

Hydrogenation Process Development in a Data-Rich Environment

Peter Sagmeister, Kensaku Matsunami, Giovanni Aprile, Darren A. Whitaker, Mohammed Janoudi, Thomas Toupy, Adrian Ramirez Galilea, Neda Nazemifard, Charles D. Papageorgiou,*
Aparajith Bhaskar, John Mack, Richard D. Braatz, and Allan S. Myerson*



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ABSTRACT: A structured, three-stage workflow was developed to accelerate hydrogenation process development, facilitate rapid scale-up translation, and maximize process understanding through data-rich experimentation. The approach integrates high-throughput batch screening, intermediate-scale catalyst evaluation, and continuous flow implementation, while allowing flexible entry at any stage depending on prior process knowledge. In Stage I, a high-throughput robotic platform enables rapid screening of catalysts, solvents, and additives under pressurized conditions, supported by automated ultra-high-performance liquid chromatography (UHPLC) method development for efficient analysis. Stage II transitions to intermediate-scale reactors for catalyst optimization and safety assessment under controlled hydrogenation conditions. In Stage III, process knowledge is transferred to continuous flow, where reaction conditions are optimized and process control strategies, including automated experimentation, dynamic experiments, and model predictive control (MPC), are implemented. The workflow was demonstrated in a case study of a catalytic nitro reduction, and reaction conditions were successfully scaled up and translated from batch to continuous flow.

KEYWORDS: *flow chemistry, hydrogenation, data-rich experimentation, model predictive control*

INTRODUCTION

Hydrogenation reactions are among the most important transformations in the pharmaceutical industry, playing a key role in the synthesis of active pharmaceutical ingredients (APIs), intermediates, and fine chemicals.^{1,2} Their ability to selectively reduce functional groups under mild conditions makes them indispensable for tuning physicochemical properties, improving bioavailability, and enables late-stage functionalization in complex molecules.³ As the industry continues to strive toward more sustainable and efficient manufacturing routes, developing robust, scalable, and safe hydrogenation processes remains a central focus.⁴

Traditionally, hydrogenations are carried out in batch reactors, where process development is relatively straightforward but frequently hindered by challenges related to reproducibility, limited mass transfer, and difficulties in scale-up.⁵ Batch-optimized conditions are frequently incompatible with continuous flow operation. Hydrogenations performed as slurry reactions in batch are often difficult to translate directly to flow and may require reduced substrate concentrations or alternative solvents. Moreover, catalysts selected for batch processing are often unavailable or unsuitable for continuous operation.

Reoptimization in a flow reactor is feasible, but screening new catalysts or solvent systems requires significant material and time due to repeated catalyst bed repacking, which limits flexibility once a catalyst is implemented in a packed-bed configuration. However, transitioning from batch to continuous flow offers numerous advantages, including improved heat and mass transfer rates, reduced costs, enhanced safety when working with pressurized hydrogen, tight control over the

reaction time and increased productivity.^{1,6–10} In continuous hydrogenation processes, well-controlled operating conditions can suppress byproduct formation and ensure consistent product quality during extended operation. For example, precise regulation of residence time and temperature enabled the kilogram-scale selective nitro reduction of a crizotinib intermediate while minimizing undesired side reactions, including dehalogenation, debenzoylation, and reduction of unsaturated functional groups.¹¹ Similarly, optimization of residence time in selective nitro-group hydrogenation minimized byproduct formation and maintained consistent product quality over extended operation periods exceeding 180 h.¹²

Several reactor technologies have been developed to address these challenges and enable robust hydrogenation in continuous flow processing.¹³ Fixed bed reactors either in trickle bed (down flow) or flooded bed (up flow) mode loaded with supported metal catalysts remain the most widely used approach due to their equipment, scalability, and compatibility with high-throughput screening.¹⁴ However, despite the straightforward hardware, these systems are not simple to characterize, as complex flow dynamics, mass transfer, and heat transfer effects must be understood for reliable operation. Recently, finely powdered catalysts ($\sim 25 \mu\text{m}$) have been successfully enmeshed within an expanded poly-

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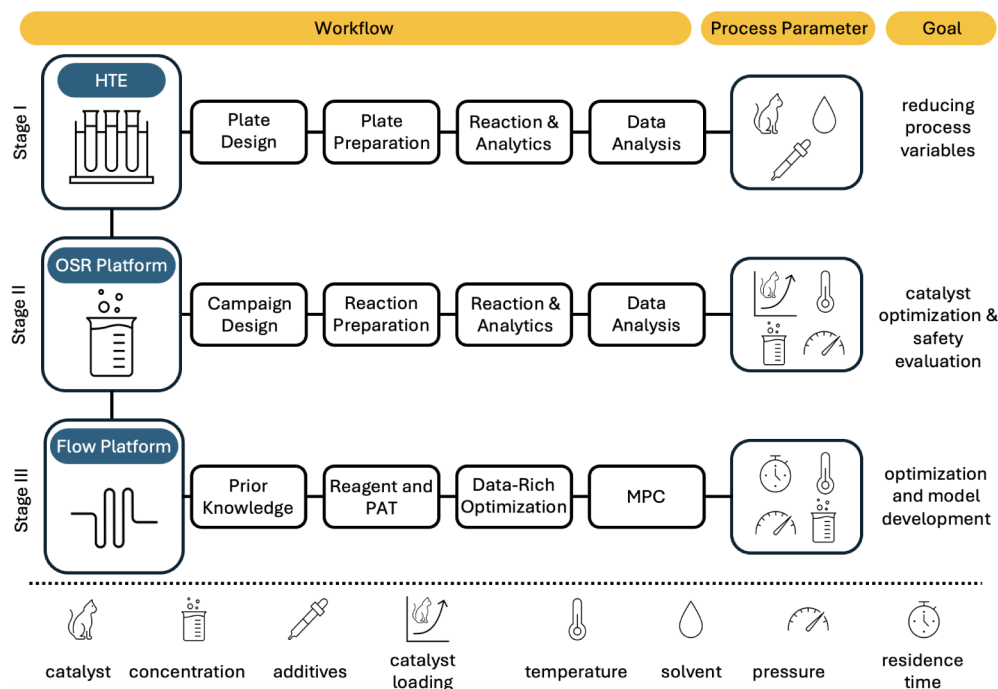


Figure 1. A schematic for the structured, three-stage workflow to quickly move from small scale batch experiments to continuous hydrogenation. Stage I is reducing the process variables during HTE campaigns. Stage II is performed in the OSR platform for further process optimization, safety and catalyst stability. Stage III is utilizing an automated flow platform which allows data-rich experimentation.

(tetrafluoroethylene) matrix and implemented in modular cartridge systems, effectively mitigating pressure drop and heat management challenges.¹⁵ Catalytic static mixers are also gaining attention as an alternative,^{16–18} offering intensified mixing, uniform gas–liquid distribution, and improved heat management, which is especially important for highly exothermic hydrogenations.¹⁹ However, the availability of catalytic static mixers may present a potential challenge because of limited suppliers.²⁰ Other approaches include membrane reactors for controlled gas dosing,^{21,22} wall-coated reactors^{23–26} and CSTRs.^{27–30} Each methodology comes with trade-offs in terms of scalability, catalyst replacement, and susceptibility to fouling, making early stage technology selection critical for efficient process development.³¹

In parallel, advances in automation and process analytical technology (PAT) are transforming how process development is conducted.^{32,33} The shift from traditional one-variable-at-a-time (OVAT) experimentation toward data-rich workflows that leverage automated design of experiments (DoE),³⁴ dynamic experimentation³⁵ and Bayesian Optimization.^{36,37} These platforms allow rapid exploration of design spaces, generation of kinetic and mechanistic models, and real-time decision-making.³⁸ When combined with inline or online PAT, such as Fourier-Transform Infrared spectroscopy (FTIR), Raman spectroscopy, or ultra-high-performance liquid chromatography (UHPLC), such systems enable continuous monitoring of conversion, selectivity, and impurity profiles, facilitating closed-loop optimization and the implementation of model predictive control (MPC).^{39–43} Recent studies highlight how integrating automated flow platforms with advanced PAT accelerates process understanding, ensures robust scale-up, and reduces material consumption.^{44–47}

Herein, we present a structured three-stage workflow that enables the rapid transition from small-scale batch experiments to an automated continuous hydrogenation platform with

MPC. The workflow is designed to address key challenges in hydrogenation process development by combining efficient catalyst and condition screening, systematic process understanding, and data-rich experimentation. By integrating batch, intermediate-scale, and continuous flow studies, this approach facilitates rapid model generation, informed decision-making, and scalable process intensification toward pilot-scale operation.

RESULTS AND DISCUSSION

We developed a structured, three-stage workflow that enables efficient hydrogenation process development, rapid scale translation, and data-rich optimization (Figure 1). This approach integrates high-throughput batch screening, intermediate-scale catalyst optimization and safety evaluation in the Optimization Sampling Reactor (OSR) platform, and continuous flow implementation to minimize material consumption while maximizing process understanding. Importantly, the workflow is flexible and can be initiated at any stage depending on the available process knowledge or project requirements.

Process Safety Considerations

Caution: Pd and Pt catalysts used for hydrogenation may be flammable or pyrophoric, especially in the dry state. Catalysts should remain wetted with solvent during handling and disposal (see ESI). Reactors charged with hydrogen must be vented and purged with nitrogen before opening.

Highly exothermic transformations, such as nitro reductions, may present thermal runaway hazards, particularly when energetic or thermally unstable nitro substrates are involved.⁴⁸ To assess the associated thermal risk, techniques such as accelerated rate calorimetry (ARC) and differential scanning calorimetry (DSC) can be employed to evaluate reaction and decomposition behavior.⁴⁹ In addition, theoretical calculations may be used to estimate the adiabatic temperature rise

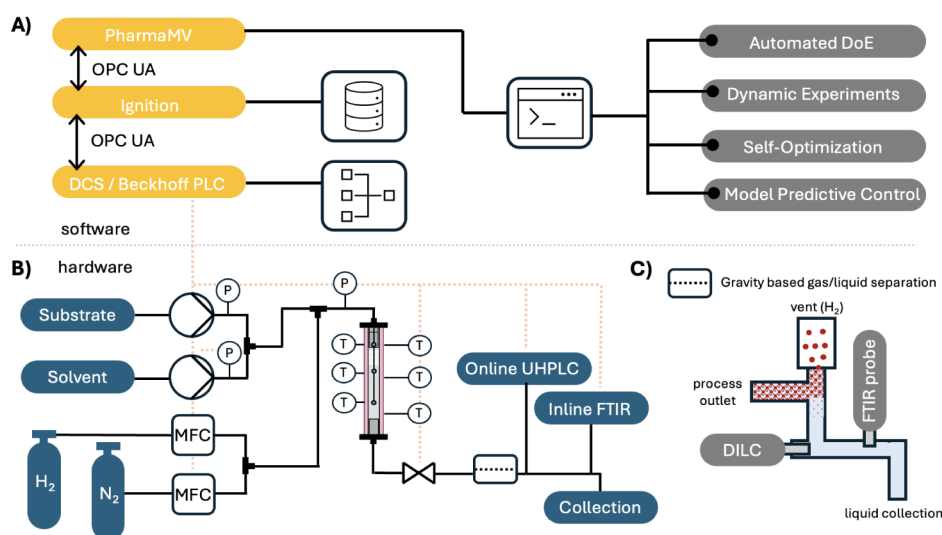


Figure 2. (A) Schematic overview of the automation layer for the continuous hydrogenation platform. (B) A simplified process diagram for the automated hydrogenation platform. (C) The gravity-based gas/liquid separation.

