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Asymmetric synthesis of (*S,S*)-(+)-1,1′-bis-(methyl-phenyl-phosphino) ferrocene

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Abstract

The asymmetric synthesis of 1,1′-bis-(methyl-phenyl-phosphino) ferrocene **1** is described using the oxazaphospholidine borane complex **5** as synthon. Two strategies were investigated, based either on P–C bond formation by ring opening of complex **5** with the 1,1′-dilithio ferrocene **10**, or on homocoupling of the cyclopentadienyl-methyl-phenyl-phosphine borane **2** anion with $FeCl_2$. The first leads to a diastereomeric mixture of the diphosphine **1** in a 55:45 ratio, and the low stereoselectivity is explained by the steric hindrance of the ferrocene dianion. In the second strategy, the (*R*)-cyclopentadienyl phosphine borane **2** (85% *ee*) was prepared by the reaction of CpNa with the optically active chlorophosphine borane **14**, derived from the aminophosphine borane **6a**. The coupling of **2** leads to the 1,1′-diphosphino ferrocene borane **13**, which is obtained diastereomerically pure by recrystallization, then decomplexed to the corresponding (*S,S*)-diphosphine **1**.

Keywords: Phosphine boranes; Chiral ligands; Ferrocene; Asymmetric synthesis; Phosphorus stereochemistry; Chlorophosphine

1. Introduction

Phosphine borane complexes have many advantages in organophosphorus synthesis, as they possess an interesting reactivity, and do not present any purification or storage problems [1–9]. In recent years, significant strides have been achieved in the asymmetric synthesis of tertiary mono- and diphosphine ligands [2–9], owing to the use of the protecting group borane (BH_3) which could be displaced under a non-racemizing decomplexation step [3,5].

Currently, this chemistry is receiving particular attention due to the remarkable results of asymmetric catalysis for the preparation of pharmaceutical, agrochemical or aromatic substances [10], thus justifying the search for original and inexpensive chiral ligands.

In spite of the numerous examples of chiral phosphorus ligands described up to date [11], the search for access to monophosphines, or new chelating diphosphines with a metallocene or a biaryl bridge, is still a challenge in phosphorus chemistry.

In continuation of our program on chiral phosphorus ligand synthesis, we present herein the asymmetric synthesis of the 1,1′-bis-(methyl-phenyl-phosphino) ferrocene. To our knowledge, the compound **1** has only been described in racemic form [12].

Two synthetic approaches were studied to synthesize the diphosphine **1**, either by P–C bond formation starting from ferrocene (Scheme 1, pathway A), or by homocoupling of the cyclopentadienyl methyl phenyl phosphine **2** with $FeCl_2$ (Scheme 1, pathway B).

2. Results and discussion

The asymmetric synthesis of mono- and diphosphines previously described by us [2–4] is based on the reaction of an organolithium reagent R_1Li with the oxazaphospholidine borane complex **5**, giving a diastereomerically pure aminophosphine borane **6** by P–O bond cleavage. Under acidic methanolysis, the compound **6** leads to the phosphinite borane **7**, which affords the phosphine borane **8** upon reaction with a second organolithium reagent R_2Li, and then the phosphine **9** after decomplexation (Scheme 2).

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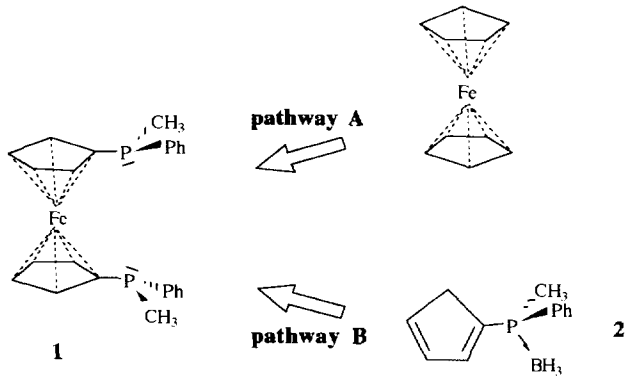


Scheme 1.

2.1. Synthesis of 1,1'-bis-(methyl-phenyl-phosphino) ferrocene 1 from ferrocene (Scheme 1, pathway A)

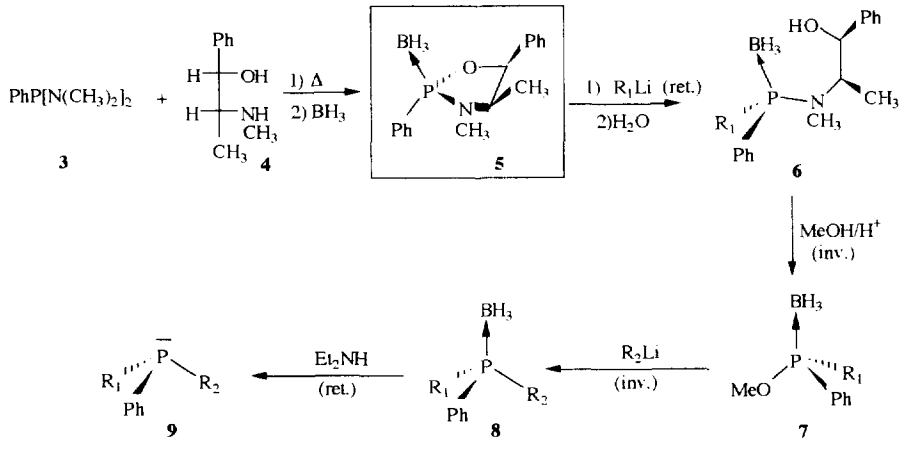
In this approach, we have investigated the condensation of 1,1'-dilithio ferrocene **10** with two equivalents of oxazaphospholidine complex **5** (Scheme 3).

The diastereomerically pure complex **5** was prepared by condensation of bis(dimethylamino)phenyl phosphine **3** with (+)-ephedrine **4**, then complexation (in situ) with $BH_3 \cdot S(CH_3)_2$ (Scheme 2). The reaction in THF at 45 °C of the dianion **10** [13] with two equivalents of complex **5** leads to the bis-aminophosphine borane **11** isolated in poor yield (10%). All attempts to increase the yield by prolonged heating, addition of LiCl, or borane to trap the TMEDA present in the medium were unsuccessful. HPLC analysis of the crude product **11** revealed the presence of three isomers, translating into a low stereoselectivity during the nucleophilic attack. Acidic methanolysis of the bis-aminophosphine **11** gives the corresponding diphosphinite borane **12** in 90% yield as a mixture of two isomers in a 3:2 ratio, observed by ^1H and ^{13}C NMR analysis. Finally, the reaction of methyl lithium (2.2 equiv.) with compound **12** leads to the corresponding diphosphine borane **13**, which is easily decomplexed by Et_2NH to give the 1,1'-bis-(methyl-phenyl-phosphino) ferrocene **1** in a diastereomeric ratio of 55:45.

