

# Continuous Amination of Aryl Fluoride/Chloride Using Aqueous Ammonia in AF-2400-Based Tube-in-Tube Micro-Reactors

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## Supporting Information

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### 1. General Experimental

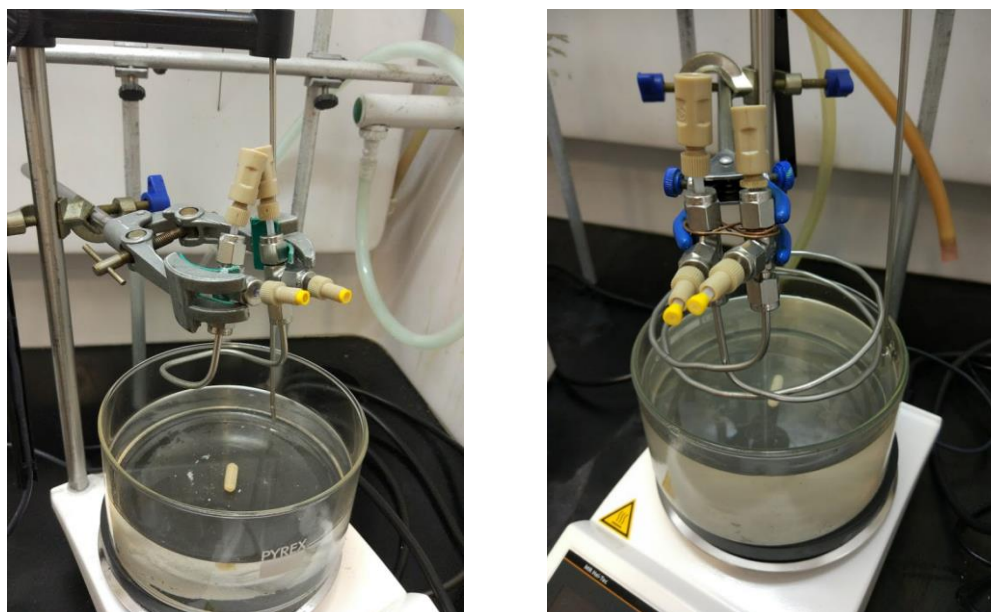
Chemicals and solvents were purchased from commercial suppliers and used as received. <sup>1</sup>H NMR, <sup>13</sup>C NMR and <sup>19</sup>F NMR spectra were recorded on a Bruker AV-III400 (400 MHz) spectrometer. Chemical shifts were calibrated using residual undeuterated solvent as an internal reference (CDCl<sub>3</sub>: 7.26 ppm <sup>1</sup>H NMR, 77.0 ppm <sup>13</sup>C NMR). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). The stainless steel micro tubing was purchased from Swagelok (USA). The membrane-based back pressure regulator was purchased from Zaiput Flow Technologies.

### 2. Tube-in-tube Reactor

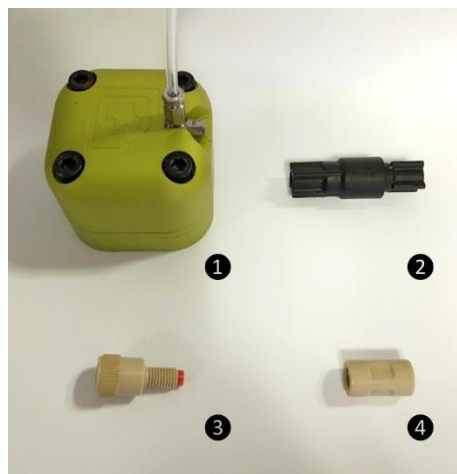
Table S1. Specifications of tube-in-tube reactors

	Material	Tube size	Volume	Length
<b>tube-in-tube reactor A (0.25 mL)</b>				
<b>Inner tube</b>	Teflon AF-2400	1/16'' od x 0.0394'' id	0.16 mL	20 cm
<b>Outer tube</b>	Stainless steel	1/8'' od x 0.08'' id	0.25 mL	20 cm
<b>tube-in-tube reactor B (1 mL)</b>				
<b>Inner tube</b>	Teflon AF-2400	1/16'' od x 0.0394'' id	0.63 mL	80 cm
<b>Outer tube</b>	Stainless steel	1/8'' od x 0.08'' id	0.99 mL	80 cm

The tube-in-tube reactor was made of PFA micro tubings and stainless steel micro tubing, according to Ley's work.<sup>[1]</sup> We made two pieces of tube-in-tube reactor using the same tubings, with different length to achieve different volume.



