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The synthesis of chiral β-ketosulfoxides by enantioselective oxidation and their stereocontrolled reduction to β-hydroxysulfoxides

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Abstract—Various chiral non-racemic β-ketosulfoxides, a class of compounds frequently used in asymmetric synthesis, were prepared in good yields by *tert*-butyl hydroperoxide oxidation of the corresponding sulfides in the presence of a complex between titanium and (*S*,*S*)-hydrobenzoin. The ee values of almost all of the purified products were >98%. As ascertained by X-ray analysis and/or by NMR spectroscopy, the use of the (*S*,*S*)-form of the ligand led to aryl β-ketosulfoxides with (R_S)-configuration and to methyl phenacyl sulfoxide with the (S_S)-configuration. Some of the aryl ketosulfoxides were subjected to reduction with DIBAL-H/$ZnCl_2$ and the corresponding β-sulfinylalcohols with an (R,R_S)-configuration produced.

1. Introduction

Enantiopure β-ketosulfoxides are of special interest in enantioselective synthetic strategies, since they are precursors of β-sulfinylalcohols. In turn, these compounds are useful building blocks in the synthesis of natural and biologically active compounds presenting a variety of structures.[1–3] An additional recent use of the same sulfinylalcohols is represented by the enantioselective protonation of lithium enolates of 2-arylcyclohexanones.[4]

The stereoselective reduction of β-ketosulfoxides represents the most convenient route to β-hydroxysulfoxides, while the alternative procedure, consisting of oxidation of the corresponding β-hydroxysulfides, is less frequently used.[5,6] In spite of their synthetic potential, the types of β-ketosulfoxides readily available are rather limited, since they are commonly prepared by the acylation[1,7,8] of (*S*)- or (*R*)-methyl *p*-tolyl sulfoxide which, in turn, is obtained by the Andersen procedure.[2,9]

In principle, in order to enlarge the number of possible structures available, chiral non-racemic β-ketosulfoxides could be produced by an enantioselective oxidation of the corresponding sulfides.[10] Various efforts have been made toward this end.[11–14] 1-(Phenylsulfinyl)-propan-2-one has been obtained by *tert*-butyl hydroperoxide (TBHP) oxidation in the presence of a complex between titanium and (+)-diethyl tartrate at −20 °C (60% ee).[11] The same compound has also been produced in up to 84% ee by dichlorocamphorsulfonyloxaziridine oxidation.[12] Phenyl phenacyl sulfoxide has been synthesized in 57% ee by an oxidation with hydrogen peroxide in the presence of chiral vanadium complexes.[13] Some β-ketosulfoxides have been obtained by oxidation with cumene-, *tert*-butyl- or furyl hydroperoxide, in the presence of a titanium/diethyl tartrate complex at −25 °C. The sulfoxides were formed with ee values between 51% and 97%, but the isolated yields were in the range

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52–66%, because relatively large amounts (30–38%) of the corresponding sulfone were produced.[14]

In recent years, work performed in these laboratories has opened a new route leading to chiral non-racemic sulfoxides by an innovative procedure involving stereocontrolled displacements of a carbanionic leaving group from a suitable sulfinyl compound.[15–21] The starting materials required for our method were often produced by different types of enantioselective hydroperoxide oxidation of the corresponding sulfide in the presence of chiral titanium complexes.[15,16,18–21] For example, dialkyl (arylsulfinyl)- or (alkylsulfinyl)methylphosphonates were synthesized in high ee values (91–>98%) by using catalytic amounts of a titanium complex with (*R*)- or (*S*)-1,1′-bi-2-naphthol (BINOL).[19,20] On the other hand, enantiopure (*R*)-benzyl *p*-bromophenyl sulfoxide, a general precursor of dialkyl sulfoxides, was obtained by using (*S*,*S*)-hydrobenzoin (HB) as a ligand in the titanium complex.[16] These procedures are simple and cheap, work at room temperature, use commercially available compounds, afford the sulfoxides in high yields and in high enantiomeric purity and can be easily scaled up to a multigram scale. Among the procedures we have reported, the oxidation with TBHP in the presence of catalytic amounts of a complex between titanium and (*S*,*S*)-hydrobenzoin[16] appeared particularly convenient for the oxidation of β-ketosulfides, in order to obtain useful chiral β-ketosulfoxides. We report herein the results concerning this oxidation process, followed by a study concerning the reduction of the carbonyl function.

