

As can be seen in Table III, the free energy of activation for the conformational flipping process (ΔG_c^\ddagger) at the coalescence temperature (T_c) appears to bear intrinsic correlation with the bond types of the bridges connecting the meta-bridged benzene and the para-linked one. Boekelheide ascribed the sharply decreased energy barrier for the exchange process in **84** as compared to **83** to two chief factors: (1) the lowering of the energy of the transition state by conjugative stabilization as the meta-bridged ring becomes coplanar with the two vinyl bridges; (2) the widening of the bridge angles from 109.5° (sp^3) to 120° (sp^2) compensates the effect of bond shortening.⁵⁵ Cyclophane **78**, whose flipping transition state is lowered by conjugative stabilization and whose bridge angles are widened to 120° , was expected to show a similar value of ΔG_c^\ddagger as in **84**. However, the ΔG_c^\ddagger of **78** is found to be intermediate between those of **84** and **83**. This phenomenon may have been caused by the unfavorable nonbonded interaction between the protons of the embedded "bi-phenyl" structural units as **78** approaches the transition state for the conformational flipping process (Scheme XXII). Such an argument is also applicable to compounds **79** and **85**.

Concluding Remarks

Despite the lack of mechanistic information about the mode of action of the low-valent-titanium reagent, the compounds so far obtained by us through this methodology should generate sufficient stimuli for future studies. Thus, the yet to be synthesized strained alkyne

(56) Wittek, M.; Vögtle, F. *Chem. Ber.* 1982, 115, 1363-1366.

6 and its derivatives are expected to display intriguing electrical properties and might therefore qualify as candidates for organic conductors.⁵⁷ Introduction of polar functional groups to the benzo-fused tetraphenylenes is anticipated to modify their abilities as host molecules in clathration. In the area of dibenzo-[2.2]cyclophanes, organometallic chemistry utilizing **65** as a novel ligand is presently under investigation by us and others.⁴⁸ In addition, more accurate determination of the ΔG_c^\ddagger for **78** can be carried out with the aid of the double-irradiation technique of Forsén and Hoffman.⁵⁸ In conclusion, we have shown the combined use of Diels-Alder cycloaddition and low-valent-titanium deoxygenation to be a powerful tool in the synthesis of novel benzenoid molecules.

I wish to thank all my collaborators, whose names are mentioned in the references, for their invaluable contribution to this program, which was initiated at the Shanghai Institute of Organic Chemistry. Dr. T.-L. Chan assisted in the preparation of this Account, and his advice and suggestions are gratefully acknowledged. Thanks are also due to Prof. T. C. W. Mak for reading the manuscript and making helpful comments. I further acknowledge with thanks financial support in the form of undergraduate summer project subsidies from Chung Chi College, New Asia College, and United College of the Chinese University of Hong Kong and in the form of graduate studentships from the Croucher Foundation (Hong Kong). The Chou's Foundation also gave partial financial support to our work through the Student Campus Work Scheme administered by the Office of Student Affairs of the Chinese University of Hong Kong.

(57) Inter alia, see: Williams, J. M.; Carneiro, K. *Adv. Inorg. Chem. Radiochem.* 1985, 29, 249-296.

(58) Forsén, S.; Hoffman, R. A. *J. Chem. Phys.* 1963, 39, 2892-2901. Forsén, S.; Hoffman, R. A. *J. Chem. Phys.* 1964, 40, 1189-1196.

Organoalkali Compounds by Radical Anion Induced Reductive Metalation of Phenyl Thioethers

THEODORE COHEN* and MAHADEVAN BHUPATHY

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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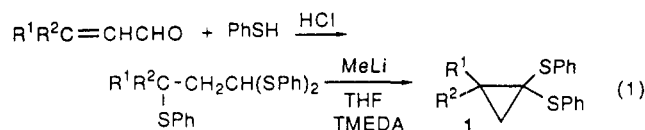
Alkylolithiums and α -Lithio Thioethers

In 1977, a visiting scientist, W. M. Daniewski, made a discovery that gave a new direction to the work in our laboratory. He found that the lithio derivatives of

Theodore Cohen was born near Boston, MA, in 1929. He received his B.S. degree from Tufts College and his Ph.D. from the University of Southern California under Jerome Berson. After a year of postdoctoral work at the University of Glasgow under Derek H. R. Barton, he was appointed to the faculty of the University of Pittsburgh, where he is Professor of Chemistry. Until the mid 1970s, his major interests were in mechanistic organic chemistry in the fields of diazonium ions, copper organic chemistry, and pyridine *N*-oxides. More recently, his main interest has been in devising novel synthetic methodology, particularly in the areas of small rings, carbanions, and sulfur organic chemistry.

Mahadevan Bhupathy was born in Madras, India, in 1953. He received his B.Sc. and M.Sc. degrees from the University of Madras and served as Scientific Officer with the Department of Atomic Energy of India in the field of high-temperature thermodynamics. His Ph.D. and postdoctoral work were done at the University of Pittsburgh with Theodore Cohen in the field of construction and ring expansions of small rings and the synthesis of pheromones. He is now a Senior Research Chemist at Merck Sharp & Dohme Research Laboratories, Rahway, NJ.

diphenyl dithioacetals bearing a 3-phenylthio substituent undergo a very efficient ring closure to form cyclopropanone dithioketals (e.g., eq 1).^{1,2} This reaction, later shown³ to be an intramolecular S_N2 reaction, permitted the synthesis of a variety of cyclopropanone dithioacetals.



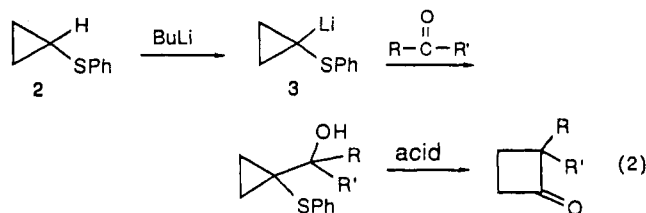
Previous to this finding, Trost had developed a useful synthesis of cyclobutanones based on the reaction of

(1) Cohen, T.; Daniewski, W. M. *Tetrahedron Lett.* 1978, 2991.

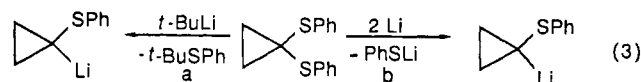
(2) Another efficient method for producing cyclopropanone dithioacetals is also available starting from epoxides. Braun, M.; Sebach, D. *Chem. Ber.* 1976, 109, 669.

(3) Cohen, T.; Matz, J. R. *J. Org. Chem.* 1979, 44, 4816.

1-lithio-1-(phenylthio)cyclopropane (**3**) with aldehydes and ketones followed by acid-catalyzed ring expansion (eq 2).⁴ However, Trost's method could not be executed with other 1-lithio-1-(phenylthio)cyclopropanes since even a methyl substituent on the cyclopropane ring severely slowed the rate of proton removal.



We perceived that a great expansion in the utility of Trost's cyclobutanone synthesis would result if cyclopropanone dithioacetals such as **1** could be converted to 1-lithio-1-(phenylthio)cyclopropanes, and we found that sulfur-lithium exchange (eq 3a) and reductive lithiation (eq 3b) were both successful in causing this transformation.⁵ Of the two forms of lithium tested for eq 3b, lithium dissolved in hexamethylphosphoric triamide (HMPA) and lithium naphthalenide (LN)^{6,7} in THF, LN was considered more practical because HMPA is carcinogenic and could also cause problems of enolate formation upon attack of the organolithium on unsaturated or enolizable ketones. Lithium in liquid ammonia also appeared to be successful in performing this reduction, but the resulting anion was apparently protonated by the solvent, producing phenyl cyclopropyl sulfide, which was reduced again; only thiophenol could be detected, due presumably to the loss of cyclopropane upon workup.



While this work was in progress, a report appeared by Screttas and Micha-Screttas⁸ showing that even simple phenyl thioethers can be reductively lithiated with LN. Primary, secondary, and tertiary alkyl phenyl thioethers were converted to alkyllithium reagents and carbonated to carboxylic acids. In some cases yields were lowered by apparent attack of the radical intermediate on the naphthalenide radical anion. However, this problem could likely be largely avoided by the use of lithium *p,p'*-di-*tert*-butylbiphenylide (LDBB),⁹ which not only is a more powerful reducing agent but is less susceptible to radical attack. Indeed, in Stork's recent synthesis of (+)-(9*S*)-dihydroerythronolide A, use is made of a primary alkyllithium formed by LDBB reduction of a phenyl thioether.¹⁰

(4) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 3088 and citations therein.

