CHEMICAL REVIEWS

REVIEW

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Asymmetric Hydrogenation of Heteroarenes and Arenes

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CONTENTS

1. INTRODUCTION

The range of application of organic compounds is enormous due to that organic compounds are structurally diverse. They either form the basis of or are important constituents of many products including plastics, drugs, petrochemicals, food, explosives, and paints. Therefore, the synthesis of more and more new compounds is one of the greatest tasks in organic chemistry. Asymmetric hydrogenation of prochiral unsaturated compounds has been intensively studied and is considered as a versatile method for the synthesis of new chiral compounds. Ketones, imines, olefins, and aromatic compounds are the common prochiral unsaturated substrates for asymmetric hydrogenation.[1] The asymmetric hydrogenation of aromatic compounds will give the greatest number of potential chiral compounds as compared to the former three types of common unsaturated substrates. Assuming that there are 10 choices for the substituents at every position of the common arene ring (benzene), up to 10^6 of substrates will be obtained for asymmetric hydrogenation

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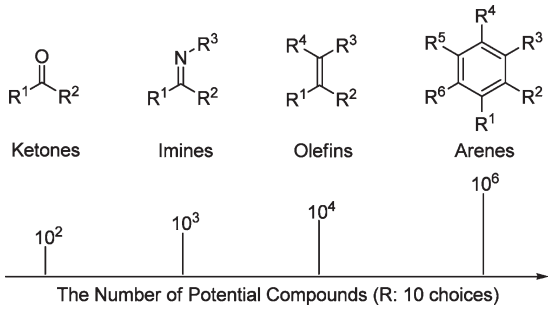
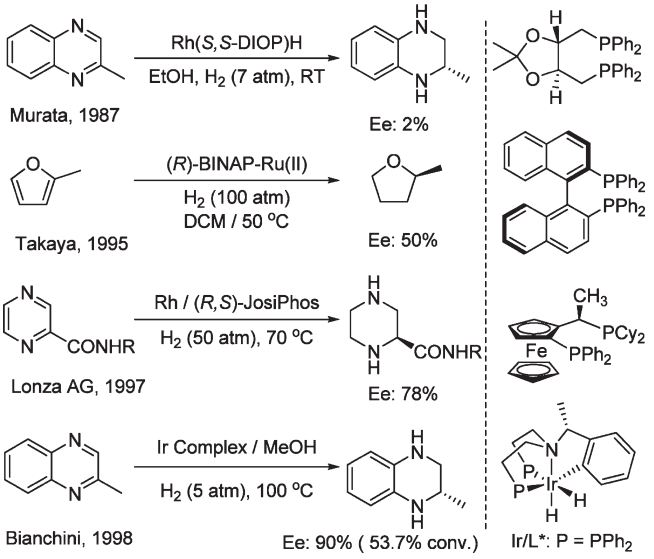


Figure 1. The number of potential substrates for asymmetric hydrogenation.

Scheme 1. Early Examples of Homogeneous Enantioselective Hydrogenation of Aromatic Compounds



(Figure 1). However, the number is relatively low in the hydrogenation of ketones (10^2), imines (10^3), or olefins (10^4). In addition, the number will be dramatically enlarged due to that aromatic rings can fuse with other rings on an edge to give polycyclic compounds such as naphthalenes, quinolines, quinoxalines, indoles, benzofurans, etc. In addition, aromatic compounds are easy to prepare from cheap starting materials, and most of them are commercially available and relatively stable. Thus, the investigation of the asymmetric hydrogenation of aromatic compounds will better promote the development of organic synthetic chemistry via producing more new chiral cyclic compounds.

Catalytic asymmetric hydrogenation of prochiral unsaturated compounds, such as olefins, ketones, and imines, has been extensively studied. In sharp contrast, the asymmetric hydrogenation of arenes/heteroarenes is a much less explored area, although it provides efficient and straightforward access to the corresponding chiral saturated and partially saturated molecules bearing cyclic skeletons, which play important roles as biologically active building blocks and key intermediates in organic synthesis. This may be ascribed to the following reasons: first, the high stability of these compounds and harsh conditions needed to destroy the aromaticity, which adversely affects the enantioselectivity;[2] and, second, some heteroaromatic compounds containing nitrogen

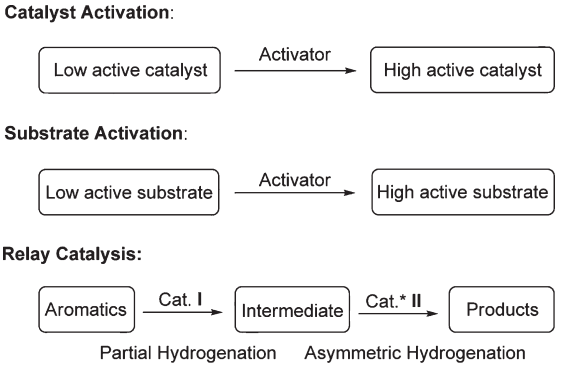


Figure 2. Some strategies for asymmetric hydrogenation of aromatics.

and sulfur atoms may poison and/or deactivate the chiral catalysts. Third, the lack of secondary coordinating group in simple aromatic compounds may be responsible for the difficulty in achieving high activity and/or enantioselectivity. Nevertheless, the low activity of aromatic compounds may be the main reason.

In addition, due to the relatively low aromaticity, bicyclic aromatic compounds are easy to hydrogenate with one aromatic ring reserved in the hydrogenation process, while the hydrogenation of single-ring aromatic compounds is much more difficult. Besides, heteroaromatic compounds containing nitrogen and oxygen atoms are also relatively easy to hydrogenate because of the low aromaticity and potential coordination with the chiral metal catalysts. For nitrogen-containing heteroaromatic compounds, those with aromatic amines as products are more ready to be hydrogenated. So, the present studies on asymmetric hydrogenation of aromatic compounds mainly focused on bicyclic aromatics and single ring heteroaromatics containing nitrogen and/or oxygen atoms.

Despite facing the above difficulties, the asymmetric hydrogenation of aromatic compounds still has been explored. The first example of homogeneous asymmetric hydrogenation of aromatic compounds was reported in 1987 by Murata and co-workers who subjected 2-methylquinoxaline under hydrogen in ethanol using Rh[(*S*,*S*)-DIOP]H as catalyst. A dismal 2% ee was obtained (Scheme 1).[3] Next, a significant improvement (50% ee) was achieved by Takaya and co-workers in 1995, in the hydrogenation of 2-methylfuran using a chiral Ru complex with (*R*)-BINAP ligand as catalyst.[4] A patent on asymmetric hydrogenation of pyrazinecarboxylic acid derivatives using homogeneous $[Rh(COD)Cl]_2$/JosiPhos at 50 atm of hydrogen gas was applied by Lonza AG in 1997, and up to 78% ee was obtained.[5] In 1998, Bianchini developed an orthometalated dihydride iridium complex for hydrogenation of 2-methylquinoxaline to 1,2,3,4-tetrahydro-2-methylquinoxaline with up to 90% ee (Scheme 1).[6] Notably, this is the first example of enantioselective hydrogenation of aromatic compounds with >90% ee, while conversion is not satisfactory. These pioneering works demonstrated the feasibility of highly enantioselective hydrogenation of aromatic compounds and have opened a new avenue to the synthesis of chiral heterocyclic compounds from readily available aromatic compounds.

Thereafter, several novel and efficient strategies, including catalyst activation, substrate activation, and relay catalysis, were developed for successful asymmetric hydrogenation of aromatic compounds (Figure 2). Catalyst activation involves the addition of additives to form more active catalyst species and by the

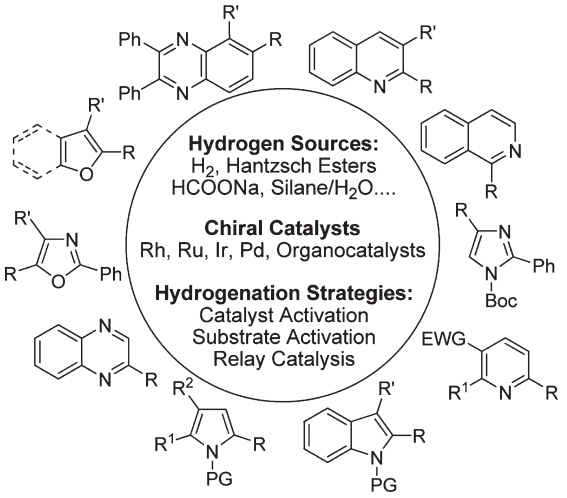


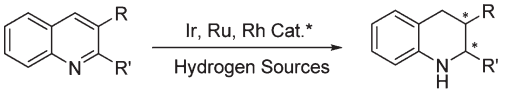
Figure 3. Catalytic enantioselective reduction of heteroarenes and arenes.

fine-tuning of steric and electronic effects of the chiral ligands. Substrate activation is achieved by introduction of activator to interact with the substrate and destroy the aromaticity partially, and a secondary coordination group to assist coordination between substrate and catalyst. Relay catalysis involves two hydrogenation catalysts for asymmetric hydrogenation of aromatic compounds: achiral catalyst **I** hydrogenates the aromatic compounds to afford the partial hydrogenation intermediates, followed by enantioselective hydrogenation of the intermediates with chiral catalyst **II** (Figure 2).

On the basis of the above principles, some important advances in homogeneous asymmetric hydrogenation of aromatic/heteroaromatic compounds were achieved using chiral organometallic catalysts and organocatalysts.[7,8] As outlined in Figure 3, various heteroarenes such as quinolines, isoquinolines, quinoxalines, pyridines, indoles, pyrroles, imidazoles, oxazoles, and furans can be smoothly hydrogenated with good to excellent enantioselectivity. In these transformations, iodine was the most common used additive to activate the catalyst. Chloroformates and Brønsted acids were successively applied to activate the substrates, and in some cases substrates were activated by introducing protecting groups on the heteroatoms, which facilitated the coordination with metal catalyst as well. One special example of asymmetric hydrogenation of carbocyclic ring of aromatic compound was also disclosed. Considering the diversity of aromatic compounds and the great importance of the corresponding hydrogenated products, a general and comprehensive summarization of the asymmetric hydrogenation of heteroarenes and arenes is necessary and helpful.

This Review is intended to provide an overview of the enantioselective hydrogenation and transfer hydrogenation of heteroarenes and arenes with both transition metal complexes and organocatalysts. However, to have a complete overview of the developments for the hydrogenation and transfer hydrogenation of heteroarenes and arenes, it is inevitable for this Review to have some overlap with the contents in previous review sections[7] or chapters of books.[8] Some specific reviews and personal accounts have been published recently, including those by Glorius,[7b] Zhou,[7c,d] and Kuwano.[7e] This Review summarizes the progress achieved in a comparably more broad area with focusing on transition metal-catalyzed homogeneous hydrogenation processes as well as organocatalyzed transfer hydrogenation. Diastereoselective hydrogenation and heterogeneous asymmetric hydrogenation will not be discussed in detail here. This Review covers the literature up to May 2011.

Scheme 2. Transition Metal-Catalyzed Enantioselective Hydrogenation of Quinolines



Hydrogen Sources: H_2; Hantzsch Esters; Et_3SiH/H_2O....

2. CATALYTIC ASYMMETRIC HYDROGENATION OF QUINOLINE DERIVATIVES

1,2,3,4-Tetrahydroquinolines are ubiquitous in naturally occurring alkaloids and artificial molecules and have found broad applications in pharmaceutical and agrochemical synthesis.[9] The asymmetric hydrogenation of readily available quinolines offers a convenient and straightforward access to these compounds in terms of simplicity and atom efficiency and have attracted considerable attention. Since the first example of highly enantioselective hydrogenation of quinolines with iridium catalyst was reported by Zhou and co-workers in 2003,[10] numerous catalysts involve various chiral transition-metal catalysts and organocatalysts have been developed for this transformation.[7d,11]

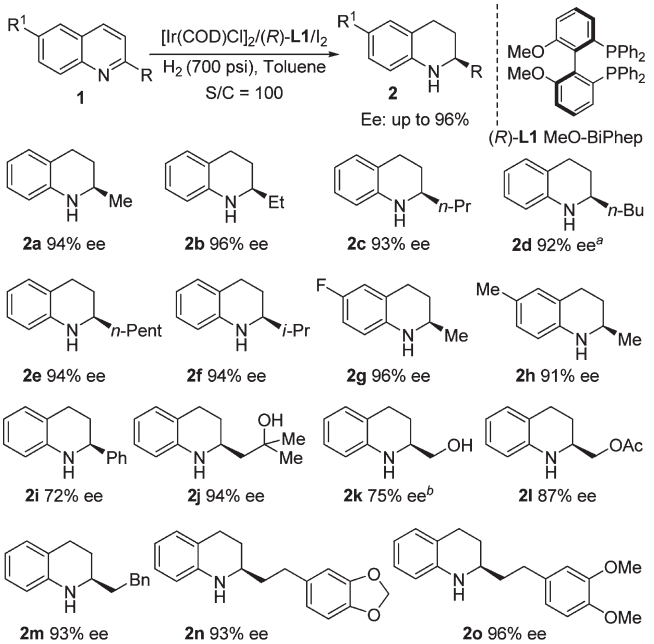
2.1. Transition Metal-Catalyzed Enantioselective Hydrogenation

Transition metal-catalyzed asymmetric hydrogenation has been extensively studied over the past decades and has achieved great success for traditional olefins, ketones, and imines.[12] In sharp contrast, its application in asymmetric hydrogenation of aromatic/heteroaromatic compounds such as quinolines is much less explored. This may be attributed to the low activity of these compounds to traditional transition metal catalysts. Nevertheless, chiral iridium, ruthenium, and rhodium catalysts were successively developed for the asymmetric hydrogenation of quinolines with activation of either catalysts or substrates (Scheme 2).

2.1.1. Ir-Catalyzed Asymmetric Hydrogenation. The first highly enantioselective hydrogenation of quinolines was realized with iridium catalyst generated in situ from $[Ir(COD)Cl]_2$ and axially chiral bisphosphine ligand MeO−BiPhep (**L1**) with the addition of iodine as activator.[10] After this successful example, much attention has being attracted to iridium-catalyzed asymmetric hydrogenation of quinolines. Most of the studies focused on finding of effective ligands to achieve high activity and enantioselectivity. Bidentate phosphorus ligands, especially atropisomeric biaryl diphosphine ligands, diphosphonite ligands, and phosphine-phosphoramidite ligands as well as other phosphorus-containing ligands such as *N,P*-ligands, *S,P*-ligands, and monodentate phosphine ligands, have been proven to be effective for iridium-catalyzed asymmetric hydrogenation of quinolines. Phosphine free ligands such as chiral diamine ligands were also successfully introduced to asymmetric hydrogenation of quinolines with iridium complex. For these catalytic systems, iodine was the most commonly used additive to activate the catalyst, chloroformates as well as Brønsted acids were employed to activate the substrates, and for certain systems additive was unnecessary.

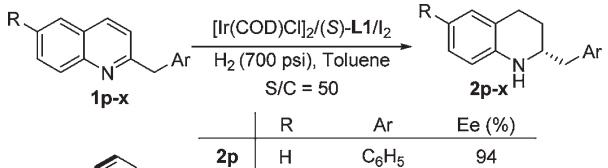
2.1.1.1. Chiral Diphosphorus Ligands. Atropisomeric Biaryl Diphosphine Ligands. At the beginning of Zhou's investigation, 2-methylquinoline **1a** was chosen as model substrate, and

Scheme 3. Ir-Catalyzed Asymmetric Hydrogenation of 2-Substituted Quinolines 1 with L1



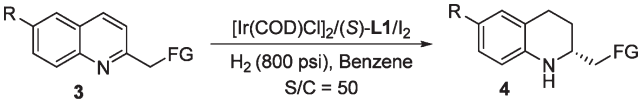
[a] With both 2-butyl and 2-(3'-butenyl)quinolines as starting materials. [b] With *i*-PrOH as solvent.

Scheme 4. Ir-Catalyzed Asymmetric Hydrogenation of 2-Benzylquinolines 1p−x



	R	Ar	Ee (%)
2p	H	C_6H_5	94
2q	H	2-MeC_6H_4	95
2r	H	2-$CF_3C_6H_4$	88
2s	H	4-$CF_3C_6H_4$	93
2t	H	4-FC_6H_4	94
2u	H	3,4-$(MeO)_2C_6H_3$	94
2v	H	1-Naphthyl	95
2w	F	C_6H_5	96
2x	Me	C_6H_5	95

Scheme 5. Ir-Catalyzed Asymmetric Hydrogenation of 2-Functionalized Quinolines 3



	R	FG	Ee (%)		R	FG	Ee (%)
4a	H	MeCO	90	**4j**	H	4-CF_3PhCO	95
4b	H	*n*-PrCO	84	**4k**	H	3,4-$(MeO)_2$PhCO	94
4c	H	$Ph(CH_2)_2CO$	87	**4l**	F	C_6H_5CO	96
4d	H	C_6H_5CO	96	**4m**	Me	C_6H_5CO	94
4e	H	4-MeOPhCO	83	**4n**	H	CO_2Me	82
4f	H	2-MeOPhCO	95	**4o**	H	CO_2Et	92
4g	H	4-MePhCO	95	**4p**	H	$CONEt_2$	80
4h	H	2-MePhCO	96	**4q**	H	$PhSO_2$	90
4i	H	4-*i*-PrPhCO	95	**4r**	H	$(CH_2)_2$OTBS	94

the reaction was carried out in CH_2Cl_2 with catalyst generated in situ from $[Ir(COD)Cl]_2$ and (*R*)-MeO−BiPhep (**L1**).[10] Unfortunately, a trace amount of 2-methyl-1,2,3,4-tetrahydroquinoline **2a** was obtained with low ee value. Subsequently, a number of additives were tested to enhance the catalytic activity of the catalyst, and iodine was proved to be the best choice with full conversion and the highest enantioselectivity. The reaction was also strongly solvent-dependent, and aromatic solvent toluene was found to be the best reaction media with regarding to enantioselectivity. Under the optimal conditions, with $[Ir(COD)Cl]_2$/**L1**/I_2/toluene as the catalytic system (S/C = 100), a series of quinolines were hydrogenated smoothly to give the corresponding products with high yields and enantioselectivities (Scheme 3, 83−94% yield, 72−96% ee). The substituent at 2-position of quinolines could be the alkyl chain ignoring the length and steric hindrance, and can also be free hydroxyl or ester. It was noteworthy that the C═C double bond in the side chain of substrate can be hydrogenated under the standard conditions. Lower enantioselectivities were obtained with 2-phenyl and 2-hydroxymethyl quinolines (**2i** and **2k**, 72% ee and 75% ee).[10] Afterward, this catalytic system was successfully applied to asymmetric hydrogenation of various substituted quinolines.

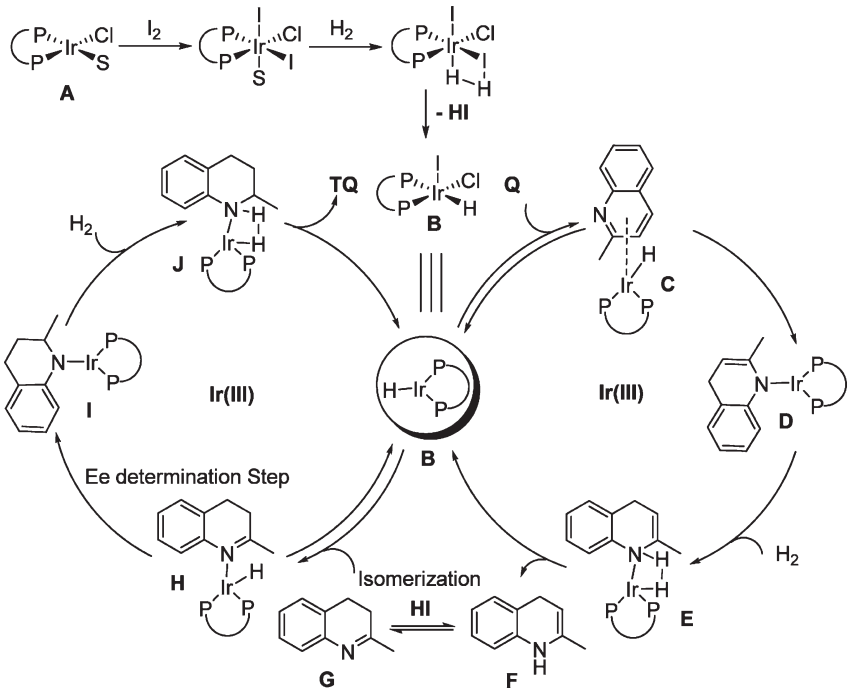
A series of 2-benzylquinolines, which were synthesized by modified literature procedures,[13] were applied to the above catalytic system by Zhou and co-workers. High yields and up to 96% ee were obtained regardless of the steric and electronic property of the aryl group (Scheme 4).[14a]

Subsequently, the tolerance of functional group with the Ir/(*S*)-MeO−BiPhep (**L1**)/I_2 catalytic system was also investigated by Zhou and co-workers. It was found that quinoline substrates with various functional groups such as ketone, ester, amide, and benzenesulfonyl at 2-position could be hydrogenated smoothly with high to excellent enantioselectivities (Scheme 5, 80−96% ee).[14a] It is noted that substrates with hydroxyl protected by TBS could also be successfully hydrogenated, and the product could be converted conveniently. In this case, benzene instead of toluene was employed as the reaction media.

