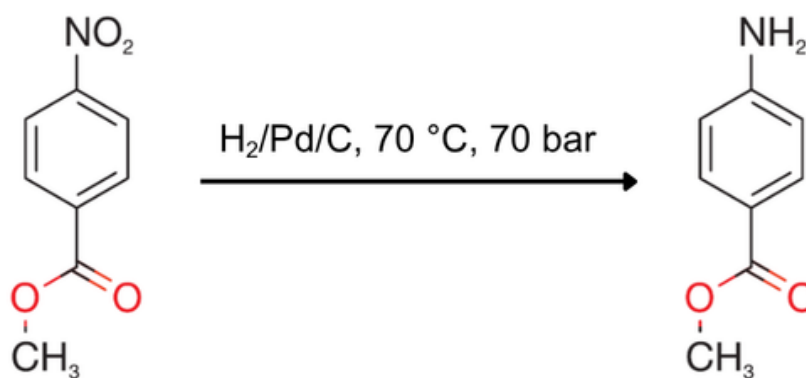


FACILE AND QUICK OPTIMIZATION OF A SMALL- AND LARGE-SCALE SYNTHESIS ON THE SAME PHOENIX™-H-GENIE® PLATFORM

INTRODUCTION

In modern synthetic laboratories, **experimental flexibility** and **operational safety** have become central priorities. As a result, many facilities seek to minimize the number of individual reactor systems in operation, reducing both **infrastructure complexity** and **operational risks**, especially when high pressure catalytic hydrogenations are the focus of their technology. Platforms capable of supporting chemical syntheses across a wide regime of scales, from **milligram-level parameter optimization** to **kilogram-scale production** offer a compelling solution to these emerging challenges. By enabling seamless scale progression on a single system, laboratories can achieve **significant space** and **cost efficiencies**, while maintaining **methodological consistency** throughout the development pipeline.

In this Application Note, we demonstrate the **scale-up capabilities** of the **Phoenix™-H-Genie® Platform**, highlighting its ability to transition seamlessly from **small-scale reaction optimization** and trials to **enhanced productivity studies**. In our model reaction (*Scheme 1*) the system enables up to a **tenfold increase** in **throughput** while facilitating catalyst activity investigations, all performed on the same reactor platform.



Scheme 1: Reduction of methyl-4-nitrobenzoate

INSTRUMENTATION AND SAFETY CONSIDERATIONS

All reactions were conducted using the **Phoenix™ II Flow Reactor system**, coupled with the **H-Genie® II hydrogen generator** as H₂ source. An **HPLC pump** delivered the liquids through the reaction line and a **Pressure Module 2.0** was employed to achieve consistent reaction pressures.

The **Phoenix™ II Flow Reactor** supports reaction temperatures of up to **450 °C** and operating pressures of up to **200 bar** for **liquid-phase reactions** and **100 bar** for **gas-liquid systems**, providing broad applicability across diverse chemical transformations. The reactor can be configured with **coiled tubing** for **homogeneous reactions** or **packed columns** containing a wide range of **catalytic materials**, offering significant flexibility for both **reaction optimization** and **catalytic process development**. The automatic pressure valve of the **Pressure Module 2.0** allows the **safe superheating** of **organic solvents**, by creating and maintaining pressures of up to **200 bar**, preventing boiling or rapid vaporization during high-temperature operation.

The **H-Genie® II** hydrogen generator can produce up to **1000 NmL/min** of **≥99.99% purity hydrogen** gas at pressures up to **100 bar**. By generating hydrogen on demand via water electrolysis, the system eliminates the need for high-pressure hydrogen cylinders and the associated gas storage requirements, providing a **safer** and **more convenient alternative** for **laboratory hydrogenation workflows**.

Each module of the **Phoenix™-H-Genie® Platform** has been engineered with safety as a core design principle. Each module of the system integrates multiple **automated safety features** and monitoring mechanisms, ensuring reliable operation under demanding reaction conditions, while providing continuous protection and operational confidence for the user.



