Enantioselective Titanium-Catalyzed Sulfides Oxidation: Novel Ligands Provide Significantly Improved Catalyst Life

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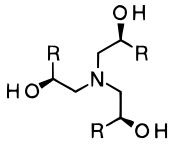
Catalytic enantioselective oxidations are among the most interesting transformations in asymmetric synthesis, as indicated by the large amount of research carried out in this field.[1] Although some very satisfactory results have already been obtained, more work is needed before procedures of general applicability and a complete understanding of species involved in the oxidative processes become available. Excellent results have been obtained in allylic alcohols[2] and sulfides oxidation[3−5] with chiral titanium peroxo species bearing C_2 symmetric diols as ligands (*e.g.* tartaric esters). A drawback of such Ti(IV)/(+)-diethyltartrate/alkyl hydroperoxide reagents is that they have a small turnover number.[6] In addition, the structure of the real oxidants and of their precursors is not well defined. In fact, owing to the presence of different species and to the complexity of the equilibrium processes occurring in solution, these systems have not yet been completely characterized.[1,7]

Aiming at overcoming these problems, we decided to investigate chiral peroxotitanium complexes containing other ligands. In particular we focused our attention on C_3 symmetric, chiral trialkanolamines **1** ligands.[8] Zirconium complexes of the (*S*,*S*,*S*)-triisopropanolamine **1a** have been successfully used in the enantioselective ring opening of *meso* epoxides with silyl azides (ee up to 93%).[9] Enantiopure homochiral trialkanolamines should be particularly suitable ligands for titanium since they are tetradentate (thus giving rise to very robust complexes) and highly symmetric ligands, and they should afford monomeric peroxotitanium species.[10]



(S,S,S)-**1a** R = Me

(R,R,R)-**1b** R = Ph

(R,R,R)-**1c** R = *t*-Bu

We now report on the synthesis of this new class of chiral titanium peroxo complexes and on their reactivity in the catalytic enantioselective oxidation of organic sulfides.[11,12]

Results and Discussion

The complex **2a** formed *in situ* by addition of titanium tetraisopropoxide to (*S*,*S*,*S*)-triisopropanolamine **1a**, affords, upon addition of *tert*-butyl hydroperoxide, the corresponding peroxo complex **3a**, as indicated by ^{1}H NMR experiments (Scheme 1).

The peroxotitanium complex **3a** is in equilibrium with its precursor **2a**. The equilibrium constant has been determined to be = 3.5 at 22 °C in deuterochloroform. The ^{1}H NMR spectrum of the peroxo species **3a**, as well as that of the precursor **2a**, shows a single set of signals at δ = 1.11, 2.82−2.91, and 5.55 ppm for the methyl, methylene, and methine groups, respectively. The peroxo species thus obtained is capable of oxidizing sulfides to sulfoxides. Reactivity and enantioselectivity have been studied by using *p*-tolyl methyl sulfide **4a** as a model substrate. The influence of parameters such as the metal/oxidant ratio and the nature of the ligand and of the hydroperoxide together with the effect of the temperature and of the solvent have also been tested.

The catalytic nature of the system is demonstrated by the experiments reported in Table 1 with ligand (*R*,*R*,*R*)-**1b**.[13]

The data of Table 1 clearly show that the system operates under truly catalytic conditions (0.01 equiv of chiral catalyst) as far as the enantioselections are concerned. At any rate, in order to speed up the reactions, 0.1 equiv of catalyst with respect to the oxidant have been routinely used (see Experimental Section).

The effect of the nature of the ligand and of the hydroperoxide has been examined. The results are collected in Table 2.

Both the nature of the ligand and of the hydroperoxide are relevant parameters. (*R*,*R*,*R*)-Tris(2-hydroxy-2-phenylethyl)amine (**1b**) and cumyl and trityl hydroperoxide (entries 5 and 6) afford the best enantioselections, even though these are still low. The sulfoxides obtained have an absolute configuration which is the opposite of that of the ligand. In all the reactions a sizeable amount of sulfone is formed (see also data in Table 1). This feature will be discussed in some more detail later. Out of trend are the results obtained with *tert*-butyl ligand **1c** that, with the three different hydroperoxides, affords rather

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(3) Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325.

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(5) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529.

(6) Lower Ti(IV)/hydroperoxide ratios (1/20 for Sharpless reagent[2] and 1/5 for the Kagan one[4b]) could be employed by carrying out the oxidations in the presence of activated molecular sieves.

(7) Conte, V.; Di Furia, F.; Licini, G.; Modena, G.; Sbampato, G. In *Dioxygen Activation and Homogeneous Catalytic Oxidation*; Simandi, L. I., Ed.; Elsevier Science Publishers B.V.: Amsterdam, The Netherlands, 1991; p 385.

