Catalytic and Chemoselective Glycosylation between "Armed" and "Disarmed" Glycosyl *p*-Trifluoromethylbenzylthio-*p*-trifluoromethylphenyl Formimidates

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Catalytic and chemoselective glycosylation between novel "armed" and "disarmed" glycosyl *p*-trifluoromethylbenzylthio-*p*-trifluoromethylphenyl formimidates was effectively performed in the presence of a catalytic amount of TfOH and MS 4A in CH_2Cl_2 at −78 °C. In addition, it was noted that highly 1,2-*cis* or 1,2-*trans* stereoselective synthesis was established when the above glycosylation was carried out at −78 °C in ^{t}BuOMe or EtCN, respectively.

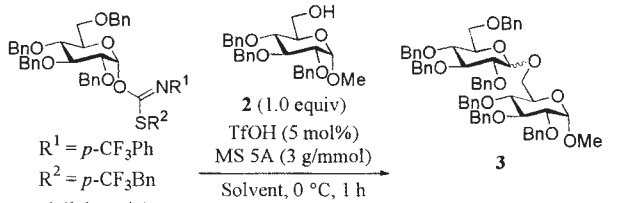
Study on establishing effective and stereoselective glycosylation is one of the most important topics in carbohydrate chemistry.[1] Recent interesting contribution to this field is the verification of the "armed-disarmed" effect proposed by B. Fraser-Reid.[2] This effect is related to the rate of formation of oxocarbonium ion at an anomeric position of a carbohydrate, which is ruled by a protecting group at the neighboring position. The oxocarbonium ion is less favorably formed when an adjacent electron withdrawing group is located in place of an adjacent alkoxy group. Pioneering reports about this effect describe "armed" derivatives of *n*-pentenyl glycoside are selectively activated by iodonium dicollidine perchlorate (IDCP) in the coexistence of "disarmed" derivatives.[3] Concerning other glycosyl donors, e.g. glycals,[4] thioglycosides,[5] glycosyl fluorides,[6] similar phenomena have also been reported: however, "armed-disarmed" glycosylation using the two corresponding glycosyl trichloroacetimidates catalyzed by TfOH has not been reported.

Very recently, a newly devised efficient "disarmed" glycosyl donor, glycosyl *p*-trifluoromethylbenzylthio-*p*-trifluoromethylphenyl formimidate, was reported from our laboratory.[7] This glycosyl donor was easily prepared in a crystalline form in good yield with high α-stereoselectivity. Catalytic glycosylation of several glycosyl acceptors with this glycosyl donor was efficiently performed in the presence of 5 mol% TfOH and MS 5A in CH_2Cl_2 at 0 °C and 1,2-*trans* stereoselectivity of the glycosides was achieved by the assistance of neighboring effect from C(2)-position. In this communication, we would like to report on catalytic, stereoselective and chemoselective glycosylation between novel "armed" and "disarmed" glycosyl *p*-trifluoromethylbenzylthio-*p*-trifluoromethylphenyl formimidates.

2,3,4,6-Tetra–*O*–benzyl-α-D-glucopyranosyl *p*-trifluoromethylbenzylthio-*p*-trifluoromethylphenyl formimidate (**1**) was also prepared easily in a crystalline form in good yields with high α-stereoselectivity. In the first place, stereoselective glycosylation of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**2**) with the glycosyl donor **1** was tried (Table 1). The glycosylations were carried out in various solvents by using 5 mol% of TfOH for 1 h at 0 °C. As a result, the reactions proceeded smoothly in almost all solvents except DMF. It should be noted that the glycosylation which afforded the glycoside in quantitative yield with 1,2-*trans* stereoselectivity proceeded when CH_3CN or EtCN was used as a solvent (entries 1,2). On the other hand, 1,2-*cis* glycoside was stereoselectively formed in quantitative yield when the same reaction was carried out in ^{t}BuOMe or Et_2O (entries 8,9).

