

Improved Continuous Flow Processing: Benzimidazole Ring Formation via Catalytic Hydrogenation of an Aromatic Nitro Compound

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Supporting Information

ABSTRACT: In the development of a new route to bendamustine hydrochloride, the API in Treanda, the key benzimidazole intermediate **5** was generated via catalytic heterogeneous hydrogenation of an aromatic nitro compound using a batch reactor. Because of safety concerns and a site limitation on hydrogenation at scale, a continuous flow hydrogenation for the reaction was investigated at lab scale using the commercially available H-Cube. The process was then scaled successfully, generating kilogram quantities on the H-Cube Midi. This flow process eliminated the safety concerns about the use of hydrogen gas and pyrophoric catalysts and also showed 1200-fold increase in space–time yield versus the batch processing.

■ INTRODUCTION

Recently we reported a new route to bendamustine hydrochloride **1** (Scheme 1), the API in Treanda, which was approved by the U.S. FDA for the treatment of chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin's lymphoma (NHL).¹ In the development of that novel route, a new and efficient approach for the construction of the 1,2-substituted benzimidazole core was established. Compound **5** can be readily produced via reduction of the two nitro groups, ring closure of the five-membered ring, and subsequent elimination of water. The hydrogenation of **4** was optimized and scaled to make kilograms of product in a pressurized batch reactor. Although successful, the scale-up presented several challenges. First, the reaction required a high inventory of available hydrogen, and hydrogen starvation led to elevated levels of impurities. Hydrogen starvation may result from inadequate inventory of hydrogen in the batch reactor or poor mixing of the four phases of reactants. However, the large amount of hydrogen gas raised a potential safety concern.² The catalytic hydrogenation of **4** consists of four phases initially, H₂ gas, solvent, substrate solid, and catalyst, and therefore the impact of mixing effects is more pronounced in the batch reaction where interfacial surface area limits mass transfer and more likely induces microzones of hydrogen starvation.³ Second, the reduction is extremely exothermic, generating 1172 kJ/mol of **4** in a single thermal event and representing a 135 °C adiabatic temperature rise. Control of this exotherm requires a system with excellent heat transfer and cooling capacity.

In a continuous flow process, the inventory of hydrogen gas is minimal but still remains at a high ratio versus substrate.⁴ Impurity issues associated with hydrogen starvation as well as safety concerns with high hydrogen inventories are therefore eliminated. In addition, a small flow reactor can provide turbulent mixing with high surface-to-volume ratios.^{5,6} This allows for excellent heat transfer and thus minimizes formation of the side products that were generated from poor

micromixing. The efficiency of energy usage is also increased with a flow process.^{6,7}

In a flow process, a sealed cartridge of catalyst can be utilized; thus, safety and handling concerns associated with weighing, transfer, and filtration of pyrophoric metal on solid support in the batch operation are eliminated.⁸ During the preparation of **5** it was necessary to complete the dehydration of intermediate **7** (Scheme 2) by treatment with acid at elevated temperatures. We hypothesized that the higher temperatures that are achievable in a continuous flow process might drive the dehydration to completion in one step and thus reduce the reaction cycle time.⁹

In short, considering cost, safety, purity and quality control, site-imposed limits on scale, and throughput of the batch process for catalytic hydrogenation of aromatic nitro compound **4**, we envisioned that a continuous flow process could be a better alternative. Interestingly, there are few literature references of continuous flow processing for these kinds of nitro reductions,¹⁰ although these reactions are industrially useful in the manufacture of vital agrochemicals, dyes, polymers, and pharmaceutical products.¹¹ Herein, we describe our efforts in converting the batch catalytic hydrogenation of **4** into a continuous flow process using the H-Cube and H-Cube Midi, two commercially available flow hydrogenation reactors.¹² Details about the challenges we encountered in investigating this technology along with the process we successfully scaled are disclosed.

