3,5-Bis(trifluoromethyl)phenyl sulfones in the direct Julia-Kocienski olefination

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1. General. Melting points are uncorrected. IR data were collected on a FTIR apparatus, and peaks are reported in cm^{-1} . Only the structurally most important IR peaks have been listed. NMR spectra were recorded on a 300 MHz apparatus for ^1H and a 75 MHz apparatus for ^{13}C , using CDCl_3 as solvent and TMS as internal standard; chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV fragment ions m/z with relative intensities (%) in parenthesis. High-resolution electron impact (DIP) mass spectra were obtained at 70 eV. Analytical TLC was visualized with UV light at 254 nm. For flash chromatographies, silica gel 60 (0.040-0.063 mm) was employed. Thin layer chromatographies were carried out on TLC plastic sheets with silica gel 60 F_{254} . Reactions under inert atmosphere (argon) were performed in oven-dried glassware, sealed with a rubber septum, and using anhydrous solvents. Compounds **12ec**, **12ad**, **12ac**, **14a-c** and **14g-i**, are commercially available. Compounds **12ae**,¹ **12ca**,² **12cf**,³ **12bb**,⁴ **12bd**,⁴ **12bg**,⁴ **12bh-bj**,⁴ (*E*)-**12bk**,⁴ (*Z*)-**12bk**,⁵ **12bl**,⁴ **14d**⁶ and **14f**⁷ have been previously reported.

2. General procedure for the synthesis of 3,5-bis(trifluoromethyl)phenyl sulfides

8. To a solution of 3,5-bis(trifluoromethyl)benzenethiol (835 μL , 5 mmol) and 95% NaH (150 mg, 6 mmol) in anhydrous MeCN (15 mL) under argon was added the corresponding alkyl bromide (5.5 mmol) at rt and the reaction was stirred at this temperature for 1d. After quenching with H_2O (20 mL), the mixture was extracted with EtOAc (2x20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford crude 3,5-bis(trifluoromethyl)phenyl sulfides **8**, which were used in the next step without further purification.

[3,5-bis(trifluoromethyl)phenyl] benzyl sulfide (8a). Colourless oil; IR (film) $\nu_{\max}$ 3030, 1601, 1455, 1354, 1278, 1182, 1135; ^1H NMR δ 7.66 (br s, 3H), 7.37-7.18 (m, 5H), 4.18 (s, 2H); ^{13}C NMR δ 140.1, 135.6, 131.9 (q, $J_{\text{C-F}} = 34.0$), 128.8, 128.7, 128.6 (m), 127.8, 123.0 (q, $J_{\text{C-F}} = 272.3$), 119.6 (m), 38.2; DIP-MS m/z 336 (M^+ , 8), 335 (48), 261 (12), 221 (18), 182 (13), 181 (84), 179 (11), 166 (13), 165 (14), 103 (13), 92 (12), 91 (100), 77 (10), 65 (11).

[3,5-Bis(trifluoromethyl)phenyl] 3,5-dimethoxybenzyl sulfide (8b). Beige solid; R_f (hexane/EtOAc: 2/1) 0.79; IR (KBr) $\nu_{\max}$ 2964, 2844, 1601, 1461, 1358, 1286, 1128, 1055; ^1H NMR δ 7.66 (s, 2H), 7.63 (s, 1H), 6.46 (s, 2H), 6.37 (s, 1H), 4.13 (s, 2H), 3.76 (s, 6H); ^{13}C NMR δ 161.0, 140.1, 137.9, 131.9 (q, $J_{\text{C-F}} = 32.9$), 128.5 (m), 123.0 (q, $J_{\text{C-F}} = 273.3$), 119.6 (m), 106.8, 99.8, 55.3, 38.4; DIP-MS m/z 396 (M^+ , 25), 151 (100).

[3,5-Bis(trifluoromethyl)phenyl] pentyl sulfide (8c). Colourless oil; IR (film) $\nu_{\max}$ 2932, 1461, 1354, 1278, 1136; ^1H NMR δ 7.65 (s, 2H), 7.61 (s, 1H), 3.01 (t, $J = 7.3$, 2H), 1.75-1.65 (m, 2H), 1.49-1.29 (m, 4H), 0.91 (t, $J = 7.1$, 3H); ^{13}C NMR δ 141.4, 131.9 (q, $J_{\text{C-F}} = 34.0$), 137.9, 131.9 (q, $J_{\text{C-F}} = 32.9$), 128.5 (m), 123.0 (q, $J_{\text{C-F}} = 273.3$), 119.6 (m), 106.8, 99.8, 55.3, 38.4; DIP-MS m/z 396 (M^+ , 25), 151 (100).

