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Ruthenium-Catalyzed Enantioselective Hydrogenation of Ferrocenyl Ketones: A Synthetic Method for Chiral Ferrocenyl Alcohols

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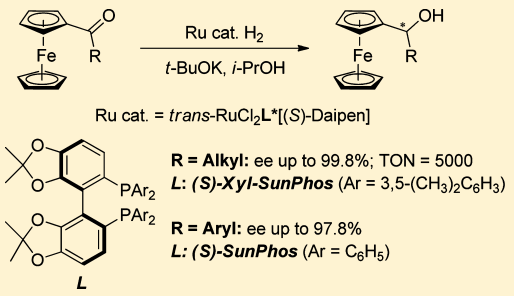
Supporting Information

ABSTRACT: Highly effective asymmetric hydrogenation of various ferrocenyl ketones, including aliphatic ferrocenyl ketones as well as the more challenging aryl ferrocenyl ketones, was realized in the presence of a Ru/diphosphine/diamine bifunctional catalytic system. Excellent enantioselectivities (up to 99.8% ee) and activities (S/C = 5000) could be obtained. These asymmetric hydrogenations provided a convenient and efficient synthetic method for chiral ferrocenyl alcohols, which are key intermediates for a variety of chiral ferrocenyl ligands and resolving reagents.



INTRODUCTION

The asymmetric hydrogenation of prochiral ketones provides a powerful access to chiral alcohols which are versatile and important building blocks for biologically active substances such as pharmaceuticals, natural products, and chiral ligands and materials.[1] Numerous catalytic systems for the asymmetric hydrogenations of ketones have been explored to achieve high efficiency and enantioselectivity.[1] For the asymmetric hydrogenation of unfunctionalized ketones, the breakthrough was made by Noyori and co-workers with a chiral ruthenium−diphosphine/diamine catalyst.[2] Subsequently, chiral bifunctional ruthenium catalysts for asymmetric hydrogenations, with combinations of mono- or bidentate phosphines and diamines, have undergone great development over the past decade: the efficiency has improved greatly and the substrate scope has been expanded extensively.[2−5] However, only a few examples regarding asymmetric hydrogenation of ferrocenyl ketones have been reported; nevertheless, most of them were limited by the substrate scope, especially for aryl ferrocenyl ketones.[4,5c,g,6] Moreover, enantiomerically pure ferrocenyl alcohols, the corresponding hydrogenated products, are important intermediates for chiral ferrocene ligands such as JosiPhos,[7] PPFA,[8] TRAP,[9] TaniaPhos,[10] PigiPhos,[11] WalPhos,[12] etc., which have been demonstrated to be of great use in asymmetric catalytic reactions.[7,8,10−13] Currently, a few methods are available for the synthesis of optically pure ferrocenyl alcohols, such as kinetic resolution,[14] asymmetric hydroboration,[15] hydrosilylation,[15f,16] transfer hydrogenation,[17] and nucleophilic addition.[18] However, these synthetic approaches suffered from low efficiency, poor enantioselectivity, or limited scope of substrates. Accordingly, the search for effective and highly enantioselective approaches to synthesize enantiomerically pure ferrocenyl alcohols is still a significant and challenging work. In this paper, we report an efficient synthetic method for chiral ferrocenyl alcohols by the asymmetric hydrogenation of ferrocenyl ketones with SunPhos derivatives as ligands which show high enantioselectivity for Ru-catalyzed asymmetric hydrogenation of various ketones,[19] including α-/β-keto acid derivatives,[19c] polyfunctionalized ketones,[19e] and simple ketones.[19b,d]

RESULTS AND DISCUSSION

We began our study with acetylferrocene (**1a**) as the model substrate, and the asymmetric hydrogenation of **1a** was carried out in *i*-PrOH containing $RuCl_2$[(*S*)-SunPhos][(*S*)-Daipen] and *t*-BuOK (S/C/B = 100/1/5) under 10 atm of H_2 at 30 °C for 15 h. The corresponding alcohol **2a** was obtained in quantitative yield and moderate enantioselectivity (Table 1, entry 1, 67.8% ee). Then a series of chiral biphosphine ligands (shown in Figure 1) were tested to explore the effect of the ligand structure on the activity and enantioselectivity for the hydrogenation of ferrocenyl ketones.[20] The results are depicted in Table 1.

Good enantiomeric excess was obtained by using (*S*)-BINAP as ligand (Table 1, entry 2, 85.4% ee), which was higher than that with other three commercially available chiral bidentate ligands: (*S*)-SegPhos, (*S*)-SynPhos, and (*S*)-C3-TunePhos (Table 1, entries 3−5, 56.6%−68.8% ee). Ligand **L1** with a 4-methyl-substituted phenyl group gave poorer stereoselectivity (Table 1, entry 6). When the xylyl-substituted ligand **L2** was used as a ligand, to our delight, the enantioselectivity was dramatically increased to 99.8% ee. The results indicate that the 3,5-dimethyl groups on the P-phenyl rings of the SunPhos

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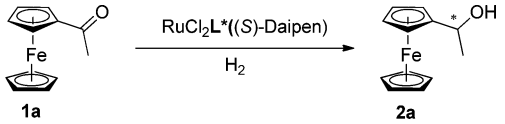
Table 1. Effects of Ligands in Asymmetric Hydrogenation of 1a[a]



entry	ligand	ee[b] (%)
1	(*S*)-SunPhos	67.8
2	(*S*)-BINAP	85.4
3	(*S*)-SegPhos	61.6
4	(*S*)-SynPhos	68.8
5	(*S*)-C3-Tunephos	56.6
6	**L1**	−7.8
7	**L2**	99.8

