# Electronic Supplementary Data

**Continuous Flow Suzuki-Miyaura Couplings Under Aqueous Micellar Conditions in a CSTR**

Cascade Catalyzed by Fe/ppm Pd Nanoparticles

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Components of CSTR

The cylinder-shaped inner chambers on the reactor block have a diameter of 13 mm and a depth of 9 mm (Figure S1). The connecting tubes between the chambers have an inner diameter of 2.5 mm. An O-ring gap (Kalrez 4079 O-Ring) surrounds the chamber. An aluminum window has dimensions of 90 mm × 25 mm × 4.8 mm. Both aluminum covers (112 mm × 46 mm × 4.8 mm) were fabricated using water jet machining (OMAX MicroMAX JetMachining Center). The PTFE reactor chamber and aluminum housing were designed with SolidWorks and manufactured by Protolabs.

Figure S1: Images of the individual reactor components.

The aluminum housing has two holes at each side to fit cartridge heaters (8376T26, McMaster-Carr Supply Company). All connection ports have 1/4-28 threads, which can be directly connected using common IDEX fittings (IDEX Health & Science LLC.) without additional adapters. All other materials for the reactor were purchased from McMaster-Carr Supply Company.

Figure S2: Miniaturized CSTR cascade showing the reactor components
Figure S3: System schematic of CSTR platform showing the various components necessary to run a reaction containing solids

Figure S4: Photograph of the CSTR setup showing the various components necessary to run a reaction containing solids

Components with model number (Figure S4): Oscillator (Model No. 306-10H, Precision Microdrives), positive displacement pump (VICI, Model M6 pump), back-pressure regulator (Model No. BPR-10, Zaiput Flow Technologies), pressure controller (Model No. PCD-500PSIG-D, Alicat Scientific).

Applications of CSTR to Suzuki-Miyaura biaryl couplings

Reaction 1. A model biaryl coupling in a CSTR platform.
Under flow conditions: \(1\) (1.25 mL, 10.0 mmol), \(2\) (1460 mg, 12.0 mmol, 1.2 equiv.), Fe/ppm Pd NPs (718 mg, 800 ppm Pd), TPGS-750-M (800 mg, 2 wt %), and \(K_3PO_4\cdotH_2O\) (3450 mg, 15.0 mmol, 1.5 equiv.) with total volume of ~40 mL (34.8 mL \(H_2O\) + 3.95 mL THFA) were distributed among three streams, as discussed below (Scheme S1).

Scheme S1. Conditions for synthesis of \(3\) in a CSTR platform.

**Syringe 1.** In glass vial containing a PTFE coated magnetic stir bar, TPGS-750-M (800 mg, 2 wt.%) was added and sealed with a rubber septum. The vial was then inerted and degassed \(H_2O\) (17.4 mL) was added under argon flow via syringe and stirred at rt for 2 h. In a separate second vial containing a PTFE coated magnetic stir bar, Fe/ppm Pd NPs (718 mg, 800 ppm Pd) were added, sealed with a rubber septum, and inerted with argon. A solution of TPGS-750-M/\(H_2O\) (17.4 mL) from the first vial was then added to the second vial via inerted syringe under an argon flow. The mixture was then stirred at rt for 1 h. This catalyst slurry was then transferred to an inerted stainless steel syringe containing a PTFE coated magnetic stir bar and attached to syringe pump 1.

**Syringe 2.** In a glass vial containing a PTFE coated magnetic stir bar, \(1\) (1.25 mL, 10.0 mmol, 1 equiv.), and \(2\) (1460 mg, 12.0 mmol, 1.2 equiv.) were added, sealed with a rubber septum, and inerted with argon. Degassed \(THFA\) (3.95 mL) was added to the vial under argon flow via inerted syringe and stirred at rt for 1 h. This solution of substrates was then transferred to inerted stainless steel syringe and attached to syringe pump 2.

