

Catalytic asymmetric oxidation of aryl methyl sulfides mediated by a (*S,S*)-1,2-diphenylethan-1,2-diol/titanium/water complex

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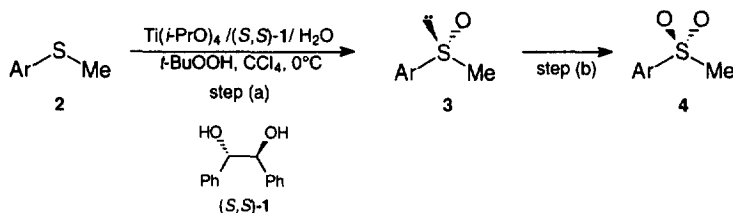
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Abstract: The asymmetric oxidation of aryl methyl sulfides to sulfoxides with hydroperoxides has been achieved using catalytic amounts of the complex formed in situ between $\text{Ti}(i\text{-PrO})_4$, (*S,S*)-diphenylethan-1,2-diol **1** and water. The sulfoxides are obtained in 60% yield and 67–80% enantiomeric excess. © 1997 Elsevier Science Ltd. All rights reserved.

Optically active sulfoxides constitute a class of compounds having a large interest as chiral auxiliaries in asymmetric synthesis¹ and as intermediates in the pharmaceutical industry.² Amongst the methods employed for their preparation, one of the most efficient is the asymmetric oxidation of prochiral sulfides with hydroperoxides in the presence of stoichiometric amounts of Ti(IV) –chiral ligand complexes, which provides aryl alkyl sulfoxides in very high ee's.³ The *catalytic* version of this reaction looks even more appealing but affords high ee only in a few cases.^{3b,4} We then started an investigation aimed at finding a simple and efficient catalytic procedure for this reaction.

Considering that the chiral ligands employed in the reported procedures are hydroxylated compounds (diethyl tartrate,^{3,4d} 2,2'-dihydroxy-1,1'-binaphthyl^{4a} and trialkanolamines^{4c}), we decided to test the catalytic efficiency of some enantiopure 1,2-diarylethan-1,2-diols. As a matter of fact early studies showed their effectiveness in Ti(IV) mediated stoichiometric asymmetric sulfoxidation,⁵ these compounds are now easily accessible by catalytic asymmetric dihydroxylation of olefins (Sharpless method)⁶ and, finally, they can be stereochemically characterized by means of a reliable and simple method recently set up.⁷ Herein we describe the results obtained in the asymmetric oxidation of aryl methyl sulfides with organic hydroperoxides in the presence of catalytic amounts of a complex formed in situ by reacting $\text{Ti}(i\text{-PrO})_4$, (*S,S*)-1,2-diphenylethan-1,2-diol **1** and water (Scheme 1).

The results obtained carrying out the enantioselective oxidation of phenyl methyl sulfide (used as test molecule) in different experimental conditions are collected in Table 1. At the beginning we adopted conditions as those described by Uemura using binaphthol as chiral ligand^{4a}: sulfide/(*S,S*)-**1**/ $\text{Ti}(i\text{-PrO})_4/\text{H}_2\text{O}=1.0/0.05/0.025/0.5$ in CCl_4 at 20°C (method A) and *tert*-butyl hydroperoxide (TBHP) as oxidant. Running the reaction in air (run 1) the phenyl methyl sulfoxide was obtained in a satisfactory



Scheme 1.

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Table 1. Catalytic asymmetric oxidation of phenyl methyl sulfide^a

run	Ar	solvent	T(°C)/time (h)	oxidant (eq.) ^b	sulfone (%)	sulfoxide (%)	ee ^c (%) (abs. conf.) ^d
1 ^e	Ph	CCl ₄	20/18	1.0	51	42	78(R)
2	Ph	CCl ₄	20/18	1.5	40	43	84(R)
3	Ph	CCl ₄	0/4→20/18	1.4	25	60	74(R)
4	Ph	CCl ₄	0/18	1.0	30	60	74(R)
5	Ph	CCl ₄	20/18	1.0 ^f	20	50	66(R)
6	Ph	CH ₂ Cl ₂	0/4→20/18	1.0	4	60	50(R)
7	Ph	THF	20/18	1.0	5	40	20(R)

