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New procedures for the enantioselective oxidation of sulfides under stoichiometric and catalytic conditions

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Abstract—Acid-catalyzed oxidation of 2-furylcarbinols with hydrogen peroxide affords alternatively 2-(1-hydroperoxyalkyl)-furans **2** or 6-hydroperoxy-2*H*-pyran-3(6*H*)-ones **3**. Compounds of the type **2** and **3** have been used as oxygen donors in efficient stoichiometric or catalytic procedures for the asymmetric sulfoxidation of prochiral sulfides in the presence of Ti(O-*i*-Pr)$_4$/*L*-DET or Ti(O-*i*-Pr)$_4$/(*R*)-BINOL/H_2O systems. Positive non linear effects, (+)-NLE, were observed in the enantioselective oxidation of methyl *p*-tolyl sulfide, promoted by enantiomerically enriched Ti(IV)/BINOL/H_2O complexes.

1. Introduction

The asymmetric oxidation of sulfides is an important preparative reaction because of the ever increasing use of chiral sulfoxides both as bioactive compounds[1] and chiral auxiliaries.[2]

In 1984 the groups of Kagan[3] and Modena[4] discovered independently that a combination of Ti(O-*i*-Pr)$_4$/(*R*,*R*)-diethyl tartrate (DET)/H_2O (1:2:1) or Ti(O-*i*-Pr)$_4$/(*R*,*R*)-DET (1:4) could be conveniently exploited for the asymmetric sulfoxidation of some sulfides with *tert*-butyl hydroperoxide (TBHP) or cumyl hydroperoxide (CHP), as oxidants.

Suitable modifications by Kagan of his original protocol have allowed the achievement of catalytic asymmetric processes. Recently other reported procedures are usually based on the in situ formation of the catalytic species by reaction of Ti(O-*i*-Pr)$_4$ with chiral binaphthols,[5] variously substituted 1,2-diols,[6] trialkanolamines.[7] Particular attention has been evidently paid to the influence of the chiral ligand on the level of efficiency and enantioselectivity of the asymmetric sulfoxidation although the structure of the used hydroperoxide has shown to be an important factor. In fact, besides the most widely used oxidants TBHP and CHP, for example, functionalized furylhydroperoxides have been successfully employed in convenient procedures for the asymmetric epoxidation of allylic alcohols,[8] the oxidation of sulfides to chiral sulfoxides and the kinetic resolution of racemic sulfoxides.[9]

One of the main targets of advanced organic synthesis is represented by the achievement of highly efficient, cheap and environmentally acceptable processes. This result allows the formation of unwanted waste to be minimized and tedious and expensive purification procedures to be avoided, so that crude intermediates or reagents can be used directly.

With these considerations in mind, our efforts have recently been addressed to the realization of a new, efficient and resource-saving procedure for the rapid synthesis of easily renewable hydroperoxides, for use in asymmetric oxidative processes.

2. Results and discussion

2.1. Synthesis of hydroperoxides 2 and 3

Hydroperoxides **2**, chosen as target compounds, proved to be easily accessible by treatment of the corresponding furylcarbinols **1** with hydrogen peroxide in 1,2-dimethoxyethane (DME) in the presence of *p*-toluenesulfonic acid (PTSA). In all the experiments reported in Table 1, the formation of **2** took place in high yield and with good selectivity (85–95%), as supported by ^{1}H NMR analysis on the isolated crude

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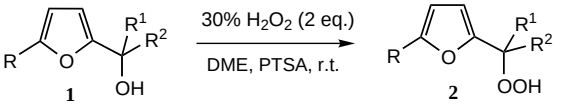
Table 1. Acid-catalyzed conversion of **1** into hydroperoxides **2** with 30% H_2O_2

Entry	R	R^1	R^2	t (h)	**2**	Yield (%)[a]
1	H	H	*n*-Hexyl	14	**2a**	65
2	H	Me	Me	3	**2b**	70
3	Me	H	*n*-Hexyl	7	**2c**	75
4	Me	H	*n*-Pentyl	8	**2d**	71
5	Me	H	*n*-Octyl	7	**2e**	65

[a] All yields refer to isolated chromatographically pure compounds **2**, whose structures were confirmed by IR, ^{1}H, ^{13}C NMR and elemental analysis data.

products **2**, that, in every case, could be easily purified by silica gel chromatography. This level of selectivity can be considered rather surprising considering of the well-known lability of the O–O peroxidic bond in acidic medium and the strong tendency of compounds of type **1** to undergo acid-catalyzed opening of the furan nucleus (Scheme 1).[10,11]



Scheme 1.

