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Highly Enantioselective Iridium-Catalyzed Hydrogenation of Quinoline Derivatives Using Chiral Phosphinite H8-BINAPO

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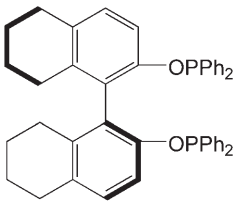
Abstract: The chiral diphosphinite H8-BINAPO derived from H8-BINOL has been used in the Ir-catalyzed asymmetric hydrogenation of quinolines, and high enantioselectivity (up to 97% ee) was obtained. Immobilization of the iridium catalyst in poly(ethylene glycol) dimethyl ether (DMPEG) is also discussed. With DMPEG/hexane biphasic system, better enantioselectivities were obtained as compared to those observed in aprotic organic solvents.

Keywords: asymmetric hydrogenation; immobilization; iridium; phosphinite ligands; poly(ethylene glycol) dimethyl ether; quinoline

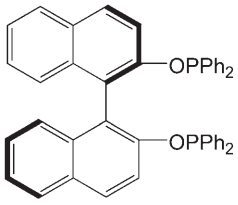
The catalytic asymmetric hydrogenation of heteroaromatic compounds as a means to prepare optically pure heterocycles is an interesting, yet challenging task in organic synthesis.[1] Although considerable effort has been made in this area, the reports on the development of highly effective catalysts are rare.[2–4] Among the reported examples, the use of chiral bidentate diphosphine ligands seems to be an important factor for high enantioselectivity.

Recently, chiral phosphinite ligands have been successfully used in the asymmetric hydrogenation of prochiral olefins.[1,5] For example, *O*-BINAPO ligands have been prepared to provide good to excellent enantioselectivities in the asymmetric hydrogenation of α-dehydroamino acids and β-aryl-β-(acylamino) acrylates.[5a] The use of carbohydrate-derived phosphinite ligands also gave good to excellent results in the enantioselective hydrogenation of α-dehydroamino acids.[5b–d] Compared with phosphine ligands, phosphinites offer the advantages of easy preparation and derivatization. In general, the phosphinites can be conveniently synthesized in good yields by reacting the corresponding alcohols with chlorophosphines in the presence of an organic base. Given the general utility of these phosphinite ligands in asymmetric hydrogenation reactions, it is very attractive to develop effective chiral phosphinite ligands for the asymmetric hydrogenation of heteroaromatics.

In our pursuit of effective chiral phosphinite ligands for asymmetric hydrogenation,[6] we demonstrated that the easily accessible H8-BINAPO ligand provided better enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of enamides and α-dehydroamino acid derivatives than their unmodified BINAPO ligand.[6c,d] Compared with the BINAPO ligand, the better performance of the H8-BINAPO ligand resulted from its more rigid structure, which made it possible to compensate for the conformational flexibility caused by the introduction of C–O–P bond.[6e] Herein we report the use of the (*S*)-H8-BINAPO (**L1**) ligand in the Ir-catalyzed asymmetric hydrogenation of quinoline derivatives in THF giving the desired products in up to 96% ee. Even higher enantioselectivities (up to 97%) were obtained when the reaction was carried out in DMPEG/hexane.



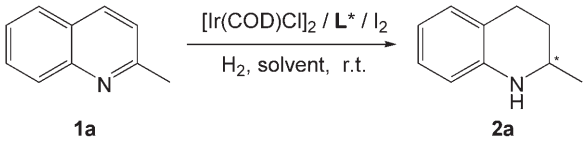
(*S*)-H8-BINAPO **L1**



(*R*)-BINAPO **L2**

We first examined the catalytic performance of **L1** ligand in the Ir-catalyzed hydrogenation of quinaldine (**1a**). For comparison, the performance of (*R*)-BINAPO (**L2**) ligand was also examined under otherwise identical conditions. The catalysts were prepared *in situ* from the phosphinites and $[Ir(COD)Cl]_2$ with I_2 as additive. Un-

Table 1. Asymmetric hydrogenation of quinoline **1a** under various conditions.[a]

