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A (−)-Sparteine-Directed Highly Enantioselective Synthesis of Boroproline. Solid- and Solution-State Structure and Properties

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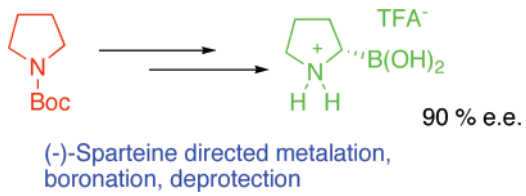
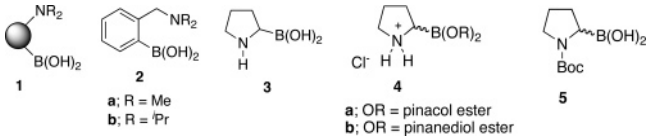


A two-step, direct asymmetric synthesis of the trifluoroacetate ammonium salt of boroproline is reported. (−)-Sparteine-mediated lithiation of *N*-Boc-pyrrolidine afforded *N*-Boc-aminoboronic acid in good yield and enantioselectivity as determined by HPLC (pinanediol ester). Deprotection using TFA yielded the ammonium salt; full characterization data are presented, and the structure in aqueous solution and the occurrence of a B−N species are discussed.

Since the report by Matteson[1] on the synthesis of (*R*)-1-acetamido-2-phenylethaneboronic acid (the boronic acid analogue of *N*-acetyl-L-phenylalanine), boronic acid analogues of amino acids and peptides have been used as enzyme inhibitors. H-Boroproline, H-boroalanine, H-boroleucine, H-borovaline, H-boronorleucine, and H-borophenylalanine are known to block the enzymatic activity of *Cryptosporidium parvum* arginine aminopeptidase (RAP).[2] Proteasome inhibitors, based upon boronic dipeptides such as PS-341 (Pyz-Phe-boroLeu),[3] have also proved to be more potent, selective, and stable than the corresponding aldehydes[4] and other natural products.[5] Boropeptides based on boroproline, such as valine−boroproline or proline−boroproline, can be used as dipeptidyl peptidase IV (DPP4, a serine protease) inhibitors,[6] while some *N*-alkylglycine−boroproline derivatives provide improved selectivity toward fibroblast activation protein-α (FAP), DPP VII, or DPP IV.[7] There are also examples of type 1 and 2 enzyme inhibitors of IgA proteinases from *Neisseria gonorrheae* and *Hemophilus influenzae*[8] and bacterial microorganisms[9] as well as activity against fibroblast activation protein-α (FAP).[10]

Our interests in aminoboronics are focused on the synthesis of bifunctional aminoboronic acids of type **1** as potential catalysts.[11] For example, the use of **2** as an efficient catalyst for amide bond formation[12] and developments in the use of organocatalysts[13] such as proline attracted us to boroproline **3** as a novel bifunctional organic catalyst. In this paper, we report a novel, simple, enantioselective synthesis of (*S*)-boroproline using an asymmetric directed metalation and subsequent study of structural and chemical properties.



The first report[8] of boroproline **3** synthesis was based on Matteson's α-amido-δ-substituted boronates;[14] however, non-enantioselective lithiation approaches from either pyrrole or pyrrolidine have been reported.[15] Only pyrrolidine boronic esters **4a** and/or **4b** have been isolated via the intermediacy of *N*-Boc-boronic acid **5**; the actual aminoboronic acid **3** has not been isolated or studied,[9] and despite diastereomers **4b** being isolated and separated, no direct enantiomeric synthesis of boroproline **3** has been reported.

