Asymmetric Homologation of Boronic Esters Bearing Azido and Silyloxy Substituents

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In the asymmetric homologation of boronic esters with a (dihalomethyl)lithium, substituents that can bind metal cations tend to interfere. Accordingly, we undertook the introduction of weakly basic oxygen and nitrogen substituents into boronic esters in order to maximize the efficiency of multistep syntheses utilizing this chemistry. Silyloxy boronic esters cannot be made efficiently by direct substitution, but a (hydroxymethyl)boronic ester has been silylated in the usual manner. Conversion of α-halo boronic esters to α-azido boronic esters has been carried out with sodium azide and a tetrabutylammonium salt as phase-transfer catalyst in a two-phase system with water and either nitromethane or ethyl acetate. These are safer solvents than the previously used dichloromethane, which can form an explosive byproduct with azide ion. Boronic esters containing silyloxy or alkoxy and azido substituents have been shown to react efficiently with (dihalomethyl)-lithiums, resulting in efficient asymmetric insertion of the halomethyl group into the carbon−boron bond.

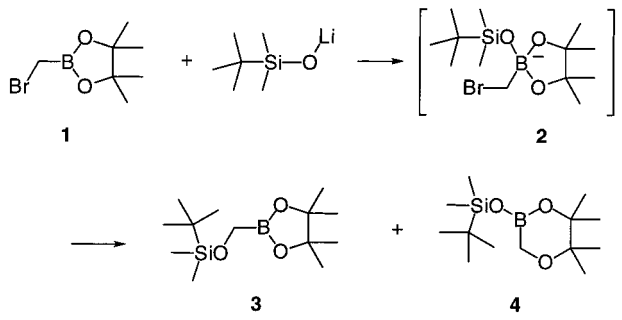
Introduction

It is well established that the highly stereoselective homologation of chiral boronic esters with (dichloromethyl)lithium works best in the absence of highly polar substituents.[1] At the outset, it was found that the reaction fails with tartrate boronates.[2] Steps in a synthesis of L-ribose proceeded efficiently in the presence of up to three benzyloxy substituents, but the yield dropped drastically after the fourth benzyloxy substituted carbon had been introduced.[3] An unexpected reaction in which a benzyloxy group was cleaved in the presence of a trityloxy group has been encountered.[4] Failure of an α-amido substituted boronic ester to undergo CHCl insertion into the carbon−boron bond has thwarted an attempted kainic acid synthesis.[5] Silylated α-amido boronic esters are similarly resistant to the homologation, though some success has been achieved with silylated aminomethyl boronic esters.[6]

The azido substituent has been found to be compatible with the homologation process,[7] and a synthesis of amino acids via azido boronic esters has been reported.[8] Thus, the azido group appeared likely to be the most useful masked amino group for this chemistry. However, the conditions previously used for the azide substitution, a phase-transfer reaction in dichloromethane/water,[7,8] are hazardous because of the possibility of generating diazidomethane.[9] For masked hydroxyl functions, it appeared likely that silyloxy groups would be ideal, but there had never been a successful synthesis of an α-silyloxy boronic ester.

Results

Silyloxy Substituents. Treatment of 2-(bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1**) with lithiated *tert*-butyldimethylsilanol yielded a gross mixture of isomers **3** and **4**. The ^{1}H NMR spectrum indicated that the ratio was ∼70/30, based on the singlets at δ 1.24 and 3.11 attributed to the pinacol methyl groups and *B*-methylene group, respectively, of **3** and the paired singlets at δ 1.16 and 1.28 and the singlet at 4.20 attributed to the distinguishable pairs of pinacol methyl groups and the *B*-methylene group of **4**. An obvious mechanism for production of **4** involves competing migration of the alkoxy and silyloxy groups from boron to the bromomethyl carbon of intermediate **2**.



Alkoxy groups such as benzyloxy and even trityloxy have invariably shown a strong migratory preference to

(1) (a) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555−10607. (b) Matteson, D. S. *J. Organomet. Chem.* **1999**, *581*, 51−65.
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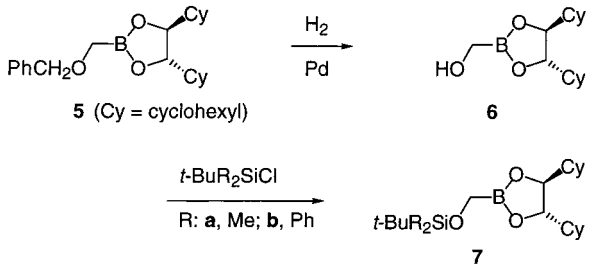
the apparent exclusion of ring expansion.[3,4,10] Silyloxy groups are evidently weaker competitors as a result of their lower nucleophilicity.