(ΔT_{ad}) based on reaction enthalpy, substrate concentration, reaction mixture density, and specific heat capacity. As a practical guideline, a 0.3 M nitro reduction may result in an adiabatic temperature rise of approximately 80 °C. The resulting thermal hazard assessment can further be interpreted using the Stoessel Criticality Classes to evaluate scale-up risks and the likelihood of reaching thermal decomposition under worst-case scenarios, such as loss of reactor cooling.⁵⁰

Stage I: High-Throughput Batch Screening. Stage I focuses on rapidly narrowing down process variables using a high-throughput experimentation (HTE) robotic platform. Plate design is guided either by operator expertise or AI-driven selection of catalysts, solvents, and additives and screened in parallel using 48-well plates under pressurized conditions. Hydrogen is charged at the start of the reaction, with no further additions during the experiment. Supported catalyst particles are selected with particle sizes compatible with fixed bed reactors (typically >250 μm), ensuring direct transferability of results to continuous processes. The substrate, additives, and catalysts are automatically dosed as solids, and the solvents are dispensed as liquids, using an Unchained Junior platform. Comparable robotic systems can also be utilized for accurate weighing and dispensing. Once the reaction plates are prepared, they are sealed and pressurized with hydrogen. Upon completion of the experiments, the samples are transferred, diluted, and subsequently analyzed using UHPLC-MS.

A key requirement for this stage is the development of a fast, reliable UHPLC method, as hydrogenation reactions, particularly nitro group reductions or debenzylations, often yield highly polar products that are challenging to separate. The detection and quantification of trace-level impurities, including potentially carcinogenic species, are of particular importance.^{51,52} To expedite this process, automated method development is typically employed, enabling rapid optimization of chromatographic parameters and ensuring robust analytical performance (see ESI). Data analysis is performed using ACD/Laboratories Catalyst D2D enabling informed decisions, by a human-in-the-loop or artificial intelligence (AI) (Atinary) on subsequent optimization generations. The outcome of Stage I provides essential information, including

the most effective catalyst type, impurity profiles, and solubility behavior. The Stage I workflow has been applied to various hydrogenations, such as nitro reduction, selective nitro reduction to prevent dehalogenation, and debenzylation (see ESI). Material requirements are modest, typically 5 mmol of substrate (0.1 M concentration per vial) and about 30–40 mg of catalyst (0.1 mol %) for one entire 48-well plate. The entire workflow, from preparation of the high-throughput plates, UHPLC method development, and analysis of the results, typically requiring 2 days and 0.25 full-time equivalent (FTE).

Stage II: Optimization in OSR Platform. The Stage II moves from 1 mL vials to larger batch reactors to investigate hydrogen uptake, conversion, impurity formation, and thermal behavior under controlled conditions (Figure 1). Using the optimal solvent and catalyst identified in Stage I, the Stage II optimization campaign is designed. Key process variables, such as catalyst loading, temperature, pressure, and substrate concentration, are systematically investigated.

Parallel experimentation is performed in an OSR reactor, which enables up to 16 reactions to be performed simultaneously under constant hydrogen pressure, therefore the hydrogen uptake can be measured. Reaction preparation is supported by automated solid and liquid dispensing systems. Process conditions employing low catalyst loadings and high hydrogen pressures are used to investigate hydrogenation kinetics independently of gas–liquid mass transfer limitations (kLa) (see ESI). Conversely, conditions involving higher catalyst loadings, extended reaction times, and elevated temperatures provide valuable insights into catalyst stability and impurity formation. Reaction performance is evaluated using analytical methods established in Stage I, and decisions regarding subsequent optimization iterations are supported by either human-in-the-loop expertise or AI.

In addition, the reaction mixture is evaluated for its thermal behavior and potential exothermicity. Such analyses offer information on the onset temperature of decomposition, heat release profiles, and overall thermal stability under process-relevant conditions. It is important to note that the assessment of safe operating temperatures differs between batch and continuous processes, as the heat transfer characteristics and reaction dynamics vary substantially.⁵³

This stage requires a larger material input compared to Stage I. Typical reaction volumes range from 3 to 10 mL, resulting in a 10- to 100-fold increase in substrate and catalyst consumption relative to HTE screening, depending on the reaction concentration and catalyst loading. Substrate and catalyst dosing can be performed automatically using powder dispensing systems; however, not all tasks in this step can be fully automated, and operator intervention is required for certain manual operations. These typically include sealing the OSR reactor to ensure pressure tightness and installing overhead stirrers. Typically, this round of optimization requires 2 working days and about 0.5 FTE.

Stage III: Continuous Flow Implementation. In Stage III, knowledge gained from Stage I and Stage II is directly translated to continuous flow, enabling rapid deployment at pilot scale (Figure 1). The experimental platform was constructed using the hardware outlined below, with a simplified schematic shown in Figure 2B. The system consisted of two liquid feeds, delivered by Knauer Azura HPLC pumps (50 mL pump heads). This configuration allowed either (i) inline dilution of the substrate by pumping the feed solution with one pump and pure solvent with the second, thereby varying the substrate concentration, or (ii) parallel pumping of the substrate with both pumps to maximize throughput. Hydrogen and nitrogen were supplied via mass flow controllers from dedicated gas cylinders. Ultra-high-purity nitrogen (5.0) was used to purge the system before and after hydrogenation runs and to store the catalyst under inert atmosphere.

The selected flow catalyst from Stage I and II is packed into a column and installed in the automated platform. Continuous process parameters, including residence time, hydrogen equivalents, temperature, pressure, and concentrations, can be optimized. Upon exiting the column, the reaction stream was chilled to ambient temperature and depressurized via an electronically controlled Equilibar back-pressure regulator. The platform was designed with a modular architecture, allowing the reactor module to be swapped easily, for example, to replace the fixed bed reactor with a Zaiput hydrogenation reactor (see ESI).

A custom, gravity-based gas–liquid separator was built in-house, capable of efficiently separating up to 50 mL/min of liquid and 500 mL/min of gas simultaneously. The separator could be equipped with two sampling ports, enabling integration with an EasySampler probe connected to a direct inject liquid chromatography (DILC) system and UHPLC for online analysis, as well as an inline FTIR probe connected to a ReactIR 702L (Mettler Toledo) for real-time spectroscopic monitoring (Figure 2C). The UHPLC and FTIR systems were rapidly calibrated using external calibration standards to enable efficient process monitoring. The UHPLC was primarily used to quantify the main components and trace impurities, providing detailed information on reaction selectivity and byproduct formation. The FTIR probe was employed for real-time monitoring of key species, such as substrate and product, allowing direct tracking of conversion during hydrogenation. For the FTIR, an additional partial least-squares (PLS) model was implemented to enhance quantitative accuracy across a wide concentration range, facilitating reliable data acquisition for dynamic experiments and model-based control.

