Titanium-Catalyzed, Asymmetric Sulfoxidation of Alkyl Aryl Sulfides with Optically Active Hydroperoxides

Waldemar Adam, Marion N. Korb,* Konrad J. Roschmann,† and Chantu R. Saha-Möller

Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97218 Würzburg, Germany

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The Ti-catalyzed, asymmetric oxidation of alkyl aryl sulfides by enantiomerically pure hydroperoxides (ee >99%) has been examined. Enantioselectivities with ee values up to ca. 80% were achieved for the oxygen transfer from (*S*)-(−)-1-phenylethyl hydroperoxide **2a** to methyl phenyl and methyl *p*-tolyl sulfide **1a** in CCl_4 as solvent, but with much overoxidation to the corresponding sulfone **4**. Detailed mechanistic studies showed that the enantioselectivity of the sulfide **1a** oxidation results from a combination of a rather low (ee values <20%) asymmetric induction in the sulfoxidation and an effective kinetic resolution (ee values ca. 80% at 85% sulfide conversion) of the sulfoxide **3a** by enantioselective oxidation to the sulfone **4a**. The overoxidation (loss of chemoselectivity) is due to sulfoxide coordination to the Ti metal to generate a template in which the oxygen atom is intramolecularly transferred from the bound and activated, optically active hydroperoxide to the ligated sulfoxide in a stereocontrolled manner.

Introduction

Optically active sulfoxides have been increasingly used as building blocks and chiral auxiliaries in the asymmetric synthesis of pharmaceutical products;[1] therefore, their enantioselective preparation is still of importance today. The main route to nonracemic sulfoxides constitutes the Andersen method,[2] namely the reaction of diastereomerically pure sulfinates with organometallic reagents. Alternatively, the asymmetric oxidation of sulfides has received much attention during the past 15 years. The use of chiral oxaziridines[3] as oxidants or the Sharpless-modified procedures of Modena[4] and Kagan[5] led to high enantioselectivities (up to ee 90%), but the sulfoxidations have been conducted stoichiometrically with respect to $Ti(O^iPr)_4$ and the chiral auxiliary. Of paramount interest is, therefore, the development of efficient catalytic systems.

In this context, besides the highly enantioselective enzyme-catalyzed sulfoxidations,[6] catalyzed sulfoxidations with (salen)manganese,[7] (salen)vanadium,[8] and titanium-containing complexes are known. For the latter, Kagan[9] optimized their Sharpless-modified titanium-catalyzed sulfoxidation [cumyl hydroperoxide/$Ti(O^iPr)_4$/(+)-DET/^{i}PrOH = 5:1:4:4] to achieve enantiomeric excesses up to 96% for alkyl aryl sulfides. Recently Scettri[10] employed furyl hydroperoxides (ee values up to >95%) instead of cumyl hydroperoxide, while Modena[11] introduced a nonracemic amino triol as chiral ligand (ee up to 84%). Uemura[12] utilized (*R*)-binaphthol as chiral auxiliary, which not only oxidizes sulfides, but also promotes the kinetic resolution of sulfoxides. The latter has also been observed for (*S*,*S*)-1,2-diphenylethane-1,2-diol[13] and for amino triol[11] as chiral auxiliaries.

In such catalytic, enantioselective oxidations, the asymmetric induction is exercised by a chiral diol ligand, e.g., tartrate or binaphthol, in combination with an achiral hydroperoxide as the oxygen donor. First attempts to use optically active sugar-derived hydroperoxides for the asymmetric sulfoxidation have been made for alkyl aryl sulfides, but only low ee values (up to 26%) were obtained for the sulfoxide.[14] In the following we report the Ti-catalyzed asymmetric oxidation of methyl *p*-tolyl sulfide **1a** (Scheme 1) with optically active hydro-

† Undergraduate research participant, Spring 1997.

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Scheme 1

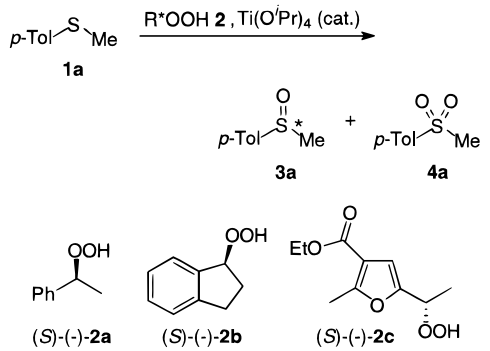

Table 1. Chemo- and Enantioselectivity of the Sulfoxidation of Methyl *p*-Tolyl Sulfide (1a) with (*S*)-1-Phenylethyl Hydroperoxide (2a) Catalyzed by Ti(O^{i}Pr)$_4$ under Various Reaction Conditions

							selectivity[a]	
entry	sulfide[b] **1a** (*M*)	R*OOH[c] **2a** (equiv)	solvent	*T* (°C)	*t* (h)	convn[a] (%)	chemo **3a**:**4a**	enantio (*S*)-(−)-**3a** ee (%)
1	0.13	1.2	CH_2Cl_2	−20	4	95	79:21	20
2	0.13	1.5	CH_2Cl_2	−20	4	98	50:50	31
3	0.13	1.5	^{i}PrOH	−20	48	>99	49:51	47
4	0.13	1.2	CCl_4	20	2	68	24:76	40
5	0.13	1.0	CCl_4	−20	3	64	36:64	52
6	0.13	1.2	CCl_4	−20	4	69	16:84	75
7	0.13	1.5	CCl_4	−20	5	88	20:80[d]	71
8	0.33	1.5	CCl_4	−20	5	95	47:53	21
9	0.13	1.2	CCl_4	−20	16	9	100:0	0

