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The search for exceptions in the highly enantioselective titanium catalysed oxidation of aryl benzyl sulfides

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ABSTRACT

After the discovery of a few cases of lower enantioselectivity in the oxidation of aryl benzyl sulfides with hydroperoxides in the presence of a complex between titanium isopropoxide and (*S*, *S*)-hydrobenzoin, a screening of the oxidation of new substrates that are related to the structures that gave low ee values, was performed. From this screening, we confirmed that only a few sulfides remain as exceptions within a framework of exceptionally high stereoselectivity of the oxidation reaction. Moreover, the exceptions are clearly identified and are connected to particular coordinating moieties present on the aryl groups.

1. Introduction

The synthesis of enantiopure sulfoxides, relevant intermediates in asymmetric organic synthesis and very useful in medicinal chemistry,[1] is an interesting research topic, as witnessed by the numerous recent literature papers.[1] In the past years, our work focused on different enantioselective oxidation reactions of sulfides.[2–4] Some of the sulfoxides that were obtained with this route were also transformed into other useful sulfinyl compounds with our strategy based upon a displacement of carbanionic leaving groups, resulting in a carbon for carbon substitution.[2–5] A large chemical library of enantiopure sulfoxides was synthesised by us by using these two strategies.[5] Our more recent research[6–12] has focused on the application of the asymmetric sulfide oxidation reaction with *tert*-butyl hydroperoxide as the oxidant in the presence of a catalytic amount of a 1:2 complex between titanium *i*-propoxide and (*S*, *S*)- or (*R*, *R*)-hydrobenzoin, a chiral ligand that is employed in many enantioselective processes.[13]

After the application of this oxidation protocol to the asymmetric synthesis of valuable intermediates, such as Sulindac alkyl esters,[6] or β-keto-sulfoxides,[7] we turned our attention to the enantioselective oxidation of aryl benzyl sulfides.[4,8–12] The corresponding sulfoxides were obtained with good yields (57–92%, with a single exception) and high ee values (81–>98% ee). In a favourable stereochemical framework, these high ee values can be increased with a crystallisation step, thus allowing us to obtain a large number of enantiopure aryl benzyl sulfoxides.[8,9] This high asymmetric induction pattern is invariantly obtained regardless of the presence of a variety of substituents (such as halogen atoms, methoxy, nitro, carbomethoxy and even bulky aryl or alkyl groups) on both the phenyl moieties on the starting sulfides.[8,9] In a subsequent step of our research,[9,10] some fluorinated aryl benzyl sulfides were oxidised with the formation of the corresponding sulfoxides always in an enantiopure form (>98% ee value) and even with higher average isolated yields (81–96%) with respect to the non-fluorinated starting materials. A theoretical calculation was able to account for the high enantioselectivity of the oxidation process, both for non-fluorinated[8] and for fluorinated substrates.[10]

Surprisingly,[10] after the synthesis of several enantiopure aryl benzyl sulfoxides, the oxidation of 2,3,4,5,6-pentafluorobenzyl pentafluorophenyl sulfide emerged as an exception. The ee value of the obtained sulfoxide lowered to 61% ee, whereas the isolated yield dropped to 19%.[10] Nevertheless, our theoretical mechanism was able to account also for this unsatisfactory result. The rationale for this uncommon reaction path was found in a different approach mode of the sulfide to be oxidised towards the titanium complex,

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an approach that was stabilised by weak interactions involving the fluorine atoms.[10]

At this point, we considered it of interest to single out further exceptions of this stereochemical framework, to better define scope and limitations of the procedure. On the basis of the results of our calculations, the investigation addressed the modifications of the approach modes of the sulfide to the titanium catalyst, due, for example, to coordinating moieties present on the phenyl groups of the substrates.

We performed a first series of tests,[11] studying the oxidation of aminophenyl or pyridyl benzyl sulfides, i.e. aryl benzyl sulfides bearing coordinating nitrogen moieties, different from the nitro-group previously investigated.[8] Actually, a decrease of the ee values of the produced sulfoxides was observed for the aminophenyl benzyl sulfide (43% ee value) and the 4-pyridyl benzyl sulfide (21% ee value).[11] Another oxidation test was performed with 2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfide,[12] that is a highly halogenated substrate similar to the 2,3,4,5,6,-pentafluorobenzyl pentafluorophenyl sulfide. However, in this case, the usual high yields (91 and 96%, according to different reaction conditions) of the enantiopure 2,4-dichlorophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (>98% ee value) were obtained.[12]

At this point, we decided to perform a further screening of the oxidation of other aryl benzyl sulfides that could have different approach modes to the titanium catalyst, thus leading to other exceptions to the highly favourable stereochemical outcome described so far.

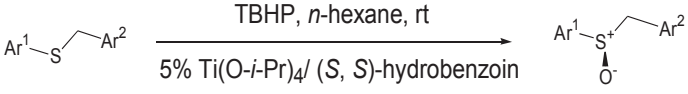
2. Results and discussion

2.1. Enantioselective synthesis of aryl benzyl sulfoxides

Aryl benzyl sulfides **1a**–**12a** were asymmetrically oxidised on a 1 mmol scale to the corresponding sulfoxides **1b**–**12b** with *tert*-butyl hydroperoxide in the presence of 5% of a 1:2 complex formed in situ by mixing titanium *i*-propoxide and (*S*, *S*)-hydrobenzoin (Table 1).

