

Supporting Information

Efficient Preparation of Nitrosoarenes for the Synthesis of Azobenzenes

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General Remarks: All reactions were conducted in flame-dried glassware under an atmosphere of dry nitrogen. Solvents were dried prior to use according to standard procedures. Compound **11** was prepared adopting a procedure by Fader¹. Thin layer chromatography was visualized by UV light, potassium permanganate stain or ninhydrine stain. Melting points were recorded on a melting point apparatus using open capillary tubes and remain uncorrected. Infrared spectra were recorded as ATR (Attenuated Total Reflectance) and are reported as wave numbers (cm⁻¹). ¹H NMR spectra were recorded at 200 MHz. Chemical shifts are given as dimensionless δ -values in ppm relative to tetramethylsilane (TMS) and coupling constants are in Hz. The residual signal of the solvent mentioned for the particular substance was used as internal standard. The number of protons was determined by integration of the signals. Multiplicities of the signals were abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad. ¹³C NMR spectra were recorded at 50.3 MHz. Solvents are mentioned for the particular substances. The chemical shifts are quoted as dimensionless δ -values in ppm using residual solvent protons as internal standard relative to TMS. The samples for high-resolution mass spectra (HRMS) were ionized at an ionization potential of 70 eV.

Tetrabutylammonium sulfanilate **1i**: Tetrabutylammonium hydroxide 30-hydrate (1.39 g, 1.73 mmol, 1.00 equiv) was dissolved in 12.5 ml of H₂O. To this solution sulfanilic acid (300 mg, 1.73 mmol, 1.00 equiv) was added and the mixture was sonified until the solid completely dissolved. Evaporation of the solvent in vacuo yielded 737 mg (quant.) **1i** as pale yellow solid. m.p. 86 °C; R_f 0.32 (DCM/MeOH 9:1); ¹H NMR (CDCl₃, 200 MHz, δ): 7.66 (d, *J* = 8.80, 2H), 6.57 (d, *J* = 8.80, 2H), 3.89 (s, br., 2H), 3.20 – 3.00 (m, 8H), 1.70 – 1.20 (m, 16H), 0.95 (t, *J* = 7.32, 12H); ¹³C NMR (CDCl₃, 50.3 MHz, δ): 147.4, 137.3, 127.3, 113.4, 58.2, 23.7, 19.4, 13.5; IR (ATR, ν): 3435 (m), 3366 (m), 3221 (m), 2961 (m), 2935 (m), 2875 (m), 1600 (m), 1206 (s), 1189 (s), 1118 (s), 1029 (s), 1006 (m), 691 (s).

Methyl 4-nitrosobenzoate **2a**: Methyl 4-aminobenzoate **1a** (5.00 g, 33.1 mmol, 1.00 equiv) was dissolved in 100 ml of DCM. To this solution Oxone (40.7 g, 66.2 mmol, 2.00 equiv) dissolved in 400 ml of water was added. The solution was stirred under nitrogen at room temperature until TLC monitoring indicated complete consumption of the starting material (0.5 h). After separation of the layers, the aqueous layer was extracted with DCM twice. The combined organic layers were washed with 1N HCl, saturated sodium bicarbonate solution, water, brine, dried (magnesium sulfate) and evaporated to dryness. The crude solid residue (5.50 g, 94% purity) was recrystallized from DCM to give 4.89 g (90%) of **2a** with a purity \geq 95%. m.p. 126 °C; R_f 0.50 (DCM); $^1\text{H NMR}$ (CDCl_3 , 200 MHz, δ): 8.29 (d, $J = 8.78$, 2H), 7.94 (d, $J = 8.78$, 2H), 3.98 (s, 3H); HR-MS: calcd for $\text{C}_8\text{H}_7\text{NO}_3$, m/e 165.0426; found, m/e 165.0423.

