Organocatalyzed Solvent-free Aza-Henry Reaction: A Breakthrough in the One Pot Synthesis of 1,2-Diamines

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Supporting Information

Contents:

Experimental details and characterization data for compounds **2b-j**, **3a**, **5b**, **5c**, **5e**, **5h**, **6b**, **6c**, **6e** and **6h**: S2-S9.

General Methods. Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification. Thin-layer chromatography (TLC) was performed on plastic plates coated with (0.20 mm) silica gel 60 F₂₅₄. Column chromatography was carried out on 70-230 mesh silica gel. Melting points were uncorrected. ¹H and ¹³C NMR spectra were recorded at 300 and 400 MHz and 75 and 100 MHz, respectively, in CDCl₃ as the solvent. Chemical shifts were reported in the δ scale relative to residual CHCl₃ (7.26 ppm) for ¹H NMR and to the central line of CDCl₃ (77.0 ppm) for ¹³C NMR. Mass spectra (MS) were obtained with an electrospray ionization source (ESIMS).

All the ESIMS spectra were performed using MeOH as the solvent. High Resolution Mass Spectra (HRMS) were recorded on a micromass LCT spectrometer using electrospray (ES⁺) ionization techniques. N-Diphenylphosphinoylimines **1a-f** were prepared according to literature or modified procedures.¹ 2-Phenylnitroethane² was prepared following literature procedures.

N-[1-(4-Chlorophenyl)-2-nitrobutyl]diphenylphosphinic amide (2b). Following the general procedure for the solvent-free aza-Henry reaction, compound **2b** was obtained as a white solid in 95% yield (81 mg) and in a 84:16 diastereomeric ratio (¹H NMR) favouring the *anti* isomer: ¹H NMR (400 MHz) δ 7.84-7.74 (m, 2H_{maj}, 2H_{min}), 7.72-7.62 (m, 2H_{maj}, 2H_{min}), 7.58-7.40 (m, 4H_{maj}, 4H_{min}), 7.38-7.21 (m, 4H_{maj}, 4H_{min}), 7.12-7.06 (m, 2H_{maj}), 7.04-6.80 (m, 2H_{min}), 4.77 (ddd, *J* = 10.3, 6.4, 3.7 Hz, 1H_{min}), 4.61 (ddd, *J* = 10.6, 6.5, 3.9 Hz, 1H_{maj}), 4.55-4.42 (m, 1H_{maj}, 1H_{min}), 4.19 (dd, *J* = 10.8, 6.9 Hz, 1H_{maj}), 3.93 (dd, *J* = 11.0, 7.5 Hz, 1H_{min}), 2.16-2.02 (m, 1H_{maj}), 2.05-1.92 (m, 2H_{min}), 1.85-1.72 (m, 1H_{maj}), 0.95 (t, *J* = 7.4 Hz, 3H_{min}), 0.93 (t, *J* = 7.6 Hz, 3H_{maj}); ¹³C NMR (100 MHz) [*anti* isomer] δ 137.3, 134.3, 132.2, 132.1, 132.0, 131.8, 130.9, 129.2, 128.9, 128.7, 128.6, 128.5, 128.4, 127.9, 95.0, 56.8, 25.1, 10.4; IR $\nu_{\max}$ (thin layer, NaCl plate) 3375, 1554, 1206 cm⁻¹; ESI-MS *m/z* 451 (M+Na⁺); Anal. Calcd for C₂₂H₂₂ClN₂O₃P: C 61.62; H 5.17; N 6.53. Found C 61.60; H 5.21, N 6.49.