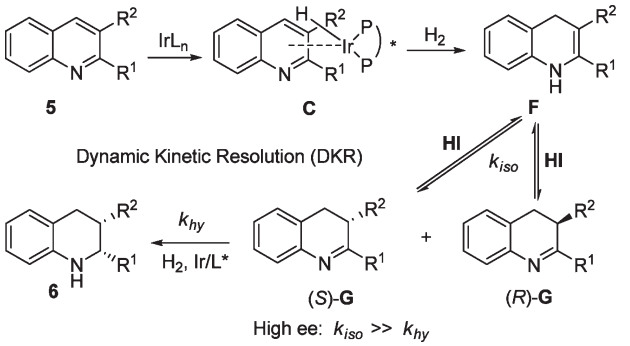
After the successful application of Ir/P−P*/I_2 catalytic system in asymmetric hydrogenation of various quinolines, systematic studies on disclosing the role of the additive iodine and the reaction process were conducted by Zhou and co-workers. It was suggested that iodine was used to activate the catalyst by oxidation of Ir(I) to more catalytic active Ir(III) species. With the combination of couples of experiments and computational study, a plausible mechanism for this process was proposed (Scheme 6).[14a]

At the beginning, Ir(I) species precursor **A** is oxidized to generate Ir(III) species in situ in the presence of I_2 (S indicates solvent), and subsequent heterolytic cleavage of H_2 can occur to form the catalytic active Ir(III)−H species **B** with release of HI (the I and Cl were omitted for clearness). The quinoline substrate **Q** could coordinate with Ir(III) species **B** to form **C**, and then 1,4-hydride transfer affords 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**. The enamine **F** isomerizes to yield imine **G**, which might be catalyzed by the above generated strong Brønsted acid HI. Imine intermediate **G** could coordinate with Ir(III)−H species **B** to form the intermediate **H**; subsequent insertion of Ir−H to the C═N forms intermediate **I** with creation of a chiral center. Finally, the

Scheme 6. Possible Mechanism of Ir-Catalyzed Hydrogenation of Quinolines



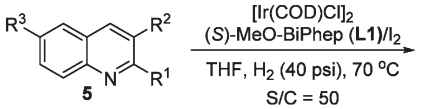
Scheme 7. Mechanism of Ir-Catalyzed Hydrogenation of 2,3-Disubstituted Quinolines 5



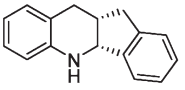
product 1,2,3,4-tetrahydroquinoline **TQ** is released via σ-bond metathesis with hydrogen from **J** and completes the catalytic cycle. Recently, Crabtree and co-workers developed a new homogeneous iridium catalyst for hydrogenation of quinolines under mild conditions.[14b] They gave an unusual stepwise outer-sphere mechanism different from the conventional inner-sphere mechanism.[14a]

The hydrogenation process of 2,3-disubstituted quinolines **5** is more complicated than that of 2-substituted quinolines.[14a] For the latter, the enantioselectivity-controlled step is the asymmetric hydrogenation of the C=N bond of the imine intermediate **G**. In contrast, the enantioselectivity-controlled step for the former is the isomerization of **F** to **G** followed by hydrogenation to give the product, which is in fact a dynamic kinetic resolution process (Scheme 7). To obtain high enantioselectivity, it should meet the condition that the rate of isomerization (k_{iso}) is faster than that of hydrogenation (k_{hy}). Therefore, high temperature and low hydrogen pressure should be employed to accelerate the isomerization and decelerate the hydrogenation, respectively.

Scheme 8. Ir-Catalyzed Hydrogenation of 2,3-Disubstituted Quinolines 5



	R^1	R^2	R^3	Ee (%)
6a	Me	Me	H	73
6b	Et	Me	H	85
6c	*i*-Pr	Me	H	86
6d	*n*-Bu	Me	H	83
6e	*n*-Pentyl	Me	H	83
6f	Phenethyl	Me	H	80
6g	Benzyl	Me	H	81
6h	C_6H_5	Me	H	38
6i	-$(CH_2)_4$-		H	39
6j	Et	Me	F	83
6k	Et	Me	Me	84
6l	Et	Me	OMe	85



6m 86% ee

Not surprisingly, very poor enantioselectivity was obtained when 2,3-dimethylquinoline **5a** was subjected to hydrogenation under high pressure at room temperature.[14a] By lowering the pressure and meanwhile elevating the reaction temperature (40 psi, 70 °C), the ee value was increased from 5% to 73%. Under optimal conditions, a series of 2,3-disubstituted quinolines **5** were hydrogenated to give products **6** with excellent diastereoselectivities (up to >20:1, major in cis isomer) and up to 86% ee (Scheme 8).

The methodology of Ir-catalyzed asymmetric hydrogenation of quinolines was also successfully applied to the synthesis of some important intermediates and naturally occurring tetrahydroquinolines alkaloids. For example, hydrogenation of quinolines as

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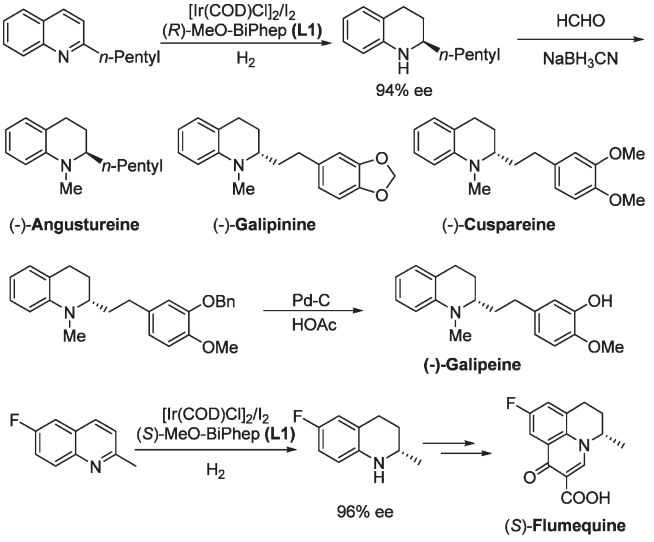
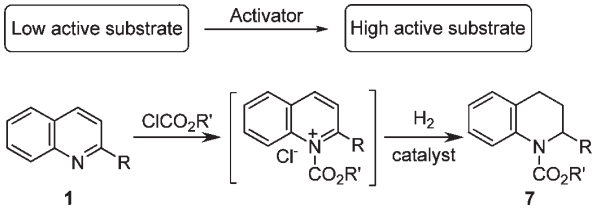
Scheme 9. Application of Ir-Catalyzed Hydrogenation of Quinolines in the Synthesis of Alkaloids and Intermediates



Scheme 10. Activation of Quinolines with Chloroformates



the key step followed by *N*-methylation of the corresponding hydrogenation products offers a convenient and economical route to (−)-angustureine, (−)-galipinine, (−)-cuspareine, and (−)-galipeine (Scheme 9, with excellent enantioselectivities and high total yields).[10,15] In addition, the hydrogenation product of 6-fluoro-2-methylquinoline is the key intermediate of the antibacterial agent of (*S*)-flumequine.[10]

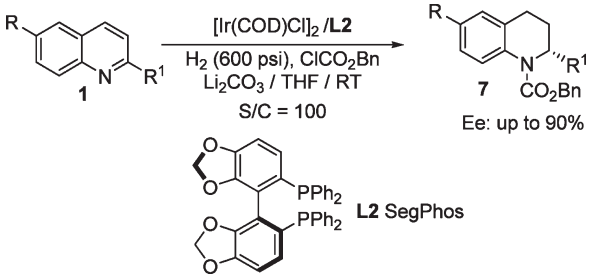
For the above successful examples of asymmetric hydrogenation of various substituted quinolines, a catalytic amount of iodine was employed as activator for catalyst. In 2006, activation strategy for substrates was also developed with addition of stoichiometric amount of chloroformates to form quinolinium salts in situ, which then were hydrogenated smoothly.[16]

Herein, the chloroformates facilitate the hydrogenation for the following reasons (Scheme 10): (1) aromaticity was destroyed partially by the formation of quinolinium salts; (2) catalyst poison was avoided with the *N*-atom bonded by the activator; and (3) CO_2R acted as a secondary coordination group to assist coordination between substrates and catalyst.

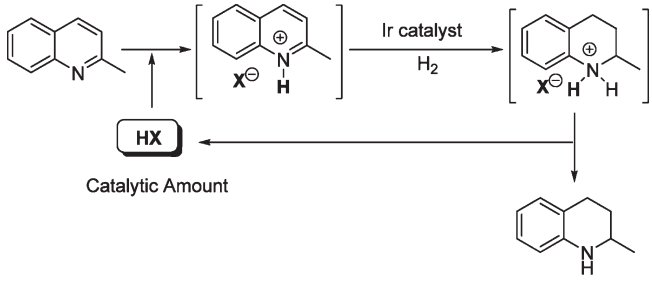
Thus, Zhou and co-workers employed the $[Ir(COD)Cl]_2$/(*S*)-SegPhos (**L2**)/$ClCO_2Bn$/Li_2CO_3 catalytic system to realize the asymmetric hydrogenation of quinolines with 88−90% ee values (Scheme 11).[16] This methodology offers an alternative access to the synthesis of optically active tetrahydroquinoline alkaloids.

For the above transformation, stoichiometric amounts of chloroformates were employed, and the activation groups were

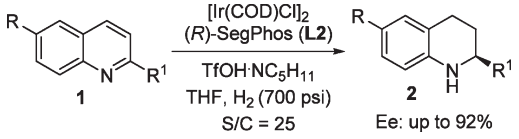
Scheme 11. Asymmetric Hydrogenation of Quinolines 1 Activated with Chloroformates



Scheme 12. Activation of Quinolines with a Catalytic Amount of Brønsted Acid



Scheme 13. Asymmetric Hydrogenation of Quinolines 1 Activated with Brønsted Acid



attached covalently at the nitrogen atoms of the products. Additional deprotection operation was needed for derivatization of the hydrogenated products, which was inconvenient. Subsequently, Brønsted acid was found to be the suitable alternative candidate for its capacity to form salt with basic quinoline substrates. Because the basicities of the product tetrahydroquinolines and the quinolines are almost equivalent, the acid can recycle in the activation process, and a catalytic amount of acid was enough for this process. It could be removed readily by simple basic workup (Scheme 12).

Catalyst with $[Ir(COD)Cl]_2$/(*R*)-SegPhos (**L2**) was found to be effective in Brønsted acids activated asymmetric hydrogenation of quinolines by Zhou and co-workers in 2010.[17] A series of Brønsted acids were examined, piperidine triflic acid was found to be the best choice in terms of enantioselectivity and conversion, and up to 92% ee was achieved (Scheme 13).

Iridium-catalyzed asymmetric hydrogenation of quinoline derivatives achieved great success; meanwhile, the asymmetric transfer hydrogenation catalyzed by iridium complex was also realized. Besides hydrogen gas, other types of hydrogen sources were also introduced with the Ir/P−P*/I_2 catalytic system. The asymmetric transfer hydrogenation of quinolines with Hantzsch ester and water in combination with silane was developed, respectively.

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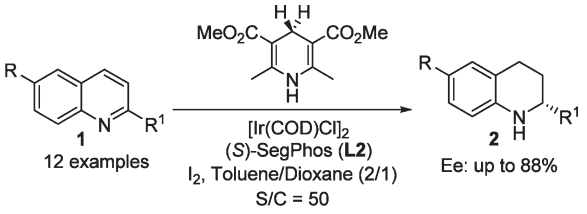
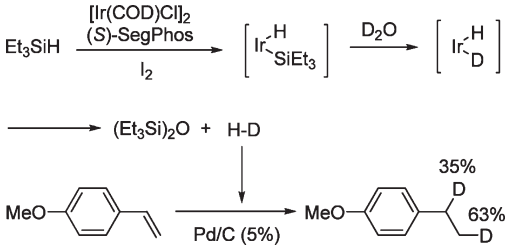
Scheme 14. Ir-Catalyzed Asymmetric Transfer Hydrogenation of Quinolines 1



Scheme 15. Generation of H_2 from Silane and Water



In 2007, Zhou and co-workers found that by replacing hydrogen gas with Hantzsch ester, which was employed as hydrogen source for chiral phosphoric acid-catalyzed asymmetric transfer hydrogenation of quinolines by Rueping et al., as the hydrogen source, 2-substituted quinolines **1** were reduced with the previous Ir/**L2**/I_2 catalytic system.[18] Up to 88% ee was obtained for a series of 2-substituted quinolines (Scheme 14).

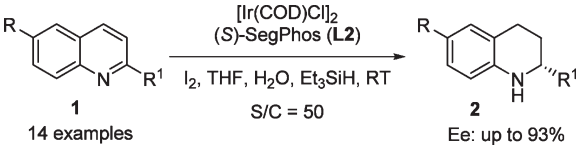
Water, the most abundant and environmentally benign source in nature, has found extensive application in organic synthesis as reagent or reaction medium. Nevertheless, it was less explored as reaction substrate in asymmetric catalysis. In 2010, the Zhou group found that water in combination with silane catalyzed by $[Ir(COD)Cl]_2$/bisphosphine/I_2 catalytic system can release hydrogen gas.[19] It was confirmed by capture of the hydrogen gas with a mixture of 4-methoxystyrene and Pd/C in another reactor, and hydrogenation product 4-methoxyphenylethane was obtained (Scheme 15). Therefore, a new strategy for generating hydrogen gas was developed.

Subsequently, it was extended to the asymmetric hydrogenation of quinolines. Conditions optimization revealed that Et_3SiH and H_2O was the proper combination; with $[Ir(COD)Cl]_2$/**L2**/I_2 as the catalytic system, a series of quinolines were hydrogenated smoothly with up to 93% ee (Scheme 16).[19]

After the pioneering work of Zhou group,[10] much attention has been attracted to the asymmetric hydrogenation of quinolines with most effort on exploring more effective ligands with both high catalytic activity and enantioselectivity. With these successful examples, excellent catalytic activities (TOF up to 4000 h^{-1}) and productivities (TON up to 43 000) were obtained. For some ligands, the formed catalysts were air-stable and could be carried out in air, and some catalysts could be reused for several cycles. In most cases, the catalysts were prepared in situ from $[Ir(COD)Cl]_2$ and the ligands with iodine as the additive. Particularly, chiral atropisomeric biaryl bisphosphine ligands were extensively studied and found their superiority in this transformation (Figure 4).

In 2005, Chan and co-workers employed P-Phos (**L3a**), which was developed by their laboratory,[20] in iridium-catalyzed

Scheme 16. Ir-Catalyzed Asymmetric Hydrogenation of Quinolines 1 with Silane/Water



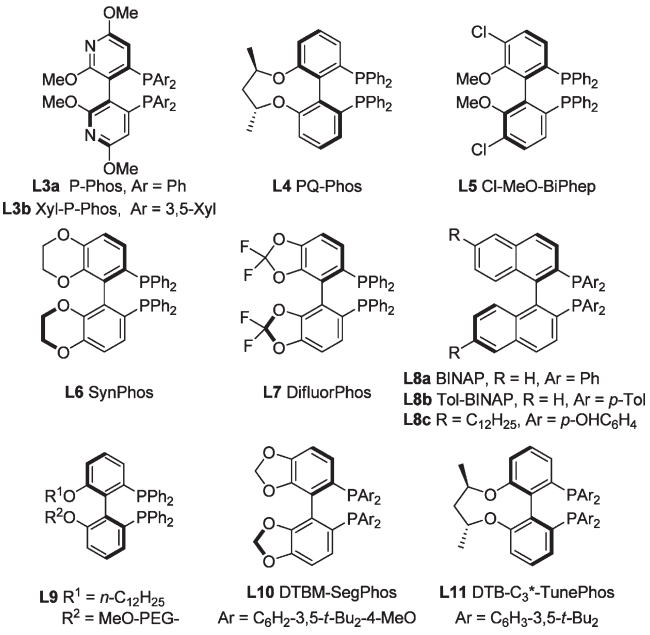


Figure 4. Atropisomeric diphosphine ligands for hydrogenation of quinolines.

asymmetric hydrogenation of quinolines, and up to 92% ee was obtained (S/C = 100).[21] It was found that the Ir-(P-Phos) catalyst was air-stable, and the reaction was carried out in undegassed THF. Subsequently, the recyclability of the catalyst was explored as the reaction could proceed well in two-phases solution of DMPEG-500/hexane with results comparable to THF. The product was easily separated via simple decantation, and the DMPEG layer was further extracted twice with hexane in air. The catalyst remaining in the DMPEG phase was recharged with substrate and hexane, and then subjected to hydrogenation again under identical conditions and could be reused eight times with retention of activity and enantioselectivity.[21] Xu and co-workers found that the catalytic efficiency of this iridium complex could be further enhanced when the reaction was carried out in a glovebox with degassed solvent.[22] It was also disclosed that the amount of additive I_2 had a critical effect on the catalytic reactivity, and decreasing the I_2 amount favored the hydrogenation at lower catalyst loadings. High S/C ratios of 2000−50 000 to produce chiral 1,2,3,4-tetrahydroquinolines in excellent yields and up to 96% ee were obtained, and, notably, up to 4000 h^{-1} TOF and 43 000 TON values were achieved.

A series of chiral diphosphine ligands denoted as PQ−Phos, which were prepared by atropdiastereoselective Ullmann coupling and ring-closure reactions in Chan's laboratory, were tested in the asymmetric hydrogenation of quinolines, and up to 93% ee was observed.[23] The dihedral angle effect of the ligands was

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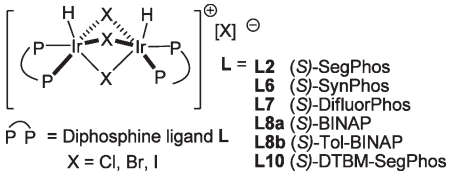


Figure 5. Cationic dinuclear triply halogen-bridged iridium(III) complexes.

disclosed as (*S*,*R*,*R*)-PQ—Phos (**L4**) to be the best one with dihedral angle = 80.0°, which was close to that of MeO—BiPhep = 83.2° (**L1**).

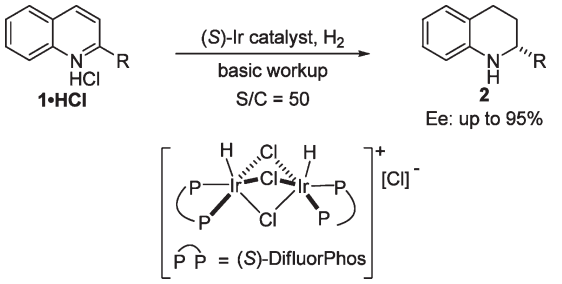
With the purpose of finding air-stable and recyclable ligands in asymmetric hydrogenation of quinolines, the performances of a series of ligands with *C*2-symmetry such as Xyl—P—Phos (**L3b**), Cl—MeO—BiPhep (**L5**), SynPhos (**L6**), and DifluorPhos (**L7**) were systematically investigated by Chan and co-workers.[24] A variety of 2-alkylsubstituted quinolines were hydrogenated smoothly to the product with these ligands, and up to 95% ee was obtained. Poor conversion and enantioselectivity were obtained when the reaction was carried out at room temperature in ionic liquids. Nevertheless, the reaction proceeded well in DMPEG-500/hexane, which would facilitate the separation of substrate and catalyst. It was found that iridium catalysts of **L3a**, **L3b**, and **L5** were air-stable, and the reactions were carried out in untreated solvents and under open atmosphere. Catalysts of SynPhos (**L6**) and DifluorPhos (**L7**) were relatively more sensitive to air. By employing 2-methylquinoline as a model substrate, the catalyst recyclability in a DMPEG/hexane biphasic system was tested. Results indicated that Ir-**L1**, Ir-**L5**, and Ir-**6** were suitable for catalyst recovery and reuse.[24] In 2010, Xu et al. revealed that the commercially available diphosphine ligand **L7** in combination with $[Ir(COD)Cl]_2$ served as an exceedingly efficient catalyst in hydrogenation of quinoline.[25] TON up to 43 000 and TOF up to 3510 h^{-1} were achieved when the reaction was carried out in THF.

In 2006, a series of mononuclear halo-carboxylate iridium(III) complexes and cationic dinuclear triply halogen-bridged iridium-(III) complexes with various axially chiral diphosphine ligands were synthesized by Mashima and Genet et al. (Figure 5). With iodine as additive, these complexes showed effectiveness in hydrogenation of quinolines.[26] Subsequently, these complexes were applied to the asymmetric hydrogenation of 2-aryl and 2-alkyl-substituted quinolinium salts without the addition of I_2. DifluorPhos (**L7**) gave the best results in terms of enantioselectivity (Scheme 17).[27] In this case, the quinolines substrates were activated by the HX acids. It was notable that an unexpected superiority of chloro- and bromo-iridium catalyst over iodo-iridium catalyst was found. With this catalytic system, 2-aryl-substituted tetrahydroquinolines were obtained with up to 95% ee.

The modification of the common used ligands provides a convenient access to find more effective ligands with improving either enantioselectivity or reactivity. In 2007, Pellet-Rostaing and co-workers synthesized electronically enriched BINAP derivatives and compared their performance in the asymmetric hydrogenation of quinolines.[28] It was found that electron-enriched 6,6′-didodecyl tetrahydroxy—BINAP (**L8c**) gave both higher conversion and enantioselectivity as compared to that of BINAP (**L8a**).

It was notable that most of the catalytic system for quinoline hydrogenation suffered from low catalytic activity as evidenced by the fact that good results could only be obtained at a low

Scheme 17. Asymmetric Hydrogenation of Quinolinium Salts



substrate-to-catalyst ratio of 100. This may be ascribed to the deactivation of iridium catalyst by formation of catalytically unreactive dimers and trimers through hydride-bridged bonds under hydrogen atmosphere.[12c,29] In 2007, the Fan group employed BINAP-cored dendrimers (**L12**) as ligands in Ir-catalyzed asymmetric hydrogenation of quinolines with dramatic enhancement of catalytic activity.[30] Good to high enantioselectivity (up to 93% ee) with TOF up to 3450 h^{-1} and TON up to 43 000 was obtained (Figure 6). The authors proposed that with the encapsulation of the iridium complex into a dendrimer framework, the dimerization was reduced, and thus the productivity of the catalyst was enhanced dramatically.

