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Asymmetric synthesis of modafinil and its derivatives by enantioselective oxidation of thioethers: comparison of various methods including synthesis in ionic liquids

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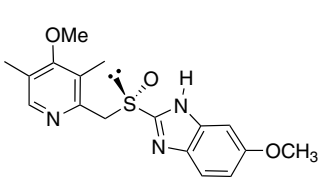
Abstract—The oxidation of 2-(benzhydrylthio)acetic acid and its derivatives was performed with various catalytic and stoichiometric enantioselective reagents, the best results being obtained with stoichiometric chiral oxaziridine **5**. The use of [bmim][PF_6] as a solvent with **5** gave slightly higher yields and, in the case of the model compound thioanisole, a reversal of the enantioselectivity.

1. Introduction

Enantiopure sulfoxides are important auxiliaries in asymmetric synthesis and chiral ligands in enantioselective catalysis.[1–4] Moreover, a few drugs which contain stereogenic sulfur in a sulfoxide unit, have emerged in the pharmaceutical industry, such as esomeprazole (a powerful proton pump inhibitor used as an anti-ulcer agent), OPC-29030 (a platelet adhesion inhibitor), or modafinil (a psychostimulant used in the treatment of sleep disorders such as narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder).



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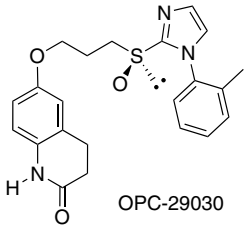

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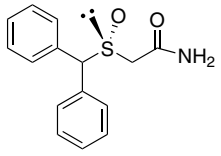

Modafinil

Several methods can be envisioned for the preparation of enantiopure sulfoxides. Andersen was the first to describe a general method using a chiral sulfinate intermediate.[5,6] Since this seminal work, a lot of effort has been devoted to the preparation of enantiopure sulfoxides, mainly via asymmetric oxidation of the corresponding thioether. The most popular method to date was discovered independently by Kagan[7,8] and Modena[9] using a modified Sharpless catalytic system (ROOH/Ti(O*i*Pr)$_4$/DET). After this success, numerous catalytic and stoichiometric methods were described, and in some cases, performances were competitive with the Sharpless/Kagan system.[2] Among these systems, a catalytic organometallic complex of a vanadium-chiral Schiff base **1** using hydrogen peroxide as a terminal oxidant was developed by Bolm.[10,11] This method was later improved by Anson using the Schiff base **2** to give higher enantioselectivities.[12] Bolm also developed a method involving iron and the Schiff base **2**.[13,14] Salen–manganese complexes, such as **3**, can also be used for the enantioselective oxidation of thioethers.[15]

Chiral stoichiometric oxidants can also be used for this reaction. Electron-deficient oxaziridines developed by Davis emerged in the eighties as a new class of stoichiometric asymmetric oxidants. Indeed, chiral oxaziridines **4** and **5**

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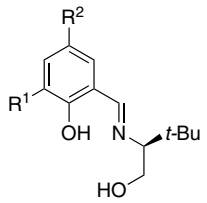
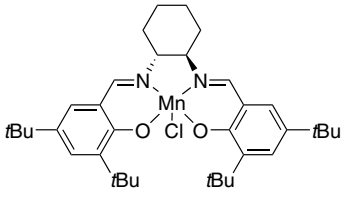


1, R^1 = *t*Bu, R^2 = NO_2
2, R^1, R^2 = I



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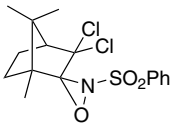

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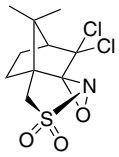

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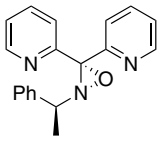
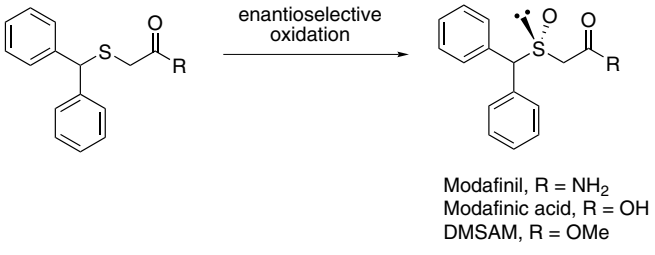


6

were designed to achieve thioether oxidation with high enantioselectivities.[16,17] Recently, Fontecave and Hamelin developed a new generation of oxaziridines such as **6**, which give high enantioselectivities when activated by a Lewis acid.[18] However, most of these systems were mainly assessed on unfunctionalized thioethers.

