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Asymmetric hydrogenation of aromatic ketones using an iridium(I) catalyst containing ferrocene-based P–N–N tridentate ligands

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ABSTRACT

Six ferrocene-based P–N–N tridentate ligands have been synthesized and applied in the Ir-catalyzed asymmetric hydrogenation of aromatic ketones. A wide range of ketones are hydrogenated enantioselectively to afford the corresponding optically active alcohols in the enantioselectivities of up to 86.6% ee. The substituent groups on the *P*-phenyl and pyridine rings play an important role with regard to the enantioselectivity.

1. Introduction

The development of new asymmetric catalytic systems is still a major challenge because of its importance in synthetic organic chemistry and manufacturing fine chemicals.[1] The reduction of ketones using molecular hydrogen is a very important process in organic synthesis due to its low cost and complete atom efficiency.[2] The catalytic asymmetric hydrogenation of simple ketones provides the most efficient process for the production of optically active secondary alcohols, which in turn, are some of the most valuable intermediates for the manufacturing of pharmaceuticals and advanced materials. For the asymmetric hydrogenation of simple aromatic ketones, the use of [(diphosphine)$RuCl_2$(diamine)] type catalytic systems (Fig. 1) pioneered by Noyori et al. is one of the most powerful and reliable procedures.[3] The general definitive feature of this catalyst is that ruthenium is coordinated with a chiral diphosphine and a chiral diamine, forming a well defined chiral *trans*-octahedral complex. The high degree of enantioselectivity was considered to be the result of a synergistic effect of the chiral diphosphine and the diamine ligands.[4] Since Noyori's original publications, there has been much interest in [(diphosphine)-$RuCl_2$(diamine)] systems, with several structurally related catalysts also showing similar excellent selectivities and reactivities for the reduction of acetophenone derivatives. Much effort has been dedicated to developing efficient phosphine ligands such as chiral phosphines, chirally flexible phosphines, and even achiral bulky monophosphine ligands. However, most phosphines have been used in conjunction with chiral DPEN and DAIPEN to mimic the Noyori catalyst.[5,6]

Recently, Zhou et al. developed chiral iridium catalysts containing a chiral SpiroPAP ligand, and these catalysts showed excellent enantioselectivities (up to 99.9% ee) and an extremely high TON (as high as 4,550,000) for the hydrogenation of simple ketones.[7] These Ir-SpiroPAP catalysts (Fig. 1) are likely to have a 'metal-ligand bifunctional catalysis' mechanism, similar to the [(diphosphine)$RuCl_2$(diamine)] catalysts.[8]

We have reported on several ferrocene-based aminophosphine ligands **1** (Fig. 2) and their application in the Ru(II)-catalyzed asymmetric hydrogenation of ketones.[9] Continuing our interest in ferrocene-based chiral ligands and their application in asymmetric catalysis[10] as well as being inspired by Zhou's results in the Ir-SpiroPAP catalyzed asymmetric hydrogenation of ketones, we herein report preliminary results regarding new ferrocene-based P–N–N ligands **2** (Fig. 2) and their Ir-complexes-catalyzed asymmetric hydrogenation of ketones.

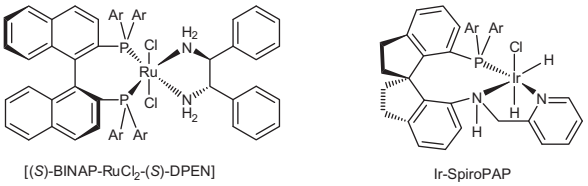

Figure 1. [(*S*)-BINAP-$RuCl_2$-(*S*)-DPEN] and Ir-SpiroPAP.

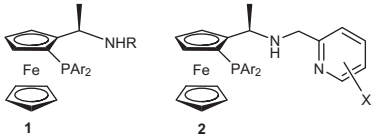

Figure 2. Ferrocene-based ligands **1** and **2**.