Additional pressure and temperature sensors were installed throughout the platform to provide detailed process monitoring. An overview of the automation structure is shown in Figure 2A. All actuators, including pumps, mass flow

controllers, thermostats, heaters, pressure transducers, and thermocouples, were connected via Modbus or analog communication to a Beckhoff PLC or the Parr Process Controller. Process variables were centralized using Open Platform Communication Unified Architecture (OPC UA) within the Ignition Supervisory Control and Data Acquisition (SCADA) platform, which served as the human–machine interface (HMI), data historian, and visualization tool. PAT tools were operated using their native control software, but all resulting data streams were transferred to Ignition via the Mettler Toledo OPC UA server, ensuring centralized data access and synchronization with other process variables.

PharmaMV software acted as the orchestration layer, controlling Ignition and thereby the entire reactor system. The process development tools within PharmaMV enabled advanced data-rich experimentation, including automated DoE, dynamic experiments, self-optimization routines, and MPC studies. This capability facilitates rapid optimization, process model development, and the implementation of process control for continuous hydrogenation.

While material consumption increases during flow optimization, a stable catalyst can be reused throughout the campaign. Catalyst stability must be periodically verified through dedicated experiments, which are repeated at key points during the optimization to ensure consistent performance. The fixed bed reactor must be packed manually by an operator, a process that typically requires approximately 2 h. Stock solutions are generally prepared by an operator; however, the integrated PAT tools and automatic experiment scheduling allow the platform to operate largely without human intervention. Depending on the desired outcomes, an optimization campaign typically spans 2–5 days and requires approximately 0.5 FTE.

Case Study – Nitro Reduction

Nitro reductions represent a key transformation in pharmaceutical process chemistry. One particularly valuable target is 3-amino-2(1H)-pyridinone (**2**), an important building block for the synthesis of APIs. This compound can be efficiently accessed via catalytic reduction of 3-nitro-2(1H)-pyridinone (**1**) (Figure 3).

Several patents have reported the nitro reduction of **1**.^{54–57} Typical literature conditions involve batch hydrogenation using palladium catalysts in alcoholic solvents at room temperature, affording yields of 69–100% with reaction times ranging from 3 to 24 h.^{58,59} Developing processes for nitro reductions on heteroaromatic systems, however, poses unique challenges. Substituted pyridines might coordinate to metal catalysts through the ring nitrogen, which can inhibit activity or alter selectivity.³² Moreover, under elevated temperatures and pressures, these systems are prone to unwanted ring hydrogenation, complicating both the reduction pathway and the impurity profile.⁶⁰

In this case study, we set out to establish the development workflow for the reduction of compound **1** (Figure 3). Extensive solubility data were already available for both **1** and **2**, which ruled out many commonly used solvents and solvent systems. The overall concentration of the process is limited by the solubility of **1** which is only 0.1 M in an EtOH/water (3:2 v/v) mixture (see ESI). As a result, the Stage I of HTE screening was intentionally omitted. The data clearly indicated that only a single solvent system was viable for continuous hydrogenation, enabling us to streamline develop-

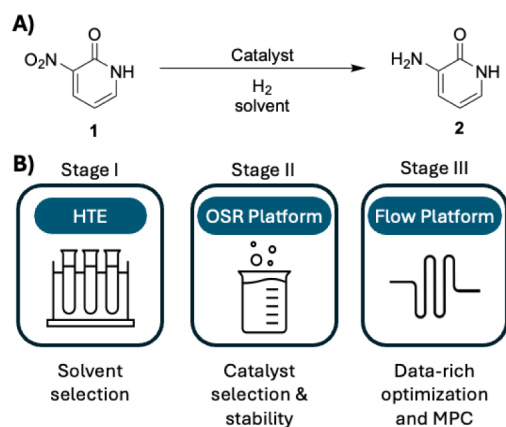


Figure 3. (A) Reaction scheme of the investigated nitro reduction used as a case study for the three-stage workflow. (B) Overview of the applied workflow: Stage I was used to identify a suitable solvent system; Stage II focused on catalyst selection, including evaluation of catalyst loading and stability; and Stage III employed the continuous flow platform with automated and dynamic experiments to derive a process model, which was subsequently used for MPC.

ment and proceed directly to catalyst screening under controlled conditions.

In Stage II, we employed an OSR platform to screen multiple catalysts appropriate for flow and experiments were performed using catalyst loadings of 0.5 and 1 mol %. Catalysts were obtained from Johnson Matthey and were all suitable for continuous flow applications; those evaluated included 3 different 5% Pd/C, three 3% Pd/Al₂O₃, one 3% Pt/C, and one 3% Pt/Al₂O₃ (for more specifications see ESI). The goal was to identify a catalyst that delivers a fast reaction with a clean impurity profile while preventing undesired over-reduction of the aromatic ring. Among those tested, the best performance was achieved with 3% Pd/Al₂O₃ (Catflo-Pd5, 0.8 mm spheres), which afforded 100% conversion and 96% selectivity under 75 psi hydrogen pressure with a reaction time of 1 h. In less optimal cases, the remaining starting material was found to stall at the hydroxylamine or hydroazo intermediates (ESI), along with minor unidentified impurities, as confirmed by UHPLC and impurity identification by UHPLC–MS.

Further screening explored the effect of catalyst loading and temperature of the selected catalyst. At higher catalyst loadings (13–26 mol %), reactions carried out below 40 °C for less than 2 h achieved selective nitro reduction without hydrogenation of the aromatic ring. However, raising the temperature to 70 °C led to significant aromatic ring reduction, especially when reaction times were extended to 16 h. Conversely, very low catalyst loadings (<1 mol %), did not show aromatic ring reduction even at elevated temperatures and prolonged reaction times.

Translating these conditions to continuous flow, the local catalyst loading is significantly higher compared to batch. Therefore, the contact time of the substrate and the catalyst should be kept to a minimum and the reaction temperature should be kept close to room temperature.

