Effective Activation of 'Armed' Thioglycoside with a New Combination of Trityl Tetrakis(pentafluorophenyl)borate [$TrB(C_6F_5)_4$] and *N*-(Ethylthio)phthalimide (PhthNSEt)

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Glycosylation of the 'armed' thioglycoside with various glycosyl acceptors is promoted by using a combination of stoichiometoric amount of *N*-(ethylthio)phthalimide (PhthNSEt) and catalytic amount of trityl tetrakis(pentafluorophenyl)borate [$TrB(C_6F_5)_4$], and is successfully applied to one-pot 'armed–disarmed' sequential synthesis of trisaccharides.

Thioglycosides[1] have attracted special attention since they were easily available as versatile glycosyl donors[2] and were stable under the conditions for protection and deprotection of hydroxy groups in the synthesis of saccharides. Many methods for the selective activation of thioglycosides by using various 'thiophilic' reagents have been reported.[1] However, most of them were moisture or light sensitive, explosive, corrosive, carcinogenic, irritant, and expensive. Thus, an efficient method for the activation of thioglycosides by using an easy-to-handle reagent was strongly desired to be developed. Recently, it was reported from our laboratory that the respective combination of a stoichiometric amount of NIS or NBS and a catalytic amount of $TrB(C_6F_5)_4$[3,4] was useful for the activation of 'disarmed' thioglycosides. In this reaction, an active halonium cation which activated aryl and alkyl thioglycosides was effectively generated by coordinating $TrB(C_6F_5)_4$ to carbonyl function of NIS or NBS. Similar methods using phthalimide derivatives were also reported by Ogawa[5] and Kusumoto[6] in which thioglycosides were activated by a combination of Lewis acids such as TMSOTf or $Mg(ClO_4)_2$ and *N*-(phenylseleno)phthalimide (PhthNSePh) to afford the corresponding disaccharides in high yields. However, it was noted there a combination of *N*-(phenylthio)phthalimide (PhthNSPh) and Lewis acid was not as effective as the seleno derivative.[5] Based on these results, it was considered that a trityl cation would mildly activate thiophthalimides to generate an active sulfenyl cation which would then activate thio-moiety of various saccharides. In this communication, we would like to report a new method for chemoselective glycosylation of 'armed' thioglycoside using a combination of $TrB(C_6F_5)_4$ and *N*-(ethylthio)phthalimide (PhthNSEt)[7] to afford disaccharides in good to excellent yields with high β stereoselectivities, and also its application to the formation of trisaccharides in an one-pot sequential 'armed–disarmed'[8] glycosylation manner.

Firstly, it was found that a combination of a catalytic amount of $TrB(C_6F_5)_4$ and a stochiometric amount of readily available and stable PhthNSEt effectively activated the 'armed' thioglycoside but not the 'disarmed' thioglycoside **2** at all (Table 1).

Next, reaction conditions were examined by taking the reaction of ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**1**) with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**3**) in order to improve the yield and β stereoselectivity without utilizing neighboring effect. By using thioglycosides **1**, the glycosylation took place effectively in a mixed solvent of trifluo-

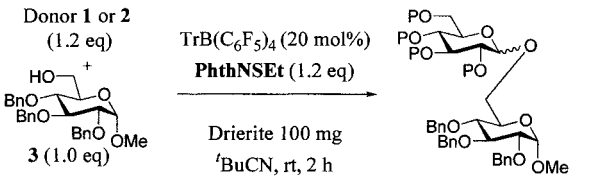
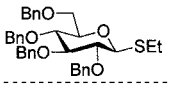
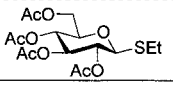


Table 1. Glycosylation of **3** with thioglycoside **1** or **2** using a combination of PhthNSEt and $TrB(C_6F_5)_4$