**Figure S1.** Tube-in-tube reactors: 0.25 mL(left) and 1.0 mL(right).

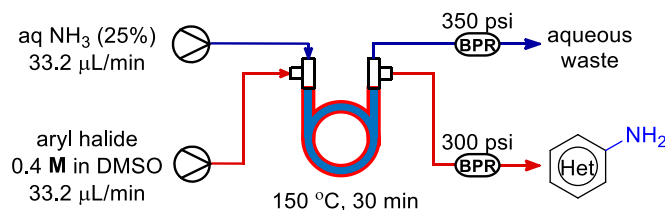


**Figure S2.** Parts required in the tube-in-tube reactor system. 1. Zaiput BPR purchased from Zaiput Flow Technologies; 2. BPR 3. Check valve 4. Connector from IDEX.

### 3. General Procedure (for 10 hrs production)

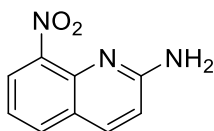
Into a 50 mL round bottom flask was charged with aryl halide (9.6 mmol) and DMSO (0.4 M, 24 mL) was stirred under vacuum for 5 min, then backfilled and protected with nitrogen. Into another 50 mL round bottom flask was charged with 25% aqueous ammonia (24 mL) and protected with nitrogen. Both solution were taken up into an Asian pump and introduced into tube-in-tube reactor B (both flowrate at 33.2  $\mu\text{L}/\text{min}$ ), and the oil bath was heated to 150  $^{\circ}\text{C}$ . After 80 mins of equilibration, the reaction mixture was collected for 10 hrs in a vial protected under nitrogen atmosphere.

Saturated NaHCO<sub>3</sub> solution was then added to the reaction mixture and extracted with ether acetate for 3 times. The combined organic layers were dried using MgSO<sub>4</sub>, concentrated, and subjected to flash column chromatography using DCM / MeOH 50:1 to 10:1 as eluent.



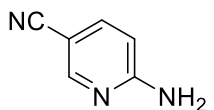
**Scheme 1.** Continuous animation of aryl fluoride/chloride using aqueous ammonia in AF-2400-based tube-in-tube micro-reactors.

The protocol for in-line titration was done in accordance to report by Ley.<sup>[2]</sup>



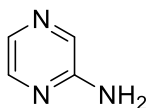
8-nitroquinolin-2-amine (**1b**)

Followed the general procedure (for 10 hrs production), reaction of 2-chloro-8-nitroquinoline (**1a**) with aq. NH<sub>3</sub> to give the product **1b** in 93% yield (1402 mg in 10 hrs). <sup>1</sup>H NMR (400 MHz, DMSO) δ 8.02 (d, *J* = 9.0 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.98 (bs, 2H), 6.87 (d, *J* = 9.0 Hz, 1H).



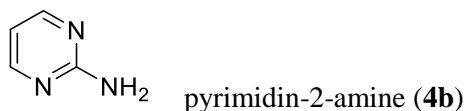
6-aminonicotinonitrile (**2b**)

Followed the general procedure (for 10 hrs production), reaction of 6-chloronicotinonitrile (**2a**) with aq. NH<sub>3</sub> to give the product **2b** in 90% yield (854 mg in 10 hrs). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.35 (d, *J* = 1.8 Hz, 1H), 7.60 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.49 (dd, *J* = 8.6, 0.7 Hz, 1H), 5.04 (bs, 2H).

