Organic LETTERS

Letter

pubs.acs.org/OrgLett

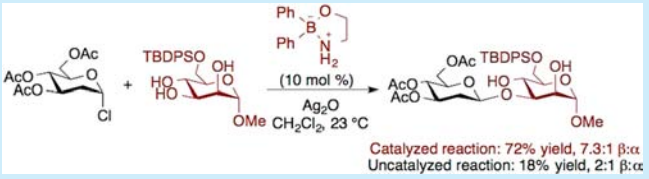
Organoboron-Catalyzed Regio- and Stereoselective Formation of β-2-Deoxyglycosidic Linkages

Thomas M. Beale, Patrick J. Moon, and Mark S. Taylor*

Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, ON M5S 3H6, Canada

Supporting Information

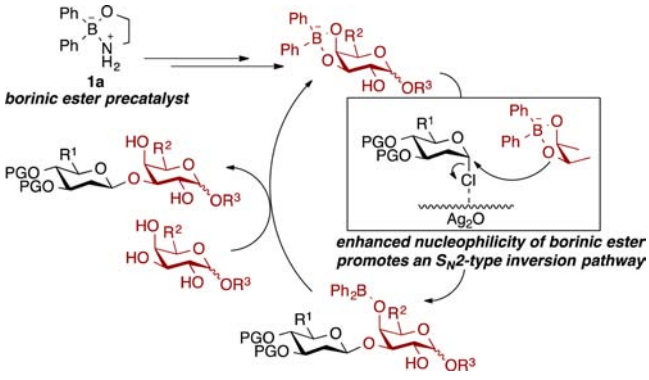
ABSTRACT: A borinic acid derived catalyst enables regioselective and β-selective reactions of 2-deoxy- and 2,6-dideoxyglycosyl chloride donors with pyranoside-derived acceptors having unprotected *cis*-1,2- and 1,3-diol groups. The use of catalysis to promote a β-selective pathway by enhancement of acceptor nucleophilicity constitutes a distinct approach from previous work, which has been aimed at modulating donor reactivity by variation of protective and/or leaving groups.



β-Configured 2-deoxyglycoside linkages are structural elements of microbial secondary metabolites having important biological effects, including antitumor, antibiotic, and cardiac activities.[1] Their stereoselective synthesis is a challenge: the lack of a hydroxyl-derived substituent adjacent to the anomeric center renders many of the established methods for the construction of equatorially oriented glycosidic bonds relatively unselective, while the anomeric effect tends to dictate a bias toward α-configured 2-deoxy glycosides.[2] A number of creative solutions, including alkylations of anomeric alkoxides,[3] chiral catalyst-controlled glycosylations,[4] *de novo* approaches,[5,6] and indirect methods mediated by a removable functional group at C-2 of the donor,[7−10] have been devised. β-Selective couplings of 2-deoxyglycosyl donors are also possible, either by diastereoselective addition to a putative oxacarbenium ion or by an S_N2-type pathway with inversion of configuration of an axially oriented leaving group. A number of useful protocols have been reported,[11−18] with thorough optimization of factors related to glycosyl donor (protective group pattern, leaving group, activation conditions) being a common theme. Herein, we describe a distinct strategy for promoting β-selective 2-deoxyglycosylations, using an organoboron catalyst to enhance acceptor nucleophilicity and thus favor an S_N2-type pathway. In the presence of the catalyst, β-2-deoxyglycosides are formed in a stereo- and regioselective fashion from readily available α-glycosyl chlorides, using acceptors having two or three potentially reactive hydroxyl (OH) groups.

The method for selective β-deoxyglycosylation disclosed here builds on our discovery that aminoethyl diphenylborinate (**1a**) promotes regioselective glycosylations of pyranoside-derived *cis*-1,2-diols at the equatorial OH group.[19] The dependence of the reaction outcome on the configuration of the glycosyl halide starting material, and the observation of first-order kinetics in the glycosyl donor, acceptor, and catalyst, suggested that the 1,2-*trans* stereochemical outcome observed for protected gluco- or galactopyranosyl halide donors was the result of an S_N2-type displacement of an Ag_2O-activated, axially oriented halide leaving group by a tetracoordinate borinate ester. We postulated that, for couplings of α-2-deoxyglycosyl halides, the borinic acid catalyst would not only influence the regioselectivity of the process by glycosyl acceptor activation but also provide selective access to the β-configured product by favoring an S_N2-type pathway (Scheme 1).

