Developments in the Simmons–Smith-Mediated Epoxidation Reaction

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Dedicated to Prof. Jean F. Normant on the occasion of his 65th birthday

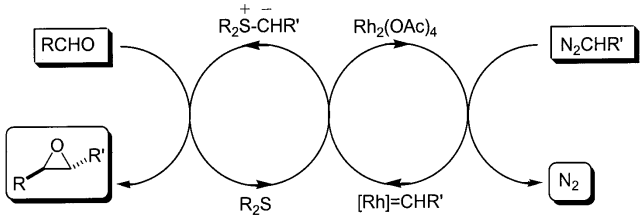
Keywords: Aziridines / Bisoxazolines / Carbenoids / Sulfur / Terminal epoxides / Ylides / Zinc

The reaction between Et_2Zn, $ClCH_2I$, sulfide, and aldehyde furnishes terminal epoxides in high yields. The reaction occurs via a zinc carbenoid, which reacts with the sulfide to furnish an ylide, which in turn reacts with the aldehyde to give the epoxide. Chiral ligands capable of chelation to zinc [1,2-amino alcohols, amino acids, bis(oxazolines), taddols] were examined, but only low enantioselectivity was observed (up to 11% *ee*). A number of chiral sulfides were also examined, but again only low enantioselectivity was observed (up to 16% *ee*). However, linking a sulfide to a metal capable of chelation to zinc [a bis(oxazoline) bearing a sulfide at the 5 position] produced a reagent that gave up to 54% *ee* in the epoxidation process. The same system was applied to the preparation of terminal aziridines from imines. The optimum group on nitrogen was a sulfonyl group, although groups capable of chelation of zinc (*o*-methoxyphenyl) were also effective. Attempts to render the aziridination process asymmetric by using the above strategy were less successful (up to 19% *ee*).

Introduction

Although there are a number of excellent methods for the asymmetric synthesis of epoxides by alkene oxidation, few are effective for the preparation of enantiopure terminal epoxides. The notable methods of Jacobsen[1] and Shi[2] provide only moderate levels of asymmetric induction for unfunctionalised terminal alkenes. In an isolated example, styrene oxide was produced in 88% yield and 86% *ee* by use of a (salen)Mn-based system prepared at −78 °C with a mixture of *m*CPBA and *N*-methylmorpholine *N*-oxide as oxidant.[3] By far the most efficient method for preparing enantiopure terminal epoxides is by kinetic resolution through ring-opening reactions with H_2O[4] or $TMSN_3$.[5]

Asymmetric epoxidation of carbonyl compounds by treatment with chiral sulfur ylides provides a complementary route to epoxides.[6] This method traditionally involved two steps: firstly alkylation of a sulfide and isolation of the sulfonium salt, followed by treatment with base in the presence of a carbonyl compound. We have reported a catalytic version of this process, which operated under neutral conditions (Scheme 1). When camphor-derived sulfides were employed, epoxides were obtained in high yields and with high enantioselectivities.[7] The process has been rendered more practical and amenable to scale-up by in situ generation of the diazo compound.[8] All attempts to extend this methodology to the synthesis of terminal epoxides by using diazomethane were unsuccessful and so we considered alternative methods for generating the intermediate metallocarbene. Whilst samarium,[9] aluminium,[10] and magnesium[11–13] carbenoids were all unsuccessful, we discovered that zinc carbenoids, generated from Et_2Zn and $ClCH_2I$,[14] efficiently transferred a methylene group to a sulfide[15] and in the presence of aldehydes furnished epoxides in good yields[16] (Scheme 2). We also reported that chiral and base-sensitive aldehydes could be converted into epoxides in high yield without any degree of racemisation.[16] In this paper we describe further developments,



Scheme 1. Application of organorhodium reagents to epoxidation

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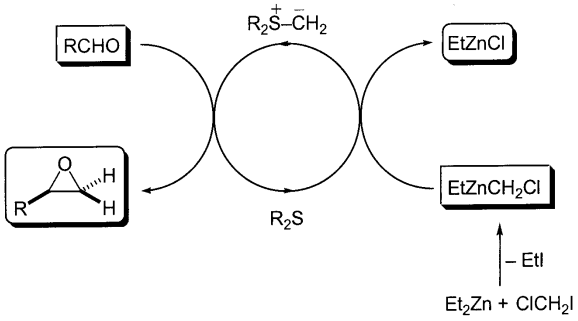
and in particular our attempts to render the process asymmetric.

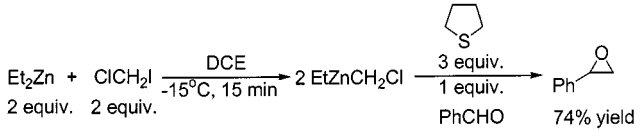


Scheme 2. Application of organozinc reagents to epoxidation

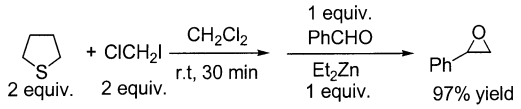
Results and Discussion

Improving the Catalytic Process

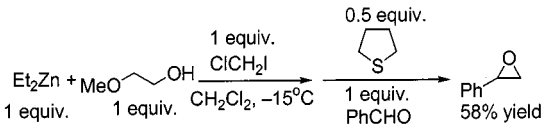
A representative example of the original process is depicted in Scheme 3. The unstable zinc carbenoid was generated at −15 °C (15 min) and the sulfide and aldehyde were then added. A threefold excess of the sulfide was required in order to obtain good yields. Ultimately it was hoped that chiral sulfides would render the epoxidation process asymmetric and so we wished to reduce the sulfide loading. It was reasoned that this could be achieved by trapping the unstable zinc carbenoid as it was formed; that is, by forming the Simmons−Smith reagent in the presence of sulfide. Indeed, a change in the order of addition of the reagents allowed quantitative conversion into styrene oxide in the presence of 2 equiv. of sulfide (Scheme 4). However, reducing the sulfide loading below 2 equiv. suppressed epoxidation. This indicated that a significant amount of the sulfide was not available for ylide formation, and was, perhaps, complexed with zinc. Bidentate ligands, when employed as additives, should compete effectively with the sulfide for coordination sites on zinc and thus allow lower sulfide loadings to be employed. We screened a range of bidentate ligands and found that a marginal improvement was observed when methoxyethanol was used; it was possible to obtain epoxide in 58% yield with 50 mol % sulfide (Scheme 5). The results shown in Schemes 4 and 5 indicate that zinc carbenoids can be efficiently generated *in the presence of sulfides and from ethylzinc alkoxides.* In contrast, Denmark[17a] has reported that ethylzinc alkoxides are poor reagents for cyclopropanations as they do not react effectively with $ClCH_2I$. Taken together, the implication is that the sulfide aids formation of the zinc carbenoid.



