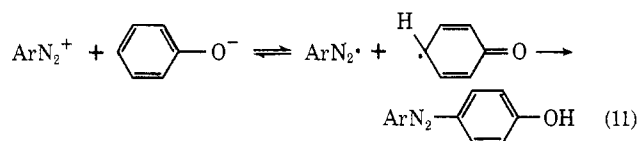in alkaline methanolic solution in the presence of phenol (conditions which favor radical formation) a homolytic diazo coupling reaction (eq 11) may take

$$ArN_2^+ + \text{(ring)}-O^- \rightleftharpoons ArN_2\cdot + \cdot\text{(ring with H)}=O \rightarrow$$

$$ArN_2-\text{(ring)}-OH \quad (11)$$

place.[64f] To the present author it seems probable that the precursor of the radical intermediates in (11) is a (covalent) aryl diazo ether.

[13]C CIDNP of p-methoxybenzenediazonium ions in $CH_3O^--CH_3OH-CH_3CN$ gives a strong positive resonance at the C_1 position of the original diazonium ion which has been tentatively attributed to a polarized diazonium salt.[64e] Polarographic data[65] are consistent with the primary formation of aryldiimine radicals.

Summarizing, it is obvious that we do not completely understand the mechanism(s) of homolytic decomposition of diazonium ions and related compounds (with the probable exception of the acylaryl-

(65) R. M. Elofson and F. F. Gadallah, *J. Org. Chem.*, 34, 854, 3335 (1969).

nitrosamine reactions). The concept of nucleofugal homolytic leaving groups and correlations with inorganic electron-transfer reactions help to rationalize the understanding of the catalytic effects in these reactions.

The question of whether there is a common intermediate for homolytic and heterolytic decompositions of diazonium ions is still open. It may be related to the $N_\alpha-N_\beta$ inversion in diazonium ions observed by Lewis,[10] a problem which also applies to the fixation of N_2 molecules by transition metal complexes (end-on and edge-on complexes).[11a,c]

As more elaborate quantum-chemical methods to consider solvation effects are not likely to be developed in the near future, we hopefully expect that the combined results from spectroscopy (esr and CIDNP) and from chain reaction kinetics will be instrumental in solving this and other problems in diazo chemistry.

The Utilization of Sulfoximines and Derivatives as Reagents for Organic Synthesis

Carl R. Johnson

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Sulfoximine[1] chemistry began in 1950, when Whitehead and Bentley discovered that the sulfoximine of methionine is the agent responsible for the toxicity of wheat flour treated with nitrogen trichloride.[2] Such treatment had been widely practiced for many years.

Our work, which commenced in 1968, has focused on the utilization of sulfoximines and their derivatives as reagents for organic synthesis. Besides novelty, these compounds have great potential for synthetic applications; they enable things to be done easily which are difficult or impossible by other methods.

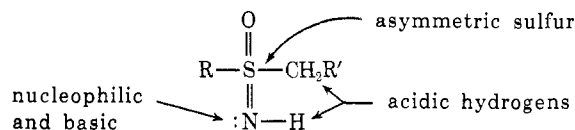The sulfoximine functional group (Figure 1) is un-

Figure 1. The sulfoximine functional group.

commonly versatile. It has acidic hydrogens on carbon and nitrogen, it is basic and nucleophilic at nitrogen, and it is potentially asymmetric.
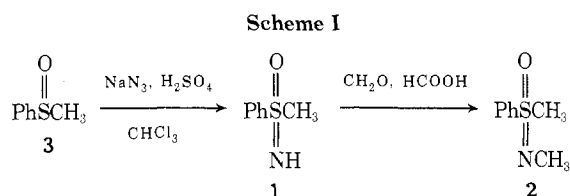
As a model system and as a starting point for much of our work we have utilized S-methyl-S-phenylsulfoximine; this Account stresses chemistry emanating from this source. The most practical method for the synthesis of 1 and its N-methyl derivative 2 is illustrated in Scheme I.

Several methods can be used for the high-yield oxidation of thioanisole to methyl phenyl sulfoxide (3).[3] We have routinely used a new laboratory meth-

(1) The IUPAC name is sulfoximide [(*Pure Appl. Chem.*, 11, 158 (1965)].
(2) H. R. Bentley, E. E. McDermott, J. Pace, J. K. Whitehead, and T. Moran, *Nature (London)*, 165 (1950); J. R. Whitehead and H. R. Bentley, *J. Chem. Soc.*, 1572 (1952).

