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Substrate Activation in the Catalytic Asymmetric Hydrogenation of *N*-Heteroarenes

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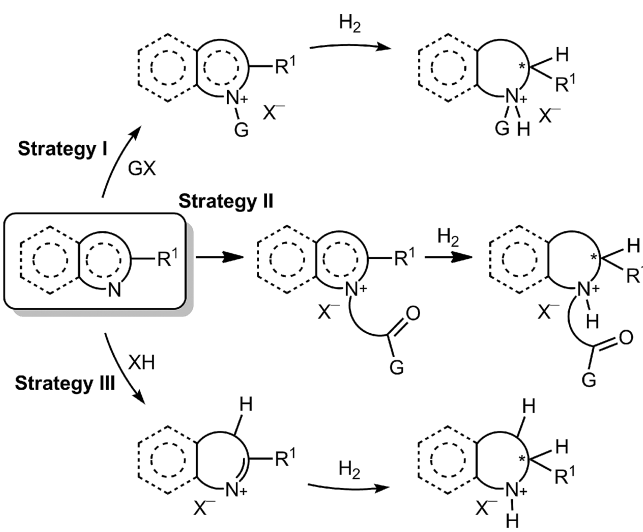
Different methods for transforming *N*-heteroarenes into more reactive derivatives for catalytic asymmetric hydrogenation are highlighted. The first strategy consists of facilitating hydrogenation by the formation of positively charged derivatives of the heteroarene. Catalyst deactivation processes arising upon binding of the substrate to the metal center can thus be prevented and, additionally, hydrogenation of positively charged heteroarenes may also be more favored than that of their neutral analogues. The second strategy is based on introducing a ligating group onto the substrate to assist its coordination to the metal center and facilitate hydrogenation by chelation assistance. The last strategy involves breaking the aromaticity of the heteroarene by inducing a double-bond migration process. This microreview summarizes advances made in the above strategies, which have allowed the development of highly enantioselective catalytic hydrogenation of *N*-heteroarenes for the production of fully or partially saturated chiral heterocycles.

Introduction

Enantiopure organic compounds are important constituents of commercially produced chemicals including plastics, active pharmaceutical ingredients, agrochemicals, food additives, etc.[1] The ever-increasing demand for compounds of this kind has fueled the development of efficient synthetic methods for their preparation.[2] Asymmetric catalysis, in which a small amount of a chiral catalyst, by virtue of being regenerated many times, yields a much larger amount of enantiomerically pure product, is a priori the most elegant, productive, and resource-efficient approach for synthesizing enantiomerically pure (or enantioenriched) compounds. Thanks to intensive research efforts in academia[2] and industry,[2,3] asymmetric catalysis has evolved significantly since its onset and now encompasses nearly all transformations subject to three-dimensional bias.

Asymmetric hydrogenation is considered to be a straightforward entry to the preparation of enantiopure compounds,[4] because many transition-metal coordination compounds (mostly phosphorus-containing complexes[5]) mediate the addition of dihydrogen to prochiral C=O, C=C, and C=N double bonds with high enantioselectivities. Thus, many highly efficient catalysts have been developed for the asymmetric hydrogenation of prochiral ketones, alkenes, and imines.[6]

Many valuable biologically active compounds contain chiral heterocyclic structural motifs.[7] Asymmetric hydrogenation of the corresponding heteroaromatic precursors can be considered one of the most practical and atom-efficient methods for synthesizing fully or partially reduced heteroaromatic derivatives in enantiomerically pure form (Scheme 1).[8] This synthetic strategy also benefits from the great diversity of starting materials. In terms of synthetic simplicity, asymmetric hydrogenation is also an attractive route, because it minimizes the need for manipulation of functional groups during the preparation of the target heterocyclic compounds in enantiomerically pure form.



Scheme 1. General representation of the substrate manipulation strategies for improving the reactivity of heteroarenes in asymmetric hydrogenation.

Despite the attractiveness of the asymmetric hydrogenation of heteroaromatic compounds, this area of chemistry

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is much less explored, with many fewer successful examples than in the cases of the asymmetric hydrogenation of prochiral ketones, alkenes, and imines. Several factors are behind the difficulties in asymmetrically hydrogenating heteroaromatic compounds:

· Firstly, heteroaromatic compounds are highly stable, which translates into a requirement for harsh hydrogenation conditions in order to break the aromaticity of the starting materials (i.e., high hydrogen pressures and temperatures). Although high pressures are normally not a problem and result only in a more demanding reaction setup, high temperatures may unfortunately be associated with low enantioselectivities in the final hydrogenated products. In this respect, there are many examples of partial hydrogenation of bicyclic heteroaromatic compounds with good enantioselectivities and with one aromatic ring being preserved, but literature examples of highly selective hydrogenation of monocyclic heteroaromatic compounds are scarce.

· Secondly, many of the heteroaromatic derivatives to be hydrogenated lack an auxiliary coordination group to the metal center. Many successful applications of enantiomerically pure transition-metal complexes in asymmetric hydrogenation rely on the ability of the substrate to form a metal chelate involving the double bond to be hydrogenated and a donor atom from the substrate (for instance, the chelation assistance of an acyl group is the classic model for achieving high reactivity and enantioselectivity in rhodium-mediated asymmetric hydrogenations).[9] A lack of auxiliary coordination between the heteroaromatic substrate and the catalyst may result in more than one low-energy direction of approach for the substrate to the metal center with overall low enantioselectivity in the transformation.

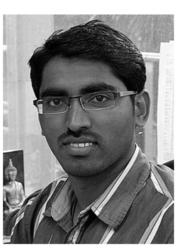
· Lastly, the activity of the catalyst may be reduced, or even suppressed altogether, by the substrates or hydrogenation products, because both compounds may contain ligating groups, such as nitrogen or sulfur, capable of coordinating to the metal center with subsequent loss of catalytic activity.

