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Cyclization by Intramolecular Carbolithiation of Alkyl- and Vinyllithiums Prepared by Reductive Lithiation: Surprising Stereochemistry in the Lithium Oxyanion Accelerated Cyclization

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The intramolecular addition of alkyl- and vinyllithiums to unactivated alkenes is rapidly growing in popularity as a preparative method for cyclopentylmethyllithiums, their heterocyclic analogues and, less effectively, the corresponding six-membered rings.[1] However, despite the highly significant work of Bailey and others, the method still has considerable limitations. A major one is the lack of general methods for preparing the organolithium. For the most part, the generation methods can only be used for primary organolithiums or those with special stabilizing features such as adjacent heteroatom groups that direct lithiations or sp^2 character of the carbon atom bearing the lithium. In most cases, the organolithium is produced by halogen−lithium or tin−lithium exchange or by heteroatom-directed lithiation. Another limitation is the paucity of functionality in the cyclized product in most cases.

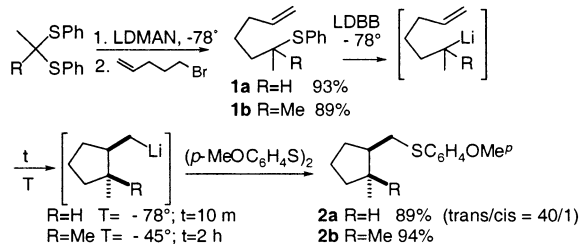
We now demonstrate the potential for very greatly extending the versatility of this cyclization method (1) by generating the organolithiums by reductive lithiation of phenyl thioethers with aromatic radical anions such as lithium 1-dimethylaminonaphthalenide (LDMAN) and 4,4′-di-*tert*-butylbiphenylide (LDBB)[2,3] and (2) by using allylic or homoallylic alcohol groups on the receiving alkene. This type of reductive lithiation allows virtually any kind of organolithium to be generated, usually in a connective manner. Furthermore, the allylic or homoallylic oxyanionic groups on the alkene *greatly accelerate the reaction and lead in most cases to completely stereoselective cyclization at −78°*. Of course, the cyclization product contains the useful alcohol function in addition to the lithiomethyl group.

Scheme 1 shows what was, when it was performed, the first example of a tertiary carbanionic cyclization[4] and it occurs at a far lower temperature than that at which such cyclizations are usually performed. It should be noted that the unique properties of sulfur allow rapid construction of the substrates **1** from the thioacetals of acetaldehyde and acetone. The high trans selectivity in the cyclization of the secondary organolithium derived from **1**a was also found by Bailey for the same organolithium produced, however, by I−Li exchange.[5]

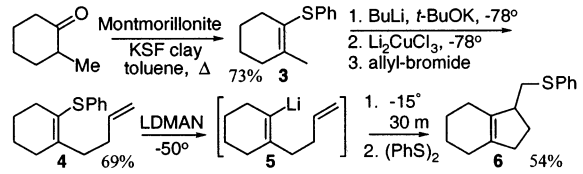
The versatility of reductive lithiation of phenyl thioethers in carbanionic cyclizations is further illustrated by generation of the fused cyclopentenylmethyllithium precursor of **6** in a three-pot sequence by ring-closure of vinyllithium **5**, derived from **4**, which is itself readily produced from **3**.[6,7] (Scheme 2).[8]

Recent work from this laboratory has demonstrated that in the cases of lithium−[9a] and magnesium−ene[9b] cyclizations, an allylic oxyanionic group on the alkene being carbometalated not only facilitates the cyclization but also exerts stereochemical control, sometimes quite high, as shown in Scheme 3 for the lithium−ene

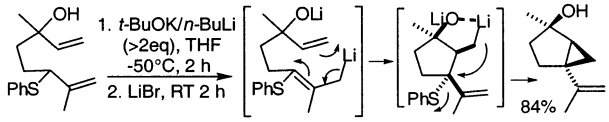
Scheme 1



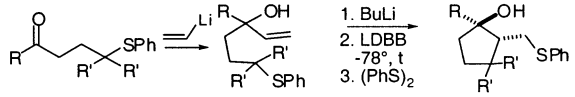
Scheme 2



Scheme 3



Scheme 4



7a R=R'=H	**8a** R=R'=H 90%	t=12 h	**9a** R=R'=H 73%
7b R=Me, R'=H	**8b** R=Me, R'=H 87%	t=12 h	**9b** R=Me, R'=H 81%
7c R=H, R'=Me	**8c** R=H, R'=Me 96%	t=1 h	**9c** R=H, R'=Me 86%
7d R=R'=Me	**8d** R=R'=Me 96%	t=1 h	**9d** R=R'=Me 80%

case. A single isomer is produced; the same cis stereochemistry between the metallomethyl group and the oxyanionic group is manifested in the Mg case.

