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Boronic Acid Catalyzed Regio- and 1,2-*cis*-Stereoselective Glycosylation of Unprotected Sugar Acceptors via S_Ni-type Mechanism

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ABSTRACT: Regio- and 1,2-*cis*-stereoselective chemical glycosylation of unprotected glycosyl acceptors has been in great demand for the efficient synthesis of natural glycosides. However, simultaneously regulating these selectivities has been a long-standing problem in synthetic organic chemistry. In nature, glycosyl transferases catalyze regioselective 1,2-*cis*-glycosylations via the S_Ni mechanism, yet no useful chemical glycosylations based on this mechanism have been developed. In this paper, we report a highly regio- and 1,2-*cis*-stereoselective S_Ni-type glycosylation of 1,2-anhydro donors and unprotected sugar acceptors using *p*-nitrophenylboronic acid (**10e**) as a catalyst in the presence of water under mild conditions. Highly controlled regio- and 1,2-*cis*-stereoselectivities were achieved via the combination of boron-mediated carbohydrate recognition and the S_Ni-type mechanism. Mechanistic studies using the KIEs and DFT calculations were consistent with a highly dissociative concerted S_Ni mechanism. This glycosylation method was applied successfully to the direct glycosylation of unprotected natural glycosides and the efficient synthesis of a complex oligosaccharide with minimal protecting groups.

INTRODUCTION

Carbohydrates play important roles in many biological processes,[1] including cell proliferation and communication, tumor metastasis, immune recognition, anticoagulation, and microbial pathogenesis. However, understanding these roles at the molecular level has been rather slow relative to comparable studies of proteins and nucleic acids due to the lack of amplification and expression methods of natural glycans. Therefore, to accelerate biological research of carbohydrates, great efforts have been devoted to the development of efficient methods for the chemical synthesis of homogeneous and structurally defined glycosides.[2] While complex natural glycosides have been synthesized in a highly stereoselective manner,[3] these synthetic schemes were highly dependent on protecting group strategies to control the regio- and stereoselectivities of each glycosylation step, leading to a decrease in step and atom economies[4] of the overall process. Therefore, regio- and stereoselective chemical glycosylation without any protecting groups has been in great demand. However, the difficulty in simultaneously regulating the glycosylation site of an unprotected glycosyl acceptor with high regioselectivity and controlling the stereochemistry of the anomeric center with high stereoselectivity is one of the biggest obstacles in protecting-group-free glycosylation.

To overcome this obstacle, regio- and stereoselective chemical glycosylations of unprotected or minimally protected sugar acceptors have been developed. The representative methods of regioselective glycosylations were based on the regioselective enhancement of nucleophilicity of the desired hydroxyl group using the recognition ability of organotin[5] or organoboron[6] compounds. In 1999, regio- and 1,2-*trans*-stereoselective Koenigs-Knorr type glycosylation of unprotected sugar acceptors via arylboronic activation was reported by Aoyama et al.[6a] Recently, Taylor et al.[6b] reported a similar but elegant method, i.e., borinic acid catalyzed regio- and 1,2-*trans*-stereoselective glycosylation of minimally protected sugar acceptors through the S_N2-type mechanism. In a different approach, Kaji et al. reported regio- and 1,2-*trans*-stereoselective glycosylations using arylboronic acid as a transient masking reagent,[7] which decreased the nucleophilicity of undesired hydroxyl groups by the formation of a corresponding cyclic boronic ester. These glycosylation methods require neighboring group participation from the 2-*O*-acyl functionality of the glycosyl donor to produce a 1,2-*trans*-glycoside with high stereoselectivity. Recently, Miller et al.[8] reported high regio- and 1,2-*trans*-stereoselective glycosylation of an unprotected sucrose and sucrose derivatives with a glycosyl fluoride under aqueous conditions. The obtained high regio- and 1,2-*trans*-stereoselectivities could be attributed to the inter-

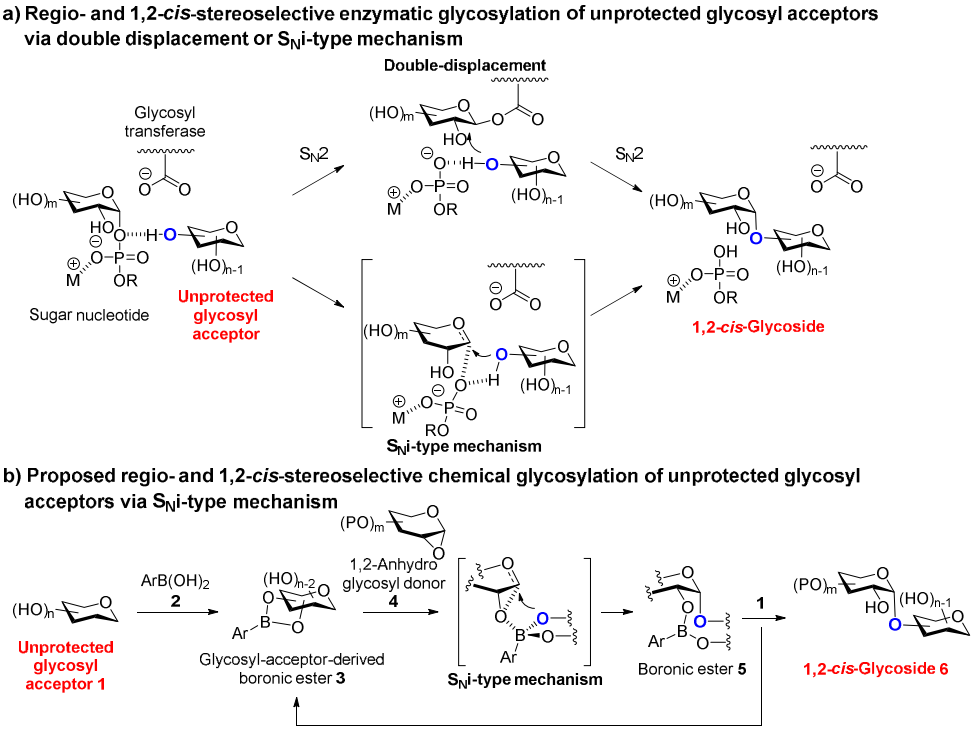


Figure 1. Regio- and 1,2-*cis*-stereoselective enzymatic and proposed chemical glycosylations of unprotected sugar acceptors.

action between a calcium ion and the sucrose moiety. However, in these chemical strategies, there are few regio- and 1,2-*cis*-stereoselective glycosylations of unprotected sugar acceptors.[5a,9]

The stereoselective synthesis of 1,2-*cis*-glycosides is challenging because glycosylations using glycosyl donors that have non-assisting functionality at C2 generally produce anomeric mixtures of glycosides.[10] Therefore, various strategies for 1,2-*cis*-stereoselective glycosylation have been reported, e.g., intramolecular aglycon delivery (IAD),[11] conformationally restrained methods,[12-15] six-membered ring neighboring group participation,[16] hydrogen bond mediated aglycon delivery (HAD)[17] and remote participation.[18] Recently, we reported 1,2-*cis*-stereoselective glycosylations utilizing glycosyl-acceptor-derived boronic[19] or borinic[20] ester catalysts. However, these methods have not been applied to regio- and 1,2-*cis*-stereoselective glycosylations of unprotected glycosyl acceptors.