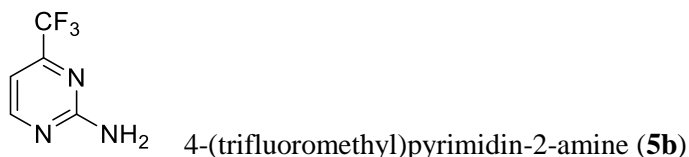


pyrazin-2-amine (**3b**)

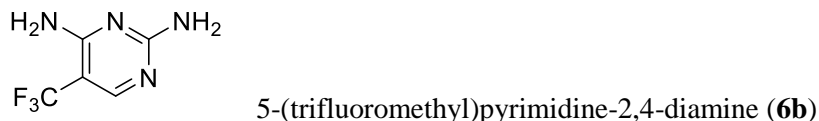
Followed the general procedure (for 10 hrs production), reaction of 2-chloropyrazine (**3a**) with aq. NH<sub>3</sub> to give the product **3b** in 55% yield (417 mg in 10 hrs). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.98 (d, *J* = 3.8 Hz, 2H), 7.89 (d, *J* = 2.6 Hz, 1H), 5.34 (bs, 2H).



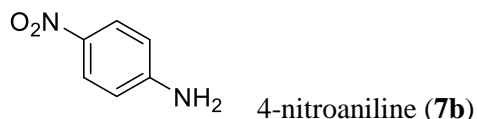
Followed the general procedure (for 10 hrs production), reaction of 2-chloropyrimidine(**4a**) with aq.  $\text{NH}_3$  to give the product **4b** in 84% yield (637 mg in 10 hrs).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.28 (d,  $J = 4.8$  Hz, 2H), 6.60 (s, 1H), 5.08 (bs, 2H).



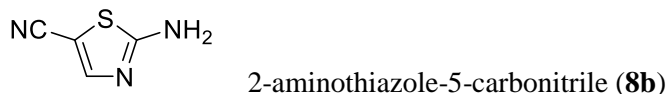
Followed the general procedure (for 10 hrs production), reaction of 2-chloro-4-(trifluoromethyl)pyrimidine (**5a**) with aq.  $\text{NH}_3$  to give the product **5b** in 97% yield (1261 mg in 10 hrs).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.49 (d,  $J = 4.9$  Hz, 1H), 6.89 (d,  $J = 4.9$  Hz, 1H), 5.50 (bs, 2H).



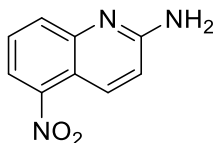
Followed the general procedure (for 10 hrs production), reaction of 0.2 M 2,4-dichloro-5-(trifluoromethyl)pyrimidine (**6a**) with aq.  $\text{NH}_3$  to give the product **6b** in 82% yield (582 mg in 10 hrs).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.00 (s, 1H), 5.66 (bs, 2H), 5.60 (bs, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  165.03 (s), 160.37 (s), 155.83 (d,  $J = 5.0$  Hz), 125.93 (d,  $J = 268.5$  Hz), 95.61 (d,  $J = 31.6$  Hz).



Followed the general procedure (for 10 hrs production), reaction of 1-fluoro-4-nitrobenzene (**7a**) with aq.  $\text{NH}_3$  to give the product **7b** in 83% yield (913 mg in 10 hrs).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.12 – 8.01 (m, 2H), 6.67 – 6.56 (m, 2H), 4.40 (bs, 2H).

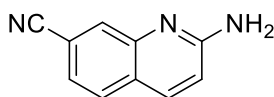


Followed the general procedure (for 10 hrs production), reaction of 2-chlorothiazole-5-carbonitrile (**8a**) with aq.  $\text{NH}_3$  to give the product **8b** in 97% yield (967 mg in 10 hrs).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.11 (bs, 2H), 7.82 (s, 1H).



