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Chemoenzymatic synthesis of enantiopure hydroxy sulfoxides derived from substituted arenes†

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Enantiopure β-hydroxy sulfoxides and catechol sulfoxides were obtained, by chemoenzymatic synthesis, involving dioxygenase-catalysed benzylic hydroxylation or arene *cis*-dihydroxylation and *cis*-diol dehydrogenase-catalysed dehydrogenation. Absolute configurations of chiral hydroxy sulfoxides were determined by X-ray crystallography, ECD spectroscopy and stereochemical correlation. The application of a new range of β-hydroxy sulfoxides as chiral ligands was examined.

1 Introduction

Ring hydroxylating arene dioxygenase enzymes, *e.g.* toluene dioxygenase (TDO), naphthalene dioxygenase (NDO), and biphenyl dioxygenase (BPDO), are best known for their ability, to catalyse the *cis*-1,2-dihydroxylation of monocyclic and polycyclic arenes and heteroarenes, in a regio- and stereo-selective manner. Enantiopure *cis*-dihydrodiol metabolites, obtained by TDO-catalysed oxidation of monocyclic arenes, have been widely used as precursors in the chemoenzymatic synthesis of chiral natural and unnatural products of value in medicinal chemistry.[1a–e] Enantiopure *cis*-diol metabolites (**a**) and (**b**), derived from bromobenzene[2a] and 2-chloroquinoline[2b] respectively, were also found to be useful precursors of chiral ligands (Scheme 1).[1b]

While arene *cis* dihydroxylation, to yield *cis*-dihydrodiols, has been the most widely studied of reactions catalysed by arene dioxygenases, much less attention has been directed to the ability of this enzyme system to catalyse other types of hydroxylation. These include: (i) benzylic monohydroxylation of alcohols to give diols,[3a–c] *e.g.* 2-hydroxyindane → *cis*-1,2-dihydroxyindane (**c**),[3c] (ii) sequential benzylic-1,3-dihydroxylation of benzocycloalkanes,[3b,c] *e.g.* indane → 1-hydroxyindane → *trans*-1,3-dihydroxyindane (**d**),[3c] (iii) sequential benzylic monohydroxylation and *cis*-dihydroxylation (trihydroxylation) of monocyclic arenes, *e.g.* ethylbenzene → 1-phenylethanol → *cis*-dihydrodiol (**e**)[4a,b] and (iv) sequential bis *cis*-dihydroxylation (tetrahydroxylation) of polycyclic arenes,[5a,b] *e.g.* chrysene → 3,4-dihydroxy-3,4-dihydrochrysene → chrysene bis *cis*-dihydrodiol (**f**).[5b] The addition of these less common types of enantiopure hydroxylated arene metabolites, into the chiral pool, has presented further opportunities for chemoenzymatic synthesis, including their application as chiral reagents, ligands or auxiliaries.

In our earlier studies,[3b,c] a series of 2-substituted indane substrates were used with *P. putida* UV4 whole cells; it resulted, initially, in TDO enzyme-catalysed benzylic monohydroxylation to give the corresponding enantiopure *cis* isomers as the main metabolites. Major objectives of the current study were to: (i) re-examine the stereochemistry and mechanism of the benzylic hydroxylation of 2-chloroindane, using *P. putida* UV4, where both mono- and di-hydroxylation at benzylic positions was observed earlier, (ii) utilize mono- and di-hydroxylated 2-chloroindane metabolites as synthetic precursors of enantiopure β-hydroxy sulfoxides, (iii) synthesise and aromatize diastereomeric monosubstituted benzene *cis*-diol sulfoxides and obtain chiral hydroxy sulfoxides *via* chiral transfer and (iv) evaluate the potential of hydroxy sulfoxides as chiral ligands.

2 Results and discussion

(i) TDO-catalysed synthesis and stereochemical assignment of hydroxylated 2-chloroindanes.

The regiochemistry and stereochemistry of TDO-catalysed benzylic hydroxylation of 2-chloroindane **1** was investigated using whole cells of *P. putida* UV4.[3c] An initial biotransformation of substrate **1** (3.0 g) yielded only the *trans*-dihydroxylated product $\mathbf{3}_{1S,3S}$ (38% yield), which in principle could be formed from either of the undetected intermediates, *cis*-$\mathbf{2}_{1S,2R}$ or *trans*- $\mathbf{4}_{1S,2S}$ chlorohydrins (Scheme 2).

When this experiment was repeated using a shorter biotransformation on a smaller scale (0.25 g), only monohydroxy-

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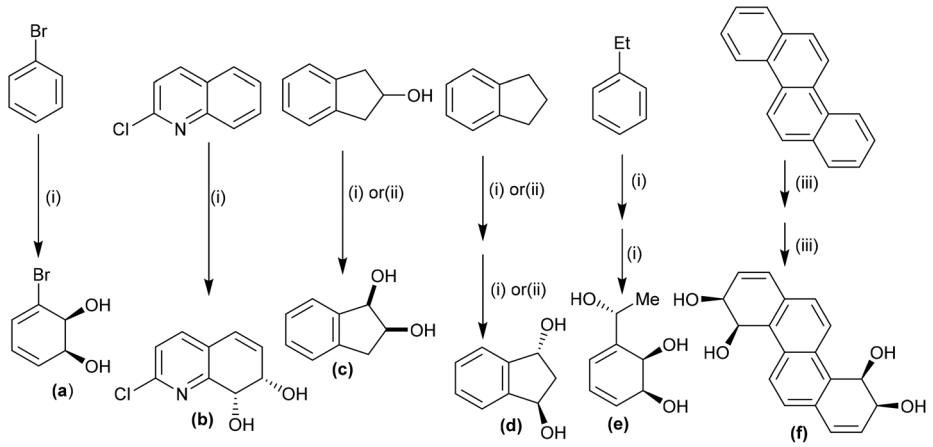
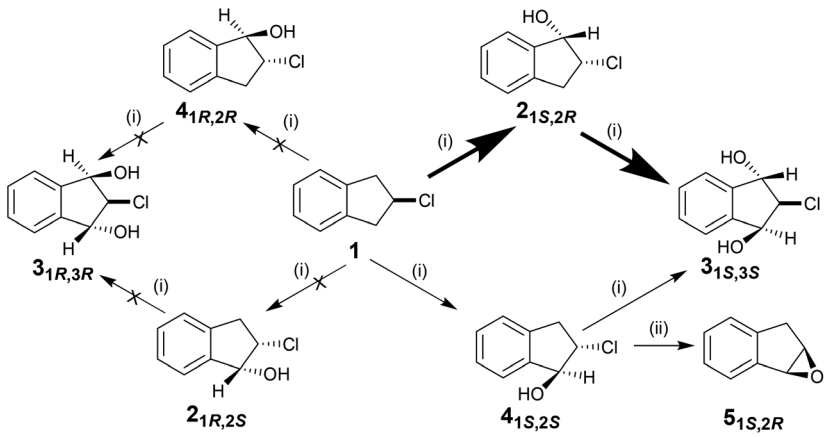


Scheme 1 Selected examples of dioxygenase-catalysed enantioselective hydroxylations including, monocyclic arene *cis*-dihydroxylation (**a**), polycyclic heteroarene *cis*-dihydroxylation (**b**), benzylic monohydroxylation (**c**), benzylic dihydroxylation (**d**), monocyclic arene trihydroxylation (**e**) and polycyclic arene tetrahydroxylation (**f**). Reagents: (i) TDO/O_2; (ii) NDO/O_2; (iii) BPDO/O_2.



Scheme 2 Biotransformation of 2-chloroindane (**1**) to yield monohydroxylated ($\mathbf{2}_{1S,2R}$ and $\mathbf{4}_{1S,2S}$) and dihydroxylated ($\mathbf{3}_{1S,3S}$) metabolites using *P. putida* UV4 as a source of TDO. Reagents: (i) TDO/O_2; (ii) NaOMe/Et_2O.

lation products were obtained.[3c] The main metabolites, *cis*-chlorohydrin $\mathbf{2}_{1S,2R}$ or $\mathbf{2}_{1R,2S}$ (90% relative yield) and *trans*-chlorohydrin $\mathbf{4}_{1S,2S}$ or $\mathbf{4}_{1R,2R}$ (10% relative yield), having very similar R_f values, were difficult to separate by chromatography. A pure sample of the main chlorohydrin **2**, obtained by fractional crystallization of the mixture, was assigned a (1*S*,2*R*) configuration. This more abundant isomer, *cis*-$\mathbf{2}_{1S,2R}$, isolated during this study, was assumed to be the precursor of the earlier isolated metabolite $\mathbf{3}_{1S,3S}$, formed *via* the metabolic sequence $\mathbf{1} \rightarrow \mathbf{2}_{1S,2R} \rightarrow \mathbf{3}_{1S,3S}$ (Scheme 2). After the removal of most *cis*-chlorohydrin $\mathbf{2}_{1S,2R}$, by repeated fractional crystallization, a small sample (*ca.* 20 mg) of the pure *trans*-chlorohydrin, $\mathbf{4}_{1S,2S}$ or $\mathbf{4}_{1R,2R}$, was separated from the residual mixture by reverse phase PLC (80% MeOH/H_2O).

Characterization of this metabolite was accomplished, by a combination of MS, IR, NMR spectroscopy, measurement of $[\alpha]_D$ and the formation of MTPA ester derivatives. ^{1}H-NMR analysis of the MTPA esters, formed using both MTPA chloride enantiomers, indicated that (+) *trans*-chlorohydrin ($\mathbf{4}_{1S,2S}$ or $\mathbf{4}_{1R,2R}$) was enantiopure (>98% ee).[3c] Based on the earlier use of NMR analysis of diMTPA ester derivatives of benzocycloalkane *cis*-diols, in the determination of absolute configurations,[3d] the (1*R*,2*R*) configuration had been tentatively assigned to metabolite **4**. It was, however, noted that this configuration was unexpected, since the benzylic (*S*) hydroxylation was preferred in the initial TDO-catalysed step, 2-chloroindane $\mathbf{1} \rightarrow$ *cis*-chlorohydrin $\mathbf{2}_{1S,2R}$. A similar (*S*) benzylic hydroxylation of *trans*-chlorohydrin $\mathbf{4}_{1R,2R}$ would thus yield compound $\mathbf{3}_{1R,3R}$ not the isolated metabolite $\mathbf{3}_{1S,3S}$.[3c]

In view of the previous reservations expressed about the reliability of the (1*R*,2*R*) absolute configuration, tentatively assigned to *trans*-chlorohydrin **4**,[3c] and the requirement to

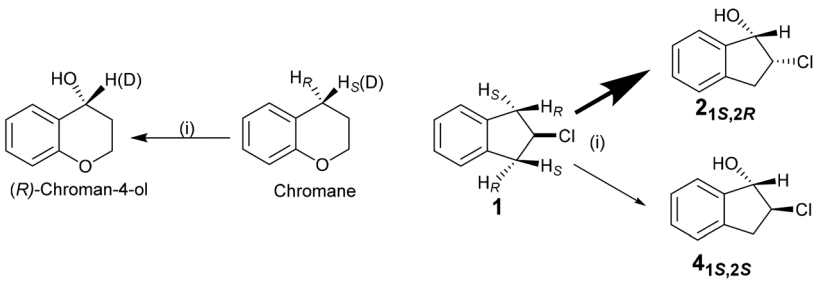
produce further quantities of metabolites $\mathbf{2}_{1S,2R}$ and $\mathbf{3}_{1S,3S}$, for potential applications in chemoenzymatic synthesis, a larger scale biotransformation of 2-chloroindane **1** (5.0 g) was carried out. The resulting crude mixture of mono- and di-hydroxylated bioproducts was partially separated by column chromatography. A pure sample of more polar *trans*-diol $\mathbf{3}_{1S,3S}$ (28% isolated yield) was obtained and the less polar *cis*- and *trans*-chlorohydrins were collected as an inseparable mixture (8 : 1). *cis*-Chlorohydrin $\mathbf{2}_{1S,2R}$ was isolated in pure form by fractional crystallization (29% yield) and the residual mixture (4 : 1; 100 mg) of *cis*- and *trans*-chlorohydrins was stirred with NaOMe in Et_2O solution. It yielded (21 mg) of enantiopure epoxide $\mathbf{5}_{1S,2R}$, $[\alpha]_D$ +55 ($CHCl_3$) of established (1*S*,2*R*) absolute configuration,[6] after PLC separation from the unreacted *cis*-isomer $\mathbf{2}_{1S,2R}$. This result showed that the (1*R*,2*R*) configurational assignment, originally assumed for the minor *trans*-chlorohydrin precursor **4**, was incorrect.[3c] It should have been (1*S*,2*S*), which is now consistent with *trans*-diol $\mathbf{3}_{1S,2S}$ metabolite being formed from both *cis*-$\mathbf{2}_{1S,2R}$ and *trans*-$\mathbf{4}_{1S,2S}$ chlorohydrin intermediates (Scheme 2).

Mechanistic studies of TDO-catalysed benzylic hydroxylation, using specifically deuterated chromane enantiomers as substrates, with *P. putida* UV4 whole cells or purified TDO, demonstrated an exclusive formation of the (*R*) enantiomer (>98% ee) with retention of configuration (Scheme 3).[7] A similar stereopreference was observed, during abstraction of prochiral benzylic hydrogen atoms in chromane and 2-chloroindane (H_R and H_S respectively, in accordance with Sequence Rule priority). A mechanism, involving benzylic radical formation and stereospecific addition of a hydroxyl group, to form a chiral benzyl alcohol with retention of configuration, was assumed to occur, during the TDO-catalysed benzylic hydroxylation of both chromane and 2-chloroindane **1**, to yield (*R*)-chroman-4-ol and chlorohydrins $\mathbf{2}_{1S,2R}$ and $\mathbf{4}_{1S,2S}$ respectively.

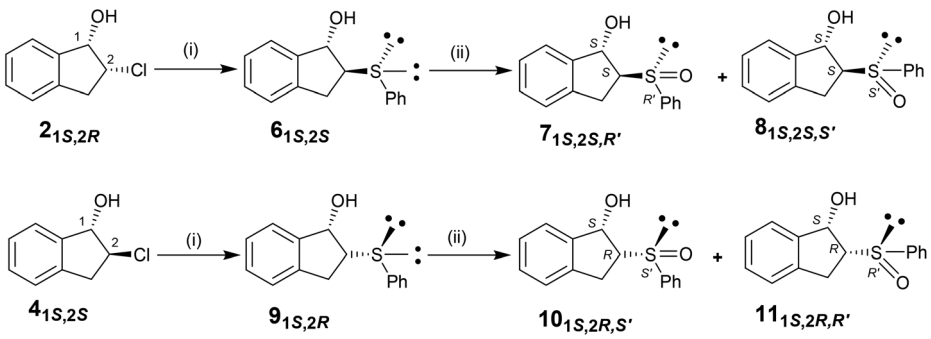
(ii) Chemoenzymatic synthesis of enantiopure β-hydroxy sulfoxides, derived from metabolites $\mathbf{2}_{1S,2R}$ and $\mathbf{3}_{1S,3S}$.

Enantiopure β-hydroxy sulfoxides have been used as chiral auxiliaries,[8a] protonating agents[8b] ligands,[8c] and synthetic precursors. Earlier approaches to the synthesis of β-hydroxy sulfoxide enantiomers have included asymmetric sulfoxidations of β-keto sulfides using chemical oxidants, *e.g.* *t*-butyl hydroperoxide, diethyl tartrate, $Ti(i\text{-}PrO)_4$ [8d] and enzymatic oxidants, *e.g.* cyclohexanone monooxygenase.[8e] In this study, chemical and enzymatic methods were combined, to provide alternative chemoenzymatic synthesis pathways to enantiopure β-hydroxy sulfoxides, involving TDO-catalysed mono- and di-hydroxylations and chemical sulfoxidations.

Treatment of the *cis*-chlorohydrin $\mathbf{2}_{1S,2R}$ with thiophenol and a base (K_2CO_3) in acetonitrile solution, resulted in a nucleophilic substitution of the Cl atom, to give β-hydroxy sulfide $\mathbf{6}_{1S,2S}$ in 80% yield. The reaction is assumed to proceed, *via* an S_N2 mechanism, with inversion of configuration at C-2 (Scheme 4). Similar treatment of the residual



Scheme 3 Stereoselectivity of TDO-catalysed benzylic hydroxylation of chromane and 2-chloroindane using *P. putida* UV4. Reagents: (i) TDO/O_2.



Scheme 4 Synthesis of β-hydroxy sulfides $\mathbf{6}_{1S,2S}$, $\mathbf{9}_{1S,2R}$. and β-hydroxy sulfoxides $\mathbf{7}_{1S,2S,R'}$, $\mathbf{8}_{1S,2S,S'}$, $\mathbf{10}_{1S,2R,S'}$, $\mathbf{11}_{1S,2R,R'}$. Reagents: (i) PhSH, K_2CO_3, MeCN; (ii) DMD/Me_2CO.

inseparable mixture (7 : 3) of chlorohydrins $\mathbf{2}_{1S,2R}$ and $\mathbf{4}_{1S,2S}$, present in the mother liquors, yielded a mixture of the β-hydroxy sulfides $\mathbf{6}_{1S,2S}$ (76% yield) and $\mathbf{9}_{1S,2R}$ (71% yield), which was separated by column chromatography.

When the hydroxy sulfide isomers $\mathbf{6}_{1S,2S}$ and $\mathbf{9}_{1S,2R}$ were separately treated with a solution of dimethyl dioxirane (DMD) in acetone, β-hydroxy sulfoxide diastereoisomeric pairs $\mathbf{7}_{1S,2S,R'}/\mathbf{8}_{1S,2S,S'}$ and $\mathbf{10}_{1S,2R,S'}/\mathbf{11}_{1S,2R,R'}$ respectively were produced (83–88% yield). Pure samples of individual diastereoisomers were obtained using multiple elution PLC. Change of configuration was assumed at C-2 (inversion), during the synthesis of β-hydroxy sulfides $\mathbf{6}_{1S,2S}$ and $\mathbf{9}_{1S,2R}$. As an exocyclic stereogenic centre was introduced during sulfoxidation, rigorous methods were required for assignment of absolute configurations to β-hydroxy sulfoxide diastereoisomers $\mathbf{7}_{1S,2S,R'}$, $\mathbf{8}_{1S,2S,S'}$, $\mathbf{10}_{1S,2R,S'}$ and $\mathbf{11}_{1S,2R,R'}$.

(iii) Stereochemical assignment of β-hydroxy sulfoxides $\mathbf{7}_{1S,2S,R'}$, $\mathbf{8}_{1S,2S,S'}$, $\mathbf{10}_{1S,2R,S'}$ and $\mathbf{11}_{1S,2R,R'}$.

Since absolute configurations had already been established for the *cis*- and *trans*-chlorohydrins, $\mathbf{2}_{1S,2R}$ and $\mathbf{4}_{1S,2S}$, a combination of spectroscopy (NMR, ECD), stereochemical correlation and X-ray crystallography was used to confirm the relative and absolute configurations at each of the three chiral centres in the derived β-hydroxy sulfoxides $\mathbf{7}_{1S,2S,R'}$, $\mathbf{8}_{1S,2S,S'}$, $\mathbf{10}_{1S,2R,S'}$ and $\mathbf{11}_{1S,2R,R'}$.

Although it is generally more difficult to assign vicinal *cis* or *trans* configurations in five-membered rings relative to six-membered rings, using NMR spectroscopy, it had earlier been established[3c] that disubstituted *cis*-1,2-indanes exhibited smaller *vicinal* coupling constants ($J_{1,2}$, Hz) than their *trans* isomers. On this basis the $J_{1,2}$ values for *cis*/*trans* disubstituted 1,2-indanes were presumed to be: $\mathbf{2}_{1S,2R}$ (5.0)/$\mathbf{4}_{1S,2S}$ (5.8), $\mathbf{9}_{1S,2R}$ (4.9)/$\mathbf{6}_{1S,2S}$ (5.7), $\mathbf{10}_{1S,2R,S'}$ (6.8)/$\mathbf{7}_{1S,2S,R'}$ (7.3) and $\mathbf{11}_{1S,2R,R'}$ (5.6)/$\mathbf{8}_{1S,2S,S'}$ (6.4).

The electronic circular dichroism (ECD) spectra of alkylaryl sulfoxide enantiomers were reported to show strong positive absorptions (Cotton effects) at *ca.* 235–255 nm for (*R*) configurations and conversely strong negative absorptions for (*S*) sulfoxides.[9a] The ECD spectrum of *trans* β-hydroxy sulfoxide $\mathbf{7}_{1S,2S,R'}$ (λ 241 nm, $\Delta\varepsilon$ +9.15), was therefore consistent with an (*R*) sulfoxide configuration and *trans* β-hydroxy sulfoxide $\mathbf{8}_{1S,2S,S'}$ (λ 245 nm, $\Delta\varepsilon$ −7.51) had the opposite (*S*) configuration at the chiral sulfoxide centre.

Similarly, ECD spectroscopy of β-hydroxy sulfoxides $\mathbf{10}_{1S,2R,S'}$ (λ 243 nm, $\Delta\varepsilon$ −8.15) and $\mathbf{11}_{1S,2R,R'}$ (λ 246 nm, $\Delta\varepsilon$ +6.53) was employed, to assign them the (*S*) and (*R*) sulfoxides configurations respectively. Unequivocal evidence of the validity of the NMR coupling constant method, for assignment of *cis* or *trans* relative configurations in five membered rings, and reliability of the ECD method for determination of absolute configurations of sulfoxides, was provided by X-ray crystal structure analysis of β-hydroxy sulfoxide $\mathbf{11}_{1S,2R,R'}$, using the anomalous dispersion method (Fig. 1). This confirmed the *cis* relationship, and absence of intramolecular H-bonding, between OH and S═O groups and the (1*S*,2*R*,*R*′) absolute configuration.

Treatment of *trans*-1,3-diol metabolite $\mathbf{3}_{1S,3S}$, in a similar manner to chlorohydrins $\mathbf{2}_{1S,2R}$ and $\mathbf{4}_{1S,2S}$ (PhSH, K_2CO_3, MeCN), yielded a mixture of two products, which were separated by column chromatography (Scheme 5). Nucleophilic substitution at C-2 yielded the expected *trans*-diol sulfide $\mathbf{12}_{1S,3S}$ as the major product (34% yield). The unexpected minor

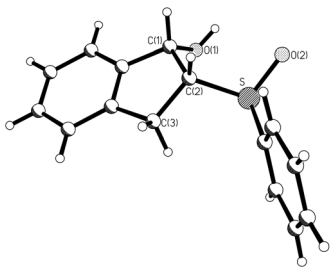
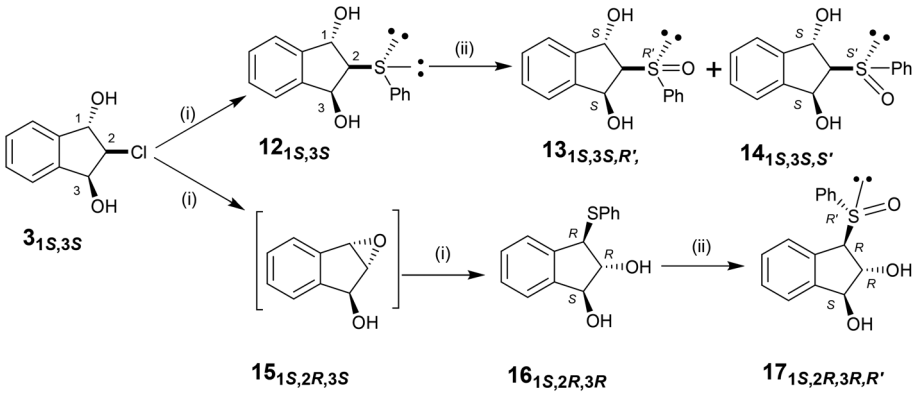


Fig. 1 X-ray crystal structure of sulfoxide $\mathbf{11}_{1S,2R,R'}$.



Scheme 5 Synthesis of β-hydroxy sulfides $\mathbf{12}_{1S,3S}$ and $\mathbf{16}_{1S,2R,3R}$ and the derived β-hydroxy sulfoxides $\mathbf{13}_{1S,3S,R'}$, $\mathbf{14}_{1S,3S,S'}$ and $\mathbf{17}_{1S,2R,3R,R'}$. Reagents: (i) PhSH, K_2CO_3, MeCN; (ii) DMD/Me_2CO.

product was identified as the more polar isomeric *trans*-1,2-diol sulfide $\mathbf{16}_{1S,2R,3R}$ (15% yield).

