A One-Pot Process for the Enantioselective Synthesis of Amines *via* Reductive Amination under Transfer Hydrogenation Conditions.

Glynn Williams,[†] Richard Pike,[†] Charles Wade[‡] and Martin Wills.[†]*

Department of Chemistry, University of Warwick, Coventry, CV4 7AL, UK. Process Chemistry Department, GlaxoSmithKline Pharmaceuticals Ltd, Gunnels Wood Road, Stevenage, Herts, SG1 2NY.

m.wills@warwick.ac.uk

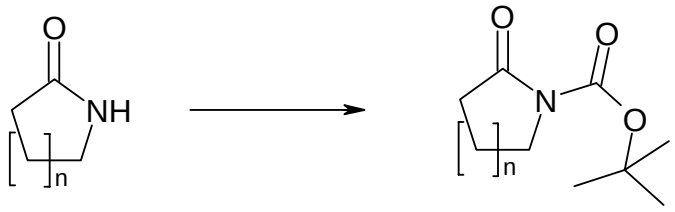
Supporting data; Experimental procedures and spectroscopic data for all new compounds.

Contents

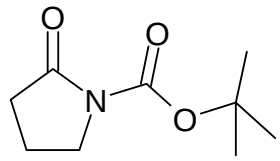
General

All reactions, unless otherwise stated, were run under an atmosphere of nitrogen at ambient temperature (18-22ºC). 0ºC refers to an ice/water slush bath and -78ºC refers to a dry ice-acetone bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by TLC using aluminium backed silica gel 60 (F254) plates, visualised using UV 254 and 2-4-dinitrophenylhydrazine, ninhydrin and potassium permanganate dips as appropriate. Flash column chromatography was carried out routinely using 60 Å silica gel (Merck). Reagents were used as received from commercial sources apart from the following exceptions, THF was distilled from sodium benzophenone ketyl, triethylamine was distilled from calcium hydride and formic acid was distilled from phthalic anhydride. NMR spectra were recorded on a Bruker DPX (300 or 400 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million downfield from TMS. Coupling constants (*J*) are measured in hertz. IR spectra were recorded on a Perkin-Elmer spectrum One FT-IR Golden Gate. Mass spectra were recorded on a 7070E VG mass spectrometer. Melting points were recorded on a Stuart Scientific SMP 1 instrument and are uncorrected.

General procedure for preparation of *t*-Boc protected lactams.[1]

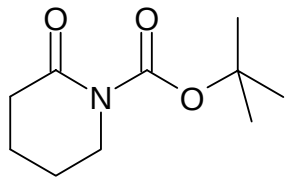


To a stirred solution of lactam (0.1 mol) in anhydrous THF (200 mL) at -78ºC was added drop wise n-BuLi (0.1 mol, 64 mL, 2.5M sol.) maintaining the temperature below -72ºC. The mixture was allowed to stir at -78ºC for 1 h before a solution of di-*tert*-butyldicarbonate (0.1 mol) in THF (25 mL) was added drop wise over 45 minutes. The reaction was allowed to stir for a further 2 h and then warmed to rt. Sat NH_4Cl (100 mL) and water (50 mL) was added and the organic layer was separated. The aqueous phase was extracted with diethyl ether (3 x 100 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (20% v/v ethyl acetate-hexanes) to afford the Boc-protected lactams.

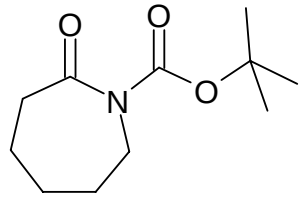


Colourless oil, (14.2 g, 77 %) ; ν_{max}(neat)/cm^{-1} 3399, 2978, 2361, 1780, 1748, 1706, 1365, 1299, 1147 ; δ_H (300.13 MHz, $CDCl_3$) 3.75 (2H, t, *J* 7.01, NC*H*$_2$), 2.51 (2H, t, *J* 8.53, COC*H*$_2$), 1.96-2.03 (2H, m, $CH_2CH_2CH_2$), 1.53 (9H, s, *t*-Bu) ; δ_C (75.5 MHz, $CDCl_3$) 174.6 (C_q), 150.4 (C_q), 82.8 (C_q), 46.8 (CH_2), 33.2 (CH_2), 28.3 (CH_3), 17.7 (CH_2); MS *m/z* (EI) 112([M+H-O*t*-Bu]$^+$, 6), 86 (37), 57 (100) ; Anal. calc. for $C_9H_{15}NO_3$: C, 58.36 ; H, 8.16 ; N, 7.56. Found: C, 58.08; H, 8.20; N, 7.30.[1]

Compound (6)

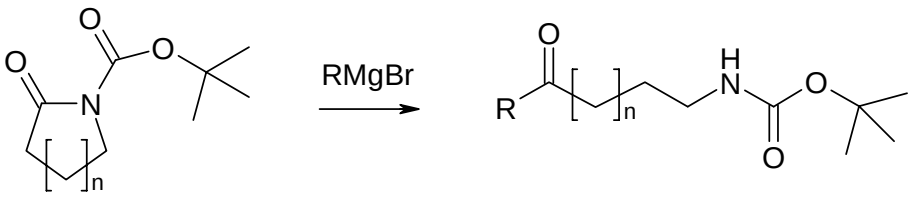


Colourless, crystalline solid, (17.9 g, 90 %) ; mp 32-34°C ; ν_{max}(neat)/cm^{-1} 3398, 2987, 2954, 2894, 2360, 1701, 1285, 1246, 1155, 1133 ; δ_H (300.13 MHz, $CDCl_3$) 3.65 (2H, m, NC*H*$_2$), 2.50 (2H, m, COC*H*$_2$), 1.82 (4h, m, $NCH_2CH_2CH_2$), 1.52 (9H, s, *t*-Bu) ; δ_C (75.5 MHz, $CDCl_3$) 171.6 (C_q), 152.9 (C_q), 82.8, (C_q), 46.4 (CH_2), 34.9 (CH_2), 28.3 (CH_3), 23.0 (CH_2), 20.8 (CH_2) ; MS *m/z* (EI) 144 ([M-*t*-Bu]$^+$, 35), 100 (17), 83 (100) ; Anal. calc. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.30; H, 8.60; N, 6.98.[1]



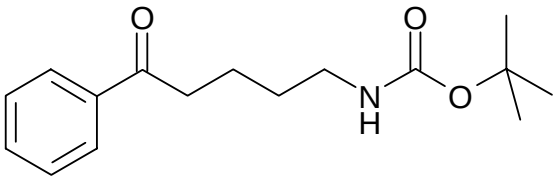
Colourless oil, (13.2 g, 62 %) ; ν_{max}(neat)/cm^{-1} 2977, 2930, 2358, 1766, 1705, 1142 ; δ_H (300.13 MHz, $CDCl_3$) 3.72-3.80 (2H, m, NC*H*$_2$), 2.62-2.70 (2H, m, COC*H*$_2$), 1.70-1.85 (6H, m, $COCH_2CH_2CH_2CH_2$), 1.52 (9H, s, *t*-Bu) ; δ_C (75.5 MHz, $CDCl_3$) 176.0 (C_q), 153.2 (C_q), 83.0 (C_q), 46.5 (CH_2), 39.8 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 28.3 (CH_3), 23.9 (CH_2) ; MS *m/z* (EI) 214 ([M+H]$^+$,45), 213 (23), 209 (100), 158 (99), 140 (17), 85 (37); Anal. calc. for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.13; H, 9.11; N, 6.46.[1]

