

Robust and Reusable Supported Palladium Catalysts for Cross-coupling Reactions in Flow

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General Considerations

Unless otherwise noted, all reagents and catalysts were commercially available and purchased from Sigma-Aldrich Ltd, Fischer Scientific Ltd., Johnson Matthey, Strem Chemical, Frontier Scientific chemical companies, and were used without further purification. All solvents were degassed before use. Continuous flow experiments were conducted using a Vapourtec R-Series instrument fitted with 6.6 mm x 100 mm Omnifit columns.¹ Silica gel plates (GF₂₅₄) were used for TLC monitoring and silica gel (230-400 mesh) was used for flash column chromatography. ¹H NMR spectra were recorded on Bruker Avance 250 and 300 MHz instruments and ¹³C NMR spectra were recorded on a Bruker Avance 300 MHz instrument, all with TMS as the internal standard. The mass spectra were run on a microTOF electrospray time of flight (ESI-TOF) coupled to an Agilent 1200 LC system (University of Bath). IR spectra were recorded on Perkin-Elmer 1600 FT IR spectrometer with only selected absorbance quoted as ν in cm⁻¹.

Experimental Procedures

Silica dioxide preparation

A solution of triethyl orthosilicate (16 mL, 72 mmol) and ammonium hydroxide (13.1 mL) in ethanol (188 mL) was stirred at room temperature for 24 hours. The product was isolated by centrifugation followed by washing with methanol (2 × 50 mL). This afforded silica dioxide as a colourless powder (10.4g).

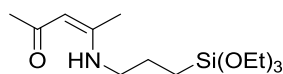
Preparation of functionalised silica (1)

A suspension of silica dioxide (1.7 g) in toluene was sonicated for 10 minutes before the addition of *N*-[3-(trimethoxysilyl)propyl]-ethyldiamine (5.7 mL). The suspension was stirred at reflux for 16 hours. Product was separated by centrifugation, washing with toluene (2 × 30 mL) and ethanol (2 × 30 mL). This afforded **1** as a light yellow powder (1.34 g).

Preparation of functionalised silica (**2**)

A suspension of silica dioxide (2.2 g) in toluene was sonicated for 10 minutes before the addition of 4-[[3-(triethoxysilyl)propyl]amino]-3-penten-2-one (13 g). The suspension was stirred at reflux for 16 hours. Product was separated by centrifugation, washing with toluene (2 × 30 mL) and ethanol (2 × 30 mL). This afforded **2** as a yellow powder (1.74 g).

Preparation of 4-[[3-(triethoxysilyl)propyl]amino]-3-penten-2-one



A solution of 2,4-pentadione (10 mL, 100 mmol) and 3-aminopropyltriethoxysilane (21 mL, 90 mmol) in methanol (60 mL) were heated to 80 °C and stirred at this temperature for 16 hours. After volatile removal 4-[[3-(triethoxysilyl)propyl]amino] 3-penten-2-one was isolated (26 g, 87 %) as a yellow oil. ¹H NMR (250 MHz, CDCl₃) δ δ 10.85 (br s, 1H), 4.94 (s, 1H), 3.81 (q, *J* = 7.0 Hz, 4H), 3.23 (q, *J* = 7.1 Hz, 2H), 1.99 (s, 3H), 1.91 (s, 3H), 1.69 (dt, *J* = 15.7, 8.0 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 6H), 0.66 (dd, *J* = 9.4, 7.1 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 194.6, 163.0, 95.1, 58.5, 45.5, 28.8, 23.9, 18.8, 18.3, 7.6. Data in accordance with literature values.²

General procedure for the preparation of Pd⁰ nanoparticles on functionalised silica

A suspension of functionalised silica (1.74 g) in ethanol (40 mL) was sonicated for 10 minutes. Pd(OAc)₂ (174 mg) was added and the mixture was stirred at room temperature for three hours. The dark solid was isolated by filtration and added to water (30 mL). The Pd^{II} species was reduced to Pd⁰ by the stepwise addition of NaBH₄ (1 g) over three hours. After complete addition the product was collected by filtration, washing with water. After drying a grey solid of Pd⁰ ligated to functionalised silica (1.2 g) was isolated.

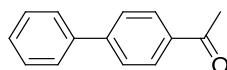
General procedure for the preparation of polymer encapsulated Pd⁰ nanoparticles

A suspension of Pd⁰ functionalised silica (0.15 g) in water (17 mL) was sonicated for 10 minutes. Allylamine (0.12 mL) and PVP (polyvinylpyrrolidinone) (250 mg) were added and the mixture was stirred at room temperature for one hour. Sodium styrene sulphonate (0.075 g), potassium peroxydisulfate (75 mg) and water (25 mL) were added and the mixture stirred for 30 minutes. Styrene (1.0 mL) and divinyl benzene (0.1 mL) were added and the mixture stirred at 80 °C for 12 hours. After filtration and washing with water the catalyst was afforded (140 mg) as a grey powder.