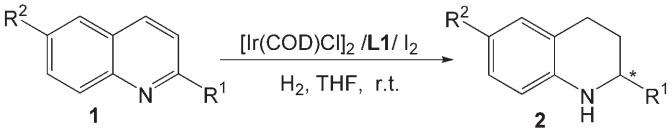


1a **2a**

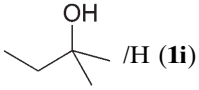
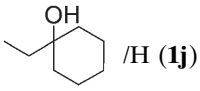
Entry	Ligand	Solvent	Conversion [%][b]	ee [%][b]
1	**L1**	toluene	>99	89
2	**L2**	toluene	92	79
3	**L1**	CH_2Cl_2	79	93
4	**L2**	CH_2Cl_2	75	91
5	**L1**	MeOH	13	68
6	**L1**	EtOH	11	41
7	**L1**	Et_2O	>99	94
8	**L2**	Et_2O	>99	80
9	**L1**	THF	>99	95
10	**L2**	THF	>99	81
11[c]	**L1**	THF	9	78
12[d]	**L1**	THF	74	90

[a] All reactions were carried out at room temperature using 1 mol % of Ir complex generated *in situ* from $[Ir(COD)Cl]_2$ and ligand, and I_2 (10 mol%) under 700 psi H_2 for 20 h.
[b] The conversion was determined by ^1H NMR, and the enantioselectivity was determined by HPLC analysis with a Chiralpak OJ-H column.
[c] $[Ir(COD)]BF_4$ was used as the precursor
[d] $[Ir(COD)]PF_6$ was used as the precursor.

Table 2. Catalytic asymmetric hydrogenation of quinoline derivatives in THF with **L1** ligand.[a]



1 **2**

Entry	R^1/R^2	Yield [%]	ee [%][b]
1	Me/H (**1a**)	98 (**2a**)	95 (*R*)
2	Et/H (**1b**)	97 (**2b**)	92 (*R*)
3	*n*-Pr/H (**1c**)	98 (**2c**)	88 (*R*)
4	*n*-Bu/H (**1d**)	99 (**2d**)	90 (*R*)
5	Ph/H (**1e**)	96 (**2e**)	84 (*S*)
6	Me/Me (**1f**)	97 (**2f**)	92 (*R*)
7	Me/MeO (**1g**)	90 (**2g**)	94 (*R*)
8	Me/F (**1h**)	99 (**2h**)	83 (*R*)
9	 /H (**1i**)	98 (**2i**)	95 (*S*)
10	 /H (**1j**)	98 (**2j**)	96 (S)

[a] All reactions were carried out in THF at room temperature using 1 mol % of Ir complex generated *in situ* from $[Ir(COD)Cl]_2$ and **L1**, and I_2 (10 mol %) under 700 psi H_2 for 20 h.
[b] The enantioselectivities of products was determined by HPLC analysis with Chiralpak OJ-H (**2a**–**e**), AS-H (**2f** and **g**), and OD-H(**2h**–**j**) columns. The absolute configurations were assigned by comparison of the HPLC retention times with the reported data.

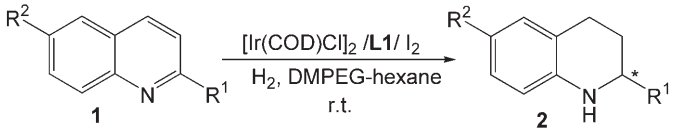
der the conditions previously optimized by Zhou and coworkers,[3] using **L1** gave promising enantioselectivity (89%), furnishing the product in more than 99% conversion. **L2** gave rise to a comparatively lower enantioselectivity (79%) with 92% conversion. Encouraged by these results, we then investigated the effect of solvent on the reaction with the objective of achieving an improvement of the enantioselectivity. The results are summarized in Table 1. It was obvious that the enantioselectivity of the reaction was sensitive to the solvents used. A higher ee value of **2a** was achieved in aprotic solvents whereas in an alcohol solvent the enantioselectivity was lower. The much lower conversion in alcohol solvent was probably due to decomposition of the Ir catalyst (entries 5 and 6). Ether solvents were more effective than other aprotic solvents (entries 7 and 9 *vs.* entries 1 and 3), and the highest enantioselectivity (95%) was obtained in THF using **L1** ligand (entry 9). It was clearly observed that Ir-**L1** performed better than Ir-**L2** in this reaction, although Ir-**L2** also displayed good catalytic performance. Therefore, we focused on the use of **L1** ligand in the subsequent study of this reaction. It should be pointed out that in all cases only the tetrahydroquinoline product was obtained and the fused aromatic ring remained intact. Furthermore, the change of Ir source to a cationic $[Ir(COD)]BF_4$ or $[Ir(COD)]PF_6$ form caused a marked decrease of yield and enantioselectivity (entries 11 and 12). We also examined a series of additives including KI, NaI, BiI_3, LiCl, tetrabutylammonium iodide, phthalimide, and I_2 was found to be the only effective additive.

