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Asymmetric version of P-S to P-C [1,3]-sigmatropic rearrangement in the ferrocene series

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Abstract—The synthesis of new 2-sulfanylferrocenylphosphonates and derivatives has been achieved through a P-S to P-C [1,3]-sigmatropic rearrangement. The asymmetric version of this reaction has been successfully performed starting from a ferrocenylphosphorodiamidothioate and afforded, as a single diastereoisomer, enantiomerically pure planar chiral *ortho*-thio-substituted ferrocenyl phosphorodiamidate.

1. Introduction

Organophosphonates have found a wide range of applications in the areas of agricultural[1] and medicinal chemistry[2] owing to their biological activity and their structural analogy with phosphates.[3] Moreover, alkylphosphonic acid derivatives such as mono (2-ethylhexyl)(2-ethylhexyl) phosphonic acid (EHEHPA) or dibutylbutylphosphonate (DBBP) have found widespread use as extractions of metals.[4] Metal complexes of thiolates have also received considerable attention,[5] because of their involvement in enzymatic[6] and non-biological catalytic processes.[7] More recently, copper arenethiolates developed by van Koten et al.,[8] have been used as catalysts in regio-[9] and enantioselective[10] allylic substitution reactions.

Compounds containing both phosphoryl and sulfanyl groups should be particularly attractive as polydentate ligands. Few examples of such compounds have been reported in the literature. Among them, 2-phosphino and 2-phosphinylbenzenethiols have been reported by Block et al.,[11] while *ortho*-mercaptoaryl, *ortho*-mercaptoheteroaryl phosphonates and their derivatives, and chiral *ortho*-thio-substituted phenylphosphonodiamidates have already been reported by some of us.[12,13]

In particular, *ortho*-sulfanyl phosphonates and phosphonodiamidates have been obtained via an *ortho*-lithiation of the aryl or heteroaryl phosphorothioate or phosphorothioamidate, followed by a P-S to P-C rearrangement ([1,3] anionic sigmatropic shift).

Ferrocene derivatives containing atoms with good donor abilities have attracted strong interest, since these complex molecules are able to act as ligands towards transition metal ions.[14] Furthermore, the sandwich structure of the ferrocene and the planar chirality, present in the derivatives with at least two different substituents in the same ring,[14] render these derivatives completely different from conventional aromatic molecules and increase their interest as chiral ligands.

Mercaptoferrocene has been used as a sulfur-based nucleophile for the synthesis of poly-heterosubstituted ferrocene derivatives with central chirality; some of these compounds have successfully been employed as ligands for palladium-catalyzed allylic substitution with asymmetric induction up to 99% ee.[15] Planar and centrally chiral ferrocenyl thiolate copper complexes have been used in the conjugate addition of Grignard reagents to enones[16] and as ligands in the enantioselective

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copper-catalyzed substitution of allylic acetate with Grignard reagents.[17]

Herein, we report our results on the synthesis of new 2-sulfanylferrocenylphosphonates and derivatives as well as the enantiomerically pure planar chiral *ortho*-thio-substituted ferrocenyl phosphonodiamidate obtained through a P-S to P-C rearrangement.

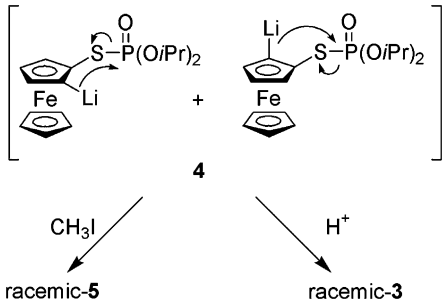
2. Results and discussion

We synthesized (*S*)-ferrocenylphosphorothioate **2** in 82% yield from sodium ferrocenyl thiolate (prepared from mercaptoferrocene **1** and sodium hydride) and diisopropyl phosphorochloridate.[12] The subsequent treatment of **2** with LDA at −5 °C in THF followed by quenching with 3.5 M H_2SO_4 solution gave 2-*O*,*O*-diisopropyl 2-sulfanylferrocenylphosphonate **3** in 86% yield as well as less than 10% of mercaptoferrocene probably arising from the nucleophilic attack of LDA on the phosphoryl centre (Scheme 1).[12b]

As previously reported,[12] the rearrangement of *O*,*O*-diisopropyl (*S*)-phenyl phosphorothioate to sulfanylphenylphosphonate takes place via an *ortho*-lithiated intermediate. In the case of ferrocene derivative **2**, the lithiation occurs at both enantiotopic *ortho*-positions to afford the lithiated racemic species **4**, which after S–C migration of the phosphonyl group and quenching with an electrophile like proton or CH_3I, led to the racemic **3** or racemic **5** (Scheme 2). ^1H NMR studies on **5** revealed that the singlet of SCH_3 ($CDCl_3$) at 2.27 ppm was split in the presence of the Pirkle alcohol into two singlets at 2.06 and 2.14 corresponding to the two enantiomers.

When the reaction was quenched with a saturated aqueous solution of NH_4Cl, it afforded an inseparable mixture of the two diastereomeric disulfides.

In order to obtain an enantiomerically pure or enantiomerically enriched planar chiral 2-sulfanylferrocenylphosphonate or its derivatives, the following methods can be envisaged: (i) an enantioselective *ortho*-lithiation reaction using (−)-sparteine as a chiral additive,[18] (ii) a diastereoselective *ortho*-lithiation of an enantiomerically pure phosphorothioate and (iii) treatment of the racemic lithium thiolate species, obtained after rearrangement of **4**, with an enantiomerically pure reagent leading to the formation of separable diastereoisomers. We have investigated the feasibility of all these three methods.

