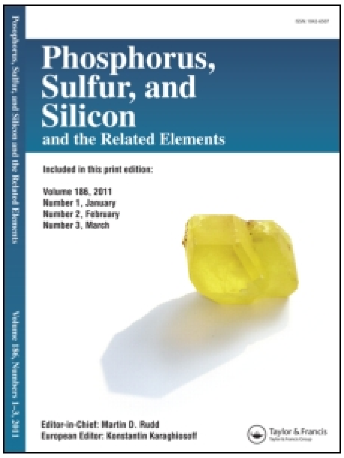

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The Versatile Phenylthio Group. A Powerful Aid in Synthesis

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THE VERSATILE PHENYLTHIO GROUP. A POWERFUL AID IN SYNTHESIS

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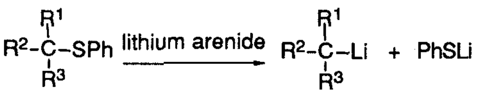
Abstract The replacement of the phenylthio group by lithium by the use of aromatic radical-anions has become one of the most powerful methods for the production of organolithium compounds. The major reasons for the power of this method are the ease of incorporation of the phenylthio group into molecules, the ability of divalent sulfur to stabilize any electronic arrangement on the atom to which it is attached, the relative ease of reductive cleavage of C-S bonds despite the stability of this type of bond under most other reaction conditions, and the fact that the rate determining step of organolithium production by this method is apparently the formation of a carbon radical. 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. Recent advances in synthetic and mechanistic chemistry based on carbanions generated by this method are presented. The dependence of the methods on the properties of divalent sulfur mentioned above and the generation and uses of heretofore virtually unavailable tertiary organolithiums are stressed. Topics covered include the production and synthetic or mechanistic uses of otherwise difficulty attainable 2-lithiotetrahydropyrans, allyllithiums, homoenolate and bis(homo)enolate anion equivalents, allylidenecyclopropyl ketones and homoallyl anions. The latter readily undergo a synthetically useful 1,2-vinyl rearrangement that is some cases leads to a ring contraction.

INTRODUCTION

Carbanions are among the most important intermediates in synthetic organic chemistry. In most synthetic applications, the carbanions used are organolithium compounds or other organometallics derived from organolithiums. In recent years, the reductive cleavage of C–S bonds of phenyl thioethers by the use of aromatic radical-anions has emerged as one of the most versatile methods for the production of organolithium compounds (fig. 1).[1,2] Among the reasons for this versatility, two are paramount.



$$R^2\text{-}\overset{R^1}{\underset{R^3}{C}}\text{-}SPh \xrightarrow{\text{lithium arenide}} R^2\text{-}\overset{R^1}{\underset{R^3}{C}}\text{-}Li + PhSLi$$

FIGURE 1 Organolithiums via reductive lithiation.

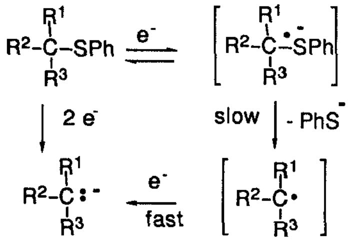


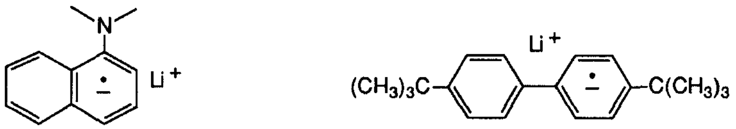
FIGURE 2 Mechanism of reductive lithiation.

Perhaps the most important reason is that divalent sulfur has remarkable chemical properties. These properties allow both great ease of incorporation of the phenylthio group into organic molecules and its ready replacement by lithium. It can enter a molecule as a nucleophile, an electrophile, or a radical. Furthermore, its divalent sulfur atom stabilizes any electronic arrangement (anion, cation, radical, carbene) on the carbon atom to which it attached. Thus, the reductive lithiation substrate can frequently be constructed by the attack of one of these fragments, stabilized by the phenylthio group. A particularly important property is that the long C–S bond is fairly weak and can be broken fairly, but not too readily; in contrast, carbon-halogen bonds are broken so readily that molecules with such bonds often cannot coexist with organolithium compounds derived from them. Two other characteristics of divalent sulfur that are sometimes of use in constructing the reductive lithiation substrates are the ability to change its oxidation number readily and its formation of complexes with certain transition metal cations such as cuprous ion.[3]

A second major reason for the versatility of reductive lithiation is that it 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.[4] 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 (Fig. 2).[1] Since the order of stability of radicals in solution is usually 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.[5] More importantly, the order of the rates of formation of organolithiums is tertiary > secondary > primary. This order is of great significance for the production of tertiary organolithiums since they tend to self-destruct by deprotonation of tetrahydrofuran. Because they form instantaneously at -78°, they can be immediately subjected to capture by an electrophile. As will be seen below, the yields of final product can be outstanding.

