Modification of a Boronic Acid Cleft Produces a Sodium–Saccharide Cotransporter†,‡

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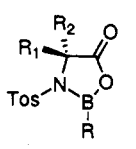
An artificial receptor molecule, which fixes a boronic acid and carboxylic acid in a cleft-like orientation 5.5 Å apart, was synthesized and characterized by spectroscopic and X-ray crystallographic methods. Further synthetic studies demonstrated how this cleft compound can be elaborated into more complicated receptors having a variety of recognition capabilities. Specifically, the cleft was conjugated with a crown ether moiety to produce the first example of a new class of artificial sodium–saccharide cotransporter. U tube transport experiments showed this carrier was able to simultaneously bind and cotransport Na^+ and *p*-nitrophenyl β-D-glucopyranoside through bulk, liquid organic membranes. At pH 6.3, the carrier did not significantly facilitate glucoside transport compared to a control system where the carrier was absent. However, at pH 11.0, transport enhancement increased to five times the background level. This enhancement was considerably better than that observed for a carrier admixture of phenylboronic acid and benzo-15-crown-5. Facilitated active glucoside transport was achieved from a departure phase containing 0.06 mM glucoside and 500 mM sodium phosphate into a receiving phase containing an equal initial glucoside concentration but only 10 mM sodium phosphate.

Introduction

Currently, there is considerable interest in utilizing the Lewis acid binding properties of organoboron receptor compounds in organic synthesis and molecular recognition. A number of chiral borane, boronate, and borate derivatives have been shown to catalyze a variety of enantioselective cycloaddition, and carbonyl addition reactions.[1] Compounds **1** and **2** (R = H, alkyl, aryl, halogen) are notable examples taken from the work of Corey[2] and Yamamoto.[3] In the field of molecular recognition, organoboron acids and their esters have been examined as Lewis acid recognition motifs for monodentate Lewis bases such as alcohols,[4] amines,[5] and anions,[6] as well as bidentate Lewis bases such as diamines,[7] diols,[8] α-hydroxy acids,[9] and α-amino acids.[10] In particular, air and water stable boronic acids have great promise as chemosensors[11] and carriers for membrane transport.[12]



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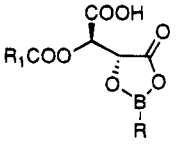

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To date, most Lewis acid catalysts have been prepared by combining an achiral organoboron with a chiral chelating moiety. Compounds **1** and **2**, for example, were prepared by this approach. Future work on organoboron catalysts is likely to focus on improving the substrate binding selectivity. In many cases, this will require the development of more sophisticated receptors. One way is to use more functionalized organoboron groups. The chiral alkyldihaloborane catalysts reported by Hawkins and co-workers[13] and the 1-boracyclopentyls prepared by Reetz[14] are two elegant examples of this approach. This strategy has also been used in molecular recognition. The various diboronic acids introduced by Shinkai and co-workers[15] and the crowned boronate esters reported by Reetz[5,6] are significant contributions. In addition, we and Shinkai have also described crowned boronic acids.[16]

† Dedicated to Professor Koji Nakanishi on the occasion of his 70th birthday.

‡ Molecular recognition with boron acids. 9. Part 8: Steiner, S. J.; Bien, J. T.; Smith, B. D. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2417–2420.

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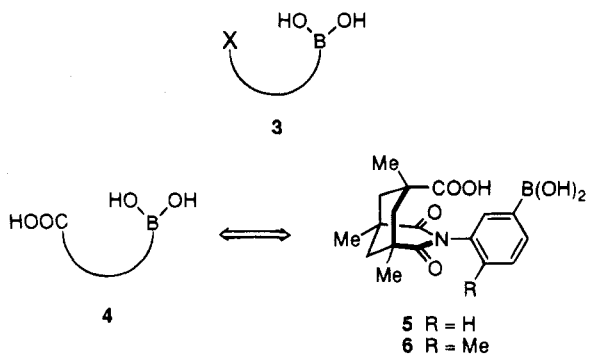
In general, the preparation of multifunctionalized organoboron compounds is not a trivial undertaking. In an effort to expedite the synthetic process we have explored a modular approach. We wished to combine a boronic acid group with a variety of other non-boron recognition functionalities, X, and produce a series of heterotopic receptors of the type shown schematically as **3**. Thus, a versatile U-shaped boronic acid scaffold, **4**, was required which could be conjugated with the various groups X. The design of compound **4** was also influenced by the following factors. (i) Our initial research goal was to produce lipophilic carriers for saccharide membrane transport; thus, arylboronic acids became the boron compounds of choice due to their air/water stability and strong Lewis acidity. (ii) Literature precedence, as well as personal experience, indicated that steric hindrance around the arylboronic acid moiety greatly decreased its diol binding ability. Therefore, the desired compound needed to be a meta-substituted arylboronic acid attached to a rigid U-shaped spacer section that terminated with a functionalizable carboxylic acid residue. The Kemp's triacid system, as exemplified by the work of Rebek, came to mind as the U-shaped spacer.[17] Thus, the boronic clefts, **5** and **6**, became the desired targets.