[3,5-Bis(trifluoromethyl)phenyl] pentyl sulfide (8c). Colourless oil; IR (film) $\nu_{\max}$ 2932, 1461, 1354, 1278, 1136; ^1H NMR δ 7.65 (s, 2H), 7.61 (s, 1H), 3.01 (t, $J = 7.3$, 2H), 1.75-1.65 (m, 2H), 1.49-1.29 (m, 4H), 0.91 (t, $J = 7.1$, 3H); ^{13}C NMR δ 141.4, 131.9 (q, $J_{\text{C-F}} = 34.0$), 127.1 (m), 123.1 (q, $J_{\text{C-F}} = 272.2$), 118.7 (m), 32.8, 30.9, 28.2, 22.1, 13.8; DIP-MS m/z 316 (M^+ , 4), 301 (13), 259 (11), 257 (17), 239 (13), 149 (14), 91 (100), 71 (14), 69 (13), 65 (12), 57 (19), 56 (21), 55 (18), 43 (31), 41 (19).
 $J_{\text{C-F}} = 34.0$, 127.1 (m), 123.1 (q, $J_{\text{C-F}} = 272.2$), 118.7 (m), 32.8, 30.9, 28.2, 22.1, 13.8; DIP-MS m/z 316 (M^+ , 4), 301 (13), 259 (11), 257 (17), 239 (13), 149 (14), 91 (100), 71 (14), 69 (13), 65 (12), 57 (19), 56 (21), 55 (18), 43 (31), 41 (19).

[3,5-Bis(trifluoromethyl)phenyl] methyl sulfide (8d). White solid; R_f (hexane/EtOAc: 8/1) 0.68; IR (KBr) $\nu_{\max}$ 1622, 1346, 1278, 1138; ^1H NMR δ 7.61 (br s, 3H); 2.57 (s, 3H); ^{13}C NMR δ 142.4, 133.4 (q, $J_{\text{C-F}} = 34.0$), 125.5 (m), 123.1 (q, $J_{\text{C-F}} = 273.3$), 118.3 (m), 15.1; DIP-MS m/z 260 (M^+ , 100), 241 (20), 239 (14), 227 (23), 225 (13), 132 (13), 69 (11).

[3,5-Bis(trifluoromethyl)phenyl] 4-nitrobenzyl sulfide (8e). Yellow oil; R_f (hexane/EtOAc: 2/1) 0.71; IR (film) $\nu_{\max}$ 3087, 1611, 1526, 1356, 1281, 1186, 1126; ^1H NMR δ 8.16 (d, $J = 8.7$, 2H), 7.69 (br s, 3H), 7.52 (d, $J = 8.7$, 2H), 4.33 (s, 2H); ^{13}C NMR δ 147.4, 143.4, 138.6, 132.2 (q, $J_{\text{C-F}} = 34.0$), 129.7, 129.0 (m), 123.9, 122.8 (q, $J_{\text{C-F}} = 273.3$), 120.3 (m), 37.7; DIP-MS m/z 381 (M^+ , 100), 362 (25), 136 (62), 106 (19), 90 (11), 89 (12), 78 (14).

3. General procedure for the synthesis of 3,5-bis(trifluoromethyl)phenyl sulfones

7. To a stirred solution of the corresponding sulfide **8** (1 mmol) and MnSO_4 monohydrate (2 mg, 1 mol%) in MeCN (23 mL) at rt was added an aqueous mixture of 30% H_2O_2 (5 mmol, 515 μL) and 0.2 M NaHCO_3 buffer solution (17 mL) previously prepared at 0 $^\circ\text{C}$. After a period of 15 to 30 min the reaction was quenched with a saturated solution of NaCl (30 mL), extracted with EtOAc (2x20 mL) and dried (Na_2SO_4). Filtration and evaporation of the solvent afforded the corresponding pure crude sulfones **7** which were recrystallized from ether/hexane.

