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Advances in Transition Metal-Catalyzed Asymmetric Hydrogenation of Heteroaromatic Compounds

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Abstract Transition metal-catalyzed asymmetric hydrogenation of heteroaromatic compounds is undoubtedly a straightforward and environmentally friendly method for the synthesis of a wide range of optically active heterocyclic compounds, which are widespread and ubiquitous in naturally occurring and artificial bioactive molecules. Over the past decade, a number of transition metal (Ir, Rh, Ru, and Pd) catalysts bearing chiral phosphorus ligands, amine-tosylamine ligands, and *N*-heterocyclic carbene ligands have been developed for such challenging transformation. This review will describe the significant contributions concerning the transition metal-catalyzed asymmetric hydrogenation of *N*-, *O*-, and *S*-containing heteroaromatic compounds, with emphasis on the evolution of different chiral ligands, related catalyst immobilization, and mechanism investigations.

Keywords Asymmetric hydrogenation · Heteroaromatic · Heterocycles · Homogeneous catalysis · Transition metal

Contents

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1 Introduction

Heterocyclic structures, saturated or unsaturated, containing *N*, *O*, *S*, and other hetero atoms in the cyclic rings are widespread and ubiquitous in naturally occurring and artificial bioactive molecules, which are widely used in pharmaceutical and agrochemical production. In recent years the synthesis of chiral heterocycles with chiral centers on the ring atoms has attracted more and more attentions based on the observation of the obvious effects of chiral centers on properties and functions of these heterocyclic compounds. On the other hand, introducing chiral centers into the ring systems will greatly extend the type and increase the amount of heterocyclic compounds, thus offering abundant opportunities for scientists to use these new molecular units in the design of novel functional molecules. Generally, the construction of chiral heterocycles has been realized through various enantioselective cyclization or cycloaddition approaches. Alternatively, catalytic asymmetric reduction of the substituted heteroaromatic compounds, which are usually easy to prepare from readily available starting materials, represents another type of feasible synthetic methods. Among them, transition metal-catalyzed asymmetric hydrogenation with hydrogen gas as the reducing agent has proven to be the most promising straightforward and atom-economic approach. Theoretically, one or more desired chiral centers can be created at the same step through precise control by the suitable match of chiral ligand and metal selection. Considering extensive applications of chiral heterocyclic

compounds in organic synthesis, it is of special interest and great significance to develop practical, highly efficient, and highly enantioselective hydrogenation protocols for heteroaromatic substrates.

Although transition metal-catalyzed asymmetric hydrogenation of prochiral olefins, ketones, and imines has been well developed for several decades based on continuing ligand and methodology exploration (For some recent comprehensive reviews, see: [1–7]), the highly enantioselective hydrogenation of heteroaromatic compounds only appeared within the last 10 years (For reviews on reduction of hereroaromatics, see: [8–15]). This delay may be due to the special chemical properties of these heteroaromatic compounds. As we know, these compounds are relatively stable owing to the aromaticity of the conjugated ring systems; and harsh reaction conditions, such as high temperature and/or high hydrogen pressure, are usually required for achieving hydrogenation and thus resulting in low enantioselectivity. In addition, the hetero atoms, such as nitrogen or sulfur atoms in the heterocyclic rings, either in the substrates or in the reduced products, even the ones in the trace impurities, may coordinate to the metal centers and thus poison and/or deactivate the catalysts.

Given the recent discovery of transition metal catalysts together with several novel catalyst or substrate activation strategies, the last 10 years have witnessed significant progress in this field [13]. To date, a number of heteroaromatic compounds, including quinolines, isoquinolines, quinoxalines, pyridines, indoles, pyrroles, furans, thiophenes, imidazoles, and oxazoles, have been successfully applied in the asymmetric hydrogenation with excellent enantioselectivities. The asymmetric hydrogenation of heteroaromatic compounds has become a highly efficient, straightforward, economical, and environmentally friendly method for the synthesis of a wide range of optically active heterocyclic compounds. In this review we would like to describe the most recent advances in homogeneous transition metal-catalyzed asymmetric hydrogenation of different types of heteroaromatic compounds, with emphasis on the evolution of different chiral ligands. Related catalyst immobilization and mechanism investigations will also be highlighted. Considering that several excellent reviews on this topic have recently been published [8–15] (in particular, a comprehensive review was published in 2011 by Zhou and co-workers [13]), it is inevitable that this review will have some overlap with the contents of these previous reviews. Other related excellent work on asymmetric hydrogenation of heteroaromatic compounds using chiral and achiral heterogeneous metal catalysts [15], and asymmetric transfer hydrogenation catalyzed by organocatalysts, will not be included in this review [13, 16, 17].

2 Asymmetric Hydrogenation of Quinolines

Optically active 1,2,3,4-tetrahydroquinoline motif is widely existent in the molecular structures of naturally occurring alkaloids, artificial pharmaceuticals, and agrochemicals [18–20]. Asymmetric hydrogenation of quinoline derivatives, which

are easily prepared from readily available starting materials, provides a direct approach for the efficient synthesis of these chiral heterocyclic compounds. To date, a wide variety of 2-substituted and 2,3-disubstituted quinolines have been successfully subjected to the asymmetric hydrogenation, and excellent enantioselectivities have been achieved.

As privileged ligands widely used in the transition metal-catalyzed hydrogenation of prochiral olefins, ketones, and imines, phosphorus-containing ligands are the first choice ligands in the asymmetric hydrogenation of quinolines and also other heteroaromatic compounds. Since the first breakthrough made by Zhou and co-workers in 2003 [21], who applied diphosphine ligand MeO-BIPHEP in the iridium-catalyzed highly enantioselective hydrogenation of 2-substituted quinolines, a large number of phosphorus-containing chiral catalysts have been well developed for this transformation. Notably, the catalytic activity was greatly enhanced by using catalysts bearing electronically deficient phosphorus ligands. Concurrent with phosphorus-containing ligand extension, substrate activation strategy by either chloroformates or Brønsted acids provided other alternatives for the asymmetric hydrogenation of quinolines [22, 23]. Another significant contribution is the application of phosphine-free diamine ligands for this transformation by Fan and co-workers [24, 25]. A broad range of quinoline derivatives were hydrogenated smoothly with diamine-containing ruthenium catalysts, giving the highest *ee* values for most substrates examined.

2.1 Chiral Diphosphine Ligands

Atropisomeric C_2-symmetric biaryl diphosphines are versatile effective ligands for asymmetric catalysis [26]. By tuning stereo and electronic properties of the ligands through rational backbone design and/or substituent modulation, the catalytic activity and stereoselectivity could be well adjusted. After the initial finding of the activation strategy with iodine additive in asymmetric hydrogenation of quinolines, Ir/diphosphine/I_2 became the most popular and widely used catalyst systems for the hydrogenation of heteroaromatic compounds [27–37], and the representative chiral diphosphine ligands used for the asymmetric hydrogenation of quinolines are listed in Fig. 1.

In 2003, Zhou and co-workers reported the first effective and highly enantioselective asymmetric hydrogenation of 2-substituted quinoline derivatives with diphosphine-iridium complex, in situ generated by mixing $[Ir(COD)Cl]_2$ (COD = 1,5-cyclooctadiene) and MeO-BIPHEP [21]. With the addition of iodine into the reaction mixture, the catalytic activity was enhanced enormously. After the optimization of the reaction conditions, a variety of 2-substituted quinoline derivatives were hydrogenated smoothly to chiral 1,2,3,4-tetrahydroquinolines in toluene in yields of 83–95% with *ee* values of 72–96%. It was noticed that the hydrogenation of most 2-alkyl-substituted quinolines gave higher enantioselectivities, while only 72% *ee* was obtained for 2-phenylquinoline. The Ir/MeO-BIPHEP/I_2 catalyst system

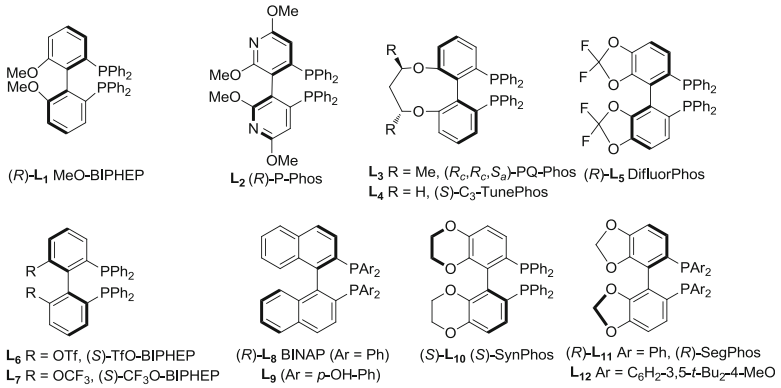
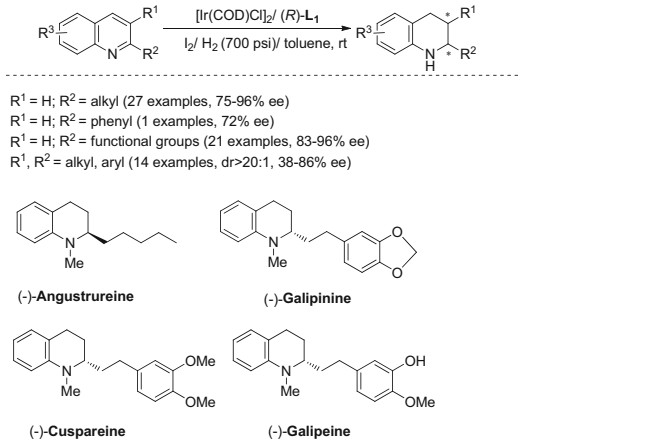


Fig. 1 Chiral diphosphine ligands for asymmetric hydrogenation of quinolines



Scheme 1 Asymmetric hydrogenation of quinoline derivatives catalyzed by $[Ir(COD)Cl]_2$/MeO-BIPHEP/I_2

also exhibited good tolerance to hydroxyl and ester groups, but lower enantiomeric excess was found for hydroxymethyl-substituted quinoline. Subsequently, this catalytic system was also applied to the asymmetric synthesis of naturally occurring alkaloids, such as (−)-angustureine, (−)-galipinine, (−)-cuspareine, and (−)-galipeine (Scheme 1) [21, 27].

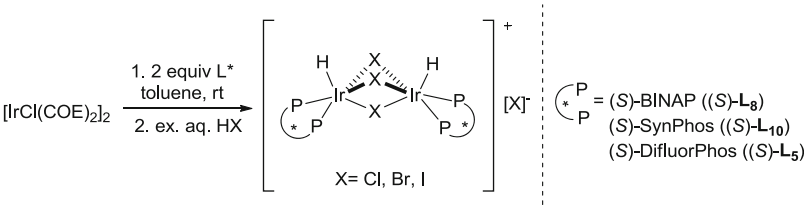
Later, Zhou and co-workers reported the asymmetric hydrogenation of 2-benzyl-substituted, 2-functionalized, and 2,3-disubstituted quinoline derivatives with the same Ir-catalyst system [28]. The enantioselective hydrogenation of 2-benzylquinolines and 2-functionalized quinolines showed high yields (65–97%) and excellent enantiomeric excesses (80–96%), which were not very sensitive to the electronic and/or steric properties of the substituents. More significantly, the

catalyst system could tolerate various functional groups, such as esters, amides, benzenesulfonyl, and TBS (*tert*-butyldimethylsilyl) protected hydroxyl groups. In the investigation of asymmetric hydrogenation with 2,3-disubstituted quinolines as substrates, excellent dr values (>20:1) were achieved, but the *ee* values were under 90%. Similarly, the key intermediates of the gephyrotoxin alkaloid were conveniently synthesized in two steps from the chiral 1,2,3,4-tetrahydroquinoline derivatives in high yields.

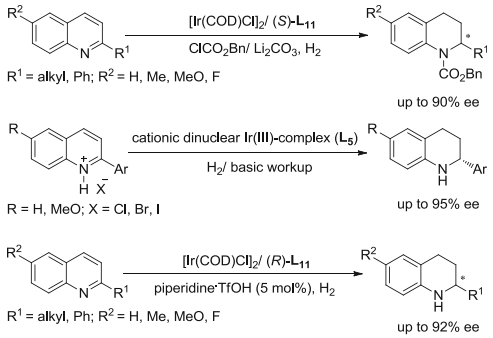
Inspired by Zhou's initial work, many other chiral diphosphine ligands were successfully introduced into this transformation. In 2005, Fan, Chan, and co-workers used P-Phos with a 2,2′-bipyridine backbone [38] for the Ir-catalyzed asymmetric hydrogenation of a series of 2-substituted quinolines [29]. The iridium catalyst proved to be air-stable even after exposing the catalyst solution to air for 24 h. The hydrogenation of 2-alkyl-substituted quinolines catalyzed by in situ generated catalyst in THF or liquid poly(ethylene glycol) dimethyl ether without degassing afforded 1,2,3,4-tetrahydroquinolines in high yields (90–99%) with excellent enantiomeric excess values (90–92% *ee*). Most recently, Xu and co-workers found that the catalytic activity was additive-controlled with the same diphosphine ligand [30]. The hydrogenation of 2-methylquinoline could be carried out at much low catalyst loading (up to 4,000 h^{-1} TOF and up to 43,000 TON, TOF = turnover frequency, TON = turnover number) by decreasing the amount of additive I_2.

In addition, the clear effect of the electronic property of diphosphine ligands on catalytic activity in the hydrogenation of quinoline derivatives was noticed by several research groups. It was found that the electron-deficient diphosphine ligands usually displayed enormously improved catalytic reactivity. Xu and co-workers reported that the commercially available and electronically deficient DifluorPhos showed excellent activity (TON up to 43,000) in the Ir-catalyzed hydrogenation of 2-alkyl-substituted quinolines [31] with high enantioselectivities (up to 96% *ee*). The same rule of electronic effect of diphosphine ligand was also demonstrated by Zhou and co-workers [32, 33]. Electron-withdrawing groups (OTf (trifluoromethanesulfonyl) and CF_3O) were introduced into the 6- and 6′-positions of BIPHEP backbone, and the iridium catalysts exhibited high *ee*s (up to 95% and 92%, respectively) and high turnover numbers (up to 14,600 and 25,000, respectively).

