Supporting Information

Contents

1. General considerations

Unless otherwise stated, all chemicals were obtained from Sigma-Aldrich, Fisher Scientific, Alfa Aesar or Fluorochem Ltd., and were used without further purification. All reaction solvents were of HPLC grade. Solvents for the asymmetric hydrogenation were dried and degassed by Freeze-pump-thaw cycling. Deuterated $CDCl_3$ was used as supplied and^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX300 (300/75 MHz) spectrometer, a Bruker AV3-400 (400/100 MHz) spectrometer or a Bruker Avance 500 (500/126 MHz) spectrometer using the residual solvent as an internal standard. Chemical shifts are reported in ppm with the multiplicities of the spectra reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br), values for coupling constants (J) are assigned in Hz.

GC measurement were performed on a HP 6890 Series GC system, 7693 injector, 7693 autosampler and 5973 mass-selective detector. Two columns were employed:

- Agilent HP-5 achiral column (30 m × 0.32 mm × 0.25 µm); H_2 (3 mL/min); injection temp, 300°C; initial column temperature, 50°C; progress rate, 30°C /min; final column temperature, 280°C.
- Agilent CP-ChirasilDex CB (25 m × 0.25 mm × 0.25 µm);H_2 (3 mL/min); injection temp,290°C; initial column temperature, 90°C; progress rate, 10°C /min; final column temperature, 195°C.

The pumps used were Jasco PU980 Intelligent HPLC pumps and Knauer K-1800. Pumps were connected to the flow reactors using PTFE tubing (1 /8” or 1 /16” O.D.) and flangeless male HPLC nuts (1 /8”) with flangeless ferrules (1 /8”).

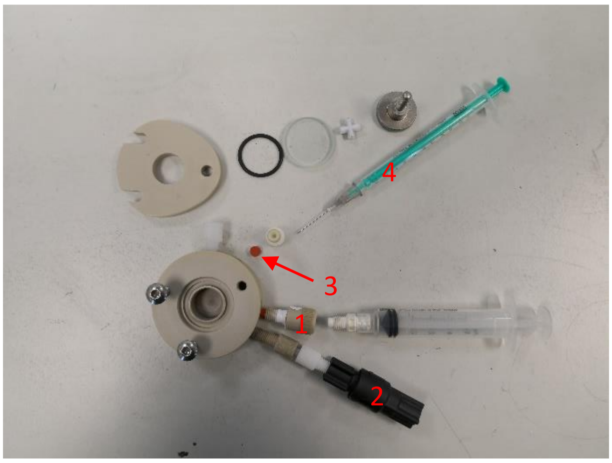
2. fReactor design and components

The fReactor material of construction is now PEEK rather than polycarbonate (Delrin) as it has resistance to a wider range of solvents and useful operating temperature of up to 140°C;[1] a more substantial steel construction unit has also been made for use of higher pressures and will be reported separately. A flat glass window replaces the watch glass, and a standard O-ring (Viton in this case) forms a better seal for operating pressurized reactions. Destructive testing has shown failure occurs in the screw fittings at 50 bar and we choose to operate up to a limit of 9 bar. The apparatus can be used with a pressure regulated gas supply or by manual injection by syringe. Each fReactor has a free volume of 1.7 mL, accounting for the volume of the cross-shaped stir bar and when configured in series for flow, an additional volume of 0.24ml per connecting pipe. fReactors with both larger, 7.5 mL, and smaller, 0.4 mL volumes have been produced, though not tested in hydrogenation. The reactors can be operated separately in batch-mode or connected in series with a short length of 1/8” PTFE tubing to give a cascade CSTR, with a multitude of smaller reactors having the advantage of a narrower residence time distribution as compared to a single larger reactor of the same combined volume. The reactor contents are efficiently mixed by a single standard magnetic stirrer on top of which sits up to five reactors located on a close-fitting aluminium plate, itself sat on a standard laboratory hotplate-stirrer, Figure S1.[2] A linear relationship has been determined between the baseplate temperature and the reactor contents, Eq. 1 (ESI 2.0).

$$\text{Reaction Fluid Temperature } {}^\circ\text{C} = (0.8 \times \text{Hotplate Temperature } {}^\circ\text{C}) + 4.4\ {}^\circ\text{C}$$

Equation S1

Standard HPLC fitments to multiple ports (1/4”-28) allow cascading of reactions, sampling or integration of in-line sensors. For the batch reactions, each fReactor was equipped with a one way check valve and a back pressure regulator (BPR). The check valve allows temporary connection of a syringe filled with a starting volume of gas. Once fully depressed, this causes a calculable and reproducible pressure rise in the reactor (details of which are given in ESI 3.1 together with access to an online calculator)[3] and is a convenient way to give high pressures when access to a gas cylinder is not available. Alternatively, hydrogen can be delivered from a regulated gas cylinder. The BPR acts as a safety relief valve, with initial pressures in the reactor selected such that after charging and heating, the maximum pressure is still lower than that required to cause the BPR to discharge pressure (ESI 3.2). The outlet of the BPR is positioned to discharge safely and experiments were carried out in a fume cupboard with a blast shield on the fReactor units. Gas leaks can be detected through either monitoring pressure prior to operation (ESI 7.0), with a fall of 0.01 bar/minute from an initial pressure of 9 bar was deemed satisfactory for reactions taking several hours. Alternatively, joints can be checked with a soap solution.



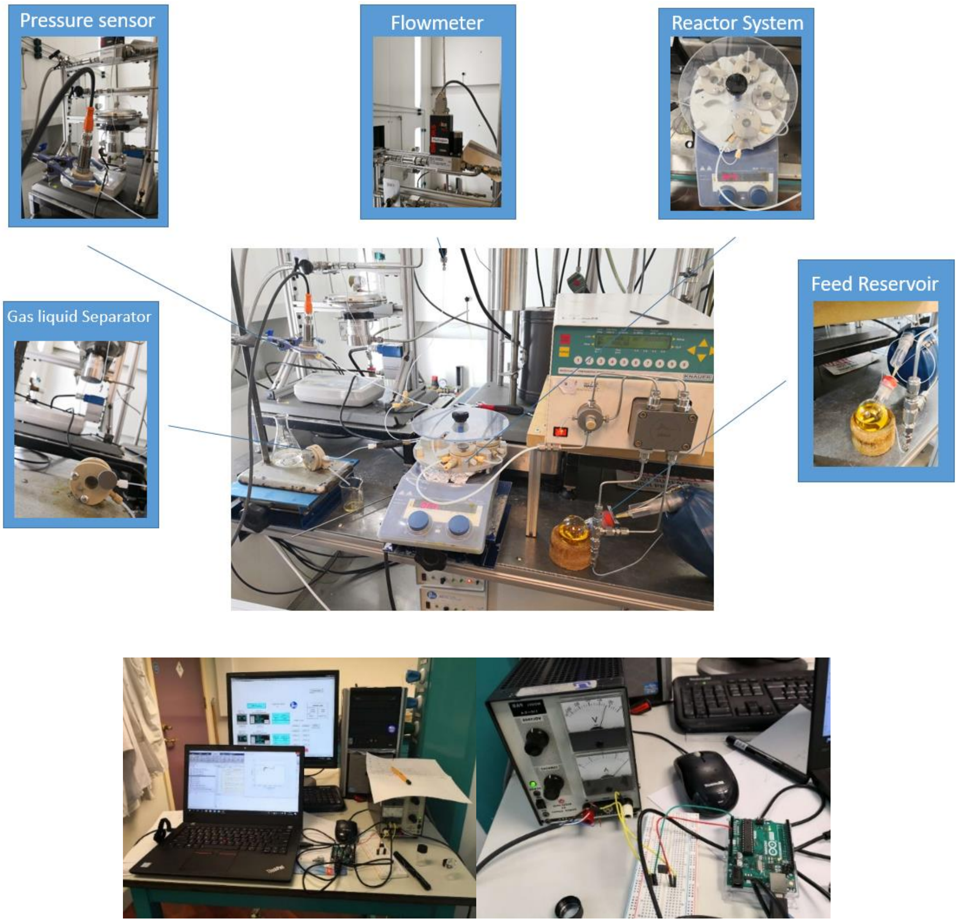


Figure S1. Pictures of components used in the continuous fReactor hydrogenation system. The computers and electronic board is used to monitor the pressure and gas flow rate.

Table S1 Components of a standard batch mode fReactor for hydrogenation

Component	Property
1. Gas inlet	Standard Inline 1/4-28 Check Valves https://www.idex-hs.com/store/fluidics/valves/flow-regulating-valves/check-valves/standard-inline-1-4-28-check-valves.html. e.g. Part CV-3301
2. Back Pressure Regulator (BPR)	Back Pressure Regulator Assemblies https://www.idex-hs.com/store/fluidics/valves/back-pressure-regulators/back-pressure-regulator-assemblies.html.
3. Septum	Low bleed red solid 5mm for high back pressure (It is added in the liquid inlet for air-sensitive reaction.).
4. Needle	27 gauge needle for adding liquid through liquid inlet septum
5. Pressure Transducer	ifm PT5404 pressure transducer
6. Arduino	https://www.arduino.cc/en/main/products
7. Power Supply	20 V power supply
8. Frit in a ferrule	https://www.idex-hs.com/store/fluidics/fluidic-connections/filters-frits/frits/frit-in-a-ferruletm.html 

Table S2 Technical Specification of continuous flow fReactor

Property	Value
Number of stages	1-5
Total assembled reactor volume	2-10 ml
Individual stage volume	2 ml (minus stir bar volume 0.3 mL)
Pressure rating – maximum advised	9 bar
Entry ports	4 x 1/4-28 flat bottomed ports per module to take standard flangeless fittings
Material: Base	PEEK
Material: Window	Toughened glass
Material: Seal	Viton
Fittings	PEEK nut and ETFE ferrule for 1/8" OD tubing; ETFE blanking nut
Tubing	PTFE 1/8 OD; 1/16 ID
Stirrer bar	PTFE cross design (0.3 mL volume)
Thermal base plate dimensions	180mm diameter. Supplied alignment pins suit hotplates 135mm or 145mm, optional pins available for square bases, or can be positioned on any flat surface without pins.
Thermal base plate	Anodized aluminium

To separate gas from liquid at the outflow, a fReactor (without a stir bar) is placed vertically,

Figure S2.

