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Kinetic resolution and asymmetric oxidation as combined routes to chiral sulfoxides

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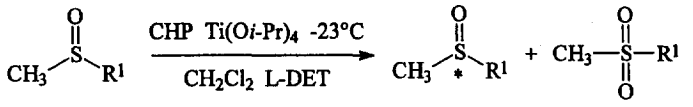
Abstract: Non-racemic sulfoxides are accessible through a modified Sharpless kinetic resolution of racemic sulfoxides. Furthermore, thanks to enantioconvergence of asymmetric oxidation and kinetic resolution a successful improvement of e.e. is achievable. © 1997 Elsevier Science Ltd

Chiral sulfoxides represent attractive compounds because of their employment as valuable auxiliaries in asymmetric synthesis[1]. The most important methods used for their preparation are: (1) the Andersen synthesis[2], concerning the reaction of diastereomeric pure sulfinates with organometallic reagents, (2) asymmetric oxidation of sulfides to chiral sulfoxides. Different approaches have been reported for the latter procedure: Sharpless modified oxidation of sulfides[3], the employment of different chiral oxaziridines[4] and enzymatic sulfoxidation[5].

In particular, *t*-butyl hydroperoxide/Ti(O*i*-Pr)$_4$/dialkyl tartrate/H_2O system gives products in enantiomeric excess in the range of 80–90%[6]. Kagan *et al.* showed the optimization of their water modified Sharpless titanium complex[7], but they asserted the necessity of careful control of experimental conditions for the preparation of the active chiral complex (temperatures, reaction times in the premixing defined addition of reagents) in order to reach high levels of enantioselectivity (e.e.>99%).

On the other hand, there are few examples of procedures based on the kinetic resolution of racemic sulfoxides: these methodologies involve the employment of titanium–binaphthol complex[8] (that catalyzes both asymmetric oxidation of sulfides and kinetic resolution of the resulting sulfoxides) and Salen manganese (III) complex as catalysts[9]. However, in both cases, kinetic resolution was found to take place with low efficiency. The paucity of results in this specific field stimulated our interest and, in particular, the possibility of exploitation of different oxidants in the asymmetric oxidation of sulfoxides was examined. In a preliminary phase a series of experiment has been performed using cumyl hydroperoxide (CHP) as oxygen donor and, under the conditions reported by Modena[3b], we found that starting racemic **1** could be enantiomerically enriched by enantioselective oxidation to sulfones[10]. (Scheme 1, Table 1).



1 **1***

Scheme 1.

Methyl aryl sulfoxides (entries 1, 2 and 3) were recovered with good yields and enantiomeric excess, deriving from the preferential oxidation of the S-enantiomer to sulfone, while the procedure appeared

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Table 1. Kinetic resolution of racemic sulfoxides with CHP

Entry	R^1	t(h)	yield 1*(%)[a]	e.e. 1*(%)[b]	E[c]
1	*p*-CH_3-C_6H_4	91	40	83 (R)	8.6
2	C_6H_5	"	39	87 (R)	9.4
3	*p*-Cl-C_6H_4	"	31	94 (R)	7.8
4	$C_6H_5CH_2$	"	31	9 (R)	1.2
5	*p*-CH_3-C_6H_4	"	75	13 (R)	2.5[d]

[a]Isolated yields. Molar ratios employed 1 / CHP / Ti(O*i*-Pr)$_4$ / L-DET 2 / 1.3 / 1 / 4 [b]E.e.s have been determined on representative samples obtained after mixing all the sulfoxide fractions coming from chromatography by ^{1}H-NMR analysis in the presence of R-(-)-(3,5-dinitrobenzoyl)-α-methylbenzyl amine as shift reagent[11]. Absolute configuration established by comparison of the specific rotation with reported values. [c]Evaluation of stereoselectivity factor[12] $E=k_R/k_S$ according to equation $E=\ln[(1-C)(1-e.e.)]/\ln[(1-C)(1+e.e.)]$. [d]*t*-butyl hydroperoxide has been employed.

