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Regioselective glycosylation of fully unprotected methyl hexopyranosides by means of transient masking of hydroxy groups with arylboronic acids

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ABSTRACT

Facile, one-pot synthesis was developed for several β(1→2)-, β(1→3)- or β(1→4)-linked disaccharides from fully unprotected methyl hexopyranosides according to the molecular recognition by arylboronic acids. The methodology was successfully applied to facile, short step assembly of the trisaccharide fragment of type II arabinogalactan.

Practical chemical synthesis of oligosaccaharide usually requires an adequate stereoselectivity and regioselectivity for glycosylation reaction, by which diversely designed oligosaccharides are provided on a preparatory scale.[1] At present, stereoselectivity of the anomeric centers has been nearly overcome by utilizing the anomeric effect and anchimeric assistance.[2] With regard to regioselective glycosylation, most of the present methods are based on the protection–deprotection method, which requires a stepwise protection of undesired hydroxy groups. In this method, after glycosylation of the desired hydroxy group, the protective groups have to be removed, and accordingly the overall synthetic scheme becomes lengthy and impractical.[3] Additional drawbacks to the protection–deprotection method seem to waste excess reagents used for protection in terms of atomic efficiency as well as time and energy for multi-step manipulation.

Recently, Hung and co-workers reported regioselective protection of sugar hydroxy groups, which has been applied to the one-pot synthesis of influenza virus-binding trisaccharide library.[4] Further novel approach for regioselective protection of hydroxy groups were provided by nonenzymatic regioselective acylation[5] as well as catalytic regioselective functionalization of 1,2-diols involving carbohydrates.[6] However, few methods have been reported for regioselective glycosylation of fully unprotected sugars without any protection on glycosyl acceptors.

The former approach of regioselective glycosylation was achieved by activation of the target hydroxy group using stannylation[7–10] or activated boronate formation.[11] These methods provided early success for regioselectivity, however, they are limited to β(1→6)-linked disaccharides only in the case of glycosylation of methyl hexopyranosides possessing both primary and secondary hydroxy groups in the same molecule. The only exception presented to our previous method was by means of ion-pair intermediates based on the stannylated methyl β-D-galactopyranoside, providing β(1→3)-linked disaccharides as the major product albeit in low yields.[10] The activating method has drawbacks limited to the primary rather than the secondary hydroxy group. Alkyl stannylene compounds also seem to be responsible for environmental preservation.

We focused on an alternative procedure without activation but with deactivation (masking) of hydroxy groups. As such, we selected boronate intermediates, since boronates are susceptible to hydrolysis for use in the protective group of diols.[12] However, they must be utilized as promising mediators for molecular recognition of carbohydrates,[13] such that boronic acids easily form sterically demanding cyclic boronates, which function as a transient masking rather than as protection for hydroxy groups.

In general (cf. Scheme 1), sugar hydroxy groups might be recognized by the boronic acids at 1,2-*cis*-diol as well as 4,6-diols of hexoses.[13] Accordingly, a glycosyl donor can conceivably attack a free hydroxy group other than masked hydroxy groups giving rise to regioselective glycosylation. After glycosylation, boronic acid should be removed easily from the reaction mixture in situ by exposure to aqueous sodium perborate.[14]

This procedure would provide a widely applicable, simple, one-pot glycosylation reaction such that the reaction would enable us