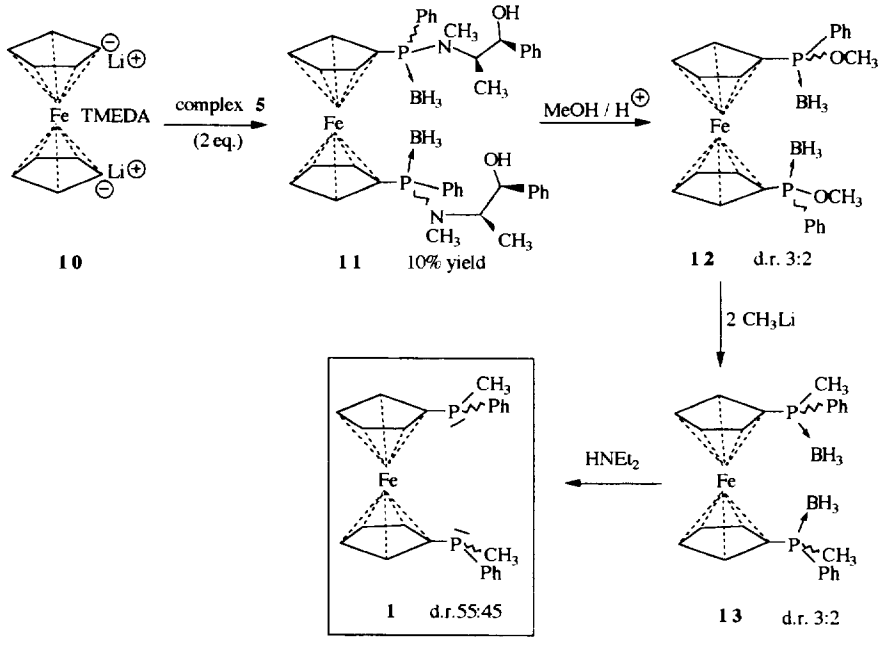
The low stereoselectivity observed in the first step could be explained by steric hindrance of the mono- and dianion derived from the ferrocene. The nucleophilic attack on complex **5** leads to the formation of an initial pentacoordinate intermediate, which evolves via two competitive pathways to the isomers, precursors of the ring-opened products with an *R* or *S* configuration at the P-center (Scheme 4).

In order to explain the stereochemical outcome of this reaction, we define the possible pentacoordinate intermediates by the P-atom substituents in apical position according to the classical convention (the pentacoordinate isomers are denoted by their apical substituents; when the upper substituent is looking towards the lower, the notation of the stereoisomer is surmounted by a bar, if the equatorial substituents are counter clockwise [14]). In addition, the substituents are ranked from 1 to 5 following their 'relative stereoapicophilicity' [15], which considers both their apicophilicity [16] and steric hindrance. This ranking leads to the following order, which increases from ferrocenyl to BH_3: $(R_{Fe}) < N(CH_3) < OCHPh < Ph < BH_3$. Thus, this order of substituents corresponds to the relative aptitude of the P-substituents to occupy an apical position and consequently leads to a decreasing stability of the pentacoordinate intermediates in the order: {12} > {13} > {14} ≈ {23} > {15} ≈ {24} > {25} ≈ {34} > {35} > {45}.

As the reaction of complex **5** with an organolithium reagent occurs with retention of configuration [4,9], explained by a nucleophilic attack opposite to the P–N bond, it is reasonable to think that {$\overline{12}$} is the initial pentacoordinate intermediate arising in the first step (Scheme 4). This intermediate must be transformed into the last pentacoordinate intermediate {13} (or {$\overline{13}$}) having the OCHPh group in axial position, and leading to



Scheme 2.



Scheme 3.

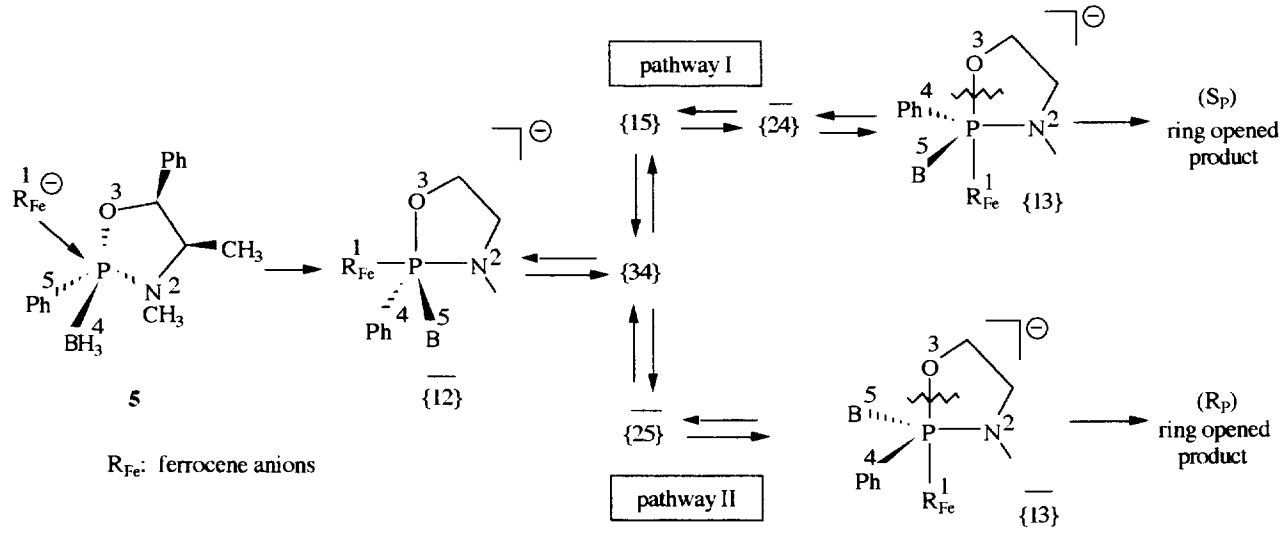
the ring-opened product by P–O[3] bond cleavage. Examination of the topological representation (Fig. 1) (pentacoordinate intermediates occupy the top of the figure in bold, while the lines represent the stereopermutations of type M1 (Berry or TR), allowing the passage from one stereoisomer to the other [17]) shows that {$\overline{12}$} begins to evolve into its isomer {34}, which is transformed into {15} (or {$\overline{25}$}), leading to the last pentacoordinate intermediate {13} (or {$\overline{13}$}). It is easy to understand the stereochemistry of each pathway leading to {13} or {$\overline{13}$}, and which are responsible for the ring-opened products with (S_P) and (R_P) configurations respectively.

