Doctoral (Ph. D.) Thesis

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

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1 Project Overview and Broader Context

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 catalyst separation, less contamination in the product, 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.[1]

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.[2]. This importance could be dramatically increased through the research carried out by Lovering et al. by analysing a database of more than two million compounds, sampled from each stage of the drug development process. Lovering et al provided evidence that the complexity of a molecule is a key determinant of success in the transition from discovery, to clinical testing, to approved drugs. The higher the complexity of a molecule the higher the chance for specific interaction with the target protein. At the same time the higher the complexity of a molecule, the more difficult to prepare/produce in a chemically and optically pure form. The authors chose two measures to reflect molecular complexity: the extent of bond saturation and the number of chiral centres. The rationale behind this choice was that increased levels of saturation —defined by the fraction of sp^3 hybridized carbons (Fsp3) — makes the compound more three-dimensional in shape and an increased number of chiral centres increases the number of potential isomers of the compound. Such effects on molecular shape might allow for improved interactions with the target protein, enhancing the potency and/or specificity of the drug candidate and increasing the probability that it will lead to a successful drug. They found that Fsp3 increased by 31% from discovery, to Phase I–III clinical trials and eventually to drug status. Finally, increased levels of saturation were shown to correlate with increased solubility, a physical property that is known to be important for success in drug discovery.[3] In short, the saturation of planar, typically aromatic-based drug candidates through hydrogenation can improve their chances of success.

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, especially in pilot plant scale and 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.

Furthermore, as a future application, the adaptation of hydrogenation to flow will allow for use of such an important reaction to be conducted in Space or areas of microgravity. As highlighted in our comment paper, New Space for Chemical Discoveries[4], the need for chemistry research in Space is paramount and the use of flow methodology to conduct the research holds the key.

The main goals of my research carried out and detailed in this thesis, were to validate and optimize the technical and chemical performance of a jointly-developed compact continuous flow hydrogenation reactor. 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. 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. This technology was then expanded, under my direction, to the development of a larger-scale pressure capable hydrogen generator for the utilization with flow reactor technology to facilitate kilo-scale flow hydrogenation.

2 Introduction

2.1 What is flow chemistry?

Flow chemistry is the pumping of a continuous flow of reaction mixture through a reactor. The reactors fall into two main types: a fixed bed type reactor, where the reaction mixture is passed through a solid catalyst or reagent, or a tubular type reactor where the starting material, reagent, or catalyst is homogeneously dissolved in solution and pumped through a heated or cooled zone. For laboratory-based systems, the internal diameter of the reaction line is typically in the micron to low millimeter range. The key point to take away from this is that reactions are performed continuously, so only a small part of the reaction mixture undergoes a reaction at any one time. Performing chemistry this way leads to a number of advantages over standard batch processes.

2.2 Typical flow chemistry set-up

A typical set-up for a flow chemistry reaction is given below in Fig. 1.[5]

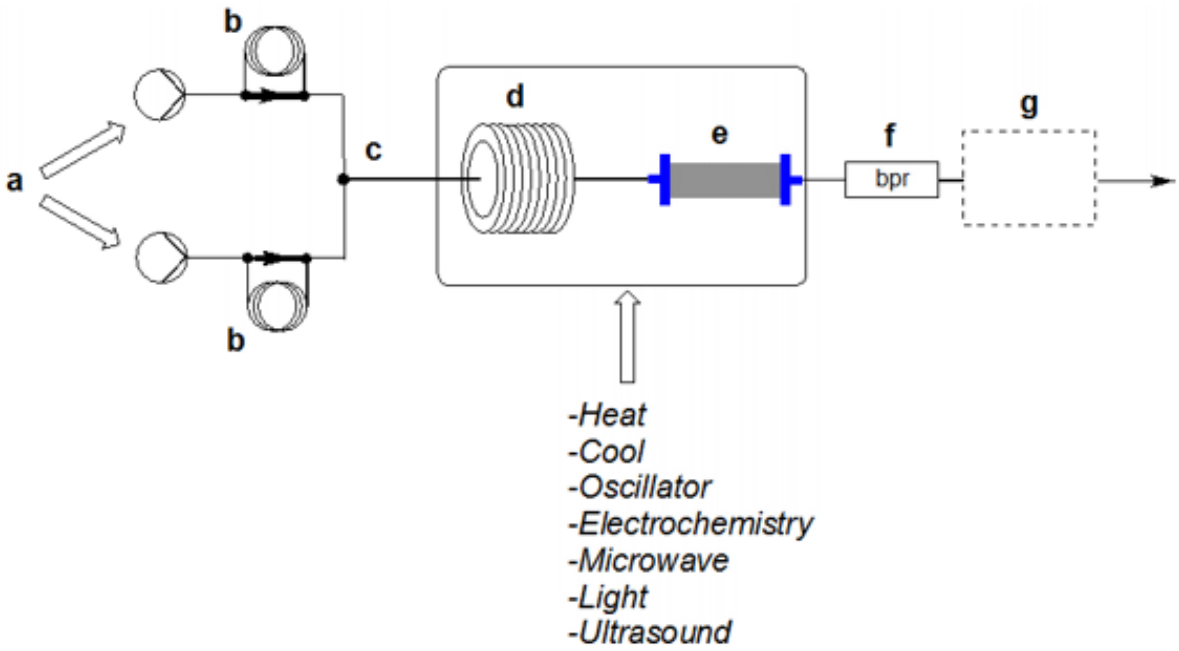


Figure 1: Typical flow chemistry set-up.

a) Pumps: used to deliver reproducible quantities of solvents and reagents; the usual types are piston, peristaltic, syringe or gear centrifugal pumps
b) Reaction injection loops: used to introduce small volumes of reagents
c) Mixer: primary mixing point, where reagents streams are combined

d) Coil reactor: provides residence time for the reaction. The residence time is defined as the time of the reaction mixture in the reaction zone.
e) Column reactor (packed bed reactor): packed with solid reagents, catalysts or scavengers
f) Back pressure regulator: controls the pressure of the system
g) Downstream unit: in-line analytics, work-up operations

2.3 Flow chemistry advantages

Performing the reaction in the above way leads to the following important advantages over carrying out a reaction in batch.

2.3.1 Improved mixing in liquid-liquid reactions

Mixing is often highly influential in the conversion and selectivity of reactions. Therefore, the degree to which mixing influences a reaction should be a major question when deciding whether or not to conduct an experiment in flow. The larger the volume of the batch reactor the more difficult it is to achieve homogeneous mixing as the below figure illustrates[6].

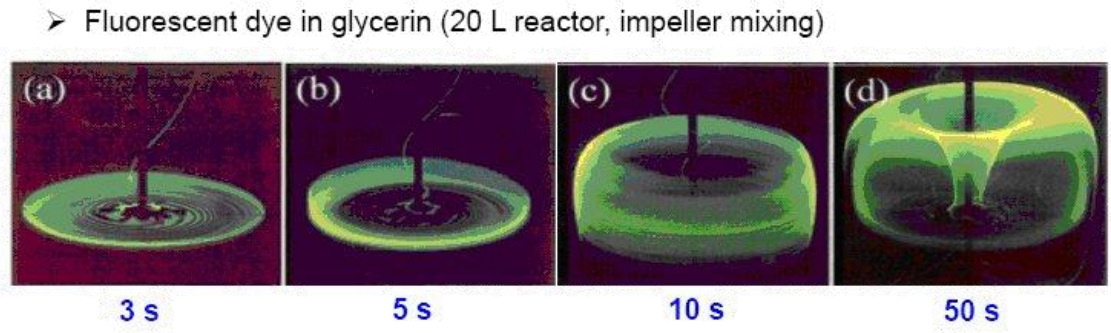


Figure 2: Fluorescent dye in a 20 L batch reactor containing glycerin.

The low volumes of flow chemistry reactors coupled with precise control of reaction mixture flow means that accurate and reproducible mixing via diffusion can be achieved over a few cms. A variety of mixers can be used to achieve different results.[7]

A couple of examples are given in Figure 3.

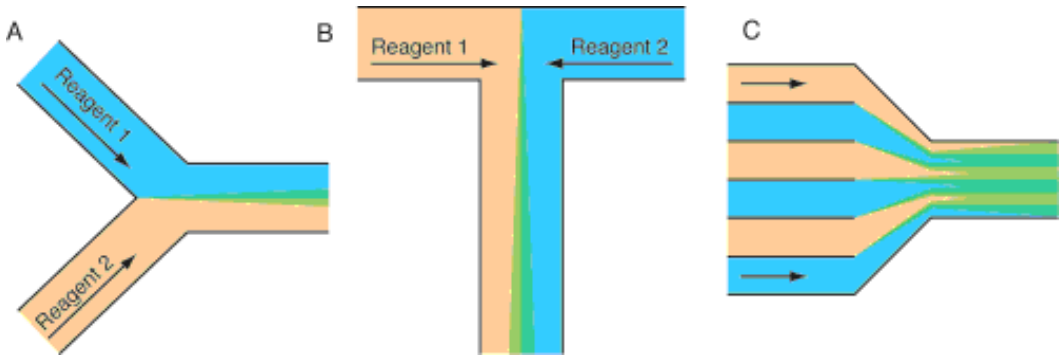


Figure 3: Schematics of different mixer units and how different liquids mix.

The rapid mixing, typically, leads to an increase in reproducibility for the reaction. Mixing, however, is more complicated than simple diffusion and requires analysis of the Damköhler number (Da). This dimensionless unit is a ratio of the rate of the reaction to the rate of mass transfer by diffusion. For reactions where Da is less than 1, mixing (>95% homogeneity) can be achieved before the reaction occurs. However, for reactions where Da is greater than 1, the reaction is faster than mass transport, causing concentration gradients within the system. This typically occurs in highly exothermic reactions and special mixers must be employed to achieve rapid mixing through deliberate turbulence. The rate of the reaction and mixing should be one of the major considerations when deciding whether or not to develop a flow process.[8]

2.3.2 Improved mixing in solid-liquid reactions

Heterogeneous reactions involving solids and liquids are especially attractive due to the ease of separation upon work-up. Heterogeneous catalysis, in particular, is an important field as many of the present industrial processes use a heterogeneous catalyst.[9] Recently, continuous flow has been exploited to enhance heterogeneous catalysis by essentially combining the reaction and separation into one step using a packed bed reactor. A schematic of such a type is given below. A wide variety of supported catalysts may be used in this type of reactor.

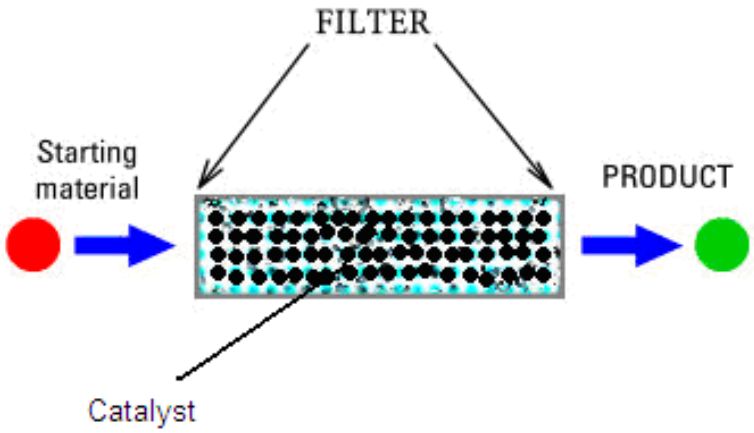


Figure 4: Schematic of a packed bed reactor.

In a fixed bed or packed bed reactor, the reaction mixture is pushed through the solid reagent or catalyst. The concentration of the catalyst/solid reagent compared to the reaction mixture in the packed bed reactor is much higher when compared to a batch reactor where the opposite is usually true. The reaction mixture travels through the channels created by the solid particles and interacts continuously as it passes down the length of the reactor. This can lead to increased reaction rates of several orders of magnitude. If you compare this to a batch reaction, the solid catalyst is stoichiometrically low in comparison to the rest of the reaction mixture, so adsorption of all the material onto the catalyst surface will take longer. Some examples of reaction times are given in Figure 5 below that highlights the time taken for reaction completion, in minutes, as a comparison between batch and flow reactors for specific reactions from internal unpublished studies.

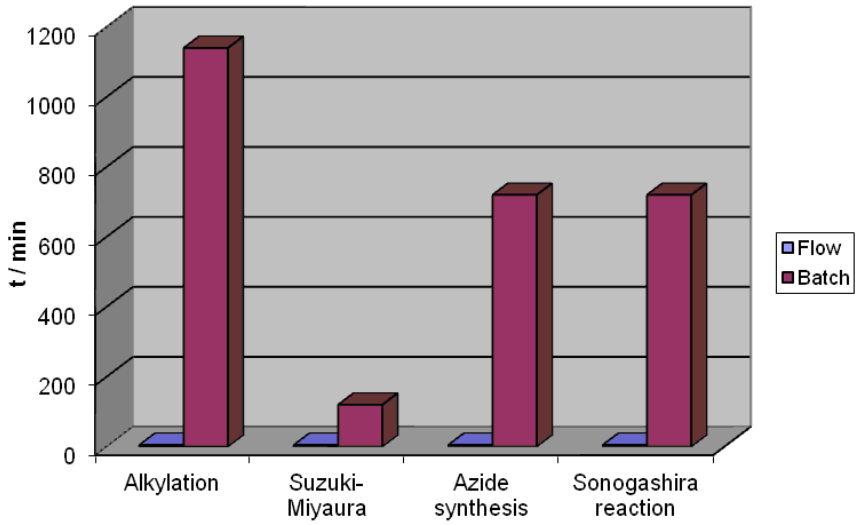


Figure 5: Reaction times for reaction examples in flow and batch reactors (own compilation).

The packed beds can also have improved lifetime due to decreased exposure to potentially catalyst poisoning products, which flow out of the catalyst bed once synthesized.[10] Additionally, the ease of screening continuous reaction parameters for a given catalyst makes continuous flow attractive. On the other hand, when a catalytic system is not purely heterogeneous, catalyst leaching is a dilemma for which flow does not offer advantages.

2.3.3 High energy reaction control

"Runaway" reactions are transformations where the heat of reaction increases the temperature of the medium, thereby increasing the rate of the reaction. This regime can lead to side-products or dangerous safety issues such as rapid boiling of solvents, occasionally resulting in an explosion. The small dimensions of tube reactors enhance the performance of these reactions not only with better mixing, but also with more efficient heat transfer. The low reaction mixture volume coupled with a high surface area to volume ratio means that any heat generated during the reaction can be removed very rapidly giving a greater degree of reaction control in flow chemistry compared to batch, as demonstrated in the lithium bromide exchange example below. This example outlines the temperature characteristic of the microreactor (inner volume 2 mL, surface to volume ratio 95) compared to a 100 mL flask (surface to volume ratio 1) in cryogenic lithium/bromide exchange experiment. Since the inner temperature of the vessel increases close to the boiling point of the solvent tetrahydrofuran (THF), the cooling system of the microreactor keeps it strictly to 0°C after a short period of equilibration.[11]

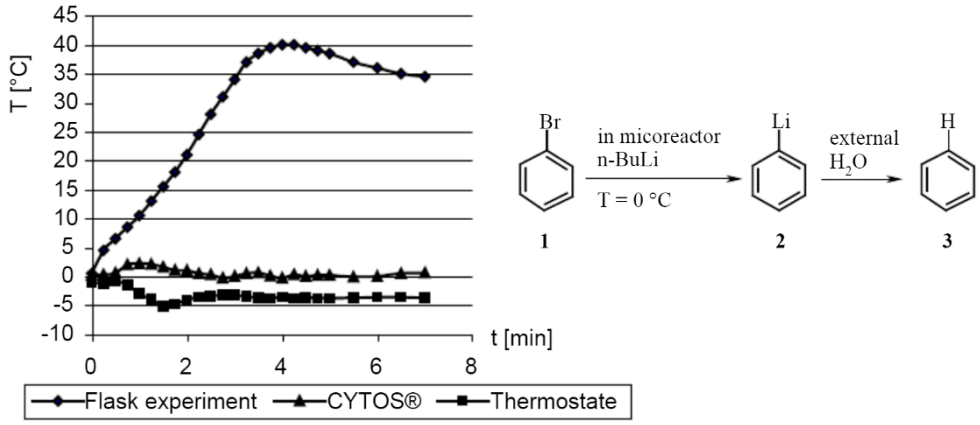


Figure 6: A chart detailing the temperature control of a bromium lithium exchange reaction in a flask and in a flow reactor (CYTOS®).

In another example, trifluoroisopropenyllithium was similarly unstable because of its propensity to form 1,1-difluoroallene via elimination of lithium fluoride. Batch reactions with trifluoroisopropenyllithium must be carried out below −100°C. Yoshida developed a three-component reaction using a trifluoroisoproenyllithium species under noncryogenic conditions (Figure 7).[12]

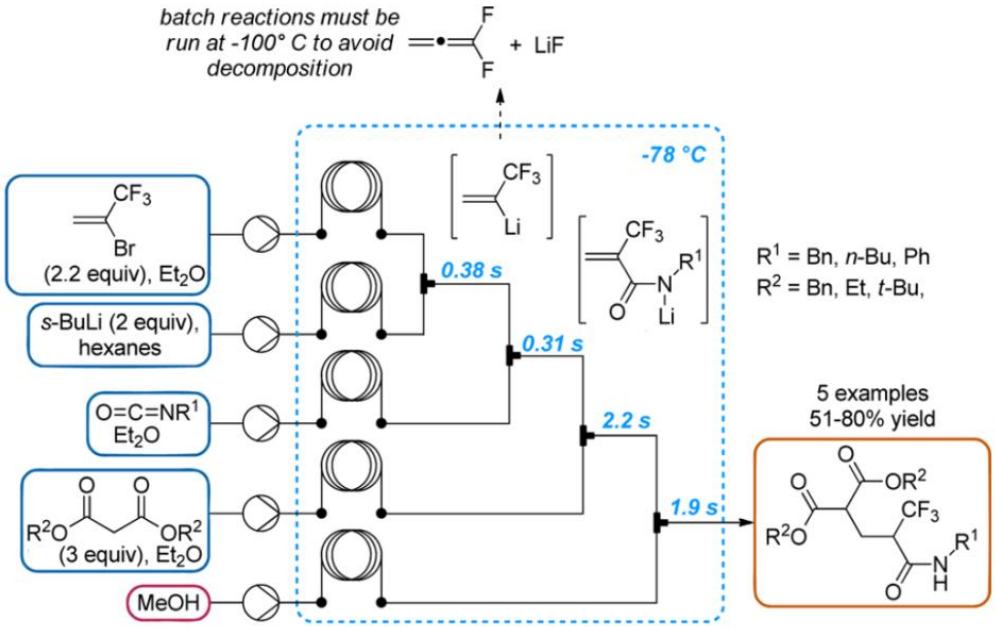


Figure 7: A schematic for the reaction of trifluoroisoproenyllithium using noncryogenic conditions

A solution of 3,3,3-trifluoropropene and sec butyllithium were mixed at −78°C to generate trifluoroisopropenyllithium and quenched with various electrophiles 0.38 s later. The authors demonstrated the utility of this setup by trapping this intermediate with various electrophiles, producing nine compounds in 62−90% yield. Batch reactions are often carried out using excess trifluoropropene and a lithium reagent. Notably, the flow conditions permitted the preparation of these substrates without excess reagents.

2.3.4 High temperature, high pressure reaction capability

The temperature dependence of reactions is typically expressed using the Arrhenius rate law (Equation 1) derived from the observation that the reaction rate increases exponentially as the absolute temperature is increased:

$$k=Ae^{-Ea/RT} \qquad \text{Equation 1}$$

Where:

k is the rate constant,

T is the absolute temperature (in Kelvin),

A is the pre-exponential factor, a constant for each chemical reaction.

E_a is the activation energy for the reaction

R is the universal gas constant

For reactions that take less than 48 h at room temperature, it may not make sense to adopt flow conditions since moderate heating (<80°C) can reduce reaction times to under an hour. However, higher temperatures are required for reactions which do not occur or take more than 48 h at room temperature. Heating a reaction mixture to higher temperatures in batch under reflux conditions necessitates high boiling solvents. This not only limits solvent options but also can complicate reaction workup and product purification[13].