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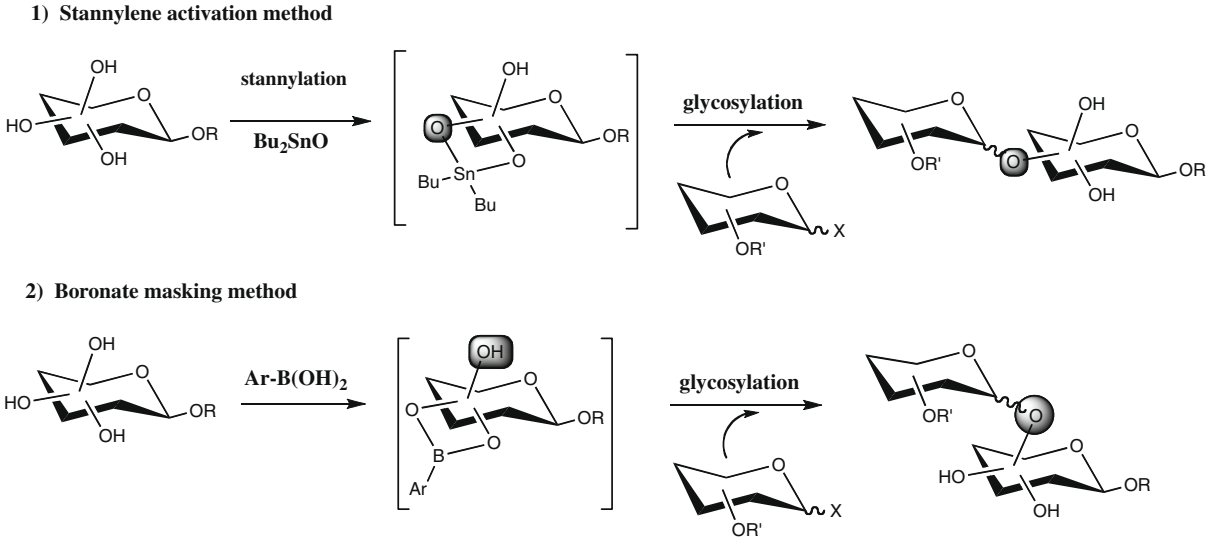


Scheme 1. General scheme for regioselective glycosylation of fully unprotected sugars.

to glycosylate any hydroxy group which has not been accessible by the previous methods.[7–11]

First, in order to achieve elucidation of structure–regioselective relationships, we set up model experimental conditions using readily available glycosyl donors and acceptors. Glycosyl bromides (**1**–**2**) functioning as reactive donors and phenyl thioglycosides (**3**–**5**) as stable, versatile donors were employed for glycosylation of several acceptors, for example, methyl hexopyranosides (**6**–**12**) in the presence of arylboronic acids (**13**–**15**) as shown in Figure 1.

The results are summarized in Table 1, where optimum reaction conditions were examined for glycosylation of methyl β-D-galactopyranoside (**7**). In both cases using bromide and phenylthio glycoside, the donor, the acceptor, and arylboronic acid were mixed in the appropriate solvent in a reaction flask to form boronic ester at room temperature for 16 h, then treated with glycosylation promoters affording the disaccharides regioselectively as depicted in Scheme 2 and Table 1. This set of reactions resulted in glycosyl-β(1→3)-galactosides in predominantly higher yields compared to the corresponding β(1→2)-linked disaccharides. The β(1→6)-galactosides were not detected from the reaction products. Accordingly, this method is applicable to the secondary hydroxy groups rather than the primary hydroxy groups. This selectivity should be rationalized by the expected masking of 4,6-hydroxy groups with arylboronic acid generating 4,6-boronate as the intermediate.[15]

Comparing with the previous method[10] providing 42% yield at best for glycosyl-β(1→3)-galactosides, the experiments described at entries 1 and 3 provide good yields with high regioselectivity. With regard to the anomeric isomers of the glycosidic linkage, β-isomers were obtained, except for entry 5, where the mannosyl

