A new enzymatic enantioselective synthesis of dialkyl sulfoxides catalysed by monooxygenases

Stefano Colonna,*[a] Nicoletta Gaggero,[a] Giacomo Carrea[b] and Piero Pasta[b]

[a] *Istituto di Chimica Organica, Facolta'di Farmacia dell'Universita', Via Venezian 21, 20133 Milano, Italy*
[b] *Istituto di Chimica degli Ormoni, CNR, Via Mario Bianco, 9, 20131 Milano, Italy*

Numerous dialkyl sulfides were enantioselectively oxidized to optically active sulfoxides catalysed by chloroperoxidase or cyclohexanone monooxygenase.

The use of sulfoxides as chiral synthons in asymmetric synthesis is well documented and reliable.[1] Intensive research has demonstrated the efficiency of sulfoxides for controlling the stereoselectivity of a large number of reaction types: alkylation of carbanions, Michael addition, aldolisation reactions, cycloadditions, Pummerer rearrangement and so on. Several sulfoxides also have attractive pharmacological or biological activities.[2] There has been extensive research in recent years trying to develop new methods for the preparation of enantiomerically pure sulfoxides.

The wider application of methodologies based on the sulfinyl function is limited, however, by the relative paucity of general one-step procedures for obtaining enantiomerically pure sulfoxides, especially dialkyl sulfoxides.

Alkyl methyl sulfoxides of high enantiomeric purity have been prepared from cholesterol methyl sulfinates. This process requires a separation of diastereoisomers which are then treated with the relevant alkyl Grignard reagent to furnish the optically active sulfoxide.[3] Similarly, diacetone-d-glucose (DAG) has been used to induce chirality at sulfur.[4] Reaction of diastereoisomerically pure DAG-alkyl sulfinates with Grignard reagents gives optically active dialkyl sulfoxides with high ee (up to ⩾98%).[4]

Optical active cyclic sulfites derived from (*S*)-ethyl lactate have also found use in the preparation of optically active dialkyl sulfoxides.[5] In this case two consecutive displacements with Grignard reagents are required before the chiral transfer agent is released, but separation of intermediate sulfinate esters is still required. Optically active oxazolidinones derived from norephedrine and phenylalanine have also been used in a chiral auxiliary based route to dialkyl sulfoxides.[6]

A different approach to optically active sulfoxides involves an asymmetric oxidation of prochiral sulfides by the Sharpless procedure, modified independently by Kagan[7] and Modena;[8] in the case of dialkyl sulfoxides the ee values ranged between 50–71%. A new catalytic asymmetric oxidation by cumyl hydroperoxide using a chiral titanium complex as catalyst has been reported by Kagan recently (68% ee in the case of octyl methyl sulfoxide).[9] The asymmetric sulfoxidation with enantiomerically pure oxaziridines has been little used for the synthesis of optically active dialkyl sulfoxides.[10,11]

An alternative to asymmetric oxidation with chiral chemical oxidants is the enzymatic oxidation.[12] The only systematic study on an enzymatic asymmetric aliphatic sulfoxidation was carried out by May and co-workers.[13] *Pseudomonas oleovorans*, a non-haem monooxygenase, catalyses stereoselective sulfoxidation of methyl thioether substrates. The ee values of the prevailing sulfoxide are in the range 2–88%, depending upon the structure of the second alkyl chain. Apart from the necessity of a terminal methyl group, the biotransformation catalysed by *Pseudomonas oleovorans* suffers from a poor chemical yield.

Here we present a new enzymatic general approach to the synthesis of dialkyl sulfoxides with high ee. The enzymes used were chloroperoxidase from *Caldariomyces fumago* (CPO) and cyclohexanone monooxygenase (CMO) from *Acinetobacter* NCIB 9871, an iron-haem and a flavin-dependent oxidoreductase, respectively.

Previously, we have shown that these enzymes can catalyse the asymmetric sulfoxidation of numerous alkyl aryl sulfides with high enantioselectivity.[14] The versatility of CMO in promoting enantioselective sulfoxidations has been recently exploited also with 1,3-dithioacetals.[15]

Yields and enantiomeric excesses of the CPO and CMO catalysed oxidation of the dialkyl sulfides tested are reported in Tables 1 and 2. Cyclopentyl methyl sulfide **1**, allyl methyl sulfide **3**, isopropyl methyl sulfide **6** and bis(thiomethyl) methane **9** are excellent substrates for CPO in terms of chemical yield and ee. The increase in the size of the cycloalkane bound to the sulfur (cyclohexyl **2** instead of cyclopentyl **1**), leads to an appreciable decrease in chemical and optical yield. The importance of steric factors on chemical yield and ee is confirmed by the results obtained with methyl sulfides with different alkyl chains **4**, **5**. An increase in the branching of the alkyl chain causes similar effects **6**, **7**. These results can be rationalized by taking into account the higher contribution of the competitive spontaneous oxidation of the more hindered starting materials for which the enzymatic oxidation is slower. As already observed for alkyl aryl sulfides,[14] the oxidation of

Table 1 CPO catalysed oxidation of sulfides to the corresponding sulfoxides [a]