A possible mechanism for the formation of sulfide $\mathbf{16}_{1S,2R,3R}$ would involve: (i) base-catalysed cyclization of *trans*-1,3-diol $\mathbf{3}_{1S,3S}$ to give the undetected epoxide intermediate $\mathbf{15}_{1S,2R,3S}$ and (ii) nucleophilic attack of thiophenoxide, at the preferred benzylic position of epoxide $\mathbf{15}_{1S,2R,3S}$, to yield *trans*-diol sulfide $\mathbf{16}_{1S,2R,3R}$. It was surprising that under similar reaction conditions *trans*-chlorohydrin $\mathbf{4}_{1S,2S}$ did not yield epoxide $\mathbf{5}_{1S,2R}$ (Scheme 2), which could also have been attacked by thiophenoxide. It is possible that, due to steric interactions, a change in preferred conformation between the *trans* OH group and Cl atom in chlorohydrin $\mathbf{3}_{1S,3S}$, relative to chlorohydrin $\mathbf{4}_{1S,2S}$, would facilitate cyclization and yield the epoxide intermediate $\mathbf{15}_{1S,2R,3S}$.

Sulfoxidation of *trans*-1,3-sulfide $\mathbf{12}_{1S,3S}$, using DMD as oxidant, gave a mixture of β-hydroxy sulfoxide diastereoisomers $\mathbf{13}_{1S,3S,R'}$ (45% yield) and $\mathbf{14}_{1S,3S,S'}$ (37% yield), which was separated by PLC. The absolute configurations of the sulfoxide chiral centres in diastereoisomers $\mathbf{14}_{1S,3S,S'}$ (λ 244 nm, $\Delta\varepsilon$ −5.28) and $\mathbf{13}_{1S,3S,R'}$ (λ 248 nm, $\Delta\varepsilon$ +4.40) were assigned as (*S*) and (*R*) respectively, based on their ECD spectra. X-ray crystal structure analysis of diastereoisomer, β-hydroxy sulfoxide $\mathbf{14}_{1S,3S,S'}$, using the anomalous dispersion method, confirmed its absolute configuration as (1*S*,3*S*,*S*′) (Fig. 2). H-bonding with allylic OH groups led to a directing effect of DMD during stereoselective epoxidations.[10] A similar rationalization could account for the formation of both diastereoisomers $\mathbf{13}_{1S,3S,R'}$ and $\mathbf{14}_{1S,3S,S'}$, with DMD directed by a benzylic OH group toward either lone pair on the sulfur atom of *trans*-1,3-sulfide $\mathbf{12}_{1S,3S}$.

Only one β-hydroxy sulfoxide isomer was obtained upon treatment of β-hydroxy sulfide $\mathbf{16}_{1S,2R,3R}$ with DMD. The structure and absolute configuration (1*S*,2*R*,3*R*,*R*′) of β-hydroxy sulfoxide $\mathbf{17}_{1S,2R,3R,R'}$ was assigned by a combination of NMR spectroscopy and X-ray crystallography, using the anomalous dispersion method (Fig. 3). The formation of a single diastereoisomer, $\mathbf{17}_{1S,2R,3R,R'}$, was again assumed to be due to H-bonding of DMD with a benzylic hydroxyl group. This directed the oxidant preferentially toward one of the lone pairs on the sulfur atom in hydroxy sulfide $\mathbf{16}_{1S,2R,3R}$, thus reducing steric interactions between the bulky phenyl group and the other aryl ring and yielding compound $\mathbf{17}_{1S,2R,3R,R'}$.

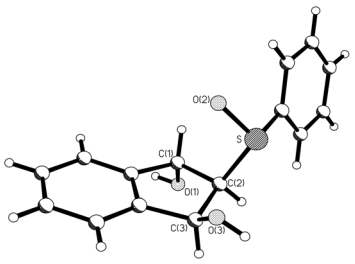


Fig. 2 X-ray crystal structure of $\mathbf{14}_{1S,3S,S'}$.

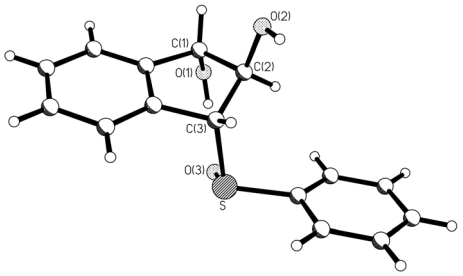


Fig. 3 X-ray structure of $\mathbf{17}_{1S,2R,3R,R'}$.

In the crystal of sulfoxide $\mathbf{17}_{1S,2R,3R,R'}$ the five-membered ring has a substantial envelope conformation, with C-2 nearly 0.4 Å out of the plane of the other four atoms. With the OH group on C-2 almost fully axial, the sulfur atom and the other OH group are thus pseudo-axial. By contrast, in hydroxy sulfoxides $\mathbf{11}_{1S,2R,R'}$ and $\mathbf{14}_{1S,3S,S'}$ the ring has a more shallow envelope conformation and thus the substituents on C-2, although tending slightly towards the axial, cannot be described as truly axial.

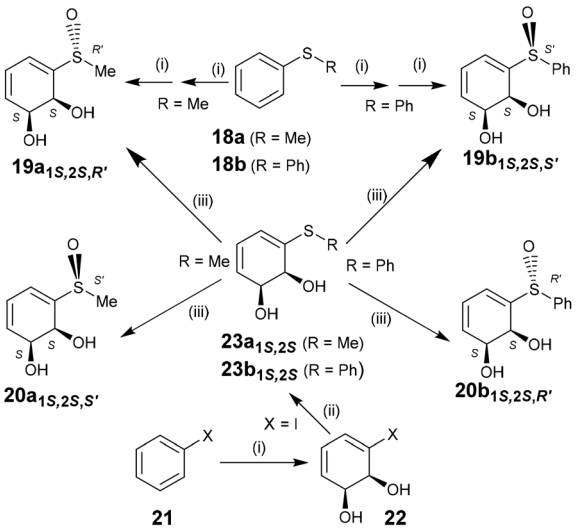
(iv) Chemoenzymatic synthesis of *cis*-diol sulfoxides $\mathbf{19b}_{1S,2S,S'}$, and $\mathbf{20b}_{1S,2S,R'}$.

Earlier tandem biotransformations of alkylaryl sulfides, using *P. putida* UV4 whole cells as a TDO source, in some cases, resulted in heteroatom oxidation to yield enantiopure sulfoxides, and further metabolism, to yield the corresponding *cis*-dihydrodiol sulfoxides. Thus, *cis*-dihydrodiol sulfoxides $\mathbf{19a}_{1S,2S,R'}$ and $\mathbf{19b}_{1S,2S,S'}$, were isolated as single diastereoisomers, *via* TDO-catalysed (*P. putida* UV4) oxidation of the alkylaryl sulfide **18a** and the diaryl sulfide **18b** respectively.[11a,b] Since no evidence of the alternative diastereoisomers $\mathbf{19a}_{1S,2S,S'}$ and $\mathbf{19b}_{1S,2S,R'}$ was found, using *P. putida* UV4, a chemoenzymatic approach to synthesise both *cis*-diol sulfoxide diastereoisomers, was adopted (Scheme 6).

cis-Diol sulfides $\mathbf{23a}_{1S,2S}$ and $\mathbf{23b}_{1S,2S}$ were obtained from the hydroxylated metabolite **22** (X = I) derived from iodobenzene **21** (X = I), *via* a palladium-catalysed cross coupling process, using tributyltin reagents (R = Me or Ph, Scheme 6).[11c] Treatment of sulfides $\mathbf{23b}_{1S,2S}$ and $\mathbf{23a}_{1S,2S}$ with DMD, gave mixtures of *cis*-diol sulfoxide diastereoisomers $\mathbf{19b}_{1S,2S,S'}$/$\mathbf{20b}_{1S,2S,R}$ and $\mathbf{19a}_{1S,2S,S'}$/$\mathbf{20a}_{1S,2S,R'}$. Diastereoisomers $\mathbf{19b}_{1S,2S,S'}$ and $\mathbf{20b}_{1S,2S,R'}$ were separated by multi elution PLC, but diastereoisomers $\mathbf{19a}_{1S,2S,S'}$/$\mathbf{20a}_{1S,2S,R'}$ could not be separated.

(v) Stereochemical assignment of sulfoxide *cis*-diol $\mathbf{20b}_{1S,2S,R'}$.

Since the metabolites $\mathbf{19a}_{1S,2S,R'}$ and $\mathbf{19b}_{1S,2S,S'}$, obtained directly from tandem biotransformations of sulfides **18a** and **18b**, were obtained as gums, their absolute configurations were assigned using ECD spectroscopy.[11a] With a crystalline sample of (+)-sulfoxide *cis*-diol $\mathbf{20b}_{1S,2S,R'}$ available, its absolute configuration was confirmed by X-ray crystallography (Fig. 4). It is noteworthy that the X-ray crystal structure of compound $\mathbf{20b}_{1S,2S,R'}$ contained equal proportions of two crystallographically



Scheme 6 TDO-catalysed oxidation of the sulfides **18a** and **18b** to yield *cis*-diol sulfoxides $\mathbf{19a}_{1S,2S,R'}$ and $\mathbf{19b}_{1S,2S,S'}$ and chemoenzymatic synthesis of *cis*-diol sulfoxides $\mathbf{19b}_{1S,2S,S'}$, and $\mathbf{20b}_{1S,2S,R'}$ from the *cis*-dihydrodiol metabolite **22** (X = I) of iodobenzene **21**. Reagents and conditions: (i) *P. putida* UV4, (ii) *n*-Bu_3SnSR, (iii) DMD, acetone.

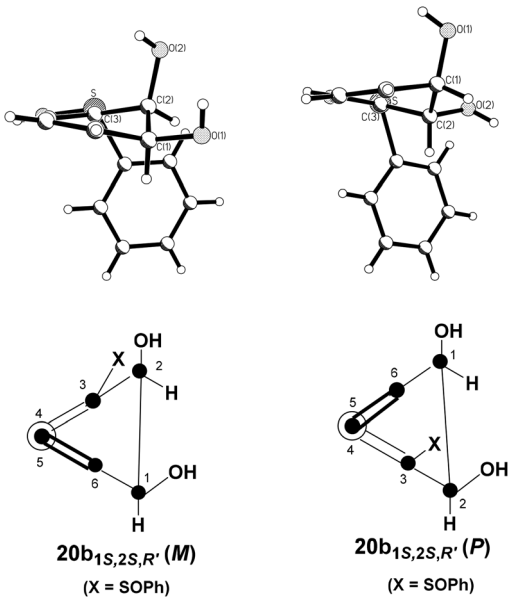


Fig. 4 X-ray crystal structures of *cis*-diol sulfoxide conformers $\mathbf{20b}_{1S,2S,R'}$ (*M*) and $\mathbf{20b}_{1S,2S,R'}$ (*P*) viewed along the diene central bond.

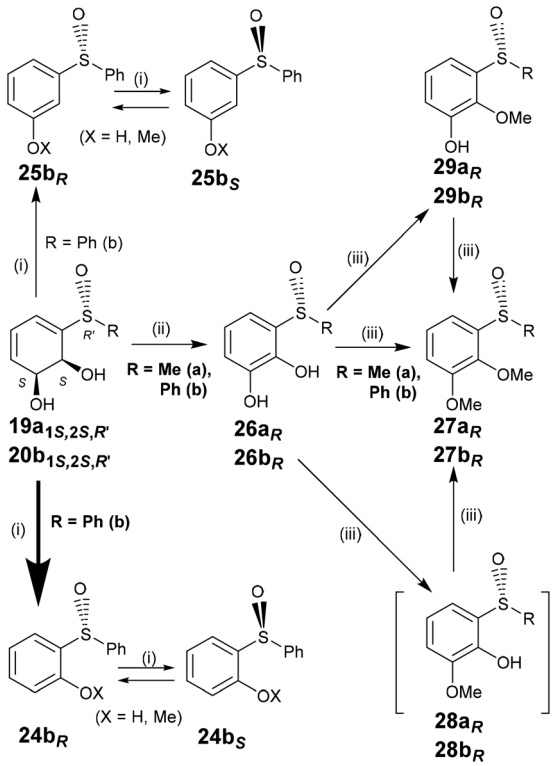
independent molecules, in the unit cell with identical 1*S*,2*S*,*R*′ absolute configurations, but with different *M* and *P* diene conformations. In the crystalline state, the *M* conformer, with torsion angle −13° along the diene unit, had a pseudo-axial OH group at C-2 and a pseudo-equatorial OH group at C-1. Conversely, the other independent molecule adopted a *P* conformation, with torsion +16° along the diene unit, leading to a pseudo-axial OH at C-1 and a pseudo-equatorial OH at C-2. In common with other *cis*-dihydrodiol metabolites **22** [X = F, Br, $CH_2(SO)Me$, $CH(CF_3)OH$] reported earlier,[11d-f] the crystal structure of $\mathbf{20b}_{1S,2S,R'}$ showed the presence of only intermolecular H-bonding between OH groups and also between OH groups and sulfoxide oxygen atoms. The *cis*-dihydrodiols **22** [X = F, Br, $CH(CF_3)OH$] and β-*cis*-diol sulfoxide **22** [X = 1,3-dithienyl sulfoxide] all crystallized out exclusively as the *M* conformers, with only crystalline *cis*-diol sulfoxide **22** [X = $CH_2(SO)Me$] having a *P* conformation.[11e] Sulfoxide $\mathbf{20b}_{1S,2S,R'}$ was thus exceptional by having both *M* and *P* conformations present in the same crystal.