General procedure for the preparation of t-Boc-amino-ketones



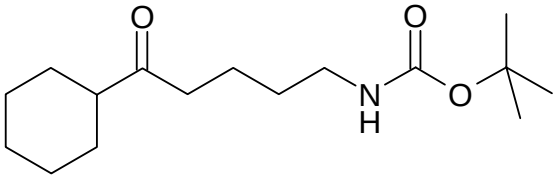
The Grignard reagent was prepared by the following procedure unless it was commercially available. To a dry 2 necked flask was added Mg (0.01mol), dry THF (5mL) and the aryl bromine (0.006mol) with stirring under N_2. Iodine crystals (catalytic) were added and the mixture was heated gently until it maintained its own reflux. When reflux had subsided external heating was applied to maintain reflux for a further 1 hour. The *t*-Boc-lactam (0.005mol) was added to a dry 3 necked round bottomed flask with a thermometer. Dry THF (20mL) was added with stirring under N_2 and the solution was cooled to -78°C. The Grignard reagent (0.006mol) was added to the t-Boc-lactam over 1 hour, maintaining the internal temperature below -70°C. The solution was warmed to room temperature and 2M HCl was added until the pH was 1-3. The aqueous layer was washed 3 x 50mL with DCM and the organic layers combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified using flash column chromatography (F.C.C.), (15-20% v/v ethyl acetate / hexane) or recrystallisation from pet. ether (40-60).

(5-oxo-5-phenyl-pentyl)-carbamic acid tert-butyl ester.[1]



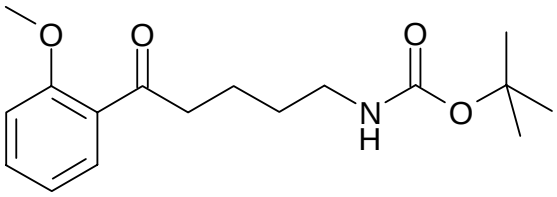
Purified by crystallisation colourless needles, (0.59 g, 43 %); mp 82-83°C; ν_{max}(neat)/cm^{-1} 3338, 2973, 2945, 2927, 2361, 2342, 1679, 1533, 1281, 1248, 1169, 1133, 730, 687, 653; δ_H (300.13 MHz, $CDCl_3$) 7.95 (2H, d, *J* 7.5, aryl H), 7.50 (3H, m, aryl H), 4.60 (1H, s, N*H*), 3.18 (2H, q, *J* 6.4, NHC*H*$_2$), 3.01 (2H, t, *J* 6.8, COC*H*$_2$), 1.78 (2H, m, NCH$_2$C*H*$_2$), 1.57 (2H, m, COCH$_2$C*H*$_2$), 1.44 (9H, s, *t*-Bu); δ_C (75.5 MHz, $CDCl_3$) 155.8 (C), 136.7 (C), 128.4 (CH_2), 127.9 (CH_2), 78.9 (C), 40.0 (CH_2), 37.7 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 21.0 (CH_3); MS *m/z* (EI) 278 ([M+H]$^+$, 14), 176 (100), 160 (99), 105 (95), 77 (54); Anal. calc: $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.34; H, 8.39; N, 5.00.

(5-oxo-5-cyclohexyl-pentyl)-carbamic acid tert-butyl ester



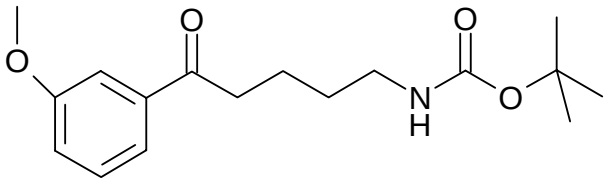
Purified by F.C.C., pale yellow crystalline solid, (0.45 g, 32 %); mp 32-35°C**;** ν_{max}(neat)/cm^{-1} 3366, 2974, 2927, 2854, 2361, 2341, 1695, 1508, 1449, 1364, 1246, 1167; δ_H (300.13 MHz, $CDCl_3$) 4.66 (1H, s, N*H*), 3.11 (2H, q, *J* 5.9, NHCH_2), 2.46 (2H, t, *J* 7.4, COCH_2), 2.41 (1H, m, COC*H*) 1.81 (4H, m, $COCH_2CH_2CH_2CH_2NH$), 1.58 (4H, m, $CH(CH_2)_2$), 1.41 (9H, s, $OC(CH_3)_3$), 1.35 (6H, m, $CH(CH_2)_2(CH_2)_3$); δ_C (75.5 MHz, $CDCl_3$) 156.4 (C), 82.5 (C), 79.4 (C), 51.2 (CH), 40.5 (CH_2), 40.3 (CH_2), 29.9 (CH_2), 29.0, (CH_2), 28.8 (CH_3), 26.2 (CH_2), 26.0 (CH_2), 21.0 (CH_2); MS *m/z* (EI) 284 ($[M+H]^+$, 35), 228 (55), 184 (100), 100 (75), 83 (84); Anal. calc: $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31; N, 4.94. found C, 67.62; H, 10.32; N 4.96.

(5-oxo-5-(2-methoxyphenyl)-pentyl)-carbamic acid tert-butyl ester



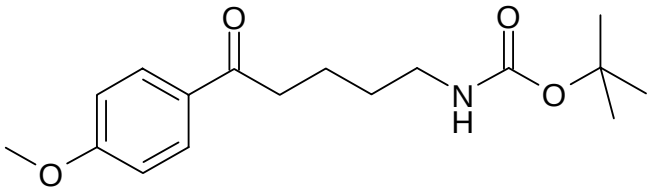
Purified by F.C.C. colourless oil, (0.64 g, 41 %); ν_{max}(neat)/cm^{-1} 3358, 2973, 2931, 2867, 1673, 1596, 1509, 1484, 1456, 1364, 1242, 1161, 1022, 981, 755, 735; δ_H (300.13 MHz, $CDCl_3$) 7.65 (1H, dd, *J* 7.6, 1.7, aryl H), 7.44 (1H, m, aryl H), 6.97 (2H, m, aryl H), 4.71 (1H, s, N*H*), 3.86 (3H, s, OCH_3), 3.14 (2H, q, *J* 6.4, HNCH_2), 2.98 (2H, t, *J* 7.1, COCH_2), 1.71 (2H, m, $COCH_2CH_2$), 1.54 (2H, m, $NHCH_2CH_2$), 1.44 (9H, s, *t*-Bu); δ_C (75.5 MHz, $CDCl_3$) 203.2 (C), 158.8 (C), 156.4 (C), 133.7 (CH), 130.5 (CH), 128.8 (C), 121.0 (CH), 111.9 (CH), 79.3 (C), 55.9 (CH_3), 43.6 (CH_2), 40.7 (CH_2), 30.0 (CH_2), 28.8 (CH_3), 21.8 (CH_2); MS *m/z* (CI) 325 ($[M+NH_4]^+$, 11), 308 (22), 269 (47), 252 (71), 234 (100), 190 (38); HRMS: $C_{17}H_{26}NO_4$ (M+H}calc 308.1856, found 308.1861.

