Carbohydrates

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Regioselective and 1,2-*cis*-α-Stereoselective Glycosylation Utilizing Glycosyl-Acceptor-Derived Boronic Ester Catalyst

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Abstract: *Regioselective and 1,2-cis-α-stereoselective glycosylations using 1α,2α-anhydro glycosyl donors and diol glycosyl acceptors in the presence of a glycosyl-acceptor-derived boronic ester catalyst. The reactions proceed smoothly to give the corresponding 1,2-cis-α-glycosides with high stereo- and regioselectivities in high yields without any further additives under mild reaction conditions. In addition, the present glycosylation method was successfully applied to the synthesis of an isoflavone glycoside.*

1,2-Cis-α-Glycosides are frequently found in many biologically active natural products and glycoconjugates, such as glycolipids, glycoproteins, and proteoglycans. To elucidate the precise biological roles of these carbohydrates, the chemically synthesized homogeneous and structurally well-defined carbohydrates have attracted much attention in chemistry, biology, and medicine.[1] In this context, development of efficient glycosylation methods for the synthesis of 1,2-*cis*-α-glycosides is becoming increasingly important in synthetic organic chemistry. From a synthetic standpoint, the efficiency of the glycosylation reaction was evaluated based on the high chemical yield, as well as α/β-stereo- and regioselectivities. In terms of α/β-stereoselectivity, the synthesis of 1,2-*cis*-α-glycosides is still a challenging task because of the non-availability of neighboring-group participation from a 2-O-acyl functionality in the glycosyl donor. To overcome this problem, efficient indirect[2] and direct[3] methods have been developed. For an example of the indirect method, there is an intramolecular aglycon delivery (IAD), which was introduced by Hindsgaul et al.[4] and extended by Stork et al.,[5] Bols,[6] and Ito and Ogawa.[7] Among them, in 1992, Bols reported a silicon-tethered IAD for the stereoselective synthesis of 1,2-*cis*-α-glycosides.[6] For an example of the direct method, in 1994, Liu and Danishefsky reported[8] a direct glycosylation of 1α,2α-anhydroglucose and stannylated glycosyl acceptors using a stoichiometric amount of $AgBF_4$ for the stereoselective synthesis of 1,2-*cis*-α-glycosides. However, the chemical yields of the obtained glycosides were low to moderate, and unfortunately, the protocol was not applicable to secondary alcohols. In terms of regioselectivity, efficient approaches utilizing not only highly toxic organotin reagents[9] but also low toxicity organoboron reagents[10–12] have been developed. In 1999, Aoyama and co-workers reported[11] a pioneering regio- and stereoselective Koenigs–Knorr-type glycosylation for the synthesis of 1,2-*trans*-glycosides using a stoichiometric quantity of a silver salt and an arylboronic acid for the activation of a glycosyl donor and a specific hydroxy group in the glycosyl acceptor, respectively. Recently, Taylor and co-workers reported[12] a similar type of regioselective Koenigs–Knorr glycosylation using a catalytic amount of an organoborinic acid to afford 1,2-*trans*-glycosides. However, to the best of our knowledge, there are few regio- and stereoselective glycosylation methods for the synthesis of 1,2-*cis*-α-glycosides. Herein, we report a novel regioselective and 1,2-*cis*-α-stereoselective glycosylation of a 1,2-anhydro glycosyl donor and a diol glycosyl acceptor utilizing a glycosyl-acceptor-derived boronic ester catalyst without any further additives under mild reaction conditions.

Our glycosylation strategy is based on the following features of an arylboronic acid, as illustrated in Figure 1:

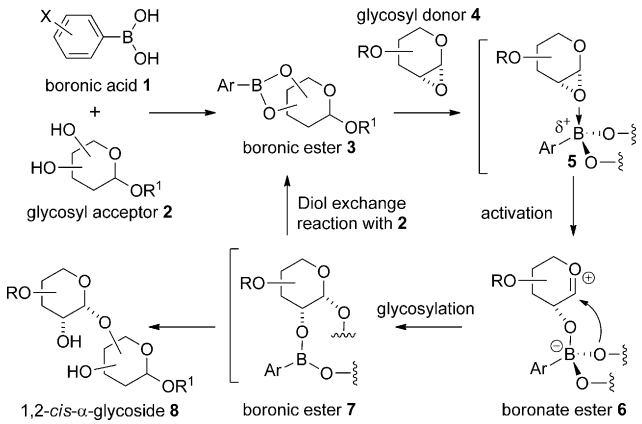

Figure 1. Regio- and 1,2-*cis*-α-stereoselective glycosylation utilizing a glycosyl-acceptor-derived boronic ester catalyst.