Synthesis of **2a** using $\text{SeO}_2/\text{H}_2\text{O}_2$: Compound **1a** (100 mg, 662 μmol , 1.00 equiv) was dissolved in 5.00 ml of DCM. To this solution SeO_2 (7.30 mg, 66.2 μmol , 0.10 equiv) and H_2O_2 (30%, 21.8 mg, 1.99 mmol, 3.4 equiv) were added. The mixture was stirred under nitrogen at room temperature until TLC monitoring indicated complete consumption of the starting material (22 h). After adding 10 ml of DCM, the layers were separated and the aqueous layer was extracted with DCM twice. The combined organic layers were washed with water, brine, dried (magnesium sulfate) and evaporated to dryness yielding **2a** as a yellow solid (109 mg, quant.) with a purity of 80% as determined by $^1\text{H NMR}$ spectroscopy.

4-Nitrosobenzoic acid **2b**: 4-Aminobenzoic acid **1b** (9.99 g, 72.8 mmol, 1.00 equiv) was dissolved in 112 ml of DCM. To this solution Oxone (89.8 g, 146 mmol, 2.00 equiv) dissolved in 450 ml of water was added. The solution was stirred under nitrogen at room temperature until TLC monitoring indicated complete consumption of the starting material (1 h). The precipitate was separated, washed with water and dried in a desiccator over sicacide[®]

to yield 11.1 g (quant.) of crude **2b** as a yellow solid with a purity of $\geq 95\%$ as determined by ^1H NMR spectroscopy. R_f 0.56 (DCM/MeOH 9:1); ^1H NMR (d_6 -DMSO, 200 MHz, δ): 13.5 (s, br., 1H), 8.27 (d, $J = 8.78$, 2H), 8.08 (d, $J = 8.78$, 2H); HR-MS: calcd for $\text{C}_7\text{H}_5\text{NO}_3$, m/e 151.0269; found, m/e 151.0273.

Methyl 3-nitrosobenzoate 2c: Methyl 3-aminobenzoate **1c** (2.00 g, 13.2 mmol, 1.00 equiv) was dissolved in 40 ml of DCM. To this solution Oxone (16.2 g, 26.5 mmol, 2.00 equiv) dissolved in 160 ml of water was added. The solution was stirred under nitrogen at room temperature until TLC monitoring indicated complete consumption of the starting material (3 h). After separation of the layers, the aqueous layer was extracted with DCM twice. The combined organic layers were washed with 1N HCl, saturated sodium bicarbonate solution, water, brine and dried (magnesium sulfate). Removal of the solvent in vacuo yielded 2.19 g (quant.) of crude **2c** as an amber solid with a purity of $\geq 92\%$ as determined by ^1H NMR spectroscopy. R_f 0.68 (DCM); ^1H NMR (CDCl_3 , 200 MHz, δ): 8.59 (s, 1H), 8.38 (d, $J = 7.80$, 1H), 7.99 (d, $J = 7.80$, 1H), 7.70 (t, $J = 7.82$, 1H), 3.99 (s, 3H); HR-MS: calcd for $\text{C}_8\text{H}_7\text{NO}_3$, m/e 165.0426; found, m/e 165.0427.

3-Nitrosobenzoic acid 2d: 3-Aminobenzoic acid **1d** (5.00 g, 36.5 mmol, 1.00 equiv) was dissolved in 100 ml of DCM. To this solution Oxone (44.9 g, 73.0 mmol, 2.00 equiv) dissolved in 400 ml water was added. The solution was stirred under nitrogen at room temperature until TLC monitoring indicated complete consumption of the starting material (3.5 h). The precipitate was separated, washed with water and dried in a desiccator over sicacide[®] to yield 5.28 g (96%) of crude **2d** as amber solid with a purity of $\geq 95\%$ as determined by ^1H NMR spectroscopy. R_f 0.53 (DCM/methanol 9:1); ^1H NMR (d_6 -DMSO,

200 MHz, δ): 13.6 (s, br., 1H), 8.50 - 8.20 (m, 2H), 8.18 (d, $J = 7.32$, 1H), 7.90-7.60 (m, 1H); HR-MS: calcd for $C_7H_5NO_3$, m/e 151.0269; found, m/e 151.0270.

