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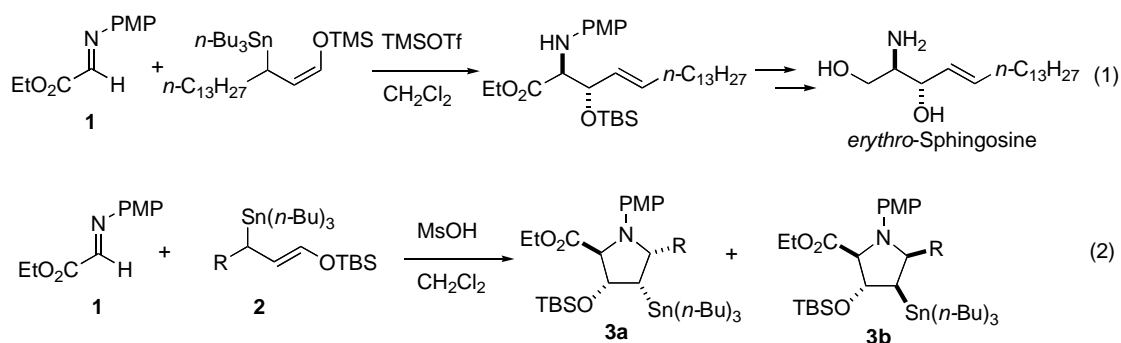
## FACILE SYNTHESIS AND RING-OPENING OF 4-(TRIBUTYLSTANNYL)PYRROLIDINE-2-CARBOXYLATES

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**Abstract** – On treatment of ethyl 2-(4-methoxyphenylimino)acetate with (*E*)-1-*tert*-butyldimethylsiloxy-3-tributylstannylalkenes in the presence of methanesulfonic acid (MsOH) at  $-78^{\circ}\text{C}$ , a ring-closing reaction proceeded to give 4-(tributylstannyl)pyrrolidine-2-carboxylates, while their ring-opening reaction was observed to give homoallylic amines under the influence of MsOH at  $-20^{\circ}\text{C}$  to room temperature.

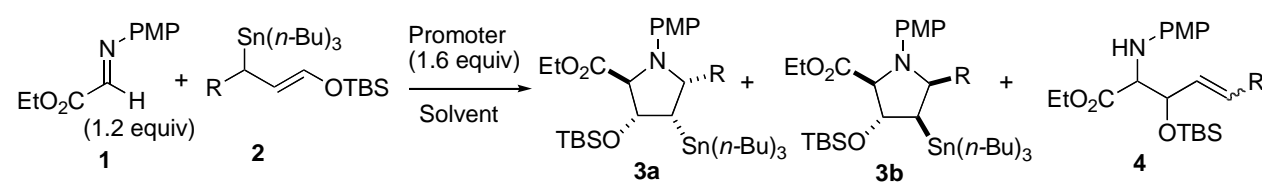
Pyrrolidine derivatives have received considerable attention as useful synthetic units for a variety of biologically intriguing materials<sup>1</sup> as well as useful catalysts for asymmetric synthesis.<sup>2</sup> We have been interested in the formation of pyrrole and pyrrolidine derivatives in a regiocontrolled manner.<sup>3</sup> We previously carried out a stereocontrolled addition of 1-*tert*-butyldimethylsiloxy-3-tributylstannylalkenes<sup>4</sup> to 2-(4-methoxyphenylimino)acetate, and this reaction was applied to the synthesis of *erythro*-sphingosine (eq 1).<sup>5</sup> During these investigations we encountered an interesting observation that under certain reaction conditions a ring-closing reaction proceeded to give 4-(tributylstannyl)pyrrolidine-2-carboxylates (**3**) as a major product (eq 2).<sup>6</sup>



**Scheme 1.** Addition of 1-trialkylsiloxy-3-tributylstannylalkenes to the imine (**1**)

This paper describes synthesis and ring-opening reaction of 4-(tributylstannyl)pyrrolidine-2-carboxylates (**3**), where allylstannanes were successfully used for the first time in the [3+2] cycloaddition with imines.<sup>7</sup> The initial examination was carried out to find the best acid activator for the formation of pyrrolidine-2-carboxylates (**3**), and Table 1 summarizes the results.

**Table 1.** Examination into the reaction conditions

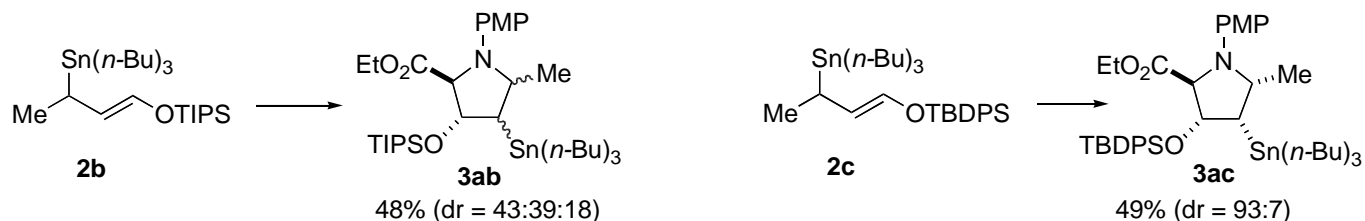


Entry	R	Promoter	Solvent	Temp (°C)	Time (min)	Yield of <b>3</b> (%) ( <b>3a:3b</b> ) <sup>a</sup>	Yield of <b>4</b> (%) (dr) <sup>a</sup>
1	Me	AlCl <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	-78	40	8 (-) <sup>b</sup>	60 (25:75)
2	Me	BF <sub>3</sub> ·Et <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	-78	20	25 (68:32)	64 (69:31)
3	Me	Et <sub>2</sub> AlCl	CH <sub>2</sub> Cl <sub>2</sub>	-78	120	12 (52:48)	32 (74:26)
4	Me	TMSOTf	CH <sub>2</sub> Cl <sub>2</sub>	-78	20	15 (71:29)	48 (69:31)
5	Me	TMSOTf	Et <sub>2</sub> O	-78 to -60	150	19 (26:74)	32 (53:47)
6	Me	TMSOTf	THF	-78	30	0	50 (56:44)
7	Me	TMSOTf	EtCN	-78 to -30	180	0	73 (61:39)
8	Me	TMSOTf	<i>n</i> -Hex	-78 to rt	1020	0	44 (58:42)
9	Me	PPTS	CH <sub>2</sub> Cl <sub>2</sub>	-78 to rt	1080	4 (-) <sup>b</sup>	23 (44:56)
10	Me	<i>p</i> -TsOH·H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	-78 to -50	120	33 (61:39)	35 (68:32)
11	Me	<i>p</i> -TsOH	CH <sub>2</sub> Cl <sub>2</sub>	-78 to -45	120	26 (66:34)	34 (68:32)
12	Me	TfOH	CH <sub>2</sub> Cl <sub>2</sub>	-78	40	36 (64:36)	57 (67:33)
13	Me	TFA	CH <sub>2</sub> Cl <sub>2</sub>	-78	30	36 (58:42)	61 (70:30)
14	Me	(+)-CSA <sup>c</sup>	CH <sub>2</sub> Cl <sub>2</sub>	-78 to -60	210	31 (65:35)	17 (66:34)
15	Me	MsOH	CH <sub>2</sub> Cl <sub>2</sub>	-78	30	64 (62:38)	28 (65:35)
16	Et	MsOH	CH <sub>2</sub> Cl <sub>2</sub>	-78	30	30 (85:15)	27 (30:70)
17	<i>n</i> -Pr	MsOH	CH <sub>2</sub> Cl <sub>2</sub>	-78	10	21 (83:17)	42 (37:63)
18	Ph	MsOH	CH <sub>2</sub> Cl <sub>2</sub>	-78	10	0	76 (17:83)
19	H	MsOH	CH <sub>2</sub> Cl <sub>2</sub>	-78	10	0	29(-) <sup>b</sup>

<sup>a</sup>Isolated yield. Ratio determined on the basis of the isolated materials and/or <sup>1</sup>H-NMR. <sup>b</sup>Ratio not determined. <sup>c</sup>(+)-Camphorsulfonic acid.

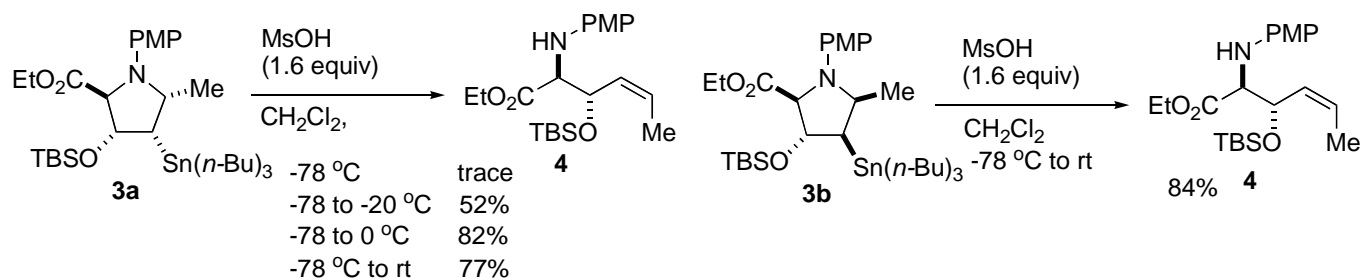
Under the influence of Lewis acids, the reaction gave the addition product (**4**) in moderate to good yields along with the pyrrolidines (**3**) in low yields (entries 1-8), in which TMSOTf was found to be the best promoter for the formation of the homoallylic amine (**4**) (entry 7). In particular, the reaction carried out in the presence of TMSOTf in relatively polar solvents or for a long time gave selectively the homoallylic amine (**4**) (entries 6-8). These observations suggested that the pyrrolidines (**3**) might undergo a ring-opening reaction to give the homoallylic amines. In contrast to the cases with Lewis acids, use of protic acids induced the formation of pyrrolidine derivatives (**3**) more effectively (entries 9-15). Among the protic acids examined methanesulfonic acid was found to be the most effective to promote the formation of the pyrrolidine (**3**) in 64% isolated yield (entry 15).<sup>8</sup> However, the pyrrolidine formation was found to have a limited generality. As can be seen from Table 1, the allylstannanes (**2**) (R = Me, *n*-Pr) gave the pyrrolidines (**3**) in low yields (entries 16 and 17), whereas formation of the pyrrolidine (**3**) was not observed with **2** (R = Ph, H), and instead, only the homoallylic amines (**4**) were obtained (entries 18 and 19).

We also examined use of other siloxyallylstannanes (**2b,c**). Both the TIPS and TBDPS derivatives (**2b,c**) gave the pyrrolidines (**3ab,ac**) in moderate yields, in which the TBDPS derivative recorded a good diastereoselectivity.



**Scheme 2.** Use of TIPS and TBDPS derivatives

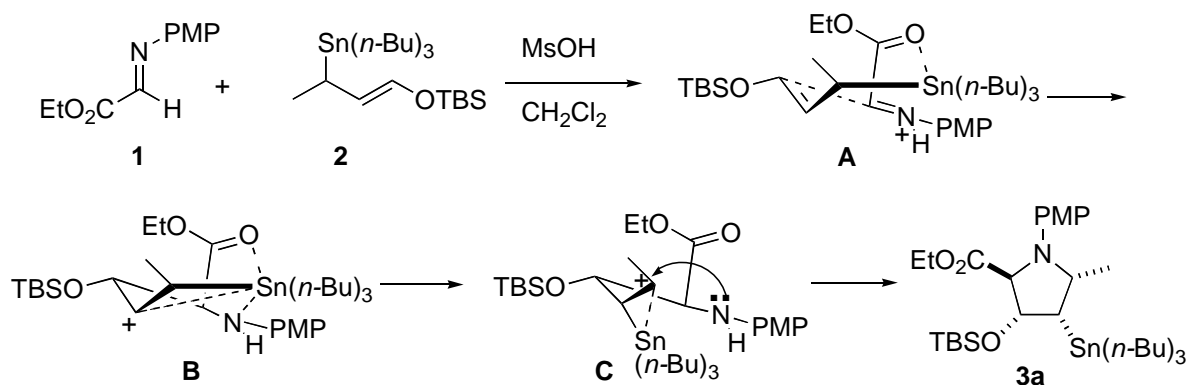
An interesting ring-opening reaction was observed with the 4-(tributylstannyl)pyrrolidine-2-carboxylates (**3a,b**). When the pyrrolidine (**3a**, R = Me) was treated with MsOH at -78 to -20 °C, the ring-opened homoallylic amine ((*Z*)-*anti*-**4**) was obtained.



