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Catalytic Regioselective Sulfonylation of α-Chelatable Alcohols: Scope and Mechanistic Insight

Michael J. Martinelli,* Rajappa Vaidyanathan,*,† Joseph M. Pawlak, Naresh K. Nayyar, Ulhas P. Dhokte, Christopher W. Doecke, Lisa M. H. Zollars, Eric D. Moher, Vien Van Khau, and Berta Košmrlj

Contribution from Chemical Process R&D, Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, Indiana 46285-4813

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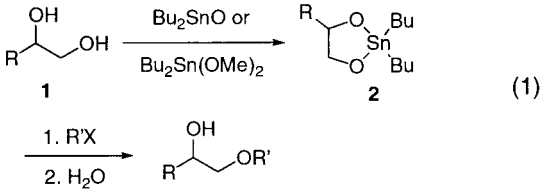
Abstract: This paper describes a convenient protocol for the regioselective sulfonylation of α-chelatable alcohols. Typically, the reaction of α-heterosubstituted alcohols with 1 equiv of *p*-TsCl and 1 equiv of Et_3N in the presence of 2 mol % of Bu_2SnO leads to rapid, regioselective, and exclusive monotosylation. The pK_a of the amine was correlated to the reaction rate. A plausible mechanism for this reaction has been proposed on the basis of ^{119}Sn NMR studies.

Introduction

The regioselective monofunctionalization of hydroxy groups in polyol substrates has been of considerable interest to organic chemists.[1] Several reports describing the use of stoichiometric reagents to effect sulfonylation,[2] alkylation,[3] and acylation[4] have appeared in the literature. Since Shanzer and co-workers first reported it,[5] the monoderivatization of diols via their stannylene acetals has been explored and reviewed thoroughly.[6] Typically, the reaction of a 1,2-diol **1** with Bu_2SnX, where X = O[2] or $(OMe)_2$,[7] is driven to completion by removal (azeotropic or desiccant) of water or methanol to afford the required stannylene acetal **2** (eq 1). After solvent exchange, these acetals undergo selective alkylation, acylation, sulfonylation, and phosphorylation, usually at the primary position, or silylation with variable regioselectivity.[8,9] This derivatization step is generally done in the presence of a catalytic amount of base (typically a tertiary amine such as triethylamine). The stannylene acetal protocol accomplishes primary hydroxyl activation and temporary secondary hydroxyl protection in a single operation.



(1)

This stannylene-based approach has been widely employed primarily because of the high yields and regioselectivities observed. However, the unavoidable coproduction of a stoichiometric amount of lipophilic tin waste, usually separable only by chromatography, poses a significant problem in large-scale applications. Dibutyltin oxide has been employed in a catalytic fashion to effect macrolactonization under neutral conditions, presumably as a template for ionic interactions with the carboxylate and alcohol termini.[10] Herradòn and co-workers reported the use of catalytic Bu_2SnO under microwave-assisted conditions to accelerate benzoylation of polyols.[11] We recently disclosed a convenient procedure for the primary selective sulfonylation of glycols using *catalytic* dibutyltin oxide in the presence of stoichiometric base.[12] Subsequently, dimethyltin dichloride was reported as a catalyst for the selective monobenzoylation of diols, with powdered K_2CO_3 as adjuvant.[13] An asymmetric version of this reaction using a chiral dialkyltin dibromide has also been reported.[14] More recently, Curran and co-workers have described the use of a recoverable fluorous tin oxide to effect regioselective monosulfonylation of diols.[15]

* To whom correspondence should be addressed. E-mail: mjm@lilly.com.
† Present address: Chemical Process R&D Division, Pharmacia Corp., 1500-91-201, 7000 Portage Road, Kalamazoo, MI 49001.

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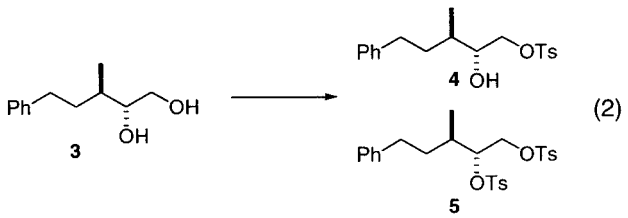
Table 1. Tosylation of Diol **3** under Various Conditions

	tin free	standard	catalytic
diol **3** (equiv)	1.0	1.0	1.0
TsCl (equiv)	1.0	1.0	1.0
Et_3N (equiv)	1.0	0.1	1.0
Bu_2SnO (equiv)	0	1.0	0.02
time (min)	1080	1080	15
% **5**	>10%	<1%	<1%

We report herein the full details of our investigation into the regioselective tosylation of α-chelatable alcohols with catalytic Bu_2SnO.

Results and Discussion

During the course of our efforts to synthesize analogues of cryptophycin,[16] we discovered the ability of Bu_2SnO to function as a catalyst in the selective monosulfonylation of diols. Mono(tosylate) **4** (eq 2) was a key intermediate in our synthetic route. The results of our preliminary experiments are listed in Table 1. Attempts to access **4** by treating diol **3** with *p*-TsCl and Et_3N ("tin-free" conditions; Table 1) led to the undesired production of the bis(tosylate) **5** (~10%) in addition to the desired mono(tosylate) **4**. Diol **3** was converted to the corresponding stannylene acetal by treatment with Bu_2SnO in toluene with azeotropic removal of water. After solvent exchange into CH_2Cl_2, the stannylene was treated with *p*-TsCl (1 equiv) and Et_3N (0.1 equiv) to furnish mono(tosylate) **4** as the exclusive product ("standard" conditions; Table 1).[17] The "standard" protocol employs 0−10 mol % Et_3N, presumably since the weak product−tin complex remains intact until workup. While the stannylene is a tight covalent complex and quite stable, its stability should be significantly diminished upon primary alcohol functionalization. We therefore speculated that excess Et_3N might enhance turnover through competitive tin binding to displace the product with concomitant neutralization of the newly formed HCl. Thus, treatment of diol **3** with *p*-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 "tin-free" protocol.



