Supporting Information

A 30 L and 20 L jacketed vessel were utilized for the bulk of the processing, with the vessel dedicated exclusively to the Pd-mediated C–N coupling (1b reaction sequence) as a "dry" vessel. Both vessels were fitted with agitator, condenser, temperature probe, heating and cooling unit, nitrogen inlet and bubbler. 30 L reactions were carried out on a 1.5 kg charge basis of **6** (9.3 moles).

Step 1a



THF (5.4 L) and water (5.25 L) were added to the 30 L reaction vessel. To this solution was then added, **4** (1.27 Kg, 11.16 moles) and potassium carbonate (1.54 kg, 11.16 moles) and stirred until all the carbonate had dissolved with agitation. A 40% (w/w) solution of **6** (3.75 kg, 9.3 moles) was added by subsurface addition tube to mitigate against HCI evolution and the biphasic reaction mixture was heated to reflux for 6 hours (typically >99% conversion). After 6 hours the reaction mixture was cooled to an internal temperature of 25 °C and the layers separated. Toluene (7.5 L) and water (4.5 L) were then added to the organic layer, agitated for 1 hour and the layers separated. The organic layer was then distilled under vacuum to a total volume of 7.5 L. The solution in the vessel was then checked for water content using KF analysis.

Water content of <1000ppm was considered acceptable to proceed with the next stage. The step 1a contents were transferred to the dry 20 L vessel for the reaction step 1b.

Step 1b



The solution from Step 1a was degassed to remove oxygen, then $PdCl_2[PhCN]_2$ (18.3 g, 0.5 mol%) and RuPhos (43.2 g, 1 mol%) were charged. LiHMDS (24 wt % 1.3 M solution in THF, 7.77 kg, 11.16 moles) was then charged and heated to reflux. After 3 hours the reaction was cooled to 20 °C and sampled for reaction completion (typically > 99% conversion). The reaction solution was then quenched with a 0.38 M solution of sodium sulfate (7.5 L) in the 30 L vessel and agitated for 1 hour. The biphasic mixture was filtered through a 5 micron filter to remove any rag layer present, and the layers were separated discarding the aqueous layer to waste.

Although the solution is telescoped through the subsequent step, a portion was isolated via the following procedure and characterized. In a clean, dry 200 mL jacketed vessel (which had been dried by refluxing with anhydrous THF before emptying the vessel and blowing dry with research grade nitrogen) at ambient temperature was charged 1-[(6-chloro-3-pyridyl)methyl]-4-ethyl-piperazine **9** (6.0 g, 25 mmol) toluene (30 mL) (which had been degassed by sparging with research grade nitrogen for 30

minutes), RuPhos (117 mg, 0.25 mmol) and PdCl₂[PhCN]₂ (46 mg, 0.12 mmol). During charging of the solid reagents a positive pressure of research grade nitrogen was maintained within the vessel. Agitation in the vessel was started and a solution of LiHMDS (23.1 mL 1.3 M in THF, 30 mmol) was added to the vessel via syringe. Upon addition of the LiHMDS solution the contents of the vessel changed colour from yellow to dark orange. The solution was then heated at reflux for 3 hours. After stirring for 3 hours at reflux the solution was cooled to 20 °C and 30 mL of an 80% saturated aqueous solution of Na₂SO₄ was added to the reaction vessel. The biphasic contents of the reaction vessel were then agitated for 10 minutes. The biphasic solution was then transferred to a 220 mL pocket filter equipped with a 5 µm PTFE 47 mm diameter filter membrane and filtered under a positive pressure of nitrogen. The filtered biphasic solution was then transferred to a separating funnel and the phases were split retaining the upper organic layer. The brown organic layer was transferred to 250 mL round bottom flask and Carbon (4g) was charged to the solution and agitated at ambient temperature for 30 minutes. After 30 minutes the black slurry was filtered through a Buchner funnel to give a pale yellow solution. The pale yellow solution was transferred to a 250 mL round bottom flask and the solvent removed on a rotary evaporator (bath temperature 55 °C) to give a yellow oil. To the yellow oil was added heptane (100 mL) which produced a suspension containing a white precipitate. This suspension was then agitated for 30 minutes before filtering through a Buchner funnel. The filtrate was then transferred to a round bottom flask and the solvent removed on a rotary evaporator

(bath temperature 55 °C) to give a colourless oil which solidified to give **11** as an offwhite solid (4.2 g, 46% yield, mostly pure, but small amount of TMS hydrolysis) when left standing at ambient temperature over 12 hours. ¹H NMR (500 MHz, CD₃CN): δ = 8.11 (d, *J* = 2.4 Hz, 1 H), 7.47 (dd, *J* = 8.2, 2.4 Hz, 1 H), 6.78 (d, *J* = 8.2 Hz, 1 H), 3.41 (s, 2 H), 2.39 (broad, 8 H), 2.33 (q, *J* = 7.2 Hz, 2 H), 1.02 (t, *J* = 7.2 Hz, 3 H), 0.16 (s, 18 H) ppm; ¹³C NMR (126 MHz, CD₃CN): δ = 162.14, 149.36, 138.87, 128.79, 121.44, 60.45, 54.06, 53.87, 53.05, 12.80, 2.83 ppm; HRMS (ESI): Calcd for C₁₈H₃₆N₄Si₂H⁺ [M + H⁺]: 365.2551, found 365.2553.

¹H NMR:



¹³C NMR:



Step 1c



Methanol (7.5 L) was charged to the organic layer. The solution was then refluxed for 7 hours and sampled for reaction completion. After the reaction was complete (typically > 99% conversion by GC) the mixture was distilled to a total volume of 6 L. Toluene (10.5 L) was added and the mixture re-distilled to a total volume of 6 L to ensure methanol removal. MeCN (9 L) was then added and the vessel heated to an internal temperature of 65 °C and held at this temperature for 1 hour to achieve full dissolution of the contents. The solution was then cooled over 1.5 hours to 46 °C (internal). If required, 1 wt% **3** (15 g) is added as seed and the solution held at 46 °C for 1 hour. The held at this temperature of -5 °C and then

the filter cake washed with MeCN (3 L) pre-cooled to -5 °C. The filter cake was then dried under vacuum at 50 °C to afford **3** (1.5 kg, 75% yield, >99% purity) identical to previously reported material.

¹H NMR:



¹³C NMR:

