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Cyclization by Intramolecular Carbolithiation of Alkyl- and Vinyllithiums Prepared by the Action of Aromatic Radical Anions on Phenyl Thioethers. High Stereoselectivity in the Cyclization Accelerated by an Allylic Lithium Oxyanion[1]

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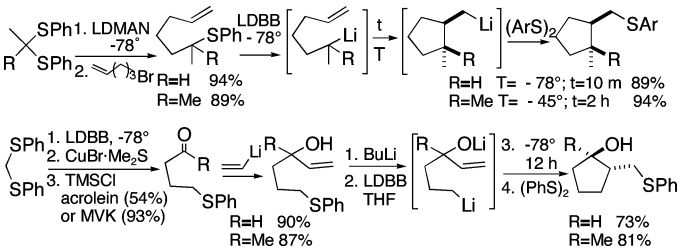

The reductive lithiation of alkyl and vinyl phenyl thioethers by aromatic radical anions is shown to be the most general method yet known for preparing organolithiums capable of intramolecular carbometalation of unactivated alkenes to produce five-membered rings and in one case a four-membered ring (in a far higher yield than known cases). The relative rates of cyclization for alkyllithiums are secondary > tertiary > primary, and the yields are very high. In the secondary case, the stereoselectivity is extremely high, producing a cyclopentylmethyllithium with a *trans*-2-alkyl substituent. A remarkable finding is that for all of the organolithiums a lithium oxyanionic group in the proximal allylic position to the alkene greatly accelerates the cyclization and leads almost exclusively to a trans relationship between the CH_2Li group and the OLi group, the opposite relationship from that observed in intramolecular carbolithiations by allyllithiums. A mechanistic rationale for this divergence is discussed. One of the two types of proximal homoallylic lithium oxyanions exerts an analogous effect. An intriguing limitation, even occurring with the highly reactive secondary organolithium and in the presence of an allylic oxyanionic group, is the failure of intramolecular carbolithiation when a methyl group is at the terminus of the alkene.

Introduction

The intramolecular addition of alkyl- and vinyllithiums to unactivated alkenes (carbolithiation) is a rapidly developing preparative method for cyclopentylmethyllithiums, their heterocyclic analogues, and in some cases, the corresponding six-membered rings.[2] The attraction of this methodology lies in its high regio- and stereoselectivity and the possibility of trapping the resulting cyclized organolithium with various electrophiles to introduce diverse functionality into the cyclized products. However, a major limitation has been the lack of truly general methods for preparing the organolithiums.

Perhaps the most widely used method to prepare organolithiums for the study of intramolecular carbolithiation has been halogen−lithium exchange. It has been used successfully to generate primary alkyllithiums,[2b,3] aryllithiums,[4] and vinyllithiums[2c,5]

(1) Taken in part from the Ph.D. thesis of Kai Deng: Deng, K. Ph.D. Thesis, University of Pittsburgh, 2004.

(2) (a) Reviews: Bailey, W. F.; Ovaska, T. V. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Greenwich, CT; 1994; Vol. 3, pp 251−273. Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *646*, 59−67. Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: New York, 2002; pp 293−335. Marek, I.; Chinkov, N.; Banon-Tenne, D. In *Metal-Catalyzed Cross-Coupling Reactions*, 2n ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, pp 395−478. Recent papers: (b) Bailey, W. F.; Jiang, X. L. *Tetrahedron* **2005**, *61*, 3183−3194. (c) Barluenga, J.; Fananas, F. J.; Sanz, R.; Fernandez, Y. *C. R. Chem.* **2004**, *7*, 855−864. (d) Coldham, I.; Price, K. N.; Rathmell, R. E. *Org. Biomol. Chem.* **2003**, *1*, 2111−2119. The earliest reports of such cyclizations involved Grignard reagents and are due to the pioneering work of Richey: (e) Richey, H. G., Jr.; Rees, T. C. *Tetrahedron Lett.* **1966**, *36*, 4297−4301. Kossa, W. C., Jr.; Rees, T. C.; Richey, H. G., Jr. *Tetrahedron Lett.* **1971**, 3455−3458.

(3) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720−5727.

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for such studies. However, the limitation of this otherwise powerful method lies in its poor performance in the generation of secondary alkyllithiums and its inability to generate tertiary organolithiums, presumably due to elimination and Wurtz-type coupling reactions of the precursor secondary and tertiary organohalides.[6]

Tin−lithium exchange is an excellent method to generate allyl- and aryllithiums as well as α-heterosubstituted organolithiums. Broka[7] and Coldham[2d,8] et al. have used this method to construct interesting tetrahydrofuran and pyrrolidine derivatives by intramolecular carbolithiation with high stereoselectivity. However, the generality of Sn−Li exchange is compromised by the limited availability of the organotin compounds.

Selenium−lithium exchange has been used by Krief[9] to generate benzyllithiums, which can form cyclopentane derivatives in excellent diastereoselectivity and good yields, but the method is limited by some of the same problems mentioned above for halogen−lithium exchange. Chamberlin[10] has used the Shapiro reaction[11] for the generation of vinyllithiums in a study of the intramolecular addition of vinyllithiums to carbon−carbon double bonds to form five-membered rings. This method is limited to vinyllithiums and by the necessity of starting with ketones.

Since its introduction,[12] reductive lithiation of phenyl thioethers using aromatic radical anions has been demonstrated to be one of the most versatile methods known for generating organolithiums.[13,14] There are two major attractions of reductive lithiation of phenyl thioethers compared with the methods discussed above. First, it is a more general method than any of the above for the generation of organolithiums. Not only primary organolithiums and many vinyllithiums but also secondary and tertiary organolithiums can be generated very efficiently. Indeed, unlike the most conventional method of organolithium preparation, electrophile removal (see above), it is often the case that the less stable the organolithium, the greater the ease of its generation by reductive lithiation.[13a,b,15] Second, phenyl thioethers are very readily available. Divalent sulfur can be introduced into a molecule as an electrophile, a nucleophile, or a radical. Furthermore, divalent sulfur stabilizes any electronic arrangement on the carbon atom to which it is attached. Despite these attractions, prior to our preliminary communication,[16] the method had rarely been used in intramolecular carbolithiation.[17]

In this paper, we present a full study of the use of reductive lithiation of phenyl thioethers to generate the required organolithiums in intramolecular carbolithiation. Since there is believed to be a radical intermediate in reductive lithiation,[13] evidence to support a organolithium cyclization, rather than a radical cyclization followed by a reduction of the cyclized radical, will also be provided. Cyclopentane rings and one cyclobutane ring have been constructed successfully in excellent yield by cyclizations of tertiary and secondary organolithiums. Moreover, it is revealed that allylic and certain homoallylic lithium oxyanions have a dramatic effect on the cyclization. Details about the rate acceleration and stereocontrol over the cyclization by these oxyanions are presented as well as certain limitations to such cyclizations.

Results and Discussion

A major purpose of the present publication is to demonstrate the striking versatility of the reductive lithiation of phenyl thioethers as a method of organolithium generation for use in intramolecular carbolithiation. A large contributor to this versatility is the ease of preparation of the reductive lithiation substrates, and therefore, these preparations are described in all cases. In the reductive lithiations that are described below, the preferred reducing agent is lithium 4,4′-di-*tert*-butylbiphenylide[18] (LDBB) because it generally gives somewhat higher yields than lithium 1-(dimethylamino)naphthalenide[12d] (LDMAN). However, the latter is generally used when the product of trapping of the resulting organolithium is relatively nonpolar and thus difficult to separate from the byproduct 4,4′-di-*tert*-butylbiphenyl; in the case of LDMAN, the byproduct, 1-(dimethylamino)-naphthalene, can be readily separated from the neutral product by a dilute acid wash.

Cyclization of a Tertiary Organolithium. Scheme 1 shows what was, when it was performed, the first example of the cyclization of a tertiary organolithium.[19] It occurs at a far lower

(4) Ross, G. A.; Koppang, M. D.; Bartak, D. E.; Woolsey, N. F. *J. Am. Chem. Soc.* **1985**, *107*, 6742−6743.

(5) Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 6787−6788.

(6) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J., Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442−2448.

(7) (a) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1338−1340. (b) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981−2984.

(8) Coldham, I.; Hufton, R.; Snowden, D. *J. Am. Chem. Soc.* **1996**, *118*, 5322−5323.

(9) Krief, A.; Barbeaux P. *J. Chem. Soc., Chem. Commun.* **1987**, *16*, 1214−1216.

(10) Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788−4796.

(11) Shapiro, R. H.; Lipton, M. F.; Kolonko, K. J.; Buswell, R. L.; Capuano, L. A. *Tetrahedron Lett.* **1975**, 1811−1814.

(12) (a) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064−1071. (b) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713−719. (c) Cohen, T.; Daniewski, W. M.; Weisenfeld, R. B. *Tetrahedron Lett.* **1978**, 4665−4668. (d) Cohen, T.; Matz, J. R. *Synthetic Commun.* **1980**, *10*, 311−317.

(13) Reviews: (a) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152−161. (b) Cohen, T. In *Heteroatom Chemistry*; Block, E., Ed.; VCH Publishers: New York, 1990; Chapter 7, pp 129−42. (c) For a review of the special method that uses a catalytic amount of the aromatic and a large excess of lithium, see: Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225−237.

(14) Recent uses of reductive lithiation of pheny thioethers: Screttas, C. G.; Heropoulos, G. A.; Micha-Screttas, M.; Steele, B. R. *Tetrahedron Lett.* **2005**, *46*, 4357−4360. Tang, T.; Ruan, Y. P.; Ye, J. L.; Huang, P. Q. *Synlett* **2005**, 231−234. de Vicente, J.; Betzemeier, B.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1853−1856. Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 569−572. Cooksey, J.; Gunn, A.; Kocienski, P. J.; Kuhl, A.; Uppal, S.; Christopher, J. A.; Bell, R. *Org. Biomol. Chem.* **2004**, *2*, 1719−1731. Streiff, S.; Ribeiro, N.; Desaubry, L. *J. Org. Chem.* **2004**, *69*, 7592−7598.

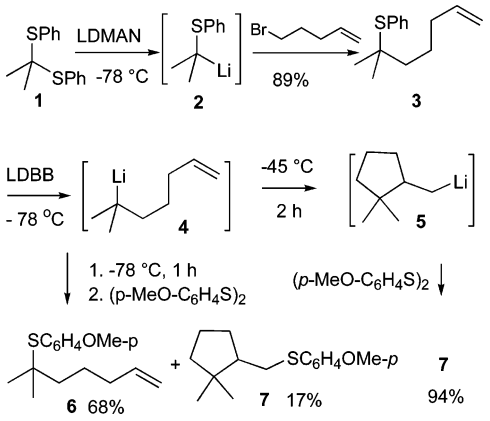
(15) Chen, F.; Mudryk, B.; Cohen, T. *Tetrahedron* **1999**, *55*, 3291−3304.

(16) Deng, K.; Bensari, A.; Cohen, T. *J. Am. Chem. Soc.* **2002**, *124*, 12106−12107.

(17) The only examples of intramolecular carbolithiation of nonconjugated alkyllithiums prepared by reductive lithiation, before our preliminary communication,[16] were by (a) Broka,[7] in which phenyl thioethers are substrates (two examples), by (b) Rychnovsky, S. D.; Hata, T.; Kim, A. I.; Buckmelter, A. J. *Org. Lett.* **2001**, *3*, 807−810 in which a nitrile was the substrate (one example), and by (c) Yus, M.; Ortiz, R.; Huerta, F. F. *Tetrahedron Lett.* **2002**, *43*, 2957−2960 (preliminary communication); Yus, M.; Ortiz, R.; Huerta, F. F. *Tetrahedron* **2003**, *59*, 8525−8542 (full paper) (three cyclizations with multiple electrophilic trapping agents) in which alkyl chlorides were the substrates. In the latter cyclizations starting with alkyl chlorides, very special conditions were required for the tertiary case. Papers b and c were first published after we had completed much of the work described in our preliminary communication.[16] After our preliminary communication, two other examples appeared in which a nitrile was the substrate: (d) Takaoka, L. R.; Buckmelter, A. J.; LaCruz, T. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 528−529. (e) Wolckenhauer, S. A.; Rychnovsky, S. D. *Tetrahedron* **2005**, *61*, 3371−3381.

