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The Use of Chiral Sulfides in Catalytic Asymmetric Epoxidation

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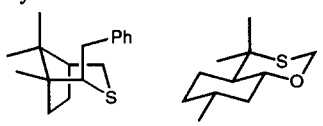
Abstract: Non racemic epoxides with ee's of 23-41% have been prepared from aldehydes and phenyl diazomethane using catalytic amounts of sulfides derived from camphor.

Non-racemic epoxides are usually prepared by catalytic asymmetric oxidation of the corresponding alkenes. Sharpless epoxidation[1] undoubtedly provides the best access to epoxides from alkenes with adjacent alcohol functionality whilst Jacobsen[2] and Katsuki[3] have independently developed strategies that utilise chiral manganese complexes as catalysts to achieve enantioselective epoxidation of non functionalised alkenes.

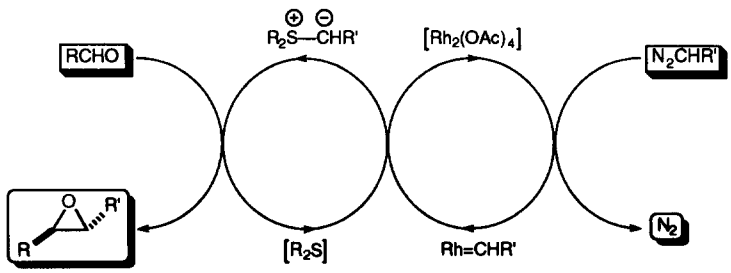
An alternative approach to the preparation of epoxides is the reaction of sulfur ylides with aldehydes and ketones.[4-6] In order to prepare non racemic epoxides, reactions of homochiral sulfur ylides with carbonyl compounds have been investigated. The best results have been achieved by Durst[7,8] and Solladie-Cavallo.[9,10] Their best results have been achieved using sulfides **1** and **2** respectively. To date, Durst has obtained the highest levels of enantioselectivity in epoxidation using sulfide **2** and various aldehydes, achieving enantiomeric excesses of 84->96% and yields of 9-38%.



1 **2**

Usually, the standard method of preparing epoxides utilising sulfur ylides[11-14] requires stoichiometric amounts of chiral sulfide precursor relative to aldehyde. This is because the process of epoxidation involves two steps. The first step is alkylation of a sulfide and subsequent isolation of the resultant sulfonium salt. The second step involves deprotonation of the sulfonium salt under basic conditions, generating sulfur ylide which then attacks the carbonyl species to give epoxide. In one exceptional case, Furukawa[15] has described the catalytic asymmetric epoxidation of aldehydes using 0.5 equivalents of sulfide in the presence of an alkyl

Scheme 1

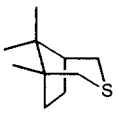


Dedicated to the memory of Professor Hidemasa Takaya, deceased on 5 October 1995

halide and base. However, the yields of epoxide were low and the reactions were not practical.

We have recently described[16] the development of a catalytic cycle for the preparation of epoxides using only catalytic quantities (0.2 eq.) of sulfide. The cycle is based upon the generation, reaction and recycling of sulfur ylides in the presence of carbonyl compounds, thus yielding epoxides, as shown in Scheme 1.

The strategy involves generation of a sulfur ylide by nucleophilic attack of a sulfide on a metallocarbene which is itself formed by reaction of metal salt with a diazocompound. The ylide thus forms with regeneration of metal. Sulfur ylide then reacts with a carbonyl compound to yield an epoxide and regenerate sulfide. Consequently, catalytic amounts of metal salt and sulfide are sufficient to obtain good yields of epoxide. The use of a chiral sulfide has resulted in the formation of non-racemic epoxides.[16] For example, catalytic amounts of sulfide **3** resulted in a 62% yield of trans-1,2-diphenyl oxirane with an enantiomeric excess of 11%.



