Pergamon

*Tetrahedron Letters*, Vol. 36, No. 12, pp. 2157-2160, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00200-6

# A New Route to Cyclic Amines by Anionic Cyclization

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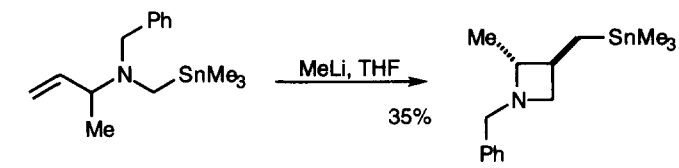
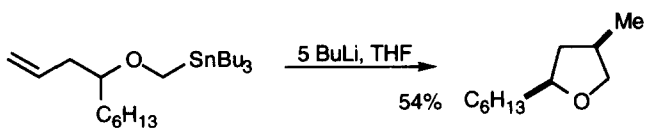
**Abstract :** Transmetallation of an aminomethylstannane gives rise to an aminomethyllithium which undergoes an anionic cyclization onto an unactivated alkene. The resulting organolithium reincorporates trimethyltin to give the product cyclic amine. The cyclization can be promoted with a catalytic amount of methyllithium. The trimethyltin group in the product can be cleaved using ceric ammonium nitrate.

In the early 1970's Peterson reported the transmetallation of a range of aminomethylstannanes and the subsequent trapping of the so-formed aminomethyllithiums with benzaldehyde.[1] This methodology has been exploited recently by a number of groups[2] for the stereo- and enantiocontrolled synthesis of amines. Here we report the intramolecular cyclization of aminomethyllithiums, generated by tin-lithium exchange, onto unactivated alkenes.

During work on the aza-Wittig rearrangement,[3] we discovered that the aminomethylstannane **1** cyclizes to the azetidine **2** on treatment with methyllithium (rather than undergoing a 1,2- or 2,3-sigmatropic shift). Anionic cyclizations of organolithiums onto unactivated alkenes have been investigated by Bailey[4] and others.[5,6] The related cyclizations of stannylmethylethers have been reported by Broka,[5] who obtained the tetrahydrofuran **4** from the stannane **3** with excess butyllithium. In this case the tin group had not been reincorporated (other than as a minor by-product).




**1** **2**

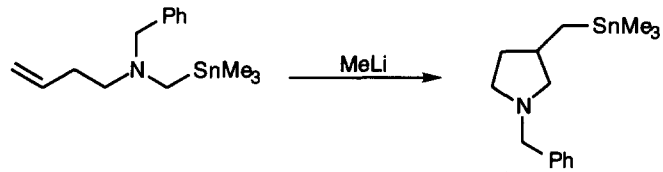



**3** **4**

In order to probe the potential for using anionic cyclizations to prepare five-membered cyclic amines, the desired aminomethylstannanes were prepared by alkylation of the secondary amine *N*-benzyl-4-amino-1-butene with iodomethyltrialkyltin.[7] Treatment of the homoallylic amine **5** with one equivalent of

methyllithium gave, as expected, the pyrrolidine **6**. Table 1 outlines an investigation of this cyclization under a range of conditions.

**Table 1 Optimization of the cyclization of amine 5**

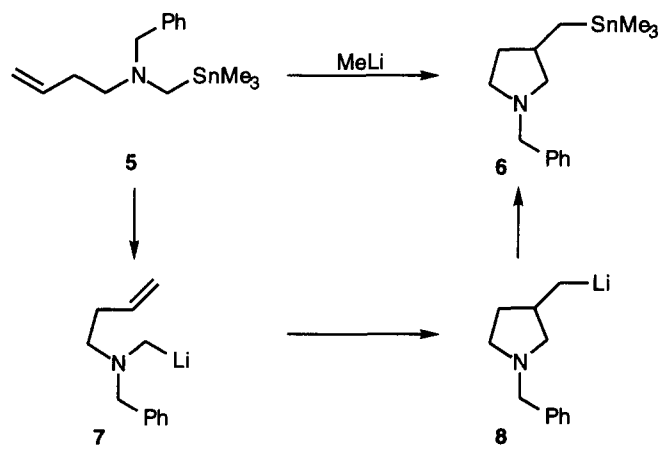



**5** **6**

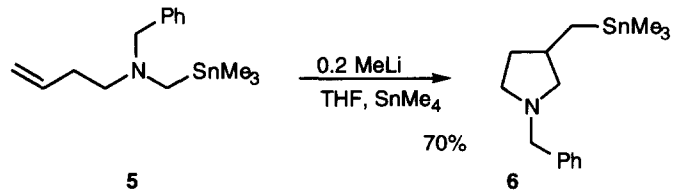
| *Entry* | *Solvent* | *Conditions* | *Yield (%)* |
|---|---|---|---|
| 1 | THF | -78 to 0 °C | 55 |
| 2 | THF, TMEDA | -45 to 0 °C | 51 |
| 3 | TMEDA | -45 to 0 °C | 44 |
| 4 | DME | -45 to 0 °C | 47 |
| 5 | Diglyme | -45 to 0 °C | 41 |
| 6 | $Et_2O$ | -78 °C to room temp. | 16[a] |
| 7 | Hexane | -78 °C to room temp. | — |
| 8 | THF (2 equiv. $SnMe_4$) | -78 to 0 °C | 72 |
| 9 | Hexane-$Et_2O$ (3:2) | -78 °C to room temp. | 40[a] |
| 10 | Hexane-$Et_2O$ (10:1) | -78 °C to room temp. | 12[a] |