The conditions identified in Stage II were successfully translated to a continuous flow setup, using 3% Pd on Al₂O₃ in a fixed bed reactor. The selected catalyst was packed in a metal column equipped with an internal three-point temperature probe. The column composition and the packing details are provided in the ESI. In brief, the column was packed with 11.7

g of catalyst, resulting in a catalyst bed approximately 10 in. long. Additionally, the column was supported with spools to minimize void volume, and included a 3-in. glass bead section for premixing prior to entering the catalyst zone. The total void volume of the catalyst bed was 2.55 mL.

Residence time distributions (RTDs) were characterized via step tracer experiments under various process conditions (see ESI). A tracer was introduced into the feed, and the outlet concentration was monitored in real time using FTIR. The RTD function, $E(t)$, was determined by taking the time derivative of the normalized outlet concentration profile. From this, the mean residence time, τ_m [s], for each condition was calculated according to eq 1 (Table 1). It is important to note

Table 1. Calculated Mean Residence Times (τ_m) for Varying Pressure, Liquid Flow Rate, and Hydrogen Flow Rate, Determined Using eq 1

$$\tau_m = \int_0^\infty tE(t)dt \quad (1)$$

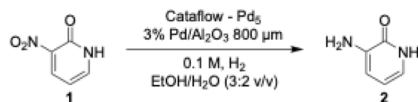
Entry	Pressure [barg]	Flow rate liquid [mL/min]	Flow rate H ₂ [mL/min]	τ_m [s]
1	10	12	174	94 ± 1
2	10	12	348	95 ± 6
3	10	6	87	176 ± 18
4	10	6	174	162 ± 0
5	10	3	43	310 ± 4
6	10	3	87	305 ± 4
7	20	12	174	91 ± 1
8	20	12	348	86 ± 0
9	20	6	87	175 ± 2
10	20	6	174	162 ± 2
11	20	3	43	339 ± 1
12	20	3	87	305 ± 4

that the RTD measurements reflect the time elapsed from the mixing point of the substrate and solvent feed to the FTIR measurement downstream of the gas–liquid separator. The mean residence time exhibited a linear decrease with increasing liquid flow rate, consistent with expectations (higher liquid flow rates correspond to shorter residence times). Interestingly, variations in hydrogen flow rate at constant liquid flow did not significantly impact the mean residence time. Similarly, changing the pressure from 10 to 20 bar had negligible impact on the mean residence time, indicating that gas flow and moderate pressure changes do not substantially influence the liquid residence time in the current setup. This approach enabled quantification of flow dynamics within the reactor, providing insight into mixing behavior and deviations from ideal plug flow under different operating conditions.

Automated Experiments

Automated optimization experiments were programmed in PharmaMV, and the hydrogenation platform automatically executed the runs. This automated screening provided a strong foundation for further investigation under continuous flow conditions. The substrate solution was prepared at 0.1 M in an ethanol–water mixture (3:2 v/v), close to the solubility limit of the substrate.

Initial screening provided valuable insights into process behavior (Table 2). The effect of residence time was examined (Entries 1–4) at a constant 12 hydrogen equivalents, 20.6 °C, and 10 bar. Surprisingly, shorter residence times gave superior

Table 2. Reaction Scheme for the Nitro Reduction Case Study^a

Entry	Hydrogen (equiv)	T [°C]	Pressure [barg]	t_{Res} [s]	LHSV [h^{-1}]	1 Conv [%] ^b	Selectivity to 2 ^b	Sum impurities [%] ^b	Space-time yield ($\text{kg L}^{-1} \text{h}^{-1}$)
1	12	20.6	10	9.6	61.74	99.1%	100.0%	0.0%	4.12
2	12	20.6	10	12.8	46.31	100.0%	100.0%	0.0%	3.12
3	12	20.6	10	19.1	30.87	96.2 ± 2.7%	97.3 ± 0.1%	2.6 ± 0.0%	1.95
4	12	20.6	10	38.3	15.44	94.6 ± 1.0%	96.2 ± 2.9%	2.9 ± 2.7%	0.95
5	9	20.6	20	19.1	30.87	98.6%	100.0%	0.0%	2.05
6	3	20.6	10	9.6	61.74	79.6%	94.3%	4.6%	3.12
7	6	20.6	10	9.6	61.74	94.1%	95.5%	4.2%	3.74
8	9	20.6	10	6.7	88.21	100.0%	100.0%	0.0%	5.94
9	5.1	20.6	10	3.8	154.36	99% ^c	100.0% ^c	ND	10.2
10	4.1	20.6	10	3.1	192.95	96% ^c	100.0% ^c	ND	12.4

^aStage III optimization table using automated experiments. ^bConversion, selectivity and impurities were calculated by UHPLC area% at 254 nm.

^cConversion and selectivity were calculated by inline FTIR.

results. Near-quantitative conversion and selectivity were achieved at 9.6 and 12.8 s, while longer residence times of 15 and 30 s led to 4–5% lower conversion and 3–4% lower selectivity.

Increasing the pressure to 20 bar had only a minor effect on conversion, but maintained quantitative selectivity compared to 10 bar. Reducing the hydrogen equivalents to 3 resulted in a ~20% drop in conversion relative to 12 equiv, while 6 equiv gave performance comparable to 12 equiv.

Given the benefits of shorter residence times, likely due to enhanced mixing, further experiments were conducted at even shorter residence times using 9 hydrogen equivalents at 10 bar. Under these conditions, the system again achieved quantitative conversion and selectivity, with a space–time yield of 5.94 kg/L/h and a liquid hourly space velocity (LHSV) of 88.21 h^{-1} .

The system was further stress-tested at residence times of 3.8 and 3.0 s, corresponding to flow rates of 40 and 50 mL/min substrate solution, respectively. At these high flow rates, the hydrogen supply (maxed at 500 mL/min) was limiting, providing only 5.1 and 4.1 equiv of hydrogen at 3.8 and 3.0 s. Despite this limitation, the 3.8 s residence time delivered an almost quantitative yield of 99% with a productivity of 10.2 kg/L/h, while the 3.0 s residence time resulted in a slight drop in yield to 96%, though with a higher productivity of 12.4 kg/L/h.

