Synthesis and Structure of Planar Chiral, Bifunctional Aminoboronic Acid Ferrocene Derivatives

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N,*N*′-Diisopropylferrocenecarboxamide is utilized for an asymmetric, directed metalation approach to several planar chiral bifunctional ferrocene derivatives. Directed metalation using *n*-butyllithium-(−)-sparteine on *N*,*N*′-diisopropylferrocenecarboxamide can be achieved to give high yields of the corresponding boronic acid; however, it was found that a sequence involving asymmetric directed metalation−bromination, followed by lithium−halogen exchange, was more convenient to access the same derivatives since this allowed straightforward determination of the enantiomeric excess. (p*R*)-2-[(*N*,*N*-Diisopropylamino)methyl]ferrocenylboronic acid and derivatives thereof could be readily accessed with high enantiomeric excess, followed by amide reduction.

Introduction

Aminoarylboronic acids have been attracting considerable interest for a wide variety of applications, including quantification of enantiomeric excess,[1] electrochemical,[2] colorimetric, or fluorescence saccharide sensor applications,[3] selective saccharide binding systems,[4] and indicators to follow reaction kinetics.[5] In addition, early studies by Letsinger et al. demonstrated the potential for such systems as bifunctional catalysts for simple alkylation and hydrolysis reactions.[6] Indeed, there have been many studies on the intramolecular interactions between boron and nitrogen[7] and how such interactions tune complexation characteristics.[8] However, the application of aminoarylboronic acids as bifunctional catalysts is largely unexplored, with a noted exception,[6] and this has led us to examine the synthesis and structure of aminoarylboronate systems[9] in order to examine their potential as catalysts for a range of organic transformations, including the important area of *in situ* direct amide formation from amines and carboxylic acids.[10] In this paper, we document the synthesis and structure of planar chiral 2-*N*,*N*′-diisopropylaminomethyferrocenylboronate derivatives, which are direct chiral analogues of a class of compounds that are valuable bifunctional catalysts for direct amide formation.[10]

Results and Discussion

2-*N*,*N*′-Diisopropylaminomethyphenylboronic acid is an exceptional catalyst for the direct amide formation of less reactive amine−carboxylic acid combinations,[10] which is partly explained by the effect of the hindered diisopropylamino function that inhibits B−N chelation in both solution and solid states.[9b] We therefore wanted to access a planar chiral version of this system to examine a range of catalytic asymmetric transformations including acylation processes. Perhaps the most direct chiral analogue of 2-*N*,*N*′-diisopropylaminomethyphenylboronic acid would be the corresponding ferrocene-based system, i.e., 2-*N*,*N*′-diisopropylaminomethyferrocenylboronic acid, since the amide derivative had already been reported by Snieckus et al.,[11] and other groups had shown that ferrocenyl-based aminoboronate systems have interesting physical and chemical properties.[8d,12]

Commercially available ferrocenecarboxaldehyde **1** was transformed into the diisopropylamide **3** using essentially literature methods,[11a,13] as shown in Scheme 1. Diisopropylamide **3** was then subjected to asymmetric directed *ortho*-metalation

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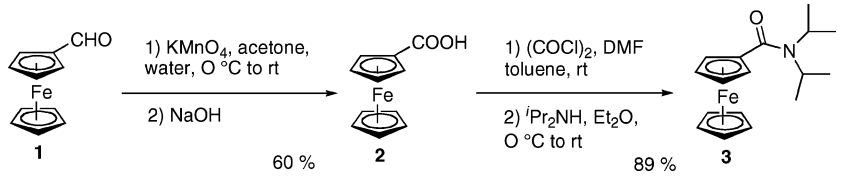
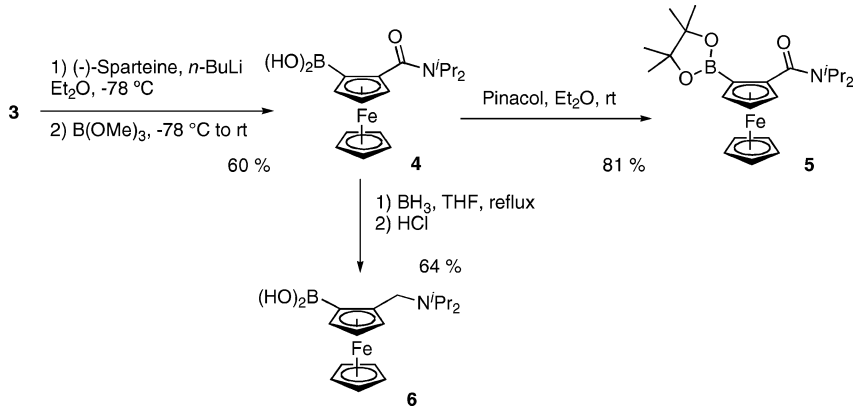
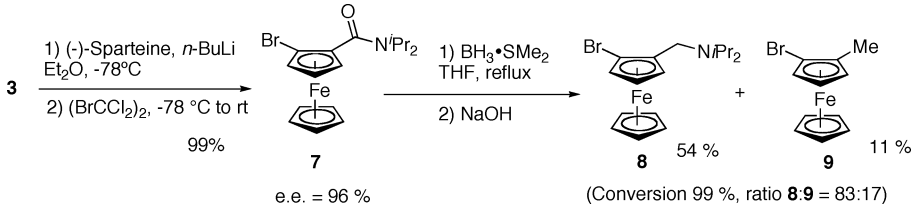
Scheme 1. Preparation of the Ferrocenecarboxylic Acid Amide 3



