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# The production of cyclopropanes from organosulfur compounds and a novel cyclopropane ring expansion

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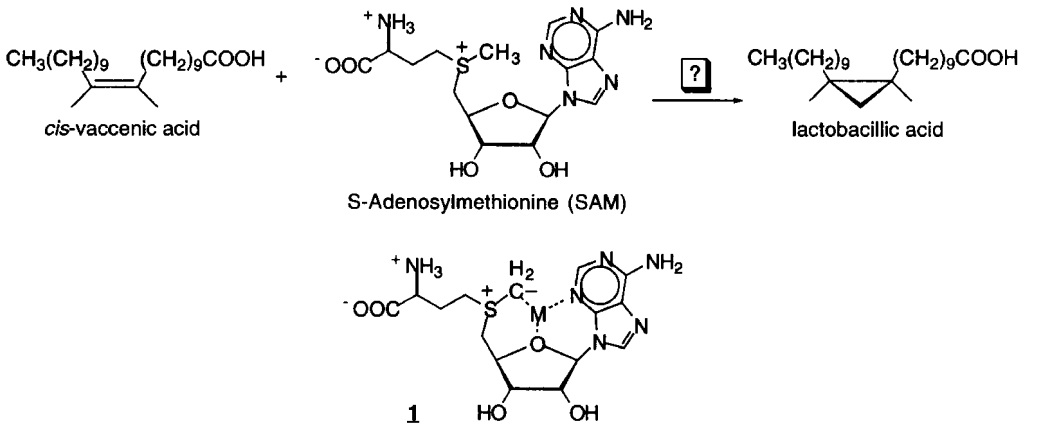
**Abstract:** The synthetic utility of the remarkable chemical properties of sulfur(II) is illustrated by several of the sulfur-based cyclopropane syntheses that have been developed in our laboratory. A newer method utilizes carbanions generated by aromatic radical-anion induced reductive lithiation of molecules bearing the phenylthio group. This very general carbanion preparation has the unusual feature that the ease of producing the carbanion is inversely correlated with its stability. Examples of this remarkable selectivity are provided. A novel diradical double ring expansion of fused bicyclic allylidenecyclopropanes derived from some of the products is also discussed.

The great versatility of sulfur(II) allows it to be introduced into a molecule as a nucleophile, an electrophile, or a radical as well as a sulfur-stabilized carbanion, carbocation, carbene, or carbon radical (1). The sulfur atom and/or nearby atoms in the resulting organosulfur compounds can be readily modified or removed. These principles are illustrated below by several of the sulfur-based cyclopropane syntheses that have been developed in our laboratory and some novel uses of sulfur - bearing cyclopropanes.

During the early 1970s, my group, in collaboration with that of Professor Toby Chapman, became interested in the question of the mechanism of the biosynthesis of those cyclopropane rings that are known to be formed by the syn addition of a methylene group, derived from S-adenosylmethionine (SAM), to an alkene (Scheme 1) (2). There had been suggestions that the methylide of SAM was involved but ylides generally do not attack unactivated double bonds. At that time, there was a major commitment in our laboratory in the organic chemistry of copper (3) and the well-known prominent role of copper in the transfer of methylene groups from diazomethane or methylene iodide to alkenes was contemplated. It was suggested that an analogous metal induced methylene transfer from the ylide of SAM to the alkene might involve a particularly attractive complex **1** between the metal M and the ylide. It is seen that two of the heteroatoms of the SAM framework participate in a chelate template that may be inviting to the metal ion as well as conducive to the electron donation by the metal that would facilitate liberation of the $CH_2$ group.