Chemists have developed various strategies for overcoming these difficulties:

· "***Ligand tuning***" has enabled the development of efficient catalytic systems for certain types of heteroaromatic compounds. Catalyst activation involving the addition of additives to form more reactive catalytic systems complements ligand design and tuning and has also been successfully exploited in this chemistry. Ligand tuning and catalyst activation have recently been reviewed and are both outside the scope of this text.[8]

· Hydrogenation or reduction of a heteroaromatic compound involves the sequential reduction of several C=C and/or C=N bonds. An elegant strategy has been devised that first involves the partial reduction of the initial heteroaromatic compound to a new prochiral heterocyclic compound by use of an achiral catalytic system. The subsequent reduction of this intermediate heterocyclic compound to the final enantiopure derivative is mediated by a second catalytic system present in the reaction mixture, which is responsible for enantioselection. This strategy is known as "***relay catalysis***" and has also recently been reviewed.[10]

· The heteroarene to be hydrogenated is synthetically manipulated and transformed into a related heterocyclic system that is more reactive in asymmetric hydrogenation ("***substrate activation***"). A first strategy consists of facilitating hydrogenation through the formation of a positively



Mr. Bugga Balakrishna obtained his degree (B.Sc.) from Acharaya Nagarjuna University (Guntur, India) in 2008 and completed his M.Sc. in Chemistry in 2010 at the Indian School of Mines in Dhanbad. After working for a year and a half as a project trainee at the Indian Institute of Chemical Technology (IICT) in Hyderabad under the supervision of Dr. B. V. Subba Reddy, he joined Prof. Anton Vidal's group at the Institute of Chemical Research of Catalonia (ICIQ) as a Ph.D. student in 2012. He works mainly on the design and development of catalytic systems derived from P-OP ligands and metal precursors for asymmetric transformations of interest.

José Luis Núñez graduated in chemistry at the University of Valladolid in Spain in 2008, moving afterwards to Tarragona (Spain) to do his doctoral thesis on the development of asymmetric synthetic methodology for metal-catalyzed transformations (Rh- and Ir-mediated asymmetric hydrogenations) at the Institute of Chemical Research of Catalonia (ICIQ) as part of Prof. Anton Vidal's group. In 2013 he joined an ongoing industrial project in the same research group for developing new production concepts for carbamates. His research interests include organometallic chemistry and homogeneous and heterogeneous catalytic solutions to problems of industrial relevance.

Anton Vidal graduated in chemical engineering in 1987 at the Institut Químic de Sarrià in Barcelona, where he completed his Ph.D. under Prof. P. Victory in 1992. He then took up two postdoctoral appointments (with Prof. J. K. M. Sanders at the University of Cambridge, 1993–1994, and with Prof. M. A. Pericàs at the University of Barcelona, 1995–1999). He gained industrial experience in several research departments at Bayer-AG (Leverkusen, Germany, 1999–2003). After his appointment as a Research Professor at ICREA (Catalan Institution for Research and Advanced Studies), he started his independent career as a Group Leader at the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona (Spain) in 2003. Prof. Vidal aims to design and develop efficient asymmetric catalytic tools.

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charged derivative of the heteroarene. Catalyst deactivation processes arising upon binding of the substrate to the metal center can thus be prevented and it is worth noting that, with this strategy, the coordinating ability of the ligating groups of the substrate and/or product toward the catalyst are neutralized (see Strategy I in Scheme 1). The hydrogenation of positively charged heteroarenes may also be more favored than that of their neutral analogues. In a second approach, the heteroarene is synthetically modified to introduce a ligating auxiliary group to assist its coordination to the metal center and facilitate hydrogenation by chelation assistance. In addition to the activation effects produced by the ligating auxiliary group, it should be noted that Strategy II also benefits from the advantages of quaternizing the sp^2-nitrogen group previously mentioned for Strategy I. Overall, the hydrogenation of the modified substrate may proceed more rapidly than that of the original derivative (see Strategy II in Scheme 1). The last strategy involves breaking the aromaticity of the heteroaromatic compound by inducing an acid- or base-mediated double-bond migration process (see Strategy III in Scheme 1). It is worth mentioning that, whereas the products arising from Strategies I and II may not correspond exactly to the hydrogenated substrate, the hydrogenated products obtained by Strategy III are formal hydrogenation products of the starting heteroarenes.

As previously indicated, several reviews deal with ligand design in the asymmetric hydrogenation of heteroaromatic compounds and highlight the different additives that increase the activity of a given catalytic system or use the concept of relay catalysis for hydrogenating heteroaromatic compounds, but none of these reviews provides a comprehensive and timely overview of the different methods for transforming the substrate into a more reactive derivative for asymmetric hydrogenation. This microreview therefore focuses on progress in synthetically manipulating heteroaromatic compounds in order to increase their reactivity in asymmetric hydrogenation mediated by enantiomerically pure transition-metal complexes.[11] The discussion is divided into three sections corresponding to these three different strategies.

1. Strategy I: Activation by Formation of Positively Charged Derivatives of the Substrate

In this strategy, the hydrogenation process is facilitated by the formation of positively charged derivatives of the heteroarene. One of the main problems to overcome in the hydrogenation of heteroarenes is catalyst deactivation due to substrate coordination to the metal center during the whole catalytic cycle. Those working on asymmetric catalysis have therefore sought to eliminate the ability of the substrate and product to bind to the catalytic metal by removing the lone pair of electrons from the ligating groups. In this strategy a dative covalent bond is formed between the lone pairs of electrons from the substrate and a suitable derivatization agent, forming positively charged species. Moreover, these substrates are activated toward hydrogenation by quaternization of the nitrogen groups. Transition-metal-mediated asymmetric hydrogenations of nitrogen-containing heteroarenes proceed in many cases by stepwise proton transfer followed by the addition of a hydride.[12] This latter step should be better favored with an iminium motif (i.e., C=N$^+$ double bond) rather than with the neutral C=N group present in the original heteroarene.

Thus, two main strategies have been devised for favoring hydrogenation through the formation of positively charged substrate derivatives:

- Firstly, the formation of positively charged derivatives of the substrate prior to the hydrogenation in a reversible manner and subsequent neutralization of the hydrogenation products.
- Secondly, formation of positively charged derivatives based on covalent chemistry.

The following discussion is divided into two sections corresponding to these two substrategies for suppressing the binding ability of the substrate to the metal center. The reader is referred to Section 2 for examples in which the formation of a positively charged derivative also involves introducing a ligating group that facilitates hydrogenation through chelation assistance.

