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Completely β-Selective Glycosylation Using 3,6-*O*-(*o*-Xylylene)-Bridged Axial-Rich Glucosyl Fluoride

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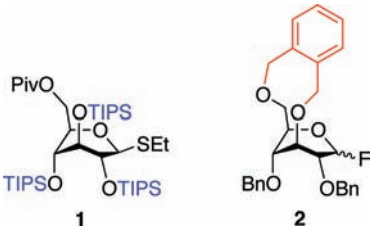
Supporting Information

ABSTRACT: A completely β-selective glycosylation that does not rely on neighboring group participation is described. The novelty of this work is the design of the glycosyl donor locked into the axial-rich form by the *o*-xylylene bridge between the 3-*O* and 6-*O* of D-glucopyranose. The synthesized 2,4-di-*O*-benzyl-3,6-*O*-(*o*-xylylene)glucopyranosyl fluoride could efficiently react with various alcohols in a $SnCl_2$–$AgB(C_6F_5)_4$ catalytic system. The mechanism composed of the glycosylation and isomerization cycles was revealed through comparative experiments using acidic and basic molecular sieves. The achieved perfect stereocontrol is attributed to the synergy of the axial-rich conformation and convergent isomerization caused by $HB(C_6F_5)_4$ generated in situ.

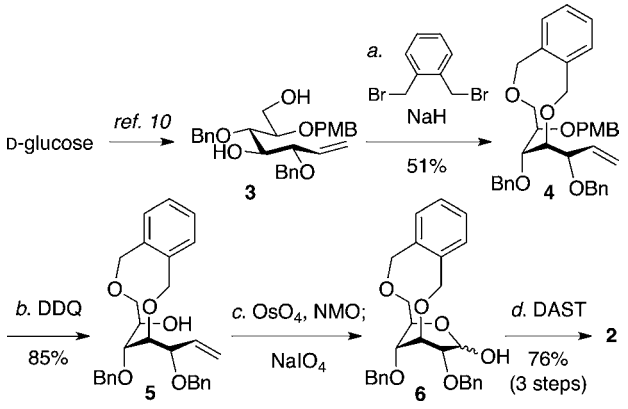
Complete control of anomeric stereoselectivity has been one of the most important needs to be achieved in chemical glycosylation. Stereocontrol on the basis of neighboring group participation (NGP) by a 2-*O*-acyl group has often fulfilled expectations to furnish 1,2-*trans*-*O*-glycosidic linkages.[1] On the other hand, stereocontrol that does not rely on the NGP strategy has also been developed, but the range of reaction conditions allowing high selectivity is narrow.[2,3] In addition, despite the high selectivity, the production of a small proportion of the undesired isomer eventually requires separation processes to obtain the pure desired isomer. In this regard, the development of a completely stereoselective glycosylation methodology has been challenging.

As a recently developed methodology for stereoselective glycosylation, the utilization of conformationally locked glycosyl donors has been discussed.[4] Bulky silyl protecting groups have often been introduced onto the adjacent *trans*-diols of carbohydrates in order to lock the conformation into axial-rich forms, which are conformations possessing more axial substituents (e.g., **1**).[5] In the case of *O*-glucosylation with conformationally locked glycosyl donors, high but incomplete β-selectivity has been observed.[6,7] In the reactions, reductions in the reactivity and migration of the trialkylsilyl groups due to the intense steric hindrance of the bulky silyl groups have been observed.[6,8,9] To resolve these problems and extend this methodology to stereocontrol based on conformational restriction, sterically less hindered, more robust, and easily removable locking methods are desired. We describe here a completely β-selective glycosylation using the novel axial-rich glycosyl donor **2**, in which the conformation is locked by a 3,6-*O*-(*o*-xylylene) bridge. We also describe the reaction mechanism.