Scheme 3. Original method for epoxidation



Scheme 4. Improved method for epoxidation



Scheme 5. Addition of chelating ligands to reduce sulfide loading

No epoxidation was observed when CH_2I_2 was employed as carbene precursor under the improved conditions. This may be due to the higher reactivity of the (chloromethyl)-zinc reagent.[17]

Development of the Asymmetric Process

(i) The Use of Chiral Ligands

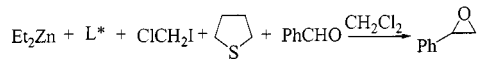
We reasoned that asymmetric induction might be achieved by the use of chiral ligands complexed to the metal ion. It is feasible that nucleophilic attack of the ylide upon the aldehyde occurs with some degree of complexation of the metal ion either to the aldehyde, or the ylide, or indeed both. The epoxidation reaction was performed in the presence of simple, readily available, chiral ligands and the results are summarised in Table 1. Again, the formation of a zinc−alkoxide bond resulted in high yields of epoxide (Entries 1 and 2). Non-racemic styrene oxide was produced in the majority of cases, albeit with low *ee* values. This demonstrates that the zinc ion is involved in the enantiodifferentiating step, but that the chiral ligands may be too remote from the reaction site to induce high levels of asymmetric induction. In view of these results, further research was directed towards the use of chiral sulfides.

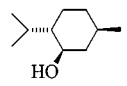
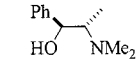
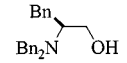
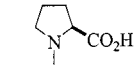
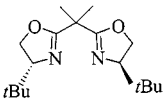
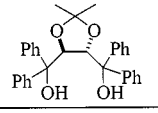
(ii) The Use of Chiral Sulfides

High enantioselectivities (> 80% *ee*) can be obtained in the transfer of benzylidene groups to carbonyl compounds using (2*R*,5*R*)-dimethylthiolane.[18] In contrast, only low enantioselectivities are observed in the transfer of a methylidene group with the same chiral sulfide.[19] It was expected that the zinc-based ylide chemistry would give different, and potentially higher, levels of asymmetric induction. A series of structurally diverse chiral sulfides was thus prepared[20] (Scheme 6) and tested in the epoxidation reaction; the results are summarised in Table 2.

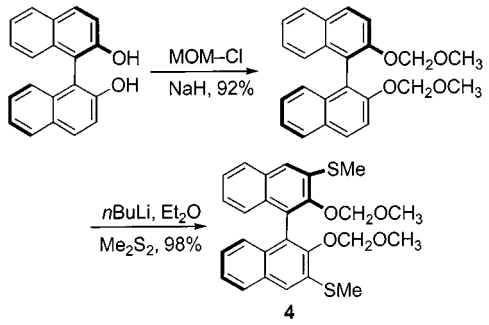
In the presence of (2*R*,5*R*)-dimethylthiolane (**1**) (Table 2, Entry 1), benzaldehyde was epoxidised with higher enantioselectivity (12%) than obtained by conventional Corey−Chaykovsky sulfur ylide chemistry (0% *ee*).[19] When methionine methyl ester (Table 2, Entry 2) and the camphor-derived sulfide **3** (Table 2, Entry 3) were employed, only traces of epoxide were detected. Given the thiophilicity of zinc,[21] it is probable that, in the case of

Table 1. Addition of chiral ligands



Entry	L*	% *ee*[a]	% Yield[b]
1		11 (*R*)	95
2		11 (*S*)	98
3		8 (*S*)	50
4		2	55
5		0	40
6[c]		13 (*R*)	68

[a] Determined by chiral gas chromatography (α-cyclodextrin column). [b] estimated by GC. [c] 1 equiv. of L* was employed.



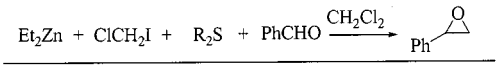
Scheme 6. Preparation of sulfide **4**

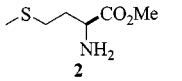
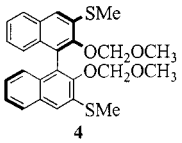
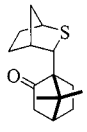
methionine, the sulfide is strongly bound to the metal ion through bidentate chelation and that ylide formation is inhibited as a result. The lack of epoxide formation when camphor-derived sulfide **3** was used was probably due to hydrolysis of the thioacetal, as the sulfide could not be reisolated from the reaction.

Sulfides **4** and **5**, containing acetals in which the sulfur was not linked to the acetal moiety, gave high epoxidation yields. In these cases, however, as with sulfide **6**, low enantioselectivities were observed. As sulfides **1** and **6** gave 0% *ee* in conventional Corey–Chaykovsky sulfur ylide chemistry, the measurable enantioselectivity observed in the zinc process suggests that the zinc ion is associated with the ylide prior to reaction and remains in close proximity during the course of the reaction (Scheme 7).

