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A highly enantioselective one-pot sulfur ylide epoxidation reaction

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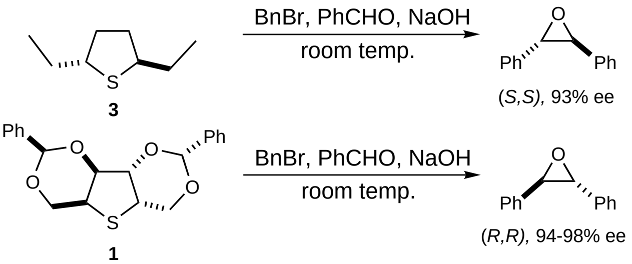
Abstract—Enantiomerically pure tricyclic C_2-symmetric sulfide **1** can be prepared in high yield and only three steps from D-mannitol. When used in a one-pot sulfur ylide mediated epoxidation reaction, between 94 and 98% enantiomeric excess was obtained; the highest reported to date for the catalytic process. Molecular modelling studies of the ylide conformation provides a basis for understanding the stereochemical outcome of the reaction. © 2002 Elsevier Science Ltd. All rights reserved.

Our aim was to design and synthesise a chiral sulfide that could be easily prepared in a few, high-yielding steps from a readily available and reasonably priced starting material, and which could find application in enantioselective epoxidation reactions and other areas of asymmetric synthesis.[1] Chiral sulfide **1** (a crystalline, odourless compound) can be prepared in three steps and 76% overall yield from D-mannitol, a readily available and cheap starting material.[2] High degrees of enantioselectivity were obtained when this sulfide was used in a one-pot sulfur ylide mediated epoxidation reaction.

Some reports in the literature described problems that had been encountered in the formation or isolation of the sulfonium salt which is an intermediate in the reaction pathway. In our case, there was concern that the steric hindrance from the groups α to the sulfur atom would hinder addition of an alkyl group, and the presence of four heteroatoms in the molecule would reduce the nucleophilicity of the sulfur to such an extent that alkylation could not occur.[3]

A catalytic process eliminates the need to isolate the intermediate sulfonium salt. The first example of this was reported by Furukawa,[4] although this method suffered from relatively low enantioselectivities. Metzner et al.[5,6] used a similar one-pot epoxidation method (Scheme 1). Using sulfides **2** and **3** (Fig. 1), stilbene oxide was produced in good yield with up to 88% and 93% enantiomeric excess, respectively, and a high degree of diastereoselectivity.

Another elegant solution to the problem of sulfide alkylation was reported by Aggarwal et al. who used an elegant rhodium-catalysed route towards enantiomerically enriched epoxides, aziridines and cyclopropanes.[7] This involved direct addition of a carbene to the sulfide, alleviating the need for an extra deprotonation step and facilitating alkyl addition to more hindered and less nucleophilic substrates.



Scheme 1. One-pot epoxidation reactions used by Metzner (top) and in this study (bottom).

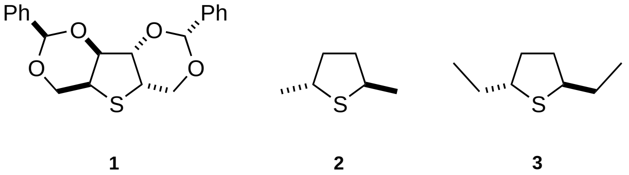


Figure 1. Chiral sulfides used in one-pot epoxidation reactions.

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Following the procedure of Metzner (Scheme 1), it was possible to form the desired product in 42% yield after 2 days stirring at room temperature in an acetonitrile:water mixture (9:1). The enantiomeric excess was found to be 94% (*R*,*R*) while the *trans*:*cis* ratio observed was 1:0.1 (Table 1, entry 1). With a longer reaction time of 7 days, the yield could be increased to 59% with no loss of enantioselectivity; 97% ee was observed (entry 3). In all cases the *trans* isomer was formed preferentially and chiral HPLC identified the major isomer as (*R*,*R*)-diphenyloxirane. In each case the sulfide was recovered in good yield, indicating that the reaction could be carried out catalytically. With 0.1 or 0.2 equiv. of sulfide (entries 4 to 8), similar high enantioselectivities were observed, but the reaction rate and yields were reduced.

The enantioselectivities observed are approximately constant, and average 96%. In a further experiment, aliquots were taken at regular intervals from a larger scale reaction set up using 0.1 equiv. of sulfide, recrystallised twice from toluene. No drop in ee was observed over 7 days (enantiomeric excesses observed range from 97 to 99%), and the *trans*:*cis* ratio was greater than 1:0.12 in all cases. The small variation in diastereoselectivity noted in Table 1 is probably not significant, as the NMR measurement of the ratio is less precise than the HPLC method used for the ee.

