Top Organomet Chem (2011) 36:313–354
DOI: 10.1007/978-3-642-19472-6_10

Adventure in Asymmetric Hydrogenation: Synthesis of Chiral Phosphorus Ligands and Asymmetric Hydrogenation of Heteroaromatics

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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),

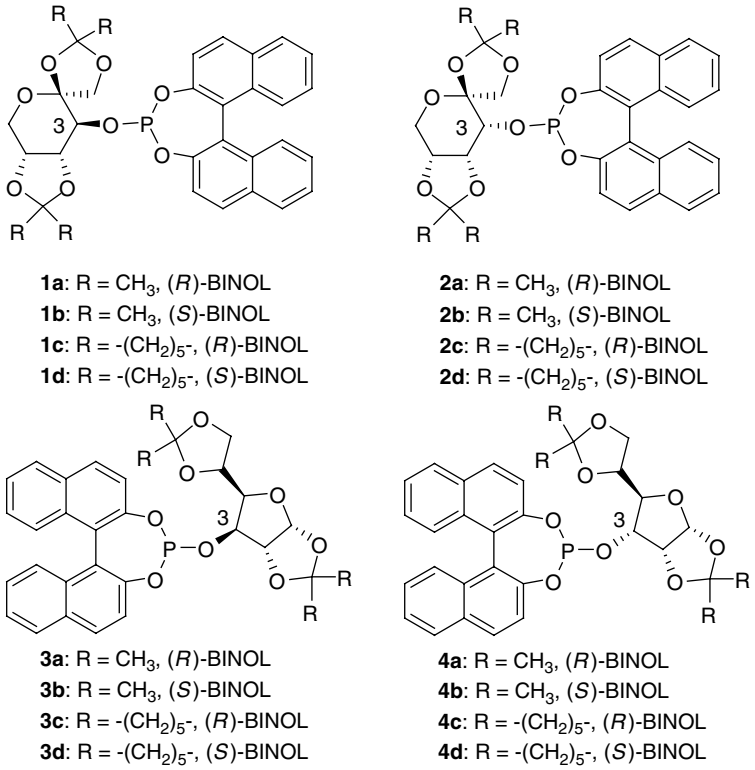
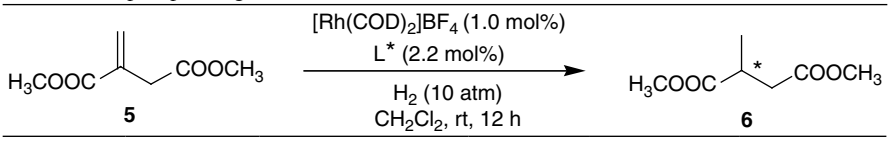


Fig. 1 D-Fructose- and D-glucose-derived monophosphite ligands **1**–**4**

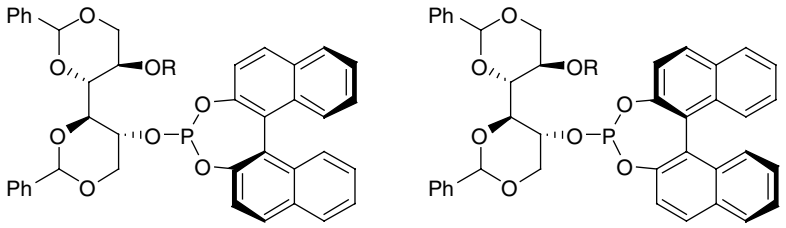
which contain additional groups in the proper spatial configuration to effectively restrain the rotation of the Rh–P bond by secondary interactions. As expected, these ligands exhibited excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of some prochiral olefins, including dimethyl 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*)

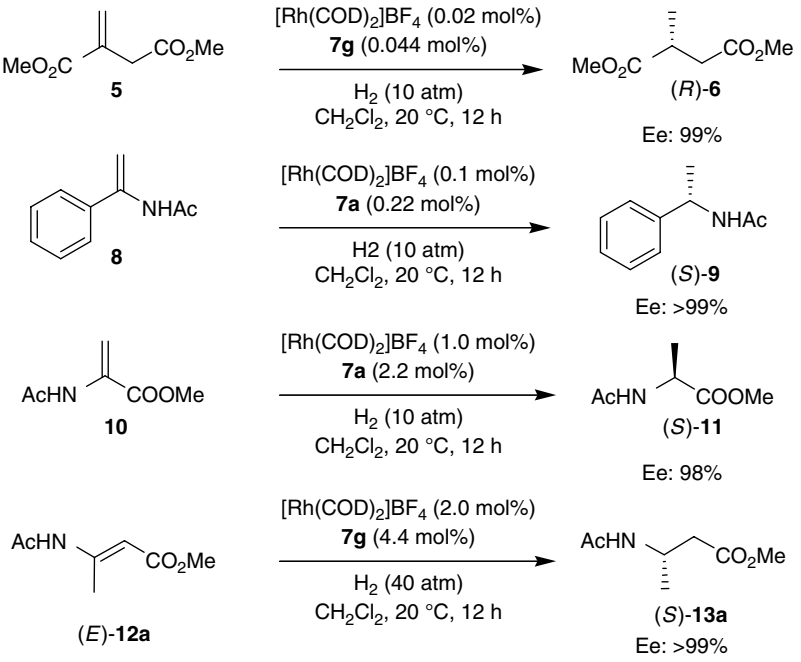


7a: R = Me
7b: R = *n*-Pr
7c: R = *i*-Pr
7d: R = *i*-Bu
7e: R = CH_2Ph
7f: R = $CHPh_2$
7g: R = 1-CH_2Nap
7h: R = CH_3
7i: R = CH_2Ph

Fig. 2 D-Mannitol-derived monophosphite ligands, ManniPhos **7**

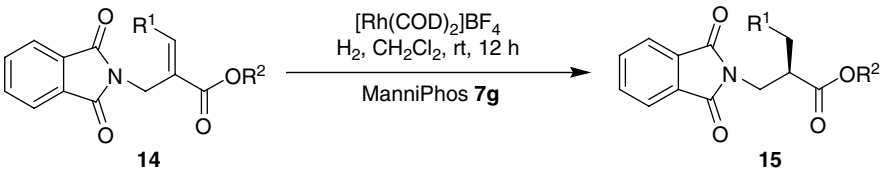
utility of this notion and enhance the versatility of this ligand type in asymmetric reactions, in 2004, we developed a new class of chiral monophosphite ligands, ManniPhos **7** (Fig. 2) [12], based on D-mannitol. These new ligands contain an extra chiral scaffold with a fair degree of rigidity and 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

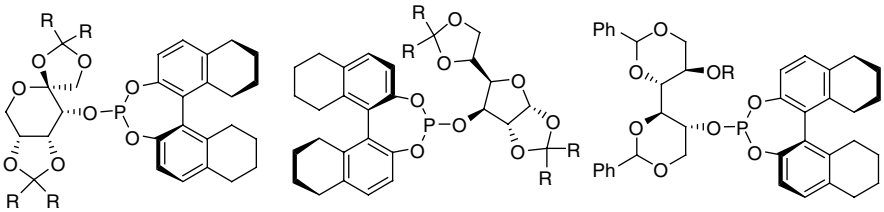


Fig. 3 Monophosphites **16–17** derived from carbohydrate and H_8-BINOL

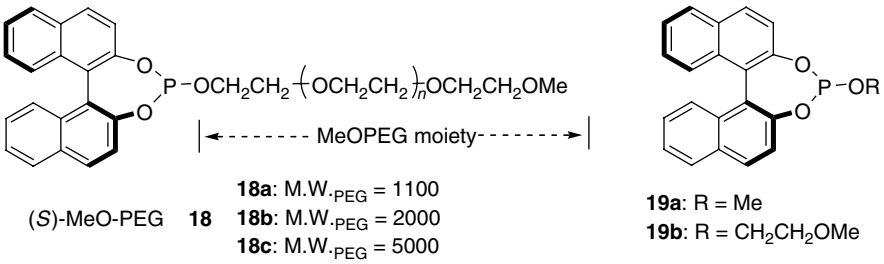
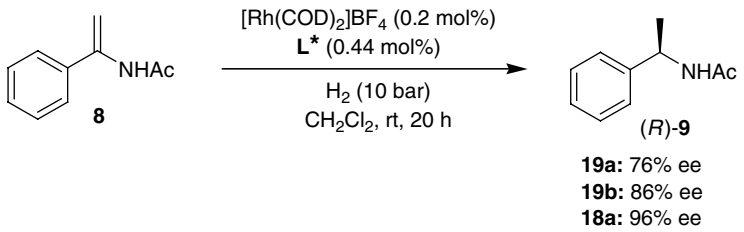


Fig. 4 MeO-PEG-monophosphite ligands **18** and relative ligands



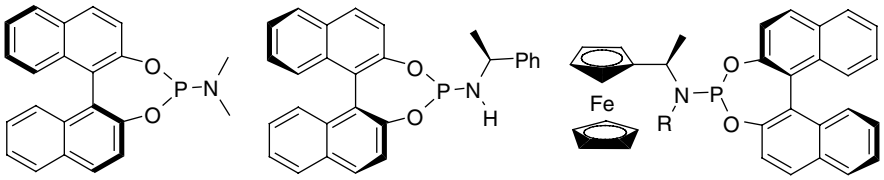
Scheme 2 Rh-catalyzed hydrogenation of N-(1-phenylethenyl)acetamide **8** with MeOPEG-monophosphite ligand **18a**

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

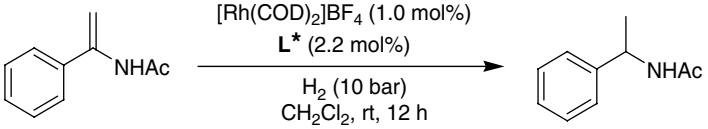


(*S*)-MonoPhos **20** (S_c,R_a)-**21**

(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**

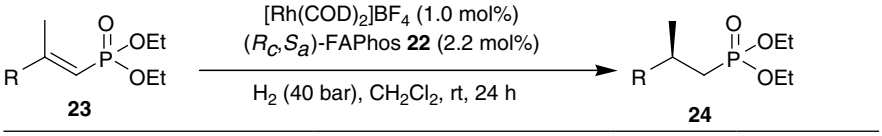
Entry	Ligand	Yield (%)	Ee (%) (config)
1	**22a**	98	99 (*R*)
2	**22b**	99	53 (*R*)
3	**22c**	<5	–
4	**22d**	98	86 (*S*)

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.

