Development of a Practical Buchwald-Hartwig Amine Arylation Protocol using a Conveniently Prepared (NHC)Pd(R-allyl)Cl Catalyst

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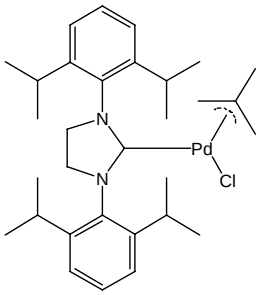
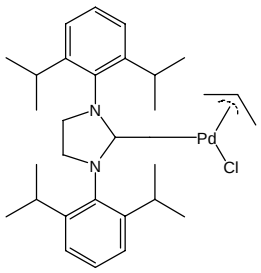
Supplementary Information

General information: All Pd-catalysed reactions were carried out under an inert atmosphere, in oven-dried Schlenk tubes, unless otherwise stated. The imidazolium salt SIPr.HCl was prepared using a literature procedure.[1] *N*-(tetrahydropyran-4-yl)methylamine, *N*,*N*,*N'*-trimethyl-1,2-diaminoethane and 7-azabicyclo[2.2.1]heptane hydrochloride were supplied by AstraZeneca Pharmaceuticals. All other chemicals were purchased from commercial sources. If liquid, the aryl halides and amines were distilled over KOH and stored over molecular sieves prior to use. All other chemicals were used as received without further purification. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates (254mm). Flash column chromatography was carried out with Kieselgel 60M 0.04/0.063mm (230-400 mesh) silica gel. All yields quoted are isolated yields. ^{1}H NMR spectra were recorded at 300MHz and ^{13}C at 75MHz on a Bruker AMX 300 at ambient temperature in $CDCl_3$. The chemical shifts (δ) for ^{1}H and ^{13}C are quoted in ppm relative to residual protiated signals of the solvent. Mass spectra were obtained on a VG70-SE mass spectrometer. Infrared spectra were obtained on a Shimadzu FTIR 8700 Spectrophotometer. Elemental analyses for novel compounds were performed at the Department of Chemistry, University College London. Melting points were measured with a Gallenkamp apparatus and are uncorrected.



(SIPr)Pd(methallyl)Cl (1). A two-necked flask with a magnetic stirrer was charged with SIPr.HCl (1.9g, 4.2mmol) and potassium *tert*-butoxide (0.4g, 3.6mmol). A septum was placed on one neck and the remaining neck was attached to a nitrogen line, after which the flask was cycled with nitrogen and vacuum three times. Under a positive flow of nitrogen, technical grade *iso*-propanol (35mL) was added *via* syringe through the septum and the mixture was stirred for 2 hours at 80^{o}C. After cooling to room temperature over 45 minutes, the septum was removed, $[Pd(methallyl)Cl]_2$ (0.55g, 1.5mmol) was added quickly and the septum was replaced. The mixture was stirred for 2 hours at room temperature, over which time its colour gradually turned grey. It was opened to the air and stirred for 15 minutes. Water (100mL) was added and a solid precipitated. The water was removed by filtration and the solid was taken up in chloroform (100mL). This solution was filtered through phase separating filter paper to remove the water and was concentrated *in vacuo* giving a yellow oil. This crude residue was purified using flash column chromatography (silica gel) with an eluent of diethyl ether/petroleum spirit (3:2) to afford the desired complex as an off-white crystalline solid (1.02g, 2.17mmol, 72%, decomposes at 155^{o}C). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.12 (s, 3H, CH_2CMeCH_2), 1.22 (d, J = 6.9Hz, 6H, $CHMe_2$), 1.29 (d, J = 6.9Hz, 6H, $CHMe_2$), 1.34 (d, J = 6.9Hz, 6H, $CHMe_2$), 1.50 (d, J = 6.7Hz, 6H, $CHMe_2$), 1.56 (s, 1H, CH_2CMeCH_2), 1.75 (s, 1H, CH_2CMeCH_2), 2.68 (d, J = 3.6Hz, 1H, CH_2CMeCH_2), 3.33-3.57 (m, 4H, $CHMe_2$), 3.69 (d, J = 3.1Hz, 1H, CH_2CMeCH_2), 3.97-4.08 (m, 4H, NCH_2), 7.25-7.19 (m, 4H, Ar), 7.34 (t, J = 7.7Hz,

2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 22.4, 23.7, 23.8, 26.6, 26.7, 28.4, 28.6, 49.5, 53.8, 72.2, 124.3, 124.4, 129.0, 129.7, 136.6, 147.1, 147.3. C.I. MS (relative intensity): 550 (10), 496 (50), 389 (10), 347 (10), 188 (15), 146 (13), 91 (31). HRMS C.I. [M^+], Calcd.: 587.23841. Actual: 587.23643. Anal. Calcd.: C 63.37, H 7.72, N 4.77. Actual: C 63.41, H 7.80, N 4.65. IR (KBr, cm^{-1}) 2962, 2925, 2868, 1448, 1425, 1382, 1363, 1326, 1267, 1240, 1055, 837, 802, 758, 731, 700, 621.