1.1. Reversible Formation of Positively Charged Derivatives of the Substrate and Subsequent Neutralization

Substrate activation should ideally be achieved with easy chemistry and in a minimum number of synthetic steps. The activating agent should also be easily removable. With these ideas in mind, activation of C=N-containing heteroarenes by protonation with Brønsted acids as activators appeared an obvious strategy to follow. A wide variety of Brønsted acids are easily available, and hydrogenated protonated products can easily be transformed into the neutral compounds by adjusting the workup conditions.

Significant progress has been made by Ohshima, Ratovelomanana, Mashima, et al.[13] in the area of asymmetric hydrogenation of quinoline derivatives by use of this activation approach.[14] These authors used the cationic dinuclear triply halogen-bridged iridium complexes **C1** as catalysts in the hydrogenation of quinolines. Interestingly, the asymmetric hydrogenation of the challenging 2-phenylquinoline in the presence of **C1** led to lower enantioselectivities than those obtained from the quinolinium analogues (increases of up to 9% in the *ee*), thus indicating that formation of quinolinium salts prior to hydrogenation was beneficial for enantioinduction. With the optimal catalyst and hydrogenation conditions in hand, the authors extended their chemistry to an array of diversely substituted quinolinium salts (13 examples) with excellent levels of conversion and enantioselectivity (up to 95% conversion and 95% *ee*; Scheme 2, a). Although the authors normally used the same halogen ligand in **C1** or in the substrate derivative, they demonstrated that the original halogen ligand in **C1** remained in the catalytically active complex (similar results

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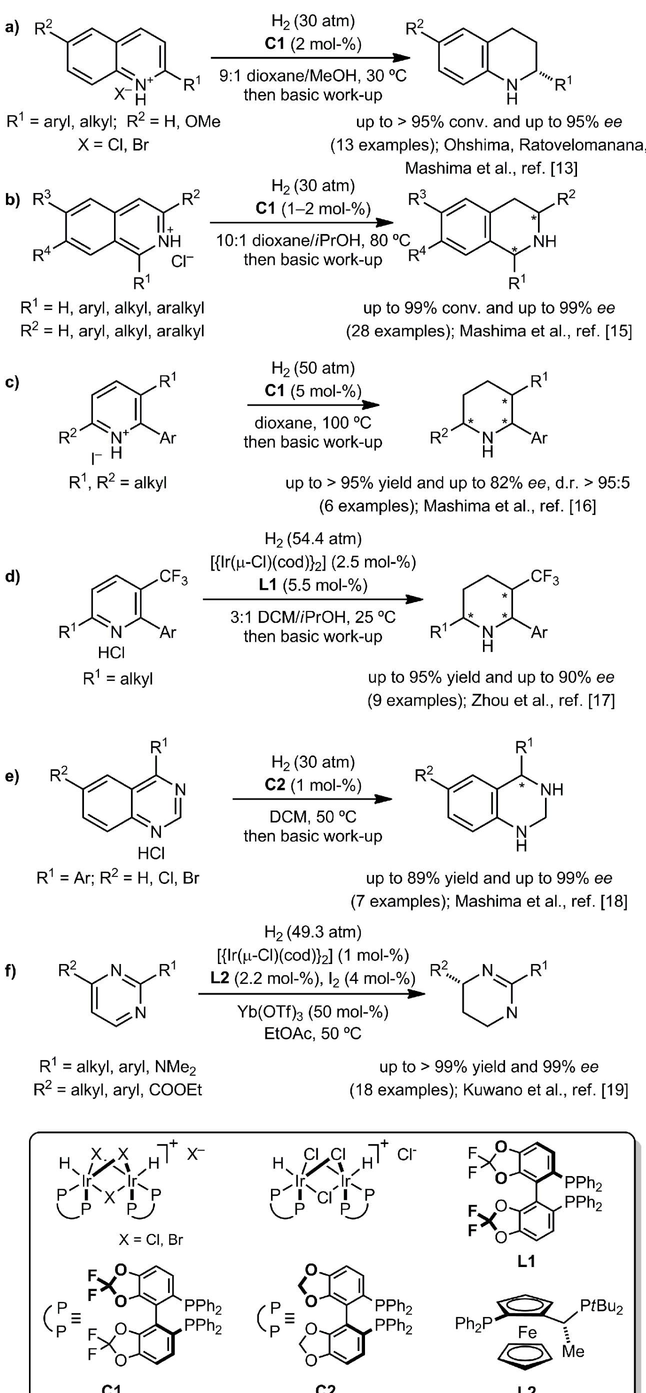
were obtained in the hydrogenation of 2-phenylquinoline hydrobromide or hydrochloride with **C1**·Cl). A series of isoquinolinium salts was also hydrogenated by Mashima et al. with outstanding results by use of the same catalytic system.[15] Interestingly, diverse substitution patterns in the isoquinolinium ring are tolerated (Scheme 2, b): 1-substitution (11 examples, up to 99% conv., up to 99% *ee*), 3-substitution (seven examples, up to 99% conv., up to 95% *ee*), 1,3-disubstitution (10 examples, up to 99% conv., up to 99% *ee*, complete *syn* selectivity), 1,4-disubstitution (one example not represented in Scheme 2 (b), up to 99% conv., *syn*/*anti* = 4:1; *ee* up to 97% for the *anti* isomer), and 3,4-disubstitution (one example not represented in Scheme 2 (b), up to 99% conv., *syn*/*anti* ≥ 95:5; 43% *ee*).



Scheme 2. Activation of C=N-containing heterocycles towards asymmetric hydrogenation by *N*-quaternization.

Mashima et al. have also reported the hydrogenation of 2-aryl-substituted pyridinium salts with a second alkyl substituent at the 3- or 6-position in the presence of **C1** as the enantioselective catalyst.[16] Even though higher catalyst amounts were used in this case (5 mol-%, Scheme 2, c), enantioselectivities were lower (up to 82% *ee*) than those reported for the quinolinium and isoquinolinium salts already discussed.

More recently, Zhou et al. also reported the hydrogenation of 3-(trifluoromethyl)pyridinium hydrochloride derivatives in the presence of an iridium catalyst based on (*R*)-difluorphos ligand **L1**. A *cis* arrangement in all three substituents was found in the corresponding piperidines after the basic workup, with enantioselectivities up to 90% *ee* (Scheme 2, d).[17]

Asymmetric hydrogenation of quinazolinium salts catalyzed by halide-bridged dinuclear iridium complexes has recently been described by Mashima et al. (Scheme 2, e).[18] Although enantioselectivities are very high (*ee* values ranging from 96 to >99%), this method suffers from low chemoselectivity for certain substrates: for R^1 = *p*-MeO-C_6H_4 significant amounts of the two partially reduced dihydroquinazolines (34%) were obtained.