The fluoroborate salts which were precursors to yl-ides **9** and **10** were prepared beginning with the appropriate sulfide *via* the sulfoxide–hydrazoic acid route. The yield of isopropyl-*p*-tolylsulfoximine was poor because of carbon–sulfur bond heterolysis. Ylide **10** was prepared also by the alkylation of **9** with methyl iodide followed by treatment of the reaction mixture with 1 equiv of base, but small amounts of **9** remained.[11] Table I includes examples of reaction of ylides **9**, **10**,[10] **11**,[12] and **12**.[13] The stabilized ylide **13**,
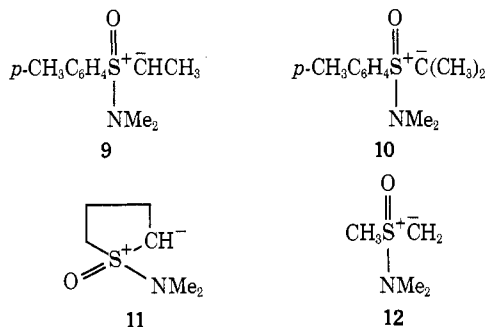
produced by reaction of **12** with benzoic anhydride, undergoes a curious cyclization catalyzed by copper sulfate (eq 2).[13]
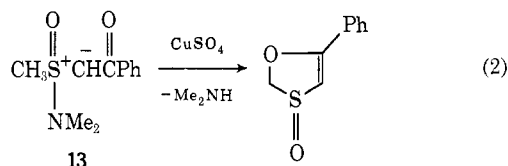
The production and utilization of cyclopropylide **14** has provided a remarkably facile synthesis of spi-ropentane derivatives.[14] Scheme II outlines alternate

Scheme II
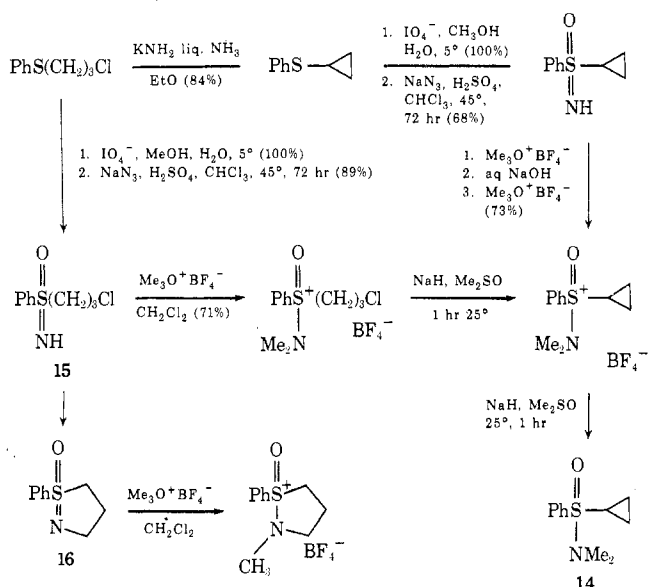
routes for the preparation of **14**. For large-scale prep-aration, the route involving cyclopropyl phenyl sul-

fide is preferable. The spontaneous cyclization of **15** to **16**[14] provided an interesting sidelight in that, at the time, **16** was the only known example of a sulfox-imine with the sulfur and nitrogen contained within a ring.[15] Some typical reactions of **14** with electro-philic olefins are shown in eq 3, 4, and 5.
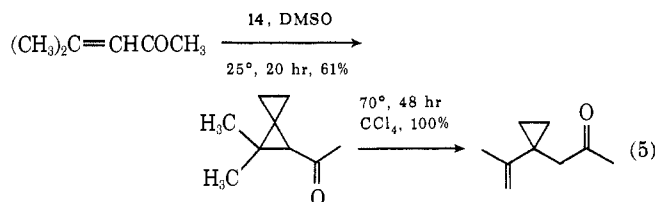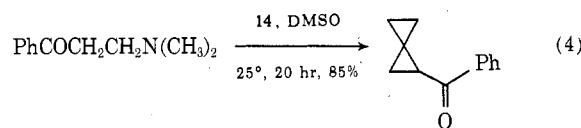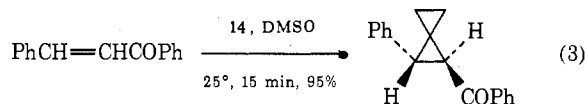
Reaction of ylide **14** with cyclohexanone produced the unstable dispiroepoxide which rearranged during isolation to give a cyclobutanone (eq 6).
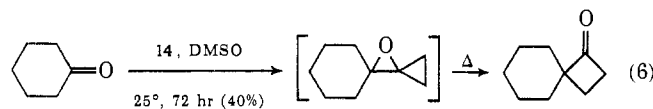
As noted above, an unsymmetrically substituted sulfoximine contains a chiral sulfur; our model sys-tem, methylphenylsulfoximine, is such a compound. Resolution of **1** has been found to be facile.[16] We have been able to obtain a high yield of the optically pure *S* enantiomer[17] after one recrystallization of di-astereomeric salts formed from racemic **1** and (+)-10-camphorsulfonic acid.[6] Exhaustive methylation of **17** followed by treatment with base resulted in the generation of chiral ylide **18**. The (*R*)-ylide **19** was produced by a scheme based on the Anderson syn-thesis of optically pure sulfoxides.[17]
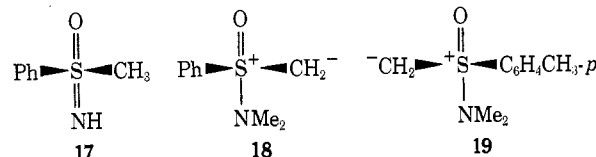
We have found that optically active methylides **18** and **19** are capable of transferring methylene in a sym-metric manner to suitably substituted electrophilic double bonds, *e.g.*, eq 7, 8, and 9.[6,18]

The complementary behavior of dimethyloxosul-
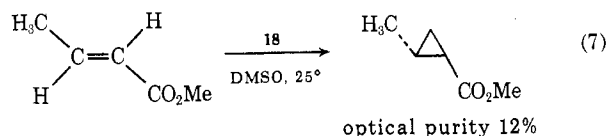
(11) E. R. Janiga, Ph.D. Dissertation, Wayne State University, 1972.