In addition to the in situ generated iridium catalysts, Genet, Mashima, Ratovelomanana-Vidal and co-workers synthesized a series of cationic triply halogen-bridged dinuclear Ir (III)-complexes of diphosphines [39, 40], including BINAP, SynPhos, and DifluorPhos (Scheme 2). These iridium complexes were further demonstrated to be highly effective in the hydrogenation of 2-substituted quinoline derivatives. With nearly quantitative conversions, the cationic triply bromo-bridged dinuclear iridium complexes of SynPhos and DifluorPhos showed good enantioselectivities (58–91% *ee*s), although the substrate scope was still limited.



Scheme 2 Preparation of cationic triply halogen-bridged dinuclear iridium(III) complexes



Scheme 3 Asymmetric hydrogenation of quinolines activated by chloroformates and Brønsted acids

The discovery of activation strategies other than catalyst activation by iodine was also explored (Scheme 3). The substrate activation could be achieved by using either chloroformates or Brønsted acids as activating agents, without adding iodine in catalyst systems [22, 41, 42]. In 2006, Zhou and co-workers realized asymmetric hydrogenation of 2-substituted quinolines by the addition of chloroformates [22] in the reaction mixture, opening a new avenue for the hydrogenation of heteroaromatic compounds. The benzyl carboxylate group on *N*-atom of the reduced products could be gently cleaved with H_2/Pd/C in THF.

Recently, Ohshima, Ratovelomanana-Vidal, Mashima, and co-workers developed the first highly enantioselective hydrogenation of 2-arylquinolinium salts by using their cationic dinuclear Ir(III) halide complexes as catalyst precursors [41]. High enantioselectivities (up to 95% *ee*) were achieved. These catalysts were also effective for 2-alkyl quinoline substrates, and all the *ee* values are above 90%.

In 2010, Zhou's group realized Ir-catalyzed hydrogenation of 2-substituted quinolines with catalytic amount of various Brønsted acids as the activator [42]. Full conversions and very good enantioselectivities (84–92% *ee*) were obtained for 2-alkyl-substituted quinolines with catalytic amounts of piperidine · OTf, but only 78% *ee* for 2-phenlyquinoline substrate.

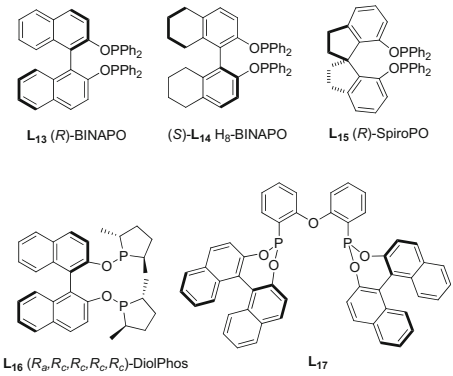


Fig. 2 Chiral diphosphinite and diphosphonite ligands for asymmetric hydrogenation of quinolines

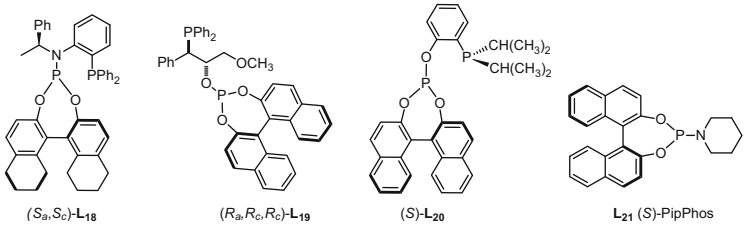


Fig. 3 Chiral phosphine-phosphoramidite, phosphine-phosphite, and monodentate phosphoramidite ligands for asymmetric hydrogenation of quinolines

2.2 *Other Chiral Phosphorus-Containing Ligands*

In addition to chiral diphosphine ligands, other chiral phosphorus-containing ligands (For selected reviews on other phosphorus-containing ligands, see: [43–46]), including diphosphinite, diphosphonite, phosphine-phosphoramidite, phosphine-phosphite, monodentate phosphoramidite and *N,P*-ligands (Figs. 2, 3, and 4) have been also successfully applied to the Ir-catalyzed asymmetric hydrogenation of quinolines [47–58].

In 2005, Fan, Chan, and co-workers first used the electron-deficient chiral diphosphinite H8-BINAPO, which was easily derived from the corresponding diols, for the Ir-catalyzed asymmetric hydrogenation of quinolines [47]. Complete conversions and excellent enantioselectivities (up to 97% *ee*) were obtained. Their further study showed that the chiral diphosphinite ligand derived from the privileged (*R*)-1,1′-spirobiindane-7,7′-diol [59] was highly effective in the Ir-catalyzed asymmetric hydrogenation of quinolines with high substrate/catalyst ratio (up to 5,000) and high enantioselectivity (up to 94% *ee*) [48].

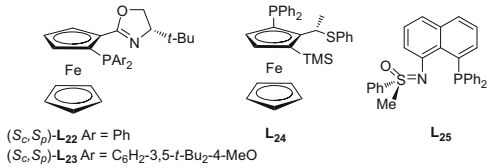


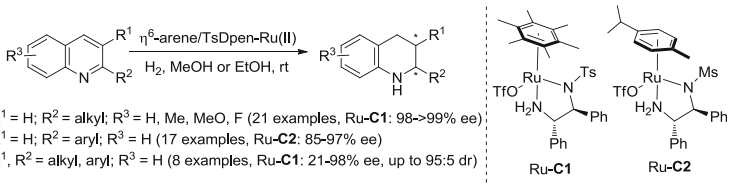
Fig. 4 Chiral *P,N*- and *P,S*-ligands for asymmetric hydrogenation of quinolines

BINOL-derived (BINOL = 1,1′-bi-2-naphthol) chiral diphosphonite ligand bearing an achiral diphenyl ether backbone was also demonstrated to be effective in the iridium-catalyzed hydrogenation of quinolines by Reetz and co-worker [49]. Interestingly, improvement of enantioselectivity was observed by the addition of achiral monodentate phosphine ligand. With this chiral diphosphonite-achiral monophosphine catalyst system, several 2-alkyl-substituted quinolines were efficiently hydrogenated with high *ee* values (up to 96% *ee*).

Most recently, three groups published their research on iridium-catalyzed asymmetric hydrogenations by using electronically dissymmetric *P,P*-ligands independently. A set of highly modular *P-OP* ligands, including various phosphine-phosphoramidites and phosphine-phosphites, were synthesized and evaluated in the iridium-catalyzed asymmetric hydrogenation of 2-substituted quinolines (Fig. 3) [50–52]. The iridium complex with ligand (S_aS_c)-**L**$_{\mathbf{18}}$ exhibited excellent enantioselectivity (up to 97% *ee*) [52]. However, much lower *ee* (81% *ee*) for 2-methylquinoline was obtained with the mismatched diastereomer.

Besides the bidentate chiral *P,P*-ligands, chiral monodentate phosphines, phosphonites, phosphites and phosphoramidites have recently been reported to present excellent performance in the asymmetric hydrogenation of functionalized olefins [45]. In 2008, the readily accessible and air-stable BINOL-derived phosphoramidite PipPhos proved to be effective in the iridium-catalyzed asymmetric hydrogenation of quinolines by Feringa and co-workers [53]. With addition of both piperidine hydrochloride and achiral monodentate phosphine ligand as additives, great enhancement in enantioselectivity was observed. Under the optimized hydrogenation conditions, a series of 2-substituted quinolines were successfully converted to 1,2,3,4-tetrahydroquinoline derivatives in high conversions with very good enantioselectivities (76–89% *ee*s).

In addition to the bidentate *P,P*-ligands, *P,N*- and *P,S*-bidentate ligands [54, 55] also exhibited good catalytic performance in the enantioselective hydrogenation of quinolines (Fig. 4). Zhou and co-workers first employed the ferrocenyloxazoline-derived *P,N*-ligand to the Ir-catalyzed asymmetric hydrogenation of quinolines [54]. With iodine as the additive, very good enantioselectivities (up to 92% *ee*) were achieved for 2-alkyl-substituted quinolines. In the case of 2-phenylquinoline, however, very poor results (45% yield with 3% *ee*) were obtained. Subsequently, they found that introducing bulky groups on the coordination phosphorus atoms could effectively prevent the formation of inactive dimer species, and thus improved the activity of the iridium catalysts [55]. Up to 93% *ee* was obtained in



Scheme 4 Asymmetric hydrogenation of quinoline derivatives with Ru-diamine catalysts

the hydrogenation of 2-alkyl-substituted quinolines with the substrate/catalyst ratio up to 25,000.

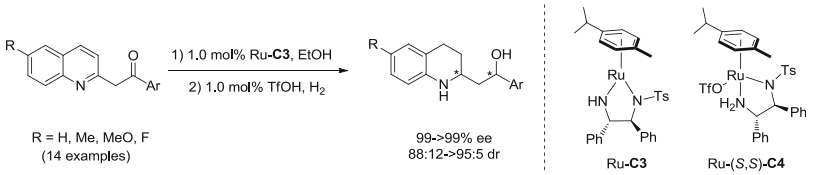
In 2008, Bolm and co-worker designed and synthesized other types of naphthalene-bridged *P,N*-type sulfoximine ligands [57]. Their iridium complexes were found to exhibit good catalytic performance in the hydrogenation of 2-alkyl-substituted quinolines. In contrast to Zhou's catalytic system, the addition of iodine gave negative results in enantioselectivity.

2.3 Chiral Diamine Ligands

In comparison with the chiral phosphorus ligands, chiral bidentate diamine ligands are more readily available, easily tunable, and air-stable [60]. Their transition metal complexes of Ru, Rh, and Ir have been extensively studied in the transfer hydrogenation of aromatic ketones and imines [61, 62].

In 2006, the chiral η^6-arene/Ts-DPEN-Ru(II) complex, which was known as an excellent catalyst only for transfer hydrogenation, proved to be an effective catalyst for asymmetric hydrogenation of simple ketones by Noyori and co-workers [63, 64]. It was found that the hydrogenation with such ruthenium catalyst could be realized simply by switching the conditions from basic to acidic. Inspired by this seminal work, Fan and co-workers first realized the highly effective asymmetric hydrogenation of basic quinoline derivatives with such a cationic ruthenium catalyst (Scheme 4) [24, 65]. Unlike hydrogenation of ketones, which occurred only in methanol or ethanol, quinolines could be hydrogenated smoothly in most common organic solvents, water, ionic liquids, and even under solvent-free/highly concentrated conditions. A comprehensive study revealed that a different catalytic mechanism was involved in the hydrogenation of quinolines as compared to that of ketones, which will be discussed later in Sect. 11.

With this catalytic system, no additive was necessary for achieving high reactivity and/or enantioselectivity. The substrate activation was achieved by the in situ generated H^+ via a ruthenium assisted hetero-split of dihydrogen. Under the optimized reaction conditions, a wide range of quinoline derivatives, including 2-alkylquinolines, 2-arylquinolines, 2-functionalized, and 2,3-disubstituted quinoline derivatives were efficiently hydrogenated to give 1,2,3,4-tetrahydroquinolines with high yields and excellent enantioselectivities (up to >99% *ee* and 5,000 TON). This



Scheme 5 Asymmetric tandem reduction of 2-(aroylmethyl)quinolines with Ru-diamine catalysts

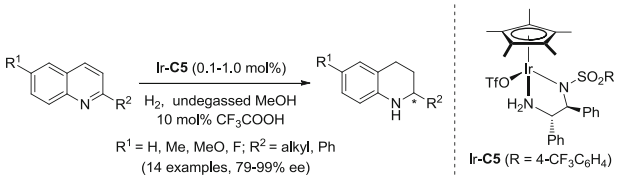
catalytic protocol was also successfully applied to the gram-scale synthesis of some biologically active tetrahydroquinoline alkaloids, such as (−)-angustureine and 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline, a key intermediate for the preparation of antibacterial agent (*S*)-flumequine.

Due to the potential poisoning of catalysts by the substrate and/or reduced product, asymmetric hydrogenation of heteroaromatic compounds under solvent-free conditions is a challenging task [66]. Recently, Fan and co-workers reported the first example of highly enantioselective hydrogenation of quinolines under solvent-free or highly concentrated conditions with the cationic Ru-diamine catalysts [67]. Under optimized conditions, a variety of 2-alkyl-substituted quinolines were hydrogenated at low catalyst loading (low to 0.02 mol%), affording 1,2,3,4-tetrahydroquinolines in high yields with excellent enantioselectivities (up to 97% *ee*). Further application of this solvent-free catalytic system to the gram-scale synthesis of the biologically active alkaloid (−)-angustureine gave 96% overall yield and 94% *ee*.

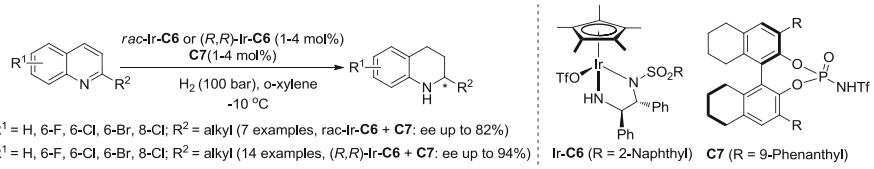
Subsequently, the same research group disclosed an asymmetric tandem reduction of 2-(aroylmethyl)quinolines (Scheme 5) based on different chemical selectivity of catalyst **Ru-C3** and **Ru-C4** for the reduction of ketone and quinoline motifs [68]. After the C = O bond was reduced under transfer hydrogenation conditions in the presence of 1.0 mol% **Ru-C3**, the asymmetric hydrogenation of quinoline was carried out under 50 atm hydrogen simply by adding 1.0 mol% TfOH (trifluoromethanesulfonic acid), which in situ generated the active hydrogenation catalyst **Ru-C4**. With such catalytic protocol, various 2-(aroylmethyl)quinolines were reduced to give the products bearing two chiral centers with up to 99% *ee* and 95:5 dr.

