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Halide promoted organotin-mediated carbohydrate benzylation: mechanism and application

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ABSTRACT

In the present study, the mechanistic origin of the promoted organotin-mediated carbohydrate benzylation by halides was explored by the comparison of the activation ability of halides on benzylation of methyl β-D-galactoside. It was demonstrated that the improvement of benzylation in terms of speed, yield and general convenience in the presence of halides was due to the formation of an activated oxide species by the coordination of halide anions to the tetracoordinate tin atoms. The halide, being able to form a stronger bond with tin, showed stronger activation ability. The catalytic amount of bromide should be preferentially chosen as an activation additive in the reaction with consideration of economy, convenience and moderate activation ability. The results were further applied to mono- and multi-benzylation of additional carbohydrate structures. A range of prototype carbohydrate structures were efficiently prepared with the guidance of the principle. In light of the previous studies and the present experimental results, the general rules for organotin-mediated benzylation of carbohydrates have been summarized.

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1. Introduction

Benzyl ethers are frequently used ether protecting groups in carbohydrate chemistry, since they are particularly stable entities, resistant to basic and acidic conditions, and also easily removed by catalytic hydrogenation.[1] Together with ester groups, they already form the selective protection and deprotection of saccharide building blocks prior to and after the glycosidic linkage step when these building blocks are used as donors or acceptors for the synthesis of oligosaccharides.[2–7] Direct benzylation of carbohydrates using benzyl halides requires extreme conditions, such as strong base in polar solvents, which is difficult to lead to highly regioselectivity for poly-hydroxyl compounds.[8–10] Selective benzylation usually requires special means, such as relying on the reductive cleavage of benzylidene acetals,[11] and depending on reagents capable of promoting regioselective alkylation of carbohydrates. These reagents could be tin (IV), boron (IV), copper (II), mercury (II) and nickel (II)-based complexes,[12–15] as well as silver carbonate.[16] However, the most widely used method for highly regioselective benzylation involves the utilization of organotin.[17,18] The regioselectivity was provided by the introduction of dibutylstannylene acetals or stannyl ethers, which was derived from the treatment of diols and polyols with organotin. Benzyl bromide was herein used as an electrophile. The reaction was normally performed in the presence of quaternary ammonium iodide,[19] quaternary ammonium bromide[19,20] or cesium fluoride[21,22] for the improvement in terms of reaction rate, yield and general convenience. However, the mechanistic origin of the improvement for the reaction by halides has not been fully clarified. For example, the improvement of the reaction by quaternary ammonium iodide cannot be simply attributed to the generation of more reactive benzyl iodide, through the replacement of bromine of alkyl bromide by iodine, since quaternary bromide and cesium fluoride are also efficient active additives.[19,23] A more reasonable explanation may involve the dibutylstannylene acetal intermediates, in which the coordination of halide anions to tin enhances the nucleophilicity of one of the bound oxygen atoms.[19] However, this interpretation was never demonstrated due to the unclear mechanism of the dibutylstannylene-mediated protection. Furthermore, although regioselective benzylation with the assistance of halides have been reported in hundreds of protocols so far,[17,18] a systematic study on how the halides influence the reaction has never been performed. Consequently, there always were some uncertainties on the utilization of halides for any a specific dibutylstannylene-mediated benzylation, including the choice of a halide (iodide, bromide, chloride or fluoride), the amount of halide salt used (catalytic, stoichiometric or excess amount), and the prediction of the benzylation outcome (regioselectivity). These uncertainties have

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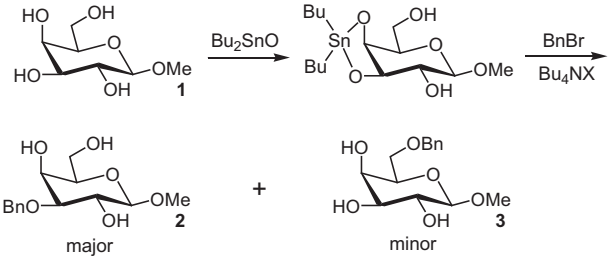
restricted the application of the method, especially on a regioselective multiple carbohydrate benzylation, which is of particular importance since two or more hydroxyl groups in polyols can be benzylated in a single-step process. In the present study, the origin of the promoted benzylation by halide anions was addressed, where the effect of the quaternary ammonium iodide, bromide, chloride, and fluoride on the dibutylstannylene-mediated benzylation of methyl β-D-galactoside was investigated, and the process was also applied on a regioselective multiple carbohydrate benzylation.

It was a general concept that the regioselectivity of the dibutylstannylene-mediated protection was controlled by complex stannylene structures.[18] However, we have recently suggested that the regioselectivity is more likely to be controlled by stereoelectronic effects of the parent carbohydrate structure,[24] which has been supported by further experiments on organoboron- and organosilicon-mediated protection.[25,26] Thereby, the origin of the regioselectivity for dibutylstannylene-mediated protection could be depicted to proceed via a selective Sn–O bond cleavage in a stannylene acetal ring, enhanced by a pentacoordinate tin atom. For dibutylstannylene-mediated benzylation (Fig. 1), as suggested, major 3-*O*-alkylated product and a minor 6-*O*-alkylated product were obtained after subsequent alkylation in toluene in the presence of tetrabutylammonium halide salts. It is not necessary to employ either stoichiometric or excess amounts of ammonium halides.[23] A tentative mechanism has been proposed to explain the absence of 4-*O*-alkylated product and the formation of 6-*O*-alkylated product.[29] Thus, we chose the 3/6-*O*-regioselective dibutylstannylene-mediated benzylation of methyl β-D-galactoside **1** as a model to investigate the effects of tetrabutylammonium halides on this simple and convenient reaction (Scheme 1).