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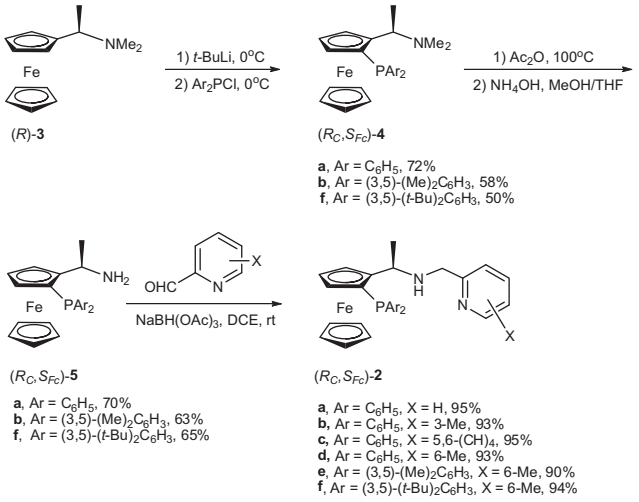
2. Results and discussion

New ferrocene-based P–N–N ligands **2** were very easily accessible from the readily available (*R*)-Ugi's amine **3** (Scheme 1). Thus, highly diastereoselective *ortho*-lithiation of amine (*R*)-**3** followed by treatment with $ClPAr_2$ gave PPFA derivatives **4**, which have an (R_C,S_{Fc})-configuration. After the reaction of **4** with Ac_2O at 100 °C, followed by treatment with a large excess of ammonia in a mixture of water, methanol, and THF at 60 °C, the dimethylamino group of **4** was substituted by an amino group to form compounds **5**. Finally, reductive amination of **5** with picolinaldehydes resulted in the formation of ligands **2a**–**f** in high isolated yields.



Scheme 1. Synthesis of P–N–N ligands **2a**–**f**.

We envisioned that the reaction of ligands **2** with [{Ir(cod)Cl}$_2$] under hydrogen would form complexes **6** (Fig. 3), which might be similar to Zhou's Ir-SpiroPAP catalysts, giving high enantioselectivity and activity in the enantioselective hydrogenation of ketones.

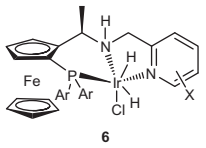
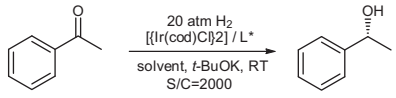


Figure 3. Plausible Ir-(R_C,S_{Fc})-**2** catalysts.

We initially chose acetophenone **7a** as the model substrate for evaluating the performance of ligands **2a**–**f** in the Ir-catalyzed asymmetric hydrogenation of ketones. All of the ligands **2a**–**f** displayed high reactivity and moderate to good enantioselectivity in the hydrogenation of acetophenone (Table 1). Thus, the complete hydrogenation of acetophenone to (*R*)-1-phenylethanol (*R*)-**8a** with 60.1% ee occurred in less than 12 h at room temperature in MeOH under an H_2 pressure of 20 atm in the presence of 0.055 mol % (R_C,S_{Fc})-**2f**, 0.025 mol % [{Ir(cod)Cl}$_2$], and 2.5 mol % *t*-BuOK (entry 1). The choice of solvent played an important role in the hydrogenation; EtOH proved to be the best solvent for Ir-**2f** (entries 2–4). Ligand screening results demonstrated that substituent groups on the pyridine and phenyl rings played only a small role in the reactivity but had a significant effect on the enantioselectivity. Of the ligands tested, the best results were obtained using **2f** in 77% ee with full conversion (entry 2), which proved that the 3,5-di-*tert*-butyl groups on the *P*-phenyl rings as well as the 6-methyl group on the pyridine ring of the ligand were the crucial factors with regard to the enantioselectivity. When the catalyst Ir-**2f** loading was lowered to 0.02 mol % (S/C = 5000), the hydrogenation product (*R*)-**8a** was still obtained with 75% ee (entry 10).

Table 1
Asymmetric hydrogenation of acetophenone catalyzed by Ir-**2a**–**f** complexes[a]

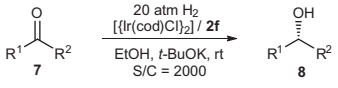


Entry	Ligand	Solvent	Time (h)	Conv[b] (%)	ee[c] (%)
1	**2f**	MeOH	12	99	60.1 (*R*)
2	**2f**	EtOH	18	99	77.0 (*R*)
3	**2f**	*i*-PrOH	18	98	23.1 (*R*)
4	**2f**	Toluene	24	97	43.0 (*R*)
5	**2a**	EtOH	18	99	44.1 (*R*)
6	**2b**	EtOH	18	99	25.1 (*R*)
7	**2c**	EtOH	18	99	57.6 (*R*)
8	**2d**	EtOH	18	99	60.5 (*R*)
9	**2e**	EtOH	18	99	69.8 (*R*)
10[d]	**2f**	EtOH	36	96	75.0 (*R*)

[a] Reaction conditions: 10 mmol substrate, 0.055 mol % **2**, 0.025 mol % [{Ir(cod)Cl}$_2$], 2.5 mol % *t*-BuOK, solvent volume = 3 mL, room temperature (25–30 °C). The catalysts were prepared in situ.
[b] Yield of isolated product.
[c] Determined by HPLC using chiral columns.
[d] S/C = 5000, 50 atm H_2.