Scheme 1. Proposal for Organoboron-Catalyzed Preparation of β-2-Deoxyglycosidic Linkages



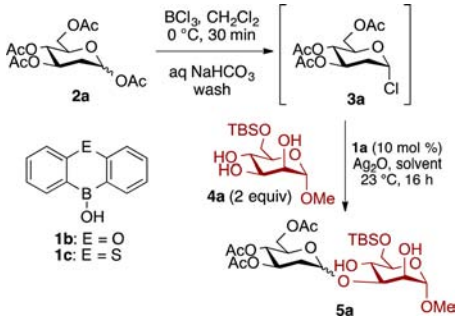
Our previous work revealed that, for more reactive "armed" donors, glycosyl chlorides provided higher levels of regiocontrol than the corresponding bromides.[19a] Thus, 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (**3a**, α:β > 20:1), generated in a straightforward fashion from glycosyl acetate **2a** by treatment with BCl_3 in CH_2Cl_2,[20] was selected as the donor to be used in optimization studies. Mannopyranoside derivative **4a**, which we have found to be among the less challenging pyranoside substrates in terms of regiocontrol,[19a,21] was employed as an acceptor with the aim of minimizing the complexity of the reaction mixtures at the optimization stage.

Received: June 12, 2014
Published: June 25, 2014

   dx.doi.org/10.1021/ol501711v | *Org. Lett.* 2014, 16, 3604−3607

The effects of varying the reaction conditions are summarized in Table 1.

Table 1. Evaluation of Reaction Conditions for Regioselective and β-Selective Coupling of 3 and 4a



entry	solvent	yield[a]	β:α[b]
1	CH_3CN (0.10 M)	44	1.6:1
2	toluene (0.10 M)	6	2.2:1
3	THF (0.10 M)	61	4.6:1
4	$^iPr_2O$ (0.10 M)	27	9:1
5	CH_2Cl_2 (0.10 M)	55	5.7:1
6	CH_2Cl_2 (0.20 M)	44	4.9:1
7	CH_2Cl_2 (0.05 M)	72	7.3:1
	Uncatalyzed reactions		
8	CH_3CN (0.10 M)	26	1:9
9	CH_2Cl_2 (0.05 M)	18	2:1
	Variation of catalyst/Ag(I) salt		
entry	variation from entry 5	yield	β:α
10	catalyst **1b** (10 mol %)	22	1.3:1
11	catalyst **1c** (10 mol %)	41	1:1.6
12	Ag_2CO_3	27	4.6:1

[a]Combined yield of α and β anomers, over two steps from **2a** (0.05 mmol scale), as determined by HPLC analysis of the unpurified reaction mixture. [b]Determined by HPLC analysis of the unpurified reaction mixture.