General procedure for Suzuki-Miyaura coupling under flow conditions

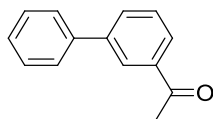
A solution of iodide (0.05 mol/L), boronic acid (0.1 mol/L) and *N*-diisopropylethyl amine (0.1 mol/L mmol) in MeOH: H₂O: DME (2:1:2) (40 mL) was pumped around the Vapourtec R-2+ module in conjunction with the R-4 reactor heater. This was fitted with a 6.6 x 100 mm Omnifit glass column containing a homogeneous mixture of polymer encapsulated catalyst 3 or 4 (200 mg) and sand (1.5 cm), to a total length of 4 cm. The reaction column was purged with MeOH: H₂O: DME (2:1:2) (5 mL) and heated to 120 °C before the reagent solution was introduced. The temperature was maintained at 120 °C throughout and an additional portion of MeOH: H₂O: DME (2:1:2) (5 mL) was pumped through the reactor after all of the reagent solution had been used.

4-phenylacetophenone



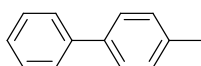
4-iodoacetophenone (492 mg, 2 mmol) and benzenboronic acid (484 mg, 4 mmol). ¹H NMR (300 MHz, CDCl₃) δ 8.03 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 6.9 Hz, 2H), 7.52 – 7.36 (m, 3H) 2.63 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 197.7, 145.7, 139.8, 135.8, 128.9, 128.9, 128.2, 127.2, 127.2, 26.7. Data in accordance with literature values.³

3-phenylacetophenone



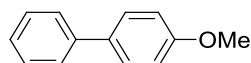
3-iodoacetophenone (492 mg, 2 mmol) and benzenboronic acid (484 mg, 4 mmol). **¹H NMR** (250 MHz, CDCl₃) δ 8.19 (t, *J* = 1.7 Hz, 1H), 7.94 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.80 (ddd, *J* = 7.7, 1.8, 1.2 Hz, 1H), 7.63 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.53 – 7.37 (m, 3H), 2.67 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 198.2, 141.8, 140.2, 137.7, 131.8, 129.1, 129.0, 127.9, 127.3, 127.0, 26.8. Data in accordance with literature values.⁴

4-methylbiphenyl



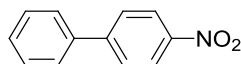
4-iodotoluene (436 mg, 2 mmol) and benzenboronic acid (484 mg, 4 mmol). **¹H NMR** (300 MHz, CDCl₃) δ 7.81 – 7.70 (m, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.59 (td, *J* = 6.7, 6.3, 1.6 Hz, 2H), 7.52 – 7.45 (m, 1H), 7.41 (d, *J* = 7.9 Hz, 2H) 2.56 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 142.1, 142.1, 135.4, 130.4, 129.9, 129.3, 128.2, 127.3, 126.9, 125.9, 20.6. Data in accordance literature values.⁵

4-methoxybiphenyl



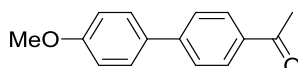
4-iodoanisole (468 mg, 2 mmol) and benzenboronic acid (484 mg, 4 mmol). **¹H NMR** (300 MHz, CDCl₃) δ 7.61 – 7.56 (m, 4H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.0 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 2H), 3.88 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 159.2, 140.9, 133.9, 128.8, 128.2, 126.8, 126.8, 114.3, 55.4. Data in accordance with literature values.⁶

4-nitrobiphenyl



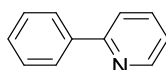
4-iodonitrobenzene (498 mg, 2 mmol) and benzeneboronic acid (484 mg, 4 mmol). **¹H NMR** (300 MHz, CDCl₃) δ 8.30 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 8.9 Hz, 2H), 7.68 – 7.59 (m, 2H), 7.57 – 7.39 (m, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 147.7, 147.1, 138.8, 129.2, 129.0, 127.8, 127.4, 124.2. Data in accordance with literature values.⁷

