Bull Soc Chim Fr (1996) 133, 1109-1115

Catalytic enantioselective oxidation of sulfides with a chiral titanium complex

Jean-Michel Brunel, Henri B Kagan*

Laboratoire de synthèse asymétrique, URA CNRS 1497,
Institut de chimie moléculaire d'Orsay, Université Paris-Sud, 91405 Orsay, France

(Received 16 September 1996; accepted 3 October 1996)

Summary — A catalytic asymmetric oxidation of sulfides by cumyl hydroperoxide in the presence of a chiral titanium catalyst is reported. The influence of the nature of the titanium alkoxide and the role of 2-propanol on the enantioselectivity have also been investigated. The most efficient catalyst has been defined as a combination Ti(O*i*-Pr)$_4$/(*R*,*R*)-(DET)/*i*-PrOH, 1:4:4, in the presence of 4 Å molecular sieves. Asymmetric oxidation of various sulfides has been achieved in enantiomeric excesses up to 96%.

asymmetric oxidation / catalytic oxidation / sulfide / chiral sulfoxide / cumyl hydroperoxide

Résumé — Oxydation catalytique énantiosélective de sulfures en présence de complexes chiraux de titane. *L'oxydation asymétrique catalytique de sulfures en présence d'un catalyseur chiral de titane par l'hydroperoxyde de cumyle a été étudiée. L'influence de la nature de l'alcoolate de titane ainsi que le rôle du 2-propanol sur l'énantiosélectivité de la réaction ont été examinés. Le catalyseur le plus efficace mis au point est une combinaison Ti(Oi-Pr)$_4$/(R,R)-(DET)/i-PrOH, 1:4:4, générée en présence de tamis moléculaires 4 Å. L'oxydation asymétrique de nombreux sulfures a été réalisée pour conduire à de bons excès énantiomériques (⩽ 96 %).*

oxydation asymétrique / oxydation catalytique / sulfure / sulfoxyde chiral / hydroperoxyde de cumyle

Introduction

Asymmetric sulfoxides are very useful chiral auxiliaries in asymmetric synthesis [1-6]. Some sulfoxides are also of interest in the pharmaceutical industry either as intermediates in multistep syntheses or as biologically active compounds [7]. The established preparation of enantiopure sulfoxides is based on the Andersen method, which uses the reaction of organometallics with chiral sulfinates [8, 9]. Various improvements widening the scope of the reaction have recently been published, such as the preparation of some alkylsulfinates from sugars [10] and the use of chiral sulfites [11] or chiral sulfinyloxazolidinones [12]. The asymmetric oxidation of sulfides is also a convenient route to sulfoxides. In the last ten years, there has been much progress in this field. Some chiral reagents give sulfoxides in enantiomeric excesses (ee) higher than 90%. This was the case for chiral oxaziridines [13], sulfonylimines (used in conjunction with hydrogen peroxide) [14] and chiral titanium complexes [15–17]. Catalytic reactions [18] giving high enantioselectivities are still uncommon except for some biosulfoxidations [19]. Recently, Uemura described a Ti(O-*i*-Pr)$_4$/BINOL/H_2O 1:1:10 system that could control the oxidation of methyl *p*-tolyl sulfide (53% ee). This titanium complex is also very effective as a catalyst for promoting the kinetic resolution of sulfoxides [20]. Jacobsen reported the use of a chiral (salen)Mn complex as catalyst and H_2O_2 as oxidant to obtain sulfoxides in moderate ee [21]. Fujita used an *N*,*N*′-disalicylidene-(*R*,*R*)-1,2-cyclohexanediamine titanium(IV) catalyst leading to chiral sulfoxides in 53% ee [22]. The best result in this field (90% ee) appears to be the oxidation of *o*-nitrophenyl methyl sulfide by PhIO in the presence of a catalytic amount of a chiral (salen)Mn complex [23]. Recently, Bolm et al discovered that a chiral (salen)vanadium complex could catalyze asymmetric sulfoxidation by H_2O_2 with ee's up to 85% [24a] while Modena and coworkers set up a new titanium catalyst with a chiral aminotriol as ligand (ee up to 84%) [24b].

In 1984 our group (in Orsay) [15, 16] and Modena's group (in Padova) [17] independently discovered that a modification of the Sharpless reagent for asymmetric epoxidation was very useful as a chiral controller in the asymmetric oxidation of some sulfides by hydroperoxides. Our reagent, called here the 'Orsay reagent', is based on the combination Ti(O*i*-Pr)$_4$/(*R*,*R*)-diethyl tartrate (DET)/H_2O 1:2:1 while the 'Padova reagent' has the composition Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET 1:4. Both reagents give similar trends in asymmetric sulfoxidations. However some differences have been noted, for

* Correspondence and reprints

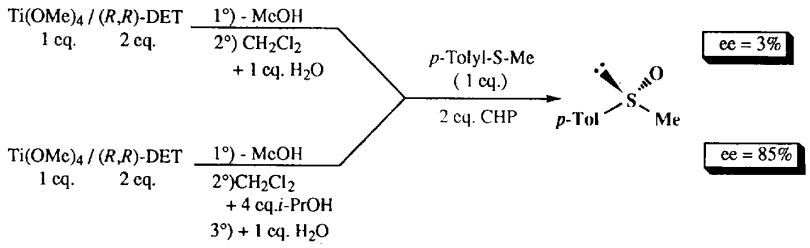


Fig 1. Experiments to probe the role of in-situ-generated alcohols during the exchange reaction. – MeOH means mixing $Ti(OMe)_4$ and (*R,R*)-DET in toluene for 30 min at room temperature, followed by addition of anhydrous degassed CH_2Cl_2 and evaporation to dryness.

