Asymmetric Hydrogenation

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Enantioselective Hydrogenation of Isoquinolines**

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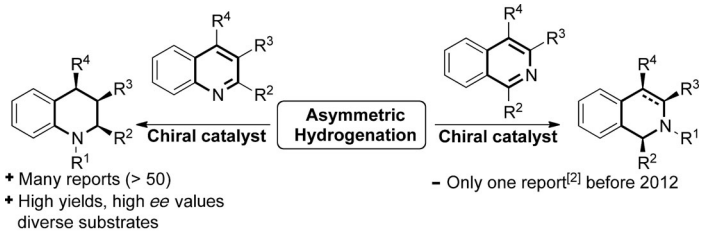
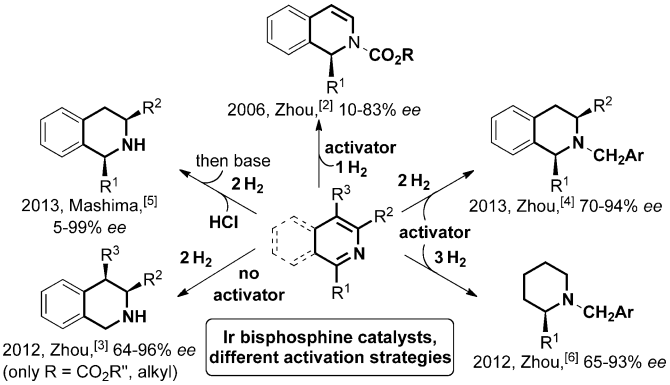
Asymmetric hydrogenation of (hetero)arenes is one of the most straightforward ways to synthesize enantiomerically pure, saturated or partially saturated cyclic molecules. Recent progress has significantly expanded the substrate scope of this reaction.[1] Whereas a number of highly efficient catalytic systems have been found for the asymmetric hydrogenation of quinolines, structurally related isoquinolines and pyridines are still regarded as challenging substrates for asymmetric hydrogenation (Scheme 1). The difficulty is presumably due



Scheme 1. Marked differences between the asymmetric hydrogenation of quinolines (left) and isoquinolines (right).

to the lower reactivity of these substrates and strong coordination to the catalyst. As chiral 1,2,3,4-tetrahydroisoquinolines and piperidines are highly important building blocks abundant in alkaloids and other biologically active compounds, the development of highly efficient catalytic systems for the hydrogenation of isoquinolines and pyridines is of great significance.

In 2006, Zhou et al. reported the first example of an asymmetric hydrogenation of isoquinolines with moderate enantioselectivities.[2] Recently, Zhou et al. and Mashima et al. further advanced the asymmetric hydrogenation of isoquinolines and pyridines with nearly simultaneous reports of the Ir-catalyzed enantioselective hydrogenation of 3,4-disubstituted isoquinolines,[3] as well as 1- or 3-substituted isoquinolinium and pyridinium salts.[4–6] Generally, four key



Scheme 2. Recent methods for the hydrogenation of substituted isoquinolines and isoquinolinium and pyridinium salts.

advances have been made in the area of asymmetric hydrogenation of isoquinolines in the last two years[3–5] (Scheme 2):

1) The development of more active (and still selective) catalysts has allowed not only partial but also full hydrogenation;
2) Less activated substrates could be used (neutral isoquinolines);
3) The diversity of substrates has increased (from monosubstituted substrates to diversely substituted substrates);
4) These activation strategies have been extended to the hydrogenation of even more challenging pyridines.[6]

It is also worth noting that all of these examples, regardless of the activation strategy, used [Ir] in combination with an axially chiral diphosphine derivative as the catalyst system (Scheme 3).

As shown in Scheme 2, in 2006 Zhou et al. envisioned that the activation of isoquinolines in the form of the corresponding N-substituted isoquinolinium salts would effectively eliminate the coordination ability of the substrate and thus greatly enhance reactivity. Thus the group reported the Ir-catalyzed asymmetric partial hydrogenation of C1-substituted isoquinolines, which were activated by stoichiometric amounts of chloroformates. However, only moderate enantioselectivities and yields were obtained.[2] Improving the versatility of this method, Zhou et al. recently found that simply changing the activator to benzyl bromide could effectively improve the reactivity and enantioselectivity to facilitate full hydrogenation of 1- and 3-substituted isoquinolinium salts by using an [Ir]-C3*-tunephos catalyst system.[4]

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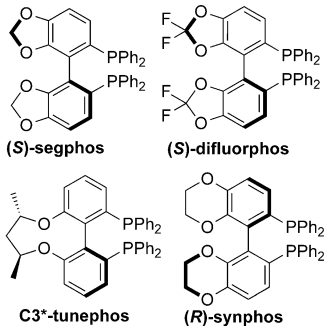
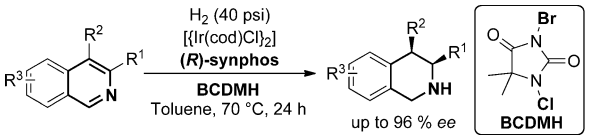


Scheme 3. Axially chiral bisphosphine ligands used as [Ir] complexes in these studies.