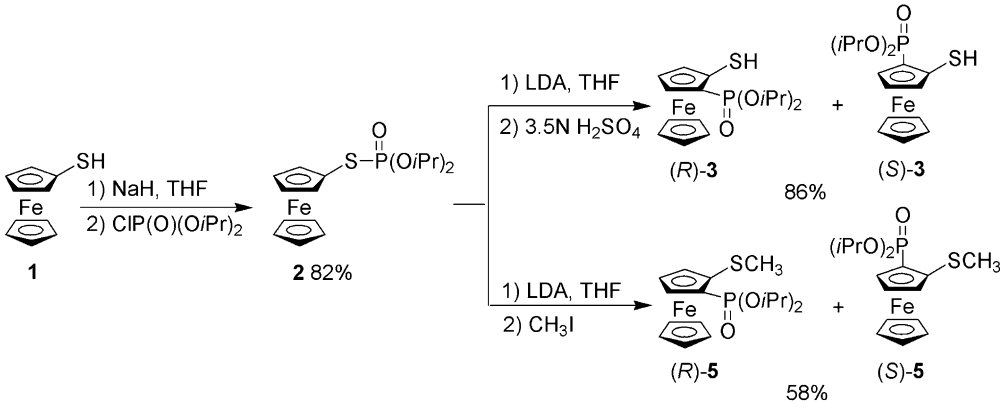


Scheme 2.

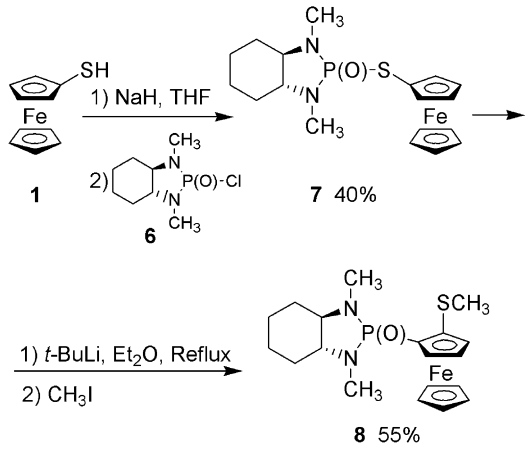
The lithiation of **2** with *n*-BuLi/(−)-sparteine and quenching with CH_3I (i) gave methylsulfanylferrocene (64%), resulting from the nucleophilic attack of *n*-BuLi on the phosphorus, and unreacted starting material (30%). The same reaction with *s*-BuLi/(−)-sparteine gave 70% of methylmercaptoferrocene and 10% of product **5** with an ee of 9% (determined by performing the ^1H NMR spectrum of the crude in the presence of Pirkle's alcohol).

The second route (ii) has been investigated using the enantiopure chlorophosphoroamidate **6**[19] as a chiral auxiliary. The reaction of **6** with mercaptoferrocene **1** gave ferrocenylphosphorodiamidothioate **7** in 40% yield (Scheme 3).

The rearrangement of **7** was attempted both with LDA (2.5 equiv at −5 °C) and with 1.1 equiv of *t*-BuLi at −10 °C in THF, but only the starting material was recovered in both cases at the end of the reaction. In contrast, the rearrangement occurs if the lithiation is performed with 1.5 equiv of *t*-BuLi in Et_2O at reflux. Under these conditions, the rearranged product **8** was obtained in 55% yield along with 17% of the starting



Scheme 1.



Scheme 3.

material and 7% of methylsulfanylferrocene (Scheme 3). With the aim of improving the yield of **8**, the same reaction was performed using 2.2 equiv of *t*-BuLi. This condition led to the disappearance of the starting material and to the formation of a large amount of methylsulfanylferrocene along with an inseparable mixture of **8** and over methylated products. Product **8** has been obtained as a single diastereoisomer, no trace of the other diastereoisomer has been found in the ^{1}H and ^{13}C NMR of the crude reaction mixture (d.r. >98:2). Its absolute configuration has been found (R,R,S_{Fc}) by X-ray analysis (Fig. 1).[20]

As far as the third approach is concerned, we have previously shown that mercaptoferrocene **1** reacts with enantiomerically pure oxiranes or amino alcohols[15] providing β-hydroxyalkyl and β-aminoalkyl ferrocenylsulfides with central chirality in good yield. The racemic ferrocenylthiol **3**, transformed into the sodium thiolate, reacted with (*S*)-(−)-propylene oxide affording a separable mixture of the two diastereomeric diisopropyl 2-(2-hydroxypropyl) sulfanylferrocenylphosphonate **9a** and **9b** in moderate yield.

These products could also be obtained via a one-pot procedure by reaction of **2** with LDA followed by quenching with (*S*)-(−)-propylene oxide (Scheme 4).

