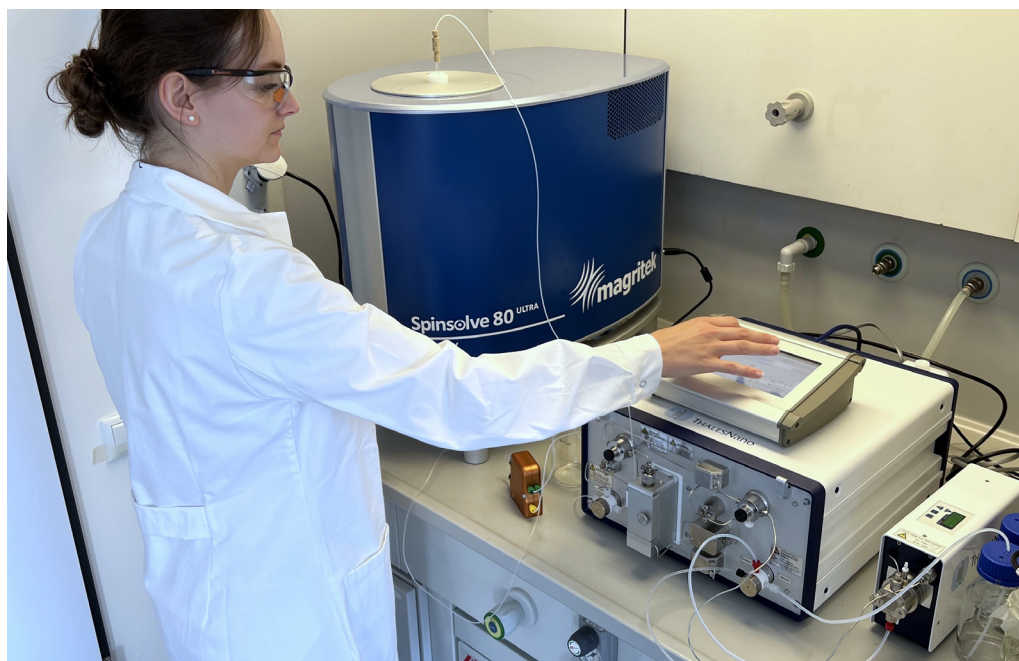


Spinsolve

Coupling a Spinsolve® NMR spectrometer to an H-Cube® Pro flow reactor for fast reaction optimization



Spinsolve 80 Ultra monitoring the hydrogenation reaction performed with an H-Cube® Pro.

The synergy between continuous flow reactors and benchtop Nuclear Magnetic Resonance (NMR) spectroscopy has attracted significant attention recently due to its transformative impact on chemical synthesis and analysis. Continuous flow reactors offer distinct advantages, including precise control over reaction parameters, enhanced safety, and improved reaction efficiency. Conversely, benchtop NMR spectroscopy provides, non-destructive, and quantitative insights into reaction kinetics, intermediates, and final products. This integration enables real-time monitoring of the conversion as a function of the reactor parameters, facilitating rapid and even automated reaction optimization. The benefits of this hybrid approach are evident in the accelerated processes of reaction discovery and optimization. Researchers can utilize real-time NMR data to make on-the-fly adjustments to reaction conditions, resulting in enhanced yields and selectivity. Furthermore, in-line analysis reduces the need for laborious sample preparation and off-line analysis, thus streamlining workflows and minimizing waste.

In this application note, we have integrated a Spinsolve 80 ULTRA benchtop NMR spectrometer from Magritek at the outlet of an H-Cube® Pro flow reactor from Thales Nano. The Spinsolve ULTRA model is a compact spectrometer that offers high-resolution capabilities, crucial for acquiring spectra of products dissolved in protonated solvents. The H-Cube® Pro, on the other hand, offers multiple advantages, including enhanced safety, precise reaction control, high efficiency, reduced catalyst loadings, and broad substrate compatibility. Its automation capabilities make it possible to streamline hydrogenation reactions in a versatile manner, making it a valuable tool in chemical synthesis and research. To showcase the benefits of combining these technologies, we optimized the reaction parameters (temperature, pressure, equivalents of H₂, and reacting mixture flow rate) to maximize the hydrogenation of cinnamyl alcohol (Figure 1). The results demonstrate that by integrating a rapid on-line analytical tool, such as NMR spectroscopy, the full spectrum of reaction parameters can be thoroughly explored within a few hours to optimize the reaction.

