Highly Enantioselective Oxidation of Sulfides Mediated by a Chiral Titanium Complex

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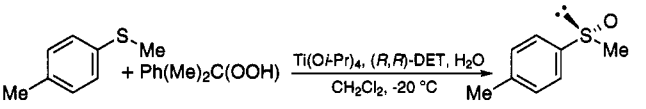
Received July 18, 1995

Chiral sulfoxides are important compounds that are finding increasing uses as chiral auxiliaries in asymmetric synthesis[1] or which can be of interest in the pharmaceutical industry.[2] Among the various ways to prepare chiral sulfoxides, the asymmetric oxidation of sulfides is one of the most attractive.[3–6] The use of a hydroperoxide in the presence of *stoichiometric amounts* of various types of chiral titanium complexes derived from the Sharpless reagent allowed us to achieve ee's up to 90–95%. We have described the usefulness of the combination Ti(O*i*-Pr)$_4$/(*R*,*R*)-diethyl tartrate (DET)/H$_2$O = 1:2:1[7] and Modena *et al.* used the combination Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET = 1:4.[8] Various chiral oxaziridines prepared by Davis *et al.* are also excellent reagents for sulfoxidation.[9] *The catalytic sulfoxidation*, where the chiral auxiliary is part of the catalyst, gave rise to promising results although the ee's remained modest except for a few cases.[10–12] In this article, we wish to describe our results concerning the optimization of the water-modified Sharpless titanium complex (Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/H$_2$O = 1:2:1) which gave rise to very high enantioselectivities (over 99%) in many cases.

Results and Discussion

Many studies in asymmetric sulfoxidation have been realized by the combination Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET/H$_2$O = 1:2:1 since we discovered this reaction in 1984[7a,b] (Scheme 1). We found that cumyl hydroperoxide is frequently superior to *tert*-butyl hydroperoxide.[7c,d] The best solvent in which to run the reaction is dichloromethane or 1,2-dichloroethane.[7e] Finally, the optimum temperature range for the oxidation is around −20 °C to −30 °C.[7b] We noticed in our laboratory that some newcomers had difficulties reproducing some of the previous results. One reason for this originated with the isolation procedure. Isolation by flash chromatography on silica gel is a good method for purification of the sulfoxides but before taking an aliquot to measure the enantiomeric excess it is necessary to mix all the sulfoxide fractions together. It has been found that enantiomeric enrichment often occured through the flash chromatography of the sulfoxides.[13] Another source of fluctuation in the ee's was the experimental conditions *for the preparation of the chiral titanium complex*.

Scheme 1



We discovered that a careful control of both the temperature and the reaction time in the premixing (in a defined order) of Ti(O*i*-Pr)$_4$, (*R*,*R*)-DET, and water was necessary in order to ensure high ee's in asymmetric oxidation of some ferrocenyl sulfides.[14] The same observation applies to sulfenyl substituted tricarbonyl(η^6-arene)chromium(0) complexes.[15] We made an extensive investigation to define the optimal conditions for the asymmetric synthesis of aryl alkyl sulfoxides, an important class of chiral sulfoxides. For that purpose, the experiments were first conducted on the asymmetric oxidation of *p*-tolyl methyl sulfide as a model reaction (Table 1). The reactions were performed in dichloromethane on 3 mmol of sulfide. The chiral titanium complex was prepared at a defined temperature (between 16 °C and 35 °C), Ti(O*i*-Pr)$_4$ was either freshly distilled or aged for one month, commercial diethyl tartrate was distilled, and cumyl hydroperoxide was used as received. For the sake of accurate data all the experiments were carried out with chemicals coming from the same supply. It was found that the highest degree of reproducibility was ensured by adding Ti(O*i*-Pr)$_4$ to diethyl tartrate and waiting for a time t_1 before adding water dropwise during time t_2. This last operation is crucial. Indeed, the partial

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Table 1. Asymmetric Oxidation of *p*-Tolyl Methyl Sulfide by Cumyl Hydroperoxide in the Presence of 1 Equiv of Ti(O*i*-Pr)$_4$/(*R,R*)-(DET)/H_2O = 1:2:1

entry	age[a] of Ti(O-*i*Pr)$_4$	T (°C)	t_1[b] (min)	t_2[c] (s)	t_3[d] (min)	t_4[e] (min)	t_5[f] (h)	yield[g] (%)	ee[h] (%)
1	10 min	16	2.5	90	20	18	23	72	>99.5
2	10 min	16	–	90	21	18	23	69	95.2
3	4 h	16	2.5	90	20	18	23	69	>99.5
4	9 h	16	2.5	90	22	20	22	72	>99.5[i]
5	24 h	16	2.5	90	21	20	22	77	99.3
6	54 h	16	2.5	90	22	20	20	74 (15)	95.5
7	54 h	15.5	2.5	–	21	20	21	72 (13)	94.2
8	54 h	15.5	2.5	45	20	19	22	71 (13)	96.2
9	54 h	15.5	2.5	90	5	19	21	76 (15)	99.5
10	54 h	15.5	2.5	90	20	20	15	73 (13)	99.2
11	54 h	15.5	2.5	90	20	6	20	74 (12)	99.0
12	1 month	15.5	2.5	90	20	20	20	68 (15)	99.2