(5) Cohen, T.; Daniewski, W. M.; Weisenfeld, R. B. *Tetrahedron Lett.* **1978**, 4665.

(6) Holy, N. L. *Chem. Rev.* **1974**, *74*, 243.

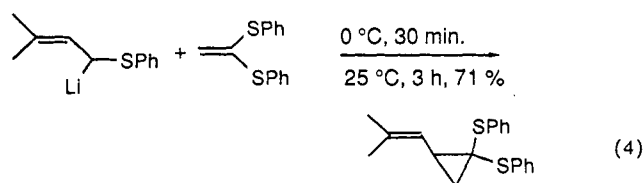
(7) The concept of using lithium naphthalenide for this transformation arose in a stimulating conversation between Dr. Theodore Cohen and Dr. William Kitching while they were both on sabbatical leave at the University of North Carolina in early 1978.

(8) Screttas, C. G.; Micha-Screttas, M. J. *J. Org. Chem.* **1978**, *43*, 1064; **1979**, *44*, 713.

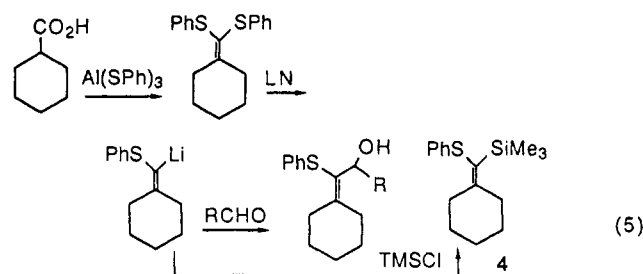
(9) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924; **1983**, *48*, 4705.

(10) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565. For the use of LN to produce a primary alkyllithium, see: Fernández, S.; Hernández, E. *Synth. Commun.* **1982**, *12*, 915.

In our own work, we were able to show that the 1-lithio-1-(phenylthio)cyclopropanes could be captured by aldehydes, ketones, carbon dioxide, and trimethylsilyl chloride.⁵ The scope of the method was greatly increased when it was found that a considerably expanded variety of reductive lithiation substrates was available by a connective variant (e.g., eq 4) of the reaction shown in eq 1.¹¹



The concept was further extended when it was found that carboxylic acids and esters could be converted to their corresponding acyl anion equivalents by treatment¹² with aluminum thiophenoxide to yield a ketene dithioacetal which was capable of reductive lithiation¹³ to a 1-lithio-1-(phenylthio)alkene (eq 5). The reduction in eq 5 was important because it hinted at the potential generality of reductive lithiation and it was the first example of the formation of a vinyl lithium by this process.



Reductive lithiation of the types of dithioacetals described above and trimethylsilylation of the resulting anions proved to be general, but substantial difficulty was encountered in separating the naphthalene from the nonpolar silylation product, a valuable substrate for further reductive lithiation (see below).^{14,15} In some cases, the naphthalene could be removed by sublimation¹³ or, in the case of liquid products, by crystallization followed by chromatography.¹⁶ This problem was solved by the use of lithium 1-(dimethylamino)naphthalenide (LDMAN),^{14,16-18} which is easily prepared by dissolving lithium in a THF solution of commercial 1-(dimethylamino)naphthalene (DMAN) at temperatures below -45 °C. The DMAN, which is the byproduct of the reductive lithiations, is readily removed from the product mixture with a dilute acid wash.¹⁴ The only disadvantage of this reagent over LN

(11) Cohen, T.; Weisenfeld, R. B.; Gapinski, R. E. *J. Org. Chem.* **1979**, *44*, 4744.

(12) Cohen, T.; Gapinski, R. E.; Hutchins, R. R. *J. Org. Chem.* **1979**, *44*, 3599. Connective syntheses of ketene dithioacetals: Seebach, D.; Gröbel, B.-T.; Kolb, M. *Chem. Ber.* **1973**, *106*, 2277. Mendoza, A.; Matteson, D. S. *J. Org. Chem.* **1979**, *44*, 1352.

(13) Cohen, T.; Weisenfeld, R. B. *J. Org. Chem.* **1979**, *44*, 3601.

(14) Cohen, T.; Matz, J. R. *Synth. Commun.* **1980**, *10*, 311.

(15) Paquette, L. A.; Wells, G. J.; Horn, K. A.; Yan, T. H. *Tetrahedron* **1983**, *39*, 913.

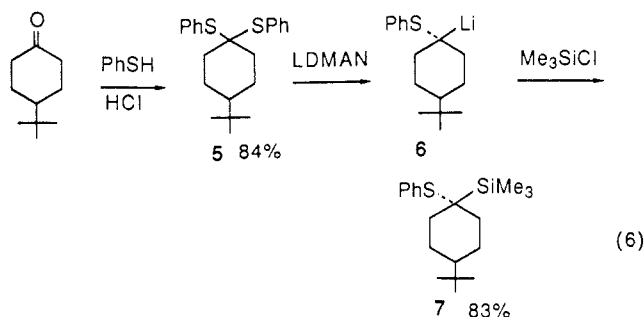
(16) Ager, D. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 183, 195.

(17) The sodium analogue was known: Bank, S.; Platz, M. *Tetrahedron Lett.* **1973**, 2097.

(18) For a detailed description of the preparation and use of this reagent, see: Cohen, T.; Sherbine, J. P.; Hutchins, R. R.; Lin, M.-T. *Organometallic Syntheses* **1986**, *3*, 361.

is that it is unstable above about $-45\text{ }^{\circ}\text{C}$, decomposing to 1-lithionaphthalene.¹⁴ Such decomposition does not interfere with reductive lithiations, which are generally performed at low temperatures, but a titratable¹⁹ stock solution cannot be used. If a higher temperature is required for the reduction, decomposition of the reagent can be avoided by using the stoichiometric quantity of lithium in the presence of far less than the stoichiometric quantity of DMAN.¹⁴ The latter acts as a conduit of electrons, and the deep blue color of the radical anion is not evident. It may be that decomposition is avoided because the low concentration of radical anion leads to a negligible concentration of the dianion,⁶ which might be the species that ejects the dimethylamide anion.

Simple dithioacetals of aldehydes^{16,20} and ketones^{8,16,21} also undergo reductive lithiation with LN^{8,16,20} or LDMAN (e.g., eq 6).^{16,21} The substrates are usually prepared by reaction of a carbonyl precursor with thiophenol and acid (eq 6),²¹ but other routes are also available.^{16,22} The reductive lithiation of dithioacetals is particularly important since the resulting tertiary anions (e.g., 6) cannot be produced satisfactorily by deprotonation or other exchange processes. They are particularly basic and can only be stored at $-78\text{ }^{\circ}\text{C}$ for short times. Fortunately, reduction of compounds such as 5 is extremely rapid due to the stability of the tertiary radical formed in the rate-determining step (see below).²¹



α -Lithio Organosilanes

The major use of the silylation products of α -lithio thioethers is as substrates for the production of α -lithio silanes via reductive lithiation (eq 7),^{15,16,21,23} although they have also been used for ketone production via sulfoxidation and sila-Pummerer rearrangement.^{16,24a,25} The α -lithio silanes are exceedingly useful in the Peterson olefination (eq 7)^{16,21} and in a related olefination proceeding through an acylsilane (e.g., eq 8).²³

Reductive lithiation is by far the most general method for production of α -lithio silanes.²¹ The major impediment to the general use of the Peterson olefination has thus been removed, and this reaction should take its place as a complement to the Wittig reaction. It is particularly promising since the anions can be treated

(19) Ager, D. J. *J. Organomet. Chem.* **1983**, *241*, 139. Screttas, C. G.; Screttas, M. M. *J. Organomet. Chem.* **1983**, *252*, 263.

(20) McDougal, P. G.; Condon, B. D.; Laffosse, M. D., Jr.; Lauro, A. M.; VanDerveer, D. V. *Tetrahedron Lett.* **1988**, *29*, 2547.

(21) Cohen, T.; Sherbine, J. P.; Matz, J. R.; Hutchins, R. R.; McHenry, B. M.; Willey, P. R. *J. Am. Chem. Soc.* **1984**, *106*, 3245.