Table 2. Kinetic resolution of racemic sulfoxides with CHP at room temperature

Entry	R^1	t(h)	yield 1*(%)[a]	e.e. 1*(%)[b]	E[c]
1	*p*-CH_3-C_6H_4	16	33	71 (R)	4.1
2	C_6H_5	"	30	77 (R)	4.2
3	*p*-Cl-C_6H_4	"	31	64 (R)	3.2
4	$C_6H_5CH_2$	"	18	6 (R)	1.1
5	*p*-Cl-C_6H_4	"	38	41 (R)[d]	2.4

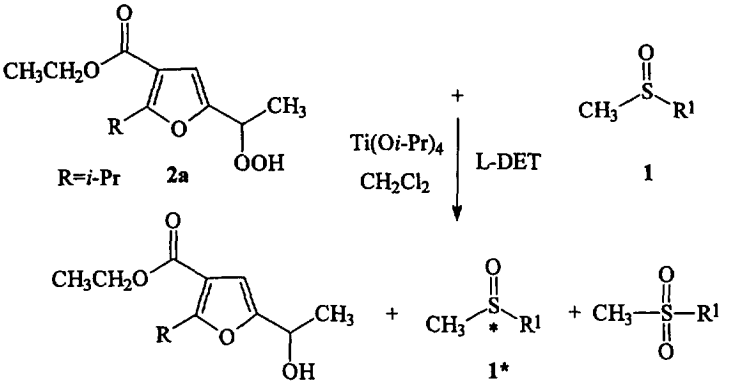
[a]Isolated yields. Molar ratios used 1 / CHP / Ti(O*i*-Pr)$_4$ / L-DET 2 / 1.3 / 1 / 4. [b]See note b in Table 1. [c]See note c in Table 1. [d]In this experiment Ti(O*i*-Pr)$_4$ has been used in catalytic amounts (20% molar) respect to sulfoxide.

unsuccessful in the case of dialkyl sulfoxide (entry 4). Poor enantiomeric excess was verified when *t*-butyl hydroperoxide was used as oxidant (last entry). Although to a lower extent, kinetic resolution proceeded at room temperature (Table 2) and under catalytic conditions (entry 5).

In the course of an investigation on the reactivity of furylhydroperoxides of type **2**, we discovered that this easily accessible class of oxidant[13] can be a valuable alternative to *t*-butyl hydroperoxide in Sharpless modified asymmetric oxidation, and, furthermore, that racemic **2** could be resolved in a significant way by asymmetric oxidation of allylic alcohols, sulfides, sulfoxides[14]. Therefore we decided to verify if the roles of **1** and **2** could be reversed, that is if **2** could be employed in the kinetic resolution of racemic sulfoxides. Compound **2a** was chosen as representative oxidant (Scheme 2) and a set of different runs was carried out adopting the conditions reported in Table 3.

Unreacted methyl aryl sulfoxides (entries 1, 2 and 3) were recovered with very high enantiomeric excess and good yields. In entry 4 the employment of D-DET allowed the sulfoxide to be obtained with still high e.e., but with the opposite absolute configuration. Very promising results both in terms of yields and enantioselectivity have been obtained at higher temperature (entries 6–10): it has to be noted that in entries 7 and 8 the values of the corresponding stereoselectivity factors, calculated by Kagan's equations[12], are respectively 17.0 and 16.2. Furylhydroperoxide **2b** (R=CH_3, entry 6) showed the same efficiency of **2a** in the kinetic resolution of sulfoxides. The procedure appeared much less efficient in the case of dialkyl sulfide (entry 5).

An interesting development of these results concerned the increase of enantiomeric excess of starting enantiomerically enriched sulfoxides **1'** (Scheme 3, Table 4).

