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Biotransformation of organic sulfides Part. 10. Formation of chiral *ortho*- and *meta*-substituted benzyl methyl sulfoxides by biotransformation using *Helminthosporium* species NRRL 4671

Herbert L. Holland *, Frances M. Brown, Ali Kerridge, Carl D. Turner

Department of Chemistry, Brock University, St. Catharines, ON, Canada, L2S 3A1

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Abstract

Benzyl methyl sulfides substituted with methyl, chloro, cyano, bromo, methoxy, nitro and amino groups in the *ortho* or *meta* positions of the aromatic ring have been converted to (*S*) sulfoxides by biotransformation using the fungal biocatalyst *Helminthosporium* species NRRL 4671. The enantiomeric excesses for *meta*-substituted examples were high in those cases where the substituent was of a polar nature, and comparable to those observed for the corresponding *para*-substituted substrates. With one exception (*o*-amino), the *ortho*-substituted examples gave sulfoxides of lower enantiomeric purity. The role of a suitably located polar substituent on an aryl ring of the substrate in ensuring a high enantiomeric excess in sulfoxidation by *Helminthosporium* species has been confirmed by the biotransformations of 4-(methylthiomethyl)benzyl alcohol and 2-(4-nitrophenyl) ethyl methyl sulfide, which give sulfoxides of much higher optical purity than those obtained from the corresponding unsubstituted substrates.

Keywords: Biotransformation; *Helminthosporium*; NRRL 4671; Sulfide; Sulfoxide

1. Introduction

Procedures that employ fungal [1–7], bacterial [8–10], yeast [11,12], or isolated enzyme [13–15] biocatalysts have been among the most actively investigated methods for the preparation of chiral sulfoxides. For several of these systems, including cyclohexanone monooxygenase from *Acinetobacter* [16,17] and the fungal biocatalysts *Mortierella isabellina* ATCC 42613 [7] and *Helminthosporium* sp. NRRL 4671 [5], enzyme active site models have been developed which allow for predictions of the substrate suitability and the stereochemical outcome of the sulfoxidation reaction. One feature of the latter model is a positive enhancement of the stereoselectivity of sulfoxidation when the substrates contain either an aromatic ring possessing a polar *para*-substituent, or an alkyl chain with a polar substituent in the terminal position, such that the polar residue was located some 8–10 Å from the site of oxidation. This effect

* Corresponding author. Tel.: +1-905-6885550 ext. 3403; Fax: +1-905-6829020; E-mail: holland@chemiris.labs.brocku.ca

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was postulated to be due to a specific binding interaction with a residue of the enzyme's active site [5]. We have now further investigated this effect by an examination of the *Helminthosporium*-catalysed oxidation of a series of *ortho*-, *meta*-, and *para*-substituted benzyl methyl sulfides, and present herein data which confirm and enhance our earlier findings [5].

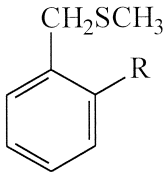
2. Results and discussion

The results of the biotransformation of *ortho*- and *meta*-substituted benzyl methyl sulfides **1** and **2** are reported in Table 1. Also presented in Table 1, for comparative purposes, are data from the corresponding unsubstituted (**1a**/**2a**/**3a**) and *para*-substituted (**3**) substrates [1,3]. The reported yields refer to isolated, homogenous material. Product structures were identified by characteristic ^{1}H and ^{13}C NMR data: these, together with supporting mass spectral data, are presented in Section 3. Enantiomeric excess (e.e.) and absolute configuration of the sulfoxide products were determined by ^{1}H NMR analysis in the presence of (*S*)-(+)-α-methoxyphenylacetic acid (mpaa), a chiral NMR shift reagent that gives consistent configurationally-dependent shifts of signals α to sulfur in chiral benzyl alkyl and dialkyl sulfoxides [18], and the assigned (*S*) configurations are consistent with the optical rotations reported below [19–21]. In all cases, the corresponding racemic sulfoxide,

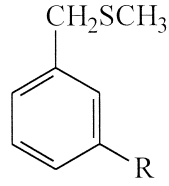
Table 1
Biotransformation of substituted sulfides by *Helminthosporium*

