1,2-Cis Selective Glycosylation with Glycosyl Fluoride by Using a Catalytic Amount of Trifluoromethanesulfonic Acid (TfOH) in the Coexistence of Molecular Sieve 5Å (MS5Å)

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Stereoselective glycosylation of several glycosyl acceptors with 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride was successfully carried out in diethyl ether by using a catalytic amount of trifluoromethanesulfonic acid (TfOH) in the coexistence of molecular sieve 5Å (MS5Å) to afford predominantly the corresponding α-linked disaccharides in high yields, which was applied to one-pot sequential syntheses of trisaccharides.

Glycosyl fluorides, as well as thioglycosides, are frequently employed in the synthesis of complex oligosaccharides[1] since they are more stable compared to the corresponding chlorides and bromides, and many methods for the activation of glycosyl fluorides have been reported[1] after our publication in 1981.[2] However, there were few effective methods for catalytic activation of glycosyl fluorides in glycosylation with various alcohols as glycosyl acceptors.[3,4] Recently, it was reported from our laboratory that the glycosylation of various glycosyl acceptors with glycosyl fluorides was successfully carried out by using a catalytic amount of trifluoromethanesulfonic acid (TfOH)[4] to afford disaccharides in high yields with β stereoselectivities. On the other hand, general methods for stereoselective syntheses of 1,2-*cis* glycosides are still needed to be developed because so-called neighboring group participation from C(2)-position has not yet been utilized while it was well known that several solvents had influence on the stereoselectivity of glycosylation. For instance, 1,2-cis glycosides are preferentially obtained when the glycosylation is carried out in diethyl ether.[2,5,6] In this communication, we would like to report a simple and effective method for 1,2-cis selective glycosylation of various glycosyl acceptors with glycosyl fluorides (**1**) by using a catalytic amount of TfOH in the co-existence of MS5Å in diethyl ether to afford predominantly α-linked disaccharides in good to excellent yields, and also its application to the formation of trisaccharides in one-pot sequential glycosylation manner.[7]

Firstly, according to our previous procedure,[4] the reaction conditions were examined in order to study the effect of solvent by taking the reaction of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride (**1**) with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**2**). These reactions were carried out in various solvents by using 5 mol% of TfOH for 2 to 7 h. As a result, the glycosylation with glycosyl fluoride **1** took place in almost all the solvents listed in Table 1 except for DMF, and 1,2-cis glycoside was predominantly obtained in ethereal solvents. Especially, the glycosylation proceeded in good yield with high 1,2-cis stereoselectivity when diethyl ether was used as a solvent (Table 1).

Next, the 1,2-cis selective glycosylation was further studied by using 20 mol% of TfOH in diethyl ether solvent in order to improve the chemical yield and stereoselectivity. The effect
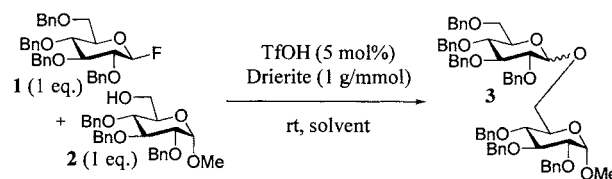
Table 1. Effect of solvents

Solvent	Time /h	Yield /%(α/β)[a]	Solvent	Time /h	Yield /%(α/β)[a]
CH_2Cl_2	2	83 (67/33)	**Et$_2$O**	7	**63 (91/9)**
Toluene	2	87 (60/40)	THF	7	13 (52/48)
Benzene	2	86 (69/31)	^{n}Pr$_2$O	7	30 (86/14)
fluorobenzene	2	86 (75/25)	DME	7	2 (86/14)
^{t}BuCN	2	83 (24/76)	^{n}Bu$_2$O	7	66 (87/13)
BTF[b]	2	90 (68/32)	THP	7	60 (82/18)
$MeNO_2$	2	63 (48/52)	^{t}BuOMe	7	24 (94/6)
AcOEt	2	70 (67/33)	(ClCH$_2$CH$_2$)$_2$O	7	83 (72/28)
1,4-dioxane	2	60 (89/11)	DMF	7	N.R.

