

# Stereoselective catalytic sulfoxidations mediated by new titanium and zirconium C<sub>3</sub> trialkanolamine complexes\*†

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**Abstract:** Monomeric Ti(IV)/C<sub>3</sub> trialkanolamine complexes are effective catalysts in the stereoselective sulfoxidation of alkyl aryl sulfides (ee's up to 84%, 0.1% of catalyst). Such complexes were shown to have a biphilic nature, behaving as electrophilic oxidants towards sulfides while a nucleophilic pathway dominates the oxidation of sulfoxides. The analogous Zr(IV) complexes, likely dimeric, are even better and more general stereoselective sulfoxidation catalysts (ee's up to 91%, 50 T.O.), affording sulfoxides with the opposite absolute configuration.

## INTRODUCTION

The development of efficient synthetic procedures for the preparation of enantiopure compounds is a well recognized target in chemistry. In the last decade, novel and highly sophisticated methodologies have been developed and remarkable results have been achieved [1]. In this field catalysis plays a particularly relevant and strategic role [2]. In fact, asymmetric catalytic processes may lead to the production of thousands or millions of optically active molecules from a single molecule of chiral, nonracemic catalyst.

Catalytic enantioselective oxidations are among the most important class of reactions in this field [3–8]. In particular, together with osmium-mediated dihydroxylation [3] and salen-catalyzed epoxidation [4], stereoselective oxidation mediated by chiral titanium(IV) alkoxide plays a unique role in such area [5–8]. This class of reactions includes fundamental stereoselective oxidative processes such as allylic alcohol epoxidation, [5]  $\beta$ -hydroxyamine *N*-oxidation, [6] sulfoxidation [7] and Baeyer–Villiger oxidation of cyclobutanones [8].

The general reaction protocols utilise titanium tetraisopropoxide as catalyst precursor in the presence of a chiral polydentate ligand and an alkyl hydroperoxide as stoichiometric oxidant. Under such conditions chiral  $\eta^2$ -alkylperoxo species have been postulated to be the reactive intermediates. [9] In the majority of the cases the ligands, which are usually the chiral source of the system, are C<sub>2</sub> symmetric diols, i.e. derivatives of tartaric acid [7a–7d], 1,1'-binaphthols [7e,f] or 1,2-diphenyl or *tert*-butyl-1,2-ethanediols [7g–7i]. Although such C<sub>2</sub>-alkoxide-titanium(IV) catalysts are highly enantioselective, they are not robust enough to survive reaction conditions employing an excess of the hydroperoxide, which is a necessary requisite for obtaining high turnover processes [10]. Furthermore, a second drawback in most of these reactions lies in the difficult characterization of the catalyst structure due to the tendency of the

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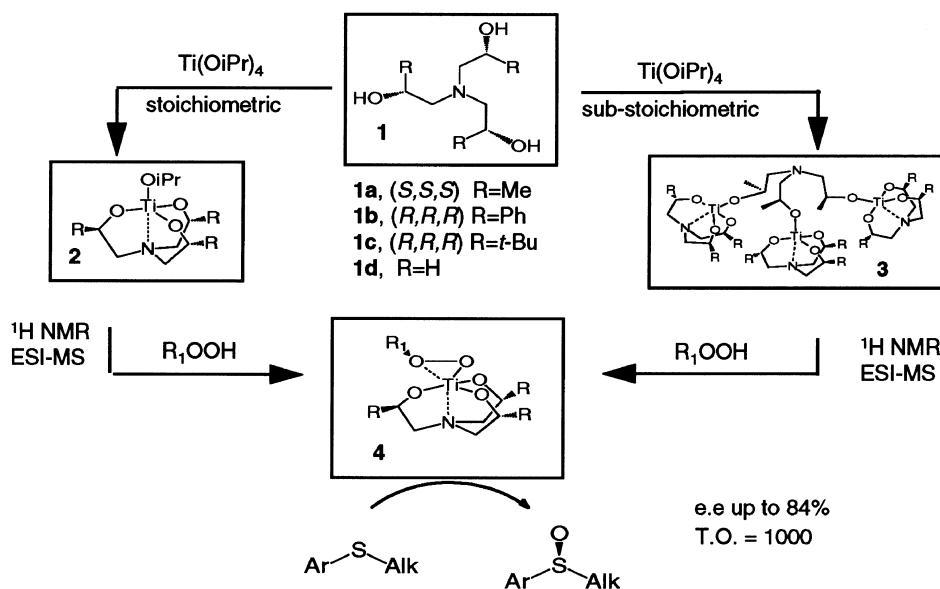
†Dedicated to the memory of Professor Fulvio Di Furia (1944–97).

