

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.

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Allylic Sulfoxides: Useful Intermediates in Organic Synthesis

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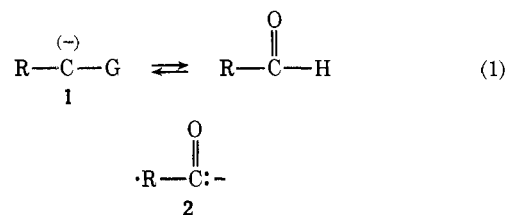
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As a consequence of the central role that polar or Lewis acid-base reactions play in the synthesis of organic molecules, organic chemists have endeavored to develop new, general ways in which such reactions can be employed in synthesis.

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,



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-

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(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.

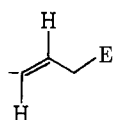
(3) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969).

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

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 \rightleftharpoons 8) that would be complementary to other methodology that has been developed for creating reversed polarity equivalents such as those cited above.

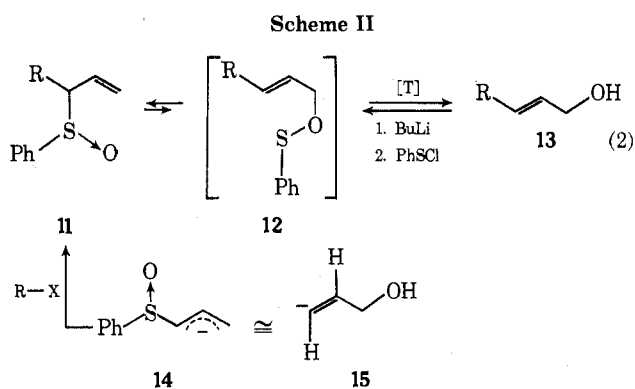
1,3 Charge Affinity Inversion Operations

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).



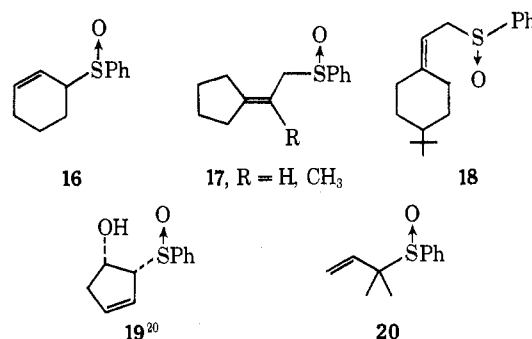
The elegant work of Mislow and coworkers on the thermal racemization of allylic sulfoxides (11, R = H) suggested that racemization could be attributed to a [2,3] sigmatropic process affording the achiral sulfenate ester 12 as an intermediate.¹⁶ We felt that if the sulfenate ester 12 could be intercepted 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.

(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.

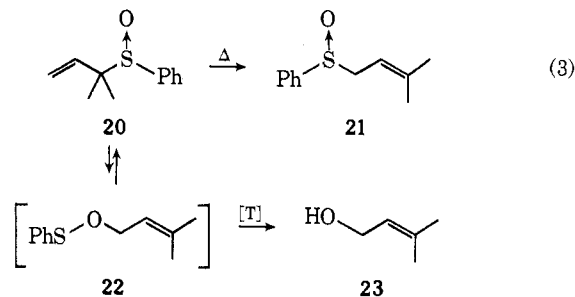
(16) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4869 (1968); R. Tang and K. Mislow, *ibid.*, **92**, 2100 (1970).

In order to assess the effect of structure on the relative sulfoxide-sulfenate equilibrium concentrations (*cf.* 11 \rightleftharpoons 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 benzenesulfonyl 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 \rightleftharpoons 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

(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*-toluenesulfonyl 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 benzenesulfonyl 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).

