

Palladium-catalysed Grignard cross-coupling using highly concentrated Grignards in methyl-tetrahydrofuran.

Edward J. Milton^[a] and Matthew L. Clarke^{*[a]}

^a School of Chemistry, University of St Andrews, EaStCHEM, St Andrews, Fife, UK. Fax: (44) 1334 463808; Tel: (44) 1334 463850; E-mail: mc28@st-andrews.ac.uk

Experimental

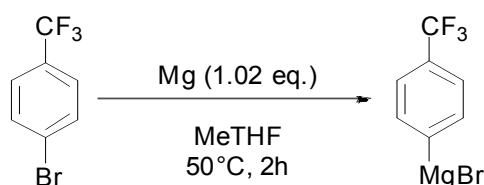
An inert atmosphere of N₂ or Argon and Schlenk line techniques were used throughout preparative procedures. *In vacuo* refers to the use of a Heidolph[®] Laborota 4000 rotary evaporator with a KNF[®] Laboport pump or a high vacuum line equipped with an Edwards[®] rotary vane pump pulling <0.5 mm Hg. Solvents were degassed by several freeze thaw cycles before use and purified *via* alumina columns in a Grubbs system Braun MSB 8000 still or distilled from sodium (Me-THF) or CaH₂ (CH₂Cl₂). Petroleum ether refers to petroleum ether 40-60°. Acetonitrile and NMR solvents (CDCl₃, CD₂Cl₂ and C₆D₆) were dried over activated 4Å molecular sieves and degassed by several freeze thaw cycles before use.

Na₂PdCl₄ was purchased from Aldrich or donated by Johnson Matthey. All ferrocene ligands were purchased from Strem or Aldrich, stored under argon and used without further purification. Reagents used for cross-coupling reactions were purchased from Aldrich. Reaction reflux conditions were obtained by using an oil bath equipped with a contact thermometer.

¹H, ¹³C, ¹⁹F and ³¹P Nuclear Magnetic Resonance (NMR) spectra were acquired with a Bruker[®] Avance DPX 300/Avance II 400 Ultrashield spectrometer at 298K in the deuterated solvent stated and referenced to Si(CH₃)₄, residual solvent resonances (¹H) or external references (¹³C, ¹⁹F and ³¹P). Signal positions were recorded in δ p.p.m with the abbreviations s, bs, d, dd, t, br and m denoting singlet, broad singlet, doublet, doublet of doublets, triplet, broad and multiplet respectively. The abbreviation Ar is used to denote aromatic. All NMR chemical shifts are quoted in ppm. All coupling constants, *J* are quoted in Hertz (Hz).

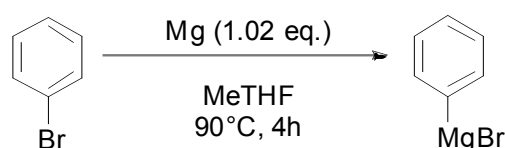
GC-MS spectra were acquired with an Agilent[®] 6890+ Series GC system equipped with an Agilent[®] 5973 Network Mass Selective Detector (MSD). Using a Supelco[®] MDN-35 column, (30 m x 250 μm, 0.25 μm) and He as the carrier gas at a constant flow rate of 1 mL/min. The temperature was ramped up from 50-280°C over a period of 26 mins, using an injection of 1 μL of sample.

Synthesis of “Super concentrated” (5M) fluorinated Grignard (F₃C-*p*)ArMgBr)



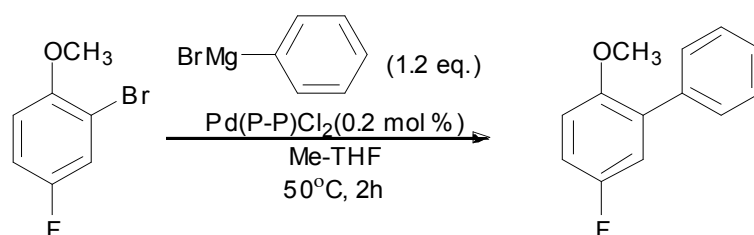
4-bromobenzotrifluoride (5 g, 3.07 mL, 22 mmol) in Me-THF (4.4 mL) was added DROPWISE to the Mg (0.545 g, 1.02 eq., 22.4 mmol) NO INITIATOR NEEDED. CAUTION, EXOTHERM! (Heat generated sufficient to maintain gentle reflux). After addition, the reaction mixture was warmed to 50°C for 2h (until the Mg was consumed) to give a dark yellow solution. An aliquot was hydrolysed with ice-cold aqueous NH₄Cl and the organics dried over MgSO₄, ¹⁹F NMR spectroscopy of the organics showed a singlet at -63.348 p.p.m for benzotrifluoride (distinguishable from starting material by spiking experiments (-63.251)). This confirms one species as the Grignard present before hydrolysis.