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metal-alkoxides to form mixtures of polynuclear species equilibrating in solution [10,11]. Titanium alkoxides are known to undergo rapid ligand exchange which further hampers the elucidation of either the catalyst structure or the mechanism of the reaction and the consequent rational catalyst engineering [9–11].

### Ti(IV)/C<sub>3</sub> TRIALKANOLAMINE MEDIATED STEREOSELECTIVE SULFOXIDATIONS

Recently we have reported that a novel series of chelating chiral alkoxide ligands, namely C<sub>3</sub> symmetric trialkanolamines **1**, provide very stable titanium(IV) complexes [10,12]. Such species efficiently catalyse the asymmetric sulfoxidation of alkyl aryl sulfides with enantiomeric excesses (ee's) up to 84% and with remarkable efficiency, reaching 50–100 turnover numbers [12] (Scheme 1).



**Scheme 1** Ti(IV)/trialkanolamines **1** complexes as chiral catalysts in stereoselective sulfoxidation.

Ligands **1** bind tightly to the titanium center in a tetradentate fashion producing complexes whose nature depends on ligand **1**:Ti(IV) ratio [13]. When a stoichiometric amount of ligand **1** and Ti(IV) is employed, catalyst **2** is obtained. Catalyst **2** affords a well resolved, highly symmetric <sup>1</sup>H NMR spectrum consistent with a monomeric structure where a single isopropoxy group is still retained in the Ti(IV) coordination sphere as an axial ligand [10,12,13].

In contrast, a complex mixture of polynuclear Ti(IV)-based species **3** forms from the interaction of Ti(IV) with excess of ligand **1**. Polynuclear aggregates **3** can be isolated as white powder by simply solvent removal and they are routinely used for the Ti(IV)/**1** mediated asymmetric sulfoxidation. In fact, system **3** is more reactive than the *in situ* formed system **2**, where three equivalents of isopropanol are liberated in solution, and offers a practical advantage in handling.

The characterization of the diverse species present in **3** has been achieved through electrospray ionization mass spectrometry (ESI-MS) combined with <sup>1</sup>H NMR evidence [13]. They consist in polynuclear Ti(IV)-based aggregates organized by the chiral trialkanolamine **1** as axial ligand of the chiral titanatrane units. Their composition corresponds to the 2:1, 3:2 and 4:3 adducts of **1** with the titanium nucleus (the higher homologue is the one reported in Scheme 1).

Both precursors **2** and **3**, in the presence of an excess of alkyl hydroperoxide, afford the same monomeric peroxocomplex **4**, which efficiently oxidizes alkyl aryl sulfides to the corresponding sulfoxides with ee's up to 84% and in the presence of 1% of chiral catalyst (Scheme 1). Recent results indicate that, under controlled conditions, even lower catalyst loading can be employed (as little as 0.1%) [14].

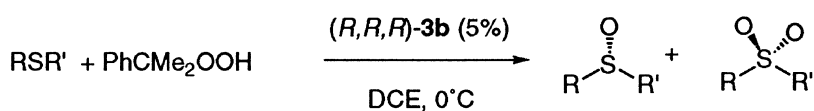
Direct evidence of the monomeric nature of the peroxospecies **4** is provided by <sup>1</sup>H NMR and ESI-MS experiments [12,13]. Peroxocomplexes **4** afford highly symmetric <sup>1</sup>H NMR spectra where the local C<sub>3</sub>

symmetry of the chiral titanatrane unit is retained. The monomeric structure of the derivatives **4** under catalytic condition is confirmed via ESI-MS spectrometry by analysis of the isotopic clusters and of the MS<sup>2</sup> spectra after collision induced dissociation. It is worthy of mention that the X-ray structure of the achiral peroxocomplex **4d** (R' = *t*-Bu) has been recently determined. It consists in a C<sub>2</sub> symmetric dimer and so far, it is the only titanium alkylperoxo species characterized at the solid state [15].