■ RESULTS AND DISCUSSION

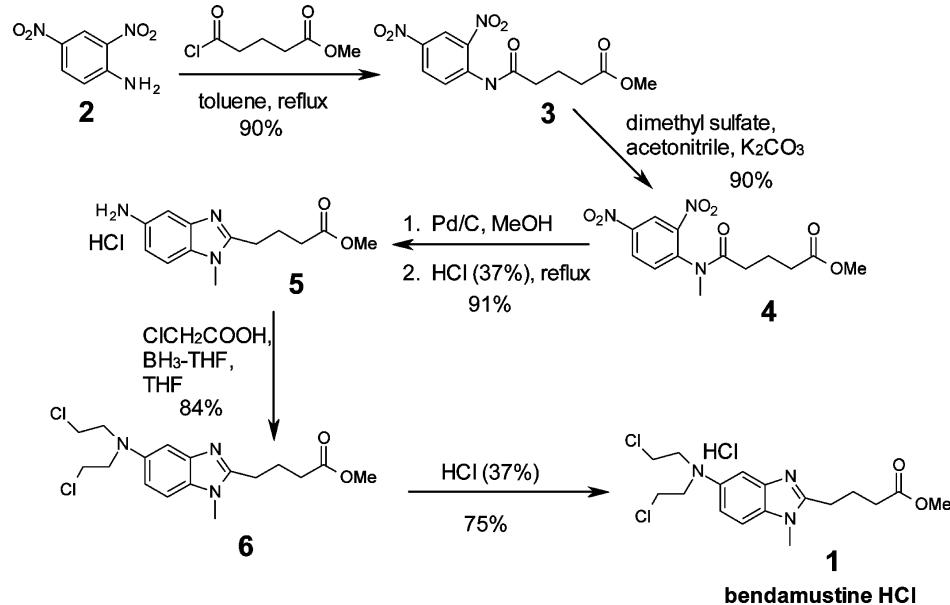
Background. In the reduction of **4**, both nitro groups are reduced (Scheme 2). The subsequent nucleophilic addition of the *ortho*-amine to the amide carbonyl generates the tertiary

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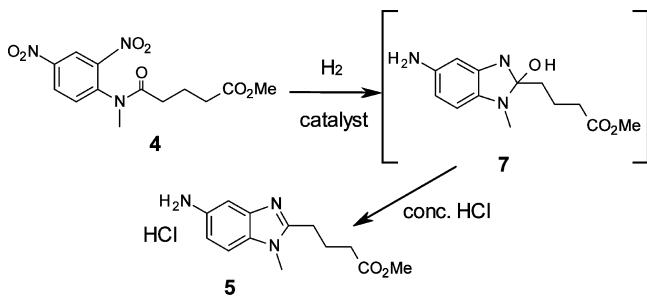
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Scheme 1. New Route to Synthesis of Bendamustine



Scheme 2. Hydrogenation of 4



alcohol 7, and this intermediate is then dehydrated with HCl to afford the imidazole ring of 5.

In the development of the batch process, the variables investigated included catalyst, hydrogen pressure, temperature, solvent, and mixing. Hydrogen pressure and temperature had the most significant impact on the rate of conversion and product quality. Below 10 °C or above 60 °C, starting material was consumed, but several impurities were generated. While a couple of side products formed at <20 psi, the reaction went to completion above 40 psi. One impurity, the N-oxide 8 (Figure 1), formed in all experiments and became a major impurity

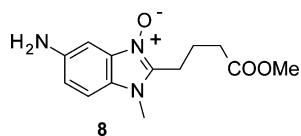


Figure 1. Structure of the N-oxide impurity.

under hydrogen starvation conditions. This impurity, once formed, cannot be further reduced through hydrogenolysis and is difficult to reject in the downstream chemistry. Four batches of this hydrogenation were run successfully at 600 g each, the maximum loading of our kilo-lab pressurized reactor, giving 95–97% of the desired products 5 and 7.