**Syringe 3.** In a glass vial containing a PTFE coated magnetic stir bar, \(K_3PO_4\cdotH_2O\) (3450 mg, 15.0 mmol, 1.5 equiv.) was added and sealed with a rubber septum. The vial was evacuated and backfilled with argon three times. Degassed \(H_2O\) (17.4 mL) was added to the vial under argon flow via inerted syringe and stirred at rt for 1 h. This solution was then transferred to an inerted stainless steel syringe and attached to syringe pump 3.

After achieving steady state (~3 residence times, 60 min), the sample was collected for 50 min and used to calculate the isolated yield of product. In 50 min, 3.3 mmol of substrate had been introduced into the reactor. The organic layer was concentrated in vacuo and then purified by flash column chromatography (\(Et_2O/hexane = 10/90\)) to afford 493 mg (2.67 mmol, ~81%) of product \(3\).

**Reaction 2:** Continuous synthesis of biaryl precursor to the sartans in flow.
Under flow conditions. 8 (1370 mg, 7.5 mmol, 1 equiv.), 9 (1220 mg, 9.0 mmol, 1.2 equiv.), Fe/ppm Pd NPs (538 mg, 800 ppm Pd), TPGS-750-M (600 mg, 2 wt %), and K₃PO₄•H₂O (2.590 g, 11.3 mmol, 1.5 equiv.) with the total volume of 30 mL (H₂O) distributed among two streams, as discussed below (Scheme S2). The flow rates of two streams were adjusted to achieve desired concentration of reagents, catalyst and the surfactant in the CSTR.

 Scheme S2. Conditions for synthesis of biaryl precursor 7 to the sartans in a CSTR platform.

Syringe 1: In a glass vial containing a PTFE coated magnetic stir bar, TPGS-750-M (600 mg, 2 wt %) was added and sealed with a rubber septum. The vial was evacuated and backfilled with argon three times. Degassed H₂O (20 mL) was added to the vial under argon flow via inerted syringe and stirred at rt for 2 h. In a separate second vial containing a PTFE coated magnetic stir bar, Fe/ppm Pd NPs (538 mg, 800 ppm Pd), 8 (1370 mg, 7.5 mmol, 1 equiv.), and 9 (1.220 g, 9.0 mmol, 1.2 equiv.) were added, sealed with a rubber septum, and inerted with argon. A solution of TPGS-750-M/H₂O (20 mL) from the first vial was then added to second vial via inerted syringe under argon flow. The mixture was then stirred at rt for 1 h. This reaction slurry was then transferred to inerted stainless steel syringe containing a PTFE coated magnetic stir bar and attached to syringe pump 1.

Syringe 2: In a glass vial containing a PTFE coated magnetic stir bar, K₃PO₄•H₂O (2.590 g, 11.3 mmol, 1.5 equiv.) was added, sealed with a rubber septum, and inerted with argon. Degassed H₂O (10 mL) was added to the vial under argon flow via inerted syringe and stirred at rt for 1 h. This solution was then transferred to an inerted stainless-steel syringe and attached to syringe pump 2.

After achieving steady state (~3 residence times, 60 min), the sample was collected for 20 min and used to calculate isolated yield of product. In 20 min, 1.32 mmol of substrate is introduced in the reactor. The organic layer of sample was concentrated in vacuo and then purified by flash column chromatography (Et₂O/hexane = 10/90) to afford 243 mg (1.26 mmol, 95%) of product 7.

Reaction 3. Continuous synthesis of a biaryl precursor to Jakafi in flow.

Under flow conditions. 13 (1830 mg, 7.5 mmol, 1 equiv.), and pinacol ester 14 (2.500 g, 9.0 mmol, 1.2 equiv.), Fe/ppm Pd NPs (538 mg, 800 ppm Pd), TPGS-750-M (600 mg, 2 wt %), Et₃N (1.57 mL, 11.3 mmol, 1.5 equiv.) with the total volume of 30 mL (28.43 mL H₂O + 1.57 mL Et₃N) were distributed among two streams as discussed below (Scheme S3).
Scheme S3. Conditions for synthesis of a biaryl precursor 15 to JAK inhibitors in a CSTR platform.

