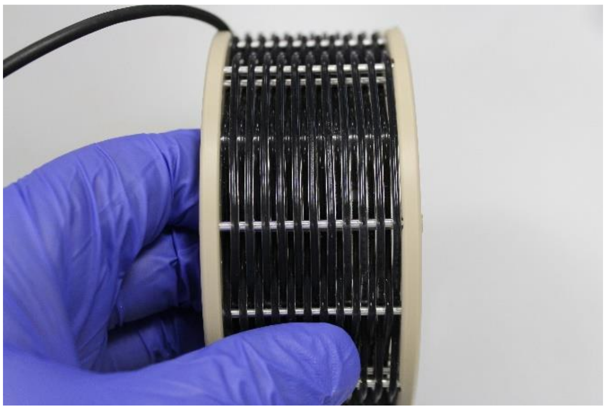
Application Note 54:

Continuous Slurry Hydrogenation with Hydrogen gas

Produced by Vapourtec



Abstract

This application note describes:

- **Selective hydrogenation** using heterogeneous catalysis, between multiple products
- Precise control of catalyst and hydrogen to substrate ratio using Vapourtec V-3 pump
- Rapid screening of conditions without the need for re-loading fixed beds
- Easy handling of a complex flow stream consisting of solid, liquid and gas
- 16 experiments at 7 bar performed in under 12 hours

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Background

Heterogeneous catalytic hydrogenation in flow. Heterogeneous catalytic hydrogenation is one of the most extensively used reactions in chemistry,[1] offering mechanistically unique routes to many compounds. However, in spite of immense efforts at development of technology suitable to execute them,[2] such as autoclaves, sealed tubes, parallel catalyst screening technology and microwave techniques, they remain somewhat challenging to develop and optimize. Frequently there is a reticence about using these reactions in a research environment, as the equipment requires some degree of specialist knowledge. Many laboratory systems are also very time consuming in terms of effort needed in order to carry out even rudimentary optimization chemistry.

Herein we present a very simple medium pressure heterogeneous catalytic hydrogenation of O-benzyl vanillin, Figure 1, combining the three phases (solid catalyst, reagent solution and gaseous hydrogen) in flow using a Vapourtec easy-MedChem E-Series. We demonstrate that it was easily possible to identify conditions which selectively gave two different products from the same substrate, simply by adjusting reaction conditions. Optimized conditions for the formation of each product were quickly established using an intuitive optimization strategy.

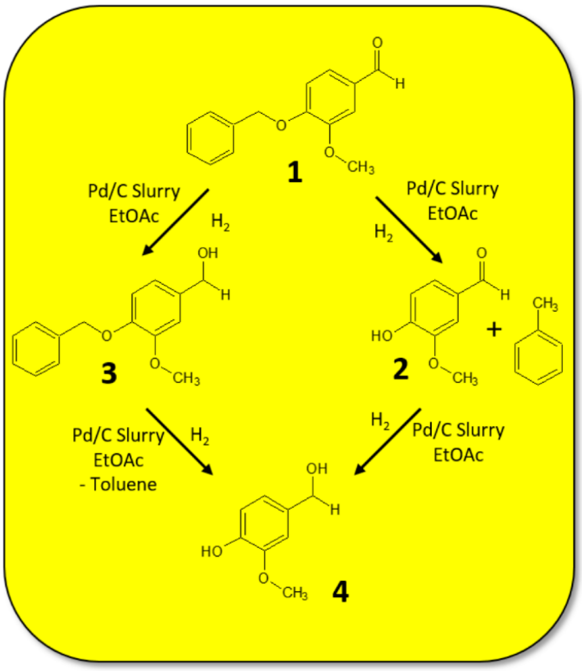

Figure 1: Heterogeneously catalyst hydrogenation of O-benzyl vanillin using hydrogen gas and a palladium on carbon slurry

Setup

All reactions were carried out using a Vapourtec 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 Figure 2. Hydrogen gas was provided from a hydrogen cylinder equipped with a low-pressure regulator, outputting 5 bar and delivered using a V-3 pump after passing through a check valve. The reagent solution contained a 0.2 M solution of O-benzyl vanillin, 1, which diluted to 0.1 M when mixed with the Pd/C slurry. A slurry of Pd/C (Aldrich 5% palladium on activated charcoal, cat. No. 75992) was prepared at the required mass per volume in ethyl acetate, and stirred continuously during aspiration. Reagent and slurry mixed in a tee-piece and mixed with the incoming hydrogen flow in a second tee-piece. The reaction mixture passed into a Vapourtec 20 ml large diameter Reactor for Rapid Mixing (PFA RRM) and into a Vapourtec SF-10 in pressure regulation mode maintaining 7 bar. The product was collected manually following depressurization and filtered prior to analysis.

