The Trityl Tetrakis(pentafluorophenyl)borate Catalyzed Stereoselective Glycosylation Using New Glycosyldonor, 3,4,6-Tri-*O*-benzyl-2-*O*-*p*-toluoyl-β-D-glucopyranosyl Phenylcarbonate

Kazuya Takeuchi, Takayuki Tamura, and Teruaki Mukaiyama
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162-8601

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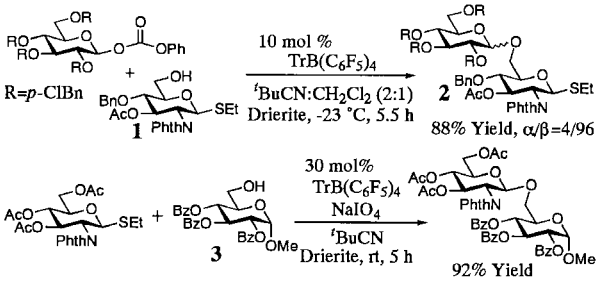
The trityl tetrakis(pentafluorophenyl)borate [$TrB(C_6F_5)_4$] catalyzed stereoselective synthesis of various disaccharides was successfully carried out by treating a new 2-*O*-acyl-protected glycosyl donor, 3,4,6-tri-*O*-benzyl-2-*O*-*p*-toluoyl-β-D-glucopyranosyl phenylcarbonate, with several glycosyl acceptors, thioglycosides, affording the corresponding disaccharides in high yields.

Development of a convenient method for preparation of complex oligosaccharides is still a significant challenging topic in the field of synthetic organic chemistry. After 1990's, a considerable progress has been made in the one-pot sequential glycosylation reaction to achieve the rapid synthesis of oligosaccharides.[1] In our previous paper,[2] a one-pot synthesis of trisaccharides by the combination of two types of $TrB(C_6F_5)_4$–catalyzed glycosylation reactions to form trisaccharide composed of three glucoses, Glcβ1-6Glcβ1-6Glc, was reported. In continuation to the above experiment, further study on several glycosylation reactions aiming to the one-pot synthesis of more complex saccharide chains was tried herein.

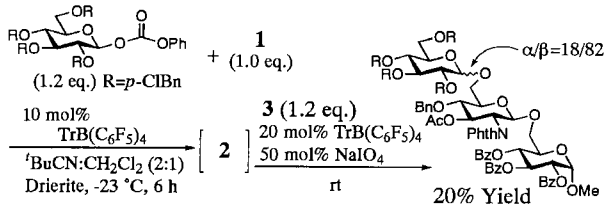
In recent years, preparation of oligosaccharides containing a variety of 2-amino-2-deoxy sugars[3] attracted great attention to understanding the biological activities of the glycoproteins, glycolipids, and other glycoconjugates. In order to accomplish the one-pot sequential synthesis of trisaccharides containing 2-amino-2-deoxy sugar as a component, the prepararion of disaccharides composed of 2-*N*-phthaloyl protected thioglycoside was studied first.

In the first place, optimizations of reaction conditions of the above two glycosylation steps were investigated to understand the effects of protecting groups of glycosyl donor and of activators (Scheme 1). *p*-Chlorobenzyl protected glycosyl



Scheme 1. $TrB(C_6F_5)_4$ catalyzed glycosylation reactions.

phenylcarbonate reacted with 2-*N*-phthaloyl protected thioglycoside (**1**) in mixed solvent containing pivalonitrile in the presence of 10 mol% of $TrB(C_6F_5)_4$ to afford the desired disaccharide (**2**) in 88% yield with high stereoselectivity (α/β=4/96). On the other hand, application of $TrB(C_6F_5)_4$–$NaIO_4$ system[4] for the activation of 2-*N*-phthaloyl protected thioglycoside corresponding to the second step of the one-pot glycosylation required careful examinations since this thioglycoside is not so reactive as a glycosyl donor. It was observed that the use of pivalonitrile as solvent was essential to the promotion of the reaction and that the reaction did not take place under the reaction temperature below 0 °C while the above reaction smoothly proceeded at room temperature when both donors and acceptors were monosaccharides (Scheme 1. below). As shown in Scheme 2, the one-pot sequential reactions under the



Scheme 2. One-Pot synthesis of trisaccharide.

above mentioned conditions, however, gave the desired trisaccharide in poor yield, unexpectedly. By identifying by-products, it was further revealed that the glycosidic bond of the disaccharide **2** was cleaved by $TrB(C_6F_5)_4$ during the second glycosylation step. Consequently, further improvement of the two coupling reactions was studied thoroughly to complete the desired one-pot trisaccharide formation. In this communication, we would like to report detailed conditions of glycosylation using glycosyl phenylcarbonates, which is the first step of the one-pot sequential glycosylation.

