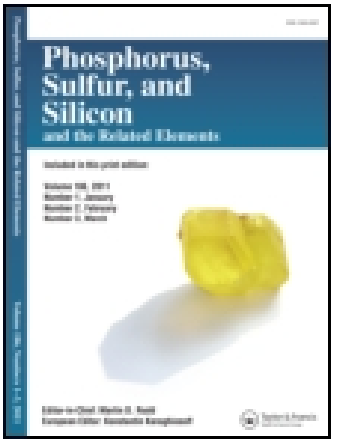


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Novel Episulfone Substitution and Ring-Opening Reactions via α-Sulfonyl Carbanion Intermediates

Nigel S. Simpkins
[a] The Department of Chemistry , The University of Nottingham , University Park, Nottingham NG7 2RD, U.K.
Published online: 17 Mar 2008.

To cite this article: Nigel S. Simpkins (1997) Novel Episulfone Substitution and Ring-Opening Reactions via α-Sulfonyl Carbanion Intermediates, Phosphorus, Sulfur, and Silicon and the Related Elements, 120:1, 197-211, DOI: 10.1080/10426509708545519

To link to this article: http://dx.doi.org/10.1080/10426509708545519

Phosphorus, Sulfur, and Silicon, 1997, Vol. 120 & 121, pp. 197–211
Reprints available directly from the publisher
Photocopying permitted by license only

Novel Episulfone Substitution and Ring-Opening Reactions via α-Sulfonyl Carbanion Intermediates

NIGEL S. SIMPKINS

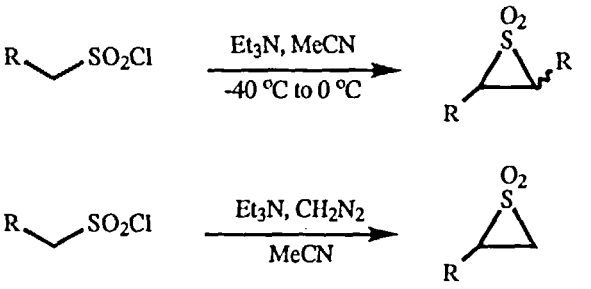
The Department of Chemistry, The University of Nottingham, University Park, Nottingham NG7 2RD, U.K.

Three-membered cyclic sulfones undergo substitution on treatment with base-electrophile mixtures, such as LDA–Me_3SiCl and ^tBu-P4-phosphazene base–PhCHO, to give either substituted episulfones or the corresponding alkenes following loss of SO_2. In the absence of Me_3SiCl, reaction of episulfones with LDA results in ring-opening to give alkenyl sulfinate intermediates, which can be alkylated to give *(E)*-alkenyl sulfone products in stereoselective fashion.

KEYWORDS episulfone, α-sulfonyl carbanion, alkenyl sulfone, episulfoxide.

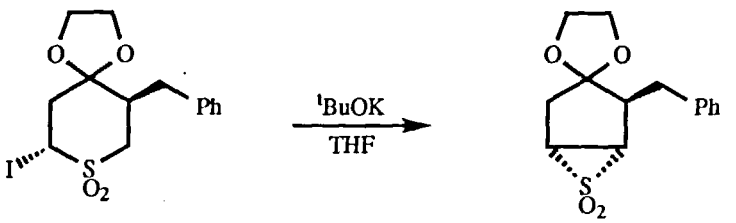
INTRODUCTION

Three-membered cyclic sulfones (thiirane 1,1-dioxides or episulfones) can be prepared by several long-established procedures, including the treatment of alkanesulfonyl chlorides with a tertiary amine base, and the reaction of alkanesulfonyl chlorides or SO_2 with diazoalkanes, especially diazomethane, Scheme 1.[1]