In 2008, Fan and co-workers extended the application of chiral diamine ligands to Ir-catalyzed asymmetric hydrogenation of quinolines [69]. A series of 2-alkyl-substituted quinolines were hydrogenated in high yields with excellent enantioselectivities (up to 99% *ee*) at a catalyst loading of 0.2 mol% (Scheme 6). More importantly, the reaction was obviously promoted by addition of a catalytic amount of TFA, and could be carried out in undegassed solvent without inert gas protection.

Most recently, Rueping and co-workers reported a Brønsted acid differentiated metal catalyzed hydrogenation of quinolines [70] by kinetic discrimination (Scheme 7). Moderate to good enantioselectivities (up to 82% *ee*) were obtained with the combination of an achiral Ir-diamine complex and a chiral *N*-triflylphosphoramide. In addition, a matched catalyst combination, including



Scheme 6 Asymmetric hydrogenation of quinoline derivatives with Ir-diamine catalyst in undegassed methanol



Scheme 7 Brønsted acid differentiated metal catalyzed hydrogenation of quinolines by kinetic discrimination

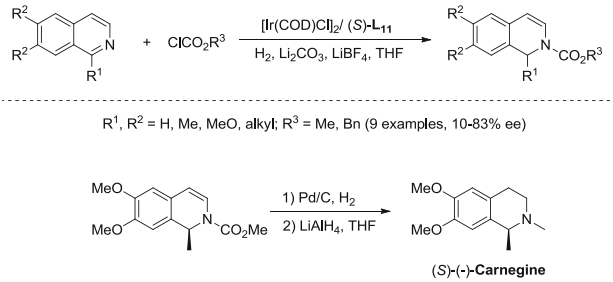
both chiral iridium-amido complex and chiral Brønsted acid, gave higher enantioselectivities (84–94% *ee*s).

3 Asymmetric Hydrogenation of Isoquinolines

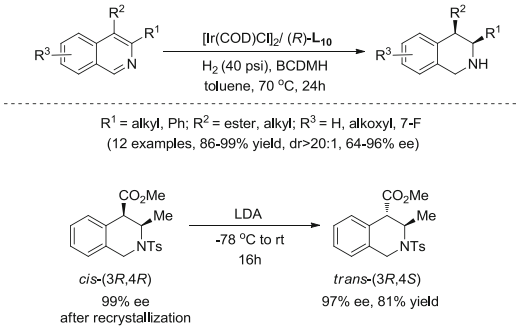
In comparison with quinolines, isoquinolines are more challenging substrates for asymmetric hydrogenation. To date, only two papers on such transformation have been published by Zhou and co-workers [22, 71], which relied on substrate or catalyst activation strategies.

In 2006, Zhou and co-workers reported the partial hydrogenation of 1-substituted isoquinolines catalyzed by Ir/(*S*)-SegPhos complex together with a substrate activation strategy (Scheme 8) [22]. Similar to the asymmetric hydrogenation of quinolines mentioned above, various 1-substituted isoquinoline derivatives were hydrogenated smoothly by using chloroformates as additives, giving the reduced 1,2-dihydroisoquinolines in 46–87% yields and 10–83% *ee*s. Upon further reduction of the products with H_2/Pd/C and $LiAlH_4$, 1,2,3,4-tetrahydroisoquinolines could be achieved, which was exemplified by the synthesis of naturally occurring alkaloid, (*S*)-(−)-carnegine.

The other example was reported recently on the hydrogenation of 3,4-disubstituted isoquinolines by catalyst activation strategy, in which a dynamic kinetic resolution was involved (Scheme 9) [71]. BCDMH (1-bromo-3-chloro-5,5-dimethyl-hydantoin) was used instead of iodine to active the in situ generated catalysts by mixing iridium precursor $[Ir(COD)Cl]_2$ and SynPhos. Lowering the hydrogenation pressure and elevating the reaction temperature led to a further increase in enantioselectivity. A set of 3,4-disubstituted isoquinolines were



Scheme 8 Asymmetric hydrogenation of activated isoquinolines and its application in the synthesis of naturally occurring alkaloid, (*S*)-(−)-carnegine

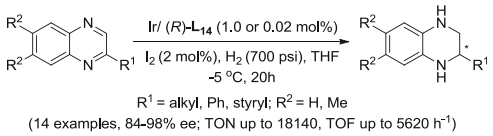


Scheme 9 Iridium-catalyzed enantioselective hydrogenation of 3,4-disubstituted isoquinolines and *cis*-*trans* transformation using LDA

hydrogenated effectively, giving *cis*-products with 86–99% yields and 64–96% *ee*s. Although it was demonstrated that the ester group at the C-4 position is not necessary for hydrogenation, lower *ee* values were observed for the 4-alkyl-substituted substrates. Subsequent treatment of *cis*-disubstituted products with LDA (lithium diisopropylamide) gave the corresponding *trans*-epimers, which is generally difficult to obtain through direct asymmetric hydrogenation. A plausible hydrogenation mechanism was also proposed, including 1,2-hydrid addition to the C = N bond, acid-catalyzed enamine-imine tautomerization, and the hydrogenation of imine.

4 Asymmetric Hydrogenation of Quinoxalines

The asymmetric hydrogenation of quinoxalines is a potentially cost-efficient and atom-economic method for the preparation of optically pure 1,2,3,4-tetrahydroquinoxaline derivatives, which are of great biological interest. Since the first example of asymmetric hydrogenation catalyzed by rhodium catalyst in 1987 [72], a variety of rhodium, iridium, and ruthenium complexes bearing chiral



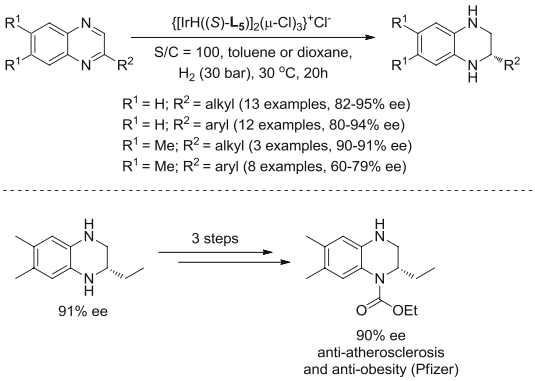
Scheme 10 Asymmetric hydrogenation of substituted quinoxalines catalyzed by Ir-(*R*)-H_8-BINAPO

phosphorus ligands have been applied to such transformation [34, 42, 50, 72–76]. Early reported catalytic systems suffered from low enantioselectivities and/or limited substrate scope [72–76]. On the basis of Zhou's Ir/diphosphine/I_2 catalytic system [21], significant progress has recently been achieved in this reaction by several research groups. In addition, some phosphine-free ligands, including chiral diamines and *N*-heterocyclic carbenes, were found to be highly efficient in the Ru-catalyzed asymmetric hydrogenation of quinoxalines. Notably, the hydrogenation by metal/Brønsted acid relay catalysis has also shown its potential in this research area.

4.1 Chiral Phosphorus-Containing Ligands

Similar to the asymmetric hydrogenation of quinolines, the iridium catalysts bearing diphosphines, diphosphinite, monodentate phosphoramidites, and phosphine-phosphite (*P-OP*) ligands were used for the asymmetric hydrogenation of quinolines [77–81]. In 2009, Fan, Chan, and co-workers reported that chiral diphosphinites derived from H8-BINOL and 1,1′-spiro-biindane-7,7′-diol showed higher enantioselectivities in the iridium catalyzed asymmetric hydrogenation of 2-methylquinoxiline compared to diphosphine-Ir catalysts under the identical reaction conditions (Scheme 10) [77]. It is noticeable that even with 0.005 mol% of Ir catalyst (substrate/catalyst ratio (S/C) = 20,000), the reaction proceeded smoothly in a slightly lowered conversion and with the same enantioselectivity. Under optimal reaction conditions, the hydrogenation of a series of 2-substituted quinoxalines was successfully realized with quantitative conversions and high *ee* values varying from 84% to 96%. It is interesting to note that the enantioselectivities were a little bit higher in some cases as the S/C elevated to 5,000/1, and the enantiomeric excess reached 98%.

At the same time, Feringa and co-worker described the enantioselective hydrogenation of 2-substituted quinoxalines with an Ir-catalyst prepared in situ from $[Ir(COD)Cl]_2$ and monodentate phosphoramidite ligand PipPhos [78]. With 10 mol% piperidine hydrochloride as additive, 71–92% yields and 75–96% *ee*s were obtained at an Ir/ligand mol ratio of 1:2.



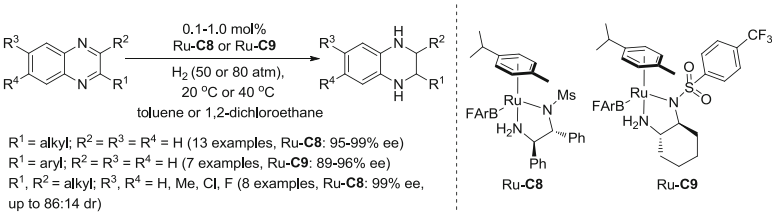
Scheme 11 Asymmetric hydrogenation of quinoxalines catalyzed by cationic dinuclear iridium (III) complex and its application in the synthesis of Pfizer's CETP inhibitor

Oshima, Mashima, and Ratovelomanana-Vidal et al. employed the cationic triply halogen-bridged dinuclear Ir(III)-complexes, mentioned above in quinoline reduction, for the asymmetric hydrogenation of 2-substituted quinoxalines (Scheme 11) [79, 80]. Without iodine as additive, DifluorPhos proved to be optimal for the hydrogenation of a series of 2-alkyl- and 2-aryl-substituted quinoxalines, furnishing 1,2,3,4-tetrahydroquinoxalines with nearly quantitative yields and high enantioselectivities (up to 95% *ee*). Moreover, to illustrate the applicability of this catalyst system, an inhibitor of cholesteryl ester transfer protein (CETP), developed by Pfizer [82], was synthesized with the asymmetric hydrogenation of 2-ethyl-6,7-dimethylquinoxaline as the key step.

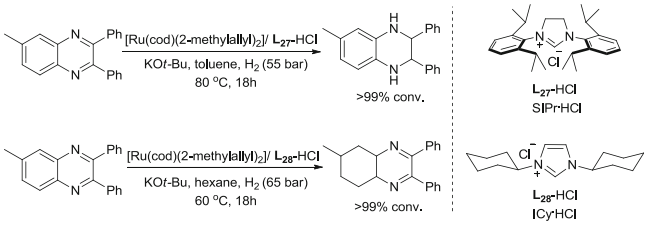
Most recently, Mashima and co-workers investigated the additive effects of achiral amines on the asymmetric hydrogenation of 2-aryl-substituted quinoxalines catalyzed by the same chiral cationic dinuclear iridium(III) complexes [81]. In the presence of *N*-methyl-*p*-anisidine (MPA), the catalytic activity was obviously enhanced and the highest enantioselectivity was observed in the hydrogenation of 2-phenylquinoxaline, which is higher than that without amine additive. The following particular mechanistic study indicated the possible existence of dual catalytic cycles in equilibrium. The addition of amine probably shifted the balance, leading to higher activity and enantioselectivity. The detailed description of the experimental processes will be included in the mechanistic study session.

4.2 Chiral Phosphine-Free Ligands

After the amazing discovery of excellent performance of chiral diamines in the ruthenium catalyzed asymmetric hydrogenation of quinolines, Fan and co-workers recently reported the extended application of such Ru-diamine catalysts in the hydrogenation of 2- and 2,3-substituted quinoxalines (Scheme 12) [83]. It was found that the weakly coordinating counteranions of the half-sandwich Ru (II) complexes showed an evident influence on the enantioselectivity and/or



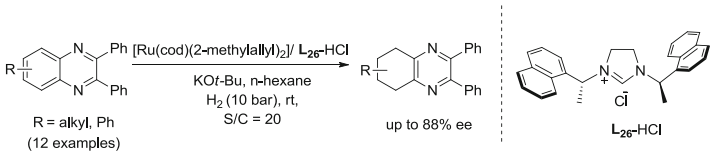
Scheme 12 Asymmetric hydrogenation of 2- and 2,3-substituted quinoxalines with chiral cationic ruthenium diamine catalysts



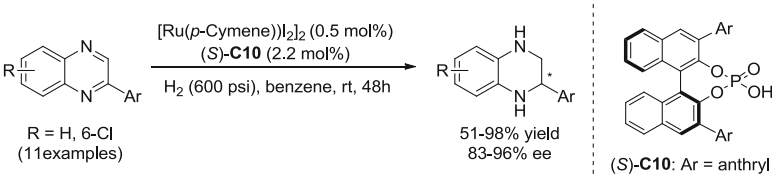
Scheme 13 Ligand-controlled regioselective hydrogenation of 6-methyl-2,3-diphenylquinoxaline

diastereoselectivity of the reaction. The Ru complexes with a bulky $BArF^-$ [tetrakis (3,5-bistrifluoromethylphenyl)borate] counteranion were selected as optimal catalyst, and were applied in the asymmetric hydrogenation of 2-alkyl-substituted, 2-aryl-substituted, and 2,3-dialkyl-substituted quinoxaline derivatives with high yields, high *ee*s, and moderate dr values. Excellent enantioselectivities ranging from 95% to 99% *ee* were achieved for 2-alkyl-substituted quinoxalines, which are the best results reported to date for this type of heteroaromatic compound.