As can be deduced from the experimental section, the operating procedure of this asymmetric oxidation reaction is simple and convenient, because it is just a 'mix-and-wait' procedure, without utilising complicated manipulations. In this respect, it is worth mentioning that our protocol is also insensitive to the presence or absence of small amounts of water.[4–8] In all the oxidation reactions collected in Table 1, the corresponding sulfone is generally absent, or present in low amounts (<5%). This evidence is useful to exclude a further enrichment of the ee values through kinetic resolution during the over-oxidation of the sulfoxide to sulfone.[9]

Table 1
Enantioselective oxidation of aryl sulfides by TBHP in the presence of a titanium/(*S*, *S*)-hydrobenzoin complex



Entry	Sulfide	Ar^1	Ar^2	Sulfoxide	Yield %[a]	ee (%)[b]
1	**1a**	4-Me-C_6H_4	C_6F_5	(*R*)-**1b**	84	>98
2	**2a**	4-O_2N–C_6H_4	C_6F_5	(*R*)-**2b**	80	>98
3	**3a**	4-MeO-C_6H_4	C_6F_5	(*R*)-**3b**	65	>98
4	**4a**	C_6F_5	2,4-$Cl_2C_6H_3$	(*R*)-**4b**	72	88 (>98)[c]
5	**5a**	C_6F_5	4-I-C_6H_4	(*R*)-**5b**	81	73 (85)[c]
6	**6a**	4-MeC_6H_4	4-I-C_6H_4	(*R*)-**6b**	84	95 (>98)[c]
7	**7a**	4-Br-C_6H_4	4-I-C_6H_4	(*R*)-**7b**	95	>98
8	**8a**	4-Br-C_6H_4	4-Br-C_6H_4	(*R*)-**8b**	80	93 (>98)[c]
9	**9a**	C_6H_5	C_6H_5	(*R*)-**9b**	87	>98
10	**10a**	4-Br-C_6H_4	C_6H_5	(*R*)-**10b**[d]	85[d]	>98[d]
11	**11a**	2-HOOC-C_6H_4	C_6H_5	(*R*)-**11b**	—	—
12	**12a**	2-HOH_2C–C_6H_4	C_6H_5	(*R*)-**12b**	74	29

[a] Yields refer to pure isolated products.
[b] Determined by HPLC.
[c] After crystallisation.
[d] Data already reported in Ref. 4.

The present research started with the oxidation of 2,3,4,5,6-pentafluorobenzyl sulfides **1a**[14]–**3a** that have methyl, nitro–or methoxy-groups in the *para*-position of the phenyl groups. This choice was determined by the partial similarity of these substrates with the problematic 2,3,4,5,6-pentafluorobenzyl pentafluorophenyl sulfide. However, good yields (65–84%, Table 1, entries 1–3) of the corresponding enantiopure (>98% ee) sulfoxides **1b**[14]-**3b** were obtained. Taking into account all the aryl 2,3,4,5,6-pentafluorobenzyl sulfides that were oxidised in the previous[9,10,12] and in the present work, the only exception to the synthesis of an enantiopure sulfoxide remains the cited 2,3,4,5,6-pentafluorobenzyl pentafluorophenyl sulfide. A further exception, limited to the lowering of the yield, in a framework of generally high isolated yields (80–96%) can be considered the oxidation of 4-methoxyphenyl pentafluorobenzyl sulfide **3a** (Table 1, entry 3), in which the yield decreases to 65%.

A further series of oxidation was performed focusing on pentafluorophenyl sulfides **4a** and **5a** (Table 1, entries 4 and 5), in which the complete fluorination was reserved only to the aryl moiety, as occurs, for example, in the case of the very successful oxidation of simple benzyl pentafluorophenyl sulfide.[10] Actually, in the oxidation of the 2,4-dichlorobenzyl pentafluorophenyl sulfide **4a**, we observed (Table 1, entry 4) only a slight decrease both of the isolated yield (72%) of sulfoxide **4b** and of the enantioselectivity of the process (88% ee value), in comparison with the very high ee values of the other reactions performed with fluorinated substrates. However, the crystallisation of sulfoxide **4b** allowed us to obtain it in an enantiopure form (>98% ee). At this point, we considered it of interest to test for the first time an iodinated sulfide as a reaction substrate. With this aim, 4-iodobenzyl pentafluorophenyl sulfide **5a** was chosen. In this case, we observed a good isolated yield (81%) of sulfoxide **5b**, but having only a 73% ee value. The crystallisation step was able to increase the ee value only to 85% (Table 1, entry 5).

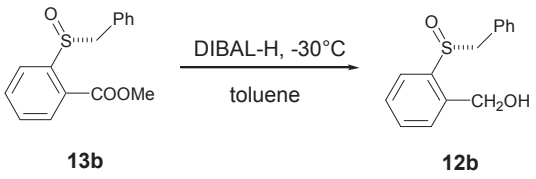
The effect of the iodine atom of the benzyl phenyl group prompted us to consider other oxidation reactions of iodinated sulfides that had not been investigated previously. Therefore, we decided to test for the first time some iodinated non-fluorinated aryl benzyl sulfides. In a first run, we chose to react *p*-tolyl 4-iodobenzyl sulfide **6a**[15] and 4-bromophenyl 4-iodobenzyl sulfide **7a**[16] (Table 1, entries 6 and 7). Good isolated yields (84% and 95% respectively) of the corresponding sulfoxides **6b**[15] and **7b**[16] were obtained having the usual high enantiomeric enrichment value (95 and>98% ee respectively). Sulfoxide **6b** was also obtained in an enantiopure form after crystallisation (Table 1, entry 6). At this stage we considered it of interest to compare the results obtained for 4-bromophenyl 4-iodobenzyl sulfoxide **7b** with the oxidation of 4-bromophenyl 4-bromobenzyl sulfide **8a**[16] (Table 1, entry 8). Only a slight decrease of the ee value was measured (93% ee) that was soon balanced by a crystallisation step that allowed us to obtain the enantiopure **8b**[16] (Table 1, entry 8). For a better comparison, we also reported in Table 1 the oxidation of the unsubstituted benzyl phenyl sulfide **9a**,[17] to give sulfoxide **9b**,[18] that had not been previously oxidised with our protocol, and the oxidation of benzyl 4-bromophenyl sulfide **10a**,[4] that was reported at the beginning of our investigation on this procedure. The inspection of the data reported in entries 6–10 of Table 1 can be considered homogeneous (84–95% isolated yields; 93- >98% ee values) upon varying the halogen atom in the *para*-position of both the aryl rings. Thus, the unusual decrease of the ee value observed for the oxidation of sulfide **5a** should be due only to a combined effect of both the iodine atom on the benzyl group and the pentafluophenyl moiety.

As a final test, taking into account the effect of the amino-group close to the reaction centre,[11] we decided to investigate the effect of the hydroxyl groups of a carboxylic acid or of an alcohol, in the *ortho*-position of the phenyl group, very close to the sulfur atom to be oxidised. To this end, we tested (2-benzylsulfanyl)benzoic acid **11a**[19] and (2-benzylsulfanyl)benzoic alcohol **12a**[20] (Table 1, entry 11 and 12). We observed that only very small quantities of sulfide **11a** were oxidised under the usual reaction conditions. Therefore, the reaction was not investigated further.

It is reasonable to believe that this inertia was due to the presence of the free carboxylic group, since the corresponding methyl (2-benzylsulfanyl)benzoate **13a** (i.e., the same sulfide, but having the carboxyl group protected as an ester) was easily oxidised with the formation of the enantiopure **13b** in our previous investigation.[8] On the other hand, sulfide **12a** was oxidised to the corresponding sulfoxide **12b**[20] with a good yield (74%) but with a low enantiomeric purity (29% ee value). According to our hypothesis, the presence of the hydroxyl moiety very close to the sulfur atom to be oxidised changes the coordination mode of the sulfide to the titanium catalyst, thus causing the decrease of the ee value of the sulfoxide **12b**, in the same way that occurred for the cited oxidation of an aminophenyl sulfide.[11]

2.2. Transformation of an enantiopure aryl benzyl sulfoxide

From the results reported above, it appears that, in spite of our efforts, the extent of the exceptions reaches a small level. Furthermore, the synthesised enantiopure sulfinyl compounds are so numerous that the request of a single sulfoxide belonging to the deviating samples could be overcome by using an indirect approach. For example, sulfoxide **12b** is an interesting structure.[20] Since the asymmetric oxidation of sulfide **12a** is not satisfactory (Table 1, entry 12), we reasoned that the previously synthesised methyl (*R*)-2-(benzylsulfinyl)benzoate **13b**[8] is a direct precursor both of the acid **11b** and of the alcohol **12b** (Scheme 1).



13b 12b

Scheme 1. Synthesis of alcohol **12b** by reducing ester **13b**.

Thus, we chose to transform ester **13b** into alcohol **12b**. After a preliminary screening of the reaction conditions, we reacted enantiopure (*R*)-**13b** with DIBAL-H in toluene at −30 °C (Scheme 1). We soon obtained enantiopure (*R*)-**12b** sulfoxide (69% yield), as checked by chiral HPLC (see Experimental Section).

2.3. Configuration assignments

2.3.1. CD spectra. According to a rule that up to now has found always confirmation,[4,6–12] when (*S*, *S*)-hydrobenzoin was used as a ligand of the titanium, (*R*)-aryl benzyl sulfoxides were obtained. The rule is immediately confirmed by the comparison of the optical rotatory values in the cases of sulfoxides **1b**[14] and **9b**,[18] that were reported in the literature. The configuration of (*R*)-**12b** was attributed from the configuration of (*R*)-**13b**, since the reduction step does not involve the stereogenic centre at the sulfur atom (Scheme 1).

As far as fluorinated sulfoxide **2b**–**5b** are concerned, it was not possible to obtain crystals suitable for the X-ray analysis, as often occurs for this type of compounds.[12] Thus, we decided to use chiroptical spectroscopy, a technique that we have demonstrated to provide sound attribution of configuration for this class of compounds with both recent theoretical and experimental investigations.[9,21,22] Actually, we found for sulfoxides **3b**–**5b** the classical Mislow pattern[23] for the (*R*)-configuration of sulfoxides (minimum at lower wavelengths and maximum at higher wavelengths in the range 200–300 nm). Fig. 1 shows the CD spectra of

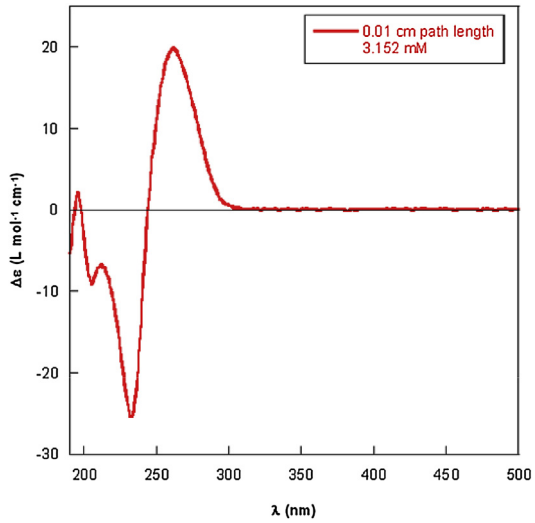


Fig. 1. 190–500 nm CD spectra (in acetonitrile) of (*R*)-4-methoxyphenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide **3b**.

3b. Thus, the (*R*)-configuration, can be safely attributed to this product.

As far as 4-nitrophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide **2b** and of pentafluorophenyl 2, 4-dichlorobenzyl sulfoxide **4b** are concerned (see Fig. S1, Supplementary Data), the lowest wavelength section of the CD spectra is more complex than usual, but similar to the pattern of, for example, the homologous non-fluorinated (*R*)-benzyl 4- nitrophenyl sulfoxide.[21]

Also in this case, the attribution of the (*R*)-configuration can be considered safe. An analogous pattern was found in the case of 4-iodobenzyl pentafluorophenyl sulfoxide **5b** (85% ee value) whose CD spectrum in the 200–300 nm range was depicted in the Supplementary Data section (Fig. S2).

2.3.2. X-ray diffraction experiments. On the other hand, single crystals of **6b**, **7b**, **8b**, obtained in the conditions outlined in the Experimental Section, together with those of the already reported (*R*)-**10b**,[4] were found to be suitable for X-ray diffraction experiments. The expected (*R*)-configuration for all the analysed sulfoxides was confirmed by anomalous-dispersion effects in diffraction measurements (Table S1, Supplementary Data).

