Supplementary Information

An Oxidatively-Activated Safety Catch Linker for Solid Phase Synthesis

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Experimental

General Experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen or argon before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[1] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$ or Na_2SO_4 as stated. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1 % aq. $KMnO_4$, or 10 % ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2/g and concentrations in g/100 mL. IR spectra were recorded on either a Perkin-Elmer Paragon 1000 FT-IR spectrometer or a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz), AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.3 MHz), Bruker DPX 250 (^{1}H: 250 MHz) or Varian 200 (^{1}H: 200 MHz) spectrometers in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. The field was locked by external referencing to the relevant deuteron resonance. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. Reverse-phase HPLC was

carried out on a Gilson instrument comprising of Gilson 306 pumps, Gilson 811C dynamic mixer, Gilson 806 manomeric module with automated injection on a Gilson 215 Liquid handler, configured with a Gilson 819 valve actuator. Separations were performed on a Hypersil® Elite C18 column (5 μm particle size, 150 x 4.6 mm). All experiments were performed under gradient elution with deionised H_2O (containing 0.1 % TFA) and MeCN, starting from 95 % H_2O, 5 % MeCN to 5 % H_2O, 95 % MeCN over 8 minutes then isocratic for 4 minutes. The flow rate was 1.0 mL/min. Detection was at λ 220, 254 and 290 nm with a Gilson 170 Diode Array Detector with equipment control and data collection managed by Gilson Unipoint LC software version 3.01. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF and were internally calibrated with polyaniline in positive and negative modes, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

General Experimental Procedures

Representative Procedure 1: carbodiimide coupling reactions in solution: To a solution of the requisite carboxylic acid in CH_2Cl_2 or DMF was added DIPEA, nucleophile (amine or alcohol), HOBt and coupling reagent (EDCI, TBTU or DIC). The reaction mixture was stirred at room temperature for 16 hours. The resulting solution was partitioned with 10 % aqueous HCl and then 2 M aqueous NaOH. The organic layer was dried (Na_2SO_4), concentrated *in vacuo* before purification as described.

Representative Procedure 2: CAN oxidation in solution: CAN (5.0 eq.) was added to a stirred solution of the requisite tertiary amine (1.0 eq.) in THF:H_2O (8:1) or MeCN:H_2O (5:1) and stirred for 16 hours at room temperature. The reaction was quenched with either a 2 M aqueous solution of NaOH or saturated aqueous bicarbonate solution ($NaHCO_3$) and extracted into ether or CH_2Cl_2. The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* and the resulting crude product purified as described.

Representative Procedure 3: carbodiimide coupling reactions on polymer support: To a suspension of the requisite carboxylic acid in CH_2Cl_2 was added DIPEA, nucleophile (amine or alcohol), HOBt and coupling reagent (EDCI, TBTU or DIC). The reaction mixture was stirred at room temperature for 16 hours. The resin was transferred to a sintered funnel, washed repeatedly with DMF, MeOH and CH_2Cl_2 then dried to a constant mass *in vacuo*.

Representative Procedure 4: Suzuki couplings on polymer support: To a stirred suspension of the polymer supported 4-iodophenyl ester (1.0 eq.) in DMF, boronic acid (4.0 eq.) and K_2CO_3 (5.0 eq.) was added Pd_2dba_3 (0.20 eq.) in 2 or 3 portions over 36 hours at 70˚C. The resin was transferred to a sintered funnel, washed repeatedly with DMF, water, THF and CH_2Cl_2 and then dried to a constant mass *in vacuo*.

Representative Procedure 5: CAN oxidation on polymer support: CAN (5.0 eq.) was added to a stirred suspension of the requisite resin (1.0 eq.) in THF:H_2O (8:1). After stirring for 16 hours the resin was transferred to a sintered funnel and washed repeatedly with THF, water, THF and CH_2Cl_2. The resin was then treated with CH_2Cl_2:NEt_3 (5:1) and the filtrate was concentrated *in vacuo*. The resulting residue was filtered through a plug of silica (EtOAc eluent) and the solvent removed *in vacuo*. The resin was dried *in vacuo* to a constant mass.

3,3-Dimethyl-5-hydroxydihydrofuran-2-one (1)

A solution of *n*-BuLi (1.6 M, 200 mL, 0.320 mol, 1.0 eq.) was added dropwise *via* cannula to a stirred solution of diisopropylamine (45.2 mL, 0.320 mol, 1.0 eq.) in THF (400 mL) at –78˚C. To the resulting solution of LDA was added *iso*-butyronitrile (28.6 mL, 0.320 mol, 1.0 eq.) in THF (300 mL) at –78˚C. After stirring for 1 hour the reaction mixture was warmed to –20˚C and bromoacetaldehyde diethyl acetal (48.0 mL, 0.320 mol, 1.0 eq.) was added dropwise *via* cannula. After the addition was complete the reaction mixture was allowed to warm slowly to room temperature and then refluxed overnight. The solvent was evaporated *in vacuo* and the resulting residue partitioned between ether (200 mL) and water (200 mL). The organic layer was washed with 10 % aqueous HCl (200 mL) and then water (200 mL). The resulting organic solution was dried ($MgSO_4$) and concentrated *in vacuo* to afford 2,2-dimethyl-4,4-diethoxy butyronitrile as a colourless oil (52.7 g, 89 %); δ_H (400 MHz, $CDCl_3$) 1.19 (6H, t, *J* 7.1, 2×CH_2CH_3), 1.36 (6H, s, CMe_2), 1.81 (2H, d, *J* 5.5, C(3)H_2), 3.51 (2H, m, dq, *J* 9.3, 7.1, CH_2CH_3), 3.64 (2H, dq, *J* 9.3, 7.1, CH_2CH_3), 4.69 (1H, t, *J* 5.5, C(4)*H*). 2,2-dimethyl-4,4-diethoxy butyronitrile (29.8 g, 0.161 mol) was refluxed overnight in a mixture of concentrated HCl, acetic acid and water (100:50:25 mL). The reaction mixture was cooled to room temperature and extracted with CH_2Cl_2 (200 mL, 2×). The aqueous layer was saturated with NaCl and re-extracted with CH_2Cl_2 (200 mL, 2×). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford **1** as an oily residue (20.2 g, 97 %). The oily residue was subsequently used for further synthesis without purification. Subsequently, an analytical sample was prepared *via* recrystallisation from EtOAc:petrol (1:1, 3 mL/g) at –20˚C to afford **1** as a crystalline yellow solid; m.p. 57 – 58˚C (lit.[2] 54 – 55˚C); δ_H (250 MHz, $CDCl_3$) 1.26 (3H, s, *Me*), 1.37 (3H, s, *Me*), 2.04 (1H,

dd, *J* 13.5, 3.4, C(4)H_2), 2.30 (1H, dd, *J* 13.5, 5.8, C(4)H_2), 4.70 (1H, br s, O*H*), 5.87 (1H, dd, *J* 5.8, 3.4, C(5)*H*).

