

Flexible Synthetic Approach to a (*S*)-Norcamphor-Based Hydroperoxide: An Efficient Oxidant for Asymmetric Sulfoxidations

Alessandra Lattanzi,^{*,[a]} Sandro Piccirillo,^[a] and Arrigo Scettri^[a]

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The renewable tertiary (*S*)-norcamphor-based hydroperoxide **3** has been efficiently obtained by a simple 4-step route. Remarkably, complete diastereocontrol was observed in the hydroperoxidation step. This oxidant, when used in the Ti-catalyzed asymmetric sulfoxidation, showed to be as reactive as previously reported hydroperoxide **2**, but more importantly,

high chemoselectivity and improved asymmetric induction were achieved. The synthetic approach used offers the opportunity for designing a variety of functionalized and potentially more efficient norcamphor-based hydroperoxides.

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Introduction

Enantiopure alkyl hydroperoxides find increased use as stereoselective oxidants in asymmetric synthesis.^[1] They offer an alternative way to classical methodologies^[2] based on metal complex/optically pure ligands and achiral alkyl hydroperoxides, since they can be used as chirality and oxygen source at the same time. Experimental data on different oxidative processes have shown that tertiary optically pure hydroperoxides performed at best in terms of efficiency and asymmetric induction.^[3] We have recently accomplished a simple synthesis of tertiary furyl hydroperoxides **1** and **2**, exploiting optically pure ketones (*R*)-camphor^[4] and (*S*)-norcamphor^[5] as chiral compounds (Figure 1). The less sterically demanding compound **2** showed to be highly reactive and furnished better levels of asymmetric induction in the epoxidation of α,β -enones^[6] and vanadium-catalyzed epoxidation of allylic alcohols (up to 67% *ee*).^[7] On the other hand, in the asymmetric sulfoxidation, sterically demanding and less reactive oxidant **1** proved to be the best reagent, affording the sulfoxides in good chemoselectivity, moderate enantioselectivity, although in modest yields.^[8]

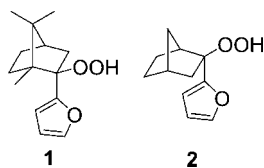
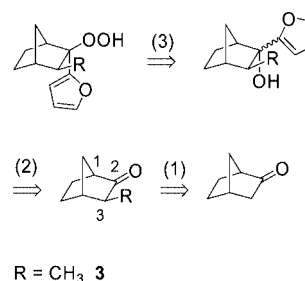


Figure 1. (*R*)-camphor- and (*S*)-norcamphor-based tertiary hydroperoxides.

Investigations on the synthesis of tertiary hydroperoxides of this type provide deeper insight into the relevant steric and electronic requirements necessary to improve their performance as stereoselective oxidants. With the aim to synthesize more efficient hydroperoxides and taking into account the synthetic approach developed to access compound **2**, one potential opportunity to retain its high reactivity and to increase the stereocontrol can be envisaged by functionalization at position 3 of the norcamphor framework, which allows the formation of an additional stereocentre close to the reactive site of the hydroperoxide. Preliminary considerations were taken for the 4-step approach to new hydroperoxides (Scheme 1).



Scheme 1. Retrosynthetic approach to functionalized (*S*)-norcamphor-based hydroperoxides.

The alkylation of norcamphor has been reported to occur in stereocontrolled manner^[9] to furnish the *exo*-alkylated ketone (step 1). The following furyllithium addition to the ketone (step 2) would have furnished a diastereoisomeric *endo/exo* mixture of alcohols. On the grounds of our results and literature reports,^[10] the final hydroperoxidation step (step 3) should have proceeded with epimerization at C-2, via the formation of an intermediate 2-norbornyl cation, to exclusively yield the *exo*-hydroperoxide. This se-

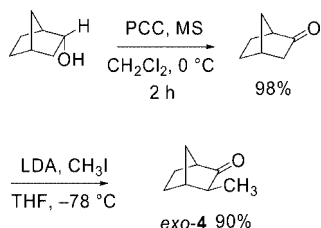
[a] Dipartimento di Chimica, Università di Salerno,
Via S. Allende, 84081, Baronissi, Italy
Fax: +39-089-965296
E-mail: lattanzi@unisa.it

quence would lead to oxidants having the same configuration at carbon 2 with respect to hydroperoxide **2** and an additional stereogenic centre. Herein, we report the synthesis of the renewable tertiary hydroperoxide **3** ($R = CH_3$) derived from (*S*)-norcamphor and its employment in Ti-catalyzed asymmetric sulfoxidation.