(12) C. R. Johnson and L. J. Pepoy, *J. Org. Chem.*, **37**, 671 (1972).

(13) C. R. Johnson and P. E. Rogers, *J. Org. Chem.*, **38**, 1793, 1798 (1973).

(14) C. R. Johnson, G. F. Katekar, R. F. Huxol, and E. R. Janiga, *J. Amer. Chem. Soc.*, **93**, 3771 (1971).

(15) For other examples see P. Stoss and G. Satlzinger, *Angew. Chem., Int. Ed. Engl.*, **10**, 79 (1971), and T. R. Williams and D. J. Cram, *J. Org. Chem.*, **38**, 20 (1973).

(16) R. Fusco and F. Tericoni, *Chem. Ind. (Milan)*, **47**, 61 (1965).

(17) K. K. Andersen, *Tetrahedron Lett.*, 93 (1962).

(18) C. R. Johnson and C. W. Schroeck, *J. Amer. Chem. Soc.*, **90**, 6852 (1968).

PhCHO $\xrightarrow[\text{DMSO, 25°}]{19}$ [structure: styrene oxide]   (8)

optical purity 20%

[structure: PhCH=CH-COPh] $\xrightarrow[\text{DMSO, 25°}]{19}$ [cyclopropyl structure Ph...COPh]   (9)

optical purity 35%
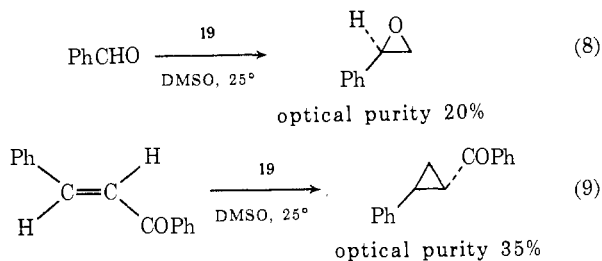
fonium methylide (4) and the simpler dimethylsulfonium methylide in their stereo- and regioselectivity is an intriguing phenomenon.[9] The reaction of 4 with 4-*tert*-butylcyclohexanone gives the (Z)-oxirane, whereas dimethylsulfonium methylide yields principally the (E)-oxirane; α,β-unsaturated ketones react with 4 to give cyclopropyl ketones but with dimethylsulfonium methylide to give vinyloxiranes. We have now gained considerable knowledge bearing on this selectivity by studies involving the independent generation[19] of the zwitterionic structures that long had been accepted as intermediates in these alkylidene transfer reactions (eq 10).

$$Z^+\!\!-\!\!CH_2^- + \;\;>\!\!C\!\!=\!\!X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[Z^+\!\!-\!\!CH_2\!\!-\!\!\overset{X^-}{\underset{|}{C}}\!\!- \right] \overset{k_2}{\rightarrow}$$

$$Z \;+\; CH_2\!\!-\!\!\overset{X}{\underset{}{C}}\!\!< \quad (10)$$
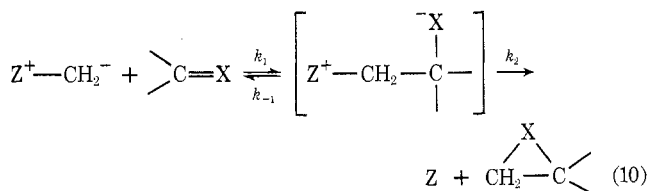
In earlier studies[10] we found that ylide 6 was similar in stability, reactivity, and selectivity to methylide 4. We considered that it would be more feasible to synthesize independently oxosulfonium betaine intermediates derived from 6 than those derived from 4. Lithium (S)-N-methylphenylsulfonimidoylmethide (20), prepared by treating (+)-2 with *n*-butyllithium, added in the conjugate manner to benzalacetophenone to give a mixture of diastereomers 21. After separation on a silica gel column, the diastereomeric adducts were methylated to give 22 and its epimer. Betaine 23, generated by treatment

Scheme III

[Scheme III structures]

Ph—S(=O)(=NMe)—CH₂Li (20) $\xrightarrow[\text{DMF}]{\text{benzalacetophenone}}$ Ph—S(=O)(=NMe)—CH₂CHCOPh (21)

1. separation
2. Me₃O⁺BF₄⁻

23 $\xleftarrow{\text{base}}$ 22

24

of 22 with base, collapsed to give optically pure cyclopropane 24 (Scheme III). The epimer of 22 led to the enantiomer of 24.

