

# FAST Hydrogenations as a Continuous Platform for Green Aromatic Nitroreductions

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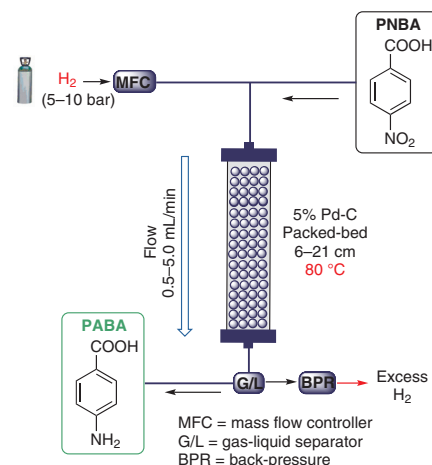
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**Abstract** A continuous-flow packed-bed catalytic reactor has been developed for hydrogenation of aromatic nitrobenzoic acids in water to produce the corresponding anilines. These hydrogenations are green, more efficient, less consumptive, and safer than the conventional reduction process. Various industrially important aromatic amines have been produced in excellent yields and with high throughput. The optimized continuous-flow reduction process produces no detectable genotoxic intermediates, unlike the corresponding batch reduction. The reactor is modular in design and can be scaled up to produce several kilograms of product per day without extensive redesign.

**Keywords** green chemistry, catalytic hydrogenation, continuous-flow packed-bed reactor, nitrobenzoic acids, anilines

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

A custom-built packed-bed flow hydrogenation rig, suitable for proof-of-concept (PoC) studies and low-kilogram levels of manufacture has been designed and built. The PoC hydrogenations reported here were carried out on

this laboratory-scale flow rig. A complementary rig offers direct scale up to a larger packed-bed reactor capable of a throughput of up to 10 kg/week. 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 by using aromatic nitrobenzoic acid substrates, exploiting their acid functionality to facilitate water-mediated processing to produce the corresponding aminobenzoic acid. This method has also resulted in critical control over the formation of genotoxic impurities (GTIs), which is of pronounced importance in the manufacture of active pharmaceutical ingredients (APIs).<sup>3</sup>

Aminobenzoic acids and their derivatives belong to an important class of chemicals that are relevant in the pharmaceutical, dye, and flavour and fragrance industries.<sup>4</sup> Catalytic hydrogenation of nitrobenzoic acids is a direct and straightforward way of accessing these aniline derivatives.<sup>5</sup> However, nitrobenzoic acids and the resulting aminobenzoic acids have limited solubility in alcohols (ethanol, methylated spirits, isopropyl alcohol, etc.), which are economic and process-friendly solvents.<sup>6</sup> Poor solubility of starting materials, products, and any intermediates or byproducts formed in a synthetic process is one of the most formidable challenges in implementing continuous-flow technology for any process chemistry and for scale up. Precipitation of any reaction component can lead to clogging of a flow reactor, back-pressure build-up, and eventual process failure. To maximize throughput from the process, the reaction concentration should be as high as possible while sufficient

solubility is ensured. In this work, the presence of the carboxylic acid moiety provides adequate solubility in aqueous alkaline solutions. This has two benefits for processing, in permitting the use of a high-concentration reaction feedstock and the use of water as a green and economical solvent. Counter to that, the use of an aqueous medium has a drawback in catalytic hydrogenation in that  $H_2$  has a lower solubility in water than in more-conventional organic solvents; for example, the solubility of hydrogen in water is least one order of magnitude lower than that in acetonitrile or ethanol.<sup>7</sup> In addition, the presence of a base (NaOH) further reduces the solubility of hydrogen.<sup>7</sup> Hence, aqueous-phase hydrogenations of nitrobenzoic acids under alkaline conditions require an elevated hydrogen pressure, which can create gas-liquid mass-transfer limitations when the reaction is scaled up, due to lowering of the gas-liquid contact area-to-volume ratio.

