Synthesis of (diarylmethyl)amines using Nicatalyzed arylation of C(sp³)-H bonds

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I. General considerations

- Aryl chlorides were used as received. Anhydrous, oxygen-free solvents (DMAc, tetrahydrofuran (THF), dimethoxyethane (DME), Dioxane and toluene) and the bases (NaOtBu, KOtBu, KHMDS, LiHMDS, NaHMDS) were stored in a glovebox and used as received. *N*-Benzylidene-*N*-(diphenylmethyl)amine (1d) was purchased from Sigma Aldrich and used as received. The well defined Ni complexes ¹ and the benzylimine substrates ² were prepared according to previously reported procedures.
- Flash chromatography was performed on silica gel 60 Å pore diameter and 40-63 μm particle size.
- ¹H, ¹³C and ¹⁹F Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker- 300, 400 or 500 MHz spectrometer at ambient temperature in CD₃OD or CDCl₃. Chemical shifts (δ) are reported in ppm, relative to the solvent residual proton peak CD₃OD (3.31 ppm for ¹H and 49.0 ppm for ¹³C) and CDCl₃ (7.26 ppm for ¹H and 77.00 ppm for ¹³C). For ¹⁹F NMR, chemical shifts refer to an external calibration using CFCl₃ (δ = 0.00 ppm). Data for ¹H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, br = broad signal, m = multiplet), coupling constants (*J*) in Hz and integration.
- HRMS analysis were performed at the EPSRC UK National Mass Spectrometry Facility (NMSF), Swansea.
- All isolated yields are an average of two runs.

II. Synthesis of imines 1a-c.

Benzophenone (3.6 g, 20 mmol), NaHCO₃ (8.4 g, 0.1 mol), the corresponding benzyl amine (21 mmol) and activated molecular sieves (4Å) were weighted in a round bottom flask under dry conditions. Then, dry toluene (40 mL) was added. The reaction was then stirred for 16 hours at 90°C. After this time, the mixture was filtered through celite. The desired imine was obtained pure after recrystallization (AcOEt:*n*-hexane).

III. Optimization data

Table 1: Selection of the precatalyst.



¹ (1) Dible, B. R.; Sigman, M. S. J. Am. Chem. Soc. 2003, 125, 872–873.

	(mol %)	(equiv.)			yield) ^[a]
1	[Ni(COD) ₂] (5)/IPr (6)	NaO <i>t</i> Bu (2.0)	Toluene (2.5)	45	-
2	[Ni(COD) ₂] (5)/IPr (6)	KO <i>t</i> Bu (2.0)	Toluene (2.5)	45	-
3	[Ni(COD) ₂] (5)/IPr (6)	NaHMDS (2.0)	Toluene (2.5)	45	-
4	[Ni(COD) ₂] (5)/IPr (6)	LiHMDS (2.0)	Toluene (2.5)	45	-
6	[Ni(COD) ₂] (5)/IPr (6)	KHMDS (1.5)	Toluene (2.5)	45	>95 (75)
7	[Ni(COD) ₂] (5)/IPr (6)	KHMDS (2.5)	Toluene (2.5)	45	>95 (72)
8	[Ni(COD) ₂] (5)/IPr (6)	KHMDS (2.0)	THF (2.5)	45	>95 (49)
9	[Ni(COD) ₂] (5)/IPr (6)	KHMDS (2.0)	DME (2.5)	45	27
10	[Ni(COD) ₂] (5)/IPr (6)	KHMDS (2.0)	DMAc (2.5)	45	-
11	[Ni(COD) ₂] (5)/IPr (6)	KHMDS (2.0)	Dioxane (2.5)	45	63
12	[Ni(COD) ₂] (5)/IPr (6)	KHMDS (2.0)	Toluene (2.5)	45	>95 (81)
13	[Ni(COD) ₂] (5)/SIPr (6)	KHMDS (2.0)	Toluene (2.5)	45	94 (65)
14	[Ni(COD) ₂] (5)/IPr* (6)	KHMDS (2.0)	Toluene (2.5)	45	>95 (60)
15	[Ni(COD) ₂] (5)/IDD (6)	KHMDS (2.0)	Toluene (2.5)	45	-
16	[Ni(COD) ₂] (5)/IMes (6)	KHMDS (2.0)	Toluene (2.5)	45	24
17	[Ni(IPr)(cin)Cl] (5)	KHMDS (2.0)	Toluene (2.5)	45	>95 (70)
18	[Ni(IPr)(all)Cl] (5)	KHMDS	Toluene (2.5)	45	70 (45)