The crystal structures of sulfoxides **6b**–**8b** and **10b** share strong similarities. Specifically, in molecule **10b** the crystal packing is mainly driven by two hydrogen bonds occurring between the sulfinyl oxygen atom, which behaves as bidentate electron density donor site, and two hydrogen atoms, one of the methylene group and one *ortho*-hydrogen of the benzyl phenyl group belonging to a translated molecule along the (−1,0,0) direction (Fig. 2).

Similar hydrogen bonding patterns are also present in the other structures. In iodinated sulfoxides **6b** and **7b**, the oxygen atom works either as bidentate electron density donor site, as occurs in **10b**, and as tridentate hydrogen bond acceptor interacting with an additional methylene hydrogen atom of adjacent molecule, while

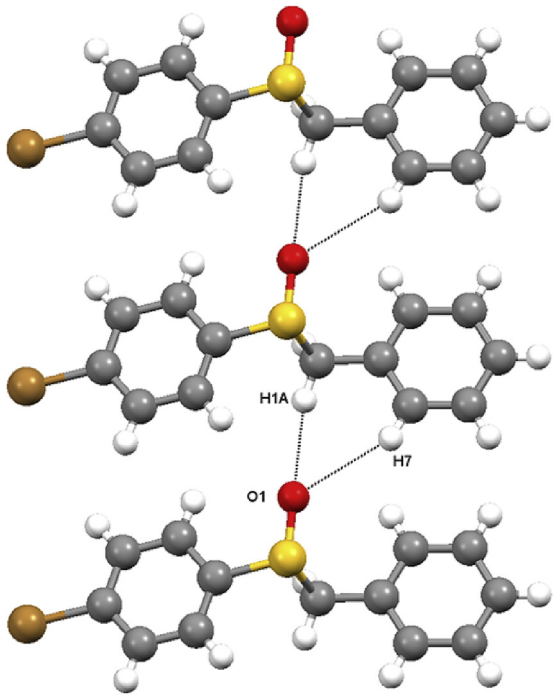


Fig. 2. Hydrogen bonding pattern in **10b**. Hydrogen bonds are pictured in black dotted lines. Colour code: C gray; H white; O red; S yellow and Br light brown.

in **8b** the hydrogen atoms involved in the hydrogen bond contacts come from two methylene units of two different molecules.

In the analysed structures, the hydrogen bond donor-acceptor distances (O···H) are in the range of 2.263 Å–2.717 Å while the angles C–H···O are in the range of 169°–141° (see Supplementary Data, Table S2, for selected distances and angles). The reported geometrical parameters classify these supramolecular contacts as medium-weak hydrogen bonds. However, their systematic occurrence suggests how the S=O···H synthon promotes and stabilises the formation of the aryl benzyl sulfoxide crystals. Recently,[12] these hydrogen bond patterns were observed in some crystal structures of similar sulfoxide derivatives and their presence clearly highlights the strong tendency of sulfinyl oxygen atom to interact with weak acidic hydrogen atoms. Interestingly, a different hydrogen bond motif is also present in iodinated sulfoxides **6b** and **7b**. The sulfur atom behaves as electron density donor site toward an *ortho*-hydrogen atom of the benzyl residue (S···H distances are: 2.96 Å in **6b** and 2.98 Å in **7b**, respectively).

Another common supramolecular motif that further stabilises the crystal packing of all systems is the interaction between some aryl hydrogen atoms and the π systems of the aryl moieties. These CH···π interactions[24] occur in a T-shape fashion (Fig. 3), meaning that the hydrogen atoms enter quasi-perpendicular to the π-cloud of the benzene ring (see also Supplementary Data, Table S2).

It is interesting to note that the presence of halogen atoms with a large polarisable electron density distribution such as bromine and iodide, namely good halogen bonding donors,[25] might give rise to the possible formation of halogen bonding interactions.[26] However, only in sulfoxide **10b** the bromine atom weakly interacts with the π system of benzyl phenyl ring (see Supplementary Data, Table S2). This suggests that the ability of the halogen atoms in this sulfoxide series to work as electron density acceptor site is quite poor and not sufficient to interfere in the formation of the hydrogen bond pattern.

3. Conclusions

The asymmetric oxidation of aryl benzyl sulfides with hydroperoxides in the presence of a complex between titanium and (*S*,*S*)-hydrobenzoin is a simple and straightforward route for the synthesis of more than thirty valuable enantiopure sulfoxides.[4,8–10,12] This highly valuable stereochemical profile was explained with a theoretical mechanism that was able to account also for the single reaction that constitutes the exception to this framework, and to suggest other possible special cases.

After further screenings, the exceptions that have been observed are sporadic and connected to sulfides bearing nitrogen coordinating groups or hydroxyl moiety on the starting sulfides, because these groups can alter the proper coordination mode of the sulfide to the metal, as drawn in our theoretical model. Two further exceptions are connected with the presence of two pentafluorophenyl moieties on the starting sulfide and, to a lower extent, to the presence of one pentafluorophenyl group together with an

