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The first application of titanocenes in the asymmetric oxidation of sulfides

Giorgio Della Sala, Alessandra Lattanzi, Tania Severino, Arrigo Scettri*

Dipartimento di Chimica, Università di Salerno, Via Allende 1, 84081 Baronissi, Salerno, Italy

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Abstract

Investigations were carried out on the oxidation of sulfides to sulfoxides catalyzed by the commercial $Cp_2Ti(X)_2$ (X=Cl, OTf)/*t*-butyl hydroperoxide (TBHP). The asymmetric version of prochiral sulfides oxidation was achieved using Cp_2TiCl_2, as transition metal catalyst, in the presence of (+)-(*R*)-BINOL, as chiral ligand and activated 4 Å molecular sieves (m.s.).

Keywords: Titanocenes; Oxidation; Sulfides; Sulfoxides; Catalysis

1. Introduction

Metallocenes complexes in their achiral or chiral forms are catalysts of interest for several organic transformations as: Ziegler-Natta polymerization [1], Diels-Alder reaction [2], Mukaiama reaction [3], ketones reduction [4], pinacol couplings [5], allylation of carbonyl compounds [6].

Their reactivity in processes of oxidation has been scarcely investigated. Titanocenes and zirconocenes have been employed in the epoxidation [7] of unfunctionalized alkenes with *t*-butyl hydroperoxide (TBHP), providing epoxides in low yields and when used as chiral complexes [8] in low enantiomeric excesses.

Indeed, we recently discovered that some commercially available titanium and zirconium cyclopentadienyl chlorides showed to be suitable catalysts for the highly diastereoselective epoxidation of allylic alcohols with TBHP in apolar solvents [9]. These promising results encouraged further work in this unexplored field and we undertook a study of their reactivity in the asymmetric oxidation of sulfides. The asymmetric oxidation of prochiral sulfides is one of the most valuable methods for the preparation of enantiomerically enriched sulfoxides which are important intermediates in organic synthesis and pharmaceuticals [10].

The ever improved procedures developed by Kagan and co-workers [11,12] and Modena and co-workers [13,14] are based on Ti(IV) as catalyst in the presence of TBHP or cumyl hydroperoxide (CHP) and tartrate esters as chiral ligands. Later on modified methodologies employing binaphtol (BINOL) [15], 1,2-diols [16], 1,2-amino alcohols [17] as chiral ligands or furyl hydroperoxides [18] as unusual oxidants have been reported. Either the structure of the chiral titanium catalytic species involved and the mechanism of these oxidations are still under debate [19,20].

* Corresponding author. Tel.: +39-89-965-374; fax: +39-898-965-296.
E-mail address: scettri@unisa.it (A. Scettri).

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2. Experimental

2.1. Materials and apparatus

Bis(cyclopentadienyl)titanium dichloride, bis(cyclopentadienyl)titanium bis(trifluoromethane-sulfonate) and sulfides were purchased from Aldrich and used as received. 4 Å molecular sieves (m.s.) were activated under vacuum overnight at 250°C. All reactions were carried out under a dry nitrogen atmosphere in flame-dried glassware. All the solvents employed were previously dried and distilled before use. Purified sulfoxides were identified by comparison with the data reported in the literature [19]. In some cases the determination of the e.e. of sulfoxides was performed by ^{1}H NMR analysis (400 MHz) in presence of *R*-(−)-3,5-dinitrobenzoyl-α-methylbenzyl amine as shift reagent [21] (1 eq compared to sulfoxide) using $CDCl_3$ as deuterated solvent.

2.2. General procedure for the asymmetric oxidation of MeSR by Cp_2TiCl_2/(+)-(R)-BINOL/TBHP/activated 4Å m.s.

In a flame dry two necked flask under argon atmosphere were added Cp_2TiCl_2 (17 mg, 0.068 mmol), (+)-(*R*)-BINOL (24 mg, 0.08 mmol) and activated 4 Å m.s. (250 mg) in dry dichloromethane (2 ml). The mixture was stirred at 40°C for 24 h. Then the dark brown solution was cooled at room temperature and TBHP 5.5 M in decane (0.110 ml, 0.60 mmol) was added and the solution was stirred for 30 min. The mixture was cooled at −20°C and the sulfide (0.5 mmol) added. The reaction was diluted with AcOEt (50 ml), then a 10% solution of Na_2SO_3 (4 ml) was added and the mixture was centrifugated. The aqueous phase with m.s. was separated from the organic phase and the last one was washed with a saturated aqueous NaCl solution. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (petrol/AcOEt mixtures) to afford pure sulfoxide.