In 2005, Cephalon patented the preparation of (*R*)-modafinil from the corresponding thioether using a Kagan system, with a good yield and excellent enantioselectivity.[19] However, this method gave disappointing results on the related compounds, modafinic acid and DMSAM. Herein, we report the assessment of alternative methods for the obtention of modafinil and its acid and methylester by enantioselective oxidation, including the first enantioselective oxidation of thioethers in an ionic liquid (Eq. 1).



(1)

2. Results and discussion

Our first study involved various catalytic systems using vanadium or iron-Schiff base complexes, as well as an Mn–salen complex, and H_2O_2 as the terminal oxidant. The results obtained are summarized in Table 1, along with the results obtained by Cephalon with the use of the Kagan system for the sake of comparison. We also checked the efficiency of these catalytic systems in our hands by running the reaction on thioanisole and comparing our results with the previously reported ones.

In stark contrast with the Kagan system, none of the three alternative catalytic systems were able to provide an acceptable yield and/or enantiomeric excess with any of the three substrates. The Mn–salen system, which performs rather poorly with thioanisole, gave the best ee on modafinil and DMSAM, whereas the two systems based on the use of a *tert*-leucine derived Schiff base, which perform rather well on thioanisole, failed to give enantiomeric excesses over 15%. No enantioselectivity could be observed with modafinic acid with any of the three catalytic systems tested.

After these rather disappointing results, we turned to the study of stoichiometric chiral oxidants **5** and **6**, using the previously described experimental conditions.[17,18] The results obtained with the three functionalized substrates, as well as with thioanisole, are summarized in Table 2.

The first results obtained with oxaziridine **6** were rather promising. Modafinil could be obtained in 70% yield with a 21% ee (entry 1). The corresponding methyl ester DMSAM was obtained in a much lower yield of 20%, but with an increased 39% ee (entry 3). Interestingly, the use of the same enantiomer of oxaziridine **6** gives modafinil and DMSAM with opposite configurations. It should be noted that oxaziridine **6** can be easily obtained as either enantiomer from the inexpensive (*R*)- or (*S*)-α-methylbenzylamine, thus allowing access to both enantiomers of modafinil and DMSAM. Disappointingly, only trace amounts of modafinic acid could be detected in the oxidation of the corresponding thioether with this oxaziridine (entry 2).

Even more interestingly, oxaziridine **5** afforded similar, or higher, enantiomeric excesses with our functionalized substrates, than with the model substrate thioanisole

Table 1. Catalytic enantioselective oxidation

	[Fe(acac)$_3$]/**2**[a]	[VO(acac)$_2$]/**2**[b]	**3**[c]	Ti(O*i*Pr)$_4$/DET
Modafinil	10% (ee 15%) (*R*)	45% (ee 12%) (*R*)	40% (ee 18%) (*S*)	70% (ee 99%) (*R*)[d,19]
DMSAM	11% (*rac*)	8% (*rac*)	70% (ee 31%) (*S*)	40% (ee 10%) (*S*)[e,19]
Modafinic acid	48% (*rac*)	5% (*rac*)	43% (*rac*)	70% (ee 50%) (*S*)[e,19]
PhS(O)Me	77% (ee 82%) (*S*)[f]	70% (ee 91%) (*S*)[g]	70% (ee 19%) (*S*)[h]	81% (ee 91%) (*R*)[e,20]

[a] [Fe(acac)$_3$] (2 mol %), **2** (4 mol %), 4-methoxybenzoic acid (1 mol %), 30% aq H_2O_2 (1.2 equiv), CH_2Cl_2, 20 °C, 16 h.
[b] [VO(acac)$_2$] (1%), **2** (1.5%), 30% aq H_2O_2 (1.2 equiv), $CHCl_3$, 0 °C, 16 h.
[c] **3** (3%), 30% aq H_2O_2 (6 equiv), CH_3CN, 20 °C, 24 h.
[d] Using (−)-DET as ligand.
[e] Using (+)-DET as ligand.
[f] Lit.[14] 63% (ee 80%) (*S*).
[g] Lit.[21] 70% (ee 97%) (*R*) using *ent*-**2** as ligand.
[h] After 3 h. Lit.[15] 72% (ee 24%) (*S*) after 1 h.

