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Synthesis and application of C_2-symmetric diamino FERRIPHOS as ligands for enantioselective Rh-catalyzed preparation of chiral α-amino acids

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Abstract

C_2-Symmetrical ferrocenyl diamino diphosphines (diamino FERRIPHOS ligands) proved to be excellent ligands for the rhodium-catalyzed enantioselective reduction of methyl α-acetamidoacrylates. The straightforward synthesis, their air stability and the easy modification of their structure makes these ligands especially interesting for transition metal-catalyzed hydrogenations. α-Amino acids with enantioselectivities greater than 95% (and up to 99.3% *ee*) were obtained with no need of further recrystallization.

1. Introduction

Homogeneous asymmetric catalysis using transition metal complexes has attracted a great deal of interest because of its high efficiency and economic feasibility in producing a broad range of optically active compounds. Many chiral bisphosphines[1] have been prepared since the late 1960s to induce enantioselective catalytic reactions, and several industrial processes use chiral phosphine transition metal complexes as catalysts, for instance, in the production of L-DOPA,[1a] L-menthol,[2] or the herbicide (*S*)-metolachlor[3] (the largest process using an asymmetric hydrogenation catalyst in quantities of over 10 000 tons per year), the latter being an example of the application of ferrocene-based ligands.

Ferrocenyl diphosphine ligands are a versatile class of compounds because they can be easily modified, benefitting from the special reactivity of the benzylic position, which allows the introduction of different nucleophiles with retention of configuration.[4] Ferrocene-based ligands incorporating both central and planar chirality is a well developed area that has found successful application in numerous asymmetric catalytic processes.[3,5] Although a great number of C_2-symmetrical diphosphine ligands have been

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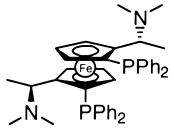
reported to catalyze the asymmetric hydrogenation of prochiral olefins,[6] few examples of synthesis and application of C_2-symmetrical ferrocenyl diphosphine ligands in metal-catalyzed processes have been described. Hayashi et al. have obtained ligand **1** via resolution of the racemic mixture and applied it to the palladium-catalyzed asymmetric cross-coupling reaction between vinylic bromides and Grignard reagents;[7] Ikeda et al. have synthesized ligands of type **2** and **3** and used them for the palladium-catalyzed asymmetric allylic substitutions.[8] To our knowledge only two examples of C_2-symmetrical ferrocenyl diphosphine ligands have been applied to the asymmetric hydrogenation of prochiral enamides.[9]



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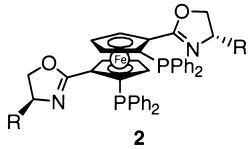

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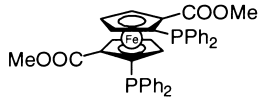


3

Recently, we have developed the synthesis of several new optically active ferrocenyl derivatives.[4b–d,11] Now we wish to report the application of some easily prepared C_2-symmetrical ferrocenyl diphosphine ligands[12] to the synthesis of optically active amino acids.

