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# Iridium-catalyzed Asymmetric Hydrogenation of Pyridinium Salts for Constructing Multiple Stereogenic Centers on Piperidines

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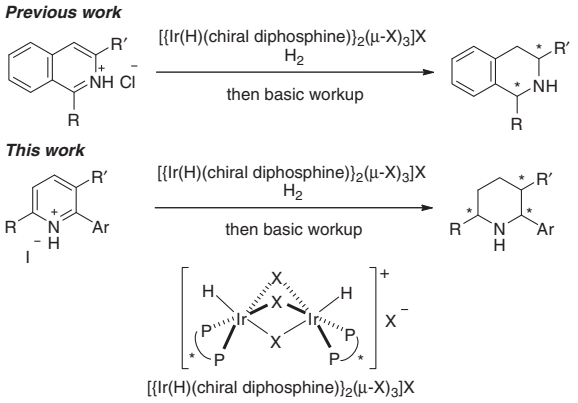
A salt formation strategy for asymmetric hydrogenation of pyridines is described. Poly-substituted pyridinium salts were successfully hydrogenated using chiral iridium dinuclear complexes to afford substituted piperidines with multiple stereogenic centers after a simple basic workup.

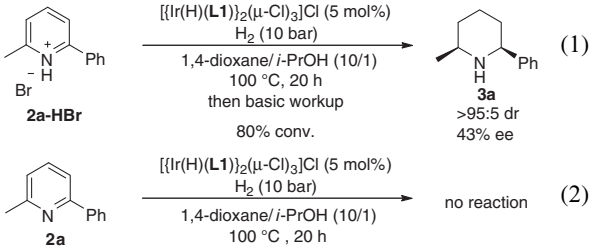
Chiral piperidine is an important structural skeleton abundant in a vast array of natural products and biologically active organic compounds, and it is often embedded within scaffolds of privileged structures recognized by medicinal chemists.[1] In this context, tremendous efforts have been focused on the development of synthetic protocols for such a prevalent motif.[2] Among them, asymmetric hydrogenation of substituted pyridines is the most straightforward and atom-economical route to concurrently constructing multiple stereocenters, but it remains a difficult task despite the recent report of the asymmetric hydrogenation of *N*-heteroaromatics.[3] Following the pioneering work by Studer et al. on the asymmetric hydrogenation of ethyl picolinate catalyzed by a rhodium complex with a chiral diphosphine ligand,[4] some synthetic studies have been devoted to the asymmetric hydrogenation of substituted pyridines.[5] Specific pyridine derivatives were successfully hydrogenated, however, such as poly-substituted pyridines bearing a chiral auxiliary,[6] 7,8-dihydroquinolin-5(6*H*)-ones,[7] *N*-iminopyridinium ylides,[8] and *N*-benzylpyridinium bromide.[3q] These systems have the potential to construct multiple stereocenters in a single operation, but there is only one case, reported by Glorius et al., in which both high ee and dr were accomplished through the hydrogenation of poly-substituted pyridines, although stoichiometric amounts of chiral auxiliary were required.[6] Accordingly, it is imperative that the general system for asymmetric hydrogenation of pyridines is established as an efficient method to prepare structurally diverse piperidines with multiple stereocenters.

We recently developed a series of asymmetric hydrogenations of *N*-heteroaromatics catalyzed by a halogen-bridged iridium dinuclear complex (Scheme 1).[9] In the course of our investigation, we found that salt formation of the substrate facilitated the asymmetric hydrogenation of isoquinolines with high enantioselectivity.[10] We achieved asymmetric hydrogenation of 1,3-disubstituted isoquinolinium salts to construct two stereocenters on a cyclic amine skeleton. Encouraged by this result, we examined the asymmetric hydrogenation of multisubstituted pyridine derivatives in which multiple stereogenic centers can be introduced to the piperidine skeleton in a single operation.

We attempted the hydrogenation of 2-methyl-6-phenylpyridinium bromide (**2a-HBr**) using iridium dinuclear complex **1** as a catalyst in a mixed solution of 1,4-dioxane/*i*-PrOH at 100 °C for 20 h under $H_2$ (10 bar), and the corresponding piperidine **3a** was obtained in 80% conv. with 43% ee after a basic workup (eq 1), whereas un-ionized pyridine was not hydrogenated under the same reaction conditions (eq 2). It is noteworthy that **3a** had only a *cis* configuration.