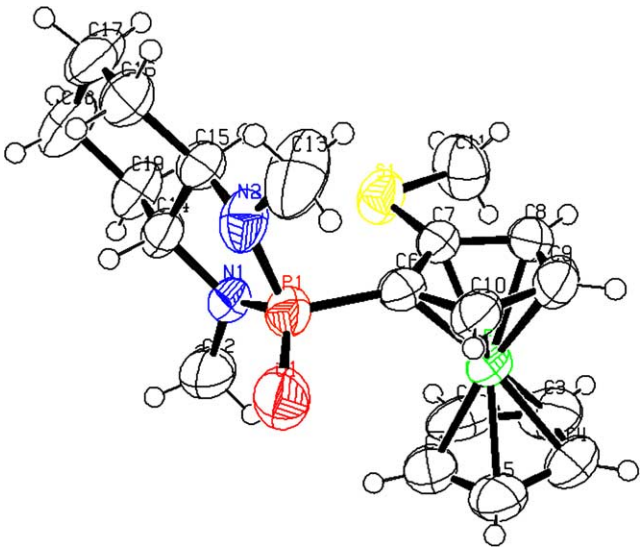


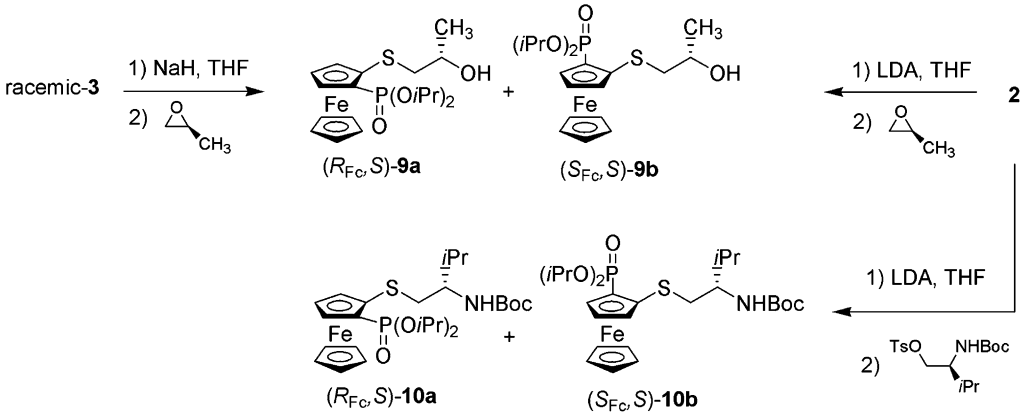
Figure 1. X-ray crystal structure of (R,R,S_{Fc})-**8**.

Using the same methodology, the synthesis of **10a** and **10b** was performed via a one-pot reaction by treatment of **2** with LDA and quenching with (*S*)−*N*-*tert*-butoxycarbonyl-2-amino-3-methyl-1-butyl-*p*-toluenesulfonate (Scheme 4).

The mixtures **9a/9b** and **10a/10b** were separated by chromatography: each product was completely characterized and showed only one set of signals in the ^{1}H and ^{13}C NMR spectra. For this reason, each separated diastereoisomer was considered enantiomerically pure. The absolute configuration of **10b** has been found to be (S,S_{Fc}) by X-ray analysis[21] (Fig. 2). On the bases of the analogies of the ^{1}H NMR spectra of **10b** in comparison with that of **9b** and **10a** with that of **9a** and on the basis of the elution order in preparative TLC, we tentatively attribute the (S,S_{Fc})-configuration to **9b**.

3. Conclusions

We have demonstrated the possibility of obtaining *ortho*-mercaptoferrocenylphosphonates and their derivatives and enantiomerically pure chiral thiosubstituted



Scheme 4.

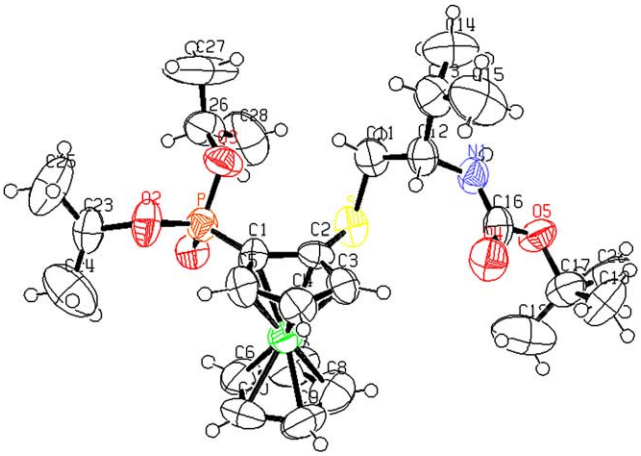


Figure 2. X-ray crystal structure of (S,S_{Fc})-**10b**.

ferrocenylphosphorodiamidates through a P-S to P-C rearrangement. The potential of these derivatives as polydentate ligands will be investigated in the near future.

4. Experimental

4.1. General remarks

Melting points (uncorrected) were determined with a Büchi melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian Gemini 300 at 300 and 75.46 MHz, respectively, or with a Varian Mercury Plus 400 at 400 and 100.57 MHz, respectively, using $CDCl_3$ solutions of the samples. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ ($\delta = 7.26$ for ^{1}H and $\delta = 77.0$ for ^{13}C). Coupling constants (J) values are given in Hz. ^{13}C NMR spectral assignments were made by DEPT experiments. ^{31}P NMR spectra were recorded with a Varian Mercury Plus 400 at 161.90 Hz, are reported in ppm and were referenced to H_3PO_4 as an external standard. IR spectra were recorded on a Perkin–Elmer Spectrum RX I FT-IR System. Mass spectra were obtained using a VG 7070-E spectrometer at an ionizing voltage of 70 eV or with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent. Optical rotation values were measured with Perkin–Elmer Polarimeter 341 and specific rotations are given in 10^{-1} deg cm^2 g^{-1}. The originality of all compounds was checked by a CAS-on-line structure search. Reactions were conducted in oven-dried (120 °C) glassware under a positive Ar or N_2 atmosphere. The transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone prior to use and stored under Ar. Et_2O was distilled from P_2O_5. Other solvents were purified by standard procedures. Light petroleum ether refers to the fraction with a bp 40–60 °C. The reactions were monitored by TLC, using silica gel plates (Baker-flex IB2-F). Column chromatography was performed with Merck silica gel 60 (70–230 mesh). Preparative thick layer chromatography was carried out on glass plates using a 1 mm layer of Merck silica gel 60 Pf 254. All chemicals were used as obtained or purified by distillation as needed.