Considering these factors, we used Almac's flow-assisted synthesis technology (FAST) platform to demonstrate the catalytic hydrogenation of nitrobenzoic acids in aqueous solutions at low  $H_2$  pressures. Model substrates were selected that are industrially relevant, namely *p*-, *o*-, and *m*-nitrobenzoic acids. Derivatives of the resulting aminobenzoic acids are used as dermatological drugs and as local anaesthetics, as well as in the dye industry and in pharmaceuticals (Figure 1).<sup>4,8</sup>

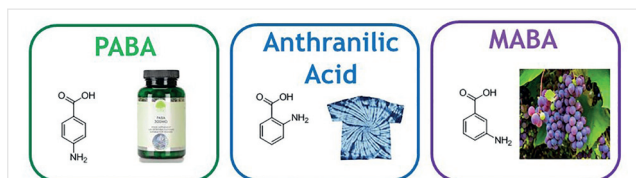
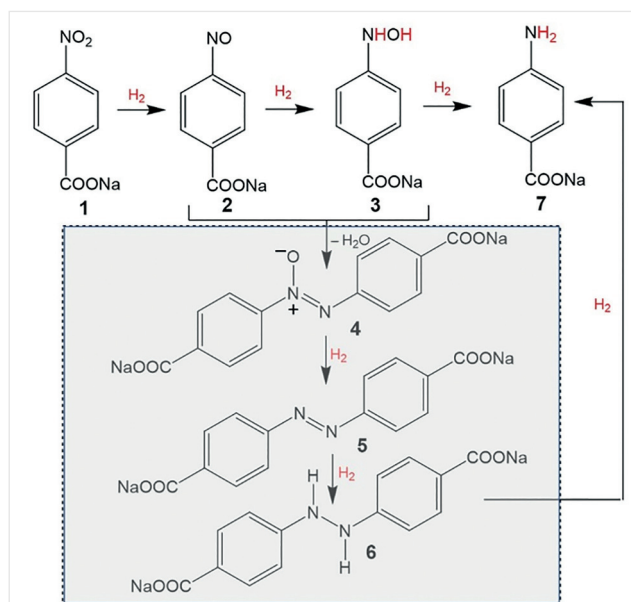


Figure 1 Model substrates for flow hydrogenations

### Batch Investigations

To establish process parameters and generate reference materials, the hydrogenation was first performed in a conventional autoclave reactor. 30 mL of an aqueous solution of *p*-nitrobenzoic acid (PNBA; 2.5 g, 0.5 M) and NaOH (0.695 g, 0.58 M) was hydrogenated at 10 bar  $H_2$  pressure and 80 °C at various catalyst loading ( $w_{\text{catalyst}}/w_{\text{substrate}}\%$ : 2, 4 and 8 wt/wt %).<sup>9</sup> Further experimental details are provided in the Supporting Information. The reaction mixture was periodically sampled and then analyzed by  $^1H$  NMR spectroscopy to determine the percentage conversion of PNBA and the percentage yield of the product and associated intermediates (Scheme 1). The rate of conversion of PNBA increased linearly with increasing loading of the palladium catalyst ( $g/cm^3$ ) in the reaction mixture, indicating an absence of external mass-transfer resistance (Figure 2).

When the hydrogen pressure was reduced from 10 bar to 5 bar with an 8 wt/wt% catalyst loading, the conversion of PNBA proceeded at a much slower rate, possibly due to



Scheme 1 Catalytic *p*-nitrobenzoate reduction mechanism

the lower concentration of hydrogen in the solution phase (Figure 3).<sup>7</sup> From analysis of the batch experiments, a key observation was that despite the complete consumption of

