# Bifunctional catalysts for catalytic asymmetric sulfur ylide epoxidation of carbonyl compounds

**Varinder K. Aggarwal,* Louise Bell, Michael P. Coogan and Philippe Jubault**

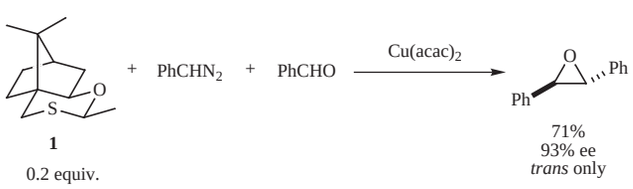
*Department of Chemistry, University of Sheffield, Sheffield, UK S3 7HF*

**Carbonyl epoxidation using diazo compounds mediated by catalytic quantities of sulfide and metal catalyst has been investigated using sulfides linked to the metal catalyst. In this study a range of bis-oxazolines with pendant sulfides were tested in the asymmetric epoxidation process using Cu(I)Br (this was the optimal metal catalyst). Although the enantioselectivity was poor (< 24% ee), it was possible to use a much lower catalyst loading (5 mol%) than we had previously achieved (20 mol% was the lower limit) without compromising the yield. This is believed to be because ylide formation is now an intramolecular process and therefore fast compared to the reaction of the metal carbenoid with the diazo compound (resulting in stilbene formation) which no longer competes significantly.**



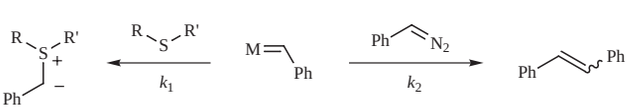
## Introduction

The catalytic asymmetric synthesis of epoxides is a high profile reaction and this interest is largely driven by industrial needs for the preparation of such intermediates in the synthesis of agrochemicals and pharmaceuticals. Considerable success has been achieved in this area most notably by Sharpless,[1] Katsuki,[2,3] Jacobsen[4] and Shi[5] who have contributed excellent processes for alkene oxidation. We have focused on carbonyl epoxidation and have developed a catalytic,[6] sulfur ylide mediated process which, with thioacetal **1**,[7] gave good yields and excellent diastereo- and enantio-control (Scheme 1).




**Scheme 1**

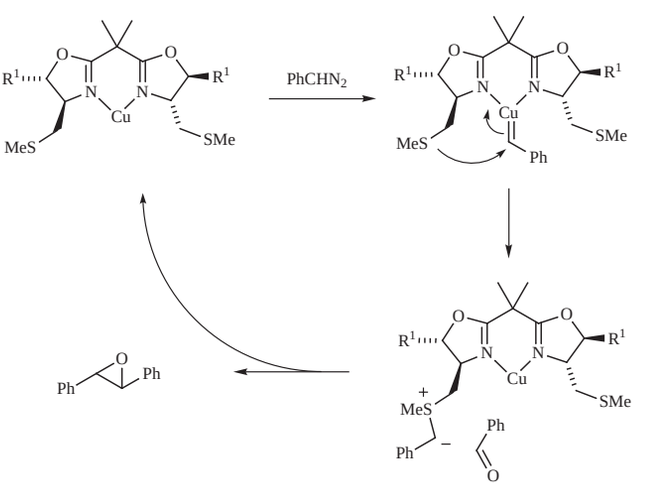
Substoichiometric amounts of sulfide can be used in this process but there is a lower limit of 20 mol%; attempts to reduce the number of equivalents of sulfide further (*e.g.* 10 mol%) resulted in greatly reduced yields (~30%).[7] The reduction in yield is due to competing reactions of the metal carbenoid. The metal carbenoid can either react with the sulfide to give the sulfur ylide or react with another equivalent of diazocompound to form stilbenes (Scheme 2). At low sulfide concentration the




**Scheme 2**

former reaction is slowed and the latter reaction begins to dominate.[6]

To achieve lower sulfide loading, the rate of reaction of the metal carbenoid with the sulfide ($k_1$) needs to be increased relative to the rate of the reaction of the metal carbenoid with diazo compound ($k_2$). This could potentially be achieved if the ylide formation was intramolecular *i.e.* the sulfide was attached in some way to the metal carbenoid. Sulfides can be covalently attached to ligands for metal complexes. Oxazoline and bis-oxazoline ligands[8,9] seemed ideal templates for this task as they readily form complexes with copper (also known to be a good metal for decomposition of diazo compounds for asymmetric cyclopropanation[10–14]) and can be easily manipulated to incorporate sulfide functionality (Scheme 3). In this paper we



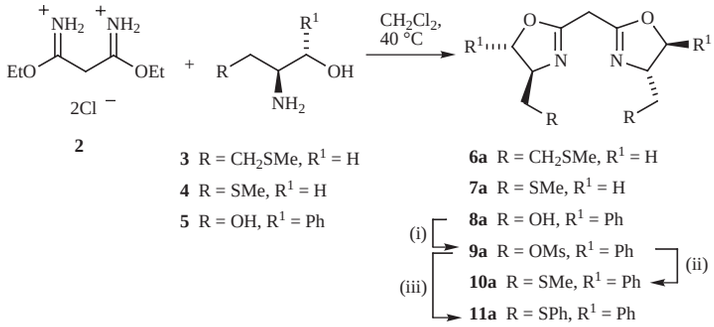

**Scheme 3**

describe the synthesis and reactivity of oxazolines bearing sulfide functionality for carbonyl epoxidation.