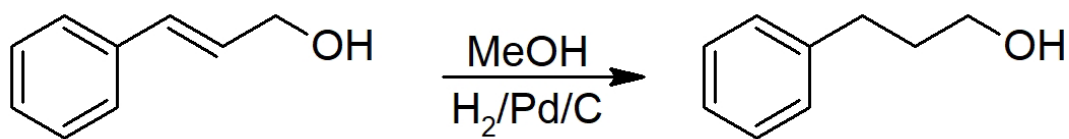


Figure 1: Hydrogenation of the double bond of cinnamyl alcohol.

In Figure 2, a photo of the setup, installed within a fume hood is presented. For these experiments, an H-Cube® Pro 2.2 from Thales Nano was equipped with an HPLC pump to precisely set the flow rate of the starting material solution. The catalyst cartridge used was the 10% Pd/C cartridge from Thales Nano. Hydrogen gas was generated via controlled electrolysis by the H-Cube® and subsequently mixed with the substrate solution before entering the catalyst. Any unreacted hydrogen gas remaining after passing through the reactor was efficiently separated at the outlet of the H-Cube® using a Zaiput "SEP-10" gas-liquid phase separator. The reaction kinetics were continuously monitored using ¹H-NMR spectroscopy with solvent suppression using a Spinsolve Ultra 80 MHz Multi-X Benchtop NMR spectrometer equipped with a reaction monitoring kit 2 (RMK2). This kit includes a glass flow cell that spans the spectrometer from top to bottom enabling the seamless pumping of the reaction mixture through the Spinsolve's sensitive volume in either continuous or stop-flow mode. In this study, we connected the output of the reactor to the flow cell and monitored the H-Cube® Pro in continuous mode, with the flow rate being easily controlled using the HPLC pump. As starting material, we prepared a solution of cinnamyl alcohol in methanol at a concentration of 0.5 molar (22.487 g / 167.59 mmol in 335 mL). The reaction mixture was monitored every 2 minutes by acquiring a 1D ¹H WET sequence with 4 scans and a 10-second repetition time. The WET sequence was set to suppress the two methanol signals at 3.3 ppm and 4.9 ppm, and the signal acquisition was performed in the presence of carbon decoupling to effectively eliminate the carbon satellites from the spectrum.

