FAST Hydrogenations as a Continuous Platform for Green Aromatic Nitroreductions

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Abstract A continuous-flow packed-bed catalytic reactor has been developed for hydrogenation of aromatic nitrobenzoic acids in water to produce the corresponding anilines. These hydrogenations are green, more efficient, less consumptive and safer reductive processes. Various industrially important aromatic amines have been produced in excellent yields and with high throughput. The optimized continuous flow reduction process produced no detectable Genotoxic Impurity (GTI) intermediates as compared with the corresponding batch mediated reduction. The reactor is modular in design and can be scaled-up for multi-kg/day product delivery without extensive re-design.

Keywords green chemistry, catalyst packed-bed, FAST (Flow Assisted Synthesis Technology), hydrogenation, nitroreduction, sustainable manufacture, aromatic acids, anilines

Approximately 25 % of marketed drugs require at least one hydrogenation step in their manufacturing process.¹ Flow-mediated hydrogenation offers many advantages over traditional batch processing including increased safety due to small dosage of hydrogen, improved temperature control and reduced solvent volumes.² It also results in improved substrate-gas-catalyst interactions, the ability for stringent reaction control and minimised side product formation (offering potential for removal of purification).

A custom built packed-bed flow hydrogenation rig suitable for Proof of Concept (PoC) studies and low kg manufacture has been designed and built. The PoC hydrogenations reported herein were carried out on this lab-scale flow rig. A complementary rig offers direct scale-up with a larger packed-bed reactor capable of producing up to 10 kg/week throughput. The critical factors for the design of a custom flow rig for nitro reductions and the process development considerations from PoC to manufacture are highlighted. The versatility of the flow hydrogenation rig has been demonstrated using aromatic nitro substrates exploiting an acid functionality which facilitates water-mediated processing

producing the corresponding amino benzoic acid. This methodology has also resulted in the critical control over Genotoxic Impurity (GTI) formation, which is of pronounced importance for active pharmaceutical ingredient (API) manufacture.³

Amino benzoic acid and derivatives belong to an important class of chemicals that are relevant in the pharmaceutical, dye and flavor and fragrance (F&F) industries.⁴ Catalytic hydrogenation of nitrobenzoic acids is a direct and straightforward way of accessing the aniline-derivatives.⁵ However, nitrobenzoic acids and the resulting aminobenzoic acids have limited solubility in alcohols which are economic and process-friendly solvents (ethanol, methylated spirit, IPA etc.).⁶ Poor solubility of starting materials, products and any intermediate/by-product formed in a synthetic process is one of the most formidable challenges in implementing continuous flow technology for any process chemistry and scale-up. Precipitation of any reaction components can lead to flow-reactor clogging, back pressure build-up and eventual process failure. In order to maximise throughput from the process, reaction concentration should be high whilst ensuring sufficient solubility. In this work, the presence of the carboxylic acid moiety is exploited affording high solubility in aqueous alkaline solution. This has double benefits for processing due to enabling high concentration in reaction feedstock and the use of water as a green, economical solvent. Counter to that, the use of aqueous media has limitations for catalytic hydrogenation due to the lower solubility of H₂ in water compared to more traditional hydrogenation organic solvents, with hydrogen solubility at least one order of magnitude lower than in acetonitrile or ethanol.⁷ In addition, the presence of base (NaOH) only further reduces hydrogen solubility.⁷ Hence, aqueous-phase hydrogenation of nitrobenzoic acids under alkaline conditions requires elevated hydrogen pressure which can create gas-liquid mass transfer limitations when the reaction is scaled-up due to the lowering of gas-liquid contact area-to-volume ratio.

Considering these factors, Almac's Flow Assisted Synthetic Technology (FAST) platform was utilised to demonstrate catalytic hydrogenation of nitrobenzoic acids in aqueous solution at low H_2 pressures. Model substrates were selected which are industrially relevant, namely para-, ortho- and meta-nitrobenzoic acid. Derivatives of amino-benzoic acids are used as dermatological drug, local anesthetics, in dye industry, and in pharmaceuticals (Figure 1).^{4,8}

Figure 1: Model substrates for flow hydrogenations.

Batch Investigations

In order to establish process parameters and generate reference materials, the hydrogenation was first performed in a conventional autoclave reactor. A 30 mL solution containing para-nitrobenzoic acid (PNBA) (2.5 g, 0.5 M), NaOH (0.695 g, 0.58 M) and catalyst loading ($wt_{catalyst}/wt_{substrate}\%$: 2, 4 and 8 wt/wt %) was hydrogenated at 10 bar H_2 pressure and 80 °C.¹³ Further experimental details are provided in the supporting information. The reaction mixture was periodically sampled and analysed by 1H NMR spectroscopy to determine the PNBA % conversion and % yield of products and associated intermediates (Scheme 1). The rate of conversion of PNBA increases linearly with increasing amount of palladium-catalyst loading (g/cm^3) in the reaction mixture indicating absence of external mass transfer resistance (Figure 2).

Figure 2: Effect of $wt_{catalyst}/wt_{substrate}\%$ on PNBA conversion under 10 bar hydrogen pressure.

When the hydrogen pressure is reduced from 10 bar to 5 bar, with 8 wt/wt % catalyst loading the conversion of PNBA takes

place at a much slower rate, which can be attributed to the lower hydrogen concentration in solution phase (Figure 3).⁷ From analysis of the batch experiments, a key observation was that despite complete consumption of PNBA which occurs at 10 min and 20 min, respectively for 10 bar and 5 bar hydrogen pressure, this does not correlate to 100% product formation. 1H NMR spectroscopy determined that significant amounts of reaction intermediates **4**, **5** and **6** (Scheme 1), potential GTIs, are present along with the target product (PABA).

Figure 3: Pressure effect on conversion and yield under batch conditions.

Nitro-to-amine reduction *via* catalytic hydrogenation is a well-studied reaction for nitro aromatic compounds.⁹ The reaction proceeds *via* one of the two alternative pathways as shown in Scheme 1. Pathway 1 involves progressing *via* nitroso **2** to hydroxylamine intermediate **3** to product **7**. Pathway 2 is *via* condensation of nitroso **2** and hydroxylamine **3** to give azoxy-derivative **4**, which goes through successive hydrogenations to produce azo- **5**, hydrazo- **6** and finally the amine product **7**.

In the batch experiments for conversion of PNBA to PABA, analysis of products observed in the liquid phase indicated that the reaction proceeds through the second pathway with evidence of all three intermediates (**4**, **5**, and **6**) but neither **2** or **3** were detectable by 1H NMR. Condensation of **2** and **3** to produce azoxy-derivative is an irreversible process and is facilitated by basic condition of the reaction mixture.^{4a} Since, the second pathway requires a total of 4.5 equivalent of hydrogen (in comparison to nitroso-hydroxylamine route which requires 3 equivalents), the equilibrium hydrogen concentration in the reaction mixture not only dictates the overall reaction rate, but also contributes in the buildup of GTI intermediates in the reaction mixture. At lower hydrogen pressure (5 bar) the reaction mixture contains more GTI intermediates at any conversion level of PNBA compared to the reaction performed at 10 bar hydrogen pressure (Figure 3). At larger scale, gas-liquid-solid mass transfer will be a decisive factor in high purity amine production to avoid the formation of GTI intermediates.

Scheme 1: Catalytic nitro reduction mechanism.

Another important economic aspect in catalytic hydrogenations is the necessity for expensive transition metal catalyst such as palladium, platinum, etc. With flow hydrogenations offering a number of advantages with respect to this. Investigations into catalyst recovery and reuse were carried out in experiments with 200 mg of 5 wt% Pd/C (8 wt/wt% catalyst loading). The rate of PNBA conversion with recycled catalyst was similar when compared to the reaction using fresh catalyst (Figure 4). However, the rate of product formation (PABA) with fresh catalyst is significantly higher than that of recycled catalyst. With recycled catalyst, faster accumulation and slower conversion of intermediates **4**, **5**, and **6** contributed to lower yields of product (PABA) even at higher PNBA conversion % (further details provided in Supporting Information).

Figure 4: Catalyst recycling under batch conditions.

Excellent multi-phase mass transfer and mixing are general attributes of continuous flow chemistry, and for gas-liquid-solid reactions in particular.¹⁰ In continuous flow catalytic reactions,

catalysts are generally packed as cartridge-type beds for continuous operation, regeneration and reusing. Under typical reaction conditions a mixture of reactive gas and liquid flowing through a packed-bed reactor assumes a trickle-flow behaviour. This results in a thin liquid film in contact with solid catalyst particles in tandem flow with the gas layer. This configuration allows fast diffusion of the gas into a liquid thin film affording rapid mixing between the dissolved gas, substrate and the catalyst and consequently a faster reaction rate.¹¹

Flow Investigations

The reduction of nitro moieties would benefit from rapid hydrogen transfer from the gaseous phase to an aqueous phase, including faster saturation of the aqueous phase with hydrogen. This will facilitate faster (higher productivity) conversion of a substrate under this continuous flow set-up. The FAST hydrogenation rig (Figure 5) was used with hydrogen (5 or 10 bar) gas metered by a mass flow controller (MFC) and mixed at a T-mixer with an aqueous solution of PNBA (0.5M) which is delivered to the system by a HPLC pump. The resulting gas-liquid mixture is trickled down the packed bed column (1.0 g of 5% Pd/C catalyst and 5.9 g of 212-300 μm glass beads). The packed bed is housed within a stainless steel tube that is externally heated to maintain a constant reaction temperature. A back pressure regulator is fitted in the downstream to maintain target pressure inside the catalyst bed. A gas-liquid separator allows facile separation of the reaction solution from unused hydrogen gas effluent. The reaction mixture is separated and analysed offline for monitoring the progress of the reaction.¹⁴

Figure 5: FAST hydrogenation flow rig.

A residence time distribution study was performed by injecting 50 μL of aminobenzoic acid (0.5 M) tracer through the packed bed (6 cm length) along with NaOH aq. Solution (2 mL/min) under 10 bar hydrogen pressure at 80 $^{\circ}\text{C}$. The effluent solution was collected and analysed with UV-Vis spectroscopy. (details of RTD

analysis provided in the Supporting Information). The mean residence time found in the RTD experiment was 6.6 min.

After reactor characterisation, model flow reactions were carried out at 5 and 10 bar hydrogen pressures (Figure 6). A 0.5 M PNBA aqueous Solution (with 0.58 M NaOH) was injected through the packed bed (6 cm length, at 80 °C) at different flow-rates: 0.5 mL/min to 5.0 mL/min. It was observed that at slower liquid flow rates (0.5 and 1.0 mL/min) complete conversion of PNBA to PABA was achieved under both 5 and 10 bar pressure. When the flow rate was increased PNBA conversion was gradually lowered. At slower liquid flow rates, PNBA spent a sufficient residence time in contact with the catalyst and hydrogen gas to ensure complete conversion into the product PABA.

Figure 6: PABA yield obtained relative to flow rates.

Figure 7: Comparison between flow and batch conditions at comparable conversion levels of PNBA (ca. 20, 40, 85 and 100%).

Under continuous flow, analysis of reaction samples by ^1H NMR found that only two reaction components were predominantly present, namely PNBA and PABA. At faster flow rates, such as 3 and 5 mL/min, < 5% of intermediates (4 and 5) were observed at

relative conversions of 22 and 42% respectively. At 2 mL/min and 0.5 mL/min flow rates, when 85 and 100% conversion were achieved, only trace or no intermediates were observed (Figure 7).¹² This indicates the hydrogenation follows the same pathway as the batch reaction, but at much faster subsequent conversion of intermediates to PABA. It should be noted that the reaction in batch process (300 mg 5% Pd/C catalyst (12 wt/wt% catalyst loading)) showed significant amounts of intermediates at comparable conversions of PNBA after 2, 6, 8 and 10 min of reaction time: conversion % (intermediate %) = 22% (11%), 42% (19%), 85% (51%) and 100% (57%). The observed differences in reaction mixture composition indicates that under continuous flow, the aqueous phase is saturated with sufficient hydrogen to convert any intermediates formed in the course of the residence time into final amine products, while in the batch conditions lack of sufficient amount of hydrogen in the solution phase resulted in accumulation of intermediates over time.

To demonstrate the robustness of the flow system and the catalyst bed for long-term efficiency over extended period of time, continuous operation was carried out over 6 hours. In comparison to the batch process, the confined catalyst packed bed showed undiminished activity over 6 hours of continuous operation with 10 bar hydrogen pressure and 0.5 mL/min flow of 0.5 M PNBA (Figure 8). In this process samples collected at regular intervals showed quantitative conversion with no GTI's identified in the product solution.

Figure 8: Catalyst packed-bed stability study with FAST hydrogenation rig.

The system was then scaled with a packed bed three-times larger as shown in Figure 9. In the larger packed bed, the flow rate could be quadrupled to 2 mL/min and quantitative conversion of PNBA to PABA was observed with the continued control over the intermediate formation. The robustness of the flow protocol developed was also demonstrated on the meta- and ortho-substituents with meta-aminobenzoic acid (MABA) and anthranilic acid both obtained respectively in quantitative yields and without any corresponding intermediates detectable.

Figure 9: Scaling-up FAST hydrogenation of nitrobenzoic acids.

Conclusion

In conclusion, the benefits of FAST hydrogenations with an environmentally favourable aqueous protocol has been demonstrated using a custom-built packed bed flow rig. The flow system used herein is superior to the batch conditions used both in terms of productivity and, minimisation of GTI formation. The robustness of the flow-mediated hydrogenation has been shown applicable for a range of ortho-, meta- and para- substituted benzoic acid substrates in aqueous alkaline conditions. The use of water increased product yield, lowered impurity levels and maximum utilisation of hydrogen gas has afforded a greener, safer chemical process.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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- (13) **General procedure for batch hydrogenation:** All conventional batch reactions were performed in an Autoclave Engineers 100 mL stainless steel stirred tank reactor. In a typical reaction, the reactor was charged with a 5 wt% Pd/C catalyst (0.02 g) and 30 mL of reaction mixture containing 2.5 g (15 mmols) para-nitrobenzoic acid PNBA with 0.695g (17.4 mmols) of NaOH. PNBA and NaOH concentrations in the aqueous solution are 0.50 M and 0.58 M, respectively. The reactor was sealed and purged three times with nitrogen before the reaction mixture was heated to 80 °C with stirring at 1250 rpm. The reactor was charged with 10 or 5 bar hydrogen pressure, at which point the reaction was started. Several samples of 200 µL of reaction mixtures were periodically withdrawn from the reactor (2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45 min, 1 h and 1.5 h). Each sample was diluted with 1.8 mL of D₂O (containing a known amount of DMSO as an external standard) and filtered through syringe filter to remove any suspending catalyst. PNBA % conversion, and % yield of PABA and intermediates were quantified from ¹H NMR analysis (based on the mole amount of internal standard DMSO present in the NMR sample) by comparing with analytical samples. For para-nitrobenzoic acid PNBA and para-aminobenzoic acid PABA, representative reference standard samples were prepared from commercially available HPLC grade reagent samples. Intermediates **4**, **5**, and **6** observed in the reaction mixtures were subsequently isolated and synthesized from separate batch reactions as described in the supporting information. Quantitative analysis of such intermediates present in the batch reaction mixtures were done by comparing with authentic samples as prepared.
- (14) **Typical procedure for flow hydrogenation:** Construction of the packed-bed reactor with necessary gas and liquid feed-lines, gas-liquid separators, etc., are described in the supporting information. For a flow experiment: initially the reactor was primed with a continuous flow of 0.58 M NaOH solution under 10 bar hydrogen pressure (gas flow rate measured using bubble-flow metre, average flow rate under atmospheric condition: 83 mL/min). Gas and liquid flow was sustained at 10 bar pressure for 30 min to

equilibrate the gas-liquid flow inside the packed bed and stabilise the gas-liquid flow through the packed bed of 5% Pd/C. Then the liquid flow was stopped and the packed bed was sealed (by closing upstream and downstream one-way valves) to maintain 10 bar hydrogen pressure at 80 °C for pre-reducing the catalyst.