2,2-Dimethyl-4-[*N*-benzyl-*N*-(2′-phenylethyl)amino]butanoic acid (2)

A solution of 2-phenylethylamine (42.2 mL, 336 mmol, 1.0 eq.), benzaldehyde (34.2 mL, 336 mmol, 1.0 eq.) and TMOF (58.8 mL, 538 mmol, 1.6 eq.) in MeOH (1.2 L) was stirred for 1 hour at room temperature. The reaction mixture was cooled to 0˚C and $NaBH_4$ (15.3 g, 403 mmol, 1.2 eq.) added portionwise. Stirring was continued for 1 hour at 0˚C and then at room temperature for 16 hours. Solvents were removed *in vacuo*, the resulting residue partitioned between water (600 mL) and EtOAc (600 mL). The aqueous layer was extracted with EtOAc (600 mL). Combined organic layers were washed with brine (1.0 L), dried (Na_2SO_4) and concentrated *in vacuo* to afford *N*-benzyl-2-phenylethylamine as a colourless oil (63.6 g, 90 %); δ_H (400 MHz, $CDCl_3$) 1.39 (1H, br s, N*H*), 2.84 – 2.96 (4H, m, NCH_2CH_2Ph), 3.83 (2H, s, NCH_2Ph), 7.12 – 7.43 (10H, m, *Ph*). A solution of *N*-benzyl-2-phenylethylamine (11.7 g, 55.4 mmol, 1.0 eq.), **1** (7.93 g, 60.9 mmol, 1.1 eq.) and TMOF (9.69 mL, 88.6 mmol, 1.6 eq.) in MeOH (1.2 L) was stirred for 2 hours at room temperature. The reaction mixture was cooled to 0˚C and $NaBH_4$ (2.51 g, 66.4 mmol, 1.2 eq.) added portionwise, stirring was continued for 1 hour at 0˚C and overnight at room temperature. The solvent was removed *in vacuo* and partitioned between water (400 mL) and CH_2Cl_2 (300 mL), the pH of the water layer was adjusted to neutral with 10 % aqueous HCl. The aqueous layer was then extracted with CH_2Cl_2 (300 mL, 3×). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound **2** as brown viscous oil (13.7 g, 76 %); ν_{max}/cm^{-1} (film) 2520, 1712; δ_H (400 MHz, $CDCl_3$) 1.10 (6H, s, CMe_2), 1.77 (2H, t, *J* 5.9, C(3)H_2), 2.81 – 2.96 (6H, m, C(4)H_2, C(1′)H_2 and C(2′)H_2), 3.85 (2H, s, NCH_2Ph), 7.12 – 7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.7, 31.5, 34.6, 42.3, 49.3, 54.3, 57.7, 126.6, 128.4, 128.6, 128.6, 128.8, 130.18, 134.1, 138.4, 180.4; *m/z* (ESI^+) 326 (MH^+, 100 %); HRMS $C_{21}H_{28}NO_2$ (MH^+) requires 326.2120; found 326.2106.

Benzyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2′-phenylethyl)amino]butanoate (3)

Following Representative Procedure **1**, to a stirred solution of **2** (250 mg, 0.769 mmol, 1.0 eq.), benzyl alcohol (0.239 mL, 2.31 mmol, 3.0 eq.), HOBt (208 mg, 1.54 mmol, 2.0 eq.) and DIPEA (0.538 mL, 3.08 mmol, 4.0 eq.) in CH_2Cl_2 (20 mL) was added EDCI (221 mg, 1.15 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours, diluted with CH_2Cl_2 (20 mL), washed with 10 % aqueous HCl (40 mL) and 2 M aqueous NaOH solution (40 mL). The resultant solution was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:petrol, 1:9) afforded the title

compound **3** as a yellow viscous oil (229 mg, 72 %); ν_{max}/cm^{-1} (film) 1728; δ_H (400 MHz, $CDCl_3$) 1.21 (6H, s, C*Me*$_2$), 1.78 – 1.82 (2H, m, C(3)*H*$_2$), 2.47 – 2.51 (2H, m, C(4)*H*$_2$), 2.65 – 2.76 (4H, m, C(1′)*H*$_2$ and C(2′)*H*$_2$), 3.61 (2 H, s, NC*H*$_2$Ph), 5.09 (2H, s, OC*H*$_2$Ph), 7.12 – 7.39 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4, 33.4, 37.4, 41.3, 49.5, 55.4, 58.4, 66.1, 125.8, 126.8, 128.0, 128.1, 128.1, 128.2, 128.5, 128.7, 128.8, 136.3, 139.6, 140.6, 177.5; *m/z* (ESI^+) 416 (MH^+, 100 %); HRMS $C_{28}H_{34}NO_2$ (MH^+) requires 416.2590; found 416.2589.

(*R*)-(*N*-α-Methylbenzyl) 2,2-dimethyl-4-[*N′*-benzyl-*N′*-(2′-phenylethyl)amino]butanamide (9)

Following Representative Procedure **1**, to a stirred solution of **2** (793 mg, 2.44 mmol, 1.0 eq.), (*R*)-α-methylbenzylamine (*R*)-**19** (1.26 mL, 9.76 mmol, 4.0 eq.), HOBt (659 mg, 4.88 mmol, 2.0 eq.) and DIPEA (1.71 mL, 9.76 mmol, 4.0 eq.) in CH_2Cl_2 (30 mL) was added EDCI (702 mg, 3.66 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours, diluted with CH_2Cl_2 (30 mL), washed with 10 % aqueous HCl (60 mL) and 2 M aqueous NaOH solution (60 mL). The solution was then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 2:98) afforded the title compound **9** as a yellow viscous oil (1.00 g, 96 %); $[\alpha]_D^{25}$ +38.8 (c 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 3339, 1634, 1530; δ_H (400 MHz, $CDCl_3$) 1.16 (6H, s, C*Me*$_2$), 1.46 (3H, d, *J* 7.0, C(α)*Me*), 1.74 (2H, t, *J* 7.8, C(3)*H*$_2$), 2.51 (2H, t, *J* 7.8, C(4)*H*$_2$), 2.65 – 2.75 (4H, m, C(1′)*H*$_2$ and C(2′)*H*$_2$), 3.62 (2H, s, NC*H*$_2$Ph), 5.13 (1H, m, C(α)*H*), 6.08 (1H, d, *J* 7.6, CON*H*), 7.13 – 7.39 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.5, 25.7, 25.9, 33.2, 37.9, 41.2, 48.5, 49.5, 55.5, 58.5, 125.8, 126.2, 126.8, 127.3, 128.2, 128.2, 128.6, 128.8, 128.8, 139.4, 140.6, 143.4, 176.3; *m/z* (ESI^+) 429 (MH^+, 100 %); HRMS $C_{29}H_{37}N_2O$ (MH^+) requires 429.2096; found 429.2094.

***N*-Benzyl-*N*-methyl 2,2-dimethyl-4-[*N′*-benzyl-*N′*-(2′-phenylethyl)amino]butanamide (10)**

Following Representative Procedure **1**, to a stirred solution of **2** (228 mg, 0.701 mmol, 1.0 eq.), *N*-benzyl-*N*-methylamine **20** (0.364 mL, 2.81 mmol, 4.0 eq.), HOBt (190 mg, 1.40 mmol, 2.0 eq.) and DIPEA (0.491 mL, 2.81 mmol, 4.0 eq.) in DMF (10 mL) was added EDCI (202 mg, 1.05 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and partitioned between CH_2Cl_2 (35 mL) and 10 % aqueous HCl (50 mL), the organic layer was washed with 2 M aqueous NaOH solution (50 mL) and then water (50 mL). The solution was dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound **10** as a yellow viscous oil (260 mg, 86 %); ν_{max}/cm^{-1} (film) 1627; δ_H (400 MHz, $CDCl_3$) 1.29 (6H, s, C*Me*$_2$), 1.76 – 1.86 (2H, m, C(3)*H*$_2$), 2.52 – 2.57 (2H, m, C(4)*H*$_2$), 2.68 – 2.85 (4H, m, C(1′)*H*$_2$ and C(2′)*H*$_2$), 2.87 (3H, s, N*Me*CH_2Ph), 3.64 (2H, s, N′C*H*$_2$Ph), 4.51 (2H, s, NMeC*H*$_2$Ph), 7.12 – 7.41 (15H, m, *Ph*); δ_C (100 MHz,

$CDCl_3$) 27.7, 34.0, 36.1, 38.8, 42.2, 50.0, 53.5, 56.3, 59.1, 126.3, 126.7, 127.3, 127.7, 128.0, 128.6, 129.0, 129.2, 129.3, 138.0, 140.1, 141.0, 176.9; *m/z* (ESI^+) 429 (MH^+, 100 %); HRMS $C_{29}H_{37}N_2O$ (MH^+) requires 429.2906; found 429.2920.