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(10) ^{1}H and ^{13}C NMR spectra and X-ray crystallographic analysis show that, unlike zirconium derivatives, titanium complexes of trialkanolamine **1a** are C_3 symmetric monomers.[8,9]

(11) Part of this work has been presented at the COFEM Conference "Giornate di Chimica Fisica Organica e Meccanicistica", Perugia, Italy, September 24−27, 1995.

(12) After our manuscript submission, the X-ray crystal structure of the achiral dimer ((η^2-*tert*-butylperoxo)titanatrane)$_2$ has been reported. Such a peroxo complex oxidizes methyl benzyl sulfide to the corresponding sulfoxide (CH_2Cl_2, 0 °C, 91% yield): Boche, G.; Möbus, K.; Harms, K.; Marsh *J. Am. Chem. Soc.* **1996**, *118*, 2770.

(13) The reactions have been performed at −20 °C in 1,2-dichloroethane, with a substrate concentration = 0.2 M and cumyl hydroperoxide as oxidant. The preformed catalyst was obtained by mixing stoichiometric quantities of Ti(*i*-PrO)$_4$ and (+)-**1b** in 1,2-dichloroethane at rt and removal of the solvent under vacuum.

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Scheme 1

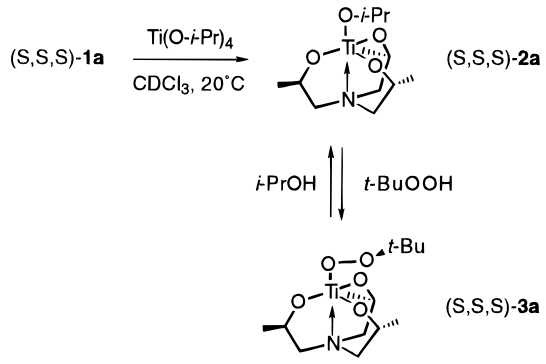
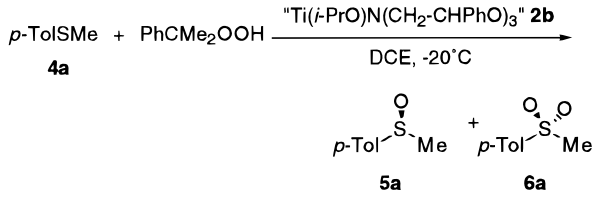


Table 1. Effect of the Ti(IV)/Cumyl Hydroperoxide Ratio on the Asymmetric Oxidation of Methyl *p*-Tolyl Sulfide (4a) Using the Preformed Catalyst 2b[12]



Substrate : Oxidant = 2 : 1

Ti(IV)/oxidant	time (h)	yield (%)[a]	**5a/6a** (%)[a]	ee **5a** (%)[b]	absol config[c]
1:2	16	100	85:15	39	*S*
1:10	16	100	84:16	38	*S*
1:25	16	100	87:13	38	*S*
1:50	56	100	84:16	40	*S*
1:100	56	84	86:14	40	*S*
1:1000	162	64	87:13	29	*S*

[a] Based on the oxidant and determined by gas chromatographic analysis. [b] Determined by ^{1}H NMR in the presence of (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol. [c] Determined by comparison with the $[\alpha]_D$ reported in the literature.[4a,14]

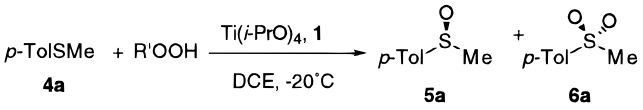
different enantioselections and the opposite absolute configuration of the sulfoxide with *tert*-butyl hydroperoxide (entry 7).

Other parameters such as the temperature and the solvent were examined. A decrease of the temperature from 20 to 0 and −20 °C results in an enhancement of the enantioselection (ee = 28, 31, and 36%, respectively). The nature of the solvent appears to have a minor effect on the enantioselectivity. At any rate, chlorinated solvents seem to be particularly suitable for these oxidations. The information so far obtained is that the most effective system involves (*R*,*R*,*R*)-tris(2-hydroxy-2-phenylethyl)amine (**1b**) as ligand and cumyl hydroperoxide as oxidant. A preliminary kinetic study on such a system has been carried out (Figure 1).

It is observed that *p*-tolyl methyl sulfone is formed from the very beginning of the reaction. Therefore, two different asymmetric processes are involved. One is the asymmetric oxidation to sulfoxide, the other is the kinetic resolution *via* oxidation to sulfone. Fortunately, both processes work in the same direction. In fact, the *S* sulfoxide is formed preferentially (ee = 29% when almost no sulfone is present), and the oxidation to the sulfone of the *R* enantiomer is faster than that of the *S* one.[15] The kinetic resolution of racemic methyl *p*-tolyl sulfoxide

(14) Sugimoto, T.; Kokubo, T.; Miyazaki, J.; Tanimoto, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1979**, 402. Sakuraba, H.; Natori, K.; Tanaka, Y. *J. Org. Chem.* **1991**, *56*, 4124.

