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An Exploratory Study of Silylated Amino Boronic Ester Chemistry

Donald S. Matteson,* Rajendra P. Singh, Christopher H. Sutton, James D. Verheyden,† and Jian-hui Lu

Department of Chemistry, Washington State University, Pullman, Washington 99164-4630

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ABSTRACT

*Diisopropyl [bis(trimethylsilylamino)methyl]-boronate, the analogous pinacol boronic ester (***3***), and pinacol [(2,2,5,5-tetramethyl-2,5,1-disilazol-1-yl)-methyl]boronate (***8***) were prepared from the corresponding (bromomethyl)boronic ester* **1** *or* **2** *and silylated lithium amide. Reaction of* **3** *or* **8** *with (dichloromethyl)lithium yielded the corresponding [1-chloro-2-(silylated amino)ethyl]boronate* **4** *or* **9**. *Further transformations of* **4** *to methylthio derivative* **5** *and dimethylamino derivative* **7** *as well as conversion of* **5** *to ureido derivatives* **6** *are described. (S,S)-1,2-Dicyclohexylethanediol [1-chloro-2-(trityloxy)-ethyl]boronate (***13***) has been converted to bis(trimethylsilyl)amino derivative* **14** *and formamido derivative* **15** *as well as to N-benzyl analogs* **18** *and* **19**. *Attempted chain extensions of* **14,** *silylated* **15,** *or* **19** *with (dichloromethyl)lithium indicated that the alkyl migration from boron to carbon is slow and incomplete.* © 1997 John Wiley & Sons, Inc. Heteroatom Chem **8:**487–494, 1997

INTRODUCTION

The chain extension of boronic esters with (dichloromethyl)lithium has provided a useful approach to asymmetric synthesis that is compatible with a considerable variety of functional substituents [1]. However, previous attempts to utilize α-bis-(trimethylsilyl)amino boronic esters in this process have yielded moisture-sensitive products that could not be purified. Instead, α-azido boronic esters were used in asymmetric syntheses of β-amino alcohols [2] and α-amino acids [3].

α-Amino boronic esters that contain an NH group are unstable toward deboronation [4], and silyl-protected amino boronic esters remain the intermediates of choice for most preparations of α-amido boronic acids, several of which are potent serine protease inhibitors [5]. We have now reinvestigated the synthesis and purification of several silylated amino boronic esters and carried out an exploratory investigation of some of their chemistry.

RESULTS AND DISCUSSION

[[Bis(trialkylsilyl)amino]methyl]boronic Esters

Diisopropyl (bromomethyl)boronate (**1**) [6] with lithio(hexamethyldisilazane) yielded crude diisopropyl [[bis (trimethylsilyl)amino]methyl]boronate, $(Me_3Si)_2NCH_2B(OCHMe_2)_2$. Because of the hydrolytic lability of the trimethylsilyl and isopropoxy groups, distillation is the only feasible means of purification. Although Si–N and B–O bonds did not undergo exchange and consequent disproportionation when $(Me_3Si)_2NCH_2B(OCHMe_2)_2$ was distilled rapidly, the compound decomposed when fractionation was attempted, and higher boiling derivatives apparently do not survive simple distillation intact.

Dedicated to Prof. William E. McEwen on the occasion of his seventy-fifth birthday.

*To whom correspondence should be addressed.
†Deceased 15 November 1992.

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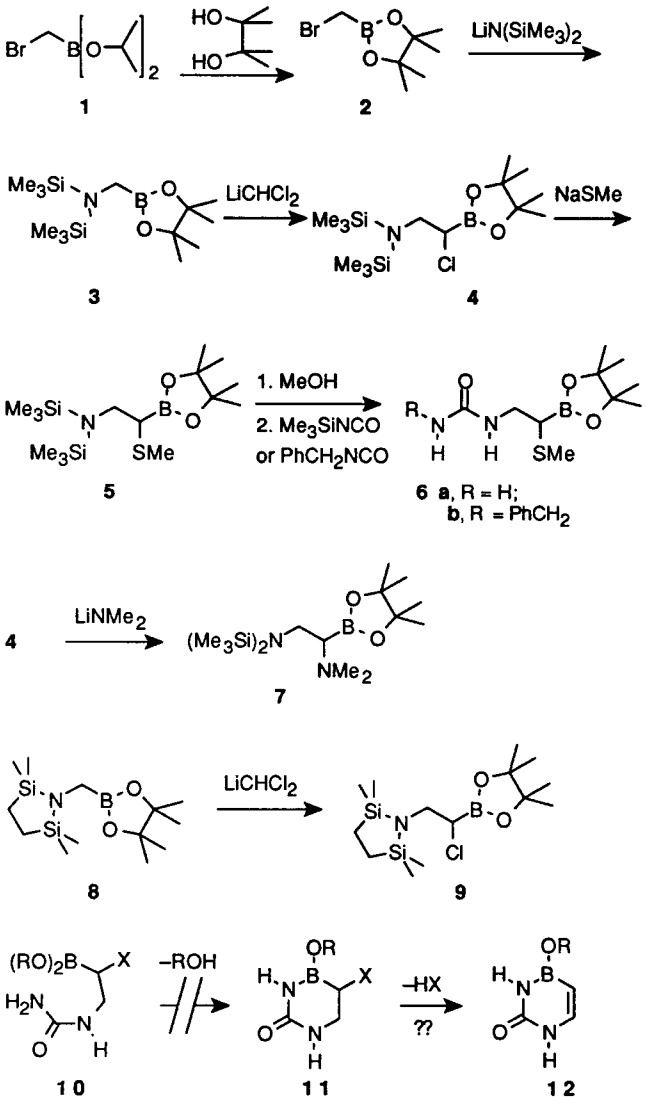
Treatment of the crude product with (dichloromethyl)lithium yielded material having the expected ^{1}H-NMR spectrum of the chain extension product, $(Me_3Si)_2NCH_2CHClB(OCHMe_2)_2$, but attempted purification failed. Hydrolysis yielded intractable polymeric powder, not monomeric (*β*-amino-*α*-chloroethyl)boronic acid, and several other attempted reactions of the diisopropyl ester yielded ambiguous results. In attempts to desilylate $(Me_3Si)_2NCH_2CHClB(OCHMe_2)_2$ to $H_2NCH_2CHClB(OCHMe_2)_2$ for possible acylation with an isocyanate, ^{1}H NMR evidence indicated that the first 2 mols of methanol displace 2-propanol from boron, and 2-propanol does not cause desilylation under mild conditions.