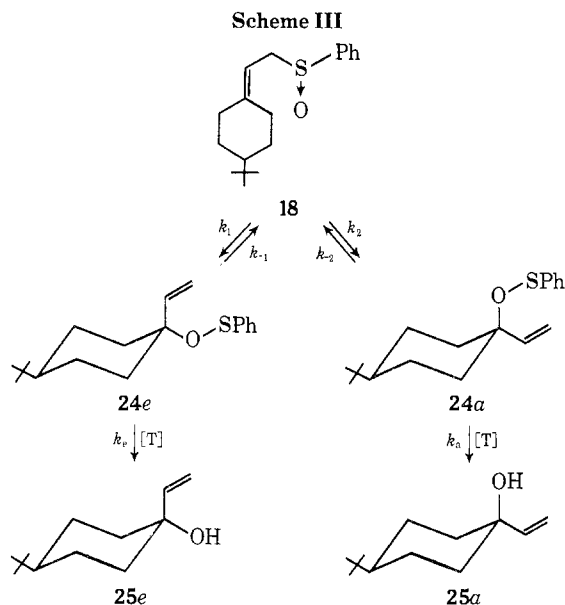


Table II
Effect of Thiophile on 25e:25a Ratio at 25°
in Methanol^a

Entry	Thiophile [T]	25e:25a, %	% conversion
i	LiBH ₃ CN	48:52	24
ii	piperidine	66:34	90
iii	C ₆ H ₅ S ⁻	88:12	99
iv	[(C ₂ H ₅) ₂ N] ₃ P	92:8	99
v	(CH ₃ O) ₃ P	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 sulfenates to alcohols, a study of the rearrangement-cleavage of sulfonate 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 sulfenates 24e and 24a followed by rapid cleavage to the isomeric alcohols 25e and 25a. The ratio of alcohols produced (25e:25a = 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

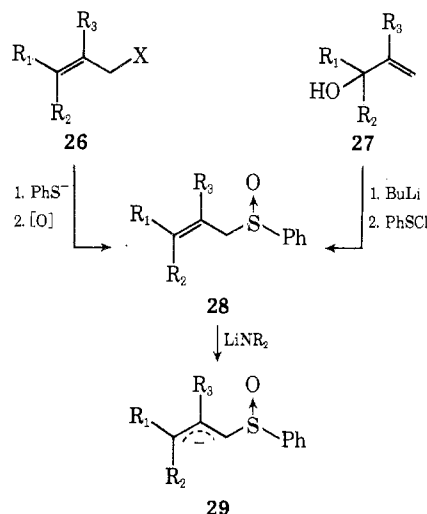
These results suggest that there are two points of stereochemical control in the interchange of sulfur and hydroxyl functions. Not only can the concerted nature of the sigmatropic rearrangement be exploited to define or transfer chirality (both from sulfur and carbon) and to create specified olefin geometries,²⁵ 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 sulfonates: G. C. Andrews, and D. A. Evans, *Tetrahedron Lett.*, 5121 (1973).

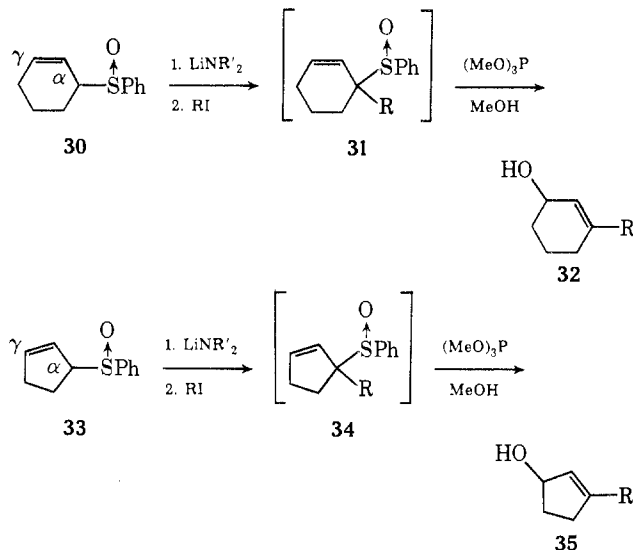
A General Synthesis of Allylic Alcohols

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 sulfenates.^{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.



