Note

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1,2-*trans*-1-Dihydroxyboryl Benzyl *S*-Glycoside as Glycosyl Donor

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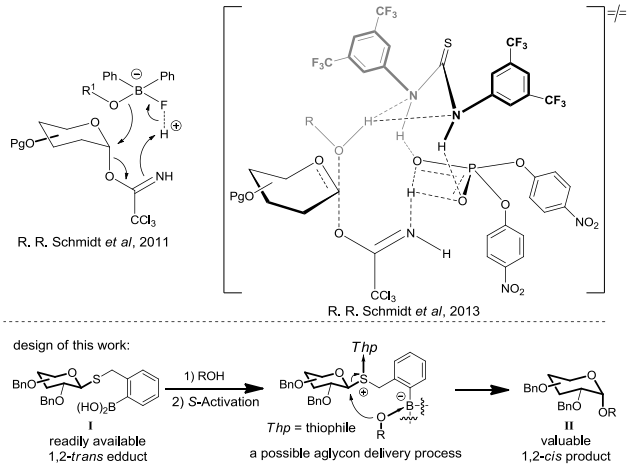
ABSTRACT

Activated by NBS, readily available 1,2-*trans*-1-dihydroxyboryl benzyl *S*-glycosides served as glycosyl donors and reacted with certain simple alcohol acceptors to produce pure 1,2-*cis*-*O*-glycosides in moderate yields. The boronic acid moiety was revealed essential in the glycosylation for product formation and good anomeric ratio. The preliminary model reactions suggested that glycosyl aryl boronic acids could be used for stereoselective glycosylation.

One of the central topics in synthetic carbohydrate chemistry is building the glycosyl bond stereoselectively. [1] Although there is no general rule to predict the stereochemistry outcome for a given reagent or condition, glycosylation reactions prefer to give 1,2-*trans* products due to the steric and stereoelectronic effects. [1,2] While 1,2-*trans* outcome can be further ensured by neighboring-group participations, the syntheses of 1,2-*cis* glycosides remain a challenge for carbohydrate chemists.

Among various methods leading to the 1,2-*cis* glycosyl bond, the conceptually intriguing intramolecular aglycon delivery is a unique solution. [3] In this method, it is necessary to tether the donor and acceptor, and the tethering strategies have been classified by R. R. Schmidt into 3 types according to the tethered position and tether nature: leaving group based, bifunctional group based, and non-reacting center based. [3b] An interesting class of leaving group based intramolecular aglycon delivery utilises non-covalent interaction such as hydrogen bonding to organize the donor and the acceptor. [4] Recently, R. R. Schmidt *et al* has developed several useful methods, [5] that employ hydrogen bonding or boron ate complex to organize the supramolecular structure. These methods belong to the category of leaving group based aglycon delivery (Scheme 1).

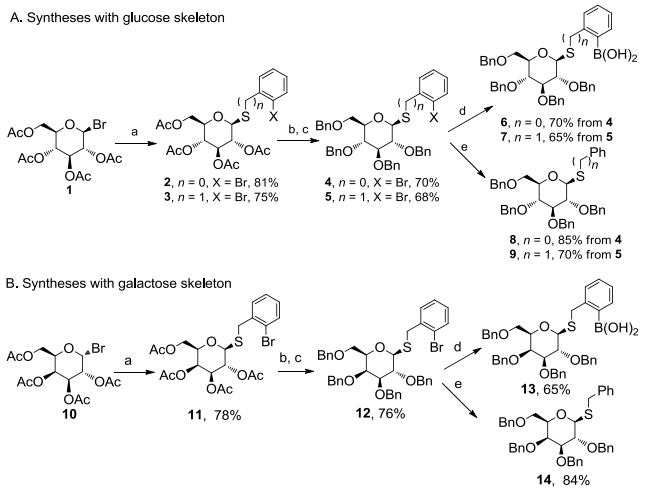
On the basis of our study on glycosyl aryl boronic acids, [6] we speculated if these compounds could be used for leaving group based aglycon delivery (Scheme 1). As the starting material, boronic acid-containing 1,2-*trans*-*S*- or *O*-Glycosides (Scheme 1, structure **I**) are readily prepared. When these boronic acids were treated with the acceptor alcohol, boronate ester or ate complex should be expected. Next, if the sulfide were activated [7] by an oxidating reagent, due to the spatial proximity and orbital arrangement, one of the oxygen nucleophiles on the boronate ester or ate complex [8] might have the opportunity to attack the C-1 center bearing the activated sulfide, with a better control of stereochemistry. Ideally, the product could be a valuable 1,2-*cis*-*O*-glycoside (Scheme 1, structure **II**).