***Scheme 1***



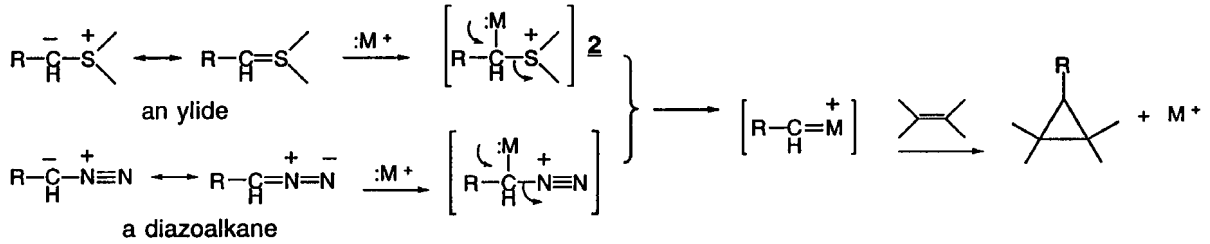




**1**

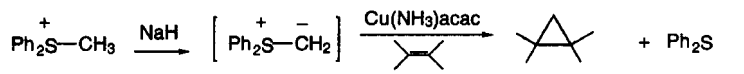
Trost (4) had already noted the analogy between diazoalkanes and ylides (Scheme 2; our assumed mechanism for methylene transfer catalyzed by a metal possessing d electrons is shown) and he had demonstrated that 7-benzoylnorcarane could be generated, albeit in very low yield, when the stabilized ylide dimethylsulfonium phenacylide was treated with cyclohexene in the presence of cupric acetylacetonate.

*Scheme 2*




The *non-stabilized* sulfur ylides required by the biosynthetic scheme could present multiple problems among which are attack on the electrophilic metal - carbenes. However, model studies on the transfer of $CH_2$ from a methylide to an unactivated alkene by treating methyl diphenyl sulfonium tetrafluoroborate with NaH *in the presence* of cupric acetylacetonate were encouraging (5). As in the biological analogs, syn cyclopropanation occurred. Subsequently, it was found that higher yields were produced when the copper(II) catalyst was replaced with an ammonia complex of cuprous acetylacetonate (6). Some results of the latter procedure are shown in Table 1. Proton exchange in the methyl group of the sulfonium salt in aqueous sodium carbonate lent credence to the biogenetic hypothesis (5). Recent reports from the laboratory of Professor Marc Julia have considerably improved and extended these results (7). Helquist has shown that an iron analog of **2** is also capable of cyclopropanating unactivated alkenes (8).

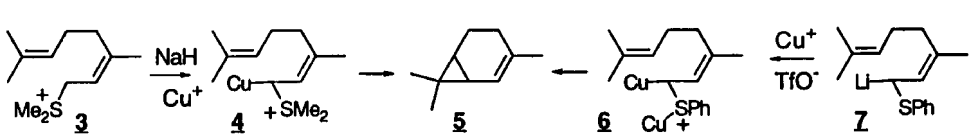
TABLE 1. Laboratory Model for Natural Cyclopropane Synthesis




| alkene | product | % yield △ | % yield $Ph_2S$ |
|---|---|---|---|
|  |  | 53 | 97 |
| $n$-$C_5H_{11}CH{=}CH_2$ | $n$-$C_5H_{11}$  | 55 | 97 |
| $Me_2CHCH_2OCH{=}CH_2$ | $Me_2CHCH_2O$  | 63 | 99 |

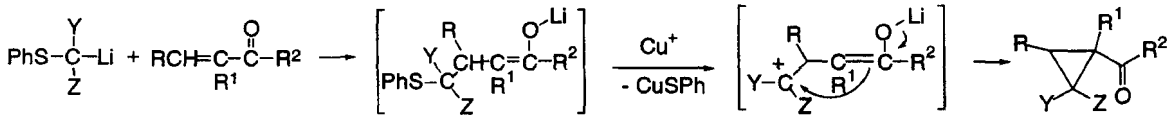
It was then speculated that natural vinylcyclopropanes such as 2-carene **5** and presqualene alcohol could be generated in nature in a similar manner. Neryl dimethyl sulfonium tetrafluoroborate **3**, was treated as above in the hope of generating **4**, a possible precursor of **5** (9). In a number of the experiments, **5** was identified as a product by GC coinjection on three columns and by its mass spectrum. However, not surprisingly, the experiments were somewhat irreproducible. Allyl sulfonium methylides undergo extremely efficient 2,3-sigmatropic rearrangements; furthermore the allylic sulfonium salt readily decomposed in the presence of cuprous ion, apparently to the neryl cation, well known decomposition products of which could be identified (10). In order to generate **6**, an analog of **4**, but from a more stable precursor, the known deprotonation product **7** of neryl phenyl sulfide was treated with cuprous triflate. Again 2-carene **5** could be identified as a product but the yields were low and again irreproducible and it was clear that the expected metal - carbene intermediate reacted more readily with its precursor than with the double bond in the same molecule (10).

