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Localized partitioning of enantiomers in solid samples of sulfoxides; importance of sampling method in determination of enantiopurity

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Localized partitioning of amorphous enantioenriched aryl benzyl sulfoxides in the solid state can lead to substantial variation in enantiopurities, even for sulfoxides which do not show detectable levels of self-disproportionation of enantiomers (SDE) during chromatography on an achiral stationary phase. The importance of preparation of representative samples of enantioenriched sulfoxides for chiral HPLC to enable reproducible results is clear.

Enantioenriched sulfoxides have attracted considerable interest in the field of asymmetric synthesis largely due to their importance as chiral auxiliaries or as synthetic intermediates with wide ranging applications. The sulfoxide moiety has been demonstrated to be an efficient chiral auxiliary in carbon–carbon and carbon–oxygen bond forming reactions, in asymmetric catalysis, in radical addition reactions, Michael reactions and in cycloaddition reactions.^{1–8} The ability of the sulfoxide moiety to promote such reactions is explained in terms of the structural features inherent to the sulfinyl group. Not only does the sulfinyl group possess a high configurational stability and there can be significant steric and stereoelectronic differences between the inequivalent organic substituents at the sulfur atom.

In addition to uses in synthetic methodology, enantiopure sulfoxides have also gained significance in the pharmaceutical industry due to their important biological activity. One of the most successful sulfoxide-containing APIs is Astra Zeneca's esomeprazole, a gastric acid secretion inhibitor, commercialized as Nexium®. Esomeprazole is the (S)-enantiomer of omeprazole, its racemic predecessor.

Synthesis of enantioenriched sulfoxides is undertaken primarily employing two principal strategies – nucleophilic displacement from sulfinate precursors,⁹ and asymmetric sulfoxidation of prochiral sulfides mediated by transition metal catalysts.^{1, 10–13} Extensive reports of asymmetric sulfur oxidation have appeared over the past 30 years since the seminal reports from Kagan^{14–15} and Modena¹⁶ utilising titanium mediated oxidation.

Central to these reports are the methods exploited for the determination of enantiopurity of the resulting sulfoxides. Chiral HPLC, whereby a chiral stationary phase is used to generate diastereomeric interactions between analyte and stationary phase, is the method of choice since its emergence as a more accurate and reproducible descriptor of enantiopurity when compared with other analytical techniques such as ¹H NMR analysis using a chiral shift reagent, or measurement of optical rotation.

Of particular interest were the seminal reports of the self-disproportionation of enantiomers (SDE) for enantioenriched sulfoxides by chromatography on an achiral phase as reported by Kagan and co-workers in 1994.^{17–18} Self-disproportionation of enantiomers in fractional crystallization of solids is well

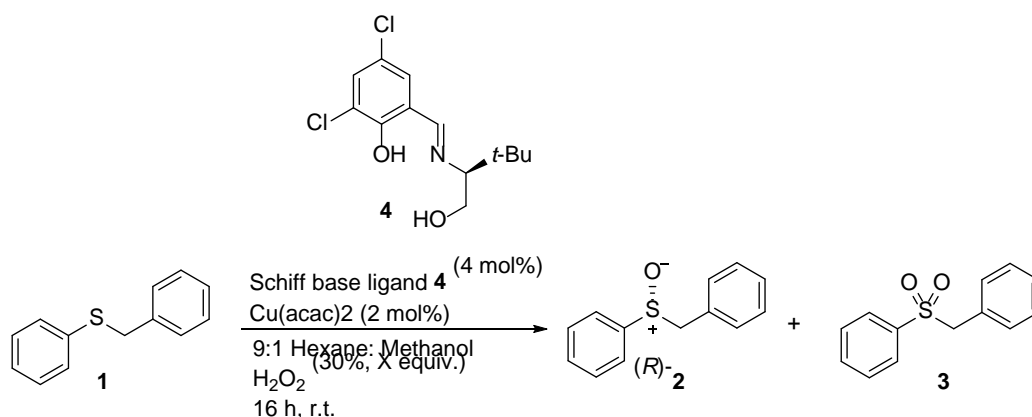
known, leading to formation of racemates and/or conglomerates, depending on the structure of a compound.¹⁹ Indeed our reports on the solid state properties of sulfoxides highlight that for benzyl *p*-tolyl sulfoxide spontaneous resolution occurs to form enantiopure crystals of the conglomerate even when a racemic synthesis is undertaken, a property not seen with other aryl benzyl sulfoxides.²⁰ Observation of this spontaneous resolution is notable, as it is believed that at most only 5–10% of crystalline racemates form conglomerates.