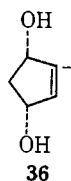
Both cyclohexenyl and cyclopentenyl phenyl sulfoxides (30 and 33) may be alkylated (R = CH₃)

(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.

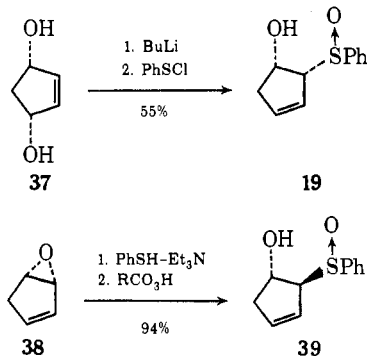
(27) (a) D. A. Evans, G. C. Andrews, T. T. Fujimoto, and D. Wells, *Tetrahedron Lett.*, 1385 (1973); (b) D. A. Evans, G. C. Andrews, T. T. Fujimoto, and D. Wells, *ibid.*, 1389 (1973).

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 than 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 sulfenyl ester.

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

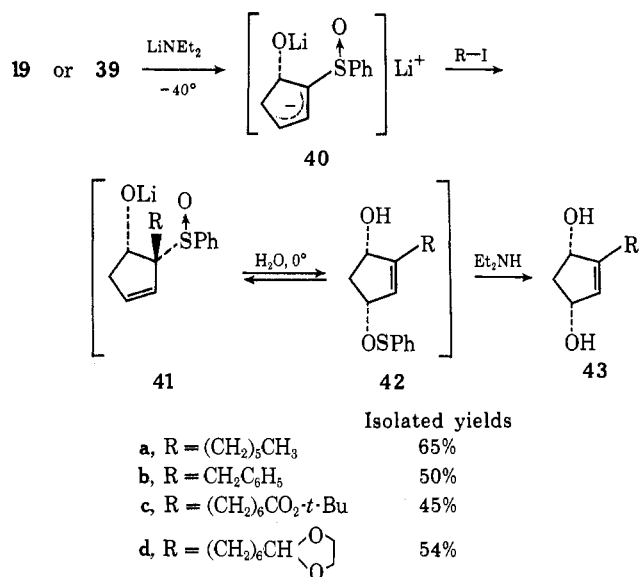


derived from the conjugate bases of either 19 or 39. The *cis*-hydroxy sulfoxide 19 may be easily prepared from the *cis*-diol 37²⁰ while the *trans*-hydroxy sulfoxide 39 can be synthesized from cyclopentadiene oxide (38) by: (a), treatment with benzenethiol-triethylamine in benzene at 25° and (b) oxidation of the resulting sulfide with *m*-chloroperbenzoic acid in dichloromethane.

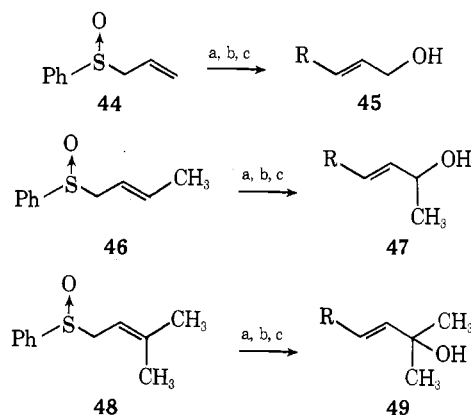


Treatment of either 19 or 39 with 2 equiv of lithium diethylamide in THF-5% hexamethylphosphoramide (HMPA) followed by the addition of the appropriate alkyl iodide at -40° presumably affords the adduct 41 which undergoes facile rearrangement to the sulfenyl ester 42 and subsequent cleavage at 0° with 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 sulfenyl 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).