**Scheme 3.** Ring-opening of pyrrolidines (**3a,b**)

The best yield (82%) was recorded in the reaction conducted at -78 to 0 °C. The same reaction with the diastereomer (**3b**, R = Me) at -78 °C to rt gave (*Z*)-*anti*-**4** in 84% yield. These results coupled with the NOE experiments<sup>9</sup> established the relative stereochemistry of the 4-(tributylstannyl)pyrrolidine-2-carboxylates (**3a,b**).

A possible reaction pathway is depicted below. First, protonation at the imino nitrogen induces the addition of the allylstannan (**2**) to form a cation intermediate (**B**), which in turn undergoes a migration of tributylstannyl group to give another cation intermediate (**C**). Cyclization gives the pyrrolidine (**3a**) as a major product.



**Scheme 4.** A possible reaction pathway

In conclusion, we have found an interesting formation of 4-(tributylstannyl)pyrrolidine-2-carboxylates from  $\gamma$ -siloxyallylstannan and  $\alpha$ -iminoacetate, where use of protic acids is crucial for this cyclization. Owing to the relatively reactive stannyl moiety, an interesting ring-opening reaction of the cyclized products was also observed at an elevated temperature to give homoallylic amines. This opening reaction may be used for the stereoselective preparation of (*Z*)-homoallylic amines. Thus, the present procedure offers a useful addition to the existing methodologies for the synthesis of highly substituted pyrrolidine-2-carboxylates in a stereocontrolled manner.

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7. [3+2] Cycloaddition using allylstannanes and  $\alpha,\beta$ -unsaturated acylirons, see: (a) J. W. Herndon, C. Wu, J. J. Harp, and K. A. Kreutzer, *Synlett*, 1991, **1**; (b) J. W. Herndon and C. Wu, *Synlett*, 1990, 411.
8. The following is a typical experimental procedure: Under an argon atmosphere, to a solution of the imine (**1**) (143 mg, 0.69 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) was added a solution of MsOH (88.4 mg, 0.92 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) at  $-78^\circ\text{C}$ . After being stirred for 10 min at  $-78^\circ\text{C}$ , a solution of (*E*)-**2** (R = Me) (276 mg, 0.58 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) was added at  $-78^\circ\text{C}$ , and the mixture was stirred at that temperature for 30 min. Sat. aq.  $\text{NaHCO}_3$  was added to quench the reaction, and the whole mixture was extracted with  $\text{Et}_2\text{O}$  (10 mL x 3). After a usual work-up, the reaction mixture was purified on preparative silica gel TLC (*n*-Hex:AcOEt = 20:1) to give **3a** ( $R_f$  = 0.26, 158 mg, 40%), **3b** ( $R_f$  = 0.35, 95 mg, 24%), and **4** ( $R_f$  = 0.21, 63.8 mg, 28% as a mixture of diastereomers in a ratio of 65:35). **3a**: Colorless oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.08 (s, 3H), 0.11 (s, 3H), 0.76-0.89 (m, 24H, including a singlet at 0.88 ppm), 1.20-1.28 (m, 9H), 1.40-1.46 (m, 9H), 1.87 (t, 1H,  $J$  = 4.8 Hz), 3.71 (s, 3H), 3.80-3.93 (m, 1H), 3.98-4.13 (m, 1H), 4.11-4.22 (m, 2H), 4.60 (t, 1H,  $J$  = 5.5 Hz), 6.38-6.42 (m, 2H), 6.78-6.83 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = -4.3, -4.6, 9.3, 13.7, 14.2, 17.9, 20.4, 25.8, 25.9, 27.5, 29.2, 40.0, 55.8, 59.3, 60.7, 72.1, 80.5, 114.8, 115.1, 139.9, 151.3, 172.4. **3b**: Colorless oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.08 (s, 3H), 0.11 (s, 3H), 0.75-0.89 (m, 24H, including a singlet at 0.86 ppm), 1.20-1.28 (m, 9H), 1.50-1.59 (m, 9H), 1.52-1.67 (m, 1H), 3.71 (s, 3H), 4.13-4.28 (m, 4H), 4.60 (br, 1H), 6.46-6.49 (m, 2H), 6.79-6.82 (m, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = -4.1, 8.5, 13.6, 21.5, 21.7, 22.0, 25.9, 27.5, 29.2, 49.3, 55.9, 58.3, 68.3, 69.7, 112.9, 114.8, 140.3, 150.9, 171.7.

9. The following NOEs were observed:

