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

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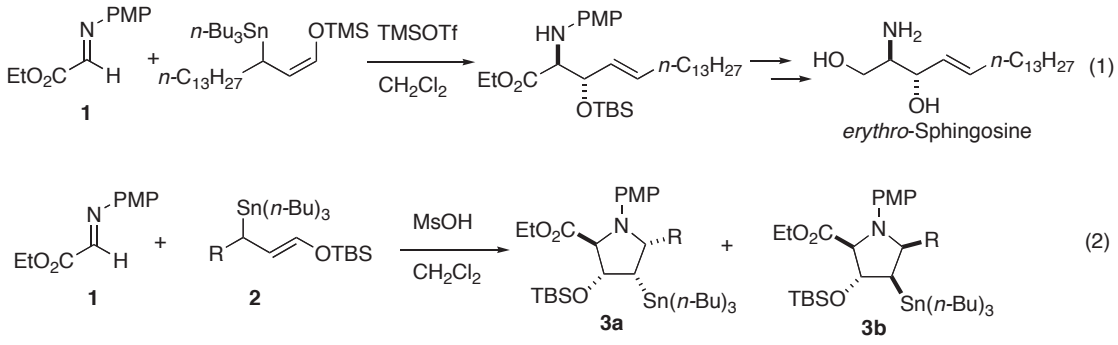
Abstract – On treatment of ethyl 2-(4-methoxyphenylimino)acetate with (*E*)-1-*tert*-butyldimethylsiloxy-3-tributylstannylalkenes in the presence of methanesulfonic acid (MsOH) *at -78 °C*, a ring-closing reaction proceeded to give 4-(tributylstannyl)pyrrolidine-2-carboxylates, while their ring-opening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

Pyrrolidine derivatives have received considerable attention as useful synthetic units for a variety of biologically intriguing materials[1] as well as useful catalysts for asymmetric synthesis.[2] We have been interested in the formation of pyrrole and pyrrolidine derivatives in a regiocontrolled manner.[3] We previously carried out a stereocontrolled addition of 1-*tert*-butyldimethylsiloxy-3-tributylstannylalkenes[4] to 2-(4-methoxyphenylimino)acetate, and this reaction was applied to the synthesis of *erythro*-sphingosine (eq 1).[5] 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).[6]

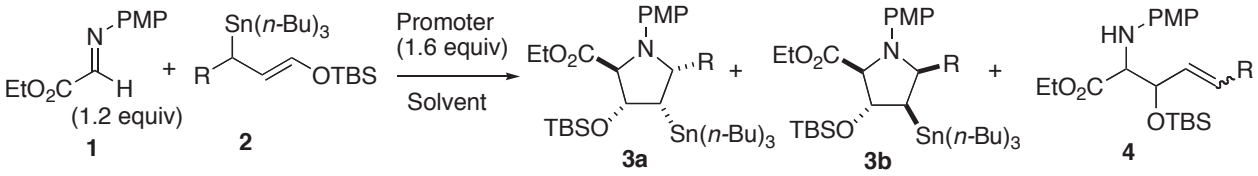


Scheme 1. Addition of 1-trialkylsiloxy-3-tributylstannylalkenes to the imine (**1**)

This paper is dedicated to Professor Akira Suzuki on the occasion of his 80th birthday.

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.[7] 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

