Asymmetric Oxidation of Sulphides to Sulphoxides Catalysed by Titanium Complexes of *N*-Salicylidene-L-amino Acids

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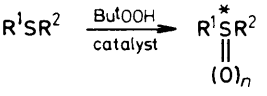
Oxidation of alkyl aryl and heterocyclic sulphides with Bu^{t}OOH and a catalytic amount of titanium *N*-salicylidene-L-amino acids (0.1 mol equiv.) affords the corresponding sulphoxides with an enantiomeric excess (e.e.) up to 21%. The use of other metal complexes with the same ligands led to racemic products.

Optically active sulphoxides constitute a group of chiral compounds for asymmetric synthesis, particularly useful in carbon–carbon bond formation.[1] They can be prepared starting from easily available, diastereoisomerically pure sulphinate esters *via* an Andersen[2] reaction with Grignard reagents, a procedure which has been recently improved by Mikolajczyk and co-workers.[3] A suitable alternative is the microbial oxidation of sulphides.[4] A third simple method for obtaining sulphoxides with high enantiomeric excess (e.e.) uses the Sharpless reagent [Ti(OPr^i)$_4$–diethyl tartrate] and Bu^{t}OOH in stoicheiometric amount.[5]

A much more difficult task is the catalytic asymmetric oxidation of prochiral sulphides by chemical means. The employment of bovine serum albumin as a chiral catalyst gives only a partial solution of this problem because of the high molecular weight of this protein.[6]

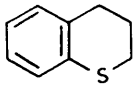
In principle, a more practical approach would be represented by transition metal-catalysed oxidations in the presence of peroxides, in spite of the low enantioselectivities reported in the literature.[7] In view of this we have studied the reactions of some representative alkyl aryl and heterocyclic sulphides with Bu^{t}OOH in the presence of catalytic amounts of a variety of transition-metal complexes derived from imines of L-amino acids as a source of chirality. Here we report our preliminary results.

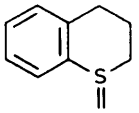
The reactions were carried out at room temperature on the sulphides (**1**)—(**7**) with Bu^{t}OOH in the presence of the catalyst and monitored by t.l.c. The crude reaction product was purified by column chromatography in order to eliminate impurities from the catalyst (or their product of degradation), capable of affecting the rotation measurements.



(**1**)–(**7**) (**8a, b**)–(**14a, b**)
a; $n = 1$
b; $n = 2$

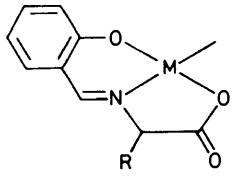
(**1**), (**8a**), (**8b**) R^1 = Me, R^2 = *p*-MeC$_6$H$_4$
(**2**), (**9a**), (**9b**) R^1 = Bu^t, R^2 = C$_6$H$_5$
(**3**), (**10a**), (**10b**) R^1 = Me, R^2 = *p*-ClC$_6$H$_4$
(**4**), (**11a**), (**11b**) R^1 = Me, R^2 = *p*-NO$_2$C$_6$H$_4$
(**5**), (**12a**), (**12b**) R^1 = *p*-NO$_2$C$_6$H$_4$, R^2 = CH$_2$CO$_2$Bu^t
(**6**), (**13a**), (**13b**) R^1 = *p*-ClC$_6$H$_4$, R^2 = CH$_2$CH$_2$OH

(**7**), 

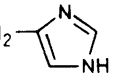
(**14a**), (**14b**), 

In the reaction mixture the sulphoxides (**8a**)—(**14a**) are generally accompanied by variable amounts of the corresponding sulphones (**8b**)—(**14b**).

The catalysts used were a series of chiral metal complexes of *N*-salicylidene-L-amino acids (sal-L-aaH$_2$) (**15**)—(**22**) and Fe(sal-L-val)Cl (**23**).



(**15**)–(**23**)

(**15**) M = TiO, R = Pr^i
(**16**) M = TiO, R = Bu^t
(**17**) M = TiO, R = CH$_2$ 
(**18**) M = MoO$_2$, R = Pr^i
(**19**) M = MoO$_2$, R = CH$_2$ 
(**20**) M = VO, R = Pr^i
(**21**) M = Cu, R = Bu^t
(**22**) M = Co, R = Pr^i
(**23**) M = Fe, R = Pr^i