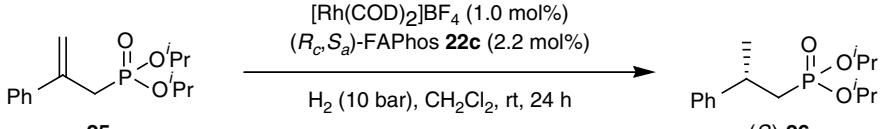
Similar results were also observed in the first Rh-catalyzed hydrogenation of β,γ-unsaturated phosphonates **25**, in which (R_c,S_a)-FAPhos **22c** with a benzyl group showed the highest enantioselectivity (Scheme 3) [23]. Interestingly, the hydrogenation of α,β-unsaturated phosphonates **23** and β,γ-unsaturated 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**

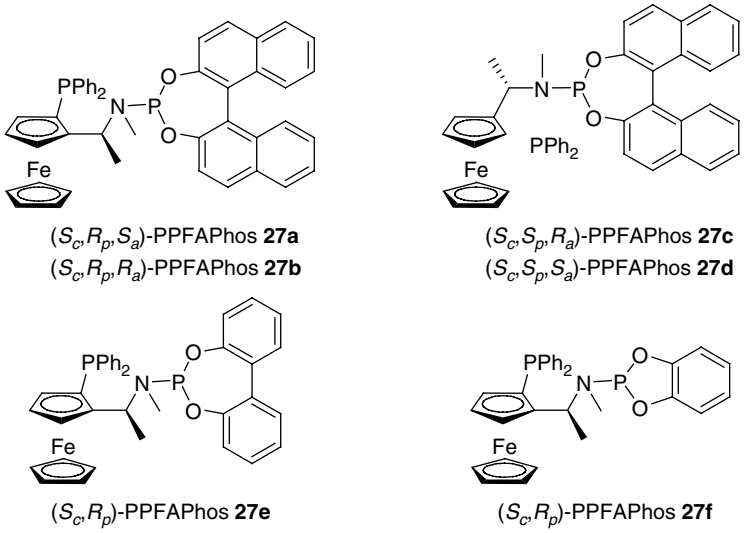
Ee: 97%

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**

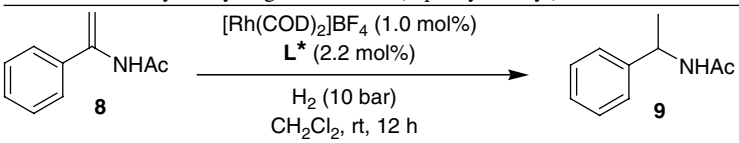
Fig. 6 Ferrocene-based phosphine-phosphoramidite ligands (PPFAPhos)

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.

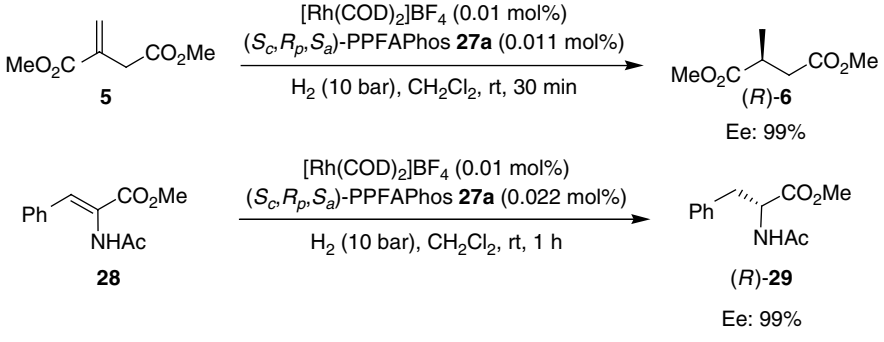
The optimized ligand, (S_c,R_p,S_a)-PPFAPhos **27a**, were demonstrated to be highly efficient in the Rh-catalyzed asymmetric hydrogenation of various functionalized olefins including enamides, dimethyl itaconate, and α-dehydroamino acid esters, normally giving over 99% ee (Scheme 4). The hydrogenation 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*)

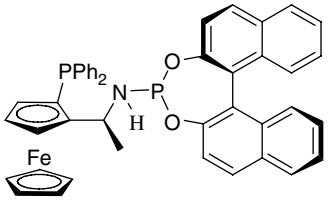


Scheme 4 Rh-catalyzed hydrogenation of olefins **5** and **28** with PPFAPhos **27a**

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].

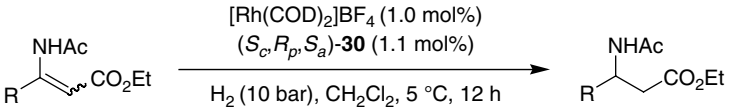
PEAPhos **36** was then prepared in good yields through a three-step transformation from commercially available and inexpensive (*S*)-1-phenylethylamine **31** as



(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**

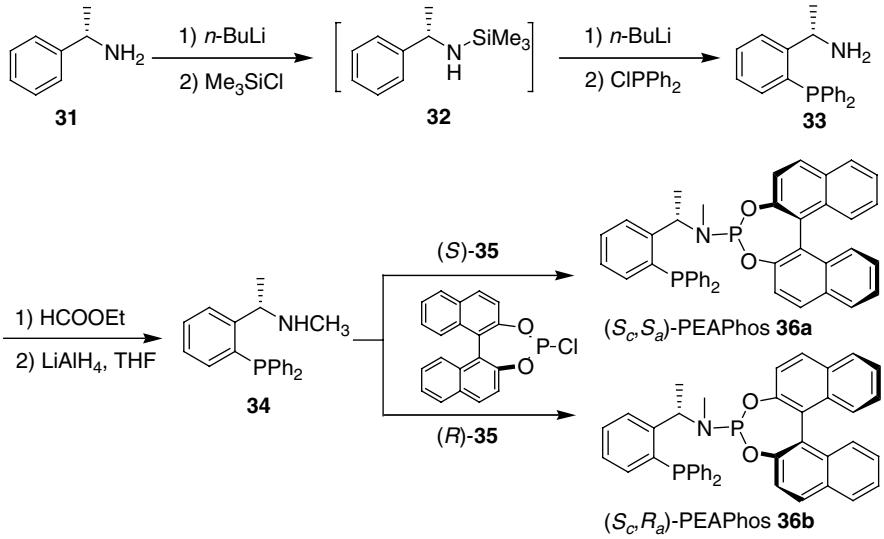


12 **13**

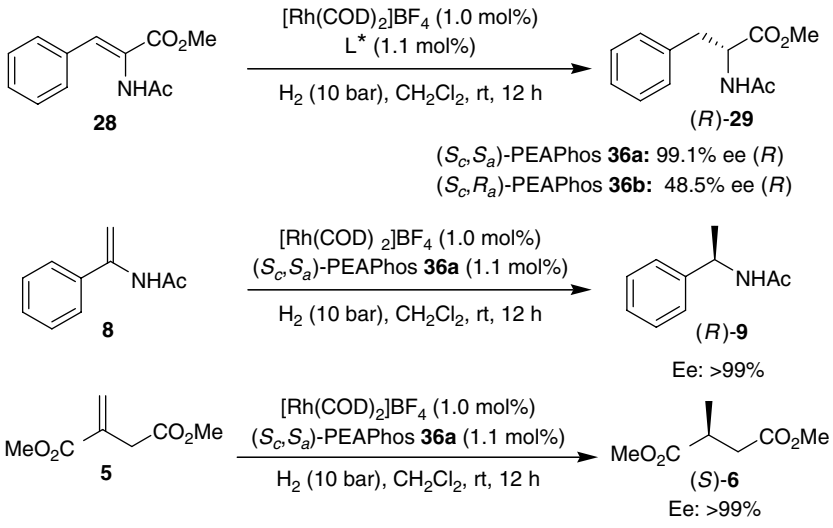
Entry	Substrate	*S*/*C*	Yield (%)	Ee (%) (config)
1	(*Z*)-**12b**: R = Ph	100	98	>99 (*R*)
2	(*Z*)-**12b**: R = Ph	5,000	96	97 (*R*)
3	(*Z*)-**12c**: R = 4-MeC_6H_4	100	98	98 (*R*)
4	(*Z*)-**12d**: R = 4-MeOC_6H_4	100	97	99 (*R*)
5	(*Z*)-**12e**: R = 4-ClC_6H_4	100	99	>99 (*R*)
6	(*Z*)-**12f**: R = Me	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



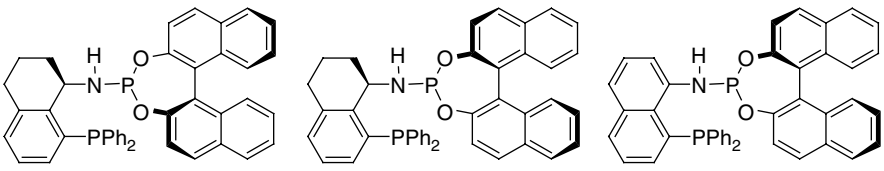
Scheme 6 Rh-catalyzed hydrogenation of olefins with ligands **36**

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).