Entry No.	Substrate	Substituent	Sulfoxide (percentage yield, configuration, e.e.)	Sulfone (%)
1[a]	**1a/2a/3a**	H	68, *S*, 62	nil
2	**1b**	*o*-CH_3	63, *S*, 57	nil
3	**2b**	*m*-CH_3	67, *S*, 12	4
4[a]	**3b**	*p*-CH_3	70, *S*, 52	3
5	**1c**	*o*-Cl	82, *S*, 79	8
6	**2c**	*m*-Cl	70, *S*, 85	1
7[a]	**3c**	*p*-Cl	71, *S*, 90	12
8	**1d**	*o*-CN	78, *S*, 60	nil
9	**2d**	*m*-CN	72, *S*, 76	nil
10[a]	**3d**	*p*-CN	96, *S*, 98	nil
11	**1e**	*o*-Br	58, *S*, 64	2
12	**2e**	*m*-Br	53, *S*, > 95	9
13[a]	**3e**	*p*-Br	71, *S*, 90	10
14	**1f**	*o*-OCH_3	82, *S*, 64	3
15	**2f**	*m*-OCH_3	88, *S*, 82	nil
16[a]	**3f**	*p*-OCH_3	86, *S*, 80	nil
17	**1g**	*o*-NO_2	81, *S*, 78	nil
18	**2g**	*m*-NO_2	82, *S*, 94	nil
19[a]	**3g**	*p*-NO_2	95, *S*, 92	nil
20	**1h**	*o*-NH_2	37, *S*, > 95	nil
			5; 6, *S*, > 95	nil
21	**2h**	*m*-NH_2	52, *S*, 82	nil
22[a]	**3h**	*p*-NH_2	62, *S*, 95	nil
23	**3i**	*p*-CH_2OH	52, *S*, 92	nil
24[b]	**4a**	H	72, *S*, 30	nil
25	**4b**	*p*-NO_2	57, *S*, 75	10
26	**4c**	*p*-NH_2	44, *S*, 40	nil

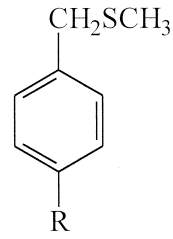
[a] Data from Ref. [3].
[b] Data from Ref. [1].



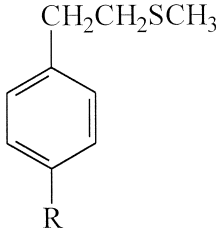
1a, R = H
b, R = CH_3
c, R = Cl
d, R = CN
e, R = Br
f, R = OCH_3
g, R = NO_2
h, R = NH_2



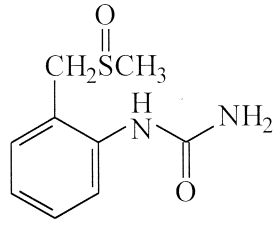
2a, R = H
b, R = CH_3
c, R = Cl
d, R = CN
e, R = Br
f, R = OCH_3
g, R = NO_2
h, R = NH_2



3a, R = H
b, R = CH_3
c, R = Cl
d, R = CN
e, R = Br
f, R = OCH_3
g, R = NO_2
h, R = NH_2
i, R = CH_2OH



4a, R = H
b, R = NO_2
c, R = NH_2



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prepared by chemical oxidation of the sulfide using sodium *meta*-periodate, was used to validate the NMR shift separations.

In the case of polar substituents possessing non-bonded electron density, (Cl, CN, Br, OCH_3, NO_2, and NH_2), the highest enantiomeric purities were found for the *para*- and *meta*-substituted examples (entries 6, 7, 9, 10, 12, 13, 15, 16, 18, 19, 21, and 22). The effect of this substitution pattern is clearly not steric, as evidenced by the results obtained from the methyl-substituted substrates **1b**, **2b**, and **3b** (entries 2–4), compared with that from the unsubstituted substrate (entry 1), where the presence of the substituent has no enhancing effect on the e.e. of sulfoxidation (and is actually detrimental when in the *meta* position). Neither is the effect due to electron donation or withdrawal into the aromatic ring, as the range of substituents examined covers both extremes of this property. The one exception to the general trend is the *ortho*-amino substituted substrate **1h** (entry 20), which gave enantiopure sulfoxide. This latter biotransformation also resulted in low-yield formation of the urea derivative **5**.