example, in oxidation of 1,1-dithianes [25] or in the influence of temperature [26]. The Orsay reagent has been postulated as a binuclear species with a Ti-O-Ti bridge resulting from partial hydrolysis of titanium alcoholates. The structure is in agreement with molecular weight determination measured in solution [16a]. For the Padova reagent the structure $Ti(DET)_4$ has been suggested [26]. A chiral 1,2-diaryl-1,2-ethanediol was not very effective as a chiral ligand in the stoichiometric combination $Ti(Oi\text{-}Pr)_4$/diol/H_2O 1:2:1, as reported by Yamamoto in 1989 [27].

Because of the availability of both enantiomers of tartaric acid, we tried to improve the efficiency of our titanium reagent. We found that a strict control of the preparation of the complex (temperature and addition rates of the various components) allowed us to enhance both reproducibility and enantioselectivity of sulfoxidation. For example, ferrocenyl phenyl sulfoxide [28] and *p*-tolyl methyl sulfoxide could be prepared in ee > 99% [29]. Here we give a full account of our efforts to generate a catalytic process retaining the high enantioselectivities of the stoichiometric reaction.

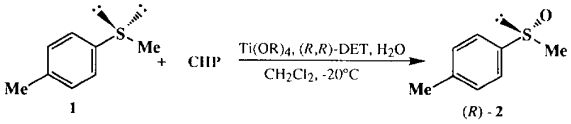
Influence of the nature of the titanium alkoxide. Preparation of a new reagent for asymmetric sulfoxidation

In order to ascertain the factors that determine the enantioselectivity of the chiral complex in the stoichiometric reaction, several experiments were carried out employing different titanium alkoxides. The oxidations were conducted under the optimal conditions described previously [29] using $Ti(OR)_4$/(*R,R*)-DET/H_2O 1:2:1. Thus, oxidation of *p*-tolyl methyl sulfide **1** was realized under stoichiometric conditions by cumyl hydroperoxide (CHP) leading to (*R*)-*p*-tolyl methyl sulfoxide **2** with an ee depending on the nature of the titanium alkoxide used and varying from 10% ($Ti(OMe)_4$) to 99% ($Ti(Oi\text{-}Pr)_4$) (table I) [30].

The influence of the titanium alkoxide on the enantioselectivities of the reaction is surprising [31]. This led us to probe the role of the in-situ-generated alcohols during the exchange reaction allowing the tartrate complexation. The following experiments were performed in CH_2Cl_2 at −20 °C using CHP as oxidant on a 3 mmol scale with 1 equiv of titanium methoxide (fig 1).

The complex was prepared by standard methods and was placed under vacuum to fully eliminate methanol. It

Table I. Influence of the nature of the titanium alkoxide used in the asymmetric oxidation of *p*-tolyl methyl sulfide by CHP in the presence of a stoichiometric amount of $Ti(OR)_4$/(*R,R*)-DET/H_2O 1:2:1.



Entry	*Titanium alkoxide*	*Yield (%)*[a]	*ee (%)*[b]
1	$Ti(OMe)_4$	75	10.3
2	$Ti(OEt)_4$	71	48.5
3	$Ti(Oi\text{-}Pr)_4$	76	>99.5
4	$Ti(On\text{-}Bu)_4$	82	82.1

[a] Isolated yield; experiment performed on the 3 mmol scale; [b] ee determined by HPLC analysis (see *Experimental section*).

was almost totally inactive, leading to the corresponding sulfoxide in poor chemical yield (19%) and low ee (3%). Nevertheless, it was reactivated for asymmetric sulfoxidation after the addition of dry 2-propanol (Ti/*i*-PrOH 1:4) and 1 equiv of water. Under these new conditions (*R*)-*p*-tolyl methyl sulfoxide was obtained in 70% chemical yield and 85% ee. These results clearly show the importance of 2-propanol in order to maintain the activity of the complex.

Influence of the amount of 2-propanol in the absence of water

The role of 2-propanol was investigated under stoichiometric conditions using the anhydrous combination $Ti(Oi\text{-}Pr)_4$/(*R,R*)-(DET) 1:2 (fig 2).

In the absence of water and 2-propanol, the reaction led to the desired sulfoxides in good chemical yield (70%) but low ee (10%). In presence of 1 equiv of 2-propanol, water was not necessary to obtain a good enantioselectivity (77% ee). Furthermore, better enantioselectivities could be reached using increasing amounts of 2-propanol (table II).

The best result (85% ee) was obtained using $Ti(Oi\text{-}Pr)_4$/(*R,R*)-(DET)/*i*-PrOH 1:2:4. However, the enantioselectivity did not reach that given (99% ee) by the reagents $Ti(Oi\text{-}Pr)_4$/(*R,R*)-(DET)/H_2O 1:2:1 (table I, entry 3) or $Ti(Oi\text{-}Pr)_4$/(*R,R*)-(DET)/H_2O/*i*-PrOH 1:2:1:1.

