron-deficient olefins, and thus are important reagents for the synthesis of epoxides. In oxidation reactions, dioxiranes can be either generated in situ from $KHSO_5$ and catalytic amount of ketones, or in isolated form.

In 1974, Montgomery reported an interesting observation that oxygen is evolved during decomposition of $KHSO_5$, with acetone as the catalyst. He suggested that the addition of a monoperoxysulfate anion to a ketone would lead to the formation of the "Criegee" intermediate, which is proposed for the Baeyer–Villiger reaction. The intermediate will then undergo decomposition to yield a dioxirane (Scheme 4).

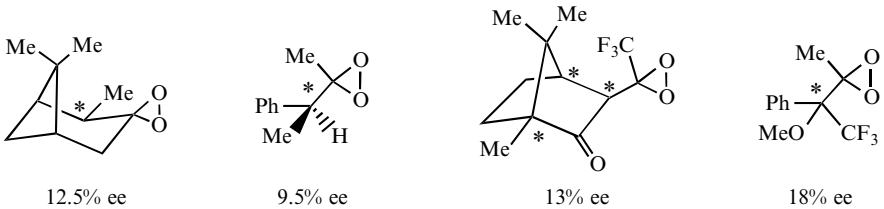


Fig. 1 Chiral ketones for asymmetric epoxidation

Fig. 2 Dioxirane

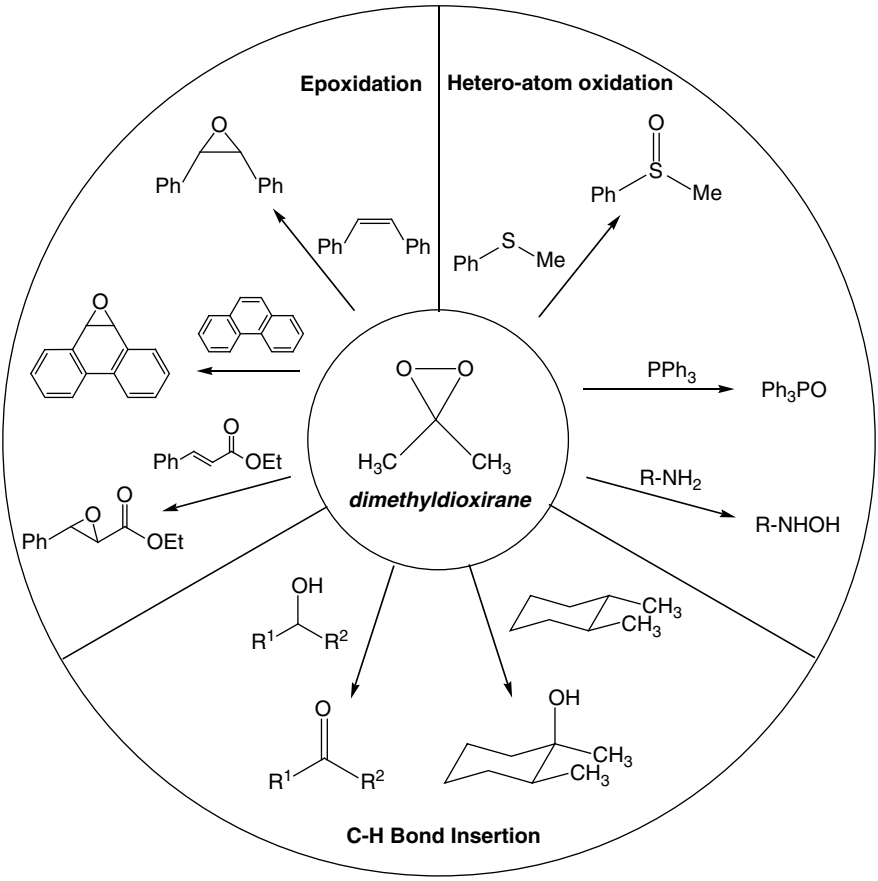
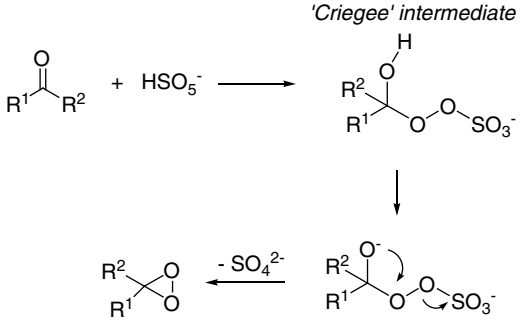


Fig. 3 Summary on the use of dimethyldioxirane



Scheme 4 Generation of dioxirane from ketone and $KHSO_5$

A brief summary of synthetic utilities of dimethyldioxirane is shown in (Fig. 3). Dimethyldioxirane is found to be very useful in mainly three types of reactions, namely: epoxidation, heteroatom oxidation, and C–H bond insertion. Through the significant

efforts by various research groups over the decades [6–16], dioxiranes have been developed as efficient oxidizing agents for organic synthesis and asymmetric epoxidation.

2 Development of Chiral Ketone Catalysts for Epoxidation

2.1 Design of the First C_2 Symmetric Chiral Ketone

Curci and coworkers [5] used acyclic chiral ketones with one stereogenic center next to the carbonyl group for asymmetric epoxidation. One possible explanation for the poor enantioselectivities inherent in this method is illustrated as follows (Fig. 4).

Consider the diastereotopic oxygen atoms of the peroxide O–O bond: the olefins can approach the chiral dioxirane functional group from two apparently different faces. Both enantiomers could be formed in the oxygen transfer process.

In order to improve the enantioselectivities, two approaches may be taken into account. The first one is to control epoxidation occurring exclusively on one face of the chiral dioxirane, with the other face totally blocked. The second one is to use a chiral dioxirane with C_2 symmetry. We first focused on designing C_2 symmetric chiral ketones (Fig. 5) [17–19].

With the use of a C_2 symmetric dioxirane, during oxygen transfer, essentially the same chiral environment will be experienced when the olefins access the chiral dioxirane from two faces. The same enantioselectivity could be attained. The facial selectivity of epoxidation would be solely dependent on the steric interactions between substituents on the olefins and those on the chiral dioxirane. The enantioselectivities could be improved by employing a C_2 symmetric chiral ketone.

Non-C_2 symmetric dioxirane:
olefins approaching from two faces, resulting in different enantioselectivites

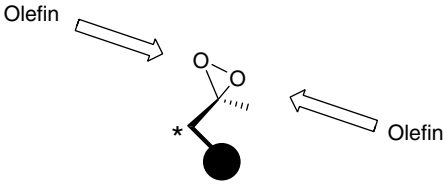


Fig. 4 Asymmetric epoxidation by dioxiranes with one adjacent chiral center

C_2 symmetric dioxirane:
olefins approaching from both faces, resulting in the same enantioselectivites

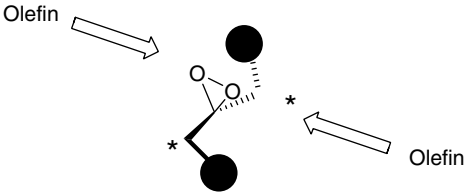


Fig. 5 Asymmetric epoxidation by C_2 symmetric dioxiranes

We first designed ketone **1** as a C_2 symmetric chiral ketone (Fig. 6). As it is well known that coplanar orientation of methoxy group and the ester carbonyl group is favorable in (R)-*O*-methyl mandelate, the methoxy groups should lie on the carbonyl plane for the most favorable conformation. The hydrogen atoms and the phenyl groups should be pointing out of the carbonyl plane such that nonbonded steric repulsion is at minimum.

The ketone (RR)-**1** has the desirable C_2 symmetry, with one small hydrogen atom and one large phenyl group on either face. The steric difference between the two group on one face of the dioxirane (RR)-**1a** should be significant enough for discriminating an aryl group or an alkyl group from a hydrogen atom on the C=C double bond (Fig. 7).

Consider a *trans*-olefin with two large and two small groups: it can be either in favored orientation or disfavored orientation when approaching the dioxirane (RR)-**1a**.

For the favored orientation (Fig. 8), the large phenyl group of the *trans*-stilbene is pointing toward the small hydrogen atom of the dioxirane (RR)-**1a** while the small hydrogen atom is pointing toward the large phenyl group of dioxirane (RR)-**1a**. Minimum unfavorable nonbonded steric interaction can be achieved in this orientation.

For the disfavored orientation (Fig. 9), there are severe nonbonded steric interactions between the large phenyl group of the olefin and the large phenyl group of the dioxirane (RR)-**1a**.

Therefore, the proposed chiral dioxirane (RR)-**1** is expected to yield high enantioselectivities for epoxidation of *trans*- and trisubstituted olefins, but not for *cis*- and

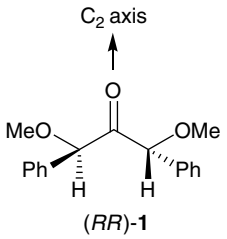


Fig. 6 Ketone **1**

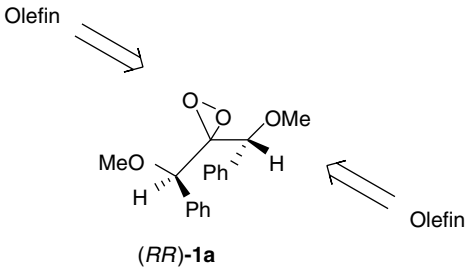


Fig. 7 Asymmetric epoxidation by dioxirane (RR)-**1a**

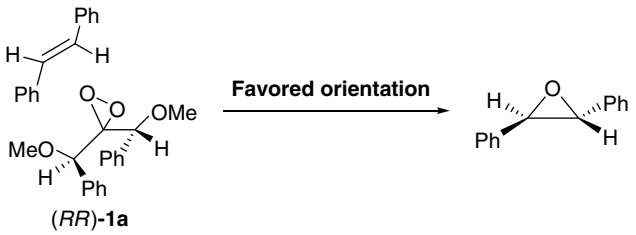


Fig. 8 Favored orientation in epoxidation of *trans*-stilbene by dioxirane (RR)-**1a**

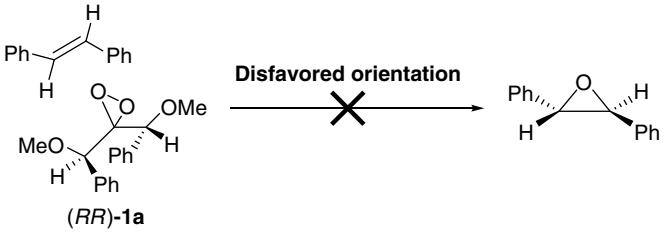


Fig. 9 Disfavored orientation in epoxidation of *trans*-stilbene by dioxirane (RR)-**1a**

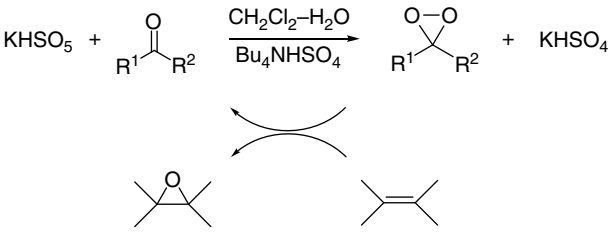
terminal olefins. The method of using C_2 symmetric chiral dioxirane is complementary to that developed by Jacobsen [2, 3] for *cis*-olefins.

The catalytic properties of the chiral ketone (RR)-**1** in asymmetric epoxidation of *trans*-β-methylstyrene were examined. However, it was found that epoxidation mediated by chiral ketone (RR)-**1** was very slow. Only background epoxidation was observed. The steric hindrance around the carbonyl group gives chiral ketone (RR)-**1** very low reactivity, which may be responsible for the poor catalytic activity.

2.2 Optimization of Reaction Conditions

Dioxiranes can be either used in isolated form, or generated in situ from Oxone® and a catalytic amount of chiral ketone (Scheme 5), as reported by Curci in 1984 [20].

Slow epoxidation rates are observed with the use of dioxiranes generated in situ from acetone, 2-butanone, and cyclohexanones. There is a lack of efficient reaction conditions



Scheme 5 Epoxidation using dioxiranes generated in situ

for generating dioxirane in situ. We believe that the poor epoxidation efficiencies may be a result of (1) the low reactivities of the dioxiranes used, and more importantly, (2) the biphasic solvent system (CH_2Cl_2–H_2O). We envision that there is a need to develop a new reaction protocol to allow more efficient epoxidations to proceed.

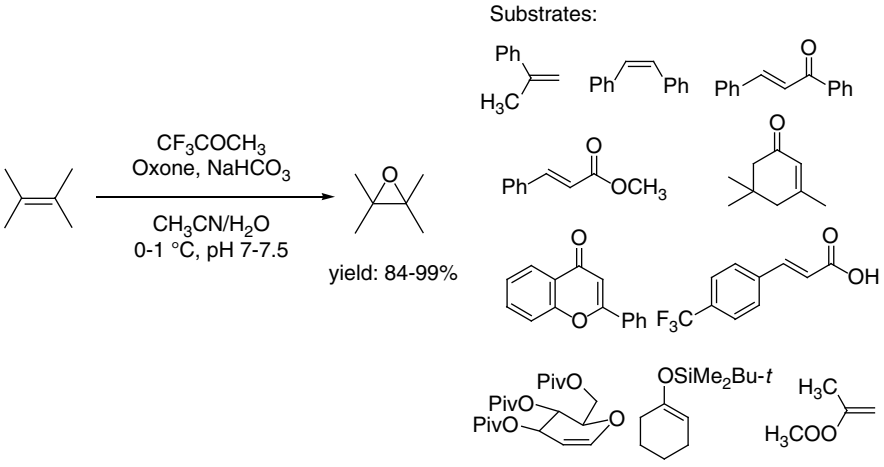
2.2.1 Homogeneous Solvent System

When water-soluble ketones are used as catalysts, dioxiranes may be generated in the aqueous phase and then go back to the organic phase for epoxidation. For water-insoluble ketones, formation of dioxirane probably relies on the anion HSO_5^- transferred to the organic phase by the phase transfer catalysts. In both cases, the inefficiencies in dioxirane formation come from the physical boundary in the biphasic system, which uncouples the processes of dioxirane formation and oxygen transfer. If the reaction is conducted in a homogeneous solvent system, the dioxirane generated can immediately transfer oxygen to the olefin without crossing the physical boundary. Accordingly, higher epoxidation efficiency is expected. With the problem of solvent system being solved, the next task at hand is to improve the reactivity of the dioxirane.

2.2.2 Reactivity of In Situ Generated Dioxiranes

Dimethyldioxirane and methyl(trifluoromethyl)dioxirane are the two most common dioxiranes used. It was reported that methyl(trifluoromethyl)dioxirane is about 1,000 times more reactive than dimethyldioxirane. When generated in situ from 1,1,1-trifluoroacetone in a homogeneous acetonitrile–water mixture, methyl(trifluoromethyl) dioxirane was found to epoxidize olefins very efficiently [21].

As illustrated (Scheme 6), unfunctionalized olefins with various substitution patterns, strongly electron-deficient olefins, and electron-rich olefins can be epoxidized

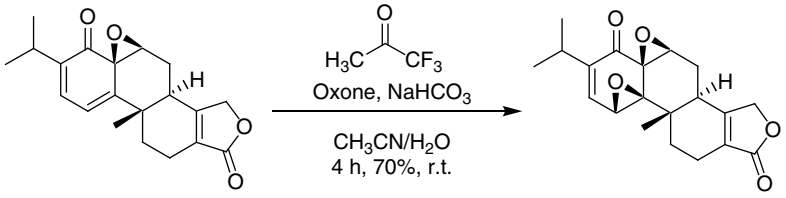


Scheme 6 Epoxidation using methyl(trifluoromethyl)dioxirane generated in situ

in excellent yields, at 0°C and neutral pH. Since potassium hydrogen sulfate, present in Oxone® and generated during the reaction, is readily neutralized by sodium carbonate buffer, various base- or acid-labile epoxides can be isolated in excellent yields under this neutral pH condition.

2.2.3 Synthesis Toward Triptolide

To further explore the utility of this efficient in situ epoxidation protocol, we applied this method in the total synthesis of triptolide (Scheme 7) [22]. We treated the dienone with methyl(trifluoromethyl)dioxirane generated in situ. The position of the second epoxide of the bis-epoxide is in *cis*-conformation to the first one and a single diastereomer in 70% yield can be obtained. The epoxidation method has also been utilized in the synthesis of other triptolide analogs.



Scheme 7 Epoxidation of a dienone intermediate for triptolide synthesis

2.3 Improvement on the Design of Chiral Ketones

In (Fig. 10), the catalytic activities of numerous ketones in the epoxidation of *trans*-stilbene are compared. In general, two trends are observed: (1) higher activities are associated with ketones with electron-withdrawing groups, such as F, Cl, and OAc, at α positions, (2) steric hindrance at α positions reduces the activities. Both electronic and steric factors have to be considered in designing efficient ketone catalysts.

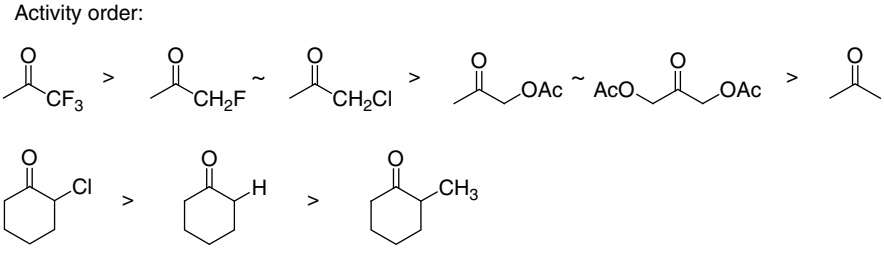


Fig. 10 Activity order of ketone catalysts for in situ epoxidation of *trans*-stilbene

2.3.1 Ideal Asymmetric Ketone Catalysts

An ideal chiral ketone with good catalytic activity and high enantioselectivity is predicted to possess: (1) electron-withdrawing groups at the α positions, (2) rigid conformations, (3) good stereochemical communications between the ketone and the substrate, and (4) C_2 symmetry if possible.

2.3.2 Development of Chiral Ketone Catalysts

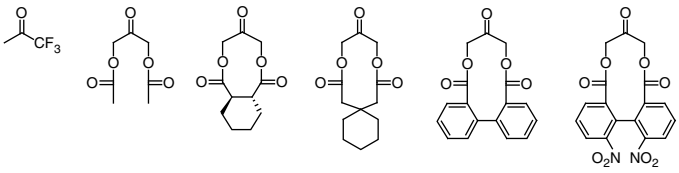
Numerous chiral ketones have been designed to catalyze in situ asymmetric epoxidation. Figure 11, summarizes the activities of several C_2 symmetric ketones.

Electron-withdrawing ester groups were added to the design of asymmetric ketone catalysts. C_2-Symmetric 1,3-diacetoxyacetone **2** exhibited good reactivity. In order to have dioxiranes with rigid conformations, cyclic analogs of 1,3-diacetoxyacetone **2** were designed and synthesized.

Several interesting features were observed in the epoxidation reactions: (1) At room temperature, with a 1:1 ketone-to-substrate ratio, epoxidation of *trans*-stilbene with cyclic ketones **3**–**6** as catalysts proceeded faster than those catalyzed by trifluoroacetone or acyclic ketone **2** alone. (2) The activities of cyclic ketones increased in the order of nine-membered-ring ketone **3** < 10-membered-ring ketone **4** < 11-membered-ring ketones **5** and **6**. Here ketone **5** gave the highest catalytic activity. (3) Cyclic ketones **3**–**6** were all stable under the reaction conditions. High yield (over 80%) of recovery could be achieved and the recovered ketones could also be reused without loss of catalytic activities.

Replacing the diphenyl unit of ketone **5** with a chiral binaphthalene unit gave the ketone (R)-**7** (Fig. 12). It is a C_2-symmetric 11-membered ring ketone. X-ray analysis revealed that ketone (R)-**7** has a rigid and C_2 symmetric structure [17]. The two-ester groups are antiparallel to each other, retaining the favorable s-*trans* geometry and being nearly perpendicular to the macrocyclic ring plane. The dihedral angle of the two naphthalene rings is ca. 70°.

The asymmetric epoxidation catalyzed by chiral ketone (R)-**7** was investigated (Fig. 13). Similar to ketone **5**, it is an effective catalyst for epoxidation reactions.



ketones:		**2**	**3**	**4**	**5**	**6**
reaction time (min):	30	50	12	10	7	6

Fig. 11 Activities of ketone catalysts for in situ epoxidation of *trans*-stilbene (ketone to substrate ratio = 1:1)

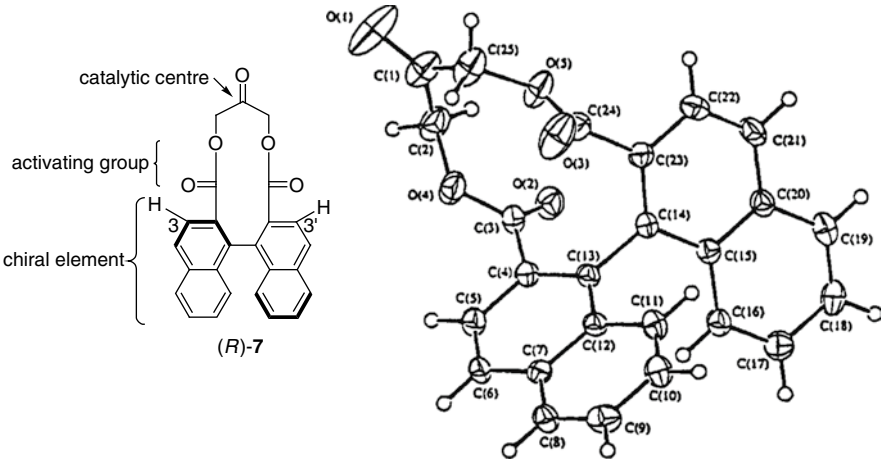


Fig. 12 Ketone (R)-**7** and its X-ray structure (right) (Permission obtained from ACS Publication)

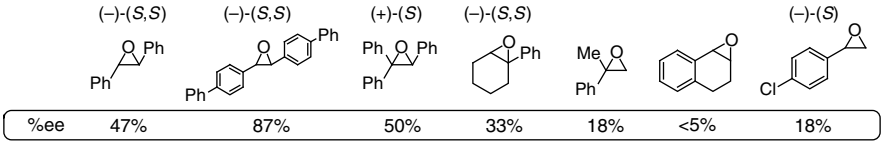


Fig. 13 Epoxidation of unfunctionalized olefins with ketone (R)-**7** as catalyst

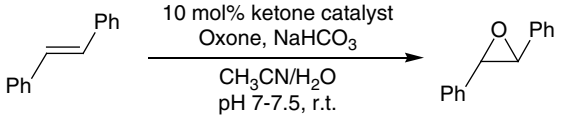
One important observation is that chiral ketone (R)-**7** yielded moderate to good enantioselectivity for epoxidation of *trans*-olefins and trisubstituted olefins but not for *cis*-olefins and terminal olefins. Even with only 10 mol% of (R)-**7**, high enantioselectivity (87% ee) was obtained for epoxidation of (E)-4,4′-diphenyl *trans*-stilbene. ^{18}O-labeling experiment was performed to prove that dioxirane intermediate (S)-**7a** is involved in the epoxidation of *trans*-stilbene catalyzed by chiral ketone (S)-**7**.

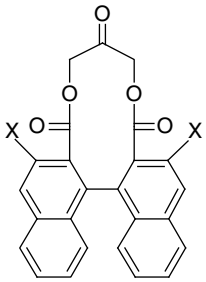
The ester groups on chiral ketone (R)-**7** are believed to serve two roles, specifically: (1) They are electron-withdrawing and able to activate the ketone group. Their corresponding ether-linked ketones were found to be much less efficient [19, 23]. (2) They further add to the rigidity of the chiral ketone. Better enantioselectivities in epoxidation of *trans*-stilbene were observed when compared to that obtained with the corresponding ether-linked ketones.

It is expected that the substituents on the 3 and 3′ positions of the naphthalene rings would be the steric recognition element (steric sensor) and exert significant influence on the enantioselectivity. A series of ketones containing different steric sensors were designed and subjected to epoxidation [18, 19]. The results are summarized in Table 1.

There are several interesting observations here: (1) When the size of the steric sensor X increased (from H to Cl to Br to I; from H to Me to CH_2OCH_3 to acetal to $SiMe_3$), the enantioselectivity first increased and then decreased. This indicates that

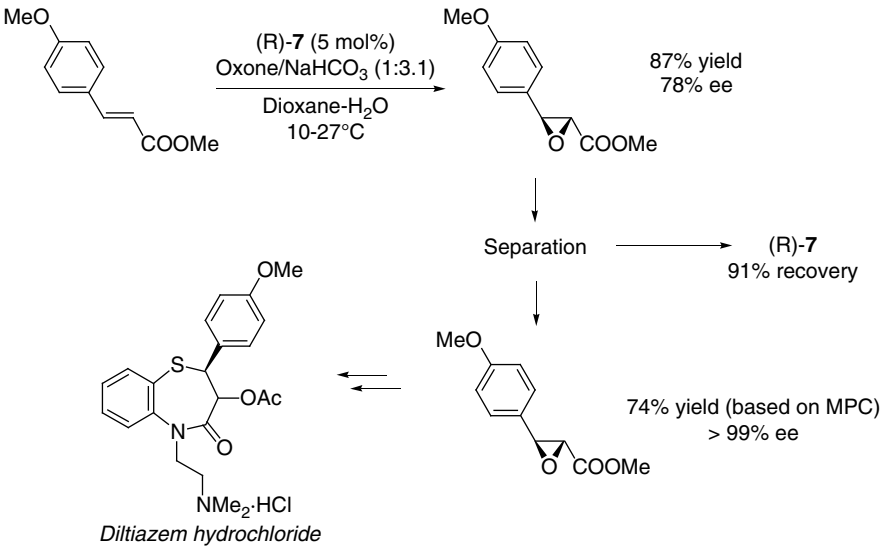
Table 1 Asymmetric epoxidation of *trans*-stilbene catalyzed by ketones **7**–**14**



	Catalyst	X	Epoxide config.	%ee
	(R)-**7**	H	(−)-(S,S)	47
	(R)-**8**	Cl	(−)-(S,S)	76
	(R)-**9**	Br	(−)-(S,S)	75
	(R)-**10**	I	(−)-(S,S)	32
	(S)-**11**	Me	(+)-(R,R)	56
	(R)-**12**	CH_2OCH_3	(−)-(S,S)	66
	(R)-**13**		(−)-(S,S)	71
	(S)-**14**	$SiMe_3$	(+)-(R,R)	44

the steric sensors should be of appropriate size. (2) With (R)-ketones as catalysts, (S,S)-epoxides of *trans*-stilbenes were obtained as the major enantiomers. This finding provides convincing evidence in the proof of transition state geometry during epoxidation, which will be discussed in the next section.

In Japan, Tanabe Seiyaku Company has applied the chiral ketone (R)-**7** for large-scale asymmetric epoxidation of methyl *p*-methoxycinnamate (MPC) (Scheme 8) [24]. Through optimization of reaction parameters, good yields and 99% ee for



Scheme 8 Asymmetric epoxidation of MPC with (*R*)-**7** as catalyst

chiral epoxidation can be achieved. The chiral epoxide product obtained is a key intermediate to synthesize the chiral drug Diltiazem hydrochloride, which is a coronary vasodilator for the treatment of angina pectoris and hypertension.

3 Asymmetric and Diastereoselective Epoxidation

3.1 Transition State Geometry in Dioxirane Epoxidation

Dioxirane epoxidation follows a concerted and stereospecific pathway, and two extreme transition states, i.e., spiro and planar, are possible (Fig. 14).

Based on the observation that certain *cis*-dialkyl alkenes were ca. 7–10 times more reactive than their *trans*-isomers, Baumstark and the co-worker proposed a spiro TS rather than a planar TS for dioxirane epoxidation. However, for phenyl-substituted alkenes, certain *trans*-isomers were slightly more reactive than *cis*-isomers.

Moreover, computational studies by Bach et al. [25] and Houk et al. [26] showed that the optimized transition state for oxygen atom transfer from dioxirane to ethylene was spiro. More recently, Breslow and Friesner have performed transition state modeling at the UB3LYP-DFT/6-31 G* level and demonstrated that enantioselectivities for various dioxirane-catalyzed asymmetric epoxidations can be modeled accurately [27].

Trans-stilbene has a large phenyl group and a small hydrogen atom on one side of the double bond. C_2 symmetric chiral dioxirane (R)-**7** can encounter *trans*-stilbene in two possible orientations, i.e., the favored and disfavored orientations, on the basis of steric effect considerations, under either a spiro or a planar transition state (Fig. 15). The orientation in which the phenyl group of *trans*-stilbene is positioned away from the naphthalene rings of the dioxirane is the favored one.

When the steric sensors at the 3 and 3′ positions of the chiral dioxirane become larger up to certain size (e.g., from H to Cl to Br), there is a minor increase of steric interactions in the favored orientation yet a significant increase in the disfavored orientation, thereby giving higher enantioselectivity. However, when steric sensors become larger (e.g., from Br to I) than certain size, the nonbonded steric interactions are increased significantly in both favored and disfavored orientations, resulting in lower enantioselectitivity and slower epoxidation.

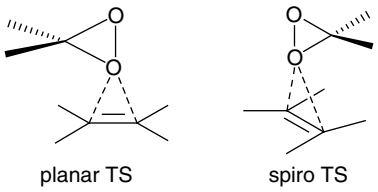


Fig. 14 Transition state geometry in dioxirane epoxidation

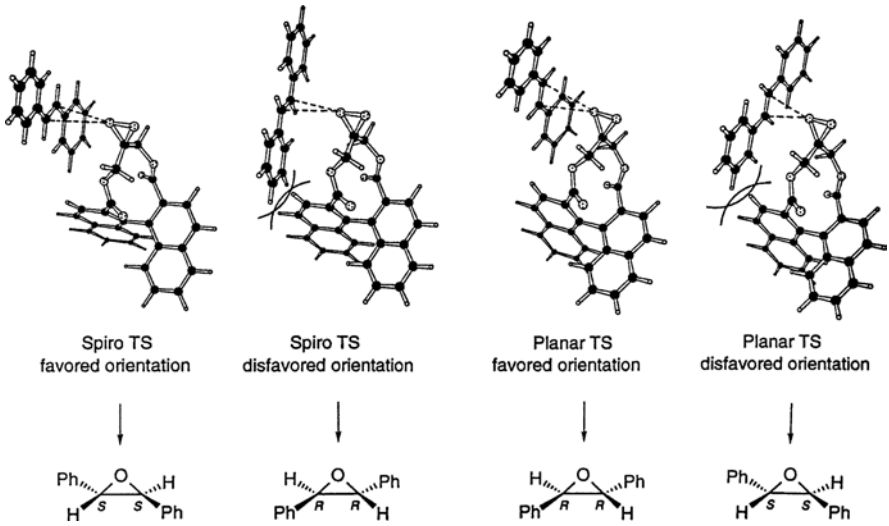


Fig. 15 Proposed transition state for epoxidation of olefins (Permission obtained from ACS Publication)

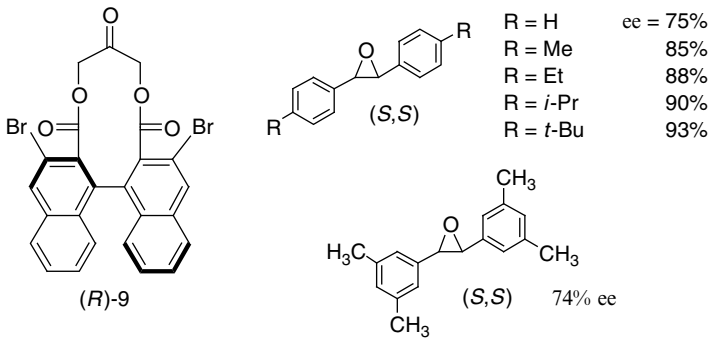


Fig. 16 Enantioselective epoxidation of *trans*-stilbene derivatives catalyzed by (R)-**9** bromo ketone

As illustrated in (Fig. 15), with chiral ketone (R)-**7** as the catalyst, (S,S)-epoxides of *trans*-stilbenes are expected to be the major products under a spiro TS, whereas (R,R)-epoxides are expected under a planar TS. All of our results have been consistent with a spiro TS [18].

In addition to the above experimental results, our docking experiments using the MacroModel program [28] suggested that the steric sensors recognize the para/meta

positions of *trans*-stilbene under a spiro TS but recognize ortho/meta positions under a planar TS.

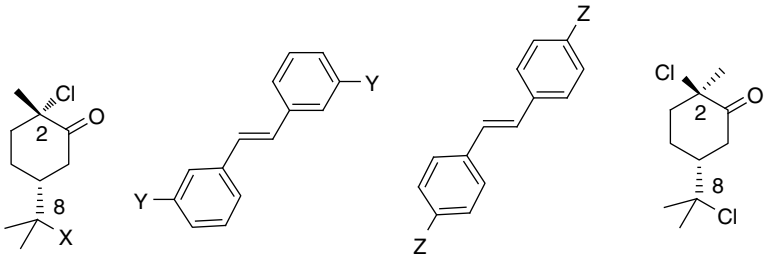
We thus expected that, under a spiro TS, higher ee values could be obtained when the para substituents of *trans*-stilbenes become larger. As shown in (Fig. 16), this was indeed the case. The meta substituents of *trans*-stilbenes seem to have little effect on enantioselectivity. Our results suggest that those chiral ketones recognize para substituents much better than meta substituents of *trans*-stilbenes.

3.2 Electronic Effect of Epoxidation Catalyzed by Chiral Ketones

In 1991, Jacobsen et al. reported their pioneering studies on the electronic effect of asymmetric epoxidation with chiral manganese-salen catalyst [29]. Since then, the electronic tuning of chiral catalyst has become a significant tool in the design of chiral catalysts.

Asymmetric epoxidation of olefins by chiral dioxiranes follows a concerted spiro transition state. The importance of steric effects of 3 and 3′ substituents of chiral binaphthyl ketones on enantioselective epoxidation has inspired us to explore whether electronic effects of remote substituents of ketone catalysts have any influence on enantioselectivity.

In 1998, our group set out to probe the effect of remote substituents, and a new series of chiral ketone catalysts **15**–**19** (prepared from (R)-carvone) were prepared (Fig. 17). Ketones **15**–**19** all have a quaternary carbon at C_2 position, but they differ in the remote substituent at C8 position. It is interesting to observe that epoxidation



15 X = F
16 X = Cl
17 X = OH
18 X = OEt
19 X = H

20
Y = Me
Y = H
Y = OMe
Y = F
Y = Cl
Y = OAc

21
Z = ^{t}Bu
Z = Me
Z = H
Z = F
Z = Br
Z = OAc

22

Fig. 17 Chiral ketones **15–19** and **22**

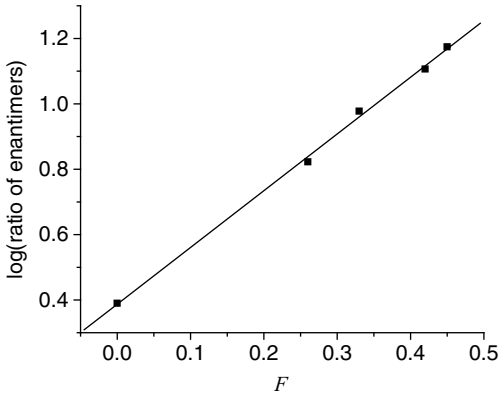


Fig. 18 Hammett plot of log(er) against *F* for asymmetric epoxidation of *trans*-stilbene catalyzed by ketones **15**–**19**. (Permission obtained from ACS Publication)

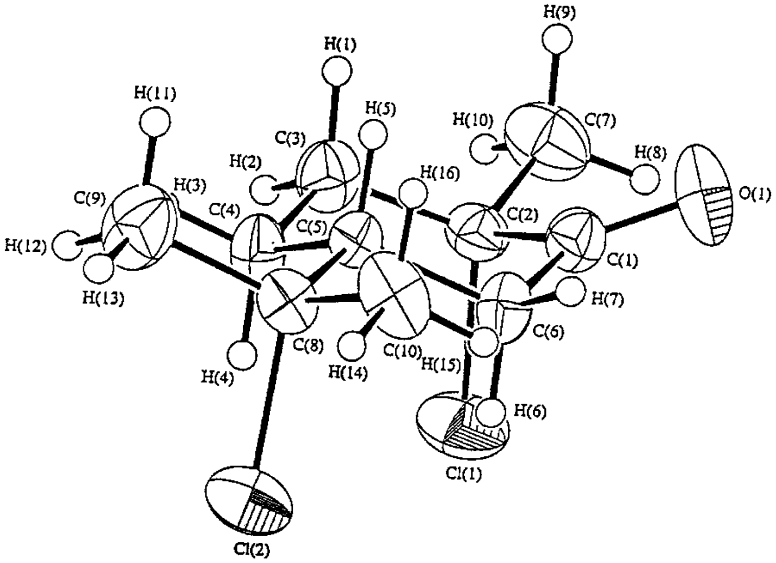


Fig. 19 X-ray structure of ketone **16** (ORTEP view) (Permission obtained from ACS Publication)

of *trans*-stilbene catalyzed by ketones **15**–**19** afforded 42–87% ee and ketones with more electron-withdrawing substituent gave faster epoxidation and higher enantioselectivity for the epoxide (Fig. 18). This study was the first to demonstrate that nonconjugated remote substituents have significant electronic effects in asymmetric catalysis [30].

According to the X-ray structure of ketone **16** (Fig. 19), (2S,5R)-dioxirane **16a** is expected to adopt the most stable chair conformation with alkyl substituents at the equatorial positions and a 2-chloro atom at the axial position (Fig. 20).

Molecular modeling suggested that the approach by bulky substrates **20** and **21** from the axial face is unlikely due to steric hindrance of the axial protons H_3 and H_5.

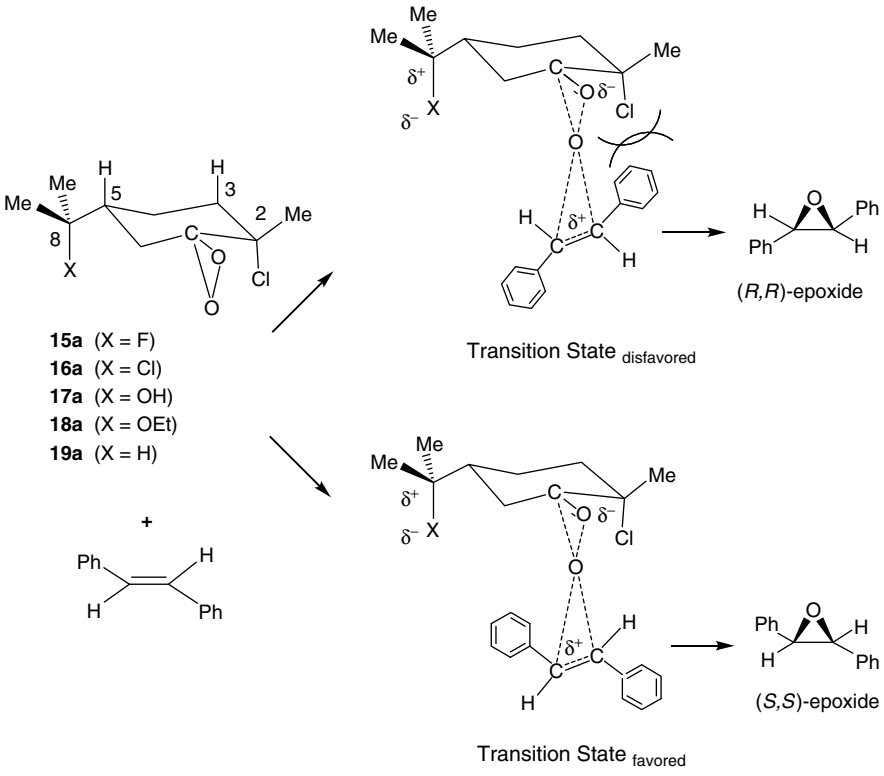


Fig. 20 Spiro transition states for dioxirane epoxidation

However, for the equatorial approach, there are two possible spiro transition states (TS). The sterically favored one (TS_f) has phenyl groups of *trans*-stilbenes positioned away from the 2-chloro atom of dioxirane **16a**, leading to the formation of (S,S)-epoxides. The disfavored one (TS_d), forming the (R,R)-epoxides, has steric clash between the 2-chloro atom and the phenyl groups. The free energy difference between TS_f and TS_d determines the enantiomeric ratio [30].

Under our previously reported in situ conditions [21], (S,S)-epoxides were formed preferentially as the major products in the epoxidation of symmetric, meta or para-substituted *trans*-stilbenes **20** and **21** catalyzed by ketone **16**. A linear relation was found in the Hammett plot (Fig. 21).

What is the significance behind the negative slope of plot A or B? Jacobsen reported in 1998 that the slope of the Hammett plot (the apparent reaction constant ρ) is equal to $\rho_f - \rho_d$, where reaction constants ρ_f and ρ_d represent the charge distributions of TS_f and TS_d, respectively.

The negative slope of plot A or plot B suggests the unfavorable n–π electronic repulsion, present in TS_d but not in TS_f, between the 2-chloro atom of the dioxirane and the phenyl groups of *trans*-stilbenes (Fig. 20).

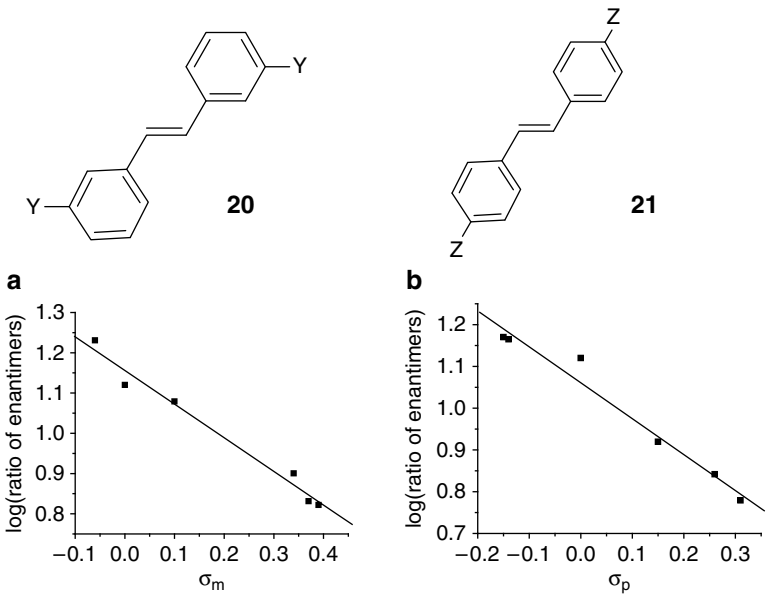


Fig. 21 Hammett plots: (**a**) asymmetric epoxidation of olefins **20** with catalyst **16** (ee range: 74–89%), slope = −0.84, R^2 = 0.989; (**b**) asymmetric epoxidation of olefins **21** with catalyst **16** (ee range: 72–87%), slope = −0.86, R^2 = 0.985. (Permission obtained from ACS Publication)

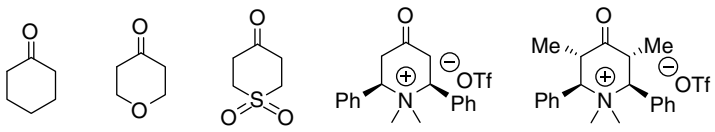
The evidence for the n–π electronic repulsion came from the observation that ketone **16** gave much higher ee (85%) than its C_2 epimer ketone **22** (32%) for epoxidation of *trans*-stilbene under the same reaction conditions though steric size of Cl atom is smaller as compared to the methyl group at C-2 position. For *trans*-stilbenes with stronger electron-donating substituents (smaller σ_m or σ_p values), the n–π electronic repulsion in TS_d becomes more severe, thereby giving higher ee.

Hence, the remote electronegative substituent at the C-8 position of the ketones **15**–**19** could stabilize the favored TS more than disfavored one by through-space electrostatic interaction (field effect), and contribute to the higher values of ee [16]. This model gives useful insights for catalyst design for asymmetric reactions.

3.3 Design of Effective Ketones for Epoxidation by the Use of Field Effect

The development of efficient catalysts for the synthesis of epoxides up to industrial scales remains a challenging yet rewarding task. In industrial applications, the catalysts employed should be inexpensive, robust, and highly efficient.

One strategy to improve the efficiency of ketone catalysts is to enhance the electrophilicity of the ketone group. We were especially excited to learn from literature that electrostatic field effect of heteroatoms has been successfully applied to improve the electrophilicity of certain enzyme inhibitors toward nucleophilic attack.



	23	**24**	**25**	**26**	**27**
Reaction Time (min)	>720	30	2–3	120	15

Fig. 22 Activities of ketones **23**–**27** in catalyzing in situ epoxidation of *trans*-stilbene with a 1:1 ketone/substrate ratio in CH_3CN–H_2O solvent system

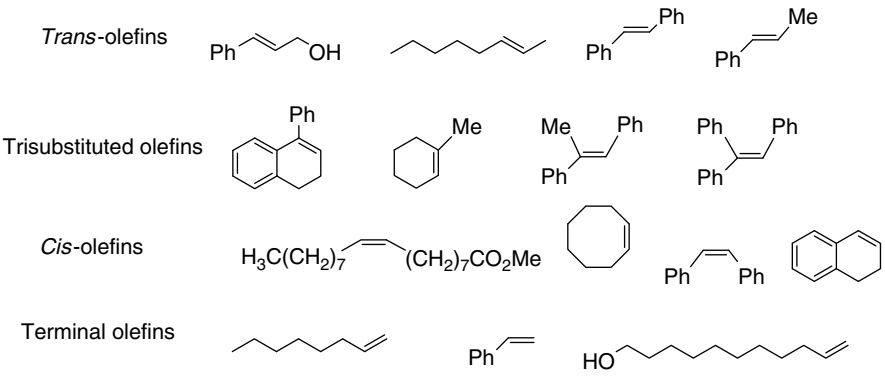


Fig. 23 Epoxidation of olefins with either ketone **25** or **27** as catalyst

In 1998, we envisaged that this concept can be used in our design of ketone catalysts [31]. Thus, a series of 4-heterocyclohexanones **24**–**27** (Fig. 22) were synthesized to investigate the influence of the field effects of hetero-substituents on the catalytic activities of ketone catalysts.

As illustrated in (Fig. 22), ketones **25** and **27** are found to be the best catalysts among the series for epoxidation of a variety of olefins in (Fig. 23). Ketones **26** and **27** with positively charged ammonium groups as the hetero-substituent are highly electrophilic because the unfavorable through-space charge-dipole repulsion (i.e., the field effect) between the ammonium group and the carbonyl group can be dissipated by rapid addition of the terminal oxidant, HSO_5^-, thus forming the corresponding dioxiranes easily.

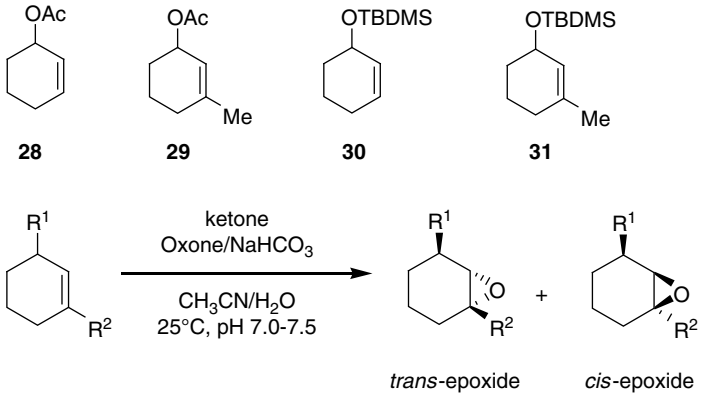
Another effective way to enhance the electrophilicity of 4-heterocyclohexanones is to introduce unfavorable through-space dipole–dipole repulsion (i.e., the field effect) between the neutral hetero-substituent and the carbonyl group as in ketones **24** and **25**. Indeed, the rates of epoxidation increase dramatically as the field effects of the hetero-substituents increase from cyclohexanone **23** to tetrahydropyran-4-one **24** to sulfone ketone **25**.

We were pleased to find that chiral ketones can perform on a large scale (20–100 mmol) directly with 5 mol% commercially available tetrahydrothiopyran-4-one that is oxidized by Oxone® to ketone **25** in epoxidation [31].

3.4 *Field Effect on Diastereoselective Epoxidation Catalyzed by Ketones*

Having grasped the importance of the field effect on enantioselectivity of epoxidation and activities of ketone catalysts, we proceeded to study this effect on diastereoselective epoxidation [32]. We began our studies on epoxidation of substrates **28–31** (Scheme 9) by using dioxiranes generated in situ from ketones **23–26** (Fig. 22) in which all the ketone catalysts have a similar steric environment at α-positions but possess different remote substituents. We found that the more polar the remote substituent of dioxirane was, the less *trans*-epoxide isomer was formed. Linear Hammett plots of the logarithm of *trans*/*cis* epoxide ratios against the field constants *F* of those remote substituents of ketones **23–26** were obtained ($\rho = -0.206$, $r = 0.974$ for **28**; $\rho = -0.319$, $r = 0.987$ for **29**; $\rho = -0.357$, $r = 0.998$ for **30**; $\rho = -0.629$, $r = 0.992$ for **31**) (Fig. 24).

Such excellent correlation suggests that the field effect may well play an important role in determining the diastereoselectivity of dioxirane epoxidation.



Scheme 9 Ketone catalyzed diastereoselective epoxidation

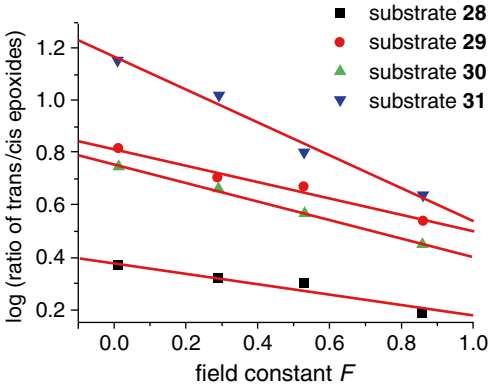


Fig. 24 Linear Hammett plots of the logarithm of *trans*/*cis* epoxide ratios against the field constants *F* of those remote substituents of ketones **23–26**

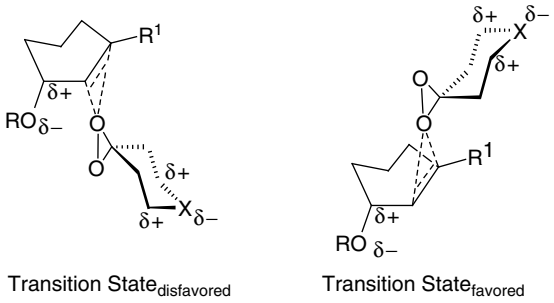
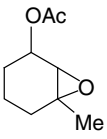
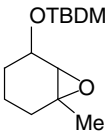
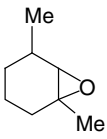


Fig. 25 Transition state geometry

Table 2 Diastereoselective epoxidation of ketone **27**

	Ratio of *trans/cis*-epoxide		
			
Oxidant			
Ketone **27** + Oxone®	15.1/1	19.7/1	18.7/1
CH_3COCF_3 + Oxone®	6.1/1	19.3/1	8.4/1
mCPBA	2.7/1	7.5/1	1.2/1

In (Fig. 25), the polar nature of the allylic C–O bond of substrates **28**–**31** makes the O atom carry δ^- charges and the allylic C atom carry δ^+ charges, additionally, the electron-withdrawing group X (O, SO_2, or $\oplus$ NMe_2) of dioxiranes gives δ^+ charges to the two adjacent C atoms. By through-space electrostatic interactions, the remote polar substituent X of dioxiranes stabilizes the disfavored TS and destabilizes the favored TS, giving lower *trans*-selectivity. This is the reason why all slopes are negative in the Hammett plots as shown in Fig. 24.

As shown in Table 2, ketone **27** exhibits diastereoselectivities (*trans*/*cis* ratio) much higher than either m-CPBA or trifluoroacetone under the in situ conditions [32].

3.5 β-Selective Epoxidation of Δ⁵-Unsaturated Steroids Catalyzed by Ketones

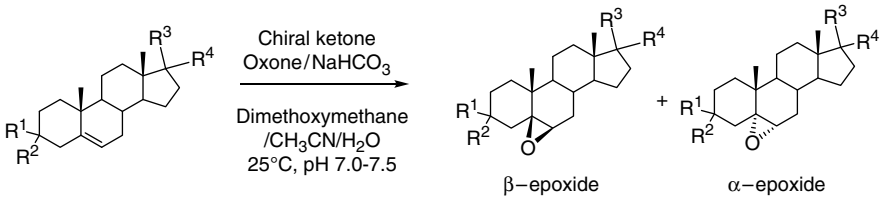
One of the important applications of ketone catalysts is α-selective epoxidation of Δ^5-unsaturated steroids. There are common organic oxidants, such as 3-chloroperoxybenzoic acid (mCPBA), which generally give α-epoxides as the product for epoxidation of 3β-substituted Δ^5-steroids. However, they display poor selectivities for epoxidation of 3α-substituted Δ^5-steroids other than epi-cholesterol.

Although 5α,6α-epoxides are readily accessible through epoxidation of Δ^5-unsaturated steroids with peracids as the oxidants, efficient methods for the synthesis of 5β,6β-epoxides of steroids remain to be developed.

Ketones **25** and **27** are efficient catalysts for olefin epoxidation and it is desirable to exploit these ketone catalysts in diastereoselective epoxidation of steroids.

After systematic screening, we found solvent system shown in (Scheme 10) should be the best way to study the interesting epoxidation reactions by ketones **25** and **27**.

In (Fig. 26), ketone **27** gives high β-selectivities (β/α-epoxide ratio > 8.5:1) in the epoxidation reactions of 3β-substituted Δ^5-steroids. Even more intriguingly, we found that ketones **25** and **27** afforded almost exclusively 5β,6β-isomeric epoxides in the epoxidation reactions of 3α-substituted Δ^5-steroids (Fig. 27).



Scheme 10 Epoxidation of steroids

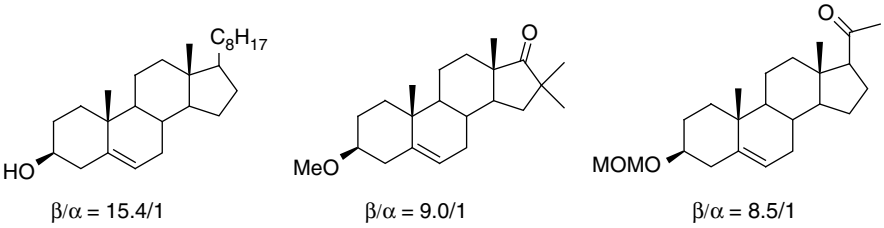


Fig. 26 Epoxidation of 3β-substituted Δ^5-steroids catalyzed by ketone **27**

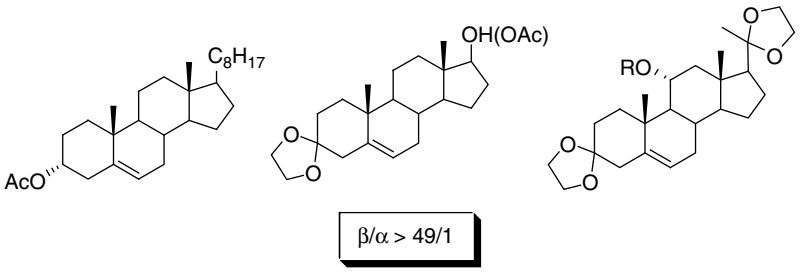
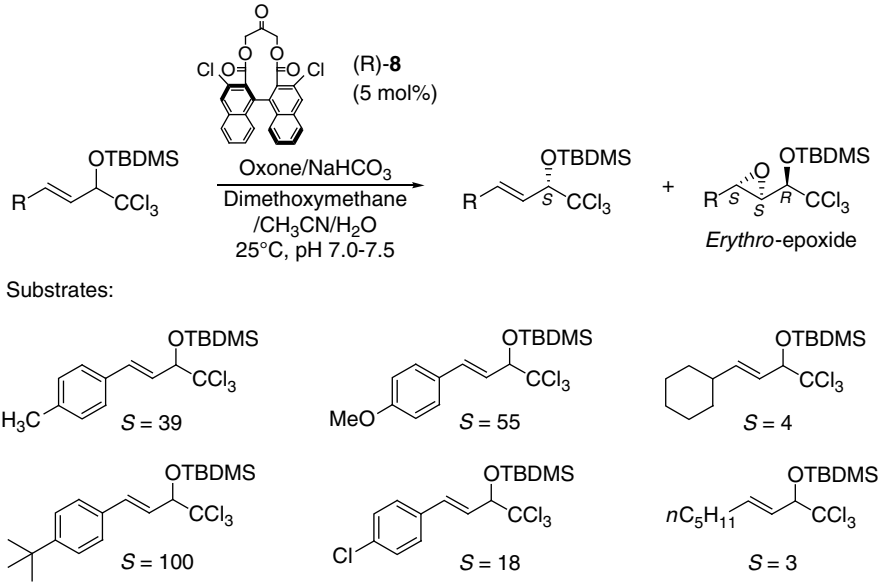


Fig. 27 Epoxidation of 3α-substituted Δ^5-steroids catalyzed by either ketone **25** or **27**

3.6 *Kinetic Resolution of Acyclic, Secondary Allylic Silyl Ethers Catalyzed by Chiral Ketones*

α-Trichloromethyl allylic alcohols and their derivatives are important intermediates in the synthesis of natural products of agricultural relevance, and serve as precursors to other useful synthons. However, preparation of enantiomerically pure or enriched α-trichloromethyl allylic alcohols remains a significant challenge, and there is no general and catalytic method available except for one enzymatic approach [33]. Kinetic resolution via enantioselective epoxidation, e.g., Sharpless asymmetric epoxidation method [34, 35], has been demonstrated as a desirable approach to resolve racemic secondary allylic alcohols. As our C_2 symmetric chiral ketones were efficient catalysts for asymmetric epoxidation of unfunctionalized olefins, we decided to explore their potential in the kinetic resolution of α-trichloromethyl allylic alcohols.

A series of TBDMS-protected α-trichloromethyl allylic alcohols were prepared and subjected to kinetic resolution conditions with chiral chloro ketone (R)-**8** as the catalyst (5 mol% loading), and the results are presented in (Scheme 11).



Scheme 11 Kinetic resolution of acyclic secondary allylic silyl ethers catalyzed by chiral ketone (R)-**8**

The recovered starting materials were enriched in the (*S*)-enantiomers, and the resulting epoxides had a (*R*)-configuration at the C-2 position as determined by X-ray crystallography [36]. Our kinetic resolution method exhibited very high diastereoselectivities such that virtually a single diastereomeric epoxide was formed with ratios of *erythro/threo*-epoxides of over 49:1. In particular, the *S* values can be up to 100, and chiral epoxides can be isolated with reasonably high enantiomeric excesses.

4 Work Performed by Others on Chiral Ketone-Catalyzed Asymmetric Epoxidation

Since our first report in 1996 on C_2 symmetric chiral ketones as catalysts for enantioselective epoxidation, many other groups have published their findings, which are briefly summarized below.

4.1 C_2 Symmetric Ketones

In 1997, Song and co-workers [37, 38] prepared C_2 symmetric chiral ketones **32** and **33** to epoxidize unfunctionalized olefins with up to 59% ee (Fig. 28). In 1997, Adam and co-workers [39] reported that ketones **34** and **35** were effective for phenylstilbene epoxidation with ee values of up to 81% (Fig. 29).

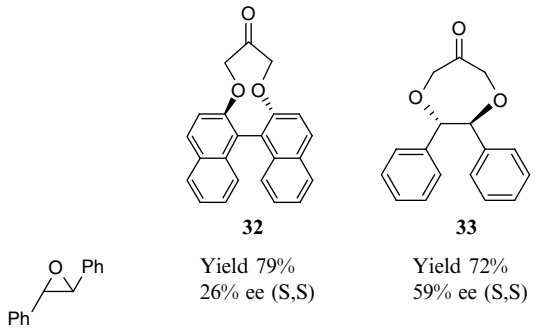


Fig. 28 C_2 symmetric chiral ketones **32** and **33**

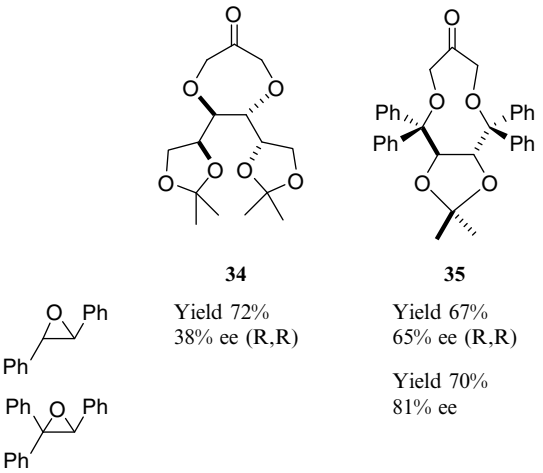


Fig. 29 C_2 symmetric chiral ketones **34** and **35**

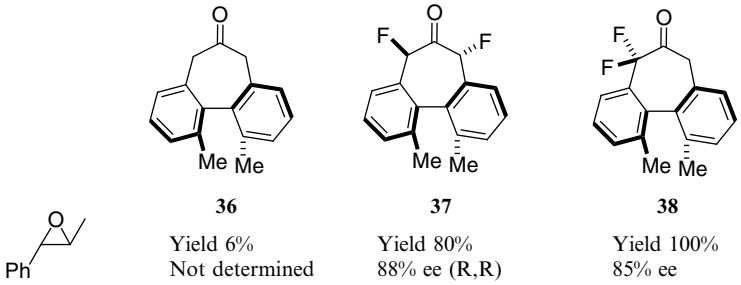


Fig. 30 C_2 symmetric chiral ketones **36**–**38**

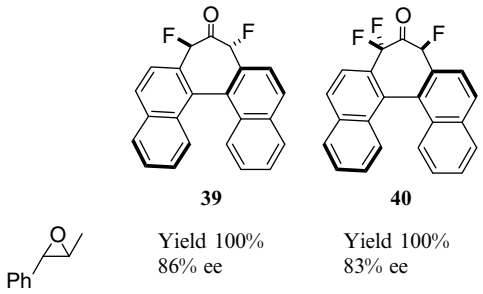


Fig. 31 C_2 symmetric chiral ketones **39** and **40**

In 1999 and 2002, Denmark and co-workers [40, 41] reported a series of fluorinated C_2 symmetric chiral ketones **37**–**38** with higher reactivity and good enantioselectivity for *trans*-olefin epoxidation (Fig. 30). In 2002, Behar and co-workers [42] designed and synthesized fluorinated C_2 symmetric chiral ketones **39** and **40** with different numbers of α-substituted fluorine atoms to modulate reactivity and enantioselectivity (Fig. 31).

4.2 Carbohydrate-Based Ketones

In 1996, Shi and co-workers reported a chiral ketone **41** prepared from ketalization and oxidation of D-fructose [43–45], and its enantiomer was synthesized from L-sorbose [46, 47]. The chiral ketones can epoxidize *trans*-olefins, allylic and homoallylic alcohols [48], conjugated dienes and enynes [49–51], enol ethers and enol esters with high yield and enantioselectivity (Fig. 32) [52].

Later the fused ketal moiety in ketone **41** was replaced by groups of higher electron-withdrawing ability to give ketone catalysts oxazolidinone (**42**) and diacetate (**43**) in which the decomposition of ketone catalyst via Baeyer–Villager oxidation was minimized (Fig. 33) [53, 54].

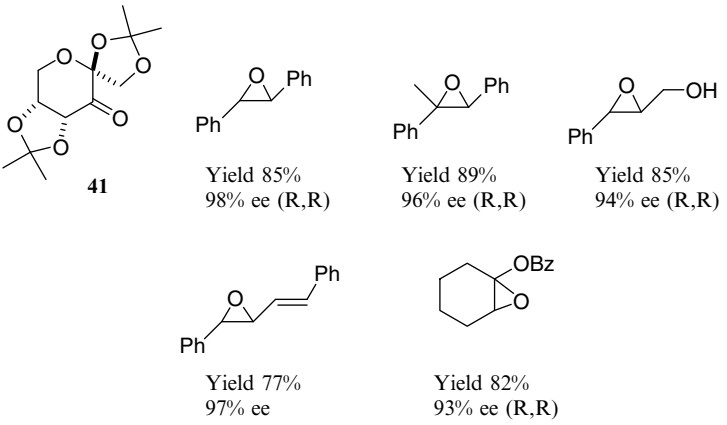


Fig. 32 Carbohydrate-based ketone **41**

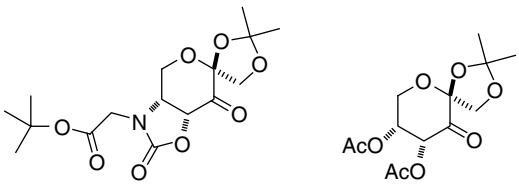


Fig. 33 Carbohydrate-based ketones **42** and **43**

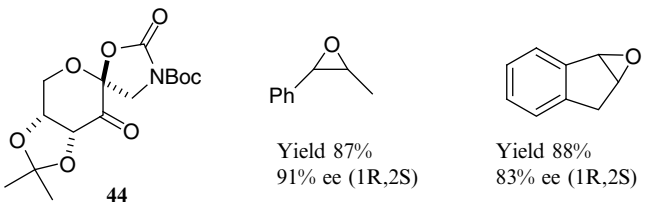


Fig. 34 Carbohydrate-based ketone **44**

In addition, Shi and co-workers reported an efficient chiral ketone catalyst, a glucose-derived ketone **44** (Fig. 34), applicable not only to *trans*-olefins but also to *cis*-olefins and terminal olefins [55–58]. Furthermore, ketone **45**, the carbocyclic analog of ketone **44**, was reported to epoxidize styrenes in high ee (Fig. 35) [59]. On the basis of this work, further achievements for asymmetric epoxidation of styrenes [60], conjugated *cis*-dienes [61], and *cis*-enynes [62] have been reported.

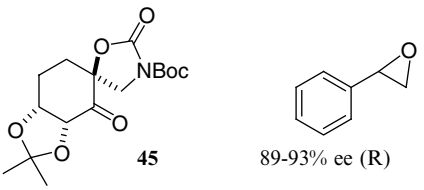


Fig. 35 Carbohydrate-based ketone **45**

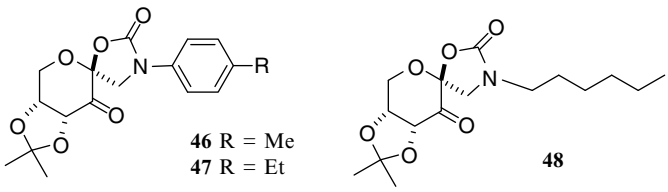


Fig. 36 Carbohydrate-based ketone **46–48**

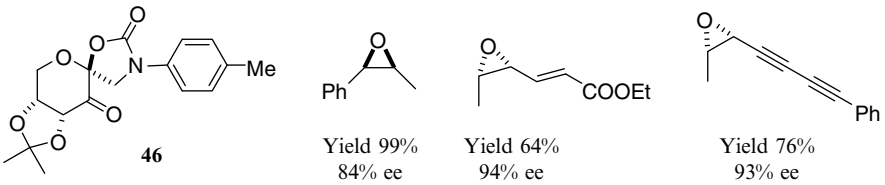


Fig. 37 Carbohydrate-based ketone **46**

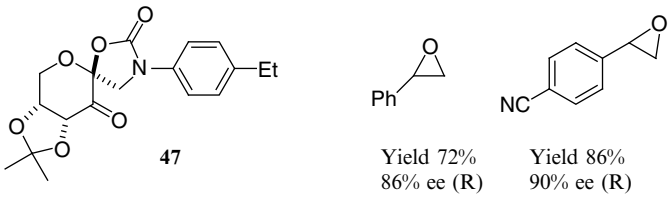
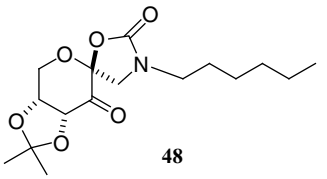


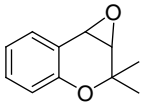
Fig. 38 Carbohydrate-based ketone **47**

The N-alkyl substituted ketones [46–48] also gave good enantioselectivity for epoxidation of chromenes (Figs. 36–39) [63, 64].

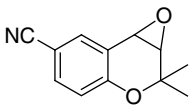
Ketone catalysts **49–50** which are arabinose-derived uloses have been developed by Shing and co-workers to give epoxide with ee values of up to 90% (Fig. 40) [65–67].



48

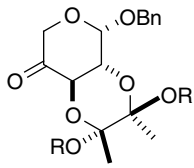


Yield 100%
84% ee



Yield 71%
89% ee (R,R)

Fig. 39 Carbohydrate-based ketone **48**



49 R = Me
50 R = ^{i}Bu

Fig. 40 Carbohydrate-based ketone **49** and **50**

5 Conclusion

In summary, ketones, despite being simple organic compounds, are surprisingly versatile catalysts for epoxidation reactions. The in situ epoxidation protocol allows reactions to be performed under environmentally benign conditions. In the past two decades, significant progress has been made in chiral ketone-catalyzed enantioselective epoxidation of olefins, which has not only addressed the urgent needs for asymmetric epoxidation of unfunctionalized *trans*-olefins and trisubstituted olefins but also extended the substrate scope to monosubstituted olefins and *cis*-olefins. The great potential of ketones in other organocatalysis reactions is worth exploring.

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Asymmetric Organocatalysis

W.J. Liu, N. Li, and L.Z. Gong

Please note the Erratum to this chapter at the end of the book

Abstract Asymmetric organocatalysis has been receiving considerable attention in the last decade and thereby made tremendous advances. Chinese researchers have also intensified efforts to investigate asymmetric organocatalysis by using diverse types of disciplines, including enamine, iminium, Brønsted acid, carbene, and Lewis base catalysis. As a result, a large number of excellent catalysts and elegant protocols have come out from China. This article summarizes the most representative achievements in enantioselective organocatalysis from Chinese groups.

Keywords Asymmetric • Organocatalysis • In China

Contents

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1 Introduction

Although asymmetric organocatalysis that exploits an organic molecule to promote an enantioselective reaction has been known for more than 100 years [1], its renaissances actually commenced with some seminal findings in the beginning of this century [2–4]. Since then, a large number of new principles, catalysts, and transformations have continuously sprung from worldwide research groups. Currently, asymmetric organocatalysis has undoubtedly been the third robust tool besides metal-based and enzyme catalysis for the bulky production of optically pure compounds. Even though with these exciting advances, the asymmetric organocatalysis is still in its infant and dynamically growing, leading to an increasing appearance of new findings.

In the past years, many chemists in China have been devoting great efforts to asymmetric organocatalysis. As a result, a wealth of elegant research works have stably come out and added some fundamentally new elements to this comparably rising field. In this review article, we will summarize some typical topics of asymmetric organocatalysis from research groups in China.

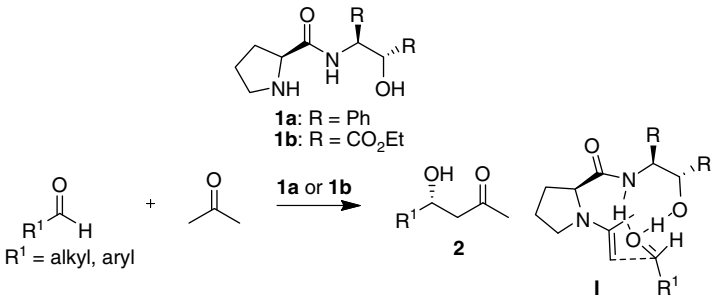
2 Enamine Catalysis

Electrophilic reactions occurring at the α-position of carbonyl compounds under the promotion of either a primary or a secondary amine via an enamine intermediate, namely enamine catalysis has been a robust principle for the design of new organocatalysts and creation of new enantioselective protocols [5–7] since seminal findings in proline catalysis, in particular proline catalyzed intermolecular direct aldol reaction, were reported [2, 3]. In China, an explosive growth in the field of enamine catalysis has also appeared.

2.1 Asymmetric Aldol Reactions

The aldol reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis. The direct aldol reaction is considered highly atom and step economy in comparison with the well-established process using enol or enolate derivatives as aldol donors.

Soon after proline-catalyzed direct intermolecular aldol reaction appeared, Gong and co-workers reported that L-prolinamides were able to efficiently catalyze direct aldol reactions [8–11]. In particular, the hydroxyl amides **1a** and **1b** exhibited high enantioselectivity for the aldol reaction of aldehydes with simple ketones (Scheme 1). Theoretical studies on the transition states revealed that the aldehyde is activated by double hydrogen bonds formed with both amide and hydroxyl protons and meanwhile the ketone donor is activated by formation of the enamine (**I**). Interestingly, the asymmetric direct aldol reaction catalyzed by L-prolinamide derivative **1a** in ionic liquid such as [bmin][BF4] led to a remarkable improvement in reaction performance in comparison with that in organic solvent [10].



Scheme 1 The asymmetric aldol reaction of acetone with aldehydes

Subsequently, a large number of proline derivatives have been identified for the direct aldol reaction including those from China (Fig. 1). To figure out a solution to the unsatisfactory stereoselectivity observed in the direct aldol reaction catalyzed by organocatalyst **1a**, Gong and co-workers designed 3-hydroxyproline-based organocatalysts **3a** and **3b** [12–14]. In the presence of 5 mol% of catalyst **3a**, the aldol reaction of cyclohexanone occurred with excellent diastereo- and enantioselectivity (up to >99/1 dr and >99% ee). More importantly, the catalyst **3a** is also efficient for the reaction of aliphatic aldehydes such as isobutyraldehyde and cyclohexanecarbaldehyde [12]. Moreover, these catalysts are able to catalyze the direct aldol reaction of cyclohexanone in water. High yields and excellent stereocontrol were achieved for a wide scope of aromatic aldehydes in the presence of 1 mol% of catalyst **3b** using water as reaction media [13]. In addition, L-prolinamide catalyst **3a** afforded highly enantioselective desymmetrization of four-substituted cyclohexanones through direct aldol reaction, creating three new stereogenic centers with excellent stereochemical control [14].

A family of proline-based organocatalysts derived from chiral diamines has been synthesized. Xiao and co-workers prepared the catalysts **4a** and **4b** that provided high stereoselectivity for the direct asymmetric aldol reaction of aromatic aldehydes with cyclohexanone and its structural analogous [15, 16]. Xiao also prepared an organocatalyst **5** by incorporation of cinchona alkaloid to proline, which delivered a highly stereoselective direct aldol reaction of acetone and 2-butanone with a wide range of aromatic and heteroaromatic aldehydes [17]. The cinchonidine backbone

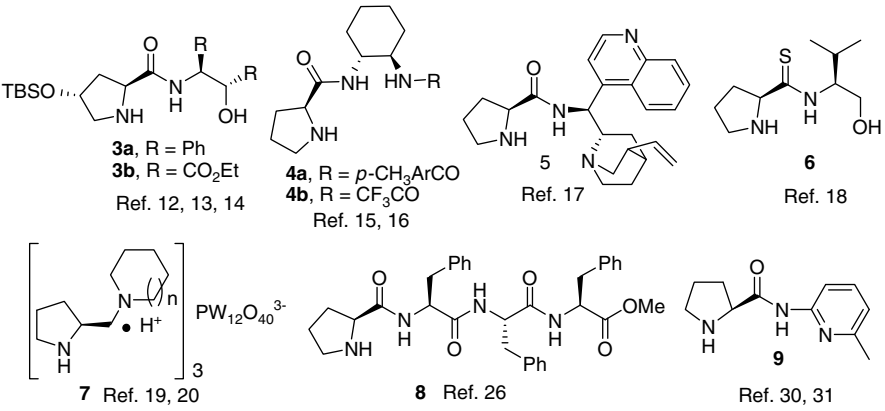


Fig. 1 Representative proline-derived organocatalysts

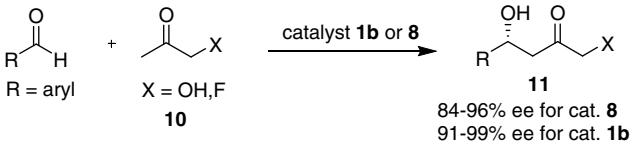
has been found to be essential to the reaction efficiency and enantioselectivity. The ion pair, formed between tertiary cinchonidine nitrogen and acid additive, was believed to give another hydrogen-bonding interaction to assist the stereocontrol.