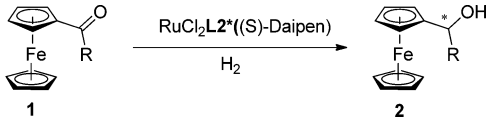
[a]All reactions were carried out with a substrate (0.25 mmol) concentration of 0.25 M in *i*-PrOH under 10 atm of H_2 at 30 °C for 15 h, with substrate/catalyst/*t*-BuOK = 100/1/5. Conversion: 100%. [b]Determined by HPLC on a Chiralpak AD-H column.

ligand significantly benefit the enantioselectivity in the hydrogenation of ferrocenyl ketones (Table 1, entry 7), and they further confirmed the "3,5-dialkyl meta-effect" in the Ru^{II}-diphosphine/diamine-catalyzed hydrogenation of simple ketones.[21] On the basis of the above results, **L2** was the ligand of choice.

After exploring the effect of ligands, we turned our attention to the effect of the solvent, reaction temperature, and hydrogen pressure, and the results are summarized in Table S1 in the Supporting Information. Solvent is important for the efficiency and enantioselectivity of the asymmetric hydrogenation. For protic solvents, *i*-PrOH was superior to EtOH and MeOH (Table S1, entry 1 vs entries 2 and 3). When aprotic solvents such as THF and DCM were applied, the reaction could hardly proceed. Thus, *i*-PrOH was the solvent of choice for this transformation. The enantioselectivity of the hydrogenation was strongly affected by the reaction temperature (Table S1, entries 6 and 7), and higher temperature decreased the enantiomeric excess. Unexpectedly, the enantioselectivity was almost independent of the hydrogen pressure between 10 and 50 atm in our optimization (Table S1, entries 8 and 9). On the basis of these results, the optimized reaction conditions were therefore set as follows: 1 mol % of $RuCl_2$[(*S*)-Xyl-SunPhos]-[(*S*)-Daipen] as the catalyst, *i*-PrOH as the solvent with a substrate concentration of 0.25 M, and *t*-BuOK as the base under 10 atm of H_2 at 30 °C for 15 h.

With the optimized conditions defined, the scope of the reaction was examined, and the results are presented in Table 2.

Table 2. Asymmetric Hydrogenation of Alkyl Ferrocenyl Ketones[a]



entry	1	R	conversion[b] (%)	ee[c] (%)
1	**1a**	Me	100	99.8
2	**1b**	Et	100	99.4
3	**1c**	*n*-Pr	100	99.2
4	**1d**	$CH_3(CH_2)_8$	100	99.4
5	**1e**	*t*-Bu	0	n.a.
6	**1f**	*i*-Pr	0	n.a.
7	**1g**	*i*-Bu	<5	n.a.
8	**1h**	$(CH_3)_2CH(CH_2)_2$	100	98.8
9[d]	**1a**	Me	100	99.8
10[e]	**1a**	Me	100	97.0
11[f]	**1a**	Me	27	98.0
12[g]	**1d**	$CH_3(CH_2)_8$	28	99.4
13[h]	**1h**	$(CH_3)_2CH(CH_2)_2$	100	98.0

[a]Unless otherwise stated, reactions were carried out with a substrate (0.25 mmol) concentration of 0.25 M in *i*-PrOH under 10 atm of H_2 at 30 °C for 15 h, with substrate/catalyst/*t*-BuOK = 100/1/5. [b]Determined by NMR analysis. [c]Determined by HPLC on a Chiralpak column. [d]Substrate/catalyst/*t*-BuOK = 1000/1/5. [e]Reaction using 5.72 g of **1a** under 50 atm of H_2 at 30 °C for 15 h, with substrate/catalyst/*t*-BuOK = 5000/1/20; isolated yield 99%. [f]Substrate/catalyst/*t*-BuOK = 10000:/1/50, under 50 atm of H_2 at 30 °C for 15 h. [g]Reaction using 1.70 g of **1d** under 50 atm of H_2 at 30 °C for 15 h, with substrate/catalyst/*t*-BuOK = 5000/1/20; isolated yield 28%. [h]Reaction using 1.28 g of **1h** under 50 atm of H_2 at 30 °C for 15 h, with substrate/catalyst/*t*-BuOK = 3000/1/20; isolated yield 98%.

A range of primary alkyl ferrocenyl ketones with different carbon chain lengths were hydrogenated smoothly in high enantioselectivity (Table 2, entries 1−4). The result showed that the length of the linear alkyl chain had no dramatic effect on the activity and enantioselectivity of the reaction. Nevertheless, when R was changed to larger alkyl groups such as *tert*-butyl and isopropyl, the hydrogenation reaction could hardly proceed (Table 2, entries 5 and 6). Only a trace amount of product was observed when R was isobutyl (Table 2, entry 7),

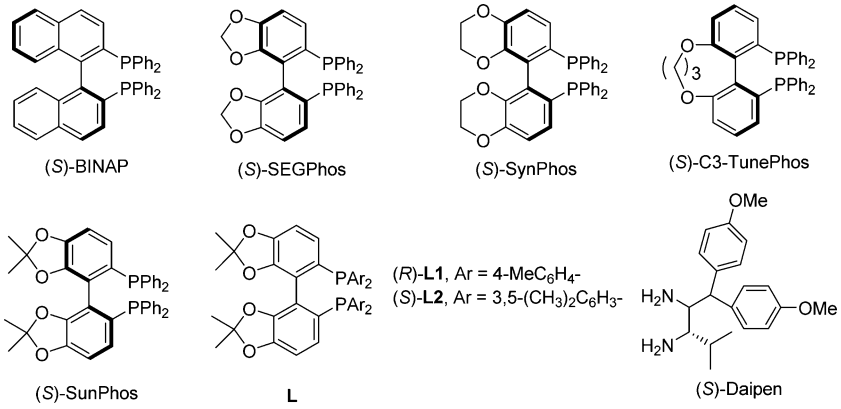


Figure 1. Structures of chiral bidentate ligands.

