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Enantioselective sulfoxidation mediated by renewable camphor-derived hydroperoxides

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Abstract—Chemoselective asymmetric oxidation of sulfides has been performed employing inexpensive and easily accessible camphor-derived hydroperoxides in the presence of catalytic loadings of $Ti(Oi\text{-}Pr)_4$ (20 mol %) and MS 4 Å. Aryl methyl sulfoxides of both absolute configurations can be obtained with enantioselectivities of up to 51%. For the first time, the kinetic resolution of racemic sulfoxides, mediated by the same chiral oxidative system has been found to be stereodivergent with respect to the sulfoxidation step. At the end of the oxidations, camphor-derived alcohols were isolated by silica gel chromatography and recycled for the synthesis of the hydroperoxides, thus providing a valuable chiral resource saving protocol.

1. Introduction

Enantioselective oxidations are amongst the most important transformations in organic synthesis. Different methodologies have been discovered, which enable access to enantiomerically pure valuable compounds such as epoxides, sulfoxides, diols, etc.[1]

Since the discovery of the Sharpless asymmetric epoxidation,[2] in the area of metal-catalyzed enantioselective oxidations, new protocols using enantiopure ligands in the presence of achiral alkyl hydroperoxides have continued to appear.[3] In response to this, asymmetric oxidative systems based on the employment of enantiomerically pure alkyl hydroperoxides, which act as stereoselective oxidants in the absence of any chiral ligand, have been studied to a limited extent.[4] The major problem associated with the second approach relies on the lack of efficient syntheses to hydroperoxides in enantiopure forms. A general methodology, via kinetic resolution of racemic hydroperoxides, performed by horseradish peroxidase (HRP), furnished enantiomerically pure secondary hydroperoxides, but was found to be unsuccessful for the resolution of tertiary hydroperoxides.[5] Secondary hydroperoxides, when used in the asymmetric epoxidation of allylic alcohols, afforded the epoxides in low ee (<25%).[6] Good ees were observed in the asymmetric sulfoxidation (up to 80%),[7] where the improvement in enantioselectivity was mainly due to the subsequent stereoconvergent kinetic resolution in the over-oxidation of enantioenriched sulfoxides to sulfones, at the expense of chemoselectivity.

As known from the results of investigations concerning the Sharpless system, tertiary hydroperoxides are required to achieve the highest levels of enantioselectivity. The only example of a tertiary hydroperoxide, synthesized from TADDOL, has indeed provided high ees in the epoxidation of α-phenyl and α-methyl cinnamyl alcohols (70–90% ee)[8] and in the asymmetric oxidation of phenyl methyl sulfide. The sulfoxide was obtained in 86% ee with the cooperative effect of the kinetic resolution, which increased the enantioselectivity of the sulfoxidation step.[9]

On the basis of these findings and in conjunction with our interest in asymmetric oxidations mediated by alkyl hydroperoxides,[10] our attention has recently focused on the synthesis of tertiary renewable hydroperoxides starting from readily available and inexpensive chiral sources, in order to set up convenient procedures for asymmetric oxidations. We succeeded in achieving a short two-step approach to a tertiary hydroperoxide starting from (+)-(1*R*)-camphor; the resulting (−)-*exo*-**1** (Fig. 1) used in $Ti(Oi\text{-}Pr)_4$-catalyzed epoxidation of allylic alcohols furnished the epoxy alcohols with up to 46% ee.[11]

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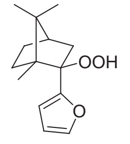


(-)-*exo*-**1**

Figure 1.

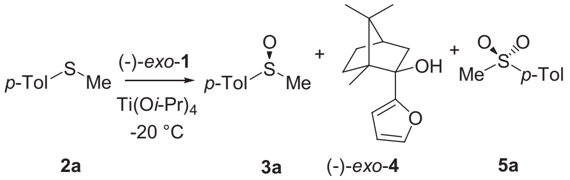
2. Results and discussion

Having in hand an easy access to *exo*-**1** in both enantiomeric forms, we decided to study their employment as stereoselective oxidants in metal-catalyzed asymmetric sulfoxidation. Methyl *p*-tolyl sulfide **2a** was chosen as the model compound for the screening of the reaction parameters (Table 1).

