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Further improvements of the dibutyl tin oxide-catalyzed regioselective diol tosylation

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ABSTRACT

In this Letter, we report that selective monotosylation of a 1,2-diol is possible using only 0.1 mol % of Bu_2SnO. More interestingly, we found that the corresponding tin acetal **3b** gave faster conversions and more reproducible reaction times. Moreover, the loading of this catalyst could be as low as 0.05–0.005 mol %.

1. Introduction

The use of dibutyl tin oxide **1** (Bu_2SnO) is well known for the regioselective derivatization of vicinal diols. Since Shanzer's original Letter,[1] the stoichiometric process has been widely applied in carbohydrate chemistry.[2,3] The reaction can be generalized to functionalize other diols as well.[4]

The catalytic process, described in 1999 by Martinelli et al.,[5] enables the selective tosylation of a diol with only 2 mol % of Bu_2SnO in the presence of a classical base such as triethylamine (Et_3N). In a more recent paper,[6] the same author detailed the mechanistic aspects of the reaction (Scheme 1): the intermediate formation of the corresponding tin acetal **3** was postulated in accordance with the reactivity of tin acetals isolated in the stoichiometric process.

Quite recently, Servi described the use of 2 mol % catalytic Sn acetal derived from the reacting diol itself.[8]

In this Letter, we wish to report the results from our own research group.[9] Most notably, we have observed: (i) that the quantity of Bu_2SnO **1** could be decreased from 2 mol % to 0.1 mol %, (ii) an important reactivity difference between **1** and the corresponding Sn acetal, (iii) that the generic Sn acetal catalyst **3b** could be used for selective diol tosylation, (iv) that the use of **3b** led to diminished catalyst loading from 0.1 mol % to 0.05 and even 0.005 mol % in some cases, and (v) the generality of the process on different commercial diol substrates.

2. Results and discussion

During the synthesis of the antipsychotic R209130, we wanted to selectively tosylate diol **2a** as shown in Scheme 2.[10]

Initially, we wanted to avoid the use of tin derivatives because of the potential toxicity associated with organotins: unfortunately, the uncatalyzed reaction gave only 76% of desired monotosyl derivative **6a**, accompanied by 8% of the starting material **2a** and 16% ditosylated product **7a**.

Given these disappointing results, we decided to use **1** in order to improve the selectivity of the tosylation. Some of our results are summarized in Table 1.

In order to limit the Sn content in the API,[11] we first decreased the quantity of the tin catalyst. To our delight, we noticed that 0.1 mol % Bu_2SnO **1** was sufficient for the reaction to proceed smoothly (entry 14). However, when the amount of **1** was decreased to 0.05%, the reaction became too slow (50% conversion after 16 h, entry 15), as in the case of the uncatalyzed reaction for which only 60% conversion was noticed after 4 days at 25 °C.

Unlike Martinelli, we observed that the use of diisopropyl ethyl amine ($^iPr_2NEt$, Hünig's base) gave product of better purity than with Et_3N.

More surprisingly, in the course of the optimization work, a rather sharp temperature peak was observed after 5 h of reaction, as shown in Scheme 3.

We assume that this induction period is due to the slow formation of the reactive tin acetal intermediate of type **3**. The subsequent steps of the catalytic cycle (selective TsCl addition, metal exchange) probably proceed much faster, as shown in Scheme 4.

To verify our assumption, we synthesized the tin acetal **3b** derived from Bu_2SnO and ethylene glycol[3] (Scheme 5).

In turn, the catalyst **3b** was used in the tosylation reaction of **2a** into **6a** (Table 3). As expected from our mechanistic insight, the reaction began immediately and went to completion with a catalyst loading as low as 0.05%. (Table 2).

In order to test the generality of our new methodology, several commercially available diols were subjected to the reaction conditions. Some pertinent results are outlined in Table 3.

It appears that the Sn-derivative-catalyzed reaction allows higher yields and better selectivities than the uncatalyzed reaction. Moreover, the use of tin acetal **3b** allows further decrease of

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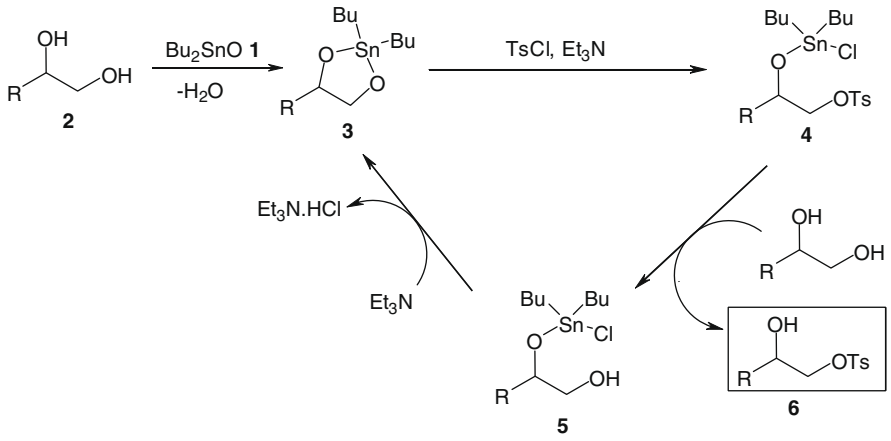
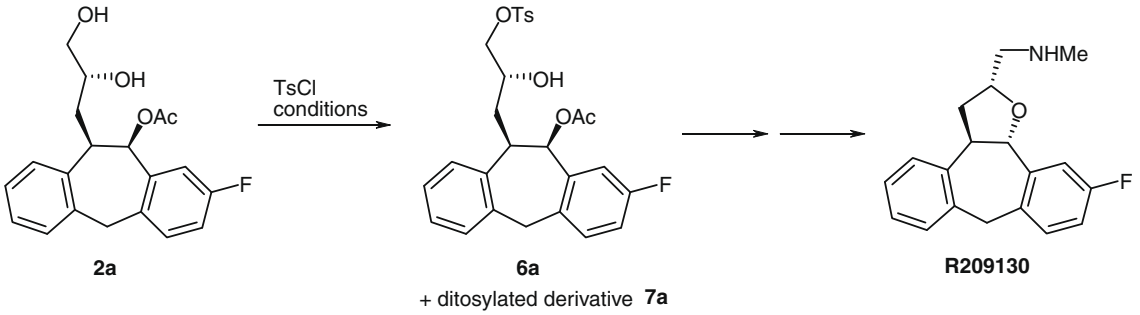


Scheme 1. Bu_2SnO-catalyzed monotosylation of a diol.[7]

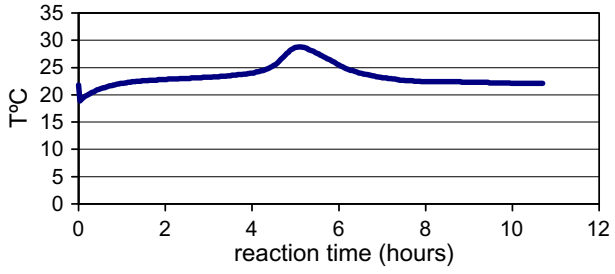


Scheme 2. Reaction of diol **2a** with TsCl.

Table 1
Optimization of reaction conditions for Bu_2SnO-catalyzed tosylation of diol **2a**

Entry	Conditions	*T* (°C)	Conversion[a]	Selectivity [**6a**]:[**7a**][a]
1	No Bu_2SnO, TsCl (1.5 equiv), pyridine (10 equiv)	25	92%	86:14
2	Bu_2SnO (10%), TsCl (1.5 equiv), Et_3N (1.5 equiv)	40	>99%	67:33[b]
3	Bu_2SnO (10%), TsCl (1.5 equiv), Et_3N (1.5 equiv)	25	>99%	90:10
4	Bu_2SnO (2%), TsCl (1.1 equiv), Et_3N (1.1 equiv)	25	>99%	94:6
5	Bu_2SnO (1%), TsCl (1.05 equiv), Et_3N (1.05 equiv)	25	>99%	94:6
6	Bu_2SnO (2%), TsCl (1.05 equiv), Et_3N (1.05 equiv)	25	>99%	96:4
7	Bu_2SnO (5%), TsCl (1.05 equiv), Et_3N (1.05 equiv)	25	>99%	96:4
8	Bu_2SnO (1%), TsCl (1 equiv), Et_3N (1.05 equiv)	25	87%	92:8
9	Bu_2SnO (0.5%), TsCl (1 equiv), iPr_2NEt (1.05 equiv)	25	97%	98:2
10	Bu_2SnO (1%), TsCl (1 equiv + 0.1 equiv), iPr_2NEt (1.05 equiv + 0.1 equiv)	25	93%	91:9
11	Bu_2SnO (0.5%), TsCl (1.1 equiv), iPr_2NEt (1.2 equiv)	25	98%	96:4
12	Bu_2SnO (0.5%), TsCl (1.05 equiv), iPr_2NEt (1.2 equiv)	25	>99%	>99:1
13	No Bu_2SnO, TsCl (1.05 equiv), iPr_2NEt (1.2 equiv)	25	Only 60% conversion after 4 days; presence of **7a** too!	
14	Bu_2SnO (0.1%), TsCl (1.05 equiv), iPr_2NEt (1.2 equiv)	25	97%	96:4
15	Bu_2SnO (0.05%), TsCl (1.05 equiv), iPr_2NEt (1.2 equiv)	25	Only 50% conversion after 16 h at rt	

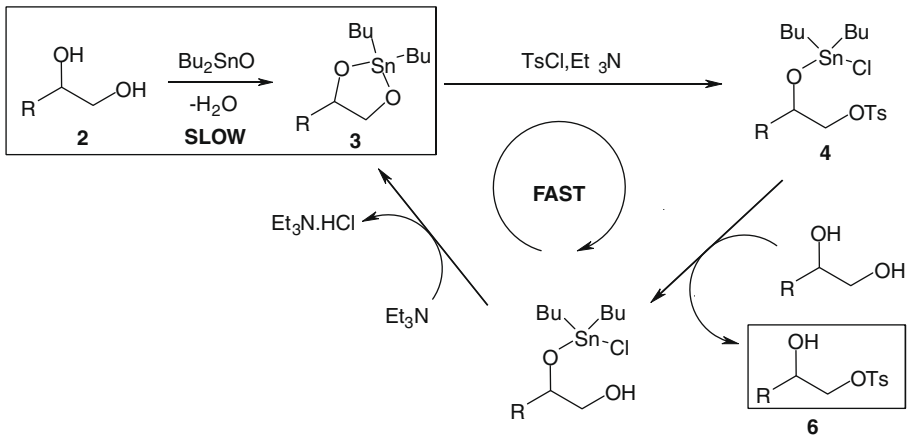
[a] HPLC, area%. Unless stated otherwise, samples were analyzed after 16 h which generally corresponds to a steady state.
[b] Formation of impurity arising mainly from ring-closure of monotosylated derivative.



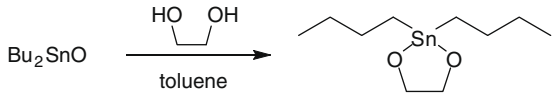
Scheme 3. Temperature evolution of the reaction.

catalyst loading, from 0.1 mol % to 0.005 mol %. Below this limit, a negative influence on the yield and/or selectively is observed.

In summary, we have shown that the loading of Bu_2SnO **1** in the tin-catalyzed selective tosylation of diols **2a** could be diminished from 2 mol % to 0.1 mol %. Moreover, the sharp exothermicity observed after 5 h led us to the hypothesis that the reactive species, the Sn acetal **3**, was formed slowly, whereas subsequent steps of the catalytic cycle were fast. In accord with this hypothesis, addition of the generic acetal **3b** instead of Bu_2SnO led to a rapid and highly selective reaction with catalyst loading that have been reduced from 0.1 mol % to 0.05 mol % and even further down to 0.005 mol % with some diol substrates.



Scheme 4. Catalytic cycle for the TsCl addition on diol **2** catalyzed by Bu_2SnO **1**.



Scheme 5. Synthesis of tin acetal derivative **3b**.

Table 2
Optimization of reaction conditions for tin acetal-catalyzed tosylation of diol **2a**

Entry	Catalyst loading [**3a**] (%)	Conversion after 24 h (%)	Selectivity [**6a**]:[**7a**]*
1	0.1	97	96:4
2	0.05	97	>99:1
3	0.005	84	>99:1

* HPLC area %.

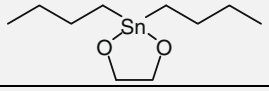
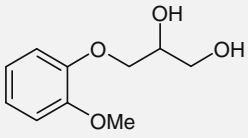
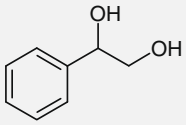
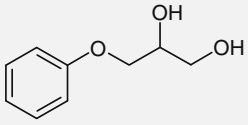
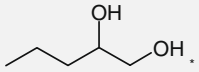
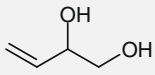
3. Experimental section

General procedures: All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen. Whereas in the lab only glass vessels were used, both steel and glass-lined vessels were used in the pilot plant. For each reaction, a sample of the reaction mixture was collected and analyzed by means of HPLC.

