Phosphinates as New Electrophilic Partners for Cross-Coupling Reactions

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Part A: Experimental Procedure for Suzuki Array Screening

The protocol used to carry out arrays of 24 Suzuki reactions using a Radley's Technologies Greenhouse Parallel Synthesiser is described in this Appendix. This procedure was adapted from one developed by Mr Ian B. Campbell of GlaxoSmithkline, Stevenage, UK and acknowledgement is made to him for the original protocol.

The conditions cover a range of catalysts, ligands, bases and solvents which have been employed regularly in Suzuki cross-coupling reactions. Arrays were carried out in a 24 array Greenhouse and followed by GC and GCMS. The reactions were carried out on 0.1 mmol scale using 3 mol% catalyst precursor, 6mol% ligand and 3 equivalents base together with 1 equivalent of dodecane as an internal standard exploring a total of 4 catalysts, 7 ligands, 10 bases, 8 solvents as described in the table below.

Table A1 Array Reaction Conditions

Greenhouse Tube	Catalyst	Ligand	Base	Solvent	% Yield by GC
A1	$Pd(PPh_3)_4$		Cs_2CO_3	DMF	N/A
A2	$Pd(PPh_3)_4$		K_3PO_4	DMF	23%
A3	$Pd(PPh_3)_4$		Na_2CO_3	DME / H_2O	no product
A4	$Pd(PPh_3)_4$		$NaHCO_3$	DME / H_2O	98%
A5	$Pd(PPh_3)_4$		$Ba(OH)_2$	DME / H_2O	72%
A6	$Pd(PPh_3)_4$		NaOH	DME / H_2O	<10%

B1	$Pd(OAc)_2$		K_2CO_3	DME / H_2O	17%
B2	$Pd(OAc)_2$	IMES	Et_3N	Toluene	<10%
B3	$Pd(OAc)_2$	IMES	Et_3N	DMF	<10%
B4	$Pd_2(dba)_3$	IMES	Et_3N	MeCN	<10%
B5	$Pd_2(dba)_3$	IMES	Et_3N	Dioxane / H_2O	11%
B6	$Pd(OAc)_2$	PPh_3	$NaHCO_3$	DME / H_2O	No product
C1	$Pd(OAc)_2$	$(2\text{-furan})_3P$	Et_3N	DMF	No product
C2	$Pd(OAc)_2$	Dppe	Et_3N	DMF	<10%
C3	$Pd(OAc)_2$	Dppb	Et_3N	DMF	<10%
C4	$Pd(OAc)_2$	Dppf	Et_3N	DMF	No product
C5	$Pd(OAc)_2$	$^tBu_2P(BiPh)$	K_3PO_4	EtOH / H_2O	44%
C6	$Pd(OAc)_2$	$^tBu_2P(BiPh)$	K_3PO_4	Toluene	<10%
D1	$Pd_2(dba)_3$		KOAc	Toluene/EtOH	31%
D2	$Pd_2(dba)_3$	IMES	Cs_2CO_3	Dioxane	<10%
D3	$Pd_2(dba)_3$	Dppf	Cs_2CO_3	DMF	No product
D4	$PdCl_2$(Binap)		$NaHCO_3$	DME / H_2O	46%
D5	$PdCl_2$(Binap)		K_3PO_4	DMF	14%
D6	$PdCl_2$(Binap)		CsF	THF / H_2O	63%

$tBu_2P(BiPh)$ =

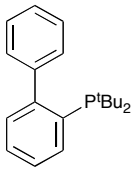


Table A2- Dispense List – The following stock solutions were prepared

A1	Enol Phosphinate **3a**	0.2 M in THF	
A1.5	Dodecane	0.	
A2	Boronic Acid **4a**	0.2 M in THF	
A3	$Pd(PPh_3)_4$	0.01 M in THF	11.55 mg/ml
A4	Pd(OAc)2	0.01 M in THF	2.24 mg/ml
A5	$Pd_2(dba)_3$	0.01 M in THF	9.14 mg/ml
A6	$Pd(Binap)Cl_2$	0.01 M in THF	8.0 mg/ml
B1	IMES	0.01 M in THF	2.02 mg/ml
B2	dppm	0.01 M in THF	3.85 mg/ml
B3	$(2\text{-furan})_3P$	0.01 M in THF	2.32 mg/ml
B4	dppe	0.01 M in THF	3.98 mg/ml
B5	dppb	0.01 M in THF	4.26 mg/ml
B6	dppf	0.01 M in THF	5.54 mg/ml
B7	$^tBu_2P(BiPh)$	0.01 M in THF	2.98 mg/ml
C1	Na_2CO_3	1.0 M in H_2O	106 mg/ml
C2	$NaHCO_3$	1.0 M in H_2O	84 mg/ml
C3	NaOH	1.0 M in H_2O	40 mg/ml
C4	Et_3N		
C5	K_2CO_3	1.0 M in H_2O	138 mg/ml
C6	K_3PO_4	1.0 M in H_2O	203 mg/ml
C7	CsF	1.0 M in H_2O	151 mg/ml
D1	DMF		
D2	DME		
D3	PhMe		
D4	MeCN		
D5	Dioxane		
D6	H_2O		
D7	EtOH		
D8	THF		

Table A3- Solid Samples were preweighed

Cs_2CO_3	3 x 97.5 mg
K_3PO_4	3 x 60.9 mg
$Ba(OH)_2$	1 x 51.3 mg
KOAc	1 x 29.4 mg

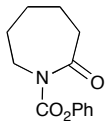
Table A4- Protocol-

1. 500 µl A1 to vessels A1 – D6 (24 dispenses)
2. 500 µl A2 to vessels A1 – D6 (24 dispenses)
3. 500 µl A3 to vessels A1 – A6 (3 dispenses)
4. 500 µl A4 to vessels B1 – C6 (Not B4 and B5) (10 dispenses)
5. 500 µl A5 to vessels D1 – D3, B4 and B5 (5 dispenses)
6. 500 µl A6 to vessels D4 – D6 (3 dispenses)
7. 500 µl B1 to vessels B2 – B5 and D2 5 dispenses)
8. 500 µl B2 to vessel B6 (1 dispense)
9. 500 µl B3 to vessel C1 (1 dispense)
10. 500 µl B4 to vessel C2 (1 dispense)

11. 500 µl B5 to vessel C3 (1 dispense)
12. 500 µl B6 to vessels C4 and D3 (2 dispenses)
13. 500 µl B7 to vessels C5 and C6 (2 dispenses)
14. All the samples were then evacuated using a Genevac vacuum centrifuge operating at full power for 12 minutes
15. 300 µl C1 to vessel A3 (1 dispense)
16. 300 µl C2 to vessels A4, D4, and B6 3 dispenses)
17. 300 µl C3 to vessel A1 (1 dispense)
18. 50 µl C4 to vessels B2 – C4 NOT B6 8 dispenses)
19. 300 µl C5 to vessel B1 (1 dispense)
20. 300 µl C6 to vessel C5 (1 dispense)
21. 300 µl C7 to vessel D6 (1 dispense)
22. 1000 µl D1 to vessels A1, A2, B3, B7 – C4, D3, D5 9 dispenses)
23. 700 µl D1 to vessel B1 (1 dispense)
24. 700 µl D2 to vessels A3 – A6, B6 and D4 6 dispenses)
25. 1000 µl D3 to vessels B2 and C6 (2 dispenses)
26. 500 µl D3 to vessel D1 (1 dispense)
27. 1000 µl D4 to vessel B4 (1 dispense)
28. 500 µl D5 to vessel B5 (1 dispense)
29. 1000 µl D5 to vessel D2 (1 dispense)
30. 300 µl D6 to vessels A3 – A6, B1, B5, B6, C5, D4 and D6 10 dispenses)
31. 700 µl D7 to vessel C5 (1 dispense)
32. 700 µl D8 to vessel D6 (1 dispense)
33. Add Cs_2CO_3 97.5 mg to vessels A1, D2 and D3
34. Add K_3PO_4 60.9 mg to vessels A2, C6 and D5
35. Add $Ba(OH)_2$ 51.3 mg to vessel A5
36. Add KOAc 29.4 mg to vessel D1
37. Reaction array was then placed in the greenhouse reactor and heated at 80°C for 18 h and then analysed by GC and GCMS

Part B: Experimental Procedures and Spectroscopic Data for Starting Lactams and all Products

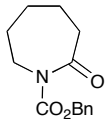
N-(Phenyloxycarbonyl)-2-oxo-azepane



To a cold (-78 °C) solution of caprolactam (1.06 g, 9.37 mmol) in dry THF (50 ml) was added *n*-BuLi (1.0 M, 11.24 ml, 11.24 mmol) dropwise *via* a syringe and the reaction mixture allowed to stir at -78 °C. After 2 h a cold (-78 °C) solution of phenyl chloroformate (2.93 g, 18.73 mmol) in dry THF (30 ml) was added *via* cannula and the resulting reaction mixture allowed to stir for an additional 3 h before warming to room temperature. The reaction was quenched with $NH_4Cl_{(aq)}$, concentrated and extracted with EtOAc (150 ml). The organic phase was washed with brine (3 x 50 ml), $NaHCO_{3\ (aq)}$

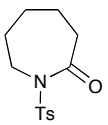
(3 x 50 ml), dried over $MgSO_4$ and concentrated affording the crude material as a yellow oil. Flash chromatography ([50:1], [19:1] DCM/EtOAc) followed by recrystallisation (pet. ether) afforded the title compound as clear crystals (1.17 g, 4.99 mmol, 53%). mp. 70-71 °C. Found; C, 66.90; H, 6.45; N, 5.90%; Calc. for $C_{13}H_{15}NO_3$; C, 66.94; H, 6.48; N, 6.00%. ν_{max} (KBr) 2938, 2861, 1778 (CH_2C=O), 1731 and 1715 (O=C-O), 1265, 1182 cm^{-1}. δ_H (500 MHz) 1.85 (6H, m, 4-*H*$_2$, 5-*H*$_2$, 6-*H*$_2$), 2.78 (2H, m, 3-*H*$_2$), 3.98 (2H, m, 7-*H*$_2$), 7.18-7.22 (2H, m, 3'-*H*, 5'-*H*), 7.23-7.29 (1H, m, 4'-*H*), 7.37-7.42 (2H, m, 2'-*H*, 6'-*H*). δ_C (125MHz) 23.8 (*C*-4), 28.9 (*C*-6), 29.4 (*C*-5), 39.7 (*C*-3), 46.9 (*C*-7), 121.8 (*C*-3'), 126.4 (*C*-4'), 129.6 (*C*-2'), 151.1 (*C*-1'), 153.4 (O*C*=O), 157.9 (*C*-2). *m/z* (ES^+) 234.1 (MH^+).