Table 2. Stoichiometric enantioselective oxidation

Entry	Sulfoxide	Oxaziridine	Yield (ee) (conf.)
1	Modafinil	**6**[a]	70% (21%) (*S*)
2	Modafinic acid	**6**[a]	—[e]
3	DMSAM	**6**[a]	20% (39%) (*R*)
4	PhS(O)Me	**6**[a,b]	80% (33%) (*S*)[f]
5	Modafinil	**5**[c]	66% (60%) (*S*)
6	Modafinic acid	**5**[c]	47% (90%) (*S*)
7	DMSAM	**5**[c]	90% (75%) (*S*)
8	PhS(O)Me	**5**[c,d]	85% (65%) (*S*)[g]

[a] **6** (0.9 equiv), $ZnCl_2$ (0.9 equiv), $CHCl_3$, 20 °C, 24 h.
[b] After 5 h.
[c] **5** (0.9 equiv), CCl_4, 20 °C, 48 h.
[d] After 3 h.
[e] Traces of racemic modafinic acid could be detected by chiral HPLC.
[f] Lit.[18] 55% (42%) (*R*) with *ent*-**6** as the oxidant and 1 h reaction time.
[g] The related *p*-tolylmethylsulfoxide was obtained with 67% ee (*S*) from the corresponding thioether.[17]

(entries 5–8). Moderate to high yields of each sulfoxide were obtained, with ees ranging from 60% to 90%. In contrast to the other oxidative systems studied so far, the best enantiomeric excess was obtained with modafinic acid (entry 6). This enantioselective oxidative system appears much more robust than the other (particularly catalytic) ones. Nevertheless, this interesting and promising result still has two drawbacks, especially for a potential development on a larger scale: first, the yields observed seem to be substrate-dependent (ranging from 47% to 90%), and second, the use of carbon tetrachloride as the solvent precludes any industrial or semi-industrial application of the method.

Ionic liquids (i.e., room temperature liquid organic salts) form a particularly attractive class of polar non-volatile and non-flammable solvents that are considered by many specialists in the field as excellent candidates for the replacement of volatile organic solvents.[22–24] In the context of green chemistry, they are strongly believed to have a promising future. Although many reports highlight the success of ionic solvents in various areas of organic reactions, particularly in the field of oxidation,[25,26] to the best of our knowledge, there is no information currently available about enantioselective oxidations of thioethers in these media. Since our research group investigates the use of ionic liquids in various applications for organic synthesis,[27–29] including asymmetric synthesis studies,[30] we evaluated the best oxidative system in our hands (i.e., Davis oxaziridine **5**) in the air and moisture stable, hydrophobic ionic liquid, [bmim][PF_6] **7**. Owing to the cost of the ionic liquid, the reactions were carried out at higher concentration in [bmim][PF_6] (1 mol/L) than in CCl_4 (0.017 mol/L). Results are summarized in Table 3.

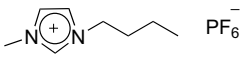


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Table 3. Asymmetric oxidation with oxaziridine **5** in ionic liquid

Entry	Sulfoxide	Yield (ee) (conf.)
1	Modafinil	73% (55%) (*S*)
2	Modafinic acid	73% (78%) (*S*)
3	DMSAM	87% (70%) (*S*)
4	PhS(O)Me	77% (33%) (*R*)

Conditions: **5** (0.9 equiv), [bmim][PF_6], 20 °C, 48 h.