Benzyl 3,5-bis(trifluoromethyl)phenyl sulfone (7a). White solid; R_f (hexane/EtOAc: 2/1) 0.65; mp 111-113 $^\circ\text{C}$; IR (KBr) $\nu_{\max}$ 1626, 1605, 1361, 1335, 1282, 1136; ^1H NMR δ 8.07 (s, 1H), 7.96 (s, 2H), 7.40-7.26 (m, 3H), 7.07 (d, $J = 7.1$, 2H), 4.39 (s, 2H); ^{13}C NMR δ 140.2, 132.6 (q, $J_{\text{C-F}} = 35.1$), 130.7, 129.5, 129.2 (m), 128.9, 127.2 (m), 127.0,

122.2 (q, $J_{\text{C-F}} = 273.3$), 62.9; DIP-MS m/z 368 (M^+ , 1), 349 (23), 213 (21), 163 (11), 92 (21), 91 (100), 65 (32); HRMS calcd. for $\text{C}_{15}\text{H}_{10}\text{F}_6\text{O}_2\text{S}$ 368.0308; found 368.0302.

3,5-Dimethoxybenzyl 3,5-bis(trifluoromethyl)phenyl sulfone (7b). Beige solid; R_f (hexane/EtOAc: 2/1) 0.59; mp 129-130 °C; IR (KBr) ν_{max} 3091, 2845, 1611, 1597, 1435, 1326, 1281, 1134, 1054; ^1H NMR δ 8.09 (s, 1H), 8.02 (s, 2H), 6.43 (br s, 1H), 6.18 (br s, 2H), 4.31 (s, 2H), 3.70 (s, 6H); ^{13}C NMR δ 161.1, 140.1, 132.6 (q, $J_{\text{C-F}} = 35.1$), 129.2 (m), 128.9, 127.2 (m), 122.3 (q, $J_{\text{C-F}} = 273.3$), 108.8, 100.9, 63.2, 55.3; DIP-MS m/z 428 (M^+ , 40), 364 (16), 213 (16), 152 (29), 151 (100), 91 (17), 78 (13), 77 (15), 65 (10); HRMS calcd. for $\text{C}_{17}\text{H}_{14}\text{F}_6\text{O}_4\text{S}$ 428.0517; found 428.0524.

Pentyl 3,5-bis(trifluoromethyl)phenyl sulfone (7c). Yellow solid; R_f (hexane/EtOAc: 2/1) 0.75; mp 65-67 °C; IR (KBr) ν_{max} 2955, 2877, 1627, 1469, 1361, 1281, 1146, 1048; ^1H NMR δ 8.38 (s, 2H), 8.17 (s, 1H), 3.19-3.13 (m, 2H), 1.83-1.73 (m, 2H), 1.44-1.24 (m, 4H), 0.89 (t, $J = 7.1$, 3H); ^{13}C NMR δ 142.2, 133.2 (q, $J_{\text{C-F}} = 34.0$), 128.5 (m), 127.3 (m), 122.3 (q, $J_{\text{C-F}} = 273.3$), 56.3, 30.2, 22.0 (2C), 13.6; DIP-MS m/z 348 (M^+ , 0.1), 331 (13), 329 (54), 279 (40), 261 (15), 255 (11), 241 (61), 227 (11), 214 (13), 213 (66), 195 (10), 194 (19), 163 (24), 144 (18), 143 (12), 71 (54), 70 (43), 69 (11), 55 (22), 43 (100), 42 (17), 41 (36); HRMS calcd. for $\text{C}_{13}\text{H}_{14}\text{F}_6\text{O}_2\text{S}$ 348.0619; found 348.0660.

Methyl 3,5-bis(trifluoromethyl)phenyl sulfone (7d). White solid; R_f (hexane/EtOAc: 2/1) 0.70; mp 133-135 °C; IR (KBr) ν_{max} 3024, 2932, 1624, 1416, 1367, 1271, 1150; ^1H NMR δ 8.42 (s, 2H), 8.17 (s, 1H), 3.16 (s, 3H); ^{13}C NMR δ 143.2, 133.4 (q, $J_{\text{C-F}} = 34.0$), 127.9 (m), 127.5 (m), 122.3 (q, $J_{\text{C-F}} = 273.3$), 44.4; DIP-MS m/z 292 (M^+ , 6), 277 (14), 273 (19), 230 (46), 213 (100), 163 (15), 63 (14); HRMS calcd. for $\text{C}_9\text{H}_6\text{F}_6\text{O}_2\text{S}$ 291.9991; found 291.9996.

