Asymmetric Hydrogenation of Heteroaromatic Compounds

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ABSTRACT
Asymmetric hydrogenation of heteroaromatic compounds has emerged as a promising new route to saturated or partially saturated chiral heterocyclic compounds. In this Account, we outline recent advances in asymmetric hydrogenation of heteroaromatic compounds, including indole, quinoline, isoquinoline, furan, and pyridine derivatives, using chiral organometallic catalysts and organocatalysts.

Introduction
Catalytic asymmetric hydrogenations of prochiral unsaturated compounds, such as olefins, ketones, and imines, have been intensively studied and are considered a versatile method for access to chiral compounds.1 On the other hand, asymmetric hydrogenation of aromatic/heteroaromatic compounds is much less explored, presumably because of the following reasons: (1) The high stability of aromatic compounds usually requires elevated temperatures and pressures and thereby adversely affecting the enantioselective reduction.2 (2) Deactivation and/or poisoning of catalysts by heteroaromatic compounds containing nitrogen and sulfur atoms may occur. (3) The lack of a secondary coordinating group in simple aromatic compounds, as contrast to functionalized alkenes and ketones, to interact with the central metal atom, must account for the difficulty in achieving enantioselective reactions.3 Despite the difficulties cited above, the search for catalysts enabling efficient asymmetric hydrogenation of aromatic/heteroaromatic compounds continues and is driven by the prospect of straightforward and efficient routes to optically active saturated or partially saturated chiral heterocyclic compounds.3

The first example of homogeneous asymmetric hydrogenation of aromatic compounds is the 1987 report by Murata and co-workers, who subjected 2-methylquinoxaline under hydrogen in ethanol using Rh[(S,S)-DIOP]H as the catalyst. A dismal 3% enantiomeric excess (ee) was obtained (Scheme 1).4 A great improvement (50% ee) was achieved by Takaya and co-workers in 1995, in the hydrogenation of 2-methylfuran5 in the presence of [(R)-BINAP](µ-Cl3)]2/Rh(I)Cl/MeOH at 50 atm. In 1998, Bianchini developed an orthometalated dihydride iridium complex for hydrogenation of 2-methylquinoline to 1,2,3,4-tetrahydro-2-methylquinoline with up to 90% ee (Scheme 1),7 although conversion is not satisfactory. These pioneering works served to demonstrate the feasibility of synthesizing chiral heterocyclic compounds from the corresponding aromatic congeners by asymmetric hydrogenation.

To date, some important advances in homogeneous asymmetric hydrogenation of aromatic/heteroaromatic compounds were achieved using chiral organometallic catalysts and organocatalysts. In this Account, we summarize our efforts in asymmetric hydrogenation of quinolines and isoquinolines and highlight the recent developments in this challenging field by other groups.

A successful asymmetric hydrogenation of aromatic compounds mainly depends upon substrate activation, catalyst activation, and dual activation (Scheme 2). Substrate activation includes the introduction of a secondary coordinating group, activators, and selection of bicyclic aromatic compounds (the aromatic stabilization of the heteroaromatic ring is reduced, thus increasing the reactivity of these substrates toward hydrogenation). Catalyst activation may be achieved by the introduction of various additives and by the fine tuning of steric and electronic effects of the chiral ligands.

Scheme 1. Pioneering Works on Asymmetric Hydrogenation of Heteroaromatic Compounds

Yong-Gui Zhou was born in 1970 in Hubei Province, China, received a B.S. degree from Huaibei Coal Industrial Teachers’ College in 1993, and earned his Ph.D. degree from Shanghai Institute of Organic Chemistry in 1998, working under the direction of Profs. Li-Xin Dai and Xue-Long Hou. He joined Xumu Zhang’s group at the Pennsylvania State University as a postdoctoral fellow that same year, and in 2002, he began his independent research career at the Dalian Institute of Chemical Physics, Chinese Academy of Sciences, where he is currently a Professor of chemistry. His research interests include the development of catalytic asymmetric reactions, mechanistic elucidation, and asymmetric synthesis.

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Asymmetric Hydrogenation of Quinoline and Isoquinoline Derivatives

Direct hydrogenation of easily available quinoline and isoquinoline derivatives is the most convenient route to synthesize the corresponding tetrahydro derivatives, which are important organic synthetic intermediates. Many alkaloids and biologically active compounds contain such structural units. Surprisingly, no report on homogeneous asymmetric hydrogenation of quinolines and isoquinolines was documented in the literature before we started this program. In our program, two kinds of strategies were considered and implemented for asymmetric hydrogenation of quinolines and isoquinolines: one of which is to develop highly reactive and enantioselective catalysts, and the other concentrates on substrate activation, e.g., by chloroformates (Scheme 3).

