perimentation, in routine analyses, and in the control of processes. Furthermore, when computer systems are properly specified and implemented their utilization results in improved measurement accuracy and control.

Conclusions

Analytical chemistry, as a service-oriented discipline, is entering a transition period when many of our instruments will be automated and placed on-line. The design of these chemical measuring systems of the future will follow improved development procedures. Many of these new measuring systems will have advanced interactive capabilities.

To summarize, there are three ways of handling difficult automation projects. First is the conventional method where the system is specified, designed, implemented, tested, and modified until operative. This is usually a long and complex procedure. A second procedure will be similar to the first but will encompass the use of such techniques as pattern recognition to help in the generation of system control and measurement specifications. However, the variables to be controlled are generally well known. It is the control algorithm that is difficult to optimize.

Therefore, a third approach to automation will utilize the capabilities of interactive experimentation and control. These systems will permit fine tuning of the control algorithms as well as rapid interrogation of data and waveforms for significant features (information) to be used together with our knowledge and intuition to reach new conclusions.

Analytical chemists already have at their command significant technology and expertise so that they can contribute to the design and implementation of automated chemical measuring systems. A partial list of that technology includes: understanding the instrumentation to be automated; designing a new instrument; writing the detailed specifications for the chemical methods; understanding the use of modeling techniques; and writing the detailed specifications for the data-reduction techniques required for processing the instrument signals, *i.e.*, spectral analysis and digital signal-processing techniques.

Analytical chemists have an exceptionally bright future, but it will require change in their skills and a significant change in the definition of their role in society.

The author wishes to express his thanks to Professors L. B. Rogers, T. A. Brubaker, S. P. Perone, G. M. Hieftje, and B. R. Kowalski, and to Dr. Michael J. Randall, Chief Biomedical Engineer, Merrell-National Laboratories, Cincinnati, Ohio, for their many helpful discussions and review of the manuscript. This work was performed under the auspices of the U. S. Atomic Energy Commission.

Allylic Sulfoxides: Useful Intermediates in Organic Synthesis

David A. Evans*[1] and Glenn C. Andrews

Contribution No. 3268 from the Department of Chemistry, University of California, Los Angeles, California 90024

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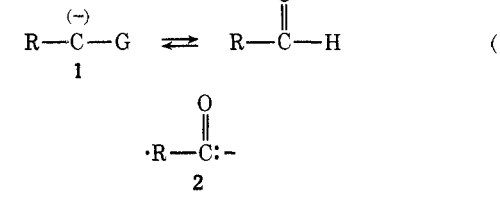
As a consequence of the central role that polar or Lewis acid–base reactions play in the synthesis of organic molecules, organic chemists have endeavored to develop new, general ways in which such reactions can be employed in synthesis.

During the last decade a great deal of effort has been focused on synthetic transformations which *invert* the inherent chemical reactivity that functional groups confer upon organic molecules. Such operations enable the chemist to reverse the Lewis acid–base properties of a given functionally activated carbon, adding new dimensions of flexibility to the design of complex molecules.

Equation 1 illustrates one such transformation. Normally, the carbonyl carbon serves as the electrophilic partner in a polar condensation process. Synthetic operations that reversibly interconvert the carbonyl function with those classes of functions, G,



(1)

which are capable of adjacent anion stabilization as indicated in **1**, enable a synthetic equivalency to be established between **1** and the inherently unstable "carbonyl anion" **2**.[2] In the literature, representations such as **1** have been referred to as either "masked" acyl anions,[3] or more recently as carbonyl anion equivalents.[4]

In the ensuing discussion, transformations which *invert* the Lewis acid–base properties of a given carbon atom *via* the interchange of activating functions (*cf.* eq 1) will be referred to as "charge affinity inver-

David Evans is Associate Professor of Chemistry at the University of California, Los Angeles. He was born in Washington, D. C., and received the Ph.D. from Caltech in 1968. His research interests lie in the area of organic synthesis, new reagent design, and molecular rearrangements. Currently he is both an Camille and Henry Dreyfus Teacher-Scholar (1971–1976) and an Alfred P. Sloan Fellow (1972–1974).

Glenn Andrews received his B.S. degree from UCLA in 1970, and is now completing doctoral work with Professor Evans.

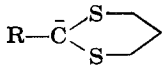
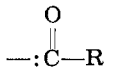
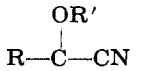
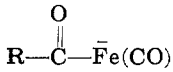
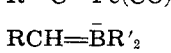
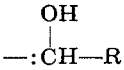
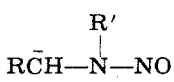
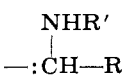
(1) After July 1, 1974: California Institute of Technology, Pasadena, Calif. 91109.

(2) L. S. Trzupek, T. L. Newirth, E. G. Kelly, N. E. Sbarbati, and G. M. Whitesides, *J. Amer. Chem. Soc.*, **95**, 8118 (1973), and references cited therein.

(3) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969).

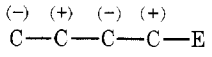
(4) J. E. McMurry, and J. Melton, *J. Amer. Chem. Soc.*, **93**, 5309 (1971).

Table I
Synthetic Equivalents to R—C(−)—E

R—C̄—G	R—C(−)—E	Ref
		14a
		4
		14b
		14c
		14d
		14e

sion" operations.[5] In biochemical processes such inversion operations on the carbonyl function are effected by the coenzyme thiamine.[6] The closest laboratory equivalent to thiamine as an *in situ* "carbonyl inversion operator" is the catalytic role of cyanide ion in the benzoin condensation.[7,8]

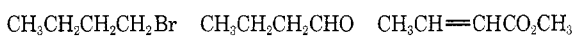
In order to correlate all the relevant literature pertaining to the development of charge affinity inversion operations *via* the interchange of functional groups, it is advantageous to define a symbol, E,[9] which represents a homogeneous class of activating functions. Each member of this class confers wholly, or in part, the *same* chemical properties upon the carbon skeleton to which it is attached.[10] *Employing the appropriate oxidation state of the carbon fragment, E functions confer the "charge affinity pattern" to the carbon residue as denoted in the general structure* **3**; *the symbol designations* (+) *and* (−) *simply denote potential electrophilic or nucleophilic site reactivity.*[11]



3

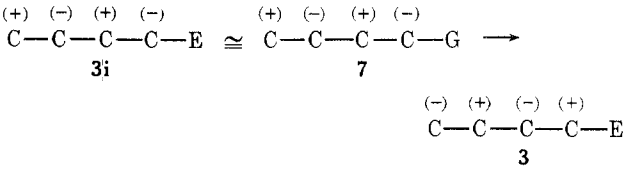
E functions, [12]=O, =NR, OR, NR_2

halogen



4 **5** **6**

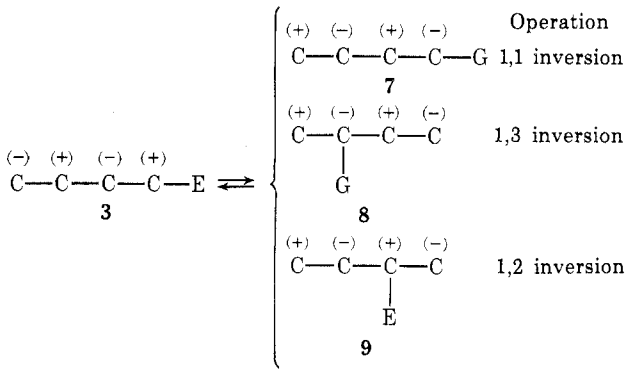
For example, the reactivity pattern of molecules **4**–**6** toward either electrophiles or nucleophiles is represented completely or in part by the common general structure **3**. In the same manner those functions, G, with opposite electronic properties may be assigned the charge affinity pattern illustrated in **7**.[10] Charge affinity inversion operations of the G ⇄ E type (*cf.* **7** → **3**) establish an equivalency between a real entity, **7**, and its reversed polarity equivalent, **3i**.



