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Selective monosulfonylation of internal 1,2-diols catalyzed by di-*n*-butyltin oxide†

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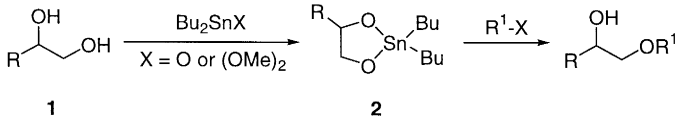
Abstract

The reaction of internal 1,2-diols with catalytic *n*-Bu_2SnO, *p*-TsCl (1.05 equiv.) and Et_3N (1.1 equiv.) led to selective monotosylation. In the case of cyclic substrates, the *cis*-1,2-diol moiety appeared best suited for optimal results, supporting the intermediacy of a five-membered chelate.

The selective monofunctionalization of diols has been of considerable interest in organic synthesis. Since Shanzer first reported it,[1] the monoderivatization of diols via their stannylene acetals has been explored and reviewed thoroughly.[2] Typically, the diol **1** is treated with a stoichiometric amount of *n*-Bu_2SnX, where X=O[3] or $(OMe)_2$,[4] with removal of water or methanol to afford the desired stannylene acetal **2**. The stannylenes then undergo selective alkylation, acylation, sulfonylation, and phosphorylation, usually at the primary position, or silylation with variable regioselectivity (Scheme 1).[5] The principal limitations of these methods are the reaction rate and the unavoidable production of a stoichiometric amount of *n*-Bu_2SnO, which is usually separable only by chromatography.



1 **2**

Scheme 1.

We recently described a convenient protocol for the primary selective sulfonylation of terminal 1,2-diols using catalytic *n*-Bu_2SnO in conjunction with stoichiometric Et_3N.[6] The reactions were extremely rapid, selective and high yielding. We report herein an extension of this method to the selective monotosylation of internal 1,2-diols.

Table 1 lists various examples of internal 1,2-diols that were subjected to the *n*-Bu_2SnO-catalyzed tosylation reaction. In the case of cyclic 1,2-diols, significant rate differences were observed between the

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† We would like to dedicate this manuscript to Professor Jose Barluenga on the occasion of his 60th birthday.

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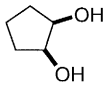
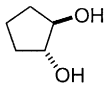
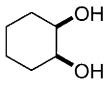
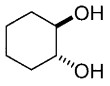
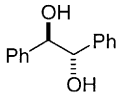
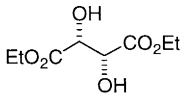
catalyzed and uncatalyzed versions. For example, *cis*-cyclopentane-1,2-diol was efficiently tosylated in the presence of catalytic *n*-Bu_2SnO within 45 min to afford the desired monotosylate in 97% yield. The corresponding uncatalyzed reaction went to approximately 13% conversion in 4 h (entry 1). A similar rate enhancement was observed in the case of *cis*-cyclohexane-1,2-diol (entry 3). The reactions of the corresponding *trans*-diols were much slower under the same conditions, and no significant rate acceleration was observed with added *n*-Bu_2SnO (entries 2 and 4). These results may be rationalized by invoking the intermediacy of a five-membered ring stannylene acetal. The formation of such a species would be more facile in the case of *cis*-1,2-diols than *trans*-1,2-diols. Interestingly, the tosylation of hydrobenzoin led to the formation of *trans*-stilbene oxide in addition to the desired monotosylate. The corresponding uncatalyzed reaction was also much slower in this case (entry 5). Sulfonylation of diethyl tartrate under the *n*-Bu_2SnO-mediated conditions led to a mixture of mono- and bis-tosylated products, the latter arising presumably due to the coordination of tin to the ester oxygen.

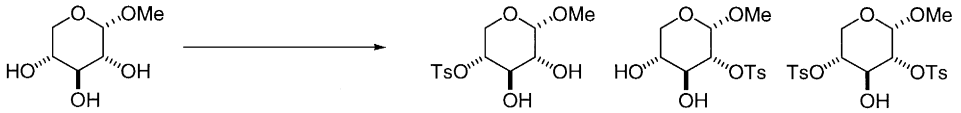
Table 1
Mono-sulfonylation of 1,2-diols catalyzed by di-*n*-butyltin oxide

		Catalyzed		Uncatalyzed	
Entry	Substrate	% Yield	Time (min)	% Yield	Time (min)
1		97	45	13	240
2		32	70	14	70
3		89	120	5	120
4		73	320	33	300
5		80[a,c]	40	<5	120
6		65[b,c]	85		

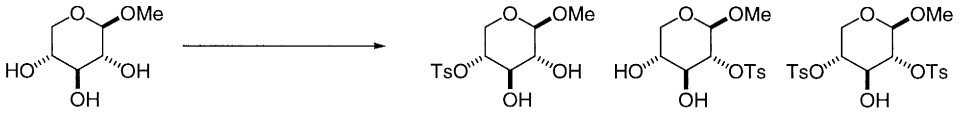
[a]A small amount of *trans*-stilbene oxide was also formed.[b]The bis-tosylate (8%) was also formed, presumably due to coordination of tin with the ester oxygen.[c]Conversion by ^1H NMR.

