Catalytic asymmetric cyclopropanation of electron deficient alkenes mediated by chiral sulfides

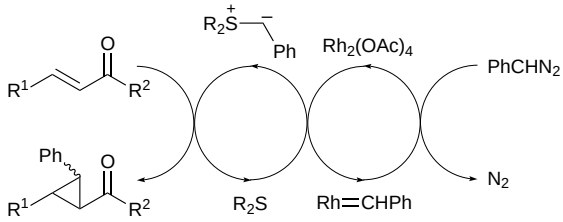
Varinder K. Aggarwal,*[a] Helen W. Smith,[a] Ray V. H. Jones[b] and Robin Fieldhouse[b]

[a] *Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, UK S3 7HF*
[b] *Zeneca Process Technology Dept., Earls Road, Grangemouth, Stirlingshire, UK*

Catalytic asymmetric cylopropanation of enones has been achieved using diazo compounds, catalytic quantities of a metal catalyst and a camphor-derived thioacetal; this sulfide shows exceptionally high levels of enantioselectivity.

Cyclopropanes are common functional groups in biologically active molecules, the most notable examples being the pyrethroids which are a highly potent class of insecticides.[1] Much effort has therefore been expended in the synthesis of cyclopropanes in racemic and more recently, in asymmetric form.[2,3] High enantioselectivity has been achieved in the Simmons–Smith[4,5] cyclopropanation of allylic alcohols using chiral promoters.[6,7] High enantioselectivity has also been achieved in metal catalysed reactions of diazocarbonyl compounds with alkenes. The chirality may be linked to the metal in the form of a chiral ligand (*e.g.* bis-oxazolines[8]) or linked to both the metal and the diazo compound to enhance the enantioselectivity.[9,10] However, in all the above cases, the metal carbenoid only reacts efficiently with electron rich alkenes[11] and so methods are required for the cyclopropanation of electron deficient alkenes. Towards this end enantiomerically pure aminosulfoxonium ylides have been successfully employed in asymmetric cyclopropanation of electron deficient alkenes.[12,13] However, such reagents have to be employed in stoichiometric amounts, and cannot be recycled. Sulfur ylides are also known to react with electron deficient alkenes to furnish cyclopropanes, but there are no asymmetric examples and so we embarked on such a study. In addition, we sought to utilise our recently reported catalytic process for asymmetric epoxidation[14,15] and aziridination[16] so that catalytic quantities of sulfides could ultimately be employed (Scheme 1). Here we report our success in achieving these goals.

Reactions were carried out on enones with phenyldiazomethane (Table 1) and we initially used tetrahydrothiophene, in stoichiometric amounts, as a representative sulfide under the conditions previously employed for the epoxidation reaction.[15] However, only low yields of cyclopropanes were obtained (entries 1 and 2). We were surprised at the low yields obtained, as high yields were obtained in the related epoxidation and aziridination reactions. We suspected that the lower reactivity of enones compared to aldehydes† and imines could have been responsible for the lower yields observed, as the ylide will have a longer lifetime in reactions with enones. This in turn would mean that the ylide might have time to undergo competitive rearrangement reactions, such as the Stevens[17,18] or the Sommelet–Hauser rearrangement,[17,18] and indeed the Sommelet–Hauser product was observed.‡ Under standard reaction conditions an excess of the sulfonium salt[22] or the ylide is typically used to cyclopropanate alkenes, perhaps for this reason.

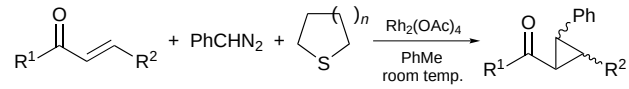


Scheme 1 Catalytic process for cyclopropanation

To reduce the extent of this rearrangement the six membered analogue, pentamethylene sulfide, was employed and, gratifyingly, high yields of cyclopropanes were obtained (entries 3–6). Even using catalytic amounts of sulfide, cyclopropanes were formed in moderate to good yields (entries 7–10). The least reactive enone (entry 10) gave reduced yields as the rearrangement of the ylide was once again a significant competing side reaction.