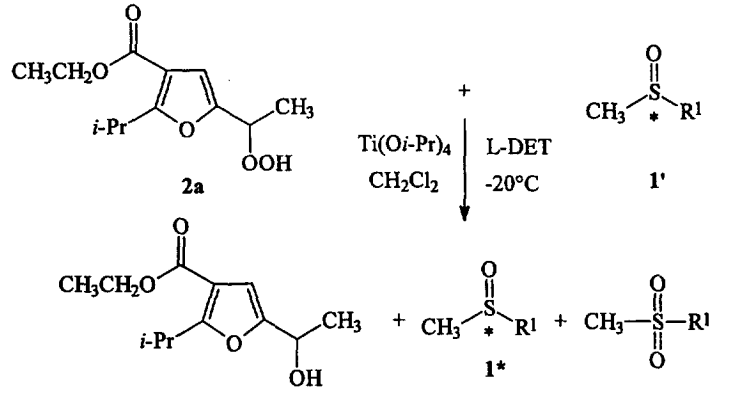


Scheme 2.

Table 3. Kinetic resolution of racemic sulfoxides with furylhydroperoxide **2a**

Entry	R^1	T(°C)	t(h)	yield 1*(%)[a]	e.e. 1*(%)[b]	E[c]
1	*p*-CH_3-C_6H_4	-23	26	38	>95 (R)	-
2	C_6H_5	"	22	38	91 (R)	10.5
3	*p*-Cl-C_6H_4	"	23	40	95 (R)	15.7
4	*p*-CH_3-C_6H_4	-15	22	49[d]	73 (S)	12
5	$C_6H_5CH_2$	-23	26	73	17 (R)	3.2
6	C_6H_5	0	21	64[e]	40 (R)	8.7
7	*p*-CH_3-C_6H_4	"	1	48	81 (R)	17.0
8	*p*-CH_3-C_6H_4	"	1	52	71 (R)	16.2
9	*p*-Cl-C_6H_4	"	6	38	76 (R)	6.0
10	C_6H_5	"	7	38	83 (R)	7.5

[a]Isolated yields. Molar ratios used **1** / **2a** / Ti(O*i*-Pr)$_4$ / L-DET 2 / 1.6 / 1 / 4. [b]See note b in Table 1. [c]See note c in Table 1. [d]In this experiment D-DET has been used. [e]In this experiment furylhydroperoxide **2b** R=CH_3 has been used.



Scheme 3.

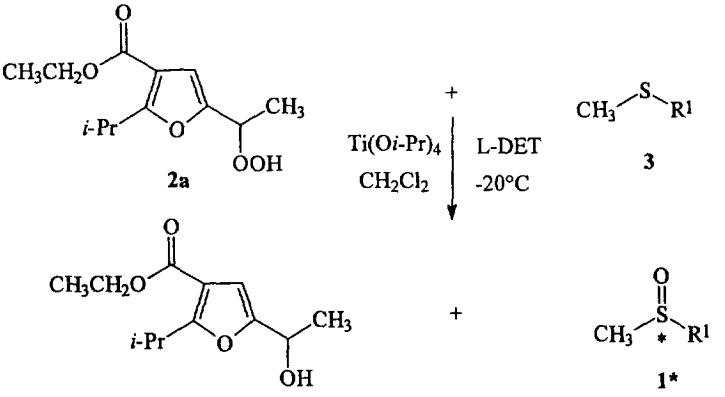
Table 4. Enantiomeric enrichment of starting chiral sulfoxides 1′

Entry	R^1	e.e.1′(%)	t(h)	yield 1*(%)[a]	e.e. 1*(%)[c]
1	*p*-CH_3-C_6H_4	73 (R)	22	82	83 (R)
2	*p*-Cl-C_6H_4	80 (R)	15	81	90 (R)
3	*n*-C_8H_{17}	65 (R)	16	76	76 (R)
4	*p*-CH_3-C_6H_4	63 (R)	22	67[b]	>95 (R)
5	C_6H_5	72 (R)	24	56[b]	>95 (R)
6	$C_6H_5CH_2$	60 (R)	18	58[b]	81 (R)

[a]Isolated yields. Molar ratios used 1′ / **2a** / Ti(O*i*-Pr)$_4$ / L-DET 1 / 0.25 / 0.25 / 1. [b]Molar ratios used 1′ / **2a** / Ti(O*i*-Pr)$_4$ / L-DET 2 / 1 / 1 / 4. [c]See note b in Table 1.

