Synthesis of 1-Amino-2-phenylethane-1-boronic Acid Derivatives

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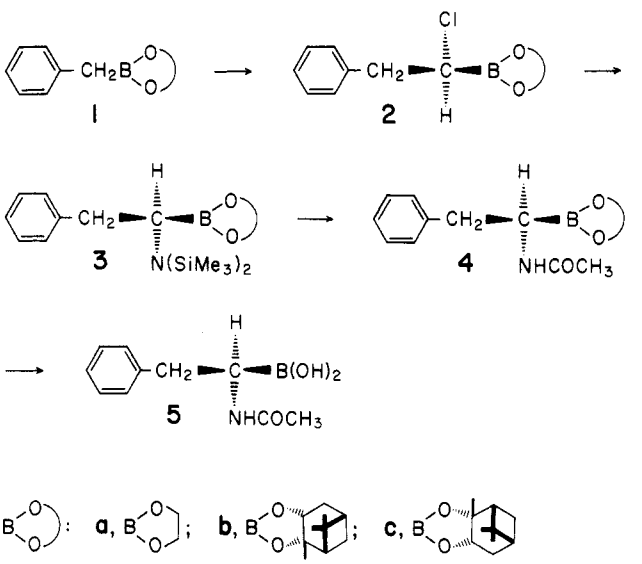
The boron analogue of *N*-acetylphenylalanine, (*R*)-1-acetamido-2-phenylethane-1-boronic acid (**5b**), has been synthesized from (+)-pinanediol phenylmethane-1-boronate (**1b**), which was converted by (dichloromethyl)lithium to the (*S*)-1-chloro-2-phenylethane-1-boronate (**2b**), then with *N*-lithiohexamethyldisilazane to the silylated 1-amino-2-phenylethane-1-boronic ester **3b**, which was desilylated and acetylated in situ to (+)-pinanediol (*R*)-1-acetamido-2-phenylethane-1-boronate (**4b**) and then cleaved to the free boronic acid **5b** with boron trichloride. 1-Amino-2-phenylethane-1-boronic esters (**6**) were found to be isolable but unstable, deboronating to 2-phenylethylamine under the influence of heat or hydroxylic solvents. 1-Amino-2-phenylethane-1-boronic acid, though not isolable, partially survives for an hour in cold aqueous solution. Attempts to synthesize the stable α-acetamido boronic esters (**4**) directly by reaction of lithioacetamide with 1-halo-2-phenylethane-1-boronic esters (**2**) have resulted in a major proportion of O-alkylation to form imino esters. Pinacol 1-acetamidino-2-phenylethane-1-boronate (**8**) has been obtained from the α-iodo boronic ester **2d** and acetamidine.

α-Amido boronic acids were proposed by G. E. Lienhard as potential serine protease inhibitors which could bind these enzymes into configurations resembling their normal transition states. A preliminary account of our synthesis of (*R*)-1-acetamido-2-phenylethane-1-boronic acid (**5b**) and Lienhard's measurement of its binding to chymotrypsin has appeared.[1] The synthetic problem had proved much more difficult than anticipated. A synthesis of ethylene glycol 1-bromo-2-phenylethane-1-boronate[2] was followed by failure of all attempts to convert this material to an α-amino or α-acetamido boronic acid. The failures were unexpected in view of earlier success in synthesizing (dimethylamino)methaneboronic acid, piperidinomethaneboronic acid, and what was believed to be phthalimidomethaneboronic acid, although aminomethaneboronic acid itself had been elusive.[3] After the report by Lindquist and Nguyen that benzamidomethaneboronic acid had been synthesized and proved to be a good inhibitor of chymotrypsin,[4] reinvestigation showed that (dialkylamino)methaneboronic esters and their quaternary ammonium derivatives are stable compounds, but reaction of dibutyl iodomethaneboronate with benzylamine followed by attempted distillation of the product resulted in disproportionation to tributyl borate and benzylmethylamine.[5]

Encouraged by Lindquist's results[4] and the development of a reasonably efficient route to pinacol 1-iodo-2-phenylethane-1-boronate (**2d**),[6] we examined reactions of **2d** with lithiobenzamide and lithioacetamide.[7] Variable yields of solid product only slightly soluble in ether or water were obtained, which typically showed significant but variable proton NMR absorptions near δ 4.3 in addition to the expected[3] absorptions near δ 3. It was tentatively concluded that the α-halo boronic ester attacks the amide anion at oxygen rather than nitrogen and that Lindquist's compound might similarly be an O-linked isomer of the expected product.[8]

Results

The successful synthetic route is based on Majumdar's observation of the stability of (dialkylamino)methaneboronic esters[5] and his efficient new synthesis of α-chloro boronic esters,[9] as well as his observation of S_N2 displacement on an α-chloro boronic ester by a highly hindered dialkylamide.[10] Thus, ethylene glycol benzylboronate (**1a**) with (dichloromethyl)lithium[9] yielded ethylene glycol 1-chloro-2-phenylethane-1-boronate (**2a**),



Series **a**, racemic; **b**, as illustrated; **c**, enantiomer of **b**

which with *N*-lithiohexamethyldisilazane yielded the stable, distillable silylated amino boronic ester **3a**. Conversion to the free amino boronic ester, which deboronates to 2-