More interestingly, the unusual oxidant system H_2O_2/PTSA showed an unprecedented reactivity towards the furan moiety of hydroperoxides **2**. In fact, under appropriate conditions (higher amounts of H_2O_2 and PTSA), starting materials **1** underwent two sequential oxidations leading, through the intermediates **2**, to compounds **3** (Scheme 2, Table 2).

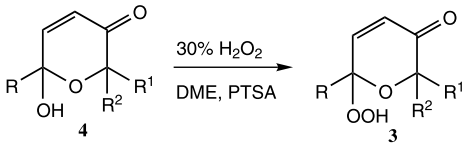
Table 2. Acid-catalyzed conversion of **1** into hydroperoxides **3** with 30% H_2O_2

Entry	R	R^1	R^2	t (h)	**3**	Yield (%)[a,b]
1	Me	H	*n*-Hexyl	18	**3a**	75 (90/10)
2	Me	H	*c*-Hexyl	23	**3b**	77 (93/7)
3	Me	H	*i*-Propyl	16	**3c**	64 (92/8)
4	Me	Me	Me	7	**3d**	77
5	Me	Et	*n*-Hexyl	5	**3e**	65 (50/50)
6	Me	H	*n*-Octyl	20	**3f**	65 (94/6)

[a] All yields refer to isolated chromatographically pure compounds **3**, whose structures were confirmed by IR, ^{1}H, ^{13}C NMR and elemental analysis data. Furthermore, **3** were reduced quantitatively by treatment with dimethyl sulfide (1.5 equiv.) in Et_2O solution a 0°C and the spectroscopic data (IR, ^{1}H, ^{13}C NMR) of the resulting compounds **4** matched with those of authentic sample prepared according to a literature procedure.[12]

[b] Values in parentheses refer to diastereomeric ratios.

Although the reaction pathway affording **3** has not yet been clarified, it seems reasonable that the formation of intermediates of the type **4** could be involved (Scheme 3).



Scheme 3.

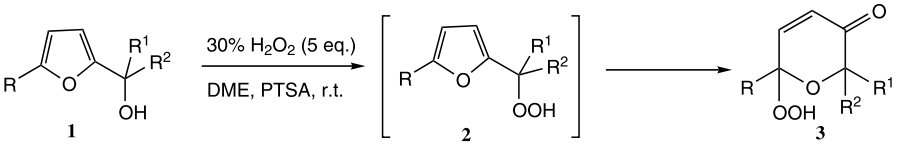
In fact, the conversion of furyl alcohols **1** into **4** with a variety of oxidants, such as *m*-chloroperbenzoic acid,[13] pyridinium chlorochromate,[14] dimethyl dioxirane[15] etc., has been widely reported in the literature; furthermore, compounds **4**, under the usual conditions, are quantitatively converted into **3**.

The achievement of a new, economical and safe approach to compounds **3** can be considered an important preparative result since, besides representing a new class of hydroperoxides, they can be quantitatively reduced (either directly in situ or after purification) to the corresponding 6-hydroxy-2*H*-pyran-3(6*H*)-one derivatives **4**, which are well-known both as bio-active compounds and versatile synthetic intermediates.[16]

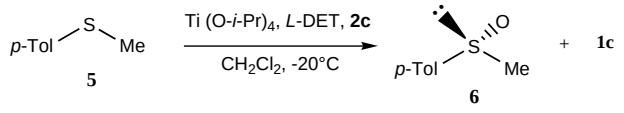
2.2. Asymmetric sulfoxidation by Modena's procedure

A set of experiments was planned in order to verify the possibility of exploiting hydroperoxides of the type **2** and **3** in the asymmetric sulfoxidation of prochiral sulfides. In the preliminary phase hydroperoxide **2c** and methyl *p*-tolyl sulfide were used as representative reagents in a modified version of the stoichiometric Modena's procedure (Scheme 4). It should be noted that compound **2c** could be obtained in ~95% yield by oxidative treatment of the corresponding furyl alcohol in acidic medium, being contaminated with very small amounts of starting material (<5%, ^{1}H NMR analysis on crude **2c**); therefore, **2c** was generally used directly without purification.

Using Modena's catalytic system, Ti(O-*i*-Pr)$_4$/*L*-DET under stoichiometric conditions gave good results and the levels of efficiency and enantioselectivity were found to depend on the amount of hydroperoxide and the reaction time (Table 3).



Scheme 2.



Scheme 4.

Table 3. Stoichiometric enantioselective oxidation of methyl *p*-tolyl sulfide by **2c**

Entry	**2c** (equiv.)	*t* (h)	Yield (%)[a]	E.e. (%)[b]
1	1.1	1.45	63 (<5)[c]	70
2	1.7	1.45	97 (nd)	74
3	2.0	18	72 (15)[c]	84
4	2.5	22	61 (30)[c]	98

[a] All yields refer to isolated chromatographically pure compound **6**, obtained with (*R*)-enantiomer in excess.
[b] E.e.s were determined by HPLC on a Daicel Chiralcel OB column.
[c] Values in parentheses refer to isolated sulfone.

In particular, a strong enhancement of the e.e. was strictly related to the amount of sulfone produced. This result suggested that a process of convergent kinetic resolution could follow the asymmetric oxidation, thus increasing the e.e. of the sulfoxide. This hypothesis was confirmed by submitting racemic methyl *p*-tolyl sulfoxide to treatment with **2c** (1.3 equiv.) under the conditions reported in Table 3. After 18 h the expected sulfone was obtained in 59% yield while the starting material was recovered in 41% yield and 98% e.e. ((*R*)-enantiomer predominant; stereoselectivity factor $S=23$, calculated according to Ref. 17).

The above procedure proved to be successful with other aryl methyl sulfides (Table 4) and good yields and moderate e.e.s were observed by carrying out the asymmetric oxidation under catalytic conditions involving the presence of only 0.2 equiv. of Ti(O-*i*-Pr)$_4$ and 0.8 equiv. of *L*-DET with respect to the starting sulfide (entry 5).

It is noteworthy that, in all the above experiments, chromatographic purification of crude sulfoxides **6** afforded **1c** in almost quantitative yield, which can be converted into **2c** according to the previously reported approach (Scheme 1).

On the basis of the results obtained by the standard Modena procedure for methyl *p*-tolyl sulfoxide (60% yield, 88.3% e.e., based on the specific rotation of the pure enantiomer), the alternative employment of **2c** allows a much higher level of enantioselectivity since **6a** was obtained in 61% yield and 98% e.e. (HPLC).
Less satisfactory results have been obtained by using hydroperoxides of the type **3**, as supported by some experiments, reported in Table 5.

Table 5. Stoichiometric enantioselective oxidation of **5** with **3d**,**f**

Entry	Ar	**3**	Yield (%)[a,b]	E.e. (%)[c]
1	*p*-MeC$_6$H$_4$	**3d**	77 (15)	68
2	*p*-ClC$_6$H$_4$	**3d**	88 (10)	64
3	*p*-MeOC$_6$H$_4$	**3f**	77 (10)	62

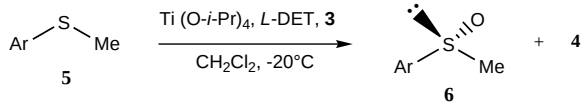
[a] All the yields refer to isolated chromatographically pure compound **6**, obtained with (*R*)-enantiomer in excess.
[b] Values in parentheses refer to isolated sulfone.
[c] E.e.s were determined by HPLC on a Daicel Chiralcel OB column.

In fact, although asymmetric oxidation was shown to proceed with good efficiency, only moderate e.e.s were observed, in spite of the formation of sulfone at levels of 10–15% (Scheme 5).

2.3. Catalytic asymmetric sulfoxidation by Uemura's procedure[5a]

Further investigations were devoted to the achievement of a catalytic procedure, leading to chiral sulfoxides, based on the use of the Ti(O-*i*-Pr)$_4$/(*R*)-BINOL/H$_2$O system. Nevertheless, the modified version, involving the use of hydroperoxide **2c** as an oxygen donor, proved to be unsuccessful: in many experiments, performed on methyl *p*-tolyl sulfide in toluene solution the formation of a white solid precipitate could be observed and the corresponding sulfoxide was usually isolated in low yields and very poor e.e.s.

On the contrary, more satisfactory results were achieved by using furylhydroperoxide **2b**, pointing out again the strong influence exerted by the structure of



Scheme 5.

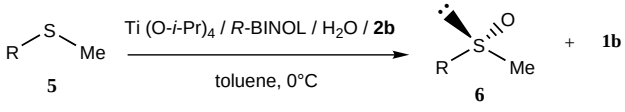
Table 4. Stoichiometric enantioselective oxidation of **5** with hydroperoxide **2c**

Entry	Ar	**5**	*t* (h)	Yield (%)[a,b]	E.e. (%)[c]
1	*p*-MeC$_6$H$_4$	**5a**	22	61 (30)	98
2	*p*-ClC$_6$H$_4$	**5b**	22	82 (16)	93
3	Ph	**5c**	22	89 (5)	78
4	*p*-MeOC$_6$H$_4$	**5d**	24	70 (30)	99
5	*p*-MeC$_6$H$_4$	**5a**	24	79 (9)	62

[a] All yields refer to chromatographically isolated pure compound **6**, obtained with (*R*)-enantiomer in excess.
[b] Values in parentheses refer to isolated sulfone.
[c] E.e.s were determined by HPLC on a Daicel Chiralcel OB column.

the oxidant on the efficiency and enantioselectivity of the reaction.