A wide range of ketones were hydrogenated over Ir-**2f** under the standard reaction conditions (Table 2). All of the aromatic ketones **7a**–**o** tested underwent hydrogenation to afford the corresponding chiral alcohols **8a**–**o** in good isolated yields and with moderate to good enantioselectivities (53.5–86.6% ee) (Table 2, entries 1–16). Of the ketones reduced, those with *meta*-substituting groups on the phenyl ring provided the best enantioselectivities (entries 6, 7, 8, 15). Electron withdrawing groups and electron donating groups on the phenyl ring, respectively, increased and decreased the activity, but seemed to only have a marginal effect on the ee values. When the catalyst loading

Table 2
Asymmetric hydrogenation of ketones with Ir-**2f**[a]



Entry	R^1	R^2	Prod	Time (h)	Yield[b] (%)	ee[c] (%)
1	C_6H_5	Me	**8a**	18	99	77.0 (*R*)
2	C_6H_5	Et	**8b**	15	99	73.6 (*R*)
3	C_6H_5	*i*-Pr	**8c**	18	99	60.8 (*R*)
4	2-$MeOC_6H_4$	Me	**8d**	12	99	69.9 (*R*)
5	2-BrC_6H_4	Me	**8e**	18	99	78.5 (*R*)
6	3-$MeOC_6H_4$	Me	**8f**	12	99	82.4 (*R*)
7	3-BrC_6H_4	Me	**8g**	18	99	86.6 (*R*)
8	3-$CF_3C_6H_4$	Me	**8h**	18	98	84.2 (*R*)
9	4-$MeOC_6H_4$	Me	**8i**	12	99	75.2 (*R*)
10	4-ClC_6H_4	Me	**8j**	12	99	70.1 (*R*)
11	4-MeC_6H_4	Me	**8k**	18	99	75.2 (*R*)
12	4-FC_6H_4	Me	**8l**	12	99	65.7 (*R*)
13	2-Furyl	Me	**8m**	12	99	53.5 (*R*)
14	1-Naphthyl	Me	**8n**	18	98	62.3 (*R*)
15	2-Naphthyl	Me	**8o**	18	98	82.6 (*R*)
16[d]	3-BrC_6H_4	Me	**8g**	36	96	85.2 (*R*)

[a] Reaction conditions: 10 mmol substrate, 0.055 mol % **2**, 0.025 mol % [{Ir(cod)Cl}$_2$], 2.5 mol % *t*-BuOK, solvent volume = 3 mL, room temperature (25–30 °C). The catalysts were prepared in situ.
[b] Yield of isolated product.
[c] Determined by HPLC using chiral columns.
[d] S/C = 5000, 50 atm H_2.

was lowered to 0.02 mol % (S/C = 5000), optically active **8g** was obtained in high yield and with little diminishment of the enantioselectivity (entry 16).

3. Conclusion

In conclusion, we have designed and synthesized a series of ferrocene-based P–N–N tridentate ligands and applied them to the Ir-catalyzed asymmetric hydrogenation of aromatic ketones. A wide range of ketones could be hydrogenated enantioselectively to afford the corresponding optically active alcohols in good isolated yields and with moderate to good enantioselectivities. The substituent groups on the *P*-phenyl and pyridine rings played a significant role with regard to the reaction enantioselectivity. Further modification of the Ar on the phosphorus and X on the pyridine ring is currently underway.

4. Experimental

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer using TMS as an internal reference. Coupling constant (J) values are given in Hz. Melting points were obtained on Micro Melting Point Instrument (XRC-1) and are uncorrected. Optical rotation analyses were performed on a Perkin–Elmer Model 343 Polarimeter. HRMS were recorded on ZAB-HS spectrometer with ES ionization (ESI). All commercially available reagents were used as received. Solvents and reagents were purified and dried by standard methods prior to use. Products were purified by flash column chromatography on silica gel purchased from Qingdao Haiyang Chemical Co., Ltd. All reactions involving air or moisture sensitive species were performed under an inert atmosphere in oven-dried glassware.

