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Dioxygenase-catalysed sulfoxidation of bicyclic alkylaryl sulfides and chemoenzymatic synthesis of acyclic disulfoxides

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Abstract—Toluene- and naphthalene-dioxygenase-catalysed oxidation of six bicyclic disulfide substrates, using whole cells of *Pseudomonas putida*, gave the corresponding monosulfoxides with high ee values and enantiocomplementarity, in most cases. Two alcohol-sulfoxide diastereoisomers, formed from the reaction of the (*R*)-1,3-benzodithiole-1-oxide metabolite with *n*-butyllithium and benzaldehyde, were separated and stereochemically assigned. Treatment, of enantiopure (1*R*,3*R*)-benzo-1,3-dithiole-1,3-dioxide, obtained by chemoenzymatic synthesis, with alkyllithium reagents, resulted in a novel ring-opening reaction which proceeded with inversion of configuration to yield a series of acyclic disulfoxides.

1. Introduction

The potential of microbial enzymes in the biocatalytic oxidation of sulfides, to yield enantiopure sulfoxides, has been recognised for many years. *t*-Butyl *p*-tolyl sulfoxide, the first reported enantiopure example of a sulfoxide produced by enzyme-catalysed oxidation of an achiral sulphide,[1] was obtained using the fungus *Aspergillus niger* (*foetidus*), a source of monooxygenase enzymes. More recent biotransformation studies, from these[2–7] and other laboratories,[8,9] have shown that the ring hydroxylating dioxygenase enzymes (Rieske non-heme iron oxygenases), present in the soil bacterium *Pseudomonas putida*, are among the most stereoselective biocatalysts, currently available, for the production of enantiopure acyclic sulfoxides. Wild-type and mutant *P. putida* strains,[2–8] and *E. coli* recombinant strains,[3,5,8,9] containing toluene dioxygenase (TDO) and naphthalene-dioxygenase (NDO), have thus, to date, yielded >30 sulfoxides with high (>90%) enantiomeric excess (ee) values.[2–9] Routes to enantiopure sulfoxides are required for asymmetric synthesis studies (e.g. as chiral auxiliaries and ligands) and for the production of pharmaceuticals including anti-ulcer drugs containing a chiral sulfoxide group (e.g. the proton pump inhibitors omeprazole, and lanzaprazole). The results, presented in this article, provide a further demonstration of the value of enantiocomplementary dioxygenase enzymes for the production of enantiopure cyclic monosulfoxides from 1,3-, 1,4- and 1,5-disulfides. The enantiopure monosulfoxide metabolite **1B**, from benzo-1,3-dithiole **1A**, and the derived disulfoxide **1C**, have, in turn, been used to investigate their reactions with alkyllithium reagents.

2. Results and discussion

2.1. Dioxygenase-catalysed monosulfoxidation of sulfides 1A–8A to yield the corresponding sulfoxides 1B–8B

The initial phase of the study involved biotransformations of bicyclic disulfide substrates **1A**–**6A** using: (i) *P. putida* UV4 (a constitutive mutant strain containing TDO), (ii) *P. putida* NCIMB 8859 (a wild-type strain containing NDO) and, to a lesser extent, (iii), *P. putida* 9816/11 (an inducible mutant strain containing NDO). These whole-cell systems provide sources of the required dioxygenase biocatalysts, under biotransformation conditions similar to those reported for earlier sulfoxidation studies.[2–9] The isolated yields, enantiopurity values, and absolute configurations of monosulfoxides **1B**–**6B** are shown in Table 1. Sulfoxides **1B**,[10] $\mathbf{2B}_{cis}$,[10] $\mathbf{2B}_{trans}$,[10] $\mathbf{3B}_{cis}$,[10] $\mathbf{3B}_{trans}$[10] and **6B**[11] had earlier been reported as single enantiomers, while sulfoxides **4B** and **5B** were obtained for the first time as single enantiomers, during the present study.

Keywords: Dioxygenase-catalysed sulfoxidation; Enantiopure bicyclic sulfoxides; Alkylithium; Acyclic disulfoxides.
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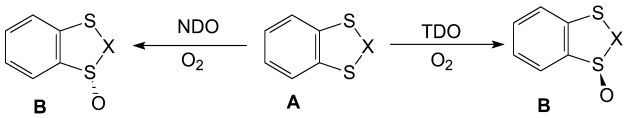
Table 1. Isolated yields (%Yld.), ee values (% ee) and absolute configurations (Ab.Con.) of sulfoxides **1B**–**8B** obtained from the corresponding sulfides **1A**–**8A** using TDO (*P. putida* UV4) and NDO (*P. putida* 8859) in whole-cell systems

Compound	TDO enzyme			NDO enzyme		
	%Yld.	% ee	Ab.Con.	%Yld.	% ee	Ab.Con.
1B	20	33	*S*	74, 72	>98	*R*
2B$_{cis}$	40, 26	>98	1*S*,2*R*	49	82	1*R*,2*S*
2B$_{trans}$	5	>98	1*S*,2S	7	38	1*R*,2*R*
3B$_{cis}$	26	>98	1*S*,2*R*	—	—	—
3B$_{trans}$	5	18	1*R*,2R	—	—	—
4B	1, 3	>98	*R*	78	>98	*S*[a]
5B	[b]	[b]	[b]	26	80 (93)[c]	*S*
6B	23	>98	*R*	60	>98	*S*
7B	5	26	*R*	21	38	*S*
8B	10	>98	*R*	2	43	*R*

[a] Predicted absolute configuration.
[b] No sulfoxide isolated; using *P. putida* 9816/11 as a source of NDO biocatalyst.
[c] Recrystallisation of bioproduct from *P. putida* 9816/11 gave an ee value of >98%.

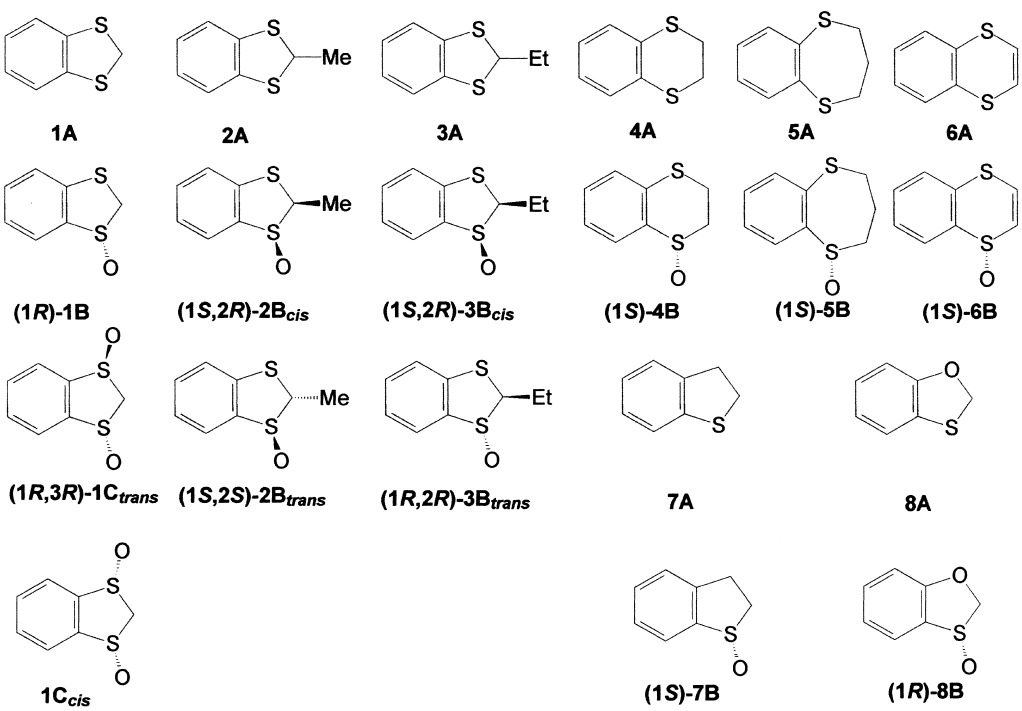
The circular dichroism (CD) spectra, of sulfoxide metabolites **1B**, **2B**$_{cis}$, **2B**$_{trans}$, **3B**$_{cis}$, and **3B**$_{trans}$, were found to have a strong absorption around 220 nm due to an n–π^* transition associated with the sulfoxide group.[10] This trend, of a positive CD absorption in the 220 nm region, was consistently associated with the rigorously established (*R*) configuration in sulfoxides **1B**, **2B**$_{cis}$, **2B**$_{trans}$, **3B**$_{cis}$, and **3B**$_{trans}$. The absolute configurations of sulfoxide enantiomers **4B**–**6B** have not been reported in the literature; no consistent CD spectral trend was evident that would allow reliable assignment of their absolute configurations. Hence, alternative approaches, to the configuration assignments for sulfoxide metabolites **4B**–**6B** were examined. Earlier studies, of the biotransformation of alkyl- and alkenylphenyl sulfides (RSPh, R=Me, Et, CH_2=CH_2, etc.), using *P. putida* UV4 (TDO), showed that an (*R*) configuration was observed in all cases.[5] This empirical method, of configuration assignment, was thus based on the assumption that the cyclic alkylaryl and alkenylaryl sulfides **4A**–**6A** would bind in a similar manner, at the active site of TDO, and would also show a preference for (1*R*) configurations for sulfoxide metabolites **4B**–**6B** (Scheme 1).

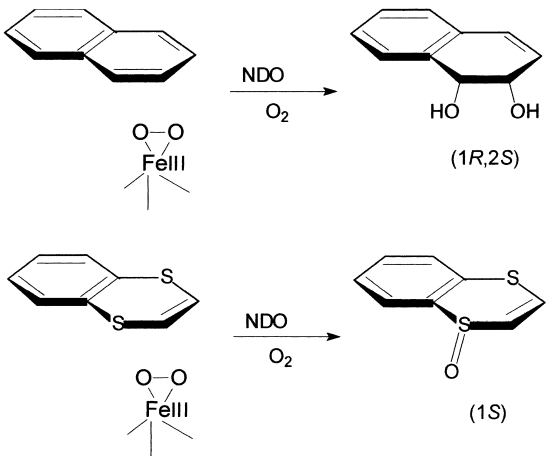


Scheme 1.