(5-oxo-5-(3-methoxyphenyl)-pentyl)-carbamic acid tert-butyl ester



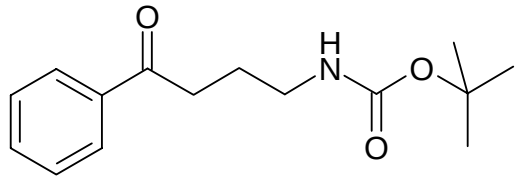
Purified by F.C.C. colourless solid, (0.62 g, 40 %); mp 46-48°C; ν_{max}(neat)/cm^{-1} 3354, 2973, 2933, 1681, 1514, 1364, 1250, 1163, 1040, 994, 781, 735, 685; δ_H (300.13 MHz, $CDCl_3$) 7.53 (1H, m, aryl H), 7.48 (1H, m, aryl H), 7.36 (1H, t, *J* 8.1, aryl H), 7.10 (1H, m, aryl H), 4.69 (1H, s, N*H*), 3.84 (3H, s, OC*H*$_3$), 3.16 (2H, q, *J* 6.8, NHC*H*$_2$), 2.99 (2H, t, *J* 7.5, COC*H*$_2$), 1.77 (2H, quin, *J* 7.5, COCH$_2$C*H*$_2$), 1.57 (2H, m, NHCH$_2$C*H*$_2$), 1.44 (9H, s, *t*-Bu); δ_C (75.5 MHz, $CDCl_3$) 200.4 (C), 160.2 (C), 156.4 (C), 138.7 (C), 130.0 (CH), 121.1 (CH), 119.8 (CH), 112.6 (CH), 79.4 (C), 55.8 (CH_3), 40.6 (CH_2), 38.5 (CH_2), 30.0 (CH_2), 28.8 (CH_3), 21.7 (CH_2); MS *m/z* (EI) 308 ([M+H]$^+$, 100), 306 (83), 300 (64), 298 (81); Anal. calc: $C_{17}H_{25}NO_4$; C, 66.43; H, 8.20; N 4.56; found C, 66.36; H, 8.20; N, 4.43.

(5-oxo-5-(4-methoxyphenyl)-pentyl)-carbamic acid tert-butyl ester



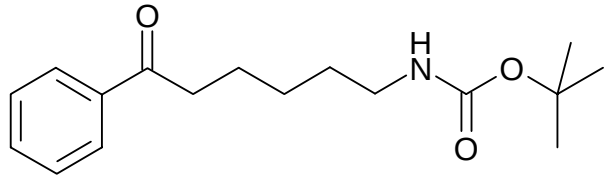
Purified by F.C.C. colourless needles, (0.67 g, 43 %); mp 75-76°C; ν_{max}(neat)/cm^{-1} 3323, 2982, 2942, 2866, 2838, 2359, 2341, 1685, 1668, 1604, 1536, 1276, 1255, 1159, 1028, 977, 822, 661; δ_H (300.13 MHz, $CDCl_3$) 7.93 (2H, d, *J* 8.9, aryl H) 6.93 (2H, d, *J* 8.9, aryl H), 4.64 (1H, s, N*H*), 3.85 (3H, s, OC*H*$_3$), 3.16 (2H, q, *J* 6.6, NHC*H*$_2$), 2.94 (2H, t, *J* 7.1, COC*H*$_2$), 1.76 (2H, quin, *J* 7.7, COCH$_2$C*H*$_2$), 1.57 (2H, m, NHCH$_2$C*H*$_2$), 1.44 (9H, s, *t*-Bu); δ_C (75.5 MHz, $CDCl_3$) 199.3 (C), 163.8 (C), 156.4 (C), 130.7 (CH), 130.4 (C), 114.1 (CH), 79.4 (C), 55.8 (CH_3), 40.6 (CH_2), 38.0 (CH_2), 30.0 (CH_2), 28.8 (CH_3), 21.8 (CH_2); MS *m/z* (EI), 307 ([M]$^+$, 30), 189 (81), 135 (100), 121 (43), 77 (30); HRMS: $C_{17}H_{25}NO_4$ calc 307.1784, found 307.1798; Anal. calc: $C_{17}H_{25}NO_4$ C 66.43, H 8.20, N 4.56, found C 66.29, H 8.10, N 4.38.

(5-oxo-5-phenyl-butyl)-carbamic acid tert-butyl ester (14)



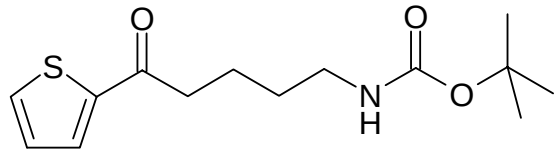
Purified by crystallisation as colourless needles, (0.84 g, 64 %); mp 95-96ºC; ν_{max}(neat)/cm^{-1} 3722, 3365, 2988, 2934, 2359, 1679, 1516, 1245, 1155; δ_H (300.13 MHz, $CDCl_3$) 7.94-7.98 (2H, m, aryl H), 7.43-7.59 (3H, m, aryl H), 4.68 (1H, bs, N*H*), 3.19-3.26 (2H, m, NCH_2), 3.03 (2H, t, *J* 7.2, COCH_2), 1.89-1.99 (2H, m, $CH_2CH_2CH_2$), 1.42 (9H, s, *t*-Bu); δ_C (75.5 MHz, $CDCl_3$) 155.8 (C_q), 136.6 (C_q), 132.9 (CH), 128.3 (CH), 127.8 (CH), 78.9 (C_q), 39.9 (CH_2), 35.5 (CH_2), 28.1 (CH_3), 24.3 (CH_2); MS *m/z* (EI) 145 ([M-(*t*-BuCO_2 + H_2O)]$^+$), 117 (60), 79 (100), 63 (50); Anal calc: $C_{15}H_{21}NO_3$: : C, 68.42; H, 8.04; N, 5.32. Found: C, 68.35; H, 8.05; N, 5.33.

(5-oxo-5-phenyl-hexyl)-carbamic acid tert-butyl ester (13)



Colourless solid, (0.62 g, 45 %); mp 35-36°C; ν_{max}(neat)/cm^{-1} 3378, 2970, 2934, 2863, 2359, 2340, 1701, 1674, 1512, 1447, 1364, 1250, 1157, 967, 747, 725, 687, 655; δ_H (300.13 MHz, $CDCl_3$) 7.95 (2H, m, aryl H), 7.55 (1H, m, aryl H), 7.46 (2H, m, aryl H), 4.8 (1H, s, N*H*), 3.13 (2H, q, *J* 6.4, NHCH_2), 2.97 (2H, t, *J* 7.4, COCH_2), 1.76 (2H, quin, *J* 7.6, $COCH_2CH_2$), 1.53 (2H, m, $NHCH_2CH_2$), 1.44 (9H, s, *t*-Bu), 1.38 (2H, m, $COCH_2CH_2CH_2$); δ_C (75.5 MHz, $CDCl_3$) 200.1 (C), 156.4 (C), 137.3 (C), 133.4 (CH), 129.0 (CH), 128.4 (CH), 79.4 (C), 40.8 (CH_2), 38.8 (CH_2), 30.4 (CH_2), 28.8 (CH_3), 26.9 (CH_2), 24.3 (CH_2); MS *m/z* (CI) 309 ([M+NH_4]$^+$, 24), 292 (27), 253 (73), 235 (100), 192 (80), 174 (58); HRMS: $C_{17}H_{26}NO_3$ (M+H) calc 292.1907, found 292.1906.