2.3. Determination of e.e. of sulfoxides by HPLC analysis

E.e. values of sulfoxides were determined by HPLC analysis using Chiralcel OB 20% 2-propanol-*n*-hexane, 0.80 ml/min, 254 nm detection.

Methyl p-tolyl sulfoxide: t_r (*S*)-enantiomer, 10.7 min; t_r (*R*)-enantiomer, 21.6 min.

Methyl phenyl sulfoxide: t_r (*S*)-enantiomer, 12.5 min; t_r (*R*)-enantiomer, 20.4 min.

Methyl p-methoxyphenyl sulfoxide: t_r (*S*)-enantiomer, 18.6 min; t_r (*R*)-enantiomer, 35.9 min.

Methyl p-bromophenyl sulfoxide: t_r (*S*)-enantiomer, 12.1 min; *t*r (*R*)-enantiomer, 15.7 min.

Methyl p-chlorophenyl sulfoxide: t_r (*S*)-enantiomer, 11.1 min; t_r (*R*)-enantiomer, 15.3 min.

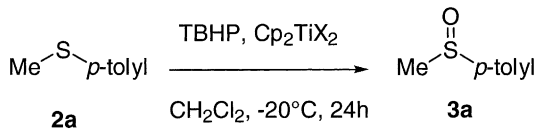
3. Results and discussion

3.1. Oxidation of a model sulfide catalyzed by Cp_2TiX_2/TBHP system

On the basis of our results obtained in the epoxidation, commercially available titanocenes (dicyclopentadienyl titanium dichloride and triflate) were employed. At the beginning it was necessary to study the efficiency of these catalysts in the sulfoxidation of a model sulfide before eventually developing an asymmetric version of the process. The reactions were carried out in CH_2Cl_2 at −20°C on methyl *p*-tolyl sulfide **2a** using TBHP and catalytic amounts of titanocene (Scheme 1, Table 1).

In all the experiments $Cp_2Ti(OTf)_2$ was more active catalyst than Cp_2TiCl_2, because the triflate is a better leaving group than chloride anion. According to the general mechanism proposed for the titanium-TBHP catalyzed oxidations of sulfides [11] (Scheme 2) the electrophilic intermediate **1** is formed after the exchange of one ligand with TBHP and this process maybe reversible. A better leaving group favors the formation of **1**, giving rise to a faster generation of the catalytic species, thence, enhancing the reaction rate.

Activated 4 Å m.s. had a beneficial effect on the reaction rate (entries 1,2) comparing to the experiments in entries 3, 4. On the other hand, they were not able



Scheme 1.

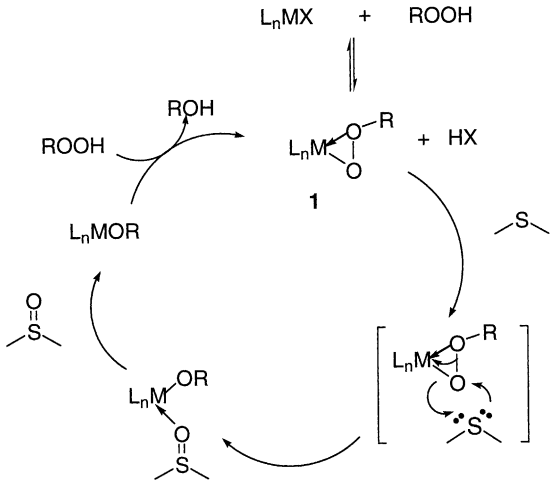
Table 1
Oxidation of methyl *p*-tolyl sulfide **2a** with TBHP catalyzed by Cp_2TiX_2[a]

Entry	Catalyst (X)	Additive	Yield (%)[b]
1	Cl	Activated 4 Å molecular sieves[c]	66
2	Otf	Activated 4 Å molecular sieves[c]	71
3	Cl	–	37
4	Otf	–	40
5	Cl	2,6-di-*t*-Butyl-4-methyl-pyridine[d]	26
6	Otf	2,6-di-*t*-Butyl-4-methyl-pyridine[d]	58
7	–	Activated 4 Å molecular sieves[c]	<1

