Captured and Cross-Linked Palladium Nanoparticles

Jin Ku Cho,[†] Romain Najman,[†] Tony W. Dean,[‡] Osamu Ichihara,[§] Christophe Muller,[§]
and Mark Bradley^{*,†}

[†] *School of Chemistry, Joseph Black Building, King's Buildings, The University of
Edinburgh, West Mains Road, Edinburgh EH9 3JJ, United Kingdom,*

[‡] *GlaxoSmithKline, Discovery Research, Gunnels Wood Road, Stevenage SG1 2NY,
United Kingdom*

[§] *Evotec Ltd, Milton Park, Abingdon, Oxfordshire OX14 4RZ, United Kingdom*

Supporting Information

Preparation of XL-RC Palladium: In the 28 mL-vial were put aminomethylated TentaGel resin (NovaSyn[®] TG amino resin HL, 1.00 g, 0.44 mmol of NH₂/g) and palladium acetate (100 mg, 0.45 mmol) and toluene (10 mL) was added. The mixture was heated to 80 °C for 10 min and shaken at room temperature for 2 h. The resin was filtered and washed with dichloromethane (5 × 20 mL), methanol (5 × 20 mL), and *N,N'*-dimethylformamide (5 × 20 mL). The resin treated with 10% hydrazine hydrate in methanol (10 mL) (*or prolonged stirring in toluene at 80 °C can also afford reduced Pd(0) without hydrazine treatment*) gave RC Pd catalyst of black color in 84% of capturing yield (0.38 mmol of Pd/g). The resulting resin was cross-linked with succinyl chloride (24 μL, 0.22 mmol) and triethylamine (184 μL, 1.32 mmol) in dry dichloromethane (10 mL). After shaking for 1 h, the resin was filtered and washed with dichloromethane (5 × 20 mL), methanol (5 × 20 mL), and *N,N'*-dimethylformamide (5 × 20

mL) and dried under reduced pressure to give final XL-RC Pd catalyst in 80% overall yield based on the amount of initially used palladium (0.36 mmol of Pd/g).

TEM analysis: Sample beads (RC-XL Pd) were embedded in Spurr resin and polymerized at 60 °C for 18 h. 100 nm sections were cut on a Reichert OMU3 ultramicrotome using a diamond knife. The sections were viewed on Hitachi H7000 transmission electron microscope.

Kinetic profile comparison: 4'-Bromoacetophenone (13 mg, 0.067 mmol), phenylboronic acid (10 mg, 0.08 mmol, 1.2 equiv), each supported palladium catalyst (10 mol%), and potassium carbonate (28 mg, 0.2 mmol, 3 equiv) were loaded in 1.5 mL eppendorf tubes (same amount of 6 samples). Water (300 µL) was added and the reaction mixture was stirred at 80 °C. Each sample was quenched by adding cold water (500 µL) and diethyl ether (500 µL) after 5 min, 10 min, 30 min, 1 h, 2 h, 4 h, respectively. The organic layer of each sample was analyzed by HPLC.

Filtration test: RC-XL Pd (140 mg, 0.36 mmol of Pd / g resin, 0.05 mmol of Pd, 10 mol%) was loaded in 2-5 mL Emrys™ Process Vials. Water (2 mL) was added and the reactor was sealed by the septum. The RC-XL Pd was stirred at 80 °C for 20 min and then filtered while still hot. The filtrate was kept at 80 °C and 4'-bromoacetophenone (99 mg, 0.5 mmol), phenylboronic acid (73 mg, 0.6 mmol, 1.2 equiv), potassium carbonate (207 mg, 1.5 mmol, 3 equiv) were added. The reaction mixture was stirred for 3 h and the resulting crude following general workup procedure was analyzed by HPLC.