*Scheme 3*

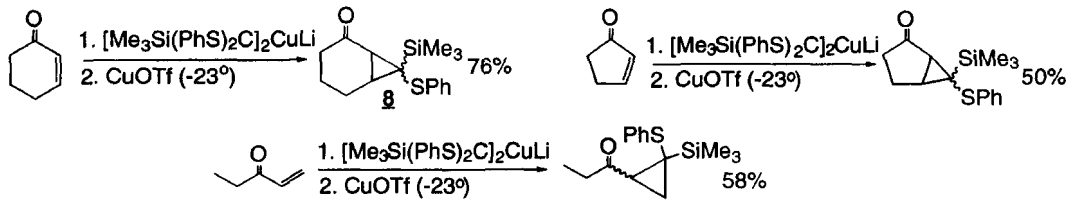


Although **6** (Scheme 3) gave only low yields of 2-carene, the experiments did show that cuprous ion is capable of efficiently removing the thiophenoxide ion from suitable molecules. We went on to produce a number of copper - carbenes in this way (10,11) but, more importantly, it could be shown that cuprous triflate (12) and in some cases even the cuprous bromide - dimethyl sulfide complex (13) is capable of removing thiophenoxide from molecules that can readily support a positive charge. Recently, this finding has been exploited in a novel and rather general method of producing usefully functionalized cyclopropyl ketones (Scheme 4). Some applications are shown in Schemes 5 and 6 (14). A novel feature of this technology is that the leaving group is stable until *activated by a Lewis acid* which is added after formation of the enolate; the thiophenoxy group, PhS, serves admirably as the masked leaving group which can be readily activated by the addition of the cuprous ion, a specific Lewis acid toward divalent sulfur.

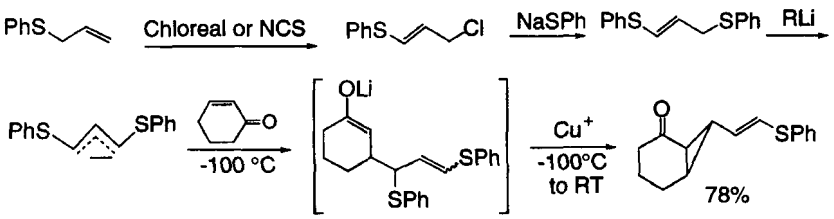
***Scheme 4***



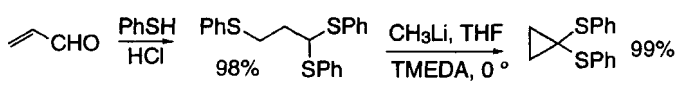
***Scheme 5***



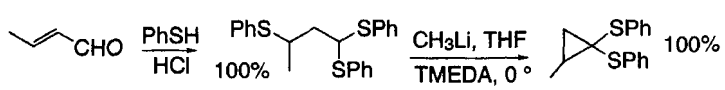
***Scheme 6***



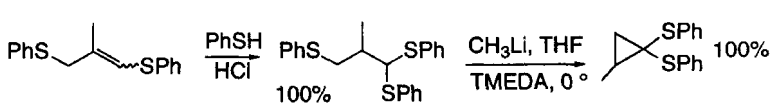
If the internal nucleophile is strong enough, a cyclopropane can be generated by expulsion of a thiophenoxide ion that is not activated by a Lewis acid. The alkyllithium induced 1,3-elimination of thiophenol from 1,1,3-tris(phenylthio)alkenes (Eq. 1-3) (15) has been shown to involve 1,3-displacement of thiophenoxide ion by the lithiothioacetal with inversion (Scheme 7) (16). The substrates are readily available by acid - induced reaction of thiophenol with enals or 1,3-bis(phenylthio)alkenes.



