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Regioselective Benzylation of Diols and Polyols by Catalytic Amounts of an Organotin Reagent

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Abstract: An efficient one-pot method for the selective benzylation of diols and polyols using 0.1 equiv. of organotin reagents and tetrabutylammonium bromide as catalyst has been developed. The diols and polyols containing a *cis*-vicinal diol were regioselectively benzylated in 70–94% isolated yields. A catalytic reaction mechanism was also proposed.

Keywords: benzylation; carbohydrates; catalysis; organotin reagents; regioselectivity

Benzyl ethers as ether protecting groups play very important roles in carbohydrate chemistry due to their particular stability and resistance to basic and acidic conditions, as well as being easily removed by catalytic hydrogenation.[1] Regioselective benzylations are often the most important part in synthesis strategies towards saccharide building blocks that are used as donors or acceptors in the synthesis of oligosaccharides.[2] Many methods have been developed to achieve selective benzylation, including employment of reagents such as tin(IV), boron(IV), silicon(IV), copper(II), mercury(II), silver(I) and nickel(II) based complexes.[3] Organotin species have become the most widely used reagents in selective benzylation for higher regioselectivities and convenient manipulation.[4] The regioselectivity originates from the generation of a dibutylstannylene acetal or stannyl ether between vicinal diol groups of the substrates and a stoichiometric amount of the organotin reagent. However, the main drawback with these reagents is the potential inherent toxicity of organotin compounds.[5] Thus, developing non-toxic reagents[6] or employing catalytic amounts of organotin reagents[7] is desirable, provided that they result in the same/better regioselectivities with similar/higher yields as when employing stoichiometric amount of organotins. Although catalytic amounts of organotins have been successfully applied in regioselective acylation,[8] sulfonylation,[9] silylation[10] and glycosylation,[11] it is hard to find their application in benzylation. The reason might be the requirement for a large amount of bromide or iodide.[4] Recently, it is reported that two hydroxy groups in polyols are selectively benzylated when 1 equiv. of dibutyltin oxide and 0.6 equiv. of tetrabutylamonnium bromide (TBAB) are used.[12] During the period after we submitted this paper, another tin-catalyzed regioselective benzylation and allylation of polyols was published, using a moderate excess of diisopropyl(ethyl)amine (DIPEA) and benzyl bromide, and 0.3 equiv. of TBAI. However, moderate yields were generally obtained under these solvent-free conditions.[13] Herein, we report an efficient one-pot method for the selective benzylation of diols and polyols using 0.1 equiv. of tetrabutylamonnium bromide (TBAB) and 0.1 equiv. of organotin reagent as catalyst (Figure 1). In this method, 0.1 equiv. of dibutyltin oxide (or dibutyltin dichloride, dimethyl-

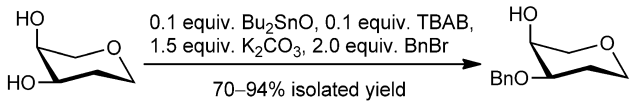


Figure 1. Regioselective benzylation of diols and polyols by a catalytic amount of organotin reagent.