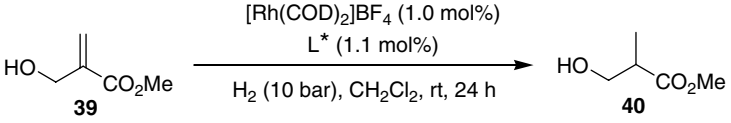
As expected, THNAPhos **37** and HY-Phos **38** provided improved enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of 2-hydroxymethylacrylate, giving the corresponding Roche ester in up to 96.7% ee (Scheme 7) [30].

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).



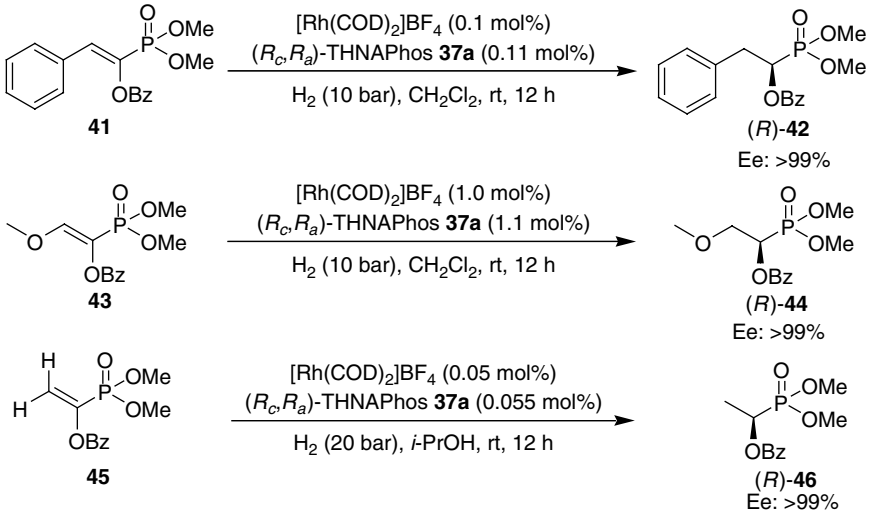
(R_c,R_a)-THNAPhos **37a** (R_c,S_a)-THNAPhos **37b** (S_a)-HY-Phos **38**

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



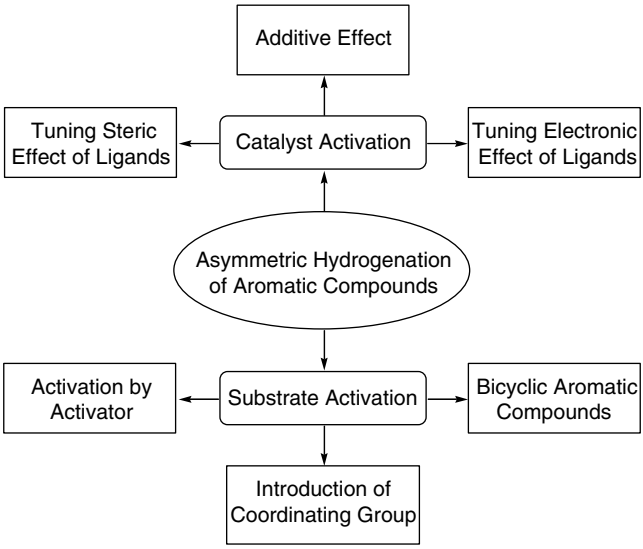
Scheme 8 Rh-catalyzed hydrogenation of α-benzoxyl phosphonates with THNAPhos **37a**

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

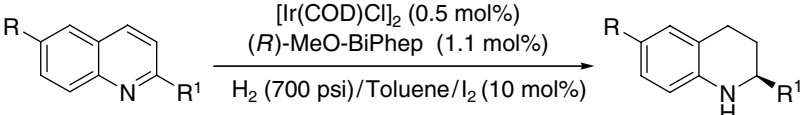
2.1.1 Transitional Metal Catalyzed Asymmetric Hydrogenation of Quinolines

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

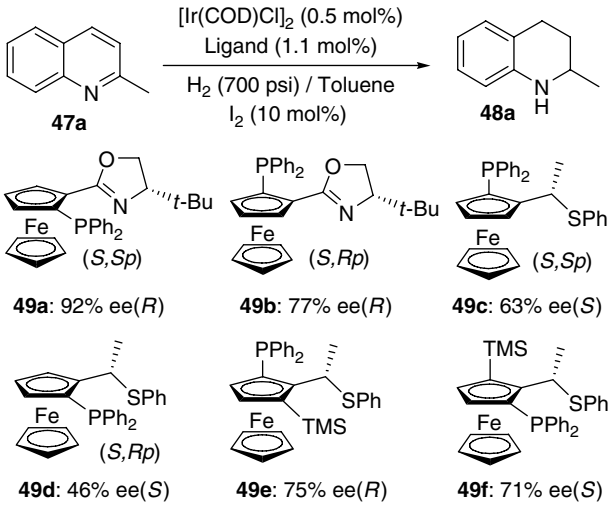
Table 7 Ir-catalyzed asymmetric hydrogenation of quinolines activated by I_2



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*)

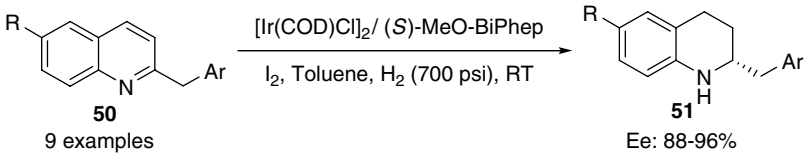
[a] C=C bond was also hydrogenated



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).

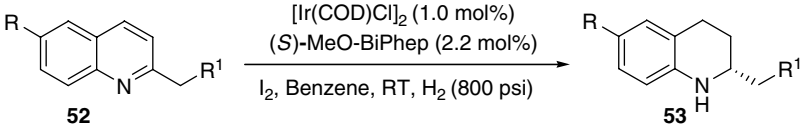


Scheme 11 Ir-catalyzed asymmetric hydrogenation of 2-benzylquinolines **50**

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

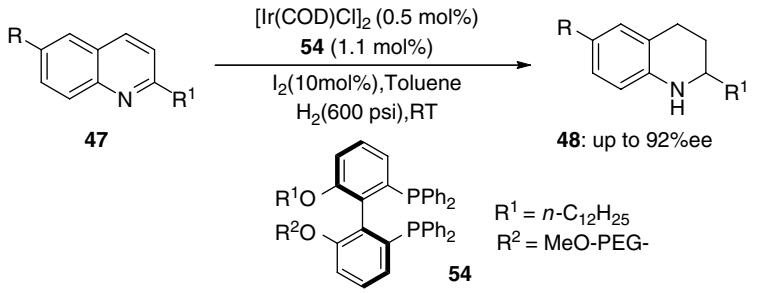


Entry	R/R[1]	Yield (%)	Ee (%)
1	H/COPh	91 (**53a**)	96 (*R*)
2	H/COMe	93 (**53b**)	90 (*R*)
3	H/CO(*n*-Pr)	91 (**53c**)	84 (*R*)
4	H/CO(*p*-MeOPh)	84 (**53d**)	83 (*R*)
5	H/CO(*o*-MeOPh)	78 (**53e**)	95 (*R*)
6	H/CO(*p*-MePh)	89 (**53f**)	95 (*R*)
7	H/CO(*o*-MePh)	97 (**53g**)	96 (*R*)
8	H/CO(*p*-*i*-PrPh)	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.

