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Enantioselective Sulfoxidation and Kinetic Resolution Combined Protocol Mediated by a Functionalized (*S*)-Norcamphor-Based Hydroperoxide/Titanium(IV) Isopropoxide System

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Abstract: A functionalized tertiary furyl hydroperoxide derived from (*S*)-norcamphor has been easily synthesized in good yield and in a highly diastereoselective manner. Good to high enantioselectivities (up to 99% *ee*) and acceptable to good yields (up to 86%) were achieved for the sulfoxides, by tandem stereoconvergent asymmetric sulfoxidation and kinetic resolution when using the novel hydroperoxide as oxygen donor and chirality source in the presence of catalytic loadings of titanium(IV) isopropoxide as the catalyst.

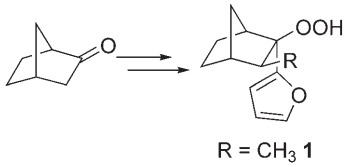
Keywords: asymmetric oxidation; kinetic resolution; optically pure alkyl hydroperoxides; sulfoxides; titanium

Introduction

Optically pure sulfoxides represent valuable compounds in asymmetric synthesis, being frequently used as chiral auxiliaries[1] and in the pharmaceutical industry due to their important biological activities.[1d,2] The most investigated approach for the synthesis of enantiomerically enriched sulfoxides is the asymmetric oxidation of prochiral sulfides by chemical and enzymatic systems.[3] Along this line, after the first reports by the Kagan and Modena groups, particular attention has been paid to metal-catalyzed sulfoxidation reactions using enantiopure ligands as diols and *tert*-butyl (TBHP) or cumyl (CHP) hydroperoxides as oxidants.[4] Another valuable method has been firstly studied by Bolm et al.,[5] using optically pure Schiff bases/$VO(acac)_2$/aqueous hydrogen peroxide and, more recently, modified versions of this system have been proposed.[6] An alternative oxidative approach can be envisioned by using an optically pure alkyl hydroperoxide as oxygen donor and chirality source in the presence of a metal catalyst. The limited number of investigations reported so far are related to the lack of efficient routes to optically pure alkyl hydroperoxides.[7] The best example of a Ti-catalyzed sulfoxidation, mediated by secondary alkyl hydroperoxides, afforded the sulfoxides in low yields (<20%) and moderate to good enantioselectivity (up to 79% *ee*).[8] The enantioselectivity originated from the asymmetric oxidation of the sulfides and concomitant kinetic resolution occurring during the overoxidation of sulfoxides to sulfones. Thanks to the stereoconvergence of the two reactions, the final sulfoxides could be isolated in satisfactory *ee*s albeit at the expense of chemical yield.

We have recently estabilished a simple approach to tertiary furyl hydroperoxides derived from (*R*)-camphor or (*S*)-norcamphor. These compounds were used as stereoselective oxygen donors in various transformations achieving up to 67% *ee*.[9] With the aim of obtaining more efficient oxidants, a modified synthetic route has been proposed starting from (*S*)-norcamphor, which afforded a hydroperoxide having a new stereocentre close to the reactive OOH group (Figure 1).[10] A minor modification (R = Me) in oxidant **1** positively influenced the reactivity and the enantioselectivity in the Ti-catalyzed asymmetric sulfoxidation in comparison to the unsubstituted compound (R = H).[9c]

The flexibility of the synthetic procedure allows the preparation of a variety of modified hydroperoxides in a stereocontrolled manner by the introduction of different R groups which can modulate the level of



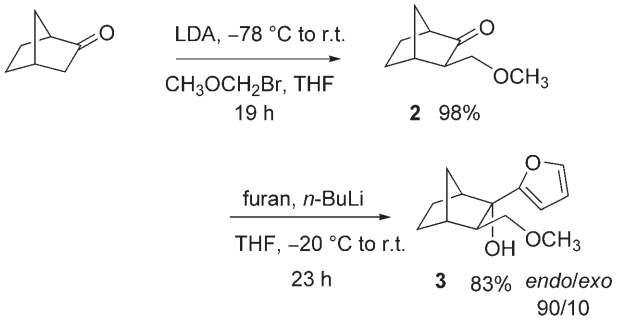
R = CH_3 **1**

Figure 1.

asymmetric induction. Herein, we report the synthesis of a novel functionalized (*S*)-norcamphor-derived hydroperoxide and its employment in the Ti-catalyzed asymmetric sulfoxidation. The first example of an efficient combined procedure of asymmetric sulfoxidation and stereoconvergent kinetic resolution for the production of sulfoxides in acceptable yields and good to high enantioselectivities has been successfully developed when using optically pure hydroperoxide/metal catalyst system.