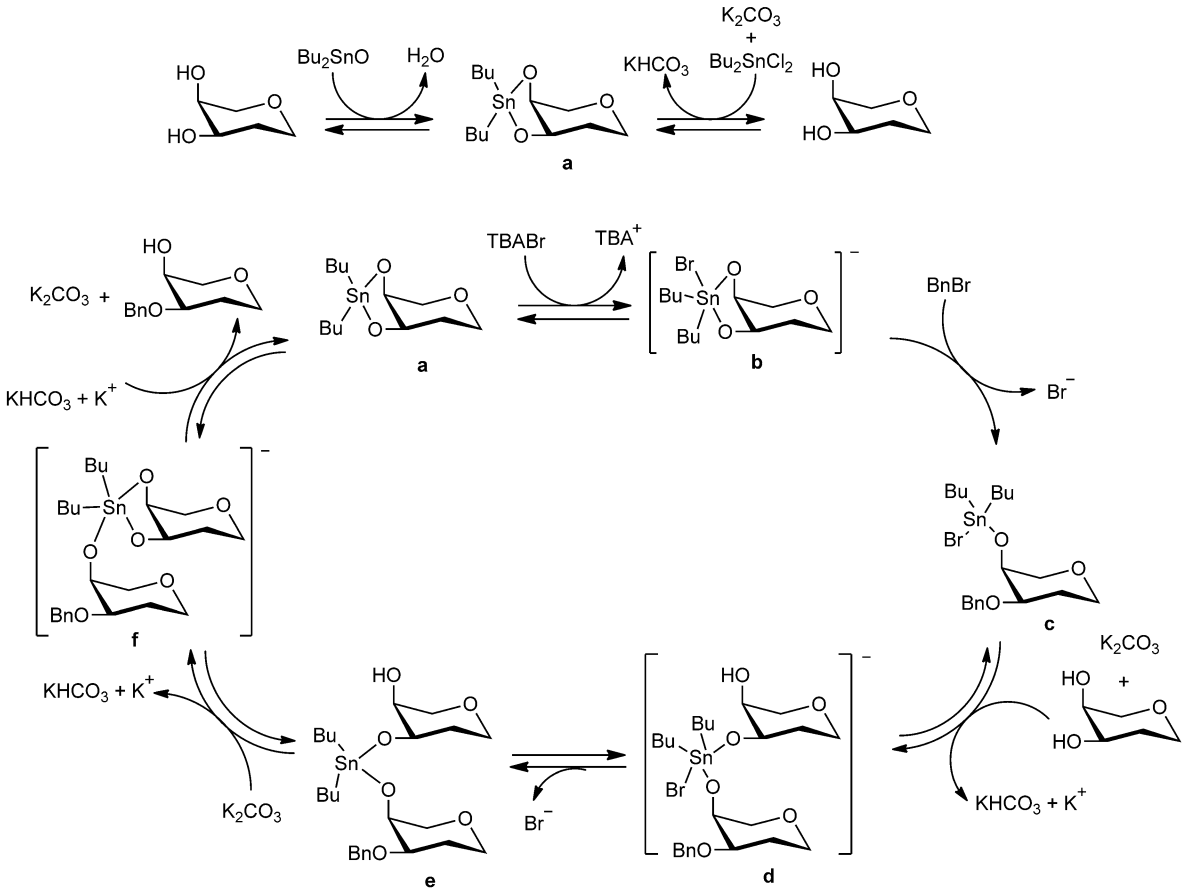
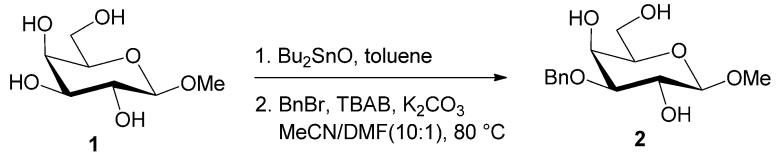


Figure 2. Proposed mechanism for the benzylation catalyzed by an organotin reagent and TBAB.

tin dichloride) was used to form a dibutylstannylene acetal with two vicinal OH groups of the substrates, 0.1 equiv. of TBAB was used to coodinate the tin atom of the dibutylstannylene acetal thus activating the reaction, and an excess amount of potassium carbonate was used to deprotonate the hydroxy group and recycle the reaction. The diols and polyols containing *cis*-vicinal diol units were regioselectively benzylated in 70–94% isolated yields, better than reported methods. Furthermore, unlike the above-mentioned solvent-free approach, this method is apparently compatible with the broadly adopted thioglycoside building blocks.

