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SPECIAL ISSUE PAPER

Regio- and stereoselective glycosylation of 2-(*o*-dihydroxyborylbenzyl) thioglucoside and unprotected methyl glycosides

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Abstract

A highly regio- and stereoselective glycosylation of a boronic acid-containing thioglucoside and unprotected methyl glycosides is described. A boronic acid moiety was installed at the *ortho*-position of the 2-*O*-benzyl group of a thioglucosyl donor. This provides transient partial protection for the unprotected glycosyl acceptor upon condensation and concomitantly prearranged the acceptor with respect to the donor for the ensuing intramolecular glycosylation.

KEYWORDS

boronic acid, glycosylation, regioselectivity, stereoselectivity

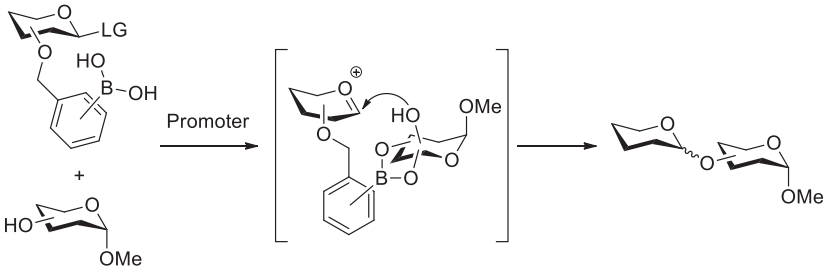
In carbohydrate chemistry, the ability to control regio- and stereoselectivity when constructing glycosidic bonds is vital for efficient synthesis of structurally well-defined oligomers. The traditional way to achieve the desired regioselectivity is by protecting all the hydroxyl groups not involving in glycosylation in the glycosyl acceptor prior to glycosylation. The tedious protecting group manipulation involved in this approach was not desirable and numerous efforts have been devoted to directly use fully unprotected or partially protected substrate for glycosylation.[1,2] The insolubility of the highly polar unprotected sugars in organic solvents, which are the usual glycosylation media, posed an additional challenge for their direct glycosylation. One way to tackle these problems in the literature was to use arylboronic acid, which is known to form cyclic boronic ester with 1,3-diol or *cis*-1,2-diol on the unprotected sugar,[3–7] to provide transient protection. This also reduced the overall substrate polarity and rendered the resulting adduct soluble in low-polarity solvents. When these arylboronic acid-sugar complexes were used as glycosyl acceptors, most of the hydroxyl groups were masked and only one or two free hydroxyl groups were available for glycosylation. Moderate to excellent regioselectivities of these intermolecular glycosylation have been achieved.[8–12] Similarly, a boronic acid moiety was incorporated in a polymeric support for regioselective solid phase glycosylations of partially protected glycosides.[13,14] In these intermolecular glycosylation, the stereochemistry of newly formed glycosidic bond was not controlled except when 2-*O*-aryl substituted glycosyl donor was used. Alteratively, the boronic acid-sugar adduct could be activated by coordination of the boron center to oxygen or nitrogen-based Lewis base so that one of bounded alkoxy groups underwent glycosylation.[15–19] An elegant work by Toshima has demonstrated that the coordination of the epoxy oxygen atom of 1,2-anhydro glycosyl

donors to the boron atom of the boronic acid-bounded glycosyl acceptors activated both entities for an intramolecular aglycol delivery that resulted in an overall highly regio- and 1,2-*cis*-stereoselective glycosylation.[20–22] Recently, a boronic acid moiety was introduced into the leaving group of thioglycosyl donors with the aim to selectively deliver the glycosyl acceptor intramolecularly from one face, though the stereoselectivities obtained were only moderate.[12,23]

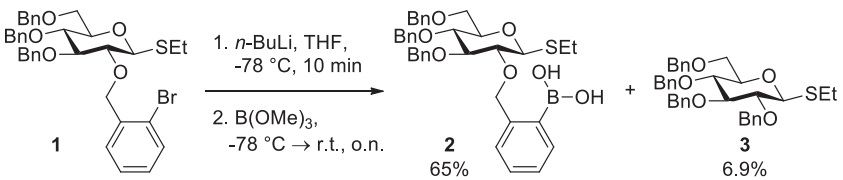
We envisioned that by incorporating a boronic acid moiety in the 2-*O*-benzyl protecting group in a per-*O*-benzylated thioglucoside, an unprotected glycosyl acceptor would anchor as a transient cyclic boronate. This preorganized donor and acceptor prior to glycosylation and would potentially bring one of the unmasked hydroxyl groups closer to and potentially from one face of the anomeric center of the glycosyl donor, thereby leading to a regio- and stereoselective glycosylation (Scheme 1). To verify this hypothesis, 2-(*o*-dihydroxyboryl)benzyl thioglucoside **2** was synthesized from 2-(*o*-bromobenzyl) thioglucoside **1**[24] by lithium-bromine exchange using *n*-butyllithium followed by quenching with trimethyl borate and hydrolysis upon acidic workup (Scheme 2).