Table 2. Effect of Ligands 1 and of the Hydroperoxide on the Asymmetric Oxidation of Methyl *p*-Tolyl Sulfide (4a)



Substrate : Oxidant = 2 : 1

no.	ligand	R′	time (h)	yield (%)[a]	**5/6** (%)[a]	ee **5** (%)[b]	absol config[c]
1	(*S*,*S*,*S*)-**1a**	*t*-Bu	240	82	86:14	11	*R*
2	(*S*,*S*,*S*)-**1a**	$PhCMe_2$	75	100	76:24	19	*R*
3	(*S*,*S*,*S*)-**1a**	Ph_3C	1320	100	76:24	13	*R*
4	(*R*,*R*,*R*)-**1b**	*t*-Bu	45	100	89:11	29	*S*
5	(*R*,*R*,*R*)-**1b**	$PhCMe_2$	40	100	84:16	36	*S*
6	(*R*,*R*,*R*)-**1b**	Ph_3C	256	98	87:13	35	*S*
7	(*R*,*R*,*R*)-**1c**	*t*-Bu	115	91	90:10	3	*R*
8	(*R*,*R*,*R*)-**1c**	$PhCMe_2$	64	100	89:11	29	*S*
9	(*R*,*R*,*R*)-**1c**	Ph_3C	1800	75	96:4	10	*S*

[a] Based on the oxidant and determined by gas chromatographic analysis. [b] Determined by ^{1}H NMR in the presence of (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol. [c] Determined by comparison with the $[\alpha]_D$ reported in the literature.[4a,14]

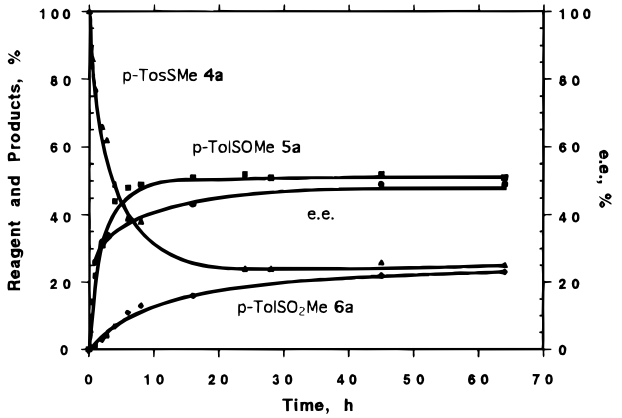


Figure 1. Dependence of the concentration of products [(▲) *p*-tolyl methyl sulfide; (■) *p*-tolyl methyl sulfoxide; (♦) *p*-tolyl methyl sulfone] (%) and of (●) the ee (%) on the time (h) in the oxidation of *p*-tolyl methyl sulfide with cumyl hydroperoxide catalyzed by (*R*,*R*,*R*)-**1b** [Ti(*i*-PrO)N($CH_2CHPhO)_3$] = 10^{-2} M in DCE at −20 °C.

3a gives the *S* sulfoxide with an ee = 33% (50% conversion). An interesting aspect, which is rather unusual in the chemistry of the titanium peroxo complexes,[16] is that the rates of the two subsequent oxidations, sulfide to sulfoxide and sulfoxide to sulfone, are comparable. This behavior deserves a more detailed investigation.

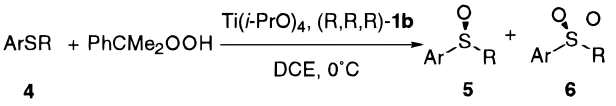
Different aryl alkyl sulfides have also been employed (Table 3). The experiments have been performed at 0 °C in order to accelerate the reactions.

The results reported in Table 3 show that both the nature of the alkyl moiety and the electronic effect of the aryl substituents play a relevant role in the enantioselections. The aryl branched alkyl sulfides **4g,h** give the best results, ee = 60 ÷ 84% (*R* = *tert*-butyl and benzyl, last three entries). Lower temperatures and an increase

(15) In sulfoxide asymmetric synthesis both enantioselective oxidation and kinetic resolution have been contemporarily observed and also in other chiral metal-catalyzed processes. Cf. ref 5. Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 7624; Nagata, T.; Imagawa, K.; Yamada, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3241.

