

## Supporting Information

Continuous Flow Metal-Free Oxidation of Picolines using Air  
Masaya Hamano, Kevin D. Nagy, and Klavs F. Jensen

### Experimental setup

The experimental setup consisted of a microreactor, syringe pump, pressure bomb, and gas cylinder. Effluent from the microreactor was collected in the bomb in a glass vial containing 0.3 mL of aqueous 2.0 M hydrochloric acid. Oxygen or air continuously was fed into the system, and back pressure was controlled by reducing or increasing the vent rate from the bomb using a needle valve. The flow rate of gas through the microreactor system was visually monitored and was controlled by adjusting the pressure drop from the feed to the bomb using a second needle valve.

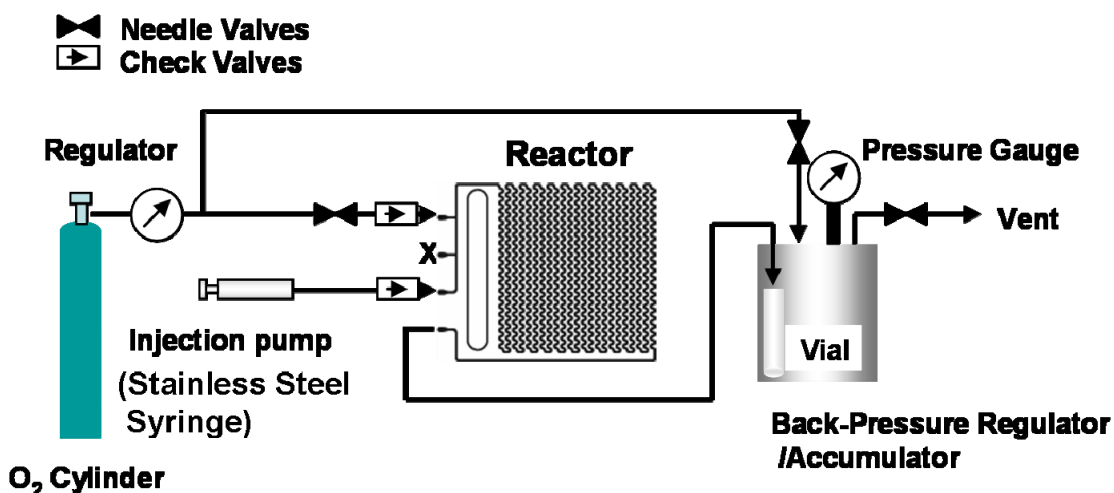


Figure S1 – Experimental setup. Use of pressurized air from a cylinder instead of oxygen enabled

This setup resulted in accumulation of oxygen in the back pressure regulator, which is potentially an explosion hazard; use of a second inert gas to provide back pressure was identified as an improvement and has been implemented in more recent endeavors in our lab.

### Experimental methods

All chemicals were purchased from commercial sources and were used as received. Solvents were anhydrous and were packaged under a polymer septum. Oxygen (AirGas, 99.8%, extra dry) and air (Airgas, dew point -80°F) were used as received. Reagent solutions were prepared in a similar fashion to the following protocol for 4-picoline with 4.4 equivalents of base.

A solution of 4-picoline (122  $\mu$ L, 1.25 mmol), potassium *t*-amylate (2.75 mL 2 M solution in THF, 5.5 mmol), and hexamethylphosphoramide (1.32 mL, 7.5 mmol) was diluted to a total of 10 mL with 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone under argon. The solution was then loaded into a stainless steel syringe (Harvard Apparatus) while taking care to maintain an

argon atmosphere. The reagent solution was stable for up to 5 hours though discoloration would start to appear after that time.

After the syringe was loaded, but before liquid was fed through the system, the system was fully pressurized by flowing oxygen or air through the system. The reagent solution was then fed into the system using a syringe pump. Three to four reactor volumes were passed through the reactor once steady state had been achieved, and the system was then decompressed. After the reaction, the channel of the reactor was washed with a mixture of 1, 2-dimethoxyethane (DME) and aqueous hydrochloric acid (1:1 v/v). The washing solution was combined with the quenched reaction mixture collected in the backpressure regulator and analyzed using HPLC.

