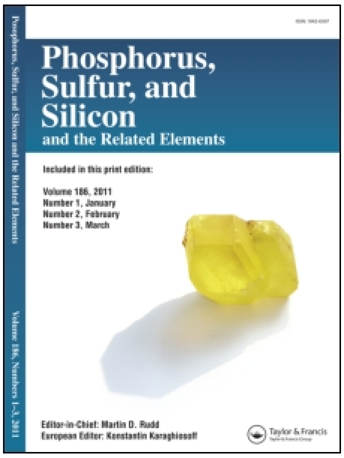

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SYNTHESIS OF CHIRAL SULFOXIDES BY ASYMMETRIC OXIDATION

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SYNTHESIS OF CHIRAL SULFOXIDES BY ASYMMETRIC OXIDATION

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The main chemical or enzymatic methods of asymmetric oxidation of sulfides are reviewed. A new approach to chiral sulfoxides is described, which uses tertiobutyl hydroperoxide in presence of a chiral titanium complex. The results obtained during the last two years are summarized. The best enantiomeric excess amounts to 95% in the case of formation of cyclopropyl phenyl sulfoxide.

INTRODUCTION

Asymmetric sulfoxides are useful chiral synthons allowing control of the formation of new asymmetric centers.[1-3] At some later stage of the synthesis the sulfinyl group can easily be removed by hydrogenolysis or thermal elimination. Among some of the achievements in asymmetric synthesis by the sulfoxide route it is appropriate to quote the preparation of β-hydroxyesters of β-hydroxy amides,[4,5] the asymmetric 1,4-addition to vinyl sulfoxides,[3] the asymmetric Diels-Alder reaction[6] and the total synthesis of hirsutene.[7] The development of the use of sulfoxides in asymmetric synthesis will depend in part of the easiness[1] to obtain both enantiomers of functionalized sulfoxides.

The main preparations of chiral sulfoxides currently available will be reviewed. Subsequently a new and simple method for the asymmetric oxidation of sulfoxides will be described. This method has been found in 1984; the results within the last two years will be summarized.[8-12]

MAIN ACCESSES TO CHIRAL SULFOXIDES

Several classes of reactions are able to produce to chiral sulfoxides (see ref[1-3] for reviews). The most useful transformation is the *Andersen method*,[13] further studied by Mislow,[14] which involves the esterification of a chiral alcohol R*OH by RSOCl. After separation of the diastereoisomeric sulfinates the desired sulfoxide is obtained by the reaction  $R-\underset{\overset{\|}{O}}{S}-OR^* + R'M \rightarrow R-\underset{\overset{\|}{O}}{S}-R'$ where R'M represents a Grignard reagent. Menthol is often used as the chiral auxiliary, some other alcohols such as cholesterol are also useful.[15] The difficulty of this process lies in the separation of the diastereomers for a wide variety of R groups.

Biochemical oxidations of prochiral sulfides were investigated by many authors. Henbest was one of the first to carry out a stereochemical study of a wide variety of sulfides using *Asp. Niger*.[16] The ee's of sulfoxides ranged between 14% (benzyl phenyl sulfoxide) and 99% (*p*-tolyl *t*-butyl sulfoxide). *Helminthosporium sp.* and

Mortarella isabellina produced methyl *p*-tolyl sulfoxide (S configuration, 100% ee) and (R configuration, 100% ee) respectively.[17] Dopamine β-hydroxylase catalyzes the conversion of phenyl 2-aminoethyl sulfides to the corresponding sulfoxides with a high stereoselectivity.[18] Reconstituted rabbit liver cytochrome P-450 was used by Oae *et al.*[19] in some asymmetric oxidations of sulfides. Thus *p*-tolyl *t*-butyl sulfoxide was obtained with 47% ee. *Cornybact. Equi.* oxidizes alkyl aryl sulfides and allyl aryl sulfides onto sulfoxides often mixed with sulfones.[20] Ee's of sulfoxides are in the range of 75 to 100%. Pig liver microsomal FAD-containing monooxygenase catalyzes oxygenation of many sulfides (ee's between 12 and 96%).[21] Oxidation by sodium metaperiodate in presence of bovine serum albumin in stoichiometric[22] or catalytic amounts[23,24] produce chiral sulfoxides (ee's $< 80\%$).

Chemical oxidation of sulfides by chiral reagents or catalysts was attempted as early as 1965. Montanari *et al.*[25] used various chiral peracids, unfortunately ee's lower than 10% were obtained. Metachloroperbenzoic acid or H_2O_2 in presence of β-cyclodextrin however are oxidant systems allowing up to 34%.[26,27]

Low ee's were also observed with a large variety of other chiral oxidants. For example iodine and a chiral diacid salt gave less than 6% ee,[28] *t*-BuOOH and $VO(acac)_2$ in presence of menthol gave ee $< 9\%$.[29] One of the most promising approaches seems to be the oxidation using a poly(L-valine)-coated platinum electrode (ee $< 93\%$).[30]

Oxygen transfer from chiral oxaziridines to sulfides was also quite successful,[31] allowing the synthesis of sulfoxides with ee's up to 70%.