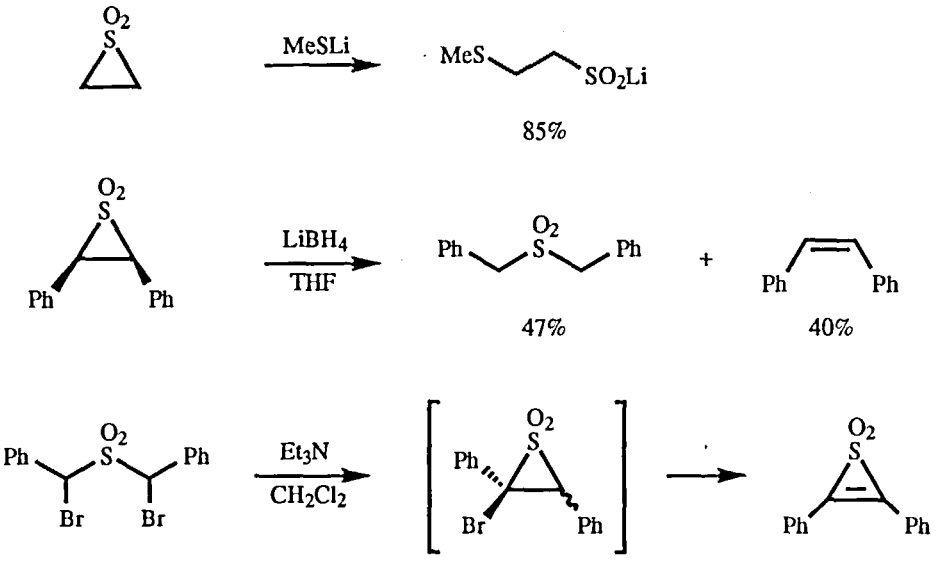
Scheme 1

Episulfones are also well established as intermediates in the classical Ramberg–Bäcklund reaction and quite recently it has been established that certain types of episulfone can be isolated from Ramberg–Bäcklund reactions, provided that modified, mild conditions are used, e.g. Scheme 2.[2]



Scheme 2

Considering the widespread interest in sulfones as synthetic intermediates, especially in C–C bond forming reactions involving α-sulfonyl carbanions, there is a dearth of synthetic methodology involving episulfones. At the outset of our studies described below, the documented chemistry of episulfones was limited mainly to studies of their SO_2 extrusion reactions to give alkenes.[3] Also a few reports describe the ring-opening reactions of episulfones with nucleophiles, which can occur via C–S cleavage, or in some cases C–C cleavage, and a few miscellaneous processes such as the dehydrobromination of episulfones to give episulfenes, e.g. Scheme 3.[4]

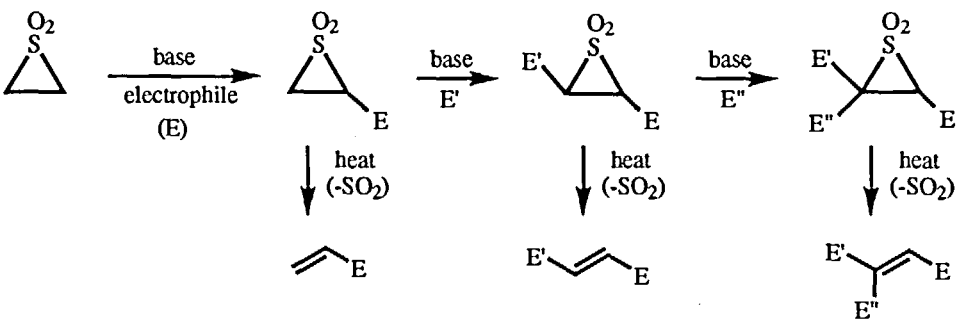


Scheme 3

We recently reported the first examples of episulfone substitution reactions involving α-sulfonyl carbanion intermediates,[5] similar transformations being also described by Taylor and co-workers,[6] and also the conversion of episulfones into alkenyl sulfones.[7] These studies are the subject of this article.

RESULTS AND DISCUSSION

We were intrigued by the possibility of carrying out substitutions of episulfones via their derived α-sulfonyl carbanions, since this should lead to useful substituted alkenes following thermal, stereospecific SO_2 extrusion, and would constitute a new approach to unsaturated products, e.g. Scheme 4.

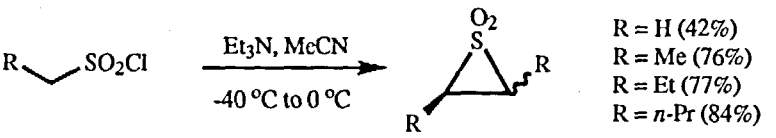


Scheme 4

Thus, in principle, a simple episulfone might undergo sequential substitution to give a range of substituted episulfones (which in turn would furnish the corresponding alkenes) provided that both the regio- and stereochemistry could be controlled. The only precedent to indicate that such episulfone substitution might be possible is the observation that, in the presence of D_2O, base-mediated desulphonylation of certain episulfones, particularly 2,3-diphenylepisulfone (stilbene episulfone), occurs with deuterium incorporation, implicating an intermediate episulfone-derived carbanion.[8]