4-Nitrobenzyl 3,5-bis(trifluoromethyl)phenyl sulfone (7e). Yellow solid; R_f (hexane/EtOAc: 2/1) 0.54; mp 168-170 °C; IR (KBr) ν_{max} 3083, 1610, 1530, 1366,

1295, 1140; ^1H NMR δ 8.22 (d, $J = 8.7$, 2H), 8.16 (s, 1H), 8.11 (s, 2H), 7.38 (d, $J = 8.7$, 2H), 4.48 (s, 2H); ^{13}C NMR δ 148.5, 140.3, 133.7, 133.3 (q, $J_{\text{C-F}} = 34.0$), 131.9, 129.0 (m), 127.8 (m), 124.1, 122.1 (q, $J_{\text{C-F}} = 273.3$), 62.10; DIP-MS m/z 413 (M^+ , 0.7), 137 (12), 136 (100), 106 (21), 90 (14), 89 (18), 78 (19); HRMS calcd. for $\text{C}_{15}\text{H}_9\text{F}_6\text{NO}_4\text{S}$ 413.0156; found 413.0160.

4. General procedure for the sulfone stability study

General procedure for the sulfone stability study with metallated bases. To a stirred solution of the corresponding sulfone **7a-d**, **9-11** (0.1 mmol) in anhydrous THF (LDA) or DME (KHMDS) (2 mL), at $-78\text{ }^\circ\text{C}$ (LDA) or $-60\text{ }^\circ\text{C}$ (KHMDS) under argon atmosphere, was added dropwise the corresponding base [LDA (0.11 mmol), KHMDS (0.11 mmol)]. After stirring at the corresponding temperature for 24 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with EtOAc (2x10 mL), and the organic phase was dried (Na_2SO_4), the solvent evaporated and the residue was purified by flash chromatography (hexane).

General procedure for the sulfone stability study with P4-*t*-Bu. To a stirred solution of the corresponding sulfone **7a-d**, **9-11** (0.1 mmol) in anhydrous THF (2 mL) at $-78\text{ }^\circ\text{C}$ under an argon atmosphere, was added dropwise a 1 M solution of P4-*t*-Bu in *n*-hexane (132 μL , 0.12 mmol). After stirring at $-78\text{ }^\circ\text{C}$ for 24 h, the reaction mixture was quenched with a saturated solution of NH_4Cl (5 mL) and extracted with EtOAc (2x10 mL). The organic phase was dried (Na_2SO_4), the solvent evaporated and the residue was purified by flash chromatography (hexane).

General procedure for the sulfone stability study with KOH. To a stirred solution of the corresponding sulfone **7a-d**, **9-11** (0.1 mmol) and TBAB (0.01 mmol) in THF (2 mL) at rt, was added KOH (54 mg, 0.9 mmol). After stirring at this temperature for 24

h, the reaction mixture was quenched with a saturated solution of NH_4Cl (5 mL) and extracted with EtOAc (2x10 mL). The organic phase was dried (Na_2SO_4), the solvent evaporated and the corresponding residue purified by flash chromatography (hexane).

5. Deuteration of benzyl 3,5-bis(trifluoromethyl)phenyl sulfone with LDA. To a stirred solution of sulfone **7a** (0.2 mmol) in 4 mL of dry THF at -78°C under argon, was added dropwise freshly prepared LDA (0.22 mmol). The mixture was then stirred for 30 min at -78°C before addition of D_2O (4 equiv). The reaction mixture was extracted with EtOAc (2x10 mL), and the organic phase was dried (Na_2SO_4), the solvent evaporated to afford the corresponding crude dideuterated sulfone. IR (KBR) ν_{max} 1659, 1363, 1295, 1150; ^1H NMR δ 8.07 (s, 1H), 7.96 (s, 2H), 7.38-7.26 (m, 3H), 7.07 (d, $J = 6.9$, 2H), 4.38 (br s, 0.41H); ^{13}C NMR δ 140.12, 132.6 (q, $J_{\text{CF}} = 35.15$), 130.7, 129.5, 129.0, 127.2, 126.6, 122.2 (q, $J_{\text{CF}} = 273.4$), 60.5; DIP-MS m/z (relative intensity) 370 (M^+ , 0.1), 149 (17), 117 (29), 93 (100), 92 (52), 91 (16).

