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5-*Exo* versus 6-*Endo* Intramolecular Carbolithiation of *N*-Allyl-*N*-(2-lithioallyl)amines

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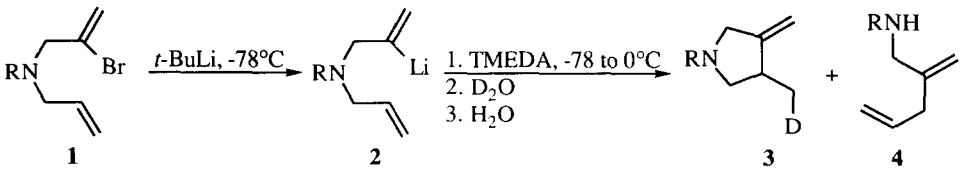
Abstract: *N*-Allyl-*N*-(2-lithioallyl)amines undergo intramolecular carbometallation *via* 5-*exo* or 6-*endo* addition. The course of the reaction depends on the nitrogen electron density. 3-Functionalized-4-methylenepyrrolidines can be synthesized. © 1997 Published by Elsevier Science Ltd.

The formation of ring systems by intramolecular carbolithiation of unsaturated alkyllithiums is an interesting synthetic transformation and provides a convenient route to five-membered carbocycles.[1] This methodology has been extended to the preparation of heterocycles such as tetrahydrofurans[2] and pyrrolidines[3] from α-alkoxy and α-aminoorganolithium compounds, respectively. On the other hand, cyclizations of vinyllithiums, rather than alkyllithiums, would also incorporate additional functionality (an alkene) into the product.[4] The intramolecular addition of vinyllithium reagents to unactivated alkenes is limited to the formation of five membered rings and only small amounts of the six-membered ring products, derived from 6-*endo* closure, are observed in some cases.[5] In this context, aryllithiums have been described to carbometallate double bonds allowing the preparation of indanes,[6] 2-cyclopropylphenol,[7] and indolines.[8] Recently we have reported the zirconium-promoted intramolecular cyclization of *N*-allyl-*N*-(2-lithioallyl)amines to afford 8-unsubstituted zirconabicyclopentenes which can be further elaborated.[9] In the present communication we describe the carbolithiation of *N*-allyl-*N*-(2-lithioallyl)amines that proceeds *via* 5-*exo* or 6-*endo* depending on the substituents bound to the nitrogen atom and the synthesis of 3-functionalized 4-methylenepyrrolidines.

Treatment of *N*-allyl-*N*-(2-bromoallyl)amines **1** with 2 eq. of *tert*-butyllithium at -78°C afforded the vinyllithium derivatives **2**.[10] These anions were stable in diethyl ether for several hours, but when 2.2 eq. of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) were added at low temperature they undergo intramolecular addition to the double bond, after removal of the cooling bath and allowing the reaction mixture to stand at 0°C. However, the outcome of the reaction depends strongly on the nature of the starting amine. So, when the reaction was carried out with **2a**, methylenepyrrolidine **3a** was obtained as the only product after deuteriolysis. Pyrrolidine derivative **3b** was also obtained when the organolithium **2b** was used as starting material. However, the treatment of **2d** and **2e** with TMEDA under the same reaction conditions led, after deuteriolysis and further hydrolysis, to minor amounts of the pyrrolidine derivatives **3d** and **3e**, but rather to the 2-methylene-4-pentenylamines **4d** and **4e**, respectively. Finally, in the case of **2c** the quenching of the reaction furnished a nearly equimolecular mixture of pyrrolidine **3c** and the secondary amine **4c** (Scheme 1).



