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Dibutyltin Oxide Catalyzed Selective Sulfonylation of α-Chelatable Primary Alcohols

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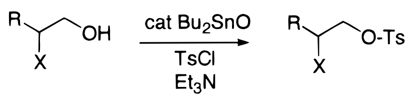
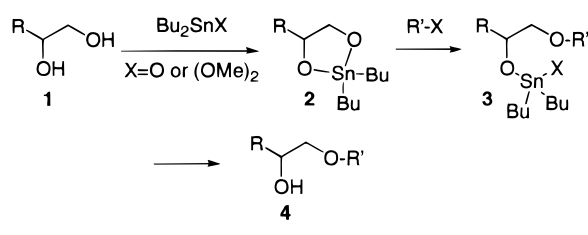
ABSTRACT



The reaction of substituted glycols with catalytic dibutyltin oxide, stoichiometric *p*-toluenesulfonyl chloride, and triethylamine in CH_2Cl_2 resulted in the complete and rapid sulfonylation at the primary alcohol. The α-heterosubstituted primary alcohol moiety appeared optimal for best results, supporting the intermediacy of a five-membered chelate. The role of the amine is discussed, in addition to catalyst requirements and solvent effects.

Selective alcohol functionalization in polyol substrates has been achieved through a variety of techniques.[1] Most cases have involved stoichiometric reagents to effect, for example, sulfonylation,[2] alkylation,[3] acylation,[4] and asymmetric variants.[5] The monoderivatization of symmetric diols using stannoxanes was first disclosed by Shanzer in 1980.[6] This stannylidene-based regioselective functionalization of glycols has been reviewed thoroughly[7] (Scheme 1). Typically, the 1,2-diol **1** is treated with Bu_2SnX, where X = O^2 or $(OMe)_2$,[8] with removal (azeotropic or desiccant) of either H_2O or MeOH to afford the requisite tin acetal **2**. Often these procedures involve solvent exchange in order to conduct the subsequent functionalization. The stannylidenes **2** then undergo selective alkylation, acylation, sulfonylation, and phosphorylation, usually at the primary position, or silylation with variable regioselectivity.[9,10] In some cases, it is possible to accomplish selective reaction without Sn, although diminished levels of selectivity are observed. The tin acetal protocol accomplishes primary hydroxyl activation and temporary secondary hydroxyl protection in a single operation. The unavoidable production or regeneration of a stoichiometric amount of lipophilic Bu_2SnO, usually separable only by chromatography, is a definite limitation for large scale application of the method. We describe herein a convenient protocol for the primary selective sulfonylation of glycols using *catalytic* dibutyltin oxide in the presence

Scheme 1



(1) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(2) O'Donnell, C. J.; Burke, S. D. *J. Org. Chem.* **1998**, *63*, 8614.
(3) Bouzide, A.; Sauvé, G. *Tetrahedron Lett.* **1997**, *38*, 5945.
(4) Sekine, M.; Kume, A.; Hata, T. 3617; Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791.
(5) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1810.
(6) Shanzer, A. *Tetrahedron Lett.* **1980**, *21*, 221.
(7) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.
(8) Boons, G.-J.; Castle, G. H.; Clase, J. A.; Grice, P.; Ley, S. V.; Pinel, C. *Synlett* **1993**, 913.
(9) Leigh, D. A.; Martin, R. P.; Smart, J. P.; Truscello, A. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1373.
(10) Reginato, G.; Ricci, A.; Roelens, S.; Scapecchi, S. *J. Org. Chem.* **1990**, *55*, 5132.

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of stoichiometric triethylamine. A dramatic rate acceleration, *vis à vis* the stoichiometric version, was also observed.

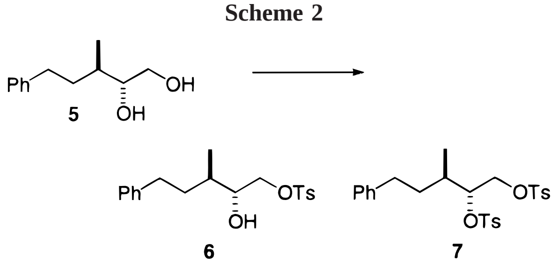
Dibutyltin oxide has been employed in a catalytic fashion to effect macrolactonization under neutral conditions,[11] presumably as a template for ionic interactions with the carboxylate and alcohol termini. Similarly, it has been used as a highly effective, intermolecular transesterification and esterification catalyst.[12] Bu_2SnX_2 has been utilized in a catalytic manner to form trimethylsilyl cyanohydrins of aldehydes and ketones.[13] A recent citation describes the use of catalytic Bu_2SnO to accelerate benzoylation of polyols.[14] This latter approach was run under conditions with a tunable microwave heater.[15] More recently, dimethyltin dichloride has been reported as a catalyst for the selective monobenzoylation of diols, with added K_2CO_3 as adjuvant.[16] Finally, application of catalytic Bu_2SnO to mediate the addition of $TMS-N_3$ to nitriles, affording tetrazoles, has been reported.[17]