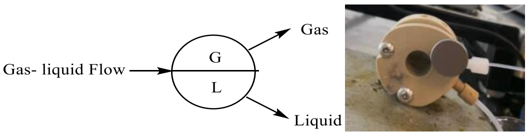


Figure S2. Gas-liquid Separator (vertical fReactor)

Table S3. Comparison of conditions used for hydrogenations using: Parr; balloon; fReactor

Property	Parr hydrogenator	Hydrogen balloon	fReactor used in batch
Reactor Volume (mL)	40-600	100	0.5-1.5
Maximum Working Pressure (bar)	70	1	9
Temperature Range (^{o}C)	-10-300	RT	-20-100
Material	Hastelloy	Glass	PEEK

3. Test of Reactors

3.1 Pressure Increasing by Hydrogen Syringe

Pressing the plunger down fully to the bottom of the syringe, the gas will be compressed into the reactor and filling the deadspace at the base of the syringe. Releasing the syringe plunger, the residual gas in the deadspace will partially expand into the filling syringe. The following equations have been used to create a modeller available at https://freactor.com/learning_PessureBatch.html

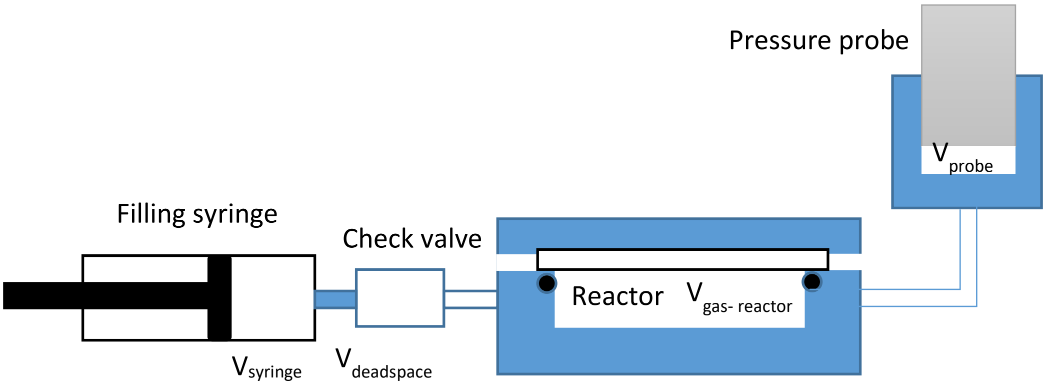


Figure S3. Schematic showing addition of gas to pressurise a reactor using a check valve

The pressure within the reactor is given by

$$P'_{reactor} = \frac{P_{syringe}V_{syringe} + P_{reactor}(V_{reactor} + V_{probe}) - P_{crack}V_{deadspace}}{V_{deadspace} + V_{reactor} + V_{probe}}$$

$P'_{reactor}$ is the final pressure within the reactor

$P_{syringe}$ is the initial pressure within the syringe

$P_{reactor}$ is the initial pressure within the reactor

P_{crack} is the cracking pressure of the check valve

$V_{syringe}$ is the initial volume of the gas within the syringe

$V_{gas\_reactor}$ is the gas volume within the reactor (ie reactor volume – liquid volume present)

V_{probe} is any additional volume e.g. in the probe adapter

$V_{deadspace}$ is the deadspace at the base of the syringe when the plunger is pushed fully down (0.23ml for a typical plastic syringe)

Example Calculation (no probe adapter present)

Charging 5ml of gas from syringe ($V_{syringe} = 5ml$) from atmospheric pressure: $P_{reactor} = 1\ bar$; $P_{syringe} = 1bar$ into a fReactor that has 0.5ml of liquid in it (ie $V_{gas\_reactor} = 1.7 - 0.5 = 1.2ml$) using a check valve with $P_{crack} = 1bar$ (e.g. component CV-3301). A typical deadspace is 0.23ml ($V_{deadspace} = 0.23ml$). Final pressure after injection is 4.17 bar.

To achieve higher pressure, you refill the syringe with gas and repeat. All figures remain as above except the starting pressure of the reactor is higher: $P_{reactor} = 4.17\ bar$. Final pressure after injection is 6.8 bar.

Heating the reactor will increase the pressure. Our experience shows it is best to ensure that the final pressure is below that of the back pressure regulator that should be fitted for safety reasons. Due to the design of spring based BPRs, on opening at the regulating pressure, the pressure will fall to below the stated value, due to the hysteresis in operation.

Heating from T1 (pressure reactor is charged at) to T2 will give a rise in pressure of

$$P'_{heated\ reactor} = P'_{reactor}\frac{T_{heated}}{T_{charged}}$$

Continuing the example, on heating the reactor from the temperature at which it was charged at 20 °C (293K) to 60 °C (333K) will give a final pressure of 7.72bar.

Note: when using a pressure probe, the additional gas within this fixture will not be heated. In this case the pressure upon heating can be calculated as:

$$P'_{heated\ reactor} = P'_{reactor}T_{heated}\left(\frac{V_{gas\_reactor} + V_{probe}}{V_{gas\_reactor}T_{charged} + V_{probe}T_{heated}}\right)$$

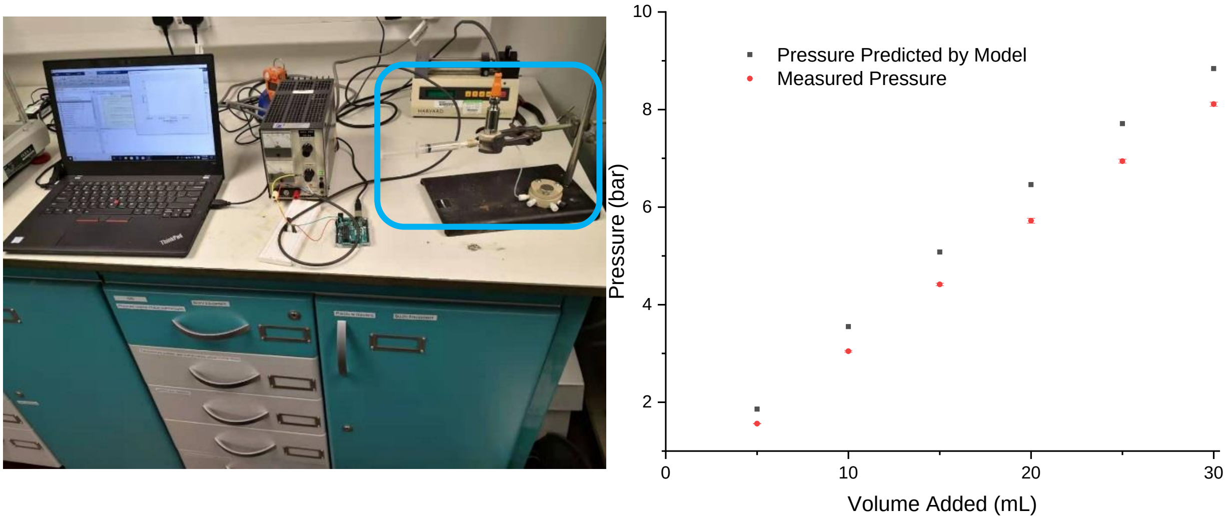


Figure S4. Left (a) Adding pressure by a 5 mL syringe pump; **Right** (b) prediction and measured value.

To evaluate the model, a syringe is charged with 5ml of gas, injected into the reactor and the pressure measured. Subseqent additions are made (ie volume added is nominal gas in syringe). Each subsequent addition increases the pressure of a fReactor system in blue frame of **Figure S4a**. The total volume is 3 mL, which includes an empty reactor (no stirring bar) and a pressure sensor holder. The syringe was filled to 5 mL and pushed to add pressure each time. Less gas than the whole 5mL is added due to the existence of dead volume in the head of syringe. **Figure S4b** shows the comparison of measured pressure and pressure predicted by model.Here the volume added is the nominal volume added (e.g. is two 5mL syringe additions, although less than 10mL will have been added due to the dead volume). The discrepency is thought to be due to the valve opening dynamics.

3.2 Residence Time Calculation

$$F_{gA} = \frac{T}{273\ K}\frac{1.01\ bar}{P}F_g \qquad (1)$$

$$F_A = F_l + F_{gA} \qquad (2)$$

$$\mathrm{t} = \frac{V}{F_A} \qquad (3)$$

F_g : Gas Flow Rate (sccm: mL/min at 273 K and atmospheric pressure)

F_l : Liquid Flow Rate (mL/min)

T: Operating Temperature (K)

P: Absolute Pressure (the pressure of back pressure regulator plus atmospheric pressure) (bar)

F_{gA} : Gas Flow Rate under Pressure (mL/min)

F_A: Total Volumetric Flow Rate (mL/min)

V: Total volume including volume of fReactor and connecting tubes (mL)

t: Residence Time (min)

Table S4. Residence time of reactions in flow

#	Liq. flow rate (mL/min)	Gas flow rate (mL/min)[5]	Total flow rate(gas+liquid)	N° of reactors	Volume of Reactors (mL)	Volume of Tubes (mL)[6]	Total Volume	T_{res} (min)
1[1]	0.2	0.68	0.88	2	3.4	0.24	3.64	4.1
2[2]	0.2	0.68	0.88	4	6.8	0.48	7.28	8.3
3[3]	0.1	0.68	0.78	4	6.8	0.48	7.28	9.3
4[4]	0.05	0.54	0.59	10	17	1.2	18.2	30

1. Residence time of Entry 24 and 25. 2. Entry 26. 3. Entry 27. 4. Entry 28, 29 and 30. 5. At 6.9 bar and 293 K. 6. Reactors are connected by PTFE tubes of 0.12 ml, 6 cm in length and 1.6 mm in inner diameter.

3.3 k_La calculations[4]

The setup was the same as that for batch mode hydrogenation. 0.5 mL or 1 mL methanol was added into the reactor. The solvent was degased by N_2 for 3 times with a stirring rate of 1200 rpm . Then the reactor was purged by H_2 for 3 times without any stirring. Then pressure was recorded by pressure sensor. The reactor was pressurized to 8 bar. Then put the reactor on the mixer with a stable stirring rate. The pressure drop was used for the calculation of k_La.

$$C_{Lsat} = \left[\frac{(P-P_E)(PM-P_E)}{(P_F-P_E)}\right].\left(\frac{V_G}{V_L}\right)\left(\frac{1}{RT}\right)t \qquad (4)$$

$$Ln\left[\frac{P_m-P_0}{(1+K)(P-P_0)-K(P_M-P_0)}\right]=k_L a\left(1+\frac{1}{K}\right)t \quad (5)$$

$$\text{with } K=\frac{P_f-P_0}{P_m-P_f}=\frac{HeV_g}{V_l RT} \quad (6)$$

$$\alpha=\frac{P_m-P_0}{(1+K)(P-P_0)-K(P_M-P_0)} \quad (7)$$

C_{Lsat} = saturation solubility of gas in the liquid phase (mol/L)

P = pressure measured in the vessel (bar)

P_m = maximum pressure after the reactor is charged with gas (bar), prior to saturation of the liquid

P_f = final pressure after gas has saturated the liquid phase (bar)

P_0 = equilibrium pressure of the liquid and vapour(bar)

V_g = volume of the gas phase (L)

V_l = volume of the liquid phase (L)

R = ideal gas constant, 0.08134 (bar·L/mole·K)

T=temperature (K)

k_La = mass transfer coefficient (s^{-1})

t = time from the onset of agitation (s)

The key assumptions of this methods are as follows: The gas follows the ideal gas law, the value of k_La is constant during the experiment and the volume of the liquid and gas phases doesn’t change during the experiment. The data presented in **Figure S5** is the pressure change of the fReactor vessel with 1 mL solvent and is then plotted according to Equation 2. The value of k_La can be calculated by identifying the gradients of the lines in **Figure S5**. The effect of gas-liquid volume ratio (r) and comparison between Parr Reactor and fReactor were also studied. The detailed calculation procedure of k_La is shown in **Figure S6**.

$$r=\frac{Volume\ of\ gas\ in\ a\ reactor}{Volume\ of\ liquid\ in\ a\ reactor} \quad (8)$$

