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Microbiological Transformations 36: Preparative Scale Synthesis of Chiral Thioacetal and Thioketal Sulfoxides Using Whole-Cell Biotransformations

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Abstract: This work describes the preparative scale enantioselective oxidation of some prochiral dithioacetals and dithioketals to their corresponding chiral monosulfoxides using whole-cell cultures of microorganisms. © 1997 Elsevier Science Ltd.

Over the last few years, enantiomerically pure sulfoxides have proved to be excellent chiral auxiliaries for asymmetric synthesis and were used in a large range of asymmetric reactions. As a consequence, they have been implied in the preparation of several enantiopure biologically active compounds as illustrated in a recent review.[1] Various chemical methods have been described for the synthesis of these chirons, including diastereoisomeric resolution,[2,3] direct asymmetric oxidation with chiral oxaziridine derivatives,[4] sulfonylimine derivatives,[5] chiral auxiliaries[6] and metal catalyzed oxidations.[7] The most successful methods - i.e. Kagan's[8] or Modena's[9] are based on the use of a modified Sharpless epoxidation reagent. Among the various types of chiral sulfoxides, those generated from dithioketals were recently described and studied.[10] They have been proved to be highly efficient for various stereoselective transformations like diastereoselective alkylation,[11] ketone reduction[12] or cycloaddition reactions.[13] However, in spite of their value, there are no direct, efficient and general methods for their preparation using conventional synthetic chemistry. In particular, the above-mentioned methods show a poor efficiency for asymmetric oxidation of 1,3-dithiane and of its 2-alkyl derivatives,[9b,10,14] leading only to sulfoxides of poor to moderate ee's. Till now, the synthesis of these chirons had to be achieved using multistep approaches involving for example (a) oxidation of an acyl-[10,15] or carboxy- derivative[16] or of substrates bearing

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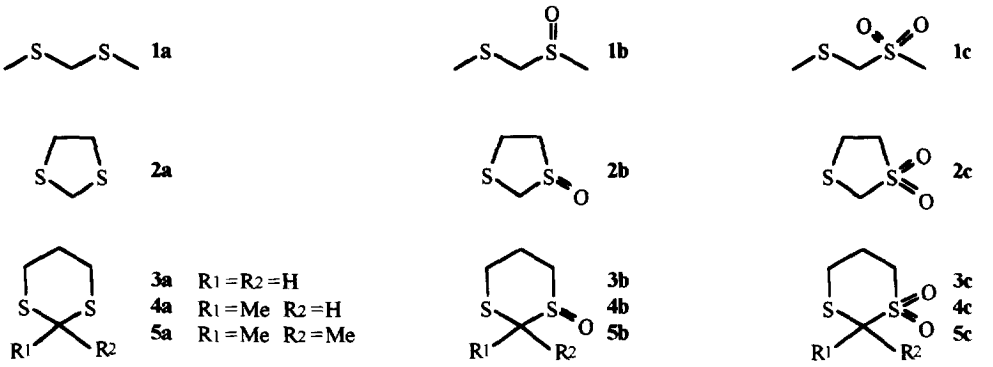
some chiral auxiliary[17] (b) subsequent elimination of these "protecting" groups and, very often, (c) final (or intermediate) recrystallization. In general, the enantiomeric purity of the resulting sulfoxides vary from modest to excellent depending on the structure of the starting material.

Because of this, the use of biocatalytic approaches has recently been explored. Thus, these techniques allow access to optically enriched sulfoxides *via* different types of biotransformations - i.e. hydrolysis of prochiral or racemic sulfoxides containing carboxyl[18] or acetoxy groups,[19] enantioselective reduction of racemic sulfoxides[20] or stereoselective oxidation of sulfides.[21-26] The latter route has been widely studied, and it has been concluded that most of the oxidative enzymes are able to oxidize sulfides to sulfoxides in a stereo- or enantioselective manner. Such oxidations have been observed with mammalian[6b,27] and microbial[28-30] monooxygenases, cytochromes P450,[31] dioxygenases[32] and peroxidases.[33] As is the case with the chemical reactions, all these biotransformations are highly substrate dependent in terms of yield and stereoselectivity. In the specific case of dithioketals, the most interesting results were those using purified cyclohexanone monooxygenase from *Acinetobacter calcoaceticus*.[34] This flavin monooxygenase is well known for its capacity to carry out stereo- and enantioselective Baeyer-Villiger oxidations[35] and sulfoxidations[28] which involve the transfer of either an electrophilic or a nucleophilic oxygen atom. Thus, 1,3-dithiane **1a**, 1,3-dithiolane **2a** and bis(methylthio)methane **3a** were transformed, using the purified enzyme, into their corresponding enantiopure *(R)*-sulfoxide (ee $\geq$ 98 %).[34a] Similarly, substituted dithianes and dithiolanes were shown to afford sulfoxides with various diastereo- and enantioselectivity.[34b] The main limitation in the exploitation of this method stems from the use of a purified enzyme which necessitates recycling of the expensive NADPH coenzyme. Although improvement of this strategy was gained using the immobilized coenzyme with a membrane reactor,[36] this technology is still unsuitable for large scale preparative applications.