Results and Discussion

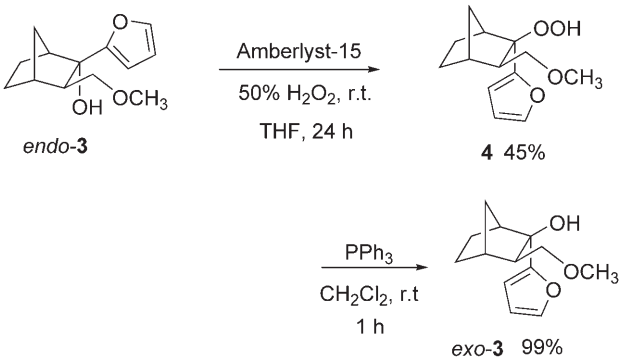
In metal-catalyzed oxidations mediated by alkyl hydroperoxides, the electrophilically active oxidative species is generated through coordination of the OOH group to the metal complex.[11] We envisioned that a chelating R group should have furnished an additional site of chelation for the hydroperoxide to the metal catalyst, giving rise to a more rigid and likely more efficient system. Hence, the alkylation of (*S*)-norcamphor[12] was carried out using methoxymethyl bromide (Scheme 1). It has been previously reported that α-alkylation reactions of norcamphor proceeded with the exclusive formation of the *exo*-product.[13] Predictably, a single diastereoisomer was isolated in high yield that was assumed to be the *exo* compound **2**.



Scheme 1.

On the grounds of our previous results,[10] furyllithium addition to ketone **2** was expected to furnish a mixture of the *endo*/*exo* alcohols with the prevalent formation of the *endo* diastereoisomer. We were pleased to observe the formation in high yield of alcohol **3** in significantly improved diastereoisomeric ratio (*endo*/*exo* = 90/10). By ^{1}H NMR NOE experiments,[14] the most abundant alcohol, isolated by flash chromatography, was confirmed to be *endo*-**3**, thus proving that compound **2** was the *exo* diastereoisomer. The enhanced stereocontrol could be explained by invoking coordination of the furyllithium reagent by the proximal methoxymethyl group, which preferentially would guide the attack of the organometallic reagent to the carbonyl group from the less sterically demanding *exo*-face of the bicyclic system.

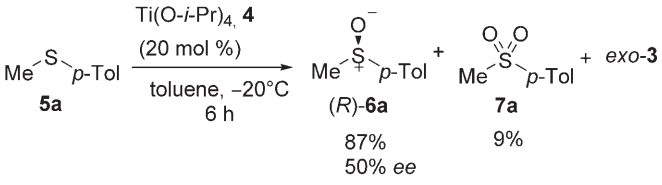
The oxidation of alcohol *endo*-**3**, performed under previously optimized conditions,[9a,c] furnished the expected *exo* hydroperoxide **4** as a single diastereoisomer in moderate yield[15] (Scheme 2). Confirmation



Scheme 2.

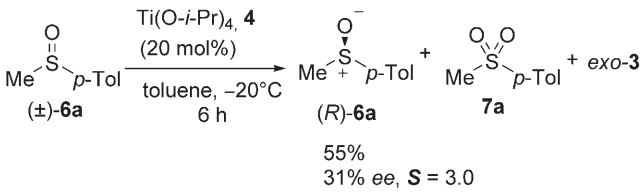
that the reaction occurred with epimerization at carbon two was achieved by reducing **4** with triphenylphosphane, which afforded alcohol *exo*-**3**. Interestingly, the oxidation of *exo*-**3**, carried out under the same conditions, led to the formation of **4** in greatly improved 75% yield. This result is particularly appealing in view of the chiral resource saving protocol we usually exploited[9,10] to regenerate these alkyl hydroperoxides.

With hydroperoxide **4** in hand, we investigated the sulfoxidation of methyl *p*-tolyl sulfide **5a** as model compound, using previously optimized conditions [titanium(IV) isopropoxide in toluene at –20 °C, Scheme 3].



Scheme 3.

Under catalytic loadings of Ti(O-*i*-Pr)$_4$, we were pleased to isolate (*R*)-sulfoxide **6a** in high yield, 50% *ee* and a small amount of sulfone **7a** was detected at the end of the reaction. Oxidant **4** provided a slightly better control of asymmetric induction with respect to compound **1**, which furnished the (*R*)-sulfoxide in 44% *ee*.[10] In order to check if the overoxidation of sulfoxide to sulfone involved a process of kinetic resolution, racemic **6a** was reacted under the same conditions (Scheme 4).