(−)-Sparteine-mediated lithiation of *N*-Boc-pyrrolidine[16,17] results in the formation of (*S*)-2-lithio-*N*-Boc-pyrrolidine, and quenching with a range of electrophiles affords the corresponding 2-substituted *N*-Boc-pyrrolidines, though not borate elec-

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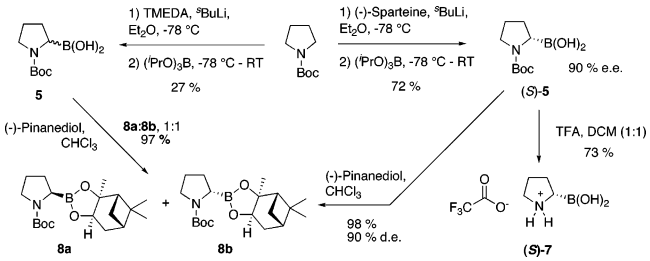
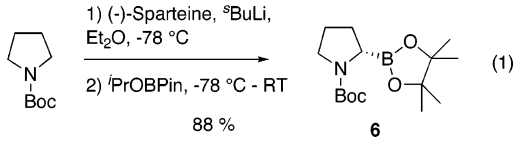
SCHEME 1. Synthesis of (*S*)-7 and Pinanediol−Pyrrolidinylboronates 8



trophiles. However, TMEDA-mediated lithiation followed by reaction with triisopropyl borate provides racemic boronic acid **5**.[15c] The synthesis of boroproline was intially approached via the *N*-Boc-protected pinacol boronate **6**, which was thought would enable isolation and purification. Hence, *N*-Boc-pyrrolidine underwent (−)-sparteine-mediated lithiation, followed by addition of isopropoxy pinacol borate to provide ester **6** (eq 1), presumably possessing the (*S*)-stereochemistry based on (−)-sparteine's usual enantioselection (vide infra).[16] Several subsequent attempts at simultaneous deprotection of *N*-Boc and pinacol ester functions under acidic conditions, followed by attempted isolation and purification using an ion-exchange resin (Dowex)[18] proved unsuccessful, and the free amino-boronic derivative could not be isolated.



An alternative approach to boroproline **3** and its derivatives was therefore examined as in Scheme 1. Racemic boronate **5** was prepared by the TMEDA-mediated lithiation of *N*-Boc-pyrrolidine (27%) followed by esterification with (−)-pinanediol to provide a 1:1 mixture diastereoisomers **8a** and **8b** (97%), as confirmed by HPLC.[19] The enantioselective synthesis of boronic acid **5** was achieved using the (−)-sparteine-mediated lithiation method to yield (*S*)-**5** in good yield and with the presumed absolute stereochemistry.[16] Subsequent formation of the (−)-pinanediol ester gave diastereosiomer **8b** with 90% de according to HPLC,[19] hence confirming the high level of asymmetric induction in the lithiation−boronation sequence providing boronic acid (*S*)-**5**.

Having isolated the (−)-pinanediol ester **8b** with the predicted absolute stereochemistry (Scheme 1), attempts were made to confirm the absolute stereochemistry of both boronic acid (*S*)-**5** and pinanediol ester **8b** by single-crystal X-ray analysis. These attempts were unsuccessfull in the case of (*S*)-**5** due to the lack of a heavy atom to assist absolute stereochemical determination (see Figure 1) and, in the case of **8b**, due to the lack of formation of suitable crystals. However, the absolute stereochemistry of

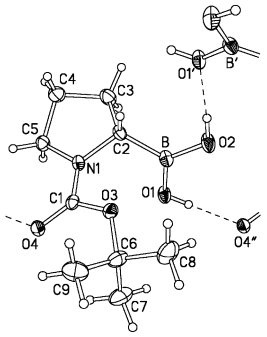


FIGURE 1. X-ray structure of (*S*)-**5**, showing hydrogen bonds (50% thermal ellipsoids). Symmetry transformations: $1 - x, y - {}^1/_2, {}^1/_2 - z$ (primed), $x - 1, y, z$ (double-primed). Absolute configuration assigned by analogy with **9**.