N-[1-(4-Methoxyphenyl)-2-nitrobutyl]diphenylphosphinic amide (2c). Following the general procedure for the solvent-free aza-Henry reaction, compound **2c** was obtained as a white solid in 92% yield (78 mg) and in a 95:5 diastereomeric ratio (¹H NMR) favouring the *anti* isomer: ¹H NMR (400 MHz) δ 7.83-7.76 (m, 2H_{maj}, 2H_{min}), 7.74-7.64 (m, 2H_{maj}, 2H_{min}), 7.56-7.40 (m, 4H_{maj}, 4H_{min}), 7.36-7.28 (m, 2H_{maj}, 2H_{min}), 7.08-7.03 (m, 2H_{maj}, 2H_{min}), 6.85-6.80 (m, 2H_{maj}, 2H_{min}), 4.76 (ddd, *J* = 10.4, 6.8, 3.6 Hz, 1H_{min}), 4.61 (ddd, *J* = 10.7, 6.8, 3.7 Hz, 1H_{maj}), 4.48-4.39 (m, 1H_{maj}, 1H_{min}), 4.05 (dd, *J* = 11.0, 6.7 Hz, 1H_{maj}), 3.80 (dd, *J* = 7.0, 4.3 Hz, 1H_{min}), 3.78 (s, 3H_{maj}, 3H_{min}), 2.14-2.00 (m, 1H_{maj}), 2.06-1.94 (m, 1H_{min}), 1.82-1.70 (m, 1H_{maj}, 1H_{min}), 0.92 (t, *J* = 7.4 Hz, 3H_{maj}, 3H_{min}); ¹³C NMR (100 MHz) [*anti* isomer] δ 159.4, 132.3, 132.2, 132.1, 132.0, 131.2, 130.8, 128.6, 128.5, 128.4, 128.3, 128.0, 127.6,

114.3, 95.5, 95.4, 57.0, 55.2, 25.1, 10.4; IR $\nu_{\max}$ (thin layer, NaCl plate) 3348, 1553, 1204 cm^{-1} ; ESI-MS m/z 447 ($\text{M}+\text{Na}^+$); Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_4\text{P}$: C 65.09; H 5.94; N 6.60. Found C 65.02; H 5.89, N 6.68.

N-[1-(2-Furyl)-2-nitrobutyl]diphenylphosphinic amide (2d). Following the general procedure for the solvent-free aza-Henry reaction, compound **2d** was obtained as a white solid in 90% yield (70 mg) and in a 95:5 diastereomeric ratio (^1H NMR) favouring the *anti* isomer: ^1H NMR (400 MHz) δ 7.82-7.71 (m, 4 H_{maj} , 4 H_{min}), 7.56-7.43 (m, 4 H_{maj} , 4 H_{min}), 7.42-7.36 (m, 2 H_{maj} , 2 H_{min}), 7.31 (dd, $J = 1.8, 0.9$ Hz, 1 H_{maj} , 1 H_{min}), 6.27 (dd, $J = 3.3, 1.9$ Hz, 1 H_{maj} , 1 H_{min}), 6.20 (dt, $J_{\text{d}} = 3.3$ Hz, $J_{\text{t}} = 0.6$ Hz, 1 H_{maj}), 6.17 (dt, $J_{\text{d}} = 3.3$ Hz, $J_{\text{t}} = 0.6$ Hz, 1 H_{min}), 4.80 (ddd, $J = 10.7, 7.1, 3.9$ Hz, 1 H_{maj} , 1 H_{min}), 4.70-4.63 (m, 1 H_{min}), 4.62 (ddd, $J = 11.2, 9.2, 7.1$ Hz, 1 H_{maj}), 3.90 (dd, $J = 11.3, 7.4$ Hz, 1 H_{maj}), 3.76 (dd, $J = 11.5, 9.0$ Hz, 1 H_{min}), 2.10-1.98 (m, 1 H_{maj} , 2 H_{min}), 1.78-1.66 (m, 1 H_{maj}), 0.96 (t, $J = 7.4$ Hz, 3 H_{min}), 0.93 (t, $J = 7.4$ Hz, 3 H_{maj}); ^{13}C NMR (100 MHz) [*anti* isomer] δ 150.9, 150.8, 142.6, 132.4, 132.3, 132.2, 132.1, 132.0, 131.9, 131.7, 131.6, 131.1, 130.9, 128.7, 128.6, 128.5, 128.4, 110.6, 108.6, 92.7, 51.3, 24.5, 10.3; IR $\nu_{\max}$ (thin layer, NaCl plate) 3376, 1557, 1208 cm^{-1} ; HRMS m/z calcd for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{NaO}_4\text{P}^+$: 407.1137. Found 407.1127 ($\text{M}+\text{Na}^+$); Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_4\text{P}$: C 62.50; H 5.51; N 7.29. Found C 62.55; H 5.49, N 7.32.

