The Enantioselective Conversion of Three-Membered Ring Sulfoxides (Episulfoxides) into Alkenyl Sulfoxides using Chiral Lithium Amide Bases

Alexander J. Blake, Susan M. Westaway and Nigel S. Simpkins*

Department of Chemistry, The University of Nottingham, University Park, Nottingham, NG7 2RD, UK

Fax (0115) 9513564; e-mail Nigel.Simpkins@Nottingham.ac.uk

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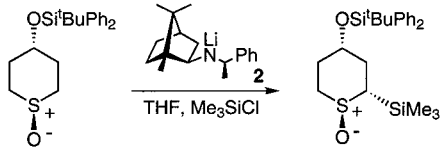
Abstract: A novel type of chiral lithium amide base reaction, involving the rearrangement of certain types of symmetrical ring-fused episulfoxides, gives alkenyl sulfoxide products in up to 88% ee. The structure of one product, including its absolute stereochemistry, was determined by X-ray crystallography, following oxidation of the sulfoxide to the corresponding alkenyl sulfone.

Some time ago we became interested in extending the applications of our chiral base methodology, which has been quite extensively demonstrated for cyclic prochiral ketones, to the asymmetric synthesis of cyclic sulfoxides.[1] The results with certain six-membered systems, although promising, were disappointing in terms of the fairly modest levels of enantiomeric excess (ee) achieved, e.g. Scheme 1.[2]



Scheme 1

Preliminary results suggested that analogous reactions of five and four-membered systems gave similarly modest levels of induction.[3]

More recently, our interest in the metallation reactions of three-membered ring sulfones (episulfones) attracted us to a well-established rearrangement reaction of the corresponding sulfoxides with LDA, to give alkenyl sulfoxides following treatment with an alkyl halide, Scheme 2.[4]

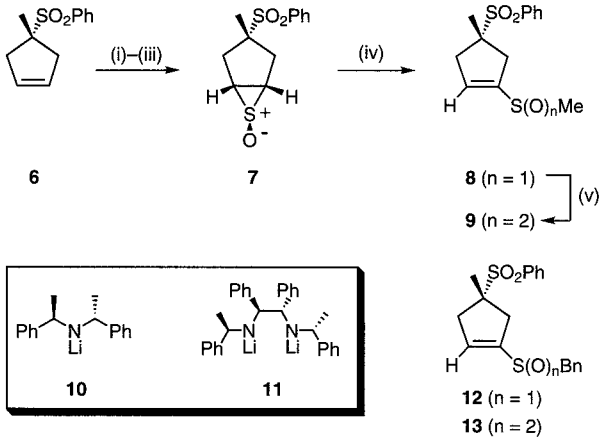
Scheme 2

We envisaged that a chiral base could be usefully applied in this reaction if a ring-fused episulfoxide derivative incorporating pro-stereogenic centres was employed as the substrate. Herein we describe our preliminary results which show that this approach does indeed allow a novel enantioselective entry to certain types of chiral alkenyl sulfoxide and derived products in up to 88% ee.

As our first substrate we employed episulfoxide **7**, derived from the sulfonyl-substituted cyclopentene **6**, Scheme 3.[5]

Synthesis of the starting episulfoxide **7** was carried out from alkene **6** via an intermediate epoxide, which was then converted into the corresponding episulfide under standard conditions.[6] Oxidation to the episulfoxide **7**, using oxone® in aqueous MeOH was highly stereoselective, furnishing only the isomer shown.[7]

Chiral base reactions of **7**, involving treatment with lithium amide **10**, followed by addition of MeI, gave the desired alkenyl sulfoxide in good chemical yield (79%) but in low ee (*ca.* 10%). However, we were



Scheme 3 Reagents: (i) mCPBA, CH_2Cl_2 (86%); (ii) Ph_3PS, TFA, PhH (49–60%); (iii) oxone®, MeOH, H_2O (81%); (iv) chiral base **10** or **11**, excess MeI, THF, -78 °C (see text); (v) oxone®, MeOH, H_2O (58%).

delighted to find that analogous reactions involving the *bis*-lithium amide **11** gave the sulfoxide **8** as a mixture of diastereomers (epimeric at sulfur, *ca.* 2:1 ratio) in 85% yield, each of which was formed in 82% ee.[8,9] As expected, the use of the enantiomeric base (ent-**11**) gave the opposite sense of asymmetric induction, leading to the enantiomer of **8** in similar chemical yield and ee.[10]