The reaction of 20 with benzaldehyde gave a mixture of diastereomers from which one was obtained pure by recrystallization. Methylation of the pure diastereomer gave 25, which upon treatment with base gave (−)-styrene oxide (26) of 22% optical purity.

[structure 25] [structure 26: styrene oxide]

25   26
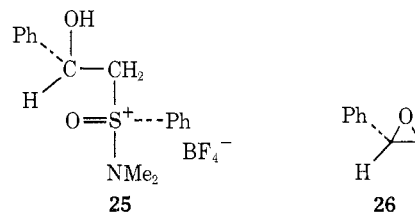
This optical purity is of the same order of magnitude as that obtained from the direct reaction of benzaldehyde with optically pure ylide 19,[18] which suggested that betaine from 25 is in equilibrium with 18 and benzaldehyde. This was confirmed by appropriate trapping experiments.[19] The result[20a] shown in eq 11 also indicates reversible addition of the oxosulfonium ylide.

[structure] $\xrightarrow{\text{base}}$ [structure]   (11)
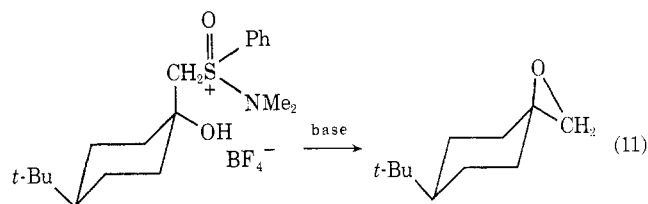
Scheme IV illustrates the independent synthesis of

Scheme IV

CH₃—S(=O)—C₆H₄CH₃-*p* $\xrightarrow[\text{ether, −78°}]{n\text{-BuLi}^{20b}}$

n-Bu—S(=O)—CH₃ $\xrightarrow{\begin{array}{l}1.\ n\text{-BuLi}\\2.\ \text{PhCHO}\\3.\ \text{recrystallization}\end{array}}$

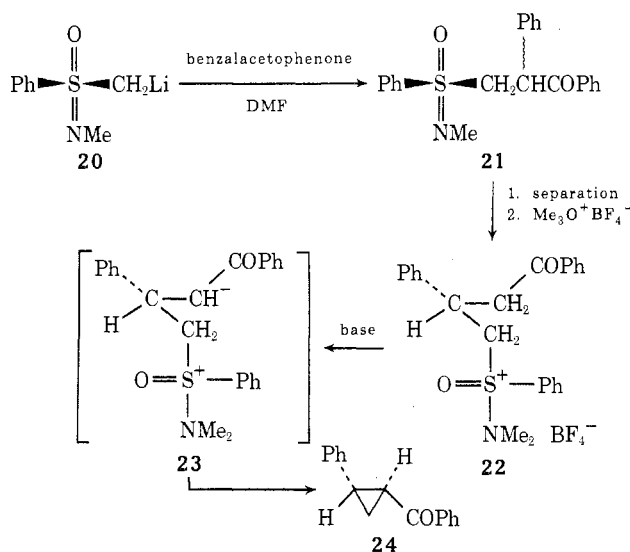[structure] $\xrightarrow[\text{H}_2\text{O, 100° 92\%}]{\text{NaHSO}_3}$ [structure] $\xrightarrow[90\%]{\text{MeI}}$

[structure] $\xrightarrow[58\%]{\text{base}}$ [structure] + *n*-BuSMe
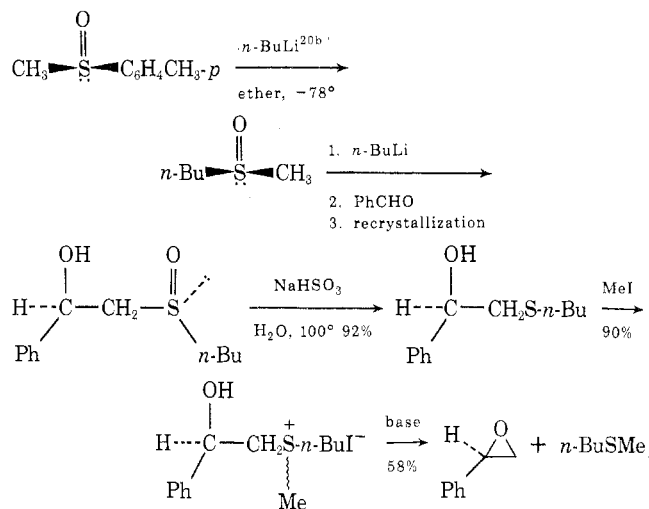
the type of betaine that would be derived from the addition of a simple sulfonium methylide to a carbonyl. The first step of Scheme IV shows that optically active *n*-butyl methyl sulfoxide is produced by reaction of *n*-butyllithium with resolved methyl *p*-tolyl sulfoxide; the reaction illustrates a new and general method for the preparation of optically active dialkyl sulfoxides.[20b] The styrene oxide obtained by this scheme was better than 90% optically pure,

(19) C. R. Johnson and C. W. Schroeck, *J. Amer. Chem. Soc.*, **93**, 5303 (1971).