2. Results and discussion

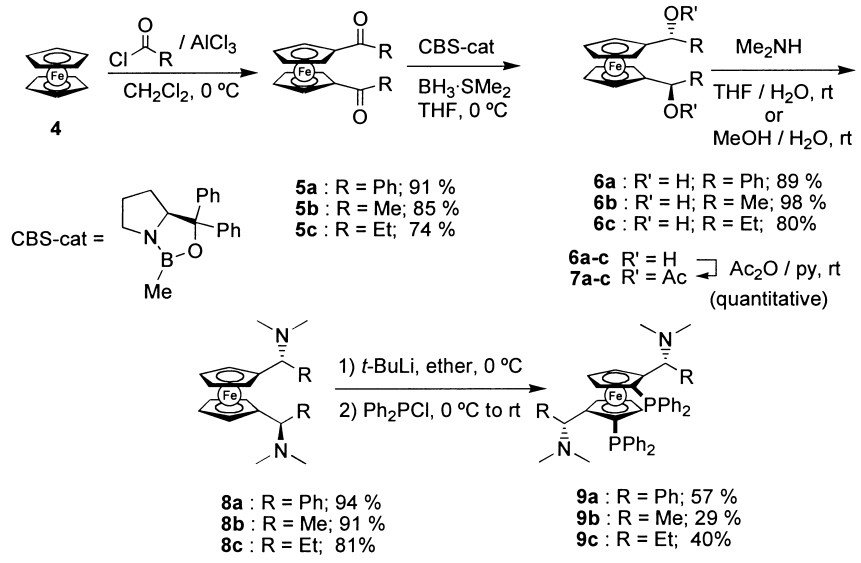
*2.1. Synthesis of ligands **9a–c***

Syntheses of ligands **9a**,**b** have already been described and will not be discussed in the present work.[12] In order to prepare ligand **9c**, a similar procedure was employed. Friedel–Crafts acylation of ferrocene (**4**) with propionyl chloride (2 equiv.) in the presence $AlCl_3$ (2 equiv.) in CH_2Cl_2 at 0°C afforded diketone **5c** in 74% yield. Asymmetric reduction of diketone **5c** with $BH_3 \cdot SMe_2$ in THF at 0°C in the presence of 60 mol% of *B*-methyl oxazaborolidine [prepared from (*S*)-2-(diphenylhydroxymethyl)pyrrolidine and methyl boronic acid;[13] CBS-catalyst† from now on] yielded diol **6c** in a 95:5 *dl:meso* ratio and *ee* 98%. Conversion to the acetate (pyridine, acetic anhydride, rt) followed by reaction with Me_2NH in a mixture of 1:1 MeOH:H_2O furnished the desired diamine **8c** in 64% yield (3 steps). Lithiation of **8c** with *t*-BuLi in ether at 0°C and quenching with $ClPPh_2$ produced diphosphine **9c** in 40% yield as a single diastereoisomer (*de* 100%; no other isomer was detected by NMR analysis) due to the well known diastereoselective *ortho* directing effect of the dimethylamino group,[15] and with an *ee* >98%. These phosphines **9a**–**c** (alkyl dimethylamino FERRIPHOS ligands)‡ are all crystalline, air stable solids (no oxidation products were observed after 3 months of air exposure) and are easily purified by recrystallization in acetone or diethyl ether/pentane (Scheme 1).

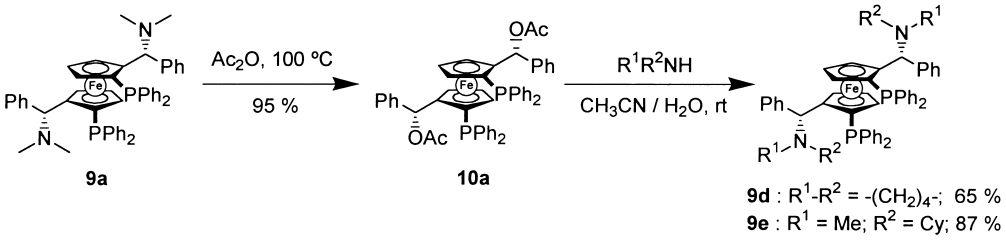
In order to obtain other ligands with a different amino group than the dimethylamino one, compound **9a** was transformed into the corresponding acetate **10a** (acetic anhydride, 100°C), and was reacted with pyrrolidine or *N*-cyclohexyl-*N*-methyl amine affording the corresponding diamino diphosphines **9d**,**e** in 65 and 87% yield as single diastereoisomers (no racemization was detected during these reactions) (Scheme 2).

† CBS≡Corey–Bakshi–Shibata, the authors who improved the method discovered by S. Itsuno for the reduction of ketones.[14]

‡ Dimethylamino alkyl FERRIPHOS is the nomenclature that we propose for a C_2-symmetrical ferrocenyl diphosphine ligand, in which the 2 position has an alkyl group and the alpha position has a dimethylamino group.



Scheme 1.



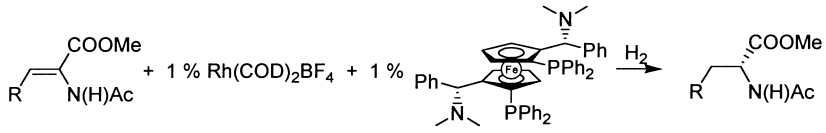
Scheme 2.

*2.2. Application of the FERRIPHOS ligands **9a–e** to the synthesis of α-amino acid derivatives*

For the evaluation of the efficiency of ligand **9a** for catalysis, rhodium-catalyzed hydrogenation of different methyl α-acetamido acrylates **11a–e** was performed. The hydrogenation reaction proceeded under very mild conditions (ca. 1 bar H_2; rt) in the presence of 1 mol% of the catalyst prepared in situ [1 mol% of $Rh(COD)_2BF_4$; 1 mol% of **9a**]. Reactions were monitored by ^1H NMR (reaction times being 2–6 h). The results obtained are summarized in Table 1.