As a conclusion, it is worth noting that protonation has activated a wide range of heteroarenes towards efficient asymmetric hydrogenation in the presence of well-established iridium catalysts.

Kuwano et al. have developed an analogous activation strategy for the hydrogenation of pyrimidines with use of Lewis acids as activators.[19] A broad range of chiral phosphines and Lewis acids were assayed in the iridium-mediated asymmetric hydrogenation of 2,3-disubstituted pyrimidines. High enantioselectivities were obtained with use of ligand **L2**, [{Ir(μ-Cl)(cod)}$_2$], iodine as additive, and an excess of Yb(OTf)$_3$ as the Lewis acid (Scheme 2, f). Enantioselectivities were high (18 examples, up to 99% *ee*) and installing a substituent at the *ortho* position of R^2 was beneficial for enantioselection. Pyrimidines bearing R^2 substituents other than aryl also underwent hydrogenation with high enantioselection.

The previously discussed activation examples involve the use of preformed *N*-protonated heteroarene salts (Scheme 2, a–e) or of an excess of a Lewis acid (Scheme 2, f). Several groups have reported the use of catalytic amounts of Brønsted acids as activators in the hydrogenation of quinolines (CF_3COOH,[20,21] piperidinium hydrochloride,[22] piperidinium triflate,[23] triflic acid,[24] or HCl[25]) and quinoxalines (piperidinium hydrochloride[26]). Despite the improvements in catalyst activity and/or selectivity induced by these additives, their role has not been elucidated until now. Because they were used in catalytic amounts with respect to the substrates, it is not possible that these Brønsted acids completely prevent the binding of

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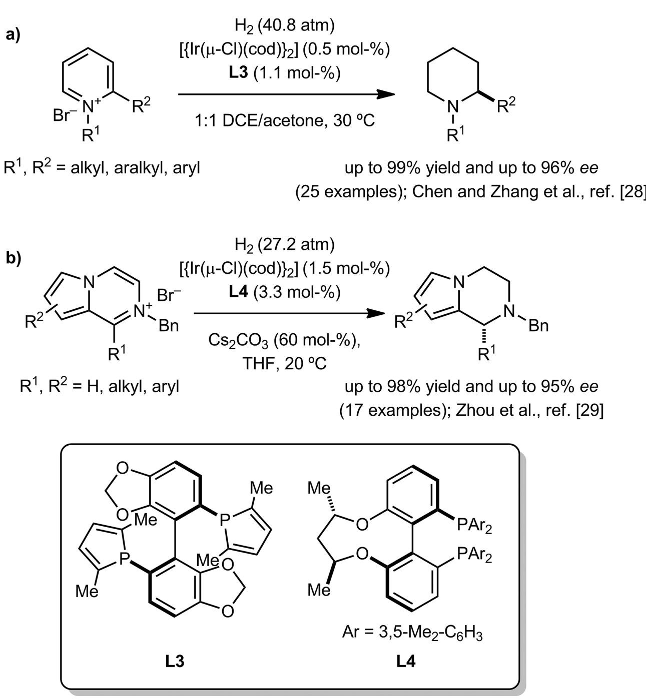
the heteroarene to the metal center. Several hypotheses have been made with regard to the role of these additives. Firstly, it has been proposed that ammonium salts (either directly added or formed in situ through reaction between the heteroarene and the additive) increase the stability of the metal catalyst with an overall increase in the catalyst activity.[22] Secondly, experimental and theoretical studies on the hydrogenation of nitrogen-containing heteroarene rings have revealed that successive additions of dihydrogen and double bond migrations may take place during hydrogenation.[12] Thus, it is also conceivable that these Brønsted acid additives facilitate the migration of double bonds in partially reduced heteroarene rings with an overall increase in catalyst activity.[27]

1.2. Substrate *N*-Derivatization

Several research groups have envisaged that the activation of simple pyridines might be achieved by derivatization at the nitrogen. Chen, Zhang, and co-workers recently reported the transformation of 2-substituted pyridines into *N*-benzylpyridinium bromides and their subsequent asymmetric hydrogenation in the presence of iridium(I) complexes derived from enantiomerically pure bisphosphines as catalysts.[28] After catalyst optimization, these authors identified that a combination of ligand **L3** and [{Ir(μ-Cl)(cod)}$_2$] (the standard iridium precursor in this chemistry) in a 1,2-dichloroethane (DCE)/acetone solvent mixture (1:1, *v*/*v*) provided very high levels of conversion and enantioselectivity (81–96% *ee*) in the hydrogenation of *N*-alkyl- or *N*-aralkyl-substituted pyridinium derivatives with aryl substituents in the 2-position (Scheme 3, a).



Scheme 3. Activation of heteroarenes by derivatization of the substrate.

On the contrary, 2-alkylpyridinium substrates were obtained with low to moderate levels of enantioselection (24–69% *ee*). Zhou and co-workers have also reported the highly enantioselective iridium-catalyzed hydrogenation of *N*-benzylated pyrrolo[1,2-*a*]pyrazinium systems (Scheme 3, b).[29] The catalytic system consisted of [{Ir(μ-Cl)(cod)}$_2$] as iridium precursor and **L4** as ligand. Interestingly, **L4** incorporates central and axial stereogenic elements and provided up to 95% *ee*.

Enantioselectivities ranged from 80 to 95% *ee* in cases involving aryl substituents in the pyrazinium ring (R^1 = substituted aryl groups), whereas the presence of alkyl substituents at the same position led to a significant drop in the enantioselectivity. The use of cesium carbonate increased the degree of conversion and inhibited racemization of the hydrogenated products.