**Syringe 1:** In a glass vial containing a PTFE coated magnetic stir bar, TPGS-750-M (600 mg, 2 wt.%) was added and sealed with a rubber septum. The vial was evacuated and backfilled with argon three times. Degassed H₂O (28.43 mL) was added to the vial under argon flow via syringe and stirred at rt for 2 h. In a separate second vial containing a PTFE coated magnetic stir bar, Fe/ppm Pd NPs (538 mg, 800 ppm Pd), 13 (1.830 g, 7.5 mmol, 1 equiv.), and 14 (2500 mg, 9.0 mmol, 1.2 equiv.) were added and sealed with a rubber septum. The vial was evacuated and backfilled with argon three times. A solution of TPGS-750-M/H₂O (28.43 mL) from the first vial was then added to second vial via syringe under argon flow. The reaction mixture was then stirred at rt for 1 h. This reaction slurry was then transferred to 50 mL stainless steel syringe containing a PTFE coated magnetic stir bar and attached to syringe pump 1.

**Syringe 2:** Second stainless-steel syringe was filled with degassed Et₃N (1.57 mL, 11.3 mmol, 1.5 equiv.) and attached to syringe pump 2.

After achieving steady state (~3 residence times, 60 min), the sample was collected for 15 min and used to calculate the isolated yield of product. In 15 min, 0.99 mmol of substrate is introduced in the reactor. The organic layer was concentrated *in vacuo* and then purified by flash column chromatography (EtOAc/hexane = 50/50) to afford 291 mg (0.81 mmol, ~82%) of product 15.

**Reaction 4.** Continuous synthesis of a biaryl precursor to Zelboraf in flow.

*Under flow conditions.* 19 (1080 mg, 3.75 mmol, 1.0 equiv.) and 20 (704 mg, 4.5 mmol, 1.2 equiv.), Fe/ppm Pd NPs (538 mg, 800 ppm Pd), TPGS-750-M (600 mg, 2 wt %), and Et₃N (1.57 mL, 11.3 mmol, 3.0 equiv.) with total volume of ~30 mL (28.44 mL H₂O + 1.57 mL Et₃N) were distributed among three streams as discussed below. The flowrates of three streams were adjusted to achieve desired concentration of reagents, nanoparticles, and the surfactant in the CSTR (Scheme S4).
Scheme S4. Conditions for synthesis of biaryl precursor 21 to Zelboraf® in a CSTR platform.

**Syringe 1:** In a glass vial containing a PTFE coated magnetic stir bar, TPGS-750-M (600 mg, 2 wt.%) was added and sealed with a rubber septum. The vial was evacuated and backfilled with argon three times. Degassed H₂O (14.22 mL) was added to the vial under argon flow via syringe and stirred at rt for 2 h. In a separate second vial containing a PTFE coated magnetic stir bar, Fe/ppm Pd NPs (538 mg, 800 ppm Pd) was added and sealed with a rubber septum. The vial was evacuated and backfilled with argon three times. A solution of TPGS-750-M/H₂O (14.22 mL) from the first vial was then added to second vial via syringe under argon flow. The mixture was then stirred at rt for 1 h. This mixture slurry of catalyst was then transferred to stainless steel syringe containing a PTFE coated magnetic stir bar and attached to syringe pump-1.

**Syringe 2:** In a glass vial containing a PTFE coated magnetic stir bar, 1-benzyl-5-bromo-1H-pyrrolo[2,3-b] pyridine 19 (1080 mg, 3.75 mmol, 1.0 equiv.) and (4-chlorophenyl) boronic acid 20 (704 mg, 4.5 mmol, 1.2 equiv.) and sealed with a rubber septum. The vial was evacuated and backfilled with argon three times. Degassed H₂O (14.22 mL) was added to the vial under argon flow via syringe and stirred at rt for 2 h. This slurry of substrates was then transferred to a stainless-steel syringe containing a PTFE coated magnetic stir bar and attached to syringe pump-2.