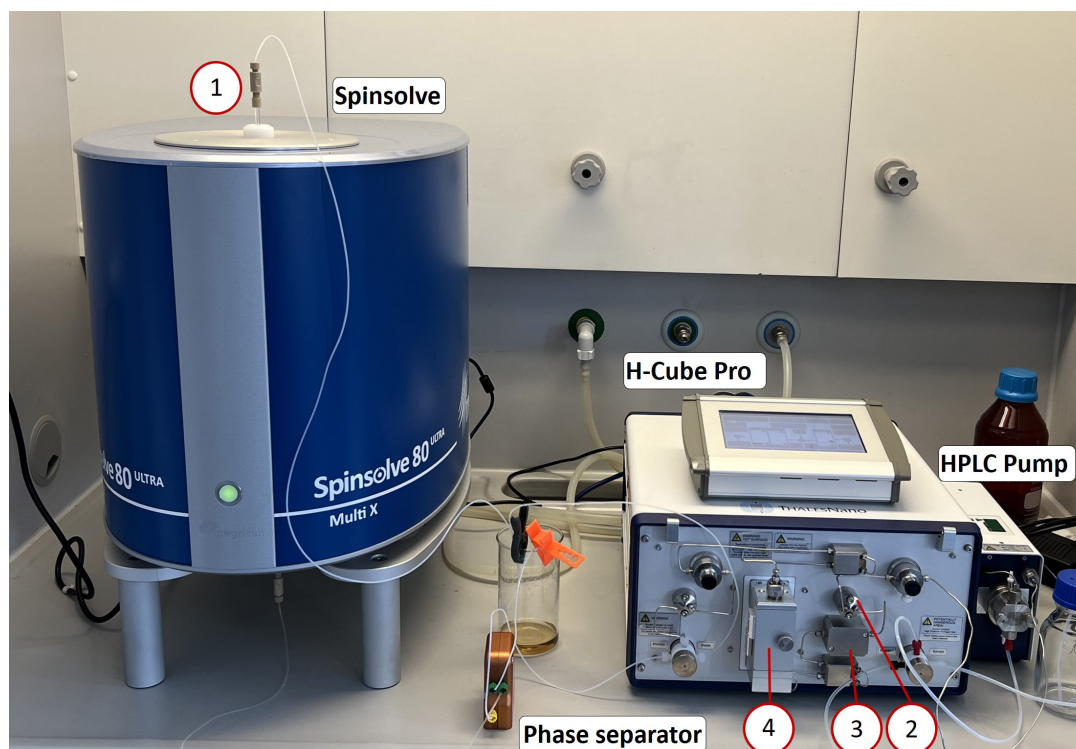


Figure 2: Picture of the setup that combines an H-Cube® Pro flow reactor with a Spinsolve 80 ULTRA for on-line reaction monitoring. The Spinsolve is equipped with a reaction monitoring kit that includes a glass flow cell (1) that makes it possible to circulate the reaction mixture through the NMR spectrometer to measure it on-line. The flow reactor produces the H₂ required for the hydrogenation in a safe mode by electrolysis and mixes it with the solution at (2). A bubble detector (3) confirms the presence of H₂. Then the starting material finally enters in the column heater containing a CatCart® catalyst at (4).

Acquiring high-resolution spectra in the presence of protonated solvents

The success of on-line monitoring by NMR spectroscopy relies on the high performance of the solvent suppression method, which attenuates the large solvent signals that would otherwise overlap with the smaller signals from the starting material and products in the sample. Figure 3 compares the spectra acquired in continuous flow mode, showing the standard proton spectrum alongside a spectrum obtained using the WET solvent suppression. The overlaid spectra demonstrate how the WET suppression significantly attenuates the methanol peaks to eliminate the overlap with the CH_2 signal at 3.5 ppm and simultaneously removes the ^{13}C satellites of the CH_3 of methanol.

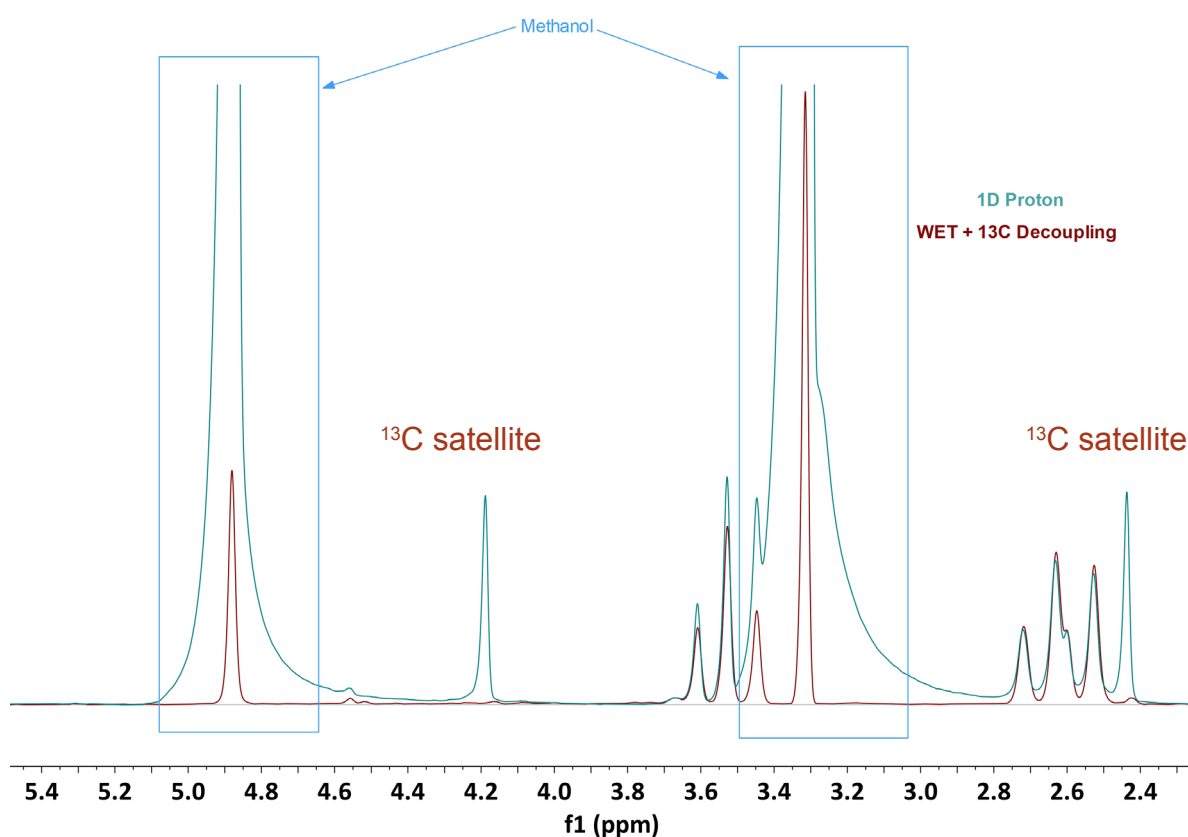


Figure 3: Comparison of the spectra acquired for the product with a standard pulse and acquire sequence (blue) and a WET suppression with carbon decoupling sequence (red). The measurements were performed under continuous flow conditions with a liquid flow rate of 1 mL/min.

The reaction was optimized by varying the temperature, pressure, hydrogen amount, and liquid flow rate were systematically varied, while spectra were continuously acquired to identify the optimal parameter combination. Figure 4 offers a subset of spectra collected during incremental variations in temperature and pressure. The signal regions corresponding to specific protons are color-coded. Protons from the double bond and the CH_2 group of the starting material are marked in red and yellow, respectively, while CH_2 protons of the product are highlighted in light blue, dark blue, and green. The graph indicates that, with increasing pressure and temperature, the signals of the starting material decrease while the signals of the product increase. To quantify reagent concentrations, the signal regions were integrated and multiplied by a single response factor to obtain absolute concentration values.

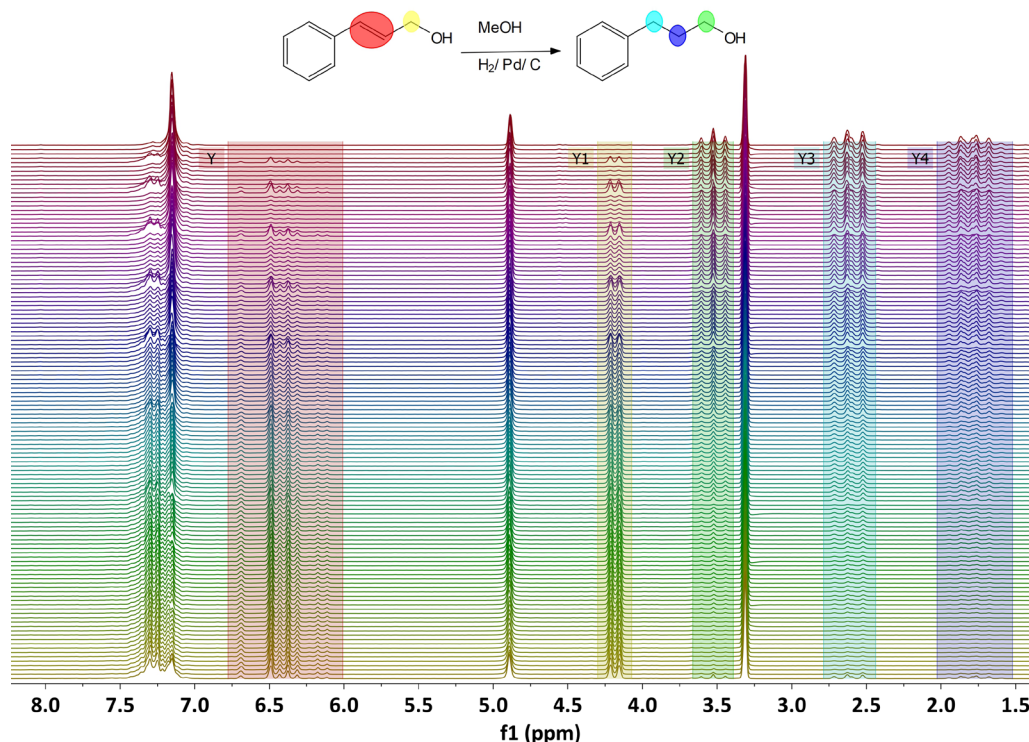


Figure 4: Spectra acquired with the Spinsolve RMX software during an optimization run of the double bond reduction of cinnamyl alcohol. The data was collected with a WET sequence set to suppress the signals of methanol at 3.3 and 4.9 ppm. To eliminate the carbon satellites, the signal was acquired in the presence of carbon decoupling.