“Synthesis of “Super concentrated” (5M) Grignard (PhMgBr)



Bromobenzene (5 g, 3.36 mL, 32 mmol) in Me-THF (6.4 mL) was added DROPWISE to the Mg (0.789 g, 1.02 eq., 32.5 mmol) *via* an addition funnel. NO INITIATOR NEEDED. CAUTION, EXOTHERM! (Heat generated sufficient to maintain gentle reflux). After addition, the reaction mixture was warmed to 90°C for 4h (until the Mg was consumed) to give a bright orange solution.

Example procedure for Grignard cross-coupling of 2-bromo-4-fluoroanisole with PhMgBr in concentrated Me-THF.



To a solution of the Grignard (PhMgBr) in Me-THF (0.24 mL, 1.2 eq., 1.2 mmol), 2-bromo-4-fluoroanisole (0.205 g, 0.13 mL, 1mmol) was added followed by the catalyst [Pd(DPPP)Cl₂] (0.2 mol %, 1.2 mg) and the reaction mixture heated to 50°C for 2h. ¹H, ¹⁹F NMR spectroscopy and GCMS showed the desired product. Excess Grignard was quenched with solid NH₄Cl, organics filtered through a plug of MgSO₄ (washed with 0.6 mL MeTHF) and concentrated *in vacuo* to give a yellow oil in essentially quantitative yield. GCMS: Retention time, MS (EI) m/z (%): 18.706 mins (96 %), [M⁺] = 202.1; C₁₄H₁₀F₄O requires 202.08. Column chromatography (Petroleum ether 40-60) yielded the product as a colourless liquid (0.173 g, 0.86 mmol, 86 %). This compound has been reported previously.² ¹H NMR (400 MHz, CDCl₃) δ= 3.82 (3H, s, OCH₃), 6.81 (1H, dd, *J*= 4.62, 8.8 Hz, ArCH), 6.87-6.94 (1H, m, ArCH), 6.96 (1H, dd, *J*= 3.2, 9.2 Hz, ArCH), 7.25 (1H, tt, *J*= 7.54, 1.4 Hz, ArCH), 7.34 (2H, t, *J*= 6.96 Hz, ArCH), 7.4-7.45 (2H, m, ArCH); ¹⁹F[¹H] NMR (376.5 MHz, CDCl₃) δ= -124.51; ¹³C NMR (100 MHz, CDCl₃) δ= 56.2, 112.3, 112.4, 114.2, 114.4, 117.3, 117.6, 127.4, 128.2, 129.4, 132.0, 132.1, 137.5, 152.7, 156.7 (d, *J*= 236.4 Hz); MS (EI) m/z (%): 202.1 (100.0) [M⁺].

Similar protocols were used for the other screening experiments, with product identities, and conversions determined by ¹H NMR spectroscopy against an internal standard, GCMS analysis and where applicable, ¹⁹F NMR spectroscopy. The data obtained matching literature values and samples previously prepared in the group by other methods.

Selected data:

Grignard cross-coupling of 2-bromo-4-fluoroanisole and 4-F₃CArMgBr

GCMS (see general experimental): Retention time, MS (EI) m/z (%): 18.345 mins (66%, [M⁺] = 270.1 (C₁₄H₁₀F₄O requires [M⁺] = 270.07. This compound has been prepared previously.¹ ¹H NMR (400 MHz, CDCl₃) δ= 3.79 (3H, s, OCH₃), 6.88-7.01 (3H, m, ArCH), 7.19-7.24 (2H, m, ArCH), 7.52-7.62 (2H, m, ArCH); ¹⁹F[¹H] NMR (376.5 MHz, CDCl₃) δ= -62.90 (s), -122.65 (s).

Grignard cross-coupling of 4-bromoanisole with PhMgBr

GCMS: Retention time, MS (EI) m/z (%): 19.578 mins (66%, [M⁺] = 184.11. (C₁₃H₁₂O requires [M⁺] = 184.09. This compound has been reported previously.³ (67 % product, 28 % SM) ¹H NMR (400 MHz, CDCl₃) δ= 3.82 (3H, s, OCH₃), 6.89 (2H, d, ArCH, ¹*J*= 7.9 Hz), 7.02-7.6 (7H, m, ArCH)

Grignard cross-coupling of 4-chlorobenzotrifluoride with PhMgBr

GCMS: Retention time, MS (EI) m/z (%): 17.287 mins (97%, [M⁺] = 222.1; C₁₃H₉F₃ requires 222.07 (93 % product, 7 % SM). This compound has been reported previously.⁴ ¹H NMR (400 MHz, CDCl₃) δ= 7.01-7.60 (9H, m, ArCH); ¹⁹F[¹H] NMR (376.5 MHz, CDCl₃) δ= -62.886

Grignard cross-coupling of 4-bromo-*N,N'*-dimethylaniline with PhMgBr

GCMS: Retention time, MS (EI) *m/z* (%): 20.9 mins (66%, [M⁺] = 197.1; C₁₄H₁₅N requires 197.12. This compound has been reported previously.⁵ ¹H NMR (400 MHz, CDCl₃) δ = 3.21 (6H, s, N(CH₃)₂), 7.01-7.58 (9H, m ArCH)