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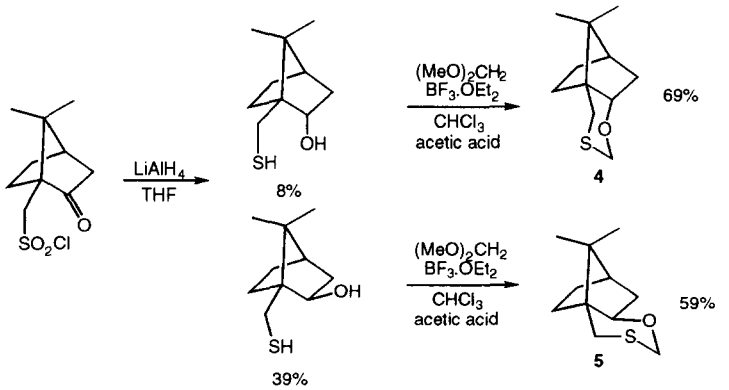
As the enantiomeric excess was low, other chiral sulfides were used in the catalytic cycle. Sulfur ylides derived from sulfide **1** were known to give epoxides with higher enantioselectivity [7,8] and so these were prepared and tested. However, no epoxide was isolated under the reaction conditions we employed; only *cis* and *trans* stilbenes were obtained. Evidently, the sulfide is too hindered to effectively intercept the carbenoid and alternative reactions occur. Consequently, we needed to develop less hindered, but chiral sulfides, for use within the catalytic cycle.

To obtain higher enantiomeric excess, it was recognised that the two groups attached to sulfur needed to be more dissimilar. Thus chiral sulfides **4** and **5** were chosen for study and were easily prepared in two steps. Reduction of (+)-(10)-camphorsulfonyl chloride with lithium aluminium hydride gave a mixture of the *endo* and *exo* products, as shown in Scheme 2.

Scheme 2



The thiols were separated by chromatography before cyclisation, using dimethoxymethane in the presence of boron trifluoride etherate and glacial acetic acid, giving sulfides **4** and **5**.

The chiral sulfides **4** and **5** were then used in our epoxidation cycle to prepare stilbene oxide. Typically, sulfide (1mmol or 0.2 mmol) and rhodium acetate (0.01mmol) were stirred at room temperature in 4ml dichloromethane. Benzaldehyde (1mmol) was then added, before the addition of phenyl diazomethane

(1.5mmol) in 6 ml dichloromethane over 24 hours. Previous work[16] had shown that slow addition of the diazo compound minimises the extent of potential side reactions. The results are shown in Table 1.

Table 1: Preparation of stilbene oxide using sulfides (4) and (5).

Entry	Sulfide	Equivalents of sulfide	Yield(%)[a] Ratio *trans:cis*	ee(%)[b,c]
1	(4)	1.0	55(4:1)	26(S,S)(-)
2	(4)	0.2	11(4:1)	23(S,S)(-)
3	(5)	1.0	70(10:1)	41(R,R)(+)
4	(5)	0.2	12(11:1)	41(R,R)(+)

(a) The total yield of *trans* and *cis* products is reported. (b) Enantiomeric excesses were determined by chiral HPLC using a chiralcel OD column. (c) Absolute configurations were determined by comparison of $[\alpha]_D$ values with literature values.[17]

Analysis of Table 1 reveals that the use of sulfides **4** and **5** in our cycle results in the formation of stilbene oxide. Sulfide **4** results in only moderate enantioselectivity, but sulfide **5** gives significantly improved ee's of 41% and a diastereoselectivity of 10:1.