2. Results and discussion

2.1. Enantioselective oxidation of sulfides 1a–7a

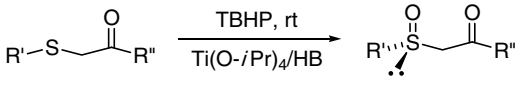
Aryl phenacyl sulfides **1a**–**4a**, methyl phenacyl sulfide **5a** and 1-arylthio-propan-2-ones **6a** and **7a** were chosen as starting materials[22–24] for our investigation on the oxidation reaction. As outlined in our project, this process was performed with TBHP at room temperature, in the presence of a complex between titanium and (*S*,*S*)-hydrobenzoin and led to the formation of the corresponding β-ketosulfoxides[25–29] **1b**–**7b** (Table 1).

2-Naphthyl phenacyl sulfide **1a** was oxidized to sulfoxide **1b** in *n*-hexane. The titanium complex was prepared with, or without, added water (Table 1, entries 1 and 2). Enantiopure (+)-**1b** was obtained, regardless of the presence of added water during the formation of the titanium active species, in similar isolated yields (57–60%). An improvement of the isolated yields (86–90%) of the same enantiopure **1b** was observed when the reaction was performed in CCl_4 (Table 1, entries 3 and 4). The enantioselective oxidation of compounds **2a**–**7a** was performed in CCl_4, without adding water. High enantiomeric purities (92–>98% ee) were also obtained in the oxidation of 4-bromophenyl phenacyl sulfide **2a**, 2-bromophenyl phenacyl sulfide **3a** and *p*-tolyl phenacyl sulfide **4a** (Table 1, entries 5–7). In particular, sulfoxide (+)-**2b** was obtained directly in an enantiopure form, whereas (+)-**3b** and (+)-**4b** increased their ee values from 92% and 96%, respectively, to >98% by crystallization. A lower enantiomeric purity (76% ee) was obtained in the case of methyl phenacyl sulfoxide (+)-**5b** (Table 1, entry 8). On the other hand, 1-arylthio-propan-2-ones **6a** and **7a** were oxidized in good yields (82–86%) to give (+)-**6b** and (+)-**7b** in enantiomerically pure forms (Table 1, entries 9 and 10).

2.2. Determination of the sulfur configuration of the β-ketosulfoxides 1b–7b

(*R*)-(+)-Benzyl *p*-bromophenyl sulfoxide was obtained by using the (*S*,*S*)-hydrobenzoin as a chiral ligand for the titanium atom in the TBHP oxidation of the corre-

Table 1. Enantioselective oxidation of β-ketosulfides



1a -7a **1b - 7b**

HB = (*S*,*S*)-Hydrobenzoin

Entry	Substrate	*R*′	*R*″	Solvent	Water[a]	Time (h)	Product	Yield[b] (%)	ee[c]
1	**1a**	2-Naphthyl	Ph	Hexane	0.5	72	(*R*)-**1b**	60	>98
2	**1a**	2-Naphthyl	Ph	Hexane	0	48	(*R*)-**1b**	57	>98
3	**1a**	2-Naphthyl	Ph	CCl_4	0.5	48	(*R*)-**1b**	86	>98
4	**1a**	2-Naphthyl	Ph	CCl_4	0	48	(*R*)-**1b**	90	>98
5	**2a**	4-Br-C_6H_4	Ph	CCl_4	0	48	(*R*)-**2b**	75	>98
6	**3a**	2-Br-C_6H_4	Ph	CCl_4	0	72	(*R*)-**3b**	81	92 (>98[d])
7	**4a**	*p*-Tolyl	Ph	CCl_4	0	48	(*R*)-**4b**	74	96 (>98[d])
8	**5a**	Methyl	Ph	CCl_4	0	24	(*S*)-**5b**	69	76
9	**6a**	2-Naphthyl	Me	CCl_4	0	24	(*R*)-**6b**	86	>98
10	**7a**	*p*-Tolyl	Me	CCl_4	0	48	(*R*)-**7b**	82	>98

[a] Water/sulfide molar ratio.
[b] Yields refer to pure isolated products.
[c] Determined by HPLC.
[d] After crystallization.

sponding sulfide.[16] Herein, the production of (+)-sulfoxides **1b**–**7b** was observed. Compounds (*R*)-(+)-**4b**[8] and (*S*)-(+)-**5b**[27] had previously been reported in the literature. The other configurations were attributed using NMR techniques, by adding (*R*)-(methoxy)phenylacetic acid[16,17,30] to an enantioenriched mixture of (+)-aryl sulfoxides **1b**–**4b** and **6b**–**7b**. Since the methylene signals of the more abundant enantiomers showed upfield shifts, the (*R*)-configuration was attributed to sulfoxides **1b**–**4b** and **6b**–**7b** according to a proposed model.[30] Furthermore, we were able to obtain suitable crystals of (+)-**3b** for an X-ray analysis. It was found that (+)-**3b** had an (*R*)-configuration (Fig. 1).