Laboratory Studies on the H-Cube. The commercially available H-Cube was selected to start our investigation. The H-

Cube is a compact, benchtop stand-alone flow apparatus that combines continuous flow microchemistry with in situ generation of hydrogen gas via the electrolysis of water, eliminating the need for a hydrogen gas cylinder.¹² The catalyst is prepacked and sealed in a disposable cartridge. Continuous hydrogenation reactions take place on the catalyst cartridge, and the cartridge can be heated to achieve higher temperatures than room temperature. A larger model, named the H-Cube Midi, is used for process scale-up.¹²

Our initial experiments using 5% Pd/C gave a mixture of 45 A% of 7 along with several other components. Upon screening of the library of marketed catalyst cartridges,¹² 10% Pd/C was found to generate a higher ratio of the desired product, 68 A% of 7. Since the 10% Pd/C cartridge for the H-Cube Midi was once found to create too high a back-pressure, we then used the Ra-Ni cartridge, also shown to be effective, for further study.

The selection of an appropriate solvent to execute the flow operation became a challenge. In batch mode, the reaction starts as a slurry of 4 in methanol. Compounds 5 and 7 are highly soluble in methanol, and as the reaction progresses, a solution is eventually obtained. Table 1 summarizes the results of solubility screening for compound 4. Tetrahydrofuran (THF), ethyl acetate, and methyl acetate, which show higher solubility of 4, emerged as potentially better replacement for

Table 1. Solubility of Compound 4

entry	solvent	solubility (mg/mL, at 22 °C)
1	MeOH	20
2	THF	204
3	acetone	326
4	acetonitrile	417
5	DMAc	435
6	EtOH	<5
7	water	<5
8	heptane	<5
9	IPA	<5
10	ethyl acetate	78
11	methyl acetate	190

methanol in the flow process where a substrate solution is required.

THF was first investigated, because it is used as the antisolvent in the subsequent crystallization of **5**. However, THF alone was found to increase the amount of a side product in the dehydration of **7**. A mixture of THF and methanol increased the solubility of **4** but gave lower conversion to the desired products than with methanol alone. Further study indicated that THF adversely impacted the performance of the catalyst and generated some unknown and highly colored impurities. Ethyl acetate showed a comparable yield and purity profile versus methanol; however, in the subsequent acid-catalyzed dehydration of **7**, transesterification was observed. Finally, methyl acetate was examined to eliminate the transesterification concern. This solvent showed a yield and purity profile similar to that of methanol, but its use resulted in an unacceptably high system pressure. A blank run with pure methyl acetate also showed this increased pressure, indicating a problem in compatibility of the cartridge with methyl acetate. Because an appropriate alternative solvent could not be found from these initial studies, it was necessary to move forward using relatively low concentrations of substrate in methanol.

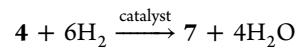
To identify the critical process parameters for optimization of the continuous flow hydrogenation process, a two-level fractional factorial design was employed for screening.¹³ The four factors selected for investigation were temperature, reaction system pressure, liquid flow rate, and concentration of **4**. The hydrogen gas flow rate is a critical process parameter but was not included in the investigational design, because it remained constant in all the experiments at approximately 30 mL/min, the highest rate achievable from the hydrogen gas generator.¹² Our exploratory experiments revealed that the best purity and yield for the reduction were obtained when using the highest hydrogen gas flow rate. Ranges for the four factors are shown in Table 2. The 2^{4-1} fractional factorial design was

Table 2. Levels of the Four Factors in the 2^{4-1} Fractional Factorial Design

variable	unit	-1	0	+1
A: temperature	°C	20	60	100
B: system pressure	bar	1	25.5	50
C: liquid flow rate	mL/min	0.3	1.65	3.0
D: concn of 4	M	0.01	0.035	0.06

constructed with one center point. Experiments were carried out in a random order, and the yield was evaluated by the total percentage of the desired products, **5** and **7**, using HPLC analysis of the reaction stream.

Analysis of the experimental data was performed using Design-Expert software¹⁴ and is depicted in Figures 2 and 3. The half-normal plot (Figure 2) indicated that the concentration of **4** (variable D) is the most significant variable impacting the yield of the desired products. The liquid flow rate (variable C) and the interaction of variables C and D are also significant. Variables A and B are less significant. Because of the complexity of this heterogeneous catalytic reduction, a number of process factors contributing to the overall conversion should be taken into account, including intrinsic chemical reaction kinetics, interphase mass transfer, intraparticle diffusion, and heat-transfer efficiency.