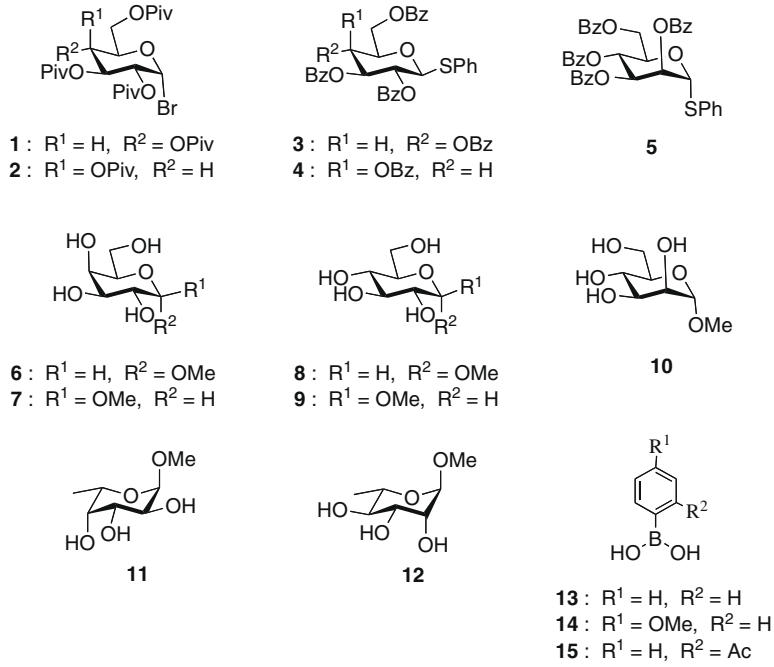
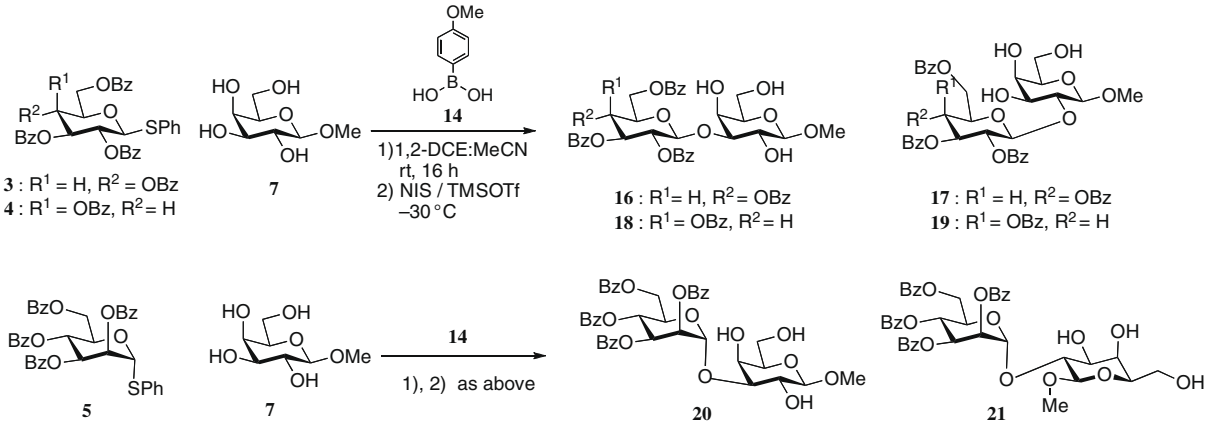


Figure 1. Glycosyl donors, acceptors, and arylboronic acids employed for regioselective glycosylation.

Table 1
Glycosylation of methyl β-D-galactopyranoside (**7**) with several glycosyl donors[a,b]

Entry	Donor	Boronic acid	Solvent[c]	Promoter[d]	Temp (°C)	Time (h)	Product	Yield (%)	Compd no.	1→3:1→2[e] (ratio)
1	**1**	**13**	DCE	A	0	24	βGlc–βGal	78	**22** + **23**	92:8
2	**2**	**14**	DCE	A	0	24	βGal–βGal	66	**24** + **25**	94:6
3	**3**	**14**	DCE–AN	B	−30	2	βGlc–βGal	71	**16** + **17**	93:7
4	**4**	**14**	DCE–AN	B	−30	2	βGal–βGal	76	**18** + **19**	91:9
5	**5**	**14**	DCE–AN	B	−30	5	αMan–βGal	73	**20** + **21**	81:19
6[f]	**3**	—	DCE–AN	B	−30	5	βGlc–βGal	—		—

[a] The reactions were performed in the presence of 1.0 equiv of arylboronic acid.
[b] Two equivalent donors were employed.
[c] DCE (1,2-dichloroethane):AN (acetonitrile) = 1:1.
[d] A: Ag(I) silica–alumina[16] (900 mg to 0.50 mmol of glycosyl bromide employed); B: *N*-iodosuccinimide–trimethylsilyl trifluoromethanesulfonate (NIS-TMSOTf).[17] NIS (0.28 mmol) and TMSOTf (0.02 mmol) were employed to 0.20 mmol of the 1-thio-glycosides.
[e] The ratio of β(1→3)-disaccharide: β(1→2)-disaccharide for entries 1–4. The ratio of α(1→3)-disaccharide: α(1→2)-disaccharide for entry 5.
[f] The reaction was carried out without boronic acid.



