Supplementary Information

Carbonylations in flow: tube-in-tube reactor vs gas-liquid slug flow

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Contents

1. General

All solvents and commercially available reagents were purchased from either Sigma–Aldrich or Strem, were reagent grade and were used as supplied without further purification. Solvents used for reaction mixtures pumped as bottle reagent were filtered using PTFE filters (Whatman 0.2 um).

Column Chromatography: CombiFlash Rf+ (Teledyne ISCO) with RediSeptSilver normal phase Silica cartridges was used for column chromatography. The unit is equipped with a UV detector, 254 nm and 280 nm wavelengths.

NMR spectroscopy: ^{1}H-NMR spectra were measured on a Bruker Avance II 400MHz spectrometer, 5mm BBO Probe-head + 1mm TXI Probe-head. [1]H resonance is reported to the nearest 0.01 Hz, and the multiplicity of the 1H signals is reported as follows: s – singlet, dd – double doublet, t – triplet. Coupling constants *J* are reported to the nearest 0.1 Hz.

UV spectroscopy: Analytical LC-MS was carried out on a Waters Acquity I-Class instrument using a Waters BEH C18 column (2.1x50mm, particle size 2.5μm) at 40°C with a mobile phase A (13 mmol/L NH_3 in water)

and B (acetonitrile) at flow rate of 0.8 ml/min. Following gradient was applied over a total of 2.1 min: 95% A to 5% A over 1.2 min, hold for 0.7 min, 5% A to 95% A over 0.2 min. Samples were analyzed at 210 nm wavelength.

CO Safety precautions

Special precautions must be taken when using CO as it is highly toxic and flammable gas (H220, H331, H360, H372, H420). All experiments were done in a well-ventilated fume hood and the levels of CO were checked by CO detectors. One detector is installed in the fume hood (Bieler & Lang) and a second portable detector from Draeger was used to check local levels. Additionally, all connections were checked using a liquid leak detector (Snoop, Supelco: 20434).

2. Experimental apparatus

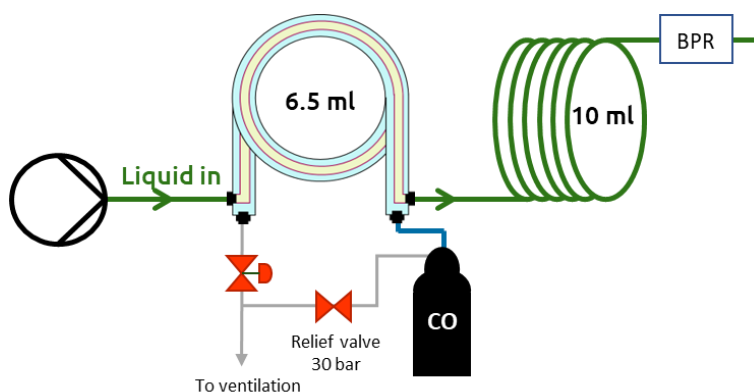Safe evacuation of CO in both apparatuses was ensured through a system of valves and bypasses.

Figure S1 Scheme of all connections on the tube-in-tube setup. BPR: Back Pressure Regulator.

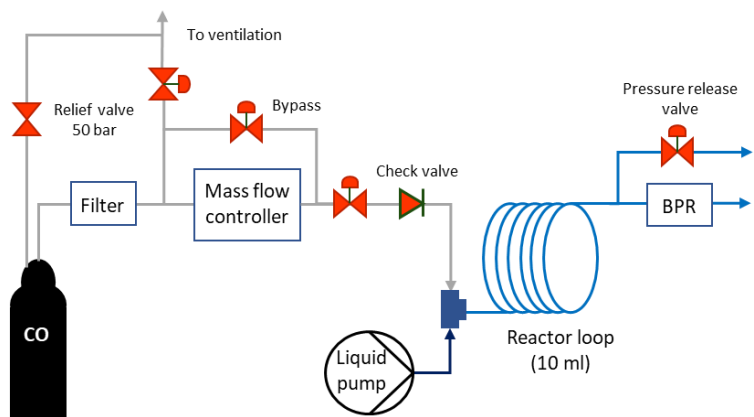

Figure S2 Scheme of all connections on the biphasic setup. BPR: Back Pressure Regulator.