Liu and co-workers found that the prolinethiamide catalyst **6** is highly efficient in catalyzing asymmetric direct aldol reaction [18]. Two mole percent of this organocatalyst is sufficient to render the reaction to proceed in high yields and excellent enantioselectivity of up to 96% ee. Moreover, excellent diastereo- and enantioselectivities were observed for the aldolization of aromatic aldehydes and cyclohexanone in water.

Besides proline amides, chiral amines derived from proline have found widespread applications in the catalytic direct aldol reactions. Significantly, Luo and Cheng demonstrated that the chiral amine-polyoxomelate hybrids **7** afforded highly efficient and enantioselective aldol reaction [19, 20]. Only 0.33 mol% of **7** is sufficient to give a clean aldol reaction with excellent enantioselectivity (up to 99% ee). More importantly, the catalyst could be recovered and reused for six times with maintained stereoselectivity. Wang and co-workers have synthesized various dendritic catalysts derived from N-prolylsulfonamide for the direct aldol reaction of cyclohexanone [21]. The dendritic catalyst could be recovered and reused at least five times without loss of catalytic activity and stereoselectivity. Additionally, other proline derivatives have also been reported to catalyze aldol reaction [22–24].

Functionalized aliphatic ketones, including hydroxyacetone, chloroacetone, and fluoroacetone, are important in the aldol reaction as donors because multiple functionalities present in the aldol products, which found widespread applications in organic synthesis [25]. As a result, aldolization involving these functional ketones has been disclosed.

Gong presented an L-proline-based peptide-catalyzed direct aldol reaction of hydroxyacetone in aqueous media (Scheme 2) [26]. Interestingly, the reaction preferentially occurred at methyl group of the hydroxyacetone, producing chiral 1,4-diols, which are disfavored adducts in similar aldol reactions catalyzed by

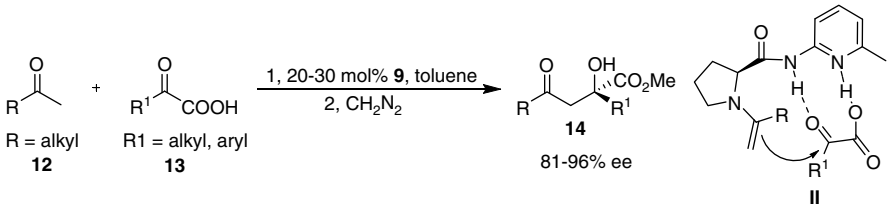


Scheme 2 The asymmetric aldol reaction of functionalized aliphatic ketones with aldehydes

either aldolase or L-proline, in high yields and enantioselectivity of up to 96% ee with catalyst peptide **8** in THF/H_2O at 0°C. However, the catalytic system is highly substrate-specific, and thus, the neutral or electron-rich aromatic aldehydes and aliphatic aldehydes are not reactive under the optimal conditions. To improve the regioselectivity, enantioselectivity and substrate scope, a family of simple L-proline amides were evaluated and proved to be effective for the aldol reaction of hydroxyacetone with aldehydes with reversed regioselectivity in aqueous media [27]. The aldolization of hydroxyacetone with a wide range of aldehydes proceeded smoothly in the presence of 20–30 mol% of the catalyst **1b** to yield chiral 1,4-diols with high regio- and enantioselectivity (91–99% ee). Similarly, fluoroacetone underwent aldolization with aldehydes in the presence of 30 mol% of the organocatalyst in aqueous media, giving otherwise disfavored products with high enantioselectivity (up to 91% ee).

In contrast to well established organocatalytic direct aldolizations with aldehydes as acceptors, those involving ketones as acceptors were scarcely reported and thus are a formidable challenge. L-Proline has been found to be effective for the direct aldol reaction of α-keto esters with a limited number of aldehydes and cyclohexanone [28, 29].

Gong and co-workers designed an organocatalyst **9** on the basis of molecular recognition to catalyze the asymmetric direct aldol reaction of ketone with α-keto acids, generating β-hydroxyl carboxylic acids with a quaternary stereogenic center with excellent enantioselectivity of up to 98% ee (Scheme 3) [30, 31]. A wide range of keto acids, regardless of the electronic and steric natures of the substituents, could participate in the reaction. Nonetheless, a range of acyclic ketones were also tolerated with excellent results. Experimental and theoretical studies on the transition states revealed that the amide N–H and the pyridine N of the organocatalyst selectively formed hydrogen bonds with the keto oxygen and the carboxylic acid hydroxyl of the α-keto acid, respectively (TS-II). These two hydrogen-bonding



Scheme 3 The asymmetric direct aldol reaction of ketone with α-keto acids

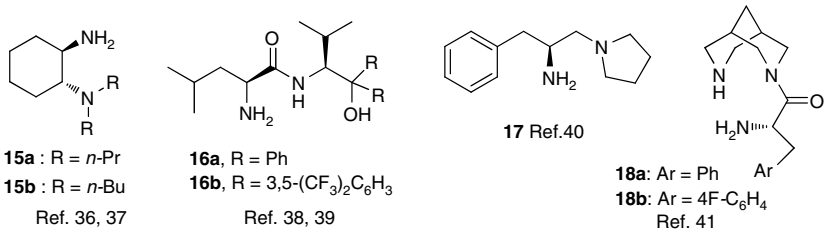
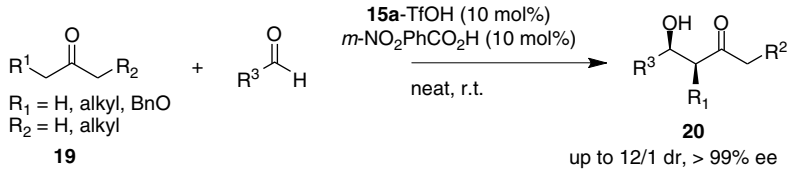


Fig. 2 Representative primary amine organocatalysts

interactions are important for the reactivity and enantioselectivity of the direct asymmetric aldol condensation.

Córdova and co-workers disclosed that naturally available primary amino acids were good organocatalysts for direct aldol reaction [32, 33]. Barbas and Lu also demonstrated that simply modified primary amino acids were efficient for highly stereoselective direct aldol reactions [34, 35]. Unlike secondary amine catalytic aldol reaction, the primary amine catalytic aldol reaction favored *syn*-selective products when the unsymmetrical aliphatic ketones were used (Fig. 2).

Luo and co-workers reported a versatile primary–tertiary diamine catalyst **15a** (Scheme 4) [36]. This catalyst in combination with either TfOH or *m*-NO_2PhOOH as an additive was able to promote a highly enantioselective aldol reaction for a wide range of aldehydes. Moreover, broad scope of aliphatic ketones was tolerated with good to high regioselectivity, *syn*-selectivity and enantioselectivity. Very recently, Xiao reported a similar catalyst **15b** [37].

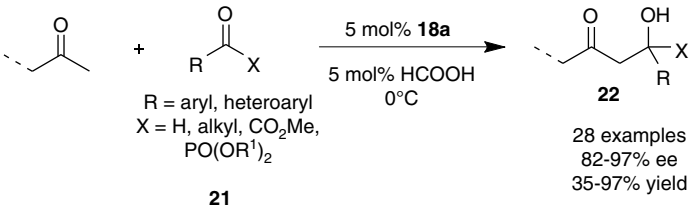


Scheme 4 The asymmetric aldol reaction of aliphatic ketones with aldehydes

Gong and co-workers designed two new organocatalysts **16a** and **16b** derived from L-leucine and (*S*)-β-amino alcohols on the basis of "enamine-double hydrogen-bonding activation" strategy [38, 39]. These catalysts offered a highly efficient syn-selective direct aldol reaction for a wide scope of aldehydes with unsymmetrical aliphatic ketones with excellent diastereo- and enantioselectivities (up to 20/1 dr and 99% ee). In addition, the catalyst **16a** was successfully applied to the direct *syn*-aldolization of dihydroxyacetone with excellent levels of stereoselectivity under the assistance of *p*-nitrobenzoic acid, which allows for an efficient synthesis of carbohydrates. Interestingly, by replacing organic solvent with brine the enantio- and diastereoselectivities were both significantly improved. As a result, a wide range of aliphatic ketones could participate in the aldol reaction in high yields and excellent diastereo- and enantioselectivities (up to >20/1 dr, >99% ee).

Luo and co-workers have also developed an excellent primary–tertiary diamine catalyst **17** to catalyze the direct aldol reaction of α-hydroxyketones. *Syn*-1,2-diol products were obtained in high yield (up to 97%) and stereoselectivity (up to 30/dr, 99% ee) [40].

Feng and Hu found an excellent primary amine organocatalyst **18a**, derived from L-phenylalanine and sparteine, delivering high yields and enantioselectivity for the direct aldol reaction of a wide scope of benzoyl phosphonates, independent of the size of phosphonate and the substitutes of the benzoyl unit (Scheme 5) [41]. Moreover, structurally diverse aryl α-keto esters could be accommodated in moderate to high yields and excellent enantioselectivity. More importantly, α,α-dialkoxy ketones could also engage in the reaction with excellent results. Theoretical study revealed that protonated piperidine was important for the reactivity and enantiocontrol.

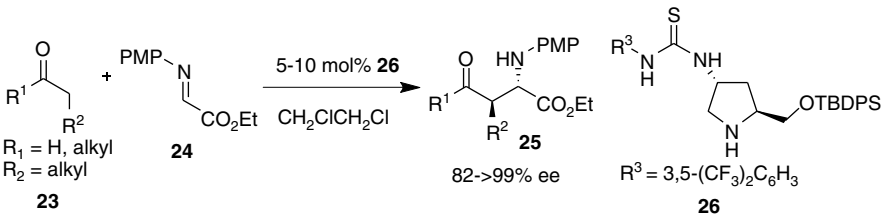


Scheme 5 The asymmetric direct aldol reaction of ketone with benzoyl phosphonates and α,α-dialkoxy ketones

Additionally, other primary amine derivatives have also been reported to catalyze aldol reaction with various enantioselectivity [42–44].

2.2 Asymmetric Mannich Reaction

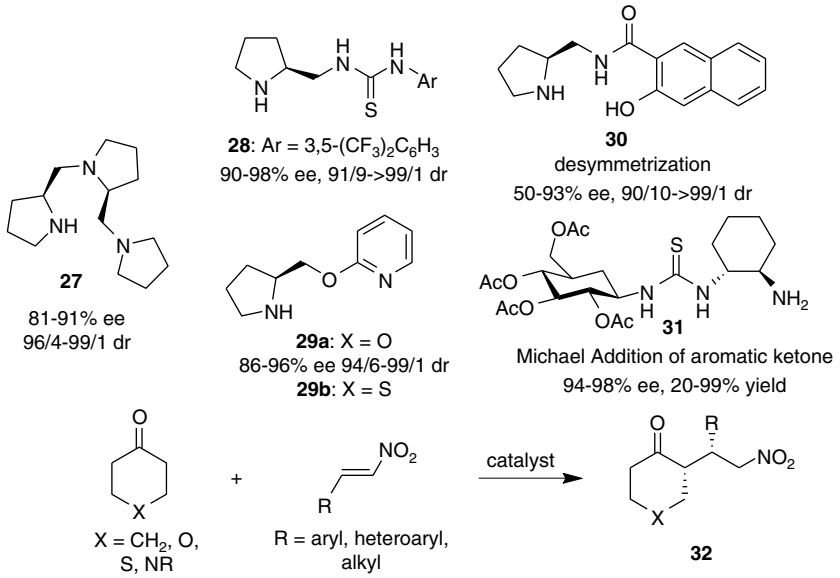
Peng and co-workers have developed a chiral secondary amine-thiourea organocatalyst, 4-aminothiourea prolinol *tert*-butyldiphenylsilyl ether **26**, which was applied to the direct *anti*-selective asymmetric Mannich reaction (Scheme 6) [45]. The direct Mannich reaction of cyclohexanone with *N*-*p*-methoxyphenyl α-iminoglyoxylate proceeded smoothly in the presence of 5–10 mol% of **26** in CH_2ClCH_2Cl to afford *anti*-product in a high yield and with excellent diastereo- and enantioselectivity. Other cyclic ketones gave moderate yields, moderate to excellent diastereo- and enantioselectivity. A wide range of unmodified aldehydes were also screened, giving *anti*-Mannich reaction products in high yields (84–89%) with excellent diastereo- and enantioselectivity (up to 89% dr, >96% ee). Notably, the reaction between isovaleraldehyde and *tert*-butyl 4-methoxybenzylidenecarbamate also occurred to yield *anti*-Mannich adduct with excellent stereochemical outcomes.



Scheme 6 The *anti*-selective direct asymmetric Mannich reaction

2.3 Asymmetric Michael Addition Reactions

Gong and co-workers designed a chiral triamine **27**, which in combination of protic acid delivered high yields and enantioselectivities in the Michael addition of cyclohexanone to nitrostyrene derivatives (Scheme 7) [46]. Slightly lower enantioselectivity was observed for the reaction involving tetrahydropyran-4-one and tetrahydrothiopyran-4-one. Principally, the large group on the pyrrolidine core, which occupies a large space to efficiently shield one side of the enamine, might be a possible reason for the high stereochemical control. Tang reported a chiral pyrrolidine–thiourea catalyst **28** capable of accelerating an asymmetric addition of simple ketones to nitroolefins [47]. The thiourea part in the catalyst activates the nitroolefins by double hydrogen-bonding interaction and meanwhile, the pyrrolidine unit activates ketones through the formation of corresponding



Scheme 7 Asymmetric Michael addition of cyclohexanone with nitroolefins

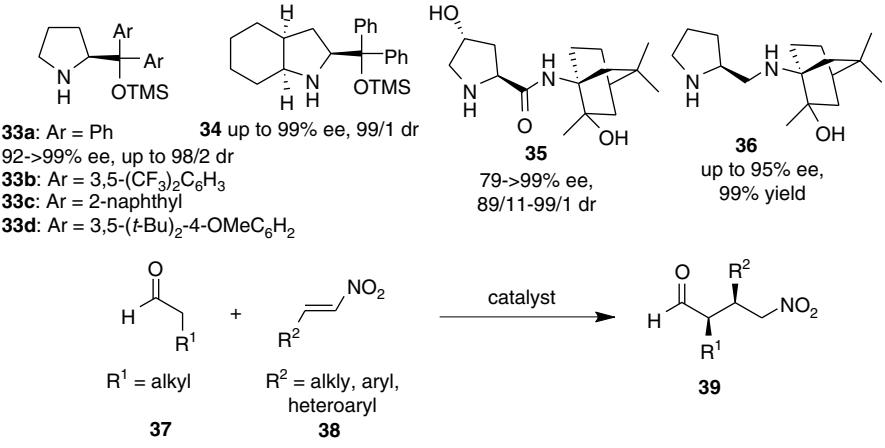
enamines. A simple pyrrolidine–pyridine-based catalyst **29a** by Wang group [48] and a primary amine-derived catalyst **18b** by Feng group [49] have been evaluated in catalyzing Michael addition reaction of ketones to nitroolefins.

Xiao and co-workers established an asymmetric desymmetrization of meso- and prochiral ketones by using direct Michael addition reaction to nitroolefins catalyzed by **30** easily accessed from 2-pyrrolidinylmethanamine and 3-hydroxy-2-naphthoic, concomitantly creating three stereogenic centers in high yields and with excellent diastero- and enantioselectivities [50].

Aromatic ketones are highly challenging donors in Michael addition reactions. Inspired by pioneering work of Jacobsen [51], Ma and co-workers synthesized a saccaride-substituted primary amine–thiourea bifunctional catalyst **31** [52]. It accelerated asymmetric Michael addition reaction of aromatic ketones to nitroolefins with excellent enantioselectivity (94–98% ee). Even for the acetone donor, the catalyst still gave excellent results (up to 94% yield, 96% ee) [53].

Ma and co-workers investigated a Michael addition of enolizable aldehydes to functionalized nitroalkene compounds and found that β-nitroacrylate compounds were suitable acceptors and water turned out to be the media of choice (Scheme 8) [54]. The Michael addition of *n*-pentanal to β-nitroacrylate proceeded smoothly in the presence of 5 mol% of catalyst **33a** under the assistance of 50 mol% benzoic acid to give a high yield (82%) and stereoselectivity (97/3 dr, >99% ee). The catalytic protocol is applicable to a large number of β-nitroacrylate, nitroalkenes, and aldehydes with excellent results. The procedure holds great potential in industrial applications. In addition, the catalyst **33a** was used to catalyze the enantioselective conjugate addition of aldehydes to α, β-unsaturated thiol esters [55].

Diphenylprolinol silyl ether has been proven to be extraordinarily efficient in catalyzing asymmetric Michael reaction of various aldehydes to nitroolefins. Luo and Chan reported that diphenylperhydroindolinol silyl ether **34** [56], which was

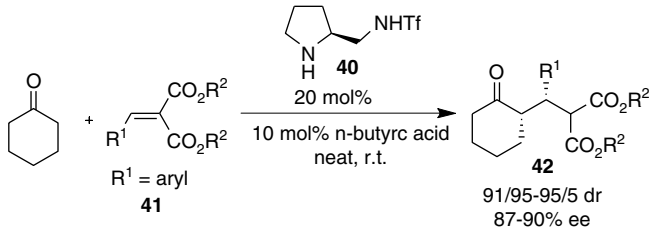


Scheme 8 Michael addition of aldehyde with nitroolefins

readily prepared from commercially available (*S*)-indoline-2-carboxylic acid, exhibited comparable or even better enantioselectivity than proline derivatives in Michael addition reaction. A variety of aldehydes and nitroalkenes could be accommodated in high yields and excellent stereochemical outcomes.

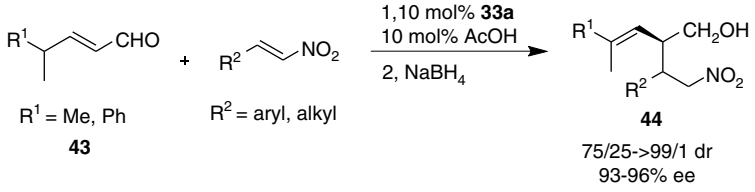
A novel prolinamide–camphor catalyst **35** has been discovered for the direct asymmetric Michael addition of aldehydes to nitroolefins in high yields and excellent diastereo- and enantioselectivities [57]. For the Michael addition of α, α-disubstituted aldehydes to nitroolefins, the pyrrolidine–camphor catalyst **36** exhibited high efficiency under neat conditions [58].

Tang and co-workers found that the pyrrolidine–thiourea-based bifunctional catalyst was also applicable to the Michael addition of cyclohexanone to dimethyl 2-(4-nitrobenzylidene) malonate in high stereoselectivity (Scheme 9) [59]. The optimal catalyst **40**, combined with *n*-butyric acid additive could provide high yields and stereoselectivity. Hydrogen bonds formed from NH in the catalyst and *n*-butyric acid with the carbonyl group of alkylidene malonates activating the substrate were believed to govern the reaction.



Scheme 9 Asymmetric Michael addition of cyclohexanone to alkylidene malonates

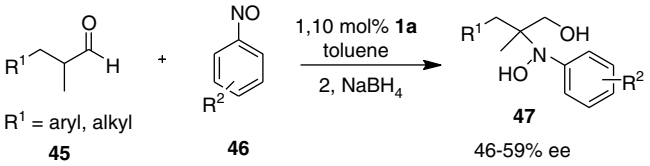
Chen and co-workers reported the first direct chem-, regio- and stereoselective Michael addition of α,β-unsaturated aldehydes **43** to nitroolefins catalyzed by **33a** (Scheme 10) [60]. This reaction is proposed to proceed via a dienamine intermediate. To inhibit the self-dimerization of α,β-unsaturated aldehydes, more bulky γ,γ-disubstituted enals were selected as the Michael donors. The reaction afforded exclusively α-regioselective products. Moderated yields, but high diastereo- and enantioselectivity were gained for a wide scope of either reaction component. More importantly, the Michael adducts could be further transformed to some valuable cyclic frameworks with scaffold diversity.



Scheme 10 Asymmetric Michael addition of α,β-unsaturated aldehydes to nitroolefins

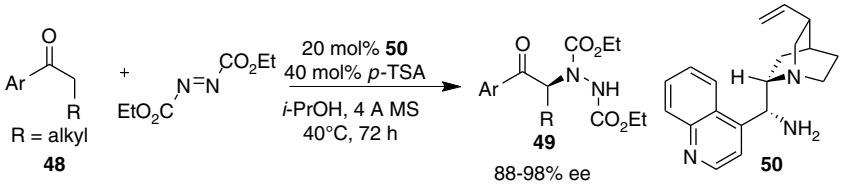
2.4 Asymmetric α-Functionalization of Carbonyl Compounds

Gong co-workers reported an enantioselective α-hydroamination of α-branched aldehydes with nitrosobenzenes catalyzed by L-prolinamide **1a** (Scheme 11) [61]. Good yields and moderate enantioselectivities have been obtained. The two protons of the amide and hydroxyl group preferentially form double hydrogen bonds with the oxygen over the nitrogen of nitroso group to render the nitrogen more reactive toward the enamine nucleophiles, leading to a distinct regioselectivity compared with the activation model by L-proline.



Scheme 11 Asymmetric α-hydroamination of aldehydes with nitrosobenzenes

Primary amine is principally more suitable for the generation of nucleophilic enamines with aryl ketones than secondary amines due to more reactivity and less sterical bulkiness. Indeed, a highly enantioselective direct α-amination of aryl ketones was realized in the presence of **50** (Scheme 12) [62]. The addition of molecular sieves facilitated the formation of enamine intermediate. Excellent enantioselectivity (88–99% ee) was achieved for aryl ketones bearing various substituents. Presumably, the protonated quinuclidine moiety of **50** acts as a Brønsted acid to activate the electrophilic azodicarboxylate through hydrogen-bonding interaction.



Scheme 12 Highly enantioselective α-amination of various aryl ketones

3 Iminium Catalysis

The condensation of a secondary amine with α,β-unsaturated aldehyde or ketone generates an unsaturated iminium species, which principally accepts the attack of nucleophiles to undergo 1, 4- or 1, 2-addition reactions. Normally, addition of acid additives to catalyst system facilitates the formation and decomposition of iminium intermediate, which is essentially important for the reaction proceeding. Iminium catalysis has been a widely applicable concept for the creation of new reactions [63].

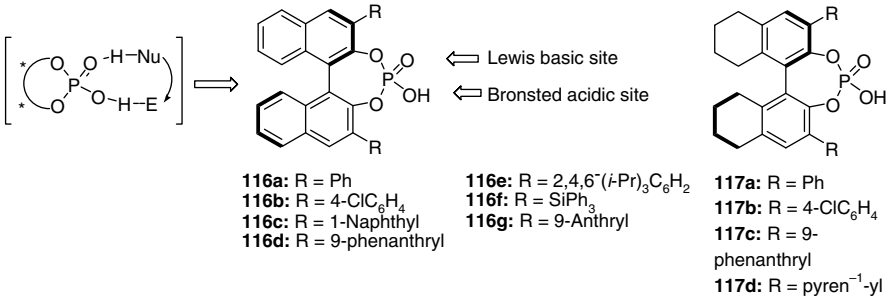
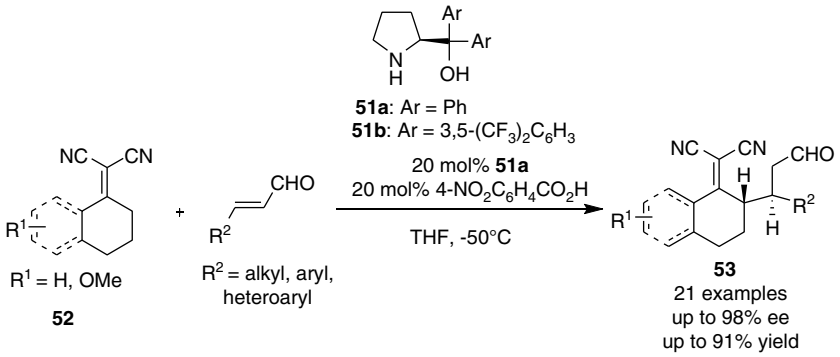


Fig. 3 Chiral binol-based phosphoric acids

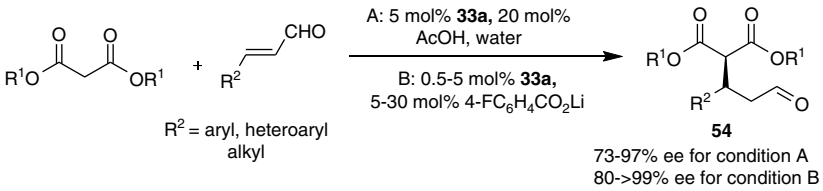
3.1 Asymmetric Michael Addition Reactions

Chen reported an asymmetric direct vinylogous Michael addition (Fig. 3) of α,α-dicyanoolefins to enals (Scheme 13) [64]. The catalyst α,α-diarylprolinol **51a** has been shown more effective than their etherified analogous. Excellent regio-, chemo-, diastereo-, and enantioselectivities were obtained for a broad scope of substrates.



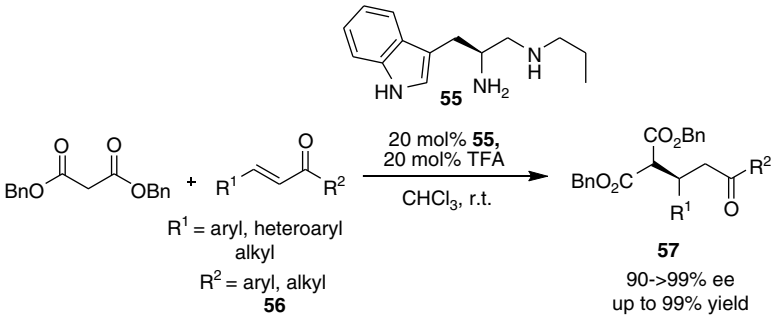
Scheme 13 Asymmetric vinylogous Michael addition reaction of α,α-dicyanoolefins with enals

For the Michael addition reaction of malonates and α,β-unsaturated aldehydes, two research groups independently improved the catalytic efficacy through different strategies (Scheme 14) [65, 66]. Ma DW reported that the use of water as the media renders the reaction to be complete within less than 24 h [65]. Liang and Ye found that the reaction proceeded smoothly with a low catalytic loading (0.5–5%) by using Brønsted base as additive [66].



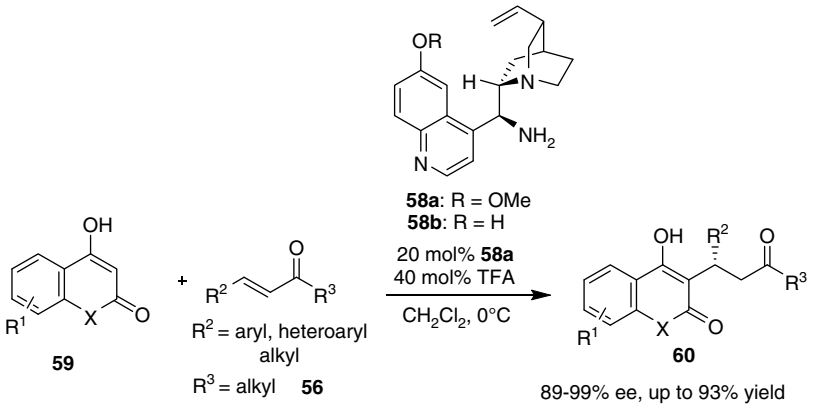
Scheme 14 Asymmetric Michael reaction of malonates with α,β-unsaturated aldehydes

A primary–secondary diamine catalyst **55** derived from L-tryptophan has been developed to catalyze the Michael addition of malonate to α,β-unsaturated ketones (Scheme 15) [67]. The length of the alkyl chain bonded to the second amine moiety had great influence on the catalytic activity. Nearly optically pure products could be obtained in excellent yields for various malonates and α,β-unsaturated ketones. The primary amine moiety activates the enone via iminium ion while the secondary amine functions as a Brønsted base to activate the nucleophile malonate, facilitating the reaction.



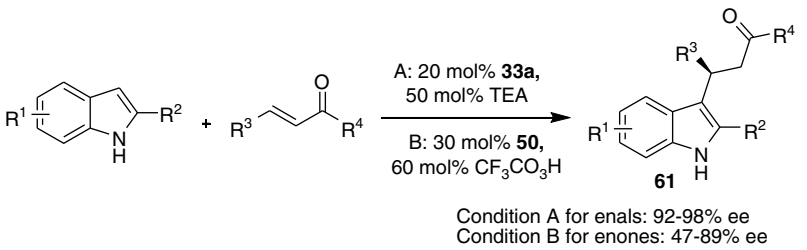
Scheme 15 Asymmetric Michael addition reaction of malonates to enones

Chen and co-workers described an enantioselective Michael addition of 4-hydroxycoumarin and its derivatives to α,β-unsaturated ketones in the presence of 9-amino-9-deoxyepiquinine **58a** and TFA (Scheme 16) [68]. Excellent enantioselectivity was achieved for a broad scope of substrates. The results were greatly improved in comparison with those with an imidazolidine catalyst [69]. Moreover, a chiral drug (*S*)-warfarin was facilely synthesized in high ee and overall yield.



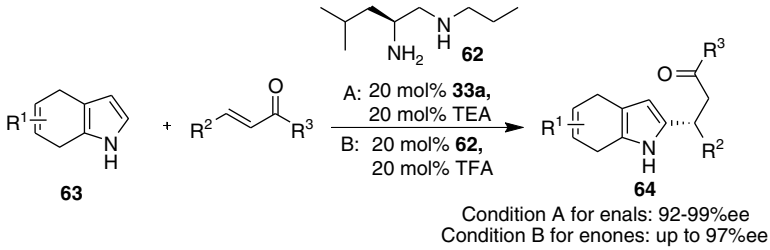
Scheme 16 Asymmetric Michael addition of 4-hydroxycoumarin and derivatives to enones

Wang and co-workers have developed an asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes catalyzed by primary amine catalyst **33a** and TEA (Scheme 17) [70]. Moderate to high yields and excellent enantioselectivity were obtained for a wide range of indoles and α,β-unsaturated aldehydes. Additionally, Chen accomplished an asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated ketones by a chiral primary amine catalyst **50** in combination of CF_3SO_3H additive, wherein moderate to high enantioselectivities have been achieved [71].



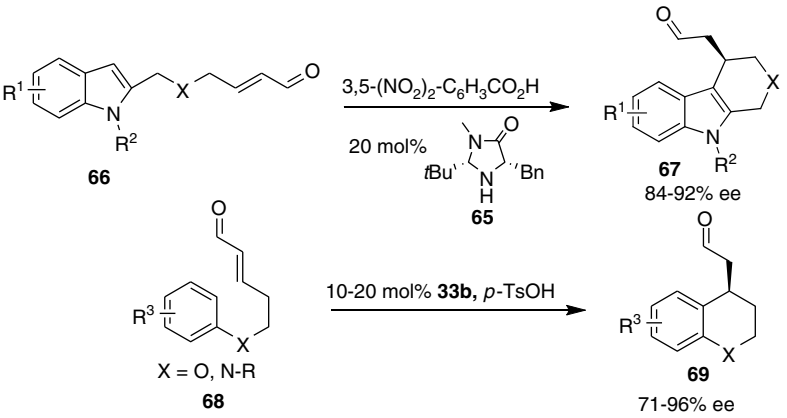
Scheme 17 Asymmetric indole alkylation of enones and enals

The asymmetric Friedel–Crafts reaction of 4,7-dihydroindoles with enals occurred smoothly under the promotion of the combined catalyst of **33a** and TEA (Scheme 18) [72], leading to the production of 2-alkylated 4,7-dihydroindoles in high yields and with excellent enantioselectivity. The reaction showed high generality for various substrates. After an oxidation, 2-alkylation indoles could be afforded. When α, β-unsaturated ketones were exploited, a primary–secondary diamine **62** was able to catalyze the transformation with excellent results [73].



Scheme 18 Asymmetric Friedel–Craft reaction of 4,7-dihydroindoles with enones and enals

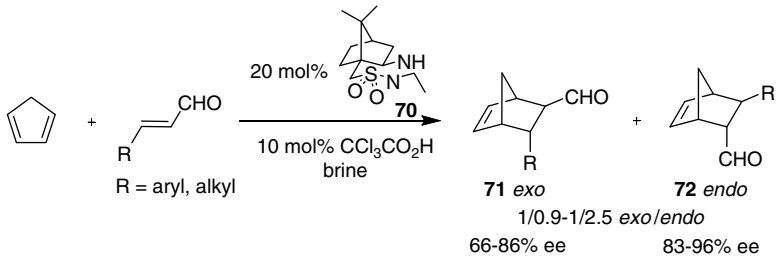
Xiao and co-workers have shown two successful examples of asymmetric intramolecular Friedel–Crafts reaction (Scheme 19) [74, 75]. The intramolecular ring-closing Friedel–Crafts-type alkylation of indolyl α,β-unsaturated aldehydes provided an enantioselective synthesis of tetrahydropyrano[3,4-b]indoles (THPIs) and tetrahydro-β-carbolines (THBCs) in the presence of a MacMillan catalyst [74]. The other intramolecular hydroarylations of ω-aryloxy- and arylamino-tethered α,β-unsaturated aldehydes enabled a straightforward access to optically active functional chromans and tetrahydroquinolines [75].



Scheme 19 Asymmetric intramolecular Michael addition of α,β-unsaturated aldehydes

3.2 Asymmetric Cycloadditions

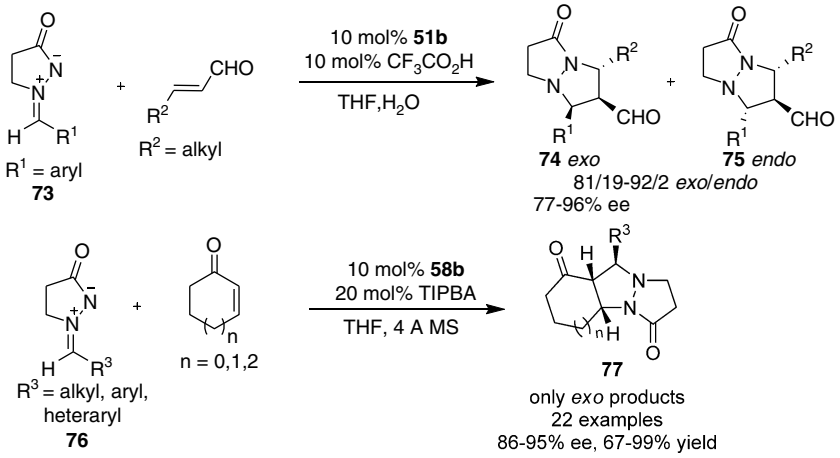
Lee designed an *N*-α-ethyl camphor sulfonyl hydrazine organocatalyst **70** and applied it to enantioselective Diels–Alder reaction (Scheme 20) [76]. The cycloaddition reaction between cyclopentadiene and various α,β-unsaturated aldehydes proceeded smoothly in the presence of 20 mol% of **72** and 10 mol% of trichloroa-



Scheme 20 Asymmetric Diels–Alder reaction between cyclopentadiene and enals

cetic acid by using brine as solvent. Good to excellent yields and enantioselectivities were obtained. In general, the enantioselectivity of the *endo* adducts was slightly higher than that of the *exo* adducts. Luo and Cheng also reported a similar reaction, in which chiral primary amine-polyoxometalate acid hybrids were used as recoverable iminium-based catalysts [77].

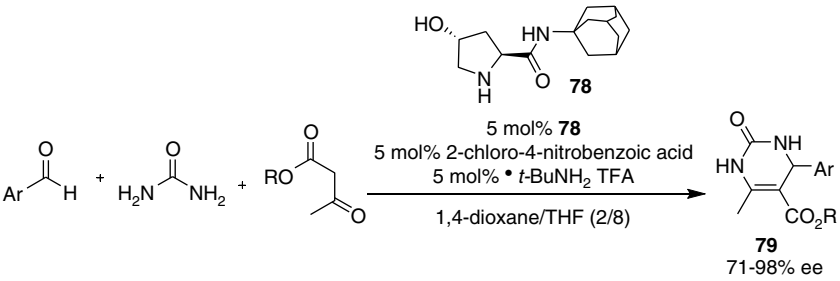
Chen presented a stereoselective [3+2] cycloaddition reaction of azomethine imines with enals catalyzed by a readily available diarylprolinol **51b** (Scheme 21). Various chiral bipyrazolin-3-one derivatives have been obtained with moderate to high enantiomerical excesses [78]. When cyclic enones were used, the combined catalyst system of **58b** and 2,4,6-triisopropylbenzenesulfonic acid (TIPBA) offered a highly enantioselective transformation (Scheme 21) [79]. A broad spectrum of substrates including cyclic enones and azomethine imines were amenable to the conditions with good to high enantioselectivities. The hydroxyl group of catalyst **58b** is essential to the stereocontrol because of an additional hydrogen bond formed between catalyst and 1,3-dipole to stabilize transition state.



Scheme 21 Asymmetric 1,3-dipolar cycloaddition reaction of azomethine imines to enals or cyclic enones

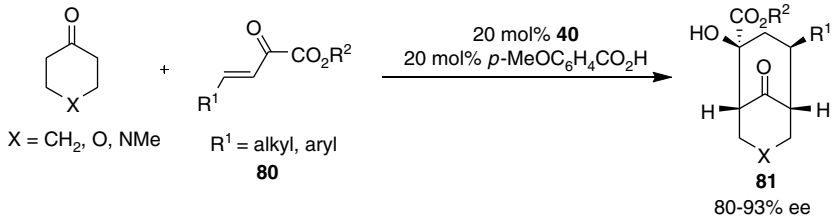
4 Asymmetric Multicomponent and Domino Reactions via Enamine and Iminium Catalysis

An asymmetric Biginelli reaction catalyzed by combination of chiral secondary amine **78** and achiral Brønsted acid in the presence of catalytic amount of an organic amino salt as additive has been developed by Feng and co-workers (Scheme 22) [80]. Fairly good yields and high enantioselectivity were obtained for a wide range of substrates. The hydroxyl group of the hydroxyl proline amide **78** has been proven to be essential to the high enantiocontrol.



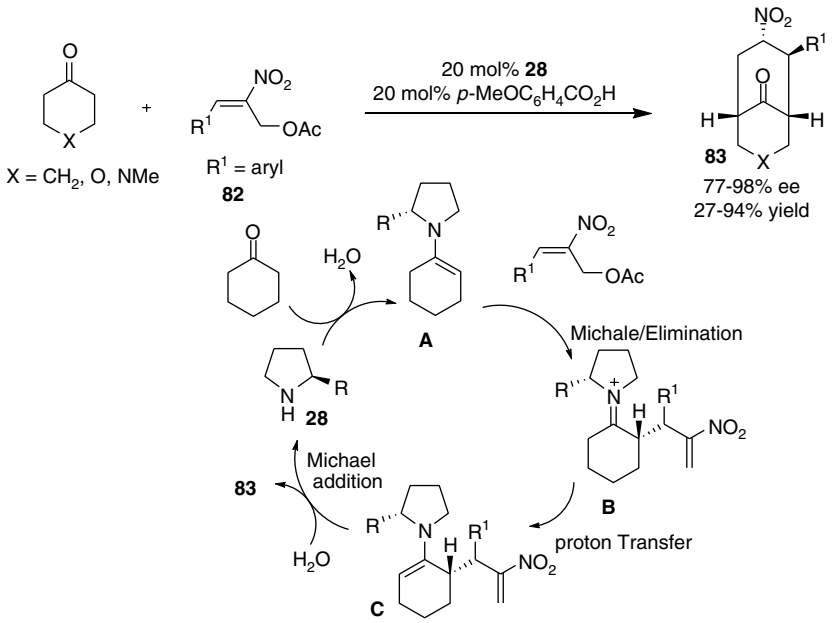
Scheme 22 Highly enantioselective Biginelli reaction catalyzed by chiral amine **78**

Tang disclosed an enantioselective formal [3+3] annulation reaction of cyclic ketones with enones, producing optically active 2-hydroxyl-9-oxo-bicyclo[3.3.1] nonane derivatives with four stereogenic centers (Scheme 23) [81]. A wide range of enone substrates were tolerated to afford desired products in good to high yields and enantioselectivities. The cascade process involves a Michael addition and a subsequent intramolecular aldol reaction.



Scheme 23 Formal [3+3] asymmetric reaction of ketones and enones

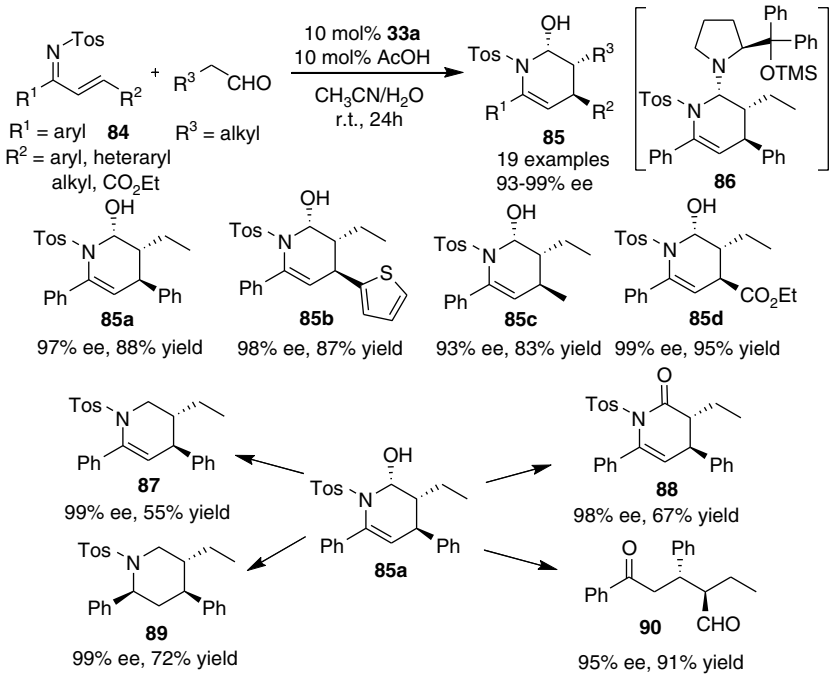
Very recently, Tang and co-workers reported a novel organocatalytic tandem reaction between cyclic ketones and (*E*)-2-nitroallycic acetates catalyzed by a pyrrolidine–urea **28** for the construction of bicyclic skeletons with four or five stereogenic centers (Scheme 24) [82]. Only one diastereomer was observed with



Scheme 24 Formal [3 + 3] asymmetric reaction of cycloketones and (e)-2-nitroallycic acetates

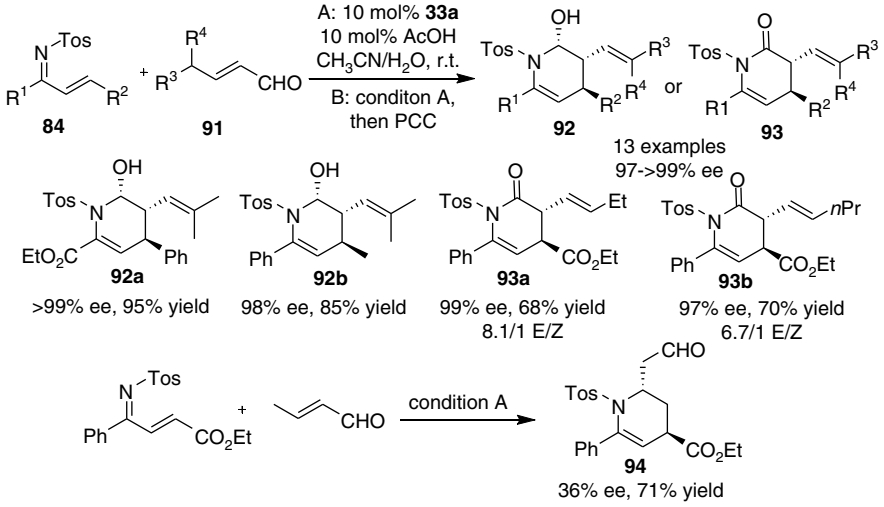
excellent results for various aromatic nitroolefins and cyclic or heterocyclic hexanones. This reaction proceeded presumably via a sequential Michael addition/elimination/Michael addition reaction.

Based on the enamine activation strategy, Chen designed a protocol to access optically pure piperidine derivatives [83]. A highly stereoselective inverse-electron-demand aza-Diels–Alder reaction of *N*-sulfonyl-1-aza-1,3-butadienes and aldehydes took place to give hemiaminals **85** in the presence of 10 mol% catalyst **33a** and AcOH. The mixture of CH_3CN and water was the best reaction media (Scheme 25). Water was found to accelerate the reaction, as water facilitates the hydrolysis of intermediate **86** to release the catalyst **33a** and thereby enabled the catalyst turnover. Excellent enantioselectivity was achieved for a wide range of substrates. Significantly, the chiral hemiaminal **85a** has been successfully transformed into a number of synthetically useful chiral building blocks such as tetrahydropyridine **87**, lactam **88**, peperidine **89**, and *anti*-1,5-dicarbonyl compound **90** in high optical purity.



Scheme 25 Asymmetric ADAR of N-tosyl-1-aza-1,3-butadienes and aldehydes and its synthetic applications

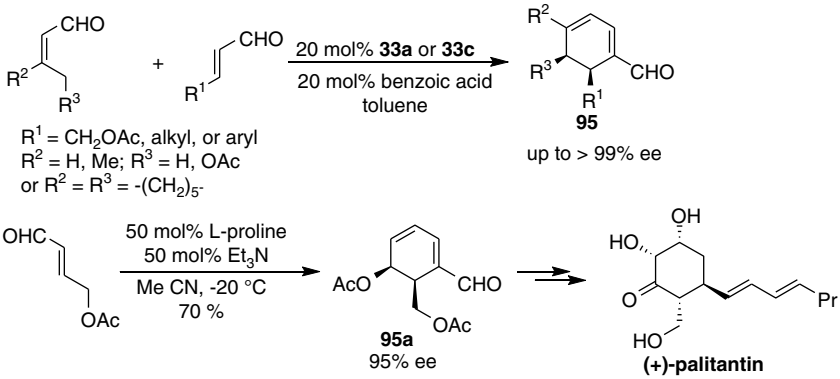
Very recently, Chen and co-workers expanded the dienamine catalysis to inverse-electron-demand aza-Diels–Alder reaction of enals with *N*-sulfonyl-1-aza-1,3-butadienes (Scheme 26) [84]. Initial investigation implied that the reaction proceeded



Scheme 26 Asymmetric ADAR of N-tosyl-1-aza-1,3-butadienes and enals

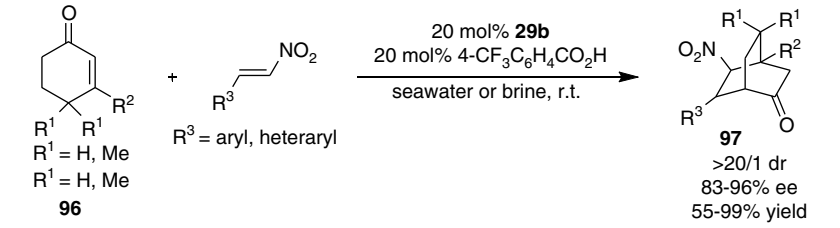
smoothly with exquisite α regioselectivity and thereby a chiral hemiaminal mixture (an *E*/*Z* mixture) was isolated. After oxidation, excellent enantioselectivity was observed for the major *E*-isomer **93**. The ratio of *E*/*Z* was 8.1/1. A broad spectrum of substrates was amenable to the catalytic conditions with excellent enantioselectivity. Impressively, these products can be readily transformed into highly synthetically useful multifunctional piperidine derivatives.

An enantioselective organocatalytic formal [4+2] reaction between α,β-unsaturated aldehydes under the promotion of prolinol derivatives **33a** or **33c** furnished optically active cyclohexa-1,3-dienyl aldehydes **95** with up to >99% ee [85]. The self [4+2] cycloaddition of (E)-3-formylallyl acetate with substoichiomeric amounts of L-proline and triethylamine at −20°C yielded a *cis*-cyclohexa-1,3-dienyl aldehyde **95a** with 95% ee. An enantioselective total synthesis of (+)-palitantin was accomplished commencing with this reaction (Scheme 27).



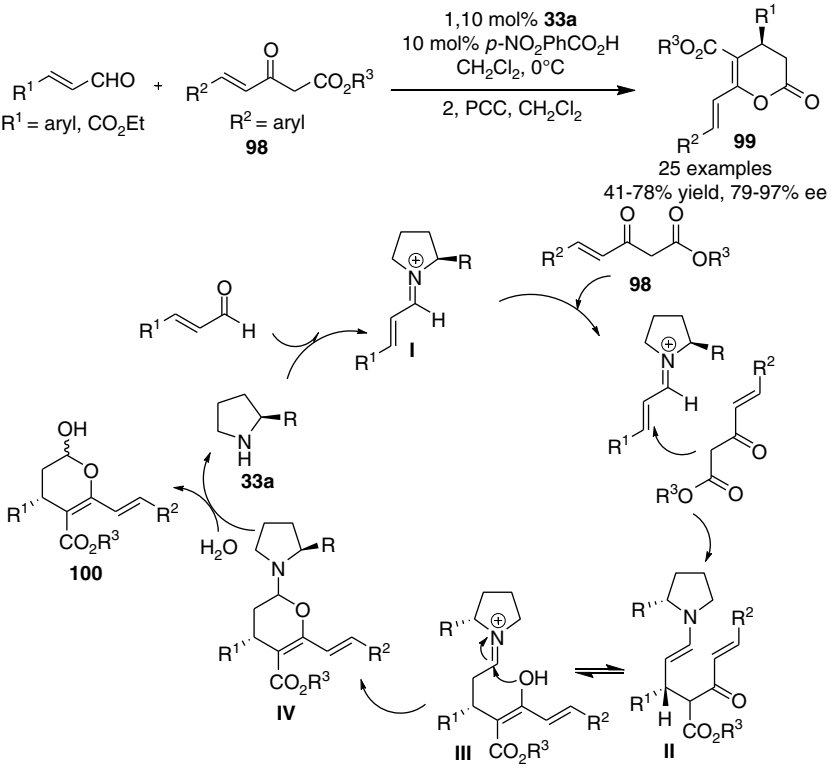
Scheme 27 Formal [4+2] reaction of enals

Xu and co-workers uncovered a highly efficient asymmetric organocatalytic Diels–Alder reaction of cyclohexenones with nitroolefins conducted in seawater or brine (Scheme 28) [86]. Excellent chem-, regio-, and stereoselectivities were observed for various aromatic nitroolefins.



Scheme 28 Diels–Alder reaction of cyclohexenones with nitroolefins in sea water and brine

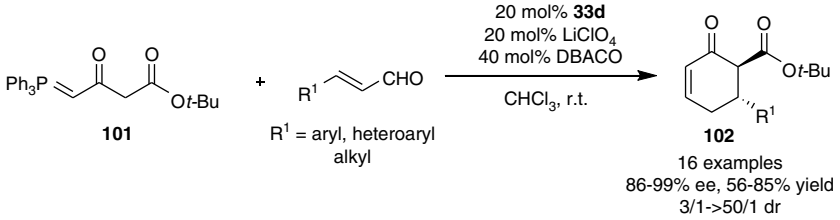
Gong and coworkers reported an asymmetric formal [3+3] cycloaddition reaction of Nazarov reagents **98** bearing an aryl group at C-5 with enals, yielding 3,4-dihydropyranols, which were readily oxidized to form chiral pyranones **99** with high enantioselectivities (Scheme 29) [87]. In this reaction, the unsaturated aldehydes first condensed with the chiral pyrrolidine **33a** to generate iminium salts **I**. Enantioselective Michael addition of Nazarov reagents **98** to the active iminium salts **I** afforded intermediates **II**, which can subsequently isomerize to **III** that undergo an intramolecular oxo-addition to form intermediates **IV**. The hydrolysis of intermediates **IV** with water generated from condensation step releases the products **100** and the organocatalyst **33a**.



Scheme 29 Asymmetric formal [3+3] cycloaddition reaction of Nazarov reagents with enals

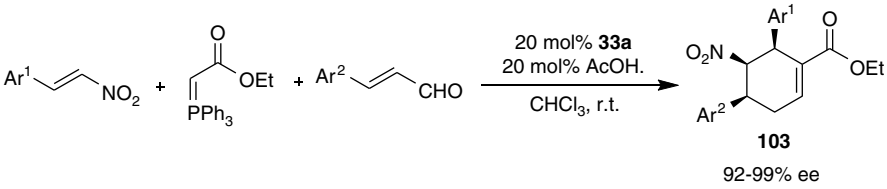
An asymmetric tandem Michaelv–Wittig reaction of enals with (3-carboxy-2-oxopropylidene)triphenylphosphorane **101** was investigated by Chen (Scheme 30) [88]. A broad spectrum of enals including aromatic, heteraromatic, and alkyl ones were tolerated. The multifunctional 6-carboxycyclohex-2-en-1-ones were isolated in moderate to high yields with excellent diastereo- and enantioselectivities (up to >50/1 dr, 99% ee).

Similarly, Hong and co-workers developed a cascade nitro-Michael–Michael–Wittig reaction for the synthesis of *all-cis*-5-nitro-4,6-dephenylcyclohex-1-



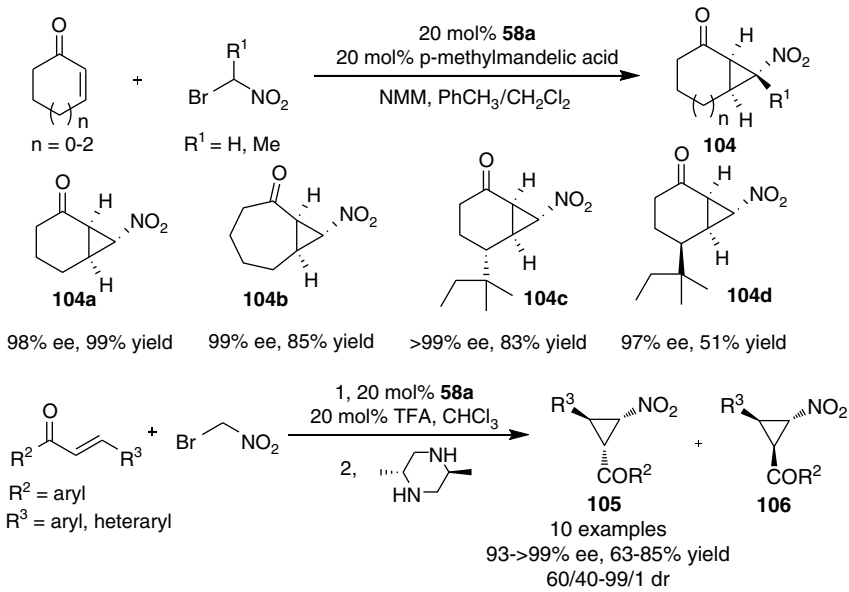
Scheme 30 Asymmetric tandem reaction of stabilized ylide and enals

enecarboxylic esters (Scheme 31) [89]. The sequential processes involved a dynamic kinetic resolution of *nitro*-Michael products.



Scheme 31 Cascade nitro-Michael/Michael/Wittig reaction

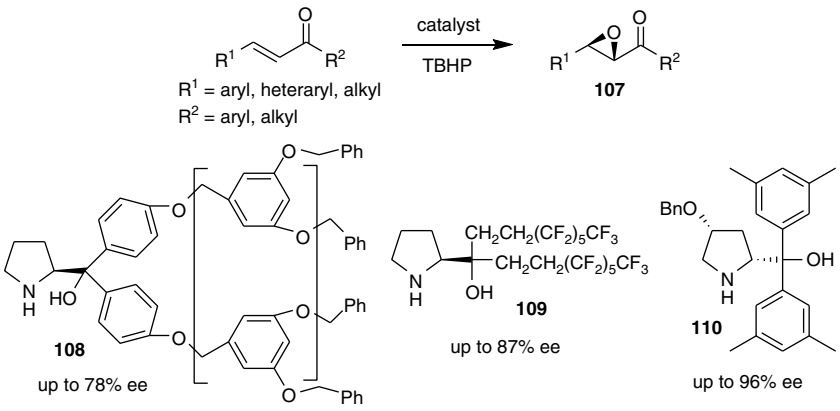
Wang and co-workers presented an asymmetric synthesis of functionalized nitrocyclopropanes by organocatalytic conjugate addition of bromonitroalkanes to enones (Scheme 32) [90]. In the presence of 9-amino-9-deoxyepiquine **58a** and



Scheme 32 Organocatalytic asymmetric Michael ring-closing reaction of bromonitroalkanes and enones

(*rac*)-4-methyl mandelic acid, the cycloaddition of cyclohexenone with bromonitro compounds furnished bicyclic products in high yields and enantioselectivities. The addition of 1 equivalent of base NMM was required. Moreover, the catalyst system also provided high selectivity in the kinetic resolution when only 0.6 equivalent of bromonitromethane was used (for example **104c** and **104d**). In addition, when chalcones were used as substrates, a stronger protic acid TFA and a chiral secondary amine were required to assist **58a** to accelerate the asymmetric cyclopropanation.

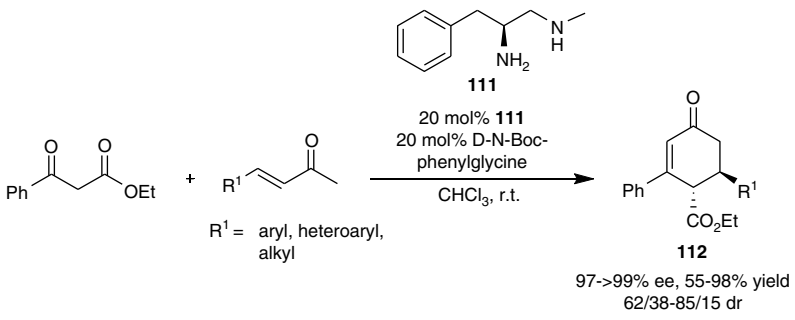
Zhao and co-workers synthesized a serious of prolinol-based organocatalysts for the asymmetric oxidation of enones (Scheme 33). Either pyrrolidinylmethanol-based dentritic catalyst **108** or fluorous α,α-diaryl-prolinol **109** was able to deliver



Scheme 33 Organocatalytic asymmetric oxidation of enones

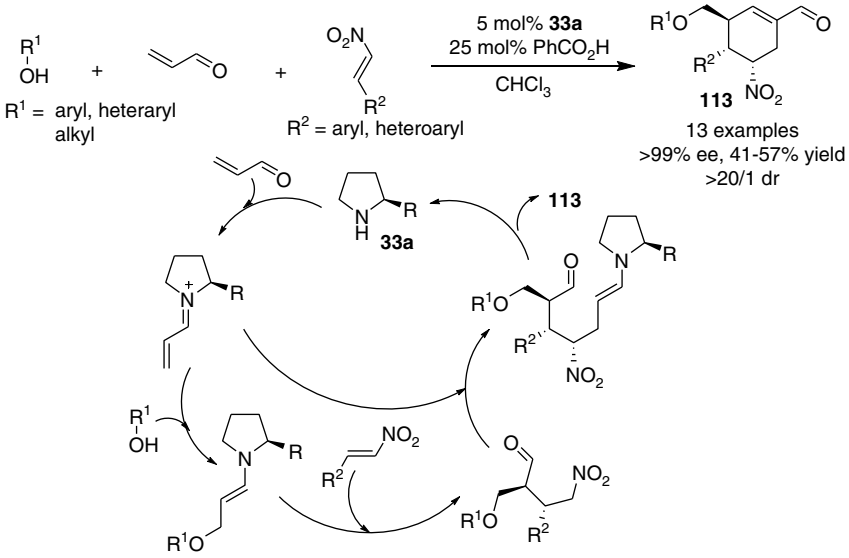
good stereoselectivity to epoxides [91, 92]. The two catalysts could be recovered and reused for several times without losing catalytic efficacy. Further modification of the catalyst found that four-substituted-α,α-diaryl-prolinol **110** was most suitable for the epoxidation, offering high enantioselectivity for a wide range of enones [93].

An asymmetric organocatalytic tandem Micheal-aldol-dehydration reaction between benzolacetates and enones could be established by using chiral primary–secondary diamine **111** as a catalyst, giving rise to cyclohexenones in excellent ee values (Scheme 34) [94].

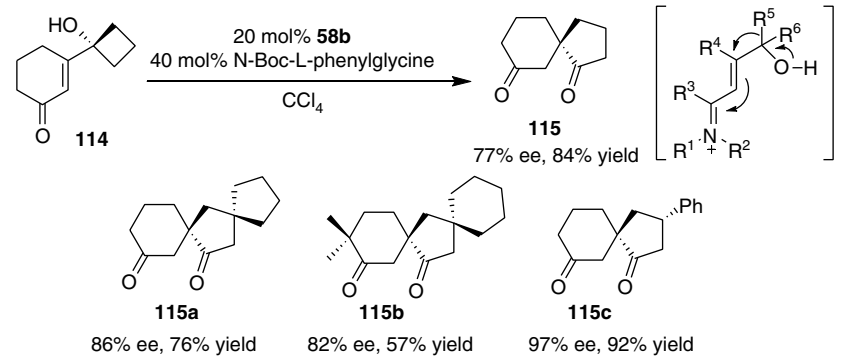


Scheme 34 Organocatalytic asymmetric Micheal-aldol-dehydration reaction between benzolacetates and enones

Gong and co-workers established an asymmetric four-component domino oxa-Michael/Michael/Micheal/aldol condensation reaction by using diphenylprolinol silyl ether **33a** as a catalyst (Scheme 35) [95]. This reaction provided a straightforward and atom economic approach to access optically active multifunctional cyclohexene carbaldehydes **113**. Various O-nucleophiles including primary, secondary alcohols and phenols, and different nitroalkenes including electron-deficient and electron-rich ones were applicable in good yields and excellent levels of stereocontrol.



Scheme 35 Organocatalytic asymmetric four-component domino oxa-Michael/Michael/Micheal/Aldol condensation reaction



Scheme 36 Organocatalytic asymmetric vinylogous α-ketol rearrangement via semipinacol-type 1,2-carbon migration

Tu and co-workers found an asymmetric vinylogous α-ketol rearrangement via semipinacol-type 1,2-carbon migration catalyzed by a cinchona-derived catalyst **58b** (Scheme 36). An all-carbon quaternary stereogenic centers in spirocyclic diketones was constructed with high levels of enantioselectivity [96].

5 Chiral Brønsted Acid Catalysis

5.1 Phosphoric Acid and Amide Catalysis

Chiral phosphoric acids of type **116**, were first demonstrated to catalyze Mannich reaction independently by Akiyama and Terada [97, 98]. This type of organocatalysts have unique structural feature containing a strong acidic hydroxy and a Lewis basic phosphoryl oxygen, which allow for the simultaneous activation of both nucleophiles and electrophiles by hydrogen bonding interactions. Moreover, the tunable 3,3′-substituents provide a diverse spectrum of catalysts for different enantioselective transformations. Indeed, they have been privileged organocatalysts widely applicable to a broad scope of asymmetric transformations (Fig. 4) [99–101].

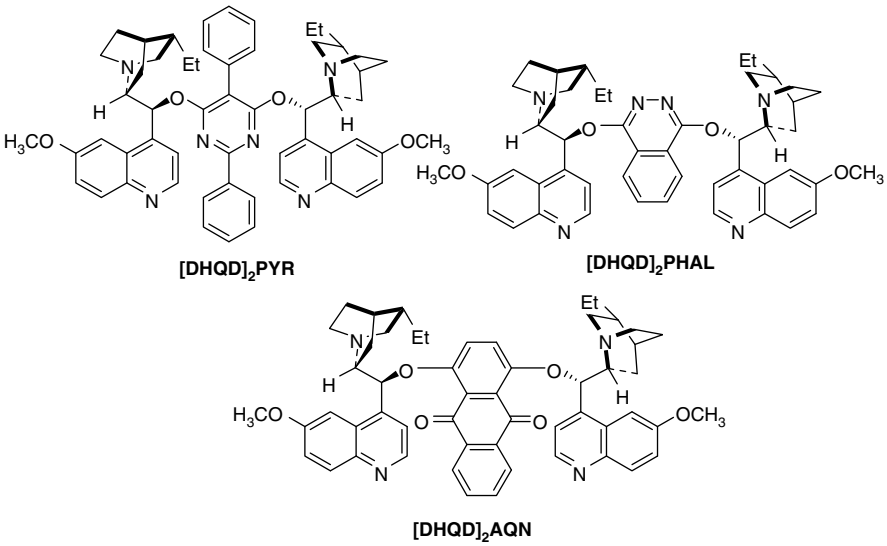
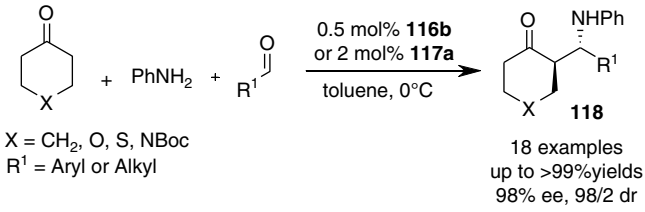


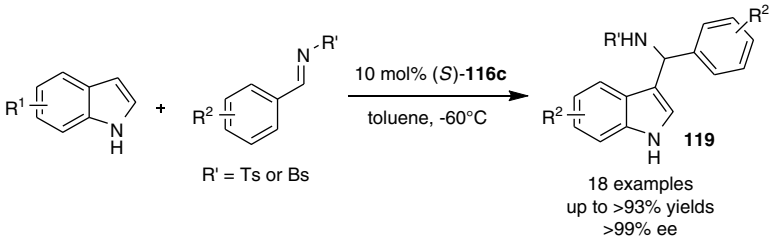
Fig. 4 Representative modified cinchona alkaloids

Gong and co-workers reported a direct asymmetric Mannich reaction catalyzed by chiral phosphoric acids (Scheme 37) [102]. The one-pot direct Mannich reaction of cyclohexanes, aniline, and benzaldehydes gave *anti*-β-amino products in high yields with excellent enantioselectivity and high diastereoselectivity in the presence of only 0.5 mol% catalyst **116b** or 2% mol% catalyst **117a**. Aliphatic aldehydes and hetero cyclohexanes also underwent a smooth Mannich reaction with excellent stereoselectivity.



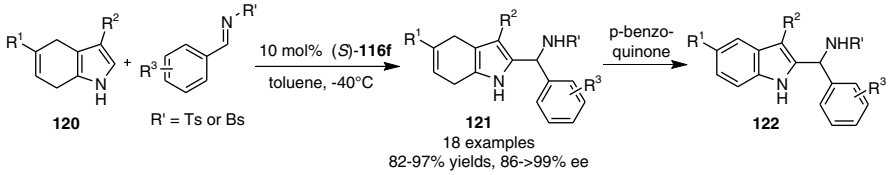
Scheme 37 Anti-selective three-component direct asymmetric Mannich reactions

You and co-workers have devoted great effort on asymmetric Friedel–Crafts reactions. They found that the Friedel–Crafts reaction of indoles with imines catalyzed by chiral phosphoric acid **116c** offered high yields and excellent enantioselectivities to a wide range of aromatic aldimines (Scheme 38) [103]. The enantioselective Friedel–Crafts reaction of indoles with ethyl glyoxylate imine has also been realized by phosphoric acid **116d** [104]. Ma and co-workers reported an enantioselective Friedel–Crafts reaction of indoles with imines generated in situ from trifluoroacetaldehyde or difluoroacetaldehyde methyl hemiacetal and aniline by utilizing chiral catalyst **116e**. High yields (80–99%) and excellent enantioselectivities (79–98% ee) have been obtained for a wide scope of indoles [105].



Scheme 38 Enantioselective Friedel–Crafts reaction of Indoles with N-sulfonyl imines

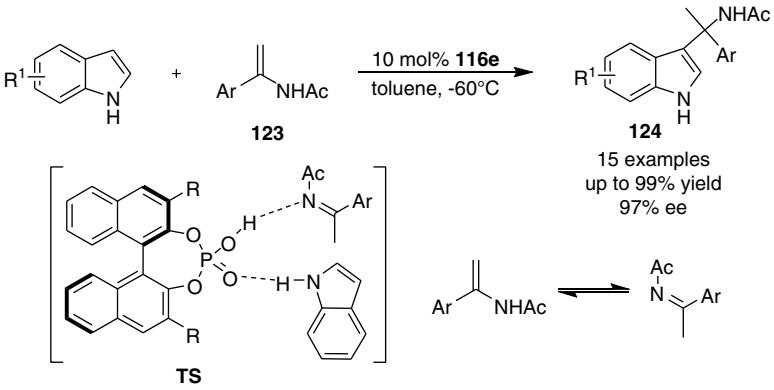
To access 2-indolyl methanamine derivatives, You developed a Friedel–Crafts reaction of 4,7-dihydroindoles with imines in the presence of catalyst **116f**, followed by oxidation, gave the desired products with excellent enantioselectivities (Scheme 39) [106]. The Friedel–Crafts reaction has been found to be general for



Scheme 39 Enantioselective Friedel–Crafts reaction of 4,7-dihydroindoles with N-sulfonyl imines

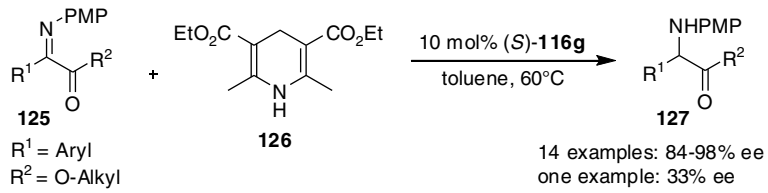
various 4,7-dihydroindoles and imines in high yields and excellent levels of enantioselectivity.

Zhou accomplished an enantioselective Friedel–Crafts reaction of indoles with α-aryl enamides catalyzed by chiral Brønsted acids (Scheme 40) [107]. In the presence of 10 mol% of chiral phosphoric acid **116e**, chiral amides with a quaternary stereogenic center were produced in high enantioselectivity. The addition of 4 Å molecular sieves was required to prevent the hydrolysis of the enamine substrates. Electronic nature of the substituent in the enamide substrates has little effect on the enantiocontrol. However, *ortho* substituents in the α-aryl enamides greatly eroded the reactivity and enantioselectivity. A wide range of substituted indoles were included with excellent results. No reaction was observed when *N*-methylindole and *N*-methyl enamide were treated with α-aryl enamide and indole, indicating that the chiral phosphoric acid catalyst activates the indole and enamine through double hydrogen-bonding interactions.



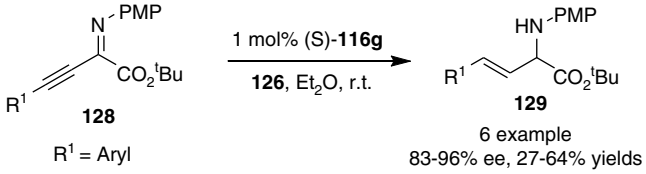
Scheme 40 Asymmetric Friedel–Crafts reaction of indoles with α-aryl enamides

You and co-workers realized a phosphoric acid catalyzed highly enantioselective transfer hydrogenation of α-imino esters (Scheme 41) [108]. The catalyst **116g** provided high enantioselectivity for a broad spectrum of substrates including aryl-, heteroaryl-, alkyl-substituted imino ester, and imino amines. However, only 33% ee was given to the methyl esters substrate.



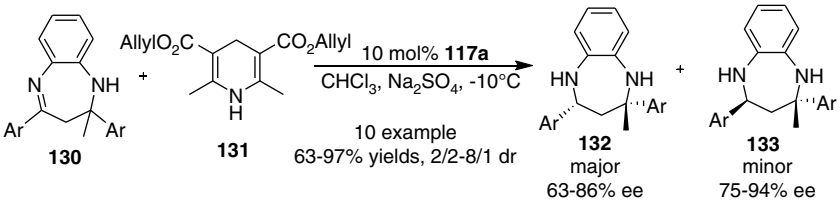
Scheme 41 Asymmetric transfer hydrogenation of α-imino esters and amides

Further studies from the same group on the transfer hydrogenation resulted in an asymmetric synthesis of *trans*-alkynyl α-amino esters from β,γ-alkynyl α-amino esters (Scheme 42) [109]. The sterically congested phosphoric acid **116g** was the catalyst of choice, delivering excellent enantioselectivity but the yield was moderate.



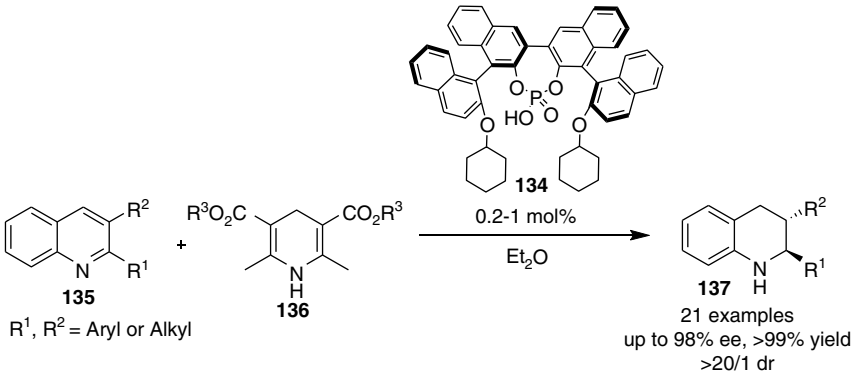
Scheme 42 Asymmetric transfer hydrogenation of β,γ-alkynyl α-amino esters

Gong discovered a method to synthesize 1,3-diamines via dynamic kinetic asymmetric transfer hydrogenation of racemic 2,4-diary-2,3-dihydrobenzo[b][1,4]diazepines catalyzed by chiral phosphoric acids (Scheme 43) [110]. H8-binol-derived phosphoric acid **117a** turned out to be the optimal catalyst. Allyl Hantzsch **131** was the best hydride source. Good to high ee for the major *syn*-products and high to excellent ee for minor *anti*-products have been obtained. The diastereomeric ratio of syn/anti ranges from 2/1 to 8/1. In this reaction, the (*S*)-**130** presumably undergoes a fast transfer hydrogenation than the (*R*)-enantiomer, while the racemization of (*R*)-enantiomer took place rapidly via reversible retro-Mannich and Mannich reaction under the catalysis of Brønsted acid.



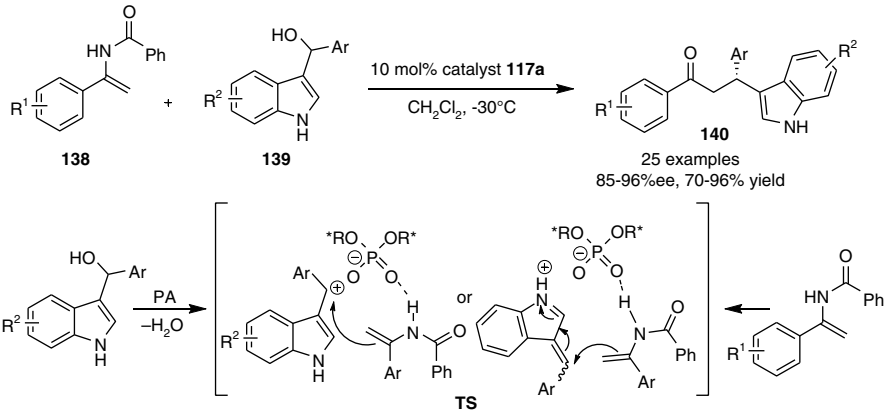
Scheme 43 Asymmetric transfer hydrogenation of 2,4-diary-2,3-dihydrobenzo[b][1, 4]diazepines

Du and co-workers designed a chiral phosphoric acid **134** and utilized it to catalyze transfer hydrogenation of quinolines (Scheme 44) [111]. Compared with the results obtained with binol-based phosphoric acids [112], this catalyst exhibited higher catalytic activity and thus only 0.2 mol% of **134** is sufficient to afford high enantioselectivity for 2-alkyl-substitued quinolines. Moreover, 2,3-disubstituted quinolines were also hydrogenated with excellent diastereo- and enantioselectivities.