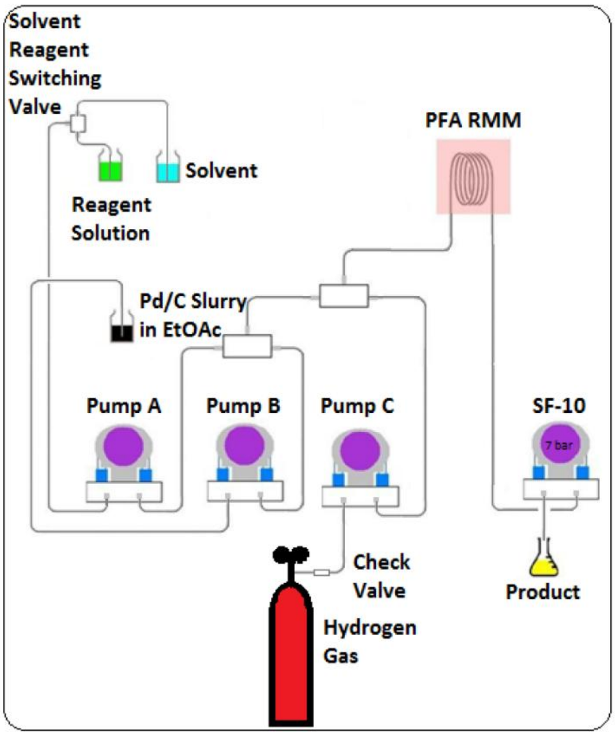

Figure 2: Schematic of the easy-MedChem configuration using an SF-10 as back pressure regulator.

Results

Effect of Temperature

The effect of temperature on the formation of 2 was determined using a catalyst loading of 15 mg/ml of Pd/C, and a 3-fold molar excess of hydrogen, Figure 3.

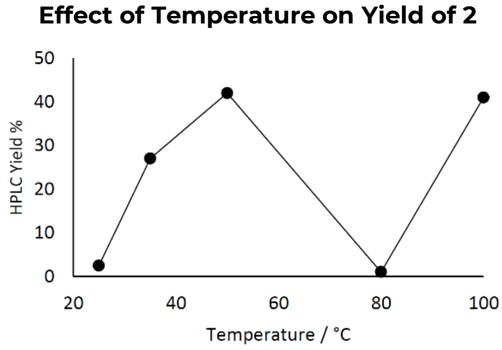

Figure 3: Effect of temperature on the yield of hydrogenation product vanillin, 2

It is clear that 25 °C is not sufficient to activate this reaction, and that 50 and 100 °C result in similar yields of 2, albeit with different ratios of other products (see Optimizing for Selectivity). Interestingly, this investigation has identified that under the conditions tested at 80 °C, the formation of 2 is suppressed almost completely despite greater than 95% conversion of 1. Instead, 3 and 4 are generated in a ratio of approximately 1:2. A possible explanation for this is that at 80 °C, further reduction of 2 to 4 occurs rapidly, whereas reduction from O-benzyl vanillyl alcohol, 3 to 4 is significantly slower under these conditions, Figure 4. Significantly, this identifies the importance of studying catalyst activity under a range of conditions to avoid regions of poor reactivity, or selectivity. Investigations of this type are particularly suited to continuous flow, as reaction conditions can be changed far more rapidly than in a batch system.

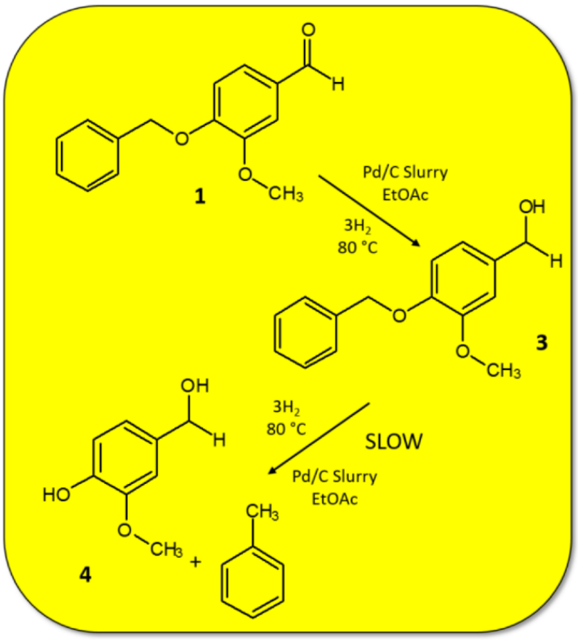

Figure 4: Possible kinetic explanation for low yield of 2 at 80 °C

The increase in yield of 2 observed at 100 °C can be attributed to a loss of activity of the catalyst under the high temperatures. In this instance, 1 is reduced to 2, but due to the loss of activity, is not able to be reduced further to 4, resulting in a higher observed yield of 2.

Optimizing for Selectivity

Reaction optimization is a critical stage of any process design, but can be resource intensive. Using the easy-MedChem it has been possible to perform an intuitive optimization for the selective hydrogenation of two products very rapidly, and using minimal reagent and catalyst. To optimize for the selective hydrogenation of 2 and 4, an initial experiment was performed under the conditions in Table 1, run 1. A mixture of products was obtained, and so a second experiment was performed with a reduced excess of hydrogen. It was observed that the formation of one product was significantly reduced, while the other two main products remained in a similar ratio. Further experiments were conducted at differing temperatures, hydrogen ratio and catalyst loadings and it was found that under the conditions of experiments 7 and 8 it was possible to selectively produce either, 2 or 4, while achieving high conversion and suppressing the formation of 3.