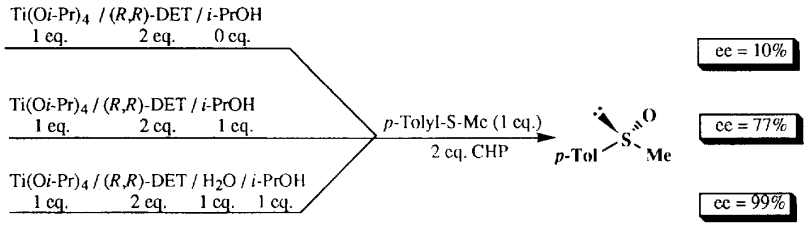


Fig 2. Experiments to determine the role of 2-propanol under stoichiometric conditions.

Table II. Influence of the amount of 2-propanol on the enantioselectivity of the asymmetric oxidation of *p*-tolyl methyl sulfide by CHP in the presence of a stoichiometric amount of Ti(O*i*-Pr)$_4$/(*R*,*R*)-(DET) 1:2.

Entry	i-*PrOH*	*Yield (%)*[a]	*ee (%)*[b]
1	0 equiv	62	10.1
2	1 equiv	77	77.3
3	2 equiv	75	80.0
4	4 equiv	78	85.2
5	10 equiv	77	69.1

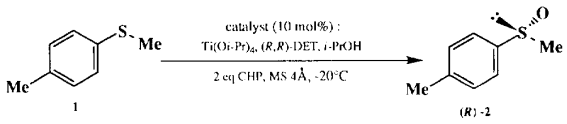
[a] Isolated yield; experiment performed on the 3 mmol scale; [b] ee determined by HPLC analysis (see *Experimental section*).

The next step in the development of asymmetric sulfoxidation is the need to find chiral titanium complexes behaving as catalysts. Our first attempts are described in the following section.

Catalytic asymmetric oxidation of sulfides

The modification of the experimental procedure in order to set up a catalytic system faces the problem of the inhibition effect of sulfoxides which are known to be good ligands for titanium alkoxides [32]. Indeed, it has been already noticed that the reagent Ti(O-*i*-Pr)$_4$/(*R*,*R*)-(DET)/H$_2$O/TBHP 1:2:1:1 at room temperature for 1 h does not oxidize *p*-tolyl methyl sulfide when 1 equiv of (*R*)- or (*S*)-*p*-tolyl methyl sulfoxide was previously added [16a]. Catalytic Sharpless epoxidation were achieved in 1986 by addition of molecular sieves, which suppress the formation of non-enantioselective complexes by moisture already present in the medium or produced during the reaction [33]. In 1987, we described the catalytic asymmetric oxidation of sulfides using a chiral titanium complex as a catalyst based on the Orsay reagent Ti(O*i*-Pr)$_4$/(*R*,*R*)-(DET)/H$_2$O 1:2:1 and molecular sieves. Addition of 4 Å molecular sieve led to enantioselectivity up to 90% under moderately catalytic conditions (20 mol% of the titanium complex). The use of lower proportions of this catalyst (10 mol%) decreased significantly the enantioselectivity (69% ee) [16b]. The beneficial effects of molecular sieves were also observed for our new combination Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/*i*-PrOH 1:2:4. Under catalytic conditions (10 mol%), (*R*)-*p*-tolyl methyl sulfoxide was obtained in 75% chemical yield and 83% ee (entry 5, table III). This result appears to be very promising for catalytic oxidation of sulfides. The beneficial effect on ee's was observed when the 4 Å molecular sieves were added before the other components. When the sieves (activated or unactivated) were added after the formation of the titanium complex, the enantioselectivity decreased significantly. Because of the various equilibria involved, many titanium species are potential catalysts. Addition of molecular sieves helps to maintain good enantioselectivity, perhaps by efficient regulation of the formation of the chiral desired titanium complex [34].

Table III. Asymmetric oxidation of *p*-tolyl methyl sulfide by CHP in the presence of 10 mol% of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/*i*-PrOH 1:2:*x* and 4 Å molecular sieve.



Entry	*Proportion*[a]	*Yield (%)*[b]	*ee (%)*[c]	*Molecular sieve*[d]
1	1:2:1	71	15.0	None
2	1:2:1	72	72.4	[e]
3	1:2:1	78	61.3	[f]
4	1:2:4	80	19.0	None
5	1:2:4	75	82.7	[e]
6	1:2:4	77	68.1	[f]

[a] Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/*i*-PrOH; [b] isolated yield; experiment performed at 3 mmol scale using 2 equiv of CHP and 10 mol% of catalyst; [c] ee determined by HPLC analysis (see *Experimental section*); [d] one weight equivalent with respect to the sulfide; [e] addition of the molecular sieves before the preparation of the catalyst; [f] addition of the molecular sieves after catalyst preparation.

Influence of the amount of (*R*,*R*)-DET

The influence of increasing amounts of ligand (*R*,*R*)-DET in the combination Ti(O*i*-Pr)$_4$/(*R*,*R*)-(DET)/*i*-PrOH (in a ratio 1:*x*:4) was also investigated under the above catalytic conditions (table IV). There was a substantial improvement of the enantioselectivity with the increase of the amount of the ligand used. The best ee was reached using 4 equiv of (*R*,*R*)-DET (with respect to the titanium alkoxide) leading to the formation of (*R*)-*p*-tolyl methyl sulfoxide in 77% chemical yield and 96% ee (entry 3).