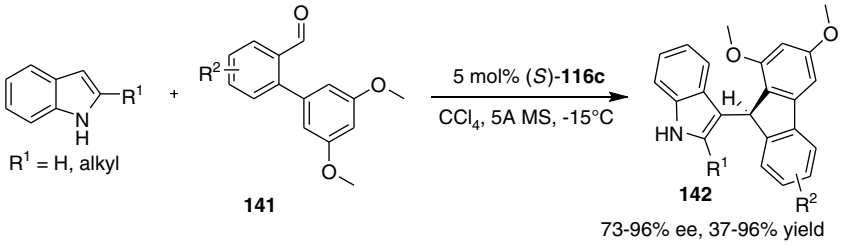
Scheme 44 Asymmetric transfer hydrogenation of quinolines

Guo and Gong very recently established a highly enantioselective alkylation reaction of enamides with indolyl alcohol (Scheme 45) [113]. The chiral phosphoric acid **117a** promoted the α-alkylation of enamides with indolyl alcohols to give β-aryl 3-(3-indolyl) propanones in high yields and with excellent enantioselectivities. In the course of the reaction, a tight chiral ion pair between the phosphate anion and the cation was generated in situ from alcohol under acidic conditions and meanwhile the Lewis basic phosphoryl oxygen in the tight ion pair activates the enamide by a hydrogen bond.



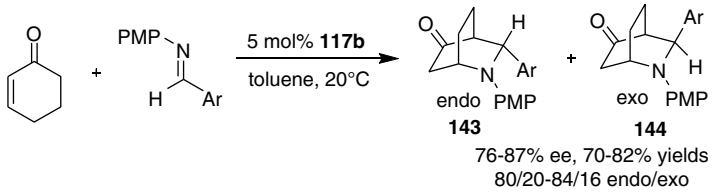
Scheme 45 Asymmetric alkylation reaction of enamides with indolyl alcohol

A phosphoric acid-catalyzed tandem double Friedel–Crafts reaction between indoles and 2-formylbiphenyls has been developed by You and co-workers (Scheme 46) [114]. In the presence of 5 mol% of chiral phosphoric acid **116c**, the cascade reaction furnished structurally different fluorene derivatives in high yields and excellent enantioselectivities.



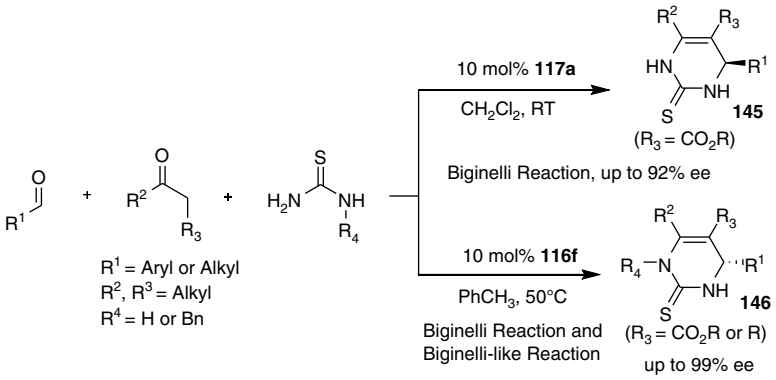
Scheme 46 Tandem double Friedel–Crafts reaction between indoles with 2-formylbiphenyls

Gong initiated a direct aza hetero-Diels–Alder reaction between aromatic aldimines and cyclohexenones catalyzed by a chiral Brønsted acid (Scheme 47) [115]. Five mole percent of phosphoric acid **117b** could promote the reaction of various aromatic aldimines in high yields and with good diastereomeric ratios and enantioselectivities. The one-pot, three-component version was also proven to be feasible without losing stereoselectivity.



Scheme 47 Asymmetric direct aza hetero-Diels–Alder reaction between aromatic aldimines with cyclohexenones

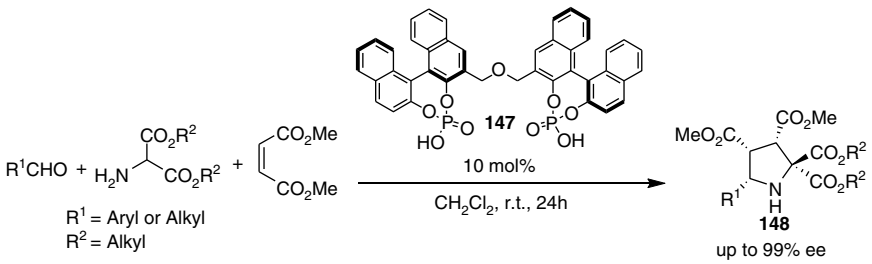
Biginelli reaction is one of most important multicomponent reactions, offering an efficient access to mutifunctionalized 3,4-dihydropyrimidine-2-(1H)-ones and related heterocyclic compounds. Gong established organocatalytic asymmetric Biginelli and Biginelli-like reactions by utilizing chiral phosphoric acid as catalyst (Scheme 48) [116, 117]. In the presence of 10 mol% chiral phosphoric acid **117a**, the Biginelli reaction of aldehydes, thiourea, and acetoacetate underwent successfully to give (*R*)-products in high yields and with excellent enantioselectivity. Aliphatic aldehydes also afforded high enantioselectivity, albeit with low yields. Further experiments revealed that the stereochemistry of the Biginelli reaction could be reversed by tuning



Scheme 48 Organocatalytic asymmetric Biginelli and Biginelli-like reaction

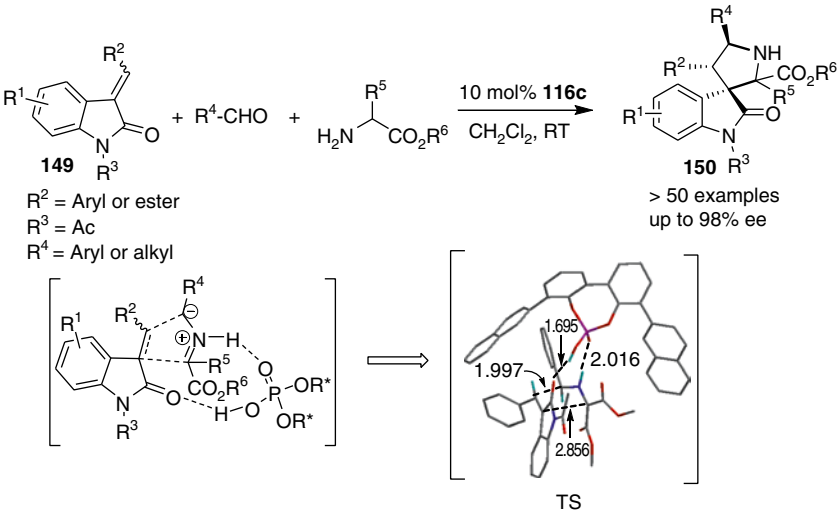
the 3,3′-disubstituents of the phosphoric acids. Using the phosphoric acid **116f** with same configuration as **117a** gave (*S*)-products with high levels of enantiocontrol. The phosphoric acid **116f** enables an asymmetric Biginelli-like reaction of benzylthiourea with aldehydes and enolizable ketones with excellent levels of enantioselectivity. Theoretical calculations revealed that imine and enol were simultaneously activated by the bifunctional chiral phosphoric acid via hydrogen bonds.

Gong also disclosed an asymmetric organocatalytic three-component 1,3-dipolar cycloaddition of aldehydes with α-amino esters and electron-deficient olefins by the employment of chiral phosphoric acid as catalyst (Scheme 49) [118]. A new bisphosphoric acid **147** was able to deliver excellent enantioselectivity for the cycloaddition of diethyl aminomalonate and maleates with a wide range of aldehydes including aromatic, aliphatic, and α,β-unsaturated aldehydes. Importantly, α-arylglycine methyl esters underwent the reaction to afford pyrrolidine derivatives with four contiguous stereogenic centers including a quaternary carbon with high enantiomeric excesses.



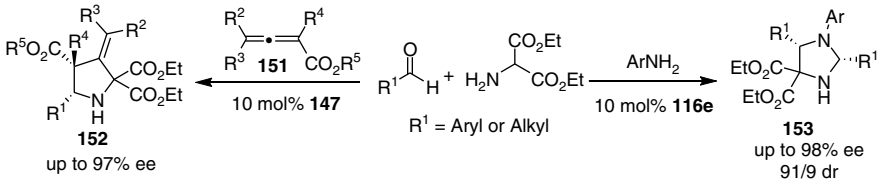
Scheme 49 Organocatalytic asymmetric three-component 1,3-dipolar cycloaddition of aldehydes with α-amino esters and electron-deficient olefins

In addition, the asymmetric 1,3-dipolar cycloaddition could be expanded to the synthesis of spiro[pyrrolidin-3,3′-oxindoles] [119]. The 1,3-dipolar cycloaddition of aldehyde, diethyl aminomalonate with methyleneindoline furnished spiro[pyrrolidin-3,3′-oxindoles] in high yields and excellent enantioselectivities (up to 98% ee) in the presence of 3,3′-β-naphthyl phosphoric acid **116c** (Scheme 50). The regiochemistry was found to be independent of electronic nature over two carbon atoms of the C=C bond of methyleneindoline and unusual regioselective 1,3-dipolar cycloaddition products were obtained. Theoretical calculations indicated that both the azomethine ylide and the methyleneindolinone are hydrogen-bonded with the phosphoric acid.



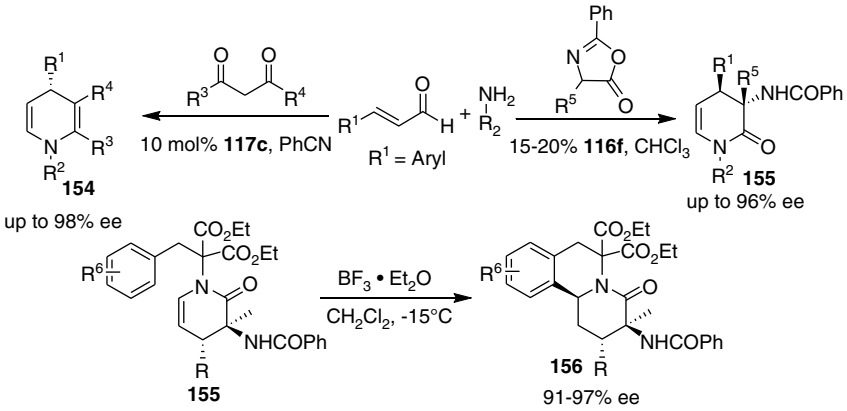
Scheme 50 Organocatalytic asymmetric three-component 1,3-dipolar cycloaddition for the synthesis of Spiro[pyrrolidin-3,3′-oxindoles]

2,3-Allenates was scarcely used as dipolarophiles for the cycloaddition. A catalytic 1,3-dipolar cycloaddition involving 2,3-allenoate dipolarophiles has been realized for the synthesis of optically active 3-methylenepyrrolidine derivatives (Scheme 51) [120]. The protocol tolerated a wide spectrum of aldehydes and 2,3-allenoates. 1,3-Dipolar cycloaddition of azomethine ylides and imines was also investigated (Scheme 51) [121]. Various synthetically useful chiral imidazolidines have been furnished with high levels of stereoselectivity (up to 98% ee and 91/1 dr).



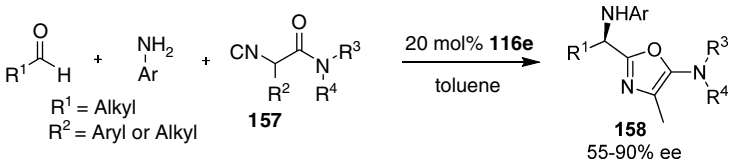
Scheme 51 Organocatalytic asymmetric three-component 1,3-dipolar cycloaddition

Gong reported a highly enantioselective three-component cyclization of cinnamaldehydes, primary amines, and 1,3-dicarbonyl compounds in the presence of chiral phosphoric acid **117c** (Scheme 52) [122]. Highly enantiomerically enriched 1,4-dihydropyridines have been obtained. Conversion of the 1,4-dihydropyridines by 1,3-dipolar addition and diastereoselective reduction to other optical active heterocyclic compounds further demonstrated the importance of the method. The



Scheme 52 Organocatalytic asymmetric cycloaddition of cinnamaldehydes and primary amines with 1,3-dicarbonyl compounds or azlactones

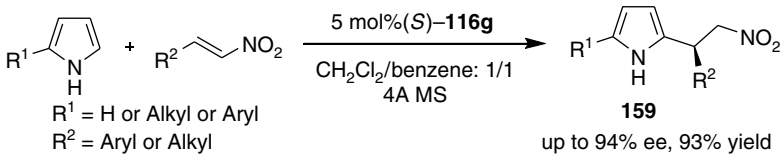
replacement of 1,3-dicarbonyl compound with azlactone led to a new enantioselective three-component cyclization reaction (Scheme 53) [123]. A wide range of 3-amino-3,4-dihydropyridinoes has been synthesized in excellent enantioselectivities (up to 96% ee). Moreover, substituted aryl ethylamines were also good reactants for this cycloaddition reaction, producing 3-amino-3,4-dihydropyridinoes able to be converted to benzo[a]quinolizidine derivatives by Lewis acid-catalyzed Pictet–Spengler reaction.



Scheme 53 Organocatalytic asymmetric α-addition of α-isocyanides to imines

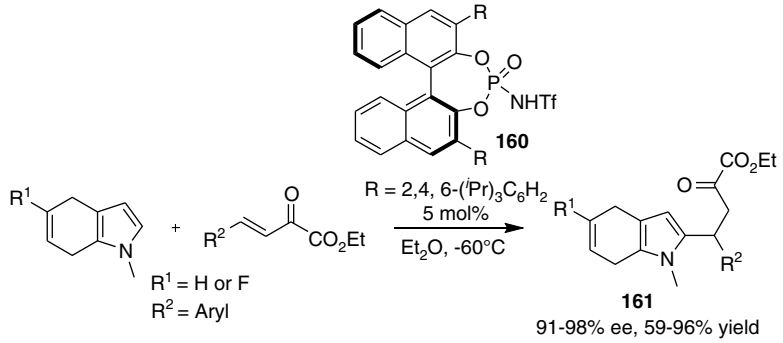
Wang, Zhu and co-workers disclosed an enantioselective three-component reaction of aldehydes and aromatic amines with α-isocyanoacetamides catalyzed by chiral phosphoric acids (Scheme 53) [124]. This is the first example of asymmetric α-addition of α-isocyanides to imines. 2-(1-Aminoalkyl)-5-aminooxazoles were obtained in moderate to high ees.

Asymmetric Friedel–Crafts alkylation of pyrroles with nitroolefins catalyzed by chiral Brønsted acids has been developed by You (Scheme 54) [125]. Various nitroolefins smoothly reacted with pyrrole or two-substituted pyrroles to give high yields and high to excellent enantioselectivity in the presence of 5 mol% of **116g**. This method has been applied to the synthesis of chiral two-substituted indoles by asymmetric Friedel–Crafts reaction of 4,7-dihydroindoles with nitroolefins and followed by oxidation [126].



Scheme 54 Asymmetric Friedel–Crafts alkylation of pyrroles with nitroolefins

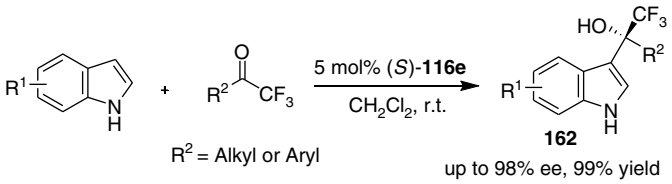
Furthermore, You and co-workers reported an asymmetric Friedel–Crafts reaction of 4,7-dihydroindoles with β,γ-unsaturated α-keto esters (Scheme 55) [127]. High yields and excellent enantiomeric excesses have been achieved by chiral N-triflyl phosphoramide **160**. The reaction was found to be general for keto esters bearing different substituents. 5-Fluoro and methoxy-4,7-dihydroindole were also appropriate substrates for this transformation. The products were easily converted to chiral two-substituted



Scheme 55 Asymmetric Friedel–Crafts reaction of 4,7-dihydroindoles with β,γ-unsaturated α-keto esters

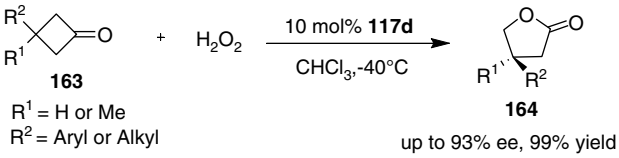
indoles through oxidation. However, chiral phosphoric acids were unable to give high enantioselectivity to the Friedel–Crafts reaction of indoles to enones [128].

Ma and co-workers developed a direct arylation of trifluoromethyl ketones with indoles (Scheme 56) [129]. Chiral phosphoric acid **116e** gave the highest enantioselectivity. Highly enantiomerically enriched trifluoromethyl-substituted tertiary alcohols have been obtained from various indoles and 2,2,2-trifluoroacetophenones. The protocol was also extended to CHF_2- and C_2F_5-arylketones with excellent enantioselectivity [130].



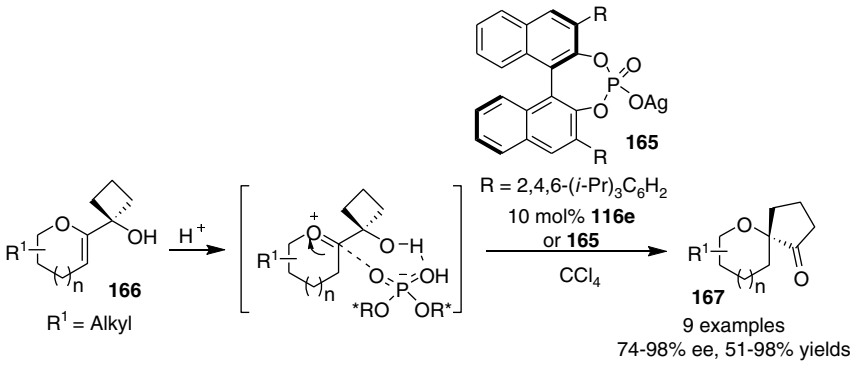
Scheme 56 Asymmetric arylation of trifluoromethyl ketones with indoles

Ding presented an asymmetric Baeyer–Villiger reaction of three-substituted cyclobutanones (Scheme 57) [131]. Strong Brønsted acids have been found to accelerate the BV reaction. The presence of 10 mol% of chiral phosphoric acid **117d** could deliver high yields and enantioselectivities (up to 93%) for various three-substituted cyclobutanones using aqueous H_2O_2 as the oxidant. A linear effect was observed to imply that one molecule of the catalyst was involved in the transition state.



Scheme 57 Asymmetric Baeyer–Villiger oxidation of three-substituted cyclobutanones

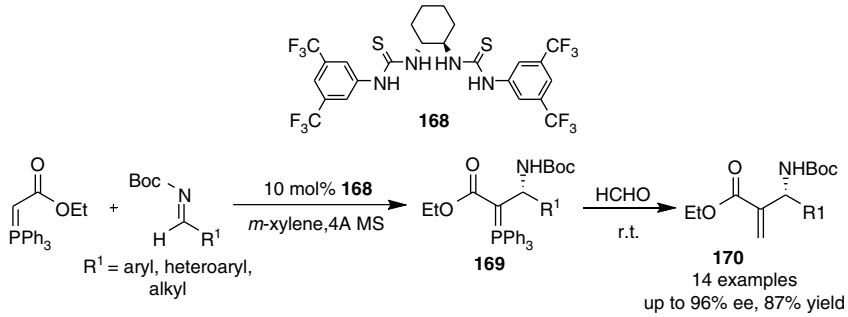
A Brønsted acid-catalyzed asymmetric semipinacol rearrangement for the synthesis of chiral spiroethers has been reported by Tu and co-workers (Scheme 58) [132]. The chiral phosphoric acid **116 e** and its corresponding sliver phosphate **165** were found to be the best catalyst for the semipinacol rearrangement of 2-oxo allylic alcohols, delivering good to high yields and high enantioselectivities. The chiral phosphoric acid that was generated in situ from sliver phosphate served as the real catalyst.



Scheme 58 Asymmetric semipinacol rearrangement of 2-oxo allylic alcohols

5.2 Chiral Thiourea

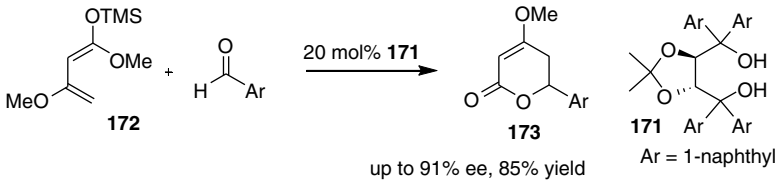
A highly enantioselective Mannich-type reaction of phosphoric ylide with N-Boc aldimines has been developed by Chen (Scheme 59) [133]. An easily available bisthiourea **168** was the best catalyst for the reaction. Moderate to high yields and excellent enantioselectivity have been obtained in most cases. A wide spectrum of N-Boc aldimines including aryl and alkyl aldimines were tolerated. The concerted hydrogen bonds might interact with both phosphoric ylide and N-Boc aldimine and thereby are able to deliver high asymmetric induction.



Scheme 59 Mannich-type reaction of phosphoric Ylide with N-Boc aldimines and subsequent synthesis of β-amino-α-methylene carboxylic esters

5.3 Weakly Acidic Chiral Brønsted Acid

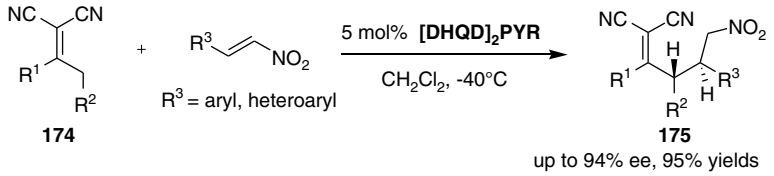
Ding group reported that a DADDOL derivative **171** enabled the Hetero-Diels–Alder reaction of Brassard's diene with aldehydes to afford δ-lactone derivatives in moderate to high yields and high enantioselectivity (Scheme 60). Hydrogen-bonding interaction between TADDOL and the carbonyl group activates the aldehydes to promote the cycloaddition reaction [134].



Scheme 60 Asymmetric hetero-Diels–Alder reaction between Brassard's diene and aldehydes

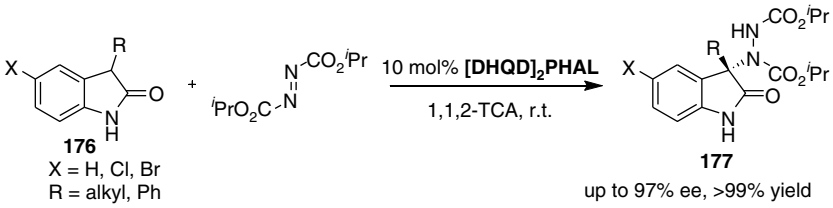
6 Chiral Organic Base Catalysis

An asymmetric direct vinylogous Michael reaction of activated vinyl malononitriles to nitroolefins catalyzed by modified cinchona alkaloid $[DHQD]_2PYR$ was reported by Chen (Scheme 61) [135]. Highly functionalized products with two vicinal chiral centers were generated with exclusive γ-selectivity and high diastereo- and enantioselectivity.



Scheme 61 Asymmetric vinylogous Michael reaction of activated vinyl malononitriles to nitroolefins

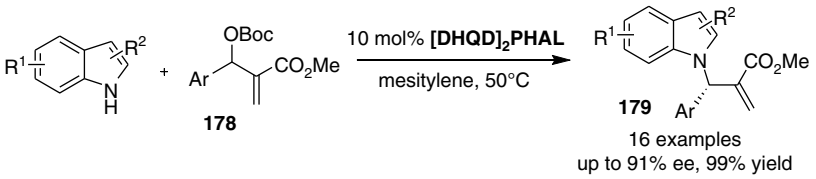
Additionally, Chen and co-workers expanded the cinchona alkaloid catalysis to an asymmetric α-amination of 2-oxindoles with diisopropyl azodicarboxylate (DIAD) (Scheme 62) [136]. Ten mole percent of $[DHQD]_2PHAL$ in 1,1,2-trichloroethane (1,1,2-TCA) provided a clean reaction of a wide range of *N*-unprotected 2-oxindoles with DIAD, furnishing (*S*)-3-amino-2-oxindoles in excellent yields and enantioselectivities.



Scheme 62 Asymmetric α-amination of 2-oxindoles

In contrast to the well-established C3-chemoselective functionalization, an asymmetric and chemoselective N-allylic alkylation of indoles with Morita–Baylis–Hillman carbonates has been less investigated. Chen found that modified cinchona alkaloid $[DHQD]_2PHAL$ is a good catalyst for the N-allylic alkylation of indoles with MHB carbonates (Scheme 63) [137]. High yields and excellent enantioselectivity were achieved.

Extensive studies from the same group on allylic alkylation reaction of Morita–Baylis–Hillman carbonate derivatives found that some other nucleophiles such as α,α-dicyanolkenes, oxindoles, cyclic imides, and even hydroperoxyalkanes were able to participate in the reaction in the presence of modified cinchona alkaloids (Fig. 5) [138–141].



Scheme 63 Asymmetric N-allylic alkylation of indoles with Morita–Baylis–Hillman carbonates

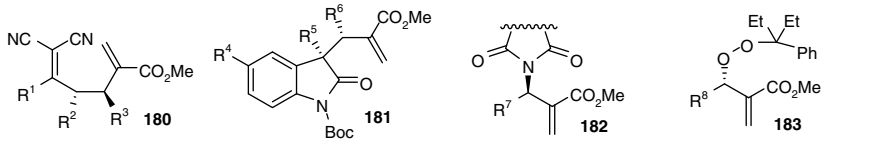
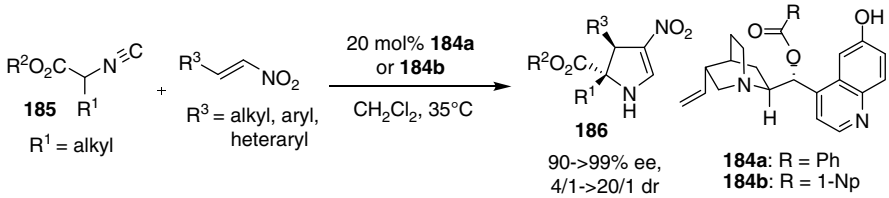


Fig. 5 Products via various reactions of Morita–Baylis–Hillman carbonates

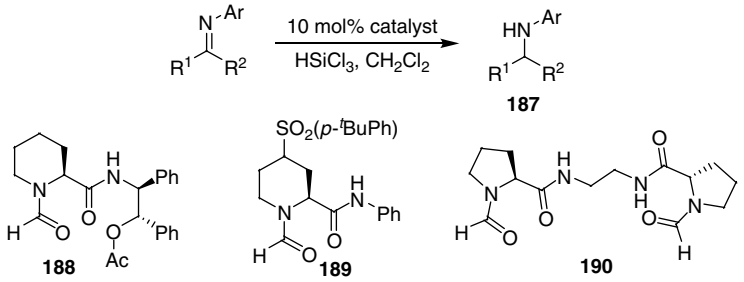
Gong and co-workers disclosed the first asymmetric catalytic cycloaddition reaction of α-substituted isocyanoesters with nitroolefins by cinchona alkaloid derivatives **184a** and **184b** to yield 2,3-dihydropyrroles with high diastereo- and enantioselectivities (Scheme 64) [142]. This reaction provides a convenient method to access multiply substituted dihydropyrroles and related heterocyclic compounds in high optical purity.



Scheme 64 Asymmetric formal [3+2] cycloaddition reaction of isocyanoesters to nitroolefins

Sun and co-workers designed a series of chiral Lewis base for the enantioselective reduction of *N*-aryl imines with trichlorosilane (Scheme 65). Catalyst **188** and **189** exhibited high asymmetric induction for aromatic and aliphatic N-aryl ketimines (87–95% ee) [143–145]. C_2-Symmetric chiral tetraamide **190** derived from L-proline was also found to be an effective Lewis base catalyst in the enantioselective reduction of ketimines, but with relative lower enantioselectivity [146].

Subsequently, Sun evaluated another easily accessible chiral Lewis base catalyst **191** bearing only a chiral sulfur center for the reduction of N-aryl imines with trichlorosilane (Fig. 6) [147]. A wide range of N-aryl imines were smoothly



Scheme 65 Asymmetric reduction of ketimines with trichlorosilane catalyzed by chiral Lewis bases

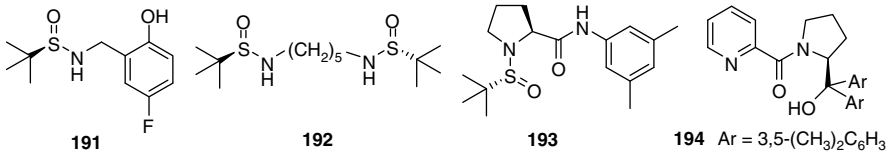
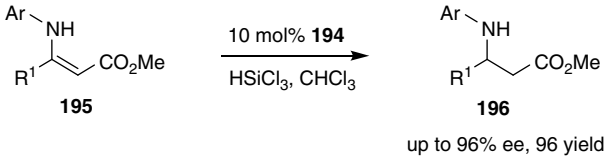


Fig. 6 Chiral Lewis base catalyst

reduced to afford amines in high yields and enantioselectivities. A profound positive nonlinear effect indicated that not only one catalyst molecule was involved in the catalytic process, instead, two molecules of catalyst were probably bound to the chlorosilane through their Lewis basic S=O groups. Thus, a bissulfinamide **192** bearing a five-methylene linkage was synthesized and indeed showed more efficient catalytic activity [148]. Recently, they disclosed a new Lewis base catalyst **193** that consists of an *S*-chiral sulfonamide group and a *C*-chiral α-amino amide moiety [149]. This catalyst enabled the reduction of aromatic *N*-alkyl ketimines by trichlorosilane in high yields and with excellent enantioselectivities of up to 99.6% ee.

Moreover, **188** could also be employed to catalyze the asymmetric reduction of ketones with trichlorosilane in high yields and enantioselectivity of up to 93% ee [150].

Zhang and co-workers developed an elegant asymmetric hydrosilylation of β-enamine esters using chiral Lewis base **194** as a catalyst (Scheme 66) [151]. High yields and enantioselectivities (up to 96% ee) were obtained for a diverse scope of β-amino acid derivatives.



Scheme 66 Asymmetric hydrosilylation of β-enamine esters catalyzed by chiral Lewis base

7 Brønsted Acid–Lewis Base Bifunctional Catalysts

7.1 Thiourea–Lewis Base Bifunctional Catalysts

Wang reported (Fig. 7) a series of bifunctional amine-thioureas bearing multiple hydrogen-bonding donors and used them to catalyze asymmetric nitro-Mannich reaction (Scheme 67) [152]. The third NH of sulfonamide on the 1,2-diphenyl-ethenediamine moiety played a significant role in the nitro-Mannich reaction. High yields and excellent enantioselectivity have been observed for the nitro-Mannich reaction between N-Boc aldimines and nitromethane catalyzed by 10 mol% of **197**. Various aromatic, heteraromatic, and alkyl N-Boc aldimines were tolerated in the reaction with excellent results. The method was extended to the nitro-Mannich reaction of N-Boc aldimines with other nitroalkanes. High yields and unprecedented diastereo- and enantioselectivities were obtained.

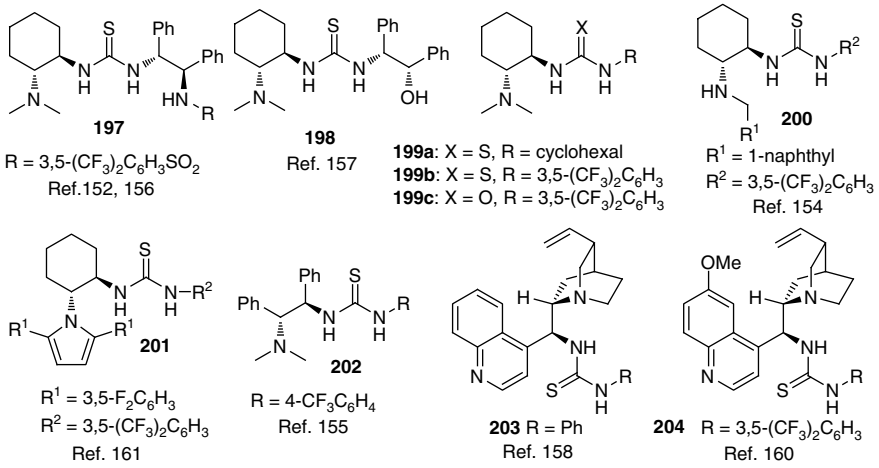
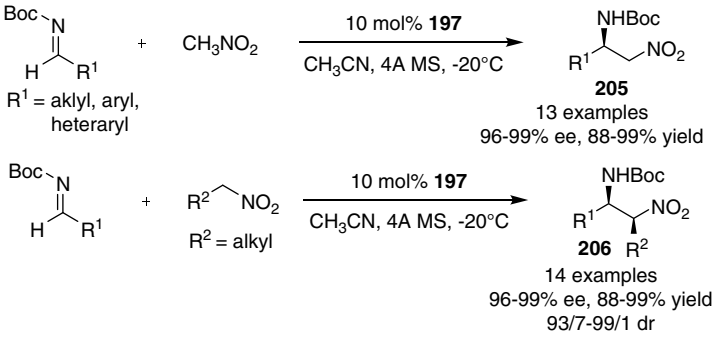
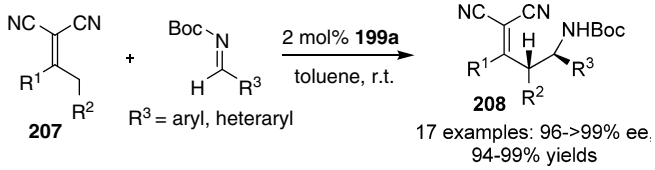


Fig. 7 Chiral bifunctional thiourea catalysts



Scheme 67 Asymmetric nitro-Mannich reaction of N-Boc aldimines with nitroalkanes

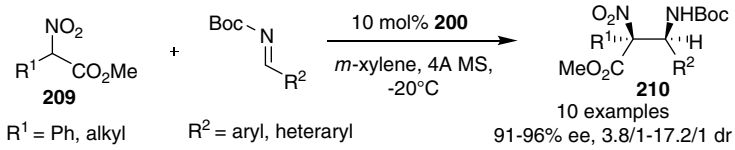
Chen and co-workers have disclosed a highly stereoselective direct vinylogous Mannich reaction of α,α-dicyanoolefins and N-Boc aldimines (Scheme 68) [153]. The bifunctional tertiary amine–thiourea **199a** was identified as the optimal catalyst. Various α,α-dicyanoolefins derived from cyclic, acyclic ketones, and aliphatic aldehydes were amenable to the catalytic system with excellent ee values. A wide scope of structurally diverse imine reactants, including aryl and heteroaryl aldimines could be operative with high enantioselectivity. More importantly, the catalyst loading could be decreased to 0.1 mol% without sacrificing the reaction



Scheme 68 Asymmetric direct vinylogous Mannich reaction of α,α-dicyanoolefins and N-BOC aldimines

stereocontrol. Moreover, the products could be converted to δ-amino acid derivatives through classical transformations.

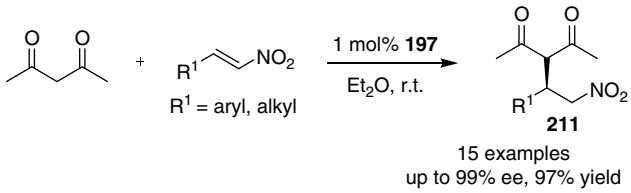
The stereoselective nitro-Mannich reaction of α-substituted nitroacetates was discovered by Chen (Scheme 69) [154]. The bifunctional thiourea/secondary-amine catalyst **200** showed highly catalytic efficiency for the reaction to furnish various



Scheme 69 Asymmetric nitro-Mannich reaction of N-Boc imines with α-substituted nitroacetates

versatile products with adjacent quaternary and tertiary chiral centers, which could be readily converted to some biologically important chiral amino acid derivatives with dense functionalities. The asymmetric Mannich reaction of three-substituted oxindoles to N-Boc imines was also developed by Chen group [155]. The bifunctional thiourea-tertiary amine catalysts **202** exhibited the highest catalytic activity and afforded high diastereoselectivity and good to excellent enantioselectivities for various substrates.

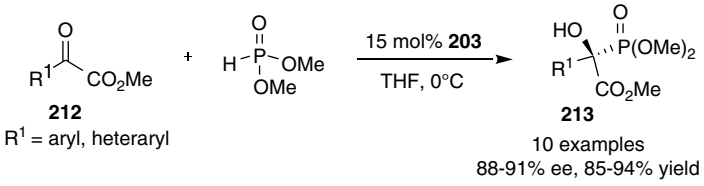
Wang found that the well-established bifunctional amine–thiourea **197** bearing multiple hydrogen-bonding donors could catalyze the asymmetric Michael addition of acetylacetone to nitroolefins (Scheme 70) [156]. Only 0.1 mol% catalyst loading was enough to ensure a complete transformation in high yields and high enantioselectivities (up to 99% ee). Both alkyl and aryl nitroolefins could participate in this



Scheme 70 Asymmetric Michael addition of acetylacetone to nitroolefins

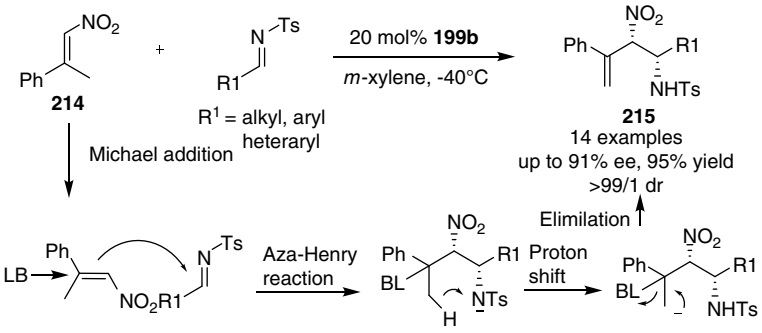
reaction with high enantioselectivity. However, the catalyst **197** delivered a very low diastereoselectivity and moderate to good enantioselectivity to the Michael addition reaction of α-substituted β-ketoesters to nitroolefins. The catalyst **198**, in which the bulky sulfonamide $NHSO_2R$ was replaced with less bulky OH group, afforded the Michael reaction of α-substituted β-ketoesters with nitroolefins in high yields and with excellent diastereo- and enantioselectivities [157].

Feng and co-workers explored an asymmetric hydrophosphonylation of α-ketoesters catalyzed by cinchona-derived thiourea catalyst **203**, offering excellent enantioselectivity for a wide scope of aromatic and hetero-aromatic α-ketoesters (Scheme 71) [158]. The thiourea moiety activates the α-ketoesters through double hydrogen-bonding interaction and the basic nitrogen activates the phosphate by the formation of another hydrogen bond with dimethyl phosphonate.



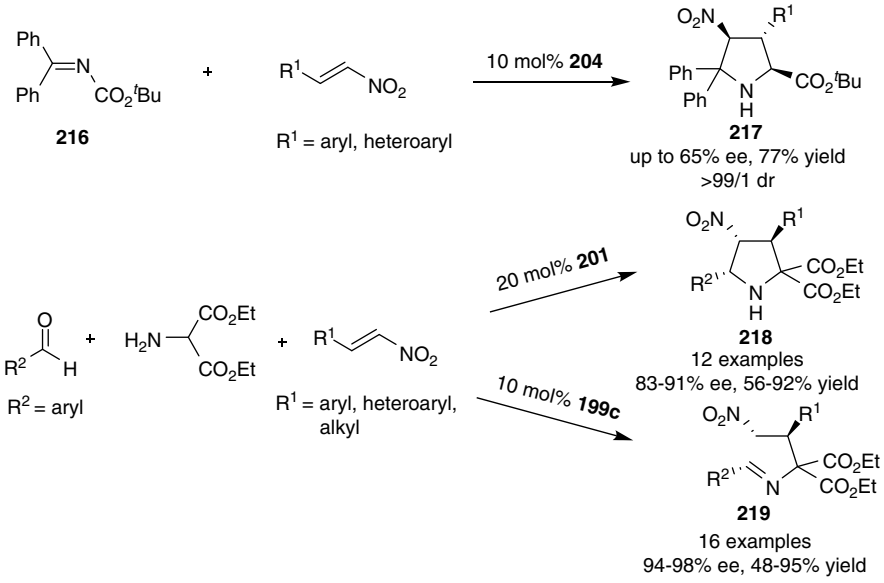
Scheme 71 Asymmetric hydrophosphonylation of α-ketoesters with dimethyl phosphite

Xu found an asymmetric Aza-MBH-type reaction of nitroalkenes with N-tosylimines (Scheme 72). Under the promotion of 20 mol% of thiourea catalyst **199b**, the reaction gave high enantioselectivity and led to a straightforward asymmetric synthesis of β-nitro-γ-enamines via tandem Michael addition/aza-Henry reaction/intermolecular proton shift/β-elimination [159].



Scheme 72 Asymmetric aza-Morita–Baylis–Hillman reaction of nitroalkenes to *n*-tosylimines

Zhang and Chen independently found a [3+2]-cycloaddition of azomethine ylides to nitroalkenes catalyzed by bifunctional thiourea catalysts. Bifunctional thiourea **204** provided moderate stereoselectivity for the cycloaddition of preformed azomethine ylides with nitroalkenes [160]. However, the thiourea **201** was capable of accelerating a one-pot, three-component reaction of aldehydes, diethyl α-aminomalonate and nitroalkenes with excellent enantioselectivity [161]. Interestingly, the Michael addition predominantly occurred with excellent enantioselectivity by using bifunctional thiourea catalyst **199c** (Scheme 73).

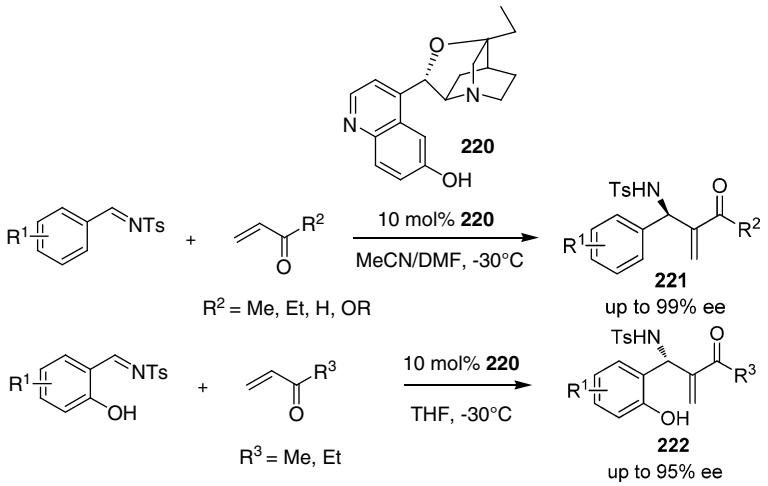


Scheme 73 Asymmetric cycloaddition and Michael reactions of azomethine ylides with nitroalkenes

7.2 *Hydroxyl–Lewis Base Bifunctional Catalysts*

In 2002, Shi and co-workers found that highly enantioselective aza-Baylis–Hillman reaction of N-sulfonated imines with activated olefins could be established by quinidine-derived chiral amines **220** (TQO or β-ICPD) [162, 163]. An interesting reversal of the asymmetric induction was observed when an ortho-phenol group would be introduced to the imine substrates (Scheme 74) [164]. Neither (+)-quinidine nor (–)-quinine exhibited catalytic activity, and *O*-methylated TQO showed lower efficiency for the reaction. These experimental results indicated that the special structural amine and the OH functionality in the catalyst **220** played an important role in controlling the stereochemistry by forming an intramolecular hydrogen bond.

The bifunctional catalysts **223**, **224**, and **225** containing phosphine functionality showed high efficiency in the catalysis of aza-MBH reaction of N-tosylimines with activated alkenes. Catalyst **226** has been applied to the asymmetric Morita–Baylis–Hillman reaction of aldehydes with activated alkenes, though with moderate yields and enantioselectivity (Fig. 8) [165–170].



Scheme 74 Asymmetric aza-MBH reaction of N-tosylimines with vinyl ketones, acrolein, and acrylates

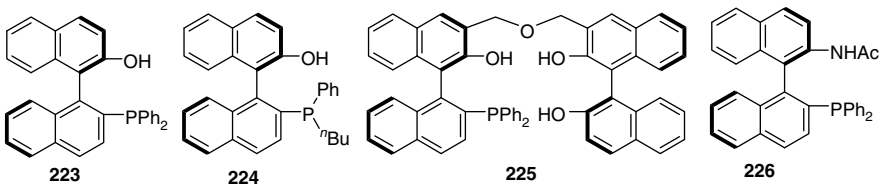
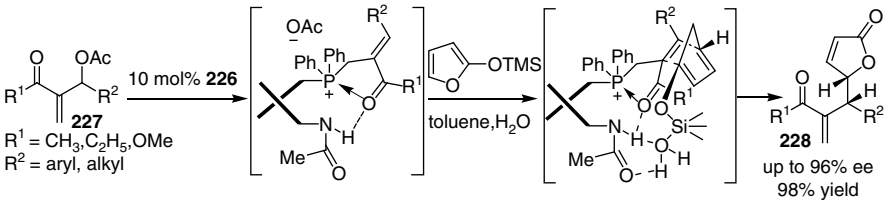


Fig. 8 Chiral bifunctional phosphine-containing catalysts

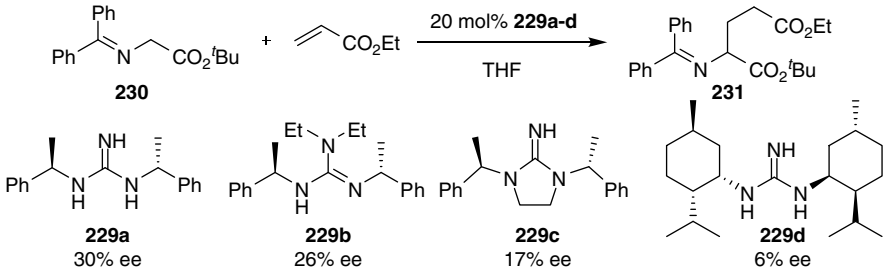
Allylic substitution of Morita–Baylis–Hillman acetates with (furan-2-yloxy)-trimethylsilane catalyzed by bifunctional phosphine catalyst **226** provided a unique entry to γ-butenolides in high yields and excellent enantioselectivity (Scheme 75) [171]. The addition of 6 equivalent of water was beneficial to the enantiocontrol. The phosphorus moiety served as Lewis base to activate Morita–Baylis–Hillman acetates by nucleophilic addition and concomitantly, the amide participates in formation of multiple hydrogen bonds for the activation of 2-trimethylailyoxy furan (Scheme 75).



Scheme 75 Allylic substitution of Morita–Baylis–Hillman acetates with (furan-2-yloxy) trimethylsilane

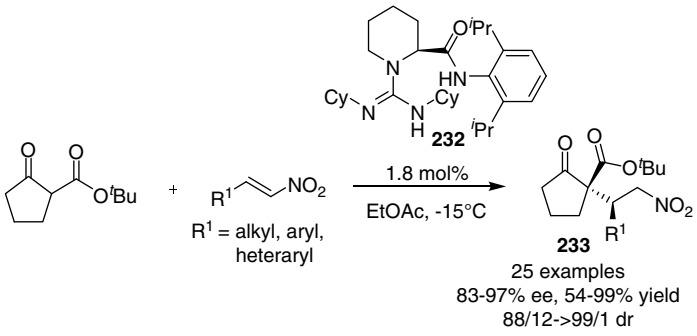
7.3 *Guanidine Catalysts*

In 1999, Ma and Cheng reported that chiral guanidines **229a–d** were able to catalyze Michael addition of imino esters to ethyl acrylate (Scheme 76) [172]. Although gave unsatisfactory enantioselectivity, the reaction represents one of early examples in asymmetric organocatalysis.



Scheme 76 Asymmetric Michael addition of glycine derivatives to acrylic esters catalyzed by guanidines

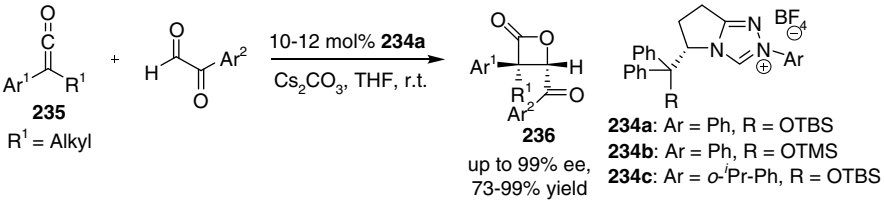
Feng designed a novel bifunctional chiral guanidine **232** and applied it to the asymmetric Michael reaction of β-ketoesters with nitroolefins, giving high yields and excellent stereoselectivity for a broad spectrum of substrates (Scheme 77) [173].

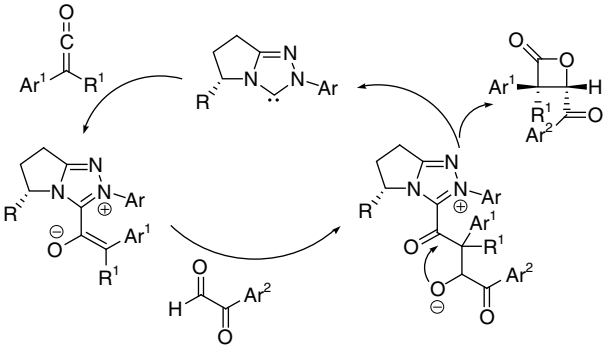


Scheme 77 Asymmetric Michael reaction of β-ketoesters with nitroolefins

8 NHC (N-Heterocyclic Carbene) Catalysis

Ye and co-workers reported a formal [2+2] cycloaddition of disubstituted ketenes with 2-oxoaldehydes catalyzed by chiral N-heterocyclic carbene **234a′** (Scheme 78) [174]. Chiral β-lactones with α-quaternary-β-tertiary stereocenters were obtained in high yields and excellent enantioselectivity. The carbene actually activates the ketene by catalytic nucleophilic addition to generate a reactive enolate intermediate, which attacks the carbonyl compound and followed by an esterification to give the observed products (Scheme 78). Moreover, β-trifluoromethyl-β-lactones and diaz-



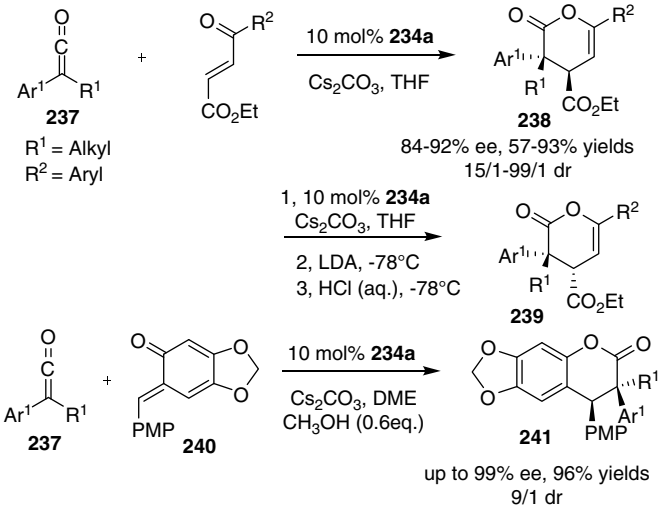


Scheme 78 Asymmetric formal [2+2] cycloaddition of disubstituted ketenes catalyzed by NHC

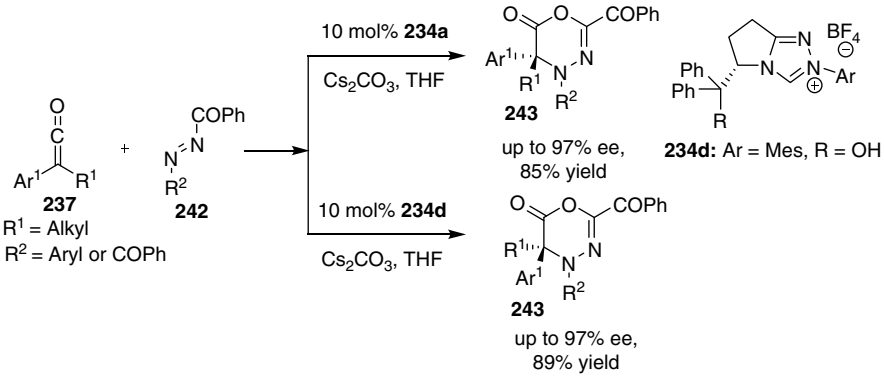
enediacarboxylates could also participate in [2+2] cycloaddition with disubstituted ketenes under the promotion of **234c** and **234b**, respectively, with high enantioselectivity [175, 176].

A formal [4+2] cycloaddition of ketenes with enones catalyzed by chiral N-heterocyclic carbene **234a** was reported by the same group (Scheme 79) [177]. The *tran*-δ-lactones were obtained in high diastereo- and enantioselectivities. The ketene generated in situ from acyl chloride was also proven to undergo the reaction. In addition, a chiral N-heterocyclic carbene-catalyzed cycloaddition of ketenes and *o*-quinone methides was accomplished for the enantioselective synthesis of dihydrocoumarins (Scheme 79) [178].

Very recently, Ye found a carbene-catalyzed asymmetric [4+2] cycloaddition reaction of ketenes with diazenes (Scheme 80) [179]. In the presence of **234a**, chi-



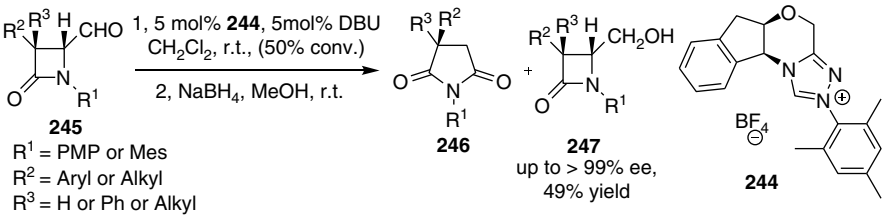
Scheme 79 Asymmetric formal [4+2] cycloaddition of ketenes catalyzed by NHC



Scheme 80 Asymmetric formal [4+2] cycloaddition of ketenes and diazenes

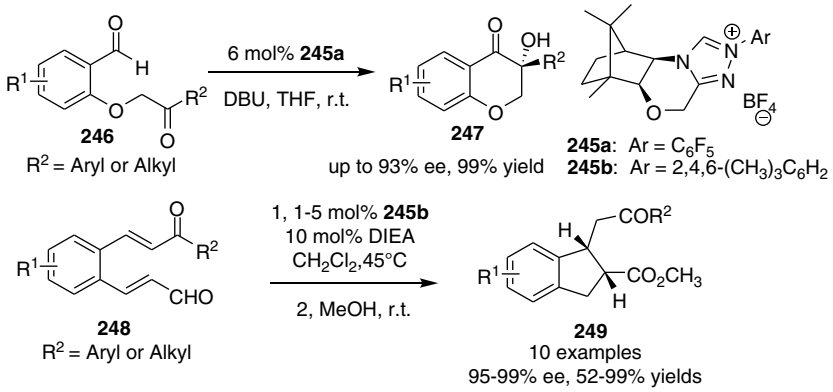
ral 1,3,4-oxadiazin-6-ones could be generated from the reaction in high yields and enantioselectivity. Interestingly, when the substituent OTBS in the catalyst **234a** was adjusted to OH, the stereochemistry of the product was completely switched.

An asymmetric synthesis of *cis*-4-formayl-β-lactams via chiral *N*-heterocyclic carbene-catalyzed kinetic resolution has been performed by You group (Scheme 81) [180]. The chiral NHC precursor **244** gave high enantioselectivity for *cis*-4-formayl-β-lactams, but low enantioselectivity for the ring-expanding products.



Scheme 81 Kinetic resolution of (±)-*cis*-4-formayl-β-lactams by chiral NHC 288

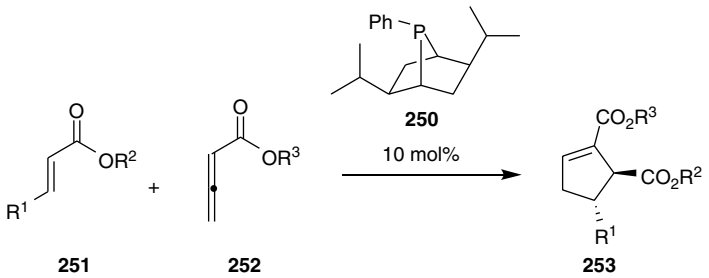
You and co-workers synthesized a new triazolium salt from D-camphor (Scheme 82). The N-heterocyclic carbene catalyst **245a** afforded an intramolecular crossed aldehyde–ketone benzoin reaction to give α-ketols containing a quaternary stereogenic center in high yields and with up to 93% ee [181]. The N-heterocyclic carbene catalyst **245b** showed high efficiency in catalyzing intramolecular Michael reaction [182].



Scheme 82 Asymmetric intramolecular crossed aldehyde–ketone benzoin reaction and intramolecular Michael addition reaction

9 Phosphorus Catalysis

Chiral phosphines have long been ligands broadly used for metal-based catalysis, while trisubstituted phosphines serving as nucleophilic catalysts were applied to organic reactions quite recently [183]. Lu pioneered a [3+2] cycloaddition of allenoate with electron-deficient olefin to generate multiply substituted cyclopetene derivatives in the presence of stoichiometric amounts of phosphines [184, 185]. Its enantioselective version was first accomplished by Zhang using chiral phosphine catalyst **250** (Scheme 83) [186]. Following this general concept, several chiral phosphine catalysts come out and showed excellent stereoselectivity [187, 188].



Scheme 83 Phosphine-catalyzed asymmetric [3+2] cycloaddition of allenoates with electron-deficient olefins

10 Conclusion

Over the past decade, great advances have been made on the asymmetric organocatalysis in China. As a result, a wealth of new chiral organocatalysts comes out to promote various important asymmetric transformations with high efficiency and stereoselectivity. Moreover, a large number of new organocatalytic protocols with great potential in organic synthesis have appeared. Currently, asymmetric organocatalysis has been a blooming research field, but is still receiving increasing attention. As such, the increasing emergence of new exciting findings from Chinese organic chemists is able to be expected.

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Enantioselective Catalysis with Structurally Tunable Immobilized Catalysts

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Abstract Immobilization of a chiral homogeneous catalyst can in principle facilitate its separation and recycling, and therefore is of considerable interest to both academia and industry. A number of methods have been developed for the immobilization of chiral catalysts, typically including using inert organic or inorganic materials as supports. However, most of the classical immobilized catalysts suffered from inferior catalytic properties to their homogeneous counterparts due to the poor accessibility, random anchoring, or disturbed geometry of the active sites in the solid matrix. In this chapter, we present the progress made in the immobilization of chiral catalysts by focusing on core-functionalized dendrimers in asymmetric catalysis, asymmetric catalysis in nanopores of mesoporous materials, and self-supported chiral catalysts for asymmetric reactions. All the three types of immobilized catalysts possess relatively well-defined structures together with a tunable chiral environment around the catalytically active centers. Representative examples selected from the researches mostly reported by Chinese chemists have demonstrated the high efficiencies and enantioselectivities of these immobilized catalysts. The impacts of supports, such as isolation or confinement effect, on the catalysis will be discussed with emphasis on their application in enantioselective synthesis.

Keywords Asymmetric catalysis • Coordination polymer • Dendrimers • Immobilization • Nanoporous solids

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Contents

1 Introduction

Homogeneous asymmetric catalysis of organic reactions to provide enantiomerically enriched products is of central importance to modern synthetic and pharmaceutical chemistry [1–4]. So far, various homogeneous chiral catalysts have been reported, and many of them are known to be highly effective in the asymmetric formation of C–H, C–C, C–O, C–N, and other bonds. However, compared with the huge amount of work devoted to the field of homogeneous asymmetric catalysis, only a few dozen processes have been industrialized [5]. One main reason for this is that the expensive homogenous chiral catalysts (with loadings usually in the range of 1–10 mol%) are often difficult to recover and reuse for homogeneous catalytic processes. In addition, the metal contaminants can sometimes leach from the homogeneous catalysts into the products, which is particularly unacceptable for pharmaceutical production. As one of the most promising solutions to these problems, immobilization of a chiral homogeneous catalyst can in principle facilitate its separation and recycling, and therefore is of considerable interest to both academia and industry [6, 7].

Over the past several decades, a number of methods have been developed for the immobilization of chiral catalysts [8, 9], typically including using inert organic or inorganic materials as the supports [10–12] or conducting the reactions in some unconventional media such as water, ionic liquids, or supercritical fluid [13–15]. In most cases, homogeneous catalysts are attached to the support by the formation of a covalent bond with the ligand. Alternatively, immobilization can be also achieved via noncovalent interactions [16], for example, by adsorption, ion-pair formation, entrapment, and so on. Despite the significant achievements made in this field, however, classical immobilized catalysts often suffer from inferior catalytic properties to their homogeneous counterparts due to the poor accessibility, random

anchoring, or disturbed geometry of the active sites in the solid matrix. The leaching of the noble metal catalyst from the support is also a serious problem because of the low stability of the immobilized catalysts. To overcome these drawbacks, major efforts have been made to develop more efficient and practical immobilization methods for homogeneous chiral catalysts. In this regard, a number of new immobilized asymmetric catalytic systems have been reported and successfully employed to a broad range of reactions during the past two decades. Various innovative techniques and new concepts for chiral catalyst immobilization have recently emerged, for example, including microencapsulated catalysts [17], dendrizyme [18], self-supported chiral catalysts [19], homochiral metal–organic frameworks (chiral MOFs) [20], chiral catalysis in nanopores [21], supported ionic liquid catalysis [22], latent biphasic catalytic system [23], and so on. Unlike most of the classical immobilized chiral catalysts, some of these newly developed immobilized chiral catalysts are designable and tunable. In most cases, their catalytic performance was comparable or even superior to those of the homogeneous counterparts.

In this chapter, we will present the progress made in the immobilization of chiral catalysts mainly from three aspects: (1) core-functionalized dendrimers in asymmetric catalysis; (2) asymmetric catalysis in nanopores of mesoporous materials; and (3) homochiral metal–organic coordination polymer catalysts (self-supported catalysts) for asymmetric reactions, focusing on the researches reported by Chinese chemists. Despite various types of immobilized catalysts, all the three types of immobilized catalysts described here have relatively well-defined structures together with a tunable chiral environment around the catalytically active centers. The impact of supports on the catalysis such as isolation effect and confinement effect of nanopores will be also discussed with emphasis on their application in enantioselective synthesis. The other types of immobilized chiral catalysts can be found in recent reviews [6–23].

2 Asymmetric Catalysis Inside Dendrimers

Dendrimers represent a new kind of polymers which possess highly branched and well-defined molecular structures with nano-scale sizes [24, 25]. Dendrimer as catalyst support has several advantages over the conventional polymer resins [26, 27]. Firstly, the dendrimer architecture offers better control of the number and the disposition of catalytic species on the support as compared to the cross-linked polymer- and the linear soluble polymer-supported catalysts. Secondly, dendrimer catalysts feature homogeneous reaction conditions and enable easy separation and recycling via solvent precipitation or nanofiltration at the end of reaction. Thirdly, the structure of dendrimer can be well characterized and analyzed by using the common analytical techniques. In addition, the well-defined molecular architecture of dendrimers allows fine-tuning of their catalytic centers by precise dendritic ligand design. Thus, such novel class of catalysts bridges the gap between homogeneous and heterogeneous catalysis, and thus combines the advantages of homogeneous and heterogeneous catalysts. Since the seminal works reported by Brunner in 1995 [18], chiral dendritic catalysts have been

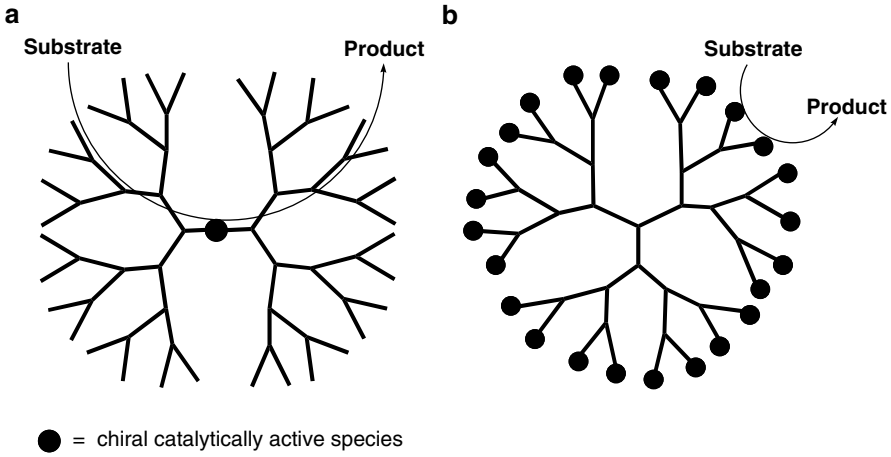


Fig. 1 Schematic representations of commonly encountered chiral catalyst immobilization on dendritic polymer supports for asymmetric reactions: (**a**) core-functionalized chiral dendrimers; (**b**) periphery-functionalized chiral dendrimers

attracting increasing attention [28, 29]. So far, a variety of chiral dendritic catalysts have been reported and successfully used in various catalytic asymmetric reactions [30, 31]. Typically, catalytically active site(s) can be attached to the periphery or the core of the dendrimer, as summarized in Fig. 1.

In the case of the core-functionalized dendrimers, it is expected that the steric shielding or blocking effect of the specific microenvironment created by the dendritic structure might influence the catalytic behavior of the core. For example, the resulting site isolation effects can be beneficial for some reactions [32, 33], whereby the catalysts often suffer from the deactivation caused by coordination saturation of the metal centers, or by the irreversible formation of an inactive metallic aggregate. On the other hand, such dendrimer catalysts have the disadvantages of low catalytic activity and low catalyst loading, particularly for the higher-generation catalysts. In this section, we attempt to summarize the recently reported core-functionalized chiral dendrimers mainly by Chinese chemists. The other type of chiral dendrimer catalysts such as periphery-functionalized chiral dendrimers can be found in recent reviews [30, 31, 34].

2.1 Core-Functionalized Dendritic Phosphorus Ligands for Asymmetric Hydrogenations

Following the pioneering contributions by Knowles and Kagan came the development of thousands of chiral phosphorus ligands for asymmetric hydrogenation [35]. High enantioselectivity and activity have been achieved using the Rh, Ru, and Ir

complexes with these ligands. However, the difficulty in recycling the often very expensive catalyst has restricted their use in industry. Recently, immobilization of phosphorus ligands in dendrimers has attracted increasing attention due to their high catalytic activity and enantioselectivity as well as recyclability [36–38].

Recently, Fan and coworkers have systemically investigated the immobilization of BINAP (BINAP = 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl) at the core of dendrimers and their application in asymmetric hydrogenation of prochiral olefins, ketone, and quinolines. Firstly, four generations of chiral BINAP-centered dendrimers were synthesized via condensation of Fréchet-type dendrons with (*R*)-5, 5′-diamino-BINAP (Fig. 2). For comparison purpose, monodendron-substituted BINAP were also synthesized by reaction of (*R*)-5-amino-BINAP with the same dendrons according to the similar synthetic method [39, 40].

The first- to the third-generation BINAP dendrimers were evaluated in the Ru-catalyzed asymmetric hydrogenation by choosing 2-[*p*-(2-methylpropyl)phenyl]-acrylic acid as a standard substrate (Fig. 2). The reaction was carried out in methanol-toluene (1:1, v/v) at room temperature under homogeneous manner. It was found that the size of the dendritic wedges influenced the reactivity of the ruthenium catalysts obviously; and the rate of the reaction increased with higher generation catalysts. In contrast, the Ru complexes with monodendron-substituted BINAP showed very similar catalytic activity to that of the corresponding homogeneous catalyst. This result indicated that the two dendritic sectors might create a unique microenvironment around Ru(BINAP), and thus play an important role on the rate enhancement. In addition, the catalyst containing the third-generation dendrimer ligand was quantitatively recovered by precipitation with methanol. The catalyst may be reused for at least three times with similar activities and enantioselectivities [39].

In the continuous study, these BINAP-cored dendrimers were employed in the Ir-catalyzed asymmetric hydrogenation of quinolines (Fig. 2), a challenging substrate for hydrogenation [41]. All the four generations of dendrimer catalysts generated in situ from BINAP-cored dendrimers and [Ir(cod)Cl_2] (cod = 1,5-Cyclooctadiene) were found to be effective even at an extremely high substrate/catalyst (*S*/*C*) ratio in the asymmetric hydrogenation of quinaldine with I_2 as an additive. Interestingly, the catalytic activity gradually increased with the increase of dendrimer generation. In particular, the reaction performed well under rather low catalyst loading in a large scale (~18 g substrate was used), affording a TON (TON = turnover number) of 43,000 which represents the highest value reported to date for such reaction. It is obvious that the isolation effect of the steric dendritic shell has significantly reduced the possibility for the formation of an inactive iridium dimer during the catalytic reaction, and therefore enhances the stability and activity of the catalyst. In addition, the third-generation dendrimer catalyst could be quantitatively recovered by precipitation with methanol, and reused at least six times with similar enantioselectivities but at the expense of slight drop of catalytic activities [42].

Fan and coworkers further extended the same method to synthesize another series of highly apolar BINAP-cored dendrimers bearing multi-alkyl chains at the periphery (Fig. 3). Their ruthenium complexes were employed in the homogeneous

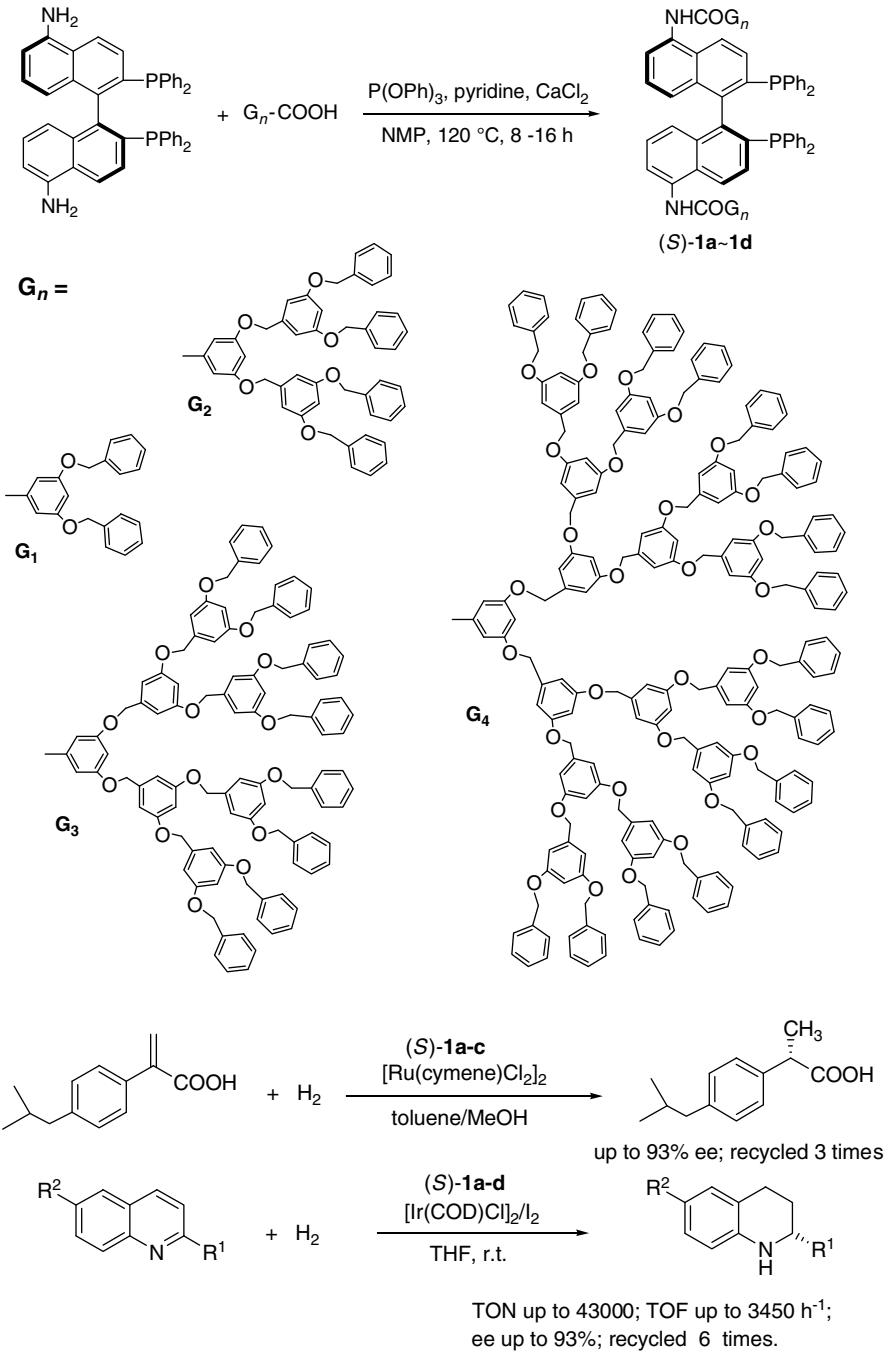


Fig. 2 Synthesis of BINAP-cored dendrimers for asymmetric hydrogenation

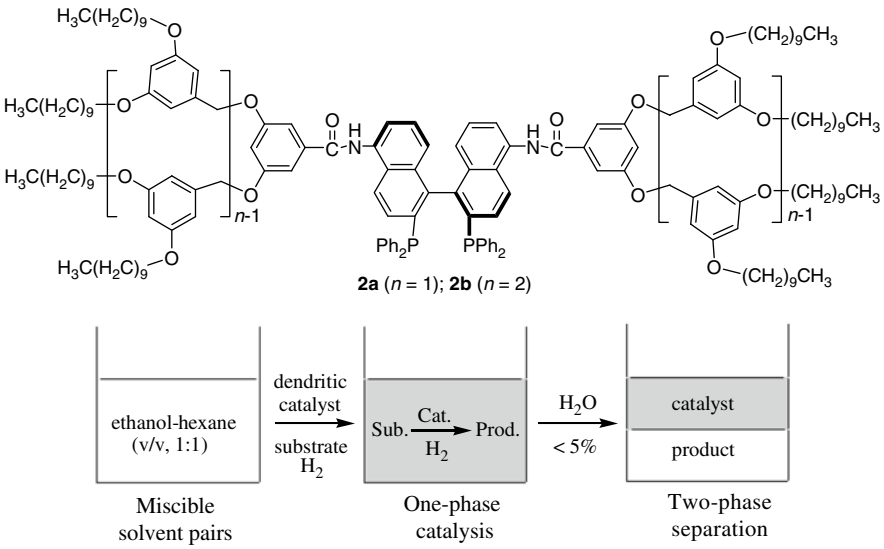


Fig. 3 Chiral BINAP-cored dendrimers for latent biphasic asymmetric hydrogenation

hydrogenation of relatively polar substrates (such as 2-phenylacrylic acid and 2-(4-isobutylphenyl)acrylic acid) in a 1:1 ethanol/hexane mixture [43]. All dendritic catalysts exhibited high enantioselectivity and activity which were almost identical to those obtained with BINAP as the ligand. Most importantly, the addition of a little amount of water could induce phase separation at the end of the reaction. The apolar dendritic catalyst in hexane layer was easily separated and reused via a liquid–liquid biphasic separation technique (the so-called "latent biphasic system" [44], as shown in Fig. 3). The number and length of the alkyl end groups on dendrimer surface could influence the recover yield of the catalyst. More than 99% of the second-generation catalyst was extracted to the hexane phase and reused at least four times without obvious loss of reactivities and enantioselectivities.

In addition, the first-generation dendritic BINAP ligand bearing long alkyl chains showed temperature-dependent solubility in 1:3 1,4-dioxane/ethanol mixture [45]. This thermomorphic dendritic catalyst performed homogeneous hydrogenation of β-ketoesters at 60°C, and could be easily recovered by simple cooling at the end of reaction (Fig. 4). Notably, slightly higher enantioselectivity was observed with this dendritic catalyst than with homogeneous Ru(BINAP) catalyst, and the dendritic catalyst could be used at least for four cycles without any loss of enantioselectivity.