Zhou and co-workers developed a divergent method for the synthesis of a series of tunable axially chiral bisphosphine ligands starting from (*S*)-MeO—BiPhep (**L1**) by introduction of different substituents at the 6,6′-positions of the biaryl backbone, and these ligands were successfully applied to asymmetric hydrogenation of quinolines.[31] After comparing investigations, **L9** bearing MeO-PEG-(1600)- and dodecanyl at the 6- and 6′-positions (Figure 4), respectively, gave the best result. Iridium catalyst with this ligand was found to be air stable and could be operated in air with the same activity and a somewhat lower ee value. The catalyst could precipitate by adding hexane to the reaction mixture and was recovered by filtering off and washing with hexane three times. The recyclability of the catalyst then was examined, and the catalytic activity and enantioselectivity were retained for five cycles.[31]

In 2010, the same group developed another strategy for inhibiting the deactivation of iridium catalyst in asymmetric hydrogenation reactions by introducing bulky substituents on the coordination atom.[32] ESI-MS studies gave strong evidence of inhibiting the formation of dimers and trimers with DTBM—SegPhos (**L10**) (Figure 4) as compared to the matrix ligand SegPhos (**L2**). The effectiveness of this strategy was confirmed by iridium-catalyzed asymmetric hydrogenation of quinolines, for which the substrate to catalyst ratio was increased from 100 to 25 000.[32]

Although P—Phos (**L3a**) has demonstrated its good catalytic performances in iridium-catalyzed asymmetric hydrogenation of quinolines by Chan and co-workers,[21] the modification of the aryl groups on the phosphorus atom was difficult. Zhang and co-workers developed a practical and convenient route to synthesize a series of C_3*—TunePhos bearing different aryl groups with small variation of the dihedral angle and tested their performance in the asymmetric hydrogenation of quinolines.[33] It was found that di-*t*-Bu-phenyl-substituted ligand **L11** gave the best result in terms of enantioselectivity (Figure 4). Interestingly, when 2-methylquinoline *N*-oxide **8** was tested in the hydrogenation

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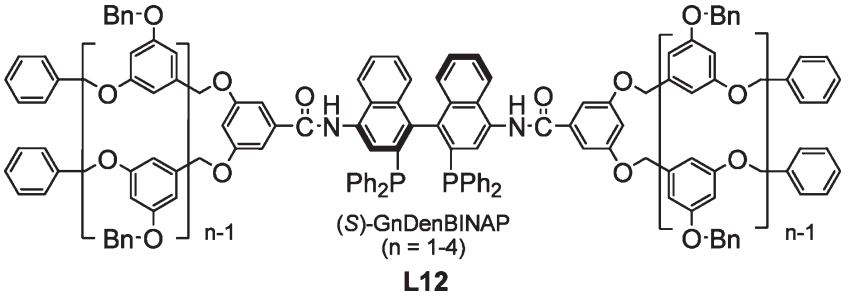
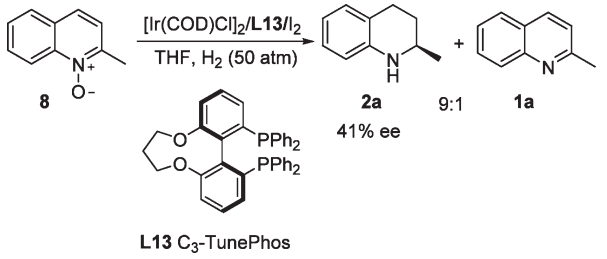


Figure 6. Dendritic GnDenBINAP ligands.

Scheme 18. Asymmetric Hydrogenation of Quinoline *N*-Oxide 8



with C_3—TunePhos (**L13**) as ligand, 2-methyltetrahydroquinoline was obtained with the opposite configuration (41% ee) and with a small portion of **1a** remaining unhydrogenated (Scheme 18).[33]

Diphosphinite and Diphosphonite Ligands. Besides axially chiral bisphosphine ligands, other types of diphosphorus ligands including diphosphinite and diphosphonite ligands were also found to work well in iridium-catalyzed asymmetric hydrogenation of quinolines with the addition of iodine (Figure 7).

Easily prepared and derived chiral diphosphinites ligands found successful applications in asymmetric hydrogenation reactions. In 2005, it was extended to asymmetric hydrogenation of quinoline derivatives by Chan's group.[34] Better performance was obtained with rigid H8-BINAPO (**L14b**) than BINAPO (**L14a**); with the former, up to 96% ee was obtained when the reaction was carried out in THF. Even higher enantioselectivities (up to 97% ee) were obtained with DMPEG-500/hexane as the reaction medium. They also tried to recycle the catalyst, but conversion and enantioselectivity dropped sharply after two runs, which may be due to the deactivation of the iridium catalyst.[34]

In 2007, Xu, Fan, and Chan et al. employed chiral phosphinite ligand SpiroPO (**L15**) derived from (*R*)-1,1′-spirobiindane-7,7′-diol in the asymmetric hydrogenation of quinolines, which exhibited high catalytic activity and enantioselectivity.[35] It was suggested that the rigidity of the spirobiindane skeleton facilitated the effective transfer of chiral information and effectively inhibited the formation of catalytically inactive species; thus up to 94% ee and a substrate/catalyst ratio of up to 5000 were obtained. The reaction could proceed well in both THF and DMPEG—hexane biphasic system. Recyclability of this catalytic system with the latter reaction medium was tested, but the conversion dropped to 40% albeit the enantioselectivity remained high.

BINOL-derived diphosphonite ligand **L16** with an achiral diphenyl ether backbone was proved to be effective in iridium-catalyzed asymmetric hydrogenation of quinolines by Reetz and co-workers (Figure 7).[36] For some substrates, the addition of

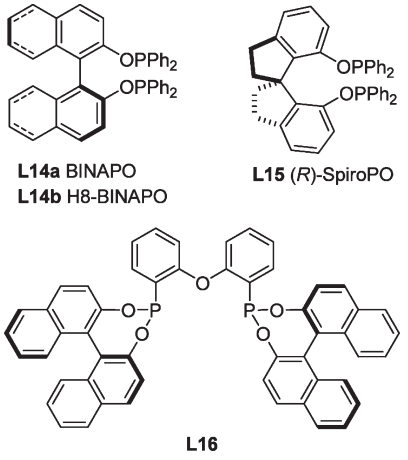


Figure 7. Diphosphinite and diphosphonite ligands.

proper achiral P-ligand in combination with iodine as additive was necessary for high enantioselectivities.

Phosphine—Phosphoramidite and Phosphine—Phosphite Ligands. Ligands that are able to generate highly active and enantioselective catalysts with different metal centers and with a broad of substrate scope are considered as privileged ligands. In 2009, Franciò and Leitner et al. developed a set of novel phosphine—phosphoramidite ligands (**L17**) with this feature, which possesses two elements of chirality and found successful application in Rh-, Ru-, and Ir-catalyzed mechanistically distinct asymmetric hydrogenation reactions (Figure 8).[37] In the Ir-catalyzed asymmetric hydrogenation of quinolines, **L17** gave up to 97% ee, and, notably, 95% ee was achieved for 2-phenylquinoline (S/C = 100).

The performance of phosphine—phosphite ligands in iridium-catalyzed asymmetric hydrogenation of quinolines was investigated by Pizzano and the Vidal-Ferran group, respectively, in 2010 (Figure 8).[38] Iodine was found not to be the proper additive with detrimental effect for enantioselectivity or no noticeable improvement for both conversion and enantioselectivity, respectively. Pizzano and co-workers found that phosphoric acids showed a beneficial effect on catalytic activity and improved the enantioselectivity somewhat with **L18** as ligand.[38a] Vidal-Ferran and co-workers found that in combination with catalytic amounts of anhydrous HCl (10 mol %), the catalytic system with **L19** exhibits excellent catalytic properties.[38b]

2.1.1.2. Other Phosphine-Containing Chiral Ligands. Ligands with only one coordinative phosphorus atom in the backbone were also found to be effective in iridium-catalyzed asymmetric hydrogenation of quinolines (Figure 9).

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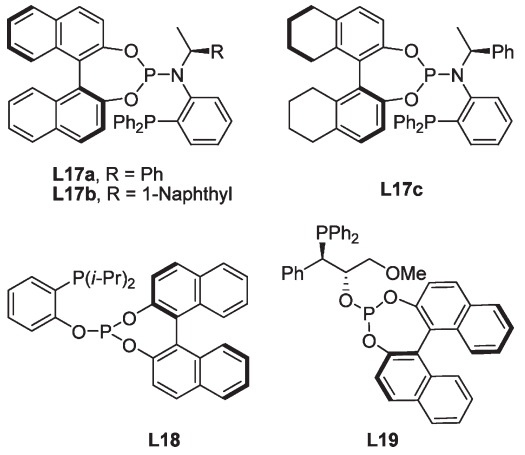


Figure 8. Phosphine−phosphoramidite and phosphine−phosphite ligands.

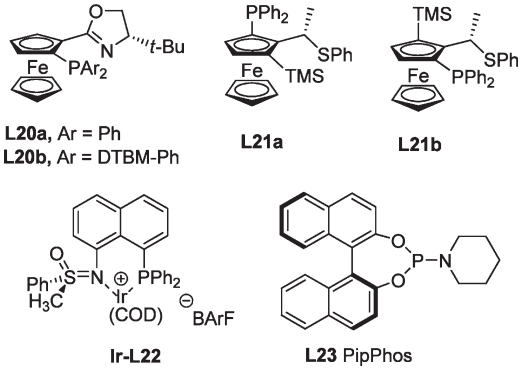


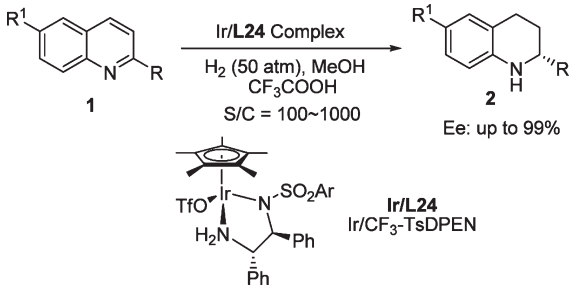
Figure 9. Other types of phosphorus-containing ligands.

The effectiveness of the ferrocenyloxazoline-derived *P,N*-ligand (**L20a**) in the asymmetric hydrogenation of quinolines was disclosed by Zhou and co-workers.[39] With iodine as the additive, up to 92% ee was obtained, and the substrate to catalyst ratio can reach 1000. It was found that central chirality dominates the absolute configuration of the products, whereas mismatched planar chirality with central chirality resulted in both lower enantioselectivity and activity. The catalytic activity was further improved via introduction of bulky aryl group on the phosphorus atom (**L20b**).[32] Subsequently, ferrocene-derived *P,S*-ligands (**L21**) were also found to be able to promote this reaction with up to 80% ee.[40] Interestingly, by introduction of a bulky trimethylsilyl group to the Cp ring of the ligands, **L21a** and **L21b** with the same central chirality and opposite planar chirality gave products with opposite absolute configuration in moderate to good enantioselectivity.

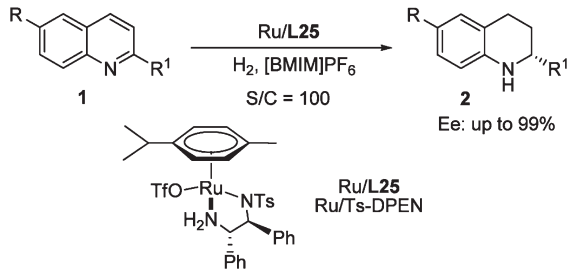
In 2008, Bolm and co-workers synthesized a series of naphthalene-bridged *P,N*-type sulfoximine ligands and disclosed the catalytic potential of their iridium complexes in asymmetric hydrogenation of quinolines.[41] With complex Ir/**L22** as catalyst, up to 92% ee was obtained (Figure 9). In this catalytic system, additives, especially iodine, showed negative effect for either activity or enantioselectivity or both.

Feringa and co-workers employed monodentate BINOL-derived phosphoramidite (*S*)-PipPhos (**L23**) as ligand to the iridium-catalyzed enantioselective hydrogenation of quinolines

Scheme 19. Ir-Catalyzed Asymmetric Hydrogenation of Quinolines with Diamine Ligands



Scheme 20. Ru-Catalyzed Asymmetric Hydrogenation of Quinolines 1



(Figure 9).[42] With this catalytic system, the addition of both chloride salts and achiral phosphine ligands as additives could dramatically enhance the enantioselectivity. Finally, when weak Brønsted acid piperidine hydrochloride in combination with tri-*ortho*-tolylphosphine was selected as the additive, the products were obtained with up to 89% ee.

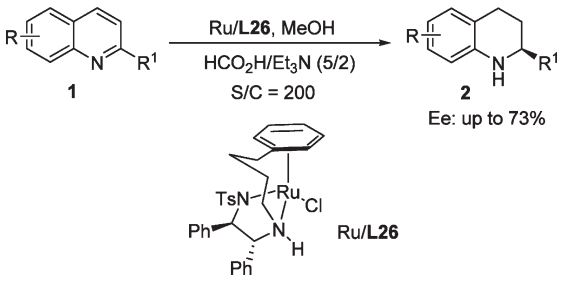
2.1.1.3. Chiral Diamine Ligands. It is noteworthy that, for the most of the successful catalytic systems of iridium-catalyzed asymmetric hydrogenation of quinolines, at least one phosphorus atom was found to be around the metal center. Nevertheless, most of these phosphine-containing catalysts are relatively air-sensitive and operation inconvenient because phosphine ligands are readily oxidized by oxygen. Thus, introducing alternative easily available and air-stable phosphine-free chiral ligands for iridium catalysts is attractive and of great significance.

In 2008, Fan and co-workers examined the performance of Ir/DPEN complexes in the asymmetric hydrogenation of quinolines and found Ir/CF_3-TsDPEN (**L24**) to be the best choice with high yield and up to 99% ee at catalyst loading of 0.2 mol % (Scheme 19).[43] In this process, a catalytic amount of TFA was added to increase the activity of the catalytic system. The reaction occurred smoothly in undegassed solvent with no need for inert gas protection.

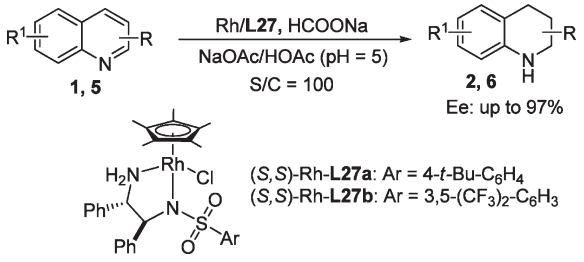
2.1.2. Ru-Catalyzed Asymmetric Hydrogenation. Air-stable Ru/Ts-DPEN catalyst has found its application in asymmetric hydrogenation of ketones and attracted much attention.[44] This catalytic system was also extended to the asymmetric hydrogenation of quinolines by Fan and Chan.[45]

Ru/Ts-DPEN (**L25**) was successfully introduced to the asymmetric hydrogenation of quinolines by them, and up to 99% ee value was obtained (Scheme 20).[45] The reaction proceeded well in both MeOH or net [BMIM]PF_6 with both high conversion and excellent enantioselectivity. The latter belongs to room temperature ionic

Scheme 21. Ru-Catalyzed Asymmetric Transfer Hydrogenation of Quinolines 1



Scheme 22. Rh-Catalyzed Asymmetric Transfer Hydrogenation of Quinolines 1 and 5



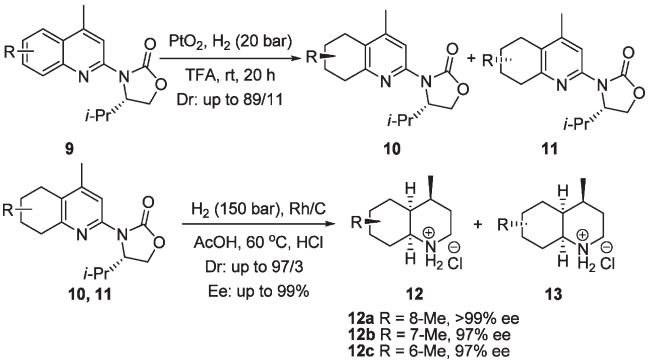
liquids (RTILs), which received considerable attention as alternative reaction media in recent years. It was found that the catalyst was stable in this media and showed the same activity and enantioselectivity after exposing to air for 30 days, while in methanol the catalyst decomposed within 1 week. The catalyst was able to be reused by separating reduced product with simple extraction with *n*-hexane, and the ionic liquid phase was recharged with the substrate and subjected to the same reaction conditions. The performance of the catalyst was maintained until the sixth run, and thereafter a slight decrease of reactivity was observed. An ionic catalytic pathway is proposed for this transformation.[45]

Subsequently, it was found that the above transformation could occur smoothly under solvent-free or highly concentrated conditions for liquid and solid substrates, respectively.[46] For the latter cases, iso-propyl alcohol was employed as the solvent with 0.1 mol % of TfOH as additive. In these cases, high activity (S/C up to 5000) and excellent enantioselectivity (up to 97% ee) were obtained, and this was the first example of enantioselective hydrogenation of heteroaromatic compounds under environmentally friendly solvent-free conditions.

Recently, the asymmetric transfer hydrogenation of quinolines with Ru/TsDPEN complex was examined by the Wills group (Scheme 21).[47] The reaction was carried out in a solution of formic acid/triethylamine/methanol, and tethered Ru(II) complex (Ru/**L26**) showed high activity but with moderate enantioselectivity in sharp contrast to the matrix Ru/TsDPEN, which gave high enantiomeric excess but with low conversion.

2.1.3. Rh-Catalyzed Asymmetric Hydrogenation. After chiral iridium and ruthenium complexes were successively applied in the asymmetric hydrogenation of quinolines, rhodium catalysts also found their positions in this field. In 2009, the Xiao group disclosed the effective transfer hydrogenation of quinolines in aqueous solution by Rh/TsDPEN (**L27**) catalytic system.[48]

Scheme 23. Heterogeneous Diastereoselective Hydrogenation of Quinolines to Decahydroquinolines



In this transformation, the pH value of the reaction medium was found to be critical for high activity, whereas the enantioselectivity showed little influence. Because this hydrogenation proceeds through an ionic mechanism, a high concentration of both formate and protonated quinolines is needed to speed up the reaction. In this context, HOAc/NaOAc buffer system at pH 5 was found as the best choice with a broad range of substrates including 2-alkyl, 2-aryl, 2,6-disubstituted, and 2,3-disubstituted quinolines, giving the desired hydrogenation products with excellent enantioselectivities and high yields (Scheme 22).[48]

The Wills group examined the asymmetric transfer hydrogenation of quinolines in a solution of formic acid/triethylamine/methanol with tethered Rh/TsDPEN complex.[47] High enantioselectivity was obtained but with uncompleted conversion even with higher catalyst loading (2 mol %).

For the homogeneous asymmetric hydrogenation of quinolines, the products were usually 1,2,3,4-tetrahydroquinolines with a newly formed stereocenter at the 2-position. In 2010, Glorius et al. then realized the diastereoselective hydrogenation of the auxiliary-substituted quinolines **9** to 5,6,7,8-tetrahydroquinolines with one heterogeneous catalyst and subsequently further hydrogenated to decahydroquinolines with traceless cleavage of the chiral auxiliary by another heterogeneous catalyst (Scheme 23).[49]

It was found that the catalyst and solvent were critical for the selective hydrogenation of benzene ring, and PtO_2 with trifluoroacetic acid (TFA) was found to be the optimal combination. Under the optimized conditions, several quinolines were hydrogenated to 5,6,7,8-tetrahydroquinolines with high yield and diastereomeric ratio up to 89/11 (**10**/**11**).[49] The obtained methyl-substituted tetrahydroquinolines were further hydrogenated to decahydroquinolines (**12**/**13** up to 97/3) with Rh/C as the catalyst. It was noteworthy that *cis*-selectivity was controlled by the chiral auxiliary over a wide distance and traceless cleavage of the chiral auxiliary occurred during the reaction course. The diastereomeric ratio of the products depends on the dr of the starting material, while the ee value of the major diastereomer was very high in each case (97−>99% ee).[49]

2.2. Organocatalyzed Enantioselective Transfer Hydrogenation

Over the past decade, chiral Brønsted acid catalysts have emerged as powerful tools for asymmetric synthesis. In 2006, Rueping developed a Brønsted acid-catalyzed highly enantioselective transfer hydrogenation of quinolines using Hantzsch esters as hydrogen source (Scheme 24),[50] which was the first

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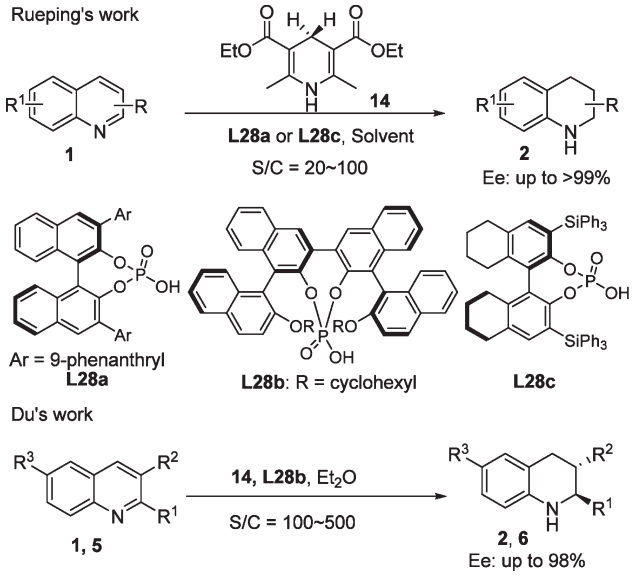
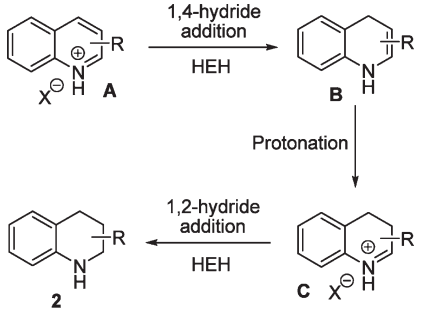
Scheme 24. Chiral Phosphoric Acids-Catalyzed Transfer Hydrogenation of Quinolines 1 and 5



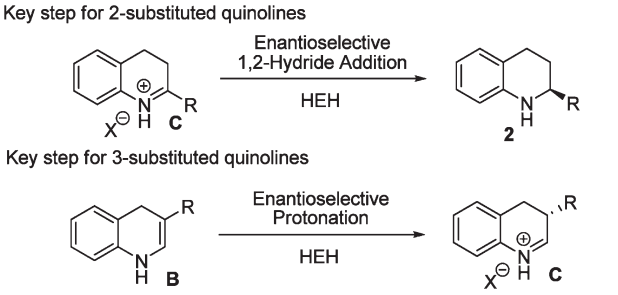
Scheme 25. Proposed Mechanism for Transfer Hydrogenation



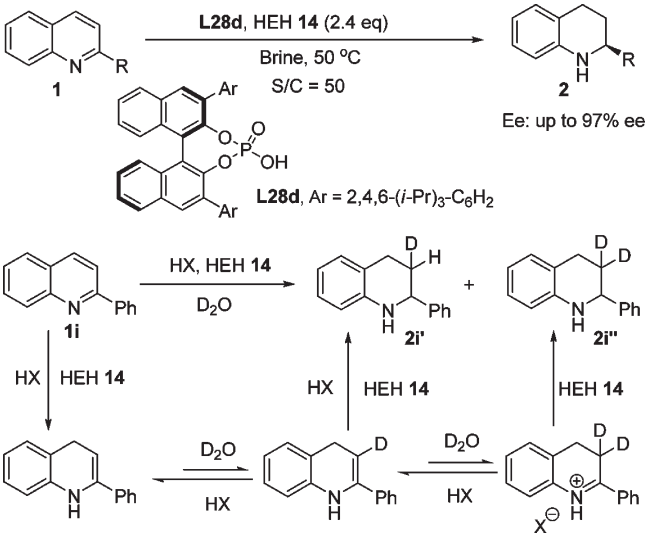
example of organocatalytic reduction of heteroaromatic compounds. Sterically congested phosphoric acid (*R*)-**L28a** (2 mol %) bearing 9-phenanthryl substituents turned out to be the best catalyst, giving 2-aryl-tetrahydroquinolines **2** in excellent enantioselectivities (91−>99%) and moderate to high yields (54−93%). A slight decrease of enantioselectivities (87−91%) was observed in the reduction of 2-alkylquinolines. The utility of the partial reduction of readily available quinolines was demonstrated by the preparation of biologically active alkaloids such as (+)-galipinine and (−)-angustureine with high total yields in only two steps. Next, the biomimetic reduction of 2- and 2,3-substituted quinolines was also investigated by Du's group to test their newly developed bis-BINOL-derived phosphoric acid **L28b** (Scheme 24).[51] With the aid of this double axially chiral phosphoric acids, lower catalyst loadings (0.2 mol %) were sufficient to afford both 2-aryltetrahydroquinoline derivatives and 2-alkyltetrahydroquinolines **1** with excellent enantioselectivities (86−98%). Furthermore, 2,3-disubstituted quinolines **5** were also hydrogenated with high diastereoselectivities and enantioselectivities (Scheme 24, 82−92% ee).