Preparation of Starting Episulfones

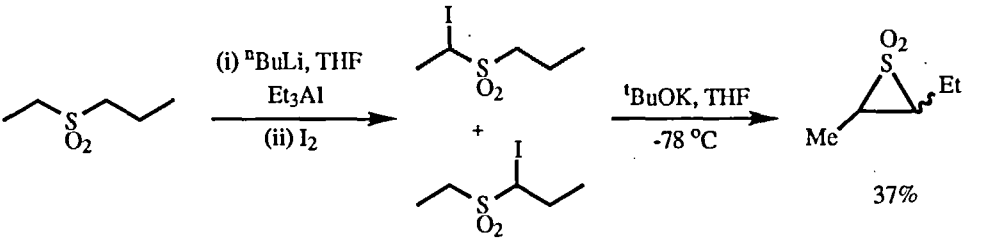
Initially, we prepared a range of simple, symmetrically-substituted episulfones by the method of Opitz, involving treatment of alkanesulfonyl chlorides with Et_3N in MeCN, Scheme 5.[1]



Scheme 5

The stereoisomeric mixtures of products could be separated by flash chromatography, enabling isolation of samples of pure *cis* and *trans* isomers, although in much of the work described below mixtures of stereoisomeric episulfones were employed.

Although most of our studies utilised these simple, symmetrical episulfones we also sought unsymmetrically substituted systems, which would be of interest in addressing aspects of regioselectivity in subsequent reactions. Established routes to such compounds include the reaction of diazoalkanes with sulfenes (generated *in situ* from the appropriate alkanesulfonyl halides as indicated in Scheme 1),[1] or the modified Ramberg-Bäcklund protocol introduced by Taylor's group.[3] In our hands, the former type of reaction, employing either diazomethane or trimethylsilyldiazomethane, proved fruitless, whilst the success of the latter procedure appears highly substrate dependent. Thus, metallation of ethyl propyl sulfone, reaction with iodine, and base treatment of the resulting mixture of α-iodosulfones gave the desired methyl ethyl episulfone in 37% overall yield, Scheme 6.[9]



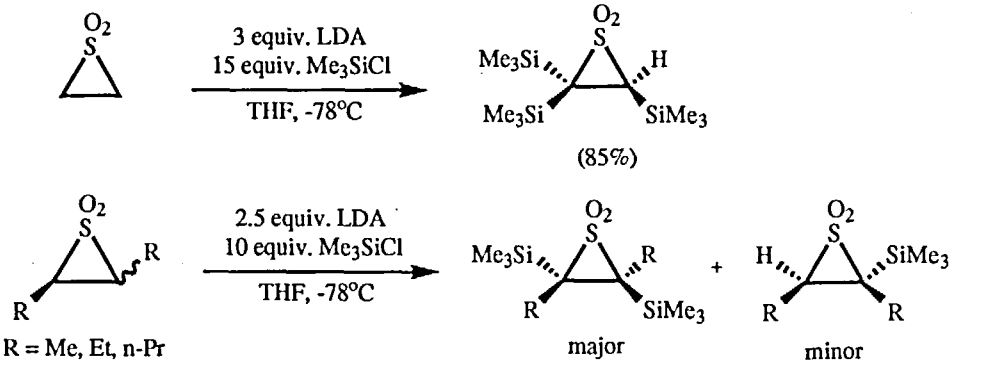
Scheme 6

Monosubstituted episulfones, such as methyl episulfone could also be obtained using similar protocols, although these preparations were not very efficient in our hands.

Episulfone Silylation using LDA-Me_3SiCl

Treatment of episulfones with a range of bases, including LDA and various alkyllithiums, in THF at low temperature, followed by quenching with typical electrophiles, such as Me_3SiCl or PhCHO, proved unrewarding. Although these conventional, external quench (EQ), type of reactions did not furnish the desired substituted episulfones, we were to find later that useful transformation of episulfones into vinyl sulfinate salts was possible this way (see below).