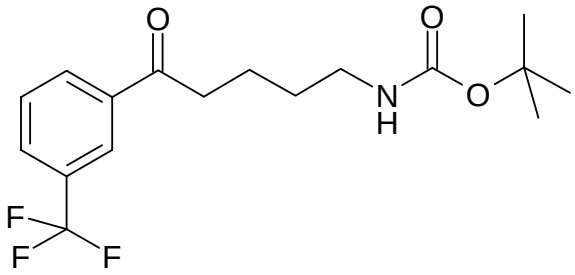
(5-oxo-5-(2-thiophene)-pentyl)-carbamic acid tert-butyl ester



Pale brown solid, (0.85 g, 72 %); mp 36-38°C; ν_{max}(neat)/cm^{-1} 3378, 2978, 2925, 2864, 1686, 1657, 1242, 1158; δ_H (300.13 MHz, $CDCl_3$) 7.70-7.73 (1H, m, thiophene C*H*), 7.60-7.63 (1H, m, COC*H*),

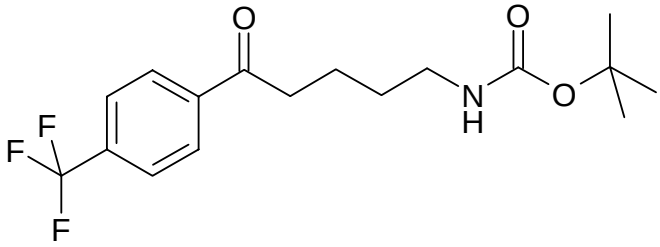
7.09-7.14 (1H, m, thiophene C*H*), 4.62 (1H, bs, N*H*), 3.12-3.20 (2H, m, NHCH_2), 2.94 (2H, t, *J* 7.2, COCH_2), 1.77-1.78 (2H, quin, *J* 7.2, $COCH_2CH_2$), 1.53-1.62 (2H, quin, *J* 7.2, $NHCH_2CH_2$), 1.43 (9H, s, *t*-Bu); δ_C (75.5 MHz, $CDCl_3$) 156.4(C_q), 144.6 (C_q), 133.9 (CH), 132.3 (CH), 128.5 (CH), 70.4 (C_q), 40.4 (CH_2), 39.1 (CH_2) 29.9 (CH_2), 28.8 (CH_3), 21.9 (CH_2); MS *m/z* (CI) 284 ($[M+H]^+$, 15), 228 (20), 166 (100), 165 (80), 111 (50); HRMS: $C_{14}H_{22}NO_3S$ calc. 284.1320, found 284.1340.

(5-oxo-5-(3-trifluoromethylphenyl)-pentyl)-carbamic acid tert-butyl ester



Pale yellow, crystalline solid, (0.85 g, 49 %); mp 32-34ºC; ν_{max}(neat)/cm^{-1} 3365, 2975, 2932, 2359, 2340, 1686, 1514, 1228, 1163, 1124; δ_H (300.13 MHz, $CDCl_3$) 8.21 (1H, s, aryl H), 8.13 (1H. d, *J* 7.5, aryl H), 7.82 (1H, d, *J* 7.5, aryl H), 7.61 (1H, t, *J* 7.5, aryl H), 4.62 (1H, bs, N*H*), 3.12-3.21 (2H, m, NHCH_2), 3.02, (2H, t, *J* 7.15, COCH_2), 1.77-1.85 (2 H, quin, *J* 7.15, $COCH_2CH_2$), 1.55-1.66 (2H,m, $NHCH_2CH_2$), 1.48 (9H, s, *t*-Bu); δ_C (75.5 MHz, $CDCl_3$) 156.6 (C_q), 137.7 (C_q), 131.6 (CH), 129.8 (CH), 129.7 (CH), 125.2 (CH), 79.6 (C_q), 40.5 (CH_2), 38.5 (CH_2), 29.9 (CH_2), 28.8 (CH_3), 21.3 (CH_2); MS *m/z* (EI) 346 ($[M+H]^+$, 35), 289 (45), 271 (65), 227 (55), 82 (100); Anal. calc. for $C_{17}H_{22}F_3NO_3$: C, 59.12; H, 6.42; N, 4.04, found C, 58.92; H, 6.47; N, 4.01.

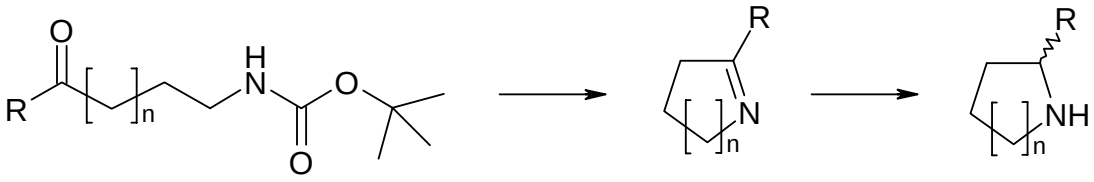
(5-oxo-5-(4-trifluoromethylphenyl)-pentyl)-carbamic acid tert-butyl ester



Pale yellow solid, (0.48 g, 28 %); mp 79-81ºC; ν_{max}(neat)/cm^{-1} 3368, 2980, 2939, 2863, 2357, 1673, 1509, 1321, 1161, 1062; δ_H (300.13 MHz, $CDCl_3$) 8.03 (2H, d, *J* 8.4, aryl H), 7.71 (2H, d, *J* 8.4, aryl H), 4.70 (1H, bs, N*H*), 3.12-3.22 (2H, m, NHCH_2), 3.02 (2H, t, *J* 7.3, COCH_2), 1.78-1.86 (2H, m, $COCH_2CH_2$), 1.58-1.67 (2H, m, $NHCH_2CH_2$), 1.42 (9H, s, *t*-Bu); δ_C (75.5 MHz, $CDCl_3$) 156.6 (C_q), 140.0 (C_q), 128.7 (CH), 126.1 (CH), 79.8 (C_q), 40.5, (CH_2), 38.6 (CH_2), 29.9 (CH_2), 28.9 (CH_3), 21.4

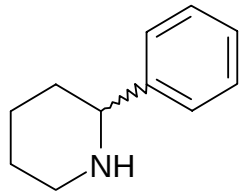
(CH_2); MS *m/z* (EI) 346 ($[M+H]^+$, 45), 290 (60), 272 (45), 246 (100), 228 (60), 173 (65), 145 (50); HRMS: $C_{17}H_{23}F_3NO_3$ calc. 346.1630, found 346.1629; Anal. Calc. for $C_{17}H_{22}F_3NO_3$: C, 59.12; H, 6.42; N, 4.04, found C, 59.03; H, 6.46; N, 3.97.

General procedure for the racemic preparation of amines



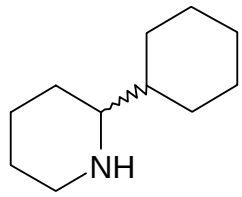
The *t*-Boc-amino-ketone (4 mmol) was stirred in TFA for 2 hrs. TLC was used to check the reaction progress. 50% w/v NaOH solution was added to the mixture until the pH was 13-14. The product was extracted 4 x 20mL with DCM and the organic layers combined, dried with $MgSO_4$ and evaporated. The product was dissolved in water / methanol (1:4, 5mL) and added to a flask followed by $NaBH_4$ (4.5 mmol). The mixture was stirred under N_2 overnight. The mixture was acidified with 1-2M HCl until the pH was 1-3 and left for 30 minutes. NaOH solution was then added until the pH was 13-14 and the product was extracted with DCM (4 x 20 mL), the organic layers were combined, dried with $MgSO_4$, filtered and evaporated to yield the product.

(±)-2-phenyl-piperidine (7)[2]



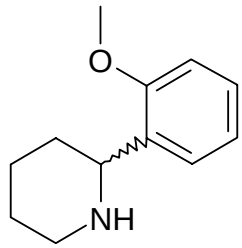
Yellow liquid, (70 mg, 60%); ν_{max}(neat)/cm^{-1} 3321, 3268, 3060, 3025, 2929, 2850, 2784, 2697, 1945, 1599, 1490, 1440, 1324, 1307, 1107, 1019, 749, 697; δ_H (300.13 MHz, $CDCl_3$) 7.29 (5H, m, aryl H), 3.58 (1H, m, NHC*H*), 3.19 (1H, m, NHCH_aH_b), 2.80 (1H, m, NHCH_aH_b), 1.85 (2H, m, CH_2), 1.66 (2H, m, CH_2), 1.52 (3H, m, N*H* and CH_2); δ_C (75.5 MHz, $CDCl_3$) 145.9 (C), 128.8 (CH), 127.4 (CH), 127.0 (CH), 62.8 (CH), 48.2 (CH_2), 35.4 (CH_2), 26.3 (CH_2), 25.8 (CH_2); MS *m/z* (EI) 161 ($[M]^+$, 57), 160 (47), 132 (76), 118 (43), 104 (100), 91 (48), 84 (44), 77 (28). HRMS: $C_{11}H_{15}N$ calc. 161.1205, found 161.1197; Anal. calc. for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69, found C, 81.70; H, 9.38; N, 8.77.