(1) Matteson, D. S.; Sadhu, K. M.; Lienhard, G. E. *J. Am. Chem. Soc.* **1981**, *103*, 5241-5242.
(2) Matteson, D. S.; Jesthi, P. K. *J. Organomet. Chem.* **1976**, *114*, 1-7.
(3) Matteson, D. S.; Cheng, T.-C. *J. Org. Chem.* **1968**, *33*, 3055-3060.
(4) Lindquist, R. N.; Nguyen, A. C. *J. Am. Chem. Soc.* **1977**, *99*, 6435-6437.
(5) Matteson, D. S.; Majumdar, D. *J. Organomet. Chem.* **1979**, *170*, 259-264.
(6) (a) Matteson, D. S.; Arne, K. *J. Am. Chem. Soc.* **1978**, *100*, 1325-1326. (b) Matteson, D. S.; Arne, K. H. *Organometallics* **1982**, *1*, 280-288.
(7) Ray, R.; Matteson, D. S., unpublished results.
(8) Amiri, P.; Lindquist, R. N.; Matteson, D. S.; Sadhu, K. M., manuscript in preparation.
(9) (a) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7588-7590. (b) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 1529-1535.
(10) Reaction of pinacol cyclohexylchloromethaneboronate[9] with lithium 2,2,6,6-tetramethylpiperidide yielded a substantial proportion of S_N2 displacement product as judged from the NMR spectrum: Majumdar, D., unpublished results.

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phenylethylamine with slight provocation, will be discussed in a subsequent section. Isolation of the unstable intermediate was avoided by treating **3a** with acetic acid and acetic anhydride, which yielded stable ethylene glycol 1-acetamido-2-phenylethane-1-boronate (**4a**) directly. The extreme water solubility of **4a**, or more properly its hydrolysis product 1-acetamido-2-phenylethane-1-boronic acid (**5a**), was unexpected. Extraction of **4a** or **5a** from water into ether proved so inefficient that only traces of **4a** were obtained after normal aqueous workup. No practical route was found for the conversion of **4a** to **5a** because of the difficulty in separating **5a** from ethylene glycol.

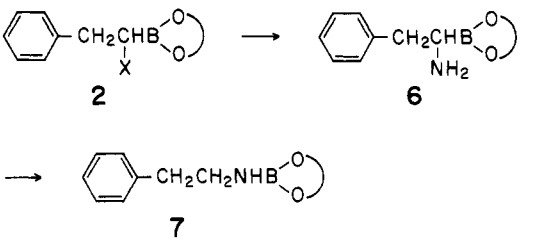
Use of (+)-pinanediol phenylmethane-1-boronate (**1b**) in the procedure of Matteson and Ray[11] readily yielded (+)-pinanediol (*S*)-1-chloro-2-phenylethane-1-boronate (**2b**), which was converted to the silylated amino boronic ester **3b**, which was not purified because of its high boiling point and hydrolytic instability but was desilylated/acetylated in situ to yield (+)-pinanediol (*R*)-1-acetamido-2-phenylethane-1-boronate (**4b**). Pinanediol esters are resistant to hydrolysis but can be cleaved with boron trichloride,[11] and application of this procedure yielded (*R*)-1-acetamido-2-phenylethaneboronic acid (**5b**).

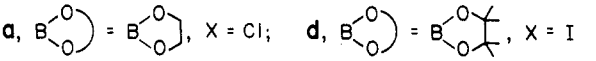
The homologation of the benzylboronic ester **1b** to the α-chloro boronic ester **2b** is best carried out with the aid of zinc chloride catalysis, which has resulted in yields up to 99%, with diastereoselectivity of 99.5%.[12] However, the reaction was first run without catalysis with diastereoselectivity of 92.7%, as shown by reaction of the α-chloro boronic ester **2b** with methylmagnesium bromide[11] and oxidation of the resulting pinanediol 1-phenylpropane-2-boronate with alkaline hydrogen peroxide to form 1-phenyl-2-propanol, 85.4% enantiomeric excess (ee). The α-amido boronic ester **4b** derived from this source was recrystallized repeatedly to constant rotation. It then showed only a single N*H* peak in the NMR, where epimers generally show separate absorptions,[13] though the other epimer was never checked in this particular case.

The boronic acid **5b** was readily converted to its anhydride by vacuum drying, as are many boronic acids. However, an unprecedented result was observed when a sample of **5b** was crystallized from a solution presumably rich in hydrochloric acid derived from the boron trichloride used to cleave the pinanediol ester (**4b**). The crystals contained approximately $^1/_2$ mol of HCl per mol of **5b** as shown by potentiometric titration[14] and chlorine analysis and otherwise functioned in the same manner as **5b** as a chymotrypsin inhibitor.[1] It would not ordinarily be possible to crystallize a tricoordinate boron halide from an aqueous solution, but perhaps the –BClOH group is acidic enough to coordinate to the amide oxygen to form a chelated structure having tetracoordinate boron.

(*S*)-1-Acetamido-2-phenylethane-1-boronic acid (**5c**) was prepared in the same manner as **5b**, but with (–)-pinanediol as the chiral directing group.

Amino Boronic Esters. Prior to the successful synthesis of the α-acetamido boronic acid **5**, an extensive investigation led to isolation of the unstable α-amino boronic esters **6**. Under the influence of heat or hydroxylic solvents, these rearrange to 2-phenylethylamine-*N*-boronic esters (**7**) or their solvolysis products. Free 1-amino-2-





phenylethane-1-boronic acid has not been purified but has been obtained as an insoluble and perhaps polymeric solid and has also been generated in cold aqueous acid and shown to have an appreciable lifetime in cold neutral aqueous solution.