Recently, it has been revealed that iridium successfully mediates asymmetric hydrogenation of imines and simple alkynes. We first examined [Ir(COD)Cl]2/MeO-Biphep, which is the common iridium hydrogenation catalyst, for hydrogenation of 2-methylquinoline. Unfortunately, it was found that the catalytic activity is very low, and only a trace amount of product with low ee was obtained when the reaction was carried out in methylene chloride at room temperature under 700 psi of hydrogen. Although the enantioselectivity and conversion are low, it is demonstrated that asymmetric hydrogenation of quinolines is feasible. The next step is how to improve the activity and enantioselectivity. A dramatic impact of additives on catalytic turnover and enantioselectivity was also noted. For example, iodine increased the reactivity of iridium-catalyzed asymmetric hydrogenation of imines, presumably via oxidation of IrI to a more catalytically active IrII state. Following this observation, we explored the highly active Ir/(R)-MeO-BiPhep/I2 system for asymmetric hydrogenation of quinolines. Using 2-methylquinoline as a model substrate, the reaction proceeded smoothly, affording 2-methyl-1,2,3,4-tetrahydroquinoline with 94% ee (Scheme 4). After screening several other additives, we concluded that only iodine and halogen analogues give excellent conversions and enantioselectivity.

Further studies showed a strong solvent dependence in that aprotic solvents, such as toluene, gave the best enantioselectivity (94%). Other commercially available chiral bidentate phosphine ligands were also examined for the hydrogenation of 2-methylquinoline, and we found that enantioselectivities decreased when (R)-BINAP (87%), (S,S)-DIOP (53%), or (R,R)-Me-DuPhos (51%) was used instead of MeO-BiPhep (94% ee) or (S)-SegPhos (94%). Thus, the optimal conditions that we established involve [Ir(COD)Cl]2/MeO-BiPhep/I2 in toluene at 700 psi of H2 (Figure 1).

A variety of substituted quinoline derivatives were hydrogenated using Ir/MeO-BiPhep/I2 as the catalyst system. Several 2-alkyl-substituted quinolines were hydrogenated with high enantioselectivities (>92% ee), regardless of the length of the side chain (entries 1–6 in Table 1). 2-ArenethyI-substituted quinolines also gave excellent asymmetric induction (entries 8–10). 2-Aryl- and 2-hydroxymethyl quinolines showed lower enantioselectivities (entries 14 and 18). While this catalytic system can tolerate hydroxyl and ester groups (entries 15–19 and 24), a C==C double bond in the side chain of the substrate (entries 5 and 21) was saturated. From the fact that three- and four-substituted quinolines gave essentially racemic products (0 and 1% ee for 3- and 4-methylquinoline, respectively) strongly indicates an intimate involvement of the heterocyclic nitrogen atom in forming intermediates.
Our recent discovery that Hantzsch esters could be dehydrogenated using the [Ir(COD)Cl]2/phosphine/I2 system16 led to an exploration of quinoline reduction. We were glad to observe that hydrogenation can proceed smoothly using [Ru(p-cymene)Cl]2/I2/tetrahydrofuran (THF) as the catalytic system with high catalytic activity [turnover number of the reaction (TON) of up to 20 000],12c but the asymmetric version gave very low enantioselectivity using the chiral diphosphine ligands or diamine ligands.

Iridium-catalyzed asymmetric hydrogenation of quinolines provides a convenient and economical route to synthesize optically active tetrahydroquinolines. This methodology can be successfully applied to the asymmetric synthesis of tetrahydroquinoline alkaloids and chiral drugs (Scheme 6).11,13 For example, the hydrogenation product of 6-fluoro-2-methylquinoline is the key intermediate of the antibacterial agent of Flumequine. N-Methylation of hydrogenation products completed the synthesis of angustureine, galipinine, and cuspareine in high total yields. A seven-step synthesis of (−)-galipeine that contains a free phenol hydroxyl group was accomplished from isovanillin with a 54% overall yield, and the work enabled an assignment of its absolute configuration.13 Similarly, absolute configurations of (+)-angustureine, (−)-galipinine, and (−)-galipeine were assigned through our synthesis.