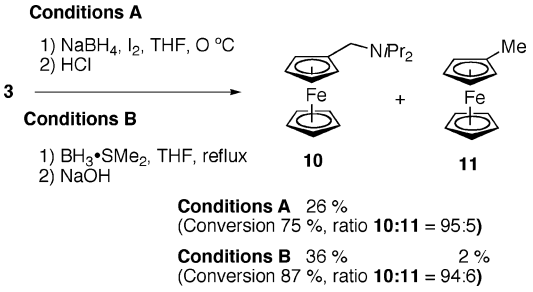
Scheme 2. Directed Metalation to Access Boronates 5 and 6



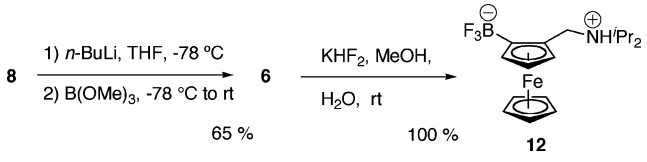
Scheme 3. Sparteine-Directed Metalation and Amide Reduction to Access (p*R*)-Bromide 8



Scheme 4. Competing Amide Reduction Providing Both Amine 10 and Methyl Derivatives 11



Scheme 5. Lithium−Halogen Exchange to Access Boronic Acid 6 and Formation of the Difluoroborane·HF Complex 12



using (−)-sparteine, as described by Snieckus,[11] to give the *ortho*-boronic acid **4** (Scheme 2), the 3D structure of which was confirmed by X-ray crystallography (Figure 1). Attempts to determine the enantiomeric excess of **4** using the methods described[11b] failed to provide any separation, as did a range of other chiral HPLC columns. It was, however, possible to verify the clean formation of the (p*R*)-boronic acid **4** by esterification to give the crystalline pinacol derivative (p*R*)-**5**, the crystal structure of which is shown in Figure 2. The expected[11a] (p*R*)-absolute stereochemistry of the main component of **4** and **5** (as shown in Figures 1 and 2) has been confirmed by anomalous X-ray scattering (see Supporting Information).

The isolation of the amide−boronic acid derivative **4** allowed us to attempt amide reduction, as developed in the corresponding benzene series.[9b] Indeed, this worked well using excess borane at reflux to provide the desired 2-[*N*,*N*′-(diisopropylamino)-methyl]ferrocenylboronic acid (**6**), which was also readily crystallized and subjected to single-crystal X-ray structure determination (Figure 3). It is noteworthy that the lone electron pair of the (amino) nitrogen atom is not donated to boron; rather it accepts an intramolecular hydrogen bond from the boronic acid moiety. Although this bond, O(2)−H···N, is somewhat weaker in **6** than in the known dimethylamino analogue[2a] (O···N 2.730(3) vs 2.672(1) Å), it is preferred over B−N chelation when there are suitably hindering substituents on nitrogen.[9b] This preference is entirely as expected from our previous observations[9] and is important for the potential application of such systems as catalysts and receptors, i.e., by being able effectively to switch off B−N chelation. This solid-state structure of **6** is also retained in solution, as indicated by the ^{11}B NMR signal at δ 32.3, characteristic of the arylboronic acid function.

Thus in **6** the boron atom maintains essentially the same planar trigonal geometry as in **4** and **5**. In all three compounds, the boronate function is approximately coplanar with the ferrocene ring, forming dihedral angles of 14.9° in **4**, 11.9° in **5**, and 18.5° in **6**. In molecule **4**, like in **6**, this type of conformation is stabilized by an intramolecular hydrogen bond,

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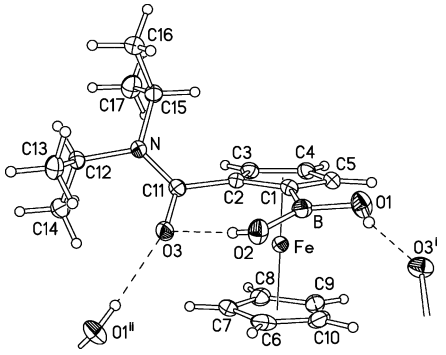

Figure 1. X-ray structure and hydrogen bonding of (p*R*)-boronic acid **4** (50% thermal ellipsoids). Symmetry codes: (i) 1−*x*, (1/2)+*y*, (1/2)−*z*; (ii) 1−*x*, *y*−(1/2), (1/2)−*z*.