After 2 hours of pre-reduction of the catalyst, the valves were opened and hydrogen flow was maintained along with the desired flow rate of PNBA (0.5 M in 0.58 M NaOH aqueous solution). Initial reaction mixture collected at the gas-liquid separator (3 times the

internal volume of the packed bed reactor column) was discarded. Reaction mixtures after the flow-equilibration and reaching steady-state were collected for ¹H NMR analysis as described in the preceding section for batch reaction analysis.

For Peer Review

Supporting Information

FAST Hydrogenations as a Continuous Platform for Green Aromatic Nitroreductions

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General experimental section

¹H and ¹³C NMR were recorded on a Bruker 400 Mz spectrometer with the residual solvent peak as the internal reference (D₂O = 4.70 ppm). ¹H resonances are reported to the nearest 0.01 ppm. ¹³C-NMR spectra were recorded on the same spectrometer with the central resonance of the dimethyl sulfoxide peak (added as external standard) as the internal reference (DMSO = 39.39). All ¹³C resonances are reported to the nearest 0.1 ppm.

The multiplicity of proton NMR (¹H) signals are indicated as: s = singlet, d = doublet, dt = doublet of triplet. Coupling constants (*J*) are quoted in Hz and reported to the nearest 0.1 Hz. Waters Xevo G2-XS QToF Mass spectrometer was used to analyse mass.

Materials

Analytical grade (>98% purity) reagents: sodium hydroxide (solid pellets), 4-nitrobenzoic acid, 3-nitrobenzoic acid, 2-nitrobenzoic acid, 4-aminobenzoic acid, 3-aminobenzoic acid, anthranilic acid were purchased from Sigma-Aldrich and used without further purification.

NMR-grade D₂O (Sigma-Aldrich) was used for ¹H and ¹³C NMR with >99.0% purity Dimethyl sulfoxide (DMSO) was used as a reference standard in the NMR solution.

Chemicals used in this work as starting materials, reference standard for products.

Deionized water was used to prepare all analytical samples and solutions of starting materials.

All standard Swagelok tube and fittings were used to construct the Hydrogenation rig.

Mass flow controller and back pressure regulator were purchased from Bronkhorst High-Tech B.V.

5% Pd/C was kindly provided by Arran Chemical Co, a partner of Almac Group.

Experimental

All conventional batch reactions were performed in a Hazard Evaluation Laboratory (HEL) autoclave reactor. The reactor was fitted with a gas inducing impeller, baffles and online hydrogen consumption monitoring. The reactor was heated by an internal heating coil and the temperature was monitored by a thermocouple.

Batch experiment (ref: Figure 2 in the manuscript): The reactor was charged with a 5 wt% Pd/C catalyst (0.02 g) and 30 mL of reaction mixture containing 2.5 g (15 mmol) *para*-nitrobenzoic acid PNBA with 0.695 g (17.4 mmol) of NaOH. PNBA and NaOH concentrations in the aqueous solution are 0.50 M and 0.58 M, respectively. The reactor was sealed and purged with nitrogen under stirring at 1250 rpm. Then the reactor temperature was set to reach 80 °C. Upon reaching 80 °C stirring was stopped to allow the solid catalyst settle at the bottom of the reactor. Then the reactor was purged with hydrogen, pressurized at 10 or 5 bar hydrogen pressure, and stirring started at 1250 rpm to allow hydrogenation reaction take place. Several samples of 200 µL of reaction mixtures were periodically withdrawn from the reactor (2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45 min, 1 h and 1.5 h). Each sample was diluted with 1.8 mL of D₂O (containing known amount of DMSO as an external standard) and filtered through syringe filter to remove any suspending catalyst. Conversion, yield and intermediate composition were analysed and quantified from ¹H NMR analysis (based on the mole amount of internal standard DMSO present in the NMR sample) by comparing with analytical samples. For *para*-nitrobenzoic acid PNBA and *para*-aminobenzoic acid PABA, representative reference standard samples were prepared from commercially available HPLC grade reagent samples as stated in the materials section. For intermediates **4**, **5** and **6**, analytical standards were prepared by the following methods.