Also, it was observed that the glycosylation with this glycosyl donor **1** proceeded smoothly even at lower temperatures (Table 2). As a result, 1,2-*trans* glycoside was formed in an almost perfectly controlled manner when the glycosylation was carried out in EtCN at −78 °C (entry 4). This perfect 1,2-*trans* stereoselectivity may be

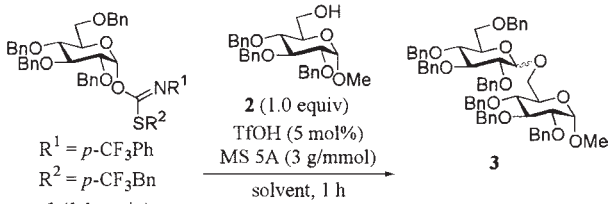
Table 1. Effect of solvent



Entry	Solvent	Yield / % (α / β)[a]	Entry	Solvent	Yield / % (α / β)[a]
1	CH_3CN	quant. (11 / 89)	8	^{t}BuOMe	quant. (88 / 12)
2	EtCN	quant. (14 / 86)	9	Et_2O	99 (86 / 14)
3[b]	^{t}BuCN	94 (25 / 75)	10	DME	quant. (82 / 18)
4	BTF	quant. (54 / 46)	11	THP	quant. (73 / 27)
5	CH_2Cl_2	98 (66 / 34)	12	$^i Pr_2O$	quant. (70 / 30)
6	Toluene	quant. (63 / 37)	13	$^n Bu_2O$	90 (65 / 35)
7	Fluorobenzene	68 (72 / 28)	14	THF	47 (42 / 58)

[a]The α / β ratios were determined by HPLC analysis. [b]The reaction was carried out at rt.

Table 2. Effect of reaction temperature



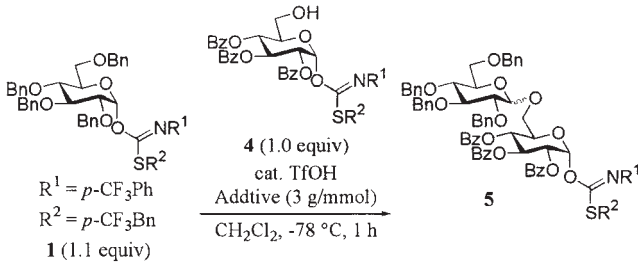
Entry	Temp./ °C	Yield / % (α / β)[a]		
		EtCN	^{t}BuOMe	CH_2Cl_2
1	0	quant. (14 / 86)	quant. (88 / 12)	98 (66 / 34)
2	-23	quant. (10 / 90)	97 (85 / 15)	quant. (59 / 41)
3	-40	quant. (3 / 97)	97 (74 / 26)	quant. (54 / 46)
4	-78	quant. (1 / 99)	95 (52 / 48)	97 (43 / 57)

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

controlled by the nature of solvent under kinetic condition.

Next, catalytic and chemoselective glycosylation between the "armed" glycosyl donor **1** and the "disarmed" glycosyl acceptor **4**[8] was examined in the presence of various additives (Table 3). As a result, the "armed-disarmed" chemoselective glycosylation proceeded smoothly and afforded the desired disaccharide **5** in high yield in the coexistence of 5–10 mol% of TfOH and MS 4A in CH_2Cl_2 at −78 °C without giving any damage to a reducing end of an acceptor (entries 7,8). The reason why the yields of the desired disaccharide **5** shown in entries 2 and 4 were low is ascribed to the hydrolysis that took place in usual work-up procedure of the initially formed **5** whose reactive leaving group still remained in.