The first α-amino boronic ester obtained was **6d** from the reaction of pinacol 1-iodo-2-phenylethane-1-boronate[6] (**2d**) with ammonia. Treatment of **2d** with ammonia at atmospheric pressure in pentane yielded an immediate crystalline precipitate which was soluble in deuteriochloroform and yielded the proton NMR spectrum of unchanged **2d**. This result is interpreted as evidence for reversible formation of a boronic ester–ammonia complex. The use of dimethylformamide or ether as solvent also led to recovery of unchanged **2d**. However, reaction of **2d** with liquid ammonia in a bomb at room temperature did result in conversion to a crystalline product which yielded the correct elemental analysis for the α-amino boronic ester **6d**. The NMR spectrum showed three inexplicably broad and shifted pinacol CH_3 peaks, the smallest at δ 0.65, the next at 0.87, and the largest at 1.10, plus two very small and sharp peaks in the normal pinacol region, 1.30 and 1.35. The NH_2 peak at δ 2.5 and C$_6H_5$ peak at 7.35 were normal, and CHCH_2 showed as an unsymmetrical unresolved multiplet near δ 3.0. This material appeared to be stable in deuteriochloroform, but in ordinary chloroform containing a little ethanol the NMR spectrum changed over the course of a few hours so that there was a single sharp pinacol CH_3 peak at δ 1.30 and a symmetrical multiplet near δ 2.9 characteristic of 2-phenylethylamine, suggesting conversion to 2-phenylethylamine-*N*-boronic ester (**7d**). Osmometric molecular weight measurements on **6d** in chloroform (with ethanol) initially yielded values 1.5 times the theoretical 247, but decreased in 30 min to 0.66 times this value. Attempts to acetylate **6d** failed. Evidence in favor of structure **6d** is provided by comparison of the proton NMR spectrum with that of the subsequently prepared and more fully substantiated ethylene glycol ester **6a**. It appears likely that **6d** exists largely as a boron–nitrogen coordinated cyclic dimer, possibly together with other subspecies.

Ethylene glycol 1-amino-2-phenylethane-1-boronate (**6a**) was prepared by methanolysis of the disilylamino precursor **3a**. Although **6a** was a crystalline solid, it was sensitive to moisture and analytical purity was not achieved. Sublimation resulted in rearrangement of **6a** to the 2-phenylethylamine-*N*-boronic ester **7a** as indicated by changes in the NMR spectrum. Structure **6a** was confirmed by oxidation with hydrogen peroxide in the presence of 2,4-dinitrophenylhydrazine and acid to yield phenylacetaldehyde 2,4-dinitrophenylhydrazone nearly quantitatively. It was demonstrated that 2-phenylethylamine does not yield aldehyde under these conditions.

(11) (a) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590–7591. (b) Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. S. *Organometallics* **1983**, *2*, 1536.

(12) (a) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077–2078. R = benzyl for compounds **1f**/**3f** (information omitted in printing error). (b) Matteson, D. S.; Sadhu, K. M., manuscript in preparation.

(13) Tsai, D. J. S.; Jesthi, P. K.; Matteson, D. S. *Organometallics* **1983**, *2*, 1543.

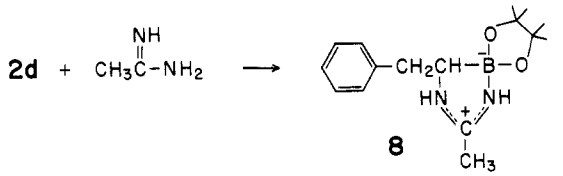
(14) Lienhard, G. E. Personal communication, 1980.

Further evidence for structure **6a** was obtained in attempts to prepare free 1-amino-2-phenylethane-1-boronic acid, which was not purified but was obtained, perhaps as a polymer, in a mixture with **6a** by treatment of **6a** with a small amount of water, which yielded an insoluble solid, which was washed with a large amount of ether and a small amount of water. Although the accidentally degenerate $CHCH_2$ absorption in the 60-MHz NMR spectrum was an uninformative singlet at δ 3.10 in D_2O/acetone-d_6/CF_3CO_2H, addition of 2-phenylethylamine yielded a superimposed characteristic symmetrical multiplet of the CH_2CH_2 group, showing that the boronic acid does not contain a significant amount of 2-phenylethylamine and is not in equilibrium with it. The residual ethylene glycol peak in this sample amounted to 25 mol %.

A neutral aqueous solution of 1-amino-2-phenylethane-1-boronic acid was prepared by dissolving **6a** in hydrochloric acid and neutralizing with sodium bicarbonate to pH 6–7. After 1 h at 5 °C, this solution was treated with sodium perborate followed by acidic 2,4-dinitrophenylhydrazine, which yielded 33% phenylacetaldehyde 2,4-dinitrophenylhydrazone.

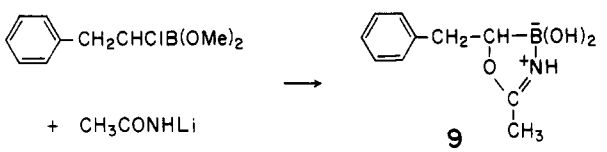
Several attempts were made to prepare tetrafluoroborate or tetraphenylborate salts of **6a** or the amino boronic acid. However, NMR and elemental analyses indicated that the recrystallized materials were mixtures containing mostly 2-phenylethylammonium salts.

