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Regioselective Alkylation of Carbohydrate Derivatives Catalyzed by a Diarylborinic Acid Derivative

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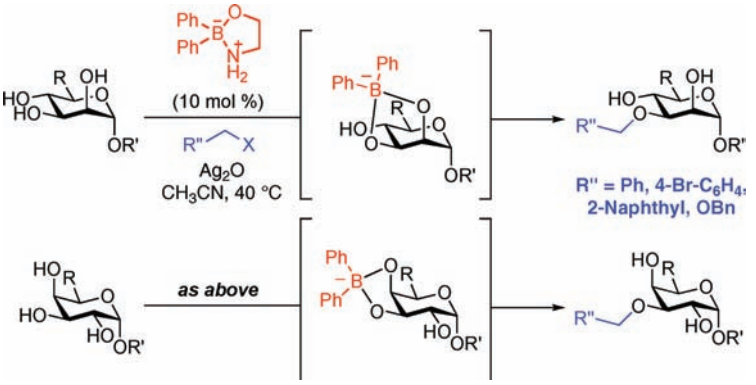
ABSTRACT



Regioselective, catalyst-controlled monoalkylations of cis-vicinal diol motifs in carbohydrate derivatives, using a diphenylborinic ester precatalyst, are described. Selective installation of benzyl, naphthylmethyl, 4-bromobenzyl and benzyloxymethyl protective groups at a single secondary hydroxy group of ten representative carbohydrate derivatives illustrates the scope of this method. This new mode of catalytic reactivity represents an operationally simple method to access useful monoalkylated building blocks while avoiding the use of stoichiometric quantities of organotin reagents.

The laboratory synthesis of oligosaccharides has been pursued for decades as a means to access new therapeutic agents and probes of biological function.[1] Crucial to such efforts are reactions that provide access to selectively protected monosaccharide building blocks for use in glycosylation reactions. Benzyl ethers and their variants are 'workhorse' protective groups in this regard, due to their favorable stability profiles, low propensities for migration, and ease of removal under mild reaction conditions.[2] Herein, we describe the regioselective alkylation of carbohydrates bearing multiple secondary hydroxy groups using a commercially available organoboron catalyst. This method enables the selective introduction of benzyl, 4-bromobenzyl, naphthylmethyl, and benzyloxymethyl protective groups to a wide range of monosaccharides, with reliable selectivity for monoalkylation at the equatorial hydroxy groups of *cis*-vicinal diol motifs.

Several methods exist for selective installation of benzyl and substituted benzyl ether groups;[3] complementary approaches based on regioselective cleavage of ether protective groups have also been developed.[4] Selective alkylation of the most acidic hydroxy group (usually at C-2) may be achieved in certain cases, with varying degrees of efficiency.[5] Reductive cleavage of benzylidene acetals

(1) (a) Varki, A.; Cummings, R. D.; Esko, J. D.; Freeze, H. H.; Stanley, P.; Bertozzi, C. R.; Hart, G. W.; Etzler, M. E. *Essentials of Glycobiology*, 2nd ed.; Cold Spring Harbor Press: New York, 2009. (b) Boltje, T. J.; Buskas, T.; Boons, G.-J. *Nature Chem.* **2009**, *1*, 611–622. (c) Seeberger, P. H.; Werz, D. B. *Nature* **2007**, *446*, 1046–1051.

(2) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; John Wiley & Sons, Inc.: NJ, 2007.

(3) Gómez, A. M. In *Glycoscience*; Fraser-Reid, B., Tatsuka, K., Thiem, J., Eds.; Springer-Verlag: Berlin, 2008; pp 103−177.

(4) For recent examples, see: (a) Lewis, J. C.; Bastian, S.; Bennett, C. S.; Fu, Y.; Mitsuda, Y.; Chen, M. M.; Greenberg, W. A.; Wong, C.-H. Arnold, F. H. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 16550–16555. (b) Yin, Z.-J.; Wang, B.; Li, Y.-B.; Meng, X.-B.; Li, Z.-J. *Org. Lett.* **2010**, *12*, 536–539.

(5) For a review, see: Garegg, P. J. *Pure Appl. Chem.* **1984**, *56*, 845–858.