(2)

In an effort to clarify the catalytic effect of dibutyltin oxide on the tosylation reaction, a rate study was conducted. Diol **6** was now chosen as the test substrate. In separate experiments, 1-phenyl-1,2-ethanediol (**6**) was treated with *p*-TsCl (1.05 equiv) and Et_3N (1 equiv) in CD_2Cl_2, in the presence of catalytic Bu_2-SnO or without added Bu_2SnO. The conversion to mono(tosylate) **7** was followed by ^1H NMR spectroscopy as a function of time (Figure 1). Analysis of the data demonstrates that the Bu_2SnO-catalyzed reaction goes to completion substantially faster than the uncatalyzed version. Apparently, in the uncatalyzed version, as the reaction time is extended, competitive secondary sulfonylation becomes significant.

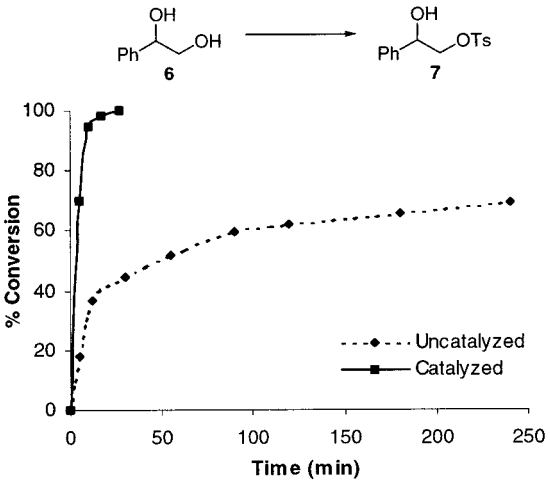


Figure 1. Rates of monotosylation of **6**.

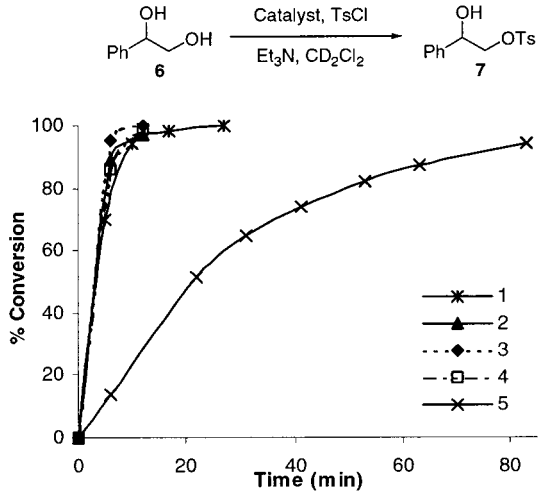


Figure 2. Variation of rate of reaction with tin species used: (1)Bu_2SnO; (2) Bu_2SnCl_2; (3) $Bu_2Sn(OMe)_2$; (4) $Bu_2Sn(OAc)_2$; (5) Bu_3SnCl.

Encouraged by these initial results, we sought to explore the scope and mechanistic aspects of this reaction. We examined the rate of the reaction and product distribution with respect to variation of several parameters, such as the Sn species used as catalyst, solvent, stoichiometry and nature of base added, and substrate structure.

Nature of Tin Species. Different tin reagents were evaluated as catalysts in the tosylation reaction. In a typical procedure, a 0.5 M solution of diol **6** in CD_2Cl_2 was treated with 1 equiv of *p*-TsCl, 0.02 equiv of the tin reagent, and 1.0 equiv of Et_3N, and the progress of the reaction was monitored by ^1H NMR spectroscopy. The results are summarized in Figure 2. Interestingly, Bu_2SnO, $Bu_2Sn(OMe)_2$, Bu_2SnCl_2, and $Bu_2Sn(OAc)_2$ exhibited essentially similar catalytic activity. Bu_3SnCl, however, proved to be a much less efficient catalyst. We believe that this trend reflects the ability of the tin reagent to readily form a strong complex with the diol (stannylene acetal). Bu_2-

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(17) Treatment of stannylene acetal **8** with 1 equiv of *p*-TsCl in the *absence* of Et_3N led to clean conversion to tosylate **7** within 15 min. The time (1080 min) under the "standard" conditions (Table 1) refers to the time required for stannylene acetal formation *and* tosylation.

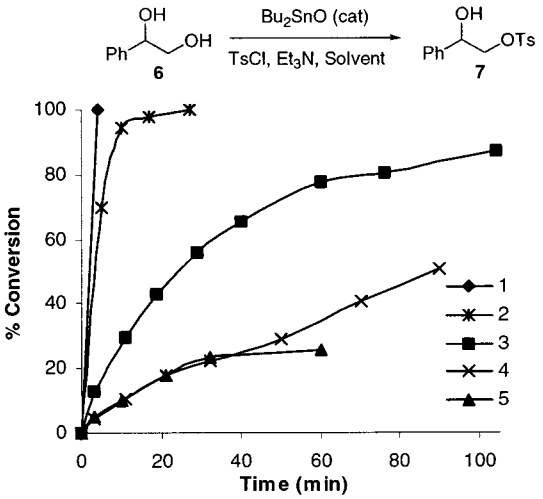


Figure 3. Variation of rate of reaction with solvent used: (1) acetonitrile; (2) methylene chloride; (3) tetrahydrofuran; (4) toluene; (5) methanol.

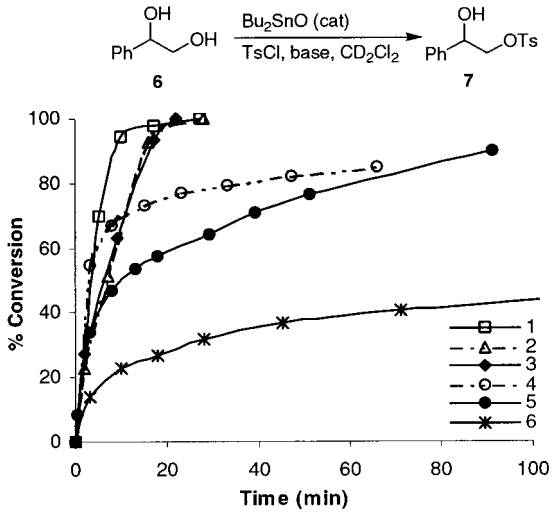


Figure 4. Variation of rate of reaction with base used. Numbers in parentheses refer to the pK_a of the conjugate acid of the base used: (1) Et_3N (10.72); (2) *i*-Pr_2NEt; (3) PMP (11.25); (4) NMM (7.13); (5) K_2CO_3; (6) pyridine (5.17).

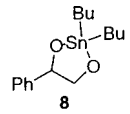


Figure 5.