Our group has previously reported on the copper mediated asymmetric oxidation of aryl benzyl sulfides to the corresponding sulfoxides, with enantioselectivities of up to 97% *ee* achieved through ligand and substrate optimization.^{21–22} During investigation of the further scope of this transformation, challenges were encountered in relation to the reproducibility of the enantioselectivities with variable outcomes in the oxidation of certain substrates. Furthermore, it is evident that the efficiency of the oxidation is very sensitive to variation in the reaction temperature.

One of our initial aims was to optimize the peroxide loading in order to maximize sulfide consumption while keeping the over-oxidation product, the sulfone, to a minimum. Therefore, the oxidation of benzyl phenyl sulfide **1** was examined using varying equivalents of hydrogen peroxide (30%) using our previously reported optimized conditions (**Table 1**). Previous work in the group demonstrated that the optimized conditions required Schiff base ligand **4** in conjunction with copper(II) acetylacetonate and a heterogenous solvent system of hexane and methanol.

We found that the use of 1.5 equivalents of H₂O₂ was necessary to ensure complete consumption of the sulfide (**Entry 3**), and while the use of more oxidant did not lead to any increase in sulfone formation, the conversion to sulfoxide was hampered, presumably due to degradation of the catalyst (**Entries 4–6**).

During optimisation studies exploring the impact of the number of equivalents of H₂O₂ we encountered some challenges in reproducibility of enantioselectivities for certain sulfur oxidations, therefore we looked in more detail at the HPLC sampling method used in conjunction with this work. Irrespective of peroxide loading, the enantioselectivity of the copper Schiff base catalysed sulfoxidation was reproducibly in the range of 52–58%, so long as the entirety of the recovered enantioenriched sulfoxide post chromatography was dissolved prior to dilution for chiral HPLC analysis; however, if instead of dissolving the complete sample recovered from chromatography, a portion of the non-crystalline solid material is extracted from the collection flask then the *ee* determined by chiral HPLC varies from the representative value.

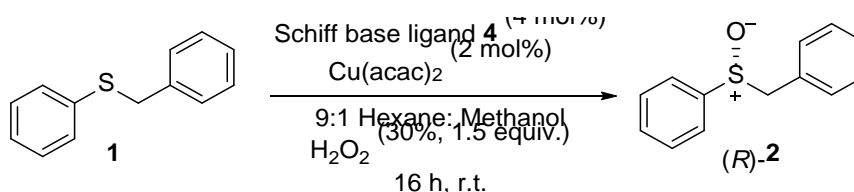
Table 1: Investigation of Peroxide Loading and HPLC sampling method

Entry	X Equiv. 30% H ₂ O ₂	1 : 2 : 3 ^a	% ee (R)-[2] ^c				% Yield [2] ^b
			Solid Sample 1 ^d	Solid Sample 2 ^d	Solid Sample 3 ^d	Representative Sample ^e	
1	1.1	56 : 44 : 0	N/A	N/A	N/A	52	29
2	1.3	6 : 93 : 1	62	62	67	56	74
3	1.5	1 : 98 : 1	79	73	60	57	75
4	1.7	4 : 95 : 1	65	61	63	56	75
5	1.9	3 : 96 : 1	70	66	64	56	70
6	2.1	10 : 89 : 1	61	60	60	58	57

- a) Ratio of **1** : **2** : **3** determined from the ¹H NMR spectrum of the crude product.
 b) After purification by column chromatography.
 c) Determined by HPLC analysis on chiral column (Chiralcel OD-H); absolute configuration determined by comparison of HPLC elution order to literature values.
 d) Solid sample obtained by taking random 3 mg of amorphous sulfoxide product and dissolving in 3 ml of HPLC grade methanol.
 e) Representative sample obtained by dissolving entirety of recovered sulfoxide post chromatography.

It is well established that the self-disproportionation of enantiomers (SDE) of sulfoxides is frequently observed during achiral chromatography,^{10, 23-28} and accordingly it is essential that representative samples are utilized for determination of enantiopurity to avoid errors in determination of %ee in individual samples. However, investigation of the enantiopurity of fractions of enantioenriched benzyl phenyl sulfoxide **2** recovered from chromatography did not display any evidence of SDE with this compound (**Table 2**).