The use of stoichiometric amounts of sulfide gives good yields of epoxide (entries 1 and 3), but as the amount of sulfide used is reduced, a notable drop in epoxide yield was observed (entries 2 and 4). Obviously with reduced amounts of sulfides, the rates of sulfur ylide formation and subsequent reactions will also be lowered and this may result in reduced yields. Therefore, in order to maintain similar rates with reduced sulfide loading it was decided to maintain the same concentration of sulfide by reducing the volume of solvent used. The reactions noted in Table 1 were carried out in a total of 10ml dichloromethane, and so when using just 0.2 equivalents of sulfide we decided to reduce the volume of solvent correspondingly to 2 ml. Under these conditions we were delighted to discover that stilbene epoxide could be prepared in 83% yield maintaining an ee of 41%. Under these new conditions, phenyl diazomethane solution could be added over three hours with no loss of epoxide yield. Encouraged by these results, a range of aldehydes were tested under these modified conditions using 0.2 equivalents of sulfide **5**. The results are shown in Table 2.

Table 2: Preparation of epoxides using 0.2 equivalents of sulfide 5.

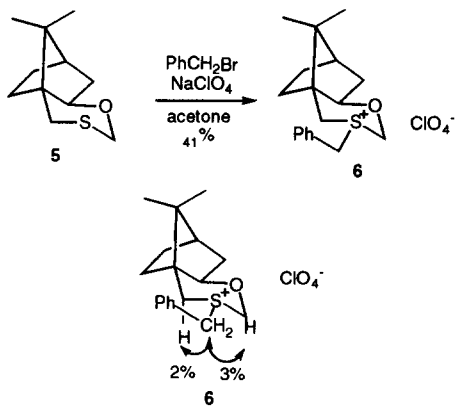
Entry	Aldehyde	Yield(%)[a] Ratio *trans:cis*	ee(%)[b,c]
1	benzaldehyde	83(7:1)	41(R,R)(+)
2	*p*-nitrobenzaldehyde	79(20:1)	34(R,R)(+)
3	*p*-chlorobenzaldehyde	59(14:1)	41(R,R)(+)
4	cyclohexanecarboxaldehyde	42(1:1)	37[d]

(a) The total yield of *trans* and *cis* products is reported. (b) Enantiomeric excesses were determined by chiral HPLC using a chiralcel OD column. (c) Absolute configurations were determined by comparison of $[\alpha]_D$ values with literatature values.[17] (d) The *cis* and *trans* isomers could not be separated. The mixture had a positive rotation.

Analysis of the results shown in Table 2 indicates that a range of aromatic and aliphatic aldehydes can be used and give epoxides with moderate to high yield and reasonable enantiomeric excess.

The origin of the enantioselectivity remains unclear at present. However we believe that a single sulfonium ylide is formed as alkylation of **5**[18] furnishes the sulfonium salt **6** (Scheme 3). The stereochemistry of **6** was confirmed by nOe studies. Irradiation of the benzylic protons gave an enhancement of the axial protons flanking the sulfide moiety, thus indicating its equatorial position and also the orientation of the phenyl group.

Scheme 3



To conclude, chiral sulfides **4** and **5**, which are easily derived from camphorsulfonyl chloride, have been used in the catalytic, asymmetric epoxidation of aldehydes giving products in good yields with reasonable enantiomeric excesses.

Acknowledgments

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Experimental

Proton and carbon-13 magnetic resonance spectra were recorded using a Bruker ACF-250 and a Bruker WH-400 (400MHz) spectrophotometer supported by an Aspect 2000 data system. Mass spectra were obtained using a Kratos MS instrument operating in E.I., C.I. mode and on a Kratos MS 80 in +ve FAB mode. Melting points (m.p.) were determined using a Kofler Hot Stage Micro Melting Point Apparatus and stand uncorrected. Enantiomeric excesses (ee) were determined by chiral HPLC using a Chiralcel OD column. Ratios of enantiomers were measured by UV monitoring at 212nm. Solvents and reagents were dried and purified prior to use according to standard procedures. Petrol refers to petroleum ether boiling range 45-60°C. Tetrahydrofuran was refluxed over potassium benzophenone under a nitrogen atmosphere until anhydrous. Benzaldehyde and benzyl bromide were distilled prior to use. Thin layer chromatography (T.L.C.) was used routinely to monitor the progress and purity of compounds. T.L.C. was performed on Merck DC-alufolien Kieselgel 60 F254 sheets containing fluorescent indicator. T.L.C. plates were visualised when possible by wavelength of 356nm ultraviolet light and by treatment with either a solution of phosphoromolybdic acid (5g in 100ml 95% absolute alcohol) or 0.5% (w/v) aqueous solution of potassium

permanganate, followed by warming of the T.L.C. plate. Chromatographic purification of compounds was achieved by medium pressure chromatography using Kieselgel 60 F254 (layer thickness 0.2mm) and on C560, 40-63 micron.