It had been a general concept that the regioselectivity of the dibutylstannylene-mediated protection originated from complex stannylene structures.[4] However, we recently suggested that the regioselectivity is more likely to be controlled by stereoelectronic effects of the parent substrate structure.[14] Under the guidance of this principle, we studied the activation ability of halides on organotin-mediated benzylation of carbohydrates and the results initially revealed the mechanism of this halide-promoted benzylation.[15] The activated benzylation by halides was attributed to coordination of the halide anion to a tetracoordinate tin atom. A catalytic amount of bromide was chosen as the best activation additive in the reaction owing to its regeneration since benzyl bromide (BnBr) has always been used as benzylation reagent. For benzylation using a stoichiometric amount of organotin, after the formation of dibutylstannylene acetals through the treatment of dibutyltin oxide with vicinal OH groups in toulene, the reaction mixture was allowed to react with an excess amount of BnBr in the presence of 0.5 equiv. of TBAB at 90–100 °C.[15] The coordination of the bromide to the tetracoordinate tin atom enhances the selective Sn–O bond cleavage to give a reactive oxygen species, followed by a nucleophilic attack of this oxygen species to an electrophile (BnBr), finally leading to a selective benzylation. The bromide regenerates from the substitution of BnBr. These results inspired us to propose a benzylation mechanism when using a cataytic amount of dibutyltin oxide, such as 0.1 equiv. of dibutyltin oxide (Figure 2). After the formation of dibutylstannylene acetal intermediate **a** between substrates and 0.1 equiv. of organotin, the intermediate **a** would further react with BnBr in the presence of 0.1 equiv. of TBAB, leading to intermediate **c** where one position is benzylated and the other occupied by the tin spe-

Table 1. Comparison of results by variation from the "standard" conditions.



Entry	Reaction conditions	Time	NMR yield [%]
1	optimized conditions[a]	3 h	96
2	no Bu_2SnO	8 h	25
3	no K_2CO_3	8 h	11
4	no TBAB	3 h	86
5	0.05 equiv. Bu_2SnO	8 h	84
6	1.5 equiv. BnBr	8 h	56
7	react at 40 °C	8 h	no reaction
8	THF only as solvent instead	8 h	low conversion
9	toluene only as solvent instead	8 h	low conversion
10	toluene/DMF (10:1)	8 h	low conversion
11	toluene/MeCN (1:1)	8 h	low conversion
12	MeCN only as solvent instead	8 h	70
13	DMF only as solvent instead	8 h	52
14	MeCN/DMF (1:1) as solvent instead	8 h	56
15[b]	Me_2SnCl_2 instead of Bu_2SnO	3 h	96
16[b]	Bu_2SnCl_2 instead of Bu_2SnO	3 h	95

[a] *Conditions:* 1) methyl β-D-galactoside **1** (100 mg), Bu_2SnO (0.1 equiv.), toluene (6 mL), 100 °C, 1 h. 2) K_2CO_3 (1.5 equiv.), TBAB (0.1 equiv.), BnBr (2 equiv.), MeCN:DMF (10:1) (2 mL), 80 °C.

[b] Methyl β-D-galactoside **1** (100 mg), Bu_2SnCl_2 or Me_2SnCl_2 (0.1 equiv.), K_2CO_3 (1.5 equiv.), TBAB (0.1 equiv.), BnBr (2 equiv.), MeCN:DMF (10:1) (2 mL), 80 °C.

cies coordinated by a bromide. Deprotonated by a base, such as potassium carbonate, the un-benzylated substrate would also coordinate to the tetracoordinate tin atom to form pentacoordinate tin intermediate **d**. After tin species exchange through intermediates **e** and **f**, the final benzylated product would be generated from intermediate **f**, leading to the regeneration of dibutylstannylene acetal **a** from the un-benzylated substrate and further starting the next cycle.