3i **7** **3**

Scheme I summarizes three distinct charge affinity inversion processes that establish equivalents to **3i**. Such functional group interconversions may be accomplished *via* the interchange of E and G functions on the same carbon (**3** ⇄ **7**) or on alternate carbon atoms (**3** ⇄ **8**). Alternatively, the transposition of an E function to an adjacent carbon (**3** ⇄ **9**) constitutes a third general example of a charge affinity inversion operation. With respect to this latter manipulation, considerable effort has been devoted to the 1,2 transposition of the carbonyl function.[13] Formally, the 1,1 and 1,3 charge affinity inversion processes **3** ⇄ **7** and **3** ⇄ **8** generate complementary sets of useful synthetic equivalents when the regioselective chemistry of functionally activated allylic carbanions is considered.

Scheme I



3 **7** **8** **9**

In recent years, the attention given to 1,1 charge affinity inversion operations that interrelate carbonyl functions to functions with reversed electronic properties (eq 1) has been impressive.[3] Table I illustrates representative examples of synthetic equivalents, R—C(−)—E, which may be created *via* such functional group interconversions.[4,14]

(5) E. J. Corey, *Pure Appl. Chem.*, 14, 19 (1967), has referred to such general processes as symmetrization operations.

(6) R. Breslow, *J. Amer. Chem. Soc.*, 80, 3719 (1958), and references cited therein.

(7) W. S. Ide and J. S. Buck, *Org. React.*, 4, 269 (1948).

(8) Recently the role of cyanide ion as a carbonyl inversion operator has been extended: H. Stetter and M. Schreckenberg, *Angew. Chem., Int. Ed. Engl.*, 12, 81 (1973).

(9) The symbol E denotes those activating functions which create an electrophilic carbon at the point of attachment either by resonance or induction.

(10) It should be pointed out that although =O and NO_2 are readily interconverted by synthetic operations, the nitro group is not considered as an E function in that its electronic properties are opposite to those of =O. Rather, the NO_2 → =O transformation is a specific example of the charge affinity transformation illustrated in eq 1.

(11) Such symbolic notation denoting electrophilic and nucleophilic site reactivity is derived from the work of Lapworth and has been extended for use in synthetic design by us and by Ugi: I. Ugi and P. Gillespie, *Angew. Chem., Int. Ed. Engl.*, 10, 915 (1971); *cf.* ref 7; M. Saltzman, *J. Chem. Educ.*, 49, 750 (1972).

(12) This operational classification scheme does not accommodate the properties of carbon monoxide, isocyanides, or cyanide ion. This restriction, however, is not serious, nor does it detract from the general concept of employing such general symbolism.

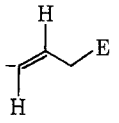
(13) E. J. Corey and J. E. Richman, *J. Amer. Chem. Soc.*, 92, 5276 (1970); J. A. Marshall and H. Roebke, *J. Org. Chem.*, 34, 4188 (1969); A. Hassner, J. M. Larkin, and J. E. Dowd, *ibid.*, 33, 1733 (1968); G. Just and Y. C. Lin, *Chem. Commun.*, 1350 (1968); J. Gore, J. P. Drouet, and J. J. Barieux, *Tetrahedron Lett.*, 9 (1969); and references cited therein.

(14) (a) D. Seebach, *Synthesis*, 17 (1969); (b) G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, 93, 5286 (1971); (c) J. P. Collman, S. R. Winter, and D. R. Clark, *ibid.*, 94, 1788 (1972); (d) G. Zweifel, R. P. Fisher, and A. Hornig, *Synthesis*, 37 (1973), and references cited therein; (e) D. Seebach and D. Enders, *Angew. Chem., Int. Ed. Engl.*, 11, 1101 (1972).

The value of employing general symbolism for homogeneous classes of activating functions and of introducing charge affinity notation to represent polar site reactivity (*cf.* **3**) lies in the organizational framework thus created. This notational scheme has suggested to us the need to develop real examples of 1,3-charge affinity inversion operations (**3** ⇄ **8**) that would be complementary to other methodology that has been developed for creating reversed polarity equivalents such as those cited above.

1,3 Charge Affinity Inversion Operations

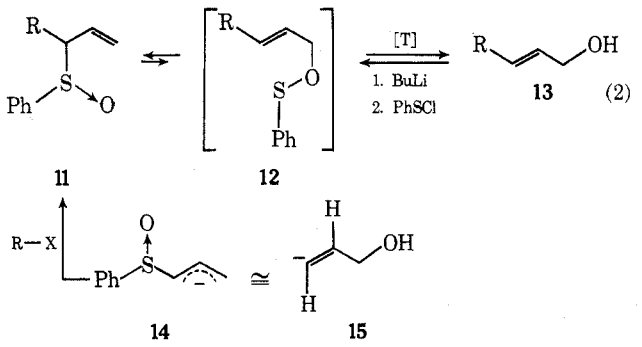
In conjunction with projects under way in our laboratories several years ago, we required a method for creating synthetic equivalents of the general structure **10**. At the time this work was initiated no such



10, E = OH, =O, halogen

equivalents had been established which embodied any degree of substrate flexibility.[15] We felt that such equivalents could be readily devised *via* the interrelation of sulfur and oxygen functions with allylic rearrangement (eq 2).

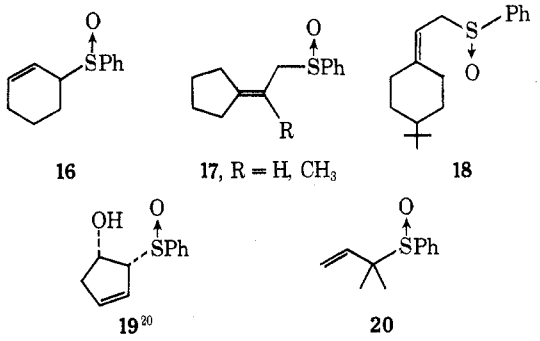
Scheme II



The elegant work of Mislow and coworkers on the thermal racemization of allylic sulfoxides (**11**, R = H) suggested that racemization could be attributed to a [2,3] sigmatropic process affording the achiral sulfenate ester **12** as an intermediate.[16] We felt that if the sulfenate ester **12** could be intercepted cleanly with thiophilic reagents (T) the 1,3 transposition of sulfoxide and hydroxyl functions could constitute the first case of a reversible 1,3 charge affinity inversion operation. Furthermore, if sulfoxide-stabilized allylic carbanions such as **14** could be alkylated regioselectively α to sulfur, the synthetic equivalency between **14** and the vinyl anion **15** would be established.