(10)-Mercaptoisoborneol and (10)-Mercaptoborneol

A solution of (+)-(10)-camphorsulfonyl chloride, $[\alpha]^{25}_D$ 32 (c 0.1 $CHCl_3$), (11.43g; 45.61mmol) in dry tetrahydrofuran (50ml) was added slowly and cautiously to a mixture of lithium aluminium hydride (3.47g; 91.12mmol) in tetrahydrofuran (50ml) at room temperature and thereafter stirred for 2 hours before being refluxed for 24 hours. The reaction mixture was then allowed to cool to room temperature. The excess hydride was quenched by the cautious addition of iced water. Stirring was continued until the evolution of gases ceased and the residues were white in colour. A large excess of ether (200ml) was then added. The precipitate was allowed to settle before the organic layer was decanted off. A large excess of ether was added a further three times, the precipitate allowed to settle and the organic layer decanted off. The organic fractions were then dried over $MgSO_4$. Removal of the solvent *in vacuo* gave the crude product which was chromatographed eluting with 98:2 petrol : ethyl acetate to give (10)-mercaptoisoborneol (3.28g; 39%) $[\alpha]^{20}_D$ −56.24 (c 5.14, $CHCl_3$). (Lit.[19] $[\alpha]^{24}_D$ -55.4 (c 10, $CHCl_3$)) and (10)-mercaptoborneol (0.65g; 8%), $\delta_H(CDCl_3)$ 0.80-2.36 (9H, m), 0.90 (6H, s), 2.52 (1H, dd, *J* 10.1), 2.73 (1H, dd, *J* 10.1), 4.31-4.39 (1H, m). (Lit. [20] $\delta_H(CDCl_3)$ 0.80-2.35 (9H, m), 0.90 (6H, s), 2.52 (1H, dd, *J* 10.1), 2.72 (1H, dd, *J* 10.1).

Oxathiane 4

A mixture of boron trifluoride etherate (0.01ml; 0.77mmol) and glacial acetic acid (0.16ml; 2.80mmol) in minimum chloroform (2ml) was stirred and refluxed under nitrogen for 15 minutes. A mixture of dimethoxymethane (0.07ml; 0.79mmol) and (10)-mercaptoborneol (0.13g; 0.70mmol) in chloroform (3ml) was then added slowly over 15 minutes. The reaction mixture was refluxed for 30 minutes, before being allowed to cool to room temperature. The reaction mixture was then washed with water (2x10ml), brine solution (2x10ml) and 10% aqueous KOH (2x10ml). The organic fraction was dried over K_2CO_3. The solvent was removed *in vacuo,* to yield the crude product which was chromatographed eluting with 85:15 petrol:ethyl acetate to produce the required oxathiane **4** (91mg; 69%), $\delta_H(CDCl_3)$ 0.72-0.90 (1H, m), 0.74 (6H, s), 0.96-1.22 (2H, m), 1.38-1.62 (2H, m), 1.91-2.13 (1H, m), 2.28 (1H, dd), 2.30-2.42 (1H, m), 2.67 (1H, d), 3.41-3.48 (1H, m), 4.67 (1H, d), 4.58 (1H, dd).(Found: M+ 198.10804, $C_{11}H_{18}SO$ requires 198.10784), m/z (+ve FAB) 198 (M^+, 100%); $[\alpha]^{25}_D$ −60 (c 0.01, $CHCl_3$).