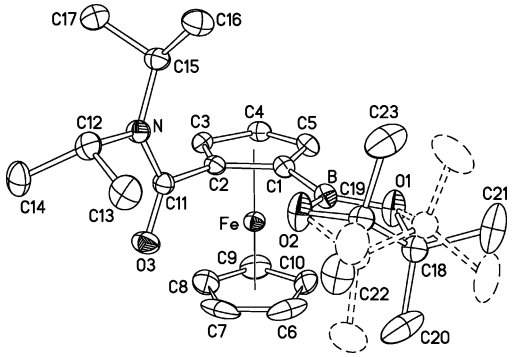

Figure 2. X-ray structure of pinacol ester of (p*R*)-**5** (30% thermal ellipsoids; H atoms are omitted for clarity). The tetramethyldioxaborolane group is disordered between two oppositely twisted conformations with the probabilities of 45% (solid) and 55% (dashed).

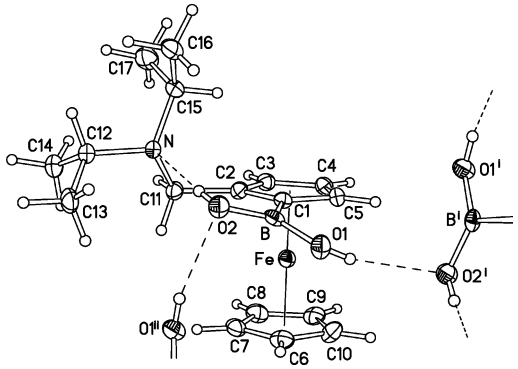

Figure 3. X-ray structure and hydrogen bonding of (p*R*)-aminoboronic acid **6** (50% thermal ellipsoids). Symmetry codes: (i) *x*+(1/2), (3/2)−*y*, 1-*z*; (ii) *x*−(1/2), (3/2)−*y*, 1−*z*.

O(2)−H···O(3), involving one of the boronic hydroxyl groups. The remaining hydroxyl forms an intermolecular hydrogen bond O(1)−H···O(3^{i}) in **4** and O(1)−H···O(2^{i}) in **6**, whereby the molecules are linked into infinite chains spiralling around the 2_1 screw axes [(1/2) *y* (1/4)] or [*x* (3/4) (1/2)], respectively. Unusually, the intermolecular hydrogen bond in **6** is directed almost perpendicular to the plane of the acceptor oxygen atom or the $B(OH)_2$ group generally.

The X-ray structure again confirms the (p*R*)-absolute stereochemistry of the main component of **6**, inherited from the parent amide **4**. However, we were unable to accurately measure the enantiopurity of this material prepared by this route using a series of different chiral HPLC columns, and we therefore examined an alternative route, which was expected to be more amenable to enantiomeric excess determination. This involved

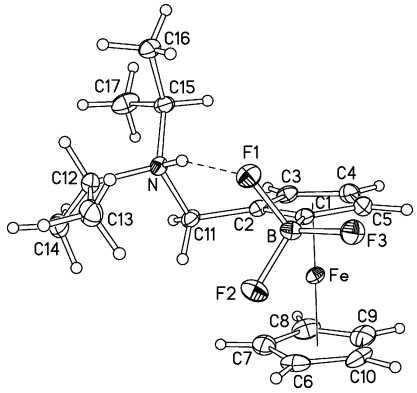

Figure 4. X-ray structure of trifluoroborate−HF complex (p*R*)-**12** (50% thermal ellipsoids).

the preparation of the corresponding ferrocene bromide **7** to enable enantiomeric excess determination, followed by an amide reduction−boronation sequence.

Therefore, we subjected amide **3** to asymmetric directed *ortho*-metalation using (−)-sparteine, as described above, followed by bromination with 1,2-dibromotetrachloroethane to provide *ortho*-bromide **7** in nearly quantitative yield (Scheme 3). It was straightforward to determine the asymmetric induction from the directed metalation step to give **7** using a Chiralcel OD HPLC column, which showed an excellent 96% enantiomeric excess. The assignment of the absolute stereochemistry of the major enantiomer of **7** as (p*R*) is based on the well-precedented control by (−)-sparteine in such systems.[11]

Once bromide **7** had been prepared, amide reduction was accomplished using excess borane−dimethylsulfide complex. Not only did this produce the expected amine **8**, but it was also accompanied by the complete reduction product **9**[14] in a crude ratio of 83:17. After separation, the major amino product **8** was isolated in a pure form in 54% yield (Scheme 3). There is another report[15] in the literature of this type of reduction with borane derivatives, which shows that ferrocenyl carbonyl compounds have this unusual ability to reduce to the methyl derivative. However, we were intrigued to look at this process further, and we therefore examined the reduction of the ferrocene amide **3** under two different reduction conditions, as outlined in Scheme 4. Generation of borane *in situ* from sodium borohydride and iodine (conditions A, Scheme 4) gave reasonable conversion and resulted in only a small amount of the methyl derivative **11**, with the amine predominating. Separation of the mixture was not straightforward, and the major product amine **10** was isolated in low yield. Similarly, the use of borane−dimethyl sulfide complex as above provided a different ratio of products; that is, at 87% conversion the amine **10** to methyl **11** ratio was 94:6, which suggests that the amount of complete reduction product depends more on the substrate rather than the reagent. Confirmation of the order of events in this reduction came from the exposure of both the ferrocene carboxaldehyde **1** and the amine **10** to the same borane−dimethylsulfide reaction conditions, which provided a quantitative conversion to the methyl ferrocene **11** in the case of the aldehyde **1** and no reduction in the case of amine **10**. This shows that it is the competing collapse of the tetrahedral complex after the first B−H addition to provide the aldehyde that drives the competing reduction to the methyl derivative. It is also

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noteworthy that the intermediate alcohol is not observed, which presumably means the corresponding borate complex readily undergoes rapid fragmentation and reduction. However, small amounts of a somewhat impure compound tentatively assigned as the corresponding primary alcohol have been observed in reactions that did not go to completion.