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).



conditions: a, LiN(*i*-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).

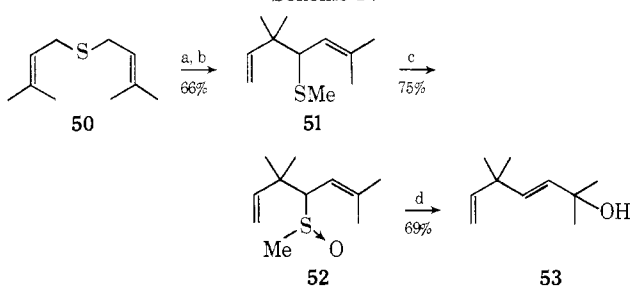
(31) B. Willhalm and A. F. Thomas, *Chem. Commun.*, 1380 (1969).

Table III
Alkylation of Allylic Anion 54^{27b}

RX	Yield, % (57E + Z)	57E:57Z	α/γ ratio ^a
CH ₃ I	75	97:3	10
<i>n</i> -C ₆ H ₁₃ I	42	96:4	2.5
(CH ₃) ₂ C=CHCH ₂ Br	46	96:4	2.0

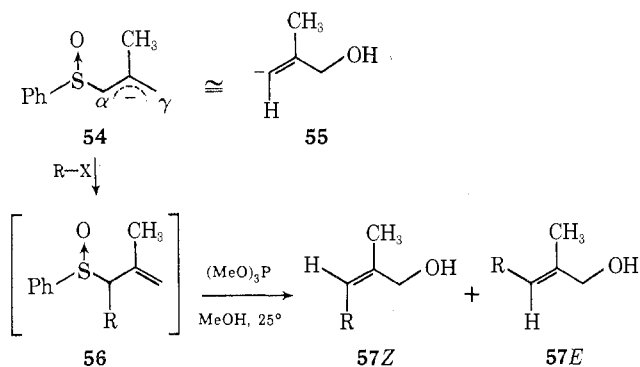
^a Relative proportion of alkylation α and γ to sulfur.

Scheme IV



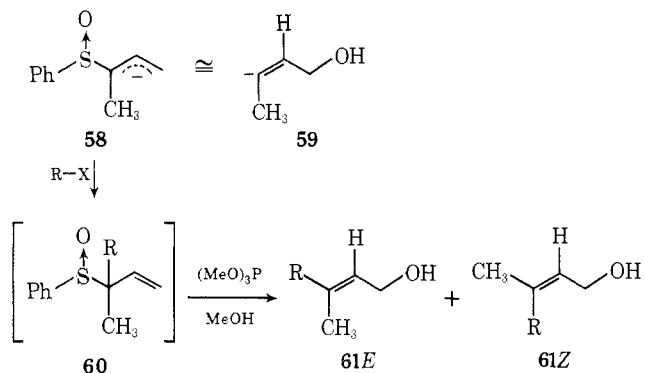
conditions: a, *n*-BuLi, THF, TMEDA; b, MeI; c, NaIO₄; d, Et₂NH-MeOH, 24 hr at 25°

respect to the vinyl anion 55 has been investigated.^{27,32}



The results summarized in Table III indicate that the *sulfonate-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-



eration of the various transition-state conformations in the rearrangement of sulfonate 60,^{16,18} when the R

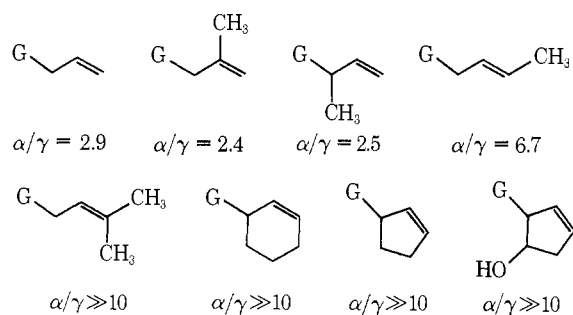
(32) P. A. Grieco, *J. Chem. Soc., Chem. Commun.*, 702 (1972).