[a] Determined by HPLC analysis of the crude reaction mixture on a chiral column (Daicel Chiralcel OD-H); error ±2% of the stated value, mass balance ≥90%. [b] 1.0 equiv of sulfide **1a** and 0.05 equiv of Ti(O^{i}Pr)$_4$ except entry 3 (0.1 equiv) and entry 9, without Ti(O^{i}Pr)$_4$. [c] ee >99%. [d] Yields of isolated products: sulfoxide **3a** (14%), sulfone **4a** (65%).

peroxides (*S*)-(−)-**2** as asymmetric inductors, readily available for the preparative scale by horseradish peroxidase-catalyzed kinetic resolution.[15] To assess the scope of this catalytic, enantioselective sulfoxidation, a variety of alkyl aryl sulfides were used in which the size of the alkyl group and the electronic properties of the aryl substituent have been probed.

Results

To establish the optimal reaction conditions for the asymmetric sulfoxidation with optically active hydroperoxides under Ti catalysis, the solvent, temperature, amount of hydroperoxide, and sulfide concentration were varied in the oxidation of methyl *p*-tolyl sulfide (**1a**) by the enantiomerically pure (ee >99%) (*S*)-(−)-1-phenylethyl hydroperoxide (**2a**). The results of these optimizations are displayed in Table 1. When CH_2Cl_2 was used as solvent, an enantiomeric excess (ee) of 20% (Table 1, entry 1) was obtained for the sulfoxide (*S*)-(−)-**3a**. By raising the amount of hydroperoxide **2a** from 1.2 to 1.5 equiv (entries 1 and 2), the sulfoxide yield was reduced from 79 to 50% due to increased overoxidation to the sulfone **4a**, while the ee values were raised from 20 to 31%. In both cases the conversion of the sulfide **1a** was almost complete. With 2-propanol as solvent (entry 3), at complete conversion, the same (49:51) sulfoxide **3a**:

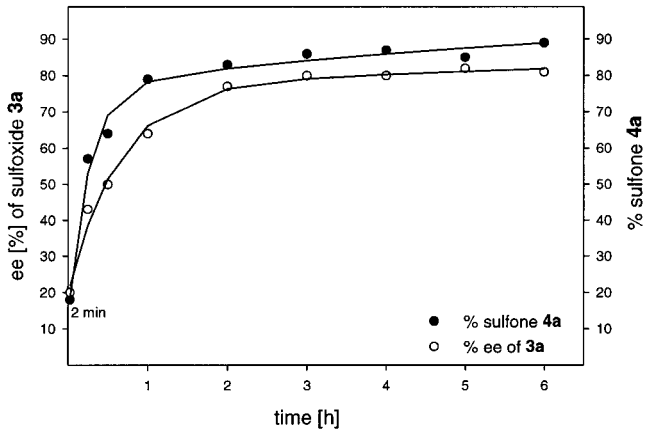

Figure 1. Time profile of the enantioselectivity (% ee of sulfoxide **3a**) and the chemoselectivity (% sulfone **4a**) in the oxidation of sulfide **1a** by R*OOH **2a**/Ti(O^{i}Pr)$_4$.

sulfone **4a** ratio was observed as in CH_2Cl_2, but with a higher ee value (47%). Still higher enantioselectivities were obtained when the reaction was conducted in CCl_4 (entry 7), but otherwise the same conditions as in entry 3 were used. Moreover, a variation of the reaction temperature from +20 to −20 °C caused a significant increase of the ee value from 40% at +20 °C (entry 4) to 75% at −20 °C (entry 6).

Most indicative is the variation of the amount of hydroperoxide **2a** that is used (entries 5−7) at −20 °C in CCl_4. An increase from 1.0 (entry 5) to 1.2 equiv (entry 6) raised the enantiomeric excess from 52 to 75%, which parallels the increase in the amount of overoxidation to the sulfone **4a** from 64 to 84%. However, when 1.5 equiv of hydroperoxide **2a** (entry 7) is employed, no significant change in the ee value or the sulfoxide **3a**:sulfone **4a** ratio is observed compared to when 1.2 equiv is used (entry 6), except that ca. 20% more of the sulfide **1a** is consumed.

Also remarkable is the concentration effect of the sulfide **1a** in this asymmetric sulfoxidation (entries 7 and 8). For the dilute (0.13 M, entry 7) solution, the ee value is drastically higher than that at 0.33 M (entry 8), i.e., 71 versus 21%. Again this trend to higher enantioselectivity parallels the extent of overoxidation, as reflected in the sulfoxide **3a**:sulfone **4a** ratio of 20:80 at 0.13 M versus 47:53 at 0.33 M (entries 7 and 8). In other words, the higher the overoxidation to sulfone **4a**, the higher the enantiomeric excess of the sulfoxide **3a**.

In a control experiment, the oxidation of sulfide **1a** by the hydroperoxide (*S*)-(−)-**2a** was conducted without Ti(O^{i}Pr)$_4$ catalyst at −20 °C (entry 9) to afford exclusively the sulfoxide **3a** in only 9% yield with no enantiomeric excess. Thus, under these conditions, the direct sulfoxidation by the optically active hydroperoxide **2a** without Ti(O^{i}Pr)$_4$ catalyst is negligible and affords racemic sulfoxide **3a**.