Isolation of (p*R*)-bromide **8** in high enantiomeric excess then allowed us to prepare the (p*R*)-boronic acid **6** by lithium−halogen exchange, followed by transmetalation with trimethyl borate, which provided clean conversion to the boronic acid in high ee (Scheme 5). Comparing the optical rotations of the sample of **6** prepared by this route (96% ee) with that produced by the initial route (Scheme 2) shows an optical purity of 70% for the direct synthesis of the boronic acid **6** from Scheme 2. This demonstrates the benefit of accessing boronic acid **6** via initial formation of the higher ee bromide **8**.

Having isolated the boronic acid **6**, it was readily converted to the corresponding trifluoroborate ammonium salt **12** with potassium hydrogen difluoride. As in the corresponding benzene series,[9b] the preferential formation of this ammonium salt rather than formation of the potassium intramolecular B−N complex[9a] is due to the more basic diisopropylamine function. The X-ray structure of (p*R*)-**12** (Figure 4) confirms its zwitterionic nature. The molecular conformation is similar to that of the corresponding (racemic) dimethylamino analogue,[8d] as well as i-Pr_2-NH−C_6H_4−BF_3.[9b] In the dimethylamino analogue,[8d] an intramolecular hydrogen bond, N−H···F (N···F 2.996(4) Å), coexists with a stronger intermolecular one (N···F 2.854(3) Å) to the same F atom, thus forming a F_2H_2 parallelogram. Structure **12** contains only the intramolecular bond, N−H···F(1), which is consequently much stronger than in the dimethylamino analogue[8d] (N···F 2.848(2) Å), while the B−F(1) bond of 1.444(2) Å is substantially longer than the other two B−F bonds (mean 1.409(2) Å). The C−B bond length in **12** (1.604(2) Å) is intermediate between those in the dimethylamino analogue (1.590(4) Å)[8d] and i-Pr_2NH−C_6H_4−BF_3 (1.618(1) Å) and similar to those in tetrabutylammonium and potassium salts of $PhBF_3^-$ (1.600(3) and 1.61(1) Å, respectively).[16] Thus, the C−BF_3 bond may be substantially weaker than the C−B bond in the boronic acids **4** (1.560(2) Å) and **6** (1.563(3) Å) and the ester **5** (1.545(4) Å).

Figure 4 also confirms the (p*R*)-absolute stereochemistry of trifluoroborate **12** and the tetrahedral nature of the boron−fluoride system, as confirmed by the ^{11}B NMR shift of δ 4.53.

Conclusions

The synthesis of planar chiral aminoboronate systems based on a ferrocene framework has been realized through (−)-sparteine-directed metalation methodology, with the more enantioselective route involving initial enantioselective bromination of amide **3**, followed by amide reduction and borylation via lithium−halogen exchange. This efficient enantioselective process is convenient for the synthesis of systems such as **6**, and subsequent structural studies, both solid and solution state, clearly show the general advantage of suitably hindered substituents on nitrogen for the effective prevention of boron−nitrogen chelation, which allow these two functional groups to act cooperatively in potential catalytic processes. Further studies in this area will be reported in due course.

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Experimental Section

Ferrocenecarboxylic Acid (2). To a solution of ferrocenecarboxaldehyde **1** (11.24 g, 52 mmol) in acetone (500 mL) at 0 °C was added a solution of $KMnO_4$ (29 g, 183 mmol) in water (100 mL). After 2 h, a solution of aqueous NaOH (20% w/v) (50 mL) was added. The reaction mixture was filtered through Celite and washed with aqueous NaOH (10% w/v) (75 mL). The filtrate was washed by diethyl ether (3 × 150 mL) to remove the ferrocene carboxaldehyde, acidified to pH 4−5 with a solution of aqueous HCl (2.4 M solution), and extracted with diethyl ether (5 × 100 mL). The combined organic phase was washed with brine (3 × 100 mL), dried, filtered, and evaporated to give ferrocenecarboxylic acid **2** (7.08 g, 60%) as orange needles: mp 205 °C (dec) [lit.[13] 210 °C (dec)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.19 (s, 5H), 4.40 (t, 2H, J = 2.0 Hz), 4.80 (t, 2H, J = 2.0).

