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A *trans*-chelating bisphosphine possessing only planar chirality and its application to catalytic asymmetric reactions

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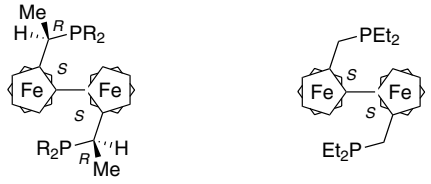
Abstract—A new chiral bisphosphine, (*S*,*S*)-2,2″-bis[(diethylphosphino)methyl]-1,1″-biferrocene [(*S*,*S*)-EtTRAP-H], was synthesized in seven steps in 45% overall yield from ferrocenyloxazoline derived from (*S*)-valinol. The new chiral phosphine has only planar chirality, and is able to form a *trans*-chelate metal complex. (*S*,*S*)-EtTRAP-H is an effective ligand in rhodium-catalyzed asymmetric hydrosilylation of ketones (up to 94% ee). In particular, the hydrosilylation of 2-octanone yielded (*S*)-2-octanol with 77% ee.

1. Introduction

Asymmetric catalysis is an important subject in synthetic organic chemistry.[1] The design of new chiral catalysts is essential for exploring new classes of catalytic asymmetric reactions as well as for achieving high enantioselectivities.[2] Typical chiral catalysts are transition metal complexes modified with optically active organic molecules, which have Lewis basic functional groups, for example, alkoxide, oxazoline, and phosphine.[3] So far, numerous chiral phosphine ligands have been developed and employed for catalytic asymmetric syntheses.[2] Various types of chirality have been utilized for design of chiral phosphines. Most of the chiral phosphines possess a stereogenic center. Many axially chiral ligands, for example, BINAP,[4] have been reported.[5] Planar chirality has frequently appeared in ferrocene-based chiral ligands along with central chirality.[6] Hayashi's ferrocenyl phosphines are typical,[7] with the role of each chiral element being investigated in asymmetric Grignard cross-coupling[8] and aldol reactions of isocyanoacetate.[9] The stereogenic center scarcely affects the enantioselectivity in the former reaction, while the enantioselectivity is controlled by the central chirality in the latter reaction. Chiral ligands, which only possess planar chirality, are relatively rare.[10]

We have designed and synthesized a new family of ferrocene-based chiral bisphosphines, TRAP **1** (Fig. 1).[11] Characteristically, TRAP forms a nine-membered chelate complex with a transition metal and is able to coordinate to a metal atom in *trans*-chelation. The ligands display high enantioselectivities for various catalytic asymmetric reactions, Michael[12] and aldol additions[13] of 2-cyanopropionates, allylation,[14] hydrosilylation of ketones,[15] hydrogenations of olefins[16–18] and indoles,[19] and cycloisomerization of 1,6-enynes.[20] (*R*,*R*)-(*S*,*S*)-TRAP ligands possess two stereogenic centers with an (*R*)-configuration at each α-position of phosphino groups as well as two chiral planes with (*S*)-configurations on the biferrocene backbone, due to the



(*R*,*R*)-(*S*,*S*)-TRAP (**1**)
1a: R = Et (EtTRAP)
1b: R = Bu (BuTRAP)

(*S*,*S*)-EtTRAP-H (**2**)

Figure 1. Structures of TRAP and TRAP-H.

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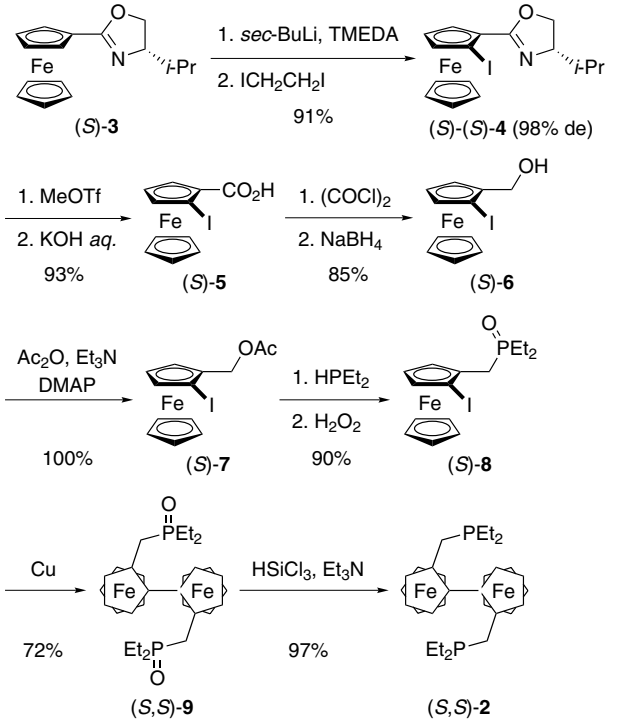
unsymmetrical disubstitution on the cyclopentadienes. We synthesized a new optically active phosphine, (*S*,*S*)-2,2″-bis[(diethylphosphino)methyl]-1,1″-biferrocene **2** [(*S*,*S*)-EtTRAP-H], in order to clarify the role of the central chirality of **1**. The TRAP-H ligand only has planar chirality for lack of methyl groups on the α-positions of diethylphosphino groups. Herein we describe the synthesis of **2** and its application to catalytic asymmetric hydrogenation of enamides and hydrosilylation of ketones. EtTRAP-H exhibited higher enantioselectivity for the asymmetric hydrosilylation than Et- or BuTRAP.[21] To the best of our knowledge, EtTRAP-H provides the highest stereoselectivity recorded to date for catalytic asymmetric reduction of linear 2-alkanone, which is one of the more challenging substrates for enantioselective reduction with asymmetric catalysis.

2. Results and discussion

2.1. Synthesis of (*S*,*S*)-EtTRAP-H

The new chiral phosphine (*S*,*S*)-EtTRAP-H was prepared from optically active ferrocenyloxazoline (*S*)-**3** derived from (*S*)-valinol (Scheme 1).[22] Diastereoselective *ortho*-lithiation of (*S*)-**3** was carried out with *sec*-butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine (TMEDA) according to Sammakia's procedure.[23] Reaction of the resulting lithioferrocene with 1,2-diiodoethane gave iodoferrocene **4** with (*S*)-planar chirality. Stereoselectivity of the *ortho*-lithiation was determined to be 98% de by ^{1}H NMR analysis of the crude product. After treatment of **4** with methyl trifluoromethanesulfonate, the resulting oxazolinium salt was hydrolyzed with aqueous KOH to give ferrocenecarboxylic acid (*S*)-**5** possessing only planar chirality. We next attempted to convert (*S*)-**5** into primary alcohol (*S*)-**6**, but an undesired deiodination side-product was yielded mainly by the use of $LiAlH_4$ and the BH_3·THF, which are typical reducing agents for carboxylic acids to primary alcohols. Treatment with $NaBH_4$ after transformation of (*S*)-**5** into acyl chloride gave the desired primary alcohol (*S*)-**6** with no formation of the deiodinated product. Esterification of (*S*)-**6** with acetic anhydride gave acetate (*S*)-**7** quantitatively. Nucleophilic substitution of the acetoxy group with diethylphosphine was conducted in acetic acid.[24] The resulting tertiary phosphine was converted into the corresponding phosphine oxide (*S*)-**8** by H_2O_2 in acetone, because the unprotected phosphine was expected to inhibit the following Ullmann coupling as well as to be readily oxidized by air. The homocoupling of (*S*)-**8** was performed with activated copper powder without the use of solvent, producing C_2-symmetric biferrocene (*S*,*S*)-**9**. Finally, the reduction of phosphine oxide **9** with $HSiCl_3$–Et_3N gave (*S*,*S*)-EtTRAP-H **2**. The new chiral phosphine (*S*,*S*)-**2** was obtained from (*S*)-**3** via seven steps in 45% overall yield.



Scheme 1. Synthesis of EtTRAP-H **2**.

EtTRAP-H as well as other TRAP ligands can be handled in the air and can be stored for over a year under argon in a freezer. The new peralkylphosphine **2**, however, is less stable to air oxidation when compared with **1a**. We previously reported that the ^{13}C resonances for α and β-carbons of the phosphorus atom of **1a** split into more than two lines because of virtual through-space ^{31}P–^{31}P coupling.[11c] The through-space coupling suggests the proximity of the two phosphorus atoms of **1a**. In contrast to **1a**, five simple doublet peaks were observed as the resonances of the 13-carbons α and β to the phosphorus atoms of **2** (Fig. 2). This observation indicates the remarkable difference between the most favorable conformations of **1a** and **2**: two phosphorus atoms in **2** cannot be located close each other.

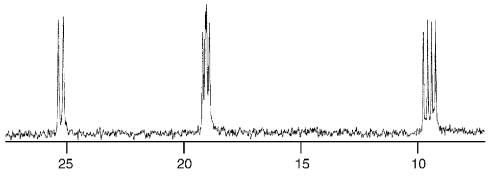


Figure 2. ^{13}C{^{1}H} NMR spectrum (75 MHz, $CDCl_3$) of **2** (alkyl region).

2.2. Rhodium complex of EtTRAP-H

To confirm whether EtTRAP-H **2** is able to form a *trans*-chelate complex or not, we conducted the reaction of the bisphosphine with 0.5 equivalent of $[RhCl(CO)_2]_2$ in CD_2Cl_2, and monitored the reaction by ^{31}P NMR measurement. The reaction went to completion immediately, forming a single rhodium complex, RhCl(CO) **2**, whose ^{31}P NMR spectrum exhibited a pair of double

doublet peaks at δ 20.8 and 26.5 ppm with $J_{P-P} = 340$ Hz (Fig. 3). The large P–P spin coupling constant is characteristic of *trans*-bis(phosphine)-metal complexes. This observation indicates that ligand **2**, as well as other TRAP ligands, is able to coordinate to a transition metal atom in *trans*-chelation.

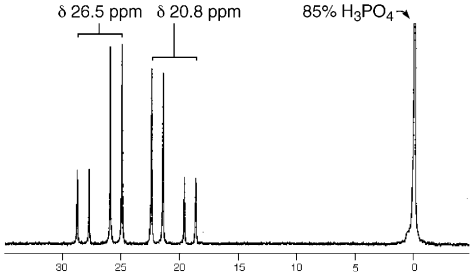
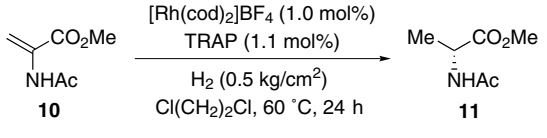


Figure 3. $^{31}P\{^1H\}$ NMR spectrum (121.5 MHz, CD_2Cl_2, 85% H_3PO_4) of *trans*-[RhCl(CO){(*S*,*S*)-EtTRAP-H}].

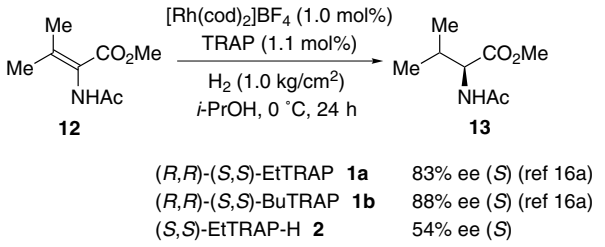
2.3. Catalytic asymmetric hydrogenations of enamides using EtTRAP-H