The use of sealed vessels permits lower boiling point solvents for high-temperature reactions since solvents can be superheated above their boiling points. In combination with microwave irradiation, high temperatures (300°C) can be achieved easily, reducing month long reaction times to mere seconds. If the solvent has a dipole moment, then microwave technology is the fastest way of heating up a solvent in a batch reaction, especially when compared to an oil bath heating method. The improved surface area to volume ratio of flow chemistry reactors means that flow chemistry reactors are also able to mimic microwave's rapid heat transfer, where reaction mixtures are heated up to the set temperature in only a few seconds. This has led to flow chemistry reactors being utilized for microwave reaction scale up.[14] The added advantage of flow reactors is that solvents without dipole moments may be used. Another advantage of utilizing flow reactors over batch for high temperature reactions is the lack of headspace. Pressurized flow reactors eliminate headspace, thereby maintaining uniform reagent concentrations, whereas in batch either solvents or reagents may vaporize into the headspace of the batch reactor causing fluctuating concentrations.

Flow chemistry reactors often adopt stainless steel HPLC (High-performance liquid chromatography) parts, which are built to withstand pressure of 100s of bars. Pressures are created using back pressure regulators, where a valve creates a resistance against the flow of reaction mixture. When combined with rapid heat transfer, low boiling point solvents may be heated up past their atmospheric boiling point. The high temperature is limited by the pressure applied and the decomposition of the solvent. This method allows the user to avoid having to use high boiling point solvents, which are either more expensive or more difficult to remove. In the below example, intramolecular thermal cyclization and benzannulation reactions of the Gould–Jacobs and Conrad–Limpach types were performed in a designed continuous flow reactor system at temperatures in the range of 300–360°C and under high pressure conditions (100–160 bar) with very short residence times (0.45–4.5 min) in THF as a low-boiling point solvent (66°C at 1 bar). Substituted heteroaromatic compounds including pyridopyrimidinones and hydroxyquinolines were synthesized in moderate to high yields. Application of the reaction conditions also allows the synthesis of naphthol and biphenyl derivatives. The procedure involves an easy work-up (evaporation of the solvent) and the non-batchwise preparative synthesis method is suitable for automation. No polymerization of the THF was noted.[15]

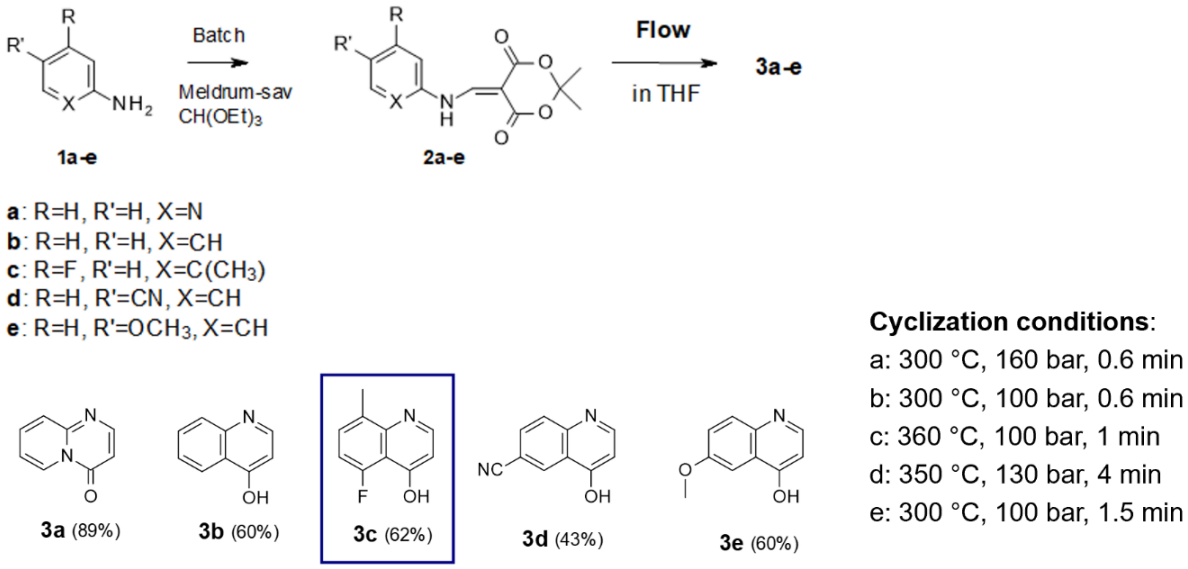


Figure 8: An overview of results from the high temperature synthesis of naphthol and biphenyl derivatives in THF using flow.

Water at very high temperature and pressure exhibits different properties than at room temperature. The polarity is lower, and the ionization constants and diffusion coefficient are increased. This helps to improve solubility of organic compounds and can increase the rates of reactions. Additionally, workup and purification procedures can be expedited after cooling back to room temperature. These benefits were exploited in the synthesis of benzazoles using water as a solvent at high temperature and pressure.[16] Benzazole derivatives have diverse applications as fluorescent molecules, pharmaceuticals, veterinary anthelmintics, and fungicides. Benzazole synthesis is commonly achieved by the reaction of ortho-phenylenediamines with carbonyls or carbonyl equivalents. For initial optimization, *N*-[2-(phenylamino)phenyl]benzamide was cylized. At 400°C and 300 bar, the corresponding benzazole was produced in 59% yield. Increasing the pressure from 300 to 450 bar increased the yield to 94%, and increasing the temperature to 445°C afforded the benzazole product quantitatively. Attempts to perform this reaction in batch were fruitless, yielding only 9−12% of the desired product after 24 h at reflux.

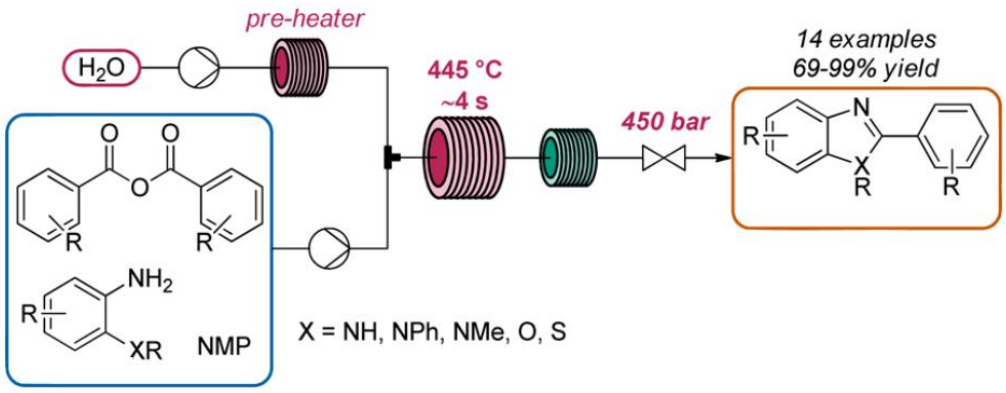


Figure 9: A schematic of the flow reactor setup for the synthesis of benzazoles using water as a solvent at high temperature and pressure.

2.3.5 Improved selectivity

Another advantage of flow chemistry is that residence time can be precisely controlled. This is useful when dealing with reactions that can generate two or more products. The residence time may be extended or shortened by adjusting the flow rate until the optimum selectivity has been achieved. Such a precise control is very difficult to achieve in batch. In the below example, it was demonstrated that radical-based dehalogenations, deoxygenations, and

hydrosilylations in flow often exhibited superior selectivity and control relative to batch comparisons.[17]

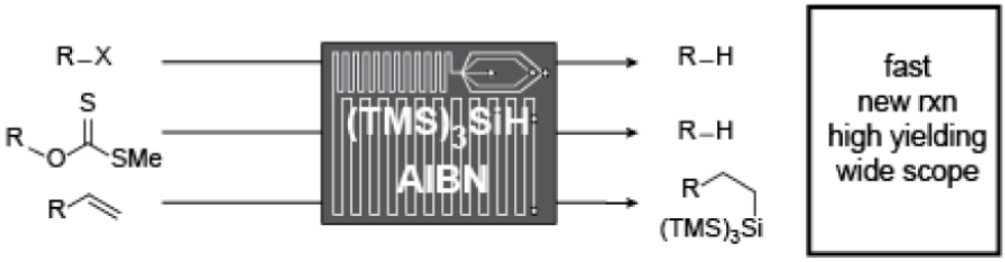


Figure 10: Radical-based dehalogenations, deoxygenations, and hydrosilylations in flow

2.3.5.1 Faster scale up or the ability to scale hazardous reactions

Continuous processes have been used for scale-up in the laboratory and pilot plants. Here, the continuous processes are used for fast reactions, requiring minutes or less. The feasibility of continuous processing can often be assessed with a modicum of effort, and sometimes batch processing cannot effectively scale up some processes. This is either due to the chemistry being too hazardous to scale, due to the hazardous nature of the materials or the reaction itself, or, as mentioned previously regarding microwave-based reactions, the technique itself is not amenable to be scaled. [18] For initial laboratory work and scale-up to the pilot plant, reactors are smaller than those used in manufacturing settings and the reaction conditions in the laboratory reactor can often be applied to the pilot plant by running a number of the lab-scale reactors in parallel, called “numbering up”, which significantly speeds up the transfer process. Despite their small size, continuous flow reactors can lead to large productivity due to rapid flow rates. [19]

2.4 Further applications

In addition to the advantages listed above, flow chemistry can be applied to, and improve upon, a number of different chemistry applications as listed below.

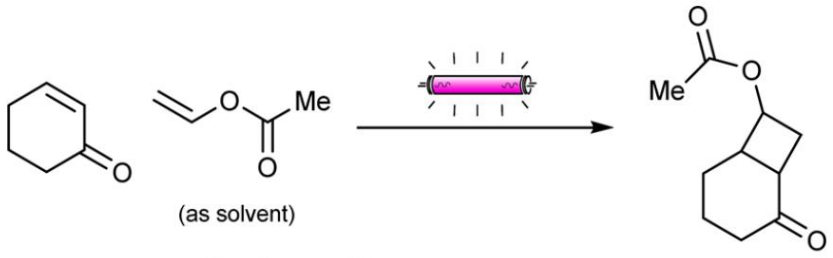
2.4.1 Efficient photochemistry

Using light to accelerate a chemical reaction is one of the most promising possibilities to access more sustainable chemical processes. In contrast to conventional reagents, photons are not only traceless but also nontoxic. However, a serious problem limiting photochemical

transformations on larger scales arises from the logarithmic decrease of the transmission of light as a function of path length through a liquid medium (Beer−Lambert−Bouguer law). Consequently, the reaction mixture is inefficiently irradiated, and low reaction rates are obtained. This issue is avoided by changing from conventional batch processes to continuous flow approaches.[20]

The large surface-to-volume ratio ensures increased irradiation efficiency for the entire solution. This not only results in significantly intensified protocols but also allows for scaling these chemistries to synthetically useful quantities. Reactions may be carried out in quartz or Teflon type reactors, which are UV transparent. Critical reaction conditions are the type of light irradiation employed and the residence time of the reaction. Maintaining reaction temperature under UV irradiation is also critical.

One of the first photocycloadditions in flow has been reported in 2004[21] where the [2 + 2] cycloaddition of cyclohexenones with vinyl acetates was demonstrated.



Microflow conditions:

Glass Microreactor (1.0 x 0.5 mm, 700 μL)
***different light sources* (see table)**

Light source	Yield	Rt	Wh	Yield / Wh
300 W Hg lamp	71%	120 min	600	**0.12**
15 W Black light	82%	120 min	30	**2.70**
1.7 W UV LED	91%	15 min	0.43	**214**

Figure 11: [2 + 2] cycloaddition of cyclohexenones with vinyl acetates.

The photomicroreactor contained a channel with a rectangular section of 0.5 × 1 mm and was irradiated with a 300 W high pressure mercury lamp. In comparison with batch, a notable decrease in reaction time was observed (71% yield in 2 h in flow, 22% in 4 h in batch). The same reaction was further investigated with respect to the nature of the light source.

Different energy saving light sources were tested, and the results underscore how uncompetitive mercury-vapor UV-lamps are in comparison with black light (UV-A light) and UV LEDs in terms of yields, irradiation times and energy consumption (0.12 yield/Wh for the mercury lamps, vs 2.70 yield/Wh for the black light and 214 yield/Wh for the UVLEDs). In the model reaction between cyclohexenone and vinyl acetate, a product yield of 71% and 82% was obtained in 2 h with mercury lamp and black light respectively, while the use of UV-LED resulted in a 91% yield in just 15 min.

2.4.2 Electrochemistry

Organic electrochemistry is a sustainable method to replace stoichiometric oxidants and reducing agents for organic transformations. The synthetic community is increasingly applying this method for the mild conditions and high chemoselectivity it offers.[22] Essentially, electrochemical reactions are redox reactions that are driven by the application of an external voltage via the incorporation of electrodes in the reaction vessel. Within the reaction media, molecules are reduced at the cathode and oxidized at the anode. In electrochemical analysis, proper placement of the electrodes is not a problem since the instrumentation employs small electrodes. In bulk electrolysis methods, however, the placement is critical. Inconsistent ohmic drops (or IR drops) produce a nonuniform potential across the working electrode which can cause undesired side reactions or ineffective use of the total electrode area.

Another challenge bulk electrolysis faces are high cell and solution resistances. As most organic transformations are performed in an organic solvent, supporting electrolytes are used to improve the conductivity of the solution. Since large scale reactions can require one or more equivalents by weight this can be costly. The supporting electrolytes must also be removed in an additional purification step that generates waste, countering the argument that the use of electrochemistry is a “green” method. Also, batch scale up can lead to an undesirable evolution of heat caused by larger distances between electrodes. Flow electrochemistry setups are advantageous to batch setups because the reaction mixture is essentially a heat exchanger fluid via the continuous flow of fluid across through the cell. When streaming a fluid in a channel between two electrodes, reducing the distance between the electrodes allows for better control of the number of electrons that are transferred to the

substrates enabling better control and selectivity of the reaction meaning that alongside more accurate product distribution you will also obtain higher yields of product.[23]

A microflow system where the current flow and liquid flow are parallel was reported.[24] Two carbon fibre electrodes were separated by a hydrophobic porous PTFE membrane (75 µm thickness). The substrate solution was fed into the anodic chamber and flowed through the membrane into the cathodic chamber, where it would leave as products. The anodic methoxylation of 4-methoxytoluene was carried out in the electrochemical cell under a constant current of 11 mA with a flow rate of 2 $mL \cdot h^{-1}$ resulting in a 90% conversion.

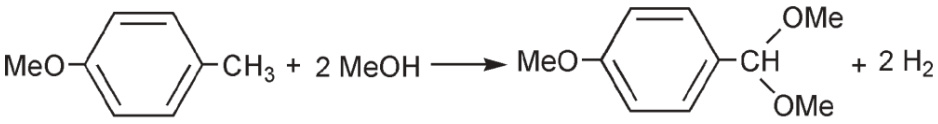


Figure 12: Anodic methoxylation of 4-methoxytoluene

2.4.3 Multi-step synthesis

Multi-step synthesis in flow chemistry, also called “telescoping”, is where the elution of product of one reactor is directly mixed with another reagent and passed through another reactor to perform another reaction, is a highly useful synthesis method, but also one of the most difficult to master. Apart from the obvious time savings of performing two or more reactions in one flow there are also other advantages. Compounds, such as azides, which may decompose explosively when formed may be immediately reacted using this type of set-up to form a more stable product. The compound need not be isolated and is only generated in small quantities continuously for added safety. The main difficulty in multi-step synthesis lies in maintaining a common solvent mixture in all steps where the starting materials, reagents, and products are all soluble. Purification between steps may also increase the difficulty.

In the below example, a 3 step synthesis of Ibuprofen is carried out.[25] The system required a batch crystallization at the end of the synthesis, but the intermediate steps required no aqueous work-up or purifications.

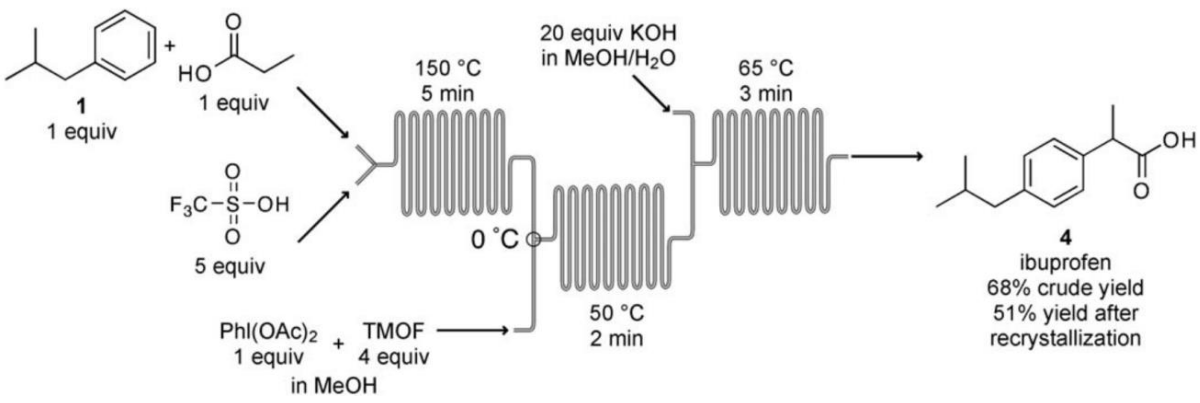


Figure 13: Reaction Schematic for the 3 step synthesis of Ibuprofen.

2.4.4 Gas-Liquid-Solid Reactions

Reactive gases are valuable reagents for a multitude of chemical transformations and serve as critical feedstocks for pharmaceuticals, crop-enhancing additives, polymers, and advanced materials. Examples of the different types of functional groups that can be made from carbon dioxide are given below (Figure 14).[26]

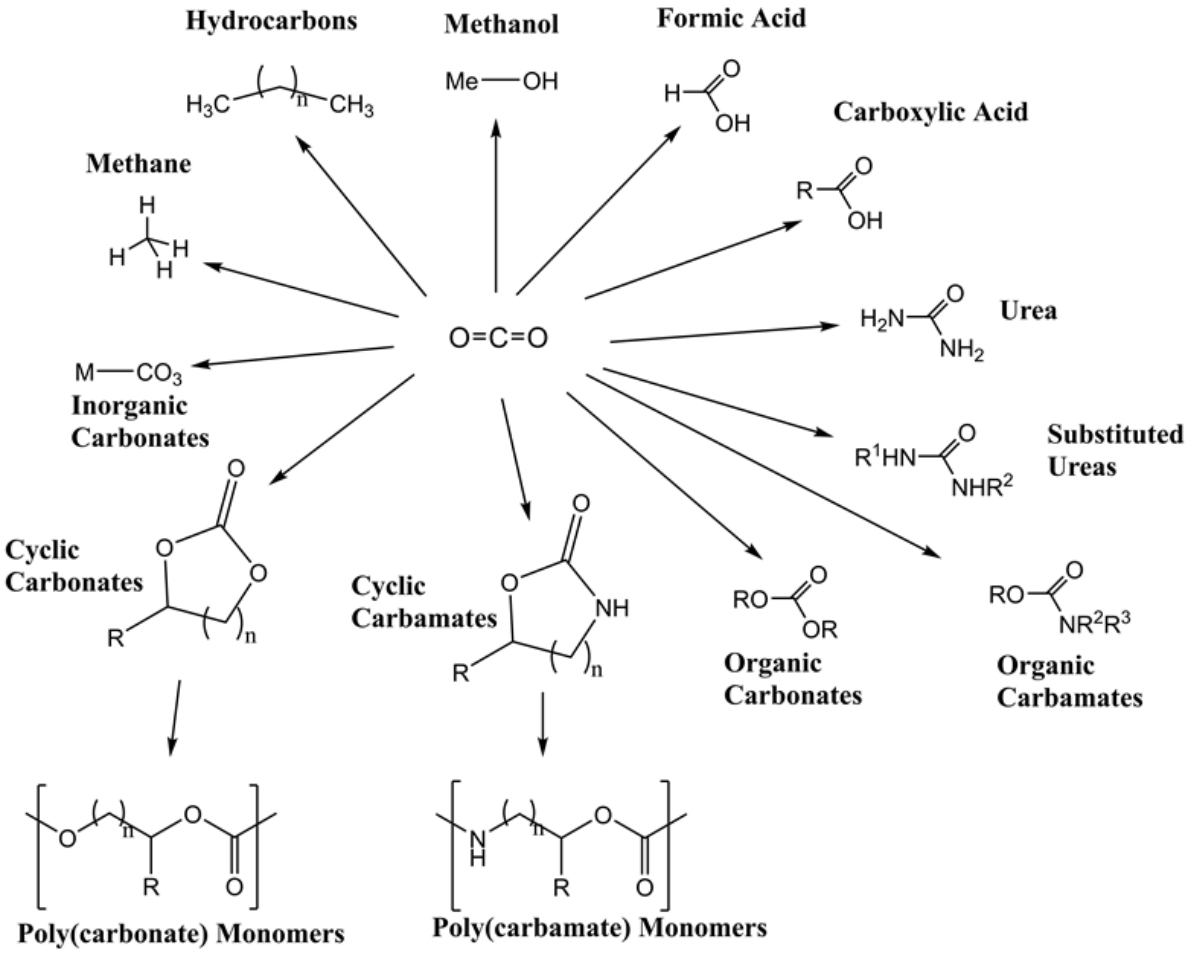


Figure 14: Functional group possibilities from a carbon dioxide source.