Scheme 1. Dibutylstannylene-mediated benzylation of galactoside **1**.

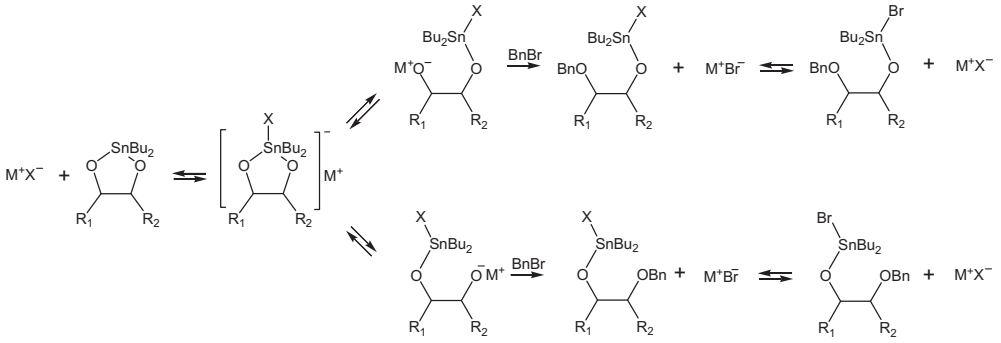


Fig. 1. A proposed mechanism for the activation of tin intermediates by halides. X=F, Cl, Br or I.

the coordination of the halide anion to the tetracoordinate tin atom enhances the selective Sn–O bond cleavage to give a reactive oxygen anion coordinated to ions (M^+), followed by a nucleophilic attack of the oxygen species to an electrophile (BnBr). Consequently, the regioselectivity was controlled by both the preferential cleavage of Sn–O bond and the nucleophilicity of the oxygen species. The formation and cleavage of Sn–X (halides) bond and Sn–O bond were reversible, and finally equilibria were likely to form. The formation of a stronger Sn–X bond would therefore lead to more reactive oxygen anions, which markedly accelerated the reaction. If this mechanism was valid, it could be proposed that the halide anion, forming stronger bond with tin, shows a higher activation ability for benzylation. This would be analogous to our previous studies where anions activated a cascade inversion by supramolecular effect.[27] Then the activation ability should follow the order: $F^->Cl^->Br^->I^-$. The bromide and iodide should not show higher activation ability than chloride and fluoride in the reaction. In order to demonstrate this, a systematic study on how the halides influence the dibutylstannylene-mediated benzylation was initiated in the following experiments.

2. Results and discussion

The 3/6-*O*-regioselectivity has been reported for the dibutylstannylene-mediated alkylation of galactosides with the activation of halide anions.[28,29] The dibutylstannylene acetals were generated by heating the unprotected galactosides with dibutyltin oxide under reflux in toluene until a clear solution was formed. A

In order to compare the activation ability of halide anions, the benzylation reactions were performed under the same conditions with various halides. The conversion rates were recorded after the same time intervals. The activation ability of various halides can be reflected by the comparison of the conversion rates. Thus, the methyl β-D-galactoside **1** (50 mg) was chosen to react with 1.1 equiv of dibutyltin oxide in toluene to form the dibutylstannylene acetals. The dibutylstannylene acetals were subsequently allowed to react with 1.5 equiv of benzyl bromide in 4 mL toluene at 90 °C for 10 h with the separate addition of 0.5 equiv of tetrabutylammonium iodide, bromide, chloride and fluoride. The conversion rates and the 3/6-*O*-benzylated product ratios were both determined by ^{1}H NMR spectra (Table S1a in SI). It can be seen in Fig. 2a. The recorded conversion rates at the 10 h time point were too subtle for the activation ability of the different halides to be distinguished. The analogous product ratios of 3/6-OBn were achieved with the separate addition of chloride, bromide and iodide; whereas more 6-OBn products formed with the addition of fluoride, in which the product ratio of 3/6-OBn with fluoride was 56/21 in comparison to 64/7 with chloride, 66/8 with bromide and 65/9 with iodide.

When the reactions were tested in 2 mL toluene under the same conditions, the analogous conversion rates were reached in 2 h (b in Fig. 2), indicating the reactions were concentration dependent. The conversion rates reached approximately 90% in 6 h. There were slight differences in the conversion rates for all the halides. More 6-OBn products formed with fluoride anion, thereby showing a poor regioselectivity. Upon analysis of the results, we realized that the reactions proceeded faster than expected. Thus the conversion

