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Ir-catalyzed asymmetric hydrogenation of β-keto esters with chiral ferrocenyl P,N,N-ligands†

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The Ir-catalyzed asymmetric hydrogenation of β-keto esters with chiral ferrocenyl P,N,N-ligands has been developed. Under the optimized conditions, a wide range of β-keto esters were hydrogenated to afford the corresponding β-hydroxy esters in good to excellent enantioselectivities (up to 95% ee).

Introduction

Transition-metal catalyzed asymmetric synthesis represents one of the most important developments in modern chemistry over the past several decades. Among the numerous catalytic methods, asymmetric hydrogenation of unsaturated olefins, ketones and imines is one of the most direct and convenient methods for the synthesis of enantiomerically pure compounds.[1] In this regard, the hydrogenation of β-keto esters yield chiral β-hydroxy esters, which are important building blocks for the synthesis of chiral drugs and nature products.[2] In 1987, Noyori[3] reported the first ruthenium catalyzed enantioselective hydrogenation of β-keto esters using BINAP[4] as a chiral ligand. Since this pioneering work, a large number of chiral ligands such as Synphos,[5] difluorphos,[6] Tunephos,[7] Segphos,[8] Solphos,[9] P-Phos,[10] PQ-Phos,[11] MeO-Naphephos,[12] Taniaphos,[13] ClickFerrophos[14] and *t*-Bu-QuinoxP*[15] have been developed and successfully applied to the ruthenium catalyzed enantioselective hydrogenation of β-keto esters. Despite these developments, most of the chiral ligands are used in combination with ruthenium as the transition metal. In contrast to chiral ruthenium catalyst, iridium catalyzed asymmetric hydrogenation of β-keto esters remains less explored, although chiral iridium complexes are among the most commonly used catalysts in asymmetric hydrogenation of olefins, ketones and imines.[16]

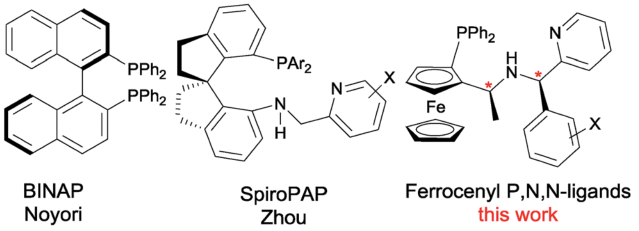
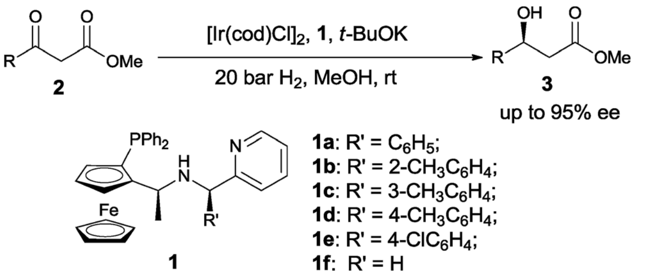


Fig. 1 Examples of efficient chiral ligands in asymmetric hydrogenation of β-keto esters.

Recently, Zhou[17] reported an iridium catalyzed enantioselective hydrogenation of β-keto esters using chiral spiro P,N,N-ligands, SpiroPAP (Fig. 1). Inspired by SpiroPAP and our recent success in the development of chiral P,N,N-ligands for asymmetric catalysis,[18] we have developed a new class of ferrocenyl P,N,N-ligands with two carbon chiral centers for iridium catalyzed asymmetric hydrogenation of α-alkyl-β-keto esters.[19] The success of this work is due to the stereo control of dynamic kinetic resolution (DKR). Considering the structural similarity, we believe that this newly developed P,N,N-ligands should be also applicable to the iridium catalyzed enantioselective hydrogenation of simple β-keto esters without DKR, as the resulting chiral β-hydroxy esters are important organic intermediates. As a result, herein, we report our studies in detail on the iridium catalyzed asymmetric hydrogenation of β-keto esters with chiral P,N,N-ligands, which provides the chiral β-hydroxy esters with good to excellent enantioselectivity (up to 95% ee) under mild conditions (Scheme 1).



Scheme 1 Ir-catalyzed asymmetric hydrogenation of β-keto esters **2** with chiral ferrocenyl P,N,N-ligands **1**.