Scheme 4.

The process was stereoconvergent with the sulfoxidation, in fact, unreacted sulfoxide was isolated as (*R*) prevalent enantiomer. The efficiency of kinetic resolution, measured by the stereoselectivity factor ***S***,[16] was significantly improved when compared to the result obtained using oxidant **1** (***S*** = 1.3).[10] This result showed that, during the oxidation, where it has been previously proposed to proceed through coordination of sulfoxide to the titanium and an intramolecular oxygen transfer to the sulfoxide by the chelated hydroperoxide,[4a,8,17] a better asymmetric control was achieved by using oxidant **4**. This could be reasonably justified by a significant effect of the methoxymethyl group on the stability of the diastereoisomeric titanium complexes made of the hydroperoxide and (*R*)-/(*S*)-sulfoxides. At present, it is difficult to speculate if the effect derives from an increased rigidity of the complex due to additional coordination of the methoxymethyl group at the titanium or if it is only of stereoelectronic nature. Nevertheless, it is an indication that kinetic resolution of sulfoxides is susceptible for significant improvement by tuning the R group in the hydroperoxide (Figure 1).

The outcome of the two oxidations on **5a** and (±)-**6a** clearly pointed out the possibility to successfully combine these reactions to prepare the final sulfoxide with a useful level of enantioselectivity and satisfactory yield. While several examples of kinetic resolution of sulfoxides have been studied using titanium and vanadium/chiral ligands-mediated oxidations,[6d,f,g,18] few reports have proposed using a metal catalyst and optically pure hydroperoxides as oxidants.[8,9b,c] However, because of the low values of the stereoselectivity factors ($1.0 < \boldsymbol{S} < 2.0$), tandem asymmetric sulfoxidation/kinetic resolution processes ususally afforded sulfoxides in significantly reduced yields and moderate to good *ee*s.[8–10]

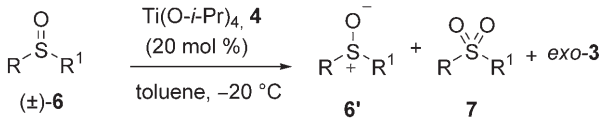
In order to evaluate the stereocontrol of kinetic resolution, it seemed appropriate to study the oxidation of different sulfoxides under the same conditions (Table 1).

From the data in Table 1 it appears that the efficiency of the process was affected by the electronic nature of the substituents on the phenyl ring (entries 1–5). The ethyl group at sulfur afforded the best result with the highest ***S*** value (entry 6). Unfortunately, no kinetic resolution was observed for the dialkyl sulfoxide **6i** (entry 8). Although the values of the stereoselectivity factor cannot be of practical use to set up an efficient access to enantiomerically enriched sulfoxides *via* kinetic resolution, they were higher than 2.0. Hence, assuming that the first asymmetric oxidation of sulfides would have taken place with moderate enantioselectivity (~50% *ee*), *in situ* subsequent kinetic resolution using hydroperoxide **4** would have afforded the sulfoxides with enhanced *ee*s and acceptable yields.

In order to prove this, we combined the stereoconvergent oxidations for different sulfides and the results are illustrated in Table 2.

Methyl aryl sulfoxides were recovered in acceptable yield and good to high enantiomeric excess (entries 1–6) and the best efficiency was observed in the

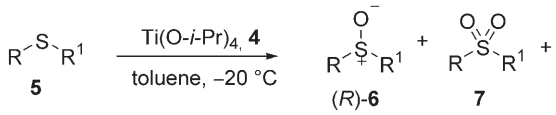
Table 1. Kinetic resolution of (±)-**6** promoted by the **4**/Ti(O-*i*-Pr)$_4$ system.[a]



Entry	**6**	Time [h]	Yield of **6'** [%][b]	*ee* of **6'** [%][c]	***S***[d]
1	R = Me, R^1 = Ph (**b**)	18	62	28 (*R*)	3.5
2	R = Me, R^1 = *p*-MeOC$_6$H$_4$ (**c**)	17	25	55 (*R*)	2.3
3	R = Me, R^1 = *p*-ClC$_6$H$_4$ (**d**)	21	61	27 (*R*)	3.2
4	R = Me, R^1 = *p*-BrC$_6$H$_4$ (**e**)	23	36	36 (*R*)	2.1
5	R = Me, R^1 = β-naphthyl (**f**)	22	40	47 (*R*)	2.9
6	R = Et, R^1 = Ph (**g**)	22	52	42 (*R*)	4.0
7	R = Ph, R^1 = Bn (**h**)	27	62	18 (*R*)	2.1
8	R = Me, R^1 = Bn (**i**)	21	42	2 (*S*)	1.1