Under the standard conditions for glycosylation catalyzed by **1a** (CH_3CN solvent, 1 equiv of Ag_2O as a halide abstracting reagent/base, 23 °C), disaccharide **5a** was obtained as a single regioisomer, but as a mixture of anomers (β:α = 1.6:1, entry 1). It should be noted that, in the absence of the catalyst, the α anomer was obtained selectively under these conditions (β:α = 1:9, entry 8). This latter result is consistent with previous work: inversion of configuration of an α-2-deoxyglycosyl halide or sulfonate generally requires a good leaving group (X = I,[16] Br[17a,d] or OSO_2R[15]), most often in combination with other features that favor an S_N2-type pathway, such as benzylidene protection of the donor, low temperature, and/or the use of an acceptor-derived alkoxide. 2-Deoxyglycosyl chlorides (activated by AgOTf in CH_2Cl_2) have been shown to provide α-configured products, although modest, acceptor-dependent levels of β-selectivity have been obtained using a benzylidene-protected donor.[17c] In any case, the results shown in entries 1 and 8 of Table 1 clearly indicate that the organoboron catalyst has a significant effect on the stereochemical outcome of this glycosylation. To improve upon the result obtained in the presence of the catalyst, solvents of lower polarity and/or Lewis basicity than acetonitrile were examined (entries 2−5), with optimal results being obtained in dichloromethane at a concentration of 0.05 M (entry 7). Enhancements in yield and β-selectivity compared to the uncatalyzed reaction were also evident under these optimized conditions (entry 9). Although we anticipated that heteroboraanthracene-derived catalysts such as **1b** and **1c** might give rise to more nucleophilic borinates and thus provide enhanced β-selectivity relative to **1a**,[22] they in fact provided inferior results (entries 10, 11). The use of Ag_2CO_3 in place of Ag_2O provided a lower yield and marginally poorer β-selectivity (entry 12).

The optimal conditions were applied to couplings of 2-deoxyglucopyranosyl or -galactopyranosyl donors with a variety of acceptors containing *cis*-1,2- or 1,3-diol motifs suitable for activation by organoboron catalyst **1a** (Table 2). In each case, either HPLC or ^1H NMR spectroscopic analysis of the unpurified reaction mixture was employed to determine the β:α selectivity. The magnitude of the $^1H-^{13}C$ ^1J coupling constant and/or ^3J coupling constants ($H1-H2_{ax}$, $H1-H2_{eq}$),[23] as well as the chemical shift of the anomeric hydrogen,[17d] were consistent with the assignment of β stereochemistry for the major disaccharide product. Isolated yields of the β-anomer after purification by silica gel chromatography are shown, for the two-step protocol starting from the peracetylated 2-deoxypyranosides. The corresponding α-configured disaccharides, along with the products of glycosyl chloride hydrolysis, accounted for the remainder of the mass balance; only in the case of **5f** and **5g** were regioisomeric 2-deoxyglycosides evident (20% and 15% yield, respectively).

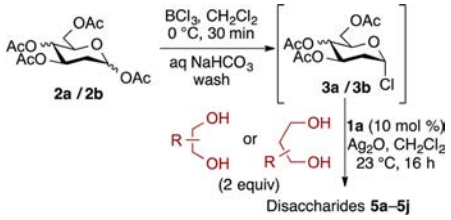
We sought to extend the method to the formation of β-2,6-dideoxy linkages, which are particularly prevalent in bioactive natural products. Diphenylborinate **1a** was found to promote β-selective reactions of 2-deoxy-L-rhamnopyranosyl chloride **3c** with a range of acceptors, as depicted in Table 3. To investigate whether there was a matching/mismatching effect between donor and acceptor,[24] glycosylations of both enantiomers of methyl β-arabinopyranoside were carried out. Similar yields and β:α selectivities were obtained for diastereomeric disaccharides **6d** and **6e**. A control experiment revealed that, in the absence of catalyst **1a**, disaccharide **6a** was obtained in 4% yield (4.3:1 β:α) under the conditions of Table 3.