		(2.0)			
19	[Ni(COD) ₂] (5)/IPr (6)	KHMDS (2.0)	Toluene (2.5)	60	>95 (72)
20	[Ni(COD) ₂] (5)/IPr (6)	KHMDS (2.0)	Toluene (1)	45	>95 (53)
21	[Ni(COD) ₂] (5)/lPr (6)	KHMDS (2.0)	Toluene (1.5)	45	>95 (85)
22	[Ni(COD) ₂] (2.5)/IPr (3)	KHMDS (2.0)	Toluene (1.5)	45	>95 (72)
23	[Ni(COD) ₂] (5)/IPr (10)	<u>KHMDS</u> (2.0)	<u>Toluene (1.5)</u>	<u>45</u>	<u>>95 (93)</u>
24	[Ni(COD) ₂] (5)/IPr (7.5)	KHMDS (2.0)	Toluene (1.5)	45	>95 (89)
25	[Ni(acac) ₂] (5)/IPr (10)	KHMDS (2.0)	Toluene (1.5)	45	traces
26	[Ni(DME)Cl ₂] (5)/IPr (10)	KHMDS (2.0)	Toluene (1.5)	45	-
27	[Ni(IPr)(cin)Cl] (5)/ IPr (5)	KHMDS (2.0)	Toluene (2.5)	45	>95 (70)

Reaction conditions: **1a** (0.5 mmol, 2.0 equiv), 4-chlorotoluene (0.25 mmol, 1 equiv). [a] Conversion calculated by NMR. NMR yield obtained using dimethylmalonate as internal reference.

IV. Experimental procedures

General procedure for the arylation of imines. Inside a glovebox, $[Ni(COD)_2]$ (0.0125 mmol,), IPr (10 or 15 mg, 2 equiv. with respect of Ni) the selected imine (0.5 mmol, 2 equiv.), KHMDS (100 mg, 0.5 mmol) were weighted in a screw cap vial equipped with a stirring bar. The aryl chloride (0.25 mmol, 1 equiv.) was added at this stage, if solid. The vial was sealed and carried out from the glovebox, where and the aryl chloride, if liquid, and the dry, degassed solvent (toluene, 1.5 ml) were added. The reaction was then stirred for 16 hours at 45°C. The reaction was then quenched adding some drops of water and filtered through Mg₂SO₄. After checking the NMR, the crude was absorbed on silica previously basified (stirring it overnight with 2% triethylamine in pentane) and purified by flash chromatography (typically with a pentane / diethyl ether = 95 / 5 eluent mixture) to afford the desired product.

Procedure for the hydrolysis of 3k. HCl 1N in diethyl ether (1 mL) was added to the solution of imine **3k** (39.7 mg, 0.1 mmol) in THF (1 mL) at 0°C. The solution was warmed to room temperature, stirred at room temperature and monitored by TLC until all the imine was consumed. The THF was evaporated under vacuum. Another 1 mL HCl (1N) was added and a white precipitate was observed. The white solid was filtered and washed with cold Et_2O (1.0 mL×3). After drying under vacuum for 12 h, the hydrochloride salt was obtained as a white solid (25.4 mg, 99% yield).

Procedure for the benzylation experiments of 1a (table2, entries 1-3). Inside a glovebox, **1a** (54 mg, 0.2 mmol, 1.0 equiv.) and the base (2.0 equiv.) were weighted in a screw cap vial equipped with a stirring bar. Outside the glovebox, toluene (0.6 mL) and benzyl chloride (0.25 μ L, 2.4 mmol, 1.2 equiv.) were added, and the reaction was then stirred at 45 °C for 3 hours. The reaction was then quenched with 2 drops of water, filtered thru MgSO₄ and dried under vacuum. The yield was then assessed *via* quantitative ¹H-NMR, using diethylmalonate as internal standard.

