Regiospecific Glycosidation of Unprotected Sugars via Arylboronic Activation

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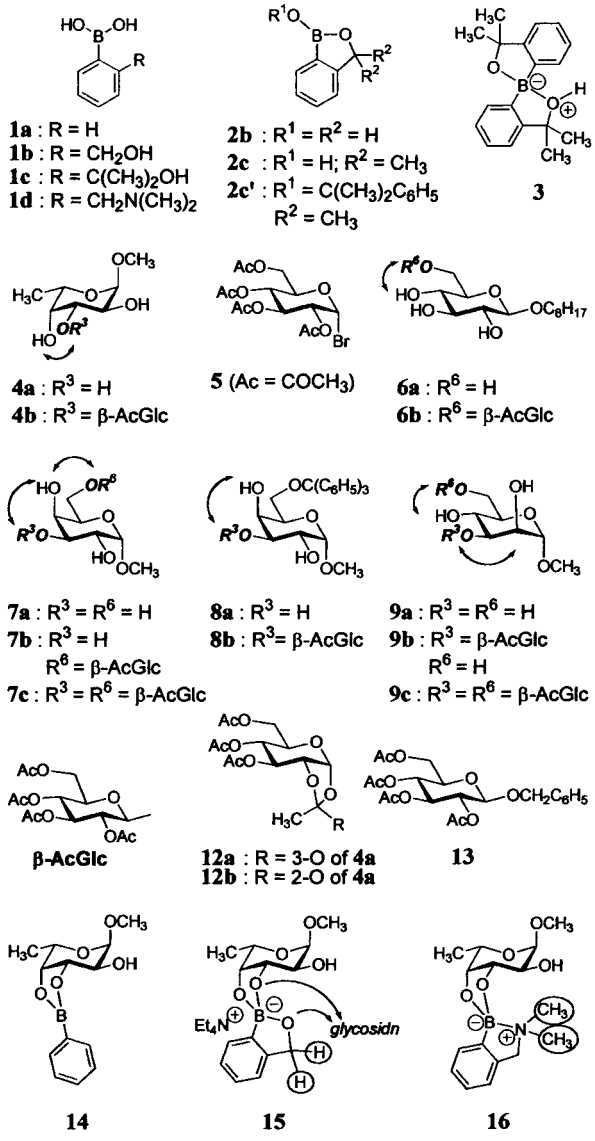
Selective functionalization (glycosidation) of sugars has so far been mostly based on tedious multistep protection/deprotection procedures, which essentially rely on selective *deactivation* of all but one OH group.[1] A potential alternative approach would involve complexation-induced *activation*, e.g., deprotonation, of a particular OH group. This is illustrated by the successful use of Sn reagents[2] in the selective alkylation,[3] acylation,[4] and sulfation[5] of unprotected sugars. To the best of our knowledge, however, the Sn-promoted glycosidation has so far been applied only to appropriately protected sugars.[6]

We are interested in the use of phenylboronic acid (**1a**, Chart 1).[7] It readily forms sugar complexes,[8] but its synthetic utility even as a protective group has been very limited.[9] We thought that the otherwise inert B−O bond might be activated (N + B−O → N^+−B···O^-) by the action of a base (N). The use of triethylamine, in fact, led to a highly regioselective alkylation, but never glycosidation, of fucoside.[7] The present work concerns intramolecular OH activation. We report here that the choice of the 2-hydroxy-2-propyl group at the ortho position as a moderately hindered intramolecular base allows direct and regiospecific glycosidation of unprotected sugars.

An attempted preparation of 2-(2-hydroxy-2-propyl)phenylboronic acid (**1c**), actually in the dehydration-cyclized form **2c**, afforded (Supporting Information) a diarylborinic acid derivative **3** (Chart 1), which turned out to be an excellent promoter of the desired reaction. Methyl α-L-fucoside (**4a**), for example, was glycosidated with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**5**; **5**/**4a** = 1.1) as a glycosyl donor in THF exclusively at the 3-position in *β* stereochemistry in the presence of the promoter **3**, $Et_4N^+I^-$, Ag_2CO_3, and molecular sieves (MS) 4 Å to give disaccharide **4b** (Scheme 1) in a 74% isolated yield[10] as the sole glycosidation product together with recovered glycosyl acceptor **4a** (24%) (Table 1, entry 1). The yield of **4b** was increased up to 93% at **5**/**4a** = 3.5 (entry 2). The silver salt and the quaternary ammonium salt $R_4N^+X^-$ with decreasing efficiencies X = I > Br ≅ Cl > F were essential; only ortho ester **12a** was obtained in the absence of the latter (refer to structure $\mathbf{5}^+$ in Scheme 1).