To obtain a more tractable series of boronic esters, **1** was transesterified to pinacol (bromomethyl)boronate [*Chemical Abstracts* name: 2-bromomethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane] (**2**) [7]. Lithio(hexamethyldisilazane) converted **2** to the [[bis(trimethylsilyl)amino]methyl]boronic ester (**3**), which with (dichloromethyl)lithium readily yielded **4.** In view of the probable incompatibility of the *α*-chloro boronic ester function with unmasked amine, displacement of chloride from **4** was tested. Lithium benzyl oxide failed, but sodiomethanethiol yielded the methylthio compound **5.**

Reaction of **5** with methanol to cleave the trimethylsilyl groups, treatment with trimethylsilyl isocyanate in situ, and a second desilylation with methanol yielded the ureido derivative **6a.** With benzyl isocyanate, **5** was converted to the benzylureido derivative **6b.**

Conversion of the chloro boronic ester **4** to the *α*-dimethylamino boronic ester **7** by treatment with lithium dimethylamide was also accomplished without difficulty. A cyclic analog of **3,** the disilazole **8,** was prepared in the hope that the protected amine function might withstand transformations that the bis(trimethylsilyl)amino group does not. Chain extension to *α*-chloro boronic ester **9** proceeded without difficulty, but an attempted displacement of chloride from **9** by lithium benzyl oxide was again unsuccessful.

We had hoped to find an *α*-substituted *β*-ureidoboronic ester **10** that could cyclize to an intermediate **11** and undergo H–X elimination to provide the boron analog of uracil **12,** which would be of interest as a possible anticancer, antiviral, or ^{10}B-neutron capture cancer therapy agent [8]. All attempts at further elaboration of **6** and **7** in this direction failed to yield products that could be purified. For example, methylation of **6a** with methyl iodide yielded amorphous material having an NMR spectrum consistent with the protodeboronation product, $H_2NCONHCH_2CH_2SMe_2^+I^-$. Deboronation was also the ultimate result of various attempted conversions of **6b** and **7** to **12.** An early unsuccessful attempt to prepare the uracil analog having B–OH in place of C=O via cyclization and dehydrogenation of a *β*-ureidoethylboronic acid has been reported [9], and benzo derivatives of **12** having the benzene ring fused to the carbon–carbon double bond have been synthesized recently [10].

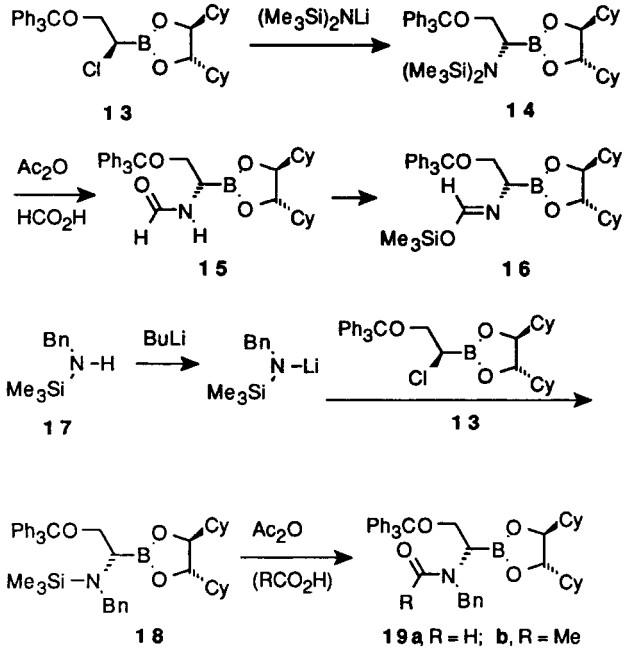


Protected [1-Amino-2-(trityloxy)ethyl]boronic Esters

We have previously reported [2-(benzyloxy)-1-chloroethyl]boronic esters [3,11,12]. Earlier attempts to convert these to [2-(benzyloxy)-1-[bis(trimethylsilyl)amino]ethyl]boronic esters and react them with (dichloromethyl)lithium failed. All of the com-

pounds were liquids that could not be chromatographed because of the hydrolytic lability of the (trimethylsilyl)amino function, and the products could not be purified and characterized.