(18) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924−1930.

SCHEME 1. Tertiary Organolithium Cyclization



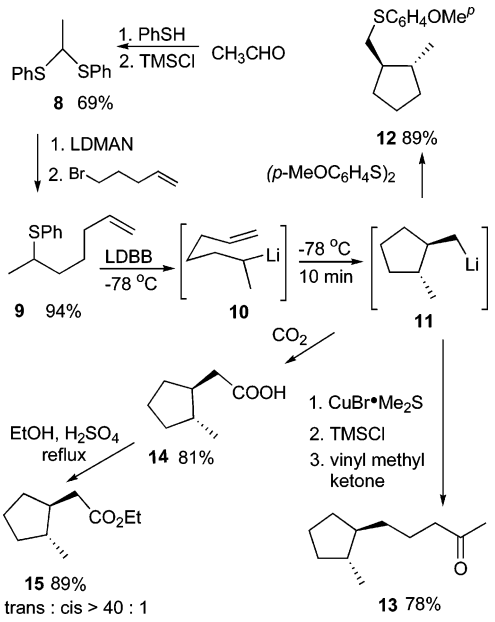
temperature than that at which cyclizations of primary alkyllithiums are usually performed.

The synthesis of 6-methyl-6-phenylthio-1-heptene **3**, the precursor of the tertiary organolithium **4**, was accomplished easily in 89% yield. Reductive lithiation of the phenyl thioacetal of acetone, 2,2-bis(phenylthio)propane **1**, with LDMAN at −78 °C, generated 2-phenylthio-2-lithiopropane **2**, which can be quenched directly by 5-bromo-1-pentene to afford the desired phenyl thioether **3**. Although 1 equiv of thiophenoxide anion is generated during the reductive lithiation, apparently the nucleophilicity of **2** is far greater than that of thiophenoxide, and no undesired attack of the latter on 5-bromo-1-pentene was observed when 1 equiv of electrophile was used.

Phenyl thioether **3** was treated with LDBB to generate the corresponding tertiary organolithium **4**, which partially cyclized when the reaction was performed at −78 °C for 1 h. After the reaction was quenched with di-*p*-methoxyphenyl disulfide, cyclized product **7** was isolated in 17% yield in addition to 68% of uncyclized product **6**.[20] Complete cyclization was achieved by performing the reaction at −45 °C for 2 h. To perform the cyclization of the primary alkyllithium, generated by I−Li exchange of 6-iodo-1-hexene in a mixture of pentane and diethyl ether, ambient temperature was required.[3] When THF was used as the reaction medium in the primary case, no cyclization occurred at all at −78 °C, and a temperature of −30 °C was required to realize cyclization.[17c] Thus, cyclization of the tertiary alkyllithium is far faster than that of a primary alkyllithium. This kinetic result is not surprising considering the fact that tertiary organolithiums are well-known to be more reactive than primary ones.

One other conclusion from Scheme 1 is that cyclizations occurring upon reductive lithiation of phenyl thioethers by preformed radical anions occur largely or completely by a carbanionic mechanism since the organolithium **4** eventually cyclizes completely; the 17% of **7** that is produced after 1 h at −78 °C could be formed by cyclization of either an organolithium or a radical. Two other observations discussed below definitively establish that all of the cyclization occurs by the carbanionic rather than the radical route.

SCHEME 2. Secondary Organolithium Cyclization



Cyclization of a Secondary Organolithium. The first case of cyclization of a secondary organolithium, 6-lithio-1-heptene **10**, was studied by Bailey in 1987 using I−Li exchange.[6] The lone secondary example in that paper proceeded in somewhat unsatisfactory yield (44%), and the reaction mixture contained hydrocarbons produced by Wurtz-type coupling, elimination, and reduction. The authors concluded that "The secondary systems are not as well behaved as are the primary alkenyllithiums." More recently, Yus[17c] examined the cyclization of a secondary organolithium, 6-lithio-1-nonene, prepared by reductive lithiation of an alkyl chloride using the catalytic method; the yields of cyclized product, captured with 3-pentanone, ranged from 45 to 62%.[21,22]

The phenyl thioacetal **8** of acetaldehyde, readily obtained by trimethylsilyl chloride mediated thioacetalization of acetaldehyde,[23] undergoes reductive lithiation with LDMAN to generate the corresponding anion, which can be quenched directly by 5-bromo-1-pentene to afford the desired phenyl thioether **9**. Reductive lithiation of **9** generates 6-lithio-1-heptene **10**, the cyclization of which provides yields from 89% to 78% of product when trapped with the same disulfide used above, CO_2, or after cuprate formation, methyl vinyl ketone (Scheme 2). In the conjugate addition to give **13**, the addition of cuprous bromide−dimethyl sulfide complex undoubtedly resulted in a mixed cuprate bearing a thiophenoxide group, a nontransferable ligand,[24] due to the presence of lithium thiophenoxide in the

(19) After our study of this cyclization was completed, ref 17b,c appeared in which tertiary organolithiums, prepared by reductive lithiation of a nitrile and an alkyl chloride, respectively, were added intramolecularly to alkenes.

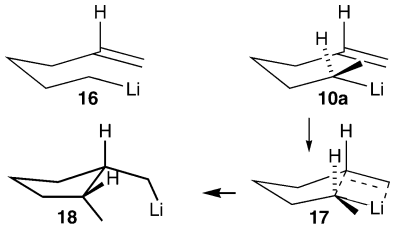
(20) It is somewhat surprising that the analogue of **4** bearing ethyl groups in place of the methyl groups of **4** was reported in ref 17c (in the preliminary communication in *Tetrahedron Lett.*, the organolithium **4** itself was erroneously drawn and the error was corrected in the *Tetrahedron* full paper) to be unstable at −78 °C, removing a proton from the solvent THF. In our experiment, **4** survived except for some cyclization to **7**. While the diethyl analogue would be expected to be more basic than **4**, it is possible that the proton that replaced the lithium was contributed by the added electrophile, 3-pentanone.

(21) Yields slightly higher and slightly lower than this range were observed when the reductive lithiation was performed in the presence of the carbonyl-trapping reagent.

(22) For the reader's guidance, it should be noted that (1) the secondary organolithium used was depicted as **10** in the preliminary communication in ref 17c, but that was acknowledged to be in error in the full paper and to be 6-lithio-1-nonene instead, and (2) the product of cyclization of the secondary organolithium in the full paper is drawn as 2-ethylcyclopentylmethyllithium whereas it must actually be 2-*n*-propylcyclopentylmethyllithium.

(23) Cohen, T., Zhang, B., Cherkauskas, J. P. *Tetrahedron* **1994**, *50*, 11569−11584.

SCHEME 3. Simple Model for Cyclization



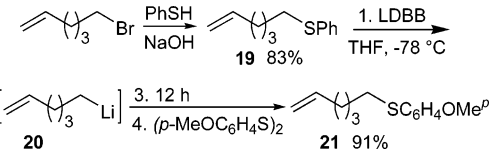
solution from the reductive lithiation. The mixed cuprate undergoes 1,4-addition to methyl vinyl ketone to give **13** in 78% yield, with only the alkyl group being transferred during the conjugate addition.

The stereochemistry of the cyclization was definitively established by Fisher esterification of **14** to the known ethyl *trans*-2-methylcyclopentyl acetate **15**. The latter had been prepared by Brown[25] by hydroboration of 1-methylcyclopentene, followed by alkylation, and its stereochemistry had been established. The spectroscopic data of **15** were identical in all respects to those of the ester described by Brown. The cyclization is almost purely trans (trans/cis > 40:1, determined by the proton NMR spectra) as Bailey had observed previously in his case of secondary organolithium cyclization.[6,26]

The almost complete trans selectivity of the cyclization is the second piece of evidence, and a more definitive one, that cyclization occurs by an anionic mechanism after reductive lithiation of the phenyl thioether by a preformed radical anion rather than by a radical mechanism during the reduction. The corresponding 5-exo secondary radical cyclization gives a mixture of two diastereomers with a cis/trans ratio of 66/34.[27]

The trans stereochemistry of the cyclization is also of interest because it is not predicted by the simple chairlike molecular model for the cyclization of 6-lithio-1-hexene **16** (Scheme 3), a model that is consistent with the computed structures for the intermediate and transition state for this type of cyclization, as developed by Bailey, Wiberg, et al.[3] This model successfully accounted for the experimentally determined stereochemistry of the products when methyl groups were at the 3-, 4-, or 5-positions of the 6-lithio-1-hexene **16**. In that paper, the correct configurations of the products are predicted if the methyl groups take up the less crowded pseudoequatorial positions during the cyclizations. Examination of the simple model of cyclization of 6-lithio-1-heptene **10** (one configuration of which is shown in Scheme 3 as **10a**) reveals that the methyl group can take up a position pointing outward, away from the remainder of the molecule, as in **10a**, or inward toward the remainder of the molecule (the epimer of **10a**). If the former, apparently less crowded, configuration were maintained in the transition state, the cis product **18** would result. A satisfactory explanation of the stereochemistry of cyclization of **10** is given in a separate computational paper in which it is revealed that solvation plays a major role.[28]

SCHEME 4. Attempted Cyclization of a Primary Alkyllithium at −78 °C



Another interesting aspect of the cyclization of the secondary alkyllithium **10**, generated by treating **9** with radical-anion reducing agent LDBB, is that it is complete in 10 min at −78 °C, a result consonant with the results of Bailey.[6] The cyclization is far faster than the corresponding tertiary and primary alkyllithium cyclizations. While tertiary organolithiums are generally more reactive than secondary organolithiums, in this case it seems reasonable to assume that the congestion of the transition state for the tertiary organolithium cyclization is responsible for the slower cyclization of the tertiary alkyllithium than that of the secondary one.

Stereoselective Intramolecular Carbolithiation of a Primary Alkyllithium Mediated by an Allyllic Lithium Oxyanion. It has been discovered in this laboratory that an allylic lithium oxyanion on the receiving alkene greatly accelerates lithium−ene[29] and magnesium−ene[30] cyclizations,[31] as well as Simmons−Smith cyclopropanations.[32] More importantly, in most cases studied, the allylic lithium oxyanionic group exerts almost complete stereocontrol over the cyclizations. In earlier work from this laboratory, it had been found that lithium oxyanionic groups elsewhere in the organolithium also accelerated cyclizations by carbolithiation to yield single isomers of three-[33] and four-membered rings.[34] It was thus of considerable interest to study the effect of allylic lithium oxyanionic groups on cyclizations of a variety of alkyllithiums, particularly because of the ease of generation of the required substrates by reductive lithiation.

Most intramolecular carbolithiations involving primary alkyllithiums are performed in pentane/ether mixtures at room temperature. THF is a much more polar solvent than either pentane or diethyl ether, and it is known to be highly lithiophilic. Bailey and co-workers found that lithiophilic reagents such as TMEDA and THF greatly increase the cyclization rate of intramolecular carbolithiation.[3] One of the strong advantages of using reductive lithiation is that it allows organolithium generation in THF. Thus, THF itself may increase the cyclization rate of primary alkyllithiums. The attempted cyclization of a primary alkyllithium *without* an oxyanionic group in THF at −78 °C is shown in Scheme 4.

The reaction of thiophenoxide anion with 6-bromo-1-hexene in S_N2 fashion afforded **19**, reductive lithiation of which afforded primary alkyllithium **20**. However, no cyclization occurred

(24) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788−7800.

(25) Brown, H. C.; Joshi, N. N.; Pyun, C.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 1754−1758.

(26) The corresponding carbomagnesiation, occurring at a higher temperature, also produces mainly trans product: Kossa, J. W. C.; Rees, T. C.; Richey, J. H. G. *Tetrahedron Lett.* **1971**, *12*, 3455−3458.