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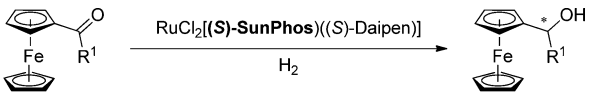
which was in sharp contrast to the results obtained by the hydrogenation of the sterically less hindered substrate **1h** (R = isopentyl; Table 2, entry 8). This result indicated that the hydrogenation reaction was significantly influenced by the steric hindrance of the alkyl group.

Additionally, the catalytic efficiency was explored with 0.1 mol % of catalyst, and acetylferrocene was completely converted to 1-ferrocenylethanol under the same conditions without any ee erosion (Table 2, entry 9). Furthermore, when the S/C value was increased to 5000, this highly active catalyst can still acquire 97.0% ee within 15 h under 50 atm of H_2 pressure (Table 2, entry 10). When the S/C value was increased to 10000, although the conversion was lowered to 27% within 15 h, excellent enantioselectivity remained (Table 2, entry 11).

Subsequently, we tried to extend the methodology to more challenging aryl ferrocenyl ketones. Unfortunately, poor results (Table 3, entry 1) were obtained by a preliminary attempt to hydrogenate the benzoylferrocene under the same conditions as described above, and similar cases had been reported by Noyori and Chan using Xyl-BINAP and Xyl-P-Phos as ligands.[6a,c] We speculate that the reason was that the catalyst having relatively larger steric P aryls in the diphosphines hampered itself from forming a stable six-membered pericyclic ring transition state with the aryl ferrocenyl ketones.[22] Thus, when **L2** was replaced by the less sterically hindered ligand (*S*)-SunPhos, as we expected, excellent activity and enantioselectivity were achieved (Table 3, entry 2).

Table 3. Asymmetric Hydrogenation of Aryl Ferrocenyl Ketones[a]



entry	3	R^1	conversion[b] (%)	ee[c] (%)
1[d]	**3a**	C_6H_5	100	0.8
2	**3a**	C_6H_5	100	90.2
3[e]	**3b**	*o*-$CH_3C_6H_5$	100	95.0
4[e]	**3c**	*o*-ClC_6H_5	100	94.8
5	**3d**	*p*-$OCH_3C_6H_5$	100	66.8
6[f]	**3e**	*p*-$CF_3C_6H_5$	100	81.8
7[g]	**3f**	1-naphthyl	100	97.8
8	**3g**	$C_6H_5CH_2$	100	85.0
9	**3h**	$C_6H_5CH_2CH_2$	100	95.2

[a]Unless otherwise stated, reactions were carried out with a substrate (0.25 mmol) concentration of 0.25 M in *i*-PrOH under 10 atm of H_2 at 30 °C for 15 h, with substrate/catalyst/*t*-BuOK = 100/1/5. [b]Determined by NMR analysis. [c]Determined by HPLC on a Chiralpak column. [d]**L2** was used as ligand. [e]Under 40 atm of H_2 at 50 °C for 48 h, with substrate/catalyst/*t*-BuOK = 100/1/20. [f]Reaction time 30 h. [g]Under 50 atm of H_2 at 30 °C for 20 h, with substrate/catalyst/*t*-BuOK = 100/1/10.

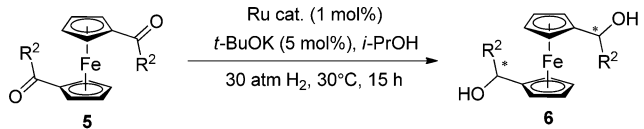
Next, a series of aryl ferrocenyl ketones bearing different substituent groups on the phenyl ring were subjected to this hydrogenation reaction under the catalysis of $RuCl_2$[(*S*)-SunPhos][(*S*)-Daipen], and the results are depicted in Table 3. The catalyst showed a good tolerance for various substituent groups on the ortho and para positions with different electronic properties. The substrates containing an ortho substituent on the phenyl ring gave higher enantioselectivities (up to 95.0% ee; Table 3, entries 3 and 4), because the ortho-substituted phenyl ring has greater steric bulk, which results in a better steric differentiation from ferrocenyl. Furthermore, substrates with an ortho chlorine atom or methyl group gave almost the same enantioselectivities, which indicated that the possible coordination interaction between the ortho chlorine atom and the Ru catalyst was not the origin of enantioselectivity (Table 3, entries 3 and 4).[15d,23] Substrates with para substituents on the aromatic ring showed a distinct influence on both reactivity and enantioselectivity. Substrate **3d** with an electron-donating methoxy group on the para position (Table 3, entry 5) was more reactive than **3e** possessing an electron-withdrawing trifluoromethyl substituent (Table 3, entry 6), but the corresponding product (**4d**) had a lower ee. Electronic influences of the para substituents were presumed to affect the coplanarity of the benzene rings with C═O in the transition state,[24] thereby generating an asymmetric bias. Additionally, other aromatic ferrocenyl ketones such as **3f**, possessing a naphthyl group, was also hydrogenated well (Table 3, entry 7). Surprisingly, the analogues 2-phenyl- and/or 2-benzyl-substituted acetylferrocene were also reactive with excellent enantiofacial discrimination under the $RuCl_2$[(*S*)-SunPhos][(*S*)-Daipen] catalyst systems (Table 3, entries 8 and 9).