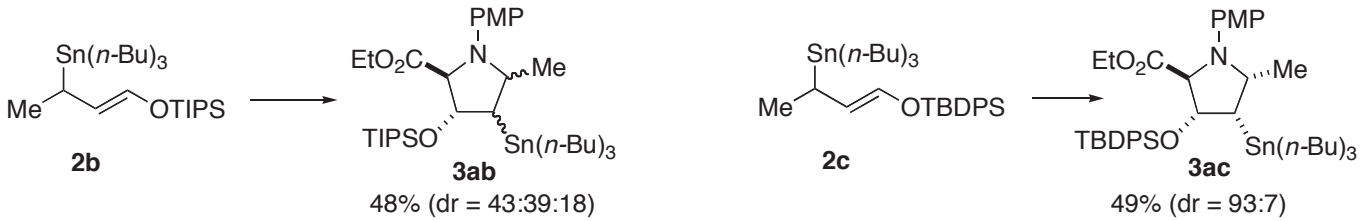


Entry	R	Promoter	Solvent	Temp (°C)	Time (min)	Yield of **3** (%) (**3a**:**3b**) [a]	Yield of **4** (%) (dr) [a]
1	Me	$AlCl_3$	CH_2Cl_2	-78	40	8 (-) [b]	60 (25:75)
2	Me	$BF_3{\cdot}Et_2O$	CH_2Cl_2	-78	20	25 (68:32)	64 (69:31)
3	Me	Et_2AlCl	CH_2Cl_2	-78	120	12 (52:48)	32 (74:26)
4	Me	TMSOTf	CH_2Cl_2	-78	20	15 (71:29)	48 (69:31)
5	Me	TMSOTf	Et_2O	-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	*n*-Hex	-78 to rt	1020	0	44 (58:42)
9	Me	PPTS	CH_2Cl_2	-78 to rt	1080	4 (-) [b]	23 (44:56)
10	Me	*p*-$TsOH{\cdot}H_2O$	CH_2Cl_2	-78 to -50	120	33 (61:39)	35 (68:32)
11	Me	*p*-TsOH	CH_2Cl_2	-78 to -45	120	26 (66:34)	34 (68:32)
12	Me	TfOH	CH_2Cl_2	-78	40	36 (64:36)	57 (67:33)
13	Me	TFA	CH_2Cl_2	-78	30	36 (58:42)	61 (70:30)
14	Me	(+)-CSA [c]	CH_2Cl_2	-78 to -60	210	31 (65:35)	17 (66:34)
15	Me	MsOH	CH_2Cl_2	-78	30	64 (62:38)	28 (65:35)
16	Et	MsOH	CH_2Cl_2	-78	30	30 (85:15)	27 (30:70)
17	*n*-Pr	MsOH	CH_2Cl_2	-78	10	21 (83:17)	42 (37:63)
18	Ph	MsOH	CH_2Cl_2	-78	10	0	76 (17:83)
19	H	MsOH	CH_2Cl_2	-78	10	0	29(-) [b]

[a]Isolated yield. Ratio determined on the basis of the isolated materials and/or ^{1}H-NMR. [b]Ratio not determined. [c](+)-Camphorsulfonic acid.

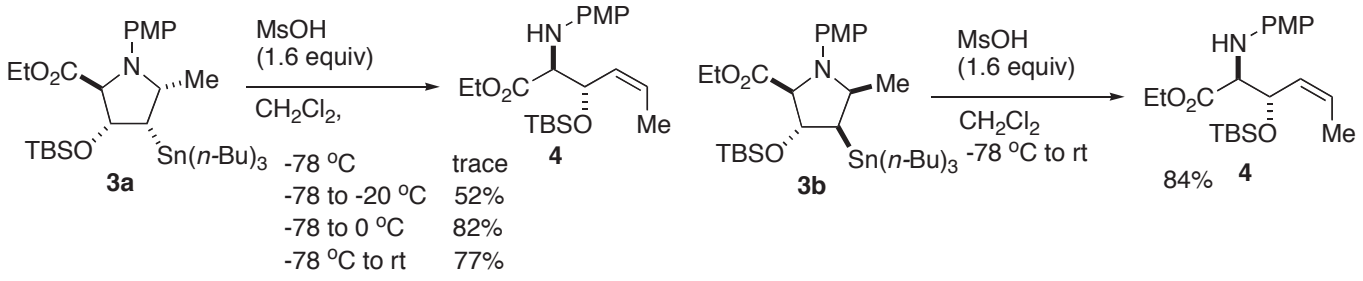
Under the influence of Lewis acids, the reaction gave the addition product (**4**) in moderate to good yields along with the pyrrolidines (**3**) in low yields (entries 1-8), in which TMSOTf was found to be the best promoter for the formation of the homoallyic amine (**4**) (entry 7). In particular, 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).[8] 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