(1)



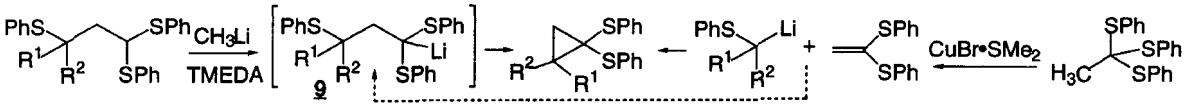
(2)

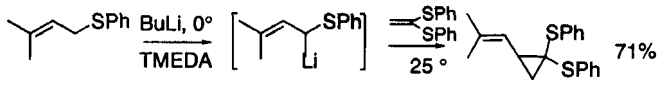


(3)

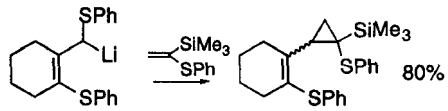
The right hand side of Scheme 7 shows a particularly versatile connective version of this cyclopropane synthesis (17). The lithiothioacetal **9** can be produced by addition of a sulfur - stabilized carbanion to a ketene bis(phenylthio)acetal. As seen in Eq. 4-6, this concept is very well suited to the production of vinylcyclopropanes. Eq. 5 and 6 indicate that 1-phenylthio-1-trimethylsilylcyclopropanes can also be generated by substituting 1-phenylthio-1-trimethylsilylethene for the ketene thioacetal (16).

*Scheme 7*

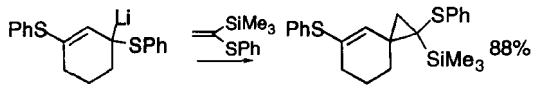




(4)



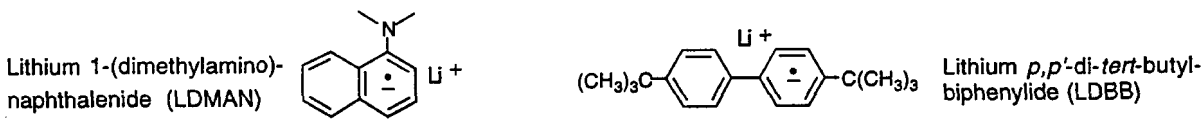
(5)



(6)

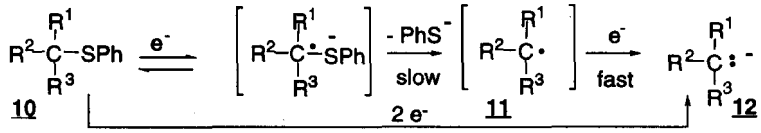
An understanding of the last method of cyclopropane synthesis that will be discussed and some of the uses of the product cyclopropanes requires a knowledge of an emerging powerful method of generating organolithium compounds by the reductive lithiation of phenylthio compounds using aromatic radical-anions (18-20). The radical-anions that are now used in our work are shown in Scheme 8. LDMAN (21) is used whenever it is important to be able readily to separate the aromatic byproduct from the material derived from the organolithium. It is a simple matter to remove the dimethylaminonaphthalene using a dilute acid wash. LDBB (22) is not only a more powerful reducing agent but is less susceptible to radical attack and we use it when there is no serious separation problem.