We also examined the asymmetric hydrogenation of ferrocenyl diketones. As illustrated in Scheme 1, the hydrogenation of the diketone **5a** catalyzed by $RuCl_2$[(*S*)-Xyl-SunPhos][(*S*)-Daipen] selectively gave only (*R*,*R*)-**6a** among the three possible stereoisomers.[15b] The aryl diketone **5b** was also hydrogenated well under 50 atm of H_2 using $RuCl_2$[(*S*)-SunPhos][(*S*)-Daipen] as catalyst. The diastereomeric ratio *dl*/*meso* of the products was 86.3/13.7 and the ee values increased to 99.9% in comparison with 90.2% ee obtained in the hydrogenation of the monoketone (**3a**).

CONCLUSION

In conclusion, we have developed a convenient, practical, efficient, and highly enantioselective protocol for the synthesis of chiral ferrocenyl alcohols by asymmetric hydrogenation. It was found that Ru-XylSunPhos-Daipen was the optimal catalyst for the hydrogenation of aliphatic acyl ferrocene (up to 99.8% ee and 5000 TON), and Ru-Sunphos-Daipen was more appropriate for the hydrogenation of aryl ferrocenyl ketones

Scheme 1. Asymmetric Hydrogenation of the Ferrocenyl Diketones



a: R^2 = CH_3, *dl*:*meso* > 99.9, *ee* > 99.9%
b: R^2 = Ph, *dl*:*meso* = 86.3:13.7, *ee* > 99.9%

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(up to 97.8% ee). This method provided crucial intermediates in the synthesis of many chiral ferrocenyl ligands, and further efforts to develop new types of ligands are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Procedures. Commercially available reagents were used throughout without further purification other than those detailed below. DMF, *i*-PrOH, and dichloromethane were distilled over calcium hydride. THF was freshly distilled from Na/benzophenone under nitrogen. MeOH and EtOH were distilled over magnesium under nitrogen. All reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques, unless otherwise noted. ^{1}HNMR spectra were recorded at 400 MHz with TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz and referenced to the central peak of 77.00 ppm for $CDCl_3$. Coupling constants (J) are reported in Hz and refer to apparent peak multiplications. HRMS were obtained on an ESI-TOF mass spectrometer. Flash column chromatography was performed on silica gel (300−400 mesh). $[\alpha]_D$ values were recorded at the D line (589 nm) of a sodium lamp in a 0.5 dm cell at 25 °C. Racemates were prepared by $NaBH_4$ reduction of the corresponding ferrocenyl ketones.

Typical Procedure for the Preparation of 1a−h and 3g,h.[25] A mixture of ferrocene (1.0 g, 5.40 mmol) and ZnO (0.5 g, 6.50 mmol) in dichloromethane (10 mL) was stirred and refluxed. The corresponding acyl chloride (16.10 mmol) in dichloromethane (10 mL) was added dropwise over 15 min and reacted for an additional 15−30 min (monitored by TLC). The resulting purplish solution was cooled to room temperature and then poured into the stirred ice water. The organic layer was separated, and the water phase was extracted with dichloromethane (8 mL × 3). The combined organic phase was neutralized with a solution of $NaHCO_3$, followed by washing with ice water and saturated brine, and dried over anhydrous Na_2SO_4. After the solvents were removed in vacuo, the crude product obtained was purified by column chromatography (PE/EA = 20/1) to give the desired compound.

*Acetylferrocene (**1a**)*:[25] red solid; 1.2 g, 97% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (t, J = 2.0 Hz, 2H), 4.50 (t, J = 2.0 Hz, 2H), 4.20 (s, 5H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.1, 79.3, 72.3, 69.9, 69.6, 27.4.

*Propionylferrocene (**1b**)*:[25] red solid; 1.2 g, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (s, 2H), 4.49 (s, 2H), 4.19 (s, 5H), 2.74 (q, J = 7.2 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 205.0, 78.9, 72.0, 69.7, 69.2, 32.7, 8.5.

*n-Butyrylferrocene (**1c**)*:[25] red solid; 1.3 g, 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (t, J = 2.0 Hz, 2H), 4.49 (t, J = 2.0 Hz, 2H), 4.20 (s, 5H), 2.68 (t, J = 7.6 Hz, 2H), 1.79−1.69 (m, 2H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 204.5, 79.2, 72.0, 69.7, 69.3, 41.6, 17.9, 14.1.

*Decanoylferrocene (**1d**)*:[26] red solid; 1.6 g, 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (t, J = 2.0 Hz, 2H), 4.49 (t, J = 2.0 Hz, 2H), 4.19 (s, 5H), 2.69 (t, J = 7.6 Hz, 2H), 1.69 (m, 2H), 1.35−1.28 (m, 12H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 204.6, 79.2, 72.0, 69.7, 69.3, 39.8, 31.9, 29.6, 29.5, 29.3, 24.6, 22.6, 14.1.

*2,2-Dimethylpropionylferrocene (**1e**)*:[25] red solid; 1.3 g, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (t, J = 2.0 Hz, 2H), 4.46 (t, J = 2.0 Hz, 2H), 4.18 (s, 5H), 1.33 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 210.3, 71.2, 71.0, 69.7, 44.2, 28.2.

*2-Methylpropionylferrocene (**1f**)*:[25] red solid; 1.3 g, 96% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (t, J = 2.0 Hz, 2H), 4.50 (t, J = 2.0 Hz, 2H), 4.19 (s, 5H), 3.16−3.06 (m, 1H), 1.21 (d, J = 7.2 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 208.6, 78.1, 72.1, 69.5, 69.4, 37.2, 19.5.