In fact, under the conditions reported in Scheme 6 and Table 6 no precipitation was observed and the formation of the expected sulfoxides took place in satisfactory yield. Furthermore, the level of enantioselectivity was again found to depend on the reaction time and the amount of sulfone produced (entries 1–4). The occurrence of a convergent process of kinetic resolution of the enantiomerically enriched sulfoxide deriving from the initial asymmetric oxidation was confirmed by submitting racemic methyl *p*-tolyl sulfoxide to reaction with **2b** in the presence of the usual amounts of the catalytic system Ti(IV)/(*R*)-BINOL/H_2O; after 19 h the corresponding sulfone was isolated in 37% yield, while the starting material was recovered in 67% yield with 41% e.e. ((*R*)-enantiomer in excess; stereoselectivity factor $S=16$). Regarding the preparative aspects, the combination of asymmetric sulfoxidation and convergent kinetic resolution afforded chiral methyl aryl sulfoxides in appreciable yield and very satisfactory e.e.s. It is noteworthy that the employment of **2b**, in place of TBHP, has allowed a significant improvement of the original Uemura's procedure, involving a moderately enantioselective sulfoxidation ($\sim$50% e.e.), while the concomitant process of kinetic resolution took place with much lower stereoselectivity factors ($S=2$–3). Consequently, chiral sulfoxides could be obtained with high e.e.s only in rather low yields. When a methyl group was replaced with an ethyl group (for example, phenyl ethyl sulfide) the starting material was recovered almost completely unreacted after prolonged treatment (24 h) under the standard conditions. In every case, moderate reactivity and enantioselectivity were observed by performing the reaction at 25°C since the



Scheme 6.

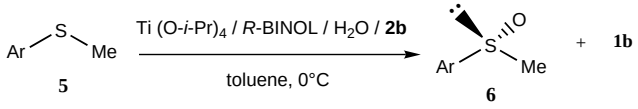
Table 6. Catalytic asymmetric sulfoxidation with Ti(O-*i*-Pr)$_4$ (0.1 equiv.)/(*R*)-BINOL (0.2 equiv.)/H_2O (20 equiv.)

Entry	R	*t* (h)	Yield (%)[a,b]	E.e. (%)[c]
1	*p*-MeC_6H_4	3	71 (nd)	49
2	*p*-MeC_6H_4	4	76 (nd)	52
3	*p*-MeC_6H_4	5.5	75 (<5)	61
4	*p*-MeC_6H_4	24	63 (37)	87
5	*p*-ClC_6H_4	16.5	67 (33)	80
6	Ph	16	69 (25)	85
7	*p*-$MeOC_6H_4$	16	56 (16)	93
8	*p*-BrC_6H_4	17	79 (21)	51
9	$C_6H_5CH_2$	23	95 (5)	51

[a] All the yields refer to isolated chromatographically pure compound **6**, obtained with (*R*)-enantiomer in excess.
[b] Values in parentheses refer to isolated sulfone.
[c] E.e.s were determined by HPLC on a Daicel Chiralcel OB column.

corresponding sulfoxide was isolated in 56% yield and 56% e.e.

Rather surprisingly, Uemura's approach afforded interesting results in the presence of reduced amounts of chiral ligand. In fact, when the catalytic system Ti(O-*i*-Pr)$_4$/*R*-BINOL/H_2O was generated according to 0.1:0.1:20 stoichiometric ratio (with respect to the starting materials), the formation of the chiral sulfoxides occurred in good yields and improved chemoselectivity (Scheme 7, Table 7).



Scheme 7.

Table 7. Catalytic asymmetric sulfoxidation by Ti(O-*i*-Pr)$_4$ (0.1 equiv.)/(*R*)-BINOL (0.1 equiv.)/H_2O (20 equiv.) system

Entry	Ar	*t* (h)	Yield (%)[a,b]	E.e. (%)[c]
1	*p*-MeC_6H_4	4	49 (nd)	47
2	*p*-MeC_6H_4	6	59 (6)	65
3	*p*-MeC_6H_4	24	79 (14)	80
4	Ph	24	77 (9)	80
5	*p*-$MeOC_6H_4$	26	66 (17)	78

[a] All the yields refer to isolated chromatographically pure compound **6**, obtained with (*R*)-enantiomer in excess.
[b] Values in parentheses refer to isolated sulfone.
[c] E.e.s were determined by HPLC on a Daicel Chiralcel OB column.

The usual process of kinetic resolution was once again found to follow the asymmetric sulfoxidation (entries 1–3). In all the experiments performed by the two procedures, the ready recovery of **1b** by chromatographic techniques allowed the regeneration of **2b** as previously reported.