We were delighted to observe that the desired sulfoxides were obtained in somewhat higher yields than in the alternative solvent. Regarding asymmetric induction, the ees were almost as high as in CCl_4. This result was not obvious since it is well documented that enantioselective oxidations with oxaziridine **5** perform generally better in apolar solvents.[31] Ionic liquids are generally considered as polar ones, and this behaviour suggests that the mechanism of oxaziridine–thioether oxygen transfer could be influenced by ionic solvents. Another unexpected result confirms this hypothesis: to our surprise, the use of oxaziridine **5** in [bmim][PF_6] on thioanisole gave the corresponding sulfoxide with 33% ee in favour of the (*R*)-enantiomer (Table 3, entry 4), whereas the same reagent favours the (*S*)-enantiomer in CCl_4 (Table 2, entry 8). This inversion of the sense of asymmetric induction was not observed in the case of functionalized sulfoxides. To rule out the difference of concentration as the reason for the observed inversion effect, the oxidation of thioanisole with oxaziridine **5** was carried out in toluene[†] at both concentrations. Increasing the concentration induced a small decrease in both yields (93% vs 98%) and enantiomeric excess (44% vs 60%): however, the sense of asymmetric induction was the same under both conditions. We are currently investigating the optimization of the procedure to improve the ees.

3. Conclusion

This study presents a series of new findings that should be useful in the field of asymmetric synthesis of functionalized sulfoxides:

- The discovery of new enantioselective oxidation systems stand generally on model reactions carried out on model substrates, typically aryl-methyl sulfides. We show that the use on functionalized substrates is not always straightforward, and requires at least a thorough re-examination of the experimental conditions.
- For the substrates used in this study, that is, the modafinil series, stoichiometric reagents such as chiral oxaziridines give a much more reliable and general performance than chiral metallo catalysts.
- Ionic liquids are appropriate media for oxaziridine–thioether oxygen transfers, opening up the way to replace halogenated solvents for this chemistry.
- Unexpected observations suggest a different mechanistic behaviour of oxidation by oxaziridines in ionic liquids with respect to molecular solvents. We think that pro-

[†] The reaction could not be run at 1 mol/L in CCl_4 owing to the poor solubility of **5** in this solvent.

gress will come from new mechanistic insights and are currently focusing on the understanding of the reaction in ionic medium.

4. Experimental

Compounds **2**,[14] **3**[15] and **6**[15] were prepared according to the literature procedures. Oxaziridine **5** was purchased from Fluka and used as received. The various thioethers were provided by Cephalon or purchased from Aldrich (for thioanisole) and used as received. Hydrogen peroxide (30% aqueous solution) was purchased from Fluka and titrated before use. The [bmim][PF_6] (99%) was purchased from Solvionics and used as received. All solvents were purified according to standard procedures. ^1H and ^{13}C NMR spectra of all the obtained sulfoxides were compared to those of authentic samples provided by Cephalon (for modafinil, modafinic acid and DMSAM) or to the literature values (for methylphenylsulfoxide).

NMR spectra were recorded on a Bruker Advance-300 instrument (300 MHz for ^1H NMR, 75 MHz for ^{13}C NMR) using $CDCl_3$ or DMSO-d_6 as solvent; δ values are quoted in ppm downfield from TMS using the residual proton signal of the solvent as reference, and J values are quoted in Hz. Liquid chromatography (HPLC) were performed on a Thermoseparation Products P100 with a UV detector UV100 set at 220, 222 and 254 nm or a Hewlett Packard series 1100 with UV detector at the same wavelength.

4.1. General procedure for oxidation catalyzed by iron/2 complex[14]

[$Fe(acac)_3$] (7.1 mg, 0.02 mmol) and ligand **2** (18.9 mg, 0.04 mmol) were dissolved in dichloromethane (0.7 mL), and the clear red solution was stirred until it turned clear brown (15 min). This solution was then added to a suspension of 4-methoxybenzoic acid (1.5 mg, 0.01 mmol) in dichloromethane (0.5 mL) in a 10 mL flask, and the resulting mixture was stirred for 10 min. A solution of thioether (1 mmol) in dichloromethane (0.8 mL) was then added to the previous solution, followed by the dropwise addition of 30% aqueous H_2O_2 solution (123 μL, 1.2 mmol, 1.2 equiv). The flask was capped, and the reaction mixture was slowly stirred at 20 °C. After 16 h, the aqueous layer was separated, and the organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The product was then purified (see below) to give the desired sulfoxide.

