Recycling the *tert*-Butanesulfinyl Group in the Synthesis of Amines Using *tert*-Butanesulfinamide

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Supporting Information

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Reagents and General methods.

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. *tert*-Butysulfinyl chloride was prepared using the previously published method.[1] Tetrahydrofuran (THF), dichloromethane, and toluene were dried over alumina under a N_2 atmosphere. Triethylamine was distilled from CaH_2 immediately prior to use. Ethyl acetate (EtOAc) and cyclopentyl methyl ether (CPME) were dried over 4 Å molecular sieves. Ammonia in $CDCl_3$ and hydrogen chloride in CPME were prepared by bubbling the each gas in the appropriate solvent at room temperature until the solutions were saturated, and the concentration of the solutions were determined prior to use by titration with methyl red or phenolphthalein as the indicators, respectively. Reactions were carried out in oven-dried glassware under a N_2 atmosphere. All temperatures listed in large scale experiments correspond to internal temperatures. Extracts were concentrated using a rotary evaporator under reduced pressure. Chromatography was carried out with 60 Å 230-400 mesh silica gel. Only partial data are listed for IR spectra. Unless otherwise noted, ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ at room temperature. Coupling constants in the NMR spectra are reported in Hz. Enantiomeric purities were determined by HPLC using Diacel CHIRALPAK AS, IB (4.6 x 250 mm) columns with UV detection at 220 nm. Melting points were determined in open Pyrex capillaries and are uncorrected.

Preparation of *N*-(1-methylcyclohexyl)-*tert*-butanesulfinamide 7.

Reaction of cyclohexanone (4.86 g, 49.5 mmol, 1.2 equiv), $Ti(OEt)_4$ (18.82 g, 82.50 mmol, 2.0 equiv), and *tert*-butanesulfinamide (5.00 g, 41.3 mmol) in THF (100 mL) according to the literature procedure[2] yielded crude sulfinyl imine. To a solution of the crude imine in CH_2Cl_2 (125 mL) was added 27.5 mL of MeMgBr (3.0 M in Et_2O, 82.5 mmol, 2.0 equiv) at -78 °C over 5 min. After 5 min, the reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction was quenched with saturated NH_4Cl (80 mL). The separated water layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (1:2 to 1:2 EtOAc/hexanes) to afford **7** (7.30 g, 81%) as a white solid. m.p. 62-64 °C. IR (neat) 3177, 2924, 1445, 1361, 1356, 1036 cm^{-1}. ^1H NMR (400 MHz) δ 1.21 (s, 9H), 1.30 (s, 3H), 1.33-1.75 (m, 10H), 3.02 (brs, 1H). ^{13}C NMR (100 MHz) δ 22.0, 22.1, 22.7, 25.6, 29.1, 38.1, 40.2, 55.0, 55.4. MS (ESI): m/z 218 (MH^+). Anal. Calcd for $C_{11}H_{23}NOS$: C, 60.78; H, 10.66; N, 6.44; S, 14.75. Found: C, 60.92; H, 10.49; N, 6.42; S, 15.13.

General Procedure A: Enantioselective formation of sulfinate esters.

A solution of proton sponge (1.2-2.5 equiv), alcohol (1.2-5.0 equiv), and catalyst (1-10 mol%) in the indicated solvent (0.50 mL, 0.20 M) and at the indicated stoichiometry was cooled to the indicated temperature and *tert*-butylsulfinyl chloride (64 μL, 0.10 mmol, 1.56 M) was added as a solution in toluene over a period of 2 min. At the indicated time, 5 equiv of ammonia in $CDCl_3$ was added to quench any remaining sulfinyl chloride and 0.10 mL of 2,6-dimethoxytoluene in $CDCl_3$ (1 mM solution, 1.0 equiv) was added as an internal standard. After the mixture was filtered, 100 μL of the filtrate was transferred to an NMR tube containing 0.8 mL of $CDCl_3$, and the yield was determined by NMR integration relative to the internal standard. Another 100 μL of the filtrate was diluted with hexanes (ca. 1.0 mL) and filtered for HPLC analysis. (For yields and % ee, see Table 1–4. See experimental procedures listed below for the preparation, characterization, and chiral HPLC conditions.)