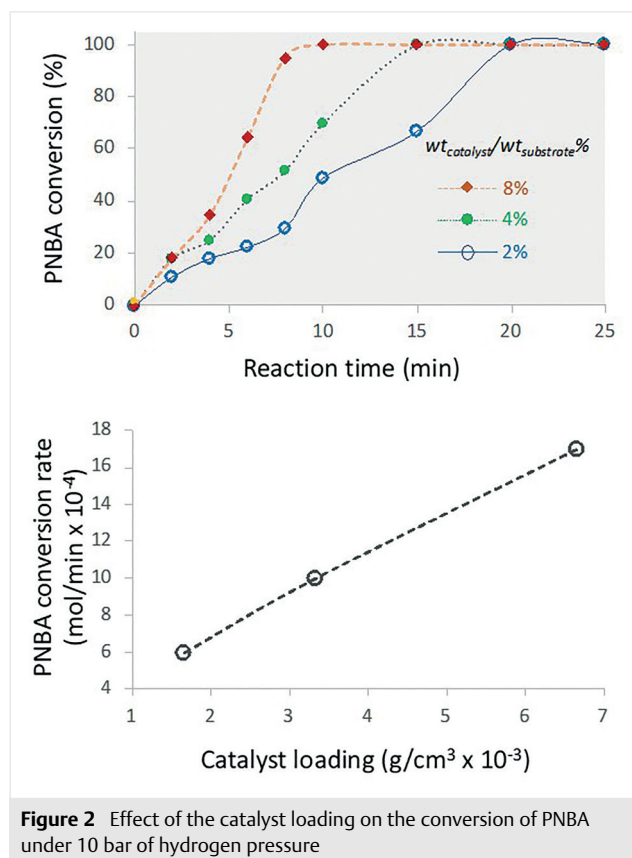
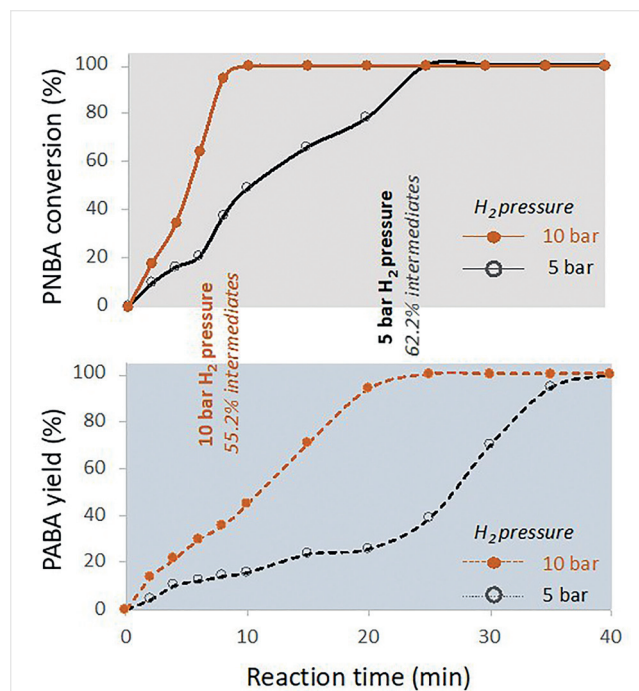


Figure 2 Effect of the catalyst loading on the conversion of PNBA under 10 bar of hydrogen pressure

PNBA, which occurred at 10 and 20 minutes at hydrogen pressures of 10 and 5 bar, respectively, this did not correlate to 100% product formation.  $^1\text{H}$  NMR spectroscopy showed that significant amounts of the reaction intermediates **4**, **5**, and **6** (Scheme 1), which are potential GTIs, were present along with the target product, PABA.



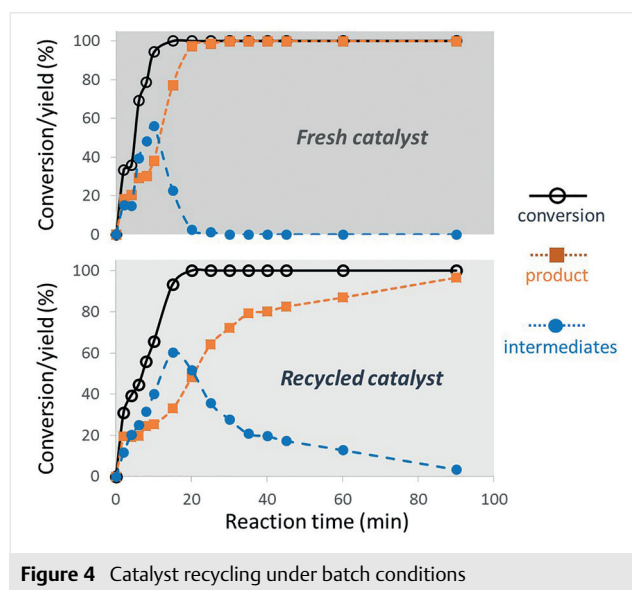
**Figure 3** Pressure effect on conversion and yield under batch conditions

