Direct Asymmetric Epoxidation of Aldehydes Using Catalytic Amounts of Enantiomerically Pure Sulfides

Varinder K. Aggarwal,*,† J. Gair Ford,† Alison Thompson,†
Ray V. H. Jones,‡ and Mike C. H. Standen‡

Department of Chemistry, University of Sheffield
Sheffield S3 7HF, England
Process Technology Department
Zeneca Manufacturing Partnership, Earls Road
Grangemouth, Stirlingshire FK3 8XG, U.K.

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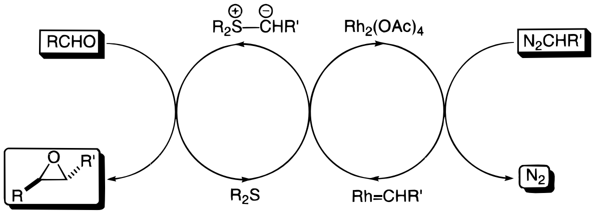
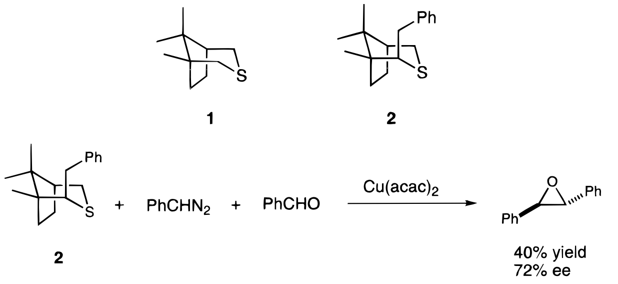
The development of catalytic methods for the synthesis of nonracemic epoxides has been a long standing goal in asymmetric synthesis.[1] Most attention has focused on the asymmetric oxidation of alkenes, and good enantioselectivities are now beginning to emerge for an increasing range of substrates.[2] Direct epoxidation of carbonyl compounds using sulfur ylides[3] has also been studied, but the process usually requires stoichiometric amounts of sulfides/sulfur ylides[4] and often only gives moderate enantioselectivities.[5] We recently described a *catalytic* process for epoxidation involving sulfur ylides which overcomes the former limitation (Scheme 1) and also described the use of sulfide **1** for the preparation of nonracemic epoxides.[5g,6] The levels of enantioselectivity were poor, and in this communication we now describe significant improvements in asymmetric induction using easily accessible chiral sulfides.

Scheme 1



Scheme 2



In our first attempts at improving enantioselectivity, we studied a more substituted analogue of **1**, as it had been previously shown by Durst that the benzyl sulfur ylide derived from sulfide **2** reacted with aldehydes to give epoxides with very high enantioselectivity.[5k,7] Sulfide **2** was prepared and tested in the catalytic cycle, but no epoxide was obtained, only stilbene.[8] However, using $Cu(acac)_2$[9] in place of $Rh_2(OAc)_4$ and employing a stoichiometric amount of the Durst sulfide **2**, we were delighted to find that epoxidation was the dominant process again (Scheme 2). The significant difference in epoxide yield using $Cu(acac)_2$ and $Rh_2(OAc)_4$ is a reflection of the difference in rate of reaction of the metal carbenoid with either the sulfide (to give ylide) or diazocompound (to give stilbene). Evidently, the copper carbenoid is less sterically hindered than the rhodium carbenoid and can therefore react with relatively hindered sulfides.[10] However, the enantiomeric excess was still only moderate,[11] so new chiral sulfides were sought. A positive feature of the Durst sulfide is that only one of the two diastereomeric lone pairs reacts with the metallocarbene, resulting in the formation of a single sulfur ylide. In the design of alternative sulfides, it was deemed important to incorporate this feature to avoid formation of diastereomeric sulfur ylides which could react with opposite enantioselectivity.[5f] A disadvantage of the Durst sulfide is that because of its lengthy synthesis it is difficult to tune the steric and/or electronic environment of the sulfur to maximize enantioselectivity. Sulfide **3** was therefore designed, as it possesses only one reactive sulfur lone pair, and, being a thioacetal, the R group is readily amenable to "tuning".