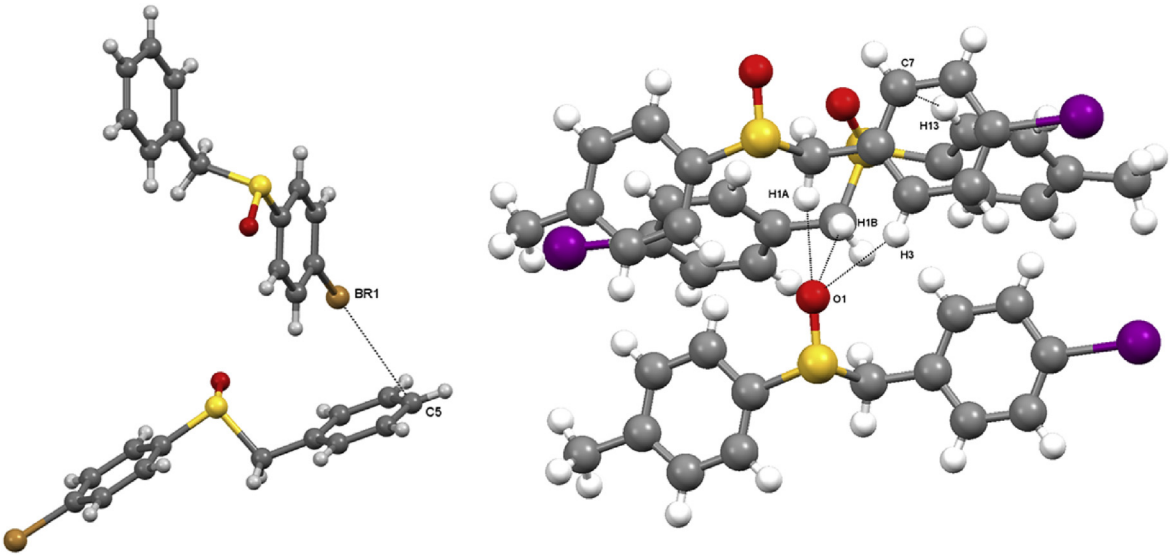


Fig. 3. Ball and stick representation of a dimeric system in **10b** (left). Ball and stick representation of three molecules of sulfoxide **5b** assembled via hydrogen bonds and C–H···π contact (right). Hydrogen bonds, halogen bonds and C–H···π interactions are pictured in black dotted lines. Colour code: C gray; H white; O red; S yellow; Br light brown and I purple.

iodine atom. However, taking into account first the high number of enantiopure sulfoxides that were synthesised against the few cases of a lower enantioselectivity, and secondly the fact that these few cases seem to be predictable on the basis of the present and the past research, we can arrive to the conclusion that nowadays this oxidation protocol is the best synthetic route to synthesise a large number of enantiopure aryl benzyl sulfoxides that, when subjected to our carbanionic leaving group strategy, should lead to a cascade of sulfoxides.

4. Experimental section

Chemicals were used as received. Elemental analyses were performed on a CHNS–O Elemental Analyzer. NMR spectra were recorded on a ^{1}H-500 MHz and ^{13}C-125 MHz spectrometer. ^{19}F spectra were recorded at 565 MHz by using trichlorofluoromethane as an internal standard. Only the absolute value of each coupling constant was reported. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publications. CCDC numbers 1031517-1031520. 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).

Sulfides **1a**–**9a** were synthesised by reacting at 50 °C for 3 h in acetone the corresponding benzyl bromides with the sodium salt of commercially available thiols on a 6 mmol scale. They were purified by distillation, but solidify on standing.

4.1. 2,3,4,5,6-Pentafluorobenzyl *p*-tolyl sulfide (1a)

Transparent oil/white solids. Kugelrohr oven temp 93–96 °C, p=0.1 mbar; mp 65–66 °C (lit.[14] mp 64–66 °C).

4.2. 4-Nitrophenyl 2,3,4,5,6-pentafluorobenzyl sulfide (2a)

Transparent yellowish oil/white solids. Kugelrohr oven temp 160–165 °C, p=0.1 mbar; mp 77–78 °C. Found: C, 46.21; H, 1.92; N, 4.50. $C_{13}H_6F_5NO_2S$ requires C, 46.57; H, 1.80; N, 4.18%. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.19–8.15 (2H, m, H_{Ar}), 7.49–7.45 (2H, m, H_{Ar}), 4.26 (2H, t, $^{4}J_{HF}$ 1.1 Hz, CH_2S). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 146.4 (C_{Ar}), 145.1 (dm, $^{1}J_{CF}$ 250 Hz, C_{Ar}), 144.1 (C_{Ar}), 140.9 (dm, $^{1}J_{CF}$ 255 Hz, C_{Ar}), 137.6 (dm, $^{1}J_{CF}$ 253 Hz, C_{Ar}), 129.1 (C_{Ar}), 124.1 (C_{Ar}), 110.8 (m, C_{Ar}), 25.0 (CH_2S). ^{19}F NMR (565 MHz, $CDCl_3$) −142.4 (dm, $^{3}J_{FF}$=21 Hz), −154.2 (tm, $^{3}J_{FF}$=21 Hz), −161.5 (m). IR (KBr) ν/cm^{-1} 2946, 1654, 1522, 1498, 1340, 986, 836.

4.3. 4-Methoxyphenyl 2,3,4,5,6-pentafluorobenzyl sulfide (3a)

Transparent oil/white solids. Kugelrohr oven temp 95–98 °C, p=0.1 mbar; mp 51–52 °C. Found: C, 52.34; H, 3.08. $C_{14}H_9F_5OS$ requires C, 52.50; H, 2.83%.^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.31–7.27 (2H, m, H_{Ar}), 6.83–6.79 (2H, m, H_{Ar}), 3.97 (2H, t, $^{4}J_{HF}$ 1.2 Hz, CH_2S), 3.80 (3H, s, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 160.3 (O-C_{Ar}), 144.8 (dm, $^{1}J_{CF}$ 252 Hz, C_{Ar}), 140.1 (dm, $^{1}J_{CF}$ 253 Hz, C_{Ar}), 137.3 (dm, $^{1}J_{CF}$ 252 Hz, C_{Ar}), 135.9 (C_{Ar}), 123.6 (C_{Ar}), 114.6 (C_{Ar}), 112.8 (C_{Ar}, m), 55.3 (OCH_3), 28.3 (CH_2S). ^{19}F NMR (565 MHz, $CDCl_3$) −143.4 (dm, $^{3}J_{FF}$=21 Hz), −156.4 (tm, $^{3}J_{FF}$=21 Hz), −162.9 (m). IR (KBr) ν/cm^{-1} 2936, 1654, 1522, 1506, 986, 830.