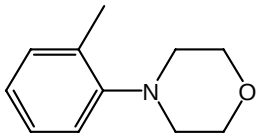
(SIPr)Pd(allyl)Cl (2).[2] A two-necked flask with a magnetic stirrer was charged with SIPr.HCl (1.9g, 4.2mmol) and potassium *tert*-butoxide (0.4g, 3.6mmol) and a septum was placed on one neck. The remaining neck was attached to a nitrogen line, after which the flask was cycled with nitrogen and vacuum three times. Under a positive flow of nitrogen, *iso*-propanol (35mL) was added *via* syringe through the septum and the mixture was stirred for 2 hours at 80 °C. After cooling to room temperature over 45 minutes, the septum was removed, $[Pd(allyl)Cl]_2$ (0.55g, 1.5mmol) was added quickly and the septum was replaced. The mixture was stirred for 2 hours at room temperature, over which time its colour gradually turned grey. It was then opened to the air and stirred for 15 minutes. Water (100mL) was added and a solid precipitated. Filtration afforded an off-white solid, which was washed with water (4x50mL). It was dried *in vacuo*, affording the desired complex (1.14g, 1.9mmol, 66%). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.15 (dd, J = 8.8Hz, 6.9Hz, 1H), 1.26 (dd, J = 11.5Hz, 6.9Hz, 12H), 1.35 (d, J = 6.4Hz, 6H), 1.45 (d, J = 6.5Hz, 6H), 2.73 (d, J =13.6Hz, 1H), 3.01

(d, *J* = 5.1Hz, 1H), 3.45 (dq, *J* = 13.2Hz, 6.4Hz, 4H), 3.87 (d, *J* = 7.4Hz, 1H), 3.97-4.10 (m, 4H), 4.74 (ddd, *J* = 18.7Hz, 13.6Hz, 7.6Hz, 1H), 7.17-7.27 (d, m, 4H), 7.33 (t, *J* = 7.7Hz, 2H). ^{13}C NMR (75MHz, $CDCl_3$): δ 23.7, 23.8, 24.2, 26.6, 28.5, 49.9, 54.0, 114.6, 124.3, 129.1, 136.3, 147.0, 147.3. C.I. MS (relative intensity): HRMS C.I. [M^++H], 1065 (28), 884 (27), 618 (25), 574 (M^+, 27), 536 (62), 391 (100), 338 (64), 188 (57), 97 (49). Calcd.: 575.23841. Actual: 575.23731. Anal. Calcd.: C 62.80, H 7.51, N 4.89. Actual: C62.06, H 7.62, N 4.72. IR (KBr, cm^{-1}) 3074, 2962, 2925, 2868, 1633, 1454, 1427, 1382, 1326, 1267, 1242, 1055, 1020, 999, 804, 758, 732.

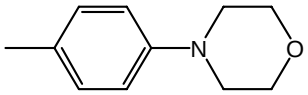
General procedure for amine arylation. An oven-dried Schlenk tube was charged with an aryl halide (1.0mmol), an amine (1.2mmol, 1.2eq.), (SIPr)Pd(methallyl)Cl (18mg, 0.03mmol, 3.0mol%) and a magnetic stirrer bar and was sealed with a septum. The flask was evacuated and backfilled with inert gas three times, after which LHMDS (1M solution in tetrahydrofuran) was added *via* syringe. The bottom of the tube was then placed in an oil bath maintained at 22°C, followed by stirring until the aryl halide had been consumed, as judged by TLC. The mixture was diluted with ethyl acetate and filtered through a short plug of silica. The solvent was removed *in vacuo* and the crude material was purified *via* flash chromatography on silica gel using an eluent of ethyl acetate with hexane or petroleum ether.

Spectroscopic Data for the Products of Amine Arylation reactions:

Morpholine Study:



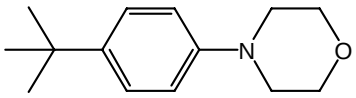
***N*-(2-methylphenyl)morpholine (Table 3, Entry 1).**[3] The coupling of morpholine and 2-bromotoluene was performed using the general procedure to afford 175mg (99%) of the title compound within 1 minute as a yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 2.33 (s, 3H, ArC*H*$_3$), 2.89-2.95 (m, 2H, NC*H*$_2$), 3.79-3.91 (m, 2H, OC*H*$_2$), 6.97-7.06 (m, 2H, Ar), 7.14-7.24 (m, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 17.9, 52.3, 67.5, 119.0, 123.5, 126.7, 131.2, 132.7, 151.4. E.I. MS (relative intensity): 204 (10), 177 (M^+, 50), 119 (100), 118 (53). HRMS E.I. [M^+], Calcd.: 177.11482. Actual: 177.11425. IR (KBr, cm^{-1}): 2957, 2853, 2816, 1599, 1491, 1450, 1373, 1298, 1254, 1225, 1117, 1043, 934, 762.



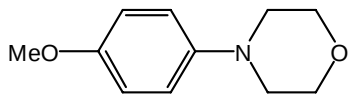
***N*-(4-methylphenyl)morpholine (Table 3, Entry 2).**[3] The coupling of morpholine and 4-bromotoluene was performed using the general procedure to afford 173mg (98% yield) of the title compound within 1 minute as an off-white solid (mp 79°C). ^{1}H NMR (300MHz, $CDCl_3$): δ 2.31 (s, 3H, ArC*H*$_3$), 3.13 (t, *J* = 4.8Hz, 4H, NC*H*$_2$), 3.88 (t, *J* = 4.8Hz, 4H, OC*H*$_2$), 6.86 (d, *J* = 8.7Hz, 2H, Ar), 7.12 (d, *J* = 8.7Hz, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 20.5, 50.0, 67.0, 116.1, 129.6, 129.8, 149.3. E.I. MS (relative intensity): 177 (M^+, 18), 119 (100), 103 (8), 91 (30). E.I. HRMS [M^+],

Calcd.: 177.11536. Actual: 177.11547. IR (KBr, cm^{-1}): 2976, 2956, 2912, 2889, 2852, 2831, 2748, 2694, 1515, 1452, 1365, 1298, 1259, 1168, 1118, 1064, 1049, 921, 819.

***N*-(4-methylphenyl)morpholine (Table 3, Entry 3).** The coupling of morpholine and *p*-tolyl triflate was performed using the general procedure to afford 124mg (70% yield) of the title compound within 1 minute. Spectra same as described above.