Table S1 Relevant fluidic components.

Part	Material	Size
Connecting tubing	PFA	1 mm ID
T-junction	PEEK	0.5 mm ID

2.1. Residence time in the gas-liquid setup

In our gas-liquid setup, we have used a T-junction for CO addition into the reactor, without any pre-mixing or gas-saturation coils. The bi-phasic mixture is entering the reactor, gas dissolves in the liquid as it flows through and ultimately some of the gas is consumed in the reaction. Thus, the residence time calculated from the gas and liquid flow rate and reactor volume is not correct, as the average density of the mixture is changing. We have measured the actual residence time of the reaction mixture by visual inspection. As the catalyst solutions were brown to dark brown, and we usually worked with 5-10 ml of reaction mixture per test, the moment the reaction mixture enters and exits the reactor can be captured.

Observed values are recorded in the plot and table below (Figure S3, Table S2). For two experiments, we measured the residence time of the front and end of the injected slug, to make sure that the dispersion of the reaction mixture is negligible (this is an expected effect, as gas bubbles block axial dispersion). Indeed, for the shorter calculated time of 16.7 min, we observe 8 and 8.7 min residence time of the front and end of the droplet respectively. For the longer theoretical time of 50 min, we captured the data at both 24 bar and 31 bar, as both pressures were tested in the optimization. At a higher pressure, more CO should be dissolved in the reaction mixture, leading to a longer residence time, visible in the plot. At higher pressure of 31 bar, the residence time of the slug front and back are respectively 28 and 31.2 min, compared to 26 min measured at lower pressure of 24 bar. Based on the small difference in the time measured for the slug front & back, we concluded that axial dispersion is negligible in our setup.
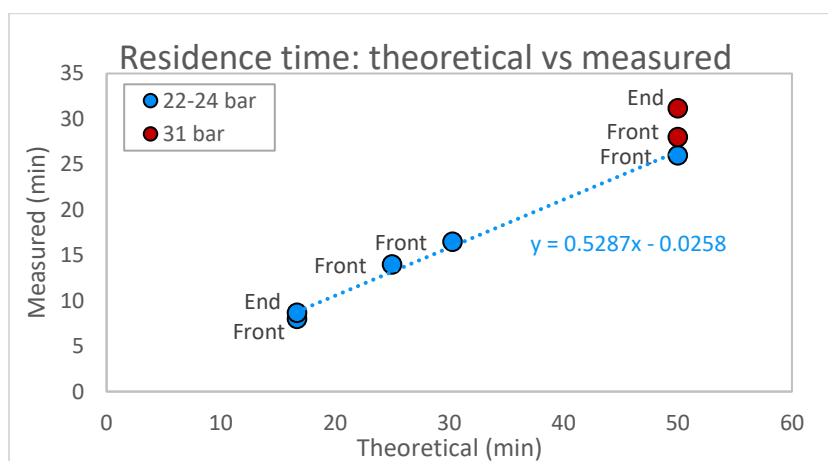
Figure S3 Theoretical vs. measured residence time

Table S2 Experimental data: residence time measurements. Experiment details + results.