Table 2: Investigation of Self-Disproportionation of Enantiomers for enantioenriched (*R*)-benzyl phenyl sulfoxide



<i>Fraction Number Post Column Chromatography^a</i>	<i>% Product 2 Recovered^b</i>	<i>% ee (<i>R</i>)-2^c</i>
1	7	58
2	26	57
3	30	58
4	17	58
5	6	59
6	2	59
7	1	57

- a) Fraction obtained post purification by flash column chromatography on silica gel using hexane: ethyl acetate (60:40) as eluent; At 1 mmol scale, each fraction was collected in a 40 ml test-tube.
- b) Each fraction was concentrated under reduced pressure prior to being dissolved in HPLC grade methanol and diluted to give a HPLC sample with a concentration of 1 mg/ml.
- c) Determined by HPLC analysis (Daicel Chiracel OD-H); absolute configuration determined by comparison of HPLC elution order to literature values.

It is clear that with sulfoxides, in addition to the possibility of SDE occurring during column chromatography, sampling of apparently amorphous solid samples of enantioenriched sulfoxides can produce samples with varying enantiopurity and accordingly extreme care must be taken when sampling solid sulfoxides even in cases where apparently homogenous non-crystalline samples are recovered through evaporation of solutions. Thus, it would seem that we are seeing an example of *localized partitioning in the solid state of amorphous solids*, even in the absence of 1) crystallization and 2) detectable levels of self-disproportionation of enantiomers via achiral chromatography.

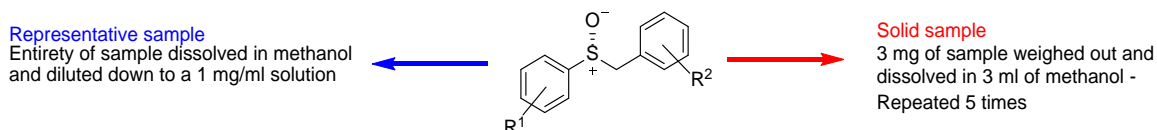
Having identified the variation in *ee* values for enantioenriched (*R*)-benzyl phenyl sulfoxide as summarized in **Table 1** it was initially thought that the variation may be consistent across a range of enantioenriched substituted aryl benzyl sulfoxides exhibiting amorphous morphology following evaporation of eluent after chromatography. To gain a better understanding of the extent of this phenomenon, a further five enantioenriched sulfoxides were generated using our copper Schiff base methodology.

For each of the five substrates, the representative *ee* was measured by combining all fractions containing the recovered enantioenriched sulfoxide following chromatography, concentrating them to dryness under reduced pressure to give an amorphous solid and dissolving the entirety of the sample in HPLC grade methanol. Once dissolved the representative sample was diluted accordingly to give a 1 mg/ml sample for chiral HPLC analysis. After analysis the representative sample was restored to the original sample, which was again concentrated under reduced pressure to give the amorphous solid. From this re-concentrated residue, five individual 3 mg solid samples were randomly selected and each dissolved in 3 ml of HPLC grade methanol.

As can be seen in **Table 3** the significant variation in enantioselectivity that was observed for enantioenriched benzyl phenyl sulfoxide **2** was not seen consistently across the series of aryl benzyl

sulfoxides studied, rather it would appear that the variation is strongly dependent on the exact substitution pattern, and therefore the structure, of the selected aryl benzyl sulfoxide. In the cases of sulfoxides **5** and **7** the representative samples and solid samples withdrawn from the amorphous sulfoxide product provided essentially similar %ee data (**Entries 1** and **3**). Sulfoxide **8** demonstrated a very minor increase in %ee when a solid sample was taken (**Entry 4**). Sulfoxide **9** however demonstrated a somewhat variable decrease in enantiopurity when analysing the solid samples (**Entry 5**). Sulfoxide **6** gave essentially reproducible solid sample data, however this ee value was approx. 10% greater than the representative enantiomeric excess of 37% (**Entry 2**).