Azoxy-intermediate (Ar-N(O)=N-Ar)

4,4'-dicarboxylate azoxybenzene disodium 4:

A batch reaction (as described in the typical batch reactor protocol section above) with 0.01 g 5 wt % Pd/C and 30 mL 0.5M PNBA (in 0.58 M NaOH aqueous solution) carried out at 80 °C under 10 bar hydrogen pressure. At 10 min of reaction time, the hydrogen pressure is rapidly reduced and the reaction mixture is purged with nitrogen to quench any hydrogenation. At this stage the reaction mixture was filtered through filter paper and plug of Celite to remove any suspending catalyst. When this reaction mixture was left at room temperature a brown solid was precipitated. This brown solid was repeatedly washed with small amount of water (10 mL each time, for 3 times) and centrifuged to give intermediate **4** (4,4'-dicarboxylate azoxybenzene disodium) as a pale brown solid upon vacuum drying. Aqueous solution of **4** was analysed by ¹H, ¹³C NMR and Mass Spectroscopy.

^1H NMR (400 MHz, D_2O): δ 8.18 (d, J = 4.0 Hz, 2H), 7.96-7.89 (d, J = 4.0 Hz, 5H), 7.82 (d, J = 4.0 Hz, 1H), ^{13}C NMR (75 MHz, D_2O): δ 175.1, 174.3, 154.5, 145.0, 148.5, 139.8, 138.5, 137.0, 124.8, 122.0.

HRMS (ESI, m/z): Molecular formula in disodium carboxylate form $\text{C}_{14}\text{H}_8\text{N}_2\text{Na}_2\text{O}_5$. Appeared as $\text{M} = \text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_5$ ($2\text{Na} \rightarrow 2\text{H}$), calculated for deprotonated form $\text{C}_{14}\text{H}_9\text{N}_2\text{O}_5$ $[\text{M}-\text{H}]^-$ 285.0511, found 285.0511

Diazo-intermediate 5 (Ar-N=N-Ar)

(4,4'-(diazene-1,2-diyl)dibenzoate disodium 5:

A batch reaction (as described in the typical batch reactor protocol section above) with 0.02 g 5 wt % Pd/C and 30 mL 0.5M PNBA (in 0.58 M NaOH aqueous solution) carried out at 80 °C under 10 bar hydrogen pressure. At 10 min of reaction time, the hydrogen pressure is rapidly reduced and the reaction mixture is purged with nitrogen to stop any hydrogenation. At this stage the reaction mixture was filtered through filter paper and plug of Celite to remove any suspending catalyst. When this reaction mixture was left at room temperature orange muddy-solid was precipitated. This orange solid was repeatedly washed with small amount of water (10 mL each time, for 3 times) and centrifuged to give intermediate **5** (4,4'-(diazene-1,2-diyl)dibenzoate disodium) as a bright orange solid upon vacuum drying. Aqueous solution of **5** was analysed by ^1H , ^{13}C NMR and Mass Spectroscopy.

^1H NMR (400 MHz, D_2O): δ 7.95 (d, J = 4.0 Hz, 4H), 6.79 (d, J = 7.79, 4.0 Hz, 4H). ^{13}C NMR (75 MHz, D_2O): δ 174.7, 153.5, 139.2, 129.9, 122.3.