4.4. 2,4-Dichlorobenzyl pentafluorophenyl sulfide (4a)

Transparent oil/white solids. Kugelrohr oven temp 150–155 °C, p=0.1 mbar; mp 54–55 °C. Found: C, 43.71; H, 1.44. $C_{13}H_5Cl_2F_5S$ requires C, 43.48; H, 1.40%.^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.37 (1H, d, $^{4}J_{HH}$ 2.0 Hz, H_{Ar}), 7.15 (1H, dd, $^{3}J_{HH}$ 8.2 Hz, $^{4}J_{HH}$ 2.0 Hz, H_{Ar}), 7.09 (1H, d, $^{3}J_{HH}$ 8.2 Hz, H_{Ar}), 4.12 (2H, s, CH_2S). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 147.8 (dm, $^{1}J_{CF}$ 246 Hz, C_{Ar}), 141.7 (dm, $^{1}J_{CF}$ 256 Hz, C_{Ar}), 137.5 (dm, $^{1}J_{CF}$ 256 Hz, C_{Ar}), 134.8 (C_{Ar}), 134.4 (C_{Ar}), 133.0 (C_{Ar}), 131.3 (C_{Ar}), 129.7 (C_{Ar}), 127.3 (C_{Ar}), 107.8 (m, C_{Ar}), 36.3 (CH_2S). ^{19}F NMR (565 MHz, $CDCl_3$) −132.1 (m), −151.8 (tm, $^{3}J_{FF}$=21 Hz), −161.1 (m). IR (KBr) ν/cm^{-1} 2941, 1655, 1514, 1477, 1097, 974, 860.

4.5. 4-Iodobenzyl pentafluorophenyl sulfide (5a)

Transparent oil/white solids. Kugelrohr oven temp 115–120 °C, p=0.1 mbar; mp 71–72 °C. Found: C, 37.30; H 1.52. $C_{13}H_6F_5IS$ requires C, 37.52; H, 1.45%.^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.63–7.56 (2H, m, H_{Ar}), 7.01–6.94 (2H, m, H_{Ar}), 3.99 (2H, s, CH_2S). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 147.5 (dm, $^{1}J_{CF}$ 244 Hz, C_{Ar}), 141.3 (dm, $^{1}J_{CF}$ 252 Hz, C_{Ar}), 137.7, 137.5 (dm, $^{1}J_{CF}$ 251 Hz, C_{Ar}), 136.0 (C_{Ar}), 130.5 (C_{Ar}), 107.9 (m, C_{Ar}), 93.4 (I-C_{Ar}), 38.4 (CH_2S). ^{19}F NMR (566 MHz, $CDCl_3$) −132.7 (m), −152.4 (tm, $^{3}J_{FF}$=21 Hz), −161.3 (m). IR (KBr) ν/cm^{-1} 2963, 1639, 1517, 1479, 1092, 977, 861.

4.6. 4-Iodobenzyl *p*-tolyl sulfide (6a)

Transparent oil/white solids. Kugelrohr oven temp 150–154 °C, p=0.1 mbar; mp 94–95 °C (lit.[15] mp 93 °C).

4.7. 4-Bromophenyl 4-iodobenzyl sulfide (7a)

White solids. Mp 126–128 °C (*n*-hexane/acetone 1:1) (lit.[16] mp 118 °C).

4.8. 4-Bromobenzyl 4-bromophenyl sulfide (8a)

Transparent oil/white solids. Kugelrohr oven temp 170–175 °C, p=0.1 mbar; mp 114–116 °C (lit.[16] mp 101 °C).

4.9. Benzyl phenyl sulfide (9a)

Transparent oil/white solids. Kugelrohr oven temp 125–130 °C, p=0.1 mbar; mp 42–43 °C (lit.[17] bp 171–193 °C at 12 Torr).

(2-Benzylsulfanyl)benzoic acid (**11a**)[19] and benzyl 2-hydroxymethylphenyl sulfide (**12a**)[20] were synthesised according to literature protocol. Racemic sulfoxides **1b**–**12b** (used in the setting up of the chiral HPLC separation) were synthesised by standard mCPBA oxidation.

4.10. Enantioselective oxidation of aryl benzyl sulfide. Representative procedure

A solution of Ti(O-*i*-Pr)$_4$ (0.014 g, 0.05 mmol) in 4 mL of *n*-hexane was added to a solution of (*S*, *S*)-hydrobenzoin (0.021 g, 0.1 mmol) in 8 mL of *n*-hexane under a nitrogen atmosphere. The mixture was stirred for 1 h at room temperature. A solution of aryl benzyl sulfide (1 mmol) (as an alternative, a suspension of low soluble sulfides) in 8 mL of *n*-hexane was added at this stage, and the mixture was stirred for 30 min. After this time, 0.14 mL of a commercial 80% solution of *tert*-butyl hydroperoxide (in di-*tert*-butyl peroxide/water 3:2) (1.1 mmol) was added and the stirring was continued for 2 days at room temperature. Finally, the solvent was removed in vacuo and the residue was subjected to column chromatography (petroleum ether/ethyl acetate 4:1).

4.11. (*R*)-2,3,4,5,6-Pentafluorobenzyl *p*-tolyl sulfoxide (1b)

White solids. Mp 138–140 °C (from ethanol), (lit.[14] mp 117–122 °C for the (*S*)-sulfoxide having a 45% ee). $[\alpha]_D^{25}$ +185.3 (*c* 0.8 in $CHCl_3$) (lit.[14] $[\alpha]_D^{25}$ −75.8 (*c* 1.0 in CH_2Cl_2) for the (*S*)-sulfoxide having a 45% ee). The ee values was measured by HPLC (Column: Chiralpak IA. Eluent: *n*-hexane/*i*-propanol 90:10).