First, we evaluated the new chiral ligand, EtTRAP-H, for the rhodium-catalyzed asymmetric hydrogenation of methyl 2-(*N*-acetylamino)acrylate **10** (Eq. 1). The hydrogenation of **10** using **2** was conducted in 1,2-dichloroethane at 60 °C and under 0.5 kg/cm^2 of partial hydrogen pressure for 24 h. The EtTRAP-H-$[Rh(cod)_2]BF_4$ complex catalyzed the hydrogenation of **10**, giving product **11** in high yield (97%). However, the enantiomeric excess of **11** was significantly low (45% ee) when compared with the enantioselectivity of the hydrogenation using **1a** (96% ee).[16a]



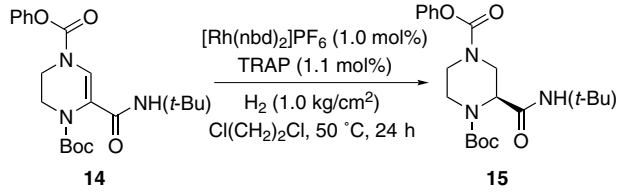
(1)

Enantioselective hydrogenation of β,β-disubstituted α-(acetamido)acrylates offers an efficient and straightforward synthetic approach to optically active β-branched α-amino acids. However, steric congestion of the tetrasubstituted olefins has made hydrogenation difficult.[25] Only a few successful examples have been reported for this asymmetric reaction so far.[26] Et- and BuTRAP are effective in the asymmetric hydrogenation of various β,β-disubstituted α-(acetamido)acrylates.[16] Hydrogenation of **12** with EtTRAP-H–rhodium catalyst was conducted in 2-propanol at 0 °C and under 1.0 kg/cm^2 of H_2 pressure for 24 h (Eq. 2). Catalytic hydrogenation gave the desired product **13** in 87% isolated yield, although the ee value was moderate.



(2)

Piperazine-2-carboxamide is a constituent of Merck HIV protease inhibitor Crixivan.[27] Some TRAP ligands showed high enantioselectivities for the hydrogenations of 1,4,5,6-tetrahydropyrazine-2-carboxamides to afford the optically active piperazine.[17,28] (*R*,*R*)-(*S*,*S*)-*i*-Bu-TRAP– and MeTRAP–rhodium catalyst gave piperazine-2-carboxamide with 97% ee (*S*) and 85% ee (*R*), respectively. The asymmetric hydrogenation of **14** using EtTRAP was less enantioselective than that with *i*-Bu- or MeTRAP, giving 35% ee of (*S*)-**15**. Hydrogenation of **14** with EtTRAP-H–rhodium catalyst was conducted under the conditions indicated in Eq. 3. In contrast to the reactions of acyclic α-(acetamido)acrylates, **10** and **12**, EtTRAP-H showed higher enantioselectivity than **1a**. However, ligand **2** was less effective than *i*-Bu- and MeTRAP.



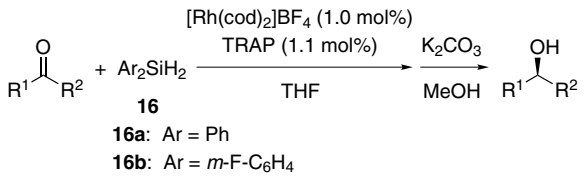
(3)

A divergent effect of the stereogenic centers of TRAP ligand was observed in the asymmetric hydrogenation of each substrate. In every case, the sense of asymmetric induction by EtTRAP-H ligand was the same as that by EtTRAP. Employment of EtTRAP-H never caused the formation of a racemic product, while the reaction proceeded with moderate to high enantioselectivity with the EtTRAP ligand. These findings suggest that stereodetermining step in the asymmetric hydrogenations using **1** was controlled predominantly by the planar chirality. The central chirality of **1** may play an important role in tuning of the chiral reaction field on asymmetric catalyst.

2.4. Catalytic asymmetric hydrosilylation of ketones using EtTRAP-H

We reported previously that rhodium complexes bearing Et- and BuTRAP are useful chiral catalysts in the enantioselective reduction of ketones with diphenylsilane **16a** (hydrosilylation).[15,29] We evaluated

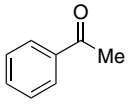
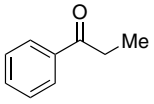
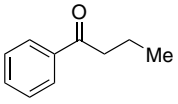
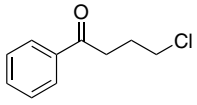
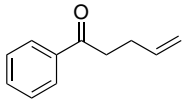
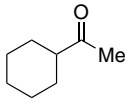
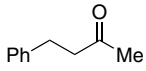
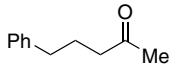
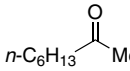
(*S*,*S*)-EtTRAP-H **2** for the asymmetric hydrosilylation of ketones (Eq. 4). The hydrosilylation of acetophenone using **2** was conducted in THF at −40 °C (Table 1, entry 3). The reaction was completed within 4 h and produced (*S*)-1-phenylethanol with 94% ee in 89% isolated yield. Using **2** enhanced both the reaction rate and enantioselectivity (entries 1, 2 vs 3). A significant improvement in reaction rate as well as enantioselectivity was obtained by use of **2** in the reaction of propiophenone (entry 5), which was hard to reduce with high ee by BuTRAP–rhodium catalyzed hydrosilylation (entry 4). These findings suggest that the methyl groups at the stereogenic centers of ligand **1** hinder the approach of propiophenone to BuTRAP–rhodium catalyst sterically. Bis(3-fluorophenyl)silane **16b** was preferable to **16a** for the asymmetric reduction of the aryl alkyl ketones (entries 5–9). Terminal chloro and olefin groups on the ketonic substrates were tolerable to the present hydrosilylation conditions.