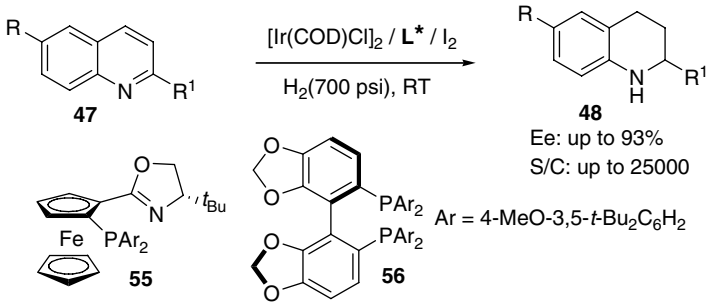
Since there is no omnipotent ligand for every substrate, the development of efficient and tunable new ligands is highly desirable. In 2008, we devised an efficient and divergent method for the synthesis of a series of tunable chiral diphosphine ligands based on (*S*)-MeO-BiPhep by introduction of different 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

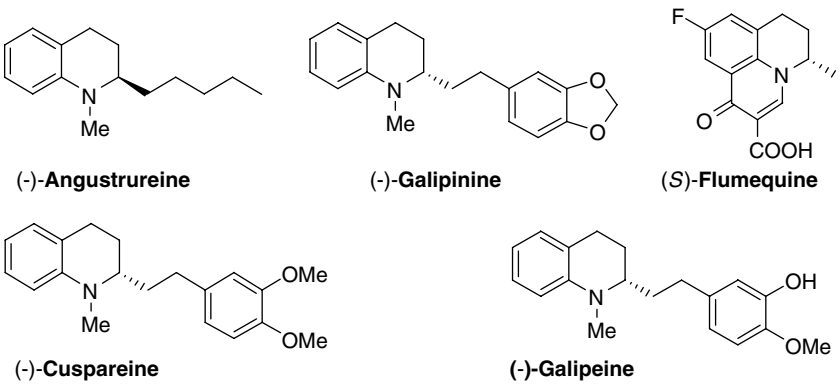
be recycled for five runs; a slightly lower enantioselectivity (84% ee) and 95% conversion were obtained in the fifth run.

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



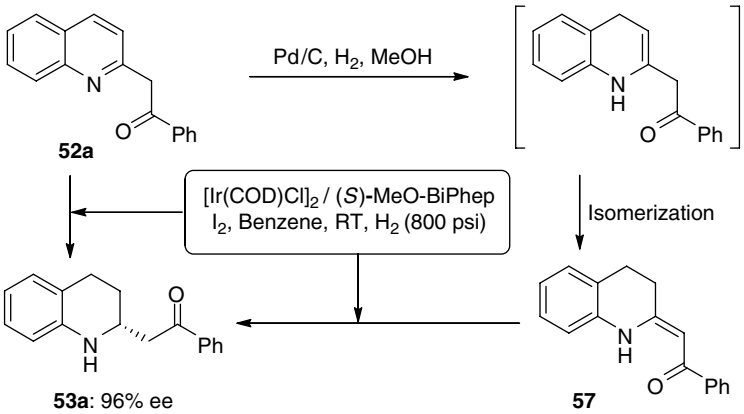
Scheme 14 Synthesis of tetrahydroquinoline alkaloids and drug flumequine

(−)-Galipeine, which contains a free phenol hydroxyl, was completed using asymmetric hydrogenation of quinoline as key step [52].

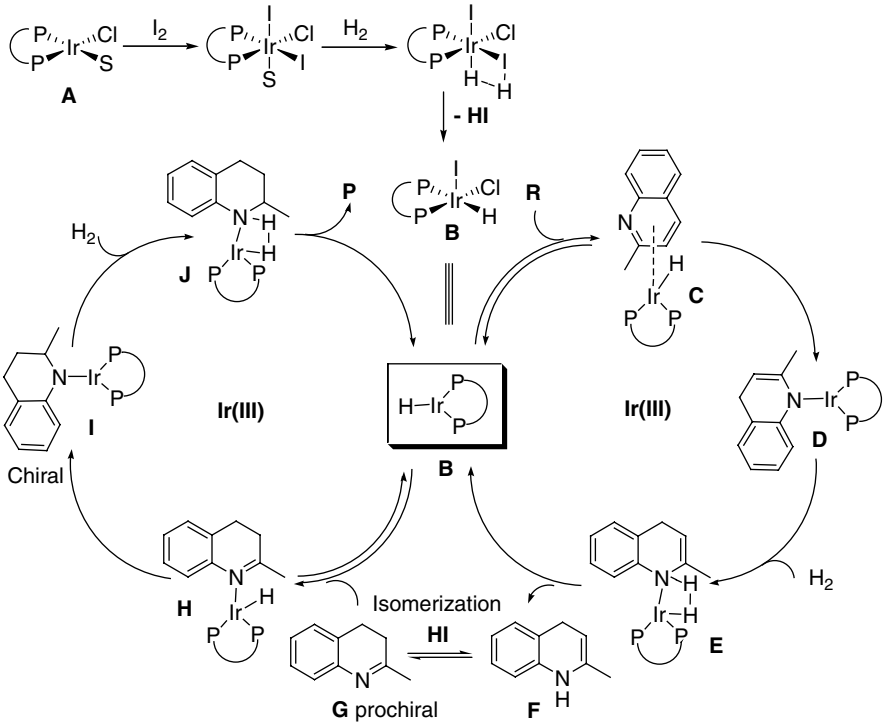
Mechanistic studies confirmed that iodine activated the catalyst in the hydrogenation of quinolines, which is in accordance with the observation of Osborn and Dorta [53, 54]. We also revealed that the hydrogenation process involves 1,4-hydride addition to quinoline, isomerization and 1,2-hydride addition, 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

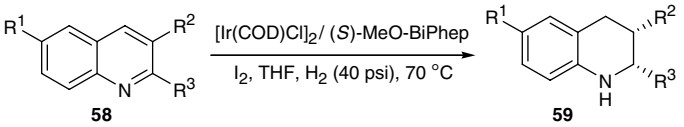
reported by Rueping [57]. Imine intermediate **G** could coordinate with Ir(III)-H species **B** to form the intermediate **H**, followed by the insertion and sigma-bond metathesis to release the product 1,2,3,4-tetrahydroquinolines **P** and regenerate **B** to complete the catalytic cycle [39].

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**

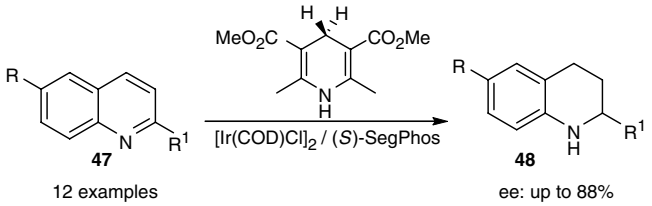


58 **59**

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

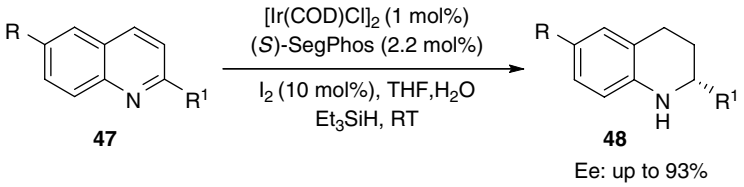
[a] The double bond in the branched chain was also hydrogenated

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].