***N*-(4-*tert*-butylphenyl)morpholine (Table 3, Entry 4).**[3] The coupling of morpholine and 4-*tert*-butylbromobenzene was performed using the general procedure to afford 199mg (91%) of the title compound as a colourless oil within 5 minutes as a white solid (mp: 59-62°C). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.37 (s, 9H, CMe_3), 3.09-3.22 (m, 4H, NCH_2), 3.81-3.95 (m, 4H, OCH_2), 6.89-6.97 (d, 2H, Ar), 7.32-7.41 (d, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$) δ 31.6, 34.0, 49.6, 67.0, 115.5, 126.0, 142.8, 149.0. E.I. MS (relative intensity): 219 (M^+, 85), 204 (100). HRMS EI [M^+], Calcd.: 219.16177. Actual: 219.16209. IR (KBr, cm^{-1}): 2976, 2835, 1519, 1450, 1363, 1299, 1261, 1176, 1120, 1070, 925, 819, 734, 553.



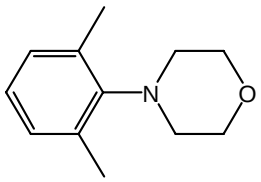
***N*-(4-methoxyphenyl)morpholine (Table 3, Entry 5).**[3] The coupling of morpholine and 4-bromoanisole was performed using the general procedure to afford 174mg (90% yield) of the title compound within 5 minutes as an off-white solid (mp: 79°C). ^{1}H NMR (300MHz, $CDCl_3$): δ 3.03-3.07 (m, 4H, OCH_2), 3.77 (s, 3H, OCH_3), 3.84-3.87 (m, 4H, NCH_2), 6.83-6.94 (m, 4H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 50.8, 55.6,

67.1, 114.5, 117.8, 145.7, 154.0. E.I. MS (relative intensity): 193 (M^+, 100), 178 (25), 135 (100), 120 (83), 92 (12). HRMS EI [M^+], Calcd.: 193.11027. Actual: 193.11000. IR (KBr, cm^{-1}): 2934, 2853, 2831, 2802, 1510, 1464, 1454, 1442, 1385, 1292, 1244, 1182, 1132, 1042, 1028, 824.

***N*-(2-methylphenyl)morpholine (Table 3, Entry 6).** The coupling of morpholine and 2-chlorotoluene was performed using the general procedure to afford 166mg (94% yield) of the title compound within 25 minutes as a yellow oil. Spectra same as described above.

***N*-(4-methylphenyl)morpholine (Table 3, Entry 7).** The coupling of morpholine and 4-chlorotoluene was performed using the general procedure to afford 168mg (95% yield) of the title compound within 5 minutes. Spectra same as described above.

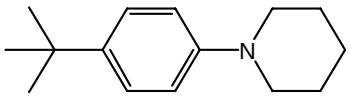
***N*-(4-methoxyphenyl)morpholine (Table 3, Entry 8).** The coupling of morpholine and 4-chloroanisole performed using the general procedure to afford 95mg (49% yield) of the title compound within 10 minutes. Spectra same as described above.



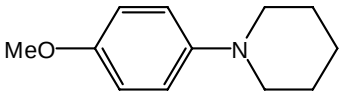
***N*-(2,6-dimethylphenyl)morpholine (Table 3, Entry 9).**[4] The coupling of morpholine and 2,6-dimethylchlorobenzene was performed using the general procedure to afford 46mg (24%) of the title compound within 60 minutes as a colourless crystalline solid (mp: 94°C). The coupling was repeated using the general

procedure at 70°C to afford 99mg (52%) of the title compound within 10 minutes. ^{1}H NMR (300MHz, $CDCl_3$): δ 2.36 (s, 6H, ArCH_3), 3.07-3.14 (m, 4H, NCH_2), 3.78-3.85 (m, 4H, OCH_2), 6.95-7.04 (m, 4H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 19.6, 50.0, 68.2, 125.4, 129.1, 137.0, 147.9. E.I. MS (relative intensity): 246 (25), 191 (M^+, 82), 190 (100), 188 (61), 146 (65), 133 (95), 132 (74), 117 (28), 86 (47), 84 (81). HRMS EI [M^+], Calcd.: 191.13047; Actual: 191.13139. IR (KBr, cm^{-1}): 2966, 2848, 2813, 2732, 2682, 1613, 1471, 1438, 1369, 1259, 1209, 1109, 1041, 937, 842, 781, 738, 673, 505.

Study of other secondary amines:

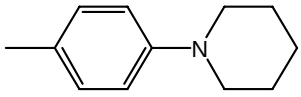


***N*-(4-*tert*-butylphenyl)piperidine (Table 4, Entry 1).**[3] The coupling of piperidine and 4-*tert*-butylbromobenzene was performed using the general procedure to afford 178mg (82% yield) of the title compound within 20 minutes as a white solid (mp 37°C). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.30 (s, 9H, CH_3), 1.53-1.60 (m, 2H, $NCH_2CH_2CH_2$), 1.68-1.76 (m, 4H, NCH_2CH_2), 3.13 (t, J = 5.5Hz, 4H, NCH_2), 6.91 (d, 2H, J = 8.9Hz, Ar), 7.29 (d, 2H, J = 8.9Hz, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 24.3, 26.0, 31.5, 33.9, 50.9, 116.3, 125.8, 142.0, 150.0. E.I. MS (relative intensity): 217 (M^+, 28), 202 (100), 149 (5). HRMS E.I. [M^+], Calcd.: 217.18304. Actual: 217.18314. IR (KBr, cm^{-1}): 2930, 2805, 2708, 1608, 1516, 1447, 1382, 1361, 1235, 1218, 1201, 1156, 1127, 1028, 920, 819.