Three phase reaction: 4'-Bromoacetophenone (199 mg, 1 mmol), resin-bound 4'-bromoaceto-phenonamide attached by Rink linker (24 mg, 0.01 mmol, 0.01 equiv), phenylboronic acid (183 mg, 1.5 mmol, 1.5 equiv), each supported palladium catalyst (5

mol%), and potassium carbonate (415 mg, 3 mmol, 3 equiv) were loaded in 2-5 mL Emrys™ Process Vials from Personal Chemistry. Water (5 mL) was added and the reactor was sealed by the septum designed by Reseal™. The reaction mixture was stirred at 80 °C for 16 h. Each resin-bound compounds and supported catalyst were filtered and washed with dichloromethane (5×3 mL) and water (5×3 mL). The combined filtrate was washed with water and the organic phase was separated and concentrated with reduced pressure. The resulting crude was purified by column chromatography on silica gel to give corresponding 4-acetyl biphenyl. On the other hand, the collected resins were treated with 90% trifluoroacetic acid in dichloromethane (3 mL) to release the products from resin. The resins was filtered and washed with dichloromethane (3×1 mL). The combined filtrates was concentrated with positive nitrogen blowing and diluted with acetonitrile for HPLC analysis.

General procedure for aqueous Suzuki Coupling of aryl halides: Aryl halide (0.5 mmol), boronic acid (0.75 mmol, 1.5 equiv), potassium carbonate (1.5 mmol, 3 equiv), and XL-RC Pd catalyst (0.05 mmol, 0.1 equiv) were loaded into 2-5 mL Emrys™ Process Vials. Water (2 mL) was added and the reactor was sealed by the septum. The reaction mixture was stirred at 80 °C for 4-16 h. At the conclusion of the reaction, the supported catalyst was filtered and washed with diethyl ether (5×3 mL) and water (5×3 mL) by turns. The combined filtrate was washed with water and the organic phase was separated and concentrated with reduced pressure. The resulting crude was purified by column chromatography on silica gel to give final biaryl product.

4-Acetylbiphenyl (Table 1, entry 1). The general procedure gave 96 mg (98 %) of white solid: ^1H NMR (300 MHz, CDCl_3) δ 8.05 (d, 2H, $J=8.1$ Hz), 7.70 (d, 2H, $J=8.7$ Hz), 7.65 (d, 2H, $J=8.1$ Hz), 7.47-7.52 (m, 2H), 7.43 (d, 1H, $J=6.6$ Hz), 2.64 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 197.8, 145.8, 140.0, 135.8, 129.0, 128.9, 128.2, 127.3, 127.2, 26.7.

4-Nitrobiphenyl (Table 1, entry 3). The general procedure gave 93 mg (93 %) of pale yellow solid: ^1H NMR (300 MHz, CDCl_3) δ 8.30 (d, 2H, $J=8.7$ Hz), 7.74 (d, 2H, $J=8.7$ Hz), 7.61-7.65 (m, 2H), 7.45-7.53 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 147.6, 138.7, 129.1, 128.9, 127.8, 127.4, 124.1.

4-Methylbiphenyl (Table 1, entry 4). The general procedure gave 70 mg (83 %) of white solid: ^1H NMR (300 MHz, CDCl_3) δ 7.62 (d, 2H, $J=6.6$ Hz), 7.54 (d, 2H, $J=8.1$ Hz), 7.46 (t, 2H, $J=7.5$ Hz), 7.36 (t, 1H, $J=7.5$ Hz), 7.29 (d, 2H, $J=7.5$ Hz), 2.44 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 141.1, 138.3, 137.0, 129.4, 128.73, 128.63, 127.1, 126.9, 21.1.

2-Methylbiphenyl (Table 1, entry 5). The general procedure gave 61 mg (72 %) of colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.42-7.47 (m, 2H), 7.34-7.39 (m, 3H), 7.26-7.30 (m, 4H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 141.9, 138.9, 135.3, 130.3, 129.8, 129.2, 128.0, 127.2, 126.7, 125.7, 20.5.

4-Methoxybiphenyl (Table 1, entry 6). The general procedure gave 87 mg (94 %) of white solid: ^1H NMR (300 MHz, CDCl_3) δ 7.52-7.56 (m, 4H), 7.41 (t, 2H, $J=7.4$ Hz), 7.30 (t, 1H, $J=7.2$ Hz), 6.98 (d, 2H, $J=8.7$ Hz), 3.84 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.1, 138.2, 133.8, 128.7, 128.2, 126.8, 126.7, 114.2, 55.4.