ID	Flow rate	CO flow rate	V_reactor	P	Residence time		Front/End
					Theoretical	Measured	
	ml/min	sccm	ml	bar	min	min	
1.	0.6	3	10	21.5	16.7	**8**	Front
						8.7	End
2.	0.4	2	10	24	25	**14**	Front
3.	0.33	1.65	10	24	30.3	**16.5**	Front
4.	0.2	1	10	24	50	**26**	Front
5.	0.2	1	10	31	50	**28**	Front
						31.2	End

2.2. Phase Sensor and Bubble Detection

To detect bubbles of gas in the liquid stream, we used a phase sensor connected to a Raspberry Pi via an analog-to-digital converter. The data was read-out in real time and recorded with a Python script. This setup required the following items:

- Raspberry Pi 4 1.5 GHz Quad-Core (Raspberry Pi)
- 4-Kanal-16-Bit-ADC für Raspberry Pi (Seeed Studio)
- OCB350L062Z phase sensor (TT Electronics/Optek Technology)

To install the converter and enable communication, we followed specification from the manufacturer.[1,2] Python code was based on the example provided on the wiki of Adafruit CircuitPython ADS1x15 library,[3,4] adapted to record measured values.

3. Methoxycarbonylation of 4-chlorobenzonitrile

Experimental procedure: methoxycarbonylation of 4-chlorobenzonitrile

Tube-in-tube setup

Exemplary procedure (amounts and conditions refer to entries 1-3 in Table S3):

4-Chlorobenzonitrile (1) (27.8 mg, 0.2 mmol, 1 eq), Palladium(II)acetate (2.25 mg, 0.01 mmol, 0.05 eq) and 1,3-Bis(diphenylphosphino)propane (8.59 mg, 0.02 mmol, 0.1 eq) were dissolved in MeOH (1 mL) and MeCN (1 mL). Triethylamine (0.0557 mL, 0.4 mmol, 2 eq) was added. The reaction mixture was injected via autosampler with 2 mL loop. Above quantities are calculated for 1 injection of 2 ml. In practice, a larger stock solution of 5 mL was prepared for each injection individually. The mixture was pumped (F= 0.626 mL/min) first through the tube in tube reactor (T= 25°C) for CO saturation (p(gas) = 18 bar) and then through a 10 mL stainless steel reactor (T= 170°C, rt= 16 min). Three 100 PSI BPRs were used to pressurize the system, resulting in the liquid pressure of 23 bar. The reaction mixture was collected using the fraction collector. Calibration curves were used to calculate conversion, yield and amount of side product: the calculated conversion is 43-49%, calculated yields of product **2**: 13-19%, and side product **3**: 8%.

Gas-Liquid Flow

Exemplary procedure (amounts and conditions refer to entry 7 in Table 2):

4-Chlorobenzonitrile (1) (139 mg, 1 mmol, 1 eq), Palladium(II) acetate (11.5 mg, 0.05 mmol, 0.05 eq) and 1,3-Bis(diphenylphosphino)propane (42.5 mg, 0.1 mmol, 0.1 eq) were dissolved in THF/MeOH (1/1) (9.5 mL). Triethylamine (0.563 mL, 4 mmol, 4 eq) was added and the mixture was degassed with N_2. This solution was filled into a 10 mL PFA loop. The mixture was pumped (F = 0.20 mL/min) and mixed with CO (2.07 mmol, 2.07 eq) at F(CO) = 1.0 sccm using a T-mixer. The combined reaction mixture was pumped through a 10 mL stainless steel heated coil reactor (T= 180°C) of the Vapourtec system. Three 150 psi BPRs and the peristaltic pump C as active BPR (5 bar) were used to pressurize the system (28-32 bar). The mixture was collected in a sealed flask flushed with N_2 and with the gas outlet directly connected to the ventilation of the hood. Theoretical residence time was 50 min. Measured residence time (as not all CO was immediately dissolved) was 31 min. Calibration curves were used to calculate conversion, yield and amount of side product: the calculated conversion is 95%, calculated yields of product **2**: 86%, and side product **3**: <2%.

LC Calibration curves: methoxycarbonylation of 4-chlorobenzonitrile

To assess conversion, yield and amount of side products obtained in the methoxycarbonylation of 4-chlorobenzonitrile, the samples were analyzed with an LC-MS and the corresponding values were derived from the calibration curves shown below. Experiments in the tube-in-tube setup and in the gas-liquid apparatus were performed at distant points in time, thus we have performed the calibration twice and used two sets of calibration curves.