In summary, the TBHP oxidation in the presence of a catalytic amount of the complex between titanium and hydrobenzoin, yielded high ee values (92–>98% ee), specifically when aryl β-ketosulfides were oxidized. A lower value was obtained in the case of the oxidation of methyl derivative **5b** (76% ee). However, this variation was not sufficient enough to establish a safe correlation between structure and ee value, since the mechanistic picture of these oxidation reactions cannot be depicted with the available data without resorting to speculation.

2.3. Reduction of β-ketosulfoxides 1b, 2b, 6b and 7b

The reduction of a β-ketosulfoxide to the corresponding sulfinyl alcohol has represented the crucial step of various procedures leading to several synthetic targets.[1,31–34] The mechanism of these reactions has been thoroughly investigated for different reagents and conditions. When hydrides were used in the presence of zinc halides,[32] the (*R*)-*p*-tolylsulfinyl group induced an almost exclusive formation of the sulfinyl alcohol with an (*R*)-configuration at the carbon stereogenic center. Thus, the reduction step appeared of interest not only for the production of the sulfinyl alcohols, but also because it allowed us to ascertain whether the same stereochemical course was also valid for groups different from the *p*-tolyl group. The β-ketosulfoxides **1b**, **2b**, **6b** and **7b** were chosen for this investigation (Table 2).

β-Ketosulfoxides **1b**, **2b**, **6b** and **7b** were reduced to the corresponding sulfinylalcohols **1c**,[35] **2c**, **6c** and **7c**[36] with DIBAL-H in the presence of a solution of zinc chloride in THF (Table 2). 2-Naphthyl phenacyl sulfoxide **1b** was reduced to **1c** in 87% de, when the hydride was dissolved in THF (Table 2, entry 1). On the other hand, complete

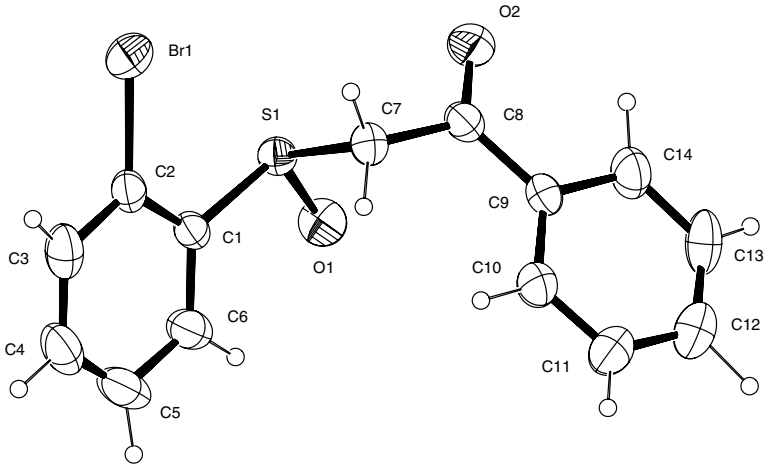
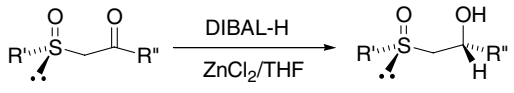


Figure 1. Asymmetric unit with atomic numbering scheme for (*R*)-(+)-**3b**. Ellipsoids drawn at 30% probability level.

Table 2. Stereoselective reduction of β-ketosulfoxides



1b, **2b**, **6b**, **7b** **1c**, **2c**, **6c**, **7c**

Entry	Substrate	*R′*	*R″*	Solvent[a]	Product	Yield[b]	de[c]
1	(*R*)-**1b**	2-Naphthyl	Ph	THF	(*R*,*R*$_S$)-**1c**	86	87
2	(*R*)-**1b**	2-Naphthyl	Ph	Toluene	(*R*,*R*$_S$)-**1c**	80	>98
3	(*R*)-**2b**	4-Br-C$_6$H$_4$	Ph	THF	(*R*,*R*$_S$)-**2c**	60	97
4	(*R*)-**2b**	4-Br-C$_6$H$_4$	Ph	Toluene	(*R*,*R*$_S$)-**2c**	93	>98
5	(*R*)-**6b**	2-Naphthyl	Me	Toluene	(*R*,*R*$_S$)-**6c**	91	86
6	(*R*)-**7b**	*p*-Tolyl	Me	Toluene	(*R*,*R*$_S$)-**7c**	70	87

[a] Solvent for DIBAL-H (see text).
[b] Yields refer to pure isolated products.
[c] Determined by HPLC or NMR.