*3-Methylbutyrylferrocene (**1g**)*:[27] red solid; 1.4 g, 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (t, J = 2.0 Hz, 2H), 4.49 (t, J = 2.0 Hz, 2H), 4.20 (s, 5H), 2.57 (d, J = 6.8 Hz, 2H), 2.32−2.22 (m, 1H), 1.00 (d, J = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 204.5, 79.8, 72.3, 70.0, 69.6, 49.0, 25.3, 23.1.

*4-Methylpentanoylferrocene (**1h**)*:[27] red solid; 1.4 g, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (t, J = 2.0 Hz, 2H), 4.49 (t, J = 2.0 Hz, 2H), 4.19 (s, 5H), 2.72−2.68 (m, 2H), 1.63−1.59 (m, 3H), 0.96 (d, J = 6.4 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 205.2, 79.4, 72.4, 70.0, 69.6, 38.0, 33.8, 28.1, 22.7.

*2-Phenylacetylferrocene (**3g**)*:[25] red solid; 1.0 g, 61% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.34 (m, 4H), 7.31−7.24 (m, 1H), 4.83 (t, J = 2.0 Hz, 2H), 4.51(t, J = 2.0 Hz, 2H), 4.11 (s, 5H), 3.98 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.10, 135.14, 129.27, 128.46, 126.77, 78.56, 72.42, 69.83, 69.73, 46.78.

*3-Phenylpropionylferrocene (**3h**)*:[25] red solid; 1.6 g, 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.29 (m, 4H), 7.24−7.21 (m, 1H), 4.77 (t, J = 2.0 Hz, 2H), 4.48 (t, J = 2.0 Hz, 2H), 4.08 (s, 5H), 3.06−3.00 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 203.0, 141.6, 128.6, 128.5, 126.1, 79.0, 72.2, 69.6, 69.3, 41.5, 30.1.

Typical Procedure for the Preparation of 3a−f and 5a,b.[28] To a stirred solution of ferrocene (1.0 g, 5.40 mmol) in CH_2Cl_2 (10 mL) was added $AlCl_3$ (0.9 g, 6.50 mmol for monoketones; 1.8 g, 13.00 mmol for diketones) in portions at 0 °C. A solution of the corresponding acyl chloride (5.90 mmol for monoketones; 11.80 mmol for diketones) in dichloromethane (10 mL) was added dropwise over 30 min while keeping the temperature at 0 °C, and then the reaction mixture was warmed to room temperature. Upon consumption of the starting material (monitored by TLC), the reaction mixture was quenched with ice water. The organic layer was separated, and the water phase was extracted with dichloromethane (8 mL × 3). The combined organic phase was neutralized with a solution of $NaHCO_3$, followed by washing with ice water and saturated brine, and dried over anhydrous Na_2SO_4. After the solvents were removed in vacuo, the crude product obtained was purified by column chromatography (PE/EA = 10/1) to give the desired compound.

*Benzoylferrocene (**3a**)*:[28] red solid; 1.2 g, 77% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.89 (m, 2H), 7.55−7.53 (m, 1H), 7.49−7.45 (m, 2H), 4.91 (t, J = 2.0 Hz, 2H), 4.59 (t, J = 2.0 Hz, 2H), 4.21 (s, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.1, 139.7, 131.4, 128.2, 128.0, 78.1, 72.5, 71.5, 70.2.

*(2-Methylbenzoyl)ferrocene (**3b**)*:[29] red solid; 1.3 g, 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.6 Hz, 1H), 7.38−7.34 (m, 1H), 7.27−7.26 (m, 1H), 7.25−7.23 (m, 1H), 4.75 (t, J = 2.0 Hz, 2H), 4.56 (t, J = 2.0 Hz, 2H), 4.25 (s, 5H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.4, 139.9, 135.6, 130.9, 129.7, 127.4, 124.9, 79.3, 72.5, 71.1, 69.9, 19.8.

*(2-Chlorobenzoyl)ferrocene (**3c**)*:[28] red solid; 1.4 g, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.49 (m, 1H), 7.47−7.44 (m, 1H), 7.42−7.32 (m, 2H), 4.74 (t, J = 2.0 Hz, 2H), 4.60 (t, J = 2.0 Hz, 2H), 4.27 (s, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.7, 139.3, 130.9, 130.7, 130.2, 128.6, 126.2, 78.4, 72.9, 71.1, 70.1.

*(4-Methoxybenzoyl)ferrocene (**3d**)*:[30] red solid; 1.2 g, 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96−7.93 (m, 2H), 6.97−6.95 (m, 2H), 4.90 (t, J = 2.0 Hz, 2H), 4.56 (t, J = 2.0 Hz, 2H), 4.20 (s, 5H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.4, 162.4, 132.3, 130.4, 113.4, 78.7, 72.1, 71.5, 70.1, 55.4.

*(4-Trifluoromethylbenzoyl)ferrocene (**3e**)*:[30] red solid; 0.74 g, 47% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.97 (m, 2H), 7.75−7.73 (m, 2H), 4.88 (t, J = 2.0 Hz, 2H), 4.64 (t, J = 2.0 Hz, 2H), 4.22 (s, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.2, 142.8, 133.4, 133.1, 132.7, 132.4 (q, J = 32.6 Hz), 128.2, 125.4, 125.3, 125.3, 125.2 (q, J = 3.8 Hz), 125.1 (q, J = 270.8 Hz), 122.4, 77.4, 73.1, 71.4, 70.3.

*(1-Naphthoyl)ferrocene (**3f**)*:[6a] red solid; 1.4 g, 76% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 7.6 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.92−7.90 (m, 1H), 7.77 (d, J = 6.8 Hz, 1H), 7.55−7.49 (m, 3H), 4.83 (s, 2H), 4.58 (s, 2H), 4.22 (s, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 201.2, 137.6, 133.7, 130.6, 130.3, 128.3, 126.9, 126.2, 125.9, 125.5, 124.2, 79.7, 72.7, 71.4, 69.9.