Results and Discussion

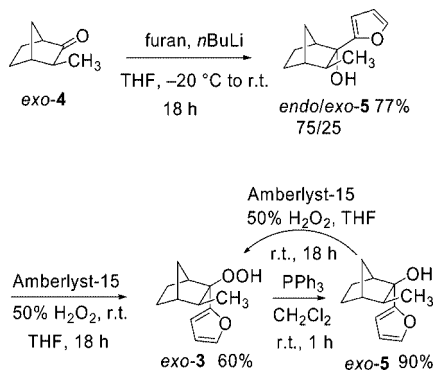
Synthesis of Hydroperoxide **3**

(*S*)-norcamphor was quantitatively obtained by pyridinium chlorochromate (PCC) oxidation of commercially available (+)-*endo*-2-norborneol (Scheme 2).^[11] We decided to carry out the α -methylation of this ketone which is the simplest modification to be introduced in the bicyclic framework. Previously reported α -methylation^[12] of (*S*)-norcamphor proceeded in high yield, affording 3-*exo*-methylnorcamphor (**4**) in highly diastereoselective manner.



Scheme 2.

The addition of 2-furyllithium to *exo*-**4** furnished the *endo*-alcohol **5** as the major diastereoisomer,^[13] which derives from the preferential attack of the organometallic reagent to the less sterically demanding *exo*-side of the bicyclic ketone **4** (Scheme 3).



Scheme 3.

The oxidation of the inseparable diastereoisomeric mixture of alcohols **5** was carried out under previously optimized conditions using 50% hydrogen peroxide solution in the presence of the heterogeneous acid catalyst Amberlyst-15 at room temperature. We were pleased to isolate the *exo* hydroperoxide **3** as sole diastereoisomer in satisfactory yield, thus confirming that complete epimerization occurred at carbon 2. In fact, the reduction of compound **3** with PPh_3 afforded exclusively the *exo*-alcohol **5**, previously

obtained as minor diastereoisomer in the furyllithium addition to *exo*-**4**. Furthermore, *exo*-**5**, when treated under the same oxidative conditions, led to the formation of **3** with the same yield. The selectivity observed in the last step is remarkable,^[14] taking into account that the reaction proceeds via the formation of a 2-norbornyl cation, which is trapped by the nucleophile H_2O_2 and products of rearrangement or elimination have not been observed. Moreover, the approach to hydroperoxide **3** is simplified, since the diastereoisomeric mixture of alcohols can be directly used in the transformation.

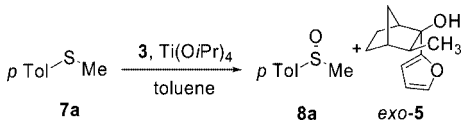
Asymmetric Sulfoxidation

Optically pure sulfoxides can serve as chiral auxiliaries in asymmetric synthesis and are important targets in pharmaceutical industry.^[15] Asymmetric sulfoxidation is the straightforward route to obtain enantioenriched sulfoxides and several successful methodologies, based on the use of a metal complex/enantiopure ligand and *tert*-butyl or cumyl hydroperoxide, have been developed in the last two decades.^[16]

Having in our hands the new oxidant, we investigated its reactivity in the sulfoxidation of methyl *p*-tolyl sulfide **7a** as test compound in the presence of $Ti(OiPr)_4$ (Table 1). The reaction was first carried out using 50 mol-% of catalyst in toluene and a good conversion to (*R*)-sulfoxide was accomplished after a short reaction time (entry 1). The enantiomeric excess of **8a** was better than the one observed when using hydroperoxide **2** under the same conditions^[5] (entry 2) and the oxidation took place with high chemoselectivity, since only traces of the sulfone were detected. When the reaction was performed in CH_2Cl_2 the sulfoxide was isolated in good yield, very high chemoselectivity and 37% *ee*. As previously observed, toluene confirmed to be the solvent of choice. A lower catalyst loading (20 mol-%) could be successfully employed in the sulfoxidation (entry 4). Decreasing the temperature to -40 °C reduced the reactivity, but without any improvement in the enantioselectivity (entry 5). When employing 10 mol-% of $Ti(OiPr)_4$ at -20 °C although a good reactivity was shown, the level of asymmetric induction dropped significantly (entry 6). Finally, the oxidation in absence of the metal catalyst was found to be a negligible process even after a long reaction time (entry 7).