1) The arylboronic acid **1** favorably and reversibly binds to either a *cis*-1,2- or 1,3-diol[13] in the glycosyl acceptor **2**; 2) the resulting glycosyl-acceptor-derived boronic ester **3** is expected to show sufficient Lewis acidity to activate the 1,2-anhydro glycosyl donor **4** without any further additives; 3) the formed oxonium cation intermediate **6**, involving a tetracoordinate boronate ester moiety, increases the nucleophilicity of the boron-bound oxygen atom,[11] and concomitant glycosylation[14] from the less-hindered B–O moiety in the boronate

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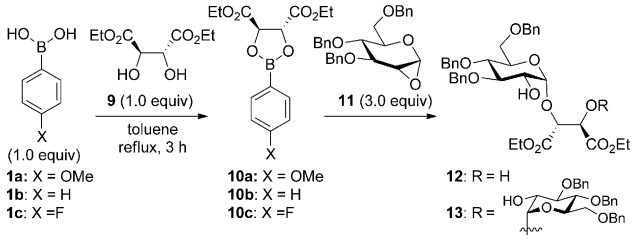
ester affords the corresponding boronic ester **7**; and 4) diol exchange reaction between **7** and **2** regenerates **3** and provides the 1,2-*cis*-α-glycoside **8**.

To investigate our hypothesis, we selected 1α,2α-anhydroglucose **11**,[15] diethyl L-tartrate (DET; **9**), and 4-methoxyboronic acid (**1a**) as the glycosyl donor, glycosyl acceptor, and arylboronic acid, respectively (Table 1). After preparation of the DET-derived boronic ester **10a** by mixing a stoichiometric amount of **1a** and **9** in refluxing toluene for 3 hours, followed by concentration in vacuo, we investigated the glycosylations of **11** and **10a** under several conditions. It was found for the first time that the glycosylation of **11** and **10a** in MeCN at −20 °C for 8 hours proceeded smoothly to give the 1,2-*cis*-α-glycoside **12** in 68 % yield with excellent stereoselectivity along with the diglycoside **13** in 10 % yield as a byproduct (entry 1). The configuration of both of the glycosidic bonds in **13** was confirmed to be α by ^{1}H NMR analysis. This result suggested that the boronic ester **15a**, which was formed by the glycosylation of **11** and **10a**, activated **11** and induced sequential α-stereoselective glycosylation to provide **13** (Figure 2).

Table 1: Glycosylations of **11** and diethyl L-tartrate-derived boronic esters **10a**–**c** under various reaction conditions.



Entry	Solvent	T [°C]	t [h]	Boronic acid	Yield [%] 12[a]	13
1	MeCN	−20	8	**1a**	68	10[a]
2	toluene	−20	8	**1a**	60	0
3	Et_2O	−20	8	**1a**	60	0
4	CH_2Cl_2	−20	8	**1a**	49	0
5	MeCN	0	8	**1a**	54	20[a]
6	MeCN	−40	8	**1a**	76	2[b]
7	MeCN	−40	2	**1a**	45	<1[b]
8	MeCN	−40	4	**1a**	71	<1[b]
9	MeCN	−40	6	**1a**	82	<1[b]
10	MeCN	−40	10	**1a**	69	10[b]
11	MeCN	−40	6	**1b**	55	<1[b]
12	MeCN	−40	6	**1c**	35	<1[b]

[a] Yield of isolated product. [b] Determined by LC/MS.

With this preliminary result in hand, we next examined the solvent effect on the glycosylation of **11** and **10a** by using toluene, Et_2O, and CH_2Cl_2. It was found that when these solvents were used, although excellent stereoselectivities were observed in all cases, chemical yields of **12** were lower than that of the reaction using MeCN under the same reaction conditions (Table 1, entries 1–4). These results indicated that MeCN was the best solvent for this reaction. Next, we optimized reaction temperature and reaction time. When the glycosylation was carried out at 0 °C, the chemical yield of **12** was lower than that obtained at −20 °C because of the increased yield of **13** (entry 5). In contrast, it was confirmed that the chemical yield of **12** increased to 76 % yield at −40 °C, because of the decreased yield of **13** (entry 6). In addition, it was found that a reaction time of 6 hours gave the highest yield of **12** (entries 7–10). Thus, it was found that the glycosylation of **11** and **10a** in MeCN at −40 °C for 6 hours gave the best result, thus producing **12** in 82 % yield.