## HPLC analysis

Reactor effluent was analyzed using a Waters UPLC with an Acquity UPLC HSS T3 C18 reverse phase column. A gradient method was used as described by Table S1

A: 10 mM ammonium formate in water

B: Methanol

Table S1 – Gradient method for HPLC analysis.

| A (%) | B (%) | Start | Stop |
|-------|-------|-------|------|
| 100   | 0     | 0     | 2    |
| 0     | 100   | 2     | 35   |
| 100   | 0     | 35    | 40   |

Conversion and yield were calculated based off of the area of HMPA (internal standard) to either the area of product or area of starting material.

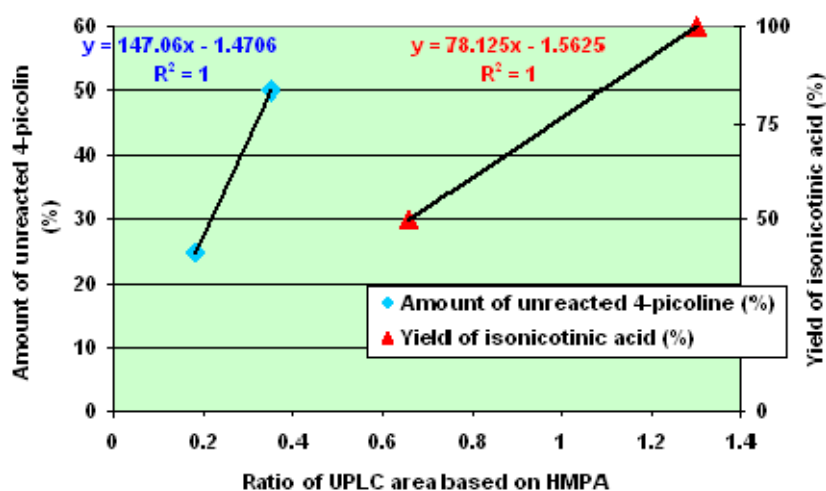


Figure S2 – Calibration curve for 4-picoline and carboxylic acid product

## Microreactor fabrication

A continuous flow microreactor platform was fabricated using previously described methodologies developed within our lab<sup>1</sup>. Silicon nitride was deposited prior to anodic bonding to enhance the chemical resistivity of the reactor<sup>2</sup>. Fluidic connections to the microreactor were achieved using compression packing<sup>3</sup> and 10-32 fittings from Swagelok and Idex Health and Science. The microreactor had 400x400 micron square channels and an internal volume of 240  $\mu\text{L}$ .

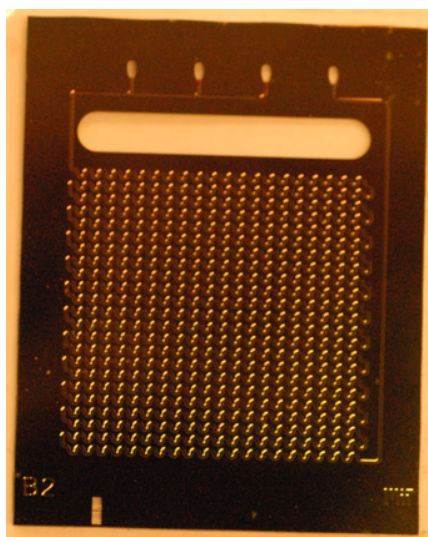


Figure S3 – Serpentine microreactor used in the study.

## Film formation

Evidence for film deposition could be seen by visual examination of the reactor. The microreactor platform could be run for ~2 hours before clogging occurred.