In light of this proposed mechanism, we started to investigate if this organotin and TBAB-catalyzed regioselective benzylation method is valid. Firstly, methyl β-D-galactoside **1** was chosen to verify this method (Table 1). The galactoside **1** (100 mg) was allowed to react with 0.1 equiv. of dibutyltin oxide (12.7 mg) in toluene (6 mL) at 100 °C for 1 h. After removal of toluene, the residue was added into a mixture of MeCN (2 mL) and DMF (0.2 mL). The addition of DMF was necessary to improve the solubility of non-protected glycosides. After reacting with 2.0 equiv. of benzyl bromide in the presence of 0.1 equiv. of TBAB and 1.5 equiv. of K_2CO_3 at 80 °C for 3 h, the expected product **2** was formed in 96% NMR yield (entry 1 in Table 1). Without dibutyltin oxide or K_2CO_3, the reactivity was dramatically decreased (entries 2 and 3 in Table 1), whereas, without TBAB the reactivity was slightly decreased (entry 4 in Table 1). With 0.05 equiv. of dibutyltin oxide or 1.5 equiv. of BnBr separately, it took 8 h to obtain an 84% or 56% yield of **2** (entries 5 and 6 in Table 1). The reaction did not appear to operate at lower temperature (entry 7 in Table 1).

Since the boiling point of THF is 66 °C, THF alone as solvent led to low conversion (entry 8 in Table 1). When using toluene or toluene mixed with DMF or acetonitrile as solvent, the poor solubility of **1** led to very low conversion (entries 9, 10 and 11 in Table 1). It took 8 h to obtain only 70% yield of **2** when using solely MeCN as solvent, indicating the necessity of the addition of DMF (entry 12 in Table 1). However, an excessive amount of DMF hindered the reaction (entries 13 and 14 in Table 1). The stannylene acetal intermediate may also be formed by the treatment of vicinal OH groups with Bu_2SnCl_2 or Me_2SnCl_2 in the presence of K_2CO_3. Thus, direct treatment of galactoside **1** with 2.0 equiv. of BnBr in the presence of 0.1 equiv. of TBAB, 1.5 equiv. of K_2CO_3 and 0.1 equiv. of Bu_2SnCl_2 or 0.1 equiv. of Me_2SnCl_2 in acetonitrile (MeCN/DMF = 10/1) gave a similar result (entries 15 and 16 in Table 1).

These experiments indicate that the mechanism proposed in Figure 2 is valid and this regioselective benzylation method can be applied to more substrates. Although the employment of Bu_2SnCl_2 or

Table 2. Selective benzylation of 1,2-diols and carbohydrates containing *cis*-diol groups.[a]

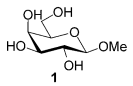
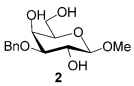
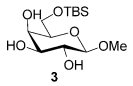
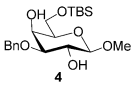
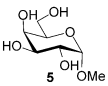
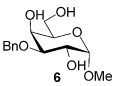
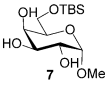
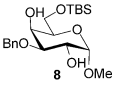
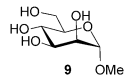
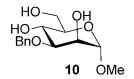
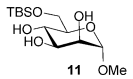
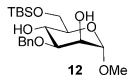
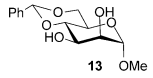
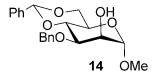
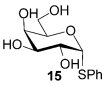
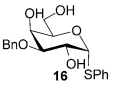
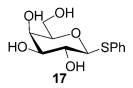
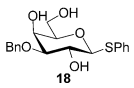
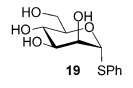
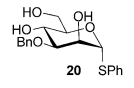
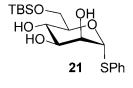
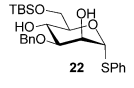
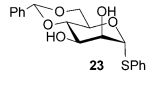
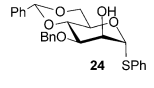
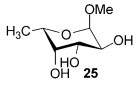
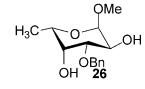
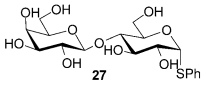
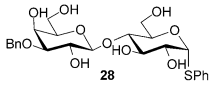
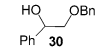
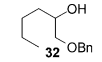
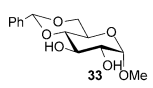
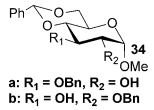
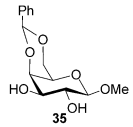
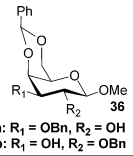
Entry	Substrate	Product	Yield [%][b]
1	 1	 2	88
2	 3	 4	90
3	 5	 6	87 (86)[c]
4	 7	 8	91
5	 9 OMe	 10 OMe	85 (82)[c]
6	 11 OMe	 12 OMe	90
7[d]	 13 OMe	 14 OMe	86 (84)[c]
8	 15 SPh	 16 SPh	79
9	 17	 18	77
10	 19 SPh	 20 SPh	82
11	 21 SPh	 22 SPh	88
12[d]	 23 SPh	 24 SPh	88
13	 25	 26	94
14	 27	 28	70
15	 29	 30	84
16	 31	 32	85
17	 33 OMe	 34 OMe a: R_1 = OBn, R_2 = OH b: R_1 = OH, R_2 = OBn	**34a** (37) **34b** (41)

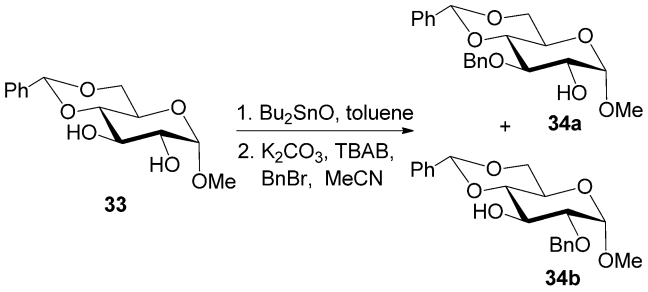
Table 2. (Continued)

Entry	Substrate	Product	Yield [%][b]
18	 35	 36 a: R_1 = OBn, R_2 = OH b: R_1 = OH, R_2 = OBn	**36a** (46) **36b** (38)

[a] *Conditions:* 1) Bu_2SnO (0.1 equiv.), toluene (6 mL), 100 °C, 1 h. 2) K_2CO_3 (1.5 equiv.), TBAB (0.1 equiv.), BnBr (2 equiv.), MeCN:DMF (10:1) (2 mL), 80 °C, 3 h.
[b] Isolated yields.
[c] The yields in brackets were obtained in experiments run on a larger scale.
[d] MeCN alone as solvent.

Me_2SnCl_2 was also efficient and more convenient, we still chose Bu_2SnO as catalyst in order to make sure of the role of the dibutylstannylene acetal intermediate in the reaction. Thus, this method was further tested with diols and polyols containing *cis*-diol groups (entries 1–14 in Table 2). It can be seen that the equatorial hydroxy groups adjacent to an axial hydroxy group in all the substrates were selectively benzylated in 70–94% isolated yields. For the dibutylstannylene acetals formed by *cis*-diols, the equatorial SnO bond preferentially breaks due to a stereoelectronic effect, thus leading to a product benzylated in an equatorial position.[14] Benzylation of non-protected glycosides could lead to a small amount of 3,6-di-benzylation products. Thus, when the 6-postion of these glycosides (compounds **1**, **5**, **9** and **19**) was protected by a TBS group (compounds **3**, **7**, **11** and **21**), better yields of 3-position benzylated products were obtained (entries 2, 4, 6 and 11 in Table 2). Since 4,6-*O*-benzylidenemannopyranosides **13** and **23** appear to show good solubility in MeCN, the employment of DMF is not necessary in these two cases (entries 7 and 12 in Table 2). The method could be further applied in the benzylation of the primary hydroxy group of 1,2-diols **29** and **31** (entries 15 and 16 in Table 2). Good selectivities and yields were also obtained when glycosides **5**, **9** and **13** were tested in a large scale (1 g), demonstrating the method's robustness (entries 3, 5 and 7 in Table 2). However, this method failed in the benzylation of substrates with *trans*-diol groups (entries 17 and 18 in Table 2). Usually, when using stoichiometric amounts of organotin reagents, protection of carbohydrates with *trans*-diol groups will not give selectivity if the adjacent substituents to the diol are either both equatorial or both axial and will give good selectivity to the hydroxy group adjacent to the equatorial substituent if the adjacent substituents are one equatorial and one axial.[14] Although benzylation of methyl 4,6-*O*-benzylidene-α-D-