We next explored asymmetric cyclopropanation (Table 2) and chose oxathiane **1** as this sulfide had previously given high enantioselectivity in epoxidation of carbonyl compounds[14] and aziridination of imines.[16] Furthermore, sulfide **1** is readily available, in either enantiomeric form, from camphorsulfonyl chloride in two steps.[14] We applied this sulfide to the 4-phenyl substituted enones (as this would give rise to a maximum of two diastereoisomers) and we were delighted to find that exceptionally high levels of enantioselectivity were obtained with both stoichiometric and catalytic amounts of sulfide.§ However, reduced yields were obtained when using catalytic compared to stoichiometric amounts of sulfide. This was also observed in the related epoxidation process[14,15] but the differences in yield are greater in cyclopropanation, presumably because of the lower reactivity of enones compared to aldehydes. The constant enantiomeric excess (no reduction observed) in reactions using catalytic quantities of sulfides indicates that no direct cyclopropanation occurs and that the sulfide reacts with the metal carbenoid (to give a sulfur ylide) at a significantly faster rate than the alkene (to give direct cyclopropanation). The major isomer of the cyclopropane is *tentatively* assigned as the *R,R*

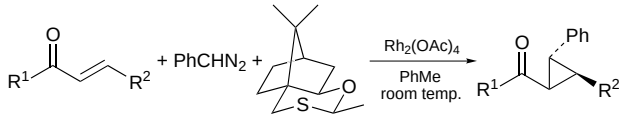
Table 1 Cyclopropanation of enones using simple sulfides



	Enone			Sulfide			
Entry	R^1	R^2	t/h[a]	n	Equiv.	Yield (%)[b]	Isomeric ratio[c]
1	Ph	Ph	3	1	1.0	40	1 : 1
2	Me	Ph	3	1	1.0	41	1 : 1
3	Ph	Ph	3	2	1.0	92	4 : 1
4	Me	Ph	3	2	1.0	80	4 : 1
5	Ph	Me	12	2	1.0	65	1 : 1 : 1
6	Me	Me	12	2	1.0	55	1 : 1 : 1
7	Ph	Ph	12	2	0.2	70	4 : 1
8	Me	Ph	12	2	0.2	82	4 : 1
9	Ph	Me	12	2	0.2	50	1 : 1 : 1
10	Me	Me	12	2	0.2	30	1 : 1 : 1

[a] Addition of $PhCHN_2$ using syringe pump. [b] Yield of *cis* and *trans* isomers. [c] Ratios determined by NMR spectroscopy.

Table 2 Cyclopropanation of enones using sulfide **1**



1

Entry	Enone R¹	Enone R²	*t*/h[a]	Sulfide (equiv.)	Yield (%)[b]	Isomeric ratio[c]	Ee (%)[d]	$[\alpha]_D^{25}$[e]
1	Ph	Ph	12	1.0	60	4 : 1	97[f]	−136
2	Ph	Ph	12	0.2	38	4 : 1	97[f]	−136
3	Me	Ph	12	1.0	55	4 : 1	> 98[g]	− 65
4	Me	Ph	12	0.2	14	4 : 1	> 98[g]	− 65

[a] Addition of $PhCHN_2$ using syringe pump. [b] Yield of *cis* and *trans* isomers. [c] Ratio determined by NMR spectroscopy. [d] Determined using HPLC (see footnote §). [e] Conditions: c = 1, CH_2Cl_2. [f] Retention times: (*R*,*R*) enantiomer, 4.41 min; (*S*,*S*) enantiomer, 4.70 min. [g] Retention times: (*R*,*R*) enantiomer, 6.10 min; (*S*,*S*) enantiomer, 6.68 min.

isomer by analogy with the epoxidation[14] and the aziridination[16] processes. In these latter cases similarly high enantioselectivity was obtained (93–97% ee) for epoxides[14] and aziridines[16] and proof of their absolute stereochemistry (*R*,*R*) was obtained.

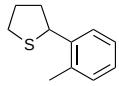
In conclusion we have developed a process for the catalytic asymmetric cylopropanation of enones, using a camphor-derived sulfur ylide which shows exceptionally high levels of enantioselectivity. We are currently extending the scope of this reaction.

Footnotes and References

* E-mail: v.aggarwal@sheffield.ac.uk

† Competetive experiments between PhCHO, chalcone and substoichiometric amounts of ylide yielded epoxide only, indicating that aldehydes were much more reactive than enones towards benzylfulfonium ylide.