4.2. Synthesis of ferrocene-based tridentate ligands 2a–f

4.2.1. General preparation of 4a, 4e, 4f

To a solution of (*R*)-Ugi's amine **3** (2.57 g, 10 mmol) in TBME (20 mL) was added 1.6 M *t*-BuLi solution in *n*-hexane (6.8 mL, 10.88 mmol) at 0 °C. After the addition was complete, the mixture was warmed to room temperature, and stirred for 1.5 h at room temperature. The mixture was then cooled to 0 °C again, and Ar_2PCl (11 mmol) was added in one portion. After stirring for 20 min at 0 °C, the mixture was warmed to room temperature, and stirred for 1.5 h at room temperature. The mixture was then quenched by the addition of saturated $NaHCO_3$ solution (20 mL). The organic layer was separated and dried over $MgSO_4$, and the solvent was removed under reduced pressure, after which the filtrate was concentrated. The residue was purified by chromatography to afford **4a**, **4e**, and **4f**.

4.2.1.1. (R_C,S_{Fc})-1-(Diphenylphosphino)-2-[1-(dimethylamino)-ethyl]ferrocene 4a[12]. Yield: 3.17 g, 72%. Red solid; mp 141–143 °C; $[\alpha]_D^{25} = -358.9$ (c 0.25, $CHCl_3$); ^{1}H NMR (500 Hz, $CDCl_3$): δ 7.62–7.56 (m, 2H), 7.37–7.32 (m, 3H), 7.22–7.14 (m, 5H), 4.37 (s, 1H), 4.25–4.24 (m, 1H), 4.16–4.14 (m, 1H), 3.94 (s, 5H), 3.86 (s, 1H), 1.77 (s, 6H), 1.26 (d, J = 7 Hz, 3H).

4.2.1.2. (R_C,S_{Fc})-1-[Bis(3,5-dimethylphenyl)phosphino]-2-[1-(dimethylamino)ethyl]ferrocene 4e[12]. Yield: 2.88 g, 58%. Red oil; $[\alpha]_D^{25} = -278.9$ (c 0.25, $CHCl_3$); ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.25–7.23 (m, 2H), 6.98 (s, 1H), 6.80–6.78 (m, 3H), 4.35 (s, 1H), 4.23–4.22 (m, 1H), 4.10–4.08 (m, 1H), 3.92 (s, 5H), 3.87 (s, 1H), 2.32 (s, 6H), 2.18 (s, 6H), 1.81 (s, 6H), 1.28 (d, J = 7 Hz, 3H).

4.2.1.3. (R_C,S_{Fc})-1-[Bis(3,5-di-*tert*-butylphenyl)phosphino]-2-[1-(dimethylamino)ethyl]ferrocene 4f. Yield: 3.33 g, 50%. Yellow foam; $[\alpha]_D^{25} = -246.8$ (c 0.25, CH_2Cl_2); ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.65–7.55 (m, 2H), 7.44 (s, 1H), 7.25–7.21 (m, 3H), 4.37 (s, 1H), 4.26 (s, 1H), 4.21–4.17 (m, 1H), 3.97 (s, 5H), 3.90 (s, 1H), 1.73 (s, 6H), 1.36 (s, 18H), 1.32 (d, J = 6.5 Hz, 3H), 1.26 (s, 18H); ^{31}P NMR (202 Hz, $CDCl_3$) δ −22.79 (s); ^{13}C NMR (126 Hz, $CDCl_3$) δ 149.8 (d, J = 7.4 Hz), 149.2 (d, J = 7.3 Hz), 138.9 (d, J = 3.8 Hz), 137.1 (d, J = 7.2 Hz), 129.5 (d, J = 22.1 Hz), 127.2 (d, J = 20.5 Hz), 122.6, 121.1, 96.2 (d, J = 22.3 Hz), 78.4 (d, J = 9.2 Hz), 71.6 (d, J = 5.4 Hz), 69.6, 69.2 (d, J = 3.8 Hz), 67.9, 57.2 (d, J = 7.2 Hz), 39.2, 34.9, 34.7, 31.6, 31.5, 10.7; HRMS (ESI) Calcd for $C_{42}H_{60}FeNP$ $[M+1]^+$: 666.3879, Found: 666.3875.