2. Strategy II: Chelation Assistance During Hydrogenation

Significant progress in the asymmetric hydrogenation of certain kinds of heteroarenes was already being made in the early 2000s. For instance, a number of efficient catalytic systems that mediate the hydrogenation of several heterocyclic systems, such as quinolines and quinoxalines, were developed. However, the hydrogenation of other kinds of relevant heterocycles such as pyridines, isoquinolines, and indoles remained a challenge. Because the hydrogenation products of these heteroarenes (i.e., piperidines, isoquinolidines, and indolines) are extremely important pharmacophores found in many bioactive compounds, chemists developed a conceptually elegant and practical synthesis of piperidines, isoquinolidines, and indolines based on chelation assistance during asymmetric hydrogenation.

The underlying principle in this strategy involved the attachment to the substrate of an auxiliary coordinating group capable of coordinating to the metal center. On the basis of the superb enantioselectivities obtained in chelation-assisted asymmetric rhodium-mediated hydrogenations,[9] it was envisaged that coordination between the substrate and the metal center would be beneficial for controlling enantioselectivity. Because an acyl group is the classical model system for achieving high enantioselectivity and reactivity in rhodium-mediated hydrogenation, the groups led by Charette,[30] Zhou,[31–33] and Andersson[34] also attached acyl motifs to various six-membered heteroarenes to be hydrogenated in the presence of iridium-based enantioselective catalysts. Examples of this strategy are shown in Scheme 4.

Charette and co-workers transformed substituted pyridines into the corresponding *N*-acyliminopyridinium ylides, which were then subjected to asymmetric hydrogenation (Scheme 4, a).[30] After screening different catalytic systems, the authors found that iridium cationic complexes derived from phosphinooxazoline ligands – **C3** – provided the highest levels of conversion and enantioselectivity. Conversion was essentially complete for all substrates tested

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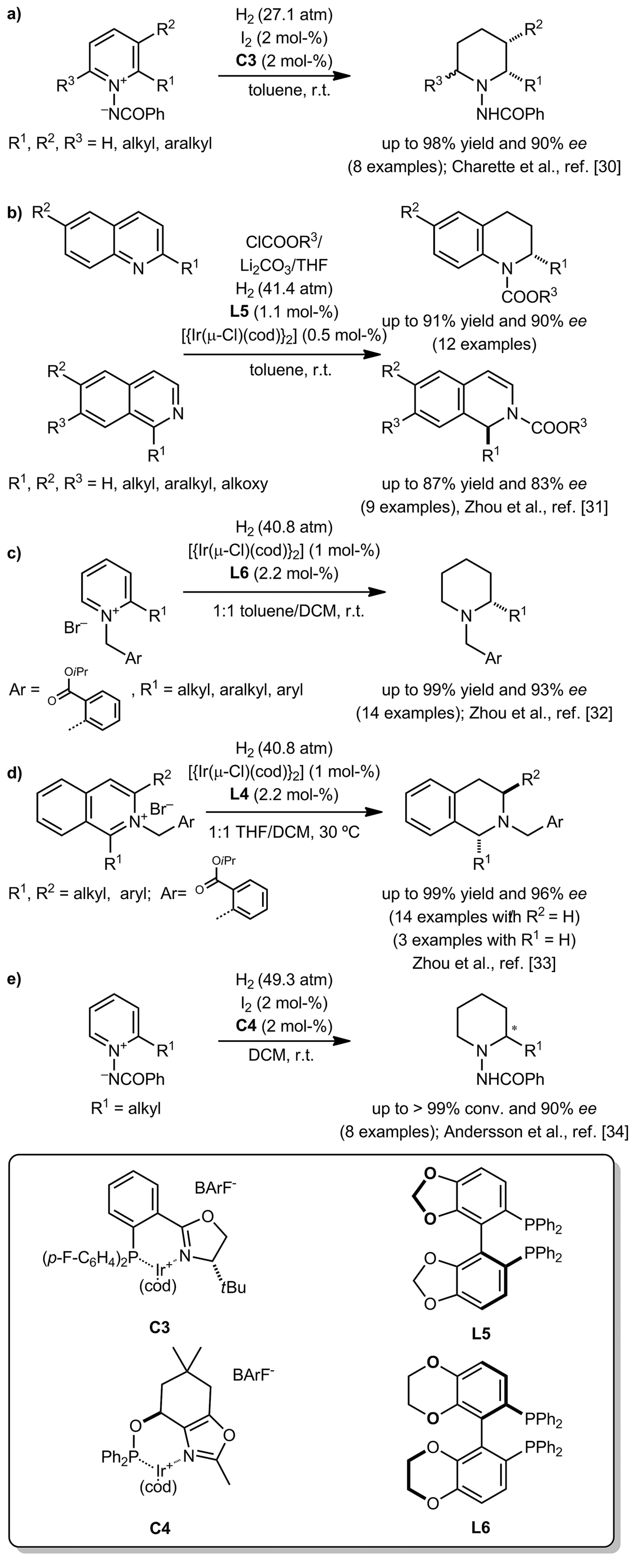

Scheme 4. Chelation assistance during asymmetric hydrogenation of six-membered heteroarenes.

(eight examples), although in some cases small quantities of partially hydrogenated compounds were detected. Enantioselectivities were generally high (up to 90%).

Disubstituted pyridinium ylides were also studied. Whereas 2,3-disubstituted compounds afforded the *cis* diastereoisomers with rather low enantioselectivities (it was observed that substitution at the 3-position was detrimental to enantioselectivities), 2,5-disubstituted pyridinium ylides were hydrogenated with high enantio- but lower diastereoselectivity. The final compounds could be efficiently converted into the corresponding piperidine derivatives by N–N bond cleavage.

An analogous strategy has been developed for the hydrogenation of quinolines and isoquinolines (Scheme 4, b).[31] Quinolines were activated by formation of the phenoxycarbonylquinolinium derivatives (R^3 = Bn) by derivatization in situ with benzyl chloroformate and a base. An array of substituted quinolines was efficiently hydrogenated with this activation strategy. 2-Alkyl-substituted quinolines were hydrogenated with high enantioselectivity regardless of the length of the alkyl chain (ca. 90% *ee*) and the reaction did not prove to be very sensitive to the substituent in the 6-position.

Isoquinolines were also activated by the same authors with use of the same strategy (Scheme 4, b). In this case, monohydrogenation took place and the corresponding 1,2-dihydroisoquinoline systems were obtained. Furthermore, conversions and enantioselectivities were lower than those observed for quinolines with the same catalytic system and activation strategy.