The stoichiometry of the hydrogenation reaction of **4** to **7** can be simply expressed by the above equation, where 1 mol of **4** requires 6 mol of hydrogen gas to complete the reaction. However, literature reports indicate that the mechanism for reducing aromatic nitro compounds to aniline via metal-catalyzed hydrogenation is not straightforward.¹⁵ Reaction pathways, reaction rate, and reaction order vary with reaction conditions. For instance, Machado reported that, in the nickel-catalyzed hydrogenation of nitrobenzene to aniline, when concentration of the aromatic nitro substrate is lower than 1.5%, the nitroso/hydroxylamine intermediates are converted to amine sequentially, but when concentration is over 1.5%, azoxy-/azo-benzene and phenylhydrazine species are prevalent.^{15h} Although the second pathway ultimately produces aniline, the reaction is much slower kinetically. Indeed, in the continuous flow hydrogenation, when the concentration of **4** is below 0.025 M, the conversion to **5** and **7** is high (>95%, Figure 3); however, with the concentrations over 0.025 M, the conversions decrease substantially, yielding multiple components in the reaction mixture. Likely, the nitro substrate and the intermediates competed with hydrogen gas for the limited surface sites of catalyst.^{15h-1} This was also supported by our experimental observation. When compound **4** at high concentrations was introduced into the flow reactor, not only were incomplete reactions noted, but also an extended time was required to elute away these species derived from an incomplete reaction in order to regenerate the catalyst. Given that the mean residence time is inversely proportional to the liquid flow rate, the effect of the liquid flow rate becomes obvious. When a slower liquid flow rate was implemented, a longer residence time was achieved and accordingly a higher conversion to the desired product was gained. As shown in Figure 3, flow rates below 0.5 mL/min gave high response. As for the interaction of variables C and D, at <0.012 M, the liquid flow rate showed little impact on yield. At higher concentrations, the lower liquid flow rates gave higher yields. The effect of hydrogen gas pressure is not significant under the investigated flow conditions, although pressure of hydrogen below 40 psi in the batch hydrogenation of **4** resulted in low product yield.^{1b} In addition, a straight line of total hydrogen uptake over reaction time with an abrupt flat end was noted in the batch operation,^{1b} suggesting a mass-transfer limitation process, and hence the reaction yield displayed pressure dependence. This pressure dependence was not observed in the flow reactor regime for the hydrogenation of **4**. In the batch hydrogenation of **4**, temperature was important, and more impurities were observed at temperatures below 10 °C or above 60 °C.¹ In the flow hydrogenation of **4**, the impact of temperature was not significant. High ratio of hydrogen and catalyst over substrate resulted in a very fast reaction even at 20 °C. Additionally, it is worth noting that efficient heat transfer and short residence time in the flow reactors eliminated formation of the impurities at temperatures higher than 60 °C that was an inherent problem in batch reactors.

With some additional experiments designed on the basis of the DoE results and solubility of compound **4**, the optimal conditions were established with Raney-nickel, 0.02 M of **4** in methanol, 0.3–0.5 mL/min flow rate, at 50–70 °C, and 1–5 bar, giving 97% of **5** and **7**. The results are consistent with the DoE model study.