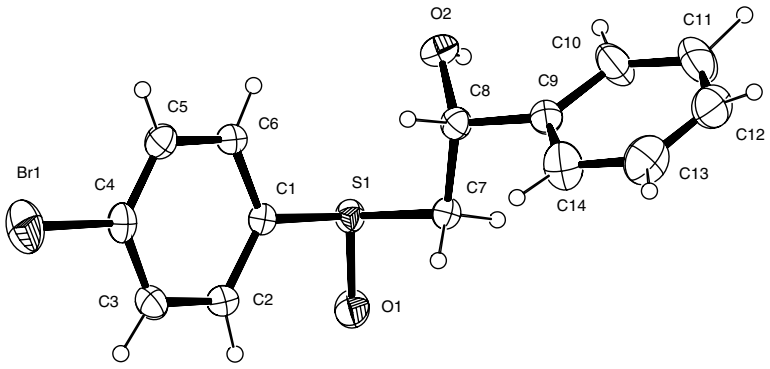


Figure 2. Asymmetric unit with atomic numbering scheme for (R,R_S)-(+)-**2c**. Ellipsoids drawn at 30% probability level.

stereoselectivity (de > 98%) was obtained by using a solution of DIBAL-H in toluene (Table 2, entry 2). In the case of *p*-bromophenyl phenacyl sulfoxide **2b**, a 97% de value was measured when a solution of DIBAL-H in THF was used (Table 2, entry 3), whereas complete stereochemical control was detected when a solution of DIBAL-H in toluene was employed (Table 2, entry 4). Thus, we decided to perform the reduction of the other substrates **6b** and **7b**, in which the less hindered methyl group is bound to the carbonyl moiety, by using DIBAL-H in toluene. In these cases, lower stereoselectivity was observed (86–87% de, Table 2, entries 5 and 6).

2.4. Determination of the configuration of the sulfinyl alcohols 1c, 2c, 6c and 7c

Compound **7c** had spectroscopic properties identical to those of (R,R_S)-**7c** sulfoxide reported in the literature.[36] The absolute configuration of the new stereogenic center of compounds **1c**, **2c**, and **6c** can be inferred from the NMR spectra of the products, according to a well-established rule.[32–34] The patterns of the ^{1}H NMR signals of the hydrogen atoms of the methylene group of β-sulfinyl alcohol is peculiar. In fact, the distances between them are greater (0.30–0.50 ppm) for the (R,S_S)- and (S,R_S)-enantiomers than for the (R,R_S)- and (S,S_S)-couple (0.17–0.27 ppm). Furthermore, a conformational analysis,[37] performed on β-sulfinyl alcohols using both NMR and IR, assigned the configurations and described the role of the hydrogen bonding. We found that the distances between the signals of the hydrogen atoms of the methylene group of the prevailing or exclusive reaction products **1c**, **2c**, **6c** and **7c** were in the region of 0.18–0.25 ppm. Furthermore, in the case of entries 1, 3, 5 and 6, it was possible to measure the distances between the signals of the corresponding residual stereoisomers, which were in the interval 0.38–0.47 ppm. Therefore, we can conclude that the main products of our reactions should have the (R,R_S)- or the (S,S_S)-configuration. Since the starting sulfoxides had an (R_S)-configuration, **1c**, **2c**, **6c** and **7c** must have the (R,R_S)-configuration. Thus, the reported rule that an (R_S)-sulfinyl group should induce the formation of an (R)-stereogenic center on the carbon atom in the hydride reduction performed in the presence of zinc halides can also be considered valid for β-ketosulfoxides **1c**, **2c** and **6c**, which have a structure different from that of *p*-tolyl sulfoxides. Finally, we succeeded in obtaining a suitable crystal of compound **2c**, for the X-ray determination of configuration. The (R,R_S)-configuration was attributed to this compound by using this technique (Fig. 2).

It is worth noting that this X-ray experiment gave a further confirmation that the β-ketosulfoxide **2b**, which is the precursor of **2c**, has the same (R_S)-configuration.