A time profile of the oxidation of **1a** with the hydroperoxide **2a** (1.5 equiv) clearly shows the dependence of the enantiomeric excess of the sulfoxide **3a** on the amount of sulfone **4a** formation (Figure 1). Remarkable is the very fast formation of the sulfone **4a**, so that after 15 min the ratio **3a**:**4a** is 43:57 at a conversion of 58%. The enantiomeric excess of the sulfoxide **3a** is only ca. 20% at the very beginning (ca. 2 min) of the reaction, when only little sulfone **4a** is formed.

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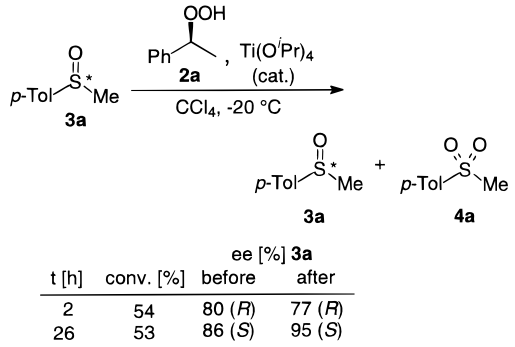
Scheme 2



t [h]	conv. [%]	ee [%] **3a** before	ee [%] **3a** after
2	54	80 (*R*)	77 (*R*)
26	53	86 (*S*)	95 (*S*)

Table 2. Kinetic Resolution of the Racemic Methyl *p*-Tolyl Sulfoxide (3a) with (*S*)-1-Phenylethyl Hydroperoxide (2a) Catalyzed by Ti(O^{i}Pr)$_4$

entry	R*OOH[a] **2a** (equiv)	Ti(O^{i}Pr)$_4$ (equiv)	*T* (°C)	*t* (h)	convn[b] **3a** (%)	ee[b] (%) (*S*)-(−)-**3a**	**s**[c]
1	0.50	0.05	20	4	57	7	1.2
2	0.50	0.05	0	7	56	10	1.3
3	0.50	0.15[d]	−20	148	53	11	1.3
4	0.75	0.25[d]	−20	96	75	30	1.6
5	0.50	1.0	−20	4	52	17	1.6
6	0.50	5.0	−20	0.75	50	19	1.7
	0.25[e]		−20	0.75	75	39	1.8
7	0.50	5.0	−20	0.5	52	22	1.8
	0.25[e]		−20	0.5	76	44	1.9

[a] ee >99%, 0.13 M sulfoxide **3a** in CCl_4 except entry 7 (0.03 M **3a**). [b] Determined by HPLC analysis of the crude reaction mixture on a chiral column (Daicel Chiralcel OD-H); error ±2% of the stated value; mass balance >90%. [c] Stereoselectivity factor, determined according to ref 16. [d] At the start 0.05 equiv of Ti(O^{i}Pr)$_4$ was added, followed by additional aliquots (0.05 equiv) of Ti(O^{i}Pr)$_4$ during the course of the reaction. [e] An additional 0.25 equiv of hydroperoxide **2a** was added.

To examine whether one of the enantiomers is preferrably oxidized to the sulfone **4a**, the separate optically active sulfoxides (*R*)-**3a** (ee 80%) and (*S*)-**3a** (ee 86%) were treated with 0.5 equiv of the hydroperoxide (*S*)-**2a** (Scheme 2). This hydroperoxide (*S*)-**2a** was consumed faster (ca. 10 times) in the reaction with the sulfoxide (*R*)-**3a** than with the enantiomer (*S*)-**3a**, and the enantiomeric excess of the sulfoxide (*S*)-**3a** increased from 86 to 95%.

All of these results evidently suggest that during the course of the sulfide **1a** oxidation the resulting sulfoxide **3a** is kinetically resolved by "overoxidation" to the sulfone **4a**. To confirm this, the racemic sulfoxide **3a** was submitted to the oxidation with hydroperoxide (*S*)-**2a** (Table 2). Whereas at 20 and 0 °C the hydroperoxide (*S*)-**2a** was completely consumed within 4−7 h (entries 1 and 2), the reaction at −20 °C (entry 3) took about 6 days with further addition of the Ti catalyst necessary. In all cases (ca. 55% conversion) the ee value of the remaining sulfoxide **3a** was around 10%, but at a conversion of 75% (entry 4) the ee value was raised to 30%. With stoichiometric or excess (5.00 equiv) amounts of the Ti catalyst, the reaction times were reduced to 45 min for ca. 50% conversion, but the ee values were only 17−19% (compare entries 5 and 6 with 4). After further addition of 0.25 equiv of hydroperoxide (*S*)-**2a**, the ee value rose to 39% (entry 6). The last run (entry 7) was conducted to test concentration effects (4 times more dilute), but there were no significant changes in the conversion and enantiomeric excess of the sulfoxide **3a**.

While the ee values (up to ca. 40%) in Table 2 definitely confirm that kinetic resolution is at play in the oxidation **3a** → **4a**, the high enantioselectivity (ee up to 80%) achieved through the "overoxidation" **1a** → **4a**, as displayed in Figure 1, could not be obtained. (This low efficiency of the kinetic resolution is also reflected in the small stereoselectivity factor **s**[16] of 1.8 and 1.9 in Table 2, entry 6 and 7.) For this reason, a number of additives were tested to assess whether they influence the enantioselectivity of the Ti-catalyzed sulfide **1a** oxidation by hydroperoxide (*S*)-**2a** (Table 3).