4.2.2. General preparation of 5a, 5e, 5f

A solution of **4** (5 mmol) in Ac_2O (20 mL) was heated to 100 °C under nitrogen conditions, and the mixture was stirred for 2 h at 100 °C. After cooling to room temperature, the orange reaction mixture was concentrated in vacuo to give an acetate. The acetate could be used in the next step without purification. To a solution of the acetate in an 80 mL mixture of MeOH and THF (1:1) was added aqueous ammonia (20 mL). The reaction was then stirred at 60 °C for 24 h. After cooling to room temperature, the mixture was quenched by the addition of ice water. The red–brown solution was extracted with ether, the organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure. After chromatographic purification, the desired products **5a**, **5e**, and **5f** were obtained in good yields.

4.2.2.1. (R_C,S_{Fc})-1-(Diphenylphosphino)-2-[(1-amino)ethyl]ferrocene 5a[9]. Yield: 1.45 g, 70%. Yellow solid; mp 132.4–132.9 °C; $[\alpha]_D^{25} = -407.2$ (c 0.25, CH_2Cl_2); ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.57–7.50 (m, 2H), 7.40–7.35 (m, 3H), 7.28–7.24 (m, 5H), 4.44 (s, 1H), 4.29–4.26 (m, 1H), 4.24–4.17 (m, 1H), 4.02 (s, 5H), 3.78–3.75 (m, 1H), 1.45 (d, J = 6.5 Hz, 3H).

4.2.2.2. (R_C,S_{Fc})-1-[Bis(3,5-dimethylphenyl)phosphino]-2-[(1-amino)ethyl]ferrocene 5e[9]. Yield: 1.48 g, 63%. Yellow solid; mp 142.3–143.1 °C; $[\alpha]_D^{25} = -305.5$ (c 0.25, CH_2Cl_2); ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.25–7.15 (d, J = 8.5 Hz, 2H), 7.05 (s, 1H), 6.95–6.85 (m, 3H), 4.30 (m, 1H), 4.30–4.20 (m, 1H), 4.07 (s, 5H), 3.62 (s, 1H), 2.36 (s, 6H), 2.26 (s, 6H), 1.88 (s, 6H), 1.49 (d, J = 6.5 Hz, 3H).

4.2.2.3. (R_C,S_{Fc})-1-[Bis(3,5-di-*tert*-butylphenyl)phosphino]-2-[(1-amino)ethyl]ferrocene 5f. Yield: 2.07 g, 65%. Yellow foam; $[\alpha]_D^{25} = -205.6$ (c 0.25, $CHCl_3$); ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.40 (s, 1H), 7.38–7.34 (m, 2H), 7.30–7.28 (m, 1H), 7.18–7.13 (m, 2H), 4.40–4.36 (m, 1H), 4.26–4.20 (m, 1H), 4.18–4.10 (m, 1H), 4.05 (s, 5H), 3.67–3.64 (m, 1H), 1.42 (d, J = 7 Hz, 3H), 1.29 (s, 18H), 1.21 (s, 18H); ^{31}P NMR (202 Hz, $CDCl_3$) δ −23.05 (s); ^{13}C NMR (126 Hz, $CDCl_3$) δ 150.4 (d, J = 6.6 Hz), 150.1 (d, J = 7.4 Hz), 138.4 (d, J = 7.8 Hz), 135.8 (d, J = 7.6 Hz), 129.1 (d, J = 21.2 Hz), 127.5 (d, J = 20.2 Hz), 122.8, 122.3, 100.0 (d, J = 10.2 Hz), 76.5 (d, J = 7.7 Hz), 71.1 (d, J = 3.5 Hz), 69.5, 68.6, 67.8 (d, J = 3.8 Hz), 45.4 (d, J = 8.8 Hz), 34.9, 34.8, 31.5, 31.4, 22.9; HRMS (ESI) Calcd for $C_{40}H_{56}FeNP$ $[M+1]^+$: 638.3578, Found: 638.3571.

4.2.3. Synthesis of ligands 2a–f

To a solution of ferrocenyl aminophosphine ligand **5** (1 mmol) and $NaBH(OAc)_3$ (2 mmol) in DCE (10 mL) was added picolinaldehyde (1.1 mmol) under a nitrogen atmosphere. The reaction mixture obtained was stirred at room temperature for 10–18 h (monitored by TLC). After being quenched with a saturated $NaHCO_3$ solution, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried with

anhydrous Na_2SO_4 and concentrated in vacuo to afford the crude product. After chromatography on silica-gel column, the corresponding P–N–N ligands **2a–f** were obtained in high yields.