Gases are ideal reagents because reaction products can often be isolated by simply venting excess gas from the reaction vessel. Raising the pressure to provide a stoichiometric excess of reagent offers a simple means of driving a reaction to completion, with the low cost of gases readily enabling such an approach. However, high pressure reactions often necessitate expensive specialized equipment or purpose-built facilities and additional safety precautions, while the use of toxic, flammable, and corrosive gases generates significant hazards that are intensified by scale.

Employing gaseous reagents in flow is particularly advantageous when looking at gas-liquid - solid reactions, where, taking into account the advantages of solid-liquid reactions outlined above, reactions take place faster because of larger interfacial areas and the short path required for molecular diffusion in the microchannels created by the packed bed. The smaller reactor size enhances safety in the cases where reagent gases are potentially hazardous. Below are various examples of where gaseous reagents have been employed in flow. The following section details examples of where flow has been utilized with reactive gases.

2.4.4.1 Reactions with carbon monoxide

Carbon monoxide is a toxic (poisoning symptoms occur above 50 ppm concentration in air) and highly flammable gas; due to its limited solubility in most organic solvents, reactions employing it are most commonly carried out at elevated pressure. This makes the use of carbon monoxide a risk, especially in standard laboratories or when large quantities are needed. However, because it is a synthetically versatile and low-cost building block, chemists have continued using it despite its associated hazards. Indeed, carbon monoxide is perhaps, behind hydrogen, one of the most used gases, and as such, it is used in several industrial process such as the Fischer–Tropsch process[27] and hydroformylation.[28] Carbon monoxide is also routinely used for the conversion of aryl halides and pseudohalides to higher oxidation level groups such as amides, esters, aldehydes, and carboxylic acids. The amino-carbonylation of halogenated aryl carboxylic acids with various amines was reported (Figure 15).[29] using a commercial pressurized continuous flow reactor. The substrates were passed through a phosphine-immobilized version of $Pd(PPh_3)_4$ to generate moderate to good yields of a variety of amide products (27–39) that were prepared in very short residence times (~2 min).

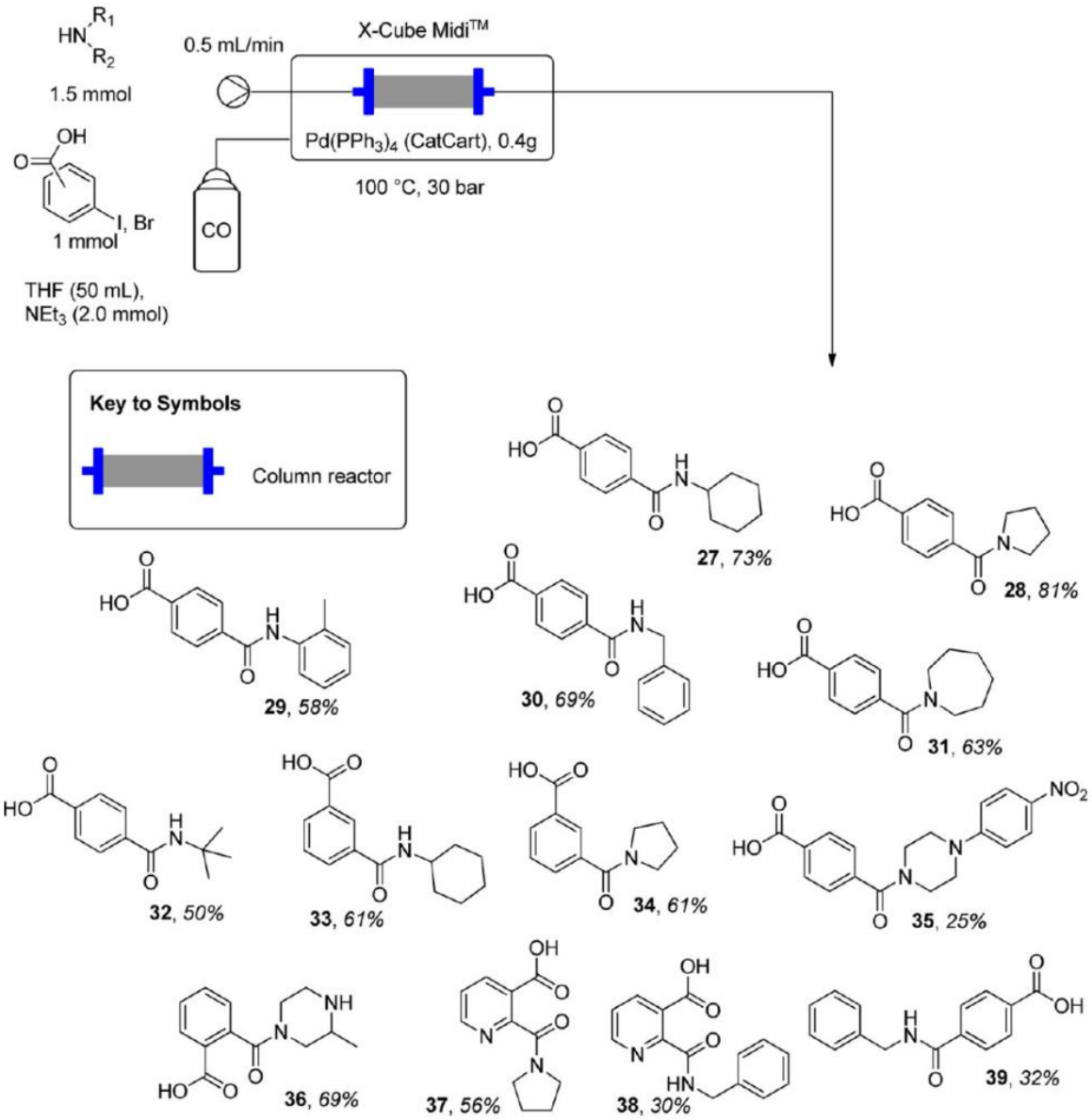


Figure 15: The amino-carbonylation of halogenated aryl carboxylic acids with various amines.

2.4.4.2 Reactions with air and oxygen

One of the most difficult reactions is the selective oxidation of alcohols to aldehydes and ketones—a process that is ubiquitous in organic chemistry, yet is also one of the least efficient, engendering the development of a large number of methodologies. One of the most attractive ways of oxidising an alcohol is to use O_2 as a terminal oxidant, where only H_2O is generated as a side-product. Although there have been a number of heterogeneous catalysts reported to facilitate the process,[30] there is a genuine concern that the process of mixing the catalyst, reactant and gaseous oxidant can lead to explosive hazards, particularly if the reaction is performed on a large scale in a batch reactor. Work has been extensively carried

out on adapting aerobic oxidation of alcohols to flow to minimize the explosion risks and to increase the efficiency of catalysts. Employing 5% Ru/Al_2O_3 under 5 bar of O_2 at 90°C, benzylic and allylic alcohols were oxidised selectively to their corresponding aldehydes and ketones, including substrates containing *N*- and *S*-heteroatoms. The rate of turnover was comparable with that previously reported using batch or microchannel reactors under optimised conditions. Some results are highlighted in the table below.[31]

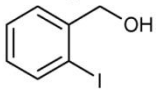
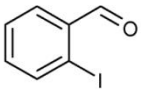
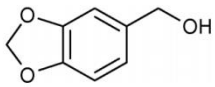
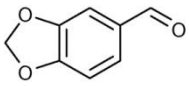
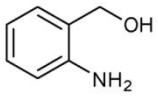
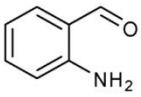
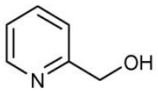
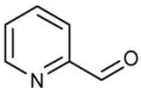
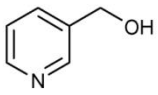
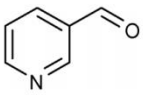
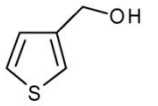
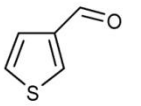
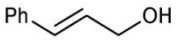
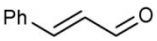
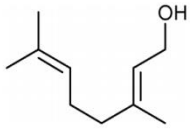
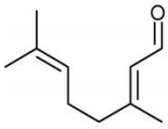
Entry	Alcohol	Product[b]	*t*/h	Conversion (%)[c]
1	$PhCH_2OH$	PhCHO	0.75	>99
2			1	>99
3			1	98
4			6	94[d]
5			7	95
6			7	97
7			1	>99
8			0.75	>99
9			2	>99

Figure 16: Table highlighting the results of oxidizing benzylic and allylic alcohols using 5% Ru/Al_2O_3.

2.4.4.3 Examples of heterogeneous hydrogenation

Of all the gas-liquid-solid reactions, heterogeneous hydrogenation is by far the most common. On solids, the accepted mechanism is the Horiuti-Polanyi mechanism[32]:

1. Binding of the unsaturated bond, and hydrogen dissociation into atomic hydrogen on the catalyst

2. Addition of one atom of hydrogen; this step is reversible
3. Addition of the second atom; effectively irreversible under hydrogenating conditions.

The popularity of hydrogenation stems from the fact the process is typically cheap, often selective, and most solvents can be used for such reactions. Moreover, the high atom economy and small amount of chemical waste is in good agreement with green chemistry principles. A plethora of heterogeneous catalysts are available, typically being noble metals (Pd, Pt, Rh, and Ni) on a solid support (carbon, alumina, silica, etc.) or finely grained alloys such as Raney nickel. Hydrogenation is widely employed across a number of industries such as food (the processing of vegetable oils[33], the petrochemical industry (conversion of alkenes and aromatics into saturated alkanes (paraffins) and cycloalkanes (naphthenes), and organic chemistry.

Heterogeneous hydrogenation's ubiquity in industry is despite the numerous safety issues associated with hydrogenation and is testament to its necessity in chemistry. The safety concerns of hydrogenation throughout the chemical industry have been well documented. The limitations of heterogeneous hydrogenation lie with the reactors, processes, and reagents used to conduct hydrogenation. 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 where reactor options are limited to balloons, autoclaves, or Parr shaker apparatus[34]. In these apparatuses, the reaction conditions are often limited to room temperature and pressure, which in turn limits the types of reactions that can be carried out. Also, analysis of the reaction mixture is invasive and reactions must be halted, depressurized, and cooled to obtain analytical samples to observe accurate reaction progress. Fast validation for the reduction of novel compounds is, therefore, difficult. The mixing of the three phases can be poor leading to low reaction rates. Heterogeneous hydrogenation, therefore, is a good candidate to adapt to continuous process in order to overcome the above.

Flow hydrogenation in the petrochemical industry has been utilized for over a century[35]. Many of the compounds found in crude oil are of little use since they contain multiple double bonds; they must be first converted to saturated compounds before use as commodities such

as petrol. Hydrocracking of heavy residues into diesel is one example. A flow process is employed due to the large production volumes necessary to fulfil global demand.

Continuous flow hydrogenation was not employed in a simple laboratory context for non-petrochemical applications until 2004, where researchers from Japan immobilized palladium into microchannels and conducted hydrogenation by passing a mixture of starting material and hydrogen over the catalysts using very low flow rates (0.1 mL/hr)[36]. Reactions were carried out in a microchannel reactor having a channel 200 µm in width, 100 µm in depth, and 45 cm in length (Figure 17). When referred to the reaction channel volume and the amount of the catalyst, the space-time yield was 140,000 times higher than those produced by ordinary laboratory flasks. A range of substrates were reacted on the microreactor over a 2 minute residence time resulting in quantitative yield in all cases.

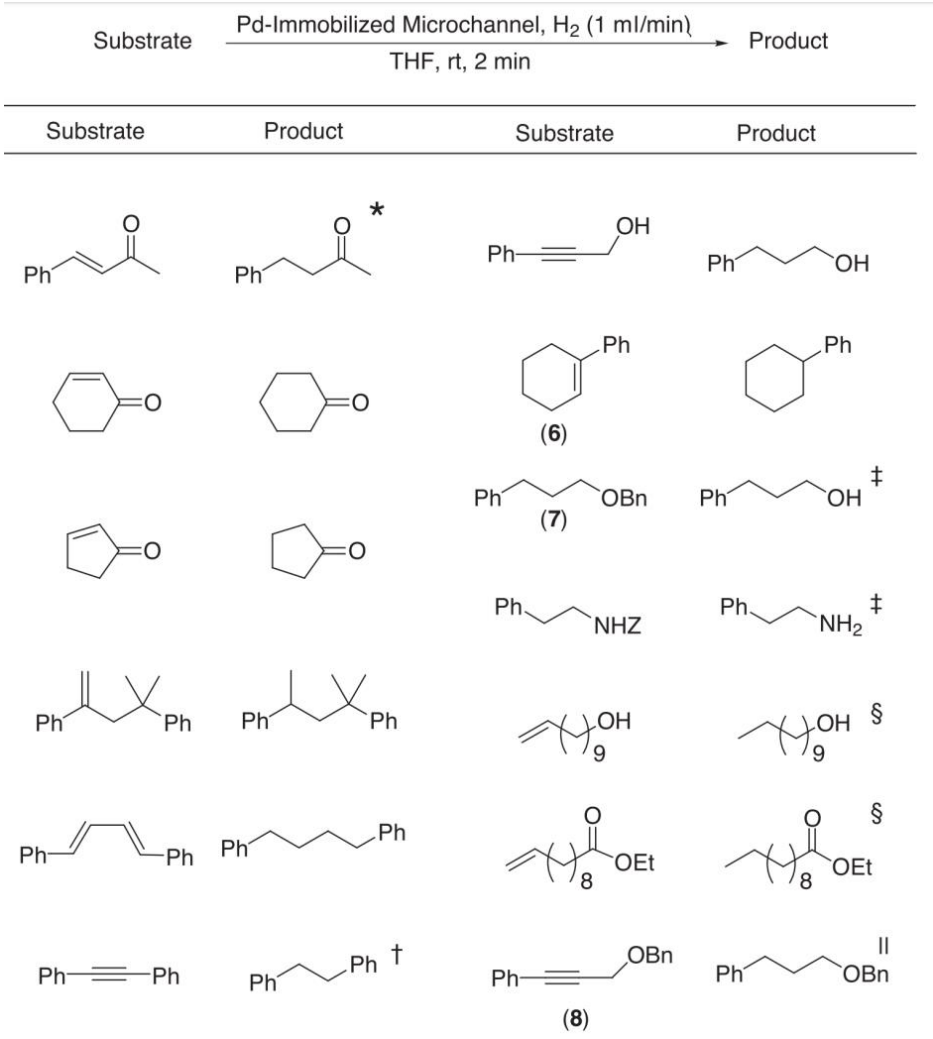


Figure 17: Table highlighting reduction of various substrates in a continuous flow hydrogenation reactor

As a proof of concept this research served as a very nice example as to the possibilities of how hydrogenation could be performed more efficiently if performed under flow conditions. However, there are a number of disadvantages to the techniques used.

1. The throughput is very low (0.1 mL/hr), so the system would need to run for days in order to generate gram scale material.
2. At the time, only palladium could be immobilized into the microchannels, so this will limit the variety of chemistry possible.
3. The system is limited in terms of temperature and pressure.
4. While this method does improve on catalyst safety, the issues regarding hydrogen source (a cylinder) are not solved.
5. The longevity of the catalyst microreactor chips have not been tested and a comparison of the costs versus normal palladium catalyst were not made.

2.4.5 Importance of automation

The pharmaceutical industry has significantly influenced laboratory automation trends in the past two decades. The need to screen large collections of chemical entities in a short time with minimised consumption of reagents has driven a strong demand of parallelisation, automation, simplification and miniaturisation solutions from the suppliers of instruments, labware and assay technologies.[37] This is also true when it comes to scale up. As contract manufacturing companies can no longer afford the costs of and time delays associated with traditional pilot-plant and scale-up developments, reactions are now typically run in parallel at a small scale, rather than one at a time at a liter or a gallon scale. This way, the rate of R&D—from discovery to scale up and commercialization—is accelerated many times over.

In today's global economy, competition is fierce, not only in costs and product performance, but also in environmental stewardship and safety as well as in speed to market. The development and use of combinatorial and high-throughput screening (HTS) tools will enable us to be safer in the workplace, because we will be more aware of potential dangerous combinations and conditions. Processes will be developed that have more benign waste streams or, perhaps in combination with recycling technologies, no waste streams at all. And of course, more and better products will be brought to the market quicker than ever.
At the time of research (2004), automation of hydrogenation was limited to batch technology, such as the one pictured below, the Auto-MATE system.[38]

Figure 18: The Auto-MATE Reactor system by HEL.

Although classed as "automated", the number of parallel reactions is limited to 8 and the addition of catalyst and work-up is performed by hand. While useful for creating and assessing calorimetric data, the above system does not come close to meeting the needs of the chemical industry in terms of high-throughput screening. Also, the source of hydrogen in this technology is still the hydrogen cylinder, so the main safety issue regarding hydrogenation is still prevalent.

Hydrogen generators have been developed to overcome the use of hydrogen cylinders in the laboratory. The systems work through generating hydrogen from the electrolysis of water, typically using polymer electrolyte membrane cells (PEMs). While inherently safer than gas cylinders, the systems are designed to supply hydrogen as a carrier gas to analytic systems and are, therefore, low in pressure. (3 bar maximum on average for laboratory systems). If connected to a reactor, this lack of pressure would severely limit the hydrogenation chemistry possible.

If laboratory hydrogenation is to remain in use against stricter and stricter safety regulations or to remain a tool of the chemist when the move towards automation shows no sign of abating, then new technologies will have to be invented to satisfy these needs.

3 Project Goals and Motivation

Based on the above explored industry and academic research requirements, the project goals for this work were as follows:

1. The adaptation of current batch process of hydrogenation to a continuous process in the form of a laboratory flow hydrogenation reactor (H-Cube®).
2. The performance of hydrogenation reactions on a wide parameter range including high pressures, from room temperature to 100°C and 1-100 bar manually.
3. Product quantity generation on the range of milligram to gram scale and above within an acceptable timeframe.
4. Incorporation of the flow reactor into an automated liquid handler towards the generation of compound libraries in a high throughput automated way.
5. The application of the invented high-pressure hydrogen cell technology towards kilo-scale per day production are explored.

Overall, the project had two motivations:

- Creation of the first fully automated flow hydrogenation platform that can be utilized in the lab of tomorrow for either reaction optimization or library synthesis.
- Creation of a hydrogenation technology that makes hydrogenation significantly safer to perform, so it may be used in any laboratory and not only in special facilities.

4 Experimental Methods

4.1 General Analytical Methods

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.

Starting materials were purchased from commercial sources. Silica gel 60 F_{254} (Merck) plates were used for TLC (Thin Layer Chromatography). Solvents were dried and purified according to the well-established methods.[39] Evaporations were carried out under reduced pressure.
All products exhibited spectral data (1H.NMR and MS) consistent with their structures.

4.2 A typical H-Cube® experimental procedure using hydrogenation of 5-nitroindole as an example.

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).

4.3 Example batch reaction using reduction of 5-nitroindole as example

5-nitroindole (16.2 mg, 0.1 mmoles) was dissolved in methanol (2 mL) and placed in a 10 mL round-bottomed flask with a stirrer bar. The flask was placed in an ice bath and a slow stream of nitrogen was flowed over the top of the flask. 145 mg of Pd/C was then added to the solution and the flask placed in a standard bomb reactor. The bomb reactor was flushed with nitrogen three times to remove any air, and then flushed with hydrogen up to a 2 atmospheres pressure. The reaction was stirred vigorously for 3 minutes before the hydrogen was released. Initial TLC results showed poor conversion. NMR analysis showed 2% conversion. The reaction was again put under hydrogen at the same pressure and left for a further 12 minutes. Analysis of the reaction mixture showed complete conversion. The total time for catalyst addition, reaction, and filtration took approximately 30 minutes.

4.4 Description of experimental method applied with Mettler Toledo's FlowIR™

Mettler Toledo's FlowIR™ is a dedicated Fourier Transform Infrared Spectroscopy (FTIR) instrument for real-time monitoring of continuous flow chemistry.

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.

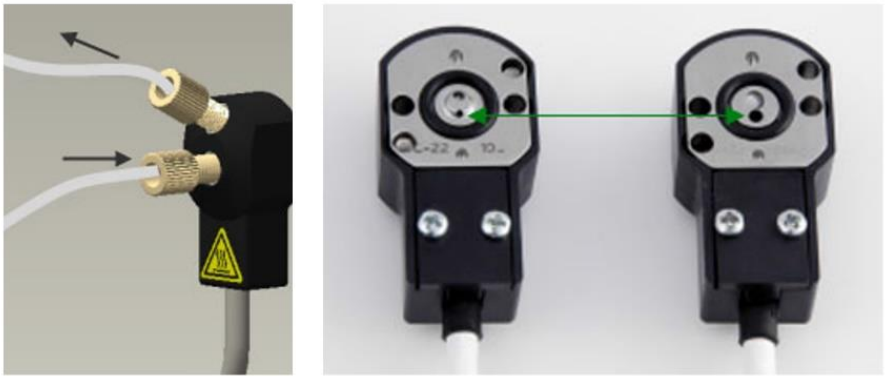


Figure 19: Mode of injection into the head (left). FlowIR volume heads- 10µL and 50µL.

Available sensor head volumes are 50 µL and 10 µL. 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.

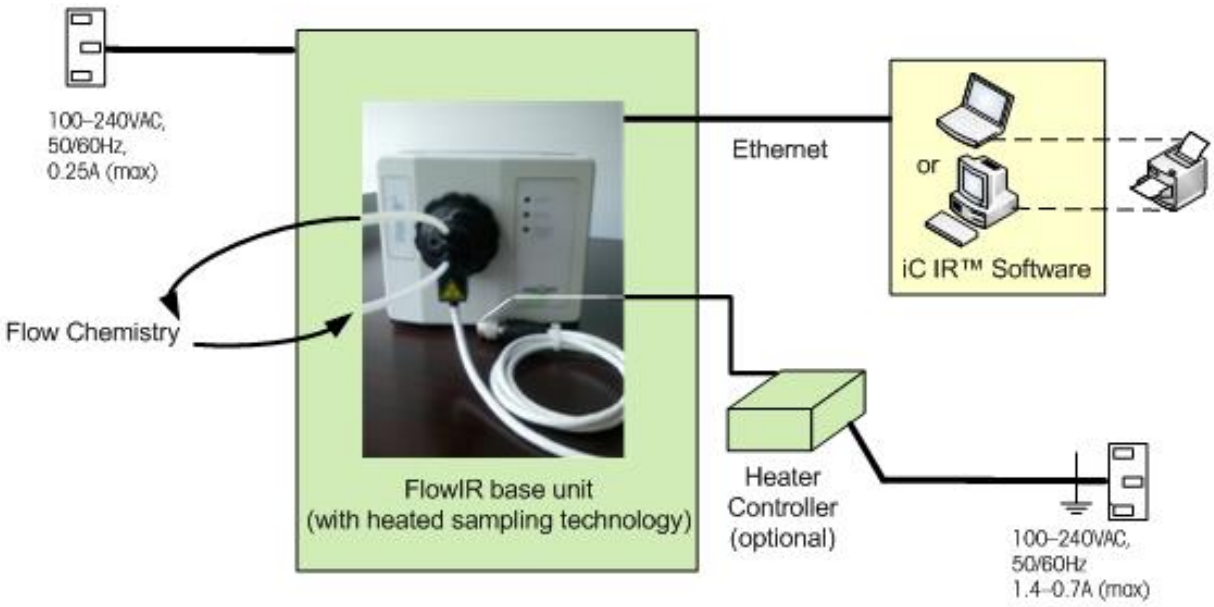


Figure 20: FlowIR connected in-line to heater controller and flow reactor.

4.5 Automated hydrogenation library production method using a nitro compound library as an example

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 (Figures 21a and b).

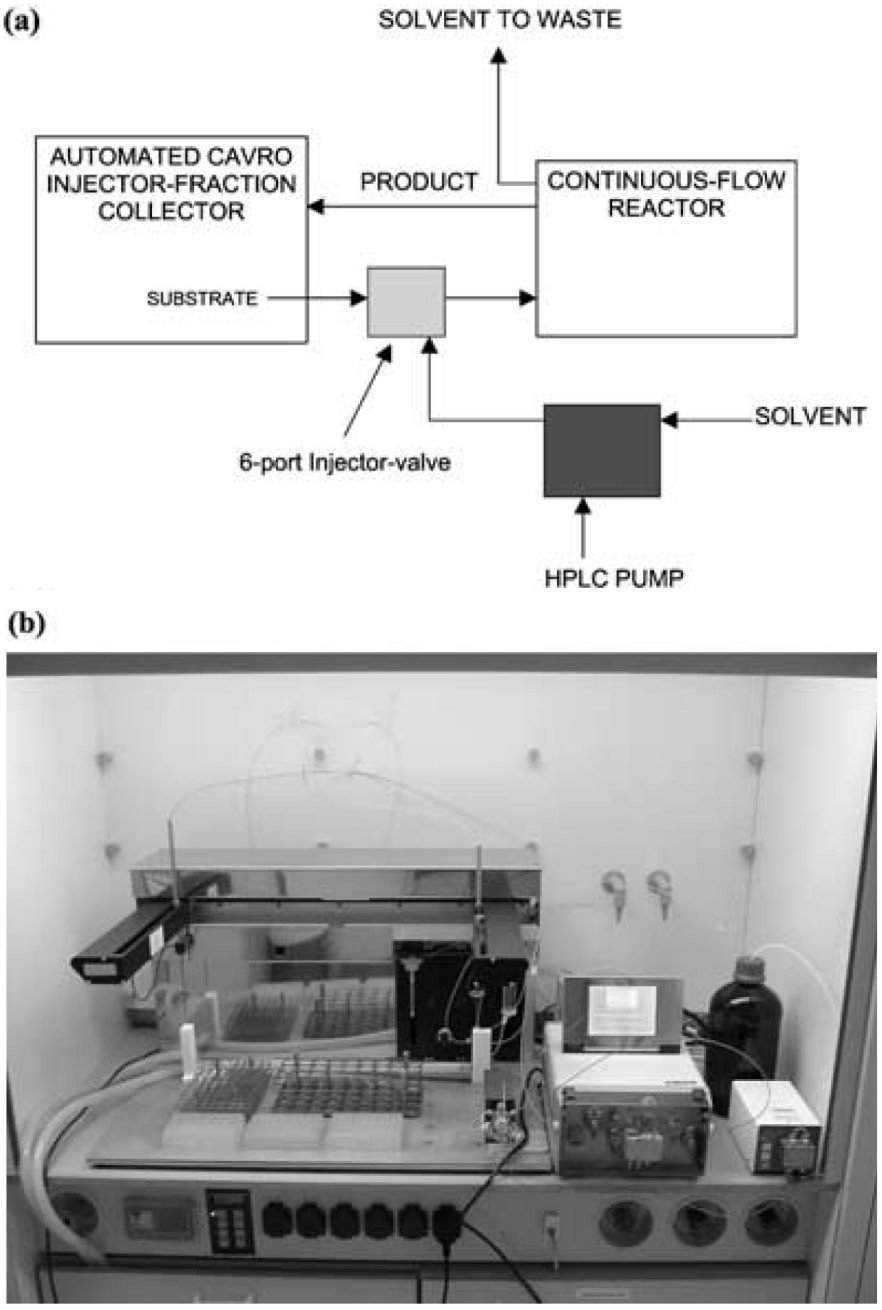


Figure 21: A continuous-flow reactor set-up for high throughput hydrogenation (a) scheme (b) photograph of set-up.

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 (see Figure 22) switches the flow of solvent from the reactor to injection loop, pushing the injected substrate out of the loop into the reactor.

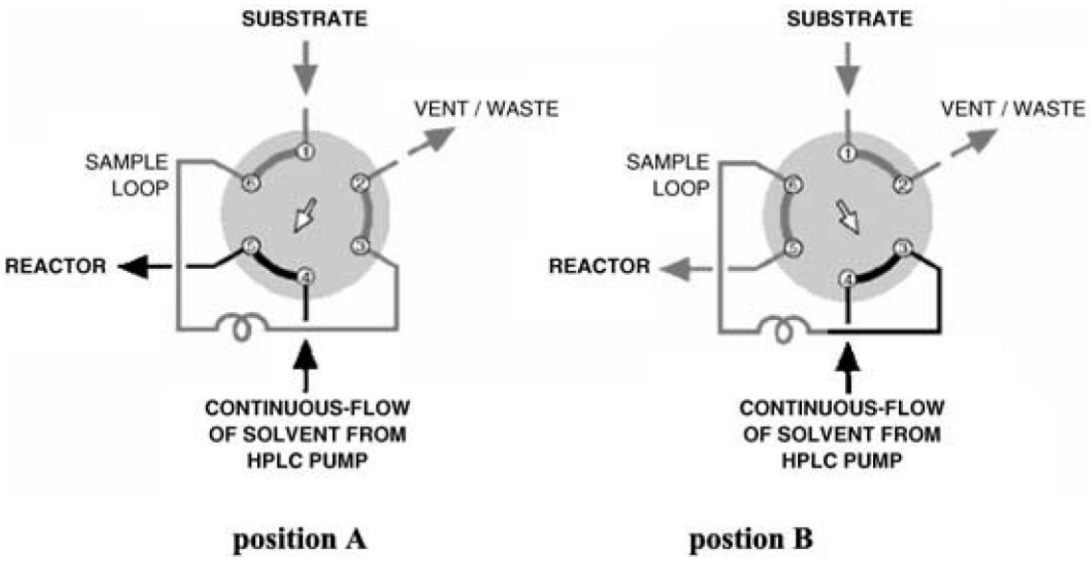


Figure 22: Flow of solvent through valve at position A and B.

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.

A catalyst cartridge containing Pd/C was placed in the H-Cube® and the pump set to a flow rate of 1 mL/min. The pump was switched on and methanol solvent passed through the H-Cube® system for 5 min to remove any air bubbles. The pump was then stopped. Portions of

0.6 mmol of 5-nitrolindole (1), 2-nitronaphthalene (2), 7- nitroindole (3), 4-nitroanisol (4), and 1-(4-nitrophenyl)piperazine (5) were dissolved in methanol in five separate vials. The vials were placed in this order in the substrate rack in the CAVRO liquid handler.
The H-Cube® was set to 30°C and the pressure to 1 atm.

The following data was loaded into the CAVRO software:
Number of reactions: 25
Fraction collection time: 6 minutes
Delay time (the time between washing and the next injection): 1 minute
Injection volume: 1 mL
The CAVRO program was then initialized. The program commences as follows:
Step 1: Injection needles and syringes are washed.
Step 2: Injection arm is moved to the sample well plate, collection arm is moved to the collection vial rack.
Step 3: Injection arm is moved to the injector port.
Step 4: Sample is injected in the sample loop.
Step 5: Injector is switched to the high-pressure side.
Step 6: Injection needle is washed two times and returned to the waste station.
Step 7: Fraction collection.
Step 8: The system is waiting.
Step 9: The system starts the next injection.
Step 10: After the final injection and collection, the needles and syringes are washed twice, and the system switches off.

4.6 Description on how to perform a reaction between the H-Genie® and Phoenix Flow Reactor

Materials preparation

10% Pd/C with particle size distribution (d10: 7 µm, d50: 35 µm, d90: 150 µm) was purchased from Johnson Matthey, glass beads unwashed (212-300 µm) and methanol from Sigma Aldrich. The catalyst was loaded into the 1" metal-metal sealed (MMS) column (L: 230 mm, ID: 21.2 mm, internal volume: 81 mL) in the following order and quantities: 4 g of glass beads, 35 g : 3.5 g of 10% Pd/C : glass beads, ~25 g glass beads.

The solution of 0.1 M of methyl-4-nitrobenzoate was prepared by dissolving 724.6 g into the 40 L of MeOH. The 1" MMS column (with the catalyst previously packed inside) was placed into its appropriate holder in the Phoenix. When the flow line was fully completed and every part was connected and tightened (gas liquid mixer, pump head, check valve from the H-Genie®, cartridge, pressure sensor, etc.), a leaking test was performed by pumping a solvent through and setting a high pressure. The water reservoir of the H-Genie® was filled with sufficient amount of MilliQ grade water and H_2 flow rate was set at 1000 NmL/min and 100 bar. When H_2 was introduced to the system, the flow rate on the HPLC pump was set at 100 mL/min using MeOH and the pressure on the Pressure Module to 70 bar. When it was stable, the temperature on the Phoenix was set to 70°C. After all parameters were stable for 5 minutes, the reaction was started by switching the inlet tubes from the MeOH flask into the stock solution of methyl-4-nitrobenzoate. Fractions were collected in order to monitor the reaction by TLC (cyclohexane:ethyl acetate 3:2) and LCMS (Liquid Chromatography-Mass Spectrometry).

To finish the reaction, the inlet tubing was switched to the solvent to wash the system for ten minutes, the different modules stopped (cooling down of the Phoenix, pressure released on the pressure Module, stop of the H_2 flowrate on the H-Genie®), and finally the HPLC Pump also stopped.

5 Results and Discussion

5.1 H-Cube® Reactor Overview

The H-Cube® system is based on the hydrogenation of a continuous flow of reactant. Additional equipment is needed to introduce the reactant into the H-Cube® device. For the most basic function where only a continuous flow of reactant is flowed through the system, only an additional HPLC pump is required. If you wish to conduct multiple injections of reactants into a continuous stream of solvent, then a loop injector valve is also required. Both set-ups are outlined in the figure below.

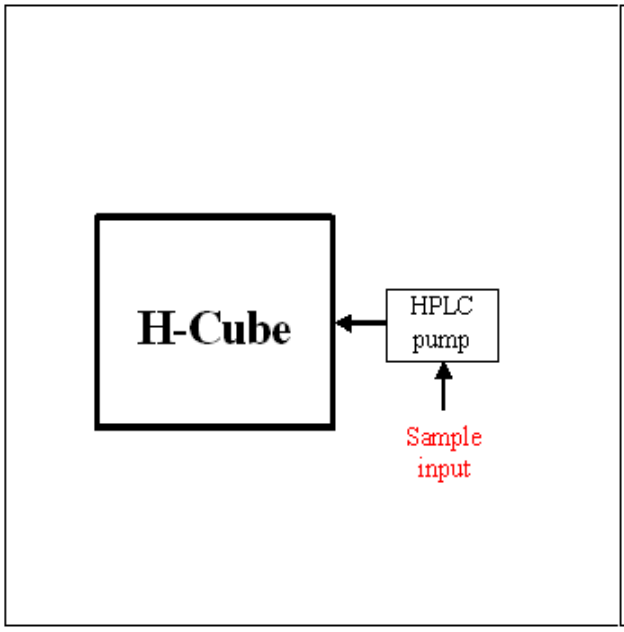


Figure 23a: H-Cube® system setup- Continuous-flow mode.

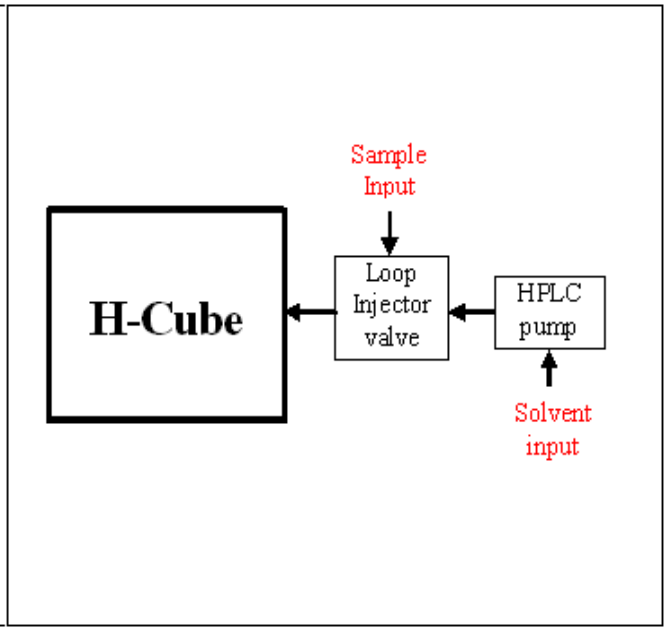


Figure 23b: H-Cube® system setup- with loop injector.

Electrolytic water decomposition within the H-Cube® generates high-purity hydrogen in the required quantity, eliminating the need for gas storage. The hydrogen gas and a solution of the reactant are mixed, pre-heated and transferred to a disposable catalyst cartridge (CatCart®) that is preloaded with the required heterogeneous catalysts. The product then flows out of the cartridge and is collected in a vial or flask. In most reactions the only work-up required is the evaporation of solvent.

5.2 How does the system work?

An overall schematic for the major functional parts within the H-Cube® is given in Figure 24.

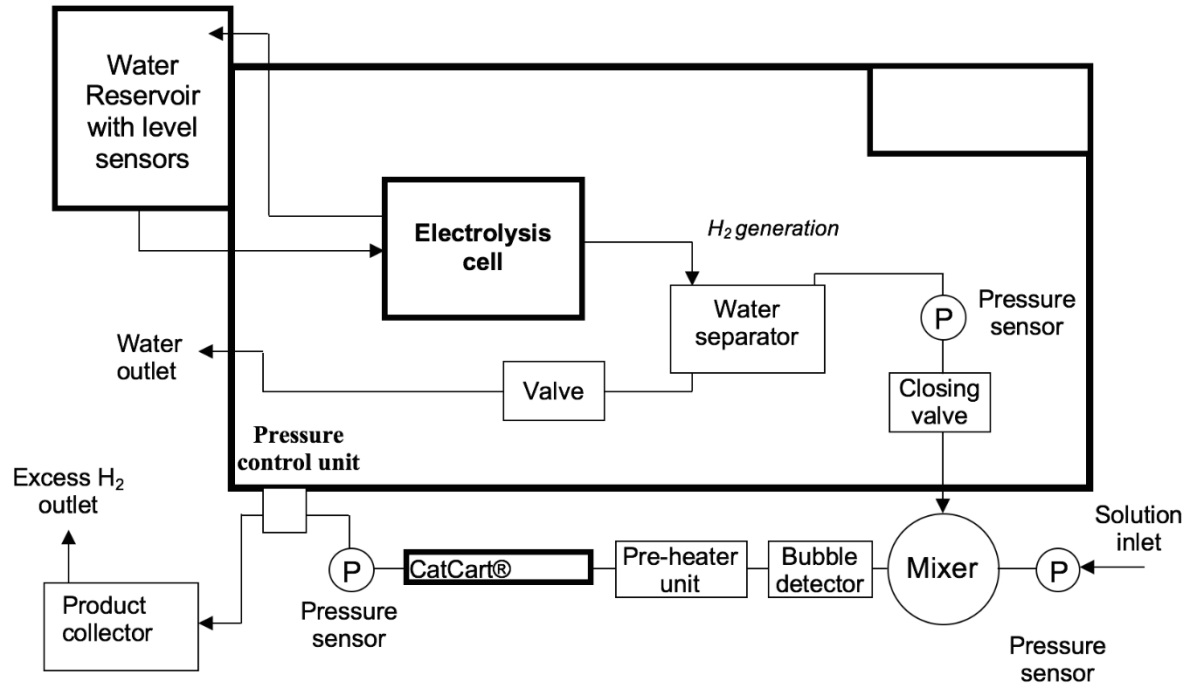


Figure 24: Schematic design of the H-Cube®.