Scheme 1. Several examples of leaving group based aglycon delivery and the design of a boronic acid directed glycosylation.

Following this design, *o*-dihydroxyboryl substituted phenyl and benzyl *S*-glucosides (compound **6** and **7**) and galactoside (compound **13**) were prepared. *O*-Bn Protections were used to minimize the unwanted interruption in the later glycosylation experiments. The syntheses were demonstrated in Scheme 2. From acetobromoglucose

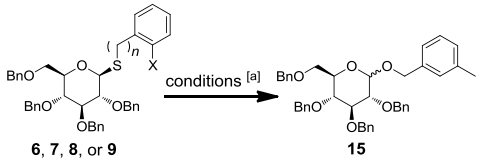
1 and *per*-*O*-acetyl galactosyl bromide **10**, standard *S*-glycosylation method was used to prepare *per*-*O*-Ac glycosides **2**, **3**, and **11**. The *O*-Ac protections on **2**, **3**, and **11** were then removed and the *O*-Bn protections were installed to yield compounds **4**, **5**, and **12**. Bromine containing glycosides **4**, **5**, and **12** were treated with *t*-BuLi and $B(OMe)_3$ successively to produce the desired boronic acids **6**, **7**, and **13** in good yields. Lithiated **4**, **5**, and **12** were also directly quenched with MeOH to give compounds **8**, **9**, and **14**, which were used as control in the following study.



Scheme 2. Preparation of glucosyl donors (**6, 7**, **8**, and **9**) and galactosyl donors (**13** and **14**). Reaction conditions and reagents: a) For compound **2**: 2-bromothiophenol, TBAHS, 1.5 M aq. Na_2CO_3, ethyl acetate, RT, 2h. For compound **3** and **11**: 2-bromobenzyl mercaptan, TBAHS, 1.5 M aq. Na_2CO_3, ethyl acetate, RT, 2h. b) NaOMe, MeOH, rt, 2h. c) NaH, TBAI, BnBr, 1,4-dioxane, 60 ^oC, overnight. d) *t*-BuLi, $B(OMe)_3$, Ether, -78 ^oC to RT. e) *t*-BuLi, CH_3OH, Ether, -78 ^oC to RT.

Glucose derivatives **6** and **7**, along with NBS as a common *S*-activator, were used for the preliminary screening. We chose *m*-methyl benzyl alcohol as glycosyl acceptor, since the glycoside product **15** showed on proton NMR distinct methyl peaks depending on the anomeric configuration. To ensure the reaction between boronic acid and acceptor alcohol, 3.0 equiv of alcohol was stirred with the sugar donor in DCM at RT for 1 h, in the presence of activated 3 Å molecular sieves. The mixture was then cooled to -40 ℃, treated with NBS, and warmed to RT overnight. The resulting mixture was subjected to aqueous workup and HPLC inspection using the purified **15** [9] as control. The results were encouraging: for the phenyl-*S*-glycoside series (Table 1, entry 1 and 2), the *alpha*:*beta* ratio from boronic acid derivative **6** was 2 times higher than that from **8**. For the benzyl-*S*-glycosides **9** and **7** (Table 1, entry 4 and 5), the results were also in favour of **7**. According to these results, it is reasonable to speculate that the boronic acid plays certain role in the delivery of the aglycon moiety. In other experiments (Table 1, entry 3 and 6), TfOH [7, 10] was added to the reaction mixture of the boronic acid derivatives **6** or **7**, and significant change of the anomeric ratio was observed for both cases. [11] In addition, when thiophilic AgOTf was used, deboronation on the starting material **6** and **7** were observed. Therefore we did not use acid or heavy metal reagents in further experiments.

Table 1. Initial screening demonstrated the importance of boronic acid for the glycosylation step.