An α-Amidino Boronic Ester. Reaction of pinacol 1-iodo-2-phenylethane-1-boronate (**2d**) with acetamidine yielded the chelated 1-acetamidino-2-phenylethaneboronic ester **8**. It was found that **8** is soluble in and stable toward



water, and not appreciably attacked by boiling aqueous sodium carbonate in 45 min.

Lithio Amide Reactions. Reaction of *N*-lithioacetamide with dimethyl 1-chloro-2-phenylethane-1-boronate in THF followed by concentration and water/ether workup yielded a voluminous, intractable white precipitate, insoluble in all common solvents except strong acid. We postulate that this is the O-alkylated acetamide **9** on the basis of the multiplet at δ 4.3 in the NMR, appropriate for O–C*H*B. The yield was only ~60%, and the most likely



other product, the acetamido boronic acid **5a**, would have been lost as a result of our ignorance at that time of its high water solubility.

In another run, water/dichloromethane workup without prior removal of the THF resulted in a much lesser amount of insoluble material. The dichloromethane extract was chromatographed on silica and eluted with methanol. A small yield of solid was obtained that was soluble in deuteriochloroform and showed unresolved broad multiplets at δ 3.1 and 4.2 as well as a broadened *C*-methyl at 2.1 and phenyl at 7.5, but nothing identified as N*H*. This material was a chymotrypsin inhibitor.[14] It was attacked slowly by atmospheric moisture, and the elemental analysis was high in boron and low in nitrogen for **9**. It is possible that **9** is unstable toward hydrolysis and likely that this product contains 1-acetoxy-2-phenylethane-1-boronic acid in some form. A 1:1 anhydride between **9** and the acetoxy compound would approximate the observed analysis.

Review of NMR spectra obtained by Ray[7] indicates that reaction of dibutyl 1-iodo-2-phenylethane-1-boronate with *N*-lithiobenzamide followed by transesterification with pinacol and chromatography yielded a mobile fraction having all of the $CHCH_2$ multiplet at δ 3.0–3.3, consistent with the benzamido analogue of **4**. Another sample shows multiplets at δ 3.1 and 4.4, consistent with the benzimido analogue of the pinacol ester of **9**. Numerous spectra of crude reaction products indicate gross mixtures of these and unidentified byproducts.

One negative result of positive future interest is the reaction of lithiodiacetamide with pinacol 1-iodo-2-phenylethane-1-boronate. No evidence for S_N2 substitution product of any kind was seen, and the major product was pinacol (*E*)-2-phenylethene-1-boronate. This is the only known example of dehydrohalogenation of an α-halo boronic ester except for the previously reported dehydrobromination of dibutyl 1-bromo-3,3,3-trichloropropane-1-boronate by *tert*-butylamine.[15]

Discussion

This work has established a good synthetic route to α-amido boronic esters and acids and proved their stability. In contrast, the stability of free α-amino boronic esters or acids is shown to be limited, though it appears that these might have sufficient stability for studies of their activity toward enzymes if generated in situ.

The baffling complexity of the results obtained from reaction of α-halo boronic esters with ammonia or lithiated amides underscores the necessity of our slightly roundabout but unambiguous route to α-amido boronic esters. The problems encountered involved not only the instability of the carbon–carbon bond but the ability of boron to coordinate with nitrogen, which makes possible a large variety of cyclic, polymeric, and cage structures.

The kinetic instability of the carbon–boron bond in α-amino boronic acids and esters was entirely unexpected and remains unexplained. Thermodynamically, the α-amino boronic ester or acid group is unstable toward rearrangement to the alkylamino-*N*-boronic function by a large amount. On the basis of the available bond energy data,[16] we estimate 20–40 kcal/mol. Data are not available for the B–NHR linkage, which tends to disproportionate. The B–NMe_2 linkage based on $B(NMe_2)_3$ is only ~8 kcal/mol stronger than typical B–C bonds, but B–OH is considerably stronger, than B–OR, and R should have a similar effect on N. The extra strength of B–O bonds is probably due to π-bonding, which should be at least as favorable with N as with O but which would be partially sterically suppressed in the only available model compound. The strength of C–H bonds is not very different from O–H or N–H bonds, as the net result is that boron is easily removed from carbon to nitrogen or oxygen in exchange for a proton. This thermodynamic argument still does not explain the kinetic instability. It is difficult to imagine a mechanism that does not involve a highly unstable carbanionic intermediate. Since no analogue of this reaction has been observed with the silylated or dialkylamino boronic esters, it may be that the critical step

(15) Matteson, D. S.; Mah, R. W. H. *J. Org. Chem.* **1963**, *28*, 2174–2176.

(16) Finch, A.; Gardner, P. J. "Progress in Boron Chemistry"; Brotherton, R. J., Steinberg, H., Eds.; Pergamon Press: Oxford, 1970; Vol 3, pp 177–210.

involves a boron–proton exchange between carbon and nitrogen.