General Procedure B: Formation of racemic sulfinate esters.

A solution of the alcohol (5.0 equiv) and triethylamine (2.0 equiv) in EtOAc (0.2 M based on *tert*-butylsulfinyl chloride) was cooled to -78 °C. *tert*-Butylsulfinyl chloride (1.0 equiv) was added as a solution in toluene, and after 5 min, the reaction vessel was removed from the cold bath. Once the reaction mixture warmed to room temperature, it was stirred for 1 h, diluted with EtOAc, and washed with 1 M HCl, saturated $NaHCO_3$, and brine and then was dried and filtered. The EtOAc was removed in vacuo, and the residue was purified via silica gel chromatography to afford pure sulfinate ester.

Ethyl *tert*-butanesulfinate 9a.[3]

Reaction of 1.37 mL (23.4 mmol, 5.0 equiv) of ethanol and 3.00 mL of *tert*-butylsulfinyl chloride solution (4.68 mmol, 1.56 M) according to General Procedure B yielded **9a** (569.1 mg, 80%) as a colorless oil after chromatography (1:8 EtOAc/hexanes). HPLC (Diacel Chiralpak AS column, 98:02 hexanes/IPA; 1.0 mL/min) t_1 = 7.3 min, t_2 = 10.9 min. ^{1}H NMR (400 MHz) δ 1.19 (s, 9H), 1.34 (t, 3H, *J* = 7.1), 4.07 (dq, 1H, *J* = 10.2, 7.1), 4.18 (dq, 1H, *J* = 10.2, 7.1). ^{13}C NMR (100 MHz) δ 15.8, 21.5, 57.0, 65.7. MS (ESI): m/z 151 (MH^+). The analytical data matched that reported in the literature**.** [3]

Propyl *tert*-butanesulfinate 9b. [3]

Reaction of 0.580 mL (7.80 mmol, 5.0 equiv) of 1-propanol and 1.00 mL of *tert*-butylsulfinyl chloride solution (1.56 mmol, 1.56 M) according to General Procedure B yielded **9b** (234.5 mg, 92%) as a colorless oil after chromatography (1:8 EtOAc/hexanes). HPLC (Diacel Chiralpak AS

column, 98:02 hexanes/IPA; 1.0 mL/min) t_1 = 6.4 min, t_2 = 9.6 min. ^{1}H NMR (400 MHz) δ 0.97 (t, 3H, *J* = 7.4), 1.20 (s, 9H), 1.68-1.77 (m, 2H), 3.94 (dt, 1H, *J* = 10.0, 6.6), 4.07 (dt, 1H, *J* = 10.0, 6.6). ^{13}C NMR (100 MHz) δ 10.3, 21.6, 23.5, 57.3, 71.5. MS (ESI): m/z 165 (MH^+). The analytical data matched that reported in the literature**.** [3]

Butyl *tert*-butanesulfinate 9c. [3]

Reaction of 1.07 mL (11.7 mmol, 5.0 equiv) of 1-butanol and 1.50 mL of *tert*-butylsulfinyl chloride solution (2.34 mmol, 1.56 M) according to General Procedure B yielded **9c** (413.7 mg, 99%) as a colorless oil after chromatography (1:8 EtOAc/hexanes). HPLC (Diacel Chiralpak AS column, 98:02 hexanes/IPA; 1.0 mL/min) t_1 = 6.0 min, t_2 = 9.5 min. ^{1}H NMR (400 MHz) δ 0.94 (t, 3H, *J* = 7.4), 1.19 (s, 9H), 1.36-1.46 (m, 2H), 1.65-1.72 (m, 2H), 3.97 (dt, 1H, *J* = 10.1, 6.6), 4.11 (dt, 1H, *J* = 10.1, 6.6). ^{13}C NMR (100 MHz) δ 13.7, 19.0, 21.6, 32.1, 57.2, 69.6. MS (ESI): m/z 179 (MH^+). The analytical data matched that reported in the literature**.** [3]

2-Methylpropyl *tert*-butanesulfinate 9d.

