Trifluoromethanesulfonic Acid (TfOH)-Catalyzed Stereoselective Glycosylation Using Glycosyl Fluoride

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Stereoselective glycosylation of 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucosyl fluoride **6** with several glycosyl acceptors is successfully carried out by using a catalytic amount of trifluoromethanesulfonic acid (TfOH).

One of the most important and fundamental topics in carbohydrate chemistry is to develop a new method for stereoselective glycosylation.[1] Among various useful glycosyl donors, glycosyl fluorides proved to be quite effective in the synthesis of many complex oligosaccharide chains because they showed more stability under various conditions compared with the corresponding chlorides or bromides. After our publication in 1981,[2] these fluorides combined with various Lewis acid activators have been frequently and successfully employed;[3-6] however, only a few examples of catalytic glycosylation have been reported.[5,6] Of a few, an effective activation of glycosyl fluoride was recently reported in the reaction with several glycosides as acceptors by using a catalytic amount of $TrB(C_6F_5)_4$.[5] On the other hand, there were no reports on a catalytic or stoichiometric amount of protic acid mediated glycosylation using glycosyl fluoride, a glycosyl donor. Considering the concept of HSAB rules, proton (H^+) is thought to be fluorophilic because of its hard character and that it should act as a catalyst for glycosylation using glycosyl fluoride. In this communication, we would like to report a new method for activation of glycosyl fluoride by using a catalytic amount of TfOH (5 mol%) to afford β-D-glucopyranosides in good to excellent yields on treatment with several glycosyl acceptors.

In the first place, 5 mol% of protic acid catalysts such as trifluoroacetic acid, methanesulfonic acid or TfOH were employed by taking the reaction of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside. As a result, it was observed that TfOH effectively accelerated glycosylation reaction of glycosyl fluoride in CH_2Cl_2 at room temperature and gave 83% yield of the corresponding disaccharide (Table 1, Entry 4) while the two former acids did not. Next, various donors which possess other types of leaving groups were studied under the same condition to evaluate the suitability of the protic acid catalyzed glycosylation (Table 1). Interestingly, glycosyl bromide and chloride were not effectively activated in contrast to glycosyl fluoride (Table 1, Entries 1-4). Glycosyl acetate, carbonate and 1-hydroxy sugar (Table 1, Entries 5-7) reacted with acceptors and furnished the desired disaccarides in moderate yields (not optimized). Since thioglycoside was not activated at all under the condition (Table 1, Entry 8), the present reaction should be applicable to the orthogonal glycosylation methodology (vide post).[7]

Various glycosyl fluorides were further examined under the above reaction condition in order to study the influence of the protecting groups of the glycosyl donor (Table 2). Both

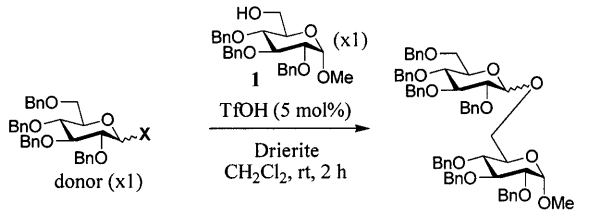


Table 1. Trifluoromethansulfonic acid catalyzed glycosylation of various glycosyl donors

Entry	X	Yield /%	α/β[a]	Entry	X	Yield /%	α/β[a]
1	Br (α)	9	45/55	5	OH (mix)	51	73/27
2	Cl (α)	6	52/48	6	OAc (α)	75	68/32
3	F (α)	87	66/34	7	OCOOPh (β)	61	72/28
4	F (β)	83	67/33	8	SEt (β)	0	—

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

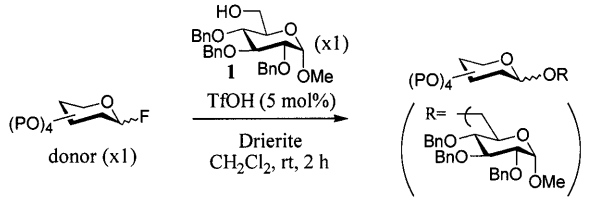


Table 2. Trifluoromethansulfonic acid catalyzed glycosylation of various glycosyl fluoride