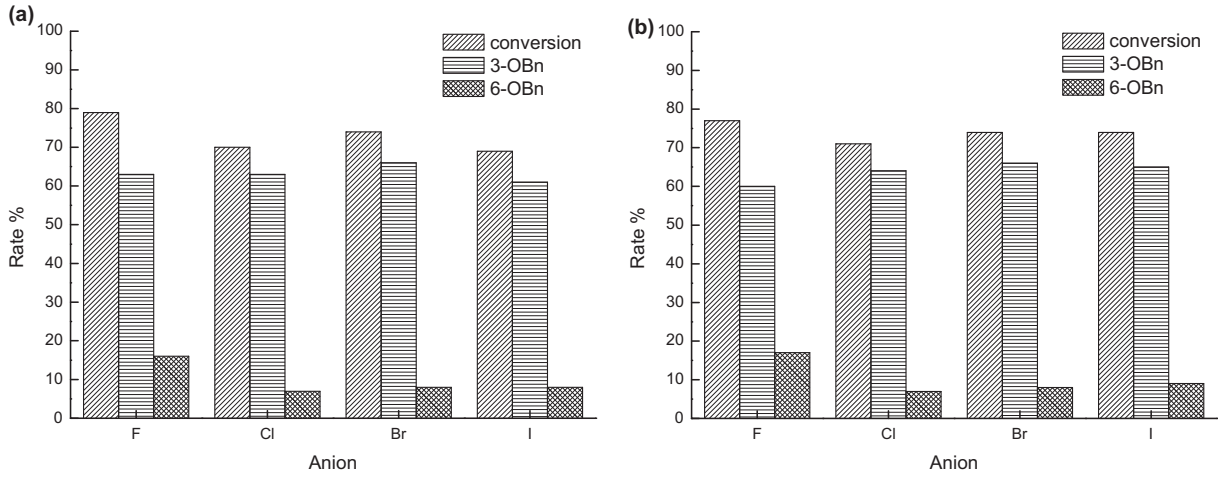


Fig. 2. The recorded conversion rates and 3/6-OBn ratios for benzylation of galactoside **1**. (a) Reaction in 4 mL toluene for 10 h; (b) reaction in 2 mL toluene for 2 h.

rates must be recorded in a suitable short reaction time period, when the conversion rates remain distinct. Therefore, in further experiments, the reactions were performed under the same conditions using less (1.1 equiv) benzyl bromide in order to avoid the formation of di-OBn products. The conversion rates and the 3/6-*O*-benzylated product ratios were determined by ^{1}H NMR spectrum with the reactions proceeding for 5 min, 2 h, 4 h and 6 h. The results were outlined in Fig. 3 (also seen in Table S2 in SI). The recorded conversion rate with fluoride at the 5 min time point was 58% in comparison to 34% with chloride, 34% with bromide and 33% with iodide, indicating a distinctly higher activation ability of fluoride than other halides. At the 2 h reaction time point, the conversion rates for all halides approached close to each other. The relative poor regioselectivity for fluoride was also shown.

The results prompted us to further investigate the effect on benzylation with the addition of varied amounts of tetrabutylammonium halides (Table S3 in SI). When 0.2 equiv of halide anions were employed, the conversion rates for all halides in 2 h were around 32–48%, indicating the decreased reactivity. When stoichiometric amounts of halides were employed, the conversion rates in 2 h were roughly analogous to those when 0.5 equiv of halides were employed. This indicated that the reactivity could not be noticeably improved by increasing the amounts of halide additives once the used amount of halide was more than 0.5 equiv. The activation ability was also compared by the comparison of the conversion rates at the 5 min time point. The rates for fluoride were 27%, 58% and 73%, respectively when 0.2, 0.5 and 1.0 equiv of fluoride anions were employed separately. However, the difference in rates for the other halides was smaller, being around 21–22%, 33–34% and 35–42% corresponding to the employment of 0.2, 0.5, and 1.0 equiv of halides. The results indicated that the fluoride showed higher activation ability as expected, which was likely to originate from the formation of strong Sn–F bond (Fig. 4a). It was supposed that the dibutyltin acetal intermediates involve benzylation as monomers in toluene at high temperature (100 °C).[24] Pentacoordinate tin atoms were thereby formed instantly when the added halides coordinated to tetracoordinate tin atom of the stannylene acetal monomers. Pentacoordinate-tetracoordinate equilibria of tin were formed then, since tetracoordinate tin atom could also generate from pentacoordinate tin atom by the breakage of the Sn–O or Sn–X (X stands for halide anions) bond (Figs. 1 and 4). The stronger Sn–X bond corresponded to the formation of more Sn–X bonds and less Sn–O bonds, leading to more oxygen anions and less X anions. Weaker Sn–X bond corresponded to the formation of less Sn–X bonds and more Sn–O bonds, leading to less oxygen anions and more X anions. Therefore, once the tetrabutylammonium fluoride was added to the reaction mixture (Fig. 4a), the fluoride coordinated to the tin atom to form stronger Sn–F

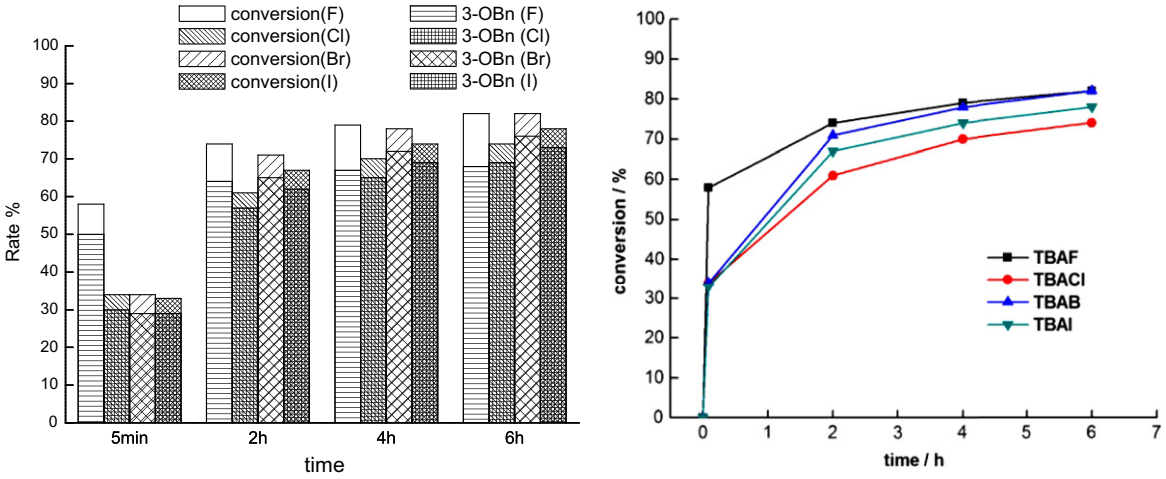


Fig. 3. The recorded conversion rates and 3/6-OBn ratios for benzylation of galactoside **1** with time.

