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Observations on Sn-Li Exchange in α-Aminoorganostannanes and the Configurational Stability of Non-stabilized α-Aminoorganolithiums

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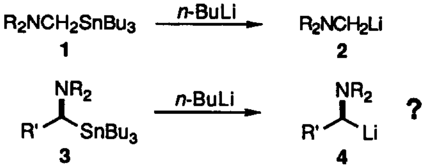
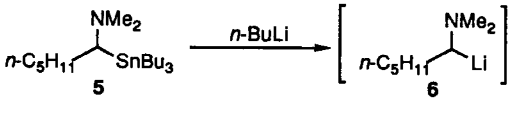
Abstract: α-Aminoorganostannanes undergo Sn-Li exchange to form carbanions which may be trapped with electrophiles if the amine moiety contains a methoxyethyl group. The α-aminoorganolithiums formed are configurationally stable for short times at low temperatures.

It was demonstrated over twenty years ago that aminomethylstannanes **1** undergo Sn-Li exchange to form aminomethyllithiums **2**.[1] However, the generation of secondary carbanions **4** from "non-stabilized"[2-4] substituted organostannanes **3** has not been reported. In principle, if organostannanes **3** could be prepared in enantiomerically pure form and if they behaved as α-alkoxyorganostannanes do (*i.e.* transmetalation/trapping proceed with retention of configuration[5]), they could be very useful for the asymmetric synthesis of amines. We now report that stannanes **3** may be successfully transmetalated if the amine contains a methoxyethyl group. Furthermore, the aminoorganolithiums formed are not as configurationally stable as α-alkoxyorganolithiums but may still be synthetically useful as they can be generated and trapped with complete retention of configuration at -95 °C.



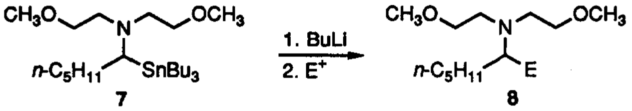
R, R' = alkyl

The simple N,N-dimethylaminoorganostannane **5** was easily prepared by treatment of the corresponding bromostannane[6] with Me_2NH (DMF, rt, 12 h). However, all attempts to generate and trap organolithium **6** were unsuccessful. At low temperatures (-78 °C, THF), no observable reaction occurred with *n*-BuLi and only stannane **5** was recovered; at higher temperatures (0 °C), stannane **5** was consumed and tetrabutyltin was formed but no other products were isolated from the reaction mixture. It is possible that the intermediate secondary organolithium **6** (as opposed to the primary organolithium **2**), which is inductively destabilized by the alkyl group, is unstable and decomposes before it can be trapped with electrophiles.



In an effort to form a more stable intermediate organolithium, the amine **7** containing methoxy groups that might provide intramolecular co-ordination was prepared. Stannane **7** underwent clean transmetalation upon treatment with *n*-BuLi (THF, -78 °C, 10 min), and the intermediate organolithium could be trapped with electrophiles (Table 1). When the electrophiles used were Me_2SO_4 or aldehydes, reasonable yields of trapped products were isolated; however, enolizable ketones provided only protonated product **8a**. Thus it seemed that "non-stabilized" secondary α-aminoorganolithiums may be prepared by Sn-Li exchange if a methoxyethyl group is present.

Table 1. Reaction of the Organolithium Derived from 7 with Electrophiles[a]



Entry	E^+	Product	E	Yield of **8** (%)[b]
1	MeOH	**8a**	H	76
2	Me_2SO_4	**8b**	Me	76
3	n-$C_5H_{11}CHO$	**8c**	n-$C_5H_{11}CH(OH)$	64[c]
4	PhCHO	**8d**	PhCH(OH)	48[d]
5	$ClCO_2Me$	**8e**	CO_2Me	78
6	MeC(O)Me	**8a**	H	90
7	$(CH_2)_5C(O)$	**8a**	H	79

[a] Reactions were run in THF at -78 °C with 1.1 eq of *n*-BuLi.

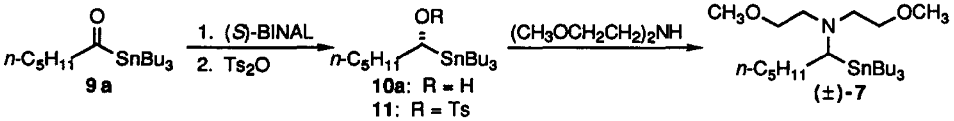
[b] Isolated yields.

[c] Isolated as a 2:1 mixture of diastereomers.

[d] Isolated as a 1:1 mixture of diastereomers.