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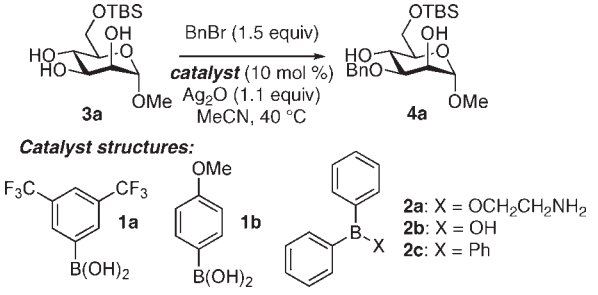
represents a general, two-step protocol for the introduction of benzyl groups at O-4 or O-6 of the pyranosides.[5] Reagents capable of promoting regioselective alkylation of sugars bearing multiple hydroxy groups have been developed, including tin(IV), copper(II), mercury(II) and nickel(II)-based complexes.[6] The most widely applied of these methods involve the use of stannylene acetals or stannyl ethers.[7] These protocols generally require the generation and isolation of the stannylated species prior to alkylation, and result in a stoichiometric amount of potentially toxic di- or trialkyltin(IV) byproducts that must be separated from the desired product.[8] Achieving *catalyst*-controlled variants of these reactions – ideally, with promoters having a safety profile more favorable than those of organotin compounds – would represent a significant advance.

Our efforts to develop an organoboron-catalyzed regioselective alkylation of sugars draw on studies by Aoyama and co-workers in which 3,4-boronate esters derived from phenylboronic acid and fucose or arabinose were alkylated at O-3 by 1-iodobutane in the presence of triethylamine and Ag_2O.[9] An 'ate' complex generated from the boronate ester and amine was proposed to undergo selective alkylation at the equatorial B–O bond. Boric acid ($B(OH)_3$, in catalytic quantities) is also known to influence the regioselectivity of methylation of pyranose sugars with diazomethane, although these reactions are variable in yield and usually result in multiple products.[10] We have recently discovered that derivatives of diphenylborinic acid (Ph_2BOH) catalyze the selective monoacylation of the equatorial hydroxy groups of *cis*-vicinal diol motifs in a wide range of carbohydrate derivatives.[11] Tetracoordinate borinic acid–carbohydrate adducts, generated by reversible covalent B–O interactions, were proposed as catalyst-substrate complexes based on data from competition experiments and computational studies. We sought to determine whether a similar mode of reactivity could be employed to achieve catalyst-controlled, regioselective monoalkylation of sugars bearing multiple secondary hydroxy groups.

Representative boron reagents were evaluated as catalysts for the monobenzylation of mannose derivative **3a** (Table 1). In the absence of catalyst, only trace amounts of 3-OBn derivative **4a** were observed: recovered starting material was the predominant component of the crude reaction mixture. Boric acid and phenylboronic acid promoted the formation of **4a** in moderate yields, along with other alkylated byproducts. The yield of **4a** was not improved by modification of the electronic properties of the arylboronic acid (catalysts **1a**–**1b**: entries 5 and 7). In contrast to the observations of Aoyama and co-workers in the context of preformed boronate esters,[9a] the addition of triethylamine suppressed the formation of **4a** (entries 4, 6 and 8). Diphenylborinate ester **2a**, the optimal precatalyst identified for the regioselective acylation of carbohydrates in our previous work, promoted high-yielding monoalkylation of **3a** at the 3-OH group (entry 9). The formation of 2-(dibenzylamino)ethanol from **2a**, benzyl bromide and Ag_2O under the reaction conditions, and the

Table 1. Evaluation of Catalysts for Regioselective Alkylation of Mannose Derivative **3a**



entry	catalyst	yield (%)[a]
1	None	<5
2	$B(OH)_3$	50
3	$PhB(OH)_2$	55
4	$PhB(OH)_2$[b]	<5
5	**1a**	55
6	**1a**[b]	<5
7	**1b**	55
8	**1b**[b]	<5
9	**2a**	90
10	**2b**	95
11	**2c**	50

[a] Yield of **3a** determined by ^1H NMR with mesitylene as a quantitative internal standard. [b] Reaction carried out in the presence of triethylamine (1.1 equiv).