In the following sections of this paper, we describe the synthesis and structural characterization of receptors **5** and **6**. In addition, we demonstrate how these compounds can be elaborated into more complicated receptors having a variety of possible recognition and catalytic abilities. Specifically, we have conjugated **6** with a crown ether moiety and produced the first example of a new class of artificial sodium saccharide cotransporter.

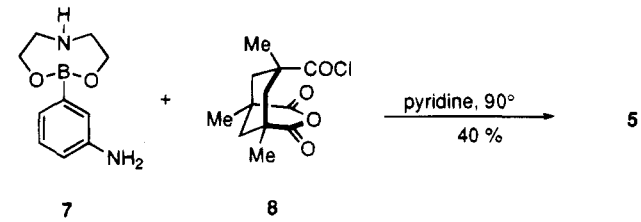
Results and Discussion

Synthesis of the Boronic Acid Cleft. Because of the commercial availability of 3-aminophenylboronic acid, cleft **5** was prepared first. As shown in Scheme 1, (3-aminophenyl)boronic acid diethanolamine ester, **7**, was condensed with Kemp's acid chloride anhydride, **8**, to give cleft **5**.[18] As expected from the work of Rebek, the 300 MHz ^{1}H NMR spectrum of **5** exhibited broadened resonances due to hindered rotation about the C_{aryl}–N bond. Coalescence for this atropisomerism was observed at −5 °C in $CDCl_3$ ($\Delta G^{\ddagger}_{268}$ = 12.7 kcal/mol).[18]

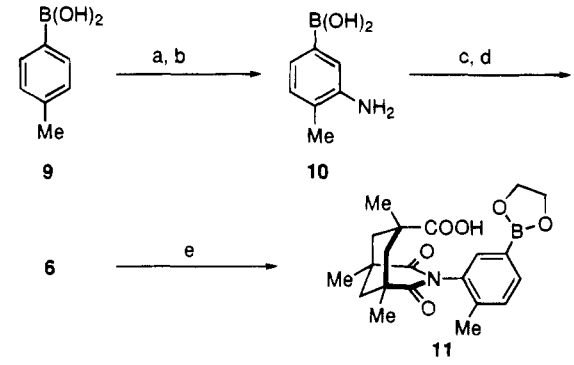
To eliminate this receptor flexibility, the conformationally locked tolyl derivative **6** was prepared by condensing the diethanolamine ester of **10** with **8** (Scheme 2). As expected, the ^{1}H and ^{13}C NMR spectra of **6** exhibited sharp resonances.[18] Compound **6** was converted to its ethylene glycol boronate ester, **11**. Single crystals of **11**, obtained from a toluene solution left standing in a freezer, were analyzed by X-ray crystallography.[19] As shown in Chart 1, the imide group in **11** is fixed in a perpendicular orientation relative to the aryl ring. Due to steric hindrance, the tolyl methyl group points away from the carboxylic acid, forcing the boronate ester into a cleft orientation. The distance between the boron and the carboxyl oxygens is about 5.5 Å. Also shown in Scheme 3 is an adventitious water molecule trapped within the cleft. This host/guest pair packed into the unit cell as a hydrogen-bonded dimer (see supplementary material for an illustration).

Modification of the Boronic Acid Cleft. With cleft **6** in hand, we explored ways of conjugating additional

Scheme 1

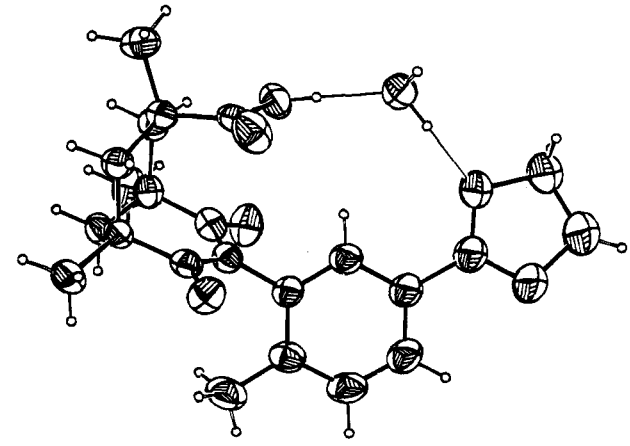


Scheme 2[a]



[a] Key: (a) Fuming nitric acid, 30%; (b) H_2, Pd/C, 76%; (c) diethanolamine, 87%; (d) **8**, pyridine, 90 °C, 80%; (e) ethylene glycol, Dean-Stark, 95%.