Under stoichiometric loadings of $\mathrm{Ti(O}i\text{-}\mathrm{Pr)_4}$ as metal catalyst (entry 1), in toluene at −20 °C, (*S*)-sulfoxide **3a** was preferentially formed in good yield, but with low ee as well as sulfone **5a** being produced in noticeable amounts. A blank experiment was carried out to assess the extent of oxidation by (−)-*exo*-**1** in the absence of the metal complex (entry 2); essentially racemic **3a** was isolated in low yield after prolonged reaction times. When reducing the catalyst loading to 50 mol% with respect to **2a** (entry 3), after 22 h an acceptable yield of **3a** with a slightly improved ee was obtained, together with better chemoselectivity. Under these conditions (50 mol% of catalyst) and for the same reaction time, different solvents were screened (entries 4–6) with toluene found to be the solvent of choice. The presence of activated molecular sieves (compare entry 7 with entry 3) improved the yields of both **3a** and **5a** with a slightly reduced enantioselectivity. Catalytic loadings of $\mathrm{Ti(O}i\text{-}\mathrm{Pr)_4}$ (20 mol%) and MS 4 Å worked favourably. In fact, the chemoselectivity increased and **3a** was isolated in good yield with a much better ee (entry 8). $\mathrm{VO(acac)_2}$ proved to be a highly active and chemoselective catalyst (entry 9), but racemic **3a** was isolated. Since the presence of MS 4 Å was beneficial, we envisaged that aging the catalyst in the presence of MS 4 Å may serve to enhance the level of enantioselectivity. In fact, stirring $\mathrm{Ti(O}i\text{-}\mathrm{Pr)_4}$ and (−)-*exo*-**1** at −20 °C for 1 h before the addition of **2a**, provided high chemoselectivity, a good yield and the best ee for **3a** (entry 10). When using the same conditions but performing the reaction at 0 °C, **3a** and **5a** were obtained in a 1/1 ratio with the ee dropping dramatically to 8% (entry 11).

Lastly, the presence of the enantiopure (+)-diethyl tartrate (L-DET) markedly slowed the reaction rate and racemic **3a** was isolated (entry 12).[12] It has to be noted that in several metal-catalyzed asymmetric sulfoxidation procedures, very high levels of enantioselectivity were obtained through the suitable exploitation of a concomitant stereoconvergent process of kinetic resolution, involving the over-oxidation of the minor enantiomer to sulfone.[3a–c,7,9,13] On the contrary, data reported in Table 1 indicated a decrease of ee for **3a**, as the amount of sulfone increased. Since a stereodivergent process of kinetic resolution could not be a priori excluded, race-

Table 1. Asymmetric sulfoxidation of **2a** by $\mathrm{Ti(O}i\text{-}\mathrm{Pr)_4}$/(−)-*exo*-**1**[a]



Entry	Solvent	$\mathrm{Ti(O}i\text{-}\mathrm{Pr)_4}$ (mol%)	Time (h)	Yield **3a**%[b]	Ee **3a**%[c]
1	Toluene	100	6	57(16)	21
2	Toluene	—	48	21(0)	3(*R*)
3	Toluene	50	22	47(10)	27
4	$\mathrm{CH_2Cl_2}$	50	22	60(8)	21
5	$\mathrm{CCl_4}$	50	22	64(13)	23
6	THF	50	41	24(0)	0
7[d]	Toluene	50	18	63(21)	22
8[d]	Toluene	20	21	56(10)	43
9[d,e]	Toluene	8	5	45(0)	3(*R*)
10[f]	**Toluene**	**20**	**22**	**64(4)**	**47**
11[f,g]	Toluene	20	22	32(37)	8
12[f,h]	Toluene	20	48	34(2)	0

[a] Molar ratios: (−)-*exo*-**1**/**2a** 1/1.

[b] Isolated products after flash chromatography. Number in parentheses refers to sulfone yield.

[c] Determined by HPLC analysis on chiral column (Daicel Chiralcel OB).

[d] Reaction performed in the presence of activated MS 4 Å (50 wt.%/**2a**).

[e] $\mathrm{VO(acac)_2}$ was used as catalyst.

[f] Reaction performed in the presence of activated MS 4 Å (100 wt.%/**2a**); 1 h of stirring the catalyst and (−)-*exo*-**1** at −20 °C before the addition of **2a**.

[g] Reaction performed at 0 °C.

