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Microbiological and Chemical Methods in the Asymmetric Oxidation of Sulfides : A Comparative Study for the Preparation of (*S*)-Vinyl Sulfoxides

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***Abstract** : The enantiogenicity of biological and chemical oxidation at the sulfur atom was studied on a series of prochiral vinyl sulfides for the preparation of sulfoxides of (S)-absolute configuration. Using either fungal cultures, Sharpless-modified reagent or chiral oxaziridine, the enantiomeric excesses varied according to the substrate's steric and/or electronic structure; the three methods were complementary.*

INTRODUCTION

The chemistry of sulfoxides has been extensively developed in recent years since chiral sulfoxides are widely used for their high diastereoselectivity as auxiliaries or reagents in asymmetric synthesis[1-7]. Chiral vinyl sulfoxides are useful dienophiles in asymmetric Diels Alder reactions[8,9]. The sulfoxide grouping is also involved in diverse biological activities and optically pure sulfoxides are of great pharmaceutical interest[10-15]. Accordingly, numerous methods have been developed for preparing sulfoxides with high enantiomeric excesses (ee > 90 %) or even optically pure[16].

We have been interested in preparing chiral vinyl sulfoxides possessing anti-anoxic activity[13] and likely to act as free radical scavengers of importance in the cardiovascular field. For pharmacological screening, both enantiomers of sulfoxides have to be synthesized in order to compare their specific activities as their pharmacological properties can differ in intensity and even be antagonistic[17]. Enantiomers of sulfoxides can be prepared by direct oxidation of the corresponding sulfides. Among the most efficient methods for the enantiogenic oxidation of prochiral thioethers are catalytic reactions using either a Sharpless-type reagent[18] or chiral oxaziridines[19], oxidation by hydroperoxides in the presence of proteins[20] or cyclodextrines[21] and oxidation by biological systems, purified enzymes, *e.g.* chloroperoxidase[22] or microorganisms[23,24].

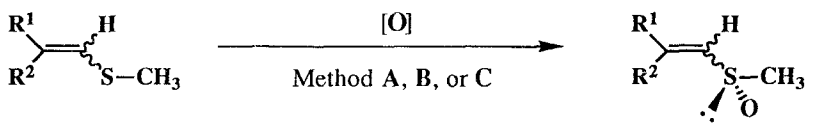
Using this last technique, Sih *et al.* reported that the two enantiomers of methyl *p*-tolyl sulfoxide could be obtained in high optical yields[25]. However, in the course of a study on preparing the required chiral vinyl sulfoxides using microorganisms, we observed that the biological oxidation of a series of prochiral sulfides by

fungi, yeasts and bacteria essentially gave sulfoxides of (*R*)-absolute configuration[26,27]. A few fungal strains yielded the (*S*)-enantiomer only with certain substrates, with enantiomeric excesses ranging from 2 % to 98 % according to the substrate, and low chemical yields. Thus, to prepare all the chiral vinyl sulfoxides of the series with (*S*)-absolute configuration and high enantiomeric excesses, we were led to also use the chemical asymmetric oxidation. Two methods are reported to give both high enantiomeric excesses (ee > 90 %) and good chemical yields (*ca* 80 %), one following a modified Sharpless procedure and described by Kagan[18] *et al.* and the other using chiral oxaziridines[19].

We report here the best results obtained using the three methods on a series of methyl aryl-vinyl sulfides. This allows comparison of the enantiogenicity of the microbiological method with that of the most efficient catalytic asymmetric oxidation methods.

RESULTS

We studied the asymmetric sulfoxidation of the major diastereomers of prochiral vinyl sulfides **1a-e** to (*S*)-sulfoxides **2 a-e** according to the following scheme and Table 1 :



1 a-e **2 a-e**

Method **A** : Bioconversion Method **B** : Sharpless-type reagent Method **C** : Chiral oxaziridine

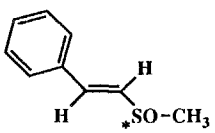
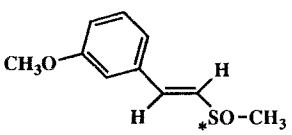
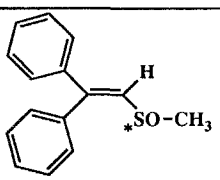
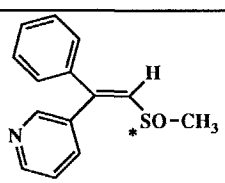
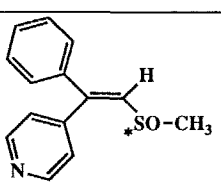
Table 1 : Diastereomers of Vinyl Sulfides **1a-e**