Chart 1. ORTEP Diagram of Compound 11



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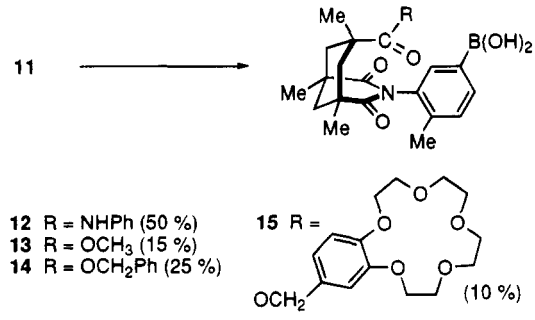
Scheme 3



functionality via the available carboxyl residue. Initial attempts to functionalize **6**, or its boronate ester **11**, by treating the activated carboxyl with nucleophiles were generally unsuccessful. Using forcing conditions, cleavage of the C–B bond was the usual side reaction. In one case, **11** was converted to its corresponding acid chloride and subsequently condensed with aniline to produce **12** in 50% isolated yield (Scheme 3). We found that a more consistent synthetic method was to reverse the polarity of the reaction and treat the carboxylate of **11** with electrophilic reagents. Using this approach, the methyl and benzyl esters **13** and **14** were prepared in low (15–25%) but reproducible yield (Scheme 3).

Crown Boronic Acid as a Sodium Saccharide Cotransporter. Previously, we have described how a boronic acid/ionophore admixture can act as a biomimetic metal cation–saccharide cotransport system.[20a] A logical improvement of this transport system is to covalently connect the boronic acid and the ionophore together, and produce a single heterotopic carrier with cotransport ability. This was achieved when the carboxylate of **11** was treated with 3-(chloromethyl)benzo-15-crown-6[21] to give the crown boronic acid **15** (Scheme 3). Compound **15** was examined as a sodium–glucoside cotransporter through bulk, liquid organic membranes. The transport of *p*-nitrophenyl β-D-glucopyranoside through a dichloroethane layer was monitored via standard U tube transport experiments.[20] Both passive (along a concentration gradient) and active (against a concentration gradient) transport experiments were conducted. The rates of passive transport were determined from the change in glucoside absorption at 302 nm in the receiving phase. The results are described in Table 1, along with some related data from a previous study. At pH 6.3, carrier **15** did not significantly facilitate glucoside transport compared to a control system where the carrier was absent (compare entries 1 and 2). At pH 11.0, transport enhancement increased to five times the background level (compare entries 5 and 6). This enhancement was considerably better than that observed for a carrier admixture of phenylboronic acid and benzo-15-crown-5 (entry 7).

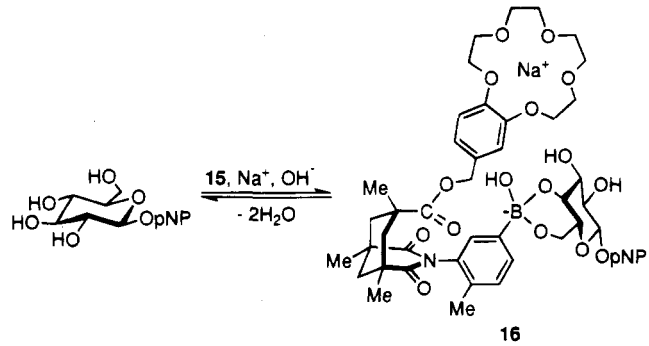
Depending on the experimental conditions boronic acids are known to transport hydrophilic diols via two distinct mechanistic pathways. One mechanism involves the reversible formation of a neutral trigonal boronate ester, whereas the other pathway is via an ion-paired,

Table 1. Rates of *p*-Nitrophenyl β-d-Glucopyranoside Transport

entry	carrier	pH	rate[a] (% extracted)[b]
1	none	6.3	4.5
2	**15**	6.3	6.8 (0.3)
3	phenylboronic acid	7.4	4.0 (0.1)[c]
4	phenylboronic acid, TOMA[d]	7.4	25 (2.0)[c]
5	none	11.0	3.5
6	**15**	11.0	18 (0.5)
7	phenylboronic acid, benzo-15-crown-5	11.0	4.8
8	phenylboronic acid, TOMA[d]	11.4	45 (26)[c]

[a] Rate (10^{-8} M min^{-1} ± 15%) that glucoside initially appeared in receiving phase. Starting conditions were 1.36 mM glucoside in departure phase and 1 mM carrier in the dichloroethane layer. [b] $[\text{Glucoside}]_{\text{extracted into org}}/[\text{glucoside}]_{\text{initially in aq}}$ ± 10%. [c] Taken from ref 20b. [d] Trioctylmethylammonium chloride.

Scheme 4



tetrahedral, "ate" anion.[20] Previous work on glucoside transport using boronic acids has shown that the ion-pair transport pathway is favored over the trigonal ester pathway, particularly when the pH is greater than the pK_a of the boronic acid.[20] The observation that extraction and transport of glucoside, mediated by carrier **15**, increased as the aqueous phase pH increased (compare entries 2 and 6 in Table 1) is strong evidence that the predominant transport mechanism is the ion-pair pathway.[20b] This implies the formation of ion-paired complex **16** and the simultaneous cotransport of both glucoside and Na^+ ion (Scheme 4).[22] We reasoned that if this mechanism was truly operating, then facilitated glucoside transport should be sensitive to Na^+ ion concentration. In particular, active glucoside transport in the direction of a Na^+ concentration gradient should occur. This was indeed the case. Considerable active glucoside transport was achieved with carrier **15** from a departure phase containing 0.06 mM glucoside and 500 mM sodium phosphate into a receiving phase containing an equal initial glucoside concentration but only 10 mM sodium phosphate (both aqueous phases were at pH 11.0). A control experiment showed that in the absence of carrier, approximately six times less active glucoside transport was observed over the same time period.