It has been established that the dihedral angles of the biaryl phosphine ligands can exert very important influence on the catalytic activity and/or enantioselectivity [46]. Fan and coworkers recently reported the synthesis of chiral BIPHEP-cored (BIPHEP = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl) dendrimers via replacing the methoxyl substituents at the 6, 6′-positions of the biphenyl backbone with sterically demanding Fréchet-type dendrons (Fig. 5). The ruthenium catalysts of these

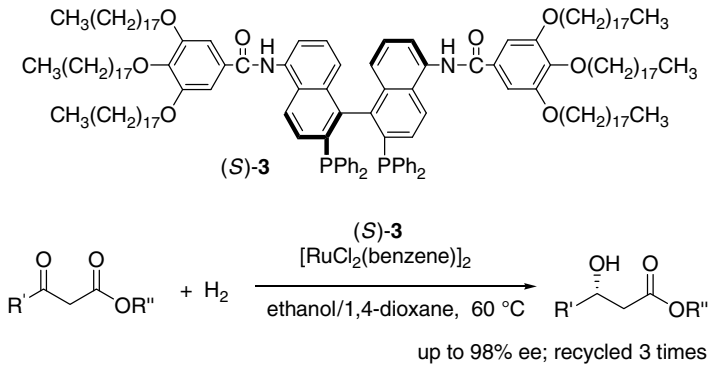
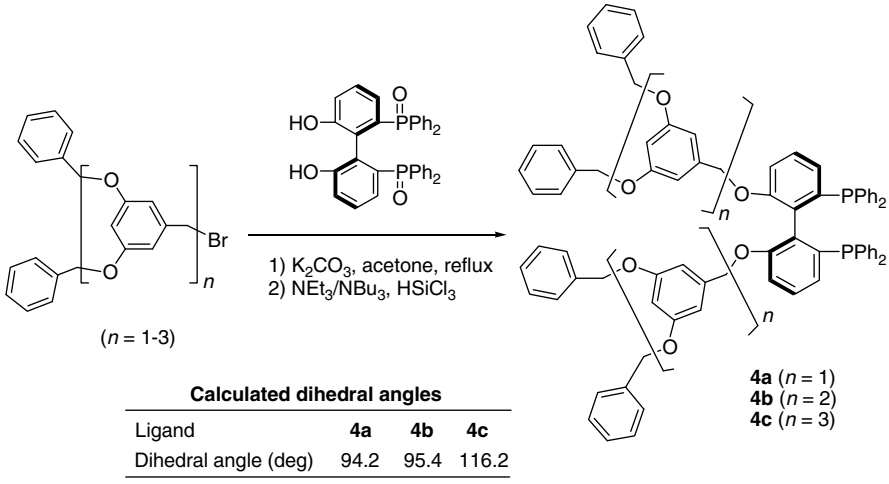


Fig. 4 Chiral BINAP-cored dendrimers for thermomorphic asymmetric hydrogenation



Calculated dihedral angles

Ligand	4a	4b	4c
Dihedral angle (deg)	94.2	95.4	116.2

Fig. 5 Synthesis of BIPHEP-cored dendrimers with tunable dihedral angles

tunable dendritic ligands were employed in the asymmetric hydrogenation of β-ketoesters, affording a very good catalytic activity while the enantioselectivity changed dramatically [47]. This result clearly indicated that the dihedral angles of the dendritic BIPHEP could be fine-tuned through the systematic adjustment of the size of the dendritic wedges.

On the other hand, the core-functionalized dendrimer catalysts show a gradual decrease of reactivity with the increase of dendrimer generation due to the steric shielding. In order to systematically study the relationship between dendrimer structure and catalytic property, Fan and coworkers synthesized two types of chiral dendrimer ligands bearing a chiral diphosphine Pyrphos (Pyrphos = 3,4-Bis(diphenylphosphino)pyrrolidine) at the focal point of the Fréchet-type polyether dendrons (Fig. 6). It was found that the primary structure and generation of the dendritic support influenced the catalytic activity significantly [48]. In the

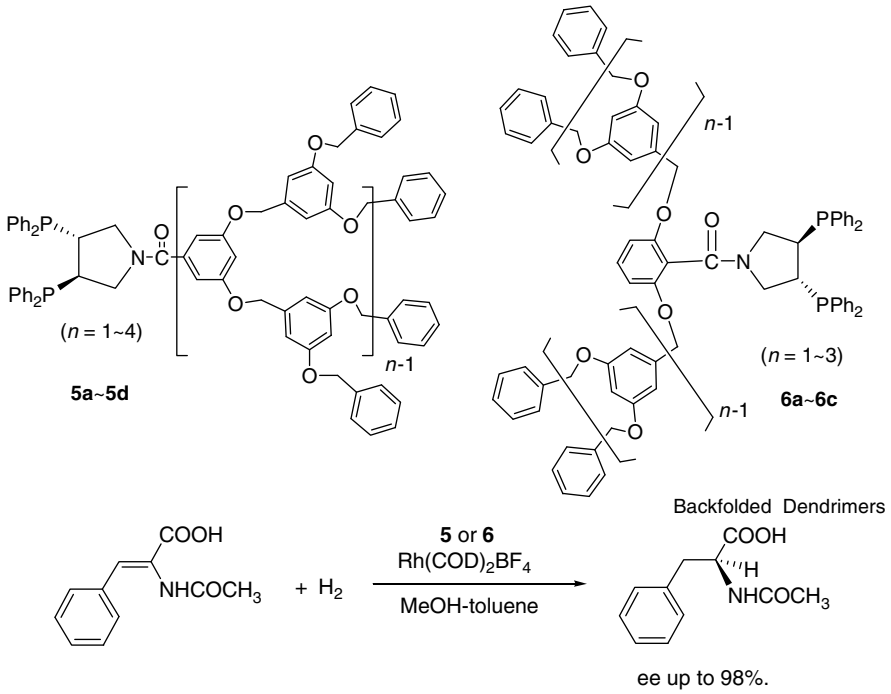


Fig. 6 Chiral dendrimers bearing Pyrphos at the focal point for asymmetric hydrogenation

Rh-catalyzed asymmetric hydrogenation of α-acetamidocinnamic acid, high enantioselectivities (up to 98%) were achieved for the first- to the fourth-generation dendrimer catalysts, while the rate of the reaction decreased when higher generation catalysts were used. Particularly, upon going from generation three to generation four, the dendrimer catalyst almost lost its catalytic activity. This obvious negative dendrimer effect might be due to the change in dendrimer conformation from a loose extended structure to a more rigid globular structure, which could encapsulate the active species. Expectedly, the backfolded dendritic catalysts showed low catalytic activity because these backfolded linkages increased the degree of steric congestion around the catalytically active core. The resulting relationship between the primary structure of the dendrimer and its catalytic properties could give a clue to more sophisticated catalyst design of dendrimer for highly asymmetric catalysis.

Recently, a variety of monodentate chiral phosphorus ligands have been developed for the Rh-catalyzed asymmetric hydrogenation of olefins [49]. To achieve facile catalyst separation, Fan and coworkers developed two types of dendritic monodentate phosphoramide ligands through substitution on the dimethylamino moiety in MonoPhos by the Fréchet-type dendritic wedges (Fig. 7). The monodendron-modified catalysts (**5a**–**5d**) were found to be effective in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters and

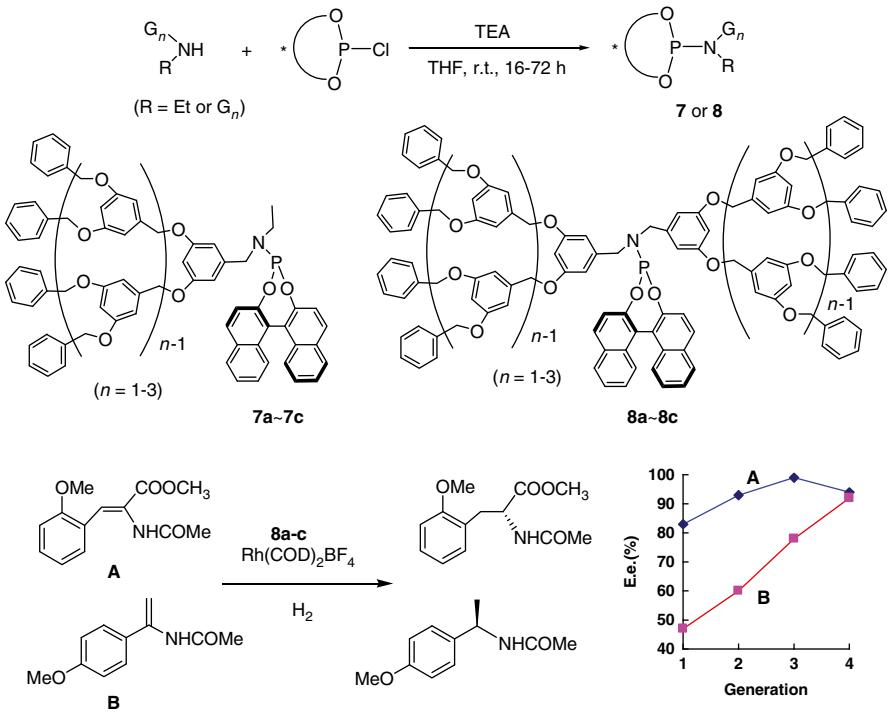


Fig. 7 Modular synthesis of MonoPhos-cored dendrimers for asymmetric hydrogenation

dimethyl itaconate, giving excellent enantioselectivities and catalytic activities which are better than or comparable to those obtained with MonoPhos. In addition, the steric shielding of the dendritic wedges could stabilize the rhodium complex against decomposition caused by the hydrolysis in protic solvents [50].

Most interestingly, the catalysts bearing two dendritic wedges on the N-atom (**6a**–**6c**) showed a gradual increase of enantioselectivity with increasing dendrimer generation in the hydrogenation of both α-dehydroamino acid esters and enamides [51]. This result was in sharp contrast to the small monodentate phosphoramidite ligands, in which large groups on the N-atom of the ligand led to poor enantioselectivity. On the other hand, these bulk dendrimer ligands afforded low reaction rate, which was probably due to the encapsulation of the catalytically active center by the dendritic wedges. In addition, the second-generation catalyst could be quantitatively precipitated by the addition of hexane and reused at least five times with similar enantioselectivity before run 5.

Noncovalent interactions have also been used for the construction of dendrimer catalysts [52]. As compared to the covalent immobilization strategy, this method could facilitate the synthesis of dendrimer and enable recycling of the often expensive dendritic support in the case of catalyst deactivation. Most recently, Fan and coworkers reported a new type of supramolecular chiral dendritic monophosphite

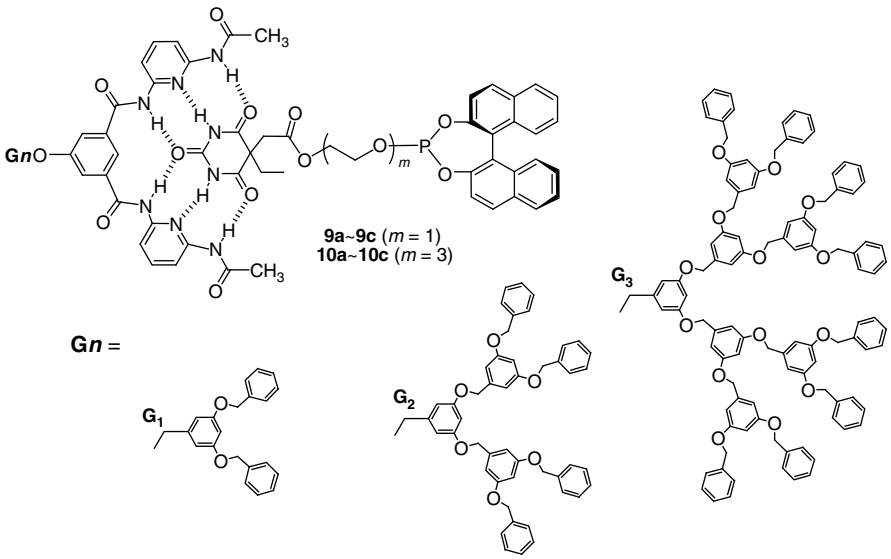


Fig. 8 Supramolecular chiral dendritic monophosphite ligands assembled by hydrogen bonding

ligands through the hydrogen-bonding assembly (Fig. 8). The Rh complexes of these supramolecular ligands were found to be effective in the asymmetric hydrogenation of enamides and dehydroamino acid derivatives with good enantioselectivities, which are comparable to those obtained with the free monophosphite ligands. In addition, the third-generation supramolecular catalyst could be easily recycled via solvent precipitation [53].

2.2 Core-Functionalized Dendritic Nitrogen-Containing Ligands for Asymmetric Catalysis

From the beginning of the 1990s, nitrogen-containing ligands have been attracting more attention in the field of asymmetric catalysis [54]. These ligands and their metallic catalysts have some distinct advantages over the phosphines, such as high air-stability, easy availability, and tailor-made modifications. Also, such homogeneous catalysts suffered from difficulty in the separation and recycling.

2.2.1 Asymmetric Transfer Hydrogenation

Since the seminal work reported by Noyori in 1995, chiral diamine ligands have been widely used in the asymmetric transfer hydrogenation [55]. Recently, Deng and Chen have developed two types of dendritic monosulfonylated diamine ligands

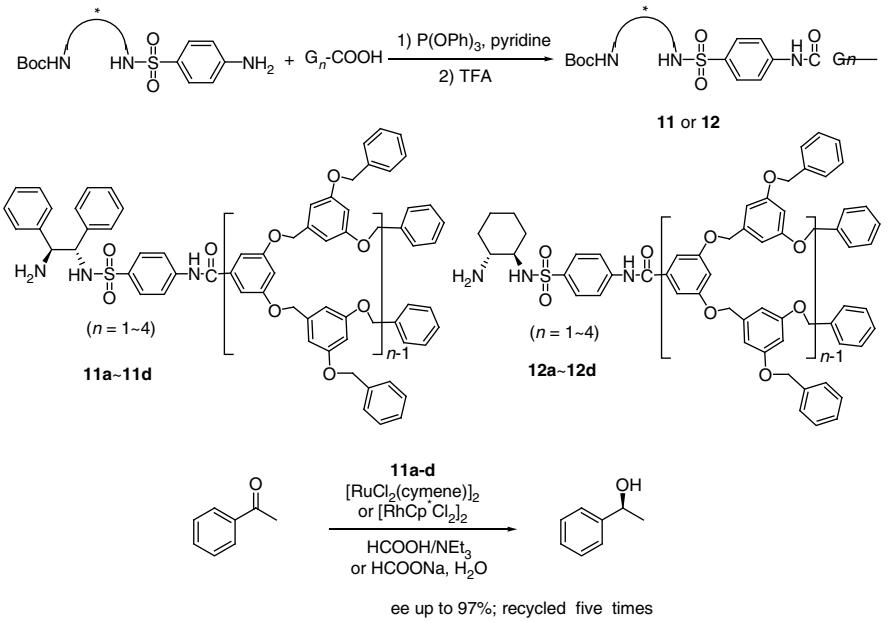
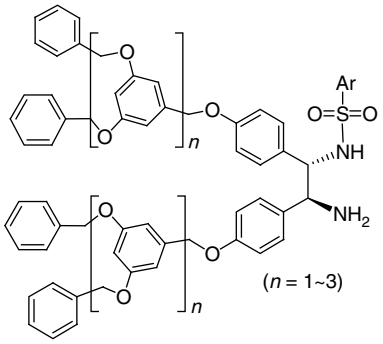


Fig. 9 Synthesis of chiral dendritic diamine ligands for asymmetric transfer hydrogenation

by attaching the monomeric diamines onto the focal point of the Fréchet's dendrons (Fig. 9). In the asymmetric transfer hydrogenation of acetophenone in HCOOH/NEt_3 mixture, slightly enhanced reactivity was observed for the dendritic Ru-TsDPEN catalysts (TsDPEN = *N*-(*p*-toluenesulfonyl) 1,2-diphenylethylenediamine) with excellent enantioselectivity. The fourth-generation catalyst could be reused at least for five times with similar enantioselectivity but at the expense of reduced reactivity [56].

The ruthenium (II) and rhodium (III) complexes of dendritic monosulfonylated DACH (DACH = 1,2-diaminocyclohexane) were also tested in the transfer hydrogenation of ketones in both organic and aqueous solution [57]. Notably, much better catalytic efficiency was achieved in an aqueous system using HCOONa as the hydrogen source. The highly hydrophobic dendritic Rh-complexes were found to be finely dissolved in the liquid substrates in the reaction mixture. Importantly, the catalyst loading could be decreased to 0.01 mol% and good conversion was still observed with excellent enantioselectivity. In addition, the dendritic catalyst could be easily precipitated from the reaction mixture by adding hexane and reused several times without obvious loss of catalytic activity and enantioselectivity.

The same group recently developed another approach toward attaching chiral DPEN (DPEN = 1,2-diphenylethylenediamine) at the core of a dendrimer [58]. Direct *N*-mono-sulfonylization of the resulting chiral dendritic vicinal diamines led to tunable dendritic N-mono-sulfonyl ligands (Fig. 10). Their ruthenium catalysts were found to be effective in the asymmetric transfer hydrogenation of an extend range of substrates, such as ketones, keto esters, and olefins with comparable



13a~**13c** (n = 1~3, Ar = 4-$CH_3C_6H_4$)
14b (n = 2, Ar = 2,4,6-Et_3-C_6H_2)
15b (n = 2, Ar = 2,4,6-$^{i}Pr_3$-C_6H_2)
16b (n = 2, Ar = 1-naphthyl)

Fig. 10 Chiral tunable dendritic diamine ligands for asymmetric transfer hydrogenation

enantioselectivities to those of the monomeric parent catalyst. Such dendritic vicinal diamines can also serve as a chiral platform for other asymmetric catalysis such as asymmetric hydrogenation [59].

2.2.2 Asymmetric C–C Bond-Forming Reactions

Chiral amino alcohols have been widely used as ligands for asymmetric catalysis [54], which are often prepared from the corresponding amino acids. Several types of chiral dendrimers bearing amino alcohol located at the core or on the periphery were reported. The representative early examples included Bolm's flexible chiral pyridyl alcohol-cored dendrimers, Meijer's and Soai's periphery-functionalized dendritic β-amino alcohols [60–62].

Recently, Zhao and coworkers have developed series of chiral pyrrolidinylmethanol-based dendritic ligands for asymmetric catalysis [63–69]. All these dendritic ligands could be readily synthesized on the basis of a convergent strategy (Fig. 11). The dendritic catalysts **17** were employed to the phenyl transfer reactions using phenyl boronic acid as the phenyl source for the first time [63]. As compared with the monomeric catalyst, the dendritic catalysts exhibited slightly higher enantioselectivities (up to 93% ee). When using $(PhBO)_3$ [$(PhBO)_3$ = triphenylcyclotriboroxane] instead of phenyl boronic acid as the phenyl source, the enantioselectivity was further enhanced to 98%. In addition, the second-generation dendritic catalyst could be quantitatively separated by precipitation with methanol and reused at least five times without obvious loss of catalytic activities and enantioselectivities. This dendritic ligand was further found to be effective in the addition of alkenylzinc reagents to aldehydes with organoboronates as the alkenyl source, providing allylic alcohols in moderate yields and good to excellent enantioselectivity [64].

Following up these investigations, the same group recently employed the chiral 2-trimethylsilanyloxy-methyl-pyrrolidine-based dendritic organocatalysts **19** for the direct asymmetric Michael addition of aldehydes to nitrostyrenes [65].

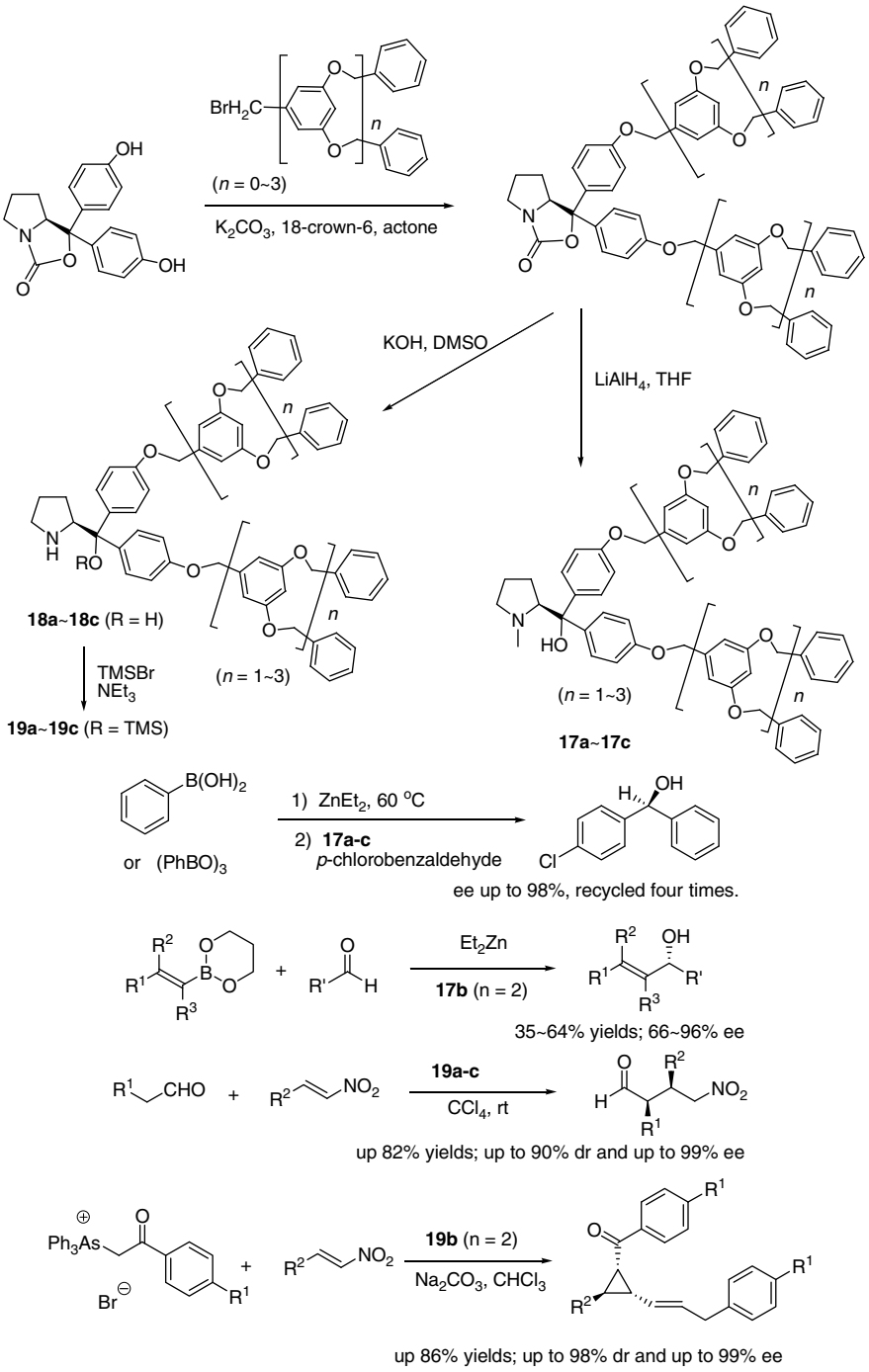


Fig. 11 Synthesis of chiral pyrrolidinylmethanol-based dendritic ligands for asymmetric C–C bond-forming reactions

Good yields (up to 82%), high diastereoselectivities (up to *syn*/*anti* = 95/5) and enantioselectivities (up to 99% ee) were observed. The second-generation dendritic catalyst could be easily recovered via precipitation with methanol and reused at least five times without obvious loss of catalytic activity and enantioselectivity. Most recently, this chiral dendritic organocatalysts were further applied to the asymmetric tandem cyclopropanation/Wittig reaction of α, β-unsaturated aldehydes with arsonium ylides [66]. It was found that the dendritic catalyst gave the products in good yields (up to 86%), and high diastereoselectivities (up to dr = 99:1) and enantioselectivities (up to 99% ee) under simple and mild reaction conditions. The catalyst can be recycled without any loss in activity.

In 2006, Zhao's and Wang's groups developed highly efficient and reusable dendritic organocatalyst derived from *N*-prolylsulfonamide for the asymmetric direct aldol reaction in water [70]. The dendritic catalysts were readily synthesized by the condensation of 4-nitrobenzsulfonamide with the Fréchet-type polyether dendritic wedges bearing a carboxyl group at the focal point (Fig. 12). It was noted that the aldol reactions proceeded efficiently in water in the presence of these hydrophobic dendrimers, providing the *anti* products as the major isomers in good to excellent yields (58–99%) with high diastereoselectivities and enantioselectivities. Interestingly, the dendritic catalysts exhibited better reactivities and higher selectivities than the monomeric catalyst. In addition, the second-generation catalyst could be quantitatively recovered by solvent precipitation and reused at least five times without any loss of reactivity and enantioselectivity.

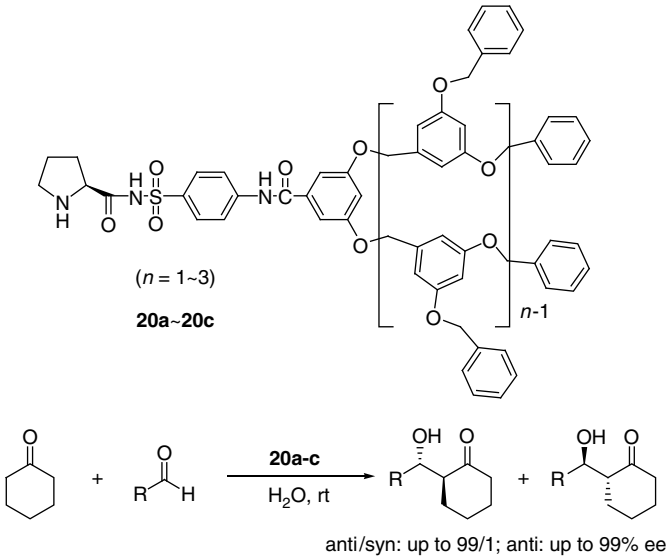


Fig. 12 Chiral N-prolylsulfonamide-based dendritic organocatalysts for asymmetric direct aldol reaction in water

2.2.3 Asymmetric Hetero-Diels–Alder Reaction

Various chiral Lewis acids including aluminum, titanium or boron, and chiral ligands such as chiral amino alcohols, diols, salen (salen = Ethylenebis(salicylimine)), bisoxazoline or *N*-sulfonylamino acids have been used as the catalysts for the asymmetric hetero-Diels–Alder (HDA) reactions [71]. Recently, Ding and coworkers developed two types of recyclable dendritic 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) ligands for the titanium-catalyzed HDA reactions of 1-methoxy-3-(trimethylsilyloxyl) buta-1,3-diene (Danishefsky's diene) with aldehydes (Fig. 13). Both dendritic catalysts showed excellent enantioselectivities (up to 97% ee) and catalytic activities (>99% yield). Enhanced enantioselectivity has been achieved through optimization of the disposition and the size of the dendritic wedges in the ligands. Notably, these dendritic catalysts showed high stability probably due to the stabilization of the titanium active species by the steric hindrance of the dendritic wedges. Furthermore, the catalyst could be quantitatively recovered by solvent precipitation and reused without further addition of the Ti source or a carboxylic acid additive for at least three cycles without obvious loss of catalytic activities and enantioselectivities. Most interestingly, a higher degree of asymmetric amplification in the catalytic HDA reactions was observed with the dendritic catalysts than with the monomeric parent catalyst [72].

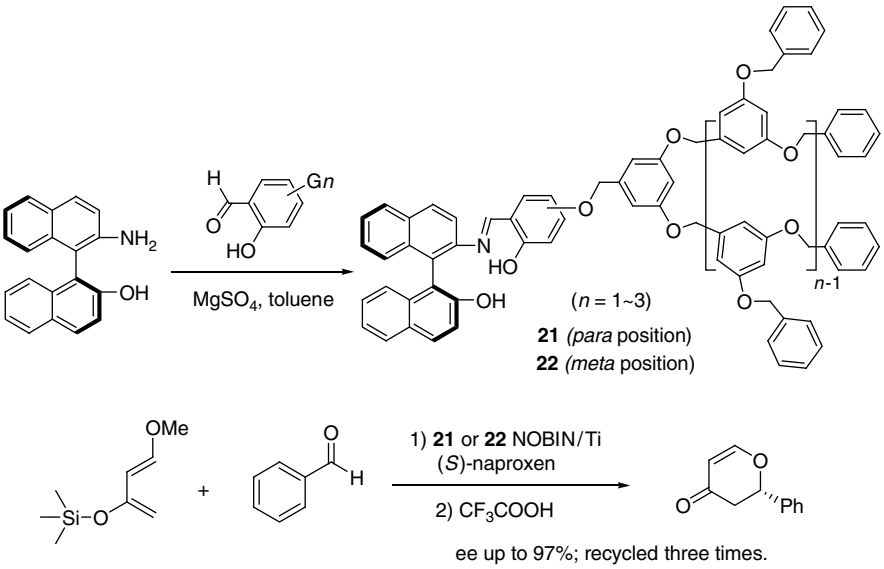


Fig. 13 Synthesis of chiral NOBIN-cored dendrimers for the titanium-catalyzed HDA reactions

3 Asymmetric Catalysis in Nanopore of Mesoporous Materials

Inorganic materials represent one type of commonly used supports for the immobilization of homogeneous chiral catalysts [11, 73]. Unlike polymers, inorganic solids prevent the intermolecular aggregations of the active species because of their rigid structure. Moreover, the inorganic materials often show higher stability under the catalytic conditions than the cross-linked polymers. Among the different types of inorganic supports reported to date, the mesoporous materials have attracted much attention because of their unique properties, such as well-ordered pore array, large surface area, uniform pore size distribution, and tunable pore diameter (4–15 nm) [74]. Unlike zeolites with channels/cavities of up to 1.0 nm, these tunable mesopores provide a large space to immobilize chiral catalysts and allow free diffusion of reactants and products. In addition, asymmetric catalysis in the nanopores of mesoporous materials can provide some unique properties, such as site-isolation, confinement, and cooperative activation effects. More importantly, the confinement effect of support, which originates from the additional non-covalent interactions (such as hydrogen bond, van der Waals force, adsorption, etc.) between catalyst/substrate and the support surfaces plays an important role when asymmetric catalysis takes place inside the nanopores (as shown in Fig. 14) [75]. Therefore, the enantioselectivity and/or catalytic activity could be improved by careful turning of this confinement effect based on the molecular design of the nanopores of mesoporous materials. In a seminal study, Thomas and coworkers reported that a chiral catalyst with the ligand 1,1′-bis(diphenylphosphino) ferrocene (dppf) anchored to the inner walls of the mesoporous support MCM-41 exhibited unprecedented high enantioselectivity (up to 99% ee) in the Pd-catalyzed allylic amination of cinnamyl

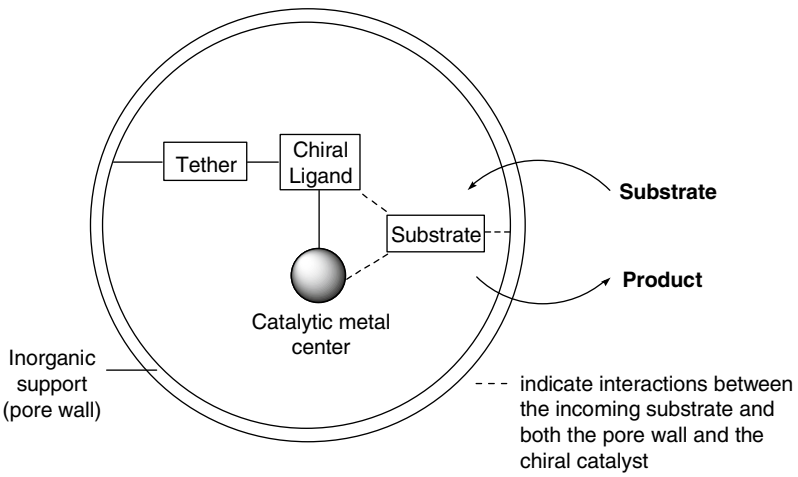


Fig. 14 Schematic representations of chiral catalyst constrained within a nanopore for asymmetric catalysis

acetate, which was far superior to those of its homogeneous counterpart and a surface-bound analog attached to nonporous silica [76]. Recently, immobilization of homogeneous chiral catalysts into inorganic solids, particularly, mesoporous materials have been attracting more and more attention [21, 75, 77, 78].

In this section, we will highlight the recent progress made in the asymmetric catalysis in nanopores of mesoporous materials and the periodic mesoporous organosilicas (PMOs), focusing on the work reported by Chinese chemists.

3.1 Immobilized Chiral Mn(salen) Catalysts in Nanopores for Asymmetric Epoxidation

Asymmetric epoxidation of unfunctionalized olefins is of great importance for the synthesis of chiral intermediates. Chiral Mn(salen) complexes are excellent catalysts for such transformation. Over the past decade, several methods have been employed to immobilize these catalysts [11, 79]. In most cases, Mn(salen) catalysts were grafted onto the supports generally via the salen ligands, which required additional functionalization of the chiral ligand. In addition, these immobilized Mn(salen) catalysts often suffered from inferior catalytic performance as compared with their homogeneous analogs.

Recently, Li and coworkers have systemically investigated the asymmetric epoxidation with Mn(salen) catalysts, which was axially immobilized in the nanopores of mesoporous materials via a non-covalent interaction strategy [21, 77, 80–84]. Various factors influencing the heterogeneous catalysts, such as the nanopores and the external surface, the linkage length, and surface hydrophobicity of the nanopores were investigated in depth. In general, the Mn(salen) catalysts anchoring into the nanopores exhibited higher enantioselectivity and/or reactivity than those immobilized on the external surface of supports for the asymmetric epoxidation of unfunctionalized olefins.

In their early report, Li and coworkers demonstrated that a phenoxide group grafted on MCM-41 was able to axially immobilize the Mn(salen) complex through the complexation of manganese by oxygen atoms (Fig. 15). In the case of asymmetric epoxidation of α-methylstyrene with aqueous NaClO, the immobilized catalyst showed a markedly higher enantioselectivity than the homogeneous catalyst (72% ee with the heterogeneous catalyst vs. 56% ee in solution). Notably, this solid catalyst could not epoxidize 1-phenylcyclohexene due to the bulkiness of the substrate, demonstrating the placement of the catalytic sites in the mesopores of the support [80]. To overcome this drawback, they further employed this method for the immobilization of three chiral Mn(salen) complexes into different mesoporous materials with large pore diameters. The resulting heterogeneous Mn(salen) catalysts showed comparable enantioselectivities for asymmetric epoxidation of styrene and 6-cyano-2,2-dimethylchromene, and much higher enantioselectivities for the epoxidation of α-methylstyrene and *cis*-β-methylstyrene than the corresponding homogeneous catalysts. Interestingly, these heterogeneous catalysts also

significantly altered the *cis/trans* ratio of epoxides for the asymmetric epoxidation of *cis*-β-methylstyrene. Notably, all these immobilized catalysts suffered from low catalytic activity due to difficulty in diffusion. This observed remarkable support effect (confinement effect) was probably attributed to the unique spatial environment constituted by the axial bulky group and the mesopores of the support. Similar confinement effect of mesoporous material in asymmetric epoxidation was also reported by Kureshy's [85, 86] and Liu's groups [87]. In addition, these immobilized catalysts were quite stable and could be recycled at least eight times without obvious loss of catalytic activity and enantioselectivity [81].

Later, the same group reported the axial immobilization of chiral Mn(salen) into inorganic mesoporous materials with different pore sizes via phenyl sulfonic groups (Fig. 16). Similar positive support effects were observed in the asymmetric epoxidation of unfunctionalized olefins [82]. For example, the solid (SBA-15) supported catalyst provided 92% ee (*cis*-epoxide) for the asymmetric epoxidation of *cis*-β-methylstyrene, which was higher than 25% ee obtained with the homogeneous

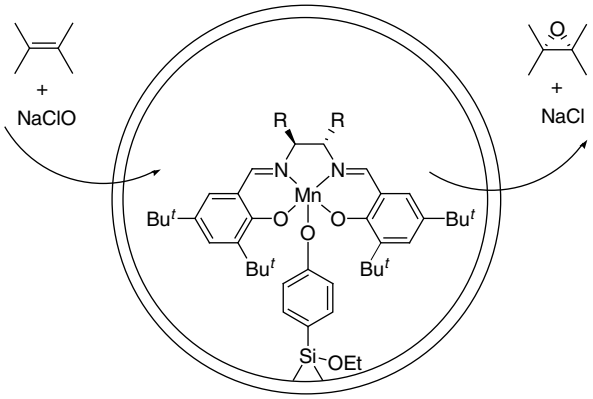


Fig. 15 Schematic representation of chiral catalyst constrained within a nanopore via phenoxyl groups for asymmetric catalysis (Chiral salen: R = Ph or R–R = –$(CH_2)_2$–. Supports: MCM-41, 2.7 nm; activated Silica, 9.7 nm; SBA-15, 7.6 and 6.2 nm)

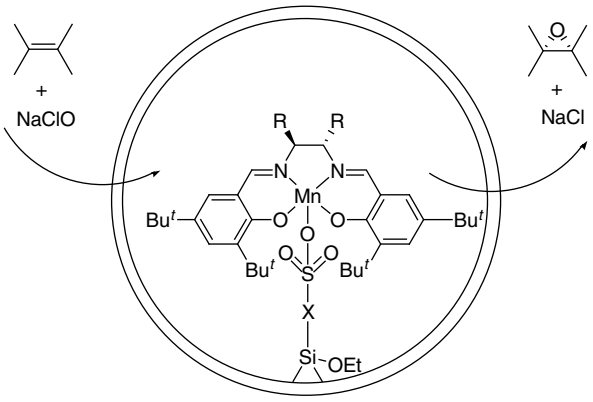
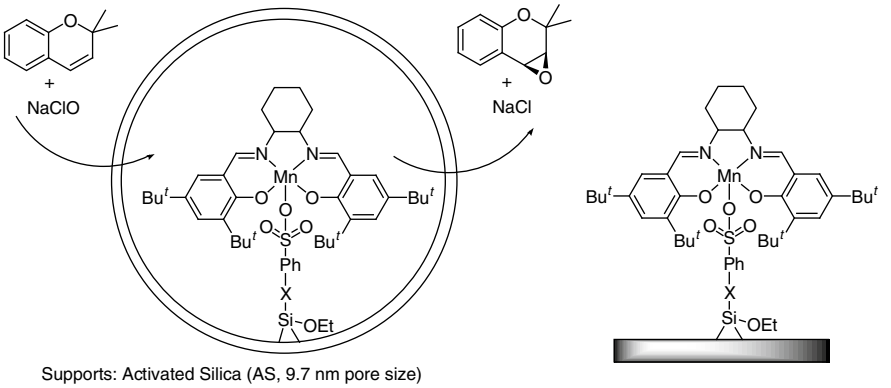


Fig. 16 Schematic representation of chiral catalyst constrained within a nanopore via organic sulfonic groups for asymmetric catalysis (Chiral salen: R = Ph or R–R = –$(CH_2)_2$–. Linkage: X = phenyl or propyl. Supports: activated Silica, 9.7 nm; SBA-15, 7.6 nm; MCM-41, 1.6 and 2.7 nm)

catalyst. The ratio of *cis*/*trans* of epoxides was also increased from 0.46 (in solution) to 7.71 (with heterogeneous catalyst) under the same reaction conditions.

In order to understand the observed confinement effect, various factors including the grafting modes (in the nanopores or on the external surface), the axial linkage rigidity and the modification of nanopores with methyl groups were systematically studied [83, 84]. A number of immobilized Mn(salen) catalysts were thus prepared by using different inorganic mesoporous materials (Figs. 16 and 17), and employed to the asymmetric epoxidation of unfunctionalized olefins. It was found that the Mn(salen) catalysts grafted through flexible propyl sulfonic groups generally exhibited higher chemical selectivity and enantioselectivity than those grafted through rigid phenyl sulfonic groups. In addition, higher enantioselectivity were achieved by increasing the axial linkage lengths for Mn(salen) catalysts immobilized in the nanopores. However, in the case of catalysts immobilized on the external surface of the support, although an increase in reactivity and chemical selectivity was observed, the enantioselectivity remained unchanged with increasing axial linkage lengths. Notably, the reactivity and enantioselectivity were further improved by methylation of the surface of nanopores. This enhancement effect was attributed to the higher



Catalyst	Time (h)	Conv. (%)	ee (%)	TOF (h^{-1})
[Mn(salen)Cl]	6	97	80	10
23	24	88	78	2
24	24	87	82	2
25	6	98	86	10
26	4.5	100	90	14
27	24	76	71	2

Fig. 17 The chiral Mn(salen) catalyst constrained within the nanopores of activated silica and on the external surface of MCM-41 for asymmetric epoxidation of 6-cyano-2,2-dimethylchromene (TOF = turnover frequency)

hydrophobicity of surface, favoring the adsorption of the more hydrophobic olefin substrates. Asymmetric epoxidation of 6-cyano-2,2-dimethylchromene with different immobilized Mn(salen) catalysts were summarized in Fig. 17.

3.2 Entrapped Chiral Catalysts in Nanopores for Asymmetric Hydrolytic Kinetic Resolution of Epoxides

Among various methods for immobilization of chiral homogeneous catalysts onto solid supports, the encapsulation is one of the most promising strategies since the properties of the trapped catalyst in principle could be kept as those of its homogeneous counterpart [88]. For this purpose, the size of the catalyst must be larger than the pore mouth of the solid support. So far, a number of entrapped chiral catalysts in nanopores of zeolites have been developed by using the "ship-in-a-bottle" approach [11, 88]. However, this method is very limited with regard to complex size, and in most cases, the immobilized catalysts suffered from inferior catalytic performance due to the poor accessibility.

In comparison with microporous zeolites, ordered mesoporous silicas have a larger pore size and volume, which enables the encapsulation of larger complexes. However, entrapping homogeneous catalyst onto the pores of such support suffered from metal leaching during the reaction. Recently, Li and coworkers described a modified method in regard to the classic "ship-in-a-bottle" approach [89]. Chiral Co(salen) complex was chosen as a model catalyst and immobilized into the nanopores of SBA-16 through the "ship-in-a-bottle" synthesis followed by tailoring the pore entrance size by using a silylation method, as described in Fig. 18. This immobilized catalyst showed excellent enantioselectivity (up to 96%) in the hydrolytic kinetic resolution (HKR) of terminal epoxides. Most importantly, the catalysts proved to be recycled ten times, indicating that the catalyst was confined stably in the nanopores of SBA-16.

Although extremely successful, the method of "ship-in-a-bottle" synthesis in mesoporous materials still suffered from some drawbacks, such as formation of undesired species in the solid matrix and limited type of metal complexes. To overcome these problems, Li and coworkers have recently developed a new approach for the encapsulation of various chiral metal catalysts in the nanopore through post-modification of the pore entrance [90]. A preformed homogeneous chiral catalyst was first introduced into the nanopores of mesoporous materials (e.g., SBA-16 with tunable small pore entrance and large cage size) by impregnation or adsorption. A subsequent treatment with an alkylsilane reduced the pore entrance size to a value small enough to entrap the complex but able to admit the diffusion of reactants and products (Fig. 19). Based on this new method, chiral catalysts Co(salen) and Ru-TsDPEN were encapsulated in the nanopores of SBA-16. The immobilized Co(salen) catalyst was found to be effective in the asymmetric HKR of terminal epoxides, providing chiral diol with excellent enantioselectivity (up to 97% ee) which are comparable to that of homogeneous counterpart. Notably, the catalyst

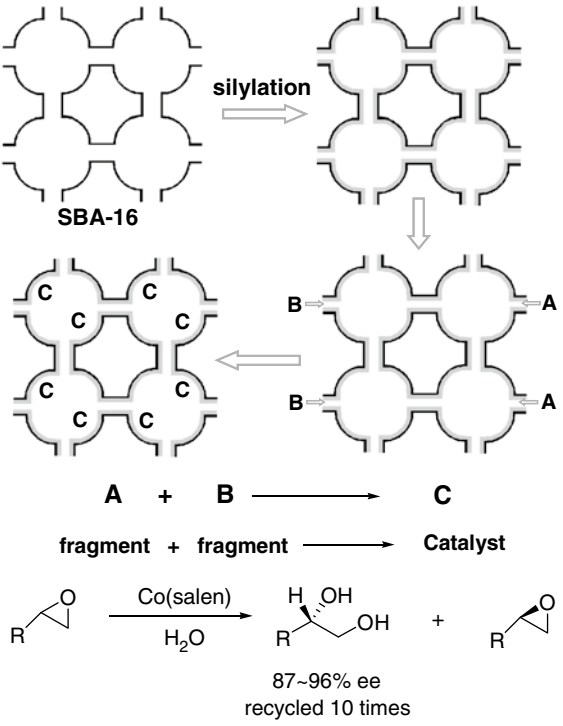


Fig. 18 Schematic representation of entrapping chiral Co(salen) catalyst within the nanopores of phenyl-modified SBA-16 for asymmetric HKR of terminal epoxides

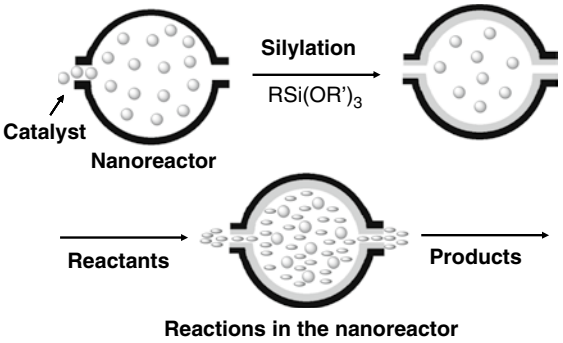


Fig. 19 Schematic representations of entrapping homogeneous chiral catalyst within the nanopores of mesoporous materials

could be recycled more than ten times without obvious loss of catalytic reactivity and enantioselectivity.

One important advantage of this method is the possibility of accommodating two or more than two chiral catalysts in the same nanocage of the support. This is of crucial importance in asymmetric catalytic reactions with a cooperative activation effect, as occurs with the HKR of epoxides [91, 92]. To demonstrate this effect, the same group chose SBA-16 as support because its nanocages are large enough to accommodate a desired number of Co(salen) complex. Immobilized catalysts with different average Co content were thus prepared, and their catalytic performance was compared [93]. It was found that the catalyst with two or more

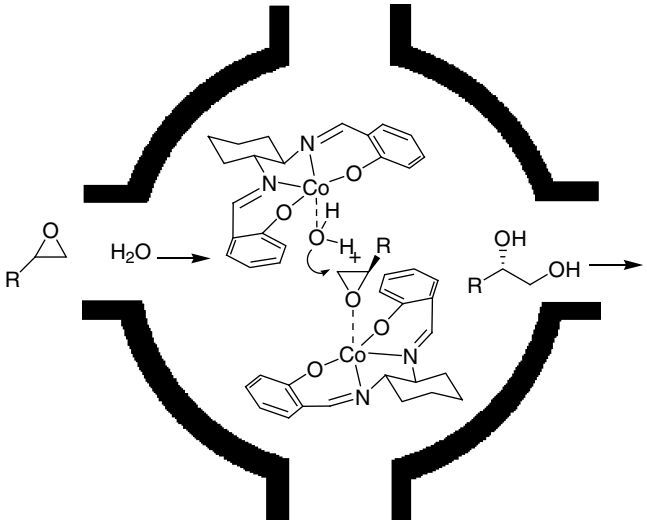


Fig. 20 Schematic representation of the Co(salen) catalyst trapped in the isolated nanopores of SBA-16 for the cooperative asymmetric HKR of terminal epoxides

than two Co(salen) complexes in each cage showed much higher activity than that obtained with homogeneous catalyst in the HKR of epoxides, demonstrating that the cooperative activation effect of Co(salen) complexes could be strengthened in the nanocages. The appropriate proximity and the free movement of Co(salen) in the confined space offered the possibility that H_2O activated by one Co(salen) complex could attack the epoxide activated by another Co(salen) complex, and then facially produce the diol with high activity (Fig. 20).

Most interestingly, this enhancement in catalytic activity and enantioselectivity became more significant with decreasing catalyst loading. For example, when the *S*/*C* ratio was increased to 4,000:1, the result obtained with the heterogeneous catalyst was better (49% conversion, TOF 163 h^{-1}, 98% ee) than that obtained in solution (34% conversion, TOF 113 h^{-1}, 98% ee diol). The difference was even much more significant when *S*/*C* was further increased to 12,000:1, 50% conversion, TOF 250 h^{-1}, 98% ee diol vs. 7% conversion, TOF 35 h^{-1}, 89% ee diol in solution. In addition, leaching of metal ions into the products was not observed, and the catalyst could be easily recovered by filtration and reused at least for eight times without any apparent loss of catalytic activity and enantioselectivity.

3.3 Immobilized Chiral Catalysts in Nanopores for Asymmetric Reduction

Since the seminal works reported by Kinting and coworkers in 1985 [94], numerous advances have been made in the heterogeneous asymmetric hydrogenations using inorganic materials. Among the reported numerous examples, chiral

catalysts immobilized in the nanopores of mesoporous materials via covalent or non-covalent strategy have attracted particular attention due to their tunable catalytic performance [11, 16]. In some cases, significant higher enantioselectivity and/or catalytic activity were observed as compared to those obtained with homogeneous counterparts due to the site-isolation effect and/or confinement effect of inorganic supports [75]. Recently, Chinese chemists also made contributions to this research field.

Liu and Li developed a mesoporous silica-supported chiral iridium catalyst with a highly ordered dimensional-hexagonal mesostructure through postgrafting the organometallic complex (1-diphenylphosphino-2-triethylsilylethane)[(*R,R*)-1,2-diphenylethylenediamine]iridium chloride on SBA-15 silica [95, 96]. Without the use of chiral diphosphine ligand, the immobilized catalyst was found to exhibit excellent enantioselectivities (up to 99% ee) and reactivities in the asymmetric hydrogenation of various simple aromatic ketones. The asymmetric induction of the heterogeneous catalyst was much superior to that of the homogeneous counterpart or IrHCl(BINAP)(DPEN) catalyst. This significant enhancement in enantioselectivity was obviously due to the confinement effect of the regular and adjustable nanopores of support. Furthermore, the catalyst could be recovered easily and used repetitively seven times without significant loss of catalytic activity and enantioselectivity.

Recently, Li and coworkers reported another type of immobilized chiral catalysts for asymmetric reduction of ketones by using periodic mesoporous organosilicas (PMOs) as support [97–100]. In comparison with mesoporous silicas, PMOs synthesized from bridged silane precursors, $(R'O)_3Si–R–Si(OR')_3$, exhibit some unique properties such as tunable surface hydrophobicity/hydrophilicity [101, 102]. Mesoporous ethane-silicas bearing chiral DACH in the nanopores was synthesized by the co-condensation of 1,2-bis(trimethoxysilyl)ethane (BTME) and DACH-containing silane precursor using triblock copolymer P123 as template [97]. The immobilized chiral catalyst generated by reaction of the resulting chiral PMOs with $[Rh(cod)Cl]_2$ showed 82–96% conversions and 19–23% ee values for the asymmetric transfer hydrogenation of acetophenone, which were much higher than those obtained with a mesoporous silica-supported catalyst. The enhancement in catalytic activity was mainly due to the increased surface hydrophobicity by ethane group modification of the mesoporous framework. In their continuing works, further enhancement in catalytic activity and enantioselectivity were achieved through the postmodification of the DACH moieties in the pore of the chiral POMs by reaction with *p*-toluenesulfonyl chloride (Fig. 21). The catalyst generated by treatment of the modified POMs with $[RhCp^*Cl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) showed moderate to high enantioselectivity (up to 81% ee) in the asymmetric transfer hydrogenation of various aromatic ketones in $HCOONa–H_2O$ [99]. Therefore, the co-condensation approach associated with the postmodification method is a promising alternative for the synthesis of mesoporous materials containing new functionalities. In addition, the catalytic properties could be also fine-tuned by systematically adjusting the pore structures [100].

Subsequently, the same group developed a new type of chiral DACH-functionalized POMs through one-step co-condensation of tetramethoxysilane with

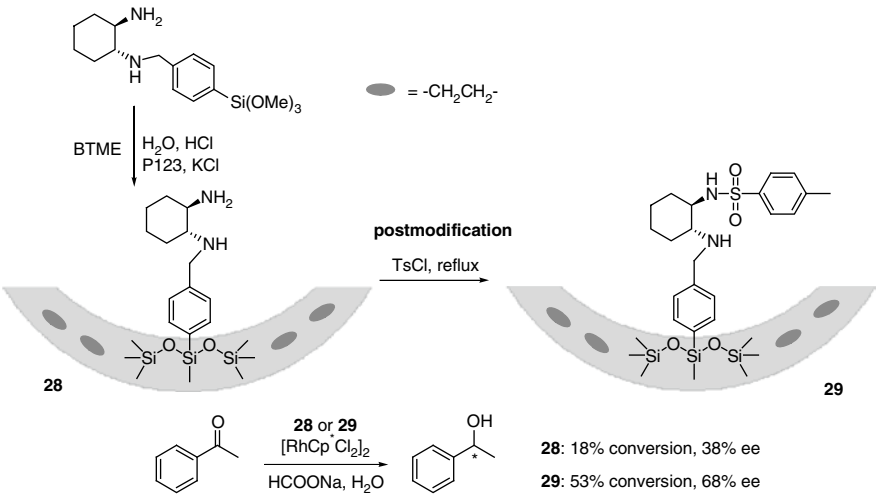


Fig. 21 Synthesis and postmodification of DACH-functionalized PMOs for asymmetric transfer hydrogenation of acetophenone

N,*N*′-bis[4-(trimethoxysilyl)benzyl]-(1*R*,2*R*)-diaminocyclohexane using cetyltrimethylammonium bromide as a structure-directing agent under basic conditions [98]. The immobilized rhodium catalyst with benzyl group as linker in the nanopores showed higher reactivity and enantioselectivity than those obtained with homogeneous counterpart in the asymmetric transfer hydrogenation of ketones. An enantioselectivity of 61% was observed in the reaction of 2-acetylnaphthalene.

4 Asymmetric Catalysis with Self-Supported Chiral Catalysts

Recently, a novel class of metal–organic hybrid material (MOHMs), also known as coordination polymers, has been developed for applications in heterogeneous catalysis [19, 20, 103–106]. As compared with the classical organic and inorganic solid-supported catalysts, such heterogeneous catalysts have several unique features. Firstly, MOHMs can be easily constructed via self-assembly of multitopic ligands with metal ions by coordination bonds without the need for an external support (self-supported catalyst [19]). Secondly, MOHMs possess infinite extended network and unprecedented high porosity with controllable pore size and shape by adjusting the organic ligand as well as the coordination preference of the metal species. Thirdly, MOHMs often display poor solubility in common organic solvents and thus enable easy separation and recycling. In addition, both the catalytic activity and the selectivity can be tuned by the pore matrices and chemical functionality of the pores through metal and ligand diversity. Thus, MOHMs as a heterogeneous catalyst may combine the advantages of both heterogeneous catalysts (e.g., facile

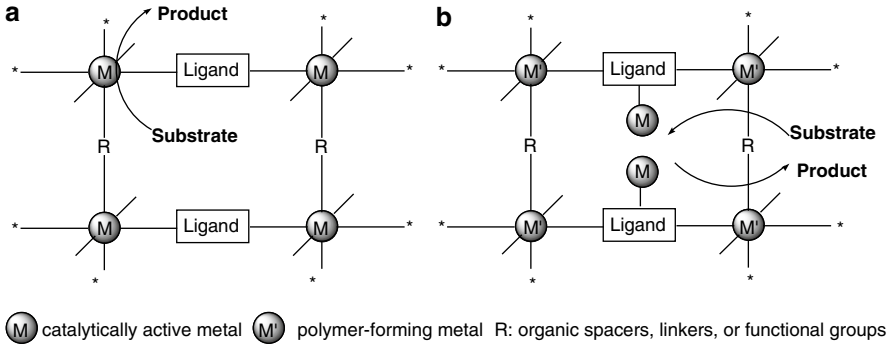


Fig. 22 Schematic representations of the construction of MOHMs catalyst for heterogeneous catalysis: (**a**) Metal–organic coordination polymers; (**b**) Organic–inorganic hybrid polymers

catalyst recovery, high stability, ease of handling) and their homogeneous counterparts (uniform active sites, high efficiency and selectivity, reproducibility).

Generally, there are two strategies for incorporating catalytically active sites into the backbone of MOHMs (As shown in Fig. 22). One strategy is to incorporate the metal centers directly into the main backbone of MOHMs by using a ditopic or polytopic ligand and catalytically active metal precursor. In such a case, the metal plays the dual role as both the structural binders and the active sites in the formed solid. The other one also uses polyfunctional ligand as the linker and metal ion or cluster as the node to construct MOHMs. In this case, however, the catalytically active sites are located as pendant auxiliaries on the main backbone of the formed MOHMs. In 2000, Kim and coworkers reported the first example of a crystalline homochiral coordination polymer for asymmetric catalysis and triggered increasing attention to this method [107]. In this section, we will summarize the recently reported chiral metal–organic coordination polymers (self-supported chiral catalysts) mainly by Chinese chemists. The second-type of chiral MOHMs for heterogeneous asymmetric catalysis can be found in recent reviews [104–106].

4.1 Self-Supported Catalysts for Asymmetric C–C Bond-Forming Reactions

The first example of self-supported chiral catalysts for heterogeneous asymmetric catalysis was independently developed by the Sasai's and Ding's groups [108–110]. Based on the facts that homo- or hetero-combination of two BINOL (BINOL = 1,1′-Bi-2-naphthol) derivatives with $Ti(O^{i}Pr)_4$ showed excellent efficiency for carbonyl-ene reaction due to the dimeric nature of the real catalytic species [111, 112], both groups designed several bridged bis-BINOLs followed by self-assembling with $Ti(O^{i}Pr)_4$ in chlorinated solvents, leading to the formation of insoluble chiral titanium-bridged polymers (Fig. 23). The resulting immobilized

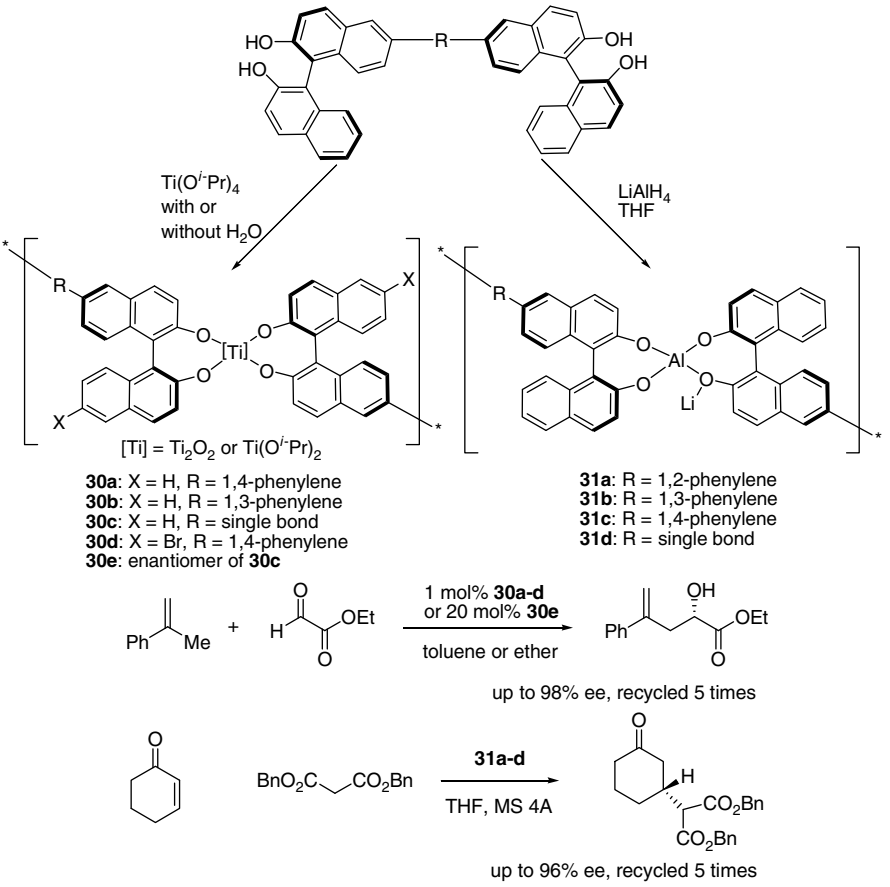


Fig. 23 Preparation of self-supported heterogeneous Ti- or Al-bridged catalysts for asymmetric carbonyl-ene reaction and Michael addition

catalysts showed excellent enantioselectivities (up to 98% ee) for carbonyl-ene reaction of α-methylstyrene and ethyl glyoxylate under heterogeneous conditions to afford the corresponding α-hydroxyl esters in high yields. Importantly, the linkers between the two BINOL units in the ligands were found to influence the enantioselectivity of reaction significantly, demonstrating the importance of the supramolecular structures of the assemblies on their catalytic performance. It is thus possible to fine-tune the immobilized chiral catalysts through modifications on the polytopic chiral ligands. In addition, the catalyst could be easily recovered by simple filtration and reused at least five times but at the expense of reduced reactivity and enantioselectivity.

This bridged bis-BINOL ligands were also used by Sasai and coworkers for the construction of Al-Li-bis(binaphthoxide) (ALB) bifunctional catalysts for asymmetric Michael reaction [108]. It has revealed that the synergistic cooperation

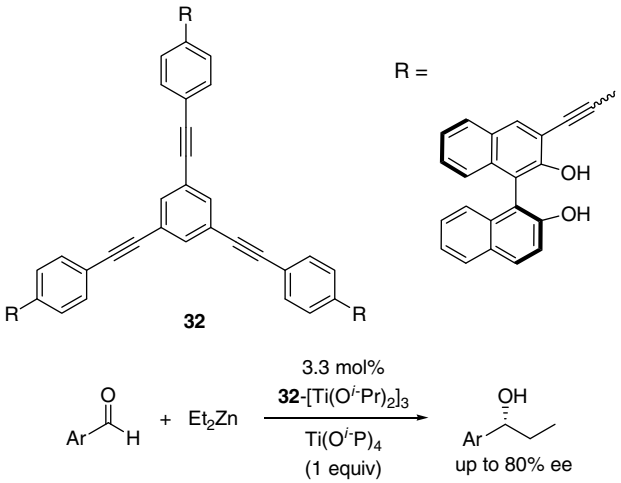


Fig. 24 Self-supported heterogeneous BINOLate Ti catalysts for asymmetric addition of diethylzinc to aldehyde

between the active sites is required for the reactivity of this bifunctional catalyst. Therefore, to achieve highly effective immobilized ALB catalyst, it is important to maintain the structural motif during immobilization. However, the conventional approach, which involves the random introduction of chiral ligand onto a sterically irregular polymer backbone, resulted in less effective catalysts. In contrast, the self-supported ALB catalysts showed comparable catalytic properties to those of homogeneous counterpart in the asymmetric Michael addition between 2-cyclohexenone and dibenzyl malonate. All these catalysts were found to be effective, leading to Michael adducts in good yields and modest to excellent enantioselectivities (up to 96% ee). The catalyst could be recycled and similar reactivity could be maintained after three catalytic runs, albeit with a decrease in enantioselectivity.

Most recently, using a similar approach, Harada and coworker developed a self-supported BINOLate/Ti(O^{i}Pr)$_4$ catalyst with a tris-BINOL ligand for the asymmetric addition of diethylzinc to aldehydes (Fig. 24). Although good enantioselectivity (up to 84% ee) was obtained and the catalyst could be recycled, leaching of some catalytic species into solution was observed [113].

4.2 Self-Supported Catalysts for Asymmetric Oxidation Reactions

Homogeneous asymmetric oxidation of sulfides with titanium complexes based on C_2-symmetric diol ligands have been successful [114]; however, little attention has been paid to the heterogeneous processes. Based on successful use of the self-supported titanium catalysts for asymmetric carbonyl-ene reaction, Ding and coworkers employed some variants of the above described Ti-bridged polymeric

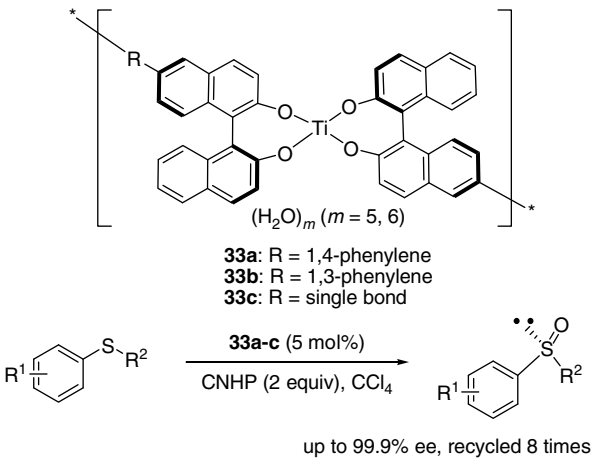


Fig. 25 Self-supported heterogeneous Ti-bridged catalysts for asymmetric oxidation of aryl alkyl sulfides

catalysts to the heterogeneous asymmetric oxidation of sulfides [110]. The reaction of the bridged BINOL ligands with $Ti(O^{i}Pr)_4$ in 1:1 molar ratio was conducted in CCl_4 followed by addition of 40 equiv of H_2O, providing the immobilized Uemura-type sulfoxidation catalysts (Fig. 25). All these catalysts were highly effective in the oxidation of aryl alkyl sulfides with cumene hydroperoxide (CNHP) as the oxidant, affording corresponding sulfoxides in moderate yields with excellent enantioselectivities (up to 99.9% ee). Notably, the catalysts were highly stable and could be readily recycled and reused for over 1 month (at least eight cycles) without significant loss of activity and enantioselectivity.

One promising advantage of self-supported catalysts is that both the catalytic activity and the enantioselectivity can be tuned through modifications on the chiral polytopic ligands. As described above, the linkers of the bridged BINOL ligands were found to play a very important role in the asymmetric carbonyl-ene reaction. Such an effect was further systematically studied by Ding and coworker in the immobilization of Shibasaki's lanthanum catalyst [115] for the asymmetric epoxidation of α,β-unsaturated ketones [116]. Three types of multitopic ligands containing different bridging linkers, including linear, bent, trigonal-planar, and tetrahedral spacers, were designed to investigate the impact of the spatial arrangement of chiral (*S*)-BINOL units on the catalytic properties of their assemblies with the lanthanum ion. The treatment of the corresponding multitopic ligands with $La(O^{i}Pr)_3$ in THF led to self-supported heterogeneous Shibasaki's BINOL/La catalysts (Fig. 26). These catalysts were subsequently applied to the epoxidation of chalcone with CNHP as the oxidant in the presence of Ph_3PO and molecular sieves, affording the products in almost quantitative yields with excellent enantioselectivities. Although the real reason was not clear, the length and the spatial orientation of the spacers in the multitopic ligands were found to have a significant impact on the enantioselectivity of the heterogeneous epoxidation. Given the modular nature of the multitopic ligands, both the reactivity and enantioselectivity of such a catalyst might be fine-tuned by judicious choice of the spacer part of the ligands. In addition, the heterogeneous nature of the catalysis was confirmed by

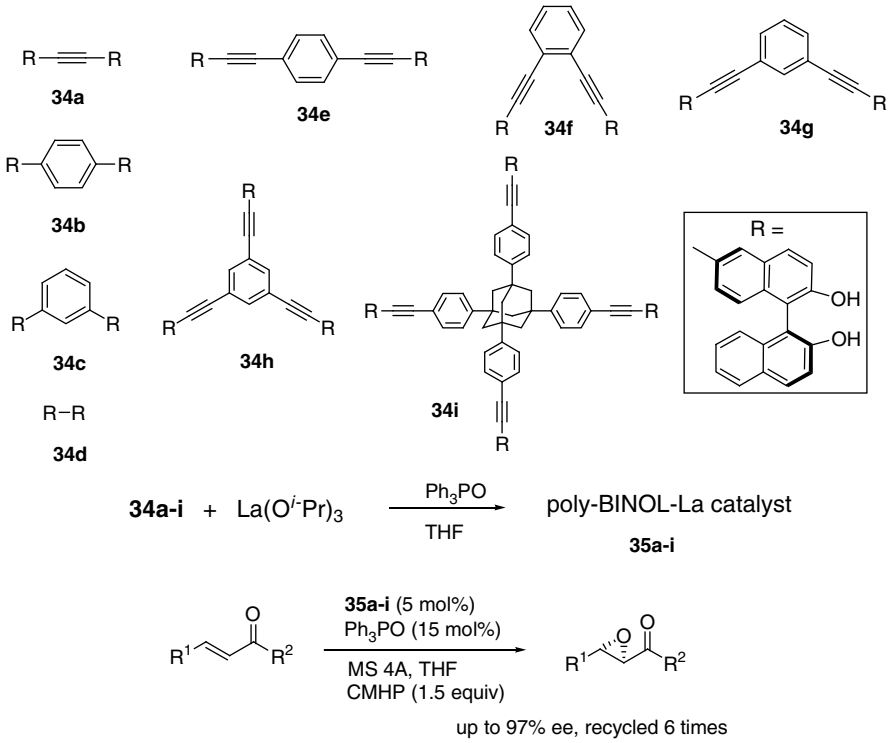


Fig. 26 Self-supported heterogeneous Shibasaki's BINOL/La catalysts for the epoxidation of α,β-unsaturated ketones

the facts of inactivity of the supernatant THF solution in the reaction system and the less than 0.4 ppm lanthanum leaching in consecutive runs as determined by inductively coupled plasma spectroscopy. The catalyst could be recovered by simple filtration under argon and reused for at least six cycles without obvious loss of enantioselectivity.

In the continuous studies, Ding and coworkers have recently developed a new class of chiral self-supported heterogeneous bis-BINOL-Zn catalysts with their bis-BINOL ligands [117]. These catalysts showed good enantioselectivity and versatility in the heterogeneous asymmetric epoxidation of α,β-unsaturated, which are comparable to those obtained with corresponding homogeneous catalyst.

4.3 Self-Supported Catalysts for Asymmetric Hydrogenations

In 2004, Ding and coworkers reported their results on the heterogenization of Ferringa's MonoPhos/Rh catalyst [118] using self-supported strategy for enantioselective hydrogenations of prochiral olefins [119, 120]. On the basis of the mechanistic

understanding that two monodentate phosphorus ligands are coordinated to Rh in the catalytically active species, they designed and synthesized various ditopic MonoPhos-based ligands bearing different linkers by the reaction of hexamethylphosphorus triamide (HMPT) with corresponding bis-BINOL derivatives. Treatment of the resulting ditopic phosphoramidites with a solution of $[Rh(cod)]BF_4$ in dichloromethane led to the formation of insoluble metal–organic coordination polymers as amorphous solids (Fig. 27). The resulting self-supported catalysts showed outstanding catalytic performance for the asymmetric hydrogenation of a number of α-dehydroamino acids and 2-aryl enamides with enantiomeric excess ranges of 94–98% and 90–98%, respectively. The linker moiety in the heterogeneous catalyst was found to influence the reactivity significantly, albeit with slight impact on the enantioselectivity. The catalyst could be easily recovered and reused at least for ten times without obvious loss of enantioselectivity, albeit a slight drop in catalytic reactivity. Furthermore, a continuous flow reaction system using an activated mixture as stationary-phase catalyst for the asymmetric hydrogenation of dehydroamino acid was successfully developed and run continuously for a total of 144 h with >99% conversion and 96–97% enantioselectivity. Importantly, the total Rh leaching in the product solution is 1.7% of that in original heterogeneous catalyst.

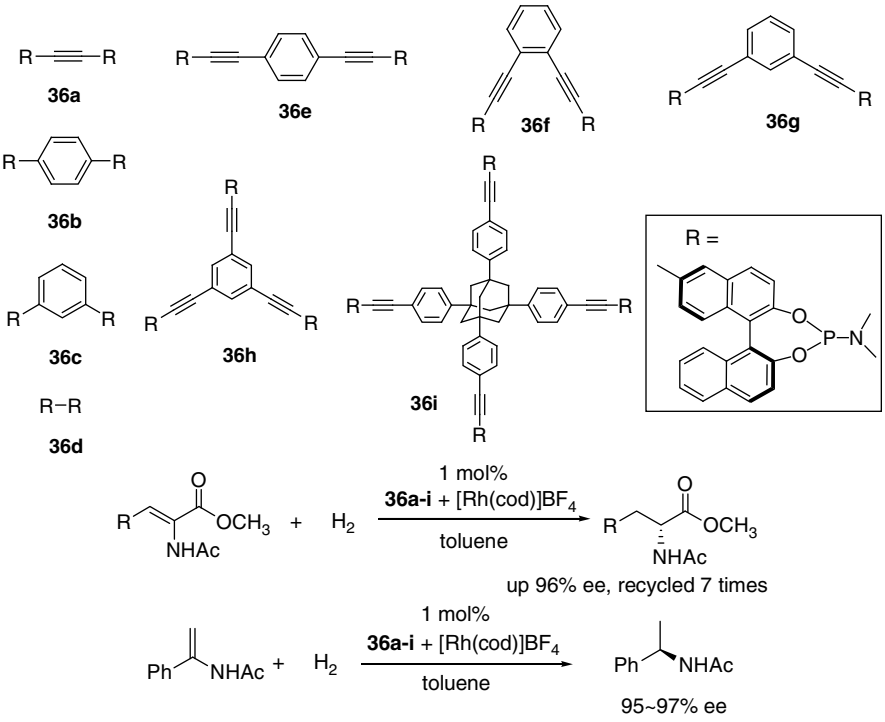


Fig. 27 Self-supported heterogeneous MonoPhos/Rh catalysts for the asymmetric hydrogenation of prochiral olefins

In order to facilitate the synthesis of self-supported chiral catalyst, the same group recently demonstrated that noncovalent interactions such as hydrogen bonding could be employed as an alternative way to synthesize the multitopic chiral ligand and further construct supramolecular metal–organic heterogeneous catalyst [121]. The well-known self-complementary hydrogen-bonding unit ureido-4[1*H*]-ureidopyrimidone (UP) was attached to the binaphthyl backbone of Feringa's MonoPhos, resulting in a new type of bis-MonoPhos ligand assembled by hydrogen bonding. Importantly, the hydrogen-bonding and ligand-to-metal coordination interactions were found to be orthogonal to each other. Therefore, treatment of the UP-modified ligand with [Rh(cod)]BF_4 resulted in the chiral supramolecular metal–organic polymer as a precipitate in toluene (Fig. 28). The obtained self-supported catalyst was demonstrated to be highly effective in the heterogeneous hydrogenation of dehydroamino acid and enamide derivatives with 91–96% ee, which were comparable to those obtained with the homogeneous counterpart. Notably, the catalyst was stable and could be recycled at least for ten times without leaching of toxic metal ions into the products although the recycled catalyst showed slightly reduced reactivity.