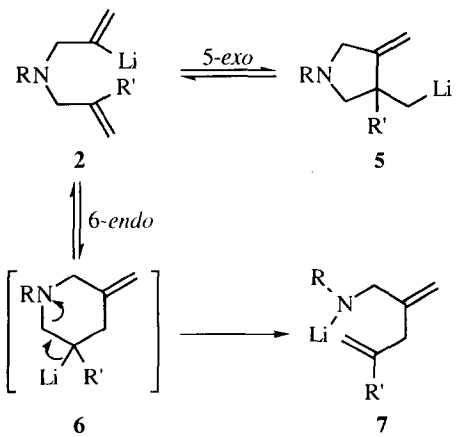
1 2 3 4

	R			Yield (%)
a	$PhCH_2$	100	0	86
b	c-C_6H_{11}	100	0	83
c	4-$MeOC_6H_4$	50	50	79
d	Ph	10	90	88
e	4-ClC_6H_4	10	90	81

Scheme 1

The formation of pyrrolidines **3** could be understood by assuming an insertion of the alkene moiety into the C-Li bond in a regiospecific 5-*exo-trig* process,[11] which generates lithiomethylpyrrolidine derivatives **5**. Their deuteriolysis leads to the deuteriated compounds **3**. Products **4** could be obtained by a 6-*endo-trig* cyclization that affords the organolithium compounds **6**, which undergo immediately a β-elimination process to give lithium amides **7**, which furnish compounds **4** after hydrolysis (Scheme 2).

The variation of the behaviour of **2** depending on the substituents bound to the nitrogen atom, could be explained on the basis of the different availability of the lone pair of the nitrogen. The ratio of the products **3** and **4** correlates with the basicity of the starting amine. The less electron density is on the nitrogen, the more favored is the product of 6-*endo* closure. In this context, in order to prepare the corresponding primary amine of type **4** , we have observed that the anion derived from *N*-Allyl-*N*-(2-bromoallyl)-*p*-toluenesulfonamide undergoes at -78°C a spontaneous β-elimination reaction to afford *N*-Allyl-*p*-toluenesulfonamide.



2 5 6 7

Scheme 2

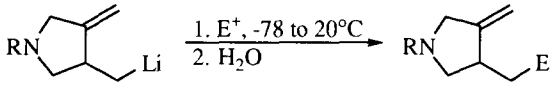
As far as we know, there are no examples of 6-*endo* ring closure in the anionic cyclization of unsaturated organolithiums. Chamberlin *et al.* have reported[5] that varying yields of methylenecyclohexanes, from 6-*endo*

closure, were obtained when the "normal" lithiomethylcyclopentanes, from 5-*exo* addition, were kept for longer times.

In order to explain these results, we suggest a simple reversion of the kinetically favored 5-*exo* product **5** to the starting vinyllithium **2**, followed by a 6-*endo* closure followed by an irreversible β-elimination of the β-nitrogen functionalized organolithium **6** (Scheme 2).[12]

In this way, when the reaction of **2** (R=Ph, R'=Me) was quenched with D_2O after 40 min at 0°C, a 3:2 mixture of deuteriated compounds corresponding to intermediates **2** and **5** along with small amounts of the hydrolysis product of secondary amide **7** (R=Ph, R'=Me) was obtained. However, when the mixture was allowed to stir at 0°C for 2h, quenching with D_2O and further hydrolysis, afforded the amine corresponding to the amide **7** (R=Ph, R'=Me) and no pyrrolidine compounds were detected. In this case, the intramolecular addition of the vinyllithium to a gem-disubstituted alkene was slower than the unsusbstituted case,[13] and this result seems to show that the initially 5-*exo-trig* addition is reversible (Scheme 2).

In order to further extend the synthetic utility of the initially formed intermediate **5** we have explored its reaction with electrophiles. So, treatment at low temperature of lithiated pyrrolidines **5a** and **5b**, derived from aliphatic amines, with different electrophiles (chlorotrimethylsilane, tri-*n*-butyltin chloride, diphenyl disulfide, benzophenone) affords, after hydrolysis and purification by column chromatography, 3-substituted-4-methylenepyrrolidines **8** in good yields[14] (Scheme 3).