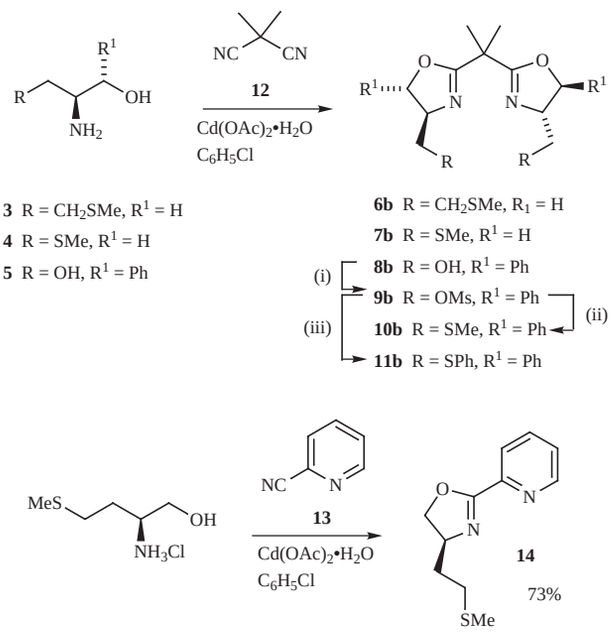
### Ligand synthesis

The required oxazolines were prepared directly by one of two methods. The unsubstituted (central carbon atom) bisoxazolines were prepared from the reaction of diethyl malonimidate with the appropriate amino alcohol (**3**,[15] **4**,[16] **5**[17]) to produce the corresponding bisoxazoline (Scheme 4, Table 1). Optimum yields were obtained using freshly prepared malonimidate, as reported by Lehn.[18] The hydroxy-bearing bisoxazolines **8a** were smoothly converted into sulfenyl-bearing bisoxazolines **10a**, **11a** by standard methods. This class of ligands would give neutral complexes with copper(I) salts.

The substituted (non-enolisable) bisoxazolines were prepared from the reaction of the amino alcohols **3**–**5** with malononitrile **12** and with 2-cyanopyridine **13** in the presence of Cd(OAc)$_2$[19,20] to give, directly, bisoxazolines **6b**–**8b** and oxazoline **14** (Scheme 5, Table 2). As before, **8b** was converted into sulfenyl-bearing bisoxazolines **10b** and **11b** by standard methods. This class of ligands would give cationic complexes with copper(I) salts.




**Scheme 4** *Reagents*: (i) MsCl, $Et_3N$, $CH_2Cl_2$ (ii) NaSMe, EtOH, 88% (iii) NaSPh, EtOH, 96%







**Scheme 5** *Reagents*: (i) MsCl, $Et_3N$, $CH_2Cl_2$ (ii) NaSMe, EtOH, 89% (iii) NaSPh, EtOH, 47%

**Table 1** Yields for direct formation of bisoxazolines

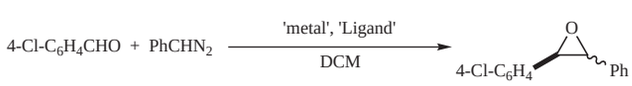
| Entry | Ligand | R | $R_1$ | Yield/% |
|---|---|---|---|---|
| 1 | **6a** | $CH_2SMe$ | H | 25 |
| 2 | **7a** | SMe | H | 30 |
| 3 | **8a** | OH | Ph | 50 |

**Table 2** Yields for direct formation of oxazolines

| Entry | Nitrile | R | $R^1$ | Ligand | Yield/% |
|---|---|---|---|---|---|
| 1 | **12** | $CH_2SMe$ | H | **6b** | 41 |
| 2 | **12** | SMe | H | **7b** | 42 |
| 3 | **12** | OH | Ph | **8b** | 50 |
| 4 | **13** | $CH_2SMe$ | H | **14** | 73 |

### Results of epoxidation

The neutral complexes formed between bisoxazolines **6a**, **7a**, **10a** or **11a** with copper salts were the first systems tested in the catalytic cycle (Scheme 6, Table 3). The bisoxazoline complexes




**Scheme 6**

(10 mol%) were preformed in dichloromethane before adding 4-chlorobenzaldehyde followed by slow addition of phenyldiazomethane over three hours. The choice of copper as the metal was based on the literature precedent for the use of this metal for efficient diazo decomposition.[10–14] Indeed, we have found it to be superior to rhodium in decomposition of phenyl diazomethane and subsequent reaction of the metal carbenoid with sulfide to give a sulfur ylide.[6] Copper(II) salts are known to be reduced to copper(I) salts by diazo compounds[21] which meant that, in principle, it did not matter whether copper(I) or copper(II) salts were used. Nevertheless, we decided to test a range of both copper(I) and copper(II) salts in our chemistry. Copper perchlorate–acetonitrile complex[22] was chosen as a copper salt because it is an air stable form of copper(I).

However, highly variable yields were obtained with different bisoxazolines and different metal salts. Copper(II) triflate gave consistently poor results (entries 1, 4). In all cases only low enantioselectivity was observed. Mass balance was generally good and in all cases where low yields of epoxides were obtained, aldehyde was recovered and phenyldiazomethane dimerised to give stilbene.[6]

We next turned our attention to the cationic complexes derived from oxazolines **6b**, **7b**, **10b**, **11b** and **14** (Table 4). As with the neutral bisoxazoline-complexes, copper(II) triflate gave poor yields (entry 1). Copper(I) salts gave consistently good yields with the cationic complexes and better than those from the neutral complexes. Copper(I) bromide proved to be particularly efficient, giving excellent yields of epoxide (entries 4, 7, 8 and 10). High yields and good diastereocontrol were observed but as before the enantiomeric excesses obtained were very low.

We investigated whether lower catalyst loading was possible and focused on bisoxazoline **7b** with the two optimum copper salts CuBr and $Cu(MeCN)_4ClO_4$. We also varied the concentration of the reaction mixture as we had previously found that low sulfide loading required higher concentrations to achieve good yields[6] and the results are shown in Table 5. It was found that good yields were maintained at low catalyst loading (entries 2 and 5) but that high concentrations were detrimental (entries 3 and 6). In these cases, precipitation of the complexes occurred and resulted in low yields of epoxides.