4.2. *O*,*O*-Diisopropyl (*S*)-ferrocenyl phosphorothioate 2

To a stirred suspension of NaH (184 mg, 4.6 mmol, 60% in mineral oil) in anhydrous THF (5 mL) under N_2 at 0 °C, mercaptoferrocene **1**[22] (785 mg, 3.6 mmol) dissolved in THF (10 mL) was slowly added. After hydrogen evolution had ceased, diisopropylchlorophosphate[23] (720 mg, 3.6 mmol) dissolved in THF (2 mL) was added dropwise. The mixture was stirred at room temperature for 20 h, and then quenched with a saturated aqueous solution of NH_4Cl, extracted with Et_2O (three times), dried, filtered and concentrated under reduced pressure. The crude was chromatographed on silica gel (light petroleum/EtOAc 10:1 and then 1:1) to give 1.15 g (82%) of **2** (solid at −20 °C). IR (CCl_4) 2981, 1366, 1253, 1106 and 990 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.28 (2d, $J = 6.4$ Hz, 12H), 4.19 (s, 5H), 4.22 (t, $J = 1.9$ Hz, 2H), 4.41 (t, $J = 1.9$ Hz, 2H), 4.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 23.61 (d, ^3J (C,P) = 5.5 Hz, CH_3), 23.83 (d, ^3J (C,P) = 5.4 Hz, CH_3), 69.45, 69.71 (CH), 72.74 (d, ^2J (C,P) = 6.7 Hz, CH), 73.93 (CH); ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm): 21.08; MS (ESI) m/z: 405 (M+Na$^+$), 382 (M$^+$). HRMS Calculated for (M$^+$) $C_{16}H_{23}FeO_3PS$: 382.0455. Found: 382.0451.

4.3. Racemic diisopropyl 2-sulfanylferrocenylphosphonate 3

To a solution of iPr$_2$NH (0.24 mL, 1.73 mmol) in THF (5 mL), under N_2 at −78 °C, n-BuLi (1.1 mL, 1.73 mmol, 1.6 M) was added. After stirring for 1 h at 0 °C, phosphorothioate **2** (300 mg, 0.785 mmol) dissolved in anhydrous THF (5 mL) was added dropwise at −78 °C. The mixture was allowed to warm at −5 °C and stirred at this temperature for 1 h, then quenched with 3.5 M H_2SO_4 (10 mL) and extracted with Et_2O. The organic layer was dried, filtered and concentrated in vacuo to afford **3** as a yellow oil (260 mg, 87%). The ^{1}H NMR of the crude revealed the presence of less than 10% of mercaptoferrocene that had not been separated. The NMR spectra have been reported detracting the signals of an authentic sample of mercaptoferrocene. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.28 (4d, $J = 6.2$ Hz, 12H), 3.77 (s, 1H), 4.22 (s, 5H), 4.41 (m, 2H), 4.46 (m, 2H), 4.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 23.95 (d, ^3J (C,P) = 4.5 Hz, CH_3), 24.09 (d, ^3J (C,P) = 4.0 Hz, CH_3), 69.60 (d, J (C,P) = 13.7 Hz, CH), 69.80 (d, J (C,P) = 13.0 Hz, CH), 70.72 (d, J (C,P) = 6.3 Hz, CH), 70.93 (d, ^2J (C,P) = 6.3 Hz, C), 71.84 (CH), 72.54 (d, ^1J (C,P) = 195 Hz, C), 73.87 (CH), 75.25 (d, J (C,P) = 13.4 Hz, CH); MS (ESI) m/z: 405 (M+Na$^+$), 382 (M$^+$).

4.4. Racemic diisopropyl 2-(methylsulfanyl)ferrocenylphosphonate 5

To a solution of iPr$_2$NH (0.24 mL, 1.73 mmol) in THF (5 mL), under N_2 at −78 °C, n-BuLi (1.1 mL,

1.73 mmol, 1.6 M) was added. After stirring for 1 h at 0 °C, phosphorothioate **2** (300 mg, 0.785 mmol) dissolved in anhydrous THF (5 mL) was added dropwise at −78 °C. The mixture was allowed to warm at −5 °C and stirred at this temperature for 1 h, then a solution of CH_3I (0.31 mL, 5 mmol) in THF (1 mL) was added and the mixture stirred at −5 °C for 3 h. The reaction was quenched with water and extracted with Et_2O. The organic layer was dried, filtered and concentrated in vacuo. Chromatography on silica gel (light petroleum/EtOAc 1:1) of the crude reaction mixture afforded methylmercaptoferrocene in 10% yield as the first R_f fraction and product **5** as the second R_f fraction as a yellow oil (180 mg, 58%). IR (CCl_4): 2974, 2920, 1550, 1244 and 1060 cm^{-1}. ^1H NMR (300 MHz, CD_2Cl_2) δ (ppm): 1.28 (d, $J = 6.1$ Hz, 6H), 1.30 (d, $J = 6.1$ Hz, 3H), 1.32 (d, $J = 6.1$ Hz, 3H), 2.27 (s, 3H), 4.24 (s, 5H), 4.30 (m, 2H), 4.45 (m, 2H), 4.71 (m, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ (ppm): 19.68 (CH_3), 23.95 (d, ^3J (C,P) = 5.2 Hz, CH_3), 23.98 (d, ^3J (C,P) = 4.4 Hz, CH_3), 24.14 (d, ^3J (C,P) = 4.6 Hz, CH_3), 24.27 (d, ^3J (C,P) = 3.6 Hz, CH_3), 70.08 (d, ^2J (C,P) = 13.1 Hz, CH), 70.29 (d, ^3J (C,P) = 3.3 Hz, CH), 70.38 (d, ^3J (C,P) = 2.8 Hz, CH), 71.26 (d, ^1J (C,P) = 218 Hz, C), 71.28 (CH), 74.03 (d, ^2J (C,P) = 14.5 Hz, CH), 74.63 (d, ^2J (C,P) = 13.1 Hz, CH), 86.9 (d, ^2J (C,P) = 14.8 Hz, C); ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm): 22.69; MS (ESI) *m/z*: 419 ($M+Na^+$), 397 (M^+). HRMS Calculated for (M^+) $C_{17}H_{25}FeO_3PS$: 396.0611. Found: 396.0615.