The active site model derived for sulfoxidation by *Helminthosporium* features a binding site located 8–10 Å from the site of oxidation which is specific for a substrate substituent with non-bonded electron density [5]. The *para*-substituted isomers (Fig. 1a) can clearly fulfil this requirement, as determined from the distance (8–10 Å) from the substituent to a putative site of oxidation determined from energy-minimised Hyperchem© structures. The *meta*-substituted isomers can also fulfil this requirement in the conformation shown in Fig. 1b: neither the *ortho*- nor other conformations of *meta*-sub-

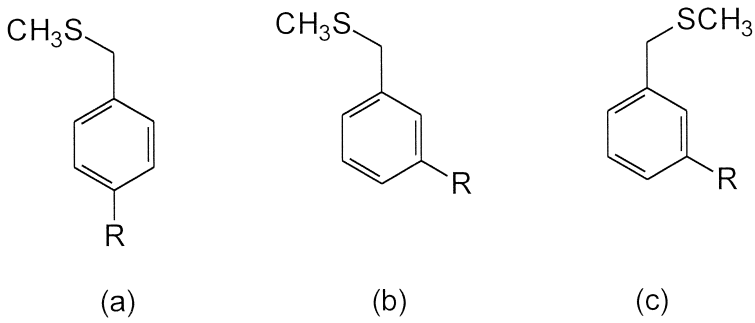

Fig. 1. Conformations of *meta*- and *para*-substituted benzyl methyl sulfides.

stituted isomers (e.g., Fig. 1c) can effectively discharge this role. The role of a polar substituent located 8–10 Å from the site of oxidation is again apparent in the biotransformation of **3i** and a comparison of entry 23 (R = *p*-CH_2OH, e.e. of sulfoxide 92%) and entry 4 (R = *p*-CH_3, e.e. of sulfoxide 52%).

This effect is also expressed in the biotransformation of the phenylethyl methyl sulfides **4**, where a *para*-nitro group (substrate **4b**, entry 25) enhances the stereoselectivity of sulfoxidation (cf. entry 24). Sulfoxidation of the *para*-amino-substituted substrate **4c** (entry 26) also shows a higher stereoselectivity than that of the unsubstituted example **4a**, but the effect is not as pronounced as that observed during sulfoxidation of **4b**. Again, as with the biotransformation of the *ortho*-amino sulfide **1h** (entry 20), the amino group shows a trend that is inconsistent with that observed for other substrates used in this study. One reason for this may be the existence of other metabolic pathways such as biological conjugation (of unknown stereoselectivity) open to the primary amino function; amino-substituted substrates consistently give only low to moderate yields of sulfoxide products (see Table 1) with little recovered starting material.

With the possible exception of the amino group, therefore, the trends observed in Table 1 are consistent with our earlier hypothesis that the stereoselectivity of sulfoxidation by *Helminthosporium* sp. NRRL 4671 is enhanced when the substrates possess an aromatic ring with a substituent having non-bonded electron density located some 8–10 Å from the site of oxidation [5]. Further refinement of this model by the use of other *ortho*- and *meta*-substituted aryl sulfide substrates is currently underway.

3. Experimental

3.1. Apparatus, materials and methods

Melting points were determined on a Kofler heating stage. Infrared spectra were recorded with a Mattson Research Series FTIR spectrometer. NMR spectra were recorded at 300 MHz (^{1}H) or 75 MHz (^{13}C) with a Bruker Avance 300 spectrometer using $CDCl_3$ as solvent and $CHCl_3$ as internal standard. Enantiomeric ratios were determined by ^{1}H NMR analysis in the presence of 3 equivalents of (*S*)-(+)-α-methoxyphenylacetic acid (mpaa) or 2 equivalents of (*R*)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine (dnb) as indicated below. Optical rotations were obtained in the stated solvent at ambient temperature with a Rudolph Autopol III polarimeter. Mass spectra (El mode except where stated otherwise) were obtained with a Kratos IS instrument. Thin layer chromatography was performed on Merck silica gel 60F-254 and flash column chromatography used silica gel, 230–400 mesh.

3.2. Maintenance of microorganisms

Helminthosporium species NRRL 4671 was obtained from the US Department of Agriculture, Northern Regional Research Laboratories, Peoria, IL, and was maintained on 4% malt agar

slopes, grown at 27°C for 4 days and then stored tightly sealed at 4°C for up to 6 months.