4′′-Benzyl-piperazin-1′′-yl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2′-phenylethyl)amino]butanamide (11)

Following Representative Procedure **1**, to a stirred solution of **2** (500 mg, 1.54 mmol, 1.0 eq.), *N*-benzyl piperazine **21** (1.07 mL, 6.15 mmol, 4.0 eq.), HOBt (416 mg, 3.08 mmol, 2.0 eq.) and DIPEA (1.08 mL, 6.15 mmol, 4.0 eq.) in CH_2Cl_2 (20 mL) was added EDCI (442 mg, 2.31 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours, washed with 10 % aqueous HCl (20 mL) and 2 M aqueous NaOH solution (20 mL). The solution was then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 2:98) afforded the title compound **11** as a yellow viscous oil (502 mg, 67 %); ν_{max}/cm^{-1} (film) 1629; δ_H (500 MHz, $CDCl_3$) 1.24 (6H, s, C*Me*$_2$), 1.76 – 1.79 (2H, m, C(3)*H*$_2$), 2.35 – 2.37 (4H, m, *C*(3′′)*H*$_2$ and *C*(5′′)*H*$_2$), 2.51 – 2.54 (2H, m, C(4)*H*$_2$), 2.74 – 2.80 (4H, m, C(1′)*H*$_2$ and C(2′)*H*$_2$), 3.48 (2H, s, N′C*H*$_2$Ph), 3.36 – 3.58 (4H, m, C(2′′)*H*$_2$ and C(6′′)*H*$_2$), 3.66 (2H, s, NC*H*$_2$Ph), 7.16 – 7.37 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.1, 33.6, 38.3, 41.4, 44.8, 49.7, 53.0, 55.8, 58.7, 62.7, 125.8, 126.8, 127.1, 128.1, 128.2, 128.2, 128.6, 128.7, 128.9, 137.7, 139.7, 140.5, 174.9; *m/z* (ESI^+) 484 (MH^+, 100 %); HRMS $C_{32}H_{42}N_3O$ (MH^+) requires 484.3328; found 484.3332.

Piperidin-4′′-yl 2,2-dimethyl-4-[*N*-benzyl-*N*-(2′-phenylethyl)amino]butanamide (13)

Following Representative Procedure **1**, to a stirred solution of **2** (200 mg, 0.615 mmol, 1.0 eq.), 4-amino piperidine (0.129 mL, 1.23 mmol, 2.0 eq.), HOBt (166 mg, 1.23 mmol, 2.0 eq.) and DIPEA (0.430 mL, 2.46 mmol, 4.0 eq.) in CH_2Cl_2 (10 mL) was added EDCI (177 mg, 0.923 mmol, 1.5 eq.). The resultant solution was stirred for 16 hours, then it was washed with water (10 mL) and 2 M aqueous NaOH solution (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford **13** in quantitative conversion. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 1:9 – MeOH, stepwise elution) afforded the title compound **13** as a colourless oil (119 mg, 47 %); ν_{max}/cm^{-1} (film) 3345, 1644; δ_H (400 MHz, $CDCl_3$) 1.12 (6H, s, C*Me*$_2$), 1.24 (2H, qd, *J* 12.0, 4.0, C(3′′)*H*$_A$ and C(5′′)*H*$_A$), 1.68 – 1.72 (2H, m, C(3)*H*$_2$), 1.81 – 1.84 (2H, m, C(3′′)*H*$_B$ and C(5′′)*H*$_B$), 2.46 – 2.50 (2H, m, C(4)*H*$_2$), 2.63 – 2.78 (6H, m, C(1′)*H*$_2$, C(2′)*H*$_2$, C(2′′)*H*$_A$ and C(6′′)*H*$_A$), 3.00 – 3.07 (3H, m, N*H*, C(2′′)*H*$_B$ and C(6′′)*H*$_B$), 3.64 (2H, s, NC*H*$_2$Ph), 3.78 – 3.85 (1H, m, C(4′′)*H*), 5.71 (1H, d, *J* 7.9, CON*H*), 7.13 – 7.29 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.8, 33.0, 33.4, 37.8, 41.1, 45.2, 46.5, 49.4, 55.5, 58.4, 125.9, 126.8, 128.1, 128.3, 128.7, 128.8, 139.4, 140.5, 176.4; *m/z* (ESI^+) 408 (MH^+, 100 %); HRMS $C_{26}H_{38}N_3O$ (MH^+) requires 408.3015; found 408.3013.

(*R*)-(α-Methylbenzyl) 2,2-dimethyl-4-[*N*-(2′-phenylethyl)amino]butanamide (15)

Following Representative Procedure **2**, CAN (2.44 g, 4.46 mmol, 5.0 eq.) was added to a stirred solution of **9** (382 mg, 0.891 mmol, 1.0 eq.) in THF:H_2O (8:1) (20 mL). After 16 hours the mixture was partitioned with 2 M aqueous NaOH solution (40 mL) and ether (40 mL). The aqueous layer was extracted with ether (40 mL). Combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 1:9 - 4:6, stepwise elution) afforded the title compound **15** as a yellow viscous oil (247 mg, 82 %); $[\alpha]_D^{25}$ +51.8 (c 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 3342, 1639, 1527; δ_H (500 MHz, $CDCl_3$) 1.19 (6H, s, C*Me*$_2$), 1.49 (3H, d, *J* 7.0, C(α)*Me*), 1.81 (2H, t, *J* 7.3, C(3)*H*$_2$), 2.72 (2H, t, *J* 7.3, C(4)*H*$_2$), 2.84 – 2.92 (4H, m, C(1′)*H*$_2$ and C(2′)*H*$_2$), 3.00 – 3.50 (1H, br s, N*H*), 5.07 (1H, m, C(α)*H*), 6.64 (1H, d, *J* 7.0 Hz, CON*H*), 7.13 – 7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.7, 26.0, 26.1, 36.0, 40.5, 41.3, 45.6, 48.6, 51.0, 126.1, 126.2, 127.2, 128.4, 128.5, 128.6, 139.7, 143.6, 176.5; *m/z* (ESI^+) 339 (MH^+, 100 %); HRMS $C_{22}H_{31}N_2O$ (MH^+) requires 339.2436; found 339.2438.