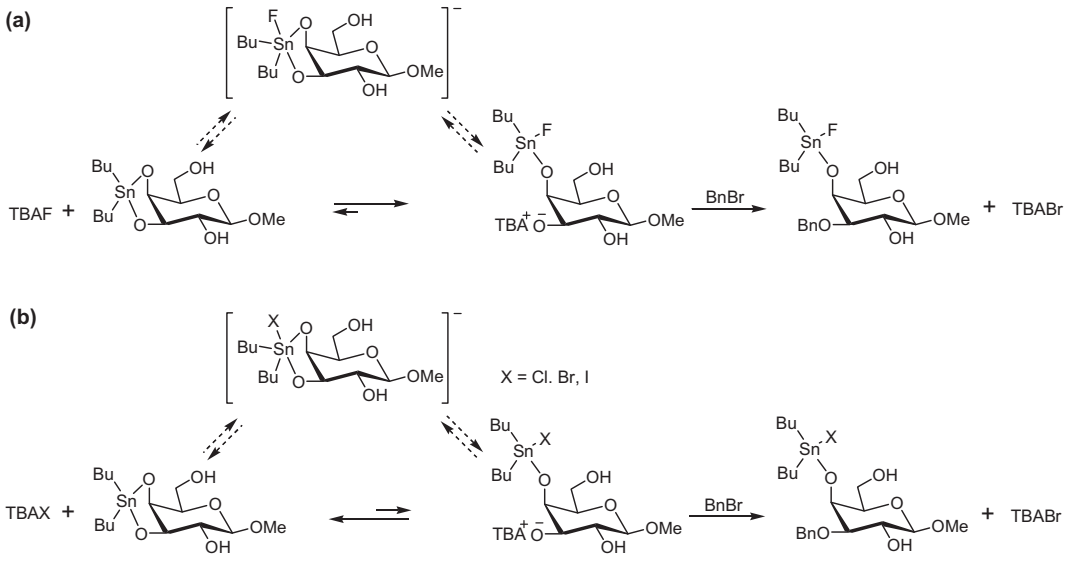


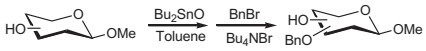
Fig. 4. Proposed approaches for promoted dibutylstannylene-mediated benzylation of galactoside **1** by halides. (a) With F^-; (b) with Cl^-, Br^- or I^-.

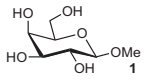
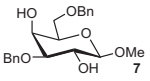
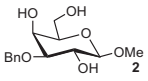
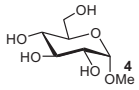
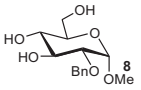
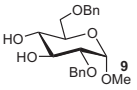
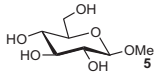
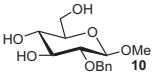
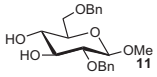
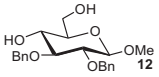
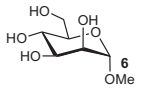
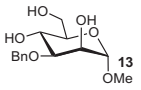
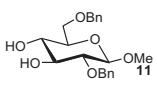
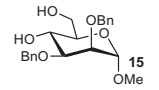
bond instantly, leading to the breakage of the weaker Sn–O bond. The benzylation then proceeded through nucleophilic attack of the oxygen species on benzyl bromide in a very short time (shorter than 5 min). With the formation of benzylation products, the bromide anions were generated, displacing the fluoride anion. When the most of the fluoride anions coordinated to the tin atoms, further benzylation was activated by the generation of bromide anions. As a result, the reaction would proceed slowly by then. That is the reason why 0.2 and 0.5 equiv of fluoride anion only led to approximately 20% and 50% conversion rate, respectively in 5 min. When chloride, bromide and iodide were employed (Fig. 4b), these anions could also coordinate to tin to form Sn–Cl, Sn–Br and Sn–I bonds, respectively. However, the Sn–O bond was stronger in this case, leading to less active oxygen species. With the formation of benzylation products, the bromide anions were also formed. As a result, there were subtle differences of activation ability among the three halides. For iodide, there was a possibility that the lower activation ability was compensated by the formation of more reactive benzyl iodide. These results demonstrated our hypothesis and also indicated that it was not a preferential choice to employ tetrabutylammonium fluoride in the reaction unless a rapid reaction was necessary and a stoichiometric amount of tetrabutylammonium fluoride additive was employed. Consequently, for organotin mediated benzylation, the optimum choice when using halides was to employ 0.5 equiv of bromide anions as activation additive, which should also be in more benzylation cases, including multiple carbohydrate benzylation.

For the dibutylstannylene-mediated multiple carbohydrate esterification, products with one or two free hydroxyl groups were produced by use of excess (2–3 equiv) organotin reagent in a one-pot process in light of description.[30,31] We wondered if the analogous product patterns could also be achieved by an organotin-mediated multiple carbohydrate benzylation, where the formed stannylene intermediates would be treated with benzyl bromide in the presence of 0.5 equiv of tetrabutylammonium bromide. Thus the results obtained from the benzylation of methyl β-D-galactoside **1** were applied to multiple benzylation and three other carbohydrate structures, methyl α-D-glucoside **4**, methyl β-D-glucoside **5**, and methyl α-D-mannoside **6** (Table 1). Although it has been reported that benzylation of two hydroxyl groups in α-D-glucoside and α-D-mannoside was made by use of 1 equiv equiv of dibutyltin oxide in the presence of *i*-Pr_2Net (DIPEA),[20] we still use excess organotin reagent in order to compare the present results with the multiple esterification. Thereby, the unprotected methyl galactoside **1**, glucosides **4** and **5**, and mannoside **6** were treated with 1.1–3.3 equiv of dibutyltin oxide to form stannylene intermediates. The intermediates were subsequently treated with 1.5–4.0 equiv of benzyl bromide in dry toluene at 100 °C for 6–12 h in the presence of 0.5 equiv of tetrabutylammonium bromide. The resulting mixtures were directly analyzed by ^{1}H NMR in DMSO-d_6 after removal of the solvent. The product distribution by NMR ratio was displayed in Table 1.

For methyl β-D-galactoside **1**, the *mono*-protection had been fully studied in the previous and present studies. The 3-hydoxyl group was regioselectively benzylated accompanied with a minor benzylation of 6-hydroxyl group, whereas the benzylation of 4-hydroxyl group was never found. Thus, the utilization of 2.2 equiv of dibutyltin oxide and 3.0 equiv of benzyl bromide led to a major expected product **7** (72%) where both the 3- and 6-hydroxyl groups were benzylated and a minor 3-position protected product **2** (28%). The regioselective *mono*-benzylation of the α-D-glucoside **4** and β-D-glucoside **5** had never been reported. Herein, the utilization of 1.1 equiv of dibutyltin oxide and 1.5 equiv of benzyl bromide led to major products **8** (67%) and **10** (65%) where the 2-hydroxyl groups were benzylated. The utilization of 2.2 equiv of dibutyltin oxide and 3.0 equiv of benzyl bromide led to major products **9** (67%) and **11** (56%) where both the 2- and 6-hydroxyl groups were benzylated. However, when we used 3.3 equiv of dibutyltin oxide and 4.0 equiv of benzyl bromide, expecting to obtain products with one free hydroxyl group, we failed and still obtained major products with two free hydroxyl groups. Even much more than 4.0 equiv of benzyl bromide were employed, the compounds with one free hydroxyl group could not be found from the reaction mixtures. An unexpected product for the multiple benzylation of methyl β-D-glucoside **5** was compound **12** (23%) where both the 2- and 3-hydroxyl groups were benzylated. Analogous results were obtained in the multiple benzylation of α-D-mannoside **6**. It was known that the utilization of 1.1 equiv of dibutyltin oxide led to a major product **13** where the 3-hydroxyl group was benzylated.[32] At present we employed 2–3 equiv of dibutyltin oxide and 3–4 equiv of benzyl bromide, which led to a major product **14** (51–69%) where both the 3- and 6-hydroxyl groups were benzylated. An unexpected product **15** was also produced in the reactions. Upon analysis of the resulting product compositions, a reactivity order of the hydroxyl

Table 1
One-pot organotin-mediated multiple carbohydrate benzylation[a]



Substrate	BnBr (equiv)	Bu_2SnO (equiv)	NMR ratio (%)					
			Product 1		Product 2		Product 3	
	3.0	2.2		72		28		
	1.5 3.0 4.0	1.1 2.2 3.3		67 33 33		33 67 67		
	1.5 3.0 4.0	1.1 2.2 3.3		65 22 21		35 56 56		22 23
	3.0 4.0 4.0	2.2 2.2 3.3		38 28 14		51 69 67		11 3 19

[a] Reaction conditions: reactant (100 mg), Bu_2SnO (1.1–3.3 equiv), TBAB (0.5 equiv), BnBr (1.1–4.0 equiv), Toluene (2 mL), 90 °C, 12 h.

groups for benzylation of β-D-galactoside was arranged as 3>6>2, 4 in comparison to the previously reported 3>6>2>4 for esterification.[31] The reactivity order for benzylation of β-D-glucoside was arranged as 2>6>3>4 in comparison to the previously reported 6>3=2>4 for esterification. The reactivity order for benzylation of α-D-glucoside was arranged as 2>6>3, 4 in comparison to the previously reported 6>2>3>4 for esterification. The reactivity order for benzylation of α-D-mannoside was arranged as 3>6>2>4 in comparison to the previously reported 6>3>2>4 for esterification. In all cases, the benzylation showed better regioselectivity. The differences in the reactivity order and the regioselectivity between benzylation and esterification were likely due to the reactivity of the electrophiles and the intermolecular migration of stannylenes.[33] The products with one free hydroxyl group were difficult to acquire, which was likely due to the deactivation of the bound oxygen atom connecting the tetracoordinate tin, which was also coordinated by bromide. The tentative explanation was outlined in Fig. 5. The oxide anion was difficult to form through the cleavage of Sn–O bond of a pentacoordinate tin coordinated by two bromides since Sn–Br bond was weaker than Sn–O bond (Fig. 5a). For example, for the benzylation of the α-D-glucoside (Fig. 5b), the oxides in 3- and 4-position were deactivated due to their connection with the tetracoordinate tin atoms, which were coordinated by a bromide. As a result, the benzylation of 3- or 4-positions could hardly occur. However, as a benefit of the outcome, it means that there will be no need to worry about per-benzylation of substrates even if a large excess amount of benzyl bromide is employed.