In 2011, Glorius and co-workers reported a ligand-controlled highly regioselective and asymmetric hydrogenation of quinoxaline derivatives for the first time by using monodentate *N*-heterocyclic carbenes (NHC) as ligand [84]. With different achiral NHC ligands, the hydrogenation of 2,3-diphenyl-6-methylquinoxaline catalyzed by the in situ formed ruthenium catalysts proceeded smoothly, affording partially reduced products, 1,2,3,4-tetrahedroquinoxaline and 5,6,7,8-tetrahydroquinoxaline, with full conversions but different regioselectivities, respectively (Scheme 13). Based on this finding, the Ru-catalyzed asymmetric hydrogenation of 2,3-diphenyl-substituted quinoxalines was realized by using chiral NHC ligands (Scheme 14). Under optimized reaction conditions, only the aromatic carbocyclic ring was selectively hydrogenated with moderate to very good enantioselectivity (up to 88% *ee*), which is totally different from the reported regioselectivity of asymmetric hydrogenation of bicyclic benzo-heteroaromatics with other types of catalyst.



Scheme 14 Asymmetric hydrogenation of 2,3-diphenyl-substituted quinoxalines with chiral ruthenium-NHC catalysts



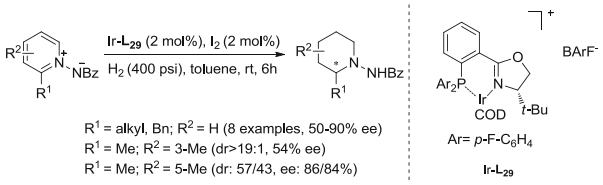
Scheme 15 Asymmetric reduction of quinoxalines through convergent disproportionation of dihydroquinoxalines using metal/Brønsted acid relay catalysis system

4.3 Metal/Brønsted Acid Catalytic System

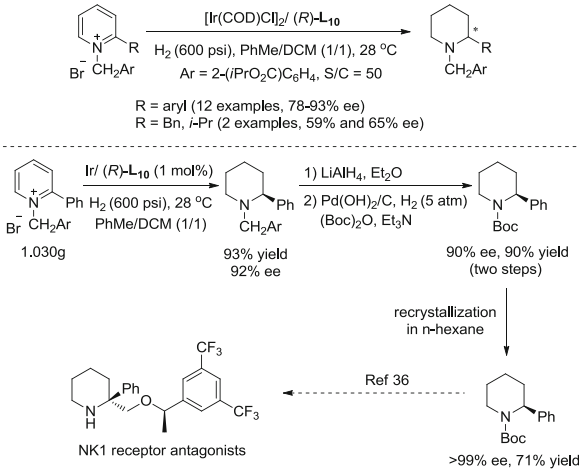
In 2011, Zhou and co-workers reported a relay catalysis to prepare chiral tetrahydroquinoxalines by using a combination of achiral ruthenium complex ([Ru(*p*-cymene)I_2]$_2$) and sterically demanding chiral Brønsted acid **(*S*)-C10** (Scheme 15) [85]. After the partial hydrogenation of 2-aryl quinoxalines, the dihydroquinoxaline intermediates were enantioselectively reduced through convergent asymmetric disproportionation, in which a self-transfer hydrogenation process was involved. With this metal/Brønsted acid relay catalyst system, a variety of quinoxalines were hydrogenated to 1,2,3,4-tetrahydroquinoxalines in high yields with good to excellent enantioselectivities (up to 96% *ee*). The proposed mechanism will be discussed later in Sect. 11.

5 Asymmetric Hydrogenation of Pyridines

As a wide-existent structural motif in natural alkaloids and many biologically active compounds, the enantioselective synthesis of chiral piperidine derivatives is of great interest [86]. Although asymmetric hydrogenation of pyridine derivatives is the most straightforward and convenient route to such chiral *N*-containing heterocyclic compounds, few successful examples were reported. Early study on this reaction focused on heterogeneous catalytic systems, which suffered from low enantioselectivities and/or reactivities, and narrow substrate scope [15]. In 2000, Studer and co-workers reported the first homogeneous transition metal-catalyzed asymmetric hydrogenation of the activated 2- and 3-pyridine carboxylic acid and their corresponding ethyl esters [87]. However, only 17–27% *ee*s were observed for



Scheme 16 Asymmetric hydrogenation of *N*-benzoyliminopyridinium ylides catalyzed by Ir-PHOX complex

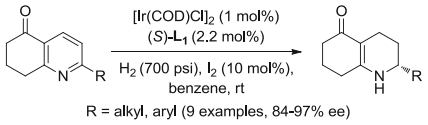


Scheme 17 Iridium-catalyzed asymmetric hydrogenation of 2-substituted pyridinium salts and its application for the formal synthesis of NK1 receptor antagonist

only four substrates tested. Recently, a breakthrough was made in the asymmetric hydrogenation of monocyclic pyridine derivatives via substrate activation strategy by Charette's and Zhou's groups, respectively.

In 2005, Charette and co-workers investigated the asymmetric hydrogenation of a special kind of activated pyridine, 2-alkyl-substituted *N*-iminopyridinium ylides (Scheme 16) [88]. A series of chiral *P*,*N*-ligands were screened in the Ir/I_2 catalyzed hydrogenations. Under the optimized reaction conditions, a set of 2-alkyl-substituted *N*-benzoyliminopyridinium ylides were successfully hydrogenated to afford chiral piperidines with modest to high yields and enantioselectivities (50–90% *ee*s). In some cases, partial reduced byproducts were observed. The hydrogenation of 2,3- and 2,5-dimethyl *N*-benzoyliminopyridinium ylides also proceeded smoothly, giving products with good stereoselectivities. In addition, the role of iodine was to oxidize the initial Ir(I) complex to the Ir(III) pre-catalyst [89].

Most recently, Zhou and co-workers described the asymmetric hydrogenation of pyridinium salts [90], another type of activated pyridine, affording 2-substituted *N*-benzyl piperidines in 60–99% yields and 59–93% *ee*s with Ir/diphosphine catalytic system (Scheme 17). Upon screening of various diphosphine ligands, the



Scheme 18 Ir-catalyzed asymmetric hydrogenation of 7,8-dihydro-quinolin-5(6*H*)-ones

electron-rich (*R*)-SegPhos and (*R*)-SynPhos displayed the highest enantioselectivity. It is noticeable that introducing an electron-withdrawing ester group at the *ortho* position of the activating benzyl group could significantly improve the enantioselectivity. Interestingly, the 2-aryl-substituted pyridines offered better reactivities and enantioselectivities than 2-alkyl-substituted pyridines. To demonstrate the practicability of this methodology, they developed a gram-scale synthesis of *N*-benzyl-2-phenyl piperidine, which was further used for the formal synthesis of an orally active NK1 receptor antagonist (Scheme 17) [91, 92].

In contrast to monocyclic pyridines, the activated bicyclic trisubstituted pyridines, 7,8-dihydro-quinolin-5(6*H*)-ones, could be hydrogenated in a relatively easy way. In 2008, Zhou and co-workers found that their Ir/diphosphine/I_2 catalytic system was also effective for the asymmetric hydrogenation of such pyridine derivatives (Scheme 18) [93]. Under optimal reaction conditions, a wide range of 2-alkyl and 2-phenyl substituted pyridines were hydrogenated smoothly, providing chiral hexahydroquinolines in moderate to high yields (up to 98%) with high enantiomeric excesses of 84–97%.

Electron deficient diphosphines, such as DifluorPhos and P-Phos, based on chiral biphenyl backbone were also employed in the Ir/diphosphine/I_2 catalyzed asymmetric hydrogenation of 7,8-dihydro-quinolin-5(6*H*)-ones by Xu and co-workers [30, 31]. Excellent enantioselectivities (up to 98% *ee*) and nearly quantitative yields were achieved for both catalysts. In contrast to the hydrogenation of quinolines with electron deficient diphosphines, no enhancement of catalytic activity was noted with pyridine substrates.

6 Asymmetric Hydrogenation of Indoles and Pyrroles

Indoline and pyrroline motifs are widely existent in the structures of naturally occurring alkaloids and other biologically active molecules [94]. The asymmetric hydrogenation of indole and pyrrole derivatives provides a straightforward method to prepare chiral compounds. Different from the basic six-membered ring pyridine and quinoline, the mono-nitrogen containing five-membered pyrroles and indoles exhibit weak acidic properties and opposite electron distribution. In most cases, the indole substrates only bearing an electron-withdrawing protecting group, such as Ac, Ts, or Boc, on the nitrogen atom could be hydrogenated. Chiral phosphorus ligands, particularly chiral diphosphines, were usually used for this transformation [95–101] and some of them are listed in Fig. 5. In addition, a breakthrough in the

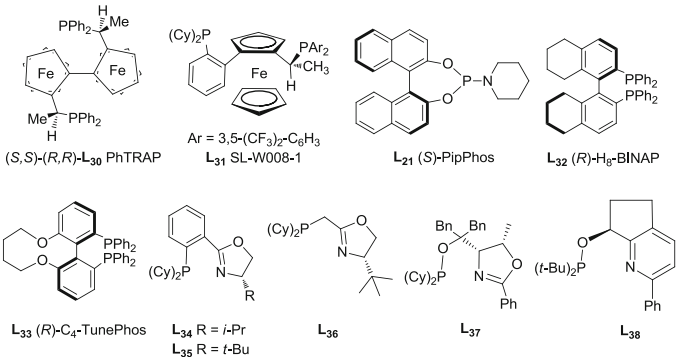
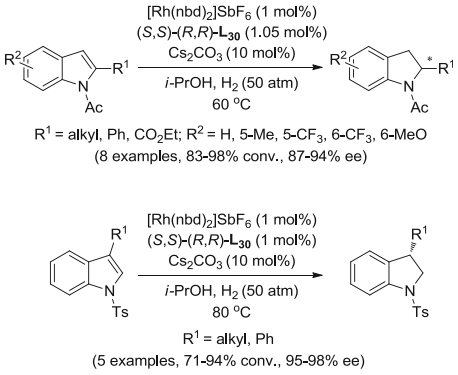


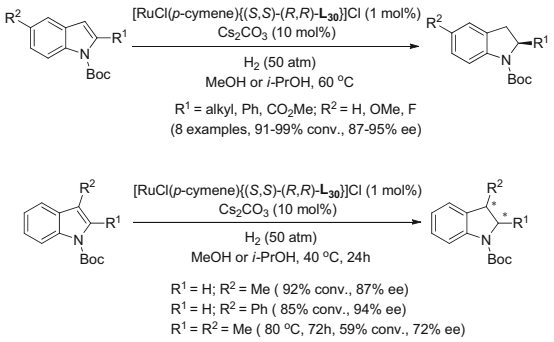
Fig. 5 Representative diphosphines and *P*,*N*-ligands for the asymmetric hydrogenation of indoles and pyrroles



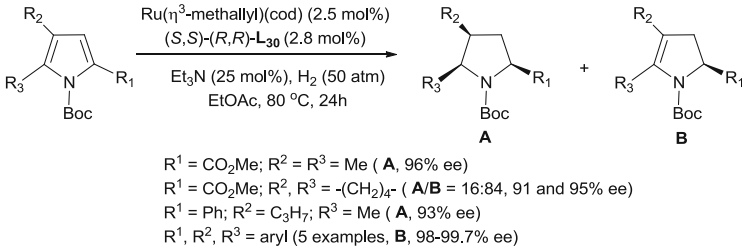
Scheme 19 Asymmetric hydrogenation of 2- and 3-substituted indoles catalyzed by $[Rh(nbd)_2]SbF_6$/PhTRAP

asymmetric hydrogenation of unprotected simple indoles was recently made by Zhou with homogeneous palladium catalytic system together with substrate activation strategy.

Early in 2000, Kuwano and co-workers reported the first efficient asymmetric hydrogenation of indoles with rhodium catalysts [95]. With a *trans*-chelating chiral diphosphine, (*S*,*S*)-(*R*,*R*)-PhTRAP, a series of 2-substituted *N*-acetyl indoles were tested, and high yields (83–98%) and excellent enantioselectivities (87–94% *ee*s) were achieved (Scheme 19). Later, they extended the substrate scope to a wide range of 2- and 3-substituted indoles with different *N*-protecting groups [96, 97]. Similarly, the combination of PhTRAP and $[Rh(nbd)_2]SbF_6$ (nbd = 2,5-norbornadiene) was demonstrated to be optimal, and excellent *ee* values were achieved for 3-substituted *N*-tosyl-protected indoles. This method was also applied to the synthesis of a Wierenga's synthetic intermediate for the left-hand segment of the antitumor agent (+)-CC-1065 [102].



Scheme 20 Asymmetric hydrogenation of *N*-Boc-protected 2-substituted indoles catalyzed by Ru-PhTRAP complex

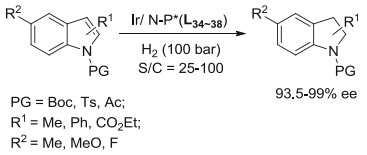


Scheme 21 Asymmetric hydrogenation of trisubstituted pyrroles catalyzed by Ru-PhTRAP complex

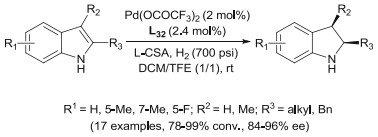
Subsequently, the same research group applied the same (*S,S*)-(*R,R*)-PhTRAP ligand in the ruthenium catalyzed hydrogenation of *N*-Boc-protected indoles [100], which could not gain satisfying stereo induction with rhodium catalysis (Scheme 20). With [RuCl(*p*-cymeme){(*S,S*)-(*R,R*)-PhTRAP}]Cl/$CsCO_3$ combination, a set of 2- and 3-substituted *N*-Boc-protected indoles were hydrogenated effectively in high yields (up to 99%) with high enantioselectivities (up to 95% *ee*). This catalytic system was also used for the hydrogenation of 2,3-dimethylindole, giving *cis*-2,3-dimethylindoline in moderate yield with good enantioselectivity.