Regarding the mechanism of this transfer hydrogenation, it is assumed that the quinoline **1** is first activated through protonation

Scheme 26. Enantioselectivity-Controlled Steps for Transfer Hydrogenation of Quinolines



Scheme 27. Transfer Hydrogenation in Aqueous Solution

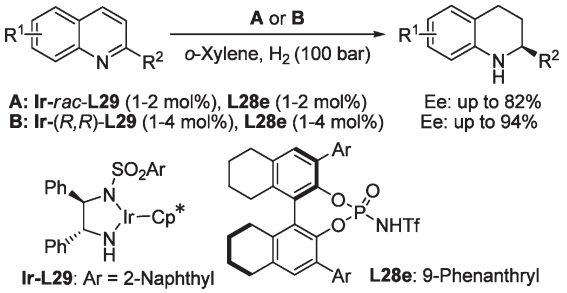


by the Brønsted acid **L28** leading to the formation of chiral ion pair **A** (Scheme 25).[50] Subsequently, **A** undergoes 1,4-hydride transfer from the Hantzsch ester **14** and gives enamine **B**, which delivers iminium **C** by isomerization in the presence of Brønsted acid. The iminium **C** undergoes 1,2-hydride addition with the second equivalent Hantzsch ester **14**, resulting in the formation of desired product tetrahydroquinolines **2**.

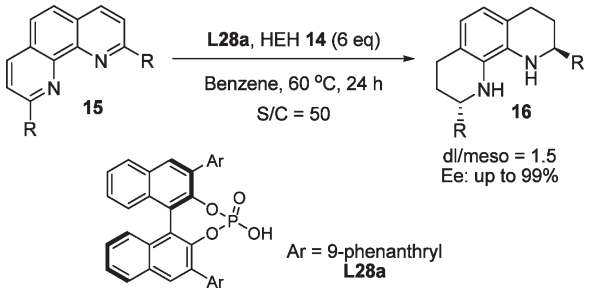
The key step in this Brønsted acid-catalyzed asymmetric transfer hydrogenation of quinolines varied with the position of substituents (Scheme 26). For 2-substituted quinolines, the key step in these reactions consists of Brønsted acid-catalyzed enantioselective 1,2-hydride addition. However, in the case of 3-substituted quinolines, the stereodetermining step in the cascade reaction must be different because 1,2-hydride addition of enamine **C** does not provide a stereogenic center. Therefore, the isomerization of **B** promoted by Brønsted acid is the enantioselective determining step in the reduction of 3-substituted quinolines. On the basis of this principle, Rueping and coworkers developed a highly enantioselective Brønsted acid-catalyzed transfer hydrogenation of 3- and 2,3-substituted quinolines through an enantioselective protonation process.[52]

Recently, organocatalytic reactions in water or aqueous media are of great interest because such systems are relevant to enzymatic reactions under physiological conditions. In 2010, Rueping described Brønsted acid-catalyzed asymmetric transfer

Scheme 28. Brønsted Acid Differentiated Ir-Catalyzed Hydrogenation



Scheme 29. Asymmetric Hydrogenation of Phenanthrolines 15



hydrogenation of 2-arylquinolines using water as a reaction medium employing the principle of hydrophobic hydration (Scheme 27).[53] As compared to previous work, a slightly decrease of enantioselectivities (83−97%) was observed due to the competition between water as a strong hydrogen-bond donor/acceptor and the chiral phosphoric acid **L28d**. Deuterated experiment was carried out to determine the source of the proton in the enamine−imine tautomerisation step of the asymmetric transfer hydrogenation in aqueous media.[53] The single and double deuterated tetrahydroquinoline **2i′** and **2i″** were isolated almost exclusively, which suggested that in aqueous reaction media the Hantzsch ester acts exclusively as a hydride source and not as the proton source. Further, the deuterium experiment shows that water acts not only as the reaction media but also plays an important role in the reaction procedure in this enantioselective Brønsted acid-catalyzed transfer hydrogenation transformation.[53]

In 2011, Rueping disclosed Brønsted acid differentiated metal-catalyzed asymmetric hydrogenation of quinolines by kinetic discrimination (Scheme 28).[54] Up to 82% ee was obtained in the hydrogenation of 2-methylquinoline using a racemic Ir(III)−amido complex and chiral Brønsted acid as catalyst. The resulting diastereomeric complexes differ in their catalytic properties, and the matched-case provides higher reactivity and selectivities. Employing combined chiral iridium−amido and Brønsted acid catalyst, higher enantioselectivities (84−94% ee) could be achieved in the hydrogenation of quinolines.[54]

In 2008, Metallinos and co-workers reported the enantioselective transfer hydrogenation of 2-substituted and 2,9-disubstituted 1,10-phenanthrolines using Brønsted acid **L28a** as catalyst (Scheme 29).[55] For the former, poor to moderate yields and moderate to high enantioselectivities were obtained for desired products (11−54% yield, 40−95% ee). Although the diastereoselectivities were not very good in reduction of 2,9-disubstituted 1,10-phenanthrolines **15**, DL-octahydrophenanthrolines **16** were obtained with excellent enantioselectivities.

In summary, several efficient catalytic systems have been successfully developed for the asymmetric hydrogenation of quinolines as shown in Table 1. These methodologies provide multiple choices for the synthesis of the corresponding chiral tetrahydroquinolines with high enantioselectivities. Noticeably, a wide range of chiral ligands have been evaluated for the iridium-catalyzed asymmetric hydrogenation of 2-substituted quinolines. Therefore, it is useful and necessary to disclose the general correlation between the structure of ligands and their catalytic performances. Commonly, the ligands suffered from low reactivity (S/C ratio of 100). Nevertheless, electron-deficient ligands such as P−Phos (**L3a**) and DifluorPhos (**L7**) were found to be more reactive (S/C ratio up to 43 000). Ligand with rigid backbone such as SpiroPO (**L15**) or with encapsulation of the ligand into a dendrimer framework (**L12**) to inhibit deactivation also increased the productivity. In the aforementioned examples of hydrogenation of quinolines, substrates bearing substituent at the 2- or 3-position or both 2- and 3-positions were hydrogenated with high enantioselectivity, whereas quinolines with the substituent at the 4-position were ignored and may be the subsequent object. The development of nonprecious metal catalysts for the asymmetric hydrogenation of quinolines and promoting this process to industry production may be the future directions.

3. CATALYTIC ASYMMETRIC HYDROGENATION OF ISOQUINOLINE DERIVATIVES

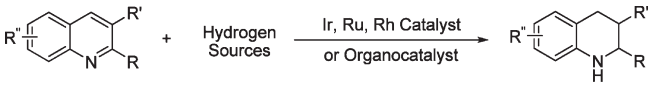
Isoquinoline is one of the most challenging substrates for asymmetric hydrogenation as it shows no activity to a number of catalytic systems, which are efficient for asymmetric hydrogenation of ketones, alkenes, and imines. Presently, only one example on asymmetric hydrogenation of isoquinolines was reported by Zhou and co-workers in 2006.[16]

As mentioned above, when chloroformates were added as the activating reagents to the reaction mixture, quinolines can be hydrogenated to tetrahydroquinolines by using $[Ir(COD)Cl]_2$/(*S*)-SegPhos (**L2**).[16] This substrate activating methodology is not only effective for hydrogenation of quinolines but also effective for isoquinolines **17**. As compared to quinolines, which can be fully hydrogenated to tetrahydroquinolines, the asymmetric hydrogenation of isoquinolines was more difficult, and partially hydrogenated 1,2-dihydroisoquinolines **18** were obtained as products. Under the optimized conditions, only 10−83% ee was achieved (Scheme 30). It is noted that this was the first and the only example for the asymmetric hydrogenation of isoquinoline derivatives, and more efficient catalyst systems are needed to be developed. Using this method, the naturally occurring tetrahydroisoquinoline alkaloids **19** and (*S*)-Carnegine were synthesized in three steps from isoquinolines: asymmetric hydrogenation, Pd−C hydrogenation, and $LiAlH_4$ reduction (Scheme 31).

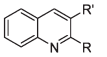
4. CATALYTIC ASYMMETRIC HYDROGENATION OF QUINOXALINE DERIVATIVES

The asymmetric hydrogenation of quinoxalines is a challenging task and provides the chiral tetrahydroquinoxalines, which are of great biological interest.[56] Various transition metal

Table 1. Asymmetric Reduction of Quinolines[a]



Organocatalyst: Chiral Phosphoric Acids
Hydrogen Sources: H_2, Hantzsch Esters, Et_3SiH/H_2O, HCOONa....

Substrates		Catalytic Systems	S/C	Ee (%)	References
 2-Substituted Quinoline	Ir	P-P*/I_2/H_2	43000	99	10,14-15,21-25,28,30-37
		P-P*/$ClCO_2R$/H_2	100	90	16
		P-P*/Brønsted acid/H_2	50	95	17,26-27,38
		P-P*/I_2/HEH	50	88	18
		P-P*/I_2/Et_3SiH, H_2O	50	93	19
		N-P*/(I_2)/H_2	1000	92	39,41
		S-P*/I_2/H_2	100	82	40
		P*/Brønsted acid/H_2	50	92	42
		N-N*/H_2	1000	99	43
	Ru	N-N*/H_2	100	99	45-46
		N-N*/HCO_2H-Et_3N	200	73	47
	Rh	N-N*/HCO_2Na	100	98	48
		N-N*/HCO_2H-Et_3N	200	94	47
	OC	CPA*/HEH	500	99	50-51,53
 2,3-Disubstituted Quinoline	Ir	P-P*/I_2/H_2	50	86	14
	Rh	N-N*/HCO_2Na	100	92	48
	OC	CPA*/HEH	100	99	51,52
 3-Substituted Quinoline	OC	CPA*/HEH	20	86	52

[a] S/C and ee indicate the highest values; P—P*, chiral bisphosphine ligand; N—P*, chiral bidentate nitrogen phosphine ligand; S—P*, chiral bidentate sulfur phosphine ligand; P*, chiral monophosphine ligand; N—N*, chiral diamine ligand; OC, organocatalyst; CPA*, chiral phosphoric acid; HEH, Hantzsch ester.

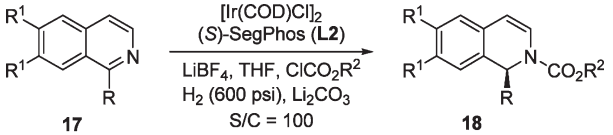
catalysts involving rhodium, iridium, and ruthenium complexes as well as organocatalysts were developed for the enantioselective hydrogenation of quinoxalines. The combination of transition metal catalyst and organocatalyst in one pot with successive hydrogenation and transfer hydrogenation sequence was also developed for reduction of quinoxalines.

4.1. Transition Metal-Catalyzed Enantioselective Hydrogenation

4.1.1. Rh-Catalyzed Asymmetric Hydrogenation. As mentioned above, the first example of asymmetric hydrogenation of quinoxaline was reported in 1987 by Murata and co-workers. Rh[(*S*,*S*)-DIOP]H was used as the catalyst for the hydrogenation of 2-methylquinoxaline (**20a**), and only 2% ee was obtained (Scheme 32).[3] Next, [(*R*,*R*)-(BDPBzP)Rh(NBD)]OTf complexes (1 mol %) were employed as the catalyst for hydrogenation of 2-methylquinoxaline, affording the corresponding hydrogenation product with 11% ee.[57]

4.1.2. Ir-Catalyzed Asymmetric Hydrogenation. In 1998, a breakthrough on asymmetric hydrogenation of aromatics was

Scheme 30. Chloroformates Activated Asymmetric Hydrogenation of Isoquinolines 17

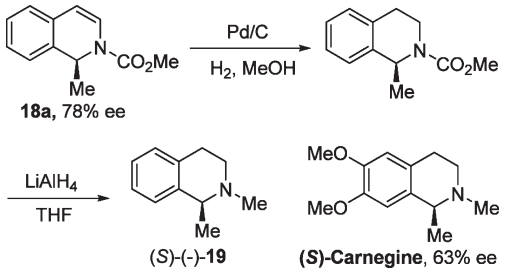


17 18

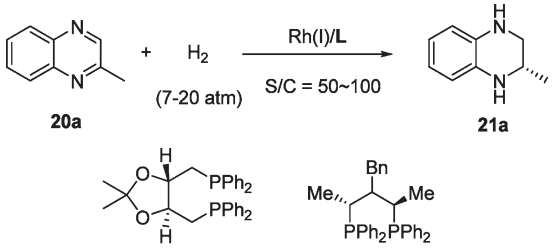
R	R^1	R^2	Yield (%)	Ee (%)
Me	H	Me	85 (**18a**)	80
Me	H	Bn	87(**18b**)	83
Et	H	Me	85 (**18c**)	62
n-Bu	H	Me	87 (**18d**)	60
Bn	H	Me	83 (**18e**)	10
Ph	H	Me	57 (**18f**)	82
Ph	H	Bn	49 (**18g**)	83
Me	MeO	Me	57 (**18h**)	63
Me	MeO	Bn	46 (**18i**)	65

dx.doi.org/10.1021/cr200328h |*Chem. Rev.* 2012, 112, 2557–2590

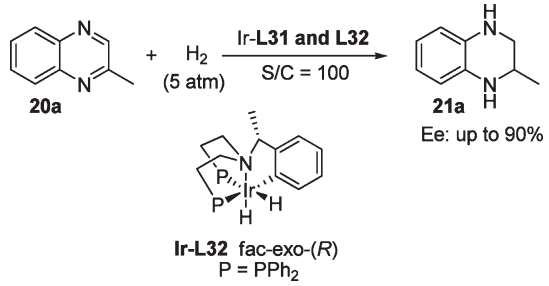
Scheme 31. Application in the Synthesis of Naturally Occurring Alkaloids



Scheme 32. Rh-Catalyzed Asymmetric Hydrogenation of 2-Methylquinoxaline 20a



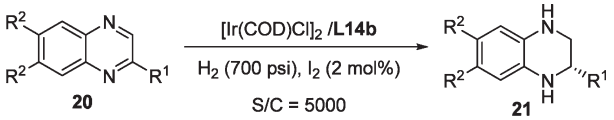
Scheme 33. Ir-Catalyzed Asymmetric Hydrogenation of 2-Methylquinoxaline 20a

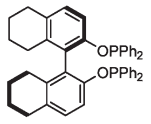


reported by the Bianchini group in hydrogenation of 2-methylquinoxaline with orthometalated dihydride iridium complex (1 mol %) as the catalyst (Ir-**L32**) (Scheme 33).[6] Excellent enantioselectivity (90%) and moderate yield (54%) were obtained in MeOH. The use of *i*-PrOH as solvent gave the highest yield (97%) but a lower enantioselectivity (73% ee). This work represented the first successful example of enantioselective hydrogenation of heteroaromatic compounds with excellent ee (>90%).[6] The same group also employed [(*R*,*R*)-(BDPBzP)Ir-(COD)]OTf complexes (1 mol %) for hydrogenation of 2-methylquinoxaline resulting in 41% yield and 23% ee.[57]

Recently, Xu, Fan, and Chan developed a highly efficient iridium-catalyzed asymmetric hydrogenation of quinoxalines at low catalyst loading (as low as 0.005 mol %) using (*R*)-H8-BINAPO (**L14b**) as the ligand.[23,58] Good to excellent enantio selectivities (81−98%) and full conversions (S/C = 5000) were obtained in the asymmetric hydrogenation of various quinoxalines **20** (Scheme 34).[58] The hydrogenation of 2-methylquinoxaline

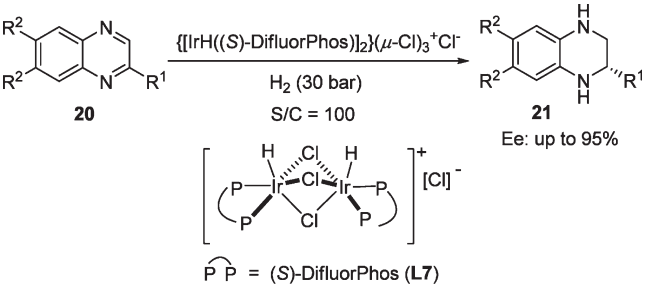
Scheme 34. Ir-Catalyzed Asymmetric Hydrogenation of Quinoxalines 20





	R^1	R^2	Ee (%)
21a	Me	H	93
21b	Et	H	89
21c	*n*-Bu	H	93
21d	*i*-Bu	H	94
21e	*t*-Bu	H	81
21f	Me	Me	87
21g	Et	Me	91
21h	Ph	H	85
21i	2-$MeOC_6H_4$	H	84
21j	$PhCH_2=CH_2$	H	97
21k	4-$MeC_6H_4CH=CH$	H	98

Scheme 35. Cationic Dinuclear Triply Halogen-Bridged Iridium Complexes for Asymmetric Hydrogenation of Quinoxalines 20



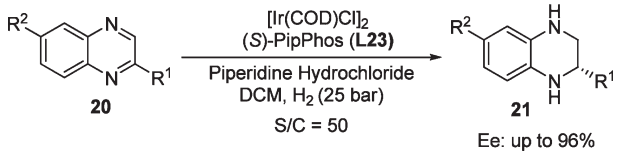
(**20a**) provided up to 5620/h TOF, which represents the highest TOF attained so far in the catalytic asymmetric hydrogenation of heteroaromatic compounds. The use of iodine is crucial for achieving excellent enantioselectivity, which is consistent with Zhou's findings for Ir-catalyzed asymmetric hydrogenation of quinolines.[10,14] Replacing iodine with other additives gave lower ee values or even racemic product.

Ohshima, Mashima, and Ratovelomanana-Vidal et al. described cationic iridium/**L7** complexes-catalyzed asymmetric hydrogenation of 2-alkyl- and 2-aryl-substituted quinoxalines (**20**) in high ee (86−95%) without the addition of iodine (Scheme 35).[59] The selection of cationic dinuclear triply halogen-bridged iridium complexes $\{[IrH((S)\text{-DifluorPhos})]_2(\mu\text{-}Cl)_3\}^+Cl^-$ bearing a chloride instead of an iodide ligand resulted in a considerable improvement in the enantioselectivity. This unprecedented halide dependence was in agreement with their previous work on the asymmetric reduction of 2-substituted quinolinium salts, where chloro- and bromo-iridium catalysts gave superior catalytic performance over the corresponding iodo-iridium catalyst.[27]

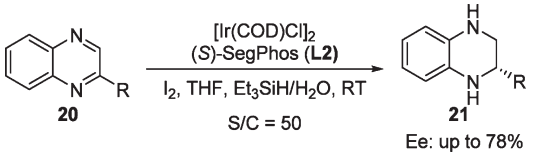
The addition of iodine was not required for the iridium/monodentate phosphoramidite ligand-catalyzed asymmetric hydrogenation of quinoxalines. de Vries, Feringa, and Minnaard developed an iridium/(*S*)-PipPhos (**L23**)-catalyzed hydrogenation of 2- and 2,6-substituted quinoxalines using piperidine

dx.doi.org/10.1021/cr200328h |*Chem. Rev.* 2012, 112, 2557–2590

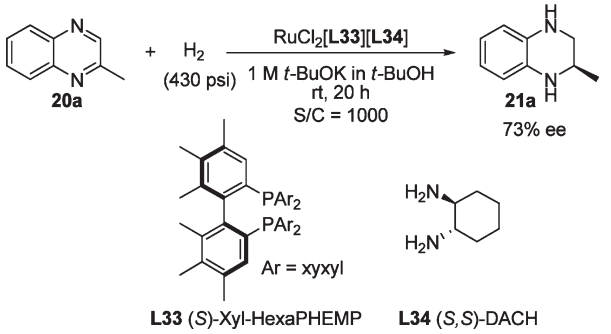
Scheme 36. Iridium/Monodentate Phosphoramidite Ligands for Asymmetric Hydrogenation of Quinoxalines 20



Scheme 37. Water/Silane as Hydrogen Source for Asymmetric Hydrogenation of Quinoxalines 20



Scheme 38. Ru-Catalyzed Asymmetric Hydrogenation of 2-Methylquinoxaline 20a



hydrochloride instead of iodine as an additive with 75−96% ee (Scheme 36).[60]

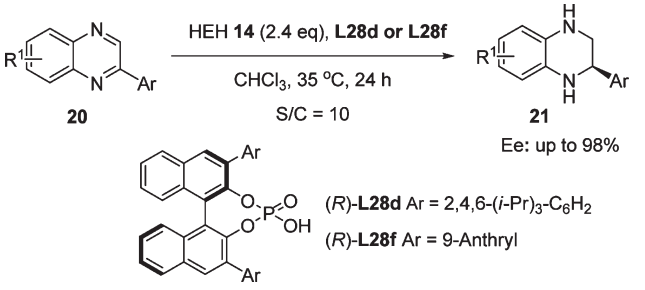
Asymmetric hydrogenation of quinoxalines using water/silane as the hydrogen source was developed by Zhou and co-workers (Scheme 37).[19] Although only moderate enantioselectivities (58−78%) were obtained, the mild autoclave-free reaction conditions make this method simpler and safer for practical operation. The previously referred [Ir(COD)Cl]$_2$/(*R*)-SegPhos (**L2**)/piperidine triflic acid catalytic system was also effective in the asymmetric hydrogenation of quinoxalines with moderate enantioselectivities.[17]

4.1.3. Ru-Catalyzed Asymmetric Hydrogenation. In 2003, Henschke and co-workers described the use of a diverse library of the related RuCl$_2$(diphosphine)(diamine) complexes in the catalytic enantioselective hydrogenation of 2-methylquinoxaline and observations concerning the effect of different diphosphine/diamine combinations.[61] In most cases, moderate enantioselectivities and excellent conversions were obtained within 20 h with a S/C ratio of 1000. The combination of Xyl-HexaPHEMP (**L33**) and (*S,S*)-DACH (**L34**) afforded the best 73% ee of enantioselectivity (Scheme 38).