For each experiment, collected volume was much larger than the volume of the starting material injected, to ensure that we collect the entire reaction mixture (as due to laminar flow and dispersion effects in tubular reactors, reaction mixture diffuses along the reactor). The samples from the collected mixture were measured using LC-MS without further dilution.

Thus, to calculate the conversion and yield, we relied on the theoretical concentration of the starting material in the collected volume $C_{SM,theoretical}$:

$$C_{SM,theoretical} = \frac{n_{SM}}{V_{collected}} \qquad (1)$$

Which in turn is based on the scale of the reaction n_{SM} (mol) and $V_{collected}$ - volume collected (ml). From there, the conversion was calculated with relevant calibration factors, e.g. for the tube-in-tube reactor:

$$conversion = 1 - \frac{A_{SM}}{608713 \times C_{SM,theoretical}} \qquad (2)$$

Where A_{SM} - UV area of the starting material peak (a.u.). The yield was calculated from the UV area of the product peak $A_{product}$ (a.u.) using the relevant calibration factor (e.g. in a tube-in-tube reactor):

$$yield = \frac{A_{Product}}{424104 \times C_{SM,theoretical}} \qquad (3)$$
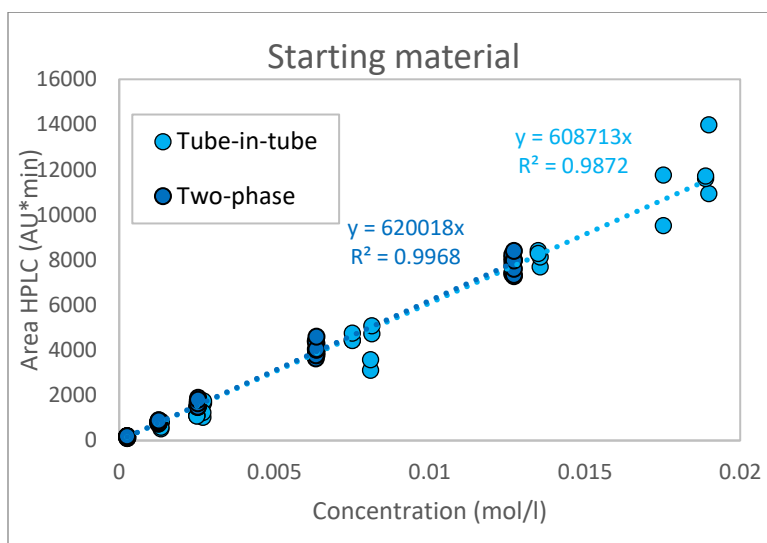

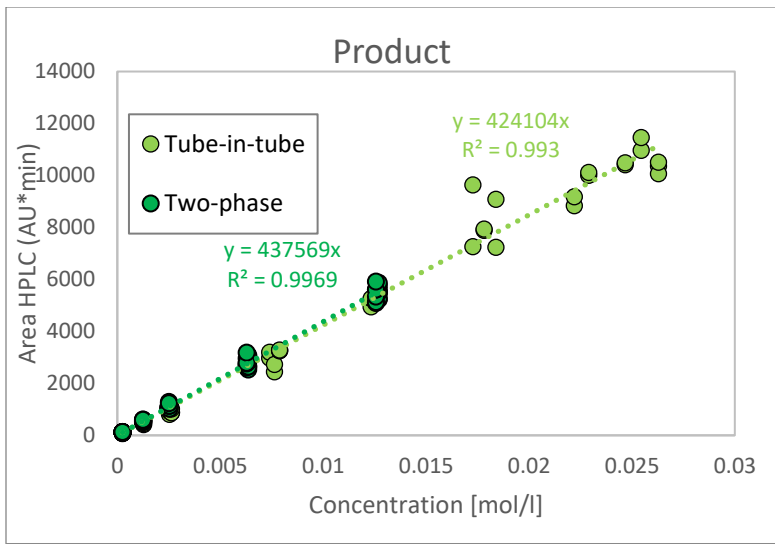*Figure S4 Calibration curves for the starting material, 4-chlorobenzonitrile.*