Although the chiral product **8** was generated in good ee, the presence of two diastereomeric sulfoxides was an unwanted complication. Oxidation using oxone® to give the corresponding sulfone **9** facilitated enantiomeric enrichment by recrystallisation, and also enabled an X-ray crystallographic determination which established the absolute configuration of this series of compounds, Figure 1.[11]

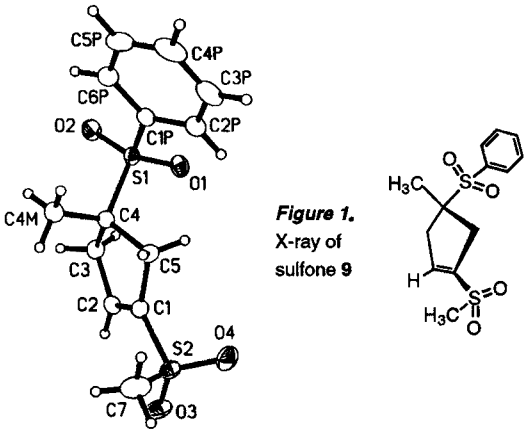
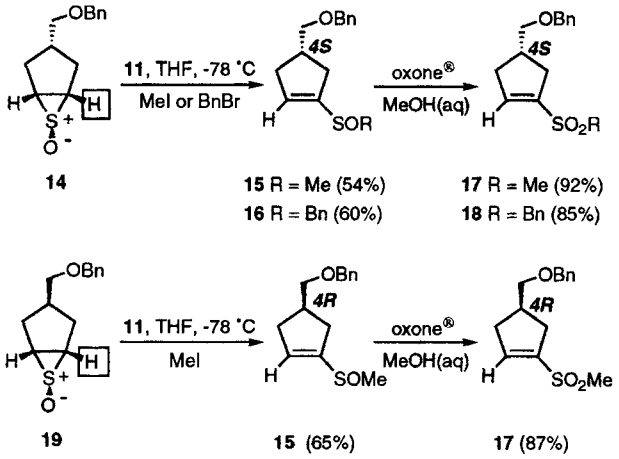


Figure 1. **X-ray of sulfone 9**

The enantioselective transformation shown in Scheme 3 could also be carried out using $PhCH_2Br$ in place of MeI, which provided alkenyl sulfoxide **12** (n = 1) in 72% yield. Oxidation to the corresponding sulfone **13** (n = 2) enabled determination of the ee (85%) using HPLC.[12]

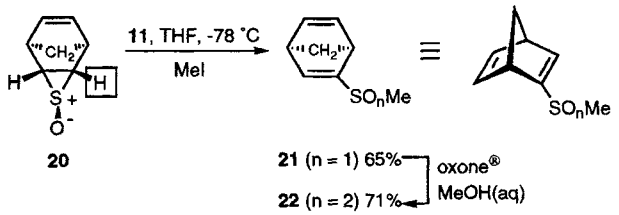
We then examined this type of transformation using the two diastereomeric episulfoxides **14** and **19**, Scheme 4.[13]



Scheme 4

In each case shown, the starting episulfoxide was converted into the alkenyl sulfoxide product, **15** or **16** in 85–88% ee, as determined by HPLC analysis of the derived alkenyl sulfones **17** and **18**. Notably, the chiral base selectivity for the highlighted hydrogen in the two episulfoxides **14** and **19**, results in these *diastereomeric* materials being converted into *enantiomeric* products.[14]

Finally, we applied the chiral base rearrangement to episulfoxide **20**,[15] which was smoothly converted into the expected alkenyl sulfoxide **21** under our standard conditions, Scheme 5.



Scheme 5

In this case the level of asymmetric induction was slightly lower (73% ee) compared with the earlier examples, the absolute configuration shown being assigned tentatively, assuming that the sense of selectivity (removal of highlighted hydrogen) follows the same pattern as before.

In conclusion, this new chiral lithium amide base mediated reaction offers a novel entry to certain types of chiral alkenyl sulfones and sulfoxides in good yield and enantiomeric excess. These products are attractive intermediates for further transformation, for example via Michael addition and cycloaddition reactions.

Acknowledgements

We are grateful to The Nuffield Foundation for support of this work.

References and Footnotes

(1) For a review, see Cox, P. J.; Simpkins, N. S. *Tetrahedron:Asymmetry* **1991**, *2*, 1.

(2) Armer, R.; Begley, M. J.; Cox, P. J.; Persad, A.; Simpkins, N.S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3099.

(3) Armer, R.; PhD Thesis, University of Nottingham, 1994.

