

Microfluidic Hydrogenation Reactions by using a Channel-Supported Rhodium Catalyst

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A glass-fabricated microfluidic device was used to screen a series of homogeneous alkene hydrogenation reactions by using Wilkinson's catalyst. Good to excellent conversions were achieved for a range of alkene substrates within short reaction times ($< 2 \min$) and low hydrogen pressures (< 0.2 MPa). During the course of the screening procedure, a metallic Rh layer was found to build up on the channels of the microfluidic device. Further investigation of this layer revealed that it was a highly active catalyst for the hydrogenation of alkenes, enones, and alkynes. Furthermore, this Rh layer catalyzed the hydrogenation of toluene to methylcyclohexane.

For over a century, catalytic hydrogenation reactions have been used for saturating double bonds and effecting functional-group conversions.^[1] Hydrogenation processes are of enormous industrial importance and are used on large scales in the petrochemical, fine chemical, and food industries. Heterogeneous catalytic hydrogenation methods were established in the early 1900s,^[2] followed by advances in homogenous catalysis by using transition-metal catalysts in the 1960s.^[3] The discovery of asymmetric transition-metal hydrogenation reactions soon followed and paved the way for highly efficient syntheses of single enantiomers.^[4] Today, catalytic hydrogenation research continues at a pace with recent notable advances in the use of cheaper transition-metal catalysts, such as iron^[5] and cobalt,^[6] and also in the area of metal-free hydrogenations.^[7] Common with all hydrogenation methods involving molecular hydrogen is the need to ensure efficient mass transport of hydrogen gas into the liquid phase. Owing to the poor solubility of molecular hydrogen in common organic solvents, hydrogenation processes are typically performed at elevated pressures and temperatures to enhance mass transport and reaction rates. Such elevated temperatures and pressures have associated safety and cost implications and require specialty high-pressure equipment. One of the key drivers for the development of new catalysts is to achieve efficient conversions at lower pressures and temperatures, which would thus alleviate the need for forcing high-temperature/pressure reaction conditions and their associated safety and cost implications.

In recent years, the development of microfluidics and micro/ meso flow reactors has impacted synthetic chemistry methodology.^[8] Such flow processes have given chemists a means of more rigorously controlling the mixing and heating regimes of

 [a] T. Haywood, Dr. P. W. Miller Department of Chemistry Imperial College London South Kensington, London SW7 2AZ (UK) E-mail: philip.miller@imperial.ac.uk chemical reactions that have been shown to impact chemical yield and selectivity. Multiphase gas-liquid and gas-liquidsolid reactions appear to be particularly suitable to the application of microfluidic flow reactors, as the higher surface area to volume ratios result in greater contact between the gas and liquid phases than that observed in traditional glassware or reactors.^[9] Additionally, there are clear safety advantages if the volumes of pressurized flammable or toxic gaseous reagents are significantly reduced in volume; for typical microfluidic and flow reactors this can range from 1 µL to 1 mL. There are now many examples of multiphase flow reactors for performing gas-liquid-phase reactions.^[10] In the area of catalytic hydrogenation commercial units, such as the H-cube reactor, typically a heterogeneous catalyst loaded onto a solid support packed into the reaction channel is used.^[11] More recently, there has been considerable interest in "tube-in-tube" reactors developed by Ley et al.^[12] for safely performing gas-liquid-phase homogenous-catalyzed hydrogenation reactions up to pressures of 2.5 MPa. The tube-in-tube reactor consists of a gas-permeable but liquid-impermeable Teflon membrane tube that is placed inside a larger stainless steel tube. By using a heated tube-in-tube reactor, Leadbeater et al.[13] demonstrated the effective hydrogenation of a number of alkene substrates by using Wilkinson's catalyst.

An alternative strategy to using either homogeneous catalysts or packed-bed heterogeneous catalysts involves supporting the catalyst directly on the channel walls of the microreactor. This can provide advantages over homogeneous catalysis for ease of catalyst separation and over-packed heterogeneous catalysts systems in terms of flow stability, lower pressure requirements, and reduced system blockages. There have been a number of successful routes to generate channel-supported catalysts including polymer coatings,^[14] immobilization of nanoparticles,^[15] and direct deposition of metals onto the channel surfaces.^[16] Herein, we report a chemical method for coating a glass-fabricated microfluidic device with an active rhodium catalyst and demonstrate its utility for the hydrogenation of alkenes. Furthermore, initial investigations of the use of this reactor for the hydrogenation of toluene are also described.