^a Method A: sulfide/(*S,S*)-1/Ti(*i*-PrO)₄/H₂O = 1.0/0.05/0.025/0.5 under N₂ atmosphere. ^b TBHP 70% in water. ^c Determined by HPLC on a Daicel Chiralcel OB column. ^d Determined by comparison of the specific rotation with reported values, see ref. 3. ^e Under aerial conditions. ^f CHP 80% in cumyl alcohol.

78% ee, but in low yield (42%) owing to an over-oxidation to sulfone which actually resulted the major product of the reaction. The formation of sulfone in addition to reduce the yield of the sulfoxide could be responsible of the ee obtained because of the phenomenon of kinetic resolution which has been observed in similar conditions.^{4,8} Since we were mainly interested in evaluating the inducing efficiency of (*S,S*)-1 in the oxidation of the sulfide only (step (a)) and to have a high chemical yield of sulfoxide, we changed the reaction conditions with the aim to minimize the formation of the sulfone and the consequent kinetic resolution process. Working under N₂ did not have much effect (run 2) neither working at lower temperature (runs 3 and 4) nor using cumene hydroperoxide (CHP) as oxidant (run 5), which in addition afforded lower ee. The effect of changing the solvent to CH₂Cl₂ (run 6) or THF (run 7) was quite beneficial, because the formation of sulfone was reduced to a few percent, but unfortunately the ee of the product became significantly lower.

Monitoring the reaction mixture by GLC-MS we observed, after 2 hours at 0°C, formation of by-products⁹ probably due to decomposition of diol 1 both *via* pinacol-type transposition and *via* degradative oxidation. At that time the yield of sulfoxide was 50–60%. The increase of conversion obtained either extending the reaction time, or adding more TBHP, or raising the temperature, only resulted in an increase of the amount of sulfone without raising neither the yield nor the ee of the sulfoxide. We then performed some exploratory runs in order to better understand the processes active in our reaction conditions. We observed that the diol 1 slightly decomposes giving the above mentioned products in presence of Ti(*i*-PrO)₄ alone, that the addition of water does not cause any other changes, while an extensive decomposition to benzaldehyde results after further addition of TBHP. From these trials we can conclude that the diol is decomposed mainly by action of TBHP and to a minor extent *via* complexation with Ti(*i*-PrO)₄. We also realized that TBHP alone does not oxidize the sulfoxide while promotes a slow oxidation of the sulfide. We can then expect that after the decomposition of the diol, and then of the chiral catalyst, we have a non-enantioselective oxidation of sulfide by TBHP alone and so further extension of the reaction time could even give rise to a decrease of ee. For these reasons and in order to limit the sulfone formation we tried to find the best conditions by speeding up the reaction. We then raised the quantity of catalyst up to 0.05 equiv., we doubled the amount of oxidant at 2 equiv., and fixed the reaction temperature at 0°C (method B).¹⁰

These conditions allowed us to perform the reaction in 2 hours, limiting the formation of sulfone and affording phenyl methyl sulfoxide in a satisfactory 60% chemical yield and 80% ee (Table 2, run 1). It is worth noting that now the optically active sulfoxide is formed only in the sulfide oxidation because the kinetic resolution process is almost completely suppressed. Using the same method B (Table 2) other sulfides have been enantioselectively oxidized (runs 2–5) affording the relative sulfoxides in fair chemical yield (50–62%) and 67–80% ee's, still maintaining the amount of sulfone below 11%.