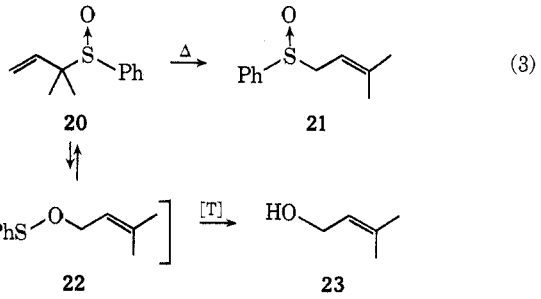
The ultimate success of the proposed allylic alcohol synthesis delineated in Scheme II depended upon the efficient 1,3 transposition of sulfur and oxygen functionality and the predictable α regioselectivity of alkylation and addition reactions with sulfur-stabilized carbanions.

In order to assess the effect of structure on the relative sulfoxide–sulfenate equilibrium concentrations (*cf.* **11** ⇄ **12**), which is known to be dependent upon electronic and medium effects,[16] the allylic sulfoxides **16–20** were synthesized in high yield from the appropriate lithium alkoxides[17,18] and benzenesulfenyl chloride.[19] In each of these cases, the sulfen-



ate–sulfoxide equilibrium constant was large enough so that no sulfenate ester was observable in the nmr spectrum (CCl_4 or $CDCl_3$). Furthermore, the lack of any isomeric sulfoxides in the synthesis of the above compounds attests to the fact that the rearrangement of the sulfenate esters occurs exclusively *via* a concerted rather than dissociation–recombination process.[21]

Attempted heating of α,α-disubstituted sulfoxides such as **20** (40°, 3 hr) has revealed that the phenylsulfinyl moiety may be induced into undergoing a clean 1,3 migration (eq 3) to the thermodynamically



more stable isomer **21**.[22] Although few cases of such 1,3-allylic migrations have been reported,[23a] they rest upon ample precedent established for the analogous rearrangements of both allylic sulfones and sulfides.[23b] Fortunately, the [2,3] sigmatropic process **20** ⇄ **22** proceeds with far greater facility, and in the presence of sulfenate ester trapping agents, T, **20** may be cleanly transformed into the rearranged alcohol **23** with no isomeric alcohol being derived from the sulfoxide **21**.[22]

(15) A synthetic equivalent of **10** (E = =O) has recently been reported: E. J. Corey, B. W. Erickson, and R. Noyori, *J. Amer. Chem. Soc.*, **93**, 1724 (1971); See also ref 14a, example **29a**.

(16) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4869 (1968); R. Tang and K. Mislow, *ibid.*, **92**, 2100 (1970).

(17) D. A. Evans, G. C. Andrews, and C. L. Sims, *J. Amer. Chem. Soc.*, **93**, 4956 (1971).

(18) V. Rautenstrauch, *Chem. Commun.* 526 (1970).

(19) Prepared according to the analogous procedure for *p*-toluenesulfenyl chloride: F. Kurzer and J. R. Powell, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 934.

(20) Prepared from *cis*-2-cyclopentene-1,3-diol (G. O. Schenck and D. E. Dunlap, *Angew. Chem.*, **68**, 248 (1956)) which was treated with 1 equiv of BuLi in THF at −60° and benzenesulfenyl chloride (D. A. Evans and T. C. Crawford, manuscript in preparation).

(21) The activation energies for concerted [2,3] sigmatropic rearrangements and competing dissociative recombination processes are frequently quite similar; *cf.* V. Rautenstrauch, *Chem. Commun.*, 4 (1970).

(22) D. A. Evans and G. C. Andrews, unpublished results.

(23) (a) S. Braverman and Y. Stabinsky, *Chem. Commun.*, 270 (1967); (b) A. C. Cope, D. E. Morrison, and L. Field, *J. Amer. Chem. Soc.*, **72**, 59 (1950); H. Kwart and N. Johnson, *ibid.*, **92**, 6064 (1970).

Scheme III

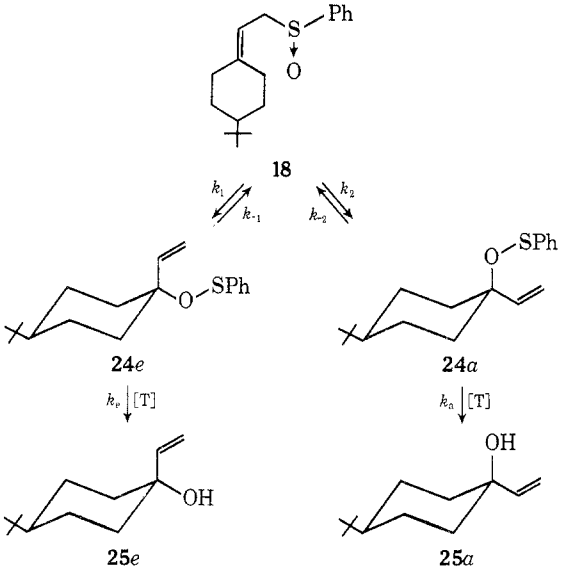


Table II
Effect of Thiophile on 25*e*:25*a* Ratio at 25° in Methanol[a]

Entry	Thiophile [T]	25*e*:25*a*, %	% conversion
i	$LiBH_3CN$	48:52	24
ii	piperidine	66:34	90
iii	$C_6H_5S^-$	88:12	99
iv	$[(C_2H_5)_2N]_3P$	92:8	99
v	$(CH_3O)_3P$	92:8	99

[a] All reactions were carried out with a 10:1 excess of thiophile for 14 days at 25°.