Experimental Section

General Data. Reactions involving carbanions were carried out under argon. Tetrahydrofuran (THF) was freshly distilled from benzophenone ketyl. Butyllithium (1.6 M in hexane) was titrated against 2-propanol to the 1,10-phenanthroline end point. Proton NMR spectra at 60 MHz were taken with a Varian EM-360 and at 200 MHz with a Nicolet NT-200 instrument and are referred to internal tetramethylsilane. ^{13}C NMR spectra were measured at 22.6 MHz with a Bruker WH-90. Optical rotations were measured at the sodium D line with a Rudolph visual polarimeter or at the mercury-546 line with a Jasco DIP-181 digital polarimeter. Melting points were taken in open capillaries in a Hoover-Thomas melting point apparatus and are uncorrected. Microanalyses were done by Galbraith Laboratories, Knoxville, TN.

Ethylene Glycol 1-(Bis(trimethylsilyl)amino)-2-phenylethane-1-boronate (3a). A solution of 25 mmol of lithiohexamethyldisilazane (from 25 mmol of butyllithium and 4.04 g of hexamethyldisilazane) in 40 mL of THF was treated with 5.04 g (24 mmol) of ethylene glycol 1-chloro-2-phenylethane-1-boronate[9] at −78 °C. A white precipitate formed after ~5 min. The mixture was kept overnight and distilled directly to yield **3a**, 8.61 g (85%), bp 110–116 °C (0.2 torr); redistilled, bp 103–104 °C (0.03 torr); 60-MHz NMR ($CDCl_3$) δ 0.15 (s, 18, $SiCH_3$), 2.95 (m, 3, $CHCH_2$), 4.23 (s, 4, OCH_2), 7.40 (s, 5, C_6H_5). Anal. Calcd for $C_{16}H_{30}BNO_2Si_2$: C, 57.30; H, 9.02; B, 3.22; N, 4.18; Si, 16.75. Found: C, 57.29; H, 9.09; B, 3.49; N, 4.43; Si, 16.54.

Ethylene Glycol 1-Amino-2-phenylethane-1-boronate (6a). A solution of 300 mg of **3a** in 1 mL of ether at 0 °C was treated with 2 mL of cold (0 °C) methanol and stirred under argon for 45 min at 0 °C. The solvent was distilled under vacuum at up to 30 °C, leaving a residue of solid **6a** (167 mg), which was treated with 15–20 mL of ether and collected (114 mg), mp 143–149 °C; 60-MHz NMR ($D_2O/CD_3COCD_3/CF_3CO_2H$) (referred to internal CD_3COCD_2H at δ 2.17) δ 3.10 (s, 3, $CHCH_2$), 3.70 (s, 4, O–CH_2), 5.25 (s, O*H*), 7.43 (s, 5, C_6H_5). Anal. Calcd for $C_{10}H_{14}BNO_2$: C, 62.87; H, 7.39; B, 5.66; N, 7.33. Found: C, 61.36; H, 7.55; B, 5.77; N, 6.86.

Attempted Isolation of 1-Amino-2-phenylethane-1-boronic Acid. Treatment of 458 mg of **3a** with 4 mL of methanol at 0 °C for 20 min, removal of the methanol under vacuum, and treatment of the residue with 1 mL of water and 20 mL of ether resulted in formation of a water/ether insoluble solid suspended in the ether phase. The aqueous phase was extracted with several portions of ether. The ether and suspended solid were washed with an additional 1 mL of water and then partially concentrated, and the finely divided solid was filtered (107 mg); 60-MHz NMR ($D_2O/CD_3COCD_3/CF_3CO_2H$) same as **6a** except that the δ 3.7 peak was reduced to ~25% of that of **6a**. Addition of 2-phenylethylamine to this solution resulted in appearance of the characteristic CH_2CH_2 multiplet at δ ~3.15 superimposed on the otherwise unaffected δ 3.1 singlet of **6a**.

Oxidation of Ethylene Glycol 1-Amino-2-phenylethane-1-boronate (6a). A 22-mg sample of **6a** was treated with 24 mg of 2,4-dinitrophenylhydrazine in 0.5 mL of sulfuric acid, 2 mL of methanol, and 2 mL of water, followed immediately by 32 mg of sodium perborate tetrahydrate, then kept overnight at 20–25 °C, and chilled for crystallization, yielding 22 mg of phenylacetaldehyde 2,4-dinitrophenylhydrazone, mp 120–124 °C; mmp 121–125 °C; 60-MHz NMR spectrum identical with that of an authentic sample.

Aqueous Stability of 1-Amino-2-phenylethane-1-boronic Acid. A solution of 46 mg of ethylene glycol 1-(bis(trimethylsilyl)amino)-2-phenylethane-1-boronate (**3a**) in 2 mL of ether was extracted with 2 mL of 1.5 M hydrochloric acid. The aqueous phase was washed with ether, neutralized with sodium bicarbonate to pH 6-7, kept at 0 °C for 1 h, and then treated with 40 mg of sodium perborate tetrahydrate followed by a solution of 27 mg of 2,4-dinitrophenylhydrazine as in the preceding paragraph. The yield of phenylacetaldehyde 2,4-dinitrophenylhydrazone was 14 mg (33%), mp 110–112 °C (low, but not depressed on admixture), verified by 60-MHz NMR.