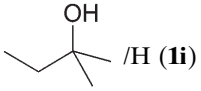
The asymmetric hydrogenation of other 2-substituted quinoline derivatives using Ir-**L1** catalyst was also carried out and the results are summarized in Table 2. Good to excellent enantioselectivities were achieved in the hydrogenation of 2-alkyl-substituted quinolines. The length of the alkyl chain did not seem to have very large effect on the ee values (entries 1–4). When the alkyl group at the 2-position was replaced by a phenyl group, a lower enantioselectivity was observed (entry 5). The introduction of electron-donating groups on the 6-position had no clear effect on the ee (entries 6 and 7). However, a 6-substituted quinoline with an electron-withdrawing group gave low enantioselectivity (entry 8). The asymmetric hydrogenation of quinolines bearing hydroxy groups proceeded smoothly, affording excellent results (entries 9 and 10). It is noted that most of these results are comparable to or better than those obtained by using Ir/MeO-BIPHEP[3] or Ir/P-Phos.[4]

Since the immobilization and recycle of chiral catalyst is of high interest,[4,7] we have also studied the immobilization of the Ir-**L1**. Room temperature ionic liquids and poly(ethylene glycol) (PEG) have recently received much attention as alternative reaction media.[7,8] We carried out the hydrogenation in these two reaction media, and found a significant reduction in both conversion and ee. For example, the reaction in ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate gave much low conversion (<10%) and poor enantioselectivity (40% ee). The use of PEG (MW = 400) brought about only 70% conversion and a lower ee of 60%. Considering the fact that this reaction worked better in less polar solvents, it was possible that the decrease in conversion and enantioselectivity was due to the high polarity of ionic liquids and PEG. A similar observation has been made in the Ir-catalyzed asymmetric hydrogenation of unfunctionalized olefins using ionic liquid as solvent.[10] On the other hand, we have recently demonstrated that the less polar biphasic system poly(ethylene glycol) dimethyl ether (DMPEG, MW = 500)/hexane is a good alternative reaction medium to THF in the Ir-catalyzed asymmetric hydrogenation of quinolines, and can be used as a new option for catalyst immobilization.[4] We thus carried out the Ir-catalyzed hydrogenation in DMPEG/hexane biphasic system. The preliminary results are shown in Table 3. To our surprise, a significant increase of enantioselectivity (up to 11%) was observed compared with those obtained in THF solvent. For example, hydrogenation of **1h** in THF only led to 83% ee (Table 2, entry 8). However, when switched to DMPEG/hexane, the same catalyst afforded the corresponding products in 94% ee (Table 3, entry 7). It was noteworthy that the hydrogenation of both substrates **1a** and **1i** gave 97% ee, which was the highest value achieved for this reaction so far (Table 3, entries 1 and 8). After the reaction, the chiral catalyst was totally soluble in the DMPEG phase, and the products were easily recovered in the upper hexane phase. It was evident that the DMPEG/hexane system had beneficial effects on enantioselectivity. A similar effect was reported by Bolm and co-workers who found that the addition of simple methoxypoly(ethylene glycol)s improved the asymmetric addition of aryl and alkyl groups to aldehydes.[11]

The recycle of the catalyst proved to be difficult. We carried out the recycling study using **1a** as a model substrate. At the end of each experiment the product was recovered *via* simple decantation of the upper hexane phase and three additional extractions with degassed hexane. The DMPEG phase was recharged with **1a**, I_2 and hexane, and was subjected to the hydrogenation conditions. Unfortunately, after two runs, the conversion and enantioselectivity were found to decrease to 65% and 72%, respectively. The replenishment of 1 mol % ligand in each run only maintained the high enantioselectivities (over 90% ee) for 3 runs, while the conversion dropped to 42% after two runs. ICP-AES analysis of the hexane layer in each recycle experiment showed a 0.2 ppm loss of iridium (0.21% of the total Ir content), indicating that no appreciable leaching of iridium occurred during the extraction of the products. It is possible that the drop in enantioselectivity and conversion was due to deactivation of the iridium catalyst. A further study to understand and eventually to resolve this problem is in progress.