In conclusion, it appears that in contrast to biochemical oxidations there does not yet exist a chemical method for sulfide asymmetric oxidation giving high ee's and with a sufficient degree of generality. Our own approach in this direction will now be described.

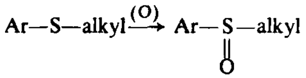
DISCOVERY OF A NEW ASYMMETRIC OXIDANT SYSTEM

Asymmetric epoxidation of allylic alcohols is now easily obtained with optical yields in the range of 95% thanks to the Sharpless procedure.[32] The Sharpless reagent is obtained by a 1 : 1 combination of $Ti(O\textit{i}Pr)_4$ and (+) diethyl tartrate (DET), the oxidant being *t*BuOOH. The stoichiometry is such that it remains around the titanium two exchangeable alkoxy group allowing coordination of the hydroperoxide and the allylic hydroxyl. By this way the epoxidation occurs intramolecularly through a highly organized transition state.

We checked that the Sharpless reagent oxidizes methyl *p*-tolyl sulfide into a mixture of racemic sulfoxide and sulfone.[8,9] However we discovered by serendipity that addition of one equivalent of water in respect to Ti suppresses the sulfone formation and gives methyl *p*-tolyl sulfoxide with ee in the range of 80%. Moreover we found it beneficial to use an excess of diethyl tartrate in respect to titanium, as also independently observed by Modena *et al.*[33]

The water-modified reagent is prepared at room temperature in CH_2Cl_2 by sequential addition to $Ti(O\textit{i}Pr)_4$ of 2 mol eq. of diethyl tartrate and 1 mol eq. of H_2O (the reverse order leads to partial hydrolysis of $Ti(O\textit{i}Pr)_4$). To the clear yellow solution is then added one equivalent of R—S—R′. The oxidation starts after

TABLE I



$$\text{Ar—S—alkyl} \xrightarrow{(O)} \text{Ar—}\underset{\underset{\displaystyle O}{\|}}{\text{S}}\text{—alkyl}$$

n°	Ar	Alkyl	Isolated[a] yield (%)	ee[b,c] (%)
1	Phe	Me	80	89
2	*p*-tolyl	Me	90	88
3	*p*-tolyl	Et	71	74
4	*p*-tolyl	n-Bu	75	20
5	*o*-tolyl	Me	75	89
6	*p*-$OMeC_2H_4$	Me	70	84
7	*o*-$OMeC_2H_5$	Me	63	77
8	1-naphthyl	Me	98	89
9	2-naphthyl	Me	88	90
10	2-naphthyl	Pr	78	24

[a] Reagent prepared with (+)-(R,R) diethyl tartrate.[9,10] Reactions performed in CH_2Cl_2, at 5 mmol scale, −20°C.

[b] Measured by ^1H nmr with a chiral shift reagent.[34]

[c] (+) sulfoxides (R-config.) are recovered.

addition of 1.1 mol eq. of *t*-BuOOH to the solution cooled at −20°C. Reaction time depends on the sulfide. After hydrolysis and filtration the optically active sulfoxide is easily recovered with a good yield by flash column chromatography. Its ee is measured by nmr, using a chiral amide as a new chiral shift reagent for sulfoxides.[34] The main results obtained at the 5 mmol scale are summarized in the next paragraphs.

OXIDATION OF ARYL ALKYL SULFIDES

Methyl aryl sulfides are oxidized in good yields and with enantiomeric excess often in the range of 80 to 90%, which is much higher than the previous asymmetric syntheses. Some representative results are indicated in Table I. Substituents on the aromatic ring do not drastically change the ee values, for example a methoxy group in ortho or para position leads to 84 and 77% ee, respectively.

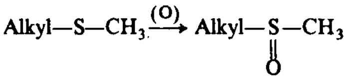
The reaction rate decreases with the introduction of electron withdrawing substituents on the aromatic system, a ρ-value of −1.02 was measured for $p\text{-R—C}_6\text{H}_4\text{—S—CH}_3$.[9]

Steric hindrance in the alkyl chain in Ar—S—alkyl gives a strong decrease in ee (for example see entries 3 and 4, Table I).

OXIDATION OF DIALKYL SULFIDES

The sulfoxides $\text{alkyl—}\underset{\underset{\displaystyle O}{\|}}{\text{S}}\text{—CH}_3$ were obtained with a reasonably good ee (50 to 70%) but always lower than when an aromatic ring is directly connected to the sulfur (Table II).

