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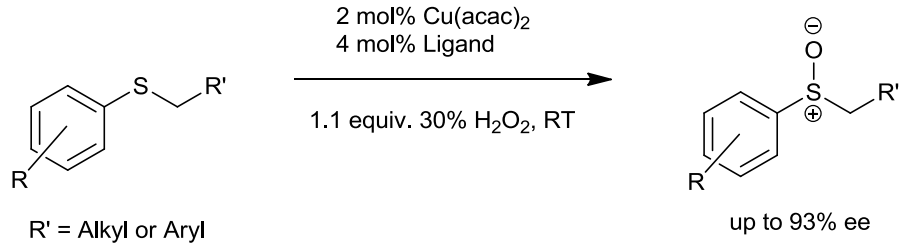
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Copper-catalyzed asymmetric oxidation of sulfides

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Abstract

Copper-catalyzed asymmetric sulfoxidation of aryl benzyl and aryl alkyl sulfides, using aqueous hydrogen peroxide as oxidant, has been investigated. A relationship between the steric effects of the sulfide substituents and the enantioselectivity of the oxidation has been observed, with up to 93% ee for 2-naphthylmethyl phenyl sulfoxide, in modest yield in this instance (up to 30%). The influence of variation of solvent and ligand structure were examined and the optimised conditions were then used to oxidise a number of aryl alkyl and aryl benzyl sulfides, producing sulfoxides in excellent yields in most cases (up to 92%), and good enantiopurities in certain cases (up to 84% ee).

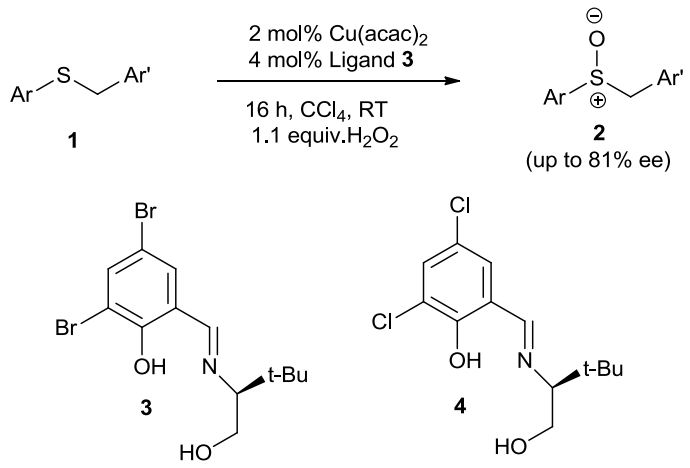
Introduction

Optically pure sulfoxides are widely used as building blocks and chiral auxiliaries in asymmetric synthesis.[1] The sulfinyl group has been shown to be an effective chiral auxiliary in a broad range of synthetic reactions from carbon-carbon bond forming reactions[2] to cycloaddition reactions.[3–5] Enantiopure sulfoxides have also found use in the pharmaceutical industry due to their important biological activity, for example esomeprazole, the (*S*)-enantiomer of omeprazole, has been one of the world's best-selling drugs since its launch in 2001. Modafinil is a psychostimulant agent that has been used for the treatment of narcolepsy; it is manufactured by Cephalon and is marketed in the racemic form as Provigil.[6] Since the 1980s, metal-catalyzed asymmetric sulfide oxidation employing titanium, vanadium and a number of other metal based systems has developed rapidly as a route to enantiopure sulfoxides.[7] The initial breakthrough came in 1984 when the research groups of Kagan[8, 9] and Modena[10] independently reported an efficient titanium-mediated sulfide oxidation based on the Sharpless asymmetric epoxidation procedure.[11] 1n 1995, Bolm reported a robust vanadium sulfoxidation procedure using a vanadium Schiff base complex.[12] The oxidation was carried out under mild conditions using hydrogen peroxide as the oxidant. A number of other metals such as iron, manganese, aluminium, niobium, zirconium, tungsten, molybdenum and osmium have also been used to catalyse asymmetric oxidation of sulfides.[7] However, there are disadvantages associated with the Kagan and Bolm procedures for asymmetric oxidation. The Kagan system is limited by its sensitivity to atmospheric moisture, low turnover numbers and it utilises a complex and expensive catalytic system.[13] Although the Bolm procedure is robust and operationally straightforward the use of vanadium is not

advantageous since vanadium is known to exert toxic, mutagenic and genotoxic effects on a variety of biological systems.[14]

Copper has received relatively little attention in metal-catalyzed asymmetric sulfoxidation. The research groups of Cross,[15] Kraemer,[16] Zhu,[17] Alcon[18] have all used copper-based systems to asymmetrically oxidise sulfides, but with limited success (enantioselectivities of 0-30% ee). In an initial study we demonstrated good enantiocontrol in copper-catalyzed asymmetric oxidation of aryl benzyl sulfides with up to 81% ee albeit with modest yields (typically 20-30%, **Scheme 1**).[19] Herein, we wish to describe the expansion of this early investigation resulting in improved yields, while retaining good enantioselectivity through variation of reaction conditions. The influence of variation of solvent, ligand and substrate structure have been examined rendering this oxidation synthetically useful.

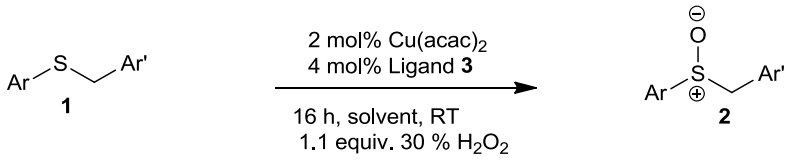
Scheme 1. Copper-catalyzed asymmetric oxidation of sulfides



Results and Discussion

The effects of varying sulfide substituents, Schiff base ligand and solvent were investigated in an attempt to optimise the asymmetric oxidation and in particular to improve the efficiency of the transformation. An initial solvent study demonstrated that CCl_4 could be replaced with toluene as solvent for copper-catalyzed asymmetric sulfoxidation with no significant loss in yield or enantioselectivity as shown in **Table 1**. An important feature of this oxidation system is that the Schiff base ligand can be recovered after chromatography and can be re-used without loss of activity.

Table 1. Investigation of Solvent



Entry	1	Ar	Ar′	Toluene				CCl_4[d]		
				1 : 2[a]	2	% Yield[b]	% ee (*R*)[c]	1 : 2[a]	% Yield[b]	% ee (*R*)[c]
1	**1a**	Ph	Ph	73 : 27	**2a**	21	58	74 : 26	27	61
2	**1b**	2-$MeOC_6H_4$	Ph	74 : 26	**2b**	19	77	57 : 43	29	79
3	**1c**	3-$MeOC_6H_4$	Ph	74 : 26	**2c**	18	73	68 : 32	24	69
4	**1d**	4-$MeOC_6H_4$	Ph	54 : 46	**2d**	33	54	63 : 37	17	39
5	**1e**	4-MeC_6H_4	Ph	78 : 22	**2e**	15	51	46 : 54	38	55
6	**1f**	4-MeC_6H_4	4'-$MeOC_6H_4$	55 : 45	**2f**	30	46	47 : 53	42	27
7	**1g**	4-FC_6H_4	Ph	75 : 25	**2g**	18	34	71 : 29	13	39

a) Ratio of **1:2** determined by ^{1}H NMR analysis of the crude product, no sulfone produced.

b) Yield of **2** after purification by column chromatography.

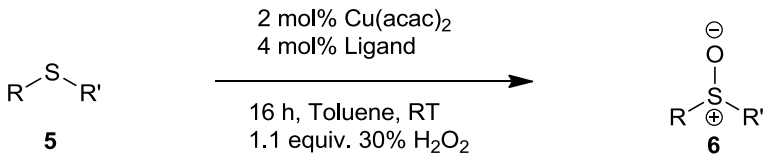
c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H); absolute configuration determined by comparison of specific rotation values for **2a**, **2e** to known literature values; for **2b**, **2c**, **2d, 2f, 2g** proposed configuration based on HPLC elution order and the direction of the specific rotations.

d) Results obtained by Kelly *et al.*[19]

We next examined the influence of steric and electronic effects on the efficiency and enantioselectivity of the oxidation. Since Schiff base ligands **3** and **4** had produced the best results in preliminary studies, these used in this investigation as shown in **Table 2**. The results indicate that the steric effect (Table 2, Entries 5 and 9) of the R′ substituent has a much stronger influence on the enantioselectivity of the oxidation than the electronic effect (Table 2, Entries 3 and 7). There is a direct trend between the size of R′ and the enantioselectivity of the oxidation for example substitution of a methyl group with an ethyl group in the R′ position results in a large increase in enantioselectivity (22% to 40% ee, Table 2, Entries 2 and 4). A similar increase in enantioselectivity is observed on replacing an isobutyl with a neopentyl group in the R′ position (Table 2, Entries 12 and 13). The oxidation of 2-naphthylmethyl phenyl sulfide produced the corresponding sulfoxide in 93% ee, the highest to date in copper-catalyzed asymmetric sulfide oxidation. We have previously shown that carrying out copper-catalyzed oxidations in the presence of NMO results in an improvement in the yield of sulfoxide.[19] Thus, the above experiments were repeated using NMO as an additive and the results are shown in **Table 2**. We found that the addition of NMO (2.5 mol%) resulted in an improvement in yield in nearly all cases. The poor yields obtained were attributed to product inhibition of the oxidation, presumably through complexation of the sulfoxide to the copper catalyst. It is believed that NMO co-ordinates to the copper catalyst, removing sulfoxide which results in an improvement in yield. Entries 10 and 12 demonstrate that the presence of a CH_2 group between the sulfur and the isopropyl

group results in improved enantioselection. However, the opposite trend was observed when the oxidation was carried out in the presence of NMO.