Donor **1** (armed)		53% yield (α/β=54/46)
Donor **2** (disarmed)		0 % yield

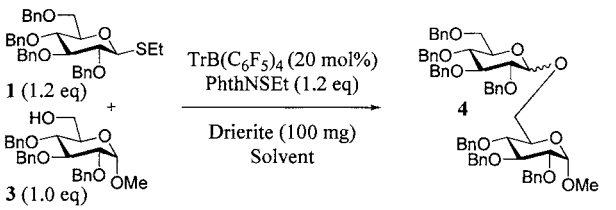


Table 2. Glycosylation of 3 with thioglycoside **1** using a combination of PhthNSEt and $TrB(C_6F_5)_4$

Entry	Solvent	Temp.	Time /h	Yield /% (α/β[a])
1[b]	BTF	rt	2	53 (54/46)
2[b]	tBuCN	rt	2	39 (65/35)
3[b]	BTF	0	5	85 (48/52)
4[b]	$PhCF_3$/tBuCN(5/1)	0	5	81 (14/86)
5[c]	**$PhCF_3$/tBuCN(5/1)**	**0**	**5**	**91 (12/88)**

[a]The α/β ratios were determined by HPLC analysis. [b]0.04 mmol/ml Concentration based on acceptor.[c] 500 mg of Drierite and 10 mol% of $TrB(C_6F_5)_4$ in 0.1 mmol/ml concentration were used.

romethylbenzene (BTF)[9] and pivaronitrile (tBuCN)[10] affording the corresponding disaccharide in 81% yield with good β stereoselectivity (Table 2, Entry 4). The above mixed solvent had known to be useful for the β-selective glycosylation of glycosyl fluoride[10] or thioglycoside,[11] as previously reported. After detailed study, the optimized reaction conditions were determined as shown in Entry 5 (10 mol% of $TrB(C_6F_5)_4$, 5g /mmol of Drierite, 0 °C, 0.1 M, 91% yield, α/β = 12/88).

As expected, the corresponding disaccharides were obtained in good to excellent yields with high β stereoselectivities under the above conditions (except for temperature and ratios of the solvents, see Table 3). Now, it is noted that chemoselective glycosylation between so-called 'armed–dis-

armed' glycosides proceeded smoothly to give the corresponding disaccharides in good yields without damaging 'disarmed' thioglycosidic linkage of the reducing end (Entries 3–5).

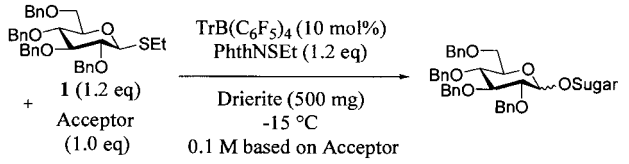
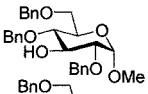
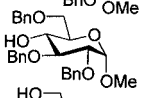
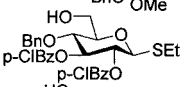
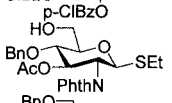
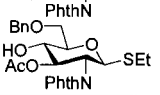


Table 3. Glycosylation of various glycosyl acceptors with thioglycoside **1**

Entry	Acceptor		Time /h	Yield /% (α/β[a])
1[b]		**5**	21	85 (9/91)
2[b]		**6**	24	77 (15/85)
3[c]		7	14	87 (9/91)
4[c]		**8**	16	86 (9/91)
5[d]		**9**	15	79 (17/83)

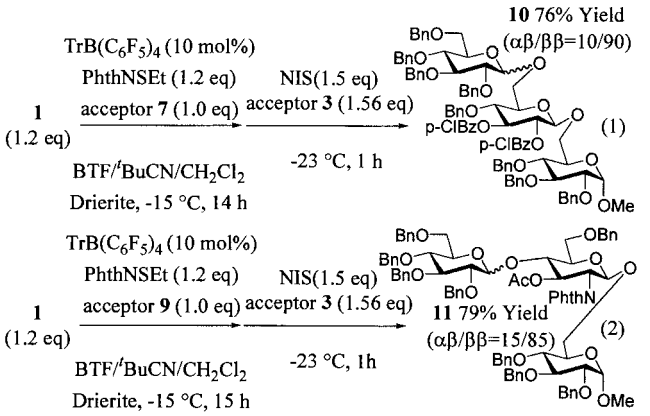
[a]The α/β ratios were determined by HPLC analysis. [b]BTF/^{t}BuCN/CH_2Cl_2 = 3/7/1.[c]$PhCF_3$/^{t}BuCN/CH_2Cl_2 = 5/5/1.[d]BTF/^{t}BuCN/CH_2Cl_2 = 10/2/1