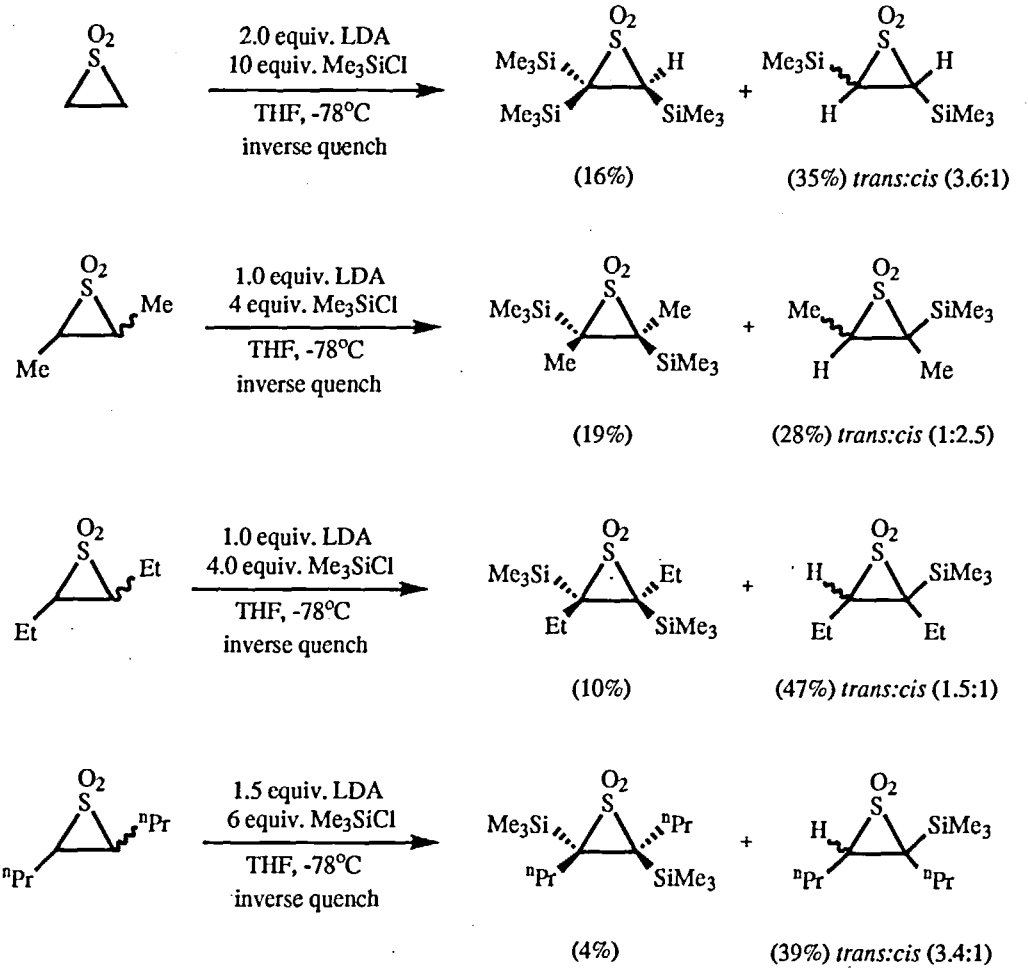
Since it quickly became clear that the difficulty in obtaining substituted episulfones from the EQ reactions was associated with the instability of the intermediate α-sulfonyl carbanion, we next turned to *in situ* quench (ISQ) reactions using Me_3SiCl as the electrophile.[10] Pleasingly, reaction of the simple episulfones with an excess of LDA in the presence of Me_3SiCl resulted in clean conversion into the silylated episulfone products shown, Scheme 7.



Scheme 7

The parent episulfone is an exceptional case, being efficiently converted into a trisilylated episulfone on treatment with 3 equivalents of LDA in the presence of a good excess of Me_3SiCl. The crystalline trisilylated episulfone proved stable enough for an X-ray structure determination, which fully confirmed the structure anticipated for this remarkable product, and revealed some notable features, such as the long C–C bond length of 1.68Å present in the three-membered ring, which is in accord with related structures described by other groups.[3c,6]

We next attempted to increase the yield of monosilylated episulfone products by conducting silylation reactions with fewer equivalents of LDA, and also by using an inverse quench procedure, whereby LDA was added to a mixture of starting episulfone and Me_3SiCl, e.g. Scheme 8.

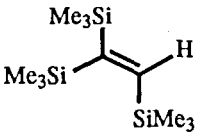


Scheme 8

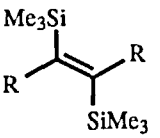
As shown, this technique enabled the isolation of a range of monosilylated derivatives in acceptable yields. These compounds proved especially useful in fluoride mediated episulfone substitution chemistry described below.

Synthesis of Silylated Alkenes by Thermal Extrusion of SO_2

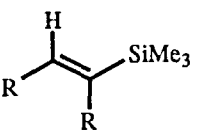
Although the silylated episulfone products obtained using the LDA–Me_3SiCl procedure proved quite stable, and could be subjected to flash column chromatography without serious loss, they were, as expected, converted cleanly into the corresponding alkenes following brief thermolysis in toluene at reflux.



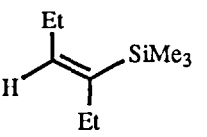
(66%)



R = Me (50%)
R = Et (82%)
R = *n*-Pr (91%)



R = Et (70%)
R = *n*-Pr (59%)



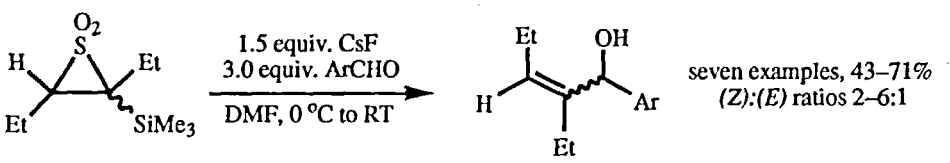
(65%)

As expected, stereoisomerically pure episulfones furnished a single alkene product, whilst mixtures of isomeric episulfones gave products having similar isomeric ratios. The episulfone silylation–SO_2 extrusion protocol can be seen to enable a short access to certain types of vinyl silane, *bis*-silane, and a *tris*-silane, in good overall yield.