*Scheme 8*




The net result is the cleavage of the C-S bond of the substrate **10** and the production of thiophenoxide ion and the carbanion **12**, usually as an organolithium compound (Scheme 9). A major reason for the great versatility of this method has to do with the remarkable properties of divalent sulfur as outline above. A second major reason is that this method is quite complementary to the removal of a proton or other electrophile by a strong base or nucleophile, the procedure that is nearly always used by synthetic chemists to produce organolithium species. In such electrophile exchange, it appears likely that the rate determining step is formation of the anion itself and there is thus a direct relationship between its stability and its ease of production. On the other hand, it is believed that in reductive lithiation the rate determining step is the generation of a carbon radical (**11**, Scheme 9) (20,23). Since the order of stability of radicals in solution is the reverse of that of carbanions, *reductive lithiation is capable of producing less stable organolithiums more rapidly and under milder conditions than more stable ones.* Thus, $sp^3$ carbanions are produced under milder conditions than the more stable $sp^2$ carbanions (24) . Furthermore, the order of the rates of formation of organolithiums is tertiary > secondary > primary. This selectivity is useful for a variety of purposes a few of which will be illustrated by the new cyclopropane synthesis outlined below.

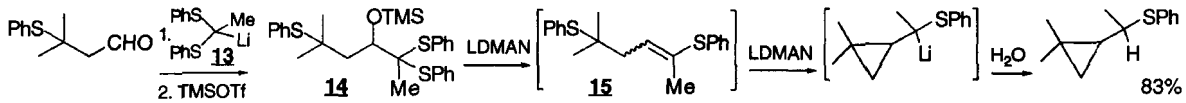
*Scheme 9*



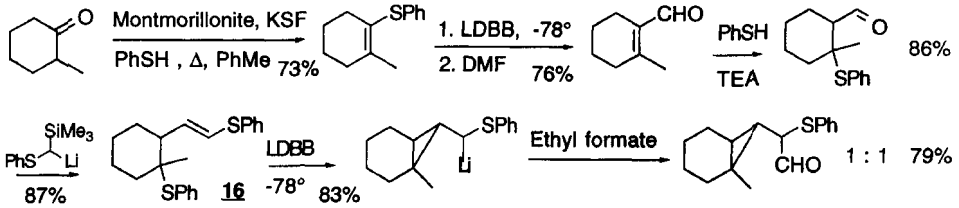

Schemes 10 and 11 demonstrate both the ease of introducing phenylthio groups into molecules and the high selectivity of reductive lithiation (25). The substrate in Scheme 10 is the adduct of thiopenol and an

enal. The nucleophile **13** is the lithio derivative of the thioacetal of acetaldehyde. The production of the enal in Scheme 11 is described in reference 24. Because of the ability of sulfur to stabilize a radical on the carbon atom to which it is attached, only one of the two types of thiophenyl groups in **14** is replaced. In **15** and **16**, only the phenylthio groups attached to the $sp^3$ carbon atoms are reductively removed. A similar selectivity is displayed in Scheme 12 (25). Analogous homoallyllithiums, but lacking the phenylthio group on the vinyl carbon atom, often undergo a similar ring closure but the resulting cyclopropylcarbinyl anions usually reopen, sometimes in the opposite sense from the ring closure to yield rearranged product (26).