3-Nitrosobenzonitrile **2e**: 3-Aminobenzonitrile **1e** (5.00 g, 42.3 mmol, 1.00 equiv) was dissolved in 250 ml of DCM. To this solution Oxone (52.0 g, 84.6 mmol, 2.00 equiv) dissolved in 500 ml water was added. The solution was stirred under nitrogen at room temperature until TLC monitoring indicated complete consumption of the starting material (3 h). After separation of the layers, the aqueous layer was extracted with DCM twice. The combined organic layers were washed with 1N HCl, saturated sodium bicarbonate solution, water, brine and dried (magnesium sulfate). Removal of the solvent in vacuo yielded 5.48 g (96%) of crude **2e** as an amber solid with a purity of $\geq 90\%$ as determined by 1H NMR spectroscopy. Column chromatography on silica gel (pentane/ethyl acetate 100:1) resulted in partial decomposition. R_f 0.77 (DCM); 1H NMR ($CDCl_3$, 200 MHz, δ): 8.18 (s, 1H), 8.13 (d, $J = 7.80$, 1H), 7.99 (d, $J = 7.80$, 1H), 7.80 (t, $J = 7.82$, 1H); HR-MS: calcd for $C_7H_4NO_2$, m/e 132.0324; found, m/e 132.0321.

1-Bromo-4-nitrosobenzene **2f**: 4-Bromoaniline **1f** (2.50 g, 14.9 mmol, 1.00 equiv) was dissolved in 45 ml of DCM. To this solution Oxone (17.9 g, 29.8 mmol, 2.00 equiv) dissolved in 180 ml of water was added. The solution was stirred under nitrogen at room temperature until TLC monitoring indicated complete consumption of the starting material (3.5 h). After separation of the layers, the aqueous layer was extracted with DCM twice. The combined organic layers were washed with 1N HCl, saturated sodium bicarbonate solution, water, brine and dried (magnesium sulfate). Removal of the solvent in vacuo yielded 2.75 g (quantitative) of **2f** as a green solid with a purity of 80% as determined by 1H NMR spectroscopy. 200 mg of the crude product were purified by sublimation ($p = 9 \cdot 10^{-3}$ mbar) to give 141 mg (70%) of **2f** as colorless crystals with a purity $\geq 95\%$ as determined by 1H NMR spectroscopy. R_f 0.88

(DCM); $^1\text{H NMR}$ (CDCl_3 , 200 MHz, δ): 7.77 (s, br., 4H), HR-MS: calcd for $\text{C}_6\text{H}_4\text{NBrO}$, m/e 184.9476; found, m/e 184.9477.

1-Ethyl-4-nitrosobenzene **2g**: 4-Ethylaniline **1g** (488 mg, 4.03 mmol, 1.00 equiv) was dissolved in 12.5 ml of DCM. To this solution Oxone (4.95 g, 8.05 mmol, 2.00 equiv) dissolved in 50 ml of water was added. The solution was stirred under nitrogen at room temperature until TLC monitoring indicated complete consumption of the starting material (12 h). After separation of the layers, the aqueous layer was extracted with DCM twice. The combined organic layers were washed with 1N HCl, saturated sodium bicarbonate solution, water, brine and dried (magnesium sulfate). After removal of the solvent the residue was distilled at ambient temperature in vacuo ($p = 7 \cdot 10^{-3}$ mbar) to give 482 mg (65%) **2g** as a green liquid with a purity $\geq 95\%$ as determined by $^1\text{H NMR}$ spectroscopy. R_f 0.77 (DCM); $^1\text{H NMR}$ (CDCl_3 , 200 MHz, δ): 7.83 (d, $J = 8.30$, 2H), 7.42 (d, $J = 7.82$, 2H), 2.74 (q, $J = 7.49$, 2H), 1.29 (t, $J = 7.80$, 3H); HR-MS: calcd for $\text{C}_8\text{H}_9\text{NO}$, m/e 135.0684; found, m/e 135.0681.