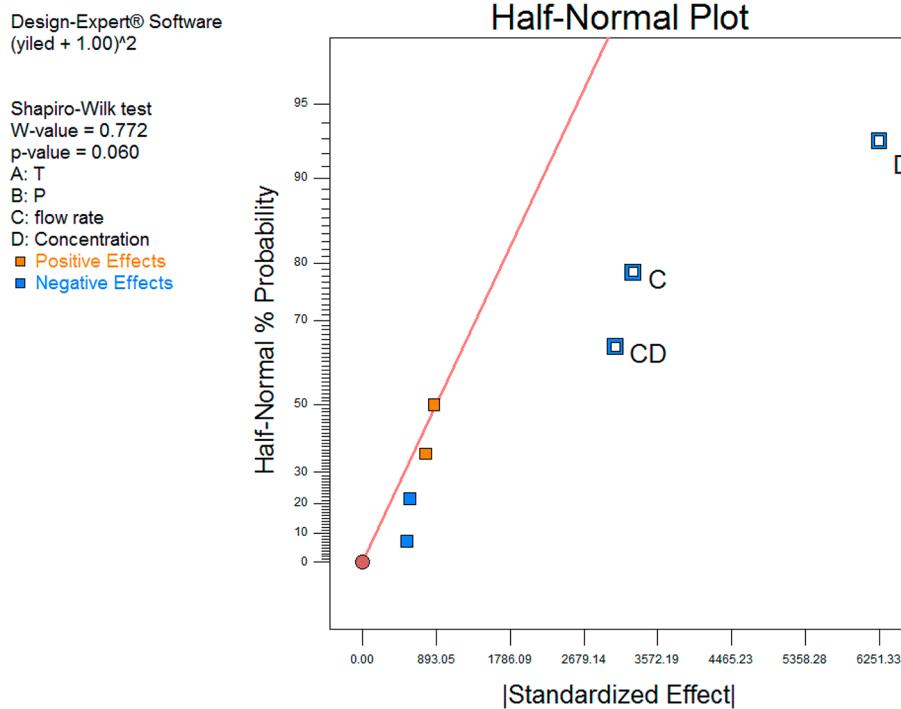


Figure 2. Half-normal plot for yield of 5 and 7.

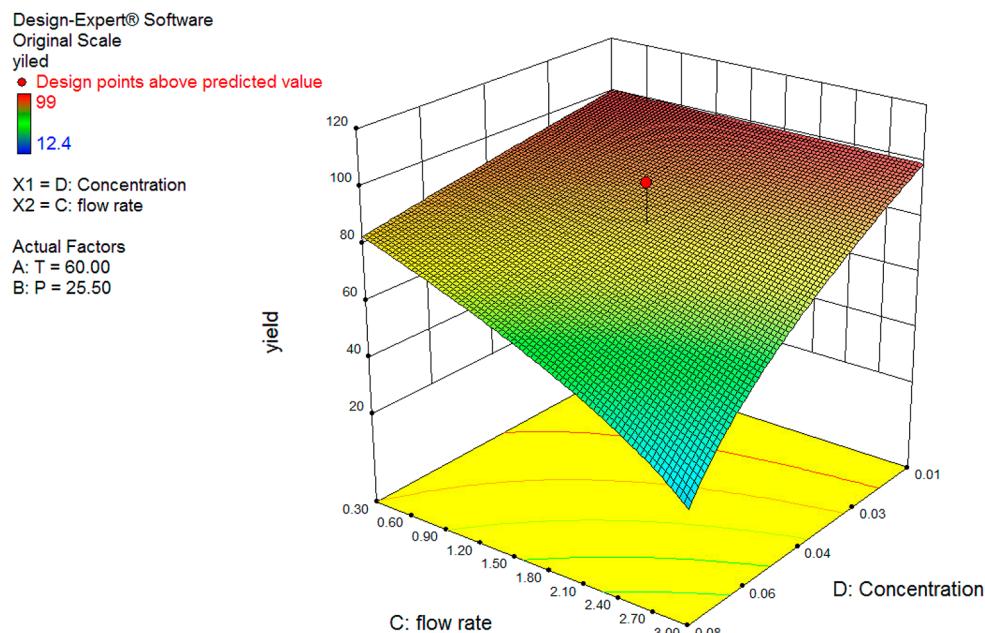


Figure 3. Effect of flow rate and concentration on percent yield of 5 and 7.

The steady-state performance of the flow hydrogenation reactor was determined by analysis of the reactant and products in the exit stream.^{10,12} After equilibrating the system with solvent under the desired reaction conditions for a period of time, feeding the solution of **4** in methanol was initialized. HPLC analysis of the reaction stream indicated that the starting material was consumed, providing a mixture of **5** (approximately 94A%) and **7** (ca. 3%). The activity of the Ra-Ni catalyst was evaluated by comparing the HPLC analysis at time intervals,^{15b,c,j} showing a constant activity over 48–50 h.