N-(Benzyloxycarbonyl)-2-oxo-azepane



To a cold (-78 °C) solution of caprolactam (0.44 M, 2.00 g, 17.66 mmol) in dry THF (40 ml) was added *n*-BuLi (2.5 M, 9.2 ml, 22.97 mmol) dropwise *via* a syringe and the reaction mixture allowed to stir at -78 °C. After 30 min benzyl chloroformate was added slowly (6.03 g, 5.04 ml, 18.73 mmol) and the resulting reaction mixture allowed to stir for 1 h before warming to room temperature. The reaction was quenched with $NH_4Cl_{(aq)}$, concentrated and extracted with EtOAc (150 ml). The organic phase was washed with brine (3 x 50 ml), $NaHCO_{3(aq)}$ (3 x 50 ml), dried over $MgSO_4$ and concentrated. Purification by flash chromatography ([4:1] DCM/EtOAc) afforded the title compound as a clear oil (2.25 g, 9.11 mmol, 52%). ν_{max} (ATR) 2932, 1767 (CH_2C=O), 1707 (O=C-O), 1378, 1264, 1163, 1014, 959, 736, 696 cm^{-1}. δ_H (500 MHz) 1.70-1.81 (6H, m, 4-*H*$_2$, 5-*H*$_2$, 6-*H*$_2$), 2.69 (2H, m, 3-*H*$_2$), 3.85 (2H, m, 7-*H*$_2$), 5.28 (2H, s, CO_2CH_2), 7.28-7.39 (3H, m, 3'-*H*, 4'-*H*), 7.43 (2H, m, 2'-*H*), 7.37-7.42. δ_C (125 MHz) 23.7, 28.9 and 29.4 (*C*-4, *C*-5, *C*-6), 39.7 (*C*-3), 46.6 (*C*-7), 68.8 (CO_2CH_2), 128.1, 128.4 and 128.8 (3 x Ar*C*-H), 135.8 (*C*-1'), 154.5 (O*C*=O), 175.9 (*C*-2). *m/z* (ES^+) 270.2 (MNa^+), 517.0 ($2MNa^+$). HRMS (ES^+) found MNa^+ 270.1101, $C_{14}H_{17}NO_3Na$ requires M^+ 270.1101.

N-([4'-Methylphenyl]sulfonyl)-2-oxo-azepane

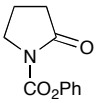


Purification by flash chromatography ([85:15], [4:1], [65:35] pet. ether/EtOAc) afforded the title compound as a white solid (1.10 g, 4.12 mmol, 46%). mp 117-120 °C. Found; C, 58.11; H, 6.28; N, 4.92%; Calc. for $C_{13}H_{17}NO_3S$; C, 58.40; H, 6.41; N, 5.24%. ν_{max} (KBr) 2941, 2861, 1697 (NC=O), 1597, 1353 (SO_2), 1168 (SO_2), 1123, 1088, 813, 549, 535 cm^{-1}. δ_H (500 MHz) 1.64-1.76 (4H, m, 4-*H*$_2$, 5-*H*$_2$), 1.81 (2H, m, 6-*H*$_2$), 2.41 (3H, s, 4'-C*H*$_3$), 2.53 (2H, t, J = 6 Hz, 3-*H*$_2$), 4.01 (2H, t, J = 5 Hz, 7-*H*$_2$), 7.29 (2H, d, J = 9 Hz, 3'-*H*, 5'-*H*), 7.87 (2H, d, J = 9 Hz, 2'-*H*, 6'-*H*). δ_C (125 MHz) 21.9 (4'-*C*H_3), 23.2 (*C*-4), 29.4 (C5), 29.6 (*C*-6), 39.0 (*C*-3), 46.7 (*C*-7), 128.8 (*C*-2'), 129.5 (*C*-3'), 136.8 (*C*-4'), 144.7 (*C*-1'), 175.1 (*C*-2). *m/z* (ES^+) 268.0 (MH^+).

N-[(4'-methylphenyl)sulfonyl]pyrrolidin-2-one

Obtained, following flash chromatography ([7:3] pet. ether/EtOAc), as a white solid (2.33 g, 9.74 mmol, 65%). mp. 139-141 °C. ν_{max} (ATR) 3028, 1737 (C=O), 1598, 1359 (NSO_2), 1238, 1217, 1169 (NSO_2), 1121, 957, 662, 596, 558 cm^{-1}. δ_H (500 MHz) 2.06 (2H, t, J = 8 Hz, 4-*H*$_2$), 2.39-2.47 (5H, m, 4'-C*H*$_3$, 3-*H*$_2$), 3.88 (2H, t, J = 7 Hz, 5-*H*$_2$), 7.33 (2H, d, J = 8 Hz, 3'-*H*), 7.91 (2H, d, J = 8 Hz, 2'-*H*). δ_C (125 MHz) 18.4 (*C*-4), 21.2 (*C*H_3), 32.5 (*C*-3), 47.5 (*C*-5), 128.3 (*C*-2'), 129.9 (*C*-3'), 135.3 (*C*-1'), 145.5 (*C*-4'), 173.7 (*C*=O). *m/z* (ES^+) 240 (MH^+). HRMS (ES^+) found MH^+ 240.0691, $C_{11}H_{14}NO_3S$ requires M^+ 240.0689, found MNa^+ 262.0509, $C_{11}H_{13}NO_3SNa$ requires M^+ 262.0508.

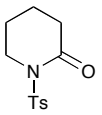
N-(Phenyloxycarbonyl)pyrrolidin-2-one



To a cold solution (-78 °C) of pyrrolidinone (0.56 g, 6.58 mmol, 1 eq) in dry THF (10 ml, 0.66 M) was added *n*-BuLi (1.6 M, 4.9 ml, 7.90 mmol, 1.2 eq) dropwise *via* a syringe. The reaction mixture was allowed to stir at -78 °C for 1 h then $Ph_2P(O)Cl$ (2.06 g, 13.16 mmol, 2 eq) was added as a cold solution in dry THF (4 ml). The reaction mixture was stirred for 1.5 h at -78 °C, warmed to room temperature and stirred for an additional 0.5 h then quenched with H_2O. The THF was removed under reduced pressure and the aqueous extracted into EtOAc (x 3), the combined organics were washed with H_2O, dried over $MgSO_4$ and concentrated to a pink solid. Purification by flash chromatography afforded the title compound as a white solid (1.01 g, 4.94 mmol, 75%). mp. 119-120 °C. Found; C, 64.33; H, 5.39; N, 6.81%; Calc. for $C_{11}H_{11}NO_3$; C, 64.38; H, 5.40; N, 6.83%. ν_{max} (ATR) 2977, 1779 (OC=O), 1697 (NC=O), 1490, 1458, 1379, 1288, 1188, 1163, 1020, 988, 751, 693 cm^{-1}. δ_H (700 MHz) 2.10 (2H, quint, J = 8 Hz, 4-*H*$_2$), 2.60 (2H, t,

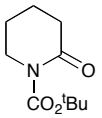
J = 8 Hz, C*H*$_2$), 3.93 (2H, t, J = 8 Hz, C*H*$_2$), 7.16 (2H, d, J = 8 Hz, 2'-*H*), 7.23 (1H, t, J = 8 Hz, 4'-*H*), 7.37 (2H, t, J = 8 Hz, 3'-*H*). δ_C (125 MHz) 17.8 (*C*-4), 33.1 (*C*H$_2$), 46.9 (*C*H$_2$), 121.7 (*C*-2'), 126.4 (*C*-4'), 129.6 (*C*-3'), 150.3 (*C*-1'), 150.5 (O*C*=O), 174.1 (*C*-2). *m/z* (ES$^+$) 206.1 (MH$^+$), 223.1 (MH$_2$O$^+$), 433.2 (2MNa$^+$).

N-[(4'-methylphenyl)sulfonyl]piperidin-2-one



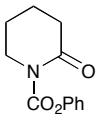
Obtained, following flash chromatography ([7:3] pet. ether/EtOAc), as a white solid (2.02 g, 7.9 mmol, 33%). mp. 136-138 °C. Found; C, 56.87; H, 5.97; N, 5.37%; Calc. for $C_{12}H_{15}NO_3S$; C, 56.90; H, 5.97; N, 5.53%. ν_{max} (KBr) 2958, 1691 (C=O), 1457, 1354 (NSO_2), 1283, 1171 (NSO_2), 1089, 969, 830, 577, 549 cm^{-1}. δ_H (400 MHz) 1.74 (2H, quint, J = 6 Hz, 4-*H*$_2$), 1.87 (2H, quint, J = 6 Hz, 5-*H*$_2$), 2.28-2.48 (5H, m, 3-*H*$_2$, 4'-C*H*$_3$), 3.88 (2H, t, J = 6 Hz, 6-*H*$_2$), 7.28 (2H, d, J = 8 Hz, 3'-*H*, 5'-*H*), 7.87 (2H, d, J = 8 Hz, 2'-*H*, 6'-*H*). δ_C (100 MHz) 20.6 (*C*-4), 21.9 (C4'-*C*H$_3$), 23.5 (*C*-5), 34.3 (*C*-3), 47.2 (*C*-6), 128.9 (*C*-2'), 129.5 (*C*-3'), 136.3 (*C*-1'), 145.0 (*C*-4'), 170.5 (*C*=O). *m/z* (ES$^+$) 254.1 (MH$^+$), 276.1 (MNa$^+$), 308.1 (MNaMeOH$^+$), 529 (2MNa$^+$). HRMS (ES$^+$) found MH$^+$ 254.0847, $C_{12}H_{16}NO_3S$ requires M$^+$ 254.0845, found MNa$^+$ 276.0666, $C_{12}H_{15}NO_3SNa$ requires M$^+$ 276.0665.

N-(tert-Butyloxycarbonyl)piperidin-2-one



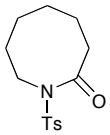
To a solution of δ-valerolactam (4.96 g, 50 mmol, 1.0 eq) in THF (100 ml) was added 4-dimethylaminopyridine (7.33 g, 60 mmol, 1.2 eq) and di-*tert*-butyldicarbonate (13.10 g, 60 mmol, 1.2 eq). The resulting mixture was stirred at room temperature for 18 h. The mixture was concentrated and the aqueous extracted with EtOAc (x 3). The combined organic phases were washed with 5% $HCl_{(aq)}$, brine then dried over $MgSO_4$ and concentrated affording the title compound as a colourless oil (8.55 g, 86%). R_f (EtOAc): 0.7. Found; C, 59.33; H, 8.40; N, 6.89%; Calc. for $C_{10}H_{17}NO_3$; C, 60.28; H, 8.60; N, 7.03%. ν_{max} (NaCl) 2977, 2947, 2879, 1773, 1732, 1480, 1459, 1392, 1243, 1134, 1057, 981, 853, 776, 660, 617 and 556 cm^{-1}. δ_H (400 MHz) 1.51 (9H, s, (C*H*$_3$)$_3$C), 1.81 (4H, m, 4-*H*$_2$, 5-*H*$_2$), 2.50 (2H, t, J = 6 Hz, 3-*H*$_2$), 3.64 (2H, t, J = 6 Hz, 6-*H*$_2$). δ_C (100 MHz) 20.6 (*C*-4), 22.9 (*C*-5), 28.1 (*C*H$_3$)$_3$C), 35.0 (*C*-3), 46.4 (*C*-6), 83.0 ((CH$_3$)$_3$*C*), 152.9 (O*C*=O), 171.5 (*C*-2). *mlz* (ES$^+$) 222.1 (MNa$^+$).