3.3. Preparation of substrates

Substrates **1b**–**1g**, **2b**–**2g**, and **3b**–**3g** were prepared from the corresponding substituted benzyl alcohol by conversion to the benzyl chloride followed by reaction with sodium thiomethylate. Substrate **4b** was prepared by conversion of 2-(4-nitrophenyl)ethanol to the mesylate ester, followed by reaction with sodium thiomethylate, and **1h** obtained from **1g**, **2h** obtained from **2g**, and **4c** obtained from **4b** by conventional reduction (Sn/HCl). All compounds gave satisfactory spectral and analytical data.

3.3.1. 4-(Methylthiomethyl)benzyl alcohol (3i)

Lithium aluminum hydride (1.94 g, 51.0 mmol) was suspended in dry ether in a two-necked flask fitted with condenser, calcium chloride drying tube and dropping funnel. A solution of methyl 4-(methylthiomethyl)benzoate (10.0 g, 51.0 mmol) in 50 ml dry ether was added by stirring at such a rate as to keep the reaction at a gentle reflux. After completion of addition, the reaction mixture was heated at reflux overnight. The reaction was cooled to room temperature and quenched (CARE!!) with water. The solids were filtered off and the two layers were separated. The aqueous layer was extracted with ether (2×100 ml) and the combined ethereal extracts dried and the solvent removed in vacuo to leave a yellow oil (93%) which needed no further purification. ^{1}H NMR δ 1.91 (3H, s), 3.59 (2H, s), 4.52 (2H, s) and 7.21 (4H, br.s) ppm; ^{13}C NMR δ 15.2, 38.4, 65.0, 127.5, 129.3, 137.8, and 140.0 ppm; MS m/z (%) 168 (68), 121 (100), 91 (24), 77 (18); Found: 168.06154 (+3.8 ppm).

3.4. Biotransformations with Helminthosporium species

Two slopes of *Helminthosporium* species NRRL 4671 were used to inoculate 15 1 dm^3 Erlenmeyer flasks each containing 200 ml of an autoclaved medium composed of V-8 vegetable juice (200 ml) and calcium carbonate (3 g) per liter of distilled water, adjusted to pH 7.2 prior to sterilization by the addition of 1 M sodium hydroxide. The flasks were allowed to stand overnight at 27°C, then placed on a 1″ rotary shaker at 180 rpm, and growth continued for a further 72 h at 27°C. The fungus was then harvested by vacuum filtration (Büchner funnel), and resuspended in 15 1 dm^3 Erlenmeyer flasks each containing 200 ml of distilled water. Substrate (1 g in 30 ml of 95% ethanol) was then distributed among the flasks, which were replaced on the rotary shaker at 180 rpm, 27°C for a further 48 h. The fungus and aqueous medium were then separated by filtration as before, the aqueous medium extracted with dichloromethane (continuous extraction, 72 h), and the fungus discarded. Concentration of the medium extract gave the crude product, which was examined by TLC, using ether or 10% methanol/ether as solvent, and then submitted to flash chromatography. The yields and e.e. values quoted in Table 1 refer to purified, homogeneous material and unless otherwise stated, arise from the combination of (only) homogeneous column fractions without further purification (e.g., crystallization) that could lead to changes in stereochemical enrichment values. Significant or hitherto unreported spectral and optical rotation data for products obtained in this study are listed below under the appropriate substrate heading.

3.4.1. 2-(Methylthiomethyl)toluene (1b)

2-(Methylsulfinylmethyl)toluene; oil; chromatography 100% ether to 100% benzene; ^{1}H NMR δ 2.31 (3H, s), 2.42 (3H, s), 3.87/4.06 (2H, ABq, $J = 12.8$ Hz), and 7.12 (4H, m) ppm; ^{13}C NMR δ 20.2, 38.0, 59.1, 126.8, 129.0, 129.1, 131.2, 131.4, and 137.7 ppm; MS m/z (%) 168 (2), 152 (3), 105 (100), 91 (4), 77 (11), found: M^+ 168.06150 (+3.6 ppm). ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.56 and 2.59 ppm, major enantiomer δ 2.56 ppm, 57% e.e.; $[\alpha]_D$ −26.94 ($c = 1$, $CHCl_3$).