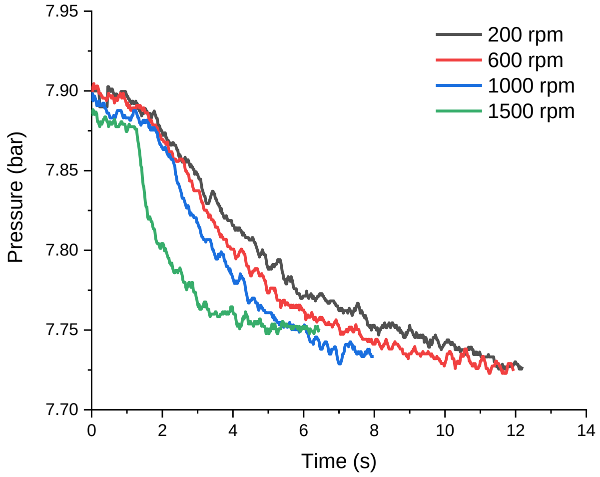
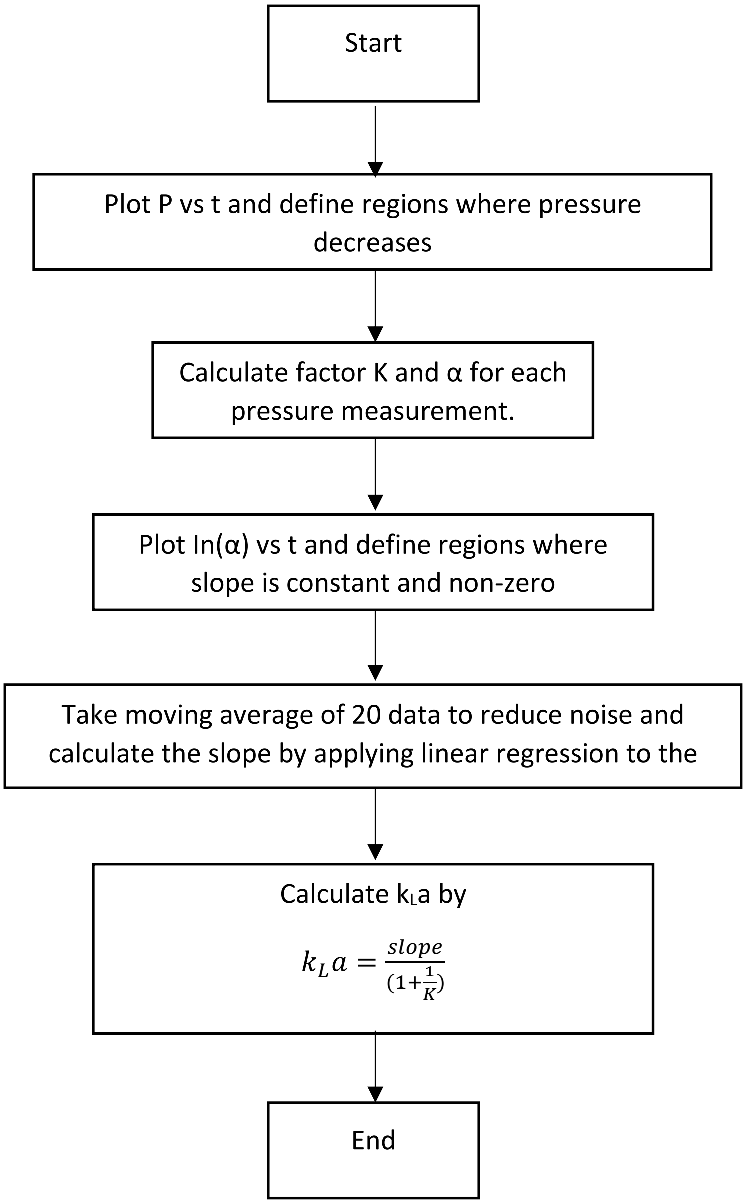


Figure S5. The pressure changing under different stirring rates with 1 mL MeOH (r = 0.7) in the reactor



Start

Plot P vs t and define regions where pressure decreases

Calculate factor K and α for each pressure measurement.

Plot In(α) vs t and define regions where slope is constant and non-zero

Take moving average of 20 data to reduce noise and calculate the slope by applying linear regression to the

Calculate k_La by

$$k_L a = \frac{slope}{(1+\frac{1}{K})}$$

End

Figure S6. Steps of Calculation of k_La

4. General procedure for batch fReactor heterogeneous hydrogenation of nitrobenzene by Pd/C.

A gas inlet check valve and 6.3 bar BPR were screwed into the fReactor. 5.3 mg of water wet (~ 50%) 10 wt. % Pd/C (2.5 μmol Pd) catalyst paste was weighed into the fReactor; the viton O-ring was seated uniformly in the groove and the reactor assembled making sure the nuts were hand-tight. The liquid medium, consisting of a nitrogen degassed solution of nitrobenzene (200 μmol) in methanol (1 mL, 0.2 M) at ambient temperature, was charged by syringe. N_2 was charged by syringe to purge the reactor three times, and released via the sealing screw. Hydrogen was charged by syringe via the check valve to 4.5 bar. Since the gas inlet check valve requires an excess pressure to let gas in, a 0.4 bar excess was used, to be certain of the desired pressure in the reactor. The reactor was placed on the mixer with a stirring frequency of 1500 rpm to start the reaction. The progress of the reaction could be monitored by taking a sample via the liquid inlet septum by a syringe. At the end of the reaction the pressure was released by the sealed screw,and the reactor disassembled. The conversion was analyzed by NMR or GC.

4.1 GC analysis of nitrobenzene and aniline

Conversion was monitored direct injection of reaction samples. The nitrobenzene calibration curve is shown below

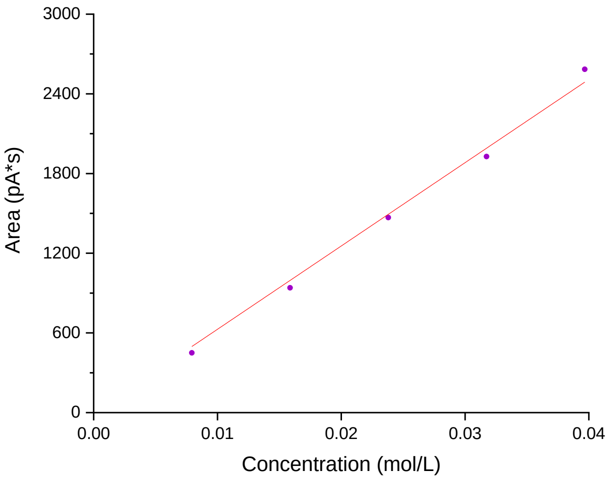


Figure S7. Nitrobenzene calibration curve

$$\text{Area (pA*s)} = 62724*\text{Concentration (mmol/mL)};\ R^2 = 0.998$$

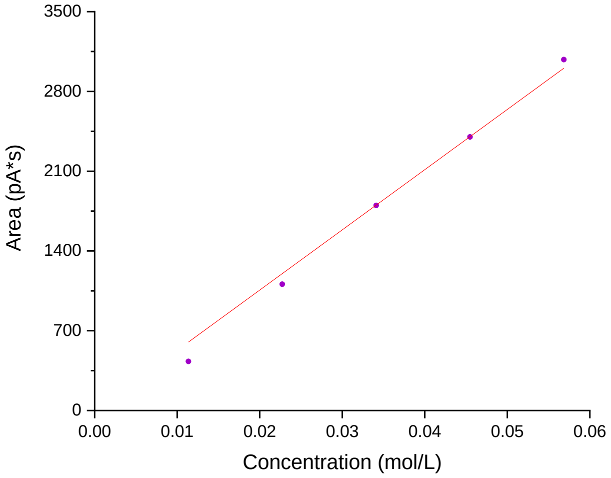


Figure S8. Aniline calibration curve

Area (pA*s) = 52839*Concentration (mmol/mL); R^2 = 0.998

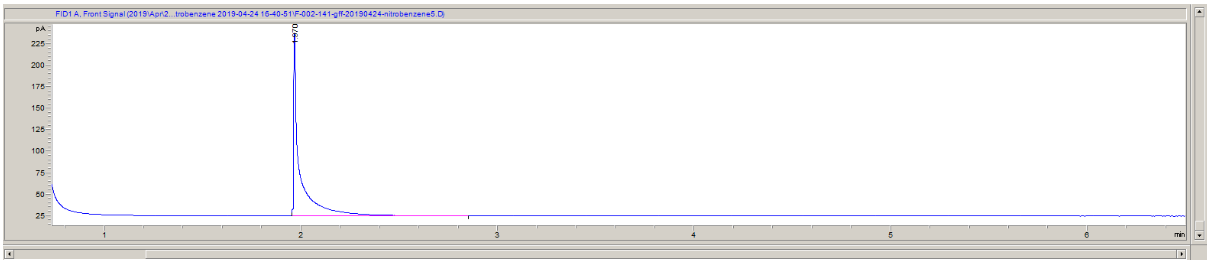


Figure S9. GC trace of nitrobenzene

```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
  1   1.970 BB    0.0271  449.82852  212.42920 1.000e2
```

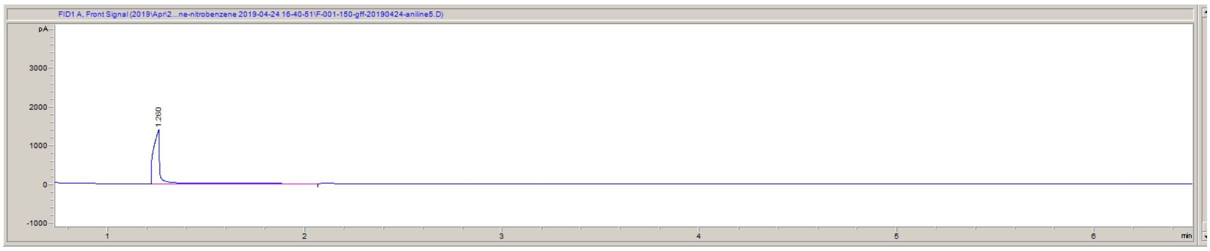


Figure S10. GC trace of aniline

```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
  1   1.260 BB    0.0386 3079.35083 1350.05786 1.000e2
```

4.2 Optimisation of batch nitrobenzene hydrogenation conditions.

The conditions required to operate continuous flow were identified using the fReactor in batch-mode. Five individual reactors were set-up with different conditions defined using design of experiment methodology (DoE); the stirrer speed was kept constant at 1500 rpm and the temperature at 293 K. The data was processed by Modde to generate an optimization model. Variable limits for entries 1-11 were defined as: pressure 1 to 4.5 bar; reaction time 10 to 30 minutes; substrate to catalyst ratio (S/C) from 200 to 2000. The results are shown in **Table S5**.

Table S5 Screening of Reaction Conditions.

#	Pressure (bar)	Reaction time (min)	S/C	Phenylhydroxyamine (%)	Yield[1] (%)
1	1	10	200	<1	22
2	4.5	10	200	<1	>99
3	1	30	200	2	25
4	4.5	30	200	<1	>99
5	1	10	2000	<1	1
6	4.5	10	2000	2	14
7	1	30	2000	<1	3
8	4.5	30	2000	1	27
9	2.75	20	1100	1	35
10	2.75	20	1100	<1	34
11	2.75	20	1100	1	31
12	6.3	2	400	2	41
13	6.3	10	400	1	99
14	6.3	2	800	3	18
15	6.3	10	800	2	70
16	6.3	2	600	4	19
17	6.3	10	600	1	97
18	6.3	6	400	1	75
19	6.3	6	800	4	36
20	6.3	6	600	3	49
21	6.3	2	400	2	41
23	6.3	10	400	1	99

1. Yield is defined as the mole percentage of aniline formeddetermined by ^{1}H NMR. Phenylhydroxyamine was the only intermediate observed.

The results of the experimental design are presented in the **Figure S11**.