Consequently, as the relative stability between the pentacoordinate intermediates is about 3–8 kcal mol^{-1} (determined by ab initio calculation [18]), the difference between the two stereochemical pathways is too small under the reaction conditions, with heating at 45 °C during 6 h, to permit a chirality control at the P-center.

2.2. Synthesis of diphosphine 1 by homocoupling of the cyclopentadienyl-methyl-phenyl-phosphine borane 2 with $FeCl_2$ (Scheme 1, pathway B)

The diphosphine **1** is obtained in the second strategy, by homocoupling of the cyclopentadienyl-methyl-phenyl phosphine **2**, which is synthesized from the oxazaphospholidine borane **5**.

As the cyclopentadienyl anion does not react cleanly,



Scheme 4.

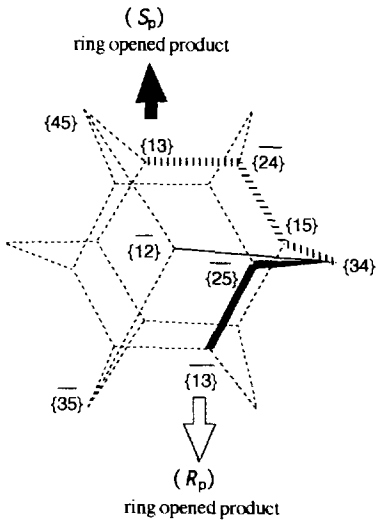
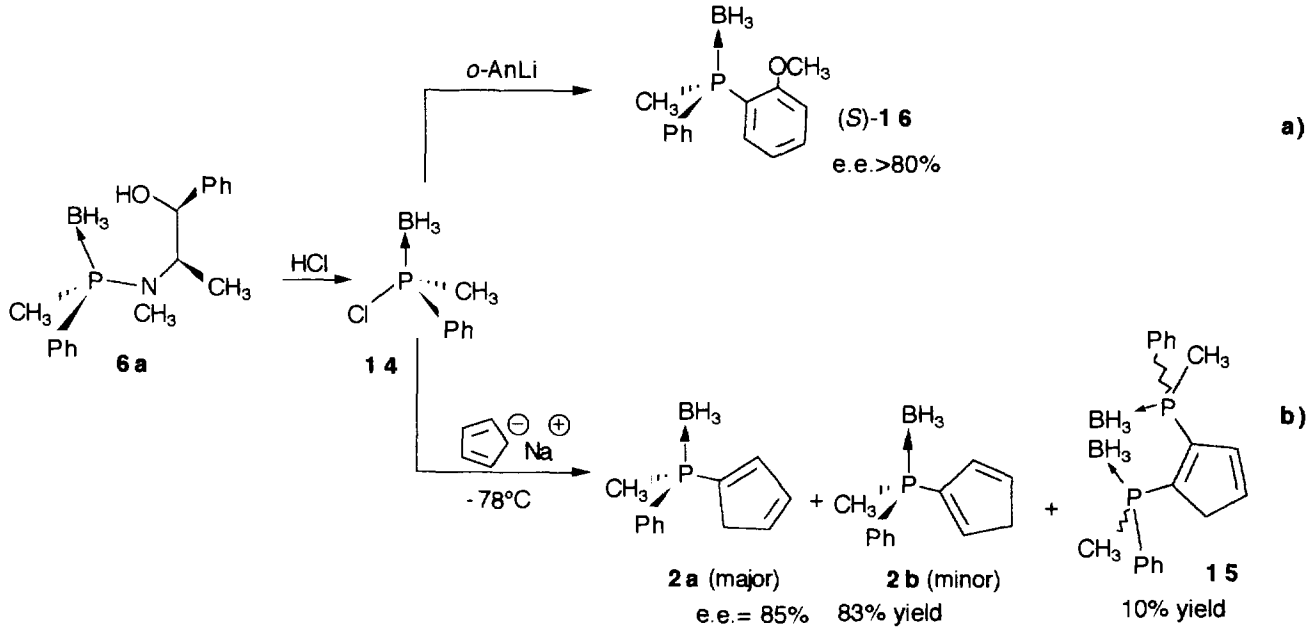


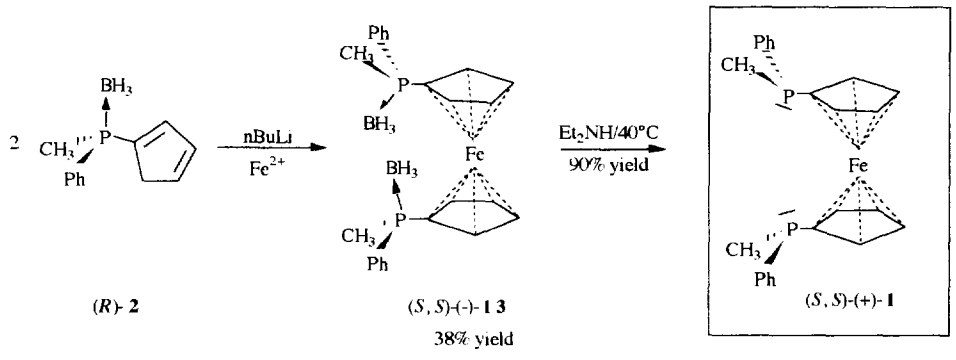
Fig. 1. Topological representations of the stereochemical pathways of the pentacoordinate intermediates towards the last {13} (or $\overline{\{13\}}$) precursor of the ring-opened product with (S_P) (or (R_P)) configuration.

either with the starting complex **5** or with the methyl phenyl phosphinite borane **7** (R_1 or R_2 = CpNa, Scheme 1), we have envisaged preparing the more reactive corresponding chlorophosphine borane **14**. Thus, this compound was prepared by P–N cleavage of the aminophosphine borane **6a** ($R_1 = CH_3$) with HCl (Scheme 5).

Preliminary results having showed that the chlorophosphine borane **14** could racemize during the work-up, we trapped it with an excess of cyclopentadienyl sodium at low temperature, after removal of the ephedrine salt by filtration. Under these conditions, the cyclopentadienyl phosphine borane **2** is obtained in 83% yield, as a mixture of two isomers **2a**,**2b** (due to the relative position of the double bonds in the ring [19]), in a ratio better than 9:1. HPLC analysis using a chiral column of the purified phosphine borane **2a** indicated an enantiomeric excess of 85%. The diphosphine borane **15** was also formed in this reaction in 10% yield,



Scheme 5.