N-(Phenyloxycarbonyl)piperidin-2-one



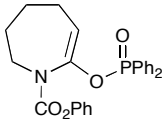
Obtained, following flash chromatography ([19:1] DCM/EtOAc) followed by recrystallisation ([10:1] pet. ether/EtOAc), as a white solid (2.94 g, 13.42 mmol, 56%). mp. 114-116 °C. Found; C, 65.49; H, 5.99; N, 6.18%; Calc. for $C_{12}H_{13}NO_3$; C, 65.74; H, 5.98; N, 6.39%. ν_{max} (KBr) 3007, 2961, 1780 (C=O), 1714 (C=O), 1417, 1356, 1226, 1149, 824 cm^{-1}. δ_H (500 MHz) 1.93 (4H, m, 4-*H*$_2$, 5-*H*$_2$), 2.63 (2H, t, J = 6 Hz, 3-*H*$_2$), 3.87 (2H, t, J = 6 Hz, 6-*H*$_2$), 7.20 (2H, d, J = 8 Hz, 2'-*H*$_2$), 7.26 (1H, t, J = 8 Hz, 4'-*H*$_2$), 7.40 (2H, t, J = 8 Hz, 3'-*H*$_2$). δ_C (125 MHz) 20.8 (*C*-4), 22.9 (*C*-5), 35.3 (*C*-3), 47.2 (*C*-6), 121.7 (*C*-2'), 126.3 (*C*-4'), 129.7 (*C*-3'), 151.0 (*C*-1'), 153.3 (O*C*=O), 171.5 (*C*-2). *m/z* (ES^+) 220.1 (MH^+), 461.1 ($2MNa^+$).

N-[(4'-methylphenyl)sulfonyl]-2-oxoazocine



Obtained, following flash chromatography ([7:3] pet. ether/EtOAc), as a white solid (3.46 g, 12.30 mmol, 80%). mp 116-118 °C. Found; C, 59.64; H, 6.82; N, 4.79%; Calc. for $C_{14}H_{19}NO_3S$; C, 59.76; H, 6.81; N, 4.98%. ν_{max} (KBr) 2938, 1687 (C=O), 1448, 1358 (NSO_2), 1211, 1167 (NSO_2), 1119, 1083, 814, 683, 634, 542 cm^{-1}. δ_H (500 MHz) 1.46 (2H, qt, J = 6 Hz, 6-*H*$_2$), 1.54 (2H, qt, J = 6 Hz, 5-*H*$_2$), 1.75 (2H, qt, J = 6 Hz, 4-*H*$_2$), 1.87 (2H, qt, J = 6 Hz, 7-*H*$_2$), 2.41 (3H, s, 4'-C*H*$_3$), 2.48 (2H, m, 3-*H*$_2$), 4.06 (2H, t, J = 6 Hz, 8-*H*$_2$), 7.28 (2H, d, J = 9 Hz, 3'-*H*, 5'-*H*), 7.90 (2H, d, J = 9 Hz, 2'-*H*, 6'-*H*). δ_C (125 MHz) 21.9 (4'-*C*H_3), 23.9 (*C*-6), 26.3 (*C*-5), 28.7 (*C*-4), 31.3 (*C*-7), 36.6 (*C*-3), 46.3 (*C*-8), 129.2, 129.4 (*C*-2', *C*-3'), 136.6 (*C*-1'), 144.8 (*C*-4'), 175.1 (*C*O). *m/z* (ES^+) 282.1 (MH^+).

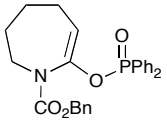
N-(Phenyloxycarbonyl)-4,5,6,7-tetrahydro-1H-azepin-2-yl diphenylphosphinate **3b**



NaHMDS Protocol: Purification by flash chromatography afforded the title compound as a white crystalline solid (1.74 g, 4.02 mmol, 79%). mp. 84-85 °C. Found; C, 69.29; H, 5.57; N, 3.12%; Calc. for $C_{25}H_{24}NO_4P$; C, 69.28; H, 5.58; N, 3.23%. ν_{max} (KBr) 3071,

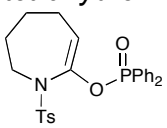
2925, 1724 (C=O), 1685 (enol ether), 1441, 1375, 1351, 1322, 1197, 1126, 1093, 1057, 993, 871 cm^{-1}. δ_H (700 MHz) 1.35-1.6 (2H, broad, 5-*H*$_2$), 1.63-1.80 (2H, broad, 6-*H*$_2$), 2.08 (2H, m, 4-*H*$_2$), 3.10-3.60 (2H, broad, 7-*H*), 5.39-5.59 (1H, m, 3-*H*), 7.05 (2H, d, J = 8 Hz, 2''-*H*), 7.19 (1H, t, J = 8 Hz, 4''-*H*), 7.33 (2H, m, 3''-*H*), 7.42 (4H, m, 3'-*H*), 7.51 (2H, t, J = 7 Hz, 4'-*H*), 7.79-7.99 (4H, m, 2'-*H*). δ_C (175 MHz) 24.2 (*C*-5), 24.8 (*C*-4), 29.3 (*C*-6), 47.3 (*C*-7), 110.8 (*C*-3), 121.7 (*C*-2''), 125.7 (*C*-4''), 128.7, 128.8 (*C*-3'), 129.5 (*C*-3''), 131.0 (*C*-1'), and 131.9, 132.0 (*C*-2'), 132.7 (*C*-4'), 144.5 (*C*-2), 151.4 (*C*-1''), 152.6 (*C*=O). δ_P (283 MHz) 29.4. *m/z* (ES^+) 433.5 (MH^+). HRMS (ES^+) found MH^+ 434.1515, $C_{25}H_{25}NO_4P$ requires M^+ 434.1515, found MNa^+ 456.1332, $C_{25}H_{24}NNaO_4P$ requires M^+ 456.1335.

N-(Benzyloxycarbonyl)-4,5,6,7-tetrahydro-1H-azepin-2-yl diphenylphosphinate **3c**



NaHMDS Protocol for phosphinate formation: Purification by flash chromatography ([4:1] DCM/EtOAc) and recrystallisation ([9:1] pet. ether/EtOAc) afforded the title compound as a crystalline solid (1.13 g, 2.53 mmol, 58%). mp. 83-85 °C. Found; C, 69.55; H, 5.81; N, 3.18%; Calc. for $C_{26}H_{26}NO_4P$; C, 69.79; H, 5.86; N, 3.13%. ν_{max} (ATR) 2936, 1701 (C=O), 1672 (enol ether), 1441, 1395, 1345, 1327, 1285, 1241, 1168, 1121, 1057, 1016, 886, 763, 728, 694 cm^{-1}. δ_H (700 MHz) 1.29-1.55 (2H, broad, 5-*H*$_2$), 1.61 (2H, m, 6-*H*$_2$), 1.98 (2H, m, 4-*H*$_2$), 3.00-3.20 (2H, broad, 7-*H*$_2$), 5.00-5.20 (2H, m, OC*H*$_2$), 5.39-5.51 (1H, m, 3-*H*), 7.25-7.45 (9H, m, 9 x Ar-*H*), 7.49 (2H, t, J = 7 Hz, 4'-*H*), 7.63-7.97 (4H, m, 4 x Ar-*H*). δ_C (176 MHz) 24.2 (*C*-5), 24.7 (*C*-4), 29.4 (*C*-6), 47.1 (*C*-7), 67.6 (O*C*H$_2$), 110.9 (*C*-3), 128.2, 128.3, 128.6, 128.7 and 132.0 (Ar*C*), 132.5 (*C*-4'), 136.5 (*C*-1'), 144.2 (*C*-2), 151.3 (*C*-1''), 154.1 (*C*=O). δ_P (283 MHz) 29.0. *m/z* (ES^+) 448.3 (MH^+), 917.3 ($2MNa^+$).

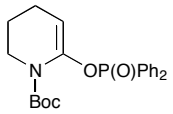
N-[(4''-Methylphenyl)-sulfonyl]-4,5,6,7-tetrahydro-1H-azepin-2-yl diphenylphosphinate **3d**



NaHMDS Protocol: The crude material was collected as a yellow soild. Purification on a Horizon® column chromatography system ([19:1], [9:1] pet. ether/EtOAc) afforded the title compound as a white solid (0.80 g, 1.71 mmol, 73%). ν_{max} (KBr) 3056, 2947, 2914, 2848, 1672, 1595, 1440, 1343, 1230, 1160, 1031, 993, 953, 869 cm^{-1}. δ_H (400 MHz)

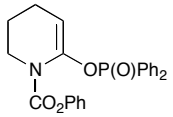
1.34 (2H, quint, J = 6 Hz, 5-*H*$_2$), 1.65 (2H, quint, J = 6 Hz, 6-*H*$_2$), 1.85 (2H, q, J = 6 Hz, 4-*H*$_2$), 2.35 (3H, s, 4''-C*H*$_3$), 3.19 (2H, m, 7-*H*$_2$), 5.52 (1H, dt, J_P = 2 Hz, J_H = 8 Hz, 3-*H*), 7.07 (2H, d, J = 8 Hz, 3''-*H*, 5''-*H*), 7.41-7.47 (4H, m, Ar-*H*), 7.52-7.57 (2H, m, 4'-*H*), 7.67 (2H, d, J = 8 Hz, 2''-*H*, 6''-*H*), 7.78-7.86 (4H, m, Ar-*H*). δ_C (100 MHz) 21.9 (4''-*C*H$_3$), 24.1 (*C*-5), 24.4 (*C*-4), 30.1 (*C*-6), 49.6 (*C*-7), 113.6 (*C*-3), 127.7 (*C*-2''), 128.8 (Ar*C*-H) 129.9 (*C*-3''), 130.3 (Ar*C*), 131.6 (Ar*C*), 132.4 (Ar*C*H), 132.8 (*C*-4'), 138.4 (Ar*C*), 143.9 (*C*-2). δ_P (162MHz,) 33.0. *m/z* (ES^+) 468.2 (MH^+), 490.3 (MNa^+), 956.8 ($2MNa^+$). HRMS (ES) found MH^+ 468.1398, $C_{25}H_{27}N_1O_4S_1P_1$ requires M^+ 468.1393, found MNa^+ 490.1214, $C_{25}H_{26}N_1O_4S_1P_1Na_1$ requires M^+ 490.1212.

1-(tert-Butyloxycarbonyl)-4,5,6-trihydro-piperidin-2-diphenylphosphinate **3e**



To a cold (-78 °C) solution of *N-(tert-Butyloxycarbonyl)piperidin-2-one* (2.23 g, 11.2 mmol, 1.0 eq) and TMEDA (1.86 ml, 12.32 mmol, 1.1 eq) in dry THF (50 ml) was added a solution of LDA (2.0 M, 6.16 ml, 12.32 mmol, 1.1 eq). The reaction mixture was stirred at -78 °C for 1 h, and diphenylphosphinic chloride (2.35 ml, 12.32 mmol, 1.1 eq) was added dropwise. The mixture was stirred at -78 °C for 1 h, and room temperature for a further 18 h. The solution was concentrated and extracted with EtOAc/brine, the organic phase was combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography ([1:1] pet. ether/EtOAc) afforded the title compound as white solid (3.987 g, 89%). R_f (EtOAc): 0.70. mp. 122 °C. ν_{max} (KBr) 3050, 2947, 1769, 1704, 1675, 1591, 1439, 1367, 1247, 1130, 953, 730, 700, 537, 524 and 436 cm^{-1}. This compound rapidly decomposed in $CDCl_3$, CD_3OD and *d*^{6}-DMSO.