Oxathiane 5

A mixture of boron trifluoride etherate (0.16ml; 13.2mmol) and glacial acetic acid (2.74ml; 47.85mmol) in minimum chloroform (2ml) was stirred and refluxed under nitrogen for 15 minutes. A mixture of dimethoxymethane (1.16ml; 13.2mmol) and (10)-mercaptoisoborneol (2.23g; 12.0mmol) in chloroform (5ml) was then added slowly over 15 minutes. The reaction mixture was maintained at reflux for 30 minutes, before being allowed to cool to room temperature. The reaction mixture was then washed with water (2x10ml), brine solution (2x10ml) and 10% aqueous KOH (2x10ml). The organic fraction was dried over K_2CO_3. The solvent was removed *in vacuo* to yield the crude product which was chromatographed eluting with 95:5 petrol : ethyl acetate to produce the required oxathiane **5** (1.54g; 59%) $[\alpha]^{25}_D$ −114 (c 1.0, $CHCl_3$) (Lit.[19] $[\alpha]^{24}_D$ -114.7 (c 16.4, EtOH)).

Sulfonium Perchlorate Salt 6.

Sulfide **5** (1.60g; 8.08mmol) was stirred with benzyl bromide (1.06ml; 8.89mmol) and sodium perchlorate (1.09g; 8.89mmol) in acetone (5ml) for 5 days at room temperature. The mixture was filtered, evaporated under reduced pressure and triturated with pentane to give the required sulfonium salt. Crystallisation from dichloromethane and pentane yielded the required sulfonium salt **6** (1.13g; 42%) as a single diastereoisomer. Equatorial benzylation was deduced to have taken place by analysis of N.O.E. studies. Temperature of decomposition 137°C; $[\alpha]^{20}_{D}$ –32.38 (c 0.8, $CHCl_3$); $\delta_H(CDCl_3)$ 7.35-7.55 (5H, m, Ph), 5.55 (1H, d, *J* 9), 5.37 (1H, dd, *J* 9, 2), 4.81 (1H, *J* 12), 4.71 (1H, *J* 12), 4.05-4.20 (1H, m), 3.92 (1H, d, *J* 11), 3.67 (1H, dd, *J* 11, 2.75), 1.13 (3H, s, Me), 0.92 (3H, s, Me), 0.85-1.95 (7H, m); δ_C 130.4(Ph), 130.2(Ph), 129.9(Ph), 126.7(Ph), 85.6, 78.7, 47.2, 45.5, 45.3, 44.8, 37.7, 36.7, 33.2, 27.1, 22.3, 19.9; (Found: M+ 289.162493, $C_{18}H_{25}SO$ requires 289.162612), m/z (+ve FAB) 289 (M+, 100%).

Preparation of Phenyl diazomethane[21]

To a stirred suspension of *p*-toluenesulfonhydrazide (30.2 g, 0.16 mol) in methanol (50 ml) was added benzaldehyde (16.5 ml, 0.16 mol). Dissolution of the hydrazide was followed by precipitation of a white solid. The cooled precipitate was filtered, washed with cold methanol and dried to give benzaldehyde toluene-*p*-sulfonylhydrazone (40.48 g, 0.15 mol, 91%). A solution of sodium methoxide was prepared by dissolving sodium cleaned in petrol (about 3 g, 0.13 mol) in methanol (100 ml). This solution was poured onto benzaldehyde toluene-*p*-sulfonylhydrazone (36.79 g, 0.133 mol). Upon complete dissolution the solvent was removed under reduced pressure to give a quantitative yield of benzaldehyde toluene-*p*-sulfonylhydrazone sodium salt as an off white solid. Benzaldehyde toluene-*p*-sulfonylhydrazone sodium salt (11.6 g, 0.04 mol) was pyrolised under vacuum (90-150 °C) using microdistillation apparatus to give the desired product, which was then redistilled (~20° C, 0.02 mm Hg) and dissolved in dichloromethane (about 8 ml) to give a deep red solution of phenyl diazomethane.