N-[2-Nitrobutyl-1-(2-thienyl)]diphenylphosphinic amide (2e). Following the general procedure for the solvent-free aza-Henry reaction, compound **2e** was obtained as a pale yellow solid in 92% yield (73 mg) and in a 95:5 diastereomeric ratio (^1H NMR), favouring the *anti* isomer: ^1H NMR (400 MHz) δ 7.90-7.82 (m, 2 H_{maj} , 2 H_{min}), 7.80-7.74 (m, 2 H_{maj} , 2 H_{min}), 7.58-7.44 (m, 4 H_{maj} , 4 H_{min}), 7.40-7.32 (m, 2 H_{maj} , 2 H_{min}), 7.23 (dd, $J = 5.1, 1.3$ Hz, 1 H_{maj} , 1 H_{min}), 6.91 (dd, $J = 5.1, 3.5$ Hz, 1 H_{maj} , 1 H_{min}), 6.87 (ddd, $J = 3.7, 1.2, 0.7$ Hz, 1 H_{maj}), 6.84-6.81 (m, 1 H_{min}), 4.90-4.82 (m, 1 H_{min}), 4.84-4.75 (m, 1 H_{maj}), 4.72 (ddd, $J = 10.3, 6.4, 4.0$ Hz, 1 H_{maj} , 1 H_{min}), 4.12 (dd, $J = 11.1, 8.0$ Hz, 1 H_{maj}), 3.78 (dd, $J = 11.3,$

7.6 Hz, 1H_{min}), 2.22-2.14 (m, 1H_{maj}, 2H_{min}), 1.98.-1.84 (m, 1H_{maj}), 0.98 (t, $J = 7.3$ Hz, 3H_{maj}, 3H_{min}); ¹³C NMR (100 MHz) [*anti* isomer] δ 142.6, 132.4, 132.3, 132.2, 132.1, 132.0, 131.9, 131.8, 131.1, 130.8, 128.7, 128.6, 128.5, 127.2, 127.0, 125.4, 125.3, 95.0, 94.9, 53.1, 25.2, 10.5; IR $\nu_{\max}$ (thin layer, NaCl plate) 3370, 1555, 1206 cm⁻¹; HRMS m/z calcd for C₂₀H₂₁N₂NaO₃PS⁺: 423.0908. Found 423.0901 (M+Na⁺); Anal. Calcd for C₂₀H₂₁N₂O₄P: C 59.99; H 5.29; N 7.00. Found C 60.05; H 5.33, N 7.04.

N-[1,2-Anti-1-(*tert*-butyl)-(2-nitrobutyl)]diphenylphosphinic amide (2f). Following the general procedure for the solvent-free aza-Henry reaction, compound **2f** was obtained as a white solid in 95% yield (71 mg) and as a single diastereoisomer (¹H NMR): mp = 220-222°C; ¹H NMR (400 MHz) δ 8.05-7.94 (m, 2H), 7.88-7.80 (m, 2H), 7.58-7.42 (m, 6H), 4.48 (dt, $J_t = 1.6$ Hz, $J_d = 11.6$ Hz, 1H), 3.38 (ddd, $J = 12.6, 10.3, 2.8$ Hz, 1H), 2.96 (dd, $J = 12.2, 5.5$ Hz, 1H), 2.46-2.34 (m, 1H), 1.72 (ddd, $J = 15.0, 7.6, 2.5$ Hz, 1H), 1.01 (s, 9H), 0.99 (t, $J = 7.1$ Hz, 3H); ¹³C NMR (100 MHz) δ 132.8, 132.6, 132.5, 132.2, 132.1, 132.0, 130.5, 128.6, 128.4, 91.2, 91.1, 62.8, 36.3, 36.2, 27.4, 22.7, 11.2; IR $\nu_{\max}$ (thin layer, NaCl plate) 3372, 1552, 1202 cm⁻¹; ESI-MS m/z 397 (M+Na⁺); Anal. Calcd for C₂₀H₂₇N₂O₃P: C 64.16; H 7.27; N 7.48. Found C 64.18; H 7.31, N 7.42.