Fluoride-Mediated Substitution of Silylated Episulfones

Naturally, we were very interested in the prospect of introducing substituents other than silicon into the episulfones, which would ultimately allow the synthesis of other types of alkenyl products. Since we had available a range of silylated episulfones, we first examined the possible conversion of such compounds into carbon-substituted derivatives, by reaction with electrophiles in the presence of fluoride.

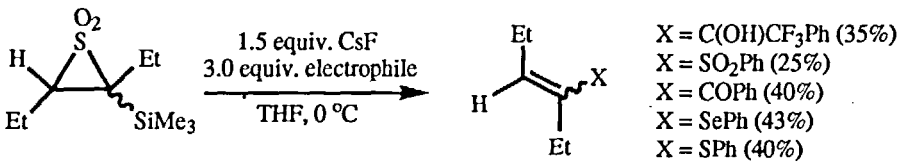
We examined various published procedures for accomplishing similar transformations,[11] and found that reaction of our monosilylated episulfones with excess CsF in THF in the presence of 18-crown-6 and aromatic aldehydes allowed the preparation of allylic alcohol products in moderate yield. Subsequently, we preferred a slightly different procedure, involving reaction of the silylated episulfone with CsF in DMF, e.g. Scheme 9.[12]



Scheme 9

Mixtures of stereoisomeric starting materials were used in all cases, giving directly the allylic alcohols as *(E):(Z)*-mixtures, in which the *(Z)*-isomer predominated, with no trace of the corresponding hydroxyalkyl-substituted episulfones, which are the presumed intermediates.

We also found that a limited range of other electrophiles could be employed in this type of reaction (using the CsF-THF-18-crown-6 method) including $PhCOCF_3$, $PhSO_2F$, PhCOF, Ph_2Se_2 and Ph_2S_2, Scheme 10.



Scheme 10

The substituted alkenyl products were isolated in modest yields and as mixtures of stereoisomers. In no case were we able to observe intermediate episulfones, even when the reactions with Ph_2Se_2 and Ph_2S_2 were started at low temperature and monitored closely by TLC.

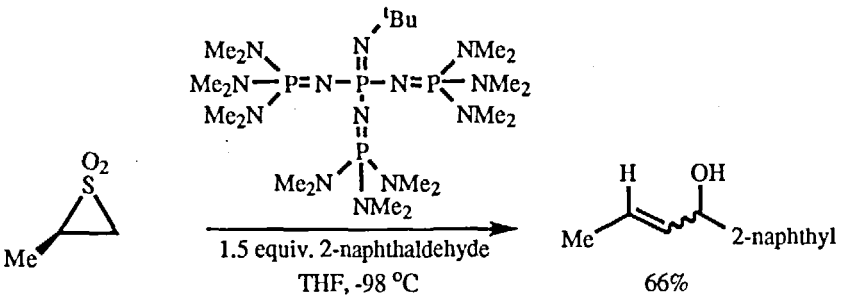
Substitution of Episulfones using a Phosphazene Base

In searching for basic conditions which would extend the repertoire of substitution chemistry available to episulfones, we briefly examined the use of Schwesinger's ^tBu-P^4-phosphazene base.[13] This base can be used in the presence of certain electrophiles, including PhCHO and some alkyl halides, and has been utilised in enolate alkylation reactions in which conventional lithium amide bases proved ineffectual.[14]

We quickly established that addition of a solution of the ^tBu-P^4-phosphazene base to a mixture of a simple episulfone, and an aromatic aldehyde, such as benzaldehyde, at

-98 °C in THF, gave allylic alcohol products, identical to those prepared by the fluoride-mediated reaction shown in Scheme 9. If the starting episulfones were used as stereoisomeric mixtures, or as single *cis*-isomers, then the allylic alcohols were obtained as *(E):(Z)* mixtures with little or no selectivity. However, we were pleased to find that the use of *trans*-episulfones in such phosphazene base substitution reactions lead to the formation of allylic alcohols with very good *(Z)*-selectivity

A single reaction was tried with methyl episulfone, involving reaction with 2-naphthaldehyde, which gave the product of deprotonation at the unsubstituted position on the ring as the only observed product, as a *ca.* 1:1 mixture of stereoisomers, Scheme 11.