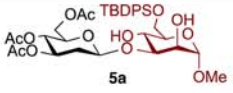
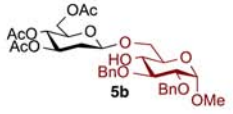
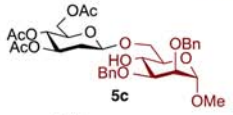
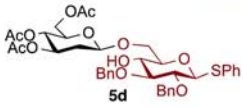
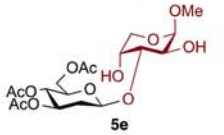
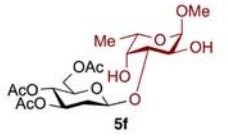
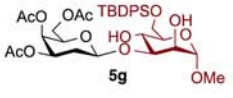
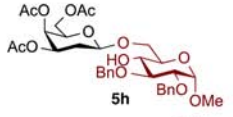
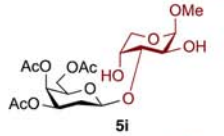
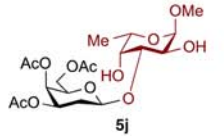
The effects of varying the protective groups of the glycosyl donor are depicted in Scheme 2. Replacement of the ester protective groups with less electron-deficient benzyl ethers was expected to favor ionization of the glycosyl chloride,[25] and thus to have a deleterious effect on the stereoselectivity of the organoboron-catalyzed reaction. Mono- and dibenzylated **3d** and **3e** were synthesized from the corresponding anomeric hemiacetals using the Ghosez reagent,[26] as reactions of the 1-OAc pyranosides with BCl_3 proved ineffective for accessing these more labile donors.[27] As shown in Scheme 2, the use of the more electron-rich, "armed" deoxyglycosyl chloride donors resulted in lower yields of disaccharide products (with glycosyl donor hydrolysis being the major side reaction) and also adversely affected the β:α ratio, consistent with the mechanistic hypothesis outlined in Scheme 1.

In summary, the use of a borinic acid derived catalyst enables regio- and stereoselective glycosylations of pyranoside-derived *cis*-1,2- and 1,3-diols, using both 2-deoxy and 2,6-dideoxyglycosyl chloride donors. Enhancement of acceptor nucleophilicity to promote a β-selective pathway constitutes a distinct approach from previous work, which has been focused on modulating donor reactivity by variation of protective and/or leaving groups.[28] The protocol is most efficient when peracetylated deoxyglycosyl halides are used. While potentially limiting the types of products that may be accessed by this approach, these peracetylated donors offer advantages in terms

dx.doi.org/10.1021/ol501711v | Org. Lett. 2014, 16, 3604−3607

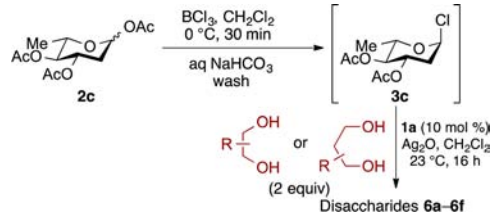
Table 2. Organoboron-Catalyzed Regioselective and β-Selective Reactions of 2-Deoxyglycopyranosyl Donors

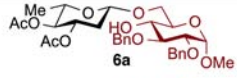
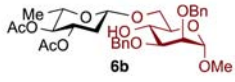
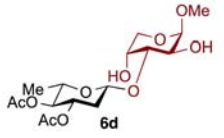
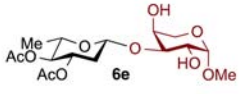
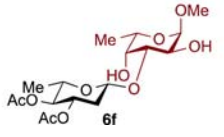


entry	product	β:α[a]	yield[c]
1	 5a	7.3:1	61%
2	 5b	16:1	77%
3	 5c	13:1	74%
4	 5d	19:1	55%
5	 5e	>19:1[b]	58%
6	 5f	7.3:1[b,c]	51%
7	 5g	5.7:1[d]	54%
8	 5h	6.7:1	68%
9	 5i	8.1:1[b]	66%
10	 5j	4.3:1[b]	51%

[a]Determined by HPLC analysis of unpurified reaction mixtures. [b]Determined by ^{1}H NMR analysis of unpurified reaction mixtures. [c]A regioisomer (20%) was identified by ^{1}H NMR analysis of the unpurified reaction mixture. [d]A regioisomer (15%) was identified by HPLC analysis of the unpurified reaction mixture. [e]Isolated yields of β-anomers after purification by silica gel chromatography, from reactions carried out on 0.1 mmol of **2a**/**2b**.