Glucoside transport through liquid organic membranes has now been examined under a variety of conditions using different boronic acid carrier systems.[20] Thus, an evaluation of the relative transport ability of carrier **15** can be made. To date, transport mediated by boronic acid/ionophore carrier systems has been significantly poorer than transport by boronic acid/quaternary ammonium systems (compare entries 2 and 4, as well as

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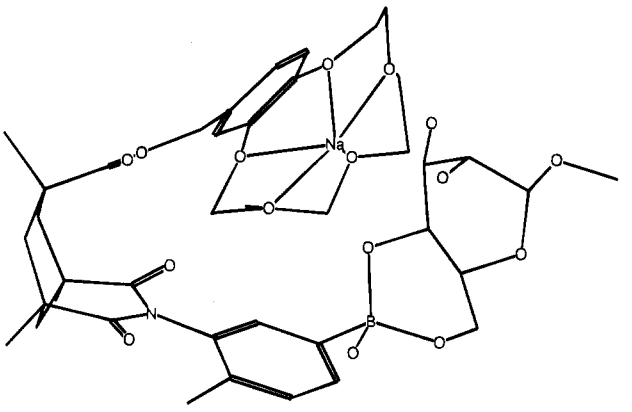

Figure 1. Low-energy conformation for complex **16** with the shortest B–Na^+ distance. For clarity, methyl β-D-glucoside is shown and all hydrogens have been omitted.

entries 6 and 8 in Table 1). This is due to the weaker glycoside extraction ability of the boronic acid/ionophore system which can be attributed to three related factors. (i) A quaternary trioctylmethylammonium cation is a superior phase transfer agent compared to a Na^+/crown complex. (ii) The entropic cost of assembling the saccharide–boronate–ionophore–metal cation complex, **16**, required for transport is higher than that associated with the corresponding saccharide–boronate–quaternary ammonium complex. (iii) The design of carrier **15** is not optimal. A molecular mechanics study of complex **16** indicated a large separation of charge which is likely to inhibit complex extraction. As expected, the modeling suggested a range of low-energy conformations with similar stabilities. The specific conformation shown in Figure 1 had one of the shortest distances between the Na^+ and the anionic boron (9.6 Å). In addition, the oxygens attached to the boron are also well beyond van der Waals contact distances with the Na^+. It appears, however, the Na^+ is capable of coordinating with the 3 or 4 position hydroxyls on the glucoside.

Transport with heterotopic carrier **15** can only occur after both a glucoside molecule and a Na^+ ion bind to the carrier. To increase glucoside transport rates through liquid membranes, both the glucoside and Na^+ extraction abilities need to be increased. There are, however, optimum extraction values to aim for. If extraction becomes greater than these optimum values both passive and active transport rates will begin to decrease.[20b] It should also be noted that although transport is quite low with bulk, liquid membranes, it may not be the case with other types of lipophilic membranes. Recently, we described boronic acid transport systems that completely failed to transport monosaccharides through liquid membranes but, nonetheless, were remarkably efficient transporters across (the much thinner) lipid bilayer membranes.[12a]

Conclusions

1. We have described the sodium–saccharide cotransporter, **15**, as the first example of a new class of heterotopic carrier. As stated previously, this is an artificial but functionally biomimetic cotransport system.[20a] Nature utilizes membrane-bound proteins to cotransport saccharides and sodium ions into cells. The ubiquitous, intracellular-directed sodium concentration gradient acts as an energy source to drive saccharide influx actively. Our eventual aim is to take advantage of this biotic energy source and use artificial cotransporters like compound **15** to not only transport but also concentrate boronic acid-binding drugs such as carbohydrates and nucleosides inside cells. Our recent discovery that boronic acids are able to transport monosaccharides through lipid bilayers augurs well for this research goal.[12a]

2. Carrier **15** was synthesized in a modular fashion, conjugating a crown ether with the boronic acid cleft, **6**. The same methodology can be used to conjugate **6** with other molecular recognition motifs, producing a range of carrier molecules with specifically designed recognition properties.

3. The boronate ester **11** and related derivatives have promise as novel Lewis acid catalysts for a range of organic transformations such as enolizations, carbonyl additions, and pericyclic reactions. Research in these areas is currently in progress.

Experimental Section

General. Unless otherwise noted, all commercial materials were reagent grade quality and were used without further purification. HPLC was conducted on a computer-controlled Waters system using UV detection. Molecular mechanics modeling used the program PC Model.