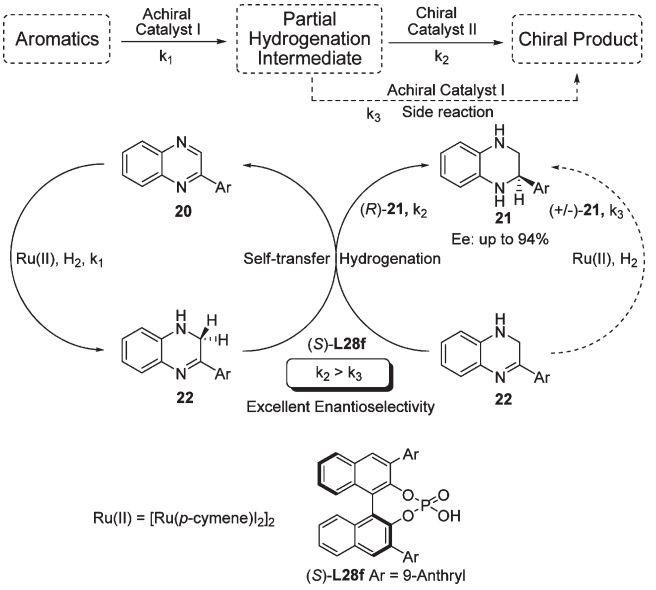
4.2. Organocatalyzed Enantioselective Transfer Hydrogenation

Recently, Rueping extended organocatalytic transfer hydrogenation to the synthesis of tetrahydroquinoxalines.[62]

Scheme 39. Organocatalyzed Asymmetric Transfer Hydrogenation of Quinoxalines 20



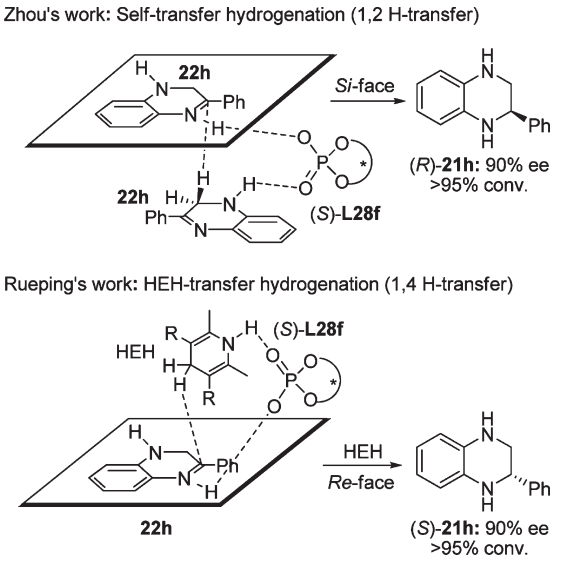
Scheme 40. Metal/Brønsted Acid Relay Catalysis for Asymmetric Reduction of Quinoxalines 20



2-Arylquinoxalines are activated with the help of catalytic amounts of BINOL phosphate (*R*)-**L28f** (10 mol %) for the reaction with Hantzsch ester to provide tetrahydroquinoxalines in good yields (73−98%) together with excellent enantioselectivities (80−98% ee) (Scheme 39).[62] Applying these reaction conditions to alkyl-substituted quinoxalines resulted in lower enantioselectivities. For example, 2-methyltetrahydroquinoxaline was obtained with 64% ee.

On the basis of a serendipitous disproportionation of dihydroquinoxaline **22**, Zhou and co-workers have successfully developed an efficient transition metal/Brønsted acid relay catalysis system for highly enantioselective hydrogenation of quinoxalines through convergent asymmetric disproportionation of dihydroquinoxalines with up to 94% ee.[63] The hydrogenation of quinoxalines **20** first generates dihydroquinoxalines **22** with ruthenium(II) as the catalyst (Scheme 40). Subsequently, the intermediates **22** undergo self-transfer hydrogenation to deliver primary starting materials **20** and final products **21** in the presence of Brønsted acid (*S*)-**L28f**. The detection of intermediate **22h** (Ar = Ph) in the hydrogenation of **20h** without the addition of Brønsted acid (*S*)-**L28f** suggests that the first hydrogenation process catalyzed by ruthenium(II) is the

Scheme 41. The Origin of Enantioreversal in the Asymmetric Reduction of Quinoxalines Resulted from Different Hydride Transfer Paths



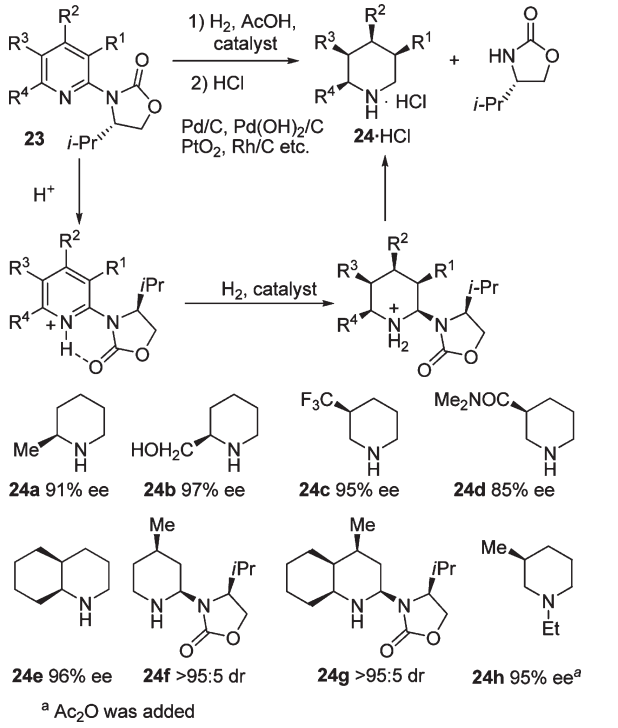
rate-determining step. Therefore, the excellent enantioselectivities observed in this transformation are attributed to that the reaction rate of this principal reaction k_2 is faster than that of the undesired side reaction k_3 ($k_2 > k_3$) (Scheme 40).

The origin of enantioreversal in the asymmetric reduction of quinoxalines can be explained by the stereochemical model as illustrated in Scheme 41.[63] For convergent disproportionation of dihydroquinoxalines, the hydrogenation of **20h** first delivers intermediate 3,4-dihydroquinoxaline **22h**, which subsequently interacts with chiral phosphoric acid (*S*)-**L28f** through two hydrogen bonds (Scheme 41). These two hydrogen bonds with the phosphate and the effect of steric hindrance build up the "three-point contact model" that determines the stereoselectivity in the disproportionation of 3,4-dihydroquinoxaline **22h**. In the pure organocatalytic process, **22h**/(*S*)-**L28f**/HEH form another "three-point contact model", leading to *Re*-face reduction based on Goodman and Himo's calculation (Scheme 41).[63] The reversal of enantioselectivity perhaps lies in the different steric demand between the 1,2-hydride transfer pathway in the self-transfer hydrogenation of **22h** and the 1,4-hydride transfer pathway using HEH (Scheme 41). DFT calculations based on B3LYP/6-31G** level were carried out to validate this proposal.[63]

5. CATALYTIC ASYMMETRIC HYDROGENATION OF PYRIDINE DERIVATIVES

Chiral piperidines are ubiquitous substructures in natural alkaloids and many biologically relevant molecules.[64] Among the numerous accessibilities, asymmetric hydrogenation of pyridine derivatives undoubtedly is the most direct and effective approach to obtain optically active piperidines. However, until now, there are only limited reports about hydrogenation of pyridine derivatives. From all of the reports, two main hydrogenation approaches were used to get chiral piperidines: the diastereoselective hydrogenation of a chiral precursor and the enantioselective hydrogenation of a prochiral substrate with a chiral catalyst. For the later one, the catalyst can be organometallic complexes or organic compounds.

Scheme 42. Diastereoselective Hydrogenation of Pyridines 23 with $Pd(OH)_2/C$



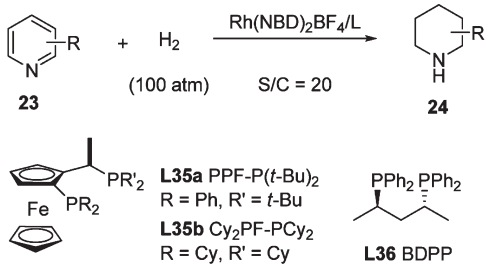
5.1. Catalytic Diastereoselective Hydrogenation

In 2000, Hegedus and co-workers reported the hydrogenation of nicotinic acid grafted to proline ester over supported metallic catalysts (Pd/C, Pt/C, Ru/C, Rh/C).[65] Using Pd/C (10%) as the catalyst, they claimed a de up to 94% was obtained for the hydrogenation of *N*-nicotinoyl-(*S*)-proline methyl ester in their original paper (10 atm H_2, 98 °C, MeOH).[65] Later, they agreed that this de was not reproducible, and the maximum de they can reach was 30%. Besson's group described the diastereoselective hydrogenation of methyl-2-nicotinic acid bonded to several optically pure auxiliaries in the presence of supported metallic catalysts. After the screening of several reaction parameters, up to 35% de was achieved when (*R*)-pantolactone was used as the chiral auxiliary (50 atm H_2, room temperature).[66] In 2003, Pinel and co-workers investigated the diastereoselective hydrogenation of 2-methyl nicotinic acid covalently bound to proline ester or pyroglutamic ester over supported metallic catalyst.[67] However, low diastereoselectivity (11−27% de) was obtained either using proline ester or using pyroglutamic ester as the chiral auxiliary.

Using a chiral oxazolidinone as the auxiliary, Glorius and co-workers reported a highly efficient diastereoselective hydrogenation of *N*-(2-pyridyl)-oxazolidinones **23** by using $Pd(OH)_2/C$ as the catalyst (Scheme 42).[68] Using this catalytic system, under a hydrogenation pressure of 100 atm, a series of mono- or multi-substituted pyridines were hydrogenated to piperidines in high yields and excellent enantioselectivities. More importantly, this transformation unites highly selective chirality transfer and nondestructive and traceless cleavage of the chiral auxiliary in one reaction. The addition of acid in this transformation is necessary. It not only activates the pyridine for hydrogenation, but also suppresses the product piperidine to poison the catalyst. The high diastereoselectivity is ascribed to strong hydrogen

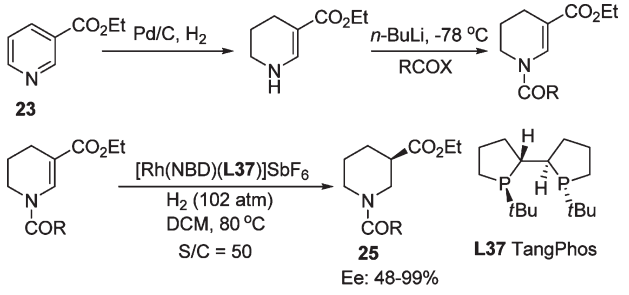
dx.doi.org/10.1021/cr200328h |*Chem. Rev.* 2012, 112, 2557–2590

Scheme 43. Rhodium-Catalyzed Asymmetric Hydrogenation of Pyridines 23



R	Ligand	Solvent	Yield (%)	Ee (%)
2-CO_2H	**L35a**	MeOH	100	25
2-CO_2Et	**L8a**	EtOH	96	25
3-CO_2H	**L35b**	MeOH	8	17
3-CO_2Et	**L36**	EtOH	45	17

Scheme 44. Rhodium-Catalyzed Indirectly Asymmetric Hydrogenation of Pyridines 23



	R	Ee (%)		R	Ee (%)
25a	Me	86	**25d**	MeO	91
25b	Ph	66	**25e**	BnO	90
25c	*t*-Bu	48	**25f**	*t*-BuO	>99

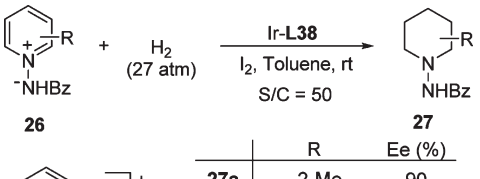
bonding between the pyridinium and oxazolidinone moiety in acetic acid.

5.2. Transition Metal-Catalyzed Enantioselective Hydrogenation

5.2.1. Rh-Catalyzed Asymmetric Hydrogenation. In 2000, Studer and co-workers investigated the asymmetric hydrogenation of 2- or 3-substituted pyridine derivatives **23** by using $Rh(NBD)_2BF_4$/diphosphine as the catalyst (Scheme 43).[69] To improve the enantioselectivity, a variety of chiral ligands, solvents, and additives were screened. However, only low enantioselectivities (up to 25%) were obtained. In this catalytic system, high H_2 pressure (100 atm), temperature (60 °C), and 5 mol % catalyst loading were needed to get reasonable conversion.

In 2008, Zhang, Lei, and co-workers reported an indirectly enantioselective hydrogenation of 3-substituted pyridine derivatives (Scheme 44).[70] Partial hydrogenation of 3-substituted nicotinates with Pd/C gave tetrahydropyridines, followed by *N*-protection with RCOX, and then enantioselective homogeneous hydrogenation using Rh(NBD)(TangPhos (**L37**))SbF_6 as the catalyst gave complete hydrogenation piperidines. The *N*-protecting group has a great influence on the enantioselectivity

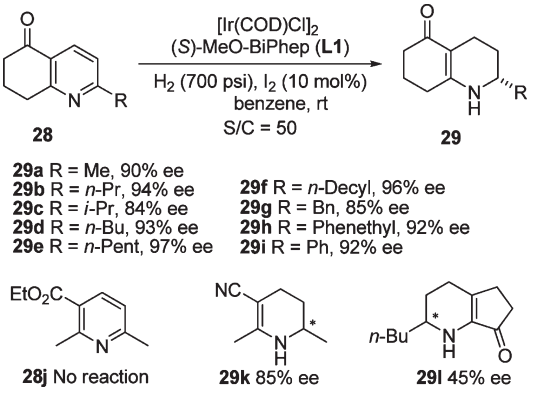
Scheme 45. Iridium-Catalyzed Asymmetric Hydrogenation of *N*-Benzoyliminopyridinium Ylides 26



	R	Ee (%)
27a	2-Me	90
27b	2-*n*-Pr	84
27c	2-Bn	58
27d	2-$(CH_2)_3OBn$	88
27e	2,3-Me_2	54
27f	2,5-Me_2	86/84[a]

[a] dr = 57/43

Scheme 46. Iridium-Catalyzed Asymmetric Hydrogenation of 7,8-Dihydroquinolin-5(6*H*)-ones 28



of the product. When carbamates were employed as the protecting groups, enantioselectivities were high, especially with the Boc protecting group giving as high as 99% ee. Nevertheless, to get practical conversion, high H_2 pressure (102 atm) and temperature (80 °C) were necessary.

5.2.2. Ir-Catalyzed Asymmetric Hydrogenation. In 2005, Charette and co-workers developed an asymmetric hydrogenation of pyridine derivatives by using an activated *N*-benzoyliminopyridinium ylides **26** as the substrates.[71] A broad screening of the different ligands and other reaction conditions revealed that cationic iridium complex of phosphinooxazoline (**L38**), with tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BAr_F) as the counterion, gave the highest enantioselectivities. The use of a catalytic amount of iodine was vital to achieve high yields, which may play an activator role for the Ir catalyst. It was well-suited for the asymmetric hydrogenation of 2-substituted *N*-benzoyliminopyridinium ylides. The products were obtained with 54−90% ee at room temperature under 27 atm of H_2 (Scheme 45). The obtained hydrogenation adducts can be converted to the corresponding piperidine derivatives with Raney nickel or lithium in ammonia to cleave the N−N bond.

In 2008, Zhou and co-workers found that the $[Ir(COD)Cl]_2$/(*S*)-MeO-BiPhep (**L1**)/I_2 catalyst system, which has been used effectively for asymmetric hydrogenation of quinolines,[10,14] is also effective for enantioselective hydrogenation of pyridine derivatives.[72] Under the optimized conditions, a variety of 2-alkyl and 2-phenyl substituted 7,8-dihydro-quinolin-5(6*H*)-ones (**28**)

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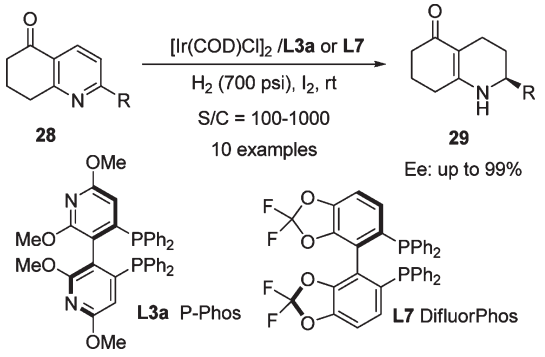
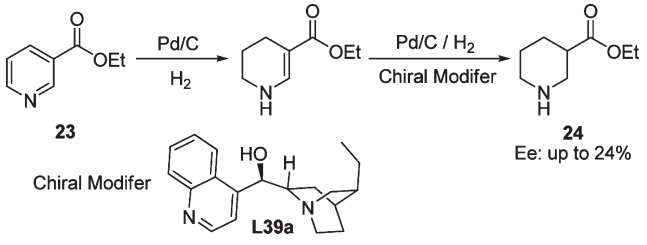
Scheme 47. Highly Active Iridium Complexes for Asymmetric Hydrogenation of 7,8-Dihydroquinolin-5(6*H*)-ones 28



Scheme 48. Heterogeneous Hydrogenation with Pd/C Modified by 10,11-Dihydrocinchonidine L39a

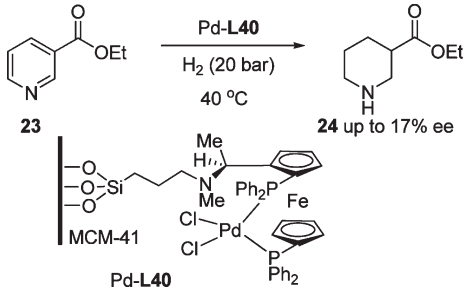


were hydrogenated to hexahydroquinolinones with good yields and excellent enantioselectivities (84−97% ee) (Scheme 46). Nevertheless, this catalyst system has no catalytic activity on acyclic trisubstituted substrate bearing ester at the 3-position (**28j**). For the 2,6-dimethylpyridine-3-carbonitrile (**28k**), low conversion of 21% and 85% ee were obtained. In contrast, substrates with acyl group at the 2-position (**28l**) can be hydrogenated with full conversion but with low ee.[72]

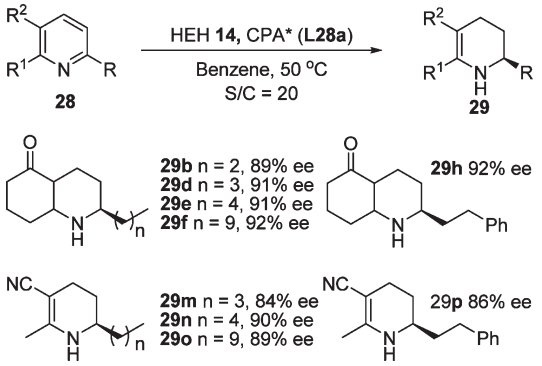
Xu and co-workers found that iridium complexes of **L3a** and **L7** were highly effective catalysts for asymmetric hydrogenation of activated pyridines **28** with up to 99% ee value and S/C ratio up to 1000 (Scheme 47).[22,25] It was found that the amount of iodine is the key issue for attaining both high activity and enantioselectivity. In contrast to asymmetric hydrogenation of quinolines, increasing the amount of iodine favored high activity and enantioselectivity for both cases (20 mol % for **L3a**, 15 mol % for **L7**).

5.2.3. Heterogeneous Asymmetric Hydrogenation. With chiral modifiers, heterogeneous asymmetric hydrogenation of pyridines was also realized.[73] In 1999, Studer and co-workers describes a two-step approach for the preparation of chiral piperidines starting with the corresponding pyridines (Scheme 48).[73a] In the first step, the starting material was converted to the 1,4,5,6-tetrahydro derivative with Pd/C. The hydrogenation of this intermediate was then catalyzed with 10,11-dihydrocinchonidine (**L39a**)-modified noble metal catalysts. However, both yield and enantioselectivity were low even after the optimization of the metal, support, solvent, and modifier concentration. Finally, with a chirally modified Pd/C catalyst, a significant ee (24%) was attained with hydrogenation of pyridine derivatives.

Scheme 49. Chiral Pd Catalyst Anchored within MCM-41



Scheme 50. Brønsted Acid-Catalyzed Enantioselective Reduction of Pyridines 28



In 2000, Thomas and Johnson reported the direct hydrogenation of ethyl nicotinate to ethyl nipecotinate using a heterogeneous chiral palladium catalyst derived from ferrocene-based diphophine ligand and anchored within MCM-41 (Pd-**L40**) (Scheme 49).[74] The catalysis was performed under mild conditions (20 atm H_2, 40 °C) and resulted in the product with 17% ee and 50% conversion.

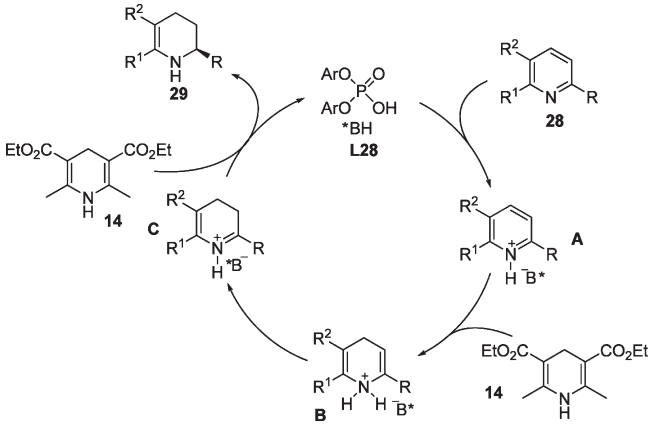
5.3. Organocatalyzed Enantioselective Transfer Hydrogenation

Recently, Rueping and co-workers reported the first example of asymmetric organocatalytic transfer hydrogenation of trisubstituted pyridine using Hantzsch esters (**14**) as hydrogen sources (Scheme 50).[75] The success of this asymmetric transfer hydrogenation was attributed to the presence of the strong electron-withdrawing substituents at the 3-position of pyridines. Excellent enantioselectivities (89−92%) and moderate to good yields (66−84%) were obtained in the reduction of 7,8-dihydroquinolin-5(6*H*)-ones **28**. For 2,6-disubstituted 3-carbonitrile pyridines (**28m**−**o**), a slight decrease of ee (84−90%) was observed.