Substrate	Diastereomer	R^1	R^2
1a	(*E*)	H	Ph
1b	(*E*)	H	3'-MeO-C_6H_4
1c	-	Ph	Ph
1d	(*Z*)	Ph	3'-pyridyl
1e	(*Z*)	Ph	4'-pyridyl

Oxidation of substrates **1a-e** by bioconversion, method A, was carried out using two strains of fungi already reported for sulfoxidation, *Helminthosporium sp.*[25,27] and *Fusarium oxysporum*[28]. After cultivation of the microorganisms, the substrates were added to the culture medium and incubated with mycelia for several hours. Reactions were stopped before completion when formation of sulfone occurred. In Table 2 are the results obtained for each substrate with the most efficient strain in providing the (*S*)-enantiomer in each case, namely *Helminthosporium. sp.*, method A-1, for **1a** and **1b** and *F. oxysporum*, method A-2, for **1c-e**. Asymmetric oxidation of sulfides **1a-e** with the Sharpless-modified reagent, method B, was carried out following a procedure described by Kagan *et al.*[29] using cumene hydroperoxide in the presence of a stoi-

chiometric amount of water-modified titanium reagent and (*S,S*)-(-)-diethyl tartrate : [Ti(O-*i*Pr)$_4$ /(-)DET /H_2O = 1:2:1] in CH_2Cl_2 at -20°C. Asymmetric oxidation catalysed by an optically pure oxaziridine, method C, was performed using (-)-α,α-dichlorocamphorbenzenesulfonyloxaziridine[19]. The reaction took place at room temperature in either CH_2Cl_2 or CCl_4. The results obtained by the three oxidation methods are given in Table 2.

Table 2 : Synthesis of (*S*)-**2a-e** Chiral Vinyl Sulfoxides : Comparative Data

Substrate	Sulfoxide	Method	e.e. (%)	yield[a] (%)	time (h)
1a		A-1 B C	≥ 98 90 42	20 39 87	22 22 18
1b		A-1 B C	≥ 98 95 40	33 41 88	22 23 6
1c		A-2 B C	29 2 68	22 50 90	70 24 6
1d		A-2 B C	66 58 64	27 62 87	48 24 6
1e		A-2 B C	≥ 98 74 65	31 40 90	72 24 6

a : after isolation of unreacted sulfide (0-30%) and/or sulfone (0-20%).

The (*S*)-absolute configuration of all the sulfoxides was assigned according to Kagan *et al.* by ^{1}H NMR using (*R*)-(-)-N-(3,5-dinitrobenzoyl)-1-phenylethylamine[30] and confirmed by X-ray analysis and optical rotation sign comparison of enantiomer **2e**[26]. Enantiomeric excesses were measured by HPLC using a chiral stationary phase for sulfoxides obtained by methods A and B, and by ^{1}H NMR using a chiral shift reagent for sulfoxides prepared by method C.

The fastest asymmetric sulfoxidation method (6 h) and the one which gave the highest chemical yields (87-90 %) was method C using the chiral oxaziridine whereas chemical yields lower than 35 % and long reaction time (22 h-72 h) were obtained with microorganisms. Conversely, the highest optical purity (ee ≥ 98 %) was obtained by microbiological oxidation for certain (*S*)-vinyl sulfoxides, **2a**, **2b** and **2e** and, to a lesser degree, using the water-modified titanium reagent (ee = 90-95 %). High enantiomeric excesses were never obtained for sulfoxide **2c**, whatever the method used. The best value, ee = 68 %, was obtained with the chiral oxaziridine, method C. Chiral sulfoxide **2d** was prepared with low enantiomeric excess by the three methods (ee = 58-66 %) but the best result was with *F. oxysporum*, method A-2. Enantiomer **2d** of (*R*)-absolute configuration and low ee (58 %) was obtained with the other strain (A-1).

DISCUSSION

Substrate specificity is evident in all three methods used in our experiments. Within this very limited series of compounds, some general comments can be made in explanation, in terms of the factors that favor enantiogenicity.

In bioconversion studies, the substrate specificity generally observed is often related to steric factors. However, no clear correlation is apparent in our series. From the results in Table 2, it can be assumed that the main contributive factor in the microbiological oxidation of certain vinyl sulfides is of an electronic nature : the enantiomeric excesses of the sulfoxides obtained by bioconversion of two sterically identical sulfides, **1d** and **1e**, are quite different (66 % and 98 % respectively). The only difference between the two substrates is the position of the hetero-atom in the pyridyl ring, resulting in different electron distribution over the molecule. When the N-atom is in the *para* position as in sulfide **1e**, its electron-withdrawing effect is associated with the strong conjugation occurring in vinyl sulfides through the participation of one of the sulfur-lone pairs in the double bonding[31]. Our results are in agreement with a mechanism involving an electron-deficient sulfur intermediate, already proposed for microbiological oxidation of alkyl-aryl sulfides[32].