*1,1′-Diacetylferrocene (**5a**)*:[15b] red solid; 1.0 g, 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (t, J = 2.0 Hz, 4H), 4.51 (t, J = 2.0 Hz, 4H), 2.35 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 200.9, 80.6, 73.4, 70.8, 27.5.

*1,1′-Dibenzoylferrocene (**5b**)*:[15b] red solid; 1.6 g, 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.77(m, 4H), 7.57−7.52 (m, 2H),

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7.44−7.40 (m, 4H), 4.92 (t, J = 2.0 Hz, 4H), 4.58 (t, J = 2.0 Hz, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.8, 139.0, 131.8, 128.2, 128.0, 79.4, 74.5, 73.0.

Typical Procedure for Asymmetric Hydrogenation. In a 25 mL Schlenk tube were placed $[RuCl_2(benzene)]_2$ (5.0 mg, 0.01 mmol) and the ligand ((*S*)-Xyl-SunPhos, 17.2 mg, 0.022 mmol; (*S*)-SunPhos 15.0 mg, 0.022 mmol). The tube was evacuated and purged with nitrogen three times before addition of freshly distilled and freeze−thaw degassed DMF (3 mL). The resulting mixture was heated at 100 °C for 12 min before it was cooled to room temperature, and then (*S*,*S*)-Daipen (6.8 mg, 0.022 mmol) was added under N_2. The tube was vacuumed and purged with nitrogen three times before it was heated to 40 °C for 4 h. The solvent was removed under vacuum to give the catalyst as a brownish yellow solid. The catalyst was dissolved in degassed *i*-PrOH (4 mL), and then the solution was equally charged into eight vials which contained 0.25 mmol of substrates, *t*-BuOK (5 equiv to catalyst), and 0.5 mL of *i*-PrOH. Then the vials were transferred into 300 mL autoclaves. The autoclaves were purged three times with H_2, and the required pressure of H_2 was set. The contents of the autoclaves were stirred under specified reaction conditions. After cooling to ambient temperature and careful release of hydrogen, the autoclaves were opened and the solvent was evaporated. The enantiomeric excess was determined by HPLC after the residue was passed through a short pad of silica gel column with ethyl acetate.

1-Ferrocenylethanol (**2a**):[6a] yellow solid; mp 76.2−80.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.58−4.52 (m, 1H), 4.22−4.16 (m, 9H), 1.84 (d, J = 4.8 Hz, 1H), 1.44 (d, J = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 94.6, 68.2, 67.8, 67.8, 66.1, 66.0, 65.5, 23.6; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 95/5, 0.6 mL/min, 210 nm) t_1 = 29.2 min, t_2 = 31.8 min; $[\alpha]_D^{25}$ = −20.3° (*c* 0.43, CH_2Cl_2), lit.[6a] $[\alpha]_D^{20}$ = +26.9° (*c* 1.15, CH_2Cl_2) for *S* enantiomer with 99.4% ee.

1-Ferrocenyl-1-propanol (**2b**):[18b] yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.26−4.23 (m, 2H), 4.20−4.16 (m, 8H), 1.94 (d, J = 2.8 Hz, 1H), 1.73−1.62 (m, 2H), 0.94 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 94.0, 70.9, 68.2, 67.7, 67.6, 67.1, 65.1, 30.9, 10.3; HPLC (Chiralcel AS-H column, hexane/*i*-PrOH = 98/2, 0.6 mL/min, 210 nm) t_1 = 13.8 min, t_2 = 14.6 min; $[\alpha]_D^{25}$ = −47.3° (*c* 0.71, CH_2Cl_2), lit.[18b] $[\alpha]_D^{20}$ = −66.5° (*c* 4.9, $CHCl_3$) for *R* enantiomer with 98% ee.

1-Ferrocenyl-1-butanol (**2c**):[31] yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.34−4.30 (m, 1H), 4.24−4.15 (m, 9H), 1.92 (d, J = 3.2 Hz, 1H), 1.69−1.60 (m, 2H), 1.50−1.42 (m, 1H), 1.39−1.32 (m, 1H), 0.92 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 94.4, 69.3, 68.2, 67.8, 67.6, 67.1, 65.1, 40.2, 19.1, 14.0; HPLC (Chiralcel IA-H column, hexane/*i*-PrOH = 95/5, 0.8 mL/min, 210 nm) t_1 = 16.7 min, t_2 = 25.0 min; $[\alpha]_D^{25}$ = −36.2° (*c* 1.22, CH_2Cl_2).

1-Ferrocenyl-1-decanol (**2d**). yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.31−4.28 (m, 1H), 4.25−4.19 (m, 9H), 1.91 (s, 1H), 1.69−1.58 (m, 2H), 1.48−1.40 (m, 1H), 1.34−1.26 (br, 13H), 0.88 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 94.5, 69.6, 68.2, 67.8, 67.6, 67.1, 65.1, 38.1, 31.8, 29.5, 29.3, 25.95, 22.6, 14.1; IR (KBr, cm^{-1}) 3928, 3564, 3445, 3094, 2953, 2924, 2853, 1716, 1647, 1465, 1411, 1378, 1275, 1233, 1105, 1040, 1021, 1001, 816, 721, 508, 485, 443; HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 99.5/0.5, 0.5 mL/min, 210 nm) t_1 = 23.1 min, t_2 = 24.2 min; $[\alpha]_D^{25}$ = −25.0° (*c* 1.03, CH_2Cl_2); HRMS-ESI (*m*/*z*) M^+ calcd for $C_{20}H_{30}FeO$ 342.1646, found 342.1654.