Table 3. Catalytic asymmetric hydrogenation of quinoline derivatives in DMPEG-hexane with **L1** ligand.[a]



Entry	R^1/R^2	Yield [%]	ee [%][b]
1	Me/H (**1a**)	98 (**2a**)	97 (*R*)
2	Et/H (**1b**)	97 (**2b**)	94 (*R*)
3	*n*-Pr/H (**1c**)	99 (**2c**)	95 (*R*)
4	*n*-Bu/H (**1d**)	99 (**2d**)	94 (*R*)
5	Ph/H (**1e**)	98 (**2e**)	87 (*S*)
6	Me/Me (**1f**)	98 (**2f**)	95 (*R*)
7	Me/F (**1h**)	96 (**2h**)	94 (*R*)
8	 /H (**1i**)	98 (**2i**)	97 (*S*)

[a] All reactions were carried out in THF at room temperature using 1 mmol % of Ir complex generated *in situ* from $[Ir(COD)Cl]_2$ and **L1**, and I_2 (10 mol %) under 700 psi H_2 for 20 h.

[b] The enantioselectivities of products was determined by HPLC analysis with Chiralpak OJ-H (**2a**–**e**), AS-H (**2f** and **g**), and OD-H (**2h**–**j**) columns. The absolute configurations were assigned by comparison of the HPLC retention times with the reported data.

In summary, we have demonstrated that the Ir-H8-BINAPO catalyst was highly effective in the asymmetric hydrogenation of quinoline derivatives. By using DMPEG/hexane as reaction medium, better enantioselectivities were obtained than in THF. The investigations on the effective recycling of the catalyst in DMPEG/hexane are still in progress.

Experimental Section

Typical Procedure for the Asymmetric Hydrogenation of Quinolines in THF and Other Solvents

A mixture of $[Ir(COD)Cl]_2$ (1.0 mg, 0.0015 mmol) and the ligand (0.003 mmol) in THF (1.0 mL) was stirred at room temperature for 30 minutes in a glovebox, and the mixture was transferred by a syringe to a stainless steel autoclave, in which I_2 (4 mg, 0.015 mmol) and substrate (0.3 mmol) in 0.5 mL THF

were placed beforehand. The hydrogenation was performed at room temperature under H_2 (700 psi) for 20 h. After carefully releasing the hydrogen, the reaction mixture was diluted with dichloromethane (5 mL), saturated sodium carbonate aqueous solution (2.0 mL) was added and stirred for 15 minutes. The aqueous layer was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were dried with sodium sulfate and concentrated under vacuum to give the crude product. Purification on a silica gel column gave the pure product. The enantiomeric excesses were determined by HPLC with chiral columns (OJ-H, OD-H, or AS-H).

Typical Procedure for the Asymmetric Hydrogenation of Quinoline in MPEG/Hexane

A mixture of $[Ir(COD)Cl]_2$ (1.7 mg, 0.003 mmol) and (*S*)-H8-BINAPO (4.0 mg, 0.006 mmol) in DMPEG (2.0 mL) was stirred at room temperature for 30 minutes in a stainless steel autoclave inside a glovebox, then I_2 (7 mg, 0.03 mmol) and substrate (0.6 mmol) together with 2 mL hexane were added and stirred for another 5 minutes. The hydrogenation was then performed at room temperature under H_2 (700 psi) for 20 h. After carefully releasing the hydrogen, the hexane layer was decanted and the product in the DMPEG phase was then further extracted with hexane (3×2 mL). The combined hexane solution was then washed with saturated sodium carbonate aqueous solution (2.0 mL) and concentrated under vacuum to give the crude product. Purification on a silica gel column led to pure product. The enantiomeric excesses were determined on an HPLC equipped with chiral columns.

Acknowledgements

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