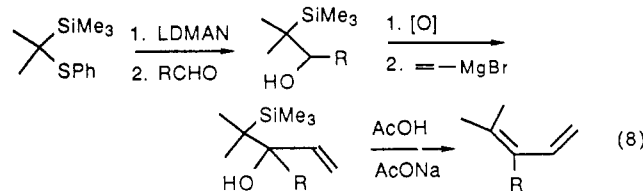
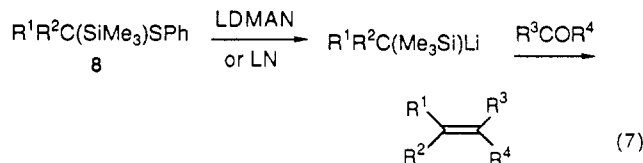
(22) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357.

(23) Jenkins, P. R.; Brown, P. A.; Bonnert, R. V.; Selim, M. R. *Tetrahedron Lett.* **1987**, *28*, 693.

(24) (a) Bhupathy, M.; Cohen, T. *Tetrahedron Lett.* **1987**, *28*, 4793.

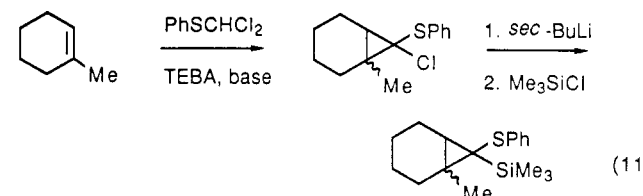
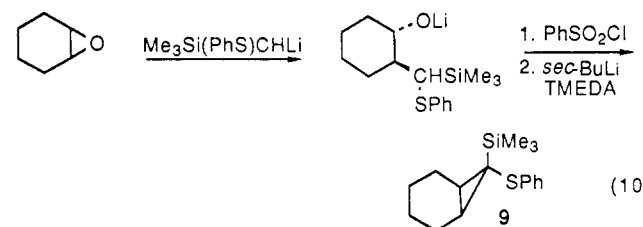
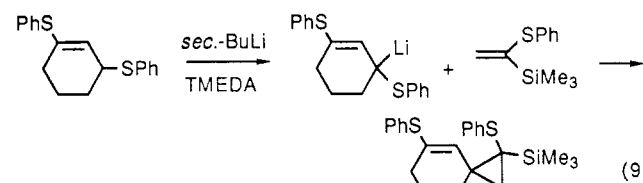
(b) Bhupathy, M.; Cohen, T. *Tetrahedron Lett.* **1987**, *28*, 4797.

(25) Review of organic compounds of sulfur and silicon: Block, E.; Aslam, M. *Tetrahedron* **1988**, *44*, 281.



with cerium(III) to generate powerful nucleophiles²⁶ toward the carbonyl group, and the resulting β -silanol can be induced to eliminate in either a syn or an anti fashion.²⁷

A most attractive use of this technology is in the preparation of alkylidene- and allylidene-cyclopropanes, compounds of considerable versatility.²¹ The substrates can be prepared as above by reductive lithiation and silylation of a cyclopropane diphenyl dithioacetal or by three other procedures exemplified by eq 9,²⁸ 10,²⁸ and 11.²⁹



The olefination procedure is exemplified in eq 12 and 13. In our original work,²¹ the alcohol corresponding to protonated 10 was isolated and the elimination was accomplished by treating it with KH in THF or diglyme. A more convenient one-pot procedure (eq 12 and 13),³⁰ leading to higher yields, involves treating the lithium alkoxide adduct (10) directly with potassium *tert*-butoxide.

The allylidene-cyclopropanes are particularly useful. Pyrolysis results in ring expansion to an alkylidene-cyclopentene.³¹ When the cyclopropane is fused to a

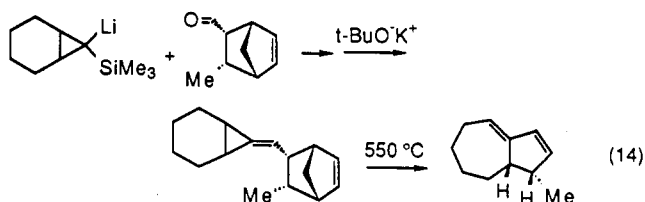
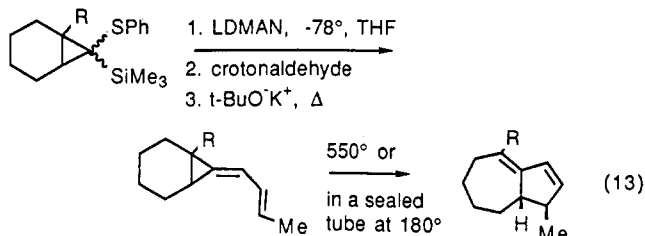
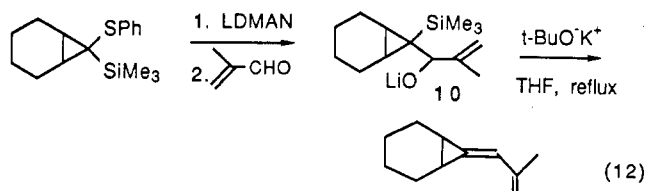
(26) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281.

(27) Hudrlik, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464.

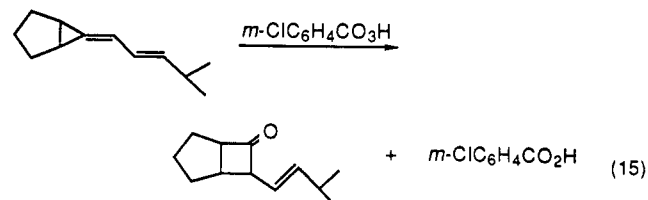
(28) Cohen, T.; Sherbine, J. P.; Mendelson, S. A.; Myers, M. *Tetrahedron Lett.* **1985**, *26*, 2965.

(29) Cohen, T.; Jung, S.-H.; Romberger, M., unpublished work. Equation 11 utilizes a modification of Makozsa's carbene-based method: Makozsa, M.; Bialecka, E. *Tetrahedron Lett.* **1971**, 4517.

(30) Cohen, T.; Jung, S.-H.; Romberger, M. L.; McCullough, D. W. *Tetrahedron Lett.* **1988**, *29*, 25.



cyclohexane ring, the process results in a double ring expansion to a hydrazulene with high stereocontrol (eq 13 and 14).³² This stereochemical result is consistent with an intermediate singlet diyl with two orthogonal odd electron arrays.³¹ When a methyl group is present at the bridgehead in the substrate, the methyl groups in the product³² of eq 13 are arranged as in the guaiane sesquiterpenes. If methyl groups are at both bridgeheads, the two are disposed in the thermolysis product as are the methyl groups in the pseudoguaianes.³² Oxidation of allylidencyclopropanes with peracids results in the production of 2-vinylcyclobutanones (e.g., eq 15),³³ which undergo a variety of ring expansions and fragmentations (see below).



α -Lithio Ethers

Early in our reductive lithiation work, it was perceived that its application to the production of unstabilized α -lithio ethers would be very rewarding, since no general preparative method was available for these species. Especially because of the many conceivable methods for production of the α -(phenylthio) ether precursors, as illustrated in eq 16–20,³⁴ reductive lithiation could be a useful complement to the more limited procedure involving tin–lithium exchange. The α -lithio silyl ethers produced in eq 18 and 19 undergo a common type of rearrangement of silicon from oxygen to carbon.³⁶

Reductive lithiation is the only general preparative method for five- and six-membered α -lithio cyclic eth-

(31) Billups, W. E.; Chow, W. Y.; Leavell, K. H.; Lewis, E. S. *J. Org. Chem.* 1974, 39, 274.