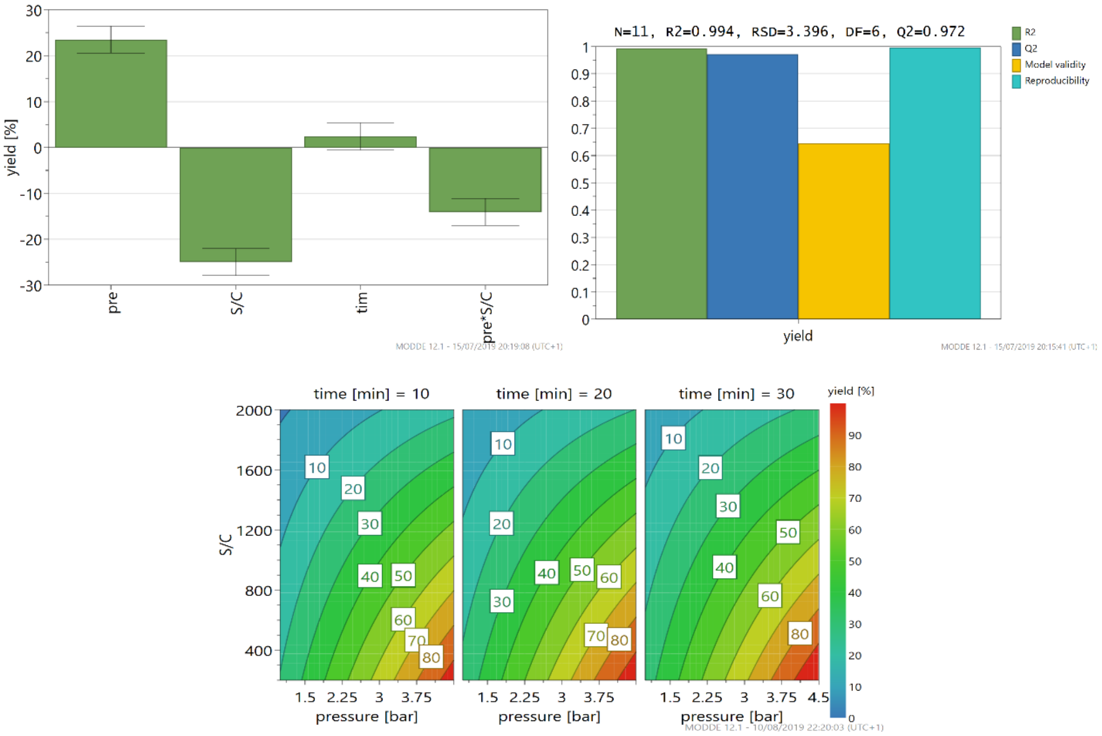


Figure S11. Results of Screening by DoE

From the coefficient plots, the variables of pressure, substrate to catalyst (S/C) loading, and the interaction between pressure and S/C were all significant terms in the model. However, the reaction time was identified as an insignificant model term, which meant that conversion didn't increase significantly as the reaction time was prolonged from 10-30 minutes. As DoE builds an empirical model, it can give a prediction of how the reaction is likely to progress. This can be used to build predicted kinetic profiles of the reaction constituents. When S/C was 2000 at 4.5 bar (**Figure S12** left), the reaction rate was so low that the yield increased only slightly during this time period. When the S/C was 200 at 4.5 bar (**Figure S12** right), the conversions were all above 90% from 10 to 30 minutes. To obtain the optimal zero order condition, the reaction was screened in a narrower area (**Table S5** Entry 12 to 23). The time period was reduced to 2-10 minutes and catalyst loading from 400-800 to reach the target conversion. Since a 6.9 bar back pressure regulator was used for both the batch and flow reactions, the actual pressure used for the optimization was 6.3 bar.

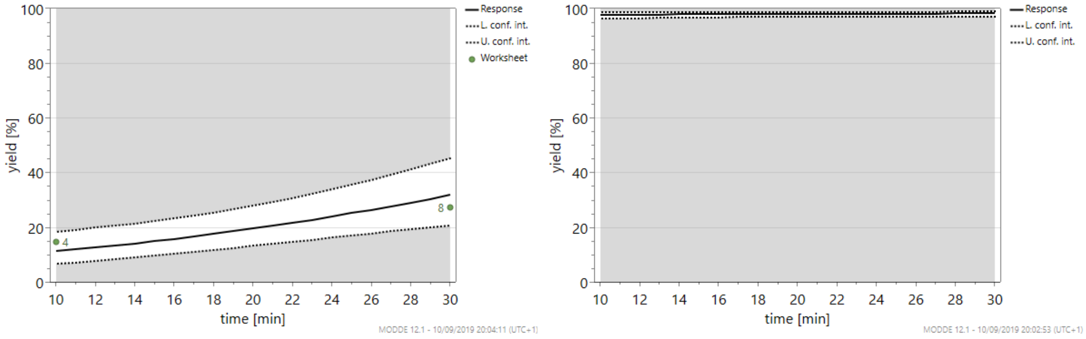


Figure S12. Predicted kinetic profiles of the reaction constituents of S/C = 2000 (left) and S/C = 200 (right) in 4.5 bar.

The coefficient plot, summary of fit and response surface plot from optimizing 11 reactions is presented in **Figure S13**. It shows that reaction time and catalyst loading are both significant factors. According to the model, the yield increased proportionally with the catalyst loading and time. **Figure S9** (lower right) is the predicted kinetic profiles, when S/C was 600. The yield increased linearly from 23% to 87%, as the reaction time increased from 2 minutes to 10 minutes. The R^2 value is 0.95 and theQ^2 value is 0.92 with model viability is 0.64 and reproducibility of 0.95. Thus, the model is reliable for prediction. It is predicted that when the catalyst loading was 400 and reaction time was 9.2 min, the yield could achieve 95% under 6.3 bar. This condition was chosen for transferring reaction to flow mode.

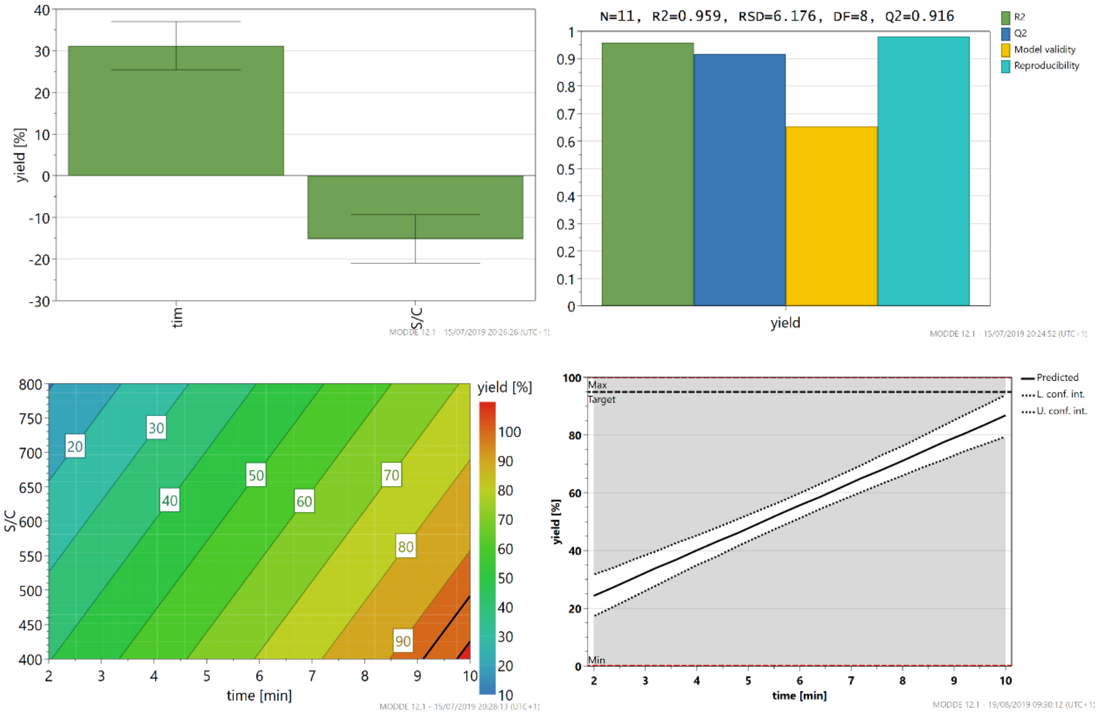


Figure S13. Results of Optimization by DoE

4.3 Procedure for Continuous Hydrogenation of Nitrobenzene by Pd/C

The reactor system was assembled and a sealing test was conducted by pressurizing the reactor. A frit-in-a-ferrule was added to each end of connecting tubes instead of normal ferrule. When the S/C = 400, nitrobenzene (6.15g, 0.05 mol) was dissolved in methanol to prepare 100 mL of a 0.5 M solution. The concentration was lowered when the S/C was 80 or 200. Then 1.4 mg catalyst (0.66 μmol) and 0.5 mL reaction medium were added to each reactor. The reactor system was pressurized to 6.5 bar, with a 6.9 bar BPR and released three times to degas the medium and purging the reactor. Hydrogen and liquid were pumped at the same time. The stirring rate was 1500 rpm. Samples were collected every

15 minutes by a vial and analyzed by GC or ^{1}H NMR. The reaction medium was collected and aniline was isolated after column chromatography, allowing calculation of the production rate and catalyst turnover. Pressure data was collected by on line pressure sensor.

Table S6 Hydrogenation of Nitrobenzene in continuous mode fReactor

#	S/C	Liq. flow rate (mL/min)	No of reactors	T_{res} (min)	Conversion[1] (%)	Predicted Conversion[2] (%)	Percentage Error[3](%)
24	80	0.2	2	4.1	88	82	6.8
25	400	0.2	2	4.1	70	58	17
26	400	0.2	4	8.3	88	92	4.5
27	200	0.1	4	9.3	95	>99	4.2

1. Average yield of steady state yield. 2. Yield predicted by DoE model. 3. Percentage error is calculated by deviding discrepency betweem experimental yield and predicted yield by experimental yield