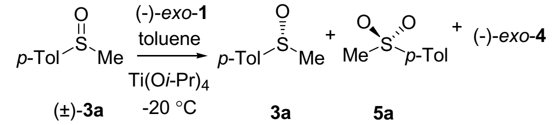
[h] Reaction perfomed in the presence of L-DET [$\mathrm{Ti(O}i\text{-}\mathrm{Pr)_4}$/L-DET 0.20/0.25].

mic **3a** was submitted to a new set of experiments (Table 2). After treatment with a Ti(O*i*-Pr)$_4$/(−)-*exo*-**1** system for prolonged reaction time (entry 1), under the conditions shown in entry 10 in Table 1, racemic **3a** was almost completely recovered, showing that the kinetic resolution is a negligible process under catalytic titanium loadings.

Nevertheless, the possibility of a stereodivergent process was confirmed by performing the reaction in the presence of a stoichiometric amount of Ti(O*i*-Pr)$_4$. In fact, when 1 equiv of the metal complex was used (entry 2), unreacted sulfoxide **3a** was isolated in 56% yield as a (*R*)-prevalent enantiomer (18% ee). Working in excess of hydroperoxide and for a prolonged reaction time, furnished a higher conversion to sulfone and hence a better ee (entry 3). A comparable result was obtained in a shorter reaction time, when using a twofold excess of titanium catalyst and (−)-*exo*-**1** (entry 4), with (*R*)-sulfoxide was isolated with 34% ee. Although a small stereoselectivity factor **S**[14] was calculated in entries 2–4, these results showed an unprecedented opposite sense of enantioselectivity in the asymmetric oxidation of sulfides and kinetic resolution of sulfoxides mediated by the same chiral oxidative system.

Under optimized conditions (Table 1, entry 10), the scope of the Ti(O*i*-Pr)$_4$/(−)-*exo*-**1**/MS 4 Å mediated sulfoxidation was evaluated (Table 3). Remarkably, only negligible amounts of sulfone were detected in all the experiments (<10%), assuring that the enantioselectivity exclusively derived from the asymmetric induction during sulfide oxidation. Preferentially enriched (*S*)-sulfoxides were isolated. The electronic properties of the substituent on the aryl group of the sulfides had noticeable effects on the enantioselectivity. Phenyl methyl sulfide was oxidized in comparable yield and enantioselectivity with respect to model sulfide **2a**

Table 2. Kinetic resolution of racemic **3a** by Ti(O*i*-Pr)$_4$/(−)-*exo*-**1**[a]



Entry	Ti(O*i*-Pr)$_4$ (mol %)	Time (h)	Yield **3a**%[b]	Ee **3a**%[c]	**S**[f]
1[d]	20	44	93(7)	0	1
2	100	22	56(44)	18	1.8
3	100	44	20(80)	29	1.8
4[e]	100	28	27(73)	34	1.7

[a] Molar ratios: (−)-*exo*-**1**/**3a** 0.7/1.

[b] Isolated products after flash chromatography. Number in parentheses refers to sulfone yield.

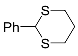
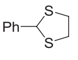
[c] Determined by HPLC analysis on chiral column (Daicel Chiralcel OB).

[d] Reaction performed in the presence of activated MS 4 Å (100 wt. %/**3a**); 1 h stirring the catalyst and (−)-*exo*-**1** at −20 °C before the addition of **3a**.

[e] Additional 1 equiv of catalyst and 0.7 equiv of (−)-*exo*-**1** were added after 6 h of reaction.

[f] Stereoselectivity factor calculated according to Ref. 14.

Table 3. Asymmetric sulfoxidation by Ti(O*i*-Pr)$_4$/(−)-*exo*-**1**/MS 4 Å system[a]

Entry	Sulfide (R,R^1)	Time (h)	Yield **3**%[b]	Ee **3**%[c,d]
1	**2a**	22	64(4)	47(*S*)
2	Me, Ph	22	52(6)	46(*S*)
3	Me, *p*-MeO–C_6H_4	23	54(9)	36(*S*)
4	Me, *p*-Cl–C_6H_4	26	39(4)	20(*S*)
5		44	52	24(*S*)[e]
6[f]		5	50	33(*S*)[e]
7	Me, Bn	24	68(8)	5(*R*)
8[g]	**2a**	22	57(5)	51(*R*)
9[g]	Me, *p*-MeO–C_6H_4	23	56(8)	37(*R*)

[a] The reactions were conducted at −20 °C in toluene using the molar ratios: (−)-*exo*-**1**/**2**/Ti(O*i*-Pr)$_4$/MS 4 Å 1/1/0.20/100 wt. %/**2**.