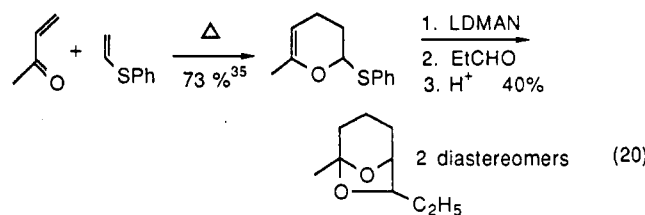
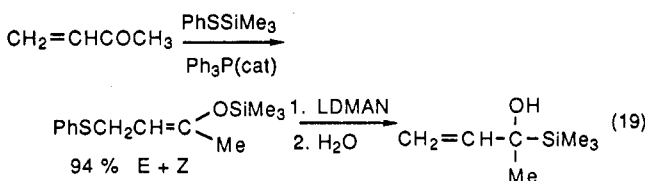
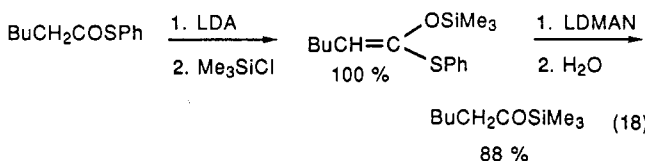
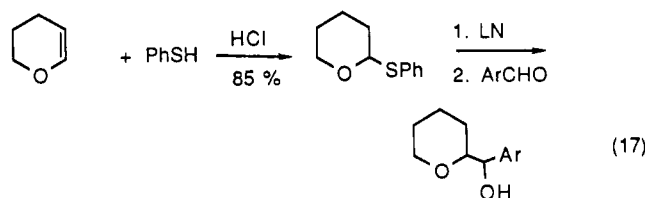
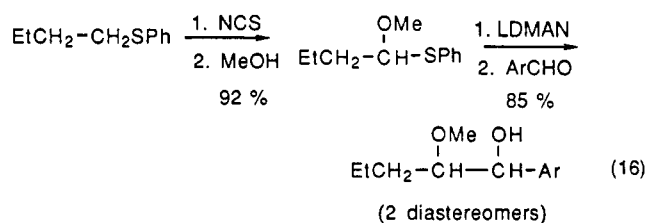
(32) Sherbine, J. P.; Jung, S.-H.; Romberger, M. L., unpublished work.

(33) Cohen, T.; McCullough, D. W. *Tetrahedron Lett.* 1988, 29, 27.

(34) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* 1980, 102, 6900.

(35) Based on consumed phenyl vinyl sulfide.

(36) Brook, A. G. *Acc. Chem. Res.* 1974, 7, 77.



ers. 2-Lithiotetrahydropyran, the intermediate in eq 17, had not been prepared previously.³⁷ Equation 20 represents a two-pot synthesis of the brevicomin, pheromones of a number of bark beetles.^{34,38}

A general and convenient method for producing the 2-phenylthio-substituted five- and six-membered ring ethers consists of reducing the corresponding lactone with diisobutylaluminum hydride (DIBAL) and treating the resulting aluminum salts of the lactols with thiophenol and boron trifluoride.^{39,40} Thus α -lithio cyclic ethers of five and six members are available by a two-pot procedure.³⁹ Scheme I³⁹ illustrates concise syntheses, using this technology, of racemic *trans*- and *cis*-rosoxide, substances that are found in roses and geraniums and are used in the perfume industry. This is the *first stereospecific synthesis of trans-rosoxide*. This scheme also illustrates another use of reductive lithiation, namely, the generation of an allyllithium (see below), which in this case results in ring fragmentation.

Reductive lithiation of the α -(phenylthio) ether derived from the corresponding 6-methyl δ -lactone also produced only the *trans* substitution product. Assuming that the methyl group is in an equatorial orientation, these results suggest that the carbon–lithium bond

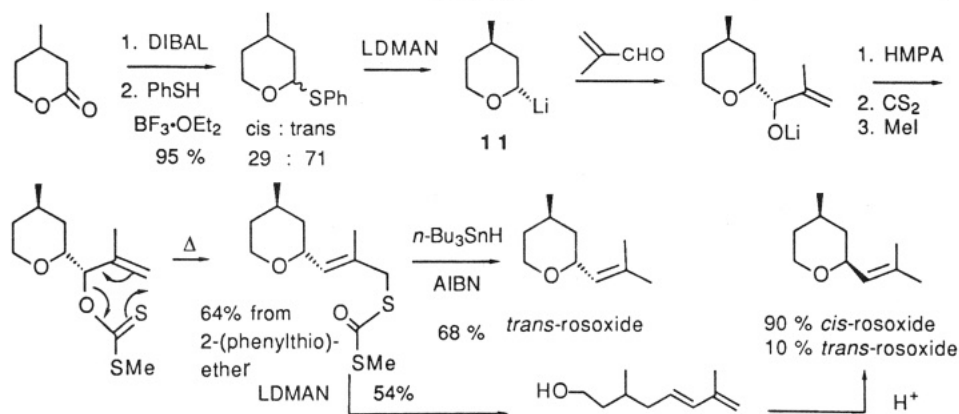
(37) It has since been prepared by tin–lithium exchange, but in considerably lower overall yield. Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* 1988, 110, 842.

(38) Cohen, T.; Matz, J. R. U.S. Patent 4,426,535, Jan 17, 1984. For a one-pot synthesis of *endo*-brevicomin, see: Cohen, T.; Bhupathy, M. *Tetrahedron Lett.* 1983, 24, 4163.

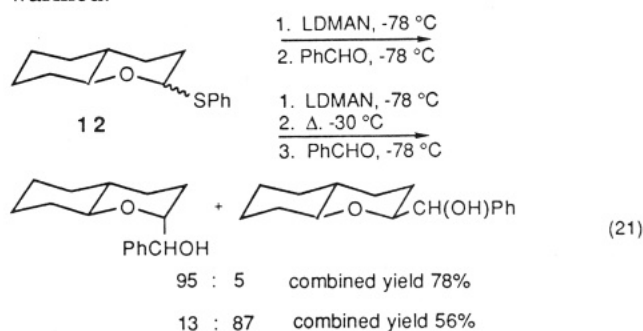
(39) Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* 1984, 106, 1130.

(40) 2-Phenylthio derivatives of seven-membered cyclic ethers could not be prepared in this way.⁴¹

Scheme I



formed by reductive lithiation is exclusively axial. This hypothesis is confirmed by the results of reductive lithiation of the epimeric mixture of trans-fused bicyclic α -(phenylthio) ethers **12**, prepared from the corresponding lactone.³⁹ When the organolithium is captured with benzaldehyde, the product is mainly the axial substitution product (eq 21),³⁹ and when it is captured by $\text{CH}_3\text{CO}_2\text{D}$, the resulting C-D bond is very largely axial. As indicated in eq 21, the first-formed axial α -lithio ether largely epimerizes upon being warmed to -30°C , an inversion that does not occur when the monocyclic organolithium **11** is similarly warmed.³⁹



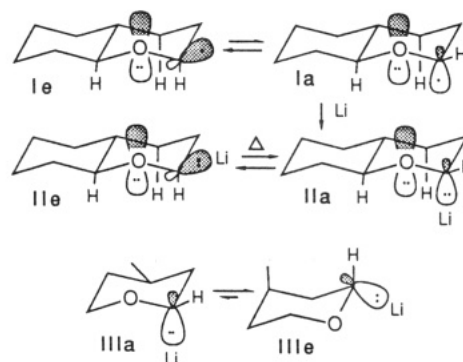
This remarkable stereochemical result is an interesting consequence of the radical nature of the key intermediates.³⁹ All of these results can be explained by an intermediate radical that is rapidly equilibrating stereochemically and that exists predominantly in the axial configuration (see I in Scheme II). There is considerable evidence that 2-tetrahydropyranyl radicals undergo rapid stereochemical equilibration at -78°C and that in the thermodynamically stable form the half-filled orbital is axially oriented, due presumably to a type of anomeric effect.^{39,41} The expected very rapid and nonselective electron transfer⁴² from the radical anion to the radical Ia provides an axial anion (IIa) that is stereochemically stable at -78°C . In the monocyclic system, the analogous anion (IIIa) can form the more thermodynamically stable⁴³ equatorial anion (IIIe) by a conformational equilibration (flip). However,

(41) Adlington, J. E.; Baldwin, J. E.; Basak, A.; Kozyrod, R. P. *J. Chem. Soc., Chem. Commun.* **1983**, 944. Giese, B.; Dupuis, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 622. Baumberger, F.; Vasella, A. *Helv. Chim. Acta* **1983**, *66*, 2210.

(42) (a) Garst, J. F. *Acc. Chem. Res.* **1974**, *4*, 400 and citations therein. (b) Andrieux, C. P.; Gallardo, I.; Savéant, J.-M.; Su, H.-B. *J. Am. Chem. Soc.* **1986**, *108*, 638 and citations therein.