Because simultaneous 3,6-bridge formation with inversion of the pyranose into an axial-rich conformation is unattainable,[10] we applied a temporary ring-opening strategy to synthesize **2** starting from known diol **3** (Scheme 1). The *o*-xylylene bridge[11] was introduced into **3** by using NaH and α,α′-dibromo-*o*-xylene to produce 3,6-*O*-bridged **4**. Treatment with DDQ removed the PMB group to provide **5**. Oxidative cleavage

Scheme 1. Synthesis of 2,4-*O*-Benzyl-3,6-*O*-(*o*-xylylene)glucopyranosyl Fluoride (2)[a]



[a]Reagents and conditions: (a) α,α′-dibromo-*o*-xylene, NaH, DMF, rt, 10 min, then 100 °C, 1 h, 51%; (b) DDQ, CH_2Cl_2, phosphate buffer (pH 7.41), 0 °C, 1.5 h, 85%; (c) OsO_4, NMO, acetone/H_2O (5/1 v/v), rt, 2 h, then $NaIO_4$, rt, 5 h; (d) DAST, THF, 0 °C to rt, 30 min, 76% for three steps; sonication in MeOH/*n*-hexane, α/β = 8/92. Abbreviations: DAST, (diethylamino)sulfur trifluoride; DDQ, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; DMF, *N*,*N*-dimethylformamide; NMO, *N*-methylmorpholine *N*-oxide; PMB, *p*-methoxybenzyl; THF, tetrahydrofuran.

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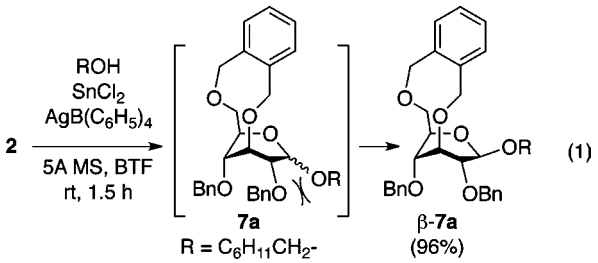
of the terminal double bond of **5** produced pyranose **6**. Fluorination at the anomeric position of **6** furnished the desired product **2** as an air-stable white powder. ^{1}H NMR analysis revealed that the pyranose ring of β-**2** is certainly locked into the axial rich $^1S_3$ conformation.[12]

To develop an efficient glycosylation using **2**, previously reported methods for activation of glycosyl fluorides were investigated.[13−15] The preliminary screening revealed that catalytic use of $SnCl_2$−$AgB(C_6F_5)_4$, as reported by Mukaiyama,[15] was promising. We thus optimized this reaction with **2** and cyclohexylmethanol as the glycosyl donor and acceptor, respectively. Finally, we chose the following reaction conditions for the completely β-selective glycosylations: **2** (1.0 equiv), ROH (1.2 equiv), $SnCl_2$ (0.2 equiv), $AgB(C_6F_5)_4$ (0.2 equiv), and 5A molecular sieves (MS) (3.0 g/mmol of **2**) in benzotrifluoride (BTF)[16] at room temperature (rt). These reaction conditions were applied in the following investigations into the scope and clarification of the reaction mechanism.

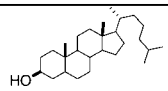
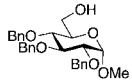
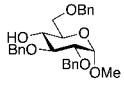
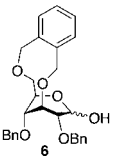
Interestingly, the optimal reaction conditions included isomerization of the α-anomeric isomer into the β-isomer (eq 1). At the beginning of the reaction, both the α- and β-isomers



were detected, and then the α-isomer disappeared gradually. This observation indicated that the β-isomer of **7a** is thermodynamically more stable than the α-isomer. Despite the existence of the *o*-xylylene bridge over the β-face of the pyranose, the thermodynamic stability was more affected by the 1,2-cis repulsion between the anomeric alkyloxy and axially oriented 2-*O*-Bn groups. Density functional theory (DFT) calculations[17] indicated that β-**7a** is 21.0 kJ/mol more stable than α-**7a**. The stereochemistry of β-**7a** was confirmed after returning the pyranose ring to the $^4C_1$ conformation by hydrogenolytic cleavage of the benzyl and *o*-xylylene groups.