The effect of parameters such as the nature of the ligand or the alkyl hydroperoxide, the temperature or the solvent on the stereoselection of the sulfoxidation reaction has been examined. As far as the reactivity and stereoselectivity are concerned, the best results were obtained by using the (*R,R,R*)-*tris*-(2-phenylethanol)amine **1b** as ligand and cumyl hydroperoxide (CHP) as primary oxidant in chlorinated solvents at -20 °C yielding sulfoxides with *S* absolute configuration, which is opposite to the absolute configuration of the chiral ligand employed [12].

The scope of **3b** based stereoselective sulfoxidation was examined with different sulfides (Table 1).

**Table 1** Stereoselective oxidation of sulfides (0.1 M) by CHP (0.1 M) mediated by **3b** ( $5.4 \times 10^{-3}$  M) in 1,2-dichloroethane (DCE) at 0 °C



Entries	R	R'	Yield (%) <sup>*</sup>	SO:SO <sub>2</sub> (%) <sup>†</sup>	ee (%) <sup>‡</sup>	Abs. conf. <sup>§</sup>
1	<i>p</i> -Tol	Me	98	62:38	45	<i>S</i>
2	2-Napt	Me	86	60:40	38	<i>S</i>
3	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	94	68:32	41	<i>S</i>
4	<i>p</i> -Tol	Et	99	64:36	38	<i>S</i>
5	<i>p</i> -Tol	<i>n</i> -Bu	99	58:42	44	<i>S</i>
6	Ph	<i>t</i> -Bu	98	60:40	60	<i>S</i>
7	Ph	Bn	94	77:23	84	<i>S</i>
8	Bn	Me	99	78:22	5	<i>S</i>
9	<i>n</i> -Oct	Me	95	83:16	5	<i>S</i>

\* Isolated yields based on the oxidant.

† Determined by <sup>1</sup>H NMR.

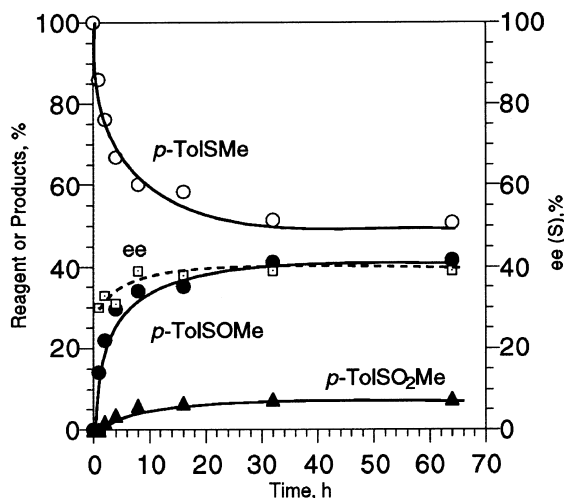
‡ Determined by <sup>1</sup>H NMR in the presence of (*R*)-(-)-1-(9-anthryl)-2,2,2-trifluoroethanol.

§ Determined by comparison with the [α]<sub>D</sub> reported in the literature.

The highest enantioselectivities were obtained with the benzyl and *tert*-butyl phenyl sulfides (ee's = 84% and 60%, respectively, entries 6 and 7). Lower ee's were obtained with the other alkyl aryl sulfides and in this case neither the presence of aromatic substituents with different electronic character (entries 1–3) nor the elongation of the alkyl chain (entries 1, 4, 5) significantly affect the enantioselection of the process (ee's = 38–45%). This last observation is in contrast with previously reported Ti(IV) mediated asymmetric oxidations [7], where a large steric differentiation between the two group linked at the sulfur atom is required for obtaining high ee's. Therefore in the Ti(IV)/trialkanolamine **1b** mediated processes a different mechanism for chiral recognition may be operating, in which secondary aromatic interactions between the substrate and the peroxocomplex **4b** could play a major role. Further support for this hypothesis is provided by the very low ee values obtained in the oxidation of dialkyl sulfides (entries 8 and 9). Studies aimed at a better understanding to this important aspect are currently under investigation.

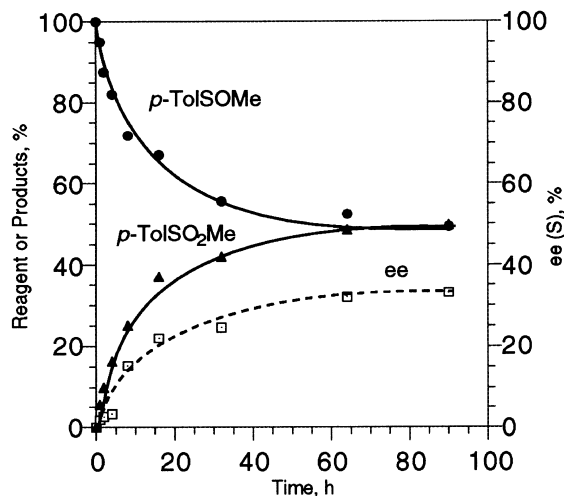
The kinetic profile of the oxidation of methyl *p*-tolyl sulfide by CHP catalyzed by **3b** (10%) is reported in Fig. 1.