Figure 1: Members of the Phoenix™-H-Genie® platform

RESULTS AND DISCUSSION

To prove the feasibility of scaling up the reaction and get familiarised with the experimental procedures, the first set of parameters were attempted on an **intermediate-scale** with a target of **100 g product**.

A **0.1 M** solution of **methyl 4-nitrobenzoate** in **methanol** was prepared by dissolving **130.4 g** of **methyl 4-nitrobenzoate** in **7.2 L** of **MeOH**. The reaction was conducted using a **MidiCart™** catalyst column loaded with **2.7 g** of **10% Pd/C** as the catalyst. The **liquid flow rate** was maintained at **10.00 ml/min** while **hydrogen** was supplied at a flow rate of **100 NmL/min**. The reaction was performed at **70 °C** under a pressure of **70 bar**.

HPLC-MS samples have been prepared every **30 minutes** during a **10-hour period**. During the first 10 hours of the reaction, the MidiCart™ showed a **conversion** of not less than **98.5%** (Figure 2).

Following the 10-hour reaction time, **87 g** of **Methyl-4-aminobenzoate** had been produced with a **yield** of **96%** (after recrystallisation) and **NMR purity** of **99%**.

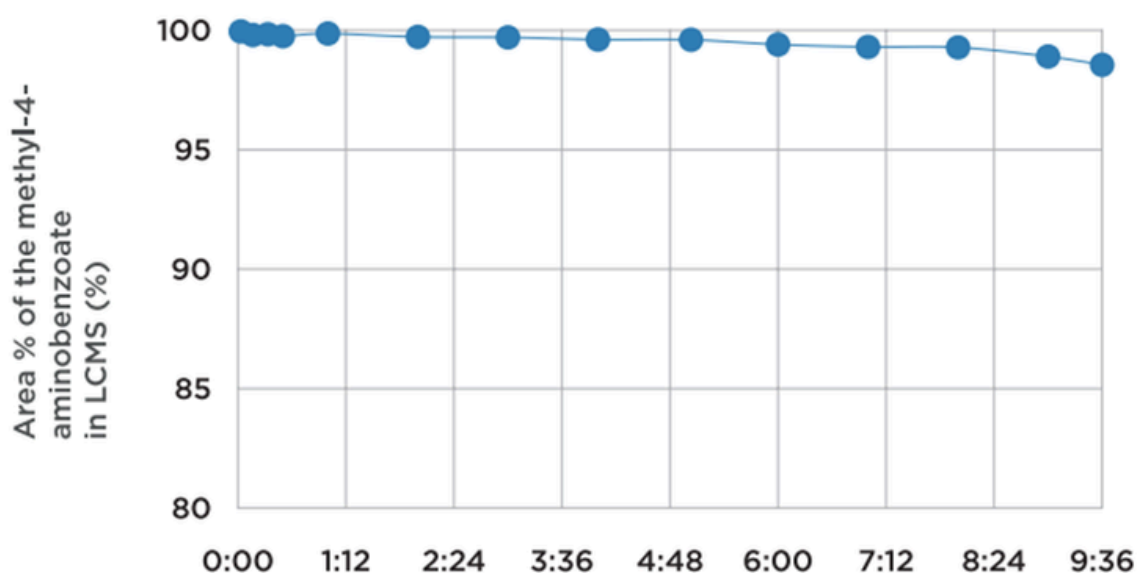


Figure 2: Conversion to methyl-4-aminobenzoate with the MidiCart™ (% LCMS)

These results demonstrate that the reactor system is suitable for the reduction of the target compound on a **100 g-scale** and confirm that the catalyst maintained adequate activity over the **12-hour reaction period**.

Encouraged by the preliminary experiments, our objective was to demonstrate that a **tenfold scale-up** could be readily achieved **within the same reactor system** by solely adjusting the **catalyst bed size** and proportionally increasing the liquid and gas flow rates.