Oxone oxidation of Tetrabutylammonium 4-aminobenzenesulfonate **1i**: Tetrabutylammonium sulfanilate **1i** (729 mg, 1.76 mmol, 1.00 equiv) was dissolved in 20 ml of DCM. To this solution Oxone (2.16 g, 3.51 mmol, 2.00 equiv) dissolved in 20 ml of water was added. The solution was stirred under nitrogen at room temperature until TLC monitoring indicated complete consumption of the starting material (0.5 h). After separation of the layers, the aqueous layer was extracted with DCM twice. The combined organic layers were washed with 1N HCl, saturated sodium bicarbonate solution, water, brine and dried (magnesium sulfate). Removal of the solvent in vacuo yielded 720 mg (97%) of crude **2i** as a dark green liquid with a purity of 85% as determined by $^1\text{H NMR}$ spectroscopy. Attempts to purify the compound by chromatography on silica gel and Florisil[®] (DCM/MeOH 15:1) resulted in partial decomposition. Characteristic data of **2i**: R_f 0.77 (DCM/MeOH 9:1); $^1\text{H NMR}$ (CDCl_3 ,

200 MHz, δ): 8.06 (d, $J = 8.28$, 2H), 7.77 (d, $J = 8.28$, 2H), 3.30 – 3.10 (m, 8H), 1.67-1.45 (m, 8H), 1.43-1.18 (m, 8H), 0.88 (t, $J = 7.32$, 12H); ^{13}C NMR (CDCl_3 , 50.3 MHz, δ): 165.1, 153.3, 127.2, 120.6, 58.5, 23.8, 19.5, 13.4; IR (ATR, ν): 3533 (m), 3477 (m), 2962 (m), 2936 (m), 2875 (m), 1522 (m), 1348 (m), 1226 (s), 1120 (s), 1031 (s), 1031 (s), 1008 (m), 738 (s).

Oxone oxidation of 4-(Hydroxymethyl)aniline **1j**: 4-(Hydroxymethyl)aniline **1j** (100 mg, 812 μmol , 1.00 equiv) was dissolved in 10 ml of $\text{CHCl}_3/\text{EtOH}$ 2:1 at 0°C . A cooled solution of Oxone (499 mg, 812 μmol , 1.00 equiv) dissolved in 10 ml of water was added. The mixture was stirred under nitrogen at 0°C until TLC monitoring indicated no further conversion of the starting material (1.5 h). After separation of the layers, the aqueous layer was extracted with DCM twice. The combined organic layers were dried over magnesium sulfate. Removal of the solvent in vacuo yielded 50 mg (45%) of crude **2j** as a green oil with a purity of 75% as determined by ^1H NMR spectroscopy. Attempts to purify the product by column chromatography on silica gel and Florisil[®] (DCM) resulted in decomposition. Characteristic data of **2j**: R_f 0.73 (DCM/MeOH 9:1); ^1H NMR (CDCl_3 , 200 MHz, δ): 7.89 (d, $J = 8.30$, 2H), 7.58 (d, $J = 7.82$, 2H), 4.79 (s, 2H), 2.41 (s, br., 1H); ^{13}C NMR (CDCl_3 , 50.3 MHz, δ): 165.6, 148.8, 126.9, 121.3, 64.3; IR (ATR, ν): 3311 (m), 2923 (m), 1677 (m), 1602 (m), 1344 (s), 1047 (m), 1012 (m), 837 (m); HR-MS: calcd for $\text{C}_7\text{H}_6\text{NO}_2$, m/e 136.0399; found, m/e 136.0398.