We carried out the reactions under the usual conditions but employing different molar ratios of **2a** with respect to 1′. The increase of e.e. is linked to stereoselectivity factors[12] E, but also to the degree of conversion C. Raising the conversion of 1′ to sulfone (entries 4, 5 and 6) in comparison to entries 1, 2 and 3 in Table 4 resulted in a better improvement of enantiomeric excess of the corresponding recovered sulfoxides **1***. Good values of e.e. were detected for dialkyl sulfoxides **1*** too (entries 3 and 6), obtained for higher conversions to sulfones because of low stereoselectivity factors.

Since asymmetric oxidation[14] and kinetic resolution showed the same sense of enantioselectivity, we exploited the two oxidation processes to obtain sulfoxides **1*** with high enantiomeric excess (Scheme 4, Table 5).



Scheme 4.

In conclusion, herein we described that furylhydroperoxides represent the most efficient oxidants to perform kinetic resolution of racemic sulfoxides under Sharpless type conditions.

Furthermore, thanks to the enantioconvergence of asymmetric oxidation and kinetic resolution we provide an alternative methodology to obtain chiral sulfoxides with high e.e. by employing simple conditions of reaction.

Experimental

^{1}H-NMR and ^{13}C-NMR spectra were recorded with Varian Gemini-200 and Varian XL-300 spestrometers. Splitting patterns are desigated as s (singlet), d (doublet), t (triplet), q (quartet), hept (heptuplet), m (multiplet), dd (double doublet), ss (sharp singlet). Chemical shifts are reported in (δ) ppm relative to internal $CDCl_3$ δ (7.26) for ^{1}H-NMR and $CDCl_3$ δ (77.0) for ^{13}C-NMR.

Table 5. Asymmetric oxidation and kinetic resolution as combined processes to chiral sulfoxides

Entry	R[1]	t(h)	yield 1*(%)[a]	e.e. 1*(%)[b]
1	*p*-CH_3-C_6H_4	63	60	>95 (R)
2	C_6H_5	63	59	>95 (R)
3	*p*-Cl-C_6H_4	67	63	92 (R)
4	*n*-C_8H_{17}	43	51[c]	73 (R)
5	$C_6H_5CH_2$	69	51[c]	70 (R)

[a]Isolated yields. Molar ratios used **2a** / **3** / Ti(O*i*-Pr)$_4$ / L-DET 1.6 / 1 / 1 / 4.[b]See note b in Table 1. [c]In these reactions L-DIPT has been used as chiral ligand.

Specific optical rotations were measured with a JASCO Dip-370 digital polarimeter at λ=589 nm at temperature of 20°C. Silica gel (230–400 mesh Merck) was used for flash chromatography. Analytical thin layer chromatography was carried out on Merck Kieselgel F_{254} plates. The enantiomeric excesses of sulfoxides were determined by ^{1}H-NMR in the presence of (R)-(−)-(3,5-dinitrobenzoyl)-α-phenylethylamine as shift reagent. Dicloromethane was strored over activated 4 Å molecular sieves (2 days at 160°C). Other chemicals (Aldrich or Fluka) were used as commercial products.

Kinetic resolution of racemic sulfoxides. General procedure

To a solution of CH_2Cl_2 (10 ml), at room temperature and under argon atmosphere are added Ti(O*i*-Pr)$_4$ (1 mmol), L-DET (4 mmol), **1** or **1′** (2 mmol). The stirred mixture is cooled to −20°C for 20 minutes. Then CHP (1.3 mmol) or **2a,b** (1.6 mmol) dissolved in 10 ml of CH_2Cl_2, is added and the reaction is monitored on TLC. Water is added (4 ml) to the solution at −20°C and a vigorous stirring is maintained for one hour at room temperature. The white gel is filtered over celite and thoroughly washed with CH_2Cl_2. The organic phase is dried over Na_2SO_4 and then evaporated. Flash chromatography of crude mixture (*n*-hexane/AcOEt) affords pure sulfoxides.