With the above optimal conditions (entry 3), we have carried out the catalytic oxidation of some aryl alkyl and dialkyl sulfides (table V). Many aryl methyl sulfoxides with various substituents on the aromatic ring

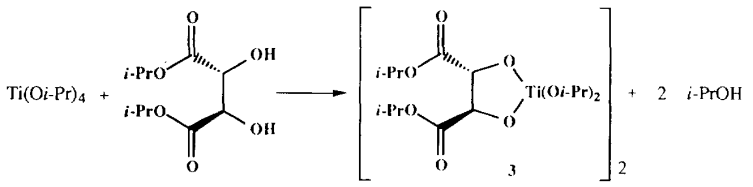
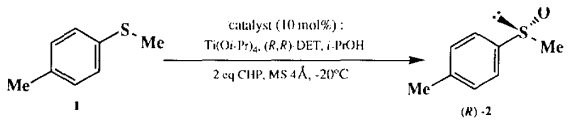


Fig 3. Reaction of Ti(O*i*-Pr)$_4$ with (*R*,*R*)-DIPT.

Table IV. Influence of the amount of (*R*,*R*)-DET on the enantioselectivity of the asymmetric oxidation of *p*-tolyl methyl sulfide by CHP in the presence of 10 mol% of Ti(O-*i*-Pr)$_4$/(*R*,*R*)-(DET)/*i*-PrOH 1:*x*:4 and 4 Å molecular sieve.



Entry	*Proportion*[a]	*Yield (%)*[b]	*ee (%)*[c]
1	1:2:4	75	82.7
2	1:3:4	73	90.4
3	1:4:4	77	95.6
4	1:5:4	78	94.1

[a] Ratio of Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/*i*-PrOH; [b] isolated yield; experiment performed at 3 mmol scale using 2 equiv of CHP and 10 mol% of catalyst; molecular sieves (one weight equivalent with respect to the sulfide) added before the preparation of the catalyst; [c] ee determined by HPLC analysis (see *Experimental section*).

gave ee > 90% (entries 1–4). Enantioselectivity is lower for oxidation of *o*-nitrophenyl methyl sulfide and *p*-tolyl ethyl sulfide (entries 5–7) but remains still respectable (90%) for the oxidation of benzyl methyl sulfide (entry 10). Finally, methyl *n*-octyl sulfoxide (entry 11) is formed in moderate ee (70%), which is lower than in our previous stoichiometric procedure (85% ee) [29].

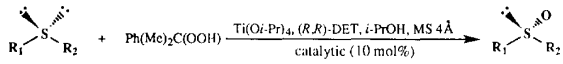
Mechanism of the reaction

The reaction of Ti(O*i*-Pr)$_4$ with (*R*,*R*)-DIPT was reported by Finn and Sharpless to proceed to give mainly the dimeric titanium compound **3** [36].

Solvate formation is often observed when transition metal alkoxides are dissolved in their parent alcohol. Solvation usually leads to a decrease in molecular complexity because it gives a different way of satisfying the coordination of the metal center [37]. According to these facts, a monomeric structure **5** may be suggested as an efficient catalyst in the above enantioselective reaction of oxidation of sulfides and a catalytic cycle is tentatively proposed as outlined in figure 4.

Dimeric complex **4** must be in equilibrium with other species and the amount of isopropanol could be crucial to optimize the formation of **5** (involving a coordination for an isopropanol molecule). When methanol is used, strong autoassociations of titanium complexes occur, as are known for example for Ti(OMe)$_4$, which has a polymeric structure [32]. Isopropoxide is present during the oxygen transfer to sulfur and may contribute to

Table V. Asymmetric oxidation of sulfides by cumyl hydroperoxide in the presence of 10 mol% of Ti(O-*i*-Pr)$_4$/(*R*,*R*)-(DET)/*i*-PrOH 1:4:4 and 4 Å molecular sieve.



Entry	R_1	R_2	*Yield (%)*[a]	*ee (%)*[b]
1	Phenyl	Me	81	91.2 (*R*)
2	*p*-Tolyl	Me	77	95.6 (*R*)
3	*p*-Anisyl	Me	73	92.1 (*R*)
4	*o*-Anisyl	Me	72	89.3 (*R*)
5	*o*-Nitrophenyl	Me	51	75.0 (*R*)
6	Phenyl	$CH{=}CH_2$	58	55.4 (*R*)
7	*p*-Tolyl	Et	68	78.1 (*R*)
8	*p*-Tolyl	*n*-Butyl	70	25.0 (*R*)
9	*o*-Anisyl	Phenyl	64	6.2 (*R*)
10	Benzyl	Me	72	90.3 (*R*)
11	*n*-Octyl	Me	69	70.7 (*R*)

[a] Isolated yield; experiment performed at 3 mmol scale using 2 equiv of CHP (see note b table IV and *Experimental section*); [b] ee determined by HPLC analysis (see *Experimental section*); absolute configurations were established by comparison of the sign of $[\alpha]_D$ to literature values [13–17].

the high enantioselectivity of the process. The excess of isopropanol should also be beneficial for displacing sulfoxide from **7** and thus restoring the catalytic activity by formation of **5**. One may envisage that the excess of isopropanol promotes the displacement of the chelated ester carbonyl group. IR study (preliminary results) rule out this hypothesis. Titanium complexes other than **5** may be candidates as the enantioselective species for the sulfoxidation, for example, dimeric complexes of the type (DET)Ti(O*i*-Pr)$_2$Ti(O*i*-Pr)$_4$. This problem is under active investigation.