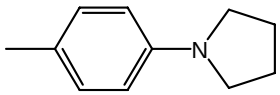
***N*-(4-methoxyphenyl)piperidine (Table 4, Entry 2).**[3] The coupling of piperidine and 4-bromoanisole was performed using the general procedure to afford 178mg (93% yield) of the title compound within 20 minutes as a colourless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.60-1.52 (m, 2H), 1.78-1.70 (m, 4H), 3.04 (t, *J* = 5.4Hz, 4H), 3.77 (s, 3H), 6.84 (d, *J* = 9.1Hz, 2H), 6.93 (d, *J* = 9.2Hz, 2H). ^{13}C NMR (75MHz, $CDCl_3$): δ 24.2, 26.2, 52.3, 55.5, 114.3, 118.8, 146.9, 153.6. E.I. MS (relative intensity): 191 (M^+, 13), 135 (100), 92 (8). HRMS E.I. [M^+], Calcd.: 191.13047. Actual: 191.12980. IR (KBr, cm^{-1}): 2933, 2792, 1511, 1463, 1452, 1442, 1383, 1292, 1233, 1217, 1181, 1121, 1041, 1027, 919, 861, 823, 795.

***N*-(4-methoxyphenyl)piperidine (Table 4, Entry 3).** The coupling of piperidine and 4-chloroanisole was performed using the general procedure to afford 82mg (43% yield) of the title compound within 15 minutes as a colourless oil. Spectra same as described above.

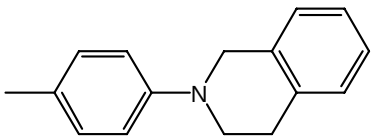


***N*-(4-methylphenyl)piperidine (Table 4, Entry 4).**[3] The coupling of piperidine and 4-bromotoluene was performed using the general procedure affording 162mg (85% yield) of the title compound within 5 minutes as a colourless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.52-1.67 (m, 2H, $N(CH_2)_2CH_2$), 1.75-1.82 (m, 4H, NCH_2CH_2), 2.34 (s, 3H, $ArCH_3$), 3.16 (t, *J* = 5.3Hz, 4H, NCH_2), 6.94 (d, *J* = 8.6Hz, 2H, Ar), 7.16 (d, *J* = 8.6Hz, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): 20.5, 24.4, 26.1, 51.4, 117.05, 128.8, 129.6, 150.4. E.I. MS (relative intensity): 175 (M^+, 88), 174 (M^+-H, 100), 146 (11),

131 (25), 119 (41), 103 (30), 91 (54). E.I. HRMS [M^+], Calcd.: 175.13609. Actual: 175.13578. IR (KBr, cm^{-1}): 2930, 2855, 2797, 1616, 1516, 1450, 1383, 1335, 1234, 1032, 918, 810.

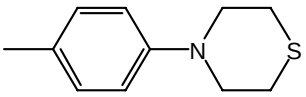


***N*-(4-methylphenyl)pyrollidine (Table 4, Entry 5).**[3] The coupling of pyrollidine and 4-bromotoluene was performed using the general procedure to afford 64mg (40%) of the title compound within 5 minutes as a colourless oil. The reaction would not go to completion. The coupling of pyrollidine and 4-bromotoluene was repeated using the general procedure except at 70°C to afford 135mg (84%) of the title compound within 2 minutes as a yellow solid (mp: 46°C). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.99-2.09 (m, 4H, NCH_2CH_2), 2.33 (s, 3H, $ArCH_3$), 3.32 (t, J = 4.7Hz, 4H, NCH_2), 6.55-6.59 (m, 2H, Ar), 7.09-7.15 (m, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 20.4, 25.5, 47.9, 111.9, 124.5, 129.7, 146.2. E.I. MS (relative intensity): 161 (M^+, 100), 160 (54), 105 (37), 86 (55). HRMS EI [M^+], Calcd.: 161.11990. Actual: 161.1928. IR (KBr, cm^{-1}): 3012, 2964, 2854, 1622, 1564, 1521, 1487, 1460, 1367, 1346, 1278, 1244, 1186, 1159, 802, 509.

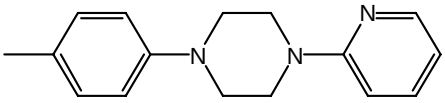


***N*-(4-methylphenyl)-1,2,3,4-tetrahydroisoqunioline (Table 4, Entry 6).** The coupling of 1,2,3,4-tetrahydroisoqunioline and 4-bromotoluene was performed using the general procedure to afford 145mg (65%) of the title compound within 30 minutes as a colourless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 2.31 (s, 3H, $ArCH_3$), 3.00 (t, J =

5.9Hz, 2H, NCH_2CH_2), 3.53 (t, J = 5.9Hz, 2H, NCH_2CH_2), 4.38 (s, 2H, NCH_2Ar), 6.93-6.96 (m, 2H, Ar), 7.06-7.21 (m, 6H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 20.4, 29.1, 47.3, 51.5, 115.9, 126.0, 126.6, 128.4, 128.6, 129.6, 134.6, 134.8, 148.7. E.I. MS (relative intensity): 237 (70), 223 (M^+, 75), 222 (40), 119 (25), 118 (100), 104 (37), 91 (48), 90 (57). HRMS EI [M^+], Calcd.: 223.13555. Actual: 223.13458. IR (KBr, cm^{-1}): 3030, 2920, 2864, 1659, 1602, 1581, 1473, 1458, 1406, 1329, 1309, 1253, 1228, 1168, 813, 761, 742.

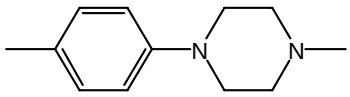


***N*-(4-methylphenyl)thiomorpholine (Table 4, Entry 7).** The coupling of thiomorpholine and 4-bromotoluene was performed using the general procedure to afford 116mg (60%) of the title compound within 10 minutes as a white solid (mp: 40°C). ^1H NMR (300MHz, $CDCl_3$): δ 2.29 (s, 3H, $ArCH_3$), 2.75-2.79 (m, 4H, SCH_2), 3.46-3.49 (m, 4H, NCH_2), 6.85 (d, J = 8.8Hz, 2H, Ar), 7.08 (d, J = 8.8Hz, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 20.5, 27.2, 52.8, 117.7, 129.6, 129.8, 149.6. E.I. MS (relative intensity): 193 (M^+, 54), 119 (100). HRMS E.I. [M^+], Calcd.: 193.09197. Actual: 193.09170. IR (KBr, cm^{-1}): 2954, 2908, 2873, 2827, 2754, 1616, 1573, 1514, 1450, 1415, 1336, 1290, 1224, 1193, 1168, 1136, 1029, 970, 893, 819, 530.