(3-Aminophenyl)boronic Acid Diethanolamine Ester, 7. (3-Aminophenyl)boronic acid (4.3 mmol) and diethanolamine (4.3 mmol) were combined in benzene (60 mL) and heated at reflux under a nitrogen atmosphere for 12 h in a Dean-Stark apparatus. Evaporation of the benzene afforded a white solid: yield 85–90%; mp 223–225 °C; IR (KBr) 3460, 3360, 3100, 1600, 1430, 1300, 1200 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 7.00 (1H, t, J = 7.5 Hz), 6.93 (1H, s), 6.91 (1H, d, J = 7.5 Hz), 6.63 (1H, d, J = 7.5 Hz), 4.01 (2H, m), 3.88 (2H, m), 3.70 (1H, br s), 3.18 (2H, m), 2.92 (2H, m); ^{13}C NMR (CD_3OD, 75 MHz) δ 147.0, 129.1, 124.2, 121.3, 116.2, 64.3, 51.7; ^{11}B (D_2O/NaOD) δ 11.2; MS (EI) m/z 206.

Acid Chloride Anhydride 8.[18] Kemp's triacid (3.9 mmol) was refluxed in thionyl chloride (20 mL) for 12 h. The thionyl chloride was removed by aspirator. The acid chloride anhydride, **8**, was recrystallized from either dry toluene or dichloromethane: yield 85–90%; IR (KBr) 2960, 2920, 1800, 1450, 1140, 1060, 1000 cm^{-1}.

Phenylboronic Acid Imide 5. (3-Aminophenyl)boronic acid diethanolamine ester, **7** (0.24 mmol), was combined with the acid chloride anhydride **8** (0.24 mmol) in anhydrous pyridine (10 mL) under nitrogen. The mixture was heated at 90 °C for 12 h, after which the pyridine was removed by evaporation. The residue was taken up in ethyl acetate (20 mL) and extracted three times with 20% HCl and once with water (20 mL). The organic phase was dried over Na_2SO_4 and evaporated to afford a solid, which was taken up in dichloromethane. Upon addition of petroleum ether, a solid formed which was collected by vacuum filtration: yield 40%; mp 193–200 °C; IR (mull) 3400, 1700, 1350 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 7.70 (1H, br d), 7.61 (1H, br s), 7.38 (1H, t, J = 7.5 Hz), 7.32 (1H, br s), 2.70 (2H, d, J = 14.5 Hz), 2.20 (1H, d, J = 13.5 Hz), 1.56 (1H, d, J = 13.5 Hz), 1.36 (2H, d, J = 14.5 Hz), 1.28 (9H, s); ^{13}C NMR (CD_3OD, 125 MHz, exchange broadened) δ 179.7, 178.8, 137.0, 134.4, 131.3, 129.1, 44.8, 44.3, 42.9, 41.8, 31.3, 26.3; HRMS (FAB) m/z 416.1847, calcd for $C_{21}H_{27}NO_7B$ [M + 57, trigonal boronate–glycerol ester + H] 416.1881.

4-Toueneboronic Acid, 9. A solution of 4-bromotoluene (146 mmol, vacuum distilled before use) in anhydrous ether (50 mL) was added dropwise to a mixture of anhydrous ether (250 mL), magnesium turnings (292 mmol), and an iodine crystal. Upon cessation of the initial exotherm, the mixture was heated at reflux for 1 h. After cooling, the Grignard reagent was slowly cannulated into a mechanically stirred solution of trimethylborate (292 mmol) in anhydrous ether (100 mL) under nitrogen at −78 °C (acetone/dry ice). The reaction

was allowed to warm to room temperature and stirring continued for a further 12 h. The solution was carefully acidified with 10% HCl (100 mL) and extracted three times with ether. The combined organic layers were dried with $MgSO_4$ and evaporated. The boronic acid **9** was recrystallized from hot H_2O: yield 49%; mp 259–260 °C; IR (KBr) 3300, 1610, 1350, 1090, 1000 cm^{-1}; ^1H NMR (D_2O, NaOD, 300 MHz) δ 7.33 (2H, d, J = 7.5 Hz), 7.02 (2H, d, J = 7.5 Hz), 2.16 (3H, s); ^{13}C NMR (D_2O, NaOD, 5% CD_3OD, 75 MHz) δ 135.9, 132.9, 132.8, 128.6, 21.2; ^{11}B (D_2O/NaOD) δ 2.65; HRMS (FAB) m/z 193.1047 calcd for $C_{10}H_{14}O_3B$ [M + 57, trigonal boronate–glycerol ester + H] 193.1038.