3. Conclusion

The enantioselective oxidation of β-ketosulfides by TBHP in the presence of a titanium complex with (S,S)-hydrobenzoin represents a convenient route to the corresponding β-ketosulfoxides in terms of reaction conditions, yields and enantioselectivities. This oxidation offers a ready access to a variety of compounds structurally different from those previously reported, which are almost invariably characterized by the presence of the *p*-tolyl group. It is worth noting that in addition to the new aryl sulfoxides which were synthesized, a high stereoselectivity in the reduction of the carbonyl moiety was observed, thus forming synthetically useful β-sulfinylalcohols in a simple and straightforward route.

4. Experimental

The purified reaction products were characterized by their ^{1}H and ^{13}C NMR spectra, recorded in $CDCl_3$ at 500 and 125 MHz, respectively. If possible, their mass spectra were determined by GC/MS analysis (70 eV). The ee values were measured by HPLC with the (R,R)-Whelk-O1 column or Chiralcel OD-H column.

The X-ray data for the *o*-bromophenyl phenacyl sulfoxide **3b** and 2-(*p*-bromophenylsulfinyl)-1-phenyl-ethanol **2c** were collected on a single-crystal Nonius Kappa CCD area detector diffractometer equipped with a fine focus sealed graphite-monochromated Mo-K_α radiation ($\lambda = 0.71073$ Å). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC 239452 **3b** and CCDC 239453 **2c**. Copies of the data can be

obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0) 1223-336033 or E-mail: deposit@ccdc.cam.ac.uk).

4.1. Materials

1-(*p*-Tolylthio)-propan-2-one **7a** is commercially available. Aryl or alkyl phenacyl sulfides **1a**–**5a** were produced by reacting bromoacetophenone with the appropriate sodium thiolate.

4.1.1. 2-Naphthyl phenacyl sulfide 1a. Mp 98–100 °C (CH_3OH) (lit.[22] mp 96.5–97.5 °C).

4.1.2. *p*-Bromophenyl phenacyl sulfide 2a. Mp 85–86 °C (CH_3OH) (lit.[23] mp 77–78 °C).

4.1.3. *o*-Bromophenyl phenacyl sulfide 3a. Mp 75–76 °C (CH_3OH). MS (70 eV): 308 (M^{+2}, 2), 306 (M^+, 2), 105 (100), 77 (33), 51 (20). ^{1}H NMR (500 MHz, $CDCl_3$). 7.99–7.94 (m, 2H), 7.61–7.57 (m, 1H), 7.55 (ddd, $J = 0.3$, $J = 1.4$, $J = 7.9$ Hz, 1H), 7.50–7.45 (m, 2H), 7.38 (ddd, $J = 0.3$, $J = 1.6$, $J = 7.9$ Hz, 1H), 7.24 (ddd, $J = 1.4$, $J = 7.4$, $J = 7.9$ Hz, 1H), 7.07 (ddd, $J = 1.6$, $J = 7.4$, $J = 7.9$ Hz, 1H), 4.33 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) 193.6, 136.0, 135.3, 133.6, 133.1, 130.3, 128.7, 128.6, 127.9, 127.8, 124.7, 40.0. Anal. Calcd for $C_{14}H_{11}BrOS$: C, 54.74; H, 3.61. Found: C, 54.55; H, 3.99.

4.1.4. *p*-Tolyl phenacyl sulfide 4a. Mp 36–37 °C (CH_3OH) (lit.[23] mp 36–37 °C).

4.1.5. Methyl phenacyl sulfide 5a. Kugelrohr oven temp 100–105 °C, $p = 0.01$ Torr (lit.[24] bp 80 °C, $p = 0.05$ Torr).

4.1.6. 1-(2-Naphthylthio)-propan-2-one 6a. Mp 50–51 °C (CH_3OH) (lit.[22] mp 46–46.2 °C) was obtained by treating chloroacetone with sodium 2-naphthalenethiolate.

Racemic sulfoxides **1b**–**7b** were prepared by peracetic acid oxidation of the sulfides.

