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Stereoselective Anionic Cyclizations to Pyrrolidines

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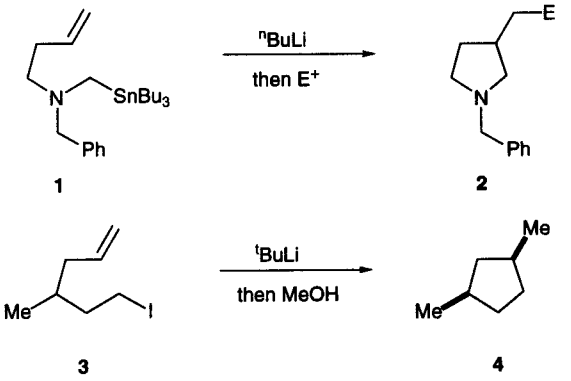
Abstract: Cyclization of α-amino-organolithiums onto unactivated alkenes results in the formation of 2,4-disubstituted pyrrolidines with high selectivities in favour of the *cis* isomers. The use of the α-methylbenzyl chiral auxiliary on the nitrogen atom gives rise to 3-substituted pyrrolidines with up to 58% d.e. Without the chiral auxiliary, enantioselectivities in the presence of (-)-sparteine are poor. © 1997 Elsevier Science Ltd.

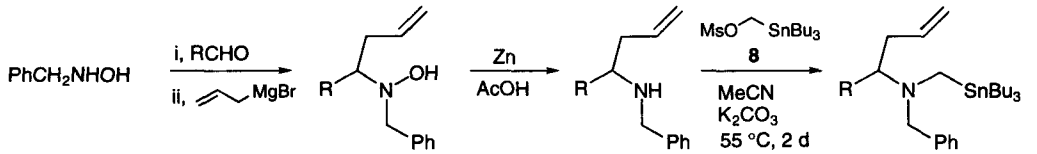
We have recently reported that aminomethyllithiums, generated by tin-lithium exchange from the stannane **1**, cyclize onto an unactivated alkene to give 3-substituted pyrrolidine products.[1-3] A variety of electrophiles can be used to trap the intermediate 3-lithiomethylpyrrolidine to give the products **2**. We wished to extend the versatility of this anionic cyclization by preparing disubstituted pyrrolidines and thereby explore the stereoselectivity of the cyclization. We report here the influence of a substituent α-to the nitrogen atom (either *endo* or *exo* to the forming ring) and the enantioselectivity on addition of the chiral ligand (-)-sparteine.

Bailey has shown that disubstituted cyclopentanes can be formed with very high stereoselectivities using an anionic cyclization.[4] For example, iodine-lithium exchange of the iodide **3** with *tert*-butyllithium, followed by trapping with methanol, results in the formation of 1,3-dimethylcyclopentane **4** (98%, 10:1 *cis*:*trans*). Anionic cyclization to 2,4-disubstituted tetrahydrofuran derivatives has also been shown to proceed with high *cis* selectivity.[5]



In order to investigate the levels of selectivity on anionic cyclization to five-membered cyclic amines, we needed access to α-substituted homoallylic amines. These were prepared by addition of allylmagnesium bromide to nitrones generated from *N*-benzylhydroxylamine **5**. Cleavage of the *N-O* bond by zinc/acetic acid under ultrasonic conditions gave the desired homoallylic amines **7a-c** (Table 1). Initial attempts to

alkylate the homoallylic amines **7** with iodomethyltributyltin[6] gave only recovered starting material. This is in contrast to the formation of the unsubstituted aminomethylstannane **1**, which proceeds smoothly with this reagent.[3] An alternative procedure, reported by Pearson and Katritzky,[7] using formaldehyde and benzotriazole resulted in [3,3]-aza-Cope rearrangement, rather than the formation of the benzotriazolylmethyl derivative. We therefore needed a new method for alkylation of the amines **7**. This was accomplished using the mesylate **8**, prepared from the corresponding alcohol and methanesulfonic anhydride.[8]

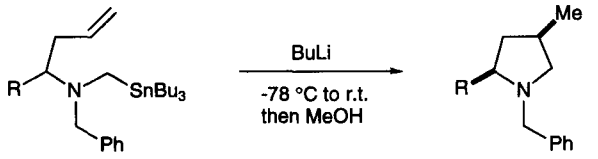


5 **6** **7** **9**

Table 1 Preparation of the stannanes 9

Entry	*R*	*Yield* **6** (%)	*Yield* **7** (%)	*Yield* **9** (%)
a	Me	85	82	57
b	^{n}Bu	52	78	45
c	^{i}Pr	89	94	14

Treatment of the stannane **9a** (R=Me) with two equivalents of *n*-butyllithium in THF gave, as expected, the pyrrolidine **10a** after quenching with methanol (Table 2). Only the *cis* isomer of **10a** was isolated under these conditions and it was not possible to observe (by ^{1}H NMR spectroscopy) any *trans* isomer.[9] This result verifies the expected *cis* selectivity. In contrast, the stannanes **9b**,**c** did not transmetallate under these conditions. The use of hexane-ether as solvent necessitated warming the reaction mixture to room temperature in order to effect transmetallation and cyclization. Under these conditions all three stannanes **9a-c** cyclized in good yield and with preference for the *cis* isomer of the pyrrolidines **10a-c**.