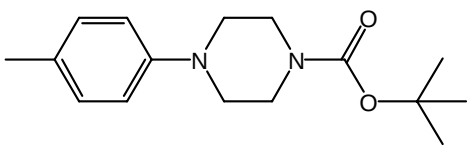


***N*-(4-methylphenyl)-1-(2-pyridyl)piperazine (Table 4, Entry 8).**[3] The coupling of 1-(2-pyridyl)-piperazine and 4-bromotoluene was performed using the general procedure to afford 243mg (96% yield) of the title compound within 5 minutes as a white solid (mp 96-98°C). ^1H NMR (300MHz, $CDCl_3$): δ 2.30 (s, 3H, $ArCH_3$), 3.25 (t,

J = 5.2Hz, 2H, NC*H*$_2$), 3.70 (t, *J* = 5.2Hz, 2H, NC*H*$_2$), 6.46-6.51 (m, 2H, Ar), 6.91 (d, *J* = 8.6Hz, 2H, Ar), 7.11 (d, *J* = 8.7Hz, 2H, Ar), 7.45-7.55 (m, 1H, Ar), 8.22-8.24 (m, 1H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 20.5, 45.4, 49.8, 107.3, 113.6, 116.8, 129.7, 129.7, 137.6, 148.0, 149.2, 159.5. E.I. MS (relative intensity): 253 (M^+, 83), 159 (66), 147 (87), 133 (38), 119 (74), 107 (100), 91 (57), 79 (89). E.I. HRMS [M^+], Calcd.: 253.15789. Actual: 253.15766. IR (KBr, cm^{-1}): 2827, 2709, 1594, 1561, 1519, 1483, 1438, 1390, 1314, 1242, 1210, 1162, 1128, 1099, 1039, 980, 955, 804, 775, 734.

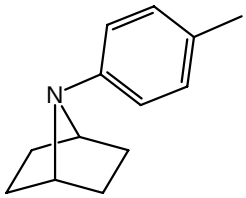


***N*-(4-methylphenyl)-*N*'-methylpiperazine (Table 4, Entry 9).** The coupling of *N*-methylpiperazine and 4-bromotoluene was performed using the general procedure to afford 153mg (80%) of the title compound within 5 minutes as a colourless solid (mp: 75°C). ^{1}H NMR (300MHz, $CDCl_3$): δ 2.28 (s, 3H, NC*H*$_3$), 2.36 (s, 3H, ArC*H*$_3$), 2.58 (t, *J* = 5.1Hz, 4H, MeNC*H*$_2$), 3.17 (t, *J* = 5.1Hz, 4H, ArNC*H*$_2$), 6.84-6.88 (m, 2H, Ar), 7.18-7.22 (m, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 20.5, 27.2, 46.2, 49.7, 55.2, 116.4, 129.1, 129.7, 149.3. E.I. MS (relative intensity): 190 (M^+, 100), 146 (18), 119 (63). HRMS E.I. [M^+], Calcd.: 190.14645. Actual: 190.1492. IR (KBr, cm^{-1}): 2964, 2937, 2918, 2837, 2790, 2748, 2700, 1616, 1515, 1452, 1379, 1336, 1294, 1267, 1242, 1211, 1159, 1078, 1008, 921, 812, 736, 526.

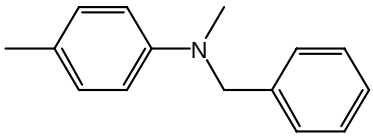


***N*-(4-methylphenyl)-*N*'-Boc-morpholine (Table 4, Entry 10).** The coupling of *N*-Boc-piperazine and 4-bromotoluene was performed using the general procedure to

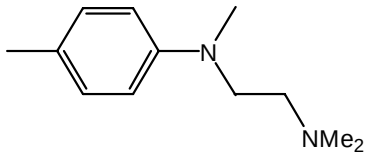
afford 264mg (96%) of the title compound within 5 minutes as a white crystalline solid (mp: 105°C). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.48 (s, 9H, C*Me*$_3$), 2.23 (ArC*H*$_3$), 3.07 (t, *J* = 5.2Hz, 4H, Boc-NC*H*$_2$), 3.57 (t, *J* = 5.2Hz, 4H, ArNC*H*$_2$), 6.84 (d, *J* = 8.5Hz, 2H, Ar), 7.08 (d, *J* = 8.5Hz, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 20.5, 28.5, 50.0, 117.0, 129.7, 149.2, 154.8. C.I. MS (relative intensity): 277 (M^++H, 34), 221 (100), 159 (14). HRMS C.I. [M^++H], Calcd.: 277.19160. Actual: 277.19112. IR (KBr, cm^{-1}): 2976, 2868, 2815, 1681, 1515, 1477, 1417, 1390, 1363, 1346, 1265, 1236, 1207, 1159, 1122, 1003, 925, 817, 738, 704.



7-(4-Tolyl)-7-azabicyclo[2.2.1]heptane (Table 4, Entry 11).[4] The coupling of 7-azabicyclo[2.2.1]heptane hydrochloride and 4-bromotoluene was performed using the general procedure at 70^{o}C and with 2.4mL LHMDS (2.4mmol, 2.4eq) to afford 16mg (9%) of the title compound within 3 hours as a white solid (mp: 175°C). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.37-1.45 (m, 4H, C*H*$_2$CH$_2$), 1.77-1.80 (m, 4H, CH$_2$C*H*$_2$), 2.25 (s, 3H, ArC*H*$_3$), 4.17 (m, 2H, NC*H*$_2$), 6.82 (d, *J* = 8.2Hz, 2H, Ar), 7.00 (d, *J* = 8.2Hz, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 20.5, 28.7, 58.1, 116.5, 128.2, 129.6, 145.7. C.I. MS (relative intensity): 216 (7), 189 (12), 188 (M^++H, 100), 187 (M^+, 70), 186 (M^+-1, 14), 158 (16). HRMS C.I. [M^++H], Calcd.: 188.14392. Actual: 188.14448. IR (KBr, cm^{-1}): 2962, 2868, 1514, 1454, 1384, 1329, 1261, 1145, 1047, 956.

