Doctoral (Ph. D.) Theses

Continuous Flow Methodologies For Safe High Pressure Catalytic Hydrogenation

Richard V. Jones

Supervisor: Dr. Csaba Janáky

Associate Professor

DOCTORAL SCHOOL OF CHEMISTRY

University of Szeged

Faculty of Science and Informatics

Department of Physical Chemistry and Materials Science

2021

1. Introduction and Project Aims

Catalytic heterogeneous hydrogenation is one of the most important and widespread techniques in the reduction of functional groups. Even with the development of homogeneous catalysis, the use of heterogeneous catalysts is still preferable and holds many advantages over their homogeneous counterparts such as easy work-up, less contamination in the products and minimizing waste. It is difficult to estimate how often hydrogenation is utilized across all chemical industries, but various sources seem to fall on an estimate of between 5-10% of all industrial reactions carried out.

The importance of hydrogenation in the pharmaceutical, agrochemical, and fine chemical industry cannot be underestimated. Approximately 25% of the synthesis of marketed drugs as well as clinical drug candidates have at least one hydrogenation step in their synthetic sequence. However, despite the prevalence of hydrogenation throughout the chemistry world, it is limited in its application due to the hazardous nature of hydrogenation itself. The addition and filtration of the hydrogen saturated pyrophoric catalysts, such as Raney nickel, in flammable solvents pose inherent safety hazards. The use of hydrogen cylinders as a hydrogen source has restricted hydrogenation to specially built facilities. In addition, high temperature (>100˚C) and pressure (>50 bar) conditions also contribute to safety hazards and limit the technology available to the chemist.

The introduction and increasing popularity of flow chemistry into the day to day chemistry laboratory affords an opportunity to, not only, adapt hydrogenation to this methodology in order to overcome the safety issues mentioned above, but also to expand the capability of hydrogenation, for the first time, towards automated generation of drug-like compounds.

Flow chemistry is the pumping of a continuous flow of reaction mixture through a reactor. The key factor is that reactions are performed in a continuous fashion, so only a small part of the reaction mixture undergoes a reaction at any one time. Therefore, performing hydrogenation in flow would reduce the exothermic hazardous elements associated with the reaction. The use of liquid starting materials would also make it suitable for automated high-throughput reaction screening.

The main aim of my research was to validate and optimize the technical and chemical performance of a jointly-developed compact continuous flow hydrogenation reactor, the first of its kind. For this purpose, the system was tested by me on a variety of different substrates with varying levels of difficulty to demonstrate improved catalytic mixing and high temperature and pressure capability. The system was tested specifically to see if it could be applied to selective reactions using residence time control. The ability to perform inline analysis using a flow FTIR probe was evaluated as a method for on-the-fly optimization. Next, I evaluated the flow system to see if the reactions could be scaled without further optimization. I then incorporated the flow hydrogenation system into an automated set-up to enable the automated high-throughput production of hydrogenated compound libraries. To the best of our knowledge, this had never been achieved before.

2. Experimental Methods

The flow hydrogenation experiments were carried out as follows. The stock solution was prepared by dissolving 5-nitroindole (0.162 g, 0.001 moles) in a 1:1 mixture of ethyl acetate and ethanol (20 mL) in a 50 mL glass vial. The sample inlet line was then placed in the reaction solution. Using the touch screen control, the pressure was set to 1 bar, the flow rate of the system to 1 mL/min, and the temperature to 30˚C. The hydrogen mode was selected to "Full Hydrogen". The reaction was started by pressing the "start" button on the touch screen control. After passing through the instrument, the total amount of reaction mixture was collected (20 mL in 20 minutes) and the column was washed with the solvent mixture (10 mL in 10 minutes) to remove any substrate still adsorbed to the catalyst. The two solutions were combined and analyzed by Thin Layer Chromatography (eluent: chloroform) which showed the total disappearance of the starting material and the formation of a product spot. The mixture was then evaporated to dryness giving the desired product (128 mg, 97% yield).