A number of new synthetic methods based on the preparation and reductive lithiation of a variety of phenylthio compounds is presented below. Many of the examples involve tertiary organolithium compounds which, except for the simplest members of the class, were virtually nonexistent prior to the discovery of reductive lithiation. The important role of the properties of divalent sulfur are emphasized.

The radical-anions that have been used in this work are shown in Fig. 3. LDMAN[6,7] 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[8] 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.



Lithium 1-(dimethylamino)-naphthalenide (LDMAN)

Lithium *p,p'*-di-*tert*-butylbiphenylide (LDBB)

FIGURE 3 Aromatic radical-anions used in this work.

MECHANISM OF THE WITTIG REARRANGEMENTS OF 2-LITHIOTETRAHYDROPYRANS

Early in our reductive lithiation work, it was demonstrated that reductive lithiation is a general method for the production of unstabilized α-lithioethers and that the substrates can be very readily prepared by a variety of methods.[9] Previously, no general preparative method had been available for these species and reductive lithiation proved to be a useful complement to the far more limited procedure involving tin-lithium exchange.[10] The application of this method to the preparation of 5-and 6-membered α-lithio cyclic ethers proved particularly rewarding since at that time these were unknown as synthetic intermediates.[11] Furthermore, the substrates could be readily prepared by the treatment with thiophenol and an acid of lactols or their diisobutylaluminum salts, themselves prepared by the reduction of lactones with diisobutylaluminum hydride, divalent sulfur thus displaying its nucleophilic character.[12] A striking finding is that regardless of the configuration of the substrate the reductive lithiation of 2-(phenylthio)tetrahydropyrans generates as proximate products almost exclusively the corresponding axial 2-lithiotetrahydropyrans,[12,13] and that in rigid systems these proximate products could be equilibrated mainly to the more stable equatorial organolithiums simply by warming.[12] The axial character of the kinetic reductive lithiation product has been attributed to the rapid attainment and stability of the conformation of the intermediate radical (e.g. **1**) in which the half filled atomic orbital is in an axial-like orientation that allows overlap with one of the orbitals on oxygen containing a non bonding electron pair.[12]

This remarkable stereoselectivity has allowed the preparation of stereochemically defined 2-lithio-6-vinyltetrahydropyrans for study of Wittig rearrangements that result in ring expansions and contractions. Evidence has been presented that these rearrangements proceed through the conformers (e.g. **4** and **5**) in which the C-Li bond is equatorially disposed and is thus anti periplanar with the C-O bond that breaks (Fig. 4).[14] Both the ring contraction to **2** and expansion to **3** occur with virtually complete stereoselectivity as shown. The synthetic promise of these novel modes of Wittig rearrangement is suggested by the new completely diastereoselective hydrazulene synthesis shown in eq. 1.

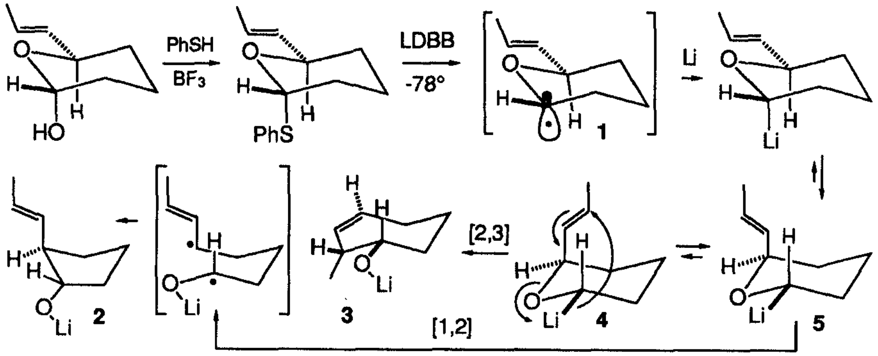
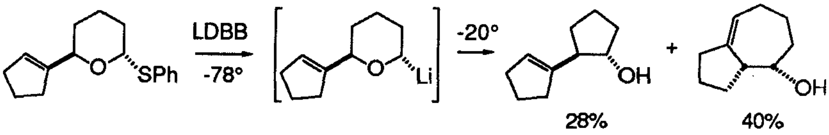


FIGURE 4 Wittig rearrangements of *trans*- 6-(*trans*-1-propenyl)-2-lithiotetrahydropyran.



(1)

A remarkable but predicted change in chemoselectivity occurs when a methyl group is substituted for a hydrogen atom at the 2-position so that the rearranging intermediate is a tertiary organolithium, undoubtedly the only unstabilized one ever to have been observed to undergo a Wittig rearrangement. The endo conformer **8**, from which the [2,3]-rearrangement presumably must proceed, should be greatly destabilized by steric congestion when R is methyl thus leading to preferential [1,2]-rearrangement that can proceed through non-endo conformers such as **7**. In accord with this expectation, **7**/**8** (R = Me) provides none of the cycloheptenol **9**, which is the major product when R = H; instead the ring contraction product **6** is formed in good yield (Fig. 5).