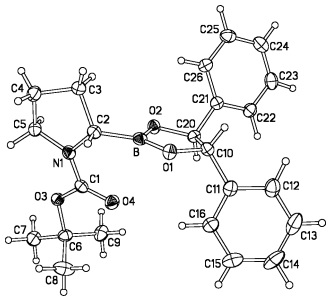
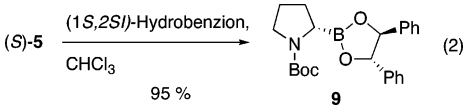


FIGURE 2. X-ray structure of (*S*)-**9** (50% thermal ellipsoids).

(*S*)-**5** was determined by formation of the (1*S*,2*S*)-hydrobenzoin ester **9** (eq 2), which provided crystals which were suitable for single-crystal X-ray analysis (Figure 2) and confirmed the (*S*)-absolute configuration at C2 in **9** and, therefore, in the parent compound (*S*)-**5**.

In both (*S*)-**5** and **9** (Figures 1 and 2, respectively), the N1 atom is sp^2-hybridized due to π-conjugation with the carboxylic group, as indicated by N1−C1 bond distances of 1.331(2) [(*S*)-**5**] and 1.341(2) Å (**9**), small (0.06 and 0.04 Å) deviations of N1 from the C1/C2/C5 plane (*A*), and the dihedral angles of 5.3° and 2.4° between the latter and the COO plane. The pyrrolidine ring conformation is intermediate between a twist and envelope conformation (C3 and C4 deviating from the *A* plane in opposite directions, by 0.15 and −0.50 Å in (*S*)-**5**, −0.47 and 0.16 Å in **9**) with the boronic substituent in a pseudo-equatorial position. The boronate B is planar-trigonal, its plane inclined by 67° [(*S*)-**5**] or 75° (**9**) to the *A* plane.



Having obtained the protected pyrrolidineboronic acid (*S*)-**5** in high ee and confirmed its absolute stereochemistry, *N*-Boc deprotection was examined using TFA. Smooth deprotection occurred, and the trifluoroacetate ammonium salt of (S)-**7** was obtained in 73% yield, notably with a ^{11}B NMR shift at δ 28 in D_2O, clearly diagnostic of a free, uncomplexed boronic acid (vide infra). Studies of intramolecular B−N interactions in aminoboronic acids have been reported,[20] which show characteristic ^{11}B NMR shifts[21] in the region ca. 10−12 ppm. The equilibria involved in the neutralization of the ammonium salts of aminoboronic acids, and eventual quaternization at B to form

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(19) HPLC conditions: Chiracel OJ, Hexane:IPA (99:1), 0.5 mL/min, λ = 210 nm; t_R (*S*) = 8.24 min, t_R (*R*) = 9.46 min.

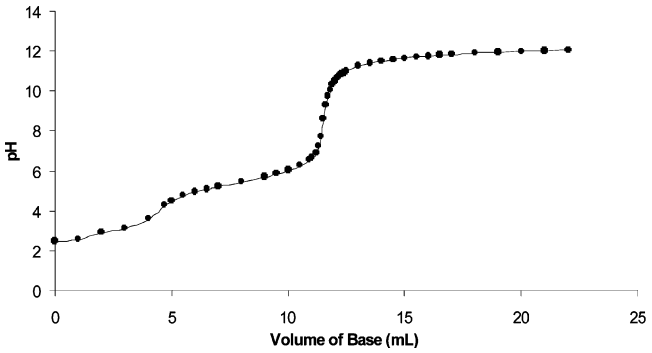
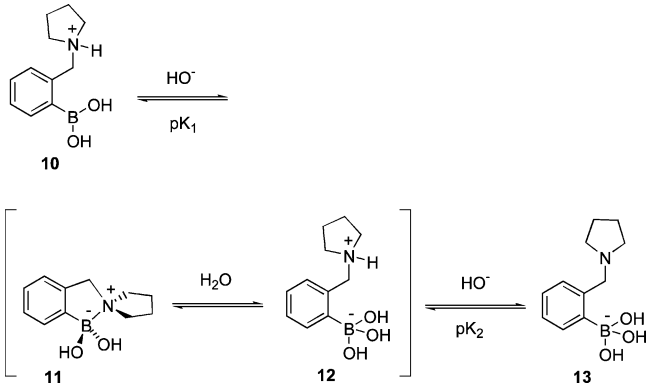


FIGURE 3. Boroproline TFA salt (S)-**7** titration with sodium deuteroxide in D_2O.