(20) (a) C. R. Johnson and J. R. Shanklin, unpublished results; (b) C. R. Johnson, J. P. Lockard, and C. W. Schroeck, *Synthesis*, 485 (1973).

which suggests that in such cases collapse of the betaine to product is much faster than reversion to ylide and carbonyl compound (see also eq 12 and 13).[20a]

(12)

(13)
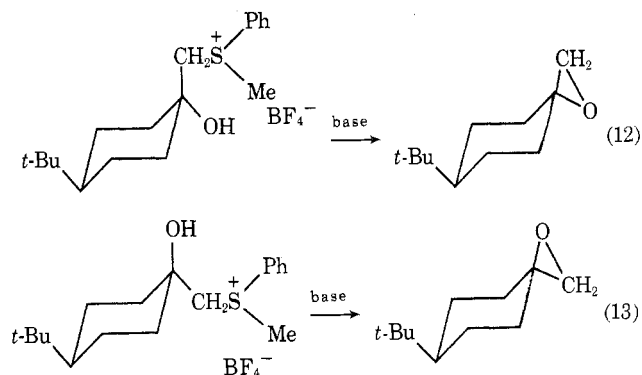
The data cited clearly implicate betaine intermediates in nucleophilic alkylidene transfer reactions of sulfonium ylides and lead to the conclusion that the initial attack of an oxosulfonium ylide at a carbonyl site is "reversible" (eq 10, $k_{-1} \geq k_2$); whereas attack by a simple sulfonium ylide is "irreversible" ($k_{-1} \ll k_2$).[21] Since oxosulfonium ylides are known to be more stable than the simple sulfonium ylides, it is not surprising that the oxosulfonium ylides are better "leaving groups." The high optical purity of cyclopropane 24 and its enantiomer indicates that for collapse of their betaine precursors $k_2 \gg k_{-1}$. All comparative results in our work and earlier studies seem to be consistent with the hypothesis that simple sulfonium ylides result in products dictated by kinetic control of betaine formation, whereas oxosulfonium ylides result in products predicted by thermodynamic considerations.[19]

Anions of *N-p-*Tolylsulfonylsulfoximines.[22] The reaction of 1 with *p*-toluenesulfonyl chloride gave 27, which could also be prepared by the copper-catalyzed reaction of *p*-toluenesulfonyl azide with methyl phenyl sulfoxide (eq 14). The latter reaction, discov-

(14)

ered by Kwart and Kahn,[23] represents a very general, high-yield method for the production of *N-p-*tolylsulfonylsulfoximines from sulfoxides. The preparation of *N-p-*tolylsulfonylsulfonimidoyl-stabilized carbanions (*e.g.,* 28) was accomplished by reaction of the *N*-tosylsulfoximines in Me$_2$SO with sodium hydride or *n*-butyllithium and in THF by treatment with *n*-butyllithium. Such anions, which are quite stable at room or slightly elevated temperatures, form another class of nucleophilic alkylidene transfer
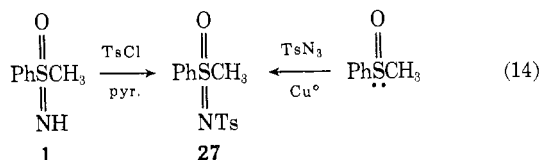
(21) For discussions of how reversibility of betaine formation might affect product stereochemistry see R. S. Bly, C. M. Dubose, and G. M. Konizer, *J. Org. Chem.,* **33**, 2188 (1968); C. E. Cook, R. E. Corley, and M. E. Wall, *Tetrahedron Lett.,* 891 (1965); and A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, Chapter 9.

(22) C. R. Johnson and G. F. Katekar, *J. Amer. Chem. Soc.,* **92**, 5753 (1970); C. R. Johnson, R. A. Kirchhoff, R. J. Reischer, and G. F. Katekar, *J. Amer. Chem. Soc.,* **95**, 4287 (1973).

(23) H. Kwart and A. A. Kahn, *J. Amer. Chem. Soc.,* **90**, 6852 (1968).

Table II
Reactions of Anions of *N*-Tosylsulfoximines

N-Tosyl-sulf-oximine	Substrate	Product	Yield, %
30	4-*tert*-Butylcyclo-hexanone		78
31	Cyclohexanone		63
27	Acetophenone		68
27	Styrene oxide		66
30	Benzalacetophenone		88
31	Benzalacetophenone		86
32	Benzalacetophenone		39
30	Benzonitrile		67

reagents derived from sulfoximines. The mechanism is similar to that of ylide reactions, but in these cases the leaving groups are water-soluble anions (*e.g.,* 29) rather than neutral molecules. The reaction of 28 with a typical substrate containing an electrophilic double bond is illustrated in eq 15.