We then turned to silylation of a 2-(hydroxymethyl)-1,3,2-dioxaborolane. Hydrogenolysis of 2-(benzyloxymethyl)-1,3,2-dioxaborolane (**5**) to the hydroxymethyl derivative **6** was followed immediately by silylation with *tert*-butyldimethylsilyl chloride to form the 2-(trialkylsilyloxymethyl)-1,3,2-dioxaborolane **7a** or with *tert*-butyldiphenylsilyl chloride to form the analogous derivative **7b**.



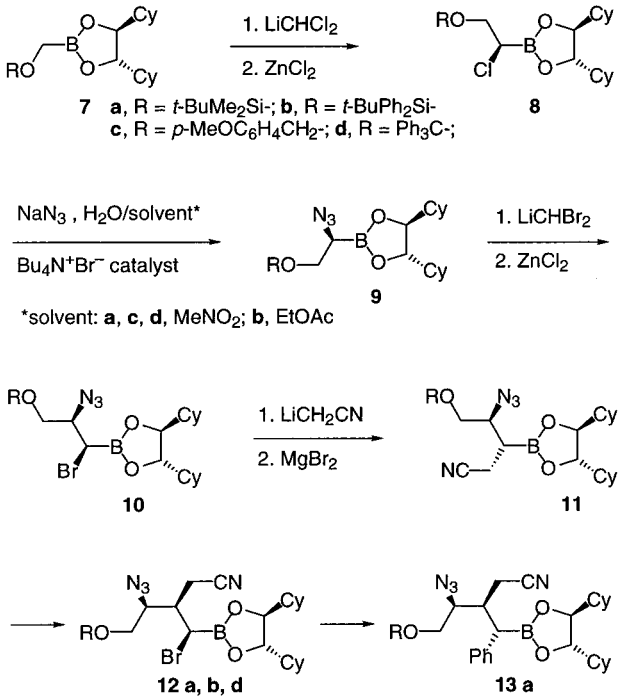
Azido Substituents. Several attempts to make an α-azido ester by reaction of an α-chloro boronic ester with an alkali metal azide in DMSO have been unsuccessful. The phase-transfer process between water and dichloromethane reported earlier has given excellent yields,[7,8] though it can be hazardous.[9] It was therefore appropriate to test alternative solvents in the hope that one could be found in which tetrabutylammonium salts would be sufficiently soluble to provide useful reaction rates.

The α-chloro-*β*-trityloxy boronic ester **8d**, which had been used as the precursor to amido boronic esters reported previously,[6] as well as the analogous *p*-methoxybenzyl boronic ester **8c**, were used as the initial test substrates. Tetrabutylammonium bromide proved insufficiently soluble in diethyl ether or diethoxymethane to provide measurable reaction rates with sodium azide. However, nitromethane was found to dissolve enough tetrabutylammonium salt to provide slow but useful reaction rates, comparable to those observed with dichloromethane, and efficient production of azido derivatives **9c** and **d**.

The availability of the silyloxy boronic esters **7a** and **b** from the route outlined above allowed the straightforward preparation of α-chloro boronic esters **8a** and **8b**. Nitromethane was used as the organic phase with **8a**, ethyl acetate with **8b**, and efficient azide substitution to form **9a** or **b** was achieved in each case.

Homologation of azido boronic esters **9** with (dibromomethyl)lithium led to α-bromo boronic esters **10**. Reaction of **10** with lithioacetonitrile, assisted by magnesium bromide as a catalyst/promoter,[11] led to **11**. This substitution was slow and inefficient without the magnesium bromide.

Beyond **11**, erratic results were obtained in the homologations and substitutions. Structures **12a**,**b**,**d** and **13a** are supported by mass spectral and NMR data but the compounds were not fully purified and characterized.



Discussion

The present investigation has provided efficient routes to boronic esters bearing (trialkylsilyl)oxy and azido substituents. Safe conditions have been found for introducing the azido group, allowing the reaction to be scaled up. It has also been shown that homologation of boronic esters with (dihalomethyl)lithiums can proceed efficiently in the presence of these useful masked hydroxy and amino substituents.