Scheme 11

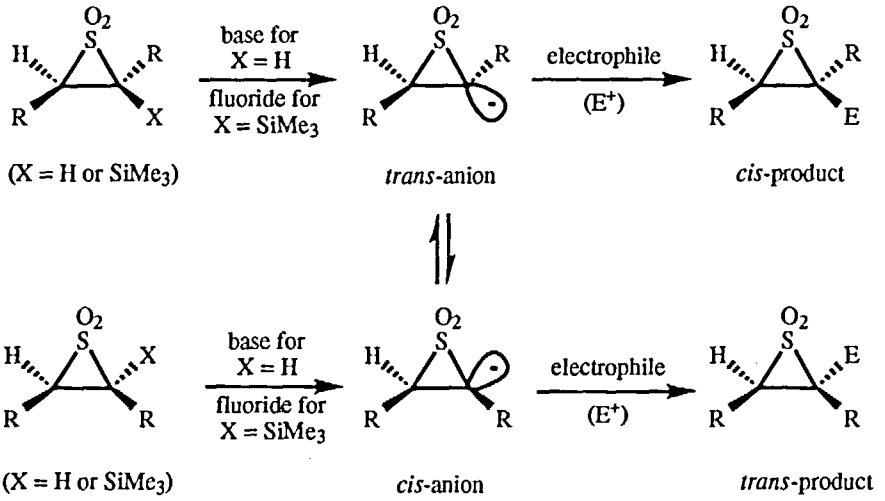
These are promising results, indicating that *trans*-disubstituted episulfones can be substituted with good stereocontrol, and that good regiocontrol in substitution of mono-substituted episulfones seems likely.

Stereochemical Aspects of Episulfone Substitution

The selectivities observed in the formation of silylated episulfones under the LDA–Me_3SiCl (ISQ) conditions can be understood by invoking a configurationally unstable intermediate episulfone α-sulfonyl carbanion, which gives monosilylated products as stereoisomeric mixtures (Scheme 8). The formation of disilylated products as single stereoisomers is presumably dictated by the severe steric interactions which would result from the formation of the alternative isomers having a *cis*-disposition of trimethylsilyl groups.

The fluoride mediated substitutions of the mono-silylated episulfones were tested mainly on *cis:trans* mixtures, with aromatic aldehydes as the electrophiles, resulting

in the formation of allylic alcohols with poor selectivity favouring the *(Z)*-isomer (usually *ca.* 2:1). Even when single isomers were employed in this type of reaction, a similar lack of selectivity was observed. These results indicate a lack of stereocontrol in the carbonyl addition reactions of the intermediate, configurationally unstable, α-sulfonyl carbanions, generated under these conditions, Scheme 12.

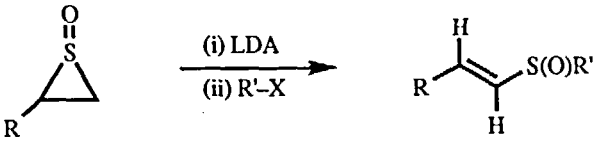


Scheme 12

Presumably, partial equilibration towards the more energetically favourable *trans*-anion is observed, leading to a predominance of *(Z)*-product in most cases (following spontaneous loss of SO_2). In the case of the highly selective phosphazene base reactions, involving *trans*-substituted simple episulfones as the starting materials, the good *(Z)*-selectivity presumably reflects the higher stability of the *trans*-anion intermediate over the corresponding *cis*-anion. Unfortunately, when starting with mixtures of isomers, the necessity for an *in situ* quench does not allow anion equilibration to take place to an extent that leads to high isomer ratios in the products.

Base-Mediated Conversion of Episulfones into Alkenyl Sulfones

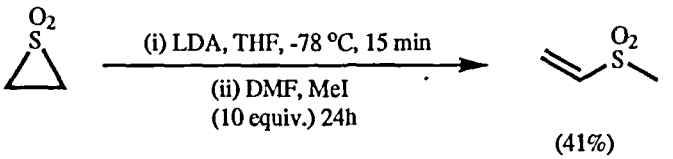
We were prompted to re-examine the reactions of episulfones with strong bases, in the absence of an ISQ, on examining reports from the group of Schwan concerning the conversion of episulfoxides into alkenyl sulfoxides, e.g. Scheme 13.[15]



Scheme 13

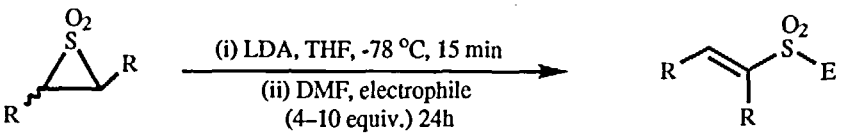
This reaction proceeds via initial deprotonation to form an intermediate episulfoxide carbanion, which then undergoes a ring-opening rearrangement process to give an alkenylsulfenic acid salt, which is alkylated on sulfur with an appropriate alkyl halide to give the observed alkenyl sulfoxide product. Although a few earlier reports give some indication that the analogous transformation of episulfones could also be achieved, this process had not been described in any detail.[16,17]