(15)
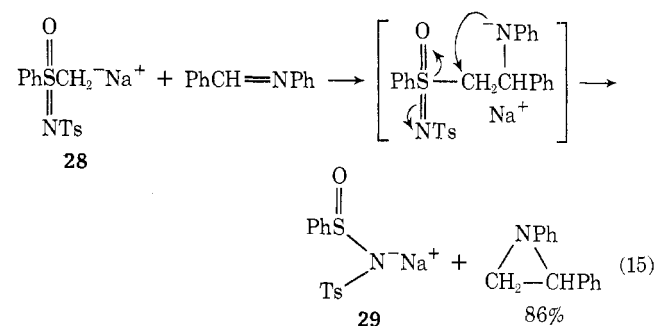
The alkylidene groups which have been transferred using reagents in this series include methylene, ethylidene, isopropylidene, benzylidene, cyclopentylidene, and cyclohexylidene.[22] Table II gives examples involving *N*-tosylsulfoximines 27, 30, 31, and 32. Reagent 30 is commercially available[24] or can be produced by the cupric ion catalyzed reaction of Chloramine-T with Me$_2$SO.[22] Our experience in working with these and other sulfonium ylide reagents leads us to the conclusion that, for simplicity of preparation and manipulation, these reagents are

(24) Columbia Organic Chemicals Co., Inc., Columbia, S. C. 29205.

Table III
Products from the Reaction of Salt 34 with Dibasic Nucleophiles[a]

(*tert*-butylamine, THF, 86%)

(α-dimethylaminostyrene, THF, 72%)

(1-pyrrolidineocyclohexene, THF, 91%)

(acetylacetone NaOMe, MeOH, 85%)

(ethyl cyanoacetate, NaOEt, EtOH, 95%)

(phenylacetonitrile, *n*-BuLi, THF, 60%)

(cyclopentadienyllithium, THF, 86%)

(nitromethane, NaOMe, MeOH, 44%)

(nitroethane, NaOMe, MeOH, 77%)
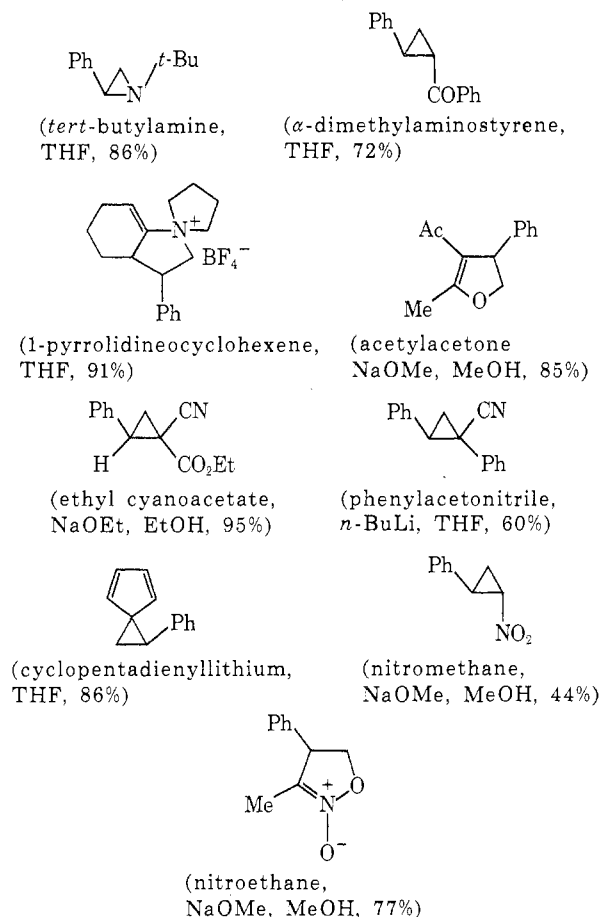
[a] All reactions were carried out at 25°. The reaction conditions, and product yields are shown in parentheses under the structures.

competitive with or superior to any others previously described for the preparation of substituted oxiranes from ketones.

CH₃SCH₃ (30), (CH₃)₂CHSCH(CH₃)₂ (31), PhS—cyclohexyl (32) with O and NTs groups

30   **31**   **32**

Electrophilic Ethylene Transfer to Dibasic Nucleophiles
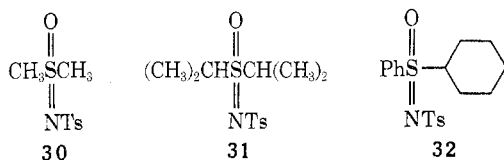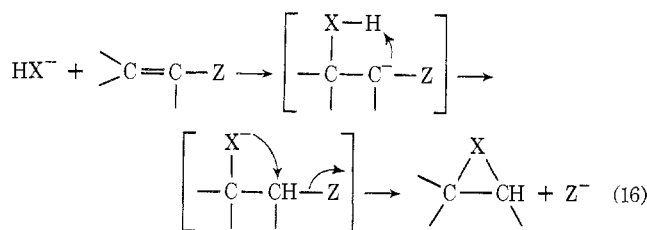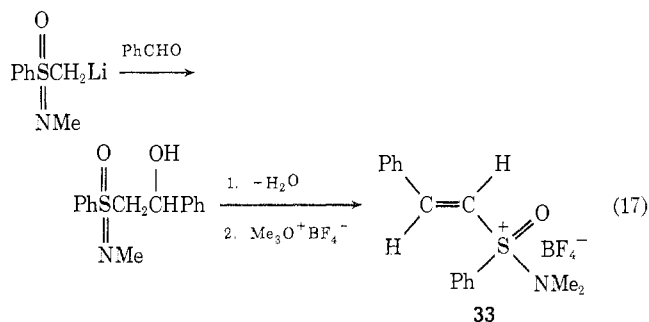
Michael receptors in which the electronegative activator (Z) is also an excellent leaving group should be capable of ethylene transfer to dibasic nucleophiles (HX⁻) (eq 16). In such reactions the intermediate,

