

Asymmetric Hydrogenation of Quinolines Catalyzed by Iridium with Chiral Ferrocenyloxazoline Derived N,P Ligands

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Abstract: Chiral ferrocenyloxazoline derived N,P ligands are used in the iridium-catalyzed asymmetric hydrogenation of quinolines, and up to 92% ee was obtained. The role of the planar chirality is also studied.

Keywords: asymmetric hydrogenation; homogeneous catalysis; N,P ligands; planar chirality; quinolines

Asymmetric hydrogenation of aromatic and heteroaromatic compounds is a very useful reaction as it provides a convenient access to numerous saturated or partially saturated chiral cyclic compounds, whose synthesis by direct cyclization is often difficult.^[1] Recently, some progress has been made in this challenging field. Ito and co-workers reported a highly effective hydrogenation of *N*-Boc- or *N*-Ac-substituted indoles using the Rh/Trap/Cs₂CO₃ catalytic system, and up to 95% ees were obtained.^[2] Bianchini realized an asymmetric hydrogenation of 2-methylquinoxaline with ees up to 90% employing an orthometalated dihydride-iridium complex.^[3] Two other systems, i.e., [Ir(COD)/(*R,R*)-BDPBzP]OTf and [Rh(NBD)/(*R,R*)-BDPBzP]OTf, developed by the same group showed low enantioselectivities.^[4] Studer and co-workers' [Rh(NBD)(DIOP)]BF₄ catalyst gave only 24–27% ee in the hydrogenation of monosubstituted pyridines and furans.^[5] 2-Methylquinoxaline was hydrogenated with Rh(DIOP)H in 3% ee.^[6] In 2003, Henschke investigated the application of Noyori's RuCl₂(diphosphine)(diamine)/base catalyst system in the hydrogenation of 2-methylquinoxaline, up to 73% ee was obtained.^[7] Some heterogeneous chirally modified catalysts and chiral auxiliary-based methods were also developed for asymmetric hydrogenation of aromatic and heteroaromatic compounds.^[8] More recently, our group reported the first catalytic asymmetric hydrogenation of quinolines with high enantioselectivities using [Ir(COD)Cl]₂/MeO-Biphep/I₂ as the catalyst system.^[9] Among the above homogenous catalytic systems, bidentate biphosphines are the more effective and widely used ligands. As far as we know, no effective

N,P ligands, which can be easily synthesized from amino acids, have been successfully used in the hydrogenation of aromatic and heteroaromatic compounds with practical optical yields. Indeed, in a patent, N,P ligands have been claimed to be used, but no detailed information was given.^[10] Intrigued by the importance of chiral tetrahydroquinolines as useful synthetic intermediates^[11] and as structural subunits existing in alkaloids and other biologically active compounds,^[12] and the success in the hydrogenation of unfunctionalized olefins and imines with N,P ligand-iridium complexes,^[13] we decided to explore the application of ferrocene derived phosphino-oxazoline ligands in the hydrogenation of quinolines and to study the role of planar chirality in this reaction.

The chiral ligands (Figure 1) used in our study were conveniently prepared according to known methods starting from commercially available optically active amino acids.^[14]

To assess the effectiveness of ligands and the impact of other factors, we chose the hydrogenation of 2-methylquinoline as the model reaction. Chiral iridium complexes prepared *in situ* from [Ir(COD)Cl]₂ and chiral N,P ligands were employed as catalysts, and the reactions were carried out in toluene at room temperature under 600 psi of hydrogen with a substrate:[Ir]:ligand:I₂ ratio of 100:0.5:1.1:5. First, we investigated the effect of substituents in the oxazoline ring on the conversion and enantioselectivities. The results are summarized in Table 1. The chiral N,P ligands of ferrocenyloxazolines derived from different amino alcohols show varied effectiveness for the enantioselectivity. The results

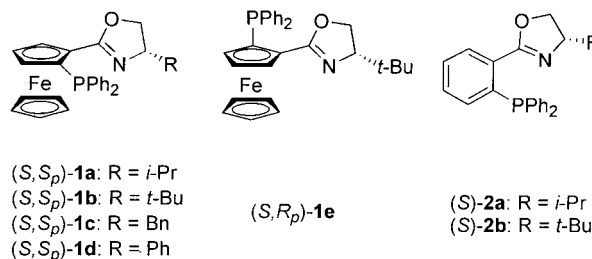


Figure 1. Chiral phosphino-oxazoline ligands derived from amino acids.