Finally, the reaction conditions were optimized in order to obtain good isolation yields (Table 2). The di-benzylation of galactoside **1** and mannoside **6** showed relatively low reactivity, requiring more benzyl bromide and longer reaction time. Consequently, the di-benzylated compounds **7** and **14** were isolated in 80% and 70% yields, respectively. However, the benzylation of glucosides **4** and **5** showed relatively high reactivity. Decreasing the amount of benzyl bromide and shortening the reaction time thereby led to high isolation yields of mono benzylated glucosides **8** (83%) and **10** (81%). The high isolated yields of di-benzylated compounds **9** (85%) and **11** (72%) were also obtained with more benzyl bromide. In

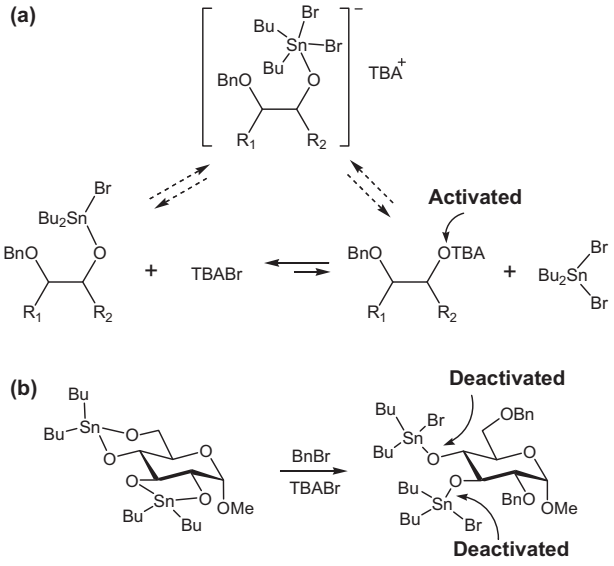


Fig. 5. The tetracoordinate tin coordinated by a bromide leading to a deactivated oxide species.

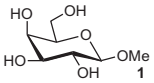
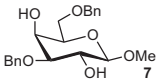
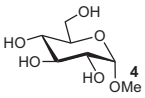
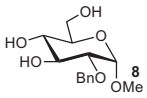
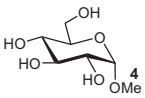
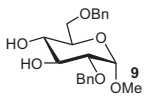
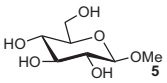
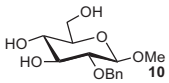
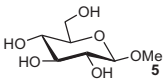
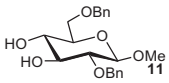
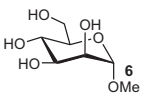
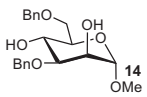
these results, one of the most valuable results was unexpectedly to obtain 2-hydroxyl group benzylated glucosides **8** and **10** in high yields. These two compounds are traditionally prepared by making use of complex reaction sequences, being potential intermediates to form important glycoside-type carbohydrate building block acceptors.

In the light of previous conducted studies[18,24] and the results of the present experiments, the general rules for organotin-mediated benzylation of carbohydrates can be summarized as follows:

2.1. For selective mono-benzylation of diols and polyols

The substrate should react with 1–1.1 equiv of dibutyltin oxide to form dibutylstannylene acetal. Then the dibutylstannylene acetal

Table 2
The optimized one-pot multiple carbohydrate benzylation

Substrate	Product	Yield (%)
		80[a]
		83[b]
		85[c]
		81[b]
		72[c]
		70[a]

Reaction conditions: [a] 2.1 equiv Bu_2SnO, 0.5 equiv TBAB, 5 equiv BnBr, 100 °C, 12 h; [b] 1.1 equiv Bu_2SnO, 0.5 equiv TBAB, 1.2 equiv BnBr, 100 °C, 8 h; [c] 2.1 equiv Bu_2SnO, 0.5 equiv TBAB, 4 equiv BnBr, 100 °C, 10 h.

should react with 1.2–1.5 equiv of benzyl bromide in a suitable volume of toluene at 90–100 °C for 6–12 h with the addition of 0.5 equiv of tetrabutylammonium bromide. For diols, the regioselectivity is controlled by steric and stereoelectronic effect of the substrate itself, and thus it can be predicted according to the parent diol structure.[24] Therefore, the hydroxyl groups adjacent to axial substituents are preferentially benzylated in the *trans*-diols; the equatorial hydroxyl groups are preferentially benzylated in the *cis*-diols; and the primary hydroxyl groups are preferentially benzylated in the 1,3-diols. For polyols, it must be confirmed, which two hydroxyl groups form the dibutylstannylene acetal with dibutyltin oxide first. Then the regioselectivity can also be predicted by the steric and stereoelectronic effect principle. Therefore, the equatorial hydroxyl group adjacent to an axial hydroxyl group is preferentially benzylated in a polyol having an axial hydroxyl group, e.g., mono-benzylation of galactoside and mannoside; and the equatorial hydroxyl group adjacent to an axial substituent or anomeric center is preferentially benzylated in a polyol without having an axial hydroxyl group, e.g., mono-benzylation of glucoside.

2.2. For selective multi-benzylation of polyols

Every two hydroxyl groups require 1–1.1 equiv of dibutyltin oxide to form dibutylstannylene acetals and 2–3 equiv of benzyl bromide to react with one dibutylstannylene acetal. Therefore, the polyols with four hydroxyl groups should react with 2–2.2 equiv of dibutyltin oxide to form dibutylstannylene acetals. The dibutylstannylene acetals should react with 4–6 equiv of benzyl bromide in a suitable volume of toluene at 90–100 °C for 6–12 h with the addition of 0.5 equiv of tetrabutylammonium bromide. The regioselectivities are dependent on the dibutylstannylene acetals and the stereoelectronic effects of diols. Thus, the regioselectivities can also be predicted by the steric and stereoelectronic effect principle mentioned above (Scheme S1 in SI).