Procedure for the bases test (table 2, entries 4-6). Inside a glovebox, **1a** (54 mg, 0.2 mmol, 1.0 equiv.) and the base (0.5 equiv.) were weighted in a screw cap vial equipped with a stirring bar. Outside the glovebox, dry degassed toluene (0.6 mL) was added using a syringe thru the septum, and the reaction was then stirred at 45 °C for 3 hours. The reaction was then quenched with 2 drops of water, filtered thru MgSO₄, dried under vacuum and analyzed via ¹H-NMR.

V. Characterization data.

N-(Diphenylmethylene)-1-phenyl-1-(*p*-tolyl)methanamine. (3a)²



From **1a** and 4-chlorotoluene, 5% [Ni] loading, isolated yield: 318 mg, 88%.

From **1d** and 4-chlorotoluene, 5% [Ni] loading, isolated yield: 304 mg, 84%.

¹**H NMR** (400 MHz, CDCl₃): δ 7.51 (m, 2H), 7.45-7.41 (m, 3H), 7.38-7.27 (m, 7H), 7.22-7.18 (m, 3H), 7.10-7.07 (m, 4H), 5.52 (s, 2H), 2.31 (s, 3H).

¹³**C NMR** (100 MHz, CDCl₃): δ 166.6, 141.9, 139.9, 136.7, 136.1, 130.0, 129.0, 128.7, 128.4, 128.4, 128.3, 127.9, 127.8, 127.5, 127.4, 126.6, 69.6, 21.1.

² Li, M.; Yucel, B.; Adrio, J.; Bellomo, A.; Walsh, P. J. Chem. Sci. 2014, 5, 2383–2391.

N-(Diphenylmethylene)-1-(4-methoxyphenyl)-1-phenylmethanamine. (3b)²



From 1a and 4-chloroanisole, 5% Ni loading, isolated yield: 325 mg, 86%.

From **1b** and chlorobenzene, 5% Ni loading, isolated yield: 325 mg, 86%.

From **1d** and 4-chloroanisole, 5% Ni loading, isolated yield: 313 mg, 83%.

¹**H NMR** (400 MHz, CDCl₃): δ 7.76 (d, J= 7.2 Hz, 2H), 7.45-7.25 (m, 10H), 7.22-7.18 (m, 3H), 7.11-7.08 (m, 2H), 7.10-7.07 (m, 4H), 6.83 (d, *J*=8.8 Hz, 2H), 5.53 (s, 1H), 3.78 (s, 3H).

¹³**C NMR** (100 MHz, CDCl₃): δ 166.57, 158.31, 145.11, 139.85, 137.15, 136.73, 129.98, 128.71, 128.58, 128.42, 128.37, 128.27, 127.96, 127.73, 127.44, 126.56, 113.70, 69.19, 55.20.

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N-(Diphenylmethylene)-1-(4-fluorophenyl)-1-phenylmethanamine. (3c)<sup>2</sup>
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From **1a** and 4-fluorochlorobenzene, 5% [Ni] loading, Isolated yield : 299 mg, 82%.

From **1c** and chlorobenzene, 5% [Ni] loading, Isolated yield : 298 mg, 82%.

From 1d and 4-fluorochlorobenzene, 5% [Ni] loading, Isolated yield : 298 mg, 82%.

¹**H NMR** (400 MHz, CDCl₃): δ 7.77 (m, 2H), 7.47-7.44 (m, 3H), 7.40-7.30 (m, 2H), 7.30-7.26 (m, 6H), 7.24-7.18 (m, 1H), 7.10-7.06 (m, 2H), 7.00-6.94 (m, 2H), 5.55 (s, 1H).

¹³**C NMR** (100 MHz, CDCl₃): δ 167.1, 162.0 (d, ¹*J*_{*C-F*}= 243.0 Hz), 144.7, 140.6 (d, ⁴*J*_{*C-F*}= 3.0 Hz), 139.7, 136.6, 130.1, 129.0 (d, ³*J*_{*C-F*}= 7.8 Hz), 128.7, 128.5, 128.4, 128.4, 128.0, 127.6, 127.4, 126.8, 115.0 (d, ²*J*_{*C-F*}= 31.2 Hz), 69.3.

¹⁹**F NMR** (376.8 MHz, CDCl₃): δ -116.4

N-(Diphenylmethylene)-1-phenyl-1-(4-(trifluoromethyl)phenyl)methanamine. (3d)²



5% [Ni] loading. Isolated yield: 328 mg, 79%.