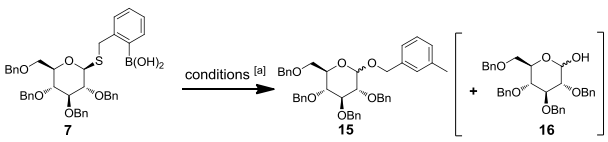


Entry	Donor	*S*-activator	Yield (*alpha*:*beta*) [b]
1	**8**	NBS	40% (2.1:1)
2	**6**	NBS	55% (4.3:1)
3	**6**	NBS, TfOH	91% (1:2.6)
4	**9**	NBS	44% (2.8:1)
5	**7**	NBS	58% (4.8:1)
6	**7**	NBS, TfOH	89% (1:1.5)

[a] Reaction conditions and reagents: 3.0 equiv of 3-methylbenzyl alcohol, 2.2 equiv of activator, 3 Å MS, DCM, -40 ^oC to RT, overnight. [b] Yields and anomeric ratios were determined by HPLC analysis using the pure anomers [9] as control.

Encouraged by the preliminary findings, we performed extensive optimization to improve the stereochemistry outcome of the glycosylation reaction. In table 1, the results from benzyl glycoside **7** and phenyl glycoside **6** were similar. We considered that the benzyl glycoside might enjoy more conformational flexibility which should benefit an efficient delivery of larger acceptors; therefore we used only benzyl glycoside **7** for further optimization. Firstly, different *S*-activators including NIS, NBS, NCS, interhalogens, [12] bromine, MeI and DMTSF (dimethyl-(methylthio)-sulfonium tetrafluoroborate) [4c] were tested (Table 2, entries 1-8). NBS and bromine both showed better stereochemistry outcome (Table 2, entries 2 and 6), and the reaction with NBS looked cleaner by TLC. In addition, one unexpected finding was that IBr gave reversed anomeric ratio in contrast to all other activators (Table 2, entry 4). Next, we kept NBS as the activator and investigated solvent effect in the glycosylation (Table 2, entries 9-12). In ether and toluene, the anomeric ratio was improved. Equally interesting observation was from acetonitrile, with which the anomeric ratio was again reversed in favor of the *beta*-amomer. Therefore, ether was used as the solvent for the third round of screening. In Table 2, entries 13-17, the equivalence of NBS and 3-methylbenzyl alcohol was further optimized. It was found that 5 equiv of NBS and 3 equiv of alcohol acceptor (both to the donor) gave the best anomeric ratio and yield. Decreasing the equivalence of acceptor to 2.0 equiv or 1.0 equiv gave less or no product **15**, and this could be regarded as another evidence supporting that the ate-complex mechanism was involved in the glycosylation. Eventually, the temperature effect was probed. The results in Table 2, entries 18 and 19 suggested that -20 ^oC was an optimal temperature for both stereoselectivity and yield. A major side product from this glycosylation was compound **16**. As a representative example, 25% of compound **16** was isolated from Table 2, entry 14. Compound **16** might come from hydrolysis (during workup procedure) of the *S*-activated intermediate.

Table 2. Optimization of the reaction condition using glucosyl donor **7**.



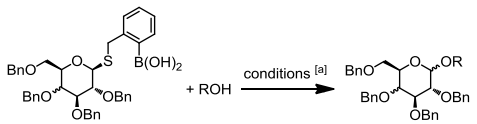
Entry	Solv.	Temp.	*S*-activator [b]	Equiv of alcohol	Yield of **15** [c] (*alpha*:*beta*)
1	DCM	-20 °C	NIS	3.0	43% (1.0:1)

2	DCM	-20 °C	NBS	3.0	49% (3.6:1)
3	DCM	-20 °C	NCS	3.0	No reaction
4	DCM	-20 °C	IBr	3.0	65% (1:10)
5	DCM	-20 °C	ICl	3.0	36% (2.0:1)
6	DCM	-20 °C	Br_2	3.0	37% (4.4:1)
7	DCM	-20 °C	MeI	3.0	No reaction
8	DCM	-20 °C	DMSTF	3.0	48% (1.2:1)
9	MeCN	-20 °C	NBS	3.0	57% (1:4.0)
10	Et_2O	-20 °C	NBS	3.0	51% (7.2:1)
11	THF	-20 °C	NBS	3.0	58% (4.0:1)
12	MePh	-20 °C	NBS	3.0	62% (5.5:1)
13	Et_2O	-20 °C	NBS[d]	3.0	42% (5.3:1)
14	Et_2O	-20 °C	NBS[e]	3.0	71% (9.4:1), with 25% of compound **16**
15	Et_2O	-20 °C	NBS[e]	2.0	31% (2.4:1)
16	Et_2O	-20 °C	NBS	1.0	Trace
17	Et_2O	-20 °C	NBS	5.0	64% (8.2:1)
18	Et_2O	-78 °C	NBS[e]	3.0	30% (3.3:1)
19	Et_2O	0 °C	NBS[e]	3.0	70% (7.8:1)

[a] Reaction conditions and reagents: 3-methylbenzyl alcohol, indicated activator, 3 Å MS, DCM, indicated reaction temperature, overnight. [b] 2.2 equiv of activator was used unless otherwise mentioned. [c] Yields after separation and NMR ratio. [d] 1.0 equiv of NBS was used. [e] 5.0 equiv of NBS was used.