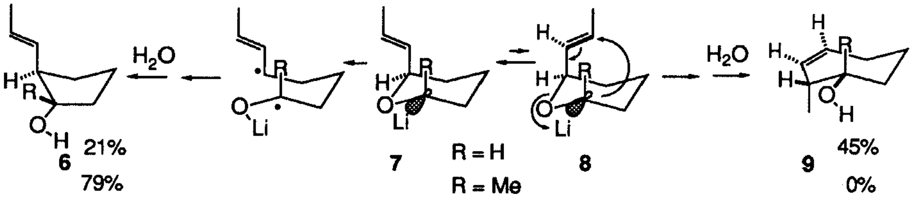
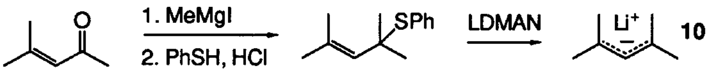


FIGURE 5 Effect on selectivity of the II° or III° nature of the carbanion.

ALLYLLITHIUMS

It has been shown that a nearly ideal general method for the regiospecific production of allyl anions is the treatment of allyl phenyl sulfides with aromatic radical anions.[15,16] The substrates can be prepared by a variety of methods and the reductive lithiation is particularly facile due to the allylic stabilization of the intermediate radical. A dramatic example of the power of this method is the two-pot preparation from mesityl oxide of 1,1,3,3-tetramethylallyllithium **10**, a substance that was needed for NMR structural studies but that did not yield to literature procedures for the production of allyl anions presumably because of its di-tertiary carbanion nature (eq. 2).[17] Once again, the nucleophilic power of divalent sulfur to displace a labile hydroxyl group is manifested and the tertiary nature of the target organolithium actually becomes an advantage in this method of carbanion generation.



(2)

When an allylic alcohol is secondary, the hydroxyl function is readily replaced by phenylthio using the *electrophilic* reagent diphenyl disulfide,[18] although the mechanistic step in which the displacement actually occurs again involves nucleophilic attack. The wide availability of allyl alcohols thus makes it possible to prepare a variety of allyllithiums. The known[19] propensity of terminally monosubstituted allyllithiums to exist mainly in the cis configuration could readily be exploited if a method could be found to allow electrophiles to attack preferentially the least substituted terminus of the allyl system. We and others had demonstrated that titanium(IV) allyls react with carbonyl groups at the most highly substituted terminus.[20] Gratifyingly, it was discovered that transmetallation of allyllithiums such as **11** with cerium trichloride followed by reaction with an aldehyde or ketone leads to predominant attack of the carbonyl group at the least substituted terminus.[16,21,22] Figure 6 illustrates how this technology can be used to synthesize a cis,cis-methylene-interrupted diene.[16,21] The acetate ester of the product **12** occurs in brown algae and **12** had been suggested as a biosynthetic precursor of the gamete attractant dictyopterene B.[23] Because of the ready availability of **12**, we were able to study its conversion to dictyopterene B for the first time and have discovered a highly stereoselective two step biogenetically inspired conversion of **12** to this gamete attractant.[21]

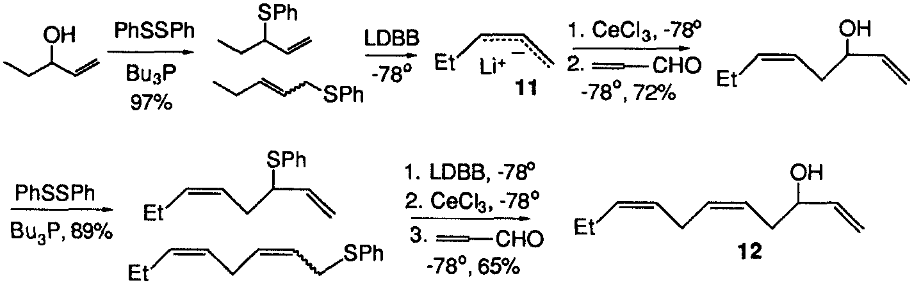


FIGURE 6 Production of a cis,cis-methylene-interrupted diene.

HOMOENOLATE AND BIS(HOMO)ENOLATE ANION EQUIVALENTS

The considerable ease of preparing 3-(phenylthio)aldehydes and -ketones (e.g. **13** and **14**, Fig. 7) has allowed the development of the most general route available to homoenolate anion equivalents.[24,25] The generally high-yield addition of thiophenol to conjugated enals and enones is usually the method of choice for production of the substrates. However, in cases in which the enone is not readily available or when the 2-position of the desired 3-(phenylthio)ketone bears no hydrogen atom, a very satisfactory method involves the attack of a sulfur-stabilized carbocation on a silyl enol ether.[26]

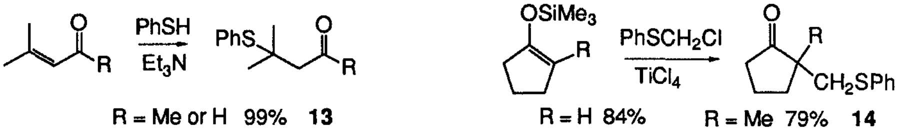


FIGURE 7 Production of 3-(phenylthio)aldehydes and -ketones.