Finally, one pot sequential glycosylation was attempted according to the above method. In the first step, **1** was treated with ethylthio glycosides **7** or **9** in the presence of a catalytic amount of $TrB(C_6F_5)_4$ and 1.2 equivalent of PhthNSEt in a mixed solvent (^{t}BuCN/BTF/CH_2Cl_2), where thioglycosides were almost completely consumed after 14 h. These were all confirmed by TLC monitoring. Next, the second glycosylation of thus formed disaccharide with glycosyl acceptor **3** was tried and the desired trisaccharides[12] were obtained stereoselectively in good yields by successive addition of NIS[3] in one-pot operation. It is noteworthy that the sequential reactions were thoroughly carried out without adding further $TrB(C_6F_5)_4$, a promoter, and that trisaccharide including 2-deoxy-2-amino sugar moiety was obtained also in high yield with good stereoselectivity.

Thus, a useful glycosylation method of armed thioglycoside by using a combination of easy-to-handle PhthNSEt and catalytic amount of $TrB(C_6F_5)_4$ was developed. It is interesting to note that trityl borate interacts with thiophthalimides to generate an active ethylsulfenyl cation which is stabilized by the borate anion and that the above cation oxidizes only the armed thioglycoside to afford the corresponding disaccharides in high yields and stereoselectivities. Then, this procedure was thus applied to the coupling of armed and disarmed thioglycosides in 'armed–disarmed' sequential trisaccharide syntheses by 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 is as follows: to a stirred suspension of Drierite (500 mg), **1** (70.5 mg, 0.12 mmol) and **7** (59.1 mg, 0.10 mmol) in ^{t}BuCN/BTF/CH_2Cl_2 (5/5/1, total 1.0 mL) was successively added $TrB(C_6F_5)_4$ (9.2 mg, 10 μmol)



Scheme 1. One pot trisacccharide syntheses using both 'armed' and 'disarmed' thioglycosides.

at –15 °C. After the reaction mixture was stirred for 14 h at –15 °C, **3** (72.4 mg, 0.16 mmol) in dichloromethane (2.5 mL) and NIS (33.8 mg, 0.15 mmol) were successively added at –23 °C. The reaction mixture was stirred for additional 1h at –23 °C and was quenched by adding saturated aqueous $NaHCO_3$. The mixture was filtered through Celite and extracted with dichloromethane (3 times). The combined organic layer was washed with 10% aqueous $Na_2S_2O_3$, H_2O and brine. Then the organic layer was dried over Na_2SO_4. After being filtered and evaporated, the resulting residue was purified by preparative TLC (silica gel) to give the desired product **10** (114 mg, 75.5 %, αβ/ββ = 10/90).

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References and Notes

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12 NMR date of **10** and **11**; **10** (major : Glcβ1–6Glcβ–6Glc): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (d, 1H, *J* = 3.4 Hz, H-1), 4.51 (d, 1H, *J* = 8.1 Hz, H-1' or H-1"), 4.52 (d, 1H, *J* = 8.1 Hz, H-1' or H-1"), ^{13}C NMR ($CDCl_3$) δ 97.9 (C-1), 100.5 (C-1'), 103.9 (C-1''); **11** (major : Glcβ1–4GlcNβ–6Glc): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (d, 1H, *J* = 3.4 Hz, H-1), 4.35 (d, 1H, *J* = 8.3 Hz, H-1"), 5.38 (d, 1H, *J* = 8.5 Hz, H-1'), ^{13}C NMR ($CDCl_3$) δ 97.7 (C-1), 98.4 (C-1'), 102.7 (C-1").