Scheme 6.

arising from the addition of a second equivalent of chlorophosphine borane **14** to the phosphine borane **2** anion. The unsymmetrical structure of **15** is proposed on the basis of ^{31}P NMR chemical shifts showing two signals at +11.3 and +3.0 ppm.

In order to determine the absolute configuration of the cyclopentadienyl phosphine borane **2**, we have studied the stereochemistry of the reaction of *o*-anisyllithium with the chlorophosphine borane **14**, which affords the (*S*)-PAMP borane **16** (Scheme 5). As it is reasonable to consider that this reaction occurs with an inversion of configuration, it derives that the chlorophosphine borane **14** has the (*R*) configuration and results from an inversion of the (S_P)-aminophosphine **6a**. Consequently, we can attribute the (*R*) configuration to the cyclopentadienyl-methyl-phenyl-phosphine borane **2** (Scheme 5).

The compound **2** is then deprotonated by ^{n}BuLi and coupled with $FeCl_2$ to afford the (*S,S*)-diphosphine borane **13** in 38% yield, following a classical procedure described in the literature [20] (Scheme 6). It is noteworthy that we do not see the formation of coupled products of the diphosphine borane **15** under the same conditions.

The diastereomerically pure (*S,S*)-(−)-diphosphine borane **13** is obtained after recrystallization, then the borane is removed by reaction with diethylamine to give the (*S,S*)-(+)-diphosphine **1**, whose ^{31}P NMR analysis indicates the presence of only one isomer at −38.3 ppm.

3. Conclusion

Two strategies for the asymmetric synthesis of 1,1′-bis-(methyl-phenyl-phosphino) ferrocene **1** have been studied, starting from the oxazaphospholidine borane complex **5** derived from (+)-ephedrine. In the first synthetic pathway (A), the diphosphine **1** was synthesized via a key step formation of two P–C bonds by ring opening of complex **5** with 1,1′-dilithio ferrocene **10**. Unfortunately, this approach led to a diastereomeric mixture of the diphosphine **1** in a 55:45 ratio, explained by the steric hindrance of the ferrocene anion, which gives a poor stereoselectivity under the reaction conditions.

In the second approach (pathway B), the diphosphine **1** was synthesized via homocoupling of the cyclopentadienyl phosphine borane **2** anion with $FeCl_2$. The (*R*)-phosphine borane **2** was prepared with an *ee* of 85% by the reaction of CpNa with the chlorophosphine borane **14**. The coupled diphosphine borane **13** was obtained diastereomerically pure after recrystallization, then decomplexed to give, in fine, the corresponding (*S,S*)-(+)-diphosphine **1**.

4. Experimental details

4.1. General

All reactions were carried out under an argon atmosphere in glassware dried overnight. All solvents were dried and freshly distilled under an argon atmosphere over sodium/benzophenone for THF and ether, and CaH_2 for toluene. Ethyl acetate and CH_2Cl_2 were of reagent grade and distilled before use. Hexane and ethanol for HPLC were of chromatography grade and used without further purification. Methyl lithium, *n*-butyl lithium, *s*-butyl lithium, $BH_3 \cdot S(CH_3)_2$ in toluene, (+)-ephedrine, $FeCl_2$ and ferrocene were purchased from Aldrich, Acros and Strem. Ephedrine was dried by azeotropic entrainment of toluene on a rotary evaporator. Commercially available 2-bromo anisol and dichlorophenyl phosphine were distilled before use. HPLC analyses were performed on a Gilson 302 UV detector. The enantiomeric excesses of the tertiary monophosphine boranes **2** and **16** were determined using a Chiracel OK column (Daicel), with a hexane/^{i}PrOH 6/4 mixture as the mobile phase, flow rate 1 ml min^{-1} and UV detection $\lambda = 240$ nm. Flash chromatography was performed on silica gel (230–400 mesh, Merck), and when necessary diastereomeric samples were obtained by preparative TLC on commercially available silica gel plates $60F_{254+366}$ (Merck)

All NMR spectra data were recorded on Bruker AM 200 (^{1}H, ^{13}C), AM and DPX 250 (^{1}H, ^{13}C, ^{31}P) spectrometers with TMS as internal reference for ^{1}H and ^{13}C NMR, and 85% phosphoric acid as external reference for ^{31}P NMR. Infrared spectra were recorded on Perkin–Elmer 297, 251, 1600 FT and Bruker FT 45 spectrometers.

Melting points were measured on a Büchi melting point apparatus and are uncorrected. Specific rotation values were determined at 20 °C on a Perkin–Elmer 241 polarimeter. Mass spectral analyses were performed on a NERMAG R10-10C and a KRATOS MS-50 for exact mass, at the Mass Spectroscopy Laboratories of the ENSCP and the Structural Chemistry Laboratories of P. et M. Curie University (Paris) respectively. The major peak m/z is mentioned with the intensity as a percentage of the base peak in brackets.

Elemental analyses were measured with a precision superior to 0.3%, at the Microanalysis Laboratories of P. et M. Curie University (Paris), and at the CNRS (Vernaison, France).

4.2. Preparation of bis(dimethylamino)phenyl phosphine 3

A 5 l, three-necked flask equipped with an efficient mechanical stirrer and a reflux condenser was charged

with 3 l of diethyl ether, 640 g of sodium hydroxide (16 mol) and 326.2 g of dimethylamine hydrochloride (4 mol). After 4 h of vigorous stirring, the organic phase was separated from the lower viscous mineral layer, and titrated with HCl M (90% yield). A 5 l three-necked flask equipped with a pressure-equalizing dropping funnel was charged with the etheral solution of dimethylamine (2 mol) and cooled to 5 °C with an ice bath. To this solution, 152 g of dichlorophenylphosphine (0.85 mol) in 50 ml of ether were slowly added under stirring (1 h), over nitrogen flush. The stirring was maintained for an additional 3 h, then the mixture was poured through a large Büchner filter funnel. After washing the solid with ether, the solvent was removed on a rotary evaporator, affording 137 g of a colorless oil (82% yield); b.p. 62 °C (0.1 mm Hg). ^{1}H NMR ($CDCl_3$): δ 2.8 (12H, d, $^3J_{PNCH}$ = 16 Hz); 7.27–7.48 (5H, m) ppm.