## Conclusions

A range of bisoxazolines with pendant sulfide moieties have been prepared and found to catalyse the epoxidation of 4-chlorobenzaldehyde in excellent yield and with high diastereoselectivity. The optimum bis-oxazolines were ones that gave rise to cationic complexes with copper(I) salts; neutral complexes gave inferior yields. The optimum copper salt was Cu(I)Br. This work represents an advance over existing technology as it allows the use of one bifunctional catalyst where two independent catalysts were previously required. In addition, the copper complexes allow lower catalyst loadings (5 mol%) than were previously possible (20 mol%) as the carbene transfer to form the ylide is now an intramolecular process.

The enantiomeric excesses were very low, however, due to poor stereocommunication between the chirality residing in the

**Table 3** Yields and enantioselectivities for epoxidation

| Entry | Ligand (equiv.)[a] | Metal[b] | Yield/%[c] | *trans*:*cis*[d] | ee/%[e] |
|---|---|---|---|---|---|
| 1 | **6a** (1) | $Cu(OTf)_2$ | 25 | 100:0 | 2 |
| 2 | **6a** (2) | $Cu(OAc)_2 \cdot H_2O$ | 79 | 94:6 | 3 |
| 3 | **6a** (1) | $Cu(MeCN)_4ClO_4$ | 76 | 92:8 | 0 |
| 4 | **7a** (1) | $Cu(OTf)_2$ | — | — | — |
| 5 | **7a** (2) | $Cu(OAc)_2 \cdot H_2O$ | 25 | 100:0 | 14 |
| 6 | **7a** (1) | $Cu(MeCN)_4ClO_4$ | — | — | — |
| 7 | **7a** (1) | CuBr | <10 | — | — |
| 8 | **10a** (2) | $Cu(OAc)_2 \cdot H_2O$ | 30 | 100:0 | — |
| 9 | **11a** (2) | $Cu(OAc)_2 \cdot H_2O$ | — | — | — |

[a] Refers to the equivalents of ligand relative to the copper salt. [b] 10 Mol% metal catalyst used. [c] Isolated yield. [d] By $^1$H NMR. [e] Measured on a Chiralcel OD column.

**Table 4** Yields and enantioselectivities for epoxidation

| Entry | Ligand | Metal[a] | Yield/%[b] | *trans*:*cis*[c] | ee/%[d] |
|---|---|---|---|---|---|
| 1 | **7b** | $Cu(OTf)_2$ | 8 | 100:0 | 12 |
| 2 | **7b** | $Cu(MeCN)_4ClO_4$ | 84 | 95:5 | 5 |
| 3 | **7b** | CuCl | 72 | 95:5 | 6 |
| 4 | **7b** | CuBr | 82 | 96:4 | 6 |
| 5 | **7b** | $CuBr_2$ | 46 | 100:0 | 24 |
| 6 | **6b** | $Cu(MeCN)_4ClO_4$ | 73 | 100:0 | 14 |
| 7 | **6b** | CuBr | 90 | 100:0 | 16 |
| 8 | **10b** | CuBr | 100 | 90:10 | 4 |
| 9 | **11b** | CuBr | 43 | 100:0 | 0 |
| 10 | **14** | CuBr | 93 | 100:0 | 6 |

[a] 10 Mol% metal catalyst used. [b] Isolated yield. [c] By $^1$H NMR. [d] Measured on a Chiralcel OD column.

oxazoline and the incoming aldehyde. Attempts to synthesise ligands which give increased enantioselectivity are progressing.

## Experimental

(*S*)-Methioninol **3**,[15] (*S*)-2-amino-3-(methylthio)propan-1-ol **4**[16] and dimethylmalonyl dinitrile **13**[19] were prepared as described in the literature. *J* Values are given in Hz.

### 4,4′,5,5′-Tetrahydro-4,4′-bis(methylthioethyl)-2,2′-methylenedioxazole 6a

(*S*)-(−)-Methioninol (1.410 g, 10.4 mmol, 2 equiv.) and diethyl malonimidate (1.201 g, 5.2 mmol, 1 equiv.) were refluxed in dichloromethane for 24 h. The mixture was allowed to cool and water (50 ml) was added. The aqueous washings were extracted with copious amounts of dichloromethane. The combined organics were dried over $MgSO_4$ and the solvent removed *in vacuo* to yield an oil. The product was purified by column chromatography (5% MeOH–$CH_2Cl_2$, $PdCl_2$ (aq.) stain; $R_f$ 0.45) and the *title material* was furnished as a white solid after Kugelrohr distillation (549 mg, 25%), mp 34–35 °C; bp 200–220 °C/0.7 mmHg; $[\alpha]_D^{21}$ −114 (*c* 1.0 in $CHCl_3$) (Found: C, 51.5; H, 7.35; N, 9.1; S, 21.15. Calc. for $C_{13}H_{22}N_2O_2S_2$: C, 51.6; H, 7.3; N, 9.3; S, 21.2%); $\nu_{max}$(liquid film)/cm$^{-1}$ 3413, 2914, 1667, 1588; $\delta_H$(250 MHz; $CDCl_3$) 1.82 (4 H, m, C$H_2$CH$_2$S), 2.09 (6 H, s, C$H_3$), 2.57 (2 H, dd, *J* 2.3, 5.8, C$H_2$S), 2.60 (2 H, dd, *J* 2.5, 6.6, C$H_2$S), 3.32 (2 H, d br, *J* 0.9, CC$H_2$C), 3.92 (2 H, t, *J* 8.0, OC$H_2$), 4.22 (2 H, m, NC*H*), 4.38 (2 H, dd, *J* 7.9, 9.8, OC$H_2$); $\delta_C$(63 MHz; $CDCl_3$) 15.5 (q), 28.3 (t), 30.5 (t), 35.1 (t), 65.3 (d), 72.8 (t), 161.9 (s); *m*/*z* (EI) 302 ($M^+$, 100%), 287 (45), 228 (23), 186 (68), 154 (49), 144 (54), 85 (75) and 61 (80) (Found: $M^+$, 302.1125. Calc. for $C_{13}H_{22}N_2O_2S_2$: *M*, 302.1123).