(27) Beckwith, A. L. J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613−1614. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959−974.

(28) Liu, H.; Deng, K.; Cohen, T.; Jordan, K. D. Submitted for publication.

(29) Cheng, D.; Knox, K. R.; Cohen, T. *J. Am. Chem. Soc.* **2000**, *122*, 412−413.

(30) Cheng, D.; Zhu, S.; Yu, Z.; Cohen, T. *J. Am. Chem. Soc.* **2001**, *123*, 30−34.

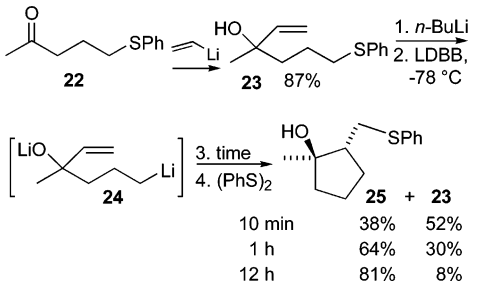
(31) Metallo−ene cyclizations are also intramolecular carbometalations resulting most usually in five-membered rings, but they differ from the cyclizations described in the present paper in that the organometallic is an allylmetal rather than an unconjugated alkylmetal.

(32) Cheng, D.; Kreethadumrongdat, K.; Cohen, T. *Org. Lett.* **2001**, *3*, 2121−2123.

(33) Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1993**, *115*, 3855−3865. Additions and corrections: Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1993**, *115*, 7932.

(34) Chen, F. P.; Mudryk, B.; Cohen, T. *Tetrahedron* **1994**, *50*, 12793−12810.

SCHEME 5. First Alkyllithium Cyclization Mediated by an Allylic Lithium Oxyanion Group

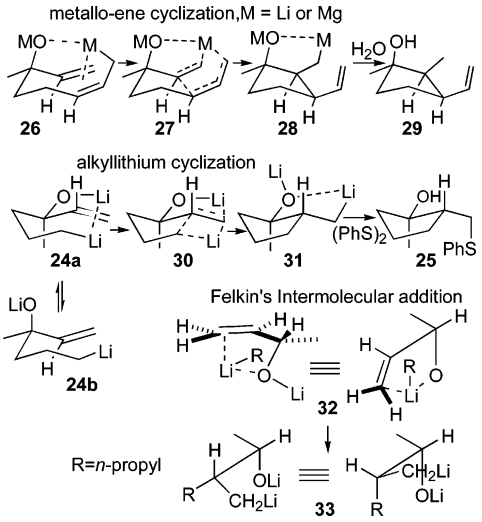


during a 12 h period at −78 °C followed by quenching with di-*p*-methoxyphenyl disulfide. Uncyclized quenched product **21** was obtained in 91% yield. After we had completed the study in Scheme 4, Yus[17c] reported that the cyclization of **20** (generated by reductive lithiation of 1-chloro-5-hexene) in THF occurred at −30 °C.

This knowledge set the stage for our examination of the effect of an allylic oxyanionic group on the cyclization of a primary alkyllithium. The first example of an allylic lithium oxyanion accelerated and directed alkyllithium cyclization is shown in Scheme 5. The cyclization substrate **23** was readily prepared by vinyllithium addition to ketone **22**, generated in high yield by the reaction of sodium thiophenoxide with commercial 5-chloropentane-2-one,[15] to afford allylic alcohol **23**, which was deprotonated and then reductively lithiated with LDBB to generate the primary alkyllithium **24**, bearing the allylic oxyanionic group. Surprisingly, the dianion **24** cyclized at −78 °C. Thus, the presence of *the lithium oxyanionic group greatly accelerates the cyclization of a primary alkyllithium*.

Another interesting finding about this reaction is that the cyclization proceeds very rapidly at the beginning, but slows with time. When the reaction was quenched immediately after the addition of LDBB (∼10 min), 38% of cyclized product **25** and 52% of uncyclized product **23** were isolated. (Since diphenyl disulfide was used to quench the reaction, the uncyclized product is starting material. When water was used, no starting material was detected, which means the reductive lithiation step is complete.) However, when the reaction was quenched after 1 h, 64% of cyclized product and 30% of uncyclized product, respectively, were isolated. After the reaction was performed at −78 °C for 12 h and quenched at this temperature, 81% of cyclized product was isolated, and 8% of uncyclized material was still isolated. It appears that the reaction is not first order, as expected for a cyclization. One possible explanation for this is that the freshly generated organolithium exists as a monomer, so that the cyclization is very fast initially. However, subsequent aggregation of the monomer reduces the reactivity of the organolithium considerably.[35] During their studies on the addition of organolithiums to chiral 1- and 2-substituted naphthalenes, Meyers and co-workers observed a similar phenomenon.[36] They found that as the organolithiums aged, they lost their ability to add to substituted naphthalenes even under prolonged contact. To obtain addition products, organolithiums have to be prepared as fresh as possible to produce monomeric organolithiums.

SCHEME 6. Models To Rationalize the Stereoselectivity of Metallo-Ene and Alkyllithium Cyclizations



However, the most surprising result in Scheme 5 is that the single diastereomer **25** obtained as cyclization product has the alcohol group and the functionality derived from the CH_2Li group on the opposite side of the cyclopentane ring.[37] The directing effect of the lithium oxyanion is complete and *in the opposite sense to that in the case of intramolecular allylmetallic carbometalations, in which an allylic oxyanionic group leads to cis products*.[29,30]

An examination of molecular models suggests an explanation for the cis stereoselectivity in the metallo-ene cyclization (M = Li or Mg) and the trans stereoselectivity in the alkyllithium cyclization as shown in Scheme 6. For the metallo-ene cyclization, the allylic oxyanion can participate as a *nucleophile* by coordination of the oxyanion with the allylic metal (**26**). A half-chair 6-center transition state **27** leads to product **28** with all-cis geometry, corresponding to the observed stereochemical result.[29,30] In the transition state **27**, the metal can coordinate both with the nonbonding electrons of the oxyanion and the π electrons[3,38] of the alkene. However, in *alkyl*lithium cyclizations, it is likely that the lithium attached to the allylic oxyanion coordinates with the double bond in an *electrophilic* fashion as in the conformation **24a**. An apparent requirement for addition of an alkyllithium to an alkene is that the C−Li bond is arranged parallel to the C═C bond to which it will add.[3,39] Because of the shorter chain length of *alkyl*lithium **24**, compared with the *allyl*lithium **26**, coordination of the lithium ion attached to carbon simultaneously with both the oxyanion and the π orbital leads to considerably greater strain than is manifested in transition state **27**. This can be gleaned from an examination of conformation **24b**, drawn from the same perspective as **26**.[40] The added strain makes nucleophilic participation of the oxyanion noncompetitive with electrophilic acceleration involving transition state **30**. In the chairlike transition state **30**, the allylic lithium oxyanion occupies the pseudoequatorial position, necessary for coordination of the Li with the π bond and

(35) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H. *J. Am. Chem. Soc.* **1985**, *107*, 1810−1815.

(36) (a) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611−4624. (b) Meyers, A. I.; Lutomski, K. A.; Laucher, D. *Tetrahedron* **1988**, *44*, 3107−3118.

(37) The spectroscopic data of **25** (^{1}H NMR and ^{13}C NMR) were identical to the literature values. Molander, G. A.; Mckie, J. *J. Org. Chem.* **1992**, *57*, 3132−3139.

(38) Rolle, T.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1953−1954.

(39) Houk, K. N.; Rondan, N. G.; Schleyer, P. R.; Kaufmann, E.; Clark, T. *J. Am. Chem. Soc.* **1985**, *107*, 2821−2823.

SCHEME 7. Preparation and Cyclization of Various Alkyllithiums Possessing Allylic Lithium Oxyanions

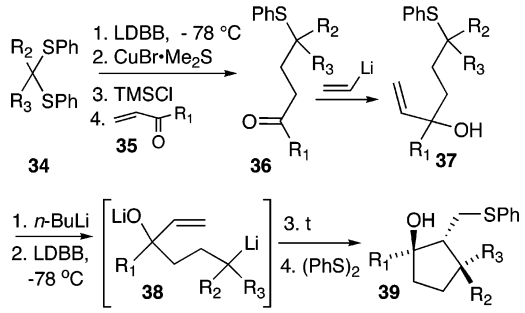


TABLE 1. Preparation and Cyclization Results of Alkyllithiums Possessing Allylic Lithium Oxyanions

entry	R_1	R_2	R_3	ketone, % yield	alcohol, % yield	time/h	product, % yield
1	H	H	H	**36a**,[a] 54	**37a**, 90	12	**39a**, 73
2	H	Me	H	**36b**[b]	**37b**, 96	1	**39b**,[c] 78
3	Me	Me	H	**36c**, 77	**37c**, 96	1	**39c**,[d] 71
4	H	Me	Me	**36d**,[a] 64	**37d**, 96	1	**39d**, 86
5	Me	Me	Me	**36e**,[e] 75	**37e**, 96	1	**39e**, 80

[a] Reference 15. [b] This aldehyde was synthesized by following ref 42 rather than conjugate addition. [c] 11% of another isomer with R_1 and $PhSCH_2-$ trans to each other was also isolated. [d] 14% of another isomer ($R_1 = R_3 = Me$, $R_2 = H$) was also isolated. [e] Reference 34.

probably also encouraged by the large size of the solvent-coordinated OLi group. This arrangement leads, after quenching, to the product **25** with trans geometry. The lithium ion on the allylic oxyanion acts as a kind of intramolecular Lewis acid, which can polarize the double bond and make it more electrophilic for the attack of the internal alkyllithium. Felkin has invoked electrophilic catalysis in the intermolecular addition of certain Grignard reagents to allylic alcohols.[41] *Intermolecular* additions of alkyllithiums to deprotonated allylic alcohols should not be subject to the restrictions mentioned above for nucleophilic participation in **24** in an *intramolecular* cyclization, and it is thus significant that the addition of *n*-propyllithium to methallyl alcohol yields with high stereoselectivity the diastereomer **33**, expected from nucleophilic participation of the oxyanionic group when the methyl group is distal (rather than proximal) to the developing CH_2Li group in the transition state.[41]

In view of the extremely high stereoselectivity of the cyclization of dianion **24** in Scheme 5, it became of interest to determine the scope of this selectivity. More specifically, it was deemed important to know if the allylic methyl group on the carbinol carbon atom plays a role in the stereoselectivity and if the latter can be extended to secondary and tertiary alkyllithium cyclizations. As indicated in Scheme 7 and Table 1, the reductive lithiation substrates **37**, except for **37c**, required for this study, were readily prepared from the thioacetals **34** of formaldehyde, acetaldehyde, and acetone by reductive lithiation, mixed cuprate formation (see discussion above, Scheme 2), addition to the appropriate enal or enone,[15,34] and addition of vinyllithium to the resulting phenylthio-substituted aldehyde or ketone **36**. Substrate **37c** was produced by vinyllithium addition to the known aldehyde **36c**, itself prepared in two steps from crotonaldehyde.[42] Treatment of **37** with *n*-BuLi/LDBB generated the dianions **38**, the cyclization substrates.

When **38a** was allowed to cyclize at −78 °C for 12 h, and the reaction mixture was quenched with diphenyl disulfide, single diastereomer **39a** was obtained, the stereochemistry of which was, again, purely trans (Table 1, entry 1). The stereochemistry of **39a** was assigned by 2D-NMR spectroscopy. The ROESY spectrum clearly shows strong interaction between the proton on the carbinol carbon atom and one of the pairs of protons on the carbon atom attached to the phenylthio group.