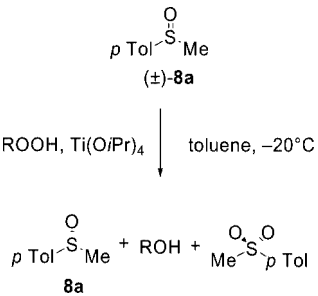
Since previous reports have pointed out the occurrence of a process of kinetic resolution accompanying the asymmetric sulfoxidation by norcamphor-based hydroperoxide **2**,^[5] racemic **8a** was chosen as representative substrate and the behaviour of hydroperoxides **3** and **2** was examined in the presence of 50 mol-% of $Ti(OiPr)_4$ (Table 2).

Under conditions depicted in entry 1, the process was found to be stereoconvergent with the sulfoxidation step since the (*R*)-sulfoxide was isolated as prevalent enantiomer. However, the kinetic resolution was poorly efficient as demonstrated by the low stereoselectivity factor,^[17] and comparable results were obtained by using hydroperoxides **3** and **2** (entries 1 and 2).

Table 1. Asymmetric sulfoxidation of **7a** by Ti(OiPr)₄/3.^[a]


Entry	<i>T</i> [°C]	Time [h]	ROOH	Ti(OiPr) ₄ [mol-%]	Yield 8a [%] ^[b]	<i>ee</i> 8a [%] ^[c]
1	−20	1.5	3	50	66(9)	43 (<i>R</i>)
2 ^[d]	−20	2	2	50	38(38)	38 (<i>R</i>)
3 ^[e]	−20	1.3	3	50	75(1)	37 (<i>R</i>)
4	−20	1.5	3	20	63(3)	44 (<i>R</i>)
5	−40	3.5	3	20	41(2)	38 (<i>R</i>)
6	−20	2	3	10	58(7)	33 (<i>R</i>)
7 ^[f]	−20	24	3	20	4	10 (<i>R</i>)

[a] Molar ratios: **3**/**7a** 1/2. [b] Isolated products after flash chromatography; yields are calculated with respect to the oxidant. Number in parentheses refer to sulfone yield. [c] Determined by HPLC analysis on chiral column (Daicel Chiralcel OB); absolute configuration was determined by the HPLC retention times reported in the literature. [d] In this reaction 4 Å MS were added. [e] The reaction was performed in CH₂Cl₂. [f] The reaction was carried out on methyl phenyl sulfide in absence of Ti(OiPr)₄.

Table 2. Kinetic resolution of racemic **8a** by Ti(OiPr)₄/3 and **2**.^[a]


Entry	Time [h]	ROOH	Ti(OiPr) ₄ [mol-%]	Yield 8a [%] ^[b]	<i>ee</i> 8a [%] ^[c]	<i>S</i> ^[d]
1	3.5	3	50	53	9 (<i>R</i>)	1.3
2 ^[e]	3.5	2	50	62	8(<i>R</i>)	1.4

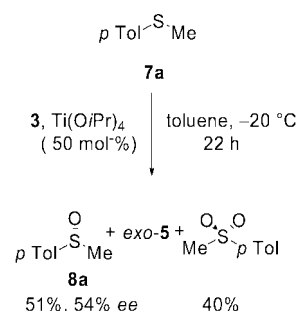
[a] Molar ratios: **8a**/**3** 1.0:0.7. [b] Isolated products after flash chromatography. [c] Determined by HPLC analysis on chiral column (Daicel Chiralcel OB); absolute configuration was determined by the HPLC retention times reported in the literature. [d] Stereo-selectivity factor *S* calculated according to ref.^[17]. [e] In this reaction molecular sieves (4 Å) were added.

The kinetic resolution plays a negligible role in affecting the asymmetric induction reported in Table 1, since the amount of sulfone is small and, consequently, the enantioselectivity originates exclusively from the oxidation of the sulfide to sulfoxide.

In order to better analyze the reactivity of **3** and compare it with hydroperoxide **2**,^[5] we studied the scope of the sulfoxidation under optimized conditions [toluene, −20 °C, 20 mol-% of Ti(OiPr)₄, (Table 3)].

