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Synthesis of Pyrrolidines by Anionic Cyclization onto Allylic Ethers, Alkynes and Carboxylic Groups

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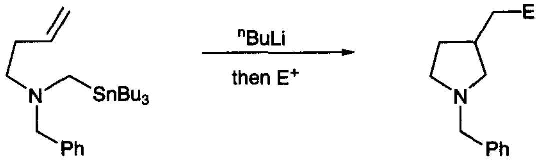
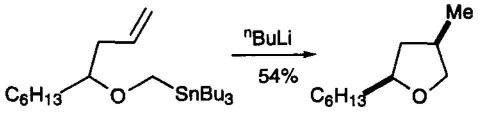
Abstract: α-Amino-methylstannanes with pendent allylic ether, alkyne or carboxylic groups, can be converted, on treatment with butyllithium, to 3-vinyl-, 3-methylene- or 3-keto-pyrrolidines by anionic cyclization. © 1997 Elsevier Science Ltd.

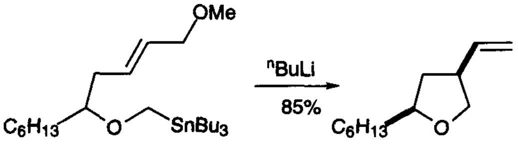
Anionic cyclizations are becoming increasingly popular for the preparation of carbocyclic and heterocyclic ring systems.[1] We have found that the stannane **1**, on transmetallation with butyllithium, gives the 3-substituted pyrrolidine products **2** after electrophilic quench.[2-4] The intermediate α-amino-methyllithium cyclizes onto the unactivated alkene to give the 3-lithiomethylpyrrolidine, which can be trapped with electrophiles. We wished to investigate the possibility that the α-amino-methyllithium would cyclize onto other functional groups, thereby giving rise to a wider variety of 3-substituted pyrrolidines. We report here successful cyclizations onto allylic ether, alkyne, carboxylic amide and carboxylate groups.

Broka has shown that anionic cyclizations onto allylic ethers proceed with greater efficiency than the corresponding cyclization onto an unactivated alkene.[5] For example, the vinyltetrahydrofuran **6** is formed in considerably improved yield in comparison with the methyltetrahydrofuran **4**. The vinyl group also provides a useful functional group for further manipulation. Lautens has reported further examples of such methodology towards heterocycles.[6]



1 **2**

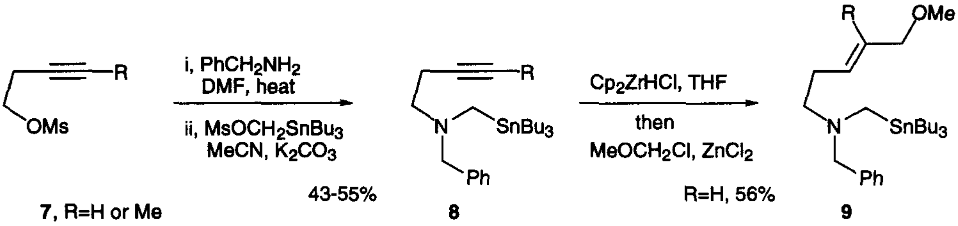




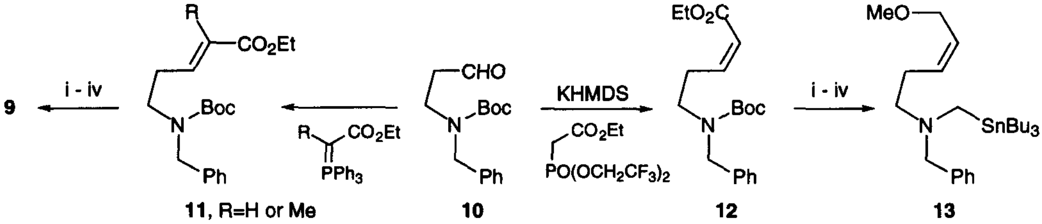
3 **4** **5** **6**

In order to test the feasibility of preparing cyclic amines by such anionic cyclizations, we have investigated two methods for the preparation of the substrates **9**, R=H and Me (Schemes 1 and 2). The shorter of these two approaches involved the carbometallation of the alkyne **8** using a procedure reported by

Srebnik and co-workers.[7] Only the desired regioisomer **9** was formed, as a single stereoisomer, using the alkyne **8**, R=H. Carbometallation of the alkyne **8**, R=Me resulted in low yields of the product **9**, R=Me. An alternative approach to the substrates **9**, R=H and Me makes use of standard Wittig chemistry from aldehyde **10**[8] (Scheme 2). This approach also allowed the preparation of the stereoisomeric alkene *Z*-**13**.



