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Catalytic enantioselective oxidation of sulfides to sulfoxides with a renewable hydroperoxide

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Abstract—The catalytic asymmetric oxidation of prochiral sulfides can be conveniently performed by using an easily accessible and renewable furyl hydroperoxide in the presence of the chiral Ti(*O*-*i*-Pr)$_4$/BINOL/H_2O system. © 2001 Published by Elsevier Science Ltd.

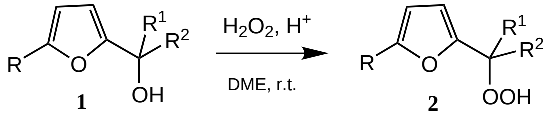
In recent years the ever increasing importance of chiral, non-racemic sulfoxides, both as bioactive compounds and chiral auxiliaries, has stimulated the development of new synthetic procedures involving stoichiometric or catalytic conditions.[1,2] In particular, the enantioselective oxidation of prochiral sulfides represents the most direct approach and many asymmetric processes are based on the use of a commercially available hydroperoxide (*t*-butyl or cumyl hydroperoxide) as oxidant and on the in situ formation of a catalytic species by reaction of Ti(*O*-*i*-Pr)$_4$ with a chiral ligand (examples of ligands used previously include tartrate esters,[3] binaphthols,[4–6] trialkanolamines[7] or variously substituted 1,2-diols[8,9]).

Our previous researches pointed out the importance of the role played by the structure of the hydroperoxide on the efficiency and enantioselectivity of the asymmetric sulfoxidation, so that high yields and enantiomeric excesses could be obtained by using functionalized furylhydroperoxides.[10,11] Furthermore, in the course of recent investigations concerning the synthesis and reactivity of renewable hydroperoxides[12] we have shown that simple secondary furylhydroperoxides of type **2** ($R=Me$, H; $R^1=H$; $R^2=$alkyl) (Scheme 1), easily accessible by treatment of the corresponding furyl alcohols **1** with H_2O_2 in acidic medium, could be very conveniently employed as oxidants for the enantioselective oxidation of sulfides in the presence of the Ti(*O*-*i*-Pr)$_4$/L-DET system under stoichiometric conditions.

Herein, we wish to report that asymmetric sulfoxidation can be achieved under catalytic conditions by a suitable modification of Uemura's approach, based on the use of the tertiary hydroperoxide **2a** ($R=H$; $R^1=R^2=Me$), available in 70% isolated yield according to the procedure reported in Scheme 1. In fact, in the presence of (*R*)-$2,2^1$-dihydroxy-$1,1^1$-binaphthyl (BINOL) (0.2 equiv.) as chiral ligand, Ti(*O*-*i*-Pr)$_4$ (0.1 equiv.) and H_2O (2 equiv.) the formation of the corresponding sulfoxides **4** took place with good yields and e.e. (Scheme 2, Table 1).

A set of experiments performed on methyl *p*-tolyl sulfide (entries 1–3) pointed out the dependence of the level of efficiency and enantioselectivity of the oxidation on the reaction time. The 49% e.e. value (entry 1), observed at the initial stage of the reaction (3 h), improved with time to 87%, while the corresponding yield of sulfoxide decreased from 71 to 63% and, furthermore, significant amounts of sulfone (37%) were isolated. These results could be explained assuming the occurrence of a kinetic resolution process that followed the asymmetric oxidation, thus enhancing the e.e. of the sulfoxide.

This assumption was confirmed by submitting (±)-methyl *p*-tolyl sulfoxide to treatment with **2a** in the presence of the usual catalytic amount of Ti(IV)/(*R*)-BINOL/H_2O system. After 19 h the expected sulfone was obtained in 37% yield, while the starting material



Scheme 1.

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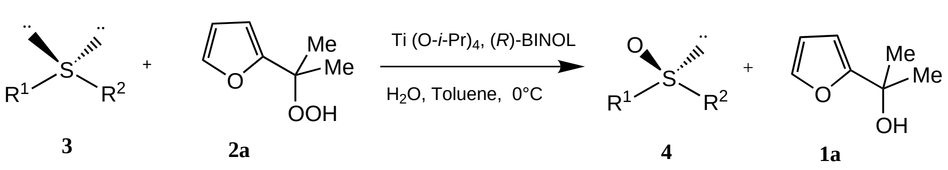

Scheme 2.