Having recently discovered that several trityloxy boronic esters are crystalline solids [13] and that **3** and **8** do undergo normal chain extension with (dichloromethyl)lithium, we decided to reexamine this chemistry with the trityloxy series. The preparation of crystalline (*S,S*)-DICHED [1-bis(trimethylsilyl)amino-2-(trityloxy)ethyl]boronate (**14**) and its formamido derivative **15** proved straightforward, and the compounds were easily purified. Since the N–H group of **15** was expected to be incompatible with (dichloromethyl)lithium, **15** was silylated to labile **16,** which was characterized only by NMR.



An alternative route to formamido boronic esters is provided by the reaction of halo boronic esters with sodiodiformimide, $NaN(CHO)_2$ [14]. We tested this route briefly with **13** as substrate in the hope that the diformylamino boronic ester might be a useful intermediate. However, NMR evidence indicated that one formyl group was cleaved during aqueous workup, and the major product was monoformamido compound **15.** Because of the labor of preparing diformimide, the route to formamido boronic esters via the bis(trimethylsilyl)amino intermediates was chosen as more convenient.

We also prepared *N*-benzyltrimethylsilazane (**17**) and used it to make the boronic ester derivative **18,** which was not purified. Desilylation with formic acid in the presence of acetic anhydride readily yielded the *N*-benzyl formamido boronic ester **19a.** Acetic anhydride alone, with no deliberate addition of a proton source before aqueous workup, produced the acetamido analog **19b.**

Attempts to carry out chain extension of **14, 16, 18,** or **19** with (dichloromethyl)lithium invariably yielded much unchanged starting material. On the basis of ^1H and ^{13}C NMR evidence, it appeared that the silyl compounds **14** and **16** slowly underwent chain extension to the extent of 30–50%, but purification was not feasible. While it might seem that synthetically useful conversions could be reached merely by waiting a few more days, the zinc chloride promoter is consumed by complexation with liberated chloride ion as the reaction proceeds, with the result that slow reactions of this type may come to a virtual standstill at a point well before completion. Epimerization of an α-chloro boronic ester, the only related process for which kinetic studies have been done [15], shows a complex relationship between the rate, concentrations, and the ratio of zinc to chloride ions.

The reaction of **19b** with (dichloromethyl)lithium clearly yielded the expected borate complex. After addition of zinc chloride (three equivalents) and stirring 20 hours at room temperature, concentration of the reaction mixture yielded a solid residue that was soluble in deuterochloroform and lacked several peaks in the ^1H and ^{13}C NMR spectra characteristic of **19b** but showed other resonances instead, plus coordinated THF (approximately four equivalents). The chlorine content of the solid was reasonably consistent with the assumption that an equivalent of $LiCHCl_2$ was retained. Aqueous workup cleaved the $CHCl_2$ group from the complex and regenerated **19b.** It may be concluded that the borate complex does not rearrange at a measurable rate in this case.

Zinc chloride was not needed for the borate rearrangement step with the pinacol boronic esters **3** or **8** but is normally required for high diastereoselectivity and useful rearrangement rates with asymmetric, functionalized boronic esters [2,12], and it would certainly appear to be essential for chain extension of compounds such as **14, 16,** or **19b.** However, complexation of zinc chloride with an adjacent amide function would make this type of substituent much bulkier and more polar than those previously used successfully in chain extensions with (dichloromethyl)lithium.

All of the asymmetric compounds **13–16** and **18–19** appeared from the NMR spectra to be single diastereomers, as expected from this type of synthesis [1], though no effort was made to detect small per-

centages of isomers. The racemic chiral compound **9** shows two narrowly separated $SiCH_3$ resonances and two narrowly separated CCH_3 resonances, in accord with the diastereotopic relationship of the C_2-symmetrical pairs of methyl substituents on the rings. The two $Si(CH_3)_3$ groups of **14** also appear as a diastereotopic pair, which was not anticipated but can be accounted for if it is assumed that rotation of the bis(trimethylsilyl)amino group is sterically restricted or that the nitrogen atom is pyramidal, and that inversion or rotation of this group is slow at room temperature on the NMR time scale.

CONCLUSIONS

Simple silylated aminomethyl boronic esters have been found to undergo chain extension with (dichloromethyl)lithium in the same manner as other boronic esters, and several transformations of the resulting masked α-chloro-β-amino boronic esters have been explored. After the chlorine has been replaced with a less reactive substituent, the amine function can be desilylated and converted to a ureido derivative, but an α-substituent that would permit cyclization to form a boron analog of uracil has not been found.

A series of asymmetric silylated (α-amino-β-trityloxyethyl)boronic esters and their formamido or acetamido derivatives has also been investigated. Most of these compounds proved to be easily purifiable solids. These compounds form borate complexes with (dichloromethyl)lithium readily enough, but the zinc chloride catalyzed rearrangement of these complexes is very slow and impractical for synthetic purposes.

EXPERIMENTAL

General Procedures

All procedures involving air-sensitive organometallic reagents were carried out under an inert atmosphere (argon). Tetrahydrofuran (THF) was rigorously dried over benzophenone ketyl. (Dichloromethyl)lithium was prepared by addition of butyllithium to dichloromethane in THF at −100°C according to the established procedure [2].