Protection of the 3-(phenylthio)aldehydes and -ketones as the dioxolanes usually occurs in excellent yield (e.g. Fig. 8). The reductive lithiations proceed uneventfully. As expected, the production of tertiary organolithiums such as **16** is especially facile, occurring instantaneously as -78°. Remarkably, such tertiary organolithiums are very well behaved. For example, **16** reacts normally and in quit good yield with an aldehyde to deliver a masked 4-hydroxyketone; unmasking (see below) would undoubtedly produce a lactol. Treatment with *N,N*-dimethylformamide provides a good yield of the monoprotected and therefore differentiated 1,4-dicarbonyl compound **17**. Treatment with cuprous bromide complexed with dimethyl sulfide at -78 °C smoothly generates the heterocuprate;[27] it obviously incorporates the phenylthio group that was released during the reductive lithiation[6] since treatment with allylic bromides (not shown) yields no allylic phenyl thioether and, judging by the excellent yields, one equivalent of the alkyllithium is not wasted. The cuprates, even tertiary ones such as that derived from **16**, add easily to enones to produce monoprotected 1,6-diketones. Deprotection is usually rapid and quantitative. In the case of **15**, the resulting diketone **18** undergoes an aldol condensation to yield diquinanes. It has also been demonstrated that cuprates derived from protected homoenolates are readily acylated by acid chlorides to provide monoprotected 1,4-diketones.[24]

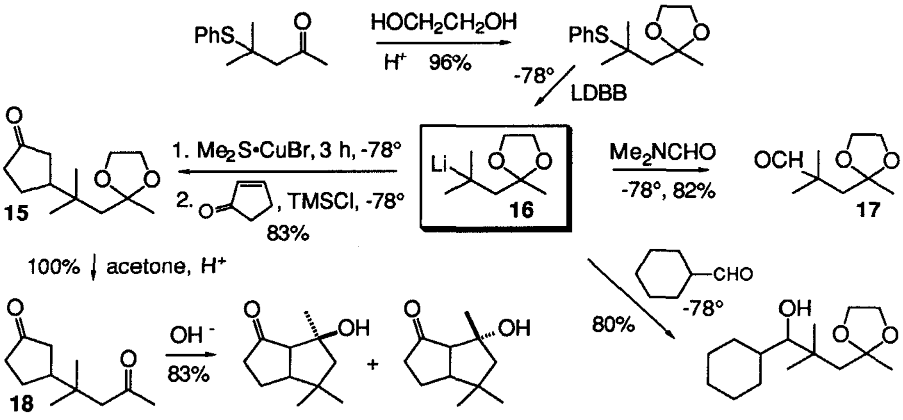


FIGURE 8 Formation and uses of a homoenolate equivalent.

In promising preliminary work,[28] a tertiary bis(homo)enolate anion equivalent[29] **21** was smoothly generated from γ-(phenylthio)ketone **19**. The latter was constructed by conjugate addition of a heterocuprate prepared from a sulfur-stabilized anion which in turn was generated by reductive lithiation of the phenyl thioacetal of acetone. The heterocuprate derived from **21** underwent efficient conjugate addition to an enone to provide the monoprotected 1,7-diketone **20** as well as allylation. The conjugate adduct **20**, upon deprotection and acid induced aldol condensation with azeotropic removal of water, produced a bicyclic enone (Fig. 9).

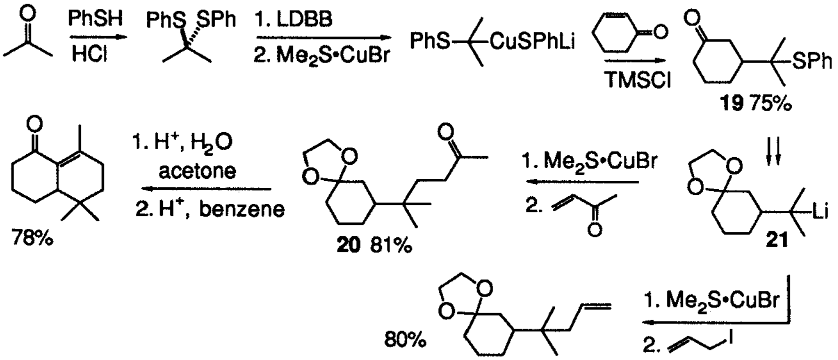


FIGURE 9 Formation and uses of a bis(homo)enolate equivalent.

GENERATION AND SYNTHETIC USES OF LITHIUM 3-LITHIOALKOXIDES

Recent work from this laboratory has demonstrated that lithium 3-lithioalkoxides such as **22**, prepared by reductive lithiation of oxetanes, are useful in the synthesis of spiroacetals (e.g. Fig. 10).[30] However, a far more versatile approach to this type of intermediate involves reductive lithiation of the adducts of organolithiums with 3-(phenylthio)aldehydes and -ketones such as **13** (Fig. 7). Thus, **26** can be prepared by the addition of 2-lithiotetrahydrofuran, generated by reductive lithiation,[9,12] to the adduct of thiophenol and acrolein; however it is accompanied by its diastereomer. Reasonable diastereoselectivity can be achieved by zinc borohydride reduction of the ketone **24**, prepared by treating the adduct **23** of thiophenol and acrylic acid with butyllithium followed by the organocerium derived from 2-lithiotetrahydrofuran. Presumably, the Cram cyclic model is followed generating a 7.5 : 1 ratio of **25** to its diastereomer. Deprotonation of **25** followed by reductive lithiation, lithium - cerium exchange,[30] addition of a lactone, and acid work-up delivers a spiroacetal **27** possessing the gross structural features of some found in nature.[31]