Table 2. Influence of Steric and Electronic Effects



Entry	Sulfide 5	R	R′	Sulfoxide 6	Ligand	No NMO			NMO[d]		
						5 : 6[a]	% Yield[b]	%ee (*R*)[c]	5:6[a,d]	% Yield[b]	% ee (*R*)[c,d]
1	**5a**	Ph	-$CH_2C_6H_4$	**6a**	**3**	79 : 21	17	58	61 : 39	30	60
2	**5b**	4-MeC_6H_4	Me	**6b**	**3**	79 : 21	15	22	65 : 35	37	21
3	**5c**	4-MeC_6H_4	-$CH_2C{\equiv}CH$	**6c**	**3**	84 : 16	8	3	83 : 17	10	6
4	**5d**	Ph	Et	**6d**	**3**	80 : 20	12	40	60 : 40	39	49
5	**5e**	Ph	-CH_2-cyclohexyl	**6e**	**3**	86 : 14	23	54	78 : 22	20	60
6	**5b**	4-MeC_6H_4	Me	**6b**	**4**	81 : 19	11	19	64 : 36	36	16
7	**5c**	4-MeC_6H_4	-$CH_2C{\equiv}CH$	**6c**	**4**	81 : 19	4	5	78 : 22	14	4
8	**5d**	Ph	Et	**6d**	**4**	72 : 28	22	46	59 : 41	40	53
9	**5e**	Ph	-CH_2-cyclohexyl	**6e**	**4**	70 : 30	19	57	71 : 29	24	63
10	**5f**	Ph	*i*-Pr	**6f**	**4**	72 : 28	19	50	69 : 31	26	64
11	**5g**	Ph	-$CH_2CH(CH_3)_2$	**6g**	**3**	82 : 18	13	51	78 : 22	17	56
12	**5g**	Ph	-$CH_2CH(CH_3)_2$	**6g**	**4**	71 : 29	15	61	76 : 24	18	61
13	**5h**	Ph	-$CH_2C(CH_3)_3$	**6h**	**4**	80 : 20	15	71	72 : 28	28	71

14	**5i**	Ph	-CH_2-2′-naphthyl	**6i**	**4**	73 : 27	23	93	45 : 55	30	93

a) Ratio of **5:6** determined by ^{1}H NMR analysis of the crude product, no sulfone produced.

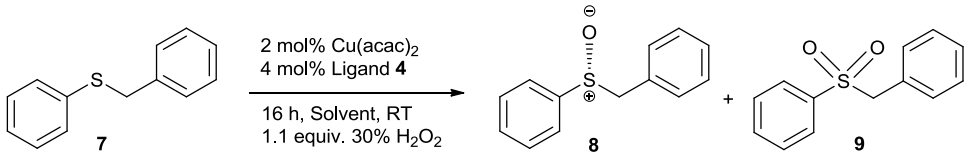
b) Yield of **6** after purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H); absolute configuration determined by comparison of specific rotation values for **6a**, **6b**, **6d**, **6e**, **6f**, **6g** to known literature values; for **6c**, **6h**, **6i** proposed configuration based on HPLC elution order and direction of specific rotations.

d) Results obtained when oxidation was carried out in the presence of 2.5 mol% NMO.

The results of the NMO study indicated that the use of more polar solvents or solvent mixtures may overcome product inhibition by co-ordinating to the copper catalyst. Katsuki reported an enhancement in the enantioselectivity of the vanadium Schiff base-catalyzed oxidation of thioanisole in the presence of a small amount of methanol.[20] An initial solvent study indicated that low polarity solvents such as toluene, benzene and CCl_4 produced the best results in terms of enantioselectivity as we had described previously (**Table 3**).[19]

Table 3. Investigation of Solvent



Entry	**Solvent**	**7 : 8 : 9**[a]	**Yield, 8 (%)**[b]	**% ee (*R*)**[c]
1	Ether	85 : 15 : 0	8	10
2	Dioxane	69 : 31 : 0	25	1
3	Toluene	79 : 21 : 0	17	58

4	CCl_4	65 : 35 : 0	27	61
5	Benzene	66 : 34: 0	26	69
6	Hexane	100 : 0 : 0	0	-
7	MeOH	40 : 60 : 0	50	24
8	MeOH[d]	19 : 81 : 0	73	29
9	50:50 toluene : MeOH	47 : 53 : 0	48	47
10	75:25 toluene : MeOH	46 : 54 : 0	47	47
11	90:10 toluene : MeOH	42 : 58 : trace	52	49
12	95:5 toluene : MeOH	48 : 52 : 0	45	46
13	90:10 hexane : MeOH	3 : 96 : 1	87	80
14	90:10 hexane : EtOH	1 : 98 : 1	90	76
15	90:10 cyclohexane : MeOH	8 : 91 : 1	85	79
16	90:10 hexane : IPA	7 : 92 : 1	83	1
17	90:10 CCl_4 : MeOH	21 : 76 : 3	70	62
18	90:10 CCl_4 : MeOH[d]	9 : 89 : 2	82	63
19	90:10 hexane : benzyl alcohol	4 : 94 : 2	87	7
20	90:10 hexane : *t*-BuOH	45 : 55 : trace	46	4
21	90:10 hexane : 2-butanol	57 : 43 : 0	38	8

a) Ratio of **7:8:9** determined by ^{1}H NMR analysis of the crude product.

b) Yield of **8** after purification by column chromatography.

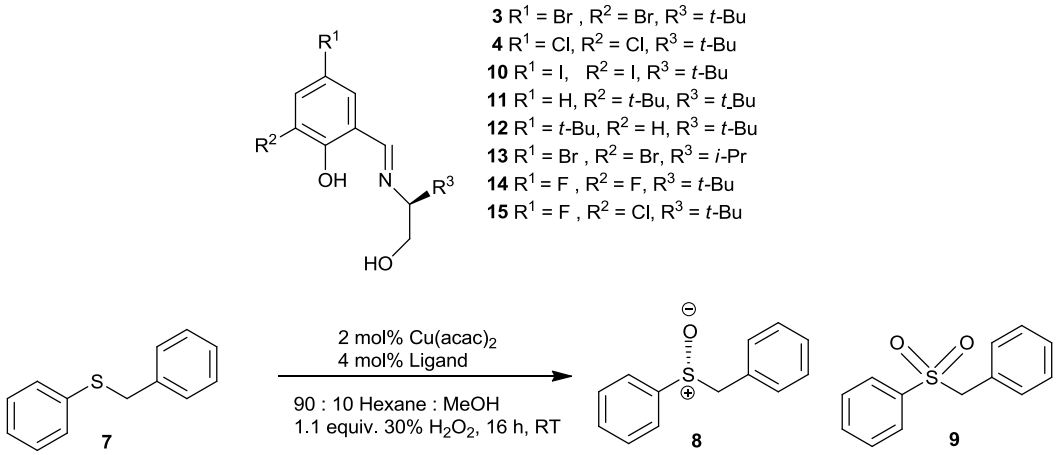
c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H); Absolute configuration determined by comparison of rotation values to literature values.

d) Oxidation was carried out in the presence of 2.5 mol% NMO.

Depending on the solvent employed the oxidation system was either monophasic or biphasic (**Table 3**). When the oxidation was carried out in methanol there was a large increase in yield but a decrease in enantioselectivity (Table 3, Entry 7) in comparison to the low polarity solvents. There was no sulfoxide produced when the oxidation was carried out in hexane (Table 3, Entry 6). Carrying out the oxidation in a mixed solvent system of toluene-methanol resulted in improved yield but with a reduced enantioselectivity (Table 3, Entries 9-12). However, using a 90:10 hexane-methanol solvent mixture produced benzyl phenyl sulfoxide in excellent yield and good enantioselectivity (Table 3, Entry 13). Similar results were achieved using solvent mixtures of hexane and ethanol, and cyclohexane and methanol (Table 3, Entries 14 and 15). Interestingly, the use of a mixture of hexane and the bulky alcohol IPA afforded practically racemic sulfoxide (Table 3, Entry 16). The use of hexane-methanol (partially miscible) and hexane-ethanol (miscible) solvent mixtures afforded sulfoxide in almost identical yield and enantioselectivity (Table 3, Entries 13 and 14). The dramatic improvements in yields using solvent mixtures of methanol is further evidence for sulfoxide inhibition. Presumably, methanol can co-ordinate to the copper catalyst, thereby displacing the sulfoxide, which results in improved yields.

An extensive ligand study was then undertaken in an attempt to find the optimum ligand for this system (**Table 4**). The results indicate that ligands **3**, **4** and **15** perform much better than the other Schiff bases in the oxidation of benzyl phenyl sulfide. Ligand **4** performed the best producing the sulfoxide in 90% yield and 79% ee. Replacement of the *tert*-butyl with an isopropyl in the R^3 position of the ligand results in a significant reduction in yield and enantioselectivity (Table 4, Entries 1 and 6). This indicates that the steric bulk at the R^3 position is crucial to maintain the enantioselectivity of the oxidation. Interestingly, the diiodo and difluoro ligands **10** and **14** perform poorly both in terms of yield and enantioselectivity (Table 4, Entries 3 and 7).