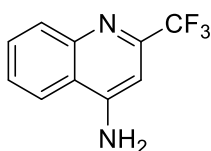
5-nitroquinolin-2-amine (**9b**)

Followed the general procedure (for 10 hrs production), reaction of 2-chloro-5-nitroquinoline (**9a**) with aq.  $\text{NH}_3$  to give the product **9b** in 70% yield (1055 mg in 10 hrs).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.34 (dd,  $J = 9.4, 0.4$  Hz, 1H), 7.88 (dd,  $J = 7.7, 1.2$  Hz, 1H), 7.79 (dt,  $J = 8.5, 1.0$  Hz, 1H), 7.62 (dd,  $J = 8.3, 7.9$  Hz, 1H), 6.99 (d,  $J = 9.4$  Hz, 1H), 6.87 (bs, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  158.63, 148.77, 145.94, 131.68, 131.59, 127.83, 118.34, 115.61, 114.53.



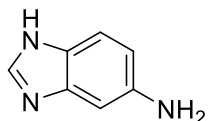
2-aminoquinoline-7-carbonitrile (**10b**)

Followed the general procedure (for 10 hrs production), reaction of 2-chloroquinoline-7-carbonitrile (**10a**) with aq.  $\text{NH}_3$  to give the product **10b** in 80% yield (1078 mg in 10 hrs).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  7.98 (d,  $J = 8.9$  Hz, 1H), 7.88 – 7.76 (m, 2H), 7.42 (dd,  $J = 8.1, 1.6$  Hz, 1H), 6.90 (d,  $J = 8.9$  Hz, 1H), 6.81 (bs, 2H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  159.28, 147.30, 136.73, 129.81, 129.08, 125.46, 122.18, 119.21, 115.44, 111.23.



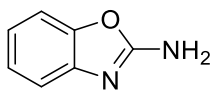
2-(trifluoromethyl)quinolin-4-amine (**11b**)

Followed the general procedure (for 10 hrs production), reaction of 4-chloro-2-(trifluoromethyl)quinolone (**11a**) with aq.  $\text{NH}_3$  to give the product **11b** in 52% yield (879 mg in 10 hrs).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.28 (d,  $J = 8.3$  Hz, 1H), 7.91 (d,  $J = 8.3$  Hz, 1H), 7.81 – 7.72 (m, 1H), 7.57 (t,  $J = 7.2$  Hz, 1H), 7.42 (bs, 2H), 6.94 (s, 1H).



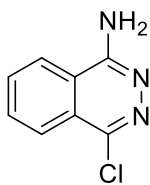
1H-benzo[d]imidazol-5-amine (**12b**)

Followed the general procedure (for 10 hrs production), reaction of 5-chloro-1H-benzo[d]imidazole (**12a**) with aq.  $\text{NH}_3$  to give the product **12b** in 90% yield (955 mg in 10 hrs).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.91 (d,  $J = 9.0$  Hz, 1H), 7.90 – 7.85 (m, 1H), 7.78 (dd,  $J = 8.0, 1.4$  Hz, 1H), 7.25 (t,  $J = 7.8$  Hz, 1H), 6.81 (d,  $J = 8.9$  Hz, 1H), 5.20 (bs, 2H).



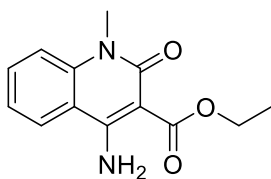
benzo[d]oxazol-2-amine (**13b**)

Followed the general procedure (for 10 hrs production), reaction of 2-chlorobenzo[d]oxazole (**13a**) with aq.  $\text{NH}_3$  to give the product **13b** in 71% yield (759 mg in 10 hrs).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  7.34 (bs, 2H), 7.30 (d,  $J = 7.5$  Hz, 1H), 7.19 (d,  $J = 7.7$  Hz, 1H), 7.08 (td,  $J = 7.6, 1.1$  Hz, 1H), 6.95 (td,  $J = 7.7, 1.2$  Hz, 1H).