Table 2. Catalytic asymmetric oxidation of aryl methyl sulfides (ArSMe)^a

run	Ar	solvent	T(°C)/time (h)	oxidant (eq.) ^b	sulfone (%)	sulfoxide (%)	ee ^c (%) (abs. conf.) ^d
1	Ph	CCl ₄	0/2.5	2.0	8	60	80(R)
2	<i>p</i> -Tolyl	CCl ₄	0/2	2.0	8	62	80(R)
3	<i>p</i> -MeOC ₆ H ₄	CCl ₄	0/2	2.0	11	56	67(R)
4	<i>p</i> -BrC ₆ H ₄	CCl ₄	0/2	2.0	4	50	67(R)
5	2-Naphthyl	CCl ₄	0/2	2.0	9	61	71(R)

^a Method B: sulfide/(*S,S*)-1/ Ti(*i*-PrO)₄/H₂O = 1.0/0.1/0.05/1.0 under N₂ atmosphere. ^b TBHP 70% in water, ^c Determined by HPLC on a Daicel Chiralcel OB column. ^d Determined by comparison of the specific rotation with reported values, see ref. 3.

Table 3. Separation of aryl methyl sulfoxides (ArSOMe) on CSP Daicel Chiralcel OB

run	Ar	eluent (hexane : IPA)	flow (mL/min)	K ₁	α	enantiomer 1 st eluted
1	Ph	80 : 20	0.8	2.69	1.95	(<i>S</i>)
2	<i>p</i> -Tolyl	80 : 20	0.8	1.86	2.74	(<i>S</i>)
3	<i>p</i> -MeOC ₆ H ₄	80 : 20	0.8	3.53	2.29	(<i>S</i>)
4	<i>p</i> -BrC ₆ H ₄	80 : 20	0.5	2.26	1.48	(<i>S</i>)
5	2-Naphthyl	80 : 20	0.5	3.17	1.47	(<i>S</i>)

The results of this sulfoxidation procedure are almost unaffected by the substituents on the aromatic ring of the substrate and we also observed that (*S,S*)-**1** always induces *R* absolute configuration in these sulfoxides. Both these behaviours parallel what is observed in sulfoxidations catalyzed by (*R,R*)-diethyl tartrate.^{3,11} A further observation concerns the determination of the ee of the products: as reported in Table 1 and Table 2 this has been carried out by means of the Chiralcel OB CSP,¹² which efficiently separates all the above compounds. Interestingly, the *S* antipode is always eluted first even changing the nature of the Ar group quite significantly (Table 3). This homogeneity of elution order could be used to assign the absolute configuration of ArSOMe and to understand the mechanism of enantioselection of this CSP.

In conclusion herein we described a novel *catalytic* system (Ti(*i*-PrO)₄, (*S,S*)-1,2-diphenylethan-1,2-diol **1** and water) for the enantioselective oxidation of aryl methyl sulfides. The use of a catalytic amount of the above system makes the workup easier and the procedure economic. This simple protocol constitutes a particularly rapid, efficient and general method for asymmetric sulfoxidation of aryl methyl sulfides.

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9. GLC-MS revealed the presence of 1,2-diphenylethan-1,2-dione, 1,2-diphenylethanone, 1,1-diphenyl-ethanone and benzaldehyde.
10. *Typical Experimental Procedure*: To a suspension of (*S,S*)-**1** (34.3 mg, 0.16 mmol) in CCl₄ (5 mL) were added in sequence and dropwise Ti(*i*-PrO)₄ (23.6 μL, 0.08 mmol) and H₂O (28.8 μL, 1.6 mmol). To the resulting homogeneous solution was added phenyl methyl sulfide (189 μL, 1.61 mmol), stirring at room temperature for 15 min. The solution was then cooled at 0°C and TBHP (70% in water, 440 μL, 3.22 mmol) added. The mixture was left stirring at 0°C for 2 hours, then diluted with CH₂Cl₂ and dried with Na₂SO₄ for a few minutes. After filtration and evaporation of solvent the residue was immediately chromatographed on a TLC plate (Et₂O as eluent) isolating the phenyl methyl sulfoxide in 60% yield.
11. (*R,R*)-diethyl tartrate despite an inversion due to the CIP rules, has the same stereostructure of (*S,S*)-**1**.
12. The CSP Daicel Chiralcel OB has been used also by other authors (ref. 4a) to separate chiral sulfoxides.

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