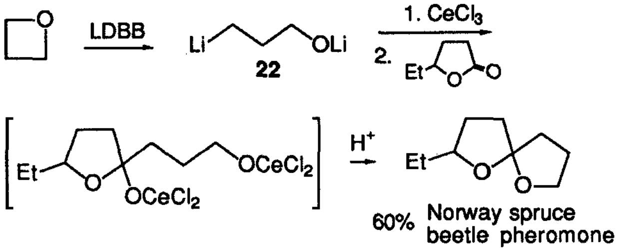


FIGURE 10 Examples of spiroacetals via reductive lithiation of oxetanes.

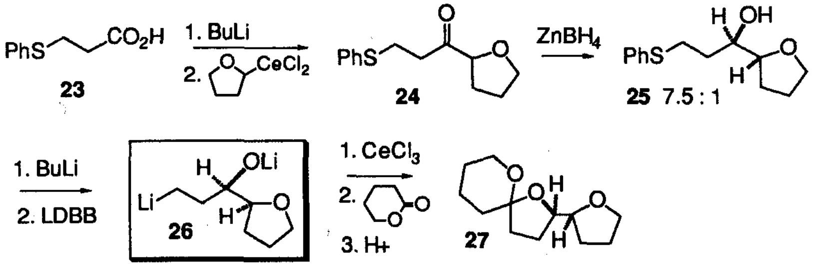


FIGURE 11 3-Lithioalkoxides and their derived spiroacetals via reductive cleavage of C–S bonds.

GENERATION AND REARRANGEMENTS OF HOMOALLYLLITHIUMS

During our study of the reductive cleavage of oxetanes, we found that it is possible to control the regiochemistry of ring opening. In the absence of Lewis acids stronger than lithium ion, opening occurs predominantly such that the least substituted organolithium is produced whereas in the presence of Lewis acids the opposite is true.[32] Reductive cleavage of **28** under the most favorable conditions for regiochemical differentiation followed by carbonation of the intermediate produced, upon acidic work-up, not the lactone expected from attack of CO_2 on the tertiary homoallylic organolithium **29** but that (**32**) expected from carbonation of the rearranged homoallylic organolithium **31**. The 1,2-vinyl migration that occurs in some homoallylic anions has been fairly well studied.[33] It is believed to proceed through a cyclopropylcarbinyllithium (**30** in the case of **29**). However, most of the known examples (usually in Grignard reagents) occur at far higher temperatures.[34] This particularly facile rearrangement prompted us to examine the scope and the synthetic aspects of homoallylic carbanion rearrangements, particularly as they apply to tertiary carbanions. In this way, we hoped to convert a process that has been merely a mechanistic curiosity into a useful synthetic procedure.

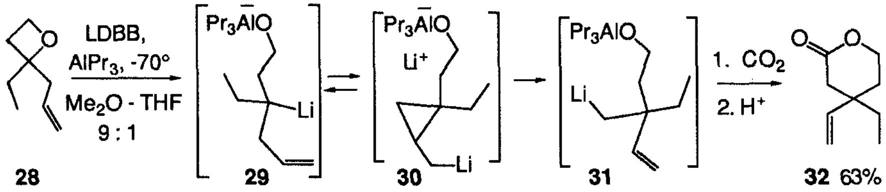
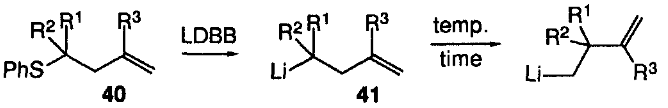


FIGURE 12 1,2-Vinyl migration during reductive lithiation of an oxetane.

Once again the great versatility of divalent sulfur helped greatly. One type of substrate (**33**) for the production of a tertiary homoallylic organolithium (**34**) could be readily prepared by reductive lithiation of the phenyl thioacetal of cyclohexanone and allylation of the heterocuprate of the resulting sulfur-stabilized organolithium (Fig. 13).[35] Carbonation of **34**, provided the carboxylic acid **39** which provided iodolactone **38** upon treatment with iodine. On the other hand, when **34** was warmed to -40 °C, it rearranged to the primary organolithium **35** which was carbonated to the unsaturated carboxylic acid **36**, capable of iodolactonization to **37**. It would be difficult indeed to conceive of preparative methods for organolithiums **34** and **35** other than reductive lithiation.

FIGURE 13 1,2-Vinyl migration to a tertiary carbanionic center.