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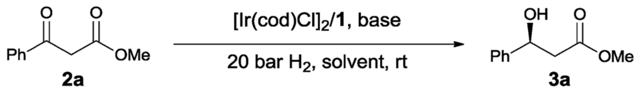
Results and discussion

As we have reported, the chiral ferrocenyl P,N,N-ligands **1** can be easily prepared from (S_c,R_p)-PPFNH$_2$ through a modular procedure.[19] With these ligands in hand, we then examined their efficiency in the iridium catalyzed asymmetric hydrogenation of β-keto esters. Methyl 3-oxo-3-phenylpropanoate (**2a**) was selected as standard substrate and the hydrogenation was carried in MeOH under 20 bar H$_2$ in the presence of 0.1 mol% catalyst prepared *in situ* from [Ir(cod)Cl]$_2$ and **1**. As we can see from Table 1, the iridium complex of ferrocenyl P,N,N-ligands displayed good performance, affording (*S*)-methyl 3-hydroxy-3-phenylpropanoate (**3a**) in full conversion and with excellent enantioselectivities (92–94% ee) (entries 1–5). Ligand (S_c,R_p,R_c)-**1c** bearing 3-methyl phenyl group at the pyridinylmethyl position gave the best enantioselectivity of 94% ee (entry 3). In sharp contrast, ligand (S_c,R_p)-**1f** with only one chiral carbon center gave disappointing enantioselectivity (entry 6), similar as the result observed in the Ir-catalyzed asymmetric hydrogenation of simple ketones.[20] Further optimization of the reaction conditions by screening different bases didn't improve the hydrogenation outcome. All of the bases tested such as *t*-BuOK, *t*-BuONa, KOH, NaOH and K$_2$CO$_3$ showed similar results (entries 6–10). The solvent effect was next investigated and an obvious solvent dependence was observed. The alcohol solvent was proved to be suitable solvent and MeOH was the best choice, while other solvents such as CH$_2$Cl$_2$ and toluene showed very low enantioselectivities (entries 11–14). When the catalyst loading was lowered to 0.02 mol% (S/C = 5000, S/C means substrate/catalyst) and 0.01 mol% (S/C = 10 000), the hydrogenation product **3a** was still obtained in full conversion and with 89% and 85% ee, respectively (entries 15–16).

Under the optimal reaction conditions, the scope of β-keto esters for this hydrogenation was investigated, and the results are shown in Table 2. The results disclosed that a wide range of β-aryl-β-keto esters **2** can be hydrogenated smoothly and afford the corresponding chiral β-hydroxy esters **3** in high yields and good to excellent enantioselectivities (85–95% ee) (entries 1–11). Although the results are not super than the best ruthenium catalysts reported, it represents a new catalyst system.[3–15] It is noteworthy that the steric and electronic effects of the group on the phenyl ring had important influence on the enantioselectivities.[17a,21] The substrate **2b** with an *ortho*-Cl in the phenyl ring tended to be hydrogenated with higher enantioselectivity than those with a *meta*- (**2c**) or *para*-Cl (**2d**) group (entries 2–4). It appeared that the electronic properties of the group at para position of the phenyl ring had some effect on the enantioselectivities, and the substrates with an electron-withdrawing group gave lower enantioselectivities than those with an electron-donating group (entries 4–8). Meanwhile, 2-naphthyl substituted substrate **2i** worked well for this reaction and gave the hydrogenation product **3i** in 92% yield and with 90% ee (entry 9). Furthermore, heteroaromatic β-keto esters **2j** and **2k** were also suitable substrates, providing the hydrogenation products **3j** and **3k** in 90% and 91% ee, respectively (entries 10 and 11). However, this catalyst system was less efficient for the

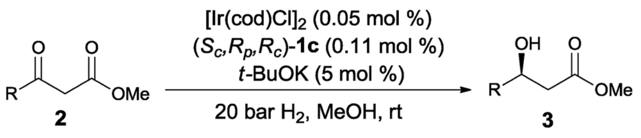
Table 1 Asymmetric hydrogenation of methyl 3-oxo-3-phenylpropanoate (**2a**): optimizing reaction conditions[a]