Figure S5 Calibration curves for the product, methyl 4-cyanobenzoate.
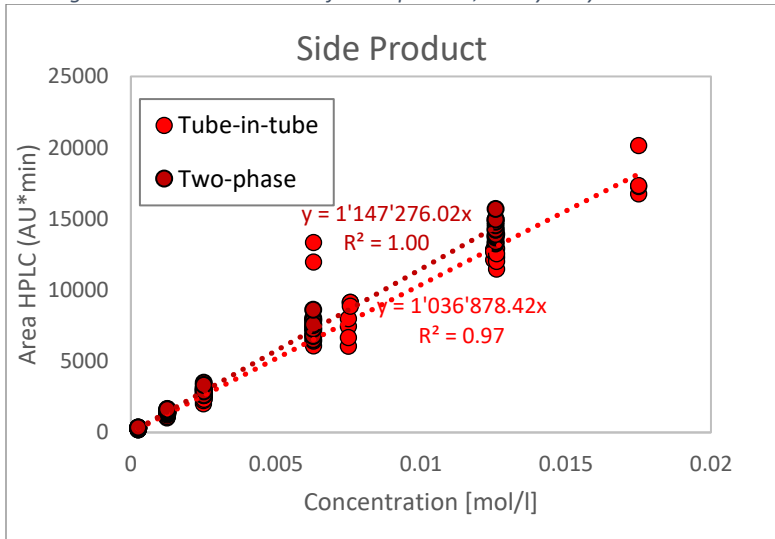
Figure S6 Calibration curves for the side product, benzonitrile.

Results: reproducibility and optimization in the tube-in-tube setup

Tube-in-tube setup: reproducibility

Table S3 Reproducibility dataset for the tube-in-tube setup. Conversion and yield in the tube-in-tube setup with following settings: 10 min at 25°C in saturation module (tube-in-tube unit), 18 bar gas pressure, 16 min residence time at 170°C and 22 bar liquid pressure in the reactor, 0.1 mol/l concentration of 4-chlorobenzonitrile, MeOH:MeCN 1:1, and 2 equivalents of Et$_3$N.

ID	Results		
	Conversion (%)	Yield (%)	Side product (%)
1	43.1	12.6	8.7
2	48.9	18.9	7.6
3	48.3	15.1	7.7
4	48.4	22.7	8.1
5	49.1	9.5	9.5
6	41.8	15.3	8.9
7	42.6	17.3	5.9
8	45.4	9.3	8.9
9	53.6	17.9	7.1
10	53.7	16.8	6.1
Average	47.5	15.5	7.9
Standard deviation	4.2	4.2	1.2

Tube-in-tube setup: Reaction Optimization

Table S4 Optimization of methoxycarbonylation of 4-chloronitrobenzene in the tube-in-tube setup. Parameters varied are highlighted in grey. Solvent used: MeOH:MeCN 1:1. Conversion and yields were calculated from integrated peaks of the HPLC-UV measurement and calibration curves.

ID	C (mol/l)	TEA equiv.	Reactor 1			Reactor 2			Results		
			T (°C)	p_{gas} (bar)	τ (min)	T (°C)	p_{liquid} (bar)	τ (min)	Conversion (%)	Yield (%)	Side product (%)
1[a]	0.1	2	25	18	10	170	22	16	47.5	15.5	7.9
2[b]	0.1	4	25	18	10	170	22	16	41.8	7.7	12.6
3[b]	0.1	4	25	18	10	170	22	16	57.7	23.7	14.5
4	0.1	2	25	18	15	170	22	23.5	62.1	37.3	5.8
5	0.1	2	25	18	15	170	22	23.5	63.9	29.4	6.6
6	0.1	2	25	18	20	170	22	30	60.7	30.0	9.4
7	0.1	2	25	18	20	170	22	30	65.6	27.1	10.0
8	0.05	2	25	18	10	170	22	16	53.0	18.4	13.1
9	0.05	2	25	18	15	170	22	24	59.2	31.4	12.7
10	0.025	2	25	18	10	170	22	16	35.7	24.2	4.3
11	0.1	2	25	18	10	190	22	16	60.2	22.7	27.0
12	0.1	2	25	18	10	210	22	16	29.2	10.5	15.1
13	0.1	2	25	18	10	230	22	16	34.1	5.7	20.8