(±)-2-cyclohexyl-piperidine



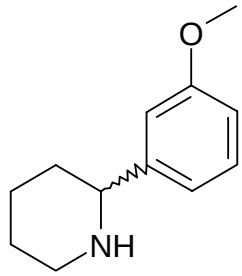
Yellow liquid, (50 mg, 68 %); ν_{max}(neat)/cm^{-1} 3344, 2920, 2851, 2698, 2502, 2408, 2358, 1673, 1447, 1200, 1175, 1130, 798, 719; δ_H (300 MHz, $CDCl_3$) 3.12 (1H, dquin, *J* 11.7, 2.1, NHC*H*), 2.9 (1H, s, N*H*), 2.62 (1H, td, *J* 11.7, 2.9, NHCH_aH_b), 2.26 (1H, m, NHCH$_a$$H_b$), 1.71 (8H, m, 4xC$H_2$), 1.21 (7H, m, N*H* and 3xCH_2), 1.00 (2H, m, CH_2); δ_C (75.5 MHz, $CDCl_3$) 62.5 (CH), 47.8 (CH_2), 43.6 (CH), 29.7 (CH_2), 29.5 (CH_2), 27.0 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 25.3 (CH_2); MS *m/z* (EI) 166 ([M-H]$^+$, 1), 149 (2), 84 (100), 78 (15), 63 (11); HRMS: $C_{11}H_{22}N$ calc. 168.1752, found 168.1758.

(±)-2-(2-methoxyphenyl)-piperidine



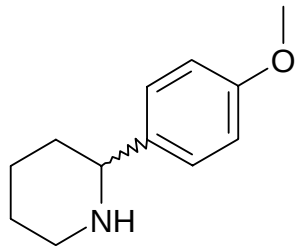
Pale yellow oil, (66 mg, 84 %); ν_{max}(neat)/cm^{-1} 2928, 2850, 2833, 2782, 2720, 1600, 1586, 1490, 1461, 1437, 1236, 1107, 1049, 1022, 750, 627; δ_H (300.13 MHz, $CDCl_3$) 7.43 (1H, dd, *J* 7.7, 1.7, aryl H), 7.20 (1H, td, *J* 7.7, 1.7, aryl H), 6.94 (1H, t, *J* 7.5, aryl H), 6.84 (1H, d, *J* 8.3, aryl H), 3.96 (1H, dd, *J* 2.4, 10.4, NHC*H*), 3.82 (3H, s, OCH_3), 3.17 (1H, d, *J* 11.7, NHCH_aCH$_b$), 2.81 (1H, m, NHCH$_a$CH_b), 2.35 (1H, s, N*H*), 1.85 (2H, m, CH_2), 1.53 (4H, m, 2xCH_2); δ_C (75.5 MHz, $CDCl_3$) 156.9 (C), 133.4 (C), 128.1 (CH), 127.2 (CH), 121.1 (CH), 110.6 (CH), 55.7 (CH_3), 48.2 (CH_2), 33.1 (CH_2), 26.5 (CH_2), 25.8 (CH_2); MS *m/z* (EI) 191 ([M]$^+$, 100), 162 (63), 134 (25), 119 (18), 91 (12), 77 (4); HRMS: $C_{12}H_{18}NO$ (M+H), calc.192.1383, found 192.1383.

(±)-2-(3-methoxyphenyl)-piperidine



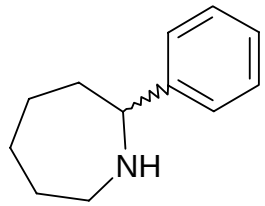
Pale yellow oil, (38 mg, 51 %); ν_{max}(neat)/cm^{-1} 3313, 2929, 2850, 2783, 2718, 2359, 2340, 1600, 1583, 1485, 1431, 1261, 1157, 1042, 845, 778, 697; δ_H (300.13 MHz, $CDCl_3$) 7.20 (1H, m, aryl H), 6.93 (2H, m, aryl H), 6.78 (1H, m, aryl H), 3.80 (3H, s, OC*H*$_3$), 3.56 (1H, m, NHC*H*), 3.17 (1H, m, NHC*H*$_a$CH$_b$), 2.77 (1H, td, *J* 11.5, 3.0, NHCH$_a$C*H*$_b$), 2.14 (1H, s, N*H*), 1.87 (1H, m, C*H*), 1.78 (1H, m, C*H*), 1.63 (1H, m, C*H*), 1.50 (3H, m, 3x C*H*); δ_C (75.5 MHz, $CDCl_3$) 160.1 (C), 147.6 (C), 129.7 (CH), 119.4 (CH), 113.1 (CH), 112.3 (CH), 62.8 (CH), 55.6 (CH_3), 48.2 (CH_2), 35.3 (CH_2), 26.2 (CH_2), 25.8 (CH_2); MS *m/z* (EI) 191 ([M]$^+$, 100), 190 (54), 162 (71), 148 (40), 134 (84), 84 (55); HRMS: $C_{12}H_{17}NO$, calc. 191.1310, found 191.1324.

(±)-2-(4-methoxyphenyl)-piperidine [4]



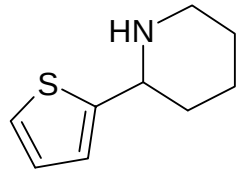
Pale yellow oil, (58 mg, 74%); ν_{max}(neat)/cm^{-1} 3324, 3268, 2996, 2928, 2849, 2782, 2716, 2359, 1609, 1510, 1440, 1302, 1238, 1172, 1109, 1035, 826, 761, 636; δ_H (300 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.9, aryl H), 6.85 (2H, d, *J* 8.3, aryl H), 3.79 (3H, s, OC*H*$_3$), 3.53 (1H, m, NHC*H*), 3.17 (1H, d, *J* 11.3, NHC*H*$_a$H$_b$), 2.78 (1H, td, *J* 11.3, 2.3, NHCH$_a$*H*$_b$), 1.97 (1H, s, N*H*), 1.89 (1H, m, C*H*), 1.74 (1H, m, C*H*), 1.63 (1H, m, C*H*), 1.49 (3H, m, C*H*); δ_C (75.5 MHz, $CDCl_3$) 158.4 (C), 137.5 (C), 127.5 (CH), 113.4 (CH), 61.5 (CH), 55.0 (CH_3), 47.6 (CH_2), 34.7 (CH_2), 25.6 (CH_2), 25.2 (CH_2); MS *m/z* (EI) 191 ([M]$^+$, 100), 162 (76), 135 (80), 121 (27), 91 (22), 77 (16); HRMS: calc. $C_{12}H_{16}NO$ 190.1231, found 190.1251.

(±)-2-phenyl-cycloheptylamine[2]



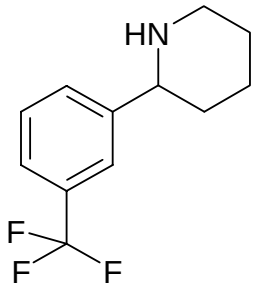
Colourless oil, (75 mg, 83 %); ν_{max}(neat)/cm^{-1} 3059, 3025, 2921, 2850, 2358, 2335, 1491, 1449, 1395, 1332, 1268, 1211, 1142, 753, 697; δ_H (300.13 MHz, $CDCl_3$) 7.25 (5H, m, aryl H), 3.75 (1H, dd, *J* 2.2, 10.1, NHC*H*), 3.12 (1H, dt, *J* 15.3, 3.6, NHCH_aH_b), 2.86 (1H, m, NHCH_aH_b), 1.95 (1H, m, C*H*), 1.71 (7H, m, 7xC*H*); δ_C (75.5 MHz, $CDCl_3$) 148.2 (C), 128.8 (CH), 126.8 (CH), 126.3 (CH), 65.3 (CH), 48.6 (CH_2), 39.4 (CH_2), 31.2 (CH_2), 27.3 (CH_2), 26.1 (CH_2); MS *m/z* (EI) 175 ([M]$^+$, 64), 132 (100), 118 (70), 104 (27), 91 (33); HRMS: $C_{12}H_{17}N$ calc. 175.1361, found 175.1359.