The kinetic behavior reported in Fig. 1 is consistent with the occurrence in solution of two consecutive reactions, namely the stereoselective oxidation to methyl *p*-tolyl sulfoxide and its kinetic resolution via further oxidation to sulfone. Both processes cooperate in building up the same enantiomer as revealed by



**Fig. 1** Plot of reagent, products (%) and ee's (%) vs. time (h) in the oxidation of methyl *p*-tolyl sulfide (0.1 M) by CHP (0.1 M) catalyzed by (*R,R,R*)-**3b** ( $1 \times 10^{-2}$  M) in DCE at  $-20^\circ\text{C}$ .

the increase of the ee during the course of the reaction. The first oxygen transfer affords preferentially the (*S*)-methyl *p*-tolyl sulfoxide (ee = 29% when almost no sulfone is present in solution) and the over-oxidation of the (*R*)-sulfoxide is faster than the (*S*)-sulfoxide [16]. Such behavior can be recognized also in the kinetic resolution of the ( $\pm$ )-methyl *p*-tolyl sulfoxide (Fig. 2).



**Fig. 2** Plot of reagent, product (%) and ee's vs. time in the kinetic resolution of methyl *p*-tolyl sulfide (0.1 M) by CHP ( $5 \times 10^{-2}$  M) catalyzed by (*R,R,R*)-**3b** ( $1 \times 10^{-2}$  M) in DCE at  $-20^\circ\text{C}$ .

Another interesting aspect that can be gathered from the kinetic profiles reported in Fig. 1 is that the rate of the two consecutive processes, oxidation of the sulfide to sulfoxide and of the sulfoxide to sulfone are comparable ( $k_S/k_{SO} = 3.2$ ). Such a behavior is quite unusual in early transition metal peroxide chemistry [17]. In fact, peroxocomplexes of  $d^0$  transition metals such as Ti(IV), V(V), Mo(VI) and W(VI) are strong electrophiles exhibiting a remarkably high selectivity in the oxidation of dialkyl and alkyl aryl sulfides; in fact  $k_S/k_{SO} > 100$  ratios are usually found, and the sulfoxide is usually the only observed product [17,18].

A mechanistic study has been carried out for a better understanding of such atypical behavior and it revealed that the peroxocomplex **4b** has a biphilic nature, behaving as a classical electrophilic oxidant towards sulfides, while a nucleophilic pathway dominates the oxidation to sulfoxides. [19]

A simple first-order dependence on the substrate and a linear Hammett correlation with negative slope ( $\rho = -0.60$ ) were obtained for the *mono*-oxidation of *para*-substituted thioanisoles by **4b** ( $R' = \text{cumyl}$ ), as

expected for an electrophilic oxidation where electron-rich substrates are the most reactive [7b, 16, 17]. In contrast, under identical experimental conditions, the oxidation of the corresponding *para*-substituted sulfoxides to sulfones gives rise to a curved Hammett plot (Fig. 3) having a concave shape with a minimum for *para*-X = H ( $\sigma = 0$ ). More specifically two intersecting linear correlations with opposite slopes can be drawn leading to a positive  $\rho = +0.43$  for electron-withdrawing substituents ( $\sigma > 0$ ), and to a negative  $\rho = -0.15$  for electron-donating ones ( $\sigma < 0$ ). A nonlinear Hammett behavior may be diagnostic of reactions which take place by two concurrent pathways having opposite electronic demand. [20]