Concerning the hydrogenation of compound **11a**, the results obtained are better than the ones reported with other ferrocenyl ligands for the same substrate (BPPFA,[10] 21% *ee*; JOSIPHOS,[16] 96% *ee*) and better or very close to the best results obtained with other ligands ([2.2]PHANEPHOS,[6f] 83% *ee*; DUPHOS derivatives,[6e] 85–>99% *ee*; DIOP,[17] 82% *ee*). Hydrogenation of (*Z*)-α-acetamidocinnamic acid was also attempted, but the corresponding amino acid derivative was only obtained in 73% *ee*. Addition of 2% of CF_3COOH to the reaction mixture previous to the hydrogenation step improved the *ee* up to 89%. Although these are only moderate results, they are still better than others previously reported for other ferrocenyl ligands (BPPFA-IP,[17] 52% *ee*; BPPFA-Ph,[17] 52% *ee*) and very close to the results obtained with other diphosphines (DIOP,[6a] 72% *ee*; BPPM,[18] 78% *ee*; JOSIPHOS,[16] 84% *ee*; PPFA,[19] 76% *ee*). The reaction described in Table 1 entry 2, was also performed with only 0.2% of rhodium complex and 0.2% of ligand **9a**, the enantiomeric excess being 97.1%. This reaction is not affected by the substrate concentration either. Repetition of the reaction in Table 1, entry 2 with a 1 M concentration of substrate afforded the expected phenylalanine derivative **17a** in 97.0% *ee*.

Table 1
Hydrogenation of methyl (*Z*)-α-acetamidoacrylates with ligand **9a**[a]

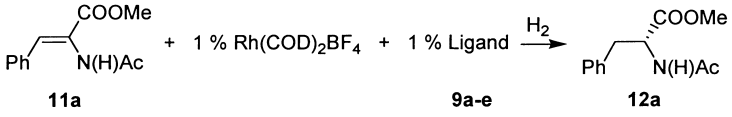


11a-e **9a** **12a-e**

Entry	R	Product	ee (%)
1	**11a** : Ph	**12a**	96.9
2[b]	**11a** : Ph	**12a**	98.0
3	**11b** : 2-Naphthyl	**12b**	95.5
4[b]	**11c** : *p*-Cl-Ph	**12c**	>99
5[b]	**11d** : *p*-F-Ph	**12d**	99.0
6	**11e** : H	**12e**	97.4

[a]Reaction conditions: 1 bar H_2; rt; 0.1 M solutions of substrates in MeOH, unless otherwise indicated. The enantiomeric excesses were determined by GC (column Chirasil-L-Val) or HPLC (column Chiralcel OD). The absolute stereochemistry was established by comparison with the literature reported values and in all cases the *R* enantiomer was obtained. [b]MeOH / toluene 1 : 1 as solvent.

Table 2
Hydrogenation of methyl (*Z*)-α-acetamidocinnamate with different ligands[a]



11a **9a-e** **12a**

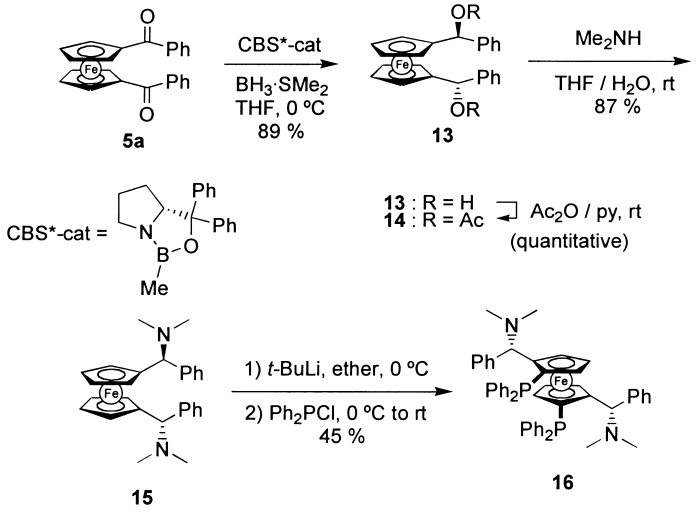
Entry	Ligand	ee (%)
1	**9a**	96.9
2	**9b**	97.6
3	**9c**	95.1
4	**9d**	97.7
5	**9e**	97.8

[a]Reaction conditions: 1 bar H_2; 0.1 M solutions of substrates in MeOH. The enantiomeric excesses were determined by GC (column Chirasil-L-Val). The absolute stereochemistry was established by comparison with the literature reported value and in all cases the *R* enantiomer was obtained.