**Syringe 3:** Third stainless-steel syringe was filled with degassed Et₃N (1.57 mL, 11.3 mmol, 3.0 equiv.) and attached to syringe pump-3.

After achieving steady state (~3 residence times, 60 min), the sample was collected for 15 min and used to calculate the isolated yield of product. In 15 min, 0.49 mmol of substrate had been introduced in the reactor. The organic layer was concentrated in vacuo and then purified by flash column chromatography (DCM/hexane = 10/90) to afford 147 mg (0.46 mmol, ~94%) of product 21.

**Batch reaction procedures**

**Reaction 1.** Batch synthesis of PFR model reaction

To a 5 mL microwave vial equipped with a PTFE coated magnetic spin vein was added 20 mg of Fe/ppm Pd NPs (800 ppm Pd), 4-bromoanisole 1 (93.52 mg, 0.5 mmol, 1.0 equiv), phenylboronic acid 2 (76.2 mg, 0.625 mmol, 1.25 equiv.), and potassium phosphate tribasic monohydrate (351 mg, 1.525 mmol, 3 equiv.). A 2 wt % solution of TPGS-750-M (0.8 mL) was added to the vial followed by tetrahydrofurfuryl alcohol (0.2 mL) and the vial was sealed using an aluminum crimp cap fitted with a PTFE
The contents of the vial were then allowed to stir at rt until a semi-homogeneous mixture had formed, and was then transferred to a microwave reactor. The contents of the vial were heated to 95 °C and stirred vigorously for 10 min. The resulting homogeneous mixture was then extracted with EtOAc (0.5 mL x 3). The organics were then evaporated under reduced pressure resulting in a crude oil, which was then taken up into 200 mL of cold water and allowed to sit cold for 30 min. The precipitate was then filtered, washed with water, and taken up in EtOAc. The crude organic mixture was then passed through a plug of silica gel to afford 89.1 mg (97%) of 4-methoxy-1,1′-biphenyl 3 as an off-white solid.

**Reaction 2.** Batch synthesis of the biaryl precursor to the sartans.

To a 4 mL reaction vial containing a PTFE coated magnetic stir bar, 19.8 mg of FePdNPs (800 ppm Pd) was added in a glove box. The reaction vial was sealed with a rubber septum. 2-bromobenzonitrile 8 (91 mg, 0.5 mmol, 1.0 equiv.), p-tolylboronic acid 9 (81.6 mg, 0.6 mmol, 1.2 equiv.) and potassium phosphate tribasic monohydrate (173 mg, 0.75 mmol, 1.5 equiv.) were added to the reaction vial under argon flow. The reaction vial was then evacuated and backfilled with dry argon three times. A solution of 2 wt % TPGS-750-M (1.0 mL) was added via syringe. The reaction vial was sealed with PTFE tape over rubber septum and then stirred vigorously at 90 °C for 20 minutes. The reaction vial was then allowed to cool to rt and the reaction mixture was extracted with EtOAc (1.0 mL X 5). The combined organic layer was dried over anhydrous Na2SO4 and solvent was removed in vacuo. Crude product was purified by flash chromatography over silica gel to afford 95.9 mg (99 %) of 2-cyano-4′-methylbiphenyl 7 as a white solid (Et2O/hexane = 6/94).