4.2. General procedure for the oxidation catalyzed by a vanadium/2 complex[21]

A solution of [$VO(acac)_2$] (5.3 mg, 0.02 mmol, 0.01 equiv) in chloroform (0.5 mL) was added to a solution of Schiff base **2** (14.1 mg, 0.03 mmol, 0.015 equiv) in chloroform (0.5 mL) and the reaction mixture was stirred for 2 h. A solution of thioanisole (237 μL, 2 mmol, 1 equiv) in chloroform (1 mL) was added and the reaction mixture stirred for 30 min at room temperature before cooling to 0 °C. After 30 min, 30% H_2O_2 (245 μL, 2.4 mmol, 1.2 equiv) was added to the reaction mixture, which was stirred vigorously at 0 °C for 16 h. The reaction was quenched with 10% $Na_2S_2O_3$ solution (10 mL) and the mixture extracted with CH_2Cl_2 (3 × 20 mL). The extracts were combined, washed with brine (3 × 20 mL), and dried over Na_2SO_4. Finally, the solvent was removed under reduced pressure. The crude product was purified (see below) to give the desired sulfoxide.

4.3. General procedure for the oxidation by manganese complex 3[15]

In a 10 mL test tube flask equipped with a magnetic stirring bar and nitrogen inlet was placed Jacobsen's catalyst **3** (15.5 mg, 0.024 mmol, 0.03 equiv) in 3 mL of MeCN thermostated at 20 °C, followed by the addition of the thioether (0.8 mmol, 1 equiv) in solution, and the addition of 30% aqueous H_2O_2 (0.49 mL, 4.8 mmol, 6 equiv). The reaction was monitored by TLC (CH_2Cl_2/MeOH 98:2). After 3–24 h, the reaction mixture was dissolved in CH_2Cl_2 and excess of H_2O_2 was quenched with 10% $NaHSO_3$ aqueous solution. The organic layer was then dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified (see below) to give the desired sulfoxide.

4.4. General procedure for oxidation with oxaziridine 6[18]

To a solution of oxaziridine **6** (0.4 mmol) in 40 mL of chloroform were successively added the desired thioether (0.44 mmol) and $ZnCl_2$ (0.4 mmol) (1:1:1.1 oxaziridine/Lewis acid/sulfide ratio) at 20 °C. The monitoring of formation of the sulfoxide was done by TLC (CH_2Cl_2/MeOH 98:2). After 24 h, the reaction mixture was quenched with water and organic later was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified (see below) to give the desired sulfoxide.

4.5. Standard conditions for the oxidation of sulfides with oxaziridine 5 in CCl_4[17]

In a 50 mL round-bottom flask equipped with a magnetic stirring bar and argon inlet was placed 0.5 mmol of (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine **5** in 30 mL of CCl_4 at 20 °C, followed by the addition of 1.1 equiv of the sulfide. After completion of the reaction as indicated by TLC, the solvent was evaporated under reduced pressure. The crude product was purified (see below) to give the desired sulfoxide.

4.6. Standard conditions for oxidation of sulfides with oxaziridine 5 in [bmim][PF_6]

In a 10 mL test tube equipped with a magnetic stirring bar and an argon inlet was placed 0.5 mmol of (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine **5** dissolved in 0.5 mL [bmim][PF_6] at 20 °C, followed by the addition of 1.1 equiv of the sulfide. The reaction was monitored by TLC (98% CH_2Cl_2/MeOH 2%). After 48 h, the ionic liquid was extracted by toluene (3–5 × 15 mL). The toluene layer was evaporated under reduced pressure and the crude product was purified (see below) to give the desired sulfoxide,

except for modafinic acid for which the ionic liquid solution was directly dissolved in dichloromethane without prior extraction.