Intense research activities are evident in metal-free enantioselective transfer hydrogenation of α,β-unsaturated carbonyl compounds and imines using organocatalysts with Hantzsch esters as the hydrogen source.14 In 2006, Rueping extended this strategy to reduce quinolines,15 employing sterically congested chiral BINOL-phosphoric acids. This reaction was found to be highly solvent-dependent, in which nonpolar (e.g., benzene) gave the best enantioselectivity. Under optimal conditions, excellent enantioselectivities (87–99% ee) were obtained for 2-substituted quinolines (Scheme 7). A possible reaction mechanism indicates the protonation of the quinolines by the chiral phosphoric acid, which allows for a 1,4-dihydride addition, isomerization, and 1,2-hydride addition to give the desirable tetrahydroquinolines.

Our recent discovery that Hantzsch esters could be dehydrogenated using the [Ir(COD)Cl]2/phosphine/I2 system16 led to an exploration of quinoline reduction. We were glad to observe that hydrogenation can proceed smoothly using [Ir(COD)Cl]2/(S)-SegPhos/I2 with 10–88% ee (Scheme 8).17

prior to hydrogen transfer; therefore, only a prochiral C-2 would have stereochemical consequences.

Ir complexes with ferrocene-based N–P and S–P ligands also promote asymmetric hydrogenation of quinolines (Scheme 5).12a,p Using the one with a N–P ligand, tetrahydroquinolines of up to 90% ee were obtained. Central chirality determined the absolute configuration of the products in iridium–ferrocenyloxazoline catalytic systems with planar chirality. For S–P ligands, S–P-1 and S–P-2 with the same central chirality and opposite planar chirality gave a product with the same absolute configuration. Interestingly, if a bulky trimethylsilyl (TMS) group (S–P-3 and S–P-4) was introduced to the Cp ring of S–P-1 and S–P-2 ligands, hydrogenation products with opposite absolute configuration were obtained in high enantiomeric purity. It is noted that hydrogenation of quinolines can also proceed smoothly in air using [Ru(p-cymene)Cl]2/I2/tetrahydrofuran (THF) as the solvent.
A natural extension of our work is to hydrogenate isoquinolines, but unfortunately the results were disappointing. We attribute the lack of reactivity to a high affinity of the hydrogenation products of isoquinolines, so that the chiral metal catalyst was not released. Accordingly, substrate modification should overcome the turnover problem. The selection of alkyl chloroformates as the modifiers is based on the following reasons (Scheme 9):

1. Aromaticity was destroyed partially by the formation of quinolinium and isoquinolinium salts.
2. Removing the lone-pair electrons from the N atom avoids strong binding to the metal center.
3. Attached CO₂R is probably important for the coordination between the substrate and catalyst.

The mechanism analysis indicated that 1 equiv of hydrogen chloride was produced during hydrogenation of quinolines and isoquinolines activated by chloroformates, which might block the reaction by the formation of the HCl salt of quinolines or isoquinolines. Therefore, the addition of a base to neutralize hydrogen chloride is necessary for substrate use. A survey of the base/solvent profile revealed that the combination of Li₂CO₃ and THF could give complete conversion. Besides alkyl chloroformates, we examined benzoyl chloride, acetyl chloride, and acetic anhydride as alternatives, but they were inefficient.

Our studies also included the screening of other commercially available chiral ligands; among them, (S)-SegPhos gave the best enantioselectivity. A variety of 2-substituted quinolines were hydrogenated using Ir/(S)-SegPhos/ClCO₂Bn/Li₂CO₃/THF with 80–90% ee (Table 2), among which only 2-phenylquinoline gave lower conversion and enantioselectivity (41% yield and 80% ee).

Extension of the work to asymmetric hydrogenation of isoquinolines resulted in only partially hydrogenated 1,2-dihydroisoquinoline. In the case of 1-methyisoquinoline,
Low enantioselectivity was obtained for 1-benzylisoquinoline, which might be due to the steric effect of the bulky phenyl group. As for 1-phenylisoquinoline, excellent enantioselectivity was obtained but the conversion was moderate, which less of the length of the alkyl chain (entries 1–4 and 7–8).

The partially hydrogenated product was obtained in 87% yield with 76% ee under the above conditions, using (S)-SegPhos as the ligand (Scheme 10). The reaction did not occur in the absence of benzyl chloroformate.