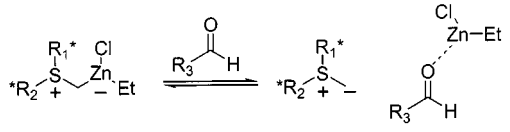
To control the spatial arrangement of the zinc species relative to the ylide, we decided to link the sulfide to a ligand capable of binding the metal ion. Bis(oxazolines) seemed

Table 2. Addition of chiral sulfides



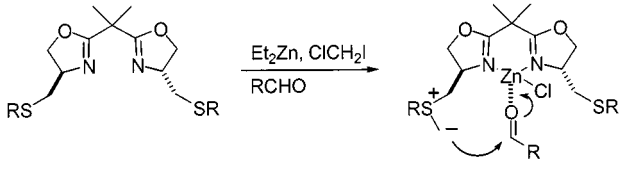
Entry	Sulfide	% *ee*[a]	% Yield[b]
1[c]	 **1**	12 (*R*)	95
2[d]	 **2**	0	<5
3[e]	 **3**	0	<5
4[e]	 **4**	4 (*R*)	86
5[c]	 **5**	11 (*R*)	72
6[c]	 **6**	16 (*S*)	93

[a] Determined by chiral gas chromatography (α-cyclodextrin column). [b] Estimated by GC. [c] $R_2S/Et_2Zn/ClCH_2I/PhCHO$ (3:2:2:1) employed, see Exp. Sect. [d] $R_2S/Et_2Zn/ClCH_2I/PhCHO$ (1:1:1:1) employed, see Exp. Sect. [e] $R_2S/Et_2Zn/ClCH_2I/PhCHO$ (2:2:2:1) employed, see Exp. Sect.



Scheme 7. Association between the sulfur ylide and the metal ion

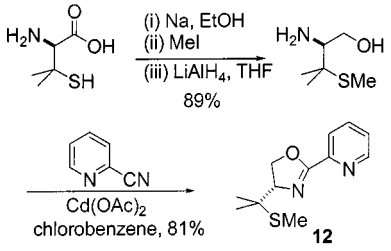
ideal ligands for this purpose, as they are known to complex metal ions and can readily be functionalised to incorporate a sulfide moiety.[22] If the metal ion were also to complex the aldehyde, the sulfur ylide reaction would become a pseudo-intramolecular process and potentially afford much higher levels of selectivity (Scheme 8).



Scheme 8. Proposed reaction pathway

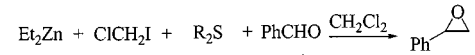
A range of oxazolines and bis(oxazolines) were prepared by conventional routes[22] (Scheme 9) and tested in the

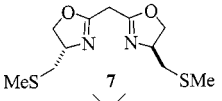
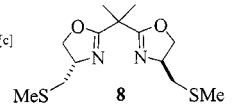
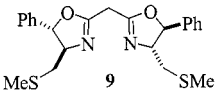
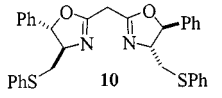
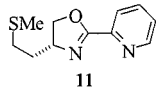
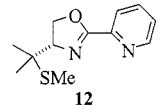
epoxidation process (Table 3). The use of pyridine-containing oxazolines **11** and **12** (Entries 5 and 6) provided styrene oxide in the highest yields, but with low enantioselectivities. When bis(oxazoline) **10** (Entry 4) was employed, the enantioselectivities were much improved (47%) but yields were only moderate (54%). The sulfur ylide derived from bis(oxazoline) **10** was also found to epoxidise cyclohexanecarboxaldehyde (Entry 4) with good levels of asymmetric induction. The enantioselectivities obtained with bis(oxazoline) **10** are the highest reported to date for this type of process (methylidene transfer).



Scheme 9. Preparation of sulfide **12**

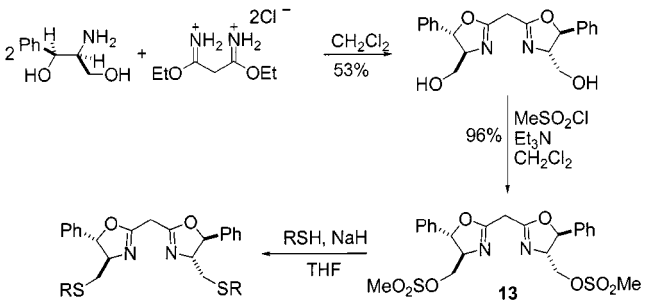
Table 3. Addition of chelating sulfides



Entry	Sulfide	% *ee*[a]	% Yield[b]
1	 **7**	13 (*S*)	16
2[c]	 **8**	3 (*S*)	35
3	 **9**	0	15
4	 **10**	47 (*S*) 54	54 30[d]
5	 **11**	4 (*S*)	98
6	 **12**	13 (*R*)	98

[a] Determined by chiral gas chromatography (α-cyclodextrin column). [b] Estimated by CG. [c] 1.4 equiv. of R_2S was employed. [d] Using $C_6H_{11}CHO$ in place of PhCHO.

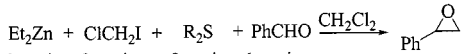
Analogues of **10** were synthesised (Scheme 10), but no improvements either in yield or in enantioselectivity were observed (Table 4). The low yields of epoxide observed with sulfides **15** and **17** are attributed to the reduced nucleophilicity of sulfur, which results from the electron-withdrawing group on the aromatic ring (NO_2) and the bulky *tert*-butyl substituent, respectively.