On the basis of the above success, in 2008 Kuwano and co-workers developed the first highly enantioselective hydrogenation of *N*-Boc protected 2,3,5-trisubstituted pyrroles with the previously reported ruthenium catalytic system [101]. Under optimized reaction conditions, a series of pyrrole derivatives were hydrogenated smoothly with their chiral Ru-PhTRAP catalyst in the presence of a suitable base, giving chiral pyrrolidines (**A**) and/or 4,5-dihydropyrroles (**B**) with full conversions and excellent *ee* values (98–99.7%) (Scheme 21).

In addition to the diphosphine-containing metal (Rh and Ru) catalysts, most recently, Pfaltz and co-worker found the cationic iridium complexes derived from



Scheme 22 Asymmetric hydrogenation of 2- and 3- substituted indoles catalyzed by iridium-*P*,*N* complex

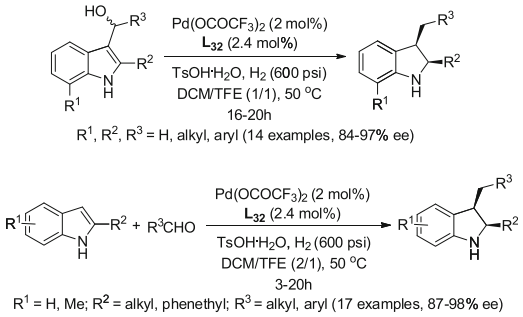


Scheme 23 Asymmetric hydrogenation of unprotected indoles using $Pd(OCOCF_3)_2$/(*R*)-H8-BINAP with a Brønsted acid as an activator

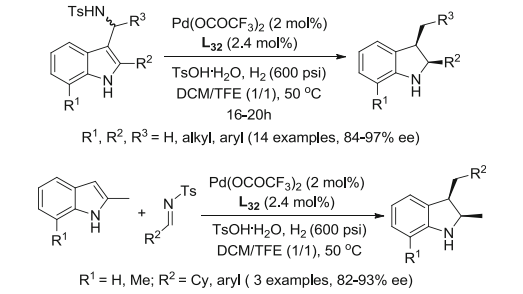
PHOX or other chiral *P*,*N*-ligands to be efficient catalysts for the asymmetric hydrogenation of *N*-protected indoles (Scheme 22) [103]. In contrast to the findings reported by Kuwano, adding a base additive to the reaction mixture led to negative results. With proper combination of the protecting group and the chiral iridium catalyst, hydrogenation of series of 2- and 3-substituted indoles proceeded smoothly with full conversions and good to excellent enantioselectivities (up to 99% *ee*).

Recently, chiral diphosphine-containing palladium complexes have proven to be effective catalysts for the asymmetric hydrogenation of imines, olefins, and ketones [104–110]. However, in contrast to the Rh, Ir, and Ru catalysts, the Pd catalysts are rarely utilized for the asymmetric hydrogenation of heteroaromatic compounds. In 2010, the first example of the Pd-catalyzed asymmetric hydrogenation of heteroaromatics was reported by Zhou and co-workers [111]. They found that the palladium complex bearing (*R*)-H8-BINAP was an efficient catalyst for the highly enantioselective hydrogenation of *N*-unprotected indoles by using a stoichiometric amount of strong Brønsted acid as activator (Scheme 23). Under optimized reaction conditions, a variety of 2-substituted indoles were hydrogenated in high yields (78–99%) with good to excellent enantioselectivities (84–96% *ee*s). The existence of a reversible process of protonation and deprotonation (enamine/imine isomerization) was demonstrated by isotopic labeling experiments; and the equilibrium proved to be faster than hydrogenation. For the hydrogenation of 2,3-disubstituted indoles, a dynamic kinetic resolution was involved; and *cis*-indolines were obtained with excellent enantioselectivities. In addition, a special mixed solvent system containing TFE (TFE = trifluoroethanol) was crucial for attaining high enantioselectivity and reactivity.

Subsequently, Zhou and co-workers found that 3-(α-hydroxy-alkyl)indoles, which were easily synthesized by nucleophilic additions, could undergo dehydration to form vinylogous iminium salts in the presence of Brønsted acid. Subsequent asymmetric



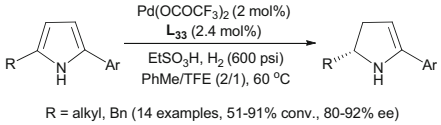
Scheme 24 Enantioselective synthesis of 2,3-disubstituted indolines *via* Pd-catalyzed asymmetric hydrogenation of 3-(α-hydroxy-alkyl)indoles and one-pot Brønsted acid/Pd-promoted tandem reactions



Scheme 25 Enantioselective synthesis of 2,3-disubstituted indolines *via* Pd-catalyzed asymmetric hydrogenation of 3-(toluenesulfonamidoalkyl)indoles and one-pot Brønsted acid/Pd-promoted tandem reactions

hydrogenation of the in situ generated vinylogous iminium intermediate [112] in the presence of Pd/H8-BINAP provided 2,3-disubstituted indolines with excellent enantioselectivities (up to 97% *ee*) (Scheme 24). Based on this finding, they further realized one-pot Brønsted acid/Pd-H8-BINAP promoted tandem Friedel-Crafts/dehydration/hydrogenation reactions with 2-substituted indoles and aldehydes as the starting materials (Scheme 24), giving 2,3-disubstituted indolines with excellent enantioselectivities (87–98% *ee*s) [113].

Very recently a series of 2-substituted 3-(toluenesulfonamidoalkyl)indoles were also synthesized by the same group and applied to the asymmetric hydrogenation [114]. Similar Brønsted acid/Pd-H8-BINAP promoted $TsNH_2$-elimination/hydrogenation processes provided 2,3-disubstituted indolines with comparable *ee* values to those obtained from 3-(α-hydroxy-alkyl)indoles as substrates. In addition, one-pot tandem Friedel-Crafts/hydrogenation reactions with *N*-tosyl imines and 2-substituted indoles as starting materials were also realized through relay catalysis by Brønsted acid/H8-BINAP/Pd (Scheme 25), giving the reduced products in high yields with excellent enantioselectivities.



Scheme 26 Asymmetric hydrogenation of 2,5-disubstituted pyrroles catalyzed by Pd-(*R*)-C_4-TunePhos complex

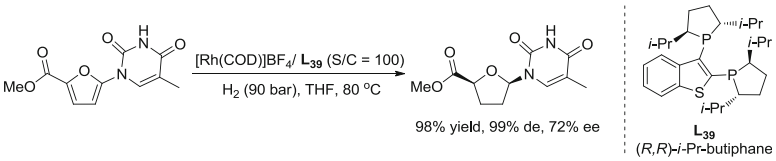
In 2011, Zhou and co-workers used a palladium/diphosphine catalytic system for the asymmetric hydrogenation of simple 2-alkyl-5-arylpyrroles [115]. With a Brønsted acid as activator and Pd/C_4-TunePhos as catalyst, a series of partially reduced chiral 2,5-disubstituted 1-pyrrolines were obtained in moderate to high yields with very good enantioselectivities (Scheme 26). It was found that the length and steric property of alkyl side chain and the electronic and steric properties of aryl substituent showed a clear influence on the enantioselectivity. Substrates with electron-withdrawing and/or steric hindered aryl substituents displayed better results.

7 Asymmetric Hydrogenation of Furans and Benzofurans

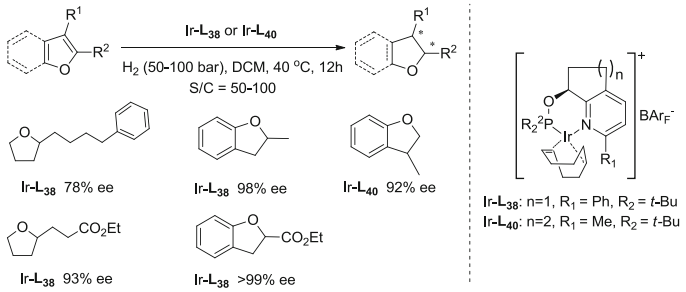
Compared to the enormous effort put into the research of asymmetric hydrogenation of *N*-containing heteroaromatic compounds, other hetero atom-containing heteroaromatics, such as furans, thiophenes, benzofurans, and benzothiophenes, are much less explored; and their highly enantioselective hydrogenations are still a big challenge in the field of asymmetric hydrogenation.

7.1 Chiral Phosphorus-Containing Ligands

Furan is among the limited compounds which were investigated in the pioneering stage of the research area of asymmetric hydrogenation of heteroaromatics (For examples of heterogeneous asymmetric hydrogenation of furans, see: [116–118]). In 1995, Takaya and co-workers published their initial results on the first homogeneous enantioselective hydrogenation of 2-methylfuran with Ru-BINAP catalyst, but only 50% *ee* of enantioselectivity was obtained under relatively harsh reaction conditions [118]. Five years later, Studer and co-workers reported the first rhodium-catalyzed asymmetric hydrogenation of 2-functionalized furans [87], including 2-furan carboxylic acid and 2-hydroxylmethylfuran. After screening of a series of diphosphine ligands, only less than 30% *ee* values were obtained, whereas the catalytic activity was pretty high. Recently, Albert and co-workers reported asymmetric hydrogenation of 2,5-disubstituted furans with cationic rhodium/



Scheme 27 Rhodium-catalyzed asymmetric hydrogenation of 2,5-disubstituted furan



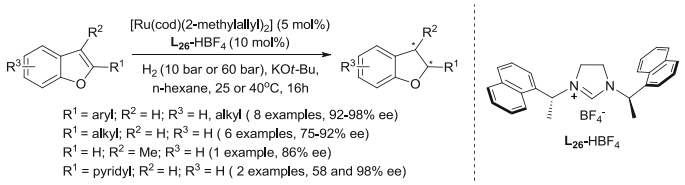
Scheme 28 Asymmetric hydrogenation of furan and benzofuran derivatives catalyzed by Ir-*P*,*N* complexes

diphosphine complex [119], giving 2′,3′-dideoxynucleoside analogue with high diastereoselectivity and moderate enantioselectivity (Scheme 27).

A breakthrough in the asymmetric hydrogenation of simple furan and benzofuran derivatives was reported by Pfaltz and co-workers in 2006 (Scheme 28) [120]. They found that iridium complexes containing pyridine-phosphinite ligand, which have proven to be excellent catalysts for the hydrogenation of unfunctionalized olefins [121], were effective for the asymmetric hydrogenation of simple furans and benzofurans. With the cationic iridium catalysts bearing a bulky electron-rich $(t\text{-Bu})_2$P group on the *P*,*N*-ligand, several 2-alkyl-substituted furans and 2- or 3-substituted benzofurans were successfully hydrogenated, providing tetrahydrofurans and benzodihydrofurans with high *ee* values (78% to >99% *ee*).

7.2 *Chiral* N-*Heterocyclic Carbene Ligands*

After the successful application and unique performance in the asymmetric hydrogenation of quinoxaline derivatives, the chiral *N*-heterocyclic carbene ligands were employed in the ruthenium-catalyzed enantioselective hydrogenation of benzofurans in 2012 by Glorius and co-workers (Scheme 29) [122]. The regioselective reduction of the heterocyclic ring was observed, offering 2,3-dihydrobenzofurans as the only products. Under the optimized reaction conditions, a series of 2-aryl and 2-alkyl substituted benzofuran derivatives were smoothly hydrogenated in the



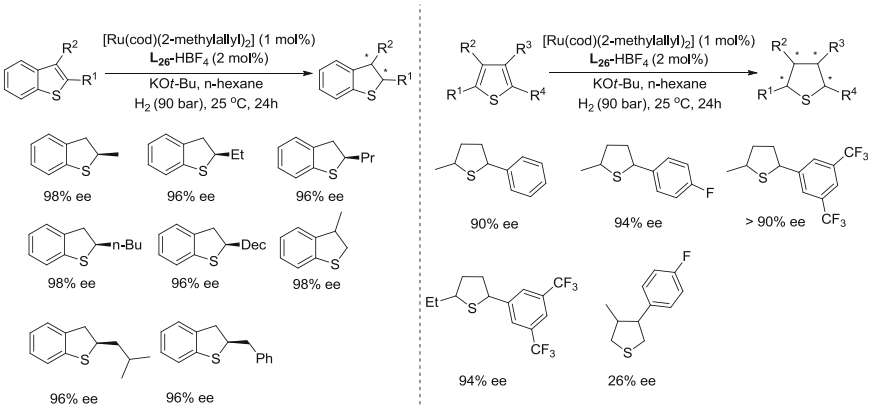
Scheme 29 Asymmetric hydrogenation of 2,3-disubstituted and 2,3,6-trisubstituted benzofuran catalyzed by Ru-NHC complex

presence of 10 mol% ruthenium catalyst under 10 or 60 bar of H_2 and mild reaction temperature. In most cases, full conversions and excellent enantioselectivities (up to 98% *ee*) were achieved. It was found that the 2-aryl substituted benzofurans bearing electron-withdrawing substituents exhibited higher reactivity than those containing electron-donating groups. In addition, higher reaction temperature and hydrogen pressure were needed for sterically demanding substrates of 2-(*o*-tolyl)-benzofuran and 2-(*tert*-butyl)-benzofuran, and lower conversions (73% and 38%) and/or enantioselectivities (92% and 75% *ee*) were observed, respectively. Further kinetic study revealed that full conversion of 2-methyl benzofuran was achieved at a catalyst loading of 0.5 mol%, providing a TON of 200 and TOF of 1,092 h^{-1}; and an induction period of 1 h was required to form the catalytically active species, and the reason was unknown.