A variety of analytical tools were employed to characterize the product composition. The ^{1}H-(400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on a Varian INOVA (400 MHz) spectrometer with TMS as an internal reference. For HPLC runs, a LaChrom system (Merck-Hitachi) connected to an autosampler and a fraction collector based on a Cavro RSP 9000 (Cavro Scientific Instruments, Inc.) robotic workstation was used. The column type used was Purospher STAR RP-18 endcapped, 3µm, 30x4 mm. The detection wavelengths were 220 or 254 nm. MS data were collected on a ZQ single-quad (Micromass-Waters) mass spectrometer using an APCI interface. HRMS experiments were performed on a MICROMASS LCT spectrometer using an electrospray interface with a lock-mass sign of tetrabutylammonium ion. IR spectra were recorded on a Nicolet FTIR MAGNA 750 spectrophotometer.

Experiments carried out by connecting the H-Cube® to a Fourier Transform Infrared Spectroscometer (FTIR) utilized Mettler Toledo's FlowIR™. Before proceeding with a reaction, the FlowIR™ system was properly configured and aligned. Background and reference spectra were collected. Mettler Toledo offers Diamond (DiComp) or Silicon (SiComp) sensor tips: both detect in the range of 4000 to 650 cm^{-1}, only differing in the sensor blind spot. A DiComp

sensor with a blind region 2250–1950 cm^{-1} was used in the here described experiments. The reactions carried out in the H-Cube® were monitored by the FlowIR™ instrument via manual injection into the sensor head or connected in-line with the flow reactor at the output side using standard HPLC Teflon fittings. Since infrared spectroscopy is highly sensitive to temperature changes, it is important to carry out the measurement at an accurately controlled, constant temperature. Therefore, a heater controller was connected to the FlowIR™, and the temperature was set during all measurements to 25°C.

The automation experiments were carried out as follows. The automated high-throughput hydrogenation system is made up of an H-Cube®, a Tecan CAVRO two-arm injector -collector, a Knauer HPLC pump, and a VICI Valco 6-port valve. The HPLC pump controls a continuous stream of solvent through the injector and then into the reactor. The temperature and pressure conditions for the reductions are set on the reactor. The CAVRO system takes up a dissolved substrate in a specific volume using one of the robotic arms and injects the substrate into the valve's injection loop. The injector valve switches the flow of solvent from the reactor to injection loop, pushing the injected substrate out of the loop into the H-Cube® reactor. The residence time of the substrate from injector to collection is approximately two minutes at 1 mL/min. The second arm of the CAVRO robotic station controls the fraction collection. The fraction collector arm positions itself over a collection vial and collects all the eluted product and solvent washing into the vial. While this process takes place, the valve positions are reset back to position A, the injection needle proceeds into a washing program and the system is ready for another sample injection. Evaporation of the solvent from the reaction mixture yields the product.

3. Summary of New Scientific Results

T1: Continuous flow hydrogenation can be safely performed in an integrated system, where in situ H_2 generation is combined with the use of a catalyst cartridge.

We created a continuous-flow hydrogenation system where a continuous steam of reactant could be reacted with *in situ* generated hydrogen, from water electrolysis, on a catalyst cartridge system at temperatures and pressures up to 100°C and 100 bar respectively.

T2: The reduction of 5-nitroindole showed a minimum 5 times higher conversion for reactions performed in continuous-flow when compared to batch.

The continuous flow hydrogenation system was compared to batch using the reduction of 5-nitroindole as a test reaction. The batch reactions showed 11 and 20% conversion compared to the continuous-flow's quantitative conversion. This suggests that the mass transfer between the gas-liquid and liquid-solid phases in a batch reactor is, therefore, lower since there is a lower interfacial area between the three phases.

T3: The continuous-flow hydrogenation reactor was able to fully reduce a pyridine ring at 100°C and 100 bar using Raney nickel as catalyst.

Alpha-picoline was hydrogenated to 2-methyl-piperidine with high conversion and yield at 100°C and 100 bar using Raney nickel as catalyst. 1H NMR analysis showed the average product selectivity of 99%, while the conversion was ca. 91% for this rather difficult hydrogenation.