showed that the *t*-Bu-substituted ligand **1b** (entry 2) is superior to **1a** (R = *i*-Pr, entry 1), **1c** (R = Bn, entry 3) and **1d** (R = Ph, entry 4). For the corresponding non-planar chiral phenyloxazoline ligands, **2b** with *t*-Bu on the oxazoline ring also shows a higher enantioselectivity than **2a** with *i*-Pr (75% vs. 63%, entries 6 and 7). Ligands without the planar chirality (**2a** and **2b**) showed lower enantioselectivities than the corresponding (oxazolonyl-ferrocenyl)phosphine ligands (**1a** and **1b**) (63% in entry 6 vs. 77% in entry 1 and 75% in entry 7 vs. 90% in entry 2). To investigate the effect of planar chirality on the enantioselectivity and absolute configuration of the products,^[15] **1e** with the same central chirality and opposite planar chirality to **1b** was synthesized and used in the hydrogenation of 2-methylquinoline. Under the same conditions, lower enantioselectivity and the same absolute configuration were observed with (*S,R_p*) ligand **1e** (77% in entry 5 vs. 90% in entry 2). It seems that the absolute configuration of the product is mainly controlled by the central chirality of the oxazoline ring. The lower ee with **1e** suggests the mismatched nature of the (*R*) planar chirality with the (*S*) central chirality on the oxazolonyl ring. Compound (*S,S_p*)-**1b** is the matched case in terms of planar and central chiralities. The ligand (*S,S_p*)-**1b** was therefore used throughout the rest of the studies.

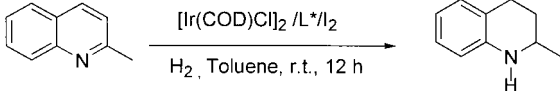
The effects of the solvents, hydrogen pressure, and temperature on the reaction conversion and enantioselectivity were also investigated using Iridium complexes of **1b** as the catalyst. The results are summarized in Table 2. Greater than 95% conversions were achieved in all solvents examined, either protic or aprotic, in 12 h. But the ees of the product are highly solvent-dependent. Non-polar solvents (entries 1, 6, 7) tend to give higher enantioselectivities than polar solvents (entries 2–5). Change in hydrogen pressure and reaction temperature

have no clear effect on the conversion and the enantioselectivities (entries 7–10). Therefore, the optimized conditions for asymmetric hydrogenation of quinolines with Ir complexes of chiral N,P ligands in the presence of I₂ are [Ir(COD)Cl]₂/(*S,S_p*)-**1b**/I₂/toluene/H₂ 600 psi/25 °C.

Under the optimized conditions, a variety of substituted quinoline derivatives were hydrogenated using the [Ir(COD)Cl]₂/(*S,S_p*)-**1b**/toluene/I₂ catalyst system. The results are shown in Table 3. Several 2-alkyl-substituted quinolines were hydrogenated with high enantioselectivities (≥90% ee) regardless of the length of the chain (entries 1–4). 2-Arenethyl-substituted quinolines also gave good asymmetric induction (entries 6 and 8). For 2-aryl-substituted quinolines (entry 7), however only 3% enantioselectivity was obtained and the reason is not clear. It is noted that a hydroxy group can be tolerated in this catalytic system. For example, both high yields and ees were achieved for substrates **3i** and **3j** with hydroxy groups (entries 9 and 10).

To evaluate further the catalytic efficiency of the [Ir(COD)Cl]₂/(*S,S_p*)-**1b**/I₂ system in asymmetric hydrogenation, we investigated the effect of the substrate-to-catalyst (S/C) molar ratio on the conversion and enantioselectivity of this reaction. 2-Methylquinoline was selected as substrate, the results (Figure 2) show that the reaction can proceed smoothly at an S/C of 500/1 or 1000/1 with complete conversion, the ee de-

Table 1. Asymmetric hydrogenation of 2-methylquinoline.^[a]



| Entry | Ligand | Conversion ^[b] [%] | ee ^[c] [%] | Configuration ^[d] |
|-------|-----------|-------------------------------|-----------------------|------------------------------|
| 1 | 1a | > 95 | 77 | (<i>R</i>) |
| 2 | 1b | > 95 | 90 | (<i>R</i>) |
| 3 | 1c | > 95 | 73 | (<i>R</i>) |
| 4 | 1d | > 95 | 73 | (<i>R</i>) |
| 5 | 1e | 85 | 77 | (<i>R</i>) |
| 7 | 2b | > 95 | 75 | (<i>R</i>) |

