

**Reaction kinetics of a water-soluble palladium- β -cyclodextrin catalyst
for a Suzuki-Miyaura cross-coupling in continuous-flow**

ELECTRONIC SUPPLEMENTARY INFORMATION

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1. Gas chromatograph – mass spectroscopy (GC-MS) results

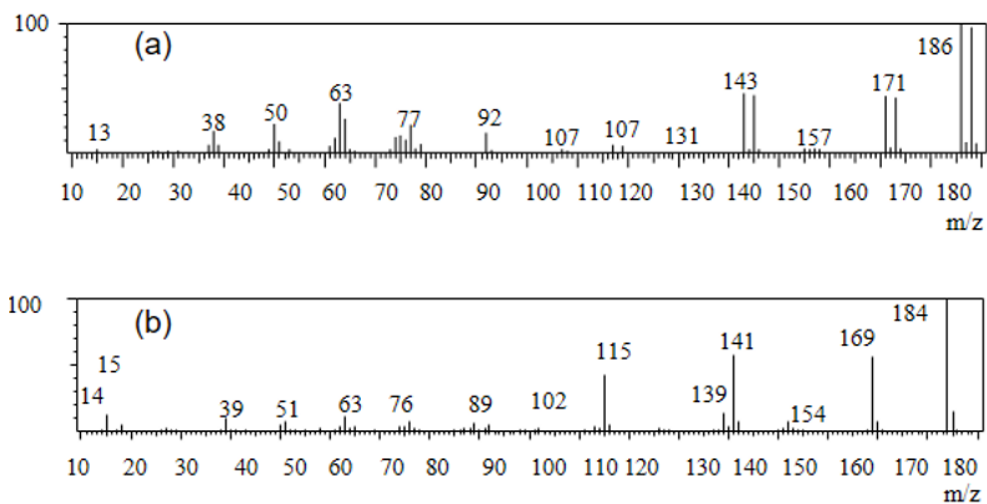


Figure S1. GC-MS results of reaction at 40 °C and 2min residence time. (a) 4-bromoanisole; (b) 4-Methoxybiphenyl

2. Hatta modulus calculations

The value of Hatta modulus is calculated by:

$$Ha = \frac{(D_A k c_A c_B^{bulk})^{\frac{1}{2}}}{k_L} \quad (S1)$$

where D_A is the diffusivity of reactant 4-bromoanisole, c_A is the concentration of 4-bromoanisole, c_B^{bulk} is the concentration of palladium catalyst, k is the rate constant of oxidative addition step, and k_L is the liquid phase mass transfer coefficient, which is estimated by:

$$k_L = \frac{D_A}{\delta} \quad (S2)$$

where δ is the film thickness.

The diameter distribution of 4-bromoanisole droplets was determined by dynamic light scattering (DLS), and the results are shown in figure S2. The diffusivity of 4-bromoanisole in water D_A is estimated to be around 2×10^{-9} m²/s at 20 °C and 3×10^{-9} m²/s at 80 °C.^{1,2} Here, c_A is 0.435 mol/L, and c_B^{bulk} is 2.17×10^{-5} mol/L. At 20 °C, rate constant k is calculated to be 348.9 L² mol⁻² s⁻¹; at 80 °C, k is evaluated as 9914.2 L² mol⁻² s⁻¹. As a worst-case scenario, the radius of the emulsion droplets is considered as the maximum possible film thickness δ .

The size distribution of 4-bromoanisole droplets before injection into the reactor and after they flowed out of the reactor were measured by DLS at 20 °C and 70 °C. The average size ranged from 236.4 nm to 809.8 nm. Size distributions by number are shown in figure S2. If the reaction was fast enough that mass transfer limitations can no longer be neglected, then the Hatta number Ha should be > 0.02 .³ At the maximum reaction rate, which appeared at 80 °C, if $Ha > 0.02$, the diameter of the 4-bromoanisole droplets should be bigger than 3000 nm. From the size distribution, it could be seen that the droplet size was always smaller than 1000 nm, and the reaction was therefore identified to be slow with respect to mass transfer. Thus, an intrinsic kinetic model could be developed.