Our preliminary experiments quickly established that reaction of an episulfone with LDA in THF, followed by addition of MeI, indeed results in the formation of the anticipated alkenyl sulfone product, but in very low yields. Since the high-yielding alkylation of sulfinate salts is known to require the use of solvents such as DMSO, or the generation of the corresponding tetraalkylammonium sulfinates,[18] we decided that the poor yields that we observed were due to the failure of the alkylation step in the THF solvent. By addition of an equivalent volume of DMF to the THF solution resulting from the LDA-mediated ring-opening of the parent episulfone, and by employing a large excess of methyl iodide (4–10 equiv.), we were able to improve the yield of methyl vinyl sulfone to 41%, Scheme 14.



Scheme 14

Presumably, our very earliest attempts at episulfone substitution had resulted in conversion of the episulfones into vinylsulfinate salts, but these had not been isolated. By following the above procedure we were able to convert other simple episulfones into vinyl sulfone products in quite respectable yields, Scheme 15.[7]



R = Me or Et

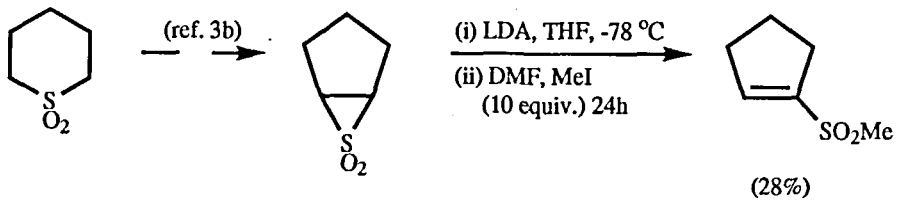
(E):(Z) ≥ 20:1

	MeI	$PhCH_2Br$	$H_2C{=}CHCH_2Br$	$ClCH_2CO_2Et$
R = Me	40	62	47	41
R = Et	56	51	65	68

Scheme 15

Notably, the vinyl sulfone products are formed in highly stereoselective fashion, irrespective of the stereochemistry of the starting episulfone, the thermodynamically favoured *(E)*-isomer predominating in every case. The *(E):(Z)* ratio of 20:1 indicated represents the lowest levels of selectivity seen, indeed, in several cases we were unable to unequivocally identify any of the minor alkenyl sulfone isomer, although some of the ^1H NMR spectra of the crude products showed minor contaminants, including very small amounts of *O*-alkylated product (i.e. sulfinate ester).

We were also able to apply the rearrangement to a bicyclic episulfone, resulting in the formation of cyclopentenyl methyl sulfone, although in modest yield, Scheme 16.



(28%)

Scheme 16

This new method should prove a useful route to certain types of vinyl sulfone, since it proceeds straightforwardly, in two steps, from commercially available alkanesulfonyl chlorides.

CONCLUSION

The carbanion chemistry of episulfones has been examined in detail for the first time. Substitution of episulfones, via intermediate α-sulfonyl carbanions, does not appear to be possible unless an ISQ procedure is adopted, the two such methods we have developed involving either lithium amide or phosphazene bases. The scope and limitations of these methods have been defined using a small number of episulfone substrates, it remains to be seen if the chemistry can be made more general and more accessible, by the development of improved routes to episulfone starting materials.

It is clear that under ISQ conditions, episulfone substitution can compete with alternative reaction modes, such as desulfonylation and ring-opening. However, this latter type of process can also be employed to provide a useful new route to vinyl sulfones.

ACKNOWLEDGEMENTS

I am grateful to the co-workers who carried out this work at Nottingham, namely Adriano B. Muccioli and Allan P. Dishington. Thanks are also due to Richard Douthwaite, who carried out the X-ray determination at Oxford. We are grateful to the Engineering and Physical Sciences Research Council (EPSRC) and to Zeneca Pharmaceuticals (Alderley Park, Macclesfield, Cheshire SK10 4TG, UK) for support of A.B.M. under the CASE scheme, we also acknowledge EPSRC for a postdoctoral fellowship to A.P.D. We would like to thank Prof. R. J. K. Taylor, University of York, for helpful discusions, and preprints of his publications in this area.

