A New Method for α-Selective Glycosylation Using a Donor, Glycosyl Methyldiphenylphosphonium Iodide, without Any Assistance of Acid Promoters

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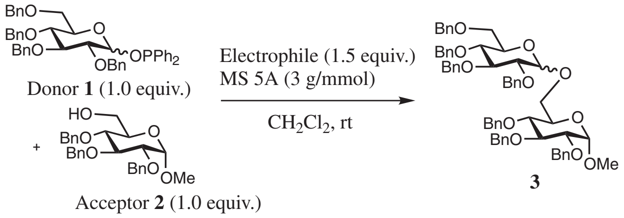
A mild and highly α-selective glycosylation of several glycosyl acceptors was performed with an in situ formed glycosyl donor, benzyl-protected glycosyl methyldiphenylphosphonium iodide, to afford the corresponding α-disaccharides in high yields in CH_2Cl_2 at room temperature without any assistance of acid promoters.

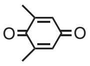
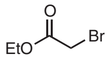
There are a number of methods reported for the stereoselective glycosylation in the syntheses of various glycosides and oligosaccharides.[1] For example, reactions of glycosyl acceptors with glycosyl donors such as glycosyl fluorides[2] or glycosyl phosphites[3] have been carried out by the promotion of Lewis acid or protonic acid to afford α- or β-glycosides stereoselectively. In most of these cases, strong acids such as Lewis acids and protonic acids or heavy metal reagents are needed and examples for mild and practical glycosylations without any assistance of acid promoters are few. Very recently, alkoxydiphenylphosphonium salts, generated from alkoxydiphenylphosphine and 2,6-dimethyl-1,4-benzoquinone[4] or iodomethane,[5] were found to react with several nucleophiles to give coupling products along with stable phosphine (V) oxide. In order to expand the scope of these reactions, application of the above concept to *O*-glycosylation reaction was considered. Thus, a highly α-selective glycosylation of glycosyl acceptors by using just a donor generated from glycosyl diphenylphosphinite **1** and iodomethane in the absence of acid promoters is described here.

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl diphenylphosphinite (**1**) was prepared easily from lithiated 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside and diphenylchlorophosphine. This reaction proceeded at room temperature and the crude product was recrystallized from *n*-hexane–ethyl acetate to afford a mixture of stereoisomers of **1**.

In the first place, glycosylation of glycosyl acceptor **2** with **1** in the presence of 2,6-dimethyl-1,4-benzoquinone in dichloromethane at room temperature was tried under the conditions reported previously. The reaction proceeded to afford the corresponding disaccharide in low yield and the stereochemistry was neither controlled (Table 1, Entry 1). When alkyl halides were used as electrophiles, the desired disaccharides were α-selectively obtained in 20 to 84% yields (Table 1, Entries 2–6). Of various electrophiles screened for the generation of active phosphonium salts, iodomethane worked out most efficiently in raising stereoselectivity and reactivity and afforded the desired disaccharide in 84% yield (Table 1, Entry 6, $\alpha/\beta = 95/5$). On the other hand, the use of glycosyl diethylphosphite as a donor under the same reaction conditions (Entry 7) gave the desired **3** in lower yield (75%) with lower stereoselectivity ($\alpha/\beta = 94/6$) even after letting it react for a duration as long as 7 days.

Table 1. Glycosylation of acceptor **2**, methyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside, with glycosyldiphenylphosphinite **1** in the presence of various electrophile



Entry	Electrophile	Time	Yield /% (α/β)[a]
1		3 days	40 (55/45)
2		2 days	45 (91/9)
3	BnBr	2 days	52 (90/10)
4	$MeOCH_2I$	20 h	45 (91/9)
5	EtI	20 h	20 (94/6)
6	MeI	20 h	**84 (95/5)**
7[b]	MeI	7 days	78 (91/9)

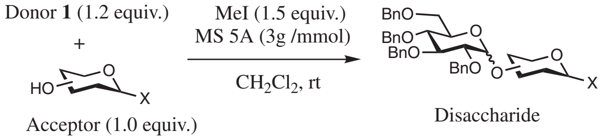
[a]The α/β ratios were determined by HPLC analysis.
[b]Glycosy diethylphoshite was used as a donor.

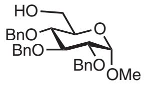
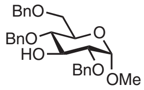
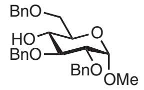
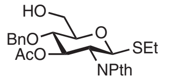
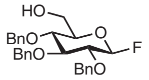
Next, the effect of solvent was examined. It was then shown that the corresponding disaccharides were obtained in 74–83% yields with α-stereoselectivities ($\alpha/\beta = 88/12$–$96/4$) when the reactions were carried out in THF, toluene, and acetonitrile. Interestingly, the use of dimethylsulfoxide gave an oxidized product, D-glucono-1,5-lactone derivative, in 39% yield. Finally, the best solvent of this glycosylation was dichloromethane (Yield = 84%, $\alpha/\beta = 95/5$).

