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The catalytic synthesis of aryl *O*-glycosides using triaryloxyboranes

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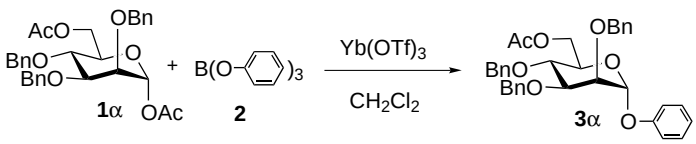
Abstract—Triaryloxyboranes worked as highly reactive glycosyl acceptors of glycosyl acetates to afford aryl *O*-glycosides in excellent yields. A catalytic amount of ytterbium(III) trifluoromethanesulfonate activated the formation reaction of aryl *O*-glycosidic linkages between the glycosyl acetates and triaryloxyboranes. © 2001 Elsevier Science Ltd. All rights reserved.

Aryl *O*-glycosidic compounds (aryl glycosides) are widely found in natural products, and their complicated structures and biological activities make them attractive target molecules in synthetic organic chemistry.[1] Some of the chemically synthesized aryl glycosides, which have a *p*-nitrophenyloxy group, a *p*-methoxyphenyloxy group and other functional groups as their aglycone moieties, are also significant substrates for enzymatic evaluations[2] and synthetic intermediates[3] in carbohydrate chemistry. Furthermore, in the recent synthesis of glycopolymers, the aglycone moieties of the aryl glycosides are often used as spacers connecting the sugars to polymers.[4]

Due to the differences in the reactivity between phenols and ordinary alcohols, the conventional syntheses of aryl glycosides by glycosylation using phenols generally need large excesses of activators and substrates,[5] and occasionally require a low temperature reaction condition to prevent the production of aryl *C*-glycoside by *O*→*C* glycoside rearrangement.[6] Although the tributyltin salts of phenols are often used as the glycosyl acceptors to improve the reactivity of phenols, they are poisonous substrates.[7]

Our recent glycosidation studies revealed that the use of boron compounds as either activators or acceptors enhanced the reactivities of the ytterbium(III) trifluoromethanesulfonate ($Yb(OTf)_3$)-promoted glycosidation using glycosyl acetates as glycosyl donors. The combined use of a catalytic amount of boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) with $Yb(OTf)_3$ as an activating system dramatically increased this glycosidation reactivity.[8] In the study of protecting the anomeric hydroxyl groups of sugars with the allyl group, triallyloxyborane, which is considered as a kind of boron alkoxide, worked as a highly reactive glycosyl acceptor to convert the glycosyl acetates into allyl glycosides.[9] The latter results suggested to us that some boron alkoxides could have the potential to function not only as glycosyl acceptors, having reactive alkoxides species, but also as receivers of the acetyloxy group from the glycosyl acetates after leaving their alkoxides. Further research on a glycoside synthesis using several trialkoxyboranes as glycosyl acceptors of glycosyl acetates determined that triaryloxyboranes worked as excellent substrates to synthesize aryl glycosides in the presence of a catalytic amount of $Yb(OTf)_3$. In this paper, we describe in detail the efficient formation reaction of the



Scheme 1.

Keywords: aryl glycoside; glycosidation; triaryloxyborane; glycosyl acetate; trifluoromethanesulfonate.

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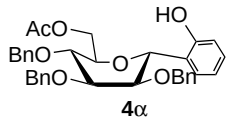
Table 1. Reaction of **1**α with **2** in the presence of $Yb(OTf)_3$

Entry[a]	Mol% of $Yb(OTf)_3$	Temp. (°C)	Yield of *O*-glycoside (%)[b]
1	10	Rt	52 (10)
2[c]	10	Rt	6
3	5	Rt	53 (12)
4	1	Rt	61 (3)
5	1	0	77

[a] Molar ratio, glycosyl acetate:$B(OPh)_3$ = 1:0.34; time, 1.5 h.
[b] Parenthesis is yield of *C*-Glycoside **4**α.
[c] PhOH was used.



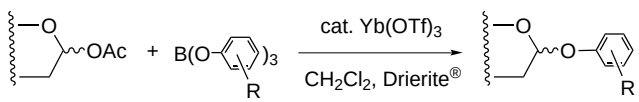
4α

Scheme 2.

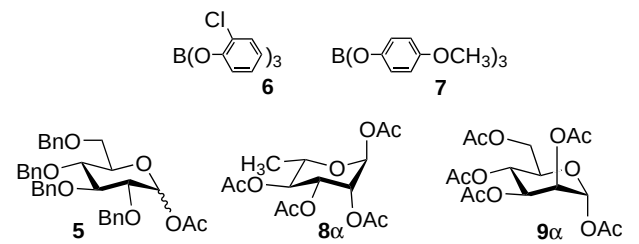
Table 2. Reaction between **1**α and **2** using various kinds of Lewis acids, solvents and molar ratios

Entry[a]	Activator (mol%)	Mol% of $B(OPh)_3$	Solvent	Yield (%)
1	$Yb(OTf)_3$ (1)	34	CH_2Cl_2	77
2	$Sc(OTf)_3$ (1)	34	CH_2Cl_2	72
3	$Zr(OTf)_2$·THF (1)	34	CH_2Cl_2	55
4	$Sn(OTf)_2$ (1)	34	CH_2Cl_2	54
5	TMSOTf (1)	34	CH_2Cl_2	52
6	$Yb(OTf)_3$ (1)	34	CH_3CN	0
7	$Yb(OTf)_3$ (1)	34	PhH	65
8	$Yb(OTf)_3$ (1)	34	THF	0
9	$Yb(OTf)_3$ (2)	50	CH_2Cl_2	80
10[b]	$Yb(OTf)_3$ (2)	50	CH_2Cl_2	86

[a] Temperature, 0°C; time, 1.5 h.
[b] Drierite® ($CaSO_4$) was added as a drying agent.