fact that diphenylborinic acid also serves as a catalyst for this reaction (entry 10), suggests that **2a** is a precatalyst from which the ethanolamine ligand is alkylated prior to displacement by carbohydrate substrate. Oxidation of triphenylborane (**2c**) to **2b**, either by adventitious oxygen or by Ag_2O, may be responsible for the moderate degree of catalyst activity observed with the former (entry 11). The efficiency of the alkylation is dependent on the halide-abstracting Ag(I) salt employed: Ag_2CO_3, AgOAc and AgOTf (with *i*-Pr_2NEt to sequester the generated triflic acid) provided inferior results. Attempts to activate the alkyl halide by addition of iodide salts (in conjunction with Brønsted bases) rather than Ag(I) reagents resulted in low reactivity. Acetonitrile was identified as the optimal

(6) (a) Eby, R.; Webster, K. T.; Schuerch, C. *Carbohydr. Res.* **1984**, *129*, 111–120. (b) Osborn, H. M. I.; Brome, V. A.; Harwood, L. M.; Suthers, W. G. *Carbohydr. Res.* **2001**, *332*, 157–166. (c) Gangadharmath, U. B.; Demchenko, A. V. *Synlett* **2004**, *12*, 2191–2193.

(7) For a review, see: David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643–663.

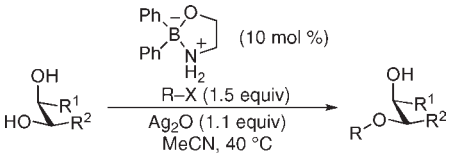
(8) Boons, G.-J.; Castle, G. H.; Clase, J. A.; Grice, P.; Ley, S. V.; Pinel, C. *Synlett* **1993**, 913–914.

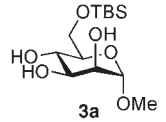
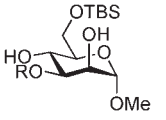
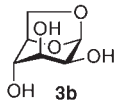
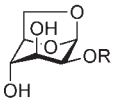
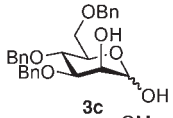
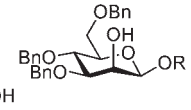
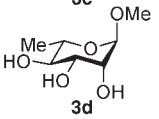
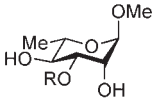
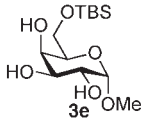
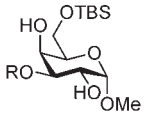
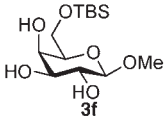
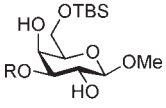
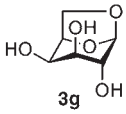
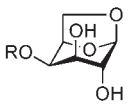
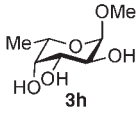
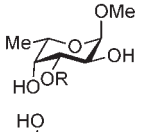
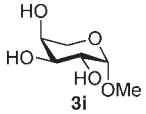
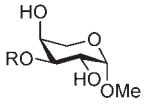
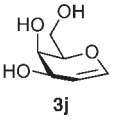
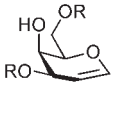
(9) (a) Oshima, K.; Kitazono, E.-i.; Aoyama, Y. *Tetrahedron Lett.* **1997**, *38*, 5001–5004. This work was later extended to include regioselective glycosylation:(b) Oshima, K.; Aoyama, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2315–2316.

(10) Evtushenko, E. V. *Carbohydr. Res.* **1999**, *316*, 187–200.

(11) Lee, D.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 3724–3727.

Table 2. Diphenylborinate-Catalyzed Regioselective Alkylation of Monosaccharides **3a**–**3j**