The investigation was further extended to a range of aldehydes (Table 2). Unfortunately, no reaction occurred when *para*-methoxybenzaldehyde was employed (presumably due to its low reactivity, entry 1), but *para*-nitrobenzaldehyde succeeded in affording the desired product, albeit with a slightly lower enantioselectivity of 84% (entry 2). *para*-Chloro- and *para*-fluorobenzaldehyde could also be employed in the same reaction, resulting in epoxides with a very high degree of enantiomeric excess (>95%, entries 3, 4), although in these cases the reaction yield is low. These results were as expected with respect to the relative reactivities of the aldehydes; the more reactive *para*-nitrobenzaldehyde gave a higher product yield but a lower selectivity than the less reactive halo-derivatives.

The enantioselectivity achieved in the epoxidation reactions may be influenced by the ylide geometry as shown in Fig. 2. Molecular mechanics calculations using the MM2* forcefield within MacroModel[8,9] were carried out on sulfide **1** to determine the lowest energy conformation. The global minimum conformation found using a Monte Carlo conformational search was used to build models of the ylide, which were minimised at RHF/6-31G**//RHF/6-31G** using GAMESS-US.[10]

The lowest energy and hence most populated ylide conformation has the phenyl group pointing away from the ring (**1b**), minimising unfavourable steric interactions between the ring substituents and the aromatic group. It may be expected that the attack of the ylide onto the aldehyde would occur from the *re* face, leading to the formation of the (*R*,*R*) epoxide, as is observed experimentally (Fig. 3).

We regard this as a mnemonic for the sense of selectivity, as it does not represent a full account of the processes going on in the reaction. It is qualitatively consistent with Metzner's results for sulfide **2**: attack

Table 1. Initial results of epoxidation studies[a]

Entry	Sulfide equiv.	Time (days)	% Yield[b]	% Sulfide recovered	*trans*:*cis*[c]	%ee[d]
1	1	2	42	81	1:0.10	94 (*R*,*R*)
2	1	5	45	70	1:0.11	96
3	1	7	59	93	1:0.08	97
4	0.2	3	27	85	1:0.07	95
5	0.1	2	20	96	1:0.20	94
6	0.1	2	16	86	1:0.11	98
7	0.1	2	14	80	1:0.17	96
8	0.1	4	41	90	1:0.11	97

[a] Reactions were conducted on a 0.1–2 mmol scale using 1 equiv. benzaldehyde, 2 equiv. benzyl bromide, 2 equiv. sodium hydroxide, in a 9:1 mixture of acetonitrile and distilled water.

[b] Isolated yield of *trans* epoxide

[c] Diastereomeric excess determined by NMR of product mixture.

[d] Enantiomeric excess determined by chiral HPLC using a Chiracel™ OD column.

Table 2. Results of epoxidation studies using a range of aldehydes[a]

Entry	R(<u>R</u>CHO)	Time (days)	% Yield	% Sulfide recovered	%de	%ee
1	p-MeOC$_6$H$_4$	2	–	75	–	–
2	p-NO$_2$C$_6$H$_4$	2	71	77	100	84
3	p-ClC$_6$H$_4$	2	20	86	100	96
4	p-FC$_6$H$_4$	3	19	83	100	98

[a] 1 equiv. of sulfide **1** was used in all reactions except entry 4, where 0.1 equiv. of sulfide were used. Reaction conditions and methods were the same as for Table 1.

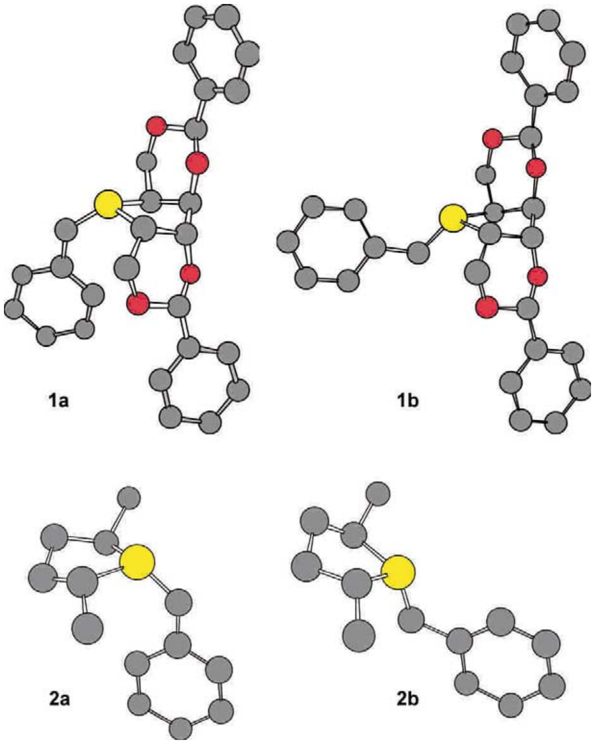

Figure 2. Two possible ylide geometries, with the phenyl ring pointing towards (**1a** and **2a**) or away (**1b** and **2b**) from the ring. Hydrogens have been omitted.