$$HX^- + \ \underset{|}{\overset{|}{>}}C=C-Z \longrightarrow \left[-\underset{|}{\overset{X-H}{C}}-\overset{-}{\underset{|}{C}}-Z \right] \longrightarrow$$

$$\left[-\underset{|}{\overset{X}{C}}-CH-Z \right] \longrightarrow \ >C-CH + Z^- \quad (16)$$

after proton transfer, would be identical with that

produced by the addition of an ylide or anion (ZCH⁻) to >C=X. Prior to the work[25] described below, relatively few examples of reactions of the type described by eq 16 were known.[26]

The preparation of our model reagent, (dimethylamino)phenyl(2-phenylvinyl)oxosulfonium fluoroborate (**33**), is shown in eq 17. Dibasic nucleophiles to

$$\underset{\underset{NMe}{\|}}{\overset{\overset{O}{\|}}{PhSCH_2Li}} \xrightarrow{\text{PhCHO}}$$

$$\underset{\underset{NMe}{\|}}{\overset{\overset{O}{\|}}{PhSCH_2}}\overset{\overset{OH}{|}}{CHPh} \xrightarrow[2. \ Me_3O^+BF_4^-]{1. \ -H_2O} \quad (17)$$
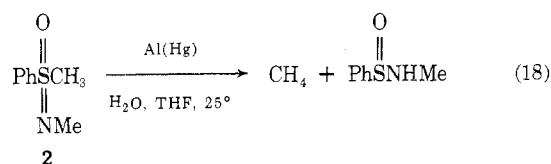
33

which ethylene transfer from salt **33** has been achieved include primary amines, enamines, and active methylene compounds. A selection of the types of compounds which have been produced is shown in Table III.[25] Note that in some instances five-membered rings are formed in preference to three-membered rings.

Optically pure (−)-(*S*)-**33** reacted with methyl cyanoacetate in methanol containing 1 equiv of sodium methoxide to give exclusively methyl (+)-(1*S*,2*R*)-1-cyano-2-phenylcylopropanecarboxylate in 81% yield with an optical purity of 25.5%. As a variant of this type of reagent we have also prepared an *S*-vinyl-*N*-tosylsulfoximine.

Aluminum Amalgam Reductions of Sulfoximines

When **2** was subjected to aluminum amalgam dissolving in aqueous THF at room temperature, carbon–sulfur hydrogenolysis occurred (eq 18).[27] This is

$$\underset{\underset{NMe}{\|}}{\overset{\overset{O}{\|}}{PhSCH_3}} \xrightarrow[H_2O, \ THF, \ 25°]{Al(Hg)} CH_4 + \overset{\overset{O}{\|}}{PhSNHMe} \quad (18)$$

2

a curious reaction not shared by simple aryl alkyl sulfoxides or sulfones; such sulfones are inert, whereas the sulfoxides are reduced to the corresponding sulfides. Moreover, dialkylsulfoximines are also inert to these conditions. Amalgamated aluminum is known to be an excellent reagent for the hydrogenolysis of the carbon–sulfur bond in β-keto sulfides,[28] sulfoxides,[29,30] sulfones,[29] and sulfonamides.[29] In these cases, it is presumed that the resonance-stabi-

(25) C. R. Johnson and J. P. Lockard, *Tetrahedron Lett.*, 4589 (1971), and unpublished results.

(26) J. Gosselck and G. Schmidt, *Tetrahedron Lett.*, 2615 (1969); G. Schmidt and J. Gosselck, *ibid.*, 3445 (1969).

(27) C. W. Schroeck and C. R. Johnson, *J. Amer. Chem. Soc.*, **93**, 5305 (1971).

(28) J. D. Dutcher, J. R. Johnson, and F. W. Bruce, *J. Amer. Chem. Soc.*, **67**, 1736 (1945); J. R. Johnson and J. P. Buchanan, *ibid.*, **75**, 2103 (1953).

(29) E. J. Corey and M. J. Chaykovsky, *J. Amer. Chem. Soc.*, **86**, 1639 (1964); **87**, 1345 (1965).

(30) P. B. Gassman and G. D. Richmond, *J. Org. Chem.*, **31**, 2355 (1966).

lized enol system (radical or anion) produced provides the necessary driving force for the reactions to occur.