The method using a chiral oxaziridine appears to be influenced by non-bonded steric interaction. This is indicated by the fact that the highest enantiomeric excess obtained in the series, ee = 68 %, is for the hindered sulfoxide **2c** bearing apolar substituents. The reaction is also more stereogenic in the series when the steric hindrance of the two groups carried by the prochiral sulfur differs : ee = 40-42 % for mono aryl-vinyl sulfoxides **2a** and **2b** and ee = 64-68 % for diaryl-vinyl sulfoxides **2c-e**.

The results obtained in our series of sulfides using the modified Sharpless reagent are more difficult to interpret as the enantiogenicity of this method seems to be influenced by both electronic (**2c** *vs* **2e**) and steric (**2b** *vs* **2c**) effects and the stereochemistry of the oxidation cannot be predicted from the substrate's steric and electronic structures.

In conclusion, there is as yet no general method for the preparation of (*S*)-vinyl sulfoxides by asymmetric oxidation of sulfides since the enantiogenicity of each method depends to a large extent on the substrate. Methods using microorganisms or chemical means are thus complementary. In view of the high enantiomeric excesses obtained using microorganisms and the great number of species available it would however be worth extending screening and optimizing the bioconversion reactions after characterization of the enzymatic systems involved.

EXPERIMENTAL

General Methods.

^{1}H NMR spectra were recorded on either a Bruker 300 MSL or a Jeol FX 90 Q instrument, in $CDCl_3$ solutions with chemical shifts reported in ppm relative to internal standard chloroform (7.27 ppm at 300 MHz). Tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato] europium (III), Eu(hfc)$_3$, was used as a shift reagent for enantiomeric excess determinations. Absolute configurations were assigned by analysis of ^{1}H NMR spectra recorded in the presence of (*R*)-(-)-N-(3,5-dinitrobenzoyl)-1-phenylethylamine[30] with reference to X-ray data[26]. HPLC experiments for enantiomeric excess determinations were performed using a Waters 600 E liquid chromatograph fitted with a Daicel Chiralcel OB column (25 cm x 0.46 cm) at room temperature. The mobile phase was *n*-hexane-isopropanol mixtures, monitored at 254 nm. Pressure and flow rate were as indicated for each sulfoxide. Retention times and area under chromatographic peaks were determined with a Shimadzu CR3A integrator, chart speed 1mm/min. Optical rotation values were measured on a Perkin-Elmer 141 polarimeter for the mercury J line (λ = 578 nm), at 25°C in acetone solutions (c in g/mL) following careful drying of the products. IR spectra were run on a Perkin-Elmer 377 spectrometer and bands are expressed in frequency units (ν cm^{-1}). Satisfactory analytical data were obtained for all new compounds (± 0.4 % for C.H.N.O.S.) at the Service Central d'Analyse du CNRS, Solaize, France.

Sulfides were prepared according to a Wittig-Horner procedure published elsewhere[33] and (*E*) and (*Z*) diastereomers were separated by MPLC using a Büchi apparatus with silica gel 60 Merck 20-45 µm and ethyl acetate in cyclohexane (5-40%) as eluent.

Method A : Microbiological Oxidation of Sulfides 1a-e.

Precultures and cultures of *Fusarium oxysporum* CBS 24801 were performed in 500-mL flasks containing 100 mL of a glucose-soyoptim medium already described (medium 1 *in* ref[34]). *Helminthosporium sp.* NRRL 4671 precultures were in corn-steep medium (medium 5 *in* ref[34]) and cultures were in medium 1. Sulfides (100 mg *per* flask) were added to 24-h old cultures under sterile conditions and incubated at 27°C in rotary shakers. Reactions were stopped by removal of the mycelium by filtration and extraction of the incubation medium with ethyl acetate overnight. Incubation times were determined by analytical kinetic studies monitored by TLC (Merck 60 F_{254}) using racemic sulfoxides and sulfones as controls and 3-25% of methanol in ethyl acetate as eluent. Quantitative assays, using the contents of ten flasks, were made for each substrate. The crude mixtures containing unreacted sulfide, sulfoxide and/or sulfone were purified by flash chromatography (Merck 40-63 µm silica gel 60) using the same eluent. Enantiomeric excesses were determined by HPLC ; (*S*)-enantiomer eluted first. Capacity factor : k'_1 = (retention time of first eluted isomer - dead time) /(dead time); dead time calculated from acetophenone peak; separation factor :α = (capacity factor of second eluted isomer)/k'_1; resolution factor; R = 2 x (retention time of second eluted isomer - retention time of first eluted isomer)/sum of baseline width of the two peaks)

Method B : Asymmetric Oxidation of Sulfides 1a-e using Sharpless-modified Reagent.