Scale-up. Because of the limits on both hydrogen gas production and liquid flow rate of the H-Cube, the H-Cube

Midi was used for scale-up. It is critical to quantify the amount of available hydrogen gas present in the reactor system for the hydrogenation of **4** and to ensure an adequate amount of hydrogen gas to drive the reaction to completion. As discussed above, **N**-oxide **8** is generated under hydrogen-starved conditions, and it is difficult to remove this impurity by downstream processing. It is challenging to quantify how much hydrogen is produced in the flow mode, as the unreacted hydrogen gas will exit the reactor in the liquid stream.¹⁶ The H-Cube system contains two bubble detectors before and after the catalyst cartridge, qualitatively indicating the amount of hydrogen gas entering into and leaving the reaction system. A

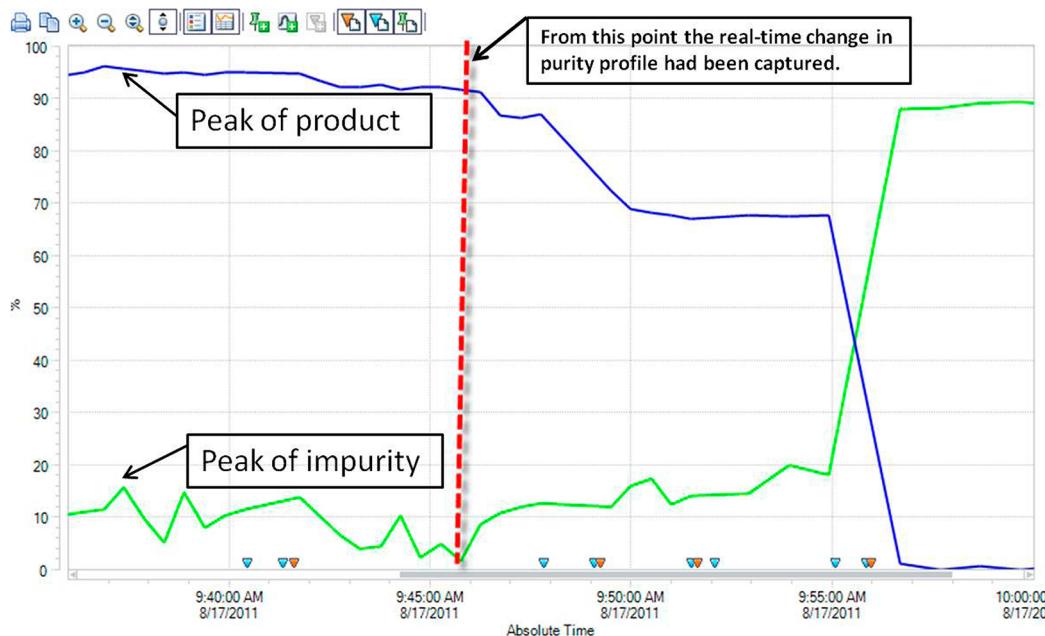


Figure 4. ReactIR spectrum for flow hydrogenation of 4.

quantitative measurement was needed to determine the ratio of hydrogen gas versus 4, but no commercial device was available that fit our needs. With some testing and modification, a commercial lab gas buret was integrated into our flow system to conveniently determine the amount of hydrogen gas being produced. Measurements could be taken during the course of the reaction without interrupting the process. When running with solvent only, the average maximum flow rate of hydrogen was determined to be 85–105 mL/min. With this number in hand, an optimal flow rate of the substrate solution, which prevented hydrogen starvation, was chosen at 5 mL/min.

Once the continuous flow process starts, any interruption will lead to a portion of the reaction stream containing partially reduced intermediates. To limit the amount of the batch potentially lost to run interruption, a fraction collector was integrated into the system with the H-Cube Midi. Fractions were collected in a 100 to 1000 mL range in approximately 50 h. The product stream contains residual hydrogen gas under reduced pressure. Although the gas pressure was low, it raised a problem in fractional collection due to solvent splashing. To separate the hydrogen gas from the liquid stream, one commercial liquid–gas separator was examined but did not work due to its low capability. The other commercially available separators are designed for the applications at the industrial but not the laboratory scale. With some investigation, we customized a device from laboratory pipet tips and inserted it in the outlet of the exit stream right prior to the fraction collector, successfully separating the residual hydrogen and reaction fluid and eliminating the problematic solvent splashing.