As illustrated in Scheme 4,[10] an allylic lithium oxyanionic group has a powerful accelerating effect in the intramolecular carbometalation by an unconjugated alkyllithium. Most intramolecular carbolithiations using primary alkyllithiums are performed in hexane/ether mixtures at room temperature. One of the strong advantages of the use of reductive lithiation is that it allows organolithium generation in THF in which cyclizations of primary alkyllithiums occur at −30°.[3c] However, the presence of *the lithium oxyanionic group allows cyclization of primary as well as tertiary alkyllithiums to occur in THF at −78°*.

However, the most surprising result in Scheme 4 is that the single diastereomers isolated in all four cases have the oxygen function and the function derived from the CH_2Li group on the opposite side of the cyclopentane ring. The directing effect of the lithium

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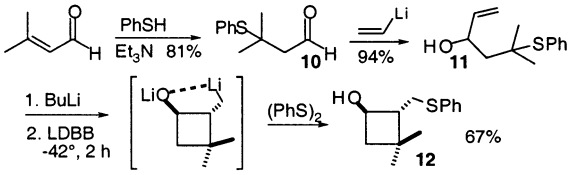
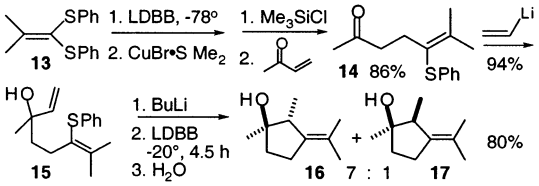
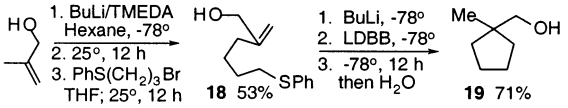
Scheme 5



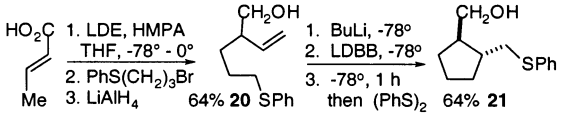
Scheme 6



Scheme 7



Scheme 8



oxyanionic group is complete and *in the opposite sense to that in the case of intramolecular allylmetallic carbometalations.*[11]

Even a cyclobutanol, **12**, can be generated by this method in a three-flask reaction from commercial reactants (Scheme 5). The stereochemistry is again exclusively trans.

As shown in Scheme 6, an sp^2 organolithium is subject to the same type of stereochemical control by an allylic lithium oxyanionic group but with somewhat less stereoselectivity. Substrate **13** is produced in one-pot from methyl isobutyrate.[12] Note that the alkene linkage is exo to the five-membered ring unlike the endo alkene that is produced upon cyclization of **5**.

In the cases of lithium oxyanionic participation in Schemes 3−6, the allylic lithium oxyanionic group is positioned such that it is a ring substituent in the cyclized organolithium. The type of allylic lithium oxyanionic participation shown in Scheme 7, in which the alcohol function is positioned exo to the ring, is seen to be equally effective at promoting cyclization. The substrate **18** was readily prepared by alkylation[13] of the dianion of methallyl alcohol with 3-phenylthio-1-bromopropane.[14]

As shown in Scheme 8, a *homoallylic* lithium oxyanion placed exo to the forming ring is even more effective than the allylic lithium oxyanionic group derived from **8** (Scheme 4) in accelerating the cyclization, and the stereochemistry of the product is still trans. The substrate **20** was readily prepared by reduction of the carboxylic acid obtained by alkylation[15] of the dianion of crotonic acid with 3-phenylthio-1-bromopropane.[14] On the other hand, we observed an apparent retardation of cyclization when the homoallylic lithium oxyanion was a substituent on the forming ring.

The combined powers of reductive lithiation of phenyl thioethers to prepare substrates and of the accelerating and remarkable directing effect of allylic and homoallylic lithium oxyanionic groups should greatly increase the versatility of intramolecular carbolithiation for cyclizations.

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Supporting Information Available: Experimental procedures and compound characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Very recently, Rychnovsky[3b] and Yus[3c] reported one tertiary example each by reductive lithiation of, respectively, a nitrile and a chloride.

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(11) We suspect that the lithium oxyanions can participate in a nucleophilic fashion in metallo−ene cyclizations, which proceed via 6-center transition states, but prefer participation in an electrophilic fashion in alkyllithium cyclizations, which proceed via 4-center transition states. This concept will be further elaborated in a full article.

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