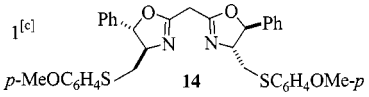
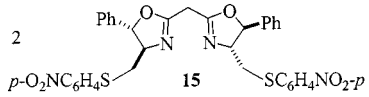
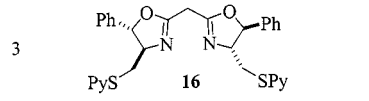
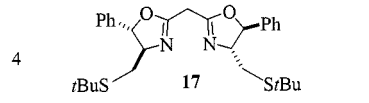


R = *p*-$MeOC_6H_4$ **14** (91%)
p-$NO_2C_6H_4$ **15** (53%)
Py **16** (75%)
*t*Bu **17** (95%)

Scheme 10. Preparation of bis(oxazoline)-based sulfides

Table 4. The effect of thio substitution in sulfide **10**



Entry	Sulfide	% *ee*[a]	% Yield[b]
1[c]	 **14**	38 (*S*)	21
2	 **15**	22 (*S*)	7
3	 **16**	10 (*S*)	30
4	 **17**	16 (*R*)	<5

[a] Determined by chiral gas chromatography (α-cyclodextrin column). [b] Estimated by ^1H NMR. [c] $R_2S/Et_2Zn/ClCH_2I/PhCHO$ (1:1:1:1) employed.

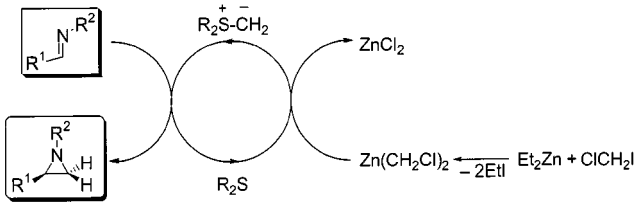
Further Studies and Mechanism

A proton NMR of the complex formed on mixing diethylzinc with **10** in $CDCl_3$ revealed that a proton from the methylene bridge was removed to give a delocalised structure. The singlet corresponding to the methylene bridge ($\delta = 3.6$) disappeared and was replaced by another singlet which was significantly shifted downfield ($\delta = 4.4$). Unfortunately, we were unable to detect the zinc carbenoid, as a mixture of products was obtained upon addition of $ClCH_2I$.

Application to Aziridination

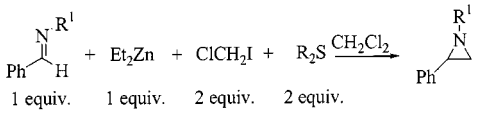
We recently reported that the Simmons−Smith reagent can also be applied to a novel process for preparing ter-

minal aziridines from imines (Scheme 11).[23] Imines derived from aromatic and aliphatic aldehydes worked well, as did the imine derived from glyceraldehyde acetonide.[23] We therefore tested a limited range of chiral sulfides, including bis(oxazoline) **10**, in the process (Table 5). As with epoxidation, high yields were obtained but enantioselectivity was poor even with sulfide **10**. This observation may reflect the poorer ability of the *N*-tosylimine to bind to zinc, thereby resulting in an "intermolecular" process.



Scheme 11. Application of organozinc reagents to aziridination

Table 5. Application of chiral sulfides to aziridination



Entry	R^1	Sulfide	% *ee*[a]	% Yield[b]
1	SO_2-C_6H_4-Me	**1**	17	69[c]
2	SO_2-C_6H_4-Me	**6**	9	82
3	SO_2-C_6H_4-Me	**10**	7	37
4	*o*-MeO-C_6H_5	**1**	19	70[d]

[a] Determined by chiral HPLC. [b] Isolated yield. [c] *N*-Benzyl-*p*-toluenesulfonamide also isolated (31%). [d] Determined by ^{1}H NMR.

Conclusions

Our preliminary communication[16] described a neutral, mild and general method for the preparation of terminal epoxides. Base-sensitive aldehydes were tolerated and those prone to racemisation underwent epoxidation without loss of optical purity. Valuable mechanistic insights have been obtained, notably the demonstration that the zinc ion is intimately involved in the epoxidation, even in cases in which the putative ylide is not bound to the metal, and also the discovery that sulfide stoichiometry can be reduced when coordinating functional groups are present, either within the sulfide structure or as chelating additives. We have found that sulfur ylides generated from Simmons−Smith reagents display lower reactivity than do ylides prepared by conventional means. This difference in behaviour was attributed to the formation of a zinc-complexed ylide.

Attempts to render this process asymmetric were only partially successful. The use of simple chiral ligands or simple chiral sulfides afforded epoxides only with low enantioselectivity. However, use of sulfides tethered to bisoxazolines gave significant improvements. When sulfide **10** was employed, both an aromatic and an aliphatic aldehyde were epoxidised with enantioselectivities of up to 54%. These enantiomeric excesses are the highest reported for the preparation of terminal epoxides by a sulfonium ylide mediated process. Further studies to improve the enantioselectivity are continuing.

Experimental Section

General: Nuclear magnetic resonance spectra were recorded with a Bruker ACF 250 instrument supported by an Aspect 2000 data system. Chemical shifts (δ_H) are quoted in ppm and are referenced relative to the residual proton signal of the deuterated solvent. Coupling constants (*J*) are measured in Hz. The following abbreviations are used for splitting patterns: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad. ^{13}C NMR were recorded using the JMOD pulse sequence and are referenced relative to the central ^{13}C signal of deuterated chloroform at δ = 77.0. Chemical shifts (δ_C) are recorded in ppm and are assigned as s, d, t, q for C, CH, CH_2, and CH_3 respectively. Elemental microanalyses were obtained by using a Perkin−Elmer 2400 Elemental CHN analyser; classical wet analysis was performed for anions (S). Mass spectra were obtained by using either a Kratos MS 25 or an MS 80 spectrometer supported by a DS 55 data system, operating in EI or positive FAB mode. Infrared spectra were recorded in the 4000−600 cm^{-1} range with a Perkin−Elmer 157G Grating FT-IR spectrophotometer. Optical rotations ($[\alpha]_D^{22}$) were recorded with a Perkin−Elmer 141 automatic polarimeter and are given in 10^{-1} $deg{\cdot}cm^2{\cdot}g^{-1}$. For epoxidation, enantiomeric excesses were determined by chiral GC (30-m α-cyclodextrin column). Styrene oxide (20 p.s.i. carrier pressure, 100 °C iso) R_T = 6.1 min (*S*), 6.3 min (*R*). Cyclohexyloxirane (16 p.s.i. carrier pressure, 45 °C iso) R_T = 51.6, 52.8 min. Ratios of benzaldehyde/styrene oxide were judged from integration of styrene oxide (vide ultra) versus benzaldehyde R_T = 3.2 min. The enantiomeric excess of *N*-(*p*-tolylsulfonyl)-2-phenylaziridine was determined by chiral HPLC (25-cm/4.6-mm Chiralcel OJ column); hexane/2-propanol (50:50, v/v), 0.7 $mL{\cdot}min^{-1}$, λ = 227 nm, R_T = 18.0, 23.7 min. The enantiomeric excess of 1-[2-methoxyphenyl]-2-phenylaziridine was determined by chiral HPLC (25-cm/4.6-mm Chiralcel OD column); hexane/2-propanol (99.5:0.5, v/v), 1 $mL{\cdot}min^{-1}$, λ = 240 nm, R_T = 18.7, 24.1 min.