4.2. Enantioselective oxidation of sulfides 1a–7a with *tert*-butyl hydroperoxide in the presence of a titanium/hydrobenzoin catalyst

A solution of Ti(O-*i*-Pr)$_4$ (51 mg, 0.18 mmol) in 5 mL of the specified solvent was added to a solution of (*S*,*S*)-hydrobenzoin (77 mg, 0.36 mmol) in 10 mL of the solvent under a nitrogen atmosphere. When necessary (Table 1, entries 1 and 3), water (3.6 mmol) was added at this stage. The mixture was stirred for 1 h at rt. A solution of sulfide (7.2 mmol) in 45 mL of the solvent was then added and the mixture was stirred for 30 min. After this time, 7.9 mmol of a commercial 80% solution of *tert*-butyl hydroperoxide (in di-*tert*-butylperoxide/water 3:2) was added and the stirring was continued for the time specified in Table 1. The solvent was then removed in vacuo and the evaporated mixture was subjected to column chromatography on silica gel (eluent methylene chloride/ethyl acetate 9:1 for compounds **1b**–**5b**, ethyl acetate/petroleum ether 8:2 for compound **6b** and ethyl acetate/petroleum ether/methanol 6:4:1 for compound **7b**). The sulfoxides were purified by crystallization.

4.2.1. (*R*)-2-Naphthyl phenacyl sulfoxide 1b. Mp 134–135 °C (hexane/EtOH 6:1) (lit.[25] racemic **1b** mp 106 °C). $[\alpha]_D^{25} = +204.5$ (c 1.01, $CHCl_3$). The ee value was measured by HPLC (Column: (*R*,*R*)-Whelk-O1, 5 μm. Eluent: hexane/*i*-propanol 60:40).

4.2.2. (*R*)-*p*-Bromophenyl phenacyl sulfoxide 2b.[26] Mp 111–113 °C (hexane/EtOH 10:1). $[\alpha]_D^{25} = +174.3$ (c 1.00, $CHCl_3$). The ee value was measured by HPLC (Column: (*R*,*R*)-Whelk-O1, 5 μm. Eluent: hexane/*i*-propanol 70:30).

4.2.3. (*R*)-*o*-Bromophenyl phenacyl sulfoxide 3b. Mp 95–96 °C, (hexane/EtOH 8:1). $[\alpha]_D^{25} = +390.4$ (c 1.01, $CHCl_3$). The ee value was measured by HPLC (Column: (*R*,*R*)-Whelk-O1, 5 μm. Eluent: hexane/*i*-propanol 70:30). ^{1}H NMR (500 MHz, $CDCl_3$) 7.96–7.92 (m, 2H), 7.88 (dd, $J = 1.6$, $J = 7.8$ Hz, 1H), 7.62–7.58 (m, 2H), 7.55 (ddd, $J = 1.2$, $J = 7.4$, $J = 7.8$ Hz, 1H), 7.49–7.45 (m, 2H), 7.39 (ddd, $J = 1.6$, $J = 7.4$, $J = 7.9$ Hz, 1H), 4.64 (d, $J = 14.2$ Hz, 1H), 4.33 (d, $J = 14.2$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) 190.9, 142.6, 136.2, 134.1, 133.0, 132.7, 128.9, 128.7, 128.6, 126.8, 118.6, 62.4. Anal. Calcd for $C_{14}H_{11}BrO_2S$: C, 52.03; H, 3.43. Found: C, 52.00; H, 3.70. *X-ray determination of configuration*: A colorless prismatic sample of $0.26 \times 0.22 \times 0.17$ mm was subjected to a single-crystal X-ray analysis. The crystal is orthorhombic, space group $P2_12_12_1$ ($Z = 4$), with the following unit cell dimensions: $a = 4.7728(1)$ Å, $b = 9.2710(2)$ Å, $c = 30.2029(7)$ Å, cell volume = 1336.44(5) Å^3, calculated density = 1.606 g cm^{-3}, $F(000) = 648$. A total of 12,777 reflections were collected at 293(2) K in the θ range of 4.03–27.99°, and then corrected for Lorentz and polarization effects, and for absorption effects ($\mu = 32.22$ cm^{-1}).[38] The number of independent reflections was 3218, with $R_{int} = 0.0612$, and omission of intensities with $I \leqslant 2\sigma(I)$ gave 2380 observed reflections employed for the structure solution by Direct Methods application (SIR97).[39] Afterwards, the structure was refined by a full matrix least squares technique (SHELXL-97):[40] all non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were localized by difference Fourier map application, with the exception of H(4) and H(10) atoms, which were placed in idealized positions and had assigned a common isotropic thermal parameter (C–H = 0.93 Å, U_{iso}-(H) = $1.2U_{iso}$(C)). Final residuals were $R = 0.0445$ and $wR = 0.0963$, using the weighting scheme $w = [\sigma^2(F_o^2) + (0.0446P)^2 + 0.3902P]^{-1}$ (where $P = (F_o^2 + 2F_c^2)/3$) and refining 199 parameters. In the final difference Fourier map, the highest residual peak has density of 0.448 e Å^{-3}. The (*R*)-configuration was attributed to the sulfur stereogenic center as determined by the Flack parameter = 0.016(13),[41] calculated after the least-squares refinement.