Table IV
Alkylation of Anion 58^{27b}

RX	Yield, % (61E + 61Z)	61E:61Z	α/γ ratio ^a
CH ₃ I	59		2.6
C ₂ H ₅ I	48	73:27	2.4
(CH ₃) ₂ C=CHCH ₂ Br	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



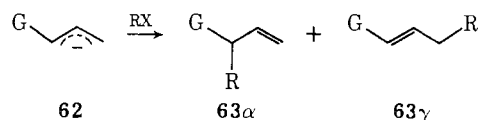
^a Anions quenched with C₂H₅I.

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 Carbanions³⁴

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-



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).

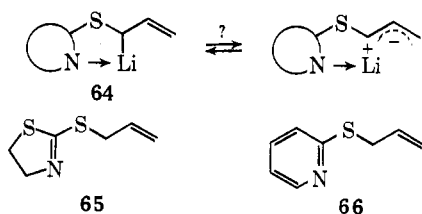
(34) D. A. Evans, and G. C. Andrews, presented at the 165th National Meeting of the American Chemical Society, Dallas, Texas, April 9, 1973.

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

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

^a Alkylation conditions: (1) *n*-BuLi, THF (-30°); (2) *n*-C₆H₁₃I (-65°). ^b Alkylation conditions: (1) *n*-BuLi, 5% HMPA-THF (-65°); (2) *n*-C₆H₁₃I (-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 65³⁵ and 66³⁶ 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).



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-pyr-

(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).

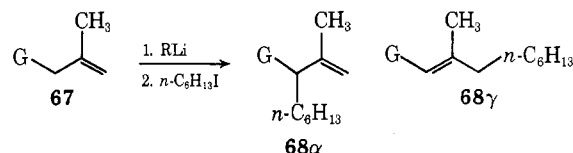
Table VII
Alkylation of $GCH_2C(CH_3)=CH_2$ (67)

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

^{a-d} See analogous footnotes in Table VI for conditions.

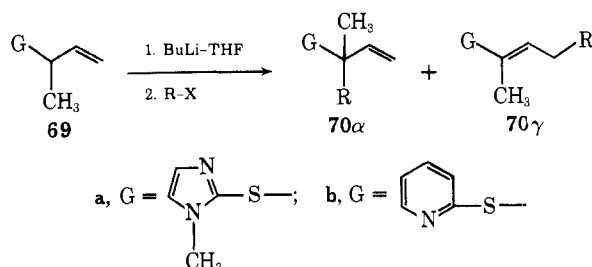
idyl sulfide (entry ii) cannot participate in intramolecular chelation, factors other than chelating capability must also be operating to alter alkylation regioselectivity. Consequently, an explanation that attributes high alkylation regioselectivity exclusively to intramolecular chelation (entries iii-v) must be considered as tenuous. Further experiments to examine this point are in progress.²²

An analogous study on the alkylation of β -methallyl sulfides 67 is equally revealing²² (Table VII). At



-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.

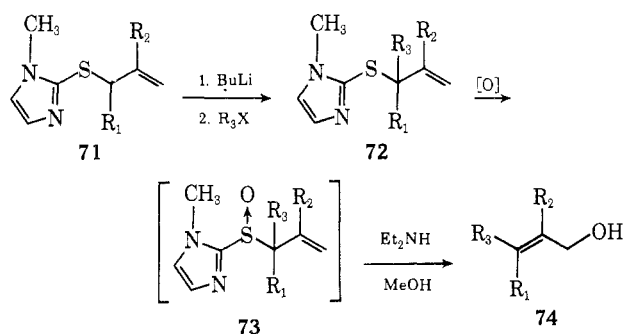
One of the unattractive features in the alkylation of the α -methallyl sulfoxide anion 58 is the rather disappointing regioselectivity toward α alkylation (Table IV). In order to determine the magnitude of the apparent directive capabilities that the heterocyclic sulfides confer upon alkylation reactions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