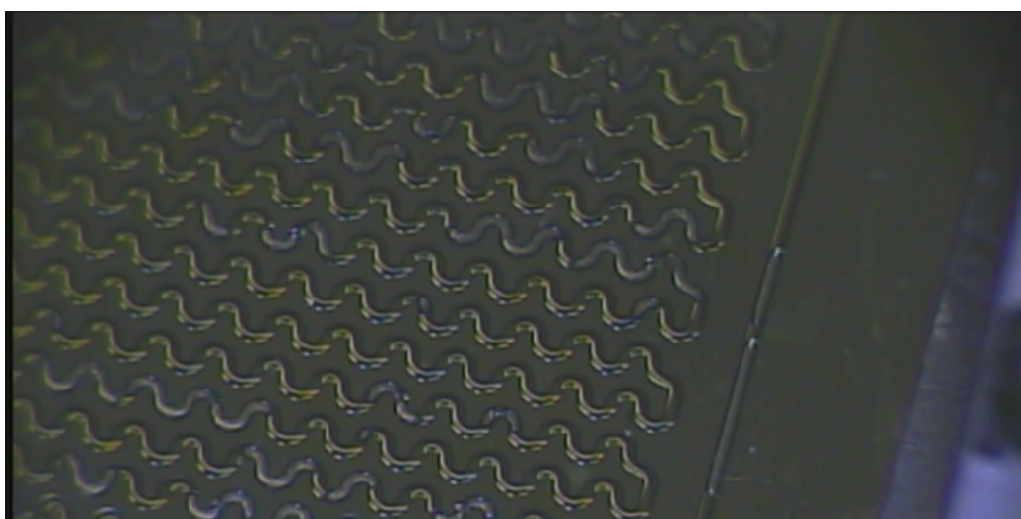


Figure S4 – Initial appearance of gas-liquid flow through the microreactor. The liquid phase is gold colored.

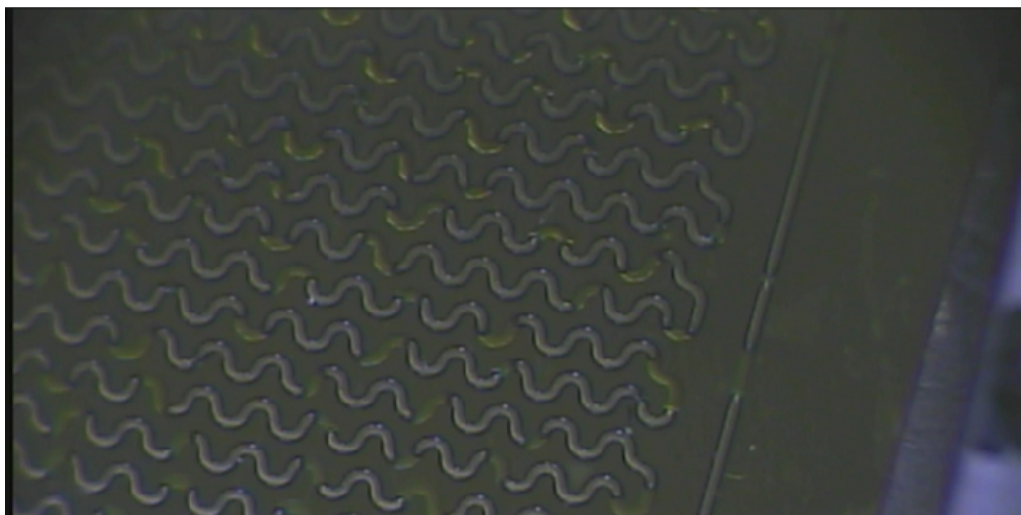


Figure S5 – Loss of iridescence of liquid slugs indicates material is accumulating on the reactor walls. Photo taken after 30 minutes of continuous operation.

## References

1. Yen, B. K. H.; Gunther, A.; Schmidt, M. A.; Jensen, K. F.; Bawendi, M. G., A microfabricated gas-liquid segmented flow reactor for high-temperature synthesis: The case of CdSe quantum dots. *Angewandte Chemie-International Edition* **2005**, 44, (34), 5447-5451.
2. Bedore, M. W.; Zaborenko, N.; Jensen, K. F.; Jamison, T. F., Aminolysis of Epoxides in a Microreactor System: A Continuous Flow Approach to beta-Amino Alcohols. *Organic Process Research & Development* **2010**, 14, (2), 432-440.
3. Marre, S.; Adamo, A.; Basak, S.; Aymonier, C.; Jensen, K. F., Design and Packaging of Microreactors for High Pressure and High Temperature Applications. *Industrial & Engineering Chemistry Research* **2010**, 49, (22), 11310-11320.