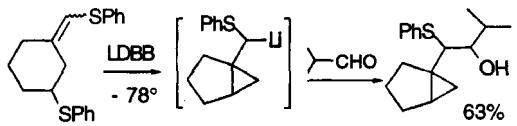
***Scheme 10***




***Scheme 11***

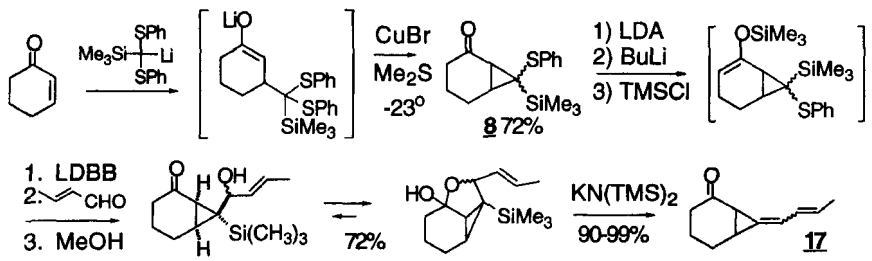



***Scheme 12***

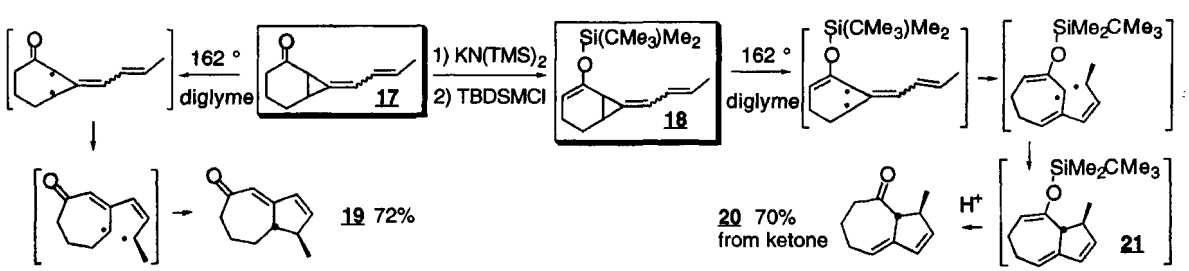



One of the synthetic uses for compounds such as **8** (13) is shown in Schemes 11 and 12. Allylidenecyclopropylketone **17** is readily available from **8** by reductive lithiation followed by Peterson olefination (27). Like other fused ring allylidenecyclopropanes, **17** undergoes smooth double ring expansion upon heating to produce, in this case, conjugated dienone **19** (28). Interestingly, the presumed diradical intermediate (29) closes in one direction only. Fortunately, the opposite regiochemistry occurs when the silyl enol ether **18** rearranges to produce **21** which hydrolyzes to the nonconjugated dienone **20**. As in other pyrolyses of this type (28), the terminal trans methyl group of the substrate ends up in the exo orientation in the ring expanded products (cis methyl groups yield endo-methyl products).

***Scheme 13***




***Scheme 14***



The novel cyclopropane syntheses outlined here depend on the weakness of the C-S bond and other properties of sulfur. In a suggested biogenetic mode, sulfide groups are expelled from a copper - ylide complex or a sulfur stabilized organocopper to provide a copper - carbene, capable of cyclopropanating alkenes. In two other methods, intramolecular nucleophilic displacements of a thiophenoxide group occurs; in one of these the nucleophile is weak and electrophilic assistance by a cuprous ion is necessary. In a final method, reductive lithiation of a thioether generates a carbanion which adds intramolecularly to an alkene activated by the presence of another sulfur group, allowing stabilization of the resulting cyclopropylcarbinyl anion. Some of the sulfur bearing cyclopropanes can be converted, also with the aid of reductive lithiation, into alkylidenecyclopropanes capable of new stereoselective and regioselective diradical ring expansions.