[a] Molar ratio: Ti(O-*i*-Pr)$_4$/**6**/**4** = 0.2/1/0.8.
[b] Yield of isolated product after flash chromatography.
[c] Determined by HPLC on chiral columns Daicel Chiralcel OB and OD. The absolute configuration was determined by comparison of the HPLC retention times with those reported in the literature.
[d] Stereoselectivity factors calculated according to ref.[16]

Table 2. Combined enantioselective sulfoxidation/kinetic resolution promoted by the **4**/Ti(O-*i*-Pr)$_4$ system.[a]



Entry	5	Yield of 6 [%][b]	*ee* of 6 [%][c]
1	R = Me, R^1 = *p*-Tol (**a**)	57	86
2	R = Me, R^1 = Ph (**b**)	30	97
3	R = Me, R^1 = *p*-MeOC$_6$H$_4$ (**c**)	39	94
4	R = Me, R^1 = *p*-ClC$_6$H$_4$ (**d**)	56	74
5	R = Me, R^1 = *p*-BrC$_6$H$_4$ (**e**)	40	68
6	R = Me, R^1 = β-naphthyl (**f**)	34	99
7	R = Et, R^1 = Ph (**g**)	47	76
8	R = Ph, R^1 = Bn (**h**)	55	96
9	R = *p*-MeC$_6$H$_4$, R^1 = Bn (**j**)	86	93
10	R = *p*-BrC$_6$H$_4$, R^1 = Bn (**k**)	57	76
11	R, *p*-Tol, R^1 = *p*-TolCH$_2$ (**l**)	50	83

[a] Molar ratio: Ti(O-*i*-Pr)$_4$/**5**/**4** = 0.2/1/2.0–2.5.
[b] Yield of isolated product after flash chromatography.
[c] Determined by HPLC on chiral columns Daicel Chiralcel OB and OD. The absolute configuration was determined by comparison of the HPLC retention times with those reported in the literature.

oxidation of sulfides having electron-donating substituents in the phenyl ring. The ethyl phenyl sulfoxide was recovered in good *ee* taking into account that the oxidation of the corresponding sulfide generally proceeds with lower enantioselectivity than methyl aryl sulfides (entry 7). Finally, remarkable results have been obtained in the oxidation of aryl benzyl sulfides (entries 8–11). They were converted into (*R*)-sulfoxides in good yield and high *ee*. In some examples, the extent of kinetic resolution was low (entry 9), showing that a high level of asymmetric induction was achieved in the first oxidation of sulfide, thus allowing isolation of the sulfoxide in high yield. It has to be noted that aryl benzyl sulfoxides are synthetically attractive compounds as chiral auxiliaries,[19] but they are difficult to oxidize with high asymmetric induction by most of the metal-chiral ligand/alkyl hydroperoxide methodologies.[20]

Conclusions

In conclusion, we have easily obtained in good yield and a highly stereoselective manner a new functionalized (*S*)-norcamphor-derived furyl hydroperoxide, which proved to be an efficient oxygen donor in the asymmetric sulfoxidation and kinetic resolution combined procedure for the synthesis of sulfoxides in good to high *ee*s. To date, these results are the first example of a highly enantioselective sulfoxidation mediated by an optically pure alkyl hydroperoxide/metal catalyst system. Hence, the methodology can be placed in the context of the metal-chiral ligand/achiral alkyl hydroperoxide protocols which have been widely developed in the last decades as the most efficient routes to enantiomerically enriched sulfoxides. From a resource-saving and economic point of view, it has to be noted that the alcohol *exo*-**3** is recovered in high yield during the purification process[21] and it can be conveniently recycled for the one-step synthesis of the oxidant **4** with improved efficiency.[22] It is evident that the performance of this class of hydroperoxides can be properly tuned according to the nature of R group introduced close to the reactive site of the oxidant. Thanks to their facile access, new stereoelectronically modified hydroperoxides will be synthesized to expand their utility as stereoselective oxygen donors.

