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Direct selective and controlled protection of multiple hydroxyl groups in polyols via iterative regeneration of stannylene acetals

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Dedicated to professor Gilbert Stork for his 60-year professorship and his many seminal contributions that helped to shape modern Chemical Synthesis.

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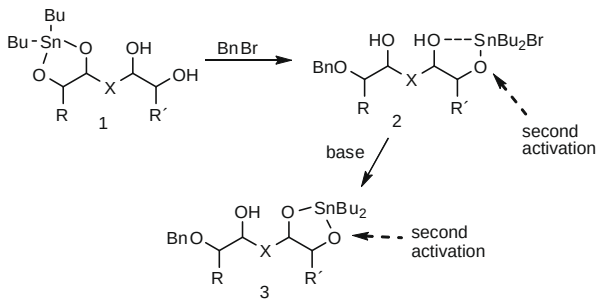
ABSTRACT

A direct selective protection (O-benzylation) of two or more hydroxyl groups in polyols displaying diverse structural patterns was made possible by the establishment of conditions that enable an efficient turnover for the Bu_2Sn group, initially at the corresponding stannylene acetals (only ~1.0 mol equiv of Bu_2SnO was employed). It was also demonstrated that one might exert control over the number of protected groups, by means of appropriate tuning of reaction conditions. The feasibility of a substoichiometric (tin source) catalytic protocol was demonstrated as well.

Protection of functional groups is a fundamental operation in total syntheses. For various reasons, it is needed along the progressive buildup of complexity in such processes.[1] Protective transformations enabling direct selective incorporation of two or more groups in multifunctional building blocks could diminish the cost of such operations on synthetic efficiency. Despite the impressive advances in Organic Synthesis, efficient and practical tools for control of regioselectivity in such contexts, particularly exploiting effects other than simple steric bias, are still needed.[2] Polyols are relevant molecular contexts for devising solutions to this problem. Selective differentiation of the hydroxyl groups in carbohydrates, for instance, is a fundamental issue in contemporary endeavors such as syntheses of complex oligosaccharides (regiospecificity regarding the free hydroxyl group for formation of a glycosidic bond). This area of study continues to provide important tools for probing intricate problems in Cell and Chemical Biology.[3,4] The regioselectivity issue also arises in the use of these substances as sources of chirality and/or functionalized carbon backbones[5] in target-oriented synthesis.[6] Herein, we report our results on the development of a methodology which addresses this problem in a conceptually different manner. We have found that selective poly-protection of hydroxyl groups in polyols may be achieved by means of a process wherein an activating group is reused controllably. It is known that hydroxyl groups at 1,2- or 1,3-diol moieties, by means of their stannylene acetal derivatives (**1**, Scheme 1),[7,8] may be selectively modified (mono-O-alkylation, acylation, sulfonylation, etc.) (such as in **1**→**2**), even in the presence of other similar diol moieties, in some cases.

Grindley's group previously reported that, in the presence of iPr_2NEt (DIPEA), reactions of monostannylene derivatives of pentaerythritol and two other similar polyols (also bearing primary hydroxyl groups), with BnBr could lead to complete mono-O-



Scheme 1. Double activation of polyols via organotin species.

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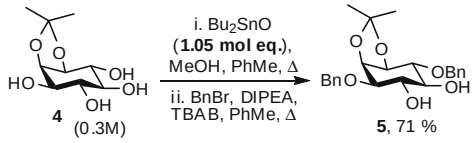


Scheme 2. Selective di-O-benzylation of **4** using equimolar Bu_2SnO.

benzylation of the 1,3-diol moieties.[9,10] Our investigations have established that halostannyl ether species (**2**) (Scheme 1) formed in the medium can engage in further activations (protections) of hydroxyl groups, either directly (from **2**) or as a reformed stannylene derivative (involving step **2**→**3**) in a controlled and tunable fashion. Besides, in both cases, activations may occur in very good selectivities in most of involved steps. In fact, we have found that this reactivity mode may be exploited in reactions wherein regioselectivity issues arise. O-Benzylations were chosen in our study because of their importance in complex carbohydrate synthesis. Moreover, the benzyl group is a model for a set of groups (displaying different aryl substituents) which allows the exploitation of protecting strategies relying on principles of orthogonal lability.[1]