**Acknowledgment**

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**References**

1. *The Chemistry of Sulfur - Containing Functional Groups*, ed. S. Patai and Z. Rappoport, Wiley Interscience, New York (1993); S. Oae, *Organic Sulfur Chemistry*, CRC Press, Boca Raton (1991); *Chemistry of Organosulfur Compounds*, ed. L.I. Belen'Kii, Ellis Horwood, New York (1990).
2. J.H. Law. *Acc.Chem.Res.* **7**, 199 (1974).
3 T. Cohen and T. Poeth, *J.Am.Chem.Soc.* **94**, 4363 (1972). T. Cohen, R.J. Lewarchik and J.Z. Tarino, *J.Am.Chem.Soc.* **96**, 7753 (1974). T. Cohen, J. Wood and A.G. Dietz, *Tetrahedron Lett.*, 3555 (1974).
4. B.M. Trost. *J.Am.Chem.Soc.* **89**, 138 (1967).
5. T. Cohen, G. Herman, T.M. Chapman and D. Kuhn. *J.Am.Chem.Soc.* **96**, 5627 (1974).
6. D. Kuhn. Ph.D. Thesis, University of Pittsburgh (1976).
7. B. Cimetiére and M. Julia. *Synlett* 271 (1991). M. Julia. *Chem.Soc.Rev. 20*, 129 (1991).
8. E. J. O'Connor, S. Brandt and P. Helquist *J.Am.Chem.Soc.* **109**, 3739 (1987).
9. J.M. Lamade. M.S. Thesis, University of Pittsburgh (1976).
10. R.B. Weisenfeld. Ph.D. Thesis, University. of Pittsburgh (1980). T. Cohen and S.M. Nolan. unpublished work.
11. A.J. Mura, Jr. Ph.D. Thesis, University of Pittsburgh (1976).
12. T. Cohen, G. Herman, J.R. Falck and A.J. Mura, Jr. *J.Org.Chem.* **40**, 812 (1975). T. Cohen, D. Kuhn and J.R. Falck. *J.Am.Chem.Soc.* **97**, 4749 (1975). T. Cohen, A.J. Mura, Jr., D.W. Shull, E.R. Fogel, R.J. Ruffner and J.R. Falck. *J.Org.Chem.* **41**, 3218 (1976). T. Cohen, R.J. Ruffner, D.W. Shull, E.R. Fogel and J.R. Falck. *Organic Synthesis* **59**, 202 (1980). T. Cohen and Z. Kosarych. *Tetrahedron Lett.* **21**, 3955 (1980).
13. T. Cohen, C.A. Shook and M. Thiruvazhi. *Tetrahedron Lett.* **35**, 6041 (1994).
14. T. Cohen and M. Myers. *J.Org.Chem.* **53**, 457 (1988). For the preparation of 1,3-bis(phenylthio)-allyllithiums, see T. Cohen, D.A. Bennett and A.J Mura, Jr. *J. Org. Chem.* **41**, 2506 (1976).
15. T. Cohen and W.M. Daniewski. *Tetrahedron Lett.* 2991 (1978).
16. T. Cohen and J.R. Matz. *J.Org.Chem.* **44**, 4816 (1979).
17. T. Cohen, R.B. Weisenfeld and R.E. Gapinski. *J.Org.Chem.* **44**, 4744 (1979). Other examples: E. Schaumann, C. Friese, C. Spanka. *Synthesis* 1035 (1986); S. Kanemasa, H. Kobayashi, J. Tanaka, O. Tsuge. *Bull.Chem.Soc.Jpn.* **61**, 3957 (1988); H. Ahlbrecht and M. Ibi. *Synthesis* 210 (1988).
18. C.G. Screttas and M. Micha-Screttas. *J.Org.Chem.* **43**, 1064 (1978); **44**, 713 (1979).
19. T. Cohen, W.M. Daniewski and R.B. Weisenfeld. *Tetrahedron Lett.* 4665 (1978).
20. T. Cohen.and M. Bhupathy. *Acc.Chem.Res.* **22**, 152 (1989); T. Cohen, in *Heteroatom Chemistry*, ed. E. Block, VCH Publishers, New York, chap. 7 (1990).
21. T. Cohen and J.R. Matz. *Synth. Commun.* **10**, 311 (1980). For the sodium analogue, see: S. Bank and M. Platz. *Tetrahedron Lett.* 2097 (1973).
22. P.K. Freeman and L.L. Hutchinson. *J.Org.Chem.* **45**, 1924 (1980); **48**, 4705 (1983).
23. M.G. Severin, M.C. Arévalo, G. Farnia and E. Vianello. *J.Phys.Chem.* **91**, 466 (1987).
24. T. Cohen and M.D. Doubleday. *J.Org.Chem.* **55**, 4784 (1990).
25. F. Chen, B. Mudryk and T. Cohen, unpublished work.
26. B. Mudryk and T. Cohen. *J.Am.Chem.Soc.* **115**, 3855 (1993).
27. D. Peterson. *J.Org.Chem.* **22**, 4737 (1968). D.J. Ager. *Synthesis* 384 (1984).
28. C.A. Shook, M.L. Romberger, S.-H. Jung, M. Xiao, J.P. Sherbine, B. Zhang, F.-T. Lin and T. Cohen. *J.Am.Chem.Soc.* **115**, 10754 (1993).
29. E.R. Davidson, J.J. Gajewski, C.A. Shook and T. Cohen, submitted for publication.