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Asymmetric Oxidation with Furylhydroperoxides

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Abstract: Chiral sulfoxides are accessible with very satisfactory enantiomeric excesses through a modified Sharpless procedure, based on the employment of furylhydroperoxides. Racemic hydroperoxides are found to undergo a kinetic resolution in the course of the asymmetric oxidation. Copyright © 1996 Elsevier Science Ltd

Optically active sulfoxides are often employed as chiral synthons or as chiral auxiliaries[1] and one of the typical procedures of synthesis involves the asymmetric oxidation of sulfides through the t-butyl hydroperoxide/$Ti(OiPr)_4$/dialkyl tartrate/H_2O system[2]. Furthermore, the introduction of an aromatic group in the oxidant (and consequently the substitution for example, of t-butyl hydroperoxide with cumyl hydroperoxide) was shown to have a beneficial effect on enantioselectivity so that, in many cases, sulfoxides can be obtained in >90% e.e.[3].

In our previous papers we reported an efficient route to a new class of hydroperoxides, i.e. furylhydroperoxides[4] of the type **1**, and their employment in a modified diastereoselective procedure of Sharpless epoxidation[5] . Since few hydroperoxides have been routinely used (essentially only t-butyl hydroperoxide and cumyl hydroperoxide) in asymmetric oxidation processes, we decided to examine the reactivity of compounds **1** , characterized by the presence of a functionalized heteroaromatic ring.

These first results refer to asymmetric oxidations of sulfides **2** under the conditions proposed by Modena[6] and the easily available hydroperoxide **1a** was chosen as representative oxidant. In effect, we have found that when the reactions were carried out using $Ti(OiPr)_4$/**1a**/**2**/L-DET in 1/1/1/4 molar ratios, the formation of chiral sulfoxides takes place in very satisfactory way (Scheme 1, Table 1).

Scheme 1

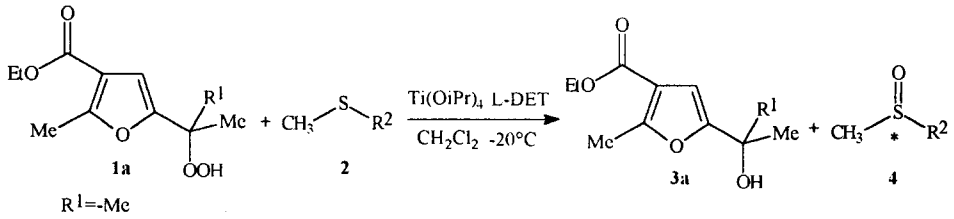


Table 1- Asymmetric oxidation of sulfides by furylhydroperoxide 1a (R^1=-Me)[a)]

Entry	R^2	Yield(%)[b)]	e.e.(%)[c)]
1	C_6H_5-	79	91
2	p-Me-C_6H_4-	53	90
3	$C_6H_5CH_2$-	75	74
4	C_8H_{17}-	77	78

[a)]All the reactions have been carried out using $Ti(OiPr)_4$/**1a**/**2**/L-DET in 1/1/1/4 molar ratio. [b)]All the yields refer to isolated chromatographically pure compounds, obtained as R prevalent enantiomer. [c)]e.e. have been determined by ^{1}H-NMR analysis in the presence of R-(-)-(3,5-dinitrobenzoyl)-α-methylbenzyl amine as shift reagent

In particular, enantiomeric excesses observed in entries 3 and 4 (Table 1) are very interesting in consideration of the fact that often asymmetric oxidation of dialkyl sulfides proceeds with moderate enantioselectivity.

Although tertiary hydroperoxides have usually afforded the best results, both in terms of chemical yields and enantiomeric excesses, a representative sulfide (methyl p-tolyl sulfide) was submitted to the action of some secondary hydroperoxides **1b-e** in order to examine the influence of a stereogenic centre in the oxidant (Scheme 2).

Scheme 2

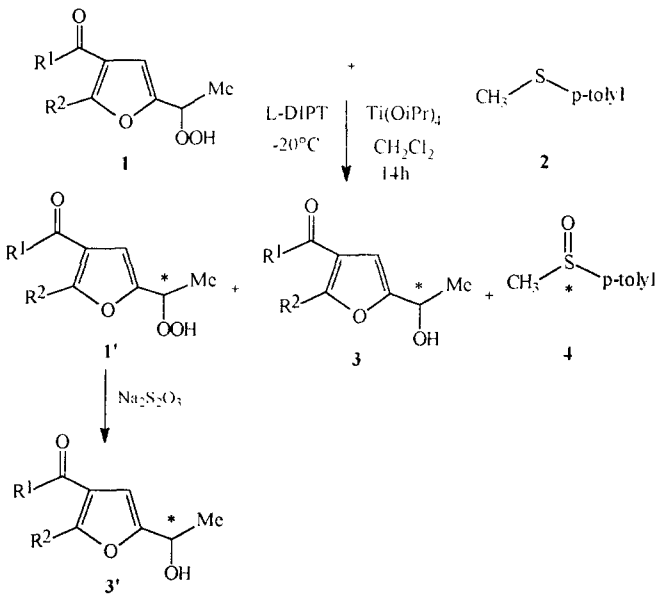


Table 2- Asymmetric oxidation of methyl p-tolyl sulfide with secondary furylhydroperoxide 1b-e[a)]