Ligands **9b**–**e** were also tested in the hydrogenation of methyl (*Z*)-α-acetamidocinnamate. The results are shown in Table 2. Good enantioselectivities were also obtained with the other ligands.

2.3. Synthesis of (S)-α-amino acid derivatives

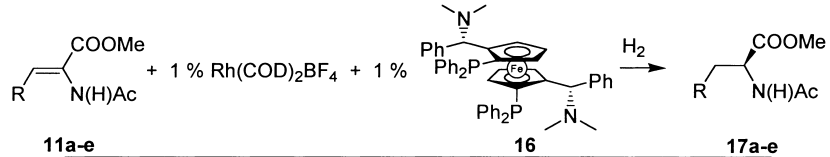
To demonstrate the versatility of the chemistry described in this paper, preparation of the other enantiomer of compound **9a** was performed (Scheme 3). The only difference resides in the choice of the other enantiomer of the CBS-catalyst [the one derived from (*R*)-proline for performing the CBS-catalyst synthesis].



Scheme 3.

This new ligand was tested for the hydrogenation of the same α-acetamido dehydroamino acids **11a–e** as in the case of ligand **9a**. The results are included in Table 3.

Table 3
Hydrogenation of methyl (*Z*)-α-acetamidoacrylates with ligand **16**[a]



Entry	R	Product	ee (%)
1	**11a** : Ph	**17a**	97.5
2	**11b** : 2-Naphthyl	**17b**	97.7
3	**11c** : *p*-Cl-Ph	**17c**	98.7
4	**11d** : *p*-F-Ph	**17d**	97.2
5	**11e** : H	**17e**	96.3

[a]Reaction conditions: 1 bar H_2; rt; 0.1 M solutions of substrates in MeOH / toluene 25 / 1. The enantiomeric excesses were determined by GC (column Chirasil-L-Val) or HPLC (column Chiralcel OD). The absolute stereochemistry was established by comparison with the literature reported values and in all cases the *S* enantiomer was obtained.

The fact that the other enantiomer of our ligands is also active in hydrogenation reactions and can be easily prepared, offers access to both enantiomers of the hydrogenated products.

3. Conclusion

In summary, we have found a new application for the previously reported diamino diphosphine ligands obtained in our group. We have also demonstrated that this wide family of FERRIPHOS ligands are excellent ligands for the asymmetric reduction of alkyl α-acetamido acrylates. Further extension to other transition metal-catalyzed reactions and to the hydrogenation of other substrates are in progress in our laboratory.

4. Experimental

4.1. General

Melting points are uncorrected. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded at room temperature in $CDCl_3$ (unless otherwise indicated) on a Bruker AC 300 spectrometer (300 MHz for proton; 75 MHz for carbon), using TMS as an internal reference. Phosphorus nuclear magnetic resonance spectra (^{31}P NMR) were recorded at room temperature in $CDCl_3$ on a Bruker AM 400 spectrometer (162 MHz for phosphorus), using H_3PO_4 85% as an external reference. Chemical shifts are given relative to the reference (TMS or H_3PO_4 85%); coupling constants are given in hertz. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Fourier transformation IR spectra were recorded on a Nicolet 510 FTIR spectrometer. Electron impact (EI, 70 eV) mass spectra were recorded on a Varian CH 7A instrument. Enantiomeric excesses were determined by HPLC. A Chiralcel OD column (Daicel Chemical Industries) was used at 30°C (unless otherwise indicated) with *n*-heptane:2-propanol, 9:1 (unless otherwise indicated) as a mobile phase and detection by a diode array UV–vis detector at 215 nm. Alternatively, enantiomeric excesses were measured by GC on a 25 m×0.2 mm fused silica WCOT Chirasil-L-Val (0.12 μm) using hydrogen (100 kPa) as the mobile phase. Racemic compounds were used as references to choose the operating conditions for the resolution of the enantiomer and/or diastereomer peaks.

4.2. Materials

THF, Et_2O and methyl *t*-butyl ether (MTBE) were distilled from sodium; CH_2Cl_2 was distilled from CaH_2; pyridine was dried over KOH. Commercial reagents were used without further purification. MeOH of technical degree (<0.1% H_2O) was used without degassing. *t*-BuLi was obtained from Chemetall GmbH as 15% solution in hexanes. Compounds **11a–d** were prepared according to literature procedures.[20] Compound **11e** was purchased from Aldrich. Compounds **5a**, **5b**, **6a**, **6b**, **7a**, **7b**, **8a**, **8b**, **9a**, **9b** were prepared as previously reported[12] with the same enantiopurities. Physical and spectroscopical data of compounds **13–16** were in accordance with the ones reported for their enantiomers,[12] except for the sign of the optical rotation. (*S*)-α,α-Diphenylprolinol[21] and CBS-catalyst[13] were prepared as previously reported.