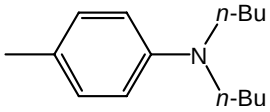


***N,N*-(4-methylphenyl)methylbenylamine (Table 4, Entry 12).**[3] The coupling of *N*-benzylmethylamine and 4-bromotoluene was performed using the general procedure to afford 175mg (83% yield) of the title compound within 5 minutes as a yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 2.40 (s, 3H, ArCH_3) 3.08 (s, 3H, NCH_3), 4.59 (s, 2H, PhCH_2), 6.80 (d, 2H, *J* = 6.7Hz, Ar), 7.14 (d, 2H, *J* = 6.7Hz, Ar), 7.32-7.43 (m, 5H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 20.4, 38.7, 57.1, 112.9, 125.9, 126.9, 127.0, 128.6, 129.8, 139.4, 147.9. E.I. MS (relative intensity): 211 (M^+, 41), 134 (32), 120 (15), 91 (100). HRMS E.I. [M^+], Calcd.: 211.13609. Actual: 211.13558. IR (KBr, cm^{-1}): 3062, 3026, 2918, 2860, 2810, 1618, 1570, 1521, 1494, 1475, 1451, 1354, 1325, 1296, 1249, 1210, 1191, 1114, 1074, 1029, 945, 803, 733, 699.

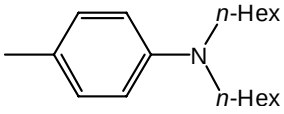


***N*-(4-methylphenyl)-*N,N',N'*-trimethyl-1,2-diaminoethane (Table 4, Entry 13).** The coupling of *N,N,N'*-trimethyl-1,2-diaminoethane and 4-bromotoluene was performed using the general procedure to afford 73mg (38%) of the title compound within 18 hours as a yellow oil. The coupling of *N,N,N'*-trimethyl-1,2-diaminoethane and 4-bromotoluene was repeated using the general procedure at 70°C to afford 163mg (85%) of the title compound within 5 hours as a yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 2.22 (s, 3H, ArCH_3), 2.30 (s, 6H, NMe_2), 2.46-2.52 (m, 2H, Me_2NCH_2), 2.93 (s, 3H, ArN*Me*), 3.37-3.46 (m, 2H, ArN(Me)CH_2), 6.68 (d, *J* = 8.3Hz, 2H, Ar), 7.05 (d, *J* = 8.3Hz, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 20.2, 38.8,

45.9, 51.4, 55.9, 112.6, 125.6, 129.8, 147.2. E.I. MS (relative intensity): 192 (M^+, 47), 135 (30), 134 (100), 120 (20), 119 (25), 118 (13), 91 (47), 86 (71). HRMS E.I. [M^++H], Calcd.: 192.16210. Actual: 192.16241. IR (KBr, cm^{-1}): 2941, 2860, 2818, 2768, 1620, 1522, 1462, 1366, 1250, 1180, 1115, 1042, 961, 802.

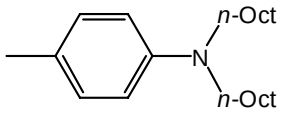


***N*-(4-methylphenyl)di-*n*-butylamine (Table 4, Entry 14).**[3] The coupling of di-*n*-butylamine and 4-bromotoluene was performed using the general procedure to afford 92mg (42% yield) of the title compound within 24 hours as a yellow oil. The coupling of di-*n*-butylamine and 4-bromotoluene was repeated using the general procedure except at 70°C to afford 188mg (86% yield) of the title compound within 1 hour as a yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.6Hz, 6H, $(CH_2)_3CH_3$), 1.25-1.45 (m, 8H, $NCH_2(CH_2)_2$), 2.30 (s, 3H, $ArCH_3$), 3.37 (q, *J* = 7.6Hz, 4H, NCH_2), 6.60 (d, *J* = 8.6Hz, 2H, Ar), 7.04 (d, *J* = 8.6Hz, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 14.1, 20.2, 20.4, 29.5, 51.0, 112.2, 124.4, 129.7, 146.2. E.I. MS (relative intensity): 218 (40), 204 (76), 188 (82), 172 (22), 158 (12), 146 (60), 130 (26), 118 (51), 97 (47), 91 (20). HRMS E.I. [M^++H], Calcd.: 220.20651. Actual: 220.20620. IR (KBr, cm^{-1}): 2957, 2930, 2866, 2361, 2332, 1618, 1518, 1460, 1367, 1290, 1221, 1184, 1148, 1103, 1016, 930, 800, 752.



***N*-(4-methylphenyl)di-*n*-hexylamine (Table 4, Entry 15).** The coupling of di-*n*-hexylamine and 4-bromotoluene was performed using the general procedure at 70°C

to afford 270mg (98%) of the title compound within 1 hour as a yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.09 (t, J = 6.3Hz, 6H, $(CH_2)_5CH_3$), 1.49 (br s, 12H, $NCH_2CH_2(CH_2)_3$), 1.72-1.76 (m, 4H, NCH_2CH_2), 2.37 (s, 3H, $ArCH_3$), 3.40 (t, J = 7.6Hz, 4H, NCH_2), 6.75 (d, J = 8.6Hz, 2H, Ar), 7.19 (d, J = 8.6Hz, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 14.1, 20.2, 22.7, 26.9, 27.3, 31.8, 51.4, 112.3, 124.5, 129.7, 146.2. E.I. MS (relative intensity): 281 (16), 275 (M^+, 6), 204 (20), 134 (27), 120 (100), 91 (14), 78 (14). HRMS E.I. [M^+], Calcd.: 275.26075. Actual: 275.26094. IR (KBr, cm^{-1}): 2955, 2928, 2858, 1620, 1520, 1466, 1369, 1292, 1254, 1188, 1109, 800.