Dynamic Experiments

To better understand the effect of residence time on hydrogenation performance, we carried out a series of dynamic experiments in which the hydrogen equivalents and residence time were systematically varied under continuous flow conditions. This approach allowed us to capture transient behavior and assess process sensitivity beyond steady-state, OVAT studies (Figure 4A).

The experiments were performed using a 0.1 M solution of 1 with hydrogen equivalents of 9, 6, and 3. The reactor was maintained at 20.6 °C and 10 barg, while residence times were varied between 7.8 and 38.3 s by adjusting flow rates from 20 mL/min to 4 mL/min.

The data (Figure 4B) revealed a surprising nonmonotonic relationship between residence time and yield. At short residence times, we observed the highest conversions. As the

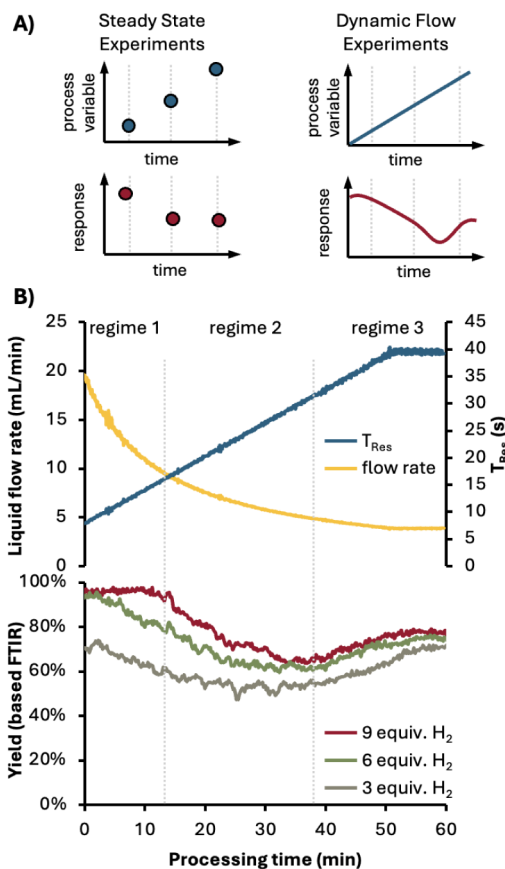


Figure 4. (A) Conceptual overview of the difference between steady-state experiments and dynamic flow experiments. (B) Process data for 3 individual dynamic experiments with a residence time sweep at different hydrogen equivalents.

residence time increased, the conversion unexpectedly dropped, before increasing again at longer residence times.

This behavior can be rationalized by considering the flow regimes in the fixed-bed reactor.⁴ At very short residence times, the catalyst bed likely operates in a pulsating flow regime, promoting excellent wetting, efficient mixing, and high hydrogen availability, which results in high conversion. At intermediate residence times, the system may transition to a

