Iridium-catalyzed asymmetric hydrogenation of pyridine derivatives, 7,8-dihydro-quinolin-5(6H)-ones

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[Ir(COD)Cl₂/MeO-BiPhep/I₂] catalyst system is highly effective for asymmetric hydrogenation of pyridine derivatives 7,8-dihydro-quinolin-5(6H)-ones with high enantioselectivities (up to 97% ee).

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Transition metal-catalyzed asymmetric hydrogenation of ketones, olefins, and imines has intensively been studied. However, enantioselective hydrogenation of heteroaromatic compounds is still a challenging task. To date, asymmetric homogeneous hydrogenation of aromatic rings with excellent enantioselectivities, such as quinolines, furans, indoles, and pyrroles has been reported. However, asymmetric hydrogenation of pyridines is a long-standing problem. To date, some progresses have been made. The pioneer work for asymmetric homogeneous hydrogenation of pyridine derivatives is done using Rh[nbd]₂BF₄/BINAP as the catalyst with moderate enantioselectivity (25% ee). Recently, Zhang’s group reported an efficient two-step asymmetric hydrogenation process of 3-substituted pyridine derivatives using a homogeneous rhodium catalyst. An efficient auxiliary-based method for the asymmetric hydrogenation of substituted pyridines has been developed by Glorious. Charette employed Iridium complex with Pfaltz’s phosphinoxazolines (PHOX) as ligands in the presence of I₂ for asymmetric hydrogenation of N-iminopyridinium ylides with modest to high enantioselectivities (54–90% ee). Very recently, Rueping and co-workers have developed highly enantioselective reaction of trisubstituted pyridine derivatives, catalyzed by chiral Brønsted acids with excellent enantioselectivities, in which Hantzsch dihydropyridine acts as hydrogen sources. In our ongoing efforts toward the development of asymmetric hydrogenation of aromatic compounds, two different systems were developed for hydrogenation of quinolines. One was the highly active iridium catalyst Ir/diphosphine/I₂, in which iodine is a crucial additive for activity and enantioselectivity. The other was Ir[P-P’]/Li₂CO₃/CICO₂R, which was involved in substrate activation to form quinolinium salts with chloroformates. The latter protocol can also be applied to asymmetric hydrogenation of isoquinolines. As an extension of our continuous work in asymmetric hydrogenation, we became interested in exploring asymmetric hydrogenation of pyridine derivatives. In this Letter, we wish to report our initial findings on the highly enantioselective hydrogenation of pyridine derivatives: 7,8-dihydro-quinolin-5(6H)-ones (1) with the catalyst Ir/MeO-BiPhep/I₂.

Based on our previous results, we firstly examined [Ir(COD)Cl₂]/(S)-MeO-BiPhep/toluene/I₂ catalyst system for hydrogenation of 7,8-dihydro-2-pentylquinolin-5(6H)-one (1a). To our delight, under the standard conditions, the reaction can run smoothly with an excellent enantioselectivity (92% ee). Encouraged by these results, we then investigated the effect of the solvent on the reaction for the sake of achieving an improvement of the enantioselectivity. The results are summarized in Table 1. Full conversions were achieved in all solvents examined in 12 h, but the ees of the products are highly solvent dependent (entries 1–4). The highest enantioselectivity (97% ee) was obtained using benzene as solvent. The use of CH₂Cl₂ and THF results in lower enantioselectivities (88% and 71% ee). Slightly lower conversion and enantioselectivity were observed under lower pressure of hydrogen gas (entry 7). The enantioselectivities of the reaction were slightly lower at higher temperature or high pressure (entries 5 and 6).

Next, the effect of various chiral ligands on the asymmetric hydrogenation of 1a was also studied. Some chiral bispinholigands were tested. The results showed that only axial chiral bisphosphine ligands exhibited good to excellent enantioselectivities with full conversions (entries 4, 8–11, and 14). The highest enantioselectivity (97% ee) was obtained using (S)-MeO-BiPhep as ligand. Whereas, the lower conversion and enantioselectivity were achieved with electron-rich (R,R)-Me-DuPhos L-6 (entry 12). Ferrocene-derived chiral N,P ligand showed excellent conversion and 72% ee (entry 13). Thus the optimized conditions are: [Ir(COD)Cl₂]/(S)-MeO-BiPhep/Benzene/I₂. It is noteworthy that the enantioselectivity achieved with Ir/(S)-MeO-BiPhep/I₂ as catalyst for the hydrogenation of pyridine derivative 1a is the highest reported to date.
Under the optimized condition, a variety of substituted 7,8-dihydro-quinolin-5(6H)-ones 1 were hydrogenated using [Ir(COD)Cl]_2/ligand catalyst system. The results are listed in Table 2. Full conversions were achieved in the hydrogenation of the 2-aryl-substituted 7,8-dihydro-quinolin-5(6H)-ones. However, the ees were slightly affected by the length of the alkyl chain and steric hindrance (entries 1–6). For 2-isopropyl substituted substrate, 84% ee was obtained (entries 3 and 6). With aryl substituted 7,8-dihydro-quinolin-5(6H)-ones, slightly low conversion and excellent enantioselectivity were obtained (92% ee, entry 7). The hydrogenation of the 2-benzyl and 2-phenethyl 7,8-dihydro-quinolin-5(6H)-ones also gave high to excellent enantioselectivities with 85% and 92% ee, respectively (entries 8 and 9).

Success of asymmetric hydrogenation of 7,8-dihydro-quinolin-5(6H)-ones 1 maybe due to the fact that the strong electron-withdrawing character of carbonyl reduces the inhibitory effect of the substrate. Thus other trisubstituted pyridine derivatives were also tested (see Scheme 1). The results showed our catalyst system has no catalytic activity on 3-electron-withdrawing substituted substrates 3 and 4. Trisubstituted pyridine derivative 5a can be hydrogenated with full conversion and 21% ee. When the phenyl group of 5a was replaced by n-butyl, slightly higher enantioselectivity was obtained (45% ee). For the 2,6-dimethylpyridine-3-carbonitrile (6), which can be hydrogenated in Rueping’s work with high ee using chiral phosphoric acid as catalyst in the presence of Hanstch ester, low conversion of 21% and 85% ee were obtained.

In summary, the [Ir(COD)Cl]_2/(S)-MeO-Biphep/I_2 catalyst system has been successfully applied in asymmetric hydrogenation of pyridine derivatives, 7,8-dihydro-quinolin-5(6H)-ones with good yields and excellent enantioselectivities. Further work will be directed toward expanding the scope of those pyridine derivatives and mechanism of the reaction.

Acknowledgments

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References and notes

3. For our recent work on asymmetric hydrogenation of quinolines and isoquinolines, see: (a) Zhou, Y.-G. Acc. Chem. Res. 2007, 40, 1357; (b) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. J. Am. Chem. Soc. 2003, 125,