Conversely, a strong preference for the opposite (*S*) sulfoxide configuration was observed earlier, using NDO with some alkylphenyl and alkenylphenyl sulfides (RSPh, R=Me, Et, CH_2=CH_2, etc.).[5] X-ray crystallographic evidence, of the substrate binding and catalytic sites of NDO, that can account for the absolute stereochemistry of the *cis*-diol metabolites of bicyclic alkenes (e.g. indene) and arenes (e.g. naphthalene), has recently been reported.[12] In view of the similarity in shape between naphthalene and the bicyclic sulfide substrates **4A** and **6A** it is probable that substrate binding and catalysis, using NDO (Scheme 2), will yield bioproducts of similar configuration (but opposite to that obtained using TDO). Thus, absolute configurations of sulfoxide metabolites **4B**–**6B** were tentatively assigned by comparison with earlier results, using the TDO and NDO enzyme systems and acyclic alkylphenyl sulfides as substrates.

Recrystallization of the bioproduct, (−)-1,2,3,4-tetrahydro-1λ^4,5-benzodithiepin-1-oxide **5B** (80–93% ee) obtained by NDO-catalysed sulfoxidation, provided an enantiopure





Scheme 2.

sample whose absolute configuration was unequivocally established, as (1*S*) by X-ray crystallography, using the anomalous dispersion method (Fig. 1). The tetrahydrodithiepine ring adopts the chair conformation, with an equatorial oxygen atom. This result lends additional support to the tentative assignments of (1*R*) and (1*S*) configurations for alkylaryl sulfoxides **4B**–**6B** formed with TDO and NDO biocatalysts, respectively.

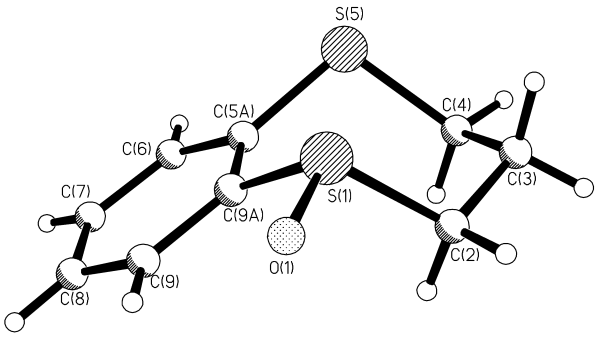


Figure 1. X-ray structure of **5B**.

As an extension to the dioxygenase-catalysed sulfoxidation study, the monosulfide isosteres **7A** and **8A**, of the parent disulfide substrate **1A**, were also examined. Thus, the corresponding enantioenriched sulfoxides, **7B** and **8B**, of known absolute configuration, were obtained with TDO and NDO as biocatalysts (Table 1). While sulfoxides **7B**, obtained using TDO and NDO, were of opposite absolute configuration, surprisingly, identical (1*R*) configurations were found for the sulfoxide metabolites **8B** using either enzyme. Sulfoxide **7B** was the most polar of the five chiral metabolites isolated with *P. putida* UV4 and 2,3-dihydrobenzo[*b*]thiophene **7A** as substrate. The structure and stereochemistry (absolute configurations and ee values) of the other metabolites, resulting from benzylic hydroxylation, desaturation and dihydroxylation of the heterocyclic and carbocyclic rings, will be discussed elsewhere.

The results, shown in Table 1, indicate that the cyclic sulfoxides were isolated in variable yields (1–78%) and that all but the sulfoxides $\mathbf{3B}_{trans}$ and **7B** could be obtained with high ee values (>90%), using either TDO or NDO as biocatalyst. The contrasting stereopreferences, previously observed for TDO- and NDO-catalysed oxidation of some acyclic alkylaryl sulfides[5] (Scheme 1), were even more common during the sulfoxidation of cyclic alkylaryl sulfides to yield sulfoxide metabolites, **1B**, $\mathbf{2B}_{cis}$, $\mathbf{2B}_{trans}$, **4B**, **6B** and **7B**. The most striking examples of enantiocomplementarity were found when TDO or NDO biocatalysts were used to produce enantiopure sulfoxides **4B** and **6B** of opposite configuration.

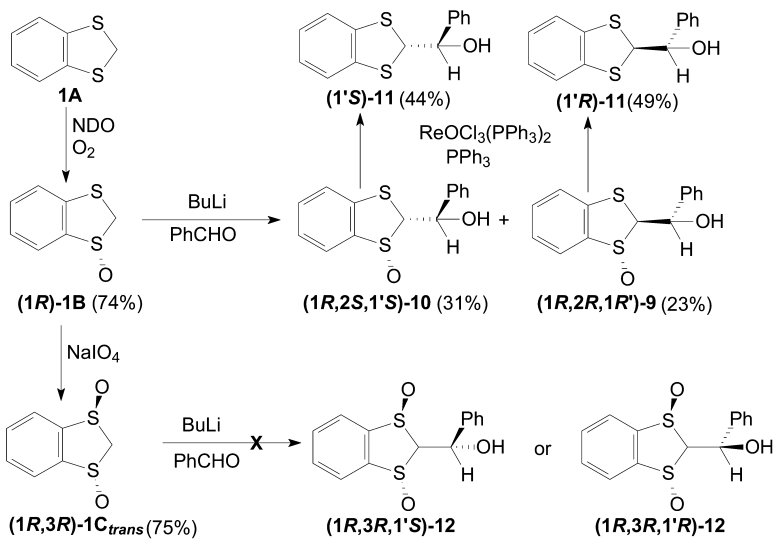
The Kagan modified Sharpless reagent, (Ti (*i*-PrO)$_4$/DET/*t*-BuOOH), had earlier[11] been used to obtain sulfoxide **6B**, as a single enantiomer (8% yield), after separation from a product mixture containing three other sulfoxidation products (92% yield). Biocatalysis now provides a complementary synthesis (asymmetric oxidation) of sulfoxide **6B** where either enantiomer is available in higher yield and state of purity. While the stereoselectivity values, found during sulfoxidations using TDO or NDO, were similar, the isolated yields were generally better, using the NDO system.

Results from earlier biotransformation studies, using both acyclic sulfides, and the corresponding racemic sulfoxides as substrates, for purified dioxygenases (TDO and NDO), or whole cell bacterial strains, containing TDO and NDO,[5,8] suggested that the enantiopure sulfoxide products were exclusively (or mainly) formed by asymmetric sulfoxidation. During the present study, the cyclic racemic sulfoxides **1B**–**8B** were also tested as substrates for the UV4 and 8859 strains of *P. putida*. With the exception of recovered sulfoxide **8B** (1*S*, 74% ee, 8859 strain), the other biotransformations showed only poor enantioenrichment of residual sulfoxides. On this basis, it would again appear that the high ee values, observed for the sulfoxide metabolites of cyclic sulfides, using TDO and NDO, were mainly the products of asymmetric sulfoxidation rather than kinetic resolution. However, during the course of these biotransformation studies of racemic sulfoxides with *P. putida* UV4, tentative evidence was found of other reactions occurring (<5% yield of bioproducts). This included evidence of a reductase-catalysed deoxygenation of sulfoxides which will be presented elsewhere.

2.2. Reaction of (*R*)-benzo-1,3-dithiole-1-oxide 1B with *n*-butyllithium and benzaldehyde

Small quantities, of enantiopure (+)- and (−)-sulfoxide **1B**, had earlier been obtained by chromatographic resolution of the racemate, using semi-preparative chiral stationary phase HPLC (CSPHPLC).[10] Treatment, of the sulfoxide enantiomers **1B** with strong base, potassium bis(trimethysilyl) acetamide, yielded a carbanion at C-2 that was used in the nucleophilic substitution of alkyl halides, to provide twelve enantiopure 2-substituted benzo-1,3-dithiole sulfoxides, including compounds $\mathbf{2B}_{cis}$, $\mathbf{2B}_{trans}$, $\mathbf{3B}_{cis}$, $\mathbf{3B}_{trans}$.[10] Absolute configuration determination, of the derived (1*S*,2*S*,2′*S*)-2-(2′-methylbutyl)-1,3-benzodithiole 1-oxide, by X-ray crystallography, allowed the configurations of the other 2-substituted benzo-1,3-dithiole sulfoxides **1B**, $\mathbf{2B}_{cis}$, $\mathbf{2B}_{trans}$, $\mathbf{3B}_{cis}$, $\mathbf{3B}_{trans}$ to be unequivocally assigned by stereochemical correlation and CD spectral comparison.

A major disadvantage of the CSPHPLC resolution procedure was that only small quantities, of each sulfoxide



Scheme 3.

enantiomer **1B** (ca: 40 mg), were obtained for reactivity studies.[10] With the availability of larger samples of the enantiopure benzo-1,3-dithiole sulfoxide **1B**, from the NDO-catalysed biotransformation route, it was possible to re-examine the reactivity of this compound and its derivatives. Thus, the second phase of the study involved the reactions of enantiopure monosulfoxide **1B** and disulfoxide $\mathbf{1C}_{trans}$ with alkyllithium reagents.

(*R*)-Monosulfoxide metabolite **1B** ($[\alpha]_D$=+505) was treated with 1 equiv. of *n*-butyllithium in dry THF (−78 °C) followed by the addition of benzaldehyde to the C-2 carbanion intermediate, to yield a diastereoisomeric mixture of 2-substituted benzo-1,3-dithiole sulfoxides **9**/**10** (Scheme 3). Separation, by PLC, gave *cis* isomer **10** as a crystalline solid (R_f 0.31, $[\alpha]_D$=+344, 31% yield) and *trans* isomer **9** as a viscous oil (R_f 0.19, $[\alpha]_D$=+116, 23% yield). X-ray crystallographic analysis (Fig. 2) confirmed the *cis* geometry of sulfoxide **10** and, using the anomalous dispersion method, allowed assignment of absolute configuration, (1*R*,2*S*,1′*S*), of the three chiral centres. The heterocyclic ring adopts an envelope conformation, with pseudoaxial oxygen and pseudoequatorial side chain at C(2).

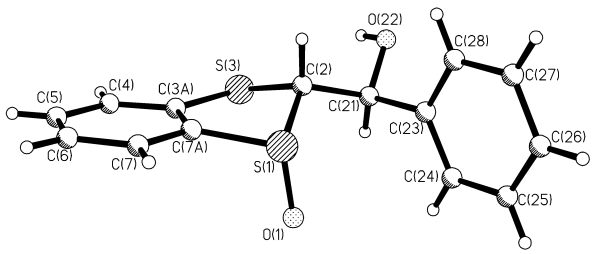
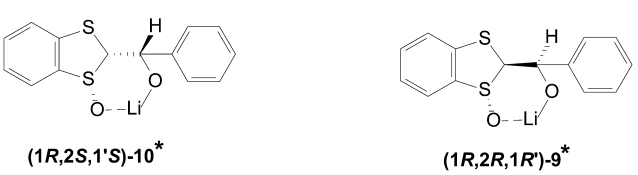


Figure 2. X-ray structure of **10**.