Most recently, Ding and coworkers further extended the noncovalent strategy to the facile generation of self-supported heterogeneous catalysts on the basis of orthogonal coordination of a bifunctional heteroditopic ligand with two different metal ions or both of which might be catalytically active, via sequential or one-pot reaction(s) [122]. Accordingly, a chiral rigid heteroditopic ligand **38** containing a 2,2′,6′,2″-terpyridine (tpy) and Feringa's MonoPhos [49] at its ends was designed

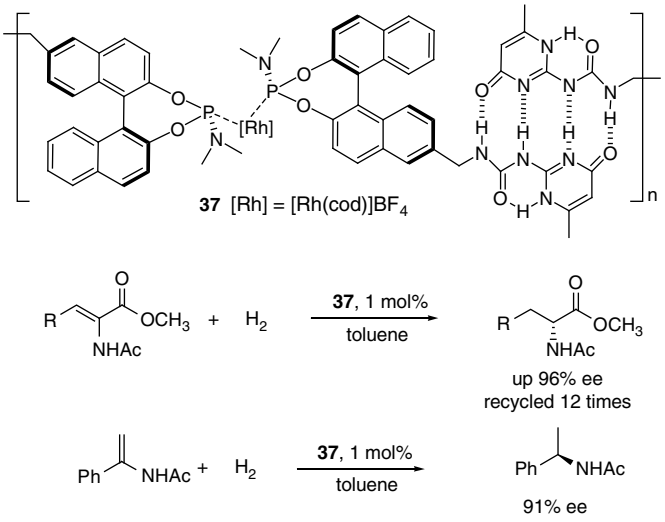


Fig. 28 Supramolecular self-supported heterogeneous MonoPhos/Rh catalysts for the asymmetric hydrogenation of prochiral olefins

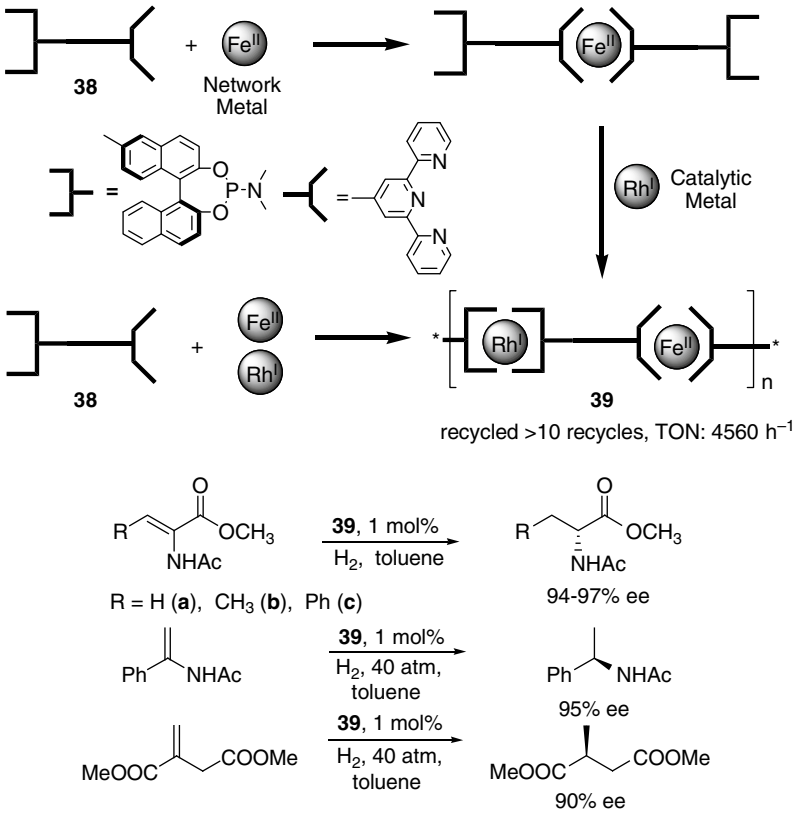


Fig. 29 Schematic representation for the synthesis of self-supported catalysts via orthogonal coordination of two different metal ions with a single ditopic ligand and their application in the asymmetric hydrogenation of prochiral olefins

and synthesized (Fig. 29). A new class of chiral bimetallic self-supported catalysts has been readily prepared by programmed assembly of **38** with Fe(II) and Rh(I) ions, respectively. The resulting heterogeneous self-supported catalyst has been successfully applied in the asymmetric hydrogenation of α-dehydroamino acid, enamide and itaconic acid derivatives with very high activity (TOF up to 4,560 h^{-1}) and excellent enantioselectivity (90–97% ee). It should be noted that the heterogeneous catalyst showed comparable activity to the homogeneous MonoPhos/Rh(I) counterpart at either ambient or higher pressure (5 atm and 40 atm) hydrogen. The assembled catalysts can be easily recovered by simple filtration and reused for more than ten times without significant loss of reactivity or enantioselectivity. The leach of metal ion in the product solution is almost negligible. It is obvious that this strategy has significantly simplified the complexity associated with the catalyst synthesis and might stimulate future research on the facile and rapid creation of chiral catalyst systems on the basis of orthogonal supramolecular interactions.

The self-supporting strategy for chiral catalyst immobilization has been also extended to the preparation of chiral heterogeneous catalyst bearing two different types of multi-topic ligands coordinated to the metal center [123]. Both bridged BINAP and diamine ligands bearing different linkers were designed and synthesized. A programmed assembly of the resulting two chiral ditopic bridging ligands with $[RuCl_2(C_6H_6)]_2$ selectively led to the formation of the self-supported catalysts, which proved to be noncrystalline solids and insoluble in isopropanol (Fig. 30). The immobilized catalysts were tested in the asymmetric hydrogenation of simple aromatic ketones, affording the corresponding chiral alcohols with the enantioselectivities (94–98% ee) comparable to those obtained with homogeneous monomeric catalyst under similar conditions. Notably, when the catalyst loading was decreased to the level of 0.01 mol%, similar enantioselectivity and reactivity were also observed. In addition, less than 0.1 ppm ruthenium leaching into the organic phase was observed, and the catalyst could be recycled at least for seven times without obvious loss of enantioselectivity and reactivity.

In their continuing study, the same group further developed a new type of self-supported Noyori-type catalysts by spontaneous hetero-coordination of an achiral bridged diphosphine and chiral bridged diamine ligands with Ru(II) metal ions according to the programmed assembly strategy [124]. The immobilized catalyst

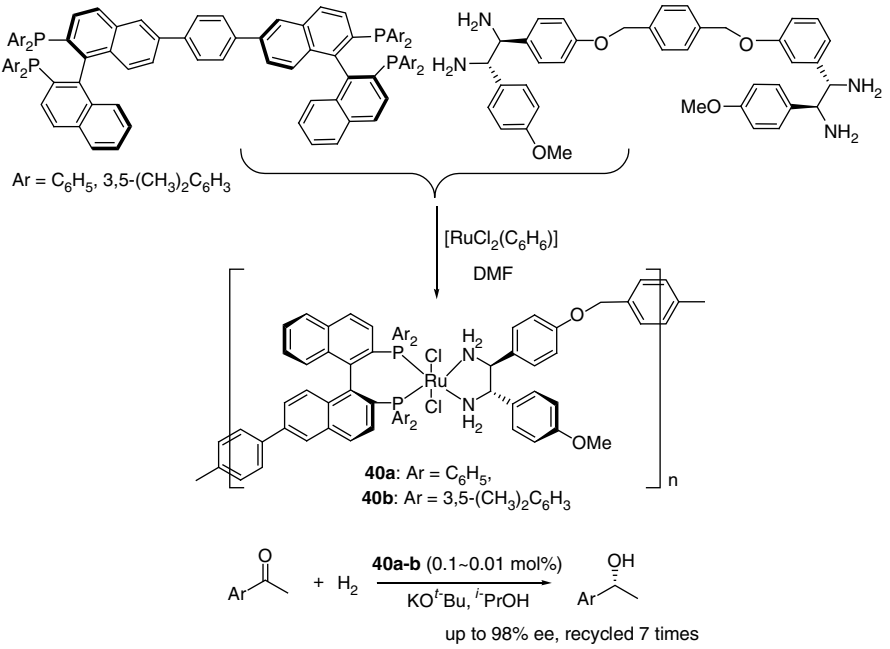


Fig. 30 Synthesis of self-supported heterogeneous Noyori's catalyst via programmed assembly for the asymmetric hydrogenation of prochiral ketones

demonstrates good enantioselectivity and activity in the heterogeneous catalysis of the hydrogenation of aromatic ketones and could be easily recovered and reused for four times with similar catalytic performance.

5 Conclusion and Perspectives

To overcome the drawbacks of classical immobilized chiral catalysts, i.e., unclear structure and low catalytic efficiency, new immobilization strategies have been developed over the past few years. As described in this chapter, immobilization of a chiral catalyst at the core of a dendrimer, into the nanopores of mesoporous materials, or via a modular assembly of chiral multitopic ligands with catalytic metal ions (self-supporting method) represent very attractive examples reported recently in this field. All the three-type recyclable immobilized chiral catalysts were utilized to catalyze several types of asymmetric organic reactions with high efficiencies and enantioselectivities comparable or even superior to those of their corresponding homogeneous counterparts. In contrast to most of the classical heterogeneous chiral catalysts, these catalysts possess well-defined and tunable structures, and their catalytic performance thus can be easily fine-tuned.

Chiral dendrimer catalysts behave like homogeneous catalysts during the reaction and can be easily separated upon completion of the reaction via solvent precipitation or nanofiltration. Incorporation of a chiral catalyst at the core of a dendrimer provides a unique microenvironment around the catalytically active metal center. The catalytic activity and enantioselectivity of the supported catalysts can be fine-tuned through systematical adjusting of the structure, size, shape, and peripheral functional groups of the dendrimer. In some particular cases, interesting dendrimer effects have been observed, including increased/decreased catalytic activity [42, 48], enantioselectivity [51], and stability [50, 72]. However, the nature of the observed dendrimer effects remains to be elucidated. In addition, finding more general and simple synthetic method for chiral dendritic catalysts is still an important challenge in this field.

The nanopore of mesoporous silicas immobilized with chiral catalysts can act as a nanoreactor for heterogeneous asymmetric catalysis. The microenvironment of the nanoreactor can be finely modified to meet the requirement of a given asymmetric reaction, such as the size of the nanopore, the hydrophilicity/hydrophobicity of the surface and electrostatic properties through direct condensation or postmodification. Particularly, the chiral catalyst encapsulated in the rigid nanopore of mesoporous materials can remain as free as the catalyst in solution since there is not a strong interaction between the metal complex and the support. In some cases, the confinement and cooperative activation effects of the nanoreactors result in much higher enantioselectivities and catalytic activities for the asymmetric catalysis (e.g., the Co(salen)-catalyzed HRK reaction of terminal epoxides [93]) than those of homogeneous catalyst. However, the nature of the confinement effect on the catalytic performance remains to be extensively investigated in the future.

The self-supported chiral catalysts through self-assembly of chiral multitopic ligands and metal ions without the use of any support have been demonstrated extremely successfully in heterogeneous asymmetric catalysis. In contrast to most other known immobilized catalysts, these catalysts possess a high density of catalytically active metal centers and asymmetric moieties, and can be used to immobilize multicomponent chiral complexes where synergistic actions are important for the catalysis. Both the catalytic activity and the enantioselectivity can be fine-tuned by the pore matrices and chemical functionality of the cavities through metal and ligand diversity. In some cases, superior catalytic performance with the self-supported catalyst was observed in comparison with the situation using homogeneous counterpart [119]. Particularly, the development of continuous-flow asymmetric catalytic reaction systems has proven advantageous for the practical application of self-supported chiral catalysts due to high stability and high total TON [120]. Although the amorphous nature of the self-supported catalyst does not deteriorate their catalytic performance, the development of structurally well-defined catalytic systems is highly desirable for mechanistic and structure–property relationship studies. In addition, the development of new analytical techniques for the characterization of the microstructure of the self-supported catalyst remains a challenge [19, 105].

In conclusion, all the three types of immobilized chiral catalysts offer a potential combination of the advantages of homogeneous and heterogeneous asymmetric catalysis, and will continue to attract increasing research interest from both academia and industry, and chemists from China will make more significant contributions to this stimulating research field.

Acknowledgments We are grateful for the financial support from the National Natural Science Foundation of China (20973178, 20821002, 20632060), National Basic Research Program of China (No. 2010CB833300 and 2009ZX09501-017), and Chinese Academy of Sciences.

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Transition Metal-Catalyzed Asymmetric Allylation

Chang-Hua Ding and Xue-Long Hou

Abstract Transition metal-catalyzed asymmetric allylation is a powerful tool for the asymmetric formation of C–C and C–X bond. This review provides a comprehensive overview of contribution made by Chinese organic chemists in these fields.

Keywords Allylation • Asymmetric catalysis • Chiral ligand • Transition metal

Contents

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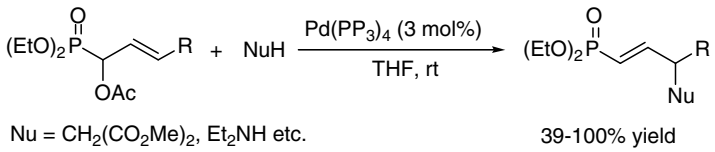
1 Introduction

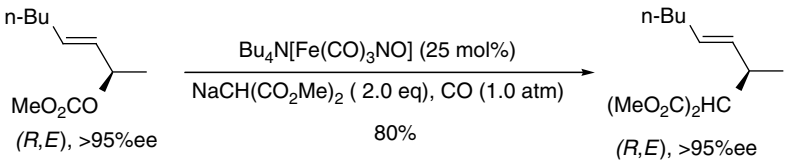
Transition metal-catalyzed asymmetric allylation usually includes the allylic substitution reactions of allyl reagents with nucleophiles catalyzed by chiral transition metal complexes and the addition reaction of carbonyl compounds with allyl reagents catalyzed by chiral Lewis acids [1–5]. Many transition metals have been applied in these reactions, which have become one of the most powerful tools for the enantioselective construction of C–C and C–X bond, affording synthetically valuable enantiopure materials. This review mainly focuses on the transition metal-catalyzed asymmetric allylic substitution reactions studied by Chinese chemists, especially on the palladium (Pd)-catalyzed ones, and the Lewis acids catalyzed addition reaction of allyl reagents to carbonyls will be discussed briefly only.

As one of the most useful reactions in asymmetric catalysis, Pd-catalyzed asymmetric allylic substitution reaction has been extensively studied. A variety of allyl reagents and nucleophiles have been successfully used. Among them, benchmark substrate, that is the 1,3-diphenylallyl acetate, has been used most often though the products from the other allyl substrates, including monosubstituted and cyclic allyl substrates are more useful in organic synthesis. The common nucleophiles include "soft" carbanion and N-, S-nucleophiles; however, the use of "hard" carbanion and O-nucleophiles has also been attracting much attention recently. Furthermore, the development of new ligands with highly catalytic activity for transition metal-catalyzed asymmetric allylation is also important. The Chinese chemists have focused on the research of all of these topics.

Transition metal-catalyzed allylation in China may be date back to 1980s. Lu's group developed a series of the Pd- and Ni-catalyzed allylic substitution reactions of various nucleophiles with a variety of allyl reagents [6–17], for example, the treatment of acetoxy allylic phosphonates with Pd(0) affording allylic phosphonate intermediate, which reacted readily with various soft carbon- and nitrogen-nucleophiles to provide corresponding allylic substituted products in 39–100% yield (Scheme 1). Xu et al. found that $Bu_4N[Fe(CO)_3NO]$ is an efficient catalyst for the alkylation reaction of allylic carbonate with malonate anion [18, 19]. In the reaction of optically active allylic carbonates with malonate in the presence of iron catalyst, nucleophile predominantly attacked the carbon atom where the leaving group was attached, affording prevailing regioisomer with high level of retention of the configuration (Scheme 2). In 1998, Dai et al. reported the design and synthesis of



Scheme 1 Pd-catalyzed allylic substitution of acetoxy allylic phosphonates



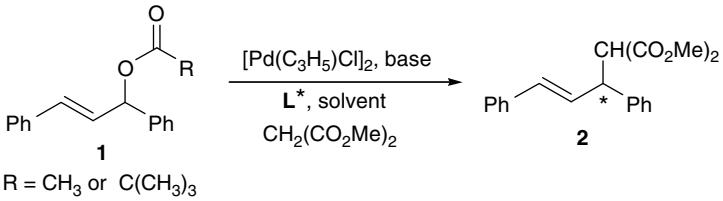
Scheme 2 Fe-catalyzed alkylation of allylic carbonate with malonate anion

several chiral ligands with ferrocene scaffold and applied them in Pd-catalyzed asymmetric allylic alkylation (AAA) reaction [20]. Since then, the field has received continuous attention from Chinese organic chemists.

2 Reactions of Symmetric 1,3-Diphenyl Allyl Acetate

2.1 With "Soft" Carbanions

The reaction of 1,3-diphenylallyl acetate with malonate has been considered as a model reaction to study the efficiency of the ligands. A variety of different types of chiral ligands with different coordinating atoms and various frameworks were created and applied in the reaction [1, 2]. In the subsection, we will discuss the application of chiral ligands developed by the Chinese organic chemists in the reaction shown in Scheme 3.

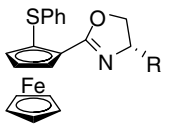


Scheme 3 Pd-catalyzed asymmetric allylic substitution with malonate

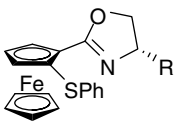
The fascinating structural properties of ferrocene and its derivatives have been the subject of increasing interest in many fields [21, 22]. Because of its adequate rigidity, steric bulkiness, and easily derivatizing as well as the stereo-electronic property and stability, ferrocene has been applied as an effective scaffold for chiral ligands. In addition, planar chirality is introduced when there are two substituents on the same ring in ferrocene. However, the understanding of the role of planar chirality had been overlooked for a long time. Some examples showed that the planar chirality has significant impact on the enantioselectivity [23–27], while in other examples it was not so apparent [28–30]. Dai and Hou designed and synthesized *S,N*- and *Se,N*-bidentate ligands and examined the role of the planar chirality

in Pd-catalyzed allylic alkylation. The ligands **3**–**6** afforded the product with similar enantioselectivities and the same absolute configuration even with different planar chirality (Fig. 1), which means that the asymmetric induction and the configuration of product were governed mainly by the central chirality of the ligands. They also synthesized *P*,*N*-bidentate ligands **7** and **8** and similar results were obtained. However, when ligand **9** with only planar chirality was applied, 54 and 76.6% ee were observed and the configuration of the products was switched to *R*. Similarly, product in 72% ee was provided when *S,N*-bidentate ligand **10c** was used. These results revealed that in 1,2-disubstituted ferrocenes, the central chirality is the main governing factor while the planar chirality should not be overlooked, and the match of planar and central chiralities is also important [20, 31].

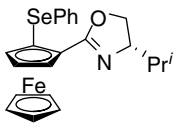
Interestingly, when the ruthenocene ligands **11** and **12** with same central chirality and opposite planar chirality, synthesized by Zhang, were applied, different results were afforded (Fig. 1). Remarkably, different enantioselectivity was observed



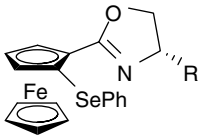
3a, R = *i*-Pr: 90.4% ee (*S*)
3b, R = *t*- Bu: 89.8% ee (*S*)



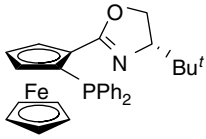
4a, R = *i*-Pr: 89.9% ee (*S*)
4b, R = *t*-Bu: 98% ee (*S*)



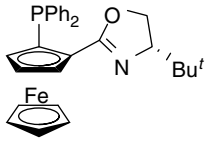
5a, R =*i*-Pr: 92.2% ee (*S*)
5b, R =*t*-Bu: 89.8% ee (*S*)



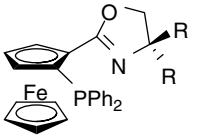
6a, R = *i*-Pr; 89.9% ee (*S*)
6b, R = *t*- Bu; 98.3% ee (*S*)



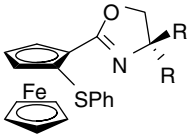
7, 94.6% ee (S)



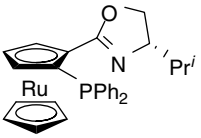
8, 92.3% ee (S)



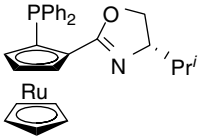
9a, R = H;76.6%ee(*R*)
9b, R = Me;54.0%ee(*R*)



10a, R = H; 8.5% ee (*R*)
10b, R = Me; 12% ee (*R*)
10c, R = Bn; 71.8% ee (*S*)



11, 87% ee (S)

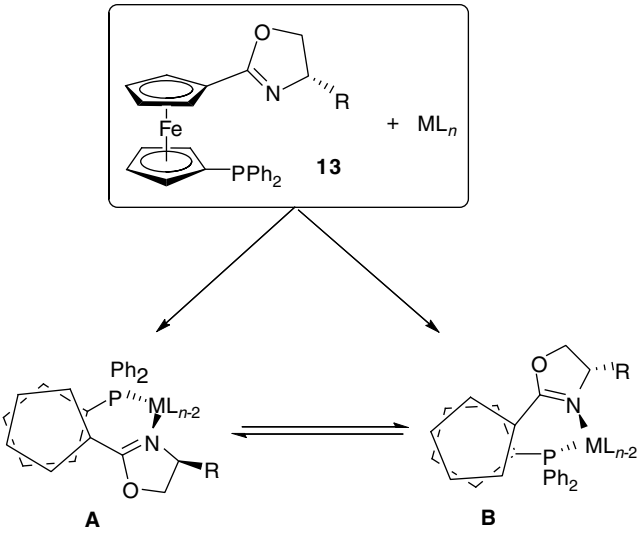


12, 59% ee (S)

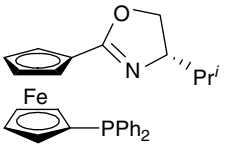
Fig. 1 Ferrocene and ruthenocene ligands

with two ligands, which demonstrated that the planar chirality with different structure of ligands has different influence on the enantioselectivity and catalytic activity [32].

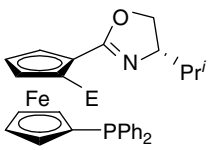
Ikeda revealed that coordination of 1,1′-disubstituted ferrocenyl ligand **13** with a metal gave rise to the two rotamers, **A** and **B**, and thus produced a new axial chirality (Scheme 4) [33]. Noting that three chiral elements (central, axial, and planar chirality) will be in one catalyst molecule after the introduction of planar chirality to ligand **13** by coordination with a metal, which should be interesting in understanding the role of planar chirality in this particular 1,1′-system and in exploring the applications of this three-chiral-element catalyst in asymmetric reactions, ligand **14** and **15** with noncoordinating group at the ortho position of the oxazoline ring were synthesized (Fig. 2). Ligand **13** gave the *S*-product with 90.8% ee configuration, while **14** afforded the *R*-product in 69.7% ee. However, if ligand **15** was used, the ee value increased dramatically to 98.5% ee forming *S*-product. Moreover, as high as 79.6–84% ee were afforded if the ligand **16** and **17** with only planar chirality were used (Fig. 2). In addition, the configuration of product was changed when the configuration of ligand was switched from *R* to *S*. These results clearly demonstrated that in this 1,1′-system, planar chirality not only determined the ee value but also controlled the absolute configuration. X-ray crystallographic structures as well as ^{1}H NMR and ^{31}P NMR spectra of η^3-diphenylallyl Pd complex of three 1,1′-*P*,*N* ferrocene ligands led to the conclusion that planar chirality influences the stereochemical outcome by changing or even inverting the ratio of the two rotamers because of the steric interaction between the third introduced noncoordinating group and the coordination site [34, 35]. Hou and Dai developed a chiral diphosphine-oxazoline ferrocenyl ligand **18** and successfully used it in the asymmetric allylic substituted reaction (Fig. 2). The enantioselectivity of the reaction was affected by the electronic



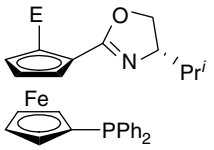
Scheme 4 Coordination of 1,1'-disubstituted ferrocenyl ligand with metal



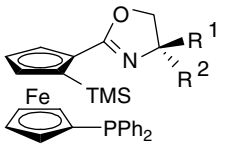
13, 90.8% ee (*S*)



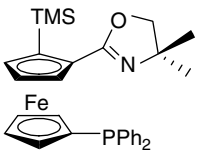
14a, E = Me, 34.2% ee (*R*)
14b, E = TMS, 69.7% ee (*R*)
14c, E = $SnBu_3$, 83.3% ee (*R*)



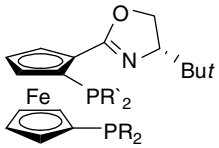
15a, E = Me, 98.5% ee (*S*)
15b, E = TMS, 98.6% ee (*S*)



16a, $R^1 = R^2 = H$, 79.6% ee (*S*)
16b, $R^1 = R^2 = Me$, 84.1% ee (*S*)

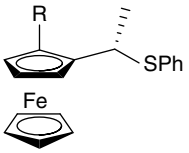


17, 81.9% ee (*R*)

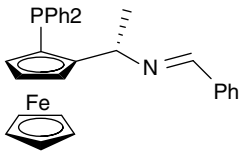


R = 4-MeO-C_6H_4
R` = 3,5-$(CF_3)_2$-C_6H_3

18, 91.5% ee (*S*)



19a, R = PPh_2, 93.8%ee(*S*)
19b, R = SPh, 75.3%ee(*R*)



20a, R = PPh_2, 71%ee(*R*)
20b, R = SPh, 86.3%ee(*R*)

Fig. 2 Ferrocene ligands

nature of the ligands. When the electronic effect was coincident with the steric effect of ligand, a higher ee (91.5%) value was observed [36].

The *trans* effect of a ligand is a kinetic phenomenon that partially describes the transition state in a substitution reaction [37–40]. For heterobidentate ligands used in catalytic allylic substitution reactions, the *trans* effects of the donor atoms can be transmitted to the allylic substrate through the metal. In this way, the reactivity and selectivity of the reaction may be finely tuned. Hou and Dai synthesized a series of planar chiral P,S-, P,(C=N)–, and S,(C=N)-bidentate ferrocenyl ligands **19** and **20** with the same central and planar chiralities (Fig. 2). On the basis of the

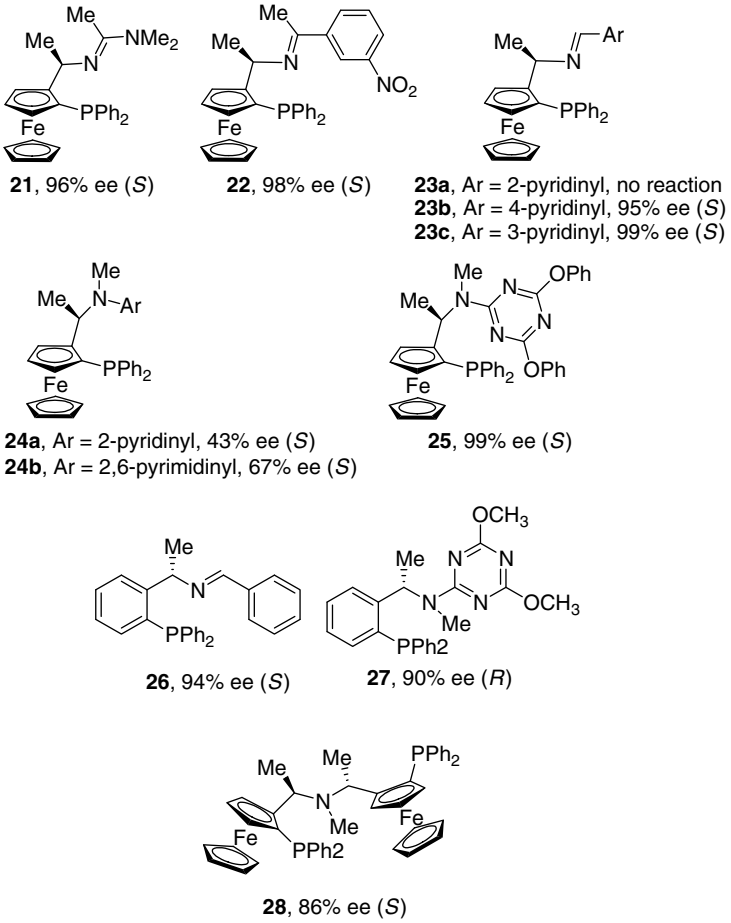


Fig. 3 Chiral ligands developed by Zheng et al.

reaction results and the study of X-ray diffraction as well as ^{1}H and ^{13}C NMR spectra of their complexes, the sequence of the *trans* effect was established as C=N>P>S in the benchmark reaction shown in Scheme 3, which was supported by molecular modeling at the PM3 level [41].

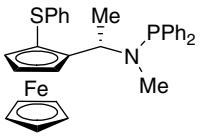
Phosphine-imines as an important class of *P*,*N* ligands are easily prepared and their electronic and steric properties can be readily modified. Zheng developed a series of chiral phosphine-imine ligands **21**–**25** with central and planar chiralities based on the ferrocene framework through different strategy (Fig. 3) [42–47]. Ligands **21** and **22** afforded the *S*-product in more than 95% ee. Pyridinyl imines **23** with an additional N donor at different position in the pyridine moiety exhibited different activity. The Pd-complex derived from the ligand **23a** with 2-pyridine showed no activity, while ligand **23c** with 3-pyridine turned out to be efficient, giving the alkylation product with an ee value of 99%.

These intriguing results showed that the presence of an additional N atom in an appropriate position of heterocyclic ring could dramatically improve the enantioselectivity. Following the observations, Zheng synthesized ligands **24** and **25** and discovered that the enantioselectivity and reactivity of the reaction are significantly increased by raising the number of N atom in heterocycle of the ligand, as high as 99% ee was obtained if ligand **25** with triazine moiety was used (Fig. 3). Later, the Zheng group synthesized two chiral phosphine-imine ligands **26** and **27** by simplifying the structure of ligands **22** and **25**. Although the ligands were slightly less effective compared to ligands **22** and **25**, still more than 90% ee was achieved [48, 49]. Zheng et al. also prepared a chiral bis(ferrocenyl) P_2N ligand **28** with C_2-symmetry through a four-step procedure from (*R*)-*N*,*N*-dimethyl-1-ferrocenylethylamine, affording the *S*-product in 86% ee [50].

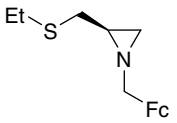
Chiral *P*,*S* ligands are unique as a class of ligands. The coordination of the sulfur donor to the metal center would create a new chiral center at sulfur, near the reaction site, in addition to other stereogenic carbon centers. Chan et al. developed a two ferrocenyl *P*,*S* ligand **29** and **30** (Fig. 4), which were proved to be highly effective. The substituents of the thioether moiety were crucial for asymmetric induction. Ligand **30** is air stable and can be handled and stored without protection from air [51, 52]. Wang synthesized enantiopure *N*-ferrocenylmethyl aziridine sulfide ligand **31** (Fig. 4), affording the *S*-product in 91% ee. They demonstrated that the three- and four-membered heterocycle-based backbone was a good chiral unit for the reaction. Moreover, it was discovered that the replacement of the phenyl group on the nitrogen atom of heterocycle by a ferrocenyl unit led to a dramatic improvement in the enantioselectivity. The origin of enantioselectivity for heterobidentate sulfide-tertiary amine ligands was rationalized by the X-ray diffraction and the solution NMR studies of the palladium-π-complex intermediate. They also demonstrated that the sulfur atom was a better acceptor than the nitrogen atom for heterobidentate sulfide-tertiary amine ligands, and the steric as well as electronic properties of the palladium allylic complexes are crucial for the enantioselectivity [53].

Chan et al. reported the use of phosphinous amide ligands **32**, and revealed that the more hindered ligand **32b** gave the less satisfactory result in comparison with its less hindered analog **32a** (Fig. 4). Thus, it demonstrated a balanced rigidity and steric hindrance of the ligand is important for the best results [54].

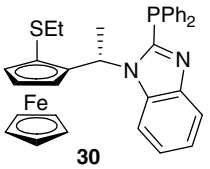
[2.2]Paracyclophane features rigid, chemically stable, and undergoes racemization only at relatively high temperature. To develop [2.2]paracyclophanes as the skeleton of chiral ligand in asymmetric catalysis, Hou designed various *N*,*S*- and *N*, *Se*-ligands with both planar and central chirality based on the [2.2]paracyclophane backbone. They observed that the benzylic substituted ligands provided far better enantioselectivity and the reactivity comparing to the corresponding benzene substituted ones (ligand **34** vs. ligand **33**) [55] (Fig. 5). Simplifying the structure of **34**, ligand **35** was designed and synthesized, which showed high catalytic activity with similar enantioselecting as compared to its benzene analog [56, 57]. In addition, other benzylic substituted ligands were also synthesized. The product formed in 96.6% ee and 86% yield when the reaction proceeded in 2 h with 2.5 mol% of $[Pd(C_3H_5)Cl]_2$ and 6 mol% of ligand **36**, while 94.4% ee and 88% yield were also



29a, 93.5% ee (*R*)

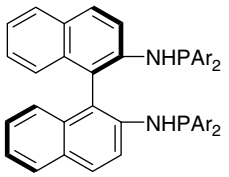


31, 91% ee (*S*)



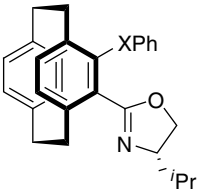
30

Nu = $CH_2(CO_2Me)_2$, 95% ee (*S*)
$BnCH(CO_2Et)_2$, 95% ee
$CHONH(CO_2Et)_2$, 96% ee
$MeCH(COMe)_2$, 96% ee

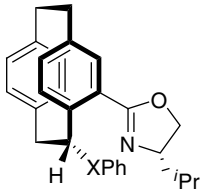


32a, Ar = Ph, 75% ee (*S*)
32b, Ar = 3,5-$(Me)_2C_6H_3$, 46% ee (*R*)

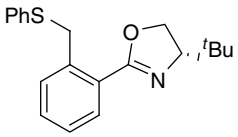
Fig. 4 Chiral ligands from the Chan and Wang groups



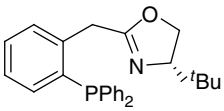
33a, X = S, 63% ee (*S*)
33b, X = Se, 73% ee (*S*)



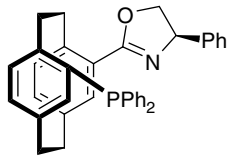
34a, X = S, 94% ee (*S*)
34b, X = Se, 93% ee (*S*)



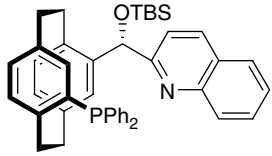
35, 0.75 h, 93% ee (*S*)



36, 96.6% ee



37, 73% ee (*R*)



38, 98% ee (*R*)

Fig. 5 Chiral ligands developed by Hou and Jiang groups

obtained when the amount of $[Pd(C_3H_5)Cl]_2$ and **36** decreased to 0.25 and 0.6 mol%, respectively, in 4 h [58]. These results clearly showed that the ligands with the substituent at benzylic position are more effective in terms of catalytic efficiency. In addition to the benzylic substituted ligands, *pseudo*-geminally disubstituted planar chiral *P*,*N*-[2.2]paracyclophane ligand **37** was also synthesized and applied, providing the *R*-product in moderate enantioselectivity (73% ee) [59].

Jiang et al. designed and synthesized another type of [2.2]Paracyclophane-derived *P*,*N*-ligand **38** featuring the structural flexibility brought by the long side chain and the rigidity originating from the paracyclophane skeleton, showing super

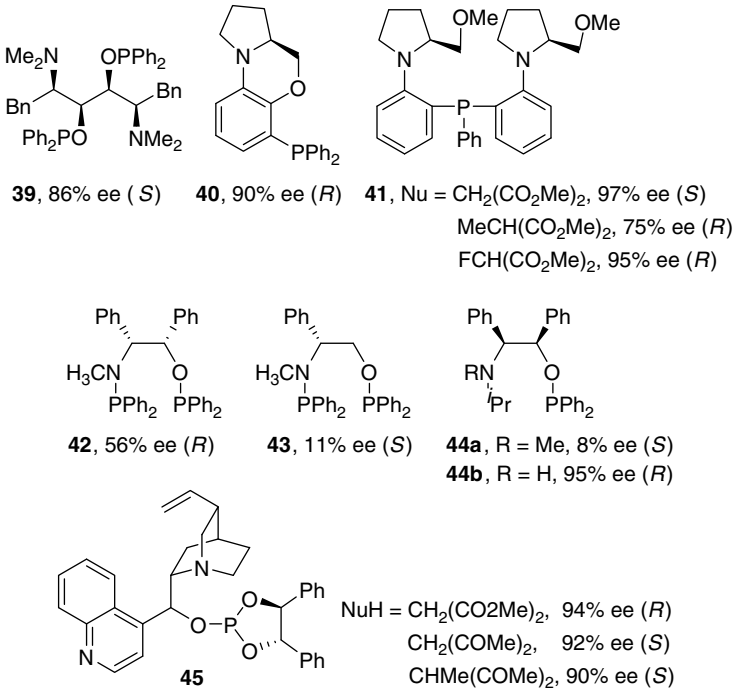
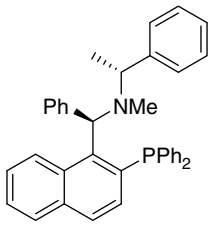


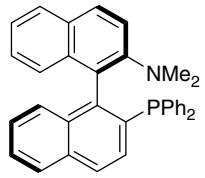
Fig. 6 Chiral ligands developed by Jiang and Mi groups

abilities of asymmetry induction (98% ee) (Fig. 5) [60]. This group also reported the synthesis and applications of several chiral amino alcohol derived ligands, such as C_2-symmetric bisphosphinites **39** [61], *P*,*O*-ligand **40** [62], and *N*,*P*,*N*-ligand **41** [63], providing good to excellent enantioselectivity (Fig. 6).Several other amino-alcohol derived ligands **42**–**44** were developed by Mi et al. (Fig. 6). Chiral amino-phosphinite ligand **44** was designed based on the findings that the stereogenic center of the carbon bonded to O-PPh_2 is important in the ligand (ligand **43** vs. ligand **42**) and represented a class of easily prepared and efficient ligand. The results showed that *N*-monosubstituted amino phosphinite **44b** (95% ee) had much better asymmetric induction properties than the *N*,*N*-disubstituted one **44a** (8% ee) [64, 65]. Another easily available bidentate chiral ligand **45** was based on cinchona alkaloid and was used as an efficient ligand with three soft nucleophiles such as $CH_2(CO_2Me)_2$, $CH_2(COMe)_2$, and $CHMe(COMe)_2$ to produce products in greater than 90% ee [66].

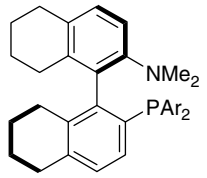
Ding et al. designed several types of chiral ligand for the Pd-catalyzed AAA reaction (Fig. 7). The chiral amino phosphine ligand **46** derived from an amino naphthol gave moderate asymmetric induction with 72% ee of the *S*-product being obtained [67]. Interestingly, chiral aminophosphine ligand **48** with H_8-MAP provided much higher enantioselectivity (82.5%) than the parent MAP ligand **47**, which affording the *S*-product product in 67.5% ee. The dramatic effect of the binaphthyl backbone



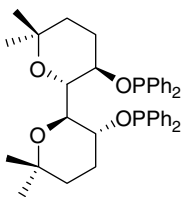
46, 72% ee (*S*)



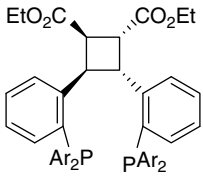
47, 67.5% ee (*S*)



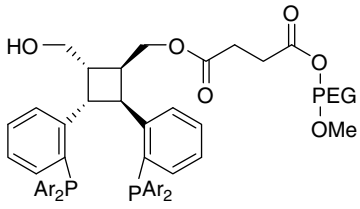
48a, Ar = Ph, 82.5% ee (*S*)
48b, Ar = 3,5-$(Me)_2C_6H_3$, 90.9% ee (*S*)



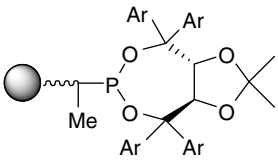
49, 91% ee (*S*)



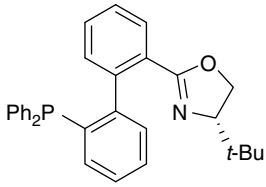
Ar = 4-$(Me)_3CC_6H_4$
50a, 98.9% ee (*S*)



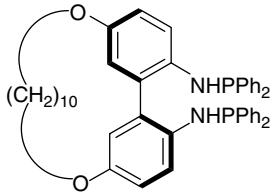
Ar = 4-$(Me)_3CC_6H_4$
50b, 97.2% ee (*S*)



Ar = 3,5-Me_2-C_6H_3
51, 64.2% ee (*S*)



52, 90% ee (*S*)



53, 58% ee (*S*)

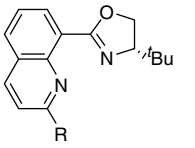
Fig. 7 Chiral ligands developed by Ding and other groups

on the enantioselectivity of the reaction can be attributed to the change of the bite angle in H_8-MAPs/Pd complexes after partial reduction of binaphthyl backbone [68, 69]. Bisphosphinite ligand **49** with C_2-symmetry from the easily available natural product D-mannitol was developed to afford the *S*-product with 91% ee [70]. C_2-Symmetric bisphosphine ligand **50a** with cyclobutane ring is even better affording *S*-product in excellent enantioselectivity (98.9% ee) [71, 72]. The ligand **50** is particularly interesting, because the MeO–PEG supported ligand **50b** has a synergistic effect on the enantioselectivity as compared with its nonsupported precursor, affording the corresponding allylation product with excellent enantioselectivities (97.2% ee). Moreover, the Pd complex of **50b** could be easily recovered and recycled several times without significant loss of enantioselectivity and activity [72].

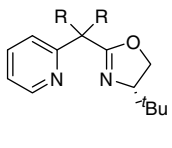
Jiang et al. reported the supported bulky monodentate phosphoramidite ligand **51** based on TADDOL backbone afforded the chiral product with *ee* up to 65% (Fig. 7); moreover, this catalyst could be recycled for three times without substantial decrease of the conversion and ee [73].

Zhang et al. reported the synthesis and application of chiral phosphine-oxazoline ligand **52** with an axial-unfixed biphenyl backbone (Fig. 7). The ligand exists as a mixture of two diastereomers in equilibrium in solution. Upon coordinated to Pd metal, however, only one of the two possible diastereomeric complexes with different axial chirality was formed. These chiral ligands afforded the *S*-product with 90% ee obtained [74, 75]. Zhang also developed an atropisomeric framework, in which the biphenyl has only two coordinating groups next to the axis, and the axial chirality of the ligand can be retained by steric hindrance of two bulky coordinating groups and macro-ring strain produced from 5,5′-linkage of biphenyls even without 6,6′-substituents. The ligand **53** with 5,5′-linked biphenyl bisaminophosphine showed such characters and demonstrated moderate asymmetric induction [76–78].

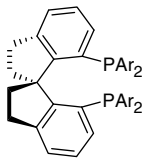
Zhou et al. prepared chiral 2-methyl-8-quinolinyloxazoline **54**, which affording the *R*-product in 78% ee (Fig. 8). The substituent on position 2 of the quinoline ring



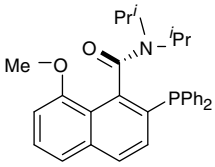
54a, R = H, 77% ee (*S*)
54b, R = Me, 78% ee (*R*)



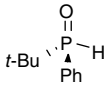
55a, R = H, 20% ee (*S*)
55b, R = Me, 88% ee (*S*)



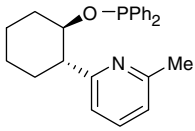
56, Ar = 4-MeO-3,5-$(Me)_2C_6H_2$
NuH = $CH_2(CO_2Me)_2$, 99% ee (*S*)
$CH_3CH(CO_2Me)_2$, 97% ee (*S*)
$CH_2(CN)_2$, 56% ee (*S*)
$CH_3COCH(CH_3)CO_2Et$ (*S*)
91&97% ee (37% de).



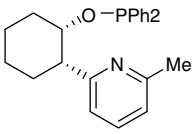
57, 94.7% ee (*S*)



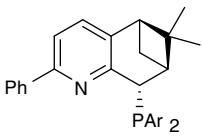
(R_p)-**58**, 79.9% ee (*S*)



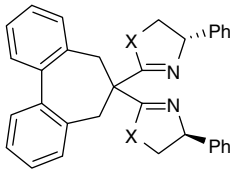
59, 84% ee (*R*)



60 , 95% ee (*R*)



61 , Ar = 2-$MeOC_6H_4$
NuH = $CH_2(CO_2Me)_2$, 92% ee (*R*)
$CH_3CH(CO_2Me)_2$, 95% ee (*R*)
$CNCH_2CN$, 64% ee (*R*)



62a, X = S, 16% ee (*R*)
62b, X = O, 87% ee (*S*)

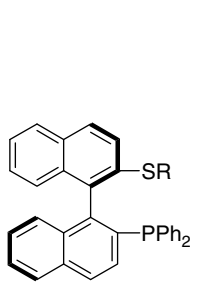
Fig. 8 Chiral ligands from the groups of Zhou and others; $CH_2(CO_2Me)_2$ used as the pronucleophile, unless otherwise stated

is crucial for stereocontrol altering the configuration of product. Ligands **54b** with same configuration as ligand **54a** yielded the alkylation product with *R* configuration, which is opposite to the configuration of the product given by ligand **54a**. The results could be explained by a late transition state [79]. This group also developed dimethyl pyridinylmethyl-oxazoline **55b** providing ee value of 88% (68% higher than unsubstituted analogs **55a**) [80]. The authors proposed that the "substituent effect" in the ligand **55b** might be attributed to the steric repulsion between R group and two heterocycles, so that the bite angle in the allylpalladium intermediates is smaller and the R group on the oxazoline ring may be closer to the reaction site, thus affecting both the equilibrium and the transition states efficiently. This type of "remote" substituent effect has been known in other asymmetric reactions such as copper-catalyzed Diels–Alder reactions [81, 82] and bisoxazoline mediated asymmetric addition of methyllithium to imines [83]. Chiral spiro diphosphine ligand **56** (SDP) developed by Zhou has shown excellent asymmetric induction power in several asymmetric reactions [84]. The evaluation of ligands indicated that the introduction of electron-donating or sterically hindered groups into the P-phenyls of SDP enhanced the enantioselectivity of the alkylation reaction. The highest enantioselectivity (99% ee) was obtained for several β-dicarbonyl nucleophiles with diethylzinc as a base (Fig. 8). An X-ray analysis of the crystal structure of the Pd-SDP complex showed that the SDP ligand created an effective asymmetric environment around the palladium, which explained the excellent selectivity [85]. The influence of electronic effect of ligands in Pd-catalyzed AAA reaction was also showed in ferrocene- and cyclophane-based ligands [41, 59].

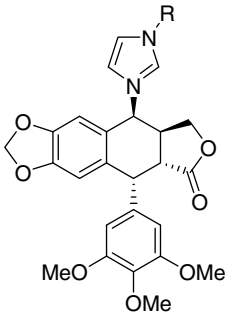
Oxygen atom is not a common coordinating atom of ligand used in the transition metal-catalyzed asymmetric catalytic reaction. However, several reports showed that excellent results could be obtained with the ligands bearing oxygen as the coordinating atom. Dai et al. prepared for the first time axially chiral nonbiaryl atropisomeric *P*,*O*-ligand **57** possessing an *N*,*N*-dialkyl-1-naphthamide skeleton and devoiding of central chirality (Fig. 8). The chiral axes in ligand **57** are quite stable at ambient temperature due to an electronic effect of the C8 oxygen with the amide carbonyl group. The ligand **57** provided the *S*-product in 94.7% ee [86]. They also developed *P*-chiral secondary phosphine oxide **58**, which is configurationally stable in the presence of metal ions both in solution and in the solid state. About 80% ee was achieved using this ligand [87].

Zhou et al. reported the synthesis of *P*,*N*-ligands **59** and **60** with a cyclohexane backbone and showed their efficiency in the reaction of Scheme 3, providing the *R*-product in 95% ee (Fig. 8). *trans*-**59** and *cis*-**60** ligands gave the products with the same absolute configuration indicating that the absolute configuration of the product was controlled by the configuration of the carbon bearing pyridine subunit in the ligand [88]. Li realized high enantioselectivity with several stablized nucleophiles in the presence of a chiral tetrahydroquinoline ligands **61** derived from chiral α-pinene, and up to 95% ee was observed [89]. Du used palladium complex of C_2-symmetric bis(oxazoline) ligand **62b** with dibenzo[*a*,*c*]cycloheptadiene as the substituent on the oxazoline ring to furnish good enantioselectivity (87% ee), while bis(thiazolines) ligand **62a** gave low enantioselectivity (16% ee) [90].

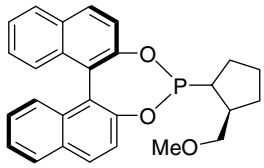
Shi found that the alkyl groups on sulfur atom of axially chiral *P*,*S*-ligands BINAPS **63** is decisive factor to control the absolute configuration in the Pd-catalyzed AAA reaction (Fig. 9). The reverse of configuration of the product was observed by changing the substituent from methyl group to isopropyl group on sulfur atom of the ligand (ligand **63a** vs. ligand **63b**). The X-ray crystallographic analysis and NMR spectroscopic indicated that the metallacycle is a pseudo-boat seven-membered arrangement, in which the alkyl group on the sulfur atom acts as a key factor in steric outcome of the reaction [91, 92]. Wang synthesized a chiral N-heterocyclic carbene (NHC) ligand precursor **64** and found that NHC-Pd-allyl complex afforded the *R*-product in 87% ee [93]. Chiral phosphoramidite ligand **65** with 1,1′-binaphthyl skeleton developed by Li furnished the *R*-products in good enantiomeric excess (up to 83% ee) [94]. Chiral *tert*-butanesulfinyl was also a useful chiral subunit in asymmetric catalysis, such as its incorporation into phosphine ligand **66**, giving the *S*-product in high enantiomeric excess (93% ee) [95]. Chiral C_2-symmetry quaterpyridine **67** reacted with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ to form a single-stranded helical binuclear palladium complex of formula $[Pd_2(\eta^3\text{-}C_3H_5)_2L]^{2+}$ with helical chirality selectively, which provided the *R*-product in 85% ee. This work represents the first application of a single-stranded helicate in asymmetric catalysis. The X-ray crystal structure and the CD analyses of the complexes confirmed the stability and integrity of the helicate both in solid and in solution states [96].



63a, R = Me, 96% ee (*S*)
63b, R = ^{i}Pr, 72% ee (*R*)

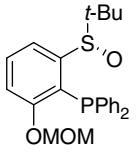


R = 2,4,6-$(Me)_3$-C_6H_2
64, 87% ee (*R*)

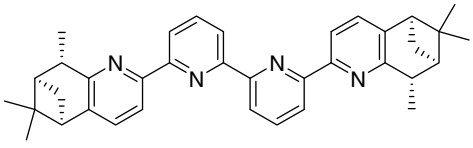


65

Nu: $CH_2(CO_2Me)_2$, 79% ee (*R*)
$CH_2(CO_2Et)_2$, 74% ee (*R*)
$CH_3CH(CO_2Me)_2$, 70% ee (*R*)
$CH_3CH(CO_2Et)_2$, 80% ee (*R*)
$CH_2(CN)_2$, 83% ee (*R*)



66, 93% (*S*)

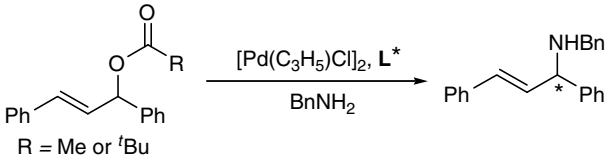


67, 85% ee (*R*)

Fig. 9 Chiral ligands used for the reaction of Scheme 3; $CH_2(CO_2Me)_2$ used as the pronucleophile, unless otherwise stated

2.2 With N-Nucleophile

In this subsection, we will discuss the Pd-catalyzed allylic amination reaction of 1,3-diphenyl allyl acetate with benzylamine (Scheme 5) in the presence of various chiral ligands developed by Chinese organic chemists. C_2-symmetric bisphosphine ligand **50c** developed by Ding et al. gave the *R*-product in 97.5% ee [71] (Fig. 10). Chiral *tert*-butanesulfinylphosphine ligand **66** was evaluated in the Pd-catalyzed amination of 1,3-diphenylallyl acetate with various amine such as benzylamine, morpholine, pyrrolidine, and dibenzylamine up to 76% ee was obtained [95]. Ligand (*R*, *R*, S_p)-**68** was found to be a better ligand containing matched chiralities (central chirality and planar chirality) and showed a higher enantioselectivity than ligand (*S*, *S*, S_p)-**68** [97]. The ferrocene-based chiral phosphine-heterocycle ligand **25** was also successfully applied to the amination reaction. A clear trend is that the enantioselectivity and reactivity would be significantly improved by increasing the number of heterocyclic N atoms in these *P*,*N* ligands, and the most efficient ones are those bearing a triazine moiety with three heterocyclic N atoms with 94% ee [47]. Zhang's group achieved 99% ee using their planar chiral ruthenocene **69a** [98, 99].



Scheme 5 Pd-catalyzed reaction of 1,3-diphenylallyl acetate with benzylamine

Planar chiral *P*,*N*-ligands **7**–**9**, **14b** and **15a** were also subjected in asymmetric amination reaction of Scheme 5 to examine the role of planar chirality (Fig. 10). With 1,2-*P*,*N*-ligand **8**, 97% ee was realized, while 96% ee was obtained with 1,1′-*P*,*N*-ferrocene ligand **15a**. High enantioselectivity was achieved even with the ligands **16** and **17** with planar chirality only, and the configuration of the product depends on the configuration of planar chirality of the ligands [31, 34, 35].

Ding et al. developed the Pd-catalyzed asymmetric allylic amination using sodium *N*,*N*-diformylamide, the advantage at which is that hydrochloride of 1,3-dephenylallyl amine could be obtained after hydrolysis of amination product. Bisphosphinite ligand **49** gave 76.7% ee in the amination reaction [70]. Excellent enantiomeric excess (94%) of amination product has been achieved with the catalysis of (*S*)-BINAP/Pd [100] (Scheme 6).

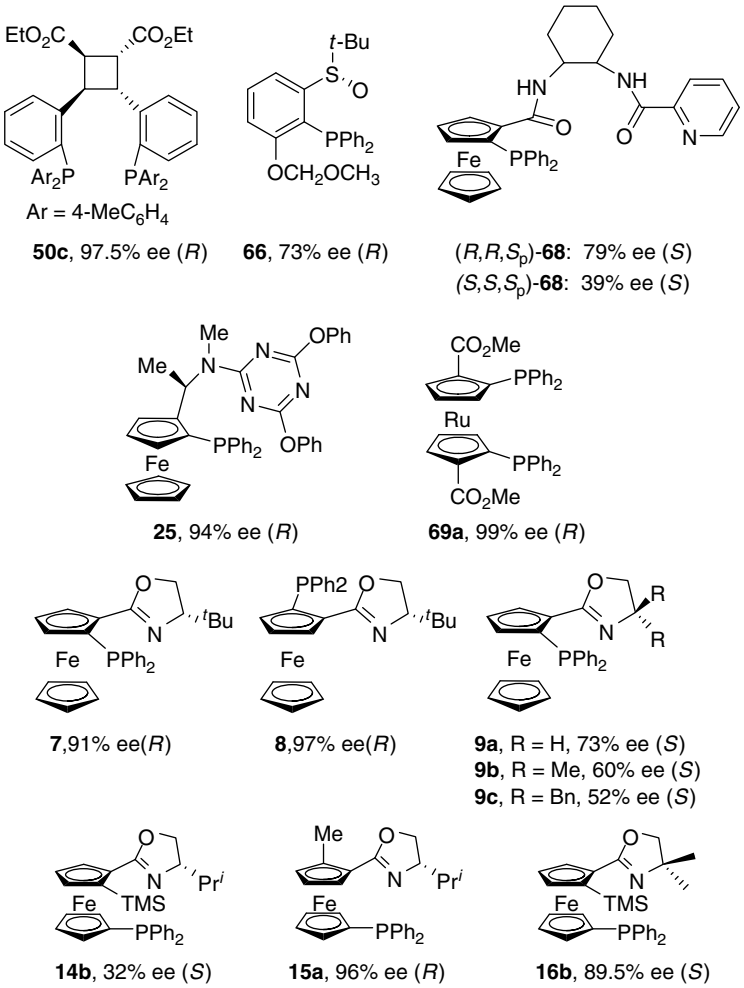
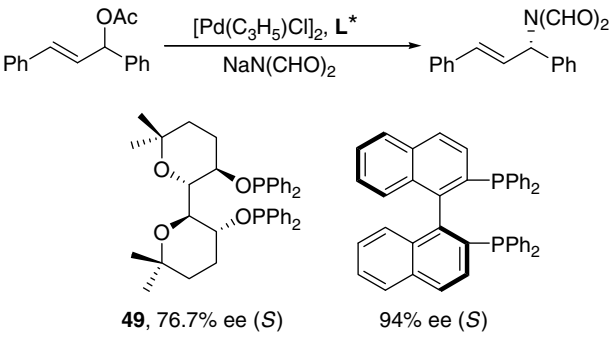


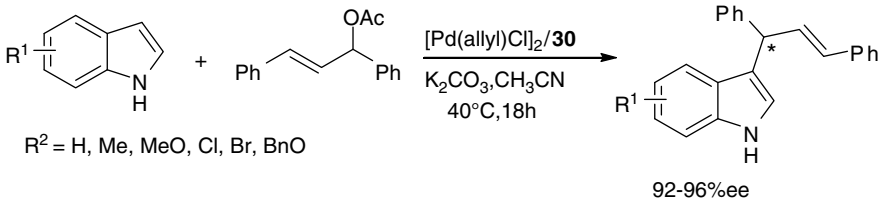
Fig. 10 Chiral ligands for Pd-catalyzed reaction of 1,3-diphenylallyl acetate with benzylamine



Scheme 6 Palladium-catalyzed asymmetric allylic amination with sodium diformylamide

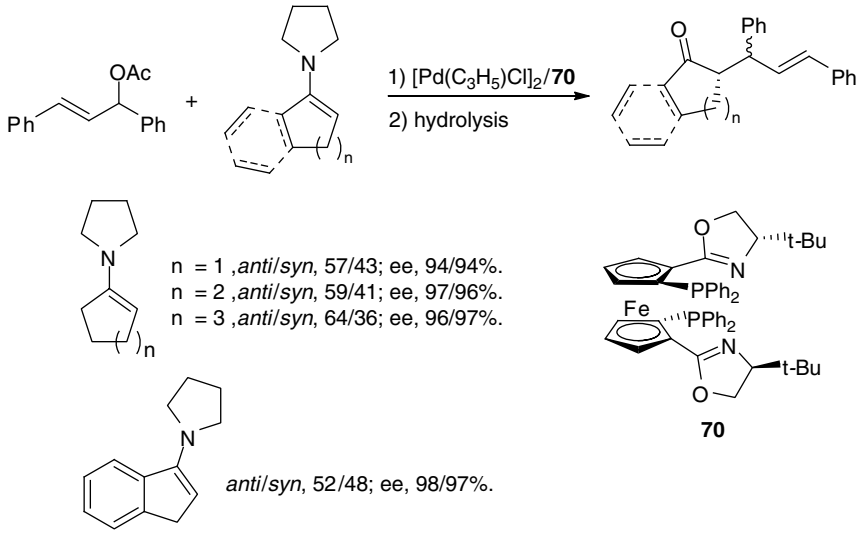
2.3 With Other Nucleophiles

Chan discovered that ligand **30** is effective for Pd-catalyzed AAA of indoles with 1.3-diphenylallyl acetate, and high enantioselectivities were achieved irrespective of the steric or electronic nature of indoles (Scheme 7). Binding mode of ligand **30** was established by an X-ray crystallographic study of [Pd(**30**)Cl_2]. It was shown that only one epimer of the ethyl substituent on the sulfur donor was observed in an *anti*-orientation with respect to the iron atom of ferrocene [101].



Scheme 7 Pd-catalyzed asymmetric allylic alkylation of indoles with 1,3-diphenylallyl acetate

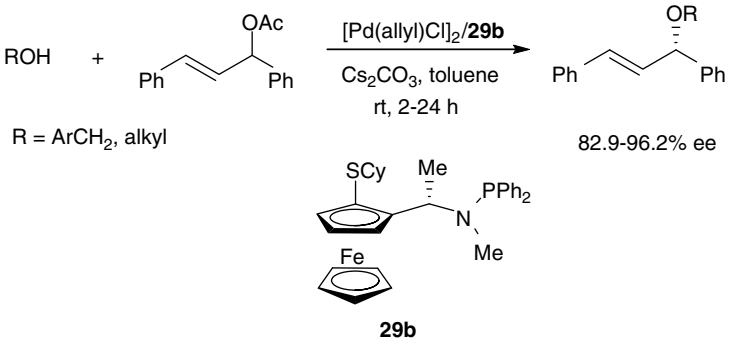
Enamines as the useful equivalent of α-carbanion of ketones have widely been used in organic synthesis. One of the advantages is that the use of strong base is not necessary. Recently, they have also been used successfully as the nucleophile in the transition metal catalyzed allylic alkylation reactions as variation of "hard" carbanions (*vide infra*) [102–104]. Zhang realized the use of enamine as nucleophile in Pd-catalyzed AAA reaction in the presence of chiral ferrocene-based phosphino-oxazoline ligand **70** for the first time (Scheme 8). It was shown that



Scheme 8 Pd-catalyzed asymmetric allylic substitution of 1,3-diphenylallyl acetate with enamines

the planar chirality plays an important role in enantioselectivity of the reaction. Excellent enantioselectivities (up to 99% ee) were obtained with pyrrolidine enamines of both aliphatic and aromatic ketone, albeit the diastereoselectivity is lower [105, 106].

The development of the synthesis of chiral compounds containing carbon–carbon or carbon–nitrogen bonds from racemic allylic electrophiles has been documented well. In contrast, the enantioselective allylic substitution of allylic acetates with relatively hard oxygen nucleophiles has only been studied sporadically. Chan reported a general Pd-catalyzed asymmetric allylic substitution of racemic 1,3-diphenylallyl acetate with aliphatic alcohols in the presence of ligand **29b** with excellent enantioselectivities (Scheme 9). They observed an intriguing relationship between the enantioselectivity of the reaction and the electronic nature of the nucleophiles, specifically, substituted benzylic alcohols. Higher enantioselectivity was observed when the benzylic alcohol contained an electron-rich para substituent, and the selectivity diminished gradually as the substituent became more electron-deficient. The electronic effect of substituted benzylic alcohols shows a linear free-energy relationship between enantioselectivity and the electronic character of the substituent. The authors suggested this observation may provide a useful tool for predicting the enantioselectivity of asymmetric allylic substitution when substituted benzylic alcohols are used as nucleophiles [107].



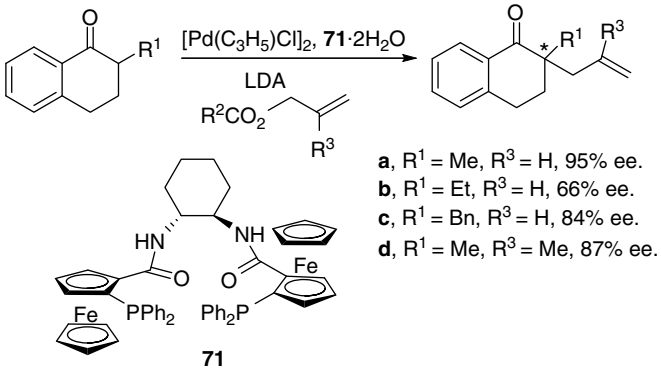
Scheme 9 Pd-catalyzed asymmetric allylic etherification of 1,3-diphenylallyl acetate with a variety of alcohols

3 Reactions of Other Allyl Substrates

3.1 Reactions of Simple Allyl Substrates

Although a variety of nucleophiles are suitable in Pd-catalyzed AAA reactions, the use of carbon nucleophiles is mainly limited to the stabilized "soft" carbanions such as β-keto ester and malonate derivatives. Because of the characters of "hard" carbanions as well as the mechanism and stereochemistry in the reaction with them,

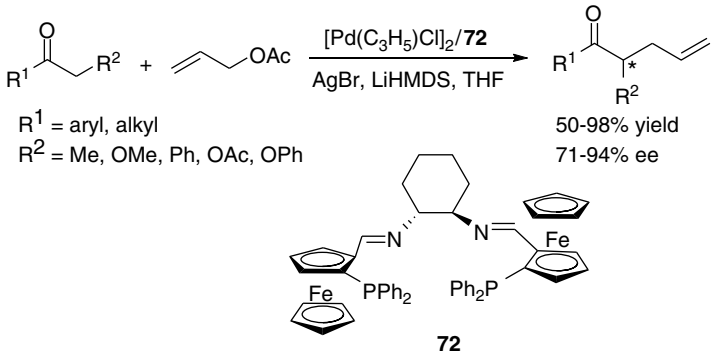
the use of "hard" carbanions in Pd-catalyzed AAA reaction remains a challenger for a long times. Simple ketone enolates are among this catalog and are an important class of nucleophiles in organic synthesis, but Pd-catalyzed AAA reaction had been ineffective with these nucleophiles because of their non stabilized character. The breakthrough came in 1999, when Trost and Schroeder obtained high enantioselectivity in Pd-catalyzed AAA reaction with tetralone and cyclohexanone derivatives by using their "chiral pocket" ligands [108]. When the α-alkyl tetralones were subjected to the reaction with simple allyl reagents, the corresponding products in high enantioselectivities were afforded if ferrocene-modified chiral pocket ligand **71**, developed by Dai and Hou, was used (Scheme 10). It was very interesting to note that ligand **71** has a chiral pocket structure containing two pairs of matched central and planar chiralities and was easily crystallized with two water molecules, which afforded higher ee value than that water-free ligand **71**, although there is no clear explanation. In addition to simple allyl reagent, 2-methyl allyl carbonate was also a suitable reagent in the reaction [109].



Scheme 10 Palladium-catalyzed asymmetric alkylation with different ketone enolates

With modified ferrocene ligand **72** containing C=N group, Hou realized the Pd-catalyzed AAA reaction of acyclic ketones with simple allyl acetate for the first time (Scheme 11). High ee was afforded when the alkoxy group was in the α-position of the carbonyl group. The presence of AgBr as additive was also crucial for both reactivity and enantioselectivity of the reaction. They also found that the enolate form of ketones dramatically affected the enantioselectivity of the reaction, and high enantioselectivity was achieved using *Z* form of the enolate [110].

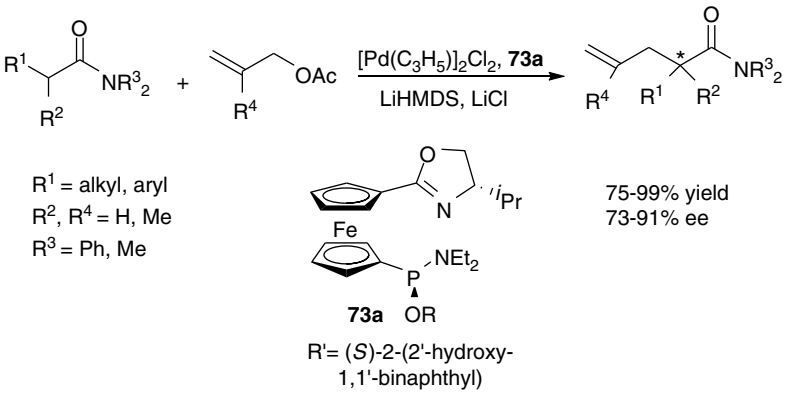
The catalytic asymmetric alkylation reaction of carboxylic acid derivatives is particularly difficult due to the lower acidity of hydrogen atom at α-position of carboxylic acid group. The even less stabilized nature of carbanions derived from carboxylic acid derivatives is another obstacle for transition metal-catalyzed AAA reactions. Hou reported the first Pd-catalyzed AAA reactions of acyclic amides, a general carboxylic acid derivative, with allyl acetates using 1,1′-*P*,*N* ferrocene



Scheme 11 Pd-catalyzed AAA reaction of acyclic ketones

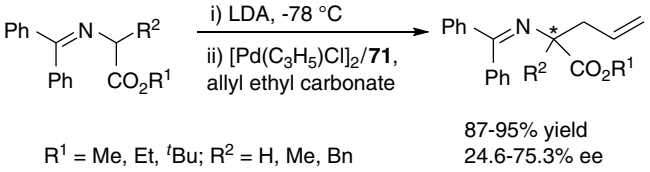
ligand **73a**, one member of the SIOCPhox ligands they developed featuring a chiral center on P-atom and a free OH functionality (Scheme 12). High yields of products with high enantioselectivities were obtained. The nature of the substituents on the nitrogen atom of the amide has a critical effect on the reactivity and stereoselectivity of the reaction, the best results were afforded when *N*,*N*-diphenyl amides were the substrates. Density functional theory (DFT) calculation revealed that the substituent of amides will influence the stability as well as reactivity of the carbanion formed during the reaction. The plausible model showed that in transition state the binol subunit of the ligand **73a** and Nu^- (the α-carbanion of the amide) are on the same side of the π-allyl moiety, which explains the observed stereochemical outcome [111].

Imino esters are useful nucleophiles in organic synthesis because they are one of the most important precursors of the relevant α-amino acids. Pd-catalyzed AAA reaction of allyl reagents with imino esters represents a straightforward way for the catalytic asymmetric synthesis of substituted α-amino acids [112–114]. However, only a few examples using such substrates in Pd-catalyzed



Scheme 12 Pd-catalyzed AAA reaction of amides

AAA reaction were reported. Dai and Hou succeeded in Pd-catalyzed AAA reaction of iminoesters with allyl ethyl carbonate in the presence of bis-ferrocene ligand **71**, giving nonracemic quaternary allylated imino esters in 77–95% yields with up to 75% ee (Scheme 13) [115].



Scheme 13 Palladium-catalyzed asymmetric allylation of imino esters

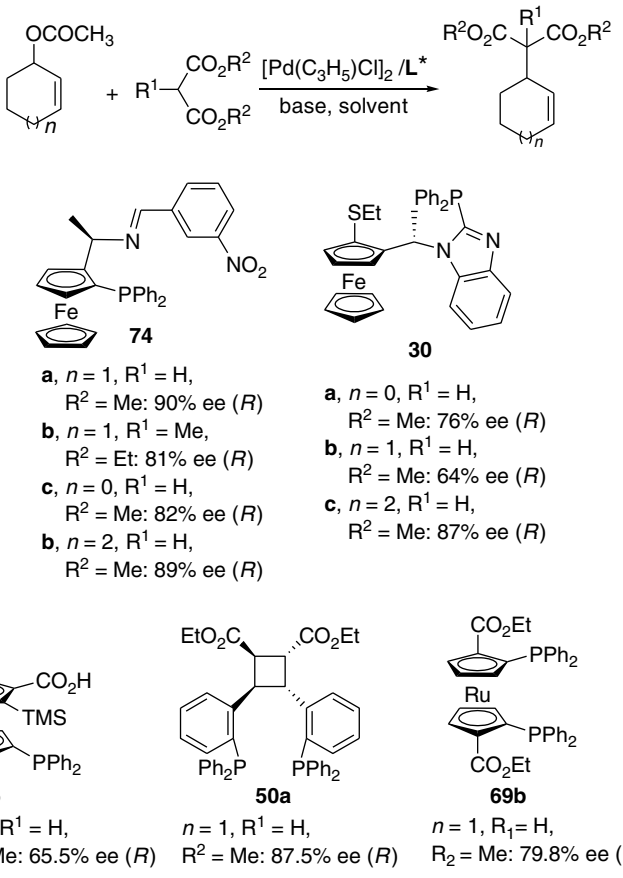
3.2 Reactions of Cyclic Allyl Substrates

Highly enantioselective transition metal-catalyzed allylic alkylation of cyclic allylic acetates, a class of nonsterically demanding substrates, with nucleophiles received less attention, and a limited number of examples with excellent enantioselectivity have been reported.

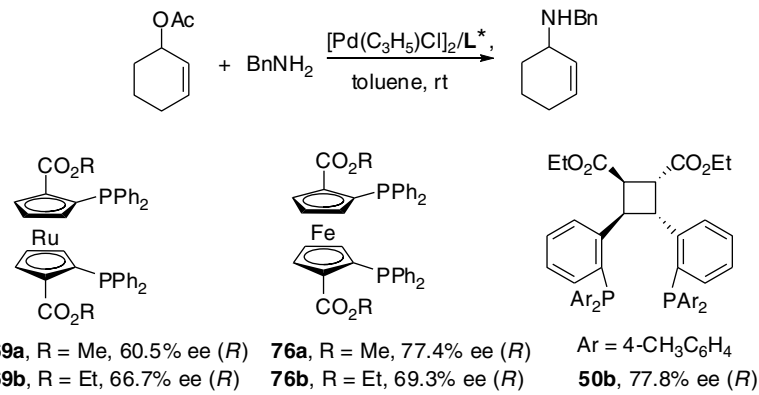
Ferrocenylphosphine-imine ligand **74** developed by Zheng was revealed to be the effective ligand in Pd-catalyzed AAA of cyclic alkenyl substrates providing corresponding alkylation product in 81–90% ee (Scheme 14) [45, 116]. High enantioselectivity was also realized when Chan used phosphine-thioether mixed donor ligand **30** they developed. The reaction of cyclic allylic acetates with different ring size with dimethyl malonate in the presence of 2.5 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 5 mol% of ligand **30** afforded good to excellent enantioselectivity (Scheme 14) [52].

Phosphinoferrocene carboxylic acid **75** with only planar chirality has been synthesized by Dai and Hou, providing allylated product in 65.5% ee (Scheme 14) [117]. The substrate extension from 1,3-diphenylallyl acetate to cyclic allylic acetate was also successful using ligand **50a** developed by Ding, with 87.5% ee [71]. A C_2-symmetric diphosphine ruthenocene ligands possessing only the planar chirality (**69b**) developed by Zhang et al. gave 79.8% enantioselectivity [98].

Zhang et al. also investigated the amination of cyclohex-2-enyl acetate using Pd-catalyst and found that ruthenocene **69** having a larger R in the ester group resulted in higher enantioselectivity while the opposite trend had been observed with ferrocene **76** (Scheme 15). By studying the X-ray structure of single crystal derived from ligand and dichlorobis(acetonitrile)palladium(II), they clarified that the twist angle of the two Cp rings in the metal complexes played the role on the enantioselectivity of the reaction [98, 99]. Ligand **50b** developed by Ding et al. is also efficient for the amination of cyclohex-2-enyl acetate, affording (*R*)-*N*-benzylcyclohex-2-enamine in 77.8% ee [71, 72].



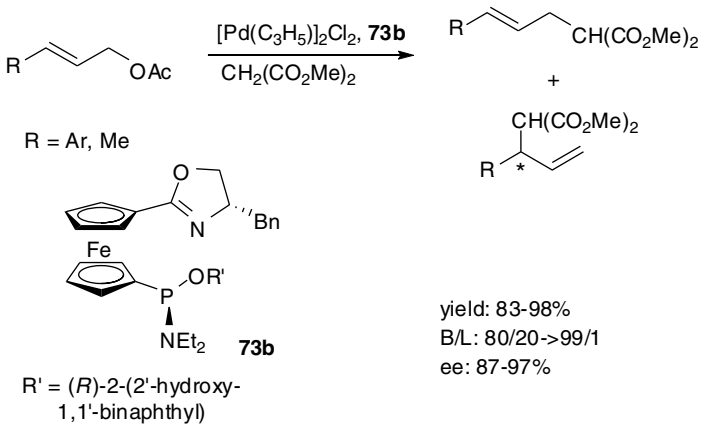
Scheme 14 Pd-catalyzed AAA reaction of cyclic allylic acetates



Scheme 15 Pd-catalyzed asymmetric amination of cyclohex-2-enyl acetate with benzylamine

3.3 *Reactions of Monosubstituted Allyl Substrates*

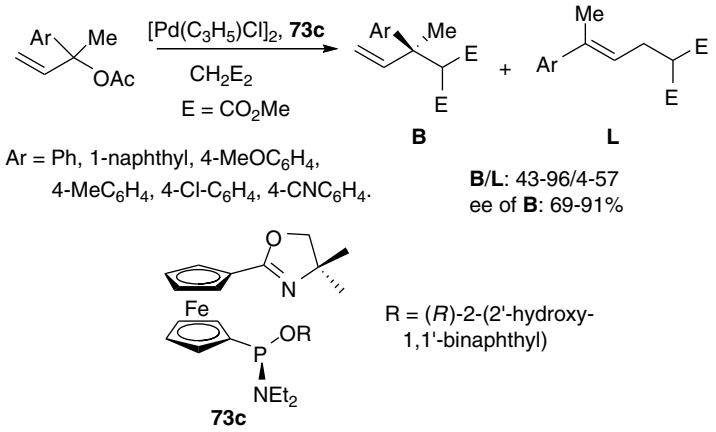
Different from symmetric 1,3-disubstituted allyl and cyclic allyl substrates, which produce only one regioisomer when react with nucleophile in the transition metal-catalysis, the reaction of monosubstituted allyl compounds with nucleophile may afford linear and branched regioisomers caused by the attack of nucleophile to different carbon terminal of η^3-ally-metal complex. Unfortunately, linear and non-optically active regioisomer is usually the major product when Pd-complexes are the catalyst. The regio- and enantio-selectivities of monosubstituted allyl substrates in Pd-catalyzed AAA reaction remain a challenge job for long time, except for a few special cases [118–122]. Based upon the mechanistic consideration and literature results, Dai and Hou designed ferrocene-based ligands, that is SiocPhox **73**. When these ligands were used in the Pd-catalyzed reaction of monosubstituted allyl acetate with malonate ester, high regio- and enantioselectivity were realized for a wide range of allyl substrates. Products in up to 99/1 of *B*/*L* ratio with 87–97% ee were given in the case of employing ligand **73b** (Scheme 16) [123].