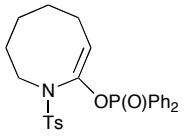
1-(Phenyloxycarbonyl)-4,5,6-trihydro-piperidin-2-diphenylphosphinate **3f**



Obtained, following flash chromatography, ([9:1] DCM/EtOAc) as a clear oil which solidified on standing (1.27 g, 3.03 mmol, 61%). mp. 97-100 °C. Found; C, 68.61; H, 5.50; N, 3.31%; Calc. for $C_{24}H_{22}NO_4P$; C, 68.73; H, 5.29; N, 3.34%. ν_{max} (KBr) 3063, 2955, 1731 (C=O), 1677 (enol ether), 1439, 1364, 1345, 1207, 1175, 1131, 837, 545, 531 cm^{-1}. δ_H (400 MHz) 1.75 (2H, quint, J = 6 Hz, 5-*H*$_2$), 2.12 (2H, m, 4-*H*$_2$), 3.49 (2H, t, J = 6 Hz, 6-*H*$_2$), 5.23 (1H, dt, $^4J_{HP}$ = 2 Hz, J = 6 Hz, 3-*H*), 7.09 (2H, dd, ^{4}J = 1 Hz,

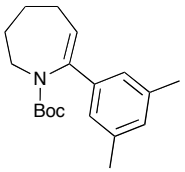
J = 8 Hz, 3''-*H*, 5''-*H*), 7.22 (1H, t, ^{4}J = 1 Hz, J = 8 Hz, 4''-H), 7.31-7.43 (6H, m, 6 x Ar-*H*), 7.50 (2H, tq, J = 8 Hz, ^{4}J = 2 Hz, 4'-*H*), 7.86-7.93 (4H, m, 3'-*H*, 5'-*H*). δ_C (100 MHz) 21.8 (*C*-5), 23.0 (*C*-4), 46.0 (*C*-6), 101.1 (*C*-3), 121.8 (*C*-3''), 125.9(*C*-4''), 128.6 (Ar*C*), 128.8 (Ar*C*), 129.6 (*C*-2''), 130.2 (*C*-2), 132.1, 132.2 (*C*-3' and *C*-5'), 132.65, 132.68 (2 x *C*-4'), 139.7, 139.8 (2 x *C*-1'), 151.2 (*C*-1''), 152.5 (*C*=O). δ_P (162 MHz) 31.1. *m/z* (ES$^+$) 420.1 (MH$^+$), 442.1 (MNa$^+$), 861.3 (2MNa$^+$).

1-Tosyl-4,5,6,7,8-quintahydro-1H-azepin-2-yl diphenylphosphinate **3g**



Obtained, following column chromatography, ([95:5], [9:1] $CHCl_3$/EtOAc) as a gummy oil which slowly solidified on standing (874 mg, 1.82 mmol, 51%). mp. 199-200 °C. HPLC, R_t = 6.02min, 98.13%. ν_{max} (KBr) 2928, 2851, 1671, 1593, 1440, 1348, 1235, 1156, 1126, 1076, 1006, 961, 874, 829, 730 cm^{-1}. δ_H (400 MHz) 1.43-1.60 (6H, m, 5-H_2, 6-H_2, 7-H_2), 2.13 (2H, m, 4-H_2), 2.36 (3H, s, 4''-CH_3), 3.31 (2H, m, 8-H_2), 5.54 (1H, dt, $^4J_{HP}$ = 2 Hz, J = 8 Hz, 3-*H*), 7.09 (2H, d, J = 8 Hz, 3''-*H*, 5''-*H*), 7.38-7.45 (4H, m, Ar-*H*), 7.51-7.57 (2H, m, 4'-*H*), 7.63-7.70 (4H, m, Ar-*H*), 7.73 (2H, d, J = 8 Hz, 2''-*H*, 6''-*H*). δ_C (100 MHz) 21.9 (4''-*C*H$_3$), 26.2 (*C*-4), 26.9 (*C*-6), 27.2 (*C*-7), 28.8 (*C*-5), 50.3 (*C*-8), 119.3 (*C*-3), 128.1 (*C*-2''), 128.8 (Ar*C*-H), 129.8 (*C*-3''), 130.5 (Ar*C*), 132.1 (Ar*C*-H), 132.8 (*C*-4'), 137.7 (Ar*C*), 138.4 (Ar*C*), 143.6 (*C*-2). δ_P (162 MHz) 32.4. *m/z* (ES$^+$) 482.1 (MH$^+$), 980.4 (2MH$_2$O$^+$). HRMS (ES$^+$) found MH$^+$ 482.1554, $C_{26}H_{29}N_1O_4S_1P_1$ requires M$^+$ 482.1550, found MNa$^+$ 504.1367, $C_{26}H_{28}N_1O_4S_1P_1Na_1$ requires M$^+$ 504.1369.

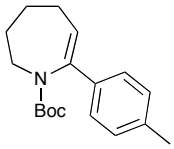
N-(tert-Butyloxycarbonyl-2-(3',5'-Dimethylphenyl)-4,5,6,7-tetrahydro-azepane **5a-i**



Suzuki protocol A: Flash chromatography ([19:1] pet. ether/EtOAc) afforded the title compound as a white solid (83%). mp. 113-115 °C. G.C. analysis: 1 peak, R_t 22.35 min. ν_{max} (KBr) 2933, 1687 (C=O), 1391, 1357, 1161 cm^{-1}. δ_H (500 MHz) 1.10 (9H, s, C(CH_3)$_3$), 1.47 (2H, m, 7-H_2), 1.79-1.89 (2H, m, 6-H_2), 2.21-2.33 (10H, m, 3'-CH_3, 5'-CH_3, 4-H_2, 5-H_2), 5.85 (1H, t, J = 7 Hz, 3-*H*), 6.88 (1H, s, Ar-*H*), 6.92 (2H, s, Ar-*H*). δ_C (125 MHz) 21.5 (*C*-5), 24.4 (*C*-3', *C*-5'), 27.7 (*C*-4), 28.2 ((C(*C*H$_3$)$_3$), 28.7 (*C*-6), 48.2 (*C*-

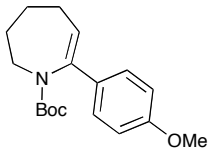
7), 79.9 (*C*(CH_3)$_3$), 122.8 (*C*-3), 123.1 (*C*-2'), 129.0 (*C*-4'), 137.7 (*C*-3'), 139.8 (*C*-2), 144.8 (*C*-1'), 153.9 (*C*=O). *m/z* (ES^+) 365 ($MNaMeCN^+$), 302 (MH^+), 246 (MH - $^tBu^+$). HRMS (ES^+) found MNa^+ 324.1934, $C_{19}H_{27}NO_2$ requires M^+ 324.1932.

N-tert-Butyloxycarbonyl-2-(4'-methylphenyl)-4,5,6,7-tetrahydro-azepane **5a-ii**



Suzuki protocol A: Purification by flash chromatography ([19:1] pet. ether/EtOAc) afforded the title compound as a white solid (0.07 g, 0.24 mmol, 81%). mp. 95-97 °C. Found; C, 75.15; H, 8.88; N, 4.87%; Calc. for $C_{18}H_{25}NO_2$; C, 75.22; H, 8.77; N, 4.87%. ν_{max} (KBr) 2979, 2933, 2856 (C-H), 1687 (C=O), 1392, 1357, 1160, 813 cm^{-1}. δ_H (400 MHz) 1.10 (9H, s, C(CH_3)$_3$), 1.46 (4H, s, 5-H_2, 7-H_2), 1.83 (2H, m, 6-H_2), 2.27 (2H, m, 4-H_2), 2.33 (3H, s, 4'-CH_3), 5.83 (1H, t, J = 7 Hz, 3-*H*), 7.09 (2H, d, J = 9 Hz, 3'-*H*), 7.19 (2H, d, J = 9 Hz, 2'-*H*). δ_C (100 MHz) 21.4 (4'-*C*H_3), 24.5 (*C*-5), 27.7 (*C*-4), 28.2 ((C(*C*H_3)$_3$), 30.0 (*C*-6), 48.1 (*C*-7), 79.9 (*C*(CH_3)$_3$), 121.9 (*C*-3), 125.0 (*C*-2'), 128.9 (*C*-3'), 137.0 (*C*-1'), 137.2 (*C*-4'), 144.6 (*C*-2), 154.6 (*C*=O). *m/z* (ES^+) 311 (MH^+), 351 ($MNaMeCN^+$), 597 ($2MNa^+$). HRMS (ES^+) found MNa^+ 310.1776, $C_{18}H_{25}NO_2Na$ requires M^+ 310.1777.

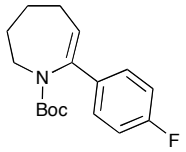
N-tert-Butyloxycarbonyl-2-(4'-Methoxyphenyl)-4,5,6,7-tetrahydro-azepane **5a-iii**



Suzuki protocol A: Purification on a Horizon® column chromatography system ([9:1] pet. ether/EtOAc) afforded the title compound as a white solid (0.06 g, 0.19 mmol, 99%).
Suzuki protocol B: Title compound isolated as a white solid (90%). mp. 72-74 °C. Found; C, 71.22; H, 8.35; N, 4.64%; Calc. for $C_{18}H_{23}NO_3$; C, 71.26; H, 8.31; N, 4.62%. ν_{max} (KBr) 2935 (C-H), 1687 (C=O), 1509, 1392, 1357, 1248, 1160 cm^{-1}. δ_H (500 MHz) 1.11 (9H, s, C(CH_3)$_3$), 1.46 (4H, m, 5-H_2, 7-H_2), 1.81 (2H, m, 6-H_2), 2.28 (2H, m, 4-H_2), 3.80 (3H, s, O-CH_3), 5.76 (1H, t, J = 6 Hz, 3-*H*), 6.82 (2H, d, J = 9 Hz, 2'-*H*, 6'-*H*), 7.25 (2H, d, J = 9 Hz, 3'-*H*, 5'-*H*). δ_C (125 MHz) 24.5 (*C*-5), 27.6 (*C*-4), 28.2 ((C(*C*H_3)$_3$), 30.0 (*C*-6),

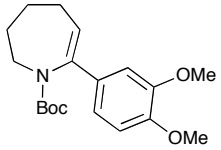
48.1 (*C*-7), 55.6 (O-*C*H_3), 79.8 (*C*$(CH_3)_3$), 113.6 (*C*-2'), 121.1 (*C*-3), 126.3 (*C*-3'), 132.6 (*C*-2), 144.3 (*C*-1'), 154.4 (*C*=O), 159.2 (*C*-4'). *m/z* (ES^+) 629 ($2MNa^+$).