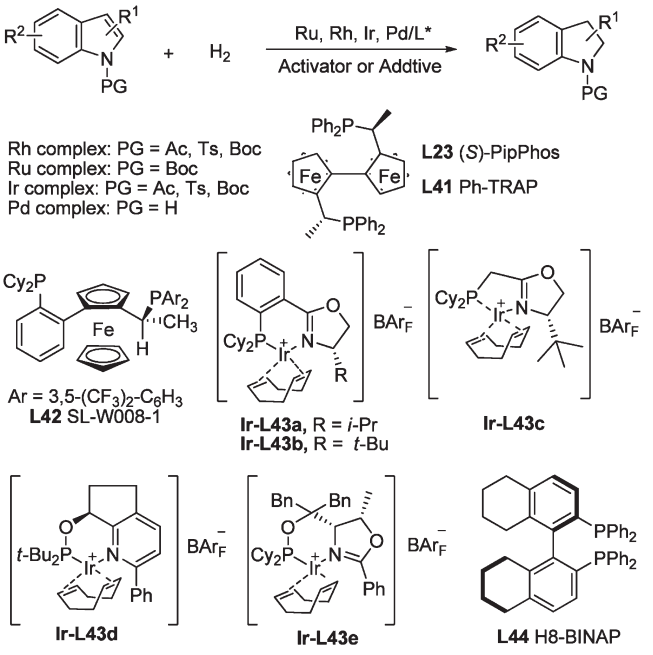
A proposed mechanism for this asymmetric transfer hydrogenation of trisubstituted pyridines is depicted in Scheme 51.[75] First, the pyridine **28** is activated by Brønsted acid **L28** through protonation and gives the iminium ion **A**, which subsequently undergoes hydride transfer from Hantzsch ester to deliver intermediate **B**. The iminium ion **C** is formed through Brønsted acid-promoted isomerization of **B**. The final product tetrahydropyridines **29** is obtained through a second hydride transfer process, which simultaneously regenerates Brønsted acid **L28** for the next catalytic cycle.

dx.doi.org/10.1021/cr200328h |*Chem. Rev.* 2012, 112, 2557–2590

Scheme 51. Mechanistic Proposal for Enantioselective Organocatalytic Reduction of Pyridines



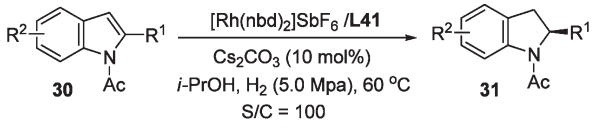
Scheme 52. Transition Metal-Catalyzed Asymmetric Hydrogenation of Indoles

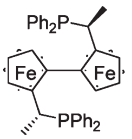


6. CATALYTIC ASYMMETRIC HYDROGENATION OF INDOLE DERIVATIVES

The asymmetric hydrogenation of the readily available indoles offers a facile access to chiral indolines, which are ubiquitous structural motifs in naturally occurring alkaloids and many biologically active molecules.[76] Since the first asymmetric hydrogenation of indoles with homogeneous rhodium complex appeared in 2000, some other catalytic systems such as ruthenium, iridium, and palladium were introduced successively (Scheme 52). Bisphosphine ligands were the commonly used ligands in these catalytic systems; other types of ligands including monodentate phosphoramidite and *P,N*-ligands were also introduced. For these successful examples, activation strategies were employed. In most of the cases, the indole substrates must bear an electron-withdrawing protecting group, such as Ac, Ts, or Boc on the nitrogen atom and with a catalytic amount of base Cs_2CO_3 or Et_3N as additive. The protecting group plays two roles: first, it acts as a secondary coordinating group; second, it avoids the catalyst deactivation and/or poison by nitrogen atom. The base additive was supposed to activate the catalyst for deprotonating from a cationic $Rh(III)H_2$ complex to generate a neutral active Rh(I)H complex. Another activation strategy was developed with a stoichiometric amount of strong Brønsted acid as activator for substrates, with which a series of *N*-unprotected indoles were hydrogenated smoothly.

Scheme 53. Rh-Catalyzed Asymmetric Hydrogenation of *N*-Ac Protected 2-Substituted Indoles 30





	R^1	R^2	Ee (%)
31a	*n*-Bu	H	94
31b	*i*-Bu	H	91
31c	Ph	H	87
31d	CO_2Me	H	95
31e	*n*-Bu	5-Me	94
31f	*n*-Bu	5-CF_3	92
31g	*n*-Bu	6-CF_3	92
31h	*n*-Bu	6-MeO	94

6.1. Rh-Catalyzed Asymmetric Hydrogenation

In 2000, Ito and Kuwano et al. employed homogeneous rhodium catalyst to realize the highly enantioselective hydrogenation of *N*-protected indoles.[77] The reaction was carried out in *i*-PrOH at 60 °C under 50 atm of H_2 with $[Rh(nbd)_2]SbF_6$/Ph-TRAP (**L41**) and 10 mol % of base Cs_2CO_3 or Et_3N as additive. Various *N*-acetylindoles **30** bearing an alkyl, aryl, or ester group at the 2-position were hydrogenated smoothly, and up to 95% ee was obtained (Scheme 53). In this catalytic system, *trans*-chelating bisphosphine ligand **L41** was crucial for high enantioselectivity, and other commercially available bisphosphine ligands gave almost racemic products. It was also found that base additive was the other key factor for both reactivity and enantioselectivity.

The effect of the protective group on the nitrogen atom was investigated, and it was found that when *N*-Boc protected substrate was applied in this catalytic system, the reaction occurred smoothly with product of slightly low enantiomeric excess (78% ee).[77] *N*-Ac protected 3-substituted indole was also tested but with undesirable alcoholysis to unprotected indole as the main product. These results provided the information that the protective group is pivotal for both reactivity and enantioselectivity, and unprotected simple indoles could not be hydrogenated under the current catalytic system.[77]

On the basis of the above findings, in 2004, the same group disclosed that *N*-Ts protected 3-substituted indoles were also hydrogenated with both high activity and enantioselectivity using Rh/Ph-TRAP (**L41**) complex as catalyst.[78] The substituent at the 3-position could be alkyl, phenyl, and functional alkyl chains, and up to 98% ee was obtained (Scheme 54).

Since the pioneering work reported, several other groups devoted their attention to the enantioselective hydrogenation of *N*-protected indoles. In 2010, the Agbossou-Niedercorn group compared the performance of a series of commercially available

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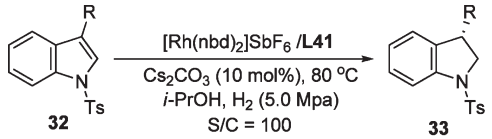
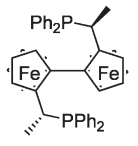
Scheme 54. Asymmetric Hydrogenation of *N*-Ts Protected 3-Substituted Indoles 32





L41 Ph-TRAP

	R	Ee (%)
33a	Me	98
33b	*i*-Pr	97
33c	Ph	96
33d	CH_2CH_2OTBS	98
33e	$CH_2CH_2CO_2t$-Bu	97
33f	CH_2CH_2NHBoc	95

chiral bisphosphine ligands in the hydrogenation of *N*-Boc protected indole-2-carboxylate.[79] It was found that Walphos-type ligands gave the best results with readily accessible $[Rh(cod)(OH)]_2$ as metal precursor, and up to 77% ee was obtained with **L42** (Scheme 52). Monodentate phosphoramidite (*S*)-PipPhos (**L23**) was also successfully applied in asymmetric hydrogenation of various *N*-protected 2-substituted indoles by Feringa and co-workers with $[Rh(cod)_2]BF_4$ as metal precursor (Scheme 52).[80] Full conversion and up to 74% ee were obtained for methyl *N*-acetylindole-2-carboxylate.

6.2. Ru-Catalyzed Asymmetric Hydrogenation

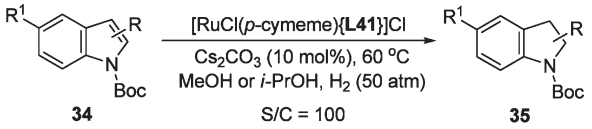
In general, *tert*-butyloxycarbonyl (Boc) was accepted both as a readily attached and detached protective group and found extensive applications in organic synthesis. Thus, the asymmetric hydrogenation of *N*-Boc-protected indoles was considered to be very attractive. Chiral ruthenium catalysts were then found to be effective for this transformation.[81]

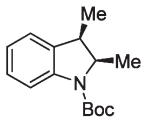
In 2006, Kuwano group employed Ru/Ph-TRAP (**L41**) catalyst to realize the asymmetric hydrogenation of various *N*-Boc protected indoles **34**.[81] In the earlier study, a variety of metal precursors including rhodium, iridium, and ruthenium were examined. Rhodium catalyst showed high activity but with lower enantioselectivity. Iridium catalyst gave both low conversion and enantioselectivity. In contrast, ruthenium catalysts with $[RuCl_2(p\text{-cymene})]_2$, $[RuCl_2(benzene)]_2$, or Ru(η^3-2-methylallyl)$_2$(COD) as precursors all gave high activities and enantioselectivities. The preformed catalyst was supposed to be [RuCl(*p*-cymeme)-{(*S*,*S*)-(*R*,*R*)-Ph-TRAP}]Cl, which exhibited the same level of catalytic activity and enantioselectivity with catalyst generated in situ by $[RuCl_2(p\text{-cymene})]_2$ and (*S*,*S*)-(*R*,*R*)-Ph-TRAP (**L41**). With [RuCl(*p*-cymeme){(*S*,*S*)-(*R*,*R*)-Ph-TRAP}]Cl as catalyst, a series of *N*-Boc protected 2-substituted indoles as well as 3-substituted indoles were hydrogenated to the corresponding indolines with excellent enantioselectivity (Scheme 55, 87–95% ee).[81] Interestingly, the facial selectivity for these two kinds of substituted indoles is opposite. The catalytic system was also suitable for *N*-Boc-2,3-dimethylindole (**34k**); in this case, the product was *cis*-2,3-dimethylindoline (**35k**) with 50% yield and moderate 65% ee.[81] The enantiomeric excess was improved to 72% when using the Ph-TRAP-ruthenium catalyst generated in situ from Ru(η^3-2-methylallyl)$_2$(cod).

6.3. Ir-Catalyzed Asymmetric Hydrogenation

Although iridium complex was extensively applied in the asymmetric hydrogenation of aromatic compounds, quinolines,[10,14] its successful application in the asymmetric hydrogenation of indoles

Scheme 55. Ru-Catalyzed Asymmetric Hydrogenation of *N*-Boc Protected Indoles 34



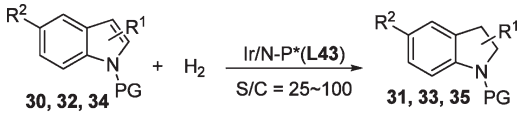


35k 72% ee[a]

[a] Ru(η^3-2-methylallyl)$_2$(cod) as metal precursor

	R	R^1	Ee (%)
35a	2-Me	H	95
35b	2-Me	MeO	91
35c	2-Me	F	90
35d	2-*n*-Bu	H	92
35e	2-Cy	H	87
35f	2-Ph	H	95
35g	2-*p*-FPh	H	93
35h	2-CO_2Me	H	90
35i	3-Me	H	87
35j	3-Ph	H	94

Scheme 56. Ir-Catalyzed Asymmetric Hydrogenation of *N*-Protected Indoles



PG = Boc, Ts, Ac
R^1 = Me, Ph, CO_2Et
R^2 = MeO, Me, F

Ee: up to 99%

was not achieved until 2010 by Pfaltz and co-workers with the employment of a series of *P*,*N*-ligands (Scheme 56).[82]

Initially, Pfaltz and co-workers started with the asymmetric hydrogenation of challenging substrates unprotected 2-methyl and 2-phenyl indoles. It showed that this kind of substrates displayed moderate activity and very low enantioselectivity.[82] After methylation of the nitrogen atom, the conversion was improved but with the sacrifice of enantioselectivity. The addition of various additives including bases led to even worse results. They then turned their attention to various *N*-protected indoles, which have been successfully hydrogenated with rhodium and ruthenium catalysts.[77−81] It was found that the protecting group influenced both activities and enantioselectivities; with the proper combination of protecting group and the chiral iridium catalyst, full conversion and excellent enantiomeric excesses could be obtained for a series of 2- or 3-substituted indoles (up to >99% ee).[82]

6.4. Pd-Catalyzed Asymmetric Hydrogenation

Homogenous palladium catalysts have been successfully applied in the asymmetric hydrogenation of imines, ketones, and olefins over the past few years.[83] In 2010, these catalysts were also successfully applied in the asymmetric hydrogenation of heteroaromatic compounds, simple indoles, by Zhou and co-workers.[84] With a stoichiometric amount of strong Brønsted acid as activator, a series of *N*-unprotected indoles were hydrogenated to the corresponding indolines. This was the first successful example for the asymmetric hydrogenation of *N*-unprotected indoles, and up to 96% ee was obtained.[84]

It is well-known that the carbon−carbon double bond of simple indoles can be protonated by a strong Brønsted acid at the

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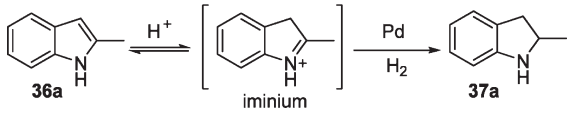
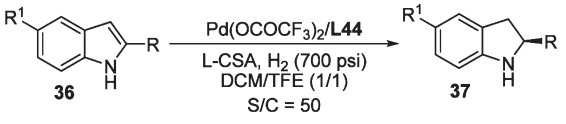
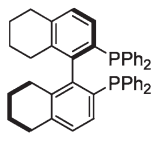
Scheme 57. Activation of Indoles with a Brønsted Acid



Scheme 58. Pd-Catalyzed Asymmetric Hydrogenation of *N*-Unprotected Indoles 36

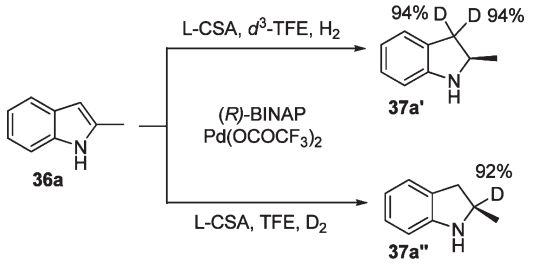


	R	R^1	Ee (%)
37a	Me	H	91
37b	*n*-Bu	H	93
37c	*n*-Pentyl	H	92
37d	Cy	H	95
37e	*c*-Pentyl	H	95
37f	Bn	H	95
37g	Me	F	88
37h	Me	Me	84
37i	2-$MeC_6H_4CH_2$	H	94
37j	3-$MeC_6H_4CH_2$	H	94
37k	4-$MeC_6H_4CH_2$	H	93
37l	1-NaphthylCH$_2$	H	96
37m	Phenethyl	H	93



L44
(*R*)-H8-BINAP

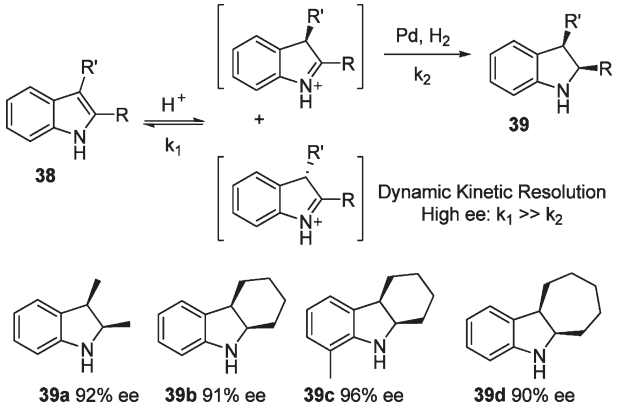
Scheme 59. Isotopic Labeling Experiments Using D_2 and d_3-TFE



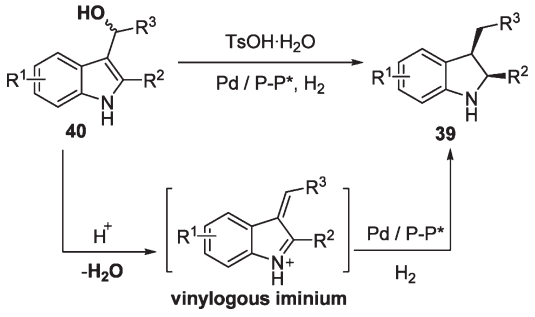
3-position and in situ form an active iminium salt intermediate for which the aromaticity was partially destroyed and prone to be hydrogenated (Scheme 57).[85] Homogenous palladium catalyst was found to be effective for the asymmetric hydrogenation of imines.[83] It could also tolerate strong acid and was found to be the proper catalyst for this transformation. Complexes of Pd-$(OCOCF_3)_2$ with various axially chiral bisphosphine ligands exhibited excellent performance, and (*R*)-H8-BINAP (**L44**) was demonstrated to be the best choice in terms of enantioselectivity and reactivity.[84] The reaction was carried out in a mixture solvent of dichloromethane and trifluoroethanol (DCM/TFE = 1/1) with L-camphorsulfonic acid (L-CSA) as the activator.

Under the optimal conditions, a variety of 2-substituted indoles **36** were hydrogenated to the corresponding indolines **37** with high yields and 84−96% ee (Scheme 58). To probe the mechanism information, two isotopic labeling experiments were conducted.[84] The reactions were carried out in deuterated TFE with hydrogen and in TFE with D_2, respectively. Two deuterium

Scheme 60. Hydrogenation Mechanism of 2,3-Disubstituted Indoles 38



Scheme 61. Dehydration Triggered Dearomatization of 3-(α-Hydroxyalkyl)indoles for Hydrogenation



atoms were incorporated to the 3-position of the indoline (**37a′**) for the former condition, which suggested that a reversible process of protonation and deprotonation existed and the equilibrium is faster than hydrogenation. 2-*deuterio*-2-Methylindoline (**37a″**) with 92% incorporation obtained in the latter case suggested that the indole was hydrogenated through the iminium intermediate activated by Brønsted acid and the indole cannot be hydrogenated in the absence of acid (Scheme 59).[84]

For the asymmetric hydrogenation of 2,3-disubstituted indoles **38**, the process was somewhat complex. Chiral iminium salt formed with protonation at the 3-position and the subsequent hydrogenation was in fact a dynamic kinetic resolution process (Scheme 60).[84] To obtain high enantioselectivity, it should meet the equation of $k_1 \gg k_2$ (k_1, rate of protonation; k_2, rate of hydrogenation), and this was confirmed by the above results. *cis*-2,3-Disubstituted indolines **39** were obtained for both 2,3-fused indoles and simple 2,3-disubstituted indoles with an ee value up to 96%.

Asymmetric hydrogenation of 2,3-disubstituted indoles offers a straightforward access to chiral 2,3-disubstituted indolines but with lack of fast approach to the starting materials. Zhou and co-workers found that various 2,3-disubstituted 3-(α-hydroxyalkyl)indoles **40** could be obtained through a divergent approach starting from the formylation of 2-substituted indoles followed by nucleophilic additions with various Grignard reagents.[86]

These 3-(α-hydroxyalkyl)indoles **40** can readily dehydrate to form vinylogous iminium salts[87] in situ in the presence of

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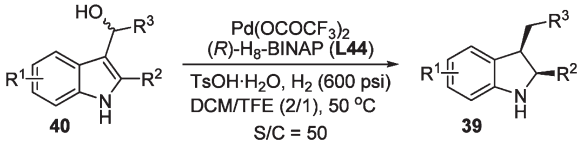
Scheme 62. Asymmetric Hydrogenation of 3-(α-Hydroxyalkyl)indoles 40



	R1	R2	R3	Ee (%)
39e	H	Me	Ph	91
39f	H	Me	4-MeC_6H_4	90
39g	H	Me	3-MeC_6H_4	90
39h	H	Me	2-MeC_6H_4	91
39i	H	Me	4-$MeOC_6H_4$	89
39j	H	Me	4-FC_6H_4	88
39k	H	Me	Cy	94
39l	H	Me	*i*-Pr	94
39m	H	*n*-Bu	Ph	94
39n	H	*n*-Bu	Cy	96
39o	H	Phenethyl	Ph	93
39p	H	Phenethyl	Cy	95
39q	5-F	Me	Ph	85
39r	5-F	Me	Cy	88
39s	7-Me	Me	Ph	97
39t	7-Me	Me	4-MeC_6H_4	96
39u	7-Me	Me	3-MeC_6H_4	95
39v	7-Me	Me	2-MeC_6H_4	94
39w	7-Me	Me	Cy	97
39x	7-Me	Me	*i*-Pr	97

Brønsted acid ($TsOH \cdot H_2O$, in this case), and the aromaticity is partially destroyed, thus facilitating hydrogenation (Scheme 61). It was found that with $Pd(OCOCF_3)_2$/**L44** as catalyst a variety of chiral 2,3-disubstituted indolines **39** were obtained with 85−97% ee (Scheme 62).[86]

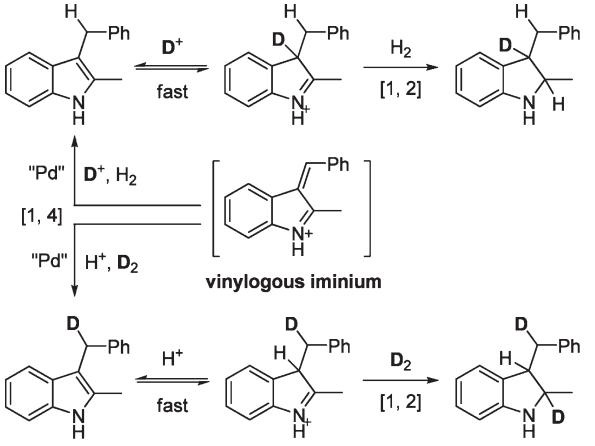
Mechanism studies disclosed that this hydrogenation reaction is driven by Brønsted acid promoting dehydration to form a vinylogous iminium in situ, which is hydrogenated stepwise with first 1,4-hydride addition to form 2,3-disubstituted indole and thus recovers its aromaticity.[86] Subsequently, further hydrogenation of the indole is activated by strong Brønsted acid to form an iminium intermediate in situ, which is hydrogenated via 1,2-hydride addition as disclosed in the previous work (Scheme 63).[84]

Subsequently, Zhou and co-workers found that the above vinylogous iminium salts could be conveniently obtained from readily available 2-substituted indoles **36** and aldehydes **41** in the presence of Brønsted acid with Friedel−Crafts/dehydration reaction sequences (Scheme 64).[88]

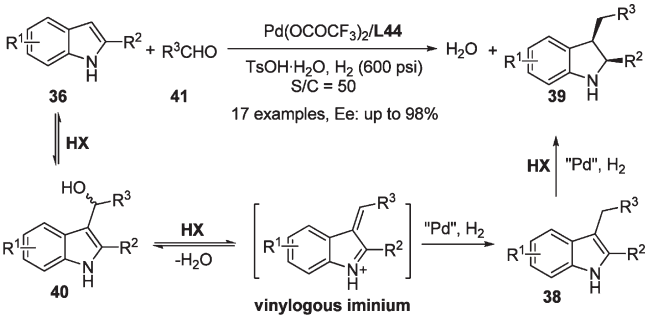
With the combination of palladium catalyst and Brønsted acid under hydrogen atmosphere, an efficient tandem reaction through consecutive Brønsted acid/Pd complex offers a fast access to chiral 2,3-disubstituted indolines **39**. Commercially available starting materials (2-substituted indoles and aldehydes), simple operation procedures, high yields, and stereoselectivity (up to 98% ee) made this method very useful for rapid and divergent synthesis of chiral 2,3-disubstituted indolines in one single operation (Scheme 64).