Table 4. Investigation of Effect of Ligand Structure



Entry	Ligand	7 : 8 : 9[a]	Yield, 8 (%)[b]	% ee (*R*)[c]
1	**3**	1 : 97 : 2	86	66
2	**4**	1 : 98 : 1	90	79
3	**10**	68 : 32 : 0	28	3
4	**11**	73 : 27 : 0	24	3
5	**12**	74 : 36 : 0	39	2
6	**13**	50 : 50 : 0	44	6
7	**14**	45 : 55 : trace	47	37
8	**15**	3 : 96 : 1	87	58

a) Ratio of **7:8:9** determined by ^{1}H NMR analysis of the crude product.

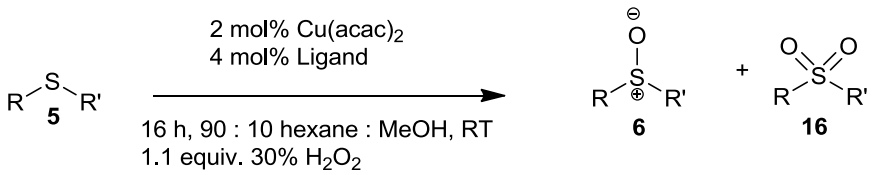
b) Yield of **8** after purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H); Absolute configuration determined by comparison of rotation values to literature values.

Having established the optimum ligand (ligand **4**) and solvent system (90:10 hexane:methanol), these conditions were then used in the asymmetric oxidation of a range of aryl benzyl and aryl

alkyl sulfides as shown in **Table 5**. Excellent yields and modest to good enantiopurities were obtained, for example benzyl phenyl sulfoxide was obtained in 90% yield and 79% ee (Table 5, Entry 1). Over-oxidation to sulfone is either entirely absent or very minimal (no more than 2%) despite the dramatic improvements in oxidation efficiency using the optimised conditions. The formation of significant amounts of sulfone would have a detrimental effect on sulfoxide yield and would lead to difficulties in isolation of the desired product. A relationship between the steric bulk of the R′ substituent of the sulfide and the enantioselectivity of the oxidation was observed again. As R′ is changed from a methyl group to an ethyl group and then to an isopropyl and neopentyl group there is an increase in enantioselectivity (Table 5, Entries 3-7). Interestingly, in **table 5** it is evident that with the different substrates, in some instances the enantiopurity achieved was higher with ligand **4**, while in others it was higher with ligand **15**, although differences are relatively modest in most cases. Thus, the optimum ligand appears to be substrate specific. Sulfide **5l** did not fully dissolve in 1 mL of 90:10 hexane:methanol and, as a result, an increased amount of solvent was used. This may have resulted in reduced enantioselectivity, as previous work in the group had demonstrated that increasing dilution had a detrimental effect on the enantioselectivity of the oxidation.[21] Sulfide **5i** was insoluble in 9:1 hexane:methanol and hence no oxidation was observed.

Table 5. Asymmetric oxidation of sulfides using optimised conditions



Entry	5	R	R′	Ligand	5 : 6 : 16[a]	6	% Yield[b]	% ee (*R*)[c]

1	**5a**	Ph	$-CH_2C_6H_4$	**4**	1 : 98 : 1	**6a**	90	79
2	**5a**	Ph	$-CH_2C_6H_4$	**15**	2 : 98 : 0	**6a**	91	58
3	**5b**	$4\text{-}MeC_6H_4$	Me	**4**	4 : 96 : trace	**6b**	90	23
4	**5d**	Ph	Et	**4**	2 : 98 : trace	**6d**	92	44
5	**5f**	Ph	i-Pr	**4**	19 : 81 : trace	**6f**	74	60
6	**5g**	Ph	$-CH_2CH(CH_3)_2$	**4**	10 : 90 : trace	**6g**	82	48
7	**5h**	Ph	$-CH_2C(CH_3)_3$	**4**	15 : 85 : 0	**6h**	79	71
8	**5i**	Ph	$-CH_2$-2′-naphthyl	**4**	100 : 0 : 0	**6i**	-	-
9	**5j**	$4\text{-}MeC_6H_4$	$-CH_2C_6H_4$	**4**	2 : 97 : 1	**6j**	91	81
10	**5j**	$4\text{-}MeC_6H_4$	$-CH_2C_6H_4$	**15**	4 : 96 : 0	**6j**	90	84
11	**5k**	$4\text{-}MeC_6H_4$	$4\text{-}MeOC_6H_4$	**4**	2 : 97 : 1	**6k**	90	47
12	**5l**	$2\text{-}MeOC_6H_4$	$-CH_2C_6H_4$	**4**	8 : 92 : trace	**6l**	85	29
13	**5m**	$3\text{-}MeOC_6H_4$	$-CH_2C_6H_4$	**4**	46 : 54 : 0	**6m**	47	21
14	**5n**	$2\text{-}MeC_6H_4$	$-CH_2C_6H_4$	**4**	1 : 98 : 1	**6n**	91	64
15	**5n**	$2\text{-}MeC_6H_4$	$-CH_2C_6H_4$	**15**	6 : 94 : 0	**6n**	88	71
16	**5o**	$3\text{-}MeC_6H_4$	$-CH_2C_6H_4$	**4**	11 : 89 : 0	**6o**	84	54
17	**5o**	$3\text{-}MeC_6H_4$	$-CH_2C_6H_4$	**15**	10 : 88 : 2	**6o**	83	69
18	**5p**	Ph	$-CH_2$- p-Tol	**4**	1 : 97 : 2	**6p**	89	55
19	**5q**	Ph	$-CH_2$-m-Tol	**4**	7 : 92 : 1	**6q**	83	50
20	**5q**	Ph	$-CH_2$-m-Tol	**15**	4 : 95 : 1	**6q**	90	46
21	**5r**	Ph	$-CH_2$-o-Tol	**4**	12 : 85 : 2	**6r**	80	47[d]

a) Ratio of **5:6:16** determined by ^1H NMR analysis of the crude product.

b) Yield of **6** after purification by column chromatography.

c) Determined by HPLC analysis on chiral column (Daicel Chiracel OD-H for **6a-6q**, Chiracel As-H for **6r**); Absolute configuration determined by comparison of rotation values for **6a**, **6b**, **6d**, **6f**, **6g** to known literature values; for **6h**, **6k**,

6l, **6m**, **6n**, **6o**, **6p**, **6q** proposed configuration based on HPLC elution order and direction of specific rotations.

d) Configuration of **6r** not determined.

Conclusion

Efficient enantioselective sulfide oxidation is effected using copper-Schiff base catalysis. The procedure employed is clean, inexpensive and is not air sensitive, utilising aqueous hydrogen peroxide as the oxidant. The use of copper as the transition metal offers significant safety benefits over other established methods, employing other toxic metals. Another important feature of this system is the absence or very limited amount of over-oxidation to produce sulfones. Use of a hexane-methanol solvent mixture overcomes catalyst inhibition by the sulfoxide and thereby leads to excellent yields. Steric effects are significant in determining the enantioselectivity of the oxidation.

Experimental Section

General: Sulfides **5a**, **5b**, **5d** were commercially available. For thin-layer chromatography (TLC), silica gel plates were used and compounds were visualised using UV. Solvents were distilled prior to use. ^{1}H (300 MHz), ^{1}H (400 MHz) and ^{13}C NMR (75 MHz) were recorded with spectrometers at 20 °C using $CDCl_3$ as solvent. Chemical shifts are given in ppm relative to TMS as the internal standard. Coupling constants (*J*) are reported in Hz. Chiral HPLC was performed using Chiralpak OD-H, OJ-H and AS-H columns; eluting with n-hexane and 2-propanol. Specific rotations were recorded at 20 °C in the solvents indicated. The Sodium D line (589 nm) was used unless otherwise indicated. Samples were analysed in a 1 mL dual-walled thermostatted glass cell of pathlength 10 cm. Sample temperature control was maintained using an immersion circulator. Absolute configurations were assigned by comparison of the specific rotations with the literature data for **6a**, **6b, 6d-g**. Notably, the direction of the specific rotations were in complete agreement with literature values, however

the magnitudes varied somewhat. Racemic sulfoxides were prepared by treatment of the sulfide with 0.6 equivalents of Oxone® in acetone at 0 °C. All reactions are carried out at room temperature unless otherwise indicated. Sulfoxides **6a**[22], **6b**[23], **6c**[24], **6d**[25], **6f**[26], **6g**[27], **6j**[28] **6k**[29], **6l**[19], **6m**[19], **6p**[30] have been reported in enantioenriched form. Sulfoxides **6e**[31], **6n**[32], **6q**[33], **6r**[34] have been reported in racemic form only. Sulfoxides **6h**, **6i**, **6o** have not been previously reported.

Experimental procedure for asymmetric sulfide oxidation

Copper(II) acetylacetonate (5.2 mg, 2.0 mol%) was added to a round bottomed flask containing Schiff base ligand **4** (11.6 mg, 4.0 mol%), and 9:1 hexane : MeOH (1 mL). The resulting solution was stirred at room temperature for 5 min, and then a solution of sulfide (1 mmol) in 9:1 hexane : MeOH (1 mL) was added. After 5 min stirring at r.t. H_2O_2 (0.130 mL, 30%, 1.1 mmol) was added in one portion, dropwise to the solution. The reaction mixture was stirred at room temperature for a further 16 h. Then H_2O (1 mL) and CH_2Cl_2 (1 mL) were added and the phases separated; the organic layer was washed with water (2 x 5 mL) and brine (5 mL), dried and concentrated under reduced pressure to give the crude product. The ratio of sulfide-sulfoxide-sulfone in the crude product was determined by ^{1}H NMR. The product was purified by column chromatography on silica gel (6:4 hexane:ethyl acetate). Schiff base ligand can be recovered after chromatography and can be re-used.