Table 3. Oxidation of Methyl *p*-Tolyl Sulfide (1a)[a] with (*S*)-1-Phenylethyl Hydroperoxide (2a)[b] in the Presence of Different Additives

entry	additive	(equiv)[d]	*t* (*h*)	convn[c] (%)	**3a**:**4a**[c]	ee (%)[c] (*S*)-(−)-**3a**
1	(*S*)-**3a** (ee 86%)	(0.05)	10	82	12:88	74
2	**4a**	(0.05)	4	80	40:60	38
3	Ph_2SO	(0.05)	7	76	33:67	53
4	R*OH[e] (ee >99%)	(1.50)	23	87	18:82	80

[a] 0.13 M sulfide **1a** in CCl_4 at −20 °C. [b] 1.2 equiv of (*S*)-(−)-**2a** (ee >99%), except run 1 and 4 (1.5 equiv). [c] Determined by HPLC analysis of the crude reaction mixture on a chiral column (Daicel Chiralcel OD-H), error ±2% of the stated value. [d] Relative to sulfide **1a**. [e] (*S*)-1-Phenylethanol (ee >99%).

Thus, equimolar (with respect to the Ti catalyst) amounts of (*S*)-sulfoxide **3a** (ee 86%) directly from the start of the sulfide **1a** oxidation (entry 1, Table 3) exercised no appreciable effect in the ee value or **3a**:**4a** ratio (compare with entry 7, Table 1), except that the reaction time was doubled for approximately the same extent of sulfide **1a** conversion. The addition of sulfone **4a** (entry 2, Table 3) or the extraneous diphenyl sulfoxide (entry 3, Table 3) actually lowered the enantioselectivity, but the extent of "overoxidation" was reduced for approximately the same amount of sulfide **1a** conversion (compare with entry 6, Table 1). Finally, when (*S*)-1-phenylethanol (entry 4, Table 3) was added at the start of the reaction, again only the reaction time was prolonged (compare with entry 7, Table 1), while the chemo- and enantioselectivities remained the same and the ee value was raised by only 9%. In view of the large amount of (*S*)-1-phenylethanol (1.5 equiv) that is present from the very beginning of the reaction, this small increase in the enantioselectivity is not sufficient to allow a conclusion that this alcohol influences the enantioselectivity significantly. Therefore, it may be stated that none of these additives promote significantly the enantioselectivity of this oxygen-transfer process.

The high extent of sulfone **4a** formation (overoxidation) implicates a pronounced nucleophilic character of the R*OOH/Ti(O^{i}Pr)$_4$ oxidant, especially since the oxidation of the sulfide **1a** by the hydroperoxide (*S*)-**2a** without the Ti catalyst (Table 1, entry 8) gave exclusively the sulfoxide **3a**, which demonstrates the electrophilic character of this hydroperoxide. To assess the electronic nature of the R*OOH/ Ti(O^{i}Pr)$_4$ oxidant, the established[17] thi-

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Table 4. Oxidation of Thianthrene 5-oxide (SSO) by (*S*)-(−)-1-Phenylethyl Hydroperoxide (2a) Catalyzed by Ti(O^{i}Pr)$_4$

solvent	R*OOH[a] **2a** (equiv)	*t* (h)	product ratio[b] ∑SOSO[c]	SSO_2[d]	$SOSO_2$[e]	X_{SO}[f]
CH_2Cl_2	0.1	0.5	70.3	21.6	7.3	0.27
CCl_4	0.1	0.5	57.6	27.9	14.5	0.37

[a] (*S*)-**2a** (ee >99%), equivalents relative to **SSO** (0.094 M). [b] Determined by HPLC analysis [reversed phase column (Knauer Eurospher 100 C-18)] error ±2% of the stated value; **SSO** conversion ca. 10%. [c] Sum of cis- and *trans*-5,10-dioxides. [d] 5,5-Dioxide. [e] 5,5,10-Trioxides. [f] Calculated according to ref 17b.

Table 5. Asymmetric Sulfoxidation of Prochiral Sulfides 1 with (*S*)-1-Phenylethyl Hydroperoxide (2a) Catalyzed by Ti(O^{i}Pr)$_4$

	sulfide[b]				selectivity[a]	
entry	R^2	R^1	*t* (h)	convn[b] (%)	chemo **3**:**4**	enantio (*S*)-(−)-**3** ee (%)
1	Me	*p*-tolyl	5	88	20:80	71
2	Et	*p*-tolyl	4	89	17:83	72
3	^{i}Pr	*p*-tolyl	57	82	21:79	65
4	^{n}Bu	*p*-tolyl	29	82	23:77	62
5	Me	phenyl	6	79	19:81	79
6	Me	*p*-anisyl	23	97	56:44	31
7	Me	*p*-nitrophenyl	6	93	41:59	15
8	Me	2-naphthyl	4	73	32:68	24 (49)[c]
9	Me	benzyl	4	93	68:32	8
10	Me	*n*-octyl	4	92	34:66	20