[a] After distillation of the commercial sample. [b] t_1: Period between the end of addition of Ti(O*i*-Pr)$_4$ on (*R,R*)-DET and beginning of addition of water. [c] t_2: Period of addition of water with a 50 μL syringe. [d] t_3: Period between last drop of water and beginning of cooling at −20 °C. [e] t_4: Period of cooling at −20 °C without stirring. [f] t_5: Period of reaction. [g] Isolated yield. Experiment performed at 3 mmol scale. Isolation by flash chromatography on silica gel (eluent:ethyl acetate). The number in parentheses is the yield of the corresponding isolated sulfone. [h] Enantiomeric excess (ee) determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane−*i*-PrOH 9:1, λ = 254 nm). [i] 95% ee for a 30 mmol scale up (unoptimized).

hydrolysis of titanium alkoxide which forms reactive oligomers may take place at the surface of water drops in dichloromethane. Because this is a two phase reaction the size of the water drops, the mode of stirring and the time of addition could play an important role in the formation of the still unknown reactive titanium complex. The rate of addition of water (see Experimental Section) is important to ensure an enantiomeric excess reproducibility.

The use of freshly distilled or aged Ti(O*i*-Pr)$_4$ has no influence on the enantiomeric excess. However, the ageing of Ti(O*i*-Pr)$_4$ favored the competitive formation of sulfones (entries 6−12). On the other hand, the ageing length t_3 (between the last drop of water and beginning of cooling at −20 °C) and the resting period t_4 at −20 °C before starting the reaction are without influence on the enantioselectivity of the oxidation. Representative experiments are listed in Table 1. The best conditions (entries 1−5) allowed us to reach repeatedly more than 99.5% ee in the asymmetric synthesis of *p*-tolyl methyl sulfoxide. This value was accurately measured by chiral HPLC on a Chiralcel OD-H column and with hexane/2-propanol (9:1) as eluent.[16]

With the above optimal conditions, we have realized the oxidation of various aryl alkyl and dialkyl sulfides (Table 2). Many aryl methyl sulfoxides with various substituents on the aromatic ring gave the same ee (>99%) (entries 1−4). Enantioselectivity is lower for oxidation of naphthyl sulfides (entries 6−7) but is still respectable (95%) for the oxidation of o-anisyl methyl sulfide and benzyl methyl sulfide (entries 5, 11). Finally, methyl *n*-octyl sulfoxide (entry 12) is formed in higher enantiomeric excess (85%) than that described by our previous procedure (81% ee).[7e]

In conclusion, a stoichiometric amount of the combination Ti(O*i*-Pr)$_4$/(*R,R*)-DET/H_2O = 1:2:1 is very useful for mediating the asymmetric oxidation of a wide range of sulfides in an highly enantioselective manner (>99% ee) which can find applications in asymmetric synthesis.[17]

Table 2. Asymmetric Oxidation of R_1SR_2 by Cumyl Hydroperoxide in the Presence of 1 Equiv of Ti(O*i*-Pr)$_4$/(*R,R*)-(DET)/H_2O = 1:2:1

entry	R_1	R_2	yield[a] (%)	ee (%)[b]
1	phenyl	Me	77	**99.2** (*R*)
2	*p*-tolyl	Me	75	>**99.5** (*R*)
3	*p*-nitrophenyl	Me	51	**99.3** (*R*)
4	*p*-anisyl	Me	78	**99.5** (*R*)
5	*o*-anisyl	Me	75	**95.3** (*R*)
6	1-naphthyl	Me	91	91.2 (*R*)
7	2-naphthyl	Me	81	77.5 (*R*)
8	*p*-tolyl	Et	82	86.6 (*R*)
9	*p*-tolyl	*n*-butyl	64	38.2 (*R*)
10	*o*-anisyl	phenyl	69	14.1 (*R*)
11	benzyl	Me	87	**95.4** (*R*)
12	*n*-octyl	Me	63	85.1 (*R*)

[a] Isolated yield. Experiment performed at 3 mmol scale. Isolation by flash chromatography on silica gel (see Experimental Section). [b] Enantiomeric excess (ee) determined by HPLC analysis on a Daicel Chiralcel OD-H column at λ = 254 nm (see Experimental Section). Absolute configurations were established by comparison of the sign of $[\alpha]_D$ to literature values.[7-9]

Well defined experimental conditions for the preparation of the titanium complex are needed to reach such high levels of enantioselectivity.

