Application Note 55:

Selective Hydrogenation with StoliCatalysts-Coated Reactors

Produced by Vapourtec

Abstract

Vapourtec have teamed up with Innovate UK award winning catalyst manufacturer Stoli Catalysts Ltd to demonstrate a new range of catalyst-coated tube reactors for continuous flow selective hydrogenation.

This application note describes:

- New catalyst-coated reactors developed by Stoli Catalysts Ltd.
- Greater than **90% selectivity** from a hydrogenation with hydrogen gas.
- Throughputs yielding **7 g/hr** of target product. Optimized reaction time of just 6 minutes.
- Long lifetime of catalysts with **less than 1 ppm of metal leaching.**
- Reactors with high surface area to volume ratio providing **excellent control** of this exothermic hydrogenation.

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Background

Regioselective heterogeneous catalytic hydrogenation forms the basis of a vast array of important industrial and laboratory based applications.[1]

It is widely recognized that variations in virtually every possible parameter can affect the regioselectivity of the reaction, including the catalyst, solvent, pressure, and temperature.[2]

With this application note we demonstrate the versatility of the Vapourtec R-Series system, equipped with a Stoli catalyst-coated reactor, in the regioselective reduction of cinnamaldehyde, Figure 1. A surprisingly complex hydrogenation, this model reaction can produce the desired cinnamyl alcohol, 2, or phenylpropanal, 3, by mono-hydrogenation, or the double hydrogenation product phenylpropanol, 4. This application readily illustrates the remarkable ease with which these reactions can be carried out and controlled using the Vapourtec R-Series.

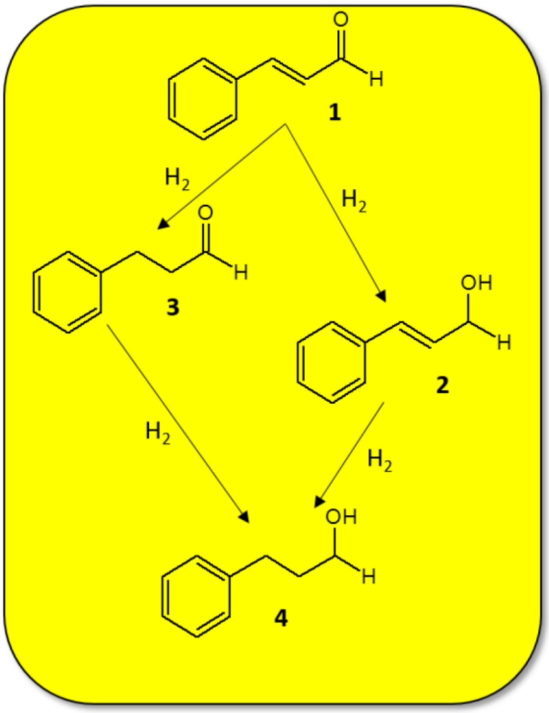

Figure 1: The hydrogenation of cinnamaldehyde as a model reaction for selective hydrogenation.

Setup

All reactions using the Stoli catalyst-coated reactors were carried out using a Vapourtec R-Series equipped with an R2C+ pump module, as shown in Figure 2. Hydrogen gas was provided from a hydrogen cylinder equipped with a low-pressure regulator and outputting 25 bar. Addition of hydrogen to the reaction was controlled using a Sierra Smart-Trak 2 mass flow controller, controlled by flow control software.

The reagent solution contained the desired concentration of 1. Reagent and hydrogen mixed in a T-piece before passing into a Stoli 5 m catalyst-coated reactor, maintained at reaction temperature by the R4, before passing through an inline Raman flow cell of Vapourtec design to permit inline monitoring. A pressure of 15 bar was maintained using an 8 bar fixed back pressure regulator (BPR) combined in series with an adjustable BPR. Automated collection was achieved using a Gilson fraction collector, under the control of flow control software. For the purpose of comparison, slurry experiments were performed using a Vapourtec E-Series easy-Medchem equipped with slurry pump manifolds and using 1.5 mm bore tubing for aspiration and all tubing carrying the slurry, as configured in Vapourtec Application Note 54.

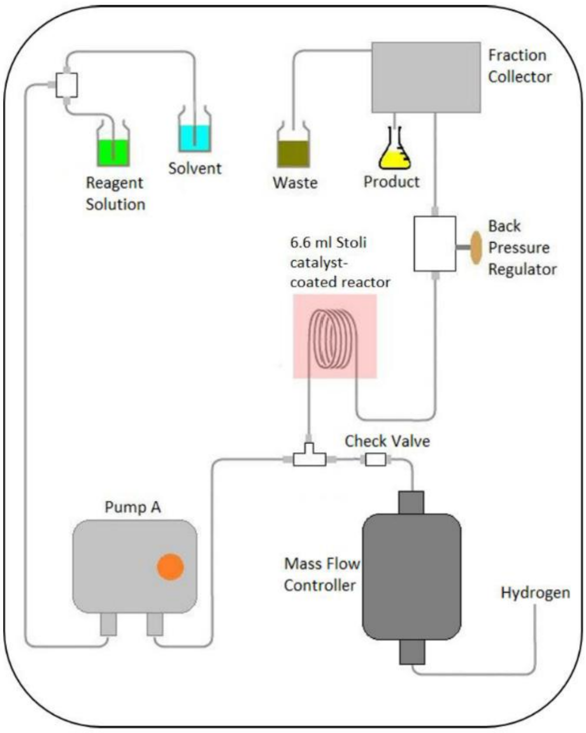

Figure 2: Schematic of the R-Series used during this application note.

Results

To demonstrate the wide-ranging benefits of the Stoli catalyst-coated reactor, several investigations were performed that explored the highest available conversion with high selectivity, long term catalyst stability and maximum throughput.

Maximization of Conversion and Selectivity

Using the Stoli catalyst-coated reactor with the Vapourtec R-Series, maintaining precise control over the reaction temperature, substrate concentration, and molar excess of gaseous hydrogen is straightforward. Flow control software was used to control these parameters, and after a brief optimization it was found that under best conditions (90 °C, 15 bar system pressure, a 0.1 M solution of 1 in iso-propanol, and a molar ratio of 1.67:1 of hydrogen to 1) it was possible to obtain a maximum conversion of 1 of 93.3% and a selectivity to 2 of 90.0% as determined by NMR. This result compares very well with the highest achievable conversion and selectivity reported using other approaches to this hydrogenation, but at significantly milder reaction conditions and with lower hydrogen excesses and pressure.

In a publication in 2016, Avril et al. of CSIRO Manufacturing, Australia, report the use of catalytic static mixers for the hydrogenation of cinnamaldehyde.3 Using a supported platinum catalyst deposited on metallic static mixers, which are inserted inside a tubular reactor, CSIRO were able to obtain 88.7% conversion with a 60.6% selectivity to 2. 140 °C, 20 bar and a four-fold excess of hydrogen was required by CSIRO to achieve their conversion using a 1.0 M solution in ethanol.

ThalesNano Nanotechnology Inc. report an application note using the H-Cube® flow reactor and a fixed bed of analogous silica supported platinum nanoparticles.4 By this approach, it is reported that a conversion of 86.3% of 1 was achieved, with a selectivity of 93.0% to 2. Significantly however, ThalesNano require a pressure of 60 bar and a very dilute 0.02 M solution of 1 in ethanol to achieve these results.

Internally at Vapourtec slurries of 5 and 10% palladium on carbon were investigated for the hydrogenation of 1 using an E-Series (application notes for the use of slurries are available at www.vapourtec.com). Using the slurry approach, it was possible to achieve full conversion of 1, interestingly though, only 25% of the reaction product was the target alcohol 2; the slurry appeared significantly more selective for phenylpropanal, 3 (75% by NMR). The full implications of this finding will be investigated in future applications.

Long Term Stability

The ability to run a synthesis using the reactor without seeing complete loss of activity or selectivity is key to many processes. To determine the long-term stability of the catalyst-coated reactors, an automated experiment was performed over 15 hours using flow control software with samples collected continuously using a fraction collector.

NMR was used to determine the reaction conversion and selectivity at the start and end of the experiment, and ICP-OES used to ascertain whether any leaching of the catalyst metal had occurred, and to what extent this changed over the duration of long use. The reaction conditions, 75 °C, 1 mlmin-1 0.1 M solution of 1 in isopropanol, 1.67:1 H2:1 at 15 bar, were chosen so that conversion of 1 was not full, enabling any loss of activity to be identified immediately, as summarized in Table 1. For a genuine production synthesis, conditions of higher temperature and or slower residence time could be selected to ensure that this effect is greatly reduced.