4.3. General procedure for the hydrogenation of dehydroamino acids

In a 25 mL Schlenk tube under argon, $Rh(COD)_2BF_4$ (0.01 mmol, 4.1 mg) and the corresponding ligand **9a**–**e**, **16** (0.01 mmol) were dissolved in MeOH or MeOH/toluene mixture. After complete solubilization of the rhodium complex, the corresponding dehydroamino acid (1 mmol) was added dissolved in MeOH. The Schlenk tube was connected to a hydrogen balloon and the inert atmosphere was replaced by hydrogen. The reactions were monitored by ^{1}H NMR. When full conversion was obtained, the solvent was removed, and the crude reaction was filtered through a short silica gel column using MTBE as eluent. Enantiomeric excesses and absolute configurations were assigned by comparison with literature data. *N*-Acetylphenylalanine methyl ester (**12a**, **17a**):[22] GC (140°C): t_R (min)=10.13 (*R*), 11.67 (*S*). *N*-Acetyl-3-(2-naphthyl)alanine methyl ester (**12b**, **17b**):[22] HPLC (flow rate of 0.6 mL/min): t_R (min)=20.09 (*R*), 23.61 (*S*). *N*-Acetyl-*p*-chlorophenylalanine methyl ester (**12c**, **17c**):[23] HPLC (flow rate of 0.8 mL/min): t_R (min)=13.14 (*R*), 17.46 (*S*); GC (160°C): t_R (min)=11.82 (*R*), 13.32 (*S*). *N*-Acetyl-*p*-fluorophenylalanine methyl ester (**12d**, **17d**):[23] HPLC (flow rate of 0.8 mL/min): t_R (min)=12.81 (*R*), 15.72 (*S*); GC (140°C): t_R (min)=11.29 (*R*), 13.25 (*S*). *N*-Acetylalanine methyl ester (**12e**, **17e**):[22] GC (80°C): t_R (min)=6.14 (*R*), 8.09 (*S*).

4.4. 1,1′-Dipropanoylferrocene **5c**

To a suspension of aluminum(III) chloride (14.67 g, 110.0 mmol) in CH_2Cl_2 (60 mL) at 0°C under argon was added propanoyl chloride (9.5. mL, 110.0 mmol). Ferrocene (9.30 g, 50.0 mmol) in CH_2Cl_2 (50 mL) was added dropwise within 30 min. The reaction was warmed to room temperature and stirred overnight. Work-up was done at 0°C by dropwise addition of ice-cold water (50 mL; caution: gas evolution!). The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed twice with saturated aqueous K_2CO_3 (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford a red solid which was washed with MTBE. A yield of 74% (11.0 g, 37.0 mmol) was obtained without further purification. Mp 50–51°C; IR (KBr): ν_{max}=3096 (w), 2934 (w), 1674 (vs), 1458 (s), 1242 (s), 1102 (m), 1048 (m), 807 (m); ^{1}H NMR δ=4.88–4.85 (m, 4H), 4.59–4.56 (m, 4H), 2.84–2.71 (m, 4H), 1.34–1.23 (m, 6H); ^{13}C NMR δ=203.68, 79.90, 72.92, 70.17, 32.68, 7.82; MS (EI, 70 eV) m/z: 298 (M^+, 100%), 269 (24), 213 (27), 186 (6), 121 (27). Anal. calcd for $C_{16}H_{18}FeO_2$: C, 64.45; H, 6.08. Found: C, 64.25; H, 6.05.