In experiments in which NMO was used (**Table 2**), NMO (2.5 mol%) was added 5 min after addition of the sulfide. The reaction mixture was then stirred for 5 min followed by addition of H_2O_2 (0.130 mL, 30%, 1.1 mmol).

(*R*)-(+)-Benzyl phenyl sulfoxide (6a, Table 5, Entry 1)[22]

Crude product contained a mixture of sulfide, sulfoxide and sulfone (1:98:1). Purification by chromatography afforded the product as a white solid (194 mg, 90%, 79% ee).

^{1}H NMR δ_H (300 MHz) 4.00 (1H, A of AB system, *J* 12.5 Hz), 4.10 (1H, B of AB system, *J* 12.5 Hz), 6.90–7.04 (2H, m), 7.19–7.32 (3H, m), 7.33–7.52 (5H, m); m.p. 125–126 °C (Lit. m.p. 127 °C)[30]; IR (KBr): v = 2961, 1455, 1442, 1084, 1033, 746 cm^{-1}; HPLC: t_R (*R*) = 17.1 min, t_R (*S*) = 21.3 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 146.5° (c 1.0, acetone) {ref.[22] $[\alpha]_D^{20}$ = - 169.8 (c 1.0, acetone) for (*S*) 79% ee}.

(*R*)-(+)-Methyl *p*-tolyl sulfoxide (6b, Table 5, Entry 3)[23]

Crude product contained a mixture of sulfide, sulfoxide and sulfone (4:96:trace). Purification by chromatography afforded the product as a clear oil (138 mg, 90%, 23% ee).

^{1}H NMR δ_H (400 MHz) 2.42 (3H, s), 2.71 (3H, s), 7.34 (2H, d, *J* 8.4 Hz), 7.54 (2H, d, *J* 8.4 Hz); HRMS (ESI): Exact mass calculated for $C_8H_{10}OS$ [$(M+H)^+$] 155.0531, Found 155.0526; HPLC: t_R (*R*) = 20.1 min, t_R (*S*) = 23.8 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (95:5); 20 °C]; $[\alpha]_D^{20}$ = + 43.6° (c 1.0, acetone) {ref.[23] $[\alpha]_D^{20}$ = + 150.4 (c 1.17, acetone) for (*R*) > 99 %ee}.

(*R*)-(+)-Ethyl phenyl sulfoxide (6d, Table 5, Entry 4)[25]

Crude product contained a mixture of sulfide, sulfoxide and sulfone (2:98:trace). Purification by chromatography afforded the product as a clear oil (142 mg, 92%, 44% ee).

^{1}H NMR δ_H (400 MHz) 1.20 (3H, t, *J* 3.5 Hz), 2.70–3.00 (2H, m), 7.46–7.57 (3H, m), 7.58–7.66 (2H, m); IR (film): v = 2935, 1479, 1444, 1087, 1021, 749 cm^{-1}; HRMS (ESI): Exact

mass calculated for $C_8H_{10}OS$ [$(M+H)^+$] 155.0531, Found 155.0532; HPLC: t_R (*R*) = 8.1 min, t_R (*S*) = 9.8 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; = + 96.1° (c 1.0, acetone) {ref.[25] $[\alpha]_D^{20}$ = + 185.6 (c 0.71, acetone) for (*R*) > 99 %ee}.

(*R*)-(+)-Isopropyl phenyl sulfoxide (6f, Table 5, Entry 5)[26]

Crude product contained a mixture of sulfide, sulfoxide and sulfone (19:81:trace). Purification by chromatography afforded the product as a clear oil (124 mg, 74%, 60% ee). ^1H NMR δ_H (400 MHz) 1.15 (3H, d, *J* 6.6 Hz), 1.23 (3H, d, *J* 6.6 Hz), 2.75–2.91 (1H, m), 7.44–7.62 (5H, m); ^{13}C NMR δ_C (75 MHz) 14.0, 15.9, 54.6, 125.0, 128.9, 131.0, 141.7; IR (KBr): v = 2970, 1464, 1444, 1088, 1023 cm^{-1}; HPLC: t_R (*R*) = 6.6 min, t_R (*S*) = 7.5 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 112.8 (c 1.0, $CHCl_3$).

(*R*)-(+)-Isobutyl phenyl sulfoxide (6g, Table 5, Entry 6)[27]

Crude product contained a mixture of sulfide, sulfoxide and sulfone (10:90:trace). Purification by chromatography afforded the product as a clear oil (149 mg, 82%, 48% ee). ^1H NMR δ_H (400 MHz) 1.07 (3H, d, *J* 6.6 Hz), 1.17 (3H, d, *J* 6.6 Hz), 2.14–2.33 (1H, m), 2.45 (1H, A of ABX system, *J* 12.0 Hz and 4.8 Hz), 2.82 (1H, B of ABX system, *J* 12.0 Hz and 4.8 Hz), 7.43–7.58 (3H, m), 7.59–7.69 (2H, m); ^{13}C NMR δ_C (75 MHz) 21.7, 22.8, 24.2, 67.6, 123.9, 129.3, 130.9, 144.7; HRMS (ESI): Exact mass calculated for $C_{10}H_{14}SO$ [$(M+H)^+$] 183.0844, Found 183.0850; IR (KBr): v = 2960, 1465, 1444, 1090, 1038, 750 cm^{-1}; HPLC: t_R (*R*) = 5.9 min, t_R (*S*) = 6.7 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 129.0 (c 1.0, $CHCl_3$).

(*R*)-(+)-Neopentyl phenyl sulfoxide (6h, Table 5, Entry 7)

Crude product contained a mixture of sulfide and sulfoxide (15:85). Purification by chromatography afforded the product as a clear oil (155 mg, 79%, 71% ee).

^{1}H NMR δ_H (300 MHz) 1.21 (9H, s), 2.54 (1H, A of AB system, *J* 13.5 Hz), 2.81 (1H, B of AB system, *J* 13.8 Hz), 7.43–7.56 (3H, m), 7.59–7.66 (2H, m); ^{13}C NMR δ_C (75 MHz) 29.8, 32.0, 73.9, 123.8, 129.2, 130.7, 145.6; (Found C, 67.10; H, 8.37; S, 16.29; $C_{11}H_{16}OS$ requires C, 67.30; H, 8.22; S 16.33); IR (film): v = 2958, 1474, 1448, 1084, 1045, 709 cm^{-1}; HPLC: t_R (*R*) = 6.6 min, t_R (*S*) = 7.6 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = +87.9 (c 1.0, $CHCl_3$).

(*R*)-(+)-Benzyl *p*-tolyl sulfoxide (6j, Table 5, Entry 8)[28]

Crude product contained a mixture of sulfide, sulfoxide and sulfone (2:97:1). Purification by chromatography afforded the product as a white solid (209 mg, 91%, 81% ee).

^{1}H NMR δ_H (300 MHz) 2.40 (3H, s), 3.97 (1H, A of AB system, *J* 12.6 Hz), 4.09 (1H, B of AB system, *J* 12.6 Hz), 7.00 (2H, dd, *J* 7.5 Hz and *J* 1.5 Hz), 7.17–7.37 (7H, m); HRMS (ESI): Exact mass calculated for $C_{14}H_{14}SO$ [$(M+H)^+$] 231.0844, Found 231.0839; IR (KBr): v = 2912, 1494, 1456, 1083, 1014, 768 cm^{-1}; HPLC: t_R (*R*) = 16.3 min, t_R (*S*) = 19.9 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 106.0 (c 1.0, acetone), {ref.[30] $[\alpha]_D^{20}$ = - 254.0 (c 0.7, acetone) for (*S*) >99% ee}.

(*R*)-(+)-4-Methoxybenzyl 4'-methylphenyl sulfoxide (6k, Table 5, Entry 10)[29]

Crude product contained a mixture of sulfide, sulfoxide and sulfone (2:97:1). Purification by chromatography afforded the product as a white solid (234 mg, 90%, 47% ee).

m.p. 123–124 ^{o}C; ^{1}H NMR δ_H (300 MHz) 2.40 (3H, s), 3.79 (3H, s), 3.93 (1H, A of AB system, *J* 12.6 Hz), 4.03 (1H, B of AB system, *J* 12.6 Hz), 6.75–6.81 (2H, m), 6.87–6.94 (2H, m), 7.19–7.32 (4H, m); ^{13}C NMR δ_C (75.5 MHz) 21.5, 55.3, 63.0, 113.9, 121.2, 124.5, 129.6,

131.6, 139.6, 141.5, 159.6; IR (KBr): v = 2961, 1610, 1514, 1036, 809 cm^{-1}; HRMS (ESI): Exact mass calculated for $C_{15}H_{16}SO_2$ [$(M+H)^+$] 261.0949, Found 261.0947; HPLC: t_R (*R*) = 12.7 min, t_R (*S*) = 15.9 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 37.9 (c 1.0, $CHCl_3$), {ref.[29] $[\alpha]_D^{20}$ = - 87 (c 0.2, $CHCl_3$) for (*S*) >99% ee}.

(*R*)-(+)-Benzyl 2-methoxyphenyl sulfoxide (6l, Table 5, Entry 11)[19]

Crude product contained a mixture of sulfide, sulfoxide and sulfone (8:92:trace). Purification by chromatography afforded the product as a white solid (209 mg, 85%, 29% ee).

m.p. 31-33 °C; ^{1}H NMR δ_H (300 MHz) 3.87 (3H, s), 3.98 (1H, A of AB system, *J* 12.0 Hz), 4.24 (1H, B of AB system, *J* 12.0 Hz), 6.90 (1H, d, J 7.8 Hz), 6.99–7.11 (3H, m), 7.17–7.30 (3H, m), 7.36-7.49 (2H, m); ^{13}C NMR δ_C (75.5 MHz) 55.8, 59.7, 110.3, 121.5, 125.8, 127.9, 128.2, 130.2, 130.3, 130.4, 132.0, 155.1; IR (KBr): v = 2959, 1596, 1496, 1086, 1032, 697 cm^{-1}; HRMS (ESI): Exact mass calculated for $C_{14}H_{14}SO_2$ [$(M+H)^+$] 247.0793, Found 247.0783; HPLC: t_R (*R*) = 16.2 min, t_R (*S*) = 18.6 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 60.3 (c 1.0, acetone), {ref.[19] $[\alpha]_D^{20}$ = + 351 (c 0.32, $CHCl_3$) for (*R*) = 81% ee}.