4.12. (*R*)-4-Nitrophenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (2b)

White solids. Mp 174–176 °C (from ethyl acetate). $[\alpha]_D^{25}$ +241.4 (*c* 0.35 in CH_3CN). The ee value was measured by HPLC (Column: Chiralcel OD-H. Eluent: hexane/*i*-propanol 70:30). Found: C, 44.36; H, 1.73; N, 4.26. $C_{13}H_6F_5NO_3S$ requires C, 44.45; H, 1.72; N, 3.99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.43–8.37 (2H, m, H_{Ar}), 7.76–7.70 (2H, m, H_{Ar}), 4.33 (1H, dt, $^2J_{HH}$ 13.4 Hz, $^4J_{HF}$ 1.2 Hz, CH_2SO), 4.13 (1H, dt, $^2J_{HH}$ 13.4 Hz, $^4J_{HF}$ 1.2 Hz, CH_2SO). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 149.9 (C_{Ar}), 149.8 (C_{Ar}), 145.5 (dm, $^1J_{CF}$ 251 Hz, C_{Ar}), 141.4 (dm, $^1J_{CF}$ 257 Hz, C_{Ar}), 137.4 (dm, $^1J_{CF}$ 254 Hz, C_{Ar}), 125.2 (C_{Ar}), 124.4 (C_{Ar}), 103.0 (m, C_{Ar}), 50.0 (CH_2SO). ^{19}F NMR (565 MHz, $CDCl_3$) −140.4 (dm, $^3J_{FF}$=21 Hz), −151.3 (tm, $^3J_{FF}$=21 Hz), −160.9 (m). IR (KBr) ν/cm^{-1} 2934, 1654, 1524, 1502, 1344, 1046, 988, 852.

4.13. (*R*)-4-Methoxyphenyl 2,3,4,5,6-pentafluorobenzyl sulfoxide (3b)

White solids. Mp 131–133 °C (from *n*-hexane/acetone 9:1). $[\alpha]_D^{25}$ +166.4 (*c* 0.7 in $CHCl_3$). The ee value was measured by HPLC (Column: Chiralcel OD-H. Eluent: *n*-hexane/*i*-propanol 70:30). Found: C, 50.25; H, 2.90. $C_{14}H_9F_5O_2S$ requires C, 50.00; H, 2.70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.46–7.42 (2H, m, H_{Ar}), 7.02–6.98 (2H, m, H_{Ar}), 4.14 (1H, dt, $^2J_{HH}$ 13.0 Hz, $^4J_{HF}$ 1.2 Hz, CH_2SO), 4.09 (1H, dt, $^2J_{HH}$ 13.0 Hz, $^4J_{HF}$ 1.2 Hz, CH_2SO), 3.87 (3H, s, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 162.7 (O-C_{Ar}), 145.4 (dm, $^1J_{CF}$ 250 Hz, C_{Ar}), 141.1 (dm, $^1J_{CF}$ 256 Hz, C_{Ar}), 137.4 (dm, $^1J_{CF}$ 252 Hz, C_{Ar}), 133.1 (C_{Ar}), 125.9 (C_{Ar}), 114.8 (C_{Ar}), 104.4 (m. C_{Ar}), 55.6 (OCH_3), 50.3 (CH_2SO). ^{19}F NMR (565 MHz, $CDCl_3$) −140.7 (m), −153.1 (tm, $^3J_{FF}$=21 Hz), −161.9 (m). IR (KBr) ν/cm^{-1} 2944, 1654, 1522, 1490, 986, 818.

4.14. (*R*)-2,4-Dichlorobenzyl pentafluorophenyl sulfoxide (4b)

White solids. Mp 94–96 °C (from ethanol). $[\alpha]_D^{25}$ +8.14 (*c* 0.5 in $CHCl_3$). The ee value was measured by HPLC (Column: Chiralcel OD-H. Eluent: *n*-hexane/*i*-propanol 70:30). Found: C, 41.64; H, 1.47. $C_{13}H_5Cl_2F_5OS$ requires C, 41.62; H, 1.34%. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.44–7.42 (1H, m, H_{Ar}), 7.27–7.24 (2H, m, H_{Ar}), 4.73–4.68 (2H, m, CH_2SO). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 145.4 (dm, $^1J_{CF}$ 252 Hz, C_{Ar}), 143.8 (dm, $^1J_{CF}$ 262 Hz, C_{Ar}), 137.5 (dm, $^1J_{CF}$ 254 Hz, C_{Ar}), 136.1 (C_{Ar}), 135.3 (C_{Ar}), 133.1 (C_{Ar}), 129.9 (C_{Ar}), 127.8 (C_{Ar}), 125.5 (C_{Ar}), 116.7 (m, C_{Ar}), 57.5 (CH_2SO). ^{19}F NMR (565 MHz, $CDCl_3$) −139.0 (m), −146.2 (tm, $^3J_{FF}$=21 Hz), −158.8 (m). IR (KBr) ν/cm^{-1} 2927, 1638, 1518, 1482, 1069, 976, 820.

4.15. (*R*)-4-Iodobenzyl pentafluorophenyl sulfoxide (5b)

White solids. Mp 180–181 °C (from acetone/*n*-hexane 1:1). $[\alpha]_D^{25}$ −19.3 (*c* 0.3 in $CHCl_3$). The ee value was measured by HPLC (Column: Whelk-O1. Eluent: hexane/*i*-propanol 70:30). Found: C, 35.95; H, 1.68. $C_{13}H_6F_5IOS$ requires C, 36.13; H, 1.40%. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.71–7.64 (2H, m, H_{Ar}), 6.98–6.91 (2H, m, H_{Ar}), 4.60 (1H, d, $^2J_{HH}$ 12.7 Hz, CH_2SO), 4.43 (1H, d, $^2J_{HH}$=12.7 Hz, CH_2SO). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 145.2 (dm, $^1J_{CF}$ 255 Hz, C_{Ar}), 143.8 (dm, $^1J_{CF}$ 251 Hz, C_{Ar}), 138.4 (C_{Ar}), 137.7 (dm, $^1J_{CF}$ 255 Hz, C_{Ar}), 131.6 (C_{Ar}), 128.1 (C_{Ar}), 116.6 (C_{Ar}), 95.3 (I-C_{Ar}), 59.7 (CH_2SO). ^{19}F NMR (565 MHz, $CDCl_3$) −138.8 (m), −146.1 (m), −158.7 (m). IR (KBr) ν/cm^{-1} 2920, 1638, 1519, 1488, 1058, 982, 834.