[a] Molar ratios: Cp_2TiX_2/**2a**/TBHP 0.14/1/1.2.
[b] Isolated yields; [sulfoxide]/[sulfone] > 15.
[c] Molecular sieves/sulfide 275 mg/0.5 mmol.
[d] 2,6-di-*t*-Butyl-4-methyl pyridine/titanocene 2.5/1.

to catalyze the sulfoxidation as checked with a control experiment in absence of the titanocene (entry 7). In entries 5, 6 when a strong non-nucleophilic base (2,6-di-*t*-butyl-4-methyl pyridine) was added to the mixture a slow down of the reaction rate was observed with Cp_2TiCl_2 (entries 3, 5) while with $Cp_2Ti(OTf)_2$ the reaction rate increased (entries 4, 6).

It is known that mineral acids can catalyze the oxidation of sulfides to sulfoxides [22]. The base removal of HX from the reaction mixture produces two effects: (I) the shift of the equilibrium towards the generation of the intermediate **1** with consequent enhancement of the reaction rate, (II) the suppression of the acid-catalyzed oxidative pathway. The two effects operate in opposite directions, one favoring, the other reducing the conversion. In the presence of the base with $Cp_2Ti(OTf)_2$ the first effect dominates while with Cp_2TiCl_2 the second effect is more relevant.



Scheme 2.

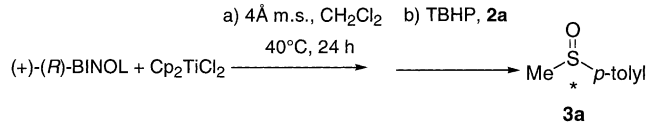
From these results it emerges that the role of m.s. is not limited to remove HX from the reaction mixture otherwise similar yields of sulfoxide should have been respectively observed in entries 1, 2 and 5, 6. The m.s. are known to catalyze the ligand exchange [23,24] leading to the formation of **1** and this effect is more evident with Cp_2TiCl_2 (entries 1, 5) than with $Cp_2Ti(OTf)_2$ (entries 2, 6) because the exchange of triflate anion is faster itself. Finally a high chemoselectivity was experienced in all the reactions as the sulfoxide/sulfone ratio was found to be higher than 15/1.

*3.2. Asymmetric oxidation of **2a** catalyzed by Cp_2TiX_2/(+)-(R)-BINOL/TBHP/4Å m.s.*

Having found out that under the conditions reported in Table 1 the $Cp_2Ti(X)_2$/TBHP system can selectively oxidize sulfides to sulfoxides, we next decided to investigate whether a chiral catalytic species generated from the achiral $Cp_2Ti(X)_2$ and a chiral ligand could have been used in reactions of asymmetric sulfoxidation. The (+)-(*R*)-BINOL was chosen as chiral ligand firstly because largely employed with Ti(IV) complexes as Ti(O*i*-Pr)$_4$ or Ti(O*i*-Pr)$_2$Cl$_2$ in many enantioselective transformations [23–27], and, furthermore, 1,4-diols are better ligands for titanocenes with respect to 1,2 or 1,3-diols [28].

As regards the generation of the chiral catalytic species we decided to exploit the strong tendency of titanium chlorides to suffer ligand exchange with protic nucleophiles: the resulting HCl could be easily eliminated by thermal treatment or trapped by m.s. Therefore, a mixture of (+)-(*R*)-BINOL, Cp_2TiCl_2 and activated 4 Å m.s. was stirred at 40°C for 24 h, then TBHP and the model sulfide **2a** were added (Scheme 3, Table 2).

The best yield and e.e. were achieved at −20°C (entry 3). When the amount of the oxidant was doubled (entry 4) a better e.e. but a lower yield of sulfoxide were obtained, a result that can be explained with a convergent process of kinetic resolution in the oxidation of sulfoxide to sulfone taking place with a poor degree of enantioselectivity. In fact, in a control



Scheme 3.

experiment a sample of racemic **3a** was reacted under the same conditions for 24 h. Starting material **3a** was recovered in 74% yield (6% e.e., *R* predominant enantiomer). The solvent effect on the sulfoxidation was investigated (entries 6–8) and CH_2Cl_2 confirmed to be the solvent of choice both for the yield and e.e. The m.s. were necessary to achieve a good level of enantioselectivity for the generation of the active catalytic species and during the oxidation step (entries 3, 9, 10).