Our reactor setup consisted of a glass microfluidic device (Figure 1) that contained an inlet for hydrogen gas and an inlet for the substrate/catalyst solution. The device contained a long (5 m) reaction channel to provide a residence delay. The exact design specifications of this device were previously reported by us.^[17] The catalytic hydrogenation reaction of styrene with the use of Wilkinson's catalyst [RhCl(PPh₃)₃] was initially investigated as a model reaction. In a typical reaction, a solution of styrene (1 molar) and Wilkinson's catalyst

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Figure 1. Glass-fabricated microfluidic device used in this study. Build-up of catalytically active Rh deposit can be observed in the first 5–6 channels. Inset: close-up of the gas-liquid inlet T-junction.

(0.5 mol%) in toluene was infused into the glass device along with a stream of hydrogen. Under liquid flow rates of $10 \,\mu\text{L}\,\text{min}^{-1}$ and a hydrogen flow rate of 2.0 sccm (0.2 MPa inlet pressure), stable annular-type flow persisted. This flow regime results in a high gas–liquid contact area within the microchannel, which thus assists the mass-transport processes. Residence times of liquid regents under these flow conditions were, however, relatively short (≈ 2 min). Despite the short residence times, conversions of styrene into ethylbenzene were found to be quantitative (Table 1, entry 1). Under our flow conditions, other substrates with terminal alkene groups (Table 1, entries 2 and 3) showed similar near-quantitative conversions



into the alkanes products. These results are in agreement with previous studies with the use of Wilkinson's catalyst, which is known to hydrogenate terminal alkene groups; however, such reactions are typically performed over much longer reaction times and at greater hydrogen pressures.^[3c]

Good to excellent conversions were observed for the double-bond saturation of α , β -unsaturated ketones (Table 1, entries 4–9). For a double bond in a sterically hindered position, the conversion was considerably lower, as seen for methylcyclohexenone (Table 1, entry 6), which has a methyl group adjacent to the double bond. Alkyne bonds can also be hydrogenated by using Wilkinson's catalyst; however, under our reaction conditions a low conversion (19%) was observed for the internal alkyne diphenylacetylene (Table 1, entry 10). Poor conversion (5%) was also seen for the sterically hindered alkene phenylcyclohexene (Table 1, entry 11).

During the course of these hydrogenation reactions, a black material suspected to be a metallic Rh deposit was seen to accumulate at the gas-liquid T-junction of the microfluidic device and along the first 4–5 reactor channels (Figure 1). Subsequent hydrogenation reactions resulted in continued buildup of this material to the point of almost complete occlusion of the channel. Such channel blockages with the use of homo-

> geneous transition-metal catalysts are a known problem and have been observed for a number of catalyzed reactions usually as a result of catalyst degradation into colloidal metallic particles. Recently, various solutions have been proposed to overcome this issue, including the use of high-frequency acoustics and tuning solvents to ensure adequate solubility.^[13,18] In our case, extensive and inconvenient cleaning procedures with the use of concentrated nitric acid was required to remove this material between reactions to regenerate a clean device.

> Given that metallic rhodium is a well-known catalyst, we also decided to investigate the catalytic activity of this coating for hydrogenation reactions. To our surprise, the infusion of a styrene solution in toluene (1 м) under similar reaction conditions (temperature, pressure, and reaction time) in the absence of added Wilkinson's catalyst resulted in quantitative conversion into ethylbenzene. In fact, this Rh coating proved to be more catalytically active than the homogeneous-based Wilkinson's catalyst for the majority of the reactions that were tested (Table 1). In control reactions under the same reaction conditions by using polytetrafluoroethylene (PTFE) tubing of similar dimensions (200 μ m \times 5 m), much lower conversions of the model styrene hydrogenation were observed (< 50%). During the course of these PTFE tube reactions, Rh particulate material was observed to form, but it passed quickly through the reactor and did not deposit on the tubing walls. This may explain the lower conversions of these tube reactions, as the catalytically active material is not retained on the walls. In comparable batch hydrogenation reactions with the use of Wilkinson's catalyst, no metallic Rh was

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observed to form; this indicates that microfluidic conditions are required for this material to form, that is, efficient contact of the gas and liquid phases is necessary. This suggests that our initial hydrogenation reactions were not solely undergoing a homogeneous catalytic process but also a heterogeneouscatalyzed process. A heterogeneous catalyst was formed in situ from the homogeneous Wilkinson's catalyst as it passed through the device and deposited on the channel walls.