Scheme 3.



Scheme 4.

aryl *O*-glycosidic linkages between the glycosyl acetates and triaryloxyboranes.

Firstly, we attempted a comparison between triphenoxyborane ($B(OPh)_3$) (**2**) and phenol concerning their reactivities as the glycosyl acceptors of 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranosyl acetate (**1**α) (Scheme 1). The reaction between 0.34 molar equivalents of **2** and **1**α using 10 mol% $Yb(OTf)_3$ in dichloromethane at room temperature gave the expected corresponding phenyl α-*O*-mannoside **3**α[10] in 52% yield and glycosyl phenol (α-*C*-glycoside) **4**α[11] (Scheme 2) in 10% yield as a by-product. The reaction under the same conditions using 1 molar equivalent of phenol afforded **3**α in only 6% yield. These results show that the triaryloxyboranes are more reactive as glycosyl acceptors of glycosyl acetates than phenols. When the reactions of **1**α with **2** using a lower amount of $Yb(OTf)_3$ were examined, the reaction with only 1 mol% $Yb(OTf)_3$ increased the yield of **3**α to 61% and decreased the yield of **4**α to 3%. Furthermore, the reaction at 0°C afforded only **3**α in a yield of 77% without producing **4**α. This indicates that all three phenoxy groups of **2** could have the potential to react. These results are shown in Table 1.

Next we examined the Lewis acids, solvents, and molar ratios for the reaction between **1**α and **2**. The Lewis acids of the trifluoromethanesulfonates used were $Yb(OTf)_3$, scandium trifluoromethanesulfonate ($Sc(OTf)_3$), zirconium trifluoromethanesulfonate·tetrahydrofuran complex ($Zr(OTf)_2$·THF), tin(II) trifluoromethanesulfonate ($Sn(OTf)_2$) and trimethylsilyl trifluoromethanesulfonate (TMSOTf). Any reaction with 1 mol% of these trifluoromethanesulfonates afforded **3**α and the yields ranged from 52 to 77%. $Yb(OTf)_3$ and $Sc(OTf)_3$ were notably effective. The effect of solvents was examined using CH_2Cl_2, CH_3CN, PhH and THF. The reactions using CH_2Cl_2 and PhH afforded **3**α in 77 and 65% yields, however, CH_3CN and THF were ineffective for this glycosidation. In the investigation of molar ratios, the reaction using 0.5 molar equivalents of **2** and 2 mol% $Yb(OTf)_3$ toward **1**α gave **3**α in 80% yield, and the addition of $CaSO_4$ to this reaction system increased the yield of **3**α to 86%. These results are shown in Table 2.

Finally, we applied this method to the synthesis of several aryl glycosides using various kinds of triaryloxyboranes and glycosyl acetates (Scheme 3). As the triaryloxyboranes[12] **2**, tris(2-chlorophenyloxy)borane (**6**), and tris(4-methoxyphenyloxy)borane (**7**) were used, and **1**α, 2,3,4,6-tera-*O*-benzyl-D-glucopyranosyl acetate (**5**), 1,2,3,4-tetra-*O*-acetyl-α-D-rhamnopyranose (**8**α), and 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose (**9**α) were used as the glycosyl acetates (Scheme 4). The reactions of the triaryloxyboranes **2**, **6** and **7** with the *O*-benzylated glycosyl acetates **1**α and **5** using 2–4 mol% of $Yb(OTf)_3$ gave the corresponding aryl glycosides in good yields. This method was also successfully applicable to the synthesis of the *O*-peracetylated aryl glycosides. The reactions of the peracetylated donors **8**α and **9**α with the triaryloxyboranes **2** and **7** in the presence of 5–15 mol% $Yb(OTf)_3$ afforded the *O*-acetylated aryl glycosides in excellent yields. These results are summarized in Table 3.

Table 3. Synthesis of several aryl glycosides using various kinds of triaryloxyboranes and glycosyl acetates

Entry[a]	Glycosyl acetate	Triaryloxyborane	Mol% of $Yb(OTf)_3$	Temp. (°C)	Time	Yield (%)	α/β (J_{C1-H1})
1	**1**α	**2**	2	0	1.5 h	86	α (171.8)
2	**1**α	**6**	4	0	5 h	61	α (171.6)
3	**1**α	**7**	4	0	5 h	96	α (170.0)
4	**5**	**2**	2	0	5 h	71	57/43
5	**5**	**6**	4	0	5 h	45	70/30
6	**5**	**7**	4	0	5 h	83	65/35
7	**8**α	**2**	5	Rt	Overnight	71	α (172.5)
8	**8**α	**7**	5	Rt	Overnight	78	α (172.5)
9	**9**α	**2**	15	Rt	2 days	75	α (174.2)
10	**9**α	**7**	15	Rt	2 days	72	α (173.4)

[a] Molar ratio, glycosyl acetate:triaryloxyborane = 1:0.5.

As mentioned above, we found that several triaryloxyboranes worked as good glycosyl acceptors of the glycosyl acetates, and an efficient glycosylation method for synthesizing aryl glycosides with only a catalytic amount of $Yb(OTf)_3$ as an activator could be developed.

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12. Triaryloxyboranes **2**, **6** and **7** were prepared by the reaction of the phenols with $B(OH)_3$ in the presence of CaH_2, as mentioned in the following reference: Cole, T. E.; Quintanilla, R.; Rodewald, S. *Synth. React. Inorg. Met.-Org. Chem.* **1990**, *20*, 55. Triphenoxyborane is also commercially available from Aldrich and Tokyo Kasei Co., Ltd.