Experimental Section

Materials. All operations were performed under argon. CH_2Cl_2 was distilled from calcium hydride and stored over 4 Å molecular sieves under argon. Ti(O*i*-Pr)$_4$ and diethyl tartrate were distilled under argon before use. The commercially available cumene hydroperoxide (80% in cumene alcohol) was purchased from Aldrich and used without further purification. HPLC analyses were performed on a 870 pump module (Du Pont Instruments) with a UV ISCO detector and a Daicel Chiralcel OD-H column.

General Procedure for Oxidation of Sulfides. A 0.84 g amount of titanium tetraisopropoxide (3 mmol) was added rapidly (10 s) to a solution of 1.24 g of (*R,R*)-diethyl tartrate (6 mmol) in 10 mL of dichloromethane at 16 °C. After 2.5 min, 54 μL of water was added slowly using a microliter syringe with vigorous stirring and an interruption of 15 s after each drop. The resulting mixture was stirred for 20 min at 16 °C, 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 3 mmol of the sulfide and 6 mmol of precooled (−22 °C) cumene hydroperoxide, 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 of ferrous sulfate heptahydrate

(16) A reference sample (1 g) of (*R*)-*p*-tolyl methyl sulfoxide of 99.5% ee was prepared by mixing weighted amounts of the two enantiopure sulfoxides. Chiral HPLC could detect the minor enantiomer which was absent on the chromatogram of the sample prepared by asymmetric oxidation.

(17) For example methyl *o*-anisyl sulfoxide obtained by asymmetric oxidation of the corresponding sulfide was subsequently transformed into the corresponding sulfoximine. This compound was used as chiral catalyst in the enantioselective trimethylsilylcyanation of aldehydes.[18]

(18) Bolm, C.; Müller, P. *Tetrahedron Lett.* **1995**, *36*, 1625.

(10.8 mmol) and 1 g of citric acid (4.8 mmol) in 30 mL of water, 15 mL of 1,4-dioxane, and 25 mL of 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 of 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 of the crude product yielded pure sulfoxide. The fractions of sulfoxide were mixed before ee measurement.[13]

All the enantiomeric excesses (ee) were measured by chiral HPLC analysis: Chiralcel OD-H column, 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 configurations were assigned by comparison of the sign of specific rotations with literature data.[7-9]

(*R*)-*p*-Tolyl Methyl Sulfoxide. Purification by silica gel chromatography (eluent ethyl acetate) afforded 347 mg (75% yield) as a white solid: t_r (*R*) = 18.5 min, t_r (*S*) = 20.4 min, ee > 99.5%;[16] $[\alpha]_D$ +145 (*c* = 2, acetone); IR (KBr) 3040, 1580, 1450, 1070, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.41 (s, 3H), 2.70 (s, 3H), 7.40–7.71 (m, 4H).

(*R*)-*p*-Nitrophenyl Methyl Sulfoxide. Purification by silica gel chromatography (eluent ethyl acetate) afforded 283 mg (51% yield) as a white solid: t_r (*R*) = 20.5 min, t_r (*S*) = 21.2 min, ee = 99.3%; $[\alpha]_D$ +156.9 (*c* = 0.75, $CHCl_3$); IR (KBr) 3086, 2992, 2906, 1642, 1580, 1504, 1418, 1330, 1113, 1089, 964, 849, 828, 735, 676, 524, 464 cm^{-1}; ^1H NMR ($CDCl_3$) δ 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).

(*R*)-*p*-Anisyl Methyl Sulfoxide. Purification by silica gel chromatography (eluent hexane:ethyl acetate, 1:1) afforded 398 mg (78% yield) as a white solid: t_r (*R*) = 20.3 min, t_r (*S*) = 21.2 min, ee = 99.5%; $[\alpha]_D$ +165.9 (*c* = 0.38, $CHCl_3$); IR (KBr) 3070, 1590, 1300, 1250, 1085, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67 (s, 3H), 3.81 (s, 3H), 7.00 (d, *J* = 9 Hz, 2H), 7.58 (d, *J* = 9 Hz, 2H).

(*R*)-*o*-Anisyl Methyl Sulfoxide. Purification by silica gel chromatography (eluent hexane:ethyl acetate, 1:1) afforded 385 mg (75% yield) as a white solid: t_r (*R*) = 20.2 min, t_r (*S*) = 20.9 min, ee = 95.3%; $[\alpha]_D$ +340 (*c* = 1, acetone); IR (KBr) 3080, 2840, 1580, 1475, 1270, 1235, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (s, 3H), 3.86 (s, 3H), 6.85 (d, *J* = 9 Hz, 2H), 7.88 (d, *J* = 9 Hz, 2H).