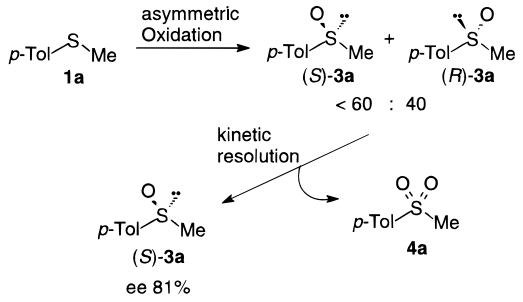
[a] Determined by HPLC analysis of the crude reaction mixture on a chiral column (Daicel Chiralcel OD-H or OB−H), error ±2% of the stated value, mass balance >90%. [b] 0.13 M in CCl_4 at −20 °C, 1.5 equiv of (*S*)-**2a** (ee >99%) and 0.05 equiv of Ti(O^{i}Pr)$_4$, preparative scale. [c] In parantheses for 1.2 equiv of hydroperoxide (*S*)-**2a**.

anthrene 5-oxide (**SSO**) probe was employed and the X_{SO} values were determined in CH_2Cl_2 and CCl_4 (Table 4). Indeed, even at as little as 10% **SSO** conversion, not only **SSO_2** (22−28%) but considerable amounts of **$SOSO_2$** (7−15%) were formed; therefore, in CCl_4 there was twice as much overoxidation as in CH_2Cl_2. These results establish unequivocally the high extent of overoxidation for the R*OOH/ Ti(O^{i}Pr)$_4$ oxidant.

To explore whether other optically active hydroperoxides are more effective in the asymmetric sulfoxidation of sulfide **1a**, the derivatives (*S*)-(−)-**2b** and (*S*)-(−)-**2c** were employed (Scheme 1) as alternatives. The oxidation of sulfide **1a** by the indanyl hydroperoxide (*S*)-(−)-**2b** (1.5 equiv) afforded after 98% conversion an enantiomeric excess of 22% for sulfoxide **3a**. In contrast to the hydroperoxide **2a**, the main sulfoxide enantiomer possessed the (*R*) configuration. With the furyl hydroperoxide (*S*)-(−)-**2c** (1.5 equiv), the sulfoxide **3a** was obtained with an ee value of only 7% after 96% conversion. In view of these low enantioselectivities, further work with these optically active hydroperoxides was abandoned.

For general scope of the asymmetric sulfoxidation by the (*S*)-(−)-1-phenylethyl hydroperoxide (**2a**), the set of structurally varied alkyl aryl sulfides (Table 5) were oxidized under the optimal conditions worked out in Table 1 [1.5 equiv of (*S*)-**2a**, CCl_4, −20 °C, ≥80% conversion of the sulfide]. Replacement of the methyl substituent in the *p*-tolyl sulfide **1** by sterically more demanding alkyl groups (Table 5, entries 1−4) resulted in no significant change in the enantioselectivity (ee values range between 62 and 72%) and the chemoselectivity [sulfoxide **3**:sulfone **4** ratio (ca. 20:80)] for this catalytic

Scheme 3



asymmetric oxidation. Of interest is the ee value of 62% for *p*-tolyl *n*-butyl sulfoxide, which is higher than reported for the modified Sharpless procedure[9] (ee 25%).

The change of the aryl group in the methyl sulfide **1** to probe electronic effects displayed no regular trends (entries 5−7) in the enantio- and chemoselectivity. The highest ee value of 79% was observed for the phenyl group (entry 5), but much lower enantioselectivities were obtained both for the electron-donating *p*-anisyl (entry 6, ee 31%) and the electron-accepting *p*-nitrophenyl group (entry 7, ee 15%). These ee values are difficult to compare because the extent of overoxidation (chemoselectivity) varies significantly (entries 5−7), since we have seen previously for the model sulfide **1a** that the enantioselectivity increases with higher amount of sulfone **4a**. Also, the oxidation of the methyl 2-naphthyl sulfide with 1.2 equiv of the hydroperoxide **2a** (entry 8) gave only a moderate enantioselectivity (ee 49%). As expected for dialkyl sulfides,[9,12] low enantioselectivities were observed in the oxidation of the benzyl (entry 9, ee 10%) and the *n*-octyl (entry 10, ee 20%) methyl sulfides. This low enantiomeric excess for the oxidation of methyl *n*-octyl sulfide was raised only to 32% by double asymmetric induction with (*S*)-(−)-1-phenylethyl hydroperoxide (**2a**) and the optically active tartrate D-(−)-DET under Kagan's[9] modified Sharpless conditions.

Mechanistic Discussion

The highest enantioselectivities (ee values up to 80%) for the Ti(O^{i}Pr)$_4$-catalyzed asymmetric oxidation of the model sulfide **1a** (0.13 M) by the hydroperoxide (*S*)-**2a** (1.5 equiv) are achieved in CCl_4 at −20 °C. More important, such a high enantioselectivity (ee value) can only be obtained at the expense of chemoselectivity (sulfide **3a**:sulfone **4a** ratio), i.e., high degree (>80%) of overoxidation of the sulfoxide **3a** to its sulfone **4a**. This is most evidently expressed in Figure 1, in which at 40% sulfide **1a** consumption (after a 2-min reaction time, during the earlier stage of the oxidation), the ee value of sulfoxide **3a** amounts to ≤20% (negligible overoxidation to sulfone **4a**), but at high (≥80%) sulfide **1a** conversion (during the later stage of the oxidation) the ee value levels off to ca. 80% (extensive overoxidation to sulfone **4a**). Loss of enantioselectivity due to the unselective, direct oxidation by the hydroperoxide (*S*)-**2a** [no Ti(O^{i}Pr)$_4$ catalyst] is negligible, as established by a control experiment (Table 1, entry 9).