The most likely reason that polar substituents can interfere with the rearrangement of (dihalomethyl)borate anions to (α-haloalkyl)boronic esters is that they complex with the required metal cation. Zinc chloride is well-known to facilitate this rearrangement,[1] and the most likely mechanism involves a zinc or other metal cation directly in the transition state.[12] This interpretation is consistent with previous observations that increasing amounts of zinc chloride were required as the number of benzyloxy substituents increased,[3] and that homologation of a *δ*-trityloxy-*γ*-benzyloxy boronic ester was accompanied by debenzylation to benzyl chloride, though the trityl group was not cleaved.[4]

A practical question of synthetic utility is whether the silyl protecting groups offer sufficient advantage over trityl or benzyl substituents to be worth the extra steps required to introduce them. It appears that they do for some multistep syntheses. The interference of multiple benzyloxy substituents with the homologation has already been noted.[3] The efficiency with which the reactions described here proceeded is encouraging. Trityloxy substituted boronic esters often yield some trityl alcohol as a byproduct, perhaps from accidental acid cleavage during workup. Cleavage of the TBDMS or TBDPS groups was not noticeable, and the homologations appeared to proceed particularly smoothly up through the formation of **10a**,**b**. The one advantage of the trityloxy compounds is their greater tendency to crystallize.

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The azido group is the only known nitrogen functionality that permits homologation chemistry to proceed in a useful manner in its presence. It is remarkable that this group is stable in the presence of boronic esters, inasmuch as any more acidic boron functionality will react with organic azides with replacement of the carbon−boron bond by a carbon−nitrogen bond.[13] Although azido boronic esters have been shown to undergo homologation and substitution previously,[7,8] the present substitution of β-azido-α-bromo boronic ester **10** by (cyanomethyl)lithium in the presence of magnesium bromide to produce **11** represents a significant extension of this chemistry. Preliminary evidence that further chain extension is possible was obtained, but results were erratic in attempted further homologation of **11** to **12** and **13**, as described further below.

The displacement of chloride by azide is inconveniently slow at room temperature, usually requiring several days to complete. Epimerization of α-chloro boronic esters by chloride produced in the displacement process is a known problem,[7] and is largely overcome by using a large excess of sodium azide. In the reactions reported here, no evidence of epimerized product or other side products was seen, but the evidence does not exclude the possibility of a few percent. The solvent systems developed here would permit acceleration of the reaction by heating, but the question of whether epimerization or side reactions would increase to significant levels at higher temperatures has not been explored.

The trityl series proceeded as far as **12d** but failed to yield **13d**. This failure was unexpected, inasmuch as homologation of the analogue of **11d** bearing a *p*-methoxybenzyloxy substituent in place of the azido group had proceeded without difficulty.[14] The problems with the trityl compounds provided the original motivation to explore the silyl series. The silylated homologation products **12a**,**b** and **13a**,**b** were obtained in highly variable yields. These compounds were not purified or fully characterized, but are strongly supported by HRMS and NMR data. While it is apparent that not all of the variables were understood and controlled, it does not appear that the azido or silyloxy substituents were the source of any problems. The cyanomethyl group has acidic protons that may become involved if excess base is present. The boronic ester intermediates were not rigorously protected from air during storage. Autocatalytic autoxidation, to which boronic esters are about as susceptible as aldehydes, may have occurred in some cases.[15]

It may be concluded that silyloxy and azido substituents are compatible with the reaction of boronic esters with (dihalomethyl)lithium and subsequent substitution of the resulting (α-haloalkyl)boronic esters. Azido substituents are the only useful protected amino functionality known for this purpose. This work does not yet prove that any transformations possible with silyloxy substituents are not possible with alkoxy substituents, but does indicate that silyloxy substituents cause minimal interference.[15] Practical means for producing azido and silyloxy substituted boronic esters are described here for the first time.