2,4-Dimethoxybiphenyl (Table 1, entry 7). The general procedure gave 67 mg (63 %) of colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.53 (d, 2H, $J=8.1$ Hz), 7.42 (t, 2H, $J=8.1$ Hz), 7.33 (d, 1H, $J=7.2$ Hz), 7.27 (d, 1H, $J=9.0$ Hz), 6.58-6.62 (m, 2H), 3.88 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 157.4, 138.3, 131.2, 129.4, 127.9, 126.5, 123.5, 104.5, 98.9, 55.5, 55.4.

4-Methyl-4'-methoxybiphenyl (Table 1, entry 8). The general procedure gave 81 mg (82 %) of white solid: ^1H NMR (300 MHz, CDCl_3) δ 7.52 (d, 2H, $J=9.0$ Hz), 7.46 (d, 2H, $J=8.1$ Hz), 7.24 (d, 2H, $J=8.1$ Hz), 6.98 (d, 2H, $J=9.0$ Hz), 3.86 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 158.9, 138.0, 136.4, 133.7, 129.5, 128.0, 126.6, 114.2, 55.4, 21.1.

2-Methyl-4'-methoxybiphenyl (Table 1, entry 9). The general procedure gave 61 mg (62 %) of colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.25-7.30 (m, 6H), 6.98 (d, 2H, $J=8.7$ Hz), 3.88 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3) δ 158.5, 141.5, 135.5, 134.3, 130.2, 129.9, 126.9, 125.7, 113.4, 55.3, 20.5.

4-Methoxy-4'-methoxybiphenyl (Table 1, entry 10). The general procedure gave 97 mg (91 %) of white solid: ^1H NMR (300 MHz, CDCl_3) δ 7.49 (d, 4H, $J=8.7$ Hz), 6.97 (d, 4H, $J=9.0$ Hz), 3.85 (s, 6H); ^{13}C NMR (300 MHz, CDCl_3) δ 158.6, 133.4, 127.7, 114.1, 55.3.

Recycle Test for aqueous Suzuki Coupling of 4-acetophenyl bromide and phenylboronic acid: After aqueous Suzuki coupling, XL-RC Pd catalyst was collected, washed, dried, and reused for next cycle. Each cycle followed the general procedure for aqueous Suzuki coupling of aryl halide to give corresponding product in 99% (1st use), 98% (2nd use), 98% (3rd use), 98% (4th use), 98% (5th use), 97% (6th use) yield based on HPLC.

Bromophenol blue derivatives (Table 2).

Bromophenol blue (0.5 mmol), carboxyphenylboronic acid (0.6 mmol, 1.2 equiv), potassium phosphate (1.5 mmol, 3 equiv), and XL-RC Pd catalyst (0.05 mmol, 0.1 equiv)

were loaded into Emrys™ Process Vials. Water (5 mL) was added and the reactor was sealed by the septum. The reaction mixture was irradiated by microwave at 120 °C for 10 min. At the conclusion of the reaction, the supported catalyst was filtered and washed with ethyl acetate, water, and saturated KHSO₄ solution by turns. The combined filtrate was extracted with ethylacetate, dried over Na₂SO₄, and evaporated under reduced pressure to afford a reddish oil. The product was isolated by column chromatography on silica gel (chloroform:methanol:acetic acid=5:1:0.06) to give the desired bromophenol blue derivative in 41% yield: ¹H NMR (400 MHz, 5% CF₃CO₂D in CD₃CN): δ= 8.03 (d, 2H, *J* = 8.4), 7.95 (d, 1H, *J* = 6.8), 7.82 (t, 1H, *J* = 7.6), 7.74 (t, 1H, *J* = 7.8), 7.58 (d, 1H, *J* = 7.6), 7.54 (d, 2H, *J* = 8.4), 7.47 (d, 1H, *J* = 2.4), 7.45 (s, 2H), 7.17 (d, 1H, *J* = 2.0); a calculated mass for C₂₆H₁₅Br₃O₇S: 711.2, found: ESI-MS, *m/z*, negative [M-H]⁻: 708.4, 710.6.

Bromocresol purple derivatives (Table 2).