[b] Isolated products after flash chromatography. Number in parentheses refers to sulfone yield.

[c] Determined by HPLC analysis on chiral column (Daicel Chiralcel OB).

[d] Configuration at sulfur (in parentheses) was determined by comparison with the $[\alpha]_D$ reported in the literature.

[e] Ee of *trans* monosulfoxide was determined by ^{1}H NMR shift experiments with Eu(hfc)$_3$.

[f] The reaction was carried out using 30% mol of Ti(O*i*-Pr)$_4$.

[g] (+)-*exo*-**1** was used as oxidant.

(compare entries 2 and 1). A slightly inferior enantioselectivity was observed in the oxidation of *p*-anisyl methyl sulfide in entry 3. The sulfide having an electron-withdrawing chloride on the aryl ring (entry 4) was less reactive and a lower enantioselectivity was found for the sulfoxide.

Appreciable results have been observed in the sulfoxidation of compounds possessing a stereogenic centre, where both diastereo- and enantioselectivity could have been investigated. The oxidation of 2-phenyl-1,3-dithiane (entry 5) yielded exclusively the *trans*-(1*S*,2*S*)-monosulfoxide with 24% ee. This result proved better than the one reported using the $Ti(Oi\text{-}Pr)_4$/L-DET/TBHP system; in fact, the monosulfoxide was obtained with *trans*/*cis* 90/10 ratio with the *trans*-(1*R*,2*R*) isomer shown to have 14% ee.[15] 2-Phenyl 1,3-dithiolane (entry 6) was converted faster into the *trans*-(1*S*,2*S*)-monosulfoxide, again with complete diastereoselectivity and an improved ee.

As expected, the dialkyl sulfoxide was isolated in good yield, but with very poor ee and preferentially enriched in the opposite (*R*)-enantiomer (entry 7). (*R*)-Sulfoxides having the same levels of enantioselectivity (compare with entries 1 and 3) were synthesized when employing (+)-*exo*-**1**, readily prepared[11] from commercially available (−)-(1*S*)-camphor (entries 8 and 9). Data in Table 3 suggest that the asymmetric induction might be dictated by noncovalent aromatic interactions of the chiral (−)-*exo*-**1**/Ti complex with the sulfide, as the aryl substituted sulfides are oxidized with higher enantioselectivity than the dialkyl sulfides, where only steric effects of the substituents can account for the chiral molecular recognition, thus allowing a lower stereochemical bias.[16] On the basis of previously suggested theoretical models for the Ti-catalyzed oxygen-transfer processes[7,17] we might assume that, under catalytic conditions (20 mol% of Ti catalyst), a mononuclear Ti/(−)-*exo*-**1** complex should form, where the hydroperoxide is electrophilically activated for oxygen transfer by further coordination of the remote oxygen atom of peroxide bond to the metal centre (Fig. 2).

Thus, considering the possible orientations of a sulfide approaching the chiral complex, two situations have to be inspected. When sulfide **2a** approaches according to pathway **A**, a significantly enhanced steric interaction should be expected for the tolyl substituent facing the C_{10}-camphor methyl of the hydroperoxide with respect to the steric interaction of the two methyl groups in **B**. According to this, the preferential formation of the (*S*)-**3a** through pathway **B** is envisaged, which is in agreement with experimental results (Table 3). An inferior discrimination between the two proposed pathways is predictable and consequently a lower enantioselectivity observed in the oxidation of dialkyl sulfides.

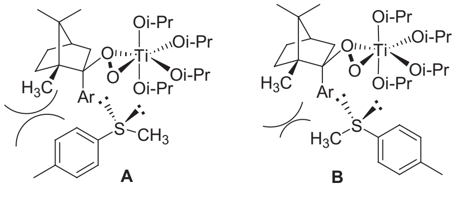


Figure 2.