(*R*)-Phenyl Methyl Sulfoxide. Purification by silica gel chromatography (eluent ethyl acetate) afforded 323 mg (77% yield) as a white solid: t_r (*R*) = 21.7 min, t_r (*S*) = 26.1 min, ee = 99.2%; $[\alpha]_D$ +135 (*c* = 1, acetone); IR (KBr) 3458, 1645, 1471, 1439, 1410, 1085, 1042, 953, 744, 687, 497 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.73 (s, 3H), 7.56–7.49 (m, 2H), 7.67–7.64 (m, 2H).

(*R*)-1-Naphthyl Methyl Sulfoxide. Purification by silica gel chromatography (eluent ethyl acetate) afforded 518 mg (91% yield) as a white solid: t_r (*S*) = 33.9 min, t_r (*R*) = 36.5 min, ee = 91.2%; $[\alpha]_D$ +407 (*c* = 1, acetone); IR (KBr) 3045, 2990, 2955, 1585, 1500, 1405, 1257, 1138, 1060, 955, 770 cm-1; ^1H NMR ($CDCl_3$) δ 2.87 (s, 3H), 7.61 (m, 2H), 7.70 (t, *J* = 7 Hz, 1H), 8.03 (m, 3H), 8.26 (d, *J* = 7 Hz, 1H).

(*R*)-2-Naphthyl Methyl Sulfoxide. Purification by silica gel chromatography (eluent ethyl acetate) afforded 462 mg (81% yield) as a white solid: t_r (*S*) = 33.9 min, t_r (*R*) = 36.5 min, ee = 77.5%; $[\alpha]_D$ +102.6 (*c* = 1.9, acetone); IR (KBr) 3040, 1580, 1030, 820, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.73 (s, 3H), 7.53 (m, 2H), 8.21 (m, 5H).

(*R*)-Benzyl Methyl Sulfoxide. Purification by silica gel chromatography (eluent ethyl acetate) afforded 402 mg (87% yield) as a white solid: t_r (*R*) = 35.8 min, t_r (*S*) = 40.8 min, ee = 95.4%; $[\alpha]_D$ +52.2 (*c* = 1.9, acetone); IR (KBr) 3040, 1490, 1450, 1370, 1295, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.96 (d, *J* = 6 Hz, 2H), 7.53 (m, 5H).

(*R*)-*p*-Tolyl Ethyl Sulfoxide. Purification by silica gel chromatography (eluent ethyl acetate) afforded 413 mg (82% yield) as an oil: t_r (*R*) = 14.9 min, t_r (*S*) = 17.5 min, ee = 86.6%; $[\alpha]_D$ +162 (*c* = 1.1, acetone); IR (KBr) 3040, 1580, 1370, 1025, 820, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (m, 3H), 2.81 (s, 2H), 2.83 (m, 3H), 7.29 (m, 2H), 7.47 (m, 2H).

(*R*)-*o*-Anisyl Phenyl Sulfoxide. Purification by silica gel chromatography (eluent ethyl acetate) afforded 505 mg (69% yield) as a white solid: t_r (*R*) = 25.1 min, t_r (*S*) = 26.0 min, ee = 14.1%; IR (KBr) 3040, 1610, 1575, 1030, 820, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.93 (s, 3H), 7.18 (m, 5H), 7.37 (m, 4H).

(*R*)-*p*-Tolyl *n*-Butyl Sulfoxide. Purification by silica gel chromatography (eluent ethyl acetate) afforded 350 mg (64% yield) as a white solid: t_r (*R*) = 15.8 min, t_r (*S*) = 16.9 min, ee = 34.2%; $[\alpha]_D$ +72 (*c* = 1, acetone); IR (KBr) 3040, 1520, 1320, 1030, 820, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (m, 3H), 1.35 (m, 2H), 2.83 (s, 3H), 2.90 (m, 2H), 7.41–7.52 (m, 4H).

(*R*)-Methyl *n*-Octyl Sulfoxide. Purification by silica gel chromatography (eluent ethyl acetate) afforded 314 mg (63% yield) as white a solid: t_r (*R*) = 16.9 min, t_r (*S*) = 20.3 min, ee = 85.1%;[19] $[\alpha]_D$ −71.3 (*c* = 1, acetone); IR (KBr) 3040, 1580, 1030, 820, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (m, 3H), 1.2–2.0 (m, 12H), 2.53 (s, 3H), 2.60 (m, 2H).

Acknowledgment. We thank CNRS for its financial support. Two of us (J.M.B. and M.D.) acknowledge Rhône Poulenc-Rorer for a postdoctoral fellowship. We thank Dr. P. Pitchen for useful discussions.

JO951290I

(19) The ee was measured by HPLC analysis of the corresponding compound obtained from *n*-octyl methyl sulfoxide by treatment with NaH and benzyl bromide.