***N*-(2′-Phenylethyl) 3,3-dimethyl-pyrrolidin-2-one (6) and (*R*)-α-methylbenzylamine hydrochloride [(*R*)-19.HCl]**

15 (207 mg, 0.612 mmol, 1.0 eq.) was refluxed in toluene (15 mL) for 24 hours. The organic layer was washed with 10 % aqueous HCl (20 mL). The organic layer was concentrated *in vacuo*. The resultant residue was partitioned between CH_2Cl_2 (20 mL) and the aqueous layer retained. The organic layer was washed with 10 % aqueous HCl (20 mL, 2×), dried (Na_2SO_4) and concentrated *in vacuo* to afford **6** (111 mg, 83 %) with identical physical and spectroscopic properties to those described above. The combined aqueous layers were co-evaporated with MeOH *in vacuo* to a constant mass to afford (*R*)-α-methylbenzylamine hydrochloride (*R*)-**19**.HCl as a white crystalline solid (87 mg, 90 %); m.p. 165 – 167˚C (lit.[3] 169 – 170˚C); $[\alpha]_D^{22}$ +2.6 (c 1.0, H_2O) {lit.[3] $[\alpha]_D^{22}$ +2.3 (c 2.9, H_2O)}; δ_H (200 MHz, CD_3OD) 1.68 (3H, d, *J* 6.9, C(α)*Me*), 4.50 (1H, q, *J* 6.9, C(α)*H*), 7.43 – 7.52 (5H, m, *Ph*). An analytical sample of the amine hydrochloride salt was treated with 2 M aqueous NaOH solution and the free amine extracted from this solution with CH_2Cl_2. The organic layer was dried and concentrated *in vacuo* to furnish (*R*)-**19**. ^1H NMR analysis of a 1:1 mixture of (*S*)-*O*-acetylmandelic acid and the amine (*R*)-**19**, and comparison with an authentic racemic standard, confirmed the e.e. to be greater than 95 %.

***N*-Benzyl-*N*-methyl 2,2-dimethyl-4-[*N′*-(2′-phenethyl)amino]butanamide (16)**

Following Representative Procedure **2**, CAN (2.86 g, 5.21 mmol, 5.0 eq.) was added to a stirred solution of **10** (447 mg, 1.04 mmol, 1.0 eq.) in THF:H_2O (8:1) (40 mL). After 16 hours the mixture was partitioned between 2 M aqueous NaOH solution (40 mL) and ether (80 mL). The aqueous layer was extracted with ether (80 mL). Combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 2:98 – 1:9, stepwise elution) afforded the title compound **16** as a yellow oil (299 mg, 85 %); ν_{max}/cm^{-1} (film) 3305, 1622; δ_H (400 MHz, $CDCl_3$) 1.31 (6H, s, C*Me*$_2$), 1.89 (2H, t, *J* 7.6, C(3)*H*$_2$), 2.77 (2H, t, *J* 7.6, C(4)*H*$_2$), 2.86 – 2.98 (7H, m, C(1′)*H*$_2$, C(2′)*H*$_2$ and N*Me*CH_2Ph), 4.39 (1H, br s, N′*H*), 4.58 (2H, s, NMeC*H*$_2$Ph), 7.14 – 7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.6, 35.1, 36.2, 40.5, 41.9, 45.6, 50.5, 53.3, 126.4, 127.3, 128.3, 128.6, 128.6, 128.7, 137.2, 138.8, 176.6; *m/z* (ESI^+) 338 (MH^+, 100 %); HRMS $C_{29}H_{37}N_2O$ (MH^+) requires 429.2906; found 429.2920.

***N*-(2′-Phenylethyl) 3,3-dimethyl-pyrrolidin-2-one (6) and *N*-benzyl-*N*-methylamine hydrochloride (20.HCl)**

16 (202 mg, 0.598 mmol, 1.0 eq.) was refluxed in toluene (20 mL) for 16 hours. The organic layer was washed with 10 % aqueous HCl (10 mL). The organic layer was concentrated *in vacuo*. The resultant residue was partitioned between CH_2Cl_2 (20 mL) and the retained aqueous layer. The organic layer was washed with 10 % aqueous HCl (10 mL, 2×), dried (Na_2SO_4) and concentrated *in vacuo* to afford **6** (128 mg, 99 %) with identical physical and spectroscopic properties to those described above. The combined aqueous layers were co-evaporated with MeOH *in vacuo* to a constant mass to afford *N*-benzyl-*N*-methylamine hydrochloride **20**.HCl as a white crystalline solid (95 mg, 100 %); m.p. 168 – 170˚C (lit.[4] 178˚C); δ_H (400 MHz, $CDCl_3$) 2.47 (3H, s, *Me*), 4.01 (2H, s, NC*H*$_2$Ph), 7.24 – 7.52 (5H, m, *Ph*), 9.50 – 10.50 (2H, br s, N*H*$_2$).

4′′-Benzyl-piperazin-1′′-yl 2,2-dimethyl-4-[*N*-(2′-phenylethyl)amino]butanamide (17)

Following Representative Procedure **2**, CAN (850 mg, 1.55 mmol, 5.0 eq.) was added to a stirred solution of **11** (150 mg, 0.310 mmol, 1.0 eq.) in THF:H_2O (8:1) (10 mL). After 3 hours the mixture was partitioned with 2 M aqueous NaOH solution (20 mL) and ether (20 mL). The aqueous layer was extracted with ether (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Filtration through silica gel afforded the title compound **17** as a colourless oil (88 mg, 72 %); ν_{max}/cm^{-1} (film) 3474, 1626; δ_H (400 MHz, $CDCl_3$) 1.26 (6H, s, C*Me*$_2$), 1.84 (2H, t, *J* 7.7, C(3)*H*$_2$), 2.39 – 2.41 (4H, m, C(3′′)*H*$_2$ and C(5′′)*H*$_2$), 2.75 (2H, m, *J* 7.7, C(4)*H*$_2$), 2.89 – 2.99 (4H, m, C(1′)*H*$_2$ and C(2′)*H*$_2$), 3.49 (2H, s, NC*H*$_2$Ph),

3.57 – 3.64 (4H, m, C(2″)H_2 and C(6″)H_2), 4.20 – 4.40 (1H, br s, N*H*), 7.16 – 7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.6, 34.9, 40.3, 41.6, 43.9, 45.4, 50.3, 53.1, 62.8, 126.4, 172.2, 128.2, 128.4, 128.6, 129.1, 137.5, 138.7, 175.0; *m/z* (ESI^+) 394 (MH^+, 100 %); HRMS $C_{25}H_{36}N_3O$ (MH^+) requires 394.2858; found 394.2858.

_N_-(2′-Phenylethyl) 3,3-dimethyl-pyrrolidin-2-one (6) and _N_-benzylpiperazine dihydrochloride (21.2HCl)

17 (53 mg, 0.135 mmol, 1.0 eq.) was refluxed in toluene (5 mL) for 16 hours. The organic layer was washed with 10 % aqueous HCl (5 mL). The organic layer was concentrated *in vacuo*. The resultant residue was partitioned between CH_2Cl_2 (5 mL) and the retained aqueous layer. The organic layer was washed with 10 % aqueous HCl (5 mL, 2×), dried (Na_2SO_4) and concentrated *in vacuo* to afford **6** (24 mg, 82 %) with identical physical and spectroscopic properties to those described above. The combined aqueous layers were co-evaporated with MeOH *in vacuo* to a constant mass to afford the *N*-benzylpiperazine **21**.2HCl as a white waxy solid (23 mg, 69 %); δ_H (200 MHz, CD_3OD) 3.64 (8H, s, CH_2), 4.53 (2H, s, CH_2Ph), 7.54 – 7.69 (5H, m, *Ph*).