Materials: Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Benzaldehyde and cyclohexanecarboxaldehyde were distilled under nitrogen prior to use. Diethyl ether and tetrahydrofuran were distilled under nitrogen from sodium benzophenone ketal and potassium benzophenone ketal, respectively. Tetrahydrothiophene and dichloromethane were dried over calcium hydride, then distilled, under nitrogen, before use. Diethylzinc was either used as a 1.1 M solution in toluene (Aldrich) or as a 1 M solution in hexanes (prepared in domo). All reactions involving diethylzinc were executed under dry argon, using oven-dried and/or flame-dried glassware that had been repeatedly evacuated and purged with argon, in efficiently degassed solvents. Flash column chromatography employed silica gel (BDH 40−63 μm). The term petroleum ether refers to the fraction with b.p. 40−60 °C.

Original Procedure for the Epoxidation of Benzaldehyde: Chloroiodomethane (0.14 mL, 2.0 mmol) was added to a stirred solu-

tion of diethylzinc (1.1 M solution in toluene, 1.8 mL) in 1,2-dichloroethane (6.0 mL) at −15 °C under nitrogen. After 15 min, tetrahydrothiophene (0.26 mL, 3.0 mmol) and benzaldehyde (0.1 mL, 1.0 mmol) were added. The reaction mixture was allowed to warm to room temperature, stirred for 48 h, and then diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography, eluting with petroleum ether/EtOAc (9:1, v/v), to afford styrene oxide as a colourless oil (78 mg, 74%). ^{1}H NMR (250 MHz. $CDCl_3$): δ = 2.85 (1 H, dd, J = 5.0 and 3.0 Hz, C*H*H′O), 3.30 (1 H, dd, J = 5.0 and 4.5 Hz, CH*H*′O), 3.85 (1 H, dd, J = 4.5 and 3.0 Hz, CHO), 7.25 (5 H, m, ArH).

Revised Stoichiometry and Order of Addition (Scheme 4)**:** Chloroiodomethane (0.15 mL, 2.0 mmol) was added to a stirred solution of tetrahydrothiophene (0.18 mL, 2.0 mmol) in CH_2Cl_2 (5 mL) at room temperature under argon. After 30 min, benzaldehyde (0.10 mL, 1.0 mmol) was added, followed by Et_2Zn (1.0 M in hexanes, 1.0 mL). After 16 h, the reaction mixture was treated with water (10 mL), extracted into CH_2Cl_2 (3 × 10 mL) and dried ($MgSO_4$). The combined organic extracts were filtered through a plug of silica (2 × 5 cm) and the solvents were evaporated to dryness. Purification by flash chromatography, eluting with petroleum ether/CH_2Cl_2 (1:1, v/v), gave styrene oxide as a colourless oil (0.12 g, 97%).

Procedure for Ligand-Assisted Epoxidations (Scheme 5)**:** 2-Methoxyethanol (0.08 mL, 1.0 mmol) was added to a solution of Et_2Zn (1.0 M in hexanes, 1.0 mL) in CH_2Cl_2 (5 mL). The solution was cooled to −15 °C and chloroiodomethane (0.07 mL, 1.0 mmol) was added. After 10 min, tetrahydrothiophene (0.045 mL, 0.50 mmol) was added, followed by benzaldehyde (0.1 mL, 1.0 mmol). After 16 h at room temperature, the reaction mixture was treated with saturated aqueous $NaHCO_3$ (5 mL), extracted into CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), and analysed by GC.

Procedure for Attempted Epoxidations with Chiral Sulfides 2 and 3: Et_2Zn (1.1 M in toluene, 1.0 mL) was added to a stirred solution of methionine methyl ester (0.16 g, 1.0 mmol) [liberated from methionine methyl ester hydrochloride with sodium carbonate as a heterogeneous mixture in CH_2Cl_2, dried (Na_2SO_4), and concentrated immediately prior to use] in CH_2Cl_2 (5 mL). The solution was cooled to 0 °C and chloroiodomethane (0.07 mL, 1.0 mmol) was added. After 10 min, benzaldehyde (0.1 mL, 1.0 mmol) was added and the reaction mixture was allowed to warm to ambient temperature. After 16 h, the reaction mixture was treated with saturated aqueous $NaHCO_3$ (5 mL), extracted into CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), and analysed by GC.

Procedure for Epoxidations with Chiral Sulfides 1, 5, and 6: Chloroiodomethane (0.07 mL, 1.0 mmol) was added to a solution of diethylzinc (1.1 M solution in toluene, 1.0 mL) in CH_2Cl_2 (3 mL) at 0 °C under argon. After 10 min, a solution of (2*R*,5*R*)-dimethylthiolane (0.17 g, 1.5 mmol) in CH_2Cl_2 (2 mL) was added, followed by benzaldehyde (0.05 mL, 0.5 mmol), and the mixture was allowed to warm to ambient temperature. After 16 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and the products were extracted into CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was filtered through a plug of silica (2 × 5 cm) and analysed by GC.