Methyl aryl sulfoxides were obtained in good yield and high chemoselectivity after short reaction times (entries

1–5). The level of asymmetric induction is moderate, but much better than the one observed when using oxidant **2**. In fact, the oxidation of **7a** carried out with **2** and quenched after 1 h, led to the formation of (*R*)-sulfoxide **8a** in 35% yield and 23% *ee*.^[5] In this case a small amount of sulfone was detected (10%), hence the level of asymmetric induction originates almost exclusively from the oxidation of the sulfide to sulfoxide. In order to obtain better enantioselectivities when using hydroperoxide **2**, we had to exploit the positive contribution of the kinetic resolution at the expense of sulfoxides yield (entries 1–4). The combined stereoconvergent oxidations, using an excess of hydroperoxide **3**, were exploited in the sulfoxidation of **7a** (Scheme 4). As predictable, (*R*)-sulfoxide **8a** was then isolated in higher *ee* and better yield when compared with oxidant **2** (Table 3, entry 1), confirming the enhanced efficiency of reagent **3**.

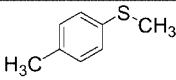
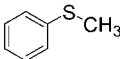
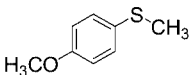
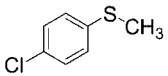
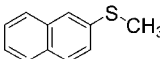
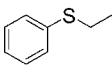
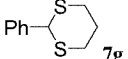
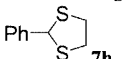
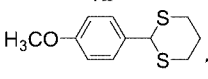
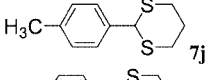
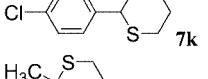
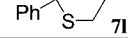
Scheme 4. Combined stereoconvergent oxidations of sulfide **7a**. Molar ratios: **7a**/**3**:1/2.

The less reactive ethyl phenyl sulfide **7f** was converted into the sulfoxide in comparable yield, but with decreased enantioselectivity (entry 6). Interestingly, 2-phenyldithianes and dithiolane were chemoselectively oxidized to give exclusively the *trans* mono-sulfoxides in high yields (entries 7–12) and comparable enantioselectivity. The level of asymmetric induction was improved when compared to that achieved with oxidant **2** for the mono-sulfoxides **8g–h** (entries 7 and 8). Finally, it is noteworthy that the bis-substituted dithiane **7l** was preferentially converted to *cis*-monosulfoxide although both diastereoisomers were recovered as almost racemic products (entry 12).

Conclusions

We have reported a simple 4-step approach to (1*S*,2*S*,3*S*,4*R*)-2-*exo*-hydroperoxy-2-*endo*-(2'-furyl)-3-*exo*-methylbicyclo[2.2.1]heptane (**3**) in 40% overall yield starting from commercially available (+)-2-*endo*-norborneol. The crucial step of hydroperoxidation proceeded with complete epimerization of the carbon at position 2 of the bicyclic framework, giving formation of the desired diastereoisomer. The new oxidant showed to be quite reactive, in a similar way to the parent hydroperoxide **2**. A significant improvement of the enantioselectivity was achieved in the Ti-catalyzed sulfoxidation of methyl aryl sulfides and 2-substituted dithianes. Moreover, the entire transformation is now highly chemoselective and, being the kinetic resolution

Table 3. Asymmetric sulfoxidation by $\text{Ti}(\text{OiPr})_4/\mathbf{3}^{[\text{a}]}$ and $\mathbf{2}^{[\text{f}]}$

		$\text{R-S-R}^1 \xrightarrow[\text{toluene, } -20^\circ\text{C}]{\mathbf{3}, \text{Ti}(\text{OiPr})_4} \text{R-S(=O)-R}^1 + \text{exo-5}$					
Entry	7	Time [h]		Yield 8 [%] ^[b]		ee 8 [%] ^[c]	
		ROOH 3		ROOH 2			
1		1.5	63 (3)	44 (R)	4	34 (55)	42 (R)
2		1	60 (3)	44 (R)	5	30 (54)	38 (R)
3		0.5	73 (6)	40 (R)	4	31 (63)	53 (R)
4		1	56 (4)	30 (R)	3	52 (23)	5 (R)
5		1	60 (5)	41 (R)	—	—	—
6		2	54 (4)	28 (R)	—	—	—
7		3	80	50 (S,S) ^[d]	2	95	32 (S,S)
8		2	74	21 (R,R) ^[d]	1.5	90	18 (S,S)
9		3	82	44 (S,S) ^[d]	—	—	—
10		2.5	80	37 (S,S) ^[d]	—	—	—
11		3	90	41 (S,S) ^[d]	—	—	—
12		5	99	16 (R,R) ^[e]	—	—	—