N-tert-Butyloxycarbonyl-2-(4'-fluorophenyl)-4,5,6,7-tetrahydro-azepane **5a-iv**



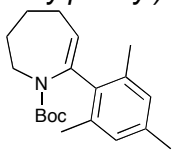
Suzuki protocol B: White solid (89%). R_f (19:1 pet. ether/EtOAc): 0.30. mp. 68 °C. Found; C, 70.31; H, 7.68; N, 4.84%: Calc. for $C_{17}H_{22}FNO_2$; C, 70.08; H, 7.61; N, 4.81%. v_{max} (KBr) 3041, 3016, 2983, 2934, 2846, 1714, 1694, 1644, 1504, 1434, 1352, 1296, 1147, 1015, 922, 893, 820 and 589 cm^{-1}. δ_H (400 MHz) 1.03 (9H, s, (C*H*$_3$)$_3$C), 1.39 (2H, br, 5-*H*$_2$), 1.77 (2H, m, 6-*H*$_2$), 2.20 (2H, m, 4-*H*$_2$), 2.80-4.40 (2H, br, 7-*H*$_2$), 5.72 (1H, t, J = 6.5 Hz, 3-*H*), 6.90 (2H, m, 3'-*H*, 5'-*H*), 7.20 (2H, m, 2'-*H*, 6'-*H*). δ_C (100 MHz) 24.2 (*C*-4), 27.6 (*C*-5), 28.1 ((*C*H$_3$)$_3$C), 29.7 (*C*-6), 48.1 (*C*-7), 80.0 ((CH$_3$)$_3$*C*), 114.9 and 115.1 (*C*-3' and *C*-5'), 122.4 (*C*-3), 126.6 & 126.7 (*C*-2' and *C*-6'), 136.1 (*C*-1'), 143.7 (*C*-2), 154.1 (O-*C*=O), 161.1 (*C*-4'). *mlz* (ES^+) 314.0 (MNa^+).

N-tert-Butyloxycarbonyl-2-(3',4'-dimethoxyphenyl)-4,5,6,7-tetrahydro-azepane **5a-v**



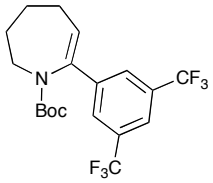
Suzuki protocol A: Flash chromatography ([4:1] pet. ether/EtOAc) afforded the title compound as a white solid (0.08 g, 0.24 mmol, 81%). mp. 95-97 °C. Found; C, 68.42; H, 8.26; N, 3.95%; Calc. for $C_{19}H_{27}NO_4$; C, 68.44; H, 8.16; N, 4.20%. v_{max} (KBr) 2936, 1688 (C=O), 1515, 1266, 1249, 1160 (C-O-C), 1140, 1027 cm^{-1}. δ_H (400 MHz) 1.12 (9H, s, C(C*H*$_3$)$_3$), 1.46 (4H, s, 5-*H*$_2$, 7-*H*$_2$), 1.83 (2H, m, 6-*H*$_2$), 2.27 (2H, m, 4-*H*$_2$), 3.87 (6H, m, 3'-OC*H*$_3$, 4'-OC*H*$_3$), 5.78 (1H, t, J = 7 Hz, 3-*H*), 6.78-6.95 (3H, m, 3 x Ar-*H*). δ_C (100 MHz) 24.4 (*C*H$_2$), 27.5 (*C*-4), 28.2 (C(*C*H$_3$)$_3$), 29.9 (*C*H$_2$), 48.2 (*C*-7), 56.1 and 56.2 (3'-O*C*H$_3$, 4'-O*C*H$_3$), 79.9 (*C*(CH$_3$)$_3$), 108.5, 110.9 and 117.6 (3 x Ar*C*-H), 121.3 (*C*-3), 133.1 (*C*-2), 144.4 (*C*-1'), 148.8 and 148.9 (*C*-OMe), 154.4 (*C*=O). *m/z* (ES^+) 688 ($2MNa^+$), 397 ($MNaMeCN^+$), 334 (MH^+), 278 (MH – ^{t}Bu$^+$).

N-tert-Butyloxycarbonyl-2-(2',4',6'-trimethylphenyl)-4,5,6,7-tetrahydro-azepane **5a-vi**



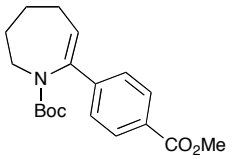
Suzuki protocol A: Purification on a Horizon® column chromatography system ([19:1] pet. ether/EtOAc) afforded the title compound as a white solid (0.12 mmol, 36%) and recovered starting material (0.02 g, isolated yield = 63%). mp. 56-58 °C. Found; C, 76.07; H, 9.39; N, 4.53%; Calc. for $C_{20}H_{29}NO_2$; C, 76.15; H, 9.27; N, 4.44%. ν_{max} (KBr) 2933 (C-H), 1681 (C=O), 1392, 1367, 1161, 853 cm^{-1}. δ_H (400 MHz) 1.07 (9H, s, C(C*H*$_3$)$_3$), 1.72-1.80 (2H, m, 5-*H*$_2$), 1.81-1.90 (2H, m, 6-*H*$_2$), 2.22 (6H, s, 2'-C*H*$_3$, 5'-C*H*$_3$), 2.25 (3H, s, 4'-C*H*$_3$), 2.29-2.39 (2H, m, 4-*H*$_2$), 3.81 (2H, t, J = 6 Hz, 7-*H*$_2$), 5.04 (1H, t, J = 5 Hz, 3-*H*), 6.79 (2H, s, 3'-*H*, 5'-*H*). δ_C (100 MHz) 21.1 (4'-*C*H$_3$), 21.5 (2'-*C*H$_3$), 24.1 (*C*-5), 27.8 (*C*-4), 27.9 (*C*-6), 28.1 (C(*C*H$_3$)$_3$), 49.8 (*C*-7), 80.2 (*C*(CH$_3$)$_3$), 122.7 (*C*-3), 128.7 (*C*-3'), 136.2 (*C*-4'), 136.7 (*C*-2'), 137.5 (*C*-1'), 140.9 (*C*-2), 154.4 (*C*=O). *m/*z (ES-$^+$) 260 (MH - ^{t}Bu$^+$), 338 (MNa$^+$).

N-tert-Butyloxycarbonyl-2-(3',5'-bis[trifluoromethyl]phenyl)-4,5,6,7-tetrahydro-azepane **5a-vii**



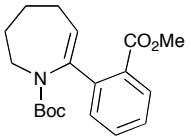
Suzuki protocol A: Purification on a Horizon® column chromatography system ([9:1] pet. ether/EtOAc) afforded the title compound as a white solid (0.09 g, 0.21 mmol, 87%). mp. 52-54 °C. Found; C, 55.79; H, 5.30; N, 3.29%: Calc. for $C_{19}H_{21}NO_2F_6$; C, 55.75; H, 5.17; N, 3.42%. ν_{max} (KBr) 3019, 2936 (C-H), 1697 (C=O), 1357, 1222, 1209, 1182, 1170, 1020, 986, 901, 846, 794, 669 cm^{-1}. δ_H (500 MHz) 1.07 (9H, s, C(C*H*$_3$)$_3$), 1.46 (2H, m, 7-*H*$_2$), 1.60 (2H, broad, 5-*H*$_2$), 1.88 (2H, m, 6-*H*$_2$), 2.35 (2H, m, 4-*H*$_2$), 5.98 (0.79H, t, J = 7 Hz, 3-*H*), 6.17 (0.21H, t, J = 7 Hz, 3-*H*) 7,72 (2H, s, 2'-*H*), 7.75 (1H, s, 4'-*H*). δ_C (125MHz) 23.9 (*C*-5), 27.95 (*C*-4), 27.99 (C(*C*H$_3$)$_3$), 29.4 (*C*-6), 48.5 (*C*-7), 80.7 (*C*(CH$_3$)$_3$), 120.8 (*C*-4'), 122.5 (*C*-3'), 125.4 (*C*-2'), 125.9 (*C*-3), 131.4-132.2 (2 x *C*F$_3$, q, J = 33 Hz), 142.3 (*C*-2), 142.7 (*C*-1'), 153.58 (*C*=O). HRMS (ES$^+$) found MNa$^+$ 432.1369, $C_{19}H_{21}NO_2F_6Na$ requires 432.1368.

N-tert-Butyloxycarbonyl-2-(4'-Methoxycarbonylphenyl)-4,5,6,7-tetrahydro-azepane **5a-viii**



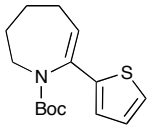
Suzuki protocol A: Purification on a Horizon® column chromatography system ([85:15] DCM/EtOAc) afforded the title compound as a white solid (0.06 g, 0.17 mmol, 72%). mp. 102-104 °C. ν_{max} (KBr) 3019, 2936, 1715 (C=O), 1694 (C=O), 1608, 1437, 1280, 1223, 1209, 795, 669 cm^{-1}. δ_H (500 MHz) 1.06 (9H, s, C(*CH*$_3$*)*$_3$), 1.44 (2H, s, 7-*H*$_2$), 1.59 (2H, broad, 5-*H*$_2$), 1.84 (2H, m, 6-*H*$_2$), 2.30 (2H, m, 4-*H*$_2$), 3.89 (3H, s, O-C*H*$_3$), 5.96 (1H, t, J = 7 Hz, 3-*H*), 7.35 (2H, d, J = 9 Hz, 2'-*H*), 7.95 (2H, d, J = 9 Hz, 3'-*H*). δ_C (125MHz) 24.2 (*C*-5), 27.9 (*C*-4), 28.2 (C(*C*H$_3$)$_3$), 29.8 (*C*-6), 48.1 (*C*-7), 52.3 (O-*C*H$_3$), 80.3 (*C*(CH$_3$)$_3$), 125.0 (*C*-3), 125.1 (*C*-2'), 129.0 (*C*-1'), 129.8 (*C*-3'), 143.9 (*C*-2), 144.6 (*C*-4'), 154.0 (N*C*=O), 167.2 (Ar*C*=O). HRMS (ES$^+$) found MNa$^+$ 354.1677, $C_{19}H_{25}NNaO_4$ requires M$^+$ 354.1676.

N-tert-Butyloxycarbonyl-2-(2'-Methoxycarbonylphenyl)-4,5,6,7-tetrahydro-azepane **5a-ix**



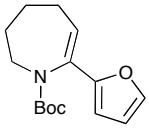
Suzuki protocol A: Stirred for 18 h at 85 °C. Purification by flash chromatography ([95:5], [6:4], [100:0] pet.ether/EtOAc) afforded the title compound as a white solid (0.60 mmol, 32%) and recovered starting material (0.19 mmol, 10%). The desired product contained a small amount of impurity due to homo coupled boronic acid which could not be removed, approx 8% by ^{1}H NMR analysis. δ_H (700 MHz) 1.02 (9H, s, C(C*H*$_3$)$_3$), 1.66 (2H, m, 5-*H*$_2$), 1.83 (2H, quint, J = 8 Hz, 6-*H*$_2$), 2.33 (2H, q, J = 8 Hz, 4-*H*$_2$), 3.64 (2H, broad, 7-*H*$_2$), 3.85 (3H, s, O-C*H*$_3$), 5.57 (1H, t, J = 8 Hz, 3-*H*), 7.27 (1H, m, 4'-*H*), 7.32-7.40 (2H, m, 5'-*H*, 6'-*H*), 7.42 (1H, m, 3'-*H*). δ_C (176MHz) 23.9 (*C*-5), 27.9 (*C*-6), 28.0 (C(*C*H$_3$)$_3$), 28.3 (*C*-4), 49.8 (*C*-7), 52.4 (O-*C*H$_3$), 80.2 ((*C*(CH$_3$)$_3$), 123.0 (*C*-3), 127.1 (*C*-4'), 128.1 (*C*-3'), 129.8 (Ar*C*-H), 130.5 (Ar*C*-H), 130.7 (*C*-2'), 140.7 (*C*-1'), 143.5 (*C*-2), 153.8 (N*C*=O), 170.1 (Ar*C*=O). *m/z* (ES$^+$) 232.1 (M – Boc$^+$), 332.1 (MH$^+$), 354.1 (MNa$^+$), 685.3 (2MNa$^+$). HRMS (ES$^+$) found MH$^+$ 332.1859, $C_{19}H_{26}NO_4$ requires M$^+$ 322.1856, found MNa$^+$ 354.1674, $C_{19}H_{25}NO_4Na$ requires M$^+$ 354.1676.