Procedure for Epoxidation with Chelating Sulfides 7, 8, 9, and 11: Chloroiodomethane (0.07 mL, 1.0 mmol) was added at 0 °C to a solution of Et_2Zn (1.1 M in toluene, 1.1 mmol) in CH_2Cl_2 (2 mL). After 10 min, a solution of sulfide (1.0 mmol) in CH_2Cl_2 (2 mL) was added, followed after 2 min by benzaldehyde (0.05 mL, 0.50 mmol). The reaction mixture was allowed to warm to ambient temperature over 16 h and then treated with saturated aqueous $NaHCO_3$ (10 mL). The products were extracted into CH_2Cl_2 (3 × 20 mL), dried (Na_2SO_4), and analysed by GC.

Optimised Procedure for the Epoxidation with Chelating Sulfides (Table 2, Entry 4; Table 3, Entries 4 and 6; Table 4)**:** A solution of sulfide **10** (0.3 g, 0.5 mmol) in CH_2Cl_2 (2.5 mL) was added to a flask containing diethylzinc (1 M solution in hexanes, 0.5 mL) at 0 °C under argon. After 10 min, chloroiodomethane (0.04 mL, 0.50 mmol) and benzaldehyde (0.025 mL, 0.250 mmol) were added. The mixture was allowed to warm to room temperature and stirred for 16 h, then quenched with saturated aqueous NH_4Cl (5 mL). Products were extracted into CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), and concentrated to dryness. The crude residue was filtered through a plug of silica (2 × 5 cm) and analysed by GC.

(−)-2,2′-Bis(methoxymethoxy)-3,3′-bis(methylthio)-1,1′-binaphthyl (4):[24] (*R*)-2,2′-Bis(methoxymethoxy)-1,1′-binaphthyl (1.50 g, 4.01 mmol) was treated with *n*BuLi (1.56 M solution in Et_2O, 7.74 mL) and dimethyl disulfide (1.32 g, 14.0 mmol) in diethyl ether (68 mL) and THF (40 mL) as described. Purification by flash chromatography, eluting with petroleum ether/EtOAc (8:2, v/v), gave the desired sulfide as a pale yellow oil (1.84 g, 98%), $[\alpha]_D^{24} = -79$ (c = 0.95 in $CHCl_3$). R_f = 0.4 (CH_2Cl_2). $C_{26}H_{26}O_4S_2$ (466.6): calcd. C 66.9, H 5.6, S 13.7; found C 66.8, H 5.7, S 13.7. IR: $\tilde{\nu}_{max}$ = 2826 (C−H), 1575 (C=C), 1159 cm^{-1} (C−O). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.60 (6 H, s, SCH_3), 2.78 (6 H, s, OCH_3), 4.67 (2 H, d, J = 5.5 Hz, 2 C*H*H′O), 4.73 (2 H, d, J = 5.5 Hz, 2 CH*H*′O), 7.15−7.23 (4 H, m, ArH), 7.39 (2 H, m, ArH), 7.62 (2 H, s, ArH), 7.79 (2 H, d, J = 8.2 Hz, ArH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.7 (2 q), 56.5 (2 q), 98.4 (2 t), 123.4 (2 d), 125.0 (2 s), 125.4 (4 d), 126.3 (2 d), 126.5 (2 d), 131.2 (2 s), 131.7 (2 s), 134.0 (2 s), 150.4 (2 s). MS (EI); m/z (%): 466 (51) [M^+], 390 (100), 315 (46).

(4*S*)-4,5-Dihydro-4-[1-methyl-1-(methylthio)ethyl]-2-(2-pyridinyl)-1,3-oxazole (12):[22,25] Sodium metal (0.23 g, 10 mmol) was added in portions to a stirred suspension of D-penicillamine (0.75 g, 5.0 mmol) in absolute ethanol (10 mL). On addition of the final piece of sodium a white solid precipitated from solution. After all the metal had dissolved, methyl iodide (0.35 mL, 5.5 mmol) was added dropwise. The solvent was removed by evaporation to the Schlenk line and THF (12.5 mL) was added. The reaction mixture was cooled to 0 °C and lithium aluminium hydride (763 mg, 20.1 mmol) was added in portions. The mixture was allowed to warm to ambient temperature and heated at reflux for 4 h. Hydrolysis was effected at 0 °C by treatment with diethyl ether (7 mL), NaOH (15% w/v, 1.25 mL), and H_2O (2.5 mL). The mixture was filtered and the filter cake was washed with copious quantities of diethyl ether (6 × 12 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield a pale yellow oil (0.67 g, 89% crude yield). The amino alcohol (0.33 g, 2.2 mmol), 2-cyanopyridine (192 mg, 1.85 mmol), and cadmium acetate dihydrate (25.0 mg, 0.092 mmol) were refluxed under argon in anhydrous chlorobenzene (9.2 mL) for 16 h. The volatile species were removed under reduced pressure and the crude material was purified by flash chromatography, eluting with EtOAc/petroleum ether (8:2, v/v). The desired sulfide was obtained as a colourless, waxy solid (0.35 g, 81%), $[\alpha]_D^{26} = +15.5$ (c = 1.1 in $CHCl_3$). R_f = 0.15 (diethyl ether). IR: $\tilde{\nu}_{max}$ = 1641 (C=N), 1246 (C−O), 1037 cm^{-1} (C−O). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.17 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 2.02 (3 H, s, SCH_3), 4.34−4.54 (3 H, m, CHN and CH_2O), 7.33 (1 H, ddd, J = 7.6, 4.9, and 1.2

Hz, PyH), 7.72 (1 H, m, PyH), 8.00 (1 H, m, PyH), 8.65 (1 H, m, PyH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 10.7 (q), 22.5 (q), 26.1 (q), 46.3 (s), 69.8 (t), 74.9 (d), 123.8 (d), 125.4 (d), 136.4 (d), 146.5 (s), 149.6 (d), 163.3 (s). MS (EI); *m*/*z* (%): 236 (18) [M^+], 148 (90), 89 (100). $C_{12}H_{16}N_2OS$ [M^+]: calcd. 236.0983; found 236.0973.