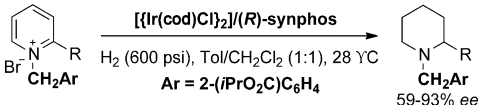
Almost at the same time, Mashima's group reported the direct asymmetric hydrogenation of 1- and 3-substituted and 1,3-disubstituted isoquinolinium chlorides in combination with a simple basic workup to give the corresponding 1,2,3,4-tetrahydroisoquinolines in high enantiomeric excess by using halogen-bridged dinuclear iridium(III) complexes $[\{Ir(H)[(S)\text{-difluorphos}]\}_2(\mu\text{-}Cl)_3]Cl$.[5] The advantages of this catalytic system are that it did not need a stoichiometric organic reagent as the activator, and it could directly access free NH-tetrahydroisoquinolines.

Despite achievements made in the hydrogenation of isoquinolinium salts, the asymmetric hydrogenation of commercially available neutral isoquinolines still remains unsolved. Neutral isoquinolines are easier to obtain than isoquinolinium salts and would not require a stoichiometric amount of activating reagent. Thus the development of an efficient method for the direct hydrogenation of neutral isoquinolines is highly desirable. Recently, Zhou et al. applied a catalyst-activation strategy to allow the direct asymmetric hydrogenation of neutral isoquinolines by treatment with $[Ir(cod)Cl]_2$/(*R*)-synphos in the presence of BCDMH [Eq. (1); cod = 1,5-cyclooctadiene].[3]

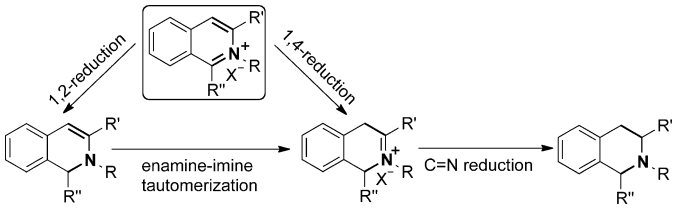


(1)

Undoubtedly, from an academic and industrial standpoint, the development of an efficient strategy for the asymmetric hydrogenation of simple pyridines is of greatest significance. Recently Zhou's group has successfully developed an iridium-catalyzed highly enantioselective hydrogenation of 2-substituted pyridinium salts by applying the same substrate-activation strategy used with isoquinolines [Eq. (2)].[6] This research indicates that those highly efficient stategies for the asymmetric hydrogenation of isoquinolines or other heteroarenes might also be applied to the hydrogenation of simple pyridines.



(2)



Scheme 4. Proposed different mechanisms for the hydrogenation of isoquinolines.

To gain insight into the reaction mechanism, a series of experiments were conducted by Zhou's and Mashima's groups (Scheme 4). Zhou et al. detected the enamine intermediate of the 1,2-hydrogenation during the hydrogenation of a 3-substituted isoquinolinium salt by ^1H NMR spectroscopy. Additionally, almost one deuterium atom was incorporated at the C4 position when a 3-substituted isoquinolinium salt was hydrogenated in THF/$[D_8]i$PrOH (4:1). Based on these results, a possible mechanism was proposed beginning with a 1,2-hydride addition to give the partially hydrogenated intermediate, followed by an acid-catalyzed enamine–imine tautomerization. Finally, a rapid hydrogenation delivers the desired product (Scheme 4). However, for Mashima's catalytic system, the authors obtained two important pieces of information by NMR monitoring: 1) asymmetric hydrogenation of the 3-phenylisoquinolinium salt under H_2 at atmospheric pressure afforded imine·HCl, which was gradually converted to the final product; and 2) under the same conditions, 1- and 4-substituted substrates could not be reduced efficiently. Based on these control experiments, Mashima et al. concluded that the hydrogenation proceeded by means of a 1,4-reduction and subsequent C=N reduction in their catalytic system (Scheme 4). More mechanistic insight is crucial for further development in the field, especially regarding the mode of enantioinduction in the C=N reduction step.

In summary, the groups of Zhou and Mashima have described the highly enantioselective hydrogenation of isoquinolines and isoquinolinium and pyridinium salts by use of different catalysts and different activation strategies. However, many challenges still remain in the enantioselective hydrogenation of these aforementioned heteroarenes:

1) a general enantioselective hydrogenation of neutral isoquinolines and simple pyridines;
2) the synthesis of molecules with multiple stereocenters;
3) high levels of functional group tolerance;
4) the development of more active catalysts and truly novel activation strategies to achieve higher turnover numbers to render the process more attractive for industry;
5) enantioselective *cis*- and *trans*-hydrogenation of these multisubstituted substrates;
6) further understanding of the reaction mechanism;
7) extension of these highly efficient catalytic systems to the hydrogenation of the other challenging (hetero)arenes.

Despite the work that remains to be done, these recent research results have advanced the field of asymmetric hydrogenation of heteroarenes to a new level. We are

convinced that these reactions will serve as role models for future work and provide new applications in the preparation of chiral N-containing cyclic molecules, especially for biologically active compounds.

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