N-(1,2-Anti-2-nitro-1-phenylheptyl)diphenylphosphinic amide (2g). Following the general procedure for the solvent-free aza-Henry reaction, compound **2g** was obtained as a white solid in 90% yield (78 mg) and as a single diastereoisomer (¹H NMR): mp = 217-219°C; ¹H NMR (400 MHz) δ 7.84-7.76 (m, 2H), 7.72-7.64 (m, 2H), 7.58-7.50 (m, 1H), 7.48-7.40 (m, 3H), 7.38-7.27 (m, 5H), 7.15-7.12 (m, 2H), 4.71 (ddd, $J = 10.9, 6.8, 4.1$ Hz, 1H), 4.49 (dt, $J_d = 6.8$ Hz, $J_t = 10.9$ Hz, 1H), 4.12 (dd, $J = 11.4, 7.3$ Hz, 1H), 2.12-2.05 (m, 1H), 1.74-1.62 (m, 1H), 1.33-1.16 (m, 6H), 0.85 (t, $J = 6.9$ Hz, 3H); ¹³C NMR (100 MHz) δ 138.8, 132.5, 132.4, 132.3, 132.2, 132.1, 131.9, 131.2, 131.1, 129.0, 128.6, 128.5, 128.4, 128.2, 126.5, 93.7, 93.6, 57.5, 31.5, 30.8, 25.5, 22.2, 13.8; IR $\nu_{\max}$ (thin layer, NaCl

plate) 3368, 1554, 1200 cm^{-1} ; ESI-MS m/z 459 ($\text{M}+\text{Na}^+$); Anal. Calcd for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_3\text{P}$: C 68.79; H 6.70; N 6.42. Found C 68.82; H 6.74, N 6.48.

N-(1,2-Anti-2-nitro-1,3-diphenylpropyl)diphenylphosphinic amide (2h). Following the general procedure for the solvent-free aza-Henry reaction, compound **2h** was obtained as a white solid in 95% yield (86 mg) and as a single diastereoisomer (^1H NMR): mp = 210-212°C; ^1H NMR (400 MHz) δ 7.88-7.82 (m, 2H), 7.72-7.65 (m, 2H), 7.59-7.53 (m, 1H), 7.52-7.40 (m, 4H), 7.36-7.20 (m, 7H), 7.19-7.16 (m, 2H), 7.12-7.09 (m, 2H), 4.96 (ddd, $J = 10.5, 6.6, 3.9$ Hz, 1H), 4.62 (dt, $J_{\text{d}} = 6.4$ Hz, $J_{\text{t}} = 10.7$ Hz, 1H), 4.20 (dd, $J = 11.2, 7.3$ Hz, 1H), 3.34 (dd, $J = 14.7, 10.6$ Hz, 1H), 3.13 (dd, $J = 14.9, 3.9$ Hz, 1H); ^{13}C NMR (d_6 -DMSO, 100 MHz) δ 139.6, 136.0, 132.5, 132.4, 132.3, 132.2, 132.1, 131.8, 129.1, 128.9, 128.8, 128.6, 128.5, 128.3, 127.8, 127.5, 95.0, 94.9, 58.9, 37.5; IR ν_{max} (thin layer, NaCl plate) 3374, 1556, 1203 cm^{-1} ; ESI-MS m/z 479 ($\text{M}+\text{Na}^+$); Anal. Calcd for $\text{C}_{27}\text{H}_{25}\text{N}_2\text{O}_3\text{P}$: C 71.04; H 5.52; N 6.14. Found C 71.09; H 5.48, N 6.20.

N-(2-Nitro-1-phenylethyl)diphenylphosphinic amide (2i). Following the general procedure for the solvent-free aza-Henry reaction, compound **2i** was obtained in 90% yield (65 mg) as a white solid: mp = 207-209°C; ^1H NMR (400 MHz) δ 7.88-7.80 (m, 4H), 7.56-7.28 (m, 11H), 4.94 (dd, $J = 12.9, 6.2$ Hz, 1H), 4.92 (dd, $J = 12.9, 5.3$ Hz, 1H), 4.90-4.82 (m, 1H), 3.92 (dd, $J = 10.6, 6.5$ Hz, 1H); ^{13}C NMR (100 MHz) δ 138.0, 137.9, 132.5, 132.4, 132.3, 131.8, 131.7, 131.4, 131.0, 130.1, 129.0, 128.7, 128.6, 128.4, 126.4, 80.9, 80.8, 53.4; IR ν_{max} (thin layer, NaCl plate) 3374, 1556, 1204 cm^{-1} ; ESI-MS m/z 389 ($\text{M}+\text{Na}^+$); Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_3\text{P}$: C. 65.57; H 5.23; N 7.65. Found C 65.52; H 5.24, N 7.71.