entry	substrate	product		yield (%)[a]
1	 **3a**		**4a** (R = Bn)	91
2			**5a** (R = 4-BrBn)	99
3			**6a** (R = Nap)	89
4			**7a** (R = BOM)	84
5	 **3b**		**4b** (R = Bn)	73
6			**5b** (R = 4-BrBn)	73
7			**6b** (R = Nap)	71
8			**7b** (R = BOM)	63
9	 **3c**		**4c** (R = Bn)	72
10	 **3d**		**4d** (R = Bn)	83
11			**5d** (R = 4-BrBn)	73
12			**6d** (R = Nap)	99
13			**7d** (R = BOM)	83
14	 **3e**		**4e** (R = Bn)	77
15			**5e** (R = 4-BrBn)	95
16			**6e** (R = Nap)	82
17			**7e** (R = BOM)	90
18	 **3f**		**4f** (R = Bn)	74
19			**5f** (R = 4-BrBn)	91
20			**6f** (R = Nap)	99
21			**7f** (R = BOM)	88
22	 **3g**		**4g** (R = Bn)	76
23			**5g** (R = 4-BrBn)	72
24			**6g** (R = Nap)	74
25			**7g** (R = BOM)	66
26	 **3h**		**4h** (R = Bn)	94
27			**5h** (R = 4-BrBn)	89
28			**6h** (R = Nap)	86
29			**7h** (R = BOM)	98
30	 **3i**		**4i** (R = Bn)	74
31			**5i** (R = 4-BrBn)	84
32			**6i** (R = Nap)	71
33			**7i** (R = BOM)	82
34	 **3j**		**5j** (R = 4-BrBn)	77[b]

[a] Isolated yield on 0.2–1.0 mmol scale. X = Br for installation of the Bn, 4-BrBn, and Nap groups; X = Cl for installation of the BOM group. [b] 2.5 equiv of 4-BrBnBr and 2.1 equiv of Ag_2O were employed.

reaction solvent: details of the optimization are provided in the Supporting Information.

A preliminary investigation of the scope of the catalytic process was undertaken using ten carbohydrate substrates derived from mannose (**3a**–**3c**), rhamnose (**3d**), galactose (**3e**–**3g**, **3j**), fucose (**3h**) and arabinose (**3i**), each containing a *cis*-diol motif (Table 2). Four alkylating agents were employed, resulting in the installation of the benzyl (Bn, **4a**–**4i**), 4-bromobenzyl (4-BrBn, **5a**–**5j**),[12] 2-naphthylmethyl (Nap, **6a**–**6i**)[13] and (benzyloxy)methyl (BOM, **7a**–**7i**) ether protective groups.

The results of Table 2 indicate that borinic ester catalysis enables reliable and high-yielding alkylation of the equatorial OH groups of *cis*-diol pairs. The method is tolerant of variation of the stereochemistry of the anomeric position (**3e** vs **3f**) and, in the *galacto* series, a sterically hindered substituent at C-5 is not essential for obtaining high regioselectivity (galactose derivative **3e** vs fucose and arabinose derivatives **3h**, **3i**). The 1,6-anhydro derivatives of mannose (**3b**) and galactose (**3g**), in which the pyranose ring adopts the $^1C_4$ (rather than the usual $^4C_1$) conformation, underwent alkylation at O-2 and O-4, respectively, complementary regiochemical outcomes to those achieved with **3a** and **3e**. Tribenzylated substrate **3c** underwent selective alkylation at O-1, delivering the challenging β-mannosyl stereochemical outcome at the anomeric position. Selective protections of the type shown in Table 2 have previously required the use of stoichiometric amounts of organotin reagents in the two-step protocols described above.[7]

Limitations of the current protocol include sugars that do not contain a *cis*-vicinal diol motif, such as glucose or xylose derivatives, which do not yield products of monoalkylation under the optimized reaction conditions. Protection of the 6-hydroxy group in the *manno* and *galacto* series is necessary to achieve efficient catalyst-controlled alkylation: for example, using methyl α-galactopyranoside as a substrate resulted in the formation of a complex mixture, presumably due to competitive binding of the boron catalyst to the 4,6- and 3,4-diol groups. However, D-galactal (**3j**) underwent selective dialkylation at O-3 and O-6 in the presence of the borinate ester catalyst (entry 34). The use of activated (benzylic or alkoxymethyl) halides seems to be essential for high reactivity with this catalyst system: neither iodomethane nor bromobutane resulted in alkylation under the conditions shown in Table 2.

