A General and Expedient One-Pot Synthesis of Sulfoxides in High Optical Purity from Norephedrine-Derived Sulfamidites.

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Supporting Information

General methods.

NMR spectra were obtained using a Bruker spectrometer (300 and 75 MHz for ^1H and ^{13}C , respectively) in CDCl_3 solutions. Melting points were measured using a Gallenkamp apparatus in open capillary tubes. Specific rotations were measured in a Perkin-Elmer 241 MC polarimeter. ee's of sulfoxides **6** were evaluated by HPLC using a Chiralcel OD (Chiralpak AS for cyclohexylisopropyl and cyclohexyldecylsulfoxides) column and hexane/isopropanol as an eluant.

Procedure for the preparation of sulfamidites **3a** and **3b**.

To a stirred solution of 1.5 g (10 mmol) of (1*R*,2*S*)-(-)-norephedrine **1** and 4.89g (40 mmol) of 4-(*N,N*-dimethylamino)pyridine in dry CH_2Cl_2 (20 mL) at 0°C , 1.5 mL of ClCO_2Bn (10.5 mmol) were added. After 5 min. the reaction was cooled to -40°C and 1.0 mL (14 mmol) of SOCl_2 were added and the mixture was stirred for 15 min. Addition of water and extraction with CH_2Cl_2 (3x20 mL) afforded a crude mixture of **3a** and **3b**. **3a** was isolated in 57% yield after chromatographic purification (CH_2Cl_2 /hexane (1:1)).

For preparation of **3b**, 2,6-lutidine should be used instead of 4-(*N,N*-dimethylamino)pyridine.

Benzyl (2*R*, 4*S*, 5*R*)-4-methyl-5-phenyl-1,2,3-oxathiazolidine-2-oxide-3-carboxylate (**3a**)

^1H NMR: δ 7.39 (m, 10H), 5.77 (d, $J = 6.4$ Hz, 1H), 5.36 and 5.27 (AB system, $J = 12.1$ Hz, 2H), 4.49 (m, 1H), 1.14 (d, $J = 6.8$ Hz, 3H).

^{13}C NMR: δ 151.8, 134.9, 133.8, 128.7, 128.6, 128.6, 128.5, 128.1, 126.2, 90.5, 68.6, 54.8, 16.8.
[α]_D: -152 (c 0.97, CHCl_3).

Benzyl (2*S*, 4*S*, 5*R*)-4-methyl-5-phenyl-1,2,3-oxathiazolidine-2-oxide-3-carboxylate (**3b**)

^1H NMR: δ 7.37 (m, 10H), 6.37 (d, $J = 5.4$ Hz, 1H), 5.29 (s, 2H), 4.49 (m, 1H), 0.87 (d, $J = 6.5$ Hz, 3H).

^{13}C NMR: δ 152.1, 135.1, 132.7, 128.8, 128.4, 128.3, 127.9, 125.9, 85.0, 68.4, 56.4, 14.5.
 $[\alpha]_{\text{D}}$: -17 (*c* 1, CHCl_3).
 m. p.: 111-112°C.

General preparation of sulfonates 4.

The procedure for one-pot preparation of sulfoxides (vide infra) was followed. 10-25 min after the addition of RMgX , the reaction is quenched with NH_4Cl (aq.), worked-up and purified by flash chromatography.

(1R, 2S)-2-[[[(Benzyloxy)carbonyl]amino]-1-phenylpropyl (S)-methanesulfonate

^1H NMR: δ 7.34 (m, 10H), 5.48 (d, J = 8.7 Hz, 1H), 5.36 (d, J = 2.1 Hz, 1H), 5.16 and 5.08 (AB system, J = 12.3 Hz, 2H), 4.08 (m, 1H), 2.74 (s, 3H), 1.05 (d, J = 6.8 Hz, 3H).
 ^{13}C NMR: δ 155.9, 137.8, 136.7, 128.6 (2C), 128.5, 128.3, 128.0, 126.1, 84.5, 66.7, 51.8, 44.9, 13.7.
 $[\alpha]_{\text{D}}$: -92 (*c* 1, CHCl_3).
 m. p.: 96-97°C.

(1R, 2S)-2-[[[(Benzyloxy)carbonyl]amino]-1-phenylpropyl (S)-ethanesulfonate

^1H NMR: δ 7.34 (m, 10H), 5.55 (d, J = 8.3 Hz, 1H), 5.36 (d, J = 2.0 Hz, 1H), 5.17 and 5.09 (AB system, J = 12.5 Hz, 2H), 4.09 (m, 1H), 2.88 (m, 2H), 1.30 (t, J = 7.5 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H).
 ^{13}C NMR: δ 155.9, 137.8, 136.8, 128.6 (2C), 128.5, 128.3, 128.0, 126.1, 84.7, 66.7, 51.9, 51.3, 13.8, 5.4.
 $[\alpha]_{\text{D}}$: -96 (*c* 1, CHCl_3).
 m. p.: 67-68°C.