SnO, $Bu_2Sn(OMe)_2$, Bu_2SnCl_2, and $Bu_2Sn(OAc)_2$ are all capable of forming stannylene acetals upon treatment with diols. Once the stannylene acetal is formed, the nature of the "nonalkyl" ligand on tin (in the catalyst) becomes irrelevant. Thus, not surprisingly, the tosylation reactions conducted in the presence of these catalysts were comparable in rate, going to completion within ca. 15 min. Bu_3SnCl, on the other hand, is incapable of forming stannylene acetals with diols. This could account for the fact that the tosylation reaction conducted in the presence of Bu_3SnCl was much slower. We chose to use Bu_2SnO for our future reactions primarily because it was a well-behaved solid, which would facilitate handling.

Solvent Study. The catalytic tosylation reaction was carried out in a variety of solvents in our quest for optimal conditions. In a typical procedure, a 0.5 M solution of diol **6** in the appropriate solvent was treated with 1 equiv of *p*-TsCl, 0.02 equiv of Bu_2SnO, and 1.0 equiv of Et_3N, and the progress of the reaction was monitored by ^1H NMR spectroscopy. The results are summarized in Figure 3. The reactions in acetonitrile and methylene chloride were essentially complete within ca. 20 min, while in THF the reactions were slower; the reaction in toluene was significantly slower, presumably due to the limited solubility of the diol in toluene. The use of MeOH as the solvent proved deleterious, probably as a result of either competitive binding of MeOH at the tin center and/or competitive tosylation of MeOH. However, it is noteworthy that tosylation of **6** went to 20% conversion even in such a large excess of *methanol*.

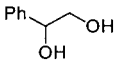
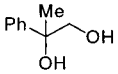
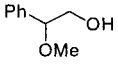
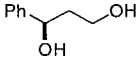
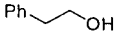
Nature and Stoichiometry of Base. To better understand the role of the amine base in the tosylation reaction, we undertook a systematic investigation. In these experiments, a solution of diol **6** in CD_2Cl_2 was treated with 1 equiv of *p*-TsCl, 0.02 equiv of Bu_2SnO, and 1.1 equiv of the appropriate base, and the reaction progress was monitored by ^1H NMR spectroscopy. The results are depicted in Figure 4. The reaction rate appears to depend on the pK_a of the conjugate acid of the base used. There was virtually no difference in rate between Et_3N, *i*-Pr_2NEt,[18] suspended K_2CO_3, and 1,2,2,6,6-pentamethylpiperidine, bases with pK_a above 10. Reactions with *N*-methylmorpholine (pK_a 7.13) and proton sponge (pK_a 12.0) were considerably slower, while pyridine (pK_a 5.17) did not progress beyond 40% conversion. The reactions using bidentate bases such as DABCO (1,4-diazabicyclo[2.2.2]octane) and TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) went to completion within 15 min, similar to Et_3N, but 1,1,3,3-tetramethylguanidine (pK_a 13.6) predominantly afforded N-tosylation. The reaction with proton sponge intermediary in effectiveness could be due to the insoluble, heterogeneous reaction mixture.

The stoichiometry of the base was then considered. The stannylene acetal of 1-phenyl-1,2-ethanediol (**8**) (Figure 5) was synthesized and subsequently treated with *p*-TsCl in CH_2Cl_2 and varying amounts of Et_3N (0.1−1.0 equiv). In all cases, clean and efficient primary regioselective tosylation was observed, irrespective of the stoichiometry of Et_3N. Treatment of stannylene acetal **8** with 1 equiv of *p*-TsCl in the *absence* of Et_3N led to clean conversion to tosylate **7** within 15 min. This suggests that, in the stoichiometric tin protocol, exclusive primary monotosylation can be obtained even in the absence of any nucleophile or base; however, for the catalytic tin protocol, a full 1 equiv of base is required to regenerate the tin catalyst.

The same net reaction in the catalytic protocol was then investigated. Diol **6** was dissolved in CD_2Cl_2 and treated with *p*-TsCl (1.05 equiv), Bu_2SnO (0.02 equiv), and varying amounts of Et_3N. We discovered that, under these conditions, the percent conversion to the tosylate was equal to the added equivalents of base. In other words, with 0.5 equiv of base, the reaction stopped at 50% conversion. It could be driven to completion by simply adding the balance of Et_3N. Thus, it is evident that, in the catalytic reaction, a full 1 equiv of the base is required, presumably to remove HCl from the cycle. From these preliminary studies, we surmised that the optimal conditions for the tosylation reaction would be catalytic Bu_2SnO and stoichiometric triethylamine in CH_2Cl_2 as the solvent.

(18) We had earlier incorrectly observed that addition of *i*-Pr_2NEt proved deleterious to the reaction rate and efficiency.[12b]

Table 2. Substrate Effect in the Monotosylation Reaction Catalyzed by Bu_2SnO

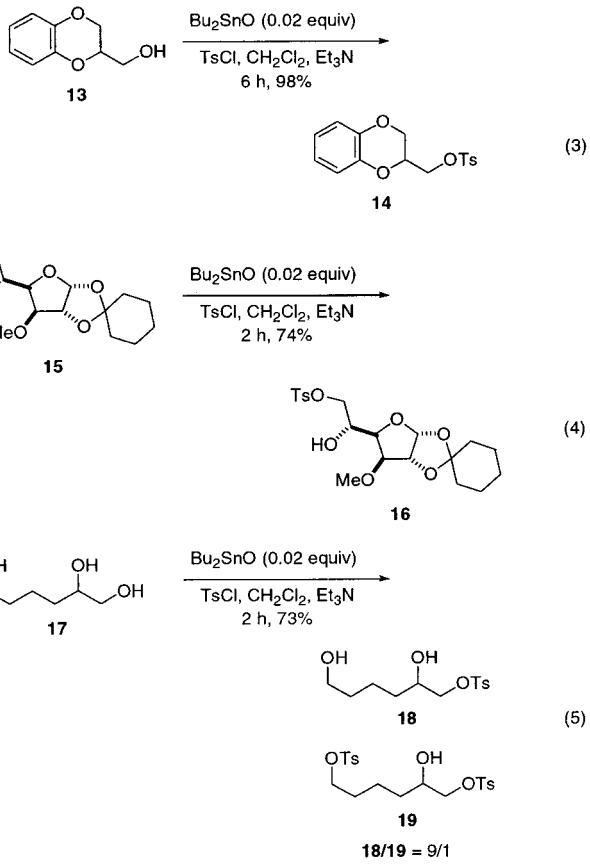
Entry[a]	Substrate	Product	Catalyzed[b]		Uncatalyzed	
			Yield[c]	t (min)	Yield[c]	t (min)
1		**7**	99	50	82	1140
2		**9**	99	120	79	1440
3		**10**	99	420	95	1550
4		**11**	92	1440	77	1260
5		**12**	86	1550	85	1550

[a] For a typical procedure, see Experimental Section. [b] Using 0.02 equiv of Bu_2SnO. [c] Refers to the isolated yield of the primary mono(tosylate).