4.2.3.1. (R_C,S_{Fc})-1-(Diphenylphosphino)-2-[1-*N*-(pyridin-2-ylmethyl)ethyl]ferrocene 2a. Yield: 0.48 g, 95%. Red solid; mp 137.3–138.2 °C; $[\alpha]_D^{25} = -320.2$ (*c* 0.25, CH_2Cl_2); ^{1}H NMR (500 Hz, $CDCl_3$) δ 8.40–8.35 (m, 1H), 7.65–7.55 (m, 2H), 7.42–7.32 (m, 4H), 7.32–7.26 (m, 2H), 7.22–7.14 (m, 3H), 7.04–6.98 (m, 1H), 6.60 (d, J = 8 Hz, 1H), 4.58–4.57 (m, 1H), 4.37–4.33 (m, 1H), 4.26–4.20 (m, 1H), 4.06 (s, 5H), 3.88–3.84 (m, 1H), 3.69 (d, ^2J = 14 Hz, 1H), 3.66 (d, ^2J = 14 Hz, 1H), 1.60 (d, J = 7 Hz, 3H); ^{31}P NMR (202 Hz, $CDCl_3$) δ −25.03 (s); ^{13}C NMR (126 Hz, $CDCl_3$) δ 159.9, 148.7, 140.1 (d, J = 10 Hz), 137.3 (d, J = 8.8 Hz), 136.0, 135.0 (d, J = 21.2 Hz), 132.6 (d, J = 18.9 Hz), 129.1, 128.3 (d, J = 6.4 Hz), 128.1, 128.0 (d, J = 2.8 Hz), 121.5, 121.3, 97.7 (d, J = 24.4 Hz), 75.1 (d, J = 7.7 Hz), 71.3 (d, J = 4.4 Hz), 69.6, 69.5 (d, J = 4.4 Hz), 69.1, 52.2, 51.3 (d, J = 9.3 Hz), 19.5; HRMS (ESI) Calcd for $C_{30}H_{29}FeN_2P$ [M+1]$^+$: 505.1496, Found: 505.1485.

4.2.3.2. (R_C,S_{Fc})-1-(Diphenylphosphino)-2-[1-*N*-(3-methylpyridin-2-ylmethyl)ethyl]ferrocene 2b. Yield: 0.46 g, 92%. Red solid; mp 103.2–104 °C; $[\alpha]_D^{25} = -353.6$ (*c* 0.25, CH_2Cl_2); ^{1}H NMR (500 Hz, $CDCl_3$) δ 8.07 (d, J = 4 Hz, 1H), 7.60–7.52 (m, 2H), 7.40–7.32 (m, 3H), 7.23–7.16 (m, 3H), 7.13–7.03 (m, 3H), 6.92–6.87 (m, 1H), 4.57 (s, 1H), 4.33–4.30 (m, 1H), 4.18–4.12 (m, 1H), 3.97 (s, 5H), 3.88–3.84 (m, 1H), 3.66 (d, ^2J = 14 Hz, 1H), 3.52 (d, ^2J = 14 Hz, 1H), 1.97 (s, 3H), 1.64 (d, J = 6.5 Hz, 3H); ^{31}P NMR (202 Hz, $CDCl_3$) δ −24.81 (s); ^{13}C NMR (126 Hz, $CDCl_3$) δ 156.9, 146.0, 140.0 (d, J = 9.2 Hz), 137.8 (d, J = 9.1 Hz), 136.9, 135.1 (d, J = 21.5 Hz), 132.3 (d, J = 18.1 Hz), 130.4, 129.0, 128.1, 128.0 (d, J = 5.8 Hz), 127.7, 121.2, 98.6 (d, J = 25.1 Hz), 74.9 (d, J = 8.3 Hz), 71.1 (d, J = 4 Hz), 69.6, 69.3 (d, J = 4.4 Hz), 69.2, 51.3 (d, J = 9.5 Hz), 49.8, 20.8, 17.7; HRMS (ESI) Calcd for $C_{31}H_{31}FeN_2P$ [M+1]$^+$: 519.1653, Found: 519.1649.