4'-acetyl-4-methoxybiphenyl



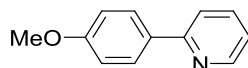
4-iodoacetophenone (492 mg, 2 mmol) and methoxyphenyl boronic acid (600 mg, 4 mmol). **¹H NMR** (300 MHz, CDCl₃) δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 2.62 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 197.8, 159.9, 145.4, 135.3, 132.2, 129.0, 128.4, 126.6, 114.5, 55.4, 26.7. Data in accordance with literature values.⁸

2-phenylpyridine



2-bromopyridine (0.19 mL, 2 mmol) and benzeneboronic acid (484 mg, 4 mmol). **¹H NMR** (300 MHz, CDCl₃) δ 8.70 (d, *J* = 5.3 Hz, 1H), 8.01 (d, *J* = 7.2 Hz, 2H), 7.70 (d, *J* = 3.7 Hz, 2H), 7.54 – 7.37 (m, 3H), 7.27 – 7.13 (m, 1H). **¹³C NMR** (75 MHz, CDCl₃) δ 157.3, 149.6, 139.3, 136.8, 128.9, 128.7, 126.9, 122.1, 120.6. Data in accordance with literature values.⁹

2-(4-methoxyphenyl)pyridine

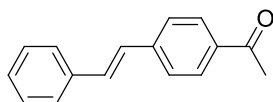


2-bromopyridine (0.19 mL, 2 mmol) and methoxyphenyl boronic acid (600 mg, 4 mmol). ^1H NMR (300 MHz, CDCl_3) δ 8.65 (d, J = 4.6 Hz, 1H), 7.95 (d, J = 8.9 Hz, 2H), 7.79 – 7.49 (m, 2H), 7.21 – 7.09 (m, 1H), 7.00 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 160.5, 157.2, 149.6, 136.8, 132.1, 128.2, 121.5, 119.9, 114.2, 55.4. Data in accordance with literature values.¹⁰

General procedure for Heck coupling under flow conditions

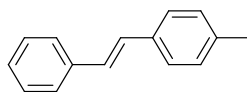
A solution of iodide (0.05 mol/L), alkene (0.1 mol/L) and 1-methyl-2-dicyclohexylamine (0.1 mol/L) in NMP (40 mL) was pumped around the Vapourtec R-2+ module in conjunction with the R-4 reactor heater. This was fitted with a 6.6 x 100 mm Omnifit glass column containing a homogeneous mixture of polymer encapsulated catalyst **3** or **4** (200 mg) and sand (1.5 cm), to a total length of 4 cm. The reaction column was purged with NMP (5 mL) and heated to 140 °C before the reagent solution was introduced. The temperature was maintained at 140 °C throughout and an additional portion of NMP (5 mL) was pumped through the reactor after all of the reagent solution had been used.

trans-4-acetylstilbene



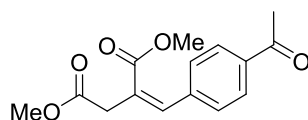
4-iodoacetophenone (492 mg, 2 mmol) and styrene (0.46 mL, 4 mmol). ^1H NMR (300 MHz, CDCl_3) δ 7.96 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 7.2 Hz, 2H), 7.39 (t, J = 7.3 Hz, 2H), 7.34 – 7.26 (m, 1H), 7.18 (d, J = 16.0 Hz, 2H), 2.61 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 197.6, 142.1, 136.7, 136.0, 131.5, 129.0, 128.9, 128.4, 127.5, 126.9, 126.6, 26.7. Data in accordance with literature values.¹¹

***trans*-4-methylstilbene**



4-iodotoluene (436 mg, 2 mmol) and styrene (0.46 mL, 4 mmol). **¹H NMR** (300 MHz, CDCl₃) δ 7.37 (d, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 7.0 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.95 (s, 2H), 2.23 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 137.5, 137.5, 134.6, 129.4, 128.7, 128.7, 127.7, 127.4, 126.5, 126.5, 21.3. Data in accordance with literature values.¹²

dimethyl 2-(4-acetylbenzylidene)malonate



4-iodoacetophenone (492 mg, 2 mmol) and dimethyl itaconate (0.62 mL, 4 mmol). **IR** (neat, cm⁻¹) ν 2101, 1738, 1706, 1673. **¹H NMR** (300 MHz, CDCl₃) δ 7.96 (d, *J* = 8.3 Hz, 2H), 7.88 (s, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 3.82 (s, 3H), 3.71 (s, 3H), 3.49 (s, 2H), 2.59 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 197.4, 171.3, 167.4, 140.9, 139.5, 137.0, 129.2, 128.6, 127.7, 52.5, 52.3, 33.5, 26.7. **HRMS** (ESI) calcd for C₁₅H₁₇O₅ [M+H]⁺: 277.1076, found 277.1055.

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