We have recently described, in a preliminary note, another approach to this problem which allows the straightforward preparative scale biooxidation of dithioacetal **1a**[37] using whole-cell bacterial cultures. In this paper, we report a more extensive study including additional substrates as well as other microorganisms.

RESULTS AND DISCUSSION

Our studies were carried out using the prochiral dithioacetals **1a**, **2a**, **3a** and **4a** as well as dithioketal **5a** as substrates. Four microorganisms, i.e. three bacterial strains[37,38] *Acinetobacter calcoaceticus* NCIMB 9871, *Acinetobacter* TD 63, *Pseudomonas* NCIMB 9872 and the fungus *Cunninghamella echimulata* NRRL 3655[39] were selected because of their known ability to achieve Baeyer-Villiger oxidations on various ketones.



Scheme 1

Analytical results

The first series of results for biosulfoxidation were obtained from analytical assays. Yields were measured by GC analysis after continuous extraction, using an internal standard. The ee's were determined by chiral GC or HPLC analysis and the absolute configurations were assigned by comparison with known data. Examination of the results summarized in Table 1 shows that: (a) all substrates were oxidized by these strains into their corresponding sulfoxides; (b) these oxidations occurred over a relatively short period of time (a few hours) with bacteria, whereas fungal oxidation was noticeably slower; (c) with bacteria, the yields as well as the enantiomeric purity of the sulfoxides were generally good to excellent (up to 98 %); (d) in most cases, the corresponding sulfone was formed but this only occurred after complete disappearance of sulfide; (e) no trace of the bissulfoxide was observed.[40]

Bis(methylthio)methane **1a** was oxidized within a few hours by either *A. calcoaceticus* NCIMB 9871 or *Acinetobacter* TD 63 strain, leading to the mono *(R)*-sulfoxide **1b** which showed ee's as high as 94 and 91 % respectively. Interestingly, the *Pseudomonas* NCIMB 9872 strain, as well as the fungus *C. echimulata,* gave the opposite enantiomer with *(S)* absolute configuration, but with ee's considerably lower (73 and 12 % respectively).

Similarly, dithiolane **2a** and dithiane **3a** were efficiently oxidized by both *A. calcoaceticus* NCIMB 9871 and *Acinetobacter* TD 63 into their corresponding *(R)*-sulfoxide enantiomer (ee's up to 96 %). Again *Pseudomonas* yielded the opposite *(S)*-enantiomere which showed only a moderate ee, but the fungus *C. echimulata* afforded the sulfoxide of *(R)* absolute configuration. This is in contrast to the oxidation of **1a** using *C. echimulata*. Yields and ee's were again rather low.

In the case of substrates **4a** and **5a**, a switch in the product enantioselectivity was observed. Indeed, whatever the microorganism, biooxidation of **4a** led predominantly to the *trans* sulfoxide of *(R)* absolute configuration at the oxidized sulfur atom, whereas compound **5a** only afforded the product of *(S)* configuration

Table 1. **Oxidation of Some Dithioacetals and Dithioketals** - (Analytical Results)