(4)

The asymmetric hydrosilylation using **2** was applicable to the enantioselective reductions of dialkyl ketones, which are more challenging substrates than aryl alkyl ketones. In particular, the asymmetric reduction of linear 2-alkanones is regarded as difficult for providing the corresponding 2-alkanols with high enantiomeric excesses. EtTRAP-H was superior to TRAP ligands in the asymmetric hydrosilylation of dialkyl ketones (entries 10–17). Cyclohexyl methyl ketone was hydrosilylated

Table 1. Asymmetric hydrosilylation of ketones using (*S*,*S*)-EtTRAP-H **2**[a]

Entry	Ketone	Temperature (°C)	Time (h)	Yield (%)[b]	Ee[c]
1[d]		−40	24	90	85 (Ref. 15b)
2[e]		−40	11	89	92 (Ref. 15b)
3		−40	4	89	94
4[e]		−10	48	73	62 (Ref. 15b)
5		−30	24	96	80
6[f]		−40	24	99	88
7[f]		−40	24	93	89
8[f]		−40	24	99	88
9[f]		−40	24	90	89
10[d,g]		−40	24	76	81 (Ref. 15b)
11		−40	4	90	89
12[e,g]		−40	30	93	70 (Ref. 15b)
13		−40	48	94	81
14[e,g]		−40	20	93	60 (Ref. 15b)
15		−40	24	99	76
16[d,g]		−30	24	88	65 (Ref. 15b)
17		−50	48	82	77

[a] Reactions were conducted in THF with **16a** as a reducing agent unless otherwise noted. The ratio of ketone/**16a**/[Rh(cod)$_2$]BF$_4$/**2** was 100:150:1:1.1.
[b] Isolated yield.
[c] Determined by chiral HPLC or GLC.
[d] Ligand **1a** was used.
[e] Ligand **1b** was used.
[f] Compound **16b** was used as a reducing agent.
[g] The reactions were conducted in DME.

with 89% ee (entry 11). It is noteworthy that the hydrosilylation of 2-octanone afforded (*S*)-2-octanol with 77% ee by the use of EtTRAP-H (entry 17). To the best of our knowledge, the ee value is the highest yet attained in the catalytic asymmetric reduction of linear 2-alkanones.[30–32] Employment of **16b**, which was effective in the hydrosilylation of aryl alkyl ketones, failed to improve the enantioselectivity (74% ee). Primary alkyl methyl ketones, which have a phenyl group at the β and γ-positions, were also reduced with good enantioselectivities by hydrosilylation using the EtTRAP-H ligand (entries 13, 15).[33]

3. Conclusion

A *trans*-chelating optically active diphosphine, (*S*,*S*)-EtTRAP-H **2**, was synthesized via seven steps in 45% overall yield from enantiomerically pure ferrocenyloxazoline derived from (*S*)-valinol and ferrocenecarboxylic acid. The new phosphine only had planar chirality and was proven able to form a *trans*-chelate complex. The new chiral phosphine **2** was evaluated for the asymmetric hydrogenation of enamides and hydrosilylation of ketones. In the former reactions, the use of **2** was less effective than those of TRAPs **1**, which possess stereogenic centers. On the other hand, ligand **2** was superior to **1** in the hydrosilylation of ketones. It is noteworthy that the highest ee value (77% ee) in the asymmetric reduction of linear 2-alkanone was recorded by the EtTRAP-H–rhodium catalyst. In all cases, the lack of a central chirality did not cause a drastic change in enantioselectivity. These observations suggest that the stereodetermining step in the asymmetric reaction using TRAP was dominantly controlled by the planar chirality. However, the central chirality of **1** may play an important role in tuning of the chiral reaction field on asymmetric catalyst.

4. Experimental

4.1. General

Melting points were measured with a Yamato-MP apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 243 polarimeter. ^{1}H, ^{31}P, and ^{13}C NMR spectra were measured with a Varian Gemini-2000 spectrometer (7.0 T magnet) at room temperature. Flash column chromatographies and preparative thin-layer chromatographies were performed with silica gel 60 (230–400 mesh, Merck) and silica gel 60 PF_{254} (Merck), respectively.

All reactions were conducted under a N_2 atmosphere except for the conversion of **4** into **5** and the oxidation of phosphine in the conversion of **7** into **8**. Solvents were distilled from the indicated drying agents: hexane (Na/benzophenone); benzene (Na/benzophenone); THF (Na/benzophenone); CH_2Cl_2 (P_2O_5); 1,2-dichloroethane (CaH_2); 2-propanol (CaH_2), Et_2O (Na/benzophenone). Diethylphosphine[34] and **3**[22] were prepared according to the literature procedures. Copper powder (300 mesh) was purchased from Lancaster.

4.1.1. (*S*)-1-Iodo-2-[(*S*)-4,5-dihydro-4-isopropyl-2-oxazolyl]ferrocene 4. A solution of *sec*-butyl lithium in cyclohexane (1.16 M, 22 mL, 26 mmol) was added dropwise to a mixture of [(*S*)-4,5-dihydro-4-isopropyl-2-oxazolyl]ferrocene **3** (5.94 g, 20 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (3.92 mL, 26 mmol) in hexane (400 mL) at −78 °C for 20 min. The mixture was stirred at −78 °C for 2 h, and then allowed to warm to 0 °C. A solution of 1,2-diiodoethane (7.89 g, 28 mmol) in THF (28 mL) was added dropwise to the reaction mixture at −78 °C for 20 min. The resulting mixture was allowed to warm to room temperature. After saturated $Na_2S_2O_3$ aq was carefully added, the mixture was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc), giving 7.64 g (91%) of (*S*)-(*S*)-**4**: Orange oil; $[\alpha]_D^{20} = -131.0$ (*c* 0.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.99 (d, $J = 6.6$ Hz, 3H), 1.06 (d, $J = 6.6$ Hz, 3H), 1.87 (octet, $J = 6.6$ Hz, 1H), 4.00–4.15 (m, 2H), 4.21 (s, 5H), 4.30 (dd, $J = 7.8$, 9.8 Hz, 1H), 4.36 (t, $J = 2.7$ Hz, 1H), 4.62 (dd, $J = 1.6$, 2.7 Hz, 1H), 4.73 (dd, $J = 1.6$, 2.7 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 18.1, 18.6, 32.5, 38.8, 69.3, 69.5, 70.9, 72.6, 78.4, 163.8; Anal. Calcd for $C_{16}H_{18}NOFeI$: C, 45.42; H, 4.29; N, 3.31. Found: C, 45.21; H, 4.19; N, 3.04.