***N,N*-Diisopropylferrocenecarboxamide (3).** To a stirred solution of **2** (12.19 g, 53 mmol) in dry toluene (90 mL) under argon were added oxalyl chloride (9.24 mL, 106 mmol) and *N,N*-dimethylformamide (0.6 mL). After 6 h, the excess oxalyl chloride was evaporated and resuspended and re-evaporated with an equal volume of toluene. Anhydrous diethyl ether (300 mL) was added, and the solution was cooled to 0 °C and treated with dry diisopropylamine (20.8 mL, 0.148 mmol). After 12 h, the mixture was diluted with saturated aqueous NH_4Cl (75 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extract was washed with H_2O (3 × 50 mL) and brine (3 × 50 mL), dried, filtered, and evaporated to give a brown residue, which was purified by silica gel chromatography (9:1, hexane/ethyl acetate as eluent) to give amide **3** as orange needles (14.7 g, 89%): mp 79−81 °C (lit.[11a] 88−91 °C). All spectroscopic and analytical properties were identical to those reported in the literature.[11a]

(p*R*)-2-(*N,N*-Diisopropylamido)ferroceneboronic Acid (4). A solution of (−)-sparteine (12.9 mL, 56.0 mmol) in diethyl ether (250 mL) was stirred at room temperature under argon for 30 min, then cooled to −78 °C and treated with *n*-butyllithium (35.0 mL of a 1.6 M solution in hexanes) over 5 min, and the resulting solution was stirred for a further 30 min. A solution of *N,N*-diisopropyl ferrocenecarboxamide **3** (8.77 g, 28.0 mmol) in diethyl ether (250 mL) was then added dropwise via syringe pump over 9 h. After a further 10 h at −78 °C, trimethylborate (9.4 mL, 84.0 mmol) was added and the solution was stirred for a further 2 h before warming to room temperature. After quenching with water (200 mL), the mixture was extracted with diethyl ether (3 × 100 mL), and the combined extracts were washed with brine (3 × 100 mL) and evaporated to give a viscous, red oil. Addition of hexane (ca. 30 mL) promoted crystallization of the desired compound **4** as small orange needles (6.0 g, 60%), which were suitable for X-ray analysis: mp 153−154 °C (lit.[11a] 148−150 °C); $[\alpha]_D^{25} = -55$ (*c* 0.006, CH_2Cl_2). All spectroscopic and analytical properties were identical to those reported in the literature;[11a] ^{11}B NMR ($CDCl_3$, 128 MHz) 30.5 (br s).

(p*R*)-*N,N*-Diisopropyl-2-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)ferrocenecarboxamide (5). Pinacol (0.195 g, 1.65 mmol) and (p*R*)-2-(*N,N*-diisopropylamido)ferroceneboronic acid **4** (0.5 g, 1.40 mmol) were dissolved in diethyl ether (10 mL) and stirred overnight. The solvent was evaporated and hexane added to precipitate the crude product. The resulting solid was then recrystallized from diethyl ether to give the ester **5** (0.5 g, 81%), crystals of which were suitable for X-ray analysis: mp = 178−179 °C; $[\alpha]_D^{25}$ = +15 (*c* 0.002, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 and 0.99 (each d, 3H, J = 6.4 Hz), 1.30 and 1.31 (each s, 6H), 1.49 (apparent t, 6H, J = 6.8 Hz), 3.36 (septet, 1H, J = 6.8 Hz), 3.54 (septet, 1H, J = 6.8 Hz), 4.33 (s, 5H), 4.34 (t, 1H, J = 2.4 Hz), 4.38 (q, 1H, J = 1.2, 2.4 Hz), 4.45 (q, 1H, J = 1.2, 2.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8, 19.9, 21.1, 21.6 (CH-CH_3), 25.0, 25.5, 45.7, 50.7, 70.4, 70.5, 71.9, 72.8, 83.4, 96.5, 168.1; ^{11}B NMR ($CDCl_3$, 160 MHz) δ 32.6 (br s); IR (nujol, cm^{-1}) 1634, 1487,

1369, 1355, 1316, 1214, 1141, 1031, 985; MS (ES+, *m/z*, %) 439 (M + H, 100). Anal. Calcd for $C_{23}H_{44}NO_3B$: C, 62.90; H, 7.80; N, 3.19. Found: C, 62.71; H, 7.76; N, 3.12.