Table 1. Asymmetric sulfoxidation under Uemura's condition using **2a**[a]

Entry	R^1	R^2	Time (h)	Yield (%)[b,c]	E.e. (%)[d]
1	Me	p-MeC_6H_4	3	71 (n.d.)[e]	49
2	Me	p-MeC_6H_4	5.5	75 (n.d.)[e]	61
3	Me	p-MeC_6H_4	24	63 (37)	87
4	Me	p-ClC_6H_4	16.5	67 (33)	80
5	Me	C_6H_5	16	69 (25)	85
6	Me	p-$MeOC_6H_4$	16	59 (16)	93
7	Et	C_6H_5	5[f]	56 (16)	56
8	Me	p-BrC_6H_4	17	79 (21)	51
9	Me	p-$CH_2C_6H_5$	23	95 (5)	51
10	Me	p-MeC_6H_4	24	79 (14)	80

[a] Typical experimental procedure: to a solution of binaphthol (0.10 mmol) in dry toluene (5.5 mL) were added Ti(O-i-Pr)$_4$ (0.050 mmol) and H_2O (1.0 mmol) under an argon atmosphere at room temperature. After the resulting brown solution was stirred at room temperature for 1 h, the sulfide (0.50 mmol) was added and the mixture was cooled to the appropriate temperature. After 0.5 h a solution of furyl hydroperoxide (1.0 mmol) in dry toluene (2.0 mL) was introduced. After TLC had shown that conversion was complete, the reaction mixture was directly filtered on a short pad of SiO_2. The crude mixture was further purified by flash chromatography to afford the pure sulfoxide.

[b] All the yields refer to isolated chromatographically pure compounds (of (R)-configuration) whose structures were confirmed by spectroscopic data (IR, ^1H and ^{13}C NMR).

[c] Values in parentheses refer to the recovered sulfone.

[d] E.e.s were determined by HPLC on a Daicel Chiralcel OB.

[e] n.d. = not determined.

[f] This reaction was performed at rt.

was recovered in 63% yield with 41% e.e. ((R)-enantiomer predominant) highlighting that the preferential oxidation of the minor component, the (S)-sulfoxide, to sulfone was responsible for the observed enantiomeric enrichment (stereoselection factor $S = 13.4$ calculated according to Ref. 13).

The reaction temperature did not appear to exert a significant influence on the oxidation step: in fact, when the experiment reported in entry 1 was repeated at room temperature, methyl p-tolyl sulfoxide was obtained in 69% yield, while a slight increase in e.e. (56% relative to 49%) was observed.

Rather interestingly, a promising result was obtained performing the reaction in the presence of 10% mol of Ti(O-i-Pr)$_4$/(R)-BINOL/H_2O system (1/1/2 molar ratio). In fact, the oxidation to sulfoxide proceeded with an appreciable level of enantioselectivity (80% e.e.) and higher efficiency and chemoselectivity since the corresponding sulfone was isolated in only 14% yield (entry 10).

It is noteworthy that, with the exception of entry 8, this catalytic procedure affords chiral aryl methyl sulfides in good yields and very satisfactory e.e. When the methyl group was replaced with an ethyl group (entry 7) the starting material was found to be almost completely unreactive under the standard conditions and the reaction had to be performed at room temperature.

In conclusion, chiral sulfoxides are conveniently available through a suitable combination of the enantioselective oxidation of sulfide and the convergent kinetic resolution of the resulting enantiomerically enriched mixture, proceeding with good stereoselection factors. This catalytic procedure proves to be more environmentally acceptable and resource-saving, since no halogenated solvent is required (as in the similar approach of Uemura) and the hydroperoxide **2a** can be easily regenerated according to Scheme 1 thanks to the efficient recover of furylalcohol **1a** by chromatographic techniques.

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