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Scheme II



in the rigid bicyclic system, the axial anion can only form the more stable equatorial anion IIe by epimerization at the anionic site, a route that becomes available at the higher temperature. Heating the monocyclic anion (III) to the same temperature causes no change in stereochemistry since the main driving force for inversion, the conversion of the C-Li bond from axial to equatorial, is no longer present. Boeckman⁴⁴ has elegantly applied this method of producing axial α -lithiotetrahydropyrans in the key step of his synthesis of (-)-X-14547A (indanomycin).

Consistent with our result is the finding by Sinaÿ⁴⁵ that reductive lithiation of either anomeric phenyl 3,4,6-tri-*O*-benzyl-1-thio- α -D-*arabino*-hexopyranoside followed by attack of carbon electrophiles results in the axial C-glycosides. Similar stereocontrol was attained by reductive lithiation of analogous chlorides⁴⁵ and sulfones.⁴⁶ The use of reductive lithiation to stereospecifically generate anions at the anomeric position of 3-deoxy sugars is a noteworthy application of this technology.^{45,46}

The method shown in eq 16 has been used by Broka and Shan⁴⁷ to prepare putative α -lithio ethers, which were cyclized to tetrahydrofurans in a very promising technique (eq 22 and 23). A related pyrrolidine synthesis has also been developed.⁴⁷

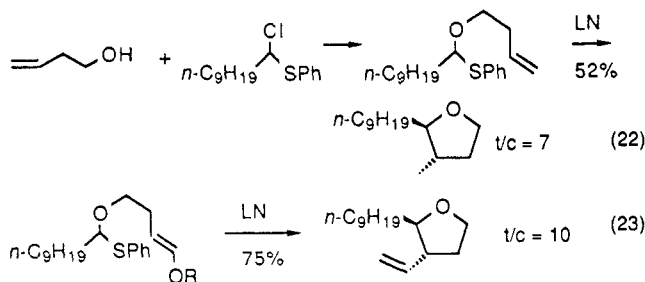
Another very versatile type of α -lithio ether is prepared by reductive lithiation of 1-alkoxy-1-(phenylthio)cyclopropanes. The simplest of these substrates

(44) Boeckman, R. K.; Enholm, E. J., Jr.; Demko, D. M.; Charette, A. B. *J. Org. Chem.* **1986**, *51*, 4745.

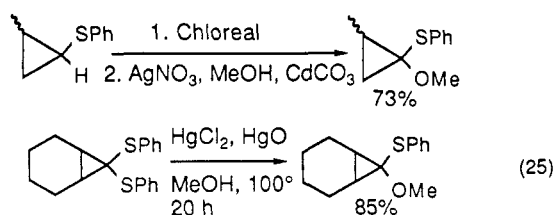
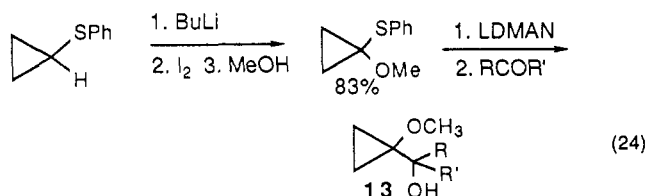
(45) Lancelin, J.-M.; Morin-Allory, L.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1984**, 355.

(46) Beau, J.-M.; Sinaÿ, P. *Tetrahedron Lett.* **1985**, *26*, 6185, 6189, 6193.

(47) Broka, C. A.; Shan, T. *J. Am. Chem. Soc.*, in press.

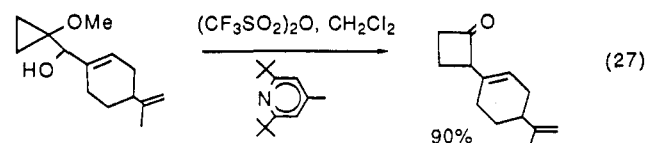
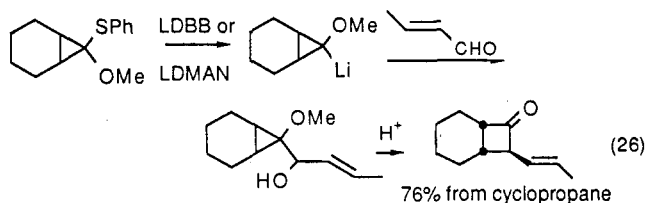


can be prepared as in eq 24.⁴⁸ Although deprotonation of 2-alkyl-substituted cyclopropyl phenyl sulfide is not practical, the same result can be attained by α -chlorination⁴⁹ followed by silver nitrate induced methanolysis (eq 25).⁴⁸ Equation 25 also shows a preparative method for such a substrate when the cyclopropane is fused to a cyclohexane;² unfortunately, when the three-membered ring is fused to a cyclopentane, this reaction is largely unsuccessful due to cyclopropane ring opening.⁴⁸ Finally, the O-methylation products of sulfinylcyclopropanes undergo the Pummerer rearrangement to produce these substrates, although the yields are also poor when a cyclopentane ring is fused to the cyclopropane.^{24b}

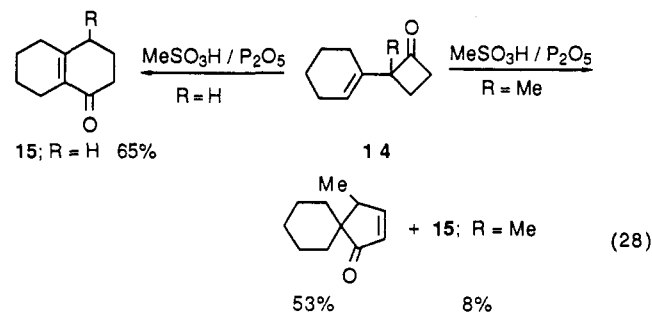


The α -lithiocyclopropyl ethers⁵⁰ arising from reductive lithiation react with aldehydes and ketones to give alcohols (e.g., 13),⁵¹ which are capable of undergoing rearrangements to cyclobutanones.^{48,52,53} These ring expansions are related to the cyclobutanone synthesis pioneered by Wenkert⁵⁴ and to that of Trost⁵⁵ shown in eq 2. Experience in our laboratory^{48,53} and in those of others^{50,56,57} indicates that the usual acid conditions for performing such rearrangements provide satisfactory yields in most cases (eq 26) and that the procedure is far more general than and gives results superior to that

utilizing the phenylthio instead of the methoxyl group on the cyclopropane ring. Since acid-sensitive groups lead to decreased yields, we have also devised a method for performing this ring expansion under nonprotic conditions (e.g., eq 27).⁵³ Even 2-furyl- and 2-nonadienylcyclobutanones are now produced in satisfactory yields.



The 2-vinylcyclobutanones which are now readily available by such procedures⁵⁸ are especially versatile synthetic intermediates.^{52,61} They undergo a variety of acid-induced ring expansions depending upon the substitution pattern.^{61,62} Considerable selectivity is often observed. For example, in the presence of protic acids, there are two modes of ring expansion of 14 depending on whether R = H or an alkyl group.⁶¹ When R = H, the product is a six-membered ring, but when R = alkyl, the product is mainly the five-membered ring (eq 28). However, in preliminary experiments, we have found that Lewis acids can force these latter cases to provide six-membered rings as well.⁶³



The alcohols derived by reduction of or addition of organometallics to the keto function of vinylcyclobutanones undergo base-induced oxyanion-accelerated [1,3]-sigmatropic rearrangements to six-membered rings,^{52,64-66} stereochemical control can be exerted by the presence or absence of a complexing agent for the metal counterion (eq 29).⁶⁶ An efficient synthesis of the eudesmane sesquiterpene (-)- β -selinene utilizes such a rearrangement of the reduction product of the vinyl-

(58) The major alternative methods for producing 2-vinylcyclobutanones are the epoxidation of allylidene cyclopropanes (see above) and the 2 + 2 cycloaddition of vinylketenes and olefins.^{59,60}

(59) Jackson, D. A.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1983**, *66*, 2330.

(60) Gadwood, R. C.; Lett, R. M. *J. Org. Chem.* **1982**, *47*, 2268.

(61) Matz, J. R.; Cohen, T. *Tetrahedron Lett.* **1981**, *22*, 2459.

(62) Jackson, D. A.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 439.

(63) Cohen, T.; Brockunier, L., unpublished observations.

(64) Wilson, S. R.; Mao, D. T. *J. Chem. Soc., Chem. Commun.* **1978**, 479.