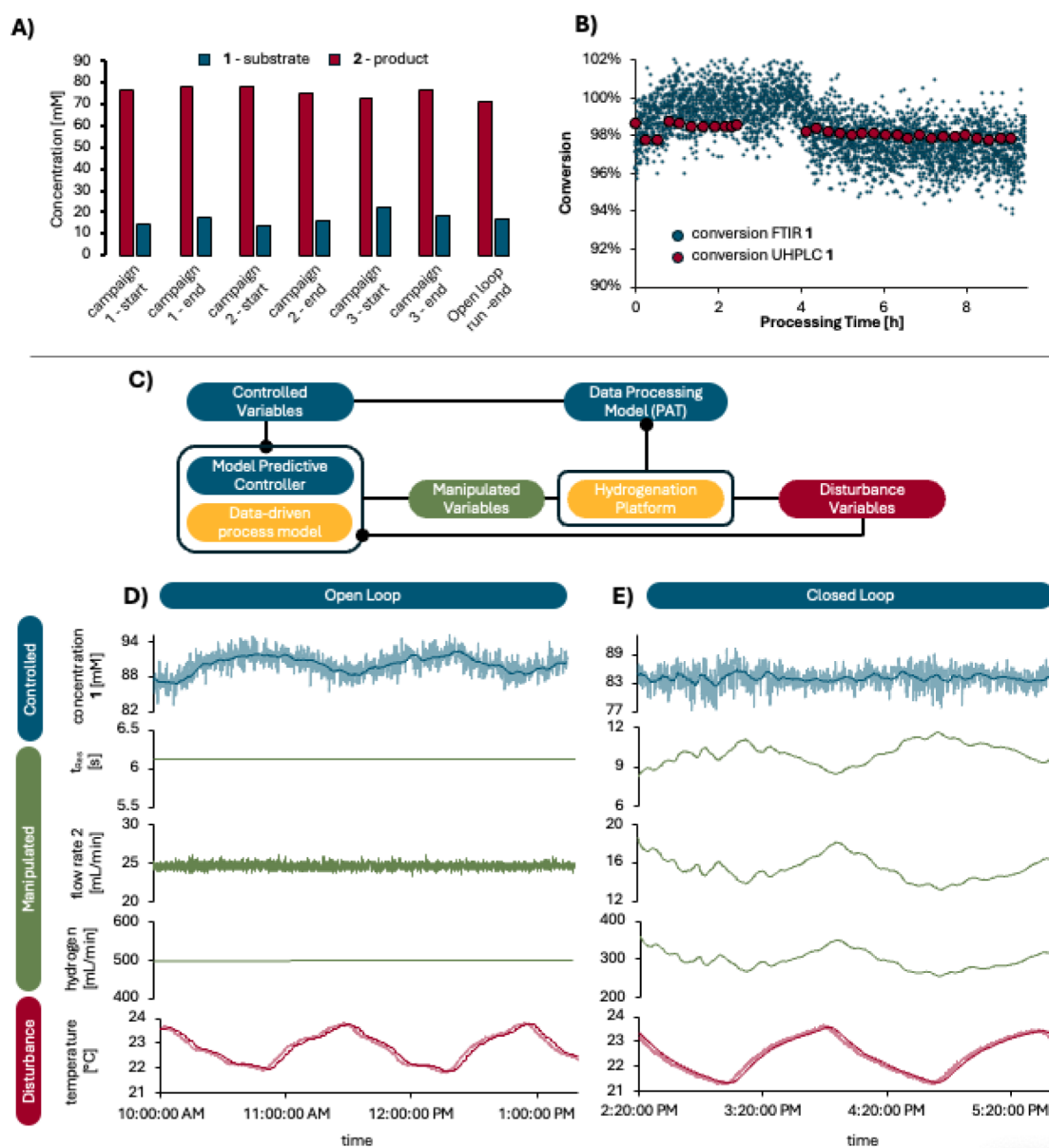


Figure 5. (A) Catalyst stability was evaluated by monitoring a single experimental set point during different optimization campaigns. (B) Open-loop run for the nitro reduction of 1 showing the conversion for the FTIR and UHPLC measurements. (C) Conceptual overview of the MPC interacting with the hydrogenation platform. (D) Process variation in open-loop configuration. (E) Process variation during closed-loop operation.

spray-like regime, reducing catalyst wetting and mass transfer efficiency, thereby causing a drop in conversion. At longer residence times, improved wetting and more intimate liquid–catalyst contact are reestablished, allowing conversion to recover as the system transitions to a trickle-flow regime.

These findings emphasize that longer residence times do not always guarantee higher conversion. Instead, flow regime transitions play a critical role in determining reaction performance. Dynamic experimentation proved valuable in revealing these nonlinear effects, which might be overlooked in traditional steady-state studies. Understanding these transitions is key for selecting optimal flow rates and ensuring robust, scalable process conditions.

Open-Loop and Model Predictive Control

Catalyst stability was regularly assessed by repeating defined process conditions. Across the entire optimization campaign, no significant catalyst deactivation was observed (Figure 5A).

To better evaluate long-term stability, conditions close to quantitative conversion and selectivity were selected. The stability run was carried out in an open-loop configuration, with process set points defined by the operator and only one manual intervention during the experiment (Figure 5B).

No evidence of catalyst poisoning was detected even after processing 15 L of reaction solution. The process was continuously monitored using FTIR and UHPLC. FTIR provided data with a 15 s sampling frequency, while UHPLC delivered data points approximately every 10 min. A single 1 h gap in UHPLC measurements occurred due to a blocked waste line in the DILC system, which was resolved by an operator. A slight decrease in pressure was observed after 5 h; without operator intervention, this likely explains the minor drop in conversion.

Since the reactor was not temperature controlled, ambient variations had a notable influence on performance. Even a 2 °C

change in room temperature correlated strongly with changes in conversion. FTIR artifacts caused by temperature shifts were ruled out, confirming that the observed effects were process-related. This external disturbance provided an excellent opportunity to implement MPC and demonstrate its capability for chemical reactions.

MPC is an advanced process control strategy that predicts and optimizes system behavior in real time based on a dynamic process model. In contrast to conventional proportional–integral–derivative (PID) controllers, MPC can effectively manage multivariable systems with strong interactions and operational constraints, making it particularly suitable for complex chemical processes. In industrial applications, the primary objective is to ensure identified quality attributes remain at their predefined set points, even in the presence of disturbances (measured or unmeasured), possible drifts and raw material variability. The objective is achieved by dynamically adjusting relevant process parameters which previously might have been held constant. By doing so, variability previously observed in quality attributes is transferred to process parameters and overall product quality and process robustness is improved.

The MPC model was developed within PharmaMV and trained using experimental process data obtained from step-change experiments performed across key process variables. These experiments were designed to capture the dynamic response of the hydrogenation system by varying the liquid flow rate, hydrogen equivalents, substrate concentration, and pressure from a nominal (midpoint) set point to both lower and higher values (see ESI).

When the liquid flow rate was varied, the system exhibited dynamic behavior consistent with the previously observed trends: at longer residence times, a decrease in product concentration (approximately 2%) was detected, indicating potential changes in the flow regime and mass-transfer characteristics.

Adjustments to the hydrogen equivalents revealed a strong positive correlation with product concentration. Operation at stoichiometric conditions (3 equiv) yielded the lowest conversion, whereas increasing to 9 equiv resulted in near-quantitative conversion and selectivity. Further increasing to 12 equiv provided no additional benefit. Conversely, substoichiometric hydrogen conditions led to a significant decrease in reaction performance, confirming hydrogen availability as a critical factor in reaction kinetics.

Variations in substrate concentration were introduced via a dedicated dilution pump, allowing controlled adjustment of feed concentration without altering total volumetric flow, ensuring a comparable contact time throughout the catalyst bed. At a concentration of 0.1 M, only partial conversion was achieved; however, upon decreasing the concentration to 0.075 and 0.05 M, full conversion was obtained at 0.05 M. This suggests that, at a constant residence time, lower substrate concentration enhances the effective catalyst-to-substrate ratio, thereby improving conversion efficiency.

Finally, stepwise variation of hydrogen pressure from 5 to 20 bar (in 5 bar increments) demonstrated a clear positive influence on conversion. This trend can be rationalized by the increased hydrogen solubility in the liquid phase at elevated pressures, which facilitates improved mass transfer and accelerates hydrogenation kinetics.

When varying the residence time at constant hydrogen equivalents, characteristic transient responses in product

concentration were observed. Due to the incompressible nature of the liquid phase, changes in liquid flow rate are transmitted almost instantaneously through the reactor. In contrast, the gaseous hydrogen phase exhibits compressibility, and the system pressure must equilibrate following each flow adjustment. As a result, increasing the liquid flow rate causes a transient rise in back pressure and temporarily reduces the effective hydrogen availability within the reactor. During this short period, the system operates under substoichiometric hydrogen conditions, leading to a momentary decrease in product concentration. Conversely, when the liquid flow rate is decreased from a higher to a lower value, an excess of dissolved hydrogen remains in the system, resulting in a temporary spike in product concentration. These dynamic effects reflect the difference in response times between the liquid and gas delivery systems, as the hydrogen feed requires a finite period to reestablish the target flow and pressure conditions. This effect was captured by changing multiple residence time steps and providing an additional tuning set for the MPC (see ESI).