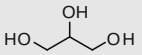
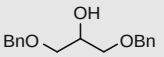
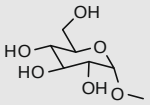
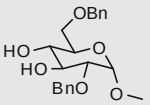
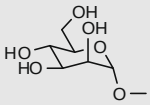
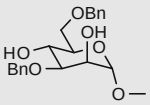
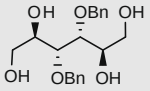
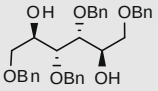
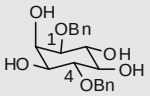
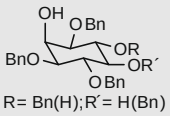
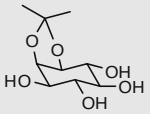
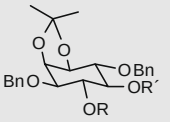
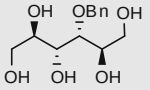
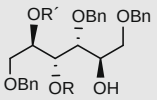
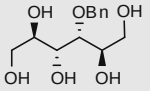
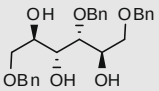
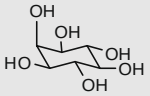
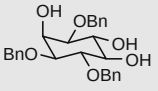
Thus, monostannylene derivative of **4** reacted with BnBr at 100, 120 °C leading to diether **5** in a single step (Scheme 2). No other di-O-benzylated compound was detected. As occurred in other experiments (See Table 1), the only significant component detected in the reaction mixture, besides the desired product, was a mixture of mono-*O*-benzyl ethers (C-3; C-6) in ~20% yield. This transformation (synthesis of **5**) could also be effected in absence of base (iPr$_2$-NEt: DIPEA) (56% yield). This additive nonetheless accelerated it, allowing it to be performed at lower temperature. This strongly indicates that, in the presence of base, formation of stannylene acetals, from the halostannyl ether precursors, occurred.[9] It is recognized that halostannyl ethers are much less reactive than stannylene acetals. Such difference in reactivity explains why mono-O-protections of polyols via monostannylenes can be realized, as commonly shown in the literature.

We found that the direct multiple protections strongly depended on the concentration of substrates in the medium. The reactions only operated efficiently in concentrated media (polyol usually at ~0.3 M). Indeed, the reaction of **4**, in the presence of DIPEA, when run at 0.1 M, instead, at 100–130 °C (18 h) afforded 53% of **5**. Through this concentration window, even halostannyl ethers, such as **2** (Scheme 1), proved themselves (absence of base) nucleophilic enough to successfully provide a second round of activation and hence, O-alkylation (Note the result with **6**, below). The interaction of the tin atom with a neighboring (1,2- or 1,3-diol moiety) hydroxyl group (as in **2**, Scheme 1) appears to significantly enhance the reactivity of halostannylethers formed after the first O-alkylation. If this interaction is not possible, the reaction stops and one hydroxyl group is retained. It is also noteworthy that these reactions (either entirely via stannylene acetals, or partially via halostannyl ethers) led to the same product (O-protections at C-3 and C-6) that was obtained via the bis-stannylene derivative of acetonide **4**.[11]

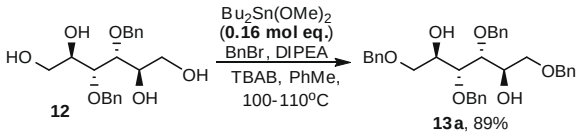
Glycerol (**6**) underwent the intended transformation at 100 °C efficiently to afford product **7** (81% without base) (Table 1, entry 1). Building on these preliminary results, this methodology was applied to glucoside **8** and mannoside **10** (100 °C) to afford selectively di-O-protected derivatives **9** and **11**, respectively (Table 1, entries 2 and 3). The formation of substances **9** and **5** (from **4**, Scheme 2) in good yields, leaving one last 1,2-diol moiety untouched, clearly indicates that, under this protocol, one can arrest the process at a certain point. Some of the following data will show that one can otherwise choose the reaction to proceed to further hydroxyl group activations.

Mannitol derivative **12** and *myo*-inositol derivative **14** (Table 1, entries 4 and 5), which bear separate 1,2-diol moieties, also reacted accordingly. Compound **14**, a hard case,[8c] offered a particularly different challenge as the reaction centers are secluded in separate

Table 1
Direct di- and poly-O-protection of hydroxyl groups[a]

Entry	Substrate	Product[b]	Yield (%)
1	 **6**	 **7**	95
2	 **8**	 **9**	89
3	 **10**	 **11**	55[c]
4	 **12**	 **13a**	88
5	 *rac*-**14**	 R= Bn(H);R´= H(Bn) **15a**(*rac*-**15b**)	47[d,e]
6	 *rac*-**4**	 R= Bn(H);R´= H(Bn) *rac*-**16a**(*rac*-**16b**)	78[f]
7	 **17**	 R= Bn(H);R´= H(Bn) **13a(13b)**	66[g]
8	 **17**	 **18**	49
9	 **19**	 *rac*-**20**, **15**	42, 34[e]