(65) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943.

(66) Bhupathy, M.; Cohen, T. *J. Am. Chem. Soc.* **1983**, *105*, 6978.

(48) Cohen, T.; Matz, J. R. *Tetrahedron Lett.* **1981**, *22*, 2455.

(49) Mura, A. J., Jr.; Bennett, D. A.; Cohen, T. *Tetrahedron Lett.* **1975**, 4433.

(50) For a convenient alternative preparation of the unsubstituted 1-ethoxy-1-lithiocyclopropane, see: Miller, S. A.; Gadwood, R. C. *Org. Synth.* **1988**, *67*, 210 and citations therein.

(51) For an application of this method, see: Kirmse, W.; Hellwig, G.; van Chiem, P. *Chem. Ber.* **1986**, *119*, 1511.

(52) Cohen, T.; Bhupathy, M.; Matz, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 520.

(53) Cohen, T.; Brockunier, L. *Tetrahedron*, in press.

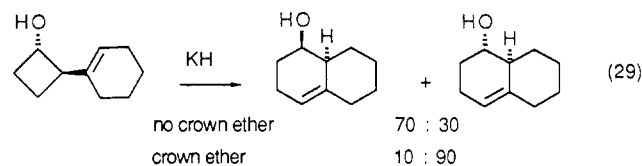
(54) Wenkert, E.; Arrhenius, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 2030.

(55) For an excellent review of Trost's extensive studies of cyclobutanone synthesis using this concept, see: Trost, B. M. *Top. Curr. Chem.* **1986**, *133*, 3.

(56) (a) Lyle, T. A.; Frei, B. *Helv. Chim. Acta* **1981**, *64*, 2598. (b) Lyle, T. A.; Mereyala, H. B.; Pascual, A.; Frei, B. *Helv. Chim. Acta* **1984**, *67*, 774.

(57) Byers, J. H.; Spencer, T. A. *Tetrahedron Lett.* **1985**, *26*, 713.

cyclobutanone derived from acid-induced ring expansion of the reaction product of (-)-perillaldehyde with 1-lithio-1-methoxycyclopropane.⁵² Thermal rearrangement of the trimethylsilyl ethers of the cyanohydrins derived from the 2-vinylcyclobutanones gives the same type of rearrangement.⁵⁷



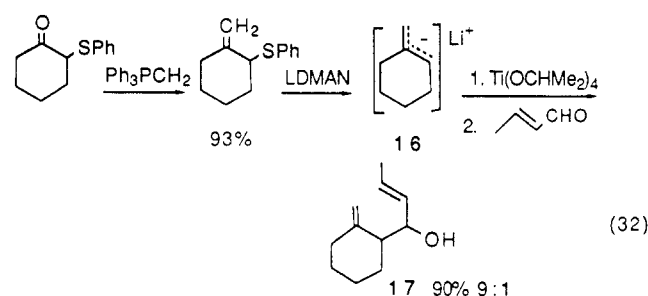
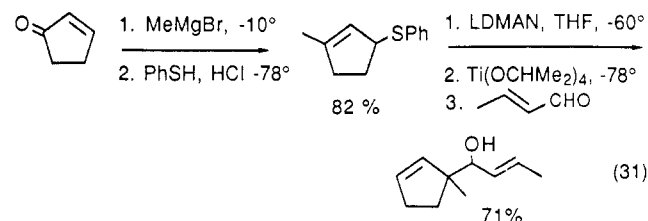
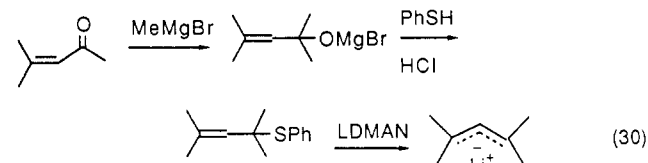
The addition of a vinylmetallic^{56b,60,67,68} to a 2-vinylcyclobutanone provides a divinylcyclobutanol, the potassium salt of which readily undergoes an oxyanion-accelerated Cope rearrangement to a cyclooctenone. An analogous result is observed with alkynylmetallics.⁶⁹

Allylmetallics

A nearly ideal general method for the regioselective production of allyl anions is the treatment of allyl phenyl sulfides with aromatic radical anions.^{70,71} While this preparative method has been used for allyl anions that are substituted at one terminus with an ether^{34,72} or thioether^{12,14,73} group, the most important uses to date have been in the formation of hydrocarbon allyl anions. The reason is that allyl anions that are substituted with a heteroatom can often be prepared in other ways,⁷⁴ whereas reductive metalation is the only general method for preparing hydrocarbon allyl anions.⁷⁰ The pioneering work of Eisch demonstrated that allyllithium itself may be prepared by the lithiation of allyl phenyl ether,⁷⁵ but more complex allylic phenyl ethers are not generally available.

It is now very clear that virtually any allyl phenyl thioether can be prepared with great ease and that the reductive lithiation step is very facile.^{70,71} An example of this technique for the preparation of a symmetrical allyllithium that could not be prepared by other procedures⁷⁶ is shown in eq 30.⁷⁷ Of course, in the case of unsymmetrical allyllithiums, regiochemical control in subsequent reactions with electrophiles is crucial to their utility. Such control has indeed been accomplished in reactions with aldehydes. Unsymmetrical allyllithiums react with aldehydes nonselectively with a slight preference for attack at the most substituted allyl terminus.⁷⁰ However, treatment of the allyllithium with titanium tetraisopropoxide leads to reaction with enals only at the most substituted terminus,⁷⁰ an effect of Ti(IV) which had been noted by others in the cases of crotyl and heteroatom substituted allyl anions. Examples are shown in eq 31 and 32. The formation of 17 also proceeded with substantial diastereoselectivity,

providing the stereoisomeric products in a 9:1 ratio. Equations 30–32 also illustrate some of the variety of synthetic methods available for the substrates required in the preparation of allyllithiums by reductive lithiation;⁷⁸ others are given below.



A major development in the field of allyl anion chemistry occurred when it was discovered⁷¹ that treatment of an unsymmetrical allyllithium with cerium(III) chloride, followed by an enal, results in addition mainly of the *least substituted* terminus to the carbonyl group. The reasoning that led to this choice was as follows. Since it is thought that a σ complex of titanium at the least hindered terminus undergoes an allylic inversion⁷⁹ upon reaction with the carbonyl component, we sought a metal that would be expected to form a π rather than a σ complex and yet would allow the allyl group to maintain its nucleophilic character. Such a complex would presumably react at the least crowded terminus. It was also necessary for the metal to be highly oxophilic in order to avoid conjugate addition to the enal. Although no allylcerium was known at that time, the three allyl lanthanides that were known were believed to involve trihapto bonding.⁸⁰ Since that time, an allylcerium has been studied by X-ray crystal structure analysis, and it is indeed a π complex.⁸¹ The pioneering work of Imamoto⁸² had indicated that alkylcerium(III) compounds behave as nucleophiles with highly oxophilic counterions and they add in a 1,2 fashion to enals. Treatment of the lithium salt 16, again prepared by reductive lithiation, with cerium(III) chloride at -78°C followed by the addition of crotonaldehyde gave mainly the 1,2-addition product at the least substituted terminus; the ratio of 18 to 17 was 18

(67) Kahn, M. *Tetrahedron Lett.* 1980, 21, 4547.

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(70) Cohen, T.; Guo, B.-S. *Tetrahedron* 1986, 42, 2803.

(71) Guo, B. S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* 1987, 109, 4710.

(72) Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* 1981, 22, 5263.

(73) Cohen, T.; Abraham, W. D.; Verner, E., unpublished work.

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(75) Eisch, J. J.; Jacobs, A. M. *J. Org. Chem.* 1963, 28, 2145.

(76) Fraenkel, G., private communication.

(77) Guo, B. S.; Doubleday, W.; Cohen, T., unpublished work.

(78) Dehydration of adducts of cycloalkanones and ((phenylthio)methyl)lithium provides allyl phenyl sulfides for reductive lithiation. Screttas, C. G.; Smonou, I. C. *J. Organomet. Chem.* 1988, 285, 143.

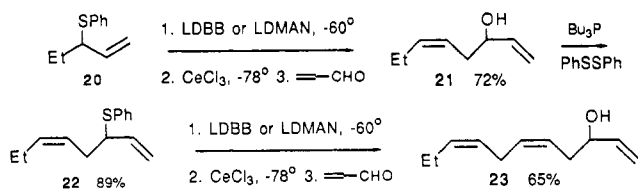
(79) Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* 1982, 21, 555.