(±)-2-Thiophenyl-2-yl-piperidine



Colourless oil, (52 mg, 79 %); ν_{max}(neat)/cm^{-1} 3310, 2930, 2850, 2789, 2359, 2341, 1439, 1308, 1105; δ_H 7.16-7.12 (1H, m, thiophene C*H*), 6.89-6.93 (2H, m, thiophene C*H*), 3.85-3.91 (1H, m, NHC*H*), 3.10-3.17 (1H, m, NHCH_aCH_b), 2.71-2.79 (1H, m, NHCH_aCH_b), 1.82-2.96 (3H, m, N*H* + CH_2) 1.42-1.63 (4H, m, 2 x CH_2); δ_C (75.5 MHz, $CDCl_3$) 150.1 (C_q), 126.7 (CH), 123.9 (CH), 122.9 (CH), 57.7 (CH), 47.9 (CH_2), 36.3 (CH_2), 26.3 (CH_2), 25.4 (CH_2); MS *m/z* (EI) 167 (M^+, 10), 85 (70), 83 (100); HRMS: calc. $C_9H_{13}NS$ calc. 167.0769, found 167.0769.

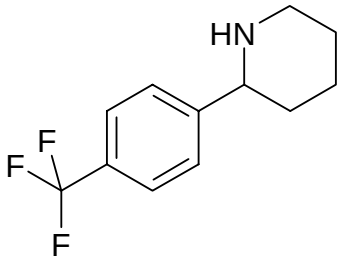
(±)-2-(3-Trifluoromethylphenyl)-piperidine



Pale yellow oil (59 mg, 65%); ν_{max}(neat)/cm^{-1} 3271, 2932, 2853, 1320, 1117, 702; δ_H 7.63 (s, 1H, aryl H), 7.39-7.59 (3H, m, aryl H), 3.60-3.68 (1H, m, NHC*H*), 3.17-3.26 (1H, m, NHCH_aCH_b), 2.76-2.84

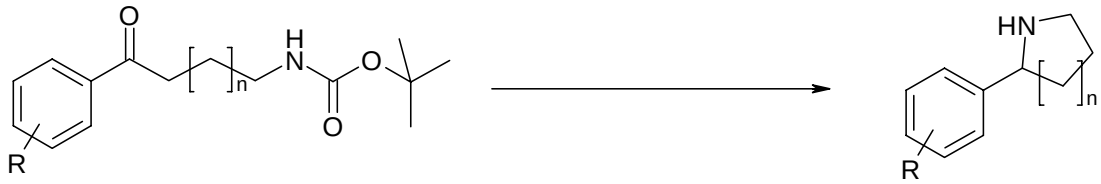
(1H, m ,NHCH$_a$C*H*$_b$), 1.47-1.92 (7H, m, N*H*CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$); δ_C(75.5 MHz, $CDCl_3$) 146.8 (C_q), 130.6 (C_q, q, *J* 24), 130.0 (CH), 129.1 (CH), 124.6(CH, d, *J* 272), 124.3 (CH), 123.9 (CH), 62.3 (CH), 48.0 (CH_2), 35.4 (CH_2), 26.1 (CH_2), 25.6 (CH_2);); MS *m/z* (EI) 229 (M^+, 65), 228 (55), 200 (80), 172 (100), 84 (86); HRMS: calc. $C_{12}H_{13}F_3N$ calc. 228.1000, found 228.0988.

(±)-2-(4-Trifluoromethylphenyl)-piperidine



Pale yellow oil (52 mg, 57%); ν_{max}(neat)/cm^{-1} 3675, 2933, 2854, 2790, 1619, 1321, 1117, 1066; δ_H 7.55 (2H, d, *J* 8.1, aryl H), 7.48 (2H, d, *J* 8.1, aryl H), 3.61-3.68 (1H, m, NHC*H*), 3.27-3.32 (1H, m, NHC*H*$_a$CH$_b$), 2.76-2.84 (1H, m, NHCH$_a$C*H*$_b$), 1.95-1.42 (7H, m, N*H*C*H*$_2$C*H*$_2$C*H*$_2$); δ_C(75.5 MHz, $CDCl_3$) 149.9 (C_q), 129.6 (C_q, q, *J* 32), 127.3 (CH), 125.7 (CH), 124.6 (C_q, q, *J* 272), 62.3 (C_q), 47.9 (CH_2), 35.44 (CH_2), 26.1 (CH_2), 25.6 (CH_2); *m/z* (EI) 229 (M^+, 40), 200 (75), 186 (35), 162 (100), 84 (95), 78 (40), 63 (50); HRMS: calc. $C_{12}H_{13}F_3N$ calc. 228.1000, found 228.0993.

Preparation (One-pot process) of piperidines.



t-Boc-amino-ketone (0.2g) was stirred in freshly distilled formic acid (1.8 mL) for 16 h. The flask was then sealed and cooled to 0ºC; triethylamine (3 mL) was added cautiously with vigorous shaking until all gas had redissolved. In a separate flask a mixture of (p-cymene) ruthenium (II) chloride dimmer (0.25 mol %) and (1*R*,2*R*)-TsDPEN (0.5 mol %), triethylamine (1 drop) and anhydrous acetonitrile (1 mL) were stirred at 28ºC for 40 min. The catalyst solution was transferred to the formic acid / triethylamine solution and the mixture stirred at 28ºC until complete by NMR. The mixture was made basic (pH 9-10) with sat. Na_2CO_3 sol. and extracted with DCM (3 x 25 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was

purified by flash column chromatography (10-15% v/v ethyl acetate / hexane on silica pre-treated with Et_3N) to afford the amines as described.

2-phenyl-piperidine (7)

Colourless oil, (110 mg, 94%); δ_H (300.13 MHz, $CDCl_3$) 7.29 (5H, m, aryl H), 3.58 (1H, m, NHC*H*), 3.19 (1H, m, NHCH_aH_b), 2.80 (1H, m, NHCH_aH_b), 1.85 (2H, m, CH_2), 1.66 (2H, m, CH_2), 1.52 (3H, m, N*H* and CH_2).

2-cyclohexyl-piperidine

Pale orange oil, (115 mg, 98%); δ_H (300.13 MHz, $CDCl_3$) 3.12 (1H, dquin, *J* 11.7, 2.1, NHC*H*), 2.62 (1H, td, *J* 11.7, 2.9, NHCH_aH_b), 2.26 (1H, m, NHCH_aH_b), 1.71 (8H, m, 7xC*H* and N*H*), 1.21 (8H, m, 8xC*H*), 1.00 (2H, m, 2xC*H*).

2-(2-methoxyphenyl)-piperidine

Yellow oil, (97 mg, 78%); δ_H (300.13 MHz, $CDCl_3$) 7.43 (1H, dd, *J* 7.7, 1.7, aryl H), 7.20 (1H, td, *J* 7.7, 1.7, aryl H), 6.94 (1H, t, *J* 7.5, aryl H), 6.84 (1H, d, *J* 8.3, aryl H), 3.96 (1H, dd, *J* 2.4, 10.4, NHC*H*), 3.82 (3H, s, OCH_3), 3.25 (1H, s, N*H*), 3.17 (1H, d, *J* 11.7, NHCH_aH_b), 2.81 (1H, td, *J* 11.7, 2.6, NHCH_aH_b), 1.85 (2H, m, CH_2), 1.53 (4H, m, 2xCH_2).