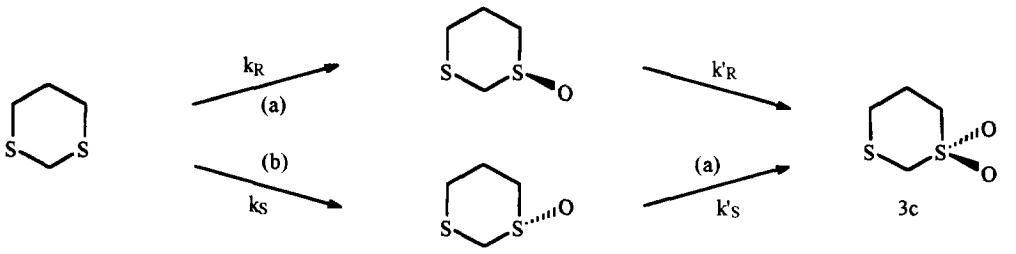
Substrate	Biocatalyst [a]	Time (h)	Residual sulfide yld (%)	Sulfoxide yld (%)	Sulfoxide ee (%)	Sulfoxide abs. conf.	Sulfone yld (%)
	A	3h	-	**79**	**94**	***R***	-
	(enzyme)	*(16h)*		*(92)*	*(98)*	*(R)*	*(8)*
1a	B	2h	-	**92**	**91**	***R***	5
	C	5h40	6	**23**	**73**	***S***	-
	D	7h30	2	**30**	**12**	***S***	-
	A	4h30	-	**71**	**> 95**	***R***	16
	(enzyme)	*(16h)*		*(94)*	*(98)*	*(R)*	*(6)*
2a	B	2h	-	**87**	**> 95**	***R***	9
	C	6h	-	**51**	**37**	***S***	10
	D	48h	12	**35**	**26**	***R***	-
	A	3h30		**74**	**93**	***R***	18
	(enzyme)	*(16h)*		*(81)*	*(98)*	*(R)*	*(19)*
3a	B	2h	-	**62**	**96**	***R***	24
	C	6h	10	**75**	**57**	***S***	3
	D	72h	9	**41**	**12**	***R***	-
	A	10h	4	*trans* : **61** *cis* : **13**	**79**	**1*R*,2*R***	-
	(enzyme)	*(2h)*		*(4/1)*	*75 (trans)*	*(1R,2R)*	
4a	B	2h	-	*trans* : **67** *cis* : **10**	**90**	**1*R*,2*R***	20
	C	6h	8	*trans* : **77** *cis* : **2**	**> 98**	**1*R*,2*R***	-
	D	48h	1	*trans* : **50** *cis* : **6**	**51**	**1*R*,2*R***	-
	A	24h	20	**66**	**60**	***S***	-
	(enzyme)	*(16h)*			*(68)*	*(S)*	
5a	B	4h	-	**92**	**65**	***S***	3
	C	19h	20	**48**	**39**	***S***	3
	D	48h	2	**38**	**9**	***S***	-

(a) Biocatalysts: *A. calcoaceticus* NCIMB 9871 **(A)**; *Acinetobacter* TD63 **(B)**; *Pseudomonas* sp. NCIMB 9872 **(C)**; *C. echinulata* NRRL 3655 **(D)**; Cyclohexanone monooxygenase from *A. calcoaceticus* NCIMB 9871 *(enzyme)*.

with moderate ee. The best biocatalyst for oxidation of **4a** appeared to be the bacteria *Pseudomonas* NCIMB 9872, which gave almost exclusively[41] the *trans*-(1*R*,2*R*)-**4b** enantiomer with excellent enantiomeric purity (ee > 98 %). The three other strains of microorganism also formed the *cis* sulfoxide.[42] Because of its substitution at the central C(2) carbon atom, substrate **4a** affords interesting additional stereochemical information. As the *trans* enantiomer is formed preferentially, it can be deduced that an equatorial oxidation is preferred. Interestingly, this is similar to the result obtained with the modified Sharpless methods.[9b,10] Additionally, preferential formation of

the sulfoxide of (1*R*,2*R*) absolute configuration shows a marked preference for addition of the oxygen atom at the *pro-R* sulfur atom. The same enantiotopic preference has been previously observed on similar compounds with the purified cyclohexanone monooxygenase[34b] as well as for the fungus *A. foetidus*.[23b,23c] It is interesting to note that optically active sulfone **4c** was obtained when the biotransformations were pursued for 24 h. *A. calcoaceticus* and *Acinetobacter* TD63 led to (*S*)-sulfone in 40 % ee (respectively in 20 and 30 % yield). The residual sulfoxide ee was 90 %. *Pseudomonas* sp. gave 39 % of (*R*)-sulfone in 70 % ee and 52 % of enantiopure *trans*-(1*R*,2*R*)-sulfoxide.