(*R*)-(+)-Benzyl 3-methoxyphenyl sulfoxide (6m, Table 5, Entry 12)[19]

Crude product contained a mixture of sulfide and sulfoxide (46:54). Purification by chromatography afforded the product as a clear oil (115 mg, 47%, 21% ee).

^{1}H NMR δ_H (300 MHz) 3.72 (3H, s), 4.00 (1H, A of AB system, *J* 12.5 Hz), 4.07 (1H, B of AB system, *J* 12.5 Hz) 6.87–7.03 (5H, m), 7.20–7.37 (4H, m); ^{13}C NMR δ_C (75 MHz) 55.5, 63.5, 108.4, 116.5, 118.1, 128.3, 128.5, 129.1, 129.8, 130.4, 144.0, 160.1; IR (KBr): v = 2907, 1594, 1481, 1248, 1031, 697 cm^{-1}; HRMS (ESI): Exact mass calculated for $C_{14}H_{14}SO_2$ [$(M+H)^+$] 247.0793, Found 247.0789; HPLC: t_R (*R*) = 12.2 min, t_R (*S*) = 14.0 min [Chiracel

OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 68.5 (c 1.0, acetone), {ref.[19] $[\alpha]_D^{20}$ = + 73.5 (c 0.17, acetone) for (*R*) = 69% ee}.

(*R*)-(+)-Benzyl *o*-tolyl sulfoxide (6n, Table 5, Entry 13)[32]

Crude product contained a mixture of sulfide, sulfoxide and sulfone (1:98:1). Purification by chromatography afforded the product as a white solid (209 mg, 91%, 64% ee).

m.p. 69-71 °C; ^{1}H NMR δ_H (300 MHz) 2.06 (3H, s), 4.00 (1H, A of AB system, *J* 12.3 Hz), 4.10 (1H, B of AB system, *J* 12.6 Hz), 6.97 (2H, dd, *J* 7.8 Hz and *J* 1.3 Hz), 7.06–7.16 (1H, m), 7.19–7.41 (5H, m), 7.67–7.78 (1H, m); ^{13}C NMR δ_C (75.5 MHz) 18.0, 62.3, 124.2, 127.1, 128.3, 128.5, 129.3, 130.2, 130.4, 130.9, 135.6, 141.3; ESI-HRMS: calcd for $C_{14}H_{14}OS$ $[(M+H)^+]$: 231.0844; found: 231.0855; (Found C, 73.06; H, 6.12; S, 14.20; $C_{14}H_{14}OS$ requires C, 73.01; H, 6.13; S 13.92); HPLC: t_R (*R*) = 11.2 min, t_R (*S*) = 13.2 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = +18.5 (c 1.0, $CHCl_3$).

(*R*)-(+)-Benzyl *m*-tolyl sulfoxide (6o, Table 5, Entry 15)

Crude product contained a mixture of sulfide, sulfoxide and sulfone (11:89:0). Purification by chromatography afforded the product as a clear oil (193 mg, 84%, 62% ee).

^{1}H NMR δ_H (300 MHz) 2.34 (3H, s) 3.97 (1H, A of AB system, *J* 12.6 Hz), 4.08 (1H, B of AB system, *J* 12.3 Hz), 7.00 (2H, dd, *J* 7.8 Hz and *J* 2.1 Hz), 7.10–7.34 (7H, m); ^{13}C NMR δ_C (75.5 MHz) 21.3, 63.7, 121.5, 124.7, 128.2, 128.4, 128.6, 129.3, 130.4, 131.9, 139.1, 142.7; IR (film): v = 2919, 1454, 1038, 766 cm^{-1}; ESI-HRMS: calcd for $C_{14}H_{14}OS$ $[(M+H)^+]$: 231.0844; found: 231.0840; (Found C, 72.96; H, 6.28; S, 14.0; $C_{14}H_{14}OS$ requires C, 73.01; H, 6.13; S 13.92); HPLC: t_R (*R*) = 15.1 min, t_R (*S*) = 18.9 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 48.6 (c 1.0, $CHCl_3$).

(*R*)-(+)-4-Methylbenzyl phenyl sulfoxide (6p, Table 5, Entry 17)[30]

Crude product contained a mixture of sulfide, sulfoxide and sulfone (1:97:2). Purification by chromatography afforded the product as a white solid (205 mg, 89%, 55% ee).

^{1}H NMR δ_H (300 MHz) 2.32 (3H, s), 3.96 (1H, A of AB system, *J* 12.6 Hz), 4.07 (1H, B of AB system, *J* 12.6 Hz), 6.87 (2H, d, *J* 7.8 Hz), 7.06 (2H, d, *J* 7.8 Hz), 7.36–7.51 (5H, m); IR (KBr): v = 2959, 1512, 1442, 1043, 687 cm^{-1}; (Found C, 73.12; H, 6.33; S, 13.94; $C_{14}H_{14}OS$ requires C, 73.01; H, 6.13; S 13.92); HPLC: t_R (*R*) = 12.7 min, t_R (*S*) = 14.3 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 42.2 (c 1.0, $CHCl_3$).

(*R*)-(+)-3-Methylbenzyl phenyl sulfoxide (6q, Table 5, Entry 18)[33]

Crude product contained a mixture of sulfide, sulfoxide and sulfone (7:92:1). Purification by chromatography afforded the product as a clear oil (191 mg, 83%, 50% ee).

^{1}H NMR δ_H (300 MHz) 2.27 (3H, s), 3.94 (1H, A of AB system, *J* 12.3 Hz), 4.08 (1H, B of AB system, *J* 12.6 Hz), 6.80 (2H, d, *J* 5.7 Hz), 7.06–7.19 (2H, m), 7.36–7.51 (5H, m); ^{13}C NMR δ_C (75 MHz) 21.3, 63.9, 124.5, 127.4, 128.4, 128.8, 129.0, 129.1, 131.1, 131.2, 138.2, 143.0; IR (KBr): v = 2967, 1604, 1444, 1040, 736 cm^{-1}; ESI-HRMS: calcd for $C_{14}H_{14}OS$ [$(M+H)^+$]: 231.0844; found: 231.0846; (Found C, 73.42; H, 6.13; S, 13.97; $C_{14}H_{14}OS$ requires C, 73.01; H, 6.13; S, 13.92); HPLC: t_R (*R*) = 16.2 min, t_R (*S*) = 18.7 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = + 36.8 (c 1.0, $CHCl_3$).

(-)-2-Methylbenzyl phenyl sulfoxide (6r, Table 5, Entry 20)[34]

Crude product contained a mixture of sulfide, sulfoxide and sulfone (12:85:2). Purification by chromatography afforded the product as a clear oil (184 mg, 80%, 47% ee).

^{1}H NMR δ_H (300 MHz) 2.18 (3H, s), 3.99 (1H, A of AB system, *J* 12.3 Hz), 4.27 (1H, B of AB system, *J* 12.3 Hz), 6.85 (1H, d, *J* 6.6 Hz), 7.02–7.25 (3H, m), 7.35–7.52 (5H, m); IR

(KBr): v = 2926, 1443, 1094, 1030, 750 cm^{-1}; (Found C, 73.19; H, 6.02; S, 13.85; $C_{14}H_{14}OS$ requires C, 73.01; H, 6.13; S, 13.92); HPLC: t_R = 67.1 min, t_R = 85.3 min [Chiracel AS-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = -16.5 (c 1.0, $CHCl_3$).

(*R*)-(+)-4-Methylphenyl prop-2'-ynyl sulfoxide (6c, Table 2, Entry 7)[24]

Crude product contained a mixture of sulfide and sulfoxide (78:22). Purification by chromatography afforded the product as a white solid (23 mg, 14%, 4% ee).

^1H NMR δ_H (300 MHz) 2.33 (1H, t, *J* 2.7 Hz), 2.44 (3H, s), 3.59 (1H, A of ABX system, J_{AB} 14.2 Hz, J_{AX} 2.6 Hz), 3.67 (1H, B of ABX system, J_{AB} 14.4 Hz, J_{BX} 2.6 Hz) 7.35 (2H, d, *J* 8.3 Hz), 7.61 (2H, d, *J* 8.2 Hz); HPLC: t_R (*R*) = 14.6 min, t_R (*S*) = 17.5 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = +5.2 (c 1.0, $CHCl_3$).

(*R*)-(+)-2-Naphthylmethyl phenyl sulfoxide (6i, Table 2, Entry 14)

Crude product contained a mixture of sulfide and sulfoxide (45:55). Purification by chromatography afforded the product as a white solid (80 mg, 30%, 93% ee).

m.p. 85-87 °C, ^1H NMR δ_H (400 MHz) 4.15 (1H, A of AB system, *J* 12.4 Hz), 4.26 (1H, B of AB system, *J* 12.4 Hz), 7.08 (1H, dd, *J* 8.6 Hz and *J* 1.6 Hz), 7.31–7.53 (8H, m), 7.66–7.85 (3H, m); ^{13}C NMR δ_C (75 MHz) 64.0, 124.5, 126.3, 126.4, 126.7, 127.7, 127.75, 127.9, 128.1, 128.9, 129.8, 131.2, 132.9, 133.1, 142.9; (Found C, 76.43; H, 5.58; S, 12.10; $C_{17}H_{14}OS$ requires C, 76.66; H, 5.30; S, 12.04) HPLC: t_R (*R*) = 32.1 min, t_R (*S*) = 40.6 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = +75.4 (c 1.0, $CHCl_3$).