The X-ray crystallographic analysis, of the minor diastereoisomer **9**, was precluded, since it could not be obtained in crystalline form. Its absolute configuration was, however, assigned by a mild rhenium-catalysed deoxygenation process.[13] Thus, using the *trans* monosulfoxide **9** and a catalytic amount of $ReOCl_3(PPh_3)_2$ in the presence of triphenyl phosphine (ambient temperature, 1.5 h), the (−)-enantiomer of 2-substituted benzo-1,3-dithiole **11** ($[\alpha]_D$=−12, 49% yield) was obtained. Similar treatment (72 h), of the more hindered *cis* sulfoxide **10**, yielded the (+)-enantiomer of 2-substituted benzo-1,3-dithiole **11** ($[\alpha]_D$=+12, 44% yield). Since the absolute configuration, of the exocyclic chiral centre of sulfoxide **10**, was established as (1′*S*) by X-ray crystallography, sulfoxide **9** must have the (1*R*,2*R*,1′*R*) configuration. The formation, of either the (1′*R*) or (1′*S*) enantiomer of alcohol **11**, provides a good example, of the transfer of chirality from a (1*R*) cyclic sulfoxide stereogenic centre in metabolite **1B**, to a new exocyclic chiral centre in alcohol **11**. The converse process, i.e. chiral relay from the chiral alcohol centres in an arene *cis*-dihydrodiol metabolite, to a new chiral sulfoxide centre of either configuration (catechol sulfoxides), has recently been reported from these laboratories.[7]

The marked degree of diastereoselectivity, found during substitution at the C-2 position for the (*R*) enantiomer of monosulfoxide **1B**, was noteworthy; thus, only two diastereoisomers, (1*R*,2*S*,1′*S*)-**10** and (1*R*,2*R*,1′*R*)-**9**, of the possible four were detected. Examination of molecular models suggests that this could be due to the preferential attractive interactions between the sulfoxide oxygen atom and the lithium alkoxide, favouring chelate formations (1*R*,2*R*,1′*R*)-**9*** and (1*R*,2*S*,1′*S*)-**10*** (Scheme 4). Similar types of chelate interactions have been suggested, to account for the diastereoselectivity associated with carbanion reactions of *trans*-1,3-dithiane 1,3-dioxide with benzaldehyde.[14]

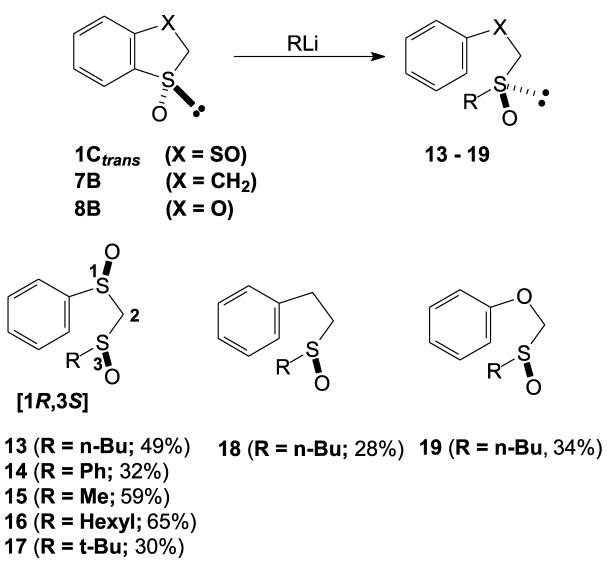


Scheme 4.

2.3. Ring-opening reactions of (1*R*,3*R*)-disulfoxide $\mathbf{1C}_{trans}$ and monosulfoxides 7B and 8B

Chemical oxidation of (+)-(*R*)-benzo-1,3-dithiole 1-oxide

1B ($[\alpha]_D$=+505), using $NaIO_4$ as oxidant, yielded enantiopure (+)-(1*R*,3*R*)-disulfoxide $\mathbf{1C}_{trans}$ ($[\alpha]_D$=+646, 75% yield, Scheme 3) as a major product. Compound $\mathbf{1C}_{trans}$ was readily separated from achiral (1*R*,3*S*) isomer $\mathbf{1C}_{cis}$ (19% yield) by flash chromatography. It was anticipated that treatment of (+)-disulfoxide $\mathbf{1C}_{trans}$ in a manner similar to (+) sulfoxide **1B**, i.e. reaction with *n*-butyllithium in dry THF (−78 °C), followed by addition of benzaldehyde, would give the two diastereoisomers of alcohol sulfoxide **12** (Scheme 3). In an earlier study,[14] on the synthesis and reaction of (±)-disulfoxide $\mathbf{1C}_{trans}$ with *n*-butyllithium and pivalaldehyde, alcohol disulfoxide diastereoisomers of similar structure to compound **12** (Ph replaced by *t*-Bu) were reported. However, spectral analysis and PLC purification indicated that only one product was formed from the reaction of *n*-butyllithum/benzaldehyde (−78 °C) with the (1*R*,3*R*) enantiomer of cyclic disulfoxide $\mathbf{1C}_{trans}$; it was identified as the acyclic disulfoxide **13** ($[\alpha]_D$=−180, 49% yield, Scheme 5). When this reaction was repeated under identical conditions, but without addition of benzaldehyde, the acyclic (−)-disulfoxide **13** was again formed (Scheme 5).



Scheme 5.

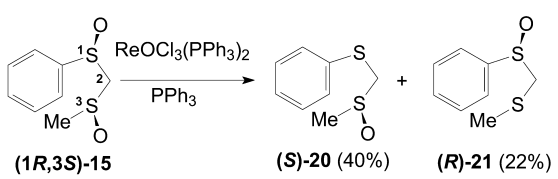
Since only a few methods are available for the synthesis of enantiopure acyclic disulfoxides, using either chemical or enzymatic approaches,[15–18] the unusual ring-opening reaction of (1*R*,3*R*)-disulfoxide $\mathbf{1C}_{trans}$ was examined further (Scheme 5). Reactions of $\mathbf{1C}_{trans}$ with other alkyllithium reagents (RLi, R=Ph, Me, $(CH_2)_5Me$, *t*-Bu) were conducted under identical conditions. ^{1}H NMR analysis, of the resulting acyclic disulfoxide products **13**–**17** indicated that in all cases single diastereoisomers were formed, albeit in relatively modest yields (28–65%, Table 2). Compound **14** was the only disulfoxide obtained without either a measurable optical rotation or CD absorption. This observation was consistent with total inversion of configuration, occurring during the ring opening process, to yield achiral *meso* isomer **14**. Comparison of the melting points and ^{1}H NMR data for disulfoxide **14** (mp 124–125 °C, $[\alpha]_D$=0), isolated during the present study, with that reported for the *meso* (mp 123 °C, $[\alpha]_D$=0) and racemic (*R*/*S* or *S*/*R*) (mp 136 °C) isomeric forms,[15,16] confirmed that it was, indeed, the *meso* compound.

Table 2. Reactions of bicyclic sulfoxides $\mathbf{1C}_{trans}$, **7B** and **8B** with alkyllithium reagents to yield the acyclic disulfoxides **13**–**17** and monosulfoxides **18** and **19**

Reactant sulfoxide		Alkyl lithium	Di- and mono-sulfoxide products			
Structure	Ab.Con.		Number	Yield	$[\alpha]_D$[a]	Ab.Con.
$\mathbf{1C}_{trans}$	1*R*,3*R*	BuLi	**13**	49	−180	1*R*,3*S*
$\mathbf{1C}_{trans}$	1*R*,3*R*	PhLi	**14**	32	[b]	[b]
$\mathbf{1C}_{trans}$	1*R*,3*R*	MeLi	**15**	59	−234	1*R*,3*S*
$\mathbf{1C}_{trans}$	1*R*,3*R*	HexylLi	**16**	65	−247	1*R*,3*S*
$\mathbf{1C}_{trans}$	1*R*,3*R*	*t*-BuLi	**17**	30	+75	1*R*,3*S*
7B	*R*	BuLi	**18**	28	−13[c]	*R*
8B	*S*	BuLi	**19**	34	+74[d]	*R*

[a] $CHCl_3$ solvent.
[b] Achiral compound.
[c] Formed from **7B** of 90% ee.
[d] Formed from **8B** of 73% ee.

The characteristic ^{1}H NMR spectral data, reported for the racemic (1*R*,3*R*/1*S*,3*S*) and (1*R*,3*S*/1*S*,3*R*) diastereoisomeric pairs of sulfoxide **15**,[15] suggested that the ring-opening product **15** ($[\alpha]_D$=−234, 59% yield) was either (1*R*,3*S*) or (1*S*,3*R*) diastereoisomer. Unfortunately an $[\alpha]_D$ value for either enantiomer of compound **15** has not been reported. The (1*R*,3*S*) configuration for (−)-sulfoxide **15** was confirmed by partial deoxygenation, using the rhenium complex-catalysed procedure (Scheme 6).[13] As expected from earlier studies,[13] the dialkyl sulfoxide group was deoxygenated more slowly compared with the alkylaryl sulfoxide group, leading to a 2:1 ratio of dialkyl sulfoxide **20** and alkylaryl sulfoxide **21**. Partial racemisation, of monosulfoxides **20** ($[\alpha]_D$=−27, 24% ee) and **21** ($[\alpha]_D$=−110, 87% ee), occurring to different degrees during the deoxygenation process, was also observed. Despite the partial racemisation, it was possible to assign (*S*) and (*R*) configurations, respectively, to monosulfoxides (−)-**20** and (−)-**21**, by comparison of the $[\alpha]_D$ values with authentic samples;[18] thus, a (1*R*,3*S*) configuration was assigned to disulfoxide **15**. The CD spectra of single diastereoisomers **13**, **15**–**17**, obtained by the ring-opening reaction of disulfoxide $\mathbf{1C}_{trans}$ (Scheme 5), displayed a similar pattern, i.e. a strong positive absorption at 218–220 nm and a strong negative absorption at 246–256 nm. The similarity in CD spectra of compounds **13**, **15**–**17** and unequivocal assignment of absolute configuration to disulfoxide **15** led us to the conclusion that in the ring-opening reactions inversion of configuration had occurred. This premise was supported by two reports in the literature,[19,20] where enantiopure acyclic alkylaryl monosulfoxides were found to react with alkyllithium reagents, to yield dialkyl sulfoxides via an S_N2 exchange process occurring with inversion of configuration. As found for acyclic alkylaryl sulfoxides,[19,20] the aryl–SO bond in the



Scheme 6.

cyclic disulfoxide **1C**$_{trans}$ was cleaved in preference to the alkyl–SO bond.

It was reported earlier[20] that alternative reactions of acyclic monosulfoxides with alkyl lithium reagents result in (a) abstraction of an α-hydrogen atom to give an α-lithiosulfoxide (carbanion formation), and (b) replacement of an aryl sulfoxide group with the alkyllithium group (group exchange). The relative proportion of either reaction was found to depend on the structure of sulfoxide (number and acidity of α-hydrogen atoms, substituent size and leaving group ability) and the type of alkyllithium reagent (size and basicity). Our observation of ring-opening reactions (group exchange), of disulfoxide **1C**$_{trans}$ with alkyllithium reagents (−78 °C), suggests that the temperature may also be an important factor. The reported[14] substitution reaction of a racemic sample of compound **1C**$_{trans}$, using *n*-butyllithium and pivalaldehyde to form *t*-butyl analogues of compounds (1*R*,3*R*,1′*S*)-**12** and (1*R*,3*R*,1′*R*)-**12** (Scheme 3), was carried out at higher temperatures (0 to −45 °C). Furthermore, ^{1}H NMR spectral analysis of the crude product mixture, obtained from the reaction of compound **1C**$_{trans}$ with *n*-butyllithium and benzaldehyde at a relatively higher temperature (−45 °C) indicated the formation of compounds (1*R*,3*R*,1′*S*)-**12** and (1*R*,3*R*,1′*R*)-**12**.

When the enantiopure monosulfoxide metabolites **4B**–**6B** containing six and seven-membered rings, were converted to the corresponding disulfoxides, and subsequently treated with alkyllithium reagents, no evidence of comparable ring-opening reactions was observed. However, under the standard reaction conditions monosulfoxide metabolites **7B** and **8B**, containing a five-membered ring, were also found to undergo a similar ring opening reaction to give the corresponding acyclic dialkyl monosulfoxides **18** and **19** in low yields (28 and 34%, Scheme 5, Table 2). Since only limited amounts of enantioenriched/enantiopure sulfoxides **7B** and **8B** were available from the small-scale biotransformations, additional samples of enantioenriched sulfoxides (−)-(*R*)-**7B** (90% ee) and (−)-(*S*)-**8B** (73% ee) were synthesised by chemical asymmetric sulfoxidation using the Kagan modified Sharpless reagent (Ti(*i*-PrO)$_4$/DET/*t*-BuOOH).[11]

It was assumed that inversion of configuration had occurred, again, during the ring-opening reaction of compound (−)-(*R*)-**7B** to yield monosulfoxide **18** ([α]$_D$=−13, 28% yield) and of compound (−)-(*S*)-**8B** to give the hemiacetal derivative **19** ([α]$_D$=+74, 34% yield). Chiral stationary phase HPLC (CSPHPLC) analysis of the sulfoxide **19** (49% ee), obtained from sulfoxide **8B** (73% ee), showed that partial racemization had occurred. The ee value for sulfoxide **18** could not be obtained using the latter CSPHPLC method.

3. Conclusions

The dioxygenase enzyme system has been shown to catalyse the enantioselective heteroatom oxidation of bicyclic sulfides (**7A**, **8A**) and disulfides (**1A**–**6A**). In many cases, the corresponding enantiopure monosulfoxides (e.g. **1B**, **2B**$_{cis}$, **2B**$_{trans}$, **3B**$_{cis}$, **4B**–**6B**) were obtained with opposite absolute configurations, using either TDO or NDO as biocatalyst. The monosulfoxide **1B** was found to undergo an α-hydrogen atom abstraction process with butyllithium followed by reaction, at low temperatures, with benzaldehyde in a diastereoselective manner, to form alcohols **9** and **10**. Under these conditions, disulfoxide **1C**$_{trans}$ was found to undergo a ring-opening reaction to yield the acyclic disulfoxides. A new chemoenzymatic route to enantiopure/enantioenriched disulfoxides (**13**, **15**–**17**) and monosulfoxides (**18** and **19**) was revealed, by the reactions of sulfoxides **1C**, **7B** and **8B**, with alkyllithium reagents.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 300 MHz (Bruker Avance DPX-300) and 500 MHz (Bruker Avance DRX-500) in $CDCl_3$ solvent, unless stated otherwise. Chemical shifts (δ) are reported in ppm relative to $SiMe_4$; coupling constants (J) are given in Hz. Mass spectra were recorded 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 standard. Elemental microanalyses were obtained on a Perkin–Elmer 2400 CHN microanalyser. HPLC analyses were carried out using a Perkin–Elmer Series 3B liquid chromatograph coupled to a Perkin–Elmer LC1-100 computing integrator. Analytical TLC was performed on Merck Kieselgel 60_{254} plastic sheets and preparative TLC (PLC) on glass plates (20 cm×20 cm) coated with Merck Kieselgel $PF_{254+366}$. Optical rotation ([α]$_D$) measurements were carried out with a Perkin–Elmer 214 polarimeter at ambient temperature (ca. 20 °C) at a concentration of ~0.01 g cm^{-3} and are given in units of 10^{-1} deg cm^2 g^{-1}. Circular dichroism spectra were recorded on a JASCO J-720 instrument, using spectroscopic grade acetonitrile as solvent. Enantiopurity of sulfoxides was determined by CSPHPLC analysis, using Chiralcel OB, OD and OJ columns and hexane/2-propanol (9/1) as eluent. The NCIMB 8859 strain of *P. putida* was acquired from the National Cultures of Industrial and marine Bacteria, Aberdeen. The 9816/11 strain of *P. putida* originated from the laboratories of Professor D. T. Gibson (University of Iowa) and the UV4 strain of *P. putida* was originally provided by Zeneca (now Avecia Lifescience Molecules, Billingham).

4.2. Synthesis and characterization of compounds 1A–8A

The di- and mono-sulfide substrates **1A**–**3A**,[10] **4A**,[21] **5A**,[22] **6A**,[23] **7A**,[24] **8A**[25] were synthesised using the reported methods.

4.2.1. 1,3-Benzodithiole 1A. Colourless oil; bp 113–114 °C/3.5 mmHg; lit.[10] 105 °C/3 mmHg; δ_H (500 MHz, $CDCl_3$) 4.48 (2H, s, CH_2), 7.00–7.02 (2H, dd, J=5.7, 3.3 Hz, 2×Ar-H), 7.19–7.22 (2H, dd, J=5.7, 3.3 Hz, 2×Ar-H).

4.2.2. 2-Methyl-1,3-benzodithiole 2A. Colourless oil; bp 98 °C/0.05 mmHg; lit.[10] 62–64 °C/0.02 mmHg; δ_H

(500 MHz, $CDCl_3$) 1.70 (3H, d, $J_{Me,H}$=6.8 Hz, Me), 4.98 (1H, q, $J_{H,Me}$=6.8 Hz, C*H*Me), 7.01–7.03 (2H, dd, *J*=5.8, 3.2 Hz, 2×Ar-H), 7.21–7.23 (2H, dd, *J*=5.8, 3.2 Hz, 2×Ar-H).

4.2.3. 2-Ethyl-1,3-benzodithiole 3A. Colourless oil; bp 70 °C/0.02 mmHg; lit.[10] 72–76 °C/0.01 mmHg; δ_H (300 MHz, $CDCl_3$) 1.02 (3H, t, J_{Me,CH_2}=7.0 Hz, CH_2Me), 1.90–1.97 (2H, m, CH_2Me), 4.76 (1H, t, $J_{CH_2,Me}$=7.0 Hz, 2-H), 6.98–7.03 (2H, m, Ar-H), 7.18–7.22 (2H, m, Ar-H).

4.2.4. 2,3-Dihydro-1,4-benzo[*d*]dithiine 4A. Yellow oil; (R_f 0.4, hexane); lit.[21] 82.5–85 °C/0.18 mmHg; δ_H (500 MHz, $CDCl_3$) 3.26 (4H, s, 2×CH_2S), 6.97–7.00 (2H, dd, *J*=5.9, 3.4 Hz, 2×Ar-H), 7.13–7.17 (2H, dd, *J*=5.9, 3.4 Hz, 2×Ar-H).

4.2.5. 3,4-Dihydro-2*H*-1λ^4,5-benzodithiepin 5A. White solid; mp 60–61 °C (from $CHCl_3$); lit.[22] 59–60 °C; δ_H (500 MHz; $CDCl_3$) 2.30 (2H, m, $CH_2CH_2CH_2$), 2.86 (4H, m, $CH_2CH_2CH_2$), 7.15–7.18 (2H, dd, *J*=5.7, 3.5 Hz, 2×Ar-H), 7.62–7.64 (2H, dd, *J*=5.6, 3.5 Hz, 2×Ar-H).

4.2.6. 1,4-Benzo[*d*]dithiine 6A. Light pink coloured oil; bp 58–60 °C/0.03 mmHg; lit.[23] 67–70 °C/0.1 mmHg; δ_H (500 MHz, $CDCl_3$) 6.52 (2H, s, 2×CHS), 7.19–7.23 (2H, dd, *J*=5.8, 3.4 Hz, 2×Ar-H), 7.26–7.29 (2H, dd, *J*=5.8, 3.4 Hz, 2×Ar-H).

4.2.7. 2,3-Dihydrobenzo[*b*]thiophene 7A. Colourless oil; bp 44–46 °C/0.15 mmHg; lit.[24] 67–69 °C/2 mmHg; δ_H (500 MHz, $CDCl_3$) 3.23–3.27 (2H, m, SCH_2), 3.30–3.34 (2H, m, CH_2Ar), 6.90–6.93 (1H, ddd, $J_{5,4}$=$J_{5,6}$=7.4 Hz, $J_{5,7}$=1.0 Hz, 5-H), 7.00–7.04 (1H, ddd, $J_{6,5}$=$J_{6,7}$=7.4 Hz, $J_{6,4}$=0.6 Hz, 6-H), 7.08–7.10 (1H, ddd, $J_{4,5}$=7.4 Hz, $J_{4,6}$=0.6 Hz, 4-H), 7.12–7.13 (1H, dd, $J_{7,6}$=7.4 Hz, $J_{7,5}$=1.0 Hz, 7-H).

4.2.8. 1,3-Benzoxathiole 8A. Colourless liquid; bp 36 °C/0.05 mmHg; lit.[25] 93–95 °C/5 mmHg; δ_H (500 MHz, $CDCl_3$) 5.66 (2H, s, CH_2), 6.81–6.83 (1H, ddd, $J_{7,6}$=8.0 Hz, $J_{7,5}$=1.2 Hz, $J_{7,4}$=0.4 Hz, 7-H), 6.85–6.89 (1H, ddd, $J_{6,7}$=8.0 Hz, $J_{6,5}$=7.0 Hz, $J_{6,4}$=1.2 Hz, 6-H), 6.97–7.00 (1H, ddd, $J_{5,4}$=7.7 Hz, $J_{5,6}$=7.6 Hz, $J_{5,7}$=1.2 Hz, 5-H), 7.15–7.17 (1H, ddd, $J_{4,5}$=7.7 Hz, $J_{4,6}$=1.2 Hz, $J_{4,7}$=0.4 Hz, 4-H).