3-Amino-4-tolueneboronic Acid, 10. 4-Tolueneboronic acid (59 mmol) was added over 1.5 h to a mechanically stirred solution of fuming nitric acid (60 mL) at −41 °C (dry ice/acetonitrile). The mixture was stirred for an additional 30 min. The product was precipitated by careful addition of the solution to crushed ice. The precipitate was collected and washed several times with cold water. Recrystallization from hot water to afforded 3-nitro-4-toluneboronic acid as yellow needles (occasionally, a small amount of 2,4-dinitrotoluene was obtained as an undesired byproduct.): yield 30%; mp 260–264 °C; IR (KBr) 3100, 1600, 1530, 1350 cm^{-1}; ^1H NMR (d_6-DMSO, 10% D_2O, 300 MHz) δ 8.30 (1H, s), 7.94 (1H, d, J = 7.5 Hz), 7.44 (1H, d, J = 7.5 Hz), 2.49 (3H, s); ^{13}C NMR (d_6-DMSO, 10% D_2O 125 MHz) δ 149.1, 139.1, 135.0, 132.6, 129.8, 19.9; ^{11}B (D_2O/NaOD) δ 2.10; HRMS (FAB) m/z 238.0889, calcd for $C_{10}H_{13}NO_5B$ [M + 57, trigonal boronate–glycerol ester + H] 238.0889. 3-Nitro-4-toluneboronic acid (21 mmol) in methanol (50 mL) was hydrogenated over catalytic amounts of Pd/C. The reduction was readily monitored by TLC; the product could be identified by its discoloration on the TLC plate. Reaction times varied from 1 to 10 h. Upon completion, the reaction mixture was filtered using a frit/Celite pad (prewashed with methanol). Removal of the methanol by rotary evaporation afforded 3-amino-4-toluneboronic acid, **10**, as a white solid: yield 76%; mp 106 °C dec; IR (KBr) 3350, 1620, 1400, 1350 cm^{-1}; ^1H NMR (D_2O/NaOD, 500 MHz) δ 6.95 (1H, d, J = 7.0 Hz), 6.90 (1H, s), 6.88 (1H, d, J = 7.0 Hz), 2.05 (3H, s); ^{13}C NMR (D_2O, NaOD, d_6-acetone, 125 MHz) δ 142.8, 129.5, 123.2, 121.7, 119.8, 16.4; ^{11}B (D_2O/NaOD) δ 2.55; HRMS (FAB) m/z 208.1139, calcd for $C_{10}H_{15}NO_3B$ [M + 57, trigonal boronate–glycerol ester + H] 208.1147.

Tolylboronic Acid Imide 6. A benzene solution (210 mL) of 3-amino-4-toluneboronic acid, **10** (12.5 mmol), and diethanolamine (12.5 mmol) was heated to reflux for 12 h in a Dean-Stark apparatus. The product, 3-amino-4-toluneboronic acid diethanolamine ester, precipitated and was collected by vacuum filtration: yield 87%; mp 125–127 °C; IR (KBr) 3420, 3350, 3120, 2920, 2860, 1660, 1400, 1270, 1070, 970 cm^{-1}; ^1H NMR (d_6-DMSO, 500 MHz) δ 6.74 (1H, s), 6.72 (1H, d, J = 7.5 Hz), 6.69 (1H, br s), 6.58 (1H, d, J = 7.5 Hz), 4.36 (2H, br s), 3.81 (2H, m), 3.74 (2H, m), 3.01 (2H, m), 2.77 (2H, m), 1.99 (3H, s); ^{13}C NMR (d_6-DMSO, 125 MHz) δ 144.8, 128.4, 121.3, 119.1, 62.8, 50.5, 17.3; ^{11}B (D_2O/NaOD) δ 10.87; HRMS (EI) m/z 220.1402, calcd for $C_{11}H_{17}N_2O_2B$ 220.1383. Using the procedure described for **5**, 3-amino-4-toluneboronic acid diethanolamine ester was condensed with acid chloride anhydride **8** to give **6** as a white solid: yield 80%; mp >260 °C; IR (KBr) 3450, 2960, 1800, 1700, 1499, 1180 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 7.74 (1H, br d), 7.50 (1H, s), 7.24 (1H, d, J = 7.5 Hz), 2.72 (2H, d, J = 14.0 Hz), 2.13 (1H, d, J = 13.5 Hz), 1.95 (3H, s), 1.63 (1H, d, J = 13.5 Hz), 1.38 (2H, d, J = 14.0 Hz), 1.29 (9H, s); ^{13}C NMR (CD_3OD, 125 MHz) δ 179.7, 178.5, 136.0, 134.7, 134.2, 130.9, 44.8, 44.6, 42.9, 42.1, 31.3, 26.2, 17.5; HRMS (FAB) m/z 430.2055, calcd for $C_{22}H_{29}NO_7B$ [M + 57, trigonal boronate–glycerol ester + H] 430.2041.

Tolyldioxaborolane imide 11. Boronic acid **6** (0.09 mmol) and ethylene glycol (0.09 mmol) were combined in benzene (75 mL) and heated at reflux in a Dean-Stark apparatus for 4 h. The benzene was removed by rotary evaporation to afford a solid; yield 95%; mp 124–126 °C; IR (KBr) 3450, 2980, 1730, 1700, 1340, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.66 (1H, d, J = 8.5 Hz), 7.62 (1H, s), 7.24 (1H, d, J = 8.5 Hz), 4.14 (4H, s), 2.85 (2H, d, J = 14.0 Hz), 2.13 (1H, d, J = 13.5 Hz), 1.99 (3H, s), 1.51 (1H, d, J = 13.5 Hz), 1.34 (6H, s), 1.32 (3H, s), 1.26 (2H, d, J = 14.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.6, 176.0, 138.7, 135.1, 133.9, 130.5, 65.9, 44.4, 44.1, 41.6, 40.9, 30.9, 25.9, 17.6; ^{11}B ($CDCl_3$) δ 30.99; HRMS (EI) 399.1874, calcd for $C_{21}H_{26}NO_6B$ 399.1853. Crystal data: $C_{21}H_{28}NO_7B$, M = 417.27, monoclinic $P2_1/c$ (No. 14), a = 11.124(2) Å, b = 12.078(2) Å, c = 16.610(2) Å, β = 97.15(2)°, V = 2214.3Å^3, Z = 4, D_c = 1.252 g/cm^3 (293 K), μ(MoKα) = 0.866 cm^{-1}, 3826 unique reflections, 2157 with $F_o^2 > 3\sigma(F_o)^2$, coordinates of all hydrogen atoms refined, R_1 = 0.039, R_2 = 0.047, gof = 1.48.