(4) (a) Bonini, B. F.; Maccagnani, G.; Mazzanti, G.; Piccinelli, P. *Tetrahedron Lett.* **1979**, 3987. (b) Bonini, B. F.; Maccagnani, G.; Mazzanti, G.; Zani, P. *Gazz. Chim. Ital.* **1990**, *120*, 115. (c) Schwan, A. L.; Pippert, M. F.; Pham, H. H.; Roche, M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1312. (d) Refvik, M. D.; Froese, R. D. J.; Goddard, J. D.; Pham, H. H.; Pippert, M. F.; Schwan, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 184.

(5) Giblin, G. M. P.; Ramcharitar, S. H.; Simpkins, N. S. *Tetrahedron Lett.* **1988**, *29*, 4197.

(6) Chan, T. H.; Finkenbine, J. R. *J. Am. Chem. Soc.* **1972**, *94*,2880.

(7) The *exo*-selective sulfoxidation of the ring-fused episulfides is to be expected, and was confirmed in the case of **7** by X-ray crystallography. At present the other examples are assumed to be analogous.

(8) For the synthesis of the chiral diamine, see Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391.

(9) *Typical experimental procedure for the asymmetric rearrangement.* A pink solution of the chiral base **11** was prepared by treatment of a solution of the corresponding amine (1.2 equiv.) with ^{n}BuLi (2.2 equiv.) in THF at -78 °C. The mixture was warmed briefly to RT (5 min) to ensure complete formation of the base and then re-cooled to –78 °C. A mixture of the episulfoxide (1 equiv.) and the appropriate electrophile (MeI or BnBr, 10 equiv.), dissolved in THF, was then added, and the resulting yellow solution stirred at –78 °C until TLC indicated complete consumption of starting material (*ca.* 45 min). The mixture was then quenched by addition of excess aqueous NH_4Cl. Extraction of the product into CH_2Cl_2, drying ($MgSO_4$), evaporation and flash chromatography on silicagel then gave the product.
Data for **8** (*ca.* 2:1 ratio of diastereomers as an oil) ν_{max}/cm^{-1} ($CHCl_3$) 2991, 2933, 2851, 1621, 1586, 1459, 1308, 1142, 1122, 989 and 959; δ_H (250 MHz; $CDCl_3$) 1.48 and 1.49 (3H, 2 x s, C–CH_3), 2.43–2.59 (2H, m), 2.60 and 2.62 (3H, 2 x s, $SOCH_3$), 3.47 (2H, m), 6.24 (1H, s, C=CH), 7.59 (2H, t, *J* 8, SO_2Ar), 7.70 (1H, t, *J* 8, SO_2Ar) and 7.92 (2H, d, *J* 8, SO_2Ar); *m/z* (EI) 284 (M^+, 6%), 188 (4), 169 (3), 143 (100), 142 (79),127 (46), 126 (22), 125 (11), 97 (74) and 95 (95) (Found: M^+,284.0534. $C_{13}H_{16}O_3S_2$ requires *M*, 284.0541).
Oxidation with oxone® then gave the sulfone **9**, which was recrystallised from ^{i}PrOH/hexane and then from ^{i}PrOH to give crystals of enantiomerically pure material for X-ray, mp 124–125 °C; $[\alpha]_D$ -24 (c 0.4, $CHCl_3$). Found: C, 51.9; H, 5.5; S, 21.1. $C_{13}H_{16}O_4S_2$ requires C, 52.0; H, 5.4; S, 21.3%.

(10) Determination of the ee of sulfoxide **8** by HPLC was possible directly, since all four stereoisomers present were separated by use of a Chiralcel OD column, using 20% ^{i}PrOH in hexane as eluant (UV detection at 254 nm).

(11) The absolute configuration was established by the collection of low-temperature data, including Friedel equivalents, and by refinement of a Flack parameter (value 0.00(6)), see Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876.

(12) Estimation of the ee of **12** was not possible. The ee of the derived sulfone **13** was determined using the same conditions used for **8**.

(13) The diastereomeric episulfoxides were obtained via the corresponding epoxides, the relative configuration of which has been assigned, see Hodgson, D. M.; Witherington, J.; Moloney, B. A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3373.

(14) The absolute configurations shown are assigned by analogy to the earlier system, shown in Scheme 3. The enantiomeric relationship of the product **17**, arising from the starting episulfoxides **14** and **19**, was clear from the HPLC analysis using a Chiralcel OD column with 10% ^{i}PrOH in hexane as eluant. The two enantiomers were eluted with retention times of *ca.* 25 and 27 minutes, with the first eluted being the major component when starting with **19**, and the second predominating in the case of **14**.

(15) The *exo*-episulfide corresponding to **20** was prepared as described previously, see Emsley, J.; Griffiths, D. W.; Jayne, G. J. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 228.