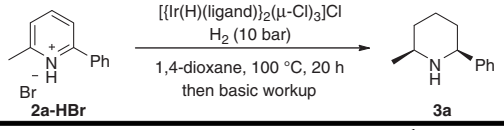

**Scheme 1.** Asymmetric hydrogenation of multisubstituted *N*-heteroaromatics.



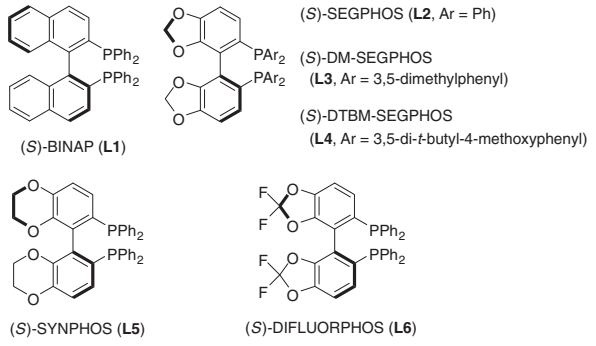

We then screened the reaction conditions. Solvent screening revealed that 1,4-dioxane was the best solvent.[13] Further optimization studies were conducted by changing the ligand to various diphosphine ligands (Table 1). The use of SEGPHOS and DIFLUORPHOS afforded higher enantioselectivity (Entries 2 and 6). DIFLUORPHOS gave the highest enantioselectivity (75% ee) and was thus selected for further investigation.

Using **L6** as a ligand, we examined the effect of halogen on both the catalyst and substrate because no halogen ligand exchange occurred on our iridium dinuclear complex, even in the presence of excess amounts of a different halogen anion (Table 2).[9a] Halogen at the substrate affected the enantioselectivity (Entries 1–3) whereas halogen at the catalyst had almost no effect on reactivity or selectivity (Entries 3–5). Iodide was determined to be the best halogen counter ion and chlorine was the best halogen ligand (Entry 3). Interestingly, the mixture of the Ir(I) complex and $I_2$ had relatively lower activity and enantioselectivity (Entry 6) than the iodide-bridged dinuclear complex (Entry 5), demonstrating that the activity of our

**Table 1.** Screening of ligands[a]

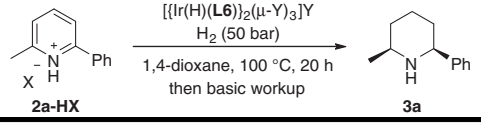



| Entry | Diphosphine | Conv.[b]/% | ee[c]/% |
|---|---|---|---|
| 1 | (*S*)-BINAP (**L1**) | 81 | 41 |
| 2 | (*S*)-SEGPHOS (**L2**) | 81 | 67 |
| 3 | (*S*)-DM-SEGPHOS (**L3**) | 61 | 52 |
| 4 | (*S*)-DTBM-SEGPHOS (**L4**) | 42 | 35 |
| 5 | (*S*)-SYNPHOS (**L5**) | 65 | 53 |
| 6 | (*S*)-DIFLUORPHOS (**L6**) | 41 | 75 |




[a]Reaction conditions: A mixture of pyridine (0.24 mmol), catalyst (12.1 μmol), and solvent (3 mL) under $H_2$ (10 bar) was heated at 100 °C for 20 h. [b]Determined by $^1$H NMR analysis after workup. [c]Determined by HPLC analysis of corresponding trifluoroacetamide.

**Table 2.** Screening of counter ions[a]



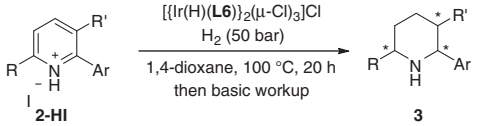

| Entry | X | Y | Conv.[b]/% | ee[c]/% |
|---|---|---|---|---|
| 1 | Cl | Cl | 51 | 69 |
| 2 | Br | Cl | 81 | 72 |
| 3 | I | Cl | 82 | 80 |
| 4 | I | Br | 70 | 76 |
| 5 | I | I | 83 | 78 |
| 6[d] | I | I | 62 | 65 |

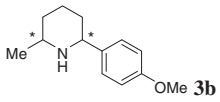
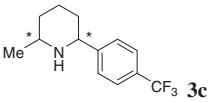
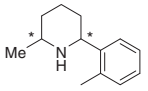
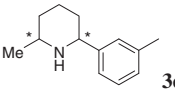
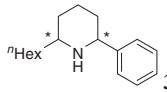
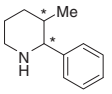
[a]Reaction conditions: A mixture of pyridine (0.08 mmol), catalyst (4.0 μmol), and solvent (6 mL) under $H_2$ (50 bar) was heated at 100 °C for 20 h. [b]Determined by $^1$H NMR analysis after workup. [c]Determined by HPLC analysis of corresponding trifluoroacetamide. [d]Mixture of $[IrCl(cod)]_2$ (5 mol %), **L6** (11 mol %), and $I_2$ (50 mol %) was used as catalyst precursor.

catalytic system differs from that of the traditional mixing system.