Secondary alkyllithium cyclizations mediated by allylic lithium oxyanions are particularly interesting as they afford products with three contiguous chiral centers. It was expected that the allylic lithium oxyanion would exert stereocontrol over the cyclization similar to that in Scheme 3 so as to result in good diastereoselectivity. As shown in entries 2 and 3, the dianions **38b** and **38c** cyclized efficiently at −78 °C to afford as major products compounds **39b** and **39c**, respectively, in satisfactory yields. Thus, three contiguous chiral centers were established in one step with good diastereoselectivity. Both products **39b** and **39c** have the by now expected trans relationship between the $PhSCH_2$ group and the alcohol. As was found for the secondary alkyllithium cyclizations lacking the allylic lithium oxyanion as well as the carbinol methyl group, both **39b** and **39c** have the expected trans relationship between the $PhSCH_2$ group and the adjacent methyl substituent. Evidence for the stereochemistry of **39b** and **39c** is provided in the Supporting Information. In each of these two cases, a minor diastereomer accompanied the major cyclized products. The 11% of the minor isomer accompanying **39b** had the $PhSCH_2$ and hydroxyl groups cis to each other, but the usual trans arrangement between the $PhSCH_2$ group and the methyl substituent. In the case of **39c**, the 14% of the minor diastereomer differed from **39c** in that the methyl substituent was cis instead of trans to the $PhSCH_2$ group.

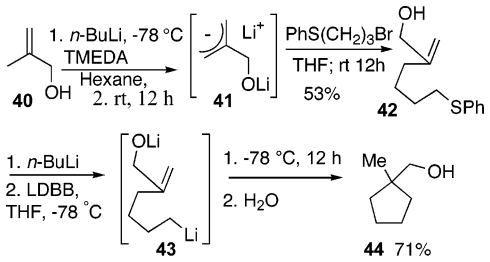
Reductive lithiation is an attractive method for the generation of tertiary organolithiums for which other methods are not generally available. After the discovery of allylic lithium oxyanion accelerated and directed primary and secondary alkyllithium cyclization, it became of interest to determine if tertiary organolithium cyclizations are affected in the same way. As shown in entries 4 and 5 of Table 1, dianions **38d** and **38e** cyclize very rapidly at −78 °C and the single diastereomers **39d** and **39e**, respectively, are obtained after the reactions are quenched with diphenyl disulfide. Compared with the primary alkyllithium cyclization mediated by an allylic lithium oxyanion (Scheme 5, 12 h at −78 °C, 81% cyclized product, 8% uncyclized product), the cyclizations of tertiary alkyllithiums are much faster. Only 1 h was needed at −78 °C to obtain complete cyclization. Compared with the corresponding tertiary anionic cyclization without the allylic hydroxyl group (Scheme 1, 1 h at −78 °C, 17% cyclized product, 68% uncyclized product), the cyclization is greatly accelerated by the allylic

(40) Bailey[2b] quite reasonably invoked coordination of the Li attached to carbon to both the axial O atom and the π bond in a conformation analogous to **24b** in a study of the cyclization of the analogue of **24** lacking the C-methyl group and with a MeO group in place of the OLi group of **24** in order to account for the modest cis selectivity under certain conditions. Such interaction appears to be weak according to the data provided, and it is not unexpected in view of the fact that the supposedly more powerful electrophilic participation that we suggest is not available in the case of the ether.

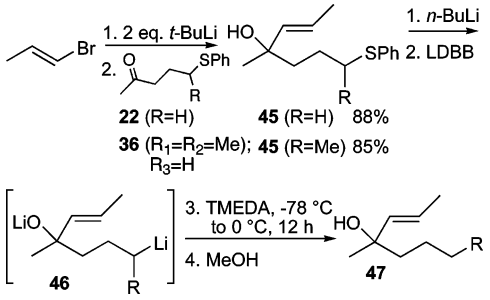
(41) Felkin, H.; Swierczewski, G.; Tambuté, A. *Tetrahedron Lett.* **1969**, *10*, 707−710 and references cited therein.

(42) Hashimoto, Y.; Sato, Y.; Takeshita, N.; Kudo, K.; Saigo, K. *Tetrahedron* **1994**, *50*, 8317−8336.

SCHEME 8. Primary Alkyllithium Cyclization Mediated by an Exo Primary Allylic Lithium Oxyanion



SCHEME 9. Attempted Cyclization of Alkyllithiums with a Terminally Methylated Alkene

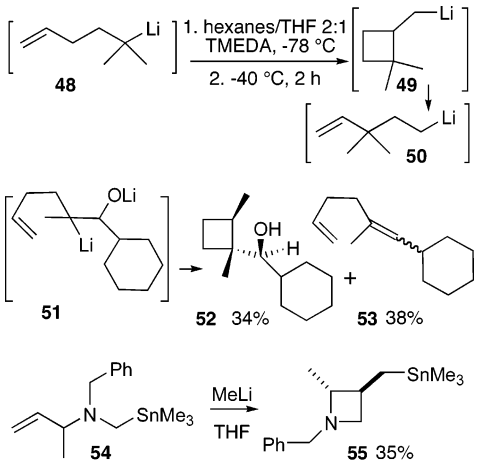


lithium oxyanion. Moreover, the cyclizations are completely stereoselective, and only the expected *trans*-diastereomers are obtained.

In the cases of oxyanionic participation discussed above and below, the allylic oxyanionic group is positioned such that it is a ring substituent in the cyclized organolithium. The type of allylic oxyanionic participation shown in Scheme 8, in which the alcohol function is positioned exo to the ring, is seen to be equally effective at promoting cyclization. The cyclization substrate **42** was readily prepared by alkylation[43] of the dianion **41** of methallyl alcohol with 3-phenylthio-1-bromopropane.[44]

A major limitation of intramolecular carbolithiation is that cyclizations are unsuccessful when an alkyl substituent is present at the terminus of the alkene,[3,7a,45] presumably due to the fact that in the transition state of the cyclization a less stable secondary anion is being generated rather than the primary one that is being generated in the absence of this alkyl group. To test whether the allylic oxyanionic effect could overcome this limitation, perhaps allowing annulation on to a cyclic alkene, the experiments in Scheme 9 were performed. Allylic alcohols **45** were prepared by the addition of *trans*-1-propenyllithium to the appropriate ketones prepared as described above. Unfortunately, dianion **46** (R = H), generated by *n*-BuLi/LDBB, failed to cyclize at −78 °C for 12 h; only uncyclized product **47** (R = H) was found after the MeOH quench. On the other hand, as pointed out by Broka[7a] in a related case, this result provides a third piece of convincing evidence for the carbanionic over the radical cyclization mechanism in the case of organolithiums produced by reductive lithiation of phenyl thioethers by preformed aromatic radical anions. The cyclization of a radical generated from substrate **45** (R = H) should be a very favorable process because a primary radical would be converted to a more

SCHEME 10. Literature Cyclizations to Cyclobutylmethyllithiums



stable secondary radical, in addition to the usual thermodynamic advantage of such cyclizations in the conversion of a π to a σ bond. Cyclization also failed to occur when the reaction mixture was allowed to warm to 0 °C. In this case, quenching with CD_3-OD gave undeuterated **47** (R = H), indicating that the primary alkyllithium in the presence of the oxyanionic group is a strong enough base to remove a proton from the THF solvent in preference to cyclizing on to the terminally methyl-substituted alkene. Neither could cyclization be induced by the addition of tetramethylethylenediamine (TMEDA) at −78 °C and then warming to 0 °C.

Even the secondary organolithium **46** (R = Me) failed to cyclize, although as outlined above, secondary organolithiums cyclize with far greater facility than primary ones. The failure of the latter cyclization, with two major accelerating factors, is intriguing in light of the fact that even relatively mildly electron-withdrawing groups, such as phenyl,[46] trimethylsilyl,[46] and phenylthio,[15,47] allow such cyclizations. It seems likely that three factors are involved, steric crowding in the transition state for cyclization, the degree of stability of the developing alkyllithium, and the greater basicity toward THF of the uncyclized alkyllithiums, due presumably to lithium bonding with the oxyanionic group. In the experiments described here, the proton removal from THF apparently competes with cyclization that requires a higher temperature than usual because of the first two factors mentioned above. This phenomenon deserves further study.

To our knowledge, the only reports of cyclobutylmethyllithiums being produced by intramolecular carbolithiations are that from earlier work from this laboratory[34] in which **48** and **51** were cyclized and the more recent report by Coldham[48] of the cyclization of the primary organolithium derived by Li−Sn exchange in **54**, all occurring in less than satisfactory yields (Scheme 10).[49] Under the conditions shown, the tertiary bishomoallyllithium **48**, produced by reductive lithiation, cyclized partially to **49**, some of which rearranged to the primary

(43) Lipshutz, B. H.; Sharma, S.; Dimock, S. H.; Behling, J. R. *Synthesis* **1992**, 191−195.

(44) Bakuzis, P.; Bakuzis, M. L.; Fortes, C. C.; Santos, R. *J. Org. Chem.* **1976**, 41, 2769−2770.

(45) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K. V. *J. Am. Chem. Soc.* **1992**, *114*, 8053−8060.

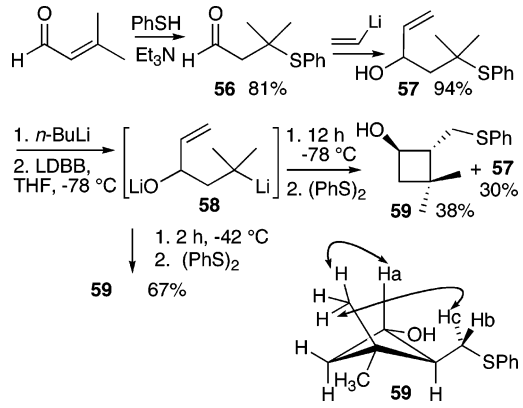
(46) Bailey, W. F.; Gavaskar, K. V. *Tetrahedron* **1994**, *50*, 5957−5970.

(47) Further examples of cyclizations of unconjugated alkyllithiums aided by a terminal phenylthio group: Kim, S.; Kim, B. S.; Jon, S. Y. *Bull. Korean Chem. Soc.* **1994**, 701−702. Ashweek, N. J.; Coldham, I.; Snowden, D. J.; Vennall, G. P. *Chem. Eur. J.* **2002**, *8*, 195−207.

(48) Coldham, I.; Hufton, R. *Tetrahedron* **1996**, *52*, 12541−12552.

(49) A satisfactory yield of a four-membered ring was obtained when an alkyllithium underwent intramolecular conjugate addition to an unsaturated ester: Cooke, M. P. J.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381−1396.

SCHEME 11. Stereoselective Cyclobutanol Formation Mediated by an Allylic Lithium Oxyanion



bishomoallyllithium **50**; the three alkyllithiums were trapped by isobutyraldehyde in yields of 21%, 31%, and 21%, respectively. Cyclization of the tertiary bishomoallyllithium **51**, bearing an oxyanionic group exo to the forming ring, produced the cyclobutane **52** along with the elimination product **53**. The organolithium derived from **54** presumably cyclized to a primary organolithium that abstracted a trimethylstannyl group from **54** to provide 35% of cyclization product **55**.

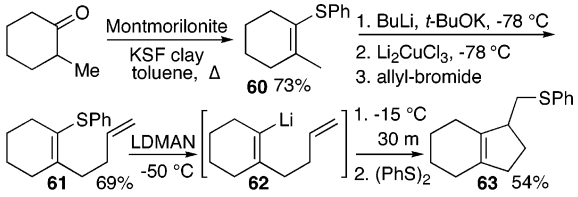
It seemed possible that cyclization in higher yield might occur with the driving force provided both by the conversion of a tertiary to a primary organolithium, as in Scheme 10, and the lower temperatures allowed by an allylic lithium oxyanion, as well as the inability of the cyclized organolithium to reopen to a less substituted organolithium as occurred with **49**.

Once again, the ease of generation of substrates containing the phenylthio group and the allylic alcohol function in the proper relationship to each other was a great help (Scheme 11). Preparation of the cyclization substrate **57** by conjugate addition of thiophenol to 2-methyl-2-propenal followed by addition of vinyllithium occurred smoothly. Dianion **58** was generated in the usual way at −78 °C. Initially, the reaction was performed at −78 °C for 12 h and quenched with phenyl disulfide. To our delight, the cyclization of dianion **58** is completely stereoselective and cyclobutanol **59** was obtained as a single diastereomer in 38% yield. Increasing the temperature from −78 to −42 °C did not affect the stereoselectivity but accelerated the cyclization rate considerably, producing **59** in 67% yield in 2 h, no starting material being detected. The stereochemistry of cyclobutanol **59** is again exclusively trans as determined by 2D NMR spectroscopy.