9 **10**

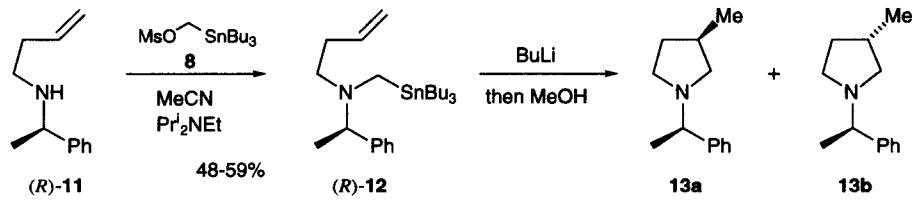
Table 2 Cyclization of the stannanes 9

		THF		Hexane-Et_2O (10:1)	
Entry	*R*	*Yield* **10** (%)	*cis:trans*	*Yield* **10** (%)	*cis:trans*
a	Me	46	>25:1	78	7:1
b	^{n}Bu	–[a]	–	50	6:1
c	^{i}Pr	–[a]	–	74	6:1

[a]Starting material **9** recovered

The difference in reactivity between the two types of solvents suggests that there are two pathways for the formation of the organolithium intermediate. In THF it is likely that a pentacoordinate stannate complex is preferred, which breaks down by loss of the most stable organolithium species (the α-amino-organolithium). However, in the less polar hexane-ether mixtures (in which transmetallation is much slower and requires warming to room temperature), a concerted transmetallation may be taking place.[10] The lower levels of selectivity in the less polar hexane-ether solvent system can be ascribed to the fact that cyclization is occurring at room temperature rather than at -78 °C in THF (for **9a**). Trapping the lithiomethylpyrrolidine intermediates with a variety of electrophiles should access different 2,4-disubstituted pyrrolidines.[2,3]

We next investigated the influence of a chiral centre *exo* to the newly-forming ring. The α-methylbenzyl substituent has recently been reported to promote very high selectivities in a related zinc enolate cyclization.[11] The stannanes (*R*)- and (*S*)-**12** were prepared by alkylation of the amines (*R*)- and (*S*)-**11** using mesylate **8**. Transmetallation and cyclization using *n*-butyllithium was effective in either THF or hexane-ether and resulted in good yields of the pyrrolidines **13a** and **13b** (Table 3). The amount of *n*-butyllithium used did not affect the yield or diastereoselectivity of the cyclization.



(*R*)-**11** (*R*)-**12** **13a** **13b**

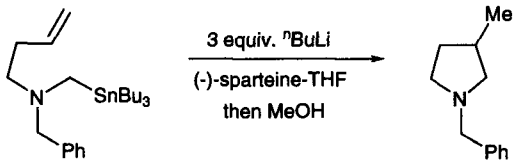
Table 3 Cyclization of the stannane 12

Entry	**12**	*equiv. BuLi*	*Conditions*	*Yield* **13** (%)	*Ratio* **13** *(d.e.)*
1	(*R*)	1.1	THF, -78 °C	78	74:26 (48)
2	(*R*)	3	THF, -78 °C	78	74:26 (48)
3	(*R*)	2	Hexane-Et_2O (10:1), 0 °C	73	50:50 (0)
4	(*R*)	3	Hexane-Et_2O (10:1), (-)-sparteine-Et_2O, 0 °C	86	50:50 (0)
5	(*R*)	3	Hexane-Et_2O (10:1), (-)-sparteine-THF, -78 °C	79	77:23 (54)
6	(*R*)	3	THF (-)-sparteine-THF, -78 °C	74	79:21 (58)
7	(*S*)	3	Hexane-Et_2O (10:1), (-)-sparteine-THF, -78 °C	73	45:55 (10)

Transmetallation and cyclization in THF at -78 °C resulted in the pyrrolidines **13a** and **13b** in approximately 3:1 ratio (48% d.e.).[12] Using hexane-Et_2O (-78 °C to 0 °C, 4 h) a 1:1 mixture of the diastereomers **13** was formed (entry 3). Addition of *n*-butyllithium/(-)-sparteine complex (dissolved in Et_2O) did not alter the diastereomer ratio (entry 4). In contrast, addition of ^nBuLi/(-)-sparteine dissolved in THF promoted transmetallation and cyclization at -78 °C (entry 5). The low temperature reaction must be due to the presence of the solvent THF. Similar results are obtained in the absence of hexane-Et_2O (entry 6). The addition of (-)-sparteine in THF therefore causes a small but significant increase in the ratio of

diastereomers. The major diastereomer was identified as pyrrolidine **13a** after hydrogenolysis of the α-methylbenzyl group and comparison of the optical rotation with the known (*R*)-3-methylpyrrolidine.[13] The mis-matched case, using stannane (*S*)-**12**, caused a loss of selectivity to -10% d.e. (entry 7).

We were interested to determine whether the presence of (-)-sparteine in the cyclization of the unsubstituted stannane **1** would result in enantioselective carbon-carbon bond formation. Somewhat disappointingly, but not unexpectedly, the cyclization took place with only low levels of enantioselectivity (26-28% e.e.) (Table 4). The use of normal or inverse addition of stannane **1** gave similar results. The enantioselectivity was determined by chiral shift ^{1}H NMR spectroscopy using the Pirkle solvating agent.[14]



1 **2**, E=H

Table 4 Cyclization of the stannane 1 in the presence of (-)-sparteine

Entry	*Conditions*	*Yield* **2**, E=H (%)	*Ratio* **2**, E=H *(e.e.)*
1	THF, -78 °C	74	63:37 (26)
2	THF, -78 °C[a]	74	64:36 (28)
3	Hexane-Et_2O (10:1), -78 °C	84	64:36 (28)
4	Hexane-Et_2O (10:1), 0 °C[b]	82	64:36 (28)

[a]Inverse addition; [b](-)-Sparteine in Et_2O.

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