4.3. (2S,4R,5S)-(−)-3,4-Dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine-2-borane 5

A 1 l, three-necked, round-bottomed flask was equipped with a mechanical stirrer, a nitrogen inlet and a short-path distillation head fitted with a dropping condenser. The flask was charged with 500 ml of toluene, (+)-ephedrine (16.5 g, 0.100 mol) and freshly distilled bis(dimethylamino)phenyl phosphine **3** (19.6 g, 0.100 mol). The solution was stirred at 105 °C for 5 h, under a gentle flow of nitrogen to remove the dimethylamine formed. The formation of the oxazaphospholidine was monitored by ^{31}P NMR (δ +142 ppm). The flask was then cooled to room temperature, and $BH_3 \cdot S(CH_3)_2$ (10 ml/10 M or 50 ml/2 M in toluene) added under stirring. After 4 h, the solvent was removed under vacuum and the crude complex **5** crystallized upon cooling. Recrystallization from ^{i}PrOH gave 20 g of complex **5**, in two crops. After concentration of the filtrate, the residue was purified on a short column of silica gel, eluting with toluene. After recrystallization, 22 g of complex **5** was obtained in addition (77% yield).

White solid: m.p. 104 °C (^{i}PrOH); $[\alpha]_D$ −4.5° (c 4, $CHCl_3$); R_F = 0.65 (toluene). ^{1}H NMR ($CDCl_3$): δ 0.2–1.7 (3H, q.l., $^1J_{BH}$ = 83.3 Hz); 0.83 (3H, d, $^3J_{HH}$ = 6.5 Hz); 2.68 (3H, d, $^3J_{PH}$ = 11 Hz); 3.67 (1H, dd., $^3J_{HH}$ = 6 Hz, $^3J_{PH}$ = 8 Hz, $^3J_{HH}$ = 6.5 Hz); 5.60 (1H, dd, $^3J_{HH}$ = 6 Hz, $^3J_{PH}$ = 3 Hz); 7.29–7.46 (5H, m); 7.46–7.59 (3H, m); 7.79–7.86 (2H, m) ppm. ^{13}C NMR ($CDCl_3$): δ 13.52 (s); 29.4 (d, $^2J_{PC}$ = 8.6 Hz); 59 (s); 84.1 (d, $^2J_{PC}$ = 9 Hz); 126.6–145.1 ppm. ^{31}P{^{1}H} NMR ($CDCl_3$): δ +133.5 (md, $^1J_{PB}$ = 100 Hz) ppm. IR (KBr): ν (3060, 2975, 2950, 2850, 2800) (C–H); (2420, 2360, 2340) (B–H); 1450; 1205; 1160; 960 (P–O–C) cm^{-1}. MS (EI) m/z (relative intensity): 285, 272 (45); 214 (19); 165 (100); 118 (99); 108 (28); 91 (33); 56 (52). Anal. Found: C, 67.46; H, 7.55; N, 4.94. $C_{16}H_{21}ONBP$ Calc.: C, 67.36; H, 7.35; N, 4.91%.

4.4. Pathway A: Preparation of diphosphine 1 from ferrocene

4.4.1. Reaction of 1,1'-dilithio ferrocene · TMEDA 10 with complex 5

4.4.1.1. Preparation of 1,1'-dilithio ferrocene · TMEDA 10 [13]. A 100 ml two-necked flask equipped with an argon inlet, magnetic stirring and a condenser fitted with a mercury overpressure valve was charged with 2.26 ml of TMEDA and 10 ml of hexane. To this solution, 6 ml of ^{n}BuLi 2 M was added and the mixture was stirred for 10 min before addition of the ferrocene (1 g, 0.005 mol) in 40 ml of hexane over a period of 30 min. After 20 h at room temperature, fine small orange crystals were formed. The supernatant liquid was then removed under argon with a syringe, and the crystals washed three times with 10 ml of hexane.

4.4.1.2. (+)-1,1'-bis-[N-Methyl,N-(1R,2S)-(2-hydroxy-1-methyl-2-phenyl)ethyl]amino-phenyl-phosphino borane] ferrocene 11. To the 1,1'-dilithio ferrocene · TMEDA **10** (5 mmol) prepared above, was successively added under stirring 50 ml of THF, 2.85 g of complex **5** (0.01 mol) and 5 ml of $BH_3 \cdot S(CH_3)_2$ (2 M in toluene, 0.01 mol). After heating at 45 °C during 6 h with an oil bath, the mixture was hydrolyzed at room temperature, and the THF removed under reduced pressure. After extraction of the aqueous layer with 4 × 20 ml of CH_2Cl_2, the organic extracts were dried over anhydrous sodium sulfate, and the solvent removed on a rotary evaporator. The residue (2.7 g) was purified by chromatography on silica with toluene as eluent, yielding 0.39 g of compound **11** (10%). HPLC analysis of compound **11** was carried out using a 250 × 4 mm^2 Hypersil column 5 μm with a cyclohexane/THF 9:1 mixture as mobile phase (flow rate 1 ml min^{-1}, UV detection λ = 328 nm). The three isomers came out at t_R = 6.5, 7.2 and 8.2 min respectively.

Orange solid: m.p. 130 °C (^{i}PrOH); $[\alpha]_D$ +56° (c 1.5, $CHCl_3$); R_F = 0.12, 0.20 (toluene/AcOEt 9:1). ^{1}H NMR ($CDCl_3$): δ 0.6–2.1 (6H, m); 1.13 (6H, d, $^3J_{HH}$ = 6.6 Hz); 2.25 (6H, d, $^3J_{PH}$ = 8 Hz); 4.01 (2H, m); 4.08 (2H, s); 4.51–4.64 (6H, m); 4.75 (2H, d, $^3J_{HH}$ = 5.6 Hz); 7.18–7.34 (20H, m) ppm. ^{13}C NMR ($CDCl_3$): δ 12.92 (s); 25.23 (s); 30.46 (s); 57.60 (d, $^2J_{PC}$ = 5.4 Hz); 72.77–76.30; 126.45–133.09 ppm. IR (KBr): ν 3512 (OH); 2920 (C–H); 2382 (B–H); 1451; 1435; 1167; 1025; 699 cm^{-1}. MS (EI) m/z (relative intensity): 483 (10); 238 (12); 146 (100); 91(60); 58 (95).

4.4.2. 1,1'-bis-(Methoxy-phenyl-phosphino borane) ferrocene 12

A 25 ml round-bottomed flask equipped with a magnetic stirrer and an argon inlet was charged with 10 ml of methanol, 756 mg (1 mmol) of compound **1** and

98 mg of sulfuric acid 98% (1 mmol). The mixture was stirred at room temperature for three days, then filtered under reduced pressure on a Büchner funnel through silica gel. The solvent was then removed and the residue purified by chromatography on silica gel with toluene/AcOEt 9:1 as eluent, yielding 440 mg of **12** (90%) as a mixture of isomers in a 3:2 ratio.