**Reaction 3.** Batch synthesis of the biaryl precursor to Jakafi.

To a 4 mL reaction vial containing a PTFE coated magnetic stir bar, 19.8 mg of FePdNPs (800 ppm Pd) was added in a glove box. The reaction vial was sealed with a rubber septum. 7-Benzyl-4-chloro-7H-pyrrolo[2,3-d]pyrimidine 13 (121.5 mg, 0.5 mmol, 1.0 equiv.) and 1-(2-tetrahydropyran-1-yl)-1H-pyrazole-4-boronic acid, pinacol ester 14 (167 mg, 0.6 mmol, 1.2 equiv) were added to the reaction vial under argon flow. The reaction vial was then evacuated and backfilled with dry argon three times. A solution of 2 wt % TPGS-750-M (1.0 mL) and Et3N (105 µL, 0.75 mmol, 1.5 equiv.) were added via syringe. The reaction vial was sealed with PTFE tape over rubber septum and then stirred vigorously at 95 °C for 20 minutes. The reaction vial was then allowed to cool to rt and the reaction mixture was extracted with EtOAc (1.0 mL X 5). The combined organic layer was dried over anhydrous Na2SO4 and solvent was removed in vacuo. Crude product was purified by flash chromatography over silica gel to afford 160.2 mg (89 %) of 7-benzyl-4-[(1-tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl]-7H-pyrrolo[2,3-d]pyrimidine 15 as a white solid (EtOAc/hexane = 1/1).

**Reaction 4.** Batch synthesis of the biaryl precursor to Zelboraf.

To a 4 mL reaction vial containing a PTFE coated magnetic stir bar, 19.8 mg of FePdNPs (800 ppm Pd) was added in a glove box. The reaction vial was sealed with a rubber septum. 1-Benzyl-5-bromo-1H-pyrrolo[2,3-b]pyridine 19 (143.5 mg, 0.5 mmol, 1.0 equiv) and 4-chlorophenylboronic acid 20 (93.6 mg, 0.6 mmol, 1.2 equiv.) were added to the reaction vial under argon flow. The reaction vial was then evacuated and backfilled with dry argon three times. A solution of 2 wt % TPGS-750-M (1.0 mL) and Et3N (105 µL, 0.75 mmol, 1.5 equiv.) were added via syringe. The reaction vial was sealed with PTFE tape over rubber septum and then stirred vigorously at 95 °C for 20 minutes. The reaction vial was then allowed to cool to rt and the reaction mixture was extracted with EtOAc (1.0 mL X 5). The combined organic layer was dried over anhydrous Na2SO4 and solvent was removed in vacuo.
Crude product was purified by flash chromatography over silica gel to afford 153.4 mg (96 %) of 1-benzyl-5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine 21 as a white solid (DCM/hexane = 1/9).

Analytical Data

4-Methoxybiphenyl  CAS: 613-37-6

\[ \text{H NMR} (500 \text{ MHz, CDCl}_3) \delta 7.61 – 7.50 (m, 4H), 7.42 (t, J = 7.8 \text{ Hz, 2H}), 7.31 (td, J = 7.3, 1.2 \text{ Hz, 1H}), 7.03 – 6.94 (m, 2H), 3.86 (s, 3H). \] [1]

\[ \text{C NMR} (126 \text{ MHz, CDCl}_3) \delta 159.31, 140.99, 133.95, 128.86, 128.30, 126.89, 126.80, 114.36, 55.50. \] [1]

2-Cyano-4′-methylbiphenyl  CAS: 114772-53-1

\[ \text{H NMR} (500 \text{ MHz, CDCl}_3) \delta 7.75 (dd, J = 7.7, 1.4 \text{ Hz, 1H}), 7.63 (td, J = 7.7, 1.4 \text{ Hz, 1H}), 7.31 (dd, J = 8.0, 1.3 \text{ Hz, 1H}), 7.49 – 7.45 (m, 2H), 7.42 (td, J = 7.6, 1.2 \text{ Hz, 1H}), 7.34 – 7.28 (m, 2H), 2.43 (s, 3H). \] [2]

\[ \text{C NMR} (126 \text{ MHz, CDCl}_3) \delta 145.65, 138.81, 135.39, 133.83, 132.88, 130.09, 129.56, 128.73, 127.39, 118.99, 111.32, 21.37. \] [2]