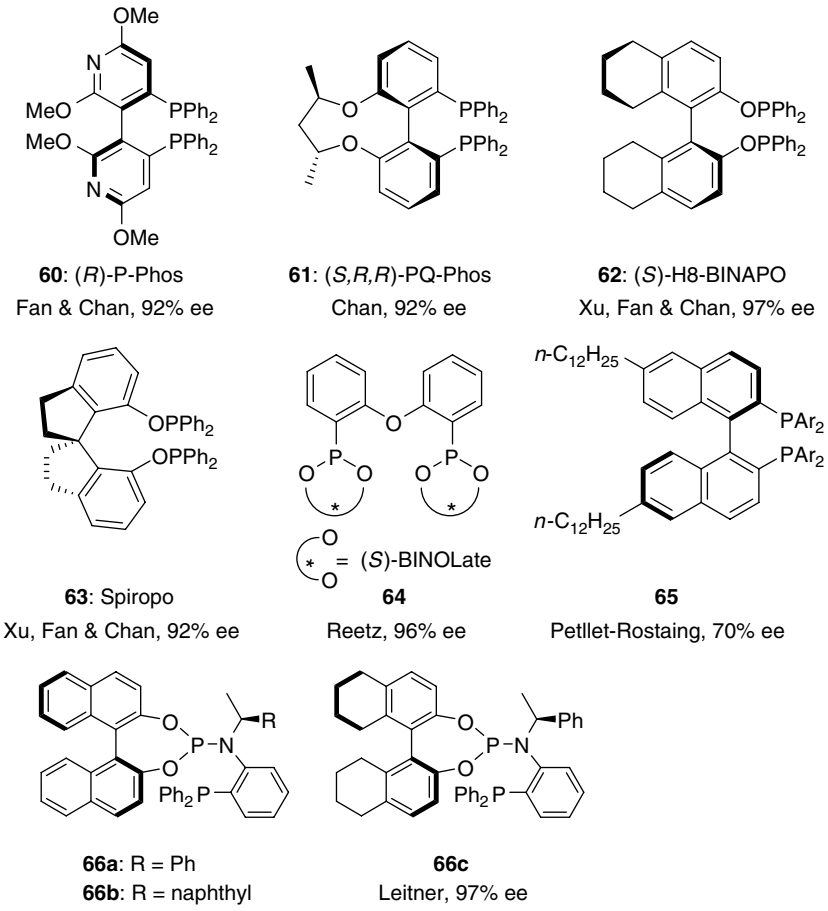


Fig. 9 Representative chiral diphosphine ligands used by other research groups

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

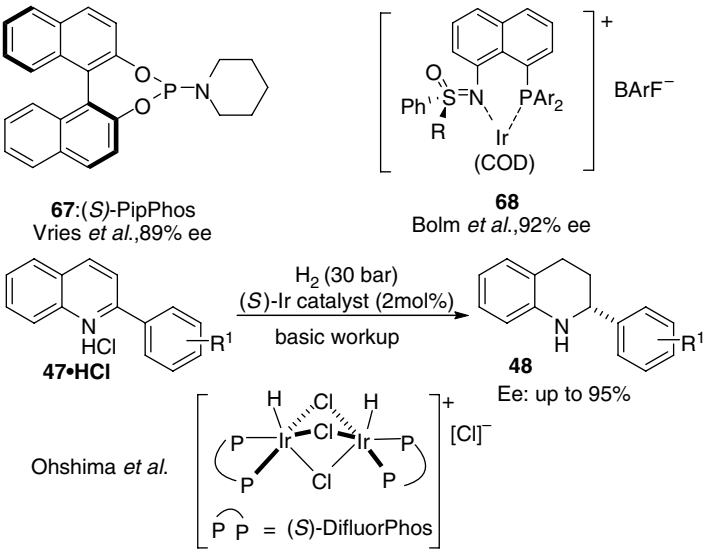


Fig. 10 Other catalytic systems for quinoline hydrogenation without iodine

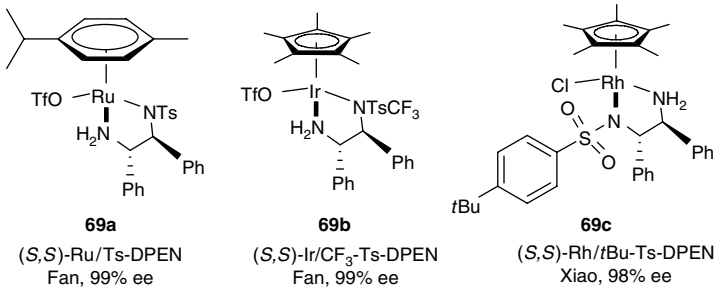
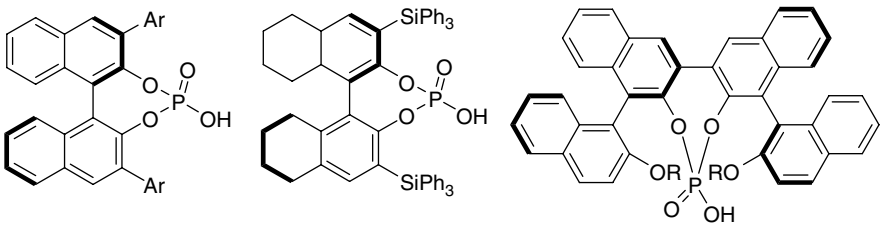


Fig. 11 Ru or Rh-catalyzed asymmetric hydrogenation of quinolines

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

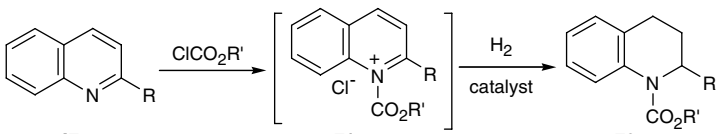
Fig. 12 Organocatalytic transfer hydrogenation with chiral Brønsted acids

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

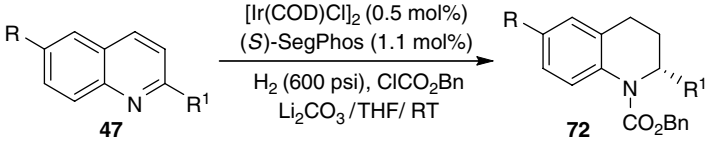
It is frustrating that the above-mentioned strategy for quinoline hydrogenation is not effective for the assorted isoquinoline and pyridine derivatives. Hence, the search for another activator to activate the substrate started. In 2006, we developed a new strategy for the asymmetric hydrogenation of 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.

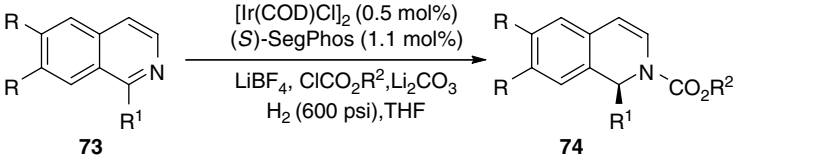
Since one molecule of hydrogen chloride is formed in this reaction, the addition of base to neutralize is necessary. Ir/(*S*)-SegPhos/$ClCO_2Bn$/Li_2CO_3 was found to be the best combination. Under the optimal conditions, a variety of 2-substituted quinolines **47** were hydrogenated with high enantioselectivities (Table 10) [83]. Therefore, this methodology offers an alternative access to tetrahydroquinoline alkaloids.

2.2 Asymmetric Hydrogenation of Isoquinolines

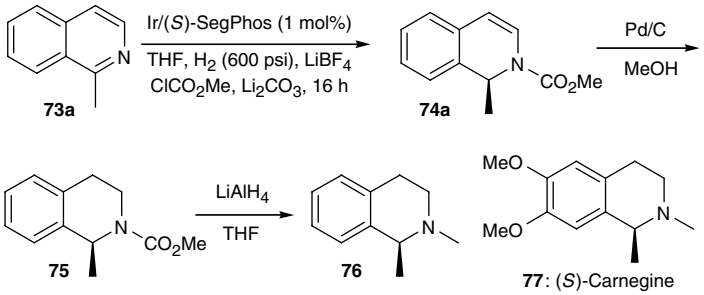
Although the asymmetric hydrogenation of isoquinolines by using iodine as the additive to activate the catalyst failed, activation with chloroformates for this type of substrates has been successful [83]. Enantioselectivity was found to be slightly higher when $LiBF_4$ or LiOTf was added as additive. 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

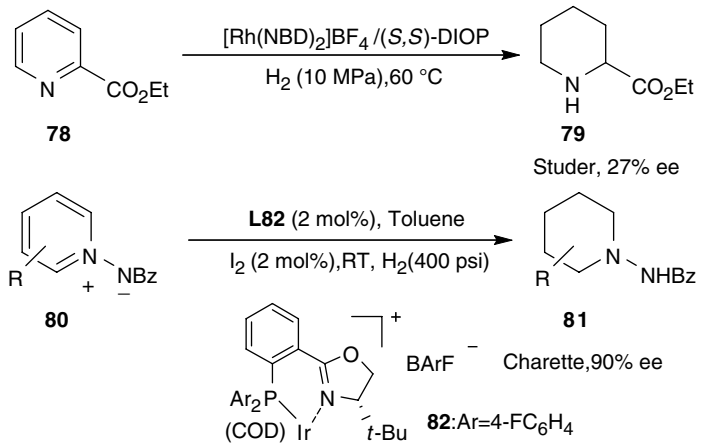
hydrogen gas to afford the corresponding 1,2,3,4-tetrahydro-isoquinoline derivatives, followed by reduction with $LiAlH_4$ to give the N-methylation products in good yield.

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.

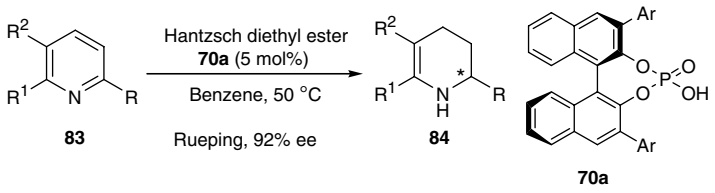
In 1999, Studer group reported the first asymmetric hydrogenation of pyridine derivatives with cinchona-modified heterogeneous Pd/TiO_2 as catalyst [84]. Afterward, the heterogeneous hydrogenation of pyridine derivatives was expanded [85–89]. Meanwhile, the homogenous asymmetric hydrogenation of pyridines 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

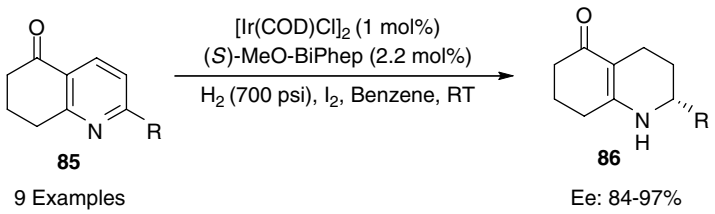
In 2007, Rueping and coworkers [93] developed the first organocatalyzed enantioselective reduction of trisubstituted pyridine derivatives **83** by using chiral Brønsted acids and Hantzsch dihydropyridine as hydrogen source with up to 92% ee (Scheme 22).