Entry	Ligand	Base	Solvent	Conv.[b] (%)	ee[c] (%)
1	(S_c,R_p,R_c)-**1a**	*t*-BuOK	MeOH	100	92
2	(S_c,R_p,R_c)-**1b**	*t*-BuOK	MeOH	100	93
3	(S_c,R_p,R_c)-**1c**	*t*-BuOK	MeOH	100	94
4	(S_c,R_p,R_c)-**1d**	*t*-BuOK	MeOH	100	93
5	(S_c,R_p,R_c)-**1e**	*t*-BuOK	MeOH	100	91
6	(S_c,R_p)-**1f**	*t*-BuOK	MeOH	76	3
7	(S_c,R_p,R_c)-**1c**	*t*-BuONa	MeOH	100	93
8	(S_c,R_p,R_c)-**1c**	KOH	MeOH	100	93
9	(S_c,R_p,R_c)-**1c**	NaOH	MeOH	100	94
10	(S_c,R_p,R_c)-**1c**	K$_2$CO$_3$	MeOH	100	93
11[d]	(S_c,R_p,R_c)-**1c**	*t*-BuOK	EtOH	100	93
12[e]	(S_c,R_p,R_c)-**1c**	*t*-BuOK	i-PrOH	100	85
13	(S_c,R_p,R_c)-**1c**	*t*-BuOK	Toluene	100	32
14	(S_c,R_p,R_c)-**1c**	*t*-BuOK	CH$_2$Cl$_2$	100	35
15[f]	(S_c,R_p,R_c)-**1c**	*t*-BuOK	MeOH	100	89
16[g]	(S_c,R_p,R_c)-**1c**	*t*-BuOK	MeOH	100	85

[a] Hydrogenation was carried out with 0.05 mol% of [Ir(cod)Cl]$_2$, 0.11 mol% of chiral P,N,N-ligands and 5 mol% of bases under 20 bar of H$_2$ at room temperature for 12 h, unless otherwise stated. [b] Conversions were determined by ^{1}H NMR analysis of the crude products. [c] Enantiomeric excesses were determined by HPLC using a chiral stationary phase. [d] The corresponding ethyl ester was obtained. [e] The corresponding isopropyl ester was obtained. [f] S/C = 5000. [g] S/C = 10 000.

Table 2 Asymmetric hydrogenation of β-keto esters **2** with Ir/(S_c,R_p,R_c)-**1c**[a]



Entry	Substrate	R	Yield[b] (%)	ee[c] (%)
1	**2a**	C$_6$H$_5$	96	94
2	**2b**	2-ClC$_6$H$_4$	95	95
3	**2c**	3-ClC$_6$H$_4$	95	88
4	**2d**	4-ClC$_6$H$_4$	94	87
5	**2e**	4-BrC$_6$H$_4$	96	85
6	**2f**	4-FC$_6$H$_4$	93	91
7	**2g**	4-MeC$_6$H$_4$	95	93
8	**2h**	4-MeOC$_6$H$_4$	95	93
9	**2i**	2-Naphthyl	92	90
10	**2j**	2-Furyl	93	90
11	**2k**	2-Thienyl	93	91
12	**2l**	i-Pr	90	64
13	**2m**	Me	90	8

[a] Hydrogenation was carried out with 0.05 mol% of [Ir(cod)Cl]$_2$, 0.11 mol% of (S_c,R_p,R_c)-**1c** and 5 mol% of *t*-BuOK under 20 bar of H$_2$ at room temperature for 12 h. [b] Isolated yields. [c] Enantiomeric excesses were determined by HPLC using a chiral stationary phase.

hydrogenation of β-alkyl-β-keto esters such as β-isopropyl-β-keto esters **2l** and β-methyl-β-keto esters **2m** (entries 12–13).

Conclusion

In conclusion, we have developed a highly efficient iridium catalyzed asymmetric hydrogenation of β-keto esters with chiral ferrocenyl P,N,N-ligands. The results suggest that a wide range of β-keto esters can be hydrogenated with good to excellent enantioselectivities under the optimized conditions. The reaction provides a readily accessible method for the synthesis of β-hydroxy esters in excellent enantioselectivities. Further application of these ferrocenyl P,N,N-ligands in asymmetric hydrogenation is still in progress.

Experimental section

General method

All reactions were carried out under N_2 atmosphere. Hydrogenation reaction was carried out in glove-box by use of a stainless steel autoclave. Solvents were purified by standard procedure. Commercial reagents were used without further purification. ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer. Chemical shifts are expressed in δ value (ppm) using tetramethylsilane (TMS) as an internal standard. HPLC analysis was performed on an Agilent 1100 series instrument with a chiralpak AS-H, chiralcel OD-H, chiralcel AD-H or chiralcel OJ-H column. Optical rotations were recorded on a JASCO P-1020 polarimeter. The absolute configurations of the products were determined by comparing optical rotation with the reported data.