The *M* or *P* diene conformations of *cis*-dihydrodiol enantiomers **22** (X = F, Br, Me, CF_3, CN), in solution, were studied earlier by both calculated and experimental ECD spectroscopy.[11d] The preferred equilibrium ratio of the *M* and *P* conformers was dependent on several factors, including intramolecular OH–OH, OH–π and OH–F hydrogen bonds. The *M* conformation, observed exclusively in the crystalline state, was found to be favoured in solutions of *cis*-dihydrodiols **22** (X = F, Br, CF_3, CN) with only *cis*-dihydrodiol **22** (X = Me) preferring the *P* conformation. It is probable that, in addition to intramolecular OH–OH, OH–π and OH–F hydrogen bonding interactions, the hydroxyl and sulfoxide groups present in sulfoxide $\mathbf{20b}_{1S,2S,R'}$ are also involved in similar interactions in solution. This will determine the *M*:*P* conformational equilibrium.

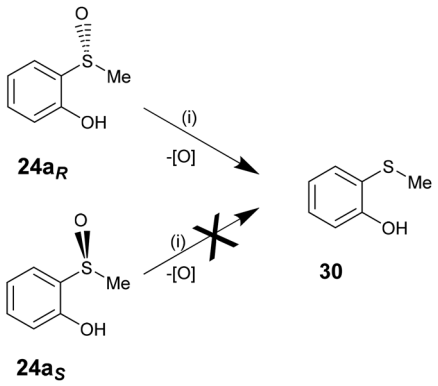
(vi) Chemical aromatization of enantiopure *cis*-diol sulfoxide $\mathbf{20b}_{1S,2S,R'}$.

Since arene *cis*-dihydrodiol enantiomers were known to aromatise under acidic or basic conditions[12a–d] and elevated temperatures, it was assumed that these characteristics would reduce their potential as chiral auxiliaries or ligands. In this context, the possibility of forming more stable phenolic sulfoxide enantiomers from the corresponding arene *cis*-diol sulfoxide diastereoisomers, *via* chirality transfer, was examined (Scheme 7).

Results from an earlier kinetic study of the aromatization of seventeen different monocyclic *cis*-dihydrodiol metabolites, under acid conditions (aq $HClO_4$, 25 °C), indicated that *ortho*-phenol sulfoxides were generally formed in preference to the *meta* isomers.[12a] Thus, GC-MS analysis showed that the major *ortho*-phenol sulfoxide $\mathbf{24b}_R$ (X = H, 78%) and minor *meta* isomer $\mathbf{25b}_R$ (X = H, 22%) were formed from a diastereoisomeric mixture of *cis*-dihydrodiol sulfoxides $\mathbf{19b}_{1S,2S,S'}$/$\mathbf{20b}_{1S,2S,R'}$ but their % ee values were not determined (Schemes 6 and 7). The acid-catalysed aromatization of *cis*-diol sulfoxide diastereoisomer $\mathbf{20b}_{1S,2S,R'}$ was repeated using aq. HCl. The phenol sulfoxides $\mathbf{24b}_R$ and $\mathbf{25b}_R$ (X = H) were methylated (CH_2N_2) to yield the corresponding ethers $\mathbf{24b}_R$ and $\mathbf{25b}_R$ (X = Me), which were used directly for chiral stationary phase HPLC (CSP HPLC) analysis. It was found that a significant degree of racemization had occurred in both *ortho* isomer $\mathbf{24b}_R$ (>98 → 68% ee) and *meta* isomer $\mathbf{25b}_R$ (>98 → 67% ee). As acid-catalysed racemization of other types of chiral sulfoxides using HCl had been observed earlier,[9b] no further aromatization



Scheme 7 Chemoenzymatic synthesis of enantioenriched phenol sulfoxides $\mathbf{24b}_R$/$\mathbf{24b}_S$, $\mathbf{25b}_R$/$\mathbf{25b}_S$ (X = H) and enantiopure alkylaryl sulfoxides $\mathbf{27a}_R$, $\mathbf{29a}_R$ and diaryl sulfoxide $\mathbf{29b}_R$. Reagents and conditions: (i) aq·HCl; (ii) *E. coli narB*; (iii) CH_2N_2, Et_2O.



Scheme 8 Dimethyl sulfoxide reductase-catalysed stereoselective deoxygenation of racemic phenol sulfoxide $\mathbf{24a}_R$/$\mathbf{24a}_S$. Reagents and conditions: (i) *C. braakii* DMSO 11.

study of sulfoxide *cis*-diol diastereoisomers was undertaken. Attempts to obtain enantiopure phenols $\mathbf{24b}_R$ and $\mathbf{25b}_R$ (X = H) by heating the *cis*-diol sulfoxide $\mathbf{20b}_{1S,2S,R'}$ (120 °C, >1 h) were also unsuccessful.

(vii) Enzymatic aromatization of enantiopure *cis*-diol sulfoxides $\mathbf{19a}_{1S,2S,R'}$ and $\mathbf{20b}_{1S,2S,R'}$.

An enzymatic approach to aromatization of *cis*-diol sulfoxides, under neutral conditions (pH 7.2), was also examined, as a possible route to chiral hydroxy sulfoxides. Biotransformations of substituted benzene *cis*-diols using whole cells of an *E. coli narB* recombinant strain, expressing naphthalene *cis*-diol dehydrogenase (NCDD), had resulted in dehydrogenation to give a wide range of the corresponding catechols.[11a,13] Under similar conditions, with sulfoxide *cis*-diols $\mathbf{19a}_{1S,2S,R'}$, and $\mathbf{20b}_{1S,2S,R'}$ as substrates, the corresponding catechol sulfoxides $\mathbf{26a}_R$ and $\mathbf{26b}_R$ were obtained (Scheme 7). The crude catechol $\mathbf{26a}_R$ (60–80% yield) was identified by NMR and MS analysis; purification by chromatography resulted in its decomposition. Catechol metabolite $\mathbf{26b}_R$ was found to be more stable and a pure sample was obtained by recrystallization. Methylation (CH_2N_2) of crude catechol $\mathbf{26a}_R$, yielded the stable derivatives $\mathbf{27a}_R$ and $\mathbf{29a}_R$. Similar treatment of crude catechol $\mathbf{26b}_R$ yielded only the dimethylated catechol $\mathbf{27b}_R$. No evidence was obtained of monomethylated catechol $\mathbf{29b}_R$ or the potentially more useful *ortho*-phenol sulfoxides $\mathbf{28a}_R$ and $\mathbf{28b}_R$. Formation of an intramolecular H-bond between the sulfoxide group and the proximate OH group in catechols $\mathbf{28a}_R$ and $\mathbf{28b}_R$ may render the other OH group more susceptible to methylation. A similar result was observed during methylation of a chiral catechol metabolite derived from *cis*-dihydrodiol **22** [X = $CH(CF_3)OH$], where *ortho* OH group was preferentially methylated due to intramolecular H-bonding.[13]

Kinetic resolution of racemic *ortho*-phenol sulfoxide substrate $\mathbf{24a}_R$/$\mathbf{24a}_S$, to yield the residual (*S*)-enantiomer $\mathbf{24a}_S$ (>98% ee) and the corresponding *ortho*-phenol sulfide **30**, was achieved by enantioselective deoxygenation (Scheme 8). This involved the use of whole cells of *Citrobacter braakii* DMSO11 expressing dimethyl sulfoxide reductase.[11b] *ortho*-Phenol sulfoxide $\mathbf{24b}_R$ (X = H) could not be obtained in enantiopure form, from the corresponding *cis*-diol sulfoxide $\mathbf{20b}_{1S,2S,R'}$ by this method (Scheme 7). As alkyl *ortho*-phenol sulfoxides have structural features similar to β-hydroxy sulfoxides $\mathbf{7}_{1S,2S,R'}$, $\mathbf{8}_{1S,2S,S'}$, $\mathbf{10}_{1S,2R,S'}$ and $\mathbf{11}_{1S,2R,R'}$, phenol sulfoxide $\mathbf{24a}_S$ was also included in a preliminary study of their value as chiral ligands.

(viii) Evaluation of β-hydroxy sulfoxide enantiomers as chiral ligands

Different types of enantiopure metabolites, (*e.g.* **a–e**, Scheme 1), obtained by TDO-catalysed hydroxylation of arenes, heteroarenes and benzocycloalkanes, have been used in the chemoenzymatic synthesis of chiral ligands and reagents (Fig. 5).[14a–c] This approach was exemplified by the use of bromobenzene *cis*-dihydrodiol (**a**, Scheme 1) in the synthesis of organophosphorus chiral ligands. Thus, the mixed phosphine–phosphine oxide enantiomer **31** was used in the asymmetric allylation of aldehydes and asymmetric hydrogenation of alkenes.[14a] Enantiopure 2,2′-bipyridines **32** and **33** and derived *N*-oxides, synthesised from a 2-chloroquinoline *cis*-dihydrodiol metabolite (**b**), also proved to be efficient chiral ligands; they were used for catalytic asymmetric allylic oxidation, cyclopropanation of alkenes, aminolysis of epoxides and allylation of aldehydes.[14b,c] The availability of enantiopure indene *cis*-diol (**c**) of

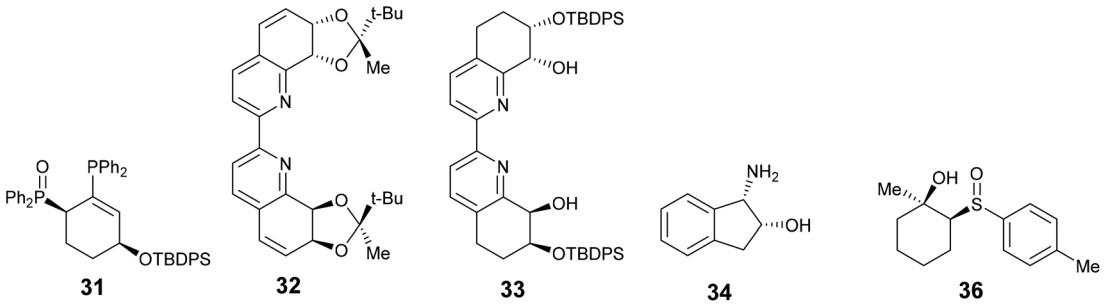


Fig. 5 Chiral ligands **31**–**34** and **36**.

either configuration by TDO- or NDO-catalysed benzylic hydroxylation of 2-indanol, was used in the chemoenzymatic synthesis of either *cis*-amino alcohol enantiomer **34** (Fig. 5).[3c] *cis*-Amino indanol enantiomers **34** are widely used as ligands in asymmetric synthesis, including aldol and cycloaddition reactions.