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

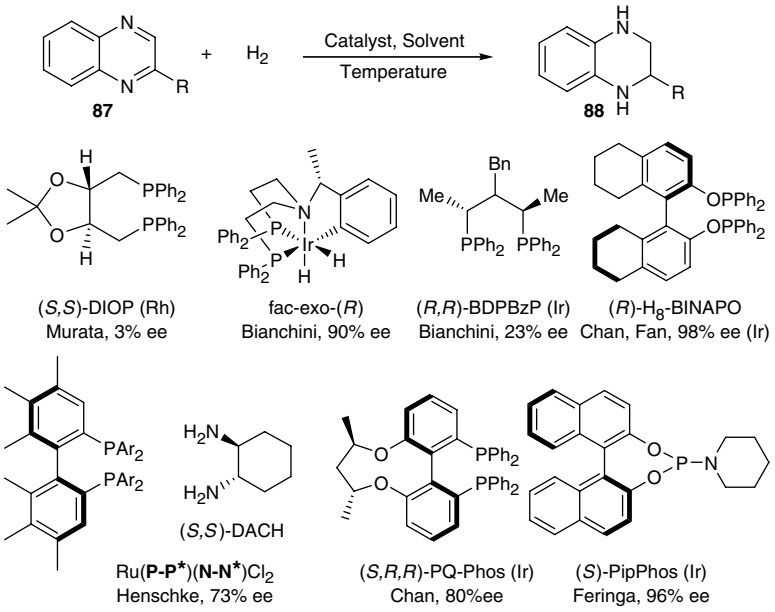
lengths of carbon chains and steric hindrance. For the methyl-substituted product, only 86% ee was obtained. With the growth of carbon chains, the enantioselectivity increased. It is noteworthy that with more steric hindrance substituent as 2-isopropyl, the enantioselectivity decreased to 84%. With the 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

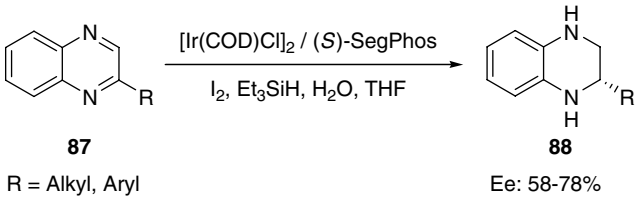
Tetrahydroquinoxalines are compounds of great biological interest, which are difficult to be obtained via stereoselective organic synthesis. Asymmetric hydrogenation tends to be an efficient method, though it is challenging. The pioneer work for homogeneous asymmetric hydrogenation of quinoxaline was 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

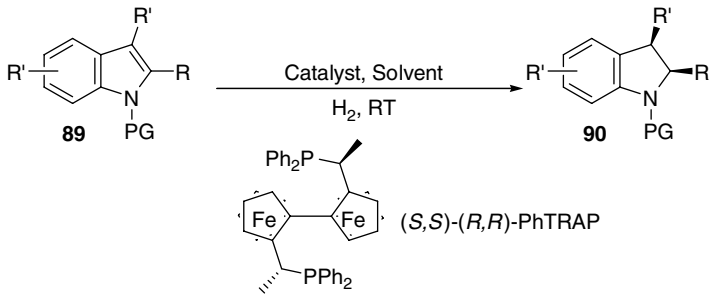


Scheme 25 Ir-catalyzed hydrogenation of quinoxalines using water/silane

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].

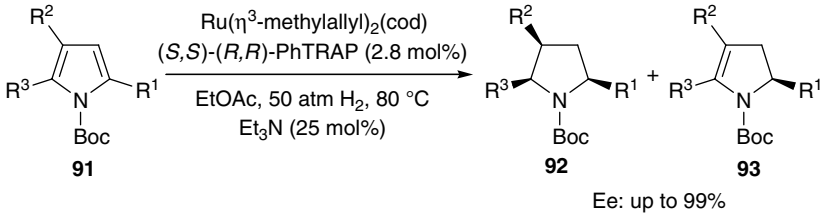


PG	Catalyst	Solvent & Additive	Ee (%)
Ac	Rh / Ph-TRAP	*i*-PrOH & Cs_2CO_3	78-95%
Ts	Rh / Ph-TRAP	*i*-PrOH & Cs_2CO_3	95-98%
Boc	Ru / Ph-TRAP	*i*-PrOH & Cs_2CO_3	72-95%

Scheme 26 Asymmetric hydrogenation of indoles

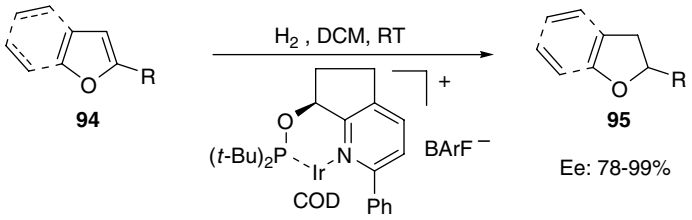
Kuwano group devoted their continuous effort to asymmetric hydrogenation of substituted indoles. In 2006, they reported the asymmetric reduction of N-Boc indoles with [RuCl(*p*-cymene){(*S,S*)-(*R,R*)-Ph-TRAP}]Cl as catalyst with great success (Scheme 26) [104]. Both for the 2-substituted and 3-substituted 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

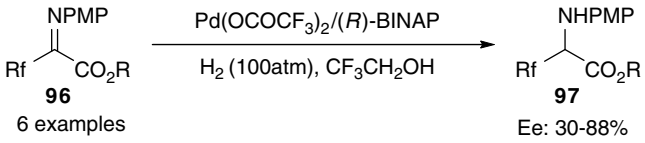
3 Palladium-Catalyzed Asymmetric Hydrogenation

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.

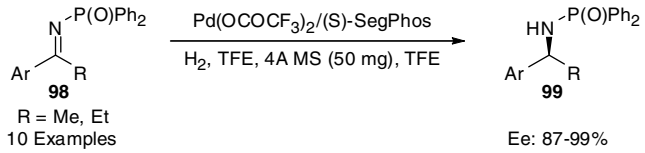
3.1 Pd-Catalyzed Asymmetric Hydrogenation of Imines

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

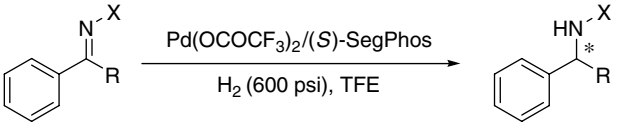


Scheme 30 Pd-catalyzed hydrogenation of N-diphenylphosphinyl ketimines

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.

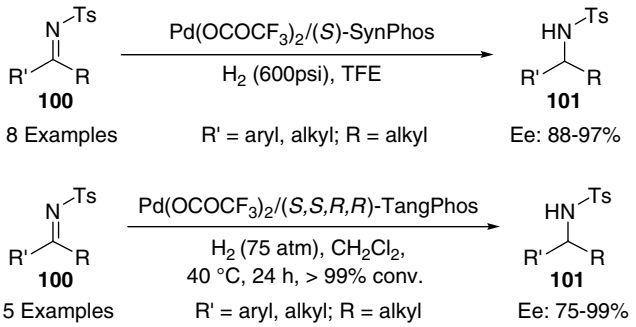
Table 12 Pd-catalyzed asymmetric hydrogenation of N-substituted imines



Entry	R/X	Temp (°C)	Conv. (%)	Ee (%)
1	Me/4-MeOC$_6$H$_4$	rt	26	94
2[a]	Me/4-MeOC$_6$H$_4$	rt	25	95
3	Me/4-MeOC$_6$H$_4$	60	9	77
4	Me/4-FC$_6$H$_4$	rt	15	N/D
5	Me/2-MeOC$_6$H$_4$	rt	24	N/D
6	Me/AcO	rt	<5	N/A
7	Me/BzNH	rt	44	58
8[b]	CO$_2$Et/PMP	rt	>95	33
9	Me/P(O)Ph$_2$	rt	85	95
10	Me/Ts	rt	>95	97

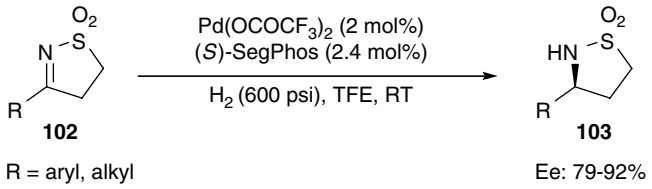
[a]4 Å MS was used
[b](*R*)-BINAP was used

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

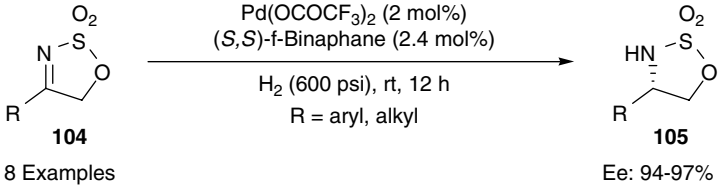
To further expand substrate scope of Pd-catalyzed asymmetric hydrogenation of imines, we synthesized a class of new activated cyclic imines **102**, the hydrogenation products are cyclic sulfonamides **103**, the sultams derivatives, which are important organic synthetic intermediates and structural 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

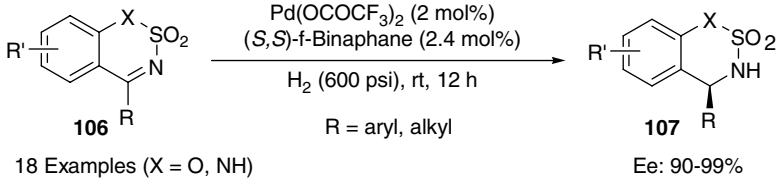
Next, we explored the practical synthesis of enantiopure cyclic sulfamidates via asymmetric hydrogenation of the corresponding activated cyclic imines **104** using $Pd(OCOCF_3)_2$/(*S,S*)-*f*-Binaphane as catalyst [125]. It is noteworthy that the (*S,S*)-*f*-Binaphane ligand is very crucial for the 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.