Because an equivalent of LiCl was produced during this reaction, the effect of lithium salt with different counterions on the enantioselectivity was investigated. The results showed that the ee slightly increased (76–83% ee) in the presence of LiBF4 or LiOTf. Ligand screening indicated that (S)-SegPhos gave the best enantioselectivity (83% ee).

Results from the hydrogenation of isoquinolines are collected in Table 3. 1-Alkylisoquinolines were hydrogenated with moderate to good enantioselectivities regardless of the length of the alkyl chain (entries 1–4 and 7–8). As for 1-phenylisoquinoline, excellent enantioselectivity was obtained but the conversion was moderate, which might be due to the steric effect of the bulky phenyl group. Low enantioselectivity was obtained for 1-benzylisoquino-

Thus, asymmetric hydrogenation of quinolines and isoquinolines activated by chloroformates provides a convenient route to synthesize optically active quinoline and isoquinoline alkaloids (Scheme 10). For instance, the reduction of hydrogenation products with LiAlH4 in Et2O afforded the N-methylation products in high yield, which are the naturally occurring tetrahydroisoquinoline alkaloids. Similarly, naturally occurring tetrahydroisoquinoline alkaloids were synthesized in three steps starting from isoquinolines (Scheme 11). For example, (S)-(−)-carnegine can be synthesized by asymmetric hydrogenation, Pd–C hydrogenation, and LiAlH4 reduction.

Since we reported our initial work on iridium-catalyzed enantioselective hydrogenation of quinoline derivatives in the presence of I2, several other groups have communicated their results in this area. Chiral bisphosphine ligands have been designed and tested. Some representative examples are shown in Figure 2.

Table 2. Hydrogenation of Quinolines Activated by ClCO2Bn

<table>
<thead>
<tr>
<th>Entry</th>
<th>R/R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H/Me</td>
<td>90</td>
<td>90 (S)</td>
</tr>
<tr>
<td>2</td>
<td>H/Et</td>
<td>85</td>
<td>90 (S)</td>
</tr>
<tr>
<td>3</td>
<td>H/n-Pr</td>
<td>80</td>
<td>90 (S)</td>
</tr>
<tr>
<td>4</td>
<td>H/n-Bu</td>
<td>88</td>
<td>89 (S)</td>
</tr>
<tr>
<td>5</td>
<td>H/n-pentyl</td>
<td>91</td>
<td>89 (S)</td>
</tr>
<tr>
<td>6</td>
<td>F/Me</td>
<td>83</td>
<td>89 (S)</td>
</tr>
<tr>
<td>7</td>
<td>Me/Me</td>
<td>90</td>
<td>89 (S)</td>
</tr>
<tr>
<td>8</td>
<td>MeO/Me</td>
<td>92</td>
<td>90 (S)</td>
</tr>
<tr>
<td>9</td>
<td>H/Ph</td>
<td>41</td>
<td>80 (R)</td>
</tr>
<tr>
<td>10</td>
<td>H/phenethyl</td>
<td>86</td>
<td>90 (S)</td>
</tr>
<tr>
<td>11</td>
<td>H/3,4-(MeO)2C6H4(CH2)2</td>
<td>80</td>
<td>90 (S)</td>
</tr>
<tr>
<td>12</td>
<td>H/3-MeO-4-BnOC6H4(CH2)2</td>
<td>88</td>
<td>88 (S)</td>
</tr>
</tbody>
</table>

* Reaction at 50 °C.

Table 3. Asymmetric Hydrogenation of Isoquinolines

<table>
<thead>
<tr>
<th>Entry</th>
<th>R/R/R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H/Me</td>
<td>Me</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>H/Me</td>
<td>Bn</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>H/Ph</td>
<td>Me</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>H/Ph</td>
<td>Bn</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>MeO/Me</td>
<td>Me</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>MeO/Me</td>
<td>Me</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>ethyl</td>
<td>Me</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>n-butyl</td>
<td>Me</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td>benzyl</td>
<td>Me</td>
<td>83</td>
</tr>
</tbody>
</table>