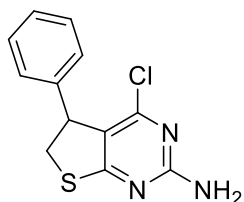
4-chlorophthalazin-1-amine (**14b**)

Followed the general procedure (for 10 hrs production), reaction of 1,4-dichlorophthalazine (**14a**) with aq.  $\text{NH}_3$  to give the product **14b** in 94% yield (1345 mg in 10 hrs).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.37 – 8.29 (m, 1H), 8.10 – 7.91 (m, 3H), 7.27 (bs, 2H).



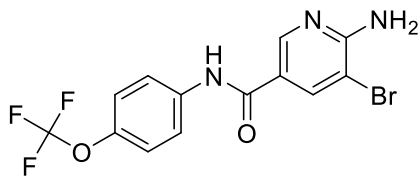
ethyl 4-amino-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**15b**)<sup>[3]</sup>

Followed the general procedure (for 10 hrs production), reaction of 0.2 M ethyl 4-chloro-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**15a**) with aq.  $\text{NH}_3$  to give the product **15b** in 92% yield (903 mg in 10 hrs).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  8.16 (dd,  $J = 8.2, 1.3$  Hz, 1H), 8.01 (bs, 2H), 7.65 (ddd,  $J = 8.5, 7.1, 1.4$  Hz, 1H), 7.41 (dd,  $J = 8.5, 0.7$  Hz, 1H), 7.23 (ddd,  $J = 8.1, 7.2, 1.0$  Hz, 1H), 4.23 (q,  $J = 7.1$  Hz, 2H), 3.47 (s, 3H), 1.31 – 1.18 (m, 3H).



4-chloro-5-phenyl-5,6-dihydrothieno[2,3-d]pyrimidin-2-amine (**16b**)

Followed the general procedure (for 10 hrs production), reaction of 0.2 M 2,4-dichloro-5-phenyl-5,6-dihydrothieno[2,3-d]pyrimidine (**16a**) with aq.  $\text{NH}_3$  to give the product **16b** in 65% yield (683 mg in 10 hrs).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  7.37 – 7.29 (m, 2H), 7.29 – 7.23 (m, 1H), 7.19 (dd,  $J = 5.3, 3.3$  Hz, 2H), 7.09 (bs, 2H), 4.70 (dd,  $J = 8.9, 2.7$  Hz, 1H), 3.96 (dd,  $J = 11.5, 9.0$  Hz, 1H), 3.14 (dd,  $J = 11.5, 2.7$  Hz, 1H).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  178.36, 163.10, 155.03, 142.35, 128.72, 127.16, 126.89, 118.70, 47.50, 38.36.



6-amino-5-bromo-N-(4-(trifluoromethoxy)phenyl)nicotinamide (**17b**)

Followed the general procedure (for 10 hrs production), reaction of 0.15 M 5-bromo-6-chloro-N-(4-(trifluoromethoxy) phenyl) nicotinamide (**17a**) with aq. NH<sub>3</sub> to give the product **17b** in 91% yield (1023 mg in 10 hrs).. <sup>1</sup>H NMR (400 MHz, DMSO) δ 10.17 (s, 1H), 8.60 (d, *J* = 2.1 Hz, 1H), 8.30 (d, *J* = 2.1 Hz, 1H), 7.88 – 7.80 (m, 2H), 7.38 – 7.29 (m, 2H), 6.95 (bs, 2H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 162.96, 158.31, 147.98, 143.72, 139.15, 138.36, 121.54, 121.40, 119.61, 118.88, 101.95.

#### 4. References and Notes:

- [1] Polyzos, A., O'Brien, M., Petersen, T. P., Baxendale, I. R., and Ley, S. V. *Angew. Chem. Int. Ed.* **2011**, 50, 1190-1193.
- [2] Pastre, J. C., Browne, D. L., O'Brien, M., and Ley, S. V. *Org. Process Res. Dev.* **2013**, 17, 1183-1191.
- [3] Ukrainets, I. V. *Chemistry of Heterocyclic Compounds*. Vol. 41, New York, United States. **2005**.