Substrate Study. Our next endeavor was to examine the range of substrates to which the catalytic reaction may be applicable. Table 2 shows a series of substrates subjected to the Bu_2SnO-catalyzed tosylation reaction. The yields refer to the amount of monotosylated product isolated, with the balance being a mixture of the starting material and the bis(tosylate). It is evident that substrates in entries 1−3 are capable of forming five-membered chelates with Bu_2SnO. In each of these cases, dramatic rate acceleration was observed in the presence of catalytic Bu_2SnO, concomitant with excellent regioselectivity. The rate differences between the diol (entry 1) and alkoxy alcohol (entry 3) substrates may be a reflection of haptophilicity. The diol in entry 4 is predisposed to form a six-membered stannylene acetal with Bu_2SnO. The catalyzed reaction in this case was virtually indistinguishable from the uncatalyzed version in terms of reaction rate.[19] The same was true in the case of phenethyl alcohol, where bidentate chelation onto tin was not possible (entry 5). From these observations, is clear that an α-chelating moiety is crucial for efficient catalysis of the tosylation reaction by Bu_2SnO.

We also examined more diverse primary alcohols with α-chelatable substituents. Alcohol **13** was sulfonylated more rapidly in the presence of catalytic Bu_2SnO to afford tosylate **14** (98% in 6 h; eq 3). The corresponding uncatalyzed reaction was much slower (95% in 23 h). Glucofuranose **15** also furnished the expected primary tosylate **16** (Eq 4) under these conditions in 74% yield within 2 h (18% yield for the uncatalyzed reaction under identical conditions). Hexane-1,2,6-triol (**17**) underwent tosylation predominantly at the 1-position to afford a 9:1 mixture of mono- and bis-primary tosylates **18** and **19,** respectively, within 2 h in 73% yield (eq 5). This example again serves to highlight the importance of the α-chelatable substituent in the catalytic tosylation reaction.

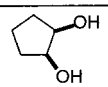
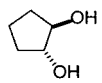
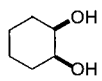
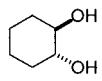
Cyclic 1,2-Diols. In the case of cyclic 1,2-diols, significant rate differences were observed between the catalyzed and uncatalyzed versions (Table 3). For example, *cis*-cyclopentane-1,2-diol was efficiently tosylated in the presence of catalytic



Bu_2SnO within 45 min to afford the desired mono(tosylate) 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 less significant rate acceleration was observed with added Bu_2SnO (entries 2 and 4). These results are consistent with the intermediacy of a five-membered ring stannylene acetal, in accordance with the stoichiometric precedent.[20] The formation of such a species would be geometrically more facile in the case of *cis*-1,2-diols than *trans*-1,2-diols.

Interestingly, the tosylation of hydrobenzoin **24** led to the formation of *trans*-stilbene oxide (**26**) (ca. 5%) in addition to

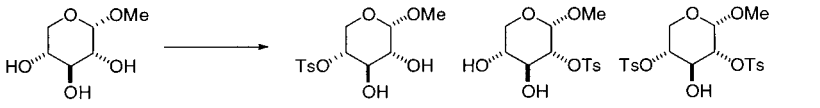
Table 3. Tosylation of Cyclic 1,2-Diols Catalyzed by Bu_2SnO[a]

Entry	Substrate	Product	Catalyzed		Uncatalyzed	
			Yield	t (min)	Yield	t (min)
1		**20**	97	45	13	240
2		**21**	32	70	14	70
3		**22**	89	120	5	120
4		**23**	73	320	33	300

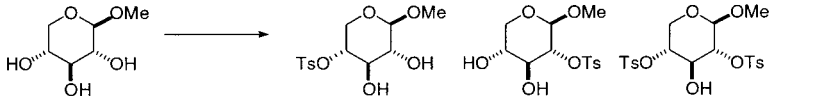
[a] All reactions were performed in CH_2Cl_2. See Experimental Section for details.

(19) However, the regioselectivity was slightly better in the catalyzed version. This suggests that the incipient stannylene acetal may be competing with the non-Sn-mediated background process.

Scheme 1

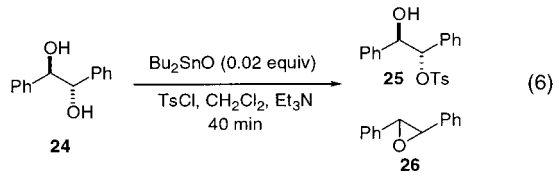


	30	31	32	33	Yield
Current work: Bu_2SnO (cat), Et_3N, TsCl, dioxane		23	77	tr.	70%
Tsuda *et al.*: 1. Bu_2SnO; 2. TsCl, DMAP (cat), dioxane		62	38	0	84%

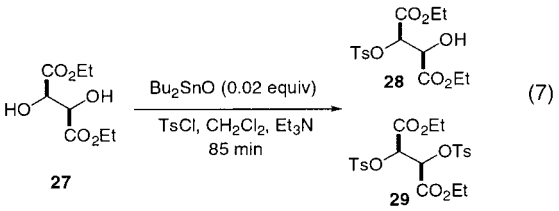


	34	35	36	37	Yield
Current work: Bu_2SnO (cat), Et_3N, TsCl, dioxane		90	10	0	40%
Tsuda *et al.*: 1. Bu_2SnO; 2. TsCl, DMAP (cat), dioxane		100	0	0	100%

the desired mono(tosylate) **25**, which was isolated in 80% yield in 40 min (eq 6).[21] The corresponding uncatalyzed reaction was much slower in this case also (<5% conversion in 2 h). Sulfonylation of diethyl tartrate (**27**) under the Bu_2SnO-mediated conditions led to a mixture of mono(tosylate) **28** (65%) and bis(tosylate) **29** (8%), the latter arising presumably due to the coordination of tin to the ester oxygen (eq 7).



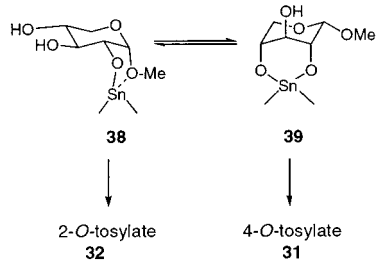
(6)



(7)

Carbohydrate Examples. Stannylene acetals have been extensively employed as intermediates in the regioselective derivatization of carbohydrates.[6b] We sought to expand the scope of our catalytic protocol to carbohydrate examples (α- and *β*-methyl-D-xylose, Scheme 1). If the hypothesis of a five-membered intermediate were correct, one would expect the α-anomer **30** to undergo preferential tosylation at the 2-position to afford **32**. However, when the Bu_2SnO-catalyzed tosylation of α-methyl-D-xylose **30** was run in CH_2Cl_2, the conversion was low (25%), and the predominant product was the 2,4-bis-(*O*-tosylate) (**33**). Similar results were obtained in the absence of Bu_2SnO. We reasoned that this was due to the higher solubility of the mono(tosylate)s **31** and **32** (compared to the starting material) in CH_2Cl_2. However, when the reaction was carried out in dioxane,[22] the 2-*O*- and 4-*O*-tosylated products

Scheme 2



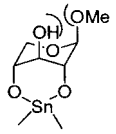
(**32** and **31,** respectively) were obtained in 70% overall yield (77:23). This is in contrast to the results of Tsuda and co-workers who observed a preponderance of the 4-*O*-tosylate **31** when they treated the stannylene acetal derived from α-methyl-D-xylose with *p*-TsCl and DMAP (cat) in dioxane (Scheme 1).[23]

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 Bu_2SnO.[12a] For cyclic compounds, we have demonstrated that a cis-α-chelatable moiety is slightly favored over the trans congener (Table 3). The *trans*-1,3-cyclohexanediol reacts about 3× slower than the *cis*-1,2-diol, with significantly lower yield. In the case of the α-anomer **30**, one may envision a five-membered intermediate arising out of tin coordination to the methoxy and 2-hydroxy groups (**38**, Scheme 2), thereby leading to tosylation at the 2-position to afford **32**. The 4-*O*-tosylate **31** may be formed either via the six-membered stannylene acetal intermediate **39** or via an uncatalyzed reaction. Since five-membered rings are kinetically favored over six-membered rings, one would expect **38** to be formed faster than **39**, 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 **39** (preformed stannylene acetal), where the 4-*O*−Sn bond is the most reactive to a bulky electrophile for steric reasons. The fact that cis-chelation is more effective than trans-chelation is well established.[20] The most spectacular example is the efficient reaction at O-3′ of methyl *β*-D-lactoside stannylene acetal with allyl bromide in the presence of six other hydroxyl moieties. The evidence in Table 2 suggests that

(20) Alais, J.; Maranduba, A.; Veyrières, A. *Tetrahedron Lett.* **1983**, *24*, 2383.
(21) Mono(tosylate) **25** is prone to decomposition and has to be isolated immediately after the reaction. The compound does not survive mass spectral conditions.
(22) The Bu_2SnO-catalyzed tosylations are slower in dioxane than in CH_2Cl_2.
(23) Tsuda, Y.; Nishimura, M.; Kobayashi, T.; Sato, Y.; Kanemitsu, K. *Chem. Pharm. Bull.* **1991**, *39*, 2883.

chelation to a *cis*-α-methoxy moiety is possible (entry 3) and could be in competition with that to a *trans*-OH (Table 3). When the stannylene acetal is formed in advance, the equilibrium is pushed to *trans*-diol complexation by removal of water. It should be recognized that alternative explanations for formation of 2-substituted products are possible, but the complexity of the system makes it difficult to rule out alternatives.

The *β*-anomer **34**, on the other hand, underwent tosylation preferentially at the 4-position to furnish **35**, consonant with Tsuda's results (Scheme 1); however, the conversion was low. In this case, the trans complexation between the less hindered hydroxy groups would be more favorable, and hence the 4-*O*-tosylate (**35**) would be formed. Moreover, the formation of the six-membered stannylene acetal **40** via tin coordination to the 4- and 2-hydroxy groups may not be favored (1,3-diaxial interaction), leading to the observed lower conversion.



40

Mechanistic Studies. Having developed the catalytic tosylation protocol, we deemed it appropriate to investigate the mechanism of this reaction. It has to be mentioned that the products of these reactions do not rearrange, unlike acylations and silylations.[24] One may also safely assume that the origin of selectivity is the same for both the stoichiometric and catalytic tosylation reactions. The selectivity observed in the sulfonylation of stannylene acetals (stoichiometric tin protocol) has been ascribed to the existence of these compounds as dimers (**41**−**43**, Figure 6).[6] However, our first approach was to determine which species, the monomer or dimer, dominated in solution.

We chose 1-phenyl-1,2-ethanediol (**6**) as our test substrate. Our attempts to identify reaction intermediates by NMR spectroscopy (^{1}H and ^{119}Sn) were hampered by the limited solubility of Bu_2SnO in CH_2Cl_2. If indeed the catalytic tosylation proceeds via the stannylene acetal intermediate (vide supra), we reasoned that the reaction could be catalyzed by the stannylene acetal **8**. Indeed, the sulfonylation of **6** using 1.05 equiv of *p*-TsCl, 1.1 equiv of Et_3N, and 2 mol % of **8** was essentially complete within ca. 8 min. Thus, acetal **8** was used instead of Bu_2SnO for our NMR studies. The ^{119}Sn NMR spectrum of acetal **8** in CD_2Cl_2 (0.2 M) at room temperature shows a broad peak around −130 ppm, similar to what was observed by Roelens,[25] indicating the presence of a pentacoordinate tin species. In an effort to mimic the reaction conditions, we acquired the ^{119}Sn NMR spectrum of a mixture of diol **6** containing 5 mol % of acetal **8**.[26] The presence of a broad peak centered around −125 ppm suggests that the stannylene acetal still exists as a dimer under the reaction conditions in the catalytic tin protocol. Three rapidly equilibrating dimeric structures are possible, namely, the 2,2-dimer (**41**), the 1,2-dimer (**42**), and the 1,1-dimer (**43**).[27] In each of the monomeric subunits in these dimers, there is one apical dicoordinate oxygen and one equatorial tricoordinate oxygen. The apical oxygen is reportedly more reactive than the tricoordinate equatorial oxygen. Although steric factors may dictate which dimer is more populated, the 1,2-dimer **42** or the 1,1-dimer **43** reacts to give the observed primary tosylate. Therefore, to simplify our discussion, we will consider only dimer **43** henceforth.