4.2.4. (*R*)-*p*-Tolyl phenacyl sulfoxide 4b. Mp 90–91 °C (hexane) (lit.[8] mp 82–83.5 °C). $[\alpha]_D^{25} = +178.0$ (c 0.99,

$CHCl_3$) {lit.[8] $[\alpha]_D = +180.9$ (*c* 1, $CHCl_3$)}. The ee value was measured by HPLC (Column: (*R*,*R*)-Whelk-O1, 5 μm. Eluent: hexane/*i*-propanol 60:40).

4.2.5. (*S*)-Methyl phenacyl sulfoxide 5b. Mp 84–85 °C (ethyl acetate/hexane), (lit.[24] racemic **5b** mp 84 °C). $[\alpha]_D^{25} = +52.0$ for a 76% ee (*c* 1.40, EtOH) {lit.[27] $[\alpha]_D = +63$ (EtOH)}. The ee value was measured by HPLC (Column: Chiralcel OD-H. Eluent: hexane/*i*-propanol 70:30).

4.2.6. (*R*)-1-(2-Naphthylsulfinyl)-propan-2-one 6b. Mp 105–107 °C (hexane/EtOH 4:1) $[\alpha]_D^{25} = +231.2$ (*c* 0.99, $CHCl_3$). The ee value was measured by HPLC (Column: (*R*,*R*)-Whelk-O1, 5 μm. Eluent: hexane/*i*-propanol 60:40). ^{1}H NMR (500 MHz, $CDCl_3$) 7.89–7.87 (m, 1H), 7.65 (d, $J = 8.5$ Hz, 1H), 7.61–7.55 (m, 2H), 7.29–7.23 (m, 3H), 3.61 (d, $J = 13.8$ Hz, 1H), 3.55 (d, $J = 13.8$ Hz, 1H), 1.91 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 199.4, 139.8, 134.6, 132.8, 129.7, 128.5, 128.0, 127.4, 124.8, 119.5, 68.4, 32.0. Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.21; H, 5.21. Found C, 67.22; H, 5.32.

4.2.7. (*R*)-1-(*p*-Tolylsulfinyl)-propan-2-one 7b. Mp 37–38 °C (hexane), (lit.[28] mp 38 °C). $[\alpha]_D^{25} = +233.8$ (*c* 1.15, $CHCl_3$) {lit.[29] $[\alpha]_D = +216.7$ (*c* 2, $CHCl_3$)}. The ee value was measured by HPLC (Column: (*R*,*R*)-Whelk-O1, 5 μm. Eluent: hexane/*i*-propanol 70:30).

4.3. Stereoselective reduction of β-ketosulfoxides

4.8 mL of a 0.5 M solution of $ZnCl_2$ in THF was added to a solution of 2 mmol of β-ketosulfoxide in 5 mL of THF at room temperature. After 30 min, the temperature was lowered to −100 °C and 4 mL of a solution of DIBAL-H 1 M in the specified solvent (Table 2) was added. The temperature was kept below −80 °C and the mixture allowed to react for 1 h. The reaction mixture was quenched with methanol and the solvent removed in vacuo. The residue was treated first with water and then with a solution of NaOH 2.5 M. The mixture was extracted three times with methylene chloride and the extracts then dried and evaporated in vacuo. The crude mixture was separated with column chromatography on silica gel, eluent methylene chloride/ethyl acetate 7:3 for compounds **1c** and **2c** and only ethyl acetate for compounds **6c** and **7c**. The stereoisomeric composition was measured by ^{1}H NMR or by HPLC. In particular, (*R*,*R*)-Whelk-O1 column was able to separate the four stereoisomers.

4.3.1. (*R*,*R*$_S$)-1-Phenyl-2-(2-naphthylsulfinyl)-ethanol 1c. Mp 128–129 °C, (hexane/EtOH 16:1). (lit.[35] racemic **1c** mp 124–126 °C). $[\alpha]_D^{25} = +55.2$ (*c* 0.98, $CHCl_3$). The diastereoisomeric composition was determined by HPLC (Column: (*R*,*R*)-Whelk-O1, 5 μm. Eluent: hexane/*i*-propanol 70:30).