Oxidation was performed on 0.5 mmole of each sulfide following the procedure described by Kagan for the preparation of (*S*)-(-)-methyl *p*-tolyl sulfoxide[29]. All reagent grades should be as stated and solvents must be carefully dried. 0.75 mL of titanium (IV) isopropoxide, Ti(O-*i*Pr)$_4$ (0.25 mmole) was introduced through the septum of a flask containing 0.85 mL of (*S,S*)-(-)-diethyl tartrate (0.5 mmole) in 30 mL of stirred methylene chloride. After a few minutes, 5 µL of distilled water (0.25 mmole) was added dropwise followed by the sulfide in solution in methylene chloride. The mixture was cooled to -30°C, stirred for 40 min and 0.1 mL of

cumene hydroperoxyde (0.5 mmole) was added dropwise. The mixture was kept at - 20°C overnight. Hydrolysis was carried out by adding 1mL of water and stirring for 90 min at room temperature. After filtration on methylene chloride-impregnated Celite, the solution was stirred with NaOH and brine as indicated by the authors. After decantation, the organic phase was dried and concentrated. Isolation of sulfoxides and enantiomeric excess determinations were as described in method A.

Method C : Asymmetric Oxidation of Sulfides 1a-e using a Chiral Oxaziridine.

In a 10 mL round-bottomed flask equipped with magnetic stirring bar and argon inlet were placed 0.25 mmoles of (-)-α,α-dichlorocamphorbenzenesulfonyloxaziridine[19] in 4 mL of CH_2Cl_2 or CCl_4, followed by 1.1 equivalent of the required sulfide in 2 mL of solvent. The mixture was stirred at room temperature, for 6 h in CH_2Cl_2 and for 18 h in CCl_4 as indicated for each substrate. The mixtures were separated by preparative TLC (silica gel G) eluting with ethyl acetate and methanol (95 : 5) and the sulfoxides, which had the lowest R_f band, were extracted with dry THF. Enantiomeric excesses were determined by ^1H NMR in the presence of Eu(hfc)$_3$ shift reagent, on the aromatic or olefinic signals

(*E*)-(*S*)-(+)-Methyl-(2-phenyl) vinyl sulfoxide 2a.

TLC : eluent AcOEt-MeOH, 97 : 3, R_f 0.4; HPLC : eluent *n*-hexane-*i*-PrOH, 90 : 10, pressure 200 psi flow rate 0.5 mL/min, t_1 33 min, t_2 46 min, $k'_1 = 10$, $k'_2 = 14.3$, $\alpha = 0.7$, $R = 2$; physical constants (mp, IR, NMR spectra) identical to those already published[27].

Method A : strain *Helminthosporium sp.* incubation time 22 h; isolated yield 20%; $[\alpha]_J^{25} = + 176$ (c = 0.010, acetone); $ee_{(HPLC)} \geq 98$ %

Method B : isolated yield 39 %; reaction time 22 h; $[\alpha]_J^{25} = + 157$ (c = 0.029, acetone); $ee_{(HPLC)} = 90$ %

Method C : solvent CCl_4; reaction time 18 h; isolated yield 87 %; [α] n.d; $ee_{(NMR)} = 42$ %, $\delta_R = 9.09$ ppm, $\delta_S = 8.95$ ppm

(*E*)-(*S*)-(+)-Methyl-[2-phen-(3'-methoxy)-yl] vinyl sulfoxide 2b.

TLC : eluent AcOEt-MeOH, 92 : 8, R_f 0.4; HPLC : eluent *n*-hexane-*i*-PrOH, 78 : 22, pressure : 474 psi, flow rate 1 mL/min, t_1 15 min, t_2 27 min, $k'_1 = 14$, $k'_2 = 26$, $\alpha = 0.5$, $R = 1.7$; mp : oil; IR 970-1030 (broad); ^1H NMR 300 MHz, $CDCl_3$: δ = 2.73 (s, 3H); 3.83 (s, 3H); 6.90 (d, 1H, J = 16 Hz); 7.25 (d, 1H, J = 16 Hz); 6.95-7.34 (m, 4H).