Sulfoxides **1B**,[10] **2B**$_{cis}$,[10] **2B**$_{trans}$,[10] **3B**$_{cis}$,[10] **3B**$_{trans}$,[10] **6B**,[11] **7B**,[26,27] and **8B**,[25] synthesised by the literature methods, were found to be spectrally identical to the metabolites isolated during the study.

4.3. Biotransformation of substrates 1A–8A using *P. putida* UV4, *P. putida* 8859 and *P. putida* 9816/11 to yield sulfoxides 1B–8B

Biotransformations of the bicyclic substrates **1A**–**8A** were carried out with whole cell preparations of *P. putida* UV4 (TDO) and *P. putida* 8859 (NDO) and *P. putida* 9816/11 (NDO), using both small-scale (<10 g) shake-flask and 10 l fermenter (>10 g) conditions reported earlier for the sulfoxidation of both acyclic[5] and cyclic sulfides.[2] The workup procedure involved extraction of the culture medium using ethyl acetate.[2,5] Yields, chiroptical and ^{1}H NMR spectral data, obtained for each biotransformation, are summarised below.

4.3.1. 1,3-Benzodithiole 1A. (i) TDO product: (*S*)-1,3-benzodithiole-1-oxide **1B**; white crystalline solid, 22 mg, 20% yield; $[\alpha]_D$=−170 (*c* 1.0, $CHCl_3$); lit.[10] $[\alpha]_D$=−505 (EtOH); 33% ee (CSPHPLC, Chiralcel OB, α=1.4); δ_H (500 MHz, $CDCl_3$) 4.18 (1H, d, $J_{A,B}$=13.0 Hz, CH_AH_B), 4.33 (1H, d, $J_{B,A}$=13.0 Hz, CH_AH_B), 7.30–7.33 (1H, m, Ar-H), 7.48–7.54 (2H, m, 2×Ar-H), 7.89–7.90 (1H, m, Ar-H).

(ii) NDO (8859) product: (*R*)-1,3-benzodithiole-1-oxide **1B**; 400 mg, 74% yield; $[\alpha]_D$=+504 (*c* 1.9, $CHCl_3$); >98% ee (CSPHPLC). A 10 litre fermenter (15 g substrate) gave sulfoxide **1B**, 12 g, 72% yield; $[\alpha]_D$=+498 (*c* 1.9, $CHCl_3$) >98% ee (CSPHPLC).

(iii) NDO (9816/11) product: (*R*)-1,3-benzodithiole-1-oxide **1B**; 60 mg, 54% yield; $[\alpha]_D$=+401 (*c* 1.3, $CHCl_3$); 81% ee (CSPHPLC).

4.3.2. 2-Methyl-1,3-benzodithiole 2A. (i) TDO products: (1*S*,2*R*)-2-methyl-1,3-benzodithiole-1-oxide **2B**$_{cis}$; white crystalline solid, 2.21 g, 40% yield; $[\alpha]_D$=−319 (*c* 0.7 $CHCl_3$); >98% ee (CSPHPLC, Chiralcel OD, α=1.33); lit.[10] $[\alpha]_D$=−68 (EtOH) for 25% ee; δ_H (500 MHz, $CDCl_3$) 1.83 (3H, d, $J_{Me,H}$=6.9 Hz, Me), 4.44 (1H, q, $J_{H,Me}$=6.9 Hz, C*H*Me), 7.26–7.30 (1H, ddd, $J_{5,4}$=7.8 Hz, $J_{5,6}$=7.0 Hz, $J_{5,7}$=1.0 Hz, 5-H), 7.43–7.46 (2H, m, 4-H and 6-H), 7.84–7.86 (1H, dd, $J_{7,6}$=7.2 Hz, $J_{7,5}$=1.0 Hz, 7-H) and (1*S*,2*S*)-2-methyl-1,3-benzodithiole-1-oxide **2B**$_{trans}$; 290 mg, 5% yield; $[\alpha]_D$=−57 (*c* 0.5, $CHCl_3$); >98% ee (CSPHPLC, Chiralcel OD, α=1.14); lit.[10] $[\alpha]_D$=−29 (EtOH) for 25% ee; δ_H (500 MHz, $CDCl_3$) 1.60 (3H, d, $J_{Me,H}$=7.4 Hz, Me), 4.59 (1H, q, $J_{H,Me}$=7.4 Hz, C*H*Me), 7.28–7.33 (1H, m, 5-H), 7.47–7.48 (2H, m, 4-H and 6-H), 7.83–7.85 (1H, dd, $J_{7,6}$=7.7 Hz, $J_{7,5}$=0.7 Hz, 7-H). When repeated on a 10 litre fermenter-scale (10.0 g of substrate **2A**), 1*S*,2*R*)-2-methyl-1,3- benzodithiole-1-oxide **2B**$_{cis}$; 2.9 g, 26% yield; $[\alpha]_D$=−316 (*c* 0.7 $CHCl_3$); >98% ee (CSPHPLC) and (1*S*,2*S*)-2-methyl-1,3-benzodithiole-1-oxide **2B**$_{trans}$; 66 mg, 1% yield; $[\alpha]_D$=−60 (*c* 0.7, $CHCl_3$); >98% ee (CSPHPLC) were obtained.

(ii) NDO (8859) products: (1*R*,2*S*)-2-methyl-1,3-benzodithiole-1-oxide **2B**$_{cis}$; 2.21 g, 40% yield; $[\alpha]_D$=+256 (*c* 1.8, $CHCl_3$); 82% ee (CSPHPLC) and (1*R*,2*R*)-2-methyl-1,3-benzodithiole-1-oxide **2B**$_{trans}$; 390 mg, 7% yield; $[\alpha]_D$=+21 (*c* 0.7, $CHCl_3$); >38% ee (CSPHPLC).

4.3.3. 2-Ethyl-1,3-benzodithiole 3A. (i) TDO products: (1*S*,2*R*)-2-ethyl-1,3- benzodithiole-1-oxide **3B**$_{cis}$; white crystalline solid, 165 mg, 55% yield; $[\alpha]_D$=−189 (*c* 0.5, $CHCl_3$); >98% ee (CSPHPLC, Chiralcel OD, α=1.36); δ_H (300 MHz, $CDCl_3$) 1.30 (3H, t, J_{Me,CH_2}=7.4 Hz, CH_2Me), 2.05–2.16 (1H, m, CH_2Me), 2.33–2.44 (1H, m, CH_2Me), 4.26 (1H, dd, $J_{H,CH2}$=7.6 Hz, 2-H), 7.25–7.28 (1H, m, Ar-H), 7.45–7.46 (2H, m, Ar-H), 7.84–7.86 (1H, d, *J*=7.7 Hz, Ar-H) and (1*R*,2*R*)-2-ethyl-1,3-benzodithiole-1-oxide **3B**$_{trans}$;white crystalline solid, 15 mg, 5% yield; $[\alpha]_D$=+24 (*c* 0.4, $CHCl_3$); 18% ee (CSPHPLC, Chiralcel OD, α=1.11); δ_H (300 MHz, $CDCl_3$) 1.18 (3H, t,

J_{Me,CH_2}=7.4 Hz, CH_2Me), 1.65 (1H, m, CH_2Me), 2.00 (1H, m, CH_2Me), 4.48 (1H, dd, $J_{2,1'A}$=8.7 Hz, $J_{2,1'B}$=6.2 Hz, H-2), 7.26–7.32 (1H, m, Ar-H), 7.47 (2H, m, Ar-H), 7.87 (1H, d, J=7.7 Hz, Ar-H).

4.3.4. 2,3-Dihydro-1,4-benzo[*d*]dithiine 4A. (i) TDO product: (*R*)-2,3-dihydrobenzo[*d*]dithiin-1-oxide **4B**; white solid, 14 mg, 13% yield; mp 104–105 °C (from $CHCl_3$); $[\alpha]_D$=+37 (*c* 1.3, $CHCl_3$); HRMS found: M^+, 184.0016, $C_8H_8OS_2$ requires 184.0017; δ_H (500 MHz, $CDCl_3$) 3.05 (1H, ddd, $J_{3A,3B}$=13.4 Hz, $J_{3A,2A}$=6.6 Hz, $J_{3A,2B}$=3.8 Hz, SCH_AH$_B$), 3.13 (1H, ddd, $J_{3B,3A}$=13.4 Hz, $J_{3B,2A}$=10.8 Hz, $J_{3B,2B}$=3.6 Hz, SCH$_A$$H_B$), 3.40 (1H, ddd, $J_{2A,2B}$=13.4 Hz, $J_{2A,3A}$=6.6 Hz, $J_{2A,3B}$=3.6 Hz, SOCH_AH$_B$), 3.76 (1H, ddd, $J_{2B,2A}$=13.4 Hz, $J_{2B,3A}$=10.8 Hz, $J_{2B,3B}$=3.4 Hz, SOCH$_A$$H_B$), 7.25–7.28 (1H, ddd, $J_{6,5}$=8.2 Hz, $J_{6,7}$=7.5 Hz, $J_{6,8}$=1.2 Hz, 6-H), 7.31–7.32 (1H, dd, $J_{5,6}$=8.2 Hz, $J_{5,7}$=1.2 Hz, 5-H), 7.37–7.40 (1H, ddd, $J_{7,8}$=7.8 Hz, $J_{7,6}$=7.5 Hz, $J_{7,5}$=1.2 Hz, 7-H), 7.73–7.75 (1H, dd, $J_{8,7}$=7.8 Hz, $J_{8,6}$=1.2 Hz, 8-H); >98% ee (CSPHPLC, Chiralcel OB, α=1.4).

(ii) NDO (8859) product: (*S*)-2,3-dihydrobenzo[*d*]dithiin-1-oxide **4B**; 85 mg, 78% yield; $[\alpha]_D$=−35 (*c* 1.1, $CHCl_3$); >98% ee (CSPHPLC).

(iii) NDO (9816/11) product: (*S*)-2,3-dihydrobenzo[*d*]-dithiin-1-oxide **4B**; 67 mg, 62% yield; $[\alpha]_D$=−37 (*c* 1.3, $CHCl_3$); >98% ee (CSPHPLC); CD (λ, nm) 313 (Δε −0.375), 271 (Δε 0.240), 256 (Δε −2.27), 242 (Δε 0.561), 229 (Δε −2.815), 213 (Δε −5.865), 194.2 (Δε 2.100).