4.16. (*R*)-4-Iodobenzyl *p*-tolyl sulfoxide (6b)

White crystals. Mp>210 °C (from *n*-hexane/acetone 2:3), (lit.[15] mp 174 °C for the racemic sulfoxide). $[\alpha]_D^{25}$ +108.6 (*c* 0.8 in $CHCl_3$). The ee value was measured by HPLC (Column: Chiralcel OD-H. Eluent: *n*-hexane/*i*-propanol 90:10).

Crystal data for $C_{14}H_{13}IOS$, M=356.20, Monoclinic, *a*=7.6569(4) Å, *b*=5.6310(4) Å, *c*=16.2048(8) Å, β=101.407(2)°, V=684.88(7) Å^3, T=103(2) K, space group $P2_1$, *Z*=2, μ(MoKα)=2.472 mm^{-1}, 20,262 reflections measured, 2437 independent reflections (R_{int}=0.0361). The final R_1 values were 0.0333 ($I>2\sigma(I)$). The final $wR(F^2)$ values were 0.0706 ($I>2\sigma(I)$). The final R_1 values were 0.0385 (all data). The final $wR(F^2)$ values were 0.0722 (all data). The goodness of fit on F^2 was 1.054. CCDC number CCDC 1031518.

4.17. (*R*)-4-Bromophenyl 4-iodobenzyl sulfoxide (7b)

White crystals. Mp 196–197 °C (from ethanol/*n*-hexane 1:1), (lit.[16] mp 171 °C for the racemic sulfoxide). $[\alpha]_D^{25}$ +113.5 (*c* 1.0 in $CHCl_3$). The ee value was measured by HPLC (Column: Chiralcel OD-H. Eluent: *n*-hexane/*i*-propanol 70:30).

Crystal data for $C_{13}H_{10}BrIOS$, M=421.08, Monoclinic, *a*=7.6772(16) Å, *b*=5.6108(12) Å, *c*=16.313(3) Å, β=101.72(2)°, V=688.0(2) Å^3, T=103(2) K, space group $P2_1$, *Z*=2, μ(MoKα)=5.363 mm^{-1}, 5163 reflections measured, 2366 independent reflections (R_{int}=0.0582). The final R_1 values were 0.0380 ($I>2\sigma(I)$). The final $wR(F^2)$ values were 0.0806 ($I>2\sigma(I)$). The final R_1 values were 0.0468 (all data). The final $wR(F^2)$ values were 0.0840 (all data). The goodness of fit on F^2 was 1.001. CCDC number CCDC 1031520.

4.18. (*R*)-4-Bromobenzyl 4-bromophenyl sulfoxide (8b)

White crystals. Mp 163–165 °C (from *n*-hexane/acetone 3:2), (lit.[16] mp 145–146 °C for the racemic sulfoxide). $[\alpha]_D^{25}$ +127.9 (*c* 0.8 in $CHCl_3$). The ee value was measured by HPLC (Column: Chiralcel OD-H. Eluent: *n*-hexane/*i*-propanol 90:10).

Crystal data for $C_{13}H_{10}Br_2OS$, M=374.09, Monoclinic, *a*=7.7288(6) Å, *b*=5.6057(5) Å, *c*=16.0226(12) Å, β=103.898(3)°, V=673.86(9) Å^3, T=103(2) K, space group $P2_1$, *Z*=2, μ(MoKα)=6.150 mm^{-1}, 12,164 reflections measured, 2249 independent reflections (R_{int}=0.0439). The final R_1 values were 0.0414 ($I>2\sigma(I)$). The final $wR(F^2)$ values were 0.0802 ($I>2\sigma(I)$). The final R_1 values were 0.0603 (all data). The final $wR(F^2)$ values were 0.0904 (all data). The goodness of fit on F^2 was 1.078. CCDC number CCDC 1031519.

4.19. (*R*)-Benzyl phenyl sulfoxide (9b)

White solids. Mp 134–136 °C (from *n*-hexane/ethyl acetate 3:2). (lit.[18] mp 138–139 °C for a sulfoxide having a 91% ee). $[\alpha]_D^{25}$ +96.5 (*c* 1.1 in $CHCl_3$). (lit.[18] $[\alpha]_D^{25}$ −135.9 (*c* 0.49 in acetone) for the (*S*) sulfoxide having a 91% ee).

4.20. (*R*)-Benzyl *p*-bromophenyl sulfoxide (10b)[4]

Crystal data for $C_{13}H_{11}BrOS$, M=295.19, Orthorhombic, *a*=5.6665(8) Å, *b*=12.081(2) Å, *c*=17.219(3) Å, V=1178.8(3) Å^3, T=93(2) K, space group $P2_12_12_1$, *Z*=4, μ(MoKα)=3.638 mm^{-1}, 19,480 reflections measured, 2404 independent reflections (R_{int}=0.1146). The final R_1 values were 0.0402 ($I>2\sigma(I)$). The final $wR(F^2)$ values were 0.0744 ($I>2\sigma(I)$). The final R_1 values were 0.0555 (all data). The final $wR(F^2)$ values were 0.0790 (all data). The goodness of fit on F^2 was 1.029. CCDC number CCDC 1031517.

4.21. (*R*)-Benzyl 2-hydroxymethylphenyl sulfoxide (12b)

Enantiopure sulfoxide **12b** was obtained by standard DIBAL-H reduction of (*R*)-benzyl 2-carboxymethylphenyl sulfoxide **13b** in toluene at −30 °C. Yield: 69%. White solids. Mp 139–141 °C (from *n*-hexane/ethyl acetate 3:2). (Lit.[20] mp 101.5–102.5 °C for a racemic

sample). $[\alpha]_D^{25}$ +124.9 (*c* 0.4 in $CHCl_3$). The ee value was controlled by HPLC (Column: Whelk-O1. Eluent: hexane/*i*-propanol 70:30).

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Supplementary data

Supplementary data (CD spectra of sulfoxides **2b**, **4b** and **5b**. Crystallographic Tables. ^1H and ^{13}C NMR spectra of already reported compounds.) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.05.036. These data include MOL files and InChiKeys of the most important compounds described in this article.

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