



# CATALYTIC HYDROGENATION OF DIFLUORO-NITROBENZENE USING THE PREMEX APART HIGH-PRESSURE REACTOR AND THE H-GENIE® HYDROGEN GENERATOR

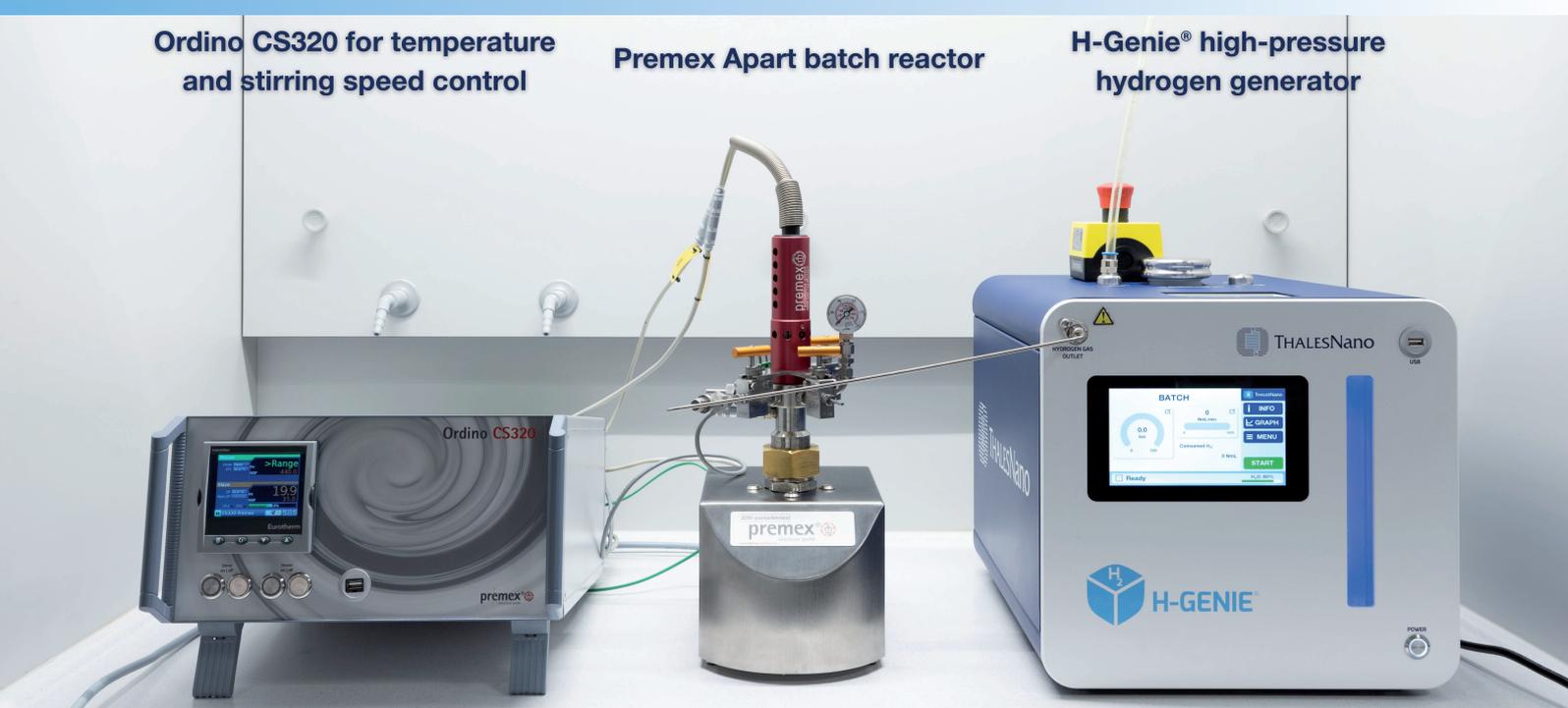
## INTRODUCTION

Catalytic hydrogenation is a cornerstone of synthetic chemistry. To this day, traditional laboratory hydrogenation reaction practices carry widely known safety concerns. **Storage and handling** of high-pressure **hydrogen cylinders**, as well as the **risks of leaks and explosions** demand specially trained personnel and infrastructure, making this crucial reaction type highly complicated for chemists and facility operators across the globe.