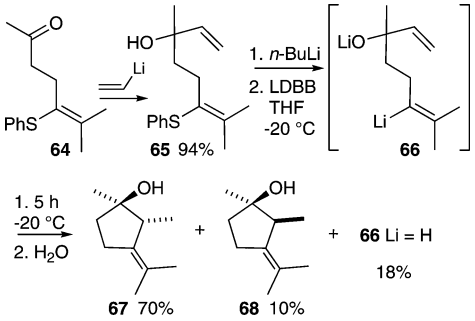
Attempted cyclization of the primary alkyllithium analogue of **58**, synthesized in the same way except preparing the substrate from acrolein, was unsuccessful at −40 °C for 5 h. The cyclization in this case may be thermodynamically unfavorable.

Vinyl Anion Cyclizations. The versatility of using reductive lithiation of phenyl thioethers in organolithium cyclizations is further illustrated by the cyclization of vinyllithiums generated in this way.[50] In the first example, shown in Scheme 12, the reductive lithiation substrate **61** is prepared in a two-pot sequence from 2-methylcyclohexanone.[51] Cyclization of the reductive lithiation product **62** yields the fused cyclopentenyl-

SCHEME 12. Formation of a Fused Ring System by Cyclization of a Cyclohexenyllithium



SCHEME 13. Vinyllithium Cyclization Mediated by an Allylic Lithium Oxyanion



methyllithium precursor of **63**. Larger ring size cycloalkenyl phenyl sulfides would very likely produce higher yields since their reductive lithiation causes cleavage almost entirely at the vinyl CS bond while in the case of cyclohexenyl phenyl sulfides, some cleavage is observed at the phenyl CS bond.[50] It should be noted that cyclization of the allylated cyclohexenyllithium, generated by the Shapiro reaction, gives a different regioisomer of **63**.[10]

As shown in Scheme 13, an sp^2 organolithium **66** is subject to the same type of stereochemical control by an allylic lithium oxyanionic group but with somewhat less stereoselectivity. The reductive lithiation substrate **65** was produced by the addition of vinyllithium to ketone **64**,[52] the conjugate addition product of the cuprate of the reductive lithiation product of 1,1-bisphenylthio-2-methylpropene, itself generated in one step from isobutyric acid and aluminum thiophenoxide.

Studies of the cyclization of dianion **66** showed that the cyclization is very sensitive to temperature. At a temperature lower than −40 °C, no cyclization was observed. When the reaction was performed at −20 °C for 5 h, two diastereomers (**67** and **68**) were formed in a ratio of 8:1 in favor to the trans diastereomer **67** (that with the hydroxyl group trans to the methyl group, generated by quenching the CH_2Li group). The two diastereomers are inseparable by flash column chromatography, so the ratio was determined by proton NMR spectroscopy. When the reaction was performed at −15 °C for 4.5 h, the diastereomeric ratio decreased to 3:1, still in favor of the trans diastereomer. In both cases (−20 and −15 °C), some product from protonation of vinyl anion **66** was also isolated. A longer time is probably needed to obtain complete cyclization. Compound **67** is known,[53] and the stereochemistry here was assigned by NMR comparison with values in the literature.

Construction of a Trans-Fused Diquinane Alcohol. Cis-fused diquinane **69c** has a lower energy than trans-fused

(50) For a discussion of the production of vinyllithiums from vinyl phenyl sulfides, see: Cohen T.; Doubleday: M. D. *J. Org. Chem.* **1990**, *55*, 4784−4786.

(51) For the use of Montmorillonite clay for the production of **60**, see: Labiad, B.; Villemin, D. Synthesis **1989**, 143−44. For the use of a cuprate for regiocontrol in the allylation, see: Giner, J. L.; Margot, C.; Djerassi, C. *J. Org. Chem.* **1989**, *54*, 2117−2125.

(52) Cohen, T.; Zhang, B.; Cherkauskas, J. P. *Tetrahedron* **1994**, *50*, 11569−11584.

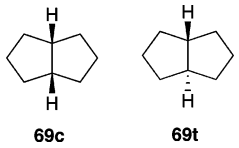


FIGURE 1. *cis*- and *trans*-diquinane.

diquinane **69t** due to the strain at the fused ring junction. According to simple AM2 calculations, the trans one **69t** is about 4 kcal/mol higher in energy than the cis one **69c** (Figure 1). However, due to the facilitating effect of the allylic oxyanionic group and the favorable thermodynamics, a relatively inaccessible *trans*-bicylo[3.3.0]octane can be prepared, albeit in reduced yield.

As illustrated in Scheme 14, for the first Michael addition step, two diastereomers were formed in yields of 63% and 4%, respectively. The trans product **70** was assumed to be the major product due to equilibration during the quenching of the enolate intermediate. Later, an X-ray crystal structure of the diquinane **72** proved the trans configuration of compound **70**.

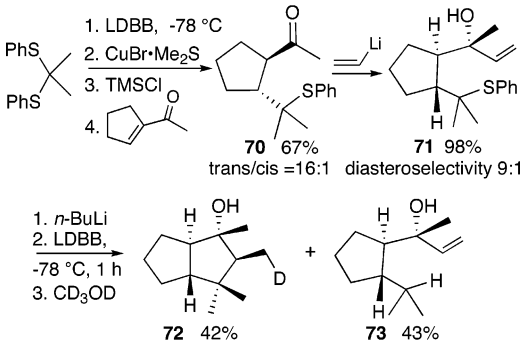
The reaction of vinyllithium with ketone **70** also occurs stereoselectively to give allylic alcohol **71**, the diastereomer predicted by the Felkin−Ahn model,[54] as the major product; the ratio or major to minor diastereomers was 9/1. The stereochemistry of **71** was deduced from the X-ray crystal structure of the diquinane **72.** Alcohol **71**, after separation from the small amount of its diastereomer, was treated with *n*-BuLi/LDBB to generate the corresponding dianion, followed by quenching with CD_3OD after the reaction had proceeded at −78 °C for 1 h. Diquinane alcohol **72** was isolated as the major cyclized product in 42% yield together with 43% of uncyclized product **73**. MS and NMR spectroscopy show that compound **72** is deuterated but that there is no deuterium at all in **73**. Some of the generated tertiary organolithium was protonated during the reaction before it could cyclize. It is likely that, as discussed above, coordination of the oxygen anion with the lithium cation associated with the tertiary organolithium makes the latter more basic than other tertiary alkyllithiums and that the proton is removed from THF even at −78 °C.

The X-ray crystal structure of compound **72** is shown in the Supporting Information. Clearly, a trans-fused diquinane has been synthesized and the stereochemistry between OH- and CH_2D is trans, similar to the results obtained in the cyclization of tertiary organolithiums **38d** and **38e**, mediated by an allylic lithium oxyanion (Scheme 14).

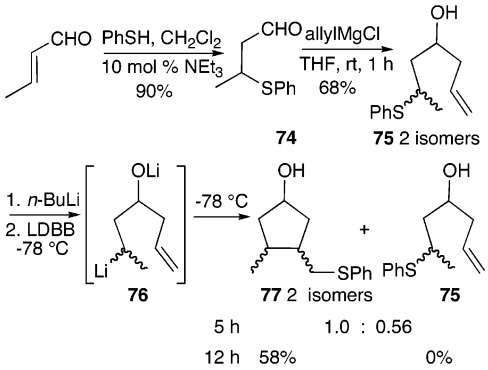
The Effect of Homoallylic Oxyanionic Groups on Intramolecular Carbolithiations. In view of the remarkable accelerating effect of allylic lithium oxyanionic groups on these cyclizations, it was of interest to determine whether *homo*allylic oxyanionic groups have a similar effect. There are two types of homoallylic analogues of the allylic oxyanionic groups that were discussed above. In one type, the oxyanionic group is within the forming ring. We term this type an endo oxyanionic group. In the second type, the homoallylic oxyanionic group is exo to the forming ring.

An examination of molecular models makes it appear unlikely that an endo oxyanionic group could provide substantial nucleophilic or electrophilic assistance. As usual, the preparation

SCHEME 14. Synthesis of a *Trans*-Fused Diquinane



SCHEME 15. Cyclizations in the Presence of an Endo Homoallylic Lithium Oxyanion



of the substrates was facile as outlined in Scheme 15. The substrates **75** for the attempted cyclization were prepared by nucleophilic allylation of the adduct **74** of thiophenol and crotonaldehyde. Deprotonation and reductive lithiation generated the dianion **76**, which was allowed to remain at −78 °C for 12 h. When the reaction mixture was quenched with diphenyl disulfide, only cyclized product **77** was isolated; its NMR spectrum indicated that it was mainly one isomer. An aliquot which had been removed at the end 5 h and quenched in the same way was found by NMR to still contain uncyclized material; the ratio of **77** to **75** was 1.0:0.56. As indicated by a comparison of this result with the complete cyclization in 10 min at the same temperature of the secondary organolithium analogue **10** of **76**, without the oxyanionic substituent, it is clear that there is no assistance to cyclization by the endo homoallylic oxyanionic group and that in this case it actually inhibits the cyclization. The inhibition of cyclization can plausibly be attributed to the stabilization of the dianion **76** by coordination of the oxyanion to the lithium ion attached to carbon that results in a five-membered ring.

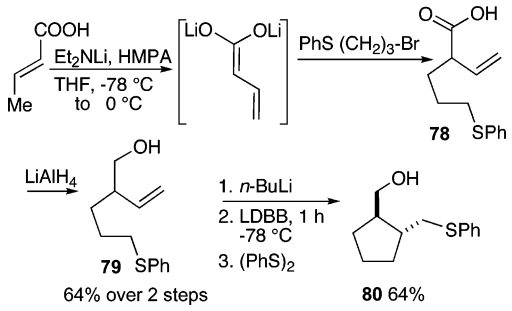
Not surprisingly, the study of the effect of an exo homoallylic lithium oxyanion proved more rewarding. The substrate **79** was readily prepared by reduction of the carboxylic acid obtained by alkylation[55] of the dianion of crotonic acid with 3-phenylthio-1-bromopropane.[44] As shown in Scheme 16, treatment with *n*-butyllithium/LDBB for 1 h at −78 °C, followed by a diphenyl disulfide quench, resulted in the production of 64% of cyclization product **80**. Thus, the acceleration afforded by the *homoallylic* oxyanion exo to the forming ring is even more effective than that provided by the exo *allylic* oxyanionic group of **42** (Scheme 8) in accelerating the cyclization. The stereochemistry

(53) Sticker, H.; Ohloff, G.; Kovats, E. *Helv. Chim. Acta* **1967**, *78*, 759−797.

(54) Wong, S. S.; Paddon-Row: M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456−458.

(55) Aurell, M. J.; Gil, S.; Mestres, R.; Parra, M.; Parra, L. *Tetrahedron* **1998**, *54*, 4357−4366.

SCHEME 16. Cyclization in the Presence of an Exo Homoallylic Lithium Oxyanion



of the product is trans as in all of the examples in which acceleration is afforded by allylic oxyanions.