In order to gain information on the trapping efficiency of thiophilic reagents, T, which could be employed in the cleavage of allylic sulfenate esters to alcohols, a study of the rearrangement–cleavage of sulfoxide **18** was undertaken (Scheme III).[24]

At 60° in methanol with trimethyl phosphite as the thiophile, the overall rate for the conversion of **18** to **25** was found to be zero order in phosphite reagent with a half-life of *ca.* 40 min. These results are consistent with the rate-determining step in the reaction scheme being the production of sulfenate esters **24***e* and **24***a* followed by rapid cleavage to the isomeric alcohols **25***e* and **25***a*. The ratio of alcohols produced (**25***e*:**25***a* = 82:18) simply reflects the k_1:k_2 ratio for the overall cleavage process. Table II summarizes the trapping efficiency of other thiophiles; apparently entries i–iii reflect situations where k_1 and k_2 are no longer rate determining.[24]

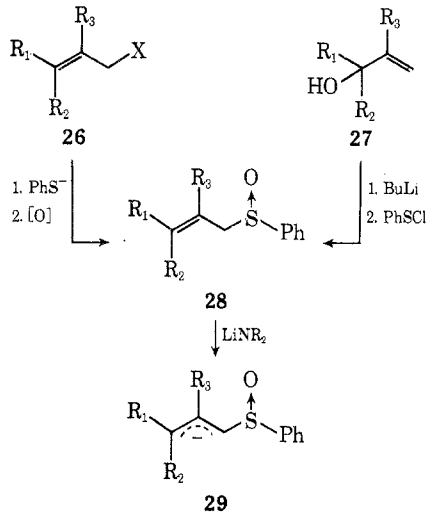
These results suggest that there are two points of stereochemical control in the interchange of sulfur and hydroxyl functions. Not only can the concerted nature of the sigmatropic rearrangement be exploited to define or transfer chirality (both from sulfur and carbon) and to create specified olefin geometries,[25] but, also, a judicious choice of sulfenate ester trapping agent can be made to alter the above stereoselective processes.

(24) D. A. Evans, and G. C. Andrews, *J. Amer. Chem. Soc.*, 94, 3672 (1972).

(25) Surprisingly similar stereochemical consequences have been observed for the [2,3] sigmatropic rearrangement of allylic sulfonium ylides and sulfoxides: G. C. Andrews, and D. A. Evans, *Tetrahedron Lett.*, 5121 (1973).

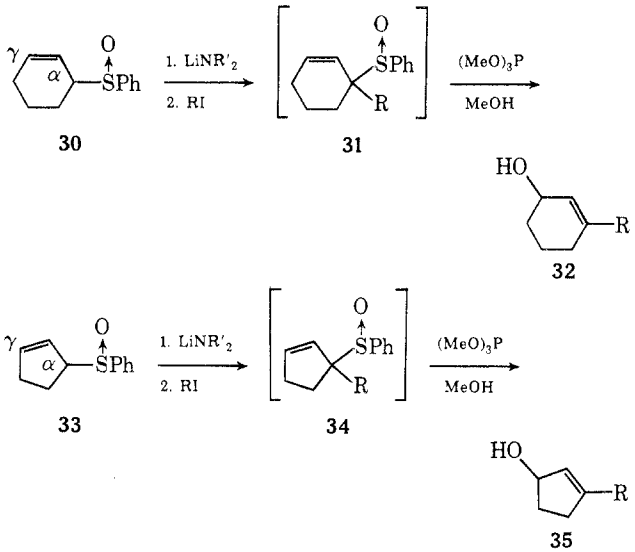
A General Synthesis of Allylic Alcohols

Depending upon practical considerations, both cyclic and acyclic allylic sulfoxides can be synthesized either from allylic halides **26** (X = halogen)[26] or from the isomeric allylic alcohols **27** *via* the corresponding sulfenate esters.[16,17] This latter procedure



complements the more classical procedures for constructing allylic sulfoxides and considerably expands the utility of the allylic alcohol synthesis outlined in Scheme II.

The formation of allylic anion **29** may be carried out in nearly quantitative yield at low temperatures (−40 to −60°) in tetrahydrofuran (THF) with a stoichiometric amount of either lithium diisopropylamide or lithium diethylamide.[27] The resulting anions may then be reacted with a variety of organic halides at the above temperatures and the resulting alkylated sulfoxides cleaved to the rearranged allylic alcohols without purification of intermediate products. Several examples are illustrated below.



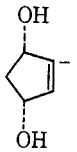
Both cyclohexenyl and cyclopentenyl phenyl sulfoxides (**30** and **33**) may be alkylated (R = CH_3)

(26) For a summary of methods for oxidizing sulfides to sulfoxides see: T. L. Ho and C. M. Wong, *Synthesis*, 561 (1972). Peracids and sodium metaperiodate prove to be the most reliable in our hands.

(27) (a) D. A. Evans, G. C. Andrews, T. T. Fujimoto, and D. Wells, *Tetrahedron Lett.*, 1385 (1973); (b) D. A. Evans, G. C. Andrews, T. T. Fujimoto, and D. Wells, *ibid.*, 1389 (1973).

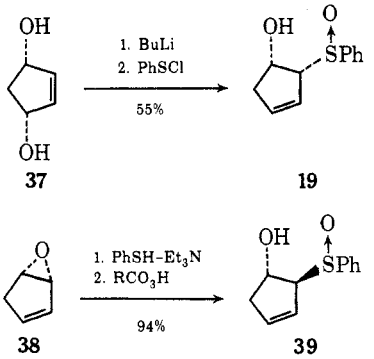
under the previously defined conditions to give quantitative yields of the adducts **31** and **34**, respectively, which may be transformed into the rearranged allylic alcohols [$(MeO)_3P$-MeOH] at 0° in high yield. There are several noteworthy features in these transformations. First, the allylic anions derived from both **30** and **33** alkylate only α to sulfur with a variety of alkyl halides; however, this degree of regioselectivity is *not* observed in condensation reactions with aldehydes, ketones, or esters.[27a] From our own work as well as that of others,[14a,28] the regioselectivity of carbonyl addition processes is lower and less predictable that the corresponding alkylation reactions for heteroatom-stabilized allylic carbanions. Second, the rearrangement-cleavage of α,α-disubstituted sulfoxides (*cf.* **20**, **31**, and **34**) occurs quite readily at 0°. This is probably a consequence of steric factors which destabilize the sulfoxide relative to the isomeric allylic sulfenate ester.

As part of a program devoted to prostaglandin synthesis, we have been interested in creating synthetic equivalents of **36**. Such equivalents are readily



36

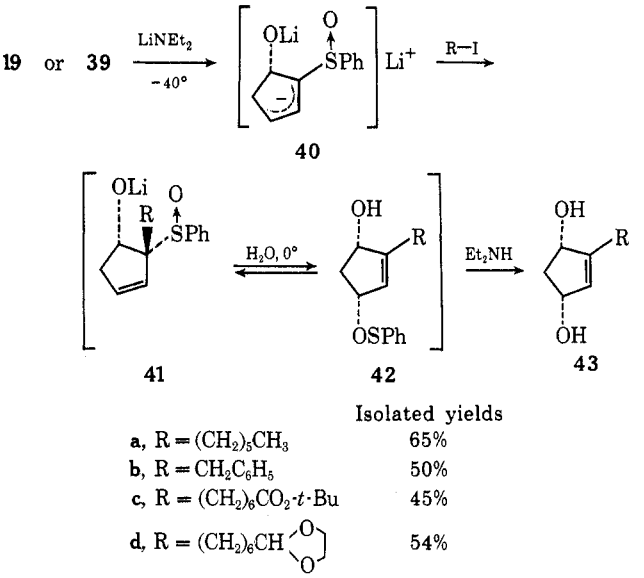
derived from the conjugate bases of either **19** or **39**. The *cis*-hydroxy sulfoxide **19** may be easily prepared from the *cis*-diol **37**[20] while the *trans*-hydroxy sulfoxide **39** can be synthesized from cyclopentadiene oxide (**38**) by: (a), treatment with benzenethiol–triethyamine in benzene at 25° and (b) oxidation of the resulting sulfide with *m*-chloroperbenzoic acid in dichloromethane.