All experiments described in Table 1 were analytical studies conducted up to the total consumption of starting material. In fact, formation of the sulfone is as a consequence of oxidation of the sulfoxide. Depending on the enantioselectivity of this second oxidation, the ee of the sulfoxide may be considerably enhanced if the opposite (minor) enantiomer is processed faster than the major one in this second enantioselective oxidation[43] (cf. Scheme 2). This phenomenon is illustrated on Figure 1 for oxidation of dithiane **3a** with *A. calcoaceticus*. This shows that the ee of the sulfoxide **3b** stayed constant (82 % ee, *(R)*) as long as the starting sulfide remained in the bioconversion medium, and increased up to 99 % afterwards. Therefore, it is possible to "tune" more precisely the preparative scale biooxidation reactions in order to prepare the desired sulfoxides in high yields and enantiomeric purity. However, in the case of the biooxidation by *Pseudomonas* sp., the *(S)*-enantiomer was formed preferentially and its ee slightly decreased as sulfone was formed, which seems to indicate that two different mechanisms may be involved. In order to check this hypothesis, oxidation of racemic sulfoxide **3b** by whole-cells of *A. calcoaceticus* and *Pseudomonas* sp. was performed (cf. Figures 3 and 4). As expected, the *(S)*-enantiomer was oxidized faster than the *(R)*-enantiomer by *A. calcoaceticus* **and** by *Pseudomonas* sp. The calculated E values were 13[44] and 2, respectively. These results indicate that the ***stereo***selectivity of the first oxidation is opposite for *A. calcoaceticus* and for *Pseudomonas* sp. whereas the ***enantio***selectivity of the second oxidative step is identical. Thus we can suppose that, for example, in the case of *A. calcoaceticus*, both oxidations took place preferentially ***on the same face and on the same sulfur atom*** (ways (a) on Scheme 2) whereas, in the case of *Pseudomonas* sp., both oxidations took place mainly on the same sulfur atom but ***not on the same face*** (way (b) then (a)).



Scheme 2

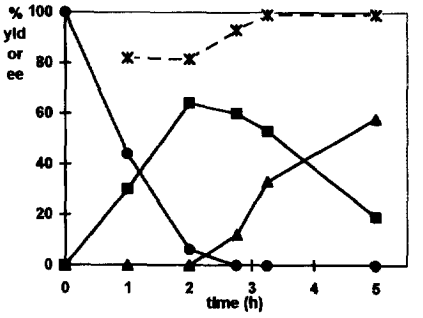


Figure 1: Biooxidation of the prochiral sulfide **3a** by *A. calcoaceticus*.

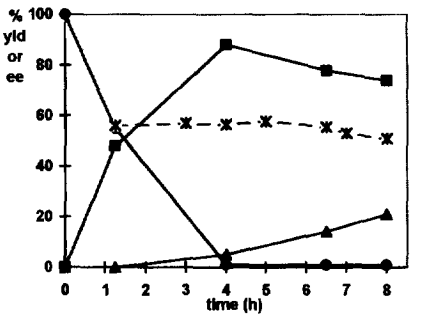


Figure 2: Biooxidation of the prochiral sulfide **3a** by *Pseudomonas* sp.

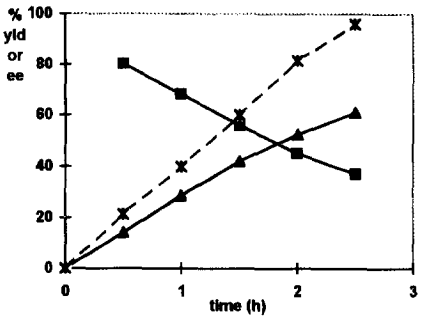


Figure 3: Biooxidation of the racemic sulfoxide **3b** by *A. calcoaceticus*.

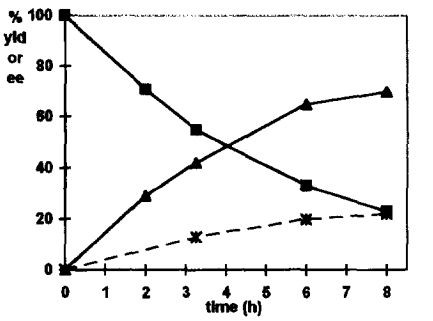


Figure 4: Biooxidation of the racemic sulfoxide **3b** by *Pseudomonas* sp.