	Initial	**Final**
Conversion / %	94.0	70.0
Selectivity / %	83.5	90.5
Metal / ppm	< 1.0	< 1.0

Table 1: Comparison of reactor performance and metal leaching following 15 hours of continuous use

These results demonstrate that even after 15 hours of continuous operation there is no loss of selectivity, and compare well to the work of CSIRO who report ppb levels of leaching of nickel, iron and chromium from reactors used in analogous reactions.3 The low levels of metal leaching also imply that the decrease in conversion is due to catalyst inhibition rather than degradation. Regeneration of the catalyst-coated reactors can be achieved by calcining in air at temperatures of 350 – 500 °C. Research is currently ongoing at Stoli to optimize the conditions for regeneration of the catalyst used in this study.

Throughput Optimization

One significant advantage of the Stoli catalyst-coated reactor is the ease of scale-up. The coated reactors generate negligible backpressure, and so maximum flow rate is only limited by reaction kinetics rather than backpressure, as is often the case for packed beds. Multiple reactors can be used in series or parallel to ensure high conversion at high flow rates and high turnover numbers allow for high concentrations of starting materials.

To demonstrate how an increased throughput can be achieved using the Stoli catalyst-coated reactors, the concentration of 1 was increased from 0.1 M to 1.5 M without any observable decrease in conversion of 1 by NMR. At 1 mlmin-1 and 110 °C a conversion of 67.4% of 1 was achieved, with a selectivity of 86.1% for the target alcohol, yielding 7 g/hr of 2. By comparison, CSIRO report a throughput that equates to 2.16 g/hr and ThalesNano achieved a throughput of 0.02 g/hr at their optimal conditions. [3,4]

Conclusion

The Stoli catalyst-coated reactor has been used to perform the hydrogenation of cinnamaldehyde with remarkable control over reaction selectivity with high conversions and reaction throughput.

Selective hydrogenation can be a challenging transformation, and we believe that being able to achieve high selectivity while maintaining throughputs of several grams per hour will add a powerful capability to the synthetic flow chemist's toolbox.

Acknowledgements

We wish to thank Stoli Catalysts Ltd for supplying the catalyst-coated reactors used during this study, and for providing technical advice and support throughout. For further information regarding the catalyst, please contact Stoli: info@StoliCatalysts.com. Our thanks also go to Tocris for undertaking the NMR analysis and Medac Ltd for the ICP-OES analysis.

Further Research

Vapourtec is very encouraged by the excellent results obtained. The selectivity for the desired product is high, leaching is below detectable levels, catalyst life appears reasonable and the catalytic reactor has proved reliable and easy to use. Vapourtec together with Stoli Catalysts Ltd are now keen to work with one or more of our Customers to evaluate the Stoli catalytic reactors applied to a pharmaceutically relevant selective hydrogenation. Vapourtec Customers interested in evaluating the Stoli catalytic reactor please contact Manuel.nuno@vapourtec.com.

Analysis

Analysis was performed by outsourced NMR. Conversion and selectivity was calculated using proton integration. Metal leaching was determined via ICP-OES.

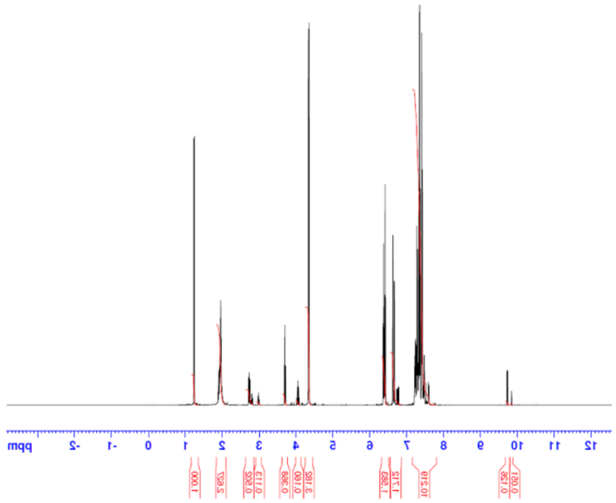

Figure 3: ^{1}H NMR ($CDCl_3$, 400 MHz) of the crude reaction mixture following evaporation of the reaction solvent.

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