Diisopropyl[[Bis(trimethylsilyl)amino] methyl]boronate

Lithio(hexamethyldisilazane) (0.16 mol) was prepared by adding butyllithium (1.5 M, 100 mL) to hexamethyldisilazane (37.2 mL) stirred at −78°C under argon. A solution of diisopropyl (bromomethyl)-boronate (**1**) [6] (35.65 g, 0.16 mol) in THF (~50mL) was added via cannula. The mixture was allowed to warm to room temperature and refluxed ~4 hours. Vacuum distillation yielded diisopropyl [[bis(trimethylsilyl)amino]methyl]boronate (bp data missing; 43.5 g, 90%); 200 MHz ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 18H), 1.13 (d, J = 6.2 Hz, 12H), 2.44 (s, 2H), 4.32 (septet, J = 6.1 Hz, 2H). Anal. calcd for $C_{13}H_{28}BNO_2Si_2$: C, 51.46; H, 11.30; B, 3.56; N, 4.62; Si, 18.51. Found: C, 51.66; H, 11.01; B, 3.81; N, 4.74; Si, 14.18. The anomalously low silicon analysis might be attributed to disproportionation and loss of isopropyl trimethylsilyl ether, though the CH_3Si ^{1}H-NMR integral at δ 0.05 was typically within ~5% of theory.

*2-Bis(trimethylsilyl)amino-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3**)*

A solution of hexamethyldisilazane (37.3 g, 0.231 moles) in THF (50 mL) was stirred magnetically under argon at −78°C, while butyllithium in hexane (144 mL, 1.6 M, 0.231 moles) was added slowly over a period of ~10 minutes. Pinacol (bromomethyl)boronate (**2**) [7] (52.1 g, 0.236 mole) was added to the stirring mixture, which promptly thickened sufficiently to stop the stirrer until the mixture was heated to distill solvents, bp 40–77°C. The pressure was gradually lowered, and a small forerun was collected, followed by **3,** bp 82–83°C (0.5 torr) (72.4 g, ~90% purity, yield of **3** ~93%); after redistillation, ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 18H), 1.22 (s, 12H), 2.43 (s, 2H), HRMS (EI) 301.2081 (M^+, calcd for $C_{13}H_{32}{}^{11}BNO_2Si_2$ 301.2065).

*4,4,5,5-Tetramethyl-2-[(2,2,5,5-tetramethyl-2,5,1-disilazol-1-yl)methyl]-1,3,2-dioxaborolane (**8**)*

A solution of 1-lithio(2,2,5,5-tetramethyl-2,5,1-disilazole) was prepared by the addition of butyllithium (1.52 M in hexanes, 87.8 mL, 133 mmol) to a stirring solution of 2,2,5,5-tetramethyl-2,5,1-disilazole (20.88 g, 130.96 mmol) in THF (30 mL) at −78°C. Pinacol bromomethylboronate (**2**) [7] (28.1 g, 127 mmol) was added neat to this solution. A white precipitate formed immediately. The mixture was allowed to warm to 20–25°C and stirred overnight. The solvents were removed by distillation at atmospheric pressure under argon. High vacuum distillation yielded **8,** bp 90–92°C (1 torr), 26.72 g, 70.3%; 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.02 (s, 12H), 0.67 (s, 4H), 1.23 (s, 12H), 2.40 (s, 2H); 75 MHz ^{13}C-NMR ($CDCl_3$) δ −0.6, 8.1, 24.8, 83.2. Anal. calcd for $C_{13}H_{30}BNO_2Si_2$: C, 52.16; H, 10.10; B, 3.61; N, 4.68. Found: C, 51.87; H, 9.83; B, 3.52; N, 4.66.

*2-[1-Chloro-2-(2,2,5,5-tetramethyl-2,5,1-disilazol-1-yl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**9**)*

(Dichloromethyl)lithium was prepared in the usual manner [2] from butyllithium (41.3 mL of 1.52 M, 62.7 mmol) and dichloromethane (12.3 g, 145 mmol) in THF (100 mL). While maintaining −100°C, 4,4,5,5-tetramethyl-2-[(2,2,5,5-tetramethyl-2,5,1-disilazol-1-yl)methyl]-1,3,2-dioxaborolane (**8**) (14.4 g, 48.26 mmol) was added to the solution via cannula. The solution was allowed to warm to room temperature and kept for 18 hours. The solvents were removed under reduced pressure. The residue was redissolved in pentane (200 mL) and filtered through a column of celite. Concentration in a rotary evaporator yielded **9,** 13.68 g, 81.6%; 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.08 (d, 6H), 0.09 (d, 6H), 0.63–0.73 (m, 4H), 1.27 (s, 6H), 1.28 (s, 6H), 3.03–3.12 (m, 1H), 3.23–3.33 (m, 2H); 75 MHz ^{13}C-NMR ($CDCl_3$) δ −0.3, 0.1, 8.1, 24.3, 24.9, 46.2, 84.2; HRMS calcd for $C_{14}H_{31}BClNO_2Si_2$ (M^+), 347.1675; found, 347.1667.