(p*R*)-2-(*N,N*-Diisopropylaminomethyl)ferrocenylboronic Acid (6). A solution of (p*R*)-2-(*N,N*-diisopropylamido)ferroceneboronic acid **4** (0.188 g, 0.52 mmol) in THF (1.8 mL) under argon was treated with borane dimethylsulfide (2.44 mL of a 2.0 M solution in THF). The solution was heated at reflux for 5 days, cooled to room temperature, and quenched with aqueous NaOH (1 mL, 5% solution) dropwise. The resulting solution was refluxed for 1 h and extracted with diethyl ether (3 × 1 mL), and the combined extracts were washed with brine (3 × 1 mL), dried, and evaporated to give a crude orange oil. The residue was purified by neutral alumina chromatography (gradient elution, hexane, hexane/ethyl acetate, ethyl acetate, ethyl acetate/methanol, and methanol) to give an orange solid, which was recrystallized from acetonitrile/water to give (p*R*)-**6** as orange needles (0.070 g, 40%): mp = 145−148 °C; $[\alpha]_D^{25} = +88$ (*c* 0.0092, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (d, 6H, $J = 6.8$ Hz), 1.05 (d, 6H, $J = 6.8$ Hz), 2.95−3.10 (m, 2H), 3.35−4.00 (dd, 2H, $J = 13.0$ Hz), 4.05 (s, 5H), 4.18−4.19 (m, 1H), 4.20 (s, 1H), 4.35 (s, 1H), 7.20−8.20 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.6, 20.8, 46.0, 47.3, 69.4, 69.5, 73.9, 75.1, 88.3; ^{11}B NMR ($CDCl_3$, 128 MHz) δ 32.3; IR (KBr, cm^{-1}) 3455, 2970, 1357, 1450, 1234; MS (ES+, *m/z*, %) 243 (100), 344 (M + H, 58), 669 (21); HRMS (ES+, *m/z*, %) found (M^+ + H) 344.14804, $C_{17}H_{27}BNO_2{}^{54}Fe$ requires 344.14788. Anal. Calcd for $C_{17}H_{26}BFeNO_2$: C, 59.52; H, 7.64; N, 4.08. Found: C, 59.61; H, 7.71; N, 3.97.

(p*R*)-2-Bromo-(*N,N*-diisopropyl)ferrocenecarboxamide (7). To a solution of (−)-sparteine (5.10 mL, 22.3 mmol) in diethyl ether (80 mL) stirred under argon at −78 °C was added *n*-butyllithium (14 mL of a 1.6 M solution in hexane) over 10 min. The resulting solution was stirred for 1 h and treated with a solution of **3** (5.37 g, 17.1 mmol) in diethyl ether (60 mL) over 30 min. After 1.5 h, a solution of 1,2-dibromotetrachloroethane (11.2 g, 34.2 mmol) in diethyl ether (60 mL) was added over 20 min. After 1 h, the mixture was warmed to room temperature, quenched with a saturated aqueous solution of NH_4Cl (75 mL), and extracted with diethyl ether (3 × 40 mL). The combined organic extract was washed with H_2O (3 × 40 mL), then brine (3 × 40 mL), dried, filtered, and evaporated to give an orange residue, which was purified by silica gel chromatography (9:1, hexane/ethyl acetate as eluent) to give (p*R*)-bromide **7** (6.7 g, >99%) as orange needles: mp = 79−80 °C; ee = 96%, Chiralcel OD, hexane/ether (0.5% of diethylamine), 80/20, 0.4 mL/min, 27.9 min, 33.2 min; $[\alpha]_D^{25}$ +36 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (d, 3 H, $J = 5.2$ Hz), 1.02 (d, 3H, $J = 6.0$ Hz), 1.43 (d, 6H, $J = 6.0$ Hz), 3.30−3.45 (m, 1H), 3.60−3.75 (m, 1H), 4.03 (t, 1H, $J = 2.6$ Hz), 4.17 (dd, 1H, $J =$ 1.2, 2.6 Hz), 4.32 (s, 5H), 4.35 (t, 1H, $J = 1.2$, 2.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 45.9, 50.9, 65.5, 66.3, 69.1, 72.4, 89.4, 89.6, 165.5; IR (KBr, cm^{-1}) 2965, 1629, 1473, 1321, 816, 487; MS (ES+, *m/z*, %) 393.0 (M + H, 100), 395.0 (M + H + 2, 82). Anal. Calcd for $C_{17}H_{22}BrFeNO$: C, 52.00; H, 5.60; N, 3.60. Found: C, 51.75; H, 5.66; N, 3.43.

(p*R*)-2-Bromo-(*N,N*-diisopropylaminomethyl)ferrocene (8). To a solution of (p*R*)-**7** (1.92 g, 4.89 mmol) in dry tetrahydrofuran (85 mL) under argon was added borane dimethylsulfide (10 mL, 20 mmol, 2 M solution in THF). The reaction mixture was stirred at reflux for 24 h, cooled at 0 °C, and quenched slowly with an aqueous solution of NaOH (10% w/v) until there was no gas evolution. The mixture was heated to reflux for 2 h, cooled to room temperature, and extracted with diethyl ether (3 × 50 mL), and the combined organic extract was washed with brine (3 × 50 mL), dried, filtered, and evaporated to give an orange residue, which was purified by silica gel chromatography (gradient elution, 9:1 hexane/ethyl acetate to ethyl acetate) to give (p*R*)-**8** (1.0 g, 54%) as a yellow oil, which solidifies upon storage in the freezer: mp 34 °C; $[\alpha]_D^{25} = -10$ (*c* 0.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (d, 6H, $J = 2.8$ Hz), 0.95 (d, 6H, $J = 3.2$ Hz), 2.85−3.10 (m, 2H), 3.45 (dd, 2H, $J = 14.4$ Hz), 3.94−3.98 (br s, 1H), 4.06 (s, 5H), 4.16−4.20 (br s, 1H), 4.26−4.30 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.3, 21.4, 42.7, 47.2, 65.6, 68.3, 69.4, 71.0, 80.1, 87.2; IR (KBr, cm^{-1}) 2962, 1360, 1233, 819, 488; MS (ES+, *m/z*, %) 278.0 (100), 280.0 (80), 379.0 (M + H, 10), 280.0 (M + H + 2, 8). Anal. Calcd for $C_{17}H_{24}BrFeN$: C, 54.00; H, 6.40; N, 3.70. Found: C, 53.88; H, 6.41; N, 3.33. (p*R*)-2-Bromomethylferrocene **9** was formed as orange crystals (0.15 g, 11%): mp 83−84 °C; $[\alpha]_D^{25} = +32.7$ (*c* 0.0052, CH_2Cl_2) {lit. (opposite enantiomer)[14] mp 82−83 °C, $[\alpha]_D^{25} = -27$ (*c* 0.11, EtOH)}; all other spectroscopic and analytical properties were identical to those reported in the literature.[14]