With the boronic acid-containing thioglucoside **2** in hand, we set out to test its reaction with unprotected glycosyl acceptors. The proposed reaction involved a formation of a condensed donor-acceptor boronate complex prior to addition of activator for an intramolecular glycosylation to proceed. In practice, the boronic acid-containing thioglucoside **2** was first treated with an equimolar unprotected methyl glycoside in dichloromethane overnight and activated molecular sieve was added to scavenger the water generated in the condensation of boronic acid and diol. The mixture was then directly subjected to glycosylation. As the cyclic boronate was readily hydrolyzed in the presence of moisture, the progress of glycosylation could easily be monitored using thin layer chrmotagraphy by tracking the disappearance of thioglucoside **2**. Upon completion of glycosylation, the reaction was quenched with trimethylamine and a few drops of saturated sodium thiosulfate. To ensure an accurate determination of glycosylation yields, all boronates were converted back to boronic acid by treating the crude mixture with acetic anhydride and pyridine overnight.[25] This concomitantly protected all the hydroxyl groups, which facilitated isolation and characterization of any glycosylation product formed.

The reaction was first examined with unprotected methyl glucoside **4**, which was known to preferentially form a 4,6-boronate with an arylboronic acid. Following the general procedure with the use of *N*-iodosaccinimide (NIS)/triflic acid (TfOH) as the promotor at −40°C, *β*-(1→3)-linked disaccharide **5** was afforded as the sole product in 35% yield (entry 1). The regio- and stereochemistry of disaccharide **5** was unambiguously determined by nuclear magnetic resonance (NMR) spectroscopy (Data S1). The reaction conditions were varied to improve the glycosylation yield. It was found that the cyclic boronic ester could alternatively be generated by refluxing thioglucosyl donor **2** and unprotected acceptor **4** in toluene overnight. However, this method required a solvent switch prior to glycosylation. The additional manipulation and the difficulty in excluding water in this process, which led to a lower glycosylation yield in general, were not desirable. When the reaction was repeated with other commonly employed glycosylation promoter system for activation of thioglycosyl donor, such as NIS/TMSOTf, NBS/TfOH, $Ph_2SO/Tf_2O/TTBP$, and *p*-TolSCl/AgOTf, either a low disaccharide yield or a complicated mixture without any identifiable product was obtained. Therefore, this glycosylation was optimized based on the initial conditions using the NIS/TfOH promoter system. The use of a larger excess of NIS failed to



SCHEME 1 Envisioned boronic acid functionality on glycosyl donor to direct regio- and stereoselective of glycosylation with unprotected glycosyl acceptor



SCHEME 2 Preparation of boronic acid-containing glycosyl donor **2**

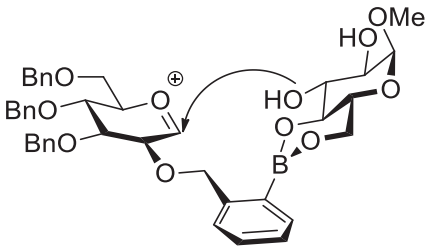
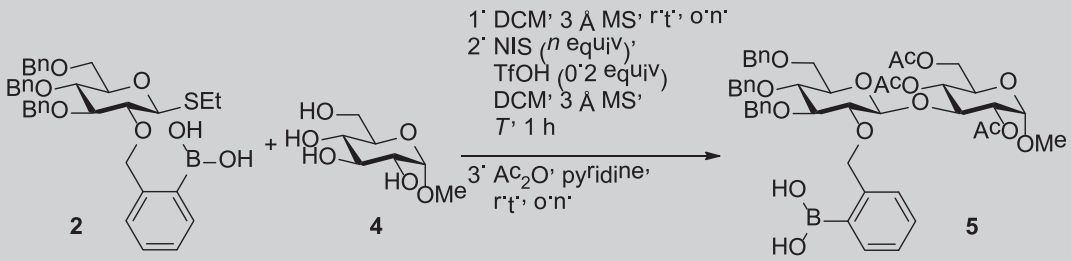