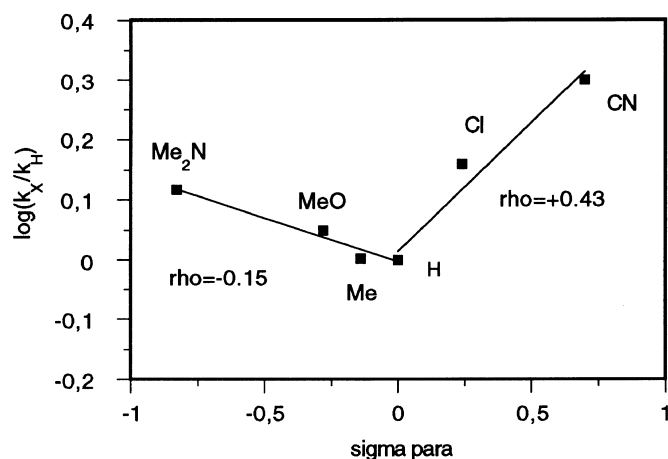


Fig. 3 Hammett plot for the oxidation of *p*-substituted aryl methyl sulfoxides by **3b**/CHP in DCE at  $-20\text{ }^{\circ}\text{C}$ .

In Fig. 4, initial rates ( $R_0$ ) of the oxidation of four representative aryl methyl sulfoxides ( $X = \text{CN}, \text{Me}, \text{MeO}, \text{Me}_2\text{N}$ ) by **3b** are plotted vs. initial substrate concentration. In all cases, a marked deviation from linearity is observed for  $[\text{substrate}]_0 > 0.2\text{ M}$ , thus indicating that the Ti(IV) oxidant displays a saturation behavior with respect to substrate concentration.

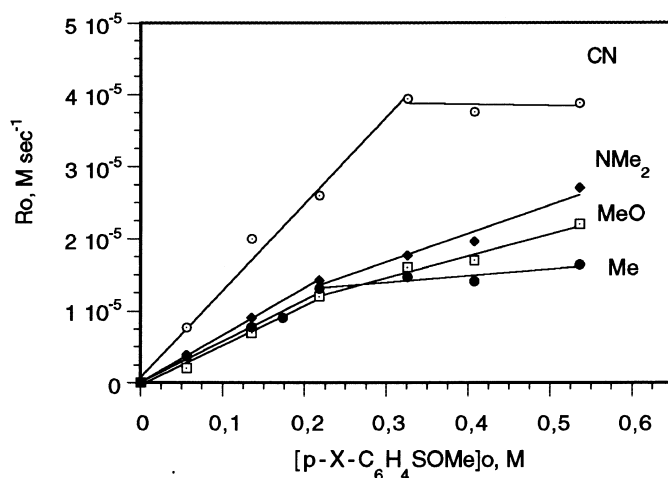
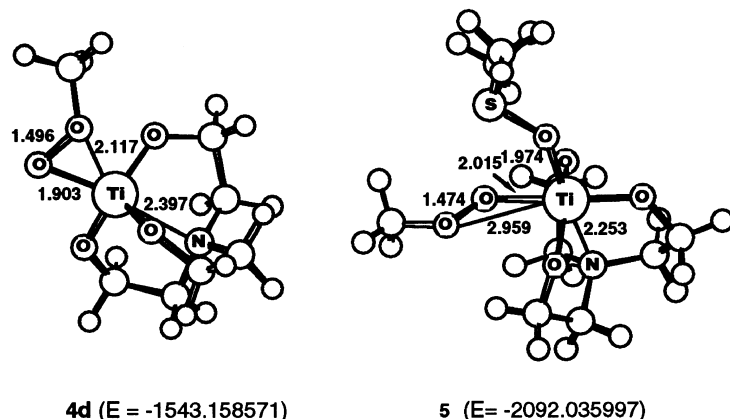


Fig. 4 Plot of initial rates ( $R_0$ ) vs. substrate concentration for *p*-X-C<sub>6</sub>H<sub>4</sub>SOMe ( $X = \text{Me}, \text{MeO}, \text{NMe}_2, \text{CN}$ ) in the oxidation by **3b**/CHP in DCE at  $-20\text{ }^{\circ}\text{C}$ .

The kinetic behavior reported in Fig. 4 affords important insight on the mechanistic behavior of the oxygen transfer to sulfoxides operated by **4b**, namely: (i) the saturation behavior fits with the occurrence of an intramolecular oxidation taking place by coordination of the sulfoxide to the Ti(IV) center; (ii) the subsequent internal oxygen transfer is likely to proceed *via* a nucleophilic pathway as indicated by the highest reactivity of the *p*-cyano substituted sulfoxide; (iii) for  $[\text{substrate}]_0 > 0.2\text{ M}$  the reaction rates further increase resulting in a second linear regime with slopes increasing in the order  $p\text{-NMe}_2 > p\text{-OMe} > p\text{-Me} > p\text{-CN}$ , reaching a definite plateau value only for the latter electron-poor

substrate. These findings suggest the concomitant presence of an electrophilic bimolecular oxidative process, simultaneous and parallel to the nucleophilic intramolecular one.