Experimental Section

General Methods. The usual procedures for handling reactive organometallic reagents were followed, including the use of an inert atmosphere (argon) and THF (tetrahydrofuran) that had been rigorously dried over sodium benzophenone ketyl. Detailed procedures for carrying out reactions of boronic esters with (dichloromethyl)lithium or (dibromomethyl)lithium have been reported previously.[2,3,7]

(4*S*,5*S*)-4,5-Dicyclohexyl-2-(benzyloxy)methyl-1,3,2-dioxaborolane (5). The pinacol boronate, 2-(benzyloxy)methyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, was prepared from 2-bromomethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and sodium benzyl oxide in DMSO according to the procedure described previously for 2-(trityloxy)methyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane; 90%.[10] A solution of the pinacol boronate (24.8 g, 100 mmol) and (*S*,*S*)-1,2-dicyclohexyl-1,2-ethanediol (22.6 g, 100 mmol) in diethyl ether (400 mL) was stirred at 20−25 °C for 20 h. The ether solution was extracted with saturated aqueous ammonium chloride, dried over magnesium sulfate, and concentrated under vacuum to viscous liquid **5** (34.9 g, 98%): became low melting solid on storage; $[\alpha]^{22}_{546}$ −32.42° ($CHCl_3$, *c* 1.65); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.83−1.76 (m, 22H), 3.34 (s, 2H), 3.91 (m, 2H), 4.52 (m, 2H), 7.24 (m, 5H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 25.9, 26.0, 26.4, 27.4, 28.3, 42.8, 56.6 (br, C−B), 75.7, 83.8, 127.5, 128.1, 128.3, 138.3; HRMS calcd for $C_{22}H_{33}BO_3$ (M^+) 356.2523, found (EI) 356.2540. No further purification was required for the analytical sample. Anal. Calcd for $C_{22}H_{33}BO_3$: C, 74.16; H, 9.34; B, 3.03. Found: C, 74.06; H, 9.42; B, 2.82.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-hydroxymethyl-1,3,2-dioxaborolane (6). A solution of **5** (17.81 g, 50 mmol) in ethyl acetate (350 mL) was hydrogenated over 5% Pd/C (4 g) at 1 atm at 20−25 °C for 24 h. Concentration under vacuum yielded analytically pure low melting solid **6** (12.77 g, 96%): $[\alpha]^{22}_{546}$ −48.21° ($CHCl_3$, *c* 1.43); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.82−1.79 (m, 22H), 2.08 (s, 1H), 3.58 (s, 2H), 3.93 (m, 2H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 25.8, 26.0, 27.3, 28.4, 42.9, 49.2 (br, C−B), 84.2; HRMS calcd for $C_{15}H_{27}BO_3$ (M^+) 266.2053, found (EI) 266.2069. Anal. Calcd for $C_{15}H_{27}BO_3$: C, 67.68; H, 10.22; B, 4.06. Found: C, 67.92; H, 10.24; B, 3.94.

(4*S*,5*S*)-4,5-Dicyclohexyl-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl-1,3,2-dioxaborolane (7a). Solid *tert*-butylchlorodiphenylsilane (17.2 g, 62.5 mmol) was added to a solution of (hydroxymethyl)dioxaborolane **6** (15 g, 56.4 mmol) in ethyl acetate (400 mL). The stirred reaction mixture was cooled with an ice bath, and a solution of imidazole (5.35 g, 78.8 mmol) in ethyl acetate (70 mL) was added dropwise (exothermic). The mixture was stirred at 20−25 °C for 24 h and then washed with ammonium chloride solution. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure to crude **7a** containing some *tert*-butyldiphenylsilanol. The product was dissolved in pentane and passed through a short column of silica gel, then concentrated to viscous liquid **7a** (17.6 g, 82%): $[\alpha]^{22}_{546}$ −42.31° ($CHCl_3$, *c* 1.35); 300 MHz ^{1}H NMR (C_6D_6) δ 0.13 (s, 6H), 0.80−1.83 (m, 22H + s, 9H at δ 1.03), 3.74 (s, 2H), 3.77 (m, 2H); 75 MHz ^{13}C NMR (C_6D_6) δ −5.3, 18.8, 26.2, 26.3, 26.4, 26.8, 27.7, 28.7, 43.3, 50.1, 84.0; HRMS calcd for $C_{17}H_{32}O_3SiB$ (M − 57) 323.2201, found (EI) 323.2201. Anal. Calcd for $C_{21}H_{41}BO_3Si$: C, 66.30; H, 10.86; B, 2.84; Si, 7.38. Found: C, 66.20; H, 10.92; B, 2.74; Si, 7.22.