Reaction of 0.720 mL (7.80 mmol, 5.0 equiv) of 2-methyl-1-propanol and 1.00 mL of *tert*-butylsulfinyl chloride solution (1.56 mmol, 1.56 M) according to General Procedure B yielded **9d** (255.2 mg, 92%) as a colorless oil after chromatography (1:10 EtOAc/hexanes). HPLC (Diacel Chiralpak AS column, 98:02 hexanes/IPA; 1.0 mL/min) t_1 = 5.8 min, t_2 = 8.5 min. IR (neat) 2961, 2874, 1471, 1392, 1364, 1130 cm^{-1}. ^{1}H NMR (400 MHz) δ 0.95 (d, 3H, *J* = 6.7), 0.96 (d, 3H, *J* = 6.7), 1.20 (s, 9H), 1.92-2.05 (m, 1H), 3.72 (dd, 1H, *J* = 9.7, 6.6), 3.88 (dd, 1H, *J* = 9.7, 6.6). ^{13}C NMR (100 MHz) δ 19.0, 21.7, 29.1, 57.4, 75.8. MS (ESI): m/z 179 (MH^+). HRMS-ESI (m/z): $[MH]^+$ calcd for $C_8H_{19}O_2S$, 179.1110; found, 179.1098.

2-Propyl *tert*-butanesulfinate 9e. [3]

Reaction of 0.600 mL (7.80. mmol, 5.0 equiv) of 2-propanol and 1.00 mL of *tert*-butylsulfinyl chloride solution (1.56 mmol, 1.56 M) according to General Procedure B yielded **9e** (128.1 mg, 50%) as a colorless oil after chromatography (1:8 EtOAc/hexanes). HPLC (Diacel Chiralpak AS column, 98:02 hexanes/IPA; 1.0 mL/min) t_1 = 5.8 min, t_2 = 9.5 min. ^{1}H NMR (400 MHz) δ 1.18 (s, 9H), 1.30 (d, 3H, *J* = 6.2), 1.37 (d, 3H, *J* = 6.2), 4.46 (sept 1H, *J* = 6.2). ^{13}C NMR (100 MHz) δ 21.6, 22.9, 23.7, 56.7, 74.0. MS (ESI): m/z 165 (MH^+). The analytical data matched that reported in the literature**.** [3]

1,1,1,3,3,3-Hexafluoro-2-propyl *tert*-butanesulfinate 9f.

Reaction of 0.820 mL (7.80 mmol, 5.0 equiv) of 1,1,1,3,3,3-hexafluoro-2-propanol and 1.00 mL of *tert*-butylsulfinyl chloride solution (1.56 mmol, 1.56 M) according to General Procedure B

yielded **9f** (335.1 mg, 79%) as a colorless oil after chromatography (1:15 EtOAc/hexanes). HPLC (Diacel Chiralpak AS column, 99.8:0.2 hexanes/IPA; 1.0 mL/min) t_1 = 8.8 min, t_2 = 11.8 min. IR (neat) 2940, 1479, 1464, 1373, 1202, 1107 cm^{-1}. ^1H NMR (400 MHz) δ 1.28 (s, 9H), 4.79 (sept, 1H, *J* = 5.8). ^{13}C NMR (100 MHz) δ 21.1, 59.9, 71.1 (sept, *J* = 34), 116.1-125.1 (m). Anal. Calcd for $C_7H_{10}F_6O_2S$: C, 30.89; H, 3.70; S, 11.78. Found: C, 30.81; H, 3.64; S, 12.14.

2-Fluoroethyl *tert*-butanesulfinate 9g.