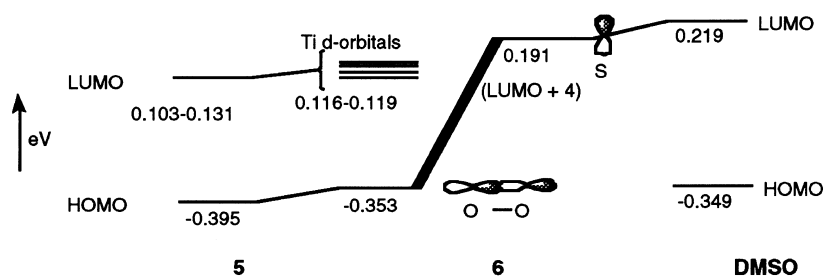
*Ab initio* calculations at the RHF/3-21G(\*) level confirmed that an intramolecular nucleophilic oxygen transfer due to the coordination of the sulfoxide to the transition metal peroxide is a feasible process. In the model chiral system ( $\eta^2$ -methylperoxy)titanatrane, **4d** ( $R' = \text{Me}$ ) interacting with dimethyl sulfoxide (DMSO), complexation of the sulfoxide to the Ti(IV) nucleus results in the formation of peroxospecies **5** with a calculated stabilization energy of 80.7 kJ/mol relative to the separated species (Fig. 5).



**Fig. 5** Optimized geometries for the model peroxospecies **4d** ( $R' = \text{Me}$ ) and the corresponding adduct **5** with DMSO at RHF/3-21G(\*) level, distances and energies are, respectively, in Angstroms and Hartrees.

Complex **5** displays an octahedral geometry in which DMSO occupies the apical position *trans* to the nitrogen atom and the peroxidic moiety moves in the equatorial plane, thus loosening the  $\eta^2$  mode of binding.

The location and the energies of the frontier orbitals of **5** are consistent with the ‘*umpolung*’ of reactivity of the peroxo functionality (Fig. 6). The HOMO of the molecule is found at  $-0.353$  eV and may be considered mainly the  $\sigma^*$  O-O orbital, while an energetically accessible LUMO (0.191 eV) may be represented by the unoccupied  $3p_y$  orbital of the sulfur atom. This implies that the electronic interaction occurring in the transition state could be described as the donation of electron density from the peroxide moiety to the sulfoxide fragment, in line with the experimental observations concerning the nucleophilic intramolecular oxygen transfer pathway (Fig. 6).



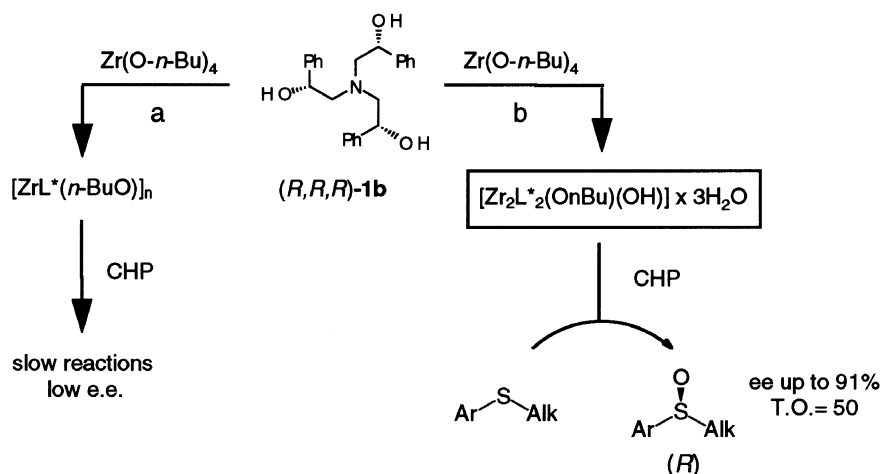
**Fig. 6** The frontier orbital energy diagram for the achiral peroxocomplex **4b** ( $R' = \text{Me}$ ), the corresponding adduct with DMSO **5** and DMSO.