In further experiments to better understand the robustness of the Rh catalytic coating, a continuous flow of 1 $\,\mathrm{M}$ styrene in toluene was infused into the device at a flow rate of 10 $\mu\mathrm{L\,min^{-1}}$ over a 24 h period. Samples were taken for GC analysis at two-hour time points to assess the styrene conversion. In all cases, the GC traces showed no deterioration in the conversion of styrene, with quantitative conversion over the entire 24 h period. Additionally, there was no visible evidence of catalyst degradation or flaking from the channel walls. This indicated that the Rh catalytic coating was robust, strongly adhered to the walls, and remained active for an extended period of time. Closer visual inspection of the coated channels indicated that the Rh layer was relatively uniform and thin (Figure 2). By using optical microscopy, the Rh layer was esti-



Figure 2. Magnified images (\times 20) of the microchannel with different levels of rhodium deposits: a) no deposit, b) partially coated, c) fully coated.

mated to be 2-10 µm in depth. Although it was not possible to easily remove the Rh layer from the enclosed glass device without chemically dissolving it by using concentrated nitric acid, the metallic Rh material could be generated by using a PTFE microreactor, as mentioned above, and collected for further analysis. Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) analysis of this Rh sample first confirmed that metallic Rh was present and that the morphology of the sample was not nanoparticulate in nature but rather amorphous (Figure 3). Powder X-ray diffraction also confirmed that the sample was not crystalline. Although this did not tell us the exact nature of the coating on the channel surface, it did suggest that metallic Rh on the glass device did not consist of nanoparticles. Attempts to prepare the Rh coating on the channel surface by using only a toluene solution of Wilkinson's catalyst and a flow of hydrogen were unsuccessful. It was necessary to have an alkene, such as styrene, in the solution to generate the coating. This suggests that an Rh-alkyl intermediate, which is known to form after the initial insertion of dihydrogen in the catalytic cycle, is the likely precursor to the deposited metallic Rh catalyst following reduction to a suspected Rh⁰ species. The formation of the Rh deposit on the mi-



Figure 3. SEM image of the rhodium deposit from the microtube reactions (20 μm scale bar).

crochannel occurs at a fast rate and can be clearly observed to form around the T-junction (Figure 1, inset) of the device once the hydrogen comes into contact with the catalyst/substrate solution. The first 4–5 channels of the device appear to be evenly coated, after which there is a thin partial coating in the next 1–2 channels. Assuming an even and thin coating of four channels as an approximation, this would give a surface area of 2.0 cm² on a device of this type.^[1]

Considering the activity of this Rh-supported catalyst for styrene hydrogenation, it was decided to reinvestigate the substrate scope again, this time without any added Wilkinson's catalyst. Results of this repeated screen are displayed in Table 1 and show in most cases that the supported catalyst outperforms the homogeneous Wilkinson's catalyst in terms of alkene conversion. One notable example is the improvement in conversion of the sterically hindered alkene methylcyclohexenone (Table 1, entry 6), which showed an improvement in the conversion from 39 to $100\,\%$ by using the supported Rh method. However, not all reactions showed improved conversions for the supported catalyst; the enone substrates (Table 1, entries 8 and 9) showed much lower conversions, which indicates that a homogenous catalytic process is favored under these particular microfluidic conditions. Conversion of the internal alkyne diphenylacetylene (Table 1, entry 10), in contrast, showed quantitative conversion for the supported catalyst system; however, the product distribution showed a 69:31 mixture of 1,2-diphenylethane/stilbene. The homogeneous system gave much lower conversions, 19%, but showed exclusive formation of 1,2-diphenylethane.

Re-examination of the GC traces of these reactions also showed noticeable conversions of toluene, used as the solvent, into methylcyclohexane (MCH) for the supported Rh catalyst. The conversion of aromatics into saturated hydrocarbon products is an important industrial process for synthetic precursors^[19] and to reduce volatile organic compounds from diesel combustion.^[20] The conversion of toluene into MCH and the reverse process to release hydrogen is currently attracting interest for hydrogen-storage and hydrogen-release applications;^[21] hence, routes to mildly and efficiently convert toluene into MCH are currently of interest. Simply passing neat toluene through the Rh-coated device at a flow rate of 10 μ Lmin⁻¹ with a flow of hydrogen (2 sccm, 0.2 MPa inlet pressure) at 120 °C resulted in a 7% conversion of toluene into MCH

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(Table 1 entry 12). Although the conversion of toluene into MCH was relatively low, it was not surprising considering the small surface area ($\approx 2 \text{ cm}^2$) of the catalyst within the device, and the relatively large volume of toluene passing rapidly through the device would result in saturation of the catalytic sites. If a dilute solution of toluene (1 m in decane) was used, conversion into MCH was found to increase markedly to 18% (Table 1 entry 13).