These results are mechanistically readily rationalized in terms of Scheme 3. The relatively ineffective (ee ≤20%) asymmetric sulfoxidation of sulfide **1a** is followed by a more efficient (ee value ca. 80%) kinetic resolution of the sulfoxide **3a** by its enantioselective oxidation to

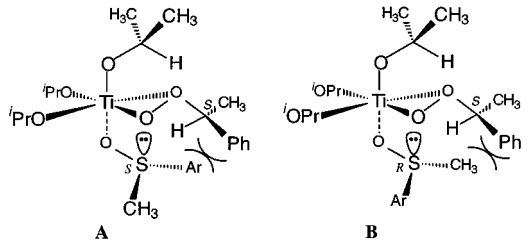


Figure 2. Postulated templates in the oxidation of (*S*)-sulfoxide **3a** (**A**) and (*R*)-**3a** (**B**) with (*S*)−(−)-1-phenylethyl hydroperoxide (**2a**) under $Ti(O^iPr)_4$ catalysis.

the sulfone **4a** (overoxidation). Precedents for such a sequence of asymmetric sulfoxidation followed by sulfoxide kinetic resolution are documented in the literature.[10−13]

Evidence for the kinetic resolution of the racemic sulfoxide **3a** in this oxidation is provided by the data in Table 2, although maximum ee values of only ca. 40% were obtained (entry 7). More significant is the fact that the (*R*) enantiomer of sulfoxide **3a** is faster oxidized by the optically active hydroperoxide (*S*)-**2a** than the (*S*) enantiomer (Scheme 2). Thus, the combination (*R*)-**3a**/(*S*)-**2a** is more effective in the $Ti(O^iPr)_4$-catalyzed oxygen transfer than the (*S*)-**3a**/(*S*)-**2a** one. This is difficult to rationalize without invoking a template effect, i.e., simultaneous coordination to the titanium metal center of both the oxygen acceptor (the sulfoxide **3a** substrate) and the oxygen donor (the optically active hydroperoxide **2a**). Moreover, the hydroperoxide **2a** is not only ligated to the titanium by means of an oxygen−metal bond but activated electrophilically for oxygen transfer by coordination of the remote oxygen atom of the peroxide bond (Figure 2). Such sulfoxide coordination to the titanium metal has been reported[18] and accounts adequately for the appreciable overoxidation even in the earlier stages of the oxidation.[19] In the proposed monomeric template, inspection of molecular models suggest that the methyl and phenyl substituents of the hydroperoxide should point away from the metal center for steric reasons. Thus, for the sulfoxide (*S*)-**3a**/hydroperoxide (*S*)-**2a** diastereomeric combination (Figure 2, complex **A**), significant steric interaction is expected between the *p*-tolyl substituents of the sulfoxide (*S*)-**3a** and the hydroperoxide (*S*)-**2a** during the oxygen transfer. This steric hindrance is reduced for the diastereomeric combination (*R*)-**3a**/(*S*)-**2a** (Figure 2, complex **B**), since now a methyl group of (*R*)-**3a** is facing the hydroperoxide phenyl substituent. In this way, the faster oxidation of the (*R*) enantiomer of the sulfoxide **3a** becomes evident and the kinetic resolution of the sulfoxide **3a** may be rationalized.

This sulfoxide coordination also explains the appreciable formation of **SSO_2** and **$SOSO_2$** at only ca. 10% consumption of **SSO** in its Ti-catalyzed oxidation by hydroperoxide (*S*)-**2a** (Table 4). Thus, the genuine electrophilic character (X_{SO} ca. 0.4 in CCl_4) of the (*S*)-**2a**/$Ti(O^iPr)_4$ oxidant is masked by coordination effects to the titanium metal.[17c,d]

Also the long reaction times (≥4 days) at −20 °C may be accounted for in the kinetic resolution of the racemic sulfoxide **3a** when only a catalytic amount of $Ti(O^iPr)_4$ is present (Table 2, entries 3 and 4). In this catalytic reaction (**3a** → **4a**), the sulfoxide concentration is much higher than in the oxidation of the corresponding sulfide **1a**, in which sulfoxide **3a** is generated *in situ*. The excess sulfoxide presumably blocks the small amount of the Ti catalyst, and thus diminution of the reaction rate is expected in the former process. Such inhibition of the Ti catalyst activity may be due to multiple sulfoxide coordination to the metal center.[5b,18] This may also be the reason why in the oxidation of the sulfide **1a** a higher amount of the hydroperoxide (*S*)-**2a** (1.5 versus 1.2 equiv, see Table 1, entry 6 and 7) does not result in a higher amount of overoxidation to the sulfone **4a** and, therefore, does not change the ee value of the sulfoxide **3a**. As a consequence, the generation of the active oxidizing species in this reaction is hindered. Consequently, to avoid such an inhibitory effect, a sufficient amount of Ti catalyst (≥1.0 equiv) must be present in the kinetic resolution of the racemic sulfoxide **3a** (Table 2, entries 5−7); however, in the presence of excess catalyst (> 1.0 equiv), lower ee values (ca. 40%) were obtained for the sulfoxide **3a** at a conversion of 75% (Table 2, entry 6 and 7) in comparison to the catalytic sulfide **1a** oxidation (ee 71−75%, Table 1, entries 6 and 7). This difference may be explained by the fact that in the case of sulfide oxidation the *enantiomerically enriched* (ee ca. 20%) sulfoxide **3a** resulting from the asymmetric sulfoxidation (**1a** → **3a**) is kinetically resolved by subsequent enantioselective oxidation (**3a** → **4a**). Therefore, at the same sulfoxide conversion, the ee values in the sulfide oxidation (**1a** → **3a**) should be at least 20% higher than in the case of the kinetic resolution of the racemic sulfoxide (**3a** → **4a**).