Ethylene Glycol 1-Acetamido-2-phenylethane-1-boronate (4a). A solution of 8.84 g (26.4 mmol) of ethylene glycol 1-(bis(trimethylsilyl)amino)-2-phenylethane-1-boronate (**3a**) in 25 mL of THF was stirred at −78 °C during the dropwise addition of 5 mL of acetic anhydride followed by 1.58 mL (27.6 mmol) of acetic acid. After reacting overnight at 25 °C, distillation yielded 5.25 g (86%) of **4a**, bp 143–145 °C (0.04 torr), which solidified and was sublimed at 70 °C (0.04 torr), mp 128 °C; 60-MHz NMR ($CDCl_3$) δ 2.04 (s, 3, CH_3), 2.75 (m, 3 $CHCH_2$), 3.90 (s, 4, OCH_2), 7.4 (s, 5, C_6H_5), 7–10 depending on concentration (s, broad, 1, N*H*); 22.6-MHz ^{13}C NMR (proton decoupled) ($CDCl_3$) δ 16.653, 36.920, 46.274 (broad, BC*H*N), 64.008, 125.978, 128.382, 128.512, 140.464, 175.801. Anal. Calcd for $C_{12}H_{16}BNO_3$: C, 61.84; H, 6.92; B, 4.64; N, 6.01. Found: C, 61.92; H, 7.00; B, 4.63; N, 5.89.

In the first successful attempt to make **4a**, the reaction mixture was worked up with water and ether and **4a** was found on evaporation of the aqueous phase. Treatment of **4a** with sodium perborate and 2,4-dinitrophenylhydrazine in the same manner described for oxidation of **3a** also yielded phenylacetaldehyde 2,4-dinitrophenylhydrazone, confirmed by mmp and 60-MHz NMR.

(+)-Pinanediol Phenylmethane-1-boronate (1b). A 2.03-g (5 mmol) sample of potassium bis[(+)-pinanediol] borate monohydrate (100% ee)[12] was treated with excess 2 M hydrochloric acid and the diol/diol boric acid liberated was extracted with 50 mL of hexanes and then stirred with 1.40 g (10.3 mmol) of phenylmethane-1-boronic acid[17] overnight. The solution was washed with water, dried over magnesium sulfate, and distilled: bp 108–110 °C (0.05–0.1 torr); 2.32 g (86%); $[\alpha]^{23}_{589}$ +31.8°, $[\alpha]^{23}_{546}$ +37.9° (*c* 6, toluene); 200-MHz NMR ($CDCl_3$) δ 0.81 (s, 3, CH_3), 1.03–2.30 (m, 12, with methyl singlets at 1.260 and 1.367, pinanyl), 2.35 (s, 2, CH_2Ph), 4.26 (dd, 1, C*H*OB), 7.05–7.28 (m, 5, C_6H_5). Anal. Calcd for $C_{17}H_{23}BO_2$: C, 75.57; H, 8.58; B, 4.00. Found: C, 75.68; H, 8.56; B, 4.07.

(+)-Pinanediol (*R*)-1-Acetamido-2-phenylethane-1-boronate (4b). A 1.38-g (5.1 mmol) sample of (+)-pinanediol phenylmethane-1-boronate (**1b**) was homologated with (dichloromethyl)lithium according to the published procedure.[9,11,18] The solution was stirred at 20–25 °C for 6 h to complete the formation of the α-chloro boronic ester **2b**, then cooled to −78 °C, and treated with 5.25 mmol of lithiohexamethyldisilazane in 15 mL of THF. The mixture was stirred overnight at 20–25 °C and the solution of **3b** was cooled to −78 °C, treated with 2 mL of acetic anhydride followed by 0.3 mL of glacial acetic acid, and then stirred at 20-25 °C for 10–12 h. The solution was concentrated under vacuum and the residue of **4b** was chromatographed through a short silica column with 5–10% ethyl acetate/hexane, yielding 1.09 g (63%); recrystallized from dichloromethane to constant rotation (three times), $[\alpha]^{18}_D$ −82.43° (*c* 5, $CHCl_3$); mp 186–188 °C; 200-MHz NMR ($CDCl_3$) δ 0.87 (s, 3, CH_3), 1.2, s, 3, CH_3), 1.40 (s, 3, CH_3), 1.42 (d, 1, *J* = 8.53 Hz, pinanyl), 1.54–2.4 (m, 5, pinanyl), 2.72 (m, 1, BC*H*N), 2.97 (m, 2, CH_2Ph), 4.23 dd, 1, C*H*OB), 6.41 (variable position, up to ~8 in more concentrated solutions, broad s, 1, N*H*), 7.26 (m, 5, C_6H_5); 22.6 MHz ^{13}C NMR ($CDCl_3$) δ 18.578, 24.164, 26.373, 27.347, 29.231, 36.441, 37.351, 38.130, 40.014, 44.301 (broad, BCHN), 52.356, 75.741, 76.391, 77.170, 78.599, 83.471, 126.214, 128.812, 140.440, 174.283. Anal. Calcd for $C_{20}H_{28}BNO_3$: C, 70.39; H, 8.27; B, 3.17; N, 4.10. Found: C, 70.53; H, 8.29; B, 2.92; N, 4.08. The foregoing procedure starting from (−)-pinanediol phenylmethane-1-boronate (**1c**) yielded (−)-pinanediol (*S*)-1-acetamido-2-phenylethane-1-boronate (**4c**), $[\alpha]^{21}_D$ +82.1° (*c* 4, $CHCl_3$); 60-MHz NMR spectrum identical with **4b**.