● sulfide **3a** (yield) ■ sulfoxide **3b** (yield) ✳ sulfoxide **3b** (ee) ▲ sulfone **3c** (yield)

It is interesting to note that the results obtained using either whole-cells of *A. calcoaceticus* or the purified cyclohexanone monooxygenase from this bacteria are very similar.[34b] The slight differences observed could derive from the fact that the biotransformations were not stopped at exactly the same stage.[45] As far as the non-substituted dithioacetals **1a**, **2a**, **3a** are concerned, *Acinetobacter* strains and *Pseudomonas* sp. led to opposite enantioselectivities,[46] the best ee's being obtained with the former microorganisms. Another interesting observation is that all oxidations using the fungi *C. echinulata* afforded low yields ($30 \leq$ yld ≤ 50 %) of sulfoxides, as well as low ee's for the products ($9 \leq$ ee ≤ 51 %). Moreover, an important loss of material was observed (balance between 32 and 57 %). This phenomenon had already been observed by Boyd and Auret on similar compounds with other fungi[23] and is probably due to the fact that fungi, being equipped with several

classes of oxidative enzymes (cytochrome P450s or peroxidases for example), lead to enantiodivergent oxidations as well as extensive degradation of the metabolites. Obviously, the use of bacterial strains seems to be a better choice for this type of biotransformations.

Preparative scale experiments

In order to illustrate these possibilities, we chose to carry out preparative scale biotransformations of compounds **1a** and **3a** using *A. calcoaceticus*, as well as oxidation of 2-methyl-1,3-dithiane **4a** with the *Pseudomonas* sp. strain. Thus, 1 g of **1a** was transformed using a 1 L culture medium. This led to 720 mg (63 % yld) of isolated *(R)*-sulfoxide **1b** in 99 % ee and 80 mg (6 % yld) of sulfone **1c**. In the same way, 1 g of dithiane **3a** led to 860 mg (76 % yld) of isolated *(R)*-1,3-dithiane-1-oxide **3b** which showed a 98 % ee. It has to be stressed that, up to now, the best preparation of 1,3-dithiane-1-oxide **1b** using conventional chemistry necessitated the use of a three-step procedure[10,15b] (overall yield 40 %), including a modified Sharpless oxidation.[47] Similarly, 695 mg (62 % yld) of enantiopure (ee > 98 %) of *trans*-(1*R*,2*R*)-2-methyl-1,3-dithiane-1-oxide **4b** were obtained from 1 g of **4a**. Preparation of **4b** *via* the three-step chemical method led to a *cis/trans* mixture (*cis*-compound major: 8/1), whereas direct oxidation of **4a** using the modified Sharpless procedure afforded the *trans*-sulfoxide which only showed a 10 % ee.[10] It is interesting to emphasize that chemical oxidation of enantiomerically enriched monosulfoxides to the corresponding disulfoxides can be achieved, using sodium periodate for instance, without loss of stereochemical integrity.[23b] Since their asymmetric synthesis is highly substrate dependent, it appears that the thioacetal biooxidation approach described here represents a good alternative to the preparation of these disulfoxides which are valuable chiral auxiliaries reacting with high diastereoselectivity on various aldehydes and ketones.[48]

In conclusion, we have shown that oxidation of prochiral dithioacetals and ketals can be efficiently performed using whole-cell cultures of bacterial strains. In some cases, this approach allows the one-step preparative scale synthesis of enantiopure monosulfoxides, as we have exemplified on substrates **1a**, **3a** and **4a**. This appears to be, at the present time, the most effective methodology allowing for the preparation of such interesting chirons. Work is in progress in our laboratories in order to further explore the scope and limitations of these biotransformations.

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EXPERIMENTAL PART

General procedures and materials

FID gas chromatography analyses were performed with a Shimadzu GC-14A chromatograph equipped with the followed capillary columns: (a) BP10 (25 m × 0.32 mm × 0.25 μm) (b) Lipodex® E (25 m × 0.25 mm, Macherey-Nagel) (c) CP-cyclodextrine (50 m × 0.25 mm, Chrompack). HPLC analyses were performed with a Shimadzu chromatograph equipped with a UV-detector (λ=220 nm) and a Chiralcel OD column (Daicel) using hexane/iPrOH as eluent. Melting points were determined on a Buchi apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer in $CDCl_3$ solutions. Chemical shifts (δ) are quoted in ppm with Me_4Si as reference and J values are in Hz. Proton and carbon attributions were made by 2D experiments, if necessary. Optical rotations were measured on a Perkin Elmer 241C polarimeter and are given in 10^{-1}deg cm^2 g^{-1}. Microorganism cultures were carried out in a 2 L or a 7 L fermentor (Setric).