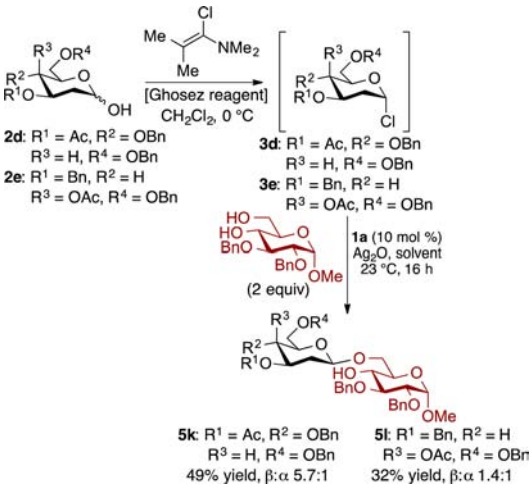
Table 3. Organoboron-Catalyzed Construction of β-2,6-Dideoxy Linkages



entry	product	β:α[a]	yield[c]
1	 6a	9:1	63%
2	 6b	10:1	60%
3	 6c	4.3:1	69%
4	 6d	4:1[b]	59%[d]
5	 6e	5.2:1[b]	69%
6	 6f	4:1[b]	46%

[a]Determined by HPLC analysis of unpurified reaction mixtures. [b]Determined by ^{1}H NMR analysis of unpurified reaction mixtures. [c]Isolated yields of β-anomers after purification by silica gel chromatography, from reactions carried out on 0.1 mmol of **2c**. [d]Isolated as a 4.9:1 β:α mixture.

Scheme 2. Organoboron-Catalyzed Glycosylations Using Benzyl-Protected 2-Deoxyglucopyranosyl Donors[a]



[a]Isolated yields from reactions carried out on 0.1 mmol scale of **2d**/**2e** are listed.

dx.doi.org/10.1021/ol501711v | Org. Lett. 2014, 16, 3604–3607

of ease of preparation and handling. Similarly, the requirement for acceptors having an unprotected *cis*-1,2- or 1,3-diol group represents a limitation,[29] but also offers the opportunity to streamline the synthesis of appropriately chosen targets. Future work will involve applications of this method to the synthesis of bioactive natural products and their analogs, as well as extensions to other challenging classes of glycosidic linkages.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds, including NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mtaylor@chem.utoronto.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Personnel Award from the Heart and Stroke Foundation of Canada (T.M.B.). Additional support was provided by NSERC (Discovery Grants Program, Canada Research Chair to M.S.T.), Boehringer Ingelheim (Canada) Ltd., the Canada Foundation for Innovation, the Province of Ontario, and the University of Toronto. M.S.T. is a Fellow of the A. P. Sloan Foundation. P.J.M. was supported by a scholarship from the University of Ottawa. NMR facilities were funded by the CFI (Project No. 19119) and the Province of Ontario.

■ REFERENCES

(1) De Lederkremer, R. M.; Marino, C. *Adv. Carbohydr. Chem. Biochem.* **2008**, *61*, 143−215.

(2) (a) Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385−8417. (b) Hou, D.; Lowary, T. L. *Carbohydr. Res.* **2009**, *344*, 1911−1940. (c) Crich, D. *J. Org. Chem.* **2011**, *76*, 9193−9209. (d) Borovika, A.; Nagorny, P. *J. Carbohydr. Chem.* **2012**, *31*, 255−283.

(3) (a) Morris, W. J.; Shair, M. D. *Org. Lett.* **2009**, *11*, 9−12. (b) Zhu, D.; Baryal, K. N.; Adhikari, S.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 3172−3175.

(4) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198−7199.

(5) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 4339−4342.

(6) McDonald, F. E.; Reddy, K. S.; Diaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304−4309.

(7) (a) Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837−8852. (b) Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; van Delft, F. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1874−1876.

(8) (a) Perez, M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 75−78. (b) Nicolaou, K. C.; Mitchell, H. J.; Fylaktakidou, K. C.; Suzuki, H.; Rodriguez, R. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1089−1093. (c) Boutureira, O.; Rodriguez, M. A.; Benito, D.; Matheu, M. I.; Diaz, Y.; Castillon, S. *Eur. J. Org. Chem.* **2007**, *21*, 3564−3572.

(9) (a) Thiem, J.; Schottmer, B. *Angew. Chem., Int. Ed.* **1987**, *26*, 555−557. (b) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541−3542. (c) Bucher, C.; Gilmour, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 8724−8728.