Reaction of 0.460 mL (7.80 mmol, 5.0 equiv) of 2-fluoroethanol and 1.00 mL of *tert*-butylsulfinyl chloride solution (1.56 mmol, 1.56 M) according to General Procedure B yielded **9g** (213.6 mg, 81%) as a colorless oil after chromatography (1:4 EtOAc/hexanes). HPLC (Diacel Chiralpak AS column, 98:02 hexanes/EtOH; 1.0 mL/min) t_1 = 8.0 min, t_2 = 9.8 min. IR (neat) 3515, 2962, 1477, 1460, 1366, 1126, 1067, 1037 cm^{-1}. ^1H NMR (400 MHz) δ 1.22 (s, 9H), 4.23-4.32 (m, 2H), 4.56-4.58 (m, 1H), 4.67-4.69 (m, 1H). ^{13}C NMR (100 MHz) δ 21.5, 57.8, 68.1 (d, *J* = 21), 82.1 (d, *J* = 172). MS (ESI): m/z 169 (MH^+). Anal. Calcd for $C_6H_{13}FO_2S$: C, 42.84; H, 7.79; S, 19.06. Found: C, 42.84; H, 8.00; S, 19.38.

1,1,1-Trifluoroethyl *tert*-butanesulfinate ester 9h.

Reaction of 0.570 mL (7.80 mmol, 5.0 equiv) of 1,1,1-trifluoroethanol and 1.00 mL of *tert*-butylsulfinyl chloride solution (1.56 mmol, 1.56 M) according to General Procedure B yielded **9h** (297.0 mg, 93%) as a colorless oil after chromatography (1:9 EtOAc/hexanes). HPLC (Diacel Chiralpak AS column, 98:02 hexanes/IPA; 1.0 mL/min) t_1 = 6.2 min, t_2 = 6.8 min. IR (neat) 2964, 1479, 1462, 1368, 1279, 1166, 1055 cm^{-1}. ^1H NMR (400 MHz) δ 1.24 (s, 9H), 4.30-4.36 (m, 2H). ^{13}C NMR (100 MHz) δ 21.3, 58.7, 64.7 (q, *J* = 36), 123.0 (q, *J* = 278). MS (ESI): m/z 205 (MH^+). Anal. Calcd for $C_6H_{11}F_3O_2S$: C, 35.29; H, 5.43; S, 15.70. Found: C, 35.38; H, 5.63; S, 15.97.

Preparation of *(Rs,S)-N*-(1-phenylethyl)-*tert*-butanesulfinamide 10.[4]

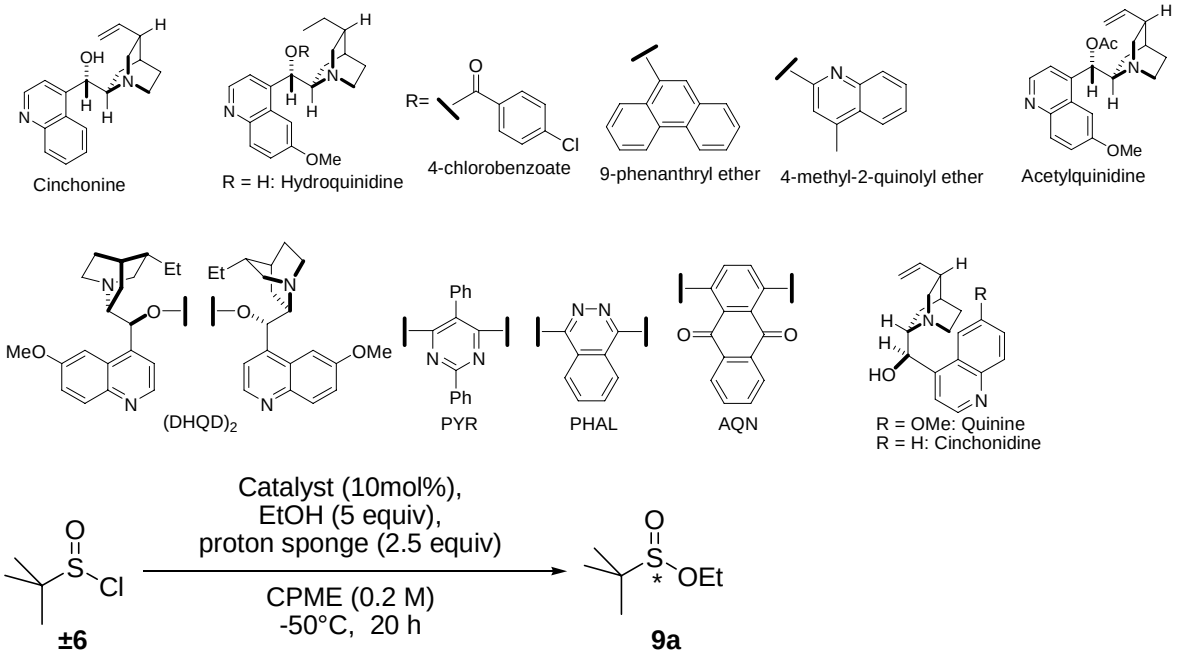
Reaction of benzaldehyde (9.63 g, 90.8 mmol, 1.1 equiv), $Ti(OEt)_4$ (37.6 g, 0.165 mol, 2.0 equiv), and *(R)-tert*-butanesulfinamide (10.00 g, 82.51 mmol) in THF (165 mL) according to the literature procedure[5] yielded crude sulfinyl imine. To a solution of the crude imine in CH_2Cl_2 (400 mL) was added 55 mL of MeMgBr (3.0 M in Et_2O, 1.65 mol, 2.0 equiv) at -48 °C over 20 min. After 5 min, the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with saturated NH_4Cl (270 mL). The separated water layer was extracted two times with 100 mL of EtOAc. The combined organic layers were dried, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (1:2 EtOAc/hexanes) to afford **10** (17.46 g, 94%, 99% dr) as a white solid. The diastereomic ratio was