[a]Pyrrolidine **10** was also isolated (19-47%)

The transformation of aminomethylstannane **5** into pyrrolidine **6** presumably occurs by way of the aminomethyllithium **7**. Cyclization onto the alkene results in the formation of the organolithium **8** which reincorporates the trimethyltin group to give the product **6**. The addition of two equivalents of tetramethyltin (entry 8) improves the yield of the pyrrolidine **6**, suggesting that the organolithium **8** incorporates the tin group from tetramethyltin.



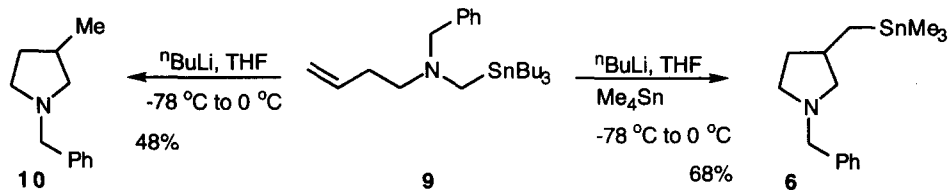
The overall transformation of **5** into **6** is a rearrangement and can be promoted with 0.4 equivalents of methyllithium (THF, -78 °C to 0 °C, 54%) or even with 0.2 equivalents of methyllithium in the presence of $SnMe_4$ (THF, -78 °C to 0 °C, 70%). The use of a catalytic amount of methyllithium is interesting as this avoids the use of stoichiometric amounts of the most reactive reagent in this process.




**5** **6**

Quenching the reaction at -78 °C indicates that both the transmetallation and cyclization occur at -78 °C in THF. The use of hexane alone does not promote transmetallation and in diethyl ether or in mixtures of hexane-diethyl ether transmetallation is slow. In these solvent systems the mixture must be warmed to at least 0 °C for transmetallation (and hence cyclization) to occur. The new organolithium **8** must pick up the trimethyltin group slowly in the less polar solvent. No products resulting from 1,2-Wittig rearrangement of the *N*-benzyl group were observed. Attempted cyclization with an *N-tert*-butyloxycarbonyl group rather than the *N*-benzyl group gave only the protodestannylated product.

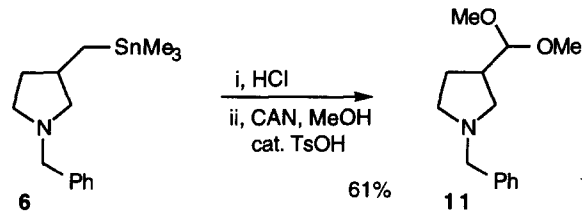
The corresponding aminomethylstannane **9** (with a tributyltin rather than a trimethyltin group) cyclizes to the pyrrolidine **10**. Reincorporation of the tin group takes place only to a minor extent (<10%), probably because of the steric bulk of the tributyltin group. Addition of two equivalents of tetramethyltin, however, allows the formation of the pyrrolidine **6** in good yield.[8]




**10** **9** **6**

The use of methyllithium to transmetallate the organostannane **9** gave the same product pyrrolidine **10**. This can be compared with the use of butyllithium to transmetallate the organostannane **5**, which gave a new pyrrolidine, in which reincorporation of the butyldimethyltin group had taken place. No pyrrolidine **6** with the trimethyltin group was observed. This result suggests that the cyclized organolithium **8** picks up the tin group from butyltrimethyltin with displacement of methyllithium rather than butyllithium. This is in accord with the known[9] order of stability of alkyllithiums (MeLi > BuLi).

Attempts to cleave the trimethyltin group from the product pyrrolidine **6** were made using ceric ammonium nitrate (CAN),[10] bromine followed by mCPBA,[11] ozone,[12] iodosylbenzene[13] and chromium trioxide.[14] Of these, the only success was obtained using CAN in methanol, which gave the pyrrolidine **11** (25%). The addition of a catalytic amount of *p*-TsOH improved the yield to 37%, but the initial formation of the hydrochloride salt of the pyrrolidine **6** followed by the use of CAN in methanol with catalytic *p*-TsOH gave the product **11** with a more respectable yield (61%).




Acknowledgements: We thank the E.P.S.R.C. for a studentship (to R.H.).

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(*Received in UK* 21 *December* 1994; *accepted* 27 *January* 1995)