During the course of our work on cryptophycin analogues,[18] we discovered the catalytic nature of Bu_2SnO in the sulfonylation of **5**. Our preliminary experiments are listed in Table 1. Under the "standard" protocol, diol **5** was converted to the corresponding stannylidene acetal by treatment with Bu_2SnO (1 equiv) in toluene with azeotropic removal of H_2O. After solvent exchange into CH_2Cl_2, the stannylidene was treated with TsCl (1 equiv) and Et_3N (0.1 equiv) for 18 h to furnish monotosylate **6** as the exclusive product. Under "tin-free" conditions where the diol was treated with TsCl (1 equiv) and Et_3N (1 equiv) in CH_2Cl_2, the byproduct bis-tosylate **7** is usually formed, accompanied by the starting diol (Scheme 2). The "standard" protocol employs 0−10 mol % of Et_3N presumably since the weak product−tin complex remains until workup. Whereas the stannylidene is a tight covalent complex and quite stable, upon primary alcohol functionalization the complex stability is significantly diminished. We therefore speculated that excess Et_3N might enhance turnover through competitive tin binding and neutralization of the newly formed HCl. Thus, treatment of diol **5** with TsCl and Et_3N (1 equiv each) and *catalytic* Bu_2SnO (2 mol %) led to the results under the "catalytic" column. It is noteworthy that excellent regioselectivity (comparable to the "standard" protocol) is achieved in this case. More significant is the observed rate acceleration under these conditions, compared with the "standard" protocol.

Table 1. Comparison of Stoichiometric and Catalytic Dibutyltin Oxide Tosylations, Relative to Tin-Free Conditions

	Standard	*Tin-free*	*Catalytic*
Diol **5**	1.0	1.0	1.0
TsCl	1.0	1.0	1.0
Et_3N	0.1	1.0	1.0
Bu_2SnO	1.0	0	0.02
Time	1080 min	1080 min	15 min
% **7**	<1%	>10%	<1%

Scheme 2



To further exemplify the catalytic effect of dibutyltin oxide on the tosylation reaction, a rate study was conducted. Diol **11** was chosen as the test substrate. In separate experiments, 1-phenyl-1,2-ethanediol **11** was treated with TsCl (1.05 equiv) and Et_3N (1 equiv) in CD_2Cl_2, in the presence and in the absence of catalytic Bu_2SnO. The conversion to monotosylate **13** was followed by ^1H NMR as a function of time (Figure 1). From this study, it is evident that the Bu_2SnO-catalyzed reaction is at least an order of magnitude faster than the uncatalyzed version.

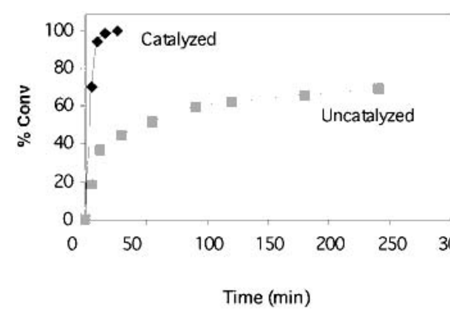


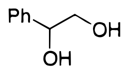
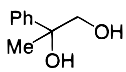
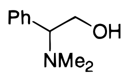
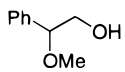
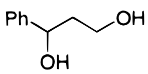
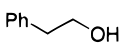
Figure 1. Rates of monotosylation of diol **11** in the presence and absence of catalytic Bu_2SnO.

A brief solvent study showed the following trend for tosylation rate and overall yield: $CH_2Cl_2 > CH_3CN >$ THF > toluene > MeOH at ambient temperature with catalytic Bu_2SnO. Toluene proved less effective due to an observed limited solubility, while methanol likely competed for binding at the tin center. Both of these aspects will manifest in less efficient reaction progress. Other Sn species were likewise evaluated in the selective tosylation process and showed this trend: $Bu_2SnO \geq Bu_2Sn(OMe)_2 > Bu_2SnCl_2 > Bu_2Sn(OAc)_2 \gg Bu_3SnCl$. We believe this trend is a reflection of the ability to both form a strong complex with the glycol and to complete catalyst turnover.