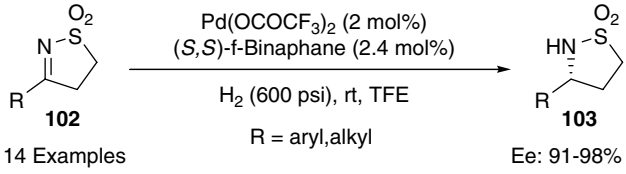
Scheme 33 Pd-catalyzed asymmetric hydrogenation of activated imine **104**

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.



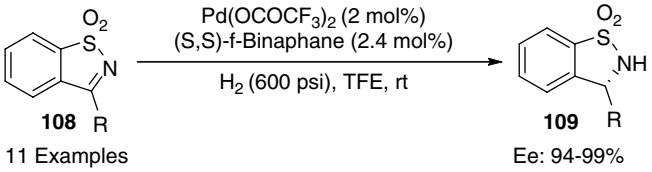
Scheme 34 Pd-catalyzed asymmetric hydrogenation of activated imine

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).



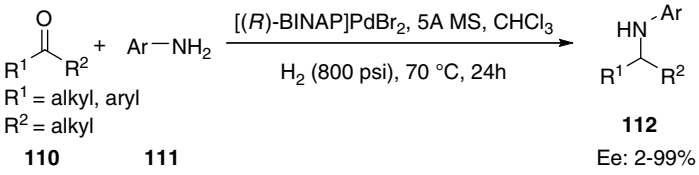
Scheme 35 Pd-catalyzed asymmetric hydrogenation of cyclic N-sulfonylimines

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**

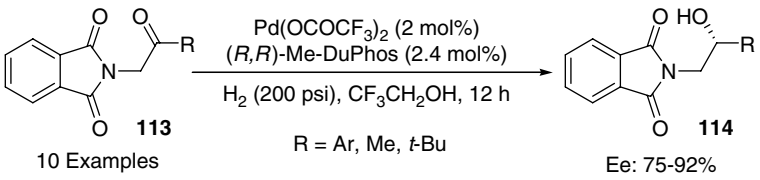
In 2009, Rubio-Perez and coworkers developed an efficient one-pot reductive amination of various carbonyl compounds and anilines using air stable [(*R*)-BINAP]$PdBr_2$ complex as catalyst (Scheme 37) [127]. They found that $CHCl_3$ was the best solvent, giving the highest enantioselectivity. For the 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

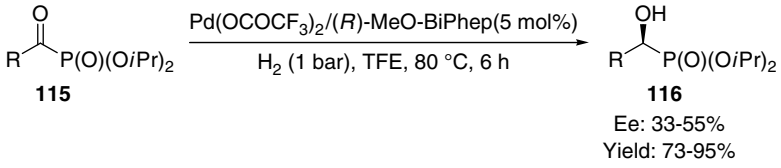
Pd complexes with chiral bisphosphines ligands are excellent catalysts for the asymmetric hydrogenation of activated imines in the presence of trifluoroethanol. And this catalytic system is also extended to asymmetric hydrogenation of ketone derivatives. In 2005, we developed Pd/bisphosphine catalyzed 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.

References

1. Blaser HU, Pugin B, Spindler F (2000) In: Applied Homogeneous Catalysis with Organometallic Compounds Cornils B, Herrmann WA (eds) 2nd edn. Chapter 3.3.1, Wiley-VCH, Weinheim
2. In: Catalytic Hydrogenation in Organic Synthesis. (1979) Rylander PN (ed) Academic, New York, p 175
3. Heller D, de Vries AHM, de Vries JG (2007) In: Handbook of Homogeneous Hydrogenation. de Vries JG, Elsevier CJ (eds) Wiley-VCH, Weinheim
4. Blaser HU, Malan C, Pugin B et al (2003) Adv Synth Catal 345:103–151
5. Tang W, Zhang X (2003) Chem Rev 103:3029–3069
6. Gillon A, Heslop K, Hyett DJ et al (2000) Chem Commun:961–962
7. Reetz MT, Mehler G (2000) Angew Chem Int Ed 39:3889–3890
8. van den Berg M, Minnaard AJ, Schudde EP et al (2000) J Am Chem Soc 122:11539–11540
9. Reetz MT, Goossen LJ, Meiswinkel A et al (2003) Org Lett 5:3099–3101
10. Huang H, Zheng Z, Luo H et al (2003) Org Lett 5:4137–4139
11. Huang H, Liu X, Chen S et al (2004) Tetrahedron: Asymmetry 15:2011–2019
12. Huang H, Zheng Z, Luo H et al (2004) J Org Chem 69:2355–2361
13. Huang H, Liu X, Deng J et al (2006) Org Lett 8:3359–3362
14. Huang H, Liu X, Chen H et al (2006) Tetrahedron: Asymmetry 16:693–697
15. Hu XP, Huang JD, Zeng QH et al (2006) Chem Commun:293–295
16. Jia X, Li X, Xu L et al (2003) J Org Chem 68:4539–4541
17. Bernsmann H, van den Berg M, Hoen R et al (2005) J Org Chem 70:943–951
18. Pêna D, Minnaard AJ, de Vries JG et al (2002) J Am Chem Soc 124:14552–14553
19. Doherty S, Robins EG, Pal I et al (2003) Tetrahedron: Asymmetry 14:1517–1527
20. Zeng QH, Hu XP, Liang XM et al (2005) Chin Chem Lett 16:1321–1323
21. Zeng QH, Hu XP, Duan ZC et al (2006) J Org Chem 71:393–396
22. Duan ZC, Hu XP, Wang DY et al (2008) Adv Synth Catal 350:1979–1983
23. Duan ZC, Hu XP, Zhang C et al (2009) J Org Chem 74:9191–9195
24. Hu XP, Zheng Z (2004) Org Lett 6:3585–3588
25. Hu XP, Zheng Z (2005) Org Lett 7:419–422
26. Huang JD, Hu XP, Duan ZC et al (2006) Org Lett 8:4367–4370
27. Wang DY, Hu XP, Huang JD et al (2007) Angew Chem Int Ed 46:7810–7813
28. Qiu M, Hu XP, Wang DY et al (2008) Adv Synth Catal 350:1413–1418
29. Yu SB, Huang JD, Wang DY et al (2008) Tetrahedron: Asymmetry 19:1862–1866
30. Qiu M, Wang DY, Hu XP et al (2009) Tetrahedron: Asymmetry 20:210–213
31. Glorius F (2005) Org Biomol Chem 3:4171–4175
32. Lu SM, Han XW, Zhou YG (2005) Chin J Org Chem 25:634–640
33. Dyson PJ (2003) Dalton Trans:2964–2974
34. Zhou YG (2007) Acc Chem Res 40:1357–1366
35. Kuwano R (2008) Heterocycles 76:909–922
36. Wang WB, Lu SM, Yang PY, Han XW, Zhou YG (2003) J Am Chem Soc 125:10536–10537
37. Lu SM, Han XW, Zhou YG (2004) Adv Synth Catal 346:909–912
38. Zhao YJ, Wang YQ, Zhou YG (2005) Chin J Catal 26:737–739
39. Wang DW, Wang XB, Wang DS, Lu SM, Zhou YG, Li YX (2009) J Org Chem 74:2780–2787
40. Crabtree R (1979) Acc Chem Res 12:331–337
41. Wang HH, Casalnuovo AL, Johnson BJ, Mueting AM, Pignolet LH (1988) Inorg Chem 27:325–331
42. Blaser HU, Pugin B, Spindler F, Togni A (2002) C R Chimie 5:379–385
43. Smidt SP, Pfaltz A (2003) Oganometallics 22:1000–1009
44. Martínez-Viviente E, Pregosin PS (2003) Inorg Chem 42:2209–2214
45. Dervisi A, Carcedo C, Ooi LL (2006) Adv Synth Catal 348:175–183