N-(2-Methyl-2-nitro-1-phenylpropyl)diphenylphosphinic amide (2j). Following the general procedure for the solvent-free aza-Henry reaction, compound **2j** was obtained in 96% yield (71 mg) as a white solid: mp = 214-215°C; ^1H NMR (400 MHz) δ 7.81-7.84 (m, 2H), 7.60-7.50 (m, 3H), 7.48-7.36

(m, 3H), 7.30-7.20 (m, 5H), 7.02-6.96 (m, 2H), 4.45 (t, $J = 11.3$ Hz, 1H), 4.38 (t, $J = 11.3$ Hz, 1H), 1.81 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz) δ 138.1, 138.1, 132.9, 132.8, 132.4, 132.1, 132.0, 131.9, 131.8, 130.9, 128.9, 128.8, 128.7, 128.5, 128.4, 127.9, 91.3, 91.2, 62.0, 26.1, 23.4; IR ν_{max} (thin layer, NaCl plate) 3396, 1542, 1205 cm^{-1} ; HRMS m/z calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3\text{P}^+$: 395.1519. Found 395.1515 ($\text{M}+\text{H}^+$); Anal. Calcd for $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_3\text{P}$: C. 67.00; H 5.88; N 7.10. Found C 67.03, H 5.92, N 7.08.

N-(2-amino-1-phenylbutyl)diphenylphosphinic amide (3a). To a magnetically stirred suspension of β -nitroamine **2a** (79 mg, 0.2 mmol) in THF/ $\text{NH}_4\text{Cl}_{\text{sat}}$ (2+0.7 mL), were sequentially added In powder (5.7 mg, 0.05 mmol) and zinc powder (117 mg, 1.8 mmol). The reaction mixture was heated to reflux with stirring. After 18h, the reaction was cooled to room temperature, poured onto sat. Na_2CO_3 , then extracted three times with CH_2Cl_2 . The organic extracts were dried over MgSO_4 , filtered and evaporated under reduced pressure. Chromatography on silica gel ($\text{CHCl}_3/\text{MeOH} = 9/1$) afforded compound **3a** as a thick colourless oil in 92% yield (67 mg) and as a mixture of diastereoisomers (*anti/syn* = 94:6, ^1H NMR of the crude product): ^1H NMR (300 MHz) δ 7.92-7.84 (m, 2H_{maj} , 2H_{min}), 7.72-7.62 (m, 2H_{maj} , 2H_{min}), 7.50-7.14 (m, 11H_{maj} , 11H_{min}), 4.71 (dd, $J = 10.5, 6.2$ Hz, 1H_{min}), 4.54 (t, $J = 8.3$ Hz, 1H_{maj} , 1H_{min}), 4.15 (dt, $J_t = 11.0$ Hz, $J_d = 4.0$ Hz, 1H_{min}), 4.04 (dt, $J_t = 10.5$ Hz, $J_d = 4.0$ Hz, 1H_{maj}), 3.05-2.94 (m, 1H_{min}), 2.89 (dt, $J_d = 7.4$ Hz, $J_t = 4.9$ Hz, 1H_{maj}), 2.05 (br s, 2H_{maj} , 2H_{min}), 1.78-1.60 (m, 1H_{maj} , 1H_{min}), 1.50-1.37 (m, 1H_{maj} , 1H_{min}), 0.92 (t, $J = 7.5$ Hz, 3H_{maj}), 0.88 (t, $J = 7.5$ Hz, 3H_{min}); ^{13}C NMR (75 MHz) [*anti* isomer] δ 142.7, 142.6, 132.6, 132.5, 131.8, 131.7, 131.5, 128.5, 128.3, 128.1, 128.0, 127.0, 126.8, 58.7, 58.4, 58.3, 26.6, 10.5; IR ν_{max} (thin layer, NaCl plate) 3410, 3330, 1199 cm^{-1} ; ESI-MS m/z 365 ($\text{M}+\text{H}^+$).