The concentrations obtained for the marked regions in Figure 4 are plotted against time in Figure 5. The left graph displays concentrations for the starting material, while the right graph shows those for the product. Each point in these curves corresponds to a spectrum in the stack plot of Figure 4, and different curves within each plot represent concentrations independently obtained from different integral regions. The excellent agreement between these curves demonstrates the accuracy and robustness of the quantification method. The minimal scatter of the points collected during each steady-state phase underscores the precision of the measurements. After altering a reaction parameter, the new steady state is typically reached within 10 minutes. Whenever a new pressure value is set on the H-Cube® (marked with a vertical line in the graphs), the signal of the starting material briefly increases before reaching a new steady state. This temporary increase occurs because the hydrogen flow is paused while the system

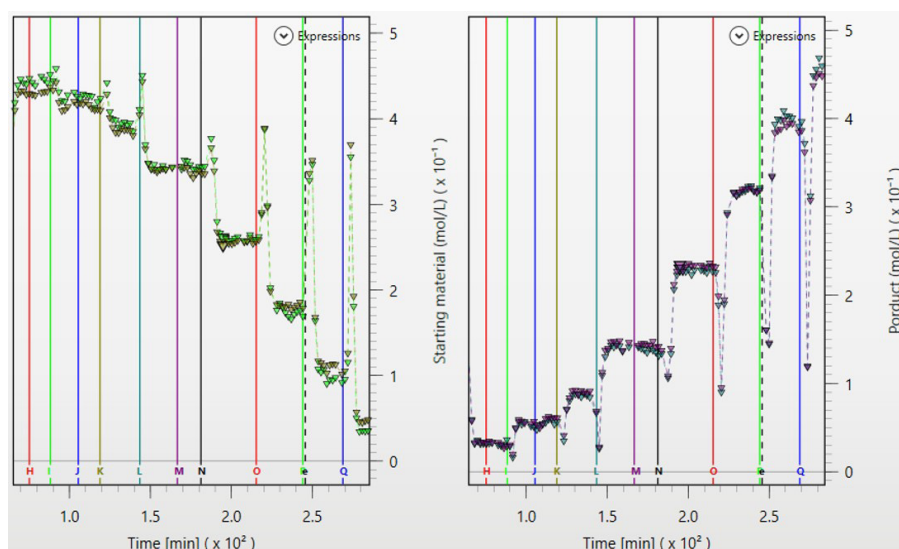


Figure 5: Screenshot of the concentration plots of the starting material (left) and product (right) as they are displayed in real time on the Spinsolve reaction monitoring software (RMX). The different curves on each plot correspond to the concentration calculated using the signal of different chemical groups available for both, starting material and product. The values are in very good agreement, showing how linear the NMR response is. It should be noticed that the calibration of the system is done using an external standard with a known concentration. The same response factor is used to quantify the concentration of both reactant and product using the different signals available in the spectrum.

adjusts the reactor pressure to the new set value. Once the reaction pressure stabilizes at the new set value, hydrogen flow is resumed, and the reactor quickly attains a steady state characterized by constant conversion. The void volume of tubing between the reaction zone and the NMR spectrometer is a couple of milliliters, therefore all of the above data is accessible in real-time during the reaction, within a couple of minutes after the mixture exits the column, enabling us to directly ascertain from the NMR data whether the steady state representative of each specific setting has been achieved or not. Figure 6 displays a subset of representative spectra collected during steady states for different temperature and pressure combinations from the optimization run depicted in Figures 4 and 5. These results indicate that, for the examined reaction, an increase in pressure significantly enhances conversion, whereas changes in temperature do not lead to a substantial increase in conversion