With the best catalyst in hand, a variety of pyridinium salts were hydrogenated (Table 3). In all cases, high diastereoselectivity was observed, and only a single isomer was observed in $^1$H NMR spectra. Substrate reactivity was affected by the substituent on the 6-phenyl group. Both electron-donating and electron-withdrawing groups retarded the reaction (Entries 1 and 2). Ortho-substituents did not inhibit the reaction, and the corresponding product was obtained with 82% ee (Entry 3). Similarly, meta-substituted substrate was hydrogenated to the corresponding product in 73% ee (Entry 4). 2-Hexyl-6-phenylpyridinium salt was also a good substrate for the present system, affording corresponding product **3f** in 66% yield with 72% ee (Entry 5). 2,3-Disubstituted substrate was also hydrogenated to give **3g**, which had only a *cis* configuration (Entry 6).

**Table 3.** Asymmetric hydrogenation of disubstituted pyridines[a]



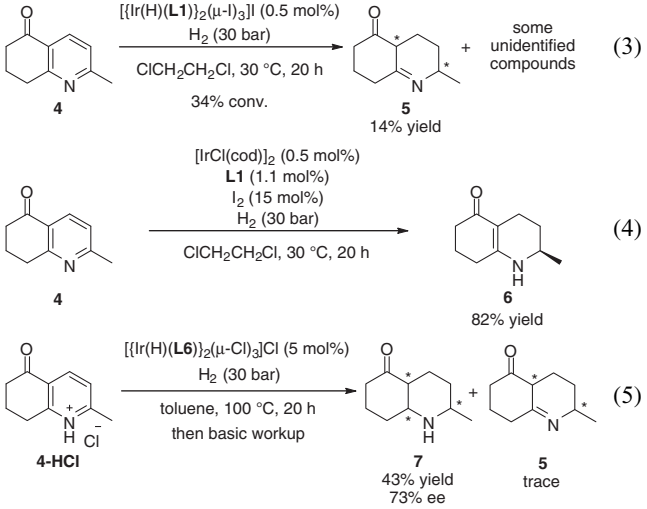

| Entry | Product | Yield[b]/% | ee[c]/% | dr[d] |
|---|---|---|---|---|
| 1[e,f] |  **3b** | 81 | 28 | >95:5 |
| 2 |  **3c** | 54 | 55 | >95:5 |
| 3 |  **3d** | >95 | 82 | >95:5 |
| 4 |  **3e** | 75 | 73 | >95:5 |
| 5 |  **3f** | 66 | 72 | >95:5 |
| 6[f,g] |  **3g** | 32 | 40 | >95:5 |

[a]Reaction conditions: A mixture of pyridine (0.24 mmol), catalyst (12.1 μmol), and solvent (6 mL) under $H_2$ (50 bar) was heated at 100 °C for 20 h. [b]Isolated yield. [c]Determined by HPLC analysis of corresponding trifluoroacetamide. [d]Determined by $^1$H NMR analysis. [e]Run at 120 °C. [f]Corresponding hydrogen chloride salt was used as a substrate. [g]Run under $H_2$ (30 bar) and toluene was used as a solvent.

We observed an interesting phenomenon that our dinuclear catalyst exhibited different activity for asymmetric hydrogenation than the complex generated from mixing the catalyst precursor and iodine, though similar active species are assumed to be generated in situ. Thus, we performed the asymmetric hydrogenation of pyridine derivative **4**, which was hydrogenated using an iridium(I) complex and iodine.[7] To our surprise, a different product was obtained when using our iridium dinuclear complex under the same reaction conditions (eq 3 vs. eq 4). Unfortunately, the produced imine **5** gradually converted to an unknown compound, even under an inert atmosphere.[12] We therefore attempted to isolate a fully hydrogenated product using our salt formation strategy. Asymmetric hydrogenation of **4-HCl**

was performed under relatively harsh conditions to afford the fully hydrogenated product **7** in 43% yield and 73% ee (eq 5), whereas a complex mixture was obtained by using Ir(I) and iodine. In contrast to disubstituted substrates in Table 3, one diastereomer was observed (major:minor = 92:8).




In summary, we developed an asymmetric hydrogenation of multisubstituted pyridinium salts to afford piperidines with multiple stereogenic centers. Our catalyst is especially advantageous for asymmetric hydrogenation of 7,8-dihydro-2-methylquinolin-5(6*H*)-one to form the product, which was not obtained using the Ir(I)–$I_2$ catalytic system. This unique activity of our complex can be used in the asymmetric hydrogenation of other substrates.

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11 See Supporting Information. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

12 Structure of **5** was determined by $^{1}$H and $^{13}$C NMR spectra of the reaction mixture.