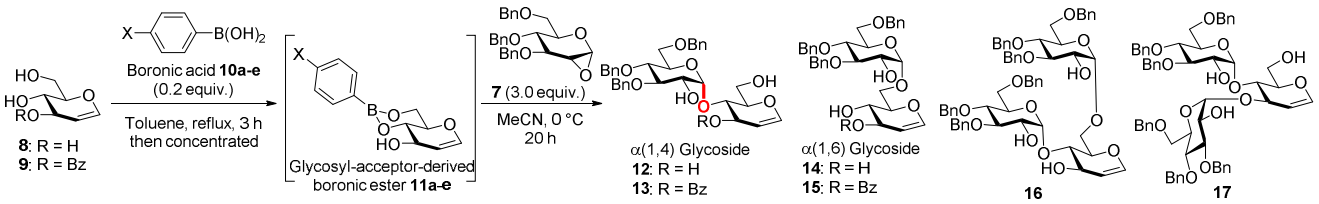
In nature, glycosyl transferases catalyze 1,2-*cis*-glycosylations[21] of nucleotide sugars and unprotected glycosyl acceptors with excellent regio- and stereoselectivities via the well-known double-displacement mechanism or S_Ni-type mechanism, which has recently been studied intensively[22] (Figure 1a). The S_Ni-type glycosylation proceeds with complete stereospecificity due to the synchronicity of the activation of the leaving group in the glycosyl donor and the front-side nucleophilic attack of the glycosyl acceptor without the assistance of the nucleophilic residue required in the double-displacement mechanism. However, no stereoselective chemical glycosylation methods based on the S_Ni-type mechanism have been developed except for the solvolysis of a glucosyl fluoride.[23] Therefore, the S_Ni-type mechanism could provide a new platform for stereoselective chemical glycosylation.

In this context, we expected that the combination of the selective recognition[24] of a diol moiety in an unprotected glycosyl acceptor with a boronic acid and the S_Ni-type mechanism could permit regio- and 1,2-*cis*-stereoselective glycosylation of unprotected glycosyl acceptors. Herein, we report the regio- and 1,2-*cis*-stereoselective glycosylation of unprotected glycosyl acceptors utilizing a boronic acid catalyst via the S_Ni-type mechanism (Figure 1b). A catalytic amount of arylboronic acid **2** selectively and reversibly binds to a diol moiety in an unprotected glycosyl acceptor **1** to give arylboronic ester **3**. The formed Lewis acidic **3** activates the epoxide of 1,2-anhydro donor **4**. Concomitantly, one of the B-O moieties, which has easy access to the anomeric position on the S_Ni-type transition state, is stereospecifically glycosylated from the same face as the 2-*O*-functionality to produce arylboronic ester **5**. An ester exchange reaction between **5** and **1** regenerates **3** and provides the desired 1,2-*cis*-glycoside **6**. To the best of our knowledge, this is the first example of a regio- and 1,2-*cis*-stereoselective S_Ni-type chemical glycosylation of unprotected glycosyl acceptors.

RESULTS AND DISCUSSION

We first selected 3,4,6-tri-*O*-benzyl-1,2-anhydroglucose (**7**) and D-glucal (**8**) as the glycosyl donor and the unprotected glycosyl acceptor, respectively. Under the reported reaction conditions,[19a] a glycosyl acceptor and a catalytic amount of *p*-methoxyphenylboronic acid (**10a**) were refluxed in toluene for 3 hours to prepare the glycosyl-acceptor-derived boronic ester. A solution of the glycosyl donor in acetonitrile was then added and the mixture was

Table 1. Regio- and stereoselective glycosylations of unprotected glycosyl acceptor 8.



Entry	R	X	H_2O (equiv.)	Yields		
				α(1,4) Glycoside	α(1,6) Glycoside	Recovery of acceptor
1	**8**: H	**10a**: OMe	0	**12**: 13	**14**: 0	**8**: 87
2	**9**: Bz	**10a**: OMe	0	**13**: 63	**15**: 0	**9**: 0
3	**8**: H	**10b**: H	0	**12**: 42	**14**: 0	**8**: 58
4	**8**: H	**10c**: F	0	**12**: 61	**14**: trace	**8**: 25
5	**8**: H	**10d**: Cl	0	**12**: 79	**14**: trace	**8**: 19
6[a]	**8**: H	**10e**: NO_2	0	**12**: 49	**14**: trace	**8**: 0
7	**8**: H	**10e**: NO_2	5	**12**: 92	**14**: 6	**8**: 0
8	**8**: H	**10e**: NO_2	10	**12**: 85	**14**: 9	**8**: 0
9[b]	**8**: H	**10e**: NO_2	5	**12**: 93	**14**: 6	**8**: 0

[a]Trisaccharides **16** and **17** were produced in 8% and 15% yields, respectively. [b]Without pre-formation of **11e**.

stirred at 0 °C for 20 h. α(1,4) Glycoside **12** was obtained in only 13% yield (Table 1, entry 1).[25] On the other hand, the use of 3-benzoylated glucal as the glycosyl acceptor under similar conditions gave the corresponding α(1,4) glycoside **13** in 63% yield (entry 2). This result suggested that the electron withdrawing effect of the benzoyl group effectively promoted the Lewis acidic boron atom to activate the 1,2-anhydro donor. Therefore, we focused on increasing the Lewis acidity of the unprotected glycosyl acceptor-derived boronic ester and investigated the electronic effect of the substituent on the benzene ring in the boronic acid. It was found for the first time that *p*-nitrophenylboronic acid (**10e**) showed the highest reactivity, producing α(1,4) glycoside **12** and overreacted trisaccharides **16** and **17** (entries 1 and 3-6). This result suggested that 9-membered boronic ester **18e**, which was formed by the glycosylation of **7** and 6-membered boronic ester **11e**, activated **7** and induced sequential α-stereoselective glycosylation to provide trisaccharides **16** and **17** (Figure 2a).[25]

To suppress this overreaction, we hypothesized that the addition of water could induce rapid hydrolysis of 9-membered boronic ester **18e**, thus inhibiting the activation of donor **7** by **18e**, producing the desired disaccharide **12** and the relatively stable 6-membered boronic ester catalyst **11e** through an equilibrium process (Figure 2b). To investigate our hypothesis, we examined the glycosylation of **7** and **8** using *p*-nitrophenylboronic acid (**10e**) in the presence of water. As expected, when 5 and 10 equivalents of water were added to the reaction mixture, the glycosylation proceeded efficiently to provide **12** in 92% and 85% yields, respectively, without any accompanying trisaccharides (entries 7 and 8). These results suggested that 6-membered boronic ester **11e** can be regenerated and act as a catalyst effectively in this glycosylation process even in the presence of an excess amount of water. In addition, since this glycosylation proceeds faster than hydrolysis by water, this glycosylation mechanism may not be the typical S_N1-type mechanism with an oxonium cation intermediate. Next, when the glycosylation of **7** and **8** using **10e** without pre-formation of **11e** was examined, a similar result was obtained (entry 9) indicating that the pre-formation of **11e** was not necessary.