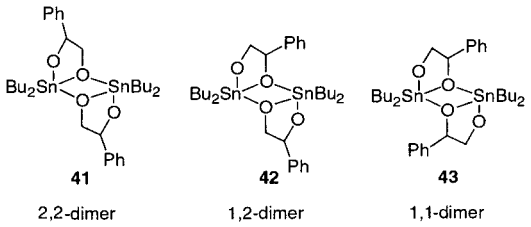


Figure 6. Dimeric structures of stannylene acetals.

It was next important to consider whether Et_3N is a ligand for tin or simply a base to neutralize the formed HCl. This would provide critical insight to whether Et_3N becomes relevant pretosylation or post-tosylation, to design catalytic systems that could employ chiral bases. Substitution of Et_3N with Bu_4NCl in the catalytic protocol did not lead to any tosylation, suggesting that the primary role of Et_3N is as a base. The utilization of suspended K_2CO_3 performed similarly to Et_3N although slower, and "proton sponge" (1,8-bis(dimethylamino)naphthalene) was only slightly less effective. These data further support the notion that the base is likely not a ligand for tin.

However, in the stoichiometric version, it has also been suggested that the amine (or nucleophile) helps break up the dimer.[6b] Grindley et al have observed significant secondary tosylation in the absence of added nucleophiles (in the stoichiometric tin protocol), especially when the group on the secondary carbon was bulky and the two alkyl groups on tin were large or rigid.[24b] This reversal in regioselectivity in the absence of added nucleophiles prompted the authors to implicate a monomeric stannylene acetal species complexed with the nucleophile (in the presence of added nucleophiles) as the reactive species. The addition of excess Bu_4NI with stoichiometric pyridine, under the standard conditions, did not provide any beneficial effect relative to the reaction without added iodide.

We also considered the fact that the catalytic reaction might proceed through such an intermediate arising out of precomplexation of the stannylene acetal dimer with Et_3N to afford a monomeric species, which would then undergo tosylation. Addition of stoichiometric Et_3N to stannylene acetal **8** did not alter either the ^{1}H or the ^{119}Sn NMR spectrum. Significant changes have been reported at lower temperatures,[6b] and this only shows that if an amine intermediate is formed, it is less stable than the dimer by >2 kcal/mol, which is significantly less than the activation barrier. These data do not support precomplexation of the stannylene acetal with Et_3N.[28]

Moreover, when the catalytic tosylation of **6** was conducted using 0.02 equiv of Bu_2SnO and 0.5 equiv of *p*-TsCl in the presence of a chiral, optically pure base such as cinchonidine or sparteine, no kinetic resolution was observed. However, modest selectivities could be detected in the presence of a chiral tin dibromide.[29] Therefore, it may be inferred that the amine is involved in the post-tosylation step. Even if the base-complexed monomer were the intermediate, the two most electronegative

(24) Roelens, S. *J. Org. Chem.* **1996**, *61*, 5257. (b) Kong, X.; Grindley, T. B. *Can. J. Chem.* **1994**, *72*, 2396.
(25) Luchinat, C.; Roelens, S. *J. Org. Chem.* **1987**, *52*, 4449.
(26) The spectrum was acquired using 52 mg of diol **6** (0.38 mmol) and 7 mg of **8** (0.02 mmol) in 0.75 mL of CD_2Cl_2.
(27) The dimers are named by using the number of the two tricoordinate oxygen atoms. See: Grindley, T. B.; Thangarasa, R. *Can. J. Chem.* **1990**, *68*, 1007.

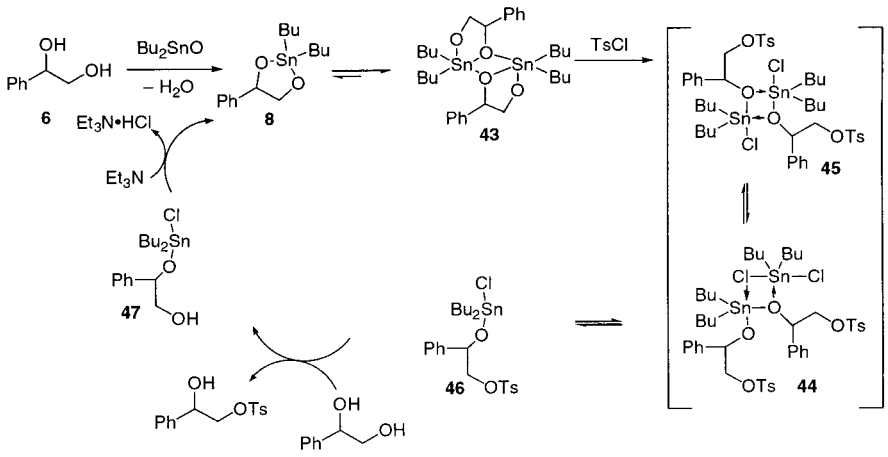


Figure 7. Proposed mechanism of the Bu_2SnO-catalyzed tosylation reaction.

oxygen atoms could not both be apical if they are in a ring. Therefore, one oxygen would be apical and the other would be equatorial, as the two butyl groups would be equatorial in the trigonal bipyramid at tin. The amine could adopt the other apical position, but the attack would occur on the more reactive apical oxygen atom, which is remote from the nitrogen substituents and unable to influence stereoselectivity. Thus, it is difficult to fully rationalize the chiral amine ligand experimental outcome without additional studies.