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† University of Sheffield.

‡ Zeneca Manufacturing Partnership.

(1) Besse, P.; Veschambre, H. *Tetrahedron* **1994**, *50*, 8885−8927.

(2) (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063−7064. (b) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378−4380. (c) Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron. Lett.* **1994**, *35*, 669−672. (d) Chang, S. B.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937−6938. (e) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333−9334. (f) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron: Asymmetry* **1991**, *2*, 481−494. (g) Hamada, T.; Irie, R.; Katsuki, T. *Synlett* **1994**, 479−481. (h) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189−214.

(3) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364. (b) Trost, B. M.; Melvin, L. S. *Sulfur Ylides*; Academic Press: New York, 1975. (c) Robertson, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 563−611.

(4) In one exceptional case Furukawa has carried out epoxidation using 0.5 equiv of sulfide in the presence of an alkyl halide, base, and aldehyde to give epoxide. However, the yields of the epoxides obtained were very low (<23% based on aldehyde), and he acknowledged that this was a poor method for the preparation of epoxides.[5b] We have also tried this method and concur with Furukawa. However, Dai and Huang have recently described essentially the same process for epoxidation and obtained surprisingly high yields of epoxides (>90%).[5j] This method is only applicable to non-enolizable aldehydes and has only been carried out using PhCHO, p-Me-C_6H_4CHO, and p-Cl-C_6H_4CHO. Our catalytic method can be used for both aliphatic and aromatic aldehydes and can also be applied to base sensitive aldehydes due to the neutral reaction conditions employed.[5h]

(5) (a) Trost, B. M.; Hammen, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 962−964. (b) Furukawa, N.; Sugihara, Y.; Fujihara, H. *J. Org. Chem.* **1989**, *54*, 4222−4224. (c) Breau, L.; Ogilvie, W. W.; Durst, T. *Tetrahedron. Lett.* **1990**, *31*, 35−38. (d) Solladie-Cavallo, A.; Adib, A. *Tetrahedron* **1992**, *48*, 2453−2464. (e) Solladie-Cavallo, A.; Adib, A.; Schmitt, M.; Fischer, J.; Decian, A. *Tetrahedron: Asymmetry* **1992**, *3*, 1597−1602. (f) Aggarwal, V. K.; Kalomiri, M.; Thomas, A. P. *Tetrahedron: Asymmetry* **1994**, *5*, 723−730. (g) Aggarwal, V. K.; Abdel-Rahman, H.; Jones, R. V. H.; Lee, H. Y.; Reid, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 5973−5974. (h) Aggarwal, V. K.; Abdel-Rahman, H.; Jones, R. V. H.; Standen, M. C. H. *Tetrahedron. Lett.* **1995**, *36*, 1731−1732. (i) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2557−2564. (j) Li, A. H.; Dai, L. X.; Hou, X. L.; Huang, Y. Z.; Li, F. W. *J. Org. Chem.* **1996**, *61*, 489−493. In several cases >90% ee has been obtained: (k) Breau, L.; Durst, T. *Tetrahedron: Asymmetry* **1991**, *2*, 367−370. (l) Solladie-Cavallo, A.; Diep-Vohuule, A. *J. Org. Chem.* **1995**, *60*, 3494−3498.

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(8) Diazocompounds readily dimerize in the presence of metal catalysts. Shankar, B. K. R.; Shechter, H. *Tetrahedron. Lett.* **1982**, *23*, 2277−2280.

(9) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300−3310.

(10) (a) Aggarwal V. K.; Abdel-Rahman H.; Li Fan; Jones R. V. H.; Standen, M. C. H. *Chem. Eur. J.*, in press. (b) For a review on ylide formation by this method, see: Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263−309.

(11) Durst reported that the benzylide of **2** reacted with benzaldehyde to give stilbene oxide with >96% ee. The enantioselectivity we obtained in our catalytic cycle was significantly lower (72% ee), and so we repeated Durst's original work but obtained only 71% ee. We have measured our ee's by chiral HPLC using a diode array detector to take a UV trace of the enantiomers as they elute. The UV traces of the two peaks were superimposable. Durst's ee's were determined by NMR using Eu shift reagents.