TABLE II

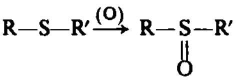


$$\text{Alkyl—S—CH}_3 \xrightarrow{(O)} \text{Alkyl—}\underset{\displaystyle O}{\overset{}{\underset{\|}{S}}}\text{—CH}_3$$

n°	Alkyl	Isolated[a] yield (%)	ee[b,c] (%)
1	*n*-octyl	77	71
2	*t*-butyl	72	53(R)
3	cyclohexyl	67	54
4	$Ph(CH_2)_3$	84	50

[a,b] See notes [a] and [b], Table I.
[c] (−) sulfoxides are recovered.

TABLE III



$$\text{R—S—R}' \xrightarrow{(O)} \text{R—}\underset{\displaystyle O}{\underset{\|}{S}}\text{—R}'$$

n°	R	R′	Isolated[a] yield (%)	ee[b] (%)
1	Ph	$CH{=}CH_2$	82	70
2	Ph	Cyclopropyl	73	95
3	Ph	CH_2CO_2Me	81	64
4	2-pyridyl	Me	63	77
5	Me	CH_2CO_2Et	84	63
6	Me	$(CH_2)_2CO_2Me$	85	64

[a,b] See notes [a] and [b] Table I.

OXIDATION OF FUNCTIONALIZED SULFIDES

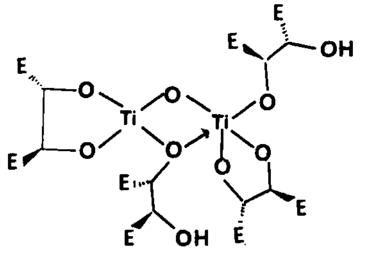
The reagent is a very smooth oxidant, which does not epoxidize double bonds (even in allylic alcohols) nor oxidize nitrogen heteroatoms. In addition it tolerates ester functions, a cyclopropane ring, ketones.... Some representative examples are indicated in Table III.

The good result obtained[10] in the oxidation of cyclopropyl vinyl sulfide is especially gratifying: there is no ring opening and the ee is close to 95%.

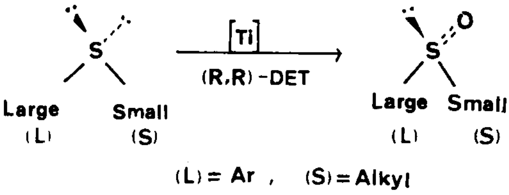
The oxidation of R—S—S—R into thiosulfinate does not give very good yield nor ee. However $\text{Me—}\underset{\displaystyle O}{\underset{\|}{S}}\text{—S—Me}$ could be isolated for the first time in an optically active form (32% ee).[12] Oxidation of R—S—CH_2—S—R into a monosulfoxide was cleanly achieved but the ee's were low (for example ee = 40% when R = Me).[10]

MECHANISM OF THE ASYMMETRIC OXIDATION

The structure of the Sharpless reagent ($Ti(O\textit{i}Pr)_4$/DET = 1 : 1) is presumably dimeric with tartrate units acting as bidentate ligands on each titanium.[35] In our case the excess of DET must replace all the O*i*Pr groups: the controlled addition of



1 (E = CO$_2$Et)



SCHEME 1

water hydrolyses Ti—OR bonds leading to Ti—OH which is prone to give Ti—O—Ti units. Molecular weight in solution for our reagent shows a dimeric structure. It is presently very difficult to propose a formula for the active species, tentatively structure **1** could be postulated for the complex formed prior to the addition of *t*-BuOOH. We believe that there is a delicate balance between several catalytic species according to the experimental conditions. For example, it was found[12] a dramatic solvent effect on the asymmetric oxidation of methyl *p*-tolyl sulfide: 85% ee in CH_2Cl_2, 70% ee in CH_3Cl and close to 0% in CCl_4.

The mechanistic details of the system (does the hydroperoxide lead to a titanium peroxide, does the sulfide coordinate to titanium prior to its oxidation?) remain to be established. The stereochemistry of the reactions is well described by Scheme 1. In this scheme L and S stand for groups sterically large and small respectively, the influence of aromatic rings seems mainly due to electronic factors. This scheme holds well for simple sulfides, polyfunctional molecules could lead to anomalies because of additional interactions with Ti.

CONCLUSIONS

A simple method is now available for the oxidation of a wide variety of prochiral sulfides. The reaction is very smooth, allowing selective oxidation of functionalized sulfides. Some improvements are however necessary: obtaining ee's above 90% e and modification of the procedure in order to use a catalytic amount of titanium complex. We are currently actively working in this area.

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