*3.4.2. 2-(Methylthiomethyl)chlorobenzene (**1c**)*

2-(Methylsulfinylmethyl)chlorobenzene, oil, chromatography 90/10 ethyl acetate/hexane; $R_f = 0.33$ (90/10 ethyl acetate/hexane); ^{1}H NMR δ 2.50 (3H, s), 4.14 (2H, s), 7.26 (2H, m) and 7.38 (2H, m) ppm; ^{13}C NMR δ 38.0, 57.8, 127.6, 128.5, 130.2, 130.3, 132.8, and 134.8 ppm; MS(FAB) m/z (%) 189 (100), 125 (74), EI found M^+ (^{35}Cl) 188.00594 (−1.7 ppm). ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.58 and 2.61 ppm, major enantiomer δ 2.58 ppm, 79% e.e.; $[\alpha]_D$ +106.5 ($c = 1$, EtOH): 2-(methylsulfonylmethyl)chlorobenzene, oil, chromatography 90/10 ethyl acetate/hexane; $R_f = 0.5$ (90/10 ethyl acetate/hexane); ^{1}H NMR δ 2.81 (3H, s), 4.48 (2H, s), 7.1–7.5 (4H, m) ppm; ^{13}C NMR δ 40.1, 58.2, 127.1, 128.0, 128.6, 132.5, 133.4, and 134.9 ppm.

*3.4.3. 2-(Methylthiomethyl)benzonitrile (**1d**)*

2-(Methylsulfinylmethyl)benzonitrile; m.p. 106–108°C; chromatography 50/50 ethyl acetate/hexane to 100% ethyl acetate; $R_f = 0.49$ (ethyl acetate); ^{1}H NMR δ 2.58 (3H, s), 4.10/4.27 (2H, ABq, $J = 13.2$ Hz), 7.42 (1H, t, $J = 7.5$ Hz), 7.47 (1H, d, $J = 7.8$ Hz), 7.60 (1H, t, $J = 7.6$ Hz) and 7.68 (1H, d, $J = 7.7$ Hz) ppm; ^{13}C NMR δ 37.8, 57.2, 113.4, 117.5, 128.9, 131.8, 133.1, and 133.6 ppm; MS(FAB) m/z (%) 180 (100), EI found M^+ 179.04085 (+2.0 ppm); ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.62 and 2.64 ppm, major enantiomer δ 2.62 ppm, 60% e.e.; $[\alpha]_D$ +111.7 ($c = 1$, EtOH); crystallization from dichloromethane/hexane gives $[\alpha]_D$ +186.2 ($c = 1$, EtOH) (92% e.e.).

*3.4.4. 2-(Methylthiomethyl)bromobenzene (**1e**)*

2-(Methylsulfinylmethyl)bromobenzene; m.p. 70–75°C; chromatography benzene to ether to 15% methanol/ether; $R_f = 0.48$ (10% methanol/ether); ^{1}H NMR δ 2.56 (3H, s), 4.20 (2H, s), 7.20–7.45 (3H, m) and 7.75 (1H, d) ppm; ^{13}C NMR δ 38.1, 60.5, 125.4, 128.3, 130.5 (2C), 132.8, and 133.6 ppm; MS m/z (%) 234/232 (3), 169/171 (100), 90 (25); ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.60 and 2.63 ppm, major enantiomer δ 2.60, 64% e.e.; $[\alpha]_D$ +69 ($c = 1$, EtOH), −4 ($c = 1$, $CHCl_3$).

*3.4.5. 2-(Methylthiomethyl)anisole (**1f**)*

2-(Methylsulfinylmethyl)anisole; semi-solid; chromatography benzene to ether to 15% methanol/ether; $R_f = 0.42$ (10% methanol/ether); ^{1}H NMR δ 2.48 (3H, s), 3.86 (3H, s), 4.04/4.16 (2H, ABq), 6.9–7.0 (2H, dd), and 7.2–7.4 (2H, m) ppm; ^{13}C NMR δ 37.9, 55.4, 55.9, 111.1, 118.7, 121.3, 130.3, 132.3, and 157.9 ppm; MS m/z (%) 168 (4), 153 (1), 121 (98) relative to 91 (100); ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.52 and 2.55 ppm, major enantiomer δ 2.52, 64% e.e.; $[\alpha]_D$ +81 ($c =$ 1.0, EtOH), −48 ($c = 1$, $CHCl_3$).