A series of homoallylic phenyl thioethers **40** was prepared from phenyl thioacetals and the organolithiums **41** derived from **40** by reductive lithiation were subjected to rearrangement conditions (eq. 3).[35] From the results of this series of experiments, it was determined that tertiary organolithiums rearrange more readily than secondary ones and that monosubstituted olefins (**41**, R^3 = H) participate more readily than disubstituted ones in which R^3 = alkyl. In the latter case, a high enough temperature is required that a serious competing reaction, deprotonation of the solvent by the highly basic tertiary organolithium, causes a decrease in the yield of products derived from the rearranged organolithium. This problem can be considerably alleviated by performing the rearrangement in a solution consisting of hexanes, THF, and tetramethylethylenediamine (TMEDA).[36] Under these conditions, certain ring contractions could be performed. Thus the homoallylic phenyl thioether **43**, prepared by Wittig olefination of the thiophenol conjugate adduct **42** of an enone, can be reductively lithiated to the tertiary organolithium **44** and the latter can be trapped in high yield by an aldehyde or it can be warmed to yield the ring contracted primary homoallyllithium **45** (Fig. 14). It appears from preliminary experiments that this type of ring contraction is more facile and occurs in higher yield starting with the corresponding methylenecycloheptene.[35]



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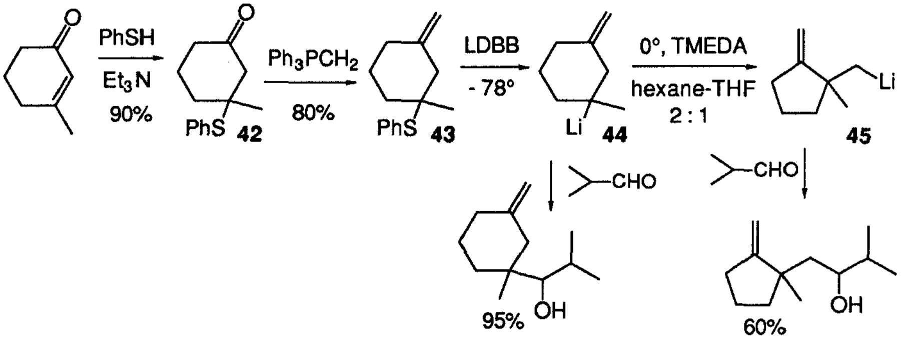

FIGURE 14 Ring contraction via the anionic 1,2-vinyl migration.

It appears from the results of our study that the extremely facile rearrangement of **29** can be partially rationalized by the tertiary nature of the rearranging organolithium. It was suspected that the oxyanionic group in the molecule also played a role. This was confirmed by the type of experiment shown in Fig. 15.[35] The presence of the organolithiums shown was demonstrated by trapping with isobutyraldehyde. It is seen that most of the first-formed organolithium undergoes rearrangement in the time that it takes to perform the reductive lithiation of **46** and to quench the product with aldehyde at -78 °C. The cyclopropylcarbinyllithium intermediate **48** can also be detected, presumably due to stabilization by chelation. At a higher temperature, **47** is virtually totally rearranged to **49**. The rearrangement is about as rapid in the analogue in which the oxyanionic group is further removed by another methylene group from the carbon atom bearing the phenylthio group, although in this case no cyclopropylcarbinyllithium can be detected. However, the special acceleration disappears when the oxyanion is replaced by a methoxy group. Presumably some type of chelation is facilitating these rearrangements; when the lithium alcoholate is external to the rearranging homoallyllithium it exerts no noticeable effect on the facility of the process.

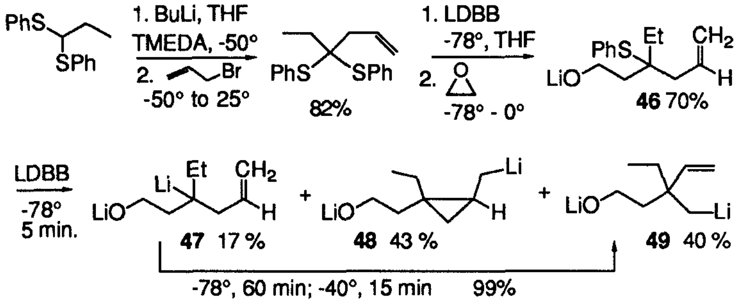

FIGURE 15 Oxyanionic acceleration of the anionic 1,2-vinyl migration.

FUSED RING ALLYLIDENECYCLOPROPYLKETONES FROM REDUCTIVE LITHIATION AND THEIR DOUBLE RING EXPANSIONS.

Earlier work from this laboratory[37] had demonstrated that some cyclopropyl ketones could be generated from enones by conjugate addition of a phenylthio-stabilized organolithium with removal of thiophenoxide at the enolate stage using cuprous triflate.[3] It had also been shown[38] that alkylidene- and allylidenecyclopropanes can be formed by reductive lithiation of 1-phenylthio-1-trimethylsilylcyclopropanes and treatment of the resulting lithiosilane with aldehydes. Recently, we have combined these two technologies into an efficient synthesis of allylidenecyclopropyl ketones (Fig. 16);[39] in this particular case, cuprous bromide can be substituted for the more reactive (and more expensive) cuprous triflate.