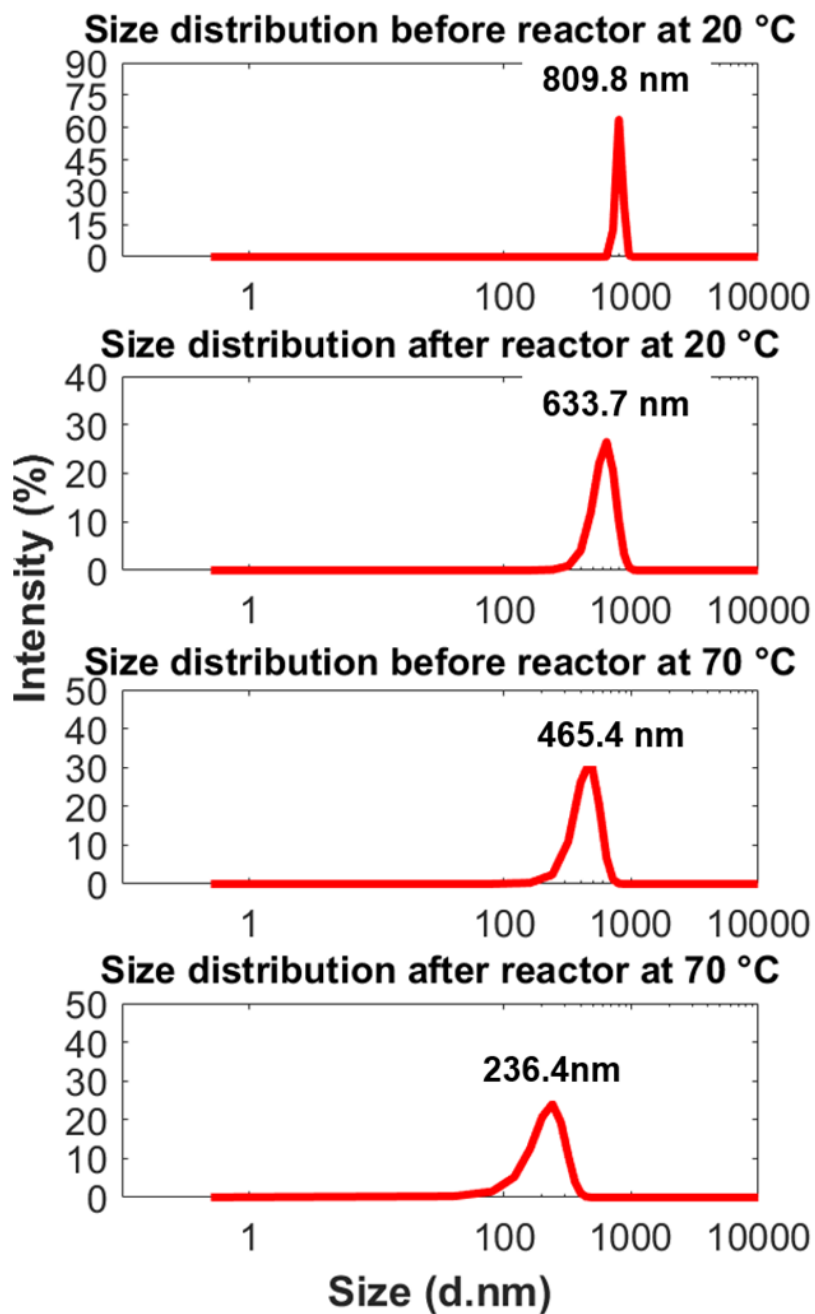


Figure S2. 4-Bromoanisole droplets size distribution before and after reagents flow through the reactor and under 20 °C, 70 °C

3. Reactor characterization

Experiments were performed to characterize the residence time distributions (RTDs) of the reactor. Illustration of the experimental setup is shown in figure S3. Water was used as the carrier fluid and was delivered to the reactor at volumetric flow rates of 33 $\mu\text{L}/\text{min}$, 50 $\mu\text{L}/\text{min}$, 100 $\mu\text{L}/\text{min}$, 133 $\mu\text{L}/\text{min}$, 200 $\mu\text{L}/\text{min}$ and 400 $\mu\text{L}/\text{min}$ using a Harvard syringe pump. Acetone was chosen as the tracer and was injected to the system through a microscale injector with an injection volume of 5 μL . The acetone tracer monitored in-line by UV-Vis absorbance spectrometry at the outlet of reactor. Both deuterium and halogen lamps on the light source were used to warm up for at least 20 min before RTD experiments. The absorbance wavelength 277 nm were chosen to maximize the signal-to-noise ratio of the measurements. A picture of the experimental setup is shown in figure S4. UV absorbance at different carrier flow rates were record as a function of time.

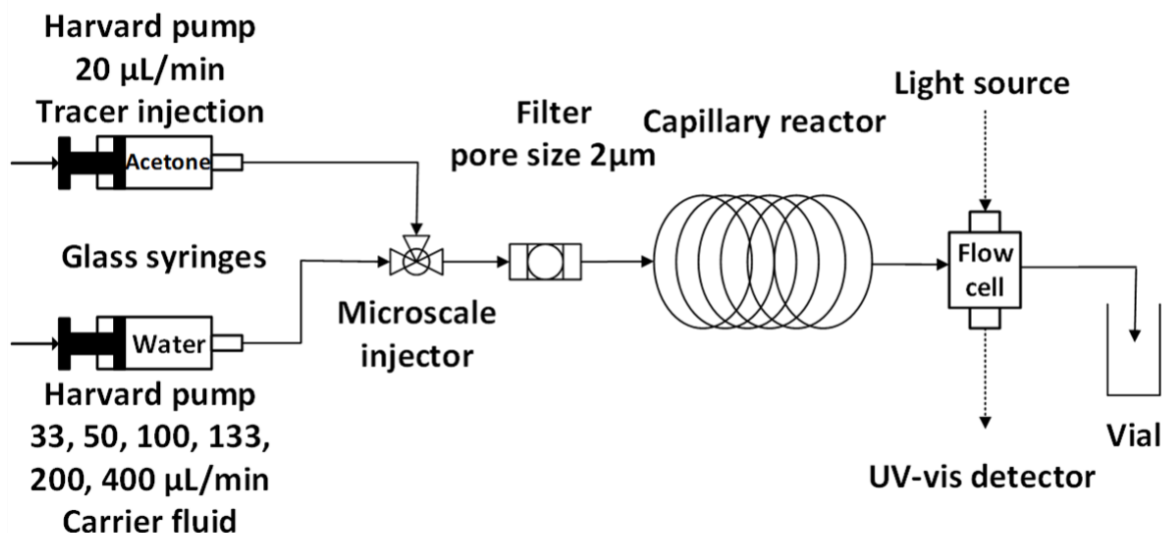


Figure S3. Process flow diagram of the continuous in-line UV-Vis spectroscopy for RTDs measurement