Viscous oil; $R_F = 0.83$ (toluene/AcOEt 9:1). ^{1}H NMR ($CDCl_3$): δ 0.1–1.6 (6H, q, $^1J_{BH} = 67$ Hz); minor isomer 3.58 (3H, d, $^3J_{POCH} = 10.2$ Hz); major isomer 3.64 (3H, d, $^3J_{POCH} = 10.2$ Hz); 4.13 (1H, s); 4.40–4.76 (7H, m); 7.44–7.62 (6H, m); 7.76–7.89 (4H, m) ppm. ^{13}C NMR ($CDCl_3$): δ 53.72 (s); 72.35–73.12 (m); 73.89–74.72 (m); 128.43–132.01 ppm. IR (KBr): ν 3057; 2998; 2942; 2840 (C–H); 2387 (B–H); 1437; 1177; 1115; 1066; 1031 (POC) cm^{-1}. HRMS (EI) Found: $[M]^+$ 490.1268. $C_{24}H_{30}B_2FeO_2P_2$ Calc.: $[M]^+$ 490.1269. MS (EI) m/z (relative intensity): 490 (2); 476 (10); 462 (100); 385 (8); 323 (16); 293 (20); 226 (18); 151 (26); 109 (43).

4.4.3. 1,1'-bis-(Methyl-phenyl-phosphino borane) ferrocene 13

A 25 ml two-necked flask equipped with a magnetic stirrer, an argon inlet and a rubber septum was charged with a solution of 0.98 g of compound **12** (2 mmol) in 2 ml of THF. To this, 2.8 ml of methyl lithium (1.6 M, 4.4 mmol) was added slowly at −78 °C, and then the reaction mixture was brought to room temperature and hydrolyzed. After removal of THF under reduced pressure, the aqueous layer was extracted with CH_2Cl_2. The solvent was removed, and the residue purified by chromatography on silica gel with toluene as eluent, to give 0.6 g of the isomers **13** in a 3:2 ratio (65% yield).

Orange solid: m.p. 132 °C (mixture of isomers); $R_F = 0.45$ (toluene). ^{1}H NMR ($CDCl_3$): δ 0.1–1.6 (6H, l); minor isomer 1.74 (3H, d, $^2J_{PCH} = 10.2$ Hz); major isomer 1.81 (3H, d, $^2J_{PCH} = 10.2$ Hz); 4.36–4.73 (8H, m); 7.41–7.48 (6H, m); 7.60–7.75 (4H, m) ppm. ^{13}C NMR ($CDCl_3$): δ minor isomer 12.83 (d, $^1J_{PC} = 42$ Hz); major isomer 13.31 (d, $^1J_{PC} = 41$ Hz); 71.62–72.19 (m); 72.96–73.93 (m); 128.49–132.17 ppm. IR (KBr): ν (3091, 3051) (C–H); (2381, 2349) (B–H); 1435; 1415; 1185; 1176; 1111; 1067; 1026 cm^{-1}. HRMS (EI) Found: $[M]^+$ 458.1358. $C_{24}H_{30}B_2FeP_2$ Calc.: $[M]^+$ 458.1358. MS (EI) m/z (relative intensity): 458 (4); 444 (28); 430 (100); 415 (45); 353 (5); 319 (4); 226 (10); 170 (8); 121 (10); 91 (10). Anal. Found: C, 62.77; H, 6.56. $C_{24}H_{30}B_2FeP_2$ Calc.: C, 62.87; H, 6.60%.

4.4.4. 1,1'-bis-(Methyl-phenyl-phosphino) ferrocene 1 from 13

A 25 ml round-bottomed flask equipped with a magnetic stirrer, a reflux condenser fitted with a rubber septum and an argon inlet was charged with 458 mg of the diphosphine borane **13** (1 mmol) and 3 ml of diethylamine. The mixture was heated at 50 °C for 14 h, then the solvent removed under reduced pressure, and the residue purified by chromatography on a short column of silica gel with toluene as eluent, giving 390 mg of the diphosphine **1** (90% yield) as a mixture of isomers in a 55:45 ratio.

Orange solid: $R_F = 0.81$ (toluene/AcOEt/hexane 70:10:20). ^{1}H NMR ($CDCl_3$): δ minor isomer 1.64 (3H, d, $^2J_{PCH} = 3$ Hz); major isomer 1.65 (3H, d, $^2J_{PCH} = 3$ Hz); 4.35–4.45 (8H, m); 7.29–7.41 (10H, m) ppm. ^{13}C NMR ($CDCl_3$): δ minor isomer 11.89 (d, $^1J_{PC} = 41$ Hz); major isomer 12.38 (d, $^1J_{PC} = 42$ Hz); 69.37; 71.30; 72.01; 74.66–75.21 (m); 127.96; 130.95; 131.33. ^{31}P NMR ($CDCl_3$): δ −38.2; −38.3 ppm. IR (KBr): ν 3063, 2969, 2906 (C–H); 1583; 1491; 1430; 1394; 1195; 1168; 1027; 875; 739; 695 cm^{-1}. HRMS (EI) Found: $[M]^+$ 430.0703. $C_{24}H_{24}FeP_2$ Calc.: $[M]^+$ 430.0702. MS (EI) m/z (relative intensity): 430 (35); 415 (25); 398 (10); 353 (3); 323 (5); 274 (8); 256 (20); 224 (17); 185 (10); 149 (12); 129 (20); 91 (40); 69 (80). Anal. Found: C, 66.84; H, 5.62. $C_{24}H_{24}FeP_2$ Calc.: C, 66.97; H, 5.62%.

4.5. Pathway B: Preparation of diphosphine 1 from cyclopentadienyl-methyl-phenyl-phosphine borane 2

4.5.1. (S_p)-(+)-N-Methyl-N-[(1R,2S)(2-hydroxy-1-methyl-2-phenyl)ethyl]amino-methyl-phenyl-phosphine borane 6a

A 25 ml two-necked flask equipped with a magnetic stirrer, an argon inlet and a rubber septum was charged with a solution of 2.85 g of the complex **5** (10 mmol) in 15 ml of THF. To this, 6.9 ml of methyl lithium (1.6 M, 11 mmol) was added slowly at −78 °C under stirring, and the reaction was maintained at this temperature for 30 min. The cooling bath was removed, and the reaction mixture allowed to warm to room temperature and hydrolyzed. The THF was removed under reduced pressure, and the aqueous layer extracted with 3 × 20 ml of CH_2Cl_2. The combined extracts were washed with H_2O, dried over $MgSO_4$, then concentrated. The residue was crystallized in ^{i}PrOH/hexane 1:1 mixture to give 2.7 g of compound **6a** (90% yield). The residue could also be purified by chromatography on a short column of silica gel with toluene/AcOEt 9:1) mixture as eluent.