4.2.3.3. (R_C,S_{Fc})-1-(Diphenylphosphino)-2-[1-*N*-(quinolin-2-ylmethyl)ethyl]ferrocene 2c. Yield: 0.53 g, 95%. Yellow foam; $[\alpha]_D^{25} = -276.8$ (*c* 0.25, CH_2Cl_2); ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.88 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 7.65–7.59 (m, 1H), 7.58–7.51 (m, 2H), 7.49–7.42 (m, 1H), 7.40–7.33 (m, 3H), 7.25–7.20 (m, 1H), 7.14–7.06 (m, 2H), 7.03–6.98 (m, 1H), 6.76 (d, J = 8.5 Hz, 1H), 4.58 (s, 1H), 4.34 (s, 1H), 4.33–4.25 (m, 1H), 4.01 (s, 5H), 3.90–3.80 (m, 3H), 1.62 (d, J = 6 Hz, 3H); ^{31}P NMR (202 Hz, $CDCl_3$) δ −25.13 (s); ^{13}C NMR (126 Hz, $CDCl_3$) δ 147.4, 140.0 (d, J = 9.5 Hz), 137.4 (d, J = 8.9 Hz), 136.0, 135.1, 134.9, 132.7, 132.5, 131.4 (d, J = 10.2 Hz), 129.1 (d, J = 9.5 Hz), 128.3 (d, J = 6.3 Hz), 128.1 (d, J = 8.1 Hz), 128.0, 127.4, 127.1, 125.8, 120.0, 97.2 (d, J = 23.7 Hz), 75.2 (d, J = 8.3 Hz), 71.4 (d, J = 4.3 Hz), 69.7, 69.6 (d, J = 4 Hz), 69.3, 52.6, 51.5 (d, J = 9.5 Hz), 19.6; HRMS (ESI) Calcd for $C_{34}H_{31}FeN_2P$ [M+1]$^+$: 555.1653, Found: 555.1644.

4.2.3.4. (R_C,S_{Fc})-1-(Diphenylphosphino)-2-[1-*N*-(6-methylpyridin-2-ylmethyl)ethyl]ferrocene 2d. Yield: 0.48 g, 93%. Red oil; $[\alpha]_D^{25} = -243.8$ (*c* 0.65, CH_2Cl_2); ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.56–7.50 (m, 2H), 7.40–7.33 (m, 3H), 7.28–7.20 (m, 3H), 7.17–7.10 (m, 3H), 6.84 (d, J = 7.5 Hz, 1H), 6.33 (d, J = 7.5 Hz, 1H), 4.53 (s, 1H), 4.33–4.28 (m, 1H), 4.25–4.17 (m, 1H), 4.00 (s, 5H), 3.85–3.80 (m, 1H), 3.62 (s, 1H), 2.41 (s, 3H), 1.55 (d, J = 6.5 Hz, 3H); ^{31}P NMR (202 Hz, $CDCl_3$) δ −25.03 (s); ^{13}C NMR (126 Hz, $CDCl_3$) δ; 159.3, 157.1, 140.1 (d, J = 9.8 Hz), 137.4 (d, J = 9.2 Hz), 136.3, 135.0 (d, J = 21.3 Hz), 132.6 (d, J = 18.6 Hz), 131.5 (d, J = 10 Hz), 129.1, 128.3 (d, J = 5.9 Hz), 128.3, 120.9, 118.3, 97.8 (d, J = 24.3 Hz), 75.1 (d, J = 8.2 Hz), 71.3 (d, J = 4 Hz), 69.6, 69.5 (d, J = 4.4 Hz), 69.1, 52.1, 51.3 (d, J = 9.2 Hz), 24.4, 19.4; HRMS (ESI) Calcd for $C_{31}H_{31}FeN_2P$ [M+1]$^+$: 519.1653, Found: 519.1645.