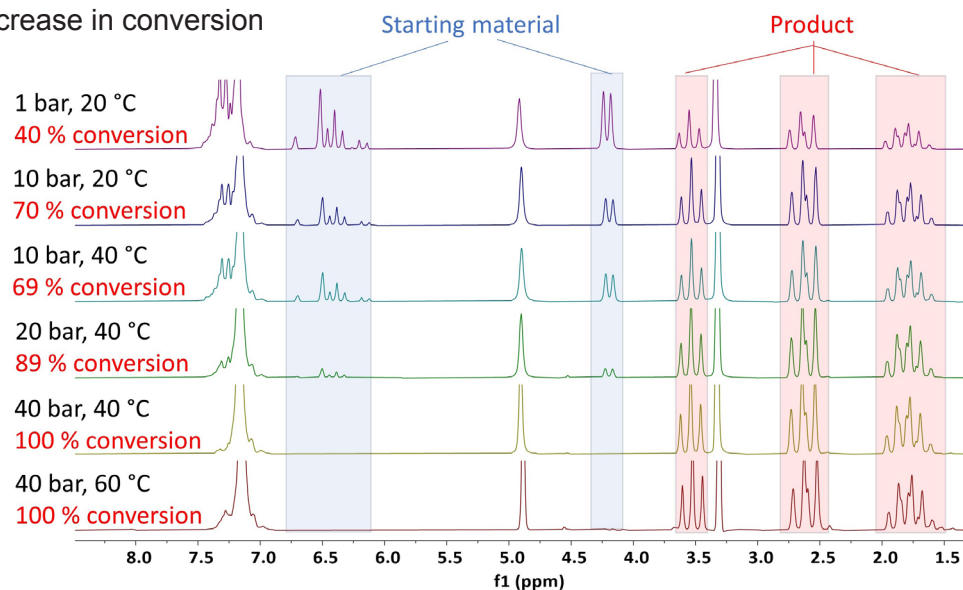


Figure 6: Spectra collected with the reactor in steady state for different values of temperature and pressure. These measurements were performed with a hydrogen amount of 42 NmL/min and a liquid flow rate of 1 mL/min.

Similarly, the dependence of the conversion on other reaction parameters was determined. Figure 7 shows the spectra collected as a function of hydrogen content for a temperature of 60 °C and a pressure of 40 bar. The curves reveal that a 42 NmL/min hydrogen is required to achieve full conversion.

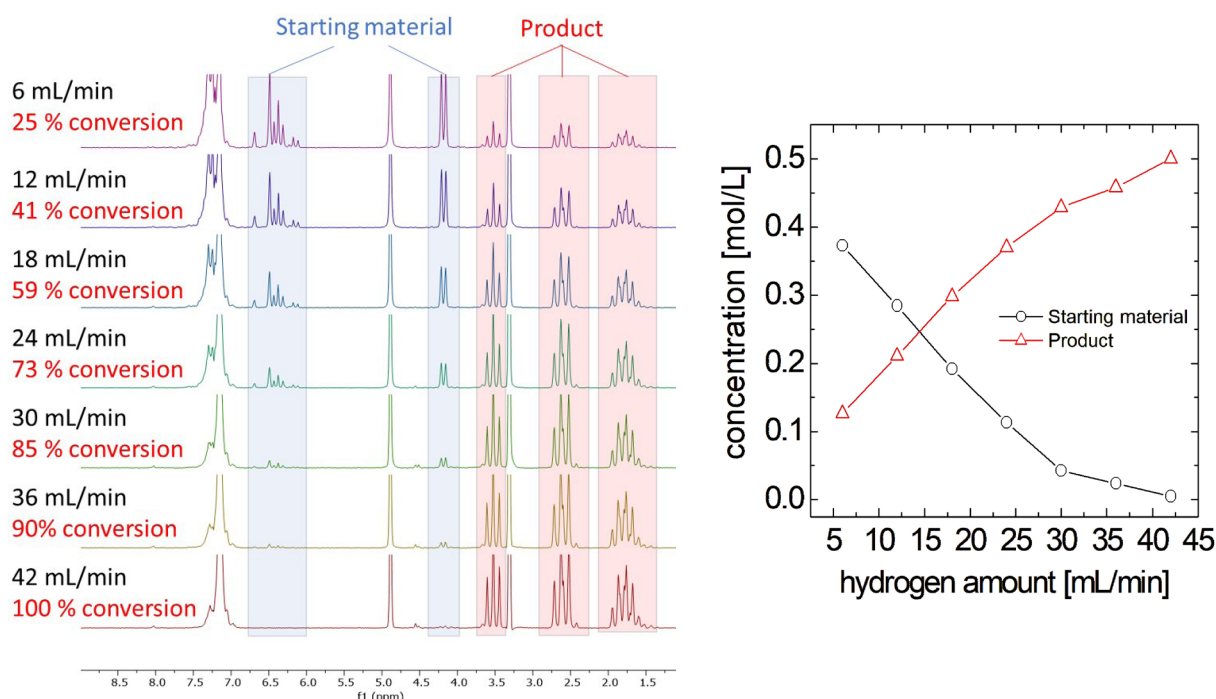


Figure 7: Optimization of the hydrogenation reaction run as a function of the hydrogen content for a temperature of 60 °C and a pressure of 40 bar.