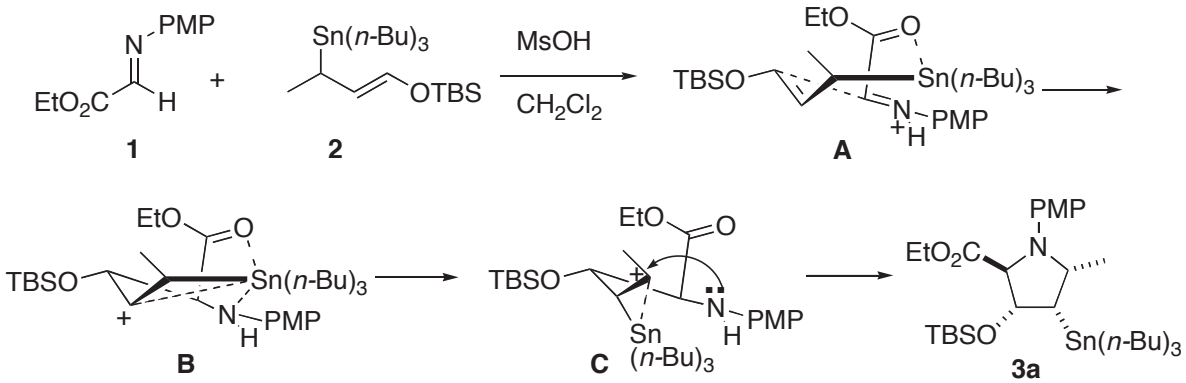
An interesting ring-opening reaction was observed with the 4-(tributylstannyl)pyrrolidine-2-carboxylates (**3a**,**b**). When the pyrrolidine (**3a**, R = Me) was treated with MsOH at -78 to -20 °C, the ring-opened homoallylic amine ((*Z*)-*anti*-**4**) was obtained.



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

The best yield (82%) was recorded in the reaction conducted at -78 to 0 ºC. The same reaction with the diastereomer (**3b**, R = Me) at -78 ºC to rt gave (*Z*)-*anti*-**4** in 84% yield. These results coupled with the NOE experiments[9] 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 γ-siloxyallylstannan and α-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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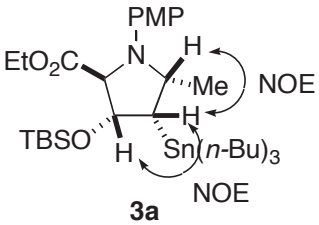
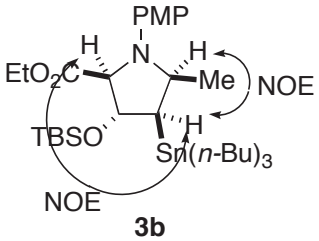
6. Similar cyclizations using allylsilanes, see: (a) N. Shindoh, H. Tokuyama, Y. Takemoto, and K. Takasu, *Heterocycles*, 2009, **77**, 187; (b) T. Akiyama, M. Sugano, and H. Kagoshima, *Tetrahedron Lett*., 2001, **42**, 3889; (c) S. Kiyooka, Y. Shiomi, H. Kira, Y. Kaneko, and S. Tanimori, *J. Org. Chem*., 1994, **59**, 1958; (d) J. S. Panek and N. F. Jain, *J. Org. Chem*., 1994, **59**, 2674.
7. [3+2] Cycloaddition using allylstannanes and α,β-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 CH_2Cl_2 (0.5 mL) was added a solution of MsOH (88.4 mg, 0.92 mmol) in CH_2Cl_2 (0.5 mL) at -78 ºC. After being stirred for 10 min at -78 ºC, a solution of (*E*)-**2** (R = Me) (276 mg, 0.58 mmol) in CH_2Cl_2 (1.0 mL) was added at -78 ºC, and the mixture was stirred at that temperature for 30 min. Sat. aq. $NaHCO_3$ was added to quench the reaction, and the whole mixture was extracted with Et_2O (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}H NMR (500 MHz, $CDCl_3$): δ = 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}C NMR (126 MHz, $CDCl_3$): δ = -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}H NMR (500 MHz, $CDCl_3$): δ = 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}C NMR (126 MHz, $CDCl_3$): δ = -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:



3a



3b