Electronic Supplementary Information (ESI)

Continuous-flow transfer hydrogenation of benzonitrile using formate as a safe and sustainable source of hydrogen

Seán D. Dempsey,[a,b,c] Ailbhe A. Ryan,[a,b,c] Megan Smyth,[b] Thomas S. Moody,[b,c] Scott Wharry,[b] Karen Fahey,[c] Andrew M. Beale,[d,e] Sofia Mediavilla Madrigal,[e,f] Paul Dingwall,[a] David W. Rooney,[a] Peter C. Knipe,[a]* Mark J. Muldoon[a]* and Jillian M. Thompson[a]*

[a] School of Chemistry & Chemical Engineering, Queen's University, Belfast, BT9 5AG, UK
[b] Almac Sciences Ltd., 20 Seagoe Industrial Estate, Craigavon, BT63 5QD, UK
[c] Arran Chemical Company, Unit 1 Monksland Industrial Estate, Athlone, Co. Roscommon, Ireland
[d] Chemistry Department, University College of London, 20 Gordon Street, London, WC1H 0AJ, UK
[e] UK Catalysis Hub, Research Complex at Harwell, Rutherford Appleton Laboratory, Didcot, OX11 0FA, UK
[f] Max Planck- Cardiff Centre on the Fundamentals of Heterogeneous Catalysis FUNCAT, Cardiff Catalysis Institute, School of Chemistry, Cardiff University, Cardiff, CF10 3AT, UK

*Emails: p.knipe@qub.ac.uk, m.j.muldoon@qub.ac.uk and jillian.thompson@qub.ac.uk

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S1. Experimental

Materials

All reagents and substrates are commercially available and were used without further purification. The catalysts used for batch reactions were sourced from various suppliers: 5 wt.% Pd on carbon (Sigma Aldrich, code number: 205680), 5 wt.% Pd on charcoal (Sigma Aldrich, code number: 75992), 5 wt.% Pd on γ-alumina (Alfa Aesar), 5 wt.% Pd on calcium carbonate (Alfa Aesar), 2 wt.% Pd on zeolite (Johnson Matthey). The catalyst used for continuous-flow experiments was a granular form of 5 wt.% Pd on carbon (Johnson Matthey, code number: 110002CPR1-5) with an average particle size of 800 μm and range of 700 – 900 μm.

Catalyst characterisation

Elemental analysis of catalysts was determined by inductively coupled plasma – optical emission spectrometry (ICP-OES) and was carried out using an Agilent Technologies 5100 ICP-OES system. Solid catalyst samples were prepared by digesting in nitric acid using a CEM Discover SPD plus microwave digester, removing excess acid by heat and making up to 25 mL in deionised water for analysis.

Attenuated total reflection-Fourier Transform infrared (ATR-IR) spectra were acquired using a Nicolet iS 10 spectrometer fitted with a Smart iTR Attenuated Total Reflectance (ATR) sampling accessory. The spectral resolution was 4 cm^{-1} and spectra were collected separately for each sample by averaging 16 scans per spectrum. Before measurement, an air background was collected.

Analysis of reactions by gas chromatography (GC)

GC analysis was carried out using an Agilent 7820A series gas chromatograph equipped with a flame ionisation detector (FID). An Agilent HP-5 column (30.0 m × 320 μm × 0.25 μm nominal) was employed for all separations. GC methods were optimised to have an injection volume of 1 μL and He flow rate of 2 mL min^{-1} along with an FID temperature of 300 °C. An initial oven temperature of 45 °C was held for 1 min followed by a temperature ramp of 20 °C min^{-1} to increase the temperature to 70 °C, which was held for 1 min. A final temperature ramp of 70 °C min^{-1} increased the temperature to 320 °C and this was held for a further 1 min. Substrate conversion, product yields and mass balances were determined using the internal standard (IS) method of quantification using dodecane or mesitylene as standard.

The IS method involved first determining the relative response factor (RF) of each analyte, which was done by analysing solutions of known concentration of analytes against known concentrations of IS. The RF for each analyte was calculated using the following equation:

$$RF = \frac{Area_{IS} \times Moles_{analyte}}{Area_{analyte} \times Moles_{IS}}$$

The average RF was obtained by analysing three standard solutions of each analyte. Addition of a known amount of internal standard to each reaction sample, allowed the number of moles of analyte to be calculated using the following equation:

$$Moles_{analyte} = \frac{RF \times Moles_{IS} \times Area_{analyte}}{Area_{IS}}$$

The substrate conversion, product yields, selectivities and mass balances were determined according to the following equations:

$$PhCN\ conversion\ (\%) = \frac{m_{PhCN}^0 - m_{PhCN}}{m_{PhCN}^0} \times 100$$

$$Product\ yield\ (\%) = \frac{m_{product}}{m_{PhCN}^0} \times 100$$

$$Product\ selectivity\ (\%) = \frac{m_{product}}{\sum m_{product}} \times 100$$

$$Mass\ balance\ (\%) = \frac{m_{PhCN} + \sum m_{product.}}{m_{PhCN}^0} \times 100$$

Where m_{PhCN}^0 refers to the initial concentration benzonitrile (in mol L^{-1}). Also, m_{PhCN} and $m_{product}$ refer to the concentrations of benzonitrile and product (in mol L^{-1}) at a given point during the reaction.

Experimental procedure for batch experiments
Batch experiments were based on the method reported by Vilches-Herrera *et al.*[1] To a 25 mL round-bottomed flask, catalyst (5 mol% Pd with respect to benzonitrile substrate) was added followed by a solution of benzonitrile (62 mg, 0.6 mmol) in THF (3 mL) along with internal standard, dodecane (153 mg, 0.9 mmol, 1.5 equiv.). To this suspension, a solution of HCOOH-NEt_3 in THF (HCOOH (10.0 M), NEt_3 (0.55 M), 18:1 molar ratio, 3 mL) was added and the flask sealed with a rubber septum. Gas evolution was observed on addition of HCOOH-NEt_3 and the rubber septum was pierced with a syringe to prevent pressure build-up inside the vessel. The flask was heated to 40 °C using an oil bath, with constant stirring (600 rpm). Samples were taken periodically from the reaction mixture to build kinetic profiles for each reaction. To sample the reaction, the flask was removed from the oil bath briefly and small portion of the reaction mixture (~ 0.25 mL) was removed using a glass Pasteur pipette and passed through a small plug of celite to remove traces of catalyst. After sampling, the reaction flask was placed back in the oil bath and reaction was resumed. Each sample taken from the reaction mixture was prepared for GC analysis by diluting the filtered sample with ethyl acetate and transferring to a GC vial.

Continuous-flow reactor setup
The catalyst bed consisted of a stainless-steel column with ¼" internal diameter containing 5 wt.% Pd on carbon granular catalyst (0.5 - 1.0 g). The catalyst was kept in place with glass beads (212-300 μm) and glass wool plugs at either end of the bed. The catalyst bed was heated using a tubular furnace (Carbolite). The liquid feed was pumped through the reactor using a peristaltic pump (Vapourtec) and a back-pressure regulator (Zaiput) was used to maintain the system pressure at 6 bar. For the most part, PTFE ⅛" tubing, connections and fittings were used, which were purchased from Kinesis. Connections and fittings at either end of the reactor were stainless steel and purchased from Swagelok.
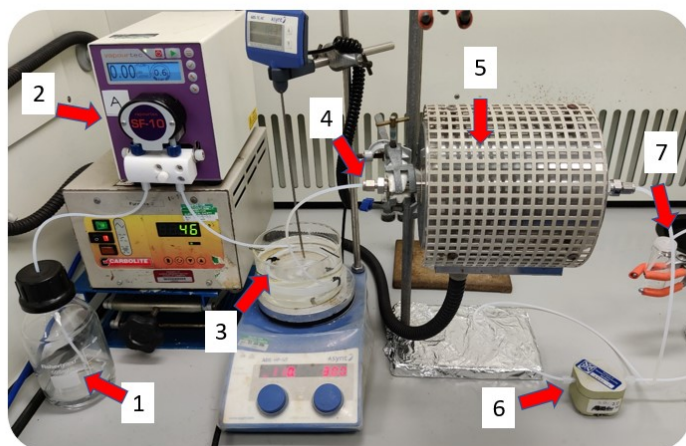
1. Feed solution
2. Peristaltic pump
3. Pre-heating loop
4. Reactor containing Pd/C catalyst bed
5. Heating furnace
6. Back pressure regulator
7. Collection flask

Figure S1: *Captured image of the experimental setup for continuous-flow experiments*

Experimental procedure for continuous-flow experiments

The reactor was heated to reaction temperature (40 °C) before reaction solvent was passed through at 1 mL min^{-1} for 20 min. The reaction feed, consisting of benzonitrile (0.1 M) and HCOOH-NEt$_3$ (HCOOH (1.0 - 10.0 M) and NEt$_3$ (0 - 0.5 M), various molar ratios) in reaction solvent, was then introduced and pumped at 1 mL min^{-1} to fill the reactor. The flow rate was altered to the reaction flow rate of 0.5 mL min^{-1} and the reaction feed solution pumped over the catalyst bed. Before taking the first sample, the system was allowed to equilibrate by allowing time for 3 passes of the feed solution through the catalyst bed. Samples were then collected periodically from the reactor outlet, with each sample collected over a 5 minute period. Samples were prepared for GC analysis by adding the appropriate amount of internal standard (mesitylene) and further diluting with solvent before transferring to GC vials for off-line analysis.

Experimental procedure for catalyst pre-treatment experiments

A. The catalyst bed was allowed to reach reaction temperature (40 °C) before pumping reaction solvent through at 1 mL min^{-1} for 20 min. Benzonitrile in THF (0.1 M) was introduced and pumped at 1 mL min^{-1} to fill reactor. The flow rate was changed to 0.5 mL min^{-1} and pumped over catalyst bed for 2 hours. The pre-mixed feed solution, containing benzonitrile (0.1 M) and HCOOH-NEt$_3$ (HCOOH (10.0 M), NEt$_3$ (0.055 M), 18:1 molar ratio) in THF was introduced and the reaction was monitored as previously described for continuous-flow experiments.

B. The catalyst bed was allowed to reach reaction temperature (40 °C) before pumping reaction solvent through at 1 mL min^{-1} for 20 min. HCOOH-NEt$_3$ in THF (HCOOH (10.0 M), NEt$_3$ (0.055 M), 18:1 molar ratio) was introduced and pumped at 1 mL min^{-1} to fill reactor. The flow rate was changed to 0.5 mL min^{-1} and pumped over catalyst bed for 2 hours. The pre-mixed feed solution, containing benzonitrile (0.1 M) and HCOOH-NEt$_3$ (HCOOH (10.0 M), NEt$_3$ (0.055 M), 18:1 molar ratio) was introduced and the reaction was monitored as previously described for continuous-flow experiments.

Experimental procedure for catalyst regeneration experiments

Three identical runs were carried out over one catalyst bed according to the general method outlined above for continuous flow experiments. The reaction feed used for each run was identical and consisted of benzonitrile (0.1 M) and HCOOH-NEt$_3$ (HCOOH (10.0 M), NEt$_3$ (0.55 M), 18:1 molar ratio) in THF. In between each run the catalyst bed was rinsed with THF for 30 min at 0.5 mL min^{-1}, followed by deionised water for 30 min at 0.5 mL min^{-1}. A sample of catalyst (~100 mg, exact mass for each sample was recorded for subsequent catalyst productivity calculations) was taken from the catalyst bed for *ex-situ* characterisation (ICP and ATR-FTIR analysis). The remaining amount of catalyst in the bed was then washed with deionised water at 2.5 mL min^{-1} for 2 or 16 hours at 40 °C. Similarly, catalyst samples were taken from the catalyst bed after regeneration for *ex-situ* characterisation. A catalyst sample was also taken after the final run in the same manner.

After being removed from the catalyst bed, each sample was treated differently depending on the type of analysis to be carried out.

- ICP-OES: Samples heated to 110 °C in oven for 60 min and left to sit at room temperature before analysis.
- ATR-FTIR: Samples heated to 60 °C in oven for 60 min and left to sit at room temperature before analysis.

Experimental procedure for extended run

Five identical runs were carried out over one catalyst bed according to the general method outlined above for continuous flow experiments. The reaction feed used for each run was identical and consisted of benzonitrile (0.1 M) and HCOOH-NEt$_3$ (HCOOH (1.0 M), NEt$_3$ (0.1 M), 10:1 molar ratio) in ethanol-water (33 vol.% H$_2$O). In between each run the catalyst bed was rinsed with ethanol for 30 min at 0.5 mL min^{-1}, followed by a wash with deionised water for 16 hours at 2.5 mL min^{-1}.

Calculating catalyst productivity

Catalyst productivity values for both batch and continuous-flow experiments were calculated using the following general equation:

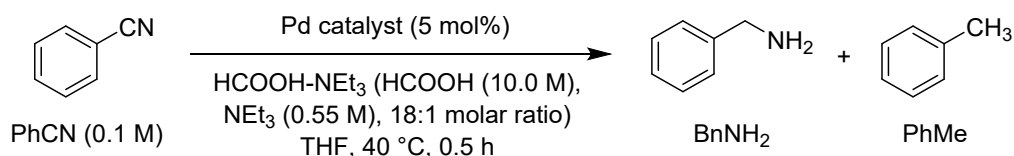$$Productivity = \frac{n_{PhCN\ conv}}{m_{cat}}$$

Where $n_{PhCN\ conv}$ refers to the number of moles of benzonitrile converted in the reaction and m_{cat} to the mass of catalyst used in grams.

S2. Catalyst screen in batch

A screen of supported Pd catalysts was carried out in batch according to the experimental method outlined in Section S1.

Table S1: *Activity and selectivity of some commercially available Pd catalysts for the CTH of benzonitrile using batch method.[1]*

PhCN (0.1 M) → Pd catalyst (5 mol%), HCOOH-NEt$_3$ (HCOOH (10.0 M), NEt$_3$ (0.55 M), 18:1 molar ratio), THF, 40 °C, 0.5 h → BnNH$_2$ + PhMe

Entry	Catalyst	Conversion (%)^a	BnNH$_2$ sel. (%)^a	PhMe sel. (%)^a
1	5 wt.% Pd on carbon	100	97	3
2	5 wt.% Pd on γ-alumina	52	97	3
3	2 wt.% Pd on zeolite	47	95	5
4	5 wt.% Pd on calcium carbonate	43	95	5
5	5 wt.% Pd on charcoal	100	95	5
6	5 wt.% Pd on carbon (granular)	56	94	6

^{a} Conversions and selectivities were determined by GC using dodecane as an internal standard and calculated using appropriate equations (see section S1).

While most of the catalysts tested gave high selectivity to benzylamine, some were more active than others for this reaction. 5 wt.% Pd on carbon (powder) exhibited complete substrate conversion, along with 5 wt.% Pd on charcoal which was tested as an additional carbon support for comparison (entries 1 and 5). Each of the other powder catalysts tested only exhibited partial conversion of substrate between 43 - 52% (entries 2 - 4). To get a better understanding of the activity of each catalyst over time, the reactions were monitored over time, and the resulting reaction profiles constructed (Figure S2). For both 5 wt.% Pd on carbon and 5 wt.% Pd on charcoal the reaction reaches completion within 5 minutes and further hydrogenolysis of benzylamine to toluene does not occur, suggesting the amine product is stable once formed. For the other powdered catalysts, the initial activity is high but after 30 - 60% substrate conversion, the rate of reaction considerably decreases, due to catalyst deactivation.
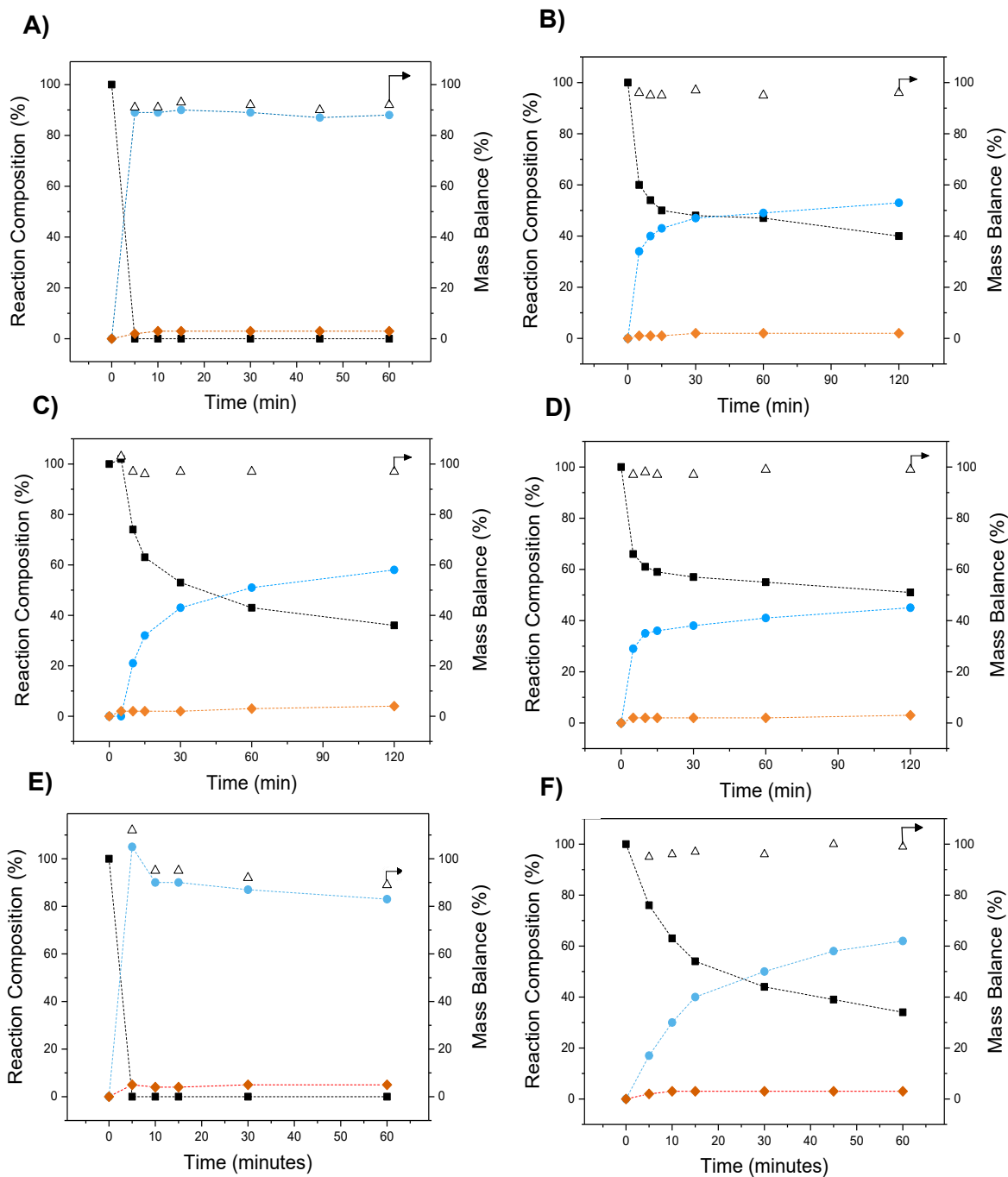
Figure S2: *Reaction profiles for CTH of benzonitrile over various catalysts in batch. Shown is (A) 5 wt.% Pd on carbon (B) 5 wt.% Pd on γ-alumina (C) 2 wt.% Pd on zeolite (D) 5 wt.% Pd on calcium carbonate (E) 5 wt.% Pd on charcoal and (F) 5 wt.% Pd on carbon (granular). Key: PhCN (■), BnNH₂ (●), PhMe (♦), mass balance (△).*

S3. Investigation of mixing in continuous-flow

Before transferring the reaction directly into flow, the manner in which the two main reaction components (benzonitrile substrate and HCOOH-NEt$_3$) were introduced into the continuous reactor required consideration. Initial mixing studies were carried out using two separate pumps, with Pump A delivering benzonitrile substrate in THF (0.2 M) and Pump B delivering HCOOH-NEt$_3$ in THF (HCOOH (10.0 M), NEt$_3$ (0.055 M), 18:1 molar ratio) to a T-piece where the two streams were combined. The mixing of the reaction was monitored visually by dying the HCOOH-NEt$_3$ solution with methyl red indicator. Figure S3 shows the formation of a biphasic liquid-liquid system with the pink HCOOH-NEt$_3$ solution forming a different layer to the clear benzonitrile solution and therefore unfavourable mixing through the reactor column. To eliminate any liquid-liquid mixing limitations, the reaction components were combined into one solution and introduced into the catalyst bed using one pump. It was confirmed that benzonitrile did not react or decompose over time in the pre-mixed feed solution.
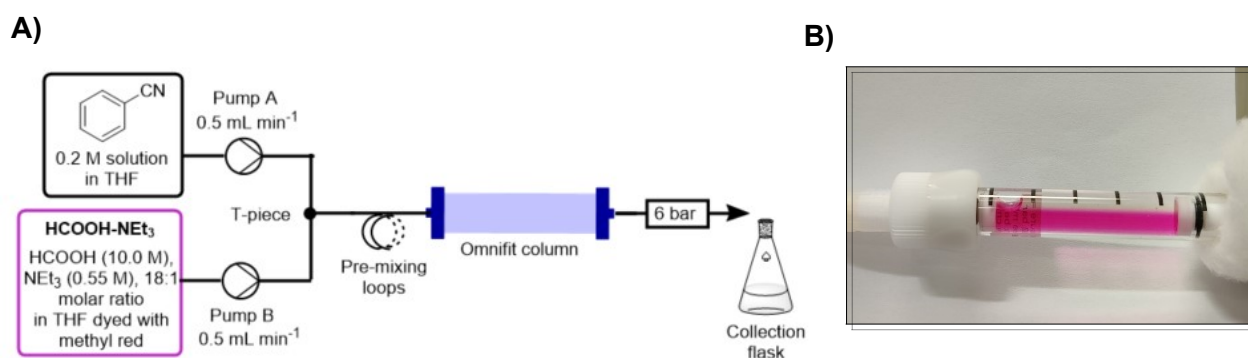
A)

B)

Figure S3: *Initial continuous-flow setup to investigate the mixing of two separate feed solutions. (A) Shows a schematic of the setup and (B) shows a captured image of the two liquid streams meeting in an empty glass column.*

S4. Investigation of back pressure

A back pressure of 6 bar was applied in continuous-flow reactions by incorporating a back-pressure regulator (BPR) in the reaction setup. This was done to control the flow of liquid and generated gas in the outlet of the reactor. However, to demonstrate that the reaction can be performed without the need for back pressure, a reaction was performed with the BPR removed. The time on stream data for reactions run with and without the BPR are shown in Figure S4, with comparable profiles observed. Note that these reactions were performed using the original conditions based on batch experiments but at a higher liquid flow rate of 2 mL min^{-1} compared to 0.5 mL min^{-1} used to produce time on stream data shown in main text (see Figure 2) explaining the lower initial conversions and yields.
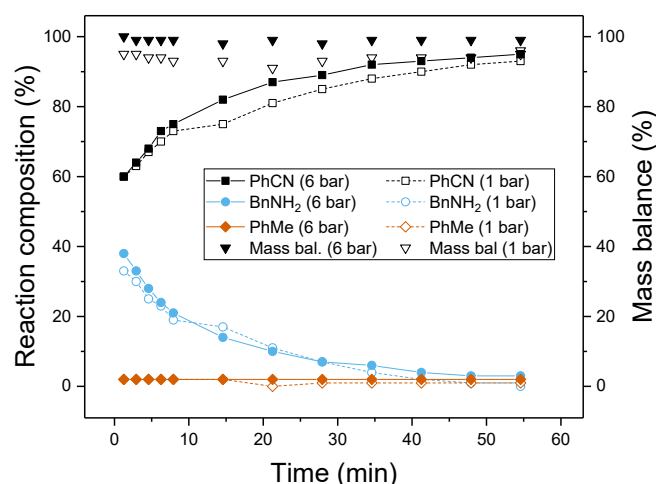

Figure S4: *Time on stream data for continuous-flow CTH of benzonitrile with and without BPR incorporated in the experimental setup. Reaction conditions: Benzonitrile (0.1 M) and HCOOH-NEt$_3$ (HCOOH (10.0 M), NEt$_3$ (0.55 M), 18:1 molar ratio) in THF was passed over 5 wt.% Pd/C (granular, 1.0 g) at 40 °C, flow rate of 2 mL min^{-1} at either 6 bar (with BPR) or ~1 bar (without BPR).*