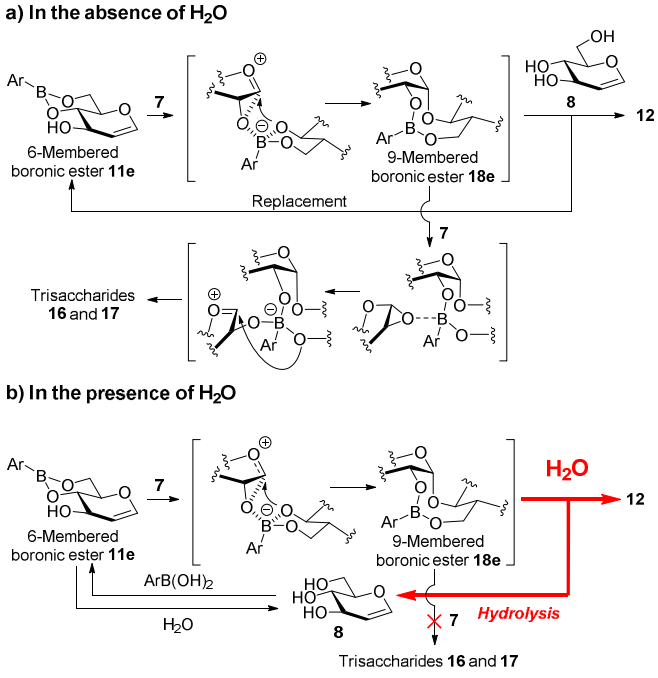
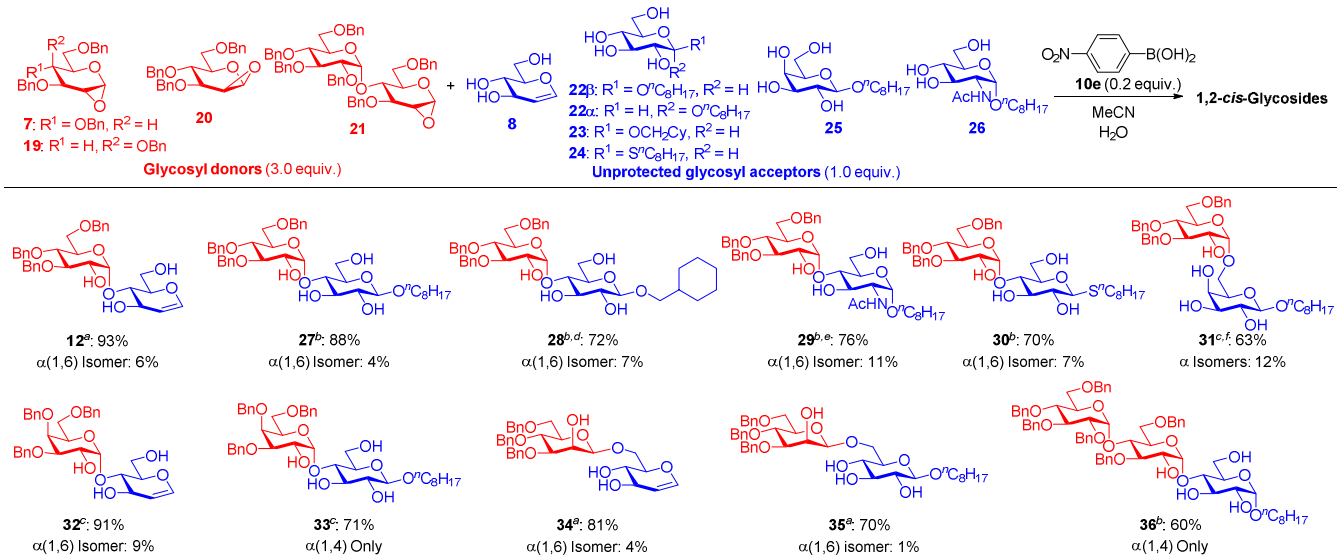


Figure 2. Proposed reaction mechanism in the absence or presence of water.

Table 2. Regio- and stereoselective glycosylations of several unprotected sugar acceptors and 1,2-anhydro donors.

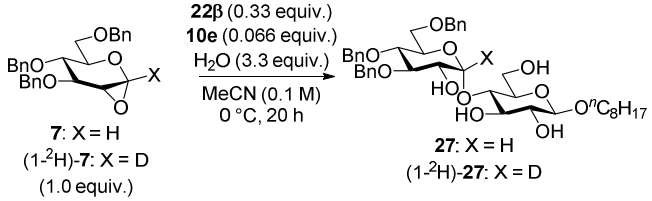


[a]5 equiv. of H_2O was added. [b]10 equiv. of H_2O was added. [c]H_2O was not added. [d]30 equiv. of DMF was added due to the low solubility of **23**. [e]60 equiv. of DMSO was added due to the low solubility of **26**. [f]Reaction was carried with **7** (1.0 equiv.) and **25** (3.0 equiv.).

The scope and selectivities of the glycosylations method were also investigated using several unprotected sugar acceptors and 1,2-anhydro donors (Table 2). 1,2-Anhydroglucose **7** can be efficiently and selectively coupled to a variety of glucose type acceptors **22β**, **23** and **26** to provide α(1,4) glucosides **27**-**29** in high yields, respectively.[25] Furthermore, the use of thioglucoside **24** containing a leaving group at the anomeric position as a glycosyl acceptor gave the corresponding α(1,4) glucoside **30**.[25] On the other hand, when galactoside **25** was used, α(1,6) glucoside **31** was obtained in good yield.[25] Unfortunately, the glycosylation using octyl α-mannoside gave a mixtures of α-glucosides with low regioselectivity (See SI). This low selectivity may be resulted from non-selective formation of 2,3- and 4,6-boronic esters with unprotected mannopyranoside, unlike unprotected gluco- and galactopyranosides, which selectively forms 4,6-boronic esters.[24c,d] α(1,4) Galactosides **32** and **33** were also obtained with similar selectivities by using 1,2-anhydrogalactose **19**.[25] In the case of the β-mannosylation using 1,2-anhydromannose **20**, β(1,6) mannosides **34** and **35** were obtained in good yields with excellent β-stereoselectivities.[25,26] In addition, disaccharide donor **21** was converted into the corresponding trisaccharide **36** in good yields with high regio- and 1,2-*cis*-stereoselectivities under similar conditions.[25] These results clearly demonstrated not only the high regio- and 1,2-*cis*-stereoselectivities but also the high generality of the present glycosylation method. All regioselectivities were consistent with those of previously reported glycosylations of protected diol acceptors.[19]

Overall, this catalytic system with a glycosyl-acceptor-derived boronic ester effectively generated 1,2-*cis*-glycosides from unprotected glycosyl acceptors with high regio- and stereoselectivities. To understand this reaction mechanism, we measured the competitive ^{13}C kinetic isotope effect[27] (^{13}C KIE) (Table 3). In general, the ^{13}C KIEs for S_N1 reactions and S_N2 reactions are 0.995-1.01 and >1.07, respectively.[28] However, in the cases of glycoside hydrolyses and glycosylation reactions, it has been reported that concerted S_N2 reactions become asynchronous S_N2 reactions, which proceed via 'exploded' transition states and display the relatively small ^{13}C KIEs due to the stabilization of partial positive charge at the anomeric position by an oxygen adjacent to the site of displacement. For examples, the ^{13}C KIEs for the spontaneous hydrolysis of

Table 3. The experimental KIEs for the glycosylation of β-glucoside 22β and the calculated KIEs for the transition states at the B3LYP/6-31G* level of theory.



Position of KIE	Experimental KIEs	Calculated KIEs	
		Initial TS	Constrained TS
1-^{13}C	0.9986 (72)[a] 0.9999 (7)[a]	1.009[b]	1.014[c]
1-^{2}H	1.055 (3)[a]	1.114[b]	1.072[c]

[a]The experimental KIEs were measured at 0 °C and were converted to 25 °C assuming $KIE_{25°C} = \exp\{(273/298)\ln(KIE_{0°C})\}$. [b]The calculations of the KIEs were performed using **TS1**. [c]The calculations of the KIEs were performed using **constrained TS** (See SI).