Thus, the present glycosylation reactions afforded the desired α-D-glucopyranosides in good to high yields with high stereoselectivities as shown in Table 2. Even when acid-labile glycosyl fluoride or thioglycosides which easily formed the sulfonium salt with iodomethane were used as acceptors, the corresponding disaccharides were obtained in good yields with high stereoselectivities as well (Table 2, Entries 4,5). However, the use of methyl 2,3,6-tri-*O*-benzyl-D-glucopyranoside gave the desired product in low yield due to the steric hindrance of hydroxyl group at 4 position (Table 2, Entry 3).

Two alternative reactive intermediates, namely, glycosyl phosphonium iodide, and glycosyl iodide are conceivable. In or-

Table 2. Glycosylation of various acceptors with donor **1**



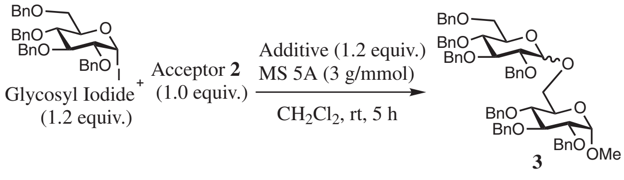
Entry	Accepto	Time	Yield /% (α/β)[a]
1		3 days	96 (96/4)
2		4 days	92 (98/2)
3		4 days	44 (99/1)
4		2 days	79 (95/5)
5		2 days	86 (91/9)

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

der to make the reaction mechanism clear, glycosyl iodides, prepared by Gervay's procedure,[6] were treated with glycosyl acceptor **2** under several conditions (Table 3). Surprisingly, the addition of diphenylmethylphosphine oxide raised reactivity and stereoselectivity in comparison to the case with tetrabutylammonium iodide. This result shows that the glycosyl phosphonium iodide, not the glycosyl iodide, is the reactive intermediate. In addition, phosphine oxide, a co-product of this reaction, is known to be a weak base but is enough to undergo full protonation to form a salt with hydrogen iodide.[7]

Thus, the present reaction is assumed to proceed via the reactive intermediates, α- and β-glycosyl phosphonium iodides which were generated from the corresponding glycosyl phosphinite and iodomethane. Glycosyl acceptors react predominantly with highly reactive β-intermediate to afford α-disaccharide and the remaining α-intermediate is therein epimerized to the reactive β-one which in turn reacts rapidly with the glycosyl acceptor (Scheme 1).

Table 3. Effect of additives on glycosylation of acceptor **2** with glycosyl iodide.



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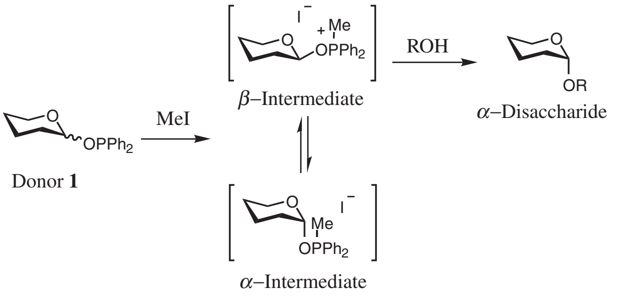
Entry	Additive	Yield /% (α/β)[a]
1	——	47 (71/29)
2	*n*-Bu$_4$NI	67 (91/9)
3	*n*-Bu$_4$NI / (*i*-Pr)$_2$NEt	42 (92/8)
4	Ph$_2$P(=O)Me	86 (94/6)

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



Scheme 1. Glycosylation of glycosyl acceptors with donor **1** and iodomethane.

The typical experimental procedure is as follows; to a stirred suspension of MS5A (300 mg), **1** (0.183 g, 0.25 mmol) and **2** (0.098 g, 0.21 mmol) in CH$_2$Cl$_2$ was added MeI (22.4 μL, 0.36 mmol) at room temperature. After stirring for 3 days, the reaction mixture was diluted with EtOAc, filtered through Celite and washed with saturated NaHCO$_3$. After having been dried over MgSO$_4$, filtered and evaporated, the resulting residue was purified by preparative TLC (silica gel) to give the desired product **3** (0.199 g, 96%, $\alpha/\beta = 96/4$).

Thus, the glycosylation using glycosyl diphenylphosphinite and iodomethane was successfully carried out without using acids which were generally used as essential promoters to afford α-disaccharide in high yield with high stereoselectivity.[8] It should be noted that the glycosyl diphenylphosphinite **1** is an easy-to-handle, stable and crystalline compound.

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References and Notes

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8 These reactions need longer reaction time (2–4 days) because formation of the corresponding quaternary salt from glycosyl diphenyphosphinites and iodomethane is quite slow. Now, the reaction of glycosyl halides and glycosyl acceptors promoted by the addition of phosphine oxide is under investigation for acceleration.

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