In conclusion the hydrogenation reaction of alkenes with the use of Wilkinson's catalyst can be rapidly and efficiently performed by using a simple glass-fabricated microfluidic device at low pressures and within short reaction times. A catalytically active Rh layer formed during the course of these reactions that robustly adhered to the wall of the channel, which made it possible to perform these reactions heterogeneously. This supported catalyst showed high catalytic activity and was able to effect the hydrogenation of toluene to MCH. Approximately 30 reactions were performed on the device, which amounts to approximately 100 h of continuous reaction time, without significant loss in activity. The exact nature of this supported Rh catalyst is under investigation, and we are currently developing methods to give greater surface-area coverage of the microchannel surface. At present, we can only achieve approximately 7% surface-area coverage of the supported catalyst; hence, significant improvements in the conversion of toluene would be expected with increased catalyst surface area. We are also investigating different flow regimes through the device. The current method benefits from the large surface areas generated from annular flow in the microchannel, but it suffers from very short residence times that clearly impact the conversion of more challenging substrates. By extending the residence times with the use of a gas-liquid segmented flow regime, it should be possible to achieve much improved alkene conversions.

Experimental Section

General

All preparations involving Wilkinson's catalyst were performed under an inert nitrogen atmosphere. Toluene was predried by using a commercial drying column. All other starting materials were of reagent grade, were purchased from Sigma–Aldrich, and were used without further purification. GC analysis was performed with a Hewlett-Packard 5890 Series II Gas Chromatograph.

Homogeneous hydrogenations

A detailed description of the microfluidic device was previously reported by us.^[17] In short, the microfluidic device was fabricated by Dolomite, Ltd., by using soda-lime glass substrates with the use of wet chemical hydrogen fluoride etching and thermally bonded. The reactor channels were 220 μ m wide and 100 μ m deep, and the main reactor channel was 5 m in length. The total volume of the device was 86 μ L. External PTFE (1/16 inch external diameter, 0.25 mm internal diameter) tubing was connected to the microfluidic reactor by using a standard Dolomite edge connector. A Harvard apparatus pump 11 elite syringe pump was used to infuse the substrate and catalyst solution. The second inlet was connected to

the H₂ gas line. Hydrogen flow was regulated by a Sierra Instruments Micro-Trak mass flow meter. In a typical reaction procedure, a toluene solution of the substrate (1 M) and Wilkinson's catalyst (0.5 mol%) was infused into the chip device at a flow rate of 10 μ Lmin⁻¹. Hydrogen gas flow was maintained at 2.0 sccm (standard cubic centimeter per minute), which resulted in annular-type flow through the device. Back pressure in the system for this particular chip device was 0.20 MPa under these flow conditions. The device was heated to 120 °C by using an aluminum heating block placed on an IKA hotplate and regulated by using an electronic contact thermometer. An aliquot (900 μ L) was collected for each sample, which was passed through a small pad of Celite prior to GC analysis.

General procedure for Rh coating

The channel surface was coated in a layer of catalytically active metallic Rh by simply passing a premixed toluene solution of styrene (1 m) and Wilkinson's catalyst (0.5 mol%) through the device at a flow rate of 10 μ L min⁻¹, hydrogen flow of 2 sccm, and heating to 120 °C. Approximately 1 mL of solution was passed through the device to generate an even coverage of the first 4–5 channels. Attempts to increase the surface coverage by infusing more catalyst/ substrate solution resulted in a deeper layer of the Rh deposit near the gas–liquid inlets; this layer restricted flow, which resulted in an undesirable increase in back pressure.

PTFE tube reactions

A 1/16 PEEK T-piece was connected to the liquid and gas inlet lines, and a 5 m reaction coil of PTFE tubing (1/16 inch external diameter, 0.2 mm internal diameter) was placed into an oil bath. Identical liquid and gas flow rates to that described above were employed. In a typical procedure, a premixed toluene solution of styrene (1 m) and Wilkinson's catalyst (0.5 mol%) was infused into the reactor. A black precipitate of metallic Rh was observed to form over the course of the reaction. This passed through the reactor without adhering to the tubing walls and was collected for analysis by TEM.

Heterogeneous reactions

An identical system to that of the homogeneous reaction system described above was used. Liquid and gas flow rates were identical in all cases. In a typical procedure, a toluene solution of the substrate (1 m) without any added catalyst was infused into the device at a flow rate of 10 μ L min⁻¹ and under gas flow of 2.0 sccm. An aliquot (900 μ L) was collected for each sample, which was analyzed directly by GC. Reactions of toluene were performed either neat or as a 1 m solution in decane, as stated in Table 1.

Acknowledgements

We are grateful to Dr. Nick Brooks for the use of a high-quality optical microscope. Dr. Mahmoud Ardakani and Mr. Richard Sweeney are acknowledged for assistance with TEM, SEM, and X-ray powder diffraction. P.W.M. is grateful to the Natural Science Foundation of China (Grant No. 21350110212) for the award of a Research Fellowship for International Young Scientists.

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Keywords: hydrogenation • microfluidic devices microreactors • rhodium • supported catalysts

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Received: December 29, 2013 Published online on March 12, 2014