



# Regioselective mono and multiple alkylation of diols and polyols catalyzed by organotin and its applications on the synthesis of value-added carbohydrate intermediates



Hengfu Xu<sup>a</sup>, Bo Ren<sup>b</sup>, Wei Zhao<sup>a</sup>, Xiaoting Xin<sup>a</sup>, Yuchao Lu<sup>a</sup>, Yuxin Pei<sup>a</sup>, Hai Dong<sup>b,\*</sup>, Zhichao Pei<sup>a,\*</sup>

<sup>a</sup> College of Science, Northwest A&F University, Yangling, 712100, Shaanxi, PR China

<sup>b</sup> Key Laboratory of Material Chemistry for Energy Conversion and Storage, Ministry of Education, Huazhong University of Science & Technology, Luoyu Road 1037, Wuhan, 430074, PR China

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## ABSTRACT

A catalytic amount of dibutyltin dichloride was used to develop regioselective alkylation of diols and multiple alkylation of polyols. Alkyl groups, including allyl, alkynyl and long-chain alkyl groups, were successfully introduced to one or two hydroxyl groups of carbohydrate and nonsugar substrates. In most cases, excellent isolation yields were obtained. The alkynylated carbohydrates may be used to synthesize oligosaccharide mimics at a high efficiency via click reaction. The carbohydrates with long-chain alkyl groups may serve as surfactants, which were further demonstrated by experiments in this study.

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## 1. Introduction

Regioselective protection of carbohydrates is often indispensable for the preparation of value-added intermediates and building blocks for oligosaccharide synthesis.<sup>1–5</sup> The method using stoichiometric amounts of organotin reagents used to be the most popular regioselective protection method.<sup>6,7</sup> However, the organotin compounds have to be either minimized in its usage to a catalytic amount,<sup>8–12</sup> or totally abandoned<sup>13–19</sup> now due to their potential inherent toxicity.<sup>20,21</sup> The regioselective alkylation of carbohydrates and polyols using a catalytic amount of organotin have been reported by two other groups<sup>22,23</sup> as well as our group<sup>24</sup> recently. Our developed method used 0.1 equiv of TBAB (tetrabutylammonium bromide) and 0.1 equiv of organotin as catalyst, and used excess amount of potassium carbonate to deprotonate the hydroxyl group and push through the reaction (Fig. 1a). We mainly used an one-pot method where first 0.1 equiv of dibutyltin oxide formed dibutylstannylene acetal with two vicinal OH of the substrates, then the concentrated dibutylstannylene acetal reacted with benzyl bromide to produce the final products in the assistance

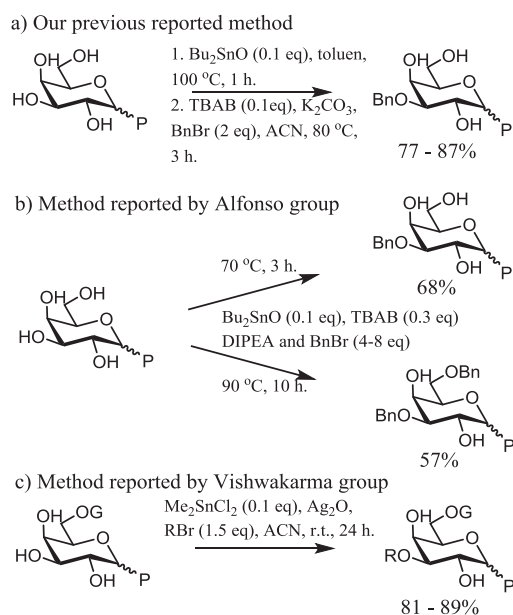


Fig. 1. Comparison of three previous reported methods.

\* Corresponding authors. E-mail addresses: [hdong@mail.hust.edu.cn](mailto:hdong@mail.hust.edu.cn) (H. Dong), [peizc@nwafu.edu.cn](mailto:peizc@nwafu.edu.cn) (Z. Pei).

of 0.1 equiv of TBAB and 1.1 equiv of  $K_2CO_3$ , indicating the key role of dibutylstannylene acetal in the reaction mechanism. In Alfonso et al.'s work,<sup>22</sup> 0.1 equiv of dibutyltin oxide was also used, but in conjuncture with 0.3 equiv of TBAB, excess amount of DIPEA (diisopropylethyl amine) and alkylation reagents (Fig. 1b). Furthermore, they expanded their method on allylation and multiple benzylation. However, in most cases, only intermediate yields were obtained in this solvent free condition used by them.