Nitro-to-amine reduction through catalytic hydrogenation is a well-studied reaction for nitroaromatic compounds.<sup>10</sup> The reaction proceeds by one of the two pathways, as shown in Scheme 1. Pathway 1 proceeds via the nitro compound **2** and the hydroxylamine intermediate **3** to give the product **7**. Pathway 2 involves condensation of nitroso compound **2** with the hydroxylamine **3** to give azoxy derivative **4**, which undergoes successive hydrogenations to produce azo compound **5**, hydrazo compound **6**, and, finally, the amine product **7**.

In the batch experiments for conversion of PNBA to PABA, analysis of products 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** nor **3** was detectable by  $^1\text{H}$  NMR. Condensation of **2** and **3** to produce an azoxy derivative is an irreversible process and is facilitated by basic conditions in the reaction mixture.<sup>4a</sup> Since the second pathway requires a total of 4.5 equivalents of hydrogen (in comparison to the 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 build-up of GTIs in the reaction mixture. At a lower

hydrogen pressure (5 bar), the reaction mixture contains more GTIs at all conversion levels of PNBA than observed in the reaction performed at 10 bar hydrogen pressure (Figure 3). At a larger scale, gas-liquid-solid mass transfer will be a decisive factor in the production of high-purity amines if the formation of GTIs is to be avoided.

Another important economic aspect of catalytic hydrogenations is the necessity for an expensive transition-metal catalyst, such as palladium or platinum. Flow hydrogenations offer a number of advantages in this respect. 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 with the reaction using fresh catalyst (Figure 4). However, the rate of formation of the PABA product with fresh catalyst was significantly higher than that with recycled catalyst. With recycled catalyst, faster accumulation and slower conversion of intermediates **4**, **5**, and **6** contributed to lower yields of the PABA product, even at higher percentage conversions to PABA; further details are provided in the Supporting Information.

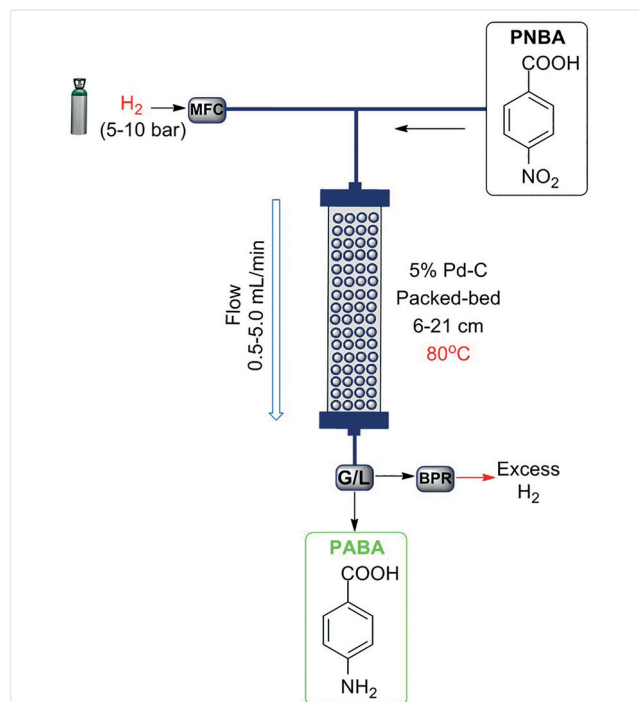


**Figure 4** Catalyst recycling under batch conditions

Excellent multiphase mass transfer and mixing are attributes of continuous-flow chemistry in general and for gas-liquid-solid reactions in particular.<sup>11</sup> In continuous-flow catalytic reactions, catalysts are generally packed in cartridge-type beds for continuous operation, regeneration, and reuse. 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 that is in contact with solid catalyst particles and in tandem flow with the gas layer. This configuration permits rapid diffusion of the gas into the thin film of liquid, resulting in rapid mixing of the dissolved gas, substrate, and catalyst, and consequently a faster reaction rate.<sup>12</sup>