Summary

This study of the scope and limitations of anionic cyclizations to five-membered rings and in one case a four-membered ring makes it clear that the reductive lithiation of phenyl thioethers by aromatic radical-anions is the most general method available for the preparation of the required alkyl- or vinyllithiums. Among the advantages of this method are the great ease of preparation of the reductive lithiation precursor resulting from the great versatility of the phenyl thioether group in organic synthesis, the ability to generate primary, secondary, and tertiary organolithiums as well as many vinyllithiums in high yield in most cases, and the use of THF, a solvent known to facilitate cyclization. The relative rates of cyclization for alkyllithiums are secondary > tertiary > primary, and in the secondary case, the stereoselectivity is extremely high, producing a cyclopentylmethyllithium or cyclobutylmethyllithium with a trans 2-alkyl substituent. An extremely useful finding is that a lithium oxyanionic group in the proximal allylic position to the alkene greatly accelerates the cyclization and leads almost exclusively to a trans relationship between the CH_2Li group and the OLi group. Thus, a valuable functionality can be incorporated in predictable stereochemistry into the cyclization product that also possesses the versatile organolithium function. The trans stereochemical relationship between the OLi and CH_2Li observed here is just the opposite of that observed in the Li− and Mg−ene cyclizations in which an *allyl*metal instead of an *alkyl*metal is used. In the latter cases, a six-center transition state is widely accepted. It is postulated that in the metallo-ene cyclizations, the flexible transition state allows the oxyanionic group to participate in a *nucleophilic* fashion whereas in the nonallylic cyclizations the much more restricted four-center transition state makes *electrophilic* acceleration, whereby the lithium counterion attached to the oxyanion activates the alkene by coordination, more favorable. A *homoallylic* oxyanionic group has an effect similar to that of an *allylic* one as long as the hydroxyl group is exo to the ring in the product. On the other hand, a homoallylic oxyanionic group that is endo to the forming ring actually substantially decreases the rate of cyclization. Finally, an interesting limitation emerged in that a terminal methyl group on the alkene completely inhibits the cyclization even when a highly reactive secondary alkyllithium is used in the presence of the usually highly activating allylic oxyanionic group.

Experimental Section

Unless otherwise indicated, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz for ^1H and 75 MHz for ^{13}C at 22 °C.

6-Methyl-6-phenylthio-1-heptene 3. A solution of 23.0 mmol of LDMAN,[56] prepared from 3.8 mL of DMAN (23.0 mmol) and 161 mg (23.0 mmol) of Li in 45 mL of THF, was cooled to −78 °C and treated with 2,2-bis(phenylthio)propane (2.90 g, 11.2 mmol) in 10 mL of THF. The dark green color of the solution turned into dark red. After 10 min of stirring, 1-bromo-4-pentene (1.39 mL, 11.2 mmol) was added. The resulting mixture was stirred at −78 °C for 2 h, and then the temperature was raised to −20 °C. After the solution had been stirred at −20 °C for 30 min, satd aq $NaHCO_3$ (30 mL) was added. The reaction mixture was extracted with ether (50 mL × 3). The combined organic layer, after being washed with 30 mL of 5% HCl (to remove DMAN) and 30 mL of brine, was dried over anhydrous $MgSO_4$, filtered through cotton, and evaporated in vacuo. The resulting residue was purified by flash chromatography with hexane to give 2.19 g (89% yield) of **3** as a yellow oil. ^1H NMR: δ 7.53−7.30 (m, 5 H), 5.83 (m, 1 H), 5.06−4.95 (m, 2 H), 2.05 (m, 2 H), 1.58 (m, 2 H), 1.49 (m, 2 H), 1.24 (s, 6 H). ^{13}C NMR: δ 138.7, 137.8 (2 C), 132.6, 128.8, 128.6 (2 C), 114.9, 49.3, 42.0, 34.3, 29.1, 24.3. IR ν_{max} (thin film): 3075, 2958, 2933, 2862, 1641, 1474, 1438, 1364, 911, 749, 694 cm^{-1}. MS (EI) *m*/*z*: 220 (M^+, 57), 179 (45), 151(65), 123 (45), 110(60), 95 (57), 81(75), 69(100), 55(75). HRMS: exact mass calcd for $C_{14}H_{20}S$ (M^+) 220.1286, found 220.1286.

1-(2,2-Dimethylcyclopentylmethylthio)-4-methoxybenzene 7. Freshly prepared LDBB[57] (3.80 mmol in 10 mL of THF) at −78 °C was cannulated to a flask containing compound **3** (220 mg, 1.53 mmol) in 10 mL of THF at −78 °C under argon. The resulting mixture was stirred at −45 °C for 2 h before it was quenched with di-*p*-methoxyphenyl disulfide (650 mg, 2.30 mmol) in 5 mL of THF. The reaction mixture was extracted with ether (20 mL × 3). The combined organic layer, after being washed with brine, was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The resulting residue was purified by flash chromatography with 1% ethyl acetate in hexane to give 360 mg (94% yield) of **7** as a pale yellow oil. ^1H NMR: δ 7.38 (d, 2 H, J = 9.4 Hz), 6.87 (d, 2 H, J = 9.4 Hz), 3.79 (s, 3 H), 3.06 (dd, 1 H, J = 12.0 Hz, 3.8 Hz), 2.61 (dd, 1 H, J = 12.0 Hz, 11.0 Hz), 2.10 (m, 1 H), 1.70−1.40 (m, 6 H), 1.05 (s, 3 H), 0.85 (s, 3 H). ^{13}C NMR: δ 158.7, 132.5 (2 C), 128.3, 114.7 (2 C), 55.3, 49.0, 42.2, 41.3, 37.6, 30.9, 28.2, 21.9, 21.4. IR ν_{max} (thin film): 2953, 2868, 1592, 1493, 1463, 1285, 1245, 1173, 1034, 825 cm^{-1}. MS (EI) *m*/*z*: 250 (M^+, 78), 153 (52), 140 (93), 125 (47), 111 (26), 96 (19), 77 (19), 69 (100), 55 (26). HRMS: exact mass calcd for $C_{15}H_{22}OS$ (M^+) 250.1381, found 250.1391.

***trans*-2-Methylcyclopentyl)acetic Acid 14.** Freshly prepared LDBB (5.40 mmol in 15 mL of THF) at −78 °C was cannulated to a flask containing 6-phenythio-1-heptene **9** (446 mg, 2.17 mmol) in 10 mL of THF at −78 °C under an argon atmosphere. The reaction mixture was stirred at −78 °C for 15 min, and CO_2 was bubbled in for about 1 h. After the addition of 5% HCl (15 mL), the temperature was allowed to rise to ambient. The mixture was extracted with Et_2O (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered through cotton, and evaporated in vacuo. The residue was purified by flash chromatography to give 250 mg (81% yield) of **14** as a pale yellow oil. ^1H NMR: δ 11.5 (br, 1 H), 2.50 (dd, 1 H, J = 15.0, 4.9 Hz), 2.16 (dd, 1 H, J = 15.0, 9.4 Hz), 2.00−1.10 (m, 8 H), 0.99 (d, 3 H, J = 6.5 Hz). ^{13}C NMR: δ 180.7, 43.8, 40.5, 39.1, 34.4, 32.4, 23.2, 18.9. IR ν_{max} (thin film): 3300−2400 (broad O−H stretch), 2954, 2870, 1708, 1410, 1289 cm^{-1}. MS (EI) *m*/*z*: 142 (M^+, 25), 127 (33), 124 (39), 113 (35), 109 (35), 99 (100), 88 (78). HRMS: exact mass calcd for $C_8H_{14}O_2$ (M^+) 142.0994, found 142.0991.

Ethyl *trans*-2-Methylcyclopentyl acetate 15. Acid **14** (161 mg, 1.13 mmol) and a catalytic amount of concd H_2SO_4 (1 drop) were

(56) Experimental details for the preparation of LDMAN can be found in the Supporting Information.

(57) Experimental details for the preparation of LDBB can be found in the Supporting Information.

added to 20 mL of EtOH in a three-neck flask (50 mL) equipped with a reflux condenser. The resulting mixture was heated at reflux for 24 h. After the reaction mixture had been cooled to room temperature, it was extracted with ether (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered through cotton, and evaporated in vacuo. The residue was purified by flash chromatography (5% ethyl acetate in hexane) to give 192 mg (89% yield) of **15** as a yellow oil. ^{1}H NMR: δ 4.11 (q, 2 H, J = 7.1 Hz), 2.43 (dd, 1 H, J = 14.7, 5.1 Hz), 2.07 (dd, 1 H, J = 14.7, 9.2 Hz), 1.14−2.00 (m, 8 H), 1.23 (t, 3 H, J = 7.1 Hz), 0.95 (d, 3 H, J = 6.6 Hz). ^{13}C NMR: δ 173.6, 60.1, 44.1, 40.5, 39.3, 34.5, 32.4, 23.2, 18.9, 14.3. IR ν_{max} (thin film): 2954, 2870, 1737, 1459, 1375, 1330, 1251, 1190, 1135, 1033, 734 cm^{-1}. MS (EI) *m*/*z*: 170 (M^+, 26), 155(7), 142(10), 125 (17), 97 (12), 88 (100), 84 (49), 67 (18), 61 (32), 55 (51). HRMS: exact mass calcd for $C_{10}H_{18}O_2$ (M^+) 170.1307, found 170.1307.

3-Methyl-6-(phenylthio)hex-1-en-3-ol 23. To freshly prepared vinyllithium (31.2 mmol) was added dropwise ketone **22** (3.10 g, 16.0 mmol) in 5 mL of Et_2O via syringe. The mixture was stirred for 2 h at −78 °C, and then the temperature was raised to −20 °C and maintained there for 30 min before the addition of 40 mL of satd aq $NaHCO_3$ (40 mL). The mixture was extracted with ether (50 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered through cotton, and evaporated in vacuo. The residue was purified by flash chromatography to give 3.07 g (87% yield) of **23** as a colorless oil. ^{1}H NMR: δ 7.36−7.18 (m, 5 H), 5.90 (dd, 1 H, J = 17.3, 10.7 Hz), 5.21 (dd, 1 H, J = 17.3, 1.2 Hz), 5.07 (dd, 1 H, J = 10.7, 1.2 Hz), 2.98−2.93 (m, 2 H), 1.80−1.60 (m, 4 H), 1.39 (s, 1 H, −OH), 1.30 (s, 3 H). ^{13}C NMR: δ 144.9, 136.9, 128.9 (4 C), 125.8, 112.1, 73.1, 41.3, 34.0, 27.9, 23.8. MS (EI) *m*/*z*: 222 (M^+, 24), 204 (19), 136 (51), 123(100), 110 (41), 95 (62), 84 (43), 79 (35), 71 (40), 55 (10). HRMS: exact mass calcd for $C_{13}H_{18}OS$ (M^+) 222.1078, found 222.1082.

(1*R,2*R**)-1-Methyl-2-(phenylthiomethyl)cyclopetan-1-ol**[58] **25.** To a stirred solution of alcohol **23** (656 mg, 2.95 mmol) in 10 mL of THF at −78 °C under argon was added *n*-BuLi (3.20 mmol, 2.00 mL) via syringe. Freshly prepared LDBB (7.40 mmol in 20 mL THF) at −78 °C was cannulated to the reaction flask. The mixture was stirred at −78 °C for 12 h before the addition of phenyl disulfide (966 mg, 4.40 mmol) in 5 mL of THF. After the mixture had been stirred for 30 min further, satd aq $NaHCO_3$ (20 mL) was added, and the mixture was allowed to warm to room temperature. The resulting mixture was extracted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton, and evaporated in vacuo. The resulting residue was purified by flash chromatography to give 531 mg (81% yield) of **25** as a yellow oil and 51 mg (8%) of **23**. ^{1}H NMR: δ 7.36−7.10 (m, 5 H), 3.05 (dd, 1 H, J = 12.4, 6.4 Hz), 2.79 (dd, J = 12.4, 8.0 Hz), 2.10−1.90 (m, 2 H), 1.80−1.40 (m, 4 H), 1.39 (m, 1 H), 1.22 (s, 3 H). ^{13}C NMR: δ 136.7, 129.16 (2 C), 129.01 (2 C), 126.1, 80.5, 48.8, 41.2, 35.0, 29.8, 22.9, 20.2. IR ν_{max} (neat) 3387 (br), 3058, 2960, 2872, 1583, 1480, 1438, 1376, 1313, 1090, 1025, 738, 691 cm^{-1}. MS (EI) *m*/*z*: 222 (M^+, 16), 204 (8), 123(12), 110 (58), 95 (44), 84 (100), 79 (14), 71 (5), 58 (7). HRMS: exact mass calcd for $C_{13}H_{18}OS$ (M^+) 222.1078, found 222.1085.