1-(4-Chlorophenyl)-1,2-butanediamine (5b). Following the general procedure for the synthesis of 1,2-diamines, crude compound **5b** was obtained as a pale yellow oil in 90% yield (36 mg) and in a 84:16 diastereomeric ratio (^1H NMR), favouring the *anti* isomer: ^1H NMR (300 MHz, CDCl_3) δ 7.44-7.33 (m, 4H_{maj} , 4H_{min}), 3.94 (d, $J = 5.7\text{ Hz}$, 1H_{min}), 3.82 (d, $J = 5.9\text{ Hz}$, 1H_{maj}), 2.93-2.85 (m, 1H_{min}), 2.85-2.76 (m, 1H_{maj}), 1.73 (bs, 4H_{maj} , 4H_{min}), 1.59-1.42 (m, 1H_{maj} , 1H_{min}), 1.41-1.18 (m, 1H_{maj} , 1H_{min}), 1.07 (t, $J = 7.1\text{ Hz}$, 3H_{min}), 1.03 (t, $J = 7.2\text{ Hz}$, 3H_{maj}).

1-(4-Methoxyphenyl)-1,2-butanediamine (5c). Following the general procedure for the synthesis of 1,2-diamines, crude compound **5c** was obtained as a pale yellow oil in 74% yield (27 mg) and in a 95:5 diastereomeric ratio (^1H NMR), favouring the *anti* isomer: ^1H NMR (300 MHz, CDCl_3) δ 7.36-7.30 (m, 2H_{maj} , 2H_{min}), 7.01-6.95 (m, 2H_{maj} , 2H_{min}), 3.90 (s, 3H_{maj} , 3H_{min}), 3.80-3.73 (m, 1H_{maj} , 1H_{min}), 2.85-2.76 (m, 1H_{maj} , 1H_{min}), 1.84 (bs, 4H_{maj} , 4H_{min}), 1.59-1.43 (m, 1H_{maj} , 1H_{min}), 1.38-1.20 (m, 1H_{maj} , 1H_{min}), 1.07 (t, $J = 7.3$, 3H_{min}), 1.02 (t, $J = 7.2\text{ Hz}$, 3H_{maj}).

1-(2-Thienyl)-1,2-butanediamine (5e). Following the general procedure for the synthesis of 1,2-diamines, crude compound **5e** was obtained as a pale yellow oil in 70% yield (24 mg) and in a 95:5 diastereomeric ratio (^1H NMR), favouring the *anti* isomer: ^1H NMR (300 MHz, CDCl_3) δ 7.35-7.29 (m, 1H_{maj} , 1H_{min}), 7.11-7.02 (m, 2H_{maj} , 2H_{min}), 4.29 (d, $J = 4.8\text{ Hz}$, 1H_{min}), 4.15 (d, $J = 5.7\text{ Hz}$, 1H_{maj}), 2.97-2.88 (m, 1H_{maj} , 1H_{min}), 1.89 (bs, 4H_{maj} , 4H_{min}), 1.71-1.53 (m, 1H_{maj} , 1H_{min}), 1.47-1.29 (m, 1H_{maj} , 1H_{min}), 1.07 (t, $J = 7.3\text{ Hz}$, 3H_{maj} , 3H_{min}).

1,2-Anti-1,3-diphenyl-1,2-propanediamine (5h). Following the general procedure for the synthesis of 1,2-diamines, crude compound **5h** was obtained as a pale yellow oil in 60% yield (28 mg) and as

single diastereoisomer (^1H NMR), favouring the *anti* isomer: ^1H NMR (300 MHz, CDCl_3) δ 7.51-7.04 (m, 10H), 3.70-3.49 (m, 2H), 2.99-2.91 (m, 1H), 2.78-2.70 (m, 1H), 1.88 (bs, 4H).