Acinetobacter calcoaceticus NCIMB 9871, *Pseudomonas* NCIMB 9872 and *Cunninghamella echinulata* NRRL 3655 were obtained from the National Collection of Industrial and Marine Bacteria (UK) and from the Culture Collection, Northern Regional Research Laboratory (USA). *Acinetobacter* TD 63 was a generous gift from Prof. P.W. Trudgill. Stock culture were grown on nutrient agar at 30 °C (for bacteria) or on Corn Steep Liquor/Glucose agar medium at 27 °C (for fungus) and stored at 4 °C.

Sulfides **1a**, **3a**, **4a** were purchased from Aldrich or Janssen. Sulfides **2a** and **5a** were obtained by the method of Hoppmann *et al.*[49] Racemic sulfoxides were obtained by oxidation of the corresponding sulfides with $NaIO_4$ in water/methanol solution, according to the general procedure by Johnson and Keiser.[50] The crude reaction products were purified by flash chromatography using diethylether/methanol mixtures as eluent.
Absolute configurations of **1b**,[3] **2b**,[23b] **3**,[15b] and **4b**[23c] and **5b**[23c] were assigned by comparison of optical rotation with literature data. The absolute configuration of **4c** was assigned by comparison of optical rotation with that of an authentic (*R*)-sulfone ($[\alpha]_D^{20}$ = -14 (c=1 $CHCl_3$)) obtained by chemical oxidation ($KMnO_4/MgSO_4/H_2O$)[51] of (1*R*,2*R*)-enantiopure sulfoxide.

Culture conditions

Bacteria: 2 L fermentor filled with 1 L minimal mineral medium culture (4 g Na_2HPO_4, 2 g KH_2PO_4, 3 g $(NH_4)_2SO_4$, 0.5 g $MgSO_4$, 0.1 g $CaCl_2$, 0.01 g $FeSO_4$, 0.2 g yeast extract) was supplemented with 1.5 *cis/trans*-1,2-cyclohexanediol (*Acinetobacter* strains) or 1.5 g cyclopentanol (*Pseudomonas* sp.) as only carbon source. In this latter case, 200 mg antifoam silicon 426 R (Prolabo) and 250 mg Pluronic PE 8100 (BASF) were added. These media were inoculated with a 6 h preculture (*Acinetobacter* strains) or a 24 h preculture (*Pseudomonas* sp.). Cells were grown for 15-20 h at 30 °C with vigourous aeration and stirring at 500 rpm.

Fungus: A 7 L fermentor, filled with 5 L Corn Steep Liquor culture medium (20 g/L CSL, 5 g/L glucose, 1 g/L KH_2PO_4, 2 g/L K_2HPO_4, 2 g/L $NaNO_3$, 0.5 g/L KCl, 0.5 g/L $MgSO_4$, 0.02 g/L $FeSO_4$) was inoculated with 2.10^7 spores from a *C. echinulata* spore suspension. Cells were grown for 60 h at 27 °C with 40 L/h aeration and 400 rpm stirring.

Biotransformation conditions

Biotransformations using bacteria were carried out at 30 °C directly in the culture medium, after growth period. The carbon source (0.5 g) was added 30 min before addition of the substrate (solubilized in ethanol at 10 % w/v). In the case of the fungus, the culture medium was filtered and the cells were used in suspension in 5 L phosphate buffer (pH 7, 4 g/L Na_2HPO_4, 2 g/L KH_2PO_4) at 27 °C. The substrate, solubilized in ethanol (10 % w/v), was added immediately.

Analytical experiments: 50 mg of substrate in ethanol were added to 50 mL of biotransformation medium in 250 mL flasks placed in a reciprocating shaker (27 °C, 100 spm). The reaction was monitored by GC (BP10) and worked up (continuous extraction by CH_2Cl_2) when the substrate had disappeared. Yields of products and residual substrates were determined by GC analysis using an internal standard.