Experimental Section

General Remarks

Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualized by UV light or by 10% H_2SO_4/ethanol spray test. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX 400 spectrometer at room temperature in $CDCl_3$ as solvent. Chemical shifts (δ) are quoted in ppm relative to internal $CDCl_3$ $\delta = 7.26$ for ^{1}H NMR and $CDCl_3$ $\delta = 77.0$ for ^{13}C NMR. Coupling constants (*J*) are given in Hz. Optical rotations were performed on a Jasco Dip-1000 digital polarimeter using the Na lamp. IR spectra were recordered as thin films unless stated otherwise on a Bruker Vector 22 instrument. IR absorptions are reported in cm^{-1}. EI-MS were performed on a Finnigan Polaris spectrometer. (+)-Norcamphor was obtained by oxidation of commercial (+)-*endo*-2-norborneol according to the literature procedure.[12]

All commercially available reagents were purchased from Aldrich. All sulfoxides are known compounds, their analytical data were identical to those reported in the literature.[4,20,23] The absolute configuration of the predominant enantiomer was determined by comparison with the HPLC retention times (Waters 486, UV detector) using Daicel Chiralcel OB and OD columns or with optical rotations reported in the literature.[4] The enantioselectivities were determined by chiral HPLC analysis.

(1*S*,3*R*,4*R*)-3-*exo*-Methoxymethylbicyclo[2.2.1]-heptan-2-one (2)

To a solution of freshly distilled diisopropylamine (2.53 mL, 17.9 mmol) in anhydrous THF (15 mL), under argon atmosphere at −78 °C, *n*-BuLi (6.56 mL, 16.4 mmol, 2.5 M solution in hexane) was added dropwise. The mixture was stirred for 20 min then a solution of (*S*)-norcamphor (1.64 g, 14.9 mmol) in 15 mL of THF was added and stirring was

maintained for 20 min. Methoxymethyl bromide (1.9 mL, 20.9 mmol) was then added and the mixture was stirred for 19 h at room temperature. After this time, the mixture was diluted with diethyl ether (50 mL) and quenched by slow addition of a saturated solution of ammonium chloride. The layers were separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine (2×50 mL) and dried over sodium sulfate. The crude product was purified by flash chromatography (*n*-pentane/diethyl ether mixtures 95/5 to 80/20) to afford **2** as a pale yellow oil; yield: 2.25 g (14.6 mmol, 98%); anal. calcd. for $C_9H_{14}O_2$: C 70.10, H 9.15%; found: C 70.23, H 9.27; $[\alpha]_D^{25}$: +60.0 (*c* 1.0, $CHCl_3$); IR: ν_{max}=2960, 2930, 2880, 1744, 1128, 1109, 1098 cm^{-1}; ^{1}HNMR (400 MHz): δ=3.46 (dd, J_1=9.7, J_2=5.1 Hz, 1H), 3.37 (dd, J_1=J_2=9.7 Hz, 1H), 3.32 (s, 3H), 2.63–2.60 (m, 1H), 2.55–2.52 (m, 1H), 2.10–2.05 (m, 1H), 1.92–1.89 (m, 1H), 1.85–1.78 (m, 2H), 1.55–1.44 (m, 3H); ^{13}CNMR (100.6 MHz): δ= 217.4, 70.6, 58.7, 54.4, 49.4, 37.8, 35.0, 27.9, 23.8; ESI-MS: *m/z*=177 ([M+Na]$^+$, 100%), 94 (20), 78 (25), 40 (60).

(1*S*,2*S*,3*R*,4*R*)-2-*endo*-Hydroxy-2-*exo*-(2′-furyl)-3-*exo*-methoxymethylbicyclo[2.2.1]heptane (*endo*-3)