4.5. (R,R)-1,1′-Bis(α-hydroxypropyl)ferrocene **6c**

Under argon, the CBS-catalyst (2.49 g, 9.0 mmol) was dissolved in THF (10 mL) and cooled to 0°C. From a syringe charged with $BH_3\cdot SMe_2$ (1 M in THF, 37.5 mL) 20% of the final amount (7.5 mL) was added to the catalyst solution. After 5 min of stirring, the remaining $BH_3\cdot SMe_2$ and a solution of the diketone **5c** (4.50 g, 15.0 mmol) in THF (30 mL) were simultaneously added within 2 h. The red color of the ketone turns to yellow upon reduction. After 5 min at 0°C the excess $BH_3\cdot SMe_2$ was quenched by dropwise addition of methanol (10 mL; caution: gas evolution!). After gas evolution had ceased, the mixture was poured onto saturated aqueous NH_4Cl (150 mL) and extracted with MTBE (200 mL). The organic layer was washed with water (2×100 mL) and brine (100 mL), dried ($MgSO_4$) and then concentrated to give an oil which was purified by column chromatography (hexanes:MTBE, 1:1). Yield: 80% [3.62 g, 12.0 mmol; *dl*:*meso*=92:8; *ee* >98%; HPLC, 5% *i*-PrOH, flow rate of 0.6 mL/min, T=20°C, t_R/min=8.35 (*SS*), 9.12 (*RS*), 11.09 (*RR*)]. Yellow oil; $[\alpha]_D^{22}$=−92.4 (*c*=1.31, benzene); IR (neat): ν_{max}=3320 (s, br), 3080 (w), 2930 (m), 2860 (m), 1460 (m), 1380 (m), 1030 (s), 810 (s); ^{1}H NMR

δ=4.42 (t, *J*=6.2, 2H), 4.26–4.12 (m, 10H), (m, 6H), 1.69–1.50 (m, 4H), 0.89 (t, *J*=7.4, 6H); ^{13}C NMR δ=93.45, 71.29, 67.34, 67.31, 66.32, 66.30, 32.69, 9.79; MS (EI, 70 eV) m/z: 302 (M^+, 22%), 284 (44), 266 (100), 255 (12), 226 (15), 178 (24), 160 (68), 91 (75). Anal. calcd for $C_{16}H_{22}FeO_2$: C, 63.59; H, 7.34. Found: C, 63.43; H, 7.41.

*4.6. (*R,R*)-1,1′-Bis(α-acetoxypropyl)ferrocene **7c***

Diol **6c** (0.60 g, 2 mmol) was dissolved in pyridine (4 mL) and acetic anhydride (2 mL) and stirred for 12 h at room temperature. Volatile matter was removed under vacuum (1 mmHg, 5 h) to yield quantitatively the acetate **7c** as a yellow oil which was already >98% pure as indicated by NMR analysis. (*dl*:*meso*=95:5; *ee* >98%); $[\alpha]_D^{22}$=−40.3 (*c*=2.06, $CHCl_3$); IR (neat): ν_{max}=1732 (vs), 1236 (vs); ^{1}H NMR δ=5.69–5.65 (m, 2H), 4.19 (s, 2H), 4.11–4.08 (m, 6H), 2.09 (s, 6H), 1.88–1.72 (m, 4H), 0.91 (t, *J*=7.3, 6H); ^{13}C NMR δ=170.61, 88.57, 73.15, 68.31, 68.51, 67.90, 67.24, 28.45, 21.16, 10,16; MS (EI, 70 eV) m/z: 380 (M^+, 10%), 326 (7), 266 (25), 220 (50), 221 (12), 161 (15). Exact mass calcd for $C_{20}H_{26}FeO_4$: 386.1180. Observed: 386.1176.

*4.7. (*R,R*)-1,1′-Bis(α-*N,N*-dimethylaminopropyl)ferrocene **8c***

The diacetate **7c** (0.97 g, 2.5 mmol) was dissolved in a CH_3OH/water mixture (20 mL). Dimethylamine (40% in water, 10 mL) was added. After stirring for 12 h at room temperature, the reaction was poured into saturated aqueous NH_4Cl (50 mL) and extracted with MTBE (100 mL). After washing with water (2×50 mL) and brine (50 mL), the organic layer was dried and concentrated to give an oil which was purified by column chromatography (hexanes:MTBE, 2:1 with 2% NEt_3) to yield diamine **8c** in 81% yield (0.72 g, 2.0 mmol; *dl*:*meso*=>99:<1) as a brown solid; mp 86–89°C; $[\alpha]_D^{22}$=−21.3 (*c*=1.43, $CHCl_3$); IR (KBr): ν_{max}=3092 (m), 1471 (s), 1450 (s), 986 (s), 827 (s); ^{1}H NMR δ=4.05–3.98 (m, 8H), 3.24 (dd, *J*=10.9, 3.3, 2H), 2.07–1.94 (m, 2H), 1.99 (s, 12H), 1.80–1.66 (m, 2H), 1.09 (t, *J*=7.3, 6H); ^{13}C NMR δ=85.81, 70.04, 68.09, 67.86, 67.64, 64.90, 40.54, 24.43, 12.29; MS (EI, 70 eV) m/z: 356 (M^+, 34%), 327 (12), 311 (29), 282 (16), 268 (33), 267 (20), 239 (100), 178 (56). Anal. calcd for $C_{20}H_{32}FeN_2$: C, 67.41; H, 9.05; N, 7.86. Found: C, 67.55; H, 8.95; N, 7.84.