White solid: m.p. 67 °C (hexane); $R_F = 0.44$ (toluene/AcOEt 9:1). ^{1}H NMR ($CDCl_3$): δ 0.00–1.60 (3H, d, $^1J_{BH} = 83$ Hz); 1.20 (3H, d, $^3J_{HH} = 7$ Hz); 1.49 (3H, d, $^2J_{PCH} = 9$ Hz); 2.07 (1H, sl); 2.43 (3H, d, $^3J_{PNCH} = 8.6$ Hz); 3.99 (1H, qd, $^3J_{HH} = 6.7$ Hz, $^3J_{PNCH} = 7.4$ Hz); 4.68 (1H, d, $^3J_{HH} = 7$ Hz); 3.04–7.11 (3H, m); 7.21–7.42 (7H, m) ppm. ^{13}C NMR ($CDCl_3$): δ 11.17 (d, $^1J_{PC} = 42$ Hz); 13.79 (s); 28.86 (s); 58.96 (d, $^2J_{PNC} = 7.6$ Hz); 77.60 (d, $^3J_{PNNC} = 5.9$ Hz); 126.64–142.55 ppm. ^{31}P NMR ($CDCl_3$): δ +66.5 (m) ppm. IR (KBr): ν 3354 (O–H); 3057, 2969, 2934, 2873 (C–H);

2376 (B–H); 1437; 1136; 1116; 1066; 1049; 906 cm^{-1}. MS (EI) m/z (relative intensity): 270 (1); 180 (100); 132 (21); 123 (54); 155 (54); Anal. Found: C, 67.75; H, 8.56; N, 4.64. $C_{17}H_{25}ONBP$ Calc.: C, 67.73; H, 8.30; N, 4.65%.

*4.5.2. (R_P)-Chloro-methyl-phenyl-phosphine borane **14***

A 250 ml two-necked flask equipped with a magnetic stirrer, an argon inlet and a rubber septum was charged with 1.2 g of the aminophosphine borane **6a** (4 mmol) and 166 ml of toluene. A solution of HCl in toluene (0.24 M, 34 ml, 8 mmol) was added at room temperature under stirring, and the reaction was monitored by TLC over silica (toluene/AcOEt 9:1). After 1 h, the ephedrine salt was filtered off with a millipore 4 μm filter, and the solution of chlorophosphine borane (90% yield) used without further purification.

After removal of the solvent, the chlorophosphine borane could be purified in a poor yield by chromatography on a short column of silica gel, previously dried overnight at 80 °C and washed with acetone then cyclohexane.

Colorless viscous oil: $R_F = 0.80$ (toluene). ^{1}H NMR ($CDCl_3$): δ 0.50–2.00 (3H, q, $^1J_{BH} = 95$ Hz); 1.20 (3H, d, $^2J_{PCH} = 11$ Hz); 7.30–7.70 (3H, m); 7.80–8.00 (2H, m) ppm. ^{13}C NMR ($CDCl_3$): δ 19.95 (d, $^1J_{PC} = 31$ Hz); 129.1 (d, $J_{PC} = 11$ Hz); 130.8 (d, $J_{PC} = 12$ Hz); 133.1 (d, $J_{PC} = 2$ Hz) ppm. ^{31}P NMR ($CDCl_3$): δ +96.8 (q, $^1J_{PB} = 47$ Hz) ppm. IR (KBr): ν 3080, 3000, 2940 (C–H); 2383 (B–H); 1437; 1119; 1062; 1049; 949; 909; 745; 690 cm^{-1}. MS (EI) m/z (relative intensity): 173 (1); 140 (20); 125 (100); 109 (64).

*4.5.3. (S_P)-o-Anisyl-methyl-phenyl-phosphine borane **16** (PAMP · BH_3) from the chloro phosphine borane **14***

A 100 ml two-necked flask equipped with a magnetic stirrer, an argon inlet and a rubber septum was charged with 55 ml of a freshly prepared solution of the chloro phosphine borane **14** in toluene (1 mmol) and cooled to −78 °C. A 50 ml two-necked flask fitted with a rubber septum and equipped with an argon inlet was charged with 0.7 ml of ^{s}BuLi (1.4 M, 1 mmol) and then 190 mg of 2-bromo-anisol was added dropwise at 0 °C. After 1 h, the mixture was cannulated to the flask containing the chlorophosphine **14**. The reaction was maintained at this temperature for 30 min, then the cooling bath was removed and the reaction hydrolyzed at room temperature. The THF was removed under reduced pressure, and the aqueous layer extracted with 3 × 20 ml of CH_2Cl_2. The combined extracts were washed with 2 × 20 ml of H_2O, dried over $MgSO_4$, then concentrated. The enantiomeric excess and the absolute configuration of the PAMP · BH_3 **16** were determined on the crude product by HPLC on a Chiracel OK Daicel column with hexane/EtOH 55:45 as eluent (flow rate 1 ml min^{-1}; major (*S*) enantiomer $t_R = 13.2$ min; minor (*R*) enantiomer $t_R = 7.7$ min; *ee* > 80%). The residue could also be purified by chromatography on a short column of silica gel with a toluene/hexane 8:2 mixture as eluent, to give 220 mg of **16** (90% yield).

White solid: $R_F = 0.52$ (toluene/hexane 8:2). ^{1}H NMR ($CDCl_3$): δ 0.40–1.50 (3H, q, $^1J_{BH} = 88$ Hz); 1.94 (3H, d, $^2J_{PCH} = 10.6$ Hz); 3.67 (3H, s); 6.90–7.90 (9H, m) ppm. ^{13}C NMR ($CDCl_3$): δ 10.7 (d, $^1J_{PC} = 42$ Hz); 55.4; 129.1 (d, $J_{PC} = 11$ Hz); 111.3–135.6; 161.5 ppm. ^{31}P NMR ($CDCl_3$): δ +9.2 (q, $^1J_{PB} = 72$ Hz) ppm. MS (EI) m/z (relative intensity): 230 (100); 199 (43); 183 (35); 91 (57).