To sum, several transition metal catalysts have been developed for the highly enantioselective hydrogenation of indoles, which offer straight and powerful accesses to enantiopure indolines as shown in Table 2.

Scheme 63. Isotopic Labeling Experiments for Mechanism Studies



Scheme 64. Tandem Reactions to Chiral 2,3-Disubstituted Indolines 39



7. CATALYTIC ASYMMETRIC HYDROGENATION OF PYRROLE DERIVATIVES

In 2001, Tungler and co-workers developed the heterogeneous asymmetric hydrogenation of a pyrrole modified with chiral auxiliary with 95% de (Scheme 65).[89] Nevertheless, it was not until very recently that the homogeneous enantioselective version of this transformation has been achieved with both ruthenium and palladium catalysts.

7.1. Ru-Catalyzed Asymmetric Hydrogenation

The pioneering work for catalytic asymmetric hydrogenation of pyrroles was reported by Kuwano and co-workers in 2008.[90] They developed a highly enantioselective hydrogenation of *N*-Boc protected 2,3,5-trisubstituted pyrroles with the chiral ruthenium complex.

They started with the asymmetric hydrogenation of methyl pyrrole-2-carboxylate (**44a**) with the previously reported catalytic system for *N*-Boc indoles,[81] with the chiral ruthenium catalyst (1%) generated in situ from Ru(η^3-methallyl)$_2$(cod) and (*S*,*S*)-(*R*,*R*)-Ph-TRAP (**L41**). The reaction occurred smoothly to afford the desired product (*S*)-*N*-Boc-proline methyl ester (**45a**) with 73% ee. To obtain high enantioselectivity, the effect of base additive as well as ligand was examined but without satisfactory results. Considering the similarity of 2,3,5-trisubstituted *N*-Boc-pyrroles and 2-substituted *N*-Boc-indoles, they directed their attention to these substrates. In these cases, chiral pyrrolidines

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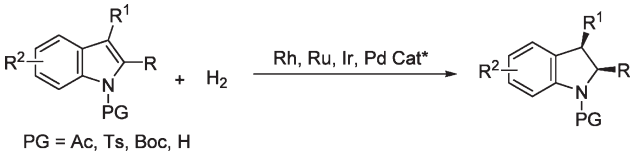
Table 2. Asymmetric Hydrogenation of Indoles[a]



Substrates		Catalytic Systems	S/C	Ee (%)	References
2-Substituted Indole	Rh	Ph-TRAP/Base/H_2 (PG = Ac, Ts)	100	98	77,78
		Walphos/Cs_2CO_3/H_2 (PG = Boc)	80	85	79
		P*/Cs_2CO_3/H_2 (PG = Ac, Boc)	20	74	80
	Ru	Ph-TRAP/Cs_2CO_3/H_2 (PG = Boc)	100	95	81
	Ir	N-P*/H_2 (PG = Ac, Ts, Boc)	100	99	82
	Pd	P-P*/Brønsted acid/H_2 (PG = H)	50	96	84
3-Substituted Indole	Rh	Ph-TRAP/Cs_2CO_3/H_2 (PG = Ts)	100	98	78
	Ru	Ph-TRAP/Cs_2CO_3/H_2 (PG = Boc)	100	94	81
	Ir	N-P*/H_2 (PG = Ts)	100	98	82
2,3-disubstituted Indole	Ru	Ph-TRAP/Et_3N/H_2 (PG = Boc)	100	72	81
	Pd	P-P*/Brønsted acid/H_2 (PG = H)	50	98	84,86,88

[a] S/C and ee indicate the highest values; Ph-TRAP, 2,2′-bis-[(diphenylphos-phino) ethyl]-1,1′-biferrocene; P*, chiral monopho-sphine ligand; N−P*, chiral bidentate nitrogen phosphine ligand; P−P*, chiral bisphosphine ligand.

(**45**) or 4,5-dihydropyrroles (**46**) were obtained, respectively, regardless of the substituents of the substrates (Scheme 66).[90]

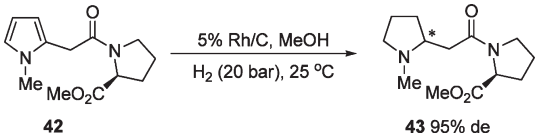
Herein, the hydrogenation proceeds stepwise through 1,2-additions of hydrogen to two C−C double bonds.[90] The less hindered double bond of pyrroles reacts with hydrogen first, followed by saturation of the remaining carbon−carbon double bond of **46**. The stereoselectivity in the additional reduction of **46** is controlled by the chirality at the 5-position. When the hindrance of the remained double bond is too big, it remains unreduced (Scheme 67).

7.2. Pd-Catalyzed Asymmetric Hydrogenation

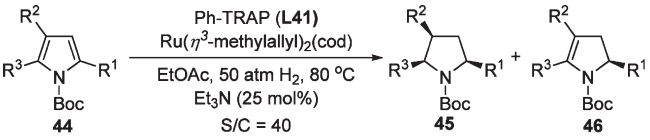
Chiral 1-pyrrolines and related compounds are ubiquitous building blocks in many biological active compounds, and their synthesis has received much attention over the past decades.[91] Among which, asymmetric hydrogenation of simple pyrroles offers the most straightforward access to these molecules. In 2011, Zhou and co-workers realized the first asymmetric hydrogenation of *N*-unprotected 2,5-disubstituted pyrroles **47** using palladium/bisphosphine complex with strong Brønsted acid as activator, and partial hydrogenation product 1-pyrrolines **48** were obtained with up to 92% ee (Scheme 68).[92]

Considering the similarity of indoles and pyrroles, both of which are electron enriched arenes and can be protonated by

Scheme 65. Heterogeneous Asymmetric Hydrogenation of Pyrrole 42

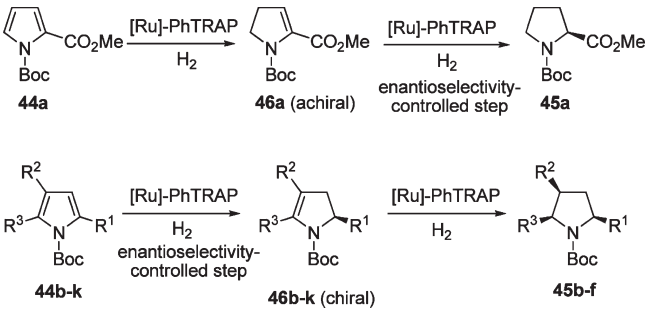


Scheme 66. Ru-Catalyzed Asymmetric Hydrogenation of Pyrroles 44



	R^1	R^2	R^3	45/46	Ee (%)	
44b	Me	Me	CO_2Me	54/46	11 (**45b**)	75 (**46b**)
44c	Me	CO_2Me	Me	98/02	74 (**45c**)	43 (**46c**)
44d	CO_2Me	Me	Me	100/0	96 (**45d**)	-
44e	Me	-$(CH_2)_4$-		16/84	91 (**45e**)	95 (**46e**)
44f	Ph	Me	*n*-Pr	100/0	93 (**45f**)	-
44g	Ph	Ph	Ph	0/100	-	99.7 (**46g**)
44h	4-F-C_6H_4	Ph	Ph	0/100	-	99.3 (**46h**)
44i	4-MeO-C_6H_4	Ph	Ph	0/100	-	98 (**46i**)
44j	Ph	Ph	4-CF_3-C_6H_4	0/100	-	99.6 (**46j**)
44k	Ph	Ph	4-MeO-C_6H_4	0/100	-	99.2 (**46k**)

Scheme 67. Pathway of Asymmetric Hydrogenation of Pyrroles



Brønsted acid, herein the previous strategy for the hydrogenation of the former was employed.[84,86,88] When 2-methyl-5-phenyl-pyrrol (**47a**) were selected as a model substrate, the reaction occurred smoothly, whereas with unexpected partially hydrogenated 5-methy-2-phenyl-1-pyrroline (**48a**) as the sole product and no complete hydrogenation, pyrrolidine was observed in the reaction mixture. A series of enantioenriched 5-alkyl-2-aryl-1-pyrrolines **48** were obtained with optimized conditions under the current catalytic system with 80−92% ee.[92]

The pyrrole can be protonated at both 3- and 4-positions in the presence of strong Brønsted acid (Scheme 69). DFT calculations based on B3LYP/cc-pVTZ(-f)//B3LYP/6-31G** level were carried out to give further insight for the selectivity.[92] The computed bond length alternation suggests that the C=N bond in intermediate **B** is better conjugated with the phenyl group (Figure 10). As a result, **B** is more stable than **A** by

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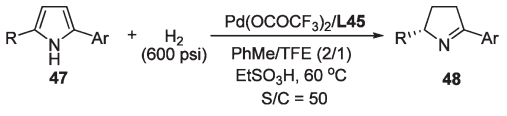
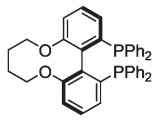
1.4 kcal/mol ($\Delta G°$ in CH_2Cl_2), and the positive charge in **B** is also more delocalized. Palladium hydride species were observed in palladium-catalyzed hydrogenation reactions and strongly suggest that it could be the true active catalyst, and the rate-determined step for the hydrogenation is most probably the hydride transfer from the catalyst to the substrate. Thus, the observed selectivity is understandable. The C=N bond in **A** is more facile for the hydride transfer because its carbon atom is more positive charged than that in **B**. To further validate this proposal, they have studied the hydride transfer reaction from ((*R*)-BINAP)Pd(H)($OCOCF_3$) to **A** and **B**. Indeed, the calculation shows that the hydride transfer barrier for **A** is 27.7 kcal/mol (relative to **47a**) lower than that for **B** by 1.8 kcal/mol.

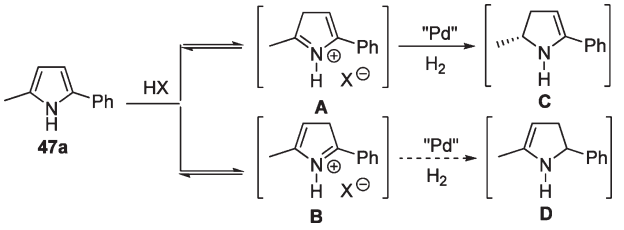
Scheme 68. Pd-Catalyzed Asymmetric Hydrogenation of Simple Pyrroles 47





	R	Ar	Ee (%)
48a	Me	Ph	92
48b	Et	Ph	80
48c	*n*-Pr	Ph	81
48d	*n*-Pentyl	Ph	85
48e	*i*-Bu	Ph	86
48f	$CyCH_2$	Ph	86
48g	Bn	Ph	80
48h	Me	4-MeC_6H_4	81
48i	Me	3-MeC_6H_4	84
48j	Me	2-MeC_6H_4	85
48k	Me	4-$CF_3C_6H_4$	89
48l	Me	4-FC_6H_4	86
48m	Me	3,5-$F_2C_6H_3$	88
48n	Me	1-Naphthyl	90

Scheme 69. Possible Pathways for Hydrogenation of Pyrroles



Therefore, on the basis of the results of the experiments and theoretical calculation, the reaction process was proposed as follows (Scheme 70):[92] simple unprotected pyrrole **47** reacts with a strong Brønsted acid to form the iminium salt by protonation of carbon−carbon double bond, and the aromaticity of pyrrole is destroyed. The in situ formed iminium salt is hydrogenated to give the intermediate enamine, followed by isomerization to a more stable imine **48** in the presence of acid, which survives under the current catalytic system.

Despite the difficulties, such as high resonance energy and sensitivity of the substrates, two effective catalytic systems were developed for the asymmetric hydrogenation of pyrroles. With ruthenium catalyst, chiral 4,5-dihydropyrroles or pyrrolidines were obtained from *N*-Boc protected 2,3,5-trisubstituted pyrroles. Chiral 1-pyrrolines were attained from simple 2,5-disubstituted pyrroles with palladium catalyst. Searching for more effective catalysts and realizing the hydrogenation of other types of substituted pyrroles may be the next objectives.

8. ASYMMETRIC HYDROGENATION OF IMIDAZOLES

Catalytic asymmetric hydrogenation of five-membered aromatic rings containing two or more heteroatoms has remained an unsettled problem for a long time. Recently, Kuwano and coworkers disclosed the first successful catalytic asymmetric hydrogenation of imidazole to optically active imidazolines.[93]

Initially, *N*-Boc-4,5-dimethyl-2-phenylimidazole was selected as a target molecule with regards to its structural similarity to 2,3,5-trisubstituted *N*-Boc-pyrrole. It was frustrating that no reaction occurred with hydrogenation conditions for the latter.[90] Gratifyingly, when *N*-Boc-4-methyl-2-phenylimidazole (**49a**) with no substituent at 5-position was subjected to hydrogenation with Ru/**L41** catalyst, *N*-Boc-imidazoline (*S*)-**50a** with 97% ee

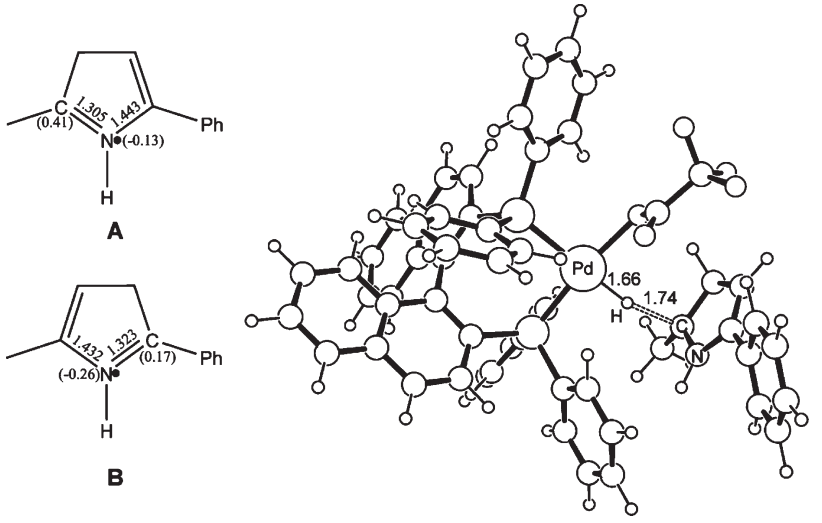


Figure 10. Left: Optimized bond lengths (in angstroms) and charges (in parentheses) for intermediates **A** and **B**. Right: The structure of the transition state for hydride transfer with **A** (bond lengths in angstroms).

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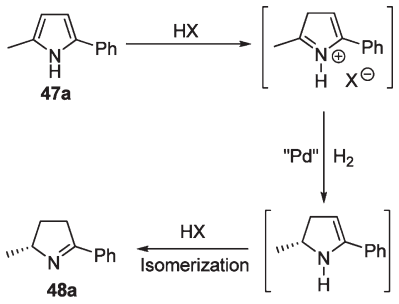
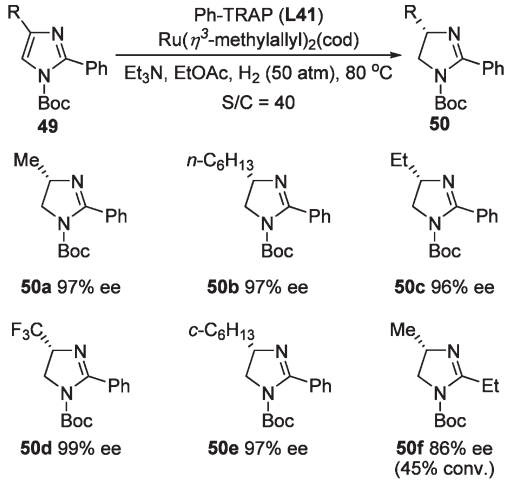
Scheme 70. Process of Pyrrole Hydrogenation



Scheme 71. Ru-Catalyzed Asymmetric Hydrogenation of Imidazoles 49



was obtained without overhydrogenation product observed (Scheme 71).[94]

A series of *N*-Boc-imidazoles **49** bearing alkyl groups of different electronic and steric properties were hydrogenated to the corresponding imidazolines **50** with excellent enantioselectivities (Scheme 71, up to 99% ee).[94] Notably, 2,4-diarylimidazoles were converted to the desired product with less than 15% yield, and replacement of the substituent at 2-position with ethyl (**49f**) resulted in deterioration in activity as well as enantioselectivity (86% ee, 45% conv).

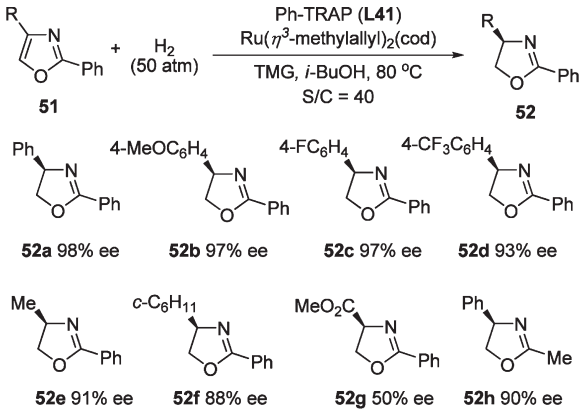
9. ASYMMETRIC HYDROGENATION OF OXAZOLES

Oxazole represents another type of five-membered aromatic compound containing two different heteroatoms, and it was also hydrogenated by the above effective catalytic system developed by Kuwano group to afford the products with high to excellent ee values.[94]

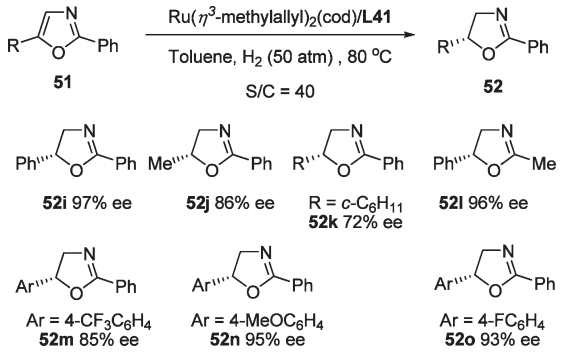
Both 2,4- and 2,5-disubstituted oxazoles **51** were hydrogenated smoothly with the Ru(η^3-methallyl)$_2$(cod) /(*R*,*R*)-(*S*,*S*)-Ph-TRAP(**L41**) complex. The addition of additional base *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) as additive was necessary for fast conversion in some cases.[94]

For 4-substituted 2-phenyloxazoles (**51a**−**h**), variations in reaction conditions barely disturbed the stereoselectivity, but

Scheme 72. Ru-Catalyzed Asymmetric Hydrogenation of 4-Substituted 2-Phenyloxazoles 51a−h



Scheme 73. Ru-Catalyzed Asymmetric Hydrogenation of 5-Substituted 2-Phenyloxazoles 51i−o



solvent affected the catalytic activity of the ruthenium complex, and isobutyl alcohol was found to be the best choice (Scheme 72).[94] TMG was also required for rapid conversion for electron-deficient and 4-alkylated substrates. 4-Carboxylate-substituted substrate (**51g**) could also be hydrogenated but with moderate ee value (50% ee). The asymmetric hydrogenation of 2-methyloxazole (**51h**) proceeded at a rate comparable to that of 2-phenyloxazole but with somewhat lower enantiomeric excess (90% ee).

For 5-substituted 2-phenyloxazoles (**51i**−**o**), the addition of TMG was unnecessary, and in these cases toluene was found to be the best solvent in terms of enantioselectivity (Scheme 73).[94] Prolonged reaction time was needed for electron-withdrawing substituted substrates but without significant deterioration of enantioselectivity. The size of the alkyl substituent on the 5-carbon affected both enantioselectivity and activity, and the *tert*-butyl group obstructed the reaction. In contrast to the hydrogenation of 4-substituted substrate, in this case the 2-methyl-substituted substrate (**51l**) caused low yield of product, while the enantioselectivity was not affected (36% yield, 96% ee).

10. CATALYTIC ASYMMETRIC HYDROGENATION OF FURAN DERIVATIVES

To date, chiral iridium complexes have been successfully introduced to the asymmetric hydrogenation of furans with excellent enantioselectivities; meanwhile, ruthenium and rhodium

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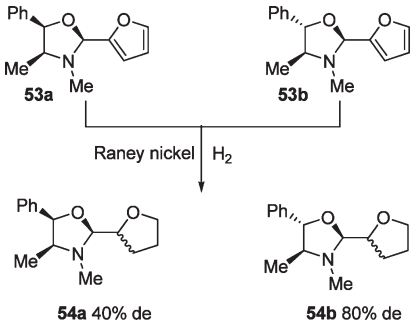
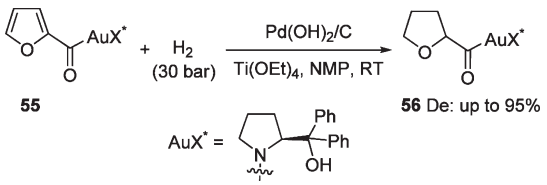
Scheme 74. Oxazolidine as Chiral Auxiliaries



Scheme 75. Pyrrolidinemethanol as Chiral Auxiliaries



catalysts were also tested together, and diastereoselective and heterogeneous-catalyzed furan hydrogenation was also developed recently.

10.1. Catalytic Diastereoselective Hydrogenation

In 1995, Polyak and co-workers reported the diastereoselective hydrogenation of the chiral 2-(2-furyl)-3,4-dimethyl-5-phenyloxazolidines **53** with Raney nickel in the presence of H_2 (Scheme 74).[95] Under the optimized conditions, the hydrogenation of the furan ring occurred, and 40−80% diastereoselectivity was obtained.