6. Experimental procedure for isomerization of compound 12bj. A stirred solution of the mixture (*Z,E*)-**12bj** (0.3 mmol) in toluene (5 mL) and a catalytic amount of I_2 , were refluxed for 12 h. The reaction mixture was dissolved in Et_2O (20 mL) and was successively washed with a saturated solution of NaHSO_3 (2x10 mL) and a saturated solution of NaCl (2x10 mL). The organic phase was dried (Na_2SO_4) and the solvent was evaporated. The obtained residue was purified by flash chromatography (hexane) to give pure (*E*)-**12bj**.

7. Synthesis of erythro and threo 2-[3,5-bis(trifluoromethyl)phenylsulfonyl]-1,2-diphenylethanol 15. To a stirred solution of the corresponding *cis*- or *trans*- epoxide

stilbene (982 mg, 5 mmol) in anhydrous MeCN (1.5 mL) under argon atmosphere at 0 °C, was added dropwise a previously prepared solution of 3,5-bis(trifluoromethyl)benzenthio (3.5 mL, 20 mmol) and 95% NaH (144 mg, 6 mmol) in MeCN (1.5 mL) at rt. After stirring for 24 h, the reaction mixture was quenched with a saturated solution of NH₄Cl (5 mL), extracted with EtOAc (2x5 mL), and the organic phase was dried (Na₂SO₄), filtered and the solvent evaporated to afford the corresponding crude alcohol, which was used in the next step without further purification. To a solution of the corresponding β -hydroxy sulfane (1 mmol) in MeOH/H₂O: 1/1 (20 mL), was added portionwise Oxone® (15.37 g, 10 mmol) at 0 °C. The mixture was stirred vigorously at rt for 1 d. The methanol was evaporated and the residue diluted with CH₂Cl₂ (20 mL) and washed with brine (2x20 mL). The organic layer was dried (Na₂SO₄). The solvent evaporated to afford the corresponding crude β -hydroxy sulfone which was purified by flash chromatography to yield pure compound **erythro-15** and **threo-15**.

erythro-2-[3,5-Bis(trifluoromethyl)phenylsulfonyl]-1,2-diphenylethanol (erythro-15). White solid; *R_f* (hexane/EtOAc:2/1) 0.76; mp 159-161 °C; IR (KBr) $\nu_{\max}$ 3528, 3098, 3028, 1635, 1455, 1353, 1314, 1285, 1130; ¹H NMR δ 7.99 (s, 3H), 7.20-7.12 (m, 8H), 7.09-6.97 (m, 2H), 5.80 (d, *J* = 9.7, 1H), 4.51 (d, *J* = 9.7, 1H); ¹³C NMR δ 141.4, 139.1, 132.4 (q, *J*_{C-F} = 35.1), 130.1, 129.9, 129.3, 129.2 (m), 128.7, 128.5, 128.4, 127.1, 126.9 (m), 122.2 (q, *J*_{C-F} = 273.3), 78.2, 74.1; DIP-MS *m/z* 474 (*M*⁺, 0.2), 105 (10), 91 (100); HRMS calcd. for C₂₂H₁₆F₆O₃S 474.0724; found 474.0724.

threo-2-[3,5-Bis(trifluoromethyl)phenylsulfonyl]-1,2-diphenylethanol (threo-15). White solid; *R_f* (hexane/EtOAc:2/1) 0.59; mp 107-109 °C; IR (KBr) $\nu_{\max}$ 3508, 3054, 1596, 1449, 1356, 1274, 1186, 1126; ¹H NMR δ 7.97 (s, 1H), 7.91 (s, 2H), 7.31-7.18 (m, 10H), 6.07 (d, *J* = 3.3, 1H), 4.31 (d, *J* = 3.4, 1H); ¹³C NMR δ 140.4, 139.2, 132.2 (q,

$J_{\text{C-F}} = 35.1$), 131.4, 129.5, 129.4 (m), 128.5, 128.4, 128.4, 128.2, 128.9 (m), 126.3, 122.2 (q, $J_{\text{C-F}} = 274.4$), 77.3, 71.5; DIP-MS m/z 474 (M^+ , 0.2), 105 (10), 91 (100); HRMS calcd. for $\text{C}_{22}\text{H}_{16}\text{F}_6\text{O}_3\text{S}$ 474.0724; found 474.0723.

8. References

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9. ^1H MNR spectra for compounds 7a-e, 8a-e, *erythro*-15 and *threo*-15

7d

erythro-15

threo-15