(Ferrocenylmethyl)diisopropylamine (10). Method A. To a suspension of $NaBH_4$ (2.9 g, 0.077 mol) in THF (60 mL) at 0 °C under argon was added a solution of iodine (8.12 g, 0.032 mol) in THF (40 mL) dropwise. The reaction was stirred for 0.5 h and allowed to warm to room temperature over 1.5 h. *N,N*-Diisopropylamidoferrocene **3** (10.0 g, 0.0319 mol) was then added portionwise over 0.5 h and the mixture refluxed overnight. After allowing the solution to cool to room temperature, dilute hydrochloric acid (200 mL of a 6 M aqueous solution) was added and the reaction stirred until no further hydrogen was evolved. After evaporation, solid sodium hydroxide was added until the pH became strongly basic (pH 12) and the solution was extracted with diethyl ether. The organic phase was then back-extracted with dilute HCl (3 × 100 mL of a 6 M aqueous solution). The aqueous phase was then basified with solid sodium hydroxide until the pH became strongly basic (pH 12) and re-extracted with diethyl ether (3 × 150 mL). The combined extracts were dried and evaporated to give a crude red oil (6.0 g), which was purified by silica gel chromatography (gradient elution, 1:1 hexane/ethyl acetate to ethyl acetate) to give **10** (2.50 g, 26%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (d, 12H, $J = 6.8$), 3.08 (septet, 2H, $J = 6.6$), 3.47 (s, 2H), 4.08 (s, 1H), 4.13 (s, 5H), 4.22 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 44.3, 47.6, 67.5, 68.7, 69.8, 88.9; IR (neat, cm^{-1}) *inter alia* 2963, 1685, 1459, 1361, 1165, 1105, 817; MS (ES+, *m/z*, %) *inter alia* 300 (M^+ + H, 39), 199 (100); HRMS (ES+, *m/z*, %) found (M + H) 300.1395, $C_{17}H_{26}N^{56}Fe$ requires 300.1415.

Method B. To a solution of **3** (0.2 g, 0.64 mmol) in dry tetrahydrofuran (11 mL) under argon was added borane dimethylsulfide (1.3 mL, 2.6 mmol, 2 M solution in THF). The reaction mixture was stirred at reflux for 24 h, cooled at 0 °C, and quenched slowly with an aqueous solution of NaOH (10% w/v) until there was no gas evolution. The mixture was heated to reflux for 2 h, cooled to room temperature, and extracted with diethyl ether (3 × 5 mL), and the combined organic extract was washed with brine (3 × 5 mL), dried, filtered, and evaporated to give an orange residue, which was purified by silica gel chromatography (gradient elution, 9:1 hexane/ethyl acetate to ethyl acetate) to give **10** (69 mg, 36%) as a yellow oil and **11** as yellow solid (3 mg, 2%), which was identical to that reported in the literature.[17]

(p*R*)-2-[(*N,N*-Diisopropylamino)methyl]ferrocenylboronic Acid (6). To a solution of **8** (2.95 g. 7.80 mmol) in 29 mL of freshly dried tetrahydrofuran under argon at −78 °C was added slowly via syringe 5.85 mL (9.36 mmol) of *n*-butyllithium. After 45 min, 0.961 mL (8.58 mmol) of trimethylborate was added via syringe at −78 °C. The reaction mixture was stirred for 45 min, then was warmed to room temperature. The reaction was quenched with water and extracted with diethyl ether (3 × 10 mL). The combined organic phase was washed with brine (3 × 15 mL), dried, filtered, and

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Table 1. Crystallographic Data