37 **19** **38** **39**

Treatment of either **19** or **39** with 2 equiv of lithium diethylamide in THF–5% hexamethylphosphoramide (HMPA) followed by the addition of the appropriate alkyl iodide at −40° presumably affords the adduct **41** which undergoes facile rearrangement to the sulfenate ester **42** and subsequent cleavage at 0° with added aqueous diethylamine to the monosubstituted cyclopentene diols **43a–d**. The primary-alkylation step (**40** → **41**) appears to be both highly stereo- and regioselective. Either trimethyl phosphite or diethylamine may be employed in the interception of sulfenate ester **42**; however, the latter reagent affords a reaction mixture from which the diols **43** can be more readily isolated.[29]

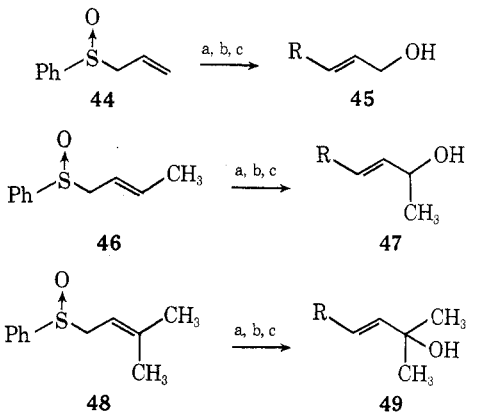
(28) (a) E. J. Corey and D. E. Cape, *J. Org. Chem.*, 34, 3053 (1969); (b) R. Kow and M. W. Rathke, *J. Amer. Chem. Soc.*, 95, 2715 (1973).



40 **41** **42** **43**

	Isolated yields
a, $R = (CH_2)_5CH_3$	65%
b, $R = CH_2C_6H_5$	50%
c, $R = (CH_2)_6CO_2$-*t*-Bu	45%
d, $R = (CH_2)_6CH$	54%

Representative sulfoxides **44**, **46**, and **48** can be employed as useful precursors to a variety of trans-1,2-disubstituted allylic alcohols, **45**, **47**, and **49**. In all cases the trans olefinic geometry, established as a consequence of the [2,3] sigmatropic rearrangement, is produced in greater than 98% isomeric purity. The isolated yields of allylic alcohols range from 50 to 85%; the only apparent side reaction appears to arise from varying amounts of alkylation γ to the sulfoxide function (*cf.* Table V).



44 **45** **46** **47** **48** **49**

conditions: a, $LiN(i\text{-Prop})_2$; b, R-I; c, $(MeO)_3P$-MeOH

In view of the utility of sulfur in [2,3] sigmatropic rearrangements,[30] the 1,3 sulfoxide–hydroxyl transformation may be employed to complement such reorganization processes.[22] The synthesis of yomogi alcohol (**53**)[31] (Scheme IV) provides an illustration of the sequential use of sigmatropic processes in a short synthetic sequence. As in the cases cited above (*cf.* **48** → **49**), the sulfoxide **52** may be transformed into yomogi alcohol (**53**) wherein the trans double bond is uniquely defined by the [2,3] sigmatropic process.

For anticipated applications of substituted allylic sulfoxides in the synthesis of trisubstituted allylic alcohols, the projected equivalency of anion **54** with

(29) D. A. Evans and T. C. Crawford, and R. C. Thomas, manuscript in preparation.

(30) (a) J. E. Bandwin, R. E. Hackler, and D. P. Kelly, *J. Amer. Chem. Soc.*, 90, 4758 (1968); (b) V. Rautenstrauch, *Helv. Chim. Acta.*, 54, 739 (1971), and references cited therein; (c) B. M. Trost, P. Conway, and J. Stanton, *Chem. Commun.*, 1639 (1971).

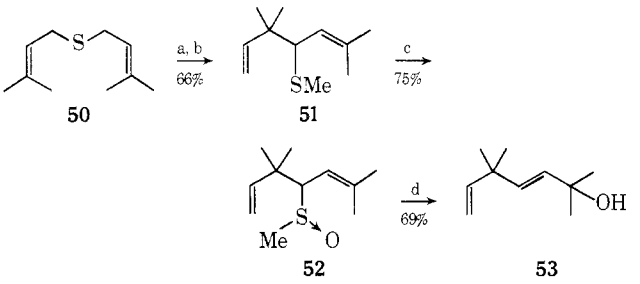
(31) B. Willhalm and A. F. Thomas, *Chem. Commun.*, 1380 (1969).

Table III
Alkylation of Allylic Anion 54[27b]

RX	Yield, % (57*E* + *Z*)	57*E*:57*Z*	α/γ ratio[a]
CH_3I	75	97:3	10
n-$C_6H_{13}I$	42	96:4	2.5
$(CH_3)_2C{=}CHCH_2Br$	46	96:4	2.0

[a] Relative proportion of alkylation α and γ to sulfur.

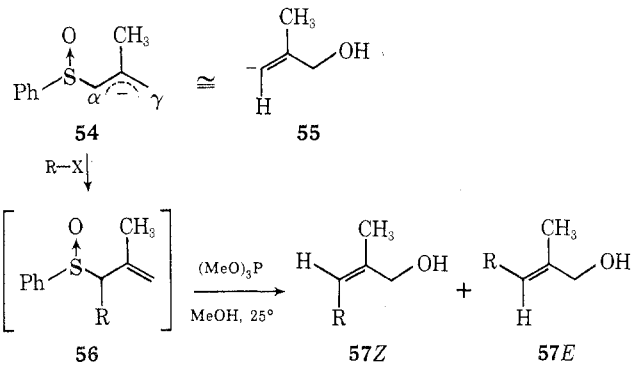
Scheme IV



50 51 52 53

conditions: a, *n*-BuLi, THF, TMEDA; b, MeI; c, $NaIO_4$; d, Et_2NH-MeOH, 24 hr at 25°

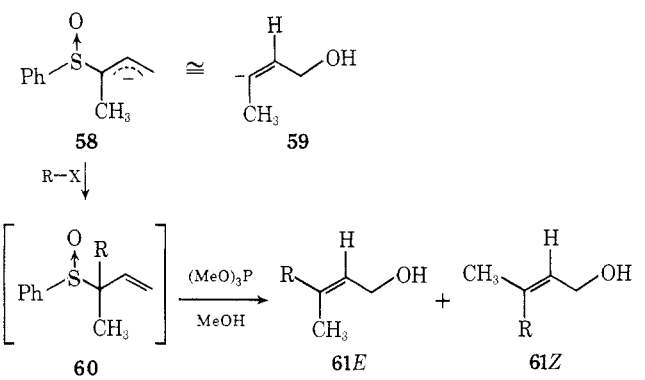
respect to the vinyl anion **55** has been investigated.[27,32]



54 55 56 57*Z* 57*E*

The results summarized in Table III indicate that the *sulfoxide-alcohol transposition* **56** → **57** *is a highly stereoselective process, the E isomer being produced nearly exclusively both with the phosphite and amine thiophiles.*[22,27b] It is presumed that the olefin geometry is established as a consequence of [2,3] sigmatropic rearrangement.

