Anionic Cyclizations of α-Aminoorganolithiums. Determination of the Stereoselectivity at the Carbanion Center and the Synthesis of (+)-Pseudoheliotridane

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The recent interest in the configurational stability of α-aminoorganolithiums by a number of research groups[1] has led to the discovery that at low temperatures both a tin−lithium exchange and quench by an external electrophile can proceed with complete configurational stability at the carbanion center. Reactions occurring with retention, inversion, and racemization of configuration are known.[1] Recently, Gawley[2] has reported that inversion of configuration occurs at the α-aminocarbanion center during a [2,3]-sigmatropic rearrangement. In this communication we report the first example of the stereoselectivity at the carbanion center during an anionic cyclization. In addition, we report the first remarkable example of an α-aminoorganolithium which is configurationally stable at room temperature.

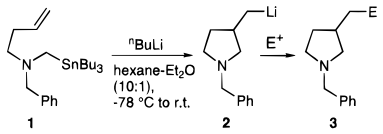
Anionic cyclizations of organolithiums[3] and other organometallics[4] onto alkenes are now a well-established method for the construction of cyclic compounds, in particular for the preparation of carbocycles. The methodology has been extended to the preparation of heterocycles such as tetrahydrofurans[5] and to a lesser extent to pyrrolidines.[5b,d,6] The cyclization proceeds through a two-electron process (rather than a radical pathway), in which the metal coordinates to the alkene prior to cyclization.[3i] Bailey has shown that the new organolithium species, formed by cyclization of a 5-hexenyllithium (prepared using iodine−lithium exchange with *t*-BuLi), can be trapped with a range of electrophiles.[3d,h,l,n] We have prepared α-aminoorganolithiums by tin−lithium exchange and have shown that these cyclize onto unactivated alkenes to give pyrrolidines.[6a,b] To our knowledge, there have been no reports of anionic cyclizations onto alkenes in which the carbanion is generated at a chiral center in enantiomerically-pure form.[6c] The ability to prepare such a configurationally-stable organolithium using tin−lithium exchange[1] led us to determine the stereoselectivity of anionic cyclizations. We describe in this communication (i) the first examples of the extension of anionic cyclizations to the preparation of a range of 3-substituted pyrrolidines, by capture of the organolithium with a variety of electrophiles, (ii) a configurationally stable carbanion at room temperature, (iii) that anionic cyclizations proceed with complete retention of stereochemistry at the carbanion center, and (iv) the use of this methodology for the very short, enantiospecific synthesis of (+)-pseudoheliotridane and other related pyrrolizidine ring systems.

Table 1. Synthesis of 3-substituted pyrrolidines **3**

E^+	E	product	yield (%)
MeOH	H	**3a**	72
Me_4Sn[a]	$SnMe_3$	**3b**	68
PhCHO	CH(OH)Ph	**3c**	90
$H_2C{=}CHCHO$	$CH(OH)CH{=}CH_2$	**3d**	71
^{t}BuCHO	$CH(OH)Bu^t$	**3e**	52
MeCHO	CH(OH)Me	**3f**	68
$H_2C{=}CHCH_2Br$	$CH_2CH{=}CH_2$	**3g**	58
CD_3OD	D	**3h**	73
$Ph_2C{=}O$	$C(OH)Ph_2$	**3i**	82

[a] THF Solvent; Me_4Sn added at −78 °C before warming to room temperature.

The stannane **1**, on treatment with *n*-butyllithium in THF, gave the pyrrolidine **3a**, E = H. Both tin-lithium exchange and anionic cyclization had therefore proceeded smoothly to give the resulting organolithium **2**, which was protonated to give the



product **3a**. This result suggested that the intermediate organolithium **2** could be trapped with electrophiles, the results of which are given in Table 1. When the cyclizations were conducted in THF, the product pyrrolidines **3c**−**i** were contaminated with significant amounts of the 3-methylpyrrolidine **3a** (presumably through competitive protonation by the solvent[7]). On switching to the less polar hexane−ether mixture, this problem was reduced or even eliminated and good yields of the pyrrolidines **3** were obtained. In the less polar solvent system, transmetallation did not take place below 0 °C and optimum conditions involved warming to room temperature for 3 h before recooling to −78 °C and adding the electrophile. Addition of aldehydes gave a mixture (1:1 to 2:1) of the two diastereomeric alcohol products.