Just recently, Vishwakarma group reported a method using 0.1 equiv of dimethyltin dichloride as catalyst with the assistance of an excess amount of silver oxide ( $Ag_2O$ ) (Fig. 1c).<sup>23</sup> Though their reported reaction condition was more mild (room temperature), the reaction required longer reaction time (24 h) and might be only applicable in a limited scope of substrates. In this study, the efficiency of our one-step method, using 0.1 equiv of dibutyltin dichloride as the catalyst, was fully demonstrated and this method was further expanded to regioselective mono-alkylation using various alkylation reagents and to regioselective multiple alkylation (Fig. 2). The regioselective alkylation mechanism should be the same as we proposed in previous studies.<sup>24</sup> In most cases, better isolation yields were obtained for both regioselective mono-alkylation and regioselective multiple alkylation of substrates. The selective multiple protections are of particularly importance since two or more hydroxyl groups in polyols can be protected in a single-step process.<sup>25–29</sup> The regioselective introduction of alkyl, allyl or alkynyl groups may supply useful value-added intermediates, which in turn can be applied in producing novel carbohydrate materials such as surfactants, hydrophilic polymers and so on.<sup>30–32</sup> Carbohydrates containing multiple alkynyl groups have been successfully used to synthesize oligosaccharide mimics via click reaction.<sup>33,34</sup> In this study, we also give examples of application in these fields and our method showed a higher efficiency compared to previously reported methods.

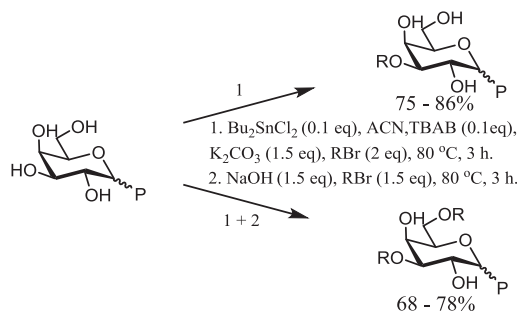


Fig. 2. Regioselective mono and multiple alkylation catalyzed by  $Bu_2SnCl_2$ .

## 2. Results and discussion

The allylation and alkylation were first tested with substrates containing a *cis*-diol moiety, compounds **1–13**, and substrates containing a 1,2-diol, compounds **14** and **15** (Table 1). These substrates were treated with 2.0 equiv of allyl bromide or alkynyl bromide in the presence of 0.1 equiv of dibutyltin dichloride, 0.1 equiv of tetrabutylammonium bromide and 1.5 equiv of  $K_2CO_3$  in a mixed solvent (MeCN:DMF, 10:1) at 80 °C for 3 h. In most of the substrates, the equatorial hydroxyl group adjacent to an axial hydroxyl group or the primary hydroxyl group of 1,2-diol was selectively alkylated in isolated yields of 75–95%. Selective protection of thioglycosides was extremely important since thioglycosides acting as significant glycosyl donors are widely used in glycosylation and oligosaccharide syntheses. The allylation and alkylation of **9**, an example of thioglycosides, gave 75–78% yields of **9a–9b**, respectively, indicating that this method can be used for the

Table 1  
Regioselective mono-alkylation of diols and polyols<sup>a</sup>

Entry	Substrate	Product	Yield (%) <sup>b</sup>
1		R=Allyl <b>1a</b>	88
2		R=Propargyl <b>1b</b>	86
3		R=Allyl <b>2a</b>	83
4		R=Propargyl <b>2b</b>	85
5		R=Allyl <b>3a</b>	82
6		R=Propargyl <b>3b</b>	86
7		R=Allyl <b>4a</b>	86
8		R=Propargyl <b>4b</b>	88
9		R=Allyl <b>5a</b>	91
10		R=Propargyl <b>5b</b>	95
11		R=Allyl <b>6a</b>	85
12		R=Propargyl <b>6b</b>	87
13		R=Allyl <b>7a</b>	87
14		R=Propargyl <b>7b</b>	89
15		R=Allyl <b>8a</b>	85
16		R=Propargyl <b>8b</b>	89
17		R=Allyl <b>9a</b>	75
18		R=Propargyl <b>9b</b>	78
19		R=Allyl <b>10a</b>	81
20		R=Propargyl <b>10b</b>	85
21		R=Allyl <b>11a</b>	89
22		R=Propargyl <b>11b</b>	90
23		R=Allyl <b>12a</b>	70
24		R=Propargyl <b>12b</b>	65
25		R=Allyl <b>13a</b>	89
26		R=Propargyl <b>13b</b>	90

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