Although the stereochemical properties of these complexes have been described elsewhere,[8] it is worth mentioning that the three donor atoms of the dianion sal-L-aa^{2-}, the phenolate oxygen, the imine nitrogen, and the carboxylate oxygen, identify the equatorial co-ordination plane of the complexes. The fourth equatorial position can then be filled by water or a donor group of a neighbouring molecule in the solid state, or by any donor molecule in solution. The chelate ring containing the amino acid residue is not planar and exhibits a marked preference for the conformation containing the amino acid side-chain in a pseudoaxial disposition. The conformation chirality for this chelate ring is of type λ when the absolute configuration of the amino acid is L.[8]

Reaction time, chemical yield, absolute configuration, and the e.e. for oxidation of the sulphides (**1**)—(**7**) in the presence of the

Table 1. Oxidation of the sulphides (**1**)—(**7**) to the sulphoxides (**8a**)—(**14a**) with the catalysts (**15**)—(**16**) and Bu^{t}OOH at room temperature

Entry	Substrate	Catalyst	Reaction time (h)	Sulphoxide yield (%)	Sulphone yield (%)	Absolute configuration	E.e. (%)
1	(**1**)	(**15**)	21	47	31	(−)-(*S*)	12.4[a]
2	(**3**)	(**15**)	23	41	34	(−)-(*S*)	13.7[b]
3	(**7**)	(**15**)	18	44	17	(+)-(*S*)	12.5[f]
4	(**1**)	(**16**)	18	54	24	(−)-(*S*)	14[a]
5	(**2**)	(**16**)	21	31	21	(−)-(*S*)	2[g]
6	(**3**)	(**16**)	23	39	36	(−)-(*S*)	18[b]
7	(**4**)	(**16**)	16	31	38	(−)-(*S*)	14[b]
8	(**5**)	(**16**)	4	25	5	*c*	21[d]
9	(**6**)	(**16**)	6	27	49	*c*	4.7[e]
10	(**7**)	(**16**)	42	55	33	(+)-(*S*)	15[f]

[a] Measured by the specific rotation of the isolated sulphoxide with use of the maximum specific rotation given in K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, Jr., *J. Am. Chem. Soc.*, 1965, **87**, 1958. [b] Based on the maximum specific rotation given in ref. 4*b*. [c] Absolute configuration unknown. [d] Measured by ^{1}H n.m.r. (200 MHz) with [Eu(hfc)$_3$] as chiral shift reagent. [e] Based on the maximum specific rotation given in ref. 5*b*. [f] Based on the maximum specific rotation given in T. Takata, M. Yamasaki, K. Fujimori, Y. H. Kim, T. Iyamagy, and S. Oae, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 2300. [g] Based on the maximum specific rotation given in ref. 6*b*.

Table 2. Oxidation of methyl *p*-tolyl sulphide (**1**) to the racemic sulphoxide (**8a**) with the catalysts (**17**)—(**23**) and Bu^{t}OOH at room temperature

Entry	Catalyst	Reaction time (h)	Sulphoxide yield (%)	Sulphone yield (%)
11	(**17**)	45	53	23
12	(**18**)	1.5	63	12
13	(**19**)	23	80	—
14	(**20**)	24	49	35
15	(**21**)	144	16	—
16	(**22**)	150	19	—
17	(**23**)	23	36	5

catalysts (**15**)—(**16**) are reported in Table 1, while Table 2 gives the experimental details for the formation of the racemic sulphoxide (**8a**) in the presence of the catalysts (**17**)—(**23**).

Initially, a systematic investigation of the effect of the structural variations in the catalysts was made for methyl *p*-tolyl sulphide as the starting material. Only the titanium complexes (**15**)—(**16**) gave asymmetric induction; for this reason they have been tested with the various sulphides reported in this paper.

The results collected in Table 1 show that the highest enantioselectivity (21% e.e.) was achieved starting from t-butyl (*p*-nitrophenylthio)acetate (**5**) with the catalyst (**16**) (entry 8). Lower stereoselectivities were observed with the alkyl aryl sulphides (**1**), (**3**), and (**4**) and with 1-thiochroman (**7**) with catalysts (**15**) and (**16**) (entries 1—4, 6, 7, and 10). t-Butyl *p*-tolyl sulphide (**2**) and 2-(*p*-chlorophenylthio)ethanol (**6**) with the catalyst (**16**) gave the corresponding sulphoxides with much lower optical purities (entries 5 and 9). The latter result is in agreement with the poor asymmetric kinetic resolution of β-hydroxy sulphides with Bu^{t}OOH and a chiral titanium catalyst recently observed by Sharpless.[9]

From the data collected in Table 1 it appears that the absolute configuration of the alkyl aryl sulphoxides (**8**)—(**11**) is (−)-(*S*) irrespective of the L-amino acid present in the chiral metal complex. In contrast, oxidation of 1-thiochroman (**7**) in the presence of the catalysts (**15**) and (**16**) gave the (+)-(*S*)-sulphoxide as the predominant enantiomer.