Improved method for preparation of Pd complexes

1,1'-bis(diisopropylphosphino)ferrocene palladium(II) dichloride [Pd(DIPPF)Cl₂]

Diisopropylphosphino ferrocene (DIPPF) (1 eq, 0.142 g, 0.339 mmol) was added to a solution of Na₂PdCl₄ (0.1 g, 0.339 mmol) in Me-THF/acetonitrile (3 mL/0.1 mL) to give a dark orange solution, which was subjected to microwave conditions at 140°C for 10 minutes at high absorption to give a red precipitate. This was filtered and washed with water (3 mL) to give a red-brown solid in quantitative yield. Examination of the filtrates in all reactions revealed no product. (0.201 g, 0.339 mmol, >99 %, >99 % purity). This compound has been reported previously by another route.⁶ ¹H NMR (300.06 MHz, CDCl₃) δ_H 4.54 (s, 4H, CpH), 4.45 (s, 4H, CpH), 2.91-2.98 (m, 4H, CHP), 1.56 (dd, 12H, *J* = 15.3, 7.1 Hz, CH₃), 1.15 (dd, 12H, *J* = 7.1, 15.3 Hz, CH₃); ³¹P[¹H] NMR (121.466 MHz, CDCl₃) δ_P 64.47 (s) [Lit (C₆D₆) δ_P 65.8 (s)]

1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium(II) dichloride [Pd(DTBPF)Cl₂]

Di-*tert*-butylphosphino ferrocene (DTBPF) (1 eq, 0.161 g, 0.339 mmol) was added to a solution of Na₂PdCl₄ (0.1 g, 0.339 mmol) in Me-THF/acetonitrile (3 mL/ 0.1 mL) to give a yellow/brown solution, which was subjected to microwave conditions at 140°C for 10 minutes at high absorption to give a red precipitate. This was filtered and washed with water (3 mL) to give a red-brown solid in quantitative yield. Examination of the filtrates in all reactions revealed no product. (0.221 g, 0.339 mmol, >99 %, ~95% purity). This compound has been reported previously by another route.⁷ ¹H NMR (300.06 MHz, CDCl₃) δ_H 4.54 (s, 4H, CpH), 4.45 (s, 4H, CpH), 1.51-1.59 (m, 36H CH₃); ³¹P[¹H] NMR (121.466 MHz, CDCl₃) δ_P 67.82 (s)

1,1'-bis(diphenylphosphino)ferrocene palladium(II) dichloride [Pd(DPPF)Cl₂]

1,1'-Bis-Diphenylphosphino ferrocene (DPPF) (1 eq, 0.188 g, 0.339 mmol) was added to a solution of Na₂PdCl₄ (0.1 g, 0.339 mmol) was dissolved in Me-THF/acetonitrile (3 mL/0.1 mL) to give a red orange solution, which was subjected to microwave conditions at 140°C for 10 minutes at high absorption to give a red precipitate. This was filtered and washed with water (3 mL) to give a red-brown solid in quantitative yield. Examination of the filtrates in all reactions revealed no product. (0.248 g, 0.339 mmol, >99 %, >99 % purity). This compound has been reported previously by another route.⁸ ¹H NMR (300.06 MHz, CDCl₃) δ_H 7.2-7.9 (m, 20H, ArH), 4.5 (s, 4H, CpH), 4.25 (s, 4H, CpH); ³¹P[¹H] NMR (121.466 MHz, CDCl₃) δ_P 35.24 (s) [Lit δ_P 34.5 (s)]⁸

1-bis(di-*tert*-butylphosphino)-1'-bis(diphenylphosphino)ferrocene palladium(II) dichloride [Pd(DTBDPPF)Cl₂]

1-(di-*tert*-butyl)-1'-(diphenylphosphino)ferrocene (DTBDPPF) (1 eq, 0.174 g, 0.339 mmol) was added to a solution of Na₂PdCl₄ (0.1 g, 0.339 mmol) in Me-THF/acetonitrile (3 mL/ 0.1 mL) to give a red solution, which was subjected to microwave conditions at 140°C for 10 minutes at high absorption to give a red precipitate. This was filtered and washed with water (3 mL) to give a red-solid in quantitative yield. Examination of the filtrates in all reactions revealed no product. (0.234 g, 0.339 mmol, 95 %, >99% purity). This compound has been reported previously by another route.⁷ mp >230°C; ¹H NMR (300.06 MHz, CDCl₃) δ_H 7.91-8.03 (m, 4H, ArH), 7.20-7.38 (m, 6H, ArH), 4.81 (s, 2H, CHP), 4.43 (s, 2H, CpH), 4.21 (s, 2H, CpH), 3.87 (s, 2H, CHP), 1.56 (d, 18H, *J* = 14.6 Hz, CH₃); ³¹P[¹H] NMR (121.466 MHz, CDCl₃) δ_P 39.57 (d, 1P) (¹*J*_{P-P} 20.9), 81.28 (d, 1P) (¹*J*_{P-P} 20.8); LR-MS: [FAB] [M-Cl]⁺ = 655.0;

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