### Flow Investigations

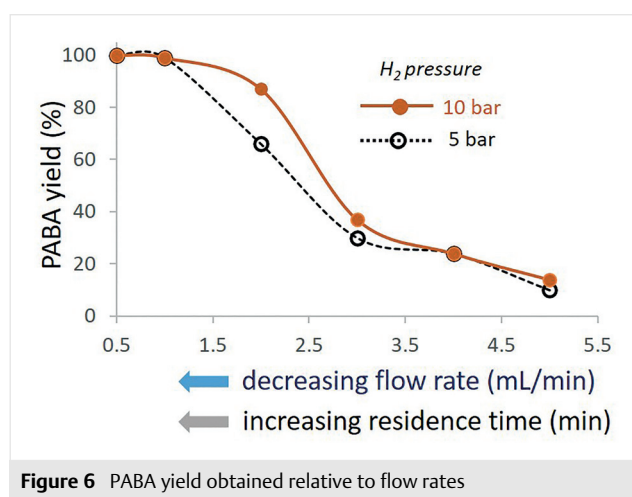
The reduction of nitro moieties should benefit from rapid hydrogen transfer from the gaseous phase to an aqueous phase and the more rapid saturation of the aqueous phase with hydrogen. This should facilitate faster (higher productivity) conversion of the substrate in a continuous-flow set-up. The FAST 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 a 0.5 M aqueous solution of PNBA delivered to the system by a HPLC pump. The resulting gas-liquid mixture trickled down a packed-bed column (1.0 g of 5% Pd/C catalyst and 5.9 g of 212–300  $\mu\text{m}$  glass beads) housed in a stainless-steel tube that was externally heated to maintain a constant reaction temperature. A back-pressure regulator (BPR) fitted downstream maintained the target pressure inside the catalyst bed. A gas-liquid separator permitted ready separation of the reaction solution from unused hydrogen gas as an effluent. The reaction mixture was subsequently separated and analyzed offline to monitor the progress of the reaction.<sup>13</sup>



**Figure 5** FAST hydrogenation flow rig. MFC = mass flow controller; G/L = gas-liquid separator; BPR = back-pressure regulator.

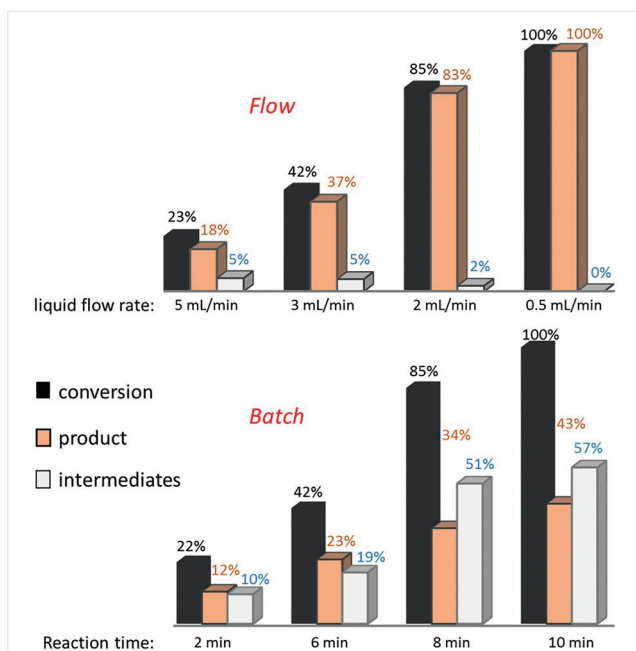
A residence-time distribution (RTD) study was performed by injecting 50  $\mu\text{L}$  of *p*-aminobenzoic acid (0.5 M) as a tracer through the packed bed (6 cm length) along with aqueous NaOH solution (2 mL/min) under 10 bar of hydrogen pressure at 80 °C. The effluent solution was collected and analyzed by UV-vis spectroscopy; details of the RTD analysis are provided in the Supporting Information. The mean residence time was determined to be 6.6 minutes.