*4.8. (*αR,α′R*)-2,2′-Bis(α-*N,N*-dimethylaminopropyl)-(*S,S*)-1,1′-bis(diphenylphosphino)ferrocene **9c***

Diamine **8c** (0.97 g, 2.9 mmol) was dissolved under argon in Et_2O (10 mL), cooled to 0°C and *t*-BuLi (*c*=1.5 M; 5.8 mL, 8.7 mmol) was added within 5 min. The solution was stirred at the same temperature for 0.5 h (the color changed from yellow to deep red). After quenching with $ClPPh_2$ (2.1 mL, 11.8 mmol) at 0°C and stirring at rt for 3 h, the mixture was poured onto a saturated solution of $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2. After drying with $MgSO_4$ and filtration, the residue was purified by column chromatography (hexanes:MTBE, 3:1 and then 1:1 with 1% of Et_3N) and recrystallized in hexanes. A yellow solid was isolated in 40% yield (0.84 g, 1.1 mmol) as a single diastereomer (*de* 100%; *ee* >98%). Mp 185–187°C; $[\alpha]_D^{22}$=−566.8 (*c*=0.66, $CHCl_3$); IR (KBr): ν_{max}=3068 (w), 3051 (w), 3026 (w), 1584 (w), 738 (s), 697 (s) cm^{-1}; ^{1}H NMR δ=7.32–7.04 (m, 20H), 4.29, 4.13 (2×br s, 2×2H), 3.81–3.78 (m, 2H), 3.02 (br s, 2H), 2.09–2.01 (m, 2H), 1.94–1.85 (m, 2H), 1.81 (s, 12H), 1.13 (t, *J*=7.4, 6H); ^{13}C NMR δ=140.54 (d, *J*=7.2), 138.47 (d, *J*=9.3), 135.01 (d, *J*=22.2), 132.11 (d, *J*=18.7), 128.55, 127.98, 127.28, 127.19, 126.99, 98.19 (d, *J*=23.6), 76.16 (d, *J*=8.9), 73.01, 72.04 (d, *J*=5.4), 70.47, 62.55 (d, *J*=7.0), 39.73, 23.55, 13.65; ^{31}P NMR δ=−23.45; MS (EI, 70 eV) m/z: 724 (M^+, 39), 679 (30), 665 (44), 664

(100), 636 (20), 635 (24), 634 (22), 339 (22), 183 (18). Anal. calcd for $C_{44}H_{50}FeN_2P_2$: C, 72.93; H, 6.95; N, 3.87. Found: C, 72.83; H, 7.08; N, 3.60.

4.9. (αR,α′R)-2,2′-Bis(α-acetoxyphenylmethyl)-(S,S)-1,1′-bis(diphenylphosphino)ferrocene ***10a***

Diamine **9a** (0.82 g, 1.0 mmol) was dissolved in acetic anhydride (4 mL) and heated at 100°C for 2.5 h. The volatiles were then removed under vacuum (1 mmHg, 3 h), affording in quantitative yield the corresponding acetate (>95% pure, NMR). Further purification could be achieved by recrystallization in diethyl ether/hexanes. Brown solid; mp 184°C (decomp.); $[\alpha]_D^{22}=-169.6$ (c=0.46, $CHCl_3$); IR (KBr): ν_{max}=1736 (vs), 1231 (vs), 737 (vs), 702 (s) cm^{-1}; ^1H NMR δ=7.27–7.03 (m, 30H), 6.58 (d, J=2.8, 2H), 4.61 (t, J=2.3, 2H), 3.96 (br s, 2H), 3.25–3.24 (m, 2H), 1.27 (s, 6H); ^{13}C NMR δ=169.03, 139.49 (d, J=10.0), 139.07, 136.29 (d, J=9.0), 134.90 (d, J=22.1), 132.61 (d, J=18.8), 129.24, 128.25, 128.22, 128.15, 128.05, 127.92, 127.84, 127.78, 127.41, 93.06 (d, J=22.9), 74.26, 73.95, 73.87, 73.75, 72.32 (d, J=4.2), 20.12; ^{31}P NMR δ=−23.75; MS (EI, 70 eV) m/z: 851 (M^+1, 5), 733 (55), 394 (22), 339 (17), 338 (69), 337 (100), 183 (38). Anal. calcd for $C_{52}H_{44}FeO_4P_2$: C, 73.42; H, 5.21. Found: C, 73.26; H, 5.29.