The H-Cube® contains a water reservoir filled with high purity deionized water (<1 µS/cm). The deionized water is the hydrogen source and is recycled through the high-pressure electrolytic cell via a water pump. The hydrogen gas is generated in the electrolytic cell.

Once the hydrogen gas is generated at the cathode side, the gas leaves the cell along with some water from the electrochemical process. The hydrogen gas passes into a water separator unit, so the gas can be dried. The water separator is a simple device that removes water mechanically by collecting the moisture from the gas. Once the moisture builds up to a certain level, an electrical water level sensor is triggered where a valve opens at the bottom of the water separator and the water is removed under positive pressure. The valve closes before the hydrogen gas can escape and depressurize the system.

The, now dry, hydrogen gas passes through a pressure sensor and into a motorized valve. The pressure sensor and valve control the elution of gas into the reaction line. The system works by always maintaining a higher positive pressure of hydrogen inside the system compared to the reaction line.

Once the hydrogen gas leaves the motorized valve, it passes through a check-valve. The check-valve is a one direction valve that allows the gas out of the reactor box, but no liquid

inside. It serves as an additional protection for the internal parts of the H-Cube®. The gas then passes through a mixer containing a titanium frit (to disperse the gas into small bubbles) and into a solvent stream. The gas has now entered the reaction line.

In the reaction line the hydrogen gas continuously saturates the reaction mixture. The gas-liquid mixture passes through a “bubble detector”. The bubble detector uses a light emitting diode (LED) and a sensor to measure how much hydrogen is contained in the gas-liquid mixture. The analysis is not truly quantitative, but gives the H-Cube® an approximate value for the amount of non-dissolved gas present in the liquid. The system will try to limit this gas amount to approximately 7%. If the amount of gas is too high, the internal motorized valve will close slowly to reduce the amount of hydrogen in the system. If the amount of gas too low, the opposite will occur.

Once the optimum gas-liquid mixture has been established it will pass into the heating unit. The heating unit heats the reaction solution to the required temperature, set by the operator using the touch-screen module. The heater unit is a “Peltier” heating system which consists of a stainless steel reaction line coil contained within a stainless steel block. The heating unit also contains the catalyst cartridge (CatCart®) where the reaction takes place. The reaction mixture will be preheated to the set temperature before flowing into the CatCart®. The components of the H-Cube® reaction line and cell, allow for reactions to be carried out up to 150°C and 100 bar.

The reaction takes place in the CatCart®. The CatCart is a tubular fixed-bed reactor packed with heterogeneous catalyst or reagent. At either end of the CatCart® is placed a metal frit and filter to allow the flow of reaction mixture into the CatCart®, but to prevent leaching of the catalyst out. For simplicity, commercially available Merck chromatography pre-columns are used with 3 different sizes (mm): 30 x 4, 55 x 4, 70 x 4. The column sizes were chosen for their small diameter and that they can hold the following catalyst dry weights: 150 mg, 300 mg, and 450 mg respectively. This would allow a reaction size range of 50 mg to 50 g. Ideal for the target lab scale reaction size. Once the fixed bed reactor sizes were chosen, the ideal catalyst particle size range was chosen.

After the reaction has taken place on the CatCart®, the reaction mixture passes through another pressure sensor and then into the back-pressure regulator valve. The back-pressure regulator valve controls the pressure in the reaction line. When the user selects a pressure on the system, the back-pressure regulator valve closes against the flow of the reaction mixture through the reaction line until the pressure sensor has detected that the pressure has risen to the set pressure. The reaction mixture, then elutes out of the system into a collection vial. A picture of the first H-Cube® system can be found in Figure 25.

Figure 25: The first H-Cube® model.

5.3 PhD applicant's contribution to H-Cube® development

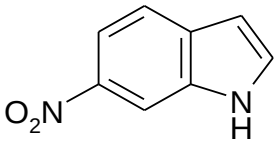
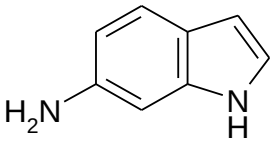
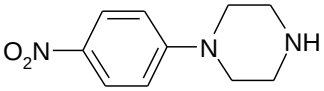
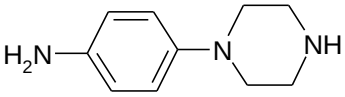
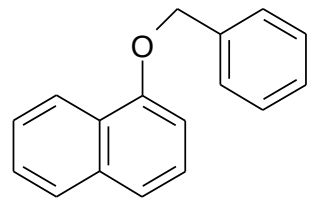
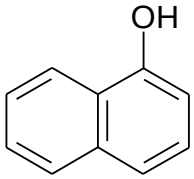
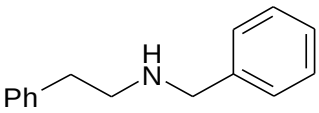
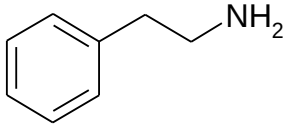
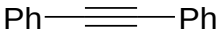
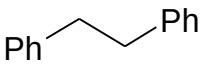
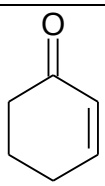
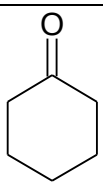
The applicant's contribution to the development of the H-Cube® was the following:

- Input as to the features necessary for the system from a chemist's perspective.
- Recommendations on necessary hydrogen quantity versus chemical throughput.
- Testing of the catalyst cartridge design and sizes and implementation of new catalyst types.
- Designing the graphical user interface from a chemist's perspective.
- Testing of the system at proof of concept and at prototype stage.
- Validation of different chemistries on the system at differing temperatures, pressures, flow-rates, and catalysts.
- Collecting feedback from beta testers.

5.4 Evaluation of H-Cube® capabilities through different chemistry examples:

5.4.1 Common functional group reductions

Once the H-Cube® was developed and considered safe for use in the laboratory, a series of reactions was chosen, at varying temperatures and pressures, to highlight the capability of the H-Cube®[40]. The functional group reductions include the most common such as nitro, deprotection, alkyne, carbonyl, oxime, and nitrile. The results are displayed in Table 1:

Substrate	Product[a]	Conditions	Yield[b]
 **(1)**		10% Pd/C or Raney-Ni, EtOAc/EtOH (1:1), Flow rate:1 mL/min, Pressure: 1 bar, Temp.:25˚C	96%
 **(2)**		Raney nickel EtOAc/EtOH (1:1), Flow rate:1 mL/min, Pressure: 1 bar, Temp.:25˚C	99%
 **(3)**		10% Pd/C, EtOAc/EtOH (1:1), Flow rate:1 mL/min, Pressure: 1 bar, Temp.:60˚C	85-97%
 **(4)**		10% Pd/C, EtOAc/EtOH (1:1), Flow rate:1 mL/min, Pressure: 1 bar, Temp.:80˚C	89%
 **(5)**		10% Pd/C, EtOH, Flow rate:1 mL/min, Pressure: 1 bar, Temp.:25˚C	94%
 **(6)**		10% Pd/C, EtOH, Flow rate:1 mL/min, Pressure: 1 bar, Temp.:25˚C	85%

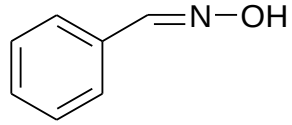
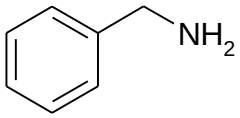
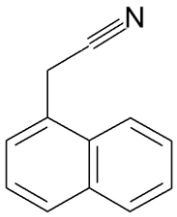
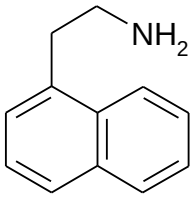
 **(7)**		Raney Ni, 2M NH_3 in methanol, Flow rate:1 mL/min, Pressure: 70 bar, Temp.:70˚C	88%
 **(8)**		Raney Ni, 2M NH_3 in methanol, Flow rate:1 mL/min, Pressure: 70 bar, Temp.:70˚C	99%

Table 1: H-Cube® benchmarking examples.

[a] All products exhibited spectral data (^{1}H.NMR and MS) consistent with their structures

[b]Yields refer to isolated pure products

All reductions detailed in Table 1 were reduced 100% after only one flow through the system. This can be attributed to the high mass transfer generated from such a high catalyst to substrate-hydrogen ratio.

5.4.2 H-Cube® and Batch Reactor Comparison

A comparison reaction was initiated to highlight the difference in conversion efficiency between batch and flow methodologies.

5-nitroindole Reduction	Conventional Batch Reactor	H-Cube Reactor
Reaction 1: RT and 30 bars; reaction time: 150 seconds	20% Conversion	100% Conversion
Reaction 2: RT and 30 bars; reaction time: 150 seconds	11% Conversion	100% Conversion

Table 2 A comparison of conversion efficiency between a batch and flow reactor.

From the results we can see that the efficiency of the H-Cube® is substantially greater than that of the batch reactor. In a typical batch reactor, a stirred suspension of substrate and catalyst is reacted under an atmosphere of hydrogen. The mass transfer between the gas-

liquid and liquid-solid phases in a batch reactor is, therefore, very low since there is a low interfacial area between the three phases.

In the H-Cube®, the dissolved substrate and hydrogen are pumped through the compressed catalyst. The interfacial area between the three phases is higher, resulting in a more efficient gas-liquid-solid reaction as demonstrated by the better product conversion in a shorter time. After this initial experiment run, further experiments with a wider parameter range and difficulty were investigated.[41] The results are summarized in Table 3 below.

5.4.3 Saturation of alpha-picoline (Entry 1).

Alpha-picoline was hydrogenated to 2-methyl-piperidine with high conversion and yield at 100°C and 100 bar using Raney nickel as catalyst. ^{1}H NMR analysis showed the average product selectivity of 99%, while the conversion was ca. 91% for this rather difficult hydrogenation. Hydrogenation of different substituted pyridines were also investigated by Prof. Kappe's group at University of Graz using the fixed-bed continuous flow hydrogenation reactor, different catalysts (Pt, Pd, Rh containing solid supported), and reaction conditions. Parameter optimization resulted in that in the case of 7 different pyridine starting materials, applying 30–80 bar of pressure, 60–80°C of temperature, and a 0.5 mL/min flow rate resulted in full conversion.[42]

5.4.4 Hydrogenation of *D*-Glucose (Entry 2).

Hydrogenation of *D*-glucose is an important process resulting in *D*-sorbitol as an artificial sweetener as well as a key biomass related product, providing a precursor for many industrial chemical agents. This reaction requires rigorous conditions and highly reactive catalysts. Therefore, continuous flow hydrogenation is ideal for this conversion due to the rate enhancement and safe operation. After placing a Raney nickel filled 70 mm long CatCarts in position, the system was washed with water until stabilization of reaction parameters were reached (150°C and 90 bar). *D*-glucose was dissolved in water and, after stabilization, the solution was passed through the system at the previously set reaction conditions and the product was collected from the product line. Finally, the product solution was concentrated

in vacuo and analyzed by ^{1}H NMR. The longer 70 mm CatCart® enabled the use of a higher reaction concentration (up to 0.4 M) and flow rate (up to 3 mL/ min) to allow higher scales of reaction to be carried out. The higher temperature (150°C instead of 100°C) and the short residence time (higher flow rate) also resulted in reaching higher conversion. It should also be noted that the notoriously difficult to use Raney Ni (due to its highly pyrophoric nature) could be used simply and safely with minimal exposure.

5.4.5 Hydrogenation of High Energy Materials

5.4.5.1 Hydrogenation of 2,4-dinitroanisole (Entry 3)

The reduction of 2,4-dinitroanisole (Entry 3) was chosen as a model reaction for a high energy species. The compound is used as an explosive substitute for TNT. The reaction has high hydrogen demand (6 mol H_2 per 1 mol substrate). The maximum concentration possible, whilst still achieving complete hydrogenation of the two nitro groups, is 0.14 M taking into account the maximum hydrogen amount. The reaction parameters were 100°C, and 100 bar. The resulted conversion was >99% and the isolated yield: 98%.

5.4.5.2 Safe hydrogenation of picric acid (Entry 4,5).

Picric acid (2,4,6-trinitrophenol) is a potential explosive, particularly in dry conditions. It requires a high hydrogen supply which also makes it difficult to selectively reduce the nitro groups to amines while retaining the aromatic species. Different catalysts were tested in a THF solution (c = 0.01 M) at a flow rate: 0.5 mL/min. At 100 bar pressure and 100 °C temperature there was a clear distinction between the catalysts. While 5% Rh/C led to the fully saturated ring (A) (selectivity: >90%), Raney Ni retained the aromatic ring (B) while reducing the nitro groups to amines (selectivity: >90%). This procedure provides a feasible technology for safe disposal of such explosives by cleanly converting them to useful intermediates.

Entry	Reactant	Solvent	Concentration	Catalyst	T °C	p (bar)	Flow rate (mL/min)	Product	Conversion (%)	Selectivity (%)
1		cyclohexane	0.05 M	Ra Ni	100	100	0.5		91	>99
2		water	0.4	Ra Ni	150	90	3		96	>99
3		EtOAc	0.14	10% Pd/C	100	100	1		>99	98
4		THF	0.01	5%Rh/C	100	100	0.5		>99	>90
5		THF	0.01	Ra Ni	100	100	0.5		>99	>90

Table 3: Summary of additional experiments performed with the H-Cube®.

5.5 The selective reduction of 4-nitro-bromo-benzene

As stated earlier, one of the key advantages of flow over batch is the ability to control precisely the residence time of the reaction mixture on the catalyst and vary it to achieve higher selectivities. Scheme 1 below is an example of where this is applied on the H-Cube®. The selective reduction of aromatic nitro groups in the presence of halogen(s) is a challenging problem for the pharmaceutical, agrochemical, dye and fine chemical industries.[43]

So far, the best results were reported with the least reactive chloro substituent in the compound 4-chloro-nitro-benzene with a 93.7% overall selectivity.[44] The intrinsic reactivity of the bromo- and iodo-groups is even higher, therefore full selectivity and 100% conversion, particularly on a large scale, are not reported in batch reactors.[45] The exothermic nature of the nitro group reduction, which may result in hot spots and/or thermal runaway, further complicates the outcome of these reactions. The effect of residence time on the selectivity between the aromatic nitro group and halogen was investigated on the model compound of 4-nitro-bromo-benzene (1A) (Figure 26).

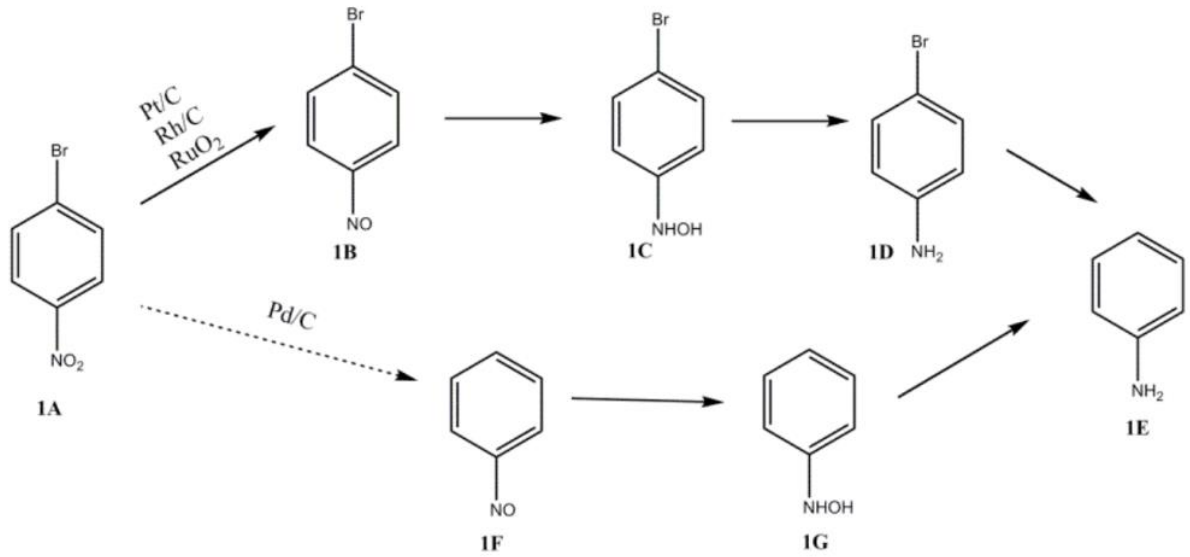


Figure 26: Different possible products during the reduction of 4-nitro-bromo-benzene.

Figure 27. summarizes our observation of the correlation between the residence time and selectivity achieving a 100% conversion rate by using the catalyst 5% Rh/C. In batch this reduction provides inconsistent results and the selectivity varied in a wide range. The best selectivity obtained was 88 % after 60 min, and in addition to aniline (1E), other oligomer

products typical in nitro reductions were also observed. In flow, at a residence time of >8 s, a 30% selectivity was achieved towards 1D, while a sharp increase can be observed between 8 seconds and 1.5 s. (Figure 27.) At a residence time of 1.5-0.6 s a 99.9% selectivity can be achieved while also maintaining a 100% conversion rate. Table 4. summarizes the product distribution found during the screening of different catalysts and the optimal residence times. In the case of Pt/C/V (Pt on carbon doped with vanadium), 100% selectivity towards 1D and 93% conversion was achieved at a < 8.4 s residence time. Au/TiO_2 catalyst, however, required a 17 s residence time to reach 100 % selectivity at a conversion rate of 94% (Table 4.). The significant difference of the optimal residence time for the three catalysts (Rh/C: 0.6 s Pt/C/V: 8.4 s, Au/TiO_2: 17 s) is in good correlation with their reported activity ranking.[46] The data suggests that the residence time to achieve the same product (while other parameters are constant) may be a practical parameter to estimate the relative activity of different catalysts in heterogeneously catalyzed reactions. The tested catalysts were found to be either non-selective or much less selective in a batch reactor (Table 4.).

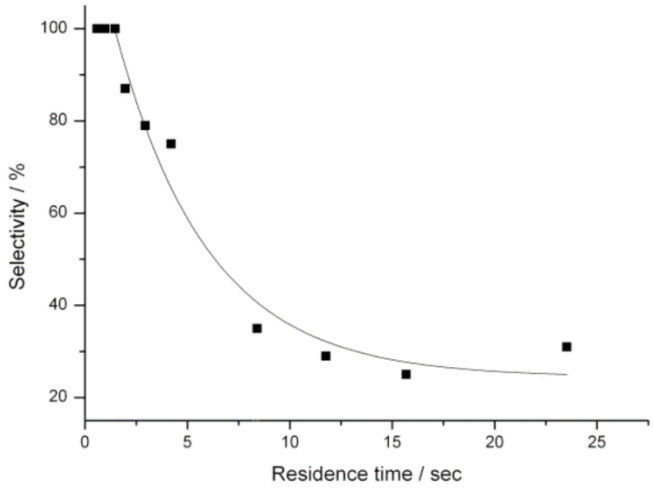


Figure 27: Effect of the mean residence time on selectivity in the hydrogenation of 4-nitrobromo-benzene (1A) to 4-bromo-aniline (1D) via flow hydrogenation using H-Cube®. 0.05M substrate solution in MeOH was passed through the CatCarts filled with the Catalyst at 30 bar hydrogen pressure, 70 °C temperature. Catalyst 5% Rh/C. The flow rate was varied between 0.5-8 mL/min.

				Product distribution (%)			
Catalyst	Method	Residence time (s)	Conversion (%)	**1B**	**1D**	**1F**	**1E**
5% Rh/C	Flow[1]	0.6 – 1.5	100	0	100	0	0
5% Rh/C	Flow[1]	24	100	0	31	0	69
5% Rh/C	Batch[2]	3600	100	0	88	0	5
RuO_2	Flow[2]	17	100	0	100	0	0
RuO_2	Flow[1]	0.35	6	100	0	0	0
RuO_2	Batch[3]	3 600	6	0	100	0	0
1% Au/TiO_2	Flow[2]	17	94	0	100	0	0
1% Au/TiO_2	Flow[1]	2.1	13	100	0	0	0
1% Au/TiO_2	Batch[3]	3 600	12	0	100	0	0
1% Pt(V)/C	Flow[1]	8.4	100	0	93	0	7
1% Pt(V)/C	Batch[3]	1 800	100	0	47	0	53
10% Pd/C	Flow[1]	>1	100	0	0	0	100
10% Pd/C	Flow[1]	0.43	27	0	0	100	0
1% Pd/C	Batch[4]	900	100	0	0	0	100

Table 4. Product distribution at different residence times for the reduction of 4-nitro-bromo-benzene 1A.