(*R*)-(+)-Benzyl 4-methoxyphenyl sulfoxide (2d, Table 1, Entry 4)[19, 35]

Crude product contained a mixture of sulfide and sulfoxide (54:46). Purification by chromatography afforded the product as a white solid (81 mg, 33%, 54% ee).

^{1}H NMR δ_H (300 MHz) 3.84 (3H, s), 3.95 (1H, A of AB system, *J* 12.0 Hz), 4.11 (1H, B of AB system, *J* 12.0 Hz), 6.89–7.02 (4H, m), 7.20-7.33 (5H, m), δ_C (75.5 MHz) 55.5, 63.8, 114.4, 126.4, 128.2, 128.5, 129.3, 130.4, 133.6, 162.0; HPLC: t_R (*R*) = 15.5 min, t_R (*S*) = 18.4 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 40 °C]; $[\alpha]_D^{20}$ = +48.2 (c 1.0, acetone), {ref.[19] $[\alpha]_D^{20}$ = + 31.9 (c 0.28, acetone) for (*R*) = 44% ee}.

(*R*)-(+)-Cyclohexylmethyl phenyl sulfoxide (6e, Table 2, Entry 5)[31]

Crude product contained a mixture of sulfide and sulfoxide (71:29). Purification by chromatography afforded the product as a clear oil that solidified to form a white solid (44 mg, 20%, 60% ee).

^{1}H NMR δ_H (300 MHz) 1.01–1.41 (5H, m), 1.60–1.83 (4H, m), 1.89–2.08 (1H, m), 2.09–2.17 (1H, m) 2.45–2.52 (1H, A of ABX system, J 12.9 Hz and 9.0 Hz), 2.76–2.82 (1H, B of ABX system, J 12.9 Hz and 4.8 Hz), 7.42–7.72 (5H, m); IR (KBr): v = 2920, 1443, 1034, 752 cm^{-1}; HPLC: t_R (*R*) = 17.3 min, t_R (*S*) = 20.3 min [Chiracel OD-H; flow rate 1mL min^{-1}; hexane-2-PrOH (90:10); 20 °C]; $[\alpha]_D^{20}$ = +47.8 (c 1.0, $CHCl_3$).

Experimental procedure for Schiff base ligand synthesis

Commercially available salicylaldehyde (1 mmol) and sodium sulfate (0.5 g) were added to a solution of (*S*)-*tert*-leucinol (1 mmol) or *L*-valinol (1 mmol) in ethanol (20 mL). The reaction mixture was stirred under reflux for 16 h, filtered and concentrated under reduced pressure. The reaction mixture was then dissolved in dichloromethane (10 mL) and washed with water (3 × 10 mL) and brine (15 mL). The organic layer was dried and concentrated under reduced pressure to leave the crude product which was purified by column chromatography on silica gel (8 : 2 hexane : ethyl acetate) to yield the pure ligand.

(*S*)-2-(*N*-3',5'-Dibromosalicylidene)-amino-3,3-dimethyl-1-butanol (3, Table 4)[36, 37]

Yellow solid, 73%, m.p. 160-162 ^{o}C; ^{1}H NMR δ_H (300 MHz) 1.01 (9H, s), 3.10 (1H, dd, *J* 9.5 Hz and 2.4 Hz), 3.11 (1H, brs), 3.70 (1H, dd, *J* 11.2 Hz and 9.8 Hz), 3.98–4.08 (1H, brm), 7.35 (1H, d, *J* 2.5 Hz), 7.58 (1H, d, *J* 2.4 Hz), 8.12 (1H, s); ^{13}C NMR δ_C (75.5 MHz) 27.3, 33.4, 62.2, 79.2, 107.9, 114.8, 118.2, 133.8, 139.1, 162.9, 164.9; m/z (ESI) [$(M+H)^+$] 378; HRMS (ESI): Exact mass calculated for $C_{13}H_{17}{}^{79}Br_2NO_2$ [$(M+H)^+$] 377.9704, Found 377.9710; $[\alpha]_D^{20}$ = -16.1 (c 1.0, acetone).

(*S*)-2-(*N*-3',5'-Dichlorosalicylidene)-amino-3,3-dimethyl-1-butanol (4, Table 4)

Yellow solid, 72%, m.p. 153–156 ^{o}C; ^{1}H NMR δ_H (300 MHz) 1.02 (9H, s), 3.11 (1H, dd, *J* 9.5 Hz and 2.4 Hz), 3.69 (1H, dd, *J* 11.2 Hz and 9.8 Hz), 3.82–4.10 (1H, brs), 3.96–4.06 (1H, brm), 7.04 (1H, d, *J* 2.5 Hz), 7.27 (1H, d, *J* 2.4 Hz), 8.12 (1H, s); ^{13}C NMR δ_C (75.5 MHz) 26.9, 32.9, 61.7, 78.5, 116.9, 120.2, 124.5, 129.6, 133.4, 162.3, 164.8; m/z (ESI) [$(M+H)^+$] 290; HRMS (ESI): Exact mass calculated for $C_{13}H_{17}Cl_2NO_2$ [$(M+H)^+$] 290.0715, Found 290.0723; IR ν_{max}/cm^{-1} (KBr) 3322, 2971, 1645, 1502 1209, 1058; (Found: C, 54.07; H, 5.91; N, 4.64. $C_{13}H_{17}Cl_2NO_2$ Requires C, 53.81; H, 5.90; N, 4.64); $[\alpha]_D^{20}$ = -23.6 (c 1.0, acetone).

(*S*)-2-(*N*-3,5-Diiodosalicylidene)-amino-3,3-dimethyl-1-butanol (10, Table 4)[22, 36]

Yellow solid, 79%, m.p. 164–165 ^{o}C (Lit. m.p. 163-164)[22], ^{1}H NMR δ_H (300 MHz) 1.00 (9H, s), 2.53 (1H, brs), 3.08 (1H, dd, *J* 9.5 Hz and 2.5 Hz), 3.68 (1H, dd, *J* 11.1 Hz and 9.8 Hz), 3.93–4.07 (1H, brm), 7.51 (1H, d, *J* 2.1 Hz), 8.01 (1H, d, *J* 2.1 Hz), 8.10 (1H, s); IR ν_{max}/cm^{-1} (KBr) 3320, 2965, 1638, 1479, 1217, 1060; $[\alpha]_D^{20}$ = -18.5 (c 0.1, acetone), Lit.[22] $[\alpha]_D^{20}$ = -16.6 (c 1.0 for *S* in acetone).

(*S*)-2-(*N*-3'-*tert*-Butylsalicylidene)-amino-3,3-dimethyl-1-butanol (11, Table 4)[37]

Yellow oil, 88%, ^{1}H NMR δ_H (300 MHz) 0.99 (9H, s), 1.44 (9H, s), 2.93 (1H, dd, *J* 9.4 Hz and 2.7 Hz), 3.73 (1H, dd, *J* 11.0 Hz and 9.7 Hz), 3.90 (1H, dd, *J* 11.1 Hz and 2.8 Hz), 6.84 (1H, t, *J* 7.5 Hz), 7.15 (1H, dd, *J* 7.6 Hz and 1.6 Hz), 7.35 (1H, dd, *J* 7.6 and 1.6 Hz), 8.42 (1H, s); IR ν_{max}/cm^{-1} (film) 3367, 2959, 1633, 1458, 1436; $[\alpha]_D^{20}$ = -54.3 (c 0.3, acetone).

(*S*)-2-(*N*-5'-*tert*-Butylsalicylidene)-amino-3,3-dimethyl-1-butanol (12, Table 4)[38]

Yellow solid, 82%, m.p. 119–120 ^{o}C; ^{1}H NMR δ_H (300 MHz) 0.96 (9H, s), 1.31 (9H, s), 1.62 (1H, brs), 2.93 (1H, dd, *J* 9.5 Hz and 2.8 Hz), 3.75 (1H, dd, *J* 11.0 Hz and 9.6 Hz), 3.92 (1H, dd, *J* 11.1 Hz and 2.8 Hz), 6.91 (1H, d, *J* 8.6 Hz), 7.26–7.28 (1H, m), 7.36 (1H, dd, *J* 8.6 Hz and 2.5 Hz), 8.36 (1H, s); ^{13}C NMR δ_C (75.5 MHz) 27.0, 31.4, 33.2, 34.0, 62.5, 81.3, 116.5, 117.8, 128.0, 129.8, 141.5, 158.9, 166.4 (HC=N); IR ν_{max}/cm^{-1} (KBr) 3422, 2958, 1633, 1493; (Found: C, 73.31; H, 9.89; N, 5.12 $C_{17}H_{27}NO_2$ Requires C, 73.61; H, 9.81; N, 5.05); $[\alpha]_D^{20}$ = -46.8 (c 0.3, acetone).