1-Ferrocenyl-4-methyl-1-pentanol (**2h**). yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.28−4.14 (m, 10H), 1.95 (s, 1H), 1.69−1.51 (m, 3H), 1.39−1.28 (m, 1H), 1.23−1.15 (m, 1H), 0.88 (d, J = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 94.6, 69.9, 68.2, 67.8, 67.6, 67.2, 65.1, 36.0, 35.1, 27.9, 22.6, 22.5; IR (KBr, cm^{-1}) 3928, 3564, 3439, 3094, 2953, 2933, 2864, 1647, 1467, 1410, 1384, 1365, 1262, 1233, 1105, 1041, 1020, 1000, 886, 816, 509, 484; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 95/5, 0.8 mL/min, 210 nm) t_1 = 14.9 min, t_2 = 18.3 min; $[\alpha]_D^{25}$ = −32.5° (*c* 0.72, CH_2Cl_2); HRMS-ESI (*m*/*z*) M^+ calcd for $C_{16}H_{22}FeO$ 286.1020, found 286.1012.

Ferrocenylphenylmethanol (**4a**):[6a] yellow solid; mp 77.5−79.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.38 (m, 2H), 7.34−7.31 (m, 2H), 7.27−7.25 (m, 1H), 5.47 (d, J = 3.2 Hz, 1H), 4.23−4.17 (m, 9H), 2.46 (d, J = 3.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.2, 128.1, 127.3, 126.1, 94.0, 71.9, 68.4, 68.0, 67.9, 67.3, 65.9; HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 210 nm) t_1 = 12.7 min, t_2 = 19.1 min; $[\alpha]_D^{25}$ = +77.0° (*c* 0.9, CH_2Cl_2), lit.[6a] $[\alpha]_D^{20}$ = −89.3° (*c* 1.01, CH_2Cl_2) for *R* enantiomer with 89% ee.

Ferrocenyl(2-methylphenyl)methanol (**4b**):[29] yellow solid; mp 106.3−108.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48−7.46 (m, 1H), 7.22−7.10 (m, 3H), 5.61 (d, J = 3.6 Hz, 1H), 4.27 (s, 6H), 4.19 (d, J = 17.3 Hz, 2H), 4.10 (s, 1H), 2.50 (d, J = 3.6 Hz, 1H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.3, 134.9, 130.1, 127.2, 125.8, 125.7, 94.5, 68.3, 68.1, 68.0, 67.7, 67.3, 66.8, 19.1; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 95/5, 0.6 mL/min, 210 nm) t_1 = 25.9 min, t_2 = 27.7 min; $[\alpha]_D^{25}$ = +134.9° (*c* 0.53, CH_2Cl_2), lit.[29] $[\alpha]_D$ = −146.7° (*c* 1.06, $CHCl_3$) for *R* enantiomer with 93% ee.

Ferrocenyl(2-chlorophenyl)methanol (**4c**):[28] yellow solid; mp 119.4−122.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.2 Hz, 1H), 7.31−7.27 (m, 2H), 7.20−7.16 (m, 1H), 5.83 (d, J = 3.2 Hz, 1H), 4.38 (s, 1H), 4.27−4.16 (m, 8H), 2.59 (d, J = 2.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 140.8, 132.1, 129.2, 128.4, 127.4, 126.8, 93.5, 68.4, 68.1, 67.9, 67.8, 67.5, 66.1; HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 95/5, 0.8 mL/min, 210 nm) t_1 = 15.5 min, t_2 = 18.3 min; $[\alpha]_D^{25}$ = +146.1° (*c* 0.76, CH_2Cl_2).

Ferrocenyl(4-methoxyphenyl)methanol (**4d**):[18a] yellow solid; mp 66.2−70.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.28 (m, 2H), 6.87−6.84 (m, 2H), 5.44 (d, J = 3.1 Hz, 1H), 4.24−4.21 (m, 6H), 4.19−4.16 (m, 3H), 3.79 (s, 3H), 2.39 (d, J = 3.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.8, 135.6, 129.0, 127.4, 113.5, 94.2, 71.6, 68.6, 68.4, 68.0, 67.9, 67.2, 65.9, 55.2. (Chiralcel OD-H column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 210 nm) t_1 = 15.3 min, t_2 = 19.0 min; $[\alpha]_D^{25}$ = +44.2° (*c* 0.28, CH_2Cl_2), lit.[18a] $[\alpha]_D^{20}$ = −12.8° (*c* 0.76, CH_2Cl_2) for *R* enantiomer with 60% ee.

Ferrocenyl(4-trifluoromethylphenyl)methanol (**4e**):[32] yellow solid; mp 64.5−68.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 5.49 (d, J = 2.0 Hz, 1H), 4.25−4.23 (m, 7H), 4.19−4.17 (m, 2H), 2.55 (d, J = 2.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 147.1, 129.9, 129.6, 129.3, 129.0 (q, J = 32.3 Hz), 128.2, 126.4, 125.5, 125.2, 125.1, 125.1, 125.1 (q, J = 3.7 Hz), 122.8, 120.1 (q, J = 270.0 Hz), 94.1, 71.3, 70.3, 68.7, 68.6, 67.7, 65.8; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 210 nm) t_1 = 24.9 min, t_2 = 29.8 min; $[\alpha]_D^{25}$ = +70.9° (*c* 0.80, CH_2Cl_2).