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

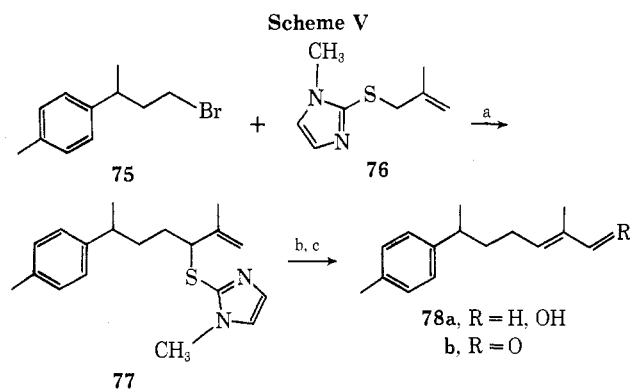
and **69b** were undertaken. As in previous cases, the imidazole sulfide **69a** may be rapidly metalated (BuLi, THF, -65°) and quenched with alkyl bromides or iodides in excellent yield to give a mixture of **70 α** and **70 γ** ($R = n\text{-C}_6\text{H}_{13}$). The observed selectivity toward α alkylation (**70 α** :**70 γ** $\geq 90:10$) was nearly identical with that observed with the β -methallyl isomer **67**. Under identical conditions sulfide **69b** exhibited somewhat lower regioselectivity (**70 α** :**70 γ** = 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:



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** ($R_1 = \text{H}, \text{CH}_3$; $R_2, R_3 = \text{alkyl}, \text{H}$). 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 -



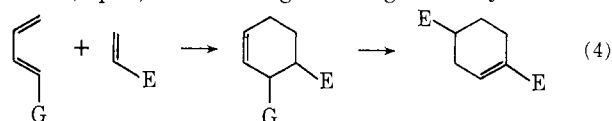
conditions: a, *n*-BuLi, -30° ; b, *m*-chloroperbenzoic acid, CH_2Cl_2 ; c, $\text{Et}_2\text{NH}\text{-MeOH}$ 26°

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

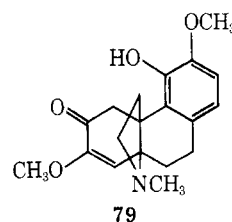
alkylated sulfide **77** in addition to the γ -alkylated isomer ($\alpha:\gamma = 90:10$) in 95% yield. Without purification, **77** was oxidized with the indicated peracid and the resulting sulfoxide cleaved with diethylamine, affording the *E* allylic alcohol **78a** along with the corresponding *Z* 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

Other Applications of 1,3 Sulfur–Oxygen Transformations

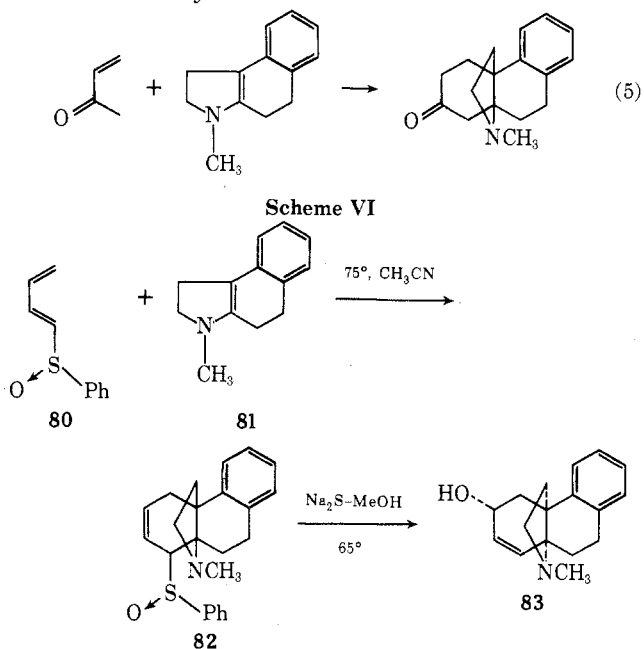
The utility of 1,3 charge affinity inversion transformations in conjunction with cycloaddition reactions appears to hold promise of the construction of cycles (eq 4).³⁹ Although the generality of such



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



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 anelation 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.