4.1.2. (*S*)-2-Iodoferrocenecarboxylic acid 5.[35] Methyl trifluoromethanesulfonate (5.97 g, 36 mmol) was added to a solution of (*S*,*S*)-**4** (7.64 g, 18 mmol) in CH_2Cl_2 (36 mL) at 0 °C. After 1 h, the mixture was concentrated under reduced pressure. The residue was dissolved in EtOH (36 mL) and 10% KOH aq (36 mL), and refluxed for 24 h. The resulting mixture was diluted with water (100 mL) and washed with Et_2O (100 mL). The aqueous layer was filtered through a Celite pad, acidified to pH 1 with concd HCl, and extracted twice with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was suspended in hexane and 6.01 g (93%) of (*S*)-**5** separated from the suspension by filtration: Orange powder; mp 172–173 °C (decomp.); $[\alpha]_D^{20} = -64.5$ (*c* 2.17, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 4.29 (s, 5H), 4.52 (t, $J = 2.7$ Hz, 1H), 4.77 (dd, $J = 1.7$, 2.7 Hz, 1H), 4.95 (dd, $J = 1.7$, 2.7 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 39.5, 69.6, 71.0, 72.9, 73.1, 80.5, 176.2.

4.1.3. (*S*)-(2-Iodoferrocenyl)methanol 6.[36] Oxalyl chloride (3.14 g, 25 mmol) and *N*,*N*-dimethylformamide (9.6 μL, 0.12 mmol) were added to a solution of (*S*)-**5** (4.42 g, 12.4 mmol) in CH_2Cl_2 (25 mL). The mixture was stirred at room temperature until the evolution of CO and CO_2 ceased (1 h), after which it was concentrated under reduced pressure. The residue was dissolved in THF (25 mL) and then sodium borohydride (1.03 g, 28 mmol) added to the solution at 0 °C. After 1 h, the

mixture was allowed to warm to room temperature and stirred for 11 h. The reaction was carefully quenched with saturated NH_4Cl aq at 0 °C. The mixture was filtered through a Celite pad and extracted twice with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc), giving 3.59 g (85%) of (*S*)-**6**: Yellow solid; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.62 (t, $J = 6.0$ Hz, 1H), 4.17 (s, 5H), 4.24 (t, $J = 2.6$ Hz, 1H), 4.33 (dd, $J = 1.4$, 2.6 Hz, 1H), 4.38 (dd, $J = 6.0$, 12.5 Hz, 1H), 4.47 (dd, $J = 1.4$, 2.6 Hz, 1H), 4.50 (dd, $J = 6.0$, 12.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 43.7, 61.3, 67.7, 69.0, 71.3, 75.1, 88.2. The enantiomeric excess of **6** was determined to be 99.1% ee by HPLC analysis with a chiral stationary phase column, CHIRALCEL OJ (4.6 mm $\phi \times 250$ mm): hexane/2-propanol = 96:4, 0.5 mL/min flow, at 35 °C, UV 254 nm detection, (*R*) $t_1 = 37.7$ min, (*S*) $t_2 = 43.4$ min.

4.1.4. (*S*)-(2-Iodoferrocenyl)methyl acetate 7. Acetic anhydride (612 mg, 6.0 mmol), triethylamine (658 mg, 6.5 mmol), and 4-(dimethylamino)pyridine (6.1 mg, 50 μmol) were added to a solution of (*S*)-**6** (1.71 g, 5.0 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at room temperature for 1 h and then saturated $NaHCO_3$ aq added. The resulting mixture was extracted twice with EtOAc. The combined organic layer was washed with brine, was dried Na_2SO_4 and evaporated to give 1.92 g (100%) of (*S*)-**7**: Orange oil; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.06 (s, 3H), 4.17 (s, 5H), 4.27 (t, $J = 2.6$ Hz, 1H), 4.36 (dd, $J = 1.4$, 2.6 Hz, 1H), 4.49 (dd, $J = 1.4$, 2.6 Hz, 1H), 4.87 (d, $J = 12.0$ Hz, 1H), 5.04 (d, $J = 12.0$ Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 20.8, 44.5, 62.9, 69.0, 69.6, 71.5, 75.5, 82.7, 170.9.

4.1.5. (*S*)-Diethyl[(2-iodoferrocenyl)methyl]phosphine oxide 8. Diethylphosphine (849 mg, 9.4 mmol) was added to a solution of (*S*)-**7** (1.81 g, 4.7 mmol) in acetic acid (50 mL) degassed by two freeze-thaw cycles. The mixture was stirred at 80 °C for 30 min. After the solvent and excess diethylphosphine were removed in vacuo, the residue was dissolved in acetone (20 mL) and then 30% H_2O_2 aq (2.0 mL) carefully added to the mixture at 0 °C. After 5 min, excess H_2O_2 was carefully decomposed with saturated $Na_2S_2O_3$ aq. The mixture was diluted with water and was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc), giving 1.82 g (90%) of (*S*)-**8**: Orange oil; $[\alpha]_D^{20} = +13.0$ (*c* 0.61, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.03 (dt, $J = 16.5$, 7.7 Hz, 3H), 1.16 (dt, $J = 16.5$, 7.8 Hz, 3H), 1.44–1.58 (m, 2H), 1.63–1.77 (m, 2H), 2.90 (dd, $J = 9.0$, 15.2 Hz, 1H), 3.02 (dd, $J = 15.2$, 17.1 Hz, 1H), 4.09 (s, 5H), 4.23 (t, $J = 2.6$ Hz, 1H), 4.36–4.41 (m, 1H), 4.43–4.48 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 5.3 (d, $J = 6$ Hz), 5.8 (d, $J = 6$ Hz), 19.2 (d, $J = 67$ Hz), 20.8 (d, $J = 65$ Hz), 30.2 (d, $J = 59$ Hz), 45.9, 67.6, 69.4, 72.0, 74.3, 81.4; $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$, 85% H_3PO_4) δ 48.2.