[a]The α/β ratios were determined by HPLC analysis. [b]BTF = trifluoromethylbenzene.
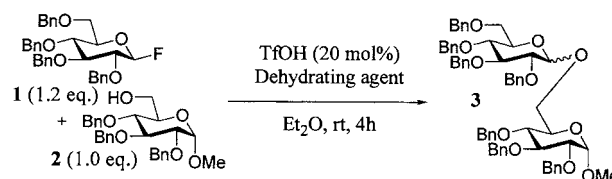
Table 2. Effect of dehydrating agents

Entry	Dehydrating agent[8]		Yield /%(α/β)[a]
1	Drierite (= $CaSO_4$)	1 g/mmol	92 (87/13)
2	Drierite (= $CaSO_4$)	3 g/mmol	88 (90/10)
3	Drierite (= $CaSO_4$)	5 g/mmol	87 (90/10)
4	MS 3Å (= K$_9$Na$_3$[(AlO$_2$)$_{12}$(SiO$_2$)$_{12}$])	3 g/mmol	N.R.
5	MS 4Å (= Na$_{12}$[(AlO$_2$)$_{12}$(SiO$_2$)$_{12}$])	3 g/mmol	N.R.
6	**MS 5Å** (= Ca$_{4.5}$Na$_3$[(AlO$_2$)$_{12}$])	3 g/mmol	**98 (88/12)**
7	None		67 (84/16)

[a]The α/β ratios were determined by HPLC analysis.

of various dehydrating agents[8] was examined in the above reaction, and both Drierite and MS5Å proved to be useful. In this reaction, MS5Å worked more effectively compared with Drierite whereas MS3Å and MS4Å did not work at all and thus no reactions were observed (Table 2). It was considered that the latter two molecular sieves captured a strong protic acid catalyst, TfOH, owing to their basic characters. As with MS5Å, on the other hand, it did not capture protic acids, and the existing TfOH activated glycosyl fluoride, which resulted in effective promotion of the glycosylation.[9]

Then, in order to extend the scope of the present reaction using MS5Å, the glycosylation of various glycosyl acceptors was examined (Table 3). As a result, the glycosylation proceeded smoothly especially in the cases of the acceptors having secondary alcohol, **4** and **5**, to afford the corresponding disaccha-

rides in excellent yields with good α-stereoselectivities (Table 3, Entries 4–9). Now, it should be noted that the chemoselective glycosylation proceeded smoothly also with thioglycosides[10] **6** and **7** to give the corresponding disaccharides in good yields without damaging the thioglycosidic linkage of reducing end (Entries 10–15).
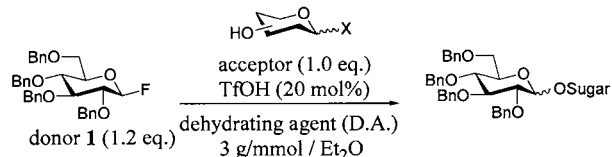
Table 3. Trifluoromethansulfonic acid catalyzed α selective glycosylation of various glycosyl acceptors with glucosyl donor **1**

| Entry	Acceptor	Product	D.A.	h	°C	Yield /% (α/β)[a]
1			Drierite	6	rt	94 (91/9)
2		**3**	MS5Å	4	rt	98 (88/12)
3	**2**		MS5Å	8	0	95 (89/11)
4			Drierite	22	rt	63 (75/25)
5		**8**	MS5Å	4	rt	97 (78/22)
6	**4**		MS5Å	12	0	97 (84/16)
7			Drierite	22	rt	24 (73/27)
8		**9**	MS5Å	5	rt	82 (73/27)
9	**5**		MS5Å	20	0	88 (81/19)
10			Drierite	4	rt	94 (84/16)
11		**10**	MS5Å	2	rt	95 (81/19)
12	**6**		MS5Å	12	0	>99 (86/14)
13			Drierite	8	rt	91 (77/23)
14		**11**	MS5Å	2	rt	98 (74/26)
15	**7**		MS5Å	12	0	>99 (80/20)

[a]The α/β ratios were determined by HPLC analysis.
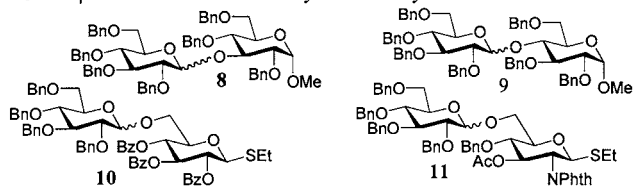
Based on the above results, one-pot sequential glycosylation was attempted. In the first step, **1** was treated with ethylthio glycosides **6** or **7** in the presence of a catalytic amount of TfOH in diethyl ether and the glycosyl fluoride was almost completely consumed, which was confirmed by TLC monitoring. Next, the second glycosylation of glycosyl acceptor **2** with thus formed disaccharide was tried, and the desired trisaccharide was obtained stereoselectively in high yield by successive addition of NIS[11] in one-pot operation. It is noteworthy that the sequential reactions were carried out without further addition of TfOH, a promoter, and that trisaccharide including 2-deoxy-2-animo sugar moiety was obtained also in high yield with good stereoselectivity.

Thus, a simple and stereoselective glycosylation method using glycosyl fluoride in the coexistence of a catalytic amount of TfOH and MS5Å was developed. This procedure was further applied to the chemoselective sequential syntheses of trisaccharides, Glcα1–6Glcβ1–6Glc and Glcα1–6GlcNβ1–6Glc, in one-pot procedure. Further study on the application of the present method to the naturally occurring oligosaccharide synthesis is now in progress.

The typical experimental procedure for the one pot glyco-
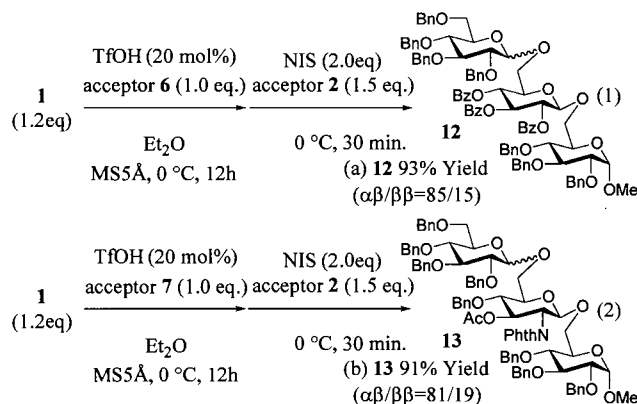
Scheme 1. One-pot trisaccharide syntheses.
(a) The αβ/ββ ratio was determined by isolation of each isomer.
(b) The αβ/ββ ratio was determined by HPLC analysis.

sylation is as follows: to a stirred suspension of MS5Å (300 mg), **1** (65.2 mg, 0.12 mmol) and **6** (53.7 mg, 0.10 mmol) in Et_2O (2.5 mL) was added TfOH (3.02 mg, 20 μmol) in toluene (0.20 mL) at 0 °C. After the reaction mixture was stirred for 12 h at 0 °C, **2** (70.0 mg, 0.15 mmol) and NIS (45.0 mg, 0.20 mmol) were successively added at 0 °C. The reaction mixture was stirred for additional 30 min at 0 °C and was quenched by adding saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc and 1 M HCl, and aqueous layer was extracted with EtOAc. The combined organic layer was washed with 10% aqueous $Na_2S_2O_3$, H_2O and brine, and dried over $MgSO_4$. After being filtered and evaporated, the resulting residue was purified by preparative TLC (silica gel) to give the desired product **12** (136.5 mg, 93.3%, αβ/ββ = 85/15).

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