Preparative experiments: Preparative biotransformations were achieved in a 2 L fermentor using experimental conditions identical to those used for the culture. 1 g of substrate, solubilized in 10 mL EtOH, was added about 30 min after addition of the carbon source (oxygen pressure came back at 100 %). The reactions were monitored by GC or HPLC analysis of samplings (1 mL culture medium was extracted by 2 mL CH_2Cl_2) and stopped when yields or ee's of sulfoxides were highest. Biotransformation media were extracted continuously with CH_2Cl_2 for 24 h. Products were purified by flash chromatography (pentane/AcOEt and AcOEt/MeOH) and identified by comparison of their spectroscopic data (^{13}C, ^{1}H NMR, IR) with those of authentic samples or with literature data.

Ee determination

Ee's of the sulfoxides and of sulfone **4c** were determined by chiral GC (Lipodex E or CP-cyclodextrine) or HPLC (Chiralcel OD - 1 mL/min - λ = 220 nm), before recrystallization.

Sulfoxide	Column	Conditions	Retention time (min)	
			(*R*)	(*S*)
1b	Chiralcel OD	Hex/iPrOH : 90/10	16	18
	Lipodex E	[170 °C]	3.5	5.1
2b	Chiralcel OD	Hex/iPrOH : 96/4	96	100
	CP-Cyclodextrine	100 °C for 30 min then 0.3 °C/min	91	90
	Lipodex E	[120°C]	63	60
3b	Chiralcel OD	Hex/iPrOH : 75/25	15.2	13.5
	Lipodex E	[100 °C]	24.5	22.5
4b	Chiralcel OD	Hex/iPrOH : 95/5	29 (1*R*,2*R*)	40 (1*S*,2*S*)
	Lipodex E		13.2	11.9
4c	Lipodex E	[175 °C]	23	18
5b	CP-Cyclodextrine	from 120 °C, 0.5 °C/min	30	31

Physical and spectroscopic properties of the obtained products

(R)-Methane(methylsulfinyl) **1b** : colourless liquid; IR (neat) 1415 cm^{-1}, 1035 cm^{-1}; ^{1}H NMR δ 2.33 (s, 3H), 2.69 (s, 3H), 3.70 (s, 2H); ^{13}C NMR δ 17.28 (CH_3), 37.68 (CH_3), 56.63 (CH_2); $[\alpha]_D^{20}$ = +105 (c=1.5 $CHCl_3$); ee 99 % (lit.[3] $[\alpha]_D$ = - 97 (c=1.44 $CHCl_3$), ee 97 %, *S*).

Methane(methylsulfonyl) **1c** : white needles; mp : 50-51 °C; IR ($CHCl_3$) 1300 cm^{-1}, 1105 cm^{-1}; ^{1}H NMR δ 2.43 (s, 3H), 3.04 (s, 3H), 3.81 (s, 2H); ^{13}C NMR δ 16.99 (CH_3), 38.05 (CH_3), 56.48 (CH_2).

(R)-1,3-Dithiolane-1-oxyde **2b** : colourless liquid; IR (neat) 1390 cm^{-1}, 1030 cm^{-1}, ^{1}H NMR δ 2.75 (m, 1H(5)), 3.45 (m, 2H(4+5)), 3.69 (m, 1H(4)), 3.89 (d, *J*=12.5Hz, 1H(2)), 3.99 (d, *J*=12.5Hz, 1H(2)); ^{13}C NMR δ 31.78 (C(4)), 55.60 (C(2)), 57.45 (C(5)); $[\alpha]_D^{20}$ = +160 (c=1.6 EtOH); (lit.[23b] $[\alpha]_D$ = + 114 (EtOH), ee 65 %, *R*).

1,3-Dithiolane-1,1-dioxyde **2c** : white crystals; mp : 75-76 °C; IR ($CHCl_3$) 1320 cm^{-1}, 1120 cm^{-1}, ^{1}H NMR δ

3.22 (m, 2H(4)), 3.34 (m, 2H(5)), 3.87 (s, 2H(2)); ^{13}C NMR δ 25.44 (C(4)), 48.53 (C(2)), 52.17 (C(5)).