The singlet in the ^1H NMR spectrum at 2.27 ppm corresponding to the SCH_3 of racemic **5** was split into two signals at 2.06 and 2.14 ppm of the two enantiomers in the presence of (*S*)-(+)-(9-anthryl)-2,2,2-trifluoroethanol as the chiral solvating agent. The singlet at 4.24 ppm corresponding to 5 FcH of the non-substituted ring was split into two signals at 4.08 and 4.12 ppm of the two enantiomers.

4.5. Phosphorothioate-mercaptophosphonate rearrangement in the presence of *s*-BuLi/(−)-sparteine or *n*-BuLi/(−)-sparteine

To a solution of (−)-sparteine (404 mg, 1.73 mmol) in THF (10 mL) at −78 °C, *s*-BuLi (1.3 mL, 1.73 mmol, 1.3 M) and thiophosphate **2** (300 mg, 0.785 mmol) were added. After stirring for 1 h at −5 °C, a solution of CH_3I (0.31 mL, 5 mmol) in THF (1 mL) was added and the mixture stirred at −5 °C for 3 h. The reaction was quenched with water and extracted with Et_2O. The organic layer was dried, filtered and concentrated in vacuo. Chromatography on silica gel (light petroleum/EtOAc 1:1) of the crude reaction mixture afforded methylmercaptoferrocene (130 mg, 72%) and product **5** (30 mg, 10%) with an ee of 9% calculated by ^1H NMR in the presence of the Pirkle alcohol.

The rearrangement performed in the same reaction conditions but using *n*-BuLi/(−)-sparteine afforded methylmercaptoferrocene (110 mg, 61%) and unreacted **2** (90 mg, 30%).

4.6. (3a*R*,7a*R*)-2-Sulfanylferrocenyl-(3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole)-2-oxide 7

To a stirred suspension of NaH (110 mg, 2.76 mmol, 60% in mineral oil) in anhydrous THF (5 mL) under N_2 at 0 °C, mercaptoferrocene (479 mg, 2.16 mmol) dissolved in THF (10 mL) was slowly added. After 30 min, a solution of (3a*R*,7a*R*)-2-chloro-(3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole)-2-oxide **6**[19] (480 mg, 2.16 mmol) in THF (15 mL) was added and the mixture stirred at room temperature for 20 h. The reaction was quenched with water and extracted with Et_2O. The organic layer was dried, filtered and concentrated in vacuo. Chromatography on silica gel (light petroleum/EtOAc 1:1 and then EtOAc) of the crude reaction mixture afforded as the higher R_f fraction ferrocenyldisulfide and the lower R_f fraction product **7** as a yellow solid (350 mg, 47%). Mp 162–165 °C; $[\alpha]_D^{20} = -163.4$ (*c* 0.74, $CHCl_3$); IR (CCl_4): 2926, 1441, 1259, 1218, 1170 and 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.75 (m, 1H, H_a-CH_2), 1.02 (m, 2H, $2H_a$-CH_2), 1.21 (m, 1H, H_a-CH_2), 1.67 (m, 2H, $2H_b$-CH_2), 1.78 (m, 1H, H_b-CH_2), 1.82 (m, 2H, H_b-CH_2, CH), 2.57 (d, $J = 13.4$, CH_3), 2.63 (d, $J = 11.4$, CH_3), 2.68 (m, 1H), 4.19 (2m, 2H), 4.20 (s, 5H), 4.22 (m, 1H), 4.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 23.97, 24.06, 27.68 (CH_2) 27.72 (d, ^2J (C,P) = 8.6 Hz, CH_3), 27.94, 28.03 (CH_2), 28.3 (d, ^2J (C,P) = 7.6 Hz, CH_3), 63.27 (d, ^2J (C,P) = 7.3 Hz, CH), 64.35 (d, ^2J (C,P) = 7.3 Hz, CH), 68.92, 69.41, 69.66, 74.20, 75.18 (CH); ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm): 44.432; MS (ESI) *m/z*: 427 ($M+Na^+$), 404 (M^+). Anal. Calcd for $C_{18}H_{25}FeN_2OPS$: C, 53.47; H, 6.23; N, 6.93. Found: C, 53.41; H, 6.35, N, 6.88.

4.7. Attempted rearrangement of 7 in the presence of LDA

To a solution of iPr_2NH (0.17 mL, 1.22 mmol) in THF (5 mL), under N_2 at −78 °C, *n*-BuLi (0.76 mL, 1.22 mmol, 1.6 M) was added. After stirring for 1 h at 0 °C, thiophosphate **7** (200 mg, 0.49 mmol) dissolved in anhydrous THF (5 mL) was added dropwise at −78 °C. The mixture was allowed to warm at −5 °C and stirred at this temperature for 1 h, then CH_3I (0.28 mL, 2.45 mmol) was added. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The organic layer was dried, filtered and concentrated in vacuo. Starting product **7** was recovered quantitatively.