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Scheme 3

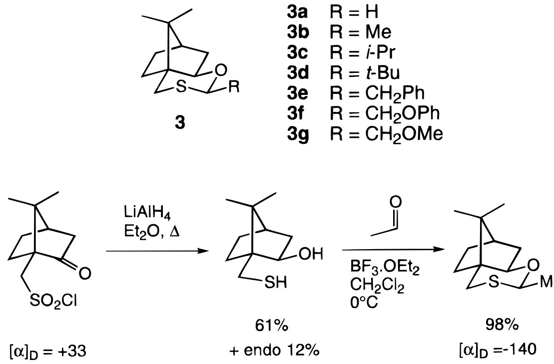
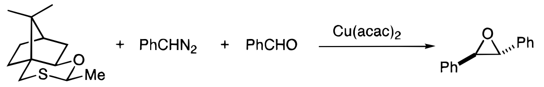


Table 1. Yields, Enantioselectivities, and Ratios of Stilbene Oxide Formed from Benzaldehyde Using 0.2 eq of Sulfides **3a**−**g**



entry	sulfide	yield %	ee %[a]	trans: cis
1	**3a**	83	41 (*R*,*R*)[b]	>98:2
2	**3b**	73	93 (*R*,*R*)[b]	>98:2
3	**3c**	45	93 (*R*,*R*)[b]	>98:2
4	**3d**	0		
5	**3e**	56	88 (*R*,*R*)[b]	>98:2
6	**3f**	43	83 (*R*,*R*)[b]	>98:2
7	**3g**	70	92 (*R*,*R*)[b]	>98:2

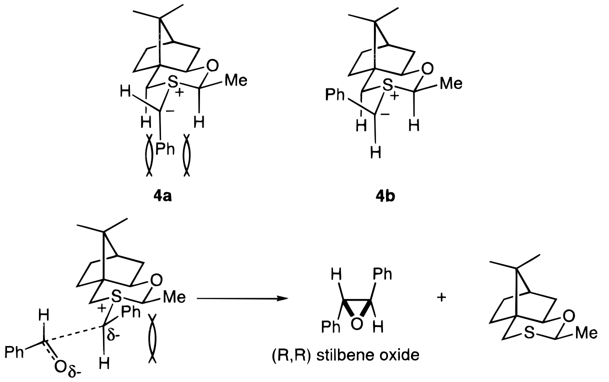
[a] Enantiomeric excess determined by chiral HPLC using a Chiralcel OD column. [b] Absolute configuration determined by comparison of [α]$_D$ values with literature values.[5b]

Table 2. Yields, Enantioselectivities, and Ratios of Epoxides Formed from Aldehydes Using 0.2 eq of Sulfide **3b**

entry	aldehyde	yield %	ee %[a]	*trans*:*cis*
1	benzaldehyde	73	93 (*R*,*R*)[b]	>98:2
2	*p*-chlorobenzaldehyde	72	92(*R*,*R*)[b]	>98:2
3	*p*-tolualdehyde	64	92(*R*,*R*)[b]	>98:2
4	cinnamaldehyde	73	89[c]	>98:2
5	valeraldehyde	35	68[c]	92:8
6	cyclohexanecarboxaldehyde	32	90[c]	70:30

[a] Enantiomeric excess determined by chiral HPLC using a Chiralcel OD column. [b] Absolute configuration determined by comparison of [α]$_D$ values with literature values.[5b] [c] Absolute configuration (*R*,*R*) assumed by analogy with entries 1−3.