3.1. 2,2-Dibutyl-[1,3,2]dioxastannolane (3b)

The following experiment was only performed at lab scale (0.1 mol).

Table 3
Monotosylation reaction of commercial diols

Entry	Substrates	Uncatalyzed	Bu_2SnO (mol %)						
		0	0.1	0.1	0.05	0.01	0.005	0.001	0.0005
		%Conversion selectivity							
1		11% 64:36	96% 95:5	97% 97:3	97% 97:3	92% 98:2	94% 95:5	85% 95:5	81% 89:11
2		40% >99:1	95% 99:1	97% >99:1	98% >99:1	92% 99:1	87% 99:1	70% 96:4	/
3		41% 54:46	95% 99:1	95% 99:1	95% 98:2	96% 95:5	92% 93:7	63% 70:30	/
4		0%	93%	88%	88%	84%	83%	0	/
5		2%	85%	86%	86%	68%	/	/	/

Substrates 1–3: % conversion and selectivity are based on HPLC area%.
Substrates 4 and 5: % conversion and selectivity are based on GC area%.
* The GC chromatogram did not show any ditosylation or starting material, analysis with HPLC showed some ditosylation.

To a suspension of **1** (24.9 g, 0.1 mol) in toluene (100 ml, 1 L/mol), ethylene glycol (28 ml, 5 equiv) was added at 25 °C. Water was removed azeotropically at 110–114 °C and the reaction mixture was stirred at that temperature for 5 h. After gradual cooling (110 °C→20 °C over 12 h), the precipitate **3b** was filtered, washed with toluene (25 ml; 0.25 L/mol), and dried at 40 °C under vacuum.

Yield: 27.4 g (93%).Mp 230–231 °C.

Compound **3b** was used as such in subsequent experiments. For analytical purposes, a 10 g sample was recrystallized from toluene (40 ml, 4 ml/g) with gradual cooling (110 °C→20 °C over 10 h).

Anal. Calcd for $C_{10}H_{22}O_2Sn$: C, 41.00; H, 7.57. Found: C, 40.68; H, 7.70.

^{1}H NMR—$CDCl_3$: δ 1.0 (6H, t, J = 7.3 Hz), 1.3 (m, 4H), 1.4 (m, 4H), 1.6 (m, 4H), 3.6 (s, 4H).

3.2. Acetic acid 8-fluoro-11-[2-hydroxy-3-(toluene-4-sulfonyloxy)-propyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-10-yl ester (6a)

Laboratory procedure (0.1 mol scale).

To a solution of **2a** (34.4 g, 0.1 mol) in toluene (1.2 L/mol) was added **1** (25 mg, 0.1 mol %) at 25 °C. The mixture was stirred for 1 h. Diisopropyl ethylamine (21 ml, 1.2 equiv) was added and the reaction mixture was stirred for 5 min. Tosyl chloride (20 g, 1.05 equiv) was added and the reaction mixture was stirred at that temperature for 16 h. Hydrochloric acid 1 N (150 ml) was added and the mixture was stirred vigorously. pH of the aqueous phase = 1–2; the organic phase was filtered over sodium sulfate and used further in the next step.

Estimated yield: 80%.[12]

Pilot plant procedure (35 mol scale).

To **2a** in toluene (34 L) was added **1** (9 g, 0.25 g/mol) and the mixture was stirred at 25 °C for 1 h. *N*,*N*-Diisopropyl ethyl amine (5.0 kg, 38.4 mol) was added, followed by tosyl chloride (7.0 kg, 36.8 mol). After stirring the reaction mixture at 25 °C for 16 h, HCl 1 N (1.35 equiv) in water was added. The pH of the aqueous layer was in the range of 1–2. The organic layer was dried over Na_2SO_4 (3.5 kg), filtered, and the crude solution was used as such in the next step.

Estimated yield: 80%.

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11. The maximum *allowed* Sn content in the drug substance was 20 ppm. Because a recrystallization is performed in a subsequent step, >99.9% Sn is removed and after crystallization of the final compound, we only find 2 ppm of Sn, which corresponds to an overall removal yield of >99.99%. Sn content is determined with Inductively Coupled Plasma (ICP) methodology.
12. Compound **6a** was an oil and we did not purify or isolate it. The yield was estimated based on the 65% yield over two steps.