According to this mechanistic picture, the Lewis acid metal center in the Ti(IV) peroxocomplex **2** plays a multiple role in activating the hydroperoxide and the sulfoxide, both by coordination, in a template oxidative process [21].

### Zr(IV)/C<sub>3</sub> TRIALKANOLAMINE MEDIATED STEREOSELECTIVE SULFOXIDATIONS

More recently, the reactivity of the analogous zirconium(IV)/trialkanolamine **1b** complexes has been investigated [22]. The zirconium complexes, prepared with the same protocols used for the titanium (see

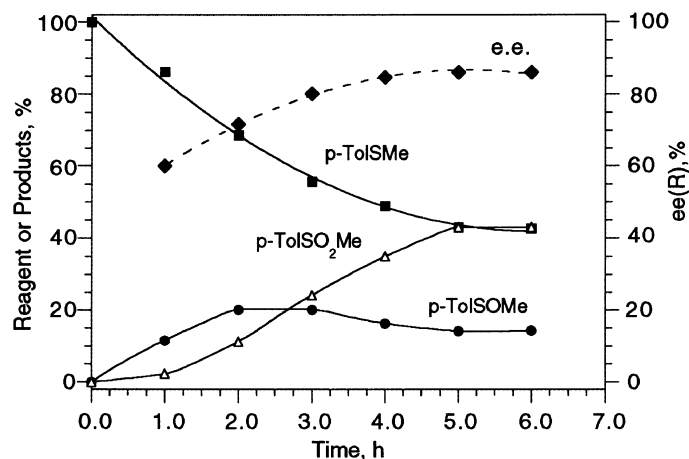
Scheme 1) were found to be poor catalysts for stereoselective sulfoxidations as far as reactivity and ee's are concerned (Scheme 2, path a). On the other hand, complex **6b**, obtained after controlled hydrolysis (addition of 2.5 equiv. of water, Scheme 2, path 2) was shown to be a much effective catalyst, affording sulfoxides with ee's up to 91% with 2% catalyst loading (Scheme 2).



**Scheme 2** Zr(IV)/trialkanolamines **1b** complexes as chiral catalysts in stereoselective sulfoxidation. Reagents and conditions: (a) Zr(*n*-BuO)<sub>4</sub> (1 equiv), DCE, 20 °C; (b) i. H<sub>2</sub>O (2.5 equiv), N<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C ii. solvent removal; iii. Zr(*n*-BuO)<sub>4</sub> (1 equiv) CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, iv. solvent removal followed by hexane stripping.

Preliminary characterizations of complex **6b** (molecular weight measurements in solution (MW ≈ 1200), <sup>1</sup>H NMR and elementary analysis) are consistent with a non-symmetric dimeric structure of general formula Zr<sub>2</sub>[NCH<sub>2</sub>CHPhO]<sub>3</sub>(*n*BuO)(OH) × 3H<sub>2</sub>O containing two trialkanolamine units and one *n*-butoxy ligand. A more detailed characterization via 2D NMR (TOCSY, HETCOR and NOESY) and ESI-MS is currently under investigation.

The kinetic profile of the oxidation of the methyl *p*-tolyl sulfide, employing a substrate:oxidant 1:1 ratio and 5% of catalyst is reported in Fig. 7.



**Fig. 7** Plot reagent, products (%) and ee's (%) on time in the oxidation of methyl-*p*-tolylsulfide (1.08 M) by CHP (1.08 M) catalyzed by (*R,R,R*)-**6b** ( $5 \times 10^{-2}$  M) in DCE at 0 °C.

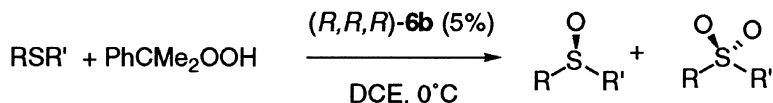
In analogy with the Ti(IV)/**1b** mediated process, also in the Zr(IV)-**6b** catalyzed sulfoxidation two independent stereoselective reactions occur in solution: the asymmetric oxidation to methyl *p*-tolyl sulfoxide and its subsequent kinetic resolution. Also in this case the ee's increase during the reaction, indicating that both processes cooperate in building up the same enantiomer. The ee's are higher compared with the analogous Ti(IV) catalyzed process, both in the stereoselective oxidation to sulfoxide