(1R, 2S)-2-[[[(Benzyloxy)carbonyl]amino]-1-phenylpropyl (S)-propane-2-sulfonate

^1H NMR: δ 7.35 (m, 10H), 5.64 (d, J = 8.7 Hz, 1H), 5.34 (d, J = 2.2 Hz, 1H), 5.17 and 5.09 (AB system, J = 12.3 Hz, 2H), 4.08 (m, 1H), 2.87 (sp, J = 7.0 Hz, 1H), 1.29 (d, J = 7.5 Hz, 3H), 1.28 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H).
 ^{13}C NMR: δ 155.7, 139.2, 137.5, 128.3 (2C), 127.9, 127.7 (2C), 125.9, 84.4, 66.4, 55.5, 51.7, 13.8, 13.6.
 $[\alpha]_{\text{D}}$: -87 (*c* 0.85, CHCl_3).

(1R, 2S)-2-[[[(Benzyloxy)carbonyl]amino]-1-phenylpropyl (S)-2-methylpropane-2-sulfonate

^1H NMR: δ 7.31 (m, 10H), 5.74 (d, J = 8.9 Hz, 1H), 5.32 (d, 2.6 Hz, 1H), 5.15 and 5.07 (AB system, J = 12.4 Hz, 2H), 4.06 (m, 1H), 1.23 (s, 9H), 1.04 (d, J = 6.8 Hz, 3H).

^{13}C NMR: δ 155.8, 137.6, 136.7, 128.6, 128.4, 128.07, 127.9, 127.9, 126.2, 84.6, 66.5, 58.0, 51.9, 21.7, 13.8.

$[\alpha]_{\text{D}}$: -92 (*c* 1, CHCl_3).

m. p.: 73-74°C.

(1*R*, 2*S*)-2-[[*(*Benzyloxy)carbonyl]amino]-1-phenylpropyl (*S*)-benzenesulfinate

^1H NMR: δ 7.75 (m, 2H), 7.56 (m, 3H), 7.37 (m, 10H), 5.56 (d, *J* = 2.0 Hz, 1H), 5.50 (d, *J* = 8.9 Hz, 1H), 5.19 and 5.11 (AB system, *J* = 12.1 Hz, 2H), 4.1 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR: δ 155.9, 145.5, 137.9, 136.8, 132.5, 129.2, 128.6, 128.6, 128.3, 128.1, 126.3, 125.1, 84.7, 66.7, 52.0, 13.8.

$[\alpha]_{\text{D}}$: -116 (*c* 1, CHCl_3).

(1*R*, 2*S*)-2-[[*(*Benzyloxy)carbonyl]amino]-1-phenylpropyl (*S*)-*p*-methoxybenzenesulfinate

^1H NMR: δ 7.68 and 7.03 (AA'BB' system, 4H), 7.36 (m, 10H), 5.59 (d, *J* = 9.1 Hz, 1H), 5.54 (d, *J* = 2.0 Hz, 1H), 5.19 and 5.10 (AB system, *J* = 12.3 Hz, 2H), 4.1 (m, 1H), 3.85 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR: δ 162.9, 155.9, 138.2, 137.1, 136.8, 128.6, 128.2, 128.0, 126.9, 126.3, 114.6, 84.1, 66.7, 55.7, 52.0, 13.8.

$[\alpha]_{\text{D}}$: -84 (*c* 1, CHCl_3).

General procedure for one-pot preparation of sulfoxides 6.

RMgX (0.3 mmol) is added to a solution of **3a** (100 mg, 0.3 mmol) in dry CH_2Cl_2 (3 mL) under argon at -78°C . After 10-25 min (TLC), HBF_4 (50 μL of a 54% wt. solution in Et_2O , 0.36 mmol) is added. 5 min later, $\text{R}'\text{MgX}$ (2.5 or 5 equiv) is added at the temperature indicated in each case (Table 1). The evolution is monitored by TLC (10-45 min). Finally, the reaction is quenched with NH_4Cl (aq.) and extracted with CH_2Cl_2 (3x5 ml). The crude mixture is purified by flash chromatography.

Table 1. Temperature and number of equivalents for the second step.