***N*-(1-(4-Chlorophenyl)-2-[(4-methylphenyl)sulfonyl]aminobutyl)-4-methylbenzenesulfonamide (6b).** Following the general procedure for the synthesis of bis-sulfonamides, compound **6b** was obtained as a white solid in 68% yield (69 mg) and in a 84:16 diastomeric ratio (^1H NMR) favouring the *anti* isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.71 (d, J = 8.5 Hz, 2H_{min}), 7.62 (d, J = 8.8 Hz, 2H_{maj}), 7.51-7.46 (m, 2H_{maj} , 2H_{min}), 7.29 (d, J = 8.1 Hz, 2H_{min}), 7.21 (d, J = 7.9 Hz, 2H_{maj}), 7.11-7.02 (m, 2H_{maj} , 2H_{min}), 6.99-6.93 (m, 2H_{maj} , 2H_{min}), 6.91-6.86 (m, 2H_{maj} , 2H_{min}), 6.41 (d, J = 8.3 Hz, 1H_{min}), 6.18 (d, J = 7.8 Hz, 1H_{maj}), 5.22 (d, J = 8.8 Hz, 1H_{maj}), 4.70 (d, J = 8.6 Hz, 1H_{min}), 4.41 (dd, J = 2.9, 8.4 Hz, 1H_{min}), 4.33 (t, J = 6.9 Hz, 1H_{maj}), 3.38-3.29 (m, 1H_{maj}), 3.28-3.20 (m, 1H_{min}), 2.42 (s, 3H_{min}), 2.39 (s, 3H_{maj}), 2.35 (s, 3H_{min}), 2.33 (s, 3H_{maj}), 1.51-1.38 (m, 1H_{maj}), 1.29-1.11 (m, 1H_{maj} , 1H_{min}), 1.02-0.86 (m, 1H_{min}), 0.57 (t, J = 7.2 Hz, 3H_{maj}), 0.47 (t, J = 7.3 Hz, 3H_{min}); ^{13}C NMR [*anti* isomer] δ 142.4, 143.2, 137.4, 136.3, 133.4, 129.6, 129.2, 128.7, 128.2, 127.3, 127.0, 126.9, 59.9, 59.7, 24.8, 21.5, 21.4, 9.6; ESI-MS m/z 507 ($\text{M}+\text{H}$) $^+$, 529 ($\text{M}+\text{Na}^+$); IR ν_{max} (thin layer, NaCl plate) 3379, 3289, 1335, 1158 cm^{-1} ; Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{ClN}_2\text{O}_4\text{S}_2$: C 56.85, H 5.37, N 5.52 Found C 56.90, H 5.38, N 5.58.

***N*-(1-(4-Methoxyphenyl)-2-[(4-methylphenyl)sulfonyl]aminobutyl)-4-methylbenzenesulfonamide (6c).** Following the general procedure for the synthesis of bis-sulfonamides, compound **6c** was obtained as a white solid in 60% yield (61 mg) and in a 95:5 diastomeric ratio (^1H NMR) favouring the *anti* isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, J = 8.1 Hz, 2H_{maj}), 7.71 (d, J = 8.4 Hz, 2H_{min}), 7.54 (d, J = 8.1 Hz, 2H_{maj}), 7.48 (d, J = 8.4 Hz, 2H_{min}), 7.30 (d, J = 8.0 Hz, 2H_{maj}), 7.33-7.28 (m, 2H_{min}), 7.15 (d, J = 8.0 Hz, 2H_{maj}), 7.09 (d, J = 7.6 Hz, 2H_{min}), 6.91 (d, J = 8.0 Hz, 2H_{min}), 6.85 (d, J = 8.5 Hz, 2H_{maj}), 6.68-6.64 (m, 2H_{maj} , 2H_{min}), 6.04 (d, J = 8.1 Hz, 1H_{min}), 5.35 (d, J = 6.4 Hz, 1H_{maj}), 4.58 (d, J =

7.9 Hz, 1H_{maj}), 4.37 (dd, $J = 2.6, 8.1$ Hz 1H_{min}), 4.20 (d, $J = 9.3$ Hz, 1H_{min}), 4.11 (dd, $J = 6.4, 7.5$ Hz, 1H_{maj}), 3.74 (s, 3H_{maj}, 3H_{min}), 3.42-3.32 (m, 1H_{maj}), 3.27-3.17 (m, 1H_{min}), 2.44 (s, 3H_{min}), 2.43 (s, 3H_{maj}), 2.37 (s, 3H_{min}), 2.35 (s, 3H_{maj}), 1.53-1.36 (m, 1H_{maj}, 1H_{min}), 1.07-0.92 (m, 1H_{maj}), 0.91-0.85 (m, 1H_{min}), 0.53 (t, 3H_{maj}, $J = 7.3$ Hz, 3H_{min}); ¹³C NMR (100 MHz) [*anti* isomer] δ 159.2, 143.6, 143.1, 137.3, 136.9, 129.7, 129.3, 128.4, 127.3, 127.2, 113.9, 60.1, 59.1, 55.2, 29.6, 24.1, 21.5, 21.4, 9.2; ESI-MS m/z 501 (M-H)⁻; IR $\nu_{\max}$ (thin layer, NaCl plate) 3379, 1332, 1159 cm⁻¹; Anal. Calcd for C₂₅H₃₀N₂O₅S₂: C 59.74, H 6.02, N 5.57. Found C 59.76, H 6.08, N 5.58.