(−)-[(4*S*,5*S*)-4,5-Dihydro-2-{[(4*S*,5*S*)-4,5-dihydro-4-{[(methylsulfonyl)oxy]methyl}-5-phenyl-1,3-oxazol-2-yl]methyl}-5-phenyl-1,3-oxazol-4-yl]methyl Methanesulfonate (13): A stirred solution of (−)-(4*S*,4′*S*,5*S*,5′*S*)-bis(4,5-dihydro-4-hydroxymethyl-5-phenyldioxazol-2-yl)methane[20] (7.36 g, 20.1 mmol) in CH_2Cl_2 (125 mL) under argon was cooled to 0 °C and treated with triethylamine (12.3 mL, 88.5 mmol). Methanesulfonyl chloride (3.43 mL, 44.3 mmol) was added dropwise and the mixture was stirred for 20 min and then allowed to warm to room temperature. After 3 h, the reaction mixture was washed with saturated aqueous $NaHCO_3$ (2 × 150 mL) and brine (150 mL), and then dried (Na_2SO_4). Concentration under reduced pressure afforded the product as a white foam (10.1 g, 96%), $[\alpha]_D^{23}$ −75 (*c* = 1.04 in EtOH). R_f = 0.5 (CH_2Cl_2/MeOH, 95:5). IR: $\tilde{\nu}_{max}$ = 1666 (C=N), 1354 (OSO_2), 1175 cm^{-1} (OSO_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.99 (6 H, s, SO_2CH_3), 3.58 [2 H, s, $CH_2C(O)$=N], 4.31 (2 H, m, CHN), 4.39 (4 H, AB part of ABX system, 2 C*HH*′OS), 5.40 (2 H, d, *J* = 6.7 Hz, PhCH), 7.26−7.38 (10 H, m, ArH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 28.5 (t), 37.4 (2 q), 69.3 (2 t), 73.5 (2 d), 83.4 (2 d), 125.8 (4 d), 128.8 (2 d), 128.9 (4 d), 138.9 (2 s), 163.2 (2 s). MS (FAB); *m*/*z* (%): 523 (100) [MH^+]. $C_{23}H_{27}N_2O_8S_2$ [MH^+]: calcd. 523.1209; found 523.1211.

Standard Procedure for the Preparation of Bis(oxazoline)-Based Sulfides: A solution of thiol (2.0 mmol) in THF (1.5 mL) was added dropwise at −78 °C under argon to a stirred suspension of sodium hydride (2.0 mmol) in THF (3.5 mL). The mixture was stirred for 10 min and then allowed to warm to room temperature. After 2 h, the reaction mixture was again cooled to −78 °C and treated with a solution of the mesylate **13** (0.67 mmol) in THF (2 mL). The mixture was allowed to warm to ambient temperature and stirred for 16 h, and then quenched with H_2O (7 mL). Products were extracted into ethyl acetate (35 mL), washed with KOH (2 N, 2 × 35 mL), H_2O (35 mL), and brine (2 × 35 mL), and then dried (Na_2SO_4). Concentration under reduced pressure afforded the crude sulfide, which was purified by flash chromatography.

(+)-(4*R*,4′*R*,5*S*,5′*S*)-Bis[4,5-dihydro-4-[4-(methoxy)phenyl]-thiomethyl-5-phenyldioxazol-2-yl]methane (14): Treatment of 4-methoxybenzenethiol (806 mg, 5.75 mmol), sodium hydride (138 mg, 5.75 mmol) and the parent mesylate **13** (1.0 g, 1.9 mmol) as above, in THF (20 mL), followed by purification by flash chromatography [gradient elution, CH_2Cl_2 to CH_2Cl_2/MeOH (99:1, v/v)] afforded the desired sulfide as a colourless oil (1.07 g, 91%), $[\alpha]_D^{23}$ = +64 (*c* = 1 in $CHCl_3$). R_f = 0.5 (CH_2Cl_2/MeOH, 95:5). IR: $\tilde{\nu}_{max}$ = 2835 (C−H), 1666 (C=N), 1246 (C−O), 1031 cm^{-1} (C−O). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.85 (2 H, dd, *J* = 13.4 and 9.2 Hz, 2 C*H*′S), 3.32 (2 H, dd, *J* = 13.4 and 4.3 Hz, 2 CH*H*′S), 3.52 [2 H, s, $CH_2C(O)$=N], 3.74 (6 H, s, OCH_3), 4.13 (2 H, m, CHN), 5.36 (2 H, d, *J* = 6.4 Hz, PhCH), 6.72 (4 H, m, ArH), 7.17 (4 H, m, ArH), 7.25−7.34 (10 H, m, ArH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 28.5 (t), 40.7 (2 t), 55.0 (2 q), 73.7 (2 d), 86.1 (2 d), 114.4 (4 d), 124.6 (2 s), 126.0 (4 d), 128.1 (2 d), 128.4 (4 d), 133.4 (4 d), 139.8 (2 s), 158.9 (2 s), 161.9 (2 s). MS (FAB); *m*/*z* (%): 611 (100) [MH^+], 471 (9), 457 (6). $C_{35}H_{35}N_2O_4S_2$ [MH^+]: calcd. 611.2038; found 611.2028.

