Asymmetric hydrogenation of quinolines with high substrate/catalyst ratio†

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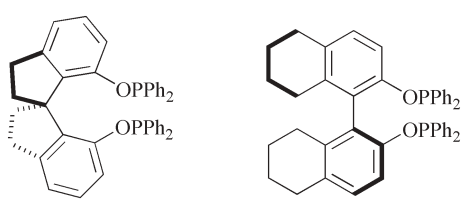
The chiral diphosphinite ligand derived from (*R*)-1,1′-spirobiindane-7,7′-diol has been found to be highly effective in the Ir-catalyzed asymmetric hydrogenation of quinolines with high substrate/catalyst ratio (up to 5000) and high enantioselectivity (up to 94% ee).

Transition metal-catalyzed asymmetric hydrogenations have been extensively studied, and are considered as a versatile method for the preparation of optically active compounds.[1,2] However, the enantioselective hydrogenation of heteroaromatic compounds, which is a convenient method for the preparation of enantiomerically pure heterocycles, still remains a challenging task. Successful examples in this type of asymmetric catalytic reactions are rare.[3–6] Recently, Zhou and co-workers found that the iridium complex generated *in situ* from $[Ir(COD)Cl]_2$ and (*R*)-MeO-BIPHEP or a ferrocenyloxazoline derived P,N-ligand was able to catalyse the enantioselective hydrogenation of quinolines with high enantioselectivities and good yields.[5a–c] Comparable results have also been achieved with the air-stable and recyclable Ir–P-Phos catalyst system.[6a] In a recent study, we found that the easily available, chiral phosphinite H8-BINAPO was an excellent ligand for the asymmetric hydrogenation of quinoline compounds with high enantioselectivities (up to 97% ee) and very good yields.[6b] Reetz and co-workers also demonstrated BINOL-derived diphosphonites with achiral P-ligands as additives to be highly efficient for the same reactions.[7] On the other hand, Zhou *et al.* disclosed a new strategy for Ir-catalyzed asymmetric hydrogenation of quinolines by using chloroformate as activating reagent, and up to 90% ee was obtained.[5d] Although moderate to excellent enantioselectivities have been achieved, almost all these reactions suffered from low catalyst efficiency as evidenced by the fact that good results could only be obtained at a low substrate-to-catalyst ratio of 100. This might be due to the instability of the catalyst. From the viewpoints of both scientific interest and practical applications, it is highly desirable to develop more efficient catalysts for the highly enantioselective reaction.

In recent years, chiral ligands based on the 1,1′-spirobiindane backbone have been shown to be highly active and enantioselective in asymmetric hydrogenations, suggesting that the rigidity of the spirobiindane skeleton facilitated the effective transfer of chiral information.[8] Following our pursuit of effective chiral phosphinite ligands for asymmetric hydrogenations,[9,10] we herein report that an iridium catalyst containing a new chiral phosphinite ligand Spiropo ($\mathbf{L_1}$) (Scheme 1) derived from (*R*)-1,1′-spirobiindane-7,7′-diol exhibited high catalytic activity (substrate/catalyst ratio up to 5000 with 91% conversion) and excellent enantioselectivity (up to 94% ee) in the asymmetric hydrogenation of quinolines.

We first examined the performance of ligand $\mathbf{L_1}$ in the Ir-catalyzed hydrogenation of quinolines with 2-methylquinoline as a model substrate (Table 1). The catalyst was prepared *in situ* from $\mathbf{L_1}$ and $[Ir(COD)Cl]_2$ with I_2 as an additive. Under our previously optimized conditions,[6b] complete conversion and 92% ee were observed (entry 1). The catalyst was very stable in THF. Even after two months under an inert atmosphere, its activity and enantioselectivity still remained unchanged (entry 2). The reaction was sensitive to the solvents used (entries 3–6), and THF provided the best results. Similar solvent effect has been reported previously.[6b] By using THF as solvent, the effects of temperature and substrate-to-catalyst (S/C) molar ratio on the rate and enantioselectivity were examined. For comparison, the performance of (*R*)-H8-BINAPO ($\mathbf{L_2}$) (Scheme 1) was also investigated under otherwise identical conditions.

Slightly higher enantioselectivity was obtained with $\mathbf{L_1}$ ligand when the reaction was carried out at 0 °C (entries 7–9). It was observed that the reaction proceeded smoothly at an S/C ratio from 100 to 2000 with complete conversions and high enantioselectivities using ligand $\mathbf{L_1}$ (entries 1, 7–9). When the S/C ratio was increased to 5000, the enantioselectivity still remained unchanged while the conversion decreased to 91% with $\mathbf{L_1}$ ligand (entry 10). It was noted that ligand $\mathbf{L_1}$ gave a high initial TOF value (2400 h^{-1} in the first hour) (entry 12). To the best of our knowledge, this is the best result reported so far for this reaction. In contrast,