Entry	R	R'	Temperature (°C)	Equiv of R'MgX
1	Ph	Me	-78	2.5
2	Ph	<i>i</i> -Pr	-78	2.5
3	Ph	Vinyl	-78	2.5
4	<i>i</i> -Pr	Et	-20	2.5
5	<i>i</i> -Pr	Ph	-20	2.5
6	<i>p</i> -Anisyl	Et	-78	2.5
7	<i>p</i> -Anisyl	<i>p</i> -Tol	-78	2.5
8	<i>p</i> -Anisyl	Vinyl	-78	2.5
9	<i>p</i> -Anisyl	<i>t</i> -Bu	-20	5.0
10	Mesityl	<i>p</i> -Tol	-20	5.0
11	Mesityl	Me	-20	5.0
12	Mesityl	Vinyl	-78	5.0
13	Me	Mesityl	-78	2.5
14	Cyclohexyl	<i>i</i> -Pr	-20	2.5
15	Cyclohexyl	Decyl	-20	2.5
16	<i>t</i> -Bu	<i>p</i> -Anisyl	r. t.	5.0

(*R*)-Methylphenylsulfoxide¹¹H NMR: δ 7.56 (m, 5H), 2.70 (s, 3H).¹³C NMR: δ 145.3, 130.7, 129.0, 123.1, 43.6.[α]_D: +137 (*c* 1, acetone) for a 93% ee.Lit.¹ [α]_D: +147.5 (acetone).**(*R*)-Isopropylphenylsulfoxide²**¹H NMR: δ 7.50 (m, 5H), 2.81 (sp, *J* = 6.9 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H).¹³C NMR: δ 141.6, 130.8, 128.7, 124.8, 54.4, 15.7, 13.8.[α]_D: +196 (*c* 1, MeOH) for a 93% ee.Lit.² [α]_D: +169.9 (*c* 1.6, acetone).**(*S*)-Isopropylphenylsulfoxide²**[α]_D: -198 (*c* 1, MeOH) for a 95% ee.**(*R*)-Phenylvinylsulfoxide³**¹H NMR: δ 7.61 (m, 2H), 7.50 (m, 3H), 6.59 (dd, *J* = 9.7 and 16.6 Hz, 1H), 6.19 (d, *J* = 16.6 Hz, 1H), 5.89 (d, *J* = 9.7 Hz, 1H).¹³C NMR: δ 143.3, 142.9, 131.1, 129.3, 124.6, 120.5.¹ Jacobus, J.; Mislow, K. *J. Am. Chem. Soc.* **1967**, 89, 5228.² Sugimoto, T.; Kokuba, T.; Miyazaki, J.; Tanimoto, S.; Okano, M. *J. Chem. Soc. Chem. Commun.* **1979**, 402.³ Benson, S. C.; Snyder, J. K. *Tetrahedron Lett.* **1991**, 32, 5885.

$[\alpha]_D$: +333 (*c* 0.98, MeOH) for a 95% ee.

Lit.² $[\alpha]_D$ (*S* config.): -376 (*c* 1, MeOH) for a >99% ee.

(*R*)-Ethylisopropylsulfoxide⁴

¹H NMR: δ 2.76 (sept, *J* = 6.8 Hz, 1H), 2.63 (m, 2H), 1.34 (t, *J* = 7.5 Hz, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.25 (d, *J* = 6.8 Hz, 3H).

¹³C NMR: δ 49.4, 41.9, 16.0, 14.5, 7.0.

$[\alpha]_D$: +20 (*c* 0.2, CHCl₃)

(*R*)-Ethyl-*p*-methoxyphenylsulfoxide⁵

¹H NMR: δ 7.52 and 6.99 (AA'BB' system, 4H), 3.82 (s, 3H), 2.78 (m, 2H), 1.14 (t, *J* = 7.3 Hz, 3H).

¹³C NMR: δ 161.9, 134.3, 126.2, 114.7, 55.6, 50.5, 6.2.

$[\alpha]_D$: +166 (*c* 1.2, CHCl₃) for a 93% ee.

(*R*)-*p*-Methoxyphenyl-*p*-tolylsulfoxide⁶

¹H NMR: δ 7.54 and 6.93 (AA'BB' system, 4H), 7.48 and 7.23 (AA'BB' system, 4H), 3.79 (s, 3H), 2.35 (s, 3H).

¹³C NMR: δ 161.8, 142.6, 141.2, 129.8, 127.0, 124.7, 114.7, 55.4, 21.3.

$[\alpha]_D$: +23 (*c* 1, CHCl₃) for a 95% ee.

Lit.⁶ $[\alpha]_D$: +24 (*c* 2.005, acetone).

(*R*)-*p*-Methoxyphenylvinylsulfoxide^{7,8}

¹H NMR: δ 7.57 and 7.01 (AA'BB' system, 4H), 6.57 (dd, *J* = 9.7 and 16.6 Hz, 1H), 6.19 (d, *J* = 16.6 Hz, 1H), 5.89 (d, *J* = 9.7 Hz, 1H), 3.85 (s, 1H).