N-tert-Butyloxycarbonyl-2-Thiophen-2-yl-4,5,6,7-tetrahydro-azepane **5a-x**



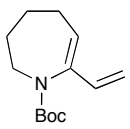
Suzuki protocol A: Purification by flash chromatography ([19:1] pet.ether/EtOAc, [4:1] DCM/EtOAc) afforded the title compound as a white solid (0.19 mmol, 38%) and recovered starting material (0.22 mmol, 44%). mp. 88-90 °C. ν_{max} (KBr) 2979, 2936, 1691 (C=O), 1388, 1367, 1255, 1163 cm^{-1}. δ_H (500 MHz) 1.40 (13H, m, 2 x C*H*$_2$, (C*H*$_3$)$_3$), 1.54 (2H, m, C*H*$_2$), 2.08 (2H, m, 4-*H*$_2$), 5.87 (1H, t, J = 7 Hz, 3-*H*), 6.81 (1H, m, 4'-*H*), 6.87 (1H, m, Ar-*H*), 6.97 (1H, m, Ar-*H*). δ_C (125 MHz) 24.3 (*C*-5), 27.4 (*C*-4), 28.0 (C(*C*H$_3$)$_3$), 29.8 (*C*-6), 47.5 (*C*-7), 79.4 (*C*(CH$_3$)$_3$), 122.0 (*C*-3), 122.7, 123.6 (*C*-2', *C*-3'), 127.1 (*C*-4'), 139.6 (*C*-2), 144.7 (*C*-1'), 153.6 (*C*=O). *m/z* (ES^+) 279.8 (MH^+), 302.2 (MNa^+), 580.9 ($2MNa^+$). HRMS (ES^+) found MNa^+ 302.1185, $C_{15}H_{21}NNaO_2S$ requires M^+ 302.1185.

N-tert-Butyloxycarbonyl-2-furyl-2-yl-4,5,6,7-tetrahydro-azepane **5a-xi**



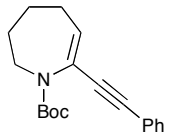
Suzuki protocol B: (90%). *Stille thermal protocol:* (89%). *Stille microwave protocol:* (91%). Pale yellow solid. R_f ([19:1] pet. ether/EtOAc): 0.3. mp. 89 °C (Lit. 87 °C). Found; C, 68.60; H, 8.11; N, 5.28%: Calc. for $C_{15}H_{21}NO_3$; C, 68.42; H, 8.04; N, 5.32%. ν_{max} (KBr) 2974, 2931, 2854, 1698, 1651, 1492, 1443, 1385, 1353, 1252, 1163, 1012, 966 and 730 cm^{-1}. δ_H (400 MHz) 1.26 (9H, s, (C*H*$_3$)$_3$C), 1.49 (2H, broad, 5-*H*$_2$), 1.80 (2H, m, 6-*H*$_2$), 2.25 (2H, m, 4-*H*$_2$), 2.70-4.30 (2H, broad, 7-*H*$_2$), 6.03 (1H, t, J = 7 Hz, 3-*H*), 6.17 (1H, d, J = 4 Hz, 2'-*H*), 6.34 (1H, m, 3'-*H*), 7.31 (1H, m, 4'-*H*). δ_C (100 MHz) 24.4 (C-4), 27.1 (C-5), 28.2 ((*C*H$_3$)$_3$C), 29.9 (C-6), 47.4 (C-7), 79.9 ((CH$_3$)$_3$*C*), 105.1 (C-3), 111.2 (C-2'), 121.5 (C-3'), 135.9 (C-2), 141.4 (C-4'), 153.0 (OC=O), 154.1 (C-1'). *mlz* (ES^+) 286.2 (MNa^+).

N-tert-Butyloxycarbonyl-2-vinyl-4,5,6,7-tetrahydro-azepane **5a-xii**



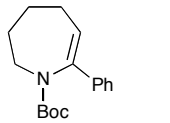
Stille thermal protocol: 82%. *Stille microwave protocol:* 85%. Colourless oil. R_f ([19:1] pet. ether/EtOAc): 0.30. Found; C, 69.11; H, 9.31; N, 6.09%: Calc. for $C_{13}H_{21}NO_2$; C, 69.92; H, 9.48; N, 6.27%. ν_{max} (NaCl) 3092, 2926, 2933, 2853, 1703, 1698, 1645, 1445, 1391, 1253, 1166, 985, 896 and 779 cm^{-1}. δ_H (400 MHz) 1.37 (9H, s, (C*H*$_3$)$_3$C), 1.47 (2H, br, 5-*H*$_2$), 1.78 (2H, quint, J = 6 Hz, 6-*H*$_2$), 2.15 (2H, m, 4-*H*$_2$), 2.90-3.70 (2H, br, 7-*H*$_2$), 4.95 (1H, d, J = 10 Hz), 5.07 (1H, d, J = 17 Hz), 5.67 (t, 1H, J = 7 Hz, 3-*H*), 6.18 (1H, dd, J = 17 Hz, J = 10 Hz). δ_C (100 MHz) 24.5 (*C*-4) 27.1 (*C*-5), 28.3 ((*C*H$_3$)$_3$C), 29.8 (*C*-6), 46.7 (*C*-7), 80.0 ((CH$_3$)$_3$*C*), 111.9 (*C*H$_2$=CH), 127.8 (*C*-3), 134.3 (CH$_2$=*C*H), 144.3 (*C*-2), 154.1 (O-*C*=O). *mlz* (ES^+) 246.0 (MNa^+).

N-tert-Butyloxycarbonyl-2-phenylethynyl-4,5,6,7-tetrahydro-azepane **5a-xiii**



Stille thermal protocol: 49%. *Stille microwave protocol:* 54%. Yellow solid. R_f ([19:1] pet. ether/EtOAc): 0.35. mp. 94 °C. Found; C, 76.23; H, 7.70; N, 4.65%: Calc. for $C_{19}H_{23}NO_2$; C, 76.73; H, 7.80; N, 4.71%. ν_{max} (KBr) 3061, 2976, 2937, 2922, 2860, 2843, 1694, 1627, 1593, 1487, 1385, 1279, 1170, 1015, 901, 860, 759, 694 and 527 cm^{-1}. δ_H (400 MHz) 1.48 (9H, s, (C*H*$_3$)$_3$C), 1.53 (2H, quint, J = 6 Hz, 5-*H*$_2$), 1.78 (2H, quint, J = 6 Hz, 6-*H*$_2$), 2.24 (2H, m, 4-*H*$_2$), 3.52 (2H, broad, 7-*H*$_2$), 6.02 (1H, t, J = 7 Hz, 3-*H*), 7.29 (3H, m, Ar-*H*), 7.41 (2H, m, Ar-*H*). δ_C (100 MHz) 23.9 (*C*-4), 27.9 (*C*-5), 28.5 ((*C*H$_3$)$_3$C), 29.7 (*C*-6), 47.4 (*C*-7), 80.5 ((CH$_3$)$_3$*C*), 86.5 (N-C=*C*), 87.8 (N-*C*=C), 123.4 (*C*), 127.6 (*C*), 128.2, 128.4, 131.4, 132.6 , 153.7 (O*C*=O). *mlz* (ES^+) 320.1 (MNa^+).

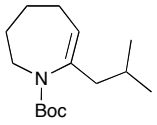
N-tert-Butyloxycarbonyl-2-phenyl-4,5,6,7-tetrahydro-azepane **5a-xiv**



Stille thermal protocol: 45%. *Stille microwave protocol:* 45%. *Stille thermal protocol:* ($PhSnMe_3$, 29%). White solid. R_f ([19:1] pet. ether/EtOAc): 0.35. mp. 85 °C (Lit. 83 °C). Found; C, 74.16; H, 8.47; N, 5.01%: Calc. for $C_{17}H_{23}NO_2$; C, 74.69; H, 8.48; N, 5.12%. ν_{max} (KBr) 3045, 2975, 2933, 2849, 1694, 1635, 1492, 1447, 1381, 1253, 1153, 1017, 892, 854, 763, 698 and 642 cm^{-1}. δ_H (400 MHz) 1.02 (9H, s, (C*H*$_3$)$_3$C), 1.47 (2H, broad, 5-*H*$_2$), 1.78 (2H, quint, J = 6 Hz, 6-*H*$_2$), 2.22 (2H, m, 4-*H*$_2$), 2.80-4.20 (2H, broad, 7-*H*$_2$),

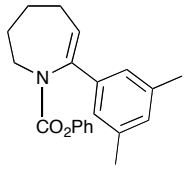
5.79 (1H, t, J = 7 Hz, 3-*H*), 7.15-7.25 (5H, m, Ar-*H*). δ_C (100 MHz) 24.3 (*C*-4), 27.6 (*C*-5), 28.0 ((*C*H_3)$_3$C), 29.8 (*C*-6), 40.1 (*C*-7), 79.8 ((CH$_3$)$_3$*C*), 122.6 (*C*-3), 125.1 (2*C*H), 127.3 (*C*H), 128.2 (2*C*H), 139.9 (*C*), 144.6 (*C*-2), 154.2 (O-*C*=O). *mlz* (ES$^+$) 296.0 (MNa$^+$).

N-tert-*Butyloxycarbonyl-2-iso-propyl-4,5,6,7-tetrahydro-azepane* **5a-xv**



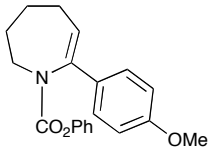
A suspension of **3a** (0.413 g, 1.0 mmol) and 1,2-bis(diphenylphosphino)ethane nickel(II) chloride (26.4 mg, 0.05 mmol) in 1:1 Et_2O/THF (18 ml) was degassed by purging Ar for 10 minutes before *iso*-propylmagnesium bromide (2.0 M solution in Et_2O, 0.75 ml, 1.5 mmol) was added. The mixture was stirred for 18h at rt. Water (0.5 ml) was added to quench the reaction, and the resulting solution was extracted by EtOAc/brine. The organic phase was combined, dried (MgSO4), filtered and evaporated. Rapid flash chromatography on silica (19:1 to 9:1 pet. Ether/EtOAc) gave the product as colourless oil (94 mg, 37%). Rf (19:1 pet. Ether/EtOAc): 0.50. Found; C, 70.76; H, 10.41; N, 5.64%: Calc. for $C_{15}H_{27}NO_2$; C, 71.10; H, 10.74; N, 5.53%. All signals in the NMR spectra were highly broadened and could not be resolved. ν_{max} (LF) 2931, 2807, 1703, 1654, 1388, 1162, 1012 and 770 cm^{-1}. *mlz* (ES+) 276.1 MNa$^+$.