2,2-Dimethyl-4-[_N_-benzyl-_N_-(but-3′-enyl)amino]butanoic acid (25)

A mixture of but-3-enylamine (10.0 mL, 98.5 mmol, 1.0 eq.), benzylamine **18** (53.8 mL, 493 mmol, 5.0 eq.) and K_2CO_3 (15.3 g, 110 mmol, 1.12 eq.) was stirred at 70˚C overnight. The reaction mixture was allowed to cool to room temperature, diluted with Et_2O (100 mL) and washed with water (100 mL, 2×). The solvent was removed *in vacuo* and reduced pressure fractional distillation afforded *N*-benzyl-but-3-enylamine as colourless liquid (11.4 g, 72 %); b.p. 100 – 120˚C, 15 mm Hg (lit.[5] 100 – 120˚C, 13 mm Hg); δ_H (400 MHz, $CDCl_3$) 1.24 (1H, br s, N*H*), 2.31 (2H, m, C(2)H_2), 2.73 (2H, t, *J* 6.8, C(1)H_2), 3.82 (2H, s, NCH_2Ph), 5.05 – 5.15 (2H, m, C(4)H_2), 5.18 (1H, ddt, *J* 17.2, 10.4, 7.0, C(3)*H*), 7.24 – 7.40 (5H, m, *Ph*). A solution of *N*-benzyl-but-3-enylamine (10.9 g, 67.6 mmol, 1.0 eq.), **1** (8.80 g, 67.6 mmol, 1.0 eq.) and TMOF (11.8 mL, 108 mmol, 1.6 eq.) in MeOH (1.0 L) was stirred overnight at room temperature. The reaction mixture was cooled to 0˚C and $NaBH_4$ (3.07 g, 81.1 mmol, 1.2 eq.) added portionwise. Stirring was continued for 1 hour at 0˚C, 2 hours at room temperature and then refluxed for 1 hour. Solvents were removed *in vacuo*, the resulting residue treated with water (250 mL) and the pH was adjusted to neutral with 10 % aqueous HCl. The aqueous layer was extracted with CH_2Cl_2 (200 mL, 3×) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (MeOH:$CHCl_3$, 1:99 – 1:9, stepwise elution) afforded **25** as a yellow viscous oil (15.0 g, 81 %); ν_{max}/cm^{-1} (film) 3070, 1710;

δ_H (400 MHz, $CDCl_3$) 1.05 (6H, s, C*Me*$_2$), 1.71 – 1.74 (2H, m, C(3)*H*$_2$), 2.37 – 2.43 (2H, m, C(2′)*H*$_2$), 2.66 – 2.70 (2H, m, C(1′)*H*$_2$), 2.75 – 2.78 (2H, m, C(4)*H*$_2$), 3.79 (2H, s, NC*H*$_2$Ph), 5.02 – 5.10 (2H, m, C(4′)*H*$_2$), 5.70 (1H, ddt, *J* 17.4, 10.2, 6.8, C(3′)*H*), 7.29 – 7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.7, 29.2, 34.4, 42.4, 49.1, 51.9, 57.5, 117.2, 128.4, 128.8, 130.2, 133.8, 134.4, 180.3; *m/z* (APCI$^+$) 276 (MH^+, 100 %); HRMS $C_{17}H_{25}NO$ (MH^+) requires 276.1964; found 276.1962.

4′′-Biphenyl 2,2-dimethyl-4-[*N*-benzyl-*N*-(but-3′-enyl)amino]butanoate (26)

Following Representative Procedure **1**, to a stirred solution of **25** (200 mg, 0.726 mmol, 1.0 eq.), 4-phenylphenol **24** (371 mg, 2.18 mmol, 3.0 eq.), HOBt (196 mg, 1.45 mmol, 2.0 eq.) and DIPEA (0.508 mL, 2.90 mmol, 4.0 eq.) in CH_2Cl_2 (15 mL) was added EDCI (209 mg, 1.09 mmol, 1.5 eq.). The resulting solution was stirred for 16 hours and washed with 10 % aqueous HCl (10 mL) and 2 M NaOH (10 mL). The solution was dried (Na_2SO_4), and concentrated *in vacuo* to afford the title product **26** as a white waxy solid (218 mg, 70 %). An analytical sample was prepared *via* recrystallization from petrol: CH_2Cl_2 (9:1) at –20˚C to afford the title compound **26** as white needles; m.p. 71 – 73˚C; $C_{29}H_{33}NO_2$ requires C 81.46, H 7.78, N 3.28 %; found C 81.47, H 7.95, N 3.48 %; ν_{max}/cm^{-1} (film) 1745; δ_H (400 MHz, $CDCl_3$) 1.36 (6H, s, C*Me*$_2$), 1.93 – 1.97 (2H, m, C(3)*H*$_2$), 2.28 – 2.34 (2H, m, C(2′)*H*$_2$), 2.59 – 2.64 (4H, m, C(1′)*H*$_2$ and C(4)*H*$_2$), 3.67 (2H, s, NC*H*$_2$Ph), 5.00 – 5.11 (2H, m, C(4′)*H*$_2$), 5.84 (1H, ddt, *J* 17.2, 10.2, 6.8, C(3′)*H*), 7.00 – 7.03 (2H, m, *Ar*), 7.26 – 7.61 (12H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 25.4, 31.6, 37.4, 41.6, 49.5, 53.3, 58.5, 115.5, 121.8, 126.8, 127.1, 127.3, 128.1, 128.2, 128.8, 128.8, 136.9, 138.7, 139.7, 140.5, 150.4, 176.3; *m/z* (ESI$^+$) 428 (MH^+, 100 %); HRMS $C_{29}H_{34}NO_2$ (MH^+) requires 428.2590; found 428.2588.

4′′′-Iodophenyl 2,2-dimethyl 4-{*N*-benzyl-*N*-[4′-(4′′-polystyrenyl)butyl]amino}butanoate (33)

Following Representative Procedure **3**, to a stirred suspension of **28** (2.23 g, 3.86 mmol, 1.0 eq.), 4-iodophenol (8.50 g, 38.6 mmol, 10.0 eq.), HOBt (1.57 g, 11.6 mmol, 3.0 eq.) and DIPEA (5.38 mL, 30.9 mmol, 8.0 eq.) in CH_2Cl_2 (40 mL) was added DIC (1.81 mL, 11.6 mmol, 3.0 eq.). After 16 hours the resin was transferred to a sintered funnel and washed repeatedly with CH_2Cl_2 and THF. The resin was dried *in vacuo* to a constant mass to afford **33** as pale brown powder (2.73 g); ν_{max}/cm^{-1} (KBr) 1749; loading 1.41 mmol/g.

[1‴,1⁗:4⁗,1⁗⁗]-Terphen-4‴-yl 2,2-dimethyl-4-{*N*-benzyl-*N*-[4′-(4″-polystyrenyl)butyl]amino}butanoate (34)

Following Representative Procedure **4**, to a stirred suspension of **29** (300 mg, 0.423 mmol, 1.0 eq.), K_2CO_3 (291 mg, 2.12 mmol, 5.0 eq.) and 4-biphenylboronic acid (335 mg, 1.69 mmol, 4.0 eq.) at 70˚C in DMF (9 mL) was added portionwise over 36 hours $Pd_2(dba)_3$ (77 mg, 0.085 mmol, 0.2 eq.). The resin was repeatedly washed with DMF, water, THF and CH_2Cl_2. The resin was dried *in vacuo* to a constant mass to afford **34** as dark brown powder (319 mg); ν_{max}/cm^{-1} (KBr) 1748; loading 1.36 mmol/g.