Ferrocenyl(1-naphthyl)methanol (**4f**):[6a] yellow solid; mp 158.2−162.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 7.6 Hz, 1H), 7.86−7.84 (m, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 6.8 Hz, 1H), 7.51−7.43 (m, 3H), 6.21 (d, J = 4.0 Hz, 1H), 4.33−4.12 (m, 9H), 2.69 (d, J = 4.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 139.0, 133.6, 130.9, 128.6, 128.1, 125.8, 125.4, 125.3, 123.9, 123.8, 94.2, 68.5, 68.1, 67.8, 67.6, 67.4; HPLC (Chiralcel AS-H column, hexane/*i*-PrOH = 98/2, 0.8 mL/min, 210 nm) t_1 = 23.1 min, t_2 = 24.4 min; $[\alpha]_D^{25}$ = +106.2° (*c* 1.13, CH_2Cl_2), lit.[6a] $[\alpha]_D^{21}$ = −92.69° (*c* 1.02, CH_2Cl_2) with 98% ee.

1-Ferrocenyl-2-phenylethanol (**4g**):[31] yellow solid; mp 68.5−70.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.27 (m, 2H), 7.24−7.17 (m, 3H), 4.60−4.56 (m, 1H), 4.27−4.26 (m, 1H), 4.19−4.06 (m, 8H), 2.95 (d, J = 7.2 Hz, 2H), 2.05 (d, J = 3.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.5, 129.4, 128.2, 126.3, 93.2, 70.8, 68.3, 67.9, 67.7, 67.2, 65.3, 44.9; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 210 nm) t_1 = 18.2 min, t_2 = 24.0 min; $[\alpha]_D^{25}$ = −4.1° (*c* 1.03, CH_2Cl_2).

1-Ferrocenyl-3-phenyl-1-propanol (**4h**):[33] yellow solid; mp 57.8−61.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.26 (m, 2H), 7.23−7.17 (m, 3H), 4.35−4.31 (m, 1H), 4.26 (s, 1H), 4.19 (s, 8H), 2.84−2.77 (m, 1H), 2.74−2.66 (m, 1H), 2.04−1.91 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.9, 128.4, 128.2, 125.7, 93.9, 68.6, 68.2, 67.9, 67.7, 67.0, 65.4, 39.5, 32.1; HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 90/10, 0.8 mL/min, 210 nm) t_1 = 14.0 min, t_2 = 21.3 min; $[\alpha]_D^{25}$ = −8.4° (*c* 0.95, CH_2Cl_2).

1,1′-Bis(1-hydroxyethyl)ferrocene (**6a**):[15b] yellow solid; mp 67.8−69.2 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.63 (q, J = 6.4 Hz, 2H), 4.20−4.15 (m, 8H), 3.11 (d, J = 2.4 Hz, 2H), 1.40 (d, J = 6.4 Hz, 6H);

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$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 95.2, 67.7, 67.6, 66.1, 66.0, 65.6, 25.5; HPLC (Chiralcel IB-H column, hexane/*i*-PrOH = 99/1, 0.6 mL/min, 210 nm) t_1 = 32.5 min, t_2 = 33.6 min (*meso*), t_3 = 37.0 min; $[\alpha]_D^{25}$ = −42.6° (*c* 0.38, $CHCl_3$), lit.[15b] $[\alpha]_D$ = −97.7° (*c* 2.34, $CHCl_3$) for *R,R* enantiomer with >99% ee (*dl*/*meso* = 98.5/1.5).

1,1′-Bis(1-hydroxyphenylmethyl)ferrocene (**6b**):[15b] yellow solid; mp 124.8−128.9 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.20 (m, 10H), 5.58 (s)/5.55 (s, *meso*; 2H total), 4.43−4.11 (m, 8H total), 3.98 (s)/3.87 (s, *meso*, 2H total); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.2, 143.7, 128.3, 128.2, 127.5, 126.2, 93.9, 93.5, 72.7, 71.9, 68.3, 68.2, 67.9, 67.7, 67.2, 66.8, 66.7, 66.4; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 95/5, 1.0 mL/min, 210 nm) t_1 = 25.3 min, t_2 = 33.1 min, t_3 = 36.0 min (*meso*); $[\alpha]_D^{25}$ = +8.6° (*c* 0.39, $CHCl_3$), lit.[18a] $[\alpha]_D^{20}$ = −34.8° (*c* 0.91, CH_2Cl_2) for *R,R* enantiomer with 94% ee.

Typical Procedure for Asymmetric Hydrogenation on a Gram Scale. The $RuCl_2$[(*S*)-Xyl-SunPhos][(*S*)-Daipen] catalyst (6.3 mg, 0.005 mmol) prepared by the above method was dissolved in degassed *i*-PrOH (2 mL) under a nitrogen atmosphere, and then the solution was charged into a 100 mL vessel which contained substrate **1a** (5.72 g, 25.00 mmol), *t*-BuOK (112.0 mg, 1.00 mmol, 20 equiv to catalyst), and 38 mL of degassed *i*-PrOH. Then the container was transferred into 300 mL autoclaves. The autoclaves were purged three times with H_2, and the required pressure of H_2 was set. The contents of the autoclaves were stirred at 30 °C for 30 h. After cooling to ambient temperature and careful release of the hydrogen in the fuming hood, the autoclaves were opened and the solvent was evaporated. The residue was purified by flash column chromatography (PE/EA = 10/1) to afforded the chiral product **2a** (5.72 g, 99% isolated yield, 96.4% ee). The substrates **1d,h** were hydrogenated through a similar procedure. After the crude products were purified by flash column chromatography (PE/EA = 10/1), 479.0 mg of **2d** and 1.31 g of **2h** were obtained in 28% yield (99.4% ee) and 98% yield (98.0% ee), respectively.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01548.

Details of the NMR and HPLC data (PDF)

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Notes

The authors declare no competing financial interest.

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