Relatively few reports have appeared on the potential of β-hydroxy sulfoxide enantiomers as chiral auxiliaries or ligands.[8a,c] Several acyclic β-hydroxy alkylaryl sulfoxides proved to be very useful chiral auxiliaries in asymmetric biaryl Suzuki reactions (>97% de).[8a] The enantioselective addition of diethylzinc to aldehydes is among the most widely studied ligand-accelerated reactions.[15a] A wide range of chiral ligands continue to be evaluated using this reaction,[15b,c] including β-hydroxy alkylaryl sulfoxides.[8c] Both cyclic and acyclic β-hydroxy sulfoxides were found to be chiral ligands, catalysing the addition of diethyl zinc to benzaldehyde (Scheme 9).[8c] When a *trans*-β-hydroxy sulfoxide moiety was part of a five-membered ring, the resulting benzylic alcohols $\mathbf{35}_{R}/\mathbf{35}_{S}$ were obtained with low ee values (2–11%); higher values (23–45% ee) resulted from the use of six-membered cyclic *cis*-β-hydroxy sulfoxide ligands.[8c] The latter study prompted this preliminary evaluation of the new hydroxy sulfoxide enantiomers $\mathbf{7}_{1S,2S,R'}$, $\mathbf{10}_{1S,2R,S'}$, $\mathbf{11}_{1S,2R,R'}$, $\mathbf{13}_{1S,3S,R'}$ and $\mathbf{24a}_{S}$ as chiral ligands (Scheme 9).

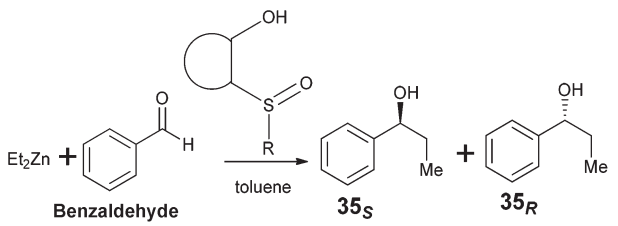
The *trans*-β-hydroxy sulfoxide $\mathbf{7}_{1S,2S,R'}$, was the first to be used as a chiral ligand. The reaction was monitored by HPLC and upon completion, 1-phenyl propanol **35** was isolated with a very low ee value (2%, CSP HPLC analysis, Table 1). Improved ee values were however obtained, using the five membered ring ligands $\mathbf{10}_{1S,2R,S'}$ (15%), $\mathbf{11}_{1S,2R,R'}$ (32%) and $\mathbf{13}_{1S,3S,R'}$ (20%), where a *cis*-β-hydroxy sulfoxide group was present in each case. The highest reported ee value (45%)[8c] of the 1-phenyl propanol product **35** from this reaction, with a β-hydroxy sulfoxide ligands, was obtained using *cis* isomer **36**. The proximity of OH and S=O groups, in the *cis* ligands $\mathbf{10}_{1S,2R,S'}$, $\mathbf{11}_{1S,2R,R'}$ and $\mathbf{13}_{1S,3S,R'}$ relative to the *trans* ligand $\mathbf{7}_{1S,2S,R'}$, appears to be an important factor, during coordination to the zinc atom, in the preferred transition state, and thus in the ee value of 1-phenyl propanol **35**.

Table 1 Enantiomeric excess values and absolute configurations of 1-phenyl propanol **35**, obtained using ligands $\mathbf{7}_{1S,2S,R'}$, $\mathbf{10}_{1S,2R,S'}$, $\mathbf{11}_{1S,2R,R'}$, $\mathbf{13}_{1S,3S,R'}$ and $\mathbf{24a}_{S}$ to catalyse the reaction of benzaldehyde with diethylzinc

Ligand	Ligand configuration	1-Phenyl propanol **35** (% ee)	Configuration
7	$\mathbf{1}S,\mathbf{2}S,\mathbf{R}'$	2	*S*
10	$\mathbf{1}S,\mathbf{2}R,\mathbf{S}'$	15	*R*
11	$\mathbf{1}S,\mathbf{2}R,\mathbf{R}'$	32	*S*
13	$\mathbf{1}S,\mathbf{3}S,\mathbf{R}'$	20	*R*
24a	$\mathbf{S}$	30	*S*

Application of *ortho*-phenol sulfoxide $\mathbf{24a}_{S}$, as a chiral ligand, resulted in a similar degree of stereoselectivity (30% ee), but of opposite absolute configuration, relative to that found using hydroxy sulfoxide $\mathbf{11}_{1S,2R,R'}$ (32% ee).

The results presented in Table 1, allied to those obtained earlier,[8c] with 45% being the maximum ee value for 1-phenyl propanol **35**, indicate that β-hydroxy sulfoxides are among the less efficient ligands used for this type of reaction.[15a–c] Nevertheless, the earlier success of β-hydroxy sulfoxide enantiomers as chiral auxiliaries,[8a] suggests that hydroxy sulfoxides $\mathbf{7}_{1S,2S,R'}$, $\mathbf{10}_{1S,2R,S'}$, $\mathbf{11}_{1S,2R,R'}$, $\mathbf{13}_{1S,3S,R'}$ and $\mathbf{24a}_{S}$ could be of more value in this context.



Scheme 9 Asymmetric synthesis of benzylic alcohol $\mathbf{35}_{S}/\mathbf{35}_{R}$ using hydroxy sulfoxides $\mathbf{7}_{1S,2S,R'}$, $\mathbf{10}_{1S,2R,S'}$, $\mathbf{11}_{1S,2R,R'}$, $\mathbf{13}_{1S,3S,R'}$, and $\mathbf{24a}_{S}$ as chiral ligands.

3 Conclusions

A range of cyclic β-hydroxy sulfoxide enantiomers was obtained, by chemoenzymatic synthesis, initiated by TDO-catalysed benzylic mono- and di-hydroxylation of 2-chloroindane, to yield both *cis*- and *trans*-chlorohydrins as single enantiomers. Nucleophilic substitution, using the thiophenolate

anion, resulted in an inversion of configuration at C-2 and formation of *cis*- and *trans*-β-hydroxy sulfides. Sulfoxidation, using DMD, yielded separable mixtures of enantiopure indane β-hydroxy sulfoxide isomers, whose absolute configurations were determined by a combination of ECD spectroscopy and X-ray crystallography.

Partially racemized *ortho*- and *meta*-phenol sulfoxides were formed, *via* chemoenzymatic synthesis and chiral transfer, involving TDO-catalysed *cis*-dihydroxylation of alkylaryl and diaryl sulfides, followed by acid-catalysed dehydration. Dehydrogenation of arene *cis*-dihydrodiol sulfoxides, catalysed by NCDD, also resulted in chiral transfer. The resulting enantiopure catechol sulfoxides were stabilized as methyl ether derivatives. A comparative study of the potential of four β-hydroxy sulfoxides and one alkyl *ortho*-phenol sulfoxide, as chiral ligands for the addition reaction of benzaldehyde with diethylzinc, was conducted.

4 Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DPX-300 and DPX-500 instruments. Mass spectra were run at 70 eV, on a VG Autospec Mass Spectrometer, using a heated inlet system. Accurate molecular weights were determined by the peak matching method, with perfluorokerosene as the standard. Elemental microanalyses were carried out on a Perkin-Elmer 2400 CHN microanalyser and IR spectra were recorded using a Perkin-Elmer Spectrum RX1 FT-IR spectrometer. ECD spectra were obtained using a Jasco J-720 instrument. A Perkin-Elmer 341 polarimeter was used for optical rotation ($[\alpha]_D$) measurements (*ca.* 20 °C, 10^{-1} deg cm^2 g^{-1}). Flash column chromatography and PLC were performed on Merck Kieselgel type 60 (250–400 mesh) and $PF_{254/366}$ respectively. Merck Kieselgel type $60F_{254}$ analytical plates were used for TLC. CSP HPLC analysis was carried out using a Shimadzu LC-A liquid chromatograph connected to Hewlett Packard diode array detector using Chiralpak AS or Chiralcel OB analytical columns. Metabolites **2**$_{1S,2R}$, **3**$_{1S,3S}$, **4**$_{1S,2S}$, **19a**$_{1S,2S,R'}$, **20a**$_{1S,2S,S'}$, **20b**$_{1S,2S,R'}$, **22** (X = I), **23a**$_{1S,2S}$ and **23b**$_{1S,2S}$, were available from earlier studies[3c,11a–c] and compounds **34** and **35** from commercial sources.

TDO-catalysed benzylic hydroxylations were conducted using *P. putida* UV4 whole cells. This is a proprietary mutant strain derived from a wild-type strain (*P. putida* NCIB 11767) originally constructed at ICI using reported methods.[1a,16a,b]

We thank Dr R. Holt (robert.holt@npilpharma.co.uk) for making this strain available to us. NCDD-catalysed dehydrogenations were conducted using whole cells of the recombinant strain *E. coli DH5α(pUC129:narB)* which was developed at the Queen's university of Belfast.[16b]

(i) Biotransformation of 2-chloro-2,3-dihydro-1*H*-indene 1 to yield (1*S*,2*R*)-2-chloro-2,3-dihydro-1*H*-inden-1-ol 2$_{1S,2R}$

The earlier biotransformation of 2-chloro-2,3-dihydro-1*H*-indene **1**[3c] (5 g), using *P. putida* UV4, was repeated and the crude mixture of bioproducts obtained was purified by column chromatography (25% EtOAc in hexane), to yield a mixture of (−)-(1*S*,2*R*)-2-chloro-2,3-dihydro-1*H*-inden-1-ol **2**$_{1S,2R}$ (1.62 g, 29%) and (+)-(1*S*,2*S*)-2-chloro-2,3-dihydro-1*H*-inden-1-ol **4**$_{1S,2S}$ (0.210 g, 4%) and also the pure more polar (−)-(1*S*,3*S*)-1,3-dihydroxy-2-chloro-2,3-dihydro-1*H*-inden-1-ol **3**$_{1S,3S}$ (1.68 g, 28%). A pure sample of (−)-(1*S*,2*R*)-2-chloro-2,3-dihydro-1*H*-inden-1-ol **2**$_{1S,2R}$ was isolated from the mixture by fractional crystallization (EtOAc/hexane). Spectra of compounds **2**$_{1S,2R}$ ($[\alpha]_D$ −52, $CHCl_3$) and **3**$_{1S,3S}$ ($[\alpha]_D$ −91 MeOH) were indistinguishable from authentic samples.[3c]

Synthesis of (+)-(1*S*,2*R*)-1a,6a-dihydro-6-*H*-indeno[1,2-*b*]-oxirene-5$_{1S,2R}$ from *trans*-chlorohydrin 4$_{1S,2S}$. A small portion (100 mg, 0.60 mmol) of the mixture (4 : 1) of (+)-chlorohydrin **4**$_{1S,2S}$ and (−)-chlorohydrin **2**$_{1S,2R}$, left after the separation of majority chlorohydrin **2**$_{1S,2R}$ was dissolved in dry Et_2O (10 mL) and stirred overnight with excess of sodium methoxide (65 mg, 1.2 mmol). The sodium salts were filtered off, and the crude product left after removal of Et_2O was purified by PLC (25% EtOAc in hexane), to give epoxide **5**$_{1S,2R}$ as an oil (21 mg, 33%); $[\alpha]_D$ +55 (*c* 0.5, $CHCl_3$); lit.,[6] $[\alpha]_D$ −55 ($CHCl_3$) for (1*R*,2*S*) enantiomer; δ_H (500 MHz, $CDCl_3$) 2.99 (1 H, dd, $J_{3,2}$ 2.9, $J_{3,3'}$ 18.0, 3-H), 3.25 (1 H, d, $J_{3',3}$ 18.0, 3′-H), 4.15 (1 H, t, $J_{2,1} = J_{2,3}$ 2.9, 2-H), 4.27 (1 H, d, $J_{1,2}$ 2.9, 1-H), 7.22–7.50 (4 H, m, Ar); *m*/*z* (EI) 132 (M^+, 73%), 104 (100).

(+)-(1*S*,2*S*)-2-(Phenylthio)-2,3-dihydro-1*H*-inden-1-ol 6$_{1S,2S}$. A solution of (−)-chlorohydrin **2**$_{1S,2R}$ (0.5 g, 3 mmol), in dry acetonitrile (10 mL) containing thiophenol (1.65 g, 15 mmol) and K_2CO_3 (0.5 g), was refluxed overnight. The cooled reaction mixture was filtered, to remove the solid salts, the filtrate concentrated under reduced pressure, and the crude product was purified by column chromatography (15% Et_2O in hexane) to give (+)-thiophenyl **6**$_{1S,2S}$ as a white crystals (0.574 g, 80%); m. p. 111 °C (from hexane); $[\alpha]_D$ +9.0 (*c* 1.1, MeOH); (Found: C, 74.0; H, 5.8. $C_{15}H_{14}OS$ requires C, 74.4; H, 5.8%); δ_H (500 MHz, $CDCl_3$) 2.90 (1 H, dd, $J_{3,2}$ 7.3, $J_{3,3'}$ 16.2, 3-H), 3.46 (1 H, dd, $J_{3',2}$ 7.8, $J_{3',3}$ 16.2, 3′-H), 3.80 (1 H, m, 2-H), 5.13 (1 H, d, $J_{1,2}$ 5.7, 1-H), 7.20–7.47 (7 H, m, Ar), 7.49–7.51 (2 H, m, Ar); δ_C (125 MHz, $CDCl_3$) 37.52, 54.88, 81.13, 124.32, 124.67, 127.01, 127.28, 128.72, 129.10 (2C), 131.43 (2C), 134.85, 140.46, 142.80; *m*/*z* (EI) 242 (M^+, 100%), 133 (92), 132 (87), 123 (75), 110 (57).