For the tenfold scale-up, a **1" MMS catalyst column** (L = 230 mm, ID = 21.2 mm, internal volume = 81 mL) was packed with **35 g** of **10% Pd/C** (particle size distribution d10: 7 µm, d50: 35 µm, d90: 150 µm). Voids have been filled with **32 g glass beads**. **Liquid** and **H₂ flow rate** were increased to **100 NmL/min** and 1000 NmL/min respectively. The rest of the reaction parameters remained constant as to the preliminary experiments.

During the run, **LC-MS** sampling have been carried out from which **>99%** conversion was observed in the first **2.5 hours**. To account for the gradual drop in catalyst activity and maintain **>90%** conversion, we have lowered the **liquid flow rate** to **80 ml/min** after **4 hours** (Figure 3). During the **7.5-hour run**, an average **productivity** of **83 g/h** and overall **isolated yield** of **pure methyl-4-aminobenzoate** (LC-MS purity: >98%) have been achieved. Table 1 summarises the key achievements and parameters from both experimental procedures.

	Liquid / H ₂ flow rate (mL/min)	Reaction time (h)	Yield (g / %)		Purity (%)	Catalyst Mass (g)	Substrate / Catalyst ratio (%)	Productivity (g/h)
MidiCart™	10 / 100	10	87	>99	99 ^a	2.2	3.4	8.7
1" MMS Column	100→80 / 1000	7	513	95 ^b	>98 ^c	35	5.6	80

Table 1: Summary of experimental differences during scale-up - ^aDetermined by ¹H NMR. ^bYield of product after recrystallisation. ^cWeighted average was calculated based on ¹H NMR spectra of fractions collected during the run.

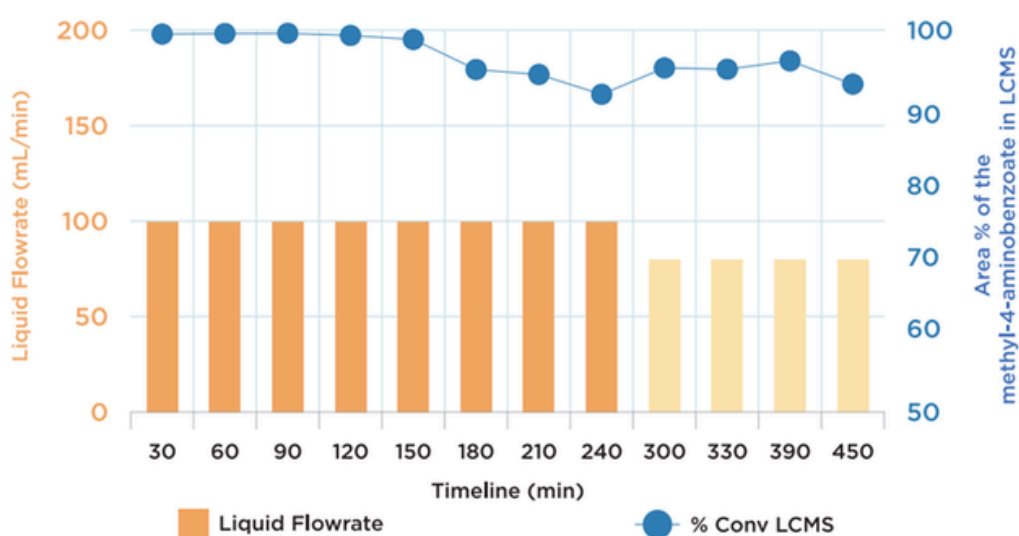


Figure 3: Conversion to methyl-4-aminobenzoate with the 1" MMS column

CONCLUSION

Using our model reaction, which requires **3 – 4.5** equivalents of **H₂**, we demonstrated that the **Phoenix™-H-Genie®** continuous-flow reactor platform enables **straightforward scale-up** through **simple adjustment** of **operating parameters** and **catalyst bed size**. The seamless and quick switching of catalyst columns can be performed in minutes, allowing a fast transformation of the system into a **kilogram-scale synthetic platform**. An approximately **tenfold increase** in **productivity** was achieved without the need for any system modifications. The flexibility of the setup allowed us to modify reaction parameters during the reaction with the aim of maintaining a desirable conversion.

For more information, please visit
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