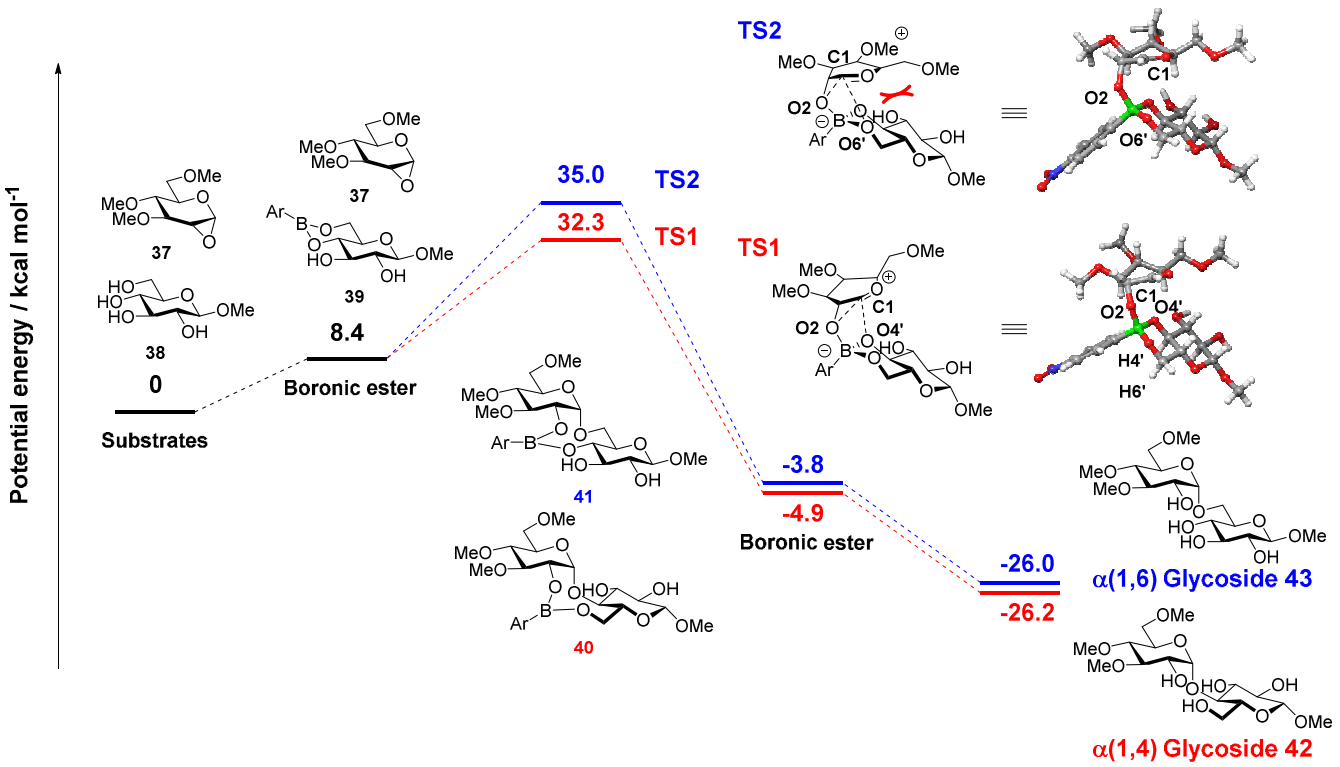


Figure 3. Potential energy surfaces for boronic acid catalyzed glycosylation.

α-glucopyranosyl fluoride, the hydroxide-catalyzed hydrolysis of 4-nitrophenyl α-mannopyranoside, and β-glucosidase catalyzed hydrolysis of methyl β-glucopyranoside were 1.032,[29a] 1.026,[29b] and 1.032,[29c] respectively. In addition, the ^{13}C KIEs for the stereospecific glycosylations with highly dissociative transition states, such as the trehalose-6-phosphate synthase (OtsA) catalyzed glycosyl transfer reaction (1.012)[22a,30] and the macrocyclic thiourea catalyzed glycosylation (1.000),[27b] have been reported to be close to around 1.00. On the other hand, in the case of the present glycosylation, the ^{13}C KIE at the anomeric carbon was determined to be 0.9986(72) and 0.9999(7) compared to the C6 and C3 carbons, used as internal standards, respectively, by the quantitative ^{13}C-NMR technique, indicating that this glycosylation can be regarded as either a S_Ni-type reaction, a highly dissociative concerted S_Ni reaction or a S_N1 with an extremely short-lived intermediate. Next, we measured the α-secondary deuterium kinetic isotope effect (α-SDKIE) for the present glycosylation (Table 3). In the cases of the epoxide ring opening reactions, it has been reported that the α-SDKIE for the S_N2-type acid-catalyzed methanolysis of *p*-nitrostyrene oxide was 1.02,[31a] and the α-SDKIEs for the S_N1-type acid-catalyzed hydrolyses of 1,2,3,4-tetrahydronaphthalene oxide and 6-methoxy-1,2,3,4-tetrahydronaphthalene oxide were 1.08[31b] and 1.05,[31b] respectively. On the other hand, the α-SDKIE for the present glycosylation was determined to be 1.055(3) by the quantitative ^1H-NMR technique using deuterium labelled **7**, (1-^2H)-**7**. Taken together, the experimental results and the previously reported data also suggested that the

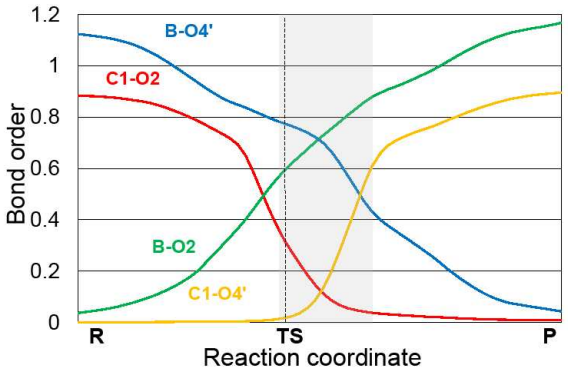


Figure 4. Evolution of the bond orders of the most relevant bonds along the reaction coordinate.

	Transition state model	
	Leads to α(1,4) glycoside	Leads to α(1,6) glycoside
1,2-Anhydroglucose or 1,2-anhydrogalactose	TS-α(1,4) Favored	TS-α(1,6) Disfavored
1,2-Anhydromannose	TS-β(1,4) Disfavored	TS-β(1,6) Favored

Figure 5. Predictive model for regioselectivity of the glycosylations using 1,2-anhydro donors.

present glycosylation proceeded via highly dissociative concerted S_Ni mechanism or a S_N1 mechanism.

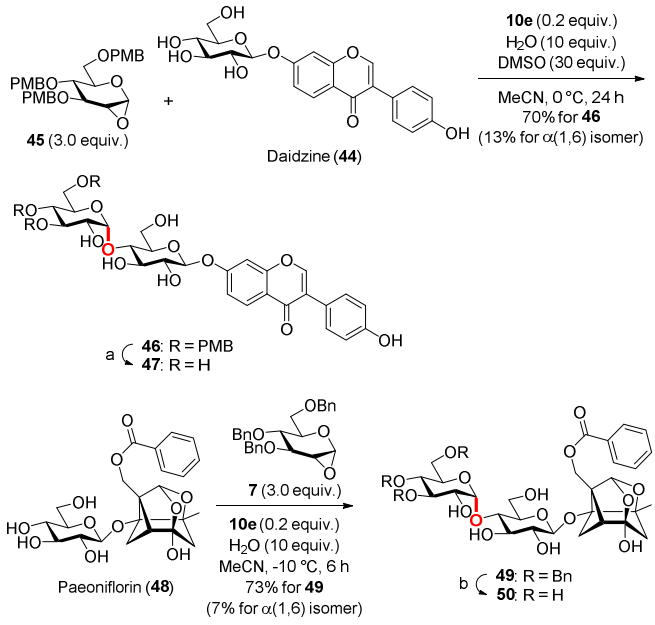
Furthermore, we investigated the reaction mechanism by DFT calculations using Jaguar version 9.1.[32] The quantum chemical level B3LYP/6-31G* was selected for structure optimization and frequency calculation. Single-point energy values were corrected at the higher B3LYP/6-31+G** level. To simplify the substrates, benzyl and octyl groups were changed to methyl groups. The transition state was found at C1-O2 = 2.03 Å and C1-O4' = 2.98 Å (Figure 3, **TS1**). The IRC scan of this TS structure indicated that the glycosylation mechanism of the 1,2-anhydro donor and glycosyl-acceptor-derived boronic ester was a concerted S_Ni mechanism. In addition, using this calculation data, the ^{13}C KIE at the anomeric carbon and the α-SDKIE were calculated by QUIVER.[33] As the results, the calculated anomeric ^{13}C KIE (1.009) was found to be close to the experimental ^{13}C KIE. On the other hand, the calculated α-SDKIE (1.114) was not consistent with the experimental α-SDKIE (1.055), because it is known that the calculated α-SDKIE was highly dependent on the anomeric C-O bond length of the TS structure.[29b] Certainly, the α-SDKIE for **constrained TS** (1.072), which was calculated by optimization the restricted structure (C1-O2 = 1.88 Å), was found to be close to the experimental α-SDKIE. Furthermore, the details of the reaction mechanism were investigated by Mayer natural bond order (NBO)[34] analysis of the reaction coordinates (Figure 4). The results showed that, in the shadowed region, a glycosidic linkage began to form before the bond breakage between the anomeric carbon and epoxy oxygen, indicating that this reaction mechanism is a concerted S_Ni mechanism.