(11) Steliou, K.; Nowosielska, A. S.; Favre, A.; Poupart, M. A.; Hanessian, S. *J. Am. Chem. Soc*. **1980**, *102*, 7579.
(12) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem*. **1991**, *56*, 5307.
(13) Whitesell, J. K.; Apodaca, R. *Tetrahedron Lett*. **1996**, *37*, 2525.
(14) (a) Morcuende, A.; Valverde, S.; Herradón, B. *Synlett* **1994**, 89. (b) Herradón, B.; Morcuende, A.; Valverde, S. *Synlett* **1995**, 455.
(15) Morcuende, A.; Ors, M.; Valverde, S.; Herradón, B. *J. Org. Chem*. **1996**, *61*, 5264.
(16) Maki, T.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett*. **1998**, *39*, 5601.
(17) Wittenberger, S. J.; Donner, B. G. *J. Org. Chem*. **1993**, *58*, 4139.
(18) Trimurtulu, G.; Ohtani, I.; Patterson, G. M.; Moore, R. E.; Corbett, T. H.; Valeriote, F. A.; Demchik, L. *J. Am. Chem. Soc*. **1994**, *116*, 4729.

With these preliminary results, we then explored the structural requirements for the substrate. Table 2 shows a series of substrates subjected to the tin-catalyzed tosylation,[19] compared with the tin-free version. The yields refer to the percentage of monotosylated product isolated, with the balance being a statistical mixture of bis-tosylate and starting material.

Table 2. Substrate Effect in the Reaction of Depicted Compound with Et_3N, TsCl, and Bu_2SnO

Entry	Substrate	Bu_2SnO (0.02 equiv)[a] % Yield[b]	t (min)	Tin-free % Yield[b]	t (min)
1		99	50	82	1140
2		99	120	79	1440
3		94	280	88	1550
4		99	420	95	1550
5		92	1440	77	1260
6		86	1550	85	1550

[a] For a typical experimental procedure, see footnote 19.
[b] Refers to the isolated yield of the primary monotosylate

Substrates in entries 1−4 are predisposed to form a five-membered chelate with Bu_2SnO, and in each case, it was possible to demonstrate a significant rate acceleration in the presence of the catalyst, concomitant with higher regioselectivity. However, entry 5 shows that the six-membered tin chelate was virtually indistinguishable from the non-chelated, noncatalyzed version in terms of reaction rate, although the product profile was much better. Finally, entry 6 was conducted to show the reaction of a simple primary alcohol under each condition, resulting in similar rate outcomes. It is interesting to compare the rate differences between the amino alcohol and the ether alcohol substrates with the parent diol (entries 3 and 4 vs entry 1) as a reflection of haptophilicity.

Additional examples with structural diversity are shown in Figure 2. Hexane-1,2,6-triol (**8**) was selectively tosylated at the 1-position, 9:1 mono:bis-primary tosylate, within 2 h in 73% yield. Primary alcohol **9** likewise underwent a more rapid catalytic tosylation, compared with the uncatalyzed version. Finally, glucofuranose **10** was converted to the primary tosylate under these conditions within 2 h in 74% yield (18% yield for the uncatalyzed reaction under identical conditions).

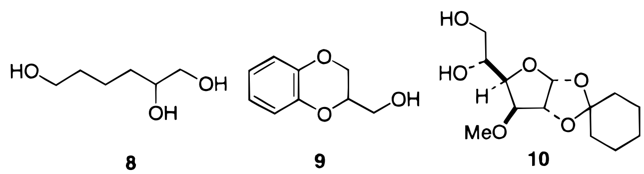
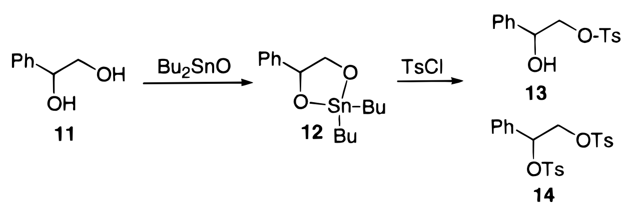


Figure 2.