[2(1*R*),4*S*,5*S*]-4,5-Dicyclohexyl-2-[1-chloro-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,2-dioxaborolane (8a). (Dichloromethyl)lithium was prepared as previously described[7] by addition of butyllithium (29.0 mmol) to dichloromethane (90 mmol) in THF (300 mL) at −100 °C under argon. A solution of silyloxy boronic ester **7a** (9.50 g,

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(15) The air oxidation hypothesis cannot be proved with the present data, but in an ongoing investigation of closely analogous chemistry involving multistep synthesis, NMR evidence of autoxidation of samples during storage has been observed, and careful protection of all intermediates from air exposure during storage has resulted in significantly improved yields in later stages of the synthesis. The *tert*-butyldiphenylsilyl protecting group has consistently given excellent results. Matteson, D. S.; Pharazyn, P. S. Unpublished results.

25 mmol) in THF (25 mL) was added via cannula. Anhydrous zinc chloride (6.8 g, 50 mmol) was added and the mixture was allowed to warm to 20−25 °C and stirred for 24 h. The solution was concentrated under vacuum. Diethyl ether was added, and the mixture was extracted with saturated aqueous ammonium chloride, dried over magnesium sulfate, and concentrated under vacuum to colorless liquid **8a** (10.4 g, 97%): $[\alpha]^{22}_{546}$ −47.37° (*c* 1.58, $CHCl_3$); 300 MHz ^{1}H NMR (C_6D_6) δ 0.01 (s, 6H), 0.87−1.80 (m, 22H + s, 9H at δ 0.95), 3.51 (t, 1H), 3.77 (d, 2H), 3.93 (m, 2); 75 MHz ^{13}C NMR (C_6D_6); δ −5.3, 18.6, 26.0, 26.2, 26.3, 26.7, 27.6, 28.5, 43.3, 65.8, 84.3; HRMS calcd for $C_{18}H_{33}O_3SiB$ (M − 57) 371.1981, found (EI) 371.1975. The analytical sample was chromatographed on a silica gel plate with 1:20 ether/pentane. Anal. Calcd for $C_{22}H_{42}BClO_3Si$: C, 61.61; H, 9.87; B, 2.52; C1, 8.27; Si, 6.55. Found: C, 61.80; H, 9.74; B, 2.36; Cl, 8.00; Si, 6.38.

[2(1*S*),4*S*,5*S*]-4,5-Dicyclohexyl-2-[1-azido-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,2-dioxaborolane (9a). A solution of chloro boronic ester **8a** (9.43 g, 22 mmol) in nitromethane (500 mL) was stirred with a solution of sodium azide (14.3 g, 220 mmol) and tetrabutylammonium bromide (1.6 g, 5 mmol) in water (120 mL) for 10 days at 20−25 °C. The organic phase was separated and concentrated under vacuum. Diethyl ether was added, and the mixture was extracted with saturated aqueous ammonium chloride. The organic phase was dried over magnesium sulfate and concentrated at reduced pressure to colorless viscous liquid **9a** (9.4 g, 98%): $[\alpha]^{22}_{546}$ −38.15° (*c* 1.32, $CHCl_3$); IR (KBr pellet): cm^{-1} 2087.5 (CN_3); 300 MHz ^{1}H NMR (C_6D_6) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.91−1.80 (m, 22H + s, 9H at δ 0.97), 2.82 (t, 1H), 3.76 (m, 2H), 3.86 (m, 2H); 75 MHz ^{13}C NMR (C_6D_6) δ −5.5, 18.5, 25.9, 26.0, 26.2, 26.8, 27.7, 28.7, 43.3, 51.0 (br, C−B), 65.5, 84.5; HRMS calcd for $C_{19}H_{33}BNO_3Si$ (M − 85) 350.2323, found (EI) 350.2317. The analytical sample was chromatographed on a silica gel plate with 1:15 ether/pentane. Anal. Calcd for $C_{22}H_{42}BN_3O_3Si$: C, 60.68; H, 9.72; B, 2.48; N, 9.65; Si, 6.45. Found: C, 60.52; H, 9.80; B, 2.36; N, 9.50; Si, 6.62.