(*S*)-2-(*N*-3',5'-Dibromosalicylidene)-amino-3-methyl-1-butanol (13, Table 4)

Yellow solid, 76%, m.p. 136–138 °C, ^{1}H NMR δ_H (300 MHz) 0.99 (3H, d, *J* 6.7 Hz), 1.01 (3H, d, *J* 6.7 Hz), 1.88–2.07 (1H, m), 3.17–3.30 (1H, m), 3.65–3.80 (1H, m), 3.99 (1H, dd, *J* 11.4 Hz and 2.6 Hz), 7.25 (1H, d, *J* 2.5 Hz), 7.60 (1H, d, *J* 2.5 Hz) 8.14 (1H, s); ^{13}C NMR δ_C (75.5 MHz) 18.4, 19.8, 29.6, 64.0, 74.8, 107.2, 114.8, 117.6, 133.5, 138.8, 163.0, 164.6; m/z IR (KBr) ν_{max}/cm^{-1} 3259, 2965, 1645, 1497, 1212, 1043, 857, 690; (Found: C, 39.73; H, 4.14; N, 3.57. $C_{12}H_{15}Br_2NO_2$ Requires C, 39.48; H, 4.14; N, 3.84); $[\alpha]_D^{20}$ = - 9.1 (c 1.0, acetone).

(*S*)-2-(*N*-3',5'-Difluorosalicylidene)-amino-3,3-dimethyl-1-butanol (14, Table 4)

Yellow solid, 57%, m.p. 161–163 ^{o}C; ^{1}H NMR δ_H (300 MHz) 0.99 (9H, s), 2.08 (1H, brs), 3.01 (1H, dd, *J* 9.6 Hz and 2.7 Hz), 3.70 (1H, dd, seen as t, *J* 9.9 Hz and 9.9 Hz), 3.99 (1H, brd, *J* 9.8 Hz), 6.75–6.82 (1H, m), 6.86–6.96 (1H, m), 8.26 (1H, s); ^{13}C NMR δ_C (75.5 MHz) 26.9, 33.1, 62.0, 80.4, 107.4-108.0 (m), 111.2-111.5 (m); 164.6; m/z (ESI) [$(M+H)^+$] 258; HRMS (ESI): Exact mass calculated for $C_{13}H_{17}F_2NO_2$ [$(M+H)^+$] 258.1328, Found 258.1317; IR (KBr) ν_{max}/cm^{-1} 3308, 2966, 1638, 1479, 1215, 1059, 857; $[\alpha]_D^{20}$ = - 35.6 (c 0.5, acetone).

(*S*)-2-(*N*-3'-Chloro-5'-fluorosalicylidene)-amino-3,3-dimethyl-1-butanol (15, Table 4)

Yellow solid, 75%, m.p. 103–105 ^{o}C; ^{1}H NMR δ_H (300 MHz) 1.00 (9H, s), 2.81 (1H, bs), 3.06 (1H, dd, *J* 9.6 Hz and 2.4 Hz), 3.70 (1H, overlapping dd, *J* 11.1 Hz and 9.6 Hz), 3.99 (1H, dd, J 11.4 Hz and 2.7 Hz), 6.87 (1H, dd, *J* 8.1 Hz and 3.0 Hz), 7.14 (1H, dd, *J* 8.1 Hz and 3.0 Hz), 8.22 (1H, s); ^{13}C NMR δ_C (75.5 MHz) 26.9, 33.0, 61.9, 79.8, 115.2, 117.0 (d, $^{3}J_{CF}$ 8 Hz), 121.0 (d, $^{2}J_{CF}$ 26 Hz), 122.8 (d, $^{3}J_{CF}$ 10 Hz) 153.4 (d, $^{1}J_{CF}$ 239 Hz) 157.0, 164.6 (d, $^{4}J_{CF}$ 3 Hz, HC=N); m/z (ESI) [$(M+H)^+$] 274; HRMS (ESI): Exact mass calculated for $C_{13}H_{17}FClNO_2$ [$(M+H)^+$] 274.1010, Found 274.1006; IR (KBr) ν_{max}/cm^{-1} 3288, 2973, 1643, 1471, 1366, 1209, 1063, 803; (Found: C, 57.41; H, 6.30; N, 5.24. $C_{13}H_{17}ClFNO_2$ Requires C, 57.04; H, 6.26; N, 5.12); $[\alpha]_D^{20}$ = - 27.4 (c 1.0, acetone).

Experimental procedure for synthesis of sulfides

Method A[39]

This method was used for the synthesis of sulfides **5e-5g**, **5i-5r** and **1d**.

The thiolate anion was first prepared by treatment of the thiol with an excess of sodium ethoxide. The thiolate anion was then treated with an equimolar amount of aryl or alkyl halide and stirred for 16 h at room temperature. Water (20 mL) and dichloromethane (20 mL)

were added to the flask. The layers were separated and the aqueous layer was extracted with dichloromethane (10 mL). The combined organic layers were washed with aqueous sodium hydroxide (2 M, 3 x 20 mL) and brine (20 mL), dried, filtered and concentrated under reduced pressure to give the sulfides which were purified by column chromatography.

Method B[40]

This method was used for the synthesis of neopentyl phenyl sulfide, **5h**

1-Bromo-2,2-dimethyl propane (3.02 g, 20 mmol), aqueous benzenethiolate (20 mmol) and aliquat 336 (0.033 mole equivalents) were added to a 2-neck round bottomed flask under nitrogen. The mixture was heated at 70 °C with vigorous stirring for 16 h. After the mixture had cooled to room temperature, the organic layer was separated and the aqueous phase was extracted with two 20 mL portions of diethyl ether. The combined organic phases were washed with 20 mL of 10% aqueous sodium chloride and dried over magnesium sulfate. After removal of the solvent the resulting residual oil was distilled using a kugelrohr apparatus to give neopentyl phenyl sulfide, b.p. 145–147° (0.1 mm. Hg).

Method C[41]

This method was used for the synthesis of 4-methylphenyl prop-2'-ynyl sulfide, **5c**.

NaH (0.72 g of 67% dispersion in mineral oil, 20 mmol) was added to a two neck flask under nitrogen. After washing with hexane (3 x 5 mL), dry dimethylformamide (DMF) (15 mL) was added to the flask and the mixture was stirred for 5 mins. The reaction mixture was cooled to 0 °C, and 4-methylbenzene thiol (20 mmol, 2.48 g) was added slowly. After stirring for 5 mins, a solution of propargyl bromide (20 mmol, 1.72 mL) in DMF (10 mL) was added. The mixture was removed from the ice-bath, allowed to return to room temperature and stirred for 16 h under nitrogen. HCl (2 M, 20 mL) and dichloromethane (20 mL) were added to the flask. The layers were separated, and the organic layers were washed with aqueous HCl (2 M, 3 x 20 mL) and brine (15 mL), dried and concentrated under reduced pressure, to yield

the crude product as yellow oil. This was purified by column chromatography on silica gel (100% hexane) to yield the product.

4-Methylphenyl prop-2'-ynyl sulfide[41] (5c)

Clear oil, 47%, ^{1}H NMR δ_H (400 MHz) 2.23 (1H, t, *J* 2.6 Hz), 2.34 (3H, s), 3.56 (2H, d, *J* 2.6 Hz), 7.14 (2H, d, *J* 8.5 Hz), 7.38 (2H, d, *J* 8.5 Hz); IR (film) ν_{max}/cm^{-1} 2117, 1231, 643.

Cyclohexylmethyl phenyl sulfide[42] (5e)

Clear oil, 95%, ^{1}H NMR δ_H (400 MHz) 0.89–1.08 (2H, m), 1.10–1.32 (3H, m), 1.45–1.80 (4H, m), 1.82–1.94 (2H, m), 2.80 (2H, d, *J* 6.8 Hz) 7.09–7.18 (1H, m), 7.21–7.38 (4H, m); IR (film) ν_{max}/cm^{-1} 2924, 1584, 1480, 1448, 736.

Isopropyl phenyl sulfide[43] (5f)

Clear oil, 70%, ^{1}H NMR δ_H (300 MHz) 1.29 (6H, d, *J* 6.9 Hz), 3.30–3.45 (1H, m), 7.18–7.33 (3H, m), 7.38–7.42 (2H, m); ^{13}C NMR δ_C (75 MHz) 23.1, 38.2, 126.7, 128.8, 131.9, 135.5; IR (film) ν_{max}/cm^{-1} 2962, 2925, 1584, 1480, 1439, 1026, 741, 692.

Isobutyl phenyl sulfide[44] (5g)

Clear oil, 97%, ^{1}H NMR δ_H (300 MHz) 1.03 (6H, d, *J* 6.6 Hz), 1.79–1.94 (1H, m), 2.81 (2H, d, *J* 6.6 Hz), 7.11–7.19 (1H, m), 7.22–7.35 (4H, m); ^{13}C NMR δ_C (75 MHz) 22.1, 28.3, 42.6, 125.6, 128.8, 128.8, 137.4; IR (film) ν_{max}/cm^{-1} 2958, 2927, 1586, 1481, 1438, 1026, 737, 690.

Neopentyl phenyl sulfide[40] (5h)

Clear oil, 37%, ^{1}H NMR δ_H (300 MHz) 1.04 (9H, s), 2.90 (2H, s), 7.10–7.18 (1H, m), 7.21–7.30 (2H, m), 7.32-7.38 (2H, m); ^{13}C NMR δ_C (75 MHz) 29.1, 32.5, 48.6, 125.5, 128.8, 128.9, 138.5; IR (film) ν_{max}/cm^{-1} 2958, 2907, 1584, 1480, 1438, 1026, 736, 690.