***N*-[4′-(4″-polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one (30) and [1,1′:4′,1″]-terphenyl-4-ol (39)**

Following Representative Procedure **5**, CAN (483 mg, 0.882 mmol, 5.0 eq.) was added to a stirred suspension of **34** (133 mg, 0.176 mmol, 1.0 eq.) in THF:H_2O (8:1) (1 mL) to furnish **39** as a pale yellow solid (22 mg, 51 %); m.p. 250 – 253˚C (lit.[6] 268 – 271˚C); HPLC (MeCN/H_2O, 254 nm) 92 %; δ_H (400 MHz, DMSO-d_6) 6.87 (2H, d, *J* 8.8, Ar), 7.34 – 7.40 (1H, m, *Ar*), 7.47 (2H, t, *J* 7.5, *Ar*), 7.55 (2H, d, *J* 8.5, *Ar*), 7.65 – 7.72 (4H, m, *Ar*), 9.60 (1H, s, O*H*). The resin was dried *in vacuo* to a constant mass (253 mg) to afford **30** with identical physical and spectroscopic properties to those described above.

4⁗⁗-Formyl-biphen-4‴-yl 2,2–dimethyl-4-{*N*-benzyl-*N*-[4′-(4″-polystyrenyl)butyl]amino}butanoate (35)

Following Representative Procedure **4**, to a stirred suspension of **29** (300 mg, 0.423 mmol, 1.0 eq.), K_2CO_3 (291 mg, 2.12 mmol, 5.0 eq.) and 4-formylphenylboronic acid (253 mg, 1.69 mmol, 4.0 eq.) at 70˚C in DMF (9 mL) was added $Pd_2(dba)_3$ (77 mg, 0.085 mmol, 0.20 eq.) portionwise over 36 hours. The resin was repeatedly washed with DMF, water, THF and CH_2Cl_2. The resin was dried *in vacuo* to a constant mass to afford **35** as a dark brown powder (292 mg); ν_{max}/cm^{-1} (KBr) 1749, 1700; loading 1.45 mmol/g.

***N*-[4′-(4″-Polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one (30) and 4′-formyl-biphenyl-4-ol (40)**

Following Representative Procedure **5**, CAN (1.09 g, 1.99 mmol, 5.0 eq.) was added to a stirred suspension of **35** (275 mg, 0.398 mmol, 1.0 eq.) in THF:H_2O (8:1) (3 mL) to furnish **40** as a yellow solid (62 mg, 79 %); m.p. 158 – 161˚C (lit.[7] 176 – 178˚C); HPLC (MeCN/H_2O, 254 nm) 90 %; δ_H (200 MHz, $CDCl_3$) 5.0 – 5.4 (1H, br s, O*H*), 6.96 (2H, d, *J* 8.7, *Ar*), 7.56 (2H, d, *J* 8.6, *Ar*), 7.72 (2H, d, *J* 8.2, *Ar*), 7.94 (2H, d, *J* 8.5, *Ar*), 10.0 (1H, s, CHO). The resin was dried *in vacuo* to a constant mass (219 mg) to afford **30** with identical spectroscopic properties to those described above.

3′′′′-Formyl-biphen-4′′′-yl 2,2–dimethyl-4-{*N*-benzyl-*N*-[4′-(4′′-polystyrenyl)butyl]amino}butanoate (36)

Following Representative Procedure **4**, to a stirred suspension of **29** (300 mg, 0.423 mmol, 1.0 eq.), K_2CO_3 (291 mg, 2.12 mmol, 5.0 eq.) and 3-formylphenylboronic acid (253 mg, 1.69 mmol, 4.0 eq.) at 70˚C in DMF (9 mL) was added $Pd_2(dba)_3$ (77 mg, 0.085 mmol, 0.20 eq.) portionwise over 36 hours. The resin was repeatedly washed with DMF, water, THF and CH_2Cl_2. The resin was dried *in vacuo* to a constant mass to afford **36** as a dark brown powder (290 mg); ν_{max}/cm^{-1} (KBr) 1749, 1698; loading 1.45 mmol/g.

***N*-[4′-(4′′-Polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one (30) and 3′-formyl-biphenyl-4-ol (41)**

Following Representative Procedure **5**, CAN (1.05 g, 1.91 mmol, 5.0 eq.) was added to a stirred suspension of **36** (262 mg, 0.382 mmol, 1.0 eq.) in THF:H_2O (8:1) (3 mL) to furnish **41** as a yellow solid (56 mg, 74 %); m.p. 130 – 133˚C; ν_{max}/cm^{-1} (KBr) 3400, 1682; HPLC (MeCN/H_2O, 254 nm) 91 %; δ_H (400 MHz, DMSO-d_6) 6.89 (2H, d, *J* 8.7, *Ar*), 7.58 (2H, d, *J* 8.8, *Ar*), 7.63 (1H, t, *J* 7.5, Ar), 7.79 – 7.81 (1H, m, *Ar*), 7.91 – 7.94 (1H, m, *Ar*), 8.10 – 8.11 (1H, m, *Ar*), 9.70 (1H, s, O*H*), 10.10 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 116.8, 127.8, 128.1, 128.8, 130.4, 130.6, 137.6, 141.87, 158.5, 194.2; *m/z* (ESI$^-$) 197 [$(M–H)^-$, 100 %]; HRMS $C_{13}H_9O$ [$(M–H)^-$] requires 197.0603; found 197.0610. The resin was dried *in vacuo* to a constant mass (214 mg) to afford **30** with identical spectroscopic properties to those described above.

4′′′′-Methoxy-biphenyl-4′′′-yl 2,2–dimethyl-4-{*N*-benzyl-*N*-[4′-(4′′-polystyrenyl)butyl]amino}butanoate (37)

Following Representative Procedure **4**, to a stirred suspension of **29** (300 mg, 0.423 mmol, 1.0 eq.), K_2CO_3 (291 mg, 2.12 mmol, 5.0 eq.) and 4-methoxyphenylboronic acid (257 mg, 1.69 mmol, 4.0 eq.) at 70˚C in DMF (9 mL) was added portionwise over 36 hours $Pd_2(dba)_3$, (77 mg, 0.085 mmol, 0.20 eq.). The resin was repeatedly washed with DMF, water, THF and CH_2Cl_2. The resin was dried *in vacuo* to a constant mass to afford **37** as a dark brown powder (282 mg); ν_{max}/cm^{-1} (KBr) 1748; loading 1.45 mmol/g.

***N*-[4′-(4′′-Polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one (30) and 4′-methoxy biphenyl-4-ol (42)**

Following Representative Procedure **5**, CAN (1.14 g, 2.07 mmol, 5.0 eq.) was added to a stirred suspension of **37** (276 mg, 0.414 mmol, 1.0 eq.) in THF:H_2O (8:1) (3 mL) to furnish **42** as an orange solid (36 mg, 43 %); m.p. 162 – 164˚C (lit.[6] 168 – 171˚C); HPLC (MeCN/H_2O, 254 nm) 89 %; δ_H (400 MHz, DMSO-d_6) 3.76 (3H, s, O*Me*), 6.82 (2H, d, *J* 8.8, *Ar*), 6.96 (2H, d, *J* 8.9, *Ar*), 7.41 (2H, d, *J* 8.8, *Ar*), 7.48 (2H, d, *J* 8.9,

Ar), 9.47 (1H, s, O*H*). The resin was dried *in vacuo* to a constant mass (253 mg) to afford **30** with identical spectroscopic properties to those described above.