Conclusion

A highly enantioselective catalytic system for the oxidation of many sulfides has been set up. It is based on the use of a titanium combination Ti(O*i*-Pr)$_4$/(*R*,*R*)-(DET)/*i*-PrOH 1:4:4 in presence of activated molecular sieves 4 Å; ee's in the range of 80–95% are often obtained, leading to the highest enantioselectivity presently achieved in catalytic asymmetric sulfoxidation by non-enzymatic methods. We are currently working to enhance the catalytic activity of the titanium complex without decrease of the enantioselectivity and to investigate the mechanistic aspects of this system including the role of the molecular sieves.

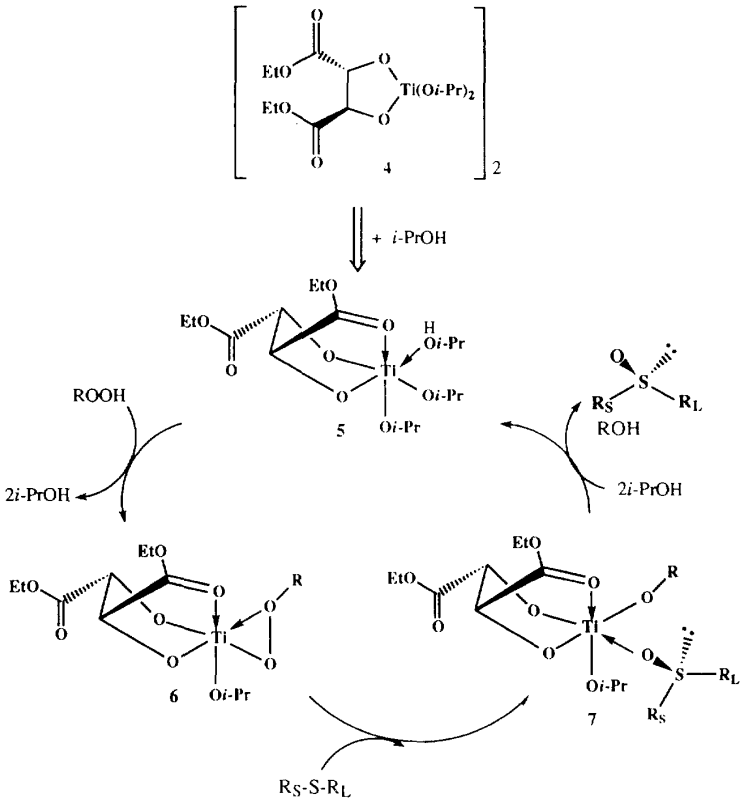


Fig 4. Tentative catalytic cycle for the enantiomeric reaction of the oxidation of sulfides.

Experimental section

General methods

All operations were performed under argon. CH_2Cl_2 was distilled from calcium hydride and stored over activated 4 Å molecular sieves under argon. Ti(O*i*-Pr)$_4$ and diethyl tartrate were distilled under argon before use. Molecular sieves (pellets, 4 Å) were purchased from Prolabo and activated at 200 °C under vacuum for 16 h and storred under argon. The commercially available cumyl hydroperoxide (80% in cumyl alcohol) was purchased from Aldrich and used without further purification. Measurements of ee's were performed by HPLC analyses on a Spectroseries P100 pump module with a Spectroseries UV 100 detector and a Daicel Chiralcel OD-H column. IR spectra (cm^{-1}) were recorded on a Perkin-Elmer 883 spectrometer in CH_2Cl_2 solution. NMR spectra were recorded on a Bruker AC250 in $CDCl_3$ and chemical shifts (δ) given in ppm with TMS as internal standard.

General procedure for catalytic oxidation of sulfides (table V)

A solution of 205 μL (*R,R*)-diethyl tartrate (1.2 mmol) in 10 mL dichloromethane at 16 °C was added under argon in a flask containing 1 weight equivalent (with respect to the sulfide) of molecular sieve 4 Å. This solution was stirred during 2.5 min and 90 μL titanium tetraisopropoxide (0.3 mmol) was slowly added. The resulting mixture was stirred for 10 min at 16 °C and 92 μL 2-propanol (1.2 mmol) was slowly added. Stirring was maintained during 10 min followed by cooling in a freezer (−22 °C) without stirring for an additional 20 min. The reaction was allowed to take place after rapid addition of the sulfide (3 mmol) and pre-cooled (−22 °C) cumyl hydroperoxide (6 mmol), with storage of the flask in the refrigerator (−22 °C) without stirring. After 16 h the mixture was poured into a solution of 3 g ferrous sulfate heptahydrate (10.8 mmol) and 1 g citric acid (4.8 mmol) in 30 mL water, 15 mL 1,4-dioxane and 25 mL diethyl ether, and was stirred for 15 min. The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic phases were stirred vigorously with 50 mL 2 M aqueous sodium hydroxide for 1 h. The aqueous solution was then extracted with diethyl ether (3 × 20 mL). The combined organic solutions were washed with brine (25 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Flash chromatography on silica gel of the crude products first afforded unreacted sulfide, sulfone and cumyl alcohol then pure sulfoxide. The fractions of sulfoxide were mixed before ee measurement [38].

All the ee's were measured by chiral HPLC analysis: λ = 254 nm, 0.5 mL/min (eluent 9:1 hexane/*i*-PrOH), except for (*R*)-*p*-anisyl methyl sulfoxide, (*R*)-*o*-anisyl methyl sulfoxide and *p*-nitrophenyl methyl sulfoxide (eluent 30:1 hexane/*i*-PrOH). Absolute configuration were assigned by comparison of the sign of specific rotations with literature data [13–17].