### 4,4′,5,5′-Tetrahydro-4,4′-bis(methylthiomethyl)-2,2′-methylenedioxazole 7a

Diethyl malonimidate (0.462 g, 2 mmol, 1 equiv.) and (+)-(*R*)-2-amino-3-(methylsulfanyl)propan-1-ol (0.497 g, 4 mmol, 2 equiv.) were refluxed in dry dichloromethane (5 ml) under argon for 48 h. Water (20 ml) was added and the product extracted into dichloromethane (3 × 50 ml). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield an oil. The product was purified by column chromatography (5% MeOH–$CH_2Cl_2$; $R_f$ 0.24) to yield the *title compound* as a white, low melting solid (0.163 g, 30%), $[\alpha]_D^{25}$ −22 (*c* 0.45 in $CHCl_3$) (Found: C, 48.0; H, 6.6; N, 10.0; S, 23.1 Calc. for $C_{11}H_{18}N_2O_2S_2$: C, 48.15; H, 6.6; N, 10.2; S, 23.4%); $\nu_{max}$(liquid film)/cm$^{-1}$ 3415, 2966, 1660, 1585, 1249, 983; $\delta_H$(250 MHz; $CDCl_3$) 2.14 (6 H, s, C$H_3$), 2.53 (2 H, dd, *J* 8.0, 13.5, C$H_2$S), 2.84 (2 H, dd, *J* 4.75, 13.5, C$H_2$S), 3.35 (2 H, s, C$H_2$), 4.10–4.24 (2 H, m, C$H_2$O), 4.30–4.42 (4 H, m, C$H_2$O + C*H*); $\delta_C$(63 MHz; $CDCl_3$) 15.9 (q), 28.3 (t), 39.9 (t), 65.9 (d), 72.4 (t), 162.6 (s); *m*/*z* (EI) 274 ($M^+$, 45%), 228 (29), 213 (100), 182 (39), 167 (24) and 61 (83) (Found: $M^+$, 274.0805. Calc. for $C_{11}H_{18}N_2O_2S_2$: *M*, 274.0809).

### (−)-(4*S*,4′*S*,5*S*,5′*S*)-4,4′,5,5′-Tetrahydro-4,4′-bis(hydroxymethyl)-5,5′-diphenyl-2,2′-methylenedioxazole 8a

(1*S*,2*S*)-(+)-2-Amino-1-phenylpropane-1,3-diol (3.373 g, 20.2 mmol, 2 equiv.) and diethyl malonimidate (2.348 g, 10.1 mmol, 1 equiv.) were refluxed for 16 h in dry dichloromethane (25 ml) under argon. Water (100 ml) was added and the product extracted into dichloromethane (5 × 50 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to yield a yellow foam. The product was purified by column chromatography (5% MeOH in $CH_2Cl_2$) and the title compound was furnished as a white solid which could be further purified by recrystallisation from ethyl acetate if required[18] (2.814 g, 79%), mp 112–113 °C (lit.,[12,18] 111 °C and 118–119 °C); $[\alpha]_D^{21}$ −75 (*c* 1.04 in EtOH) (lit.,[18] $[\alpha]_D^{23}$ −77.3 (*c* 1.04 in EtOH); $\nu_{max}$(Nujol mull)/cm$^{-1}$ 2851, 1656; $\delta_H$(250 MHz; $CDCl_3$) 3.47 (2 H, s, NC$H_2$N), 3.56 (2 H, dd, *J* 3.3, 12.0, C$H_2$OH), 3.87 (2 H, dd, *J* 2.8, 12.0, C$H_2$OH), 4.04 (2 H, m, NC*H*), 5.45 (2 H, d, *J* 6.5, PhC*H*), 7.16–7.28 (10 H, m, ArH); $\delta_C$(63 MHz; $CDCl_3$) 28.4 (t), 63.3 (t), 75.8 (d), 83.6 (d), 125.8 (d), 128.6 (d), 128.8 (d), 139.8 (s), 163.9 (s).

### (4*R*,4′*R*,5*S*,5′*S*)-4,4′,5,5′-Tetrahydro-4,4′-bis(methylthiomethyl)-5,5′-diphenyl-2,2′-methylenedioxazole 10a

(−)-(4*S*,4′*S*,5*S*,5′*S*)-4,4′,5,5′-Tetrahydro-4,4′-bis(hydroxymethyl)-5,5′-diphenyl-2,2′-methylenedioxazole **8a** (228 mg, 0.65 mmol, 1 equiv.) was dissolved in dichloromethane (20 ml) under argon and cooled to 0 °C. Triethylamine (0.4 ml, 2.86 mmol, 4.4 equiv.) was added followed by methanesulfonyl chloride (0.11 ml, 1.43 mmol, 2.2 equiv.). The reaction was allowed to warm to room temperature and stirred for 2 h. An aqueous work up was then performed, extracting into dichloromethane (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting mesylate (0.931 g, 1.78 mmol) was added neat to a solution of sodium methyl thiolate (0.5 g, 7.1 mmol, 4 equiv.) in absolute ethanol (20 ml) and heated briefly to dissolve the mesylate. The mixture was then stirred for 16 h at ambient temperature and the solvent was removed by distillation. Brine (20 ml) was added and the aqueous phase extracted with dichloromethane

**Table 5** Yields for epoxidation of 4-$ClC_6H_4CHO$

| Entry | Ligand | Metal[a] | Total vol.[b] | Yield/%[c] | *trans*:*cis*[d] |
|---|---|---|---|---|---|
| 1 | **7b** (10 mol%) | $Cu(MeCN)_4ClO_4$ | 1 ml | 84 | 95:5 |
| 2 | **7b** (5 mol%) | $Cu(MeCN)_4ClO_4$ | 1 ml | 60 | 100:0 |
| 3 | **7b** (5 mol%) | $Cu(MeCN)_4ClO_4$ | 0.6 ml | 4 | 100:0 |
| 4 | **7b** (10 mol%) | CuBr | 1 ml | 82 | 96:4 |
| 5 | **7b** (5 mol%) | CuBr | 1 ml | 78 | 100:0 |
| 6 | **7b** (5 mol%) | CuBr | 0.6 ml | 56 | 100:0 |

[a] 1:1 Ratio of ligand to metal. [b] Volume after addition of the diazo compound, reactions performed with 0.5 mmol of aldehyde. [c] Isolated yield. [d] Determined by $^1$H NMR. All ees ~5%.