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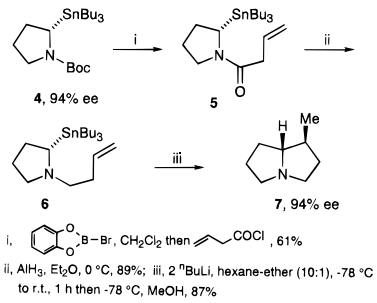
In order to test the stereospecificity of the anionic cyclization at the carbanion center, the stannane **6** was prepared from the known[1b] stannane **4**. Stannane **4** was prepared according to



Beak, and its optical rotation corresponded with the literature value[1b,h] for an enantiomeric excess of 94%, $[\alpha]_D$ −136 (*c* 2.7, $CHCl_3$). This was confirmed by removal of the Boc group using *B*-bromocatechol borane[8] and trapping with (*S*)-(−)-PhC(OMe)-(CF_3)COCl (MTPA-Cl) to verify the high enantiomeric excess. Removal of the Boc group and trapping with but-3-enoyl chloride gave the amide **5**. Reduction with AlH_3 (or $LiAlH_4$) gave the amine **6**. Transmetallation of the amine **6** with *n*-butyllithium in hexane−ether (10:1) (−78 °C to room temperature) and trapping the resulting organolithium with methanol gave the pyrrolizidine alkaloid (+)-pseudoheliotridane **7** as a single diastereomer.[9,10] The optical rotation of **7** was measured as $[\alpha]_D$ +6.8 (*c* 0.5, EtOH) [lit.[10e,11] $[\alpha]_D$ +7.0 (*c* 0.5, EtOH)]. Chiral shift studies[12] confirmed the high enantiomeric ratio (94% ee) and that there had been no loss of enantiomeric purity. This is a notable result as it represents the first configurationally-stable α-aminoorganolithium at room temperature. This presumably arises due to the nonpolar, poor donor nature of the solvent and chelation of the lithium atom to the alkene, followed by intramolecular anionic cyclization at room temperature. Gawley[2] has recently reported an α-aminoorganolithium possessing "remarkable configurational and chemical stability". In his case an alkene also was present, which presumably stabilizes the organolithium such that at 13 °C for 2 h the enantiomeric excess had dropped only to 65%.

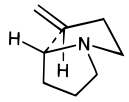


Figure 1.

Table 2. Synthesis of Pyrrolizidines **8**

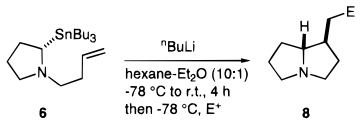
E^+	E	product	yield (%)
CD_3OD	D	**8a**	50
$Ph_2C{=}O$	$C(OH)Ph_2$	**8b**	62
Me_3SiCl	$SiMe_3$	**8c**	63
PhCHO	CH(OH)Ph	**8d**	41[a]

[a] **8d** was a mixture (1:1) at the alcohol center.

In our case, transmetallation occurs slowly (1−2 h) at this temperature, and there is no loss in optical purity.

Anionic cyclization of amine **6** completes a short (four steps from *N*-Boc pyrrolidine), efficient and enantioselective synthesis of (+)-pseudoheliotridane, together with the determination that anionic cyclizations proceed with complete retention of configuration at the carbanion center. The anionic cyclization of amine **6** gives a single diastereomer **7**, as expected from related anionic cyclizations[3e] with the preference for reaction *via* a chairlike conformation (Figure 1). This places the two hydrogen atoms *trans* to each other, resulting in the formation of pseudoheliotridane, rather than its diastereomer heliotridane. This is in contrast to the related radical cyclization which is known to give racemic heliotridane and very little of the diastereomer pseudoheliotridane.[13]

The ability to trap the organolithium, resulting from the anionic cyclization, with a range of electrophiles has led to the synthesis of the derivatives **8** of pseudoheliotridane, as shown



in Table 2.[14] Further anionic cyclizations−electrophilic quenches will allow the synthesis of a variety of cyclic amine products with stereochemical control.

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Supporting Information Available: A procedure for the anionic cyclization, electrophilic quench of aminomethylstannane **1**, and spectroscopic data for compounds **3a**−**i**, **5**−**7**, and **8a**−**d** (8 pages). Ordering information is given on any current masthead page.

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(9) ^1H NMR (300 MHz) indicates a ratio of >98:2 for the two diastereomers pseudoheliotridane and heliotridane, based on the doublet for the CH_3 group for pseudoheliotridane picrate 1.21 ppm; lit.[10] 1.23 ppm, heliotridane picrate 1.14 ppm.

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(12) The Pirkle solvating agent [(*R*)-(−)-9-anthryl-2,2,2-trifluoroethanol] splits the CH_3 group of pseudoheliotridane in the ^1H NMR spectrum (see supporting information).

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(14) We have not been able to determine the enantioselectivity of the cyclizations to the derivatives **8**. It is anticipated, however, that there would be no loss of optical purity [*e.g.* **8b** $[\alpha]_D$ +19.6 (*c* 0.5, EtOH)], as the external electrophilic quench occurs after stereospecific cyclization.