The **H-Genie®** hydrogen generator mitigates these challenges by **generating high-pressure H<sub>2</sub> gas in-situ** on demand. Acting as a high-pressure H<sub>2</sub> source, the H-Genie® eliminates the need for hydrogen storage and cylinders in the laboratory. This approach enhances operational safety, simplifies laboratory workflows, and enables chemists to perform high-pressure catalytic hydrogenations with greater confidence and compliance.

An emerging trend today is the combined application of batch and continuous flow systems resulting in **semi-continuous, mixed technologies**. The instruments featured in this Application Note can also provide a seamless opportunity for building such a mixed system.

In this Application Note, we demonstrate the ease of use and seamless operation of a **Premex Apart high-pressure batch reactor** and an **H-Genie® hydrogen generator system** for a **heterogeneous catalytic pharmaceutical model reaction** (depicted on picture 1). Using the injected hydrogen amount monitoring function of the H-Genie®, as well as the temperature probe of the Premex Apart reactor, the conversion of the reaction can be followed.



Picture 1: Experimental setup used in the catalytic hydrogenation of difluoro-nitrobenzene

## INSTRUMENTATION AND SAFETY CONSIDERATIONS

Using patented technology, the H-Genie® can generate  $\geq$  **99.99% purity hydrogen gas** at up to **1000 NmL/min flow rate** and **100 bar pressure** via water electrolysis from **Type I quality water**. The built-in Mass Flow Controller enables accurate control of the generated gas flow rate and tracking of the injected hydrogen. The „consumed hydrogen” function allows users to monitor a **batch reaction’s hydrogen uptake** which is directly in correlation with the conversion. Multiple day reactions requiring hydrogen are also feasible for the H-Genie® with the inclusion of the **Automatic Water Filler** attachment.

The H-Genie® was designed with safety as its utmost priority, featuring a multitude of automated safety features, including a **built-in H<sub>2</sub> sensor, water leak detection, a gas leakage test** during every initialization, and overpressure detection. The **internal gas circuit** of the generator is designed to be as small as possible, minimizing the amount of released hydrogen during the unlikely event of an emergency shutdown. The H-Genie® is also equipped with an **external emergency button** which allows users to quickly shut down the system.

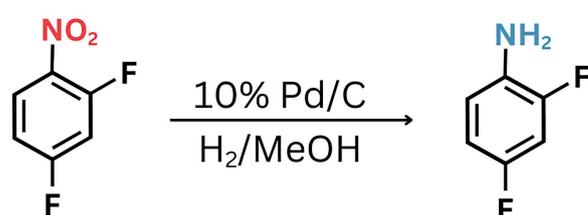
**Water quality** is a critical parameter influencing the operational lifetime of the electrolytic cell in the H-Genie® system. The instrument **continuously monitors the conductivity of the water** in the internal reservoir. If an increase in conductivity is detected, the device issues a warning message prompting the user to replace the water. In cases of sustained elevated conductivity, the system initiates an automatic and safe shutdown procedure to protect the electrolytic cell from potential damage. To ensure consistently low water conductivity, the internal reservoir is equipped with an **integrated ion-exchange cartridge** containing a **mixed-bed resin**.

Used for heterogeneous catalytic reactions, the **Premex Apart reactor** is a highly configurable **high-pressure** and **high-temperature benchtop batch reactor**. The reactor used in our experiments had a **60 mL nominal volume** and was configured for working temperatures up to **200°C** and pressures up to **200 bar**. The reactor is available with a **100 mL reactor volume** and operating limits of up to **300°C** and **480 bar**. The reactor zone is double sealed using an O-ring and metal-metal cutting ring for confident leak-tight assembly. The autoclave lid features **multiple gas connections** with **needle valves**, a fully integrated **magnetic feedthrough**, and a **micromotor**. The needle valves can be configured with an **immersion sampling tube**. In our experiments, an immersion temperature probe was used to track reaction temperatures inside the reaction chamber. **Electric or fluid heating** specifications are both available. **Reaction heating, stirring, temperature monitoring** and **logging** duties specific to the reactor were carried out using the **Ordino CS320 control unit** also supplied by Premex. Although we employed the Apart reactor to conduct our experiments, other reactors from Premex (such as the Twister and Pinto high pressure reactor systems) are also suitable for this application depending on the requirements of the user.

## DISCUSSION AND RESULTS

### Catalytic hydrogenation of difluoro-nitrobenzene using the H-Genie® and Premex Apart

To demonstrate the chemoselective reduction of a nitro group in the presence of an aromatic ring and halogen substituents, the hydrogenation of difluoro-nitrobenzene was selected as a model reaction using 10% Pd/C catalyst (Scheme 1). A **30 mL, 1 M methanolic solution** of the nitrobenzene



Scheme 1: Reduction of difluoro-nitrobenzene

was prepared and filled into the reactor along with **80 mg** of **10% Pd/C catalyst**, equating to a catalyst loading of **10Wt%**. To eliminate any oxygen from the reaction atmosphere, two flushing sequences using hydrogen gas, generated by the H-Genie® were carried out by letting **5 bar** of **pressure** to build up in the head space, followed by releasing it via the opening of a needle valve.

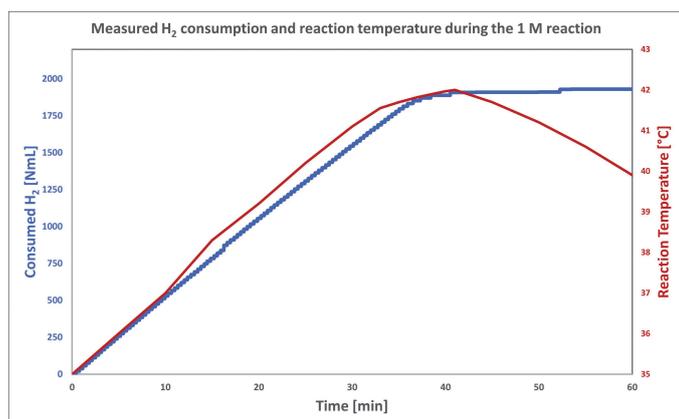


Figure 1: Reaction monitoring based on the H-Genie's consumed hydrogen function and temperatures recorded by the Premex Apart reactor.

Subsequently **reaction pressure** of **30 bar** was set on the H-Genie® and the reactor was pressurised. During pressurization, the **reaction temperature** of **35°C** was set, and heating was initiated using the **Ordino CS320**. After stabilization of temperature and pressure, **stirring** was commenced at **400 RPM** and the “consumed hydrogen” value on the H-Genie® was reset. This procedure allowed precise quantification of hydrogen consumption by the reaction.

Throughout the reactions, **hydrogen uptake** was continuously monitored, and **temperature profiles** were recorded. To study the **exothermic nature** of the catalytic process, temperature regulation was suspended during reactions.

**Monitoring** both the **reaction temperature** and **hydrogen consumption** enabled reliable determination of reaction completion. As shown in **Figure 1**, the reaction was considered complete at approximately **41 minutes**, as indicated by the onset of a temperature plateau and the absence of further hydrogen uptake.