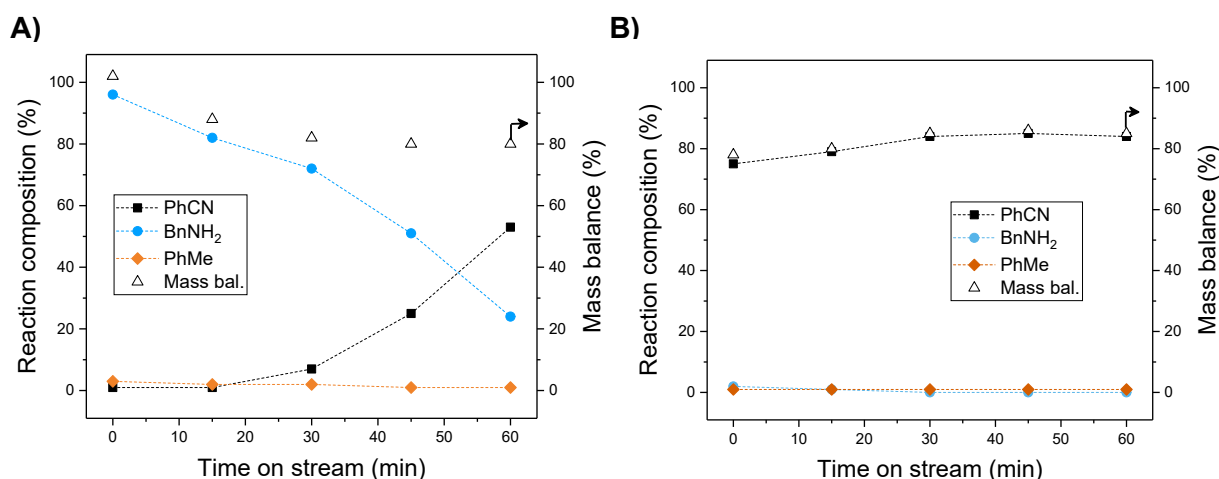## S5. Catalyst pre-treatment studies

Figure S5: *Time on stream data for continuous-flow CTH of benzonitrile after pre-treatment of catalyst bed with (A) benzonitrile substrate in THF (0.1 M) and (B) HCOOH-NEt$_3$ in THF (HCOOH (10.0 M), NEt$_3$ (0.55 M), 18:1 molar ratio) for 120 min prior to sample collection. Reaction conditions: Benzonitrile (0.1 M) and HCOOH-NEt$_3$ (HCOOH (10.0 M), NEt$_3$ (0.55 M), 18:1 molar ratio) in THF was passed over 5 wt. % Pd/C (granular, 1.0 g) at 40 °C, flow rate of 0.5 mL min^{-1} and 6 bar back pressure.*

S6. Additional data for process development in continuous-flow

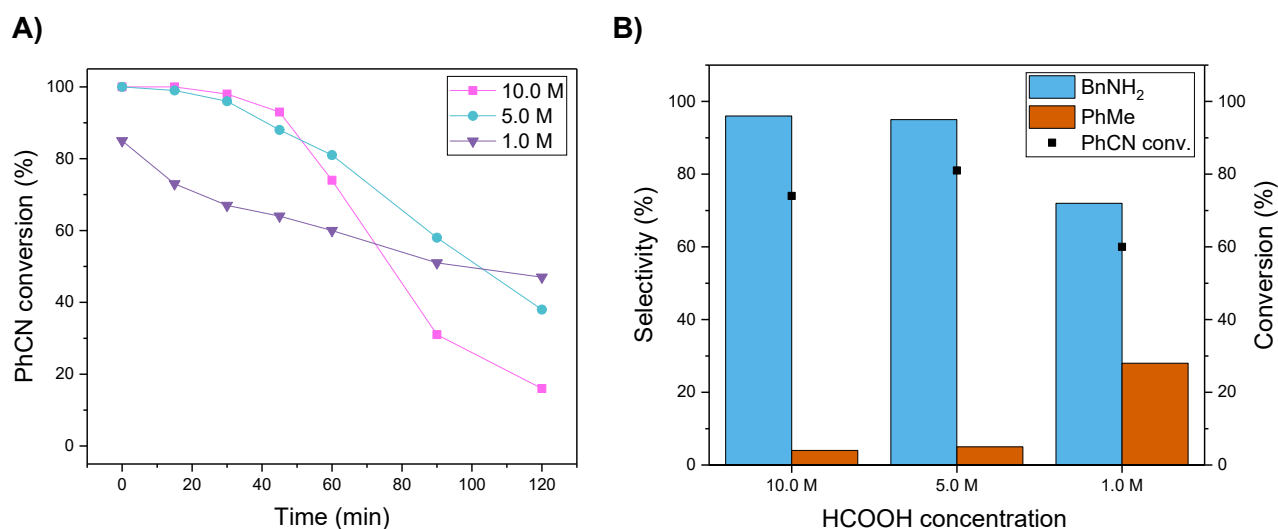## Effect of HCOOH concentration

A)

B)

Figure S6: The effect of HCOOH concentration on (A) benzonitrile conversion as a function of time on stream and (B) product selectivities after 60 min on stream for the continuous-flow CTH of benzonitrile. Reaction conditions: Benzonitrile (0.1 M) and HCOOH-NEt$_3$ (HCOOH (1 - 10 M), NEt$_3$ (0.055 – 0.5 M), 18:1 molar ratio) in THF was passed over 5 wt.% Pd/C (granular, 1.0 g) at 40 °C, liquid flow rate of 0.5 mL min^{-1} and 6 bar back pressure.

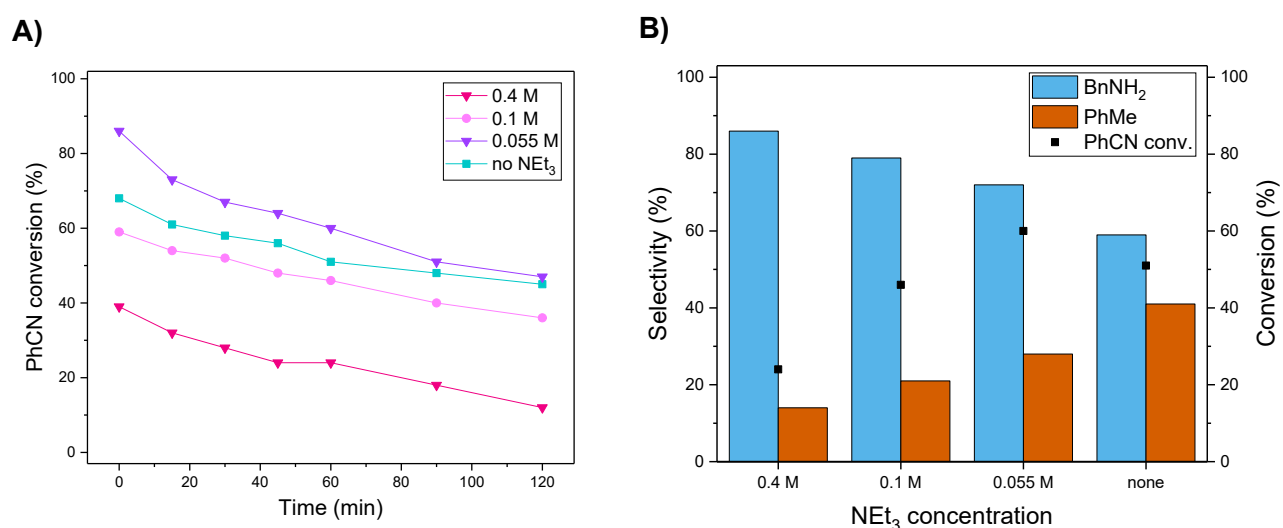## Effect of HCOOH-NEt$_3$ molar ratio

A)

B)

Figure S7: The effect of NEt$_3$ concentration on (A) benzonitrile conversion as a function of time on stream and (B) product selectivities after 60 min on stream for the continuous-flow CTH of benzonitrile. Reaction conditions: Benzonitrile (0.1 M) and HCOOH-NEt$_3$ (HCOOH (1.0 M), NEt$_3$ (0 - 0.4 M)) in THF was passed over 5 wt. % Pd/C (granular, 1.0 g) at 40 °C, liquid flow rate of 0.5 mL min^{-1} and 6 bar back pressure.

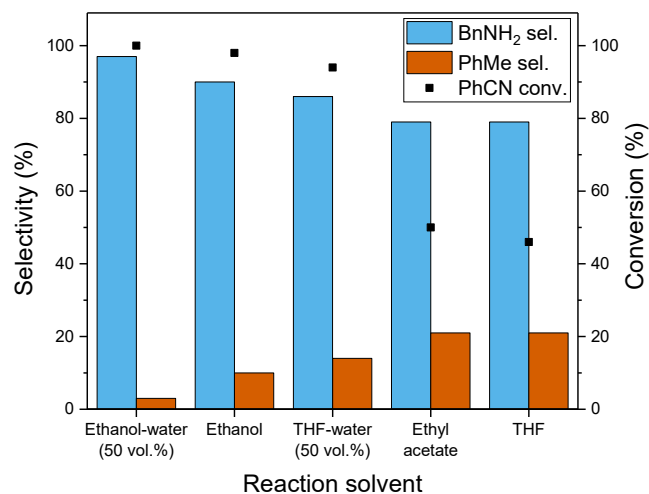## Effect of solvent choice on selectivity

Figure S8: *The effect of reaction solvent on benzylamine selectivity after 60 min on stream for the continuous-flow CTH of benzonitrile. Reaction conditions: Benzonitrile (0.1 M) and HCOOH-NEt$_3$ (HCOOH (1.0 M), NEt$_3$ (0.1 M), 10:1 molar ratio) in various solvents was passed over 5 wt.% Pd/C (granular, 1.0 g) at 40 °C, liquid flow rate of 0.5 mL min^{-1} and 6 bar back pressure.*

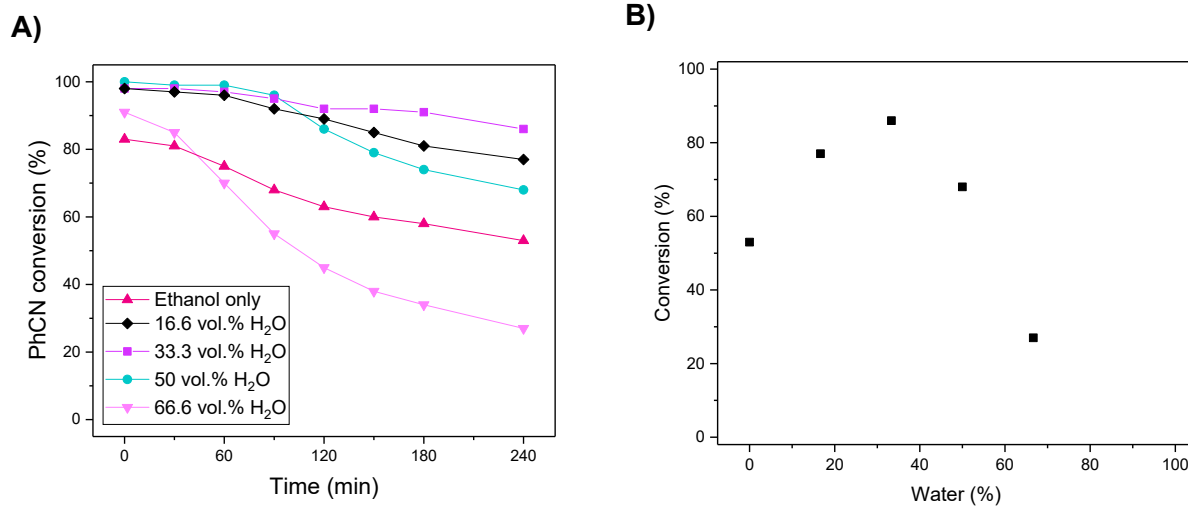## Effect of volume percent water in reaction solvent