To a solution of freshly distilled furan (2.0 mL, 27.4 mmol) in anhydrous THF (14 mL), under argon atmosphere at −20 °C, *n*-BuLi (12 mL, 29.7 mmol, 2.5 M solution in hexane) was added dropwise. The mixture was stirred at −20 °C for 1 h then a solution of **2** (11.9 mmol, 1.84 g) in 20 mL of THF was added and stirring was maintained at room temperature overnight. After this time, the mixture was diluted with diethyl ether (50 mL) and quenched by slow addition of a saturated solution of ammonium chloride. The layers were separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine (2×50 mL) and dried over sodium sulfate. The crude product was purified by flash chromatography (petrol/diethyl ether mixtures 90/10 to 70/30) to afford *endo*-**3** as a pale yellow oil; yield: 1.97 g (8.88 mmol, 75%); anal. calcd. for $C_{13}H_{18}O_3$: C 70.24, H 8.16%; found: C 70.40, H, 8.28; $[\alpha]_D^{23}$: +46.0 (*c* 1.0, $CHCl_3$); IR: ν_{max}=3407 (O−H), 2957, 2927, 2871, 1458, 1388, 1302, 1190, 1153, 1119, 1100, 1057, 1014, 733 cm^{-1}; ^{1}HNMR (400 MHz): δ=7.35–7.34 (m, 1H), 6.33–6.31 (m, 1H), 6.27–6.24 (m, 1H), 3.17 (s, 3H), 3.14 (dd, J_1=12.8, J_2=9.9 Hz, 1H), 2.81 (dd, J_1=J_2=9.9, 1H), 2.47–2.45 (m, 1H), 2.31–2.28 (m, 1H), 2.17–2.09 (m, 1H), 2.06–2.03 (m, 1H), 1.93–1.90 (m, 1H), 1.73–1.67 (m, 1H), 1.47–1.39 (m, 3H); ^{13}CNMR (100.6 MHz): δ=158.2, 141.2, 109.8, 105.5, 79.6, 72.8, 58.6, 57.2, 47.8, 39.8, 37.3, 29.1, 21.6; EI-MS: *m/z*=222 (M$^+$, 3%), 190 (40), 162 (50), 149 (45), 123 (100), 95 (70), 81 (20).

(1*S*,2*R*,3*R*,4*R*)-2-*exo*-Hydroxy-2-*endo*-(2′-furyl)-3-*exo*-methoxymethylbicyclo[2.2.1]heptane (*exo*-3): pale yellow oil, yield: 217.0 mg (0.98 mmol, 8%); anal. calcd. for $C_{13}H_{18}O_3$: C 70.24, H 8.16%; found: C 70.35, H 8.24; $[\alpha]_D^{25}$: +50.0 (*c* 1.0, $CHCl_3$); IR: ν_{max}=3492 (OH), 2956, 2925, 2874, 1456, 1291, 1156, 1098, 1061, 1013, 885, 736 cm^{-1}; ^{1}HNMR (400 MHz): δ=7.40–7.37 (m, 1H), 6.30–6.28 (m, 1H), 6.27–6.25 (m, 1H), 3.59–3.50 (m, 2H), 3.32 (s, 3H), 3.19 (bs, 1H), 2.55–2.52 (m, 1H), 2.34–2.29 (m, 1H), 2.11–2.08 (m, 1H), 1.99–1.97 (m, 1H), 1.51–1.45 (m, 1H), 1.40–1.32 (m, 1H), 1.24–1.15 (m, 3H); ^{13}CNMR (100.6 MHz): δ= 159.4, 141.9, 110.0, 106.8, 79.9, 73.2, 58.9, 50.7, 48.5, 39.2, 35.5, 29.1, 23.3; EI-MS: *m/z*=222 (M$^+$, 5%), 190 (40), 162 (60), 149 (45), 123 (100), 95 (65).

(1*S*,2*R*,3*R*,4*R*)-2-*exo*-Hydroperoxy-2-*endo*-(2′-furyl)-3-*exo*-methoxymethylbicyclo[2.2.1]heptane (4)

To a stirred solution of **3** (1.26 mmol, 280 mg) in anhydrous THF (13 mL) under argon atmosphere, were added, at room temperature, a solution of 50% aqueous H_2O_2 (12.6 mmol, 726 μL,) and Amberlyst-15 (290 mg). The mixture was stirred overnight at room temperature. Then, the mixture was diluted with diethyl ether (50 mL), washed with brine (3×20 mL) and the organic phase was dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (petrol/diethyl ether 90/10) to afford **4** as a yellow oil; yield: 135 mg (0.57 mmol, 45%); anal. calcd. for $C_{13}H_{18}O_4$: C 65.53, H 7.61%; found: C 65.41, H 7.48; $[\alpha]_D^{25}$: +6.9 (*c* 1.0, $CHCl_3$); IR: ν_{max}=3431 (OH), 2964, 2934, 2878, 1634, 1453, 1150, 1135, 1113, 1089, 1005, 884, 737 cm^{-1}; ^{1}HNMR (400 MHz): δ=9.92 (s, 1H), 7.47–7.44 (m, 1H), 6.42–6.39 (m, 1H), 6.37–6.34 (m, 1H), 3.82 (dd, J_1=J_2=9.6 Hz, 1H), 3.49 (dd, *J*= 12.8, 9.6, 1H), 3.41 (s, 3H), 2.75–2.73 (m, 1H), 2.48–2.44 (m, 1H), 2.10–2.08 (m, 1H), 1.94–1.90 (m, 1H), 1.53–1.40 (m, 2H), 1.23–1.14 (m, 2H), 0.92–0.75 (m, 1H); ^{13}CNMR (100.6 MHz): δ=155.1, 142.6, 110.2, 109.9, 91.8, 72.8, 59.0, 51.6, 46.6, 40.3, 35.5, 28.6, 24.4; EI-MS: *m/z*=175 (60), 154 (100), 139 (20), 123 (20), 95 (50).

