Trityl Tetrakis(pentafluorophenyl)borate Catalyzed Stereoselective Glycosylation Using Glycopyranosyl Fluoride as a Glycosyl Donor

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A catalytic and stereoselective glycosylation of glycosyl fluorides with several glucosides is successfully performed by using a catalytic amount of trityl tetrakis(pentafluorophenyl) borate.

Development of stereoselective glycosylation reaction is a most foundamental topic in carbohydrate chemistry. In these 20 years, various types of new glycosyl donors and activators have been studied[1] to develop useful glycosylation methods after classical Köenigs-Knorr type reactions. Among these methods, the use of glycosyl fluoride, which is more stable glycosyl donor compared with the corresponding chlorides or bromides, proved to be quite effective in carbohydrate chemistry and has widely been used for the synthesis of many complex oligosaccharide chains after our publication in 1981.[2] These fluorides can be activated in the presence of various Lewis acids such as SnCl$_2$-AgClO$_4$,[2] SnCl$_2$-TrClO$_4$,[3] SiF$_4$,[4] Me$_3$SiOTf,[4] TiF$_4$,[5] BF$_3$·OEt$_2$,[6] Tf$_2$O,[7] Cp$_2$MCl$_2$-AgClO$_4$ (M=Ti, Zr, Hf),[8] Me$_2$GaCl,[9] Yb(OTf)$_3$[10] and La(ClO$_4$)$_3$·nH$_2$O.[11] Though many kinds of Lewis acids were examined to activate glycosyl fluoride, only a few example of catalytic glycosylation of glycosyl fluorides with trimethylsilyl ethers have been reported.[4,6,11] And to the best of our knowledge, the use of various alcohols and saccharides as glycosyl acceptors in the catalytic glycosylation of glycosyl fluorides have not yet been reported. In this communication, we would like to report a new method for activation of glycosyl fluorides with several glucosides as acceptors by using a catalytic amount of trityl tetrakis(pentaflurophenyl)borate to afford β-D-glucopyranosides in good yields and high stereoselectivities.

It was firstly reported from our laboratery that triphenylcarbenium ion (trityl cation) could activate 1-*O*-acetyl-sugars in catalytic manner like ordinary Lewis acids.[12]

Recently, we focused on a new trityl salt, trityl tetrakis(pentafluorophenyl)borate,[13] to apply it for catalytic activation of various types of glycosyl donors such as 1-OH sugar,[14] 1-*O*-acyl sugar[15] and thioglycosides(activated in the coexistence with oxidant).[16] These results led us to attempt further catalytic activation of anomeric C-F bond by trityl salt in order to show the usefulness of this catalyst.

Firstly, the effects of a dehydrating agent, an additive, and a solvent were examined taking the reaction of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride **1** with methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside **2** as a model (Table 1). These reactions were carried out in the presence of 20mol% of trityl tetrakis(pentafluorophenyl)borate as a catalyst in various solvents with or without dehydrating agents. As a result, it was observed that the use of Drierite and pivalonitrile[17] enhanced reactivity and the latter additionally improved stereoselectivity of this reaction.[18]

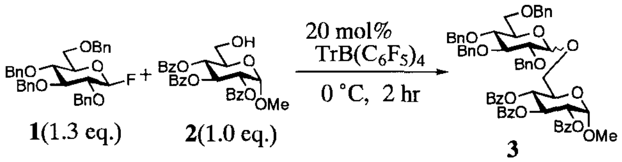


Table 1. Effects of dehydrating agents and solvents

Enrty	Dehydrating agent[a]	Solvent	Yield /%	α / β
1	MS3A	CH$_2$Cl$_2$	41	49 / 51
2	MS4A	CH$_2$Cl$_2$	9	—
3	MS5A	CH$_2$Cl$_2$	38	50 / 50
4	**Drierite**	**CH$_2$Cl$_2$**	**42**	**49 / 51**
5	—	CH$_2$Cl$_2$	17	47 / 53
6	—	Et$_2$O	9	—
7	—	Toluene	5	—
8	—	EtCN	51	13 / 87
9	—	**^{t}BuCN:CH$_2$Cl$_2$ (5:1)**	**89**	**10 / 90**

[a] 50 mg was used in 0.1mmol scale of the reaction.