[a] Molar ratios: $\mathbf{3}/\mathbf{7a-f}/\text{Ti}(\text{OiPr})_4$ 1:2:0.2; $\mathbf{3}/\mathbf{7g-k}/\text{Ti}(\text{OiPr})_4$ 1:1.5:0.2. [b] Isolated products after flash chromatography; yields are calculated with respect to the oxidant. Number in parentheses refer to sulfone yield. [c] Determined by HPLC analysis on chiral columns (Daicel Chiralcel OB and OD); absolute configuration was determined by the HPLC retention times reported in the literature. [d] *trans/cis* >99/<1 Diastereoisomeric ratio was determined by ^1H NMR (400 MHz) analysis of the crude reaction mixture. [e] *trans/cis*, 45:56 Diastereoisomeric ratio was determined by ^1H NMR (400 MHz) analysis of the crude reaction mixture; the *ee* reported refers to the *trans* isomer, the *cis* product was found to be racemic.

a negligible process, the asymmetric induction exclusively originates during the oxidation of the sulfides to sulfoxides.^[18] This investigation clearly indicates that the presence of the stereocentre close to the reactive site of the norcamphor-based hydroperoxide **3** is beneficial and it can help to enhance the enantioselectivity in the asymmetric sulfoxidation. On the basis of the synthetic approach reported in Scheme 1, functionalized and potentially more efficient hydroperoxides are accessible in stereocontrolled manner. In fact, α -alkylation of (*S*)-norcamphor with a variety of alkyl halides allows to introduce substituents with different steric, electronic and chelating properties nearby the reactive site of the oxidant. Further studies in this direction are ongoing in our laboratory.

Experimental Section

General Remarks: All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of argon. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride under argon. CH_2Cl_2 and toluene were distilled from calcium hydride under argon. 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 10% H_2SO_4 /ethanol spray test. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). IR spectra were recorded as thin films unless stated otherwise on a Bruker

Vector 22 instrument. IR absorptions are reported in cm^{-1} . ^1H 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 ^1H NMR and CDCl_3 $\delta = 77.0$ for ^{13}C NMR spectroscopy. Coupling constants (J) are given in Hz. Optical rotations were performed on a Jasco Dip-1000 digital polarimeter using the Na lamp. EIMS spectra were performed on a Finnigan–Polaris spectrometer. (+)-Norcamphor was obtained by oxidation of commercial (+)-*endo*-2-norborneol according to the literature procedure.^[11] (1*S*,3*S*,4*R*)-*exo*-3-Methylbicyclo[2.2.1]heptane-2-one (*exo*-4) was synthesized according to the literature procedure.^[12]

Diastereoisomeric Mixture of *endolexo* (1*S*,3*S*,4*R*)-2-(2'-Furyl)-2-hydroxy-3-*exo*-methylbicyclo[2.2.1]heptane (5): To a solution of freshly distilled furan (0.8 mL, 11 mmol) in anhydrous THF (7 mL), under argon atmosphere at -20°C , *n*BuLi (4.9 mL, 12 mmol, 2.5 M solution in hexane) was added dropwise. The mixture was stirred 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 with sodium sulfate. The crude product was purified by flash chromatography (petroleum ether/diethyl ether, 90:10) to yield the *endolexo* mixture of alcohols **5** as pale yellow oil; yield: 694 mg (77%); major diastereoisomer. ^1H NMR (400 MHz, ppm): $\delta = 7.35\text{--}7.34$ (m, 1 H), 6.31–6.29 (m, 1 H), 6.25–6.24 (m, 1 H), 2.49–2.48 (m, 1 H), 2.07–2.03 (m, 2 H), 1.89–1.88 (m, 1 H), 1.65–1.61 (m, 1 H), 1.46–1.42 (m, 2 H), 1.40–1.36 (m, 2 H), 0.68 (d, $J = 7.0$ Hz, 3 H). ^{13}C NMR (100.6 MHz, ppm): $\delta = 158.9$, 141.1, 109.6, 105.3, 81.4, 52.0, 47.7, 44.7, 36.9, 29.1, 21.4, 17.0. EI-MS: $m/z = 192$ (M^+ , 20%), 174 (25), 164 (80), 146 (60), 136 (40), 123 (100), 110 (30), 95 (65).