The aluminum amalgam reduction of optically active arylsulfoximines which proceeds with retention of configuration at the chiral sulfur provides a useful method for the correlation of absolute configurations.[27] More importantly, the method allows the production of arenesulfinamides of high optical purity. The synthesis of these materials in high optical purity is difficult to achieve due to racemization under the more usual reaction conditions. Optically active primary sulfinamides had not been previously prepared (eq 19).

$$\text{(19)}$$
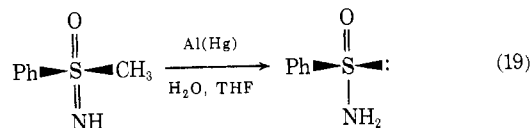
Sulfoxides are produced by the aluminum amalgam reduction of (dialkylamino)oxosulfonium salts; this reaction allows optically active sulfoximines to be converted to optically active sulfoxides with retention of configuration at sulfur.

The aluminum amalgam reduction of sulfoximines is a key step in a general method under development in our laboratory for the production of optically pure alcohols. The method is illustrated by example in eq 20.[27] Reduction of the β-hydroxysulfoximine **34** pro-

$$\text{(20)}$$
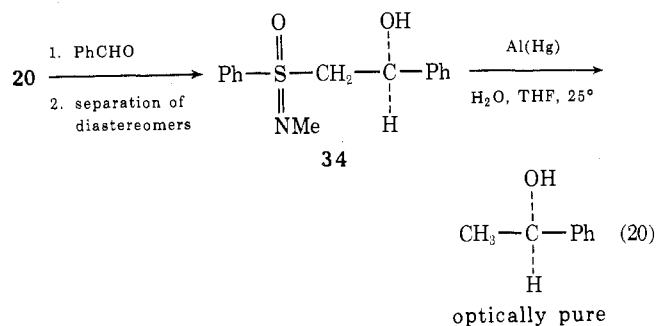
optically pure

duced optically pure (+)-(R)-1-phenylethanol. Under these mild conditions no hydrogenolysis or racemization occurred at the benzylic carbon.

It seemed logical to us that in these reductions of sulfoximines the carbon departed the sulfur as a carbanion. If so, one should be able to generate olefins by the reduction of compounds with suitable leaving groups β to the sulfoximine (eq 21). A surprisingly simple modification of the reaction condi-

$$\text{(21)}$$
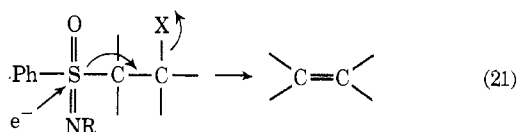
tions noted above for the synthesis of alcohols proved effective for the production of olefins.[31] This consisted of the addition of acetic acid to the reaction medium. Although the acid may play a more complex role, its function could well be the conversion of the hydroxyl group to a better leaving group by protonation. Several examples of this olefin-forming reaction are illustrated in eq 22 and 23.

$$\text{(22)}$$

$$\text{(23)}$$
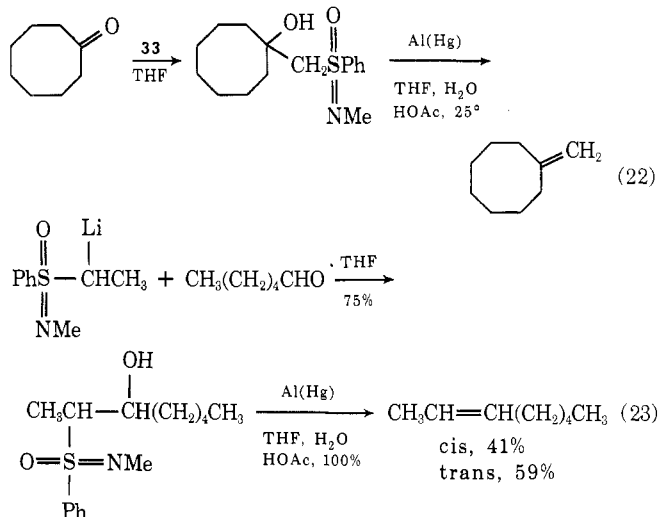
Although the method is still in the development stage the early results have been so encouraging that we expect the method may be a reasonable alternative to the Wittig reaction for the conversion of carbonyl groups to carbon–carbon double bonds.

Conclusion

Sulfur bound in organic molecules can exist in a number of stable oxidation states which provide for a wide variety or regional and stereochemical substitution patterns. This unique structural versatility allows the tailoring of sulfur molecules to perform specific functions. In this Account we have examined variations on sulfoximine chemistry and have attempted to provide a new prospect of the potentiality of organic sulfur chemistry in organic synthesis. We have shown sulfoximines and their derivatives to be useful in the synthesis of oxiranes, aziridines, cyclopropanes, alcohols, and alkenes. All except the latter class have been prepared in optically active forms using chiral sulfoximines for their synthesis.

(31) C. R. Johnson, J. R. Shanklin, and R. A. Kirchoff, *J. Amer. Chem. Soc.*, **95**, 6462 (1973).