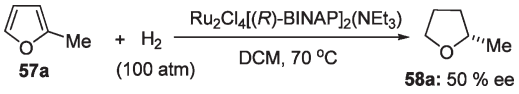
Recently, Börner, Jähnisch, and co-workers investigated the diastereoselective hydrogenation of furan 2-carboxylic acid derivatives modified with chiral auxiliaries on heterogeneous catalyst.[96] Among the various heterogeneous catalysts, $Pd(OH)_2/C$ was proved to be most effective. Chiral auxiliaries, solvents, and additives were optimized to improve the diastereoselectivity. By using (*S*)-α,α-diphenyl-2-pyrrolidinemethanol as the auxiliaries, *N*-methyl-pyrrolidin-2-one (NMP) as the solvent, and the Ti(IV) alkoxides as additives, furan 2-carboxylic acid derivatives **55** can be hydrogenated to tetrahydrofuran derivatives **56** with up to 95% de (Scheme 75).

10.2. Transition Metal-Catalyzed Enantioselective Hydrogenation

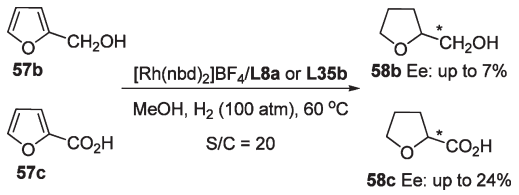
10.2.1. Ru-Catalyzed Asymmetric Hydrogenation. Asymmetric hydrogenation of 2-methylfuran (**57a**) was first reported by Takaya and co-workers using the complex Ru_2Cl_4-[(*R*)-BINAP]$_2$(NEt_3) as the catalyst.[4] Only this furan derivative was investigated, and possibly it is regarded as a functionalized olefin substrate in their studies. To ensure full conversion, the reaction was carried out at 70 °C under 100 atm of H_2, providing the product 2-methyltetrahydrofuran **58a** with 50% ee (Scheme 76).

10.2.2. Rh-Catalyzed Asymmetric Hydrogenation. In addition to investigating the hydrogenation of pyridine derivatives, Studer and co-workers also studied the asymmetric hydrogenation of 2-substituted furans.[69] Although rhodium precursors

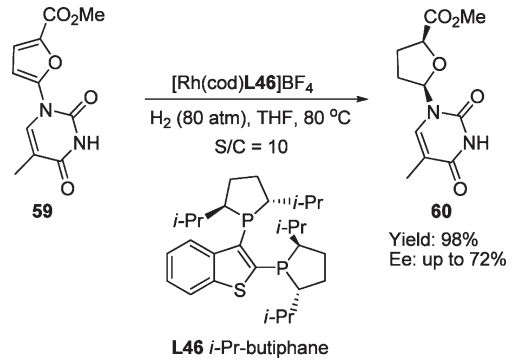
Scheme 76. Ruthenium-Catalyzed Asymmetric Hydrogenation of 2-Methylfuran 57a



Scheme 77. Rhodium-Catalyzed Asymmetric Hydrogenation of Furan Derivatives



Scheme 78. Rhodium Complex-Catalyzed Asymmetric Hydrogenation of Furan Derivative 59



and different bidentate diphosphine ligands were screened, low enantioselectivities (7−24% ee) were obtained. Notably, all of the reactions were carried out using 5 mol % of catalyst at 60 °C under 100 atm of H_2 (Scheme 77).

Albert and co-workers investigated the asymmetric hydrogenation of 5-thyminyl-2-furoate **59** in detail from their practical need.[97] After the screening of metals, ligands, additives, solvents, and other reaction conditions, the combination of cationic $[Rh(COD)_2]BF_4$ and *i*-Pr-butiphane (**L46**) was found to be most effective, yielding the desired *cis*-product **60** with 72% ee and 99% de (Scheme 78). It was noteworthy that high hydrogen pressure (80 atm), high temperature (80 °C), and 10 mol % of catalyst loading were needed to obtain a reasonable yield, and only *cis*-hydrogenation products (de values >99%) were obtained in these experiments.

10.2.3. Ir-Catalyzed Asymmetric Hydrogenation. Chiral iridium complexes based on the *P,N*-ligands were often applied in the hydrogenation of unfunctionalized olefins. During their research works, Pfaltz and co-workers found that pyridine−phosphinite-ligated iridium complexes (with BAr_F as the counterion), which possess bulky electron-rich (t-Bu)$_2$P group, were effective for the asymmetric hydrogenation of simple furans and benzofurans **57**.[98] Iridium complexes Ir-**L43d** (Scheme 52) and Ir-**L43f** were demonstrated to be the most effective catalysts for

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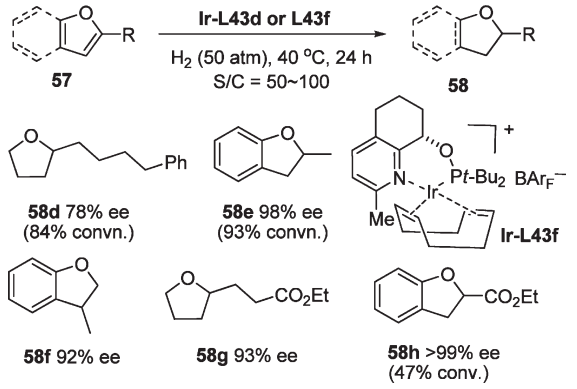
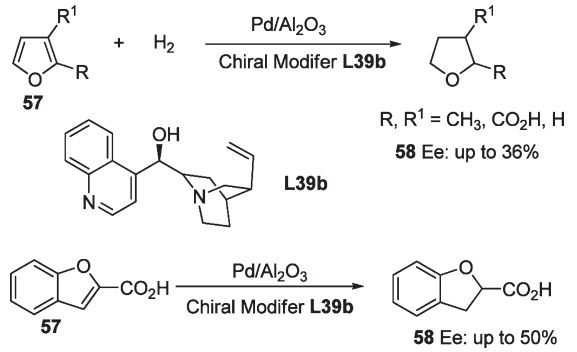
Scheme 79. Iridium-Catalyzed Asymmetric Hydrogenation of Furan Derivatives 57



Scheme 80. Heterogenous Pd-Catalyzed Asymmetric Hydrogenation of Furans 57

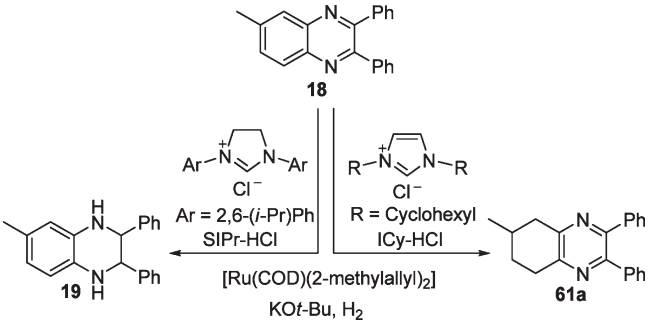


asymmetric hydrogenation of 2-substituted furans and benzofurans, affording the corresponding chiral tetrahydrofuran and dihydrobenzofurans **58** with 78−93% ee and 92−>99% ee, respectively, under 50 or 100 atm of H_2 at 40 °C (Scheme 79). The substituents at the phosphorus atom have an important impact on the reaction activity and the enantioselectivity. Replacement of the *t*-butyl by cyclohexyl group lowers conversion and enantioselectivity.

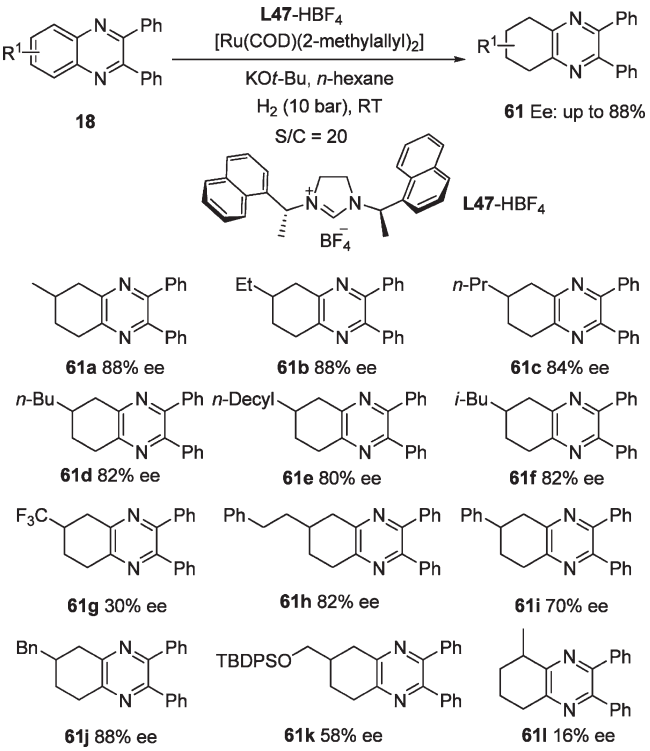
Heterogeneous catalysts were also applied in the asymmetric hydrogenation of furans. In 2003, Baiker and coworkers utilized a cinchonidine-modified 5 wt % Pd/Al_2O_3 catalyst for the enantioselective hydrogenation of furan and benzofuran carboxylic acids (Scheme 80).[99] At room temperature and 30 bar of H_2, this heterogeneous catalyst can hydrogenate furan carboxylic acids, giving tetrahydrofuran-2-carboxylic acid with 22% yield and 36% ee in 2-propanol. If the reaction was carried out in toluene, tetrahydrofuran-2-carboxylic acid was obtained with 95% yield and 32% ee. For the hydrogenation of benzofuran-2-carboxylic acid, 50% ee was obtained at 29% conversion. For the other furan derivatives, very low enantioselectivities were obtained.

Although the asymmetric hydrogenation of furan has achieved some progress, excellent enantioselectivities were obtained only with iridium catalysts (up to 99% ee). In contrast, ruthenium and rhodium catalysts gave poor to moderate ee. Therefore, more effective catalysts need to be developed in this field.

Scheme 81. Ligand-Controlled Regioselective Hydrogenation of Quinoxaline 18



Scheme 82. Ru/NHC-Catalyzed Asymmetric Hydrogenation of Carbocyclic Ring of Quinoxalines 18



11. ASYMMETRIC HYDROGENATION OF CARBOCYCLIC RING OF AROMATIC COMPOUNDS

Asymmetric hydrogenation of arenes is the most challenging subject in asymmetric catalysis due to the strong aromaticity and low coordinating ability of these compounds. At present, some efforts have been tried, but very poor enantioselectivity was obtained. Chaudret[100] and Claver[101] tried to explore the asymmetric hydrogenation of 2-methoxytoluene using ruthenium nanoparticles stabilized with chiral *N*-donor ligands and chiral diphosphite ligands derived from the chiral carbohydrates, respectively, both with poor results. The main reason for these poor results may be the low reactivity of the substrates, and a novel activation strategy still needs to be developed for asymmetric hydrogenation of simple arenes.

For the above reduction of nitrogen-containing bicyclic heteroaromatic compounds, usually the heterocycles were selectively

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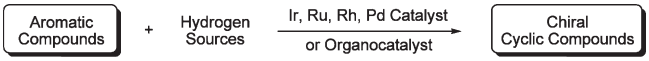
Table 3. Typical Catalytic Systems for Asymmetric Hydrogenation of Heteroarenes and Arenes[a]



Organocatalyst: Chiral Phosphoric Acids
Hydrogen Sources: H_2, Hantzsch Esters, Et_3SiH/H_2O, HCOONa....

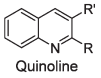
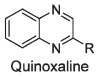
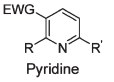
Substrates		Catalytic Systems	S/C	Ee (%)	Scheme/Figure	References
 Quinoline	Ir	P-P*/I_2/H_2	43000	99	Scheme 3-5,8,18 Figure 4-8	10,14-15 21-25,28 30-37
		P-P*/$ClCO_2R$/H_2	100	90	Scheme 11	16
		P-P*/Brønsted acid/H_2	50	95	Scheme 13,17 Figure 8	17,26-27,38
		P-P*/I_2/HEH	50	88	Scheme 14	18
		P-P*/I_2/Et_3SiH, H_2O	50	93	Scheme 16	19
		N-P*/(I_2)/H_2	1000	92	Figure 9	39,41
		S-P*/I_2/H_2	100	82	Figure 9	40
		P*/Brønsted acid/H_2	50	92	Figure 9	42
		N-N*/H_2	1000	99	Scheme 19	43
	Ru	N-N*/H_2	100	99	Scheme 20	45-46
		N-N*/HCO_2H-Et_3N	200	73	Scheme 21	47
	Rh	N-N*/HCO_2Na	100	98	Scheme 22	48
		N-N*/HCO_2H-Et_3N	200	94	-	47
	Pt	PtO_2/H_2 (Diastereoselective)	5 (wt)	>99	Scheme 23	49
	OC	CPA*/HEH	500	99	Scheme 24, 27-29	50-53
 Isoquinoline	Ir	P-P*/$ClCO_2R$/H_2	100	83	Scheme 30	16
 Quinoxaline	Rh	P-P*/H_2	100	11	Scheme 32	3, 57
	Ir	P-P*/H_2	5000	98	Scheme 33-35	6,17 23,58-59
		P*/H_2	50	96	Scheme 36	60
	Ru	N-N*-P-P*/H_2	1000	73	Scheme 38	61
	OC	CPA*/HEH	10	98	Scheme 39	62
	Ru	H_2/CPA* (Relay catalysis)	100	94	Scheme 40	63
 Pyridine	Pd	$Pd(OH)_2/C/H_2$ (Diastereoselective)	-	97	Scheme 42	65-68
	Rh	P-P*/H_2 (3 steps)	50	>99	Scheme 43-44	69-70
	Ir	N-P*/I_2/H_2 (*N*-Ylide)	50	90	Scheme 45	71
		P-P*/I_2/H_2	1000	99	Scheme 46-47	22,25,72
	OC	CPA*/HEH	20	92	Scheme 50	75

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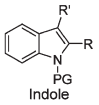
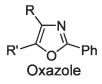
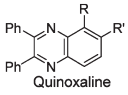
Table 3. Continued

Substrates		Catalytic Systems	S/C	Ee (%)	Scheme/Figure	References
 Indole		Ph-TRAP/Base/H_2 (PG = Ac, Ts)	100	98	Scheme 53-54	77,78
	Rh	Walphos/Base/H_2 (PG = Boc)	80	85	Scheme 52	79
		P*/Base/H_2 (PG = Ac, Boc)	20	74	Scheme 52	80
	Ru	Ph-TRAP/Base/H_2 (PG = Boc)	100	95	Scheme 55	81
	Ir	N-P*/H_2 (PG = Ac, Ts, Boc)	100	99	Scheme 56	82
	Pd	P-P*/Brønsted acid/H_2 (PG = H)	50	98	Scheme 58,60,62,64	84,86,88
 Pyrrole	Ru	Ph-TRAP/Base/H_2	40	99	Scheme 66	90
	Pd	P-P*/Brønsted acid/H_2 (PG = H)	50	92	Scheme 68	92
 Imidazole	Ru	Ph-TRAP/H_2	40	99	Scheme 71	94
 Oxazole	Ru	Ph-TRAP/H_2	200	98	Scheme 72-73	94
 Furan	Ru	P-P*/H_2	500	50	Scheme 76	4
	Rh	P-P*/H_2	10	72	Scheme 77-78	69,97
	Ir	N-P*/H_2	100	>99	Scheme 79	98
 Quinoxaline	Ru	NHCs*/H_2	20	88	Scheme 82 (Reduction of carbocyclic ring)	102

[a] S/C and ee indicate the highest values; P−P*, chiral bisphosphine ligand; N−P*, chiral bidentate nitrogen phosphine ligand; S−P*, chiral bidentate sulfur phosphine ligand; P*, chiral monophosphine ligand; N−N*, chiral diamine ligand; OC, organocatalyst; CPA*, chiral phosphoric acid; HEH, Hantzsch ester; NHCs*, chiral *N*-heterocyclic carbenes.

reduced due to their lower aromatic stabilization.[7,8] In 2011, Glorius and co-workers found that the selectively enantioselective hydrogenation of the aromatic carbocyclic ring of substituted quinoxalines could be realized by using a homogeneous chiral ruthenium NHC (*N*-heterocyclic carbene) complex.[102] Notably, this is the first example of homogeneous catalytic asymmetric hydrogenation of carbocyclic ring of aromatic compounds.

It was found that Ru/NHC complexes formed in situ from [Ru(cod)(2-methylallyl)$_2$] and monodentate NHCs were found to be very reactive catalytic systems for the hydrogenation of quinoxalines. Further studies revealed that the regioselectivity of hydrogenation was completely controlled by the choice of NHC ligands; using ruthenium complex with aryl-substituted NHCs ligand as catalyst, only hydrogenation product with the reduction of nitrogen-containing ring was obtained, but alkyl-substituted NHCs ligands completely reversed regioselectivity to aromatic carbocyclic ring hydrogenation of quinoxalines. Therefore, on the basis of the above findings, a novel asymmetric hydrogenation of the carbocyclic ring was successfully developed (Scheme 81).[102] Under the optimal conditions, a series of 2,3-diphenyl-5- and 6-substituted quinoxalines **18** were hydrogenated smoothly in high yields with excellent regioselectivity (>99/1) and up to 88% ee (Scheme 82).

12. CONCLUDING REMARKS

As mentioned in this Review, during the past few years, a number of effective catalytic systems including transition metal and organocatalysts have been successfully developed for the asymmetric hydrogenation of heteroarenes, and a breakthrough with asymmetric hydrogenation of carbocyclic ring of special quinoxaline substrates was also achieved (Table 3). They offered straightforward and facile access to a wide range of chiral compounds bearing cyclic skeletons with or without heteroatoms at the chiral center. For the hydrogenation of quinolines, iridium complex with chiral diphosphine ligands was studied extensively with two kinds of activation strategies. One is catalyst activation with iodine as an additive to form a more active iridium catalyst.

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The other is substrate activation with chloroformate and Brønsted acid to form more active reactant. Phosphine-free catalytic systems with Ir, Ru, Rh complexes of chiral diamines ligands as well as organocatalysts were also successfully developed. A single example of asymmetric hydrogenation of isoquinolines was reported with Ir/diphosphine complex in the presence of chloroformates. Highly enantioselective hydrogenation of quinoxalines was obtained using Ir complexes and chiral organophosphoric acid as catalyst. Notably, an efficient metal/Brønsted acid relay catalytic system for highly enantioselective hydrogenation of quinoxalines through convergent asymmetric disproportionation of dihydroquinoxalines was also founded. Pyridine derivatives with a chiral auxiliary and an achiral auxiliary can be efficiently hydrogenated using heterogeneous catalysts and homogeneous Ir/N−P catalysts in the presence of iodine, respectively. Pyridines with an electron-withdrawing group at the 3-position can be successfully reduced using chiral organophosphoric acid or Ir complexes in the presence of iodine. *N*-Protected indoles and pyrroles can be effectively hydrogenated using Rh or Ru complexes with privileged trans-chelating bisphosphines ligands Ph−TRAP. Simple indoles and pyrroles can be hydrogenated with the stoichiometric amount of Brønsted acid as activator using Pd/diphosphine complexes with excellent enantioselectivities. Asymmetric hydrogenation of 5-membered aromatic rings containing two or more heteroatoms, imidazoles and oxazoles, were disclosed with Ru/Ph−TRAP complex. Furan derivatives were also hydrogenated with iridium and rhodium complexes. Regioselective asymmetric hydrogenation of the carbocyclic ring of special quinoxalines was developed using the chiral Ru/NHCs complexes.

Despite the gratifying results obtained in asymmetric reduction of heteroarenes and arenes, it is especially important to point out that this field is still far from being mature and is still in its infancy and full of challenges. For instance, the asymmetric hydrogenation of easily accessible phenols, anilines, simple pyridines, and arenes is among the most attractive targets. New and highly efficient chiral catalysts and activation strategies for such transformations are expected in the coming years. First, the development of new activation strategy for arenes and heteroaromatic compounds is highly desirable, and super acids, acidic ionic liquids, and Lewis acid may be the best choice. The combination of two catalysts in one pot with relay hydrogenations to the target molecules was another promising candidate. Second, explorations of new highly active homogeneous catalyst, new metal precursors, chiral ligands, and additive effect should be screened extensively. Third, the design and development of a new organocatalyst type is a good direction due to the compatibility of the functional group and simple operation of the organocatalytic process. Fourth, chiral-modified heterogeneous catalysts should also be explored for asymmetric hydrogenation of aromatic compounds due to recyclability of chiral catalysts and simple purification procedure, especially for cheap heterogeneous nickel, cobalt, iron, and copper hydrogenation catalysts. Fifth, a thorough understanding of mechanistic details of these successful hydrogenation reactions might eventually lead to the next generation of general asymmetric hydrogenation methods for arenes and heteroarenes.

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BIOGRAPHIES

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Qing-An Chen was born in Fujian Province, China, in 1984. After receiving his B.S. degree from University of Science and Technology of China in 2007, he joined the research group of Zhou at Dalian Institute of Chemical Physics, Chinese Academy of Sciences. He is currently working on his Ph.D. thesis, and his research interests are centered on the combination of transition metal and organocatalyzed asymmetric hydrogenation reaction as well as ligand synthesis for asymmetric reactions.

Sheng-Mei Lu was born in 1977. She received her B.S. degree and M.S. degree from Central China Normal University in 1999 and 2002, respectively. In 2006, she received her Ph. D. degree in organic chemistry under the supervision of Profs. Xiu-Wen Han and Yong-Gui Zhou at Dalian Institute of Chemical Physics, Chinese Academy of Science. After a short time working in Prof. Zhou's group, she worked as a postdoctoral fellow (Alexander von Humboldt Foundation Fellowship) with Prof. Carsten Bolm at RWTH Aachen University for 2 years. During her Ph.D. and postdoctor, she worked on the asymmetric hydrogenation of the compounds containing more than one double bond. In 2009, she joined Prof. Can Li's group, State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences. Her research interests involve asymmetric catalysis with homogeneous and heterogeneous metal catalysts.

Yong-Gui Zhou was born in Hubei Province, China, in 1970. He received his B.S. degree from Huaibei Coal Industrial Teachers' College in 1993 and Ph.D. degree from Shanghai Institute of Organic Chemistry in 1999, under the supervision of Profs. Li-Xin Dai and Xue-Long Hou. He joined Xumu Zhang's group at the Pennsylvania State University as a postdoctoral fellow that same year, and in 2002 he began his independent research career at the Dalian Institute of Chemical Physics, Chinese Academy of Sciences, where currently he is a professor of chemistry. His research interests include the development of catalytic asymmetric reactions, mechanistic elucidation, and asymmetric synthesis.

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