After characterization of the reactor, model flow reactions were carried out at hydrogen pressures of 5 and 10 bar (Figure 6). A 0.5 M aqueous solution of PNBA with 0.58 M NaOH was injected through the packed bed (6 cm length) at 80 °C and various flow rates from 0.5 to 5.0 mL/min. At slower liquid flow rates (0.5 or 1.0 mL/min), complete conversion of PNBA to PABA was achieved at both 5 and 10 bar of hydrogen pressure. When the flow rate was increased, the PNBA conversion gradually fell. 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.



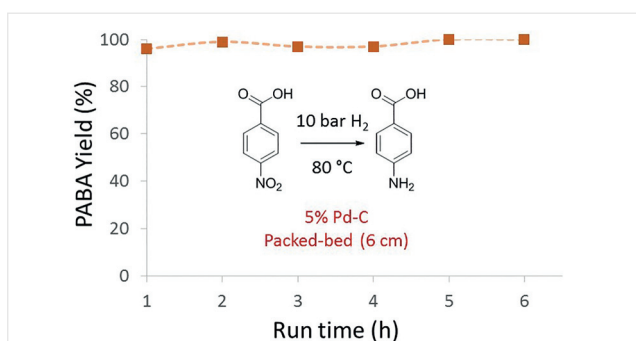
**Figure 6** PABA yield obtained relative to flow rates

Under continuous flow, <sup>1</sup>H NMR analysis of the reaction samples showed that only two reaction components were predominantly present: PNBA and PABA. At faster flow rates, such as 3 or 5 mL/min, <5% of intermediates **4** and **5** were observed at relative conversions of 22 and 42%, respectively. At flow rates of 2.0 or 0.5 mL/min, when 85 and 100% conversion was achieved, only traces of intermediates or no intermediates were observed (Figure 7).<sup>14</sup> This indicates that the hydrogenation follows the same pathway as the batch reaction, but with much faster subsequent conversion of intermediates into PABA. Note that the reaction in a batch process (300 mg 5% Pd/C catalyst; 12 wt/wt% catalyst loading) showed the presence of significant amounts of intermediates at comparable conversions of PNBA after 2, 6, 8, or 10 minutes of reaction time: percentage conversion (percentage intermediate) = 22% (11%), 42% (19%), 85% (51%), and 100% (57%), respectively. The observed differences in the composition of the reaction mixture indicates that under continuous flow, the aqueous phase is saturated with sufficient hydrogen to convert any intermediates formed during the residence time into the final amine product, whereas under batch conditions, a lack of sufficient of hydrogen in the solution phase results in the accumulation of intermediates over time.



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

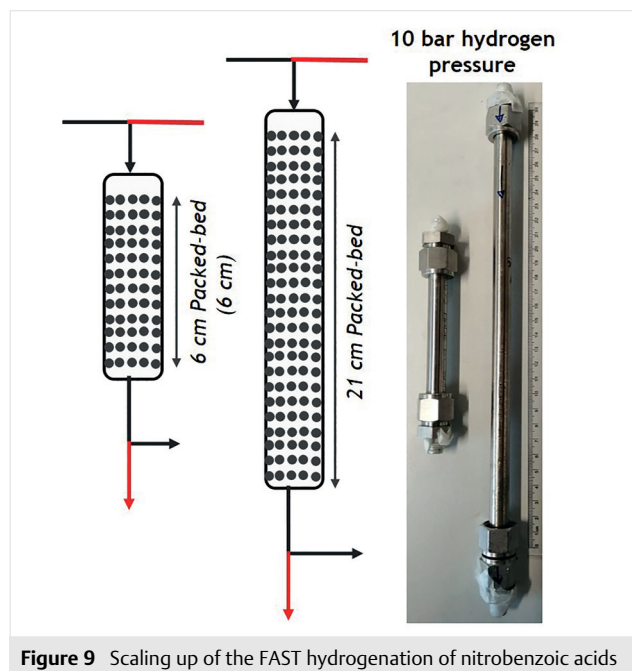
To demonstrate the robustness of the flow system and the catalyst bed for long-term efficient operation over an extended period of time, a continuous operation was carried out over six hours. In comparison with the batch process, the confined catalyst packed bed showed undiminished activity over six hours of continuous operation at 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 GTIs identified in the product solution.