Determination of Concentration of Phenyl diazomethane

Phenyl diazomethane solution (50µl), as prepared above, was stirred with toluic acid (0.065g; 0.48mmol; excess) and dichloromethane (5.0ml) for 5 minutes at room temperature whereby the initial red colour gradually disappeared until the solution became colourless. The solvent was then removed *in vacuo* to yield the benzyl ester of toluic acid along with the remainder of the toluic acid which was used in excess. ^1H N.M.R. studies and subsequent integration and comparison of the benzyl signal of the ester (δ=5.27) relative to the tosyl signals of the ester and excess acid (δ=2.29-2.35) revealed the percentage of the toluic acid (14%) which had reacted with phenyl diazomethane. Since a known quantity (0.48mmol) of toluic acid had been used, it was possible to establish the concentration of the phenyl diazomethane solution (0.14 x 0.48 = 0.067) which was found to be 0.067M.

Preparation of enantiomerically enriched epoxides

General Procedure

To a stirred solution of chiral sulfide (0.2 eq.), rhodium acetate (0.01 eq.) and benzaldehyde (1 eq.) in dichloromethane (1 ml), was added a solution of phenyl diazomethane (1.5 eq.) in dichloromethane (1 ml) at room temperature over a period of three hours *via* a syringe pump. Upon completion of the addition, the solvent was removed *in vacuo* and the residue chromatographed using silica gel eluting with dichloromethane:petrol 40:60 to yield epoxide.

Reaction with benzaldehyde

Using the above method, a solution of phenyl diazomethane (1.5mmol in 1ml of dichloromethane) was added to a solution of chiral sulfide 5 (40mg; 0.2mmol), rhodium acetate (4mg; 0.01mmol) and benzaldehyde (101µl; 1.0mmol) in dichloromethane (1ml). Chromatography yielded *trans*-1,2-diphenyl oxirane (147mg, 74%), $[\alpha]^{25}_D$ +131 (c 0.1 EtOH) and *cis*-1,2-diphenyl oxirane (20mg, 9%).

Reaction with *p*-nitrobenzaldehyde

Using the above method, a solution of phenyl diazomethane (1.13mmol in 0.75ml of dichloromethane) was added to a solution of chiral sulfide 5 (30mg; 0.15mmol), rhodium acetate (4mg; 0.008mmol) and *p*-nitrobenzaldehyde (181mg; 0.75mmol) in dichloromethane (0.75ml). Chromatography yielded *trans*-1-*p*-nitrophenyl-2-phenyl oxirane (143mg, 79%), $[\alpha]^{25}_D$ +84 (c 0.1 EtOH).

Reaction with *p*-chlorobenzaldehyde

Using the above method, a solution of phenyl diazomethane (1.5mmol in 1ml of dichloromethane) was added to a solution of chiral sulfide 5 (40mg; 0.2mmol), rhodium acetate (4mg; 0.01mmol) and *p*-chlorobenzaldehyde (141mg; 1.0mmol) in dichloromethane (1ml). Chromatography yielded *trans*-1-*p*-chlorophenyl-2-phenyl oxirane (127mg, 55%), $[\alpha]^{20}_D$ +110 (c 0.1 EtOH)) and *cis*-1-*p*-chlorophenyl-2-phenyloxirane (9mg, 4%).

Reaction with cyclohexanecarboxaldehyde

Using the above method, a solution of phenyl diazomethane (1.5mmol in 1ml of dichloromethane) was added to a solution of chiral sulfide 5 (40mg; 0.2mmol), rhodium acetate (4mg; 0.01mmol) and cyclohexanecarboxaldehyde (141mg; 1.0mmol) in dichloromethane (1ml). Chromatography yielded an inseperable mixture of *trans*-1-cyclcohexane-2-phenyl oxirane and *cis*-1-cyclohexane-2-phenyloxirane (84mg, 42%). $[\alpha]^{20}_D$ +8 (c 0.1 $CHCl_3$). The *trans* isomer had an ee of 37%.

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