Tolylboronic Acid Imide Anilide 12. Dioxaborolane **11** (0.075 mmol), *N,N*-diisopropylethylamine (Hünig's base, 1.6 mmol), and DMF (1 drop) were combined in dry acetonitrile (10 mL). Thionyl chloride (1.6 mmol) was added and the solution stirred overnight. Diisopropylethylamine (1.6 mmol) and aniline (0.075 mmol) were added, and the solution was stirred overnight. The reaction was quenched with 20% HCl (2 mL). Evaporation of the acetonitile resulted in the precipitation of the anilide **12**. The precipitate was collected and dried in vacuo: yield 50%; mp 235–237 °C; ^1H NMR (d_6-DMSO, 10% D_2O, 500 MHz) δ 9.20 (1H, s), 7.72 (2H, d, J = 7.5 Hz), 7.69 (1H, s), 7.54 (1H, d, J = 7.5 Hz), 7.20 (2H, t, J = 7.5 Hz), 7.11 (1H, d, J = 7.5Hz), 6.93 (1H, t, J = 7.5 Hz), 2.77 (2H, d, J = 14 Hz), 2.06 (1H, d, J = 13.5 Hz), 1.84 (3H, s), 1.62 (1H, d, J = 13.5 Hz), 1.39 (2H, d, J = 14 Hz), 1.28 (3H, s), 1.22 (6H, s); ^{13}C NMR (d_6-DMSO, 10% D_2O, 125 MHz, quaternary signals absent) δ 176.6, 176.1, 160.9, 135.1, 129.0, 128.5, 122.9, 119.9, 43.2, 42.7, 31.1, 26.2, 17.2; HRMS (FAB) m/z 505.2501, calcd for $C_{28}H_{34}N_2O_6B$ [M+57, trigonal boronate–glycerol ester + H] 505.2515.

Tolylboronic Acid Imide Methyl Ester 13. Dioxaborolane **11** (0.25 mmol), trimethyloxonium tetrafluoroborate (0.27 mmol), and *N,N*-diisopropylethylamine (Hünig's base, 0.25 mmol) were combined in dichloromethane (10 mL) and stirred overnight. Dichloromethane (30 mL) was added and the solution extracted with 10% HCl solution (the organic layer was filtered after the first extraction), saturated $NaHCO_3$, and brine. The product **13** was obtained as a white powder: yield 15%; HRMS (FAB) m/z 444.2195, calcd for $C_{23}H_{31}NO_7B$ [M + 57, trigonal boronate–glycerol ester + H] 444.2194. Compound **13** was converted to the corresponding 1,3,2-dioxaborolane by esterification with ethylene glycol using a Dean-Stark apparatus: yield 95%; mp 222–224 °C; IR (mull) 3020, 1730, 1680, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.66 (1H, d, J = 7.5 Hz), 7.64 (1H, s), 7.23 (1H, d, J = 7.5 Hz), 4.31 (4H, s), 3.76 (3H, s), 2.88 (2H, d, J = 14.0 Hz), 2.12 (1H, d, J = 13.0 Hz), 1.99 (3H, s), 1.49 (1H, d, J = 13.0 Hz), 1.33 (6H, s), 1.28 (3H, s), 1.26 (2H, d, J = 14.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.2, 175.9, 138.0, 135.0, 134.7, 130.4, 66.0, 52.8, 44.4, 44.1, 42.2, 40.9, 31.0, 26.1, 17.6; HRMS (EI) m/z 413.2008, calcd for $C_{22}H_{28}NO_6B$ 413.2009.