Sulfide	Conversion (%)	Ee (%)	Configuration
1 Cyclopentyl methyl sulfide	⩾98	⩾98	*R*[b]
2 Cyclohexyl methyl sulfide	85	85	*R*
3 Allyl methyl sulfide	⩾98	⩾98	*R*
4 Pentyl methyl sulfide	75	⩾98	*R*
5 Octyl methyl sulfide	40	54	*R*
6 Isopropyl methyl sulfide	⩾98	⩾98	*R*
7 *tert*-Butyl methyl sulfide	80	85	*R*
8 *tert*-Butyl ethyl sulfide	30	35	*R*
9 Bis(thiomethyl)methane	75	⩾98	*R*

[a] The sulfide (0.42 mmol) and CPO (Sigma) (6.7×10^{-6} mmol) were magnetically stirred in 40 ml of 0.05 mol dm^{-3} citrate buffer, pH 5 at 25 °C for 5 min. H_2O_2 (0.42 mmol) in 480 μl of buffer, pH 5, was added in 18 aliquots at 3 min intervals. The reaction was quenched with sodium sulfite, extracted with diethyl ether and dried. The enantiomeric excesses of sulfoxides were determined by chiral HPLC on a Chiralcel OB column (Daicel), using the proper mixture of hexane and propan-2-ol as the mobile phase. The absolute configuration of sulfoxides was determined by comparison with authentic samples prepared by Sharpless oxidation and using chiral HPLC. [b] The absolute configuration of cyclopentyl methyl sulfoxide was determined by analysis of its ^{1}H NMR spectrum in the presence of the chiral shift reagent (*S*)-(+)-α-methoxy-α-phenylacetic acid (ref. 17).

Table 2 CMO catalysed oxidation of sulfides to the corresponding sulfoxides [a]

Sulfide	Conversion (%)	Ee (%)	Configuration
1 Cyclopentyl methyl sulfide	80	⩾98	*R*[b]
2 Cyclohexyl methyl sulfide	86	⩾98	*R*
3 Allyl methyl sulfide	82	⩾98	*R*
4 Pentyl methyl sulfide	58	60	*S*
5 Octyl methyl sulfide	50	50	*S*
6 Isopropyl methyl sulfide	75	⩾98	*R*
7 *tert*-Butyl methyl sulfide	85	⩾98	*R*
8 *tert*-Butyl ethyl sulfide	30	35	*R*
10 *tert*-Butyl vinyl sulfide	78	⩾98	*R*
11 Cyclohexyl ethyl sulfide	8	47	*R*
12 4-Hydroxyethyl methyl sulfide	80	33	*R*

[a] The sulfide (0.1 mmol) was magnetically stirred in 4 ml of 0.05 mol dm^{-3} Tris–HCl buffer, pH 8.6, containing 2 μmol NADPH, 0.4 mmol glucose-6-phosphate, 5 units of CMO and 10 units of glucose-6-phosphate dehydrogenase. After overnight reaction, the solution was extracted with 4 portions (4 ml each) of diethyl ether and the organic extract was dried and evaporated. The enantiomeric excesses of sulfoxides were determined by chiral HPLC on a Chiralcel OB column (Daicel), using the proper mixture of hexane and propan-2-ol as the mobile phase. The absolute configuration of sulfoxides was determined by comparison with authentic samples prepared by Sharpless oxidation and using chiral HPLC. [b] The absolute configuration of cyclopentyl methyl sulfoxide was determined by analysis of its ^{1}H NMR spectrum in the presence of the chiral shift reagent (*S*)-(+)-α-methoxy-α-phenylacetic acid.[17]

dialkyl sulfides affords predominantly or exclusively the corresponding (*R*)-sulfoxide.

For CMO promoted sulfoxidation, high enantioselectivity is observed for cycloalkyl methyl sulfoxides (**1**, **2**), and methyl sulfoxides with a linear or branched alkyl chain of up to four carbon atoms (**3**, **6**, **7**). In all these cases the absolute configuration of the prevailing enantiomer is *R*. A longer alkyl chain not only causes a drastic drop in the chemical and optical yield **4**, **5**, but also changes the stereochemical course of the sulfoxidation, since the resulting enantiomer now has the *S* absolute configuration.

The predictive active site model for the cyclohexanone monooxygenase catalysed oxidation of sulfides to sulfoxides, already proposed by us,[16] is compatible with these results but does not offer conclusive evidence due to the high conformational freedoms of dialkyl sulfides.

A comparison of the results obtained in the oxidation of dialkyl sulfides with CPO and CMO leads to the following conclusions: (i), both enzymes exibit high enantioselectivity in the oxidation of cycloalkyl methyl and alkyl methyl sulfides with limited steric requirements; (ii), the two enzymatic systems are enantiocomplementary for pentyl methyl sulfide and for octyl methyl sulfide, leading in all other cases to the (*R*)-sulfoxides; (iii) chloroperoxidase is more convenient than cyclohexanone monooxygenase since it is commercially available, uses hydrogen peroxide as oxidant and does not require the regeneration of the cofactor, as in the case with CMO.

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