8 Asymmetric Hydrogenation of Thiophenes and Benzothiophenes

Optically active dihydro- and tetrahydrothiophene structures are widely existent in naturally occurring and artificial bioactive molecules [123]. Asymmetric hydrogenation of the corresponding aromatic organosulfur compounds is undoubtedly a straightforward and efficient method for the synthesis of such chiral heterocyclic compounds. However, thiophene, particularly substituted thiophene derivatives, are challenging substrates for homogeneous catalysis, probably due to its aromaticity and the strong coordination/poisoning ability of the substrate and/or the reduced products. To date, the only successful example of asymmetric hydrogenation of thiophenes and benzothiophenes was reported in 2012 by Glorius and co-workers [124].

It was found that the Ru/NHC complex generated in situ from Ru(COD)(2-methylally)$_2$ and monodentate NHC **L26** was a highly efficient catalyst for the hydrogenation of thiophenes and benzothiophenes. Under optimized reaction conditions, hydrogenation of a series of 2-alkyl-substituted benzothiophenes proceeded smoothly, providing chiral 2,3-dihydrobenzothiophenes in moderate to high yields with excellent enantioselectivities of 96–98% *ee*s (Scheme 30). Similarly, 3-methylbenzothiophene could also be reduced in 79% yield with 98% *ee*. However,

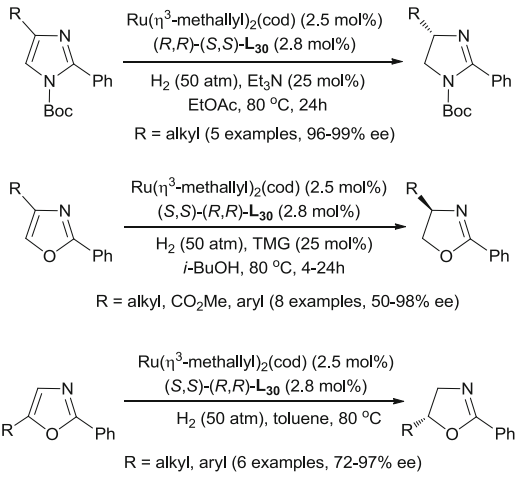


Scheme 30 Asymmetric hydrogenation of substituted benzothiophenes and thiophenes catalyzed by Ru-NHC complex

no conversion of arylated substrates was observed. In the case of thiophenes, it was found that the hydrogenation of 2- and 3-alkyl, and 2-aryl substituted thiophenes proceeded smoothly, but giving racemic tetrahydrothiophenes. Remarkably, 2,5-disubstituted thiophene derivatives could be hydrogenated to tetrahydrothiophenes with moderate to high yields and perfect diastereoselectivities (only *cis*-products were observed) and excellent enantioselectivities (up to 94% *ee*). In addition, a 3,4-disubstituted thiophene was also hydrogenated to give the reduced product in good yield but with lower enantioselectivity (26% *ee*).

9 Asymmetric Hydrogenation of Imidazoles and Oxazoles

Like thiophenes and benzothiophenes, the catalytic asymmetric hydrogenation of five-membered heteroaromatic rings containing two or more heteroatoms are less studied. The only example of highly enantioselective hydrogenation of such monocyclic heteroaromatics was reported by Kuwano and co-workers in 2011 [125]. With chiral Ru-PhTRAP complex as the catalyst, which has been successfully applied for the asymmetric hydrogenation of indoles and pyrroles, both imidazoles and oxazoles were hydrogenated smoothly, giving partially reduced chiral imidazolines and oxazolines, respectively (Scheme 31). It was found that excellent *ee* values (96–99% *ee*) were achieved for the hydrogenation of 2-phenyl-4-alkyl-substituted *N*-Boc-imidazoles. In the case of oxazoles, both 4- and 5-substituted 2-phenyloxazoles were smoothly hydrogenated to chiral oxazolines with good to excellent enantioselectivities (72–98% *ee*s). In most cases, adding TMG (*N*,*N*,*N*′,*N*′-tetramethylguanidine) as a base was necessary for fast conversions. In addition, subsequent hydrolysis of the obtained chiral imidazolines and oxazolines provided acyclic chiral 1,2-diamine and β-amino alcohols, respectively, which are widely used as chiral auxiliaries in organic synthesis.



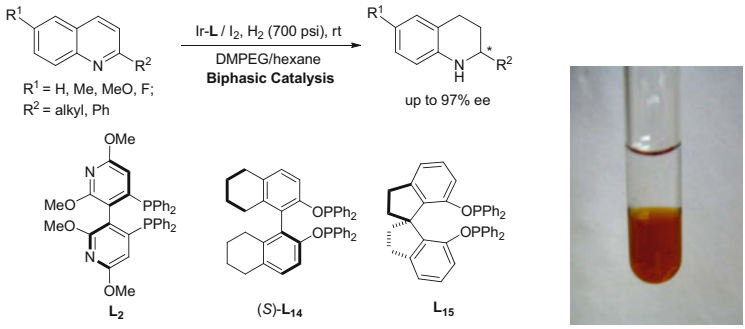
Scheme 31 Asymmetric hydrogenation of *N*-Boc-protected imidazoles and oxazoles catalyzed by Ru-PhTRAP complex

10 Catalyst Immobilization

As described above, various transition metal catalysts involving rhodium, iridium, ruthenium, and palladium complexes bearing different types of chiral ligands have proven to be effective in the asymmetric hydrogenation of *N*-, *O*-, and *S*-containing heteroaromatic compounds. However, most catalytic systems suffered from low catalyst efficiency as evidenced by the fact that good results could only be obtained at a low substrate-catalyst ratio of 100. Considering that all these catalysts bearing noble metals and chiral ligands are very expensive and also toxic, immobilization of these catalysts is highly desirable. To date, a number of methods for recycling homogeneous chiral catalysts have been developed over the past several decades [126–131]. However, only a few examples have been reported on the immobilization of transition metal catalysts in the asymmetric hydrogenation of quinoline derivatives.

10.1 Biphasic Catalytic Systems

Recently, liquid polyethylene glycol (PEG) has been adopted as a new approach for catalyst recycling due to their benign characteristics [132, 133]. In 2005, Fan, Chan, and co-workers developed the first immobilized iridium catalytic system for the asymmetric hydrogenation of heteroaromatics (Scheme 32) [29, 134]. At the beginning, ionic liquids and PEG instead of organic solvents were used in the Ir/P-Phos catalyzed asymmetric hydrogenation of quinolines. However, poor conversion and/or enantioselectivity were observed. When the less polar



Scheme 32 Biphasic catalytic asymmetric hydrogenation of quinolines with iridium catalysts in DMPEG/hexane

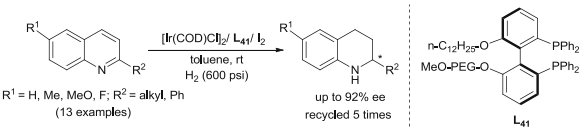
polyethylene glycol dimethyl ether (DMPEG) was used as the solvent, complete conversion and very good enantioselectivity were obtained. To facilitate the separation of the product and the recycling of the catalyst, the DMPEG/hexane biphasic catalytic system was applied in this reaction. A series of 2-substituted quinolines were hydrogenated to 1,2,3,4-tetrahydroquinolines in high yields with excellent enantioselectivities, which were comparable to those obtained in THF. More importantly, the reduced product could easily be separated via simple decantation and the DMPEG layer containing the iridium catalyst was used in the next catalytic run. The catalyst was reused at least eight times without obvious loss of reactivity and enantioselectivity [29].

Subsequently, this immobilization approach was extended to the iridium complexes bearing chiral diphosphinites H8-BINAPO and SpiroPO [47, 48]. When the reactions were carried out in a biphasic DMPEG/hexane system, comparable and even higher enantioselectivities were observed as compared to those obtained in aprotic organic solvents [47]. Similarly, the catalyst could be reused for several times, but the recovered catalyst showed decreased reactivity due to the possible decomposition of the catalyst in the course of recycling.

10.2 Catalyst Immobilization with Soluble Linear Polymer

Unlike the cross-linked polymer-supported homogeneous chiral catalysts, the linear polymeric chiral catalysts bearing catalytically active units on the main chain catalyze organic reactions in a completely homogeneous manner, similar to the conventional homogeneous catalytic reaction. When the reaction is complete, the catalyst can be separated by either solvent precipitation or membrane filtration. Therefore, soluble polymers as alternative catalyst supports have recently attracted much attention [135, 136].

Recently, Zhou and co-worker developed a series of tunable axial chiral diphosphine ligands by attaching MeO-BIPHEP onto soluble polyethylene glycol



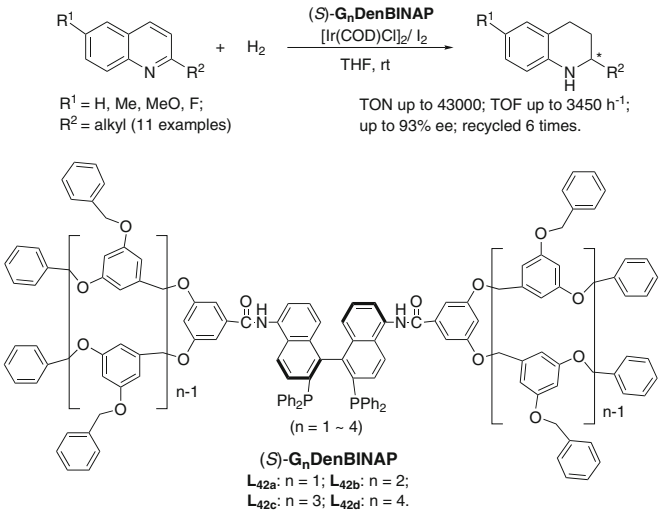
Scheme 33 Asymmetric hydrogenation of quinolines with PEG-supported iridium catalysts

(PEG, Mw = 1,000, 1,600, and 5,000) support via covalent bonding (Scheme 33) [137]. MeO-PEG (1,600)-based chiral ligands bearing different alkyl substituents gave 80–91% *ee*s in the Ir-catalyzed asymmetric hydrogenation of 2-methyl quinoline. The different enantioselectivities might be due to the varying of the dihedral angle of the chiral backbone. The attachment of PEG support with different molecular weight onto the ligand had no obvious effect on the *ee* values. With MeO-PEG (1,600)-supported MeO-BIPHEP as the ligand, a series of 2-substituted quinolines were hydrogenated to 1,2,3,4-tetrahydroquinolines in high yields (85–97%) with very good *ee* values (89–92% *ee*s). Interestingly, the MeO-PEG-supported iridium catalyst was found to be more air-stable and could be recovered by solvent precipitation. The catalyst was reused at least five times with the maintenance of the reactivity, but the enantioselectivity gradually decreased from 91% *ee* to 84% *ee* during the process.

10.3 Chiral Dendrimeric Catalyst

In recent years, attachment of homogeneous catalysts to dendrimers has been attracting considerable attention owing to its well-defined molecular architecture (For recent reviews on organometallic dendrimer catalysts, see [138–143]). Unlike traditional polymer-supported catalysts, dendrimeric catalysts offer opportunities for the study of support-catalyst interactions to fine-tune both catalytic activity and stereoselectivity through systematic adjusting of their structure, size, shape, and solubility. In the case of the core-functionalized dendrimers, it is expected that the steric shielding or blocking effect of the specific microenvironment created by the branched shell could modulate the catalytic behavior of the core.

In 2007, Fan and co-workers applied their BINAP-cored poly(benzyl ether) dendrimers to the iridium catalyzed asymmetric hydrogenation of 2-alkyl-substituted quinolines (Scheme 34) [144, 145]. All four generations of dendrimer catalysts, generated in situ from BINAP-cored dendrimers and $[Ir(COD)Cl_2]$, were found to be effective even at an extremely high substrate/catalyst ratio in the asymmetric hydrogenation of 2-methyl quinoline with I_2 as the additive. It was found that the catalytic activity gradually increased with increasing dendrimer generation, and the maximum initial TOF from the third-generation catalyst could reach 3,450 h^{-1}, which represents the highest TOF obtained so far for the asymmetric hydrogenation of quinolines. In addition, the reaction proceeded smoothly



Scheme 34 Asymmetric hydrogenation of quinolines with dendrimeric iridium catalysts

under rather low catalyst loading in a large scale reaction (~18 g substrate) to give a TON of 43,000, which is also the highest TON reported to date for such a reaction.

This rate enhancement of the dendrimer catalysts was further demonstrated by the time-conversion curves (Fig. 6). This was probably due to the encapsulation of such an iridium complex into a dendrimer framework, which would reduce the formation of inactive iridium dimer and therefore enhance the productivity of the catalyst. In addition, the third-generation dendrimer catalyst could be quantitatively recovered by precipitation with methanol, and reused at least six times with similar enantioselectivities but at the expense of relatively low catalytic activities.

10.4 Catalyst Immobilization in Ionic Liquid

The use of room temperature ionic liquids as alternative reaction media is particularly good in enhancing catalyst stability and reaction rates, and improving stereoselectivity in transition metal-catalyzed asymmetric hydrogenation. In addition, ionic liquids have served as a promising means to immobilize catalysts, therefore facilitating product isolation and offering an opportunity to reuse the catalyst [146–150].