- *(R)-Phenyl methyl sulfoxide*

Purification by silica-gel chromatography (eluent ethyl acetate) afforded 374 mg (81% yield) as white solid.

$[\alpha]_D$ +124.1 (*c* = 1, acetone).

IR: 3 458, 1 645, 1 471, 1 439, 1 410, 1 085, 1 042, 953, 744, 687, 497.

^{1}H NMR: 2.73 (s, 3H); 7.56–7.49 (m, 3H); 7.67–7.64 (m, 2H).

HPLC: tr (*R*) = 21.7 min, tr (*S*) = 26.1 min, ee = 91.2%.

• *(R)-p-Tolyl methyl sulfoxide*

Purification by silica-gel chromatography (eluent ethyl acetate) afforded 356 mg (77% yield) as white solid.

$[\alpha]_D$ +139.0 (*c* = 2, acetone).

IR: 3 040, 1 580, 1 450, 1 070, 1 030.

^{1}H NMR: 2.41 (s, 3H); 2.70 (s, 3H); 7.40–7.71 (m, 4H).

HPLC: tr (*R*) = 18.5 min, tr (*S*) = 20.4 min, ee = 95.6%.

• *(R)-p-Anisyl methyl sulfoxide*

The starting sulfide was purified by flash chromatography on silica-gel in order to remove some impurities which perturb HPLC analysis. Purification of the crude sulfoxide by silica-gel chromatography (eluent hexane/ethyl acetate, 1:1) afforded 372 mg (73% yield) as white solid.

$[\alpha]_D$ +153.5 (*c* = 0.38, $CHCl_3$).

IR: 3 070, 1 590, 1 300, 1 250, 1 085, 1 020.

^{1}H NMR: 2.67 (s, 3H); 3.81 (s, 3H); 7.00 (d, *J* = 9 Hz, 2H); 7.58 (d, *J* = 9 Hz, 2H).

HPLC: tr (*R*) = 20.3 min, tr (*S*) = 21.2 min, ee = 92.1%.

• *(R)-o-Anisyl methyl sulfoxide*

Purification by silica-gel chromatography (eluent hexane/ethyl acetate, 1:1) afforded 370 mg (72% yield) as white solid.

$[\alpha]_D$ +318.6 (*c* = 1, acetone).

IR: 3 080, 2 840, 1 580, 1 475, 1 270, 1 235, 1 015.

^{1}H NMR: 2.72 (s, 3H); 3.86 (s, 3H); 6.85 (d, *J* = 9 Hz, 2H); 7.88 (d, *J* = 9 Hz, 2H).

HPLC: tr (*R*) = 20.2 min, tr (*S*) = 20.9 min, ee = 89.3%.

• *(R)-o-Nitrophenyl methyl sulfoxide*

Purification by silica-gel chromatography (eluent ethyl acetate) afforded 283 mg (51% yield) as white solid.

$[\alpha]_D$ +118.5 (*c* = 0.75, $CHCl_3$).

IR: 3 086, 2 992, 2 906, 1 642, 1 580, 1 504, 1 418, 1 330, 1 113, 1 089, 964, 849, 828, 735, 676, 524, 464.

^{1}H NMR: 2.18 (s, 3H); 6.60 (t, *J* = 7.8 Hz, 1H); 6.93 (t, *J* = 7.8 Hz, 1H); 6.99 (dd, *J* = 0.9 and 7.8 Hz, 1H); 8.03 (dd, *J* = 1.5 and 7.8 Hz, 1H).

HPLC: tr (*R*) = 20.5 min, tr (*S*) = 21.2 min, ee = 75.0%.

• *(R)-Phenyl vinyl sulfoxide*

Purification by silica gel chromatography (eluent hexane/ethyl acetate, 1:1) afforded 236 mg (58% yield) as white solid.

$[\alpha]_D$ +168.2 (*c* = 1.05, acetone).

IR: 3 045, 3 020, 1 610, 1 580, 1 438, 1 080, 1 040, 750.

^{1}H NMR: 5.85 (d, *J* = 9 Hz, 1H); 6.17 (d, *J* = 16 Hz, 1H); 6.65 (dd, *J* = 9, 16 Hz, 1H); 7.0–8.0 (m, 5H).

ee = 55.4%.

• *(R)-p-Tolyl ethyl sulfoxide*

Purification by silica-gel chromatography (eluent ethyl acetate) afforded 342 mg (68% yield) as an oil.

$[\alpha]_D$ +146.1 (*c* = 1.1, acetone).

IR: 3 040, 1 580, 1 370, 1 025, 820, 755.

^{1}H NMR: 1.20 (m, 3H); 2.81 (s, 2H); 2.83 (m, 3H); 7.29 (m, 2H), 7.47 (m, 2H).

HPLC: tr (*R*) = 14.9 min, tr (*S*) = 17.5 min, ee = 78.1%.

• *(R)-p-Tolyl n-butyl sulfoxide*

Purification by silica-gel chromatography (eluent ethyl acetate) afforded 383 mg (70% yield) as white solid.

$[\alpha]_D$ +72.0 (*c* = 1, acetone).

IR: 3 040, 1 520, 1 320, 1 030, 820, 755.

^{1}H NMR: 1.18 (m, 3H); 1.35 (m, 4H); 2.83 (s, 3H); 2.90 (m, 2H); 7.41–7.52 (m, 4H).

HPLC: tr (*R*) = 15.8 min, tr (*S*) = 16.9 min, ee = 25.0%.