(16) Bonchio, M.; Campestrini, S.; Conte, V.; Di Furia, F.; Moro, S. *Tetrahedron* **1995**, *51*, 12363.

Table 3. Asymmetric Oxidation of Aryl Methyl Sulfides 4



Substrate : Oxidant = 1 : 1

no.	Ar	R	yield (%)[a]	5/6 (%)[b]	ee 5 (%)[c]	absol config[d]
4a	*p*-Tol	Me	98	62:38	45	*S*
4b	2-Napt	Me	86	60:40	38	*S*
4c	*p*-$NO_2C_6H_4$	Me	88	26:74	15	*S*
4d	*p*-$MeOC_6H_4$	Me	94	68:32	41	*S*
4e	*p*-Tol	Et	99	64:36	38	*S*
4f	*p*-Tol	*n*-Bu	99	58:42	44	*S*
4g	Ph	*t*-Bu	98	60:40	60	*S*
4g	Ph	*t*-Bu	96	63:37	66[e]	*S*
4h	Ph	CH_2Ph	94	77:23	84	*S*

[a] Isolated yields based on the oxidant. [b] Determined by ^{1}H NMR. [c] Determined by ^{1}H NMR in the presence of (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol. [d] Determined by comparison with the $[\alpha]_D$ reported in the literature.[4a,14] [e] Reaction performed at −20 °C.

of the kinetic resolution, assuming a behavior similar to that of methyl *p*-tolyl sulfide, are expected to further increase the ee's. The elongation of the linear chain does not affect significantly the ee's (substrates **4a**, **4e**, and **4f**) meanwhile a stronger effect is observed in the presence of aryl groups with different electronic properties (substrates **4a**−**d**). This is again at variance with the behavior of the Ti(IV)/(+)-DET/TBHP reagents. Therefore, to some extent, these Ti(IV)/trialkanolamines peroxo complexes complement the other Ti(IV)−diethyltartrate based chiral oxidizing reagents. The oxidations by the latter, in fact, are almost unaffected by the substituents on the aromatic ring, while any increase or branching of the aliphatic chain dramatically decreases their enantioselectivity in comparison with aryl methyl sulfides.

Experimental Section

General Methods. ^{1}H NMR spectra were determined on a Bruker WP200 (200 MHz) instrument. Specific rotations were obtained with a Perkin-Elmer 241 polarimeter operating at λ = 589 nm corresponding to the sodium D line. Radial chromatography was performed on a Chromatotron 7924 T (Harrison Research) over silica gel 60 (Merck, TLC PF 254). Gas chromatographic analyses were performed on a Varian 3700 GC equipped with a 0.5 m × 2 mm glass column packed with 3% FFAP on Chromosorb W AW DMCS (80−100 mesh), eicosane as external standard.

Chemicals. *tert*-Butyl hydroperoxide (Fluka, 80%, 20% di-*tert*-butyl peroxide) was purified by distillation under vacuum (bp 31 °C/16 Torr) and stored at 0 °C. Cumene hydroperoxide (Fluka) was stored under molecular sieves at 0 °C. Trityl hydroperoxide was prepared following a literature procedure.[17] Titanium(IV)−tetraisopropoxide (Aldrich) was distilled under vacuum (bp 60−63 °C/0.1 Torr). 1,2-Dichloroethane was washed three times with 10% concentrated H_2SO_4 and with several times until pH = 7, dried overnight over $CaCl_2$, distilled over P_2O_5, and stored over molecular sieves. Sulfides were prepared accordingly to the literature by alkylation of the corresponding thiols. Enantiopure trialkanolamines **1a**−**c** were prepared following the literature procedure.[8]

Asymmetric Oxidation. A typical procedure is the following: in a 10 mL volumetric flask Ti(*i*-PrO)$_4$ (0.015 mL, 0.054 mmol), (−)-(*R*,*R*,*R*)-tris(2-hydroxy-2-phenylethyl)amine (24.5 mg, 0.065 mmol) and the methyl *p*-tolyl sulfide (**2a**) (150 mg, 1.084 mmol) are dissolved in dry 1,2-dichloroethane. After cooling to −20 °C, cumyl hydroperoxide (0.040 mL, 0.544 mmol) is added under magnetic stirring. The solution is stirred at −20 °C until disappearance of the oxidant, warmed at room temperature, and poured into a 5% sodium metabisulfite aqueous solution. After filtration through Celite, the mixture is extracted with chloroform. The organic layers are washed once with NaOH 5% aqueous solution and with brine and dried over $MgSO_4$, and the solvent was removed under vacuum. The products are purified *via* radial chromatography over silica gel (petroleum ether/ethyl acetate). Ee's were determined directly on the reaction mixture before purification by ^{1}H NMR in the presence of (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol (Fluka).

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