Entry	1	R^1	R^2	4		1'		3	
				(yield%)[b)]	(e.e.%)[c)]	(yield%)[b)]	(e.e.%)[d)]	(yield%)[b)]	(e.e.%)[e)]
1	b	-OEt	-Me	51	81	20	68	72	23
2	c	-OMe	$-(CH_2)_2OMe$	74	77	24	63	68	28
3	d	-OEt	-iPr	75	95	25	81	68	30
4	e	$-(CH_2)_5-$		48	>95	22	78	74	23

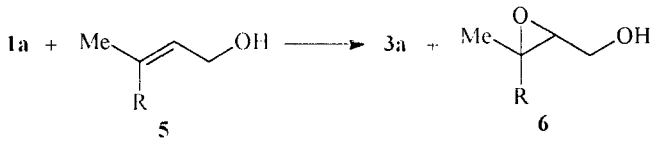
[a)]All the reactions have been carried out using Ti(OiPr)4/L-DIPT/1/sulfide in 1/4/2/1 molar ratios.[b)]All the yields refer to isolated chromatographically pure compounds. In all entries methyl p-tolyl sulfone was isolated in about 15% yield as over-oxidation product.[c)]e.e. have been determined by ^{1}H-NMR analysis in the presence of R-(-)-N-(3,5-dinitrobenzoyl)-α-methylbenzyl amine as shift reagent.[d)]e.e. have been determined by ^{1}H-NMR analysis in the presence of tris[3-(heptafluoropropylhydroxymethylene-(+)-camphorato]europium(III) as shift reagent on the corresponding 3'.[e)]e.e. have been determined by ^{1}H-NMR analysis in the presence of tris[3-heptafluoropropylhydroxymethylene-(+)-camphorato]europium(III) as shift reagent

In effect we have found, that, under conditions reported in Table 2, the formation of the chiral sulfoxide again takes place with very high enantioselectivity (entries 3 and 4) and more interestingly, the asymmetric oxidation involves a kinetic resolution of the racemic hydroperoxides **1**. Since unreacted hydroperoxide **1'** can be easily reduced to the corresponding alcohol by treatment with aqueous 0.1 M $Na_2S_2O_3$, it has to be noted that four enantiomerically enriched compounds can be obtained simultaneously.

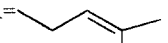
This promising result has to be considered one of the few examples of kinetic resolution of hydroperoxides by non-enzymatic catalysts[7]; the opportunity of obtaining optically active hydroperoxides is of particular interest in asymmetric synthesis, because they can be used as stereoselective oxidizing reagents. Moreover this route also gives access to enantiomerically enriched 2-furylcarbinols and these compounds are important building blocks for the synthesis of natural products such as monosaccharides, pheromones, pyranones[8].

Finally, the first attempts to use **1a** in a modified procedure for Sharpless epoxidation of allylic alcohols[9] have afforded encouraging results since epoxyalcohols **6a,b** have been obtained with very high enantiomeric excesses[10] (Scheme 3).

Scheme 3



6a: R=-Me yield 50% e.e.> 95%

6b: R=  yield 75% e.e.> 95%

Experimental: in a typical experimental procedure a mixture of $Ti(OiPr)_4$ (1mmol), L-DET (4mmol), **2** (1mmol) in 7 ml. of CH_2Cl_2, stored on molecular sieves, is stirred at -20°C for 20 minutes. Then **1**, dissolved in

7 ml. of CH_2Cl_2 is added and the reaction is monitored on TLC. Water (0.4 ml.) is added to the solution at -20°C and a vigorous stirring is maintained for one hour at room temperature. The gel is filtered over celite and thoroughly washed with CH_2Cl_2.The crude product is purified by flash chromatography. Elution with n-hexane/ethyl acetate mixtures affords pure **1**, **3**, **4**. For the epoxidation of **5a** and **5b** we used the stoichiometric Sharpless procedure.

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10. e.e. have been determined by ^{1}H-NMR analysis on the corresponding acetyl derivatives in the presence of tris[3-(heptafluoropropylhydroxy-methylene-(+)-camphorato]europium(III) as shift reagent.

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