General procedure for asymmetric hydrogenation of β-keto esters

In a nitrogen-filled glovebox, a stainless steel autoclave was charged with $[Ir(COD)Cl]_2$ (0.34 mg, 0.005 mmol) and (S_c,R_p,R_c)-**L1c** (0.66 mg, 0.011 mmol) in 1.0 mL of dry MeOH. After stirring for 1 h at room temperature, a solution of the substrates **2** (1.0 mmol) and *t*-BuOK (5.6 mg, 0.05 mmol) in 2.0 mL of MeOH was added to the reaction mixture, and then the hydrogenation was performed at room temperature under an H_2 pressure of 20 bar for 12 h. The solvent was then evaporated and the residue was purified by flash column chromatography to give the corresponding hydrogenation product which was analyzed by chiral HPLC to determine the enantiomeric excesses.

(*S*)-Methyl 3-hydroxy-3-phenylpropanoate 3a.[22,23] Colorless oil was obtained in 96% yield. 94% ee was determined by chiral HPLC (chiralcel OD-H, *n*-hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, 210 nm, 40 °C): t_R (S) = 11.5 min, t_R (R) = 16.8 min. $[\alpha]_D^{28} = -45.5$ (c 1.01, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44–7.27 (m, 5H), 5.14 (dd, J = 8.8, 4.0 Hz, 1H), 3.72 (s, 3H), 2.97–2.67 (m, 3H).

(*S*)-Methyl 3-(2-chlorophenyl)-3-hydroxypropanoate 3b.[4b] Colorless oil was obtained in 95% yield. 95% ee was determined by chiral HPLC (chiralcel OJ-H, *n*-hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, 210 nm, 40 °C): t_R (R) = 9.4 min, t_R (S) = 10.7 min. $[\alpha]_D^{28} = -79.6$ (c 1.03, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63 (d, J = 7.6 Hz, 1H), 7.38–7.28 (m, 2H), 7.27–7.20 (m, 1H), 5.50 (d, J = 9.6 Hz, 1H), 3.75 (s, 3H), 2.92–2.83 (m, 1H), 2.65–2.55 (m, 1H).

(*S*)-Methyl 3-(3-chlorophenyl)-3-hydroxypropanoate 3c.[22] Colorless oil was obtained in 95% yield. 88% ee was determined by chiral HPLC (chiralcel AD-H, *n*-hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, 210 nm, 40 °C): t_R (R) = 9.8 min, t_R (S) = 10.8 min. $[\alpha]_D^{28} = -38.4$ (c 1.05, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43–7.37 (m, 1H), 7.29–7.23 (m, 3H), 5.11 (dd, J = 7.0, 5.8 Hz, 1H), 3.73 (s, 3H), 2.75–2.69 (m, 2H).

(*S*)-Methyl 3-(4-chlorophenyl)-3-hydroxypropanoate 3d.[22,23] Colorless oil was obtained in 94% yield. 87% ee was determined by chiral HPLC (chiralpak AS-H, *n*-hexane/i-PrOH = 95/5, 0.8 mL min^{-1}, 210 nm, 40 °C): t_R (R) = 18.4 min, t_R (S) = 20.2 min. $[\alpha]_D^{28} = -37.6$ (c 1.02, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35–7.28 (m, 4H), 5.11 (dd, J = 8.1, 4.7 Hz, 1H), 3.73 (s, 3H), 2.75–2.67 (m, 2H).

(*S*)-Methyl 3-(4-bromophenyl)-3-hydroxypropanoate 3e.[22,23] Colorless oil was obtained in 96% yield. 85% ee was determined by chiral HPLC (chiralpak AS-H, *n*-hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, 210 nm, 40 °C): t_R (R) = 12.1 min, t_R (S) = 13.0 min. $[\alpha]_D^{28} = -31.7$ (c 1.08, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 5.09 (dd, J = 7.9, 4.8 Hz, 1H), 3.72 (s, 3H), 2.78–2.63 (m, 2H).

(*S*)-Methyl 3-(4-fluorophenyl)-3-hydroxypropanoate 3f.[22] Colorless oil was obtained in 93% yield. 91% ee was determined by chiral HPLC (chiralpak AS-H, *n*-hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, 210 nm, 40 °C): t_R (R) = 11.6 min, t_R (S) = 12.7 min. $[\alpha]_D^{28} = -42.6$ (c 1.03, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40–7.30 (m, 2H), 7.10–6.98 (m, 2H), 5.12 (dd, J = 8.7, 4.1 Hz, 1H), 3.73 (s, 3H), 2.80–2.66 (m, 2H).