*2-[1-Methylthio-2-bis(trimethylsilyl)amino]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5**)*

Freshly distilled **3** (38.7 g, 0.128 mole, purity ~85%) was added to (dichloromethyl)lithium generated from dichloromethane (25 mL, 0.39 mol) and butyllithium (106 mL of 1.65 M, 0.175 mole) at −100°C. After the mixture had warmed to room temperature, ^{1}H NMR analysis indicated complete conversion of **3** to **4** [^{1}H NMR ($CDCl_3$) δ 0.14 (s, 18H), 1.274 (s, 6H), 1.278 (s, 6H), 3.12 (dd, 1H,J = 16.0 Hz, J = 10.6 Hz), 3.30 (m, 2H); ^{13}C NMR ($CDCl_3$) 2.39, 24.4, 24.7, 46.2 (broad), 48.4, 84.2.], with ~20% of other products present. Powdered sodio(methanethiol) (8.37 g, 0.119 mole) was added via a powder funnel under an argon purge to the reaction mixture at room temperature. There was no immediate change in appearance of the suspended salt. After stirring 3 days, ^{1}H NMR analysis indicated complete conversion of **4** to **5.** Vacuum distillation yielded yellow oily **5,** bp 106–119°C (0.5 torr), 26.0 g, 56.2%, estimated purity ≥90%: ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 18H), 1.255 (s, 6H), 1.264 (s, 6H), 2.07 (dd, partly obscured, J = 8.3, 7.3 Hz, ~1H), 3.03 (dd, J = 7.2, 14.1 Hz, 1H), 3.19 (dd, J = 8.6, 14.1 Hz, 1H), 2.10 (s, 3H).

*2-[1-Methylthio-2-N-ureido]ethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6a**)*

Methanol (2.28 g, 0.71 mol) was added dropwise to a solution of freshly distilled **5** (12.85 g, 0.036 mole, ca. 90% pure) in anhydrous acetonitrile (25 mL) under argon. After stirring 15 minutes, a copious white precipitate formed. Stirring was continued an additional 10 minutes. Trimethylsilyl isocyanate (3.37 g, 0.036 mole) was added. The precipitate dissolved and an exothermic reaction occurred (flask hot to touch). After cooling to room temperature, the solvent was distilled under vacuum (0.2 torr). The yellow amorphous solid (9.8 g) was washed with pentane. Attempted recrystallization from ether-pentane or dichloromethane caused partial decomposition, as indicated by a doublet at 2.79 ppm in the ^{1}H NMR spectrum. Chromatography on silica (hexane; ethyl acetate/acetone 8:2) yielded **6a,** 2.18 g, 24%; TLC, acetone, R_f = 0.37; ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 12H), 2.08 (s, 3H), 2.17 (t, J = 6.5 Hz, 1H), 3.42 (m, 2H), 4.99 (br, 2H), 5.97 (br, 1H). Anal. calcd for $C_{10}H_{21}BN_2O_3S$: C, 46.17; H, 8.14; B, 4.16; N, 10.77; S, 12.33. Found: C, 46.23; H, 7.81; B, 3.64; N, 10.53; S 11.45.

*2-[1-Methylthio-2-(N′-phenylmethyl-N-ureido)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6b**)*

Methanol (1.89 g, 59 mmol) was added to a solution of freshly distilled **5** (10.67 g, 29.5 mmol) in anhydrous acetonitrile (30 mL) under argon. After 25 minutes, a white precipitate had formed and benzyl isocyanate (3.93 g, 29.5 mmol) was added dropwise. As the addition neared completion, the precipitate dissolved, and an exothermic reaction became evident. After stirring overnight the solution was concentrated under vacuum to a very viscous, almost solid residue (11.46 g). Treatment with excess methanol and 2,2-dimethoxypropane and concentration under vacuum yielded semisolid **6b** (10.82 g, 105% crude). A portion was recrystallized from diethyl ether; ^{1}H NMR (CD_3CN) δ 1.21 (s, 12H), 2.04 (s, 3H), 2.14 (br t, J = 7.26 Hz, 1H), 3.30 (dd, J = 5.73, 7.20 Hz, 2H), 4.24 (d 2H), 5.37 (br t, J = 5.4 Hz, 1H), 5.65 (br t, J = 1H), 7.36–7.19 (m, 5H); HRMS (EI) 350.1857 (M^+ calcd for $C_{17}H_{27}{}^{11}BN_2O_3S$ 350.1835).

*2-[1-Dimethylamino-2-bis(trimethylsilyl)amino]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**7**)*

Lithio(dimethylamine) was prepared by addition of butyllithium (30 mL, 1.6 M, 48 mmol) to a large excess of dimethylamine in tetrahydrofuran (150 mL) at −78°C. Crude **4** was prepared from **3** (10.0 g, 33.3 mmol) in the same manner as described under the preparation of **5,** but it was only partially concentrated. The **4** was added to the cold lithio(dimethylamine) solution via cannula over a period of 5 minutes. When the mixture had warmed to ~0–20°C, the

solution was concentrated under vacuum to a semisolid residue (17.6 g). The ^{1}H NMR spectrum indicated complete reaction of **4.** Vacuum distillation yielded **7,** bp 108–112°C, 8.6 g (72%, purity ~90%); ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 18H), 1.258 (s, 6H), 1.265 (s, 6H), 2.13 (br t, J = 7.68 Hz, 1H), 2.31 (s, 6H), 3.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 2.5, 24.8, 25.3, 44.8, 45.0, 57.2 (br), 83.1; HRMS (EI) 359.2715 ($M^+ + H$, calcd for $C_{11}H_{19}{}^{11}BNO_2$ 359.2721).