Scheme 16 Pd-catalyzed allylic alkylation with ligand **73b**

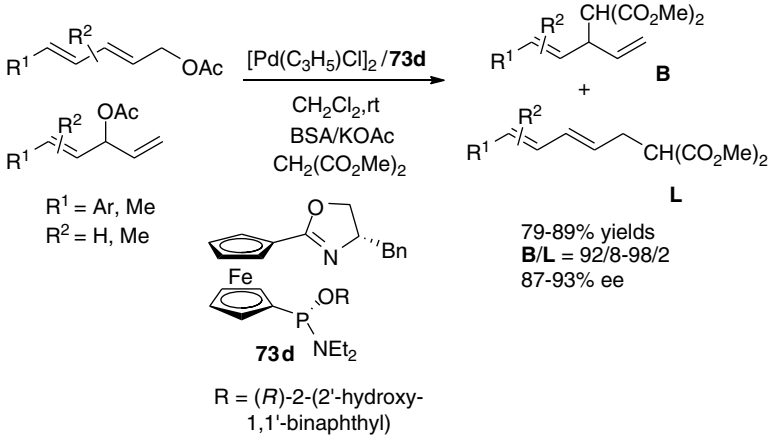
Construction of a chiral quaternary carbon center by catalytic asymmetric reactions represents a demanding and challenging area in organic synthesis because of its great importance for the synthesis of enantiomerically pure natural products and pharmaceuticals [124, 125]. Formation of an all-carbon-substituted chiral quaternary carbon center on a monosubstituted allyl substrates using Pd-catalyzed allylic alkylation is particularly difficult because of the regioselectivity issue. Based on the success of ligand **73** in the highly regio- and enantioselective Pd-catalyzed AAA reaction of monosubstituted allyl substrates, Hou et al. modified the ligands through the introduction of an additional group on oxazoline ring, and thus making the oxazoline ring devoid of chiral center. The modified ligand **73c** was successfully applied in the reaction of substituted allyl acetates with malonate ester to install all

carbon chiral quaternary carbon center with high regio- and enantioselectivities, *B*/*L* ratio being 43–96/4–57 and enantioselectivity being 69–91 for a wide range of allyl substrates (Scheme 17) [126].



Scheme 17 Formation of all-carbon-substituted chiral quaternary carbon center by Pd-catalyzed regio- and enantioselective allylic alkylation reaction

The allylic alkylation reaction of polyenyl esters, a special variant of monosubstituted allylic esters, usually provides linear products under Pd-catalyzed conditions. To address the issue of regioselectivity as well as enantioselectivity in allylic substitution reactions of polyenyl esters, some metal complexes such as Mo [127] and Ir [128–130] were employed. Hou group realized a high regio- and enantioselective Pd-catalyzed AAA reactions of 2,4-dienyl esters in the presence of ferrocene-based chiral ligand **73d** with *B*/*L* ratio ranging from 92/8 to 98/2 and enantioselectivities being 87–93% ee (Scheme 18). These results demonstrated the

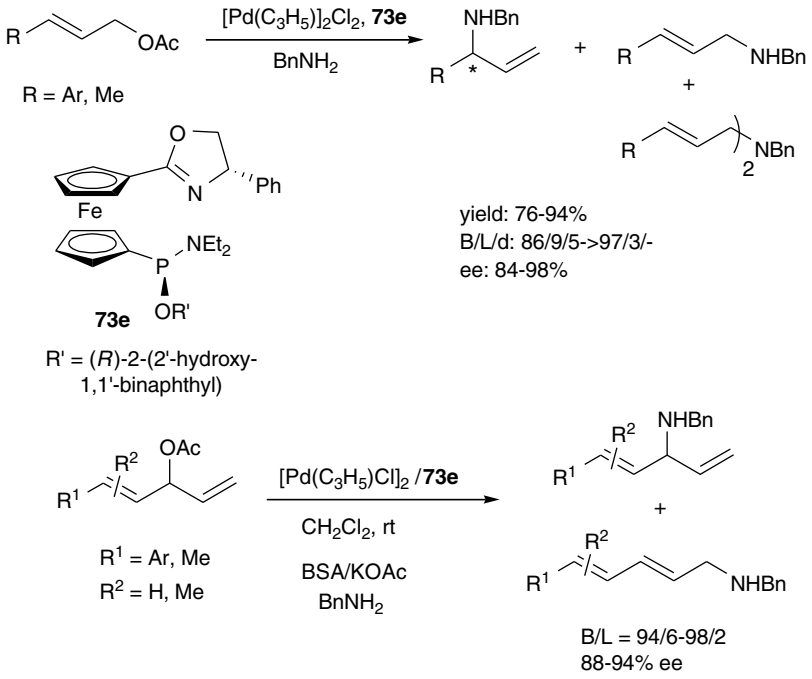


Scheme 18 Pd-catalyzed asymmetric allylic substitution reactions of polyenyl esters with malonate

usefulness of this type of ligands in the control of regio- and enantioselectivities of the reactions with different types of allyl substrates [131].

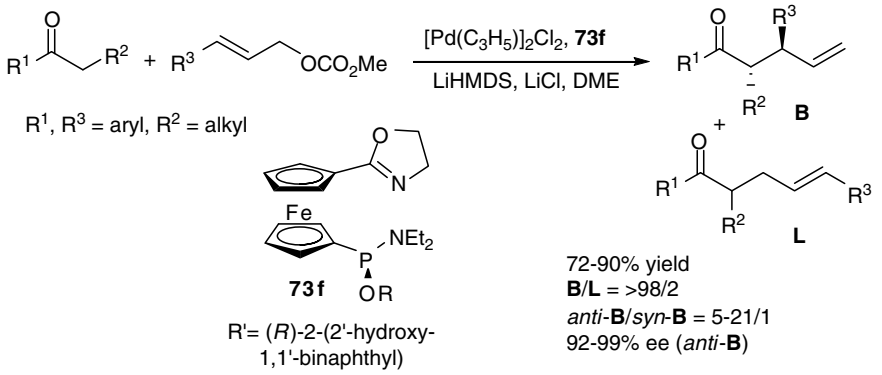
High regio- and enantioselectivities in Pd-catalyzed allylic amination of monosubstituted allyl acetates were also realized for a wide range of substrates by using ferrocene ligand **73e** (ee ranging from 84 to 98%, the ratio of branch-linear up to 97/3) (Scheme 19). Experiments demonstrated that the presence of the free hydroxyl group in the ligands is crucial for the stereoselectivity and reactivity of the reaction. When the ligand with the hydroxyl group being protected as methylether was used, the reaction needed more time to completion and the regio- and enantioselectivities decreased dramatically. Interaction between the free OH group and nucleophile directs the nucleophile to attack inside carbon of allyl complex in an intramolecular mode [123]. The 1,1′-*P,N*-ferrocene ligand **73e** also showed excellent control of regio- and enantioselectivity in the amination reaction of pentadienyl branched allyl acetate with benzylamine [131].

Hou et al. explored the possibility of generating two chiral centers by transition metal-catalyzed asymmetric reaction of simple ketone enolates and monosubstituted allyl substrates, a more challenging job, based on their success of Pd-catalyzed AAA reaction of monosubstituted allyl substrates with stabilized carbanion as well as the use of "hard" carbanions in the reactions [109–111, 123, 126, 131]. 1,1′-*P,N*-ferrocene **73f** with no chiral center on the oxazoline ring is the best ligand in the reaction of aryl ketones with cinnamyl derivatives, forming two vicinal



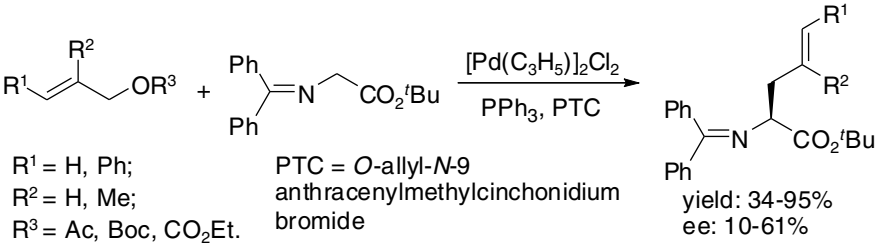
Scheme 19 Pd-catalyzed asymmetric amination reactions with ligand **73e**

chiral centers in high yields with high regio-, diastereo-, and enantioselectivities (Scheme 20). Both solvents and additives had great impact on the reaction selectivities. The presence of LiCl or CuCl favored the formation of branched products while CuI gave linear products predominantly. In addition, the reaction in DME gave the products in much better diastereoselectivity than that in THF (6:1 vs. 2:1) [132].



Scheme 20 Pd-catalyzed AAA reaction of monosubstituted allyl substrates with acyclic ketone enolates

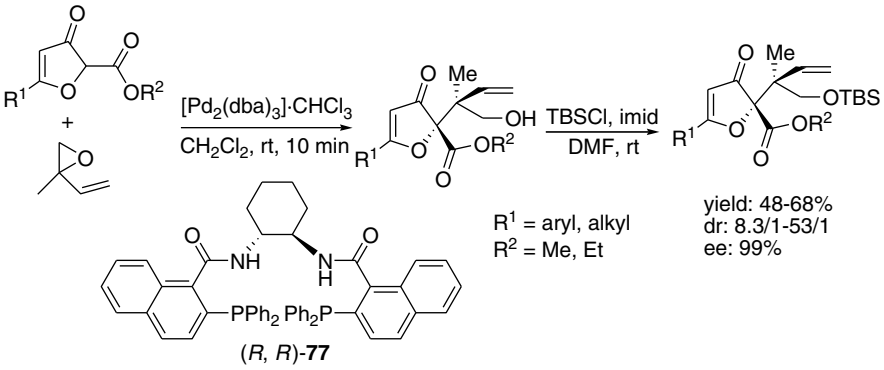
Gong and Mi realized the Pd-catalyzed allylic alkylation of glycine derivatives with simple allyl esters in the presence of a chiral quaternary ammonium salt. The molecular sieves was found to have a beneficial effect on the enantioselectivity of the reaction by scavenging water from the system. Alkylated products with ee of up to 61% were obtained from the attack of nucleophile at the unsubstituted site of allyl substrate (Scheme 21) [133].



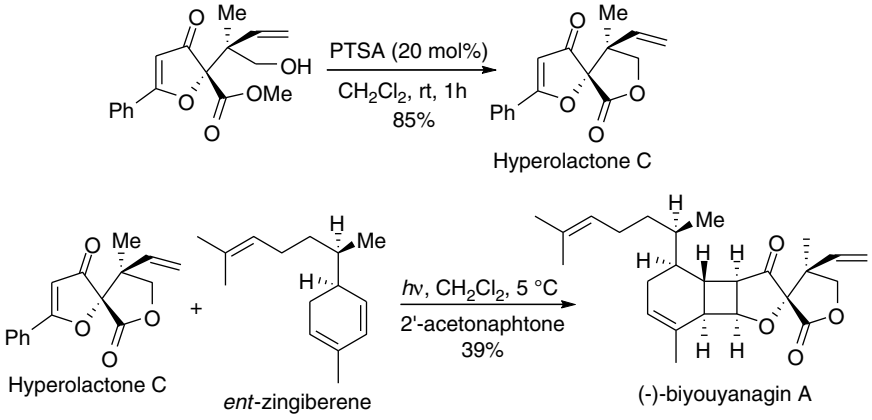
Scheme 21 Pd-complex catalyzed allylic alkylation of imino ester with allyl acetates under PTC condition

The motif of two vicinal quaternary carbon centers is found in a wide range of bioactive natural products such as hyperolactones A–C [134, 135] and (−)-biyouyanagin A [136]. In general, the stereoselective construction of two

vicinal quaternary carbon centers relies on substrate control. The catalytic asymmetric synthesis of two vicinal quaternary carbon centers with high diastereoselectivity and enantioselectivity remains a formidable challenge. Xie et al. developed a successful strategy for the construction of two vicinal quaternary carbon centers with high diastereoselectivity and excellent enantioselectivity by using a Pd-catalyzed AAA reaction with Trost's ligand **77** (Scheme 22) [137–139]. This strategy has enabled the concise and efficient total syntheses of natural products hyperolactone C and (−)-biyouyanagin A from benzaldehyde in only six and seven steps with total yields of 20% and 8%, respectively. The unnatural enantiomer enthyperolactone C and (+)-biyouyanagin A were also prepared by simply switching the configuration of chiral ligand in the Pd-AAA reaction and by changing the coupling partner in the final photoinduced [2 + 2] cycloaddition reaction (Scheme 23) [140].



Scheme 22 Pd-catalyzed AAA reaction of ketones with isoprene monoepoxide

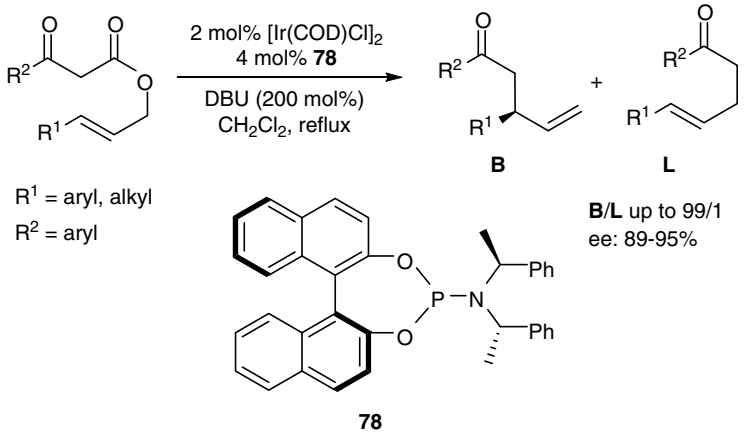


Scheme 23 Total synthesis of natural (−)-biyouyanagin A

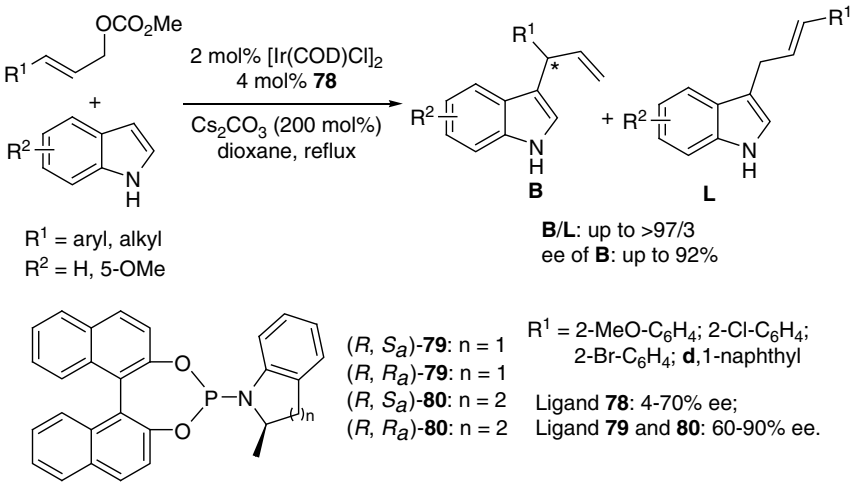
4 The Allylation Catalyzed by Other Metals

As mentioned earlier, the allylic substitution reactions may also be catalyzed by many other transition metal complexes, such as Ir, Ru, Cu, Mo, with different outcome [2]. Usually, the branched products are predominantly produced when Ir- and Cu-catalysts are used. In addition, Pd-catalyzed AAA reaction usually requires stablized nucleophiles such as malonate esters and some other 1,3-dicarbonyl compounds. In contrast, "hard" carbanions, for example, Grignard reagents, organozinc and organolithium compounds, have been used in the Cu-catalyzed reaction, which is complementary to palladium catalysis [141].

You et al. succeeded in the Ir-catalyzed decarboxylative allylic alkylation with unsymmetrical allylic substrates. A catalyst derived from $[Ir(COD)Cl]_2$ and Feringa's phosphoramidite **78** was found to be efficient for the highly regio- and enantioselective decarboxylative alkylation of γ-substituted allyl β-ketocarboxylates, affording the branched products with *B*/*L* ratio up to >99/1 and 96% ee (Scheme 24) [142]. Crossover experiment excluded the possibility that the alkylation products are produced through intramolecular rearrangement or the cage ion pairs. The utilization of neutral conditions and the possibility to prepare products that are not accessible by traditional Tsuji–Trost allylic alkylation make the transition metal catalyzed decarboxylative allylic alkylation interesting in organic synthesis [143–145]. The same catalyst system was applied by authors to a highly regio- and enantioselective Friedel–Crafts-type allylic alkylation of indoles, affording the branched products with up to >97/3 branched-linear ratio and 92% ee (Scheme 25) [146]. However, the reaction suffered from low enantioselectivity when the ortho-substituted cinnamyl carbonates were substrate. To address the issue, they developed new phosphoramidite ligands **79** and **80** from enantiopure BINOL and 2-methylindoline or 2-methyl-1,2,3,4-tetrahydroquinoline, which were proved to



Scheme 24 Ir-catalyzed asymmetric decarboxylative allylic alkylation

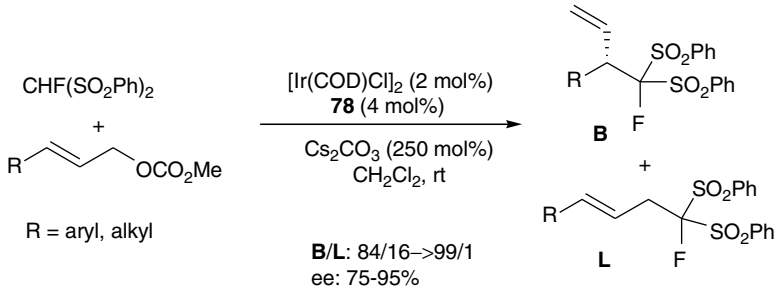


Scheme 25 Ir-catalyzed regio- and enantioselective Friedel–Crafts-type allylic alkylation of indoles

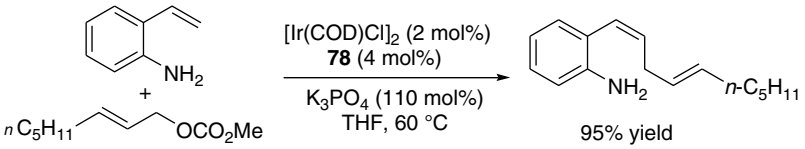
be effective for ortho-substituted cinnamyl carbonates, providing much higher enantioselectivity than ligand **78** (Scheme 25) [147].

The catalyst derived from $[Ir(COD)Cl]_2$ and phosphoramidite **78** was utilized by You and Zhao for Ir-catalyzed allylic alkylation of monofluoro-bisphenylsulfonylmethane (FBSM) with 1,3-unsymmetrical allylic substrates, affording the enantiopure fluorobis(phenylsulfonyl) methylated compounds bearing a terminal C=C bond with highly regio- and enantioselectivities. The resulted monofluoromethylated products may be converted to monofluorinated ibuprofen and naproxen in a highly efficient manner (Scheme 26) [148].

You et al. observed an unprecedented *cis*-Heck-type product, a skipped *Z*, *E* diene, during the study of $[Ir(COD)Cl]_2$/ligand **78**-catalyzed allylic substitution reactions of *o*-amino styrene with allylic carbonates (Scheme 27) [149]. Based on the results, You et al. designed $[\{Ir(cod)Cl\}_2]$/phosphoramidite **78** catalyzed

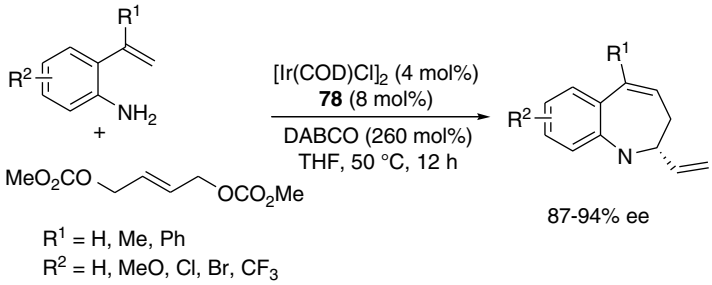


Scheme 26 Ir-catalyzed regio- and enantioselective allylic alkylation of fluorobis(phenylsulfonyl) methane



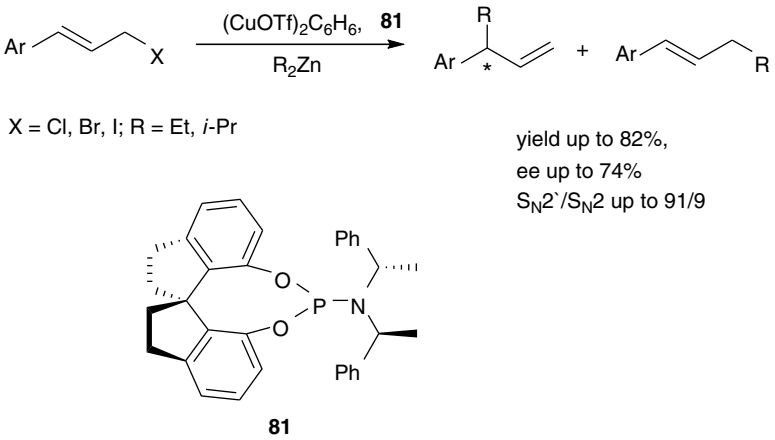
Scheme 27 Ir-catalyzed cross-coupling of styrene with allylic carbonates

tandem allylic vinylation and amination reaction of (*E*)-but-2-ene-1,4-diyl dimethyl dicarbonate with ortho-amino styrene derivatives, affording the 2,3-dihydro-1*H*-benzo[*b*]azepines with high enantioselectivity (87–94% ee) (Scheme 28) [150].



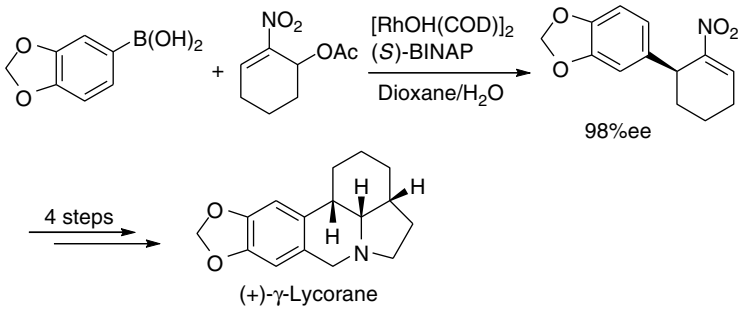
Scheme 28 Ir-catalyzed asymmetric tandem allylic vinylation/amination reaction

Zhou's group realized high regio- and enantioselectivities in the Cu-catalyzed AAA reaction of cinnamyl halides with dialkylzincs using chiral spiro phosphoramidite ligand **81** (Scheme 29) [151].



Scheme 29 Cu-catalyzed regioselective asymmetric allylic alkylation with dialkylzincs

Gong described the first enantioselective allylic arylation of 2-nitrocyclohex-2-enol esters with arylboronic acids catalyzed by complex of $[RhOH(COD)]_2$ and (*S*)-BINAP, providing enantioselectivities ranging from 90 to 99% ee for various arylboronic acids. A concise total synthesis of optically pure (+)-γ-lycorane in overall 38% yield was achieved based upon this new methodology (Scheme 30) [152].



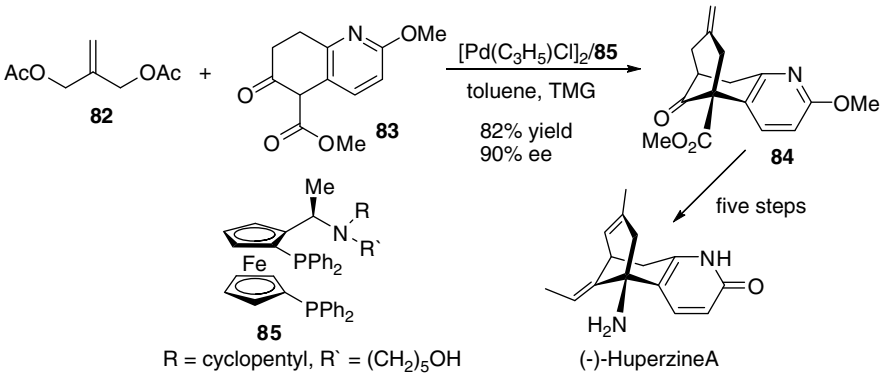
Scheme 30 Rh-catalyzed enantioselective nitroallylation of 2-nitrocyclohex-2-enol ester with arylboronic acid

5 Cyclization by Pd-Catalyzed Allylation and Lewis Acid Catalyzed Allylation

Lu et al. developed Pd-catalyzed racemic reaction of 2-methylene propan-1,3-diol diacetate (**82**) with di-carbanions to afford the carbon skeleton of bicycle[3.3.1] nonane derivatives [8, 9]. Bai's group realized an enantioselective reaction of β-ketoester **83** with allylic agent **82**, providing tricyclic intermediate **84** in 90% ee through a bicyclic annulation manner using the chiral ferrocenylphosphine ligand **85**. This allylation product was used successfully in the total synthesis of enantiopure (−)-huperzine A, a Lycopodium alkaloid isolated from Chinese herb *Huperzia serrata*a, which was approved in China as a new drug for the treatment of Alzheimer's disease (Scheme 31) [153, 154].

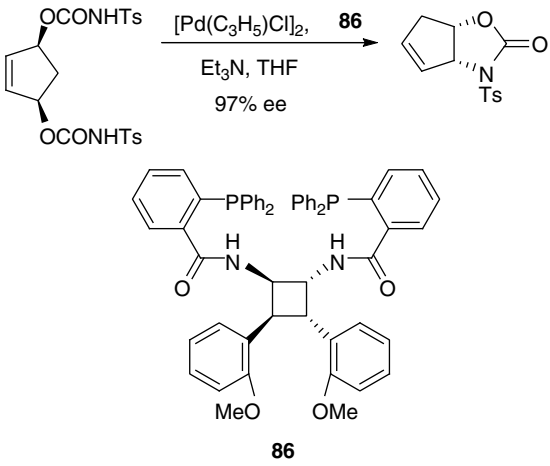
Ding developed a new class of bisphosphine ligand **86** with a cyclobutane backbone on the basis of a privileged C_2 scaffold of head-to-head coumarin dimer, which showed excellent activity and enantioselectivity in Pd-catalyzed desymmetrization of the biscarbamate of *meso*-cyclopent-2-en-1,4-diol, affording oxazolidin-2-one in 97% ee (Scheme 32) [155].

Ma reported an enantioselective cyclic allylation based on the carbopalladation of 3,4-allenyl hydrazines using catalyst from Pd(0)/bisoxazoline ligand **87a** with a spiro skeleton and a α-naphthylmethyl substituent, and optically active pyrazolidine derivatives was obtained with ee values ranging from 92 to 95%. The reaction may proceed via the oxidative addition, intermolecular carbometallation of the allene moiety forming a π-allyl palladium intermediate, and the intramolecular enantioselective allylation (Scheme 33) [156, 157]. By means of similar strategy,



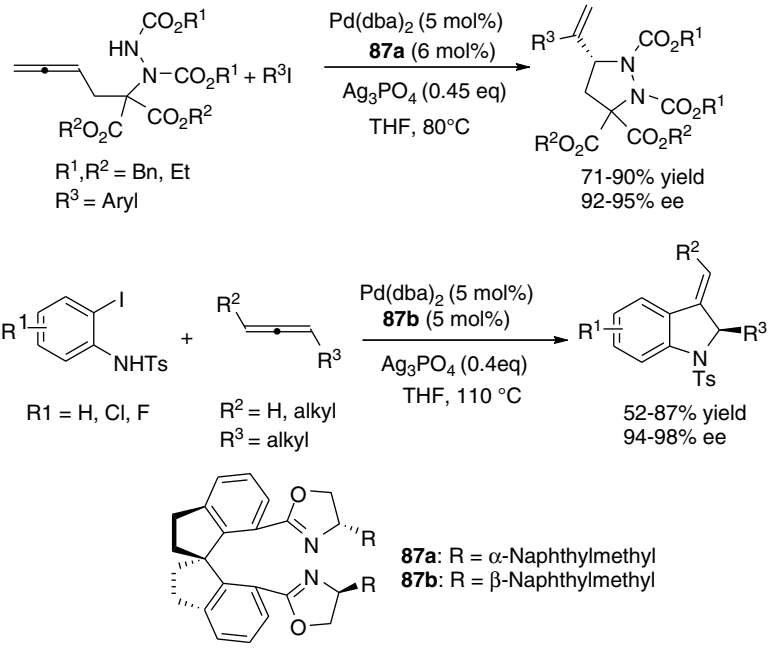
Scheme 31 Pd-catalyzed enantioselective bicycloannulation of β-keto-ester **83** with allylic agent **82**

Scheme 32 Pd-catalyzed desymmetrization of *meso*-cyclopent-2-en-1, 4-diol biscarbamate

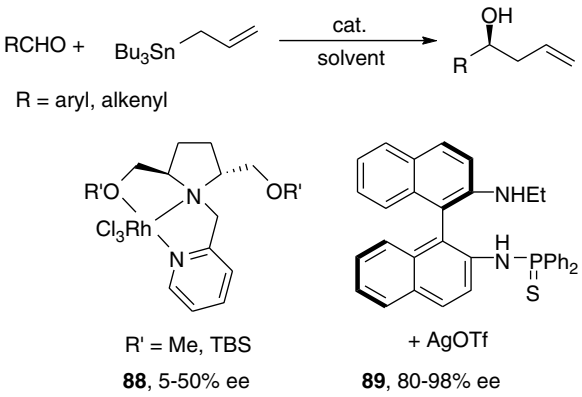


the Pd-catalyzed asymmetric allylic annulation of readily available 2-iodoanilines with simple allene was realized by the same group using a β-naphthylmethyl substituent spiro-BOX ligand **87b**, affording the 3-alkylideneindolines in good yields with high to excellent enantiomeric excesses (94–98% ee) [158].

Optically active homoallylic alcohols and amines are useful intermediates in organic synthesis. The Lewis acid catalyzed stereoselective addition of allyl organometallics to carbonyl compounds and imines is one of the most concise ways to such motif. Shi et al. used in situ generated cationic chiral rhodium complexes **88** as catalyst for the enantioselective allylation of arylaldehydes with allyl stannane albeit in 5–50% ee (Scheme 34) [159]. To improve the selectivity, they devised a new chiral bidentate diphenylthiophosphoramide **89** and applied it as the ligand in the Ag(I)-catalyzed enantioselective allylation reaction of arylaldehydes with allyltributyltin, affording homoallylic alcohols in high enantioselectivities (Scheme 34) [160, 161].

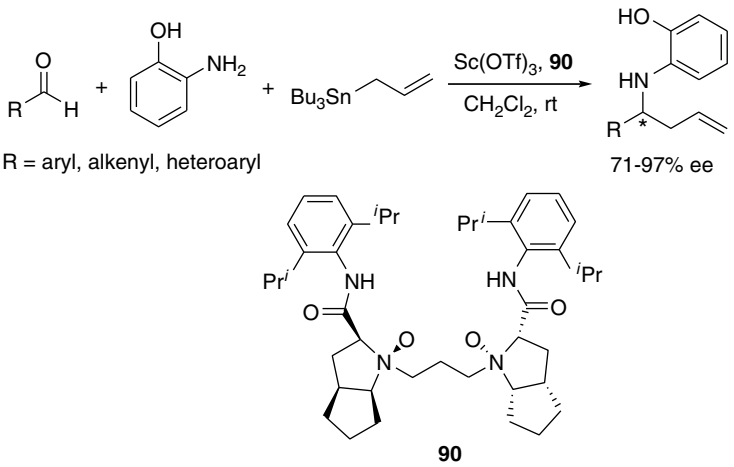


Scheme 33 Pd-catalyzed enantioselective cyclization with spiro-BOX ligand **87**



Scheme 34 Ag-catalyzed enantioselective allylation of aldehydes

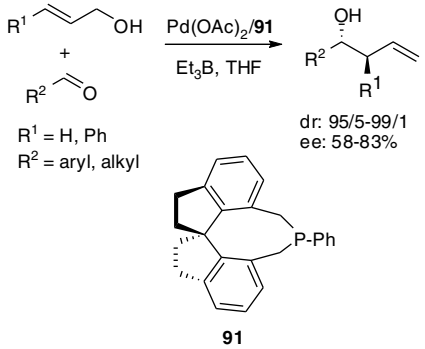
Feng developed the catalytic asymmetric three-component allylation with aldehydes, amine and allyl stannane by using readily accessible and tunable C_2-symmetric *N*,*N*′-dioxide **90**-Sc(III) complex as catalyst. A wide range of homoallylic amines were obtained with high enantioselectivities under mild conditions. The operational simplicity, practicability, and mild reaction conditions render it an attractive approach for the asymmetric reactions (Scheme 35) [162].



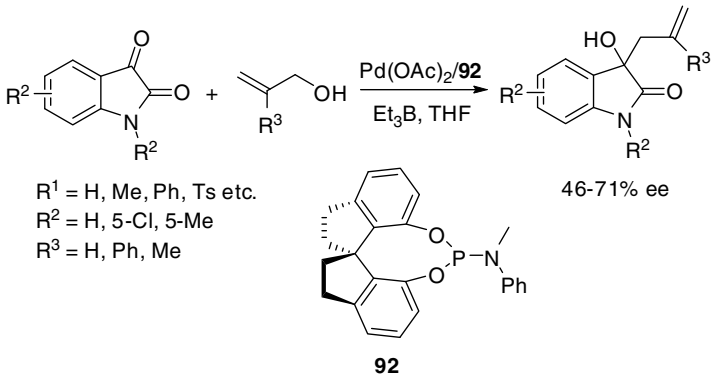
Scheme 35 Catalytic asymmetric three-component allylation of aldimines catalyzed by C_2-Symmetric *N*,*N*′-dioxide–Sc^{III} complex

The enantioselective allylation of benzaldehyde by umpolung of π-allylpalladium complexes is another useful route to homoallylic alcohols. Zhou used allylic alcohol instead of allyl ester as allyl donor in Pd-catalyzed allylation of aldehydes in the presence of ligand **91** and Et_3B with high diastereo- and enantioselectivities. A variety of aromatic, heteroaromatic, and aliphatic aldehydes were suitable substrate (Scheme 36) [163]. They also reported a Pd-catalyzed asymmetric allylation of isatins with allylic alcohols. With chiral spiro phosphoramidite ligand **92** containing an aniline moiety, various homoallylic alcohols, such as 3-allyl-3-hydroxy-2-oxindoles, were obtained directly from the allylic alcohols in one step with moderate enantioselectivities. This represents the first example of using allylic alcohol as the allylation reagent in catalytic asymmetric allylation of ketones (Scheme 37) [164].

Hou's group synthesized a chiral 4-substituted [2.2]paracyclophane monophosphine **93**, which was employed as ligand in the Pd-catalyzed umpolung allylation

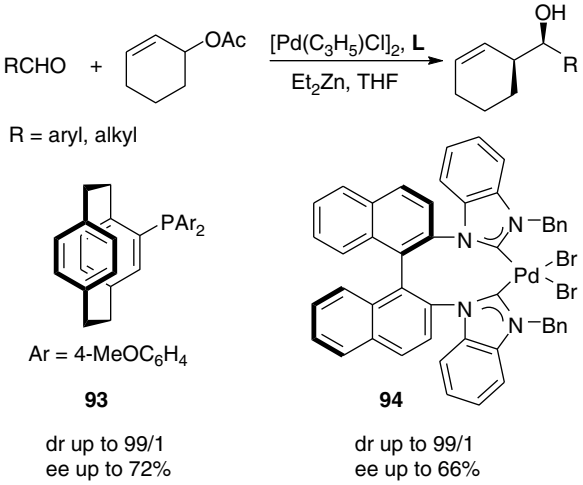


Scheme 36 Pd-catalyzed asymmetric allylation of aldehydes with allylic alcohols



Scheme 37 Pd-catalyzed asymmetric allylation of isatins with allylic alcohols

of aldehydes with 2-cyclohexenyl acetate, affording *syn*-homoallyl alcohols in 38–95% yields, 80–98% dr and 7–72% ee (Scheme 38) [165]. Shi reported the use of axially chiral bis(NHC)-Pd(II) complex **94** as catalyst in enantioselective umpolung allylation of aldehydes with cyclohexenyl acetate to produce the products in modest enantioselectivities and good to excellent syn diastereoselectivities (Scheme 38) [166].



Scheme 38 Pd-catalyzed asymmetric allylation of aldehydes with cyclohexenyl acetate

6 Summary and Outlook

In past decades, the transition metal-catalyzed allylation reactions received much attention all over the world as well as in China. A variety of chiral ligands have been designed and synthesized, which demonstrated their catalytic activity as well

as stereochemistry control ability in the reaction. Many strategies have been developed to explore the way to address the challenges of the reactions. In spite of great achievements in transition metal-catalyzed asymmetric allylation have been made, there are still some limitations. In the future, it is desirable to uncover the use of monosubstituted allyl reagents as well as the use of "hard" carbon nucleophiles in addition to enolates. The applications of the reactions in organic synthesis still also await exploration.

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Enantioselective Reactions with Trisoxazolines

Jian Zhou and Yong Tang

Abstract A series of homochiral and heterochiral trisoxazolines were synthesized by a direct or modular approach. These trisoxazoline-derived metal complexes function as enantioselective Lewis acid catalysts for Friedel–Crafts, Kinugasa, 1,3-dipolar cycloaddition, cyclopropanation, and Diels–Alder reaction. In these catalyzed processes, trisoxazoline-derived chiral metal complexes exhibit excellent reactivity, good to excellent selectivity, and high tolerance towards moisture. In some cases, the reaction selectivity could be easily tuned by changing reaction parameters such as temperature and solvent. In these reactions, trisoxazoline-derived chiral catalysts achieved better enantiofacial control, higher catalytic activity, and higher tolerance of impurities than the corresponding bisoxazoline derived ones. In light of these features, it is assumed that the coordination of the oxazoline sidearm to the metal center improves the stability, activity, and chiral environment of the catalyst.

Keywords Trisoxazoline • Enantioselective • Catalysis • Sidearm

Contents

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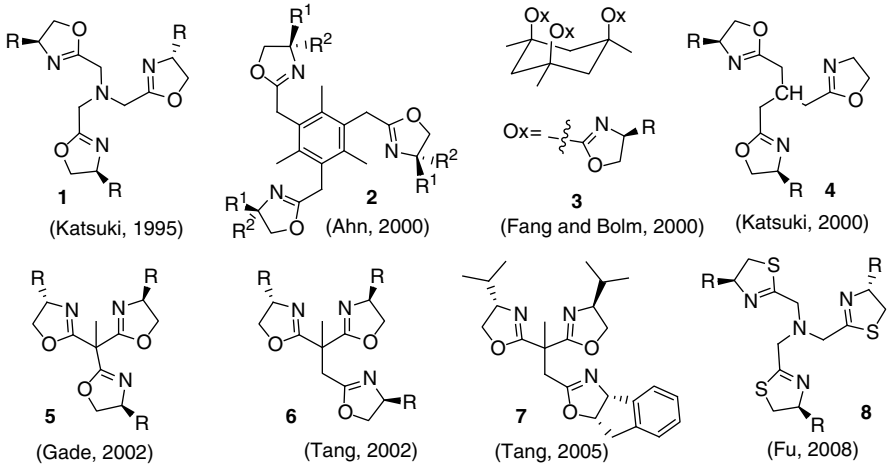
1 Introduction

The search for superior chiral catalysts represents fundamental endeavors in synthetic organic chemistry [1]. Although asymmetric organocatalysis has been efficiently developed in the past decade [2, 3], the development of new chiral ligands that upon coordination to a metal realizes enantioselective reactions of interests is still one of the central research areas in asymmetric catalysis.

Since Nozaki and Noyori developed the first example of asymmetric catalysis using a chiral metal complex [4], asymmetric metal catalysis has attracted much attention, and been thriving for tens of years. Numerous chiral ligands have been synthesized and applied into many types of metal-catalyzed asymmetric reactions; however, only a handful of them belong to "privileged" chiral ligands [5]. Bisoxazolines have already been established as a kind of powerful ligands in asymmetric metal catalysis and been applied to a series of metal-catalyzed C–C bond formation reactions [6–8]. Still much effort has been devoted to variation of linkages, backbones, and aminoalcohols to develop super ligand [9], owing to the intrinsic advantages of oxazoline ligands, such as easy accessibility and structural elaboration, stability towards hydrolysis and oxidation, and facile coordination to a wide range of transition metals. Furthermore, an important advantage of bisoxazolines is that chiral induction is direct and strong in the reaction process, because the two stereogenic centers neighboring the coordinating nitrogen atom of the oxazoline ring are held in close proximity to the metal [10].

Inspired by the versatility of bisoxazolines, chemists become interested in the synthesis and application of trisoxazolines, with the anticipation that trisoxazolines could have the following important advantages: (1) increase ligand diversity: [11] homochiral or heterochiral, C_3-symmetric or pseudo-C_3-symmetric, and tridentate or multidentate trisoxazolines can be synthesized via direct or modular synthesis; (2) improve catalyst stability: [12] trisoxazolines form more stable chiral complexes than bisoxazolines for the formation of more chelation ring. The stronger chelation effect could suppress the competitive coordination of mulitidentate products to metal center in some cases, and increase the tolerance of catalyst to impurities; (3) create tunable chiral space: the presence of a pendant oxazoline ring creates a more sterically encumbered chiral space than bisoxazolines, which might reduce disadvantages such as rotation and flexibility in enantiofacial control; (4) while it is believed that C_2 symmetry might reduce the number of possible diastereomers in catalytic intermediates with square planar geometry, C_3 symmetry can do the same for octahedral intermediates. In this light, C_3-symmetric trisoxazolines might be versatile in metal-catalyzed asymmetric reactions involving octahedral intermediates (For a detailed discuss of C3 symmetry and C2 symmetry, please see a comprehensive review: [13]).

Pioneered by Katsuki et al. in 1995, the first chiral trisoxazoline metal complex was successfully applied in asymmetric Kharash–Sosnavsky reaction [14–16]. Gradually following this report, several types of trisoxazolines have been developed



Scheme 1 Representative trisoxazoline ligands applied in asymmetric catalysis

and found utility in asymmetric catalysis and molecular recognition (For a review: [17]). The representative trisoxazolines were shown in Scheme 1. These ligands have been applied to an array of asymmetric reactions: Trisoxazolines **1**[14–16] and **4** [18] developed by Katsuki et al. and the analogue **8** [19] were mainly applied to the copper catalyzed enantioselective allylic oxidation of alkenes and could achieve 93% ee in the oxidation of cyclopentene; Chang et al. found that isopropyl-substituted trisoxazoline **1** could catalyze the addition of Et_2Zn to aldehyde to give secondary alcohol with up to 90% ee [11c]. Noticeably, tridentate (N, N, N) ^{i}Pr-PYBOX afforded only 20% ee in this case under the same reaction condition, suggesting that chiral space created by trisoxazoline **1** was more effective in this reaction than the relative PYBOX. Trisoxazolines **3** derived from Kemp's acid were also used in the allylic oxidation of the cyclopentene, but only moderate ee was obtained [94% yield and 45% ee (S)] [20]. The benzene-based trisoxazoline **2** was mainly applied in molecular recognition by Ahn's group [21–24] and it turned out to be especially promising for the selective recognition of NH_4^+, alkylammonium ions, and the enantiomeric recognition of α-chiral primary ammonium ions and β-chiral primary ammonium ions. Trisoxazoline **2** was only tried in the Michael addition of methyl phenylacetate to methyl acrylate, and *tert*-butyl-substituted trisoxazoline **2** in combination with KOBu^t could promote the reaction of phenylacetate with methyl acrylate in up to 82% ee [25].

The most versatile C_3-symmetric trisoxazolines **5** were developed by Gade et al. (for a review, see: [26]). While previously trisoxazolines were all prepared via direct synthesis, Gade et al. first introduced a modular strategy when preparing trisoxazolines **5** [27]. The modular synthesis turned out to be a powerful strategy to synthesize trisoxazolines and improved the diversity because it enables facile synthesis of homochiral and hetereochiral trisoxazolines. From the view point of ligand design, the possibility of introducing and combining different

substituents at the oxazoline rings, chiral or achiral units, even oxazoline ligands with opposite absolute configuration within the same tripodal ligand system allowed a straightforward access to a large variety of such systems. They also applied trisoxazolines in a number of enantioselective transformations, including cyclopropanation [28], amination [29], Mannich reaction [30], and kinetic resolution by transesterification [31].

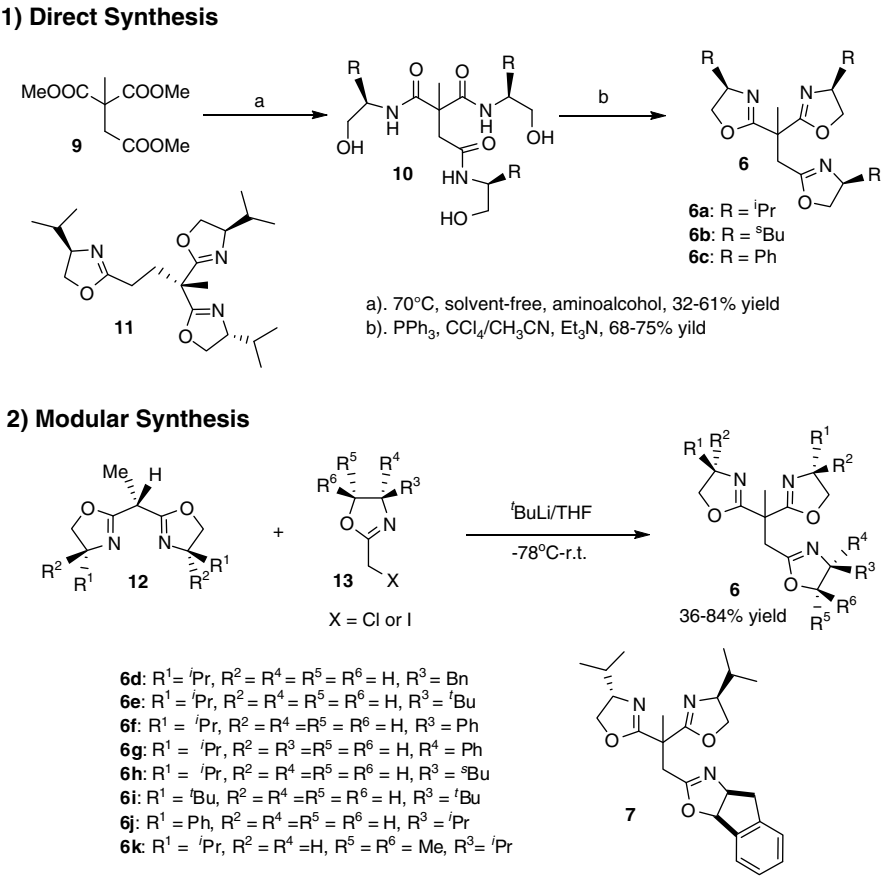
In contrast to the aforementioned efforts in the development of C_3-symmetrical trisoxazolines, we designed a pseudo-C_3-symmetric trisoxazoline construct **6** using a sidearm approach [32]. With an additional carbon on the linker, the third oxazoline might be regarded as a sidearm to a classical bisoxazoline, which might improve the catalyst stability and create a tunable chiral environment. Interestingly, we report our results with trisoxazoline **6** the same time Gade reported their trisoxazoline **5** in 2002. The only difference between trisoxazoline **5** and **6** is that the latter has a more flexible sidearmed oxazoline ring because of the additional methylene group on the sidearm. During our investigation of trisoxazoline **6** and **7** in asymmetric reactions, we also examined how this small difference influenced the catalytic properties. Here we summarize our studies in the development and application of pseudo-C_3-symmetric trisoxazoline construct **6** in asymmetric catalysis.

2 The Synthesis of Trisoxazolines 6 and 7

Trisoxazoline **6** was initially obtained via a direct synthesis from triester **9** and corresponding aminoalcohols in two steps. For example, triester **9** reacted with L-valinol without solvent at 70°C to afford white hydroscopic solid **10a** in 61% yield. Treatment of compound **10a** with PPh_3/CCl_4 afforded desired trisoxazoline **6a** as colorless oil in 75% yield [32]. Another type of pseudo-C_3-symmetric trisoxazoline **11**, with two CH_2 groups on the bridge, was also prepared in the same manner [33].

Although the direct synthesis allows facile preparation of trisoxazoline **6** in relatively short steps, it suffers from several drawbacks: (1) it fails to prepare heterochiral trisoxazolines or homochiral trisoxazolines with bulkier group such as benzyl and *tert*-butyl group; (2) in the key step of triamide **10** forming reaction, the yield is low in some cases; (3) although the PPh_3/CCl_4-mediated cyclization to afford trisoxazolines is mild and convenient, the separation of Ph_3PO from the final product entails careful choosing of eluent for column chromatography. In light of this, we turned to modular synthesis. Modular synthesis of trisoxazolines was developed by Florio and Gade. Florio et al. developed a novel tris(oxazolinyl)-cyclopropane via "trimerization" of metalated 2-chloroalkyl-2-oxazolines [34]. Almost at the same time, Gade and coworkers reported the preparation of C_3-symmetric trisoxazolines from bisoxazoline by addition–elimination reaction [27].

By modular synthesis, we successfully expanded the pseudo-C_3-symmetric trisoxazoline **6** based ligand library (Scheme 2). This improvement allows the incorporation of a wide variety of substituents such as benzyl, *t*-butyl, and indenyl



Scheme 2 The synthesis of trisoxazolines

groups to the stereogenic center to construct homochiral and heterochiral trisoxazolines. It should also be noted that homochiral trisoxazoline **6i**, which could not be prepared by the direct synthesis previously used, has been obtained successfully, demonstrating the superiority of the modular synthesis [35].

Experimental procedures for the synthesis of trisoxazolines:

By direct synthesis: (a) Under an atmosphere of N_2, to a Schlenk tube were added trimethyl 1,2,2-propanetricarboxylate **9** (3.72 g, 17 mmol) and L-valinol (7.04 g, 68 mmol). The resulting mixture was stirred at 70°C. After 10 h, the mixture was cooled down to 30°C, and the generated methanol was removed under reduced pressure. Then the reaction was heated to 70°C again. Repeat the same operation for six times (total reaction time: 70 h). The mixture was cooled to room temperature and was purified by chromatography on silica gel (pure ethyl acetate) to give **10a** as highly hydroscopic white solid (4.52 g, 61% based on the amount of **9**). (b) To a solution of compound **10a** (503 mg, 1.17 mmol) and triphenylphosphine

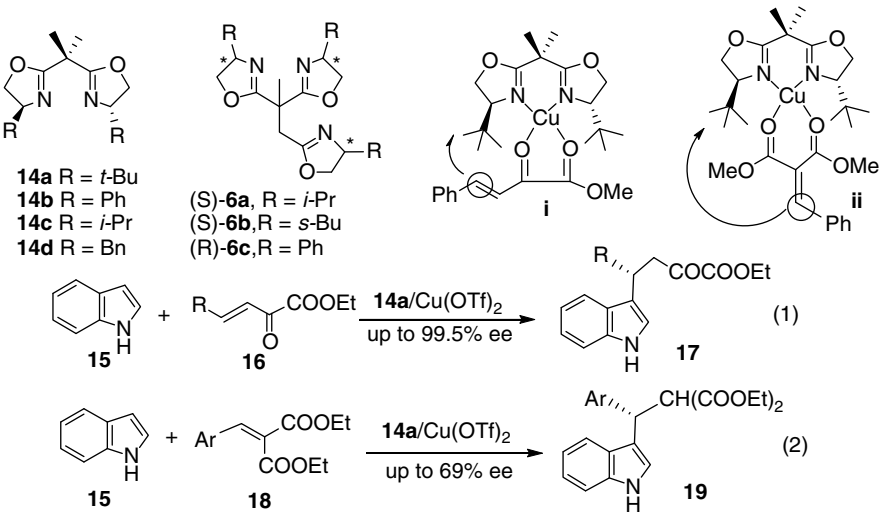
(1.84 g, 7.00 mmol) in a mixture of CCl_4 (5 mL) and CH_3CN (13 mL) was added 5 mL of triethylamine at 25°C under N_2. After 24 h, the mixture was diluted with ethyl acetate (10 mL) and washed with saturated aqueous $NaHCO_3$ (3 mL). The organic layer was separated. And the aqueous layer was extracted with ethyl acetate (5 × 3 mL). The combined organic layer was washed with saturated aqueous NaCl (5 × 2 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (acetone/petroleum ether, 1/4, v/v) to afford crude **6a** as pale yellow oil. The pure product was obtained by flash column chromatography on silica gel (ethyl acetate/petroleum ether, 1/1, v/v then ethyl acetate). Yield: 329 mg (75%).

By modular synthesis: (a) General Procedure for the Synthesis of 2-Chloromethyl Oxazolines **13**: To a stirred milky solution of methyl chloroacetimidate hydrochloride (5.5 mmol) in CH_2Cl_2 (15 mL) was added a solution of amino alcohol **6** (5.0 mmol) in CH_2Cl_2 by syringe, followed by the dropwise addition of triethylamine (0.75 mL, 5.5 mmol) at 0°C under nitrogen. The resulting mixture was stirred for 6–8 h at 20°C until the color of reaction mixture became pink. The solvent was removed under reduced pressure and the resulting paste was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were concentrated in vacuo to afford the crude product, which was purified by flash chromatography (petroleum ether/ethyl acetate = 1/6, containing 3% triethylamine) to give the pure product. (b) To a solution of bisoxazoline **12** (2.0 mmol) in dried THF (30 mL) was added dropwise *t*-BuLi (1.3 mL, 1.7 M in hexanes, 2.2 mmol) within 15–20 min at −78°C under nitrogen. The resulting yellow solution was stirred for an additional 1 h at this temperature. Then a solution of 2-chloromethyl oxazoline (2.8 mmol) in THF (10 mL) was added dropwise at −78°C over 10 min. The solution was slowly warmed to room temperature and was stirred for further 10 h. The mixture was diluted with CH_2Cl_2 (20 mL) and was washed with H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL) and the combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (petroleum ether/acetone = 1/10) to give the desired product.

3 The Application of TOX 6 and 7 in Asymmetric Reactions

Since the third oxazoline ring might be regarded as a sidearm to bisoxazoline **14**, trisoxazolines **6** were first employed to reactions catalyzed by BOX **14** derived chiral catalyst to evaluate the sidearm effect. The moment we obtained trisoxazoline **6a**, Jørgensen et al. reported asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated ketoesters **16** [36] (eq 1, Scheme 3) and alkylidene malonates **18** (eq 2) [37]. Interestingly, under the catalysis of ^{t}Bu-bisoxazoline **14a**/Cu(II) complexes, up to 99.5% ee was achieved in the addition of indole to ketoester **16** (eq 1), while only 50–69% ee in the case of alkylidene malonate **18** (eq 2).

The difference is probably due to the fact that the complexation of alkylidene malonates to copper would place the reacting center on the ligand C_2 axis and the prochiral center of the BOX/Cu-alkylidene malonate complex would not reside near the ligand chirality (**ii,** Scheme 3), in comparison with the unsaturated α-ketoester-Cu(II) complex (**i**, Scheme 3) [38].



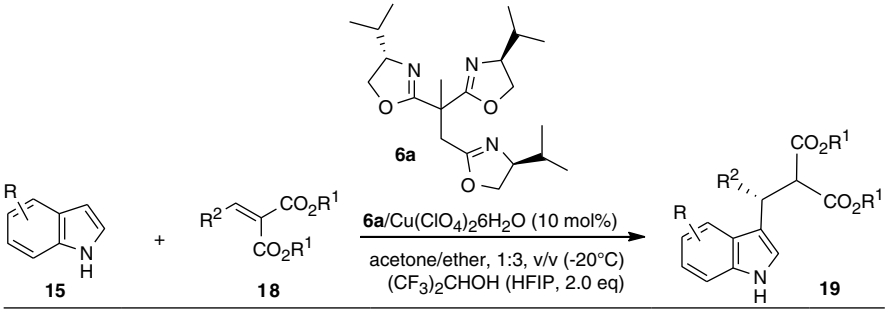
Scheme 3 The difference of enantiofacial control between the BOX **14a**/Cu(II) copper-catalyzed Michael addition of indole to ketoester **16** and alkylidene malonate **18**

3.1 Friedel–Crafts Reaction Catalyzed by Trisoxazoline 6a Copper Catalyst

Considering the structure difference between bisoxazoline and pseudo-C_3-symmetric trisoxazoline **8**, it was assumed that the sidearm might provide better face discrimination in the case of alkylidene malonates. TOX **6a** was first tried in the Friedel–Crafts reaction of indole with alkylidene malonates [32]. Initial study revealed that chiral catalyst **6a**/$Cu(ClO_4)_2 \cdot 6H_2O$ is water- and air-stable, and the reaction could be carried out in air. Up to 93% ee and 99% yield was achieved at −20°C in a mixed solvent of acetone and ether (1/3, v/v), with the aid of 2 eq of HFIP relative to malonates **23** to accelerate the reaction (Table 1). Different substituted indoles and arylidene malonates worked well at −20°C to afford excellent enantioselectivity. Ethylidene malonate is more reactive, so the reaction could be carried out at −78°C, and the enantioselectivity was improved to 85% (entry 11, Table 1).

During the investigation of the role of HFIP to accelerate the reaction, it was found that use of alcohols as the solvent could greatly accelerate this reaction and allow for the reaction to be carried out whilst exposed to air. Furthermore, the

Table 1 TOX **6a**/Cu(II) complex in Friedel–Crafts reaction



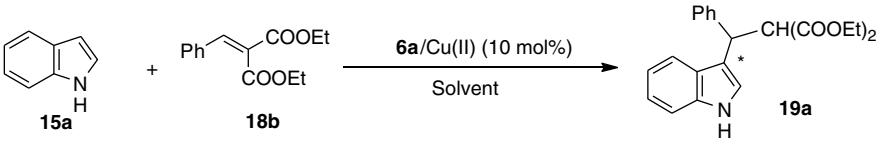
Entry	22	23	Yield (%)	Ee%
1	**15a**: R = H	**18a**: R^1 = Me, R^2 = Ph	98%	88%
2	**15a**: R = H	**18b**: R^1 = Et, R^2 = Ph	84%	89% (S)
3	**15b**: R = 4-methoxy	**18b**: R^1 = Et, R^2 = Ph	97%	91%
4	**15c**: R = 5-methoxy	**18b**: R^1 = Et, R^2 = Ph	73%	91%
5	**15d**: R = 5-methyl	**18b**: R^1 = Et, R^2 = Ph	92%	93%
6	**15a**: R = H, R_1 = Et	**18c**: R = 2-ClPh	99%	92%
7	**15a**: R = H, R_1 = Et	**18d**: R = 4-ClPh	84%	90%
8	**15a**: R = H, R_1 = Et	**18e**: R = 3-NO_2Ph	99%	91%
9	**15a**: R = H, R_1 = Et	**18f**: R = 4-NO_2Ph	99%	91%
10	**15a**: R = H, R_1 = Me	**18 g**: R = 4-NO_2Ph	99%	91%
11	**15a**: R = H, R_1 = Et	**18 h**: R^2 = Me (−78 °C)	84%	85%

enantioselectivity for S-enantiomer was found to be dependant on the alcohol solvent, the bulkier the alcohol the better the enantioselectivity (see control experiment A, Table 2). Very interestingly, a reversal of enantioselectivity was observed just by changing coordinating solvents to weakly coordinating solvents such as halogenated solvents, using the same ligand **6a** and the same Lewis acid $Cu(OTf)_2$. The triflate is important for the high ee of R-enantiomer (see control experiment B, Table 2 [39]).

After careful optimization, up to 98% ee for the S-enantiomer could be achieved when using isobutyl alcohol as the solvent at −25°C in the presence of TOX **6a**/$Cu(OTf)_2$, with the ratio of ligand **6a** to $Cu(OTf)_2$ being 1.2:1.0, while up to 89% ee for the R-enantiomer was obtained when using 1,1,2,2-tetrachloroethane (TTCE) as the solvent at 0°C, with the ratio of ligand **6a** to $Cu(OTf)_2$ being 1.0:1.5 (NOT 1.2/1.0!) (Scheme 4).

The synthetic utilization of the alkylation adducts was demonstrated by the transformation to the corresponding β-substituted tryptophans, one of useful tools in medicinal chemistry (for reviews, see: [40]). For example, treating adducts **7a** and **7h** with KOH in the mixed solvent of THF and ethanol (1:1, v/v) afforded hemiacid esters **20** and **22** in high yields, which could be readily converted to the corresponding β-substituted tryptophans **21** and **23** using the documented procedures (Scheme 4). One of the advantages of this process is that both enantiomers

Table 2 Control experiments

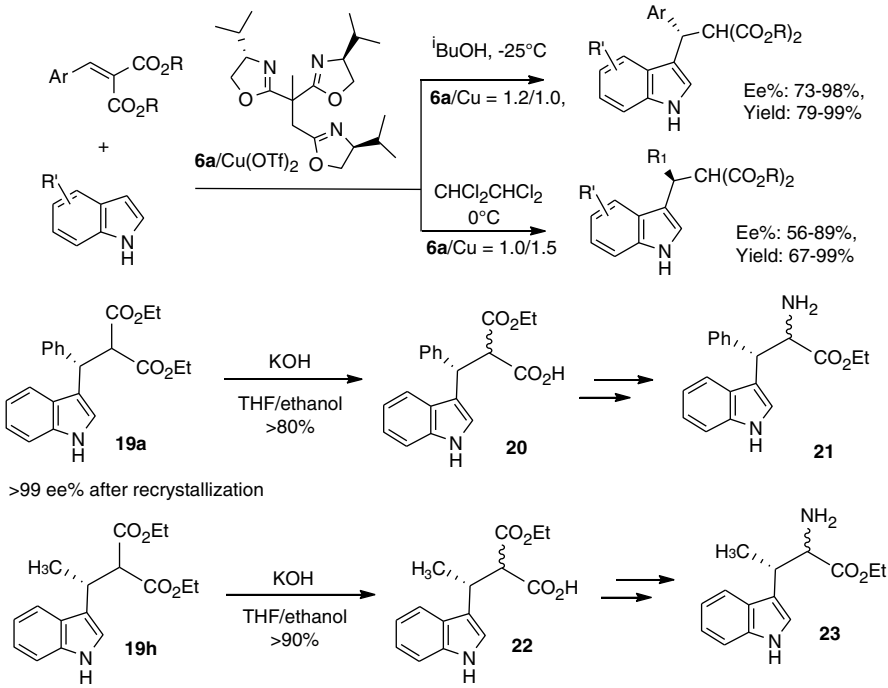


A: The influence of alcohol solvent on ee for *S*-enantiomer using **6a**/$Cu(OTf)_2$ (at 15°C)

Entry	Solvent	ee (%)
1	MeOH	48 (S)
2	EtOH	63 (S)
3	*n*-PrOH	85 (S)
4	*i*-PrOH	88 (S)
5	*i*-BuOH	90 (S)

B: Counteranion effect in $CHCl_2CHCl_2$ for *R*-enantiomer (at 0°C)

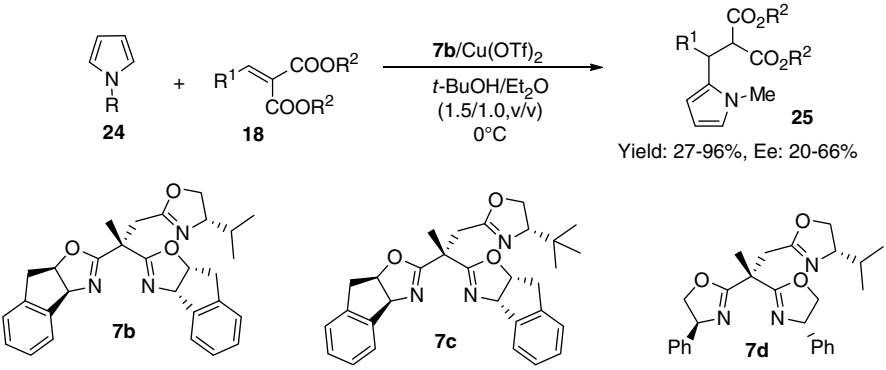
Entry	Catalyst	KOTf/Cu	ee (%)
1	**6a**/$Cu(ClO_4)_2 \cdot 6H_2O$ = 1.0/1.5	0	35 (R)
2	**6a**/$Cu(ClO_4)_2 \cdot 6H_2O$ = 1.0/1.5	5	74 (R)
3	**6a**/$Cu(OTf)_2$ = 1.0/1.5	0	80 (R)



Scheme 4 Reversal of enantioselectivity and product elaboration

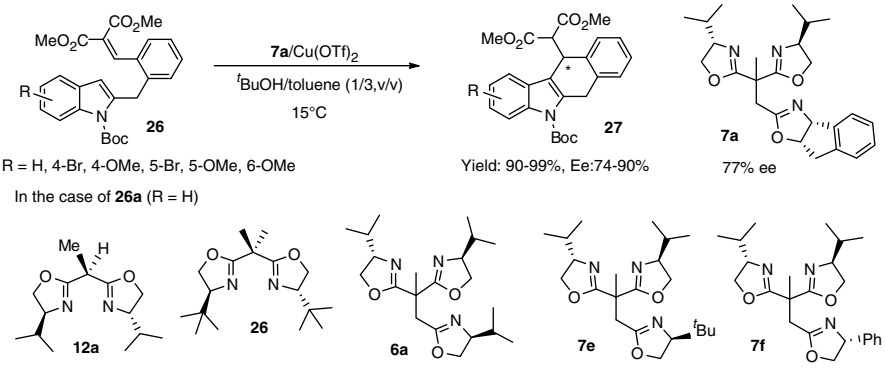
of the alkylation adduct **19a** can be obtained under mild conditions with high ee (both 99% ee after recrystallization) from the same catalyst, i.e., trisoxazoline **6a**/$Cu(OTf)_2$ complex, just by changing the solvent from isobutanol to TTCE (Scheme 4).

We also applied our trisoxazolines in the copper-catalyzed enantioselective addition of pyrrole to alkylidene malonates [41]. In this case, the hetereochiral trisoxazoline **7b** turned out to be the most enantioselective chiral ligand, with up to 66% ee. Other trisoxazolines, **7c** and **7d** for example, are less effective than **7b**, suggesting that the match of the substituent of the sidearmed oxazoline with that of the parent bisoxazoline would benefit the enantiofacial control (Scheme 5).



Scheme 5 Trisoxazoline **7b**/Cu(OTf)$_2$ catalyzed addition of pyrroles with alkylidene malonates

Very recently, we developed an enantioselective intramolecular Friedel–Crafts reaction of indolyl alkylidene malonates [42]. Some typical results are included in Scheme 6. As is clear, bisoxazolines **12a** and **26** afforded obviously inferior enantioselectivity, and all trisoxazolines provided better enantioselectivity. In this case, hetereochiral trisoxazolines again turned out to be superior to homochiral trisoxazolines. Trisoxazoline **7a** derived copper complex could afford the product in 74–90% ee in this transformation with excellent yields. This protocol provides a facile synthesis of polycyclic indole framework, a privileged subunit in products with biological activity.



Scheme 6 Intramolecular Friedel–Crafts reaction

*General Procedure for the preparation of the (+)-enantiomer of **19** using trisoxazoline **6a**/Cu(ClO$_4$)$_2$·6H$_2$O as the chiral catalyst*. To a Schlenk tube were added Cu(ClO$_4$)$_2$·6H$_2$O (0.10 eq) and (*S*)-isopropyl trisoxazoline **6a** (0.12 eq) in a mixed solvent of acetone–ether (1:3,v/v) under N$_2$ atmosphere. The solution was stirred at room temperature for 2 h and a mixture of malonate **18** (1.0 eq) and HFIP (2.0 eq) were added. The concentration of Cu^{2+} was maintained at 0.015 mol/mL. The resulting mixture was kept stirring for 15 min, then cooled to −20°C, and stirred for another 15 min before the indoles (1.2 eq) were added. After the reaction was complete (monitored by TLC), the solution was concentrated. The residue was purified by flash column chromatography on silica gel [eluted with CH$_2$Cl$_2$/petroleum ether (1/1, v/v) then pure CH$_2$Cl$_2$] to afford the desired product.

*General Procedure for the preparation of the (+)-enantiomer of **19** using trisoxazoline **6a**/Cu(OTf)$_2$ as the chiral catalyst in isobutanol*. Under air atmosphere, to a Schlenk tube was added Cu(OTf)$_2$ (0.10 eq), followed by (*S*)-isopropyl-trisoxazoline **6a**. Then ^{i}BuOH was added, and the concentration of Cu^{2+} was maintained at 0.005 mol/mL. The resulting blue-green solution was stirred at room temperature (10–25°C) for 2 h before alkylidene malonate (1.0 eq) was added into the mixture. The resulting mixture was kept stirring at room temperature for 15 min, then cooled to −25°C, and stirred for another 15 min before the indoles (1.2 eq) were added. After the reaction was complete (monitored by TLC), the reaction mixture was concentrated under reduced pressure at room temperature, and the residue was purified by flash column chromatography on silica gel [eluted with CH$_2$Cl$_2$/petroleum ether (1/1, v/v) then pure CH$_2$Cl$_2$] afforded the desired product.

*General Procedure for the preparation of the (−)-enantiomer of **19** using trisoxazoline **6a**/Cu(OTf)$_2$ as the chiral catalyst in TTCE*. 1,1,2,2-tetrachloroethane (TTCE) was purified as follows: TTCE (200 mL) was stirred with conc. H$_2$SO$_4$ at 80°C for about 10 min. Then the yellow acid layer was removed. This operation was repeated for several times until that conc. H$_2$SO$_4$ no longer turned yellow. The organic layer was washed successively by water, saturated NaHCO$_3$, and saturated NaCl solution. The resulting white emulsion was dried over Na$_2$SO$_4$, distilled under reduced pressure over P$_2$O$_5$, then over CaH$_2$, and stored under N$_2$ for use. It should be noted that oil temperature should keep below 80°C during the course of distillation, to avoid the decomposition of 1,1,2,2-tetrachloroethane. Under N$_2$ atmosphere, to a Schlenk tube was added Cu(OTf)$_2$ (0.10 eq), followed by (*S*)-isopropyl-trisoxazoline **6a** (0.067 eq). Then 1,1,2,2-tetrachloroethane was added. The concentration of Cu^{2+} was maintained at 0.01 mol/mL. The resulting blue cloudy solution, if catalyst solution is green, TTCE needs to be repurified, was stirred at 20°C for 2 h before alkylidene malonate (1.0 eq) was added into the mixture. The resulting mixture was stirred at 20°C for 30 min until the mixture was clear. Then the reaction system was cooled to 0°C and stirred for another 15 min before the indoles (1.2 eq) were added. The reaction mixture was quenched by silicon gel when the reaction was complete (monitored by TLC). Purification by flash column chromatography on silica gel [eluted with CH$_2$Cl$_2$/petroleum ether (1/1, v/v), then pure CH$_2$Cl$_2$] afforded the desired product.

*General Procedure for the preparation of **25** using trisoxazoline **7b**/Cu(OTf)$_2$ as the chiral catalyst*. A mixture of Cu(OTf)$_2$ (9.0 mg, 0.025 mmol) and ligand **7b** (14 mg, 0.03 mmol) was stirred in *t*-BuOH (1.5 mL) at room temperature for 0.5 h. Then a solution of malonate **18** (62 mg, 0.25 mmol) in ether (1 mL) was added. The resulting mixture was stirred at 0°C for 20 min and *N*-methyl pyrrole (0.044 mL, 0.3 mmol) was added. After the reaction was complete (monitored by TLC), the mixture was filtered rapidly through a glass funnel with a thin layer of silica gel and eluted with dichloromethane. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography.

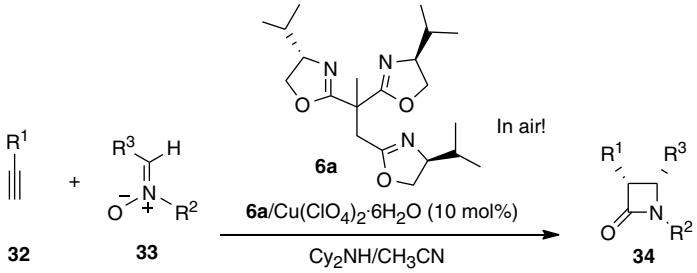
*General Procedure for the preparation of **27** using trisoxazoline **7a**/Cu(OTf)$_2$ as the chiral catalyst*. A mixture of Cu(OTf)$_2$ (0.01 mmol) and TOX **7a** (0.012 mmol) in toluene/^{t}BuOH (3 mL/1 mL) was stirred at 40°C for 2 h under nitrogen atmosphere. After the mixture was cooled to 15°C, substrate **26** (0.1 mmol, 45 mg) was added and the resulting mixture was stirred at 15°C until the reaction is complete (determined by ^{1}H NMR analysis). The mixture was filtered through a thin layer (40 mm) of silica gel (300–400 mesh), and eluted with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography.

3.2 Kinugasa Reaction

Although this reaction was developed in 1972 and has been regarded as an efficient protocol for the preparation of β-lactams, previously reports were all focused on the use of Cu(I) salts as the catalyst, so that the reaction must be performed under an inert atmosphere to suppress the Glaser oxidative coupling (for a highlight about Kinugasa reaction, please see: [43]). With trisoxazoline **6a**, we found for the first time that Cu(II) salts worked well in this reaction (Table 3). Trisoxazoline **6a**/Cu(ClO$_4$)$_2$·6H$_2$O could promote this reaction well under an aerobic atmosphere, greatly simplified the procedures. Bases were found to strongly influence the course of the reaction, and dicyclohexylamine turned out to be the best base. Different aromatic substituted nitrones **33** readily reacted with four different alkynes **32** to afford the desired lactams. Up to 97/3 *cis*/*trans* selectivity and 85% enantioselectivity for *cis* isomer was achieved when the secondary amine dicyclohexylamine was used as a base [44]. This reaction now has a limitation: only aromatic substituted nitrones worked well.

In this reaction, it is possible to employ ^{13}C NMR technique to investigate the role of the sidearm oxazoline in trisoxazoline **6a**, since both Cu(II) and Cu(I) could promote the reaction well under the same conditions, although Cu(I) demonstrated lower selectivity [45]. Considering that Cu(II) is paramagnetic and Cu(I) was the possible catalytic species in the reaction, CuCl was used for the ^{13}C NMR study instead of Cu(ClO$_4$)$_2$·6H$_2$O. In the absence of CuCl, the ^{13}C chemical shifts of the three sp^2 carbon atom of oxazolines in TOX **6a** appeared at δ 163.71, 167.38, and 167.43 ppm. However, after complexation with CuCl, the ^{13}C signals merged at

Table 3 Trisoxazolines in Kinugasa reaction



32 **33** **34**

Entry	R^1	R^2/R^3	*cis/trans*	ee (*cis*,%)	Yield (%)
1	Ph	Ph/Ph	94/6	82	56
2	Ph	*o*-MeC_6H_4/Ph	95/5	82	36
3	Ph	*o*-$MeOC_6H_4$/Ph	97/3	84	36
4	Ph	*o*-BrC_6H_4/Ph	93/7	74	70
5	Ph	*o*-$EtO_2CC_6H_4$/Ph	91/9	70	98
6	Ph	Ph/*o*-MeC_6H_4	95/5	82	50
7	Ph	Ph/*o*-$MeOC_6H_4$	95/5	83	58
8	Ph	Ph/*o*-$CF_3C_6H_4$	93/7	82	75
9	Ph	Ph/2-Furanyl	67/33	85	56
10	Ph	Ph/Ph	96/4	84	35
11	p-CF_3Ph	Ph/Ph	75/25	73	65
12	Cyclohexyl	Ph/Ph	93/7	72	35
13	EtO_2C	Ph/Ph	86/14	80	50
14	Me_3Si	Ph/Ph	No reaction		

164.32 ppm, and the merging was also observed for both the O- and N-bound sp^3 carbons. These results suggested that all three nitrogen atoms of TOX **6a** might coordinate to copper in the catalyst–substrate complex. After the addition of equimolar phenylacetylene **32a** and Cy_2NH, the single signal of the ^{13}C signals of three sp^2 carbon of oxazolines and the O- and N-bound sp^3 carbons split again into three peaks. The ^{13}C analysis suggested that decoordination of the pendant oxazoline might occur when copper(I) phenylacetylide formed, consistent with the coordination/decoordination equilibrium proposed by Gade et al. in the trisoxazoline **5a/**Cu(II) catalytic system [46].