T4: The continuous-flow hydrogenation system was utilized in the selective reduction of 4-bromo-nitrobenzene. Standard transition metal-based catalysts on charcoal, considered to be non-selective in batch-based hydrogenations, were turned into fully selective ones by using flow-based hydrogenation in a bench top flow hydrogenation reactor.

The key parameter for reaching the high selectivity was the residence time that could be fine-tuned to seconds and milliseconds. Even the most commonly used catalysts, such as Pd/C or Pt/C, were turned selective. The results suggest that catalyst selectivity achieved in batch does not reflect the true nature and selective properties of catalysts since the reaction times

achievable are orders of magnitude away from the optimal reaction time. The potential to increase catalyst selectivity through flow offers a greener alternative for the currently utilized batch-based organic synthesis methods.

T5: Continuous flow hydrogenation system can be connected to an inline FTIR system to monitor reaction conversion during the reaction. Reaction conditions can be modified to achieve optimum conversion.

The H-Cube® was connected to Mettler Toledo's ReactIR™ FTIR system. The set-up was tested with a carbonyl reduction and the reduction of D-glucose to D-sorbitol. Using the reaction mixture spectra, optimum reaction conditions were quickly achieved during the reaction itself and without stopping. Results were comparable to offline optimization.

T6: The ability to scale flow hydrogenations without modification of reaction parameters was demonstrated by transferring reactions to a 17 times larger continuous-flow hydrogenation system.

A series of reactions were run on a 17 times larger continuous flow hydrogenation reactor to assess the throughput of the system with different functional groups. The reactions were first performed on the H-Cube® and the optimized reaction parameters (temperature, pressure, and catalyst), were immediately transferred to the H-Cube Midi™. These include a ketone reduction, a nitro reduction, double bond saturation, and a carbobenzyloxy group deprotection. In the reduction of benzaldehyde, 74 g, was reduced in 80 minutes. The nitro reduction, which can lead to catalyst deactivation, produced 92 g in 6 hours without any catalyst poisoning.

T7: Continuous flow hydrogenation unit can be coupled with an automatic liquid handler to conduct fully automated hydrogenation as a part of a chemical library production

The system was optimized using 5-nitroindole before a 5 membered library production was carried out. A total of 25 reactions were run (5 reactions per each compound, run alternately). NMR and LCMS results show complete conversion to the corresponding amine for all twenty-five injections. The results for each substrate remain constant throughout each injection demonstrating the system's ability to reproduce results. The high level of conversion over all

of the twenty-five injections indicates that catalyst activity was high throughout the experiment with no sign of deactivation. This result suggests that a greater number of compounds could be reduced on the same catalyst column. The total time for the 25 reactions was 3 hours.

T8: A stand-alone hydrogen generator can generate gaseous hydrogen up to 1 NL/min, 100 bar, and 4.0 purity for use with kilogram-scale in-house built or commercial flow reactors.

We created the first commercial hydrogen gas generator with the capability to connect to any flow reactor equipment. The system generates hydrogen gas from water up to 100 bar and 1 NL/min at a 4.0 purity. Due to the proposed technological novelties as well as the modular construction, the created electrochemical cell architecture is highly scalable and flexible. The cell can be easily scaled up, both in terms of its size/dimensions and the number of stacks made use of, while maintaining pressure tolerance. The system was validated in combination with a commercial flow reactor for the nitro reduction of methy-4-nitrobenzoate where a throughput of 83 g/hr of product was achieved.

4. Publication List

Hungarian Scientific Bibliography (MTMT) identifier: 10078947

Publications related to the scientific topic of the dissertation:

1) **R. Jones**, L. Gödörházy, D Szalay, J. Gerencsér, G. Dormán, L. Urge, and F. Darvas
   A Novel Method for High-throughput Reduction of Compounds Through Automated Sequential Injection into a Continuous-flow Microfluidic Reactor
   QSAR & Combinatorial Science, 24(6), 722-727 (2005)
   IF_{2005} = 2.024
2) **R. Jones**, L. Gödörházy, N. Varga, D Szalay, and F. Darvas
   Continuous-flow High Pressure Hydrogenation Reactor for Optimization and High-throughput Synthesis
   Journal of Combinatorial Chemistry, 8(1), 110-116. (2006)
   IF_{2006} = 3.295
3) G. Dormán, L. Kocsis, **R. Jones**, and F. Darvas
   A Benchtop Continuous-flow Reactor: A Solution to the Hazards Posed by Gas Cylinder-based Hydrogenation
   Journal of Chemical Health and Safety, 20 (4), 3–8(2013)
   IF_{2013} = 0.389
4) **R. Jones**, C. Csajagi, Z. Szekelyhidi, I. Kovacs, B. Borcsek, L. Urge, and F. Darvas
   The Application of Flow to Reaction Optimization, Compound Library Synthesis, and Scale up.
   Chemistry Today, 26(3), 10-14 (2008)
   IF_{2008} = 0.565
5) C. Janaky, E. Kecsenovity, A. Danyi, B. Endrődi, V. Török, F. Darvas, and **R. Jones**
   Modular Electrolyzer Cell to Generate Gaseous Hydrogen at High Pressure and with High Purity
   PCT Patent, Publication Number WO/2020/039218

Other publications:

1) I. Kovacs, **R. Jones**, K. Niesz, C. Csajagi, B. Borcsek, L. Urge, and F. Darvas
   Automated Technology for Performing Flow-Chemistry at Elevated Temperature and Pressure
   Journal of the Association for Laboratory Automation, 12(5), 284-290 (2007)
   IF_{2007} = N/A
2) J. M. Tukacs, **R. Jones**, F. Darvas, G. Lezsák, G. Dibó, and L. T. Mika
   Synthesis of γ-Valerolactone Using a Continuous-flow Reactor
   RSC Advances, 3, 16283-16287 (2013)
   IF_{2013} = 3.119
3) L. Lengyel, T. Nagy, G. Sipos, **R. Jones**, Gy. Dorman, L. Ürge, and F. Darvas
   Highly Efficient Thermal Cyclization Reactions of Alkylidene Esters in Continuous-flow to give Aromatic/Heteroaromatic Derivatives
   Tetrahedron Letters, 53, 738-743(2012)
   IF_{2012} = 2.397
4) C. Spadoni, **R. Jones**, L. Urge, and F. Darvas

The recent advancement of hydrogenation technology and their implications for drug discovery research
Chemistry Today, January/February, 36-39(2005)
IF_{2005} = 0.321

5) B. Endrodi, G. Bencsik, F. Darvas, **R. Jones**, K. Rajeshwar, and C. Janaky
Continuous-flow Electroreduction of Carbon Dioxide
Progress in Energy and Combustion Science, 62, 133-154(2017)
IF_{2017} = 29.85

6) **R. Jones**, F. Darvas, and C. Janaky
New Space for Chemical Discoveries
Nature Reviews Chemistry, 1, Article number: 0055 (2017).
IF_{2017} = N/A

5. Co-Authors' declaration

We, the undersigned, as the co-authors of the Modular Electrolyzer Cell to Generate Gaseous Hydrogen at High Pressure and with High Purity. PCT Patent, Publication Number WO/2020/039218. associated with the doctoral dissertation of Richard V. Jones PhD candidate entitled as Continuous Flow Methodologies For Safe High Pressure Catalytic Hydrogenation hereby declare that the role of the candidate was decisive in achieving the scientific results related to this publication and the candidate's thesis point 8, therefore these results have not been used to obtain a PhD degree so far, and we will not do so in the future.

Egon Kecsenovity

Antal Danyi

Viktor Török

6. Supervisor's declaration

I, the undersigned, as the supervisor of the PhD candidate Richard V. Jones in connection with the doctoral dissertation entitled as Continuous Flow Methodologies For Safe High Pressure Catalytic Hydrogenation hereby declare regarding the publications listed in the Thesis booklet as "Publications related to the scientific topic of the dissertation" and the candidate's thesis points T1-T8 that the results used in this dissertation reflect the PhD candidate's independent contribution.

Dr. Csaba Janáky