(10) (a) Auzanneau, F.-I.; Bundle, D. R. *Carbohydr. Res.* **1991**, *212*, 13−24. (b) Zuurmond, H. M.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1993**, *49*, 6501−6514. (c) Hou, D.; Taha, H. A.; Lowary, T. L. *J. Am. Chem. Soc.* **2009**, *131*, 12937−12948.

(11) (a) Hashimoto, S-i.; Sano, A.; Sakamoto, H.; Nakajima, M.; Yanagiya, Y.; Ikegami, S. *Synlett* **1995**, 1271−1273. (b) Pongdee, R.; Wu, B.; Sulikowski, G. A. *Org. Lett.* **2001**, *3*, 3523−3525.

(12) Tanaka, H.; Yoshizawa, A.; Takahashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 2505−2507.

(13) Kim, K. S.; Park, J.; Lee, Y. J.; Seo, Y. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 459−462.

(14) (a) Junnemann, J.; Lundt, I.; Thiem, J. *Liebigs Ann. Chem.* **1991**, 759−764. (b) Toshima, K.; Nagai, H.; Kasumi, K-i.; Kawahara, K.; Matsumura, S. *Tetrahedron* **2004**, *60*, 5331−5339.

(15) (a) Crich, D.; Vinogradova, O. *J. Org. Chem.* **2006**, *71*, 8473−8480. (b) Issa, J. P.; Lloyd, D.; Steliotes, E.; Bennett, C. S. *Org. Lett.* **2013**, *15*, 4170−4173. (c) Issa, J. P.; Bennett, C. S. *J. Am. Chem. Soc.* **2014**, *136*, 5470−5744.

(16) Lam, S. N.; Gervay-Hague, J. *Org. Lett.* **2003**, *5*, 4219−4222.

(17) (a) Binkley, R. W.; Koholic, D. J. *J. Org. Chem.* **1989**, *54*, 3577−3581. (b) Zhang, Z.; Magnusson, G. *J. Org. Chem.* **1996**, *61*, 2383−2393. (c) Verma, V. P.; Wang, C.-C. *Chem.—Eur. J.* **2013**, *19*, 846−851. (d) Kaneko, M.; Herzon, S. B. *Org. Lett.* **2014**, *16*, 2776−2779.

(18) Ma, Y.; Li, Z.; Shi, H.; Zhang, J.; Yu, B. *J. Org. Chem.* **2011**, *76*, 9748−9756.

(19) (a) Gouliaras, C.; Lee, D.; Chan, L.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 13926−13929. (b) Beale, T. M.; Taylor, M. S. *Org. Lett.* **2013**, *15*, 1358−1361.

(20) Niggeman, J.; Lindhorst, T. K.; Walfort, M.; Laupichler, L.; Sajus, H.; Thiem, J. *Carbohydr. Res.* **1993**, *246*, 173−183.

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

(22) Dimitrijevic, E.; Taylor, M. S. *Chem. Sci.* **2013**, *4*, 3298−3303.

(23) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293−297.

(24) (a) Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed.* **1991**, *30*, 180−183. (b) Cid, M. B.; Alonso, I.; Alfonso, F.; Bonilla, J. B.; López-Prados, J.; Martín-Lomas, M. *Eur. J. Org. Chem.* **2006**, 3947−3959.

(25) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584.

(26) Ernst, B.; Winkler, T. *Tetrahedron Lett.* **1989**, *30*, 3081−3084.

(27) A control experiment revealed that the method of preparation of **3c** (1-OAc pyranoside/BCl_3 versus 1-OH pyranoside/Ghosez reagent) did not influence yield or β-selectivity in the synthesis of **6a**. See the Supporting Information.

(28) For studies of the influence of acceptor nucleophilicity on the stereochemical outcomes of 2-deoxyglycosylation reactions under S_N1-type conditions, see: (a) Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 8039−8050. (b) Beaver, M. G.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 1107−1118.

(29) When 1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose was coupled with **3a** under the conditions of Table 2, disaccharide was obtained in 21% yield (1:1 β:α).