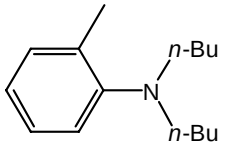


***N*-(4-methylphenyl)di-*n*-octylamine (Table 4, Entry 16).** The coupling of di-*n*-butylamine and 4-bromotoluene was performed using the general procedure at 70°C to afford 273mg (86%) of the title compound within 1 hour as a yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 0.97 (t, J = 7.0Hz, 6H, $(CH_2)_7CH_3$), 1.33-1.38 (br s, 20H, $NCH_2CH_2(CH_2)_5$), 1.61-1.66 (m, 4H, NCH_2CH_2), 2.32 (s, 3H, $ArCH_3$), 3.29 (t, J = 7.6Hz, 4H, NCH_2), 6.64 (d, J = 8.6Hz, 2H, Ar), 7.08 (d, J = 8.6Hz, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 14.2, 20.2, 22.8, 27.4, 29.5, 29.6, 30.4, 32.0, 51.4, 112.2, 124.3, 129.8, 146.3. E.I. MS (relative intensity): 480 (14), 479 (23), 331 (M^+, 55), 233 (29), 232 (100), 134 (65) 120 (19). HRMS E.I. [M^+], Calcd.: 331.32335. Actual: 331.32269. IR (KBr, cm^{-1}): 3009, 2924, 2855, 1620, 1520, 1464, 1393, 1367, 1234, 1186, 1111, 800, 723.

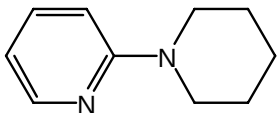
***N*-(4-methylphenyl)di-*n*-butylamine (Table 4, Entry 17).** The coupling of di-*n*-butylamine and 4-chlorotoluene was performed using the general procedure except at

70°C to afford 22mg (10% yield) of the title compound within 30 minutes as a yellow oil. Spectra the same as above.

***N*-(4-methylphenyl)di-*n*-hexylamine (Table 4, Entry 18).** The coupling of di-*n*-hexylamine and 4-chlorotoluene was performed using the general procedure except at 70°C to afford 69mg (25% yield) of the title compound within 30 minutes as a yellow oil. Spectra the same as above.



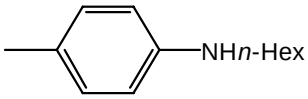
***N*-(4-methylphenyl)di-*n*-butylamine (Table 4, Entry 19).**[5] The coupling of of di-*n*-butylamine and 2-bromotoluene was performed using the general procedure at 70°C to afford 44mg (20%) of the title compound within 90 minutes as a yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 0.86 (t, J = 7.2Hz, 6H, $(CH_2)_3CH_3$), 1.22-1.42 (m, 8H, $NCH_2(CH_2)_2$), 2.29 (s, 3H, $ArCH_3$), 2.90 (t, J = 7.1Hz, 4H, NCH_2), 6.93-6.99 (m, 1H, Ar), 7.06-7.18 (m, 3H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 14.0, 18.3, 20.5, 53.7, 122.1, 123.0, 125.9, 130.8, 135.0, 150.7. E.I. MS (relative intensity): 219 (M^+, 11), 176 (100), 134 (42), 120 (48), 91 (41). HRMS E.I. [M^+], Calcd.: 219.19815. Actual: 219.19847. IR (KBr, cm^{-1}): 2960, 2931, 2869, 1616, 1539, 1456, 1382, 1363, 1326, 1261, 1056, 804.



***N*-(2-pyridyl)piperdine (Table 1, Entry 20).**[3] The coupling of piperidine and 2-bromopyridine was performed using the general procedure to afford 147mg (91%

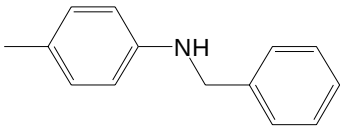
yield) of the title compound within one minute as a yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.62 (s, 6H, $NCH_2(CH_2)_3$), 3.50 (s, 4H, NCH_2), 6.53-6.55 (m, 1H, Ar), 6.62 (d, *J* = 8.6Hz, 1H, Ar), 7.39-7.45 (m, 1H, Ar), 8.15-8.17 (m, 1H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 24.8, 25.5, 46.3, 107.1, 112.4, 137.3, 147.9, 159.7. E.I. MS (relative intensity): 162 (60), 146 (10), 133 (63), 119 (42), 107 (50), 94 (23), 84 (100). HRMS E.I. [M^+], Calcd.: 162.11569. Actual: 162.11518. IR (KBr, cm^{-1}): 2999, 2932, 2853, 2818, 1595, 1485, 1439, 1383, 1312, 1246, 1161, 1130, 1024, 978, 932, 853, 772, 733.