(80) Tsutsui, M.; Ely, N. *J. Am. Chem. Soc.* 1975, 97, 3551.

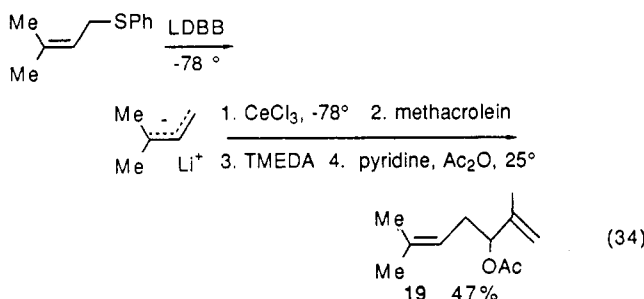
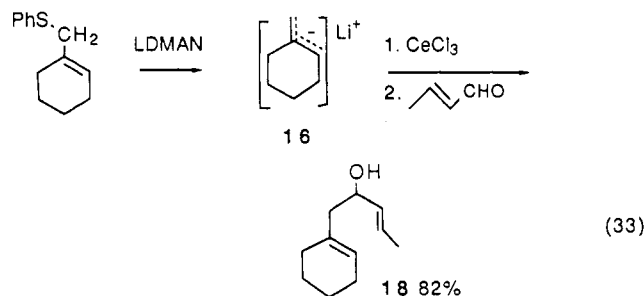
(81) Huang, Z.; Chen, M.; Qui, W.; Wu, W. *Inorg. Chim. Acta* 1987, 139, 203.

(82) Imamoto, T.; Sugiura, T.; Takiyama, N. *Tetrahedron Lett.* 1984, 25, 4233.

Scheme III



(eq 33).⁷¹ This novel regioselectivity has made possible a highly efficient synthesis of the pheromone of the Comstock mealybug (19),⁸³ a very significant agricultural pest (eq 34).^{84,85}



Since terminal allyllithiums exist at equilibrium largely in the *cis* configuration, the ability of cerium to force substitution at the least substituted terminus permits a useful synthesis of *cis*-alkenes. Scheme III⁷¹ shows a simple method of iteratively creating *cis*-alkene linkages and its application to the production of compounds 21 and 23, which are believed to be biogenetic precursors of various gamete attractants in marine algae. Although unpublished experiments with the production of (1-*n*-pentylallyl)lithium and (1-ethylallyl)potassium (see below), both of which isomerize more slowly than (1-ethylallyl)lithium and the isomeric (1-(2-pentenyl)allyl)lithiums, indicate that the allyl anions are produced mainly in the *trans* configuration, *trans* olefins were detected as relatively minor contaminants. The methylene-interrupted *cis,cis* diene functionality of the type found in 23 is widespread in biologically active natural products. The Biellmann⁸⁶ method (see Scheme IV) used to prepare the substrate 20 and that used to replace the hydroxyl group of 21 with a phenylthio group have been found generally useful in our laboratory for the preparation of the precursors of allyl anions.^{70,71}

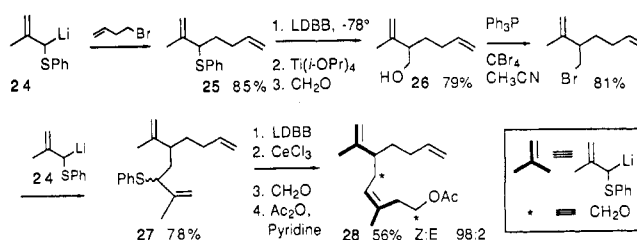
(83) Fall, Y.; Bac, N. V.; Langlois, Y. *Tetrahedron Lett.* 1986, 27, 2611 and citations therein.

(84) Cohen, T.; Bhupathy, M.; McCullough, D. W., unpublished work. In the case of certain 1,1-disubstituted allyl anions, better regioselectivity than we reported⁷¹ can be attained by allowing the lithium-cerium exchange to continue for 3 h rather than 1 h.

(85) A related synthesis, but without the use of cerium(III), provided a poor yield. Ushida, M.; Nakagawa, K.; Negishi, T.; Asano, S.; Mori, K. *Agric. Biol. Chem.* 1981, 45, 369.

(86) Atlani, P. M.; Biellmann, J. F.; Dube, S.; Vicens, J. J. *Tetrahedron Lett.* 1974, 2665.

Scheme IV



The use of titanium to control regiochemistry and of cerium to control both regiochemistry and stereochemistry is demonstrated by an economical synthesis (Scheme IV)⁸⁷ of the pheromone 28 of the California red scale, a serious world-wide citrus pest.^{88,89} As the inset indicates, the bold parts of the drawing represent both fragments that were inserted as the Biellmann anion 24 and the two starred atoms were inserted in the form of formaldehyde. The latter attacks the allyl anion derived from 25 exclusively at the most substituted terminus under the influence of Ti(IV) but the allyl anion derived from 27 mainly at the least substituted terminus under the influence of Ce(III). Although in the latter case 9% of the undesired regioisomer is formed as well, the *Z:E* ratio (98:2) is unusually favorable, thanks to the methyl group on the central carbon atom of the allyl system.⁹⁰

One can also improve the thermodynamic *E:Z* ratio by use of potassium rather than lithium allyls.⁹¹ We have found⁹² that the treatment of an allyl phenyl sulfide with potassium 1-(dimethylamino)naphthalenide (KDMAN) results in the formation of an allylpotassium which is a powerful enough base, even at -78°C , to frequently deprotonate the starting material, particularly if it is a primary phenyl thioether.⁹³ With regard to secondary thioethers, the yield of allylpotassium derived from 20 was sharply decreased by this phenomenon but that from 3-(phenylthio)-1-octene was only marginally affected; apparently steric hindrance to proton removal is significant. The allylpotassiums generated in this way are mixtures of *cis* and *trans* isomers, and the rate of equilibration of these highly ionic species to the more stable *cis* isomer is impractically slow^{92,94} at the low temperatures necessary to avoid anion decomposition. However, a catalytic quantity of magnesium bromide (allylmagnesiums are largely nonionic⁹⁵) causes rapid equilibration.⁹²

An alternative method of generating allylpotassiums is by deprotonation of alkenes by the use of butyllithium-potassium *tert*-butoxide.⁹¹ However, we have found that the alcoholate anion deactivates the magnesium ion catalyst so that equilibration is not possible. Butyllithium can also be used to deprotonate alkenes, but its generation requires the use of poisonous

(87) Cohen, T.; Piccolino, E.; McCullough, D. W., unpublished work.

(88) Roelofs, W.; Gieselmann, M.; Cardé, A.; Tashiro, H.; Moreno, D. S.; Hendick, C. A.; Anderson, R. J. *J. Chem. Ecol.* 1978, 4, 211.

(89) Syntheses: Oppolzer, W.; Stevenson, T. *Tetrahedron Lett.* 1986, 27, 1139 and citations therein.

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(91) Schlosser, M.; Hartmann, J. *J. Am. Chem. Soc.* 1976, 98, 4674.

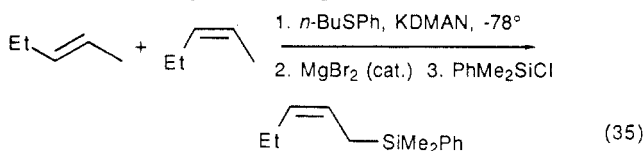
(92) Cohen, T.; Guo, B. S.; Doubleday, W.; McCullough, D. W., unpublished work.

(93) Hoffmann⁷² has generated an alkoxy-substituted allylpotassium from such a substrate by performing the reduction at a very low temperature in the presence of the chloroborane electrophile.