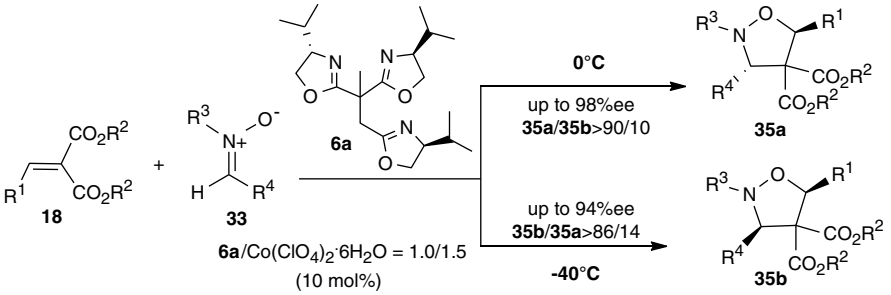
*General Procedure for the preparation of lactam of **34a** using trisoxazoline **6a/**$Cu(ClO_4)_2 \cdot 6H_2O$ as the chiral catalyst*. A mixture of $Cu(ClO_4)_2 \cdot 6H_2O$ (9.3 mg, 0.025 mmol) and (*S*)-isopropyl trisoxazoline **6a** (11.3 mg, 0.03 mmol) in CH_3CN (4 mL) was stirred under air atmosphere at 15°C for 2 h. The solution was cooled to 0°C and then Cy_2NH (50 μL, 0.25 mmol) was added. After 10 min, alkyne (0.375 mmol) was added. When the color of the resulting mixture turned light yellow, we added nitrone (0.25 mmol) to the solution. After the reaction was complete (monitored by TLC), the mixture was passed through a short silica gel column (neat CH_2Cl_2 as the eluent). The filtrate was concentrated, and the residue was purified by flash chromatography (PE/CH_2Cl_2) to afford the product. The diastereoselectivity

was determined by ^{1}H NMR spectroscopic analysis of the crude product. The determination of enantioselective excess of the *cis*-isomer was performed by chiral HPLC with a Daicel Chiralcel OD-H column (eluent: hexane/^{i}PrOH 80/20, flow rate: 0.7 mL/min).

3.3 1,3-Dipolar Cycloaddition

Since TOX **6a** derived copper catalyst was capable of providing enough face discrimination for alkylidene malonates, our new reaction design was based on this type of substrates. Alkylidene malonates could be easily prepared from aldehyde and malonates via Knoevenagel condensation. This type of substrates has high reactivity towards nucleophiles and might form stable six-membered ring after complexation with metal cations, which is important to achieve high selectivity. We tried our pseudo-C_3-symmetric TOX **6a** in the dipolar cycloaddition of nitrones **18** and alkylidene malonates **33** [47], because the reaction of nitrones with electro-deficient olefins could provide highly substituted isoxazolidines with multiple stereocenters. This versatile and atom-economical process has been applied to the preparation of both β-lactams and β′-hydroxy-β-amino acids, which are important motifs in many biologically active molecules [48–50]. TOX **6a** in combination with $Co(ClO_4)_2{\cdot}6H_2O$ proved to be excellent chiral catalyst in this case (Table 4). It should be noted that much better enantioselectivity was observed when the ratio of trisoxazoline **6a** and

Table 4 Trisoxazolines in 1,3-dipolar cycloaddition



			0°C			−40°C		
Entry	R^1/R^2	R^3/R^4	Yield(%)	**35b/35a**	ee (%)	Yield(%)	**35b/35a**	ee (%)
1	*p*-BrC_6H_4/Et	Ph/Ph	99	95/5	95	88	5/95	80
2	*p*-$NO_2C_6H_4$/Et	Ph/Ph	93	97/3	94	99	10/90	83
3	*p*-MeC_6H_4/Et	Ph/Ph	95	95/5	92	99	14/86	88
4	Ph/Et	Ph/Ph	94	97/3	95	81	11/89	93
5	Ph/Et	*p*-MeC_6H_4/Ph	94	99/1	91	77	14/86	87
6	Ph/Et	*p*-BrC_6H_4/Ph	76	99/1	95	90	10/90	80
7	Ph/Bu^i	*p*-BrC_6H_4/Ph	95	99/1	96	38	12/88	94
8	*c*-Hex/Et	*p*-BrC_6H_4/Ph	91	90/10	89	99	14/86	71

$Co(ClO_4)_2 \cdot 6H_2O$ was 1.0/1.5 rather than 1.2/1.0, the same feature was also observed in the synthesis of R-enantiomer in the indole alkylation shown in Table 1.

General procedures for cycloaddition between nitrones and alkylidene malonates to give exo products using trisoxazoline ***6a****/*$Co(ClO_4)_2 \cdot 6H_2O$ *as the chiral catalyst.* A mixture of $Co(ClO_4)_2 \cdot 6H_2O$ (4.6 mg, 0.013 mmol, 5 mol%) and ligand **6a** (3.1 mg, 0.0087 mmol, 3.3 mol%) in the mixture of toluene and isopropyl acetate (1.5 mL) was stirred at 50°C for 4 h under N_2 atmosphere. After cooling to room temperature, the pale amaranth solution was added into a reaction tube with powdered MS 4 Å (250 mg). To this mixture was added the solution of alkylidene malonate (0.3 mmol) in the mixture of toluene and isopropyl acetate (1 mL). After stirring for 0.5 h at 0°C, nitrone (0.25 mmol) was added. The resulting suspension was stirred for 20 h at 0°C. Then 0.5 mL of TMEDA was added and stirred for additional 10 min. After the reaction was finished (monitored by TLC), the reacting mixture was filtrated through silica gel and eluted with ethyl acetate. The filtrate was concentrated under reduced pressure to give crude product, which was used to determine the diastereomer ratio by ^{1}H NMR. The residue was purified by flash chromatography (silica gel, petroleum ester/ethyl acetate) to afford the pure product. The ee was determined by HPLC analysis using a chiral column (Chiralcel AD column with hexane/*i*-PrOH as eluent).

General procedures for cycloaddition between nitrones and alkylidene malonates gave endo products catalyzed by Co(II)/TOX. A mixture of $Co(ClO_4)_2 \cdot 6H_2O$ (4.6 mg, 0.013 mmol, 5 mol%) and TOX **6a** (3.1 mg, 0.0087 mmol, 3.3 mol%) in the appropriate solvent (1.5 mL) was stirred at 30°C for 4 h under N_2 atmosphere. To the pale amaranth solution was added flame-activated MS 4 Å powder 250 mg and alkylidene malonate in the mixture of toluene and isopropyl acetate (1 mL). After stirring for 0.5 h at −40°C, nitrone was added. The resulting suspension was stirred for the appropriate time at −40°C. After the reaction was finished (monitored by TLC), 1.0 mL of TMEDA was added. After stirring for additional 30 min at −40°C, the resulting mixture was filtrated through silica gel (eluted with ethyl acetate). The filtrate was concentrated under reduced pressure to give crude product. The ratio of diastereoisomers was determined by ^{1}H NMR. The residue was purified by flash chromatography (silica gel, petroleum ester/ethyl acetate) to afford the desired product. The ee was determined by chiral HPLC.

3.4 Diels–Alder Reaction

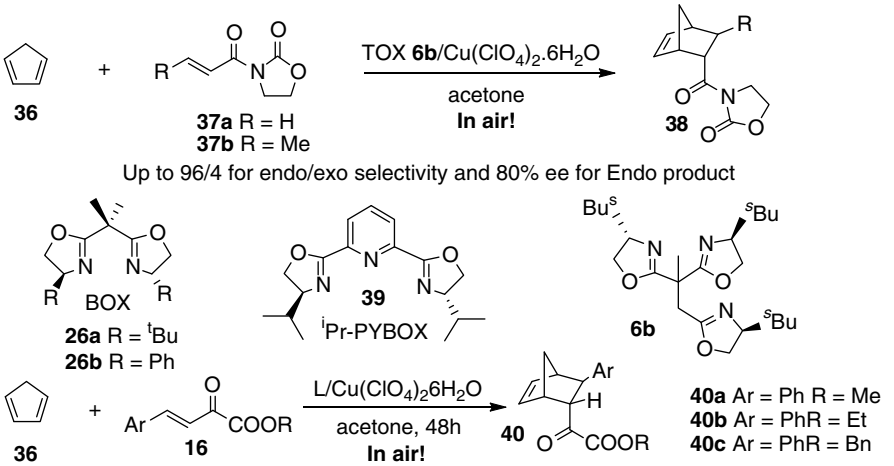
Since Diels–Alder reaction of cyclopentadiene **36** with 2-oxazolidinone **37** is very important to enantioselectively construct six-membered carbocycles [51], we also examined the efficiency of trisoxazoline derived catalyst in this reaction.

When using acetone as the solvent in air, ^{s}Bu-substituted trisoxazoline **6b**/$Cu(ClO_4)_2 \cdot 6H_2O$ complex could afford up to 80% ee for the endo product (96/4 endo/exo) in the case of oxazolidinone **37**, which is inferior to the results obtained

with bisoxazoline **26a**. But in the reaction of ketoester **16** with cyclopentadiene, 71% ee for endo product (97/3 endo/exo) could be achieved. Several frequently used bisoxazolines were also examined in the cycloaddition of cyclopentadiene with ketoesters. However, *tert*-butyl and phenyl substituted BOX **26a** and **26b** failed to achieve better results than trisoxazoline **6b** (Table 5). Noticeably, ^{i}Pr-substituted PYBOX **39** showed much lower catalytic activity than other ligands, higher temperature (0°C) was required to complete the reaction, whilst −35°C was sufficient for others.

General procedures for catalytic Asymmetric Diels–Alder Reaction using trisoxazoline ***6b/Cu(ClO$_4$)$_2$·6H$_2$O*** *as the chiral catalyst*: To a Schlenk tube was added Cu(ClO$_4$)$_2$·6H$_2$O (0.10 eq), followed by trisoxazoline **6b** (0.12 eq), then acetone under air atmosphere. The concentration of chiral catalyst was maintained at 0.02 mol/mL. The solution was stirred at room temperature for 2 h, and acryloyl-2-oxazolidinones or ketoester (1.0 eq) was added. The resulting mixture was kept stirring for 15 min, then cooled to the indicated temperature, and stirred for another 15 min before the cyclopentadiene (5.0 eq) was added. After the reaction was complete (monitored by TLC), the solution was concentrated. The residue was purified by flash column chromatography on silica gel to afford the desired product.

Table 5 Trisoxazolines in Diels–Alder reaction



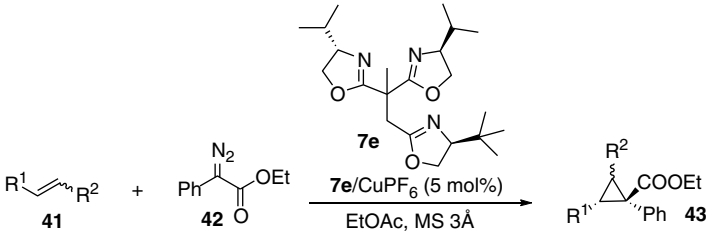
Entry	Ligand	**16**	Temp (°C)	Yield (%)	Endo/exo	ee% (endo)
1	**26a**	**16a**	−35	52	8/92	53
2	**26b**	**16a**	−35	58	8/92	0
3	**39**	**16a**	0	63	12/88	4
4	**6b**	**16a**	−35	64	3/97	71
5	**6b**	**16b**	−35	82	3/97	64
6	**6b**	**16c**	−35	47	3/97	62

3.5 Cyclopropanation Reaction

Cyclopropane derivatives are valuable synthetic building blocks in organic synthesis [52–55]. While chiral rhodium catalysts achieved good diastereoselectivity and enantioselectivity in the cyclopropanation of styrene with aryldiazoacetates [56–64], nonrhodium catalysts failed to work well. We found that hetereochiral trisoxazoline **7e** in combination with $CuPF_6$ worked efficiently in cyclopropanation of alkenes **41** and aryldiazoacetate **42**, affording tri- or tetra-substituted cyclopropane derivatives **43** with high diastereoselectivity and enantioselectivity. Solvent significantly influenced this reaction: no cyclopropanation product could be detected in hexane or toluene, and reaction proceeded well in coordinating solvents. EtOAc was the optimal solvent for this reaction, and the desired product could be obtained in excellent selectivity. The generality of this reaction was good, a series of alkenes worked well in this reaction, and only single diastereomers could be detected in all the cases (Table 6) [65].

*General procedures for catalytic asymmetric Cyclopropanation reaction using trisoxazoline **7e/**$CuPF_6$ as the chiral catalyst*. A mixture of $CuPF_6(CH_3CN)_4$ (7.7 mg, 0.021 mmol), trisoxazoline **7e** (9.0 mg, 0.023 mmol), alkene **41** (1.9 mmol, 5 eq) in ethyl acetate (1 mL) was stirred at room temperature for 2 h. The resulting mixture was heated to 40°C and then MS 3 Å (200 mg) was added. To this solution was injected ethyl phenyldiazoacetates **42** (78 mg, 0.42 mmol) in 2 mL of ethyl acetate via a syringe pump within 6 h. After the reaction was complete (monitored by TLC), the mixture was filtered rapidly through a glass funnel with a thin layer of silica gel and eluted with dichloromethane. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate) to afford the desired product.

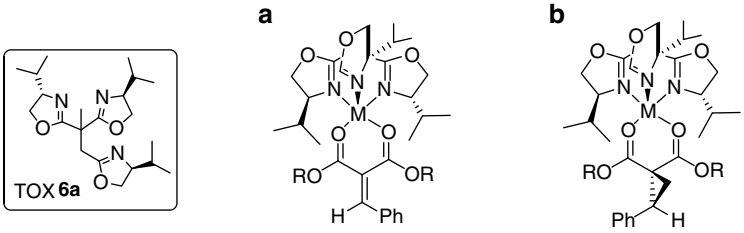
Table 6 Trisoxazolines in cyclopropanation reaction



Alkenes				BuO	Ph	Ph
Yield	85%	80%	86%	99%	51%	99%
ee	87%	83%	90%	82%	82%	89%

3.6 Cycloaddition of Cyclopropanes with Nitrones

Trisoxazoline **6** and **7** in combination with suitable metal salts have been successfully applied for some enantioselective transformations involving alkylidene malonates **18**. In these transformations, it was assumed that malonates coordinated to the metal center in a bidentate fashion to maximize the activation (**A**, Scheme 7), and trisoxazoline **6** could provide enough chiral discrimination to achieve excellent selectivity. Naturally, we speculated that cyclopropane-1,1-dicarboxylates might coordinate to TOX **6** derived chiral Lewis acid in the same way as alkylidene malonates do (**B**, Scheme 7), so it is possible to achieve high enantioselectivity in catalytic transformations employing cyclopropane-1,1-dicarboxylates as the substrates.

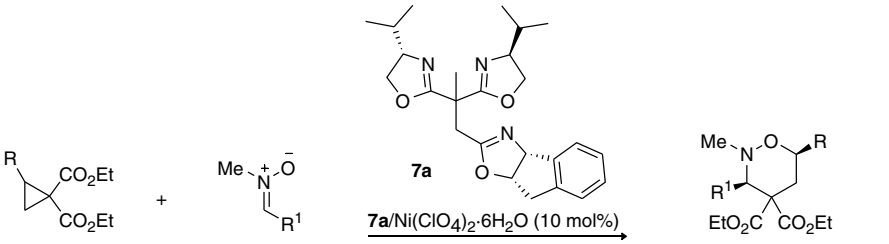


Scheme 7 Proposed coordination fashion of alkylidene malonates and cyclopropane-1,1-diesters to TOX/M^{n+} complex

In light of the above analysis, we tried the dipolar homo [3+3] cycloaddition between cyclopropane-1,1-dicarboxylates and nitrones, which provides an easy access to both optically active tetrahydro-1,2-oxazine derivatives and 2-substituted cyclopropane-1,1-dicarboxylates with high enantioselectivity, which has been applied to the total synthesis of natural products [66, 67]. Chiral catalyst TOX **7a**/$Ni(ClO_4)_2 \cdot 6H_2O$ turned out to be a powerful catalyst for this kinetic resolution, which provided optically active tetrahydro-1,2-oxazine derivatives in high diastereoselectivity and enantioselectivity (Table 7) [68]. Both electron-deficient and electron-rich α-aryl nitrones worked well with high selectivity. A styryl-substituted nitrone also afforded good selectivity. The effect of substituents on 2-position of cyclopropane-1,1-dicarboxylates was also examined, showing that 2-vinyl and styryl substituted cylcopropane **44** afforded lower selectivity than phenyl substituted one.

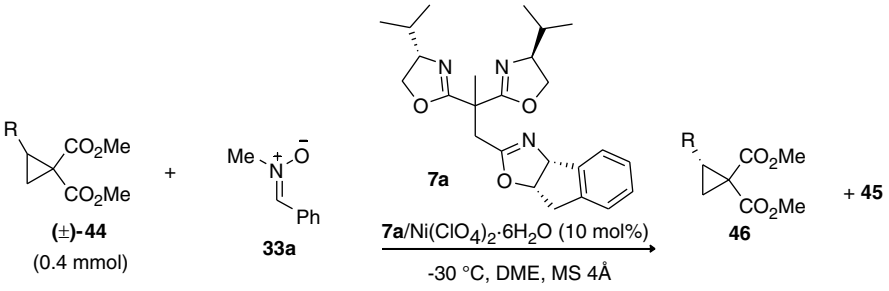
During the studies on the [3+3] cycloaddition described in Table 7, we found that it needed 2 eq of cyclopropane-1,1-dicarboxylate **44** to ensure high enantioselectivity and diastereoselectivity, and very interestingly, cyclopropane **44** could be recovered with high enantioselectivity. Since two-substituted cyclopropane-1,1-dicarboxylates **44** are very useful synthetic intermediate in organic synthesis, it is important to develop new method to obtain enantiopure compounds. We next carefully checked the effect of substrates ratios on the enantioselectivity of recovered

Table 7 Asymmetric cycloaddition of cyclopropanes with nitrones



Entry	R	R_1	*T* (days)	Yield (%)	Dr (%)	ee (%)
1	Ph	Ph	4	88	11:1	95
2	Ph	4-BrC_6H_4	4	85	12:1	97
3	Ph	4-MeO_2CC_6H_4	4	97	11:1	97
4	Ph	4-MeC_6H_4	4	80	12:1	96
5	Ph	4-MeOC_6H_4	4	92	13:1	90
6	Ph	2-furyl	4	99	13:1	93
7	Ph	Styryl	3	76	4:1	92
8	Vinyl	Ph	3	88	6:1	80
9	Styryl	Ph	5	84	5:1	80
10	Ph	Ph	5	74	11:1	93

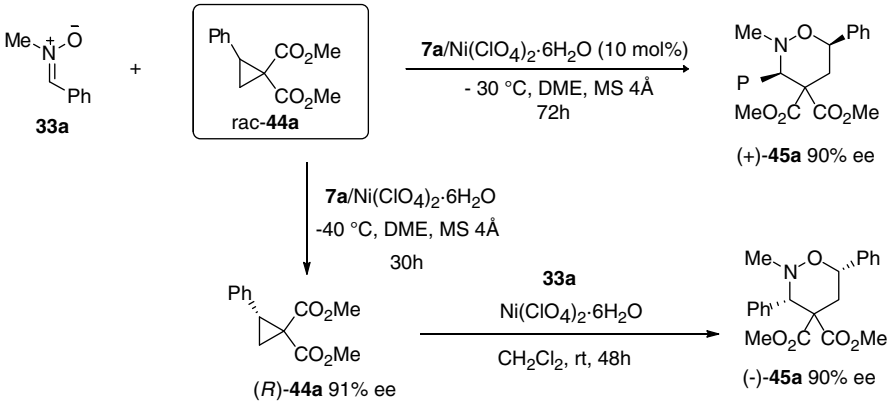
Table 8 Kinetic resolution of 2-substitutedcyclopropane-1,1-dicarboxylates



Entry	R	**33a** (mmol)	*S*	*T* (h)	ee (%)	Recovery of **44** (%)
1	Ph	0.40	16	30	91	43
2	4-MeC_6H_4	0.25	97	48	96	49
3	4-BrC_6H_4	0.23	81	67	95	49
4	4-F_3CC_6H_4	0.23	97	168	96	49
5	4-$NO_2C_6H_4$	0.23	36	96	97	45
6	4-ClC_6H_4	0.23	70	72	94	49
7	4-MeOC_6H_4	0.23	13	48	92	40

cyclopropane. The ee of recovered (*R*)-**44** highly depends on substrates ratio and conversion of **44**. Basically, a little bit excess of nitrone (see Table 8) could ensure the high ee of the recovered cyclopropanes. Seven cyclopropane-1,1-dicarboxylate **44** could be recovered in high enantioselectivity.

We also found that optically active cyclopropane-1,1-dicarboxylate **44a** could readily react with nitrone **33** in the presence of $Ni(ClO_4)_2{\cdot}6H_2O$ catalyst, to afford the corresponding tetrahydro-1,2-oxazine **45a** in high yield without loss of enantioselectivity. With this aid, both enantiomers of the tetrahydro-1,2-oxazine could be prepared from racemic 2-phenyl cyclopropane **44a** by TOX **7a**/$Ni(ClO_4)_2{\cdot}6H_2O$-catalyzed cycloaddition with nitrone or kinetic resolution followed by cycloaddition with the nitrone (Scheme 8).



Scheme 8 Synthesis of both enantiomers of the 1,2-oxazine **45a**

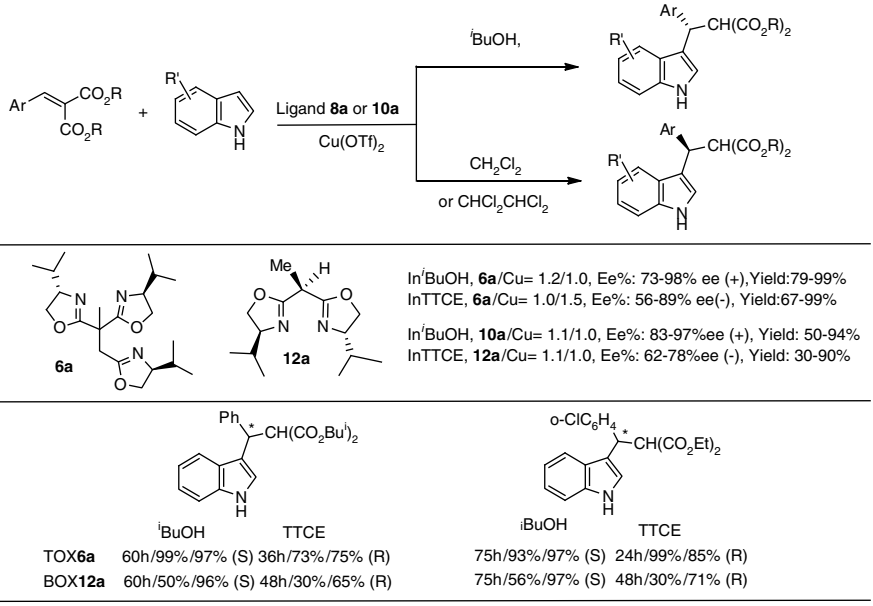
General procedures for catalytic asymmetric [3+3] cycloaddition using trisoxazoline ***7a****/Ni(ClO*$_4$*)*$_2$*·6H*$_2$*O as the chiral catalyst*. Typical procedure for the enantioselective [3+3] cycloaddition: A mixture of $Ni(ClO_4)_2{\cdot}6H_2O$ (0.040 mmol) and the trisoxazoline **7a** (0.044 mmol) in dimethoxyethane (1 mL) was stirred at 50°C for 2 h under nitrogen. The mixture was then cooled to room temperature and added to the cyclopropane diester **44** (0.44 mmol) with a syringe. Activated molecular sieves 4 Å (100 mg) was added to the resulting solution. The mixture was stirred at −30°C for 30 min, and then the nitrone (0.20 mmol) was added. When the reaction was complete (monitored by TLC), the mixture was passed rapidly through a glass funnel with a thin layer (20 mm) of silica gel (300–400 mesh), which was then washed with CH_2Cl_2 (50 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography to afford the product.

The general procedure for the kinetic resolution of two-substituted cyclopropane 1,1-diesters is similar to that for the enantioselective [3+3] cycloaddition. The reaction was carried out at the desired temperature, and the ratio of the nitrone **33a** to the racemic 2-substituted cyclopropane diester **44** was changed (see Scheme 15). The reaction was quenched when the conversion of **44** was equal to or higher than 50% (monitored by H NMR spectroscopy).

4 Trisoxazoline vs. Bisoxazoline

As our trisoxazoline could be regarded as a sidearmed bisoxazoline, with a pendant sidearm oxazoline ring as the sidearm, it is very interesting to evaluate how the sidearm influences the catalyst properties, for the modification and improvement of new ligand. We first checked the sidearm effect in the Friedel–Crafts reaction of indoles and alkylidene malonates, since it was found that the use of isobutyl alcohol as the solvent could greatly improve the reactivity and enantioselectivity in the presence of trisoxazoline **6a**/$Cu(OTf)_2$ as the chiral catalyst. It was speculated that the coordination of the isobutyl alcohol to the copper center made the chiral environment more effective. Based on this analysis, we further checked that if the use of isobutanol as the solvent could achieve excellent enantioselectivity when using a simple isopropyl substituted bisoxazoline as the chiral ligand, and finally developed a highly tunable and enantioselective indole alkylation with alkylidene malonates using cheap and simple bisoxazoline **12a** (Scheme 9) [69]. This made a detailed comparison possible between trisoxazoline **6a** and bisoxazoline **12a**.

Generally, as compared to bisoxazoline **12a**, trisoxazoline **6a**/Cu(II) complexes showed higher catalytic activity, better enantiofacial control, and broader substrate scope, as well as better enantioselectivity under milder reaction conditions. We listed two examples in Scheme 9 for a brief comparison: when using ^{i}BuOH as solvent, although the ee for the *S*-enantiomer was similar, BOX **12a** afforded obviously poorer yield and could only achieve above 90% ee (for S-enantiomer) at low



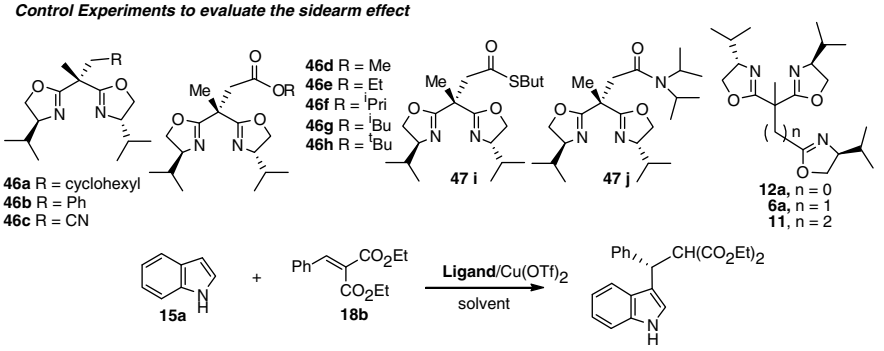
Scheme 9 The comparison of BOX 12a with TOX **6a** in the Friedel–Crafts reaction

temperature (−25°C) using ^{i}BuOH, whereas TOX **6a** could achieve the same levels of enantioselectivity even at 15°C. When using CH_2Cl_2 or $CHCl_2CHCl_2$ as the solvent, BOX **12a** was significantly inferior to TOX **6a** in respect to both reactivity and enantioselectivity.

Compared to its bisoxazoline congener, it was believed that the coordination of the sidearm oxazoline to the copper center significantly improved the catalytic properties (both electronic and steric). Unfortunately, we tried in vain to get the single crystal of chiral **6a**/Cu(II) complex or chiral **6a**/Cu(II)-malonate **18** complex. To obtain substantial evidence for understanding the role of the sidearm, we synthesized a variety of bisoxazoline **46**, substituting the third oxazoline ring by a range of functional group sidearms, including noncoordinating or coordinating, small or bulkier sidearm [33]. Evaluation of sidearm effects was conducted with the model reaction of indole **15a** with benzylidene malonate **18b**. Results shown in Scheme 10 strongly supported the coordination of the sidearm oxazoline of TOX **6a** to the copper center. In THF, when a noncoordinating bulky group such as cyclohexyl was employed as a sidearm, only moderate ee (48%) was obtained; in sharp contrast, even the relatively small coordinating sidearm in a cyano group improved the ee to 61%. Furthermore, the bulkier the coordinating sidearm, the better the ee. The length of the sidearm oxazoline also significantly influenced both the reactivity and enantioselectivity (A, Scheme 10). These results supported the idea that coordination of the sidearmed oxazoline in TOX **6a**, tuned the electronic and steric properties of the catalyst to influence the enantioselectivity and reactivity.

In the following studies, we continued to pay attention to the investigation of the difference of bisoxazoline **12a** and trisoxazoline **6** or **7**, aiming at providing more information on how sidearm influenced the catalyst property. Table 9 summarized the published results demonstrating the difference between the two types of chiral

Control Experiments to evaluate the sidearm effect

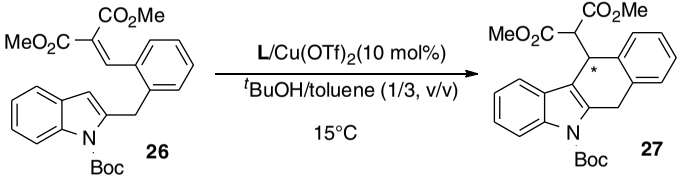
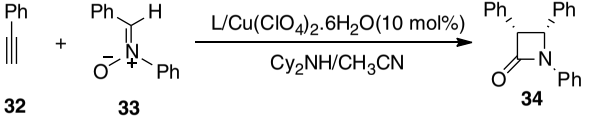
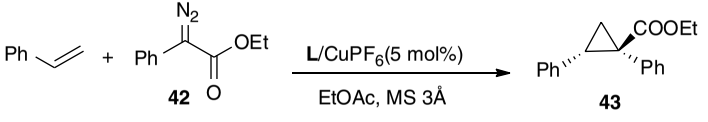
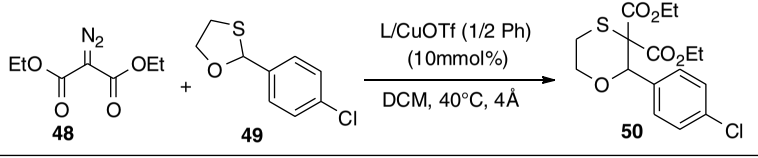


A: Evaluation of the side-arm effects in THF

Ligand	46a,	46b,	46c,	46d,	46e,	46f,	46g,	46h,	46i,	46j,	46a,	6a,	11
ee% (+)	48	37	61	73	72	73	74	79	80	72	60	82	67

Scheme 10 Evaluation of sidearm effects in the Friedel–Crafts reaction

Table 9 The differences between BOX **12a** and TOX **6** or **7** in some asymmetric reactions

Entry	Model reaction	**12a**	**6** or **7**
1		Time: 10 h Yield: 99% Ee: 41%	L: TOX **7a** Time: 4 h Yield: 99% Ee: 77%
2		Time: 6 d Yield: 33% Dr: 43:1 Ee: 36%	L: TOX **6a** Time: 15 h Yield: 60% Dr: 13:1 Ee: 80%
3		Yield: 80% Ee: 68%	L: TOX **7e** Yield: 92% Ee: 92%
4		Time: 39 h Yield: 65% Ee: 52%	L: TOX **7a** Time: 39 h Yield: 44% Ee: 80%

ligands. These results demonstrated that the introduction of a sidearmed oxazoline ring to bisoxazoline framework indeed significantly influenced the catalyst property, so that enantioselectivity could be obviously improved in most cases. In the intramolecular Friedel–Crafts reaction, hetereochiral trisoxazoline **7a** afforded obviously higher reactivity and ee (entry 1, Table 9).

The most significant difference was observed in the Kinugasa reaction. While the reaction catalyzed by trisoxazoline **6a-**derived copper catalyst could proceed efficiently in air, it took as long as six days for the corresponding bisoxazoline **12a** to obtain full conversion, with much inferior yield and enantioselectivity (entry 2). The reason might be due to the fact that trisoxazolines provided stronger chelation with copper center than bisoxazolines to prevent effectively phenylethynylcopper from its coordination polymerization. During the reaction, we did observe a small amount of yellow precipitation formed in the bisoxazolines **12a**/Cu(II) reaction system, but a clear solution occurred in the case of trisoxazolines. In the cyclopropanation reaction, the heterochiral trisoxazoline **7e** also achieved much better enantioselectivity than bisoxazoline **12a** (entry 3).

Another result should be mentioned is observed in enantioselective asymmetric [1, 2]-Stevens rearrangement of sulfur ylides via decomposition of diazomalonates (entry 4) [70]. Although trisoxazoline **6a** could provide good enantioselectivity than bisoxazoline **12a**, it showed lower reactivity. In this reaction, bisoxazoline with a pendant phenyl group as the sidearm finally turned out to be the best chiral ligand. We speculate that the diminished yield in the case of trisoxazoline **6a** resulted from the tenuated Lewis acidity of copper catalyst, due to the coordination of the sidearm with strong Lewis basity, which retarded the formation of metallocarbene intermediate. This result suggested that the coordinating ability of the sidearm really influenced the Lewis acidity of the metal cations. It needs careful balance between reactivity and enantiofacial control when introducing the sidearm.

5 Conclusion

During the past decade, we have been interested in the development and application of pseudo-C_3-symmetric trisoxazolines in the catalytic asymmetric C–C bond forming reactions. With direct or modular approaches, we successfully obtained serials of homochiral and heterochiral trisoxazolines. These ligands could form stable complexes with a wide range of metal cations, and their derived Cu(II), Cu(I), Co(II), Ni(II) complexes have been successfully applied in several enantioselective reactions. In almost all the reactions, our trisoxazoline ligand afforded higher reactivity, better enantiofacial control, and high stability and tolerance to impurities such as moisture. These results finally suggested the introduction of a sidearm to bisoxazoline is a useful and fruitful approach to design and develop new ligands with novel property.

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Adventure in Asymmetric Hydrogenation: Synthesis of Chiral Phosphorus Ligands and Asymmetric Hydrogenation of Heteroaromatics

Xiang-Ping Hu, Duo-Sheng Wang, Chang-Bin Yu, Yong-Gui Zhou, and Zhuo Zheng

Abstract Catalytic asymmetric hydrogenations of prochiral unsaturated compounds, such as olefins, ketones, and imines, have been intensively studied and are considered as a versatile method of the synthesis of chiral compounds due to atom economy and operational simplicity. Since 2002, we mainly focused on synthesis of new phosphorus ligands, asymmetric hydrogenation of heteroaromatic compounds and palladium-catalyzed asymmetric hydrogenation. Significant contribution was made in the Dalian Institute of Chemical Physics. In this chapter, we hope to share our experience and adventure in the development of chiral monophosphite ligands and phosphine–phosphoramidite ligands, asymmetric hydrogenation of heteroaromatic compounds, and the development of new homogeneous palladium catalytic hydrogenation system, which have a wide range of applications in synthesis of chiral compounds.

Keywords Catalytic asymmetric hydrogenation • Chiral phosphorus ligand • Iridium • Isoquinolines • Palladium • Quinolines • Rhodium

Contents

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1 Synthesis of Chiral Phosphorus Ligands

The rhodium-catalyzed asymmetric hydrogenation is arguably one of the most powerful tools for the preparation of a wide range of enantiomerically pure or enriched compounds [1–3]. Although significant progress has been made in this area, the development of new phosphorus-containing ligands with properties superior to their predecessors remains a central task for chemists. An optimum catalytic system should hold the following criteria: (1) high efficiency, i.e., the ability to operate at low levels of catalyst under the mild hydrogenation conditions, (2) broad substrate scope, (3) air and moisture stability, (4) and the direct and simple ligand synthesis, with the starting material being inexpensive or readily available from single-step synthesis. Our research in the past few years is largely stimulated by our ambition in the development of a unique ligand that could fully fulfill the above criteria, which now proves to be a rather difficult task. However, our efforts in ligand design have led to some exciting outcomes, although they are still far from our goal.

1.1 Chiral Monodentate Phosphorus-Containing Ligands for Catalytic Asymmetric Hydrogenation

Despite the encouraging performance of chelating bisphosphorus ligands in catalytic asymmetric hydrogenation, the past decade has witnessed a renewed interest in the development of chiral monodentate phosphorus ligands [4, 5]. This resurgence of monodentate ligands is partly due to the ready accessibility of a diverse range of ligand structures, and the nature of lower cost when compared to bidentate ligands. Pioneering studies from the groups of Pringle [6], Reetz [7], and Feringa [8] have disclosed that chiral monodentate phosphonite, phosphite, and phosphoramidite ligands also yield highly active and selective Rh catalysts for the hydrogenation of a variety of alkenes, giving comparable or sometimes better results than those obtained with bidentate ligands. However, the efficiency of the catalyst with chiral monophosphorus ligands is not always sufficiently high, which to some extent may be due to the free rotation of M–P bond.

To overcome this problem, in 2003, Reetz's [9] group and ours [10] independently developed some carbohydrate-based monophosphite ligands **1**–**4** (Fig. 1),

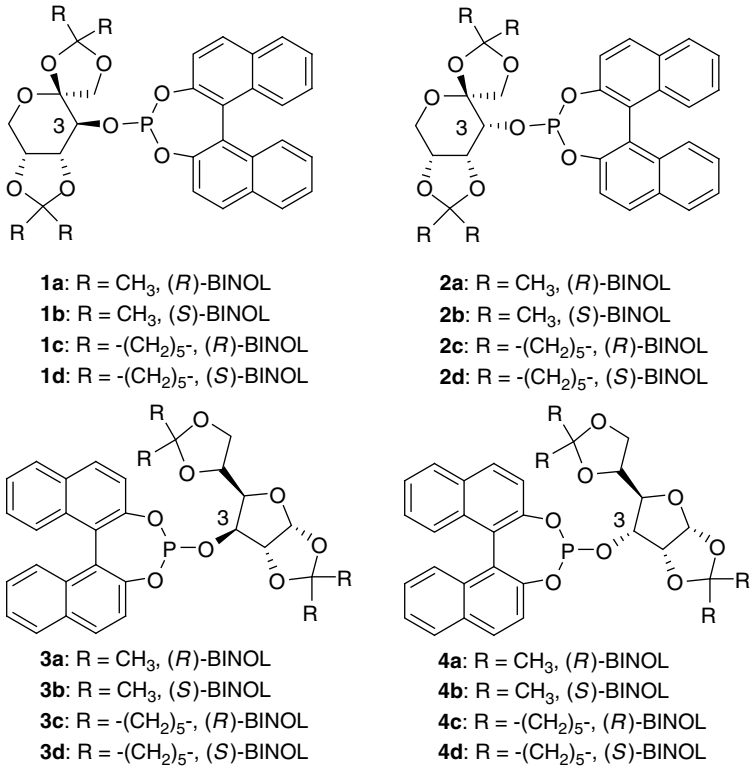
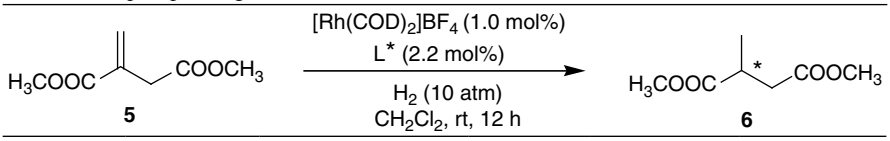


Fig. 1 D-Fructose- and D-glucose-derived monophosphite ligands **1**–**4**

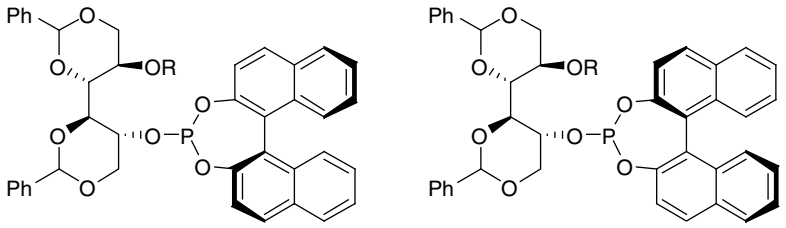
which contain additional groups in the proper spatial configuration to effectively restrain the rotation of the Rh–P bond by secondary interactions. As expected, these ligands exhibited excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of some prochiral olefins, including dimethyl itaconate, enamides, α-dehydroamino acid esters, and β-dehydroamino acid esters [10, 11]. The results in Table 1, based on the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate **5**, disclosed that the enantioselectivities were dramatically influenced by the structure of the ligands, and the absolute configuration of carbon atom at C-3 in the carbohydrate backbone has a predominating role in the enantioselectivities. In general, fructose-derived ligands **2a**–**d**, with *R*-configuration on C-3, displayed much higher enantioselectivities than ligands **1a**–**d** with the opposite configuration on C-3. Interestingly, for ligands **1a**–**d**, (*S*)-BINOL is matched cooperatively to the corresponding carbohydrate fragment, while (*R*)-BINOL and the carbohydrate components are matched in ligands **2a**–**d**. Similar observations were also made with ligands **3** and **4** derived from D-glucose.

Excellent enantioselectivities and the pronounced effect of carbohydrate backbones in ligands **1**–**4** indicated that additional groups orientated in a spatial configuration in monophosphites improved the enantioselectivity. To establish the general

Table 1 Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate with carbohydrate-derived monophosphite ligands



Entry	Ligand	Ee (%) (config)	Entry	Ligand	Ee (%) (config)
1	**1a**	49.7 (*R*)	9	**3a**	92.8 (*R*)
2	**1b**	82.5 (*S*)	10	**3b**	99.1 (*S*)
3	**1c**	18.5 (*R*)	11	**3c**	92.9 (*R*)
4	**1d**	91.5 (*S*)	12	**3d**	96.9 (*S*)
5	**2a**	99.6 (*R*)	13	**4a**	93.6 (*R*)
6	**2b**	99.1 (*S*)	14	**4b**	77.5 (*S*)
7	**2c**	99.4 (*R*)	15	**4c**	84.3 (*R*)
8	**2d**	90.3 (*S*)	16	**4d**	81.0 (*R*)

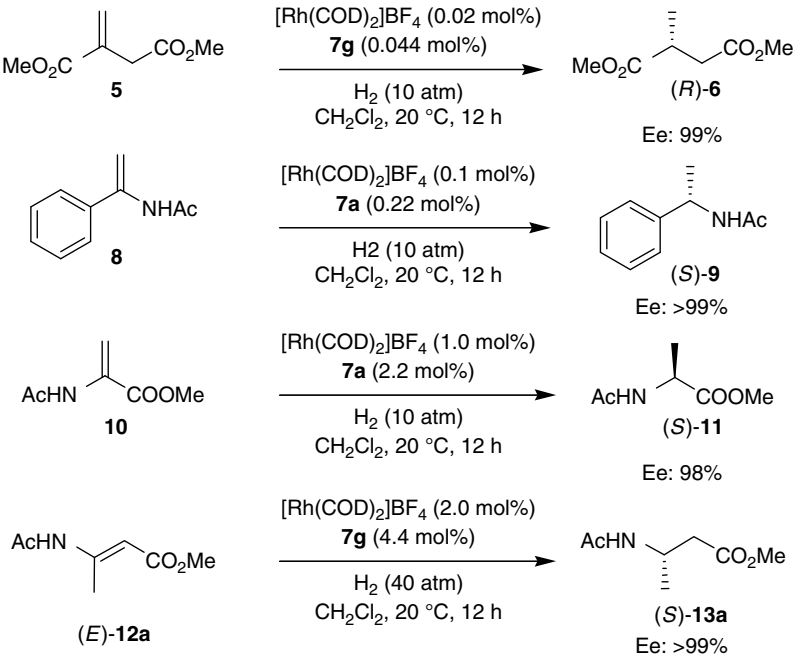


7a: R = Me
7b: R = *n*-Pr
7c: R = *i*-Pr
7d: R = *i*-Bu
7e: R = CH_2Ph
7f: R = $CHPh_2$
7g: R = 1-CH_2Nap
7h: R = CH_3
7i: R = CH_2Ph

Fig. 2 D-Mannitol-derived monophosphite ligands, ManniPhos **7**

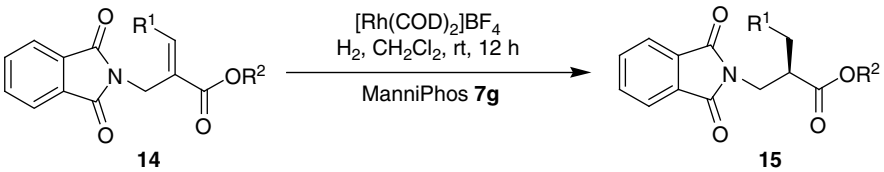
utility of this notion and enhance the versatility of this ligand type in asymmetric reactions, in 2004, we developed a new class of chiral monophosphite ligands, ManniPhos **7** (Fig. 2) [12], based on D-mannitol. These new ligands contain an extra chiral scaffold with a fair degree of rigidity and flexibility in attaching additional groups in a proper spatial configuration such that the ligands may not only offer the effect of additional groups but also act like hemilabile ligands to enhance the enantioselectivity. It is exciting that these ligands do show excellent catalytic activity and enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate, enamides, α-dehydroamino acid esters, and β-dehydroamino acid esters (Scheme 1).

More importantly, ManniPhos **7g** was found to be highly efficient in the first Rh-catalyzed asymmetric hydrogenation of α-phthalimidomethyl acrylates **14** for the enantioselective synthesis of β^2-amino acid esters [13]. The results in Table 2 indicated that the substrates without a substituent in the β-position of



Scheme 1 Rh-catalyzed asymmetric hydrogenation of functionalized olefins

Table 2 Rh-catalyzed hydrogenation of α-phthalimidomethyl acrylates **14** with ligand **7g**



Entry	Substrate (R^1, R^2)	$P(H_2)$ (atm)	*S/C*	Conv (%)	Ee%
1	**14** (H, Et)	10	100	>99	99.1 (*R*)
2	**14** (H, Me)	10	100	>99	98.3 (*R*)
3	**14** (H, Et)	10	1,000	>99	97.7 (*R*)
4	**14** (C_6H_5, Me)	85	25	82	92.0 (*R*)
5	**14** (4-ClC_6H_4, Me)	85	25	>95	86.4 (+)
6	**14** (4-FC_6H_4, Me)	85	25	>95	95.9 (+)
7	**14** (4-$CF_3C_6H_4$, Me)	85	25	>95	94.6 (+)
8	**14** (2-$MeOC_6H_4$, Me)	85	25	87	85.4 (+)
9	**14** (4-MeC_6H_4, Me)	85	25	73	76.0 (+)
10	**14** (2-thienyl, Me)	85	25	60	55.4 (+)
11	**14** (*i*-Pr, Me)	85	25	91	49.5 (–)

the carbon–carbon double bond could give full conversion and excellent enantioselectivity even in 0.1 mol% of catalyst loadings. However, this catalyst system is not efficient for the hydrogenation of β-substituted substrates, giving only low conversion. When the hydrogenation was performed under a hydrogen pressure of 85 atm and a catalyst loading of 4.0 mol%, some β-aryl substituted substrates could be hydrogenated to yield the corresponding β-amino acid precursors in good enantioselectivities.

By replacing BINOL with H_8-BINOL, we developed a series of new carbohydrate-based monophosphite ligands **16–17** (Fig. 3) [14]. These ligands also displayed excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of various functionalized olefins such as enamides and dimethyl itaconate.

The pronounced effect of the carbohydrate backbone in catalytic activity and enantioselectivity indicated that the additional oxygen-containing groups orientated in a spatial configuration in the alkoxy moiety of monophosphites may act as hemilabile ligands in catalytic hydrogenation, forming only weak metal–oxygen bonds that may be cleaved reversibly. This secondary interaction between the oxygen donor and central metal can effectively restrain the rotation of the Rh–P bond, and make the empty coordination sites available, when needed, in the course of catalytic cycles, leading to a high enantioselectivity. With this in mind, we surmised that the introduction of a polyethylene glycol (PEG) structure as the alkoxy moiety of the monophosphite ligand might result in a new class of highly effective "polymer-monophosphites" for the Rh-catalyzed asymmetric hydrogenation, due to the potential for secondary interactions between the oxygen atoms abundant in the PEG structure and the central metal. A series of soluble PEG monomethyl ether-derived polymer-monophosphites (MeOPEG-monophosphites, **18**, Fig. 4) were then prepared and subjected to the hydrogenation [15].

As expected, these MeOPEG-monophosphite ligands **18** provided a greatly improved enantioselectivity, in comparison with methanol and glycol monomethyl ether-derived monophosphites **19a** and **19b**, in the hydrogenation of *N*-(1-phenylethenyl)acetamide **8** (Scheme 2). Various functionalized olefins including enamides and β-dehydroamino acid esters were also hydrogenated with the present catalytic system in high enantioselectivities. Besides the high efficiency in the Rh-catalyzed asymmetric hydrogenation, another salient and practical

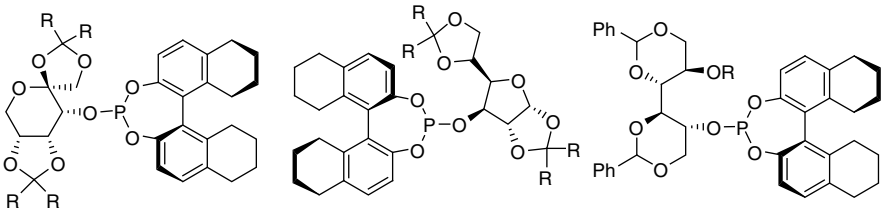


Fig. 3 Monophosphites **16–17** derived from carbohydrate and H_8-BINOL

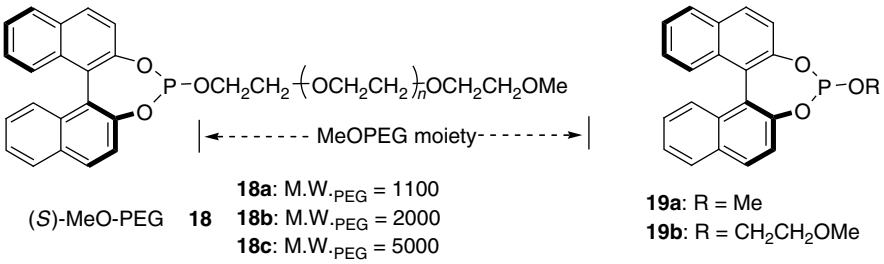
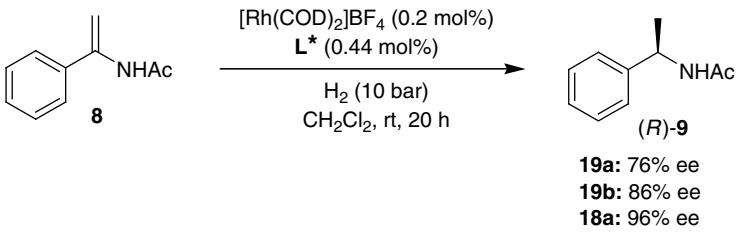


Fig. 4 MeO-PEG-monophosphite ligands **18** and relative ligands



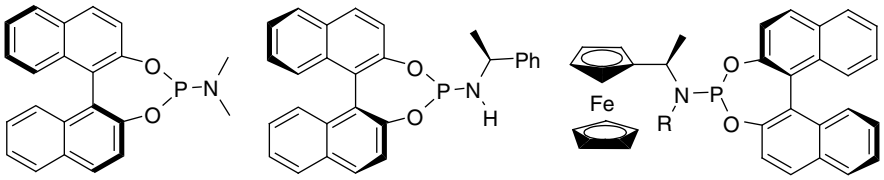
Scheme 2 Rh-catalyzed hydrogenation of N-(1-phenylethenyl)acetamide **8** with MeOPEG-monophosphite ligand **18a**

feature of the present catalytic system is that they are easily separated and recovered from the reaction mixture. After the completion of the hydrogenation, ether was added to the reaction mixture and the precipitate was formed immediately. Simple filtration under an Ar atmosphere recovered the precipitated catalyst and left products in solution. The recovered catalyst could be recycled four times with only a slight loss in the enantioselectivity (from 97% ee in the first run to 91% ee in the fourth run).

A shortcoming of these carbohydrate-derived monophosphite ligands is that they are somewhat sensitive to air and moisture. Considering that monophosphoramidite ligands normally display better air stability than monophosphite ligands, we set out to develop a new class of monophosphoramidite ligands by the modification of MonoPhos **20** [8], the simplest member of the monodentate phosphoramidites based on axially chiral 2,2′-binaphthol. Structural modification of the MonoPhos backbone can be carried out either by introducing substituents onto the binaphthyl moiety or by replacing the dimethylamino group with other C_2-symmetric amines [16, 17]. However, introduction of substituents onto the binaphthyl moiety of MonoPhos has usually resulted in diminished enantioselectivities and reaction rates. In contrast, replacement of the dimethylamino group with other C_2-symmetrical amino groups has proved to be more successful. Strangely, replacement of the dimethylamino group with an unsymmetrical amino moiety has not been investigated as thoroughly. With the exception of one report showing that α-phenylethylamine-derived monophosphoramidite **21** displayed excellent enantioselectivity in the Rh-catalyzed

asymmetric hydrogenation of β-dehydroamino acid esters [18], few monodentate phosphoramidites with unsymmetrical amino groups have exhibited high enantioselectivities in asymmetric catalytic hydrogenation [19, 20]. We surmised that the introduction of an unsymmetrical chiral amino group into the monophosphoramidite structure may lead to a desirable chiral environment around the central metal due to the presence of the additional stereogenic center. We then initiated a study on the synthesis of a series of monodentate phosphoramidites (abbreviate as FAPhos, **22**, Fig. 5) derived from unsymmetrical 1-ferrocenylethylamine and the investigation of their efficiency in the Rh-catalyzed asymmetric hydrogenation [21].

As expected, these newly developed monophosphoramidite ligands **22** showed excellent enantioselectivities for a broad range of substrates, including α-dehydroamino acids esters and aromatic enamides, providing comparable or higher efficiency than that obtained with the most efficient monophosphoramidites reported so far, with the hydrogenation performing under much milder conditions. An investigation on the hydrogenation of *N*-(1-phenylethenyl)acetamide **8**, as shown in Table 3, indicated that the substituent on the amino group has a dramatic influence on both the catalytic activity and enantioselectivity, and ligand with a bulkier substituent on the amino group tended to show lower

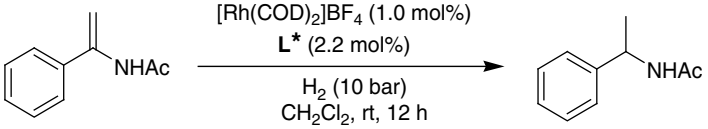


(*S*)-MonoPhos **20** (S_c,R_a)-**21**

(R_c,S_a)-**22a**: R = Me
(R_c,S_a)-**22b**: R = Et
(R_c,S_a)-**22c**: R = Bn
(R_c,R_a)-**22d**: R = Me

Fig. 5 Monophosphoramidite ligands **20**–**22**

Table 3 Rh-catalyzed hydrogenation of N-(1-phenylethenyl)acetamide **8** with FAPhos **22**



8 **9**

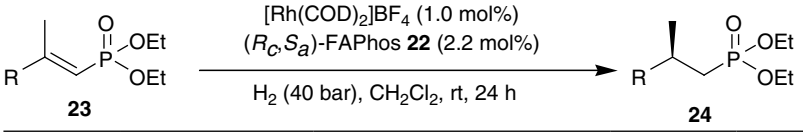
Entry	Ligand	Yield (%)	Ee (%) (config)
1	**22a**	98	99 (*R*)
2	**22b**	99	53 (*R*)
3	**22c**	<5	–
4	**22d**	98	86 (*S*)

catalytic activity and enantioselectivity. The result also suggested that the binaphthyl moiety controls the chirality of the hydrogenation product and the matched stereogenic elements are (R_c)-central and (S_a)-axial absolute configurations.

Subsequent studies disclosed that FAPhos is unique for asymmetric hydrogenation of some new phosphonate substrates. Thus, in the first Rh-catalyzed asymmetric hydrogenation of β-substituted-α,β-unsaturated phosphonates **23**, FAPhos displayed excellent enantioselectivities, providing up to 99.5% ee for the hydrogenation of (*E*)-substrates and 98.0% ee for (*Z*)-substrates (Table 4) [22]. The substituent on the amino moiety of FAPhos significantly affected both the reactivity and enantioselectivity, and the best result was obtained with (R_c,S_a)-FAPhos **22b** bearing an ethyl group.

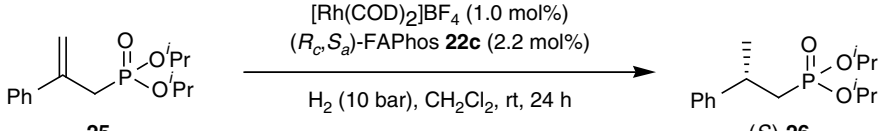
Similar results were also observed in the first Rh-catalyzed hydrogenation of β,γ-unsaturated phosphonates **25**, in which (R_c,S_a)-FAPhos **22c** with a benzyl group showed the highest enantioselectivity (Scheme 3) [23]. Interestingly, the hydrogenation of α,β-unsaturated phosphonates **23** and β,γ-unsaturated phosphonates **25** with (R_c,S_a)-FAPhos ligands gave products with the opposite configuration.

Table 4 Rh-catalyzed hydrogenation of β-substituted-α,β-unsaturated phosphonates with FAPhos



23 **24**

Entry	Ligand	Substrate (R)	Yield (%)	Ee (%) (config)
1	(R_c,S_a)-**22a**	(*E*)-**23a**: R = Ph	98	95.6 (*R*)
2	(R_c,S_a)-**22b**	(*E*)-**23a**: R = Ph	98	98.3 (*R*)
3	(R_c,S_a)-**22c**	(*E*)-**23a**: R = Ph	61	93.4 (*R*)
4	(R_c,S_a)-**22b**	(*E*)-**23b**: R = 4-MeC_6H_4	99	98.8 (+)
5	(R_c,S_a)-**22b**	(*E*)-**23c**: R = 4-$CF_3C_6H_4$	96	99.0 (+)
6	(R_c,S_a)-**22b**	(*E*)-**23d**: R = 4-ClC_6H_4	99	98.7 (+)
7	(R_c,S_a)-**22b**	(*E*)-**23e**: R = 2-thienyl	95	99.5 (+)
8	(R_c,S_a)-**22b**	(*E*)-**23f**: R = $PhCH_2CH_2$	98	98.2 (+)
9	(R_c,S_a)-**22b**	(*Z*)-**23f**: R = $PhCH_2CH_2$	99	98.0 (−)



25 (*S*)-**26**

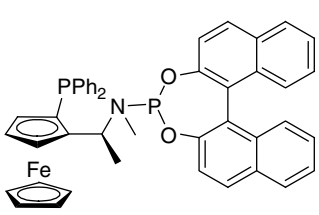
Ee: 97%

Scheme 3 Rh-catalyzed hydrogenation of **25** with ligand FAPhos **22c**

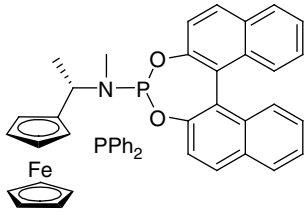
1.2 Chiral Phosphine–Phosphoramidite Ligands for Catalytic Asymmetric Hydrogenation

C_2 symmetry has been an important principle in designing efficient bisphosphorus ligands for catalytic asymmetric hydrogenation. It is commonly believed that ligands with two different coordinating functionalities are capable of generating a larger number of diastereomeric transition states than those with C_2 symmetry, which makes the stereocontrol of the process more difficult. However, this does not mean that C_2 symmetry is essential for ligand design. In fact, two equal coordinating groups in C_2-symmetrical bisphosphorus ligands influence the reactivity and selectivity of the corresponding metal catalyst in different manners, resulting in an unsymmetrical metal–ligand–substrate intermediate. Therefore, the greater complexity introduced by unsymmetrical ligands may be more advantageous in achieving desired chiral environments by individually optimizing two different coordinating atoms that is impossible with C_2-symmetrical ligands. Following this assumption, in 2004, we developed our first generation of highly unsymmetrical hybrid phosphine–phosphoramidite ligands (PPFAPhos **27**, Fig. 6), based on a planar-chiral ferrocene backbone [24].

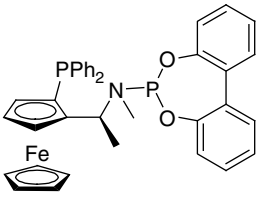
The synthesis of these ferrocene-based phosphine–phosphoramidite ligands, despite their complex appearance and holding three stereogenic elements, is convenient, and all four of their diastereoisomers were prepared in high yields. These PPFAPhos ligands exhibit excellent air and moisture stability. For example, (S_c,R_p,S_a)-PPFAPhos **27a** did not show any change in its ^{1}H or ^{31}P NMR spectra even after being held at ambient temperature in open air for more than 6 months. This advantage makes PPFAPhos ligands highly practical for general laboratory preparations as well as scale-up operations.



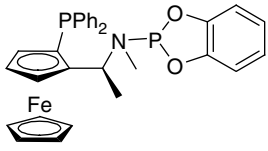
(S_c,R_p,S_a)-PPFAPhos **27a**
(S_c,R_p,R_a)-PPFAPhos **27b**



(S_c,S_p,R_a)-PPFAPhos **27c**
(S_c,S_p,S_a)-PPFAPhos **27d**



(S_c,R_p)-PPFAPhos **27e**



(S_c,R_p)-PPFAPhos **27f**

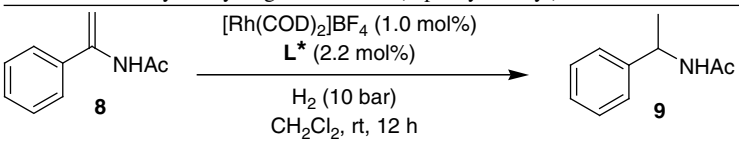
Fig. 6 Ferrocene-based phosphine-phosphoramidite ligands (PPFAPhos)

The hydrogenation of *N*-(1-phenylethenyl)acetamide **8** as a model reaction, as shown in Table 5, discloses some interesting information on the ligand structure: (1) binaphthyl moiety plays a crucial role in the enantioselectivity, and controls the chirality of the hydrogenation product; (2) *S*-central, *R*-planar, and *S*-axial chiralities are the matched stereogenic elements.

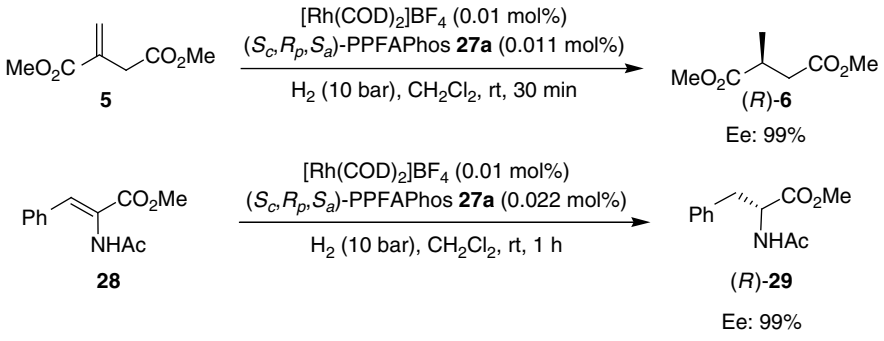
The optimized ligand, (S_c,R_p,S_a)-PPFAPhos **27a**, were demonstrated to be highly efficient in the Rh-catalyzed asymmetric hydrogenation of various functionalized olefins including enamides, dimethyl itaconate, and α-dehydroamino acid esters, normally giving over 99% ee (Scheme 4). The hydrogenation can be performed even under a catalyst loading as low as 0.01 mol%, without loss of the catalytic activity and enantioselectivity.

However, these PPFAPhos ligands exhibited a very low enantioselectivity in the hydrogenation of β-(acylamino)acrylates. Further ligand-optimizing experiments disclosed that an N–H proton on the amino unit of these phosphine-phosphoramidite ligands have a crucial role in achieving high stereocontrol in the hydrogenation of β-(acylamino)acrylates, presumably due to a potential second interaction between the N–H proton in the ligand and the substrate [25].

Table 5 Rh-catalyzed hydrogenation of N-(1-phenylethenyl)acetamide **8** with PPFAPhos



Entry	Ligand	*S*/*C*	Yield (%)	Ee (%) (config)
1	(S_c,R_p,S_a)-**27a**	100	99	99.6 (*R*)
2	(S_c,R_p,R_a)-**27b**	100	99	10.6 (*S*)
3	(S_c,S_p,R_a)-**27c**	100	98	99.6 (*S*)
4	(S_c,S_p,S_a)-**27d**	100	99	82.6 (*R*)
5	(S_c,R_p)-**27e**	100	97	81.5 (*S*)
6	(S_c,R_p)-**27f**	100	98	78.1 (*R*)
7	(S_c,R_p,S_a)-**27a**	5,000	96	99.3 (*R*)

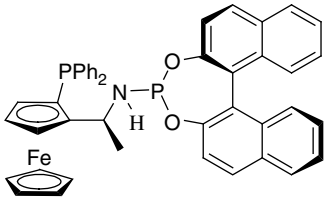


Scheme 4 Rh-catalyzed hydrogenation of olefins **5** and **28** with PPFAPhos **27a**

Thus, (S_c,R_p,S_a)-PPFAPhos-H **30** with an N–H proton on the amino unit (Fig. 7), was found to be highly efficient for the Rh-catalyzed asymmetric hydrogenation of a variety of β-(acylamino)acrylates (Table 6), in particular (*Z*)-β-aryl-β-(acylamino)acrylates, which remains a challenging task in catalytic asymmetric hydrogenation. Good performance was achieved even at the catalyst loadings as low as 0.02 mol% (*S*/*C*=5,000), representing one of the most efficient catalytic system in the catalytic hydrogenation of (*Z*)-β-aryl-β-(acylamino)acrylates reported so far. More interestingly, our research indicates that individual hydrogenation of *E*- and *Z*-isomers can be performed under identical catalytic conditions by the use of the present catalytic system, affording β-amino acid derivatives in excellent enantioselectivities but with the opposite configuration.

Although these ferrocene-based PPFAPhos ligands are highly efficient in the Rh-catalyzed asymmetric hydrogenation of various functionalized olefins, the cost for the synthesis of PPFAPhos, which is prepared from ferrocene through an eight-step transformation including a tedious resolution procedure, is expensive. Considering the structural similarity between 1-ferrocenylethylamine and 1-phenylethylamine and low cost of chiral 1-phenylethylamine, we then surmised that 1-phenylethylamine-derived phosphine-phosphoramidite ligand (abbreviated as PEAPhos, **36**) may be a good alternative to ferrocene-based PPFAPhos ligands [26].

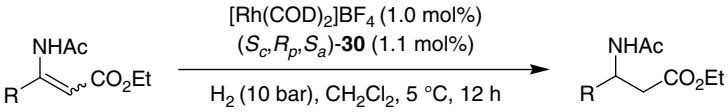
PEAPhos **36** was then prepared in good yields through a three-step transformation from commercially available and inexpensive (*S*)-1-phenylethylamine **31** as



(S_c,R_p,S_a)-PPFAPhos-H **30**

Fig. 7 Ferrocene-based phosphine–phosphoramidite ligand **30** with an N–H proton

Table 6 Rh-catalyzed hydrogenation of β-(acylamino)acrylates with PPFAPhos-H **30**

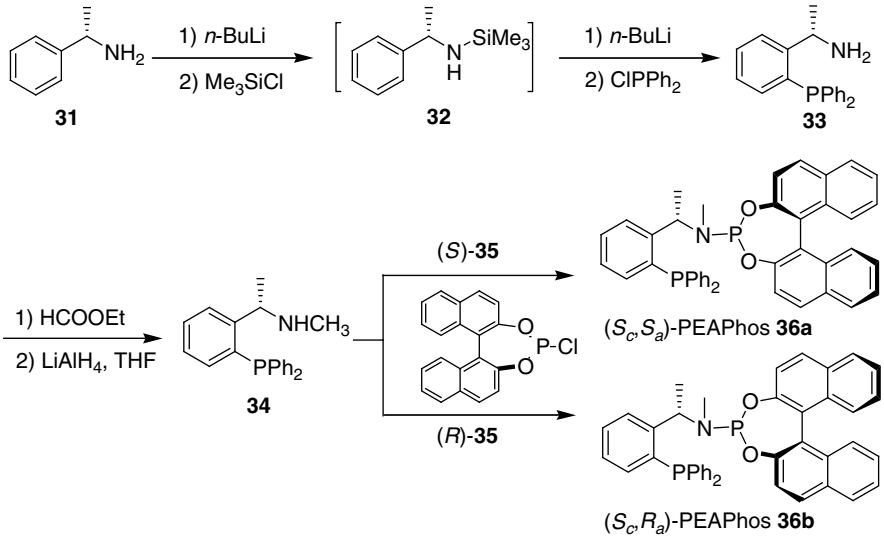


12 **13**

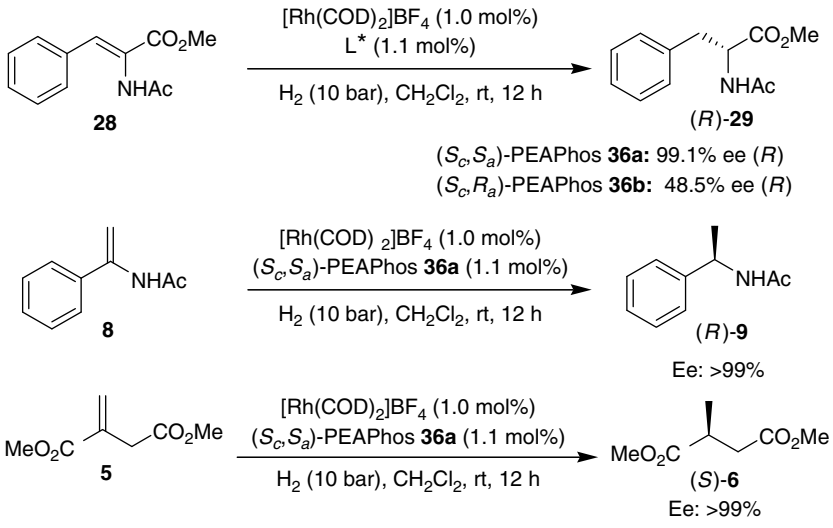
Entry	Substrate	*S*/*C*	Yield (%)	Ee (%) (config)
1	(*Z*)-**12b**: R = Ph	100	98	>99 (*R*)
2	(*Z*)-**12b**: R = Ph	5,000	96	97 (*R*)
3	(*Z*)-**12c**: R = 4-MeC_6H_4	100	98	98 (*R*)
4	(*Z*)-**12d**: R = 4-MeOC_6H_4	100	97	99 (*R*)
5	(*Z*)-**12e**: R = 4-ClC_6H_4	100	99	>99 (*R*)
6	(*Z*)-**12f**: R = Me	100	95	93 (*S*)
7	(*E*)-**12f**: R = Me	100	95	97 (*R*)

outlined in Scheme 5. These ligands are also air and moisture stable, and can be held in open air for several months.

The research disclosed that PEAPhos **36** is highly efficient for the Rh-catalyzed asymmetric hydrogenation of a variety of substrates including α-dehydroamino acid esters, enamides, and dimethyl itaconate (Scheme 6), in which up to 99.9% ee was obtained for all of these kinds of substrates. Most interestingly, the central



Scheme 5 Synthesis of 1-phenylethylamine-derived phosphine-phosphoramidite ligands



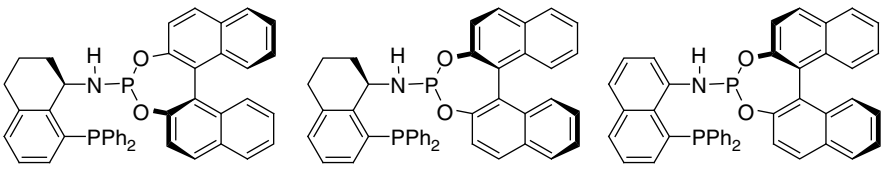
Scheme 6 Rh-catalyzed hydrogenation of olefins with ligands **36**

chirality in the 1-phenylethylamine backbone decides the absolute configuration of the hydrogenation product, no matter the (*R*)- or (*S*)-configuration of binaphthyl moiety, contrary to the results obtained with PPFAPhos in which the binaphthyl moiety controls the chirality of the hydrogenation product.

The rigidity of a ligand structure has a significant influence on the enantioselectivity. Despite the high efficiency of (S_c,S_a)-PEAPhos **36a** in the Rh-catalyzed asymmetric hydrogenation of some traditional substrates, this ligand provided insufficient selectivity in some challenging hydrogenation such as Rh-catalyzed hydrogenation of 2-hydroxymethylacrylate, presumably because of its flexible backbone. We therefore introduced two new class of phosphine-phosphoramidite ligands with more rigid backbone: one based on 1,2,3,4-tetrahydro-1-naphthylamine structure (abbreviated as THNAPhos, **37**) [27, 28] and other on 1-naphthylamine (abbreviated as HY-Phos, **38**) [29] (Fig. 8).

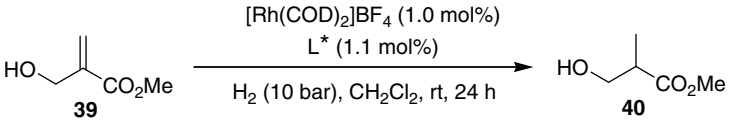
As expected, THNAPhos **37** and HY-Phos **38** provided improved enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of 2-hydroxymethylacrylate, giving the corresponding Roche ester in up to 96.7% ee (Scheme 7) [30].

Besides its successful application in the Rh-catalyzed asymmetric hydrogenation of traditional substrates including α-dehydroamino acid esters, enamides, α-dehydroamino acid esters, and dimethyl itaconate [28], the most important application of (R_c,R_a)-THNAPhos **37a** is in the catalytic asymmetric hydrogenation of various α-enol ester phosphonates and α-enamido phosphonates. Catalytic asymmetric hydrogenation of α-enol ester phosphonates, especially those bearing β-ary or β-alkoxy substituents, is still a challenge. To our delight, we found that (R_c,R_a)-THNAPhos **37a** could provide unprecedented enantioselectivities (normally over 99% ee) and catalytic activity (*S*/*C* >1,000) in Rh-catalyzed asymmetric hydrogenation across a broad range of α-enol ester phosphonates bearing β-aryl, β-alkoxy, and β-alkyl substituents (Scheme 8).