2.4. Non-linear effects (NLE) in the asymmetric sulfoxidation

In recent years particular attention has been paid to the detection of NLE in a variety of asymmetric reactions,[18] since they can be used to prepare compounds with high e.e.s starting from only enantiomerically enriched ligands or auxiliaries and, furthermore, to obtain mechanistic information.

As regards the asymmetric sulfoxidation, Kagan pointed out a negative NLE, (–)-NLE, for the oxidation of methyl *p*-tolyl sulfide in the presence of the modified Sharpless reagent Ti(O-*i*-Pr)$_4$/*L*-DET/H_2O, that affected the level of enantioselectivity until the value of 70% e.e. was reached for diethyl tartrate; then, the linear relationship was observed until enantiomerically pure *L*-DET was used.[19]

In Table 8 the results from the asymmetric sulfoxidation of methyl *p*-tolyl sulfide with **2b**, performed in the

presence of partially resolved BINOL, according to the above procedures, are reported.

Table 8. (+)-NLE in the asymmetric sulfoxidation of methyl *p*-tolyl sulfide with Ti(IV) (0.1 equiv.)/(*R*)-BINOL (0.2 equiv.)/H_2O (20 equiv.) system

Entry	(*R*)-BINOL (e.e.)	Yield (%)[a,b]	E.e. (%)[c]
1	23	50 (3)	22
2	44	85 (6)	41
3	59	69 (2)	49
4	100	76 (3)	52

[a] All the yields refer to isolated chromatographically pure compound **6**, obtained with (*R*)-enantiomer in excess.
[b] Values in parentheses refer to isolated sulfone.
[c] E.e.s have been determined by HPLC on a Daicel Chiralcel OB column.

Short reaction times (4 h for Ti(O-*i*-Pr)$_4$ (0.1 equiv.)/(*R*)-BINOL (0.2 equiv.)/H_2O (20 equiv.) system) were chosen in order to minimize the formation of sulfone and, consequently, to reduce the superimposition of the process of kinetic resolution. A (+)-NLE was detected and it has to be noted that very close values of e.e.s have been obtained with 59% e.e. and enantiopure (*R*)-BINOL (Fig. 1).

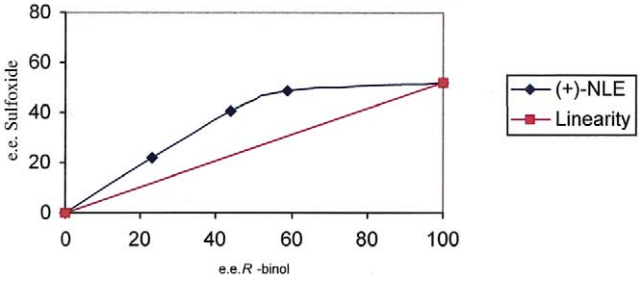


Figure 1. Ti(IV)/(*R*)-BINOL = 1/2; react. time = 4 h.

3. Conclusion

In conclusion two new classes of hydroperoxides, easily accessible by a simple and inexpensive procedure, have shown their synthetic utility both as key intermediates and reagents in asymmetric oxidative processes. In particular, chiral sulfoxides have been obtained in very satisfactory yields and e.e.s by stoichiometric or catalytic procedures involving the employment of a secondary or a tertiary furyl hydroperoxide, respectively, in the presence of different Ti(IV) chiral complexes. More interestingly, the unprecedented detection of a (+)-NLE was pointed out in the asymmetric oxidation of methyl *p*-tolyl sulfide catalyzed using a Ti(O-*i*-Pr)$_4$/(*R*)-BINOL/H_2O system.

4. Experimental

4.1. Materials and general methods

CH_2Cl_2 and toluene were dried over calcium hydride and distilled before use. Light petroleum refers to the fraction of petroleum ether boiling in the range 40–60°C. The sulfoxidation reactions were carried out under an argon atmosphere and using flame dried glassware. Flash chromatography and TLC were performed on Merck silica gel. Proton (400 MHz) and carbon (100 MHz) NMR spectra were recorded on a Bruker DRX 400. Chemical shifts are reported in (δ) ppm relative to internal $CDCl_3$ δ (7.26) for ^{1}H NMR and $CDCl_3$ (77.0) for ^{13}C NMR. IR spectra were recorded on a Bruker Vector 22 (frequencies 400–4000 cm^{-1}, resolution 2 cm^{-1}). Starting materials **1** were prepared by reacting 2-formyl-furan, 5-methyl-2-formyl-furan or 2-acetyl furan with the appropriate Grignard reagent and their structure were confirmed by ^{1}H and ^{13}C NMR analysis.