It should be noted that although the epoxide ring opening reactions in generally have early TSs[29b,35] due to the release of the large strain energy (~27 kcal/mol)[36] and low activation energy, the present reaction has a relatively late stage TS and high activation energy probably because of the 1,3-diaxial interaction between aryl group and hydrogen atoms (H4' and H6') in **TS1** derived from a change in boron geometry from trigonal planar as in the 6 membered ring boronic ester **39** to tetrahedral for the 6 membered ring boronate ester **TS1**. Similar 1,3-diaxial interaction in the 6-membered ring boronate complex was reported by Bowie et al.[37]

Next, we searched the transition states in the production of the α(1,6) isomer to rationalize the high regioselectivity of the glycosylation. This transition state was found at C1-O2 = 2.08 Å and C1-O6' = 3.19 Å (Figure 3, **TS2**). We confirmed by IRC scan that the reaction mechanism of glycosylation at the 6 position is also a S_Ni-type mechanism. The difference in activation energy of the glycosylations at the 4 and 6 positions was 2.7 kcal/mol, indicating that the glycosylation at the 4 position is kinetically more favorable. These results are in good agreement with the experimental observations. From transition state structures, the regioselectivity was attributed to the overlap between glycosyl donor and glycosyl acceptor moieties that destabilizes the transition state of the glycosylation at the 6 position. In the case of the glycosylation of galactoside **25**, the high α(1,6) selectivity of the product may be rationalized by similar transition states (See SI). Also, the observed regioselectivities in the β-mannosylations were completely opposite to those in the α-glucosylations and α-galactosylations. The differences in regioselectivities derived from the structure of the glycosyl donor can be easily predicted by the following transition state models (Figure 5). In **TS-α(1,4)**, the glycosyl donor moiety exists apart from the glycosyl acceptor moiety. Conversely, **TS-α(1,6)** is destabilized by the significant overlap between them. In the case of 1,2-anhydromannose **20**, the favorable direction toward the boronic ester was reversed due to the opposite stereochemistry of C2. Therefore, **TS-β(1,6)** is more stable than **TS-β(1,4)**, leading to the production of β(1,6) mannosides **34** and **35** with high regioselectivities.

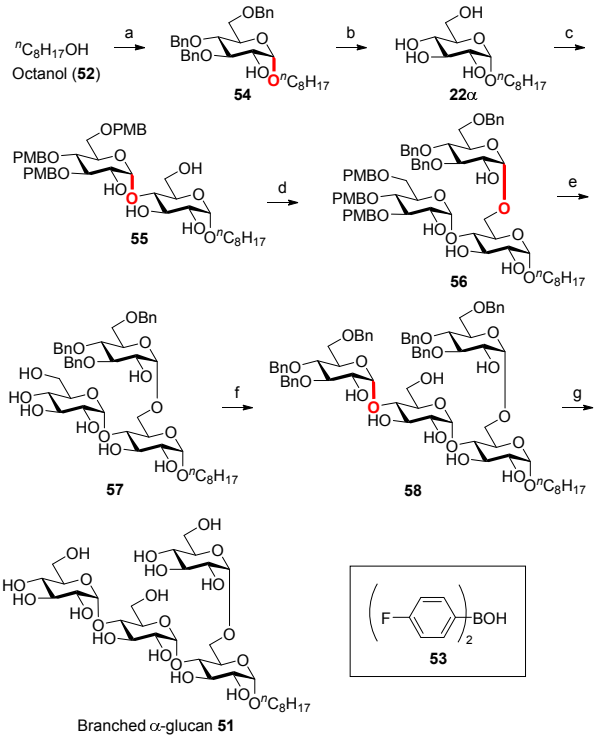
Next, we applied our strategy to the direct glycosylation of unprotected natural glycosides (Scheme 1). The glycosylation using daidzine (**44**), which has five free hydroxyl groups including a phenolic one, as an unprotected glycosyl acceptor and donor **45** proceeded smoothly to give desired α(1,4) glycoside **46** in high yield with high regio- and stereoselectivities. The removal of PMB groups of **46** gave the isoflavone glycoside **47**. Furthermore, when paeoniflorin (**48**), which is a herbal medicine, was employed as an unprotected glycosyl acceptor, desired α(1,4) glycoside **49** was obtained in high yield with high regio- and stereoselectivities. Removal of the benzyl groups of **49** provided α-glycoside **50**. These results indicated that using this glycosylation method, various natural glycosides can be glycosylated with high regio- and stereoselectivities under mild conditions without any modification to the natural glycosides.

Scheme 1. Direct glycosylation of unprotected natural glycosides.[a]



[a]Reagents and conditions: (a) TFA, CH_2Cl_2, 0 °C, 1 h, 90%; (b) $Pd(OH)_2/C$, H_2, THF, MeOH, rt, 20 min, 95%

Scheme 2. The efficient synthesis of branched α-glucan 51 via boronic and borinic acid catalyzed regio- and 1,2-*cis*-α-stereoselective glycosylations.[a]



[a]Reagents and conditions: (a) **7**, **53**, THF, -60 °C, 24 h, 71% (36% for **7**) (α only); (b) Pd/C, H_2, MeOH, rt, 14 h, 99%; (c) **45**, **10e**, H_2O, MeCN, rt, 6 h, 72% (α(1,4) only); (d) **7**, **53**, THF, -80 °C, 16 h, 73% (α(1,6) only); (e) TFA, CH_2Cl_2, rt, 30 min, quant.; (f) **7**, **10e**, H_2O, MeCN, -10 °C, 24 h, 59% (α(1,4) only) (73% BRSM); (g) Pd/C, H_2, MeOH, rt, 18 h, 83%

Finally, we applied the present glycosylation method to the synthesis of branched α-glucan **51** (Scheme 2). Similar oligosaccharides were synthesized by Boons et al.[38] and Demchenko et al.[39] In our synthetic strategy, α(1,4) glycosidic linkages would be constructed using cyclic 4,6-boronic ester catalysts, whereas the other α-glycosidic linkages would be constructed using acyclic borinic ester catalysts derived from a borinic acid and highly reactive primary alcohols in the glycosyl acceptors which does not have a diol group that can form a cyclic complex. Initially, α-glucoside **54** was prepared as a single isomer by the highly 1,2-*cis*-stereoselective glycosylation of 1,2-anhydroglucose **7** and octanol (**52**) using borinic acid catalyst **53**.[20a] Deprotection of the benzyl groups of **54** gave the unprotected sugar **22α** in 99% yield. Next, glycosylation of **45** and **22α** using a catalytic amount of boronic acid **10e** proceeded effectively to provide α(1,4) glycoside **55** in 72% yield with excellent regio- and stereoselectivities. Subsequently, borinic acid catalyzed regio- and stereoselective glycosylation of **7** and **55**, which has four free hydroxyl groups, gave α(1,6) glycoside **56** as a single isomer in 73% yield. Deprotection of the PMB groups of **56** gave trisaccharide **57** which possesses seven free hydroxyl groups. The next boronic acid catalyzed glycosylation gave α(1,4) glycoside **58** in 59% yield (73% BRSM) with excellent regio- and stereoselectivities in the presence of water under mild conditions. Finally, deprotection of the benzyl groups gave branched α-glucan **51**. The anomeric configurations and glycosylated positions were confirmed by coupling constants of anomeric protons and HMBC correlations of benzoylated **58** (See SI).