Next, in order to extend the applicability of the present reaction, several solvents and temperatures were examined taking the reaction of **1** with methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside **4** which had lower nucleophilicity than **2** as a model (Table 2). The β-selectivity was nearly the same when the ratio of pivalonitrile:dichloromethane was reduced to 1:10 (Entry

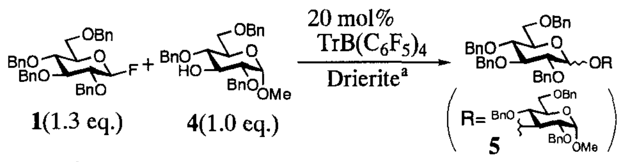


Table 2. Effects of solvents and temperatures

Entry	Solvent	temp. /°C	time /hr	Yield /%	α / β
1	^{t}BuCN:CH$_2$Cl$_2$ (5:1)	0	4	80	17 / 83
2	^{t}BuCN:CH$_2$Cl$_2$ (1:10)	0	4	75	20 / 80
3	^{t}BuCN:Toluene (1:10)	0	4	90	17 / 83
4	^{t}BuCN:BTF (1:10)	0	4	94	17 / 83
5	^{t}BuCN:BTF (1:5)	0	4	95	18 / 82
6	^{t}BuCN:BTF (1:1)	0	4	81	16 / 84
7	**^{t}BuCN:BTF (1:5)**	**- 10**	**14**	**93**	**9 / 91**

[a] 100 mg was used in 0.1 mmol scale of the reaction.

1, 2). The yield was much increased when benzotrifluoride (BTF) was used as a co-solvent for pivalonitrile. It was recently reported[19] that BTF was not only a useful alternative solvent for organic reactions currently conducted in dichloromethane but also was a robust compound with relatively low toxicity and price. The pivalonitrle:BTF=1:5 mixed solvent gave a better result (Entry 4-6) and the stereoselectivity was further improved when the reaction was carried out at -10 °C for 14 hours.

Several examples of the present glycosylation reaction are demonstrated in Table 3. In every case, the desired β-D-glucopyranosides were obtained in good to high yields with high stereoselctivities.

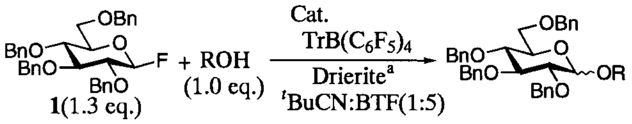
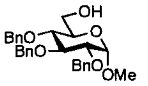
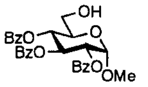
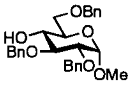


Table 3. Synthesis β-D-glucopyranosides

ROH	Cat. /mol%	temp /°C	time /hr	Yield %	α / β
	20	- 10	4	91	3 / 97
	10	0	1.5	96	5 / 95
	20	- 10	4	95	8 / 92
	10	0	1.5	95	11 / 89
	20	- 10	16	63	9 / 91
	20	0	6	82	16 / 84

[a] 100 mg was used in 0.1 mmol scale of the reaction.

The typical experimental procedure is as follows: to a stirred suspension of trityl tetrakis(pentafluorophenyl)borate (18.5 mg, 0.02 mmol) and Drierite (100 mg) in mixed solvent (benzotrifluoride/pivalonitrile=5/1, 3.0 ml) was successively added methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside **4** (46.5 mg, 0.10 mmol) and 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride **1** (70.5 mg, 0.13 mmol) in the above mixed solvent (1.5 ml) at -10 °C. The reaction mixture was stirred for 14 hours at -10 °C, then it was quenched by adding saturated aqueous sodium hydrogen carbonate (10 ml). The mixture was filtered through Celite and extracted with dichloromethane (3 times, each of 20 ml). The combined organic layer was washed with brine (5 ml) and dried over Na_2SO_4. After filtration and evaporation, the resulting residue was purified by preparative TLC (silica gel), and thus methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside **5** (91.6 mg, 93% yield) was isolated. The ratio of anomers was determined by HPLC analysis.

A catalytic and stereoselective glycosylation of glycosyl fluoride with several glucosides was successfully developed by using trityl salt as a catalyst and several disaccharides were obtained in high yields and high stereoselectivities. It is noted that the reaction is the first example of activating anomeric C-F bond by using a typical Lewis acid as trityl cation.

Further investigation of this novel glycosylation method to the oligosaccharide synthesis is now in progress.

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