Chart 1



Control runs reveal the following elementary processes (Scheme 1). (1) In the presence of Ag_2CO_3, borinate **3** in THF undergoes facile intramolecular protonolysis of the B−C bond to give the dimethylbenzyl derivative (**2c′**, $\delta_B = 11$)[11] of the targeted cyclized boronate **2c**. (2) Upon treatment with fucoside **4a** in THF in the presence of $Et_4N^+I^-$ and MS 4 Å, boronate **2c′** thus formed and freed from the silver salt readily undergoes an alcohol/sugar exchange to give the sugar 3,4-boronate complex, or boron−acetal

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(10) All of the glycosidation products in an analytical purity were isolated by chromatography on silica and assigned as such or after further conversion to peracetylated derivatives on the basis of $^1H-^1H$ and $^1H-^{13}C$ COSY spectra.

(11) It is well-known (e.g., Oshima, K.; Toi, H.; Aoyama, Y. *Carbohydr. Lett.* **1995**, *1*, 223−230) that the ^{11}B NMR chemical shifts (δ_B) for arylboronic acid derivatives depend on coordination numbers and are around 10 and −10 ppm for tricoordinated sp^2 and tetracoordinated sp^3 species, respectively.

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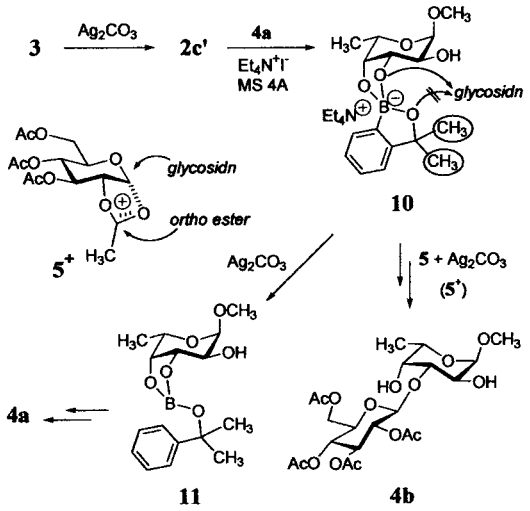
Table 1. Glycosidation of Various Acceptors (A) with Donor **5**[a]

entry	A	**5**/A	products (%)[b]		recovered A (%)[c]
1	**4a**	1.1	**4b** (74)		**4a** (24)
2	**4a**	3.5	**4b** (93)		**4a** (~0)
3	**6a**[d]	1.1	**6b** (15)		**6a** (71)
4	**6a**[d]	3.5	**6b** (24)		**6a** (nd)[e]
5	**7a**	1.1	**7b** (35)	**7c** (19)	**7a** (41)
6	**7a**	2.1	**7b** (29)	**7c** (46)	**7a** (20)
7	**7a**	7.1	**7b** (<1)	**7c** (84)	**7a** (~0)
8	**8a**	1.1	**8b** (41)		**8a** (54)
9	**8a**	3.5	**8b** (91)		**8a** (~0)
10	**9a**	1.1	**9b** (32)	**9c** (12)	**9a** (47)
11	**9a**	2.1	**9b** (26)	**9c** (44)	**9a** (23)
12	**9a**	7.1	**9b** (9)	**9c** (84)	**9a** (~0)

[a] A (0.42 mmol), $Et_4N^+I^-$ (0.48 mmol), and MS 4A (1.5 g) in THF (20 mL) at 50 °C for 20−48 h with a molar ratio of A:**3**:**5**:Ag_2CO_3 = 1:1.1:1.1:1.2 for entries 1, 3, 5, 8, and 10; 1:2.1:2.1:2.1 for entries 6 and 11; 1:1.1:3.5:1.2 for entries 2, 4, and 9; or 1:2.1:7.1:2.1 for entries 7 and 12. [b] Isolated yields. [c] Isolated yields (for **6a** and **8a**) or analytical (HPLC) yields for **4a**, **7a**, and **9a**. [d] Complexation-independent reaction occurs only in this case to give a very small amount of 2-*O*-glycosidated product. [e] Not determined.

Scheme 1



10 having a tetracoordinated (sp^3) boron center ($\delta_B = -8$).[11] (3) Addition of the glycosyl donor **5** and Ag_2CO_3 to the above mixture affords disaccharide **4b** and the starting acceptor **4a** in a ratio which depends on the amount of donor **5** used. (4) Hydrolysis of benzyl boronate **2c′** gives rise to the target compound **2c** (Supporting Information) ($\delta_B = 12$),[11] which is also effective in the regiospecific conversion of fucoside **4a** to disaccharide **4b**.