The tuning of the protecting groups of glycosyl phenylcarbonate was examined in order to enhance the stability of glycosidic bond. When 2,3,4,6-tetra-*O*-benzoyl glucosyl phenylcarbonate was used in the $TrB(C_6F_5)_4$–catalyzed glycosylation reaction, the reactivity of the donor decreased dramatically compared to that of *p*-chlorobenzyl protected glycosyl phenylcarbonate (Table 1). Actually, no reaction took place under low temperatures ranging from -40 ˚C ~ 0 ˚C when glycosylation of 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl phenylcarbonate with methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (**3**) was tried in the presence of 30 mol% of $TrB(C_6F_5)_4$. The reaction began very slowly at 0 °C and final-

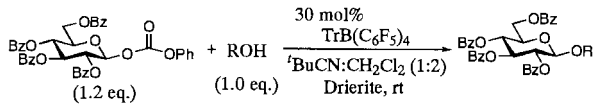


Table 1. Glycosylation with per-acylprotected glycosyl donor

Entry	ROH	time /h	Yield /%
1	**3**	12	80
2	**1**	4	63
3	**4**	4	N.D.

ly, it proceeded smoothly at room temperature and afforded the corresponding disaccharide in 80% yield. On the other hand, the desired disaccharide was not formed in the case of glycosylation using an inactive glycosyl acceptor, ethyl 3-*O*-acetyl-6-*O*-benzyl- 2-*N*-phthaloyl-2-deoxy-1-thio-β-D-glucopyranoside (**4**) since the cleavage of the anomeric ethylthio group took place prior to the coupling reaction (Table 1. Entry 3).

In order to accomplish a successful preparative method for various oligosaccharides, enhancement of reactivities of glycosyl donors is always required. S. V. Ley reported[5] the precise data on the reactivity of rhamnose and mannose derivatives and revealed that the 3-, 4-, and 6-benzoyl protecting groups showed significant deactivation compared with benzyl protected ones. They concluded that, except for the neighboring C-2 substituent, proximity of electron withdrowing protecting groups to the ring oxygen was more influential compared with their distance from the anomeric position. Then, it was planned to prepare a modified glycosyl donor in which only C-2 hydroxy group was protected by benzoyl (Bz) group and other hydroxy groups were protected by benzyl (Bn) group.[6] As summarized in Table 2, reactivity of the modified glycosyl donor was dramatically improved compared with that of perbenzoylated one. The new glycoyl donor, 3,4,6-tri-*O*-benzyl-2-*O*-*p*-toluoyl-β-D-glucosyl phenylcarbonate[7] (**5**), reacted smoothly with **3** in the presence of a catalytic amount of $TrB(C_6F_5)_4$ at -15 ˚C to afford the corresponding disaccharide stereoselectively in high yield (Entry 1). 2-*N*-Phthaloyl protected or 2-*O*-benzoyl protected ethyl thioglycosides having 6-OH group reacted with **5** at -20 °C to yield the desired products in high yields. However, the glycosylation using an inactive acceptor (**4**) did not give a satisfactory result since the cleavage of the anomeric ethylthio group took place prior to the coupling reaction (Table 2. Entry 5). It had already been known in our laboratory that the use of pivalonitrile as solvent quite smoothly promoted replacement of the leaving group with an acceptor and also the cleavage of glycosidic linkage.[8] Then, the reaction was next examined in dichloromethane alone and much improvement was observed concerning chemical yield though the reaction time became longer (Entry 3, 7).

Thus, catalytic and stereoselective syntheses of various disaccharides by using a 2-*O*-acyl-protected glycosyl donor, 3,4,6-tri-*O*-benzyl-2-*O*-*p*-toluoyl-β-D-glucosyl phenylcarbonate, was successfully developed. It is noted that 2-*O*-acyl-protected glycosyl donor was suitable for the catalytic stereoselective glycosylation because of its high reactivity and its high stereoselectivity.

Further study on the application of this glycosylation method to a one-pot sequential glycosylation will be reported in the paper to follow.

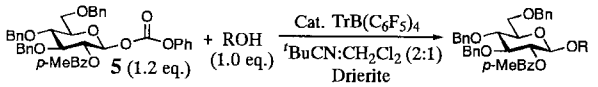
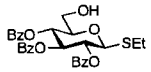


Table 2. Glycosylation with 2-*O*-acylprotected glycosyl donor

Entry	ROH	Cat. /mol%	temp. /˚C	time /h	Yield /%
1	**3**	30	-15	2	98
2	**1**	30	-15	2	86
3[a]	**1**	30	-15	6	73
4	**1**	10	-20	6	91
5		10	-20	6	88
6	**4**	30	-15	4	38
7[a]	**4**	30	-15	21.5	84

[a] Only dichloromethane was used as solvent.

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References and Notes

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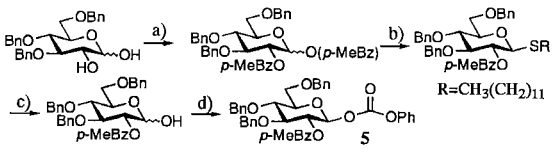
7 The donor **5** was prepared from 3,4,6-tri-*O*-benzyl glucose[9] according to the following equation. 2-*O*-Benzoyl and 2-*O*-*p*-chlorobenzoyl analogs were similarly prepared, however, they were not employed as donors in the present experiment because of their low solubilities.



a) *p*-Toluoyl chloride, DMAP / pyridine / 0 °C ~ rt / 89%, b) $CH_3(CH_2)_{11}SH$, BF_3•OEt_2 / CH_2Cl_2 / 0 °C ~ rt / 78%, c) 30 mol% TfOH (70% aq.), 40 mol% n-Bu_4NIO_4 / MeCN / 0 °C / 90% (Ref. 10), d) Phenyl chloroformate, Et_3N / CH_2Cl_2 / rt / 48% (1st crop). Yields were not optimized.

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