FIGURE 1 Plausible reaction intermediate responsible for the regio- and stereoselectivity observed in the reaction with unprotected methyl glucoside **4**

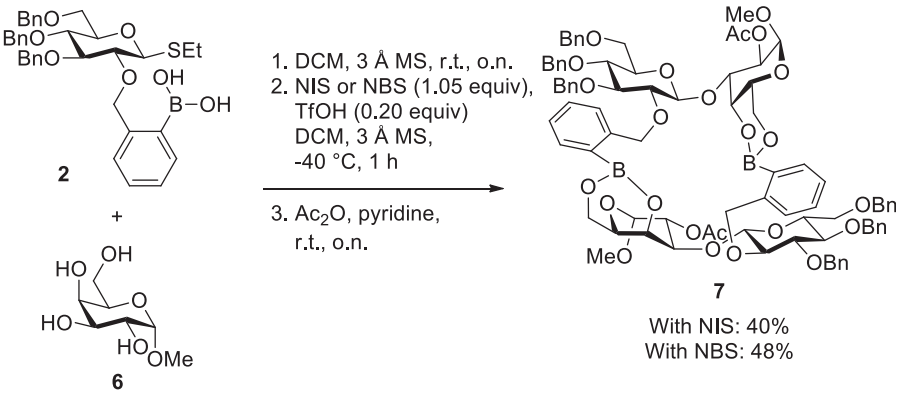
improve the glycosylation. Instead, there was more severe decomposition and as a result, a reduced amount of disaccharide **5** was isolated (entry 2). The reaction concentration effect was studied (entry 1, 3–4). A more dilute condition was advantageous for this intramolecular glycosylation. A slightly diminished glycosylation yield was obtained when the glycosylation was carried out at a higher (entry 5) or lower temperature (entry 6). The addition of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to reduce the acidity in the reaction mixture during glycosylation only attenuate the donor reactivity and the reaction

TABLE 1 Glycosylation of thioglucoside **2** and unprotected methyl glucoside **4**



Entry	Concentration	*n*	*T* (°C)	Yield[a]
1	0.05 M	1.05	−40	35%
2	0.05 M	1.20	−40	19%
3	0.02 M	1.05	−40	36%
4	**0.01 M**	**1.05**	**−40**	**45%**
5	0.01 M	1.05	−20	30%
6	0.01 M	1.05	−60	37%
7[b]	0.01 M	1.05	−40	39%
8[c]	0.01 M	1.05	−40	21%

[a]Isolated yield.
[b]Addition of 0.2 equiv DTBMP in step 2.
[c]1.5 equiv of thioglucoside **2** was used.



SCHEME 3 Reaction of boronic acid-containing thioglucoside **2** and unprotected methyl galactoside **6**

outcome was not affected, though a longer reaction time was required for complete consumption of the thioglucosyl donor (entry 7). To our surprise, when an excess amount of the boronic acid-containing donor **2** was employed aiming to ensure a more complete formation of cyclic boronate with the unprotected acceptor **4**, the disaccharide yield dropped dramatically (entry 8). In all cases, disaccharide **5** was the only isolatable glycosylation product.

The regio- and stereoselectivity observed was rationalized by the plausible reaction intermediate depicted in Figure 1. The unprotected methyl glucoside **4** preferentially form a 4,6-cyclic boronate with the boronic acid moiety in thioglucoside **2** and this brought the 3-hydroxyl group close in proximity to the top face of anomeric center after activation using NIS/TfOH (Table 1).

Having identified the optimal conditions for the reaction between glucosides, the reactions with other unprotected glycosides were studied. It was found that the reaction was substrate dependent and different reaction outcomes were obtained when using different glycosyl acceptors. When the same reaction conditions were employed in the reaction with unprotected galactoside **6**, a macrocyclic β-(1→3)-linked disaccharide dimer **7** was afforded as the only product (Scheme 3). Using NBS in place of NIS slightly improved the yield to 48%. The formation of the disaccharide dimer was confirmed by mass spectroscopy, while the regio- and stereochemistry of the dimer was determined by NMR spectroscopy. The unusual upfield shift of proton signal of the 2-acetyl group in ^{1}H NMR spectrum indicated that the acetyl group was shielded by the macrocycle. It was postulated that a six-membered 4,6-boronate was preferentially formed over a five-membered *cis*-3,4-boronate after condensation between the boronic acid moiety of thioglucoside **2** and galactoside **6** under thermodynamic conditions, leaving the 2- and 3-hydroxyl group on the galactoside available for glycosylation. However, unlike the boronate formed with the glucoside acceptor, this condensed species had two free hydroxyl groups oriented further away from the reactive anomeric center and this prevented any intramolecular reaction from proceeding (Figure 2). Instead, intermolecular reaction was geometrically favorable, leading to the formation of the macrocyclic dimer **7** of β-(1→3)-linked disaccharide.