Enantioselectivities were close to 80% in most cases for monosubstituted isoquinolines (R^2 = H), although substitution in the carbocyclic ring (R^2 = OMe) led to a drop in enantioselectivity and conversion (ca. 64% *ee*). The authors do not provide any direct evidence of the participation of the acyl groups in the coordination sphere of the metal in the examples indicated in Scheme 4. However, the hydrogenation of derivatives analogous to the heterocycles indicated in Scheme 4 (a, b), but without a chelating substituent, either did not proceed[30] or led to hydrogenated products with lower enantioselectivity.[35]

More recently, Zhou and co-workers reported the transformation of 2-substituted pyridines into *N*-aralkylpyridium bromides and subsequent asymmetric hydrogenation in the presence of iridium(I) complexes derived from enantiomerically pure bisphosphines as catalysts.[32] A benzyl group with a CO_2*i*Pr substituent at its *ortho*-position (Scheme 4, c) was crucial in achieving high enantioselectivity; the C=O group on the benzyl group is probably coordinated to the metal center of the catalyst, thus favoring control of enantioselectivity. After catalyst optimization, these authors demonstrated that the combination of ligand **L6** with the standard iridium precursors in this chemistry, in a toluene/dichloromethane solvent mixture (1:1, *v*/*v*), provided very high levels of conversion and enantioselectivity in the hydrogenation of *N*-substituted pyridinium derivatives with alkyl, benzyl, and aryl substituents in the 2-position. Whereas iridium catalysts derived from **L6** enabled enantioselectivities ranging from 78 to 93% *ee* in the aryl-substituted hydrogenated products, the presence of alkyl or benzyl substituents at the 2-position provoked a drop in enantioselectivity.

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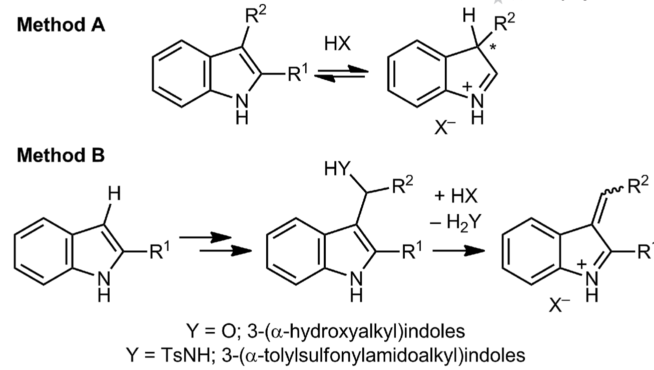
The same authors have described an analogous approach for the asymmetric hydrogenation of isoquinolium salts.[33] The catalytic system involves ligand **L4**, which incorporates central and axial stereogenic elements. Excellent enantioselectivities are obtained for 1-aryl-substituted substrates (up to 96% *ee*) and, once again, the presence of a chelating C=O motif is crucial for controlling enantioselection (Scheme 4, d). As had also been observed for 2-alkyl-substituted *N*-benzylpyridines, isoquinolinium derivatives alkyl-substituted at the 1- and 3-positions (Scheme 4, d) were hydrogenated with much lower *ee* values (43–74% *ee*).

Andersson et al. reported the hydrogenation of *ortho*-substituted *N*-iminopyridinium ylides mediated by the iridium complex **C4**. Eight substrates were explored, and the *ee* values of the hydrogenated products ranged from 10 to 90% *ee* (Scheme 4, e). Substrate chelation proved to be beneficial in achieving high levels of stereoselection.[34]

With regard to catalytic enantioselective hydrogenations of five-membered heteroaromatic rings, those long remained a challenge until Kuwano and co-workers reported that ruthenium complexes of enantiopure bisphosphines efficiently catalyzed the highly enantioselective hydrogenation of *N*-acylindoles.[36] Although each of their hydrogenated indole derivatives contains a *N*-acyl group, which is a priori capable of coordinating to the metal center, Kuwano and co-workers do not attribute any effect of the potential coordination of the substrate to the metal center to the outstandingly high levels of conversion and enantioselectivity achieved. Further examples of successful hydrogenation of indole derivatives with *N*-Ac, *N*-Boc, and *N*-Tos substituents were reported by the same research group,[37] by Pfaltz and co-workers,[38] and by Feringa, de Vries, and co-workers.[39] The results described for *N*-acetyl, *N*-Boc, and *N*-tosylindoles by all these research groups demonstrate that the substituent at the nitrogen greatly influences the level of conversion and the enantioselectivity achieved in the hydrogenation processes.[36–39] However, no conclusive evidence on the coordination of the *N*-substituents to the metal center is provided by the authors.

3. Strategy III: Hydrogenation After Breaking the Aromaticity

The stability of these heteroaromatic compounds can result in the need for harsh hydrogenation conditions for breaking their aromaticity and low enantioselectivities of the hydrogenated products due to the high temperatures normally required. Breaking the aromaticity of a heteroarene to be hydrogenated is not feasible for all kinds of substrates, but it was considered an intuitive step to undertake in order to facilitate hydrogenation whenever aromaticity could be broken. For instance, it was known that simple unprotected indoles reacted with strong Brønsted acids to form iminium derivatives through protonation of the C=C double bond of the five-membered ring (Method A in Scheme 5).[40]



Scheme 5. Strategies for breaking aromaticity in indoles.

Zhang, Zhou, and co-workers developed this idea and envisaged that the iminium compounds produced in situ according to Method A in Scheme 5 might be more prone to hydrogenation than the original indole derivatives. Catalyst screening studies in the hydrogenation of 2-methylindole identified palladium complexes incorporating ligand **L7** as the most efficient catalyst. The combined use of these palladium complexes and L-camphorsulfonic acid (L-CSA) in a mixture of dichloromethane and trifluoroethanol (TFE) as a solvent mediated the asymmetric hydrogenation of 2-methylindole with high levels of conversion (>95%) and enantioselectivity [91% *ee* in favor of the (*R*) enantiomer of the corresponding indoline].[41] Under the optimized reaction conditions, an array of diversely substituted indoles (13 examples), each possessing only one substituent in the five-membered ring, was hydrogenated with excellent yields (up to 99%) and enantioselectivities (up to 96% *ee*; Scheme 6, a).[41,42]