4.2. Standard procedure for synthesis of 2-(1-hydroperoxyalkyl)furans, 2

To a solution of **1** (4.0 mmol), in 1,2-dimethoxyethane (DME, 40 mL) was added 30% aqueous H_2O_2 (0.820 mL, 8 mmol) and *p*-toluenesulfonic acid (PTSA, 84 mg, 0.45 mmol). The mixture was stirred at room temperature for the appropriate reaction time (see Table 1). At the end of the reaction, the mixture was diluted with Et_2O (160 mL) and washed with saturated $NaHCO_3$ solution (2×10 mL) and saturated NaCl solution (3×10 mL) and finally dried over dry Na_2SO_4 for a few minutes. After filtration and evaporation of the solvent, the crude product was purified by flash chromatography (95/5 light petroleum/Et_2O) to afford pure 2-(1-hydroperoxyalkyl)-furans **2**.

4.2.1. 1-(Furan-2-yl)-hept-1-yl-hydroperoxide, 2a. Pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.87 (t, 3H, *J* 7.2 Hz), 1.0–1.5 (m, 8H), 1.82 (m, 1H), 1.93 (m, 1H), 4.90 (t, 1H, *J* 7.2 Hz), 6.37 (bs, 2H), 7.42 (bs, 1H), 8.00 (s 1H). ^{13}C NMR ($CDCl_3$, 100.16 MHz) δ: 14.0, 22.5, 25.5, 28.9, 30.7, 31.5, 80.8, 109.0, 110.2, 142.5, 153.1. IR *v* (neat, cm^{-1}): 3398, 2936, 2864, 1559, 1470, 1332, 1034, 797. Anal. calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.76; H, 9.26%.

4.2.2. 2-(Furan-2-yl)-prop-2-yl-hydroperoxide, 2b. Pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.60 (s, 6H), 6.34 (m, 2H), 7.39 (bs, 1H), 7.71 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100.16 MHz) δ: 24.0, 80.4, 108.0, 110.7, 142.7, 156.7. IR *v* (neat, cm^{-1}): 3300, 2986, 2939, 1575, 1380, 1362, 1276, 1164, 1018, 822. Anal. calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.22; H, 7.20%.

4.2.3. 1-(5-Methyl-furan-2-yl)-hept-1-yl-hydroperoxide, 2c. Pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.87 (t, 3H, *J* 6.9 Hz), 1.0–1.5 (m, 8H), 1.81 (m, 1H), 1.91 (m, 1H), 2.30 (s, 3H), 4.83 (t, 1H, *J* 7.2 Hz), 5.94 (d, 1H, *J* 02.5 Hz), 6.25 (d, 1H, *J* 2.5 Hz), 7.81 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.16 MHz) δ: 13.6, 14.0, 22.5, 25.6, 28.9, 30.6, 31.5, 81.0, 106.1, 150.9, 512.4. IR *v* (neat, cm^{-1}): 3380, 2921, 2851, 1567, 1468, 1223, 1015, 778. Anal. calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.70; H, 9.61%.

4.2.4. 1-(5-Methyl-furan-2-yl)-hex-1-yl-hydroperoxide, 2d. Pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.87 (t, 3H, *J* 5.7 Hz), 1.0–1.5 (m, 6H), 1.80 (m, 1H), 1.92 (m, 1H), 2.29 (s, 3H), 4.82 (t, 1H, *J* 7.2 Hz), 5.94 (d, 1H, *J* 3.0 Hz), 6.24 (d, 1H, *J* 3.0 Hz). ^{13}C NMR ($CDCl_3$, 100.16 MHz) δ: 13.5, 13.9, 22.4, 25.3, 30.5, 31.5, 81.0, 106.1, 110.0, 151.0, 152.4. IR *v* (neat, cm^{-1}): 3396, 2944, 2870, 1560, 1460, 1229, 1024, 789. Anal. calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.52; H, 9.07%.

4.2.5. 1-(5-Methyl-furan-2-yl)-non-1-yl-hydroperoxide, 2e. Pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.87 (t, 3H, *J* 7.2 Hz), 1.0–1.5 (m, 12H), 1.77 (m, 1H), 1.90 (m, 1H), 2.26 (s, 3H), 4.79 (t, 1H, *J* 7.2 Hz), 5.91 (d, 1H, *J* 3.0 Hz), 6.21 (d, 1H, *J* 3.0 Hz), 8.35 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.16 MHz) δ: 13.4, 14.0, 22.6, 25.6, 29.1, 29.2, 30.5, 31.7, 80.8, 106.0, 110.0, 151.0. IR *v* (neat, cm^{-1}): 3384, 2924, 2855, 1563, 1465, 1222, 1020, 784. Anal. calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.09; H, 9.97%.