SCHEME 2. Effects of Changes in pH upon the Solution Behavior of Aminoboronic Acid Derivatives



the boronate "ate" complex, were initially thought to proceed via intermolecular B−N chelation;[22,23] however, more recent investigations using ^{11}B NMR titrations indicate that the first equilibrium is that of the quaternization of B leading to a B−N chelated species **11** in equilibrium in solution with the solvated zwitterion **12** (Scheme 2).[24]

A comparison of these observations was made in D_2O for TFA salt (*S*)-**7**, involving the addition of hydroxide (1 equiv). ^{1}H and ^{11}B NMR spectroscopy revealed the occurrence of structural changes to amino-boronate (*S*)-**7**; in the ^{11}B NMR spectrum the boronate shifted from 28 ppm to ca. 2 ppm, which confirmed the formation of the expected "ate" complex.[25] Titration of (*S*)-**7** with hydroxide (Figure 3) confirmed the presence of an intermediate species en route to the fully quaternized boron "ate" complex, with p*K* values of 5.2 and 11.2. This is in good agreement with reported data for *o*-(*N*,*N*-dimethylaminomethyl)benzene[20b,22a] and for the process shown in Scheme 2. However, the physical relative position of the boron and amino functions in boroproline systems such as **7** means that an intramolecular complex cannot be the intermediate species.

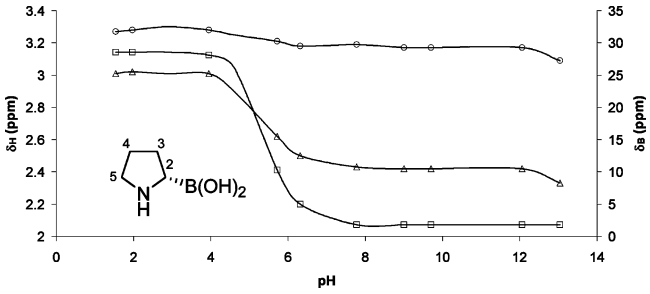


FIGURE 4. Variation of ^{1}H and ^{11}B NMR shifts with pH. □: B chemical shifts. Δ: H2 chemical shifts. ○: H5 + H5′ chemical shifts. For full chemical shifts listings, see the Supporting Information.

In order to study this further, both ^{1}H and ^{11}B NMR spectra were also recorded at various pH values as (*S*)-**7** was titrated with deuteroxide in D_2O (Figure 4); the pH profile of the ^{11}B NMR shifts shows the transition that must occur between the sp^2 boronic acid and sp^3 boronate "ate" complex. Similar to literature reports,[24] no evidence was obtained for this transition occurring after pH 7. This behavior confirms that the first equilibrium is that of boronate hydroxylation to form a trihydroxyboronate complex, and a p*K* value of 5.3 can be calculated (Figure 4) which agrees with the value of 5.2 determined by titration. Further, it appears that the pK_a of the boronic acids in aminoboronic acids of type (*S*)-**7** are essentially defined by the stabilization of the trihydroxyboronate complex by ion pairing with the ammonium ion. Indeed, the pK_a value quoted herein (5.3) compares well to those reported for arylaminoboronic acids,[20b,22a,24] despite the lower Lewis acidity of alkylboronic acids compared to arylboronic acids.[26]