4.3.5. 3,4-Dihydro-2*H*-1λ^4,5-benzodithiepin 5A. (i) NDO (8859) product: (*S*)-1,2,3,4-tetrahydro-1λ^4,5-benzodithiepin-1-oxide **5B**; colourless crystalline solid, 30 mg, 26% yield; mp 120–121 °C (from $CHCl_3$/hexane); $[\alpha]_D$=−71 (*c* 1.4, $CHCl_3$); Found: C, 54.7; H, 5.0; $C_9H_{10}OS_2$ requires C, 54.5; H, 5.1%; δ_H (500 MHz, $CDCl_3$) 2.41–2.49 (2H, m, 4-H), 2.61–2.63 (1H, m, 3-H$_A$), 2.87–2.88 (1H, m, 3-H$_B$), 2.97–3.00 (1H, m, 2-H$_A$), 3.25–3.27 (1H, m, 2-H$_B$), 7.38–7.41 (1H, td, $J_{7,6}$=$J_{7,8}$=7.5 Hz, $J_{7,9}$=1.4 Hz, 7-H), 7.58–7.59 (2H, m, 6-H and 8-H), 7.87–7.89 (1H, dd, $J_{9,8}$=7.7 Hz, $J_{9,7}$=1.4 Hz, 9-H); 80% ee (CSPHPLC, Chiralcel OB, α=1.25).

(ii) NDO (9816/11) product: (*S*)-1,2,3,4-tetrahydro-1λ^4,5-benzodithiepin-1-oxide **5B**; 20 mg, 10% yield; $[\alpha]_D$=−82 (*c* 0.8, $CHCl_3$); 93% ee (CSHPLC, Chiralcel OB, α=1.25); CD (λ, nm) 265 (Δε −2.162), 250 (Δε 0.439), 236 (Δε −1.243), 228 (Δε 0.448), 220 (Δε −1.423), 215 (Δε −0.589), 198 (Δε −7.96).

4.3.6. X-ray crystal structure analysis of (*S*)-1,2,3,4-tetrahydro-1λ^4,5-benzodithiepin-1-oxide 5B. Recrystallization of compound **5B** (93% ee) gave a sample whose X-ray crystal structure analysis showed it to be of >98% ee and of the (*S*) configuration.

Crystal data for **5B**: $C_9H_{10}OS_2$, M_r=198.3, orthorhombic, a=8.106(4), b=9.043(3), c=13.042(6) Å, V=956.0(7) Å^3, T=293 K, Cu Kα radiation, λ=1.54178 Å, space group $P2_12_12_1$, Z=4, D_x=1.378 g cm^{-3}, 0.50×0.40×0.34 mm^3, μ=4.63 mm^{-1}, F(000)=416, Siemens P3/V2000 diffractometer, ωscan, 10<2θ<110°, measured/independent reflections: 5093/1195, direct methods solution, full matrix least squares refinement on F_0^2, anisotropic displacement parameters for non-hydrogen atoms, hydrogens located in difference Fourier but included at positions calculated from the geometry of the molecule using the riding model, $R1$=0.044 for 1115 data with $F_0 > 4\sigma(F_0)$, 111 parameters, $wR2$=0.113 (all data), GoF=1.07, Flack absolute structure parameter x=−0.09(4) establishes the absolute configuration as (1*S*), $\Delta\rho_{min,max}$=−0.30/0.23 e Å^{-3}. CCDC reference number 212386, Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax:+44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3.7. 1,4-Benzo[*d*]dithiine 6A. (i) TDO product: (*S*)-1,4-benzo[*d*]dithiin-1-oxide **6B**; white solid, 25 mg, 23% yield; $[\alpha]_D$=−376 (*c* 0.5, $CHCl_3$); lit.[11] $[\alpha]_D$=−383 ($CHCl_3$); >98% ee (CSPHPLC, Chiralcel OB, α=1.17); δ_H (500 MHz, $CDCl_3$) 7.05 (1H, d, $J_{3,2}$=9.4 Hz, SCH), 7.31 (1H, d, $J_{2,3}$=9.4 Hz, S(O)CH), 7.51–7.54 (1H, ddd, $J_{6,5}$=$J_{6,7}$=7.6 Hz, $J_{6,8}$=1.4 Hz, 6-H), 7.56–7.60 (1H, ddd, $J_{7,6}$=$J_{7,8}$=7.6 Hz, $J_{7,5}$=1.3 Hz, 7-H), 7.60–7.62 (1H, dd, $J_{5,6}$=7.6 Hz, $J_{5,7}$=1.3 Hz, 5-H), 7.94–7.96 (1H, dd, $J_{8,7}$=7.6 Hz, $J_{8,6}$=1.4 Hz, 8-H); CD (λ, nm) 311 (Δε 0.522), 272 (Δε −0.444), 255 (Δε 3.357), 243 (Δε −0.675), 229 (Δε+3.657), 213 (Δε 7.470).

(ii) NDO (8859) product: (*R*)-benzo[*d*]dithiin-1-oxide **6B**; 66 mg, 60% yield; $[\alpha]_D$=+373 (*c* 1.0, $CHCl_3$); >98% ee (CSPHPLC).

(iii) NDO (9816/11) product: (*R*)-benzo[*d*]dithiin-1-oxide **6B**; 47 mg, 43% yield; $[\alpha]_D$=+373 (*c* 1.0, $CHCl_3$); >98% ee (CSPHPLC).

4.3.8. 2,3-Dihydrobenzo[*b*]thiophene 7A. (i) TDO product: (*R*)-2,3-dihydrobenzo[*b*]thiophene-1-oxide **7B**; white solid, 40 mg, 5% yield; $[\alpha]_D$=−59 (*c* 1.0, $CHCl_3$); lit.[27] $[\alpha]_D$=−285 (Me_2CO); 26% ee (CSPHPLC, Chiralcel OB, α=1.7); δ_H (500 MHz, $CDCl_3$) 3.23–3.26 (1H, m, 3-H$_A$), 3.28–3.34 (1H, m, 3-H$_B$), 3.39–3.40 (1H, m, 2-H$_B$), 3.83–3.91 (1H, m, 2-H$_A$), 7.41–7.44 (1H, ddd, $J_{5,4}$=$J_{5,6}$=7.4 Hz, $J_{5,7}$=0.5 Hz, 5-H), 7.46–7.47 (1H, dd, $J_{4,5}$=7.4 Hz, $J_{4,6}$=1.2 Hz, 4-H), 7.50–7.53 (1H, ddd, $J_{6,5}$=$J_{6,7}$=7.4 Hz, $J_{6,4}$=1.2 Hz, 6-H), 7.83–7.85 (1H, dd, $J_{7,6}$=7.4 Hz, $J_{7,5}$ 0.5, 7-H).

(ii) NDO (8859) product: (*S*)-2,3-dihydrobenzo[*b*]thiophene-1-oxide **7B**; 48 mg, 21% yield; $[\alpha]_D$=+95 (*c* 1.1, $CHCl_3$); 38% ee (CSPHPLC); CD (λ, nm) 263 (Δε 0.882), 231 (Δε 0.733), 217 (Δε −2.586), 198 (Δε 5.447).

(iii) NDO (9816/11) product: (*S*)-2,3-dihydrobenzo[*b*]thiophene-1-oxide **7B**; 19 mg, 17% yield; $[\alpha]_D$=+27 (*c* 1.0, $CHCl_3$), 11% ee (CSPHPLC).

4.3.9. 1,3-Benzoxathiole 8A. (i) TDO product: (*R*)-benzo[1,3]oxathiol-3-oxide **8B**; white solid, 11 mg, 11% yield; $[\alpha]_D$=+194 (*c* 1.0, $CHCl_3$); >98% ee (CSPHPLC, Chiralcel OB, α=1.3); δ_H (500 MHz, $CDCl_3$) 4.98 (1H, d,

$J_{A,B}$=11.0 Hz, CH_AH$_B$), 5.49 (1H, d, $J_{B,A}$=11.0 Hz, CH$_A$$H_B$), 7.18–7.20 (1H, ddd, $J_{4,5}$=7.6 Hz, $J_{4,6}$=1.2 Hz, $J_{4,7}$=0.5 Hz, 4-H), 7.22–7.24 (1H, ddd, $J_{5,4}$=7.6 Hz, $J_{5,6}$=7.2 Hz, $J_{5,7}$=1.2 Hz, 5-H), 7.56–7.59 (1H, ddd, $J_{6,7}$=7.7 Hz, $J_{6,5}$=7.2 Hz, $J_{6,4}$=1.2 Hz, 6-H), 7.88–7.90 (1H, ddd, $J_{7,6}$=7.7 Hz, $J_{7,5}$=1.2 Hz, $J_{7,4}$=0.5 Hz, 7-H); CD (λ, nm) 285 ($\Delta\varepsilon$ −2.831), 215 ($\Delta\varepsilon$ 6.55), 208 ($\Delta\varepsilon$ 5.259), 199 ($\Delta\varepsilon$ 15.600).

(ii) NDO (8859) product: (*R*)-benzo[1,3]oxathiol-3-oxide **8B**; 50 mg, 2% yield; $[\alpha]_D$=+87 (*c* 0.5, $CHCl_3$); 43% ee (CSPHPLC)

(iii) NDO (9816/11) product: (*R*/*S*)-benzo[1,3]oxathiol-3-oxide **8B**; 200 mg, 70% yield; $[\alpha]_D$=0 (*c* 0.5, $CHCl_3$); racemic (CSPHPLC).

4.4. Reaction of (+)-(*R*)-benzo-1,3-dithiole-1-oxide 1B with *n*-butyllithium and benzaldehyde

n-Butyllithium solution in hexane (1.6 M, 1.6 ml) was added to a stirring solution of (+)-(*R*)-benzo-1,3-dithiole-1-oxide **1B** (300 mg, 1.7 mmol in 10 ml of dry THF) kept under nitrogen at −78 °C. After 0.5 h, benzaldehyde (186 mg, 1.7 mmol) was added to the reaction mixture; it was allowed to warm to room temperature and stirred for another 0.5 h. The reaction mixture was then carefully poured into water (50 ml), the products extracted with ether (3×25 ml), the extract washed with water (30 ml) and dried ($MgSO_4$). Removal of the solvent yielded the crude product mixture which on separation by PLC (1% MeOH in $CHCl_3$) afforded pure samples of *cis*-(1*R*,2*S*,1′*S*)-2-(1′-phenylmethanol)-benzo-1,3-dithiole-1-oxide **10** and the more polar *trans*-(1*R*,2*R*,1′R)-2-(1′-phenylmethanol)-benzo-1,3-dithiole-1-oxide **9**.