(*R*)-1-Acetamido-2-phenylethane-1-boronic Acid (5b). (+)-Pinanediol (*R*)-1-acetamido-2-phenylethane-1-boronate (**4b**) in dichloromethane was added to excess liquid boron trichloride at −78 °C, allowed to warm to 25 °C, and concentrated under a stream of argon as described by Matteson and Ray.[11] The boronic acid **5b** was purified by dissolving it in water, extracting bypro-

(17) Boronic acids: Washburn, R. M.; Levens, E.; Albright, C. F.; Billig, F. A. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, pp 68–72.

(18) It is preferable to use the newer procedure with zinc chloride catalysis,[12] in which case the zinc chloride must be separated from the α-chloro boronic ester **2b** before reaction with the lithiohexamethyldisilazane.

ducts with ether, and lyophilizing the aqueous solution. Residual boric acid was removed by addition of methanol and distillation of the methyl borate/methanol azeotrope, and the **5b** was recrystallized from aqueous THF; yield 82%. Depending on the time of drying, either the boronic acid or its anhydride was obtained; anhydride, mp 205 °C, $[\alpha]^{22}_D$ −195.8° (*c* 0.6, H_2O); 200-MHz NMR (CD_3OD) δ 2.10 (s, 3, $COCH_3$), 2.55 (m, 1, BC*H*N), 2.87 (m, 2, CH_2Ph), 4.89 (s, O*H*), 7.12–7.33 (m, 5, C_6H_5); 22.6-MHz ^{13}C NMR (D_2O) δ 16.108, 36.180, 49.562 (broad, BC*H*N), 126.212, 128.552, 128.681, 140.569, 176.360; IR (KBr) 3700–2800 (OH/NH), 1635, 1540, 1500, 1460, 1385, 1270, 800, 740, 700 cm^{-1}. Anal. (Acid) Calcd for $C_{10}H_{14}BNO_3$: C, 58.01; H, 6.82; B, 5.22; N, 6.77. Found: C, 58.12; H, 6.64; B, 5.08; N, 6.51. (Anhydride) Calcd for $C_{10}H_{12}BNO_2$: C, 63.54; H, 6.40; B, 5.72; N, 7.41. Found: C, 63.38; H, 6.54; B, 5.54; N, 7.27. A sample crystallized from the strongly acidic solution resulting from addition of water immediately after the evaporation of the boron trichloride had a composition approximately corresponding to a 1:1 mixture of boronic half acid chloride and anhydride. Anal. Calcd for $C_{20}H_{27}BClN_2O_5$: C, 55.54; H, 6.29; B, 5.00; Cl, 8.20; N, 6.48. Found: C, 55.98; H, 6.22; B, 5.36; Cl, 9.30; N, 6.51.

Application of the same procedure to the enantiomer **4c** yielded (*S*)-1-acetamido-2-phenylethane-1-boronic acid (**5c**):proton NMR and IR spectra identical with **5b**, $[\alpha]^{22}_D$ as anhydride +195° (*c* 0.7, H_2O). Anal. Calcd for $C_{10}H_{12.5}BNO_{2.25}$ (75% anhydride, 25% acid): C, 62.06; H, 6.51; B, 5.59; N, 7.24. Found: C, 61.98; H, 6.30; B, 5.82; N, 6.96.

Pinacol 1-Acetamidino-2-phenylethane-1-boronate (8). A suspension of 0.65 g (6.9 mmol) of acetamidine hydrochloride in 20 mL of THF was stirred at −78 °C during the dropwise addition of 6.9 mmol of butyllithium in hexane. On warming to 0 °C the solid dissolved. The mixture was again cooled to −78 °C, and 1.09 g (3.04 mmol) of pinacol 1-iodo-2-phenylethane-1-boronate (**2d**) in ~3 mL of ether was added. The mixture was kept overnight at 20–25 °C and concentrated under vacuum. The residue was treated with water (~50 mL) and dichloromethane (~50 mL), and the organic phase was concentrated to yield a solid residue of **8**, which was recrystallized from ether/petroleum ether: 0.51 g (58%); mp 189–192 °C; 100-MHz NMR ($CDCl_3$) δ 1.19 (s, 12, O-CCH_3), 1.99 (s, 3, N-CCH_3), 2.6–3.0 (m, 3, C*H*CH_2), 5.46 (s, ~12 Hz wide at half-height, 1, N*H*), 5.80 (s, ~12 Hz wide 1, N′*H*), 7.28 (m, 5, C_6H_5). Anal. Calcd for $C_{16}H_{25}BN_2O_2$: C, 66.68; H, 8.74; B, 3.75; N, 9.72. Found: C, 66.80; H, 8.82; B, 3.68; N, 9.87.

Dehydrohalogenation of Pinacol 1-Iodo-2-phenylethane-1-boronate (2d). Treatment of 0.10 g (1 mmol) of diacetamide in 10 mL of THF at 0 °C with 1 mmol of butyllithium was followed by addition of 0.36 g (1 mmol) of **2d** in ~2 mL of petroleum ether. The mixture was stirred for 2 h at 20–25 °C, concentrated, and worked up with water and ether. Evaporation of the ether phase yielded 0.23 g of residue shown to be ~30% unchanged **2d** and ~70% pinacol (*E*)-2-phenylethene-1-boronate[19,20] by its NMR spectrum, which showed the characteristic =C*H*B doublet (J = 18 Hz) at δ 6.23 (lit.[19] δ 6.12 for the ethylene glycol ester).