[a] General conditions (See Supplementary data): (i) Bu_2SnO (1.05–1.10 mol equiv), MeOH/toluene, 100 °C, 3 h; (ii) BnBr, DIPEA, Bu_4NBr (TBAB) (0.6 mol equiv), toluene (0.3 M), 100–130 °C.
[b] Pure compounds: only the specific regioisomers presented here were detected.
[c] 16% of mono-O-benzylated (C-3) product was also formed.
[d] 21% of *rac*-**20** was formed as well.
[e] **15a**/**15b** ratio = 1.5–2.0:1.0, respectively.
[f] **16a**/**16b** ratio = 1.5–2.0:1.0, respectively.
[g] **13a**/**13b** ratio = 3–4:1, respectively.



Scheme 3. Catalyzed di-O-benzylation of **12**.

parts of a more rigid molecule. Notwithstanding the formation of regioisomers (**15a**,**b**), resulting from low selectivity in the mono-protection of the C4,C5-diol moiety, high chemoselectivity is maintained: only mono-O-benzylation at this moiety is observed.[12] We have not attempted to improve the yield of **15a**,**b**.

Furthermore, the feasibility of selective activation of multiple hydroxyl groups was proven through reactions of tetrol **4** and pentol **17** (Table 1, entries 6 and 7), which led to products of tri-O-benzylation **16a** and **13a** as major regioisomers, respectively, in good overall yields. In the case of reaction of compound **4**, reaction channeling to the formation of tri-O-protected product relied on the reaction temperature (130 °C instead of 100 °C, 120 °C). As it occurred in transformation **4**→**5** (Scheme 2), BnBr and DIPEA were not used in large excesses. Thus, temperature plays a key role in reaction tuning. We were also able to convert **17** into product of di-O-alkylation **18** by simply using less BnBr (3.0 mol equiv) and monitoring the reaction progress closely (Table 1, entry 8). In an attempt to suppress formation of products of tribenzylation **13**, lower reaction temperature (80–85 °C, 11 h) was tried, but it led to lower yield of **18** (41%). This result suggests that, in cases of difficulty in controlling the number of O-protections, it might be more rewarding to maintain the reaction fast (higher temperature) and to adjust the stoichiometry (BnBr).

An even more challenging substrate would be *myo*-inositol itself, **19**. Gratifyingly, in an exploratory experiment, mono-stannylene of **19**, despite its low solubility at the outset, reacted at 120–130 °C giving triether **20**,[13] as major product, in a single step (Table 1, entry 9).[14] Ongoing investigation suggests that the yields of products like **20** (directly from **19**) may be significantly increased by minimizing formation of tetra-O-protected derivatives.

With the realization that a turnover process for the Bu_2Sn group was taking place in these transformations, we envisaged that a substoichiometric catalytic procedure could be put forward.[15,16] The successful reaction of tetrol **12** catalyzed by preformed $Bu_2Sn(OMe)_2$ shows its feasibility (Scheme 3). In this experiment, starting material (and intermediate triether, likely) remained mostly in a second liquid phase before their consumption.

The underlying turnover of the activating group (Bu_2Sn) relies, most likely, on different dynamical processes allowing its mobility, which include (intramolecular) migrations and intermolecular transfers of this group.[17] The latter processes are favored in more concentrated mixtures.

In summary, a methodology for direct selective activation (and protection) of multiple hydroxyl groups in polyols, exemplified by reactions of O-benzylation, has been established as a consistent synthetic tool. This establishes the selective protections of polyols via stannylene acetals as a more atom-economical methodology.[18] Medium dilution and careful tuning of appropriate reaction conditions (temperature, more importantly) were identified as fundamental requisites for the needed turnover of the Bu_2Sn group to operate efficiently. This work also demonstrated that one can exert significant control over the number of hydroxyl group activations, which greatly enhances the flexibility of the methodology. Such control is a corollary of the efficiency (adequate rates) and flexibility (tuning ability) of this reactivity mode for stannylene acetals.

Due to its broad scope, this methodology may be regarded as a valuable alternative for fast access to selectively protected polyol derivatives (synthetic blocks, etc.). We believe that these results motivate further developments in this important area.

Acknowledgments

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Supplementary data

Supplementary data (experimental details and physical data for products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.114.

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