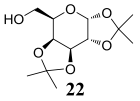
Using the optimized condition described in Table 2, entry 14, we took some simple glycosyl acceptors to study the stereochemistry outcome on donor **7**. Aliphatic alcohols gave moderate yields which seemed not to be affected by the steric hindrance. The stereoselectivity was quite reliable with pure 1,2-*cis* outcomes (Table 3, entries 1-2). To further study the glycosylation, donor **7** was first reacted with 2 equiv. of EtOH at RT and then 1 equiv. *i*-PrOH at -40 °C. At the end, corresponding *alpha*-ethyl and *alpha*-isopropyl glucosides were obtained with 2:1 ratio. Cyclic aliphatic alcohols, as well as the sugar alcohol **22**, gave low to moderate yields, too. Although the anomeric ratio was still good, the erosion of anomeric stereochemistry control indicated that the glycosylation mechanism already changed in these cases (Table 3, entries 4-6). The same reaction condition was applied to galactosyl donor **13** as well and the yields were again moderate (Table 3, entries 7-8). Concerning the stereochemistry, isopropanol consistently gave perfect result, while the sugar alcohol **22** provided lower anomeric ratio. Although the formation of 1-OH pyranoses again significantly diminished yields in all cases in Table 3, the good to perfect 1,2-*cis* glycosylation outcome suggested that glycosyl aryl boronic acid could be a useful glycosyl donor.

Table 3. Screening the cceptors using glucosyl donor **7** and galactosyl donor **13**.



7, config. = *gluco*-
13, config. = *galacto*-

17-21, and **23**, config. = *gluco*-
24-25, config. = *galacto*-

Entry	Donor	ROH	Product, yield (*alpha*:*beta*) [b]
1	**7**	EtOH	**17**, 47% (*alpha* only)
2	**7**	*i*-PrOH	**18**, 42% (*alpha* only)
3	**7**	EtOH: *i*-PrOH = 2:1[c]	**17**:**18** = 2:1, 40% in total (*alpha* only for both) [d]
4	**7**	*t*-BuOH	**19**, 41% (*alpha* only)
5	**7**		**20**, 42% (6.7:1)
6	**7**		**21**, 35% (8.5:1)
7	**7**	 **22**	**23**, 49% (9.8:1)
8	**13**	*i*-PrOH	**24**, 34% (*alpha* only)
9	**13**	**22**	**25**, 45% (5.1:1)

[a] Reaction conditions and reagents: 3 equiv Of acceptor, 5 equiv of NBS, 3 Å MS, ether, -40 °C to -20 °C, overnight. [b] Yields after separation and NMR ratio. [c] 2 equiv of EtOH was mixed with 7. The mixture was stirred at RT for 1 h, cooled to -40 °C, treated with 1 equiv of *i*-PrOH, stirred at -40 °C for 10 min, and then activated by NBS. See supporting information for details. [d] Compounds **17** and **18** were collected as a mixture and analyzed by quantitative ^{13}C-NMR.

Although various results in table 1 and 2 suggested that the glycosylation was related to the boronate ester or boron ate complex intermediate, further control experiments were still desirable. Thus, glycosyl donors **5**, **9**, **12** and **14**, bearing no boronic acid on the phenyl ring, were tested with the optimized glycosyation condition. Except for donor **9**, which gave low yield (11%) of product **15**, essentially no reaction could be observed with donors **5**, **12**, and **14**. These results further indicated that the boron-glycosyl acceptor complex was involved in the aglycon delivery process. It should be noted, however, that at this stage, a detailed mechanistic picture is not clear and different possibilities remain. More studies on related reactions are ongoing.

Table 4. Further experiments showed that the boronic acid is crucial for the glycosylation.