*4.5.4. (R_P)-Cyclopentadienyl-methyl-phenyl-phosphine borane **2** from the chloro phosphine borane **14***

To a 250 ml two-necked flask equipped with an argon inlet and a rubber septum and charged with 5.87 g of white crystalline C_5H_5Na · DME (33 mmol) [21], the chloro phosphine borane **14** (4 mmol) in 200 ml of toluene was added under stirring at −78 °C. The reaction was maintained at this temperature for 1.5 h, then the cooling bath was removed and the mixture allowed to warm to room temperature. After 12 h, the mixture was passed through Celite and washed with CH_2Cl_2. After removal of the solvent, the residue was purified by chromatography on silica gel with toluene as eluent, yielding 670 mg of the cyclopentadienyl-phosphine borane **2** (83% yield) as a mixture of two isomers **2a**,**2b** in a ratio better than 9:1. In addition, 140 mg of the diphosphine borane **15** as a mixture of isomers was also obtained (10% yield).

*4.5.4.1. (R_P)-Cyclopentadienyl-methyl-phenyl-phosphine borane **2a**.* The enantiomeric excess and the absolute configuration of the phosphine borane **2a** were determined by HPLC on a Chiracel OK Daicel column with hexane/^{i}PrOH 6:4 as eluent (flow rate 1 ml min^{-1}; minor (*S*) enantiomer $t_R = 10$ min; major (*R*) enantiomer $t_R = 21$ min; *ee* 85%).

Colorless viscous oil: $[\alpha]_D$ −4 (c 0.6, $CHCl_3$); $R_F = 0.55$ (toluene). ^{1}H NMR ($CDCl_3$): δ 0.00–2.00 (3H); 1.60 (3H, d, $^2J_{PCH} = 10$ Hz); major isomer **2a** 3.00 (2H, m); minor isomer **2b** 3.10; 6.90–7.20 (5H, m) ppm. ^{13}C NMR ($CDCl_3$): δ 10.75 (d, $^1J_{PC} = 41$ Hz); 44.2 (d, $^1J_{PC} = 41$ Hz); 127.9; 128.1; 130.5–130.6 ppm. ^{31}P NMR ($CDCl_3$): δ +0.9 (q, $^1J_{PB} = 71$ Hz) ppm.

*4.5.4.2. 1,2-bis-(Methyl-phenyl-phosphino borane) cyclopentadiene **15**.* Colorless viscous oil: mixture of isomers $R_F = 0.23$ (toluene). ^{1}H NMR ($CDCl_3$): δ 0.00–2.00 (3H); 1.45 (3H, d, $^2J_{PCH} = 12$ Hz); 1.60 (3H, d, $^2J_{PCH} = 12$ Hz); 2.85 (2H, m); 7.30–7.60 (6H, m); 7.6–7.8 (4H, m) ppm. ^{13}C NMR ($CDCl_3$): δ 5.80–7.19 (m); 8.87–10.23 (m); major isomer 50.43 (d, $^1J_{PC} = 30$ Hz); minor isomer 50.62 (d, $^1J_{PC} = 27$ Hz); 127.6–127.8;

130.51–131.38 ppm. ^{31}P NMR ($CDCl_3$): δ +10.4 (m); +2.2 (m, $^1J_{PB}$ = 69 Hz) ppm. MS (EI) m/z (relative intensity): 279 (10); 201 (13); 188 (100); 173 (70); 149(69); 123(21); 77(36).

*4.5.5. (S,S)-(−)-1,1′-bis-(Methyl-phenyl-phosphino borane) ferrocene **13** by homocoupling of **2** with $FeCl_2$*

A 100 ml two-necked flask equipped with a magnetic stirrer, an argon inlet and a rubber septum was charged with 600 mg of the phosphine borane **2** (2.97 mmol) in 3 ml of THF, and 2.5 ml of ^{n}BuLi (1.25 M, 3.2 mmol) was added at −78 °C under stirring. After half an hour, a suspension of 190 mg of $FeCl_2$ (1.5 mmol) in 2 ml of THF was added, and the reaction allowed to warm to room temperature for an additional 4 h before hydrolysis. The solvents were removed under reduced pressure and the aqueous layer extracted with 4 × 20 ml of CH_2Cl_2. The combined extracts were washed with H_2O, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel with a toluene/cyclohexane 40:60 mixture as eluent, yielding 260 mg of the diphosphine borane **13** (38% yield), which was recrystallized from a cyclohexane/^{i}PrOH 8:2 mixture.

Orange solid: m.p. 188 °C (cyclohexane/^{i}PrOH 8:2); $[\alpha]_D$ −92.8 (c 0.6, $CHCl_3$); R_F = 0.45 (toluene). ^{1}H NMR ($CDCl_3$): δ 0.1–1.6 (6H, l); 1.77 (3H, d, $^2J_{PCH}$ = 10.1 Hz); 4.32 (2H, sl); 4.49 (2H, sl); 4.57 (2H, sl); 4.59 (2H, sl); 7.41–7.45 (6H, m); 7.62–7.67 (4H, m) ppm. ^{13}C NMR ($CDCl_3$): δ 13.40 (d, $^1J_{PC}$ = 42 Hz); 72.19 (d, J_{PC} = 8 Hz); 72.41 (d, $^1J_{PC}$ = 64 Hz); 73.14 (d, J_{PC} = 11 Hz); 73.76 (d, J_{PC} = 15 Hz); 73.87 (d, J_{PC} = 15 Hz); 128.58; 128.74; 131.11; 131.15; 131.20; 131.35 ppm. ^{31}P NMR ($CDCl_3$): δ +5.9 (q, $^1J_{PB}$ = 74 Hz) ppm. MS (EI) m/z (relative intensity): 458 (30); 444 (53); 430 (100); 415 (64); 353 (5); 319 (5); 226 (10).

*4.5.6. (S,S)-(+)-1,1′-bis-(Methyl-phenyl-phosphino) ferrocene **1***

170 mg of the diphosphine borane **13** prepared from **2** was heated at 45 °C in 5 ml of diethylamine. After 2 h the solvent was removed under reduced pressure, and the residue purified by chromatography on a short column of silica gel with a hexane/AcOEt 8:2 mixture as eluent, giving 144 mg of the diphosphine **1** (90% yield).

Orange solid: m.p. 124 °C; R_F = 0.75 (toluene); $[\alpha]_D$ +15.8 (c 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.53 (6H, d, $^2J_{PCH}$ = 3 Hz); 4.23 (4H, sl); 4.29–4.30 (4H, m); 7.29–7.41 (10H, m) ppm. ^{31}P NMR ($CDCl_3$): δ −38.3 ppm. MS (EI) m/z (relative intensity): 430 (60); 415 (100); 400 (1); 353 (9); 307 (5); 226 (10).

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