General Procedure for the Kinetic Resolution

To a stirred solution Ti(O-*i*-Pr)$_4$ (14.7 μL, 0.050 mmol) in anhydrous toluene (0.4 mL) a solution of the racemic sulfoxide (±)-**6** (0.243 mmol) in anhydrous toluene (0.6 mL) was added under argon atmosphere at −20 °C. The mixture was stirred for 10 min at −20 °C and then to it was added a solution of **4** (50 mg, 0.210 mmol) in anhydrous toluene (1.5 mL). The reaction progress was monitored by TLC analysis. At the end of reaction, water (240 μL) was added and the mixture was stirred for 1 h at room temperature. After filtration of the mixture over a celite bed with ethyl acetate (70 mL), the solvent was evaporated under vacuum and the crude reaction mixture was purified by flash chromatography (from petrol/ethyl acetate mixtures 90/10 to pure ethyl acetate) to give *exo*-**3** (80–90% recovery with respect to **4**) and (*R*)-**6′**.

General Procedure for the Combined Asymmetric Sulfoxidation and Kinetic Resolution

To a stirred solution of Ti(O-*i*-Pr)$_4$ (10.2 μL, 0.035 mmol) in anhydrous toluene (0.45 mL) **5** (0.174 mmol) was added under an argon atmosphere at −20 °C. After stirring for 5 min, a solution of **4** (83 mg, 0.348 mmol) in anhydrous toluene (2.0 mL) was added. In some examples, the total amount of the oxidant was divided into two equivalent portions and the second addition of a toluene solution of **4** was made after 4–5 h of reaction. The reaction progress was monitored by TLC analysis. At the end of the reaction, water (300 μL) was added and the mixture was stirred for 1 h at room temperature. After filtration of the mixture

over a celite bed with ethyl acetate (40 mL), the solvent was evaporated under vacuum and the crude reaction mixture was purified by flash chromatography (from petrol/ethyl acetate mixtures 90/10 to pure ethyl acetate) to give *exo*-**3** (80–90% mol recovery with respect to **4**) and **6**. Spectroscopic data of sulfoxides **6** were in agreement with those reported in the literature.[4] Enantiomeric excesses and absolute configurations were determined by HPLC analysis on chiral column (Daicel Chiralcel OB and OD columns) with UV detection at 254 nm according to the literature.[4,20,23]

(*R*)-4-Tolyl methyl sulfoxide (6a): ^{1}H NMR (400 MHz): δ = 7.53 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.71 (s, 3H), 2.42 (s, 3H); HPLC: t_r (*R*) = 20.5 min, t_r (*S*) = 9.7 min (Chiralcel OB; flow rate 0.8 mL min^{-1}; hexane/*i*-PrOH, 8/2).

(*R*)-Phenyl methyl sulfoxide (6b): ^{1}H NMR (400 MHz): δ = 7.65–7.63 (m, 2H), 7.54–7.52 (m, 3H), 2.72 (s, 3H); HPLC: t_r (*R*) = 20.2 min, t_r (*S*) = 12.1 min (Chiralcel OB; flow rate 0.8 mL min^{-1}; hexane/*i*-PrOH, 8/2).

(*R*)-4-Methoxyphenyl methyl sulfoxide (6c): ^{1}H NMR (400 MHz): δ = 7.61–7.58 (d, *J* = 8.9 Hz, 2H), 7.04–7.02 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 2.71 (s, 3H); HPLC: t_r (*R*) = 33.7 min, t_r (*S*) = 16.3 min (Chiralcel OB; flow rate 0.8 mL min^{-1}; hexane/*i*-PrOH, 8/2).

(*R*)-4-Chlorophenyl methyl sulfoxide (6d): ^{1}H NMR (400 MHz): δ = 7.59 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 2.73 (s, 3H); HPLC: t_r (*R*) = 15.2 min, t_r (*S*) = 10.5 min (Chiralcel OB; flow rate 0.8 mL min^{-1}; hexane/*i*-PrOH, 8/2).