Primary Amines Study

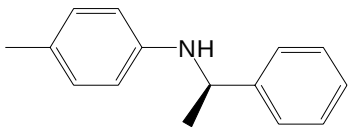


***N*-(4-methylphenyl)*n*-hexylamine (Table 5, Entry 1).**[3] The coupling of *n*-hexylamine and 4-bromotoluene was performed using the general procedure except at 70^{o}C and with 4.0eq of amine to afford 122mg (64% yield) of the title compound within 1 hour as a white crystalline solid (mp: 49°C). ^{1}H NMR (300MHz, $CDCl_3$): δ 0.90-1.00 (m, 3H, $(CH_2)_5CH_3$), 1.25-1.50 (m, 8H, $CH_2(CH_2)_4CH_3$), 2.26 (s, 3H, $ArCH_3$), 3.10 (t, *J* = 7.6Hz, 2H, NCH_2), 3.20-3.50 (br s, 1H, NH), 6.75 (d, *J* = 8.6Hz, 2H, Ar), 7.01 (d, *J* = 8.6Hz, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 14.1, 20.4, 22.7, 26.9, 29.6, 31.7, 44.5, 113.0, 126.3, 129.7, 146.3. E.I. MS (relative intensity): 192 (M^++H, 20), 191(M^+, 95), 120 (100). HRMS E.I. [M^+], Calcd.: 191.16739. Actual: 191.16745. IR (KBr, cm^{-1}): 2924, 2855, 1616, 1522, 1470, 1313, 1254, 1223, 1182, 1126, 1042, 806, 729. ***N*,*N*-bis(4-methylphenyl)*n*-hexylamine (Table 5, Entry 1).** This coupling also afforded 34mg (12% yield) of the bisarylation product within 1

hour as a yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 0.90-1.00 (m, 3H, $(CH_2)_5CH_3$), 1.25-1.45 (m, 8H, $CH_2(CH_2)_4CH_3$), 2.33 (s, 6H, $ArCH_3$), 3.66 (t, J = 7.7Hz, 2H, NCH_2), 6.91 (d, J = 8.6Hz, 4H, Ar), 7.09 (d, J = 8.6Hz, 4H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 14.1, 20.6, 22.7, 26.9, 27.5, 31.7, 52.5, 120.9, 129.8, 130.2, 146.1. E.I. MS (relative intensity): 282 (M^++H, 100), 281 (M^+, 72), 211 (62), 210 (98), 196 (30), 180 (48), 118 (88), 91 (49). HRMS E.I. [M^+], Calcd.: 281.21434. Actual: 281.21437. IR (KBr, cm^{-1}): 2926, 2860, 1612, 1510, 1458, 1367, 1252, 1188, 1136, 1080, 1043, 808.

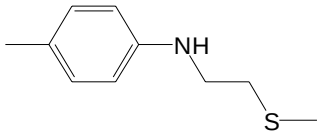


***N*-(4-methylphenyl)benzylamine (Table 5, Entry 2).** The coupling of benzylamine and 4-bromotoluene was performed using the general procedure at 70°C and with 4.0eq of amine to afford 79mg (40%) of the title compound within 30 minutes as a yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 2.31 (s, 3H, $ArCH_3$), 3.92 (br s, 1H, N*H*), 4.36 (s, 2H, NCH_2Ph), 6.62 (d, J = 8.2Hz, 2H, Ar), 7.05 (d, J = 8.2Hz, 2H, Ar), 7.35-7.45 (m, 5H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 20.5, 48.7, 113.1, 126.8, 127.2, 127.6, 128.7, 129.8, 139.8, 146.0. E.I. MS (relative intensity): 197 (M^+, 100), 196 (44), 91 (90). HRMS E.I. [M^+], Calcd.: 197.11990. Actual: 197.11944. IR (KBr, cm^{-1}): 3416, 3028, 2918, 2862, 1618, 1520, 1495, 1470, 1321, 1302, 1265, 1250, 1182, 1126, 808, 743, 723, 698.



***N*-(4-methylphenyl)-1-phenylethylamine (Table 5, Entry 3).** The coupling of 1-phenylethylamine and 4-bromotoluene was performed using the general procedure at

70°C and with 4.0eq of amine to afford 148mg (70%) of the title compound within 30 minutes as a yellow solid (mp: 70°C). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.55 (d, *J* = 6.7Hz, 3H, NCHC*H*$_3$), 2.25 (s, 3H, ArC*H*$_3$), 3.95 (br s, 1H, N*H*), 4.51 (q, *J* = 6.7Hz, 1H, NC*H*), 6.49 (d, *J* = 8.4Hz, 2H, Ar), 6.96 (d, *J* = 8.4Hz, 2H, Ar), 7.25-7.30 (m, 1H, Ar), 7.36-7.44 (m, 4H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 20.4, 25.1, 53.7, 113.5, 125.9, 126.4, 126.9, 128.7, 129.7, 145.1, 145.5. E.I. MS (relative intensity): 211 (M^+, 50), 196 (100), 107 (18), 105 (34). HRMS E.I. [M^+], Calcd.: 211.15550. Actual: 211.13497. IR (KBr, cm^{-1}): 3409, 2967, 2862, 1618, 1519, 1488, 1448, 1357, 1317, 1298, 1255, 1205, 1182, 1143, 1066, 1012, 806, 756, 702, 574, 509.



***N*-(4-methylphenyl)-2-(Methylthio)ethylamine (Table 5, Entry 4).** The coupling of 2-(methylthio)ethylamine and 4-bromotoluene was performed using the general procedure at 70°C and with 4.0eq of amine to afford 25mg (14%) of the title compound within 1 hour as a colourless oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 2.11 (s, 3H, SC*H*$_3$), 2.25 (s, 3H, ArC*H*$_3$), 2.76 (t, *J* = 6.4Hz, 2H, NCH$_2$C*H*$_2$S), 3.34 (t, *J* = 6.4Hz, 2H, NC*H*$_2$), 3.90 (br s, 1H, N*H*), 6.58 (d, *J* = 8.4Hz, 2H, Ar), 7.00 (d, *J* = 8.4Hz, 2H, Ar). ^{13}C NMR (75MHz, $CDCl_3$): δ 15.0, 20.4, 33.7, 42.3, 113.4, 127.1, 129.8, 145.5. E.I. MS (relative intensity): 181 (M^+, 14), 120 (100), 91 (8), 86 (13). HRMS E.I. [M^+], Calcd.: 181.09197. Actual: 181.09131. IR (KBr, cm^{-1}): 2960, 2916, 2866, 1618, 1519, 1425, 1319, 1257, 1045, 808.

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