¹**H NMR** (400 MHz, CDCl₃) : δ 7.77 (m, 2H), 7.55 (app. d, J= 8.4 Hz, 2H), 7.48-7.26 (m, 12H), 7.25-7.21 (m, 1H), 7.24-7.18 (m, 1H), 7.09-7.05 (m, 2H), 5.61 (s, 1H).

¹³**C NMR** (100 MHz, CDCl₃) : δ 167.7, 148.8, 144.0, 139.5, 136.5, 130.3, 129.0, 128.8, 128.7, 128.5, 128.0, 127.8, 127.6, 127.0, 125.3 (q, J_{C-F}= 3.4 Hz), 123.4 (q, J_{C-F}= 270.1 Hz), 69.5

¹⁹**F NMR** (376.8 MHz, CDCl₃) : δ -62.4



5% [Ni] loading. Isolated yield: 301 mg, 77%.

¹**H NMR** (400 MHz, CDCl₃) : δ 7.75 (m, 2H), 7.45-7.42 (m, 3H), 7.37-7.33 (m, 5H), 7.29-7.25 (m, 3H), 7.20-7.08 (m, 4H), 6.74 (m, 1H), 6.70 (m, 1H), 6.59 (ddd, *J*= 8.4 Hz, 2.8 Hz, 0.8 Hz, 1H),5.51 (s, 2H), 2.90 (s, 6H).

¹³**C NMR** (125 MHz, CDCl₃) : δ 166.52, 150.59, 145.55, 145.03, 139.95, 136.75, 129.89, 128.92, 128.72, 128.36, 128.28, 128.19, 127.92, 127.87, 127.48, 126.47, 116.20, 112.01, 111.04, 77.00, 70.21, 40.65.

1-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-(diphenylmethylene)-1-phenylmethanamine. (3f)



³ Li, M.; Berritt, S.; Walsh, P. J. Org. Lett. 2014, 16, 4312-4315.

5% [Ni] loading. Isolated yield: 337 mg, 86%.

HRMS: [M-H]⁺, m/z calculated : 390.1489; observed: 390.1481.

¹**H NMR** (400 MHz, CDCl₃): δ 7.79 (m, 2H), 7.48-7.28 (m, 11H), 7.26-7.20 (m, 1H), 7.13 (d, *J*= 2 Hz, 1H), 7.11 (m, 1H), 6.95 (d, *J*= 1,6 Hz, 1H), 6.78 (dd, *J*¹=8.4 Hz, *J*²=1.6 Hz, 1H), 6.74 (d, *J*= 8 Hz, 1H), 5.92 (s, 2H), 5.51 (s, 1H).

¹³**C NMR** (100 MHz, CDCl₃): δ 166.75, 147.58, 146.23, 144.91, 139.74, 138.96, 136.62, 130.05, 128.71, 128.46, 128.38, 128.30, 127.97, 127.68, 127.33, 126.66, 120.43, 108.26, 107.91, 100.79, 69.44.

4-(((Diphenylmethylene)amino)(phenyl)methyl)phenyl)(phenyl)methanone. (3g)



5% [Ni] loading. Isolated yield: 402 mg, 89%.

HRMS: [M-H]⁺, m/z calculated : 450.1852; observed: 450.1548

¹**H NMR** (500 MHz, CDCl₃): δ 7.85-7.80 (m, 6H), 7.59 (t, *J*= 7.5 Hz, 1H), 7.53-7.47 (m, 7H), 7.45-7.39 (m, 5H), 7.35 (t, *J*= 7.5 Hz, 2H), 7.29-7.24 (m, 1H), 7.14-7.11 (m, 2H), 5.69 (s, 2H), 2.31 (s, 3H).

¹³**C NMR** (125 MHz, CDCl₃): δ 196.40, 167.60, 149.59, 144.09, 139.53, 137.67, 132.22, 130.32, 130.25, 129.96, 128.73, 128.62, 128.47, 128.16, 128.03, 127.59, 127.52, 127.36, 126.97, 69.67.

4-(((Diphenylmethylene)amino)(phenyl)methyl)benzonitrile. (3h)²



5% [Ni] loading. Isolated yield: 297 mg, 80%.

¹**H NMR** (400 MHz, CDCl₃): δ 7.76-7.73 (m, 2H), 7.57 (d, J= 8.4 Hz, 2H), 7.47-7.36 (m, 15H), 7.06-7.3 (m, 2H), 5.57 (s, 2H).