Pinacol 1-Amino-2-phenylethane-1-boronate (6d). A 1.06-g (2.96-mmol) sample of pinacol 1-iodo-2-phenylethane-1-boronate (**2d**) was placed in a Parr bomb purged with argon and equipped with a magnetic stirrer, and the bomb was cooled with a dry ice/acetone bath while ~12 mL of anhydrous ammonia was distilled into it from sodium metal. The mixture was allowed to warm to 20–25 °C and was stirred 3 h, after which the bomb was vented. The residue was treated with ~50 mL of dichloromethane and filtered under argon to remove 0.37 g (86%) of ammonium iodide. The dichloromethane solution was concentrated under vacuum and the solid residue was washed with three 5–10-mL portions of ether. The residue nearly all dissolved in 20 mL of warm dichloromethane (under argon). The solution was concentrated slowly under reduced pressure, and when crystals began to form, 10 mL of ether was added to promote crystallization. The yield of **6d** was 0.26 g (35%), mp 117–127 °C dec in an open capillary, mp 195-197 °C in sealed, evacuated capillary; 60-MHz NMR ($CDCl_3$) δ 1.07 (br s, side peaks at 0.87 and 0.75, 12, CCH_3), 1.40 (s, sharp, ~0.5) 2.50 (br s, 2, NH_2), 3.05 (asymmetric unresolved m, 3, CH_2C*H*), 7.35 (s, 5, C_6H_5). (For comparison, the CH_2CH_2 of 2-phenylethylamine is a symmetrical, resolved multiplet at δ 2.93, and the NH_2 is at 1.23.) Anal. Calcd for $C_{14}H_{22}BNO_2$: C, 68.04; H, 8.97; B, 4.37; N, 5.67. Found: C, 68.24; H, 8.85; B, 4.21; N, 5.56. M_r (osmometric in $CHCl_3$): after 4 min, 370; 8 min, 337; 12 min, 304; 16 min, 272; 20 min, 240; 30 min, 163; calcd for monomer is 247. After recrystallization from ether and standing several weeks in contact with air, a sample of what had been **6d** yielded an NMR spectrum corresponding largely to hydrated **7d**: ($CDCl_3$) δ 1.20 (s, 12, CCH_3), 2.93 (m, symmetrical, only ~2–3, CH_2CH_2), 3.60 (broad s, 3, N*H* + O*H*), 7.35 (s, 5, C_6H_5).

Reaction of Dimethyl 1-Chloro-2-phenylethane-1-boronate with Lithioacetamide. A 713-mg (12 mmol) sample of acetamide partially dissolved in 20 mL of THF at 0 °C was treated with 11 mmol of butyllithium, resulting in immediate precipitation of lithioacetamide. The mixture was stirred 15 min at 25 °C, then cooled to 0 °C, and treated with 2.23 g (10.5 mmol) of dimethyl 1-chloro-2-phenylethane-1-boronate, which resulted in immediate dissolution of the precipitate. After 16 h at 25 °C the solution was concentrated and the residue was treated with 50 mL of water, 1.5 mL of 85% phosphoric acid (final pH 3–4), and 150 mL of ether. A voluminous white precipitate resulted, 1.85 g (72%). This material was insoluble in Me_2SO-d_6/$CDCl_3$. It was soluble in aqueous 6 M hydrochloric acid and reprecipitated by sodium bicarbonate: 60-MHz NMR (D_2O/CF_3CO_2D) δ 2.1 (s, 3, C–CH_3), 2.8–3.1 (m, 2, PhCH_2), 4.3 (m, 1, O–C*H*–B), 6.3 (O*H*), 7.35 (s, 5, C_6H_5). The elemental analysis corresponds to a dihydrate except that H is low. Anal. Calcd for $C_{10}H_{18}BNO_5$: C, 49.41; H, 7.46; B, 4.45; N, 5.76. Found: C, 49.48; H, 5.53; B, 4.01; N, 5.55.

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Registry No. **1a**, 35895-82-0; **1b**, 78922-83-5; **1c**, 88824-36-6; **2a**, 88765-78-0; **2b**, 78902-03-1; **2c**, 88824-37-7; **2d**, 79121-47-4; **3a**, 88765-79-1; **3b**, 78902-04-2; **3c**, 88824-38-8; **4a**, 88765-80-4; **4b**, 78902-05-3; **4c**, 88824-39-9; **5a**, 88765-81-5; **5b**, 78902-01-9; **5c**, 78902-02-0; **6a**, 88765-82-6; **6d**, 88765-83-7; **7d**, 88765-84-8; **8**, 88765-85-9; $CH_3CONHLi$, 88765-87-1; lithiohexamethyldisilazane, 4039-32-1; 1-amino-2-phenylethane-1-boronic acid, 88765-86-0; potassium bis[(+)-pinanediol] borate, 88851-51-8; phenylmethane-1-boronic acid, 4463-42-7; (dichloromethyl)lithium, 2146-67-0; acetamidine hydrochloride, 124-42-5; pinacol (*E*)-2-phenylethene-1-boronate, 83947-56-2; 1-chloro-2-phenylethane-1-boronate, 87100-19-4.

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