• *(R)-o-Anisyl phenyl sulfoxide*

Purification by silica-gel chromatography (eluent ethyl acetate) afforded 468 mg (64% yield) as white solid.

IR: 3 040, 1 610, 1 575, 1 030, 820, 760.

^{1}H NMR: 2.93 (s, 3H); 7.18 (m, 5H); 7.37 (m, 4H).

HPLC: tr (*R*) = 25.1 min, tr (*S*) = 26.0 min, ee = 6.2%.

• *(R)-Benzyl methyl sulfoxide*

Purification by silica-gel chromatography (eluent ethyl acetate) afforded 333 mg (72% yield) as white solid.

$[\alpha]_D$ +49.4 (*c* = 1.9, acetone).

IR: 3 040, 1 490, 1 450, 1 370, 1 295, 1 015.

^{1}H NMR: 2.42 (s, 3H); 3.96 (d, *J* = 6 Hz, 2H); 7.53 (m, 5H).

HPLC: tr (*R*) = 35.8 min, tr (*S*) = 40.8 min, ee = 90.3%.

• *(R)-Methyl n-octyl sulfoxide*

Purification by silica-gel chromatography (eluent ethyl acetate) afforded 344 mg (69% yield) as white solid.

$[\alpha]_D$ −59.2 (*c* = 1, acetone).

IR: 3 040, 1 580, 1 030, 820, 755.

^{1}H NMR: 0.9 (m, 3H); 1.2–2.0 (m, 12H); 2.53 (s, 3H); 2.60 (m, 2H).

HPLC: tr (*R*) = 16.9 min, tr (*S*) = 20.3 min, ee = 70.7% [39].

Acknowledgments

We thank CNRS and Institut universitaire de France for its financial support. One of us (JMB) acknowledges Rhône Poulenc for a postdoctoral fellowship. We thank P Pitchen for useful discussions.

References and notes

1 For some reviews on the synthesis and application of chiral sulfoxides, see:
a) Solladié G, *Synthesis* (1981), 185 and references therein
b) Andersen KK, In: *The Chemistry of Sulfones and Sulfoxides*, Patai S, Rappoport Z, Stirling CJM, eds, John Wiley & Sons, Chichester, UK, 1988, Chapter 3, p 55
c) Posner GH, In: *The Chemistry of Sulfones and Sulfoxides*, Patai S, Rappoport Z, Stirling CJM, eds, John Wiley & Sons, Chichester, UK, 1988, Chapter 16, p 823

2 Carreño MC, *Chem Rev* (1995) 95, 1717

3 Barbachyn JD, Johnson CR In: *Asymmetric Synthesis*, Morrison JD, Scott JW, eds, Academic Press, New York, 1983, Vol 4, p 227

4 Kagan HB, Rebiere F, *Synlett* (1990) 643

5 a) Posner GH, *Acc Chem Res* (1987) 20, 72
b) Mikolaczyk M, Drabowicz J, *Top Stereochem* (1982) 13, 333

6 a) Pyne SG, Bloem P, Chapman SL, Dixon CE, Griffith R, *J Org Chem* (1990) 55, 1086
b) Hua DH, Bharathi SN, Takusagawa F, Tsujimoto A, Panagan JAK, Hung MH, Bravo A, Erplelding AM,

J Org Chem (1989) 54, 5659
c) Bolm C, Müller P, *Tetrahedron Lett* (1995) 36, 1625

7 a) Pitchen P, France CJ, McFarlane IM, Newton CG, Thompson DM, *Tetrahedron Lett* (1994) 35, 485
b) Pitchen P, *Chem Ind* (1994) 636
c) Matsugi M, Hashimoto K, Inai M, Fukuda N, Furuta T, Minamikawa JI, Otsuka S, *Tetrahedron: Asymmetry* (1995) 12, 2991

8 Andersen KK, *Tetrahedron Lett* (1962) 3, 93 and refs [1b–3] therein

9 Whitesell JK, Wong MS, *J Org Chem* (1994) 59, 597

10 a) Fernandez I, Khiar N, Llera JM, Alcudia F, *J Org Chem* (1992) 57, 6789
b) Guerrero de la Rosa V, Ordonez M, Llera JM, Alcudia F, *Synthesis* (1995) 761

11 a) Rebiere F, Samuel O, Ricard L, Kagan HB, *J Org Chem* (1991) 56, 5991
b) Rebiere F, Kagan HB, *Tetrahedron Lett* (1989) 30, 3659
c) Pelloux-Léon N, Gautier-Lumeau I, Wendt S, Vallée Y, *Tetrahedron: Asymmetry* (1996) 7, 1007

12 Evans DA, Faul MM, Colombo L, Bisaha JJ, Clardy J, Cherry DJ, *J Am Chem Soc* (1992) 114, 5977

13 a) Davis FA, Sheppard AC, *Tetrahedron* (1989) 45, 5703
b) Davis FA, Reddy RT, Weismiler MC, *J Am Chem Soc* (1989) 111, 5964
c) Davis FA, Weismiler MC, Murphy CK, Reddy RT, Chen BC, *J Org Chem* (1992) 57, 7274
d) Davis FA, Reddy RT, Han W, Carroll PJ, *J Am Chem Soc* (1992) 114, 1428