Lowering of the temperature results in modest enhancement in stereoselectivity: thus, oxidation of (**1**) with catalyst (**16**) at 0 °C for 29.5 h gave the corresponding sulphoxide (**8a**) in 60% yield (22% e.e.) together with the corresponding sulphone (**8b**) in 11% yield. Use of a stoicheiometric amount of catalyst in place of 0.1 mol equiv. failed to influence substantially the enantioselectivity: the sulphide (**1**) reacted in the presence of the catalyst (**16**) to give (**8a**) in 61% yield (21.3% e.e.). Asymmetric induction is accompanied by kinetic resolution: starting from the racemic sulphoxide (**8a**) and Bu^{t}OOH in the presence of (**15**) we recovered after 23 h (−)-(*S*)-methyl *p*-tolyl sulphoxide (**8a**) in 37% yield (7.6% e.e.). The sulphoxides are optically stable under our reaction conditions.

Apart from the stereochemical aspects of the work, the data collected in Tables 1 and 2 give additional information on the effect of the metal complexes on the sulphoxidation reaction. Thus, the molybdenum complex (**18**) is the most efficient catalyst (entry 12), while the copper complex (**21**) is relatively inefficient (entry 16). The chemical conversions appear to be independent of the presence of electron-donating or electron-withdrawing substituents in the starting material (entries 1, 2, 4, and 6—9).

In all cases examined the sulphoxides were contaminated by the corresponding sulphones. The metal complexes probably favour the second oxidation step, as indicated by the oxidation of the sulphide (**1**) by the catalyst (**18**) (entry 12), and by the fact that in the absence of catalyst only the sulphoxide (**8a**) was formed (*ca.* 5% yield).

The modest asymmetric induction shown by the catalysts in the sulphoxidation is probably associated with scarce or very weak interaction between the substrates and the chiral centres of the complexes in the course of the reaction. This seems confirmed, for instance, by the negligible influence exhibited by both the structural features of the substrates and the concentration of the catalyst. Furthermore, by following the oxidation of the sulphide (**1**) in the presence of the catalyst (**16**) by circular dichroism, we found that there was no significant build-up during the reaction of any adduct of the catalyst. While at this stage the low level of enantioselectivity induced by the sulphoxidation with Bu^{t}OOH catalysed by the titanium complexes of *N*-salicylidene-L-amino acids is clearly of limited synthetic utility, we wish to stress that the process is catalytic and competes favourably with similar asymmetric syntheses reported in the literature.[7]

Experimental

^{1}H N.m.r. spectra were recorded on a Varian 390 instrument, using tetramethylsilane as internal standard and $CDCl_3$ as solvent. Optical rotations were measured on a Perkin-Elmer 241 spectrometer. Enantiomeric excesses were determined by ^{1}H n.m.r. with the aid of [Eu(hfc)$_3$] as shift reagent using a Varian XL 200 instrument. The c.d. spectra were recorded on a Jasco J-500 C Dichrograph calibrated with a solution of

isoandrosterone in dioxane. The Bu^{t}OOH in anhydrous benzene was prepared according to Sharpless and his co-workers.[10] The preparation of the metal complexes of *N*-salicylidene-L-amino acids is described elsewhere.[8]

Preparation of the Sulphides (**1**)—(**7**).—Starting sulphides were synthesized following the method described in the literature.[6]

Oxidation: Typical Procedure.—The sulphide (1 mmol) and the catalyst (0.1 mmol) suspended in anhydrous benzene were magnetically stirred at room temperature, and then Bu^{t}OOH in anhydrous benzene (1.2 mmol) was added and the mixture was stirred for the appropriate time (see Tables 1 and 2). The reaction mixture was cooled, washed with freshly prepared aqueous sodium sulphite, and the aqueous phase extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which was purified by flash chromatography [diethyl ether—methanol (95:5 v/v) as eluant]. Reaction times, and chemical and optical yields are reported in Tables 1 and 2.

Characteristics of the Sulphoxides (**8a**)—(**14a**) *and of the Sulphones* (**8b**)—(**14b**).—Both the optically active and racemic forms of the sulphoxides (**8a**)—(**14a**) are known[6] and the physical properties of our specimens were in agreement with those reported.

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