The Et_3N stoichiometry was next considered as a critical feature. To address this aspect, initial experiments were conducted with the stannylidene of 1-phenyl-1,2-ethyleneglycol (**12**, Scheme 3). The stannylidene was treated with TsCl in CH_2Cl_2 and varying amounts of Et_3N (0.1−1.0 equiv). In all cases, clean and efficient regioselective tosylation was observed.[20]

Scheme 3



Next, we investigated the same net tosylation reaction in the catalytic version. Thus, 1-phenyl-1,2-ethyleneglycol (**11**) was dissolved in CD_2Cl_2 and treated with TsCl (1.05 equiv), Bu_2SnO (0.02 equiv), and varying amounts of Et_3N. Under these conditions, the percent conversion to the primary tosylate was *equal* to the added equivalents of Et_3N. With <1.0 equiv of Et_3N, the reaction proceeded to the extent predicted and stopped. It could be driven to completion simply by adding the balance of Et_3N.[20] Since the reaction produces an equivalent of HCl, it might be expected that the amine base is simply acting as an acid scavenger. Substitution of $(i\text{-Pr})_2NEt$ for the Et_3N proved deleterious to the reaction rate and efficiency, resulting in a much slower reaction even with a full equiv of $(i\text{-Pr})_2NEt$. This is presumably due to the increased steric requirements and ineffectiveness as a ligand. On the basis of these data, we concluded that Et_3N is important as a ligand on Sn, as well

(19) **General Experimental Procedure for the Sulfonylation of α-Chelatable Alcohols.** To a solution of the alcohol (10 mmol) in CH_2Cl_2 (20 mL) were added Bu_2SnO (0.2 mmol), *p*-TsCl (10 mmol), and Et_3N (10 mmol). The reaction mixture was stirred until TLC indicated complete consumption of the starting material. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was crystallized or chromatographed to afford the desired monotosylate. All tosylation products were characterized by the usual techniques (^{1}H and ^{13}C NMR, IR, HRMS, EA) and were compared to literature values or commercial samples whenever possible.

(20) None of the bis-tosylate **14** was detected by ^{1}H NMR.

as an HCl scavenger. Preliminary ^{1}H NMR analysis, however, did not reveal any chemical shift difference upon the addition of an equivalent of Et_3N to stannylidene acetal **12**. This ambiguous role of the amine, as a ligand and as an HCl quench, remains the topic of our continued investigations. It is noteworthy that the key difference between the catalytic and the stoichiometric versions appears to be the role of the amine base/ligand.

It has long been recognized that stannylidenes form dimeric species as determined by ^{1}H, ^{13}C, and Sn NMR,[21] although the oligomerization is concentration dependent.[22] The analysis can be further complicated by the use of racemic diols in the measurements, due to the statistical mixture of (*R*,*R*)-, (*S*,*S*)-, and (*R*,*S*)-dimers.[23] Nonetheless, upon formation of the stannylidene and dimerization, the Sn center may undergo ligation with Et_3N. Reaction with TsCl followed by expulsion of $Et_3N{\cdot}HCl$ then affords a vacant binding site on Sn. A new substrate molecule can then bind to Sn and, due to its bidentate capability, displaces the product to complete the catalytic cycle.[24] This mechanistic proposal is consistent when taken together with the substrate structural requirements shown in Table 2 and the added efficiency of Et_3N over $EtN(i\text{-}Pr)_2$. It is not clear at this time whether monomeric or dimeric stannylidene species are involved in the reaction. Although the mechanistic aspects of this reaction require further elucidation, its utility in organic synthesis seems clear.

In conclusion, we have demonstrated the feasibility of a catalytic Bu_2SnO-mediated sulfonylation with high regioselectivity. Salient features of this reaction include the use of *only* 2 mol % of the catalyst and rapid, exclusive monotosylation. Some of the important reaction features (solvent and base) are disclosed, as well as the critical substrate structural requirements. The role of the Et_3N also was critical and will be the subject of further investigation. The use of catalytic Bu_2SnO to effect functionalization affords dramatic rate acceleration relative to the noncatalyzed version, improved product quality, and minimal waste. Additionally, this protocol avoids the need for extensive chromatographic removal of lipophilic tin oxides.

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(21) (a) Wrackmeyer, B. *Ann. Rep. NMR Spectrosc*. **1985**, *16*, 73. (b) Roelens, S.; Taddei, M. *J. Chem. Soc., Perkin Trans. 2* **1985**, 799. (c) Otera, J.; Yano, T.; Okawara, R. *Chem. Lett*. **1985**, 901. (d) Otera, J.; Yano, T.; Okawara, R. *Organometallics* **1986**, *5*, 1167.

(22) Luchinat, C.; Roelens, S. *J. Org. Chem*. **1987**, *52*, 4449.

(23) (a) Shanzer, A.; Libman, J.; Gottlieb, H. E. *J. Org. Chem*. **1983**, *48*, 4112. (b) Luchinat, C.; Roelens, S. *J. Am. Chem. Soc*. **1986**, *108*, 4873.

(24) Roelens, S. *J. Org. Chem*. **1996**, *61*, 5257.