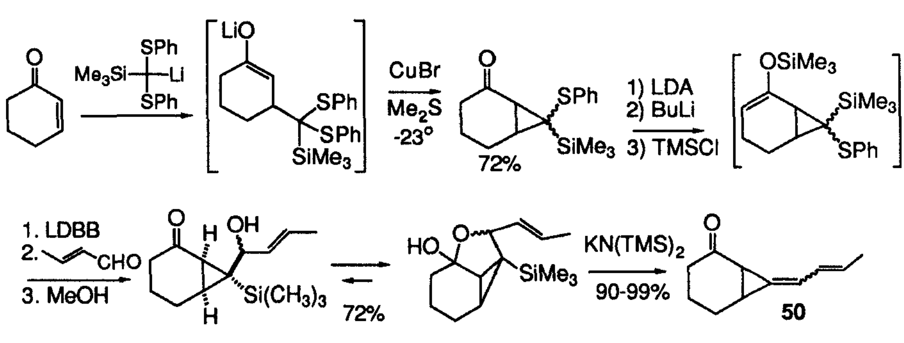

FIGURE 16 Synthesis of an allylidenecyclopropyl ketone from an enone.

Extensive work in this laboratory[40] had revealed that a highly stereoselective double ring expansion occurs upon thermolysis of fused ring allylidenecyclopropanes. It has now been found[39] that **50** is no exception. Not only is the double ring expansion very highly stereoselective but it is essentially completely regioelective as well; none of the regioisomeric double ring expansion product **54** can be detected (Fig. 17). Gratifyingly, it is possible to generate **54** exclusively by performing the rearrangement on the enol silyl ether **51** of **50**. In general, it appears that this sulfur driven chemistry provides a selective novel route to fused ring systems such as the hydrazulenes shown here.

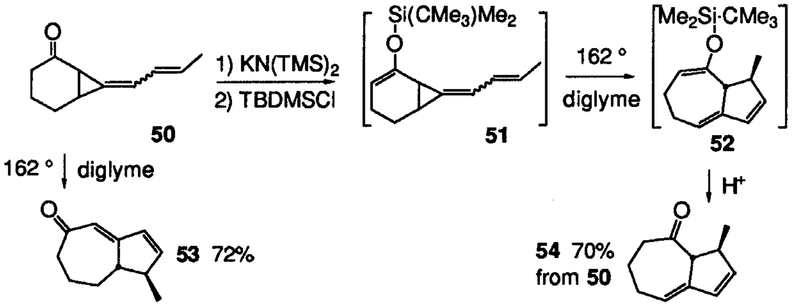

FIGURE 17 Regio- and stereoselective double ring expansion of an allylidenecyclopropylketone and its enol silyl ether.

CONCLUSION

Because of the unique properties of divalent sulfur, it is frequently a simple matter to construct molecules in which the phenylthio group resides at any desired position. A wide variety of organolithium intermediates can be generated by replacing the phenylthio group with lithium by the agency of aromatic lithium radical-anions. The method is especially useful for preparing heretofore exceedingly rare tertiary organolithiums. A number of recent examples from this laboratory of the preparation and use of these organolithiums as nucleophiles and as rearrangement substrates has been presented. It is likely that the synthetic potential of this method of production of organolithiums will gain substantial recognition in the future.

ACKNOWLEDGMENT

I am most grateful to my talented and enthusiastic colleagues who helped to design and who totally executed the work described here. Their names are indicated in the references. I also thank the National Institutes of Health and the National Science Foundation for their support of this work.