1: 70 bar, 30°C

2: 72 mg catalyst, 25 bar, room temperature, 7% other oligomer side products were observed.

3: 360 mg catalyst, 25 bar, room temperature

4: 120 mg catalyst, 1 bar, room temperature

The reduction of nitro groups to amino groups consists of different intermediates that could also react with each other (Scheme 1.). The first step of the sequence is the very fast addition of one H_2 molecule resulting in a nitroso intermediate that is usually not observed in the products during batch-based experiments. Studying this reaction in detail using batch-based hydrogenation is rather difficult because of the fast intrinsic reaction rate and the high exothermicity. In order to investigate if the elemental steps can be distinguished, we further fine-tuned the residence time. At a residence time of 11.2 s for Au/TiO_2 and 4.2 s for RuO_2 the anticipated intermediate (nitroso-4-bromo-benzene, 1B) started to appear in the reaction mixture. By decreasing the residence time step by step we were able to find the optimal

residence time to achieve 100 % selectivity towards the 1B intermediate with the Au/TiO_2 at a residence time of 2.1 s and with RuO_2 at a residence time of 0.35 s, although at a lower conversion rate (Table 4.). Contrary to the above, using 10% Pd/C as catalyst at longer residence times (1.0 - 8.4 seconds), the only product observed was aniline. Further reduction of the residence time to 0.47 s resulted in the exclusive formation of nitroso-benzene (1F) with 100% selectivity at 27% conversion. This indicates that the intrinsic reactivity ranking of the nitro reduction and the hydrogenolysis of the bromine-carbon bond is either the same, or the hydrogenolysis occurs faster on the Pd catalyst. To the best of our knowledge, this is the first report, where the parameters of the aromatic nitro reduction could be adjusted to stop the reaction at the nitroso intermediate stage with these transition metal catalysts leading to the exclusive formation of the nitroso derivative 1B or 1F, which can be an important intermediate. It is interesting to note, that the hydroxylamine intermediate 1C could not be detected at any residence times tested. The above experiments show, that by using this residence time controlled method, we were able to focus the synthesis individually on three different elemental reactions in the reaction sequence resulting in three different products (1B, 1D, 1E) to an extent that has never been reported before. The results indicate that this flow-based method offers a powerful alternative to studying the intrinsic reaction kinetics of catalytic hydrogenations.

5.6 Monitoring continuous flow hydrogenation using inline analytics

The above example highlights the amount of data that can be gained from a single experiment, where reactions parameters are changed during the reaction and analytical samples taken for off-line analysis. Being able to monitor analytically continuous flow chemistry while in operation allows for rapid screening of reaction conditions, leading to faster process optimization. In batch a separate reaction and analysis must be made for each set of reaction conditions. Infrared spectroscopy offers an alternative detection method for chemistries that are difficult to follow by conventional analytical methods such as gas chromatography or liquid chromatography. Based on the above, the utilization of FTIR for “on the fly” optimization of hydrogenation experiments was explored. The below experiments were carried out connected to Mettler Toledo’s ReactIR system.

5.6.1 Carbonyl Reduction Example

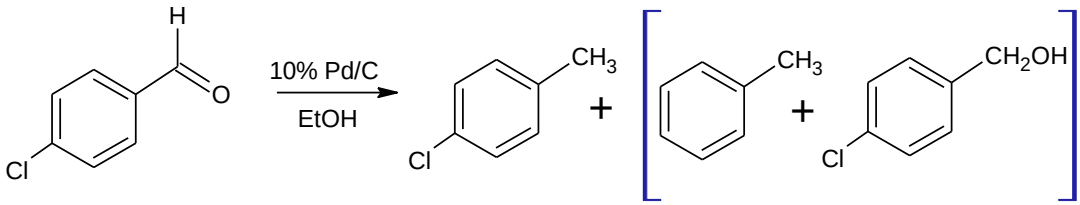


Figure 28: Possible products from reduction of 4-chlorobenzaldehyde.

4-Chlorobenzaldehyde was selectively reduced to 4-chlorotoluene using the H-Cube® flow reactor and a catalyst cartridge filled with 10% Pd/C catalyst. (Reaction parameters are shown in Table 5.)

Sample	Temp. (°C)	P (bar)	Flow rate (ml/min)	Conversion (GC-MS)	Selectivity (GC-MS)
1	0 (starting material)				
2	70	38	1.5	100	5
3	70	62	1.5	100	8
4	100	50	1.5	100	30
5	80	50	2.1	100	9
6	97	70	1.9	100	24
7	115	51	2.2	100	20
8	128	64	1.6	100	4
9	92	54	2	100	43
10	59	72	1	100	72
11	57	36	0.7	100	68
12	39	58	1	100	81
13	10	58	0.3	100	91

Table 5: Reaction parameters and their results, determined by GC-MS.

The hydrogenation reaction was monitored using the FlowIR™ instrument after manual injection of the samples. Using the iC IR™ program, the spectra of the samples were analyzed. After solvent subtraction, characteristic wavelengths were chosen for the starting compound (1210 cm^{-1}) and for the desired product (1495 cm^{-1})(Figure 29). The reaction samples were also analyzed by GC-MS, to confirm the IR spectroscopy results.

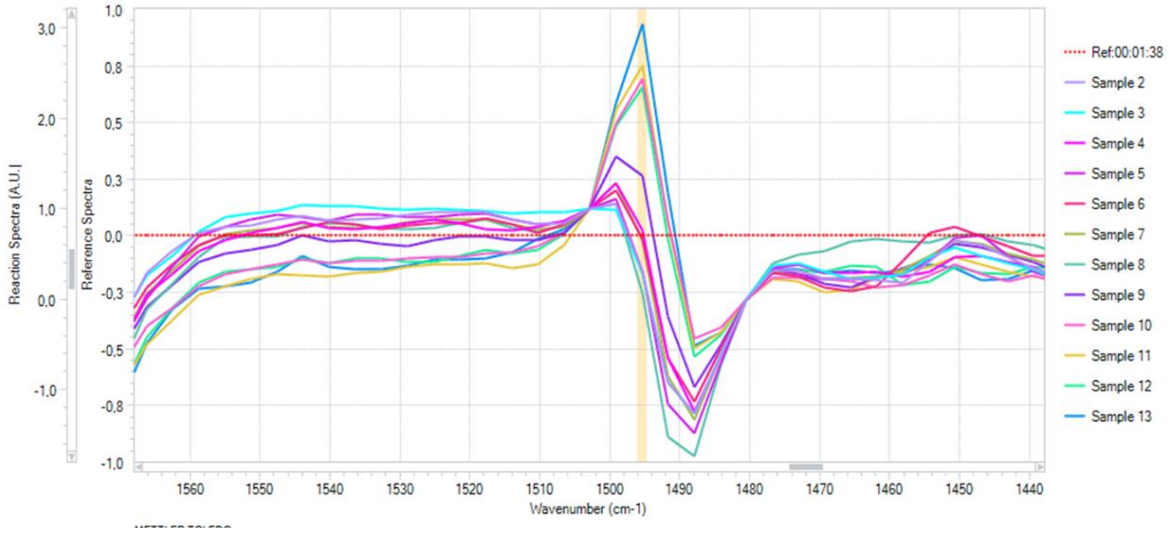


Figure 29: IR spectrum of the reaction mixtures. Ref 00:01:38 is the starting material, extracted from the spectra.

By following the intensity of the selected wavelengths, the changes in the amount of starting material as well as the product were monitored (Figure 30).

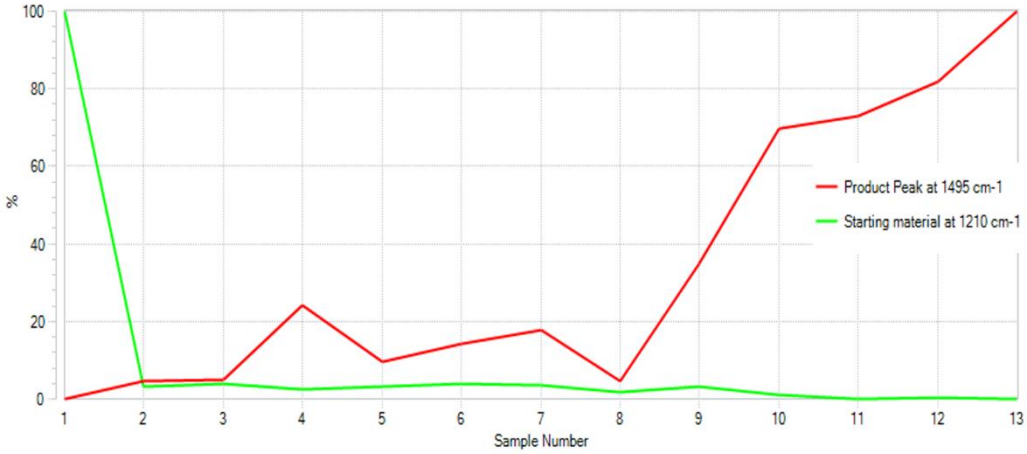


Figure 30: Trends of product and starting material peaks.

The red line in Figure 30. follows the same trend as the selectivity values for 4-chlorotoluene obtained by GC-MS. The peak at 1495 cm^{-1} represents exclusively the 4-chlorotoluene product. The green line decreases to a near-zero value after Sample 1, that is in agreement with the 100 % conversion values given by GC-MS (Table 5).

Reaction parameters for the optimization were determined by the Simplex algorithm. The optimal conditions were found to be 10°C, 58 bar pressure and 0.3 mL/min flow rate. The optimal temperature is low because at higher temperatures dehalogenated product may form. The reaction, however, requires a low liquid flow-rate. When the residence time chosen is shorter, then hydrogenation gives the benzylalcohol product.

5.6.2 Reduction of *D*-Glucose to *D*-Sorbitol

Reduction of *D*-glucose to *D*-sorbitol was carried out in the H-Cube® and optimized using in-line infrared analysis.

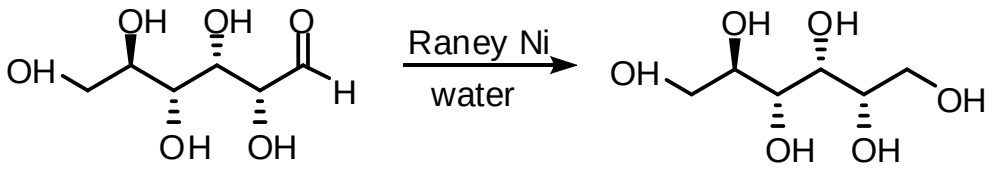


Figure 31: Reduction of *D*-glucose to *D*-sorbitol.

Firstly, mixtures of glucose and sorbitol were prepared (0-100%) in a 0.1M total concentration. These standard solutions were then manually injected into the FlowIR instrument and the infrared samples collected. After collecting these spectra, the most appropriate wavelength was chosen (1050 cm^{-1}) for monitoring the reaction.

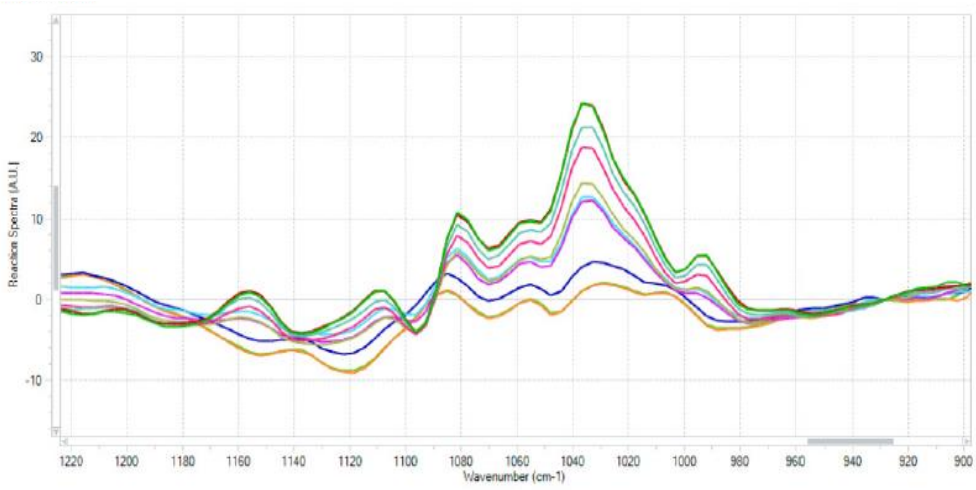


Figure 32: A section of the infrared spectra.

A calibration line was drawn from the measured intensities (Figure 33). This shows that the peak intensity of 1050 cm^{-1} is in linear correlation with the glucose concentration.

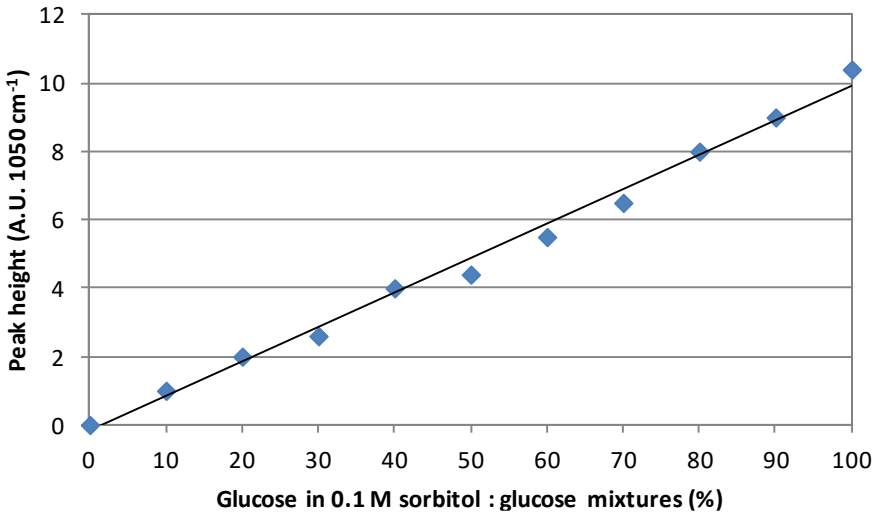


Figure 33: Calibration line for glucose content of standard solutions.

During the hydrogenation experiment, the FlowIR™ spectrometer was connected in-line with the H-Cube® instrument. The IR spectra were collected automatically every 30 seconds by the iC IR™ program. Conversion rates of the reaction (Sample 1-5.) were determined by reading the intensity of the 1050 cm^{-1} peak and the new reaction parameters were determined based on the results. Further analysis was obtained through GC-MS and the results presented in Table 6.

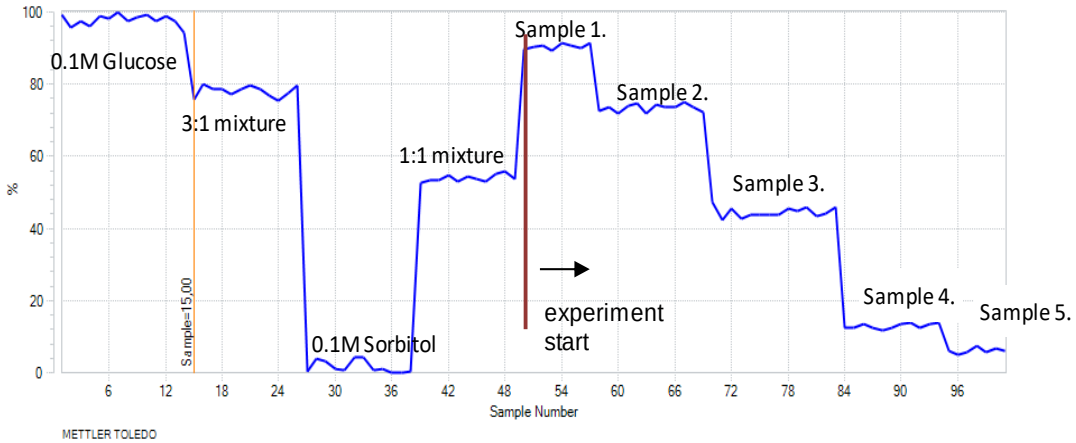


Figure 34: Detection of Glucose content of 4 standard solutions and reaction samples (1-5).

Sample	T (°C)	p (bar)	H_2 (%)	Flow rate (ml/min)	c (M)	Conversion* (%)
1	50	20	100	1	0.1	10
2	80	20	100	1	0.1	30
3	100	80	100	1	0.1	55
4	110	80	100	0.8	0.1	85
5	120	80	100	0.7	0.1	95

Table 6: Reaction parameters and conversion values of sample 1-5.

Using the real-time analysis data allowed optimization of the reaction very quickly and the ability to reach 95% conversion using a single sample. The optimal conditions for the reduction of glucose are 120°C, 80 bar pressure, and 0.7 mL/min flow rate.

5.7 A brief study concerning the scale-up of flow heterogeneous hydrogenation[47]

The difficulties involved with scaling up reactions from laboratory to process scale are well known.[48] Reaction pathways are often designed in laboratories on a small scale. Laboratory experiments carried out in test tubes or small flasks produce the required chemicals or products, but may not sufficiently highlight problems that can occur when the reaction is scaled. These include formation of by-products and release of gases or vapours, which may be toxic or flammable. Heat releases may be absorbed by the equipment or surroundings and go unnoticed. In the laboratory, reactions are carried out in glass vessels, while in scale-up other materials may be used which may result in unexpected reactions or problems including catalytic and inhibition effects. Consequently, when target compounds are identified and prepared for transfer to production, the synthetic route frequently requires re-optimization.

A flow hydrogenation system, called the H-Cube Midi™, was designed to shorten the time between identifying a target compound and scaling up the reaction (Figure 35). The system works in the same way as the aforementioned H-Cube®, but is designed with a higher throughput capability. The system has a larger hydrogen gas production rate (125 mL/min) and a large catalyst column size (90 x 9.5 mm). Up to 4.5 moles of compound can be processed in a 24-hour period. The parameters of the catalyst column were designed, so that users can

directly apply the optimized temperature and pressure identified on the small scale H-Cube® to the larger scale system. If minor adjustments to parameters need to be performed, they can be adjusted during a reaction. As demonstrated earlier, this method can significantly reduce the optimization time.

Figure 35: H-Cube Midi™

A series of reactions were run on the H-Cube Midi™ to assess the throughput of the system with different functional groups. These include a ketone reduction, a nitro reduction, double bond saturation, and a carbobenzyloxy group deprotection. The results are displayed in Table 7. 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. A longer catalyst lifetime can be attributed to the flow process. Any product formed that can deactivate the catalyst, such as a primary amine, passes out of the column and is replaced by the starting material. The deactivating product does not remain on the catalyst long enough to poison the catalyst leading to increased catalyst longevity and the possibility of catalyst recycling.