4.3.2. (*R*,*R*$_S$)-1-Phenyl-2-(*p*-bromophenylsulfinyl)-ethanol 2c. Mp 129–131 °C, (hexane/EtOH 10:1). $[\alpha]_D^{25} = +72.6$ (*c* 0.99, $CHCl_3$). The diastereoisomeric composition was determined by HPLC (Column: (*R*,*R*)-Whelk-O1, 5 μm. Eluent: hexane/*i*-propanol 70:30). ^{1}H NMR (500 MHz, $CDCl_3$) 7.69–7.65 (m, 2H), 7.55–7.51 (m, 2H), 7.40–7.27 (m, 5 H), 5.35 (dd, $J = 2.7$, $J = 9.8$ Hz, 1H), 4.12–3.87 (m, 1H), 3.21 (dd, $J = 9.8$, $J = 13.1$ Hz, 1H), 2.96 (dd, $J = 2.7$, $J = 13.1$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) 142.7, 141.7, 132.6, 128.7, 128.3, 125.9, 125.7, 125.5, 70.8, 64.3. Anal. Calcd for $C_{14}H_{13}BrO_2S$: C, 51.70; H, 4.03. Found: C, 51.84; H, 4.36. *X-ray determination of configuration*: A colorless prismatic sample of $0.50 \times 0.28 \times 0.14$ mm was subjected to a single-crystal X-ray analysis. The crystal is orthorhombic, space group $P2_12_12_1$ ($Z = 4$), with the following unit cell dimensions: $a = 5.7750(1)$ Å, $b = 10.8140(2)$ Å, $c = 22.0340(4)$ Å, cell volume = 1376.04(4) Å^3, calculated density = 1.570 g cm^{-3}, $F(000) = 656$. A total of 17,026 reflections was collected at 293(2) K in the θ range of 2.10–30.06°, and they were corrected for Lorentz and polarization effects, and for absorption effect ($\mu = 31.30$ cm^{-1}).[38] The number of independent reflections was 4011, with $R_{int} = 0.0482$, and omission of intensities with $I \leqslant 2\sigma(I)$ gave 3488 observed reflections employed for the structure solution by Direct Methods application.[39] Afterwards, the structure was refined by a full matrix least squares technique. All non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were localized by difference Fourier map application. Final residuals were $R = 0.0359$ and $wR = 0.0865$, using the weighting scheme $w = [\sigma^2(F_o^2) + (0.0421P)^2 + 0.4116P]^{-1}$ (where $P = (F_o^2 + 2F_c^2)/3$) and refining 215 parameters. In the final difference Fourier map, the highest residual peak has density of 0.521 e Å^{-3}. The (*R*)-configuration was attributed to both the sulfur and the carbon stereocenter, as Flack parameter = −0.004(9),[41] calculated after least-squares refinement.

4.3.3. (*R*,*R*$_S$)-1-(2-Naphthylsulfinyl)-propan-2-ol 6c. Mp 108–110 °C, (hexane/EtOH 15:1). $[\alpha]_D^{25} = +239$ (*c* 1.00, $CHCl_3$) for an 86% de. The diastereoisomeric composition of the (*R*,*R*$_S$)/(*S*,*R*$_S$)-mixture was determined by HPLC (Column: (*R*,*R*)-Whelk-O1, 5 μm. Eluent: hexane/*i*-propanol 85:15). ^{1}H NMR (500 MHz, $CDCl_3$) 8.21–8.19 (m, 1H), 8.00 (d, $J = 8.7$ Hz, 1H), 7.96–7.90 (m, 2H), 7.65–7.59 (m, 3H), 4.58–4.51 (m, 1H), 3.92–3.39 (m, 1H), 3.05 (dd, $J = 9.1$, J=13.2 Hz, 1H), 2.87 (dd, $J = 2.5$, J=13.2 Hz, 1H), 1.33 (d, $J = 6.4$ Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) 140.7, 134.5, 132.8, 129.8, 128.5, 128.1, 128.0, 127.5, 124.5, 119.5, 65.2, 63.4, 23.3. Anal Calcd. for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.02. Found: C, 66.85; H, 6.34.

4.3.4. (*R*,*R*$_S$)-1-(*p*-Tolylsulfinyl)-propan-2-ol (7c). Colorless oil. $[\alpha]_D^{25} = +241.0$ (*c* 1.00, $CHCl_3$) for a 87% de {lit.[36] $[\alpha]_D = +273$ for a > 90% de (*c* 1.1, $CHCl_3$)}. The diastereoisomeric composition of the (*R*,*R*$_S$)/(*S*,*R*$_S$)-mixture was determined by HPLC (Column: (*R*,*R*)-Whelk-O1, 5 μm. Eluent: hexane/*i*-propanol 80:20).

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