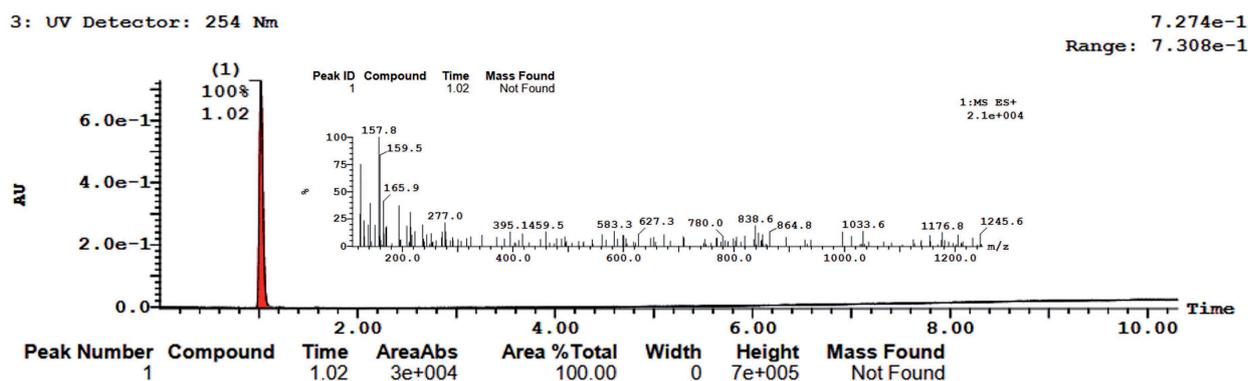


Figure 2: Starting material HPLC-MS measurements

To prove the accuracy of the method, the reaction mixture was filtered, and samples were prepared for **HPLC-MS analysis**. LC-MS analysis of the starting material mixture shows a single peak at **1.02 minute elution time** with an **m/z value** of **159** consistent with the unfragmented molecule-ion from difluoro-nitrobenzene starting material (Figure 2). The product mixture, taken directly from the filtered reaction solution without further work-up, also consists of a single peak at **0.30 min elution time** and **m/z value** of **130**. This corresponds to the **[M+1]<sup>+</sup> peak** of the **difluoro-aniline product** which is rationalised by the HPLC method that involved **TFA** in the eluent which protonates the molecule ion.

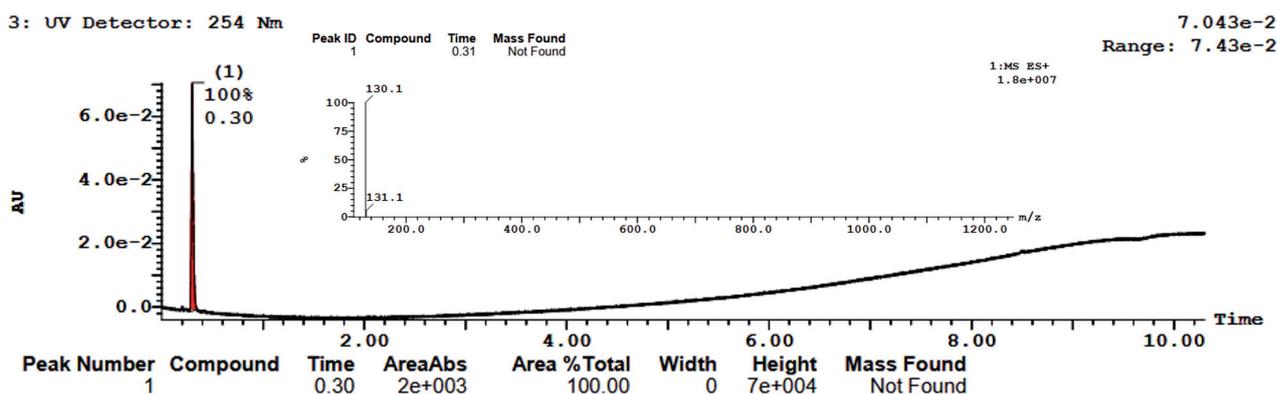


Figure 3: Product HPLC-MS measurements

HPLC-MS analysis of samples has confirmed quantitative conversion, indicated by the lack of hydrogen uptake measured by the H-Genie®. The analysis also confirms the intended chemoselectivity, as only a single peak was observed in the reaction mixture.

### Effects of substrate concentration on reaction performance

To investigate the effect of **substrate concentration** on reaction performance, **0.1 M** and **5 M solutions** were prepared, both reactions were carried out at **50°C reaction temperature**. In the dilute (**0.1 M**) solution, rapid reaction completion was observed within approximately **1.3 minutes**, rendering real-time monitoring challenging based solely on hydrogen uptake measurements. In this case, measured thermal data provided detailed insight into the reaction progression (**Figure 4**, stirring started after **50°C** was reached at the **170 second** mark).

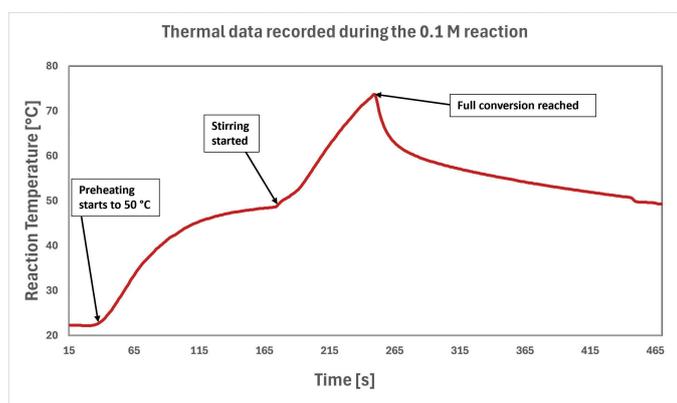


Figure 4: Thermal measurement exported from the Ordino CS320 control unit during 0.1 M experiment

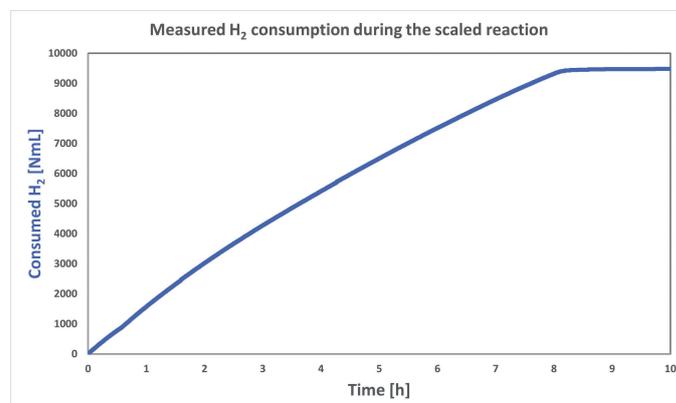


Figure 5: Reaction monitoring of the 5 M batch based on the H-Genie®'s consumed hydrogen function

In contrast, the reaction conducted at **5 M** required **8.2 hours** to reach completion, with a total hydrogen consumption of **9.5 L**, in close agreement with the calculated stoichiometric demand (**Figure 5**).

## SUMMARY AND CONCLUSIONS

The integration of the H-Genie® hydrogen generator with Premex high pressure reactors provides a **safe** and **user-friendly** solution for laboratories routinely performing **high-pressure batch hydrogenations**. The technique demonstrated shows how workflows can be enhanced through real time experimental data combined from both units. The accuracy of consumption monitoring of the H-Genie® provides a great improvement compared to working with conventional hydrogen cylinders.



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**ThalesNano Inc.**  
 Záhony utca 7. | H-1031 Budapest | Hungary  
**Phone:** +36 1 880 8500  
**Fax:** +36 1 880 8501  
**Email:** [sales@thalesnano.com](mailto:sales@thalesnano.com)  
[www.thalesnano.com](http://www.thalesnano.com)

**US Office**  
 50 S. Penn St. Suite B-2  
 Hatboro PA. 19040  
 USA  
**Phone:** 215-534-3365  
**E-mail:** [USAsales@thalesnano.com](mailto:USAsales@thalesnano.com)