The pronounced retardation of the oxidation in ^{i}PrOH compared to that in CCl_4 (Table 1, entries 3 and 7) becomes also interpretable in terms of sulfoxide coordination to the titanium center. On one hand, the sulfoxide **3a** is more strongly solvated in the protic ^{i}PrOH and should, therefore, diminish sulfoxide coordination; on the other hand, ^{i}PrOH competes with sulfoxide coordination by facile ligand exchange.

Conclusion

The asymmetric sulfoxidation of aryl alkyl sulfides by (*S*)-(−)-1-phenylethyl hydroperoxide (**2a**) at −20 °C in CCl_4 affords good to high enantiomeric excesses for methyl phenyl and *p*-tolyl alkyl sulfides (ee up to ca. 80%) at the expense of substantial overoxidation to the sulfone. Neither electronic (variation of the aryl group) nor steric (variation of the alkyl group) effects helped to enhance the enantiomeric excess. A time profile of the oxidation of the model substrate *p*-tolyl methyl sulfide (**1a**) with (*S*)-(−)-1-phenylethyl hydroperoxide (**2a**) showed that the asymmetric induction of the sulfoxidation is rather low (ee <20%), but the enantioselectivity is significantly enhanced through concomitant kinetic resolution of the sulfoxide **3a**; however, this comes at the expense of chemoselectivity through overoxidation. Sulfoxide coordination to the titanium center is responsible for the kinetic resolution through a template effect. Thus, the oxygen atom is transferred intramolecularly between the hydroperoxide and sulfoxide, which are simultaneously

(18) (a) Bonchio, M.; Calloni, S.; Di Furia, F.; Licini, G.; Modena, G.; Moro, S.; Nugent, W. A. *J. Am. Chem. Soc.* **1997**, *119*, 6935−6936. (b) Bonchio, M.; Licini, G.; Modena, G.; Moro, S.; Bortolini, O.; Traldi, P.; Nugent, W. A. *Chem. Commun.* **1997**, 869−870.

(19) For convenience and simplicity, we assume a mononuclear template with one Ti atom, but little if any structural data are available for such metal complexes. The recently suggested theoretical model (ref 18) is adopted for the Ti-catalyzed oxygen-transfer process.

ligated to the titanium metal. For high enantioselectivities, the *in situ* generation of the sulfoxide by asymmetric sulfide oxidation with R*OOH/Ti(O^iPr)$_4$ is more effective than employing racemic sulfoxide.

Experimental Section

General Procedure. For the sulfoxidation reactions, all glassware was dried under vacuum (ca. 150 °C/0.1 Torr) and all reactions were run under an argon gas atmosphere. CH_2Cl_2 and CCl_4 were distilled under an argon gas atmosphere from CaH_2 and ^{i}PrOH from magnesium; Ti(O^iPr)$_4$ was distilled prior to use. The optically active hydroperoxides (*S*)-(−)-**2a-c** were prepared by kinetic resolution of the racemic hydroperoxide with horseradish peroxidase as previously described.[15b] Horseradish peroxidase was obtained from Boehringer, Mannheim. The sulfides **1** were prepared according to literature procedures.[20]

Enantiomeric excesses of the sulfoxides **3**, the conversions of the sulfides **1**, and the sulfoxide **3**:sulfone **4** ratios were determined directly on the crude production mixture by HPLC analysis on chiral columns (Daicel Chiralcel OD-H column, 35 × 0.46 cm), with UV detection at 220 nm, *n*-hexane/2-propanol (9:1) as eluent and a flow rate of 0.5 mL/min (reactions with *p*-Tol-S-Me, *p*-Tol-S-Et); *n*-hexane/2-propanol (99:1), a flow rate of 0.5 mL/min (reactions with *n*-octyl-S-Me) or Daicel Chiralcel OB-H, *n*-hexane/2-propanol (8:2), a flow rate of 0.6 mL/min (reactions with *p*-Tol-S-*i*-Pr); *n*-hexane/ethanol (8:2), a flow rate of 0.4 mL/min (reactions with *n*-Bn-S-Me) or of 0.5 mL/min (reactions with Ph-S-Me, 2-naphthyl-S-Me) or of 0.6 mL/min (reactions with *p*-nitrophenyl-S-Me); *n*-hexane/ethanol (95:5) → *n*-hexane/2-propanol (8:2); a flow rate of 0.5 mL/min (reactions with *p*-Tol-S-*n*-Bu); *n*-hexane/2-propanol (8:2) → (7:3), a flow rate of 0.5 mL/min (reactions with *p*-anisyl-S-Me).

On the OD-H column the (*R*) enantiomer of sulfoxide **3** always eluted before the (*S*) one; on the OB-H column the (*S*)-enantiomer eluted first.