46. Wang ZJ, Deng GJ, Li Y, He YM, Tang WJ, Fan QH (2007) Org Lett 9:1243–1246
47. Wang XB, Zhou YG (2008) J Org Chem 73:5640–5642
48. Wang DS, Zhou J, Wang DW, Guo YL, Zhou YG (2010) Tetrahedron Lett 51:525–528
49. Keay JG (1991) Comprehensive organic synthesis, vol 8. Pergamon, Oxford, p 579
50. Katrizky AR, Rachwal S, Bachwal B (1996) Tetrahedron 52:15031–15070
51. Barton DH, Nakanishi K, Meth-Cohn O (1999) In: Comprehensive natural products chemistry, Elsevier, Oxford, vol 1–9
52. Yang PY, Zhou YG (2004) Tetrahedron: Asymmetry 15:1145–1149
53. Chan YNC, Osborn JA (1990) J Am Chem Soc 112:9400–9401
54. Dorta R, Broggini D, Stoop R, Ruegger H, Spindler F, Togni A (2004) Chem Eur J 10:267–278
55. Xiao DM, Zhang XM (2001) Angew Chem Int Ed 40:3425–3428
56. Chi YX, Zhou YG, Zhang XM (2003) J Org Chem 68:4120–4122
57. Rueping M, Theissmann T, Raja S, Bats JWP (2008) Adv Synth Catal 350:1001–1006
58. Guo QS, Du DM, Xu J (2008) Angew Chem Int Ed 47:759–762
59. Wang DW, Zeng W, Zhou YG (2007) Tetrahedron: Asymmetry 18:1103–1107
60. Tokunaga M, Larrow JF, Kakiuchi F, Jacobsen EN (1997) Science 277:936–938
61. Ready JM, Jacobsen EN (2001) J Am Chem Soc 123:2687–2688
62. ten Brink GJ, Arends IWCE, Sheldon RA (2000) Science 287:1636–1639
63. Narayan S, Muldoon J, Finn MG, Fokin VV, Kolb HC, Sharpless KB (2005) Angew Chem Int Ed 44:3275–3279
64. Hayashi Y, Sumiya T, Takahashi J, Gotoh H, Urushima T, Shoji M (2006) Angew Chem Int Ed 45:958–961
65. Wang DW, Wang DS, Chen QA, Zhou YG (2010) Chem Eur J 16:1133–1136
66. Xu LJ, Lam KH, Ji JX, Wu J, Fan QH, Lo WH, Chan ASC (2005) Chem Commun:1390–1392
67. Qiu L, Kwong FY, Wu J, Lam WH, Chan S, Yu WY, Li YM, Guo R, Zhou Z, Chan ASC (2006) J Am Chem Soc 128:5955–5965
68. Lam KH, Xu LJ, Feng LC, Fan QH, Lam FL, Lo WH, Chan ASC (2005) Adv Synth Catal 347:1755–1758
69. Tang WJ, Zhu SF, Xu LJ, Zhou QL, Fan QH, Zhou HF, Lam K, Chan ASC (2007) Chem Commun:613–615
70. Reetz MT, Li XG (2006) Chem Commun:2159–2160
71. Jahjah M, Alame M, Pellet-Rostaing S, Lemaire M (2007) Tetrahedron: Asymmetry 18:2305–2312
72. Eggenstein M, Thomas A, Theuerkauf J, Franciò G, Leitner W (2009) Adv Synth Catal 351:725–732
73. Mršić N, Lefort L, Boogers JAF, Minnaard AJ, Feringa BL, de Vries JG (2008) Adv Synth Catal 350:1081–1089
74. Lu SM, Bolm C (2008) Adv Synth Catal 350:1101–1105
75. Yamagata T, Tadaoka H, Nagata M, Hirao T, Kataoka Y, Ratovelomanana-Vidal V, Genet JP, Mashima K (2006) Organometallics 25:2505–2513
76. Deport C, Buchotte M, Abecassis K, Tadaoka H, Ayad T, Ohshima T, Genet JP, Mashima K, Ratovelomanana-Vidal V (2007) Synlett:2743–2747
77. Tadaoka H, Cartigny D, Nagano T, Gosavi T, Ayad T, Genet JP, Ohshima T, Ratovelomanana-Vidal V, Mashima K (2009) Chem Eur J 15:9990–9994
78. Zhou HF, Li ZW, Wang ZJ, Wang TL, Xu LJ, He YM, Fan QH, Pan J, Gu LQ, Chan ASC (2008) Angew Chem Int Ed 47:8464–8467
79. Wang ZJ, Zhou HF, Wang TL, He YM, Fan QH (2009) Green Chem 11:767–769
80. Wang C, Li CQ, Wu XF, Pettman A, Xiao JL (2009) Angew Chem Int Ed 48:6524–6528
81. Li ZW, Wang TL, He YM, Wang ZJ, Fan QH, Pan J, Xu LJ (2008) Org Lett 10:5265–5268
82. Rueping M, Antonchick AP, Theissmann T (2006) Angew Chem Int Ed 45:3683–3686
83. Lu SM, Wang YQ, Han XW, Zhou YG (2006) Angew Chem Int Ed 45:2260–2263
84. Blaser HU, Honig H, Studer M, Wedemeyer-Exl C (1999) J Mol Catal A: Chem 139:253–257

85. Raynor SA, Thomas JM, Raja R, Johnson BFG, Bell RG, Mantle MD (2000) Chem Commun:1925–1926
86. Hegedus L, Hada V, Tungler A, Mathe T, Szepesy L (2000) Appl Catal A 201:107–114
87. Douja N, Besson M, Gallezot P, Pinel C (2002) J Mol Catal A: Chem 186:145–151
88. Ouja N, Malacea R, Banciu M, Besson M, Pinel C (2003) Tetrahedron Lett 44:6991–6993
89. Glorius F, Spielkamp N, Holle S, Goddard R, Lehman CW (2004) Angew Chem Int Ed 43:2850–2852
90. Studer M, Wedemeyer-Exl C, Spindler F, Blaser HU (2000) Monatsh Chem 131:1335–1343
91. Legault CY, Charette AB (2005) J Am Chem Soc 127:8966–8967
92. Lei A, Chen M, He M, Zhang XM (2006) Eur J Org Chem:4343–4347
93. Rueping M, Antonchick AP (2007) Angew Chem Int Ed 46:4562–4566
94. Wang XB, Zeng W, Zhou YG (2008) Tetrahedron Lett 49:4922–4924
95. Murata S, Sugimoto T, Matsuura S (1987) Heterocycles 26:763–766
96. Bianchini C, Barbaro P, Scapacci G, Farnetti E, Graziani M (1998) Organometallics 17:3308–3310
97. Bianchini C, Barabro P, Scapacci G (2001) J Organomet Chem 621:26–33
98. Cobley CJ, Henschke JP (2003) Adv Synth Catal 345:195–201
99. Henschke JP, Burk MJ, Malan CG, Herzberg D, Peterson JA, Wildsmith AJ, Cobley CJ, Casy G (2003) Adv Synth Catal 345:300–307
100. Tang WJ, Xu LJ, Fan QH, Wang J, Fan BM, Zhou ZY, Lam KH, Chan ASC (2009) Angew Chem Int Ed 48:9135–9138
101. Mrsic N, Jerphagnon T, Minnaard AJ, Feringa BL, de Vries JG (2009) Adv Synth Catal 351:2549–2552
102. Kuwano R, Sato K, Kurokawa T, Karube D, Ito Y (2000) J Am Chem Soc 122:7614–7615
103. Kuwano R, Kaneda K, Ito T, Sato K, Kurokawa T, Ito Y (2004) Tetrahedron: Asymmetry 17:521–535
104. Kuwano R, Kashiwabara M (2006) Org Lett 8:2653–2655
105. Kuwano R, Kashiwabara M, Ohsumi M, Kusano H (2008) J Am Chem Soc 130:808–809
106. Ohta T, Miyake T, Seido N, Kumobayashi H, Takaya H (1995) J Org Chem 60:357–363
107. Maris M, Huck WR, Mallat T, Baiker A (2003) J Catal 219:52–58
108. Feiertag P, Albert M, Nettekoven U, Spindler F (2006) Org Lett 8:4133–4135
109. Kaiser S, Smidt SR, Pfaltz A (2006) Angew Chem Int Ed 45:5194–5197
110. Blaser HU, Malan C, Pugin B, Spinder F (2003) Adv Synth Catal 345:103–151
111. Enders D, Reinhold U (1997) Tetrahedron: Asymmetry 8:1895–1946
112. Bloch R (1998) Chem Rev 98:1407–1438
113. Alvaro G, Savoia D (2002) Synlett:651–673
114. Mao J, Baker DC (1999) Org Lett 1:841–843
115. Uemastu N, Fujii A, Hashiguchi S, Ikariya T, Noyori R (1996) J Am Chem Soc 118:4916–4917
116. Verdaguer X, Lange UEW, Buchwald SL (1998) Angew Chem Int Ed 37:1103–1107
117. Ringwald M, Sturemer R, Brintzinger HH (1999) J Am Chem Soc 121:1524–1527
118. Moessner C, Bolm C (2005) Angew Chem Int Ed 44:7564–7567
119. Abe H, Amii H, Uneyama K (2001) Org Lett 3:313–315
120. Suzuki A, Mae M, Amii H, Uneyama K (2004) J Org Chem 69:5132–5134
121. Nanayakkara P, Alper H (2003) Chem Commun:2384–2385
122. Wang YQ, Zhou YG (2006) Synlett:1189–1192
123. Wang YQ, Lu SM, Zhou YG (2007) J Org Chem 72:3729–3734
124. Yang Q, Deng JG, Zhang XM (2006) Angew Chem Int Ed 45:3832–3835
125. Wang YQ, Yu CB, Wang DW, Wang XB, Zhou YG (2008) Org Lett 10:2071–2074
126. Yu CB, Wang DW, Zhou YG (2009) J Org Chem 74:5633–5635
127. Rubio-Perez L, Perez-Flores FJ, Sharm P, Velasco L, Cabrera A (2009) Org Lett 11:265–268
128. Wang YQ, Lu SM, Zhou YG (2005) Org Lett 7:3235–3238
129. Goulioukina NS, Bondarenko GN, Bogdanov AV, Gavrilov KN, Beletskaya IP (2009) Eur J Org Chem:510–515