4-Methyl-N-[2-[(4-methylphenyl)sulfonyl]amino-1-(2-thienyl)butyl]benzenesulfonamide (6e)

Following the general procedure for the synthesis of bis-sulfonamides, compound **6e** was obtained as a white solid in 58% yield (55 mg) and in a 95:5 diastomeric ratio (¹H NMR) favouring the *anti* isomer: ¹H NMR (400 MHz, CDCl₃) δ 7.79-7.73 (m, 2H_{maj}, 2H_{min}), 7.60 (d, $J = 8.2$ Hz, 2H_{maj}), 7.52 (d, $J = 8.2$ Hz, 2H_{min}), 7.36-7.08 (m, 5H_{maj}, 5H_{min}), 6.82-6.61 (m, 2H_{maj}, 2H_{min}), 5.85 (d, $J = 8.3$ Hz, 1H_{min}), 5.20 (d, $J = 6.8$ Hz, 1H_{maj}), 4.67 (dd, $J = 2.2, 8.6$ Hz, 1H_{min}), 4.57 (d, $J = 8.5$ Hz, 1H_{maj}), 4.56-4.47 (m, 1H_{maj}, 1H_{min}), 3.50-3.40 (m, 1H_{maj}), 3.36-3.27 (m, 1H_{min}), 2.45 (s, 3H_{min}), 2.44 (s, 3H_{maj}), 2.39 (s, 3H_{maj}), 2.37 (s, 3H_{min}), 1.20-1.04 (m, 1H_{maj}, 1H_{min}), 0.98-0.77 (m, 1H_{maj}, 1H_{min}), 0.61 (t, $J = 7.5$ Hz, 3H_{maj}, 3H_{min}); ¹³C NMR (100 MHz) [*anti* isomer] δ 143.6, 143.4, 140.3, 137.2, 136.7, 129.7, 129.4, 127.3, 127.2, 126.7, 126.3, 125.5, 59.3, 56.2, 29.6, 24.0, 21.5, 9.5; ESI-MS m/z 477 (M-H)⁻; IR $\nu_{\max}$ (thin layer, NaCl plate) 3377, 1332, 1160 cm⁻¹; Anal. Calcd for C₂₂H₂₆N₂O₄S₃: C 55.20; H 5.48; N 5.85. Found C 55.25, H 5.42, N 5.90.

N-1-benzyl-2-[(4-methylphenyl)sulfonyl]amino]-2-phenylethyl-1-ethanesulfonamide (6h)

Following the general procedure for the synthesis of bis-sulfonamides, compound **6h** was obtained as a white solid in 55% yield (58 mg) and as a single diastereoisomer: mp = 176-178 °C. ¹H NMR (400

MHz, CDCl₃) δ 7.58 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.18-6.97 (m, 12H), 6.84 (d, J = 7.6 Hz, 2H), 5.81 (bs, 1H), 4.90 (bs, 1H), 4.44 (t, J = 6.2 Hz, 1H), 3.80-3.70 (m, 1H), 2.95 (dd, J = 5.3, 13.9 Hz, 1H), 2.36 (s, 3H), 2.34 (s, 3H), 2.25 (dd, J = 8.1, 13.9 Hz, 1H); ¹³C NMR (100 MHz) δ 143.5, 143.2, 137.5, 137.0, 136.7, 129.8, 129.6, 129.5, 128.9, 128.7, 128.6, 128.1, 127.7, 127.5, 127.1, 126.7, 60.2, 59.9, 37.4, 21.7, 21.6; ESI-MS m/z 535 (M+H)⁺, 557 (M+Na)⁺; IR ν_{max} (thin layer, NaCl plate) 3371, 1334, 1188, 1161 cm⁻¹; Anal. Calcd for C₂₉H₃₀N₂O₄S₂ : C 65.14; H 5.66; N 5.24; Found C 65.18; H 5.70, N 5.22.

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Graphical Abstract.