Finally, to monitor the reaction progress and detect any system failure, a ReactIR system was used to examine the outlet stream.¹⁷ When the reaction was running well, the IR spectrum of the product stream looked stable; when the incompletely reduced reaction occurred, the ReactIR captured the change instantly (Figure 4). The results indicated that this PAT tool could immediately detect the presence of the intermediate resulting from incomplete reduction. Along with other real-time

data, it was plausible to quickly identify the problems with the system in the course of the reaction.

Optimized Conditions and Scale-up Results. Based on the data from H-Cube and some exploratory experiments on the H-Cube Midi, the optimized conditions for the flow hydrogenation of 4 were determined to be Raney-nickel catalysis, 4 in methanol at 0.05 M, 5 mL/min, at 70 °C, and atmospheric pressure. Using the integrated flow reactor system (Figure 5), five batches were run on approximately 250 g each, yielding the desired product in >97 A% purity and with 85% isolated yield of 5 after dehydration. These results are comparable to those from the optimized batch process (see Table 3). The ratio of catalyst versus substrate was decreased by 10-fold.

Summary. A successful conversion of a batch process for catalytic heterogeneous hydrogenation of compound 4 to a continuous flow process has been described. The continuous operation holds several advantages over the batch process. In particular, the continuous operation requires a smaller equipment foot-print, less catalyst utilization, and less time for reaction optimization and development. It also provides better mixing, mass and heat transfer, and control over process and process safety. Easy scalability makes the flow operation an attractive alternative to batch processing, which usually requires additional investigation on the scale-dependent factors. In contrast to being in place for many decades in the bulk chemicals and petrochemical industries, continuous flow hydrogenation is still a relatively new manufacturing operation in the fine chemical and pharmaceutical industries. There are still challenges in hardware and technology of flow hydrogenation reactors, in particular, for the catalytic heterogeneous reactions with high hydrogen demand. However, applications of flow technologies are gaining favor in pharmaceutical manufacturing. Overcoming a number of challenges initially encountered in the flow hydrogenation of 4, we successfully scaled up the continuous process to kilogram scale with the desired results. The 10-fold improvement in catalyst utilization and 1200-fold increase in space–time yield¹⁸ versus the