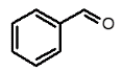
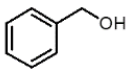
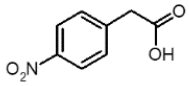
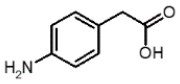
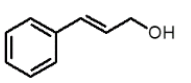
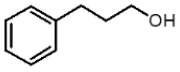
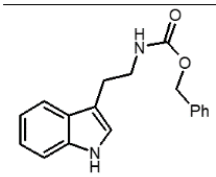
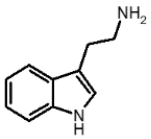
Starting Material	Product	Reaction Conditions	Amount Processed/ Time	Calc. amount for 8 hours	Yield
		Flow-rate: 10mL/min Temperature: 40°C Pressure: 70 bar Solvent: methanol Catalyst: 10% Pd/C (10.8 g) Concentration: 0.35M	74 g in 1.33 hours	445.2g	72%
		Flow-rate: 30mL/min Temperature: 30°C Pressure: 30 bar Solvent: methanol Catalyst: 10% Pd/C (2,81 g) Concentration: 0.05M	46.2 g in 3 hours	123g	90%
		Flow-rate: 10mL/min Temperature: 90°C Pressure: 10 bar Solvent: ethanol Catalyst: Raney Cu (17,4 g) Concentration: 0.2M	92 g in 6 hours	122.66g	82%
		Flow-rate: 10mL/min Temperature: 60°C Pressure: 50 bar Solvent: ethanol Catalyst: 10% Pd/C (3,1 g) Concentration: 0.05M	13.9 g in 1.5 hours	74g	95%

Table 7: Reactions performed on the H-Cube Midi™ including results and reaction conditions

5.8 Automating the flow hydrogenation process to enable high-throughput synthesis

With the impact of genomics and proteomics generating a large number of drug targets, the need for pharmaceutical companies to generate drug candidates in the fastest time possible is paramount. In order to achieve this, the pharmaceutical industry has made major investments in the development of new high-throughput techniques in the fields of genomic and proteomic research, chemical synthesis, and biological screening.[49] The biggest bottleneck in the drug discovery process is the synthesis of novel compounds, and interest has focused on this stage in particular towards developing high-throughput technologies, which produce large numbers of diverse compounds in the fastest and most inexpensive ways possible.[50] Chemical reduction through catalytic hydrogenation has numerous applications in drug synthesis and industrial processes.[51] When carried out in the laboratory using batch

reactors such as autoclaves and bomb reactors there are practical disadvantages. The removal of air from the reactor, priming, filtration, and washing of the pyrophoric catalyst are necessary steps for each reduction. Batch catalytic hydrogenation is therefore, a time-consuming and hazardous process to perform, making the technique impractical for automated high-throughput synthesis on a small scale.

Chemists have sought to overcome the disadvantages of batch reactor catalytic hydrogenation by limiting the use of the hydrogenation to an early stage in the synthesis sequence and in large batches. Benzyl protecting groups which are cleaved using hydrogen over a catalyst[52] may be substituted for other protecting groups such as di-tert-butyldicarbonate (BOC)[53] and Methoxymethyl Ether (MOM).[54] BOC and MOM are cleaved through the addition of a strong acid[55] and can be employed during combinatorial procedures, such as Suzuki coupling[56], where deprotection may be carried out simply on hundreds of compounds overnight.

These methods also carry inherent disadvantages. The large-scale reduction of a nitro group to an amine at the beginning of the synthesis can create further additional steps involving the protection and de-protection of said amine. The use of strongly acidic or basic conditions to deprotect compounds can lead to decomposition of the products during the deprotection step.[57] In comparison, protecting groups such as benzyl or 2-phenylethyl carbamate groups[58], which are removed under much milder conditions, are stable in most acidic and basic conditions. The stability of benzyl groups in these conditions is highly useful in synthesis where they may be employed at an early stage in the synthesis and will not conflict with any subsequent acid/base-catalyzed steps.[59] The infrequent use of catalytic hydrogenation with combinatorial chemistry is due mainly to the difficulties associated with high-throughput hydrogenation technology rather than their chemical efficacy. The development of high-throughput hydrogenation technology that can be relatively easily handled for use in compound library synthesis would, therefore, be a highly valued tool in the drug discovery field. Below, an efficient continuous-flow hydrogenation reactor and its novel application to the high-throughput reduction of small-scale compounds through automated sequential injection is reported.

The reduction of a nitro group to an amine as a final step in drug synthesis has played important roles in the synthesis of potential drugs, such as Amprenavir.[60] The reduction would therefore be a useful high-throughput synthetic step for the generation of similar drug candidate libraries.

To demonstrate this high-throughput application, a single aromatic nitro substrate was repeatedly injected into the reactor. The reduction of 5-nitroindole was chosen as an example reaction. 25 samples of 5-nitroindole (0.1 mmoles, 16.2 mg) were injected automatedly into a continuous-flow of ethyl acetate: ethanol (1:1) solvent at 6 minute intervals. The reductions were carried out at room temperature and atmospheric pressure and 1 mL/min flow-rate. 140 mg of 10% palladium on charcoal was used as the catalyst in the column. Each sample was analysed by LCMS and then NMR. A graph of the results is given below, in Figure 36.

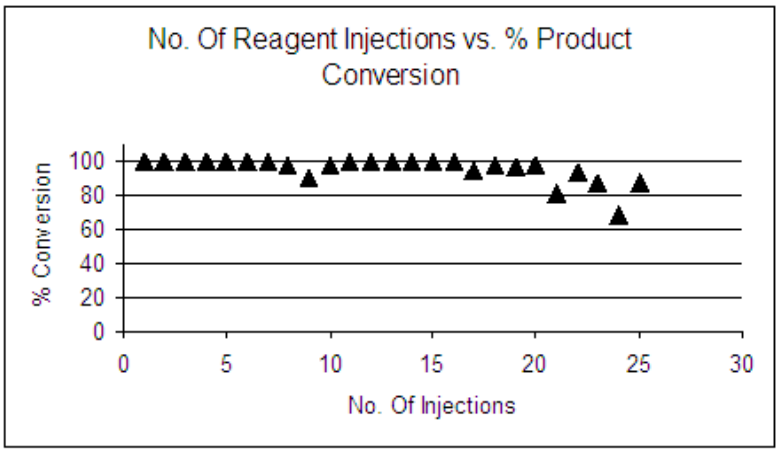


Figure 36: Chart showing the product conversion (%) for each injection

The first twenty injections proceeded favourably with all maintaining a high conversion rate of >90% and a quantitative yield. The remaining 5 injections deteriorated in conversion to below 70% which is attributed to the deactivation of the catalyst due to poisoning by the amine product. The same nitro reductions performed on a batch reactor[61] required over 30 minutes per reduction, including catalyst addition, purging of air, pressurization, 15 minutes reaction time for completion, depressurization and filtration. The overall result is that five reactions can be performed on the H-Cube® system in the same time it takes to perform one reaction on a batch reactor. The other benefits include that the whole process was automated, obtaining the product only entailed removal of solvent which eliminated the

potentially hazardous step of filtering the hydrogen-saturated catalyst from the reaction mixture using flammable solvent. The catalyst was also recycled between reactions limiting waste generation.

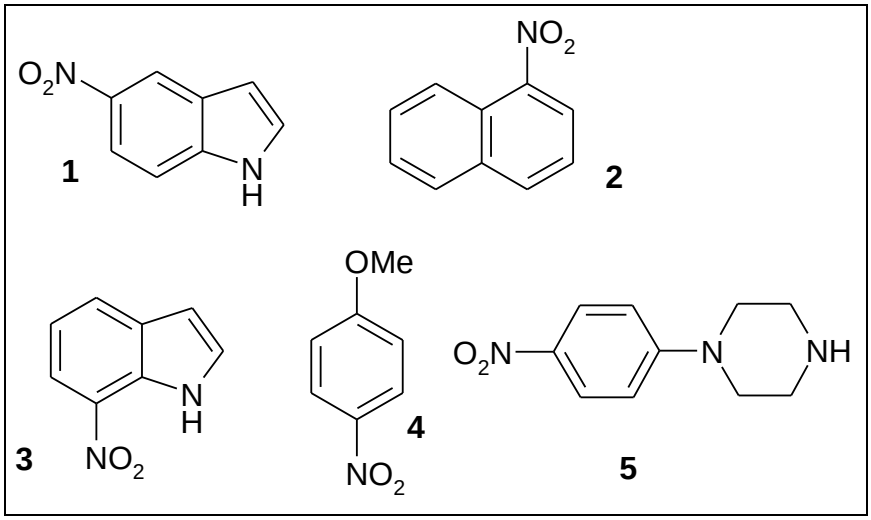


Figure 37: A small aromatic nitro group containing library.

As a further investigation, the reduction of several aromatic nitro compounds was chosen as a sample library to test the automated set-up. The five different nitro compounds (see Figure 41, 0.1 mmol, 1 mL) were automatically injected into a continuous flow of methanol solvent every seven minutes (2 min reaction time, 4 min washing, and 1 min delay). The reductions were carried out at 30 °C and atmospheric pressure and a 1 mL/min flow rate. 140 mg of 10% palladium on charcoal was used as the catalyst in the column. The catalyst was pre-treated by flowing a mixture of hydrogen, reactant, and solvent through the catalyst at 30 °C and 1 bar for 10 min. The procedure progressed as follows. 5-nitroindole (1) was injected, then after seven minutes, 2-nitronaphthalene (2) was injected and run through the system. This process continued until the final compound, 1-(4-nitrophenyl)piperazine (5) had been injected and flushed into the system.

Once this process was complete, the injection sequence was repeated. The sequence was repeated four times giving twenty-five injections in total. LCMS samples were taken of every fraction to determine product conversion and level of contamination. The whole process took less than three hours. The results are shown in Figure 38. The 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.

As a comparison, a 5-nitroindole reduction was carried out in a batch reactor to measure the time taken for each reduction. Each reduction was performed for three minutes (the residence time of the substrate in the reactor), using the same pressure, temperature, catalyst amount, and solvent. After 3 min, less than 2% conversion was noted. The reaction was resealed and refilled with hydrogen and reacted for a further 17.5 min. After this period of time, TLC showed complete conversion. The reaction was filtered and reduced to dryness. The flow method has a higher rate of reaction, most likely due to the higher interaction between the three phases when compared to the batch reactor. In the H-Cube®, a stream of substrate/hydrogen is flowed through a packed catalyst bed, so the active surface of the catalyst, in contact with the substrate/hydrogen mixture, is very high at all times. In the batch reactor, a suspension of catalyst/substrate is stirred under an atmosphere of hydrogen, so the interaction between the three phases is much lower giving lower reaction rates. From start to finish the whole process, including catalyst addition and filtration, took approximately thirty minutes. To perform all twenty-five reductions in batch mode, the total amount of time can be calculated as 12.5 h which is over four times longer than the same process using automated sequential injection into the H-Cube®. Moreover, the H-Cube® can handle higher temperatures and higher pressures in a standard laboratory, the need for such conditions is sometimes a bottleneck in medicinal chemistry laboratories.

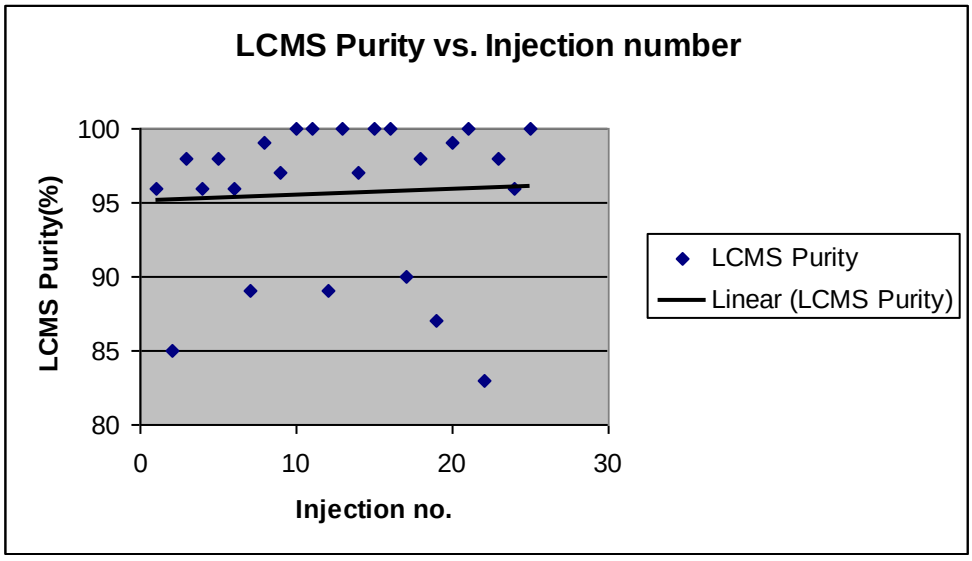


Figure 38: Product purity over twenty-five injections.

5.9 The development of a high-pressure gas generator to facilitate the safe scale-up of kilo-scale per day continuous-flow hydrogenation

5.9.1 Background

In meetings held with Mettler Toledo the following data was presented:

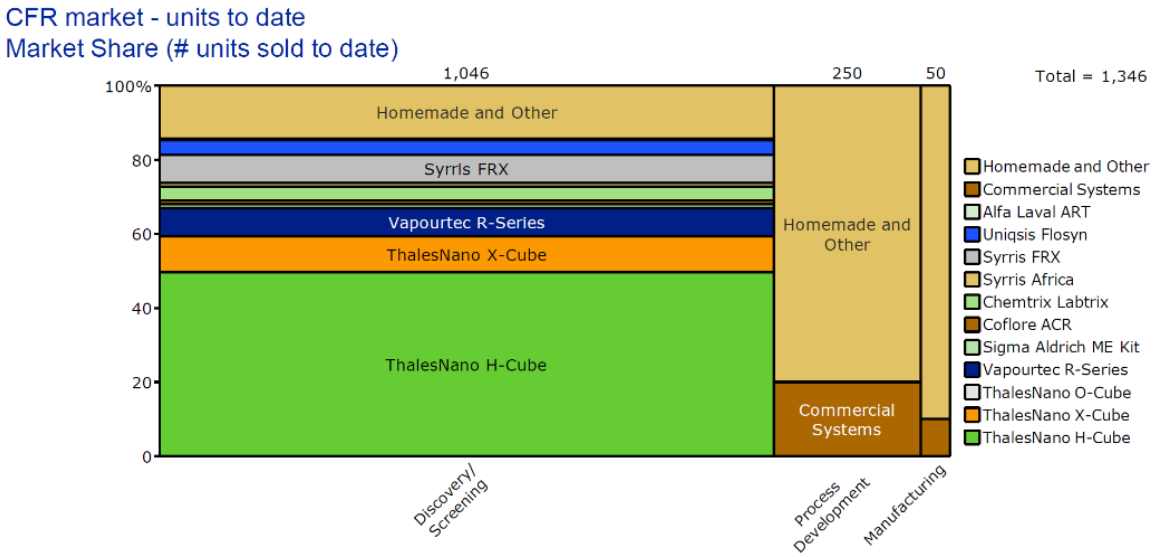


Figure 39: The cumulative continuous-flow reactor (CFR) market (#units sold to date (2010)) by department.

The data highlights that in departments where larger scale chemistry (100 g and above) is performed, namely the process development and manufacturing departments, over 80% of flow reactors used are not commercial, but developed in-house. There are two main reasons for this:

(i) The size and complexity of the equipment necessary for this scale is either not yet available commercially or is prohibitively more expensive than building a system of your own.

(ii) The commercially available equipment is not suitable for a specific application.

The drivers for utilizing continuous-flow technology at this scale are similar to those highlighted previously:

Safety

- Enabler for more exotic/hazardous chemistries. Inherent control of exo- and endothermic reactions, fast chemistry, multi-stage chemistry, unstable compounds
- Exposure / Operator safety: Orders of magnitude smaller volumes of material/solvents, Lower concentration/amounts of toxic reagents/materials

Speed

- “On-demand” product manufacturing
- Faster & easier development / scale up – time to market

Increased Efficiency: Quality and Cost of Product

- Better controlled processes, less batch failures
- FDA filings: Process Analytical Technology (PAT) & Quality by design (QbD) – control space
- Savings: $ / kg material (productivity): yield, reaction & process time, manufacturing space

However, when considering hydrogenation for large scale manufacturing, the source of hydrogen is a major factor when considering the safety of the process. Especially when considering the quantity of hydrogen necessary for the reaction. Based on this feedback, I designed a gas generator (H-Genie®, Fig. 40) that could provide high pressure hydrogen to work with home-made or commercial flow systems. After a market study, the system was designed with the following two main features:

- On-demand generation of 4.0 purity hydrogen from water at a pressure range of 1-100 bar (14.5-1450 psi).
- A mass flow controller to provide an accurate gas flow-rate range of 100-1000 NmL/min for connection with flow reactors and to log how much hydrogen is consumed during a reaction.

5.9.2 How does the system work?

The high pressure hydrogen generator works by generating hydrogen gas up to 4.0 purity from deionized water using a patented electrolytic cell. The hydrogen gas is dried through a two-stage water separation system, mechanical separation and thermal separation. The water removed is then drained through an external vent. The now dry hydrogen gas enters the mass flow controller (MFC), which controls precisely the flow rate of hydrogen out of the generator between 100 and 1000 NmL/min. The generator then generates hydrogen gas to the required pressure (up to 100 bar) by continuously generating hydrogen until this pressure is reached. In flow mode, it will do this internally first, before releasing the hydrogen at the set pressure. The generator will then continuously generate hydrogen to maintain that pressure.

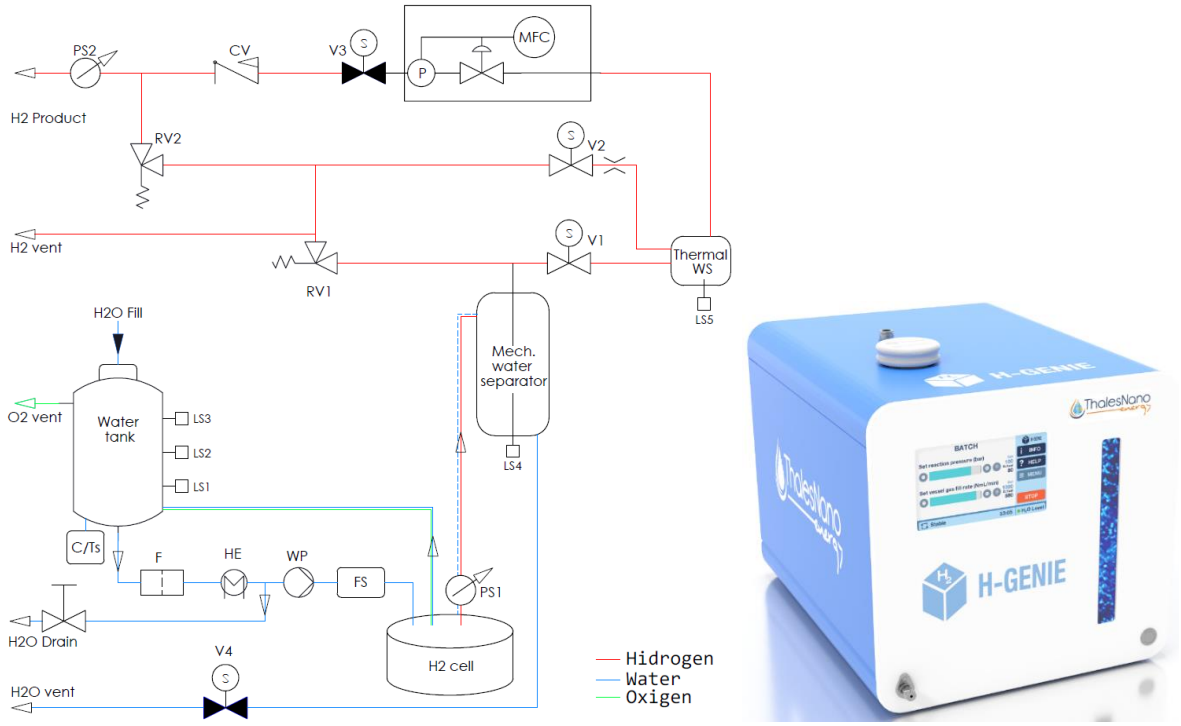


Figure 40: Schematic design of the H-Genie®.