Allylic anion **58**, a synthetic equivalent of **59**, also has potential utility in the stereoselective synthesis of trisubstituted olefins.[27b] As predicted from consid-



58 59 60 61*E* 61*Z*

eration of the various transition-state conformations in the rearrangement of sulfoxide **60**,[16,18] when the R

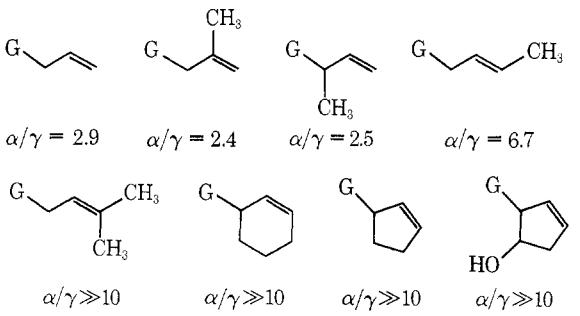
(32) P. A. Grieco, *J. Chem. Soc., Chem. Commun.*, 702 (1972).

Table IV
Alkylation of Anion 58[27b]

RX	Yield, % (61*E* + 61*Z*)	61*E*:61*Z*	α/γ ratio[a]
CH_3I	59		2.6
C_2H_5I	48	73:27	2.4
$(CH_3)_2C{=}CHCH_2Br$	35	93:7	1.1

[a] Relative proportion of alkylation α and γ to sulfur.

Table V
Alkylation Ratios for Allylic Sulfoxides (PhS(→O)G)[a]



α/γ = 2.9 α/γ = 2.4 α/γ = 2.5 α/γ = 6.7

α/γ ≫ 10 α/γ ≫ 10 α/γ ≫ 10 α/γ ≫ 10

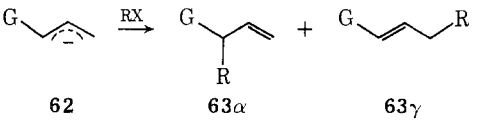
[a] Anions quenched with C_2H_5I.

moiety gets progressively larger than methyl the stereoselectivity in the product-forming step increases, affording higher ratios of the *E* isomer. However, as with anion **54**, the relative proportion of α *vs.* γ alkylation observed with **58** detracts from the general utility of this allylic alcohol synthesis (Table IV).

From our own work we have found two inherent shortcomings in the chemistry of sulfoxide-stabilized allylic anions. Relatively reactive alkyl or allylic halides are required in the substitution reactions of these carbon nucleophiles. Secondly, the variable regioselectivity which is observed in the alkylation reactions of these ambident anions is highly substrate dependent (Table V). This latter problem has been one of long-standing concern in related synthetic studies.[14a,28,33] The following section presents solutions to both of the above limitations.

Regioselective Alkylation of Sulfur-Stabilized Allylic Carbanions[34]

In general, the reactions of functionally activated anions **62** with electrophiles afford varying amounts of α alkylation (**63**α) and γ alkylation (**63**γ), the rel-



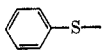
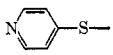
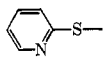
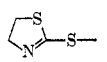
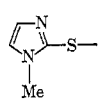
62 63α 63γ

ative ratio of products being system dependent (Table V). Several years ago we undertook a study directed at the problem of controlling the site reactivity of such ambident carbon nucleophiles.[22,34] We were particularly interested in the effect of internal metal chelation in compounds denoted by general structure **64** on α-alkylation regioselectivity. Dur-

(33) (a) J. F. Biellmann and J. B. Ducep, *Tetrahedron Lett.*, 5629 (1968); (b) P. L. Stotter and R. E. Hornish, *J. Amer. Chem. Soc.*, **95**, 4444 (1973); (c) K. Oshima, H. Yamamoto, and H. Nozaki, *ibid.*, **95**, 7926 (1973).

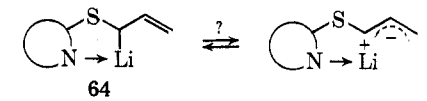
(34) D. A. Evans, and G. C. Andrews, presented at the 165th National Meeting of the American Chemical Society, Dallas, Texas, April 9, 1973.

Table VI
Alkylation of $GCH_2CH{=}CH_2$ (62)

Entry	G	Yield, % (63α + 63γ)	Ratio (THF)[a] 63α:63γ	Ratio (5% HMPA)[b] 63α:63γ
i		93	75:25[c]	68:32
ii		78		88:12
iii		90	99:1	>99:1
iv		95	*d*	>99:1
v		92	99:1	>99:1

[a] Alkylation conditions: (1) *n*-BuLi, THF (−30°); (2) *n*-$C_6H_{13}I$ (−65°). [b] Alkylation conditions: (1) *n*-BuLi, 5% HMPA–THF (−65°); (2) *n*-$C_6H_{13}I$ (−65°). [c] As in footnote *a* but *sec*-BuLi (−78°) used to generate anion. [d] HMPA required.

ing the course of our own work, two independent alkylation studies on the anions derived from **65**[35] and **66**[36] were reported. Both communications claimed exclusive α alkylation, although with the former sulfide the material balance was less than 50% with three different alkylating agents.[35c] Apparently these low yields result from attack by butyllithium (THF) on the thiazoline ring which accompanies allylic metalation.[22] Yields of metalation apparently can be improved *via* the use of modified metalation conditions (*n*-BuLi, THF, HMPA).[35a] In order to directly compare **65** and **66** with other promising chelating heterocycles under investigation in our laboratory, we have reinvestigated these as well as other systems (Table VI).



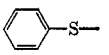
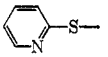
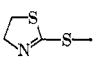
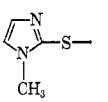
64

65 **66**

These results indicate that, in contrast to phenyl allyl sulfide (entry i), the allyl sulfides containing lithium chelating capabilities (entries iii–v) exhibit dramatic selectivity toward α alkylation. While the thiazoline derivative (entry iv) requires 5% HMPA for rapid clean lithiation, both the 2-pyridyl and imidazolyl sulfides are smoothly lithiated in THF with exceptional facility in the absence of cation complexing bases.