(−)-(1*S*,2*R*)-2-(Phenylthio)-2,3-dihydro-1*H*-inden-1-ol 9$_{1S,2R}$. Thiophenol (0.65 g, 5.9 mmol) and K_2CO_3 (0.5 g) were added to a mixture (7 : 3) of (−)-chlorohydrin **2**$_{1S,2R}$ and (+)-chlorohydrin **4**$_{1S,2S}$ (0.170 g, 1 mmol), in dry acetonitrile (5 mL). The reaction mixture was refluxed overnight, worked up in a similar manner to the preceding synthesis. The resulting two thiophenyl products **6**$_{1S,2S}$ (0.131 g, 76%, less polar) and **9**$_{1S,2R}$ were separated by column chromatography (15% Et_2O in hexane). Thiophenyl compound **9**$_{1S,2R}$ was obtained as white crystalline solid (52 mg, 71%); m. p. 92–93 °C (from hexane); $[\alpha]_D$ −51.1 (*c* 0.8, MeOH); (Found: C, 74.3; H, 5.7. $C_{15}H_{14}OS$ requires C, 74.4; H, 5.8%); δ_H (500 MHz, $CDCl_3$) 3.10 (1 H, dd, $J_{3,2}$ 8.0, $J_{3,3'}$ 15.9, 3-H), 3.30 (1 H, dd, $J_{3',2}$ 7.6, $J_{3',3}$ 15.9, 3′-H), 4.05 (1 H, m, 2-H), 4.7 (1 H, br, OH), 5.08 (1 H, d, $J_{1,2}$ 4.9, 1-H),

7.21–7.32 (6 H, m, Ar), 7.48–7.50 (3 H, m, Ar); δ_C (125 MHz, $CDCl_3$) 36.96, 54.55, 74.77, 124.67, 125.37, 127.23, 127.30, 128.91, 129.16 (2C), 130.84 (2C), 134.88, 141.39, 142.87; *m*/*z* (EI) 242 (M^+, 98%), 132 (97), 133 (97), 123 (100), 110 (77).

(−)-(1*S*,3*S*)-2-(Phenylthio)-2,3-dihydro-1*H*-indene-1,3-diol $12_{1S,3S}$ and (+)-(1*S*,2*R*,3*R*)-3-(phenylthio)-2,3-dihydro-1*H*-indene-1,2-diol $16_{1S,2R,3R}$. A mixture of (−)-(1*S*,3*S*)-1,3-dihydroxy-2-chloro-2,3-dihydro-1*H*-inden-1-ol $3_{1S,3S}$ (0.750 g, 4 mmol), thiophenol (2.2 g, 20.0 mmol) and K_2CO_3 (1.5 g) in dry acetonitrile (15 mL) was refluxed overnight. Workup procedure similar to that used for the synthesis of compounds $6_{1S,2S}$ and $9_{1S,2R}$, followed by column chromatography (25% Et_2O in hexane), gave two thiophenyl compounds $12_{1S,3S}$ and $16_{1S,2R,3R}$. (−)-Thiophenyl compound $12_{1S,3S}$; semisolid from less polar fraction (0.358 g, 34%); $[\alpha]_D$ −76 (*c* 0.6, MeOH); (Found: M^+, 258.0718. $C_{15}H_{14}O_2S$ requires 258.0715); δ_H (500 MHz, $CDCl_3$) 3.77 (1 H, dd, $J_{2,1}$ 5.1, $J_{2,3}$ 7.3, 2-H), 4.63 (2 H, br s, 2 × OH), 5.10 (1 H, d, $J_{1,2}$ 5.1, 1-H), 5.24 (1 H, d, $J_{3,2}$ 7.3, 3-H), 7.26–7.57 (9 H, m, Ar); δ_C (125 MHz, $CDCl_3$) 64.41, 72.44, 78.18, 124.13, 125.67, 127.48, 129.14 (2C), 129.34, 129.65, 131.16 (2C), 134.22, 141.02, 143.28; *m*/*z* (EI) 258 (M^+, 53%), 148 (100), 131 (85), 120 (55).

(+)-Thiophenyl compound $16_{1S,2R,3R}$; colourless crystals from more polar fraction (0.162 g, 15%); m. p. 97–99 °C (from EtOAc/hexane); $[\alpha]_D$ +7 (*c* 0.4, MeOH); (Found: C, 69.5; H, 5.3. $C_{15}H_{14}O_2S$ requires C, 69.8; H, 5.4%); δ_H (500 MHz, $CDCl_3$), 4.23 (1 H, m, 2-H), 4.38 (1 H, d, $J_{1,2}$ 6.8, 1-H), 5.02 (1 H, m, 3-H), 7.25–7.49 (9 H, m, Ar); δ_C (125 MHz, $CDCl_3$) 60.40, 79.60, 86.73, 124.25, 125.26, 125.86, 127.45, 128.77, 129.14, 129.19 (2C), 131.64 (2C), 141.01, 142.82; *m*/*z* (EI) 258 (M^+, 12%), 240 (16), 109 (32), 57 (100).

(ii) General procedure for sulfoxidation of phenyl sulfides using dimethyldioxirane

Dimethyldioxirane (DMD) was prepared as a solution in acetone by the addition of potassium peroxymonosulfate (Oxone) to a mixture of water, acetone and sodium bicarbonate in accordance with the literature procedure.[17] A solution of dimethyldioxirane (DMD) (*ca.* 0.08 M) was added dropwise, to a stirring solution of the phenyl sulfide maintained at 0 °C in acetone solution. The progress of the reaction was constantly monitored by TLC. When the starting compound was just consumed, the reaction was terminated by removal of the solvent *in vacuo* and the mixture of sulfoxide diastereoisomers was separated by PLC (40–100% EtOAc in hexane). Phenyl sulfoxides $7_{1S,2S,R'}$ and $8_{1S,2S,S'}$ (from sulfide $6_{1S,2S}$), $10_{1S,2R,S'}$ and $11_{1S,2R,R'}$ (from sulfide $9_{1S,2R}$), $13_{1S,3S,R'}$ and $14_{1S,3S,S'}$ (from sulfide $12_{1S,3S}$), $17_{1S,2R,3R,R'}$ (from sulfide $16_{1S,2R,3R}$), $20b_{1S,2S,R'}$ and $19b_{1S,2S,S'}$ (from sulfide $23b_{1S,2S}$) were synthesised by the procedure.

(+)-(1*S*,2*S*)-2-[(*R*′)-Phenylsulfinyl]-2,3-dihydro-1*H*-inden-1-ol $7_{1S,2S,R'}$. Less polar crystalline white solid (58 mg, 45%); m. p. 128–129 °C; $[\alpha]_D$ +217 (*c* 0.9, MeOH); (Found: C, 69.5; H, 5.3. $C_{15}H_{14}O_2S$ requires C, 69.8; H, 5.4%); δ_H (500 MHz, $CDCl_3$) 2.57 (1 H, dd, $J_{3,2}$ 8.4, $J_{3,3}$ 16.1, 3-H), 3.27 (1 H, dd, $J_{3',2}$ 9.0, $J_{3',3}$ 16.1, 3′-H), 3.46 (1 H, ddd, $J_{2,1}$ 7.3 = $J_{2,3'}$ 9.0, $J_{2,3}$ 8.4, 2-H), 5.64 (1 H, d, $J_{1,2}$ 7.3, 1-H), 7.13 (1 H, m, Ar–H), 7.24 (2 H, m, Ar–H), 7.28 (1 H, m, Ar–H), 7.54 (3 H, m, Ar–H), 7.68 (2 H, m, Ar–H); δ_C (125 MHz, $CDCl_3$) 26.78, 72.83, 75.32, 124.07, 124.30 (2C), 124.86, 127.46, 128.88, 129.29 (2C), 131.09, 139.12, 142.04, 142.20; ν_{max}/cm^{-1} 3290 (OH), 1028 (SO); ECD (MeOH): λ/nm 241 ($\Delta\varepsilon$ +9.15), 218 ($\Delta\varepsilon$ −12.9).

(−)-(1*S*,2*S*)-2-[(*S*′)-Phenylsulfinyl]-2,3-dihydro-1*H*-inden-1-ol $8_{1S,2S,S'}$. More polar white crystalline solid (56 mg, 43%); m. p. 112–113 °C; $[\alpha]_D$ −137 (*c* 1.1 MeOH); (Found: C, 69.3; H, 5.3. $C_{15}H_{14}O_2S$ requires C, 69.8; H, 5.4%); δ_H (500 MHz, $CDCl_3$) 2.94 (1 H, dd, $J_{3,2}$ 8.8, $J_{3,3}$ 16.1, 3-H), 3.03 (1 H, dd, $J_{3',2}$ 8.8, $J_{3',3}$ 16.1, 3′-H), 3.54 (1 H, ddd, $J_{2,1}$ 6.4, $J_{2,3'}$ = $J_{2,3}$ 8.8, 2-H), 4.7 (1 H, br s, OH), 5.80 (1 H, d, $J_{1,2}$ 6.4, 1-H), 7.15 (1 H, m, Ar–H), 7.25 (2 H, m, Ar–H), 7.40 (1 H, m, Ar–H), 7.57 (3 H, m, Ar–H), 7.76 (2 H, m, Ar–H); δ_C (125 MHz, $CDCl_3$) 30.90, 72.77, 76.35, 124.41(2C), 124.45, 124.53, 127.66, 128.78, 129.55 (2C), 131.71, 138.31, 142.28, 142.89; ν_{max}/cm^{-1} 3326 (OH), 1011 (SO); ECD (MeOH): λ/nm 245 ($\Delta\varepsilon$ −7.51), 218 ($\Delta\varepsilon$ +11.7).

(−)-(1*S*,2*R*)-2-[(*S*′)-Phenylsulfinyl]-2,3-dihydro-1*H*-inden-1-ol $10_{1S,2R,S'}$. Less polar colourless crystalline diastereoisomer (14 mg, 25%); m. p. 106–107 °C (from EtOAc/hexane); $[\alpha]_D$ −171 (*c* 0.81, MeOH); (Found: M^+, 258.0717. $C_{15}H_{14}O_2S$ requires 258.0714); δ_H (500 MHz, $CDCl_3$) 2.79 (1 H, dd, $J_{3,2}$ 8.6, $J_{3,3}$ 16.7, 3-H), 3.58 (1 H, ddd, $J_{2,1}$ 6.8, $J_{2,3'}$ 7.8, $J_{2,3}$ 8.6, 2-H), 3.72 (1 H, dd, $J_{3',2}$ 7.8, $J_{3',3}$ 16.7, 3′-H), 5.38 (1 H, d, $J_{1,2}$ 6.8, 1-H), 7.25–7.28 (3 H, m, Ar), 7.51–7.55 (4 H, m, Ar), 7.71–7.31 (2 H, m, Ar); δ_C (125 MHz, $CDCl_3$) 27.97, 67.60, 76.28, 124.46 (2C), 124.94, 125.10, 127.56, 129.23 (2C), 129.57, 130.92, 140.98, 142.72, 142.89; ν_{max}/cm^{-1} 3400 (OH) 1034 (SO); ECD (MeOH): λ/nm 243 ($\Delta\varepsilon$ −8.15), 216 ($\Delta\varepsilon$ +15.1).

(+)-(1*S*,2*R*)-2-[(*R*′)-Phenylsulfinyl]-2,3-dihydro-1*H*-inden-1-ol $11_{1S,2R,R'}$. More polar colourless crystalline diastereoisomer (32 mg, 57%); m. p. 149–150 °C (from EtOAc); $[\alpha]_D$ +100 (*c* 0.8, MeOH) (Found: C, 69.7; H, 5.1. $C_{15}H_{14}O_2S$ requires C, 69.8; H, 5.4%); δ_H (500 MHz, $CDCl_3$) 2.59 (1 H, dd, $J_{3,2}$ 8.2, $J_{3,3}$ 16.0, 3-H), 3.21 (1 H, dd, $J_{3',2}$ 8.8, $J_{3',3}$ 16.0, 3′-H), 3.62 (1 H, ddd, $J_{2,1}$ 5.6, $J_{2,3'}$ 8.8, $J_{2,3}$ 8.2, 2-H), 4.72 (1 H, br s, OH), 5.59 (1 H, d, $J_{1,2}$ 5.6, 1-H), 7.20–7.26 (4 H, m, Ar–H), 7.56–7.58 (3 H, m, Ar–H) 7.80–7.82 (2 H, m, Ar–H); δ_C (125 MHz, $CDCl_3$) 31.35, 60.41, 65.86, 75.70, 124.79, 125.20 (2C), 125.30, 127.71, 129.43 (2C), 131.75, 140.55, 142.59, 142.72; ν_{max}/cm^{-1} 3353 (OH), 1013 (SO); ECD (MeOH): λ/nm 246 ($\Delta\varepsilon$ +6.53), 216 ($\Delta\varepsilon$ −12.3).

Crystal data for compound $11_{1S,2R,R'}$. $C_{15}H_{14}O_2S$, M = 258.3, monoclinic, a = 8.6093(11), b = 6.0390(7), c = 11.4715(14) Å, U = 596.3(2) Å^3, T = 153(2) K, space group $P2_1$ (no. 4), Mo-Kα radiation, λ = 0.71073 Å, Z = 2, $F(000)$ = 272, D_x = 1.439 g cm^{-3}, μ = 0.261 mm^{-1}, Bruker SMART CCD diffractometer, ϕ/ω scans, 3.6° < 2θ < 56.8°, measured/independent reflections: 6656/2573, R_{int} = 0.042, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; all hydrogen atoms located in a difference Fourier synthesis but included at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. R_1 = 0.040 for 2392 data with $F_o > 4\sigma(F_o)$, 164 parameters, ωR_2 = 0.095 (all data), GoF = 1.02, $\Delta\rho_{min,max}$ = −0.24/0.32 e Å^{-3}. CCDC1413402.

The absolute configuration is confirmed as (1*S*,2*R*,*R*′) from the anomalous scattering arising from the sulfur atom; Flack parameter $x = -0.05(8)$.

(+)-(1*S*,3*S*)-2-[(*R*′)-Phenylsulfinyl]-2,3-dihydro-1*H*-inden-1-ol 13$_{1S,3S,R'}$. More polar diasteroisomer, a viscous oil (47 mg, 45%); $[\alpha]_D$ +99.0 (*c* 0.9, MeOH); (Found: M^+ 274.0669 $C_{15}H_{14}SO_3$ requires 274.0664); δ_H (500 MHz, $CDCl_3$) 2.43 (1 H, br s, OH), 3.25 (1 H, dd, $J_{2,1}$ 5.5, $J_{2,3}$ 7.1, 2-H), 4.72 (1 H, br s, OH), 5.49 (1 H, d, $J_{1,2}$ 5.5, 1-H), 5.65 (1 H, d, $J_{3,2}$ 7.1, 3-H), 7.34 (4 H, m, Ar–H), 7.59 (3 H, m, Ar–H), 7.85 (2 H, m, Ar–H); δ_C (125 MHz, $CDCl_3$) 73.31, 74.45, 75.47, 124.31, 124.93, 125.17 (2C), 129.36, 129.66 (2C), 129.86, 131.93, 141.16, 141.63, 143.27; *m*/*z* (LSIMS) 297 [(M + Na)$^+$, 47%], 275 [(M + H)$^+$, 100%]; ν_{max}/cm^{-1} 3350 (OH), 1015 (SO); ECD (MeOH): λ/nm 248 ($\Delta\varepsilon$ +4.40), 216 ($\Delta\varepsilon$ −8.20).

(−)-(1*S*,3*S*)-2-[(*S*′)-Phenylsulfinyl]-2,3-dihydro-1*H*-inden-1-ol 14$_{1S,3S,S'}$. Less polar colourless crystalline diastereoisomer (39 mg, 37%); m. p. 155 °C; $[\alpha]_D$ −144 (*c* 1.0, MeOH); (Found: C, 65.4; H, 5.0. $C_{15}H_{14}O_3S$ requires C, 65.7; H, 5.1%); δ_H (500 MHz, $CDCl_3$) 2.21 and 2.87 (1 H each, br s, OH), 3.39 (1 H, dd, $J_{2,1}$ 6.3, $J_{2,3}$ 6.6, 2-H), 5.10 (1 H, d, $J_{1,2}$ 6.3, 1-H), 6.06 (1 H, d, $J_{3,2}$ 6.6, 3-H), 7.34 (2 H, m, Ar–H), 7.43 (2 H, m, Ar–H), 7.60 (3 H, m, Ar–H), 7.88 (2 H, m, Ar–H); δ_C (125 MHz, $CDCl_3$) 73.91, 74.76, 77.51, 124.39 (2C), 124.69, 126.04, 129.38, 129.51 (2C), 130.40, 131.50, 138.67, 140.68, 143.27; ν_{max}/cm^{-1} 3308 (OH), 1010 (SO); ECD (MeOH): λ/nm 244 ($\Delta\varepsilon$ −5.28), 216 ($\Delta\varepsilon$ +9.67).

Crystal data for compound 14$_{1S,3S,S'}$. $C_{15}H_{14}O_3S$, M = 274.3, orthorhombic, a = 5.4884(5), b = 11.4294(9), c = 19.5736(16) Å, U = 1227.8(2) Å^3, T = 153(2) K, space group $P2_12_12_1$ (no. 19), Mo-Kα radiation, λ = 0.71073 Å, Z = 4, F(000) = 576, D_x = 1.484 g cm^{-3}, μ = 0.264 mm^{-1}, Bruker SMART CCD diffractometer, ϕ/ω scans, 4.1° < 2θ < 56.9°, measured/independent reflections: 13 801/2821, R_{int} = 0.065, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; all hydrogen atoms located in a difference Fourier synthesis but included at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. R_1 = 0.039 for 2504 data with $F_o > 4\sigma(F_o)$, 174 parameters, ωR_2 = 0.91 (all data), GoF = 1.01, $\Delta\rho_{min,max}$ = −0.27/0.40 e Å^{-3}. CCDC 1413403. The absolute configuration is confirmed as (1*S*,3*S*,*S*′) from the anomalous scattering arising from the sulfur atom; Flack parameter $x = -0.05(8)$.

(+)-(1*S*,2*R*,3*R*)-3-[(*R*′)-Phenylsulfinyl]-indan-1,2-diol 17$_{1S,2R,3R,R'}$. Colourless crystalline solid compound 17$_{1S,2R,3R,R'}$ (53 mg, 62%); m. p. 180–81 °C; $[\alpha]_D$ +50 (*c* 0.51, $CHCl_3$); (Found: C, 65.5; H, 4.9. $C_{15}H_{14}O_3S$ requires C, 65.7; H, 5.1%); δ_H (500 MHz, $CDCl_3$) 2.95 and 3.21 (1 H each, br s, OH), 4.57 (1 H, m, 1-H), 4.66 (1 H, m, 2-H), 4.90 (1 H, m, 3-H), 7.17–7.88 (9 H, m, Ar–H); *m*/*z* (LSIMS) 297 [(M + Na)$^+$, 100%], 275 [(M + H)$^+$, 23%).

Crystal data for compound 17$_{1S,2R,3R,R'}$. $C_{15}H_{14}O_3S$, M = 274.3, orthorhombic, a = 7.292(2), b = 11.750(3), c = 14.698(4) Å, U = 1259.4(6) Å^3, T = 153(2) K, space group $P2_12_12_1$ (no. 19), Mo-Kα radiation, λ = 0.71073 Å, Z = 4, F(000) = 576, D_x = 1.447 g cm^{-3}, μ = 0.258 mm^{-1}, Bruker SMART CCD diffractometer, ϕ/ω scans, 4.4° < 2θ < 57.3°, measured/independent reflections: 13 537/2915, R_{int} = 0.089, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; all hydrogen atoms located in a difference Fourier synthesis but included at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. R_1 = 0.061 for 2303 data with $F_o > 4\sigma(F_o)$, 174 parameters, ωR_2 = 0.157 (all data), GoF = 0.98, $\Delta\rho_{min,max}$ = −0.64/0.74 e Å^{-3}. CCDC 1413404. The absolute configuration is confirmed as (1*S*,2*R*,3*R*,*R*′) from the anomalous scattering arising from the sulfur atom; Flack parameter $x = 0.10(14)$.

(+)-(1*S*,2*S*)-1,2-Dihydroxy-3-(*S*′)-phenylsulfinyl-cyclohexa-3,5-diene 19b$_{1S,2S,S'}$. Light yellow coloured gum (102 mg, 18%); R_f 0.56 (6% MeOH/$CHCl_3$); $[\alpha]_D$ +263 (*c* 0.6, MeOH); (Found: M^+, 236.0510. $C_{12}H_{12}O_3S$ requires 236.0507); δ_H (500 MHz, $CDCl_3$) 3.05 (1 H, d, $J_{OH,1}$ 7.7, OH), 3.21 (1 H, d, $J_{OH,2}$ 7.4, OH), 4.20 (2 H, m, 1-H, 2-H), 6.11 (1 H, ddd, $J_{6,5}$ 9.5, $J_{6,1}$ 3.6, $J_{6,4}$ 1.0, 6-H), 6.16 (1 H, ddd, $J_{5,6}$ 9.5, $J_{5,4}$ 5.4, $J_{5,1}$ 1.0, 5-H), 6.72 (1 H, dd, $J_{4,5}$ 5.4, $J_{4,6}$ 0.8, 4-H), 7.48–7.52 (3 H, m, Ar–H), 7.72–7.74 (2 H, m, Ar–H); δ_C (125 MHz, $CDCl_3$) 66.00, 67.70, 123.30, 124.98, 125.43, 129.45 (2C), 131.51 (2C), 132.99, 142.53, 144.7; ECD (MeOH): λ/nm 273 ($\Delta\varepsilon$ +4.64), 217 ($\Delta\varepsilon$ −9.77).

(+)-(1*S*,2*S*)-1,2-Dihydroxy-3-(*R*′)-phenylsulfinyl-cyclohexa-3,5-diene 20b$_{1S,2S,R'}$.[11c] White crystalline solid (0.153 g, 27%), m. p. 110–112 °C (from EtOAc/hexane); R_f 0.46 (6% MeOH/$CHCl_3$); $[\alpha]_D$ +297 (*c* 1.0, MeOH); (Found: M^+, 236.0519. $C_{12}H_{12}O_3S$ requires 236.0507); δ_H (500 MHz, $CDCl_3$) 2.98 (1 H, d, $J_{OH,1}$ 8.9, OH), 3.44 (1 H, d, $J_{OH,2}$ 3.1, OH), 4.19 (1 H, dd, $J_{2,OH}$ 8.4, $J_{2,1}$ 6.4, 2-H), 4.30 (1 H, dd, $J_{1,2}$ 6.1, $J_{1,6}$ 2.7, 1-H), 6.09 (2 H, m, 5-H, 6-H), 6.75 (1 H, m, 4-H), 7.50–7.55 (3 H, m, Ar–H), 7.63–7.65 (2 H, m, Ar–H); δ_C (75 MHz, $CDCl_3$) 64.41, 69.27, 121.73, 124.66, 129.42, 129.53 (2C), 131.22 (2C), 137.06, 141.90, 142.27; ECD (MeOH): λ/nm 228 ($\Delta\varepsilon$ +10.13), 228 ($\Delta\varepsilon$ −9.52).