CONCLUSION

In conclusion, the highly regio- and 1,2-*cis*-stereoselective S_Ni-type glycosylation of 1,2-anhydro donors and unprotected sugar acceptors has been developed using *p*-nitrophenylboronic acid (**10e**) as a catalyst in the presence of water under mild conditions. Highly controlled regio- and 1,2-*cis*-stereoselectivities were achieved via the combination of the boron-mediated carbohydrate recognition and S_Ni-type mechanism. Mechanistic studies using the KIEs indicated that this glycosylation can be regarded as a highly dissociative concerted S_Ni reaction or a S_N1 with an extremely short-lived intermediate. Furthermore, computational analysis supported the feasibility of the highly dissociative concerted S_Ni mechanism and the high regioselectivity of this glycosylation. Our mechanistic studies showed that the 1,2-*cis*-glycosylations based on the similar hypotheses, such as borinic acid catalyzed glycosylation[20] and Me_3Al mediated glycosylation,[40] might proceed through S_Ni mechanism. The picture that emerges for the present boronic acid catalyzed glycosylation involves a stereospecific S_Ni mechanism induced by the simultaneous activation of glycosyl donor and glycosyl acceptor. This occurs in a manner similar to those employed by natural glycosyltransferases that generate 1,2-*cis*-*O*-glycosides through the S_Ni mechanism, suggesting the possibility of the development of other S_Ni type glycosylations using unprotected glycosyl acceptors. Moreover, this glycosylation method was applied successfully to the direct glycosylation of unprotected natural glycosides and the efficient synthesis of branched α-glucan **51** with minimal protecting groups. Further applications of this glycosylation method to the synthesis of biologically active oligosaccharides, glycoconjugates, and natural products are now in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information.
Experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(25) The glycosidic linkage of the obtained glycoside was confirmed by acetylation, and subsequent ^{1}H NMR analysis of the corresponding acetylated glycoside. see the Supporting Information.

(26) The anomeric configurations of the obtained mannoside was determined from the $^{1}J_{CH}$ coupling constants. see the Supporting Information.

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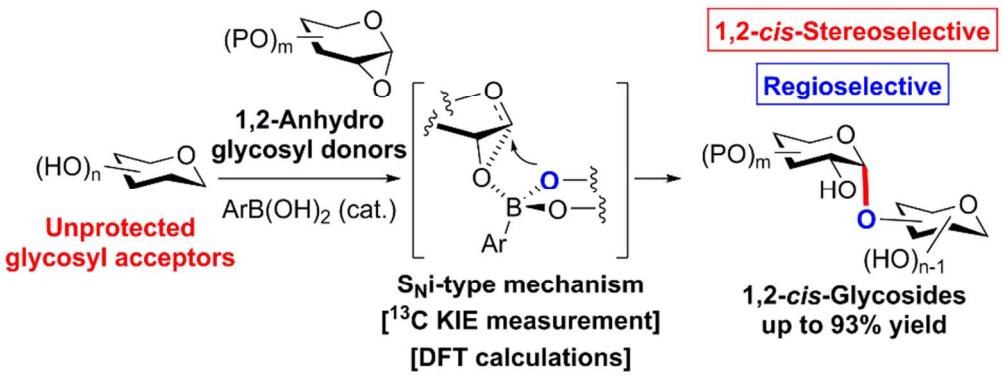

Graphical abstract

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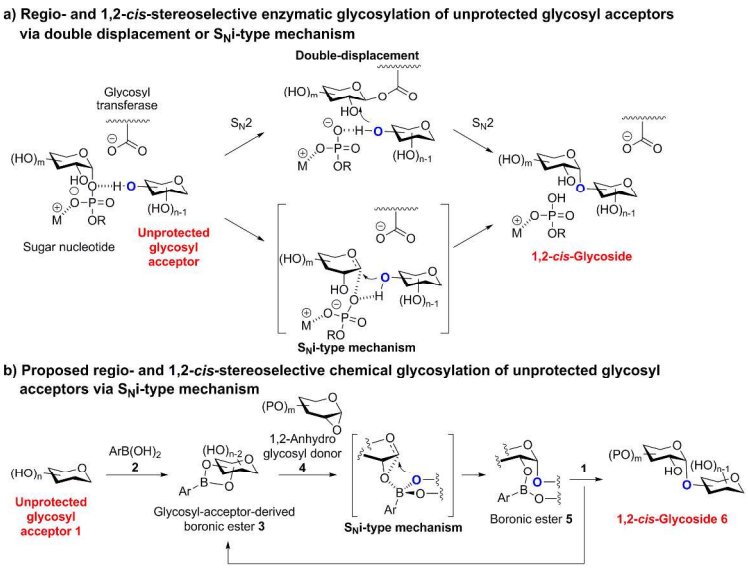

Figure 1

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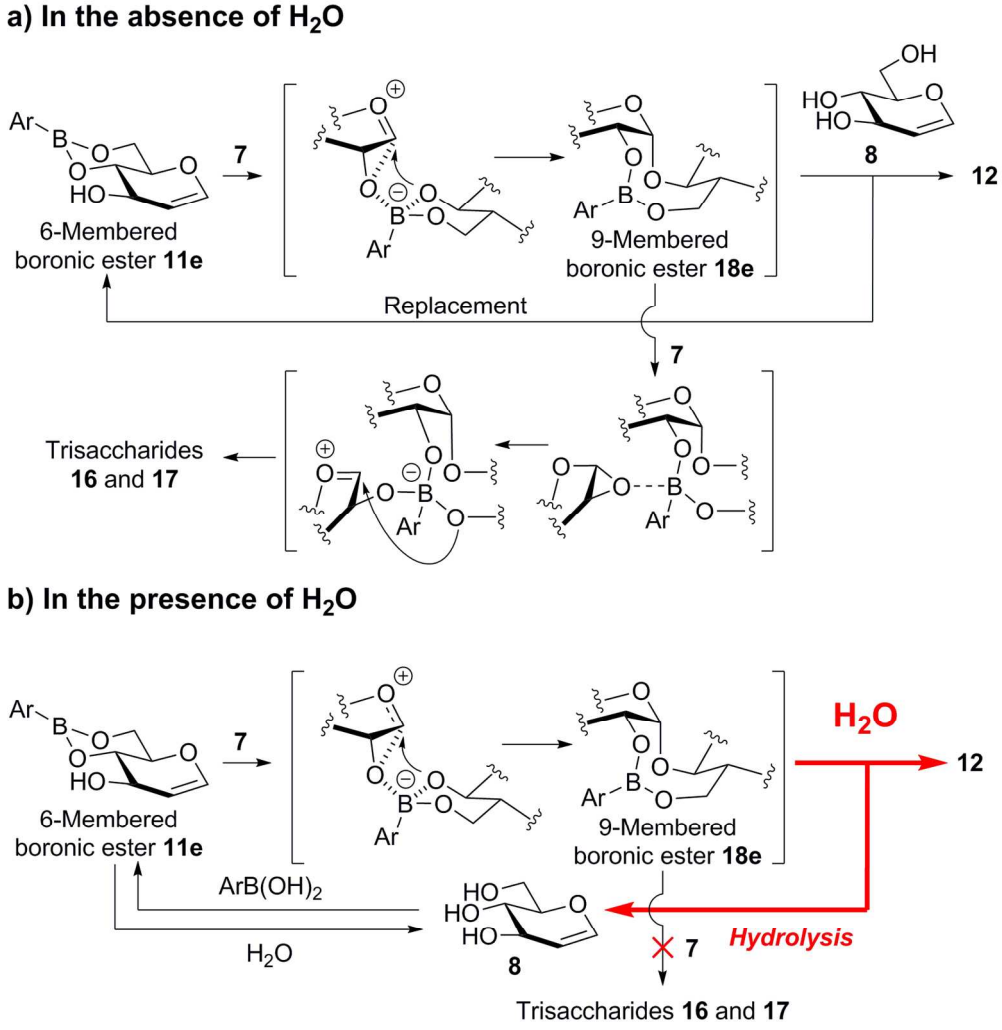