The opposite sense of enantioselectivity observed during kinetic resolution might be explained by invoking a different steric control in the second oxidation step. In fact, sulfoxides are known to coordinate to titanium,[17] so, in this case, the oxygen would be delivered intramolecularly by the chelated hydroperoxide to the sulfoxide.[18]

Confirmation that the stereodivergent kinetic resolution was a general process was provided by employing both enantiomers of *exo*-**1**, under stoichiometric amounts of $Ti(Oi\text{-}Pr)_4$ (Table 4). It is well established in asymmetric synthesis, that absolute configuration of enantiopure ligands determines the asymmetric induction. Accordingly, the access to the final product in both absolute configurations relies on the pertinent choice of the enantiomeric ligands, when both are available (e.g., L- or D-DET in Sharpless asymmetric epoxidation). To achieve the same goal, in metal-catalyzed oxidations mediated by enantiopure alkyl hydroperoxides, both enantiomers have to be accessible, which, in general, is not straightforward.[19]

3. Conclusion

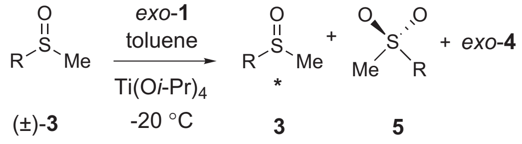
In conclusion, we have reported a chemoselective process of asymmetric sulfoxidation, in the presence of low $Ti(Oi\text{-}Pr)_4$ loadings, which allows to obtain enantiomerically enriched sulfoxides of both absolute configurations, using easily accessible and renewable camphor-derived hydroperoxides. In spite of the moderate levels of enantioselectivity genuinely achieved in the sulfoxidation, the observed ees proved to be among the best reported so far with the use of enantiopure hydroperoxides as stereoselective oxidants.[20] Employing the same chiral promoter, the stereodivergent kinetic resolution offers an alternative route to enantiomerically enriched sulfoxides of opposite absolute configuration. Furyl alcohols (−)-*exo*-**4** and (+)-*exo*-**4**, by-products of the sulfoxidation, can be isolated by silica gel chromatography (70–80% yield) and recycled for the one-step synthesis of the hydroperoxides, with the advantage of providing a less-consuming chiral reagent protocol. Further investigations on the synthesis of stereoelectronically modified tertiary camphor-based hydroperoxides are underway in order to clarify the factors, which affects the enantioselectivity of the oxidations and to develop a better control of the asymmetric induction in the same processes.

4. Experimental

4.1. Materials and general methods

All reactions were performed under an argon atmosphere in flame dried glassware. Solvents such as tetra-

Table 4. Kinetic resolution of racemic sulfoxides[a]



Entry	R	Time (h)	Yield **3**%[b]	Ee **3**%[c]	S[g]
1[d]	*p*-MeO–C_6H_4	16	39(61)	25(*R*)	1.7
2[d,e]	Ph	28	20(78)	39(*R*)	1.7
3	*p*-Cl–C_6H_4	28	23(77)	49(*R*)	2.0
4[f]	*p*-Tol	22	57(43)	13(*S*)	1.7
5[f]	*p*-MeO–C_6H_4	16	37(63)	22(*S*)	1.6

[a] Molar ratios: *exo*-**1**/**3**/Ti(O*i*-Pr)$_4$ 0.7/1/1.

[b] Isolated products after flash chromatography. Number in parentheses refers to sulfone yield.

[c] Determined by HPLC analysis on chiral column (Daicel Chiralcel OB).

[d] (−)-*exo*-**1** was used as oxidant.

[e] Additional 1 equiv of catalyst and 0.7 equiv of (−)-*exo*-**1** were added after 6 h of reaction.

[f] (+)-*exo*-**1** was used as an oxidant.

[g] Stereoselectivity factor calculated according to Ref. 14.

hydrofuran and toluene were distilled over sodium using benzophenone as an indicator. Dichloromethane was distilled from calcium hydride. Petrol refers to the fraction of petroleum ether boiling in the range of 40–60 °C. Standard techniques were used in handling air sensitive reagents. All commercially available reagents were purchased from Aldrich and Fluka. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualized by UV light or by a 10% H_2SO_4/ethanol spray test. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). NMR spectra were recorded in $CDCl_3$ solutions on a Bruker DRX 400 spectrometer (400 MHz) at room temperature. Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: $\delta_H = 7.26$). Optical rotations were performed on a Jasco Dip-1000 using the Na lamp. The synthetic sequence to compound (+)-*exo*-**1** and (+)-*exo*-**4** was previously reported.[11] Specific rotation data for (+)-*exo*-**1** $\{[\alpha]_D^{24} = +49.9$ (c 1.00, $CHCl_3$)$\}$ matched those of (−)-*exo*-**1**; specific rotation data of (+)-*exo*-**4** $\{[\alpha]_D^{24} = +41.0$ (c 1.58, $CHCl_3$)$\}$ matched those of (−)-*exo*-**4**.