4.3. Standard procedure for the synthesis of 6-hydroperoxy-2*H*-pyran-3(6*H*)-ones, 3

The products **3** were prepared treating a solution of **1** (4 mmol) in DME (20 mL) with 30% aqueous H_2O_2 (2.0 mL) and PTSA (323 mg, 1.7 mmol). The resulting mixture was stirred at room temperature for the appropriate time (see Table 2). At the end of the reaction, the mixture was diluted with Et_2O (80 mL) and washed with saturated $NaHCO_3$ solution (2×10 mL) and saturated NaCl solution (3×10 mL) and finally dried over dry Na_2SO_4 for a few minutes. After filtration and evaporation of solvent, the crude product was purified by flash chromatography (85/15 light petroleum/Et_2O) to afford pure 6-hydroperoxy-2*H*-pyran-3(6*H*)-ones **3**.

4.3.1. 2-Hexyl-6-hydroperoxy-6-methyl-2*H*-pyran-3(6H)-one, 3a. Viscous oil. Mixture of inseparable diastereoisomers (90/10 ratio). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.87 (m), 1.30 (m), 1.41 (m), 1.57 (s), 1.66 (s), 1.73 (m) 1.92 (m), 4.20 (dd, J_1 7.6 Hz, J_2 3.9 Hz), 4.50 (dd, J_1 7.6 Hz, J_2 3.9 Hz), 6.15 (d, *J* 10.1 Hz), 6.16 (d, *J* 10.4 Hz), 6.68 (d, *J* 10.1 Hz), 6.89 (d, *J* 10.4 Hz), 7.90 (bs), 8.40 (bs). ^{13}C NMR ($CDCl_3$, 100.16 MHz) δ: 14.1, 20.5, 22.6, 23.2, 42.8, 29.0, 30.0, 31.4, 31.7, 73.1, 75.9, 78.2, 128.8, 129.5, 143.8, 148.0, 196.0, 201.0. IR *v* (KBr, cm^{-1}): 3347, 2932, 1670, 1630, 1380, 1095, 842. Anal. calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.01; H, 8.95%.

4.3.2. 2-Cyclohexyl-6-hydroperoxy-6-methyl-2*H*-pyran-3(6*H*)-one, 3b. Viscous oil. Mixture of inseparable diastereoisomers (93/7 ratio). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.0–1.4 (m), 1.5–1.75 (m), 2.06 (m), 4.03 (d, *J* 3.0 Hz), 4.33 (d, *J* 2.1 Hz), 6.14 (d, *J* 10.1 Hz), 6.67 (d, *J* 10.1 Hz), 6.92 (d, *J* 10.1 Hz), 8.54 (bs), 8.82 (bs). ^{13}C NMR ($CDCl_3$, 100.16 MHz) δ: 23.1, 26.0, 26.4, 29.1, 39.3, 80.2, 100.1, 129.0, 129.8, 144.3, 149.1, 196.9, 201.1. IR *v* (KBr, cm^{-1}): 3340, 2919, 1675, 1620, 1380, 1085, 859. Anal. calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.53; H, 7.90%.

4.3.3. 6-Hydroperoxy-6-methyl-2-*i*-propyl-2*H*-pyran-3(6*H*)-one, 3c. Viscous oil. Mixture of inseparable diastereoisomers (92/8 ratio). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.82 (d, *J* 6.8 Hz), 0.93 (d, *J* 6.8 Hz), 1.50 (s), 1.62 (s), 2.34 (m), 4.05 (d, *J* 6.8 Hz), 1.50 (s), 1.62 (s), 2.34 (m), 4.05 (d, *J* 2.9 Hz), 4.37 (d, *J* 3.0 Hz), 6.13 (d, *J* 10.1 Hz), 6.68 (d, *J* 10.1 Hz), 6.90 (d, *J* 10.3 Hz), 8.87 (s), 9.04 (s). ^{13}C NMR ($CDCl_3$, 100.16 MHz) δ: 15.9, 16.48, 18.8, 19.8, 23.1, 29.6, 80.3, 82.0, 100.0, 128.9, 129.9, 144.6, 149.4, 197.1, 201.4. IR *v* (KBr, cm^{-1}): 3357, 2942, 1677, 1618, 1395, 1078, 861. Anal. calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.89; H, 7.70%.

4.3.4. 6-Hydroperoxy-2,2,6-trimethyl-2*H*-pyran-3(6*H*)-one, 3d. Viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.41 (s, 3H), 1.57 (s, 3H), 1.65 (s, 3H), 6.12 (d, 1H, *J* 10.2 Hz), 6.71 (d, 1H, *J* 10.2 Hz), 8.00 (bs). ^{13}C NMR ($CDCl_3$, 100.16 MHz) δ: 24.4, 26.4, 26.9, 79.4, 100.3, 127.1, 144.3, 198.9. IR *v* (KBr, cm^{-1}): 3340, 2932, 1679, 1625, 1405, 1058, 831. Anal. calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.95; H, 6.90%.