14 Bulman Page PC, Heer JP, Bethell D, Collington EW, Andrews DM, *Synlett* (1995), 773

15 Pitchen P, Kagan HB, *Tetrahedron Lett* (1984) 25, 1049

16 a) Pitchen P, Duñach E, Deshmukh MN, Kagan HB, *J Am Chem Soc* (1984) 106, 8188
b) Zhao S, Samuel O, Kagan HB, *Tetrahedron* (1987) 43, 5135
c) Zhao S, Samuel O, Kagan HB, *Org Synth* (1989) 68, 49
d) Kagan HB, Duñach E, Nemecek C, Pitchen P, Samuel O, Zhao S, *Pure Appl Chem* (1985) 57, 1911

17 a) Di Furia F, Modena G, Seraglia G, *Synthesis* (1984), 325
b) Bortolini O, Di Furia F, Licini G, Modena G, Rossi M, *Tetrahedron Lett* (1986) 27, 6257

18 Kagan HB, In: *Catalytic Asymmetric Synthesis*, Ojima I, ed, VCH, 1993, 203

19 a) Holland HL, *Chem Rev* (1988) 88, 473
b) Allen CC, Boyd DR, Dalton H, Sharma ND, Haughey SA, Austin R, McMordie S, McMurray BT, Sheldrake GN, Sproule K, *J Chem Soc, Chem Commun* (1995), 119
c) Ottolina G, Pasta P, Carrea G, Colonna S, Dallavalle S, Holland HL, *Tetrahedron: Asymmetry* (1995) 6, 1375

20 a) Komatsu N, Hashizume M, Sugita T, Uemura S, *J Org Chem* (1993) 58, 4529
b) Komatsu N, Hashizume M, Sugita T, Uemura S, *J Org Chem* (1993) 58, 7624

21 Palucki M, Hanson P, Jacobsen EN, *Tetrahedron Lett* (1992) 33, 7111

22 Nakajima K, Sasaki C, Kojima M, Aoyama T, Ohba S, Saito Y, Fujita J, *Chem Lett* (1987) 2189

23 Noda K, Hosoya N, Irie R, Yamashita Y, Katsuki T, *Tetrahedron* (1994) 32, 9609

24 a) Bolm C, Bienwald F, *Angew Chem Int Ed Engl* (1995) 34, 2640
b) Di Furia F, Licini G, Modena G, Motterle R, Nugent WA, *J Org Chem* (1996) 61, 5175

25 Aggarwal VK, Evans G, Doya E, Dowden J, *J Org Chem* (1992) 57, 6390

26 Conte V, Di Furia F, Licini G, Modena G, Sbampato G, In: *Dioxygen Activation and Homogeneous Catalytic Oxidation*, Simandi LI, ed, Elsevier Science Publishers, Amsterdam, 1991, 385

27 Yamamoto K, Ando H, Shuetake T, Chikamatsy H, *J Chem Soc, Chem Commun* (1989) 754

28 Diter P, Samuel O, Taudien S, Kagan HB, *Tetrahedron: Asymmetry* (1994) 5, 549

29 Brunel JM, Diter P, Duetsch M, Kagan HB, *J Org Chem* (1995) 60, 8086

30 A similar observation on the advantage of using Ti(O-*i*-Pr)$_4$ as titanium alkoxide for preparation of a chiral catalyst has been reported in the enantioselective trimethylsilylcyanation of aldehydes. Hayashi M, Miyamoto Y, Inoue T, Oguni N, *J Org Chem* (1993) 58, 1515

31 Recently, a combination Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/*i*-PrOH 1:1:1 has been used in enantioselective trimethylsilylcyanation of aldehydes catalyzed by titanium alkoxide–diethyl tartrate complexes in presence of *i*-PrOH as additive.
a) Hayashi M, Matsuda T, Oguni N, *J Chem Soc, Chem Commun* (1990) 1364
b) Hayashi M, Matsuda T, Oguni N, *J Chem Soc, Perkin Trans I* (1992) 3135

32 Bradley DC, Mehrotra RC, Gaur DP, In: *Metal Alkoxides*, Academic Press, London, New York, 1978

33 Hanson RM, Sharpless KB, *J Org Chem* (1986) 51, 1922

34 Recently, Posner decribed that surface chemistry/morphology and control of moisture content within the molecular sieves proved to be extremely significant variables for asymmetric Diels–Alder cycloadditions catalyzed by a chiral titanium complex. Thus, an increase in enantioselectivity with increasing sieve hydration has been observed [35a]. Such an observation has been also reported in a catalyzed palladium cyclization of *cis*-1,2-divinylcyclohexane [35b]

35 a) Posner GH, Dai H, Bull DS, Lee JK, Eydoux F, Ishihara Y, Welsh W, Pryor N, Petr S, *J Org Chem* (1996) 61, 671
b) Tottie L, Baeckström P, Moberg C, Egenfeldt T, Heumann A, *J Org Chem* (1992) 57, 6579

36 Finn MG, Sharpless KB, *J Am Chem Soc* (1991) 113, 113

37 This has been observed on a acac-modified titanium butoxide with an equilibrium between [Ti(O*n*-Bu)$_3$(acac)]$_2$ and Ti(O*n*-Bu)$_2$(acac)$_2$ in *n*-butanol. Blanchard J, Bardoux-Boeuff S, Maquet J, Sanchez C, *New J Chem* (1995) 19, 929

38 Diter P, Taudien S, Samuel O, Kagan HB, *J Org Chem* (1994) 59, 370

39 The ee was measured by HPLC analysis of the corresponding homologous sulfoxide obtained from *n*-octyl methyl sulfoxide by treatment with NaH and benzyl bromide