Table 1: Early experiments and conditions that gave selective production of 2 and 4. Pd/C loading measured in mg/ml of catalyst in EtOAc. [a] as determined by HPLC area

Run	T/°C	Pd/C	H_2:1	2/%[a]	4/%[a]
1	50	15	3	42	15
2	50	15	1	29	4
7	80	3	3	6	94
8	80	3	1	71	5

Effect of Catalyst Loading

The effect of catalyst loading was investigated using different Pd/C density slurries. By pumping the catalyst as a slurry, it is also possible to adjust this ratio by varying flow rates from a stock solution. The effect of loading at 80 °C was investigated using a loading of 1, 3 and 15 mg/ml of Pd/C (0.5, 1.4 and 7 mol% respectively) in ethyl acetate and a 1:1 ratio of hydrogen to substrate, Figure 5.

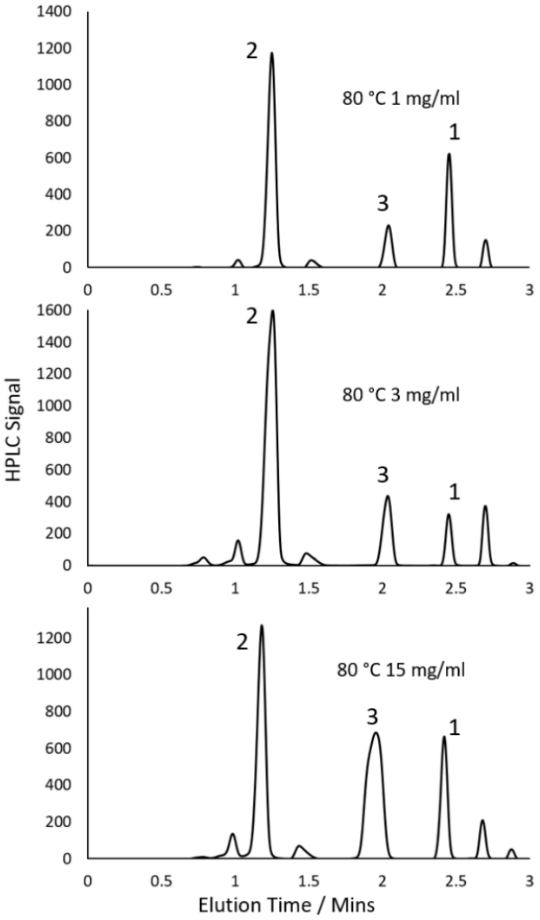

Figure 5: The effect of different catalyst loadings at 80 °C

It is clear that catalyst loading has a significant influence over the output of the reaction, and demonstrates the major advantage of performing heterogenous catalysis as a slurry; the ratio of catalyst to substrate can be tightly controlled. At 1 mg/ml loading, the selectivity to 2 is high, but conversion is low. A 3-fold increase to 3 mg/ml loading has greatly improved conversion while maintaining selectivity to the desired product. At a loading of 15 mg/ml selectivity to 2 has dropped considerably, with large quantities of 3 being formed, and the conversion has fallen. It is suspected that this fall in conversion is due to hydrogen adsorption onto the large catalyst surface area, reducing its effective concentration relative to the substrate.

Conclusion

Using the Vapourtec easy-MedChem it has been possible to rapidly optimize a catalytic hydrogenation using a palladium on carbon slurry, and hydrogen gas. Using the V-3 pump to control the hydrogen gas flow allows for a much more precise control over the hydrogen to substrate ratio than is easily possible using batch methodologies. As a result, it has been possible to identify reaction conditions that are product selective through control of the hydrogen stoichiometry.

By pumping the catalyst as a slurry, it was also possible to directly control and change the ratio of catalyst to substrate, which had a considerable influence on the reaction completion and selectivity. This control cannot be easily achieved using a packed bed because, although the amount of catalyst packed can be controlled, it is inherently far more than is necessary. However, using a slurry allows a range of different loadings to be examined while retaining the same residence time in the reactor. Using the catalyst in this way increases the number of optimizable parameters of this reaction, and permits enhanced control over reaction and process design.

It is also possible to assess a range of reaction conditions quickly without the need to re-pack a fixed bed with fresh catalyst between experiments, and without experiencing the heat transfer limitations that can be observed using a fixed bed. Pumping the Pd/C as a slurry in this manner also avoids the scale limiting nature of a fixed bed.

The use of the stand-alone SF-10 peristaltic pump expanded the system capability, and made it possible to access high reaction pressure even in the presence of the slurry.

This application note demonstrates the versatility of the E-series and V-3 pumps, which have made possible the rapid investigation of a complex mixture of solid, liquid and gas in continuous flow, and demonstrated control of selectivity through precise regulation of hydrogen and catalyst stoichiometry and mixing environment. In addition, we have shown the simplicity and speed of optimizing reaction conditions in flow.

Analysis

Analysis of each experiment was performed using HPLC. Characterization was achieved using an outsourced laboratory LCMS service.