Deboronation of **6a** *with Methyl Iodide*

Methyl iodide (0.80 g, 5.64 mmol) was added dropwise to a solution of recrystallized urea derivative **6a** (0.90 g, 3.46 mmol) in acetonitrile under argon. After a night, concentration and heating (~100°C) under vacuum yielded an amorphous fluffy solid mixture of pinacol borate and (2-*N*-ureidoethyl)(dimethyl)-sulfonium iodide; ^{1}H NMR (CD_3CN/DMSO-d_6) δ 1.17 (s, 70% of 12H, pinacol borate), 2.91 (s, 6H), 3.42 (m, 2H), 3.48 (m, 2H), 5.40 (br s, 2H), 6.36 (br m, 1H); impurities at 5.48 (s, 0.4H) and 7.41 (s, 0.4H).

{4S-[2(R),4α,5β]}-2-[1-Bis(trimethylsilyl)amino-2-(triphenylmethoxy)ethyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (***14***)*

A solution of {4S-[2(S*),4α,5β]}-2-[1-chloro-2-(triphenylmethoxy)ethyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (**13**) [7] (12 g, 21.6 mmol) in THF (50 mL) was added slowly via cannula to a stirred solution of lithiohexamethyldisilazane, which had been prepared by addition of butyllithium (1.6 M in hexane, 15 mL, 24 mmol) to hexamethyldisilazane (3.87 g, 24 mmol) in THF (50 mL) at −78°C. The mixture was allowed to warm to 20–25°C and stirred for 16 hours. This solution was used directly in the next step for preparation of **15.** Isolation of **14,** mp 135–137°C, was achieved by concentration of the solution and treatment of the residue with pentane to precipitate lithium chloride. Evaporation of the pentane yielded a crystalline residue that had the elemental composition of **14;** 84%; 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.00 (s, 9H), 0.05 (s, 9H), 1.01–1.92 (m, 22H), 2.83 (dd, J = 7.1, 14 Hz, 1H), 2.99 (dd, J = 6.0, 14.7 Hz, 1H), 3.37 (dd, J = 8.2, 16.5 Hz, 1H), 3.84–3.86 (m, 2H), 7.10–7.53 (m, 15H); 75 MHz ^{13}C-NMR ($CDCl_3$) δ 1.0, 1.9, 25.8, 26.0, 26.5, 27.8, 28.9, 41.4 (broad), 43.2, 67.0, 84.0, 86.4, 127.8, 128.9, 130.4, 144.5. MS calcd for $C_{41}H_{60}NO_3Si_2B$ ($M+H$): 682, found: 682. Anal. calcd for $C_{41}H_{60}NO_3Si_2B$: C, 72.22; H, 8.87; B, 1.59; N, 2.05; Si, 8.24. Found: C, 72.28; H, 8.49; B, 1.70; N, 1.58; Si, 8.32.

{4S-[2(R),4α,5β]}-2-[1-Formamido-2-(triphenylmethoxy)ethyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (***15***)*

The solution containing **14** (21.6 mmol) prepared as described in the preceding paragraph was cooled to −78°C. Acetic anhydride (6.73 g, 6.22 mL, 66 mmol) was added, followed by formic acid (96%, 1.10 g, 0.9 mL, 24 mmol). The mixture was stirred at 20–25°C for 16 hours. The solution was concentrated under vacuum, and the residue was treated with ether (300 mL), washed with water (3 × 300 mL), dried over magnesium sulfate, and filtered. Concentration yielded crude **15,** which was washed with pentane (50 mL), 9.35 g (78%). An analytical sample was recrystallized from ether/pentane (40:60), mp 159–160°C; $[\alpha]^{23}_{546}$ = +23.11° (c = 1.04 in $CHCl_3$), 300 MHz ^{1}H-NMR ($CDCl_3$) δ 1.56–1.81 (m, 22H), 3.34 (m, 2H), 3.58 (m, 1H), 3.85–3.91 (m, 2H), 6.23 (br d, 1H), 7.19–7.42 (m, 15H), 8.07 (s, 1H); 75 MHz ^{13}C-NMR ($CDCl_3$) δ 25.8, 26.0, 26.4, 27.7, 28.7, 37.2 (broad), 42.8, 64.5, 84.2, 86.6, 127.0, 127.8, 128.6, 143.9, 161.5. HRMS calcd for $C_{36}H_{43}BNO_4$ ($M-1$): 564.3285. Found: 564.3300. Anal. calcd for $C_{36}H_{44}BNO_4$: C 76.45; H, 7.84; B, 1.91; N, 2.48. Found: C, 76.53; H, 7.87; B, 1.61; N, 2.52.

{4S-[2(R),4α,5β]}-2-[1-[(Trimethylsilyloxymethylene)imino]-2-(triphenylmethoxy)ethyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (***16***)*

A solution of sodium iodide (0.64 g, 4.2 mmol) and **15** (2.26 g, 4 mmol) in anhydrous acetonitrile (500 mL) was treated with chlorotrimethylsilane (0.65 g, 6 mmol) followed by triethylamine (0.50 g, 5 mmol) at room temperature. Monitoring by NMR indicated that the reaction was complete after 35 hours. After concentration under vacuum, the product was extracted into 1:1 ether/pentane (100 mL). Concentration yielded moisture-sensitive solid **16,** 2 g (78%); 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.37 (s, 9H), 0.80–1.87 (m, 22H), 3.30 (m, 2H), 3.40 (m, 1H), 3.70 (m, 2H), 7.28–7.48 (m, 15H), 7.82 (s, 1H); 75 MHz ^{13}C-NMR ($CDCl_3$) δ 1.0, 25.9, 26.1, 26.4, 26.6, 28.5, 43.0, 67.6, 77.0, 82.6, 126.8, 127.7, 128.8, 144.0, 169.1.