The ^{1}H NMR spectra of (*S*)-**7** in D_2O (Figure 4) also show the changes in the electronic environments at C2 and C5. Both quaternization at boron and neutralization of the ammonium salt are clear, causing increased shielding of the vicinal protons. A significant shift of ca. 0.6 ppm for the C2 proton occurs at pH > 4, compared to a smaller shift (ca. 0.1 ppm) at C5. This is in good agreement with the signals recorded in the ^{11}B NMR spectrum, indicating that quaternization at boron also occurs. A second change in the same proton's chemical shift was observed at higher pH, where deprotonation of the ammonium ion is expected to occur.[27] However, it is not possible to unambiguously identify the structure of the transient species involved, though clearly it cannot be an intramolecular B−N complex such as **11** (Scheme 2). It is likely that in boroamino acids such as (*S*)-**7**, zwitterionic and bimolecular species are involved as transition species in the pH titration curves (Figure 4). The most likely explanation for the observed ^{1}H and ^{11}B NMR shifts (Figure 4) is explained as in Scheme 3; i.e., the TFA ammonium salt (*S*)-**7** undergoes neutralization with hydroxide to form the doubly zwitterionic dimer **14**, which is solvated to give trihydroxyboronate complex **15**. Further increases in pH eventually transform the boroproline system fully to the neutral amine trihydroxybornate species **16**.

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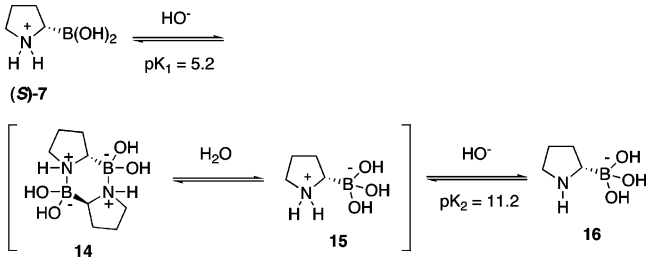
(27) pK_a of pyrrolidine = 11.27: Hall, H. K., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5441−5444.

SCHEME 3. Prediction of Effects of Changes in pH upon the Solution Behavior of Boroproline Aminoboronic Acid (*S*)-7



We have reported the direct, highly enantioselective synthesis of boroproline and isolated it as the trifluoroacetate salt (*S*)-**7** which shows similar properties to other amino boronate systems when exposed to pH titration.[24] It is proposed that a bimolecular 6-membered ring complex **14** is involved as a transition species, and hydroxylation of the boronate function precedes neutralization of the ammonium ion with p*K* values of 5.2 and 11.2, respectively. The impact of such equilibria and pH effects on the ability of the aminoboronic acid to act as a catalyst for organic reactions is being investigated.

Experimental Section

(*S*)-*N*-(1,1-Dimethylethoxycarbonyl)pinacol (Pyrrolidin-2-yl)-boronate (6). *s*-BuLi (4.80 mL, 5.6 mmol) was added dropwise to a stirred solution of (−)-sparteine (1.27 mL, 5.6 mmol) in Et_2O (24 mL) at −78 °C under Ar. The solution was stirred at −78 °C for 30 min. Boc-pyrrolidine (0.82 mL, 4.66 mmol) in Et_2O (2 mL) was added dropwise. The mixture was stirred at −78 °C for 4 h. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxoborolane (1.30 g, 7.0 mmol) was added dropwise and the solution allowed to warm to rt overnight. The reaction was quenched with satd aq NH_4Cl, the mixture was extracted with DCM (2×), the pH was adjusted to 7, and the mixture was extracted further with DCM (2×). The combined organic extracts were dried ($MgSO_4$) and evaporated. Purification by SiO_2 chromatography (3:1, petroleum ether−EtOAc as eluent) gave **6** (1.20 g, 88%) as a white solid: mp 107 °C dec; $[\alpha]^{23}D$ +50.6 (*c* 0.035, DCM); IR (neat) 2976, 1682, 1367, 1144; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 12H), 1.37 (s, 9H), 1.50−2.00 (m, 4H), 2.90−3.40 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.4, 24.5, 25.0, 27.2, 27.7, 28.5, 45.9, 78.8, 83.4, 154.9; ^{11}B NMR (128 MHz, $CDCl_3$) δ 32; *m*/*z* (ES+) 298.2 (100).