7-Benzyl-4-chloro-7H-pyrrolo[2,3-d]pyrimidine CAS: 16019-34-4

\[ \text{H NMR} (500 \text{ MHz, CDCl}_3) \delta 8.67 (s, 1H), 7.35 – 7.27 (m, 3H), 7.21 (dd, J = 6.0, 2.7 \text{ Hz, 3H}), 6.61 (d, J = 3.5 \text{ Hz, 1H}), 5.45 (s, 2H). \]

\[ \text{C NMR} (126 \text{ MHz, CDCl}_3) \delta 152.33, 151.29, 151.00, 136.37, 129.18, 129.07, 128.32, 127.74, 117.60, 100.10, 48.59. \]
7-Benzyl-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidine

1H NMR (500 MHz, CDCl$_3$) $\delta$ 8.86 (s, 1H), 8.42 (s, 1H), 8.29 (s, 1H), 7.31 (tt, $J = 7.0, 6.1$ Hz, 3H), 7.25 – 7.21 (m, 2H), 7.20 (d, $J = 3.6$ Hz, 1H), 6.76 (d, $J = 3.6$ Hz, 1H), 5.48 (s, 3H), 4.13 – 4.06 (m, 1H), 3.80 – 3.71 (m, 1H), 2.17 (dt, $J = 6.2, 1.8$ Hz, 2H), 2.10 – 2.01 (m, 1H), 1.78 – 1.57 (m, 4H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 151.85, 151.68, 151.18, 139.56, 136.99, 129.00, 128.60, 128.47, 128.09, 127.70, 122.12, 114.32, 100.34, 88.01, 67.88, 48.04, 30.71, 25.07, 22.32.

HRMS: (ESI, [C$_{21}$H$_{21}$N$_5$O + H]) calcd, 360.1824; found m/z: 360.1825.

1-Benzyl-5-bromo-1H-pyrrolo[2,3-b]pyridine

1H NMR (500 MHz, CDCl$_3$) $\delta$ 8.37 (d, $J = 2.2$ Hz, 1H), 8.04 (d, $J = 2.2$ Hz, 1H), 7.30 (dddd, $J = 12.3, 7.0, 4.6, 2.3$ Hz, 3H), 7.23 – 7.15 (m, 3H), 6.43 (d, $J = 3.5$ Hz, 1H), 5.46 (s, 2H).[3]

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 146.20, 143.66, 137.46, 130.91, 129.47, 128.88, 127.89, 127.57, 122.12, 111.86, 99.80, 48.16.[3]

Benzyl-5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine
\textbf{^1H NMR} (500 MHz, CDCl$_3$) $\delta$ 8.55 (d, $J = 2.1$ Hz, 1H), 8.07 (d, $J = 2.2$ Hz, 1H), 7.55 (d, $J = 8.5$ Hz, 2H), 7.44 (d, $J = 8.5$ Hz, 2H), 7.35 – 7.27 (m, 3H), 7.24 (dd, $J = 7.5$, 2.4 Hz, 3H), 6.54 (d, $J = 3.5$ Hz, 1H), 5.53 (s, 2H).

\textbf{\textsuperscript{13}C NMR} (126 MHz, CDCl$_3$) $\delta$ 147.52, 142.33, 138.33, 137.76, 133.19, 129.17, 129.02, 128.87, 128.72, 128.61, 127.80, 127.57, 127.24, 120.56, 100.54, 48.11.

\textbf{HRMS:} (ESI, [C$_{20}$H$_{15}$ClN$_2$ + H]) calcd, 319.1002; found m/z: 319.1003.
NMR Spectra

4-Methoxybiphenyl (CAS: 613-37-6)
2-Cyano-4'-methylbiphenyl (CAS: 114772-53-1)
7-Benzyl-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (CAS:16019-34-4)
7-Benzyl-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-7H-pyrrolo[2,3-d]pyrimidine
1-Benzyl-5-bromo-1H-pyrrolo[2,3-b]pyridine
1-Benzyl-5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine
References


Author Contributions

*These authors contributed equally to this work.