Crystal data for compound 20b$_{1S,2S,R''}$. $C_{12}H_{12}O_3S$, M = 236.3, orthorhombic, a = 8.108(3), b = 11.284(4), c = 24.513(8) Å, U = 2242.7(14) Å^3, T = 293(2) K, space group $P2_12_12_1$ (no. 19), Mo-Kα radiation, λ = 0.71073 Å, Z = 8, F(000) = 992, D_x = 1.400 g cm^{-3}, μ = 0.276 mm^{-1}, Siemens P3 diffractometer, ω scans, 3.3° < 2θ < 65.1°, measured/independent reflections: 4569/4569, direct methods solution, full-matrix least squares refinement on F_o^2, anisotropic displacement parameters for non-hydrogen atoms; all hydrogen atoms located in a difference Fourier synthesis but included at positions calculated from the geometry of the molecules using the riding model, with isotropic vibration parameters. R_1 = 0.049 for 3069 data with $F_o > 4\sigma(F_o)$, 294 parameters, ωR_2 = 0.120 (all data), GoF = 1.03, $\Delta\rho_{min,max}$ = −0.25/0.33 e Å^{-3}. CCDC 1413405. The structure comprises two crystallographically-independent molecules. The absolute configuration in both is confirmed as (1*S*,2*S*,*R*′) from the anomalous scattering arising from the sulfur atom; Flack parameter $x = 0.00(9)$.

Biotransformation of (1*S*,2*S*)-1,2,3-(*R*′-methylsulfinyl)cyclohexa-3,5-diene-1,2-diol 19a$_{1S,2S,R'}$ to yield 3-(*R*)-methylsulfinyl-

1,2-dihydroxybenzene 26a$_R$. *cis*-Diol sulfoxide diastereoisomer **19a$_{1S,2S,R'}$**[11a] was used as substrate with whole cells of *E. coli narB*[11a,13] (19 h), to yield catechol **26a$_R$**. Ethyl acetate extraction of the centrifuged medium, containing the biotransformed products, yielded a crude sample of 3-methylsulfinyl-1,2-dihydroxybenzene **26a$_R$**, which was found to decompose during attempted chromatographic purification. A crude sample of catechol **26a$_R$** was characterized by NMR and MS spectra analyses before methylation. Catechol **26a$_R$** was obtained as a light brown gum (0.57 g, 72% crude yield); R_f 0.18 (60% EtOAc/hexane); (Found: M^+, 172.0192. $C_7H_8O_3S$ requires 172.0194); δ_H (500 MHz, $CDCl_3$) 2.97 (3 H, s, Me), 6.59 (1 H, dd, $J_{6,5}$ 7.9, $J_{6,4}$ 1.5, 6-H), 6.84 (1 H, t, $J_{5,4} = J_{5,6}$ 7.9, 5-H), 7.03 (1 H, dd, $J_{4,5}$ 7.9, $J_{4,6}$ 1.5, 4-H), 10.71 (1 H, br s, OH); *m*/*z* (EI) 172 (M^+, 98%), 157 (52), 111 (100), 97 (49), 83 (58), 57 (60), 55 (54).

Biotransformation of (1*S*,2*S*)-1,2,3-(*R*′- and *S*′-phenylsulfinyl)-cyclohexa-3,5-diene-1,2-diol 20b$_{1S,2S,R'}$ and 19b$_{1S,2S,S'}$ to yield 3-phenylsulfinyl-1,2-dihydroxybenzene enantiomers 26b$_R$ and 26b$_S$. *cis*-Diol sulfoxides 1,2-diol **20b$_{1S,2S,R'}$** (150 mg, 0.64 mmol) and **19b$_{1S,2S,S'}$** (0.5 g, 2.12 mmol) were metabolized, separately, using *E. coli narB* (18 h). Ethyl acetate extraction of the centrifuged culture media yielded the corresponding catechol sulfoxides, 3-[(*R*)-phenylsulfinyl]benzene-1,2-diol **26b$_R$** (90 mg, 60% crude yield) and 3-[(*S*)phenylsulfinyl]-benzene-1,2-diol **26b$_S$** (0.4 g, 81% crude yield). Small portions of catechol sulfoxide enantiomers **26b$_R$** and **26b$_S$** were purified by recrystallization for characterization. The remaining crude samples were methylated with diazomethane.

Catechol **26b$_S$** was obtained as white solid; m. p. 153–154 °C; $[\alpha]_D$ +298 (*c* 0.36, MeOH); (Found: M^+, 234.0340. $C_{12}H_{10}O_3S$ requires 234.0351); δ_H (500 MHz, $CDCl_3$) 5.86 (1 H, br s, OH), 6.76 (1 H, dd, $J_{6,5}$ 7.9, $J_{6,4}$ 1.5, 6-H), 6.83 (1 H, t, $J_{5,4} = J_{5,6}$ 7.9, 5-H), 7.00 (1 H, dd, $J_{4,5}$ 7.9, $J_{4,6}$ 1.5, 4-H). 7.51 (3 H, m, Ar–H), 7.69–7.70 (2 H, m, Ar–H), 10.72 (1 H, br s, OH); δ_C (125 MHz, $CDCl_3$) 116.71, 117.92, 120.33, 122.77, 124.84, 129.57 (2C), 131.63 (2C), 143.40, 146.22, 146.31; *m*/*z* (EI) 234 (M^+, 15%), 186 (5), 91 (38), 85 (91), 83 (100), 47 (22); ECD (MeOH): λ/nm 237.2 ($\Delta\varepsilon$ −3.642), 220.2 ($\Delta\varepsilon$ +2.171), 208.4 ($\Delta\varepsilon$ −6.918), 194.8 ($\Delta\varepsilon$ +10.840).

Catechol **26b$_R$**; $[\alpha]_D$ −303 (*c* 0.59, MeOH); ECD (MeCN): λ/nm 238.0 ($\Delta\varepsilon$ +4.992), 220.0 ($\Delta\varepsilon$ −2.358), 208.0 ($\Delta\varepsilon$ +9.994), 194.6 ($\Delta\varepsilon$ −16.400).

(iii) Methylation using diazomethane

A sample of catechol (*e.g.* **26a$_R$**; 100 mg) in methanol solution (5 mL) was treated at 0 °C with excess of freshly prepared solution of diazomethane in ether. After leaving the mixture in an ice bath (1 h), the solvents were removed and the crude mixture of methylated product/s separated by PLC (50% EtOAc in hexane). Methylated catechols **29a$_R$** and **27a$_R$** (from **26a$_R$**), **27b$_S$** (from **26b$_S$**) and **27b$_R$** (from **26b$_R$**) were synthesised by the same procedure.

(+)-2-Methoxy-3-[(*R*)-methylsulfinyl]phenol 29a$_R$. White crystalline solid (40 mg, 37%); R_f 0.1 (50% EtOAc/hexane); m. p. 135–38 °C (from EtOAc); $[\alpha]_D$ +229 (*c* 0.36, $CHCl_3$); (Found: M^+, 186.0359. $C_8H_{10}O_3S$ requires 186.0351); δ_H (500 MHz, $CDCl_3$) 2.83 (3 H, s, –SOMe), 3.93 (3 H, s, –OMe), 7.13 (1 H, dd, $J_{6,5}$ 7.9, $J_{6,4}$ 1.6, 6-H), 7.19 (1 H, dd, $J_{5,4} = J_{5,6}$ 7.9, 5-H), 7.33 (1 H, dd, $J_{4,5}$ 7.9, $J_{4,6}$ 1.6, 4-H); δ_C (125 MHz, $CDCl_3$) 41.98, 61.35, 115.04, 119.81, 125.55, 137.89, 142.71, 149.44; *m*/*z* (EI) 186 (M^+, 40%), 183 (36), 169 (100), 141 (93), 111 (63), 51 (48).

(+)-1,2-Dimethoxy-3-[(*R*)-methylsulfinyl]benzene 27a$_R$. Light yellow oil (57 mg, 50%); R_f 0.17 (50% EtOAc/hexane); $[\alpha]_D$ +220 (*c* 0.47, $CHCl_3$); (Found: M^+, 200.0500. $C_9H_{12}O_3S$ requires 200.0507); δ_H (500 MHz, $CDCl_3$) 2.78 (3 H, s, –SOMe), 3.91 (3 H, s, –OMe), 3.92 (3 H, s, –OMe), 7.05 (1 H, dd, $J_{6,5}$ 8.0, $J_{6,4}$ 1.5, 6-H), 7.28 (1 H, dd, $J_{5,4} = J_{5,6}$ 8.0, 5-H), 7.42 (1 H, dd, $J_{4,5}$ 8.0, $J_{4,6}$ 1.5, H-4); δ_C (125 MHz, $CDCl_3$) 42.16, 56.07, 61.05, 114.90, 115.66, 125.07, 139.15, 144.02, 152.05; *m*/*z* (EI) 200 (M^+, 93%), 185 (89), 184 (94), 168 (86), 127 (82), 109 (100), 77 (94); ECD (MeOH): λ/nm 287 ($\Delta\varepsilon$ +3.152), 241 ($\Delta\varepsilon$ +38.08), 226 ($\Delta\varepsilon$ +27.11), 210 ($\Delta\varepsilon$ −35.14), 200 ($\Delta\varepsilon$ +3.305), 195 ($\Delta\varepsilon$ −3.717), 192 ($\Delta\varepsilon$ +1.308).

(+)-3-[(*S*)-Phenylsulfinyl]-1,2-dimethoxybenzene 27b$_S$. Light yellow oil (32 mg, 90%); R_f 0.80 (3% MeOH/$CHCl_3$); $[\alpha]_D$ +161 (*c* 0.32, $CHCl_3$); (Found: M^+, 262.0662. $C_{14}H_{14}O_3S$ requires 262.0664); δ_H (500 MHz, $CDCl_3$) 3.80 (3 H, s, OMe), 3.85 (3 H, s, OMe), 7.00 (1 H, dd, $J_{6,5}$ 8.1, $J_{6,4}$ 1.4, 6-H), 7.23 (1 H, t, $J_{5,4} = J_{5,6}$ 8.1, 5-H), 7.41 (3 H, m, Ar–H), 7.47 (1 H, dd, $J_{4,5}$ 8.1, $J_{4,6}$ 1.4, 4-H), 7.73 (2 H, m, Ar–H); δ_C (125 MHz, $CDCl_3$) 56.00, 60.73, 114.98, 115.84, 124.88, 125.31, 129.09 (2C), 130.90 (2C), 139.22, 145.09, 145.90, 152.32; *m*/*z* (EI) 262 (M^+, 8%), 247 (7), 246 (22), 245 (100), 91 (23), 77 (21), 51 (25); ν_{max} (KBr)/cm^{-1} 3156, 3064, 2962, 2941, 2838, 1590, 1480, 1272, 1035 (S═O), 782, 690.

(−)-3-[(*R*)-Phenylsulfinyl]-1,2-dimethoxybenzene 27b$_R$. (19 mg, 74%); $[\alpha]_D$ −159 (*c* 0.43, $CHCl_3$).

Aromatization of sulfoxide *cis*-diol 20b$_{1S,2S,R'}$. A small sample (*ca.* 10 mg) of enantiopure sulfoxide *cis*-diol **20b$_{1S,2S,R'}$** was treated with aq. HCl (0.5 M, 5 mL). The reaction mixture was left overnight at room temperature, extracted with EtOAc, the extract concentrated, and the residue treated at 0 °C with ether solution of diazomethane. The mixtures of methyl ethers, **24b$_R$**/**24b$_S$** and **25b$_R$**/**25b$_S$** (X = Me) of phenols **24b$_R$**/**24b$_S$** and **25b$_R$**/**25b$_S$** (X = H), obtained were analysed by CSPHPLC (Chiralpak AS column, 0.5 mL min^{-1}, 20% IPA/hexane). The elution profiles of enantiomers **24b$_R$** (52.9 min, 64%), **24b$_S$** (71.2 min, 12%), **25b$_S$** (58.8 min, 4%), **25b$_R$** (62.0 min, 20%), and their relative ratios provided unequivocal evidence of racemization.

Asymmetric alkylation of benzaldehyde to form alcohol 35. Diethyl zinc solution in hexane (0.1 mL, 1 M) was added to a stirred solution of benzaldehyde (100 mg, 1 mmol) and hydroxy sulfoxide ligand (Table 1, 0.02 mmol) in dry toluene (3 mL) under a nitrogen atmosphere. When the reaction was complete (monitored by TLC), saturated solution of NH_4Cl (5 mL) was added and the stirring continued for 10 min. The product was extracted with EtOAc (2 × 5 mL), the extract dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by PLC (25% Et_2O in hexane) to give 1-phenylpropanol **35**. The absolute configuration of the

product was determined by comparison of its $[\alpha]_D$ value with that reported in the literature. Enantiomeric purity values (*S* isomer 10.7 min, *R* isomer 12.5 min) were confirmed by CSP HPLC analysis (Chiralcel OB column, 10% IPA in hexane).

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