tert-Butyl 4-nitrosobenzylcarbamate **2l**: *tert*-Butyl 4-aminobenzylcarbamate **1l** (500 mg, 2.25 mmol, 1.00 equiv) was dissolved in 20 ml of DCM. To this solution Oxone (2.07 g, 3.38 mmol, 1.50 equiv) dissolved in 20 ml of water was added. The solution was stirred under nitrogen at room temperature until TLC monitoring indicated complete consumption of the starting material (9.5 h). After separation of the layers, the aqueous layer was extracted with DCM twice. The combined organic layers were washed with 1N HCl, saturated sodium

bicarbonate solution, water, brine and dried (magnesium sulfate). After removal of the solvent the mixture of nitro and nitroso compound was separated from the azoxybenzene by column chromatography on Florisil[®] (pentane/ethyl acetate 20:1). Recrystallization of this mixture from ethyl acetate/pentane yielded 318 mg of **2l** (60%) as a green solid with a purity $\geq 95\%$ as determined by ¹H NMR spectroscopy. m.p. 80 °C; R_f 0.44 (DCM); ¹H NMR (CDCl₃, 200 MHz, δ): 7.84 (d, *J* = 8.30, 2H), 7.50 (d, *J* = 8.30, 2H), 5.07 (s, br., 1H), 4.38 (d, *J* = 5.86, 2H), 1.45 (s, 9H); ¹³C NMR (CDCl₃, 50.3 MHz, δ): 165.5, 155.9, 147.3, 127.7, 121.3, 80.0, 44.2, 28.3; IR (ATR, ν): 3342 (m), 2978 (m), 1692 (s), 1511 (s), 1456 (m), 1366 (m), 1274 (m), 1251 (m), 1168 (s), 1117 (m), 1049 (w), 865 (w), 784 (w); HR-MS: calcd for C₁₂H₁₆N₂O₃, *m/e* 236.1161; found, *m/e* 263.1167.

Methyl 4-methyl-3-nitrosobenzoate **2m**: Methyl 3-amino-4-methylbenzoate **1m** (3.00 g, 18.2 mmol, 1.00 equiv) was dissolved in 60 ml of DCM. To this solution Oxone (22.3 g, 36.3 mmol, 2.00 equiv) dissolved in 240 ml of water was added. The solution was stirred under nitrogen at room temperature until TLC monitoring indicated complete consumption of the starting material (3.5 h). After separation of the layers, the aqueous layer was extracted with DCM twice. The combined organic layers were washed with 1N HCl, saturated sodium bicarbonate solution, water, brine and dried (magnesium sulfate). Removal of the solvent in vacuo yielded 3.15 g (96%) crude **2m** as an amber solid with a purity of $\geq 95\%$ as determined by ¹H NMR spectroscopy. The purity could not be improved by sublimation. m.p. 85 °C; R_f 0.36 (DCM); ¹H NMR (CDCl₃, 200 MHz, δ): 8.26 (dd, *J* = 7.82, 1.96, 1H), 7.64 (d, *J* = 7.82, 1H), 6.88 (d, *J* = 1.96, 1H), 3.90 (s, 3H), 3.41 (s, 3H); ¹³C NMR (CDCl₃, 50.3 MHz, δ): 166.0, 163.6, 146.6, 135.7, 133.2, 128.0, 108.4, 52.4, 17.5; IR (ATR, ν): 2954 (m), 1722 (s), 1491 (m), 1435 (m), 1290 (s), 1256 (s), 1117 (m), 757 (m); HR-MS: calcd for C₉H₉NO₃, *m/e* 179.0582; found, *m/e* 179.0589.