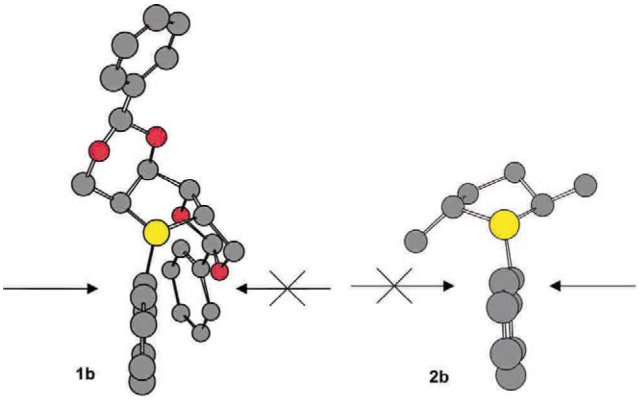

Figure 3. For sulfide **1**, attack from the *re* face is less hindered than attack from the *si* face. The expected, lower energy ylide conformation (with the phenyl group pointing away from the ring) is shown. For Metzner's sulfide **2**, *si* face attack is less hindered. Hydrogens have been omitted.

occurs from the *si* face of the favoured ylide conformation **2b** (Fig. 3) leading to the formation of the (*S*,*S*) epoxide. The larger substituents on sulfide **1** (with respect to the methyl groups adjacent to the sulfur atom in Metzner's compound **2**) are responsible for the increased enantioselectivity observed.

The energy difference between the ylide conformations **1a** and **1b** was calculated to be 8.5 kJ/mol. Using Boltzmann factors[11] to compute relative populations of the conformations at 298 K, this energy difference corresponds to a limiting enantiomeric excess of 94%; remarkably close to that observed experimentally. However, the calculated energy difference between the ylide conformations for sulfide **2** corresponds to an ee of just 17%; a much smaller enantioselectivity than that observed in the reaction. This indicates that the ylide conformation is not the only important factor in controlling the stereoselectivity of these reactions.[12] The close agreement of the initial calculation may be fortuitous; a higher level of calculation including solvent effects may enable further insights.[13]

In conclusion, we have shown that readily accessible, crystalline C_2-symmetric sulfide **1** can be used in catalytic, transition-metal free, sulfur ylide mediated epoxidation reactions. The enantioselectivities obtained (averaging 96%) are, as far as we are aware, the highest reported to date for this reaction, except for the work of Solladié-Cavallo et al., which requires a two-step epoxidation procedure.[14] Future prospects include the extension of the scope of this reaction and the application of sulfide **1** to other asymmetric reactions.

Acknowledgements

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References

1. Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341–2372.
2. (a) Rao, A. V. R.; Reddy, K. A.; Gurjar, M. K.; Kunwar, A. C. *J. Chem. Soc., Chem. Commun.* **1988**, 1273–1274; (b) Winn, C.; Goodman, J. M. *Tetrahedron Lett.* **2001**, *42*, 7091–7093.
3. Durst, T.; Breau, L.; Ben, R. N. *Phosphorus, Sulfur, Silicon* **1993**, *74*, 215–232.
4. Furukawa, N.; Sugihara, Y.; Fujihara, H. *J. Org. Chem.* **1989**, *54*, 4222–4224.
5. (a) Julienne, K.; Metzner, P.; Henyron, V.; Greiner, A. *J. Org. Chem.* **1998**, *63*, 4532–4534; (b) Julienne, K.; Metzner, P.; Henyron, V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 731–735; (c) Julienne, K.; Metzner, P.; Greiner, A.; Henyron, V. *Phosphorus, Sulfur, Silicon* **1999**, 341–342; (d) Metzner, P.; Alayrac, C.; Julienne, K.; Nowaczyk, A. *Actualité Chim.* **2000**, 54–59.
6. Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem.* **2001**, *66*, 5620–5623.
7. (a) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem., Int. Ed. Engl.* **2001**, *8*, 1430–1433; (b) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed. Engl.* **2001**, *8*, 1433–1436.
8. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, C.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440–467.
9. Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 440–467.

10. Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347–1363.
11. Goodman, J. M.; Kirby, P. D.; Haustedt, L. O. *Tetrahedron Lett.* **2000**, *41*, 9879–9882 on line calculation of population from relative energies can be found at http://www.ch.cam.ac.uk/magnus/boltz.html.
12. Other computational approaches to prediction of enantioselectivity include: (a) Myllimäki, V. T.; Lindvall, M. K.; Koskinen, A. M. P. *Tetrahedron* **2001**, *57*, 4629–4635; (b) Lindvall, M. K.; Koskinen, A. M. P. *J. Org. Chem.* **1999**, *64*, 4596–4606.
13. Aggarwal, V. K.; Harvey, J. N.; Richardson, J. *J. Am. Chem. Soc.* **2002**, *124*, 5747–5756.
14. Solladié-Cavallo, A.; Diep-Vohuule, A.; Sunjic, V.; Vinkovic, V. *Tetrahedron: Asymmetry* **1996**, *7*, 1783–1788.