We then sought to expand the scope of this reaction to carbohydrate examples (α- and β-methyl-D-xylose, Scheme 2). If the hypothesis of a five-membered intermediate were correct, one would expect the α-anomer **3** to undergo preferential tosylation at the 2-position to afford **5**. However, when the *n*-Bu_2SnO-catalyzed tosylation of α-methyl-D-xylose **3** was run in CH_2Cl_2, the conversion was low (25%), and the predominant product was the 2,4-bis-*O*-tosylate (**6**). Similar results were obtained in the absence of *n*-Bu_2SnO. We reasoned that this was due to the higher solubility of the monotosylates **4** and **5** (compared to the starting material) in CH_2Cl_2. However, when the reaction was carried out in dioxane,[7] the 2-*O*- and 4-*O*-tosylated products (**5** and **4**, respectively) were obtained in 70% overall yield

(77:23). This is in contrast to the results of Tsuda and co-workers who observed a preponderance of the 4-*O*-tosylate **4** when they treated the stannylene acetal derived from α-methyl-D-xylose with *p*-TsCl and DMAP (cat.) in dioxane (Scheme 2).[8]



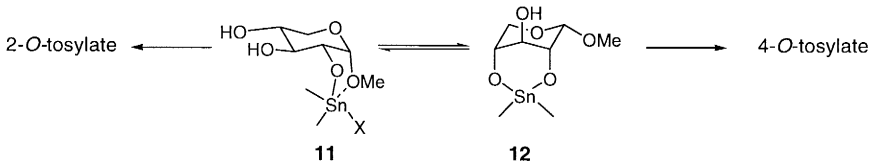
3	**4**	**5**	**6**	**Yield**
Current work: Bu_2SnO (cat), Et_3N, TsCl, dioxane	23	77	tr.	70%
Tsuda *et al.*: 1. Bu_2SnO; 2. TsCl, DMAP (cat), dioxane	62	38	0	84%



7	**8**	**9**	**10**	**Yield**
Current work: Bu_2SnO (cat), Et_3N, TsCl, dioxane	90	10	0	40%
Tsuda *et al.*: 1. Bu_2SnO; 2. TsCl, DMAP (cat), dioxane	100	0	0	100%

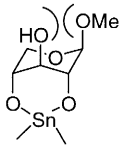
Scheme 2.

This trend may be explained as follows: We have already shown that an α-chelatable moiety should be present for efficient catalysis of tosylations by *n*-Bu_2SnO.[6a] For cyclic compounds, we have demonstrated that this α-chelatable moiety should be *cis* to the hydroxy group (Table 1). In the case of the α-anomer **3**, one may envision a five-membered intermediate arising out of tin coordination to the methoxy and 2-hydroxy groups (**11**, Scheme 3), thereby leading to tosylation at the 2-position to afford **5**. The 4-*O*-tosylate **4** may be formed either via the six-membered stannylene acetal intermediate **12**, or via an uncatalyzed reaction. Since five-membered rings are kinetically favored over six-membered rings, one would expect **11** to be formed faster than **12**, leading to the observed product distribution. On the other hand, the product distribution observed by Tsuda and co-workers may be attributed to the greater contribution of intermediate **12**, where the 4-O–Sn bond is the most reactive to a bulky electrophile for steric reasons.



Scheme 3.

The β-anomer **7**, on the other hand, underwent tosylation preferentially at the 4-position to furnish **8**, consonant with Tsuda's results (Scheme 2); however, the conversion was low. In this case, the *trans* relationship between the methoxy and 2-hydroxy groups would preclude the formation of a five-membered chelate, and hence the 2-*O*-tosylate would not be formed. Moreover, the formation of the six-membered stannylene acetal **13** via tin coordination to the 4- and 2-hydroxy groups may not be favored (1,3-diaxial interaction), leading to a lower conversion.



13

In summary, we have demonstrated the feasibility of selective monotosylation of internal diols using catalytic amounts of *n*-Bu_2SnO (ca. 2 mol%). Additionally, we have demonstrated that, for efficient catalysis in the case of cyclic substrates, an α-chelatable moiety *cis* to the hydroxy group should be present. The use of catalytic *n*-Bu_2SnO to effect sulfonylation affords dramatic rate enhancement relative to the uncatalyzed version, and minimal waste. This protocol obviates the need for extensive chromatographic removal of stoichiometric lipophilic tin waste.

Acknowledgements

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8. Tsuda, Y.; Nishimura, M.; Kobayashi, T.; Sato, Y.; Kanemitsu, K. *Chem. Pharm. Bull.* **1991**, *39*, 2883.
9. Typical experimental procedure: To a solution of the diol (2.5 mmol) in CH_2Cl_2 (5 mL) were added *n*-Bu_2SnO (0.02 equiv.), TsCl (1.05 equiv.) and Et_3N (1.1 equiv.). The reaction mixture was stirred at room temperature until TLC indicated disappearance of starting material. The mixture was filtered, and the filtrate was concentrated.