(*R*)-4-Bromophenyl methyl sulfoxide (6e): ^{1}H NMR (400 MHz): δ = 7.68 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 2.72 (s, 3H); HPLC: t_r (*R*) = 14.3 min, t_r (*S*) = 11.0 min (Chiralcel OB; flow rate 0.8 mL min^{-1}; hexane/*i*-PrOH, 8/2).

(*R*)-2-Naphthyl methyl sulfoxide (6f): ^{1}H NMR (400 MHz): δ = 8.22 (s, 1H), 8.00–7.98 (d, *J* = 8.8 Hz, 1H), 7.94–7.92 (m, 2H), 7.61–7.59 (m, 3H), 2.80 (s, 3H); HPLC: t_r (*R*) = 20.4 min, t_r (*S*) = 14.8 min (Chiralcel OB; flow rate 0.8 mL min^{-1}; hexane/*i*-PrOH, 8/2).

(*R*)-Phenyl ethyl sulfoxide (6g): ^{1}H NMR (400 MHz): δ = 7.62–7.60 (m, 2H), 7.53–7.51 (m, 3H), 2.86–7.83 (m, 2H), 1.20 (t, *J* = 7.4 Hz, 3H); HPLC: t_r (*R*) = 17.8 min, t_r (*S*) = 9.5 min (Chiralcel OB; flow rate 0.8 mL min^{-1}; hexane/*i*-PrOH, 8/2).

(*R*)-Benzyl phenyl sulfoxide (6h): ^{1}H NMR (400 MHz): δ = 7.50–7.35 (m, 5H), 7.31–7.20 (m, 3H), 7.00–6.95 (m, 2H), 4.08 (d, *J* = 12.6 Hz, 1H), 3.98 (d, *J* = 12.6, 1H); HPLC: t_r (*R*) = 10.3 min, t_r (*S*) = 12.1 min (Chiralcel OD; flow rate 0.8 mL min^{-1}; hexane/*i*-PrOH, 8/2).

(*R*)-Benzyl methyl sulfoxide (6i): ^{1}H NMR (400 MHz): δ = 7.40–7.23 (m, 5H), 4.07 (d, *J* = 12.8 Hz, 1H), 3.93 (d, *J* = 12.8 Hz, 1H), 2.46 (s, 3H); HPLC: t_r (*R*) = 16.5 min, t_r (*S*) = 13.0 min (Chiralcel OB; flow rate 0.8 mL min^{-1}; hexane/*i*-PrOH, 8/2).

(*R*)-Benzyl 4-tolyl sulfoxide (6j): ^{1}H NMR (400 MHz): δ = 7.34–7.20 (m, 7H), 7.02–6.98 (m, 2H), 4.10 (d, *J* = 12.6 Hz, 1H), 3.94 (d, *J* = 12.6 Hz, 1H), 2.40 (s, 3H); HPLC: t_r (*R*) = 9.8 min, t_r (*S*) = 11.4 min (Chiralcel OD; flow rate 0.8 mL min^{-1}; hexane/*i*-PrOH, 8/2).

(*R*)-Benzyl 4-bromophenyl sulfoxide (6k): ^{1}H NMR (400 MHz): δ = 7.58–7.53 (m, 2H), 7.32–7.25 (m, 3H), 7.22–7.18 (m, 2H), 7.00–6.95 (m, 2H), 4.09 (d, *J* = 12.6 Hz, 1H), 3.97 (d, *J* = 12.6 Hz, 1H); HPLC: t_r (*R*) = 12.9 min, t_r (*S*) = 14.3 min (Chiralcel OD; flow rate 0.8 mL min^{-1}; hexane/*i*-PrOH, 8/2).

(*R*)-4-Methylbenzyl-4′-tolyl sulfoxide (6l): ^{1}H NMR (400 MHz): δ = 7.32–7.17 (m, 4H), 7.04 (d, *J* = 7.0 Hz, 2H), 6.85 (d, *J* = 7.0 Hz, 2H), 4.06 (d, *J* = 12.5 Hz, 1H), 3.93 (d, *J* = 12.5 Hz, 1H), 2.40 (s, 3H), 2.32 (s, 3H); HPLC: t_r (*R*) = 17.0 min, t_r (*S*) = 18.6 min (Chiralcel OD; flow rate 0.7 mL min^{-1}; hexane/*i*-PrOH, 9/1).

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