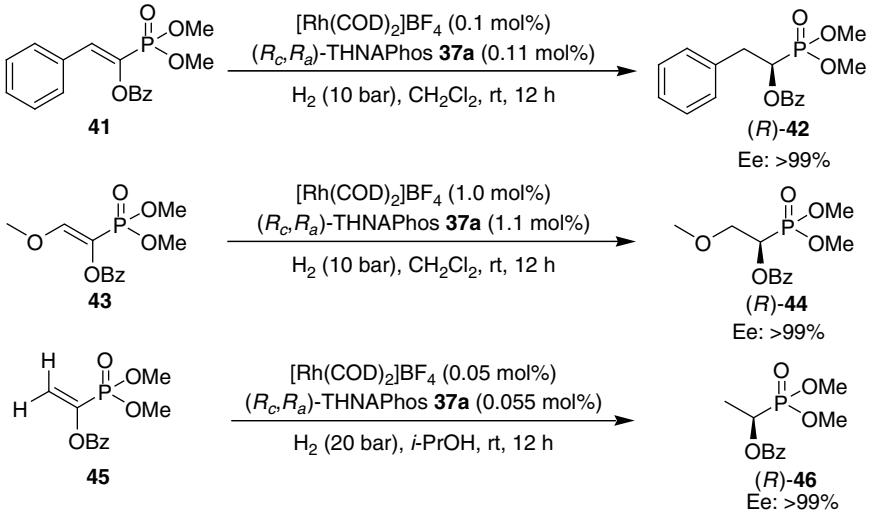
(R_c,R_a)-THNAPhos **37a** (R_c,S_a)-THNAPhos **37b** (S_a)-HY-Phos **38**

Fig. 8 Phosphine–phosphoramidite ligands THNAPhos **37** and HY-Phos **38**



(S_c,S_a)-PEAPhos **36a :** 93.8% ee (*S*)
(R_c,R_a)-THNAPhos **37a:** 96.7% ee (*R*)
(S_a)-HY-Phos **38:** 94.1% ee (*S*)

Scheme 7 Rh-catalyzed hydrogenation of 2-hydroxymethylacrylates



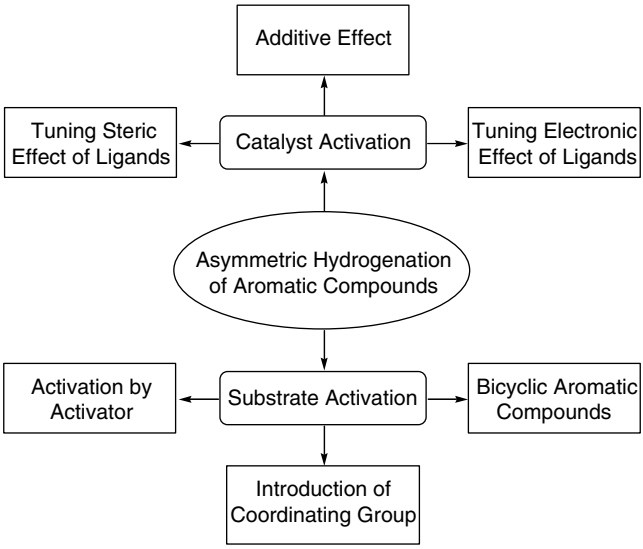
Scheme 8 Rh-catalyzed hydrogenation of α-benzoxyl phosphonates with THNAPhos **37a**

In summary, we have developed a series of chiral monodentate phosphorus-containing ligands and chiral phosphine-phosphoramidite ligands, which have a wide range of applications in the Rh-catalyzed asymmetric hydrogenation of various functionalized C=C double bonds. It is our hope that our experience in the ligand development will provide some useful information for those who are interested in ligand design.

2 Asymmetric Hydrogenation of Heteroaromatics

The asymmetric hydrogenation of prochiral unsaturated compounds, such as olefins, imines, and ketones, provides a straightforward access to the corresponding optically active compounds, and has been extensively studied [1–3]. In contrast, the asymmetric hydrogenation of heteroaromatic compounds is much less explored [31–35]. Difficulties encountered in the asymmetric hydrogenation of these compounds make this phenomenon rational. Commonly, rigorous conditions are needed to hydrogenate more than one type of double bonds simultaneously and meanwhile destroy aromaticity [34]. Despite all these difficulties, great progress on the asymmetric hydrogenation of heteroaromatic compounds, especially quinolines and isoquinolines, has been achieved in the past few years [34]. Therefore, in this section, we will focus on the asymmetric hydrogenation of heteroaromatics, quinolines, and isoquinolines.

Activation strategies, including catalyst activation and substrate activation, are needed for successful asymmetric hydrogenation of aromatic compounds (Scheme 9) [34]. Catalyst activation involves the introduction of additive to form more active catalyst species and developing more effective ligands by fine-tuning of their steric



Scheme 9 Activation strategies for asymmetric hydrogenation of aromatic compounds

and electronic properties. Substrate activation may be achieved by introduction of activator to act with the substrate and destroy the aromaticity partially, and a secondary coordination group to assist coordination between substrate and catalyst. Owing to relatively weak aromaticity of bicyclic aromatics, bicyclic aromatic compounds are easy to be hydrogenated.

2.1 Asymmetric Hydrogenation of Quinolines

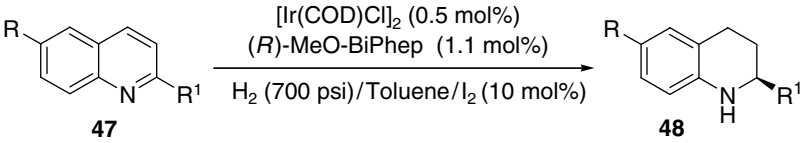
2.1.1 Transitional Metal Catalyzed Asymmetric Hydrogenation of Quinolines

Based on the above analysis, bicyclic heteroaromatic compounds with weak aromaticity, quinolines, and isoquinolines were subjected to asymmetric hydrogenation study using the activation strategy. A breakthrough was made by us for the asymmetric hydrogenation of quinolines in 2003. A number of additives were investigated to activate the iridium catalyst, iodine was found to be most effective and we realized the first highly enantioselective hydrogenation of quinolines [36]. We employed $[Ir(COD)Cl]_2$/MeO-BiPhep as catalyst using iodine as additive, while the hydrogenation reaction could not take place in the absence of iodine. Detailed studies showed this reaction was highly solvent dependent, and toluene was the best solvent, and axial chiral diphosphine ligand (*R*)-MeO-BiPhep was the best choice with 94% ee. Thus, optimal conditions were established as: $[Ir(COD)Cl]_2$/MeO-BiPhep/I_2/toluene.

Under the optimal conditions, the scope of this new strategy was explored. A variety of 2-substituted and 2,6-disubstituted quinoline derivatives were hydrogenated smoothly to give the desired products in excellent yields and enantioselectivities (Table 7). 2-Alkyl substituted quinolines were hydrogenated with high enantioselectivities regardless of the length of side chain. 2-Arenethyl substituted quinolines also gave excellent asymmetric induction. 2-Phenylquinoline was hydrogenated with lower enantioselectivity. Gratifyingly, the catalytic system could also tolerate hydroxyl group. It was found that this catalytic system was effective for 2-substituted quinolines; however, very poor enantioselectivity and reactivity were obtained for 3- and 4-substituted quinoline derivatives.

In 2004, we revealed that ferrocene phosphine-oxazoline ligands (N,P ligand) were also effective in the Ir-catalyzed asymmetric hydrogenation of quinolines with up to 92% ee (Scheme 10) [37]. It was found that the central chirality governed the absolute configuration of the products, and (S,S_p) was a well-matched combination. In 2005, ferrocene-based S–P ligands were also found to be effective in the asymmetric hydrogenation of quinolines [38]. In consistency with our former study, the absolute configuration of the product was also determined by the central chirality

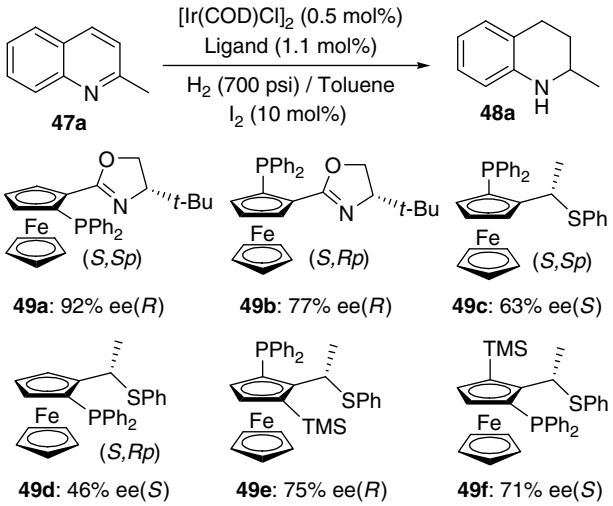
Table 7 Ir-catalyzed asymmetric hydrogenation of quinolines activated by I_2



47 **48**

Entry	R/R[1]	Yield (%)	Ee (%)
1	H/Me	94	94 (*R*)
2	H/Et	88	96 (*R*)
3	H/*n*-Pr	92	93 (*R*)
4	H/*n*-Bu	86	92 (*R*)
5	H/3-Butenyl[a]	91	92 (*R*)
6	H/*n*-Pentyl	92	94 (*R*)
7	H/*i*-Pr	92	94 (*S*)
8	H/Phenethyl	94	93 (*R*)
9	H/3,4-$(OCH_2O)C_6H_3(CH_2)_2$–	88	93 (*R*)
10	H/3,4-$(MeO)_2C_6H_3(CH_2)_2$–	86	96 (*R*)
11	F/Me	88	96 (*R*)
12	Me/Me	91	91 (*R*)
13	MeO/Me	89	84 (*R*)
14	H/Ph	95	72 (*S*)
15	H/$Me_2CH(OH)CH_2$–	87	94 (*S*)
16	H/*c*-$C_6H_{11}(OH)CH_2$–	89	92 (*S*)
17	H/$Ph_2CH(OH)CH_2$–	94	91 (*S*)
18	H/CH_2OH	83	75 (*S*)
19	H/CH_2OCOCH_3	90	87 (*S*)

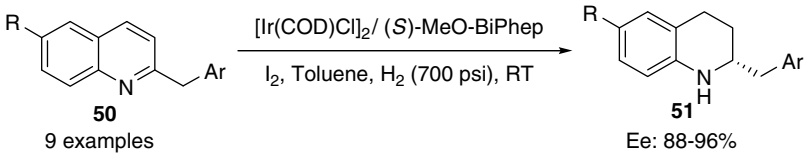
[a] C=C bond was also hydrogenated



Scheme 10 Asymmetric hydrogenation of quinaldine with N,P and S,P ligands

of the ligand. Interestingly, by introducing a bulky trimethylsilyl group to the Cp ring of the ligands (**49e** and **49f**), the hydrogenation products with opposite absolute configuration were obtained in moderate enantioselectivity.

Considering high enantioselectivity of catalytic system $[Ir(COD)Cl]_2$/MeO-BiPhep/I_2, we extended this catalytic system to challenge 2-benzylquinolines **50** and 2-functionalized quinolines **52** [39]. Under the former optimized conditions, all the 2-benzylquinoline derivatives were reduced smoothly to the corresponding 1,2,3,4-tetrahydro-benzylquinolines with excellent enantioselectivities and high yields regardless of the electronic and steric properties of the substituent groups (Scheme 11).

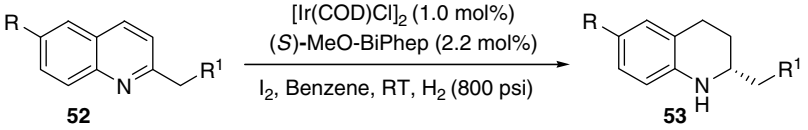


Scheme 11 Ir-catalyzed asymmetric hydrogenation of 2-benzylquinolines **50**

As summarized in Table 8, a variety of 2-functionalized quinoline derivatives could be successfully hydrogenated [39]. For the substrates bearing alkyl or aryl ketones, the tetrahydroquinoline derivatives were obtained with good to excellent enantioselectivities. Interestingly, the system could even tolerate the esters, amide, benzenesulfonyl or OTBS groups, and all these substrates were hydrogenated with 80–92% ee.

Despite the great progress achieved in the asymmetric hydrogenation of quinoline derivatives, there were still some unsolved issues. It was observed that a general

Table 8 Ir-catalyzed hydrogenation of 2-functionalized quinolines

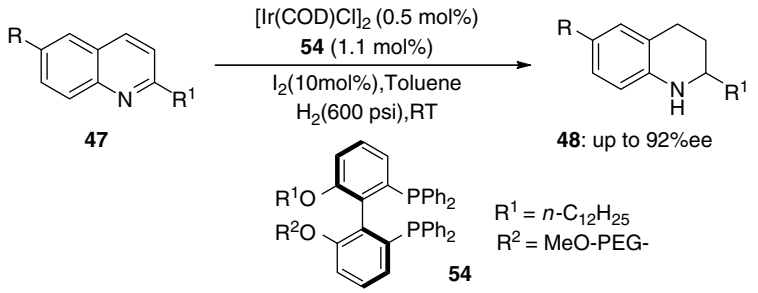


Entry	R/R[1]	Yield (%)	Ee (%)
1	H/COPh	91 (**53a**)	96 (*R*)
2	H/COMe	93 (**53b**)	90 (*R*)
3	H/CO(*n*-Pr)	91 (**53c**)	84 (*R*)
4	H/CO(*p*-MeOPh)	84 (**53d**)	83 (*R*)
5	H/CO(*o*-MeOPh)	78 (**53e**)	95 (*R*)
6	H/CO(*p*-MePh)	89 (**53f**)	95 (*R*)
7	H/CO(*o*-MePh)	97 (**53g**)	96 (*R*)
8	H/CO(*p*-*i*-PrPh)	97 (**53h**)	95 (*R*)
9	H/CO(*p*-CF_3Ph)	90 (**53i**)	95 (*R*)
10	H/CO(1-Naphthyl)	89 (**53j**)	95 (*R*)
11	H/CO$(CH_2)_2$Ph	90 (**53k**)	87 (*R*)
12	Me/COPh	82 (**53l**)	94 (*R*)
13	F/COPh	92 (**53m**)	96 (*R*)
14	H/CO(3,4-$(MeO)_2$Ph)	95 (**53n**)	94 (*R*)
15	H/*p*-MeOPhCH=CH[a]	80 (**53o**)	95 (*S*)
16	H/COOMe	88 (**53p**)	82 (*R*)
17	H/COOEt	93 (**53q**)	92 (*R*)
18	H/$CONEt_2$	98 (**53r**)	80 (*R*)
19	H/SO_2Ph	97 (**53s**)	90 (*R*)
20	H/$(CH_2)_3$OTBS	90 (**53t**)	94 (*S*)
21	H/$(CH_2)_4$OTBS	65 (**53u**)	89 (*S*)

[a] The double bond was also hydrogenated

drawback of Ir/P,P and Ir/N,P catalysts in the asymmetric hydrogenation reactions is the deactivation by the irreversible formation of inactive dimers and trimers through hybrid-bridged bonds in the presence of hydrogen gas [3, 40–45]. Thus, in iridium-catalyzed asymmetric hydrogenation of quinolines, the *S*/*C* ratios were usually limited to 100. In 2007, Fan and coworkers introduced BINAP-cored dendrimers to the iridium-catalyzed hydrogenation of quinolines, excellent enantioselectivities and activities were obtained [46]. With the encapsulation of the iridium complex into the dendrimer framework, site-isolation effect was achieved; and reduced dimerization therefore enhanced the efficiency of the catalyst.

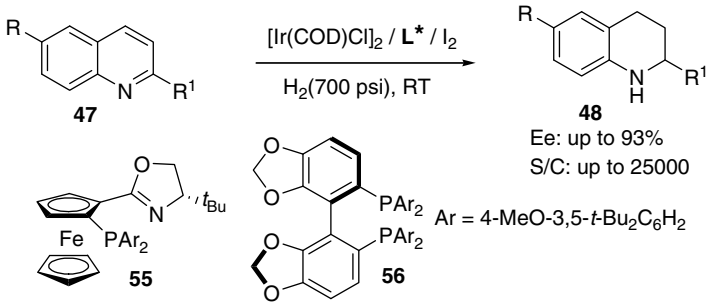
Since there is no omnipotent ligand for every substrate, the development of efficient and tunable new ligands is highly desirable. In 2008, we devised an efficient and divergent method for the synthesis of a series of tunable chiral diphosphine ligands based on (*S*)-MeO-BiPhep by introduction of different substituents at the 6,6′-positions of the biaryl backbone (Scheme 12) [47]. The iridium complexes of these ligands were successfully applied in the asymmetric hydrogenation of quinolines. When introduced one PEG group and the other as a linear alkyl (R^1=*n*-$C_{12}H_{15}$, R^2=MeO-PEG-1,600) to the ligand, best result was obtained (92% ee). In addition, this catalytic system could



Scheme 12 Tunable axially chiral diphosphine ligands for hydrogenation of quinolines

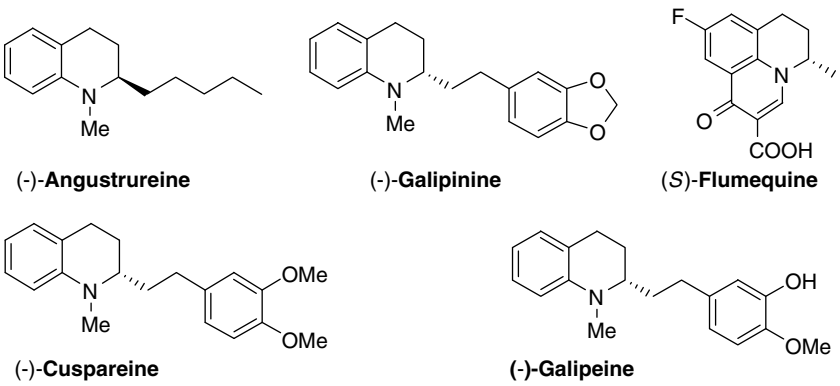
be recycled for five runs; a slightly lower enantioselectivity (84% ee) and 95% conversion were obtained in the fifth run.

Very recently, we described a new strategy, by introducing bulky substituents on coordination atoms, to block the formation of inactive dimer species, and consequently improve the activity of the Ir catalysts in the hydrogenation of quinolines [48]. It was found that the reaction proceeded smoothly to obtain the products with moderate to excellent enantioselectivities at high substrate/catalyst ratio (up to 25,000) (Scheme 13). Importantly, it has been further demonstrated that inhibition of the formation of dimers and/or trimers was responsible for this profound activity enhancement, as evidenced by the experimental results of ESI-MS analysis.



Scheme 13 Effective strategy for inhibiting deactivation

Asymmetric hydrogenation of quinoline derivatives provides a convenient and straight access to the optically active 1,2,3,4-tetrahydroquinolines, which are commonly present in natural alkaloids and have found broad application in pharmaceutical and agrochemical synthesis [49–51]. Since 2003, we applied our methodology to the asymmetric synthesis of tetrahydroquinoline alkaloids and chiral drugs (Scheme 14). For example, the hydrogenated product of 6-fluoro-2-methylquinoline is the key intermediate of antibacterial agent of Flumequine (Scheme 14) [36]. Furthermore, some naturally occurring tetrahydroquinoline alkaloids such as angustrureine, galipinine, and cuspareine were easily synthesized by N-methylation of hydrogenated products with high overall yields [36]. A total synthesis of alkaloid



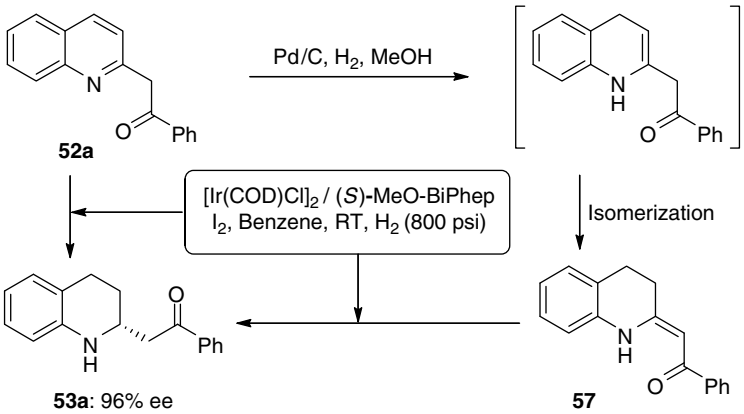
Scheme 14 Synthesis of tetrahydroquinoline alkaloids and drug flumequine

(−)-Galipeine, which contains a free phenol hydroxyl, was completed using asymmetric hydrogenation of quinoline as key step [52].

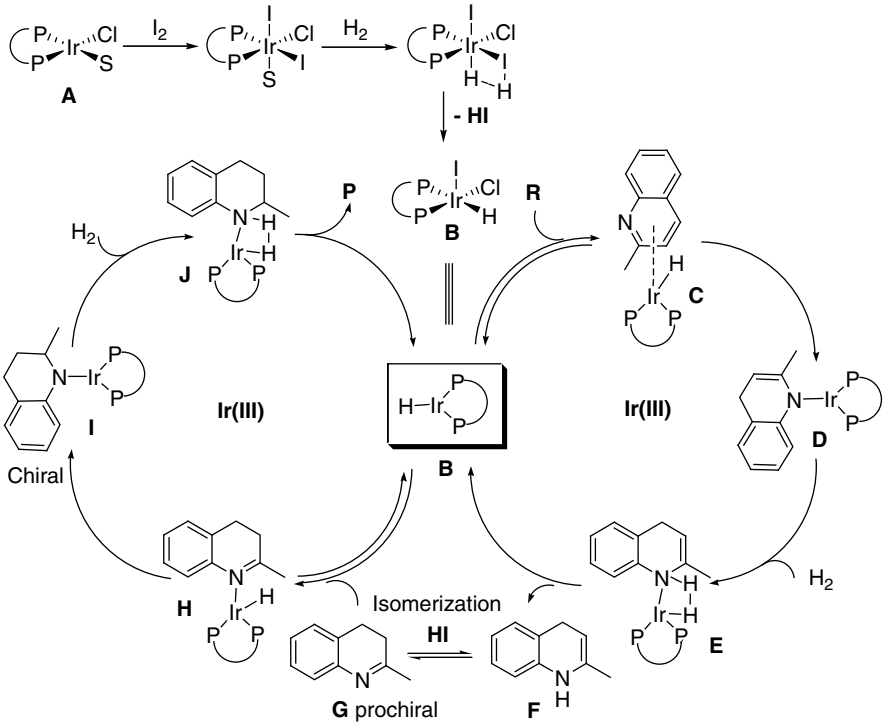
Mechanistic studies confirmed that iodine activated the catalyst in the hydrogenation of quinolines, which is in accordance with the observation of Osborn and Dorta [53, 54]. We also revealed that the hydrogenation process involves 1,4-hydride addition to quinoline, isomerization and 1,2-hydride addition, and the catalytically active species may be Ir(III) complex [39].

The synthesis and isolation of the possible reaction intermediate, which is usually unstable with a short lifetime, is very important and sometimes could provide a direct proof to support the mechanism. Therefore, 2-functionalized quinoline **52a** was selected as the starting material, which was treated with Pd/C under hydrogen in MeOH. The steady **57** was achieved after isomerization from the unstable intermediate and could be isolated. When **57** and **52a** were subjected to the identical hydrogenation conditions (Scheme 15), the desired product **53a** was obtained with the same enantioselectivity (96% ee). The existence of intermediate **57** could also be detected in the direct hydrogenation of compound **52a** under a lower pressure of hydrogen and with a shorter reaction time. Subsequent computational results also suggested that 1,4-hydride addition was more favorable than 1,2-hydride addition as the first step.

Based on the theoretical and experimental results mentioned above, together with suggestions of Zhang and Rueping group,[55–57] a plausible mechanism was suggested as follows (Scheme 16): The oxidative addition of I_2 to the Ir(I) species precursor **A** generates the Ir(III) species. Subsequent heterolytic cleavage of H_2 may form the Ir(III)-H species **B** with the elimination of hydrogen iodide. The quinoline substrate could coordinate with Ir(III) species **B** (I and Cl were omitted for clearness), and then 1,4-hydride transfer to afford the intermediate **D**. Subsequently, the heterolytic cleavage of H_2 with the intermediate **D** gives an enamine **F** and regenerates the Ir(III)-H species **B**. Then, enamine **F** isomerizes to yield imine **G**, which might be catalyzed by the in situ generated Brønsted acid HI, as



Scheme 15 Synthesis and hydrogenation of intermediate enamine **57**



Scheme 16 Proposed mechanism for Ir-catalyzed hydrogenation of quinolines

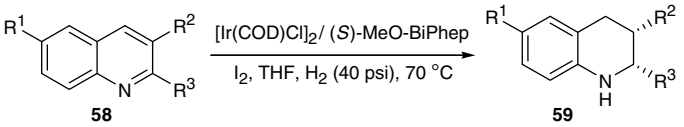
reported by Rueping [57]. Imine intermediate **G** could coordinate with Ir(III)-H species **B** to form the intermediate **H**, followed by the insertion and sigma-bond metathesis to release the product 1,2,3,4-tetrahydroquinolines **P** and regenerate **B** to complete the catalytic cycle [39].

Compared to 2-substituted quinolines, 2,3-disubstituted quinolines were less studied and remaining a challenge. We reasoned that the hydrogenation mechanism of 2,3-disubstituted quinolines was somewhat different from that of 2-substituted quinolines [39]. For the hydrogenation of 2-substituted quinolines, the hydrogenation of C=N bond is the enantioselectivity-control step (Scheme 16, **H** to **I**), while the enantioselectivity-control step of the former is the isomerization of enamine to imine combined with the hydrogenation of C=N bond, which is in fact a dynamic kinetic resolution process. To achieve high enantioselectivity, it should meet the equation $K_{iso} \gg K_{hy}$. It is obvious that higher temperature could accelerate the rate of isomerization (K_{iso}), and lower pressure of hydrogen can decrease the rate of hydrogenation (K_{hy}). Therefore, the asymmetric hydrogenation reactions of 2,3-disubstituted quinolines should perform under high reaction temperature and low hydrogen pressure. Detailed experiments showed that the best combination was 70°C and 40 psi of hydrogen in THF.

In general, with both 2,3-disubstituted quinolines and 2,3,6-trisubstituted quinolines, the reactions proceeded well with good enantioselectivities and diastereoselectivities (Table 9). Interestingly, the cyclic product **59l** was also obtained mainly with the *cis* configuration (entry 12), which was complementary for the *trans*-selectivity reported by Du using chiral phosphoric acid as catalyst [58]. The successful hydrogenation of 2,3-disubstituted quinolines provided new evidence to the mechanism suggested by us for the hydrogenation of quinolines [39].

During the studies on the hydrogenation mechanism of quinolines, we found that the dehydroaromatization reactions of 1,4-dihydropyridines (Hantzsch esters) could be realized with our catalytic system. The hydrogen gas generated in this reaction

Table 9 Iridium-catalyzed asymmetric hydrogenation of 2,3-disubstituted quinolines **58**

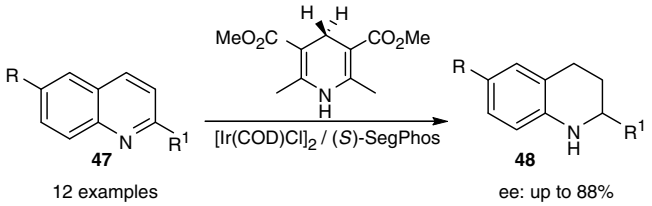


58 **59**

Entry	$R^1/R^2/R^3$	Yield (%)	Syn/Anti	Ee (%)
1	H/Me/Me	92 (**59a**)	>20:1	73
2	H/Me/Et	93 (**59b**)	>20:1	85
3	H/Me/*i*-Pr	94 (**59c**)	>20:1	86
4	H/Me/*n*-Bu	94 (**59d**)	>20:1	83
5	H/Me/*n*-Pentyl	91 (**59e**)	>20:1	83
6	H/Me/3-Butenyl	90 (**59d**)[a]	>20:1	83
7	H/Me/Phenethyl	97 (**59g**)	>20:1	80
8	H/Me/Benzyl	98 (**59h**)	>20:1	81
9	Me/Me/Et	91 (**59i**)	>20:1	84
10	F/Me/Et	89 (**59j**)	>20:1	83
11	MeO/Me/Et	76 (**59k**)	>20:1	85
12	H/$(CH_2)_4$	96 (**59l**)	>20:1	39
13	H/Me/Ph	90 (**59m**)	>20:1	38

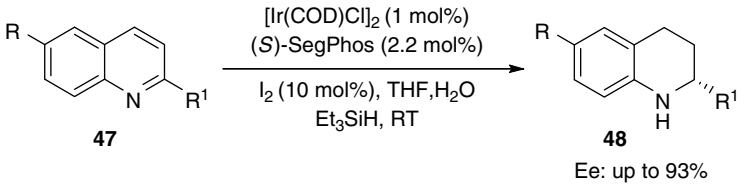
[a] The double bond in the branched chain was also hydrogenated

was subsequently applied in the iridium-catalyzed asymmetric transfer hydrogenation, and two reactions were combined (Scheme 17). Thus, a mild asymmetric transfer hydrogenation of quinolines was realized with $[Ir(COD)Cl]_2$/(*S*)-SegPhos/I_2 in the presence of Hantzsch esters with up to 88% ee [59]. Compressed hydrogen gas was avoided and this glovebox-free condition is convenient in laboratory.



Scheme 17 Asymmetric transfer hydrogenation of quinolines

Water, for being abundant and environmentally benign, has been applied to organic synthesis as a reaction reagent and medium [60–64]. Meanwhile, silanes have been extensively applied for asymmetric hydrosilylation. It is interesting to combine them in one catalytic reaction to serve as hydrogen source. Owing to the high oxyphilicity of organic silicon compounds, we envisioned that metal–hydride bond can be conveniently formed via the reaction of readily available metal-silyl compounds with water, which can be applied to the asymmetric hydrogenation reaction. Thus, we developed the first asymmetric hydrogenation of quinolines with water/silane as hydrogen source under mild autoclave-free reaction conditions with up to 93% ee (Scheme 18) [65]. For this hydrogenation reaction, two hydrides are from silanes and the other two are from water.



Scheme 18 Asymmetric hydrogenation of quinolines with water and silanes

Since our first report on Ir-catalyzed enantioselective hydrogenation of quinoline derivatives with iodine as activator, several other groups consecutively reported their results in this area (Fig. 9). Chan and coworkers developed a serial of effective diphosphine ligands, such as axially chiral P-Phos [66], PQ-Phos,[67] phosphinite ligands H_8-BINAPO [68], and Spiropo [69] with high activity and can be immobilized in DMPEG (poly(ethylene glycol) dimethyl ether) for recycling. Reetz's group found that BINOL-derived diphosphonites linked to an achiral diphenyl ether unit were also effective [70]. Pellet-Rostaing and coworkers devised an effective approach to synthesize more electron-donating BINAP ligands and examined their performance in the asymmetric hydrogenation of 2-methylquinoline [71]. Leitner and coworkers developed a series of new phosphine-phosphoramidite ligands, which can be prepared via a modular approach, with two elements of chirality [72].

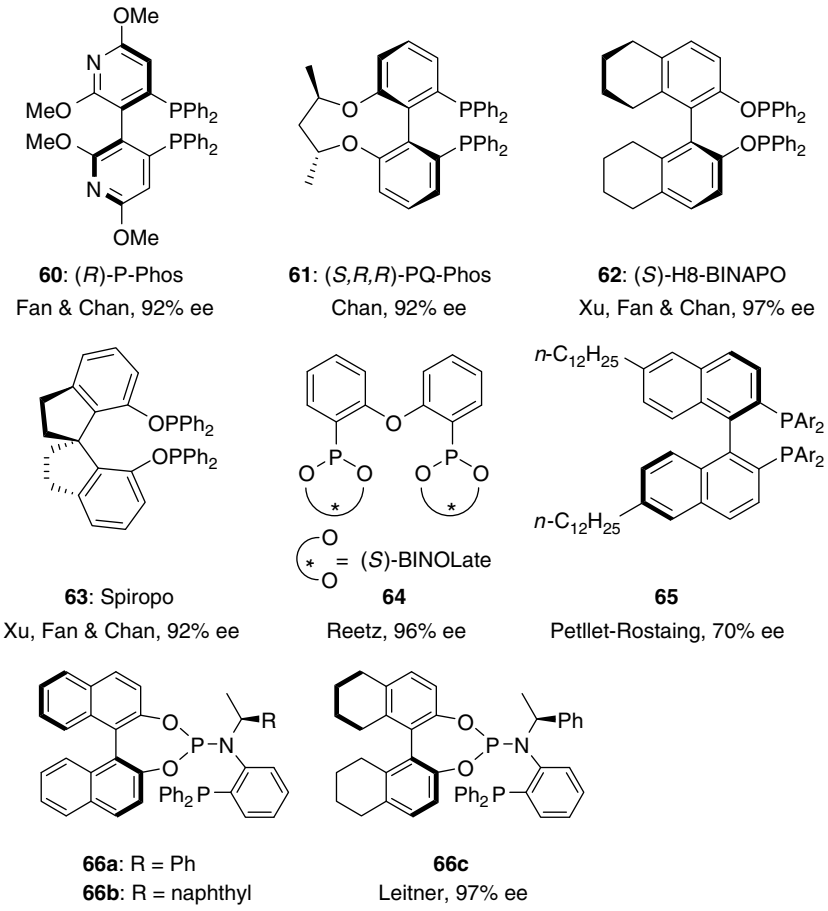


Fig. 9 Representative chiral diphosphine ligands used by other research groups

Furthermore, monodentate BINOL-derived phosphoramidites [73] and sulfoximine-derived P,N ligands [74] were also introduced to the asymmetric hydrogenation of quinolines by de Vries and Bolm (Fig. 10), respectively. In these catalytic systems, the addition of iodine was not required. Mashima and coworkers introduced the preformed cationic dinuclear triply halogen-bridged Ir(III) complexes with diphosphine ligands in the asymmetric hydrogenation of quinolines [75–77]. In 2009, they reported the asymmetric hydrogenation of quinoline hydrogen chloride salts using Ir-complexes with Difluorphos, with up to 95% ee [77]. This is the first example of effective hydrogenation of 2-arylquinolinium salts.

In addition, ruthenium and rhodium complexes were successively introduced to the asymmetric hydrogenation of quinolines by Fan [78, 79] and Xiao [80] groups with phosphine-free ligands, and the catalysts were air stable (Fig. 11). Fan and coworkers reported the first phosphine-free cationic Ru/Ts-DPEN catalyst in asymmetric hydrogenation of quinolines with unprecedented reactivity and high enantioselectivity [78]. Subsequently, they found this catalytic system was effective

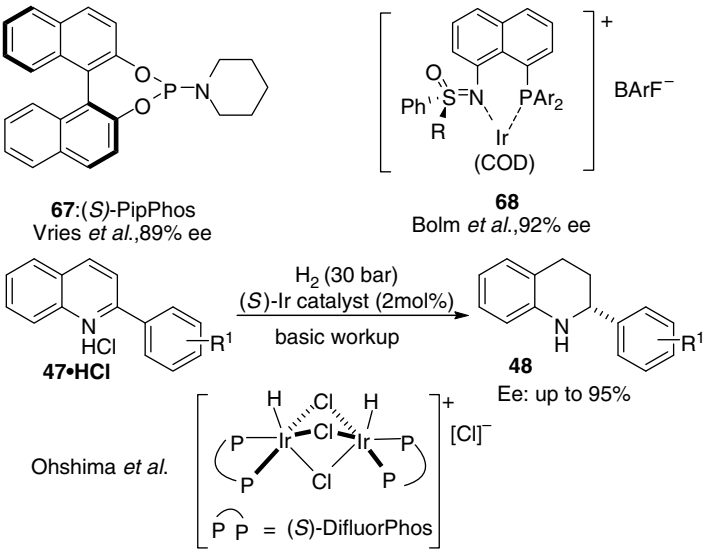


Fig. 10 Other catalytic systems for quinoline hydrogenation without iodine

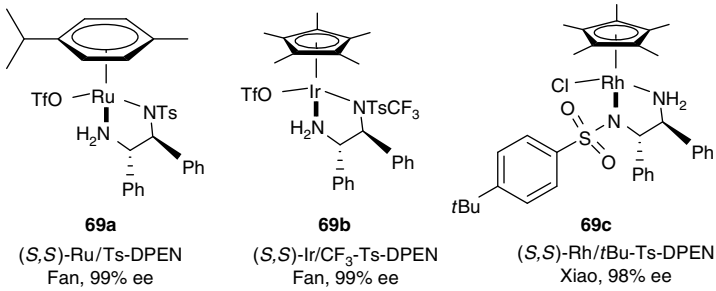
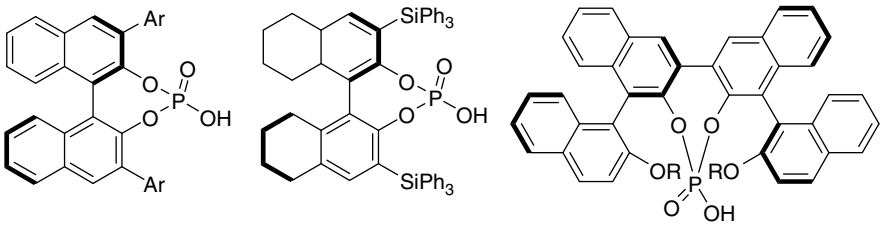


Fig. 11 Ru or Rh-catalyzed asymmetric hydrogenation of quinolines

under more environmentally friendly solvent-free or highly concentrated conditions [79]. Iridium complexes with this type of chiral diamine as ligands were also found to be effective, with up to 99% ee [81]. In 2009, Xiao and coworkers reported the first Rh-catalyzed asymmetric transfer hydrogenation of quinolines in an aqueous formate solution with excellent enantioselectivities [80].

2.1.2 Organocatalyzed Asymmetric Transfer Hydrogenation of Quinolines

In contrast to conventional transition metal catalysts, organocatalyst seems to be more attractive in recent years. Biomimetic, highly enantioselective organocatalytic transfer hydrogenation of α,β-unsaturated carbonyl compounds and imines has been independently carried out by MacMillan, List, and Rueping using Hantzsch



70a
Rueping, 99% ee

70b
Rueping, 86% ee

70c
Du, 98% ee

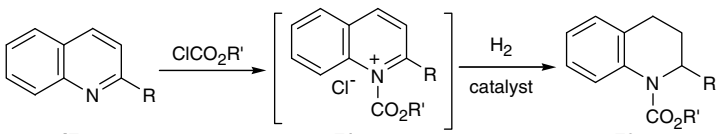
Fig. 12 Organocatalytic transfer hydrogenation with chiral Brønsted acids

esters as the hydrogen source. This strategy has also been extended to the asymmetric transfer hydrogenation of quinolines (Fig. 12).

In 2006, Rueping reported the first example of asymmetric transfer hydrogenation of quinolines under metal-free conditions [82]. Catalysts are sterically congested chiral BINOL-phosphoric acids (**70a**). Nonpolar and aromatic solvents are more effective for this catalytic system, and benzene gave the best enantioselectivity. Under optimal conditions, excellent enantioselectivities (up to 99% ee) were obtained for 2-substituted quinolines [82]. It was observed that higher enantioselectivities were obtained for 2-aryl substituted substrates than 2-alkyl-substrates. A mechanistic elucidation was suggested. First step is the activation of quinolines by the protonation with chiral phosphoric acid followed by a 1,4-dihydride addition. Subsequent, isomerization and 1,2-hydride addition gave the desirable tetrahydroquinolines. Subsequently, they extended this strategy to 3-substituted quinolines with up to 86% enantioselectivity [57]. In 2008, Du and coworkers [58] designed and synthesized novel double axially chiral phosphoric acid catalysts based on BINOL (**70c**), and applied these catalysts to asymmetric transfer hydrogenation of 2-substitued and 2,3-disubstituted quinolines with excellent enantioselectivities and diastereoselectivities.

2.1.3 Asymmetric Hydrogenation of Quinolines by Substrate Activation

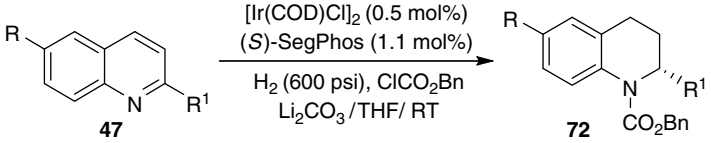
It is frustrating that the above-mentioned strategy for quinoline hydrogenation is not effective for the assorted isoquinoline and pyridine derivatives. Hence, the search for another activator to activate the substrate started. In 2006, we developed a new strategy for the asymmetric hydrogenation of quinolines activated by chloroformates [83] (Scheme 19). The chloroformates were crucial for the following reasons: (1) aromaticity



47 **71** **72**

Scheme 19 Asymmetric hydrogenation of quinolines activated by chloroformates

Table 10 Asymmetric hydrogenation of quinolines activated by chloroformates



Entry	R/R[1]	Yield (%)	ee (%)
1	H/Me	90	90 (*S*)
2	H/Et	85	90 (*S*)
3	H/*n*-Pr	80	90 (*S*)
4	H/*n*-Bu	88	89 (*S*)
5	H/*n*-Pentyl	91	89 (*S*)
6	F/Me	83	89 (*S*)
7	Me/Me	90	89 (*S*)
8	MeO/Me	92	90 (*S*)
9	H/Ph	41	80 (*R*)
10	H/Phenethyl	86	90 (*S*)
11	H/3,4-$(MeO)_2C_6H_3(CH_2)_2$	80	90 (*S*)
12	H/3-MeO-4-$BnOC_6H_3(CH_2)_2$	88	88 (*S*)

was destroyed partially by the formation of quinolinium salts; (2) catalyst poison may be avoided with the N-atom bonded by the activator; (3) CO_2R may act as secondary coordination group to assist the coordination between substrate and catalyst.

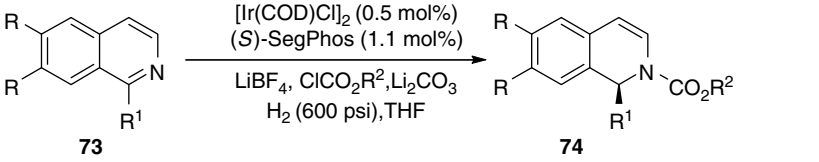
Since one molecule of hydrogen chloride is formed in this reaction, the addition of base to neutralize is necessary. Ir/(*S*)-SegPhos/$ClCO_2Bn$/Li_2CO_3 was found to be the best combination. Under the optimal conditions, a variety of 2-substituted quinolines **47** were hydrogenated with high enantioselectivities (Table 10) [83]. Therefore, this methodology offers an alternative access to tetrahydroquinoline alkaloids.

2.2 Asymmetric Hydrogenation of Isoquinolines

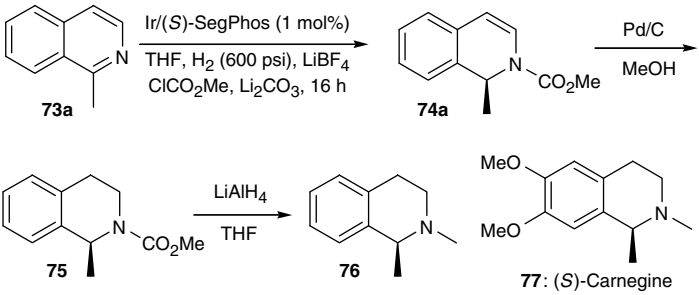
Although the asymmetric hydrogenation of isoquinolines by using iodine as the additive to activate the catalyst failed, activation with chloroformates for this type of substrates has been successful [83]. Enantioselectivity was found to be slightly higher when $LiBF_4$ or LiOTf was added as additive. In contrast to quinolines, all the isoquinolines were hydrogenated to give the corresponding dihydroisoquinolines with one double bond remaining as enamine which is difficult to hydrogenate. Moderate to good enantioselectivities and good yields were achieved for the selected examples (Table 11).

Asymmetric hydrogenation of isoquinolines also provides a convenient and straight route to optically active isoquinoline alkaloids. We applied this methodology to the synthesis of (*S*)-(−)-carnegine **77**, which is the natural tetrahydroisoquinoline alkaloid (Scheme 20) [83]. The hydrogenated products were treated by Pd/C in MeOH with

Table 11 Hydrogenation of isoquinolines activated by chloroformates



Entry	$R/R^1/R^2$	Yield (%)	ee (%)
1	H/Me/Me	85	80 (*S*)
2	H/Me/Bn	87	83 (*S*)
3	H/Ph/Me	57	82 (*S*)
4	H/Ph/Bn	49	83 (*S*)
5	MeO/Me/Me	44	63 (*S*)
6	MeO/Me/Bn	46	65 (*S*)
7	H/Et/Me	85	62 (*S*)
8	H/*n*-Bu/Me	87	60 (*S*)
9	H/Bn/Me	83	10 (*S*)



Scheme 20 Asymmetric synthesis of some isoquinoline alkaloids

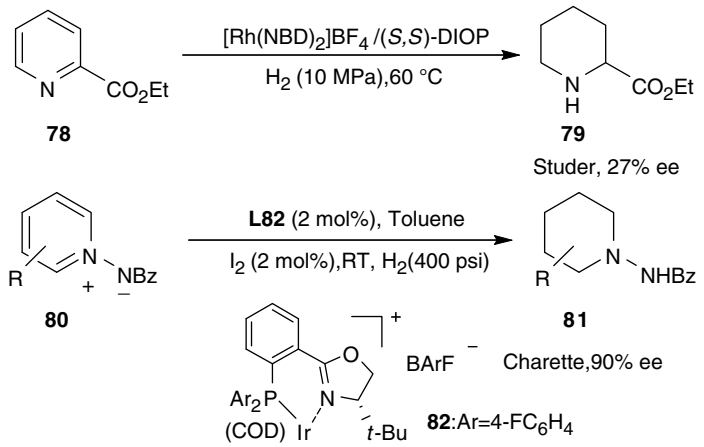
hydrogen gas to afford the corresponding 1,2,3,4-tetrahydro-isoquinoline derivatives, followed by reduction with $LiAlH_4$ to give the N-methylation products in good yield.

2.3 Asymmetric Hydrogenation of Pyridines

Chiral piperidine derivatives are important building blocks for many biologically active compounds, and asymmetric hydrogenation is one of the efficient methods to attain these compounds. Recently, some progress has been made in this field.

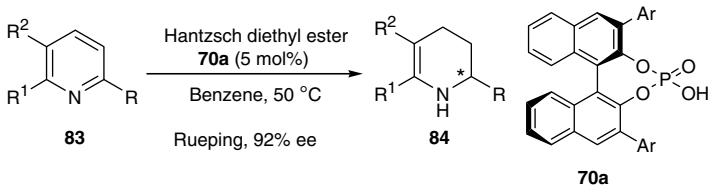
In 1999, Studer group reported the first asymmetric hydrogenation of pyridine derivatives with cinchona-modified heterogeneous Pd/TiO_2 as catalyst [84]. Afterward, the heterogeneous hydrogenation of pyridine derivatives was expanded [85–89]. Meanwhile, the homogenous asymmetric hydrogenation of pyridines was also started by Studer and coworkers. In 2000, they reported the homogeneous hydrogenation of simple monosubstituted pyridines using the $Rh(NBD)_2BF_4$/

bisphosphine ligands as catalysts with somewhat low enantioselectivity [90]. In 2005, Charette group reported Ir-catalyzed asymmetric hydrogenation of N-iminopyridinium ylides with up to 90% ee (Scheme 21) [91]. In 2006, Zhang, Lei and coworkers developed an efficient two-step method for the preparation of chiral nipecotic acid derivatives through asymmetric hydrogenation of enamides using Rh(NBD)(Tang-Phos)SbF_6 with 48–99% ee [92].



Scheme 21 Direct homogenous asymmetric hydrogenation of pyridines

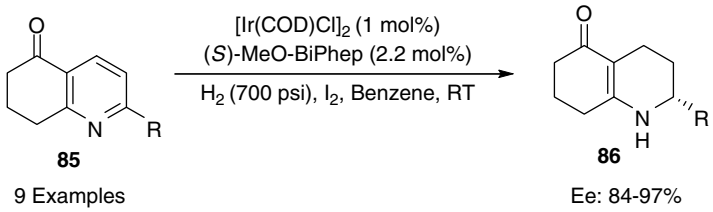
In 2007, Rueping and coworkers [93] developed the first organocatalyzed enantioselective reduction of trisubstituted pyridine derivatives **83** by using chiral Brønsted acids and Hantzsch dihydropyridine as hydrogen source with up to 92% ee (Scheme 22).



Scheme 22 Organocatalyzed asymmetric transfer hydrogenation of pyridines

Very recently, we extended our catalytic system to pyridine substrates. The asymmetric hydrogenation of 7,8-dihydro-quinolin-5(6*H*)-ones was realized using the catalytic system $[Ir(COD)Cl]_2$/MeO-BiPhep/I_2 [94]. The enantioselectivity of the products is highly solvent dependent. The highest ee value was obtained with benzene as the solvent. The axially chiral bisphosphine ligand (*S*)-MeO-BiPhep showed high reactivity and enantioselectivity (97% ee).

Under the optimized conditions, all the alkyl substituted substrates were hydrogenated smoothly (Scheme 23), while the enantioselectivity was different with the



Scheme 23 Ir-catalyzed asymmetric hydrogenation of pyridines

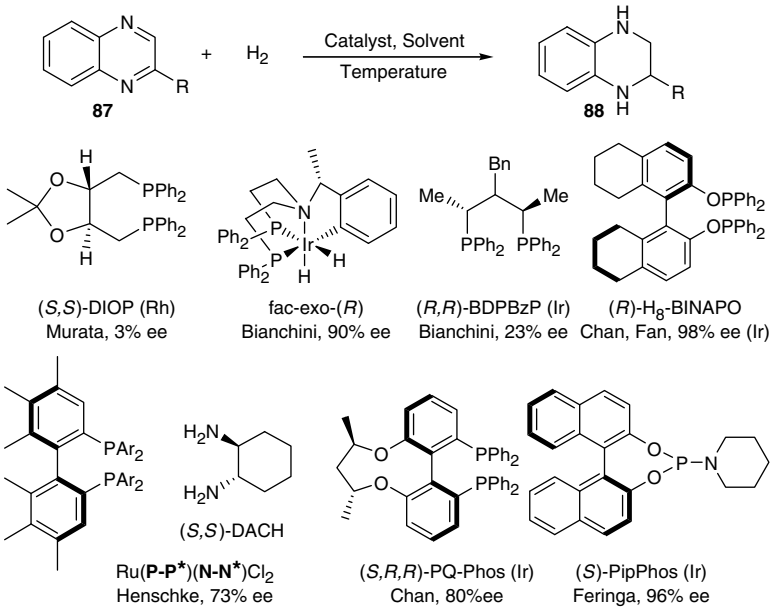
lengths of carbon chains and steric hindrance. For the methyl-substituted product, only 86% ee was obtained. With the growth of carbon chains, the enantioselectivity increased. It is noteworthy that with more steric hindrance substituent as 2-isopropyl, the enantioselectivity decreased to 84%. With the 2-phenyl substituted pyridine, slightly low conversion with excellent enantioselectivity was observed (entry 7, 92% ee). The hydrogenation of the 2-benzyl and 2-phenethyl 7,8-dihydro-quinolin-5(6*H*)-ones also exhibited 85% and 92% ee, respectively.

2.4 Asymmetric Hydrogenation of Quinoxalines

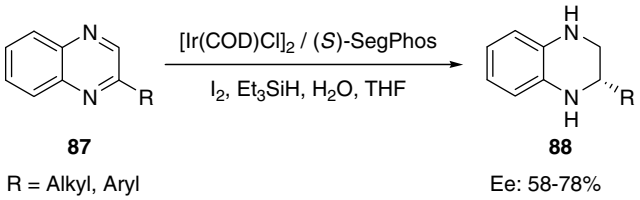
Tetrahydroquinoxalines are compounds of great biological interest, which are difficult to be obtained via stereoselective organic synthesis. Asymmetric hydrogenation tends to be an efficient method, though it is challenging. The pioneer work for homogeneous asymmetric hydrogenation of quinoxaline was reported by Murata group in 1987; 2-methyltetrahydroquinoxaline was obtained by using (+)-(DIOP)RhH prepared in situ with enantioselectivity of only 3% [95]. Then, in 1998, Bianchini and coworkers realized the hydrogenation of 2-methylquinoxaline using an orthometalated dihydride iridium complex in MeOH with up to 90% ee [96]. Subsequently, the same group applied [(*R,R*)-(BDPBzP)Ir(COD)]OTf and [(*R,R*)-(BDPBzP)Rh(NBD)]OTf complexes to the asymmetric hydrogenation of 2-methylquinoxaline with 23% ee and 11% ee, respectively [97].

In 2003, Henschke group reported asymmetric hydrogenation of 2-methylquinoxaline by using Noyori's catalytic system $RuCl_2$(diphosphine)(diamine) with moderate enantioselectivity [98, 99]. Chan group reported the hydrogenation of 2-methylquinoxaline using the Ir-PQ-Phos complex as catalyst with up to 80% ee in the presence of iodine [67]. Very recently, Chan, Xu, and Fan reported the asymmetric hydrogenation of quinoxalines using $[Ir(COD)Cl]_2/H_8$-BINAPO/I_2 with up to 98% ee (Scheme 24) [100]. Meanwhile, Feringa and coworkers described the hydrogenation of 2-substituted quinoxalines with Ir-PipPhos as catalyst with up to 96% ee [101].

In 2009, we reported the asymmetric transfer hydrogenation of quinolines with $[Ir(COD)Cl]_2$/(*S*)-SegPhos/I_2 as catalyst using silane and water as hydrogen source [65]. This new strategy was also successfully applied to the asymmetric hydrogenation of quinoxalines **87** (Scheme 25). Alkyl or aryl substituted quinoxalines can be reduced smoothly with full conversion and 58–78% ee.



Scheme 24 Asymmetric hydrogenation of quinoxalines

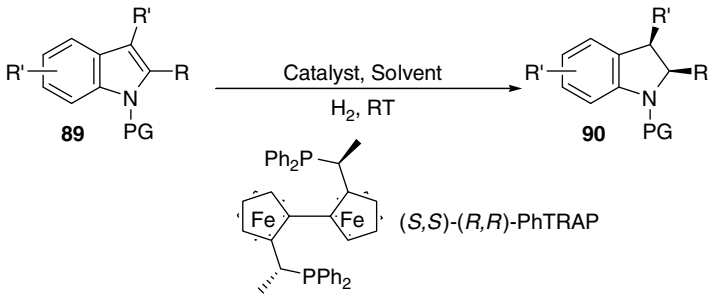


Scheme 25 Ir-catalyzed hydrogenation of quinoxalines using water/silane

2.5 *Asymmetric Hydrogenation of Indoles, Pyrroles, and Furans*

The hydrogenated product of substituted indoles is regarded as a privileged structure because this skeleton has been found as a substructure in a huge number of alkaloids and natural products. Direct hydrogenation of indoles is the most convenient route to obtain these compounds.

In 2000, Kuwano and coworkers reported a highly effective hydrogenation of N-Boc or Ac-substituted indoles by using chiral $[Rh(nbd)_2]SbF_6$/(*S*,*S*)-(*R*,*R*)-PhTRAP complex (Scheme 26) [102]. It is noteworthy that most chiral bisphosphine ligands failed to achieve efficient chiral induction, yielding almost racemic products. The PhTRAP-rhodium catalyst showed high enantioselectivity for the hydrogenation of N-Boc or Ac-protected 2-substituted indoles, for Ac-protected 3-substituted indole, the above catalytic system gave the major undesirable alcoholysis product. In 2004, they used Ts as protecting group of 3-substituted indoles to yield the products with high enantioselectivities and conversions [103].

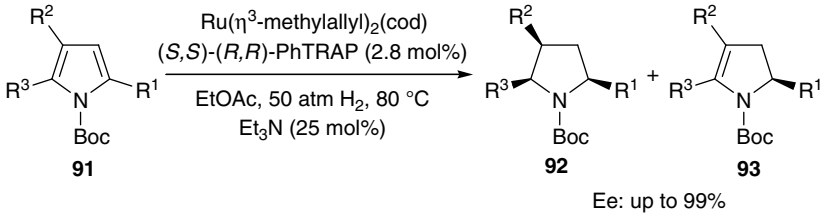


PG	Catalyst	Solvent & Additive	Ee (%)
Ac	Rh / Ph-TRAP	*i*-PrOH & Cs_2CO_3	78-95%
Ts	Rh / Ph-TRAP	*i*-PrOH & Cs_2CO_3	95-98%
Boc	Ru / Ph-TRAP	*i*-PrOH & Cs_2CO_3	72-95%

Scheme 26 Asymmetric hydrogenation of indoles

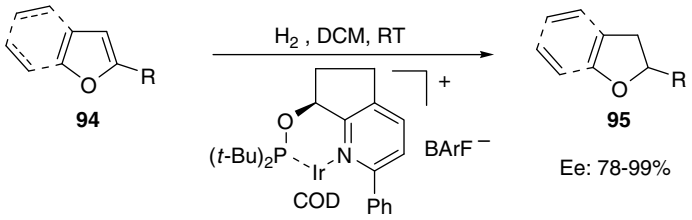
Kuwano group devoted their continuous effort to asymmetric hydrogenation of substituted indoles. In 2006, they reported the asymmetric reduction of N-Boc indoles with [RuCl(*p*-cymene){(*S,S*)-(*R,R*)-Ph-TRAP}]Cl as catalyst with great success (Scheme 26) [104]. Both for the 2-substituted and 3-substituted indoles, high enantioselectivities were obtained except 2-cyclohexylindole. For 2,3-disubstituted indoles, only the *cis*-2,3-dimethylindoline was formed with moderate enantioselectivity (72% ee) and conversion.

In 2008, Kuwano and coworkers extended their catalytic system to the asymmetric hydrogenation of N-Boc-pyrroles using Ru(η^3-methylallyl)$_2$(cod)/(*S,S*)-(*R,R*)-PhTRAP as catalyst (Scheme 27) [105]. The selectivity can be improved by adding a catalytic amount of triethylamine with 99% ee.



Scheme 27 Ru-catalyzed asymmetric hydrogenation of 2,3,5-trisubstituted pyrroles

The first example of asymmetric hydrogenation of furans was reported by Takaya using Ru_2Cl_4[(*R*)-BINAP]$_2$(NEt_3) as the catalyst with moderate ee (50%) [106]. Subsequently, some efforts were tried with low enantioselectivity [90, 107, 108]. By far, the best result in enantioselective hydrogenation of furans was achieved by Pfaltz and coworkers [109] with up to >99% ee using pyridine-phosphinite-ligated iridium complex as the catalyst (Scheme 28).



Scheme 28 Asymmetric hydrogenation of furans

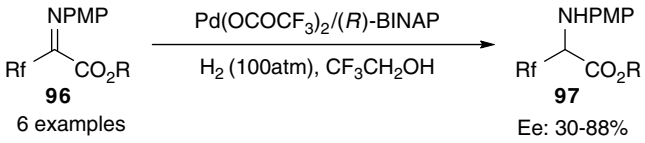
3 Palladium-Catalyzed Asymmetric Hydrogenation

Although a large number of Pd-catalyzed reactions have been developed, very little attention has been paid to palladium-catalyzed homogeneous asymmetric hydrogenation reactions. Some successful examples of heterogeneous asymmetric hydrogenation reactions catalyzed by Pd(0) have been reported [110]. Recently, Pd-catalyzed homogeneous asymmetric hydrogenation of activated imines and functionalized ketones has been developed by us, Amii, and the others.

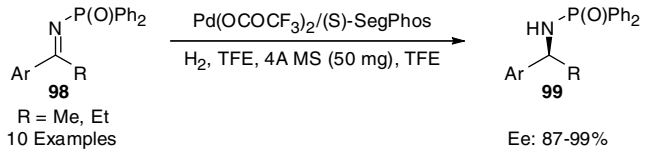
3.1 Pd-Catalyzed Asymmetric Hydrogenation of Imines

Chiral amines are ubiquitous in natural products and drugs and serve as building blocks, chiral ligands, and chiral auxiliaries in asymmetric synthesis. Accordingly, the development of efficient synthetic methods for chiral amines is one of the most challenging tasks for organic chemists [111–113]. The asymmetric hydrogenation of the C=N bond is considered to be the most convenient and efficient route. Recently, a number of transition metal-based catalysts, such as those containing Rh, Ru, Ti, Zr, and Ir, have been applied to asymmetric hydrogenation of imines [98, 114–118]. In the past decades, some progresses have been achieved in the hydrogenation of imines with Pd(II) complexes. In 2001, Amii and coworkers reported the first highly enantioselective hydrogenation of α-fluorinated iminoesters **96** with a $Pd(OCOCF_3)_2$/BINAP complex to afford chiral fluoro amino acids **97** with moderate ee values (Scheme 29) [119]. Subsequently, some optically active β,β-difluoroglutamic acid and β,β-difluoroproline derivatives were synthesized with the same catalyst system [120]. In 2003, Alper and coworkers reported the Pd-catalyzed asymmetric double carbohyoamination of iodobenzene for the synthesis of chiral α-aminoamides with high enantioselectivity [121]. The reaction was suggested to involve a Pd-catalyzed asymmetric hydrogenation of α-aminoamide intermediates.

In 2006, we reported the highly enantioselective hydrogenation of *N*-diphenylphosphinyl ketimines **98** using $Pd(OCOCF_3)_2$/(*S*)-SegPhos as catalyst [122]. This reaction was highly solvent dependent, and 2,2,2-trifluoroethanol was the best solvent. The scope of the Pd-catalyzed asymmetric hydrogenation of *N*-diphenyl phosphinyl ketimines **98** was explored (Scheme 30). Both electron-deficient and



Scheme 29 Pd-catalyzed asymmetric hydrogenation of α-fluorinated iminoesters

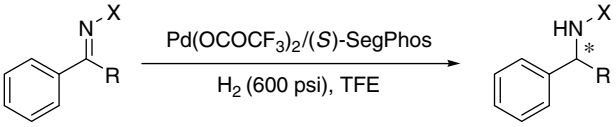


Scheme 30 Pd-catalyzed hydrogenation of N-diphenylphosphinyl ketimines

electron-rich aryl imines can be hydrogenated with high enantioselectivities [122]. *ortho*-Methoxy-substituted aryl imines gave the highest ee of 99%.

As an extension of Pd-catalyzed asymmetric hydrogenation of N-diphenyl phosphinyl imines, the detailed studies on Pd-catalyzed asymmetric hydrogenation of varied kinds of N-substituted imines was reported [123]. The preliminary investigations of the asymmetric hydrogenation of imines with Pd complex catalysts suggested that the suitable N-substituent is crucial in achieving good reactivity (Table 12). We speculated that the strong electron-withdrawing character of tosyl and diphenylphosphinyl reduces the inhibitory effect of the starting material and product on the catalyst. So, for Pd-catalyzed asymmetric hydrogenation of imines, activated imines are good substrates in view of reactivity and enantioselectivity.

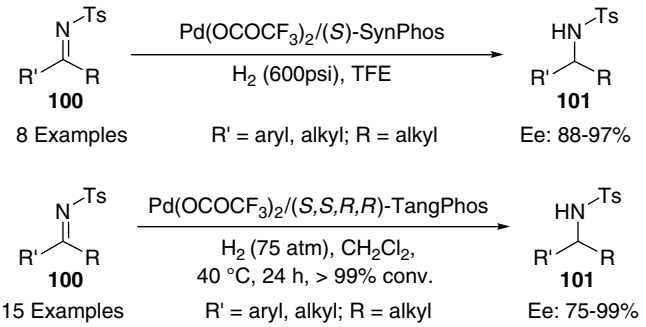
Table 12 Pd-catalyzed asymmetric hydrogenation of N-substituted imines



Entry	R/X	Temp (°C)	Conv. (%)	Ee (%)
1	Me/4-$MeOC_6H_4$	rt	26	94
2[a]	Me/4-$MeOC_6H_4$	rt	25	95
3	Me/4-$MeOC_6H_4$	60	9	77
4	Me/4-FC_6H_4	rt	15	N/D
5	Me/2-$MeOC_6H_4$	rt	24	N/D
6	Me/AcO	rt	<5	N/A
7	Me/BzNH	rt	44	58
8[b]	CO_2Et/PMP	rt	>95	33
9	Me/$P(O)Ph_2$	rt	85	95
10	Me/Ts	rt	>95	97

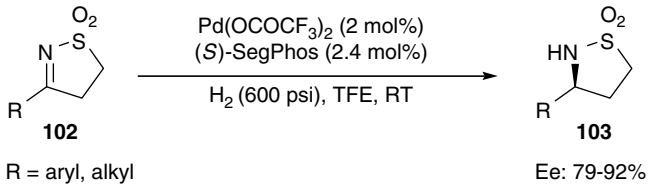
[a]4 Å MS was used
[b](*R*)-BINAP was used

The Pd(OCOCF$_3$)$_2$/(*S*)-SynPhos system was also efficient for enantioselective hydrogenation of N-tosyl substituted imines derivatives. Under the optimized condition, all the N-tosyl imines **100** were hydrogenated completely to give the corresponding amines derivatives (Scheme 31). Excellent enantioselectivities and high yields were obtained regardless of the electronic properties and steric hindrance of substituent groups [123]. In the same year, Zhang and coworkers also reported asymmetric hydrogenation of N-tosylimines **100** using a Pd(OCOCF$_3$)$_2$-TangPhos complex at 40°C in methylene chloride with up to 99% ee, independently (Scheme 31) [124].



Scheme 31 Pd-catalyzed asymmetric hydrogenation of N–Ts imines

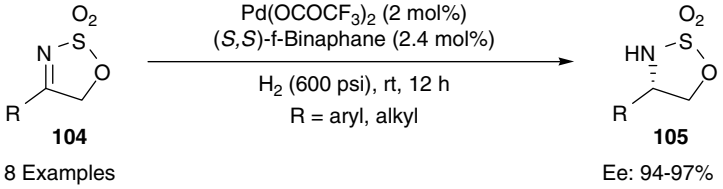
To further expand substrate scope of Pd-catalyzed asymmetric hydrogenation of imines, we synthesized a class of new activated cyclic imines **102**, the hydrogenation products are cyclic sulfonamides **103**, the sultams derivatives, which are important organic synthetic intermediates and structural units of agricultural and pharmaceutical agents. The asymmetric hydrogenation of cyclic N-sulfonylimines was studied using Pd(OCOCF$_3$)$_2$/(*S*)-SegPhos system at ambient temperature under H_2 pressure of 600 psi. A variety of cyclic N-sulfonylimine derivatives could be successfully hydrogenated to afford their corresponding sultams **103** (Scheme 32) with 79–92% ee [123].



Scheme 32 Pd-catalyzed asymmetric hydrogenation of cyclic N-sulfonylimines

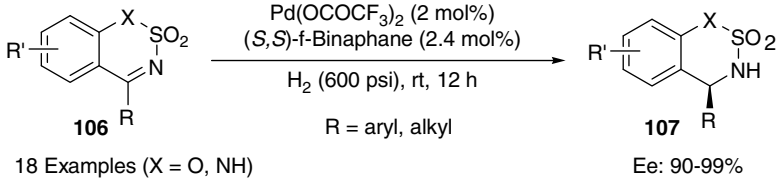
Next, we explored the practical synthesis of enantiopure cyclic sulfamidates via asymmetric hydrogenation of the corresponding activated cyclic imines **104** using Pd(OCOCF$_3$)$_2$/(*S,S*)-*f*-Binaphane as catalyst [125]. It is noteworthy that the (*S,S*)-*f*-Binaphane ligand is very crucial for the hydrogenation of this kind of substrates.

Under the optimal reaction conditions, a wide variety of imines **104** were hydrogenated with full conversions. Substrates with electron-donating or electron-withdrawing aryl substituents (Scheme 33) can be successfully hydrogenated to give the corresponding cyclic sulfamidates **105**. For alkyl substituted imines, high enantioselectivities and full conversions were also obtained. It should be noted that the asymmetric hydrogenation can be also operated in air with almost the same enantioselectivity and reactivity.



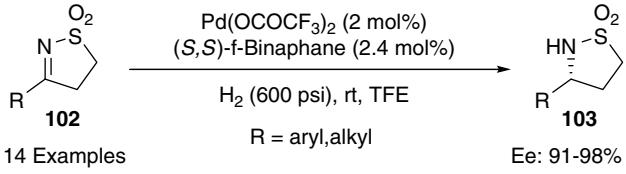
Scheme 33 Pd-catalyzed asymmetric hydrogenation of activated imine **104**

The assorted benzo-fused six-membered imine **106** were also explored [125]. As shown in Scheme 34, the above Pd catalyst was also effective for a variety of imines **106** to give the corresponding chiral benzo-fused oxathiazinanes **107** with 90–99% ee.



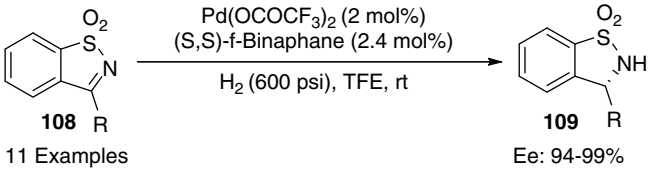
Scheme 34 Pd-catalyzed asymmetric hydrogenation of activated imine

To further improve the enantioselectivity of the asymmetric hydrogenation of cyclic imine **102**, the effect of ligands on the enantioselectivity was systematically screened. Interestingly, when a Pd catalyst containing (*S,S*)-*f*-Binaphane ligand was used in the asymmetric hydrogenation of imine **102a**, a significant increase in the ee value was obtained in comparison with the result of (*S*)-SegPhos (98% ee vs. 79% ee) [126]. Inspired by the result, a series of cyclic N-sulfonylimines **102** were hydrogenated with high enantioselectives and yields (Scheme 35).



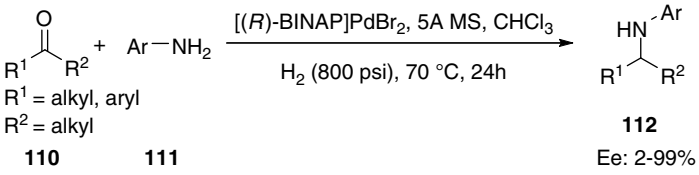
Scheme 35 Pd-catalyzed asymmetric hydrogenation of cyclic N-sulfonylimines

The above chiral palladium catalytic system $Pd(OCOCF_3)_2$/(*S,S*)-*f*-Binaphane can also be extended to asymmetric hydrogenation of assorted benzo-fused imines **108** (Scheme 36). A variety of aryl- and alkyl-substituted cyclic sultams could be obtained in 94–99% ee values with full conversion [126]. The electronic and steric characteristics of substituents in the substrates have no significant influence on the enantioselectivity and reactivity. Notably, the palladium catalytic system can tolerate hydroxyl and TBSO groups with 98 and 99% ee, respectively.



Scheme 36 Pd-catalyzed asymmetric hydrogenation of activated imines **108**

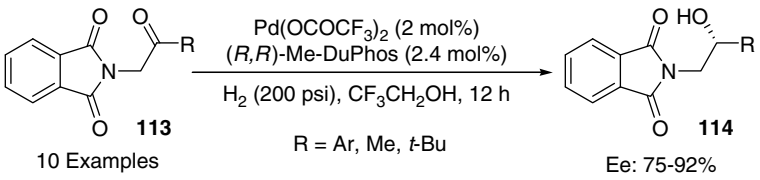
In 2009, Rubio-Perez and coworkers developed an efficient one-pot reductive amination of various carbonyl compounds and anilines using air stable [(*R*)-BINAP]$PdBr_2$ complex as catalyst (Scheme 37) [127]. They found that $CHCl_3$ was the best solvent, giving the highest enantioselectivity. For the alkyl ketones, high enantioselectivity was obtained; however, when aryl ketones were subjected to the asymmetric reductive amination, moderate yields and relatively low enantiomeric excess were obtained.



Scheme 37 Pd-catalyzed asymmetric reductive amination of ketones

3.2 Pd-Catalyzed Asymmetric Hydrogenation of Ketones

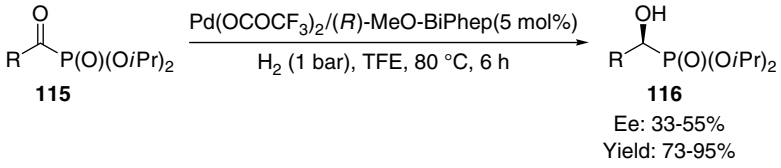
Pd complexes with chiral bisphosphines ligands are excellent catalysts for the asymmetric hydrogenation of activated imines in the presence of trifluoroethanol. And this catalytic system is also extended to asymmetric hydrogenation of ketone derivatives. In 2005, we developed Pd/bisphosphine catalyzed hydrogenation of N-phthalimide ketones **113** with up to 92% ee, which provided an efficient method to chiral amino alcohols **114** (Scheme 38) [128]. This reaction was also strongly solvent-dependent, and only TFE is efficient in terms of the conversion and enantioselectivity. (*R,R*)-Me-DuPhos emerged as the best ligand with respect to the activity and selectivity.



Scheme 38 Pd-catalyzed asymmetric hydrogenation of functionalized ketones

In general, N-phthalimide aryl ketones bearing either electron-withdrawing or electron-donating groups were hydrogenated with high enantioselectivities and complete conversions. In the case of alkyl ketones, excellent enantioselectivities were also obtained. However, for bromo-substituted aryl ketone, no hydrogenated product was obtained probably due to oxidative addition of palladium with the aromatic bromide.

Recently, Goulioukina reported the asymmetric hydrogenation of α-ketophosphonates **115** catalyzed by $Pd(OCOCF_3)_2$/(*R*)-MeO-BiPhep in TFE under atmospheric hydrogen pressure with up to 55% ee (Scheme 39) [129].



Scheme 39 Pd-catalyzed asymmetric hydrogenation of α-keto phosphonates

4 Summary

This chapter focused on recent advances in homogeneous asymmetric hydrogenation in Dalian Institute of Chemical Physics. Three sections, namely, the synthesis of chiral phosphorus ligands, asymmetric hydrogenation of heteroaromatics, and homogeneous palladium catalyzed asymmetric hydrogenation, were reviewed. We have developed a series of chiral monodentate phosphorus-containing ligands and chiral phosphine–phosphoramidite ligands, which have a wide range of applications in the Rh-catalyzed asymmetric hydrogenation of various functionalized C=C double bonds. Two types of systems were developed for hydrogenation of heteroaromatics. One is the highly active iridium catalyst Ir/diphosphine/I_2, in which the additive iodine is crucial for activity and enantioselectivity. The other is Ir/diphosphine in the presence of chloroformates, which is able to activate quinolines by the formation of salt. The latter can also be applied to asymmetric hydrogenation of isoquinolines. The efficient homogeneous palladium catalytic systems were developed for the functionalized ketones and activated imines. We hope that our experience in asymmetric hydrogenation will provide some useful information and hints for those who are interested in ligand design, mechanistic elucidation, and development of asymmetric reactions.

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DOI: 10.1007/978-3-642-19472-6_11

Erratum to: Asymmetric Organocatalysis

W.J. Liu, N. Li, and L.Z. Gong

Erratum to:
Shengming Ma (ed.), Asymmetric Catalysis from a Chinese Perspective
Top Organomet Chem (2011) 36:153–206
DOI 10.1007/978-3-642-19472-6_6

In this Chapter, the citations of Fig. 3 "Chiral binol-based phosphoric acids" and Fig. 4 "Representative modified cinchona alkaloids" are incorrect.

Fig. 3 is erroneously cited on p. 164, in the first sentence of Sect. 3.1:

3.1 Asymmetric Michael Addition Reactions

Chen reported an asymmetric direct vinylogous Michael addition (~~**Fig. 3**~~) of α,α-adicyanoolefins to enals (Scheme 13) [64. …

Fig. 3 should correctly replace the citation of Fig. 4 on p. 177, in Sect. 5.1:

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The online version of the original chapter can be found at DOI 10.1007/978-3-642-19472-6_6

5.1 Phosphoric Acid and Amide Catalysis

Chiral phosphoric acids of type **116**, were first demonstrated to catalyze Mannich reaction independently by Akiyama and Terada [97, 98]. This type of organocatalysts have unique structural feature containing a strong acidic hydroxy and a Lewis basic phosphoryl oxygen, which allow for the simultaneous activation of both nucleophiles and electrophiles by hydrogen bonding interactions. Moreover, the tunable 3,3'-substituents provide a diverse spectrum of catalysts for different enantioselective transformations. Indeed, they have been privileged organocatalysts widely applicable to a broad scope of asymmetric transformations (~~Fig. 4~~ **Fig. 3**) [99–101].

Fig. 4 should correctly be cited on p. 189, Sect. 6:

6 Chiral Organic Base Catalysis

An asymmetric direct vinylogous Michael reaction of activated vinyl malononitriles to nitroolefins catalyzed by modified cinchona alkaloid $[DHQD]_2PYR$ (**Fig. 4**) was reported by Chen (Scheme 61) [135]. Highly functionalized products with two vicinal chiral centers were generated with exclusive γ-selectivity and high diastereoand enantioselectivity.

Index