[2(1*S*),4*S*,5*S*]-4,5-Dicyclohexyl-2-[1-azido-2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-1,3,2-dioxaborolane (9b). The conditions were the same as for the conversion of **8a** to **9a** except that **8b** (12.16 g, 22 mmol) was used in place of **8a** and ethyl acetate (250 mL) was used in place of nitromethane, yielding colorless low melting solid **9b** (12.1 g, 98%): $[\alpha]^{22}_{546}$ −34.83° ($CHCl_3$, *c* 1.40); IR (KBr pellet) 2087 cm^{-1} (CN_3); 300 MHz ^{1}H NMR (C_6D_6) δ 0.84−1.87 (m, 22H + S, 9H at δ 1.21), 2.86 (t, 1H), 3.80 (m, 2H), 3.99 (m, 2H), 7.24 (m, 6H) 7.85 (m, 41); 75 MHz ^{13}C NMR C_6D_6) δ 19.4, 26.1, 26.3, 26.7, 27.0, 27.8, 28.7, 43.3, 51.3 (broad, C−B), 66.1, 84.7, 128.2, 130.0, 130.1, 133.5, 133.7, 136.1; HRMS calcd for $C_{32}H_{46}BNO_3Si$ (M − 28) 531.3340, found (EI) 531.3346. The analytical sample was chromatographed. Anal. Calcd for $C_{32}H_{46}BN_3O_3Si$: C, 68.68; H, 8.29; B, 1.93; N, 7.51; Si, 5.02. Found: C, 68.68; H, 8.33; B, 1.80; N, 7.30; Si, 5.12.

[2(1*R*,2*R*),4*S*,5*S*]-4,5-Dicyclohexyl-2-[2-azido-l-bromo-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-1,3,2-dioxaborolane (10a). A solution of LDA (11 mmol, 1.5 M in hexane) was added dropwise to a stirred solution of azido boronic ester **9a** (7.83 g, 18 mmol) and dibromomethane (3.8 mL, 9.38 g, 54 mmol) in THF (200 mL) at −78 °C under argon. Anhydrous zinc chloride (7.4 g, 54 mmol) was added. The solutions was allowed to warm to 20−25 °C, stirred for 24 h, and concentrated under vacuum. Diethyl ether (400 mL) was added, the mixture was extracted with saturated ammonium chloride (2 × 400 mL), and the organic phase was dried over magnesium sulfate. Concentration under vacuum yielded viscous liquid **10a** (8.5 g, 95%): $[\alpha]^{22}_{546}$ −51.62° (*c* 1.67, $CHCl_3$); IR (KBr) cm^{-1} 2099 (CN_3); 300 MHz ^{1}H NMR (C_6D_6) δ 0.02 (s, 6H), 0.82−1.75 (m, 22H + s, 9H at δ 0.90), 3.58, (d, 1H), 3.66 (m, 1H), 3.72 (m, 2H), 3.78 (m, 2H); 75 MHz ^{13}C NMR (C_6D_6) δ −5.4, 18.4, 26.0, 26.2, 26.3, 27.5, 28.5, 43.3, 65.3, 65.6, 84.5; HRMS calcd for $C_{19}H_{34}BBrNO_3Si$ (M − 85) 442.1584, found (EI) 442.1599. The analytical sample was chromatographed on a silica gel plate with 1:14 ether/pentane. Anal. Calcd for $C_{23}H_{43}BBrN_3O_3Si$: C, 52.28; H, 8.20; B, 2.05; Br, 15.12; N, 7.95; Si, 5.32. Found: C, 52.50; H, 8.14; B, 1.88; Br, 15.16; N, 7.72; Si, 5.48.

[2(1*R*,2*S*),4*S*,5*S*]-4,5-Dicyclohexyl-2-[2-azido-1-cyanomethyl-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-1,3,2-dioxaborolane (11a). Lithioacetonitrile was prepared by dropwise addition of LDA (10 mmol, 1.5 M solution in hexane) to a solution of acetonitrile (0.41 g, 0.52 mL, 10 mmol) in THF (150 mL) at −78 °C. After 5 min, a solution of bromo boronic ester **10a** (4.23 g, 8 mmol) in THF (10 mL) was added via cannula. After an additional 5 min stirring at −78 °C, magnesium bromide (16 mmol, from magnesium metal and 1,2-dibromoethane) in THF was added via cannula. The bath temperature was allowed to rise to 20−25 °C and stirring was continued for 24 h. The solution was concentrated at reduced pressure. Diethyl ether was added, and the solution was extracted with saturated ammonium chloride. The organic phase was dried over magnesium sulfate and concentrated to a viscous liquid mixture of ∼80% **11a** and ∼20% unchanged bromo boronic ester **10a** as estimated by ^{1}H NMR analysis (3.6 g). Chromatography on silica with 1:20 ether/pentane yielded colorless viscous liquid **11a** (2.8 g, 72%): IR (KBr pellet) cm^{-1} 2098 (CN_3), 2197 (CN); 300 MHz ^{1}H NMR (C_6D_6) δ 0.05 (s, 6H), 0.83−1.71 (m, 22H + s, 9H at δ 0.93), 2.05 (m, 2H), 3.58, (m, 2H), 3.67 (m, 2H), 3.86 (m, 1H); 75 MHz ^{13}C NMR (C_6D_6) δ −5.4, 16.5, 18.3, 25.2, 26.0, 26.2, 26.3, 26.7, 27.6, 28.6, 43.1, 65.4, 66.0, 84.3, 119.1; HRMS calcd for $C_{31}H_{36}BN_4O_3Si$ (M − 57) 431.2650, found (EI) 431.2657.