(1*S*,2*S*,3*S*,4*R*)-2-*endo*-(2'-Furyl)-2-*exo*-hydroperoxy-3-*exo*-methylbicyclo[2.2.1]heptane (*exo*-3): To a stirred solution of *endolexo*-**5** (422 mg, 2.2 mmol) in anhydrous THF (22 mL) under argon atmosphere, were added, at room temperature, a solution of 50% aqueous H_2O_2 (1.2 mL, 22 mmol) and Amberlyst-15 (400 mg). The mixture was stirred overnight at room temperature. Then, the mixture was diluted with diethyl ether (50 mL) and washed with brine (3×20 mL); then the organic phase was dried with sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (petroleum ether/diethyl ether, 90:10) to yield *exo*-3 as yellow oil; yield: 274 mg (60%); $[\alpha]_{\text{D}}^{25} = +44.7$ ($c = 0.67$, CHCl_3). IR: $\tilde{\nu}_{\text{max}} = 3369$ (O–H), 2959, 2873, 1457, 1151, 1014, 981, 884 cm^{-1} . ^1H NMR (400 MHz, ppm): $\delta = 7.43\text{--}7.42$ (m, 1 H), 7.31 (br. s, 1 H), 6.37–6.35 (m, 2 H), 2.79–2.78 (m, 1 H), 2.18–2.16 (m, 2 H), 2.03 (d, $J = 9.5$ Hz, 2 H), 1.94–1.92 (m, 1 H), 1.56–1.46 (m, 3 H), 1.16 (d, $J = 7.0$ Hz, 3 H). ^{13}C NMR (100.6 MHz, ppm): $\delta = 155.0$, 142.0, 109.9, 109.2, 90.6, 47.6, 44.3, 44.1, 34.1, 29.0, 23.5, 15.1. EI-MS: $m/z = 190$ (35%), 161 (40), 124 (100), 95 (70). $\text{C}_{12}\text{H}_{16}\text{O}_3$ (208.11): calcd. C 69.21, H 7.74; found C 69.17, H 7.69.

(1*S*,2*S*,3*S*,4*R*)-2-*endo*-(2'-Furyl)-2-*exo*-hydroxy-3-*exo*-bicyclo[2.2.1]heptane (*exo*-5): To a stirred solution of **3** (62 mg, 0.3 mmol) in CH_2Cl_2 (4 mL) under argon atmosphere was added Ph_3P (79 mg, 0.3 mmol). The mixture was stirred at room temperature for 1 h. The solvent was then removed under vacuum and purification of the residue by flash chromatography (petroleum ether/ Et_2O , 90:10) gave *exo*-**5** as a pale yellow oil; yield: 52 mg (90%); $[\alpha]_{\text{D}}^{25} = +50.0$ ($c = 1.0$, CHCl_3); IR: $\tilde{\nu}_{\text{max}} = 3467$ (O–H), 2957, 2872, 2359, 1458, 1151, 1010, 979 cm^{-1} . ^1H NMR (400 MHz, ppm): $\delta = 7.36\text{--}7.34$

(m, 1 H), 6.30–6.28 (m, 1 H), 6.22–6.20 (m, 1 H); 2.44–2.43 (m, 1 H), 2.06–2.03 (m, 2 H), 1.92–1.90 (m, 1 H), 1.85–1.84 (m, 1 H), 1.46–1.34 (m, 2 H), 1.25–1.17 (m, 2 H), 1.03 (d, $J = 7.2$ Hz, 3 H). ^{13}C NMR (100.6 MHz, ppm): $\delta = 158.4$, 141.8, 109.7, 106.1, 79.5, 48.9, 45.8, 43.8, 34.4, 29.1, 23.2, 14.1. EI-MS: $m/z = 192$ (M^+ , 20%), 174 (30), 164 (90), 146 (60), 136 (40), 123 (100), 110 (30), 95 (70). $\text{C}_{12}\text{H}_{16}\text{O}_2$: (192.12): calcd. C 74.97, H 8.39; found C 74.92, H 8.43.