(39) D. A. Evans, C. A. Bryan, and C. L. Sims, *J. Amer. Chem. Soc.*, **94**, 2891 (1972).

(40) M. Tomita and M. Kozuka, *Tetrahedron Lett.*, 6229 (1966).

(41) D. A. Evans, C. A. Bryan, and G. M. Wahl, *J. Org. Chem.*, **35**, 4122 (1970).

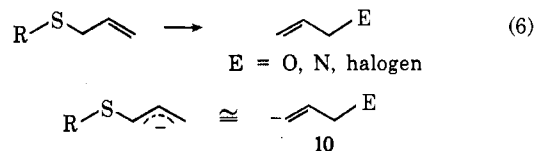
Conclusions

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-stabi-

(42) P. A. Brisco, F. Challenger, and P. S. Duckworth, *J. Chem. Soc.*, 1755 (1956).

(43) E. Block, *J. Chem. Educ.*, 48, 814 (1971).



lized 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.

The authors are greatly indebted to their coworkers, T. C. Crawford, R. C. Thomas, T. T. Fujimoto, and C. A. Bryan, and to the National Science Foundation, the National Institutes of Health, and The Petroleum Research Fund, administered by the American Chemical Society, for generous support of this research.

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

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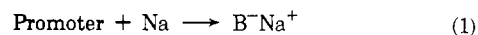
Acid-catalyzed conversions of hydrocarbons have been widely studied and reported in the chemical literature.¹ Many important petrochemical processes involve catalysis by acids. In contrast, the use of bases as catalysts for hydrocarbon reactions has received until recently relatively little attention, 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 cyclenes³ 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 ethylenediamine⁴ 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 dehydrogenation and aromatization reactions of hydrocarbons.

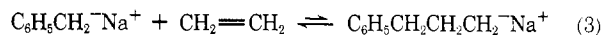
Base-catalyzed carbon-carbon addition reactions are of synthetic interest because they afford hydrocarbons and related compounds in good yields by a simple one-step procedure. These reactions are made possible by the fact that hydrocarbons and related compounds having a benzylic or allylic hydrogen are 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



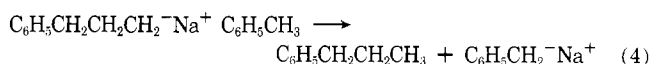
Initiation



Addition



Propagation



(1) "Friedel-Crafts and Related Reactions," Vol. I-IV, G. A. Olah, Ed., Interscience, New York, N. Y., 1965.

(2) H. Pines and L. A. Schaap, *Advan. Catal. Relat. Subj.*, 12, 117 (1960).

(3) (a) H. Pines, J. A. Vesely, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, 77, 347 (1955); (b) H. Pines and H. E. Eschinazi, *ibid.*, 77, 6314 (1955); 78, 1178, 5950 (1956); (c) H. Pines and W. O. Haag, *J. Org. Chem.*, 23, 328 (1958).

(4) L. Reggel, S. Friedman, and I. Wender, *J. Org. Chem.*, 23, 1136 (1958).

(5) A. Schriesheim, J. E. Hofmann, and C. A. Rowe, *J. Amer. Chem. Soc.*, 83, 3731 (1961).

(6) A. J. Hubert and H. Reimlinger, *Synthesis*, 3, 97 (1969) (review).

(7) For general discussion of carbon acids see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965.