Our working mechanistic model for the regioselectivity observed in the acylation and alkylation reactions involves the formation of tetracoordinate borinate complexes of *cis*-diol motifs (Figure 1). Previous computational studies from our group suggested an electronic basis for the observed selectivity: the highest values of the condensed Fukui indices f^- for nucleophilic reactivity[14] were observed at O-3 for borinate esters derived from representative substrates in both the *manno* and *galacto* series (**3d** and **3h**).[11] Calculations of this type (DFT, B3LYP/6-311+G(d,p)) modeling the adducts of anhydro[1,6]galactose (**3b**) and

(12) Plante, O. J.; Buchwald, S. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2000**, *122*, 7148–7149.

(13) (a) Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *63*, 4172–4173. (b) Xia, J.; Alderfer, J. L.; Piskorz, C. F.; Matta, K. L. *Chem.—Eur. J.* **2001**, *7*, 356–367.

(14) Yang, W.; Mortier, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 5708–5711.

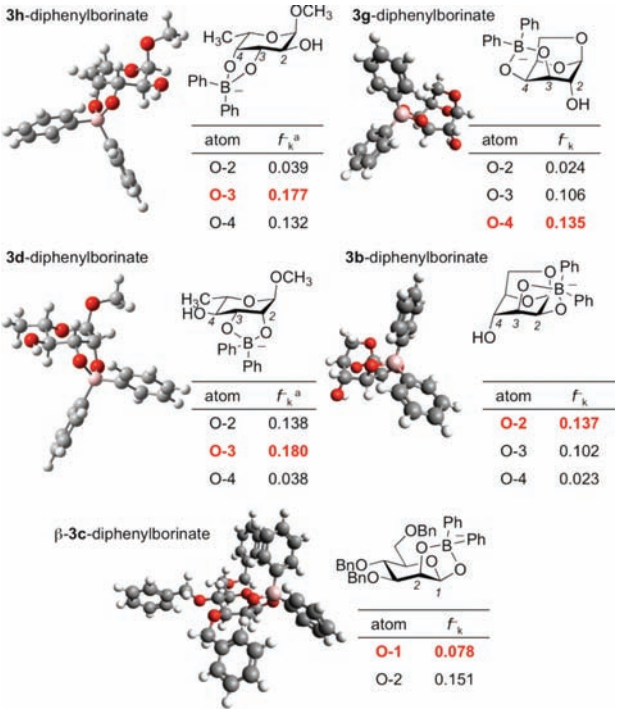


Figure 1. Calculated structures and condensed Fukui indices (B3LYP/6-311+G(d,p)) of diphenylborinates of **3b**−**3d**, **3g**, and **3h**. The site of observed reactivity under the catalytic reaction conditions is indicated in bold type (red color). [a]From ref 11.

anhydro[1,6]mannose (**3g**) provide additional support for this model: the Fukui indices indicate highest nucleophilicity at O-4 and O-2, respectively, consistent with the experimental data (Figure 1). On the other hand, the selective alkylation of mannose derivative **3c** at O-1 cannot be rationalized by calculations of this type: Fukui index calculations indicate that O-2 is the more nucleophilic position of the borinate ester, as would be expected given the electron-deficient nature of the C1 position. Selective alkylation of the more acidic 1-OH group may indicate a role for proton transfer equilibria in the regiochemical outcome observed for this substrate.[15] Selective alkylation of the dibutylstannylene acetal derived from **3c** occurs at the 1-OH group: a mechanistic rationale for this behavior has not been advanced.[16]

In conclusion, borinic acid catalysis represents an efficient and broadly applicable method for the regioselective alkylation of carbohydrate derivatives bearing multiple secondary hydroxy groups. The operational simplicity of this method, and the ability to avoid the use of stoichiometric quantities of organotin-based reagents, are attractive features for applications in the preparation of selectively protected carbohydrate derivatives. In a more general context, the catalyst-controlled alkylation of amines and alcohols is a challenging and underdeveloped mode of reactivity: nucleophilic catalysis, the strategy applied most broadly to influence the outcome of acylation, phosphorylation, sulfonylation, and silylation reactions,[17] has proven difficult to adapt to alkyl halides and related electrophiles. The nucleophile activation strategy developed here may present new opportunities in this regard: exploiting this method to achieve other challenging manipulations of unprotected carbohydrate derivatives and developing chiral catalysts for asymmetric alkylation of alcohols represent interesting directions for future research.

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Supporting Information Available. Experimental procedures, details of computational studies, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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