Bromocresol purple (0.5 mmol), carboxyphenylboronic acid (0.6 mmol, 1.2 equiv), potassium phosphate (1.5 mmol, 3 equiv), and XL-RC Pd catalyst (0.05 mmol, 0.1 equiv) were loaded into Emrys™ Process Vials. Water (5 mL) was added and the reactor was sealed by the septum. The reaction mixture was irradiated by microwave at 120 °C for 10 min. At the conclusion of the reaction, the supported catalyst was filtered and washed with ethyl acetate, water, and saturated KHSO₄ solution by turns. The combined filtrate was extracted with ethylacetate, dried over Na₂SO₄, and evaporated under reduced pressure to afford a reddish oil. The product was isolated by column chromatography on silica gel (chloroform:methanol=5:1) to give the desired bromocresol purple derivative in 57% yield: ¹H NMR (400 MHz, 5% CF₃CO₂D in CD₃CN): δ= 8.03 (d, 2H, *J* = 8.0 Hz), 7.91 (d, 1H, *J* = 8.0 Hz), 7.78 (t, 1H, *J* = 7.6 Hz), 7.71 (t, 1H, *J* = 7.6 Hz), 7.51-7.54 (m, 3H), 7.27 (d, 1H, *J* = 2.4 Hz), 7.11 (d, 1H, *J* = 2.4 Hz), 7.09 (s, 2H, *J* = 2.8 Hz), 6.99 (d, 1H, *J* = 2.8 Hz), 2.23 (s, 3H), 2.21 (s, 3H); a calculated mass for C₂₈H₂₁BrO₇S: 581.4, found: ESI-MS, *m/z*, negative [M-H]⁻: 579.3, 581.3.

Bromothymol blue derivatives (Table 2).

Bromothymol blue (0.5 mmol), carboxyphenylboronic acid (0.6 mmol, 1.2 equiv), potassium phosphate (1.5 mmol, 3 equiv), and XL-RC Pd catalyst (0.05 mmol, 0.1 equiv) were loaded into Emrys™ Process Vials. Water (5 mL) was added and the reactor was sealed by the septum. The reaction mixture was irradiated by microwave at 120 °C for 10 min. At the conclusion of the reaction, the supported catalyst was filtered and washed with ethyl acetate, water, and saturated KHSO₄ solution by turns. The combined filtrate was extracted with ethylacetate, dried over Na₂SO₄, and evaporated under reduced pressure to afford a reddish oil. The crude product was purified by column chromatography on silica gel (chloroform:methanol = 5:1) to give the desired bromothymol blue derivative in 28% yield: ¹H NMR (400 MHz, 5% CH₃CO₂D in (CD₃)₂SO, 100 °C): δ= 7.94-8.01 (m, 3H), 7.16-7.36 (m, 6H), 6.93 (t, 1H, *J* = 7.6 Hz), 2.96-3.12 (br, 2H), 2.19 (s, 1.5H, rotamer), 2.11 (s, 1.5H, rotamer), 1.63 (s, 1.5H, rotamer), 1.54 (s, 1.5H, rotamer), 0.97-1.03 (m, 12H); a calculated mass for C₃₄H₃₃BrO₇S: 665.6, found: ESI-MS, *m/z*, negative [M-H]⁻: 664.6, 662.7.

IR spectra

(A) Original aminomethylated TentaGel resin

(B) Resin-captured (RC) Pd(OAc)₂

(C) RC Pd after NH₂NH₂·H₂O treatment

Figure S1. IR spectra of RC Pd after NH₂NH₂·H₂O treatment.

- (A) Original aminomethylated TentaGel resin
(B) Resin-captured (RC) Pd(OAc)₂
(C) RC Pd after prolonged stirring in toluene at 80 °C

Figure S2. IR spectra of RC Pd after prolonged stirring in toluene at 80 °C.

SEM

Figure S3. SEM of XL-RC Pd.

SEM-EDX

Figure S4. SEM-EDX of XL-RC Pd.

TEM

(a) XL-RC Pd

(b) XL-RC Pd after 2nd use

(c) XL-RC Pd after 5th use

(d) XL-RC Pd after 6th use

Figure S5. TEM images of XL RC Pd after reuses (scale bar: 10 nm).