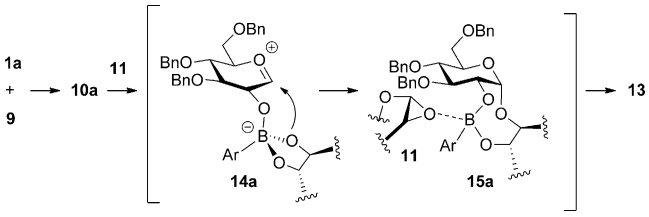


Figure 2. Proposed mechanism for the generation of **13**.

Next, we examined the glycosylations of **11** with **10b** and **10c**, which were prepared from **9** with **1b** and **1c**, respectively, to investigate the electrostatic effect of the substituents on the benzene ring in the boronic esters. It was found that when **10b** and **10c** were used, the chemical yields of **12** were lower than that obtained using **10a**, which possesses an electron-donating methoxy group. In addition, **10c**, possessing an electron-withdrawing fluorine group, gave the lowest yield (35 %) of **12** (Table 1, entries 11 and 12). According to the chemical features of the boronic esters, it is reasonable to assume that the electron-withdrawing group in **10c** increases both the Lewis acidity of the boron atom and the activation rate, but reduces both the nucleophilicity of the boron-bound oxygen atom in the boronate ester and the glycosylation rate, whereas the electron-donating group in **10a** reduces both the Lewis acidity of the boron atom and the activation rate, but increases both the nucleophilicity of the boron-bound oxygen atom in the boronate ester and the glycosylation rate (Figure 3). Taken together, the experimental results and these features of the boronic esters suggest that the rate-determining step of this reaction is the glycosylation step.

Next, we examined the glycosylation of **11** and **9** using a catalytic amount of **10a**. After several attempts to optimize the reaction conditions, it was found that the glycosylation of **11** and **9** in the presence of **10a** in MeCN at −20 °C for

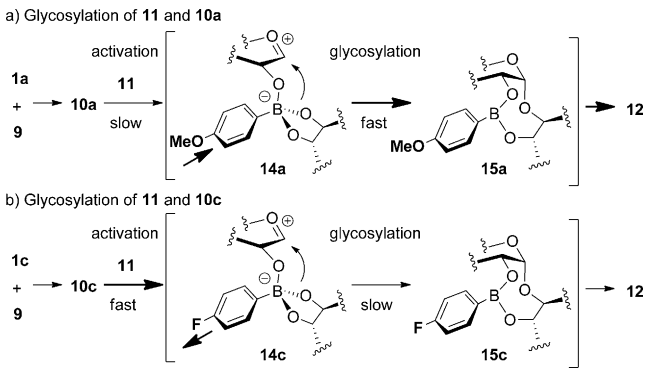


Figure 3. The electrostatic effect of the substituents on the benzene ring in **10a** and **10c** in the glycosylations with **11**.

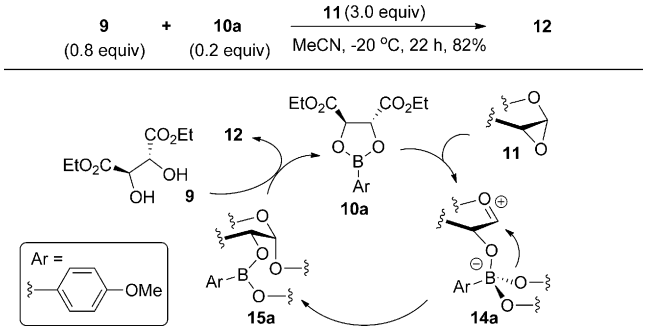
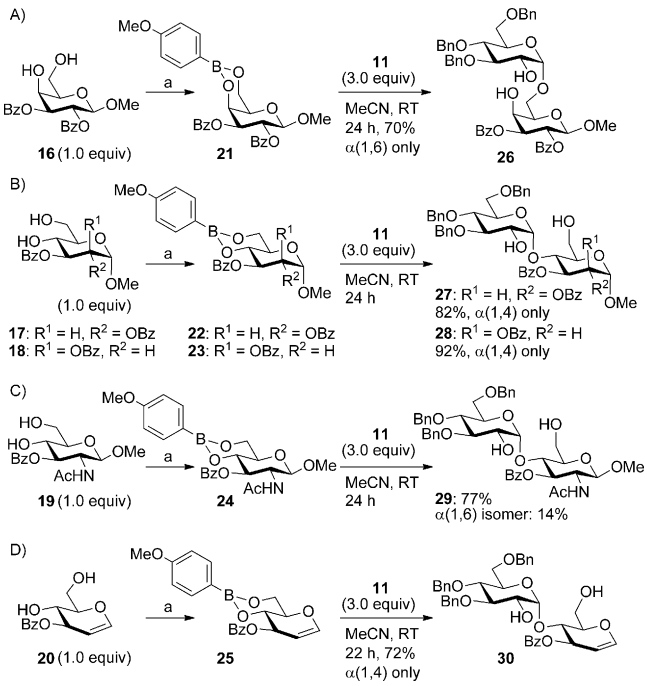


Figure 4. Proposed catalytic cycle for the glycosylation of **11** and **9** using **10a**.

22 hours proceeded effectively to provide **12** as a single isomer in high yield (82%). This result clearly indicates that the diol exchange reaction between **9** and the boronic ester **15a** proceeded smoothly to provide **10a** for re-entry into the catalytic cycle (Figure 4).

With these favorable results in hand, we next examined the regioselectivity and generality of the present glycosylation method using several 1,3-diol sugar acceptors (**16**–**20**; Scheme 1). It was found that when the galactoside **16** and boronic ester **21** were used, excellent regio- and α-stereoselectivities were observed, and only the α(1,6) glycoside **26** was obtained as a single isomer in good yield (Scheme 1 A).[16] Interestingly, when the glucoside **17**, mannoside **18**, glucosaminide **19**, and glucal **20** were employed in the glycosylations using the corresponding boronic esters **22**–**25** it was also found that good to excellent regioselectivities and excellent α-stereoselectivities were observed, and in these cases, the α(1,4) glycosides **27**–**30** were obtained in high yields in the absence of any additives under mild reaction conditions (Scheme 1 B–D).[16]



Scheme 1. Glycosylations of **11** with several 1,3-diol sugar acceptors (**16**–**20**) using the corresponding glycosyl-acceptor-derived boronic ester catalysts **21**–**25**. Reagents and conditions: a) **1a** (0.2 equiv), toluene, reflux, 3 h. Bz = benzoyl.

The observed high regioselectivities may be rationalized by consideration of the following transition states. In the glycosylation of **11** and **16** using **21**, **11** approaches from the equatorial face of the boron atom in **21** to minimize steric hindrance, and generate the oxonium cation involving the boronate ester. At this stage, since significant steric hindrance between the anomeric proton of the oxonium cation and the benzene ring of the boronate ester destabilizes the transition-state TS-1, glycosylation from the oxygen atom at the 6-position takes place through the favored TS-2 to give **26** (Figure 5 a). In contrast, in the glycosylation of **11** and **17** using **22**, a similar steric hindrance between the anomeric proton of the oxonium cation and the benzene ring of the boronate ester destabilizes TS-3 (Figure 5 b). Thus, **27** is regioselectively obtained through the favored TS-4. These models are also consistent with the observed regioselectivities in the glycosylations of **11** and **18** using **23**, **11** and **19** using **24**, and **11** and **20** using **25**.

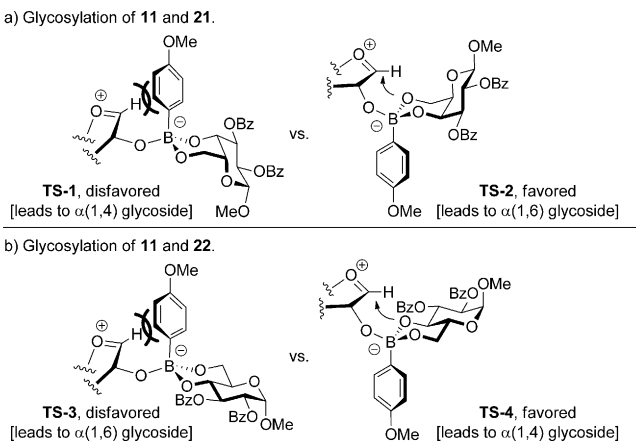
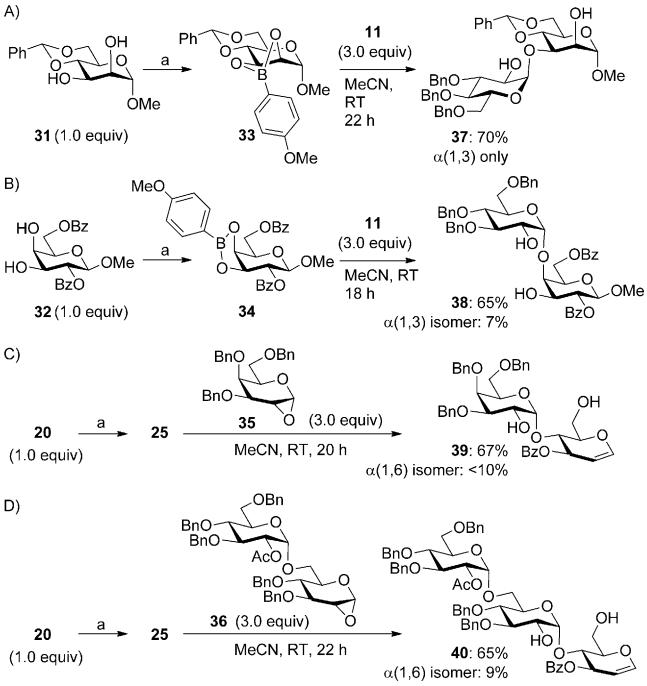
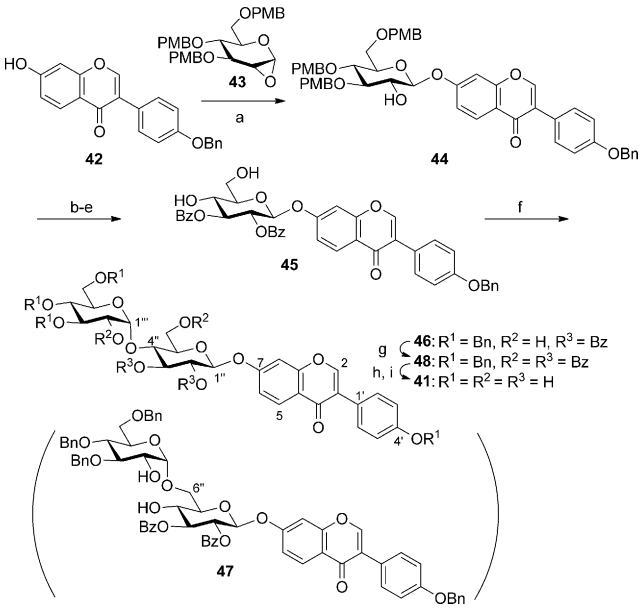


Figure 5. Proposed rationale for the regioselectivity in the glycosylations of a) **11** and **21**, and b) **11** and **22**.

To investigate further the generality of this present method, we next examined the glycosylations of **11** with *cis*-1,2-diol sugar acceptors, that is the mannoside **31** and galactoside **32**. When the glycosylation of **11** and **31** using the boronic ester **33** was conducted, the α(1,3) glycoside **37** was obtained in 70% yield as a single isomer with excellent α-stereoselectivity (Scheme 2 A).[16] When the glycosylation of **11** and **32** using the boronic ester **34** was conducted, it was found that glycosylation at an axial 4-OH in **34** preferentially proceeded to give the α(1,4) glycoside **38** in 65% yield with high regioselectivity [α(1,4)/α(1,3) = 9.3:1] and excellent α-stereoselectivity (Scheme 2 B).[16] Next, we turned our attention to the type of glycosyl donor used. When the 1α,2α-anhydrogalactose **35**[17] and 1α,2α-anhydroisomaltose **36**[8] were employed as glycosyl donors, the glycosylations with **20** using **25** were found to proceed effectively to afford the α(1,4) glycosides **39**[18] and **40**, respectively, with good regio-



Scheme 2. Glycosylations of **11** and the *cis*-1,2-diol sugar acceptors **31** and **32** using the corresponding catalysts **33** and **34** (A and B). Glycosylations of **20** and 1,2-anhydro sugars **35** and **36** using the catalyst **25** (C and D). Reagents and conditions: a) **1a** (0.2 equiv), toluene, reflux, 3 h.