4.8. Attempted rearrangement of 7 in the presence of *t*-BuLi at 0 °C in THF

To a solution of **7** (200 mg, 0.49 mmol) in THF (10 mL) at 0 °C under N_2, a solution of *t*-BuLi 1.7 M in pentane (0.54 mmol, 0.32 mL) was added. The mixture was allowed to warm at −5 °C and stirred at this temperature for 1 h, then CH_3I (2.70 mmol, 0.2 mL) was added and the mixture was stirred at room temperature for 4 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The organic layer was dried, filtered and concentrated in vacuo.

The starting product **7** was then quantitatively recovered.

4.9. Rearrangement of 7 in the presence of *t*-BuLi at room temperature in Et_2O: synthesis of (3a*R*,7a*R*)-[(S_{Fc})-(2-methylsulfanyl)ferrocenyl]-(3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole)-2-oxide 8

To a solution of **7** (200 mg, 0.49 mmol) in anhydrous Et_2O (30 mL) under N_2 at room temperature, a solution of *t*-BuLi 1.7 M in pentane (0.76 mmol, 0.44 mL) was added. The mixture was stirred at reflux for 1 h, then CH_3I was added (2.7 mmol, 0.2 mL) and the mixture refluxed for an additional 4 h. The reaction was then quenched with a saturated aqueous solution of NH_4Cl, extracted with Et_2O, dried, filtered and concentrated under reduced pressure. The crude was chromatographed on silica gel (EtOAc) to give as the higher R_f fraction 8 mg (7%) of methylmercaptoferrocene, as the second R_f fraction the starting product **7** (34 mg, 17%) and as the lower R_f fraction product **8** (113 mg, 0.27 mmol, 55%) mp 115–118 °C; $[\alpha]_D^{20} = -426.5$ (*c* 0.31, $CHCl_3$); IR (CCl_4): 2939, 2867, 1256, 1214, 1177 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 1.25 (m, 1H, H_a-CH_2), 1.31 (m, 2H, CH_2), 1.41 (m, 1H, H_a-CH_2), 1.81 (m, 2H, CH_2), 1.91 (m, 1H, H_b-CH_2), 2.05 (m, 1H, H_b-CH_2), 2.27 (d, $J = 11.4$, 3H, CH_3), 2.34 (s, 3H, SCH_3), 2.77 (m, 1H, CH), 2.84 (d, $J = 11.4$, CH_3), 2.89 (m, 1H, CH), 4.31 (s, 5H), 4.39 (m, 1H), 4.43 (m, 1H), 4.61 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 17.72 (SCH_3), 24.26, 24.49 (CH_2), 27.96 (d, ^2J (C,P) = 10.3 Hz, CH_3) 28.25 (d, ^2J (C,P) = 8.7 Hz, CH_3), 29.06 (d, ^3J (C,P) = 4.0 Hz, CH_2), 29.75 (d, ^3J (C,P) = 1.8 Hz, CH_2), 63.35 (d, ^2J (C,P) = 7.5 Hz, CH), 64.99 (d, ^2J (C,P) = 6.3 Hz, CH), 69.35 (d, ^3J (C,P) = 11.5 Hz, FcCH), 69.98 (d, ^3J (C,P) = 10.9 Hz, FcCH), 70.91 (5 FcCH), 74.36 (d, ^2J (C,P) = 13.2 Hz, CH), 88.71 (d, ^2J (C,P) = 12.7 Hz, FcC), 87.26 (d, ^1J (C,P) = 255 Hz, C); ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm): 38.162; MS (ESI) *m/z*: 441 ($M+Na^+$), 419 ($M+1^+$). Anal. Calcd for $C_{19}H_{27}FeN_2OPS$: C, 54.55; H, 6.51; N, 6.70. Found: C, 54.50; H, 6.57, N, 6.74.

4.10. (R_{Fc})- and (S_{Fc})-diisopropyl[2-((2*S*)-2-hydroxypropyl)sulfanylferrocenyl]phosphonate 9a and 9b

4.10.1. Method A. To a stirred suspension of NaH (12 mg, 0.29 mmol, 60% in mineral oil) in anhydrous THF (5 mL) under N_2 at 0 °C, racemic thiol **3** (88 mg, 0.23 mmol) dissolved in THF (5 mL) was slowly added. After 30 min, a solution of (*S*)-(−)-propylenoxide (13 mg, 0.23 mmol) in THF (2 mL) was added dropwise. The mixture was stirred at room temperature for 24 h. The reaction was then quenched with a saturated aqueous solution of NH_4Cl, extracted with Et_2O, dried, filtered and concentrated under reduced pressure. The crude mixture was separated by preparative TLC on silica gel (EtOAc) affording as the higher R_f fraction **9a** as a yellow solid in 18% yield (18 mg) and as the second R_f fraction **9b** as a yellow oil in 18% yield (18 mg) containing 10% of the other diastereoisomer. This product has been characterized without further purification while the NMR spectra have been reported detracting the signals of the other diastereoisomer. The lower R_f fraction was the disulfide arising from the thiol **3** (20 mg, 23%).