Tolylboronic Acid Imide Benzyl Ester 14. Dioxaborolane **11** (0.075 mmol), *N,N*-diisopropylethylamine (Hünig's base, 0.83 mmol), and benzyl bromide (0.30 mmol) were combined in dry DMF (10 mL) under nitrogen and heated to 90 °C overnight. The DMF was evaporated and the residue taken up in ethyl acetate (40 mL) and washed with 10% HCl (2 × 20 mL), H_2O (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4 and evaporated to affored a tan residue. Purification by C18 reversed-phase HPLC (7.8 × 300 mm bondapak column) using water/methanol (30:70, 2 mL/min) afforded **14** (retention time = 13.6 min) as a tan residue. The compound could be precipitated as a solid using dichloromethane/petroleum ether: yield 25%; mp 133–140 °C; ^1H NMR (d_6-acetone, 10% D_2O, 300 MHz) δ 7.78 (1H, s), 7.72 (1H, d, J = 8 Hz), 7.33 (5H, m), 7.21 (1H, d, J = 8 Hz), 5.25 (3H, s), 2.74 (2H, d, J = 13.5 Hz), 2.18 (1H, d, J = 13 Hz), 1.96 (3H, s), 1.67 (1H, d, J = 13 Hz), 1.42 (2H, d, J = 13.5 Hz), 1.27 (6H, s), 1.21 (3H, s); ^{13}C NMR (d_6-acetone, 10% D_2O, 125 MHz) δ 176.6, 176.3, 137.9, 137.2, 136.3, 135.8, 134.4, 130.3, 129.1, 129.0, 128.8, 67.9, 44.1, 42.8, 41.5, 31.1, 26.2, 17.6; HRMS (FAB) m/z 520.2512, calcd for $C_{29}H_{35}NO_7B$ [M + 57, trigonal boronate–glycerol ester + H] 520.2513.

Tolylboronic Acid Imide Methylbenzo-15-crown-5 Ester 15. Dioxaborolane **11** (0.30 mmol), *N,N*-diisopropylethylamine (Hünig's base, 0.33 mmol), and 3-(chloromethyl)benzo-

15-crown-6[21] (0.30 mmol) were combined in dry DMF (10 mL) under nitrogen and heated to 90 °C overnight. The DMF was evaporated and the residue taken up in ethyl acetate (40mL) and washed with 10% HCl (2 × 20mL), H_2O (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4 and evaporated to afforded a tan residue. Purification by column chromatography (neutral alumina) using dichloromethane/methanol (25:1) afforded **15** (R_f = 0.55) as a tan residue. The compound could be precipitated as a solid using dichloromethane/petroleum ether: yield 10%; ^{1}H NMR (d_6-acetone, 10% D_2O, 500 MHz) δ 7.78 (1H, s), 7.72 (1H, d, J = 7.5 Hz), 7.22 (1H, d, J = 7.5 Hz), 6.86 (1H, s), 6.84 (2H, d, J = 8.5 Hz), 5.16 (2H, s), 4.07 (2H, m), 3.90 (2H, m), 3.81 (2H, m), 3.73 (2H, m), 3.64 (8H, m), 2.73 (2H, d, J = 14 Hz), 2.18 (1H, d, J = 13 Hz), 1.96 (3H, s), 1.66 (1H, d, J = 13 Hz), 1.41 (2H, d, J = 14 Hz), 1.26 (6H, s), 1.21 (3H, s); ^{13}C NMR (d_6-acetone, 10% D_2O, 75 MHz) δ 176.6, 176.4, 149.8, 137.0, 136.3, 135.8, 134.4, 130.3, 129.9, 122.2, 115.2, 114.2, 71.8, 71.7, 71.2, 71.1, 70.1, 70.0, 69.8, 69.2, 68.2, 44.1, 44.0, 42.8, 41.5, 31.3, 26.3, 17.6; HRMS (FAB) m/z 732.3174, calcd for $C_{37}H_{49}NO_{12}B$ [M + 79, trigonal boronate–glycerol ester + Na] 732.3190.

Transport and Extractions. The transport and extraction experiments reported in Table 1 used the same apparatus and procedures described previously.[20c] Nonetheless, transport rates in this study were slightly faster than identical runs made in the previous work; the difference was attributable to slight changes in operator technique. The dimensions of the U tubes were as follows: internal diameter 1.20 cm, height 10 cm, and 2.5 cm between the arms. Both aqueous phases were 3.5 mL, and the organic layer was 7.0 mL. Only the organic layer was stirred (475 ± 15 rpm, determined using a stroboscope). Starting concentrations for passive transport experiments were as follows: departure phase, 1.36 mM glucoside in 10 mM sodium phosphate buffer; organic layer, 1 mM of carrier in dichloroethane; receiving phase, 10 mM sodium phosphate buffer. The rates of passive transport were determined from the change in glucoside UV absorption (λ_{max} = 302 nm, ϵ = 9800 M^{-1} cm^{-1}) in the receiving phase. Control experiments without added glucoside confirmed that the increase in absorption was not due to decomposition of the carrier. In fact, the carrier was stable enough for recycling. Starting conditions for the active transport experiments were as follows: departure phase, 0.06 mM glucoside in 500 mM sodium phosphate buffer, pH 11.0; organic layer, 1 mM of carrier in dichloroethane; receiving phase, 10 mM sodium phosphate buffer, pH 11.0. All experiments were reproduced at least in duplicate. The reproducibility of observed transport rates was always less than 20% and usually less than 10%. Reproducibility of the extractions was ±10%.

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Supplementary Material Available: ^{1}H NMR spectra of **12–15**; ORTEP diagram of **11**/water complex showing dimerized packing arrangement (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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