*N-Benzyltrimethylsilazane (***17***)*

Benzylamine (2.14 g, 20 mmol) in THF (100 mL) was stirred at 0°C during the dropwise addition of butyllithium (1.6 M in hexane, 12.5 mL, 20 mmol). After stirring for 3 hours at 20–25°C, the mixture was again cooled to 0°C and chlorotrimethylsilane (2.17 g, 20 mmol) was added slowly. The mixture was stirred for 8 hours at 20–25°C, then concentrated un-

der vacuum. Pentane (50 mL) was added to the residue, and lithium chloride was removed by filtration. Concentration of the solution yielded **17** as a liquid, 3.45 g (96.4%), 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.2 (s, 9H), 0.84 (broad t, 1H), 4.0 (d, 2H), 7.42–7.34 (m, 5H); 75 MHz ^{13}C-NMR ($CDCl_3$) δ 0.3, 44.38, 126.23, 126.81, 130.53, 144.16. MS calcd for $C_{10}H_{17}NSi$ (M^+): 153; found: 153. Anal. calcd for $C_{10}H_{17}NSi$: C, 67.03; H, 9.49; N, 7.82; Si, 15.64. Found: C, 67.27; H, 9.34; N, 7.63; Si, 15.69.

{4S-[2(R),4α,5β]}-[1-(N-Benzylformamido)-2-(triphenylmethoxy)ethyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (***19a***)*

Butyllithium (1.6 M in hexane, 4.37 mL, 7 mmol) was added slowly to a stirred solution of *N*-benzyltrimethylsilazane (**17**) (1.253 g, 7 mmol) in THF (40 mL) at −78°C to form the lithio derivative. The mixture was stirred for 4 hours at −78°C. A solution of **13** (3.90 g, 7 mmol) in THF (20 mL) was added via cannula to the above reaction mixture. The mixture was slowly allowed to warm to room temperature and stirred for 14 hours to complete the formation of **18,** then cooled to −78°C. Acetic anhydride (2.693 g, 2.48 mL, 26 mmol) was added followed by formic acid (0.427 g, 0.35 mL, 9.2 mmol). The bath was slowly allowed to warm to room temperature, and the mixture was stirred an additional 14 hours. The solution was concentrated in a rotary evaporator. Ether (200 mL) was added, and the solution was washed with water (3 × 300 mL). The ether solution was dried over magnesium sulfate and filtered. Concentration yielded solid **19a,** 4.12 g (90%). An analytical sample was recrystallized from 30:70 ether–pentane, mp 70–71°C, $[\alpha]_{546}^{23}$ +66.9° (*c* 1.0, $CHCl_3$), 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.85–1.07 (m, 22H), 3.00 (d, J = 9.9 Hz, 1H), 3.22 (dd, J = 10.1 and 11.2 Hz, 1H), 3.54 (dd, 2H), 3.63 (d, J = 11.4 Hz, 1H), [3.45 (m), 3.80 (m), 4.46 (m), 5.0 (m), impurity at ~5–10%], 4.70 (d, J = 15.3 Hz, 1H), 4.76 (d, J = 15.1 Hz, 1H), 7.40–7.21 (m, 20H), 8.57 (s, 1H); 300 MHz ^{13}C-NMR ($CDCl_3$): δ 25.9, 26.1, 26.7, 28.5, 29.3, 42.9, 47.0 (broad), 52.5, 65.5, 82.8, 87.3, 126.9, 128.3, 128.8, 143.9, 164.8. HRMS calcd for $C_{43}H_{49}NO_4B$ (M-H): 654.3755; found, 654.3728. Anal. calcd for $C_{43}H_{50}NO_4B$: C, 78.77; H, 7.69; B, 1.65; N, 2.14. Found: C, 78.72; H, 7.48; B, 1.47; N, 2.29.

{4S-[2(R),4α,5β]}-[1-(N-Benzylacetamido)-2-(triphenylmethoxy)ethyl]-4,5-dicyclohexyl-1,3,-2-dioxaborolane (***19b***)*

Butyllithium (1.6 M in hexane, 3.74 mL, 6 mmol) was added slowly to a stirred solution of *N*-benzyltrimethylsilazane (1.074 g, 6 mmol) in THF (40 mL) at −78°C. The mixture was stirred at −78°C for 3 hours. A solution of **13** (3.34 g, 6 mmol) in THF (20 mL) was added via cannula. The mixture was allowed to warm to room temperature slowly and stirred for 14 hours, then cooled to −78°C and treated with acetic anhydride (2.24 g, 2.0 mL, 22 mmol). The mixture was again stirred for 14 hours at room temperature, then concentrated on a rotary evaporator and treated with ether (300 mL). The ether solution was washed with water (3 × 300 mL), dried over magnesium sulfate, and filtered. Concentration yielded **19b** as a solid, mp 75–76°C, 3.81 g (95%), $[\alpha]_{546}^{23}$ +70° (*c* 1.1, $CHCl_3$); 300 MHz ^{1}H-NMR ($CDCl_3$): δ 1.63–0.83 (m, 22H), 2.06 (s, 3H), 3.08 (dd, J = 11.4 Hz, 1H), 3.20 (d, J = 9.9 Hz, 1H), 3.45 (dd, 2H), 3.65 (d, J = 10.5 Hz, 1H), 4.78 (d, J = 16.5 Hz, 1H), 5.04 (d, J = 16.5 Hz, 1H), 7.33–7.71 (m, 20H); 75 MHz ^{13}C-NMR ($CDCl_3$) δ 16.2, 25.9, 26.3, 26.7, 28.8, 29.4, 43.1, 51.0, 66.9, 82.2, 87.1, 126.8, 127.7, 127.9, 128.9, 143.9, 176.1. HRMS calcd for $C_{44}H_{51}NO_4B$ (M–H): 668.3911; found: 668.3930. Anal. calcd for $C_{44}H_{52}NO_4B$: C, 78.91; H, 7.83; N, 2.09; B, 1.61. Found: C, 78.66; H, 7.91; N, 1.66; B, 1.48.