(*S*)-Methyl 3-hydroxy-3-(p-tolyl)propanoate 3g.[21a] Colorless oil was obtained in 95% yield. 93% ee was determined after conversion into the corresponding benzoate by chiral HPLC (chiralcel OD-H, *n*-hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, 210 nm, 40 °C): t_R (R) = 9.0 min, t_R (S) = 9.8 min. $[\alpha]_D^{28} = -44.7$ (c 1.04, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30–7.23 (m, 2H), 7.16 (d, J = 7.9 Hz, 2H), 5.09 (dd, J = 9.2, 3.8 Hz, 1H), 3.70 (s, 3H), 2.87–2.62 (m, 2H), 2.40 (br, 1H), 2.34 (s, 3H).

(*S*)-Methyl 3-(4-methoxyphenyl)-3-hydroxypropanoate 3h.[22] Colorless oil was obtained in 95% yield. 93% ee was by chiral HPLC (chiralcel AD-H, *n*-hexane/i-PrOH = 95/5, 0.8 mL min^{-1}, 210 nm, 40 °C): t_R (R) = 27.0 min, t_R (S) = 28.5 min. $[\alpha]_D^{28} = -38.5$ (c 1.00, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 5.09 (dd, J = 9.2, 3.6 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.10 (br, 1H), 2.84–2.64 (m, 2H).

(*S*)-Methyl 3-hydroxy-3-(naphthalen-2-yl)propanoate 3i.[21a] Colorless oil was obtained in 92% yield. 90% ee was by chiral HPLC (chiralpak AS-H, *n*-hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, 210 nm, 40 °C): t_R (R) = 13.3 min, t_R (S) = 14.6 min. $[\alpha]_D^{28} = -38.6$ (c 1.05, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.88–7.77 (m, 4H), 7.54–7.42 (m, 3H), 5.30 (dd, J = 8.6, 4.1 Hz, 1H), 3.72 (s, 3H), 3.05 (br, 1H), 2.90–2.75 (m, 2H).

(*S*)-Methyl 3-(furan-2-yl)-3-hydroxypropanoate 3j.[23] Colorless oil was obtained in 93% yield. 90% ee was by chiral HPLC (chiralcel OD-H, *n*-hexane/i-PrOH = 50/50, 0.8 mL min^{-1}, 210 nm, 40 °C): t_R $(S) = 5.4$ min, t_R $(R) = 8.0$ min. $[\alpha]_D^{28} = -23.4$ (*c* 1.01, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28–7.23 (m, 1H), 7.02–6.94 (m, 2H), 5.38 (dd, $J = 8.0$, 4.6 Hz, 1H), 3.74 (s, 3H), 2.92–2.83 (m, 2H).

(*S*)-Methyl 3-hydroxy-3-(thiophen-2-yl)propanoate 3k.[23] Colorless oil was obtained in 93% yield. 91% ee was by chiral HPLC (chiralcel OD-H, *n*-hexane/i-PrOH = 50/50, 0.8 mL min^{-1}, 210 nm, 40 °C): t_R $(S) = 5.4$ min, t_R $(R) = 8.0$ min. $[\alpha]_D^{28} = -24.9$ (*c* 1.05, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.29–7.25 (m, 1H), 7.04–6.93 (m, 2H), 5.38 (dd, $J = 8.0$, 4.6 Hz, 1H), 3.74 (s, 3H), 2.93–2.83 (m, 2H).

(*S*)-Methyl 3-hydroxy-4-methylpentanoate 3l.[24] Colorless oil was obtained in 90% yield. 64% ee was determined after conversion into the corresponding benzoate by chiral HPLC (chiralcel AD-H, *n*-hexane/i-PrOH = 95/5, 0.8 mL min^{-1}, 210 nm, 40 °C): t_R $(R) = 7.8$ min, t_R $(S) = 9.0$ min. $[\alpha]_D^{28} = -22.0$ (*c* 1.18, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.82–3.75 (m, 1H), 3.72 (s, 3H), 2.69–2.37 (m, 3H), 1.78–1.65 (m, 1H), 0.94 (dd, $J =$ 11.2, 6.8 Hz, 6H).

(*S*)-Methyl 3-hydroxybutanoate 3m.[7a] Colorless oil was obtained in 90% yield. 8% ee was determined after conversion into the corresponding benzoate by chiral HPLC (chiralcel AD-H, *n*-hexane/i-PrOH = 95/5, 0.8 mL min^{-1}, 210 nm, 40 °C): t_R $(S) = 8.1$ min, t_R $(R) = 8.8$ min. $[\alpha]_D^{18} = +14.9$ (*c* 1.05, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.28–4.14 (m, 1H), 3.72 (s, 3H), 2.87 (br, 1H), 2.53–2.38 (m, 2H), 1.24 (d, $J = 6.3$ Hz, 3H).

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