2-(3-methoxyphenyl)-piperidine

Pale yellow oil, (120 mg, 96%); δ_H (300.13 MHz, $CDCl_3$) 7.20 (1H, t, *J* 7.8, aryl H), 7.03 (1H, s, aryl H), 6.97 (1H, d, *J* 7.9, aryl H), 6.78 (1H, dd, *J* 7.8, 1.8, aryl H), 3.75 (3H, s, OCH_3), 3.00 (1H, m, NHC*H*), 2.62 (1H, td, *J* 11.5, 3.0, NHCH_aH_b), 1.90 (3H, m, NHCH_aH_b and CH_2), 1.68 (3H, m, N*H* and CH_2), 1.52 (2H, m, CH_2).

2-(4-methoxyphenyl)-piperidine

Brown oil, (117 mg, 94%); δ_H (300.13 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.9, aryl H), 6.85 (2H, d, *J* 8.3, aryl H), 5.05 (1H, s, N*H*), 3.79 (3H, s, OCH_3), 3.59 (1H, m, NHCH_aH_b), 3.09 (1H, d, *J* 11.3, NHCH_aH_b), 2.78 (1H, m, C*H*), 1.89 (1H, m, C*H*), 1.78 (1H, m, C*H*), 1.61 (3H, m, C*H* and CH_2), 1.48 (1H, m, C*H*).

2-(3-Trifluoromethylphenyl)-piperidine

Yellow oil, (131 mg, 99%), δ_H (300.13 MHz, $CDCl_3$) 7.63 (s, 1H, aryl H), 7.39-7.59 (3H, m, aryl H), 3.60-3.68 (1H, m, NHC*H*), 3.17-3.26 (1H, m, NHCH_aCH$_b$), 2.76-2.84 (1H, m ,NHCH$_a$CH_b), 1.47-1.92 (7H, m, N*H*CH$_2$CH_2CH_2CH_2).

2-(4-Trifluoromethylphenyl)-piperidine

Yellow oil, (130 mg, 98%), δ_H (300.13 MHz, $CDCl_3$) 7.55 (2H, d, *J* 8.1, aryl H), 7.48 (2H, d, *J* 8.1, aryl H), 3.61-3.68 (1H, m, NHC*H*), 3.27-3.32 (1H, m, NHCH_aCH$_b$), 2.76-2.84 (1H, m, NHCH$_a$CH_b), 1.95-1.42 (7H, m, N*H*CH_2CH_2CH_2).

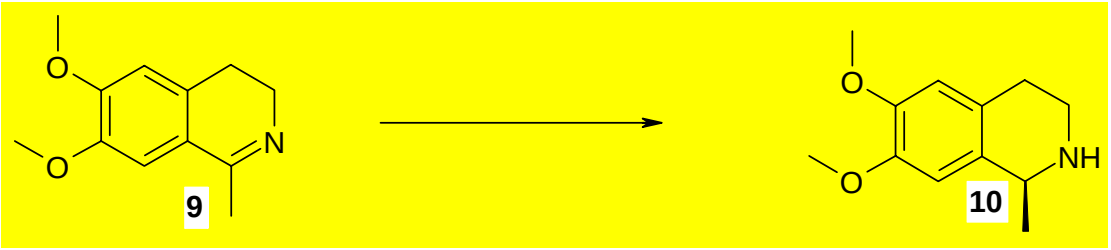
2-Thiophenyl-2-yl-piperidine

Yellow oil (40 mg, 20%), δ_H (300.13 MHz, $CDCl_3$) 7.16-7.12 (1H, m, SC*H*), 6.89-6.93 (2H, m, SCHC*H*C*H*), 3.85-3.91 (1H, m, NHC*H*), 3.10-3.17 (1H, m, NHCH_aCH$_b$), 2.71-2.79 (1H, m, NHCH$_a$CH_b), 1.82-2.96 (3H, m, N*H* + CH_2) 1.42-1.63 (4H, m, 2 x CH_2).

2-phenyl-cycloheptylamine

Colourless oil, (24 mg, 12%), δ_H (300.13 MHz, $CDCl_3$) 7.25 (5H, m, aryl H), 3.75 (1H, dd, *J* 2.2, 10.1, NHC*H*), 3.12 (1H, dt, *J* 15.3, 3.6, NHCH_aH$_b$), 2.86 (1H, m, NHCH$_a$$H_b$), 1.95 (1H, m, C*H*), 1.71 (7H, m, 7xC*H*).

Asymmetric reduction of 9 to 10.[6]

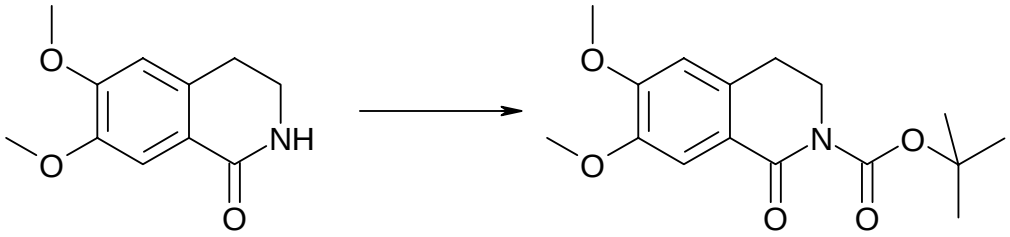


A mixture of (p-cymene) ruthenium (II) chloride dimer (2.3mg, 0.0037 mmol) and (1R,2R)-TsDPEN (2.7 mg, 0.0073 mmol) in a 5:2 formic acid-triethylamine mixture (4mL) was stirred at 28ºC for 30 min. A solution of imine (300 mg, 1.5 mmol) in anhydrous acetonitrile (2ml) was added and the solution was stirred for 16h. The solution was poured onto saturated Na_2CO_3 solution (10 mL) and extracted with DCM (3 x 20 mL). Combined organics were washed with brine (10 mL) and dried ($MgSO_4$), the solvent was removed under reduced pressure and the residue purified by flash column chromatography (50-100 % v/v ethyl acetate-hexanes gradient elution) to afford (S)-(-)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline **10**[5] as a pale orange oil which crystallised on

$[\alpha]_D^{22}$

standing (296 mg, 95 %); -52.0 (*c* 1g/100 mL, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3270, 2929, 1511, 1452, 1252, 1220, 1114, 784; δ_H(300.13 MHz, $CDCl_3$; $(CH_3)_4Si$) 6.61 (1H, s, Ph H), 6.56 (1H, s, Ph H), 4.06 (1H, q, J 6.7, CH_3CH), 3.85 (3H, s, OCH_3), 3.22-3.33 (1H, m, CH_2), 2.97-3.07 (1H, m, CH_2), 2.76-2.85 (1H, m, CH_2), 2.62-2.67(1H, m, CH_2), 1.46 (3H, d, J 6.4, $CHCH_3$); δ_C (75.5 MHz, $CDCl_3$) 147.7 (C_q), 147.6 (C_q), 132.9 (C_q), 127.3 (C_q), 112.2 (CH), 109.5 (CH), 56.4 (CH_3), 56.3 (CH_3), 51.7 (CH), 42.3 (CH_2), 30.0 (CH_2), 23.3 (CH_2); MS m/z (EI) 207 (M^+, 15), 206 (20), 193 (30), 192 (100); HRMS: calc. $C_{12}H_{17}N0_2$ calc. 207.1259, found 207.1255. The ee was determined to be 88 % by derivatisation of (S)-(-)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline with 5(*R*)-methyl-1-(chloromethyl)-2-pyrrolidinone (**8**) and the integration of the doublets at 1.33 ppm and 1.40 ppm in the ^{1}H NMR were used to calculate ee%.