Method A : strain *Helminthosporium sp.*, incubation time 22 h; isolated yield 33%; $[\alpha]_J^{25} = + 157$ (c = 0.012, acetone); $ee_{(HPLC)} \geq 98$ %

Method B : isolated yield 41 %; reaction time 23 h; $[\alpha]_J^{25} = + 141$ (c = 0.081, acetone); $ee_{(HPLC)} = 95$ %

Method C : solvent CH_2Cl_2; reaction time 6 h; isolated yield 88 %; [α] n.d; $ee_{(NMR)} = 40$ %, $\delta_R = 6.16$ ppm, $\delta_S = 5.89$ ppm

(*S*)-(-)-Methyl-(2,2-diphenyl) vinyl sulfoxide 2c.

TLC : eluent AcOEt-MeOH, 92 : 8, R_f 0.5; HPLC : eluent *n*-hexane-*i*-PrOH, 94 : 6, pressure : 108 psi flow rate 0.2 mL/min, t_1 106 min, t_2 130 min, $k'_1 = 9.6$, $k'_2 = 12$, $\alpha = 0.8$, $R = 1.1$; physical constants (mp, IR, NMR spectra) identical to those already published[27].

Method A : strain *F. oxysporum*, incubation time 70 h; isolated yield 22%; $[\alpha]_J^{25} = - 25$ (c = 0.008, acetone); $ee_{(HPLC)} = 29$ %

Method B : isolated yield 50 %; reaction time 24 h; $[\alpha]_J^{25} = - 2$ (c = 0.009, acetone); $ee_{(HPLC)} = 2$ %

Method C : solvent CH_2Cl_2; reaction time 6 h; isolated yield 90 %; [α] n.d; $ee_{(NMR)} = 68$ %, $\delta_R = 7.96$ ppm, $\delta_S = 7.77$ ppm.

(Z)-(*S*)-(-)-Methyl-(2-phenyl-2-pyrid-3'-yl) vinyl sulfoxide 2d.

TLC : eluent AcOEt-MeOH, 75 : 25, R_f 0.5; HPLC : eluent *n*-hexane-*i*-PrOH, 90 : 10, pressure 160 psi, flow rate 0.5 mL /min, t_1 66 min, t_2 84 min, $k'_1 = 21$, $k'_2 = 27$, $\alpha = 0.8$, $R = 0.7$; mp 38-40°C; IR 970-1030 (broad); ^1H NMR 300 MHz, $CDCl_3$: δ = 2.80 (s,3H); 6.95 (s,1H); 7.35-7.50 (m,7H); 8.67-8.75 (m,2H).

Method A : strain *F. oxysporum*, incubation time 48 h; isolated yield 27%; $[\alpha]_J^{25} = -23$ (c = 0.019, acetone); $ee_{(HPLC)} = 66$ %

Method B : isolated yield 62 %; reaction time 24 h; $[\alpha]_J^{25} = -25$ (c = 0.050, acetone); $ee_{(HPLC)} = 58$ %

Method C : solvent CH_2Cl_2; reaction time 6 h; isolated yield 87 %; [α] n.d; $ee_{(NMR)} = 64$ %, $\delta_S = 6.78$ ppm, $\delta_R = 6.33$ppm.

(Z)-(*S*)-(-)-Methyl-(2-phenyl-2-pyrid-4'-yl) vinyl sulfoxide 2e.

TLC : eluent AcOEt-MeOH, 75 : 25, R_f 0.5; HPLC : eluent *n*-hexane--PrOH, gradient 5-8% in 20 min, pressure 220 psi, flow rate 0.5 mL /min, t_1 60 min, t_2 80 min, $k'_1 = 59$, $k'_2 = 79$, $\alpha = 0.7$, $R = 0.8$; physical constants (mp, IR, NMR spectra) identical to those already published[27].

Method A : strain *F. oxysporum*, incubation time 72 h; isolated yield 31%; $[\alpha]_J^{25} = -45$ (c = 0.013, acetone); $ee_{(HPLC)} \geq 98$ %

Method B : isolated yield 40 %; reaction time 24 h; $[\alpha]_J^{25} = -23$ (c = 0.010, acetone); $ee_{(HPLC)} = 74$ %

Method C : solvent CH_2Cl_2; reaction time 6 h; isolated yield 90 %; [α] n.d; $ee_{(NMR)} = 65$ %, $\delta_S = 10.0$ ppm, $\delta_R = 9.74$ ppm.

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