In entries 11 and 13 the addition of the base to the reaction mixture slightly affected the e.e. of the product, supporting that m.s. were not simply involved in the removal of the acid and that the acid-catalyzed oxidative pathway was not operative (entry 11).

A greater amount of the titanocene/chiral ligand ratio gave the sulfoxide in lower yield and e.e. (entry12).

We next investigated other parameters as the nature of the titanocene, the hydroperoxide, the chiral ligand and the type of m.s. (Scheme 4, Table 3).

With the employment of CHP **3a** was obtained with essentially the same e.e. but in lower yield. When using (−)-(*S*)-BINOL, as predictable, **3a** was recovered preferentially enriched in the *S*-enantiomer.

Table 2
Asymmetric oxidation of **2a** by Cp_2TiCl_2/(+)-(*R*)-BINOL/TBHP/activated 4 Å m.s.[a]

Entry	Solvent	*T* (°C)	*t* (h)	Yield **3a** (%)[b]	e.e. **3a** (%)[c]	Absolute configuration
1	CH_2Cl_2	Room temperature	2	53[d]	25	*R*
2	CH_2Cl_2	0	7	50[e]	39	*R*
3	CH_2Cl_2	−20	24	95	45[f]	*R*
4[g]	CH_2Cl_2	−20	48	58[h]	53[f]	*R*
5	CH_2Cl_2	−45	8	20	23	*R*
6	Toluene	−20	23	57[i]	33	*R*
7	THF	−20	23	66	23	*R*
8	CCl4	−20	23	66	28	*R*
9[j]	CH_2Cl_2	−20	24	9	17	*R*
10[k]	CH_2Cl_2	−20	24	63	33	*R*
11[l]	CH_2Cl_2	−20	24	93	33[f]	*R*
12[m]	CH_2Cl_2	−20	22	47	38	*R*
13[n]	CH_2Cl_2	−20	24	21	26[f]	*R*

[a] Molar ratios: Cp_2TiCl_2/(+)-(*R*)-BINOL/**2a**/TBHP/m.s. 0.14/0.17/1/1.2/500 mg.

[b] Isolated yields; [sulfoxide]/[sulfone] > 15.

[c] The e.e. values were determined by ^{1}H NMR analysis (400 MHz) in the presence of (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine as shift reagent.

[d] [Sulfoxide]/[sulfone] = 1.1.

[e] [Sulfoxide]/[sulfone] = 6.1.

[f] The e.e. value was measured by HPLC using OB column.

[g] Molar ratio TBHP/sulfide 2/1.

[h] [Sulfoxide]/[sulfone] = 1.2.

[i] [Sulfoxide]/[sulfone] = 10.4.

[j] Reaction performed in absence of m.s.

[k] The m.s. were added only after the generation of the catalyst.

[l] Cp_2TiCl_2/2,6-di-*t*-butyl-4-methyl pyridine 1/2.5.

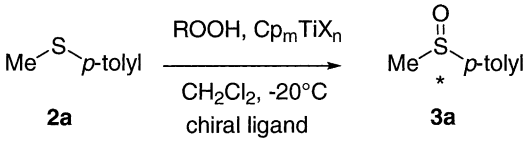
[m] Cp_2TiCl_2/(+)-(*R*)-BINOL/sulfide 0.25/0.25/1.0.

[n] 2,6-di-*t*-Butyl-4-methyl pyridine was used in absence of m.s. since the generation of the catalytic species.

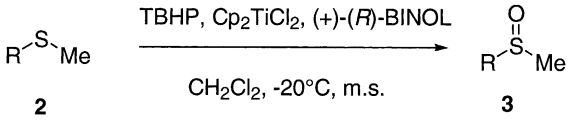
Table 3
Influence of the parameters: titanocene, hydroperoxide, chiral ligand and type of molecular sieves in the asymmetric sulfoxidation of **2a**[a]