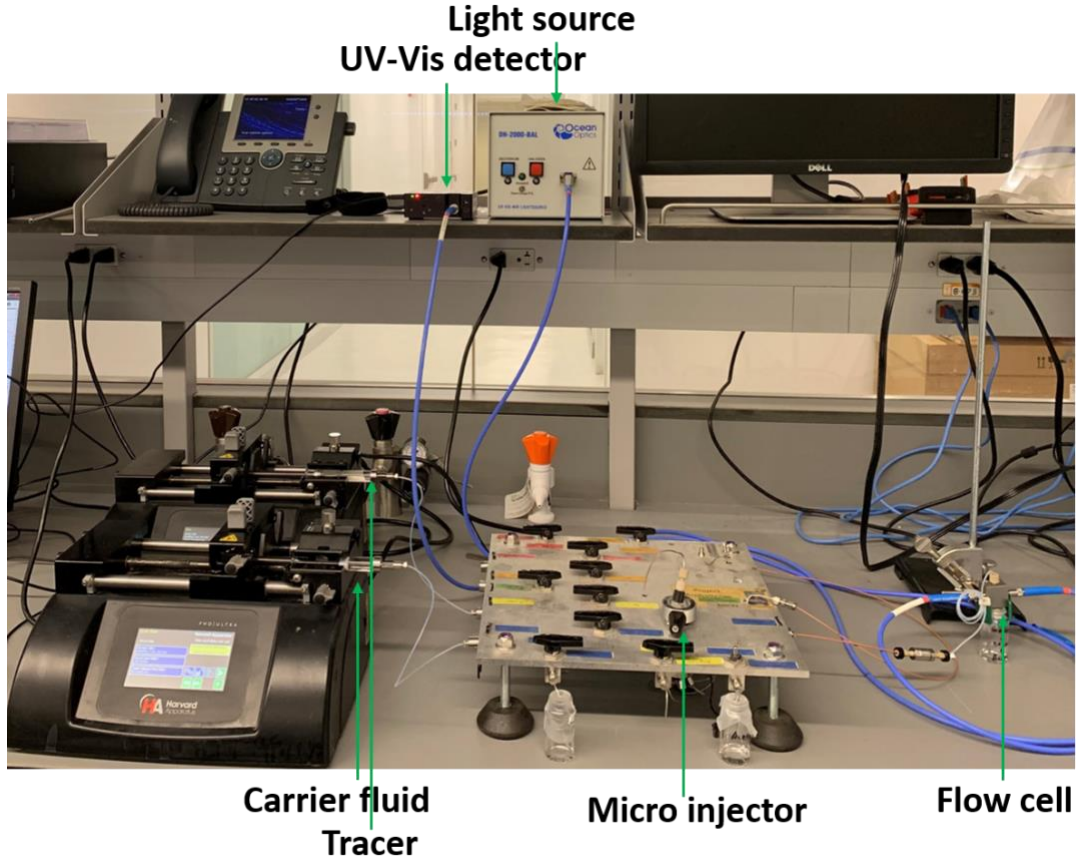


Figure S4. Photo of RTD measurement experiments

The mean residence time τ was calculated by:

$$\tau = \frac{\int_0^{\infty} tA(t)dt}{\int_0^{\infty} A(t)dt} \quad (\text{S3})$$

where $A(t)$ is the tracer absorbance at 277 nm. The tracer was injected into the system at $t = 0$, and $\int_0^{\infty} A(t)dt$ is the area under the absorbance curve. With i an integer and l the total number of signals obtained in one RTD experiment, the area under the absorbance curve was calculated by:

$$\int_0^{\infty} A(t)dt = \sum_{i=1}^{l-1} (t_{i+1} - t_i) \times \frac{A_{i+1} + A_i}{2} \quad (\text{S4})$$

Similarly,

$$\int_0^{\infty} tA(t)dt = \sum_{i=1}^{l-1} \frac{t_i + t_{i+1}}{2} \times (t_{i+1} - t_i) \times \frac{A_{i+1} + A_i}{2} \quad (\text{S5})$$

Then $C(t)$ was normalized to $E(\Theta)$ by,

$$E(\Theta) = \tau \times A(\Theta) \quad (S6)$$

In which,

$$\Theta = t/\tau \quad (S7)$$

$$A(\Theta) = \frac{A(t)}{\int_0^{\infty} A(t) dt} \quad (S8)$$

The absorbance and their corresponding normalized RTD functions at different flow rates are shown in figures S5-S10.

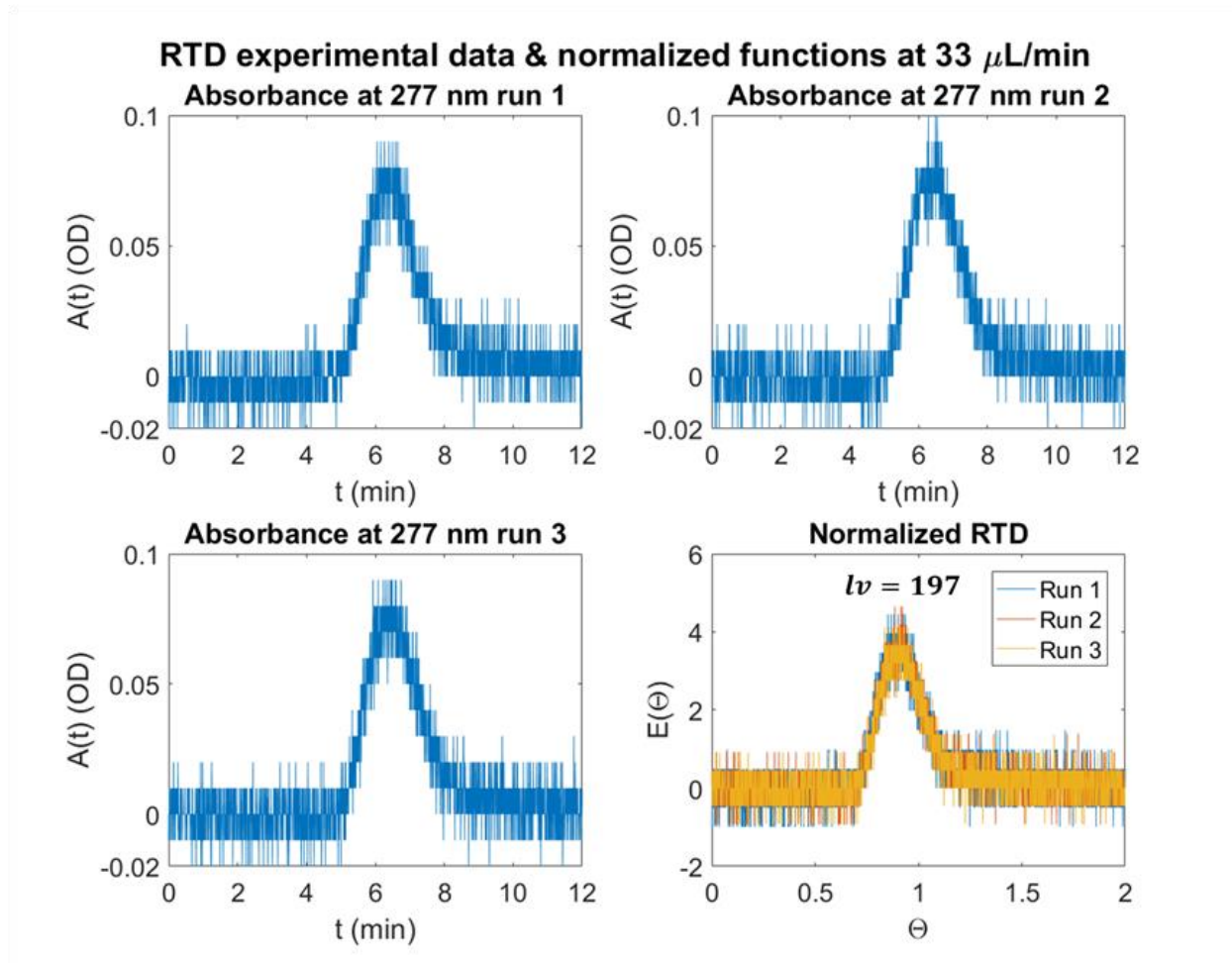


Figure S5. UV-vis absorbance over time and normalized RTD functions at carrier volumetric flow rate 33 $\mu\text{L}/\text{min}$

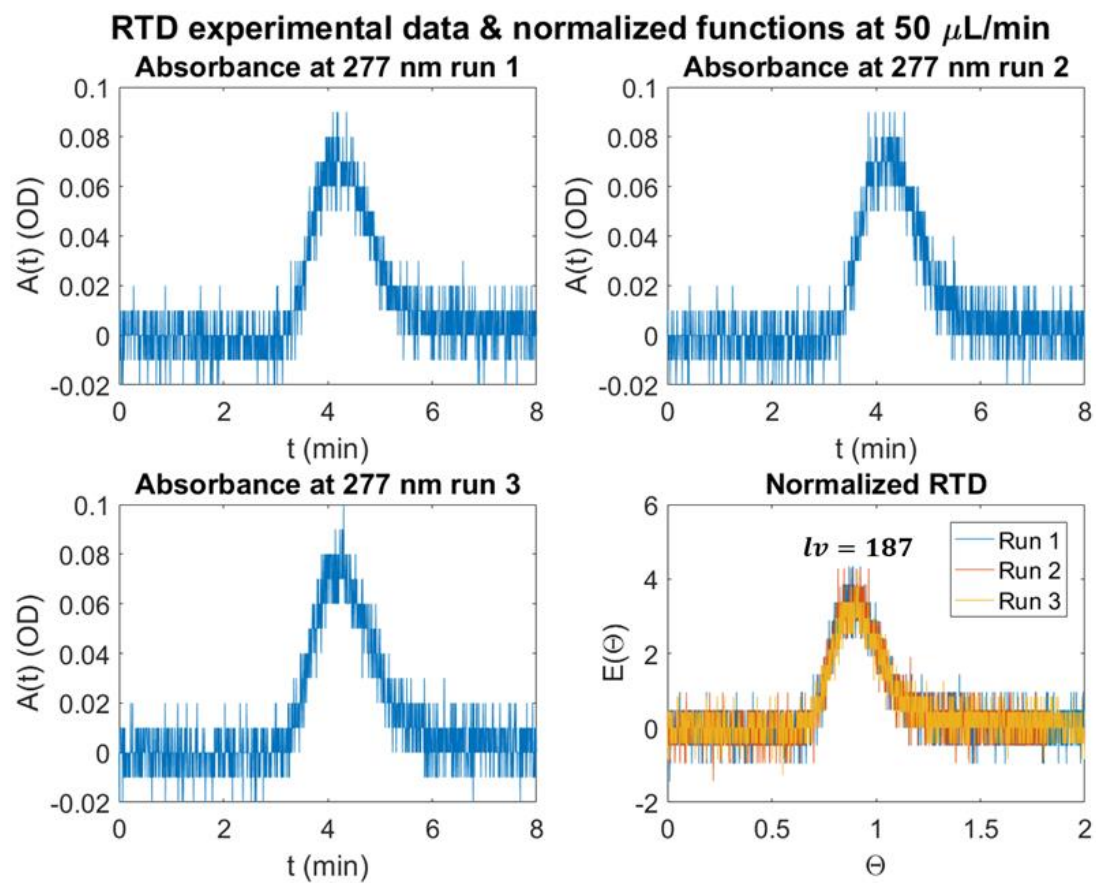


Figure S6. UV-vis absorbance over time and normalized RTD functions at carrier volumetric flow rate 50 $\mu\text{L}/\text{min}$

RTD experimental data & normalized functions at 100 $\mu\text{L}/\text{min}$

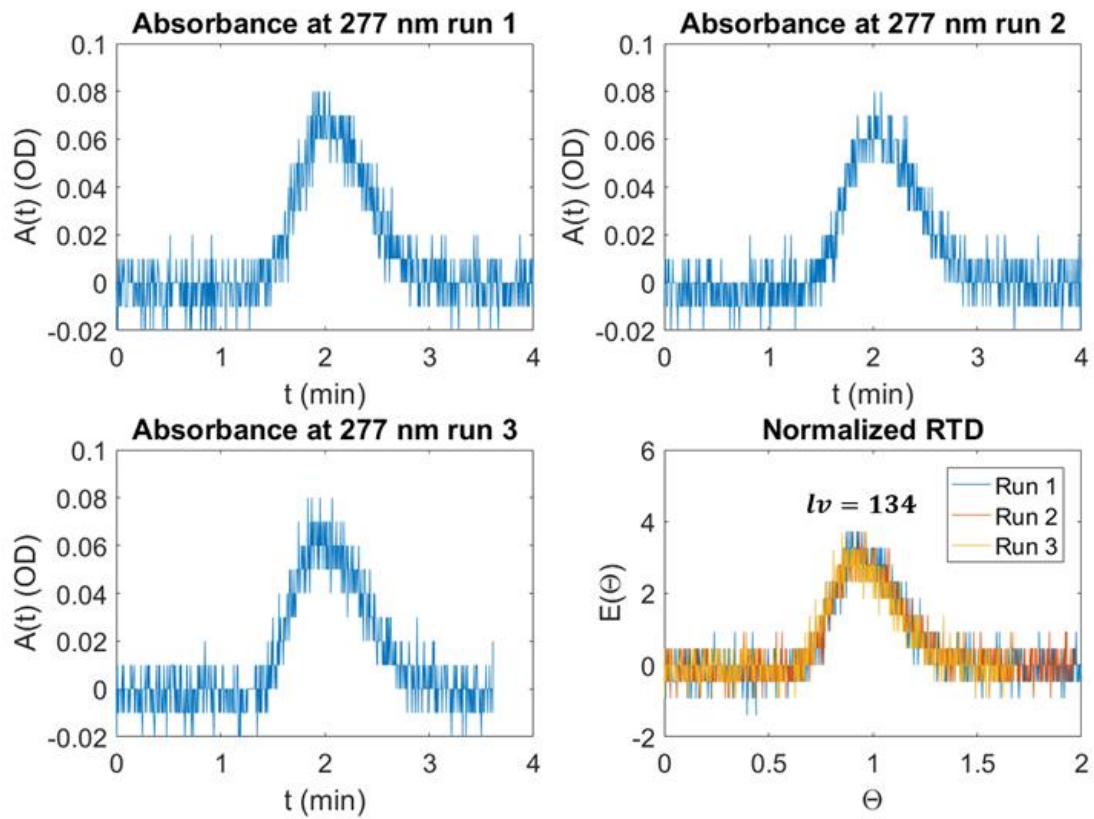


Figure S7. UV-vis absorbance over time and normalized RTD functions at carrier volumetric flow rate 100 $\mu\text{L}/\text{min}$

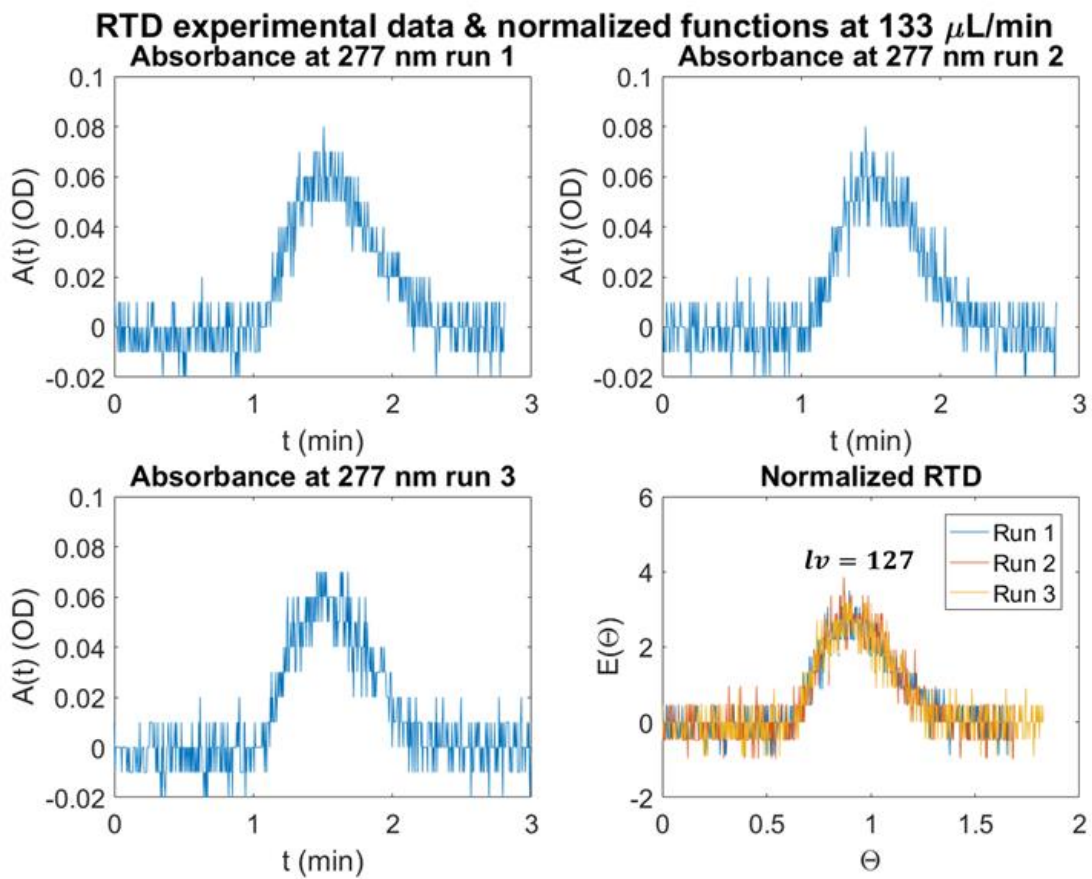


Figure S8. UV-vis absorbance over time and normalized RTD functions at carrier volumetric flow rate 133 $\mu\text{L}/\text{min}$

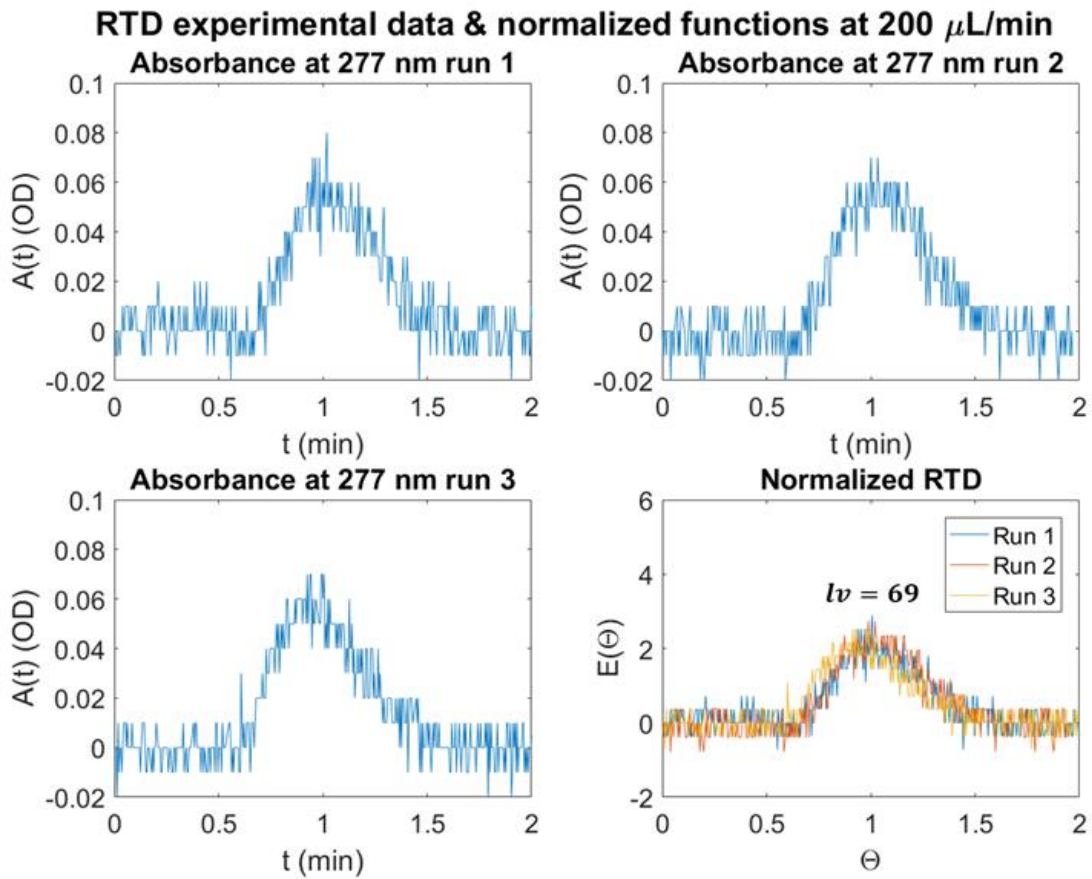


Figure S9. UV-vis absorbance over time and normalized RTD functions at carrier volumetric flow rate 200 $\mu\text{L}/\text{min}$

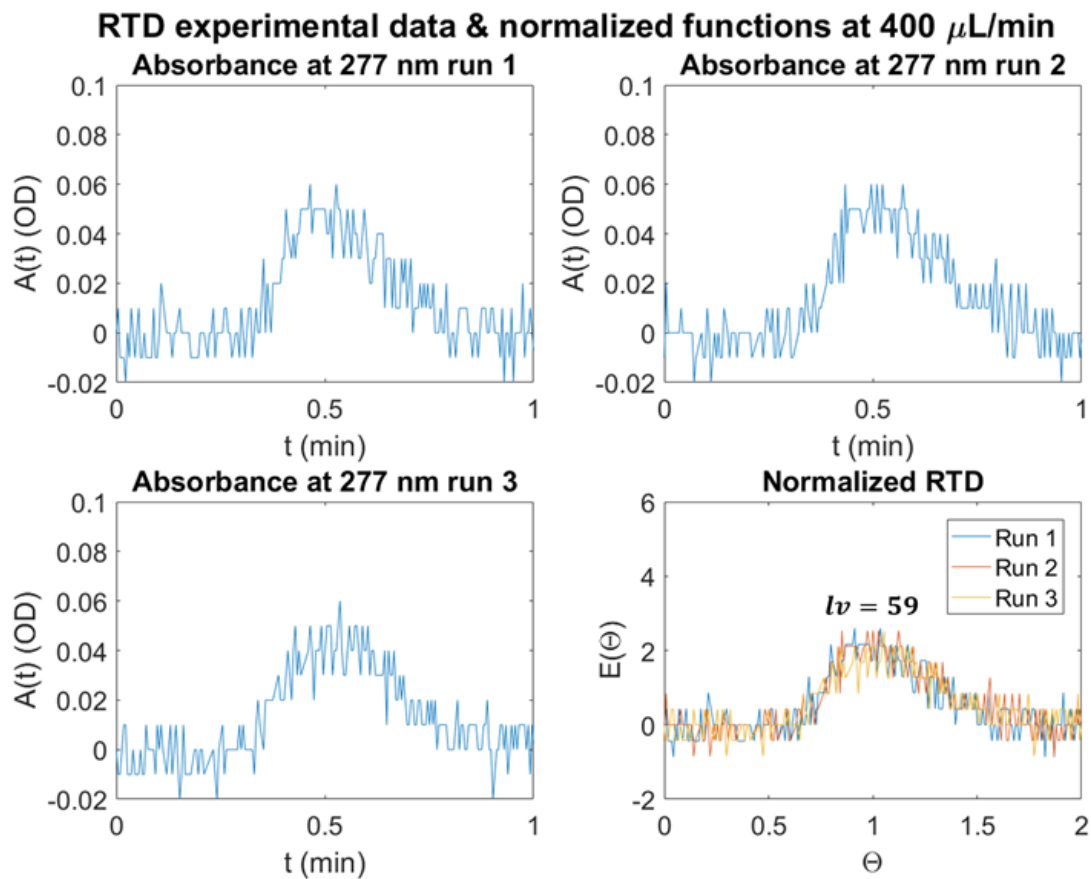


Figure S10. UV-vis absorbance over time and normalized RTD functions at carrier volumetric flow rate 400 $\mu\text{L}/\text{min}$

The length to diameter ratio of the reactor is 10^3 , which yields the Bodenstein number B_o ,

$$B_o = \frac{ud_t}{D} \quad (S9)$$

where d_t is the diameter of the tubing, D is the diffusivity of bromoanisole in water at 80 °C, and u is the superficial velocity. Estimated values of B_o at different flow rates are listed in table S1.

Table S1. Bodenstein number B_o at different flow rates

Volumetric flow rate v_0 ($\mu\text{L}/\text{min}$)	Superficial flow rate u (cm/s)	B_o
33	0.28	466.9
50	0.42	707.4
100	0.89	1414.7
133	1.13	1881.6
200	1.70	2829.4
400	3.40	5658.8

According to O. Levenspiel, for $L/d_t = 10^3$, and B_o in the range of 10^3 , the Taylor expression for the dispersion should be used³:

$$D = \frac{u^2 d_t^2}{192D} \quad (S10)$$

The extent of axial distribution was then measured by Levenspiel number lv :

$$lv = \frac{uL}{D} \quad (S11)$$

where D is the dispersion coefficient, u is the superficial velocity, and L is the reactor length. Combining (S10) and (S11), the relationship between the Levenspiel number and the velocity can be seen as,

$$lv = \frac{192DL}{d_t^2} \cdot \frac{1}{u} \quad (S12)$$

Indicating that the lv number decreases as velocity increases, which is consistent with our findings.

Values of lv were estimated by:

$$E(\Theta)_{max} = \frac{1}{\sqrt{4\pi \cdot \frac{1}{lv}}} \quad (S13)$$

where $E(\Theta)_{max}$ is the maximum value of $E(\Theta)$ at different flow rates. For flow rates from 33 $\mu\text{L}/\text{min}$ to 400 $\mu\text{L}/\text{min}$ (see figure S5-S10), $E(\Theta)_{max}$ ranges from 2-4. Values of lv are then calculated to be 58.96 to 197.46. Values of Levenspiel number at different flow rates are shown in table S2. For $lv > 50$, the dispersion causes insignificant impact on conversions.⁴ Thus flow in the reactor is considered as plug flow and the dispersion can be neglected.

Table S2. Estimated Levenspiel number lv at different flow rates

Flow rate ($\mu\text{L}/\text{min}$)	$E(\Theta)_{max}$	Levenspiel number
33	3.964	197.46
50	3.855	186.75
100	3.267	134.12
133	3.174	126.60
200	2.350	69.40
400	2.166	58.96

Assuming plug flow, the reactor volume V was then evaluated by the mean residence time,

$$V = v_0 \tau \quad (S14)$$

where v_0 is the volumetric flow rate and τ is corresponding residence time. The value of V is $216.4 \pm 20 \mu\text{L}$. Dead volume of the RTD experiments setup is the connecting tubing before the reactor with 31 cm total length and 500 μm inner diameter (total volume 63 μL), and an inline solvent filter with 12.3 μL swept volume. So, the reactor volume was measured to be $141.1 \pm 20 \mu\text{L}$.

4. Catalytic mechanism model fitting

According to the catalytic cycle, the rate of formation of 4-methoxybiphenyl at 20 °C could be written as:

$$\frac{dc_m}{d\tau} = \frac{1}{\frac{1}{k_1 \times c_{pd} \times c_b^2} + \frac{1}{k_2 \times c_{pd} \times c_{base}^2} + \frac{1}{k_3 \times c_{pd} \times c_p^2} + \frac{1}{k_4 \times c_{pd}}} \quad (S15)$$

where c_m is the concentration of product, τ is the mean residence time under different flow rates, c_b is the concentration of 4-bromoanisole, c_{pd} is the concentration of catalyst in the reaction mixture, c_{base} is the concentration of OH⁻ at 20 °C, and c_p is the concentration of phenylboronic acid.

For 20 °C, since there is dead volume before and after the reactor caused by 10 cm of tubing connecting to the mixer and 10 cm of tubing leading to the collection vial, the residence time at different flow rates were recalibrated by,

$$\tau = \frac{V_{reactor} + V_{deadvolume}}{v_0} \quad (S16)$$

where $V_{reactor}$ is the volume of reactor equal to 100 μ L, $V_{deadvolume}$ is the summation of the 20 μ L dead volume before the reactor and 20 μ L dead volume after the reactor equal to 40 μ L, and finally v_0 is experimental volumetric flow rate of 400 μ L/min, 200 μ L/min, 133 μ L/min, 100 μ L/min, 50 μ L/min, and 33 μ L/min.

The concentration of 4-methoxy biphenyl was fitted to time t by using MATLAB *nlinfit*,

$$c_m = \alpha_1 \times \left(1 - \frac{1}{1 + \alpha_2 \times \tau}\right) \quad (S17)$$

The fitted parameters were found to be $\alpha_1 = 0.2196$, $\alpha_2 = 0.5506$ with $R^2 = 0.93$.

Then values of the rate of formation of 4-methoxybiphenyl r_{m20} could be estimated by taking the derivative of 4-methoxybiphenyl concentration with respect to time,

$$r_{m20} = \frac{\alpha_1 \times \alpha_2}{(1 + \alpha_2 \times \tau)^2} \quad (S18)$$

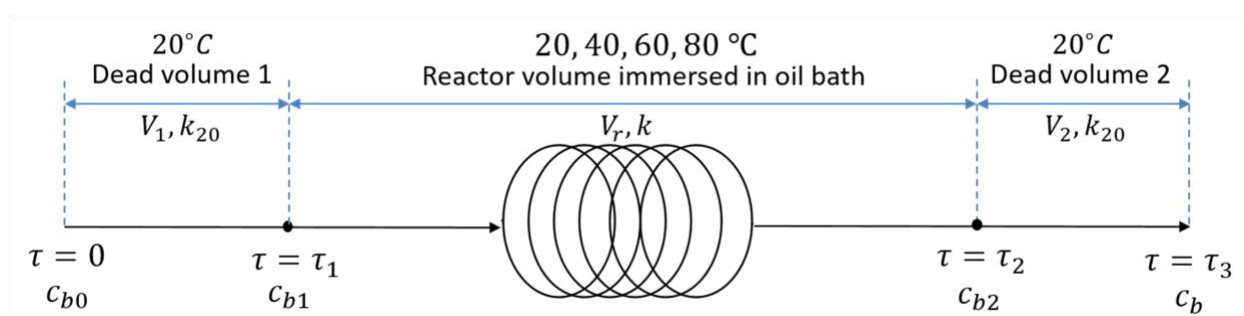
The experimental data was then fitted into the above relationship by MATLAB *nlinfit* and the determined values of rate constants are reported in table S3 with $R^2 = 0.84$.

Table S3. Rate constants fitting results

Rate constant	Value	Unit
k_1	1.547×10^4	$L^2 mol^{-2} min^{-1}$
k_2	1.023×10^{14}	$L^2 mol^{-2} min^{-1}$
k_3	9.271×10^{12}	$L^2 mol^{-2} min^{-1}$
k_4	1.518×10^{16}	min^{-1}

Since the rate constants of the transmetalation and the reductive elimination steps are several orders of magnitude larger than that of the oxidative addition step. The oxidative addition step is then considered to be the rate limiting step. The rate constants of the oxidative addition step at different conditions were then calculated.

The residence times after the mixing of reagents, at the end of the first dead volume, at the end of the effective reactor volume, and at the end of the second dead volume were $\tau = 0, \tau = \tau_1, \tau = \tau_2$, and $\tau = \tau_3$, respectively. The corresponding 4-bromoanisole concentrations at above points were $c_{b0}, c_{b1}, c_{b2}, c_b$. Here, c_{b0} is the initial concentration of 4-bromoanisole in feeding stream, and c_b was measured by gas chromatography. The first dead volume, reactor volume, second dead volume were V_1, V_r , and V_2 , respectively. The temperature in V_1 and V_3 were ambient temperature ($20^\circ C$), whereas the temperatures in the reactor were $20, 40, 60$, and $80^\circ C$. A configuration of the reactor with its dead volumes is shown in figure S11.

**Figure S11.** Configuration of reactor and its dead volumes

Assuming the Graetz-Nusselt heating and cooling of the microchannel is much faster than any residence time, the design equations with boundary conditions could be written as,

For $\tau = 0$ to $\tau = \tau_1, T = 20$ °C:

$$\int_{c_{b0}}^{c_{b1}} \frac{dc_b}{c_b^2} = \int_0^{\tau_1} (-k_{20} c_{pd}) d\tau \quad (S19)$$

For $\tau = \tau_1$ to $\tau = \tau_2, T = 20, 40, 60, 80$ °C:

$$\int_{c_{b1}}^{c_{b2}} \frac{dc_b}{c_b^2} = \int_{\tau_1}^{\tau_2} (-k_{20/40/60/80} c_{pd}) d\tau \quad (S20)$$

For $\tau = \tau_2$ to $\tau = \tau_3, T = 20$ °C:

$$\int_{c_{b0}}^{c_{b1}} \frac{dc_b}{c_b^2} = \int_{\tau_2}^{\tau_3} (-k_{20} c_{pd}) d\tau \quad (S21)$$

where k_{20} is the rate constant of oxidative addition step at 20 °C, $k_{20/40/60/80}$ is the rate constant of oxidative addition step at 20, 40, 60, and 80 °C, respectively.

Separation of variables and integration yields the relationship of c_b to τ at 20 °C:

$$c_b = \frac{1}{k_{20} c_{pd} \tau_3 + \frac{1}{c_{b0}}} \quad (S22)$$

The value of k_{20} was then obtained by fitting c_b and τ into the above equation using MATLAB *nlinfit*.

The relationship of c_b to τ at 40, 60, 80 °C were also obtained by combining the solutions of (S19) into (S20) and the result into (S21),

$$c_b = \frac{1}{k_{20} c_{pd} \tau_1 + k_{40/60/80} c_{pd} (\tau_2 - \tau_1) + k_{20} c_{pd} (\tau_3 - \tau_2) + \frac{1}{c_{b0}}} \quad (S23)$$

The regressions were then solved by MATLAB *nlinfit* to obtain the rate constants for 40, 60, 80 °C.

5. Activation energy estimation

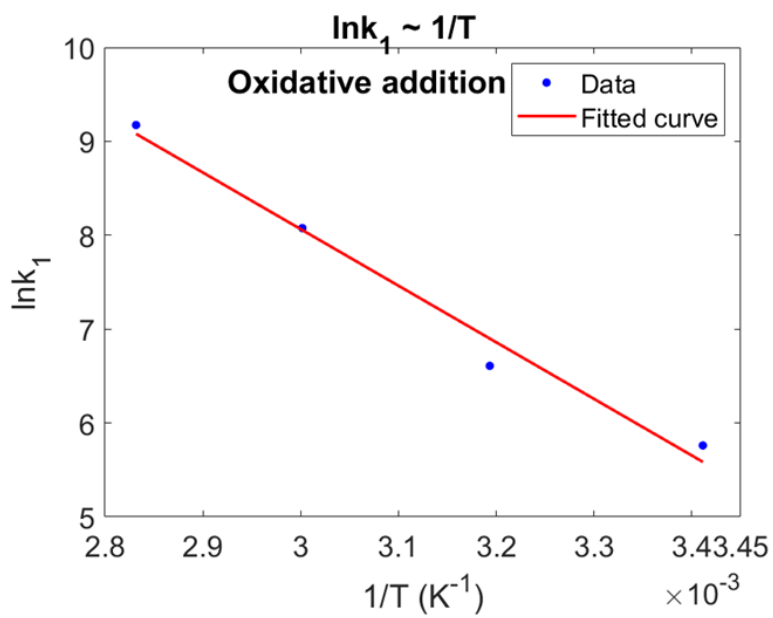


Figure S12. Linear regression for the activation energy for oxidative addition step

6. Error of the activation energy:

According to propagation of uncertainty, error of rate constant ε_k could be calculated as,

$$\varepsilon_k = \left| -\frac{2}{cpd} \cdot r_m \cdot c_b^{-3} \right| \cdot |\varepsilon_b| \quad (\text{S24})$$

where r_m is the rate of formation of product at different temperatures. Values of ε_k were determined by the maximum errors.

Error of the activation energy was determined by the maximum error value calculated by the equation,

$$\varepsilon_E = \left| -RT \cdot \frac{1}{k} \right| \cdot |\varepsilon_k| \quad (\text{S25})$$

where k , ε_k are the rate constants fitted by nonlinear regression, and the corresponding errors at each temperature. k_1 is the rate constant of oxidative addition step at each temperature, ε_{k1} is the maximum error of k_1 at each temperature, and ε_E is the error of the activation energy of oxidative addition step at each temperature. Values of k_1 , ε_{k1} , ε_E are listed in table S4 using a value of the gas constant $R = 8.314 \text{ J}/(\text{mol}\cdot\text{K})$. Error of the activation energy ε_{E_total} was then determined by the summation of ε_E at each temperature, and its value was estimated to be 4.7 kJ/mol .

Table S4. Errors of rate constant at each temperatures

Temperature (K)	$k_1 (L^2 \text{mol}^{-2} \text{s}^{-1})$	$\varepsilon_{k1} (L^2 \text{mol}^{-2} \text{s}^{-1})$	$\varepsilon_E (\text{Jmol}^{-1})$
293.15	317.46	88.56	681.5
313.15	741.33	267.98	941.2
333.15	3213.88	1773	1528.0
353.15	7637.94	3262	9940.4

7. Reaction at longer residence time for full conversion

Experiments at 10 min and 20 min residence times at 80 °C were also carried out. As can be seen in Figure S13, the conversion reached $98.3 \pm 2.91\%$ after 10 min of reaction.

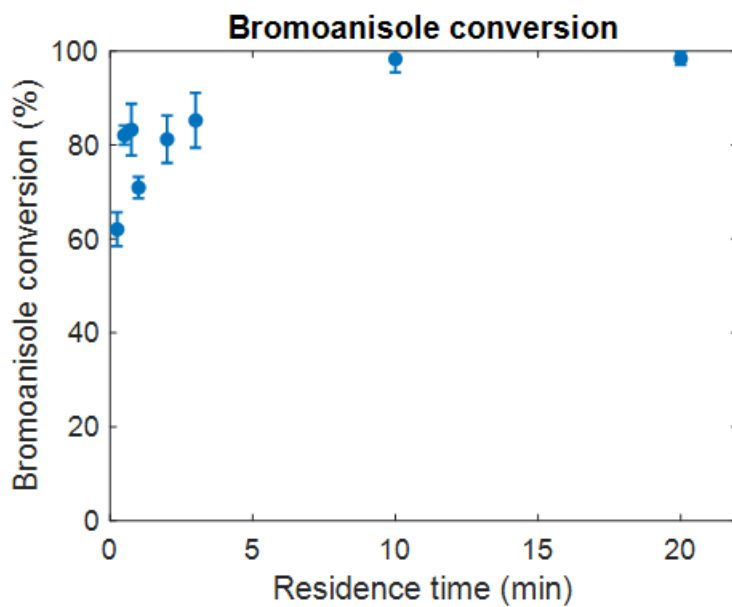


Figure S13. 4-bromoanisole conversion for extended residence time at 80 °C

8. Heat transfer evaluation

For capillary reactors, the temperature profile of Graetz-Nusslet problem along $r = 0$ predicts the heating time for fluid in the center in a reactor of length L where the heat flux at the wall is constant:

$$t = \frac{z}{2v_{avg}} = \frac{\rho C_p R^2}{k} \quad (S26)$$

In which z is the axial distance, v_{avg} is the fluid velocity at the center of the tubing, ρ is the density of the fluid inside the tubing, at 20 °C, 50% ethanol in water mixture density is $859.3 \frac{kg}{m^3}$,^{5,6}. C_p is the heat capacity and is $11.46 \frac{J}{K \cdot mol}$ for our solvent system.⁷ k is the thermal conductivity, at 66 °C, its value of 50 % ethanol in water is $0.329 \frac{W}{m \cdot K}$.⁸ R is the tubing radius 250 μm . The estimated maximum values of t is $0.0058 s \ll \tau_{min} = 15s$.

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