Next, the ^{119}Sn NMR spectrum of a mixture of diol **6** in the presence of **8** (5 mol %) and *p*-TsCl (1 equiv) was acquired.[30] The ^{119}Sn NMR spectrum of this sample contains two equally intense peaks at −140.97 and −91.97 ppm. By analogy to literature data,[31] these peaks may be attributed to a [$Bu_2Sn(OR)_2^{\bullet}$] and a [$Bu_2SnCl_2^{\bullet}$] fragment, respectively. Thus, one can postulate structure **44** for this complex (Figure 7).[31] The dibutyltin dichloride may be loosely bound to the dialkoxytin fragment allowing for rapid intra- and intermolecular exchange of Bu_2SnCl_2. The ^{119}Sn NMR spectrum also shows three other significant peaks at −120.48, −374.91, and 108.37 ppm. The peak at −120.48 ppm may arise from the stannylene acetal dimer **43**. The peak at −374.91 ppm could be due to the presence of higher oligomeric species. The upfield peak at 108.37 may be attributed to the presence of monomeric Bu_2SnCl_2.[32]

On the basis of our observations and literature precedent, a plausible mechanistic postulate for the catalytic protocol is outlined in Figure 7. The reaction of the diol with Bu_2SnO produces the stannylene acetal **8** in situ, which exists as a dimeric species **43**. Sulfonylation by *p*-TsCl leads to intermediates **44** and **45**. Et_3N could break up the dimer to give a species such as **46**. Displacement of the tosylate by another molecule of the diol would furnish intermediate **47**. Triethylamine can then scavenge HCl to regenerate the stannylene acetal **8** and complete the catalytic cycle.

This mechanism accounts for the following observations: (1) The stannylene acetal catalyzes the tosylation just as Bu_2SnO does. (2) The stannylene acetal exists as a dimer under the reaction conditions. (3) 1 equiv amount of base is required to ensure complete reaction. (4) The extent and rate of reaction depend on the pK_a of the conjugate acid of the base used. (5) The acetoxy, alkoxy, oxo, or halogen ligands on tin have little effect on the reaction rate, although other alkyl ligands have been shown to play a significant role.[24b] (6) This catalytic version may contrast the stoichiometric, in which added nucleophiles can alter the regioselectivity.[24b]

Conclusion. We have described a convenient protocol for the regioselective sulfonylation of α-chelatable alcohols using catalytic amounts (2 mol %) of Bu_2SnO. The reactions are extremely rapid and highly selective. We varied several reaction parameters and described the optimal reaction conditions. The role of the amine has been elucidated, and a plausible mechanism for the Bu_2SnO-catalyzed tosylation reaction has been proposed. The proposed mechanism is based on our observations and literature precedent. These new insights will provide a good starting point for the design of novel chiral and resin-bound tin reagents. This catalytic procedure obviates the need for extensive chromatographic removal of lipophilic tin oxides. The high regioselectivity and the dramatic rate enhancement observed render this reaction particularly attractive for large-scale sulfonylations.

Experimental Section

Materials. All chemicals were purchased from Aldrich Chemical Co. and were used as received, unless otherwise stated. (*R*)-1-Phenyl-1,3-propanediol was purchased from Fluka. The carbohydrate samples, α- and β-methyl-D-xylosides, were purchased from Pfaltz and Bauer, Inc., and were used as received.

General Procedure for Kinetics Experiments. To a solution of alcohol **6** (5 mmol) in the appropriate deuterated solvent (10 mL) were added the appropriate tin reagent (0.1 mmol), *p*-TsCl (5.25 mmol), and the appropriate base (5 mmol). The reaction mixture was stirred at room

(28) Matsumura and co-workers have obtained high primary selectivity in the presence of a non-nucleophilic base (K_2CO_3 or Na_2CO_3) while using both a sterically "unencumbered" tin species (Me_2SnCl_2)[13] as well as a sterically demanding binaphthyl tin species[14] as the catalyst. In the former case, the reactions were faster with Et_3N than K_2CO_3, but no differences in regioselectivity were observed. In the latter case, there was no difference in regioselectivity in the presence of a coordinating base (Et_3N) or a noncoordinating base (Na_2CO_3), although there were differences in yields and enantioselectivities. In other words, there was no reversal in regioselectivity due to either the steric bulk of the alkyl group on tin or the nature of the base used; however, it must be reiterated that the catalytic reaction does not proceed in the absence of the base, and hence, the product distribution in the *absence* of base cannot be determined! These results, coupled with the lack of spectroscopic evidence for monomeric tin species in the presence of Et_3N, lead us to believe that the catalytic reaction proceeds via the dimeric species.

(29) Martinelli, M. J.; Vaidyanathan, R. Unpublished results. See also ref 14.

(30) The spectrum was acquired using 52 mg of diol **6** (0.38 mmol), 7 mg of **8** (0.02 mmol), and 72 mg of *p*-TsCl (0.38 mmol) in 0.75 mL of CD_2Cl_2.

(31) Bredenkamp, M. W.; Spies, H. S. C.; van der Merwe, M. J. *Tetrahedron Lett.* **2000**, *41*, 547.

(32) The complexity of the ^{119}Sn and ^{1}H NMR spectra of a mixture of acetal **8** and *p*-TsCl and the fact that there is no obvious general relationship between $\delta(^{119}\text{Sn})$ and other empirical parameters preclude a more rigorous interpretation of the data.

temperature. Aliquots (0.3 mL) were withdrawn at different time intervals, and the percent conversion was determined by ^{1}H NMR spectroscopy.

General 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 reaction was quenched with water, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layers were washed sequentially with water and brine, dried (Na_2SO_4), and filtered, and the filtrate was concentrated in vacuo. The residue was crystallized or chromatographed to afford the desired mono(tosylate).

General Procedure for the Sulfonylation of α- and *β*-Methyl-D-xylosides. To a solution of the xyloside (2.5 mmol) in dioxane (5 mL) were added Bu_2SnO (0.05 mmol), *p*-TsCl (2.63 mmol), and Et_3N (2.75 mmol). The reaction mixture was stirred at room temperature overnight and concentrated in vacuo. The residue was chromatographed (SiO_2, 60% EtOAc/hexanes) to afford the mono(tosylates).

Sulfonylation Products. Tosylates **7**,[33] **9**,[34] **10**,[35] **11**,[36] **12**,[37] **28**,[38] **31**,[23] **32**,[23] **33**,[23] **35**,[23] **36**,[23] and **37**[23] were characterized by ^{1}H and ^{13}C NMR and were compared to literature values or commercial samples, as appropriate.

^{119}Sn NMR Experiments. ^{119}Sn NMR spectra were collected on a Varian Inova 500 MHz spectrometer at a frequency of 186.52 MHz. Unless stated, all spectra were accumulated at a probe temperature of 25 °C. Data were collected using the INEPT pulse sequence with a sweep width of 119.9 kHz using a 64K data set. The pulse width was approximately 70° with an acquisition time of 0.192 s coupled with a 2 s recycle delay. Data were accumulated using ^{1}H decoupling and transformed using a 3 Hz line broadening. Tetramethyltin was used as the standard.