4.10.1.1. (R_{Fc})-Diisopropyl[2-((2*S*)-2-hydroxypropyl)-sulfanyl ferrocenyl]phosphonate 9a. Mp 86–88 °C; $[\alpha]_D^{20} = +196.3$ (*c* 0.40, $CHCl_3$); IR (CCl_4): 3383, 2987 and 984 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.11 (d, $J = 6.4$ Hz, 3H, CH_3), 1.38 (d, $J = 5.8$ Hz, 3H, CH_3), 1.40 (d, $J = 5.8$ Hz, 3H, CH_3), 1.44 (d, $J = 6.4$ Hz, 3H, CH_3), 1.47 (d, $J = 6.4$ Hz, 3H, CH_3), 2.43 (dd, $J_1 = 13.6$, $J_2 = 9.8$ Hz, 1H, H_a-CH_2), 2.75 (dd, $J_1 = 13.6$, $J_2 = 2.1$ Hz, 1H, H_b-CH_2), 3.51 (m, 1H, OH), 4.29 (s, 5H), 4.37 (m, 1H), 4.52 (br s, 1H), 4.58 (br s, 1H), 4.81 (m, 1H, CH), 5.06 (m, 2H, 2CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.89 (CH_3), 23.99 (d, ^3J (C,P) = 6.6 Hz, CH_3), 24.12 (d, ^3J (C,P) = 4.8 Hz, CH_3), 24.20 (d, ^3J (C,P) = 4.0 Hz, CH_3), 24.40 (d, ^3J (C,P) = 2.6 Hz, CH_3), 47.56 (CH_2), 62.82 (CH), 70.6 (d, ^3J (C,P) = 6.5 Hz, CH), 71.06 (d, ^2J (C,P) = 13.2 Hz, CH), 71.34 (5CH), 71.58 (d, ^3J (C,P) = 6.3 Hz, CH), 73.28 (d, ^1J (C,P) = 220.3 Hz, C), 73.68 (d, ^2J (C,P) = 14.8 Hz, CH), 78.38 (d, ^2J (C,P) = 13.5 Hz, CH), 81.20 (d, ^2J (C,P) = 15.3 Hz, C); ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm): 24.332; MS (ESI) *m/z*: 463 ($M+Na^+$), 441 ($M+1^+$), 440 (M^+). Anal. Calcd for $C_{19}H_{29}FeO_4PS$: C, 51.83; H, 6.64. Found: C, 51.78; H, 6.69.

4.10.1.2. (S_{Fc})-Diisopropyl[2-((2*S*)-2-hydroxypropyl)-sulfanyl ferrocenyl]phosphonate 9b. $[\alpha]_D^{20} = -106.1$ (*c* 0.33, $CHCl_3$); IR (CCl_4): 3373, 2988 and 984 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.11 (d, $J = 6.3$ Hz, 3H, CH_3), 1.37 (d, $J = 6.3$ Hz, 6H, $2CH_3$), 1.41 (d, $J = 6.4$ Hz, 3H, CH_3), 1.42 (d, $J = 6.1$ Hz, 3H, CH_3), 2.46 (dd, $J_1 = 13.7$, $J_2 = 9.5$ Hz, 1H, H_a-CH_2), 2.90 (dd, $J_1 = 13.7$, $J_2 = 2.6$ Hz, 1H, H_b-CH_2), 3.79 (m, 1H, CH), 3.96 (m, 1H, OH), 4.29 (s, 5H), 4.35 (m, 1H), 4.52 (m, 1H), 4.53 (m, 1H), 4.78 (m, 1H, CH), 4.92 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 22.05 (CH_3), 23.99 (d, ^3J (C,P) = 5.9 Hz, CH_3), 24.13 (d, ^3J (C,P) = 4.4Hz, CH_3), 24.39 (d, ^3J (C,P) = 3.1 Hz, CH_3), 47.30 (CH_2), 66.53 (CH), 70.47 (d, ^3J (C,P) = 6.5 Hz, CH), 70.76 (d, ^2J (C,P) = 13.6 Hz, CH), 70.97 (d, ^3J (C,P) = 6.2 Hz, CH), 71.28 (5CH), 73.29 (d, ^1J (C,P) = 240 Hz, C), 74.30 (d, ^2J (C,P) = 15.1 Hz, CH), 78.58 (d, ^2J (C,P) = 13.1 Hz, CH), 82.02 (d, ^2J (C,P) = 15.7 Hz, C); ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm): 23.589; MS (ESI) *m/z*: 463 ($M+Na^+$), 441 ($M+1^+$), 440 (M^+).

4.10.2. Method B. To a solution of iPr$_2$NH (0.24 mL, 1.73 mmol) in THF (5 mL), under N_2 at −78 °C, *n*-BuLi (1.1 mL, 1.73 mmol, 1.6 M) was added. After stirring for 1 h at 0 °C, phosphothioate **2** (300 mg, 0.785 mmol) dissolved in anhydrous THF (5 mL) was added dropwise at −78 °C. The mixture was allowed to warm at −5 °C and stirred at this temperature for 1 h, then a solution of (*S*)-(−)-propylenoxide (68 mg, 1.17 mmol) in THF (1 mL) was added and the mixture stirred at room temperature for 20 h. The reaction was then quenched with a saturated aqueous solution of NH_4Cl, extracted with Et_2O,

dried, filtered and concentrated under reduced pressure. The crude mixture was separated by preparative TLC of silica gel (EtOAc) affording as the higher R_f fraction **9a** as a yellow solid in 19% yield (65 mg) and as the second R_f fraction **9b** as a yellow oil in 20% yield (67 mg) containing 10% of the other diastereoisomer. The lower R_f fraction was the disulfide arising from the thiol **3** (20 mg, 23%).