4.10. (αR,α′R)-2,2′-Bis(α-pyrrolidinophenylmethyl)-(S,S)-1,1′-bis(diphenylphosphino)ferrocene ***9d***

Diacetate **10a** (300 mg, 0.35 mmol) was treated with pyrrolidine (1.46 mL, 17.5 mmol) in CH_3CN (2 mL)/H_2O (0.2 mL) at 90°C for 12 h. The solvents were removed under vacuum and the residue dissolved in MTBE and washed with brine. After removal of solvents, the residue was purified by column chromatography (hexanes:MTBE, 5:1) to yield the corresponding product in 65% yield (198 mg, 0.23 mmol) as an orange solid; mp 242°C (decomp.); $[\alpha]_D^{22}=-317.7$ (c=0.53, $CHCl_3$); IR (KBr): ν_{max}=3067 (w), 3024 (w), 1601 (w), 1585 (w), 737 (s), 698 (s) cm^{-1}; ^1H NMR δ=7.30–6.88 (m, 30H), 4.65 (d, J=4.6, 2H), 4.26, 3.09, 2.95 (3×br s, 3×2H), 1.97–1.93 (m, 4H), 1.81–1.77 (m, 4H), 1.28–1.19 (m, 4H), 1.08–1.03 (m, 4H); ^{13}C NMR δ=142.81, 139.93 (d, J=7.5), 138.07 (d, J=10.3), 135.03 (d, J=23.2), 132.45 (d, J=18.9), 128.80, 128.58, 128.19, 128.08, 127.92, 127.65, 127.57, 127.42, 126.51, 99.62 (d, J=23.5), 75.44 (d, J=10.0), 73.23, 72.06, 71.45, 65.74 (d, J=11.2), 51.43, 22.73; ^{31}P NMR δ=−23.46; MS (EI, 70 eV) m/z: 872 (M^+, 30), 803 (19), 802 (100), 734 (48), 733 (69), 732 (72), 724 (28), 464 (31), 463 (62), 401 (19), 395 (76), 394 (72), 393 (24), 337 (30), 239 (30), 183 (77), 160 (53). Exact mass calcd for $C_{56}H_{54}FeN_2P_2$: 872.3112. Observed: 872.3133.

4.11. (αR,α′R)-2,2′-Bis[α-(N-cyclohexyl-N-methylamino)phenylmethyl]-(S,S)-1,1′-bis(diphenylphosphino)ferrocene ***9e***

Diacetate **10a** (160 mg, 0.18 mmol) was treated with *N*-cyclohexyl-*N*-methylamine (1.2 mL, 9.3 mmol) in CH_3CN (2 mL)/H_2O (0.2 mL) at 90°C for 12 h. The solvents were removed under vacuum and the residue taken up in MTBE and washed with brine. After removal of solvents, the residue was purified by column chromatography (hexanes:MTBE, 5:1) to yield the corresponding product in 87% yield (150 mg, 0.16 mmol) as a pale yellow solid; mp 224°C (decomp.); $[\alpha]_D^{22}=-290.2$ (c=0.57, $CHCl_3$); IR (KBr): ν_{max}=3071 (w), 3053 (w), 3001 (w), 1600 (m), 1584 (w), 741 (s), 701 (s) cm^{-1}; ^1H NMR δ=7.24–7.03 (m, 30H), 4.95 (d, J=4.7, 2H), 4.34, 3.31, 3.06 (3×br s, 3×2H), 2.12–2.05 (m, 2H), 1.51–1.47 (m, 4H), 1.43 (s, 6H), 1.34–1.31 (m, 4H), 0.91–0.66 (m, 12H); ^{13}C NMR δ=142.77, 139.95 (d, J=7.8), 138.34 (d, J=10.2), 135.58 (d, J=23.4), 132.58 (d, J=18.8), 128.60, 128.50, 128.12, 128.01, 127.42, 127.33, 127.17, 126.37, 98.75 (d, J=23.4), 76.10 (d, J=11.4), 73.74, 72.92 (d, J=5.5), 71.18, 64.28 (d, J=11.2), 60.07, 32.02, 29.22, 26.22, 26.04, 26.00; ^{31}P NMR δ=−24.80; MS (EI, 70 eV) m/z: 958 (M^+1, 17), 845 (51),

764 (25), 763 (52), 762 (100), 735 (32), 733 (27), 506 (20), 395 (29), 183 (20). Exact mass calcd for $C_{62}H_{66}FeN_2P_2$: 956.4051. Observed: 956.4064.

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