4.2.3.5. (R_C,S_{Fc})-1-[Bis(3,5-dimethylphenyl)phosphino]-2-[1-*N*-(6-methylpyridin-2-ylmethyl) ethyl]ferrocene 2e. Yield: 0.52 g, 90%. Yellow foam; $[\alpha]_D^{25} = -262.4$ (*c* 0.25, CH_2Cl_2); ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.28–7.23 (m, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.04 (s, 1H), 6.92–6.84 (m, 3H), 6.74 (s, 1H), 6.30 (d, J = 8 Hz, 1H), 4.55 (s, 1H), 4.34–4.30 (m, 1H), 4.29–4.22 (m, 1H), 4.08 (s, 5H), 3.87–3.82 (m, 1H), 3.63 (d, ^2J = 14.5 Hz, 1H), 3.61 (d, ^2J = 14.5 Hz, 1H), 2.47 (s, 3H), 2.35 (s, 6H), 2.11 (s, 6H), 1.58 (d, J = 6.5 Hz, 3H); ^{31}P NMR (202 Hz, $CDCl_3$) δ −25.14 (s); ^{13}C NMR (126 Hz, $CDCl_3$) δ 159.5, 157.0, 139.4 (d, J = 9.3 Hz), 137.6 (d, J = 6.7 Hz), 137.4 (d, J = 7.9 Hz), 136.8 (d, J = 8.9 Hz), 136.2, 132.6, 132.5, 130.6 (d, J = 25.1 Hz), 130.2 (d, J = 28.7 Hz), 120.7, 117.8, 97.3 (d, J = 23.9 Hz), 75.8 (d, J = 7.8 Hz), 71.4 (d, J = 4 Hz), 69.6, 69.5 (d, J = 3.9 Hz), 68.7, 51.8, 51.1 (d, J = 9.6 Hz), 24.4, 21.4, 21.2, 19.1; HRMS (ESI) Calcd for $C_{35}H_{39}FeN_2P$ [M+1]$^+$: 575.2279, Found: 575.2273.

4.2.3.6. (R_C,S_{Fc})-1-[Bis(3,5-di-*tert*-butylphenyl)phosphino]-2-[1-*N*-(6-methylpyridin-2-ylmethyl)ethyl]ferrocene 2f. Yield: 0.69 g, 94%. Yellow foam; $[\alpha]_D^{25} = -184.6$ (*c* 0.25, CH_2Cl_2); ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.42–7.37 (m, 3H), 7.24 (s, 2H), 7.23–7.21 (m, 1H), 7.17–7.10 (m, 1H), 6.81 (d, J = 7.5 Hz, 1H), 5.89 (d, J = 8 Hz, 1H), 4.51 (s, 1H), 4.30–4.23 (m, 2H), 4.06 (s, 5H), 3.75 (s, 1H), 3.54 (d, ^2J = 14.5 Hz, 1H), 3.48 (d, ^2J = 14.5 Hz, 1H), 2.39 (s, 3H), 1.55 (d, J = 6.5 Hz, 3H), 1.29 (s, 18H), 1.13 (s, 18H); ^{31}P NMR (202 Hz, $CDCl_3$) δ −24.98 (s); ^{13}C NMR (126 Hz, $CDCl_3$) δ 159.4 (d, J = 5.9 Hz), 157.1, 150.5 (d, J = 6.6 Hz), 150.0 (d, J = 7.4 Hz), 138.5 (d, J = 7.7 Hz), 136.3, 135.6 (d, J = 7.3 Hz), 129.1 (d, J = 21.4 Hz), 127.4 (d, J = 20.7 Hz), 125.3, 122.7 (d, J = 20.5 Hz), 120.8, 117.8, 96.9, 75.1 (d, J = 14.1 Hz), 71.1 (d, J = 4.2 Hz), 69.6, 69.4 (d, J = 3.8 Hz), 68.6, 51.8, 51.1 (d, J = 10.1 Hz), 34.9, 34.8, 31.5, 31.3, 24.3, 19.2; HRMS (ESI) Calcd for $C_{47}H_{63}FeN_2P$ [M+1]$^+$: 743.4157, Found: 743.4148.

4.3. Typical procedure for the asymmetric hydrogenation of ketones 7a–o[11]

To a 20 mL hydrogenation vessel were added the catalyst precursor [{Ir(cod)Cl}$_2$] (1.7 mg, 2.53 μmol), ligand **2f** (4.5 mg, 6.06 μmol), and anhydrous EtOH (3 mL) under a nitrogen atmosphere. The mixture was stirred for 1.0 h at 25–30 °C to give a clear yellow solution. After placing the vessel in an autoclave, the ketone (10 mmol) and *t*-BuOK (28 mg, 0.253 mmol) were added. The autoclave was replaced with H_2 three times, and the reaction mixture was stirred at room temperature until no obvious hydrogen pressure drop was observed. After releasing the hydrogen pressure, the reaction mixture was filtered through a short silica gel column. The solvent in the filtrate was removed to determine the yield and the product obtained was analyzed by HPLC to determine the enantiomeric excess.

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