4.11. (R_{Fc})- and (S_{Fc})-diisopropyl-2-((2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutylsulfanyl)-ferrocenylphosphonate 10a and 10b

The reaction was performed following the previously reported method B. Starting from LDA (1.73 mmol) and **2** (0.785 mmol) and quenching the reaction mixture with a solution of (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutyl-*p*-toluensolfonate[15] (280 mg, 0.785 mmol). After 30 h of stirring and the usual work-up chromatography on preparative TLC (EtOAc) of silica gel afforded as the higher (R_f) diastereoisomer **10a** as a yellow solid in 15% yield (65 mg) and the lower (R_f)-diastereoisomer **10b** in 16% yield (70 mg).

4.11.1. (R_{Fc})-diisopropyl[2-((2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutylsulfanyl)ferrocenyl]phosphonate 10a.

Mp 90–93 °C; $[\alpha]_D = +66.7$ (*c* 0.33, $CHCl_3$); IR (CCl_4): 3276, 2978, 1707, 1498 and 998 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ (ppm): 0.62 (d, $J = 6.7$ Hz, 3H, CH_3), 0.81 (d, $J = 6.7$ Hz, 3H, CH_3), 1.088 (d, $J = 6.2$ Hz, 3H, CH_3), 1.094 (d, $J = 6.1$ Hz, 3H, CH_3), 1.13 (d, $J = 6.2$ Hz, 3H, CH_3), 1.20 (d, $J = 6.2$ Hz, 3H, CH_3), 1.28 (s, 9H, CH_3), 2.16 (m, 1H, CH), 2.95 (m, 2H, CH_2), 3.41 (m, 1H, CH), 3.82 (m, 1H), 4.06 (s, 5H), 4.30 (m, 2H), 4. 70 (m, 1H, CH), 4.89 (m, 1H, CH), 6.39 (br d, $J = 8.5$ Hz, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 19.29, 19.57 (CH_3), 23.89 (d, ^3J (C,P) = 6.0 Hz, CH_3), 23.96 (d, ^3J (C,P) = 4.6 Hz, CH_3), 24.09 (d, ^3J (C,P) = 4.1 Hz, CH_3), 24.25 (d, ^3J (C,P) = 2.6 Hz, CH_3), 28.41 (CH_3), 29.77 (CH), 40.82 (CH_2), 56.99 (CH), 69.89 (d, ^3J (C,P) = 6.2 Hz, CH_3), 70.44 (d, ^3J (C,P) = 6.0 Hz, CH_3), 70.66 (d, ^2J (C,P) = 13.4 Hz, CH), 71.41 (CH), 73.71 (d, ^2J (C,P) = 15.0 Hz, CH), 72.62 (d, ^1J (C,P) = 220 Hz, C), 77.33 (C), 78.26 (d, ^2J (C,P) = 13.0 Hz, CH), 84.85 (d, ^2J (C,P) = 15.9 Hz, C), 155.51 (CO); ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm): 23.335; MS (ESI) *m*/*z*: 590 ($M+Na^+$), 567 (M^+). Anal. Calcd for $C_{26}H_{42}FeNO_5PS$: C, 55.03; H, 7.46; N, 2.47. Found: C, 55.19; H, 7.39, N, 2.40.

4.11.2. (S_{Fc})-diisopropyl[2-((2*S*)-2-[(*tert*-butoxycarbonyl)-amino]-3-methylbutylsulfanyl)ferrocenyl]phosphonate 10b.

Mp 99–100 °C; $[\alpha]_D = -64.0$ (*c* 0.285, $CHCl_3$); IR (CCl_4): 3300, 2967, 1710, 1498, and 950 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ (ppm): 0.56 (d, $J = 6.7$ Hz, 3H, CH_3), 0.59 (d, $J = 6.7$ Hz, 3H, CH_3), 1.08 (d, $J = 5.9$ Hz, 3H, CH_3), 1.09 (d, $J = 5.9$ Hz, 3H, CH_3), 1.19 (d, $J = 5.8$ Hz, 3H, CH_3), 1.21 (d, $J = 5.8$ Hz, 3H, CH_3), 1.37 (s, 9H, CH_3), 1.55 (m, 1H, CH), 2.51 (m, 1H, H_a-CH_2), 2.87 (dd, $J_1 = 13.9$, $J_2 = 3.5$ Hz, 1H, H_b-CH_2), 3.66 (m, 1H), 3.85 (m, 1H, CH), 4.10 (s, 5H), 4.39 (m, 1H), 4.53 (m, 1H), 4.66 (m, 1H, CH), 4.97 (m, 1H, CH), 5.29 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 18.12, 19.93 (CH_3), 24.01 (d, ^3J (C,P) = 5.4 Hz, $2CH_3$), 24.05 01 (d, ^3J (C,P) = 4.0 Hz, CH_3), 24.35 (d, ^3J (C,P) = 2.8 Hz, CH_3), 31.50 (CH), 40.24 (CH_2), 55.49 (CH), 69.68 (d, ^3J (C,P) = 6.3 Hz, CH_3), 70.30 (d, ^3J (C,P) = 5.9 Hz, CH_3), 70.42 (d, ^2J (C,P) = 13.6 Hz, CH), 71.37 (CH), 74.24 (d, ^1J (C,P) = 220.3 Hz, C), 74.65 (d, ^2J (C,P) = 14.9 Hz, CH), 77.91 (C), 78.48 (d, ^2J (C,P) = 12.9 Hz, CH), 82.94 (d, ^2J (C,P) = 15.9 Hz, CH), 155.97 (CO); ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm): 22.888; MS (ESI) *m*/*z*: 590 ($M+Na^+$). Anal. Calcd for $C_{26}H_{42}FeNO_5PS$: C, 55.03; H, 7.46; N, 2.47. Found: C, 55.15; H, 7.51, N, 2.50.

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21. Crystallographic data for compound **10b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 273576. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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