Entry	Titanocene	H_2O in m.s. (%)	Chiral ligand	ROOH	*t* (h)	Yield **3a** (%)[b]	e.e. **3a** (%)[c]	Absolute configuration
1	Cp_2TiCl_2	Activated	(+)-(*R*)-BINOL	CHP	24	65	41	*R*
2	Cp_2TiCl_2	Activated	(−)-(*S*)-BINOL	TBHP	24	95	38	*S*
3	Cp_2TiCl_2	Activated	(*R*,*R*)-(+)-hydrobenzoin	TBHP	24	36	28	*S*
4	Cp_2TiCl_2	4	(+)-(*R*)-BINOL	TBHP	24	73	42	*R*
5	Cp_2TiCl_2	10	(+)-(*R*)-BINOL	TBHP	24	79	41	*R*
6	Cp_2TiCl_2	18	(+)-(*R*)-BINOL	TBHP	24	80	38	*R*
7	$CpTiCl_3$	Activated	(+)-(*R*)-BINOL	TBHP	24	79[d]	6[e]	*R*
8	$Cp_2Ti(OTf)_2$	Activated	(+)-(*R*)-BINOL	TBHP	24	90	37	*R*

[a] Molar ratios: Cp_mTiX_n/chiral ligand/**2a**/ROOH/m.s. 0.14/0.17/1/1.2/500 mg.
[b] Isolated yields; [sulfoxide]/[sulfone] > 15.
[c] The e.e. values were measured by HPLC using OB column.
[d] [Sulfoxide]/[sulfone] = 8.9.
[e] The e.e. values were determined by ^{1}H NMR analysis (400 MHz) in the presence of (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine as shift reagent.



Scheme 4.



Scheme 5.

With (*R*,*R*)-(+)-hydrobenzoin (a 1,2-diol), **3a** was obtained in low yield, lower e.e. and preferentially as *S*-entiomer. The percentage of water has influence on the enantioselectivity of this type of oxidations [11–13,15], so we performed some reactions with m.s. containing variable percentages of water (entries 4–6), but the yields and the e.es. were only marginally affected. Finally with $CpTiCl_3$ the reaction proceeded with very low enantioselectivity (entry 7), while $Cp_2Ti(OTf)_2$ furnished almost the same results of Cp_2TiCl_2 (last entry and entry 3 in Table 2).

3.3. Asymmetric oxidation of sulfides catalyzed by Cp_2TiCl_2/(+)-(R)-BINOL/TBHP/activated 4Å m.s.

Having optimized the sulfoxidation conditions, we performed the oxidation reactions on a range of sulfides (Scheme 5, Table 4).

Table 4
Asymmetric oxidation of methyl sulfides with Cp_2TiCl_2/(+)-(R)-BINOL/TBHP/activated 4 Å m.s.[a]

Entry	*R*	*t* (h)	Yield **3**%[b]	e.e. **3**%[c]	Absolute configuration
1	*p*-Me-C_6H_4 (a)	24	95	45	*R*
2	C_6H_4(b)	26	65	39	*R*
3	*p*-MeO-C_6H_4 (c)	25	80	40	*R*
4	*p*-Br-C_6H_4 (d)	24	83	37	*R*
5	*p*-Cl-C_6H_4 (e)	28	81	38	*R*
6	*p*-NO_2-C_6H_4 (f)	48	61	15	*R*
7	$C_6H_5CH_2$ (g)	24	80	12	*R*
8	$CH_3(CH_2)_7$ (h)	23	84	14	*R*

[a] Molar ratios: Cp_2TiCl_2/(+)-(*R*)-BINOL/**2**/ROOH/m.s. 0.14/0.17/1/1.2/500 mg.
[b] Isolated yields; [sulfoxide]/[sulfone] > 8.
[c] The e.e. values were measured by HPLC using OB column.

The level of enantioselectivity and the yields were similar in the oxidation of methyl aryl substituted sulfides, except for methyl *p*-nitro phenyl sulfide. This substrate proved to be less reactive having a poorer sulfur nucleophile. These results are in agreement with the involvement of an electrophilic active species in the oxidation. As generally reported for titanium–TBHP mediated asymmetric sulfoxidation the level of enantioselectivity reached for dialkyl sulfoxides **3g**, **h** (entries 7, 8) was quite low.

4. Conclusions

In conclusion we have disclosed a new system based on $Cp_2Ti(X)_2$ (X = Cl, OTf)/TBHP/activated 4 Å m.s. for the chemoselective oxidation of sulfides to sulfoxides. Furthermore, we have found out that the asymmetric oxidation of sulfides to sulfoxides is feasible with Cp_2TiCl_2/(+)-(*R*)-BINOL/activated 4 Å m.s./TBHP system. Methyl aryl sulfoxides are isolated in good yields and moderate e.es.

Acknowledgements

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