(−)-(4*R*,4′*R*,5*S*,5′*S*)-Bis{4,5-dihydro-4-[4-(nitrophenyl)thiomethyl]-5-phenyldioxazol-2-yl}methane (15): Treatment of *p*-nitrothiophenol (0.62 g, 4.0 mmol), sodium hydride (97 mg, 4.0 mmol) and the parent mesylate **13** (700 mg, 1.34 mmol) in THF (14 mL) followed by purification by flash chromatography [gradient elution, CH_2Cl_2 to CH_2Cl_2/MeOH (99:1, v/v)] afforded the desired sulfide as a yellow foam (0.45 g, 53%), $[\alpha]_D^{23}$ = −92 (*c* = 1 in $CHCl_3$). R_f = 0.45 (CH_2Cl_2/MeOH, 98:2). IR: $\tilde{\nu}_{max}$ = 1663 (C=N), 1510 (NO_2), 1338 cm^{-1} (NO_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.17 (2 H, dd, *J* = 13.1 and 7.6 Hz, 2 C*H*′S), 3.45 (2 H, dd, *J* = 13.1 and 5.2 Hz, 2 CH*H*′S), 3.55 [2 H, s, $CH_2C(O)$=N], 4.29 (2 H, m, CHN), 5.33 (2 H, d, *J* = 6.7 Hz, PhCH), 7.25−7.34 (14 H, m, ArH), 8.04 (4 H, m, ArH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 28.5 (t), 37.0 (2 t), 73.6 (2 d), 86.2 (2 d), 123.9 (4 d), 125.9 (4 d), 127.0 (4 d), 128.7 (2 d), 128.8 (4 d), 139.1 (2 s), 145.4 (2 s), 145.7 (2 s), 162.5 (2 s). MS (FAB); *m*/*z* (%): 641 (52) [MH^+], 472 (10), 154 (96), 136 (100). $C_{33}H_{29}N_4O_6S_2$ [MH^+]: calcd. 641.1529; found 641.1565.

(−)-(4*R*,4′*R*,5*S*,5′*S*)-Bis[4,5-dihydro-4-(2-pyridinylthiomethyl)-5-phenyldioxazol-2-yl]methane (16): Treatment of 2-mercaptopyridine (0.23 g, 2.0 mmol), sodium hydride (48 mg, 2.0 mmol), and mesylate **13** (0.35 g, 0.67 mmol) in THF (7 mL), followed by purification by flash chromatography [gradient elution, CH_2Cl_2 to CH_2Cl_2/MeOH (98:2, v/v)] afforded the desired sulfide as a colourless oil (0.28 g, 75%), $[\alpha]_D^{23}$ = −39 (*c* = 1 in $CHCl_3$); R_f = 0.45 (CH_2Cl_2/MeOH, 95:5). IR: $\tilde{\nu}_{max}$ = 1664 (C=N), 1578 (C=C), 1414 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H = 3.44 (2 H, dd, *J* = 13.7 and 6.7 Hz, 2C*H*′S), 3.61 [2 H, s, $CH_2C(O)$=N], 3.77 (2 H, dd, *J* = 13.7 and 4.9 Hz, 2 CH*H*′S), 4.38 (2 H, m, CHN), 5.39 (2 H, d, *J* = 6.7 Hz, PhCH), 6.96 (2 H, ddd, *J* = 7.3, 4.9 and 1.2 Hz, PyH), 7.18 (2 H, m, PyH), 7.24−7.35 (10 H, m, ArH), 7.44 (2 H, m, PyH), 8.38 (2 H, ddd, *J* = 4.9, 1.8 and 0.9 Hz, PyH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 28.6 (t), 34.0 (2 t), 74.4 (2 d), 85.5 (2 d), 119.5 (2 d), 122.3 (2 d), 125.7 (4 d), 128.0 (2 d), 128.5 (4 d), 135.8 (2 d), 140.1 (2 s), 149.2 (2 d), 157.7 (2 s), 162.1 (2 s). MS (FAB); *m*/*z* (%): 553 (100) [MH^+], 124 (33). $C_{31}H_{29}N_4O_2S_2$ [MH^+]: calcd. 553.1732; found 553.1752.

(−)-(4*R*,4′*R*,5*S*,5′*S*)-Bis[4-(*tert*-butylthiomethyl)-4,5-dihydro-5-phenyldioxazol-2-yl]methane (17): Treatment of 2-methyl-2-propanethiol (518 mg, 5.75 mmol), sodium hydride (138 mg, 5.75 mmol), and the parent mesylate **13** (1.0 g, 1.9 mmol) in THF (20 mL) following the order of addition shown above, gave the desired sulfide as a colourless oil (926 mg, 95%), $[\alpha]_D^{20}$ = −58 (*c* = 0.65 in $CHCl_3$). R_f = 0.4 (CH_2Cl_2/MeOH, 95:5). IR: $\tilde{\nu}_{max}$ = 1665 (C=N), 1390 [$C(CH_3)_3$], 1364 cm^{-1} [$C(CH_3)_3$]. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32 [18 H, s, $C(CH_3)_3$], 2.67 (2 H, dd, *J* = 11.9 and 9.2 Hz, 2 C*H*′S), 2.99 (2 H, dd, *J* = 11.9 and 4.7 Hz, 2 CH*H*′S), 3.58 [2 H, s, $CH_2C(O)$=N], 4.18 (2 H, m, CHN), 5.34 (2 H, d, *J* = 6.1 Hz, PhCH), 7.26−7.37 (10 H, m, ArH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 28.7 (t), 30.9 (6 q), 33.6 (2 t), 42.4 (2 s), 74.7 (2 d), 86.1 (2 d), 125.9 (4 d), 128.2 (2 d), 128.6 (4 d), 140.2 (2 s), 161.8 (2 s). MS (FAB); *m*/*z* (%): 511 (100) [MH^+], 407 (33). $C_{29}H_{39}N_2O_2S_2$ [MH^+]: calcd. 511.2453; found 511.2430.

Standard Procedure for the Simmons−Smith-Based Aziridination (Table 5)**:** Diethylzinc (1.1 M solution in toluene, 1.0 mL) was added to a stirred solution of imine (1.0 mmol), chloroiodomethane (0.15 mL, 2.0 mmol), and chiral sulfide (2.0 mmol) in CH_2Cl_2 (5 mL) at room temperature under a positive pressure of argon. After 16 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and the reaction products were extracted into CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with triethanolamine (2 N, 2 × 10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford the crude aziridine, which was purified by flash chromatography.

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