¹³C NMR: δ 162.2, 143.0, 140.8, 127.2, 120.2, 114.9, 55.5.

ee: 93%

(*R*)-*tert*-Butyl-*p*-methoxyphenylsulfoxide⁵

¹H NMR: δ 7.51 and 6.99 (AA'BB' system, 4H), 3.85 (s, 3H), 1.15 (s, 9H).

¹³C NMR: δ 162.1, 131.0, 127.9, 114.0, 55.6, 55.5, 22.8.

$[\alpha]_D$: +116 (*c* 0.9, CHCl₃) for a 76% ee.

⁴ Mohammed, M. S. *Iraqi J. Sci.* **1990**, 30, 455.

⁵ Maccagnani, G.; Taddei, F. *Boll. Sci. Fac. Chim. Ind. Bologna* **1965**, 23, 381.

⁶ Andersen, K. K.; Gaffiel, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, 86, 5637.

⁷ Bader, A.; Wuensch, J. R. *Macromolecules* **1995**, 28, 3794.

⁸ It was isolated partially impurified with ca. 10% of both di-*p*-methoxyphenylsulfoxide and divinylsulfoxide.

(R)-Mesityl-*p*-tolylsulfoxide⁹

¹H NMR: δ 7.29 and 7.20 (AA'BB' system, 4H), 6.84 (s, 2H), 2.40 (s, 6H) 2.35 (s, 3H), 2.26 (s, 3H).

¹³C NMR: δ 142.0, 141.2, 139.9, 139.7, 136.7, 130.7, 129.5, 124.5, 21.2, 21.1, 19.3.

[α]_D: +273 (c 1, CHCl₃) for a 97% ee.

Lit.⁶ [α]_D (*S* config.): -279 (c 0.953, CHCl₃).

(R)-Mesitylmethylsulfoxide¹⁰

¹H NMR: δ 6.84 (s, 2H), 2.83 (s, 6H) 2.53 (s, 3H), 2.26 (s, 3H).

¹³C NMR: δ 141.1, 137.9, 136.1, 131.0, 38.5, 21.0, 18.9.

[α]_D: +243 (c 1, CHCl₃) for a 97% ee.

(S)-Mesitylmethylsulfoxide¹⁰

[α]_D: -241 (c 1, CHCl₃) for a 98% ee.

Lit.¹⁰ [α]_D: -390 (c 1, CHCl₃).

(R)-Mesitylvinylsulfoxide¹¹

¹H NMR: δ 6.84 (s, 2H), 6.62 (dd, *J* = 9.9 and 16.5 Hz, 1H), 6.11 (d, *J* = 16.5 Hz, 1H), 5.93 (d, *J* = 9.9 Hz, 1H), 2.48 (s, 6H), 2.26 (s, 3H).

¹³C NMR: δ 141.7, 139.3, 139.2, 133.6, 130.9, 120.1, 21.1, 19.0.

[α]_D: +589 (c 1.1, CHCl₃) for a 95% ee.

(R)-Cyclohexylisopropylsulfoxide¹²

¹H NMR: δ 2.80 (sp, *J* = 7.0 Hz, 1H), 2.53 (m, 1H), 2.3-1.2 (m, 10H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.26 (d, *J* = 7.0 Hz, 3H).

¹³C NMR: δ 55.4, 45.9, 27.2, 25.7, 25.6, 25.3, 24.5, 17.4, 13.9.

[α]_D: -18 (c 1.2, CHCl₃) for a 90% ee.

Lit.¹² [α]_D (*S* config.): +20.5 (c 1, CHCl₃) for a >98% ee.

(R)-Cyclohexyldecylsulfoxide¹²

¹H NMR: δ 2.58 (m, 2H), 2.49 (m, 1H), 2.10 (m, 1H), 2.0-1.6 (m, 6H), 1.5-1.1 (m, 19H), 0.84 (m, 3H).

¹³C NMR: δ 58.9, 48.9, 31.9, 29.5, 29.4, 29.3, 29.2, 29.0, 26.5, 25.6, 25.5, 25.3, 24.9, 22.8, 22.7, 14.2.

[α]_D: +22 (c 1, CHCl₃) for a 93% ee.

Lit.¹² [α]_D (*S* config.): -22.1 (c 1, CHCl₃) for a >98% ee.

⁹ Shimizu, T.; Kobayashi, M. *J. Org. Chem.* **1987**, 52, 3399.

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¹¹ Shibata, N.; Fujimori, C.; Fujita, S.; Kita, Y. *Chem. Pharm. Bull.* **1996**, 44, 892.

¹² Annunziata, M.; Capozzi, M.; Cardellicchio, C.; Naso, F.; Spina, G.; Tortorella, P. *J. Org. Chem.* **2001**, 66, 5933.