Table 3: Comparison of sampling methods for substituted aryl benzyl sulfoxides

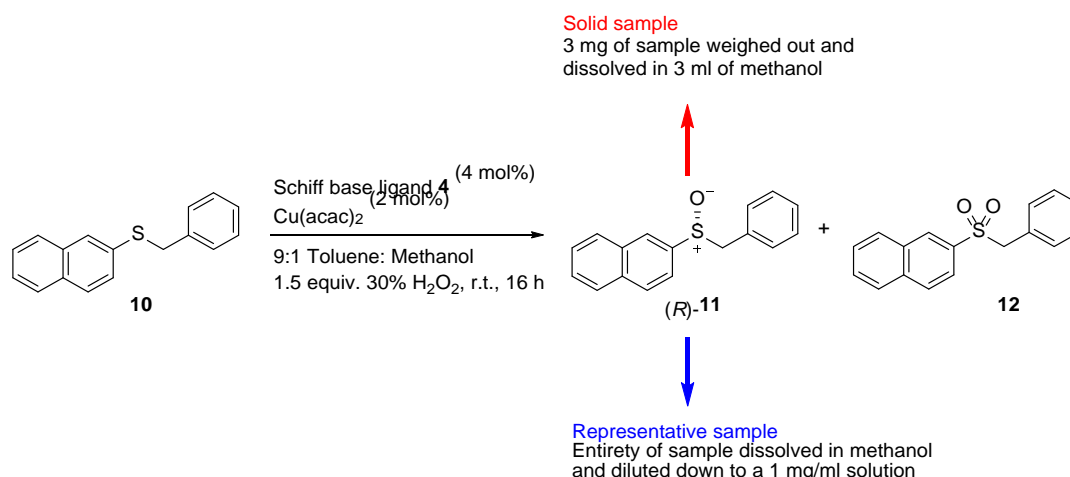


Entry	Sulfoxide ^a	R ¹	R ²	Representative %ee (R) ^b	Solid Sample ^b				
					% ee (R) Sample 1	% ee (R) Sample 2	% ee (R) Sample 3	% ee (R) Sample 4	% ee (R) Sample 5
1	[5]	3-Me	-	31	30	28	32	30	32
2	[6]	4-MeO	-	37	48	48	47	47	47
3	[7]	2-Me	-	71	72	71	72	71	70
4	[8]	4-Me	-	55	60	58	56	57	55
5	[9]	-	4-Cl	55	51	42	56	39	50

a) Sulfoxides **5–9** were generated as per 'Experimental Procedure for Asymmetric Sulfide Oxidation'

b) Determined by HPLC analysis (Chiralpak IB for sulfoxide **5**, Phenomenex Lux Amylose-1 for sulfoxides **6–9**); absolute configuration determined by comparison of HPLC elution order to literature values.

Thus far, all HPLC sampling of the solid amorphous material had been carried out in a random manner, so that no indication could be made as to whether the partitioning of the solid state was occurring in an ordered predictable manner while evaporated under reduced pressure. Thus enantioenriched 2-naphthyl benzyl sulfoxide **11** was generated using our copper Schiff base methodology to give a sample with 62% ee (**Entry 1, Table 4**). As in previous instances the representative sample was restored to the bulk sample, dissolved, and concentrated under reduced pressure in a 100 ml round bottom flask. Solid amorphous material was collected from both the upper and lower parts of the flask to give a %ee of 59% and 73% respectively (**Entries 2** and **3**), indicating *localized partitioning of the enantiomers* of the sulfoxide throughout the evaporation process. Thus the degree of partitioning is dependent on several factors which may include size of collection vessel post chromatography, choice of eluent system for chromatography, and relative rate of evaporation of solvents during solid acquisition post chromatography, in addition to the exact sulfoxide structure.

Table 4: HPLC sampling of enantioenriched (R)-2-naphthyl benzyl sulfoxide

Entry	HPLC sampling method used	Part of 100 ml round bottom flask sample taken from	% ee (R) 11
1	Representative sample	Entirety	62
2	3 mg/ml solid sample	Bottom	73
3	3 mg/ml solid sample	Top	59

a) Determined by HPLC analysis (Phenomenex Lux Amylose-1); absolute configuration determined by comparison of HPLC elution order to literature values.