(3 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by column chromatography (5% MeOH–$CH_2Cl_2$; $R_f$ 0.44) to yield the *title material* as an oil (0.67 g, 88%), $[\alpha]_D^{21}$ +17 (*c* 0.59 in $CH_2Cl_2$); $\nu_{max}$(Nujol mull)/cm$^{-1}$ 3054, 2831, 1664, 1605, 1551; $\delta_H$(250 MHz; $CDCl_3$) 2.08 (6 H, s, SC$H_3$), 2.65 (2 H, dd, *J* 7.5, 12.5, C$H_2$S), 2.95 (2 H, dd, *J* 5.0, 12.5, C$H_2$S), 3.59 (2 H, s, NC$H_2$N), 4.23 (2 H, q, *J* 5.0, C$H$C$H_2$S), 5.37 (2 H, d, *J* 7.5, C$H$Ph), 7.33 (10 H, m, ArH); $\delta_C$(63 MHz; $CDCl_3$) 15.7 (q), 28.7 (t), 38.9 (t), 74.2 (d), 87.9 (d), 125.8 (d), 128.2 (d), 128.7 (d), 140.1 (s), 161.9 (s); *m*/*z* (EI) 426 ($M^+$, 6%), 365 (100), 317 (15), 117 (28) and 91 (39) (Found: $M^+$, 426.1429. Calc. for $C_{23}H_{26}N_2O_2S_2$: *M*, 426.1435).

**(4*R*,4′*R*,5*S*,5′*S*)-4,4′,5,5′-Tetrahydro-4,4′-bis(phenylthiomethyl)-5,5′-diphenyl-2,2′-methylenedioxazole 11a**

(−)-(4*S*,4′*S*,5*S*,5′*S*)-4,4′,5,5′-Tetrahydro-4,4′-bis(hydroxymethyl)-5,5′-diphenyl-2,2′-methylenedioxazole **8a** (0.298 g, 0.84 mmol, 1 equiv.) was dissolved in dichloromethane (20 ml) and cooled to 0 °C. Triethylamine (1 ml, 7.4 mmol, 8.8 equiv.) was added followed by methanesulfonyl chloride (287 μl, 3.7 mmol, 4.4 equiv.). The reaction was allowed to warm to room temperature and stirred for an hour. A further equivalent of both triethylamine and methanesulfonyl chloride were added and the reaction stirred for another hour. The reaction was judged to be complete by TLC and an aqueous work up was performed, extracting into dichloromethane (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. A flask charged with sodium hydride (60% in oil, 0.78 g, 19.5 mmol, 2.5 equiv.) was washed with light petroleum (20 ml) the solvent decanted and the flask treated with 10 ml THF sealed under argon and cooled to −78 °C before dropwise treatment with benzenethiol (2 ml, 19.5 mmol, 2.5 equiv.). After stirring for 30 min as the mixture attained ambient temperature, the resultant thick paste was treated with the mesylate prepared as above (4 g, 7.6 mmol) as a solution in THF (15 ml) dropwise. The mixture was stirred for 16 h before treatment with aqueous sodium hydroxide (2 M, 20 ml) and extracted into dichloromethane (3 × 20 ml). The combined organic extracts were washed with brine (saturated, 20 ml) dried ($Na_2SO_4$) and the solvent removed *in vacuo*. The product was purified by column chromatography (2% MeOH–$CH_2Cl_2$; $R_f$ 0.24) to yield the *title material* as a white crystalline compound (4.010 g, 96%), mp 100–101 °C; $[\alpha]_D^{21}$ −19 (*c* 0.36 in $CH_2Cl_2$); $\nu_{max}$(Nujol mull)/cm$^{-1}$ 1663, 1221, 742; $\delta_H$(250 MHz; $CDCl_3$) 2.98 (2 H, dd, *J* 9.0, 13.3, C$H_2$S), 3.44 (2 H, dd, *J* 4.6, 13.3, C$H_2$S), 3.55 (2 H, s, NC$H_2$N), 4.22 (2 H, m, C$H$C$H_2$S), 5.38 (2 H, d, *J* 6.3, C$H$Ph), 7.18–7.29 (20 H, m, ArH); $\delta_C$(63 MHz; $CDCl_3$) 28.6 (t), 38.8 (t), 73.8 (d), 86.1 (d), 125.9 (d), 126.4 (d), 128.3 (d), 128.6 (d), 128.9 (d), 129.8 (d), 134.9 (s), 139.9 (s), 162.1 (s); *m*/*z* (FAB) 551 ($M^+$, 100%), 503 (9), 441 (14) and 427 (13) (Found: $M^+$, 551.1817. Calc. for $C_{33}H_{30}N_2O_2S_2$: *M*, 551.1826).

**General procedure for the formation of oxazolines using cadmium acetate hydrate**

The amino alcohol (2.5 mmol, 2.5 equiv.) and dimethylmalononitrile (1 mmol, 1 equiv.) were refluxed for 24 h in chlorobenzene (3 ml) in the presence of cadmium acetate hydrate (13 mg, 5 mol%). After cooling the crude material was purified by column chromatography.