2′′′′-Trifluoromethyl-biphen-4′′′-yl 2,2–dimethyl-4-{*N*-benzyl-*N*-[4′-(4′′-polystyrenyl)butyl]amino}butanoate (38)

Following Representative Procedure **4**, to a stirred suspension of **29** (300 mg, 0.423 mmol, 1.0 eq.), K_2CO_3 (291 mg, 2.12 mmol, 5.0 eq.) and 2-(trifluoromethyl)phenylboronic acid (321 mg, 1.69 mmol, 4.0 eq.) at 70˚C in DMF (9 mL) was added $Pd_2(dba)_3$ (77 mg, 0.085 mmol, 0.20 eq.) portionwise over 36 hours. The resin was repeatedly washed with DMF, water, THF and CH_2Cl_2. The resin was dried to a constant mass *in vacuo* to afford **38** as a dark brown powder (289 mg); ν_{max}/cm^{-1} (KBr) 1750; loading 1.37 mmol/g.

***N*-[4′-(4′′-Polystyrenyl)butyl]-3,3-dimethyl-pyrrolidin-2-one (30) and 2′-trifluoromethyl biphenyl-4-ol (43)**

Following Representative Procedure **5**, CAN (1.10 g, 2.00 mmol, 5.0 eq.) was added to a stirred suspension of **38** (273 mg, 0.400 mmol, 1.0 eq.) in THF:H_2O (8:1) (3 mL) to furnish a 86:13 mixture of product **43** (70 mg, 74 %); HPLC (MeCN/H_2O, 254 nm) 59 %; δ_H (400 MHz, $CDCl_3$) 6.83 (2H, d, *J* 8.6, *Ar*), 7.13 (2H, d, *J* 8.0, *Ar*), 7.38 (2H, d, *J* 7.0, *Ar*), 7.53 – 7.61 (1H, m, *Ar*), 7.66 – 7.70 (1H, m, *Ar*), 7.73 – 7.83 (1H, m, *Ar*), 9.63 (1H, s, O*H*); *m/z* (ESI⁻) 237 ([M-H]⁻, 100 %) and 4-iodophenol respectively. The resin was dried *in vacuo* to a constant mass (209 mg) to afford **30** with identical spectroscopic properties to those described above.

(*S*)-4-(4′-Hydroxybenzyl)-5,5-dimethyloxazolidin-2-one (45)

To a slurry of L-tyrosine **44** (200 g, 1.10 mol, 1.0 eq.) and boiling chips in MeOH (1 L) at 0˚C was added thionyl chloride (0.69 mol, 50 mL, 0.63 eq.) dropwise. The resulting solution was refluxed for 12 hours after which time the reaction was allowed to cool to room temperature and the volatiles removed *in vacuo*. The resulting solid was dissolved in EtOAc (1.5 L) and partitioned with saturated aqueous $NaHCO_3$ (1 L). The organic layer was washed with water (1 L), brine (1 L), dried with $MgSO_4$ and the solvent removed *in vacuo* to afford L-tyrosine methyl ester. The crude reaction product was partially dissolved in ethanol (1 L) and the resulting stirred mixture was cooled to 0˚C. $NaHCO_3$ (278 g, 3.31 mol, 3.0 eq.) was added in portions, followed by Boc_2O (253 g, 1.16 mol, 1.05 eq.). The mixture was allowed to warm to room temperature and then stirred for 48 hours. After this time the slurry was filtered through Celite® which was subsequently washed with ether (2×500 mL). The solvent was removed from the combined filtrate *in vacuo*,

the product re-dissolved in ether (1 L) and filtered through Celite® washing with further ether (2×500 mL). Solvent removal *in vacuo* afforded *N*-Boc-L-tyrosine methyl ester as a pale yellow oil (296 g, 91 % over two steps); δ_H (200 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 3.00 (2H, m, C*H*$_2$), 3.72 (3H, s, O*Me*), 4.54 (1H, m, C*H*NH), 5.01 (1H, br d, *J* 8.4, N*H*), 6.74 – 6.97 (4H, m, *Ar*). A 5 L flask fitted with a silicone oil filled bubbler and a mechanical stirrer was dried by the passage of hot air through the apparatus. The flask was allowed to cool to room temperature under an Ar atmosphere and MeMgBr (3.0 M in ether, 1.67 L, 5.0 mol, 5.0 eq.) added *via* cannula. The stirred MeMgBr solution was cooled to –78˚C and a solution of *N*-Boc-L-tyrosine methyl ester (296 g, 1.0 mol, 1.0 eq.) in THF (1.5 L) was added *via* cannula over 1 hour forming a white solid. After addition was complete further ether (1 L) and THF (0.5 L) were added *via* cannula and the reaction allowed to warm to room temperature. The white coagulate was broken down with a glass rod after 12 hours and the resulting slurry was stirred for 72 hours. Saturated aqueous NH_4Cl (500 mL) was added (initially dropwise until the effervescence subsided) and the resulting mixture extracted into EtOAc (3×2 L). The combined organic layers were washed with brine (5 L), dried ($MgSO_4$) and the solvent removed *in vacuo* to afford (*S*)-*N*-tert-Butoxycarbonyl 2-amino-1-(4′-hydroxyphenyl)-3-methyl-butan-3-ol as a yellow crystalline solid (285 g, 96 %); δ_H (MeOD-*d*$_4$, 200 MHz) 1.36 (3H, s, C*Me*$_2$), 1.42 (3H, s, C*Me*$_2$), 1.46 (9H, s, C*Me*$_3$), 2.55 (1H, dd, *J* 13.4, 11.8, C*H*$_2$Ph), 3.18 (1H, dd, *J* 13.4, 1.4, C*H*$_2$Ph), 3.74 (1H, m, C*H*NH), 6.51 (1H, d, *J* 10.0, N*H*), 6.86 – 7.21 (4H, m, *Ar*). (*S*)-*N*-tert-Butoxycarbonyl 2-amino-1-(4′-hydroxyphenyl)-3-methyl-butan-3-ol (40.2 g, 0.136 mol, 1.0 eq.) was dissolved in THF (1 L) and stirred mechanically. To the stirred solution was added ^{t}BuOK (33.5 g, 0.299 mol, 2.2 eq.) and stirring continued at room temperature for 10 min. The resulting slurry was refluxed for 30 min and then allowed to cool to room temperature and H_2O (500 mL) added. Volatiles were removed *in vacuo* and the yellow aqueous layer washed with ether (500 mL). The aqueous layer was acidified to pH 4 with a 2 M aqueous HCl solution and the organic material extracted with EtOAc (3×500 mL), washed with brine (500 mL), dried with $MgSO_4$ and the solvent removed *in vacuo* to give the crude product as brown crystals (28.1 g). Recrystallization (hot EtOAc / hexane) afforded the title compound **45** as yellow platelet crystals (25.2 g, 84 % after 4 crops). A small sample was recrystallized from toluene to afford beige platelet crystals: mp 141 – 142˚C; $C_{12}H_{15}NO_3$ requires C 65.1, H 6.8, N 6.3 %; found C 65.25, H 6.9, N 6.3 %; $[\alpha]_D^{24}$ –85.0 (c 0.96, MeOH); ν_{max}/cm^{-1} (KBr) 3267, 1718, 1616; δ_H (MeOD-*d*$_4$, 400 MHz) 1.55 (3H, s, C*Me*$_2$), 1.58 (3H, s, C*Me*$_2$), 2.82 – 3.01 (2H, m, C*H*$_2$Ar), 3.98 (1H, dd, *J* 9.2, 5.6, C*H*NH), 6.94 – 7.26 (4H, m, *Ar*); δ_C (MeOD-*d*$_4$, 100 MHz) 22.4, 28.2, 37.4, 64.9, 85.4, 116.9, 129.7, 131.5, 157.7, 161.4; *m/z* (APCI$^-$) 220 (M$^-$, 100 %).