In conclusion, observation of localized partitioning of enantiomers in amorphous non-crystalline samples of sulfoxides even in the absence of detectable levels of self-disproportionation of enantiomers via chromatography on an achiral phase can be rationalized on the basis of the strong intermolecular non-covalent interactions in the solid state between R and S enantiomers of sulfoxides. Observation of this behaviour with highly polar compounds such as sulfoxides, and moreover considering the significant variation in the nature of the substituents on sulfur as opposed to stereogenic carbon, is arguably not surprising. According to Hunter's hydrogen-bond parameter table sulfoxides are among the most potent hydrogen bond acceptors leading to strong intermolecular interactions in the solid state.²⁹ Accordingly, when conducting studies in asymmetric sulfoxidation additional care should be taken to eliminate potential errors in the determination of enantiomeric excess not only via self-disproportionation of enantiomers in sulfoxide samples through chromatography, but also through localized partitioning in the solid state, even in the absence of crystallisation.

Experimental Section

General Procedures: All solvents were distilled prior to use by the following methods: methanol was distilled from magnesium methoxide and stored over 3Å molecular sieves; toluene was distilled from sodium benzophenone ketyl; ethyl acetate was distilled from potassium carbonate; and hexane was distilled prior to use. All commercial reagents were used without further purification unless otherwise stated. Hydrogen peroxide was standardised by titration using potassium permanganate.

¹H (300 MHz) NMR spectra were recorded on a Bruker Avance 300 NMR spectrometer. All spectra were recorded at 300 K in deuterated chloroform (CDCl₃) using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ_H) are reported in parts per million (ppm) relative to TMS, and coupling

constants are expressed in hertz (Hz). Splitting patterns in ^1H NMR spectra are designated as s (singlet), d (doublet), dd (doublet of doublets) and m (multiplet).

Flash column chromatography was carried out using Kieselgel silica gel 60, 0.035–0.075 mm (Merck). Thin-layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF254). Visualization was achieved by UV (254 nm).

The enantiopurity of chiral compounds was measured using chiral stationary phase high-performance liquid chromatography (HPLC), carried out on either a Chiralcel OD-H, Phenomenex Lux Amylose-1, or a Chiralpak IB column. Details of the column conditions and mobile phase employed are included in the Experimental Section; data for the plots were extracted at 254 nm, at which wavelength all of the compounds exhibited good absorption. In all instances baseline resolution was obtained, and injection of racemic reference samples for each run confirmed the accuracy of the integration of the chromatograms, regardless of retention time.

HPLC analysis was performed on a Waters alliance 2695 separations module with a Waters alliance 2996 photodiode array detector. High temperature chiral HPLC analysis was obtained using an Igloo[®] column heater/cooler.

Experimental Procedure for Asymmetric Sulfide Oxidation: Copper(II) acetylacetonate (5.2 mg, 2.0 mol %) was added to a 25 ml round-bottom flask containing Schiff base ligand **4** (11.6 mg, 4.0 mol%), and 9:1 hexane (or toluene)/methanol (1 ml). The resulting mixture was stirred at r.t. for 5 min, and then a solution of sulfide (1 mmol) in 9:1 hexane (or toluene)/methanol (1 ml) was added. After a further 5 min of stirring at r.t., hydrogen peroxide (0.170 ml, 30%, 1.5 mmol) was added dropwise to the mixture. The reaction mixture was stirred at r.t. for a further 16 h. Water (10 ml) and dichloromethane (10 ml) were then added and the phases separated; the organic layer was washed with water (2 x 10 ml) and brine (10 ml), dried with MgSO_4 , filtered, and concentrated under reduced pressure to give the crude product. The product was purified by flash column chromatography on silica gel (60:40 hexane/ ethyl acetate) to afford the enantioenriched sulfoxide as an amorphous white solid. Each of sulfoxides **2**, **5–9** and **11** were prepared and purified using these conditions.

(*R*)-(+)-Benzyl phenyl sulfoxide **2** (Table 1, Entry 3)^{21, 30}

White solid (162 mg, 75%, 57% ee); ^1H NMR (CDCl_3 , 300 MHz) 7.51–7.34 (m, 5H), 7.33–7.20 (m, 3H), 7.03–6.94 (m, 2H), 4.10 (d, 1H, $J = 12.5$ Hz), 3.99 (d, 1H, $J = 12.5$ Hz); HPLC: t_R (R) = 18.6 min, t_R (S) = 22.5 min [Chiralcel OD-H; flow rate 1 ml min⁻¹; hexane/2-PrOH (95:5); 40°C].³¹

(*R*)-(+)-Benzyl *m*-tolyl sulfoxide **5** (Table 3, Entry 1)^{21, 32}

White solid (199 mg, 86%, 31% ee); ^1H NMR (CDCl_3 , 300 MHz) 7.33–7.11 (m, 7H), 7.04–6.94 (m, 2H), 4.05 (d, 1H, $J = 12.5$ Hz), 3.95 (d, 1H, $J = 12.5$ Hz), 2.32 (s, 3H); HPLC: t_R (R) = 23.1 min, t_R (S) = 25.6 min [Chiralpak IB; flow rate 0.5 ml min⁻¹; hexane/2-PrOH (90:10); 20°C].