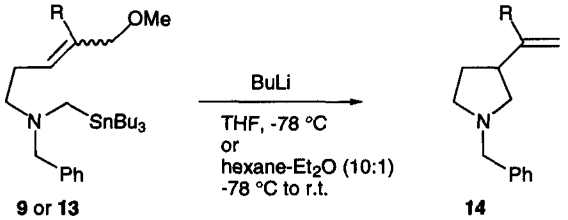
Scheme 1



i, DIBAL, PhMe (90-94%); ii, NaH, MeI (92-96%); iii, TFA (100%); iv, $MsOCH_2SnBu_3$ (48-70%)

Scheme 2

We were pleased to find that treatment of the stannanes **9** or **13** with two equivalents of *n*-butyllithium in THF or hexane-Et_2O (10:1) gave the pyrrolidines **14**, R=H or Me (Scheme 3). The cyclization proceeds in good yield, particularly in hexane-Et_2O, with either the *E* or the *Z* isomer (Table 1). Of significance is the fact that the alkene can be trisubstituted (R=Me), despite the fact that alkyl substituents at the position of build-up of negative charge disfavour anionic cyclization.[5,9]

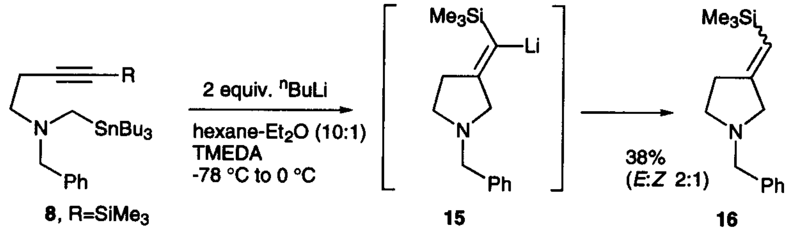


Scheme 3

Table 1 Cyclization of the stannanes 9 and 13

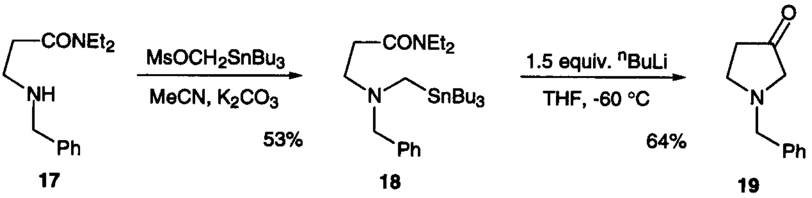
Compound	*Stereoisomer*	*R*	*Yield* **14** *(%) using THF*	*Yield* **14** *(%) using hexane-Et_2O (10:1)*
9	*E*	H	55	81
9	*E*	Me	22	64
13	*Z*	H	–	79

The alkynes **8** were prepared *en route* to the allylic ethers **9**, as outlined in Scheme 1. Bailey has shown that anionic cyclizations onto alkyl-, aryl- or silyl-substituted alkynes to give cyclopentanes work well.[10] However, treatment of the alkynes **8**, R=H or Me with butyllithium did not give any pyrrolidine products. We therefore prepared the alkyne **8**, R=$SiMe_3$ in which an anion-stabilising group was present at the terminus of the triple bond. Anionic cyclization using butyllithium gave the *E*- and *Z*-3-trimethylsilyl-methylene pyrrolidines **16** as a mixture of stereoisomers (Scheme 4). It is likely that anionic cyclization occurs to give initially only the *E*-vinyllithium **15**, which can isomerise to the *Z*-isomer.



Scheme 4

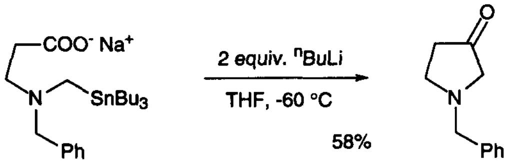
Finally, we have investigated the possibility that the α-amino-organolithium would cyclize onto a carbonyl group. Anionic cyclizations of organolithiums onto carboxylic amide groups have been documented.[11] We therefore prepared the carboxylic amide **18** by addition of benzylamine to *N*,*N*-diethyl acrylamide, followed by alkylation of the resulting secondary amine **17** with *O*-methanesulfonyl-tributylstannylmethanol (Scheme 5). Transmetallation was very sluggish in the less polar hexane-Et_2O mixes. Satisfactory results were obtained using THF as the solvent, with warming from -78 °C to -60 °C, giving rise to *N*-benzyl-3-keto-pyrrolidine **19**.



Scheme 5

Brief studies using a carboxylic ethyl ester group as the electrophile resulted in preferential attack by *n*-butyllithium onto the carbonyl group, rather than tin-lithium exchange. Attempts, however, to effect cyclization using a carboxylate group as the electrophile were successful (Scheme 6).[12] Treatment of the salt **20** with two equivalents of butyllithium in THF resulted in the formation of the pyrrolidine **19**. Therefore, the carboxylic amide or carboxylate groups are both suitable electrophiles, disfavouring intermolecular, but allowing intramolecular addition with an organolithium species.

Further studies on the anionic cyclization of α-amino-organolithium species onto various electrophiles and the application of this methodology to the preparation of target cyclic amines is in progress and will be reported in due course.



20 **19**

Scheme 6

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