Table 3. Catalytic "armed-disarmed" glycosylation



Entry	Additive	TfOH / mol%	Yield / % (α / β)[a]	Recovery of **4**
1	MS 5A	5	77 (65 / 35)	14
2	MS 5A	10	trace	-
3	Drierite	5	51 (54 / 46)	14
4	Drierite	10	14 (40 / 60)	-
5	MS 3A	5	88 (66 / 34)	10
6	MS 3A	10	66 (61 / 39)	-
7	MS 4A	5	89 (66 / 34)	10
8	MS 4A	10	89 (65 / 35)	-

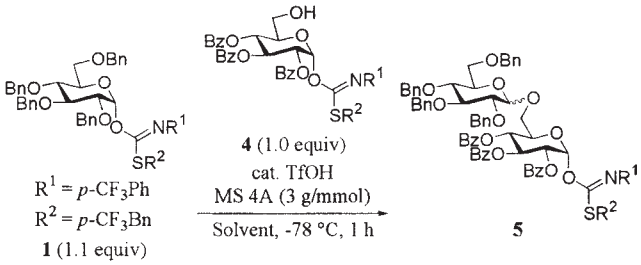
[a]The α / β ratios were determined by HPLC analysis.

Finally, the above glycosylation was tried in EtCN at −78 °C and the glycoside was formed in good yield with high 1,2-*trans* stereoselectivity, as expected (Table 4, entry 3). It is surprising to note that the glycoside was also formed in good yield with extremely high 1,2-*cis* stereoselectivity at −78 °C when ^{t}BuOMe was used as solvent (entry 6). It is explained by considering the bulkiness of acceptor **4** which is making it more difficult to approach oxocarbonium ion of the donor from β-side than acceptor **2**.

The typical experimental procedure is as follows: to a stirred suspension of MS 4A (88 mg), **1** (29.1 mg, 0.032 mmol) and **4** (25.0 mg, 0.029 mmol) in ^{t}BuOMe (2.0 mL) was added a toluene solution (ca. 0.1 mL) of TfOH (0.48 mg, 3.2 μmmol) at −78 °C. The reaction mixture was stirred for 1 h at the same temperature and was quenched by adding saturated aqueous $NaHCO_3$. The mixture was filtered through the pad of celite, and aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, and dried over Na_2SO_4. After filtration and evaporation, the resulted residue was purified by preparative TLC (hexane/EtOAc 4 : 1) to give the desired product **5** (37.4 mg, 93%, $\alpha/\beta = 95 : 5$).

Thus, catalytic, highly 1,2-*cis* or 1,2-*trans* stereoselective and chemoselective glycosylation between novel "armed" and "disarmed" glycosyl *p*-trifluoromethylbenzylthio-*p*-trifluoromethylphenyl formimidates was effectively performed in the presence of a catalytic amount of TfOH and MS 4A at −78 °C in ^{t}BuOMe or EtCN, respectively. It is expected that these glycosylations using "armed" and "disarmed" glycosyl *p*-trifluoromethylbenzylthio-*p*-trifluoromethylphenyl formimidates in appropriate solvents would be applicable to the efficient one-pot glycosylation.

Table 4. Catalytic and stereoselective "armed-disarmed" glycosylation



Entry	Solvent	TfOH / mol%	Yield / % (α / β)[a]	Recovery of **4**
1	EtCN	5	9 (2 / 98)	85
2	EtCN	10	42 (2 / 98)	56
3	EtCN	15	82 (4 / 96)	15
4	EtCN	20	77 (3 / 97)	-
5	^{t}BuOMe	5	77 (95 / 5)	19
6	^{t}BuOMe	10	93 (95 / 5)	-
7	^{t}BuOMe	15	80 (95 / 5)	-

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

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References and Notes

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8 "Disarmed" glycosyl acceptor **4** was synthesized by 4 steps procedure from ethyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside as follows; 1) TBDPSCl, imidazole/DMF, 2) 70% TfOH aq., *n*-Bu_4NIO_4/MeCN, 0 °C, 3) KHMDS, *p*-CF_3PhNCS/THF, −78 °C, then *p*-CF_3BnBr, 0 °C, 4) TBAF, AcOH/THF.