*3.4.6. 2-(Methylthiomethyl)nitrobenzene (**1g**)*

2-(Methylsulfinylmethyl)nitrobenzene; oil; chromatography benzene to ether to 15% methanol/ether; $R_f = 0.31$ (10% methanol/ether); ^{1}H NMR δ 2.62 (3H, s), 4.10/4.62 (2H, Abq), 7.50–7.70 (3H, m), and 8.15 (1H, d) ppm; ^{13}C NMR δ 39.1, 58.4, 126.0, 126.7, 130.1, 134.2, 134.4, and 149.0 ppm; MS m/z (%) 199 (3), 136 (100), 78 (70); ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.69 and 2.73 ppm, major enantiomer δ 2.69, 78% e.e.; $[\alpha]_D$ +170 ($c = 1.0$, EtOH), +130 ($c = 1$, $CHCl_3$).

*3.4.7. 2-(Methylthiomethyl)aniline (**1h**)*

2-(Methylsulfinylmethyl)aniline; m.p. 118–120°C; chromatography; benzene to ether to 15% methanol/ether; $R_f = 0.32$ (10% methanol/ether); ^1H NMR δ 2.55 (3H, s), 3.85/4.20 (2H, ABq), 6.80 (2H, dd), 7.0 (1H, d), and 7.18 (1H, t) ppm; ^{13}C NMR δ 37.6, 56.9, 116.7, 117.8, 119.2, 130.1, 132.7, and 147.8 ppm; MS m/z (%) 169 (5), 146 (5), 131 (3), 106 (100); ^{1}H NMR (mpaa or dnb) no detectable splitting of S-CH_3 or -CH_2S- signals, > 95% e.e.; $[\alpha]_D$ +120 ($c = 1$, EtOH), +100 ($c = 1$, $CHCl_3$). Also obtained and purified by chromatography (ethyl acetate/methanol 97.2/2.5), $R_f = 0.37$ (10% methanol/ether) was 2-(methylsulfinyl methyl)phenyl urea **5**;

semi-solid; ^{1}H NMR δ 2.56 (3H, s), 3.80/4.10 (2H, ABq), 6.70 (1H, d), 7.0 (1H, d), 7.10 (1H, dd), and 7.30 (1H, d) ppm; ^{13}C NMR δ 37.7, 56.4, 118.6, 118.7, 119.0, 129.9, 132.4, and 144.8 ppm; MS m/z (%) 203 (8), 170 (2), 152 (10), 140 (100); ^{1}H NMR (mpaa or dnb) no detectable splitting of S-CH_3 or -CH_2S- signals, > 95% e.e.; $[\alpha]_D$ +130 (c = 1, EtOH).

*3.4.8. 3-(Methylthiomethyl)toluene (**2b**)*

3-(Methylsulfinylmethyl)toluene; oil; ^{1}H NMR δ 2.33 (3H, s), 2.43 (3H, s), 3.85/4.01 (2H, ABq, J = 12.8 Hz), 7.07 (2H, m), 7.14 (1H, d, J = 7.5 Hz) and 7.25 (1H, m) ppm; ^{13}C NMR δ 21.7, 37.7, 60.7, 127.4, 129.2, 129.6, 130.0, 131.1, and 139.1 ppm; MS m/z (%) 168 (1), 152 (5), 105 (100), 91 (6), 77 (10), found M^+ 168.06079 (−0.6 ppm). ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.53 and 2.55 ppm, major enantiomer δ 2.53 ppm; 12% e.e.; $[\alpha]_D$ −25.9 (c = 1, $CHCl_3$): 3-(methylsulfonylmethyl)toluene; oil; ^{1}H NMR δ 2.39 (3H, s), 2.74 (3H, s), 4.20 (2H, s), and 7.0–7.3 (4H, m) ppm; MS m/z 184 (M^+).

*3.4.9. 3-(Methylthiomethyl)chlorobenzene (**2c**)*

3-(Methylsulfinylmethyl)chlorobenzene; m.p. 94–96°C; chromatography 50/50 ethyl acetate/hexane to 100% ethyl acetate; R_f = 0.24 (50/50 ethyl acetate/hexane); ^{1}H NMR δ 2.48 (3H, s), 4.10 (2H, ABq, J = 14.3 Hz), 7.20 (1H, m) and 7.33 (3H, m) ppm; ^{13}C NMR δ 37.9, 59.9, 128.7, 129.1, 130.4, 130.6, 132.1, and 135.2 ppm; MS(FAB) m/z (%) 189 (100), EI found M^+ (^{35}Cl) 188.00701 (+3.9 ppm). ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.52 and 2.55 ppm, major enantiomer δ 2.52 ppm, 85% e.e.; $[\alpha]_D$ +105.1 (c = 1, EtOH): 3-(methylsulfonylmethyl)chlorobenzene, ^{1}H NMR δ 2.80 (3H, s), 4.23 (2H, s), 7.2–7.45 (4H, m).

