Tetrahedron Letters,Vol.25,No.10,pp 1049-1052,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

AN EFFICIENT ASYMMETRIC OXIDATION OF SULFIDES TO SULFOXIDES

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Abstract

The Sharpless reagent ($Ti(OiPr)_4$ + 1 mol eq. diethyl tartrate (DET) + 2 t-BuOOH) modified by addition of one mol eq. H_2O gives a new homogeneous reagent which cleanly oxidizes sulfides into sulfoxides in dichloromethane. The best results were obtained for the stoichiometry Ti/DET/H_2O/t-BuOOH = 1:2:1:2. The e.e. observed ranged from 4 to 93% with the highest beeing observed in the case of methyl p-tolyl sulfoxide.

Chiral sulfoxides are gaining considerable importance in synthesis as chiral synthons for asymmetric C-C bond formation[1-4]. The main synthesis of chiral sulfoxides is based on the separation of intermediate diastereomeric menthyl sulfinates[5-8]. Chemical asymmetric oxidation of prochiral sulfides is not a preparative method for chiral sulfoxides although moderate to high enantiomeric excesses have been observed in some cases[9-13]. We wish to present a simple method for the oxidation of some sulfides into optically active sulfoxides, with e.e. up to 93% in one case. We found that the Sharpless reagent for asymmetric epoxidation of allylic alcohols[14] can be used for the sulfide oxidation with a modified procedure.

We selected methyl p-tolyl sulfide (1) as a model substrate. The standard Sharpless method for epoxidation of allylic alcohols ($Ti(OiPr)_4$, (R,R)-diethyl tartrate (DET), t-BuOOH (TBHP), 1:1:2 in CH_2Cl_2, - 20°C) leads to racemic methyl p-tolyl sulfoxide(2). However, the combination $Ti(OiPr)_4$/(R,R)-DET/H_2O/TBHP, 1:(1 or 2):1:2, gives a dramatic change in the enantiomer composition (84 or 91% e.e. respectively, at - 20°C). A perfectly soluble species is formed in these conditions and it is critical to avoid an excess of water (> 4-5 equivalents), which leads to precipitation (presumably TiO_2). The chemical yield is satisfactory and sulfone formation is always negligible.

The procedure for sulfide oxidation is exemplified in the case of 1. $Ti(OiPr)_4$ (1.49 mL, 5 mmol) and (R,R)-DET (1.71 mL, 10 mmol) are dissolved at 25°C in 50 mL CH_2Cl_2 under nitrogen. H_2O 90 µl, 5 mmol) is introduced through a septum via microsyringe. Stirring is maintained until the yellow solution becomes homogeneous (15-20 min) and 1 (0.7 g, 5 mmol) is added. The solution is cooled to - 20°C, and 5 mL (10 mmol) of a CH_2Cl_2 solution of TBHP (2M)[14a] is introduced. The solution is kept at - 20°C for 4 h. Introduction of 10 mL of H_2O to this cooled solution gives a white gel which is stirred 1 h (- 20°C → + 20°C) and filtered. The filtrate is well washed with CH_2Cl_2. The combined organic layers are then washed with NaOH (1N) and brine, dried over Na_2SO_4 and concentrated to give a white paste. Chromatography (AcOEt, cyclohexane 1:1) on silica gel gives 0.7 g (90%) of (R)-2 ; $\{\alpha\}_D^{20}$= + 132.5° (c=2, acetone), mp 67-69°C (lit. data for pure (R)-2 : $\{\alpha\}_D^{20}$ = + 145.5° (acetone) ; mp 73-74.5°C)[6].

The reagent was used for asymmetric oxidation of several types of sulfides. The results are indicated in Table 1, taking - 20°C as standard reaction temperature. It appears that in the series of S-alkyl p-tolyl sulfide the optimum e.e. is obtained when alkyl = Me. It is interesting to see that a substrate such as 1, which is not able to form a chelate on titanium, leads to almost enantiomerically pure sulfoxide 2. We established that the sulfoxide is not obtained by a combination of asymmetric synthesis and kinetic resolution (of sulfoxide). Treatment of racemic sulfoxide 2 by the reagent does not produce sulfone.

It has been assumed that the system ($Ti(OiPr)_4$ + DET, 1:1) is a dimer with alcohol interchanges giving two tartrate units acting as bridges between the two metal centers[16]. Infra-red spectroscopy shows two ester-bands (1735 cm^{-1} free ; 1635 cm^{-1} chelated). We found the following situation after the controlled addition of 1 equivalent of water to ($Ti(OiPr)_4$ + DET ; 1:1) : the two band system (1735 cm^{-1}, 1635 cm^{-1}) immediately transformed into a new one (1740 cm^{-1}, 1670 cm^{-1}), almost superimposable on the one obtained with two equivalents of DET versus $Ti(OiPr)_4$. It appears that a similar species has been obtained and indeed we observed that the combination 2 DET + 1 $Ti(OiPr)_4$ is almost as stereoselective as the reagent incorporating water (in the conditions of Table 1, - 20°C, (R)-methyl p-tolyl sulfoxide was thus obtained with 70% e.e.). Finally, we got the best result with a reagent containing 2 diethyl tartrate and 1 water equivalent. The water molecule presumably promotes the formation of an oxo bridge between two titaniums.

We are currently investigating the scope and various mechanistic and synthetic aspects of this new asymmetric synthesis of sulfoxides, where the highest enantiomeric excesses known for asymmetric oxidation of sulfides by a purely chemical system were obtained.

Table 1

Asymmetric oxidation of various sulfides

Sulfide	Reactions conditions[a]		e.e.(%)[b]	Sulfoxide configuration	Yield(%)[c,d]
Methyl p-tolyl sulfide 1	- 20°C	4 h	91	(R)	90
"	- 40 → - 24°C	12 h	93	(R)	95
"	+ 1°C	1.5 h	75	(R)	90
"	+ 21°C	20 min	47	(R)	90
"	+ 41°C	10 min	21	(R)	90
Ethyl p-tolyl sulfide	- 20°C	3 h	74	(R)	71
i-propyl p-tolyl sulfide	- 20°C	3 h	63	(R)	56
n-butyl p-tolyl sulfide	- 20°C	3 h	20	(R)	28
Benzyl p-tolyl sulfide	- 20°C	12 h	7	(R)	41
Mesityl p-tolyl sulfide	- 20°C	24 h	-	-	0
t-butyl (p-toluene-thio) acetate	+ 20°C	1 h	4	(R)	66
Methyl phenyl sulfide	- 20°C	12 h	89	(R)	81

a $[\text{Sulfide}] = [\text{Reagent}] = 2\text{x}10^{-1}$ M in CH_2Cl_2, under nitrogen atmosphere. Reagent :$Ti(OiPr)_4$ + (R,R)-diethyl tartrate + H_2O + TBHP (1:2:1:2).

b Measured by the specific rotation of isolated sulfoxides using for the maximum specific rotations the values given in ref[2,6].

c Isolated yields for reactions at the 5 mmol scale and expressed with respect to $Ti(OiPr)_4$

d The starting material accounts for the remainder, sulfone was not detected.

Acknowledgements

We thank CNRS for its financial support. One of us (P.P.) acknowledges DGRST for a fellowship.

We thank Professor K.B.Sharpless for useful discussions and communication of unpublished data.

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(Received in France 9 December 1983)