**2,2-Bis[(4*S*)-4-methylthioethyl-5-phenyl-1,3-oxazolin-2-yl]-propane 6b**

The crude was purified by column chromatography (5% MeOH in $CH_2Cl_2$) to yield the *title compound* as a clear oil (1.071 g, 74%), $[\alpha]_D^{25}$ −156 (*c* 1.0 in $CHCl_3$) (Found: C, 54.2; H, 7.9; N, 8.8; S, 19.4. Calc. for $C_{15}H_{26}N_2O_2S_2$: C, 54.6; H, 7.9; N, 8.5; S, 19.4%); $\nu_{max}$(liquid film)/cm$^{-1}$ 3414, 2916, 1659; $\delta_H$(250 MHz; $CDCl_3$) 1.48 [6 H, s, C(C$H_3$)$_2$], 1.81 (4 H, m, C$H_2$CH$_2$S), 2.09 (6 H, s, SC$H_3$), 2.54 (4 H, t, *J* 7.5, C$H_2$S), 3.91 (2 H, dd, *J* 6.8, 7.8, OC$H_2$), 4.21 (2 H, tdd, *J* 6.3, 6.3, 12.5, C$H$), 4.32 (2 H, dd, *J* 7.8, 9.5, OC$H_2$); $\delta_C$(63 MHz; $CDCl_3$) 15.5 (q), 24.3 (q), 30.2 (t), 35.1 (t), 38.5 (s), 65.0 (d), 72.5 (t), 169.1 (s); *m*/*z* (EI) 330 ($M^+$, 32%), 256 (16), 231 (15) and 187 (100) (Found: $M^+$, 330.1431. Calc. for $C_{15}H_{26}N_2O_2S_2$: *M*, 330.1435).

**2,2-Bis[(4*S*)-4-methylthiomethyl-1,3-oxazolin-2-yl]propane 7b**

The crude was purified by column chromatography (5% MeOH–$CH_2Cl_2$) to yield the *title compound* as a clear oil (0.066 g, 38%), $[\alpha]_D^{21}$ −46 (*c* 0.48 in $CH_2Cl_2$) (Found: C, 51.1; H, 7.4; N, 9.3; S, 21.4. Calc. for $C_{13}H_{22}N_2O_2S_2$: C, 51.6; H, 7.3; N, 9.3; S, 21.2%); $\nu_{max}$(liquid film)/cm$^{-1}$ 3381, 2918, 1651, 1519, 1257, 977; $\delta_H$(250 MHz; $CDCl_3$) 1.48 (6 H, s, C$H_3$), 2.11 (6 H, s, SC$H_3$), 2.48 (2 H, dd, *J* 1.8, 7.0, C$H_2$S), 2.80 (2 H, dd, *J* 4.8, 13.8, C$H_2$S), 4.12 (2 H, d, *J* 1.5, OC$H_2$), 4.33 (4 H, m, OC$H_2$, C$H$); $\delta_C$(63 MHz; $CDCl_3$) 16.1 (q), 24.3 (q), 38.7 (s), 39.3 (t), 65.7 (d), 72.4 (t), 170.1 (s); *m*/*z* (EI) 302 ($M^+$, 51%), 256 (38), 241 (68), 173 (78), 105 (43) and 61 (100) (Found: $M^+$, 302.114. Calc. for $C_{13}H_{22}N_2O_2S_2$: *M*, 302.1122).

**(−)-2,2-Bis[(4*S*,5*S*)-4-hydroxymethyl-5-phenyl-1,3-oxazolin-2-yl]propane 8b**

(1*S*,2*S*)-(+)-2-Amino-1-phenylpropane-1,3-diol (6.221 g, 37.3 mmol, 2.5 equiv.), dimethylmalonyldinitrile (1.400 g, 14.9 mmol, 1 equiv.) and cadmium acetate hydrate (0.198 g, 5 mol%) were refluxed in chlorobenzene (70 ml) for 16 h. The reaction was judged to have proceeded to completion (by TLC) and the reaction mixture was purified by column chromatography (5% MeOH in $CH_2Cl_2$; $R_f$ 0.22). The product was further purified by recrystallisation from ethyl acetate and furnished white crystals[19,20] (2.506 g, 43%), mp 150–152 °C (lit.,[19,20] 157 °C); $\delta_H$(250 MHz; $CDCl_3$) 1.70 (6 H, s, C$H_3$), 3.67 (2 H, br d, *J* 10.0, C$H_2$OH), 3.84 (2 H, br s, O$H$), 3.96 (2 H, dd, *J* 2.5, 10.0, C$H_2$OH), 4.13 (2 H, m, C$H$), 5.52 (2 H, d, *J* 7.5, PhC$H$), 7.30 (10 H, m, Ph).

**(−)-2,2-Bis[(4*R*,5*S*)-4-methylthiomethyl-5-phenyl-1,3-oxazolin-2-yl]propane 10b**

The dihydroxybisoxazoline **8b** (1.200 g, 3 mmol, 1 equiv.) was dissolved in dichloromethane (60 ml) and cooled to 0 °C. Triethylamine (3.7 ml, 26.4 mmol, 8.8 equiv.) was added dropwise followed by methanesulfonyl chloride (1.0 ml, 13.2 mmol, 4.4 equiv.). The reaction was allowed to warm to room temperature and stirred for 4 h after which time the reaction was complete (by TLC). Water (50 ml) was added and the product extracted into dichloromethane (3 × 100 ml). The combined organic

extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to furnish an oil. The oil was dissolved in absolute ethanol (55 ml) and sodium methylthiolate (1.050 g, 15 mmol, 5 equiv.) added. The mixture was refluxed for 16 h after which time the reaction was complete (by TLC). Water (50 ml) was added and the aqueous phase was extracted with copious amounts of dichloromethane (5 × 100 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by column chromatography (5% MeOH–$CH_2Cl_2$; $R_f$ 0.5) and the *title material* was furnished as a pale solid (1.218 g, 89%), mp 68 °C (pentane); $[\alpha]_D^{21}$ +25 (*c* 0.28 in $CH_2Cl_2$) (Found: C, 65.8; H, 6.8; N, 6.0; S, 13.85. Calc. for $C_{25}H_{30}N_2O_2S_2$: C, 66.1; H, 6.6; N, 6.2; S, 14.1%); $\nu_{max}$(Nujol mull)/cm$^{-1}$ 2921, 1655, 1147, 1119; $\delta_H$(250 MHz; $CDCl_3$) 1.62 (2 H, s, $H_2O$), 1.70 (6 H, s, C$H_3$), 2.64 (2 H, dd, *J* 8.5, 13.8, C$H_2$S), 2.94 (2 H, dd, *J* 4.3, 13.8, C$H_2$S), 4.22 (2 H, ddd, *J* 4.3, 6.5, 8.5, CHC*H*CH$_2$), 5.35 (2 H, d, *J* 6.5, C*H*CHCH$_2$), 7.29 (10 H, m, Ph); $\delta_C$(63 MHz; $CDCl_3$) 15.8 (q), 24.7 (q), 39.1 (t), 74.2 (d), 85.8 (d), 125.9 (d), 128.1 (d), 128.7 (d), 140.6 (s), 169.4 (s); *m*/*z* (EI) 454 (M$^+$, 24%), 393 (100), 186 (28) and 61 (50) (Found: M$^+$, 454.1733. Calc. for $C_{25}H_{30}N_2O_2S_2$: *M*, 454.1748).

### (−)-2,2-Bis[(4*R*,5*S*)-4-phenylthiomethyl-5-phenyl-1,3-oxazolin-2-yl]propane 11b

The dihydroxybisoxazoline **8b** (1.000 g, 2.5 mmol, 1 equiv.) was dissolved in dichloromethane (50 ml) and cooled to 0 °C. Triethylamine (3.1 ml, 22 mmol, 8.8 equiv.) was added dropwise followed by methanesulfonyl chloride (0.85 ml, 11 mmol, 4.4 equiv.). The reaction was allowed to warm to room temperature and stirred for 4 h after which time the reaction was complete (by TLC). Water (50 ml) was added and the product extracted into dichloromethane (3 × 100 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to furnish an oil. The oil was dissolved in absolute ethanol (55 ml) and sodium phenylthiolate (1.650 g, 12.5 mmol, 5 equiv.) was added. The mixture was refluxed for 16 h after which time the reaction was complete (by TLC). Water (50 ml) was added and the aqueous phase was extracted with copious amounts of dichloromethane (5 × 100 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by column chromatography (5% MeOH in $CH_2Cl_2$; $R_f$ 0.5) and the *title material* was furnished as a pale solid (0.675 g, 47%), mp 78 °C (pentane); $[\alpha]_D^{21}$ +18 (*c* 0.22 in $CH_2Cl_2$) (Found: C, 72.1; H, 6.0; N, 4.7; S, 11.2. Calc. for $C_{35}H_{34}N_2O_2S_2 \cdot 1/4H_2O$: C, 72.1; H, 6.0; N, 4.8; S, 11.0%); $\nu_{max}$(Nujol mull)/cm$^{-1}$ 2921, 1655, 1147, 1119; $\delta_H$(250 MHz; $CDCl_3$) 1.65 (6 H, s, C$H_3$), 2.97 (2 H, dd, *J* 9.0, 13.3, C$H_2$S), 3.45 (2 H, dd, *J* 3.7, 13.3, C$H_2$S), 4.22 (2 H, m, NC*H*), 5.39 (2 H, d, *J* 6.5, PhC*H*), 7.21 (20 H, m, ArH); $\delta_C$(63 MHz; $CDCl_3$) 24.5 (q), 38.9 (t), 39.0 (s), 73.7 (d), 85.9 (d), 126.1 (d), 126.3 (d), 128.2 (d), 128.5 (d), 128.8 (d), 129.8 (d), 135.1 (s), 140.2 (s), 169.5 (s); *m*/*z* (EI) (M$^+$ − 1, 38%), 469 (85), 455 (43), 186 (21), 123 (100) (Found: M$^+$, 579.2121. Calc. for $C_{35}H_{34}N_2O_2S_2$: *M*, 579.2139).

### (*S*)-2-(2-Pyridyl)-4,5-dihydro-4-(methylthioethyl)oxazole 14

(*S*)-Methioninol **3** (1.350 g, 10 mmol, 1.2 equiv.), 2-cyanopyridine (0.866 g, 8.3 mmol, 1 equiv.) and cadmium acetate hydrate (0.133 g, 5 mol%) were refluxed in chlorobenzene (10 ml) for 24 hours under argon. The reaction mixture was then purified by column chromatography (5% MeOH in $CH_2Cl_2$; $R_f$ 0.30) and the *title material* obtained as a pale yellow oil (1.207 g, 58%), $[\alpha]_D^{25}$ −117 (*c* 0.35 in $CH_2Cl_2$) (Found: C, 59.15; H, 6.45; N, 12.58; S, 14.18. Calc. for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.34; N, 12.60; S, 14.42%); $\nu_{max}$(liquid film)/cm$^{-1}$ 2919, 2253, 1646, 1470, 1365, 1264, 1098; $\delta_H$(250 MHz; $CDCl_3$) 1.74–2.01 (2 H, m, C$H_2$), 2.03 (3 H, s, C$H_3$), 2.60 (1 H, dd, *J* 4.0, 7.0, C$H_2$S), 2.63 (1 H, dd, *J* 4.0, 6.5, C$H_2$S), 4.04 (1 H, t, *J* 8.0, C$H_2$O), 4.40 (1 H, m, C*H*), 4.53 (1 H, dd, *J* 8.0, 9.8, C$H_2$O), 7.30 (1 H, ddd, *J* 1.3, 4.8, 7.8, Ar), 7.69 (1 H, td, *J* 7.8, 2.0, Ar), 7.93 (1 H, dt, *J* 7.5, 1.3, Ar), 8.62 (1 H, 'dq', *J* 4.8, 1.3, Ar); $\delta_C$(63 MHz; $CDCl_3$) 15.1 (q), 30.3 (t), 34.9 (t), 65.6 (d), 72.5 (t), 123.5 (d), 125.2 (d), 136.2 (d), 146.2 (d), 149.3 (d), 162.4 (s); *m*/*z* (EI) 222 (M$^+$, 29%), 175 (13), 161 (27), 148 (100), 123 (26) and 106 (38) (Found: M$^+$, 222.0837. Calc. for $C_{11}H_{14}N_2OS$: *M*, 222.0827).