‡ Sulfide **I** was formed in 20% yield as a result of ylide equilibration and Sommelet–Hauser rearrangement from the reaction. Ylide equilibration and rearrangement has been reported (refs. 19–21).



I

§ A typical procedure for asymmetric cyclopropanation reaction: Chalcone (0.5 mmol), oxathiane **1** (0.5 mmol) and $Rh_2(OAc)_4$ (1 mol%) were dissolved in toluene (0.5 ml) under N_2. A solution of phenyldiazomethane in toluene (1.5 mmol) was added over 12 h *via* an inverted syringe pump. The crude mixture was purified by column chromatography to furnish the cyclopropane as a white solid (60%). The enantiomeric excess was determined by chiral HPLC on Hichrom column, stationary phase D-phenylglycine, using Pr^iOH–light petroleum (0.7 : 99.3) as eluent with a flow rate of 2 ml min^{-1}. The *R*,*R* enantiomer eluted at 265 s and the *S*,*S* enantiomer at 282 s.

1 H. N. C. Wong, M. Y. Hon, C. W. Tse, Y. C. Yip, J. Tanko and T. Hudlicky, *Chem. Rev.*, 1989, **89**, 165; T. Hudlicky and J. W. Reed, *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 5, p. 899.
2 J. Salaun, *Chem. Rev*., 1989, **89**, 1247.
3 V. K. Singh, A. DattaGupta and G. Sekar, *Synthesis*, 1997, 137.
4 H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, 1958, **80**, 5323.
5 H. E. Simmons, T. L. Cairns, S. A. Vladuchick and C. M. Hoiness, *Org. React.*, 1973, **20**, 1.
6 A. B. Charette and H. Juteau, *J. Am. Chem. Soc.*, 1994, **116**, 2651.
7 A. B. Charette, S. Prescott and C. Brochu, *J. Org. Chem.*, 1995, **60**, 1081.
8 D. A. Evans, K. A. Woerpel, M. M. Hinman and M. M. Faul, *J. Am. Chem. Soc.*, 1991, **113**, 726.
9 H. M. L. Davies, N. J. S. Huby, W. R. Cantrell, Jr and J. L. Olive, *J. Am. Chem. Soc.*, 1993, **115**, 9468.
10 R. E. Lowenthal and S. Masumune, *Tetrahedron Lett.*, 1991, **32**, 7373.
11 For an example of metal carbenoid addition to an electron deficient alkene, see T. Hudlicky and R. P. Short, *J. Org. Chem.*, 1982, **47**, 1522. However, in this example the reaction is intramolecular, which no doubt facilitates the process. It was also noted in this example that marginally higher yields were obtained in the presence of sulfides, suggesting the intermediacy of a sulfur ylide. We thank one of the referees for bringing this paper to our attention.
12 C. R. Johnson and C. W. Schroek, *J. Am. Chem. Soc.*, 1973, **95**, 7418.
13 S. G. Pyne, Z. Dong, B. W. Skelton and A. H. White, *J. Org. Chem.*, 1997, **62**, 2337.
14 V. K. Aggarwal, J. G. Ford, A. Thompson, R. V. H. Jones and M. Standen, *J. Am. Chem. Soc.*, 1996, **118**, 7004.
15 V. K. Aggarwal, H. Abdel-Rahman, F. Li, R. V. H. Jones and M. C. H. Standen, *Chem. Eur. J.*, 1996, **2**, 1024.
16 V. K. Aggarwal, A. Thompson, R. V. H. Jones and M. C. H. Standen, *J. Org. Chem.*, 1996, **61**, 8368.
17 E. Block, *The Chemistry of the Sulphonium Group*, ed. C. J. M. Stirling and S. Patai, Wiley, New York, 1981, p. 673.
18 I. E. Markó, *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 3, p. 913.
19 W. Ando, M. Yamada, E. Matsuzaki and T. Migita, *J. Org. Chem.*, 1972, **37**, 3791.
20 N. A. Nesmayanov and V. A. Kalyavin, *Org. Soedin. Sery*, 1980, **2**, 330 *Chem. Abstr.*, 1981, **94**, 192 063.
21 M. Yoshimine and M. J. Hatch, *J. Am. Chem. Soc.*, 1967, **89**, 5831.
22 M. Hetschko and J. Gossleck, *Chem. Ber.*, 1973, **106**, 996.

Received in Liverpool, UK, 16th June 1997; 7/04214K