Table 3. Benzylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside by the use of various amounts of Bu_2SnO.[a]



Entry	Bu_2SnO	Yield[b]	Ratio (**a**:**b**)
1	0.1 equiv.	72%	0.9:1
2	0.2 equiv.	77%	0.8:1
3	0.4 equiv.	94%	0.7:1
4	0.6 equiv.	90%	0.6:1
5	0.8 equiv.	93%	0.5:1
6	1.1 equiv.	87%	0.3:1

[a] *Conditions:* 1) Bu_2SnO, toluene (6 mL), 100 °C, 1 h. 2) K_2CO_3 (1.5 equiv.), TBAB (0.5 equiv.), BnBr (2.0 equiv.), MeCN (2 mL), 80 °C, 24 h.

[b] Isolated yields.

glucopyranoside **33** and 4,6-*O*-benzylidene-β-D-galactopyranoside **35** gave good selectivities when using stoichiometric amounts of organotin,[14] it did not give selectivities in this method (entries 17 and 18 in Table 2).

In order to explore why this method failed in the benzylation of compounds **33** and **35**, compound **33** was benzylated through the employment of various amounts of dibutyltin oxide (Table 3). It was observed that the yield of product **34a**, where the 3-position was benzylated, decreased with increases in the amount of dibutyltin oxide. The experimental results clearly indicate that the dibutylstannylene acetal initially formed with catalytic amounts of dibutyltin oxide cannot be regenerated with *trans*-diol under the prevailing conditions, thus leading to no selectivity. Consequently, only the starting dibutylstannylene acetals lead to some selectivities.

In conclusion, in light of the principle that the regioselectivity in organotin-mediated protection is controlled by stereoelectronic effects of the parent carbohydrate structure, an organotin-catalyzed benzylation mechanism has been proposed in this paper. According to the proposed mechanism, a method for the highly regioselective benzylation of diols and polyols employing a catalytic amount of an organotin reagent was developed. The organotin reagents could be any organotin reagent as long as they can form stannylene acetals with the substrates, such as dibutyltin oxide, dibutyltin dichloride or dimethyltin dichloride. The method employing 0.1 equiv. of dibutyltin oxide to substrates containing *cis*-diol groups has been proven to be highly efficient. The convenient protocol using dibutyltin dichloride or dimethyltin dicholoride can be carried out as a one-step reaction. This method appeared convenient, efficient, and environmentally friendly, and is also associated with high regioselectivity.

Experimental Section

General Procedure for Selective Monobenzylation of Diols and Polyols

Method a: Diol or polyol (100 mg) and dibutyltin oxide (0.1 equiv.) were added in 6 mL toluene, and refluxed for 1 h. Then, after evaporation of the solvent under vacuum, the residue was disolved in a mixture of 2 mL MeCN and 0.2 mL DMF in the presence of K_2CO_3 (1.5 equiv.) and benzyl bromide (2 equiv.)

Method b: Diol or polyol (100 mg) and dibutyltin chloride (0.1 equiv.) were added in a mixture of 2 mL MeCN and 0.2 mL DMF in the presence of K_2CO_3 (1.5 equiv.) and benzyl bromide (2 equiv.). The reaction was allowed to proceed at 80 °C for 3 h. After the removal of the solvents, the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 1:1 to 0:1) to give the desired pure product;

Large scale: Diol or polyol (1 g) and dibutyltin chloride (0.1 equiv.) were added in a mixture of 20 mL MeCN and 2 mL DMF in the presence of K_2CO_3 (1.5 equiv.) and benzyl bromide (2 equiv.). The reaction was allowed to proceed at 80 °C for 3 h. After the removal of the solvents, the residue was purified by column chromatography (*n*-hexane/ethyl acetate = 1:1 to 0:1) to give the desired pure product.

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