### General procedure for epoxidation using bisoxazolines/oxazolines and copper(II) triflate, copper(I) bromide, copper(II) bromide and copper(II) chloride

The bisoxazoline or oxazoline (0.1 mmol, 1 equiv.) in dichloromethane (0.5 ml) was added to copper triflate (0.033 g, 0.1 mmol, 1 equiv.) under argon. An immediate darkening of the solution was observed. The solution was stirred at ambient temperature for 3 h before the addition of *p*-chlorobenzaldehyde (0.140 g, 1 mmol, 10 equiv.) in dichloromethane (0.5 ml). Phenyldiazomethane (2 mmol, 20 equiv.) in dichloromethane (1 ml) was then added over 3 h and the reaction stirred at room temperature overnight. The product was purified by column chromatography (10% $CH_2Cl_2$–petrol).

### General procedure for epoxidation using bisoxazolines and copper acetate

The bisoxazoline (0.2 mmol, 2 equiv.) was dissolved in methanol (1 ml) and copper(II) acetate (0.1 mmol, 1 equiv.) in methanol (2 ml) was added. An immediate deep purple colour was observed. The reaction was stirred at room temperature for an hour before the solvent was removed. The residue was purified by flushing through a short column of neutral alumina (MeOH spiked $CH_2Cl_2$). The complex and *p*-chlorobenzaldehyde (0.140 g, 1 mmol, 10 equiv.) were dissolved in dichloromethane (1 ml) under argon and phenyldiazomethane (2 mmol, 20 equiv.) in dichloromethane (1 ml) added over 3 h. The reaction was stirred at room temperature overnight before being purified by column chromatography (10% $CH_2Cl_2$–petrol).

### General procedure for epoxidation using bisoxazolines and a copper(I) perchlorate complex

The bisoxazoline (0.1 mmol, 1 equiv.) in dichloromethane (0.5 ml) was added to $Cu(MeCN)_4ClO_4$ (0.1 mmol, 1 equiv.) under argon. The reaction was stirred at room temperature for 3 h during which time the solid slowly dissolved to form a pale solution. *p*-Chlorobenzaldehyde (140 mg, 1 mmol, 10 equiv.) in dichloromethane (0.5 ml) was added, then phenyldiazomethane (2 mmol, 20 equiv.) in dichloromethane (1 ml) was added over 3 h and the reaction stirred at room temperature overnight. The product was purified by column chromatography (10% $CH_2Cl_2$–petrol).

## Acknowledgements

We thank EPSRC for support, and Gair Ford and Rachel Stenson for help with the preparation of the manuscript and for additional experiments.

## References

1 R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, ed. A. Ojima, VCH, New York, 1993, p. 103.
2 T. Katsuki and V. S. Martin, *Org. React.*, 1996, **48**, 1.
3 T. Katsuki, *Coord. Chem. Rev.*, 1995, **140**, 189.
4 E. N. Jacobsen, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 1993, p. 159.
5 Z.-W. Wang, Y. Tu, M. Frohn, J.-R. Zhang and Y. Shi, *J. Am. Chem. Soc.*, 1997, **119**, 11 224.
6 V. K. Aggarwal, H. Abdel-Rahman, L. Fan, R. V. H. Jones and M. C. H. Standen, *Chem. Eur. J.*, 1996, **2**, 212.
7 V. K. Aggarwal, J. G. Ford, A. Thompson, R. V. H. Jones and M. C. H. Standen, *J. Am. Chem. Soc.*, 1996, **118**, 7004.
8 A. Pfaltz, *Acc. Chem. Res.*, 1993, **26**, 339.
9 A. Pfaltz, *Acta Chem. Scand.*, 1996, **50**, 189.

10 R. E. Lowenthal, A. Abiko and S. Masamune, *Tetrahedron Lett.*, 1990, **31**, 6005.
11 R. E. Lowenthal and S. Masamune, *Tetrahedron Lett.*, 1991, **32**, 7373.
12 D. Müller, G. Umbricht, B. Weber and A. Pfaltz, *Helv. Chim. Acta*, 1991, **74**, 232.
13 D. A. Evans, K. A. Woerpal, M. M. Hinman and M. M. Faul, *J. Am. Chem. Soc.*, 1991, **113**, 726.
14 D. A. Evans, K. A. Woerpel and M. J. Scott, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 430.
15 H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo and S. Yamada, *Chem. Pharm. Bull.*, 1965, **13**, 995.
16 D. A. Dickman, A. I. Meyers, G. A. Smith and R. E. Gawley, *Org. Synth.*, 1990, **Coll. Vol. VII**, 530.
17 This amino alcohol is commercially available.
18 J. Hall, J.-M. Lehn, A. Decian and J. Fischer, *Helv. Chim. Acta*, 1991, **74**, 1.
19 G. Koch, *Dissertation Thesis*, *University of Basel*, 1995. See also: H. Witte and W. Seeliger, *Liebigs Ann. Chem.*, 1974, 996. We thank Prof. A. Pfaltz for bringing this method to our attention.
20 $ZnCl_2$ has also been used as a catalyst for this type of transformation: C, Bolm, K. Weickhardt, M. Zehnder and T. Ranff, *Chem. Ber.*, 1991, **124**, 1173; M. Nakamura, A. Hirai and E. Nakanmura, *J. Am. Chem. Soc.*, 1996, **118**, 8489. However, we observed only partial formation of the bisoxazolines (formation of the non-symmetrical oxazoline).
21 R. G. Salomon and J. K. Kochi, *J. Am. Chem. Soc.*, 1973, **95**, 3300.
22 G. J. Kubas, B. Monzyk and A. L. Crumbliss, *Inorg. Synth.*, 1979, **19**, 90.

*Paper* 8/02362J
*Received* 26*th March* 1998
*Accepted* 12*th May* 1998