(*S*)-*N*-(1,1-Dimethylethoxycarbonyl)(pyrrolidin-2-yl)boronic Acid ((*S*)-5). *s*-BuLi (4.66 mL, 6.5 mmol) was added to a stirred solution of (−)-sparteine (1.50 mL, 6.5 mmol) in Et_2O (48 mL) at −78 °C under Ar. After 10 min, Boc-pyrrolidine (0.88 mL, 5.0 mmol) in Et_2O (2 mL) was added dropwise. After 4 h, triisopropyl borate (1.15 mL, 5 mmol) was added dropwise and the solution allowed to warm to rt overnight. The reaction was quenched with aq HCl (20 mL, 5%), the mixture was separated separated, and the aqueous phase was extracted with Et_2O (50 mL, 3×). The combined extracts were dried ($MgSO_4$), evaporated, washed with hexane, and filtered to give (*S*)-**5** (0.77 g, 72%) as a white solid: mp 107 °C dec; $[\alpha]^{23}D$ +69.5 (*c* 1.06, DCM); IR (KBr) 3365−3150, 1667, 1350, 1243 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.43 (s, 9H), 1.65−1.87 (m, 2H), 1.91−2.10 (m, 2H), 2.93 (dd, 1H, J = 11.2, 6.8 Hz), 3.20−3.30 (m, 1H), 3.40−3.50 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.8, 27.6, 28.5, 47.4, 80.2, 157.2; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31; *m*/*z* (CI) 70.1 (100), 170.2 (80), 591.4 (boroxine, 20). Anal. Calcd for $C_9H_{18}BNO_4$: C, 50.3; H, 8.4; N, 6.5. Found: C, 49.9; H, 8.55; N, 6.4.

***N*-(1,1-Dimethylethoxycarbonyl)(pyrrolidin-2-yl)boronic Acid (5).** *s*-BuLi (4.66 mL, 6.5 mmol) was added to a stirred solution of TMEDA (0.97 mL, 6.5 mmol) in Et_2O (48 mL) at −78 °C under Ar. After 10 min, Boc-pyrrolidine (0.88 mL, 5 mmol) in Et_2O (2 mL) was added dropwise. After 4 h, triisopropyl borate (1.15 mL, 5 mmol) was added dropwise and the solution allowed to warm to rt overnight. The reaction was quenched with aq HCl (20 mL, 5% solution), the mixture was separated, and the aqueous phase was extracted with Et_2O (50 mL, 3×). The combined organic extracts were dried ($MgSO_4$), evaporated, washed with hexane, and filtered to afford **5** (0.23 g, 27%) as a white solid: IR (KBr) 3360−3155, 1666, 1356, 1245 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.42 (s, 9H), 1.63−1.85 (m, 2H), 1.93−2.09 (m, 2H), 2.92 (dd, 1H, J = 11.2, 6.8 Hz), 3.19−3.29 (m, 1H), 3.38−3.48 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.8, 27.6, 28.5, 47.4, 80.2, 157.2; ^{11}B NMR (128 MHz, $CDCl_3$) δ 31; *m*/*z* (CI) 70.1 (100), 170.2 (80), 591.4 (boroxine, 20).