and in the kinetic resolution [23]. In fact, at product distribution methyl *p*-tolyl sulfoxide: methyl *p*-tolyl sulfone = 84:16, the **6b** and **3b** systems afford ee's values = 60% and 33%, respectively. Likewise, in the kinetic resolution of ( $\pm$ )-methyl *p*-tolyl sulfoxide at 35% conversion ee's of 41% and 22%, respectively, were obtained. It is worthy of notice that in the Zr(IV) **6b** mediated oxidation, the *R* sulfoxide is preferentially obtained when (*R,R,R*)-**1b** is used as chiral ligand, with an opposite stereochemical outcome of the oxygen transfer in respect with the Ti(IV) catalyzed process. Therefore, both enantiomeric sulfoxides can be prepared by using the same chiral ligand simply by switching the metal ion from Ti(IV) to Zr(IV). The reverse stereoselection afforded by Ti(IV) and Zr(IV) catalysts may be due to the different geometry and structures of the active species which, as we already discuss above, are monomeric in the first case and likely polynuclear in the second.

Another piece of information that derives from the analysis of the kinetic profiles reported in Fig. 7 is that, also in the Zr(IV) **6b** mediated process, the two consecutive oxidative processes afford a reactivity ratio,  $k_s/k_{so} = 0.4$ . Such an inversion of the selectivity indicates that in this case the oxygen transfer to the sulfoxide is the fastest of the two oxidative processes. This observation, which may reflect a metal-promoted nucleophilic oxidation of the sulfinyl moiety is currently under investigation and may be due both to the more Lewis acidic character of Zr(IV) and to the presence of two zirconium nuclei in close proximity performing the simultaneous activation of the hydroperoxide and of the substrate. The cooperative effect of two zirconium atoms in the activation of both substrate and nucleophile was previously proposed in the stereoselective ring opening of *meso*-epoxides by silylazides catalysed by hydrolyzed Zr(*t*-BuO)<sub>4</sub>/**1a** complexes [24,25].

The stereoselective sulfoxidation mediated by **6b** was tested with a series of alkyl aryl and dialkyl sulfides (Table 2).

**Table 2** Stereoselective oxidation of sulfides (1.08 M) by CHP (1.08 M) mediated by **6b** ( $4.6 \times 10^{-2}$  M) in 1,2-dichloroethane (DCE) at 0 °C



Entries	R'	R	SO:SO <sub>2</sub> *†	ee (%)†‡	Abs. conf.§
1	Ph	Me	29:71*	87‡	( <i>R</i> )
2	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub>	Me	25:75*	89‡	( <i>R</i> )
3	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub>	Me	32:68†	89†	( <i>R</i> )
4	<i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub>	Me	32:68†	86†	( <i>R</i> )
5	2-Naph	Me	52:48†	88†	( <i>R</i> )
6	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub>	<i>n</i> -Bu	37:63*	91‡	( <i>R</i> )
7	<i>p</i> -Me-C <sub>6</sub> H <sub>4</sub>	<i>i</i> -Pr	28:72*	91‡	( <i>R</i> )
8	Ph	<i>t</i> -Bu	44:56*	77‡	( <i>R</i> )
9	Ph	Bn	22:78*	79‡	( <i>R</i> )
10	Bn	Me	60:40*	14†	( <i>S</i> )
11	<i>n</i> -Oct	Me	60:40*	8†	( <i>S</i> )

\* Determined by GC analysis.

† Determined by <sup>1</sup>H NMR analysis.

‡ Determined by HPLC analysis.

§ Determined by comparison with the  $[\alpha]_D$  reported in the literature.

The method appears to be fairly general for the alkyl aryl sulfides since ee's in the range 80–90% are obtained for the oxidation of a variety of substrates with different stereoelectronic features. Neither the presence of aromatic substituents with diverse electronic character (entries 1–4) nor substitution with a 2-naphthyl group (entry 5) has a meaningful effect on the enantioselectivity of the process. Likewise, enantioselectivity is not significantly diminished by elongation (entry 6) or increased bulkiness (entries



7–9) of the alkyl substituent. On the other hand, dialkyl sulfides (entries 10 and 11) afford the corresponding sulfoxides in very low ee's and with the opposite absolute configuration. Therefore, inspection of data reported in Table 1 and 2 seems to indicate that the molecular recognition mechanism of the chiral Ti(IV) and Zr(IV)/**1b** based oxidants operate through non-covalent aromatic interactions (*edge to face* or *face to face*) with the substrate [26].

## ACKNOWLEDGEMENTS

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