[a] average from Table S3.

[b] entries 2 and 3: reaction was performed at identical conditions, but conversion and yield deviate significantly. As both are within the variability expected from the reproducibility example (Table S3) and we have not identified any potential reasons to disqualify any of the measurements, we decided to report both values here.

4. Scale-up: Methoxycarbonylation of 2-bromo-5-(1,1-difluoroethyl)pyridine

Experimental Procedure: methoxycarbonylation of 2-bromo-5-(1,1-difluoroethyl)pyridine

To showcase the scale-up method and to calculate the reaction throughput, the product was isolated.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.90 (dd, *J* = 2.4, 1.0 Hz, 1H), 8.22 (dd, *J* = 8.1, 0.9 Hz, 1H), 8.00 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.06 (s, 3H), 2.00 (t, *J* = 18.3 Hz, 3H).

Tube-in-tube setup

Exemplary procedure (amounts and conditions refer to entry 12 in Table S5):

2-bromo-5-(1,1-difluoroethyl)pyridine (1850 mg, 8 mmol, 1 eq), Palladium(II)acetate (89.8 mg, 0.4 mmol, 0.05 eq) and 1,3-Bis(diphenylphosphino)propane (344 mg, 0.8 mmol, 0.1 eq) were dissolved in MeCN (80 mL). Triethylamine (2.23 mL, 16 mmol, 2 eq) in MeOH (80 mL) was added. The reaction mixture was saturated with CO in the tube-in-tube reactor at room temperature and then pumped through a 10 mL stainless steel coil reactor (residence time = 80 min; T= 110°C) of the Vapourtec system. Two 150 psi BPRs and one 100 psi BPR were used to pressurize the system (22 bar liquid pressure). The reaction mixture was collected in a sealed flask flushed with N$_2$ and a gas outlet directly connected to the ventilation. The reaction ran for 27 h. The reaction mixture was concentrated under reduced pressure and purified by

Column Chromatography using CombiFlash (EtOAc/Heptane gradient) to give 1.18 g (73% yield) of **5** as a colorless liquid.

Gas-Liquid Flow

Exemplary procedure (amounts and conditions refer to entry 5 in Table S6):

2-bromo-5-(1,1-difluoroethyl)pyridine (4) (1500 mg, 6.42 mmol, 1 eq), Palladium(II) acetate (36 mg, 0.16 mmol, 0.025 eq), 1,3-Bis(diphenylphosphino)propane (135 mg, 0.321 mmol, 0.05 eq) were dissolved in MeOH (31.4 mL) and THF (31.4 mL), Triethylamine (1.79 mL, 12.8 mmol, 2 eq) was added and the mixture was sonicated. This solution was pumped as bottle reagent (F = 0.66 mL/min) and mixed with CO (16 mmol, 2.5 eq) at F(CO) = 4.0 sccm using a T-mixer. The combined reaction mixture was pumped through a 10 mL stainless steel coil reactor (theoretical residence time = 15 min; T = 170°C) of the Vapourtec system. Three 150 psi BPRs and pump C acting as active BPR (5 bar) were used to pressurize the system (25 bar). The reaction mixture was collected in a sealed flask flushed with N_2 and a gas outlet directly connected to the ventilation. The reaction mixture was concentrated under reduced pressure and purified by Column Chromatography using CombiFlash (EtOAc/Heptane gradient) to give 1.19 g (92% yield) of **5** as a colorless oil.

Results: optimization in the tube-in-tube setup and the gas-liquid flow setup

Tube-in-tube setup: Reaction Optimization

*Table S5 Optimization of Methoxycarbonylation of 2-bromo-5-(1,1-difluoroethyl)pyridine in the tube-in-tube setup. Varied parameters highlighted in **bold**. *Conversion was estimated from the UV area of the product and starting material peaks assuming that starting material was converted only to product (no side products were observed). Conversion was calculated as Area of Product/(Area of Product + Area of Starting Material).*

ID	Scale (mmol)	C (mol/l)	TEA eq.	Reactor 1		Reactor 2			Estimated conversion* (%)	Isolated yield (%)
				T (°C)	p_{gas} (bar)	T (°C)	p_{liquid} (bar)	τ (min)		
1	0.2	0.1	2	rt	17.5	**110**	24	**16**	29%	12%
2	0.2	0.1	2	rt	17.5	**90**	24	**30**	31%	15%
3	0.2	0.1	2	rt	17.5	**150**	24	**24**	61%	35%
4	0.2	0.1	2	rt	17.5	**130**	24	**50**	88%	45%
5	**1**	0.1	2	rt	17.5	130	22.5	50	36%	33%
6	0.2	0.1	2	rt	17	110	21.8	**60**	76%	65%
7	0.2	0.1	2	rt	17.5-18	110	19-20.7	**80**	80%	
8	**1**	0.1	2	rt	18	110	21.5-23	80	48%	
9	0.1	**0.05**	2	rt	17.5-18	110	19.8-21.4	80	100%	
10	**0.5**	0.05	2	rt	17.5-18	110	23	80	75%	63%
11	**1**	0.05	2	rt	17.5-18	110	21.5-23.4	80	74%	
12	**8**	0.05	2	rt	17.5-18	110	21.5-23.4	80	78%	73%

Gas-Liquid Flow: Reaction Optimization

*Table S6 Optimization of Methoxycarbonylation of 2-bromo-5-(1,1-difluoroethyl)pyridine in the biphasic setup. Varied parameters highlighted in **bold**. *Conversion was estimated from the UV area of the product and starting material peaks assuming that starting material was converted only to product (no side products were observed). Conversion was calculated as Area of Product/(Area of Product + Area of Starting Material).*

ID	Scale (mmol)	C (mol/l)	TEA equiv.	CO equiv.	T (°C)	p_{liquid} (bar)	τ (min)	Results	
								Estimated Conversion* (%)	Isolated Yield (%)
1	0.5	0.1	2	2.5	**150**	15-17	15	67%	-
2	0.5	0.1	2	2.5	**170**	25	15	100%	66%
3	**0.5**	0.1	2	2.5	**160**	15-17	15	94%	-
4	**1.5**	0.1	2	2.5	170	25	15	100%	89%
5	**6.42**	0.1	2	2.5	170	25	15	100%	92%

References

(1) 4-Channel 16-Bit ADC for Raspberry Pi (ADS1115) | Seeed Studio Wiki https://wiki.seeedstudio.com/4-Channel_16-Bit_ADC_for_Raspberry_Pi-ADS1115/ (accessed Jan 19, 2024).

(2) 4-Channel 16-Bit ADC for Raspberry Pi (ADS1115) https://www.seeedstudio.com/4-Channel-16-Bit-ADC-for-Raspberry-Pi-ADS1115.html (accessed Jan 19, 2024).

(3) Introduction — Adafruit CIRCUITPYTHON_ADS1X15 Library 1.0 documentation https://docs.circuitpython.org/projects/ads1x15/en/latest/ (accessed Jan 19, 2024).

(4) Adafruit 4-Channel ADC Breakouts https://learn.adafruit.com/adafruit-4-channel-adc-breakouts/python-circuitpython (accessed Jan 19, 2024).