* Without LiBF4.
Asymmetric Hydrogenation of Indole Derivatives

In 2000, Ito and co-workers reported a breakthrough in asymmetric hydrogenation of aromatic compounds in that the hydrogenation of N-Boc or Ac-substituted indoles with the use of a Rh/Ph-TRAP/Cs$_2$CO$_3$ catalyst in isopropanol at 60 °C is highly effective, and up to 95% ee was obtained (Scheme 12). It is noteworthy that both activity and enantioselectivity are significantly dependent upon the use of base. The addition of 10 mol % of Cs$_2$CO$_3$ or Et$_3$N improved enantioselectivity and catalytic activity remarkably. The chiral ligand is crucial for enantioselectivity. Only trans chelating bisphosphine ligand PhTRAP gave a high ee, and other commercially available bisphosphine ligands gave almost racemic products. The protecting group (e.g., Ac and Boc) on the nitrogen atom of indole is also important for enantioselectivity, because it acts as a secondary coordinating group. For 3-substituted N-acetyl-indoles, undesirable alcoholysis intervened. Using Ts as the protecting group, the indole derivatives underwent hydrogenation satisfactorily (high conversion and 95–98% ee).

Ru-catalyzed asymmetric hydrogenation of N-Boc indoles using a readily prepared catalyst, [RuCl(p-cymene)-RhTRAP][Cl], was developed by the same group in 2006 with 90–95% ee (Scheme 13). 2,3-Disubstituted indoles only furnished moderate enantioselectivity (72% ee).

For the above hydrogenation of indole derivatives, successful factors include (1) the introduction of protecting groups, Ac, Boc, or Ts, which may act as a secondary

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**FIGURE 2.** Representative chiral bisphosphine ligands used by other research groups.
Asymmetric Hydrogenation of Pyridine Derivatives

Thousands of pyridine derivatives are commercially available, and numerous others can be prepared by existing methods. In addition, chiral piperidine derivatives are important synthetic intermediates and the structural unit of many biologically active compounds. Therefore, a general method for asymmetric hydrogenation of pyridine derivatives would be highly desirable.

At present, the best results obtained for asymmetric homogeneous hydrogenation of pyridine derivatives is 25% ee using 5 mol % of Rh(nbd)_2BF_4/BINAP as the catalyst. High temperature and pressure are crucial for full conversion. A cinchona-modified heterogeneous catalyst (up to 19% ee) was found inefficient (Scheme 14). Recently, two successful examples on the asymmetric hydrogenation of auxiliary-substituted pyridines and a two-step asymmetric hydrogenation process of 3-substituted pyridine derivatives using a homogeneous rhodium catalyst were reported.

In 2004, Glorius and co-workers reported a highly efficient asymmetric hydrogenation of chiral N-(2-pyridyl)-oxazolidinones with up to 98% ee in acetic acid using commercially available heterogeneous catalysts (Scheme 15). The substrate is easy to synthesize from 2-bromopyridines and chiral oxazolidinone; the purification procedure is simple; and chiral auxiliary can be conveniently recovered and reused. Products with multiple stereocenters can be prepared in high yield with excellent optically purity. The high diastereoselectivity was ascribed to strong hydrogen bonding between the pyridinium and oxazolidinone moiety in acetic acid.

Charette and co-workers developed an asymmetric hydrogenation of pyridine derivatives with an activating achiral auxiliary and N-benzyliminopyridinium ylides, with 54–90% ee (Scheme 16). N-Benzyliminopyridinium ylide acts as the role of the activator of the substrate and secondary coordinating group. The highest enantioselectivities were obtained with cationic iridium complexes of phosphinoxazoline, with tetrakis(3,5-bis(trifluoromethy)phenyl)borate (BARF) as the counterion. The use of a catalytic amount of iodine is vital to achieve high yields, which may play an activator role for the Ir catalyst. This is a successful example based on the principle of simultaneous activation of the substrate and catalyst. It is well-suited for the asymmetric hydrogenation of 2-substituted N-benzyliminopyridinium ylides. The hydrogenation adducts obtained can be converted to the corresponding piperidine derivatives using Raney nickel or lithium in ammonia to cleave the N–N bond.

Zhang, Lei, and co-workers reported a highly enantioselective hydrogenation process of ethyl nicotinate, which consists of an efficient partial hydrogenation of nicotinate with Pd/C and a subsequent highly enantioselective homogeneous hydrogenation using Rh(NBD)(TangPhos)SbF_6 as the catalyst, with >99% ee (Scheme 17).

Asymmetric Hydrogenation of Furan Derivatives

Hydrogenation of furan derivatives is also less explored. In 2006, two groups reported the efficient asymmetric hydrogenation of furan derivatives (Scheme 18). According to Pfaltz and co-workers, Ir catalysts derived from the pyridine–phosphinite ligand delivered tetrahydrofuran derivatives with 78–99% ee, and this is the best result for the asymmetric hydrogenation of furan derivatives to date. The P substituent in the bidentate pyridine–phosphinite ligand is crucial for the enantioselectivity, and the...
the Pd(OCOCF₃)₂/acyclic ketimines, up to 99% ee can also be obtained using 19). Two kinds of cyclic agents. For and structural units for agricultural and pharmaceutical derivatives, which are important synthetic intermediates.

Hydrogenation of Activated Imines

Studies have shown that a few other heteroaromatic compounds underwent hydrogenation with moderate enantioselectivity. For example, 2-methylquinoxaline can be hydrogenated using Noyori’s RuCl₂(bisphosphine) (1,2-diamine) catalyst (73% ee) and the [Ir(COD)Cl]₂/PQ-Phos/I₂ system (72% ee).

Miscellaneous Work on Pd-Catalyzed Hydrogenation of Activated Imines

In the course of exploring the asymmetric hydrogenation of aromatic compounds using the activation strategy, we developed the Pd-catalyzed hydrogenation of activated imines to acquire chiral heterocycles using the Pd(OCOCF₃)₂/diphosphine complex in trifluoroethanol (Scheme 19). Two kinds of cyclic N-p-toluenesulfonyl imines can also be hydrogenated with high enantioselectivity using Pd(OCOCF₃)₂/(S)-SegPhos. To our delight, this methodology provides a new access to chiral heterocyclic sultam intermediates and structural units for agricultural and pharmaceutical agents. For N-p-toluenesulfonyl and N-diphenylphosphinyl acyclic ketimines, up to 99% ee can also be obtained using the Pd(OCOCF₃)₂/(S)-SynPhos or (S)-SegPhos complex as the catalyst. The exclusive E configuration of the imines and the strong electron-withdrawing character likely contributed to the success of the asymmetric hydrogenation.

Summary and Outlook

This Account focused on recent advances in homogeneous asymmetric hydrogenations of heteroaromatic compounds. Two different systems were developed for the hydrogenation of quinolines. One is the highly active iridium catalyst Ir/diphosphate/I₂, in which iodine is a crucial additive for activity and enantioselectivity. The other was Ir/diphosphate/I₂/CO₂ and involves derivatization to form quinolinium salts with chloroformates. The latter protocol can be applied to the asymmetric hydrogenation of isoquinolines. A highly enantioselective organocatalytic asymmetric transfer hydrogenation of quinolines is to use a chiral BINOL-derived Brønsted acid as the catalyst. Protected indoles can be hydrogenated efficiently using Rh or Ru complexes with trans chelating bisphosphines. Pyridine derivatives with chiral and achiral auxiliaries can be efficiently hydrogenated using heterogeneous catalysts and homogeneous Ir/N–P catalysts in the presence of iodine, respectively. Furan derivatives can be hydrogenated with high enantioselectivity using Ir catalysts derived from pyridine–phosphinite.

Although some promising results have been obtained in the asymmetric hydrogenation of aromatic compounds, it should be emphasized that a great deal of effort is required to work out satisfactory protocols for various situations. All of the above examples are confined to bicyclic heteroaromatic compounds possessing quinoline, isoquinoline, quinoxaline, or indole skeletons, in which aromatic stabilization of the heteroaromatic ring is reduced, thus rendering their susceptibility to hydrogenation. For the monocyclic heteroaromatic compounds, only furan derivatives gave the excellent enantioselectivity. Low enantioselectivity was obtained for the direct hydrogenation of pyridine derivatives. The asymmetric hydrogenation of common phenols, anilines, and arenes is largely unsuccessful. Future work may then focus on the following: (1) The development of a new activation strategy for arenes and heteroaromatic compounds; perhaps superacids and Lewis acids deserve a closer look. (2) Exploration of new homogeneous catalysts, containing new combinations of metal precursors, chiral ligands, and additives. (3) Rueping’s organocatalytic hydrogenation of quinolines opened a new access to the asymmetric hydrogenation of heteroaromatic compounds; therefore, the design and development of a new organocatalyst type are a good direction because of the compatibility of the functional group and simple operation of the organocatalytic process. (4) Heterogeneous catalysts capable of asymmetric hydrogenation should also be explored, because their recyclability should be simpler. (5) A fuller understanding of the mechanistic details of these successful reactions might eventually lead to the next generation of general asymmetric hydrogenation methods for aromatic compounds.

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