$\mathbf{L_1}$ $\mathbf{L_2}$

Scheme 1

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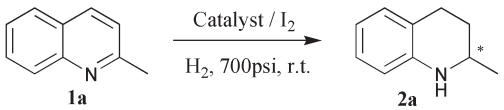
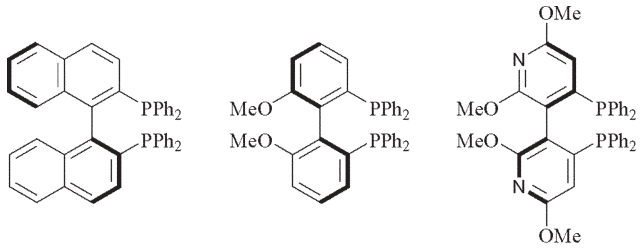
Table 1 The catalytic activity of ligands $\mathbf{L_1}$ and $\mathbf{L_2}$ in the asymmetric hydrogenation of quinaldine[a]



Entry	L*	Solvent	S/C	Conv.[c] (%)	Ee[c] (%)
1	$\mathbf{L_1}$	THF	100	100	92
2[b]	$\mathbf{L_1}$	THF	100	100	92
3	$\mathbf{L_1}$	Toluene	100	100	89
4	$\mathbf{L_1}$	Et_2O	100	100	91
5	$\mathbf{L_1}$	CH_2Cl_2	100	72	71
6	$\mathbf{L_1}$	CH_3OH	100	10	16
7	$\mathbf{L_1}$	THF	500	100	92 (94)[d]
8	$\mathbf{L_1}$	THF	1000	100	92 (94)[d]
9	$\mathbf{L_1}$	THF	2000	100	92 (94)[d]
10[a]	$\mathbf{L_1}$	THF	2000	100	92
11	$\mathbf{L_1}$	THF	5000	91	92
12[a]	$\mathbf{L_1}$	THF	5000	48	92
13	$\mathbf{L_2}$	THF	100	100	95 (96)[d]
14	$\mathbf{L_2}$	THF	500	48	76
15	$\mathbf{L_2}$	THF	1000	26	65
16	$\mathbf{L_2}$	THF	2000	16	61
17	$\mathbf{L_2}$	THF	5000	7	67

[a] All reactions were carried out at room temperature with 0.15 mmol quinaldine (0.3 mmol for S/C 2000/1 and 0.75 mmol for S/C 5000/1) using Ir complex generated *in situ* from $[Ir(COD)Cl]_2$, ligand $\mathbf{L_1}$ or $\mathbf{L_2}$, and I_2 (1%) under 700 psi H_2 for 20 h (except for entries 10 and 12, 1 h) in 2 ml THF. [b] The catalyst was stored as a THF solution for two months before use. [c] The conversion was determined by ^1H NMR and the enantioselectivity was determined by HPLC analysis with a Chiralpak OJ–H column. The product was in *R*-configuration. [d] The data in parentheses were obtained from reactions carried out at 0 °C.

although ligand $\mathbf{L_2}$ displayed somewhat better enantioselectivity at an S/C ratio of 100 (entry 13), both conversion and enantioselectivity dropped dramatically when the S/C ratio was increased from 500 to 5000 (entries 14–17). The effect of S/C ratio on catalysts with other bidentate phosphine ligands was also examined (Scheme 2). Considering the importance of solvent effect in this reaction, we employed the best solvent for each ligand employed: *i.e.* toluene for MeO-BIPHEP and BINAP, THF for P-Phos. With BINAP and MeO-BIPHEP, only 7 and 9% conversions at an S/C ratio of 2000 in 20 h were obtained, respectively, while with the P-Phos ligand, a complete conversion and 86% ee were observed under identical conditions. It was noted when the reaction time was reduced to 1 h, the (P-Phos)–Ir system provided the same enantioselectivity but substantially lower conversion (32%) compared to ligand $\mathbf{L_1}$ (entry 10). In a similar manner, ferrocenyloxazoline ligand by Zhou[5c] only led to 67% conversion and 82% enantioselectivity in 12 h when the S/C ratio was 2000.



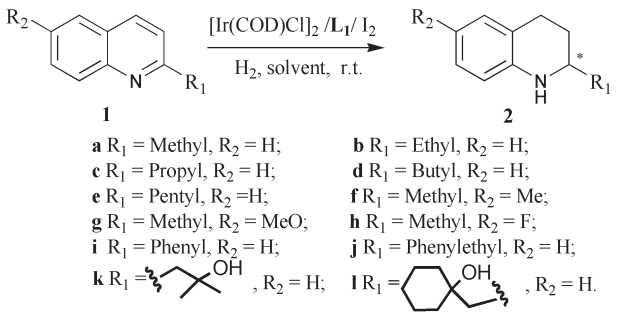
(*S*)-BINAP (*S*)-MeO-BIPHEP (*R*)-P-Phos

Scheme 2

The asymmetric hydrogenation reactions of other 2-substituted quinoline derivatives were also carried out under a high S/C ratio of 1000, and the results were summarized in Table 2. In general, all substituted quinolines studied were hydrogenated with complete conversions (except entry 7) and good enantioselectivities (except entry 9) regardless of the length of the alkyl chain (entries 1–5) of the 2-alkyl-substituted quinolines. The introduction of electron-donating and/or electron-withdrawing groups on the 6-position had no significant effect on the ee values (entries 6–8). When the alkyl group at the 2-position was replaced by a phenyl group or a phenylethyl group, lower enantioselectivities were observed (entries 9 and 10). The hydrogenation of quinolines with hydroxyl groups also proceeded smoothly, affording excellent results (entries 11 and 12).