For the conditions to determine the ee values of the isolated sulfoxides **3**, see ref 9b.

Absolute configurations of the sulfoxides **3** were assigned by direct comparison of the specific rotation determined on a polarimetric Chiralyser with literature values.[5b,9b]

General Procedure of the Oxidation of the Sulfide 1a in CCl_4 with the Optically Active Hydroperoxides (*S*)-(−)-2a−c on the Analytical Scale. To a solution of 5.9 μL (20.0 μmol) of Ti(O^iPr)$_4$ in 1 mL of CCl_4 was added a solution of sulfide **1a** (400 μmol) in 1 mL of CCl_4. The mixture was stirred for 10 min at room temperature (ca. 20 °C) and then cooled to −20 °C. After 5 min, a solution of the hydroperoxide [480 μmol (1.2 equiv) or 600 μmol (1.5 equiv)] in 1 mL of CCl_4 was added, and the reaction mixture was stirred at −20 °C for the time stated in Table 1. The reaction progress was monitored by TLC or ^{1}H NMR analysis directly on the reaction mixture. After complete consumption of the hydroperoxide, the catalyst was destroyed by the addition of 20 μL of aqueous, saturated NH_4F solution, and the mixture was stirred for 1−1.5 h at room temperature. After filtration of the suspended material over Celite and thorough washing of the residue with CH_2Cl_2 (5 × 2 mL), the solvent was evaporated (20 °C/20 Torr). The enantiomeric excess of the sulfoxide **3a**, the conversion of the sulfide **1a**, and the sulfoxide **3a**:sulfone **4a** ratio were determined on the crude reaction mixture as described above.

General Procedure of the Oxidation of the Sulfides 1 in CCl_4 with the Optically Active Hydroperoxides (*S*)-(−)-2a on the Preparative Scale. The reaction was carried out as described above by starting with 14.8 μL (50.0 μmol) of Ti(O^iPr)$_4$ in 3.5 mL of CCl_4 and the addition of a solution of sulfide **1** (1.00 mmol) in 2 mL of CCl_4 and a solution of 82.9 mg (1.5 mmol) of hydroperoxide (*S*)-**2a** in 2 mL of CCl_4. After workup and the determination of the enantiomeric excess of the sulfoxide **3**, the conversion of the sulfide **1**, and the sulfoxide **3**:sulfone **4** ratio as described above, the products were isolated by flash column chromatography [silica gel, petroleum ether (30−50 °C)/diethyl ether (1:1) → EtOAc]. The spectral data of the sulfoxides **3** matched those reported.[5d]

Procedure for the Kinetic Study of the Ti-Catalyzed Oxidation of Methyl *p*-Tolyl Sulfide (1a) with the Hydroperoxide (*S*)-2a. The reaction solution was prepared as described above and stirred at −20 °C. After the reaction times stated in Figure 1, 0.1 mL of the mixture was taken out and immediately hydrolyzed with 8−10 drops aqueous, saturated NH_4F solution at room temperature. After 5 min of stirring, this sample was diluted with 1 mL of CH_2Cl_2 and dried over molecular sieves (4 Å), and the suspended material was filtered. After the solvent was evaporated (20 °C/20 Torr), the enantiomeric excess of the sulfoxide **3a**, the conversion of the sulfide **1a**, and the sulfoxide **3a**:sulfone **4a** ratio were determined as described above.

General Procedure of the Kinetic Resolution of Racemic Methyl *p*-Tolyl Sulfoxide (3a) by (*S*)-(−)-1-Phenylethyl Hydroperoxide (2a). To a solution of Ti(O^iPr)$_4$ (0.05−5.0 equiv) and (*S*)-(−)-1-phenylethyl hydroperoxide (**2a**) (0.5−0.75 equiv) in 2 mL of CCl_4 was added at −20 °C a solution of 61.7 mg (400 μmol) of methyl *p*-tolyl sulfoxide (**3a**) in 1 mL of CCl_4. The mixture was stirred at −20 °C until the hydroperoxide (*S*)-**2a** was consumed as demonstrated by a negative peroxide test (KI). The solution was worked up, and the enantiomeric excess of the sulfoxide **3a** and the sulfoxide **3a**:sulfone **4a** ratio were determined on the crude reaction mixture as described above.

General Procedure for the Oxidation of Thianthrene 5-Oxide (SSO) by (*S*)-(−)-1-Phenylethyl Hydroperoxide (2a)/Ti(O^iPr)$_4$. To a solution of 186 mg (800 μmol) of thianthrene 5-oxide (**SSO**) in 8 mL of CCl_4 or CH_2Cl_2 was added 11.8 μL (40.0 μmol) of Ti(O^iPr)$_4$. After the mixture was stirred for 10 min at room temperature, a solution of 11.1 mg (80.0 μmol) of (*S*)-(−)-1-phenylethyl hydroperoxide (**2a**) in 0.5 mL of solvent was added. Stirring was continued at room temperature until the entire hydroperoxide (*S*)-**2a** was consumed (30 min), as confirmed by the negative peroxide test. After addition of 40 μL of aqueous, saturated NH_4F solution, the mixture was worked up as described above. The product ratios (Table 4) were determined by HPLC analysis of the crude product mixture on a reversed phase column (Knauer Eurospher 100 C-18) with UV detection at 254 nm, methanol/water/acetonitrile (64:34:2) as eluent, and a flow rate of 0.4 mL/min.

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