5-(1-Hydroperoxyethyl)-3-ethoxycarbonyl-2-isopropylfuran ***2a***

White needles; ^{1}H-NMR ($CDCl_3$): 1.24 (d, 6H, *J*=7.0 Hz), 1.32 (t, 3H, *J*=7.0 Hz), 1.52 (d, 3H, *J*=7.0 Hz), 3.73 (hept, 1H, *J*=7.0 Hz), 4.26 (q, 2H, *J*=7.0 Hz), 5.00 (q, 1H, *J*=7.0 Hz), 6.62 (s, 1H), 7.83 (ss, 1H). ^{13}C-NMR ($CDCl_3$): 13.9, 15.9, 20.3, 27.1, 60.0, 75.9, 109.4, 112.1, 151.2, 164.2, 167.4. Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.48; H, 7.49%. Found: C, 59.40; H, 7.41%.

5-(1-Hydroperoxyethyl)-3-ethoxycarbonyl-2-methylfuran ***2b***

White needles; ^{1}H-NMR ($CDCl_3$): 1.32 (t, 3H, *J*=7.0 Hz), 1.52 (d, 3H, *J*=6,8 Hz), 2.56 (s, 3H), 4.26 (q, 2H, *J*=7.0 Hz), 4.99 (q, 1H, *J*=6.8 Hz), 6.62 (s, 1H), 8.20 (ss, 1H); ^{13}C-NMR ($CDCl_3$): 13.5, 13.9, 15.9, 60.2, 75.8, 109.6, 114.0, 151.6, 159.6, 164.4. Anal. Calcd.for $C_{10}H_{14}O_5$: C, 56.05; H, 6.59%. Found: C, 56.10; H, 6.64%.

(R)-p-Tolyl methyl sulfoxide

White solid; $[\alpha]_D^{20}$ +141.8 (c=1.5, acetone) ^{1}H-NMR ($CDCl_3$): 2.40 (s, 3H), 2.68 (s, 3H), 7.30–7.70 (m, 4H).

(R)-Phenyl methyl sulfoxide

White solid; $[\alpha]_D^{20}$ +142.2 (c=1.1 acetone) ^{1}H-NMR ($CDCl_3$): 2.70 (s, 3H), 7.50–7.55 (m, 3H), 7.63–7.68 (m, 2H).

(R)-p-Chlorophenyl methyl sulfoxide

White solid; $[\alpha]_D^{20}$ +114.5 (c=1.8 acetone) ^{1}H-NMR ($CDCl_3$): 2.72 (s, 3H), 7.50–7.60 (m, 4H).

(R)-Benzyl methyl sulfoxide

White solid; $[\alpha]_D^{20}$ −67.1 (c=2.0 ethanol) ^{1}H-NMR ($CDCl_3$): 2.42 (s, 3H), 3.98 (dd, 2H, *J*=13.0 Hz).

(R)-Methyl n-octyl sulfoxide

White solid; $[\alpha]_D^{20}$ −59.8 (c=1.6 acetone) ^{1}H-NMR ($CDCl_3$): 0.87 (m, 3H), 1.26–1.90 (m, 12 H), 2.54 (s, 3H), 2.66 (m, 2H).

Asymmetric oxidation and kinetic resolution combined processes to chiral sulfoxides

To a solution of CH_2Cl_2 (7 ml), at room temperature and under argon atmosphere are added Ti(O*i*-Pr)$_4$ (1 mmol), L-DET (4 mmol), **3** (1 mmol). The stirred mixture is cooled to −20°C for 20 minutes. Then **2a** (1.6 mmol) dissolved in 7 ml of CH_2Cl_2, is added and the reaction is monitored on TLC. Water is added (4 ml) to the solution at −20°C and a vigorous stirring is maintained for one hour at room temperature. The white gel is filtered over celite and thoroughly washed with CH_2Cl_2. The organic phase is dried over Na_2SO_4 and then evaporated. Flash chromatography of crude mixture (*n*-hexane/AcOEt) affords pure sulfoxides.

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