Entry	Donor	Product	Yield /%	α/β
1	**2**		83	67/33[a]
2	**3**		87	66/34[a]
3	**4**		11	β
4	**5**	—	0	—
5	**6**		80	β
6[b]	**6**		97	β

[a]The α/β ratios were determined by HPLC analysis. [b]1.2eq of the donor was used at 0 °C for 4 h.

armed sugars **2** and **3** (Table 2, Entries 1, 2) reacted smoothly with **1** in the presence of 5 mol% TfOH while disarmed sugars **4** and **5** gave poor results (Table 2, Entries 3, 4). On the other hand, 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl protected glycosyl fluoride **6**[8] was effectively activated and gave the corresponding glucoside stereoselectively in good yield (Table 2, Entry 5). The reactivity of glycosyl fluoride increased drastically compared to Entries 4 and 5 by just changing 3,4,6-*O*-Bz protecting groups to Bn ones.[9] Also the neighboring group participation worked effectively to prepare 1,2-trans glycosidic bond. After having studied the reaction in detail, the optimized reaction condition was determined as shown in Entry 6 (0 °C, donor **6**, 1.2 eq, acceptor **1**, 1.0 eq, 97% yield).

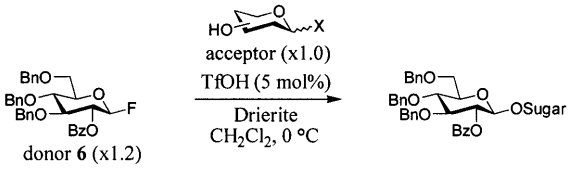
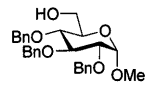
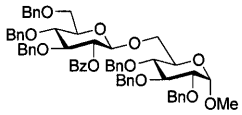
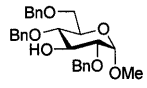
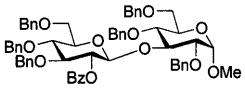
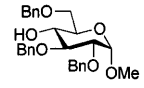
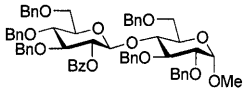
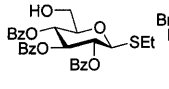
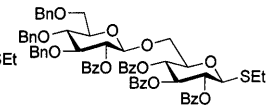
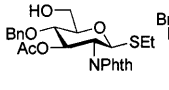
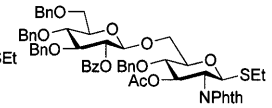


Table 3. Trifluoromethansulfonic acid catalyzed β selective glycosylation of glucosyl donor **6** with various glycosyl acceptors

Entry	Acceptor	Product	Time /h	Yield /%
1			4	97
2			6	87
3			18	67
4			5	85
5			8	81

Under the conditions described above, the corresponding disaccharides were expectedly obtained in good to excellent yields with β fashion as summarized in Table 3. Now, it should be pointed out that orthogonal glycosylation proceeded to give disaccharides in good yields without damaging the thioglycosidic linkage of reducing end (Table 3, Entries 4, 5).

The typical experimental procedure is as follows: to a stirred suspension of Drierite (100 mg), 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride (66.8 mg, 0.12 mmol) and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (46.5 mg, 0.10 mmol) in dichloromethane (2.5 mL) was successively added TfOH (0.75 mg in toluene, 0.04 mL, 5.0 μmol) at 0 °C. The reaction mixture was stirred for 4 h at 0 °C, then it was quenched by adding saturated aqueous sodium hydrogen carbonate (2 mL). The mixture was diluted with EtOAc and 1 M HCl, and aqueous layer was extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over $MgSO_4$. After filtration and evaporation, the resulting residue was purified by preparative TLC (silica gel) to afford methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2'-*O*-benzoyl-3',4',6'-tri-*O*-benzyl-β-D-glucopyranosyl)-α-D-glucopyranoside (97.2 mg, 97.1% yield).

Thus, a catalytic and stereoselective glycosylation of glycosyl fluoride **6** with several glycosyl acceptors was successfully carried out in the presence of 5 mol% of TfOH and several disaccharides were obtained in high yields with definite stereoselectivities. It is noted that the present reaction is the first example of activating anomeric C-F bond by using a catalytic amount of protic acid.

Further investigations on the present glycosylation method for constructing the 1,2-cis-gluco type glycosidic linkage and the synthesis of oligosaccharide are now in progress.

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