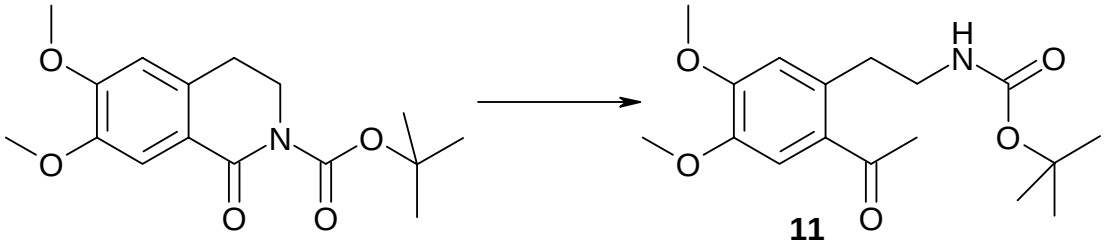
Preparation of 11 from lactam 6,7-dimethoxy-3,4-dihydro-2H-isoquinolin-1-one.



To a suspension of hexane washed NaH (0.82 g, 60% suspension in oil, 0.020 mol) in anhydrous THF (30 mL) at 0°C was added drop wise a solution of 6,7-dimethoxy-3,4-dihydro-2H-isoquinolin-1-one (3.92 g, 0.19 mol), the resulting suspension was stirred at 0°C for 1 hr. Boc_2O (4.05g, 0.19 mol) was added in 4 portions over 30 min, a thick suspension was formed so THF (20 mL) was added and the reaction allowed to warm to rt and stirred for 4 hr until complete by TLC. Water (20 mL) was added cautiously and the phases were separated. The aqueous layer was extracted with Et_2O (2 x 50 mL) and the organics combined, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. Residual DMF was removed azeotropically with EtOAc/Heptane (1:9) under reduced pressure to afford 6,7-dimethoxy-1-oxo-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester as an off white solid (4.95 g, 86%); mp 116-119°C; ν_{max}(neat)/cm^{-1} 2976, 2360, 2342,1749, 1661, 1155; δ_H(300.13 MHz, $CDCl_3$; $(CH_3)_4Si$) 7.64 (1H, s, aryl H), 6.65 (1H, s, aryl H), 3.98 (2 H, t, *J* 6.2,NC*H*$_2$CH$_2$), 3.93 (3H, s, OC*H*$_3$), 3.91 (3H, s, OC*H*$_3$), 2.95 (2H, t, *J* 6.2, NCH$_2$C*H*$_2$), 1.60 (9H, s, *t*-Bu); δ_C (75.5 MHz, $CDCl_3$) 164.3 (C_q), 153.8 (C_q), 153.3 (C_q), 148.5 (C_q), 134.3 (C_q), 122.1 (C_q), 111.6 (CH), 109.5 (CH), 83.4 (C_q), 56.5 (CH_3), 56.4 (CH_3), 45.1 (CH_2), 28.5 (CH_3), 28.4 (CH2); MS

m/z (CI) 307 (M^+, 80), 207 (100), 178 (40), 150 (30); HRMS: calc. $C_{16}H_{21}N0_5$ calc. 307.1420, found 307.1407; Anal. calc. for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56, found C, 62.47; H, 6.82; N, 4.49.

Preparation of 11.[3]



11

To a stirred solution of 6,7-dimethoxy-1-oxo-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (1 g, 3.3 mmol) in THF (20 mL) at -78°C was added drop wise a solution of methyllithium (0.086 g, 1.6 mol in THF) over 1 hr. 2N HCl (10 mL) was added and the reaction warmed to rt. The layers were separated and the aqueous layer extracted with DCM (2 x 20 mL), the organics were combined, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure. The crude oil was purified by flash column chromatography (0-15 % v/v ethyl acetate-hexanes gradient elution) to afford [2-(2-acetyl-4,5-dimethoxy-phenyl)-ethyl]-carbamic acid tert-butyl ester (11)[3] as a pale yellow powder (0.5 g, 47%); mp 107-110°C; ν_{max}(neat)/cm^{-1} 3312, 2969, 2936, 1680, 1539, 1147; δ_H(300.13 MHz, $CDCl_3$; $(CH_3)_4Si$) 7.21 (1H, s, aryl H), 6.73 (1H, s, aryl H), 5.03 (1H, bs, N*H*), 3.92 (6H, s, 2 x OC*H*$_3$), 3.37 (2H, m, NHC*H*$_2$), 3.02 (2 H, t, *J* 7.0, NHCH$_2$C*H*$_2$), 2.58 (3H, s, $COCH_3$), 1.41 (9H, s, *t*-Bu); δ_C (75.5 MHz, $CDCl_3$) 156.5 (C_q), 152.1 (C_q), 147.0 (C_q), 134.9 (C_q), 129.9 (C_q), 114.7 (CH), 113.6 (CH), 79.3 (C_q), 56.6 (CH_3), 56.4 (CH_3), 42.5 (CH_2), 34.4 (CH_2), 29.8 (CH_3), 28.8 (CH_3); MS m/z (EI) 323 (M^+, 4), 206 (80), 205 (100), 57 (25); HRMS: calc. $C_{17}H_{25}N0_5$ calc. 323.1734, found 323.1729; Anal. calc. for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33, found C, 63.22; H, 7.77; N, 4.28.

Conversion of 11 to 9 using the one-pot protocol.

The conversion of **11** to **9** was carried out in 85% yield following the general procedure described above for the monocyclic compounds. The resulting product had identical ^{1}H and ^{13}C spectra to that of reduction of **9**. The ee was determined to be 88 % by derivatisation of (S)-(-)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline with 5(*R*)-methyl-1-(chloromethyl)-2-pyrrolidinone (**8**) and the integration of the doublets at 1.33 ppm and 1.40 ppm in the ^{1}H NMR were used to calculate ee%.

$[\alpha]_D^{22}$ -51.7 (*c* 1g/100 mL, $CHCl_3$);

General procedure for determination of enantiomeric excess.

To a suspension of sodium hydride (0.13 mmol, washed with hexanes and dried under vacuum) in DCM (1 mL) at 0ºC was added a solution of amine (0.12 mmol) in DCM (0.5 mL), the resulting suspension was stirred for 1 hr before a solution of halide **8** (0.13 mmol) in DCM (0.25 mL) was added and stirred for 2 hrs. Water (1 mL) was added cautiously and the organic layer was separated, the aqueous layer was extracted with further DCM (2 x 1 mL), the organic extracts were combined, dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to afford the crude products. These were analysed without purification. The e.e. was determined from the 2 methyl doublets around 1 ppm, a CH_2 signal around 3 ppm or an AB system around 4 ppm.

References.

1) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J.Org.Chem*., **1989** *54*, 228-234.

2) Willoughby, C. A.; Buchwald, S. L. *J.Am.Chem.Soc*., **1994**, *116*, 1994; 8952-8965.

3) Lenz, G. R.; Woo, C.-M.; Hawkins, B. L. *J.Org.Chem*., **1982**, *47*, 3049-3053.

4) Hunt, J. C. A.; Laurent, P.; Moody, C. J. *J.Chem.Soc.Perkin Trans.1*, **2002**, 2378 - 2389.

5) Pedrosa, R.; Andres, C.; Iglesias, J. M. *J.Org.Chem*. **2001**, *66*, 243 - 250.

6) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori R., *J. Am. Chem. Soc.*, **1996**, *118*, 4916-17.