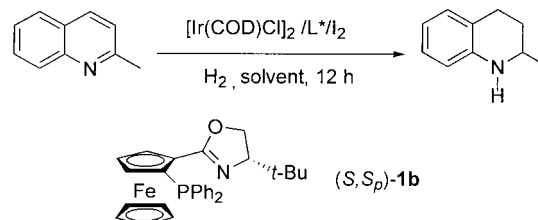
^[a] Reaction conditions: 1 mmol scale, quinoline/[Ir(COD)Cl]₂/chiral ligand/I₂ = 100/0.5/1.1/5, 5 mL toluene, 600 psi H₂

^[b] Determined by ¹H NMR analysis of the crude products.

^[c] Determined by HPLC analysis with a Chiralpak OJ-H column.

^[d] The absolute configuration of product is assigned by comparison of rotation sign with literature data.

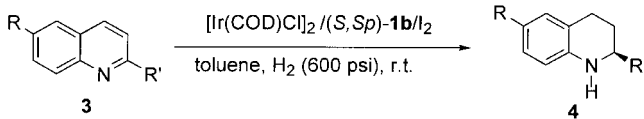
Table 2. Asymmetric hydrogenation of 2-methylquinoline.^[a]

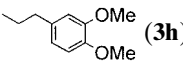
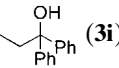
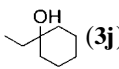


| Entry | H ₂ [psi]; T [°C] | Solvent | ee ^[b] [%] |
|-------|------------------------------|---------------------------------|-----------------------|
| 1 | 600; 25 | CH ₂ Cl ₂ | 87 |
| 2 | 600; 25 | THF | 14 |
| 3 | 600; 25 | EtOAc | 44 |
| 4 | 600; 25 | MeOH | 18 |
| 5 | 600; 25 | <i>i</i> -PrOH | 51 |
| 6 | 600; 25 | benzene | 88 |
| 7 | 600; 25 | toluene | 90 |
| 8 | 600; 0 | toluene | 90 |
| 9 | 300; 25 | toluene | 89 |
| 10 | 100; 25 | toluene | 90 |

^[a] Reaction conditions: 1 mmol scale, quinoline/[Ir(COD)Cl]₂/chiral ligand/I₂ = 100/0.5/1.1/5, 5 mL solvent, H₂, the absolute configuration of product is *R*; conversion is determined by ¹H NMR analysis of the crude products and is > 95% in all cases.

^[b] Determined by HPLC analysis with a Chiralpak OJ-H column.

Table 3. Iridium-catalyzed asymmetric hydrogenation of quinolines **3**.^[a]


| Entry | R/R' of 3 | Yield [%] ^[b] | ee [%] ^[c] | Configuration ^[d] |
|-------|---|--------------------------|-----------------------|------------------------------|
| 1 | H/Me (3a) | 95 (4a) | 90 | <i>R</i> |
| 2 | H/Et (3b) | 95 (4b) | 91 | <i>R</i> |
| 3 | H/ <i>n</i> -Pentyl (3c) | 94 (4c) | 92 | <i>R</i> |
| 4 | Me/Me (3d) | 93 (4d) | 92 | <i>R</i> |
| 5 | F/Me (3e) | 86 (4e) | 89 | <i>R</i> |
| 6 | H/Phenethyl (3f) | 92 (4f) | 72 | <i>R</i> |
| 7 | H/Ph (3g) ^[e] | 45 (4g) | 3 | <i>S</i> |
| 8 | H /  (3h) | 82 (4h) | 87 | <i>R</i> |
| 9 | H /  (3i) | 89 (4i) | 80 | <i>S</i> |
| 10 | H /  (3j) | 82 (4j) | 79 | <i>S</i> |

^[a] Reaction conditions: 1 mmol scale, quinoline/[Ir(COD)Cl]₂/chiral ligand/I₂ = 100/0.5/1.1/5, 5 mL toluene, 600 psi H₂

^[b] Yield of isolated product based on the quinolines by column chromatography

^[c] Determined by HPLC analysis with Chiral column (see experimental section).