Figure S9: *The effect of water percentage in ethanol solvent on benzonitrile conversion (A) as a function of time on stream and (B) as a function of percentage water in solvent after 4 hours on stream for the continuous-flow CTH of benzonitrile. Reaction conditions: Benzonitrile (0.1 M), HCOOH-NEt$_3$ (HCOOH (1.0 M), NEt$_3$ (0.1 M), 10:1 molar ratio) in solvent was passed over 5 wt.% Pd/C (granular, 0.5 g) at 40 °C, liquid flow rate of 0.5 mL min^{-1} and 6 bar back pressure.*
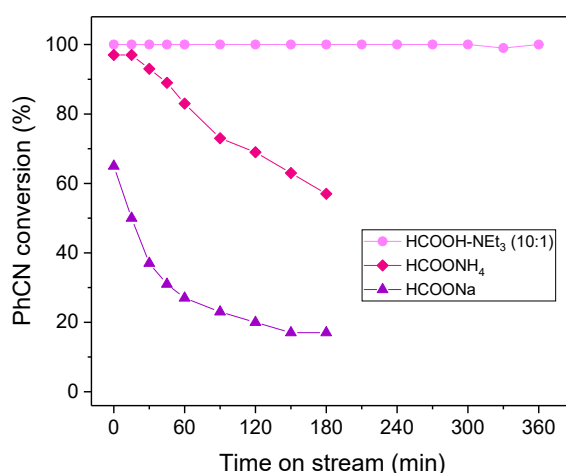
Effect of reducing agent

Figure S10*: The effect of formate reducing agent on benzonitrile conversion as a function of time on stream for the continuous-flow CTH of benzonitrile. Reaction conditions: Benzonitrile (0.1 M) and reducing agent (1.0 M) in ethanol-water (33 vol.%) was passed over 5 wt. % Pd/C (granular, 1.0 g) at 40 °C, liquid flow rate of 0.5 mL min^{-1} and 6 bar back pressure.*

Optimisation of catalyst regeneration

It was previously shown that catalyst regeneration could be achieved by washing with deionised water and the extent of regeneration depended on the amount of time taken for the wash step (Figure 3-A). To investigate if catalyst regeneration is more influenced by (i) the volume of water passed over the catalyst bed or (ii) the flow rate of the water passed over the catalyst bed an experiment was carried out in which the same volume of water (480 mL) was passed over a catalyst bed during regeneration but at different flow rates (Figure S11). The results of this experiment demonstrate that using faster flow rates during the water wash leads to more effective regeneration of catalyst activity for the CTH of benzonitrile, with the wash at 2.5 mL min^{-1} for 3.2 h resulting in an increase in conversion from 89% to 95%, while the wash at 0.5 mL min^{-1} for 16 h resulted in no increase in conversion. Therefore, the faster flow rate of 2.5 mL min^{-1} was chosen for catalyst regeneration during the extended run.
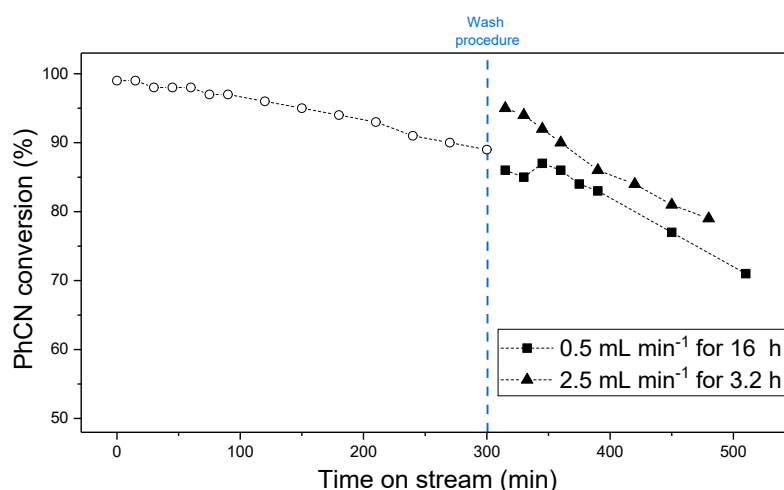

Figure S11*: The change in benzonitrile conversion over time to determine the effect of flow rate on catalyst regeneration for the continuous-flow CTH of benzonitrile.*
Reaction conditions: Benzonitrile (0.1 M) and HCOOH-NEt$_3$ (HCOOH (1.0 M), NEt$_3$ (0.1 M), 10:1 molar ratio) in ethanol-water (33 vol.% H$_2$O) was passed over 5 wt.% Pd/C (0.5 g) at 40 °C, liquid flow rate of 0.5 mL min^{-1} and 6 bar back pressure.

References

1. M. Vilches-Herrera, S. Werkmeister, K. Junge, A. Börner and M. Beller, *Catal. Sci. Technol*., 2014, **4**, 629–632.