To investigate the scope and limitations of this reaction, the optimal reaction conditions were applied to several alcohols (Table 1). The perfect β-stereoselectivity observed in all cases was noteworthy; the α-isomers were not detected by ^{1}H NMR analysis of the crude products. The yields of the glucosides were good to excellent. With simple aliphatic alcohols (entries 1 and 2), the β-glycosylation proceeded quite smoothly, providing the glycosides in >90% yield, even with the tertiary alcohol. With partially protected sugars (entries 3 and 4), the yields were ∼80%. As described above, convergent anomeric isomerization was induced in the β-selectivity. Since the α-methoxy groups of the glycosyl acceptors survived without being isomerized, the isomerization rate for the axial-rich glycosides would be faster than for the equatorial-rich glycosides. This phenomenon could be explained by the conformational-arming theory reported by Bols and co-workers,[9,18] which states that an axially oriented polar substituent stabilizes a positive charge (oxocarbenium ion in this case) more effectively than the corresponding equatorial equivalent. To show the effectiveness of this new β-

Table 1. β-Glycosylation Reaction Using Glucosyl Fluoride 2 with Various Glycosyl Acceptors

Entry	ROH	Time (h)	Product[a]	Yield (%)[b]
1		5.5	β-7**b**	92
2		4	β-7**c**	96
3[c]		3	β-7**d**	83
4[c]		3.5	β-7**e**	82
5[d]		3	β,β-7**f**	92

[a]The stereochemistries of β-7**b**−**f** were confirmed after removal of the benzyl and *o*-xylylene groups. [b]Isolated yields. [c]1.5 equiv of glycosyl acceptor was used. [d] The reaction temperature was 0 °C.

glycosylation reaction, we applied this method to the synthesis of β,β-trehalose, which possesses a 1,1-β,β-glycosidic linkage. Pyranose **6** successfully coupled with **2** (entry 5) to provide only the β,β-trehalose derivative **7f**, although glycosyl acceptor **6** was a mixture of anomers.

We next investigated the reaction mechanism and found that this complete β-glycosylation is composed of glycosylation and isomerization cycles (Scheme 2). The glycosylation cycle is triggered by the generation of $SnB(C_6F_5)_4Cl$ (**8**) as the actual catalyst.[15] The catalyst activates glucosyl fluoride **2**, generating oxocarbenium ion **9** along with SnClF. Intermediate **9** couples with an alcohol to provide glycoside **7**, initially as an anomeric mixture. This glycosylation is accompanied by the formation of $HB(C_6F_5)_4$ (**10**), which reacts with SnClF to regenerate **8**. In the isomerization cycle, **10** isomerizes α-**7** into the thermodynamically more stable β-isomer via oxocarbenium ion **9** to afford β-**7** only. The following paragraphs describe in detail the investigations into the mechanism.

The reaction between **9** and an alcohol provides glycoside **7** along with the protic acid **10**, which has been reported by Mukaiyama to be an effective catalyst for activating a glycosyl fluoride.[19] These facts prompted the following question: which species is the real catalyst of this reaction: **8** or **10**? To clarify the actual catalytic species experimentally, we utilized the properties of molecular sieves: acidic 5A MS[20] and basic 4A and 3A MS.[21,22]

Table 2 summarizes the results of comparative experiments using the acidic and basic MS. The two reagents **8** and **10** were generated according to eqs 2 and 3,[14,15] respectively. When **10** activated **2** (entries 1−4), differences appeared in the yield. An approximately 80% yield of β-**7a** was produced without MS or with 5A MS (entries 1 and 2), whereas no reaction occurred with 4A and 3A MS (entries 3 and 4). In the former two entries, **10** could act as the actual catalyst. In contrast, the basic

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Scheme 2. Possible Catalytic Cycle

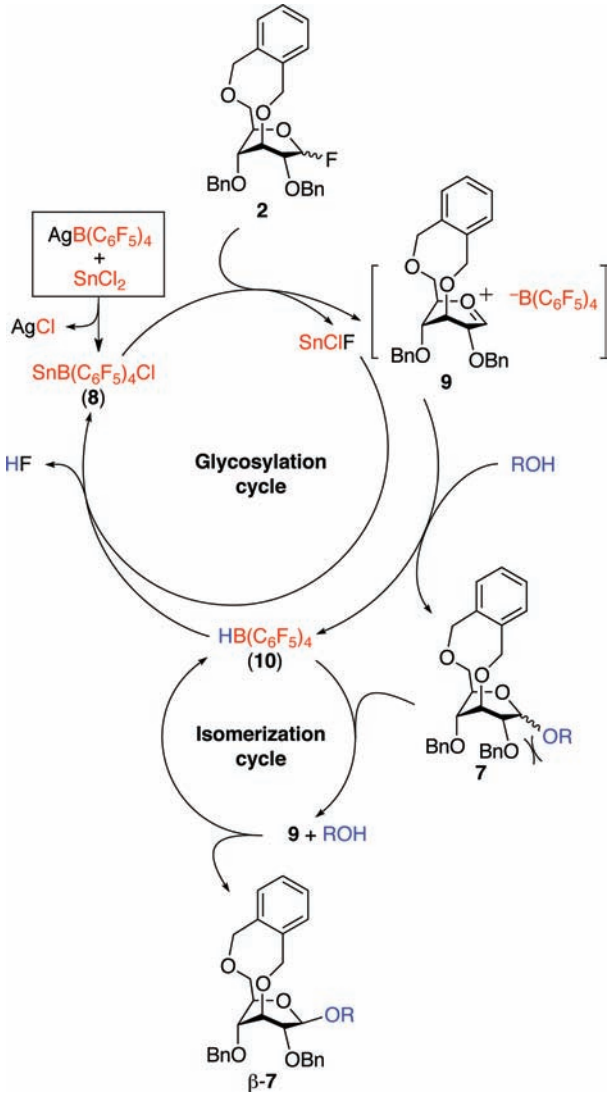


Table 2. Effects of MS in the Glycosylation Reactions Catalyzed by $SnB(C_6F_5)_4Cl$ (8) or $HB(C_6F_5)_4$ (10)

$$\mathbf{2} + \underset{(1.2\ \text{equiv})}{C_6H_{11}CH_2OH} \xrightarrow[\text{MS, BTF, rt}]{\text{reagent (0.2 equiv)}} \mathbf{7a}$$

entry	reagent	MS	actual catalyst	yield (%)	α/β ratio
1	**10**	none	**10**	78	>1/99
2	**10**	5A	**10**	80	>1/99
3	**10**	4A	none	0[a]	–
4	**10**	3A	none	0[a]	–
5	**8**	none	**8** or **10**	96	>1/99
6	**8**	5A	**8** or **10**	98	>1/99
7	**8**	4A	**8**	95	60/40
8	**8**	3A	**8**	90	67/33

[a]No reaction.

MS shown in the latter two entries deactivated the protic acid **10**; therefore, no "actual catalyst" existed in the reaction system.[23] These results show that **10** can catalyze the glycosylation reaction under acidic conditions but not under basic conditions.

$$AgB(C_6F_5)_4 + t\text{-BuBr} \rightarrow \underset{(\mathbf{10})}{HB(C_6F_5)_4} + H_2C{=}CMe_2 + AgBr \quad (2)$$

$$SnCl_2 + AgB(C_6F_5)_4 \rightarrow \underset{(\mathbf{8})}{SnB(C_6F_5)_4Cl} + AgCl \quad (3)$$

When **8** was applied as the reagent (entries 5–8), **7a** was provided in >90% yield. Differences appeared in the anomeric ratio. Under acidic reaction conditions (entries 5 and 6), both **8** and **10** could act as the actual catalyst, but **8** was likely to be more efficient because the yield of **7a** was 10–20% lower when only **10** was applied (entries 1 and 2 vs 5 and 6). With the basic MS (entries 7 and 8), the MS could counteract **10** generated by the glycosylation reaction (see Scheme 2), and thus, only **8** remained as the actual catalyst. These results demonstrate that **8** is not affected by the basic MS and is the actual catalyst in these reactions. Thus, there should be a pathway to revive **8** as the final step of the glycosylation cycle.