In all cases, the *trans*-diols having higher reactivity,[33] require less benzyl bromide (1.2 equiv), lower reaction temperature and shorter reaction time. The *cis*-diols and 1,3-diols having lower reactivity,[33] require more benzyl bromide (1.5–2.5 equiv), higher reaction temperature and longer reaction time. The amount of solvent used should be as little as possible to increase the concentration of the substrate. The polar solvent DMF can be used instead of the non-polar solvent toluene, which will increase the reactivity since DMF molecules can also coordinate to the tin atoms and polar solvent favors S_N^2 reaction. In addition, any anion can be employed in the reaction instead of bromide in principle. However, with consideration of economy, convenience and moderate activation ability, the catalytic amount of tetrabutylammonium bromide should be preferentially chosen as the activation additive. The studies on benzylation by employing catalytic amount of dibutyltin oxide could also be guided by the above general rules and are in proceeding.

3. Conclusions

By the study of the activation ability of halides on organotin-mediated benzylation of methyl β-D-galactoside, the mechanism of the halide promoted benzylation was initially revealed, suggesting an activated oxide species forming from the coordination of the halide anion to the tetracoordinate tin atom. It was also demonstrated that the halide, which could form a stronger bond with tin showed stronger activation ability, thereby fluoride being the strongest activation additive to the benzylation. However, a catalytic amount of bromide was employed as the best activation additive in the reaction owing to its regeneration and moderate activation ability. The results were further applied to additional carbohydrate structures and multiple carbohydrate benzylations. A range of prototype carbohydrate structures were efficiently prepared with the guidance of the principle. General rules for organotin-mediated benzylation of carbohydrates have been summarized in present studies.

4. Experimental section

4.1. General

All commercially available starting materials and solvents were reagent grade and used without further purification. Chemical reactions were monitored with thin-layer chromatography using precoated silica gel 60 (0.25 mm thickness) plates (Macherey–Nagel). Flash column chromatography was performed on silica gel 60 (SDS 0.040–0.063 mm). ^{1}H NMR spectra were recorded with a Bruker Avance 400 instrument at 298 K in DMSO-d_6, using the residual signals from DMSO-d_6 (^{1}H: δ=2.50 ppm) as internal standard. ^{1}H peak assignments were made by first order analysis of the spectra, supported by standard ^{1}H–^{1}H correlation spectroscopy (COSY).

4.2. General procedure for benzylation

The starting material (0.515 mmol) and dibutyltin oxide (1.1–3.3 equiv) was dissolved in 20 mL anhydrous toluene, and refluxed for 1 h. After evaporation of the solvent till 2 mL, benzyl bromide (1.1–4.5 equiv) was added dropwise, and then allowed to react at 90–100 °C for 6–12 h. The resulting mixture was directly analyzed by ^{1}H NMR in DMSO-d_6.

4.3. Methyl 3,6-di-*O*-benzyl-β-D-galactopyranoside (7)[32]

Methyl β-D-galactopyranoside (200 mg, 1.03 mmol) and dibutyltin oxide (566 mg, 2.266 mmol) was dissolved in 40 mL

anhydrous toluene, and refluxed for 1 h. After evaporation of the solvent till 4 mL remained, benzyl bromide (612 μl, 5.15 mmol) was added dropwise, and then allowed to react at 100 °C for 12 h. The resulting mixture was directly purified by flash column chromatography (hexane/ethyl acetate, 2:1). To give 309 mg of product (80%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ=7.26–7.43 (m, 10H, 2×Ph), 5.11 (d, J=5.2, 1H, 2-OH), 4.52–4.70 (m, 4H, 2×PhCH$_2$), 4.64 (d, J=5.6, 1 H, 4-OH), 4.06 (d, J=7.6, 1H, 1-H), 3.89 (s, 1H, 4-H), 3.47–3.64 (m, 4H, 2-H, 5-H, 6$_a$-H, 6$_b$-H), 3.39 (s, 3H, OMe), 3.25–3.28 (dd, J_1=3.2, J_2=9.6, 1H, 3-H) ppm.

4.4. Methyl 2-*O*-benzyl-α-D-glucopyranoside (8)[34]

Methyl α-D-glucopyranoside (200 mg, 1.03 mmol) and dibutyltin oxide (282 mg, 1.133 mmol) was dissolved in 40 mL anhydrous toluene, and refluxed for 1 h. After evaporation of the solvent till 4 mL remained, benzyl bromide (122 μl, 1.236 mmol) was added dropwise, and then allowed to react at 100 °C for 8 h. The resulting mixture was directly purified by flash column chromatography (hexane/ethyl acetate, 1:1). To give 243 mg of product (83%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ=7.24–7.41 (m, 5H, Ph), 5.10 (d, J=6, 1H, 4-OH), 4.97 (d, J=7.2, 1H, 3-OH), 4.78 (s, 2H, PhCH$_2$), 4.51–4.55 (m, 2H, 1-H, 6-OH), 3.62–3.66 (m, 1H, 6$_a$-H), 3.43–3.50 (m, 2H, 3-H, 6$_b$-H), 3.30–3.35 (m, 2H, 2-H, 5-H), 3.29 (s, 3H, OMe), 3.23–3.27 (m, 1H, 4-H) ppm.