4.2. General procedure for the sulfoxidation

To a solution of Ti(O*i*-Pr)$_4$ (25 µL, 0.085 mmol) in 1 mL of dry toluene and activated MS 4 Å (100%/weight based on the sulfide), under argon atmosphere, was added, at −20 °C, a solution of (−)-*exo*-**1** (100 mg, 0.424 mmol) in 1.5 mL of dry toluene. The mixture was stirred for 1 h at −20 °C and then a solution of sulfide **2** (0.424 mmol) in 0.75 mL of dry toluene added. The reaction progress was monitored by TLC analysis. At the end of the reaction, water (85 µL) was added and the mixture stirred for 1 h at room temperature. After filtration of the mixture over Celite with ethyl acetate (40 mL), the solvent was evaporated under vacuum and the crude reaction mixture purified by flash chromatography (from petrol/diethyl ether mixtures 90/10 to pure ethyl acetate) to give (−)-*exo*-**4** (70–80 mol% recovery with respect to **1**) and **3**. Enantiomeric excesses were determined by HPLC analysis on chiral column (Daicel Chiralcel OB column) with UV detection at 254 nm, *n*-hexane/2-propanol 8/2 as eluent and a flow rate of 0.5 mL/min (for *p*-tolyl methyl sulfoxide, phenyl methyl sulfoxide, *p*-anisyl methyl sulfoxide, *p*-chlorophenyl methyl sulfoxide); *n*-hexane/2-propanol 9/1 as eluent and a flow rate of 0.8 mL/min for benzyl methyl sulfoxide. Enantiomeric excesses for *trans* 2-phenyl-[1,3]-dithiane-1-oxide and *trans* 2-phenyl-[1,3]-dithiolane-1-oxide were measured by ^1H NMR shift experiments with Eu(hfc)$_3$ according to Ref. 15.

4.3. General procedure for kinetic resolution

To a solution of Ti(O*i*-Pr)$_4$ (126 µL, 0.424 mmol) in 1 mL of dry toluene, at −20 °C and under argon atmosphere, was added a solution of the racemic sulfoxide (0.424 mmol) in 0.75 mL of dry toluene. The mixture was stirred at −20 °C for 10 min and then a solution of (−)-*exo*-**1** (70 mg, 0.297 mmol) in 1.5 mL of dry toluene added. At the end of the reaction, water (424 µL) was added and the mixture stirred for 1 h at room temperature. After filtration of the mixture over Celite with ethyl acetate (40 mL), the solvent was evaporated under vacuum and the crude reaction mixture purified by flash chromatography (from petrol/ethyl acetate mixtures 1/1 to pure ethyl acetate) to give the unreacted sulfoxide.

Acknowledgements

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18. The simultaneous coordination of hydroperoxide and sulfoxide (template effect) has been postulated to rationalize the over-oxidation to sulfone, hence the kinetic resolution.[7] Hypotheses on the transition states involved in the oxidations, at the moment, would be highly speculative even in consideration of the complex equilibria that different Ti-species can provide in solution.[1,2]
19. In the case of the most broadly applicable approach to enantiopure hydroperoxides via HRP, only hydroperoxides of one absolute configuration can be obtained.[5] When starting their synthesis from the chiral pool, in general one enantiomer of the chiral source is available; the other enantiomer has to be prepared or is highly expensive.
20. During the earlier stages of asymmetric sulfoxidation of **2a** by (*S*)-1-phenylethyl hydroperoxide/Ti(O*i*-Pr)$_4$ system, when either the over-oxidation to sulfone and the positive contribution by kinetic resolution were negligible, the ee of **3a** was determined to be <20%.[7] An example of chemoselective sulfoxidation of methyl phenyl sulfide with enantiopure tertiary hydroperoxide TADOOH, in THF at −30 °C for 3 days, furnished the sulfoxide in 61% yield and 80% ee.[9]