***N*-(1,1-Dimethylethoxycarbonyl)-(1*S*,2*S*,3*R*,5*S*)-pinanediol (Pyrrolidin-2-yl)boronate (8a + 8b).** Compound **5** (0.108 g, 0.5 mmol) in $CHCl_3$ (10 mL) was treated with (−)-pinanediol (85 mg, 0.5 mmol). After 12 h, the solvent was evaporated to give **8a** + **8b** (0.17 g, 97%) as a clear oil. Analytical and spectroscopic properties were identical to those reported in the literature.[15a]

(*S*)-(Trifluoroacetate)(pyrrolidin-2-ium)boronic Acid ((*S*)-7). (*S*)-**5** (0.50 g, 2.33 mmol) in DCM (15 mL) was treated with TFA (15 mL). After 3 h, water was added, the DCM layer was separated, and the aqueous phase was evaporated to give a residue which was recrystallized from DCM to afford (*S*)-**7** (0.39 g, 73%) as a beige solid: mp 103.2 °C; $[\alpha]^{23}D$ +50.1 (*c* 0.20, DCM); IR (KBr) 3300−3000, 1755, 1674, 1385, 1200 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 1.73−1.81 (m, 1H), 1.85−2.00 (m, 2H,), 2.11−2.17 (m, 1H,), 2.94 (m, 1H, J = 9.4 Hz), 3.20 (t, 2H, J = 7.4 Hz); ^{13}C NMR (126 MHz, D_2O) δ 24.5, 26.6, 46.1, 47.9 (br), 116.4 ($^1J_{CF}$ = 292 Hz), 162.9 ($^2J_{CF}$ = 36.5 Hz); ^{11}B NMR (128 MHz, D_2O) δ 28; ^{19}F NMR (188 MHz, D_2O) δ −76.1; *m*/*z* (ES+) 115.9 (100), 114.9 (25); *m*/*z* (ES−) 112.9 (100); HRMS (ES+) $[M]^+$ calcd for $C_4H_{11}NO_2B^+$ 116.0877, found 116.0879.

(*S*)-*N*-(1,1-Dimethylethoxycarbonyl)-(1*S*,2*S*,3*R*,5*S*)-pinanediol (Pyrrolidin-2-yl)boronate ((*S*)-8). (*S*)-**5** (0.215 g, 1 mmol) in $CHCl_3$ (25 mL) was treated with (−)-pinanediol (0.17 g, 1 mmol). After 12 h, the solvent was evaporated to afford (*S*)-**8** (0.34 g, 98%) as a clear oil. Analytical and spectroscopic properties were identical to those reported in the literature.[15a]

(*S*)-*N*-(1,1-Dimethylethoxycarbonyl)-(4*S*,5*S*)-4,5-diphenylethanediol (Pyrrolidin-2-yl)boronate ((*S*)-9). (*S*)-**5** (40 mg, 0.19 mmol) in $CHCl_3$ (25 mL) was treated with (*S*,*S*)-hydrobenzoin (40 mg, 0.19 mmol). After 12 h, the solvent was evaporated and recrystallized from THF to afford (*S*)-**9** (70.2 mg, 95%) as white needles: mp 109 °C dec; $[\alpha]^{23}D$ −29.3 (*c* 0.016 in DCM); ν_{max}(neat)/cm^{-1} 2980, 2922, 2878, 1658, 1417, 1125; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 1.81−2.29 (m, 4H), 3.09−3.59, (m, 3H), 5.07 (s, 1.5H), 5.20 (s, 0.5H), 7.20−7.42 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 27.6, 27.9, 28.5, 28.7, 29.3, 29.7, 45.3, 46.5, 79.1, 81.1, 86.4, 86.6, 126.3, 126.9, 127.9, 128.1, 128.5, 128.7, 139.8, 141.0, 157.3; ^{11}B NMR (128 MHz, $CDCl_3$) 33; *m*/*z* (ES+) 394.0 (55), 416.3 (56); HRMS (ES+) $[M]^+$ calcd for $C_{23}H_{28}NO_4BNa$ 416.2009, found 416.2004.

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Supporting Information Available: General experimental methods, X-ray crytallographic data for compounds **5** and **9**, and ^1H, ^{13}C, ^{11}B, and ^{19}F NMR spectra (as appropriate) for compounds **5**−**7** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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