Scheme 2. Regioselective glycosylation of fully unprotected methyl β-D-galactopyranoside.

donor (**5**) provided only the α-anomer as generally anticipated. For glycosylation with bromide (**1**), 1,2-dichloroethane (DCE) is the favored solvent, while with the thioglycoside, the mixed solvent system using DCE/MeCN (1:1) provided better yields, probably due to good solubility of the thioglycosides, acceptors, and promoters in the mixed solvent employed in the glycosylation. Glycosylation of the galactoside **7** without boronic acid resulted in product mixture hardly isolable as a pure product (cf. Table 1, entry 6).

Structures of the disaccharides obtained were unambiguously elucidated on the basis of their MS, ^{1}H and ^{13}C NMR spectra.[18] The intersaccharide linkages were defined by the deshielding effect of the ^{13}C NMR chemical shift, where the O-glycosylated carbon atom sizably shifted to a lower magnetic field.[10] Further, HMBC and NOESY data supported the above statement by the corresponding crossed signals of the second order analyses. As for the glycosylation of methyl β-D-galactopyranoside (**7**), β(1→3)-linked disaccharides (**16** and **18**) have been obtained predominantly. This selectivity would be rationalized by the generation of the 4,6-boronate intermediate,[15] which could be glycosylated in situ to give the β(1→3)- and β(1→2)-linked disaccharides. The β(1→3)-selectivity is probably due to the steric effect, where the electrophiles seem to attack the 3-hydroxy group in preference to the 2-hydroxy group. In the galactopyranoside there would be more enough space around the 3-hydroxy group because of the neighboring axial hydroxy group at position 4. This assumption might be supported by further experiments using methyl anomeric D-glucopyranosides (**8** and **9**) as the acceptors, where glucose acceptors having no such space around the 3-OH group result in reversed regioselectivity affording β(1→2)-linked disaccharides in the glycosylation (cf. Table 2, entries 2 and 3).

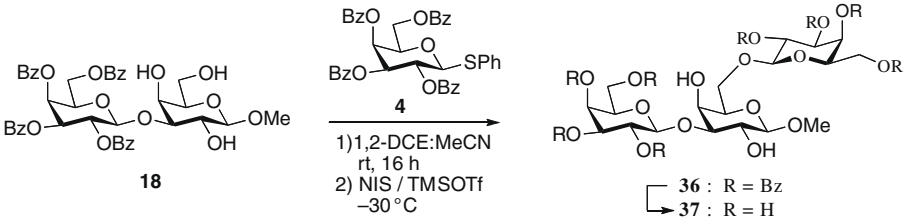
Glycosylation of various glycosyl acceptors with such glycosyl donors as bromide (**1** and **2**) and phenylthio glycoside (**3**) are summarized in Table 2. Glycosylation of α-galactoside (**6**) with **1** provided β(1→3)-disaccharide predominantly with less selectivity compared with the β-galactoside probably due to steric relief around the C-2 hydroxyl group (entry 1). In contrast, glycosylation of α-D-glucopyranoside (**8**) afforded β(1→2)-linked disaccharide in preference to β(1→3)-disaccharides in the ratio of ca. 7:1 (entries 2 and 3). In the case of α-D-glucopyranoside (**8**) as the acceptor, the donor attacks the 2-hydroxy group easier than the 3-hydroxyl group according to the steric surroundings, affording β(1→2)-disaccharide predominantly. The β-D-glucopyranoside acceptor (**9**) is found to have less selectivity comparing the α-anomer (**8**) affording the β(1→2)-: β(1→3)-disaccharides in the ratio of ca. 7:3 (entries 4 and 5). The relatively low yields (35–44%) were observed at the entries 2, 3, and 5, whereas the starting materials as well as other products were not isolable from the reaction mixture. For 6-deoxyhexopyranosides (**11** and **12**), masking of the *cis*-diol leaves only one hydroxy group free, which causes the entire regioselectivity affording β(1→2)-disaccharide for α-L-fucopyranoside (entry 6) as well as β(1→4)-disaccharide for α-L-rhamnopyranoside (entry 7) in good yields.

Furthermore, utility of our method was evaluated by a facile assembly of the trisaccharide fragment (**37**) [Gal*p*-β1→3 (Gal*p*-β1→6)-Gal*p*-β1→Me] of type II arabinogalactan (a Chinese medicine, *Ohgi*).[19–21] For construction of the trisaccharide (**37**) we employed the disaccharide **18** obtained by regioselective glycosylation at a 69% yield (cf. entry 4 in Table 1). Although the disaccharide **18** has three free hydroxy groups, the C-6 hydroxy group was selectively glycosylated with **4** to afford the desired trisaccha-

Table 2
Glycosylation of various acceptors with the glycosyl donors **1**–**3**[a]

Entry	Donor/acceptor	Boronic acid	Solvent[b]	Promoter[c]	Temp (°C)	Time (h)	Products[d]	Yield (%)	Compd no.	β1→3:β1→2[e] (ratio)
1	**1**/**6**	**14**	DCE	A	0	24	βGlc–αGal	58	**26** + **27**	86:14
2	**1**/**8**	**14**	DCE	A	rt	24	βGlc–αGlc	43	**28** + **29**	14:86
3	**3**/**8**	**15**	DCE–AN	B	−10	1	βGlc–αGlc	44	**30** + **31**	12:88
4	**3**/**9**	**13**	DCE	B	−10	0.3	βGlc–βGlc	63	**32** + **33**	30:70
5	**3**/**9**	**15**	DCE	B	−10	0.2	βGlc–βGlc	35	**32** + **33**	28:72
6	**3**/**11**	**14**	DCE	B	−30	0.5	βGlc–αFuc	74	**34**	0:100[f]
7	**3**/**12**	**14**	DCE	B	−30	0.3	βGlc–αRha	89	**35**	100:0[g]

[a] Two equivalent donors were employed.
[b] DCE (1,2-dichloroethane):AN (acetonitrile) = 1:1.
[c] A: Ag(I) silica-alumina; B: *N*-iodosuccinimide–trimethylsilyl trifluoromethanesulfonate (NIS-TMSOTf). Quantities of the promoters employed were same as described in Table 1.
[d] The disaccharide obtained by the combination of the donor and the acceptor employed for regioselective glycosylation.
[e] The ratio of β(1→3)-disaccharide: β(1→2)-disaccharide.
[f] Only the β(1→2)-disaccharide was obtained.
[g] Only the β(1→4)-disaccharide was obtained.



Scheme 3. Synthesis of the trisaccharide fragment of type II arabinogalactan.

ride **36** in 70% yield, which was easily deprotected to give the target trisaccharide **37** in 85% yield. Accordingly, the trisaccharide **37** has been obtained in only three steps from methyl β-D-galactopyranoside (**7**) (Scheme 3).

In summary, a simple, one-pot, regioselective glycosylation has been developed for fully unprotected methyl hexopyranosides with several glycosyl donors (glycosyl bromides and phenylthio glycosides) in the presence of arylboronic acids: (1) Various β(1→2)-linked disaccharides for methyl α- and β-D-glucopyranosides, and β(1→3)-linked disaccharides for methyl α- and β-D-galactopyranosides were obtained regioselectively even in the presence of the primary hydroxy group. (2) Glycosylation of methyl α-L-fuco- and α-L-rhamnopyranoside resulted in complete regioselection affording β(1→2)-linked disaccharide and β(1→4)-linked disaccharide, respectively. (3) It only took three steps using our method for facile assembly of the trisaccharide fragment of the arabinogalactan. Research into further applications of our method to facile one-pot assembly of complex oligosaccharides is still in progress.

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Supplementary data

Supplementary data (experimental procedures and compound characterization) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.048.

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