In light of our recent finding that the less polar biphasic solvent system of poly(ethylene glycol) dimethyl ether (DMPEG, MW = 500)–hexane was a good replacement for THF in Ir-catalyzed asymmetric hydrogenation of quinolines when ligand $\mathbf{L_2}$ was employed,[6] we also examined the DMPEG–hexane biphasic system with $\mathbf{L_1}$ in this study. The solvent effect was not found to be as remarkable as observed in the reactions mediated by $\mathbf{L_2}$. For most of the substrates, a significant increase of enantioselectivity

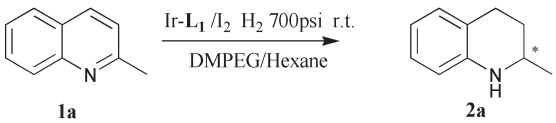
Table 2 Asymmetric hydrogenation of quinoline derivatives catalyzed by Ir–$\mathbf{L_1}$ complex at high substrate/catalyst ratio in THF or DMPEG–hexane solvent systems[a]



Entry	Sub.	Conv.[b] (%)	Ee[b] (%) in THF	Ee[b] (%) in DMPEG–hexane
1	**1a**	100 (100)[c]	92 (92)[c]	92
2	**1b**	100 (100)[c]	87 (88)[c]	87
3	**1c**	100 (100)[c]	90 (90)[c]	91
4	**1d**	100 (100)[c]	87 (90)[c]	87
5	**1e**	100	90	90
6	**1f**	100	92	92
7	**1g**	66 (100)[c]	92 (92)[c]	92[c]
8[b]	**1h**	100	87	89
9	**1i**	100	43	65
10	**1j**	100	83	83
11[b]	**1k**	100	91	91
12[b]	**1l**	100	92	92

[a] All reactions were carried out at room temperature with 0.15 mmol quinolines with an Ir complex generated *in situ* from $[Ir(COD)Cl]_2$ (0.05%) and ligand (0.1%), and I_2 (1%) under 700 psi H_2 for 20 h in 2 ml THF and/or MeO-PEG–hexane (1 : 1, v/v). [b] The conversions were determined by ^1H NMR and the enantioselectivities were determined by HPLC analysis with a Chiralpak OJ–H (**1a–1g**), OD–H (**1h** and **1k**), AS–H (**1i** and **1j**) and OJ (**1l**) columns. The absolute configurations were assigned by comparison of the HPLC retention time with the reported data (all products were in *R*-configuration except for entries 8, 11 and 12). [c] Data were obtained at a substrate/catalyst ratio of 100.

Table 3 Recycling of the Ir–$\mathbf{L_1}$ catalyst in the hydrogenation of quinaldine[a]



1a **2a**

Run	1	2	3	4	5
Conv.[b] (%)	>99	75	62	43	40
Ee[b] (%)	92	91	90	89	86

[a] The reaction was carried out at room temperature with 3 mmol quinaldine using Ir catalyst (0.1%) under 700 psi H_2 for 20 h in DMPEG–hexane (5 ml, 1 : 1, v/v). [b] The convention was determined by ^{1}H NMR and the ee value was determined by chiral OJ–H column.

was not observed in comparison with those obtained in THF solvent. The only exception was 2-phenylquinoline (**1i**) (Table 2, entry 9), which gave 65% ee in DMPEG–hexane in comparison to the lower ee of 43% in THF.

The immobilization of chiral homogeneous catalysts have attracted much attention recently since it affords an attractive approach for the separation of product from the catalytic system and the recycling of the catalyst.[11] Following our effort in this area,[11a,12] we have recently found that the asymmetric hydrogenation of quinolines could be carried out smoothly in a DMPEG–hexane biphasic system, resulting in efficient separation and recycling of the catalyst.[6a] The recyclability of the complex Ir–$\mathbf{L_1}$ in DMPEG–hexane was studied with the hydrogenation of **1a** as a model reaction. At the end of each experiment the product was separated *via* simple decantation of the upper hexane layer followed by three additional extractions with degassed hexane. The results were summarized in Table 3. The conversion and enantioselectivity were consistent with the results obtained in THF in the first run. Although the conversion dropped to 40% after four runs, the enantioselectivities remained high. The decrease of conversion might be due to the decomposition or a certain degree of leaching of the catalyst in the course of recycling.

In conclusion, we have developed a highly effective catalyst for the asymmetric hydrogenation of quinolines with high substrate/catalyst ratio (up to 5000) and high enantioselectivity (up to 94%). In view of the high activity of the catalyst and the ready accessibility of the ligand, the method described here provides a practical route to optically active tetrahydroquinoline derivatives.

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