The conversion from **10** and SnClF to **8** (eq 4) is considered to be possible on the basis of the acidities of HF (pK_a = 3.2) and **10**. Although the pK_a value of **10** is not described in the literature, $B(C_6F_5)_4^-$ is known as an activated anion whose nucleophilicity and coordination ability have been reported to be quite low.[24] Accordingly, the acidity of **10** should be much stronger than that of HF, shifting the equilibrium in eq 4 to the right.

$$\underset{(\mathbf{10})}{HB(C_6F_5)_4} + SnClF \rightleftarrows \underset{(\mathbf{8})}{SnB(C_6F_5)_4Cl} + HF \quad (4)$$

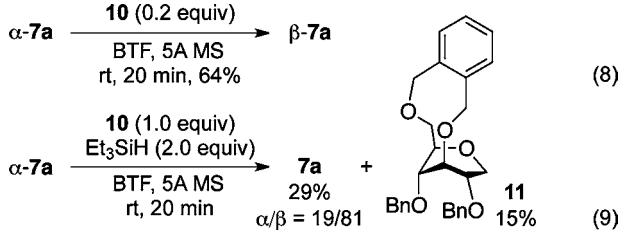
This consideration was supported by experiments. Although SnF_2 did not induce the glycosylation reaction (eq 5), the simultaneous use of SnF_2 and **10** gave glycoside **7** (eq 6). In this experiment, 4A MS was applied to hinder the reaction caused by **10** itself. This successful glycosylation revealed that the transformation described in eq 7 could be possible, supporting the production of **8** via eq 4.

$$\mathbf{2} + \underset{(1.2\ \text{equiv})}{C_6H_{11}CH_2OH} \xrightarrow[\text{BTF, rt, 44 h}]{SnF_2\ (0.2\ \text{equiv})} \text{no reaction} \quad (5)$$

$$\mathbf{2} + \underset{(1.2\ \text{equiv})}{C_6H_{11}CH_2OH} \xrightarrow[\text{BTF, rt, 16 h, 81\%}]{\substack{SnF_2\ (0.3\ \text{equiv}) \\ \mathbf{10}\ (0.2\ \text{equiv}),\ 4A\ MS}} \mathbf{7a}\ \ \alpha/\beta{=}61/39 \quad (6)$$

$$\mathbf{10} + SnF_2 \rightleftarrows SnB(C_6F_5)_4F + HF \quad (7)$$

In the isomerization cycle (Scheme 2), it was clear that **10** dominates the cycle. Thus, in Table 2, when **8** worked as the actual catalyst (entries 7 and 8), low stereoselectivity was observed. In contrast, when **10** was the actual catalyst (entries 1, 2, 5, and 6), complete β-selectivity was obtained. In addition, isomerization of α-**7a** to β-**7a** using **10** was confirmed (eq 8),



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which experiment also corroborated the generation of **9**. Despite the potential isomerization pathway via an endocyclic cleavage,[25] the isomerization involving exocyclic cleavage is more probable, as the isomerization reaction in the presence of Et_3SiH provided **11** (eq 9).

In conclusion, we have developed a completely β-selective glycosylation that does not rely on the NGP strategy. To realize this, we designed and synthesized the 3,6-*O*-(*o*-xylylene)-bridged axial-rich glucosyl fluoride **2**. The β-glycosylation reaction using **2** and $SnCl_2$–$AgB(C_6F_5)_4$ catalyst was stably applicable to several types of alcohols. In these reactions, the actual catalyst might be $SnB(C_6F_5)_4Cl$, generated in situ. The perfect β-selectivity arises from isomerization of the α-anomeric isomer into the β-isomer, which is catalyzed by $HB(C_6F_5)_4$ that is also generated in situ. This novel glycosylation offers a fundamental concept for new trends in the design of chemical glycosylation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all reactions and products, including ^1H NMR and ^{13}C NMR spectra, the results of DFT calculations, and complete ref 17 (as SI ref 3). 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 interest.

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