*3.4.10. 3-(Methylthiomethyl)benzonitrile (**2d**)*

3-(Methylsulfinylmethyl)benzonitrile; m.p. 57–60°C; chromatography 80/20 ethyl acetate/hexane to 10/90 methanol/ethyl acetate; R_f = 0.18 (ethyl acetate); ^{1}H NMR δ 2.53 (3H, s), 3.93 and 4.04 (2H, ABq, J = 13.0 Hz), 7.51–7.62 (3H, m) and 7.68 (1H, m) ppm; ^{13}C NMR δ 38.0, 58.8, 113.3, 118.6, 130.1, 132.0, 132.3, 133.9, and 135.0 ppm; MS m/z (%) 179 (5), 163 (4), 146 (2), 130 (4), 116 (100), 89 (16), found M^+ 179.04077 (+1.5 ppm). ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.56 and 2.58 ppm, major enantiomer δ 2.56 ppm, 76% e.e.; $[\alpha]_D$ +148.8 (c = 1.95, EtOH).

*3.4.11. 3-(Methylthiomethyl)bromobenzene (**2e**)*

3-(Methylsulfinylmethyl)bromobenzene; m.p. 105–107°C; chromatography benzene to ether to 15% methanol/ether; R_f = 0.38 (10% methanol/ether); ^{1}H NMR δ 2.48 (3H, s), 3.90/3.98 (2H, ABq), 7.20 (2H, m) and 7.45 (2H, m) ppm; ^{13}C NMR δ 37.9, 59.8, 123.3, 129.1, 130.9, 132.0, 132.4, and 133.3 ppm; MS m/z (%) 232/234 (5), 216/218 (6), 171/169 (100), 90 (23); ^{1}H NMR (mpaa or dnb) no detectable splitting of S-CH_3 or -CH_2S- signals, > 95% e.e.; $[\alpha]_D$ +125 (c = 1, EtOH), −100 (c = 1, $CHCl_3$). Also obtained was 3-(methylsulfonylmethyl)bromobenzene; m.p. 84–86°C; ^{1}H NMR δ 2.80 (3H, s), 4.20 (2H, s), and 7.20–7.50 (4H, m) ppm; ^{13}C NMR δ 39.7, 61.0, 123.4, 129.6, 130.7, 131.0, 132.8, and 133.8 ppm; MS m/z (%) 248/250 (10), 169/171 (100), 90 (20).

*3.4.12. 3-(Methylthiomethyl)anisole (**2f**)*

3-(Methylsulfinylmethyl)anisole; oil; chromatography benzene to ether to 15% methanol/ether; R_f = 0.36 (10% methanol/ether); ^{1}H NMR δ 2.48 (3H, s), 3.82 (3H, s), 3.90/4.07 (2H, ABq), 6.80–9.95 (3H, m) and 7.30 (1H, d) ppm; ^{13}C NMR δ 37.7, 55.7, 60.7, 114.3, 115.9, 122.6, 130.4, 131.5, and 160.3 ppm; MS m/z (%) 121 (100), 91 (14); ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.51 and 2.53 ppm, major enantiomer 2.51, 82% e.e.; $[\alpha]_D$ zero (EtOH), −50 (c = 1, $CHCl_3$).

*3.4.13. 3-(Methylthiomethyl)nitrobenzene (**2g**)*

3-(Methylsulfinylmethyl)nitrobenzene; m.p. 103–104°C; chromatography benzene to ether to 15% methanol/ether; R_f = 0.25 (10%

methanol/ether); ^{1}H NMR δ 2.56 (3H, s), 3.98/4.12 (2H, ABq), 7.60–7.72 (2H, m), 8.18 (1H, s) and 8.24 (1H, d) ppm; ^{13}C NMR δ 38.1, 59.1, 123.8, 125.3, 130.3, 132.2, 136.7, and 148.8 ppm; MS m/z (%) 199 (6), 183 (2), 136 (100), 90 (49); ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.585 and 2.605, major enantiomer 2.585, 94% e.e.; $[\alpha]_D$ +166 (c = 1, EtOH), +71 (c = 1, $CHCl_3$).