In 2008, Fan and co-workers first used phosphine-free cationic Ru-TsDPEN catalyst for the asymmetric hydrogenation of quinolines [24] and found that the

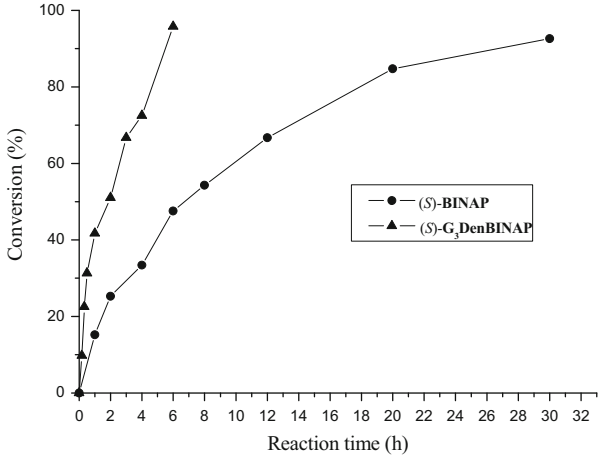
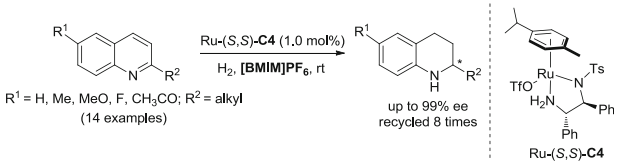


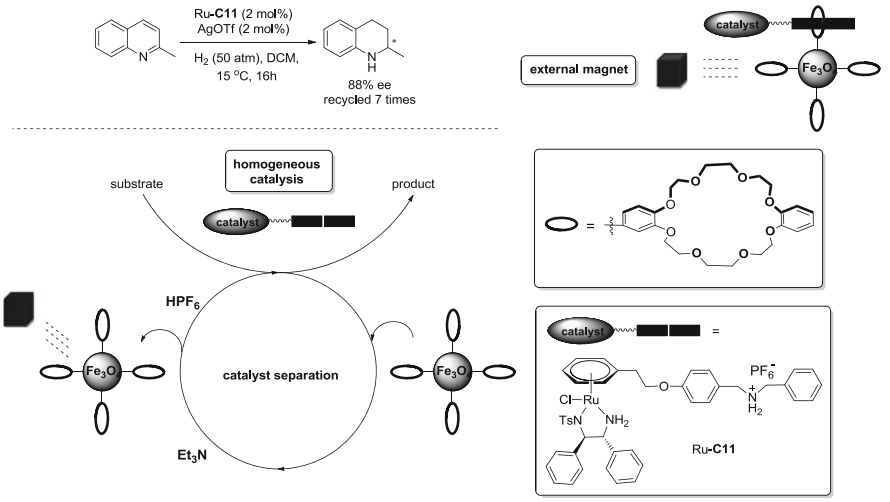
Fig. 6 Time course curves for the Ir-catalyzed hydrogenation of 2-methyl quinoline using the third-generation dendrimer and BINAP



Scheme 35 Asymmetric hydrogenation of quinolines with ruthenium catalyst in ionic liquid

reaction proceeded smoothly in neat ionic liquid [BMIM]PF_6 (Scheme 35, BMIM = 1-*n*-butyl-3-methylimidazolium). Unlike the Ir/diphosphine/I_2 catalytic system, which gave unsatisfactory results in ionic liquid [29], unprecedented reactivities and excellent enantioselectivities were achieved, which are better than those in methanol. Under the optimized reaction conditions, a variety of 2-alkyl quinolines were hydrogenated to tetrahydroquinolines in high yields (87–97%) with excellent enantioselectivities (96–99% *ee*). More interestingly, it was found that the hydrogenation in ionic liquid was selective for the C = N (quinoline) over the C = O bond, which were both reduced in methanol.

In addition, the catalyst stability was obviously enhanced in ionic liquid. Even after exposing the catalyst solution to air for 30 days, almost the same activity and enantioselectivity were observed. In contrast, the catalyst in methanol was found to be decomposed within 1 week under otherwise identical conditions. The dramatic enhancement of the catalyst stability by an ionic liquid was probably a result of the solvation effect of [BMIM]PF_6 on the cationic Ru catalyst and the very low solubility of oxygen in the ionic liquid. On the basis of the high stability of the catalyst in ionic liquid, manipulation of catalyst recycling was easy and reliable. Upon completion of the reaction, the reduced products were separated by extraction



Scheme 36 Homogeneous asymmetric hydrogenation of 2-methylquinoline and catalyst recycling by heterogeneous magnetic nanoparticles through supramolecular protocol

with *n*-hexane. The ionic liquid layer was recharged with quinoline and subjected to the next catalytic run. The ruthenium catalyst was reused at least eight times without obvious decrease in reactivity and enantioselectivity.

10.5 Catalyst Immobilization with Magnetic Nanoparticles

Nanoparticles are considered to be robust and readily available heterogeneous catalysts as well as catalyst supports for catalytic transformations due to their high surface area [151–155]. Based on its heterogeneous nature, covalently bonded nanoparticle-immobilized catalysts are still suffering from decreased catalytic activity and selectivity. By introducing non-covalent interactions between the nanoparticle support and homogeneous catalyst, both homogeneous catalysis and heterogeneous catalyst separation could be realized in the same reaction. In recent years, magnetic nanoparticles as solid support for catalysis have attracted more and more attentions due to its simple separation from liquid reaction mixtures with the aid of an external magnet [154, 155].

In 2011, a homogeneous catalyst/heterogeneous catalyst separation protocol combining the use of magnetic nanoparticles and host-guest assembly was developed by Fan and co-workers [156]. This novel approach was applied in the Ru-catalyzed asymmetric hydrogenation of 2-methylquinoline (Scheme 36). After the homogeneous hydrogenation catalyzed by the chiral Ru-diamine catalyst bearing a dialkylammonium salt tag, crown ether functionalized magnetic nanoparticles were added to facilitate host-guest assembly. The assembled

heterogeneous catalyst was readily recovered by magnet-assisted decantation, and was further basified to release the tagged catalyst. The recycled catalyst was then acidified and reused in the hydrogenation again by recharging 2-methylquinoline. The catalyst was reused seven times with similar *ee* values (88–89%) and nearly quantitative conversions.

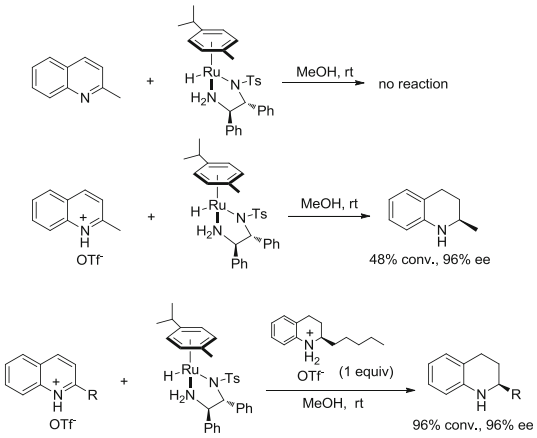
11 Mechanistic Aspects

As one of the most straightforward and powerful approaches for the creation of optically active heterocyclic compounds, asymmetric hydrogenation has been successfully used for different types of heteroaromatics, including quinolines, isoquinolines, quinoxalines, pyridines, indoles, pyrroles, furans, thiophenes, imidazoles and oxazoles, with excellent enantioselectivities. However, only a few detailed studies of the reaction mechanism have been published to date. This might be, on one hand, due to the short history of research in this topic. On the other hand, such transformations are more complicated relative to hydrogenation of alkenes, ketones, and imines, which generally involve reduction of different types of double bonds, together with isomerization and dehydrogenation processes. Most recently, efforts have been devoted to the mechanism studies of ruthenium and iridium catalyzed asymmetric hydrogenation of quinolines and quinoxalines. Both stepwise inner-sphere and stepwise outer-sphere pathways were proposed, depending on the catalytic system, addition of additives, and substrate used.

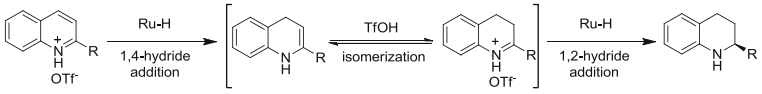
11.1 Mechanism for Asymmetric Hydrogenation of Quinolines

In general, the reduction of quinolines includes a hydrogenation sequence of C = C and C = N bonds. In 2008, Fan and co-workers proposed an ionic and cascade reaction pathway, including 1,4-hydride addition, isomerization, and 1,2-hydride addition for the asymmetric hydrogenation of quinolines in ionic liquid [24]. Subsequently, Fan, Yu, and co-workers further investigated the catalytic pathway of this reaction systematically by using a combination of stoichiometric reaction, intermediate characterization and isotope labeling patterns together with DFT (density functional theory) calculations [65].

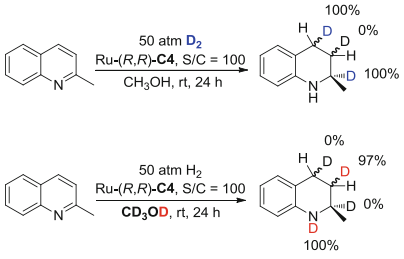
In the stoichiometric reaction between 2-substituted quinolines and ruthenium hydride complex, it was found that the addition of 2 equiv. of Brønsted acid was crucial for full conversion. Unlike the hydrogenation of aromatic ketones with a similar ruthenium catalyst, quinolines should be activated by the Brønsted acid before hydrogenation (Scheme 37). In addition, the existence of an imine intermediate was confirmed by the evidence from ^{1}H NMR (nuclear magnetic resonance)



Scheme 37 Stoichiometric reduction of quinoline with isolated Ru-H hydride



Scheme 38 The possible hydrogenation pathway of quinoline with Ru-H hydride



Scheme 39 Deuterium-labeling studies

and ESI-MS (electrospray ionization-mass spectrometry) characterization. These observations suggested a possible ionic catalytic pathway including 1,4-hydride addition, isomerization, and then 1,2-hydride addition process (Scheme 38). The deuteration study further provided positive evidence, such as that 100% deuterium at both C-2 and C-4 positions were observed when D_2 was employed, and 97% deuterium at the C-3 position was observed when CD_3OD was used as the solvent (Scheme 39). Furthermore, the 1,4-hydride addition step proved to be reversible by deuterium scrambling into recovered 2-phenyl quinoline at the C4-position, and 1,2,3,4-tetrahydroquinoline at the C2- and C4-positions.

To further understand the mechanism and the origins of enantioselectivity, theoretical calculations were carried out to study the hydrogenation process of the

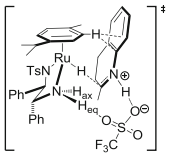
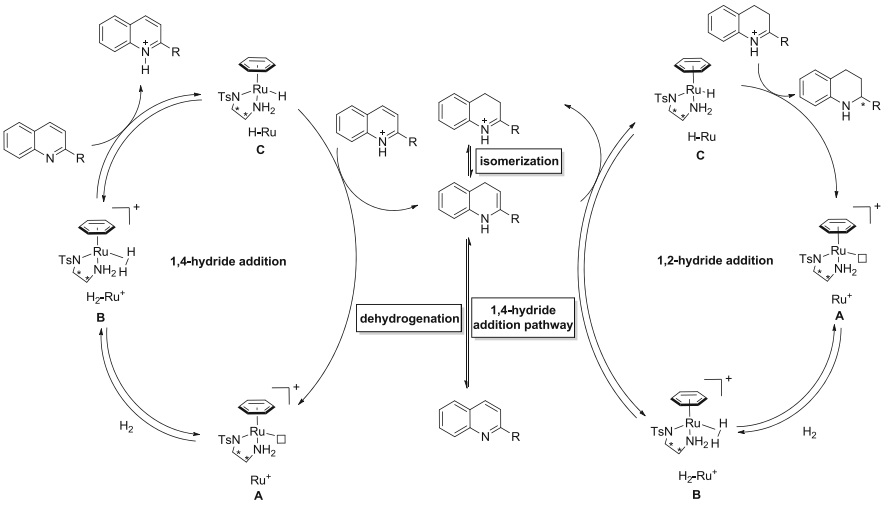


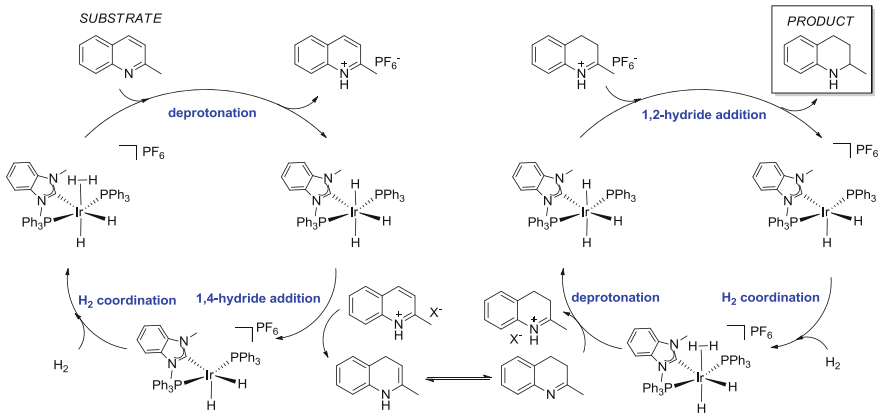
Fig. 7 Calculated transition structures for the hydride transfer to imine



Scheme 40 Catalytic cycle proposed for the asymmetric hydrogenation of quinoline using Ru(II)-TsDPEN catalyst (ethylenediamine ligand and OTf^- are omitted for clarity)

protonated imine intermediate in situ generated by the 1,4-hydride addition and isomerization. The computational results indicated that the final 1,2-hydride addition should proceed through an ionic pathway involving the following transition state (Fig. 7). Similar to the ketone reduction reported by Noyori and co-workers [157, 158], the enantioselectivity originated from the CH/π attraction between the η^6-arene ligand in the Ru-complex and the fused phenyl ring of dihydroquinoline via a 10-membered ring transition state with the participation of TfO^- anion. This proposed transition state also offered new insights into the mechanism of other imine reduction involved reactions with similar ruthenium catalysts [159].