***(R)*-1-Phenyl-1,3-propanediol 3-tosylate (11):**[36] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2 H), 7.36−7.26 (m, 7 H), 4.81 (m, 1 H), 4.28 (m, 1 H), 4.08 (m, 1 H), 2.45 (s, 3 H), 2.03 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 142.5, 142.0, 132.0, 129.8, 127.8, 121.6, 121.4, 117.1, 117.0, 70.1, 67.1, 64.0, 21.4

2-((Tosyloxy)methyl)-1,4-benzodioxan (14): mp = 79−81 °C; IR ($CHCl_3$) 3035, 1597, 1494, 1369, 1269, 1177 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 6.75 (m, 4 H), 4.41−4.00 (m, 5 H), 2.45 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 142.5, 142.0, 132.0, 129.8, 127.8, 121.6, 121.4, 117.1, 117.0, 70.1, 67.1, 64.0, 21.4; HRMS found *m*/*z* 320.0713 (M^+), calcd for $C_{16}H_{16}O_5S$ *m*/*z* 320.0718.

1,2-*O*-Cyclohexylidene-3-*O*-methyl-α-D-glucofuranose 6-tosylate (16): IR ($CHCl_3$) 3029, 2941, 2865, 1600, 1450, 1368, 1177 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 5.84 (d, J = 3.5 Hz, 1 H), 4.54 (d, J = 3.0 Hz, 1 H), 4.27−4.25 (m, 1 H), 4.16−4.15 (m, 1 H), 4.09−4.03 (m, 2 H), 3.88 (d, J = 3.0 Hz, 1 H), 3.43 (s, 3 H), 2.91 (d, J = 6.5 Hz, 1 H), 2.43 (s, 3 H), 1.72−1.38 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 132.4, 129.9, 128.0, 112.6, 104.6, 84.2, 80.9, 78.9, 72.3, 67.3, 57.9, 36.3, 35.6, 24.8, 23.8, 23.5, 21.6; HRMS found *m*/*z* 446.1838 $(M + NH_4)^+$, calcd for $C_{20}H_{32}NO_8S$ *m*/*z* 446.1848.

***cis*-Cyclopentane-1,2-diol 1-tosylate (20):** IR ($CHCl_3$) 3022, 1743, 1728, 1600, 1362, 1176 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, J = 7.0 Hz, 2.0 Hz, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 4.64 (ddd, J = 6.0 Hz, 6.0 Hz, 4.0 Hz, 1 H), 4.10 (ddd, J = 6.0 Hz, 6.0 Hz, 4.0 Hz, 1 H), 3.05 (br s, 1 H), 2.42 (s, 3 H), 1.84−1.75 (m, 4 H), 1.69−1.64 (m, 1 H), 1.49−1.45 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 133.4, 129.8, 127.7, 84.1, 72.7, 29.8, 27.7, 21.6, 18.7; HRMS found *m*/*z* 257.0828 $(M + H)^+$, calcd for $C_{12}H_{17}O_4S$ *m*/*z* 257.0848.

***trans*-Cyclopentane-1,2-diol 1-tosylate (21):** IR ($CHCl_3$) 2969, 1600, 1358, 1189, 1176 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.5 Hz, 2 H), 7.33 (d, J = 8.5 Hz, 2 H), 4.58−4.55 (m, 1 H), 4.26−4.23 (m, 1 H), 2.89 (br s, 1 H), 2.42 (s, 3 H), 2.01−1.90 (m, 2 H), 1.70−1.63 (m, 1 H), 1.49−1.45 (m, 3 H), 1.56−1.50 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 133.7, 130.2, 128.0, 89.2, 77.3, 31.7, 30.1, 21.9, 20.7; HRMS found *m*/*z* 257.0831 $(M + H)^+$, calcd for $C_{12}H_{17}O_4S$ *m*/*z* 257.0848.

***cis*-Cyclohexane-1,2-diol 1-tosylate (22):** IR ($CHCl_3$) 3028, 2946, 2869, 1704, 1600, 1449, 1361, 1175 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.5 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 2 H), 4.59 (ddd, J = 8.0 Hz, 3.0 Hz, 3.0 Hz, 1 H), 3.80−3.79 (m, 1 H), 2.42 (s, 3 H), 2.20 (br s, 1 H), 1.92−1.85 (m, 1 H), 1.75−1.69 (m, 1 H), 1.62−1.45 (m, 4 H), 1.31−1.23 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 134.0, 129.8, 127.6, 83.1, 68.9, 30.1, 27.6, 21.6, 21.5, 20.7; HRMS found *m*/*z* 271.0987 $(M + H)^+$, calcd for $C_{13}H_{19}O_4S$ *m*/*z* 271.1004.

***trans*-Cyclohexane-1,2-diol 1-tosylate (23):** IR ($CHCl_3$) 2947, 2868, 1600, 1454, 1360, 1175 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, J = 2.5 Hz, 8.0 Hz, 2 H), 7.34 (dd, J = 2.5 Hz, 8.0 Hz, 2 H), 4.31−4.25 (m, 1 H), 3.59−3.54 (m, 1 H), 2.44 (s, 3 H), 2.38 (br s, 1 H), 2.04−1.95 (m, 2 H), 1.67−1.66 (m, 2 H), 1.47−1.39 (m, 1 H), 1.32−1.19 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 133.9, 129.9, 127.7, 86.7, 72.0, 32.3, 30.8, 23.8, 23.2, 21.6; HRMS found *m*/*z* 271.1004 $(M + H)^+$, calcd for $C_{13}H_{19}O_4S$ *m*/*z* 271.1004.

Hydrobenzoin tosylate (25):[21] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.07 (m, 14 H), 5.45 (d, J = 3.5 Hz, 1 H), 5.10 (d, J = 3.5 Hz, 1 H), 2.35 (s, 3 H), 1.98 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 138.3, 134.3, 133.5, 129.4, 128.7, 128.1, 128.0, 127.8, 127.7, 127.1, 126.9, 86.2, 76.2, 21.5.

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Supporting Information Available: ^{119}Sn NMR spectra of stannylene acetal **8** under both reaction conditions (with and without TsCl) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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