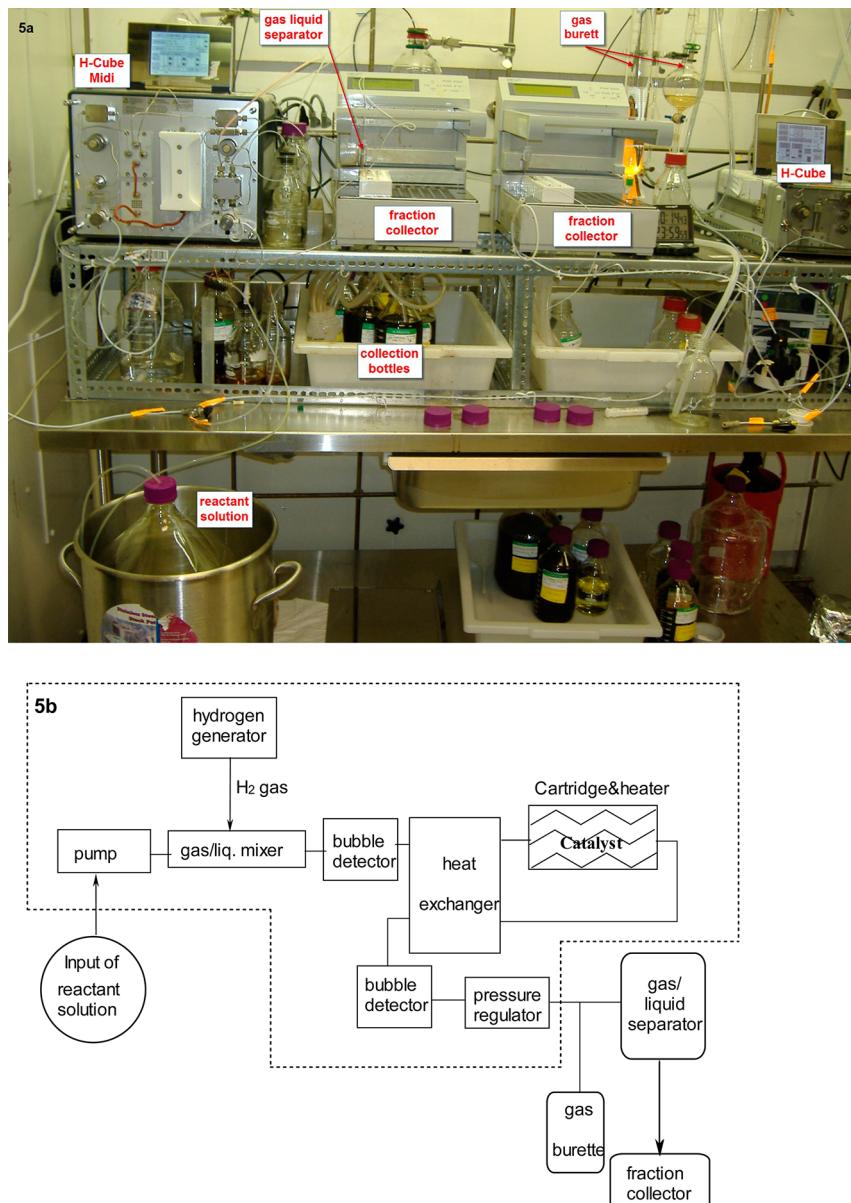


Figure 5. Photo (5a) and diagram (5b) of the integrated flow reactor system for continuous hydrogenation of 4. The parts within the dotted lines are those of the H-Cube or H-Cube Midi.

Table 3. Comparison of Hydrogenation of 4 in Batch and Continuous Flow Operation

mode	temp (°C)	pressure (barg)	ratio of catalyst/substrate (w/w)	A% by HPLC		
				N-oxide ^a	5 ^{a,b}	7 ^a
batch	20–55	4	0.1:1	0.5	3.0	93.3
flow	70	1	0.01:1	not detectable	2.5	95.3

^aAveraged values for comparison. ^bNeutral form of 5.

conventional batch operation clearly show the sustainability of a continuous heterogeneous hydrogenation process.

EXPERIMENTAL SECTION

General Method. Reverse-phase HPLC analyses were performed on an Agilent-1100 machine using a Waters X-Terra MS C-18 column using 10 mM aqueous ammonium bicarbonate and acetonitrile at a flow rate of 1 mL/min. The identity of the peaks in the chromatogram were confirmed by LC-MS and ¹H NMR. HPLC analysis results are described as

area % (A%) (see the details in Supporting Information). All continuous flow hydrogenation reactions were performed in the stainless steel microreactors H-Cube and H-Cube Midi (Thalesnano Inc.), respectively. The flow product stream was continuously collected using a Super Fraction Collector CHF122SC (Advantec MFS, Inc.). The FTIR spectroscopy was measured using a ReactIR 45m (Mettler Toledo) instrument equipped with a diamond probe.

Representative Flow Hydrogenation Process. Under nitrogen atmosphere, compound 4 (250 g, 0.769 mol) was

completely dissolved in methanol (15.3 L) in a 20-L jacketed reactor at room temperature. The reaction parameters, including temperature, pressure, liquid flow rate, and hydrogenation gas pressure, were selected on the H-Cube Midi, and the system was conditioned by pumping only pure solvent (methanol) through the flow reactor for at least 25 min. The production of hydrogen gas was measured using a gas buret to ensure that the desired reaction parameters were achieved, gaining a stable processing state. At this point, the substrate solution was introduced. The reaction was complete after a single passage through the apparatus, and the product stream was continuously collected in 1-L flasks using an automated fraction collector. The process was followed by HPLC analysis. Typically the product stream contained approximately 3 A% of 7 and 94 A% of 5 by HPLC analysis. Once the batch was completed, the product streams were combined and used directly in the next dehydration stage.

■ ASSOCIATED CONTENT

S Supporting Information

HPLC method and additional experimental data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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