*3.4.14. 3-(Methylthiomethyl)aniline (**2h**)*

3-(Methylsulfinylmethyl)aniline; oil; chromatography; benzene to ether to 15% methanol/ether; R_f = 0.18 (10% methanol/ether) ^{1}H NMR δ 2.48 (3H, s), 3.78/4.0 (2H, ABq), 6.60–6.71 (3H, m), and 7.12 (1H, t) ppm; ^{13}C NMR δ 37.7, 60.8, 115.4, 116.6, 120.0, 130.2, 131.0, and 147.7 ppm; MS m/z (%) 169 (8), 153 (3), 106 (100), 77 (11); ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.49 and 2.52 ppm, major enantiomer 2.49, 82% e.e.; $[\alpha]_D$ +14 (c = 1, EtOH), −68 (c = 1, $CHCl_3$).

*3.4.15. 4-(Methylthiomethyl)benzyl alcohol (**3i**)*

4-(Methylsulfinylmethyl)benzyl alcohol; semi-solid; chromatography ethyl acetate; ^{1}H NMR δ 2.46 (3H, s), 3.80/3.90 (2H, ABq, J = 12.9 Hz), 4.71 (2H, s), 7.33 (2H, m) and 7.41 (2H, m) ppm; ^{13}C NMR δ 37.3, 59.8, 64.3, 127.7, 128.6, 130.8, and 142.4 ppm; MS(FAB) m/z (%) 185 (57), 121 (100), EI found M^+ 184.05583 (0.1 ppm). ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.48 and 2.51 ppm, major enantiomer δ 2.48 ppm, 92% e.e.; $[\alpha]_D$ +63.5 (c = 1, EtOH). Crystallisation from ethyl acetate/hexane gives m.p. 88–90°C; $[\alpha]_D$ +69.5 (c = 1, EtOH), > 95% e.e.

*3.4.16. 2-(4-Nitrophenyl)ethyl methyl sulfide (**4b**)*

2-(4-Nitrophenyl)ethyl methyl sulfoxide; m.p. 95–98°C; chromatography (70/30 ethyl acetate/hexane to 10/90 methanol/ethyl acetate); R_f = 0.15 (10/90 methanol/ethyl acetate); ^{1}H NMR δ 2.62 (3H, s), 2.97 (2H, m), 3.23 (2H, t, J = 7.6 Hz), 7.43 (2H, d, J = 8.3 Hz) and 8.17 (2H, d, J = 8.6 Hz) ppm; ^{13}C NMR δ 28.9, 39.1, 55.3, 124.4, 129.9, 146.9, and 147.3 ppm; MS(FAB) m/z (%) 214 (100), found M^+ 214.05948 (+26.5 ppm). ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.66 and 2.69 ppm, major enantiomer δ 2.66 ppm, 75% e.e.; $[\alpha]_D$ +84.6 (c = 1, EtOH). Crystallization from dichloromethane/hexane gave m.p. 99–100°C; $[\alpha]_D$ + 100.9° (c = 1, EtOH), 90% e.e.: 2-(4-nitrophenyl)ethyl methyl sulfone; ^{1}H NMR δ2.94 (3H, s), 3.33 (4H, m), 7.45 (2H, d, J = 8.4 Hz) and 8.21 (2H, d, J = 8.4 Hz) ppm; ^{13}C NMR δ 28.4, 41.6, 55.6, 124.6, 129.8, 130.3, and 145.4 ppm.

*3.4.17. 2-(4-Aminophenyl)ethyl methyl sulfide (**4c**)*

2-(4-Aminophenyl)ethyl methyl sulfoxide; oil; chromatography 90/10 ethyl acetate/hexane to 10/90 methanol/ethyl acetate); R_f = 0.40 (10/90 methanol/ethyl acetate); ^{1}H NMR δ 2.58 (3H, s), 2.85–3.05 (4H, m), 3.97 (2H, br.s), 6.67 (2H, m) and 7.05 (2H, m) ppm; ^{13}C NMR δ 28.3, 39.0, 57.0, 115.8, 128.9, 129.8, and 145.9 ppm; MS(FAB) m/z (%) 184 (100), EI found M^+ 183.07218 (+2.1 ppm). ^{1}H NMR (mpaa) S-CH_3 splits to δ 2.60 and 2.62 ppm, major enantiomer δ 2.60 ppm, 40% e.e.; $[\alpha]_D$ +56.4 (c = 1, EtOH).

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