Figure 2

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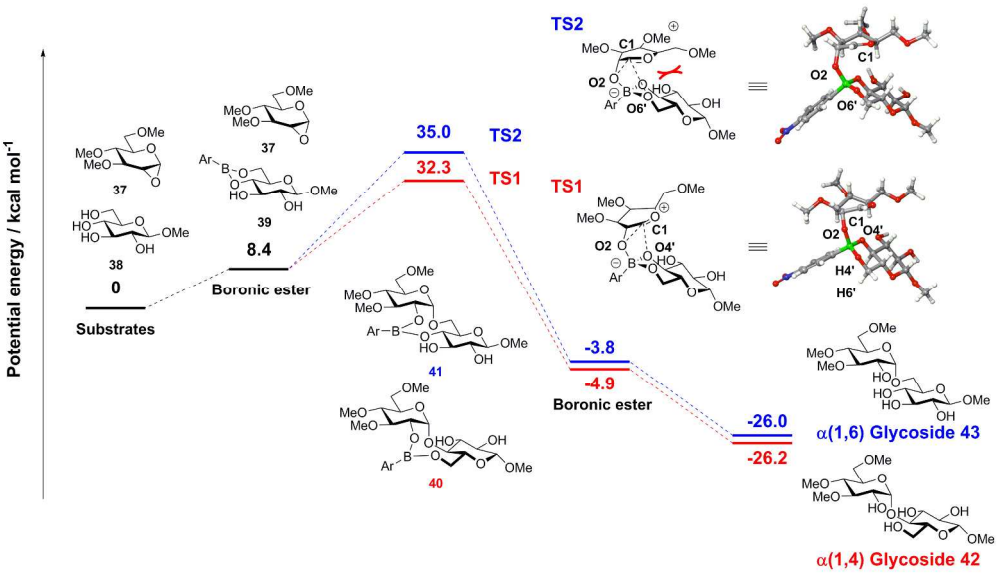

Figure 3

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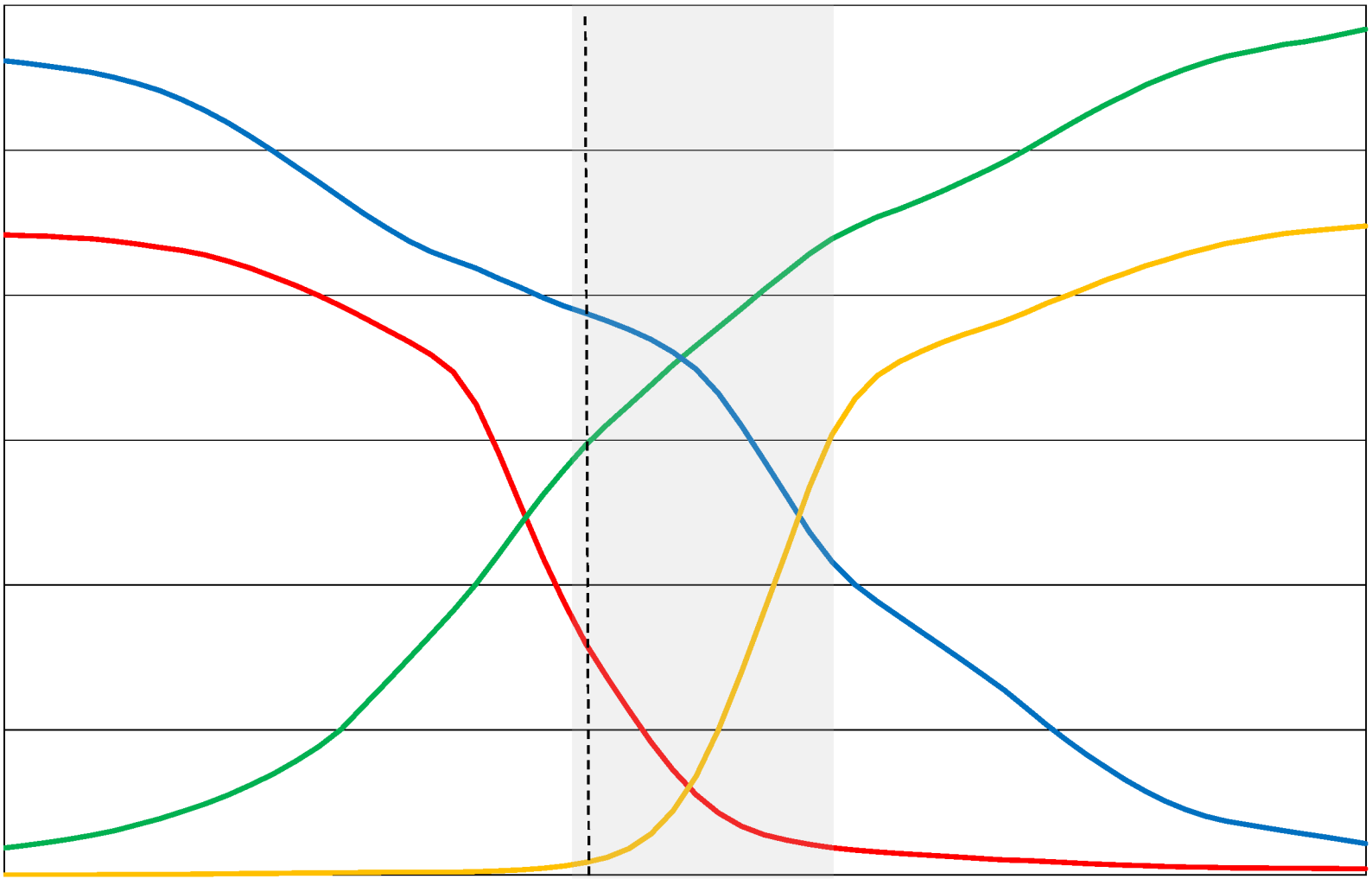


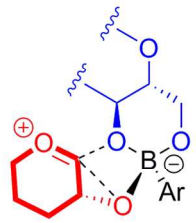
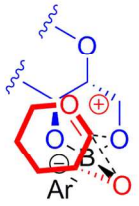
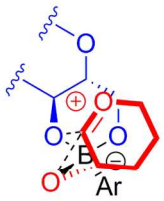
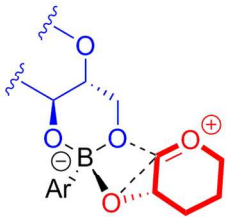
	Transition state model	
	Leads to α(1,4) glycoside	Leads to α(1,6) glycoside
1,2-Anhydroglucose or 1,2-anhydrogalactose	 TS-α(1,4) Favored	 TS-α(1,6) Disfavored
1,2-Anhydromannose	 TS-β(1,4) Disfavored	 TS-β(1,6) Favored