Scheme 4



Sulfides **3a**−**g** were prepared as shown in Scheme 3[12] (**3b** shown; see supporting information for **3a, 3c**−**g**) and incorporated in the catalytic cycle with benzaldehyde (Table 1). It was found that high enantioselectivity could be obtained provided that the thioacetal was substituted at the 2 position (entries 2−7). Sterically hindered (entries 2, 3, 4, and 5) or electron-withdrawing groups (entries 6 and 7) resulted in lower yields in the epoxidation process. The optimum sulfide in terms of yield (73%) and enantioselectivity (93%) was **3b** (entry 2).[13,14] *This is the highest enantioselectivity yet reported for trans-stilbene oxide formation by any method and uses an easily accessible sulfide, employed in only catalytic quantities.* Sulfide **3b** was tested with a range of aldehydes, and the results are summarized in Table 2. It was found that high enantioselectivity was maintained with both aromatic and aliphatic aldehydes. Aliphatic aldehydes gave lower yields compared to aromatic aldehydes and gave a mixture of *trans* and *cis* epoxides, *whereas aromatic aldehydes only gave trans epoxides.* This contrasts with sulfides **1** and **2** in which mixtures of *trans*:*cis* epoxides were obtained with benzaldehyde.[5k]

Our mechanistic rationale for the high asymmetric induction observed is depicted in Scheme 4. The ylide can adopt two conformations **4a** or **4b**, but **4a** suffers from 1,3 diaxial interactions of the phenyl group with the axial H's. **4b** may also suffer from 1,3 interactions between the phenyl and methyl groups, but as the carbon-bearing ylide is likely to be between sp^2 and sp^3 hybridized, this interaction may be smaller than that encountered in **4a**. The aldehyde can attack either face of ylide **4b**, but the equatorial methyl group hinders *Si* face attack and hence *Re* face attack is preferred. [In the absence of this group, both faces of the ylide can be attacked, resulting in much reduced enantioselectivity (Table 1, entry 1)]. Since the *trans* epoxide is obtained, this dictates the orientation of the aldehyde as it approaches the *Re* face of the ylide (assuming an end-on approach rather than a [2 + 2] addition,[15] Scheme 4) and gives the (*R*,*R*)-epoxide.

In summary, we have discovered new conditions under which hindered sulfides can participate in our catalytic cycle for direct epoxidation of aldehydes and found simple, tuneable, chiral sulfides which give very high levels of asymmetric induction.

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Supporting Information Available: Method for the preparation and analytical data of thioacetals **3a**−**g**, method for the asymmetric epoxidation process, and assay methods for the product epoxides (7 pages). See any current masthead page for ordering and Internet access instructions.

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[12] (a) Eliel, E. L.; Frazee, W. J. *J. Org. Chem.* **1979**, *44*, 3598−3599. (b) de Lucchi, O.; Lucchini, V.; Marchioro, C.; Valle, G.; Modena, G. *J. Org. Chem.* **1986**, *51*, 1457.

[13] (a) Using stoichiometric amounts of sulfide **3b**, high yield (90%) and high enantioselectivity (93% ee) were obtained with benzaldehyde, but with 0.2 equiv of sulfide a slightly lower yield (73%) but the same enantioselectivity was obtained. To obtain reasonable yields when using substoichiometric amounts of sulfide, it was found necessary to conduct reactions at the same effective concentration of sulfide. This presumably resulted in similar rates of ylide formation and reaction with the aldehyde and therefore allowed the sulfide to be returned and recycled at the same rate as that of the stoichiometric process.

[14] While commercial Cu(acac)$_2$ worked well with sulfide **2**, no epoxide was obtained with sulfide **3b**. However, using Cu(acac)$_2$ prepared by adding saturated sodium carbonate to a suspension of copper oxide and acetylacetone in H$_2$O (see: Bryant B. E.; Fernelius W. C. *Inorg. Synth.* **1957**, *5*, 115), the yields reported in Tables 1 and 2 were obtained. The following general procedure was used in all of the reactions: To a stirred solution of sulfide **3b** (0.2 mmol), Cu(acac)$_2$ (0.05 mmol), and the aldehyde (1 mmol) in dichloromethane (0.5 mL) under nitrogen was added a solution of phenyldiazomethane (1.5 mmol in 0.5 mL of dichloromethane) at room temperature over a period of 3 h using a syringe pump. After the solution was stirred for an additional 1 h, the solvent was removed *in vacuo* and the residue was chromatographed on silica gel.

[15] It has not been established whether sulfur ylide additions to carbonyl compounds occur via a [2 + 2] cycloaddition analogous to the phosphorus ylide reaction or a head to tail addition. However, most literature examples use the head to tail addition mode to account for the stereoselectivity observed.[5c]