N-Phenyloxycarbonyl-2-(3',5'-dimethylphenyl)-4,5,6,7-tetrahydro-azepane **5b-i**



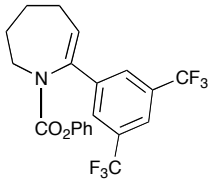
Suzuki protocol A: Purification by flash chromatography ([9:1], [1:1] pet.ether/EtOAc) afforded the title compound as a clear oil (69 mg, 0.21 mmol, 82%). ν_{max} (ATR) 2932, 1717 (C=O), 1382, 1352, 1196, 1170, 748, 688 cm^{-1}. δ_H (500 MHz) 1.97 (2H, m, CH_2), 2.34 (6H, m, Ar-CH_3), 2.42 (2H, q, J = 7 Hz, 4-H_2), 2.69 (1H, broad, 7-H*H*), 4.32-4.74 (1H, broad, 7-*H*H), 6.16 (1H, t, J = 7 Hz, 3-*H*), 6.75 (2H, d, J = 8 Hz, 2''-H_2), 6.96 (1H, s, 4'-*H*), 7.08 (2H, s, 2'-H_2), 7.11 (1H, t, J = 8 Hz, 4''-*H*), 7.24 (2H, t, J = 8 Hz, 3''-H_2). δ_C (125 MHz) 21.6 (Ar-*C*H$_3$), 24.4 (*C*-5 or 6), 27.6 (*C*-4), 30.0 (*C*-5 or 6), 48.9 (*C*-7), 121.9 (*C*-2''), 122.7 (*C*-2'), 124.1 (*C*-3), 125.4 (*C*-4''), 129.2 (*C*-3''), 129.7 (*C*-4'), 138.2 (*C*-3'), 138.3 (*C*-1'), 144.0 (*C*-2), 151.5 (*C*-1''), 153.7 (*C*=O). *m/z* (ES$^+$) 322.3 (MH$^+$), 339.3 (MH$_2$O$^+$) 665.6 (2MNa$^+$). HRMS (ES$^+$) found MNa$^+$ 344.1621, $C_{21}H_{23}NO_2Na$ requires M$^+$ 344.1621.

N-Phenyloxycarbonyl-2-(4'-methoxyphenyl)-4,5,6,7-tetrahydro-azepane **5b-ii**



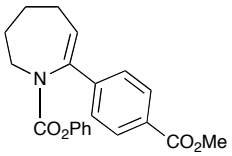
Suzuki protocol A: Purification by flash chromatography ([9:1] pet. ether/EtOAc) afforded the title compound as a crystalline solid (0.06 g, 0.19 mmol, 81%). mp. 92-94 °C. Found; C, 73.78; H, 6.50; N, 4.13%: Calc. for $C_{20}H_{21}NO_3$; C, 74.28; H, 6.55; N, 4.33%. ν_{max} (ATR) 2931, 1710 (C=O), 1641, 1608, 1512, 1384, 1353, 1252, 1197, 1175, 1034, 812, 731 cm^{-1}. δ_H (500 MHz) 1.69 (2H, m, 7-*H*$_2$), 1.91-2.07 (4H, m, 5-*H*$_2$, 6-*H*$_2$), 2.40 (2H, m, 4-*H*$_2$), 3.85 (3H, s, O-C*H*$_3$), 6.08 (1H, t, J = 6 Hz, 3-*H*), 6.78 (2H, m, 2 x Ar-*H*), 6.91 (2H, d, J = 9 Hz, 3'-*H*, 5'-*H*), 7.10 (1H, m, 4''-*H*), 7.22 (2H, m, 2 x Ar-*H*), 7.38 (2H, d, J = 9 Hz, 2'-*H*, 6'-*H*). δ_C (125MHz) 24.8 (*C*-5), 27.9 (*C*-4), 30.1 (*C*-6), 49.0 (*C*-7), 55.9 (O-*C*H_3), 114.1 (*C*-3'), 122.0 (Ar*C*), 123.0 (*C*-3), 125.2 (*C*-4''), 126.1 (*C*-2'), 129.7 (Ar*C*), 131.2 (*C*-1'), 143.7 (*C*-2), 151.8 (*C*-1''), 153.9 (*C*=O), 159.5 (*C*-4'). *m/z* (ES^+) 323.5 (MH^+). HRMS (ES^+) found MH^+ 324.1592, $C_{20}H_{22}NO_3$ requires M^+ 324.1594.

N-Phenyloxycarbonyl-2-(3',5'-bis[trifluoromethyl]phenyl)-4,5,6,7-tetrahydro-azepane **5b-vi**



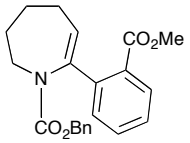
Suzuki protocol A: Purification by flash chromatography ([1:1] $CHCl_3$/pet. ether) afforded the title compound as a white solid (83 mg, 0.19 mmol, 69%). mp 111-113 °C. Found; C, 58.18; H, 3.99; N, 3.08%: Calc. for $C_{21}H_{17}NO_2F_6$; C, 58.74; H, 3.99; N, 3.26%. ν_{max} (ATR) 2948, 1712 (C=O), 1354, 1279, 1203, 1179, 1165, 1121, 1110, 978, 898, 754, 731, 683 cm^{-1}. δ_H (500 MHz) 1.59-1.90 (3H, broad, 5-*H*$_2$, 7-H*H*), 2.01 (2H, m, 6-*H*$_2$), 2.48 (2H, m, 4-*H*$_2$), 3.91 (1H, broad, 7-*H*H), 6.35 (1H, t, J = 7 Hz, 3-*H*), 6.74 (2H, d, J = 8 Hz, 2''-*H*, 6''-*H*), 7.13 (1H, t, J = 8 Hz, 4''-*H*), 7.25 (2H, t, J = 8 Hz, 3''-*H*, 5''-*H*), 7.08 (1H, s, 4'-*H*), 7.88 (2H, s, 2'-*H*, 6'-*H*). δ_C (125 MHz) 23.9 (*C*-5), 27.9 (*C*-4), 29.4 (*C*-6), 49.2 (*C*-7), 121.4 (*C*-2''), 121.7 (*C*-4'), 124.8 (*C*-2'), 125.8 (*C*-4''), 128.2 (*C*-3), 129.5 (*C*-3''), 129.6 (*C*-3'), 131.8-132.6 (2 x *C*F_3, q, J = 33 Hz), 140.8 (*C*-1'), 141.5 (*C*-2), 151.0 (*C*-1''), 153.1 (*C*=O). *m/z* (ES^+) 430.3 (MH^+) 447.3 (MH_2O^+) 493.3 ($MNaMeCN^+$), 881.5 ($2MNa^+$). HRMS (ES^+) found MH^+ 430.1237, $C_{21}H_{18}NO_2F_6$ requires 430.1236.

N-Phenyloxycarbonyl-2-(4'-carbomethoxyphenyl)-4,5,6,7-tetrahydro-azepane **5b-viii**



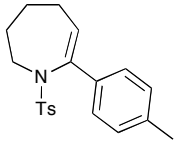
Suzuki protocol A: Purification by flash chromatography ([9:1] pet. ether/EtOAc) afforded the title compound as a clear oil (35 mg, 0.01 mmol, 37%). v_{max} (ATR) 2954, 1725 (C=O), 1710 (C=O), 1381, 1263, 1200, 1086, 767, 732, 688 cm^{-1}. δ_H (500 MHz) 1.75 (2H, quint, J = 6 Hz, 5-*H*$_2$), 1.92 (2H, quint, J = 6 Hz, *6*-*H*$_2$), 2.42 (2H, q, J = 6 Hz, 4-*H*$_2$), 3.76-3.94 (5H, m, 7-*H*$_2$, C*H*$_3$), 5.79 (1H, t, J = 6 Hz, 3-*H*$_2$), 6.64 (2H, d, J = 8 Hz, 2''-*H*, 6''*H*), 7.07 (1H, m, 4''-*H*), 7.19 (2H, t, J = 8 Hz, 3''-*H*, 5''-*H*), 7.30 (1H, t, J = 8 Hz, 4'-*H*), 7.39 (1H, t, J = 8Hz, 5'-*H*), 7.45 (1H, d, J = 8 Hz, 6'-*H*), 7.52 (1H, d, J = 8 Hz, 3'-*H*). δ_C (125 MHz) 23.9 (*C*-5), 28.2 (*C*-4), 28.3 (*C*-6), 50.7 (*C*-7), 52.6 (*C*H$_3$), 121.5 (*C*-2''), 125.0 (*C*-3), 125.4 (*C*-4''), 127.6 (*C*-4'), 128.4 (*C*-3'), 129.2 (*C*-3''), 129.8 (*C*-6'), 130.6 (*C*-2') 130.9 (*C*-5'), 139.6 (*C*-1'), 142.5 (*C*-2), 151.2 (*C*-1''), 153.2 (N*C*=O), 170.0 (*C*O$_2$Me). ***m/z*** (ES^+) 352.3 (MH^+), 374.3 (MNa^+), 415.3 ($MNaMeCN^+$), 725.5 ($2MNa^+$). HRMS (ES^+) found MNa^+ 374.1362, $C_{21}H_{21}NO_4Na$ requires 374.1363.

N-Benzyloxycarbonyl-2-(2'-methylbenzoate)-4,5,6,7-tetrahydro-azepane **5c-viii**



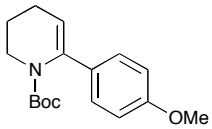
Suzuki protocol A (trifluoroborate salt): Reaction mixture stirred at 85 °C for 3 h. Purification by flash chromatography ([8:2], [6:4] pet. ether/EtOAc) afforded the title compound as a colourless oil (71 mg 0.20 mmol, 58%). v_{max} (ATR) 2930, 1726 (C=O), 1698 (C=O), 1398, 1254, 1162, 1112, 1085, 1022, 757, 696 cm^{-1}. δ_H (700 MHz) 1.64 (2H, m, 5-*H*$_2$), 1.85 (2H, t, J = 6 Hz, 6-*H*$_2$), 2.30 (2H, q, J = 6 Hz, 4-*H*$_2$), 3.70 (2H, broad, 7-*H*$_2$), 3.79 (3H, s, C*H*$_3$), 4.82 (2H, s, OC*H*$_2$), 5.66 (1H, t, J = 6 Hz, 3-*H*), 6.68 (2H, d, J = 8 Hz, 2''-*H*, 6''*H*), 7.11 (2H, t, J = 8 Hz, 3''-*H*, 5''-*H*), 7.16 (1H, t, J = 8 Hz, 4''-*H*), 7.22-7.36 (3H, m, 3 x Ar-*H*), 7.38 (1H, d, J = 8 Hz, 6'-*H*). δ_C (176 MHz) 23.8 (*C*-5), 28.2 (*C*-4), 28.3 (*C*-6), 50.6 (*C*-7), 52.5 (*C*H$_3$), 67.6 (O*C*H$_2$), 124.8 (*C*-3), 127.3 (Ar*C*-H), 127.7 (*C*-4''), 127.9 (*C*-2''), 128.2 (*C*-3''), 128.3 (*C*-6'), 129.4 (Ar*C*-H), 130.60 (Ar*C*-H), 130.64 (C-2'), 136.1 (*C*-1''), 139.5 (*C*-1'), 142.5 (C-2), 154.8 (N*C*=O), 170.0 (*C*O$_2$Me). ***m/z*** (ES^+) 366.3 (MH^+), 753.6 ($2MNa^+$). HRMS (ES^+) found MNa^+ 388.1518, $C_{22}H_{23}NO_4Na$ requires 388.1519.