Hydrogenation of 2,3-disubstituted indoles by this methodology deserves special mention,[42] because it results in the formation of two contiguous stereogenic centers, one of which (the one corresponding to C3) should be formed during protonation and the other (the one relating to C2) during the hydrogenation process (Scheme 6, b). The authors reasoned that if protonation could be made to take place at a higher rate than hydrogenation, the overall process could be driven under dynamic kinetic resolution conditions and might benefit from a reduction in the number of formed stereoisomers. The use of the palladium complexes incorporating ligand **L7** in combination with a protic acid different from that used for monosubstituted indoles (*p*-TsOH instead of L-CSA) at a higher reaction temperature in the same solvent mixture enabled the efficient preparation of 2,3-disubstituted indolines. Under these conditions, a variety of 2,3-substituted indoles (17 examples) were hydrogenated with excellent yields (up to 97%) and diastereo- (only *cis* diastereoisomers were obtained) and enantioselectivities (up to 98% *ee*; Scheme 6, b). Alkyl, aryl, and aralkyl substituents were tolerated in the indole ring, though enantioselectivities for 3-benzyl-substituted indoles were slightly lower than those for their 3-alkyl analogues. Fused-ring substrates were also satisfactorily hydrogenated (up to 96% *ee*). The effects of substituents on the carbocycle were

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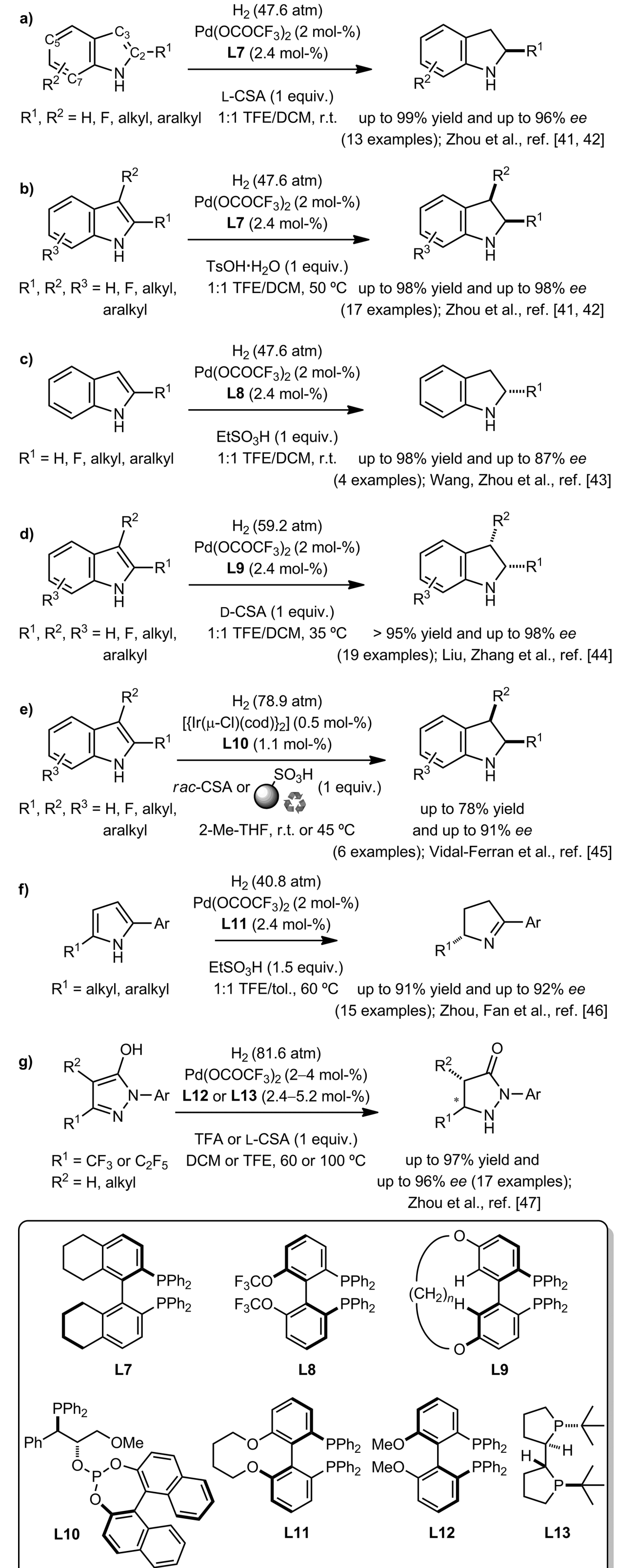

Scheme 6. Asymmetric hydrogenation of indoles and pyrroles.

not extensively studied, although trisubstituted indoles with a 5-F substituent displayed slightly lower *ee* values than their F-unsubstituted analogues (up to a 4% decrease in the *ee*). Combined experimental and theoretical studies suggest that the bisphosphine-palladium complexes mediated the hydrogenations through an outer-sphere mechanism with stepwise proton and hydride transfers.[42] The authors reported the hydrogenation of unprotected indoles by the same strategy with ligand **L8** and $EtSO_3H$ as additive, although the results obtained in terms of enantioselectivity were not as good (up to 87% *ee*; Scheme 6, c) as with *p*-TsOH (Scheme 6, b).[43]

Liu, Wang, and co-workers also reported the hydrogenation of indole systems with Pd^{II} complexes derived from the BridgePhos ligand **L9**, which exhibits a large bite angle, with excellent enantioselectivities (up to 98% *ee*; 19 differently substituted indoles with D-CSA as activator; Scheme 6, d).[44]

Although the above examples constituted efficient asymmetric hydrogenation of indoles, several practical challenges remained. First and foremost, stoichiometric amounts of a Brønsted acid are required, which calls for the recycling and reuse of the activator. Secondly, relatively high catalyst loadings (2 mol-% of palladium precursor and 2.4 mol-% of ligand) are used. Vidal-Ferran and co-workers reported the use of neutral iridium complexes of enantiomerically pure P-OP ligand **L10** (1 mol-%) and (reusable) Brønsted acids for the efficient conversion of unprotected indoles into enantiomerically enriched indolines (six examples, up to 78% isolated yield and up to 91% *ee*; Scheme 6, e).[45] Interestingly, the DOWEX™ resin used in this approach was recovered, recycled, and reused up to twice, giving comparable catalytic activity.