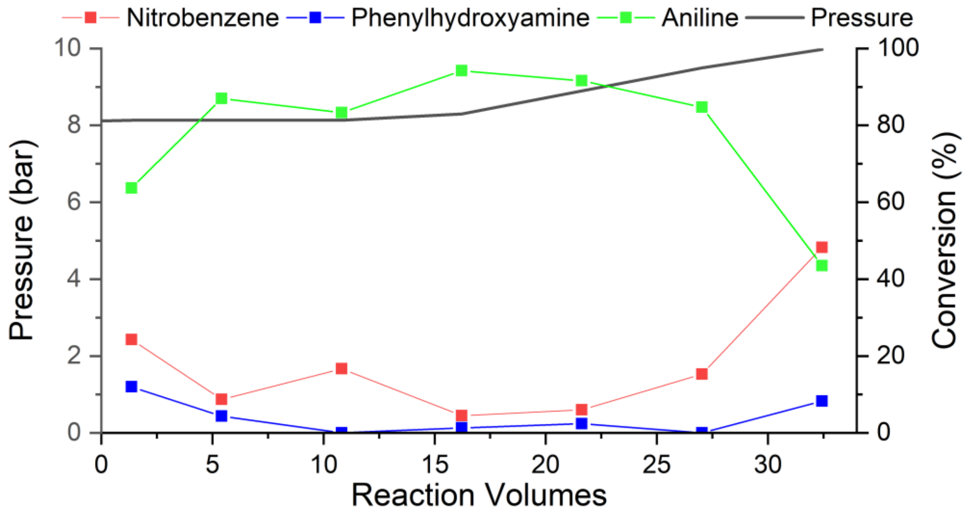


Figure S14. Continuous hydrogenation of nitrobenzene Entry 24

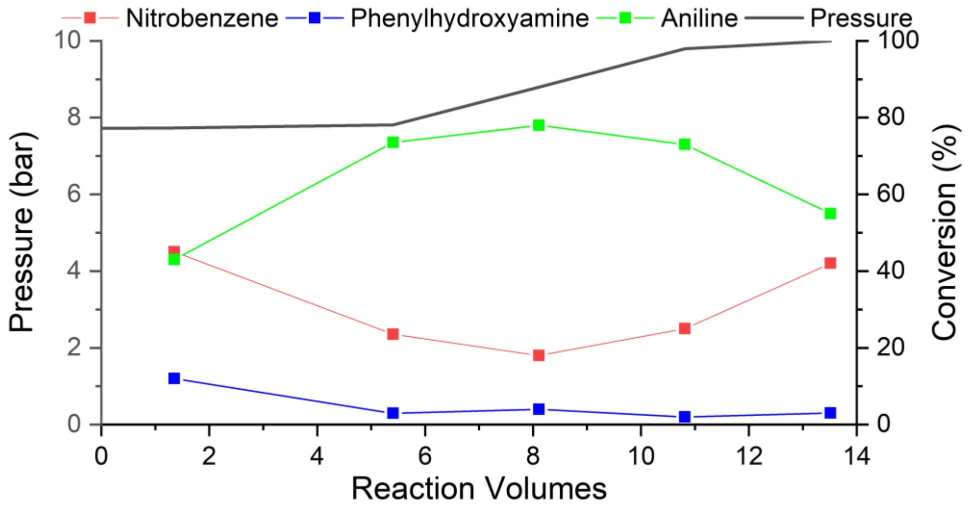


Figure S15. Continuous Hydrogenation of Nitrobenzene Entry 25

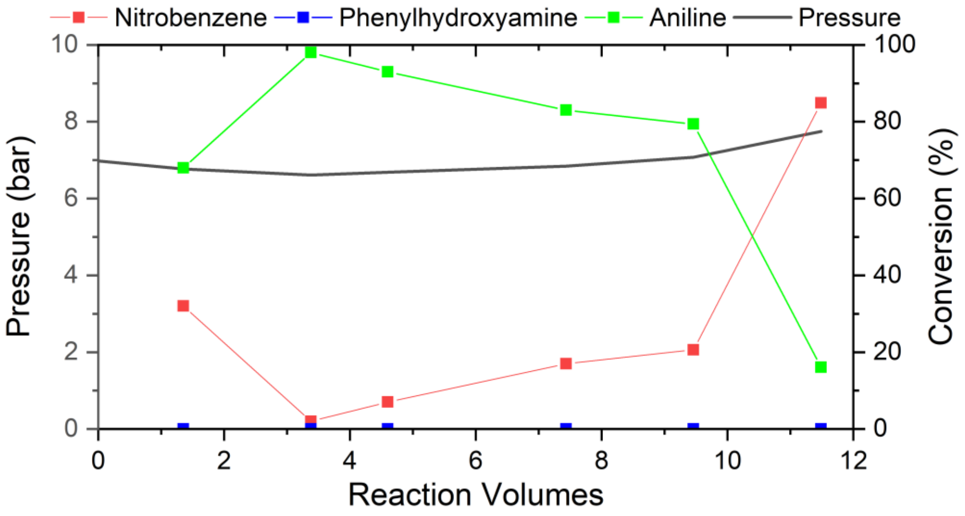


Figure S16. Continuous Hydrogenation of Nitrobenzene Entry 26

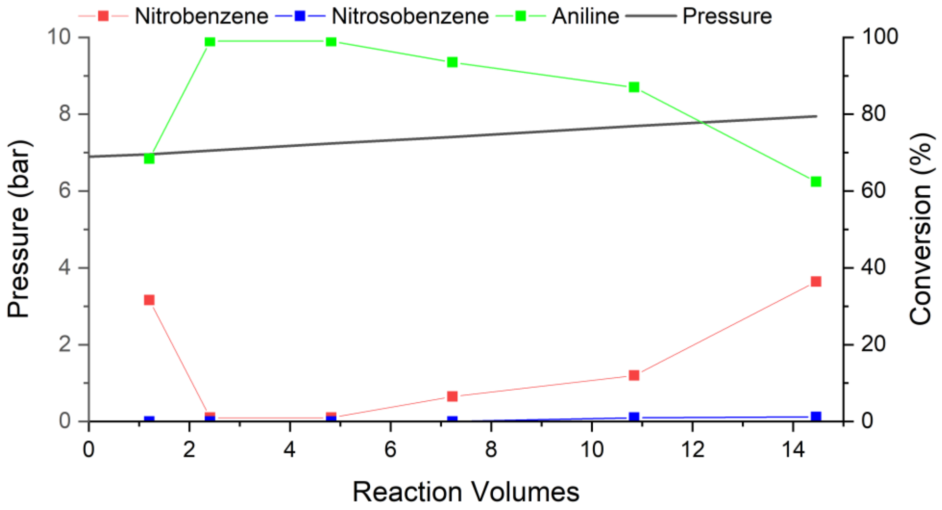


Figure S17. Continuous Hydrogenation of Nitrobenzene of Entry 27

5. General procedure for batch-mode heterogeneous hydrogenolysis of (*S*)-3-benzyl-1-palmitoyl-glycerol.

(*S*)-3-benzyl-1-palmitoyl-glycerol (200 mg) was dissolved in 0.5 mL dichloromethane and charged by syringe to a batch fReactor containing a degassed slurry of wet 10% Pd/C (5 mg) in 0.5 mL dichloromethane. The fReactor was pressurised to 9 bar at ambient temperature three times to ensure a completely hydrogen atmosphere (see previous description of how to do this), and mixed at 1500 rpm for 1 hour. After releasing the pressure, separating the Pd/C over a small plug of silica, evaporating the dichloromethane eluent and redissolving the solid product in $CDCl_3$, ^{1}HNMR analysis showed >90% loss of the benzyl group.

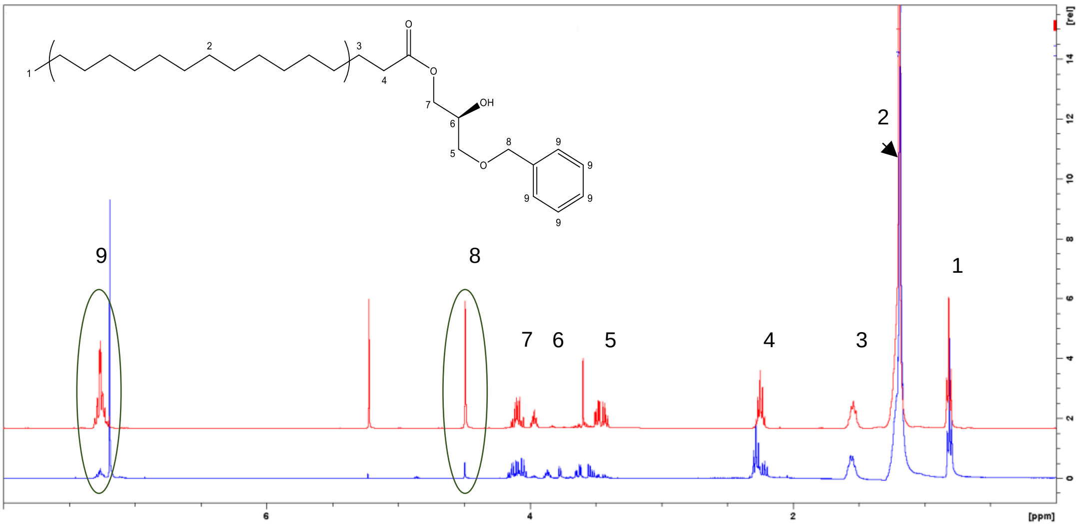


Figure S18. ^{1}HNMR showing the starting material (red) and product after hydrogenolysis, (blue) with greatly reduced benzylic protons (ringed signals).

6. General procedure for batch-mode homogenous hydrogenation of (*E*) and (*Z*)-methyl-3-acetamido-2-butenoate.

6.1 Synthesis of (*E*) and (*Z*)-methyl-3-acetamido-2-butenoate.

A 250 mL round-bottomed flask was charged with methyl 3-aminocrotonate (5 g, 0.043 mol) and 43 mL THF. Acetic anhydride (22.3mL, 0.24 mol) and pyridine (5.7 mL, 0.0714 mol) were added. The reaction mixture was stirred under reflux at 75 °C for 15 h. The reaction was quenched with 100 mL saturated K_2CO_3 solution and extracted with ethyl acetate for three times. The combined organic phases were washed with 100 mL K_2CO_3, thrice with 50 mL K_2HPO_4, then 50mL brine, dried over Na_2SO_4 and concentrated *in-vacuo*. The crude materials were purified by biotage column (60 mL 10-90% ethyl acetate in petroleum ether, then 120 mL 20-80% ethyl acetate and 240 mL 60-40% ethyl acetate) to afford methyl-(*E*)-3-acetamido-2-butenoate (yellow solid) 6.7% yield, and methyl-(*Z*)-3-acetamido-2-butenoate (white solid) 37% yield.

(*Z*)^{1}H NMR (500 MHz, $CDCl_3$) δ 11.10 (s, 1H), 4.91 (d, J = 1.1 Hz, 1H), 3.70 (s, 3H), 2.38 (d, J = 1.1 Hz, 3H), 2.15 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 169.59 (s), 169.00 (s), 155.27 (s), 95.99 (s), 77.29 (s), 76.78 (s), 51.05 (s), 25.28 (s), 21.94 (s). Same as literature.[2]

(*E*)^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, J = 0.6 Hz, 1H), 6.71 (s, 1H), 3.68 (s, 3H), 2.36 (d, J = 0.8 Hz, 3H), 2.12 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 168.69 (s), 148.52 (s), 102.32 (s), 50.94 (s), 25.13 (s), 18.72 (s). Same as literature.[2]

6.2 Synthesis of racemic methyl 3-acetamidobutanoate

A Parr hydrogenator was used for the reaction. All manifold valves, cylinder regulator and isolation valves were checked. The process controller and computer were turned on and the temperature and pressure alarms were tested. The reaction medium consisting of methyl-3-acetamido-2-butenoate (1 g, 6.4 mmol) in methanol (40 mL) were added into vessel along with 10% Pd/C (50% water content) (640 mg) and purged, by filling under pressure and emptying, with nitrogen 5 times then hydrogen 5 times. The agitator was set at 1000 rpm and temperature at 25 °C. The bypass hydrogen valve was closed and pressure was set to 4 bar. The reaction was monitored by hydrogen uptake for 8 hours, the agitator stopped and the reactor depressurized and purged with nitrogen 5 times. The reaction medium was collected catalyst separated over a plug of silica, washed with methanol and the solvent removed *in vacuo* to give racemic methyl 3-acetamidobutanoate (white solid) in 96% yield. The product was analysed by chiral GC and NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (s, 1H), 4.41 – 4.28 (m, 1H), 3.70 (s, 3H), 2.62 – 2.46 (m, 2H), 1.96 (s, 3H), 1.22 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.26 (s), 169.28 (s), 51.67 (s), 41.92 (s), 39.68 (s), 23.49 (s), 19.98 (s). Same as the literature.[5]

6.3 GC analysis of (*E*) and (*Z*)-methyl-3-acetamido-2-butenoate and racemic methyl 3-acetamidobutanoate.

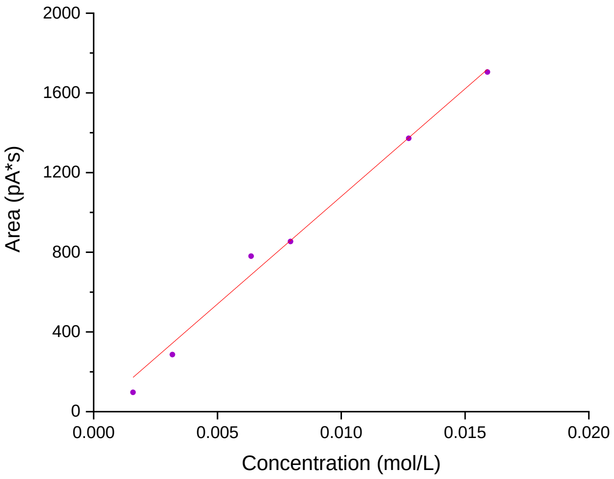


Figure S19. (*Z*)-methyl-3-acetamido-2-butenoate calibration curve

Area (pA*s) = 108027*Concentration (mmol/mL); $R^2 = 0.990$

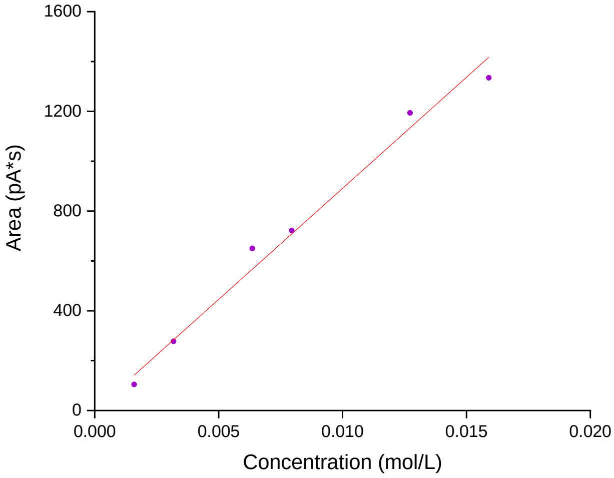


Figure S20. (*E*)-methyl-3-acetamido-2-butenoate calibration curve

Area (pA*s) = 89104*Concentration (mmol/mL); R^2 = 0.995

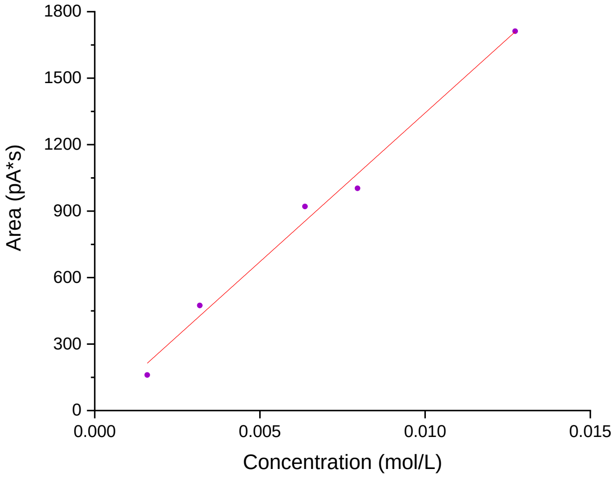
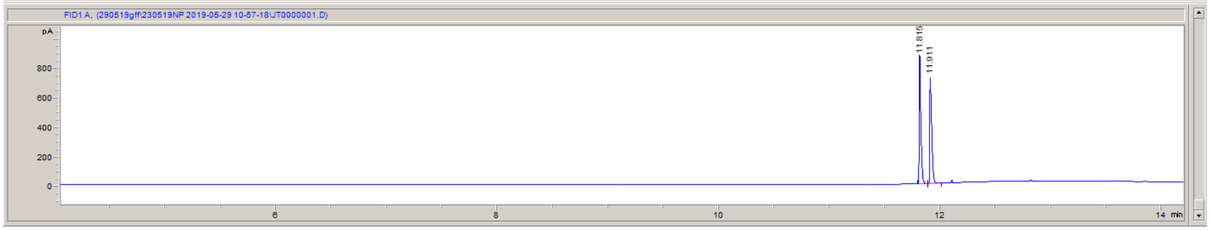


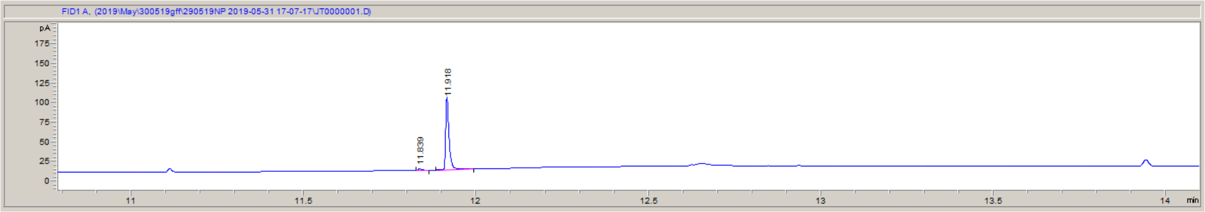
Figure S21. racemic methyl 3-acetamidobutanoate calibration curve

Area (pA*s) = 134312*Concentration (mmol/mL); R^2 = 0.997



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  11.815 BB    0.0152  898.97290  874.37762 49.94991
   2  11.911 BB    0.0186  900.77576  718.89716 50.05009
```

Figure S22. Racemic methyl 3-acetamidobutanoate

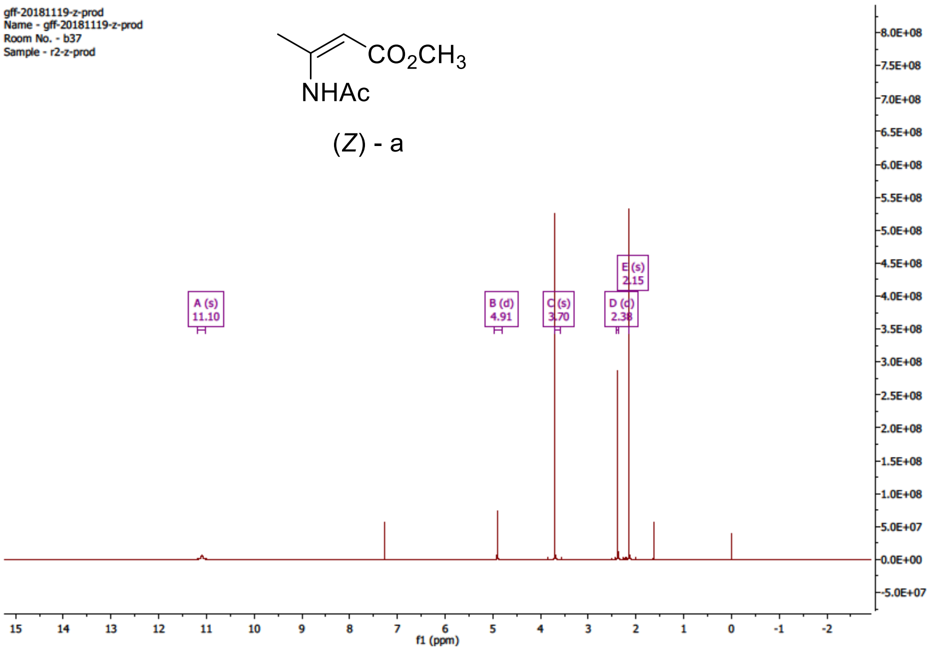


```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  11.839 BB    0.0126    1.43343    1.77222  2.22764
   2  11.918 BB    0.0107   62.91411   88.16644 97.77236
```

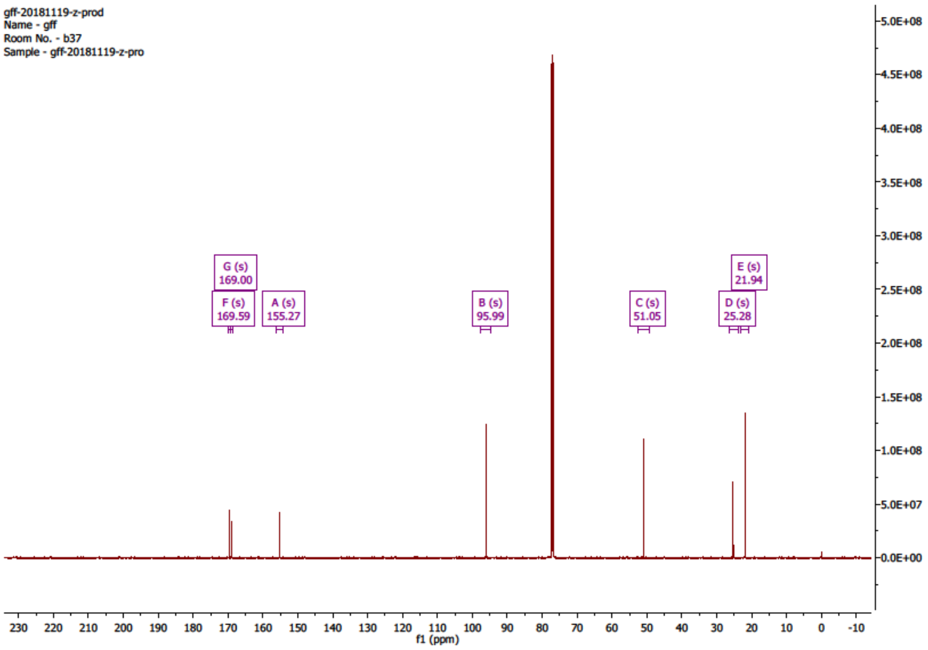
Figure S23. (*S*)-methyl 3-acetamidobutanoate by hydrogenation of (*E*)- methyl 3-acetamidobutanoate

6.4 NMR analysis of (*E*) and (*Z*)-methyl-3-acetamido-2-butenoate, racemic methyl 3-acetamidobutanoate

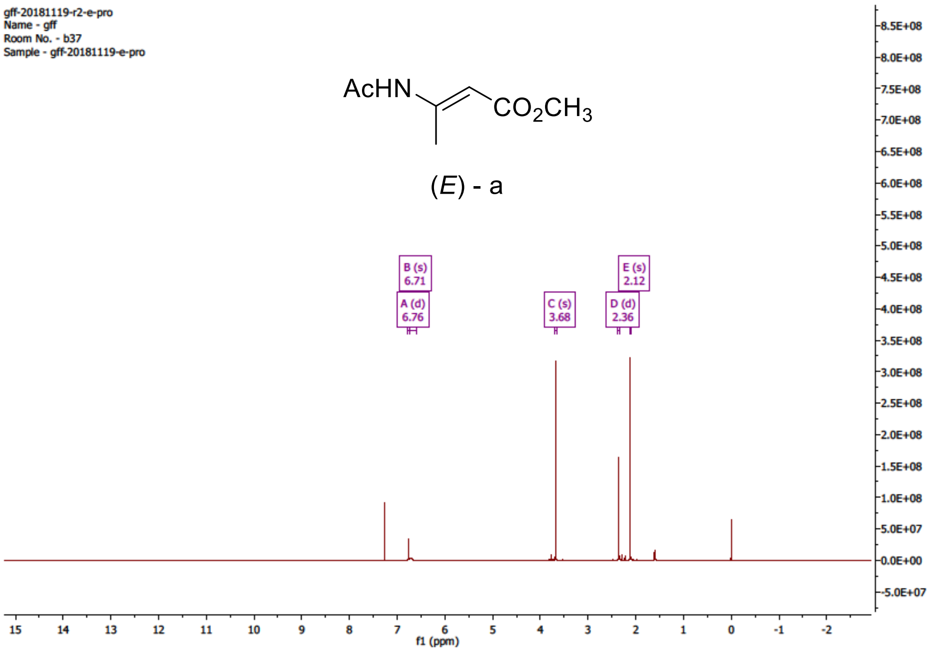
(*Z*)-methyl 3-acetamidobutanoate (^{1}H-NMR):



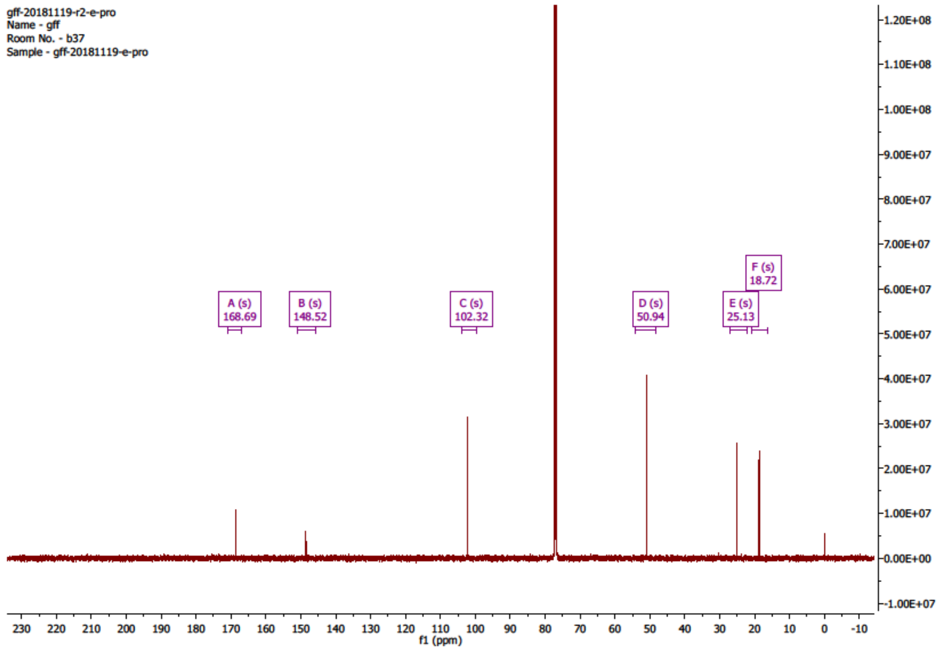
(*Z*)-methyl 3-acetamidobutanoate (^{13}C-NMR):



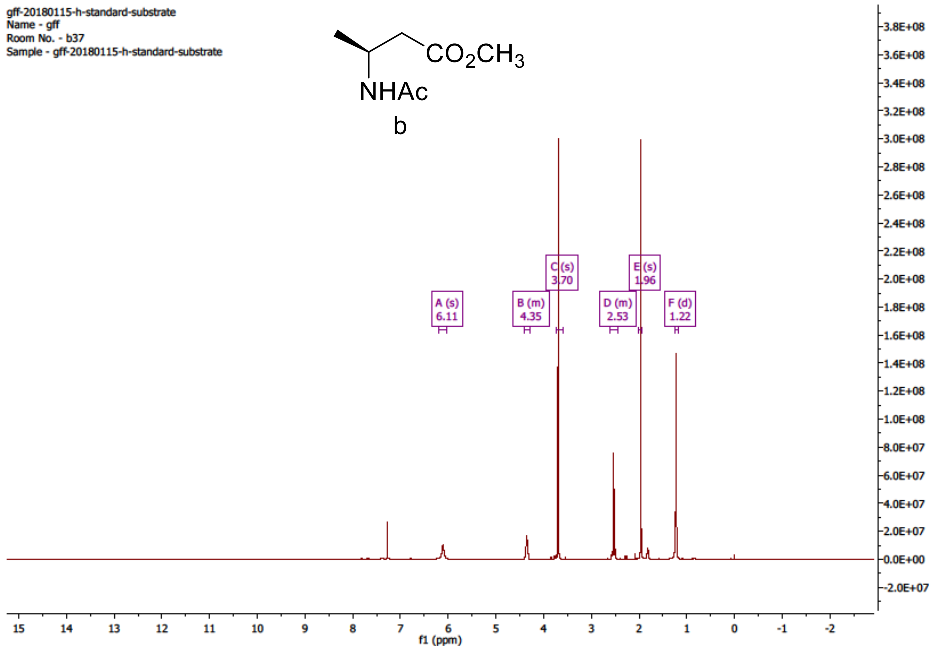
(*E*)-methyl 3-acetamidobutanoate (^{1}H-NMR):



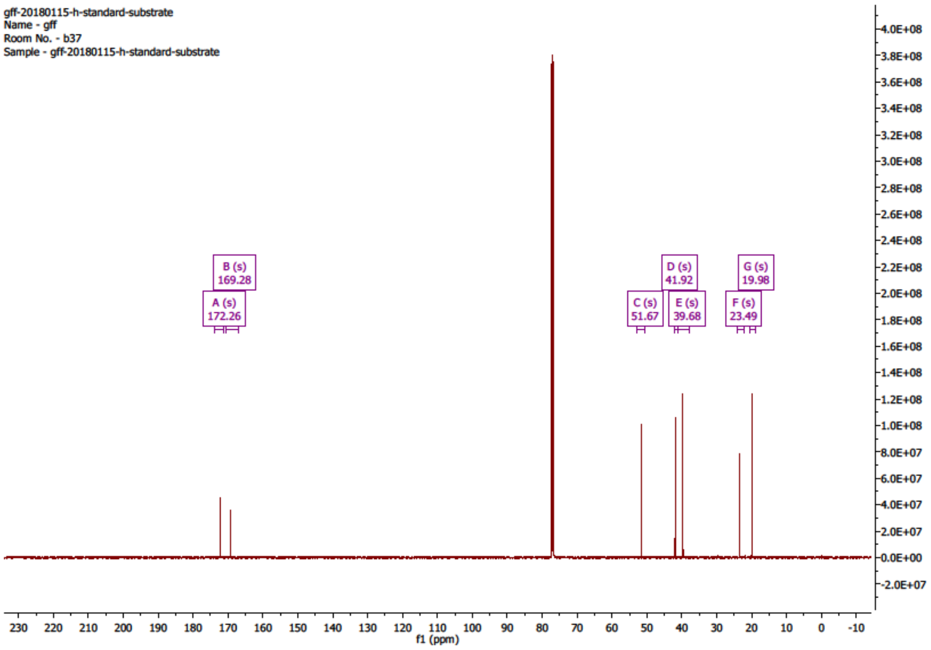
(*E*)-methyl 3-acetamidobutanoate (^{13}C-NMR):



(*S*)-methyl 3-acetamidobutanoate (^{1}H-NMR):



(*S*)-methyl 3-acetamidobutanoate (^{13}C-NMR):



6.5 Procedure for batch mode and continuous mode fReactor (air-sensitive) asymmetric homogeneous hydrogenation

Batch Mode Asymmetric Hydrogenation:

The reaction medium was prepared and reactor was assembled in a glovebox. The solvent was degassed using the freeze-pump-thaw method. (+)-1,2-Bis[(*2R,5R*)-2,5-diethylphospholano]benzene (1.5 mg, 0.0041 mmol), and Bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate catalyst precursor (1.6 mg, 0.004 mmol） were dissolved in 1 mL dry DCM. The mixture was stirred for 30 minutes, then, the substrate (62.8 mg, 0.4 mmol) was added into 1 mL catalyst medium with S/C of 100. 0.5 mL reaction medium was charged to the reactor. The reactor was sealed and then taken out of the glove box. It was pressurized to the desired level with hydrogen supplied from a syringe or a cylinder. The stirring rate was 1500 rpm. Samples were taken from the septum port to monitor reaction. When reaction was finished, gas was released form one port slowly and a sample was collected by pipette from reactor. The metal catalyst was removed by filtering over a silica pad, and after removing the solvent the conversion and ee were analyzed by NMR and GC.

Flow Mode Asymmetric Hydrogenation:

(+)-1,2-Bis[(*2R,5R*)-2,5-diethylphospholano]benzene (58 mg, 0.164 mmol), and Bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate catalyst precursor (64 mg，0.16 mmol） were dissolved in 40 mL dry and degassed DCM. The medium was mixed for 30 minutes, then, the substrate (1256 mg, 8 mmol) was added into 1 mL catalyst medium with S/C of 50. The fReactor flow system was assembled and a sealing test conducted. The reactor was purged by pressurising with N_2 5 times. The empty reactor system was then pressurized to 6.5 bar (6.9 bar BPR) with H_2 supplied from a regulated cylinder and mass flow controller, and the liquid was pumped simultaneously. The stirring rate was 1500 rpm. Samples were collected every 15 minutes in an empty vial. The metal catalyst was removed by filtering over a silica pad, and after removing the solvent the conversion and ee were analyzed by NMR and GC. When reaction finished, system was depressurized by disassembling the BPR slowly, and washed by pumping DCM.

Table S6 Asymmetric Hydrogenation in continuous mode fReactor

#	Substrate	S/C	Liquid flow rate (mL/min)	Residence time (min)	Yield in steady state[1] (%)	ee. (%)
28	(*Z*)-a	50	0.05	27	80	80
29	(*E*)-a	50	0.05	27	93	98
30	(*Z*)-a	100	0.05	27	56	71

1. Average yield of steady state yield.

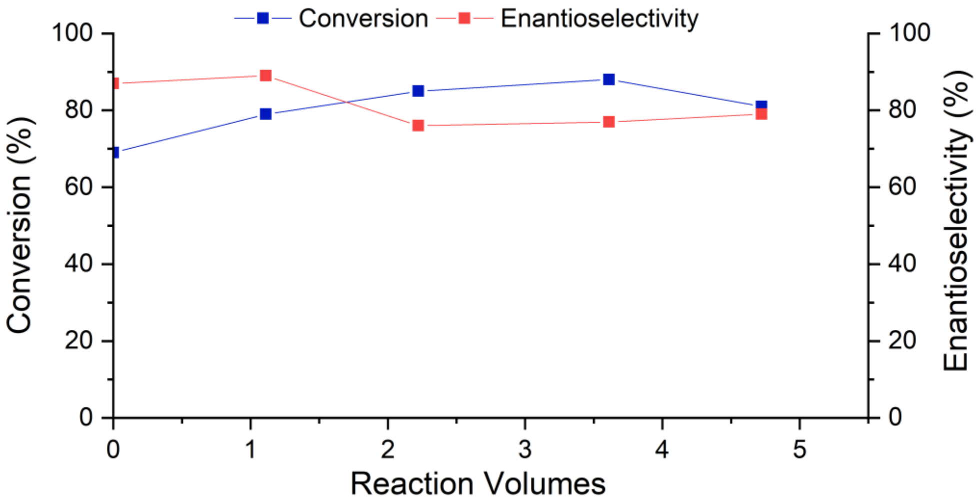


Figure S24. Continuous Asymmetric Hydrogenation of Entry 28 ((*Z*)-a)

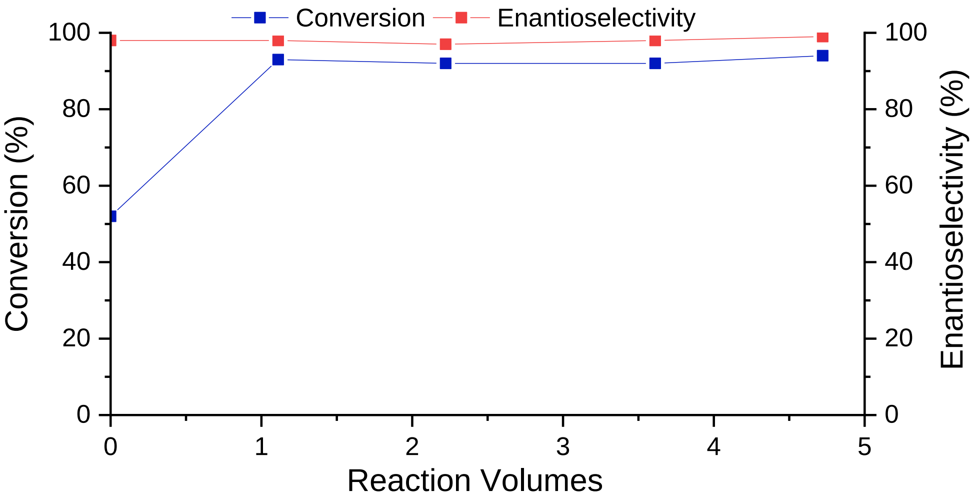


Figure S25. Continuous Asymmetric Hydrogenation of Entry 29 ((*E*)-a)

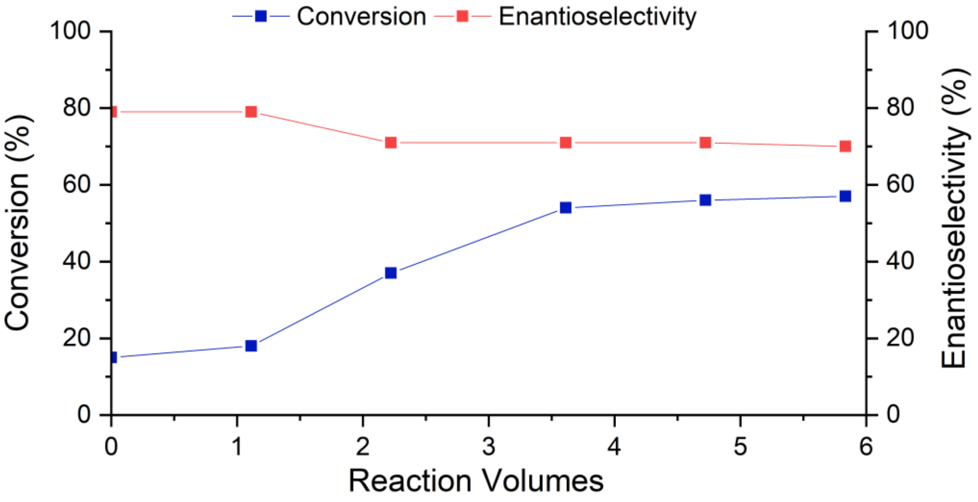


Figure S26. Continuous Asymmetric Hydrogenation of Entry 30 ((*Z*)-a)

7. Avoidance of leaking:

Leaks can be identified using a pressure sensor attached to the fReactor (see ESI 1.0), or after pressurising the fReactor, with a bubble solution (snoop). PTFE pipe tape is recommended to improve sealing performance if leaks are found at screw fittings. It It is critical to sit the Viton O-ring correctly in the groove to achieves a gas-tight condition. Make sure it is clean and seated uniformly; checked by gently pressing the glass window against the O-ring. If it is observed that the O-ring is deformed uniformly, this means it can hold pressure. If there is part that is not pressed by the window, the O-ring has to be cleaned and placed properly. The Viton O-ring can swell considerably in contact with THF, slightly with MeOH, and not in contact with DCM. If it does swell, it is recommended to change it for a new one. Other materials are available that offer different resistance to solvents. Old seals can recover to normal state after the solvent evaporates. When assembling the fReactor, it is important to tighten the screws in turn to keep the gap between the top and base plate even, i.e. even pressure applied.

8. The MatLabCode for Pressure Sensor

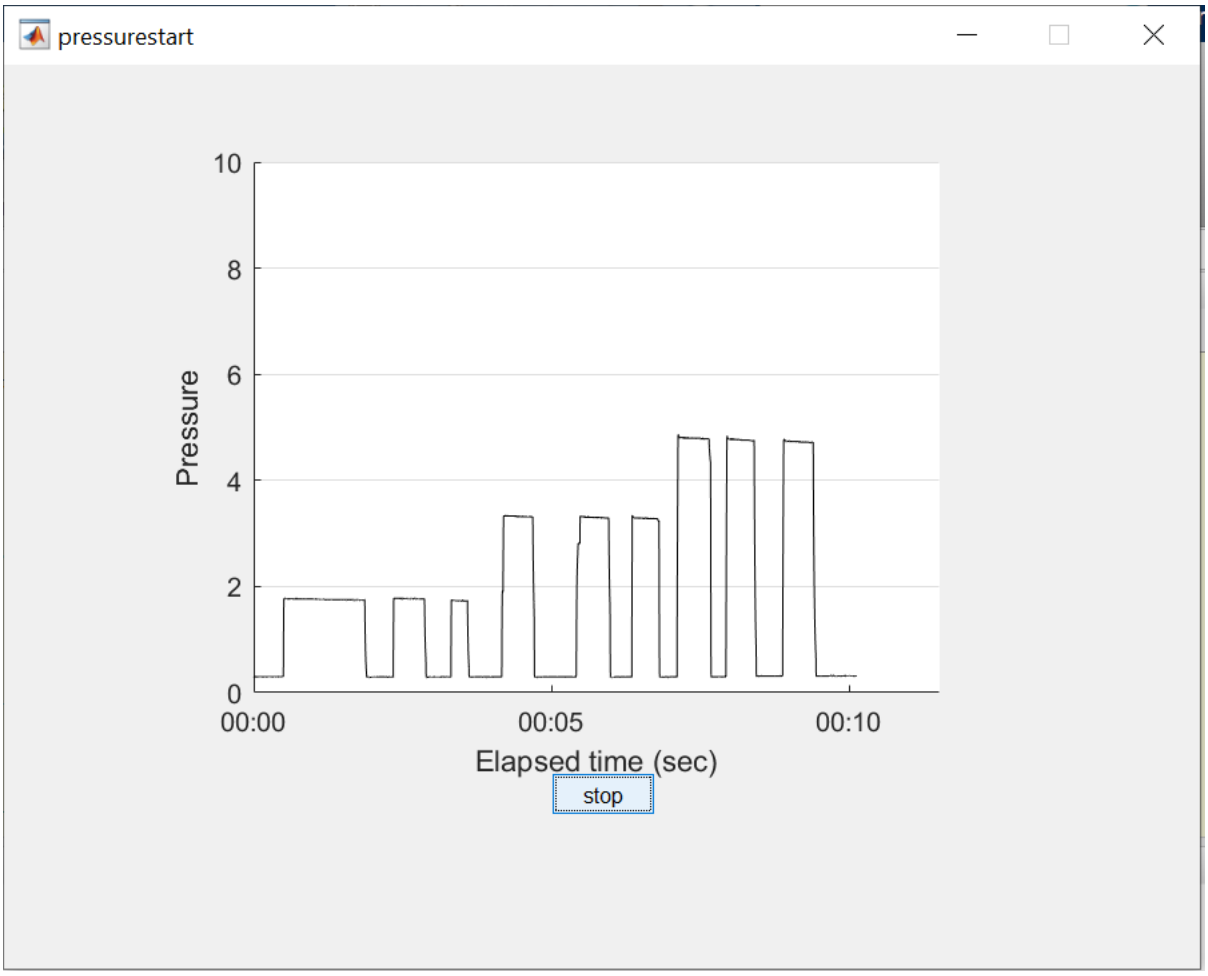


Figure S27. Matlab interface of Pressure Measurement

Figure S28. pressure sensor and pressure sensor holder

```
function varargout = pressurestart(varargin)
% PRESSURESTART MATLAB code for pressurestart.fig
%      PRESSURESTART, by itself, creates a new PRESSURESTART or raises the existing
%      singleton*.
%
%      H = PRESSURESTART returns the handle to a new PRESSURESTART or the handle to
%      the existing singleton*.
%
%      PRESSURESTART('CALLBACK',hObject,eventData,handles,...) calls the local
%      function named CALLBACK in PRESSURESTART.M with the given input arguments.
%
%      PRESSURESTART('Property','Value',...) creates a new PRESSURESTART or raises the
%      existing singleton*.  Starting from the left, property value pairs are
%      applied to the GUI before pressurestart_OpeningFcn gets called.  An
%      unrecognized property name or invalid value makes property application
%      stop.  All inputs are passed to pressurestart_OpeningFcn via varargin.
%
%     *See GUI Options on GUIDE's Tools menu.  Choose "GUI allows only one
%      instance to run (singleton)".
% See also: GUIDE, GUIDATA, GUIHANDLES

% Edit the above text to modify the response to help pressurestart

% Last Modified by GUIDE v2.5 29-May-2019 23:11:23

% Begin initialization code - DO NOT EDIT
gui_Singleton = 1;
gui_State = struct('gui_Name',       mfilename, ...
                   'gui_Singleton',  gui_Singleton, ...
                   'gui_OpeningFcn', @pressurestart_OpeningFcn, ...
                   'gui_OutputFcn',  @pressurestart_OutputFcn, ...
                   'gui_LayoutFcn',  [] , ...
                   'gui_Callback',   []);
if nargin && ischar(varargin{1})
```

```
    gui_State.gui_Callback = str2func(varargin{1});
end

if nargout
    [varargout{1:nargout}] = gui_mainfcn(gui_State, varargin{:});
else
    gui_mainfcn(gui_State, varargin{:});
end
% End initialization code - DO NOT EDIT

% --- Executes just before pressurestart is made visible.
function pressurestart_OpeningFcn(hObject, eventdata, handles, varargin)
% This function has no output args, see OutputFcn.
% hObject    handle to figure
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)
% varargin   command line arguments to pressurestart (see VARARGIN)

% Choose default command line output for pressurestart
handles.output = hObject;

% Update handles structure
guidata(hObject, handles);

% UIWAIT makes pressurestart wait for user response (see UIRESUME)
% uiwait(handles.figure1);

% --- Outputs from this function are returned to the command line.
function varargout = pressurestart_OutputFcn(hObject, eventdata, handles)
% varargout  cell array for returning output args (see VARARGOUT);
% hObject    handle to figure
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)
```

```
% Get default command line output from handles structure
varargout{1} = handles.output;

% --- Executes on button press in stop.
function stop_Callback(hObject, eventdata, handles)
% hObject    handle to stop (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Hint: get(hObject,'Value') returns toggle state of stop
stop = get(hObject,'Value')

% --- Executes on button press in togglebutton1.
function togglebutton1_Callback(hObject, eventdata, handles)
% hObject    handle to togglebutton1 (see GCBO)
% eventdata  reserved - to be defined in a future version of MATLAB
% handles    structure with handles and user data (see GUIDATA)

% Hint: get(hObject,'Value') returns toggle state of togglebutton1
 % Use the arduino command to connect to an Arduino device.
clear a
a = arduino;

%% Take a single temperature measurement
% The datasheet for the TMP36 temperature sensor tells us that the voltage
% reading is directly proportional to temperature in Celsius with an
% offset of 0.5V and a scale factor of 10 mV/°C (equivalent to 100 °C/V).
% Therefore the conversion can be represented as
%
% $T_C = (V-0.5)*100$
% We can read the output voltage, convert it to Celsius and convert the
% result to Farenheit as follows:
v = readVoltage(a,'A1');
sv = (v*5.0)/1024.0;
```

```
pressure_bar = (sv-1.0)/(4.0)*(10.0-0.0);

fprintf('Pressure Reading',pressure_bar)

h = animatedline;

stop = false

ax = gca;

ax.YGrid = 'on';

ax.YLim = [0 10];

startTime = datetime('now');

while ~stop

  % Read current voltage value

  v = readVoltage(a,'A1');

  sv = (v*5.0)/1024.0;

  % Calculate temperature from voltage (based on data sheet)

  pressure_bar = (sv-1.0)/(4.0)*(10.0-0.0);

  [timeLogs,ECGLogs] = getpoints(h);

  f = [timeLogs,ECGLogs];

  % Get current time

  t = datetime('now') - startTime;

  % Add points to animation

  addpoints(h,datenum(t),pressure_bar)

  datetick('x','keeplimits')

  drawnow;

  stop = get(hObject,'Value')

end

%% Plot the recorded data

plot(timeLogs,ECGLogs)

xlabel('Elapsed time (sec)')

ylabel('Pressure')

%% Save results to a file


T = table(timeLogs',ECGLogs','VariableNames',{'Time_sec','pressure'});

filename = 'pressure_Data.xlsx';

% Write table to file

writetable(T,filename)
```

9. References

1. Material Properties Data: Polyetheretherketone (PEEK) www.makeitfrom.com [last accessed 12/02/20].

2. Commercially available from www.asynt.com/product/freactor-complete-kit/ [last accessed 12/02/20]

3. www.freactor.com [last accessed 12/02/20]

4. R. Machado, Fundamentals of mass transfer and kinetics for the hydrogenation of nitrobenzene to aniline. *Air Products and Chemicals*, 2007, **1**, 1-14

5. G. Zhu, Z. Chen and X. Zhang, Highly efficient asymmetric synthesis of β-amino acid derivatives via rhodium-catalyzed hydrogenation of β-(Acylamino) acrylates. *J. Org. Chem.*, 1999, **64**, 6907-6910.