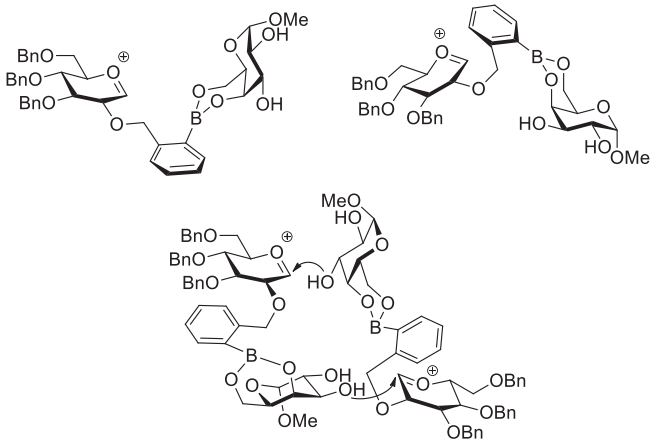
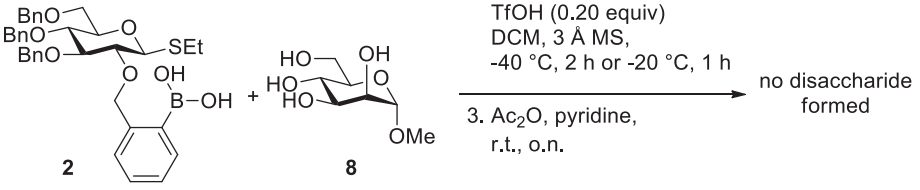


FIGURE 2 Plausible reaction intermediates responsible for the regio- and stereoselectivity observed in the reaction with unptorected methyl galactoside **7**

When unprotected methyl mannoside **8** was used as the glycosyl acceptor, no disaccharide was formed under any glycosylation conditions attempted (Scheme 4). Thioglucoside **2** decomposed while mannoside **8** was acetylated. Presumably, the availability of two orthogonal sites for the formation of cyclic *cis*-2,3- and 4,6-boronate on the unprotected methyl mannoside **8** was responsible for this reaction outcome. The initially insoluble unprotected mannoside **8** became soluble after the formation of the first cyclic boronate and this promoted the rapid formation of the second boronate, leaving no free hydroxyl group available for glycosylation. As there was only one equivalent of boronic acid in the mixture, the other half equivalent of mannoside remained uncondensed. The insolublity of the unprotected mannoside in dichloromethane prevented it from undergoing any glycosylation.

To conclude, we have demonstrated that a boronic acid moiety installed at the *ortho*-position of the 2-benzyl group of thioglucoside was able to act as a transient protecting group for the unprotected methyl glucosyl and galactosyl acceptors to partially shield the hydroxyl groups and as a molecular clamp to bring the acceptor into a specific orientation with respect to donor. The reaction outcome was highly substrate dependent. In other words, the success of glycosylation was governed



SCHEME 4 Attempts in reaction of boronic acid-containing thioglucoside **2** and unprotected methyl mannoside **8**

by the ability to selectively form a condensed boronate intermediate that possess one or more free hydroxyl groups, in which one of them is in a closer proximity to the reactive anomeric center where glycosylation took place possibly also from one face. This was the case for the glucoside acceptor and a β-(1→3)-linked disaccharide was afforded as the sole product. For galactoside acceptor, although intramolecular glycosylation of the condensed 4,6-boronate was not favorable, an intermolecular glycosylation proceeded with high regio- and stereoselectivity, resulting in a formation of a β-(1→3)-linked disaccharide dimer. The inability of mannoside acceptor to form a condensed boronate with any free hydroxyl groups was postulated to be the reason for the failure of glycosylation. In general, excellent regio- and stereoselective glycosylations of unprotected glycosides were achieved when glycosylation of the condensed boronate complex was possible. The highly specific formation of glycosidic bond using unprotected glycosyl acceptor is desirable in complex oligosaccharides synthesis. Thus, the idea of placing a boronic acid moiety at the other positions of per-*O*-benzylated glycoside donors may possibly lead to formation of disaccharides with a different glycosyl linkage and merit further investigation.

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