Based on these experimental and theoretical results, a plausible mechanism for this process was thus proposed (Scheme 40). First, dihydrogen is reversibly coordinated to the ionized ruthenium complex **A**. The formed dihydrogen complex **B** is then deprotonated by quinoline to generate both the active ruthenium hydride species **C** and the activated substrate. A subsequent 1,4-hydride transfer affords the enamine intermediate and the regenerated **A**. Similarly, the enamine serves as a base to deprotonate the dihydrogen ligand, resulting in species **C** and the iminium cation.

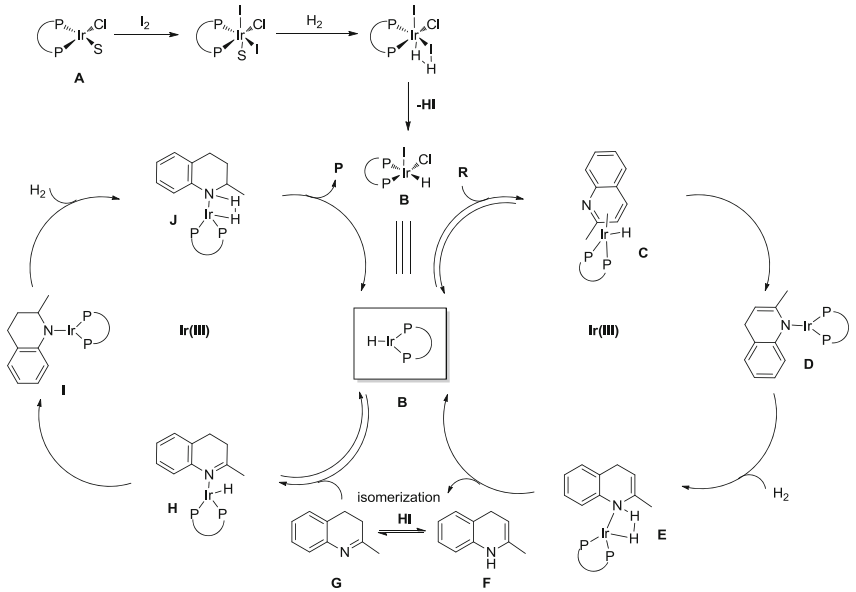


Scheme 41 Catalytic cycle proposed for the hydrogenation of 2-methylquinoline using Ir(I)-NHC catalyst

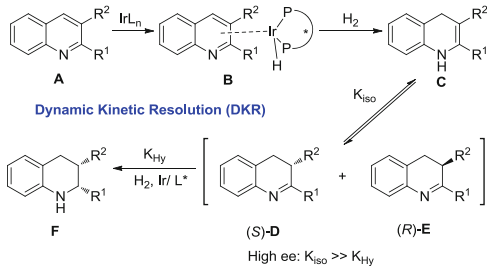
Finally, 1,2-hydride transfer via a ten-membered ring transition state as described above gives 1,2,3,4-tetrahydroquinoline enantioselectively, and regenerates ruthenium complex **A**.

In 2011, Crabtree and co-workers developed a new homogeneous achiral iridium catalyst for the hydrogenation of quinolines under mild conditions [160]. Based on experimental and theoretical results, a similar ionic and cascade reaction pathway and an unusual stepwise outer-sphere mechanism were proposed (Scheme 41).

As described in Sect. 2, the first highly enantioselective hydrogenation of quinolines was realized with iridium/diphosphine/I_2 catalytic system. In 2009, Zhou and co-workers proposed two possible hydrogenation pathways depending on the initial 1,2- or 1,4-hydrogen addition [28]. A combination of experimental and theoretical studies indicated that hydrogenation of quinolines favored an initial 1,4-hydride transfer tandem reaction pathway. A conventional inner-sphere mechanism was proposed through a cascade reaction of 1,4-hydride addition, enamine-imine isomerization, and 1,2-hydride addition (Scheme 42). First, the oxidative addition of I_2 to the Ir(I) catalyst precursor **A** results in Ir(III) species, which was involved in the subsequent heterolytic cleavage of the H_2 to form the catalytic active Ir(III)-H species **B**. Then quinoline (**R**) coordinates with **B** to form **C**, followed by 1,4-hydride transfer to give the intermediate **D**. Subsequent heterolytic cleavage of H_2 with **D** affords the enamine intermediate and the regenerated **B**. The enamine isomerizes to imine catalyzed by the in situ generated HI. Similarly, coordination of the formed imine with **B** gives the intermediate **H**. Subsequently, the enantioselective 1,2-insertion of C = N bond into the Ir-H bond gives the intermediate **I**. Finally, the reduced product 1,2,3,4-tetrahydroquinoline (**P**) is released via hydrogenolysis.

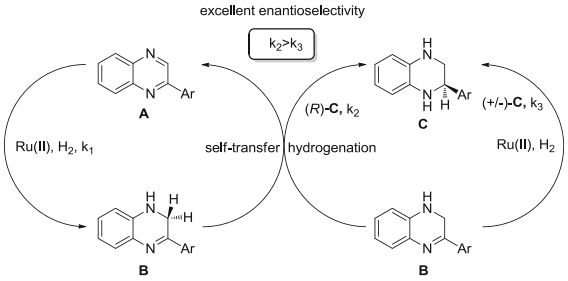


Scheme 42 Catalytic cycle proposed for the asymmetric hydrogenation of quinoline using Ir/MeO-BIPHEP/I_2 catalytic system

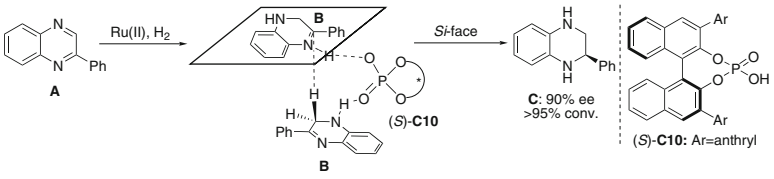


Scheme 43 Plausible mechanism for Ir-catalyzed asymmetric hydrogenation of 2,3-disubstituted quinolines via dynamic kinetic resolution

In addition, the hydrogenation process of 2,3-disubstituted quinolines is more complicated than that of 2-substituted quinolines. The enantio-determining steps include the isomerization of enamine to imine and subsequent hydrogenation of the C = N bond (Scheme 43). The first step is in fact a dynamic kinetic resolution process. It was found that high enantioselectivities were observed under high temperature and low hydrogen pressure, which accelerate the isomerization and slow down the hydrogenation. In both cases, the origin of enantioselectivity was still untouched and awaits further exploration.



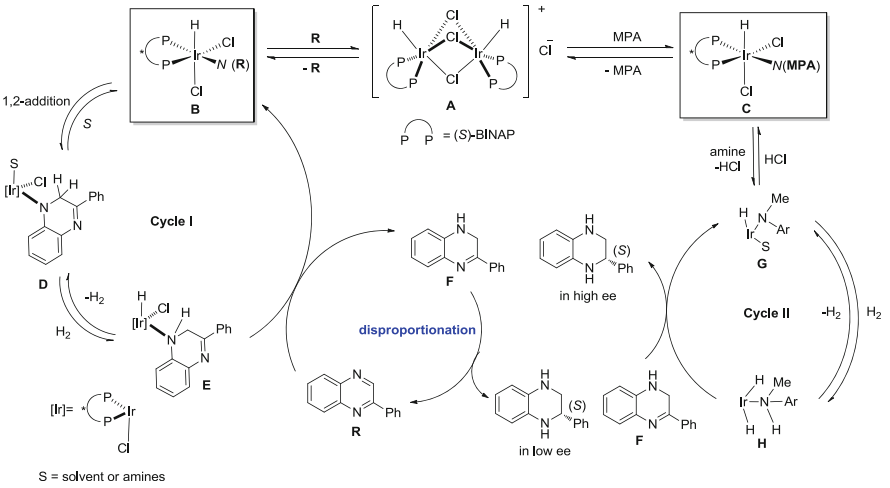
Scheme 44 Catalytic cycle proposed for the metal/Brønsted acid induced asymmetric hydrogenation of 2-aryl quinoxalines



Scheme 45 The proposed "three-point contact model" for the self-transfer hydrogenation

11.2 Mechanism for Asymmetric Hydrogenation of Quinoxalines

Over the past few decades, several homogeneous catalytic systems have been developed for the highly enantioselective hydrogenation of quinoxalines. However, fewer mechanistic studies of this reaction have been reported than those of quinolines. In 2011, Zhou and co-workers described the first mechanistic study [85] related to the convergent asymmetric disproportionation of dihydroquinoxalines induced by chiral phosphoric acid in a transition metal/Brønsted acid catalyzed asymmetric hydrogenation of 2-aryl quinoxalines. In their proposed mechanism (Scheme 44), hydrogenation of quinoxaline **A** first generates the intermediate dihydroqinoxaline **B** by using achiral ruthenium(II) as the catalyst. Subsequently, the intermediate **B** undergoes self-transfer hydrogenation catalyzed by chiral phosphoric acid, giving the starting material **A** and the final product 1,2,3,4-tetrahydroquinoxaline **C**. The intermediate **B** was observed in the hydrogenation of **A** in the absence of phosphoric acid, suggesting that the first hydrogenation process catalyzed by ruthenium complex is the rate-determining step. The observed high enantioselectivities were thus due to the fact that the reaction rate of the chiral phosphoric acid-catalyzed self-transfer hydrogenation is higher than that of the achiral ruthenium-catalyzed hydrogenation of **B**. To understand the origin of enantioselectivity, a "three-point contact model" was also proposed on the basis of experimental results and DFT calculations (Scheme 45).



Scheme 46 Catalytic cycles proposed for the asymmetric hydrogenation of quinoxalines using chiral cationic dinuclear iridium complexes

For asymmetric hydrogenation of *N*-heteroaromatic compounds with diphosphine ligands, addition of additives is crucial for achieving high reactivity and/or enantioselectivity. Most recently, Mashima and co-workers discovered the additive effects of amine in the asymmetric hydrogenation of 2-aryl quinoxalines with their chiral cationic dinuclear triple-halide-bridged iridium complexes [81]. The pK_a value and amount of amine additive were found to be crucial for the enhancement of catalytic activity. With the addition of 1 equiv. of the optimal amine *N*-methyl-*p*-anisidine (MPA), a series of 2-aryl quinoxalines were hydrogenated in nearly quantitative conversions with high *ee* values. The remarkable additive effects were then investigated in detail by solution dynamics studies of iridium complexes in the presence of MPA and by labeling experiments, which revealed a plausible dual mechanism comprised of two individual catalytic cycles in equilibrium (Scheme 46). Each of the proposed intermediates in these cycles was either isolated or spectroscopically characterized.

At the beginning, the reversible and competing coordination of substrate (cycle I) and amine additive MPA (cycle II) to the dinuclear iridium precursor **A** generates two active catalytic species **B** and **C**, respectively. For cycle I, reversible 1,2-insertion of the C = N bond of quinoxaline (**R**) into the Ir–H bond of **B** gives the intermediate **D**, followed by the addition of H_2 to the Ir–N bond to produce the intermediate **E**. Subsequent replacement reaction of **E** with the substrate gives the partially reduced product **F** and the regenerated **B**. Then acidic protons derived from catalyst **A** induce rapid racemic disproportionation of the partially reduced product **F** to give quinoxaline and racemic tetrahydroquinoxaline; at the same time, the iridium catalyst induces slow asymmetric hydrogenation to give the chiral product, thus resulting in low enantioselectivity at the early stage of hydrogenation. As the reaction proceeds, accumulation of amine product may suppress the acid-catalyzed racemic disproportionation.

For cycle II, addition of excess amounts of MPA shift the equilibrium to the formation of catalytic species **C**. Subsequent elimination of HCl from **C** affords the amide-hydride species **G**, which reacts with H_2 to give an amine-dihydride species **H**. Finally, asymmetric hydrogenation of the C = N bond of dihydroquinoxaline and quinoxaline with the catalytic species **H** to give tetrahydroquinoxaline with high enantioselectivity through the bifunctional outer-sphere mechanism, similar to that described by Noyori and co-workers [157, 158]. The amine additive MPA serves not only as a ligand to generate the highly reactive and enantioselective Ir-amide species but also as a Brønsted base to bypass the acid-catalyzed racemic disproportionation of half-reduced compounds. Similarly, the amine product also exhibits additive effects as well as positive feedback enhancement [161], which was observed for the first time in asymmetric hydrogenation.

12 Summary and Perspectives

As reviewed in this chapter, transition metal-catalyzed asymmetric hydrogenation of *N*-, *O*-, and *S*-containing heteroaromatic compounds, which are generally regarded as more challenging substrates, has received increasing attention in recent years. A number of transition metal (Ir, Rh, Ru, and Pd) catalysts bearing chiral phosphorus ligands, amine-tosylamine ligands, and *N*-heterocyclic carbene ligands have been examined. Different types of heteroaromatics, including quinolines, isoquinolines, quinoxalines, pyridines, indoles, pyrroles, furans, thiophenes, imidazoles and oxazoles, have been successfully applied to such transformations, providing a facile and economic access to a variety of optically active heterocycle compounds. The significant progress made in this challenging hydrogenation reaction was mainly attributed to the discovery of new catalytic systems, and the development of new catalyst and substrate activation strategies. Furthermore, several recoverable catalytic systems have also been developed and found to be highly efficient in the asymmetric hydrogenation of quinolines. Mechanistic studies on the hydrogenation of quinolines and quinoxalines have revealed the catalytic pathway and/or offered some insight into the origin of enantioselectivity. However, despite significant progress having been made, this field is still far from being mature as compared to the asymmetric hydrogenation of prochiral olefins and ketones, and there are still many challenges which limit its application. The focus for further research in this area is expected to be the development of more efficient homogeneous and heterogeneous chiral catalysts and the extension of substrate scope. In addition, detailed mechanistic investigations for different heteroaromatic compounds will form part of future studies, which are likely to be beneficial for the discovery of new generation catalysts and new substrates of heteroaromatics for asymmetric hydrogenation.

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