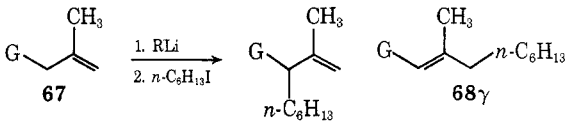
A comparison of the relative alkylation regioselectivities of entries i–iii is revealing. Both the 2- and 4-pyridyl sulfides show a higher propensity for α alkylation than the phenyl derivative. Since the 4-pyridyl sulfide (entry ii) *cannot* participate in intramolecular chelation, factors *other* than chelating capability must also be operating to alter alkylation regioselectivity. Consequently, an explanation that attributes high alkylation regioselectivity exclusively to intramolecular chelation (entries iii–v) must be considered as tenuous. Further experiments to examine this point are in progress.[22]

Table VII
Alkylation of $GCH_2C(CH_3){=}CH_2$ (67)

Entry	G	Yield, % (68α + 68γ)	Ratio (THF)[a] 68α:68γ	Ratio (5% HMPA)[b] 68α:68γ
i		84	75:25[c]	70:30
ii		79	90:10	79:21
iii		94	*d*	80:20
iv		86	92:8	84:16

[a–d] See analogous footnotes in Table VI for conditions.

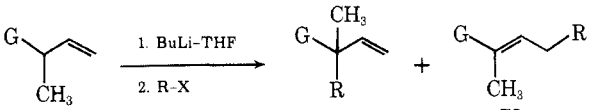
An analogous study on the alkylation of β-methallyl sulfides **67** is equally revealing[22] (Table VII). At



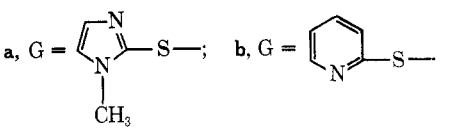
67 **68α** **68γ**

−65° in the absence of HMPA both the 2-pyridyl and imidazole sulfides (entries ii, iv) again show high α regioselectivity toward alkylation. That internal chelation *may* be playing a role in defining this regioselectivity is suggested by the results of alkylation in the presence of HMPA. Such cation coordinating cosolvents appear partially to "wash out" the directive effect of the heterocyclic ligand.[37] This is unfortunate in the case of thiazoline sulfide (entry iii) which can only be lithiated in the presence of HMPA, an observation that detracts from the utility of this heterocyclic sulfide.

One of the unattractive features in the alkylation of the α-methallyl sulfoxide anion **58** is the rather disappointing regioselectivity toward α alkylation (Table IV). In order to determine the magnitude of the apparent directive capabilities that the heterocyclic sulfides confer upon alkylation reactions in allylic systems containing this substitution pattern, the lithiation and subsequent alkylation of sulfides **69a**



69 **70α** **70γ**



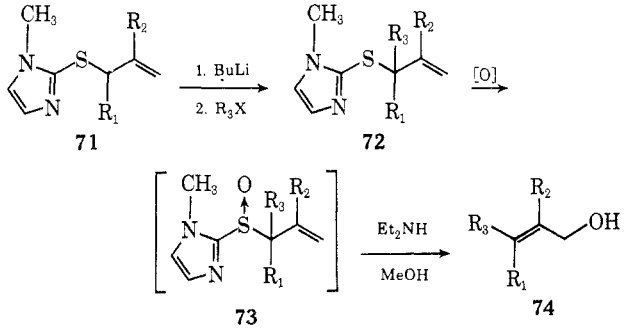
(35) (a) K. Hirai and Y. Kishida, *Tetrahedron Lett.*, 2743 (1972); (b) K. Hirai and Y. Kishida, *ibid.*, 2117 (1972); (c) K. Hirai, H. Matsuda, and Y. Kishida, *ibid.*, 4359 (1971).

(36) (a) T. Mukaiyama, K. Narasaka, K. Maekawa, and M. Furusato, *Bull. Chem. Soc. Jap.*, 44, 2285 (1971); (b) K. Narasaka, M. Hayashi, and T. Mukaiyama, *Chem. Lett.*, 259 (1972).

(37) The effects of higher concentrations of HMPA further lower the α:γ ratio: at 20% HMPA (entry iv), 68α:68γ = 75:25.

and **69b** were undertaken. As in previous cases, the imidazole sulfide **69a** may be rapidly metalated (BuLi, THF, −65°) and quenched with alkyl bromides or iodides in excellent yield to give a mixture of **70α** and **70γ** (R = n-C_6H_{13}). *The observed selectivity toward α alkylation (**70α**:**70γ** ≥ 90:10) was nearly identical with that observed with the β-methallyl isomer* **67**. Under identical conditions sulfide **69b** exhibited somewhat lower regioselectivity (**70α**:**70γ** = 80:20). As in prior cases, the effect of added cation complexing bases such as HMPA in lowering the relative percentage of α-alkylation is dramatic.

The allylic imidazole sulfides, as well as the allylic sulfoxide systems, serve admirably well in the 1,3 transposition of sulfur and oxygen functions. In general terms the sulfide **71** may be transformed into the allylic alcohol **74** without the purification of *any* intermediates under the following set of conditions:

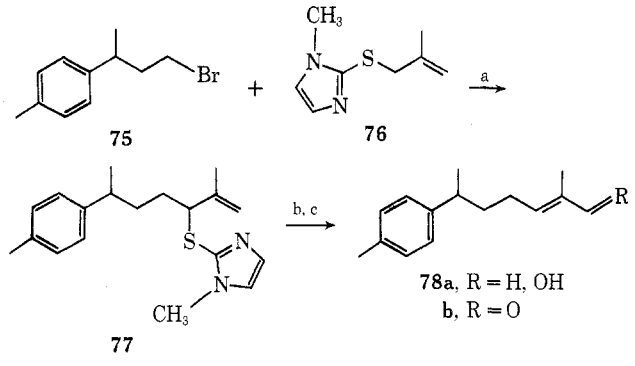


71 **72** **73** **74**

Oxidation of **72** to **73** with m-chloroperbenzoic acid (CH_2Cl_2, 0°) followed by the addition of excess diethylamine in methanol (25°, 24 hr) affords excellent yields of the allylic alcohol **74** (R_1 = H, CH_3; R_2, R_3 = alkyl, H). In a variety of cases studied in our laboratory, yields of allylic alcohols **74** based on sulfide **71** ranged from 80 to 90%. *In addition to the high regioselectivity as well as nucleophilicity exhibited by the anions derived from the imidazole sulfide* **71**, *all by-products resulting from the alkylation (e.g. γ-alkylation) and sulfoxide-cleavage steps are conveniently removed by extraction.*[22]

A simple synthesis of the sesquiterpene nuciferal (**78b**)[38] serves to illustrate the potential applicability of this allylic alcohol synthesis to related terpenoid substances.[27b] Lithiation of sulfide **76** followed by alkylation with 1 equiv of bromide **75** affords the α-alkylated sulfide **77** in addition to the γ-alkylated isomer (α:γ = 90:10) in 95% yield. Without purification, **77** was oxidized with the indicated peracid and the resulting sulfoxide cleaved with diethylamine, affording the E allylic alcohol **78a** along with the corresponding Z isomer in 80–85% yield (E:Z > 97:3) based on the initial sulfide **76**. Final oxidation of **78a** to nuciferal (**78b**) was accomplished with manganese dioxide (99%).[22]

Scheme V



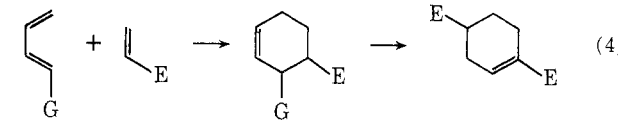
75 **76** **77**

conditions: a, n-BuLi, −30°; b, m-chloroperbenzoic acid, CH_2Cl_2; c, Et_2NH-MeOH 26°

(38) T. Sakai, K. Nishimura, and Y. Hirose, *Bull. Chem. Soc. Jap.*, 38, 381 (1965).