	4	5	6	12
CCDC deposit no.	622148	622149	622150	622151
formula	$C_{17}H_{24}BFeNO_3$	$C_{23}H_{34}BFeNO_3$	$C_{17}H_{26}BFeNO_2$	$C_{17}H_{25}BF_3FeN$
fw	357.03	439.17	343.05	367.04
T (K)	120	200	120	120
cryst syst	orthorhombic	monoclinic	orthorhombic	orthorhombic
space group (no.)	$P2_12_12_1$ (# 19)	$P2_1$ (# 4)	$P2_12_12_1$ (# 19)	$P2_12_12_1$ (# 19)
a (Å)	8.1087(8)	7.3099(4)	7.1359(4)	10.842(1)
b (Å)	12.016(1)	10.2092(5)	11.753(1)	11.304(1)
c (Å)	17.531(2)	15.5910(7)	20.110(2)	13.971(1)
β (deg)	90	97.41(1)	90	90
V (Å^3)	1708.1(3)	1153.8(8)	1686.6(2)	1712.3(3)
Z	4	2	4	4
ρ_{calcd} (g cm^{-3})	1.388	1.264	1.351	1.424
μ (mm^{-1})	0.90	0.68	0.90	0.91
no. of reflns total	18 775	16 066	23 970	18 515
no. of unique reflns	3836, 3710[a]	6714, 5147[a]	4914, 3839[a]	6168, 5488[a]
R_{int}	0.024	0.036	0.083	0.028
R_1,[a,b] wR_2[c]	0.021, 0.053	0.043, 0.107	0.038, 0.075	0.030, 0.074
Flack param	0.019(9)	−0.021(15)	−0.028(15)	−0.003(9)

[a] Reflections with $I > 2\sigma(I)$. [b] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [c] $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2}$.

concentrated *in vacuo*. The orange residue was purified by flash chromatography on aluminum oxide using a graduated elution (hexane, hexane/ethyl acetate, ethyl acetate, ethyl acetate/methanol, methanol as eluent). The fractions containing the boronic acid and the methylboronate ester were concentrated, and the solid was recrystallized from acetonitrile/water. Filtration gave **6** (1.50 g, 65%) as orange needles, which were suitable for X-ray analysis: mp = 144−150 °C; $[\alpha]_D^{25} = +121$ (c 0.01, $CHCl_3$). All spectroscopic and analytical properties were identical to those reported above.

(*pR*)-*N*-{[2-(Difluoroborylferrocenyl]methyl}-*N*,*N*-diisopropylamine Hydrofluoride (12). (p*R*)-2-(*N*,*N*-Diisopropylaminomethyl)-ferrocenylboronic acid **6** (1.0 g, 3.0 mmol) was dissolved in methanol (25 mL) and treated with a solution of KHF_2 (1.4 g, 17.9 mmol) in water (5 mL). After stirring the resulting suspension for 0.5 h, acetone (50 mL) was added and the resulting solution stirred for a further 0.5 h. Evaporation gave a yellow residue, which was extracted with DCM (ca. 30 mL), filtered, and re-evaporated to give the HF salt **12** as a yellow powder in quantitative yield. Slow evaporation from acetone/DCM gave crystals suitable for X-ray analysis: mp = 80 °C (dec); $[\alpha]_D^{25} = +183$ (c 0.0012, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15, 1.28, 1.43, and 1.57 (each d, 3H, J = 6.8 Hz), 3.53 (septet, 1H, J = 6.8 Hz), 3.64−3.76 (m, 2H), 4.02 (br s, 1H), 4.13 (t, 1H, J = 2 Hz), 4.19 (s, 5H), 4.46 (s, 1H), 4.68 (dd, 1H, J = 1.9, 12.6 Hz), 7.46 (v br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 18.5, 18.8, 20.4, 48.7, 51.6, 52.2, 68.2, 69.1, 70.0, 74.6, 77.2; ^{11}B NMR ($CDCl_3$, 128 MHz) δ 4.53 (br s); ^{19}F NMR ($CDCl_3$, 188 MHz) δ −133.2 (br s); MS (ES+, *m*/*z*, %) *inter alia* (M + H) 368 (49), 199 (100); IR (nujol, cm^{-1}) 3121, 3077, 1400, 1343, 1310, 1277, 1228, 1188, 1151, 1134, 1119, 1103, 1067, 1036, 1012, 983, 965, 936, 897, 814; HRMS (ES+, *m*/*z*, %) found (M + H) 368.1475, $C_{17}H_{26}BNF_3{}^{56}Fe$ requires 368.1460.

X-ray Crystallography. Single-crystal diffraction data were collected on a Bruker three-circle diffractometer with a SMART 6K CCD area detector, using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) and Cryostream (Oxford Cryosystems) open-flow N_2 cryostat and corrected for absorption by a semiempirical method based on Laue equivalents.[18] The structures were solved by direct methods and refined by full-matrix least-squares against F^2 of all unique data, using SHELXTL software.[19] Absolute configurations of all compounds were determined reliably from anomalous scattering, using the Flack method.[20] On cooling, monoclinic crystals of **5** underwent a reversible, second-order phase transition into a triclinic (pseudomonoclinic) phase. The α and γ angles began to deviate significantly from 90° around 145 K; at 120 K the lattice parameters are a = 7.295(2) Å, b = 10.163(2) Å, c = 15.595(3) Å, α = 90.28(1)°, β = 97.52(1)°, γ = 91.88(1)°, V = 1145.7(7) Å^3. Crystal data and other experimental details are listed in Table 1.

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Supporting Information Available: General experimental methods, ^{1}H and ^{13}C NMR spectra for compounds **8** and **10**, and crystallographic information (in CIF format) for **4**, **5**, **6**, and **12** are available free of charge via the Internet at http://pubs.acs.org.

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