4.7. (Benzhydrylsulfinyl)-acetic acid (modafinic acid)

Modafinic acid was purified by extraction with an aqueous K_2CO_3 solution (0.5 M) of the crude product dissolved in dichloromethane (20 mL), the separation of the aqueous layer and acidification to pH 1 to precipitate the modafinic acid, which was collected by filtration and oven dried at 50 °C to give a white solid. ^{1}H NMR (DMSO-d_6): δ 13.22 (br s, 1H, CO_2H) 7.3–7.53 (m, 10H, Ar-H) 5.41 (s, 1H, CH) 3.49 (d, 1H, $J = 14.3$ Hz, CH_2) 3.37 (d, 1H, $J = 14.3$ Hz, CH_2). ^{13}C NMR (DMSO-d_6): δ 167.4, 136.6, 134.9, 129.6, 129.1, 128.6, 128.5, 128.1, 128, 69.3, 55.4. Enantiomeric excess was determined by chiral HPLC on a Chiralpak AD-H (250 × 4.6 mm) column eluting with a hexane/isopropanol/triethylamine/TFA (85:15:0.1:0.1) mixture (0.7 mL/min, $\lambda = 220$ nm, retention times 16.8 min for (*S*)-(+)-modafinic acid and 20.2 min for (*R*)-(−)-modafinic acid). $[\alpha]_D^{20} = +39.1$ (*c* 1.0, MeOH) for ee = 90% (*S*).

4.8. Methyl(diphenylmethanesulfinyl)-acetate (or DMSAM)

DMSAM was purified by flash chromatography on silica gel (Et_2O 100%) to give a white solid. ^{1}H NMR ($CDCl_3$): δ 7.27–7.39 (m, 10H, Ar-H) 5.13 (s, 1H, CH) 3.67 (s, 3H, OCH_3) 3.49 (d, 1H, $J = 13.9$ Hz, CH_2) 3.37 (d, 1H, $J = 14.3$ Hz, CH_2). ^{13}C NMR ($CDCl_3$): δ 166, 135.4, 133.9, 129.7, 129.4, 129, 128.9, 128.7, 128.6, 71.7, 54.2, 52.9. Enantiomeric excess was determined by chiral HPLC on a Chiralpak AD-H (250 × 4.6 mm) column eluting with isopropanol (0.5 mL/min, $\lambda = 222$ nm, retention times 15.2 min for (*S*)-(+)-DMSAM and 24.3 min for (*R*)-(−)-DMSAM). $[\alpha]_D^{20} = +15.1$ (*c* 1.0, MeOH) for ee = 75% (*S*).

4.9. (Benzhydrylsulfinyl)-acetamide (modafinil)

Modafinil was purified by flash chromatography on silica gel (Et_2O 100%, then CH_2Cl_2/MeOH 97:3) to give a white solid. ^{1}H NMR (DMSO-d_6): δ 7.69 (s, 1H, CO–NH) 7.50–7.53 (m, 4H, Ar-H) 7.33–7.44 (m, 7H, Ar-H+CONH) 5.35 (s, 1H, CH) 3.40 (d, 1H, $J = 13.5$ Hz, CH_2); 3.25 (d, 1H, $J = 13.9$ Hz, CH_2). ^{13}C NMR (DMSO-d_6): δ 166.4, 137.2, 134.9, 129.7, 129.1, 128.5, 128, 127.9, 68.8, 56.2. Enantiomeric excess was determined by chiral HPLC on a Chiralpak AS (250 × 4.6 mm) column eluting with ethyl alcohol (0.5 mL/min, $\lambda = 220$ nm, retention times 10.2 min for (*S*)-(+)-modafinil and 14.7 min for (*R*)-(−)-modafinil). $[\alpha]_D^{20} = +14.1$ (*c* 1.0, MeOH) for ee = 60% (*S*).

4.10. Methyl phenyl sulfoxide

Methyl phenyl sulfoxide was purified by flash chromatography on silica gel (Et_2O 100%, then CH_2Cl_2/MeOH 98:2) to give a colourless liquid. ^{1}H NMR ($CDCl_3$): δ 7.64–7.66 (m, 2H); 7.51–7.54 (m, 3H); 2.73 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 145.7, 131.2, 129.5, 123.6, 44.0. Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD-H (250 × 4.6 mm) column eluting with a heptane/isopropanol (90:10) mixture (0.5 mL/min, $\lambda = 254$ nm, retention times 22.9 min for (*R*)-methylphenylsulfoxide and 25.7 min for (*S*)-methylphenylsulfoxide).

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