Scheme 3. Total synthesis of the isoflavone glycoside **41** by glycosylation using **1a**, **11**, and **45**. Reagents and conditions: a) *t*BuOK, DMF, 60 °C, 24 h, 65%; b) DDQ, CH_2Cl_2/1,4-dioxane/phosphate buffer (20 mM, pH 7.2; 1:1:1, v/v/v), RT, 12 h, 96%; c) $tBu_2Si(OTf)_2$, pyridine, DMF, −40 to 0 °C, 2 h, 89%; d) BzCl, pyridine, RT, 1 h, 92%; e) TBAF, AcOH, THF, RT, 3 h, 91%; f) **1a**, toluene, reflux, 3 h; then **11**, MeCN/THF (3:1, v/v), RT, 24 h, 77% for **46**, 4% for **47**; g) BzCl, DMAP, pyridine, 40 °C, 2 h, 98%; h) BCl_3, CH_2Cl_2, −78 °C, 2 h, 50%; i) NaOMe, MeOH, 40 °C, 2 h, 92%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMF = *N*,*N*-dimethylformamide, PMB = *p*-methoxybenzyl, TBAF = tetra-*n*-butylammonium fluoride, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

and excellent α-stereoselectivities (Scheme 2C and D).[16] These results clearly indicated not only the good to high regioselectivity and high α-stereoselectivities but also the high generality of the present glycosylation method.

Finally, we applied the present glycosylation method to the synthesis of the isoflavone glycoside **41** (Scheme 3). The isoflavone glycoside was enzymatically synthesized by Hamada and co-workers in 2008.[19] The synthetic scheme for **41** is summarized in Scheme 3. First, the daidzein 7-*O*-β-glucoside **44** was synthesized by a β-stereoselective glycosylation using **43**[20] and 4′-*O*-benzyl-daidzein (**42**)[21] in the presence of *t*BuOK. The compound **44** was converted into the glycosyl acceptor **45** in four steps (1. de-*p*-methoxybenzylation; 2. silylenation; 3. benzoylation; 4. desilylenation). Next, we conducted the glycosylation of **45** and **11** using a catalytic amount of **1a** in MeCN/THF (3:1) at room temperature. It was found that the desired α(1,4) glycoside **46** was obtained in 77% yield with excellent α-stereoselectivity and good regioselectivity along with the minor α(1,6) glycoside **47** in 4% yield. These results also demonstrated the high efficiency and generality of the present glycosylation method. Next, benzoylation of the free hydroxy groups in **46** provided **48**. At this stage, the α(1,4) linkage in **46** was confirmed on the basis of the downfield chemical shift changes for the 6″-H protons in the ^{1}H NMR spectrum, and a correlation peak at 1‴-C with 4″-H in the HMBC spectrum. Finally, removal of the Bn groups in **48** with BCl_3 and subsequent removal of the Bz groups, gave the isoflavone glycoside **41**. ^{1}H NMR, ^{13}C NMR, and HRMS (ESI-TOF) data for an analytical sample of synthetic **41** was found to be identical in all respects with the reported data.[19]

In conclusion, we have developed the first regio- and 1,2-*cis*-α-stereoselective glycosylation utilizing a glycosyl-acceptor-derived boronic ester catalyst without any further additives under mild reaction conditions. The use of 1α,2α-anhydro glycosyl donors and 4-methoxyboronic acid (**1a**) in MeCN was found to be effective for the glycosylations with several diol acceptors. Furthermore, we successfully applied the present glycosylation method to the synthesis of the isoflavone glycoside **41**. Detailed mechanistic studies of this method, application to other types of donors, and synthetic studies of other compounds using the present method are now in progress in our laboratory.

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[18] Since the minor α(1,6) isomer of **39** was not obtained in a completely pure form at this stage, the chemical structure was confirmed by acetylation, purification, and subsequent ^{1}H and ^{13}C NMR analysis. See the Supporting Information.

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