REFERENCES

1. (a) G. Opitz, K. Rieth, and T. Ehlis, *Chem. Ber.*, 1990, **123**, 1563 and 1989. (b) G. Opitz, T. Ehlis, and K. Rieth, *Tetrahedron Lett.*, 1989, **30**, 3131. (c) For a review, see N. H. Fischer, *Synthesis*, 1970, 393.
2. (a) L. Ramberg and B. Bäcklund, *Arkiv Kemi, Mineral. Geol.*, 1940, **13A**, No. 27. For reviews, see: (b) N. S. Simpkins, *Sulfones in Organic Synthesis*, Pergamon Press, Oxford, 1993. (c) J. M. Clough, in *Comprehensive Organic*

Synthesis, B. M. Trost and I. Fleming (Eds), Pergamon Press, Oxford, 1991, **3**, 861.

3. (a) A. G. Sutherland and R. J. K. Taylor, *Tetrahedron Lett.*, 1989, **30**, 3267. (b) R. A. Ewin, W. A. Loughlin, S. M. Pyke, J. C. Morales, and R. J. K. Taylor, *Synlett,* 1993, 660. (c) S. M. Jeffery, A. G. Sutherland, S. M. Pyke, A. K. Powell, and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1,* 1993, 2317.
4. For a review see U. Zoller in *The Chemistry of Sulphones and Sulphoxides*, John Wiley and Sons, New York, 1988, S. Patai, Z. Rappoport and C. J. M. Stirling (Eds), Chapter 9, p. 379. See also reference 2b.
5. A. B. Muccioli, N. S. Simpkins, and A. B. Mortlock, *J. Org. Chem.,* 1994, **59**, 5141.
6. (a) A. E. Graham, W. A. Loughlin, and R. J. K. Taylor, *Tetrahedron Lett.*, 1994, **35**, 7281. (b) A. E. Graham, W. A. Loughlin, M. H. Moore, S. M. Pyke, G. Wilson, and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1,* 1996, 661.
7. A. P. Dishington, A. B. Muccioli, and N. S. Simpkins, *Synlett*, 1996, 27.
8. (a) F. G. Bordwell, J. M. Williams Jr., E. B. Hoyt Jr., and B. B. Jarvis, *J. Am. Chem. Soc.*, 1968, **90**, 429. (b) N. P. Neureiter, *J. Am. Chem. Soc.*, 1966, **88**, 558.
9. T. Imamoto and H. Koto, *Synthesis*, 1985, 982.
10. Corey, E.J.; Gross, A.W. *Tetrahedron Lett.,* 1984, **25**, 495.
11. M. Lamothe, M. B. Anderson, and P. L. Fuchs, *Synth. Commun.,* 1991, **21**, 1675.
12. R. S. Atkinson and B. J. Kelly, *J. Chem. Soc., Chem. Commun.*, 1989, 836.
13. (a) R. Schwesinger and H. Schlemper, *Angew. Chem. Int. Ed. Engl.,* 1987, **26**, 1167. (b) R. Schwesinger, C. Hasenfratz, H. Schlemper, L. Walz, E-M. Peters, K. Peters, and H. G. von Schnering, *Angew. Chem. Int. Ed. Engl.,* 1993, **32**, 1361.
14. See for examples (a) T. Pietzonka and D. Seebach, *Chem. Ber.*, 1991, **124**, 1837. (b) A. Solladié-Cavallo, A. G. Csaky, I. Gantz, and J. Suffert, *J. Org.*

Chem., 1994, **59**, 5343. (c) H-J. Gais, J. Vollhardt, and C. Krüger, *Angew. Chem. Int. Ed. Engl.*, 1988, **27**, 1092.

15. (a) A. L. Schwan, M. F. Pippert, H. H. Pham, and M. R. Roche, *J. Chem. Soc., Chem. Commun.*, 1993, 1312. (b) M. D. Refvik, R. D. J. Freose, J. D. Goddard, H. H. Pham, M. F. Pippert, and A. L. Schwan, *J. Am. Chem. Soc.*, 1995, **117**, 184.
16. (a) S. Matsumura, T. Nagai, and N. Tokura, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 2672. (b) B. B. Jarvis, W. P. Tong, and H. L. Ammon, *J. Org. Chem.*, 1975, **40**, 3189.
17. Vinylogous variants of this process, involving sulfolene starting materials, are well established, see for example (a) R. L. Crumbie and D. D. Ridley, *Aust. J. Chem.*, 1981, **34**, 1017. (b) F. Naf, R. Decorzant, and S. D. Escher, *Tetrahedron Lett.*, 1982, **23**, 5043. Analogous reactions of thiirene dioxides, to give acetylenic sulfinate products have also been observed, see for example (c) L. A. Carpino, L. V. McAdams, III, R. H. Rynbrandt, and J. W. Spiewak, *J. Am. Chem. Soc.*, 1971, **93**, 476.
18. For a discussion of sulfinate alkylation, see reference 2b, p. 11.