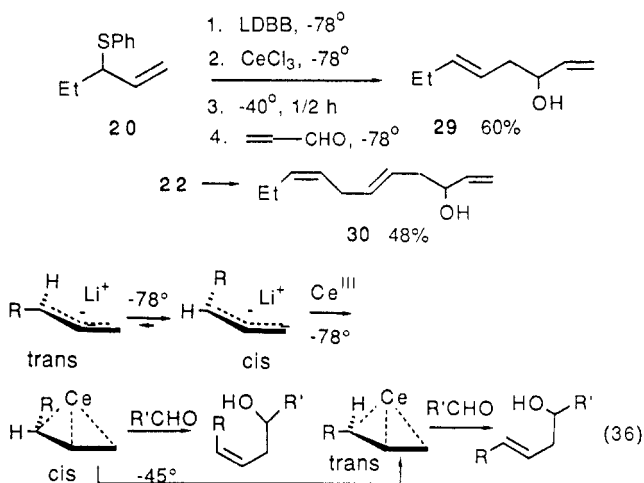
(94) Thompson, T. B.; Ford, W. T. *J. Am. Chem. Soc.* 1979, 101, 5459.

(95) Hutchison, D. A.; Beck, K. R.; Benkeser, A.; Grutzner, J. B. *J. Am. Chem. Soc.* 1973, 95, 7075.

and expensive dibutylmercury.⁹⁶ We have had some success at generating alkylpotassiums for use in allyl-potassium production by simple reductive potassiation of alkyl phenyl sulfides.⁹⁷ When butylpotassium is generated in the presence of commercial *cis*-2-pentene and the resulting alkylpotassium is captured with phenyldimethylsilyl chloride, 1-(phenyldimethylsilyl)-2-pentene, with a *cis*:*trans* ratio of 98.6:1.4, is produced in 65% yield. When the same deprotonation is performed on the much cheaper mixture of *cis*- and *trans*-2-pentene, and the product is treated with catalytic magnesium bromide before silylation, the same product is formed with a ratio of 97:3 (eq 35). The major competing reaction, destruction of the butyl phenyl sulfide by the butylpotassium, is minimized by using isobutyl phenyl sulfide and by slow addition techniques. Work is continuing on this promising method of allylpotassium production.



Remarkably, *trans* allyl anions can be produced with high selectivity simply by warming the solutions of *cis*-allylceriums from -78 to -40 °C. Thus, **29** and **30**, the *trans* analogues of **21** and **23**, can be generated from **20** and **22**, respectively.⁷¹ This stereochemical control is possible because of the fortunate circumstance that the mainly ionic allyllithiums are more stable in the *cis* configuration while the allylcerium π complexes are more stable in the *trans* configuration (eq 36).



Miscellaneous Anions and the Scope of Reductive Metalation

Reductive lithiation has been used in the preparation of 2-alkylcyclobutanones by alkylating the enolate of 2-(phenylthio)cyclobutanone and then removing the phenylthio group with LDMAN via the enolate anion.⁹⁸ The method is uniquely successful since Raney nickel caused ketone reduction as well as desulfurization while lithium in ammonia⁹⁹ led to an amide by ring cleavage.

(96) Hart, A. J.; O'Brien, D. H.; Russel, C. R. *J. Organomet. Chem.* 1974, 72, C19.

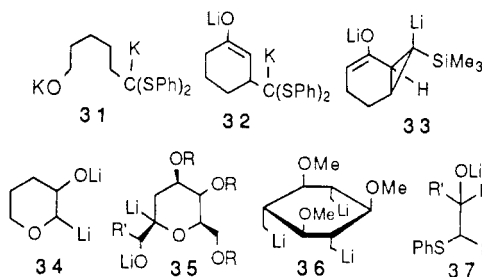
(97) Cohen, T.; Doubleday, W., unpublished work.

(98) Cohen, T.; Ouellette, D.; Senaratne, K. P. A.; Yu, L.-C. *Tetrahedron Lett.* 1981, 22, 3377. Cohen, T.; Yu, L.-C.; Daniewski, W. M. *J. Org. Chem.* 1985, 50, 4596.

(99) Coates, R. M.; Pigott, H. D.; Ollinger, J. *Tetrahedron Lett.* 1974, 3955.

The enolate of a β -lactam has been generated by treatment of the α -phenylseleno derivative with LN.¹⁰⁰

Di- and polyanions have also been prepared by reductive metalation. Dianions **31**¹⁰¹ and **32**¹⁰² have been prepared by treatment of the corresponding phenylthio precursors with potassium naphthalenide, and dianion **33** has been prepared by treatment of the enolate of the (phenylthio)cyclopropyl ketone¹⁰³ precursor with LDB-B.¹⁰⁴ However, dianion **34** and hydroxyl-protected analogues in the sugar series could not be produced from the phenylthio precursor by the use of LN,¹⁰⁵ starting material was recovered. On the other hand, a β -oxyanionic substituent is not detrimental if the phenylthio group is benzylic,⁸ and the dianion **35** could be generated by Beau and Sinaÿ from the more easily reducible phenylsulfonyl precursor by using LN.⁴⁶ Trianion **36** was prepared from the tris(phenylthio) precursor with LDBB.¹⁰⁶ When a 2-(phenylthio) epoxide was treated with LDBB, a C-O bond instead of the C-S bond was cleaved, resulting in dianion **37**;¹⁰⁷ this epoxide cleavage is a useful synthetic method.^{107,108}



Although a number of vinylolithiums have been prepared by reductive lithiation of vinyl phenyl sulfides, difficulties can be encountered when the phenylthio group is attached to an sp^2 carbon atom. Examples of sulfur- and oxygen-substituted vinylolithiums produced in this way are shown in eq 5 and 18. A silicon-substituted vinylolithium has been obtained by reductive lithiation of **4** (eq 5).²¹ Although reductive lithiation with LN of a 1-(phenylthio)-2-(dialkylamino)alkene was successful,¹⁰⁹ that of 1-(phenylthio)cyclohexene and 2-(phenylthio)furan below 0 °C was not.¹¹⁰ When 1-(phenylthio)cyclohexene was warmed to ambient temperature with LN, reductive cleavage occurred to the extent of 60% at the vinyl carbon atom and 40% at the phenyl carbon atom. Finally, LDMAN has been used for production of a (2-((trialkylsilyloxy)vinyl)lithium from the corresponding vinyl phenylseleno ether.¹¹¹

Mechanism and Concluding Remarks

A number of observations in our laboratory lead to the conclusion that a radical intermediate is involved in these reductive lithiations and that it is formed in the rate-determining step. Such a mechanism would

(100) Agawa, T.; Ishida, M.; Ohshiro, Y. *Synthesis* 1980, 933.

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be consistent with that believed to occur upon reduction of alkyl phenyl sulfides with sodium in HMPA at 100 °C, although in that case the selectivity is lower.¹¹² It is also consistent with that of single-electron reduction of organyl halides.⁴² Since LDBB executes reductive lithiations with much greater ease than LN or LDMAN, the rate or degree of electron transfer also must affect the overall rate. We assume that either the electron transfer to the phenyl thioether is concerted with rupture of the C-S bond, as in the reduction of alkyl halides,^{42a} or a rapid and reversible electron transfer to the substrate precedes a rate-determining bond rupture, as occurs with aryl halides.^{42b}

The observations are as follows. The stereochemistry of α -lithio ether production in five-membered rings has already been discussed. Furthermore, the ease of reduction of a thioether is related to the stability of the putative radical intermediate. In general, the ease of formation decreases in the order alkylolithiums > cyclopropylolithiums > vinyl- or aryllithiums,^{18,21,110} more highly substituted alkylolithiums are formed more rapidly than less highly substituted ones,¹¹³ and 1,1-bis-(phenylthio)cyclopropane is reduced more rapidly than 1-(phenylthio)-1-(trimethylsilyl)cyclopropane.²¹ Indeed, this pattern is a major reason for the attractiveness of this method of anion production, for reductive metalation is quite complementary to the removal of a pro-

ton or other electrophile by a strong base or nucleophile, the method that is nearly always used by synthetic chemists to produce organolithium species.¹¹⁴ In such electrophile exchange, the rate-determining step is apparently formation of the anion itself, and there is thus a direct relationship between its stability and its ease of production. *Since the stability order of radicals is frequently opposite that of anions in solution, the rate-determining radical formation in reductive metalation has profound consequences with regard to ease of anion production and, as demonstrated above, interesting stereochemical consequences as well.*

The other major attractions of this relatively new method of anion production are that the substrates are very readily available, due to the remarkably versatile properties of sulfur, and that they are usually stable in the presence of the anionic products. These properties contrast sharply with those of organyl halides, which are occasionally used in synthetic chemistry as substrates for aromatic radical anions.¹¹⁵ As this methodology becomes better known, it seems inevitable that it will become one of the dominant methods to produce carbanions for synthetic purposes.

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