Figure 5

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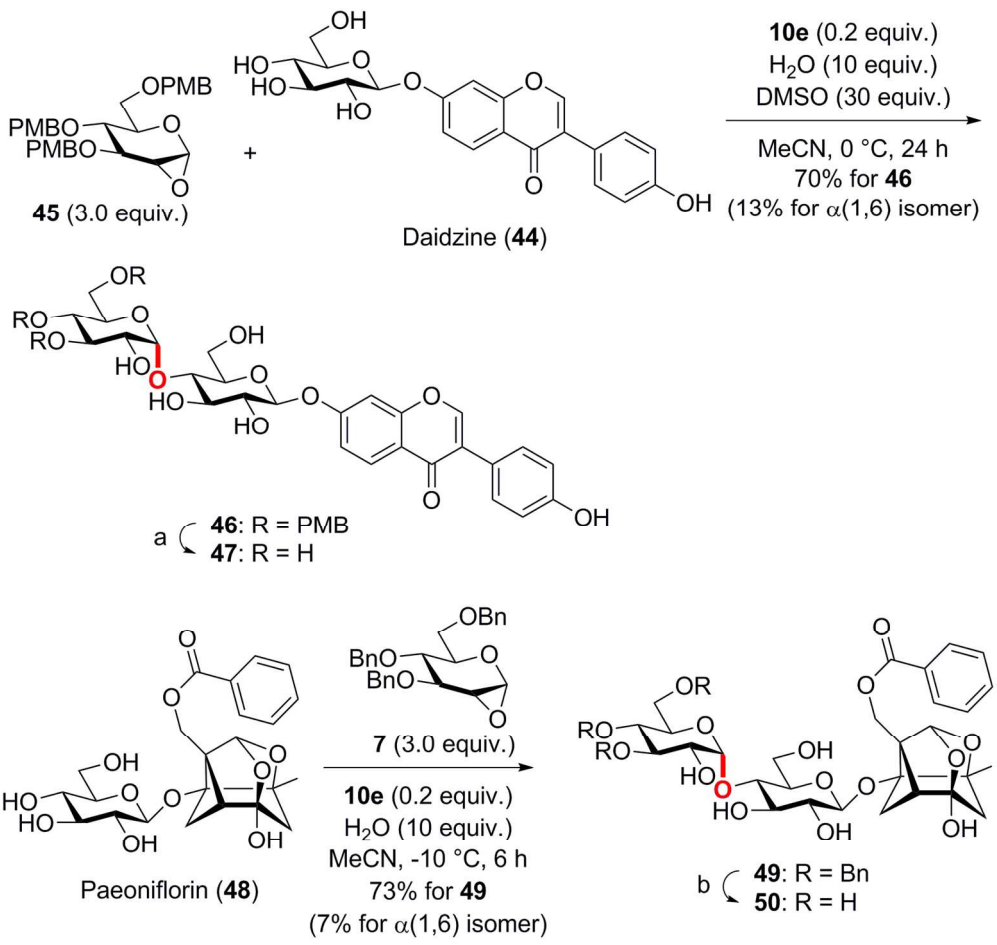
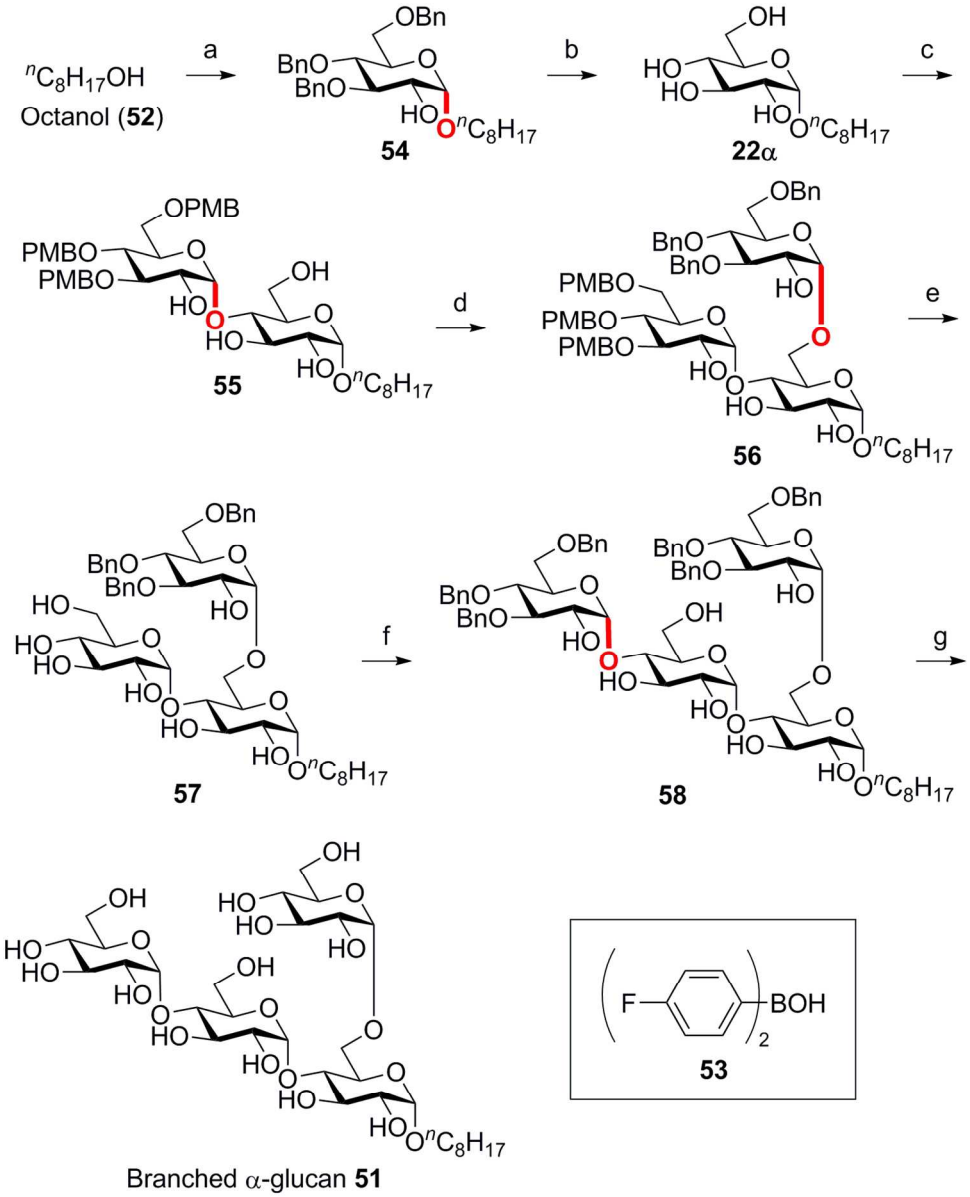


Scheme 1

145x136mm (300 x 300 DPI)



Scheme 2

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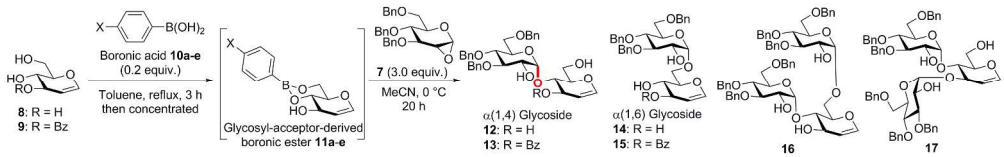

Table 1

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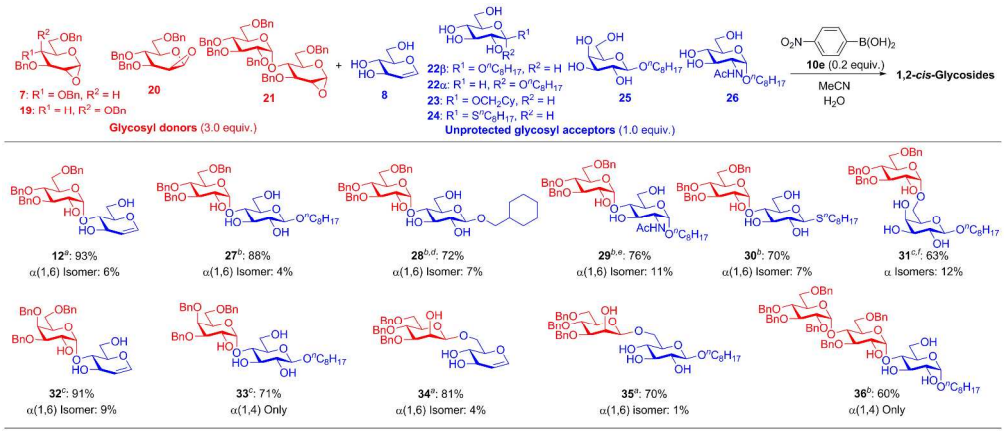

Table 2

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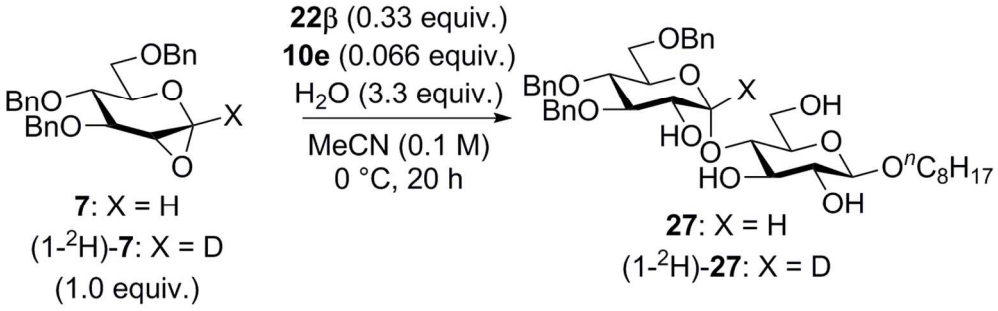

Table 3

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