Another set of control runs reveals the roles of respective functional moieties. (5) Phenylboronic acid (**1a**) forms the corresponding 3,4-boronate (**14**, $\delta_B = 13$),[11] which is mostly recovered unreacted under the present conditions. This indicates that the intramolecular coordination on boron of the ortho substituent in the key sugar complex **10** (Scheme 1) is essential for the activation of the 3-O nucleophile. (6) The use of the hydroxymethyl derivative **1b** in the cyclized form **2b**[12] led to the formation of disaccharide **4b** (10%) at **5**/**4a** = 1.1. In this case, however, glycosidation to a significant extent (10%) also occurs not unexpectedly at the coordinating benzyl oxygen site (structure **15**), giving rise to benzyl glycoside (**13**) upon subsequent protonolysis of the B−C bond. These results reveal the role of the two vicinal methyl groups in promoter **3**; they block the coordinating oxygen atom and prevent it from undergoing glycosidation reactions on itself (structure **10** in Scheme 1). (7) *N*,*N*-dimethylaminomethyl derivative **1d**[13] ($\delta_B = -9$)[11] forms a tetracoordinated boronate, or boron−acetal **16** ($\delta_B = -5$),[11] which is nonreactive under the conditions. In this case, the two methyl groups on the coordinating nitrogen are apparently so close to the reaction center that glycosidation is completely inhibited.[14]

The present method (**3**/**5**/Ag_2CO_3/$Et_4N^+I^-$/MS in THF) is also applicable to other alkyl glycosides (Table 1).[10] Octyl β-glucoside (**6a**) is glycosidated at 6-O to give **6b**. Methyl α-galactoside (**7a**) gives rise to 6-*O*-monoglycosidated disaccharide **7b** and 3,6-*O*,*O*-diglycosidated trisaccharide **7c**. When a 6-trityl derivative **8a** is used, exclusive reaction occurs at 3-O to give **8b**. Methyl α-mannoside (**9a**), on the other hand, affords a mixture of 3-mono- and 3,6-disubstituted products **9b** and **9c**. As suggested above in item 3, the desired glycosidation is in competition with the Ag^+-assisted nonproductive B−C bond cleavage in the key intermediate (**10** in Scheme 1) to give borate **11** as a protected form of the starting acceptor. Thus, in reference to Table 1, the total glycosidation yields, although not very high and acceptor-dependent at a stoichiometric donor/acceptor ratio **5**/A = 1.1 or 2.1 (entries 1, 3, 5, 6, 8, 10, and 11), can be enhanced up to ≥84% simply at a higher donor excess (entries 2, 7, 9, and 12) except for one notable case of the least reactive glucoside **6a** (entry 4). In this way, selective one-pot synthesis of trisaccharides **7c** and **9c** becomes feasible (entries 7 and 12), although that of precursor disaccharides **7b** and **9b** cannot be achieved (entries 5 and 6 and 10 and 11).

The observed regiospecificity is readily understood on the basis that (1) the site of boronate formation in the present substrates (**4a** and **6a**−**9a**) is a cis vicinal diol moiety or a 1,3-diol involving an exocyclic 6-OH, as shown by arrows in Chart 1 (R^3, R^6 = H) and (2) reaction occurs at the less hindered B−O moiety (i.e., primary > secondary and equatorial > axial) in the resulting boronate. The sites (OH) of glycosidation expected along these lines, shown in bold italic letters, are exactly where the reactions take place.

In summary, **1c**-related boronic (borinic) acid derivatives **3** (**2c** or **2c′**) allow selective and direct glycosidation at the 3- and/or 6-positions of glucoside, galactoside, mannoside, and fucoside, which are all important constituents of naturally occurring oligosaccharides. This is due to a remarkable cooperation of selective complexation, intramolecular activation, and steric manipulation, thus converting an otherwise protective boron cap into an activator. The present work may thus open a hitherto-unexplored route to oligosaccharides without involving protection/deprotection procedures. Further work is now under way to apply the present method to various glycosyl donors under milder donor-activation conditions and also to find out the method of 4-O activation in 3,4- and 4,6-boronates.

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Supporting Information Available: Preparation of compounds **3** and **2c**, typical glycosidation procedure, and Chart 2 (structural formulas with TLC R_f values) and Tables 2 (^{1}H NMR data), 3 (^{13}C NMR data), and 4 (elemental analysis and HRMS data) for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) When the strong activator $AgClO_4$ is used, the less hindered remote 2-O reacts with 5^+ to give ortho ester **12b**.