(*R*)-(+)-Benzyl *p*-methoxy sulfoxide **6** (Table 3, Entry 2)^{22, 33}

White solid (143 mg, 58%, 37% ee); ^1H NMR (CDCl_3 , 300 MHz) 7.35–7.18 (m, 5H), 7.03–6.86 (m, 4H), 4.10 (d, 1H, $J = 12.4$ Hz), 3.95 (d, 1H, $J = 12.4$ Hz), 3.82 (s, 3H); HPLC: t_R (R) = 49.7 min, t_R (S) = 54.4 min [Lux Amylose-1; flow rate 0.5 ml min⁻¹; hexane/2-PrOH (90:10); 20°C].

(*R*)-(+)-Benzyl *o*-tolyl sulfoxide **7** (Table 3, Entry 3)^{21, 34}

White solid (174 mg, 76%, 71% ee); ^1H NMR (CDCl_3 , 300 MHz) 7.74–7.66 (m, 1H), 7.37–7.16 (m, 5H), 7.13–7.06 (m, 1H), 7.00–6.92 (m, 2H), 4.07 (d, 1H, $J = 12.6$ Hz), 3.98 (d, 1H, $J = 12.6$ Hz), 2.06 (s, 3H);

HPLC: t_R (R) = 24.3 min, t_R (S) = 26.9 min [Lux Amylose-1; flow rate 0.5 ml min⁻¹; hexane/2-PrOH (90:10); 20°C].

(R)-(+)-Benzyl *p*-tolyl sulfoxide **8** (Table 3, Entry 4)^{21, 35}

White solid (150 mg, 65%, 55% ee); ¹H NMR (CDCl₃, 300 MHz) 7.32–7.14 (m, 7H), 7.05–6.92 (m, 2H), 4.07 (d, 1H, J = 12.6 Hz), 3.96 (d, 1H, J = 12.6 Hz), 2.38 (s, 3H); HPLC: t_R (R) = 29.4 min, t_R (S) = 33.0 min [Lux Amylose-1; flow rate 0.5 ml min⁻¹; hexane/2-PrOH (90:10); 20°C].

(R)-(+)-4-Chlorobenzyl phenyl sulfoxide **9** (Table 3, Entry 5)^{22, 33}

White solid (88 mg, 35%, 55% ee); ¹H NMR (CDCl₃, 300 MHz) 7.52–7.32 (m, 5H), 7.25–7.18 (m, 2H), 6.94–6.84 (m, 2H), 4.02 (d, 1H, J = 12.8 Hz), 3.96 (d, 1H, J = 12.8 Hz); HPLC: t_R (S) = 68.4 min, t_R (R) = 70.9 min [Lux Amylose-1; flow rate 0.5 ml min⁻¹; hexane/2-PrOH (95:5); 20°C].

(R)-(+)-2-Naphthyl benzyl sulfoxide **11** (Table 4, Entry 1)^{22, 33}

White solid (186 mg, 70%, 62% ee); δ_H (300 MHz, CDCl₃) 7.93–7.78 (m, 4H), 7.62–7.51 (m, 2H), 7.41 (dd, 1H, J = 8.6, 1.8 Hz), 7.31–7.17 (m, 3H), 7.02–6.96 (m, 2H), 4.17 (d, 1H, J = 12.6 Hz), 4.08 (d, 1H, J = 12.6 Hz); HPLC: t_R (R) = 46.7 min, t_R (S) = 55.3 min [Lux Amylose-1; flow rate 0.5 ml min⁻¹; hexane/2-PrOH (90:10); 20°C].

Supporting Information

Copies of chiral-phase HPLC chromatographs for compounds **2**, **5–9** and **11**

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Notes

There are no conflicts to declare

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TOC/Graphical Abstract