Cyclized products **39a**−**e** were obtained by treating their THF solution with *n*-BuLi and LDBB sequentially, and the reactions were performed at the indicated temperatures and times. See the preparation of cyclized product **25** for a representative procedure.

***trans*-2-(Phenylthiomethyl)cyclopentan-1-ol 39a.** ^{1}H NMR: δ 7.42−7.19 (m, 5 H), 4.02 (m, 1 H), 3.01 (m, 2 H), 2.60 (br, 1 H, −OH), 2.12−1.85 (m, 3 H), 1.90−1.50 (m, 3 H), 1.50−1.30 (m, 1 H). ^{13}C NMR: δ 136.8, 129.2 (4 C), 126.1, 78.7, 47.3, 37.8, 34.5, 30.2, 21.9. MS (EI) *m*/*z*: 208 (M^+, 20), 190 (8), 123 (17), 110 (100), 98 (96). HRMS: exact mass calcd for $C_{12}H_{16}OS$ (M^+): 208.0922, found 208.0917.

3-Methyl-2-(phenylthiomethyl)cyclopentan-1-ol 39b. Two diastereomers were obtained in a ratio of 7:1. Major diastereomer **39b**: 71% yield. Minor diastereomer **39b-minor**: 11% yield.

39b. ^{1}H NMR: δ 7.51−7.30 (m, 5 H), 4.19 (m, 1 H), 3.33 (dd, 1 H, J = 12.8, 4.7 Hz), 3.02 (dd, J = 12.8, 8.3 Hz), 2.92 (s, 1 H, −OH), 2.05−1.50 (m, 6 H), 1.19 (d, 3 H, J = 6.2 Hz). ^{13}C NMR: δ 136.9, 129.1 (2 C), 128.9 (2 C), 126.0, 78.7, 54.6, 38.5, 36.5, 33.3, 31.5, 20.0. MS *m*/*z*: 222 (M^+, 59), 123 (19), 100 (100), 97 (53), 70 (64), 55 (18). HRMS: exact mass calcd $C_{13}H_{18}OS$ (M^+) 222.1078, found 222.1073.

39b-minor. ^{1}H NMR: δ 7.39−7.17 (m, 5 H), 4.39 (m, 1 H), 3.18 (dd, 1 H, J = 12.2, 4.4 Hz), 3.01 (dd, 1 H, J = 12.2, 11.0 Hz), 2.02−1.10 (m, 6 H), 1.52 (s, 1 H, −OH), 1.04 (d, 3 H, J = 6.5 Hz). ^{13}C NMR: δ 136.8, 129.05 (2 C), 128.90 (2 C), 126.0, 73.95, 51.9, 37.2, 32.29, 32.25, 31.5, 19.1. MS *m*/*z*: 222 (M^+, 31), 123 (13), 100 (69), 95 (44), 84 (100), 70 (64). HRMS: exact mass calcd $C_{13}H_{18}OS$ (M^+) 222.1078, found 222.1077.

(1*R,2*R**,3*S**)-1,3-Dimethyl-2-(phenylthiomethyl)cyclopentan-1-ol 39c.** Two diastereomers were obtained in a ratio of 6:1. Major diastereomer **39c**: 78% yield. Minor diastereomer **39c-minor**: 14% yield.

39c. ^{1}H NMR: δ 7.43−7.23 (m, 5 H), 3.10 (dd, 1 H, J = 12.6, 5.1 Hz), 2.99(dd, 1 H, J = 12.6, 8.5 Hz), 2.74 (br, 1 H), 1.93−1.66 (m, 5 H), 1.36 (m, 1 H), 1.33 (s, 3 H), 1.14 (d, 3 H, J = 6.0 Hz). ^{13}C NMR: δ 136.7, 129.1 (2 C), 129.0 (2 C), 126.1, 81.1, 55.7, 40.1, 38.6, 33.9, 30.3, 24.1, 20.9. MS *m*/*z*: 236 (M^+, 26), 218 (19), 178 (8), 123 (10), 100 (100), 69 (17), 59 (23). HRMS: exact mass calcd $C_{14}H_{20}OS$ (M^+) 236.1235, found 236.1236.

39c-minor. ^{1}H NMR: 7.39−7.19 (m, 5 H), 3.05−2.91 (m, 2 H), 2.42 (m, 1 H), 2.17 (m, 1 H), 1.97 (m, 1 H), 1.85−1.64 (m, 3 H), 1.30 (s, 3 H), 0.94 (d, 3 H, J = 7.2 Hz). ^{13}C NMR: δ 136.8, 129.05 (2 C), 128.90 (2 C), 126.0, 73.95, 51.9, 37.2, 32.3, 31.5, 19.1. MS *m*/*z*: 236 (M^+, 22), 218 (25), 178 (6), 123 (14), 110 100), 69 (22), 55 (12). HRMS: exact mass calcd $C_{14}H_{20}OS$ (M^+) 236.1231, found 236.1235.

***trans*-3,3-Dimethyl-2-(phenylthiomethyl)cyclopentan-1-ol 39d.** ^{1}H NMR: δ 7.40−7.20 (m, 5 H), 4.17 (m, 1 H), 3.21 (dd, 1 H, J = 12.9, 3.93 Hz), 2.79 (dd, 1 H, J = 12.9, 11.1 Hz), 2.11 (m, 1 H), 1.70−1.20 (m, 4 H), 1.05 (s, 3 H), 0.85 (s, 3 H). ^{13}C NMR: δ 136.1, 129.2 (4 C), 126.4, 79.9, 56.2, 41.6, 39.3, 34.0, 31.5, 29.0, 23.1. IR ν_{max} (neat): 3401(br), 3058, 2953, 2867, 1584, 1480, 1463, 1439, 1366, 1090, 1061, 1026, 739, 691 cm^{-1}. MS(EI) *m*/*z*: 236 (M^+, 45), 218 (7), 126 (40), 110 (100), 97 (18), 70 (99), 55 (39). HRMS: exact mass calcd for $C_{14}H_{20}OS$ (M^+) 236.1235, found 236.1236.

(1R*,2S*)-1,3,3-Trimethyl-2-(phenylthiomethyl)cyclopentan-1-ol 39e. ^{1}H NMR: δ 7.42−7.13 (m, 5 H), 3.06 (dd, 1 H, J = 12.6, 5.1 Hz), 2.91 (dd, 1 H, J = 12.6, 10.4 Hz), 2.2 (br, 1 H, −OH), 1.93−1.69 (m, 4 H), 1.46 (m, 1 H), 1.38 (s, 3 H), 1.11 (s, 3 H), 0.91 (s, 3 H). ^{13}C NMR: δ 136.3, 129.1 (4 C), 126.2, 81.3, 58.3, 41.0, 39.8, 39.0, 30.92, 30.86, 25.6, 23.4. MS *m*/*z* 250 (M^+, 30), 232 (16), 123 (100), 110 (67), 81 (58), 67 (29), 55 (40). HRMS: exact mass calcd for $C_{15}H_{22}OS$ (M^+) 250.1391, found 250.1379.

2-(4-Phenylsulfanylbutyl)prop-2-en-1-ol 42. To a flame-dried, three-neck round-bottom flask equipped with an argon inlet, a magnetic stirring bar, and a rubber septum, to a solution of TMEDA (1.66 mL, 11.0 mmol) in hexane (2 mL) was added *n*-BuLi (1.66 mL, 1.51 M solution in hexane, 11.0 mmol) while the mixture was maintained below −10 °C. A vigorous reaction occurred, resulting in a thick white slurry, which was stirred at this temperature for 30 min. After the reaction mixture had been cooled to −78 °C, a solution of 2-methyl-2-propen-1-ol **40** (421 μL, 5.00 mmol) in 2 mL of hexane was added dropwise. The mixture was allowed to stir overnight (∼12 h) before it was warmed to ambient temperature. Then, the mixture was cooled to −78 °C, and phenyl 3-bromopropyl sulfide (965 mg, 4.16 mmol) in 2 mL of THF was added. The mixture was allowed to warm slowly to ambient temperature overnight (∼ 12 h), and the reaction was quenched with satd aq

(58) "*" Means that the compound is racemic and thus that these are relative configurations.

NH_4Cl. The organic layer from the ether extraction was washed with brine and concentrated in vacuo. Column chromatography on silica gel using 20% of EtOAc in hexane afforded 485 mg (53% yield) of **42** as a colorless oil. ^{1}H NMR: 7.17−7.35 (m, 5 H), 5.03 (s, 1 H), 4.87 (s, 1 H), 4.07 (s, 2 H), 2.94 (t, 2 H, J = 6.9 Hz), 2.09 (t, 2 H, J = 7.5 Hz), 1.58−1.73 (m, 4 H). ^{13}C NMR: 148.4, 136.6, 128.83, 128.75, 125.7, 109.4, 65.6, 33.3, 32.3, 28.7, 26.7. MS (EI) *m*/*z*: 222 (M^+, 28), 194 (35), 135 (10), 123 (65), 110 (100), 95 (35), 84 (32), 77 (39), 72 (56), 65 (36), 58 (55). HRMS (EI): calcd for $C_{13}H_{18}OS$ 222.1078, found 222.1077.

(1-Methylcyclopentyl)methanol 44.[59] A solution of 444 mg (2.00 mmol) of **42** in 5 mL of THF was cooled to −78 °C and added to 1.60 mL of *n*-BuLi (2.21 mmol, 1.38 M solution in hexane). After being stirred for 15 min, the resulting yellowish solution was transferred to a solution of LDBB in THF (5.00 mmol, 16.7 mL) at −78 °C and left at this temperature for 12 h. The reaction was quenched with 5 mL of water. The mixture was diluted with ether, and the extract was washed with brine, dried over $MgSO_4$, and concentrated on the rotary evaporator. The crude mixture was purified by flash chromatography with 10% of EtOAc in hexane to give 162 mg of colorless oil (71% yield). ^{1}H NMR: 3.38 (s, 2 H), 1.27−1.71 (m, 8 H), 1.01 (s, 3 H). ^{13}C NMR: 65.7, 32.6, 31.3, 29.9, 29.7, 22.4, 13.9. MS (EI) *m*/*z*: 114 (M^+, 15), 97 (14), 81 (48), 69 (76), 57 (100).

***trans*-3,3-Dimethyl-2-(phenylthiomethyl)cyclobutan-1-ol 59.** To a stirred solution of alcohol **57** (300 mg, 1.35 mmol) in 10 mL of THF at −78 °C under argon was added *n*-BuLi (0.93 mL, 1.5 mmol) via syringe. Freshly prepared LDBB (3.40 mmol in 10 mL of THF) at −78 °C was cannulated to the reaction flask. The reaction mixture was stirred at −42 °C for 2 h before the addition of phenyl disulfide (471 mg, 2.16 mmol) in 5 mL of THF. After the mixture had been stirred for 30 min more, 10 mL of satd $NaHCO_3$ solution was added. The resulting mixture was extracted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton, and evaporated in vacuo. The residue was purified by flash chromatography (10% ethyl acetate in hexane) to afford 201 mg (67% yield) of **59** as a yellow oil. ^{1}H NMR: δ 7.40−7.16 (m, 5 H), 3.95 (m, 1 H), 3.04−3.00 (m, 2 H), 2.13−2.02 (m, 2 H), 1.76 (m, 1 H, −OH), 1.58 (m, 1 H), 1.16 (s, 3 H), 1.04 (s, 3 H). ^{13}C NMR: δ 136.7, 129.1 (4 C), 126.1, 69.1, 53.6, 43.4, 33.2, 31.2, 30.5, 23.2. IR ν_{max} (neat): 3332(br), 3058, 2954, 2930, 2863, 1585, 1481, 1439, 1066, 737, 690 cm^{-1}. MS (EI) *m*/*z* 222 (M^+, 35), 178 (17), 149 (9), 123 (15), 110 (100), 95 (26), 69 (95), 57 (43). HRMS: exact mass calcd for $C_{13}H_{18}OS$ (M^+) 222.1078, found 222.1071.