5

a R=$PhCH_2$
b R=c-C_6H_{11}

8

	R	E	Yield (%)
aa	$PhCH_2$	$SiMe_3$	77
ab	$PhCH_2$	$SnBu_3$	71
ac	$PhCH_2$	SPh	74
ad	$PhCH_2$	$C(OH)Ph_2$	75
ba	c-C_6H_{11}	$SiMe_3$	73
bb	c-C_6H_{11}	$SnBu_3$	70

Scheme 3

In conclusion we have described the first 6-*endo* intramolecular carbolithiation of a terminal alkene *versus* the more favored 5-*exo* addition, due to a lower electron density on the nitrogen atom in aromatic amines. Moreover, functionalized pyrrolidines have been synthesized using this methodology.

Acknowledgements

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References and Notes

1. (a) Bailey, W. F.; Ovaska, T. V. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 3, Mechanisms of Importance in Synthesis, pp. 251-273, (b) Bailey, W. F.; Patricia, J. J.; Del Globo, V. C.; Jarret, R. M.; Okarma, P. J. *J. Org. Chem.* **1985**, *50*, 1999-2000, (c) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442-2448, (d) Bailey, W. F.; Rossi, K. *J. Am. Chem. Soc.* **1989**, *111*, 765-766, (e) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thid, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720-5727, (f) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K. V. *J. Am. Chem. Soc.* **1992**, *114*, 8053-8060.
2. (a) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336-1338, (b) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981-2984, (c) Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954-1964.
3. (a) Coldham, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1275-1276, (b) Coldham, I.; Hufton, R. *Tetrahedron Lett.* **1995**, *36*, 2157-2160, (c) Coldham, I.; Hufton, R. *J. Am. Chem. Soc.* **1996**, *118*, 5322-5323.
4. (a) Chamberlin, A. R.; Bloom, S. H. *Tetrahedron Lett.* **1986**, *27*, 551-554, (b) Bailey, W. F.; Jiang, X.-L., McLeod, C. E. *J. Org. Chem.* **1995**, *60*, 7791-7795.
5. Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788-4796.
6. Ross, G. A.; Koppang, M. D.; Bartak, D. E.; Woolsey, N. F. *J. Am. Chem. Soc.* **1985**, *107*, 6742-6743.
7. Bailey, W. F.; Punzalan, E. R. *Tetrahedron Lett.* **1996**, *37*, 5435-5436.
8. (a) Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1996**, *61*, 2594-2595, (b) Bailey, W. F.; Jiang, X.-L. *J. Org. Chem.* **1996**, *61*, 2596-2597.
9. Barluenga, J.; Sanz, R.; Fañanás, F. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1009-1010.
10. (a) Corey, E. J.; Cane, D. E.; Libit, L. *J. Am. Chem. Soc.* **1971**, *93*, 7016-7021, (b) Barluenga, J.; Foubelo, F. Fañanás, F.J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 553-557, (c) Barluenga, J.; Canteli, R. M.; Flórez, J. *J. Org. Chem.* **1994**, *59*, 602-606, 1586-1588.
11. *Exo* and *endo* are defined according to Baldwin's system; Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.
12. Alternatively, the 5-*exo* product could rearrange to the 6-*endo via* a cyclopropyl derivative. See ref. 5.
13. (a) Bailey, W. F.; Khanolkar, A. D. *J. Org. Chem.* **1990**, *55*, 6058-6061, (b) Bailey, W. F.; Khanolkar, A. D. *Tetrahedron* **1991**, *47*, 7727-7738. Cyclization of 1,2-disubstituted alkenes is only possible with an activating group such as phenyl, trimethylsilyl, or cyclopropyl: Bailey, W.F.; Gavaskar, K. V. *Tetrahedron* **1994**, *50*, 5957-5970.
14. All the yields refer to isolated chromatographically pure compounds whose structures have been confirmed by IR, HRMS, ^{1}H and ^{13}C NMR data.

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