5 (X= Br) and **9** (X= H) , config. = *gluco*-
12 (X= Br) and **14** (X= H) , config. = *galacto*-

15, config. = *gluco*-
26, config. = *galacto*-

Entry	Donor	Product, yield (*alpha*:*beta*) [b]
1	**5**	No reaction
2	**9**	**15**, 11% (6.2:1)
3	**12**	No reaction
4	**14**	No reaction

[a] Reaction conditions and reagents: a) 3.0 equiv of 3-methylbenzyl alcohol, 5.0 equiv of NBS, 3 Å MS, ether, -40 °C to -20 °C, overnight. [b] Yields after separation and NMR ratio.

In conclusion, we prepared a new type of glycosyl donor and attempted a 1,2-*cis* glycosylation method. From readily available glycosyl bromides, through *S*-glycosylation, protection manipulation, and lithiation, 1-dihydroxyboryl phenyl and benzyl *beta*-*S*-glucosides as well as 1-dihydroxyboryl benzyl *beta*-*S*-galactosides were efficiently prepared in good yields as starting materials. Activated by

NBS, 1-dihydroxyboryl benzyl *S*-glucosides served as glycosyl donors for *O*-glycosylation. It was found that the boronic acid moiety was essential in the glycosylation for product formation and good anomeric ratio. After optimization of the glycosylation step, some simple 1,2-*cis*-*O*-glycosides could be prepared with good to perfect anomeric ratio. Although there is room to improve the glycosylation yield and broaden the substrate scope, the preliminary model reactions suggested that glycosyl aryl boronic acids could be used for stereoselective glycosylation.

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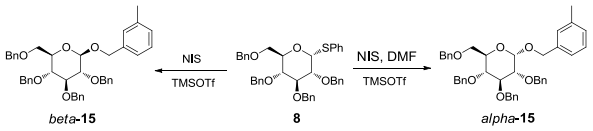
[9] Both anomers of **15** were prepared from compound **8** according to literature procedures. For DMF assisted 1,2-*cis*-glycosylation, see S.-R. Lu, Y.-H. Lai, J.-H. Chen, C.-Y. Liu, K.-K. T. Mong, *Angew. Chem. Int. Ed.* **2011**, *50*, 7315-7320; For experimental details, see supporting information.



[10] G. H. Veeneman, S. H. van Leeuwen, J. H. van Boom, *Tetrahedron Lett.* **1990**, *31*, 1331-1334.

[11] Addition of TfOH could facilitate the departure of the sulphide leaving group, thus reduced the directing effect of boronic acid. Consequently, the native reactivity of cyclic carbohydrate led to a 1,2-*trans* glycoside.

[12] (a) A. Meijer, U. Ellervik, *J. Org. Chem.* **2004**, *69*, 6249-6256; (b) A. Meijer, U. Ellervik, *J. Org. Chem.* **2002**, *67*, 7407-7412; (c) K. P. R. Kartha, L. Ballell, J. Bilke, M. McNeil, R. A. Field, *J. Chem. Soc. Perkin. Trans. 1* **2001**, 770-772; (d) K. P. R. Kartha, P. Cura, M. Aloui, S. K. Readman, T. J. Rutherford, R. A. Field, *Tetrahedron: Asymmetry* **2000**, *11*, 581-593.

Supplementary Material

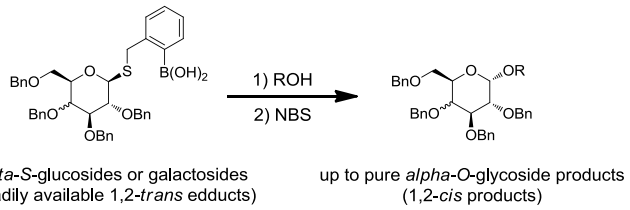
Experimental details and copies of NMR spectra.

Highlights:

- 1,2-*trans*-1-dihydroxyboryl benzyl *S*-glycosides were readily prepared.
- From these compounds, glycosylation with simple alcohols gave pure 1,2-*cis*-*O*-glycoside outcome.
- Boronic acid moiety was found essential for the reaction and the anomeric ratio.

1,2-*trans*-1-Dihydroxyboryl Benzyl *S*-Glycoside as Glycosyl Donor

Xiao Liu, Bingbing Zhang, Xiangying Gu, Guohua Chen, Lin Chen, Xin Wang, Bing Xiong, Qi-Dong You*, Yue-Lei Chen*, and Jingkang Shen*



beta-*S*-glucosides or galactosides (readily available 1,2-*trans* edducts)

up to pure *alpha*-*O*-glycoside products (1,2-*cis* products)