2-Naphthylmethyl phenyl sulfide[45] (5i)

White solid, 82%, ^{1}H NMR δ_H (300 MHz) 4.26 (2H, s), 7.11–7.27 (3H, m), 7.28–7.36 (2H, m), 7.38–7.51 (3H, m), 7.63–7.85 (4H, m); ^{13}C NMR δ_C (75 MHz) 39.5, 125.8, 126.1, 126.5, 127.0, 127.4, 127.7, 127.7, 128.3, 128.9, 130.1, 132.6, 133.3, 134.9, 136.3 ($C_{Ar(q)}$); IR (KBr) ν_{max}/cm^{-1} 3048, 2917, 1438, 832, 738.

Benzyl-(4-methylphenyl)-sulfide[39] (5j)

White solid, 76%, m.p. 42–43 ^{o}C, (Lit. 45 ^{o}C)[8]; ^{1}H NMR δ_H (300 MHz) 2.30 (3H, s), 4.06 (2H, s), 7.05 (2H, d, *J* 8.2 Hz), 7.15–7.32 (7H, m); ^{13}C NMR δ_C (75.5 MHz) 21.0, 39.7, 127.1, 128.4, 128.8, 129.6, 130.7, 132.4, 136.5, 137.8; ν_{max}/cm^{-1} (KBr) 2921, 1494, 1454, 1265, 740, 697;

4-Methoxybenzyl-(4'-methylphenyl)-sulfide[39] (5k)

White solid, 75%, m.p. 65–67 ^{o}C, (Lit. 67 ^{o}C)[46]; ^{1}H NMR δ_H (300 MHz) 2.30 (3H, s,), 3.78 (3H, s), 4.03 (2H, s), 6.76–6.84 (2H, m), 7.03–7.11 (2H, m), 7.13–7.28 (4H, m); ^{13}C NMR δ_C (75.5 MHz) 21.0, 39.2, 55.3, 113.9, 129.6, 129.8, 129.9, 130.7, 132.7, 136.5, 158.7; IR ν_{max}/cm^{-1} (KBr) 2958, 2833, 1609, 1510, 1492, 1241, 1174, 1030, 799; m/z (ESI) [(M+OH)$^{+}$] 261; HRMS (ESI): Exact mass calculated for $C_{15}H_{16}OS$ [(M+OH)$^{+}$] 261.0949, Found 261.0937.

Benzyl-(2-methoxyphenyl)-sulfide[47,48] (5l)

White solid, 55%, m.p. 68–70 ^{o}C, ^{1}H NMR δ_H (300 MHz) 3.88, 4.09 (2H, s), 6.79–6.91 (2H, m), 7.12–7.35 (7H, m); ^{13}C NMR δ_C (75.5 MHz) 37.3, 55.8, 110.5, 121.0, 124.5, 127.0, 127.6, 128.4, 128.9, 130.5, 137.5, 157.6; IR ν_{max}/cm^{-1} (KBr) 2934, 1577, 1476, 1245, 1071,

1025, 747; m/z (ESI) [(M+OH)$^+$] 247.; HRMS (ESI): Exact mass calculated for $C_{14}H_{14}OS$ [(M+OH)$^+$] 247.0793, Found 247.0799.

Benzyl-(3-methoxyphenyl)-sulfide[47] (5m)

Clear oil, 83%, ^{1}H NMR δ_H (300 MHz) 3.73 (3H, s,), 4.12 (2H, s), 6.67–6.75 (1H, m), 6.80–6.85 (1H, m), 6.87–6.94 (1H, m), 7.12–7.35 (6H, m); ^{13}C NMR δ_C (75.5 MHz) 38.9, 55.2, 112.2, 114.8, 121.8, 127.2, 128.5, 128.8, 129.7, 137.4, 137.8, 159.7; IR ν_{max}/cm^{-1} (film) 3062, 3029, 2936, 1590, 1479, 1249, 1043, 769; m/z (ESI) [(M+OH)$^+$] 247; HRMS (ESI): Exact mass calculated for $C_{14}H_{14}OS$ [(M+OH)$^+$] 247.0793, Found 247.0796.

Benzyl *o*-tolyl sulfide[49] (5n)

Clear oil, 90%, ^{1}H NMR δ_H (300 MHz) 2.32 (3H, s), 4.08 (2H, s), 7.04–7.18 (3H, m), 7.19–7.33 (6H, m); ^{13}C NMR δ_C (75.5 MHz) 20.3, 38.3, 126.1, 126.4, 127.2, 128.5, 128.8, 128.9, 130.1, 135.8, 137.2, 137.9; IR (film) ν_{max}/cm^{-1} 3061, 3029, 1469, 1454, 1066, 744, 697; (Found C, 78.50; H, 6.62; $C_{14}H_{14}S$ requires C, 78.46; H, 6.58); m/z (ESI) [(M+OH)$^+$] 231; HRMS (ESI): Exact mass calculated for $C_{14}H_{14}S$ [(M+OH)$^+$] 231.0844, Found 231.0848.

Benzyl *m*-tolyl sulfide (5o)

Clear oil, 91%, ^{1}H NMR δ_H (300 MHz) 2.29 (3H, s), 4.11 (2H, s), 6.95–7.02 (1H, m), 7.07–7.34 (8H, m); ^{13}C NMR δ_C (75.5 MHz) 21.4, 39.0, 126.7, 127.2, 128.5, 128.8, 128.9, 130.4, 136.2, 137.6, 138.6; IR (film) ν_{max}/cm^{-1} 3029, 2921, 1592, 1495, 1453, 770, 693; (Found C, 78.55; H, 6.62; S, 14.93; $C_{14}H_{14}S$ requires C, 78.46; H, 6.58; S 14.96); m/z (ESI) [(M+OH)$^+$] 231; HRMS (ESI): Exact mass calculated for $C_{14}H_{14}S$ [(M+OH)$^+$] 231.0844, Found 231.0843.

4-Methylbenzyl phenyl sulfide[50] (5p)

White solid, 87%, m.p. 69-71 °C, (Lit. 63.5-64.4 ^{o}C)[50]; ^{1}H NMR δ_H (300 MHz) 2.32 (3H, s), 4.09 (2H, s), 7.03–7.36 (9H, m); ^{13}C NMR δ_C (75.5 MHz) 21.1, 38.7, 126.2, 128.7, 128.8, 129.2, 129.6, 134.3, 136.7, 136.8; IR (film) ν_{max}/cm^{-1} 3058, 2918, 1582, 1479, 1435, 1090, 738, 690; (Found C, 78.13; H, 6.59; S, 15.30; $C_{14}H_{14}S$ requires C, 78.46; H, 6.58; S 14.96); m/z (ESI) [(M+OH)$^{+}$] 231; HRMS (ESI): Exact mass calculated for $C_{14}H_{14}S$ [(M+OH)$^{+}$] 231.0844, Found 231.0849.

3-Methylbenzyl phenyl sulfide (5q)

Clear oil, 77%, ^{1}H NMR δ_H (300 MHz) 2.31 (3H, s), 4.09 (2H, s), 7.00–7.37 (9H, m); ^{13}C NMR δ_C (75.5 MHz) 21.3, 39.0, 125.9, 126.3, 128.0, 128.4, 128.8, 129.6, 129.7, 136.6, 137.3, 138.2; IR (film) ν_{max}/cm^{-1} 3057, 2920, 1584, 1480, 1438, 1089, 738, 690; (Found C, 78.20; H, 6.51; S, 15.3; $C_{14}H_{14}S$ requires C, 78.46; H, 6.58; S 14.96); m/z (ESI) [(M+OH)$^{+}$] 231; HRMS (ESI): Exact mass calculated for $C_{14}H_{14}S$ [(M+OH)$^{+}$] 231.0844, Found 231.0843.

2-Methylbenzyl phenyl sulfide (5r)

Clear oil, 86%, ^{1}H NMR δ_H (300 MHz) 2.39 (3H, s), 4.10 (2H, s), 7.02–7.37 (9H, m); ^{13}C NMR δ_C (75.5 MHz) 19.2, 37.4, 126.0, 126.5, 127.5, 128.9, 129.8, 130.3, 130.5, 135.1, 136.7, 136.8; IR (film) ν_{max}/cm^{-1} 3060, 2929, 1583, 1479, 1438, 737, 690; (Found C, 78.61; H, 6.32; S, 15.02; $C_{14}H_{14}S$ requires C, 78.46; H, 6.58; S 14.96); m/z (ESI) [(M+OH)$^{+}$] 231; HRMS (ESI): Exact mass calculated for $C_{14}H_{14}S$ [(M+OH)$^{+}$] 231.0844, Found 231.0844.

Benzyl-(4-methoxyphenyl)-sulfide[47,48] (1d)

White solid, 95%, m.p. 47–49 ^{o}C, (Lit. 48–49 ^{o}C)[9]; ^{1}H NMR δ_H (300 MHz) 3.77 (3H, s), 3.98 (2H, s), 6.73–6.83 (2H, m), 7.13–7.31 (7H, m); ^{13}C NMR δ_C (75.5 MHz) 41.2, 55.3, 114.4, 126.1, 127.0, 128.4, 128.9, 134.1, 138.1, 159.2; IR ν_{max}/cm^{-1} (KBr) 2920, 2834, 1595, 1493, 1288, 1246, 1179, 1026, 810.

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Supporting Information: ^{1}H NMR spectra are available for compounds **5o**, **5r**, **5q**, **6a**, **6b**, **6c**, **6d**, **6e**, **6f**, **6g**, **6h**, **6i**, **6j**, **6k**, **6l**, **6m**, **6n**, **6o**, **6p**, **6q**, **6r**, **2d**, **4**, **13**, **14** and **15**. ^{13}C NMR spectra are available for compounds **5o**, **5r**, **5q**, **6h**, **6i**, **4**, **13**, **14** and **15**. HPLC data are available for sulfoxides **6i** and **6h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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