Additionally, the impact of the liquid flow rate on the conversion was investigated, as depicted in Figure 8. Here, it is observed that an increase in flow rate, while keeping all other parameters constant, results in a decrease in conversion. This is an expected phenomenon due to the decreased residence time of the substrate on the column resulting from the higher liquid flow rate.

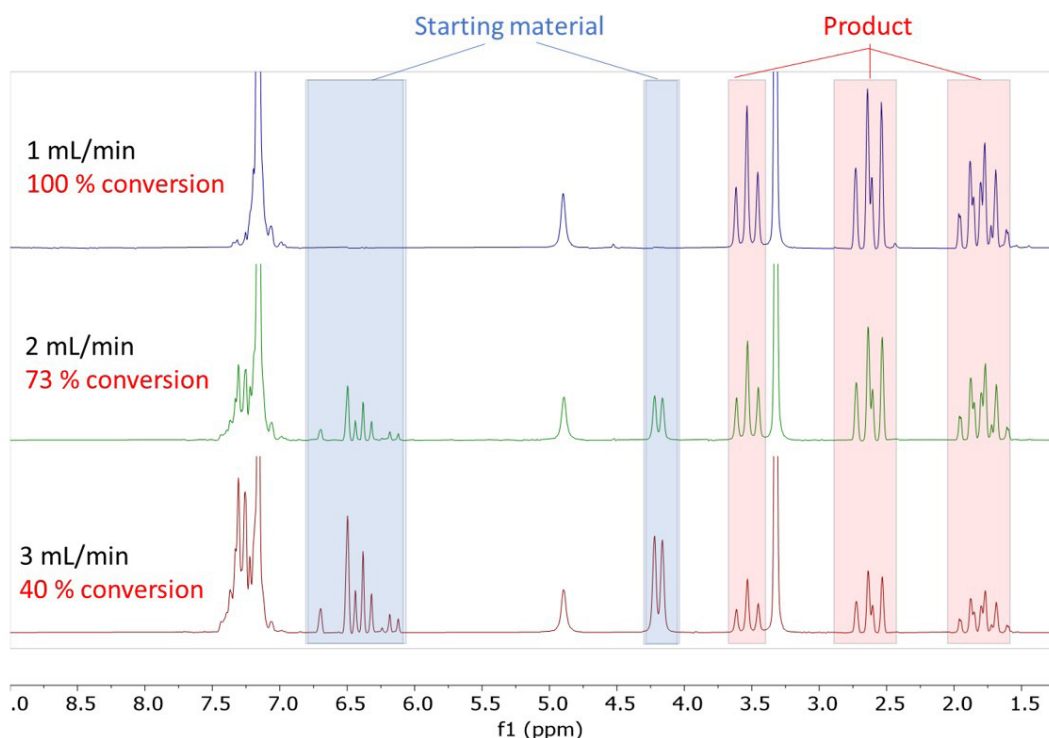


Figure 8: Conversion as a function of the flow rate for a temperature of 40 °C, a pressure of 40 bar, and a hydrogen amount of 42 mL/min.

Overall, this application note demonstrates the usefulness of combining a continuous flow reactor with an on-line NMR spectrometer for immediate reaction monitoring. This technique offers various advantages compared to conventional batch protocols and off-line analysis – since the steady state is achieved within 10-15 minutes after inserting new reaction conditions, a research chemist can easily analyze at least 30 different combinations of parameters in a single day, significantly facilitating and speeding up the optimization process. We see the combination of benchtop NMR and H-Cube® as a time- and cost-saving option to efficiently optimize hydrogenation reactions. It is also worth highlighting that the H-Cube® and the Spinsolve spectrometer behaved very stable and robust during the whole reaction optimization run, delivering consistent and reproducible conversion values.

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