REFERENCES

1. T. Cohen.and M. Bhupathy, Acc. Chem. Res., 22, 152 (1989). T. Cohen, in Heteroatom Chemistry, edited by E. Block (VCH Publishers, New York, 1990), Chapter 7.
2. Original discovery of this method of producing organolithiums: C. G. Screttas and M. Micha-Screttas, J. Org. Chem., 43, 1064 (1978). T. Cohen, W. M. Daniewski, and R. B Weisenfeld, Tetrahedron Lett., 4665 (1978).
3. T. Cohen, G. Herman, J. R. Falck, and A. R. Mura, Jr., J. Org. Chem., 40, 812 (1975). T. Cohen, D. Kuhn, and J. R. Falck, J. Am. Chem. Soc, 97, 4749 (1975).
4. T. Durst, in Comprehensive Carbanion Chemistry. Part B, edited by E. Buncel and T. Durst (Elsevier, New York, 1984), Chapter 5.
5. T. Cohen and M. D. Doubleday, J. Org. Chem., 55, 4784 (1990).
6. T. Cohen and J. R. Matz, Synth. Commun., 10, 311 (1980).
7. The sodium analogue was known: S. Bank and M. Platz, Tetrahedron Lett., 2097 (1973).
8. P. K. Freeman and L. L. Hutchinson, J. Org. Chem., 45, 1924 (1980); 48, 4705 (1983).
9. T. Cohen and J. R. Matz, J. Am. Chem. Soc., 102, 6900 (1980).
10. Footnote 8, p 133, of U. Schöllkopf, in Methoden der Organischen Chemie, 4th ed., Part 1, Vol. 13, edited by E. Müller, (Houben-Weyl, Georg Theime Verlag, Stuttgart, 1970), p 87. D. Peterson, J. Organomet. Chem. Rev., Sect. A, 7, 295 (1972). W. C. Still, J. Am. Chem. Soc., 100, 1481 (1978). W. C. Still and A. Mitra, Ibid., 100, 1927 (1978). See also: D. Seebach and N. Meyer, Angew. Chem. Int. Ed. Engl., 15, 438 (1976).
11. They have since been prepared by tin-lithium exchange, albeit in considerably lower overall yield. J. S. Sawyer, A. Kucerovy, T. L. Macdonald, and G. J. McGarvey, J. Am. Chem. Soc., 110, 842 (1988).
12. T. Cohen and M.-T. Lin, J. Am. Chem. Soc., 106, 1130 (1984).
13. J. -M. Lancelin, L. Morin-Allory, and P. Sinaÿ, J. Chem. Soc., Chem. Commun., 355 (1984).
14. E. Verner and T. Cohen, J. Am. Chem. Soc., 114, 375 (1992). E. Verner and T. Cohen, J. Org. Chem., 57, 1072 (1992).
15. T. Cohen, and B.-S. Guo, Tetrahedron, 42, 2803 (1986).
16. B. S. Guo, W. Doubleday, and T. Cohen, J. Am. Chem. Soc., 109, 4710 (1987).
17. J. A. Cabral, T. Cohen, W. W. Doubleday, E. F. Duchelle, G. Fraenkel, B.-S Guo, and S. H. Yü, J. Org. Chem., in press.
18. I. Nakagawa and T. Hata, Tetrahedron Lett., 1409 (1975). T. Mukaiyama, R. Matsueda, and M. Suzuki, Ibid., 1901 (1970).
19. M. Schlosser, J. Hartmann, and V. David, Helv. Chim. Acta , 57, 1567 (1974). R. B. Bates and W. A. Beavers, J. Am. Chem. Soc., 96, 5001 (1974). K. N.

Houk, R. W. Strozier, N. G. Rondan, R. R. Fraser, and W. Chauqui-Offermanns, J. Am. Chem. Soc., 102, 1426 (1980).

20. Reference 15 and citations therein.
21. W. D. Abraham and T. Cohen, J. Am. Chem. Soc., 113, 2314 (1991).
22. D. W. McCullough, M. Bhupathy, E. Piccolino, and T. Cohen, Tetrahedron, 47, 9727 (1991).
23. R. E. Moore, Acc. Chem. Res., 10, 40 (1977).
24. J. P. Cherkauskas and T. Cohen, J. Org. Chem., 57, 6 (1992).
25. Reviews of homoenolate equivalents: (a) I. Kuwajima and E. Nakamura, Topics in Current Chemistry, 155, 1(1990). (b) D. Hoppe, Angew. Chem. Int. Ed. Engl., 23, 932 (1984). (c) J. C. Stowell, Chem. Rev., 84, 409 (1984). N. H. Werstiuk, Tetrahedron, 39, 205 (1983).
26. I. Paterson and I. Fleming, Tetrahedron Lett., 995 (1979). I. Paterson, Tetrahedron, 44, 4207 (1988).
27. G. H. Posner, C. E. Whitten, and J. J. Sterling, J. Am. Chem. Soc., 95, 7788 (1973).
28. J. P. Cherkauskas, B. Zhang, and T. Cohen, unpublished work.
29. For a method of producing the primary organolithium analogues, see. D. J. Ramón and M. Yus J. Org. Chem., 56, 3825 (1991).
30. B. Mudryk, C. A. Shook, and T. Cohen, J. Am. Chem. Soc., 112, 6389 (1990).
31. T. L. B. Boivin, Tetrahedron, 43, 3309 (1987).
32. B. Mudryk and T. Cohen, J. Org. Chem., 56, 5760 (1991).
33. A review of some earlier examples: E. J. Grovenstein, Angew. Chem., Int. Ed. Engl., 17, 313 (1978).
34. For an apparent exception in a system with a special driving force, see: A. Maercker, M. Bsata, W. Buchmeier, and B. Engelen, Chem. Ber., 117, 2547 (1984).
35. B. Mudryk and T. Cohen, unpublished results.
36. Rychnovsky had shown that organolithiums are far less destructive of THF when the latter is diluted with a substantial amount of hexane: S. C. Rychnovsky, J. Org. Chem. 54, 4982 (1989).
37. T. Cohen and M. Myers, J. Org. Chem., 53, 458 (1988).
38. T. Cohen, S.-H. Jung, M. L. Romberger, and D. W. McCullough, Tetrahedron Lett., 29, 25 (1988).
39. C. A. Shook and T. Cohen, unpublished results.
40. J. P. Sherbine, Ph. D. Thesis, University of Pittsburgh, 1985; M. L. Romberger, Ph. D. Thesis, University of Pittsburgh, 1989; S.-H. Jung, M. Xiao and T. Cohen, unpublished results.