General Procedure for Asymmetric Sulfoxidation: To a stirred solution of $\text{Ti}(\text{O}i\text{Pr})_4$ (10.3 μL , 0.035 mmol) in anhydrous toluene (0.5 mL) compound **7** (0.350 mmol) was added under argon atmosphere at -20°C . After stirring for 5 minutes, a solution of **3** (36 mg, 0.175 mmol) in anhydrous toluene (1.2 mL) was added. The reaction progress was monitored by TLC analysis. At the end of the reaction, water (50 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 petroleum ether/diethyl ether mixtures 90:10 to pure ethyl acetate) to give (+)-*exo*-**5** (65–75% mol recovery with respect to **3**) and **8**. Spectroscopic data of sulfoxides **8a–I** were in agreement with those reported in the literature.^[16] 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.^[16]

(R)-Methyl 4-Tolyl Sulfoxide (8a): ^1H NMR (400 MHz, ppm): $\delta = 7.53$ (d, $J = 8.0$ Hz, 2 H), 7.33 (d, $J = 8.0$ Hz, 2 H), 2.71 (s, 3 H), 2.42 (s, 3 H). HPLC: $t_{\text{r}}(\text{R}) = 20.5$ min, $t_{\text{r}}(\text{S}) = 9.7$ min (Chiralcel OB; flow rate 0.8 mL/min; hexane/*i*PrOH, 8:2).

(R)-Methyl Phenyl Sulfoxide (8b): ^1H NMR (400 MHz, ppm): $\delta = 7.65\text{--}7.63$ (m, 2 H), 7.54–7.52 (m, 3 H), 2.72 (s, 3 H). HPLC: $t_{\text{r}}(\text{R}) = 20.2$ min, $t_{\text{r}}(\text{S}) = 12.1$ min (Chiralcel OB; flow rate 0.8 mL/min; hexane/*i*PrOH, 8:2).

(R)-4-Methoxyphenyl Methyl Sulfoxide (8c): ^1H NMR (400 MHz, ppm): $\delta = 7.61\text{--}7.58$ (d, $J = 8.9$ Hz, 2 H), 7.04–7.02 (d, $J = 8.9$ Hz, 2 H), 3.86 (s, 3 H), 2.71 (s, 3 H). HPLC: $t_{\text{r}}(\text{R}) = 33.7$ min, $t_{\text{r}}(\text{S}) = 16.3$ min (Chiralcel OB; flow rate 0.8 mL/min; hexane/*i*PrOH, 8:2).

(R)-4-Chlorophenyl Methyl Sulfoxide (8d): ^1H NMR (400 MHz, ppm): $\delta = 7.60\text{--}7.58$ (d, $J = 8.6$ Hz, 2 H), 7.52–7.50 (d, $J = 8.6$ Hz, 2 H), 2.73 (s, 3 H). HPLC: $t_{\text{r}}(\text{R}) = 15.2$ min, $t_{\text{r}}(\text{S}) = 10.5$ min (Chiralcel OB; flow rate 0.8 mL/min; hexane/*i*PrOH, 8:2).

(R)-Methyl 2-Naphthyl Sulfoxide (8e): ^1H NMR (400 MHz, ppm): $\delta = 8.22$ (s, 1 H), 8.00–7.98 (d, $J = 8.8$ Hz, 1 H), 7.94–7.92 (m, 2 H), 7.61–7.59 (m, 3 H), 2.80 (s, 3 H). HPLC: $t_{\text{r}}(\text{R}) = 20.4$ min, $t_{\text{r}}(\text{S}) = 14.8$ min (Chiralcel OB; flow rate 0.8 mL/min; hexane/*i*PrOH, 8:2).

(R)-Ethyl Phenyl Sulfoxide (8f): ^1H NMR (400 MHz, ppm): $\delta = 7.62\text{--}7.60$ (m, 2 H), 7.53–7.51 (m, 3 H), 2.86–2.80 (m, 2 H), 1.20 (t, $J = 7.4$ Hz, 3 H). HPLC: $t_{\text{r}}(\text{R}) = 17.8$ min, $t_{\text{r}}(\text{S}) = 9.5$ min (Chiralcel OB; flow rate 0.8 mL/min; hexane/*i*PrOH, 8:2).

trans-(S,S)-2-Phenyl-1,3-dithiane 1-Oxide (8g): ^1H NMR (400 MHz, ppm): $\delta = 7.45\text{--}7.36$ (m, 5 H), 4.56 (s, 1 H), 3.60–3.57 (m, 1 H), 2.94–2.90 (m, 1 H), 2.77–2.76 (m, 1 H), 2.72–2.70 (m, 1 H), 2.59–2.49 (m, 1 H), 2.45–2.31 (m, 1 H). HPLC: $t_{\text{r}}(\text{R}) = 40.9$ min, $t_{\text{r}}(\text{S}) = 17.2$ min (Chiralcel OD; flow rate 0.5 mL/min; hexane/*i*PrOH, 7:3).