4.3.5. 2-Ethyl-2-hexyl-6-hydroperoxy-6-methyl-2*H*-pyran-3(6*H*)-one, 3e. Viscous oil. Mixture of inseparable diastereoisomers (50/50 ratio). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.79–0.86 (m), 0.95 (t, *J* 7.5 Hz), 1.20–1.4 (m), 1.64 (s), 1.8–1.9 (m), 6.10 (bd, *J* 10.2 Hz), 6.67 (d, *J* 10.2 Hz), 6.68 (d, *J* 10.2 Hz), 8.16 (s), 8.21 (s). ^{13}C NMR ($CDCl_3$, 100.16 MHz) δ: 14.0, 22.5, 23.2, 23.3, 24.4, 29.5, 29.6, 29.8, 31.4, 31.6, 36.4, 38.3, 71.8, 85.1, 100.3, 100.4, 128.2, 143.6, 143.8, 198.6. IR *v* (KBr, cm^{-1}): 3390, 2972, 1680, 1625, 1387, 1075, 882. Anal. calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.71; H, 9.55%.

4.3.6. 6-Hydroperoxy-2-octyl-6-methyl-2*H*-pyran-3(6*H*)-one, 3f. Viscous oil. Mixture of inseparable diastereoisomers (94/6 ratio). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.86 (m), 1.24 (m), 1.38 (m), 1.55 (s), 1.63 (s), 1.88 (m), 4.20 (dd, J_1 7.0 Hz, J_2 4.0 Hz), 4.52 (dd, J_1 7.0 Hz, J_2 4.0 Hz), 6.13 (d, *J* 10.1 Hz), 6.69 (d, *J* 10.1 Hz), 6.89 (d, *J* 10.3 Hz), 8.72 (bs), 8.80 (bs). ^{13}C NMR ($CDCl_3$, 100.16 MHz) δ: 14.7, 21.1, 23.2, 23.8, 24.7, 25.1, 25.4, 25.8, 26.2, 29.8, 30.0, 30.1, 30.8, 32.0, 32.4, 76.6, 78.8, 100.8, 102.7, 129.2, 129.9, 145.1, 149.1, 196.7, 197.5. IR *v* (cm^{-1}): 3342, 2922, 1673, 1628, 1389, 1089, 852. Anal. calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.41; H, 9.58%.

4.4. Standard procedure for stoichiometric asymmetric sulfoxidation

A solution of titanium tetraisopropoxide (0.142 g, 0.50 mmol), (*R*,*R*)-diethyl tartrate (0.415 g, 2.0 mmol) and sulfide (0.50 mmol) in dry CH_2Cl_2 (3.2 mL) under an argon atmosphere was stirred at room temperature for 5 min. Then the temperature was cooled to –20°C and after 20 min a solution of hydroperoxide **2** or **3** (1.25 mmol in 3.2 mL of dry CH_2Cl_2) was slowly added. After the appropriate reaction time, water (2 mL) was added and the solution was stirred for about 1 h. Then the resulting gel was recovered with ethyl acetate (20 mL) and filtered on a short pad of SiO_2. After remov-

ing the solvent under reduced pressure, the crude oil was purified by silica gel flash chromatography (eluent starting from Et_2O to a mixture 1/1 Et_2O/ethyl acetate) to afford the pure sulfoxide.

4.5. Standard procedure for stoichiometric kinetic resolution

The above reported procedure for stoichiometric sulfoxidation was used with the substitution of sulfide with racemic methyl *p*-tolyl sulfoxide (0.50 mmol).

4.6. Standard procedure for catalytic asymmetric sulfoxidation

A solution of (*R*)-(+)-binaphthol (14 mg, 0.050 mmol or 28 mg, 0.10 mmol), in dry toluene (5.2 mL) at room temperature under an argon atmosphere was treated by dropwise addition (via syringe) of titanium tetraisopropoxide (14.2 mg, 0.050 mmol) and H_2O (18 mg, 1.0 mmol). After stirring for 1 h, the sulfide (0.50 mmol) was added and then the mixture was cooled to 0°C. After 30 min a solution of hydroperoxide (**2b**, **2c** or **2e**, 1.0 mmol) in dry toluene (2.3 mL), was slowly added and the mixture was stirred for the appropriate reaction time. The reaction mixture was filtered through a short pad of silica gel and the product eluted with ethyl acetate. After removing the solvent under reduced pressure, the crude oil was purified by flash chromatography on silica gel (eluent starting from Et_2O to a mixture 1/1 Et_2O/ethyl acetate) to afford the pure sulfoxide.

4.7. Standard procedure for catalytic kinetic resolution

The above reported procedure for catalytic sulfoxidation was used with the substitution of sulfide with racemic methyl *p*-tolyl sulfoxide (0.50 mmol).

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