[2(1*R*,2*R*,3*S*),4*S*,5*S*]-4,5-Dicyclohexyl-2-[3-azido-l-bromo-2-cyanomethyl-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-butyl]-1,3,2-dioxaborolane (12a). A solution of cyano boronic ester **11a** (2.92 g, 6 mmol) and dibromomethane (0.83 mL, 2.08 g, 12 mmol) in THF (60 mL) was stirred at −78 °C under argon during the dropwise addition of LDA (6.0 mmol, 1.5 M in hexane). Anhydrous zinc chloride (3.26 g, 24 mmol) was added, and the mixture was allowed to warm to 20−25 °C and stirred for 24 h. The solution was concentrated at reduced pressure. Diethyl ether was added, and the solution was extracted with saturated ammonium chloride. The organic phase was dried over magnesium sulfate and concentrated to a viscous liquid mixture of −65% bromo boronic ester **12a** and ∼35% unchanged **11a** as estimated by ^{1}H NMR analysis (3.1 g). Chromatography on silica gel with 1:20 ether/pentane yielded **12a** (1.2 g, 35%): $[\alpha]^{22}_{546}$ −46.23° (*c* 1.7, $CHCl_3$); IR (neat) cm^{-1} 2098.8 (CN_3), 2280.3 (CN); ^{1}H NMR (C_6D_6) δ 0.02 (s, 6H), 0.92 (s, 9H), 0.71−1.78 (m, 23H), 2.20 (m, 2H) 3.48 (d, 1H), 3.57 (m, 2H), 3.70 (m, 1H), 3.83 (m, 2H); 75 MHz ^{13}C NMR (C_6D_6) δ −3.6, 16.4, 18.2, 26.0, 26.3, 26.4, 26.6, 27.7, 29.0, 32.0, 43.6, 64.7, 65.2, 65.3, 84.4, 117.6; HRMS calcd for $C_{26}H_{47}BBrN_4O_3Si$ (M + 1), 581.2694, found, 581.2780.

[2(1*S*,2*R*,3*S*),4*S*,5*S*]-4,5-Dicyclohexyl-2-[3-azido-2-cyanomethyl-4-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-1-phenylbutyl]-1,3,2-dioxaborolane (13a). Phenylmagnesium bromide (1.72 mmol, 1 M in THF) was added dropwise to a stirred solution of bromo boronic ester **12a** (1.0 g, 1.72 mmol) in THF (10 mL) at −78 °C. After being stirred for 15 h at 20−25 °C, the solution was concentrated under vacuum. Dimethyl sulfoxide (2 mL) was added and the solution was stirred for 8 h at 20−25 °C. Diethyl ether was added, and the solution was extracted with saturated ammonium chloride. The organic phase was dried over anhydrous magnesium sulfate and concentrated at reduced pressure to **13a** (0.90 g, 90%): IR (neat) cm^{-1} 2099 (CN_3); ^{1}H NMR (C_6D_6) δ 0.21 (s, 6H), 1.13 (s, 9H), 0.71−1.78 (m, 24H), 2.04 (m, 2H) 3.55 (m, 2H), 3.96 (m, 2H), 4.06 (m, 1H); ^{13}C NMR (C_6D_6) δ −3.6, 1.4, 25.8, 26.3, 26.4, 26.4, 27.7, 29.1, 32.0, 44.2, 62.4, 65.5, 66.0, 82.3, 119.2; HRMS calcd for $C_{28}H_{42}BN_4O_3Si$ (M − 57) 521.3119, found 521.3107.

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Supporting Information Available: Preparative information and physical properties of compounds **7b**,**c**, **8b**,**c**, **9c**,**d**, **10b**,**c**,**d**, **11b**,**c**,**d**, and **12b**,**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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