(R)-1,3-Dithiane-1-oxide **3b**[17] : cubic white crystals; mp : 108.5-110.5 °C; IR (CH_2Cl_2) 1420 cm^{-1}, 1050 cm^{-1}; ^{1}H NMR [52] δ 2.1-2.3 (m, 1H(5)), 2.4-2.7 (m, 4H), 3.2-3.4 (m, 1H(6)), 3.65 (d, *J*=13Hz, 1H(2)), 4.02 (dd, *J*=13Hz, J=3Hz, 1H(2)); ^{13}C NMR[53] δ 27.55 (C(5)), 28.84 (C(4)), 51.20 (C(2)), 52.84 (C(6)); $[\alpha]_D^{20}$ = +210.6 (c=1.0 CH_2Cl_2); ee = 98 %; (lit.[15b] $[\alpha]_D^{20}$ = -210 (c=1 CH_2Cl_2), ee>98 %, *S*).

1,3-Dithiane-1,1-dioxyde- **3c** : white powder; mp : 140-141 °C; IR (CH_2Cl_2) 1305 cm^{-1}, 1285 cm^{-1}, 1135 cm^{-1}, 1105cm^{-1}; ^{1}H NMR δ 2.55-2.70 (m, 2H(5)), 2.70-2.80 (m, 2H(4)), 3.05-3.20 (m, 2H(6)), 3.91 (s, 2H(2)); ^{13}C NMR δ 27.55 (C(4)), 28.84 (C(5)), 51.20 (C(2)), 52.84 (C(6)).

(1R,2R)-trans-*2-Methyl-1,3-dithiane-1-oxide* **4b** : white crystals, mp : 118-121 °C; IR ($CHCl_3$) 1410 cm^{-1}, 1020 cm^{-1}; ^{1}H NMR[52] δ 1.65 (d, *J*=7Hz, 3H), 2.20-2.40 (m, 1H(5)), 2.40-2.85 (m, 4H), 3.35-3.50 (m, 1H(6)), 3.65 (q, *J*=7Hz, 1H(2)); ^{13}C NMR[53] δ 15.24 (CH_3), 29.63 (C(5)H_2), 30.18 (C(4)H_2), 53.63 (C(6)H_2), 60.29 (C(2)H); $[\alpha]_D^{20}$ = +57.6 (c=1.0 EtOH); ee > 98 %; (lit.[23c] $[\alpha]_D^{20}$ = +62.1 (c=1 EtOH)).

(R)-2-Methyl-1,3-dithiane-1,1-dioxide **4c** : white crystals, mp: 79-81 °C; IR ($CHCl_3$) 1310 cm^{-1}, 1295 cm^{-1}, 1135 cm^{-1}, 1105 cm^{-1}; ^{1}H NMR[52] δ 1.59 (d, *J*=7Hz, 3H), 2.40-2.75 (m, 3H(5)), 2.75-3.10 (m, 2H), 3.10-3.30 (m, 1H), 4.11 (q, *J*=7Hz, 1H(2)); ^{13}C NMR[53] δ 11.0 (CH_3), 28.7 (C(4)H_2), 29.5 (C(5)H_2), 52.4 (C(6)H_2), 58.8 (C(2)H); $[\alpha]_D^{20}$ = -9.5 (c=1.1 $CHCl_3$); ee = 70 %, op = 68 %.

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38. Whole-cells of *A. calcoaceticus* NCIMB 9871 and of *Pseudomonas* NCIMB 9872 were already used for sulfoxidation of alkyl aryl sulfides[29] or alkyl alkyl sulfides.[30]

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40. One can however not exclude, in particular in the cases were the balance is lower than 100 %, that these disulfoxides can be degraded to higher water soluble compounds.[23a]

41. The *cis/trans* ratio measured by GC was: 38/1.

42. Hovewer, we were not able to determine its ee composition because of the apparent lack of chiral discrimination on our analytical chiral columns.

43. A similar phenomenon was already described during oxidation of linear sulfides with a titanium-binaphtol complex,[7c] with a (Salen) manganese complex[7e] or using modified Sharpless method (Scettri, A.; Bonadies, F.; Lattanzi, A.; Senatore, A.; Sorriente, A. *Tetrahedron: Asymmetry* **1996**, *7*, 657-658). In contrast, when applied to prochiral sulfides, this latter method allowed the preparation of optically active disulfoxides.[10,16]

44. Slightly lower to the one determined for the purified CMO enzyme ($E \approx 20$).[34a]

45. This point could explain the variations of ee observed in different publications.[28e,29]

46. An inversion of absolute configuration between these two microorganisms had been already described for some alkyl aryl sulfoxides by Kelly *et al.*[30]

47. If the Sharpless oxidation is carried out directly on 1,3-dithiane **3a**, ee's were lower than 30 %.[10,15b,16]

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