**Figure 8** Catalyst packed-bed stability study with the FAST hydrogenation rig

The system was then scaled up 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 a quantitative conversion of PNBA into PABA was observed with

continued control over the formation of intermediates. The robustness of the flow protocol developed was also demonstrated for *meta*- and *ortho*-substituents, *m*-aminobenzoic acid (MABA) and anthranilic acid both being obtained in quantitative yields and without the presence of any detectable intermediates.



**Figure 9** Scaling up of the FAST hydrogenation of nitrobenzoic acids

In conclusion, the benefits of FAST hydrogenations with an environmentally favourable aqueous protocol have been demonstrated by using a custom-built packed-bed flow rig. This flow system gave superior results to those achieved under batch conditions in terms of both productivity and minimization of GTI formation. The robustness of this flow-mediated hydrogenation has been shown by its application to a range of *ortho*-, *meta*-, and *para*-substituted benzoic acid substrates under aqueous alkaline conditions. The use of water increased the product yield, lowered impurity levels, and maximized the utilization of hydrogen gas, affording a greener and safer chemical process.

## Funding Information

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## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1610751>.

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- (9) **Batch Hydrogenation of *p*-Nitrobenzoic Acid**  
The batch reactions were all performed in a 100 mL stainless-steel stirred-tank reactor (Autoclave Engineers, Erie, PA). In a typical reaction, the reactor was charged with 5 wt% Pd/C catalyst (0.02 g) and an aqueous mixture (30 mL) of *p*-nitrobenzoic acid (PNBA; 2.5 g, 15 mmol) and NaOH (0.695 g, 17.4 mmol). The concentrations of PNBA and NaOH in the aq solution were 0.50 M and 0.58 M, respectively. The reactor was sealed and purged three times with N<sub>2</sub>, and then the mixture was heated to 80 °C with stirring at 1250 rpm. The reactor was pressurized to 10 or 5 bar with H<sub>2</sub>, at which point the reaction started. 200 μL aliquots of the reaction mixtures were withdrawn from the reactor at 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45, 60, and 90 min. Each sample was diluted with 1.8 mL of D<sub>2</sub>O containing a known amount of DMSO as an external standard, and filtered through a syringe filter to remove any suspended catalyst. The percentage conversion of PNBA and the percentage yields of *p*-aminobenzoic acid (PABA) and its various intermediates were quantified by means of <sup>1</sup>H NMR analysis. Reference samples for PNBA and PABA were prepared from commercially available HPLC-grade reagent samples. Intermediates **4**, **5**, and **6**, observed in the reaction mixtures, were subsequently isolated and synthesized by separate batch reactions, as described in the Supporting Information. Quantitative analysis of these intermediates in the batch reaction mixtures was performed by comparison with these authentic samples.
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- (13) **Flow Hydrogenation of *p*-Nitrobenzoic Acid**  
The construction of the packed-bed reactor and its associated gas- and liquid-feed lines, gas-liquid separators, etc., are described in the Supporting Information. For a flow experiment, the reactor was primed with a continuous flow of 0.58 M NaOH solution under 10 bar of hydrogen pressure. The gas flow rate was measured by using bubble flowmeter; the average flow rate under atmospheric conditions was 83 mL/min. The gas and liquid flow were kept under 10 bar pressure for 30 min to equilibrate the gas-liquid flow inside the packed bed and to stabilize the gas-liquid flow through the packed bed of 5% Pd/C. The liquid flow was then stopped and the packed bed was sealed by closing the upstream and downstream one-way valves to maintain a 10 bar hydrogen pressure at 80 °C to prereducate the catalyst. After 2 h of prereducate of the catalyst, the valves were opened and hydrogen flow was maintained along with the desired flow rate of the PNBA solution (0.5 M in 0.58 M NaOH aq solution). The initial reaction mixture (three times the internal volume of the packed-bed reactor column) collected at the gas-liquid separator was discarded. The subsequent mixtures, after flow equilibration and attainment of a steady state, were collected for <sup>1</sup>H NMR analysis as described for the batch reaction.<sup>9</sup>
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