¹³**C NMR** (100 MHz, CDCl₃): δ 168.12, 150.21, 143.57, 139.34, 136.31, 132.22, 130.44, 128.74, 128.61, 128.56, 128.19, 128.10, 127.50, 127.48, 127.23, 119.01, 110.46, 69.47.

N-(Diphenylmethylene)-1-phenyl-1-(pyridin-2-yl). (3i)



7.5% [Ni] loading. Isolated yield: 310 mg, 89%.

HRMS: [M-H]⁺, m/z calculated : 347.1543; observed: 347.1539.

¹**H** NMR (500 MHz, CDCl₃): δ 8.47 (d, J= 4.5 Hz, 1H), 7.83-7.77 (m, 3H), 7.67 (dt, *J*= 7.5, 1.5 Hz, 1H), 7.42-7.35 (m, 8H), 7.28 (t, *J*= 7.5 Hz, 2H), 7.22-7.18 (m, 1H), 7.12-7.09 (ddd, *J*= 7.5 Hz, 4 Hz, 1 Hz, 1H), 7.07-7.04 (m, 2H), 5.77 (s, 2H).

¹³**C NMR** (125 MHz, CDCl₃) : δ 167.93, 163.87, 148.88, 143.96, 139.82, 136.66, 136.33, 130.15, 128.77, 128.58, 128.42, 128.36, 128.00, 127.72, 127.46, 126.82, 122.03, 121.80, 71.89.

N-(Diphenylmethylene)-1-phenyl-1-(o-tolyl)methanamine. (3j)²



¹**H NMR** (400 MHz, CDCl₃): δ 7.77-7.74 (m, 2H), 7.71 (d, J= 7.6 Hz, 1H), 7.46-7.18 (m, 13H), 7.09-7.06 (m, 3H), 5.76 (s, 1H), 1.97 (s, 3H).

¹³**C NMR** (100 MHz, CDCl₃) : δ 166.76, 144.00, 142.74, 139.77, 137.01, 135.34, 130.34, 129.99, 128.72, 128.53, 128.43, 128.21, 127.96, 127.62, 126.59, 126.46, 126.06, 66.68, 19.53.

Naphthalen-1-yl(phenyl)methanaminium chloride. (3k)²



7.5% [Ni] loading. Isolated yield: 143 mg, 61% (overall yield after hydrolysis)

¹**H NMR** (400 MHz, CDCl₃): δ 8.01-7.94 (m, 3H), 7.72-7.63 (m, 2H), 7.56-7.37 (m, 7H), 6.44 (s, 1H).

¹³**C NMR** (100 MHz, CDCl₃): δ 138.77, 135.55, 131.43, 130.64, 130.30, 130.24, 130.11, 129.13, 128.51, 128.03, 127.40, 126.15, 124.40, 124.15, 56.05.

N-(Diphenylmethylene)-1-phenylmethanamine. (1a)²



Chemical Formula: C₂₀H₁₇N Molecular Weight: 271,36

¹**H NMR** (400 MHz, CDCl₃): δ 7.71-7.65 (m, 2H), 7.51-7.34 (m, 10H), 7.25-7.20 (m, 3H), 4.62 (m, 3H), 7.10-7.07 (m, 4H), 5.52 (s, 2H), 2.31 (s, 3H).

N-(Diphenylmethylene)-1-(4-methoxyphenyl)methanamine. (1b)²



Chemical Formula: C₂₁H₁₉NO Molecular Weight: 301,38

¹**H NMR** (400 MHz, CDCl₃): δ 7.69-7.65 (m, 2H), 7.51-7.34 (m, 6H), 7.26-7.19 (m, 4H), 6.89 (m, 2H), 4.55 (s, 2H), 5.52 (s, 2H), 3.80 (s, 3H).

N-(Diphenylmethylene)-1-(4-fluorphenyl)methanamine. (1c)²

Chemical Formula: C₂₀H₁₆FN Molecular Weight: 289,35 Ph

OMe

¹**H NMR** (400 MHz, CDCl₃): δ 7.72-7.68 (m, 2H), 7.51-7.28 (m, 8H), 7.23-7.19 (m, 2H), 7.05-6.99 (m, 2H), 4.58 (s, 2H).













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-30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210













220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