(2-But-3-enylcyclohex-1-enylsulfanyl)benzene 61. To 5 mL of a dry THF solution of 1-phenylthio-2-methylcyclohexene **60** (1.02 g, 5.00 mmol) at −78 °C under argon was successively added 3.72 mL of 1.48 M *n*-BuLi in hexane (5.51 mmol) and 6 mL of a 1.0 M solution of *t*-BuOK in THF (6.00 mmol). The reaction mixture was maintained at −78 °C with stirring for 3 h. To the allylmetallic prepared in this way at −78 °C was added 1.25 mL of a 1.00 M solution of Li_2CuCl_3 in THF, prepared from 516 mg of CuCl (5.20 mmol) and 452 mg of LiCl (10.6 mmol) in 5 mL of dry THF. The clear orange solution immediately became black. Upon shaking, it quickly lightened to a tan color and had a gelatinous consistency. After the solution had been stirred for 1 h at the same temperature, 605 μL (7.00 mmol.) of allyl bromide was added at once, and the mixture was allowed to warm slowly to room temperature overnight. During the course of the reaction, the mixture became black and less viscous. The mixture was poured into water and extracted with ether. Filtration of the reaction mixture on Celite improved the separation of the phases. After the usual workup, the crude product was purified by flash chromatography on silica gel using hexane to give 842 mg (69% yield) of colorless oil. ^{1}H NMR: 7.03−7.27 (m, 5H), 5.75−5.86 (m, 1H), 4.93−5.09 (m, 2H), 2.48 (t, 2H, J = 7.7 Hz), 2.16−2.21 (m, 6H), 1.64−1.68 (m, 4H). ^{13}C NMR: 144.9, 138.4, 136.7, 128.8, 128.2, 125.2, 114.6, 34.9, 32.6, 31.6, 30.9, 24.2, 22.8. MS (EI) *m*/*z*: 244 (M^+, 65), 203 (100), 169 (20), 161 (22), 147 (65), 141 (18), 135 (70), 123 (55), 109 (35), 91 (85), 77 (80), 65 (52), 55 (35). HRMS (EI): calcd for $C_{16}H_{20}S$ 244.1286, found 244.1275.

1-Phenylsulfanylmethyl-2,3,4,5,6,7-hexahydro-1*H*-indene 63. To a cooled (−78 °C) 0.30 M solution of LDMAN in THF (5.82 mmol, 19.5 mL) was added a solution of 570 mg of **61** (2.33 mmol) in 5 mL of THF. The reaction mixture was allowed to warm to −15 °C and to remain at that temperature for 30 min. A solution of 610 mg of phenyl disulfide (2.80 mmol) in 2 mL of THF was slowly added, and the mixture was stirred for an additional 1 h. The reaction mixture was poured into aq HCl (2 N) and worked up in the usual manner. The crude material was purified by flash chromatography with hexane to give 307 mg (54%) of **63** as a colorless oil. ^{1}H NMR: 7.14−7.50 (m, 5 H), 3.19 (dd, 1 H, J = 1.4, 8.6 Hz), 2.72−2.79 (m, 2 H), 1.88−2.25 (m, 6 H), 1.55−1.61 (m, 6 H). ^{13}C NMR: 137.7, 136.5, 135.2, 131.0, 128.7, 125.4, 47.4, 38.3, 34.7, 28.6, 25.9, 24.1, 22.93, 22.88. MS (EI) *m*/*z*: 244 (M^+, 20), 186 (15), 135 (15), 121 (100), 91 (20), 84 (26), 79 (30), 67 (21). HRMS (EI) calc for $C_{16}H_{20}S$ 244.1286, found 244.1280.

(1*R,2*R**)- and (1*R**,2*S**)-1,2-Dimethyl-3-(methylethylidene)-cyclopentan-1-ol 67 and 68.** To a stirred solution of alcohol **65** (266 mg, 1.06 mmol) in 10 mL of THF at −78 °C under argon was added *n*-BuLi (1.17 mmol, 0.74 mL) via syringe. Freshly prepared LDBB (2.65 mmol in 7 mL of THF) at −78 °C was cannulated to the reaction flask. The temperature was then raised to −20 °C, and the reaction mixture was stirred at that temperature for 5 h. After the addition of 20 mL of satd $NaHCO_3$ solution, the resulting mixture was extracted with ether (20 mL × 3). The extract was dried over $MgSO_4$, filtered through cotton, and evaporated in vacuo. The residue was purified by flash chromatography (10% ethyl acetate in hexane) to afford 135 mg (80%) of a mixture of **67** and **68** in a major/minor ratio of 7:1. 3,7-dimethylocta-1,6-dien-3-ol (31 mg, 18%) was also isolated. Major diastereomer (1*R**,2*R**)-**67**. ^{1}H NMR: δ 2.42−2.25 (m, 3 H), 1.88−1.65 (m, 2 H), 1.66 (s, 3 H), 1.60 (s, 3 H), 1.26 (s, 3 H), 0.87(d, 3 H, J = 7.2 Hz). ^{13}C NMR: δ 139.3, 124.0, 81.9, 48.8, 37.0, 27.1, 23.5, 21.0, 20.8, 17.2. Minor diastereomer (1*R**,2*S**)-**68**. ^{1}H NMR ($CDCl_3$) δ 2.42−2.25 (m, 3 H), 1.88−1.65 (m, 3 H), 1.64 (s, 3 H), 1.55 (s, 3 H), 1.20 (s, 3 H), 0.96 (d, 3 H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 137.8, 123.5, 79.3, 46.6, 37.3, 27.9, 26.8, 20.8, 20.6, 14.5. MS *m*/*z*: 154 (M^+, 40), 136 (53), 121 (91), 111 (43), 107 (52), 96 (62), 81 (100), 69 (85), 55 (90). HRMS: exact mass calcd for $C_{10}H_{18}O$ 154.1358, found 154.1357.

2,3,4,4-Tetramethylbicyclo[3.3.0]octan-2-ol 72. To a stirred solution of alcohol **71** (304 mg, 1.05 mmol) in 10 mL of THF at −78 °C under argon was added *n*-BuLi (0.74 mL, 1.20 mmol) via syringe. Freshly prepared LDBB (2.63 mmol in 7 mL of THF) at −78 °C was cannulated to the reaction flask. The resulting mixture was stirred at −78 °C for 1 h before the addition of 1 mL of CD_3-OD. The reaction mixture was extracted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton, and evaporated in vacuo. The residue was purified by flash chromatography (10% ethyl acetate in hexane) to give 80 mg cyclized product **72** (42%) as a white solid. Uncyclized product **73** (82 mg, 43%) was also isolated as a pale yellow oil.

72. ^{1}H NMR: δ 2.01−1.88 (m, 3 H), 1.60−1.42 (m, 3 H), 1.25−1.13 (m, 3 H), 1.03 (s, 3 H), 0.91(s, 3 H), 0.83 (m, 2 H), 0.81 (s, 3 H). ^{13}C NMR: δ 61.4, 59.1, 58.1, 34.5, 26.94, 26.89, 26.2, 21.8, 20.5, 17.3, 9.3 (t, J = 16.3 Hz). IR ν_{max} (thin film): 3334 (br), 2955, 2872, 1458, 1365, 1098, 978, 938 cm^{-1}. MS *m*/*z* 165 (M^+-H_2O, 33), 150 (100), 136 (30), 122 (54), 111 (82), 93 (38), 79 (41), 67 (29), 55 (26). HRMS: exact mass calcd 165.1628 (M^+ − H_2O), found 165.1635.

73. ^{1}H NMR: δ 5.93 (dd, 1 H, J = 17.3, 10.8 Hz), 5.20 (dd, 1 H, J = 17.3, 1.4 Hz), 5.05 (dd, 1 H, J = 10.8, 1.4 Hz), 1.87−1.42 (m, 9 H), 1.25 (s, 3 H), 0.90 (d, 3 H, J = 6.6 Hz), 0.81 (d, 3 H, J

(59) Shiner, V. J., Jr.; Tai, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 436−442.

= 6.5 Hz). ^{13}C NMR: δ 144.51, 111.89, 75.91, 52.06, 45.94, 31.69, 29.27, 27.65, 26.93, 26.31, 22.62, 17.46.

2-(3-Phenylsulfanylpropyl)but-3-en-1-ol 79. Crotonic acid (860 mg, 10.0 mmol) in 10 mL of THF was slowly added at −78 °C to a stirred lithium diethylamide solution (generated from 22 mmol of 1.5 M solution of *n*-BuLi and 22 mmol of diethylamine in 10 mL of THF at 0 °C). The resulting solution was allowed to warm to 0 °C and to remain at this temperature for an additional 30 min before being cooled again to −78 °C. 3-Bromo-1-(phenylthio)-propane (10 mmol) was added dropwise, and the solution was stirred at ambient temperature for 1 h. Water was added, and the mixture was extracted twice with ether. The aqueous layer was acidified by careful addition of concd HCl and then extracted three times with ethyl acetate. The extract was washed with aq NaCl and dried over $MgSO_4$. Evaporation of the solvent gave crude acid **78**, which was spectroscopically pure and was submitted directly to reduction with an equimolar amount of lithium aluminum hydride (LAH) in THF at ambient temperature for 1 h. The excess of LAH was quenched by diluting carefully with ethyl acetate and then water. After the usual workup, the crude alcohol **79** was purified by flash chromatography with 10% EtOAc in hexane to give an overall yield of 64%. ^{1}H NMR: 7.15−7.36 (m, 5 H), 5.11−5.25 (m, 2 H), 3.57 (dd, 1 H, J = 5.2, 10.5 Hz), 3.42 (dd, 1 H, J = 8.2, 10.5 Hz), 2.85−2.99 (m, 2 H), 2.17−2.27 (m, 1 H), 1.54−1.71 (m, 4 H). ^{13}C NMR: 139.3, 136.6, 128.9, 128.80, 125.75, 117.7, 65.5, 46.6, 33.5, 29.6, 26.5. MS (EI) *m*/*z*: 222 (M^+, 25), 204 (25), 194 (23), 136 (75), 123 (100), 110 (82), 95 (50), 79 (45), 65 (35), 55 (35). HRMS (EI): calcd for $C_{13}H_{18}OS$ 222.1078, found 222.1071.

***trans*-(2-Phenylsulfanylmethylcyclopentyl)methanol 80.** A solution of 444 mg (2.00 mmol) of **79** in 5 mL of THF was cooled to −78 °C and added to 1.60 mL of *n*-BuLi (2.21 mmol, 1.38 M in hexane). After being stirred for 15 min, the resulting yellowish solution was transferred to a solution of LDBB in THF (5.0 mmol, 16.7 mL) at −78 °C and left at this temperature for 1 h. The reaction mixture was then quenched with a solution of phenyl disulfide (655 mg, 3.00 mmol) in 2 mL of THF. The mixture was diluted with ether, and the extract was washed with brine, dried over $MgSO_4$, and concentrated on the rotary evaporator. The crude mixture was purified by flash chromatography with 10% of EtOAc in hexane to give 284 mg (64% yield) of **80** as a colorless oil. ^{1}H NMR: 7.15−7.36 (m, 5 H), 3.57 (m, 2 H), 3.07 (dd, 1 H, J = 5.43, 12.4 Hz), 2.93 (dd, 1 H, J = 6.6, 12.4 Hz), 1.37−1.91 (m, 8 H). ^{13}C NMR: 128.9, 128.8, 125.7, 66.5, 47.7, 41.9, 39.5, 32.9, 29.5, 24.4. MS (EI) *m*/*z*: 222 (M^+, 54), 136 (10), 123 (74), 110 (100), 94 (63), 81 (49), 67 (48), 55 (42). HRMS (EI): calcd for $C_{13}H_{18}OS$ 222.1078, found 222.1076.

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Supporting Information Available: Experimental procedures and compound characterization, including NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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