4.1.6. (*S*,*S*)-2,2″-Bis[(diethylphosphinyl)methyl]-1,1″-biferrocene 9. Copper powder (15 g)[37] was shaken with iodine (1.5 g) in acetone until the brown color of iodine disappeared, and then successively washed with acetone, acetone/concd HCl = 1/1, and then acetone. The activated copper powder was dried in vacuo.[38] The freshly activated copper powder (13.1 g, 206 mg-atom) was added to a solution of (*S*)-**8** (1.77 g, 4.1 mmol) in CH_2Cl_2 (10 mL). Immediately, the mixture evaporated in vacuo. The mixture was heated at 80 °C for 24 h under an argon atmosphere. The mixture was dissolved in EtOAc, filtered through a Celite pad and evaporated. The residue was purified by flash column chromatography on silica gel (EtOAc/diethylamine), giving an orange solid. The orange solid was recrystallized from CH_2Cl_2/EtOAc/hexane, giving 895 mg (72%) of (*S*,*S*)-**9**: Orange solid; $[\alpha]_D^{20} = -773.7$ (*c* 0.49, $CHCl_3$); mp 160–165 °C (decomp.); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.00 (dt, $J = 16.5$, 7.8 Hz, 3H), 1.03 (dt, $J = 16.5$, 7.7 Hz, 3H), 1.32–1.65 (m, 4H), 2.68 (dd, $J = 11.4$, 15.6 Hz, 1H), 2.87 (dd, $J = 14.7$, 15.6 Hz, 1H), 4.30 (s, 5H), 4.32 (t, $J = 2.5$ Hz, 1H), 4.47 (d, $J = 2.5$ Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 5.6 (d, $J = 6$ Hz), 5.7, 19.9 (d, $J = 65$ Hz), 20.4 (d, $J = 66$ Hz), 27.5 (d, $J = 62$ Hz), 67.2, 69.1, 70.3, 79.9, 84.6 (d, $J = 5$ Hz); $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$, 85% H_3PO_4) δ 49.1.

4.1.7. (*S*,*S*)-2,2″-Bis[(diethylphosphino)methyl]-1,1″-biferrocene 2 [(*S*,*S*)-EtTRAP-H]. Trichlorosilane (400 mg, 3.0 mmol) was added at 0 °C to a mixture of (*S*,*S*)-**9** (303 mg, 0.50 mmol) and triethylamine (410 mg, 4.0 mmol) in benzene (2.5 mL) in a glass tube. The tube was cooled to −78 °C and sealed in vacuo. The mixture was heated at 100 °C for 10 h. After being cooled to −78 °C, the tube was opened. The excess trichlorosilane was carefully decomposed with 15% NaOH aq. The resulting mixture was filtered through a Celite pad and extracted twice with benzene. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by a short column chromatography on activated alumina (benzene/Et_2O = 10/1), giving 278 mg (97%) of (*S*,*S*)-**2**: Orange oil; $[\alpha]_D^{24} = -750.2$ (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 0.81–1.14 (m, 12H), 1.14–1.33 (m, 8H), 2.28 (dd, $J = 2.3$, 14.9 Hz, 1H), 2.37 (d, $J = 14.9$ Hz, 1H), 4.19 (s, 2H), 4.27 (s, 5H), 4.4 (s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 9.3 (d, $J = 13$ Hz), 9.7 (d, $J = 14$ Hz), 19.0 (d, $J = 13$ Hz), 19.1 (d, $J = 12$ Hz), 25.2 (d, $J = 15$ Hz), 66.0, 68.5 (d, $J = 7$ Hz), 69.7, 70.5, 84.6, 86.8 (d, $J = 12$ Hz); $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$, 85% H_3PO_4) δ −17.7.

4.1.8. ^{31}P NMR study for the reaction of EtTRAP-H with $[RhCl(CO)_2]_2$. $[RhCl(CO)_2]_2$ (1.94 mg, 5.0 μmol) was added to a solution of **2** (5.75 mg, 10 μmol) in CD_2Cl_2 (0.7 mL) at room temperature. After 10 min, the resulting solution was transferred to an NMR tube equipped

with a septum rubber. $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$, 85% H_3PO_4) δ 20.8 (dd, $J_{P-Rh} = 119$ Hz, $J_{P-P} = 340$ Hz), 26.5 (dd, $J_{P-Rh} = 120$ Hz, $J_{P-P} = 340$ Hz).

4.1.9. Catalytic asymmetric hydrogenation of 10. A solution of $[Rh(cod)_2]BF_4$ (2.0 mg, 5.0 μmol) and (*S*,*S*)-**2** (3.2 mg, 5.6 μmol) in 1,2-dichloroethane (0.5 mL) was stirred at room temperature for 10 min and then **10** (71.6 mg, 0.50 mmol) added. Immediately, the flask was cooled to −78 °C, repeatedly evacuated and filled with H_2–N_2 1:1 mixture. The reaction mixture was stirred at 60 °C for 24 h. After the solvent had evaporated, the residue was passed through a short column chromatography on silica gel (hexane/EtOAc = 1:3), giving 70.7 mg (97%) of **11**: ^1H NMR (200 MHz, $CDCl_3$, TMS) δ 1.41 (d, $J = 7.1$ Hz, 3H), 2.02 (s, 3H), 3.76 (s, 3H), 4.59 (quintet, $J = 7.3$ Hz, 1H), 6.08 (br d, 1H). The enantiomeric excess of **11** was determined to be 45% ee (*R*) by HPLC analysis with a chiral stationary phase column, SUMICHIRAL OA-3000 (4.0 mm $\phi \times 250$ mm): hexane/1,2-dichloroethane/ethanol = 100:20:1, 1.0 mL/min flow, at 35 °C, UV 230 nm detection, (*R*) $t_1 = 20.0$ min, (*S*) $t_2 = 25.1$ min.