trans-(R,R)-2-Phenyl-1,3-dithiolane 1-Oxide (8h): ^1H NMR (400 MHz, ppm): $\delta = 7.54\text{--}7.48$ (m, 2 H), 7.42–7.31 (m, 3 H), 5.41 (s, 1 H), 3.87–3.84 (m, 1 H), 3.63–3.60 (m, 1 H), 3.38–3.35 (m, 1

H), 2.96–2.89 (m, 1 H). HPLC: $t_r(R)$ = 24.2 min, $t_r(S)$ = 19.6 min (Chiralcel OD; flow rate 0.5 mL/min; hexane/*i*PrOH, 7:3).

trans-(S,S)-2-(4'-Methoxyphenyl)-1,3-dithiane 1-Oxide (8i): ^1H NMR (400 MHz, ppm): δ = 7.35–7.32 (m, 2 H), 6.92–6.90 (m, 2 H), 4.51 (s, 1 H), 3.80 (s, 3 H), 3.59–3.51 (m, 1 H), 2.93–2.62 (m, 3 H), 2.56–2.26 (m, 2 H). HPLC: $t_r(R)$ = 44.6 min, $t_r(S)$ = 24.3 min (Chiralcel OD; flow rate 0.5 mL/min; hexane/*i*PrOH, 7:3).

trans-(S,S)-2-(4'-Methylphenyl)-1,3-dithiane 1-Oxide (8j): ^1H NMR (400 MHz, ppm): δ = 7.34–7.13 (m, 4 H), 4.52 (s, 1 H), 3.59–3.50 (m, 1 H), 2.92–2.22 (m, 5 H), 2.34 (s, 3 H). HPLC: $t_r(R)$ = 21.9 min, $t_r(S)$ = 10.5 min (Chiralcel OD; flow rate 0.8 mL/min; hexane/*i*PrOH, 7:3).

trans-(S,S)-2-(4'-Chlorophenyl)-1,3-dithiane 1-Oxide (8k): ^1H NMR (400 MHz, ppm): δ = 7.38–7.35 (m, 4 H), 4.54 (s, 1 H), 3.61–3.51 (m, 1 H), 2.83–2.63 (m, 3 H), 2.56–2.26 (m, 2 H). HPLC: $t_r(R)$ = 36.0 min, $t_r(S)$ = 11.4 min (Chiralcel OD; flow rate 0.8 mL/min; hexane/*i*PrOH, 7:3).

trans-(R,R)-2-Methyl-2-phenyl-1,3-dithiane 1-Oxide (trans-8l): ^1H NMR (400 MHz, ppm): δ = 7.66 (m, 2 H), 7.41 (m, 2 H), 7.33 (m, 2 H), 2.88–2.60 (m, 4 H), 2.53–2.43 (m, 1 H), 2.09–1.96 (m, 1 H), 1.92 (s, 3 H). HPLC: $t_r(R,R)$ = 16.9 min, $t_r(S,S)$ = 22.5 min (Chiralcel OD; flow rate 0.5 mL/min; hexane/*i*PrOH, 7:3).

cis-2-Methyl-2-phenyl-1,3-dithiane 1-Oxide (cis-8l): ^1H NMR (400 MHz, ppm): δ = 8.00 (m, 2 H), 7.43 (m, 2 H), 7.36 (m, 1 H), 2.91 (m, 1 H), 2.79–2.65 (m, 2 H), 2.47–2.28 (m, 3 H), 1.93 (s, 3 H).

General Procedure for Kinetic Resolution: To a stirred solution $\text{Ti}(\text{O}i\text{Pr})_4$ (60.4 μL , 0.205 mmol) in anhydrous toluene (0.7 mL) a solution of the racemic sulfoxide ($\pm$)-**8a** (109 mg, 0.709 mmol) in anhydrous toluene (1 mL) was added under argon atmosphere at -20°C . The mixture was stirred for 10 min at -20°C and then was added a solution of **3** (68 mg, 0.327 mmol) in anhydrous toluene (1.5 mL). The reaction progress was monitored by TLC analysis. At the end of the 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 petroleum ether/diethyl ether mixtures 90:10 to pure ethyl acetate) to give (+)-*exo*-**5** (65–75 mol-% recovery with respect to **3**) and (*R*)-**8a** as white solid; yield 59 mg (54%).

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