Before transferring the control strategy to the actual process, PharmaMV's simulation environment was used to tune and evaluate the MPC *in silico*. This simulation-based methodology minimizes material consumption during MPC commissioning. Following this step, the control strategy was transferred to the continuous flow platform. For the closed-loop experiment, the MPC was implemented to stabilize the hydrogenation process in the presence of disturbances arising from ambient temperature fluctuations (Figure 5C). The controlled variable was the product amine concentration, monitored continuously by FTIR spectroscopy, with real-time quantification provided by a Partial Least Squares (PLS) calibration model. The manipulated variables were the residence time (adjusted via the liquid flow rate) and the hydrogen flow rate (simultaneously adapted to maintain a constant hydrogen-to-substrate ratio). A target product concentration of 84 mM was defined, and the controller's objective was to maintain this set point despite external disturbances by optimally coordinating adjustments to the manipulated variables (Figure 5D).

The standard deviation of the concentration of the product 2 could be reduced by 51% compared to the open loop run. This shows the strength of MPC for disturbance rejection and could be further improved for a manufacturing environment. Additionally, MPC can be further used for set point tracking. In this case we changed the set point of the controlled variable from 88 mM to 85 mM and the controller was capable to adjust the concentration to the desired concentration within 15 min.

CONCLUSION

A modular, three-stage hydrogenation workflow was developed to enable efficient process development, rapid scale translation, and robust data generation. The workflow is highly flexible and can be initiated at any stage depending on existing process knowledge and project requirements. Stage I employs high-throughput robotic screening to rapidly identify suitable solvents, catalysts, and additives. Using the optimal solvent–catalyst combination from Stage I, Stage II systematically explores key process parameters—including catalyst loading, temperature, pressure, and substrate concentration—while also assessing catalyst stability. Both early stages are accelerated through automated UHPLC method development, enabling rapid impurity profiling and efficient analytical support.

In Stage III, the acquired process understanding is translated to a fully automated continuous hydrogenation platform capable of performing automated DoE, self-optimization, and dynamic studies. The workflow was demonstrated through the nitro reduction of **1**, successfully transferring the process from batch to continuous operation. Space–time yields up to 12.4 kg L⁻¹ h⁻¹ were achieved under optimized conditions. Furthermore, an MPC strategy was implemented to compare open- and closed-loop operation, clearly illustrating the advantages of data-driven, feedback-controlled continuous hydrogenation.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its [Supporting Information](#).

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.oprd.6c00149>

Further details of reaction setups, residence time distributions, and experimental results data ([PDF](#))

■ AUTHOR INFORMATION

Corresponding Authors

Allan S. Myerson – Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; [orcid.org/0000-0002-7468-8093](#); Email: myerson@mit.edu

Charles D. Papageorgiou – Process Engineering and Technology, Synthetic Molecule Process Development, Takeda Development Center Americas, Inc., Cambridge, Massachusetts 02142, United States; [orcid.org/0000-0001-7959-6289](#); Email: charles.papageorgiou@takeda.com

Authors

Peter Sagmeister – Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; [orcid.org/0000-0002-4326-1775](#)

Kensaku Matsunami – Davidson School of Chemical Engineering, Purdue University, West Lafayette, Indiana 47906, United States; [orcid.org/0000-0002-8831-018X](#)

Giovanni Aprile – Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; [orcid.org/0000-0001-6549-3107](#)

Darren A. Whitaker – Process Engineering and Technology, Synthetic Molecule Process Development, Takeda Development Center Americas, Inc., Cambridge, Massachusetts 02142, United States

Mohammed Janoudi – Process Engineering and Technology, Synthetic Molecule Process Development, Takeda Development Center Americas, Inc., Cambridge, Massachusetts 02142, United States

Thomas Toupy – Process Engineering and Technology, Synthetic Molecule Process Development, Takeda Development Center Americas, Inc., Cambridge, Massachusetts 02142, United States

Adrian Ramirez Galilea – Process Engineering and Technology, Synthetic Molecule Process Development, Takeda

Development Center Americas, Inc., Cambridge, Massachusetts 02142, United States

Neda Nazemifard – Process Engineering and Technology, Synthetic Molecule Process Development, Takeda Development Center Americas, Inc., Cambridge, Massachusetts 02142, United States

Aparajith Bhaskar – Modersys, Vanguard House, Daresbury WA4 4AB, U.K.

John Mack – Modersys, Vanguard House, Daresbury WA4 4AB, U.K.

Richard D. Braatz – Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States; [orcid.org/0000-0003-4304-3484](#)

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acs.oprd.6c00149>

Author Contributions

Conceptualization: P.S., D.A.W., and A.S.M. Methodology: P.S., K.M., G.A., D.A.W., T.T., M.J., A.R.G., and A.B. Investigation: P.S., K.M., D.A.W., T.T., and A.B. Funding acquisition: N.N., C.P., R.D.B., and A.S.M. Supervision: D.A.W., N.N., R.D.B., and A.S.M. Writing—original draft: P.S. Writing—review and editing: all authors.

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■ ABBREVIATIONS

API, active pharmaceutical ingredient; ARC, accelerated rate calorimetry; BPR, back pressure regulator; CSTR, continuous stirred-tank reactor; ΔT_{ad} , delta adiabatic temperature; DILC, direct inject liquid chromatography; DoE, Design of Experiments; DSC, differential scanning calorimetry; EtOH, ethanol; ESI, electronic supporting information; FTE, full-time equivalent; FTIR, Fourier-transform infrared spectroscopy; HTE, high-throughput experimentation; LHSV, liquid hourly space velocity; MPC, model predictive control; OPCUA, open platform communication Unified Architecture; OSR, Optimization Sampling Reactor; OVAT, one-variable-at-a-time; PAT, process analytical technology; PID, proportional–integral–derivative; PLS, Partial Least Squares; RTD, residence time distribution; SCADA, Supervisory Control and Data Acquisition; UHPLC, ultra-high-performance liquid chromatography.

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