4.1.10. Catalytic asymmetric hydrogenation of 12. A solution of $[Rh(cod)_2]BF_4$ (2.0 mg, 5.0 μmol) and (*S*,*S*)-**2** (3.2 mg, 5.6 μmol) in 2-propanol (0.5 mL) was stirred at room temperature for 10 min and **12** (85.6 mg, 0.50 mmol) then added. Immediately, the flask was cooled to −78 °C, repeatedly evacuated and filled with H_2. The reaction mixture was stirred at 0 °C for 24 h. After the solvent had evaporated, the residue was passed through a short column chromatography on silica gel (hexane/EtOAc = 1:3), giving 75.5 mg (87%) of **13**: ^1H NMR (200 MHz, $CDCl_3$, TMS) δ 0.91 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 2,05 (s, 3H), 2.15 (double septet, $J = 5.0$, 6.6 Hz, 1H), 3.75 (s, 3H), 4.57 (dd, $J = 5.0$, 8.9 Hz, 1H), 5.96 (br d, 1H). The enantiomeric excess of **13** was determined to be 54% ee (*S*) by HPLC analysis with a chiral stationary phase column, SUMICHIRAL OA-3000 (4.0 mm $\phi \times 250$ mm): hexane/1,2-dichloroethane/ethanol = 100:20:1, 1.0 mL/min flow, at 35 °C, UV 230 nm detection, (*R*) $t_1 = 11.2$ min, (*S*) $t_2 = 15.9$ min.

4.1.11. Catalytic asymmetric hydrogenation of 14. A solution of $[Rh(nbd)_2]PF_6$ (1.1 mg, 2.5 μmol) and (*S*,*S*)-**2** (1.6 mg, 2.8 μmol) in 1,2-dichloroethane (1.0 mL) was stirred at room temperature for 20 min and **14** (100.4 mg, 0.25 mmol) then added. Immediately, the flask was cooled to −78 °C, repeatedly evacuated and filled with H_2. The reaction mixture was stirred at 50 °C for 24 h. After the solvent had evaporated, the residue was passed through a short column chromatography on silica gel (hexane/EtOAc = 1:3), giving 93.2 mg (92%) of **15**: ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.35 (s, 9H), 1.51 (s, 9H), 3.02–3.43 (br m, 3H), 3.84–4.10 (br m, 2H), 4.32–4.82 (br m, 2H), 5.93 (br s, 1H), 7.04–7.24 (m, 3H), 7.35 (t, 2H). The enantiomeric excess of **15** was determined to be 57% ee (*S*) by HPLC analysis with a chiral stationary phase column, SUMICHIRAL OA-2000 (4.6 mm $\phi \times 250$ mm): hexane/2-propanol/methanol = 90/10/0.5, 1.0 mL/min flow, at 35 °C, UV 254 nm detection, (*S*) $t_1 = 23.3$ min, (*R*) $t_2 = 26.0$ min.

4.1.12. Bis(3-fluorophenyl)silane 16b. 3-Fluorophenylmagnesium bromide was prepared from 3-bromofluorobenzene (9.63 g, 55 mmol) and magnesium turnings (55 mg-atom) in THF. The Grignard reagent was added dropwise to a solution of tetrachlorosilane (4.24 g, 25 mmol) in THF (25 mL) at 40 °C for 1 h. After being stirred for 2 h, the resulting mixture was added dropwise to a suspension of lithium aluminum hydride (1.42 g, 37 mmol) in Et_2O (20 mL) at room temperature for 1 h. After 16 h, the mixture was carefully added to saturated NH_4Cl aq (100 mL) at 0 °C, filtered through a Celite pad and extracted with Et_2O. The organic layer was dried over $CaSO_4$ and was evaporated. The residue was purified by vacuum distillation (0.3 mmHg), giving 3.26 g (59%) of **16b**: Colorless oil; ^1H NMR (200 MHz, $CDCl_3$, TMS) δ 4.91 (s, 2H), 7.04–7.45 (m, 8H).

4.1.13. General procedure for catalytic asymmetric hydrosilylation of ketones. A solution of $[Rh(cod)_2]BF_4$ (2.0 mg, 5.0 μmol) and **2** (3.2 mg, 5.6 μmol) in THF (0.5 mL) was stirred at room temperature for 10 min. Ketone (0.50 mmol) and **16** (0.75 mmol) were added to the mixture at the temperature indicated in Table 1. After 24 or 48 h, a solution of K_2CO_3 (0.5 mg) in MeOH (0.5 mL) was added to the resulting mixture. The mixture was stirred at room temperature for 4 h and evaporated. The residue was purified by preparative thin-layer chromatography or by medium-pressure liquid chromatography after passing through a short column chromatography on silica gel (hexane/EtOAc).

4.1.13.1. 1-Phenylethanol (Table 1, entry 3). ^1H NMR (200 MHz, $CDCl_3$, TMS) δ 1.48 (d, $J = 6.4$ Hz, 3H), 1.98 (br s, 1H), 4.87 (q, $J = 6.4$ Hz, 1H), 7.19–7.41 (m, 5H). The enantiomeric excess of the product was determined by GLC analysis with a chiral stationary phase column, Chiraldex G-TA (0.25 mm $\phi \times 30$ m): at 95 °C, (*S*) $t_1 = 9.8$ min, (*R*) $t_2 = 10.6$ min.

4.1.13.2. 1-Phenylpropanol (Table 1, entries 5 and 6). ^1H NMR (200 MHz, $CDCl_3$, TMS) δ 0.91 (t, $J = 7.4$ Hz, 3H), 1.61–1.91 (m, 2H), 1.95 (br s, 1H), 4.58 (t, $J = 6.6$ Hz, 1H), 7.20–7.42 (m, 5H). The enantiomeric excess of the product was determined by HPLC analysis with a chiral stationary phase column, CHIRALCEL OB-H (4.6 mm $\phi \times 250$ mm): hexane/2-propanol = 9:1, 0.5 mL/min flow, at 35 °C, UV 254 nm detection, (*S*) $t_1 = 11.8$ min, (*R*) $t_2 = 13.5$ min.