A similar strategy combining enantiomerically pure palladium complexes derived from ligand **L11** and ethanesulfonic acid as activator enabled the efficient hydrogenation of 2-alkyl-5-aryl-substituted pyrroles (15 examples, up to 91% yield, up to 92% *ee*) to afford the corresponding 3,4-dihydro-2*H*-pyrrole derivatives (Scheme 6, f).[46]

Very recently, Zhou et al. reported the asymmetric hydrogenation of fluorinated pyrazol-5-ols by capturing one of the tautomers with the aid of a strong Brønsted acid as activator. Two catalytic systems were developed for 4-unsubstituted of 4-substituted pyrazol-5-ols, based on the use of ligand **L12** or **L13** and TFA or L-CSA as activators, respectively (Scheme 6, g).[47] The hydrogenation of 17 examples was reported, with overall enantioselectivity in the corresponding substituted hydrogenated compounds ranging from 82 to 96% *ee*.

Because partially saturated indoles represent an interesting class of organic molecules that can be found in many bioactive compounds, other activation methods for increasing the reactivity of indole derivatives towards hydrogenation, involving C=C double bond migration, have also been developed (Method B in Scheme 5).[48] Easily available 3-(α-hydroxyalkyl)indoles can readily be dehydrated in the presence of a Brønsted acid to form conjugated iminium derivatives, in which the aromaticity has been partially broken.[49] Zhou, Jiang, et al. took advantage of some of the palladium-based enantioselective catalytic systems described previously (see Scheme 7) for the hydrogenation of

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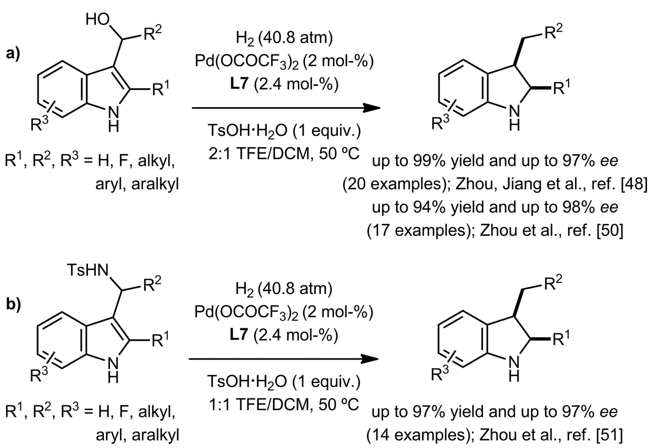
3*H*-indol-1-ium derivatives.[48] In this case, the iminium derivatives (produced in situ) were efficiently hydrogenated in the presence of the standard palladium precursor and ligand **L7** in high yields (up to 99%) and with enantioselectivities ranging from 85 to 97% (Scheme 7, a). This methodology provided an efficient route to enantiomerically enriched 2,3-disubstituted indolines (20 examples), all possessing relative *cis* stereochemistry of the two substituents of the indoline ring. A wide variety of aryl and aralkyl substituents at the 2- and 3-positions of the indole system did not provoke major changes in the enantioselectivities (*ee* values ranged from 88 to 94% *ee*). Substitution at the 5-position of the indole with a fluoro group brought *ee* values to the lowest levels seen in the series, due to steric and electronic effects, whereas the highest enantioselectivities were obtained with a methyl group at the 7-position, probably due to steric effects.[48]



Scheme 7. Elimination-triggered asymmetric hydrogenation of indoles.

Zhou and co-workers[50] prepared a set of enantioenriched indolines analogous to that reported by Zhou, Jiang, and co-workers[48] by use of an elegant tandem condensation and hydrogenation process. The tandem process involved a Brønsted-acid-promoted Friedel–Crafts reaction of the C3-unsubstituted indole to yield the corresponding 3-(α-hydroxyalkyl)indoles, which were directly hydrogenated in the presence of the catalytic system incorporating ligand **L7** (Scheme 7, a). The overall selectivity of the process is similar regardless of how the 3-(α-hydroxyalkyl)indoles are prepared (preformed in Zhou's and Jiang's method[48] or generated in situ in Zhou's tandem process[50]).

Analogous 2,3-disubstituted indolines were obtained from 3-(tolylsulfonamidoalkyl)indoles (Scheme 7, b). Their asymmetric hydrogenation, catalyzed by palladium complexes of ligand **L7**, was triggered by acid-mediated elimination of toluenesulfonamide ($TsNH_2$). This method also proved to be highly efficient, and 14 di- or trisubstituted indolines were efficiently prepared (up to 97% yield and 97% *ee*) by this approach.[51]

As a conclusion to this section, asymmetric hydrogenation of indoles triggered either by protonation or by double bond migration has enabled access to a wide variety of mono-, di-, or trisubstituted indolines with high enantioselectivities. Palladium- or iridium-based hydrogenation catalysts have been used for this transformation. A strategy for recovering, recycling, and reusing the stoichiometric amounts of the required Brønsted acids has also been developed. However, the main limitation lies in the fact that triggering hydrogenation by protonation or double bond migration can intrinsically only be applied to a reduced number of heteroarenes (for instance, indole, pyrrole, and pyrazole derivatives, as has been demonstrated to date).

Conclusions and Future Outlook

In this review we have focused on the various strategies devised to activate heteroaromatic substrates towards asymmetric hydrogenation by manipulation of their structures. The published examples have been classified into three different strategies, and the most relevant experimental details (catalyst employed, reaction conditions used, type of heteroarene, structural diversity, and catalyst activity in terms of conversion and enantioselectivity) have been highlighted in the different schemes throughout the text. These strategies include the formation of positively charged derivatives of the heteroarene (Strategy I), the introduction of a coordinating group that facilitates the hydrogenation by chelation assistance (Strategy II), and hydrogenation after breaking of the aromaticity (Strategy III). The use of an appropriate activation strategy for a given type of heteroarene has enabled access to a wide variety of fully and partially hydrogenated mono- and bicyclic heterocyclic compounds with excellent levels of conversion and enantioselectivity. In view of the wide repertoire of available ligand scaffolds and the ever-increasing number of reports on the application of substrate manipulation as a tool for improving the reactivity of heteroarenes in asymmetric hydrogenation, one can only imagine that the near future will witness several new examples of successful application of this methodology.

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