Attempted Homologation of {4S-[2(R),4α,5β]}-2-[1-Bis(trimethylsilyl)amino-2-(triphenylmethoxy)ethyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (***14***)*

A solution of **14** (5.28 g, 7.75 mmol) in THF (15 mL) was added via cannula to (dichloromethyl)lithium prepared in the usual way from butyllithium (9 mmol) and dichloromethane (2.5 mL, 24.8 mmol) in THF (50 mL) at −100°C. Zinc chloride (2.9 g) was added. After 28 hours at room temperature, the solution was concentrated. The residue was treated with 1:1 ether/pentane, filtered through magnesium sulfate, and concentrated to a solid. The NMR spectra indicated an ~1:1 mixture of **14** and its chain extension product. Absorptions not attributable to **14** include the following: 300 MHz ^{1}H-NMR ($CDCl_3$) δ 0.15 (s, 9H), 0.18 (s, 9H), 1.0–1.92 (m, 2H), 3.9 (m, 2H), 4.0 (m, 1H); 75 MHz ^{13}C-NMR δ 2.8, 4.3, 25.66, 26.2, 27.1, 27.6, 28.5, 42.4, 58.4, 67.9, 84.0, 87.1, 127.6, 128.5, 128.7, 143.5.

Attempted Reaction of {4S-[2(R),4α,5β]}-2-[1-[(Trimethylsilyloxymethylene)imino]-2-(triphenylmethoxy)ethyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (***16***) with (Dichloromethyl)lithium*

Freshly prepared **16** (2.0 g) was dissolved in a small amount of THF, transferred into a flask containing

(dichloromethyl)lithium made in the usual way from butyllithium (4 mmol) and dichloromethane (8 mmol) in THF (50 mL) at −100°C, and treated with zinc chloride (1.6 g, 12 mmol). After 60 hours at 20–25°C, the solution was concentrated under vacuum, and the residue was worked up with ether and aqueous ammonium chloride in the usual way. Concentration of the ether phase yielded 1.4 g of material that appeared by ^{1}H-NMR analysis to contain 30–50% of the chain extension product, {4*S*-[2(*S**,*S**),4α,5β]}-2-[1-chloro-2-[formamido]-3-(triphenylmethoxy)ethyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane in a mixture with recovered **15;** 300 MHz ^{1}H-NMR ($CDCl_3$) peaks in addition to those of **15:** δ 3.22 (m, 2H) 3.50 (m, 1H), 3.66 (d, 1H), 3.75 (m, 2H), 6.63 (br d, 1H), 8.87 (s, 1H); 75 MHz ^{13}C-NMR ($CDCl_3$) peaks in addition to those of **15:** **δ** 25.7, 26.0, 26.3, 27.5, 29.0, 42.7, 63.3, 76.8, 83.8, 87.0, 127.2, 127.6, 128.5, 143.8, 162.0.

Attempted Homologation of {4S-[2(R),4α,5β]}-[1-(N-Benzylacetamido)-2-(triphenylmethoxy)ethyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (***19b***)*

A solution of **19b** (0.5 mmol) in THF (15 mL) was added to (dichloromethyl)lithium (0.8 mmol) in THF (25 mL) in the usual way and treated with zinc chloride (1.5 mmol). After 20 hours at 20–25°C, the solution was concentrated, dissolved in ether (50 mL), passed through a column of magnesium sulfate, and concentrated to a solid; 300 MHz ^{1}H-NMR ($CDCl_3$) 1.16–2.0 (m, ~38H), 3.2 (m, 2H), 3.6 (d, 1H), 3.9 (m, ~17H), 4.17 (m, 1H), 5.0 (dd, 2H), 7.17–7.44 (m, 15H); 75 MHz ^{13}C-NMR ($CDCl_3$) δ 15.0, 25.7, 26.0, 26.3, 28.3, 29.3, 42.7, 50.1, 52.5, 65.9, 82.1, 87.0, 126.9, 127.7, 128.7, 143.2, 146.6. Anal. calcd for $C_{61}H_{85}BCl_{8.5}Li_{1.5}NO_8Zn_3$ (**19b** + $LiCHCl_2$ + 0.5LiCl + $3ZnCl_2$ + $4C_4H_8O$): C, 49.5; H, 5.8; B, 0.7; Cl, 20.4; N, 1.0; Zn, 13.3. Found: C, 47.1; H, 5.3; B, <0.7 (not detected); Cl, 19.0; N, 0.8; Zn, 13.7%. This material was treated with ether and water, and concentration of the ether phase yielded solid recovered **19b,** verified by ^{1}H-NMR analysis.

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