HRMS (ESI, m/z): Molecular formula in disodium carboxylate form $\text{C}_{14}\text{H}_8\text{N}_2\text{O}_4\text{Na}_2\text{O}_4$. Appeared as $\text{M} = \text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_4$ ($2\text{Na} \rightarrow 2\text{H}$), calculated for protonated form $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 271.0719, found 271.0717, calculated for deprotonated form $\text{C}_{14}\text{H}_9\text{N}_2\text{O}_4$ $[\text{M}-\text{H}]^-$, found 269.0562, found 269.0562.

Hydrazo-intermediate 6 (Ar-NH-NH-Ar)

4,4'-(hydrazine-1,2-diyl)dibenzoate disodium 6

Generation of diazo-derivative **6** was observed in the reaction mixtures (^1H NMR) from batch reactions. However, it is known that hydrazo group aerobically oxidises to corresponding azo-functionality ($\text{Ar-NH-NH-Ar} \rightarrow \text{Ar-N=N-Ar}$) under alkaline and aqueous condition [Ref: Zhang, L.; Xia, J.; Li, Q.; Li, X; Wang, S. *Organometallics* **2011**, 30, 3, 375.]

Hence, isolation of diazo-derivative 4,4'-(hydrazine-1,2-diyl)dibenzoate disodium **6** from the hydrogenation reaction mixture was not possible. However, it was synthesized via a literature procedure [Ref: Bouillon, M. E.; Meyer, H. H. *Tetrahedron* **2016**, 72(23), 3151.]

In a 50 mL two-neck round-bottom flask was taken 100 mg of 4,4'-(diazene-1,2-diyl)dibenzoate disodium **5** with 300 mg of ammonium chloride and 500 mg of zinc dust in 5 mL deionized water. The reaction mixture was purged with nitrogen gas to remove any dissolved air/oxygen. The reaction mixture was then stirred at room temperature under nitrogen blanket (nitrogen balloon at atmospheric pressure). After 6 hours of stirring the mixture was allowed to settle, a small portion of the supernatant solution was filtered through a small Celite plug to remove all insoluble inorganics. ^1H NMR in D_2O of the reaction mixture showed production of 4,4'-(hydrazine-1,2-diyl)dibenzoate. In agreement with literature data (^1H NMR spectrum) of similar 4,4'-substituted 1,2-diarylhydrazines [Ref: Wang, F.; Planas, O.; Cornella, J. *J. Am. Chem. Soc.*, **2019**, *141*, 4235] and matches with the diazo-derivatives observed in the course of hydrogenation reactions.

^1H NMR (400 MHz, D_2O): δ 7.65 (dt, $J = 8.0, 4.0$ Hz, 4H), 6.79 (dt, $J = 8.0, 4.0$ Hz, 4H).

Catalyst recycling study:

For catalyst recycling (ref: Figure 4 in the manuscript) 0.20 g of 5 wt% Pd/C catalyst was taken with 5 mL of water in an autoclave reactor described above. The mixture was purged with hydrogen under stirring and pressurized at 10 bar hydrogen pressure. The mixture was then heated at 80 °C and stirred under 10 bar hydrogen pressure for 2 hours to accomplish reduction of all palladium present in the mixture. Stirring and heating was stopped. As the catalyst settled down at the bottom of the reactor, the reactor was opened and quickly added to it 25 mL aqueous solution of 2.5 g PNBA with 0.695 g NaOH. The final concentration of PNBA and NaOH became 0.50M and 0.58M, respectively. Then the mixture was purged with nitrogen at 5 bar pressure and reaction temperature was raised to 80 °C. At this point, stirring was stopped to allow all catalyst settle down at the bottom, nitrogen atmosphere was exchanged with hydrogen under no stirring and agitation. Once the hydrogen pressure was set at 10 bar, stirring started and analytical samples (200 μL of reaction mixtures) were withdrawn from the reactor at regular interval (2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45 min, 1 h and 1.5 h). Each sample were diluted with 1.8 mL of D_2O (containing known amount of DMSO as an internal standard) and filtered thorough syringe filter to remove any suspending catalyst. Conversion, yield and intermediate composition were analysed and quantified from ^1H NMR analysis (based on the mole amount of internal standard DMSO present in the NMR sample) by comparing with analytical samples.