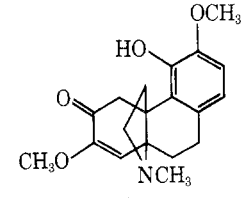
Other Applications of 1,3 Sulfur–Oxygen Transformations

The utility of 1,3 charge affinity inversion transformations in conjunction with cycloaddition reactions appears to hold promise of the construction of cycles (eq 4).[39] Although the generality of such



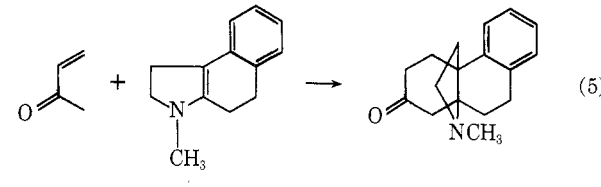
(4)

merged synthetic operations has not been defined, we have explored the applicability of such methodology to the synthesis of the hasubanan alkaloid cepharamine (**79**).[40] In model studies the dienyl sulf-



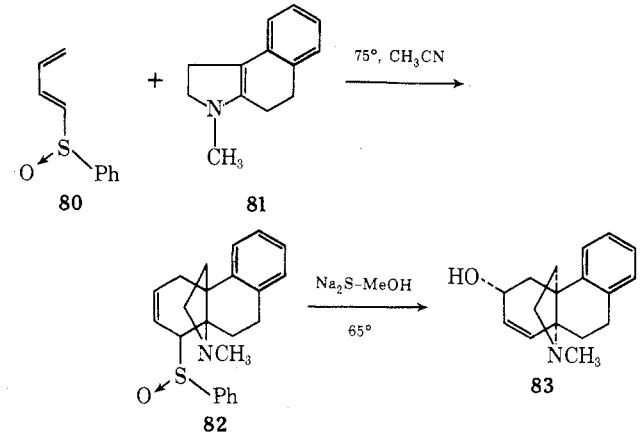
79

oxide **80** and endocyclic enamine **81** undergo cycloaddition at 75° to give the adduct **82** which may be transformed into the tetracyclic alcohol **83** in an overall yield of 30% (Scheme VI). This unusual annelation sequence, which nicely complements the more traditional use of methyl vinyl ketone with similar substrates (eq 5),[41] should find additional use in alkaloid synthesis.



(5)

Scheme VI



80 **81** **82** **83**

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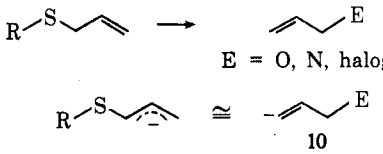
Conclusions

Through our own work as well as that of others, there now exist efficient means for the allylic interchange of sulfur with other atoms such as oxygen, nitrogen,[42] and halogen[35a] (eq 6). Consequently, the synthetic applications of anion equivalents such as **10** may be considerably expanded beyond the examples included in this Account.

During the last few years the number of new innovations in synthetic organic chemistry that have involved the use of the sulfur atom has been quite exciting.[43] Throughout much of this work sulfur-stabilized carbanions have played a prominent role. In this regard the future use of sulfur derivatives of 2-mercapto-1-methylimidazole in reagent design appears quite promising.



(6)

10

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Base-Catalyzed Carbon–Carbon Addition of Hydrocarbons and of Related Compounds

Herman Pines

The Ipatieff Catalytic Laboratory, Department of Chemistry, Northwestern University, Evanston, Illinois 60201

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Acid-catalyzed conversions of hydrocarbons have been widely studied and reported in the chemical literature.[1] Many important petrochemical processes involve catalysis by acids. In contrast, the use of bases as catalysts for hydrocarbon reactions has received until recently relatively little attention, except for the conversion of conjugated dienes and styrenes to high molecular compounds using alkali metals as catalysts.[2]

The discovery that sodium in the presence of small amounts of organosodium compounds, produced *in situ* or deposited on alumina, acts as an effective catalyst for double bond isomerization of alkenes and cyclenes[3] triggered much research in this field.[2] It was subsequently discovered that base-catalyzed isomerization of olefins may proceed in homogeneous solutions using lithium ethylenediamine in ethylenediamine[4] or potassium *tert*-butoxide (*t*-BuOK) in dimethyl sulfoxide (DMSO).[5]

Since base-catalyzed isomerization of olefins has been adequately reviewed,[6] the present Account is limited to the title subject only. However it omits reactions leading to the formation of macromolecules.

Herman Pines received a degree in Chemical Engineering from the Ecole Supérieure de Chimie Industrielle, Université de Lyon, Lyon, France, and his Ph.D. from the University of Chicago. During 1930–1952 he was Research Chemist and later Coordinator of Exploratory Research, Universal Oil Products Company. Also, during 1941–1952, he held an adjunct professorial appointment at Northwestern University. He then became Vladimir Ipatieff Professor of Chemistry and Director of the Ipatieff High Pressure and Catalytic Laboratory, and since 1970 has enjoyed emeritus status. During 1971–1973 he has been intermittently Visiting Professor at the University of Bar Ilan and the Weizmann Institute of Science in Israel, and the Federal University of Rio de Janeiro, Brazil. His research concerns applications of heterogeneous catalysis to dehydration and aromatization reactions of hydrocarbons.

Base-catalyzed carbon–carbon addition reactions are of synthetic interest because they afford hydrocarbons and related compounds in good yields by a simple one-step procedure. These reactions are made possible by the fact that hydrocarbons and related compounds having a benzylic or allylic hydrogen are carbon acids, having a pK_a of about 35 to 37; they can donate a proton to a base and thus become carbanions.[7] These carbanions can add to olefinic hydrocarbons. The steps involved in the catalytic chain reactions are illustrated by the following set of equations, using toluene and ethylene as reactants, and sodium as catalyst:[8]

$$\text{Promoter} + \text{Na} \longrightarrow \text{B}^-\text{Na}^+ \quad (1)$$

Initiation

$$\text{C}_6\text{H}_5\text{CH}_3 + \text{B}^-\text{Na}^+ \rightleftharpoons \text{C}_6\text{H}_5\text{CH}_2^-\text{Na}^+ + \text{BH} \quad (2)$$

Addition

$$\text{C}_6\text{H}_5\text{CH}_2^-\text{Na}^+ + \text{CH}_2{=}\text{CH}_2 \rightleftharpoons \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2^-\text{Na}^+ \quad (3)$$

Propagation

$$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2^-\text{Na}^+ \ \text{C}_6\text{H}_5\text{CH}_3 \longrightarrow \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_3 + \text{C}_6\text{H}_5\text{CH}_2^-\text{Na}^+ \quad (4)$$

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