4.4.1. (1*R*,2*S*,1′*S*)-2-(1′-Phenylmethanol)-benzo-1,3-dithiole-1-oxide 10. Colourless crystals, 147 mg, 31% yield; R_f 0.31 (1% MeOH in $CHCl_3$); mp 163–164 °C (from $CHCl_3$/hexane); $[\alpha]_D$=+344 (*c* 0.49, $CHCl_3$); HRMS found: M^+276.0278, $C_{14}H_{12}O_2S_2$ requires 276.0278; δ_H (300 MHz, $CDCl_3$) 4.23 (1H, d, $J_{OH,1'}$ 1.7, OH), 4.65 (1H, d, $J_{2,1}$=4.8 Hz, 2-H), 5.77 (1H, d, $J_{2,1'}$=4.8 Hz, 1′-H), 7.25–7.28 (1H, m, Ar-H), 7.36–7.46 (5H, m, Ar-H), 7.54 (2H, d, *J*=7.1 Hz, Ar-H), 7.77 (1H, d, *J*=7.6 Hz, Ar-H); *m*/*z* 276 (M^+, 7%), 259 (13), 229 (30) and 153 (100).

4.4.2. X-ray crystal structure analysis of (1*R*,2*S*,1′*S*)-2-(1′-phenylmethanol)-benzo-1,3-dithiole-1-oxide 10. *Crystal data for* **10**: $C_{14}H_{12}O_2S_2$, M_r=276.4, orthorhombic, *a*=5.531(1), *b*=10.410(3), *c*=21.931(7) Å, *V*=1262.8(6) Å^3, *T*=293 K, Cu Kα radiation, λ=1.54178 Å, space group $P2_12_12_1$, *Z*=4, D_x=1.45 g cm^{-3}, 0.56×0.49×0.43 mm^3, μ=3.74 mm^{-1}, Siemens P3/V2000 diffractometer, ωscan, $8 < 2\theta < 150°$, measured/independent reflections: 2748/2303, direct methods solution, full matrix least squares refinement on F_0^2, anisotropic displacement parameters for non-hydrogen atoms, hydrogens located in difference Fourier but included at positions calculated from the geometry of the molecule using the riding model, *R*1=0.071 for 2181 data with $F_0 > 4\sigma(F_0)$, 165 parameters, *wR*2=0.188 (all data), *GoF*=1.05, Flack absolute structure parameter *x*=0.00(4) establishes the absolute configuration as (1*R*,2*S*,1′*S*), $\Delta\rho_{min,max}$=−0.47/0.54*e* Å^{-3}. CCDC reference number 212387.

4.4.3. (1*R*,2*R*,1′*R*)-2-(1′-Phenylmethanol)-benzo-1,3-dithiole-1-oxide 9. White solid, 108 mg, 23% yield; R_f 0.19 (1% MeOH in $CHCl_3$); $[\alpha]_D$=+116 (*c* 1.2, $CHCl_3$); HRMS found: M^+276.0291, $C_{14}H_{12}O_2S_2$ requires 276.0278; δ_H (300 MHz; $CDCl_3$) 4.68 (1H, d, $J_{2,1'}$= 10.0 Hz, 2-H), 4.93 (1H, br s, OH), 5.32 (1H, d, $J_{1',2}$=10.0 Hz, 1′-H), 7.22–7.44 (6H, m, Ar-*H*), 7.49–7.52 (2H, m, Ar-*H*), 7.83 (1H, d, *J*=7.8 Hz, Ar-*H*); *m*/*z* 276 (M^+, 4%), 259 (11), 229 (28) and 153 (100).

4.4.4. Deoxygenation of (1*R*,2*S*,1′*S*)-2-(1′-phenylmethanol)-benzo-1,3-dithiole-1-oxide (10) and (1*R*,2*R*,1′*R*)-2-(1′-phenylmethanol)-benzo-1,3-dithiole-1-oxide 9. To each sample of monosulfoxides **10** and **9** (20 mg, 0.72 mmol), dissolved separately in CH_2Cl_2 (3 ml), was added triphenyl phosphine (25 mg, 0.1 mmol) and a catalytic amount of trichlorooxobis(triphenyl phosphine)-rhenium. The two reaction mixtures were allowed to stir at room temperature (sulfoxide **9** for 2 h and sulfoxide **10** for 72 h). The products were purified by PLC to give the corresponding sulfides (+)-(1′*S*)-**11**; 8 mg, 44% yield; $[\alpha]_D$=+12 (*c* 0.75, Me_2CO) from 1*R*,2*S*,1′*S*-**10** and (−)-(1′*R*)-**11**; 9 mg, 49% yield; $[\alpha]_D$=−12 (*c* 0.9, Me_2CO) from 1*R*,2*R*,1′*R*-**9**); HRMS found: M^+260.0342, $C_{14}H_{12}OS_2$ requires 260.0330; δ_H (300 MHz, $CDCl_3$) 4.66 (1H, d, *J*=8.2 Hz, 2-H), 4.89 (1H, d, *J*=8.2 Hz, 1′-H), 7.03–7.06 (2H, m, Ar-H), 7.18–7.25 (3H, m, Ar-H), 7.32–7.40 (5H, m, Ar-*H*); *m*/*z* 260 (M^+, 9%) and 153 (100).

4.4.5. Sodium periodate oxidation of (+)-(*R*)-1,3-benzodithiole-1-oxide 1B. (+)-(*R*)-1,3-Benzodithiole-1-oxide **1B** (260 mg, 1.52 mmol) in methanol (15 ml) was oxidized using a solution of sodium periodate (360 mg, 1.68 mmol) in water (10 ml) at 50 °C for 24 h. PLC (5% MeOH in $CHCl_3$), of the reaction mixture, afforded pure samples of (1*R*,3*R*)-1,3-benzodithiole-1,3-dioxide **1C**$_{trans}$ and the more polar *cis*-1,3-benzodithiole-1-oxide **1C**$_{cis}$.

(1R,3R)-1,3-Benzodithiole-1,3-dioxide **1C**$_{trans}$. White crystalline solid, 156 mg, 75% yield; R_f 0.33 (5% MeOH in $CHCl_3$); mp 123–126 °C (from $CHCl_3$/hexane); $[\alpha]_D$=+646 (*c* 1.5, $CHCl_3$); HRMS found: M^+185.9810, $C_7H_6O_2S_2$ requires 185.9809; δ_H (300 MHz; $CDCl_3$) 4.46 (2H, s, CH_2), 7.82–7.85 (2H, m, Ar-H), 7.99–8.02 (2H, m, Ar-H); *m*/*z* 186 (M^+, 32%) and 156 (100). Benzo-1,3-dithiole-1,3-dioxide **1C**$_{cis}$. 40 mg, 19% yield; R_f 0.22 (5% MeOH in $CHCl_3$); mp 179–180 °C; HRMS found: M^+185.9814, $C_7H_6O_2S_2$ requires 185.9809; δ_H (300 MHz, $CDCl_3$) 4.24 (1H, d, $J_{A,B}$=13.2 Hz, CH_AH$_B$), 5.03 (1H, d, $J_{B,A}$=13.2 Hz, CH$_A$$H_B$), 7.85–7.88 (2H, m, Ar-*H*), 8.08–8.11 (2H, m, Ar-*H*); *m*/*z* 186 (M^+, 33%) and 156 (100).

4.5. Ring opening reactions of bicyclic disulfoxide 1C$_{trans}$ and monosulfoxides 7B and 8B with alkyl and aryllithium reagents

4.5.1. Reaction of (1*R*,3*R*)-1,3-benzodithiole-1,3-dioxide 1C$_{trans}$ with *n*-butyllithium and benzaldehyde. *n*-Butyllithium solution in hexane (1.6 M, 0.53 ml) was added to stirred solution (1*R*,3*R*)-1,3-benzodithiole-1,3-dioxide

1C$_{trans}$ (100 mg, 0.54 mmol, $[\alpha]_D$=+646) in dry THF at −78 °C. After 0.5 h, benzaldehyde (0.06 ml, 0.6 mmol) was added to the reaction mixture; it was allowed to warm to room temperature, stirred overnight, and worked up as described earlier. Purification by PLC (5% MeOH in $CHCl_3$) afforded a pure sample of (−)-(butane-1-sulfinyl-methanesulfinyl)-benzene **13**; white solid, 64 mg, 49% yield; R_f 0.43 (5% MeOH in $CHCl_3$); mp 82–84 °C (from CH_2Cl_2/hexane); $[\alpha]_D$=−180 (*c* 1.69, $CHCl_3$); HRMS found: M^+244.0582, $C_{11}H_{16}O_2S_2$ requires 244.0592; δ_H (500 MHz, $CDCl_3$) 0.93 (3H, t, *J*=7.5 Hz, $(CH_2)_3$*Me*), 1.46–1.53 (2H, m, $(CH_2)_2CH_2CH_3$), 1.75–1.82 (2H, m, $CH_2CH_2CH_2CH_3$), 3.03–3.09 (1H, m, CH_AH_B-$(CH_2)_2CH_3$), 3.18–3.24 (1H, m, $CH_AH_B(CH_2)_2CH_3$), 3.91 (1H, d, *J*=13.3 Hz, SO−CH_AH_B−SO), 4.15 (1H, d, *J*=13.3 Hz, SO−CH_AH_B−SO), 7.55–7.59 (3H, m, Ar-*H*), 7.68–7.71 (2H, m, Ar-*H*); *m/z* 244 (M^+, 2%) and 126 (100); CD (λ, nm) 251 (Δε −11.18), 220 (Δε 16.67).

4.5.2. Reaction of (+)-(1*R*,3*R*)-benzo-1,3-dithiole-1,3-dioxide with phenyllithium. *General procedure*. The lithium reagent (1.1 molar equiv.) was added to a stirring solution (−78 °C, under nitrogen) of the disulfoxide (**1C**$_{trans}$) or mono-sulfoxide (**7B**, **8B**) (1.0 mmol in ~20 ml of dry THF). The reaction mixture was allowed to warm up to room temperature, stirred overnight, and then quenched with water; it was extracted with ethyl acetate, the extract dried ($MgSO_4$), concentrated under reduced pressure, and the crude product purified by PLC.