N-[(4''-Methylphenyl)sulfonyl]-2-(4'-methylphenyl)-4,5,6,7-tetrahydro-azepane **5d-ii**



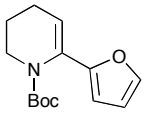
Suzuki protocol A: Degassed by passing a stream of nitrogen through mixture prior to adding catalyst. Purification on a Horizon® column chromatography system ([19:1] DCM/EtOAc) afforded recovered starting material (114 mg, 0.24 mmol, 33%) and the title compound as a white solid (110 mg, 0.32 mmol, 43%). ν_{max} (ATR) 2938, 2918, 1440, 1334, 1150, 1087, 1058, 950, 814, 763, 704 cm^{-1}. δ_H (400 MHz,) 1.43 (2H, m, 5-*H*$_2$), 1.83 (2H, quint, J = 6 Hz, 6-*H*$_2$), 2.06 (2H, q, J = 6 Hz, 4-*H*$_2$), 2.34 (3H, s, C*H*$_3$), 2.41 34 (3H, s, C*H*$_3$), 6.04 (1H, t, J = 6 Hz, 3-*H*), 7.04 (2H, d, J = 8 Hz, 2 x Ar-*H*), 7.18 (4H, d, J = 8 Hz, 2 x Ar-*H*), 7.55 (2H, d, J = 8 Hz, 2 x Ar-*H*). δ_C (100 MHz) 19.8 (*C*H$_3$), 20.2 (*C*H$_3$), 22.3 (*C*-5), 25.3 (*C*-4), 28.6 (*C*-6), 49.3 (*C*-7), 124.7 (Ar*C*-H), 126.1 (Ar*C*-H) 126.9 (*C*-3), 127.4 (Ar*C*-H) 127.9 (Ar*C*-H), 134.4 (Ar*C*), 136.2 (*C*-2), 137.4 (Ar*C*), 141.6 (Ar*C*), 141.7 (Ar*C*). *m/z* (ES^+) 342.3 (MH^+), 359.4 (MH_2O^+), 700.6 ($2MH_2O^+$). HRMS (ES^+) found MH^+ 342.1523, $C_{20}H_{24}NO_2S$ requires 342.1522, found MNa^+ 364.1342, $C_{20}H_{23}NO_2SNa$ requires 364.1342.

N-(tert-Butyloxycarbonyl)-2-(4'-methoxyphenyl)-4,5,6-trihydro-piperidine **5e-iii**



Obtained, following flash chromatography, as a white solid (41%). R_f ([19:1] pet. ether/EtOAc): 0.25. mp. 99 °C. ν_{max} (KBr) 3042, 3004, 2931, 2838, 11693, 1644, 1609, 1509, 1365, 1246, 1153, 1033, 993, 831, 778 and 593 cm^{-1}. δ_H (400 MHz) 1.09 (9H, s, (C*H*$_3$)$_3$C), 1.80 (2H, m, 5-*H*$_2$), 2.24 (2H, td, J = 7 Hz, 4 Hz, 4-*H*$_2$), 3.64 (2H, m, 6-*H*$_2$), 3.77 (3H, s, OC*H*$_3$), 5.27 (1H, t, J = 4 Hz, 3-*H*), 6.85 (2H, d, J = 9 Hz, 3'-*H*, 5'-*H*), 7.19 (2H, d, J = 9 Hz, 2'-*H*, 6'-*H*). δ_C (100 MHz) 24.2 (*C*-4), 24.4 (*C*-5), 28.0 ((*C*H$_3$)$_3$C), 45.4 (*C*-6), 55.9 (*C*H$_3$O), 80.6 ((CH$_3$)$_3$*C*), 114.2 (*C*-3' and *C*-5'), 114.6 (*C*-3), 127.3 (*C*-2' and *C*-6'), 134.5 (*C*-1'), 140.9 (*C*-2), 154.7 (O*C*=O), 159.8 (*C*-4'). *mlz* (ES^+) 312.3 (MNa^+).

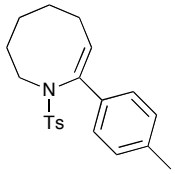
N-(tert-Butyloxycarbonyl)-2-furan-2'-yl-4,5,6-trihydro-piperidine **5e-x**



Obtained, following flash chromatography, as a pale yellow solid (29%). R_f ([19:1] pet. ether/EtOAc): 0.4. mp. 54 °C. ν_{max} (KBr) 3151, 2979, 2928, 2890, 2837, 1694, 1681,

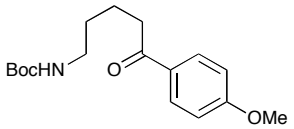
1644, 1455, 1361, 1253, 1154, 1003, 919, 879, 755, 689 and 599 cm^{-1}. δ_H (400 MHz) 1.23 (9H, s, (CH_3)$_3$C), 1.80 (2H, m, 5-H_2), 2.24 (2H, td, J = 7 Hz, 4 Hz, 4-H_2), 3.58 (2H, m, 6-H_2), 5.53 (1H, t, J = 4 Hz, 3-*H*), 6.25 (1H, dd, J = 3, 1 Hz, 5'-*H*), 6.39 (1H, dd, J = 3 Hz, 2 Hz, 4'-*H*), 7.40 (1H, dd, J_1 = 2 Hz, 1 Hz, 3'-*H*). δ_C (100 MHz) 23.7 and 24.2 (*C*-4 and *C*-5), 28.0 ((CH_3)$_3$C), 44.9 (*C*-6), 80.9 ((CH_3)$_3$*C*), 105.7 (*C*-3), 111.9 (*C*-2'), 115.2 (*C*-3'), 132.5 (*C*-2), 141.6 (*C*-4'), 153.9 (O-*C*=O), 154.6 (*C*-1'). *mlz* (ES^+) 272.3 (MNa^+).

N-[(4''-Methylphenyl)sulfonyl]-2-(4'-methylphenyl)-4,5,6,7,8-quintahydro-1H-azocine **5g-ii**



Purification on a Horizon® column chromatography system ([100:0], [95:5], [7:3] EtOAc/$CHCl_3$) afforded recovered starting material **3g** (164 mg, 0.34 mmol, 33%) and the title compound as a white solid (214 mg, 0.60 mmol, 58%). ν_{max} (KBr) 2924, 2855, 1691, 1447, 1340, 1155, 1118, 1086, 1010, 874, 815, 708 cm^{-1}. δ_H (400 MHz) 1.60 (4H, m, 5-H_2, 6-H_2), 1.72 (2H, m, 7-H_2), 2.31 (3H, s, CH_3), 2.36 (2H, m, 4-H_2), 2.40 (3H, s, CH_3), 3.63 (2H, m, 8-H_2), 6.39 (1H, t, J = 8 Hz, 3-*H*), 6.97 (2H, d, J = 8 Hz, Ar-*H*), 7.07 (2H, d, J = 8 Hz, Ar-*H*), 7.16 (2H, d, J = 8 Hz, Ar-*H*), 7.52 (2H, d, J = 8 Hz, Ar-*H*). δ_C (100 MHz) 21.0 (*C*H_3), 21.4 (*C*H_3), 26.5 (*C*-4), 27.0 (*C*-5 or 6), 27.4 (*C*-7), 28.3 (*C*-5 or 6), 52.6 (*C*-8), 125.7 (Ar*C*-H), 127.4 (Ar*C*-H), 128.8 (Ar*C*-H),129.1 (Ar*C*-H), 132.4 (*C*-3), 134.1, 137.3, 138.0, 138.2 and 142.7 (tertiary-*C*). m/z (ES^+) 356.3 (MH^+), 373.2 (MH_2O^+), 728.4 ($2MH_2O^+$). HRMS (ES^+) found MH^+ 356.1680, $C_{21}H_{26}NO_2S$ requires 356.1679, found MNa^+ 378.1498, $C_{21}H_{25}NO_2SNa$ requires 378.1498.

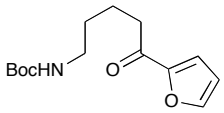
5-(N-tert-butoxycarbonylamino)-1-(4'-methoxyphenyl)pentan-1-one



Compound **5e-iii** (0.1 mmol) was dissolved in $CDCl_3$ (0.5 ml) and monitored by NMR and TLC. The sample completely converted into the title compound after 3 days. R_f ([1:1] pet. ether/EtOAc): 0.85. δ_C (100 MHz) 1.42 (9H, s, (CH_3)$_3$C), 1.56 (2H, quint, J = 8 Hz, 2-H_2), 1.75 (2H, quint, J = 8 Hz, 3-H_2), 2.94 (2H, t, J = 7 Hz, 4-H_2), 3.15 (2H, 1-H_2), 3.86 (3H, s, OCH_3), 4.64 (1H, broad, N*H*), 6.92 (2H, d, J = 9 Hz, 8-*H*), 7.93 (2H, d, J = 9 Hz, 7-*H*). δ_C (100 MHz) 21.6 (*C*-3), 28.5 ((CH_3)$_3$C), 29.8 (*C*-2), 37.7 (*C*-4), 40.4 (*C*-1), 55.6 (*C*H_3O),

79.2 ($(CH_3)_3C$), 113.8 (*C*-3' and *C*-5'), 130.1 (*C*-1'), 130.4 (*C*-2' and *C*-6'), 156.2 (O-*C*=O), 163.5 (*C*-4'), 198.8 (Ar-*C*=O).

5-(N-tert-butoxycarbonylamino)-1-(2'-furyl)pentan-1-one



Compound **5e-xi** (0.1 mmol) was dissolved in $CDCl_3$ (0.5 ml) and monitored by NMR and TLC. After 4 days 75% of the sample completely converted into the title compound. R_f ([1:1] pet. ether/EtOAc): 0.80. δ_C (100 MHz) 1.42 (9H, s, $C(H_3)_3C$), 1.54 (2H, quint, J = 8 Hz, 2-H_2), 1.73 (2H, quint, J = 8 Hz, 3-H_2), 2.83 (2H, t, J = 7 Hz, 4-H_2), 3.14 (2H, m, 1-H_2), 4.62 (1H, broad, N*H*), 6.51 (1H, dd, J = 4 Hz, J = 2 Hz, 3'-*H*), 7.18 (1H, d, J = 4 Hz, 2'-*H*), 7.56 (1H, d, J = 2 Hz, 4-*H*). δ_C (100 MHz) 21.3 (*C*-3), 28.6 ($(CH_3)_3C$), 29.7 (*C*-2), 38.0 (*C*-4), 40.3 (*C*-1), 79.3 ($(CH_3)_3C$), 112.3 (*C*-2'), 117.1 (*C*-3'), 146.4 (*C*-4'), 152.9 (*C*-1'), 156.2 (O-*C*=O), 189.4 (Ar-*C*=O).

Part C 500 MHz ^{1}H NMR spectra for **5a-i** in $CDCl_3$ at rt and 60 ˚C to illustrate presence of rotomers