^[d] Determined by comparison of rotation sign with literature data or by analogue.

^[e] The conversion is 50%.

creased slightly (90% ee vs. 88% ee, 86% ee). But when the S/C is 2000/1, the conversion is only 67%, although the ee is 82%.

In conclusion, Ir complexes with chiral N,P ligands are effective catalysts for the asymmetric hydrogenation of heteroaromatic compounds such as quinolines, and up to 92% ees were obtained. Central chirality dominates the absolute configuration of the products in iridium-ferrocenyloxazoline catalytic systems with planar chirality. The method described provides an effective, mild and convenient route to synthesize chiral tetrahydroquinoline derivatives.

Experimental Section

General Experimental Procedure for Hydrogenation

A mixture of [Ir(COD)Cl]₂ (3.4 mg, 0.005 mmol) and (*S,S,P*)-**1b** (5.5 mg, 0.011 mmol) in toluene (5 mL) was stirred at room temperature for 30 min in a glove-box. The mixture was transferred by a syringe to a stainless steel autoclave in which I₂ (12.7 mg, 0.05 mmol) and substrate (1.0 mmol) were placed beforehand. The hydrogenation was performed at room temperature under H₂ (600 psi) for 12–16 h. After carefully releasing the hydrogen, the reaction mixture was diluted with dichloromethane (20 mL). Saturated sodium carbonate solution (5 mL) was added and the mixture was stirred for 15 min. Layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers

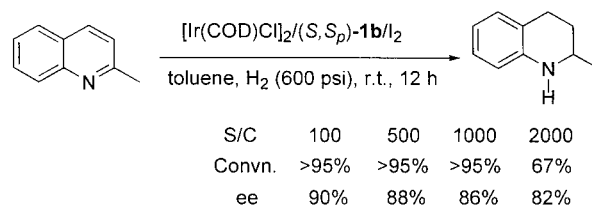


Figure 2. Effect of the S/C on the conversion and enantioselectivity.

were dried over sodium sulfate and concentrated to afford the crude product. Purification was performed on a silica gel column eluted with hexane/EtOAc to give pure product. The enantiomeric excesses were determined by HPLC with chiral columns (OJ-H, OD-H, or AS-H). **4a**: HPLC OJ-H, elute: hexane/*i*-PrOH = 95/5, flow rate: 1.0 mL/min, (*S*) t₁ = 12.1 min, (*R*) t₂ = 13.5 min; **4b**: HPLC OJ-H, elute: hexane/*i*-PrOH = 95/5, flow rate: 1.0 mL/min, (*S*) t₁ = 10.2 min, (*R*) t₂ = 11.4 min; **4c**: HPLC OJ-H, elute: hexane/*i*-PrOH = 95/5, flow rate 0.5 mL/min, (*S*) t₁ = 14.7 min, (*R*) t₂ = 16.2 min; **4d**: HPLC OJ-H, elute: hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, (*S*) t₁ = 15.1 min, (*R*) t₂ = 19.2 min; **4e**: HPLC OD-H, elute: hexane/*i*-PrOH = 94/6, flow rate: 1.0 mL/min, (*S*) t₁ = 5.3 min, (*R*) t₂ = 6.6 min; **4f**: HPLC AS-H, elute: hexane/*i*-PrOH = 94/6, flow rate 1.0 mL/min, (*S*) t₁ = 5.2 min, (*R*) t₂ = 5.6 min; **4g**: HPLC AS-H, elute: hexane/*i*-PrOH = 94/6, flow rate 1.0 mL/min, (*S*) t₁ = 5.5 min, (*R*) t₂ = 14.7 min; **4h**: HPLC AS-H, elute: hexane/*i*-PrOH = 94/6, flow rate: 1.0 mL/min, (*S*) t₁ = 11.3 min, (*R*) t₂ = 12.4 min; **4i**: HPLC OD-H, elute: hexanes/*i*-PrOH = 94/6, flow rate: 1.0 mL/min, (*S*) t₁ = 1.8 min, (*R*) t₂ =

14.1 min; **4j**: HPLC OD-H, elute: hexane/*i*-PrOH = 97/3, flow rate: 0.5 mL/min, (S) *t*₁ = 25.5 min, (R) *t*₂ = 26.9 min.

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