(*S*)-4-(4′-*tert*-Butyldimethylsilyloxybenzyl)-5,5-dimethyloxazolidin-2-one (46)

To a stirred solution of **45** (20.0 g, 90.6 mmol, 1.0 eq.) in CH_2Cl_2 (700 mL) was added TBDMSCl (20.5 g, 135.9 mmol, 1.5 eq.) and imidazole (9.26 g, 136.0 mmol, 1.5 eq.). The reaction mixture was stirred for 24 hours at room temperature, forming a white slurry. The reaction products were filtered through a plug of Celite® followed by further CH_2Cl_2 (200 mL). The solvent was then removed *in vacuo* from the filtrate to produce a white solid. The crude reaction product was recrystallised (hot hexanes) to afford the title compound **46** as white needles (27.3 g, 90 %): mp 95 – 96˚C; $C_{18}H_{29}NO_3Si$ requires C 64.4, H 8.7, N 4.2 %; found C 64.6, H 8.4, N 4.1 %; $[\alpha]_D^{24}$ –68.5 (c 0.98, MeOH); ν_{max}/cm^{-1} (KBr) 3273, 1752, 1725; δ_H ($CDCl_3$, 400 MHz) 0.19 (6H, s, Si*Me*$_2$), 0.99 (9H, s, SiC*Me*$_3$), 1.45 (3H, s, C*Me*$_2$), 1.48 (3H, s, C*Me*$_2$), 2.61 (1H, dd, *J* 13.4, 10.9 Hz, C*H*$_2$Ar), 2.77 (1H, dd, *J* 13.4, 3.8 Hz, C*H*$_2$Ar), 3.65 (1H, dd, *J* 10.8, 3.8 Hz, NHC*H*), 4.83 (1H, br s, N*H*), 6.81 – 7.03 (4H, m, Ar); δ_H ($CDCl_3$, 100 MHz) –4.5, 18.2, 21.9, 25.6, 27.5, 36.2, 63.1, 83.2, 120.6, 129.3, 129.8, 154.8, 157.9; m/z (APCI$^+$) 336 (MH^+, 22 %), 279 (79), 221 (100).

(*S*)-3-Propanoyl-4-(4′-*tert*-butyldimethylsilyloxybenzyl)-
5,5-dimethyloxazolidin-2-one (47)

A solution of **46** (24.5 g, 73.0 mmol, 1.0 eq.) in THF (400 mL) under Ar was cooled to –78˚C and *n*-BuLi (2.5 M in hexanes, 32.1 mL, 80.3 mmol, 1.1 eq.) added dropwise over 2 min. The resulting solution was stirred at –78˚C for 30 min before addition of propanoyl chloride (8.10 g, 7.61 mL, 87.6 mmol) dropwise. After 1 h, the resulting solution was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and allowed to warm to room temperature. Volatiles were removed *in vacuo* and the product mixture extracted with EtOAc (2×150 mL). The combined organic layers were washed with 2 M aqueous HCl solution (100 mL), saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL), dried with $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by passing through a plug of silica eluting with hexanes followed by 40 % EtOAc in hexanes. Solvent removal from the more polar fractions *in vacuo* afforded the title compound **47** as a pale yellow oil which crystallised on standing to give colourless rods (27.5 g, 97 %): mp 60 – 62˚C; $C_{21}H_{33}NO_4Si$ requires C 64.4, H 8.5, N 3.6 %; found C 64.4, H 8.6, N 3.5 %; $[\alpha]_D^{24}$ –29.0 (c 1.31, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 1777, 1701; δ_H ($CDCl_3$, 400 MHz) 0.18 (6H, s, Si*Me*$_2$), 0.97 (9H, s, SiC*Me*$_3$), 1.13 (3H, td, *J* 7.4, 2.3, CH_2CH_3), 1.35 (3H, s, C*Me*$_2$), 1.37 (3H, s, C*Me*$_2$), 2.81 (1H, dd, *J* 14.4, 9.5, C*H*$_2$Ar), 2.92 (2H, qd, J 7.4, 2.3, C*H*$_2$CH$_3$), 3.06 (1H, dd, *J* 14.4, 3.8, C*H*$_2$Ar), 4.44 (1H, dd, J 9.5, 3.8, NC*H*), 6.77 – 7.11 (4H, m, *Ar*); δ_C ($CDCl_3$, 100 MHz) –4.5, 8.3, 18.2, 22.2, 25.6, 28.5, 29.3, 34.5, 63.5, 82.2, 120.2, 129.5, 130.0, 152.7, 154.4, 174.2; m/z (APCI$^+$) 392 (MH^+, 23 %), 336 (21), 275 (17), 221 (100).

(*S*)-3-Propanoyl-4-(4′-hydroxybenzyl)-5,5-dimethyloxazolidin-2-one (48)

To a stirred solution of **47** (12.3 g, 31.5 mmol, 1.0 eq.) in THF (500 mL) was added TBAF (1.1 M in THF, 28.6 mL, 31.5 mmol, 1.0 eq.). The resulting yellow solution was stirred for 1 hour and then sufficient 2 M aqueous HCl solution was added to quench out the colouration. Volatiles were removed in vacuo and the organic products were extracted into EtOAc (2×250 mL). The combined organic layers were washed with brine (250 mL), dried with $MgSO_4$ and the solvent removed *in vacuo* to afford a pale cream solid. Purification via column chromatography (30:70, EtOAc:hexanes) afforded the title compound **48** as a white solid (8.12 g, 93 %): mp 125 – 128˚C; $C_{15}H_{19}NO_4$ requires C 65.0, H 6.9, N 5.05 %; found C 64.9, H 6.9, N 5.0 %; $[\alpha]_D^{22}$ –43.2 (c 1.00, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3298, 1789, 1666; δ_H ($CDCl_3$, 400 MHz) 1.15 (3H, t, *J* 7.3, CH_2CH_3), 1.37 (3H, s, CMe_2), 1.40 (3H, s, CMe_2), 2.84 (1H, dd, *J* 14.4, 9.3, CH_2Ar), 2.93 (2H, q, *J* 7.3, CH_2CH_3), 3.04 (1H, dd, *J* 14.4, 4.0, CH_2Ar), 4.44 (1H, dd, *J* 9.3, 4.0, NC*H*), 5.21 (1H, s, O*H*), 6.78 – 7.13 (4H, m, *Ar*); δ_C ($CDCl_3$, 100 MHz) 8.4, 22.2, 28.6, 29.3, 34.5, 63.6, 82.3, 115.5, 128.8, 130.2, 152.8, 154.4, 174.5; m/z (APCI$^-$) 276 (M^-, 91 %), 220 (100).

References and notes

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