4.5. Methyl 2, 6-di-*O*-benzyl-α-D-glucopyranoside (9)[20]

Methyl α-D-glucopyranoside (200 mg, 1.03 mmol) and dibutyltin oxide (566 mg, 2.266 mmol) was dissolved in 40 mL anhydrous toluene, and refluxed for 1 h. After evaporation of the solvent till 4 mL remained, benzyl bromide (490 μl, 4.412 mmol) was added dropwise, and then allowed to react at 100 °C for 10 h. The resulting mixture was directly purified by flash column chromatography (hexane/ethyl acetate, 2:1). To give 327 mg of product (85%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ=7.26–7.39 (m, 10H, 2×Ph), 5.11 (d, J=6, 1H, 4-OH), 5.07 (d, J=5.2, 1H, 3-OH), 4.71 (d, J=3.6, 1H, 1-H), 4.59–4.68 (m, 2H, PhCH$_2$), 4.50 (s, 2H, PhCH$_2$), 3.67–3.69 (d, J=9.2, 1H, 6$_a$-H), 3.50–3.56 (m, 3H, 3-H, 5-H, 6$_b$-H), 3.26 (s, 3H, OMe), 3.18–3.21 (dd, J_1=3.6, J_2=9.6, 1H, 2-H), 3.11–3.13 (m, 1H, 4-H) ppm.

4.6. Methyl 2-*O*-benzyl-β-D-glucopyranoside (10)[35]

Methyl β-D-glucopyranoside (200 mg, 1.03 mmol) and dibutyltin oxide (282 mg, 1.133 mmol) was dissolved in 40 mL anhydrous toluene, and refluxed for 1 h. After evaporation of the solvent till 4 mL remained, benzyl bromide (122 μl, 1.236 mmol) was added dropwise, and then allowed to react at 100 °C for 8 h. The resulting mixture was directly purified by flash column chromatography (hexane/ethyl acetate, 1:1). To give 237 mg of product (81%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ=7.26–7.40 (m, 5H, Ph), 5.16 (d, J=5.2, 1H, 3-OH), 5.02 (d, J=4.8, 1H, 4-OH), 4.67–4.76 (m, 2H, PhCH$_2$), 4.57 (t, J=2.4, 1H, 6-OH), 4.23 (d, J=8, 1H, 1-H), 3.67–3.68 (dd, J_1=4, J_2=12, 1H, 6$_a$-H), 3.45–3.48 (m, 1H, 6$_b$-H), 3.43 (s, 3H, OMe), 3.28–3.31 (m, 1H, 3-H), 3.08–3.15 (m, 2H, 4-H, 5-H), 3.00 (t, J=4, 1H, 2-H) ppm.

4.7. Methyl 2, 6-di-*O*-benzyl-β-D-glucopyranoside (11)[36]

Methyl β-D-glucopyranoside (200 mg, 1.03 mmol) and dibutyltin oxide (566 mg, 2.266 mmol) was dissolved in 40 mL anhydrous toluene, and refluxed for 1 h. After evaporation of the solvent till 4 mL remained, benzyl bromide (490 μl, 4.412 mmol) was added dropwise, and then allowed to react at 100 °C for 10 h. The resulting mixture was directly purified by flash column chromatography (hexane/ethyl acetate, 2:1). To give 277 mg of product (72%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ=7.23–7.39 (m, 10H, 2×Ph), 5.21 (d, J=5.6, 1H, 4-OH), 5.17 (d, J=6, 1H, 3-OH), 4.53–4.49 (m, 4H, 2×PhCH$_2$), 4.27 (d, J=8, 1H, 1-H), 3.74–3.77 (d, J=12, 1H, 6$_a$-H), 3.51–3.55 (dd, J_1=4, J_2=10, 1H, 6$_b$-H), 3.43 (s, 3H, OMe), 3.30–3.41 (m, 2H, 4-H, 5-H), 3.09–3.15 (m, 1H, 3-H), 3.02 (t, J=8, 1H, 2-H) ppm.

4.8. Methyl 3, 6-di-*O*-benzyl-α-D-mannopyranoside (14)[20]

Methyl α-D-mannopyranoside (200 mg, 1.03 mmol) and dibutyltin oxide (566 mg, 2.266 mmol) was dissolved in 40 mL anhydrous toluene, and refluxed for 1 h. After evaporation of the solvent till 4 mL remained, benzyl bromide (612 μl, 5.15 mmol) was added dropwise, and then allowed to react at 100 °C for 12 h. The resulting mixture was directly purified by flash column chromatography (hexane/ethyl acetate, 2:1). To give 270 mg of product (70%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ=7.26–7.43 (m, 10H, 2×Ph), 5.08 (d, J=6.4, 1H, 4-OH), 4.89 (d, J=4.8, 1H, 2-OH), 4.68–4.55 (m, 4H, 2×PhCH$_2$), 5.56 (d, J=1.6, 1H, 1-OH), 3.87 (s, 1H, 2-OH), 3.74 (d, J=9.6, 1H, 6$_a$-H), 3.50–3.72 (m, 3H, 4-H, 5-H, 6$_b$-H), 3.40 (dd, J_1=3.2, J_2=9.2, 1H, 3-OH), 3.25 (s, 3H, OMe) ppm.

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Supplementary data

Table S1, Table S2, Table S3, Scheme S1, ^{1}H NMR data of compounds **2**, **3**, **12**, **13**, **15** and ^{1}H NMR-spectra of compound **7**, **8**, **9**, **10**, **11**, and **14**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.02.024.

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