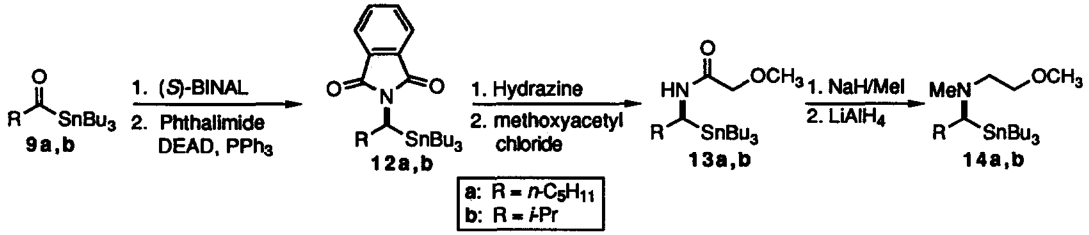
In order to study the configurational stability of such α-aminoorganolithiums, a route to enantiomerically enriched aminostannanes was required. Hence the sequence shown in Scheme 1 was carried out. Although hydroxystannane **10a** was readily prepared in 96% ee[7], conversion of **10a** to tosylate **11**, and treatment with $(MeOCH_2CH_2)_2NH$ provided aminostannane **7** in racemic form. This observed racemization was initially quite unexpected but may be due to an S_N1-like displacement occurring in the reaction of the amine with stannane **11**.

Scheme 1



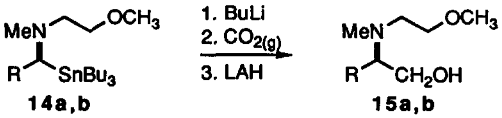
Fortunately, enantiomerically-enriched aminostannanes may be accessed via Mitsunobu chemistry.[8] The sequence shown in Scheme 2 was carried out and furnished stannanes **14a** and **14b** in 94% ee.

Scheme 2



Stannane **14a** readily underwent transmetalation (1.1 eq *n*-BuLi, THF, -95 °C, 10 min) to form the corresponding organolithium. The configurational stability of this organolithium was assessed by transformation to β-amino alcohol **15a** (CO_2; LAH) and HPLC analysis of MTPA[9] esters. Results are shown in Table 2. It may be seen that conversion of **14a** to **15a** may be carried out with high overall efficiency and complete retention of configuration if the intermediate organolithium is generated at low temperatures (-95 °C) and quickly

Table 2. Configurational Stability of Organolithiums Derived from Stannanes **14a** and **14b**[a]



Entry	R	Solvent	Temp (°C)	Time[b] (min)	Yield of 15[c] (%)	ee[d] (%)
1	*n*-C_5H_{11}	THF	-95	10	95	94
2	*n*-C_5H_{11}	THF	-95	180	48	90
3	*n*-C_5H_{11}	THF	-78	20	70	83
4	*n*-C_5H_{11}	DME	-78	20	77	27
5	*n*-C_5H_{11}	DME	-78	20	44	25[e]
6	*i*-Pr	DME	-78	20	57	0[e]

[a] Stannanes **14a** and **14b** were each of 94% ee (based on HPLC analysis of MTPA[9] amides of the 1° amine precursors.) Reactions were run with 1.1 eq of *n*-BuLi unless otherwise noted.

[b] Time between addition of *n*-BuLi and CO_2 (g).

[c] Isolated yields of chromatographed products.

[d] Determined by HPLC (silica, CH_2Cl_2-EtOAc, 9:1 for **15a**) or ^{19}F NMR (for **15b**) analysis of MTPA[9] esters.

[e] Reaction was run with 5 eq of *n*-BuLi.

treated with CO_2 (entry 1). After 3 h at -95 °C (entry 2), a slight deterioration in enantiomeric purity was observed along with a dramatic decrease in yield, presumably reflecting slow racemization along with decomposition of the organolithium. At a slightly higher temperature (-78 °C, entry 3), marked racemization occurred even after only 20 min. Under the same reaction conditions (-78 °C, 20 min), but with DME instead of THF as solvent, considerably more racemization was observed (entry 4). This degree of configurational stability is comparable to, but slightly less than, that recently noted for *t*-BOC protected α-aminoorganolithiums.[10]

The more sterically hindered stannane **14b** proved to be more resistant to transmetalation. Essentially no reaction was observed in THF with 1.1 eq of *n*-BuLi; only partial (~50%) reaction took place with 5 eq of *n*-BuLi, -78 °C). With a large excess (5 eq) of *n*-BuLi in DME, >90% reaction was noted but the amino alcohol eventually isolated was completely racemic (Table 2, entry 6). Under the same reaction conditions, stannane **14a** gave rise to alcohol **15a** with 25% ee. Thus it seems that stannane **14b** is not only more difficult to transmetalate than **14a** but the derived organolithium is also more configurationally labile.

In summary, "non-stabilized" secondary aminoorganolithiums may be prepared from α-aminoorganostannanes in selected cases. In addition, such organolithiums may be sufficiently configurationally stable that they may be useful as enantiomerically-enriched nucleophilic reagents.

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