After the reaction mixture was cooled down to room temperature, hydrogen gas was released, the reactor was cooled to room temperature, and reactor content was taken in a centrifuge tube. Centrifugation at 5000 rpm for 30 min, separated the catalyst from the reaction mixture. Careful decantation of the mother liquid left moist catalyst bed at the bottom of the centrifuge tube. Care was taken so that the decantation did not allow any loss of solid catalyst. The recovered catalyst was washed 3 more times with 0.58 M NaOH solution (30 mL each time) to remove any residual PNBA, PABA or intermediates. Then the solid catalyst was mixed with a fresh batch of 5 mL of water, pre-reduced with hydrogen gas as described above. After releasing the hydrogen as the reaction mixture cooled off to room

temperature, 25 mL of PNBA in NaOH aq. solution (to achieve final solution concentration: 0.50 M PNBA with 0.58 M NaOH) was added quickly to the pre-reduced palladium catalyst. Hydrogenation of the mixture and sampling for analysis were performed in the same manner as described above.

Continuous flow reaction:

Packed-bed column preparation:

A 12 cm long ½" Swagelok tube (internal diameter 0.94 cm) is sequentially filled with: quartz wool (packing length 1 cm), 212-300µm acid-washed glass beads (2 cm), mixture of 1.0 g 5 wt% Pd/C and glass beads (catalyst bed-length 6 cm), glass beads (2 cm) and quartz wool (1 cm). The choice of the material was made to ensure the beads are clean and free from any contamination and inert under the reaction conditions. The dimensions of the beads were selected in the range of 212-300 µm, to ensure the similar aspect ratio as that of the catalyst particle size. This is done to achieve uniform packing across the catalyst bed and to avoid channelling of liquid and gas flow through the catalyst bed. Top-end of the packed bed column was connected to a liquid feed line (via Shimadzu LC-20AD HPLC pump) and hydrogen gas cylinder (via Mass flow controller). The bottom-end of the packed-bed column was connected to a sample port (via gas-liquid separator) and back pressure regulator. Packed-bed column was wrapped with flexible heating tape which maintained 80 °C reaction temperature. The flow rig was then primed by flowing 0.58 M NaOH solution under 10 bar hydrogen pressure (gas flow rate measured using bubble-flow metre, average flow rate under atmospheric condition: 83 mL/min). Gas and liquid flow was sustained at 10 bar pressure for 30 min to equilibrate the gas-liquid flow inside the packed bed. Then the liquid flow was stopped and the packed bed was sealed (by closing upstream and downstream one-way valves) to maintain 10 bar hydrogen pressure at 80 °C for pre-reducing the catalyst.

After 2 hours of pre-reduction of the catalyst, valves were opened and hydrogen flow is maintained along with desired flow rate of PNBA (0.5 M in 0.58 M NaOH aqueous solution). Initial reaction solution collected at the gas-liquid separator (3 times the internal volume of the packed bed reactor column) was discarded. Reaction mixtures after the flow-equilibration and reaching steady-state were collected for ¹H NMR analysis as described in the preceding section for batch reaction analysis.

Reaction with 5 bar Hydrogen pressure were conducted exactly under same conditions as applied for 10 bar hydrogen pressure. Gas flow rate was maintained at 83 mL/min by adjusting the cylinder pressure (rather than changing the MFC input/output settings).

Larger packed-bed column for scaling up was prepared based on the catalyst-filler (quartz wool, glass beads) ratio used above, however this case: 3.0 g of 5 wt% Pd/C was used.

Residence time distribution:

A residence time distribution study was performed by injecting 50 μL of aminobenzoic acid (0.5 M) tracer through the packed bed (6 cm length) along with NaOH aq. solution under 10 bar hydrogen pressure and 80 $^{\circ}\text{C}$. The effluent solution was collected and analyzed with UV-Vis spectroscopy. Analysis of residence time distribution function $E(t)$ versus the sampling time showed that at 2 mL/min flowrate of liquid, 60% of tracer exited the reactor between 4-8 min.