4.1.13.3. 1-Phenylbutanol (Table 1, entry 7). ^1H NMR (200 MHz, $CDCl_3$, TMS) δ 0.93 (t, $J = 7.2$ Hz, 3H), 1.20–1.92 (m, 5H), 4.69 (dd, $J = 5.9$, 7.4 Hz, 1H), 7.22–7.48 (m, 5H). The enantiomeric excess of the product

was determined by HPLC analysis with a chiral stationary phase column, CHIRALCEL OB-H (4.6 mm $\phi \times 250$ mm): hexane/2-propanol = 96:4, 0.5 mL/min flow, at 35 °C, UV 254 nm detection, (*S*) $t_1 = 14.4$ min, (*R*) $t_2 = 16.6$ min.

4.1.13.4. 4-Chloro-1-phenylbutanol (Table 1, entry 8). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.57 (br s, 1H), 1.70–2.09 (m, 4H), 3.48–3.67 (m, 2H), 4.67–4.78 (m, 1H), 7.22–7.45 (m, 5H). The enantiomeric excess of the product was determined by HPLC analysis with a chiral stationary phase column, CHIRALCEL OD-H (4.6 mm $\phi \times 250$ mm): hexane/2-propanol = 96:4, 0.5 mL/min flow, at 35 °C, UV 254 nm detection, (*S*) $t_1 = 31.9$ min, (*R*) $t_2 = 34.2$ min.

4.1.13.5. 1-Phenyl-4-pentenol (Table 1, entry 9). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.65–2.27 (m, 5H), 4.71 (dd, $J = 5.7$, 7.4 Hz, 1H), 4.95–5.12 (m, 2H), 5.85 (ddt, $J = 10.3$, 17.1, 6.6, 1H), 7.22–7.47 (m, 5H). The enantiomeric excess of the product was determined by HPLC analysis with a chiral stationary phase column, CHIRALCEL OB-H (4.6 mm $\phi \times 250$ mm): hexane/2-propanol = 96:4, 0.5 mL/min flow, at 35 °C, UV 254 nm detection, (*S*) $t_1 = 17.1$ min, (*R*) $t_2 = 20.4$ min.

4.1.13.6. 1-Cyclohexylethanol (Table 1, entry 11). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 0.81–1.37 (m, 6H), 1.15 (d, $J = 6.3$ Hz, 3H), 1.53–1.92 (m, 6H), 3.54 (quintet, $J = 6.3$ Hz, 1H). The enantiomeric excess of the product was determined by HPLC analysis of its *N*-(3,5-dinitrophenyl)carbamate derivative with a chiral stationary phase column, SUMICHIRAL OA-4500 (4.0 mm $\phi \times 250$ mm): hexane/1,2-dichloroethane/ethanol = 50:15:1, 1.0 mL/min flow, at 35 °C, UV 254 nm detection, (*S*) $t_1 = 25.1$ min, (*R*) $t_2 = 28.1$ min. The *N*-(3,5-dinitrophenyl)carbamate derivative was prepared as follows. A mixture of the alcohol (ca 1 mg), 3,5-dinitrophenylisocyanate (ca 5 mg), and pyridine (50 μL) in toluene (0.5 mL) was vigorously stirred at 75 °C for 30 min and then concentrated in vacuo. The residue was purified by a preparative thin-layer chromatography (hexane/EtOAc).

4.1.13.7. 4-Phenyl-2-butanol (Table 1, entry 13). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.22 (d, $J = 6.2$ Hz, 3H), 1.57 (br s, 1H), 1.65–1.88 (m, 2H), 2.57–2.85 (m, 2H), 3.81 (sextet, $J = 6.2$ Hz, 1H), 7.10-7.41 (m, 5H). The enantiomeric excess of the product was determined by HPLC analysis with a chiral stationary phase column, CHIRALCEL OD-H (4.6 mm $\phi \times 250$ mm): hexane/2-propanol = 9:1, 0.5 mL/min flow, at 35 °C, UV 254 nm detection, (*R*) $t_1 = 13.8$ min, (*S*) $t_2 = 17.2$ min.

4.1.13.8. 5-Phenyl-2-pentanol (Table 1, entry 15). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 1.17 (d, $J = 6.2$ Hz, 3H), 1.33–1.88 (m, 5H), 2.63 (t, $J = 7.5$ Hz, 2H), 3.80 (sextet, $J = 6.2$ Hz, 1H), 7.10–7.41 (m, 5H). The enantiomeric excess of the product was determined by HPLC analysis with a chiral stationary phase column, CHIRALCEL OJ (4.6 mm $\phi \times 250$ mm): hexane/2-propanol = 96:4, 0.5 mL/min flow, at 35 °C, UV 254 nm detection, (*S*) $t_1 = 23.2$ min, (*R*) $t_2 = 25.9$ min.

4.1.13.9. 2-Octanol (Table 1, entry 17). ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 0.80–0.98 (m, 3H), 1.19 (d, $J = 6.1$ Hz, 3H), 1.14–1.53 (m, 11H), 3.80 (sextet, $J = 6.1$ Hz, 1H). The enantiomeric excess of the product was determined by HPLC analysis of its *N*-(3,5-dinitrophenyl)carbamate derivative with a chiral stationary phase column, SUMICHIRAL OA-4500 (4.6 mm $\phi \times$ 250 mm): hexane/1,2-dichloroethane/ethanol = 50:15:1, 1.0 mL/min flow, at 35 °C, UV 254 nm detection, (*S*) $t_1 = 35.4$ min, (*R*) $t_2 = 40.4$ min.

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