determined by HPLC analysis (Microsorb-100 Å Si column, 90:10 hexanes/IPA; 1.0 mL/min; 222 nm) t_1 = 6.3 min (minor diastereomer), t_2 = 8.5 min (minor diastereomer). m.p. 75-77 °C, ^{1}H NMR (400 MHz) δ1.20 (s, 9H), 1.54 (d, 3H, *J* = 6.7), 3.31 (d, 1H, *J* = 3.0), 4.58 (dq, 1H, *J* = 3.0, 6.7), 7.24-7.61 (m, 5H). ^{13}C NMR (100 MHz) δ 22.5, 25.2, 54.6, 55.5, 126.9, 127.5, 128.5, 143.4. MS (ESI): m/z 226 (MH^+). The analytical data matched that reported in the literature**.** [6]

Catalyst screen

We performed a cinchona alkaloid catalyst screen using ethanol in CPME (Table 1). Cinchonine resulted in an excellent yield but the selectivity was moderate (entry 1). Acetyl quinidine, which was reported as an effective sulfinyl transfer reagent for dynamic kinetic resolution,[6] was not effective in this system (entry 2). Hydroquinidine and its ester and ether derivatives resulted in lower yields and less selectivities (entries 3–6). Generally, ether derivatives were more active and selective than ester derivatives. Dimeric derivatives gave high conversions but poor selectivities (entries 7–9). The use of quinine and cinchonidine, the pseudo enantiomers of quinidine and cinchonine, led to the opposite sense of induction (entries 10 and 11). All cinchona alkaloids resulted in moderate to excellent yields. However, enantioselectivities were below that observed for quinidine.

Table 1. Catalyst Screen Using Ethanol



entry	catalyst	yield (%) [a]	ee (%) [b]
1	Cinchonine	>99 [c]	75 [c]
2	Acetylquinidine	64	22
3	Hydroquinidine	77	82
4	Hydroquinidine 9-phenanthryl ether	97	82
5	Hydroquinidine 4-methyl-2-quinolyl ether	94	56
6	Hydroquinidine 4-chlorobenzoate	72	38
7	$(DHQD)_2PYR$	92	68
8	$(DHQD)_2PHAL$	>99	33
9	$(DHQD)_2AQN$	95	4
10	Quinine	81	72 [d]
11	Cinchonidine	99	62 [d]

a) Yields determined by NMR with 2,6-dimethoxytoluene as an internal standard. b) Enantiomeric excess determined by chiral HPLC. c) Catalyst did not dissolve completely. d) Opposite sense of induction was observed.

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