(1R,3R)-Benzo-1,3-dithiole-1,3-dioxide **1C**$_{trans}$. (50 mg, 0.27 mmol, $[\alpha]_D$=+646) and phenyllithium solution in cyclohexane (1.8 M, 0.25 ml) yielded meso *bis*-(phenylsulfinyl) methane **14**; white solid, 23 mg, 32% yield; mp 124–125 °C (from $CHCl_3$); lit.[14] 123 °C; R_f 0.25 ($CHCl_3$); δ_H (500 MHz; $CDCl_3$) 4.10 (1H, d, $J_{A,B}$=12.7 Hz,−SO−CH_AH_B−SO−), 4.20 (1H, d, $J_{B,A}$=12.7 Hz,−SO−CH_AH_B−SO−), 7.51–7.59 (6H, m, Ar-H), 7.68–7.74 (4H, m, Ar-H).

4.5.3. Reaction of (+)-(1*R*,3*R*)-benzo-1,3-dithiole-1,3-dioxide 1C$_{trans}$ with methyllithium. (1*R*,3*R*)-Benzo-1,3-dithiole-1,3-dioxide **1C**$_{trans}$ (45 mg, 0.24 mmol, $[\alpha]_D$=+646) and methyllithium solution in hexane (1.6 M, 0.25 ml) yielded (−)-(1*R*)-[(3*S*)-methylsulfinyl] methylphenyl sulfoxide **15**; white solid, 38 mg, 59% yield; mp 135 °C (from $CHCl_3$); R_f 0.22 ($CHCl_3$); $[\alpha]_D$=−234 (*c* 0.8, $CHCl_3$); HRMS found: M^+202.0118, $C_8H_{10}O_2S_2$ requires 202.0122; δ_H (500 MHz, $CDCl_3$) 2.98 (3H, s, *Me*), 3.91 (1H, d, $J_{A,B}$=13.1 Hz, CH_AH_B), 4.13 (1H, d, $J_{B,A}$=13.1 Hz, CH_AH_B), 7.55–7.60 (3H, m, Ar-H), 7.67–7.70 (2H, m, Ar-H); *m/z*: 202 (M^+1%),139 (26), 125 (53), 109 (72), 91 (100); CD (λ, nm) 251 (Δε −18.15), 220 (Δε 20.42).

4.5.4. Deoxygenation of disulfoxide 15. To a solution of (−)-(1*R*)-[(3*S*)-methylsulfinyl] methylphenyl sulfoxide **15** (22 mg, 0.11 mmol, $[\alpha]_D$=−234) in CH_2Cl_2 (3 ml) was added triphenylphosphine (25 mg, 0.1 mmol) along with a catalytic amount of trichlorooxobis(triphenylphosphine)-rhenium; the reaction mixture was stirred (2 h) at room temperature. Triphenylphosphine oxide was removed from the reaction mixture by reverse phase PLC (70% MeOH in H_2O). The product was further separated into two sulfoxides by PLC on silca gel (5% MeOH in $CHCl_3$); (−)-(*S*)-(phenylsulfanylmethyl)methyl sulfoxide **20**; 8 mg, 40% yield; $[\alpha]_D$=−27 (*c* 0.81, $CHCl_3$); 24% ee (Chiralcel OJ) and (−)-(*R*)-(methylsulfanylmethyl)phenyl sulfoxide **21**; 5 mg, 22% yield; $[\alpha]_D$=−110 (*c* 0.45, $CHCl_3$); 87% ee (Chiralcel OD). Spectral data for sulfoxides **20** and **21** were in agreement with the literature values.[6]

4.5.5. Reaction of (+)-(1*R*,3*R*)-benzo-1,3-dithiole-1,3-dioxide 1C$_{trans}$ with *n*-hexyllithium. (1*R*,3*R*)-Benzo-1,3-dithiole-1,3-dioxide **1C**$_{trans}$ (40 mg, 0.22 mmol, $[\alpha]_D$=+646) and *n*-hexyllithium solution in hexane (2.0 M, 0.15 ml) yielded (−)-(1*R*)-[(3*S*)-*n*-hexylsulfinyl]-methylphenyl sulfoxide **16**; white solid, 38 mg, 65% yield; mp 128–130 °C (from benzene); R_f 0.2 ($CHCl_3$); $[\alpha]_D$=−247 (*c* 1.7, $CHCl_3$); HRMS found: M^+272.0902, $C_{13}H_{20}O_2S_2$ requires 272.0905; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, J_{Me,CH_2}=7.1 Hz, Me), 1.30–1.34 (4H, m, $(CH_2)_3$-$(CH_2)_2$Me), 1.45–1.47 (2H, m, $(CH_2)_2CH_2(CH_2)_2$Me), 1.77–1.82 (2H, m, $CH_2CH_2(CH_2)_3$Me), 3.04–3.08 (1H, m, CH_AH_B−$(CH_2)_4$Me), 3.16–3.21 (1H, m, CH_AH_B−$(CH_2)_4$Me), 3.90 (1H, d, $J_{A'B'}$=13.2 Hz, SO−$CH_{A'}H_{B'}$−SO), 4.13 (1H, d, $J_{B'A'}$=13.2 Hz, SO−$CH_{A'}H_{B'}$−SO), 7.55–7.60 (3H, m, Ar-H), 7.68–7.71 (2H, m, Ar-H); *m/z* 272 (M^+, 1%), 210 (5), 126 (81) and 43 (100); CD (λ, nm) 256 (Δε −21.39), 221 (Δε 23.55).

4.5.6. Reaction of (+)-(1*R*,3*R*)-benzo-1,3-dithiole-1,3-dioxide 1C$_{trans}$ with *t*-butyllithium. (1*R*,3*R*)-Benzo-1,3-dithiole-1,3-dioxide **1C**$_{trans}$ (60 mg, 0.32 mmol) and *t*-butyllithium solution in pentane (1.7 M, 0.3 ml) yielded (+)-(1*R*)-[(3*S*)-*t*-butylsulfinyl]methylphenyl sulfoxide **17** as a light yellow coloured oil, 20 mg, 30% yield; R_f 0.2 ($CHCl_3$); $[\alpha]_D$=+75 (*c* 1.0, $CHCl_3$); HRMS found: M^++H 245.0666, $C_{11}H_{16}S_2O_2$+H requires 245.0670; δ_H (500 MHz; $CDCl_3$) 1.21 (9H, s, Bu^t), 3.91 (1H, d, J_{AB}=12.4 Hz, CH_AH_B), 3.95 (1H, d, J_{BA}=12.4 Hz, CH_AH_B), 7.58 (3H, m, Ar-H), 7.79 (2H, m, Ar-H); *m/z* (CI) 245 (M^++H, 7%), 189 (15), 126 (96) and 57 (100); CD (λ, nm) 250 (Δε −14.66), 218 (Δε 26.49).

4.5.7. Reaction of (−)-(*R*)-2,3-dihydrobenzothiophene-1-oxide 7B with *n*-butyllithium. *n*-Butyllithium solution in hexane (1.6 M, 0.53 ml) and (−)-(*R*)-2,3-dihydrobenzo[*b*]thiophene-1-oxide **7B** (90% ee) (118 mg, 0.78 mmol) yielded (−)-(*R*)-*n*-butylphenethyl sulfoxide **18** as a colourless oil, 45 mg, 28% yield; R_f 0.51 (5% MeOH in $CHCl_3$); $[\alpha]_D$=−13.3 (*c* 1.98, $CHCl_3$); HRMS found: M^+210.1072, $C_{12}H_{18}OS$ requires 210.1078; δ_H (500 MHz; $CDCl_3$) 0.95 (3H, t, $J_{1,2}$=7.4 Hz, Me), 1.39–1.55 (2H, m, CH_2Me), 1.71–1.78 (2H, m, $CH_EH_FCH_2$Me), 2.60–2.66 (1H, ddd, $J_{C,D}$=13.0 Hz, $J_{C,A}$=9.0 Hz, $J_{C,B}$=8.5 Hz, $PhCH_2$−H_CH_D), 2.70–2.76 (1H, ddd, $J_{D,C}$=13.0 Hz, $J_{D,A}$=7.8 Hz, $J_{D,B}$=5.9 Hz, $PhCH_2$−H_CH_D), 2.86–2.93 (1H, ddd, $J_{E,F}$=12.8 Hz, $J_{E,G}$=10.0 Hz, $J_{E,H}$=7.2 Hz, $SOCH_EH_F$), 2.93–2.98 (1H, ddd, $J_{F,E}$=12.8 Hz, $J_{F,G}$=9.3 Hz, $J_{F,H}$=5.6 Hz, $SOCH_EH_F$), 3.04–3.10 (1H, ddd, $J_{A,B}$=14.0 Hz, $J_{A,C}$=9.0 Hz, $J_{A,D}$=7.8 Hz, Ph−CH_AH_B), 3.11–3.17 (1H, ddd, $J_{B,A}$=14.0 Hz, $J_{B,C}$=8.5 Hz, $J_{B,D}$=5.9 Hz, Ph−CH_AH_B), 7.23–7.26 (3H, m, Ar-H), 7.31–7.34 (2H, m, Ar-H); *m/z* (EI) 210 (M^+, 13%), 194 (24), 193 (32), 154 (7), 135 (8), 105 (100), 91 (69), 77 (57), 57 (92), 41 (47), 29 (55).

4.5.8. Reaction of (−)-(*S*)-1,3-benzoxathiole 8B with *n*-butyllithium. *n*-Butyllithium solution in hexane (1.6 M, 0.16 ml) and (−)-(*S*)-1,3-benzoxathiole-1-oxide **8B** (73% ee) (35 mg, 0.23 mmol) yielded (+)-(*R*)-*n*-butylphenoxymethyl sulfoxide **19** as an oil; 16 mg, 34% yield; R_f 0.52 (5% MeOH in $CHCl_3$); $[\alpha]_D$=+74 (*c* 0.6, $CHCl_3$); HRMS found: M^+, 212.0866, $C_{11}H_{16}O_2S$ requires 212.0871; *m/z* 212 (M^+, 70%), 108 (97), 107 (88), 94 (96), 79 (95), 77 (87), 65 (92), 57 (66), 55 (99), 51 (94), 41 (97), 39 (95), 29 (100), 27 (95); δ_H (500 MHz; $CDCl_3$) 0.98 (3H, t, $J_{CH_2,Me}$=7.3 Hz, Me), 1.44–1.59 (2H, m, CH_2Me), 1.78–1.85 (2H, m, CH_2CH$_2$Me), 2.80–2.91 (2H, m, CH_2CH$_2$CH$_2$Me), 4.92 (1H, d, $J_{A,B}$=10.2 Hz, OCH_AH$_B$), 5.02 (1H, d, $J_{B,A}$= 10.2 Hz, OCH$_A$$H_B$), 7.02–7.08 (3H, m, Ar-H), 7.31–7.33 (2H, m, Ar-H); 49% ee (CSP-HPLC, Chiralcel OD Column α=1.1).

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