Methyl 4-(4-bromo-phenylazo)-benzoate **3a**: Crude **2a** (577 mg, 3.49 mmol, 1.20 equiv) was dissolved in 25 ml of acetic acid. To this solution was added 4-bromoaniline (501 mg, 2.91 mmol, 1.00 equiv). The resulting mixture was stirred at room temperature for 24 h (TLC monitoring). The precipitate was separated by filtration, washed with water and dried in a desiccator over sicacide[®]. Purification by chromatography (DCM/pentane 4:1, silica gel) yielded 922 mg (98%) of **3a** as an orange solid. m.p. 176 °C; R_f 0.73 (DCM/pentane 4:1); ¹H NMR (CDCl₃, 200 MHz, δ): 8.19 (d, *J* = 8.78, 2H), 7.94 (d, *J* = 8.78, 2H), 7.83 (d, *J* = 8.78, 2H), 7.66 (d, *J* = 8.78, 2H), 3.96 (s, 3H); ¹³C NMR (CDCl₃, 50.3 MHz, δ): 166.4, 154.9, 151.8, 132.4, 132.0, 130.6, 126.2, 124.6, 122.7, 52.4; IR (ATR, ν): 2952 (w), 1722 (s), 1440 (w), 1407 (w), 1298 (m), 1283 (s), 1195 (w), 1112 (m), 1099 (m), 1011 (w), 1099 (w), 865 (m), 832 (m), 773 (m), 708 (m); HR-MS: calcd for C₁₄H₁₁N₂O₂Br, *m/e* 318.0004; found, *m/e* 318.0000.

tert-Butyl 4-(4-bromo-phenylazo)-benzoate **3b**: Crude **2f** (5.90 g, 32.3 mmol, 2.00 equiv) was dissolved in 300 ml of acetic acid. To this solution was added *tert*-butyl 4-amino-benzoate (3.12 g, 16.2 mmol, 1.00 equiv). The resulting mixture was stirred at room temperature for 6 d (TLC monitoring). The precipitate was separated by filtration, washed with water and dried in a desiccator over sicacide[®]. Recrystallization from pentane yielded 5.16 g (89%) of **3b** as an orange solid. m.p. 96 °C; R_f 0.75 (DCM/pentane 1:1); ¹H NMR (CDCl₃, 200 MHz, δ): 8.14 (d, *J* = 8.78, 2H), 7.92 (d, *J* = 8.78, 2H), 7.83 (d, *J* = 8.78, 2H), 7.67 (d, *J* = 8.78, 2H), 1.63 (s, 9H); ¹³C NMR (CDCl₃, 50.3 MHz, δ): 165.1, 154.6, 151.2, 134.0, 132.4, 130.4, 126.1, 124.6, 122.6, 81.5, 28.2; IR (ATR, ν): 2977 (w), 1710 (s), 1572 (w), 1477 (m), 1460 (m), 1367 (m), 1097 (m), 1007 (m), 866 (m), 834 (m), 755 (m), 710 (m); HR-MS: calcd for C₁₇H₁₇N₂O₂Br, *m/e* 360.0474; found, *m/e* 360.0471.

Fmoc-AMPB-OH **3c**: Crude **2b** (10.0 g, 66.2 mmol, 2.00 equiv) was suspended in 900 ml of AcOH/DMSO 1:1 and the suspension was sonified until the solid completely dissolved. To the solution was added *N*-(4-aminobenzyl)carbamic acid *9H*-fluorenylmethyl ester (11.1 g, 33.6 mmol, 1.00 equiv). The mixture was stirred for 36 h at room temperature (TLC monitoring). The product was precipitated by careful addition of water, separated and washed with water. Recrystallization from acetone/H₂O yielded 14.5 g (quant.) of **3c** as a red solid. m.p. 240 °C (decomp.); R_f 0.47 (DCM/MeOH 9:1); ¹H NMR (d₆-DMSO, 200 MHz, δ): 13.3 (s, br., 1H), 8.14 (d, *J* = 8.30, 2H), 8.05 – 7.80 (m, 6H), 7.71 (d, *J* = 7.32, 2H), 7.50 – 7.24 (m, 6H), 4.50 – 4.00 (m, 5H); HR-MS: calcd for C₂₉H₂₃N₃O₄, *m/e* 477.1689; found, *m/e* 477.1680.

References

(i) Fader, L. D. *Org. Lett.* **2002**, *4*, 63-66.