5.9.3 The development of a novel large-scale high pressure cell

In order to create the high-pressure hydrogen generator a completely novel cell (Fig. 41) had to be invented. (International patent no. WO 2020/039218 A1). In particular, the invention relates to new components and a new assembly of a water electrolyzer cell capable of operating at high differential pressures. It is based on the electrochemical reduction ($2H_2O + 2e = H_2 + 2\ H_2O$) and oxidation ($H_2O - 2e^- = 2H^+ + 0.5\ O_2$) of water ($H_2O$) on the cathode and anode sides, respectively. Due to the proposed technological novelties as well as the modular construction, the presented 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 catalytic recombiners integrated into the electrolyzer cell allow high gas purity over a wide range of pressures and H_2 flow-rates. This allows the application of the invented electrolyzer cell in various industries, such as the chemical, pharmaceutical, and energy industry. High pressure and high purity are especially important in synthetic organic chemistry (both in pharmaceutical and chemical industries) and in the field of energy storage, especially in the automobile sector. One of the new components made use of in the water electrolyzer cell according to the invention is a modular

bipolar plate. Instead of the conventional single-item bipolar plates, two-component bipolar plate assemblies are employed in the cell, said assemblies being built up of two separate plate components fabricated also separately. Between the two components, circular cavities are introduced that were found to be effective gas transportation avenues to the channels connecting the adjacent stacks. The two-component design results in thinner bipolar plates when assembled, and an overall lighter cell. In addition, if needed because of any reasons, the half of said bipolar plate assembly, i.e. one of its two components can be changed independently of the other component, further increasing thereby the flexibility of the cell. In addition to the above, the cell contains a number of other novelties:

- A H_2 /O_2 recombiner that is integrated into the cavities formed within the separate components of the two-component bipolar plate assembly. The H_2 /O_2 recombiner, provided in the form of a large surface mesh, helps to increase the purity of the gaseous streams (H_2, O_2) generated within the electrolyzer cell.
- A custom designed and assembled current collector made of titan (Ti) frits (Ti-frits). Said Ti-frits are made of a catalyst-coated Ti powder provided in the form of individually coated Ti-particles of different average particle size, wherein a nanoparticulate catalyst is deposited by wet chemical processes on the surface of each Ti-particle before the Ti-frits are actually manufactured by pressing the catalyst-impregnated Ti-particles. In this way, the effective surface area of the active catalyst is significantly increased which results in the enhancement of the purity of the gaseous hydrogen generated in the electrolyzer cell according to the present invention.
- A fluid channel sealing assembly that provides a watertight sealing between two catalyst-coated membranes arranged in adjacent electrolyzer stacks.
- A pressure chamber at both ends of the cell formed within specific pressure chamber plates arranged at both ends of the cell. These special plates provide adaptive pressure control on the stacks from both sides, thus providing uniform pressure distribution throughout the stacks. This construction inhibits deformation of the cell body, and thus avoids the decrease in the contact area between the internal components, such as e.g. the catalyst-coated membrane and the Ti-frit and/or the Ti-frit and a Ti-plate. This results in a stable cell resistance even at elevated pressures.

Importantly, the application of said pressure chamber plates eliminates the requisite of any moving parts (such as pistons or valves) or elastic plastic elements as pressure controlling means within the cell, which is the current state-of-the-art.

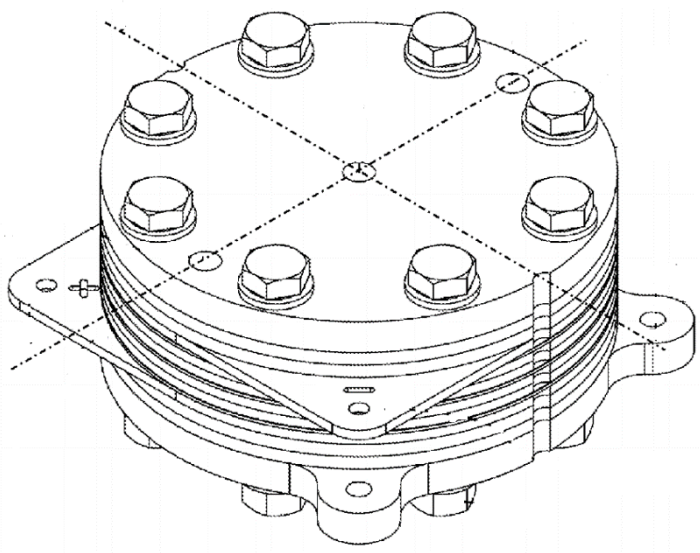


Figure 41: A diagram of the novel high-pressure cell.

5.9.4 Gas flow accuracy measurements

Once the system was created, a number of functional tests were carried out. When conducting experiments with continuous processes, it is important to have accurate flow rates. The flow rates are controlled through an internal mass flow controller (MFC), which also logs the amount of hydrogen released from the system (important in the case of logging hydrogen uptake during a reaction).

The generator was tested over a series of flow-rates multiple times and an average taken. Results are displayed in the table below.

Flowrate	Average (Nml/min)	% Difference from setpoint	Max (Nml/min)	Min (Nml/min)
100	99.59	-0.41	108.39	96.16
500	509.16	+1.83	516.01	496.61
1000	1010.48	+1.05	1045.79	999.03

Table 8: Hydrogen gas flow-rate measurement accuracy.

Overall, the generator performed well in this test. The percentage difference between the setpoint and measured value was <2% for all tests. This is negligible due to the use of excess hydrogen in current applications.

5.9.5 Chemical tests

The gas generator was connected to the Phoenix Flow Reactor via a gas-liquid mixer (ThalesNano assembled mixer). A high flowrate HPLC pump (1-100 mL/min, Teledyne SSI) was used to create the flow and a back-pressure module (ThalesNano Pressure Module) to build the pressure in the system. The pump delivers the liquid through the gas-liquid mixer, where the generated hydrogen gas from the H-Genie® is mixed with the liquid. The gas-liquid mixture flows through the temperature-controlled catalyst bed packed inside the metal-metal sealed (MMS) column, placed in the Phoenix. Finally, the mixture flows through the pressure sensor and the back-pressure regulator before being collected in a flask or vial (Figure 42.).

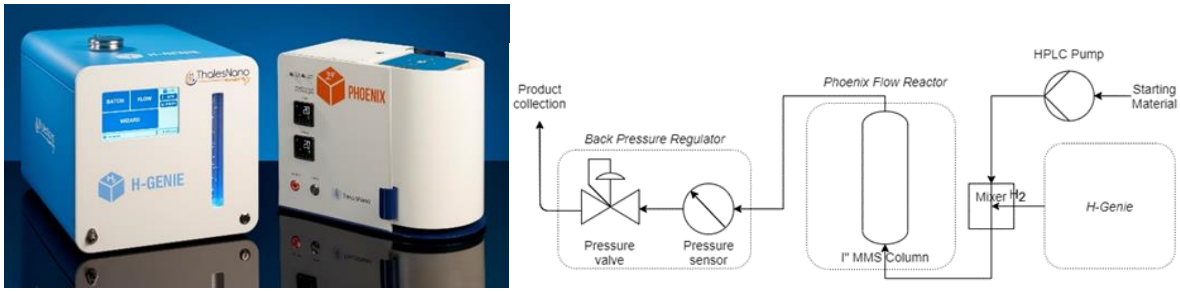


Figure 42. Schematic representation of Phoenix-H-Genie® system.

The nitro reduction of methy-4-nitrobenzoate was chosen as the benchmark reaction (Fig. 43.) because it had already been performed on a H-Cube Midi™ and scale up the reaction. The previous reaction on the H-Cube Midi™ using a 5% Pd/C catalyst over 12 h resulted in a yield of 89% with an NMR purity of 98%. It was decided to scale-up this reaction to reach an input of 0.6 mol / hour of starting material.

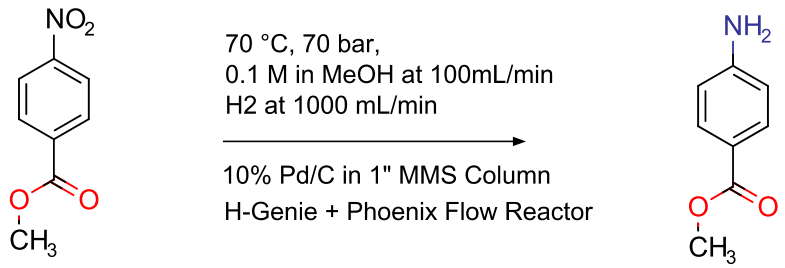


Figure 43. Nitro reduction of methy-4-aminobenzoate.

The repeat of this reaction, using the same conditions except for the catalyst (10% Pd/C), over 10 hours, performed on a MidiCart, showed a conversion not less than 98.5% at the end of the run (Figure 44).

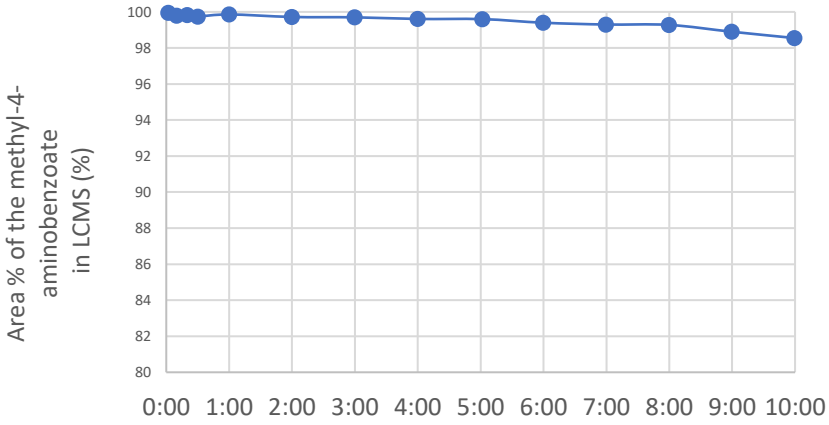


Figure 44. Conversion to methyl-4-aminobenzoate with the MidiCart (% LCMS).

The reaction was then scaled up by a factor 10 (catalyst volume, liquid and hydrogen flow rates) to demonstrate the capabilities of the different modules to achieve higher throughputs. A 7-hour long run was performed on a 1" metal-metal sealed (MMS) column and showed a stable conversion (> 99%) for the first 150 mins before dropping (Figure 45.).

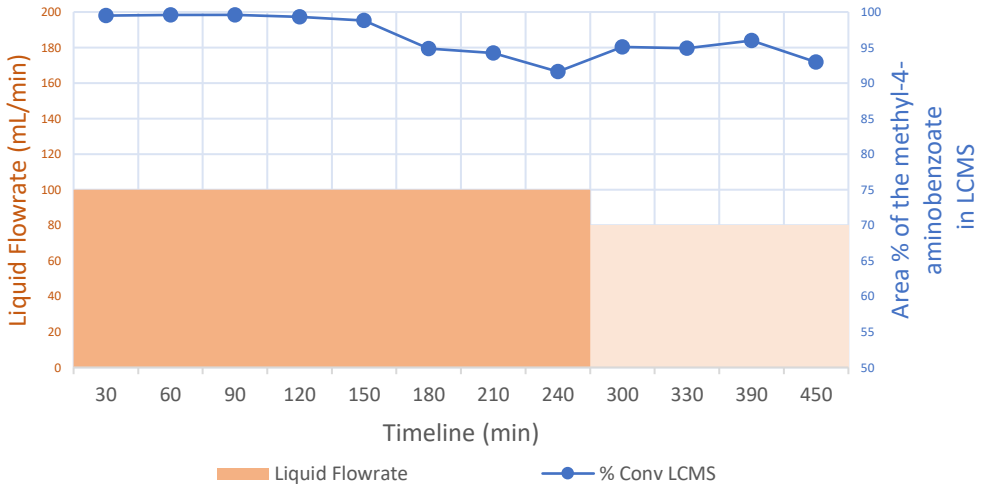


Figure 45. Conversion to methyl-4-aminobenzoate with the 1" MMS column.

A decrease in liquid flow rate (from 100 to 80 mL/min), resulting in an increase in both the residence time and hydrogen equivalency, could partially overcome this decrease in catalytical activity by maintaining the conversion above 90% for the remaining runtime. An

average productivity of 83 g / h with an overall isolated yield of pure methyl-4-aminobenzoate (LCMS purity > 98%) was achieved.

	Pump / H_2 flow rate (mL/min)	Time of use (h)	Yield (g / %)		Purity (%)	Substrate / Catalyst ratio	Productivity (g/h)
MidiCart	10 / 100	10	87	>99	>99[a]	3.4%	8.7
1" MMS Column	100-80 / 1000	7	513	95[b]	>98[c]	5.6%	83

[a] Determined by ^{1}H NMR. [b] Yield of product after recrystallisation. [c] Weighted average was calculated based on ^{1}H NMR spectra of fractions collected during the run.

Table 9. A comparison of results between H-Cube Midi™ and H-Genie®-Phoenix combined.

5.10 Further development and Outlook

5.10.1 Electrochemical conversion of CO_2

CO_2 is a greenhouse gas therefore, using renewable energy to convert CO_2 to transportation fuels and commodity chemicals is a value-added approach to simultaneous generation of products and environmental remediation of carbon emissions.[62] The large amounts of chemicals produced worldwide (Figure 46) that can be potentially derived from the hydrogenation of CO_2, highlights further the importance of this strategy. Several industrial entities are interested in such technologies, ranging from energy/utilities companies through cement producing and processing firms to oil and gas companies.

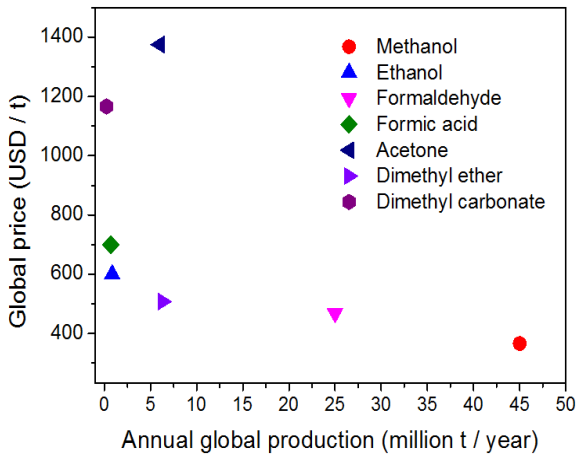


Figure 46. Global market of the most important CO_2-utilization products.

There are numerous routes for converting CO_2 to transportation fuels and other chemicals. The following three major pathways delineate how sunlight can be used to generate such products (e.g., CH_4 or CH_3OH) from CO_2:

- Photochemical (PC) or photosynthetic methods: Directly use sunlight to photochemically convert CO_2 to fuels using molecular- or suspended semiconductor (SC) photocatalysts
- Electrochemical (EC) approaches: Here sunlight is first converted to electricity by a photovoltaic solar cell (PV) and CO_2 is then reduced electrochemically.
- Photoelectrochemical (PEC) route: Photogenerated electrons are utilized to reduce CO_2 either directly at a SC/electrolyte interface or indirectly employing a redox mediator.

With the recent rapid drop in the cost of Si solar cells, the price of solar electricity has decreased to a level that in over 20 countries translates to grid parity. A recent study concluded that on a 20–25 year term it is not likely that any solar energy utilization pathways other than Si solar photovoltaic panels will have an industrially relevant role. Another techno-economic analysis suggested that PV + EC conversion setups may attain »14% solar to H_2 efficiency (20% PV, 70% EC) in an economically feasible manner as the electricity price drops (which is clearly the case for both solar and wind power). These factors suggest that CO_2 conversion, at least on a short to intermediate term, will be driven in an EC configuration.

To increase the CO_2 conversion rate to a level of practical significance, electrochemical (EC) CO_2 reduction must be performed in a continuous-flow setup to overcome mass-transport limitations. We note that there is a striking difference here compared to water splitting, where ample amounts of water molecules (55.5 M!) are available for the reaction. Interestingly, despite some successful pioneering studies[63], very little attention has been devoted to EC CO_2 reduction in continuous flow mode. Only a minor fraction (»5%) of the articles report on studies performed under such flow conditions. In fact, this trend can also be very problematic in the sense that conclusions drawn from batch experiments cannot be directly translated to flow situations (unlike for water splitting).

There are a few reviews on electrochemical cell designs for CO_2 reduction: namely microfluidic reactors and polymer electrolyte membrane (PEM) electrolyzers, so this is an area in need of further development.

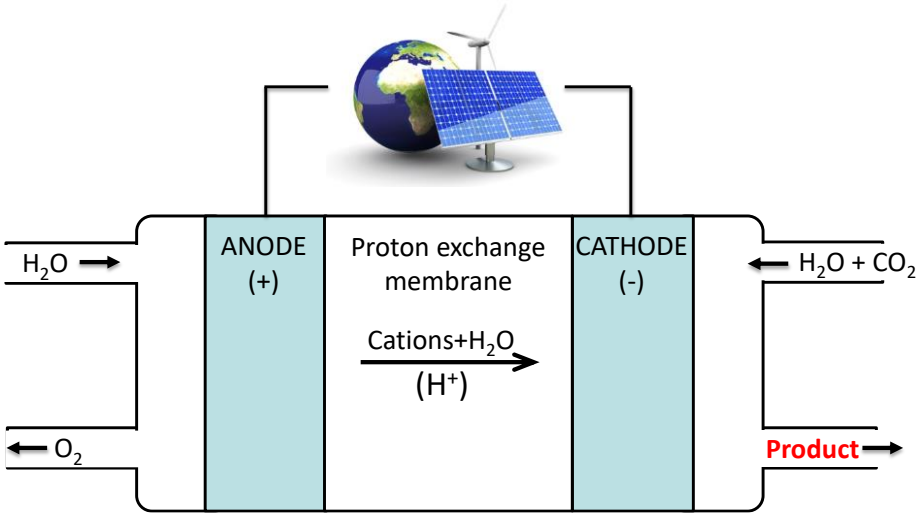


Figure 47. Typical cell design outline.

The overall design of the cell would be very similar setup to water electrolyzers, such as that in the H-Cube® (but feeding CO_2 together with water to the cathode compartment). The anode reaction is simply the production of molecular oxygen from water (formation of other value-added products can also be envisioned). The possible reduction products are carbon monoxide, formic acid, methane, methanol, and ethanol.

Future work will concentrate on the following:

- The adaptation of water electrolyzing H-Cube® technology to designing a flow-based electrochemical CO_2 converter.
- Work will focus particularly on the following development aspects:
    - Reactor cell design and the materials used for the construction
    - Catalysts and supports used for the electrochemical process.
    - Optimization of each process based on feed types.
- The adaptation of CO_2 conversion to generate syngas products toward utilization in the Fischer-Tropsch synthesis.

5.10.2 Chemistry as an aid towards space exploration

Interest in deep-space exploration includes possibilities such as manned missions to Mars, as well as future efforts towards the colonization of the Moon and/or Mars. However, for such

goals to be realized there are first many hurdles to overcome, many of which that require a chemistry solution. The main one being, the limitation of food, fuel, or chemical resources on long duration missions. We can only use what we take with us and this must be maximized and recycled to prolong trips as long as possible. Until now, there is very little precedent for synthetic chemistry in space. I believe this is mainly because of concerns with performing traditional batch chemistry in a low- or zero-gravity environment due to the poor mixing and reproducibility. As discussed previously, flow chemistry is possible solution to this issue because it is amenable to both automation (and therefore remote operation from Earth) and synthesis under zero gravity and other harsh conditions.

Based on the above research, there are two projects in particular where we will seek to exploit our technology:

- Create a 'drug-on-demand' chemistry system in which a variety of pharmaceuticals can be synthesized, analysed, purified and formulated — fresh and when needed — from basic chemical building blocks. This will provide the supply of medical treatments for astronauts on long-duration spaceflights. Note that the current shelf life for pharmaceuticals is typically less than 1 year, which is inadequate for longer spaceflight durations.
- Convert the waste materials that are generated during the voyage and/or the natural resources of alien planets into usable chemicals to sustain human life or to further exploration. Such studies include the electrochemical recovery of O_2 from CO_2, as well as the generation of other basic building blocks to enable chemical transformations to more complex molecules.

Consider, for example, that the Martian atmosphere consists of 96% CO_2; thus, this is the only viable source of O_2 as well as any carbon-based chemicals (for uses such as fuel and food). Sunlight is available (with a significant UV component); therefore, solar panels could provide electricity, or sunlight could potentially even be used directly in photosynthetic or photoelectrochemical cells to convert CO_2 to useful products.

6 Executive Summary

The first commercial continuous-flow hydrogenation system, called H-Cube®, was developed. The H-Cube® works by combining a continuous production of hydrogen, generated *in situ* through the electrolysis of deionized water, with a continuous flow of reaction mixture and reacting the mixture on a catalyst cartridge, a CatCart®.

Figure 48. The H-Cube® and CatCart®.

The H-Cube® advances the performing of hydrogenation in the laboratory, both from a safety and performance standpoint. The H-Cube® improves safety on several different levels.

1. The development of an in-built hydrogen cell, which negates the use of hydrogen cylinders in the process. Hydrogen is generated up to 100 bar “on demand” from water.
2. The design and implementation of a catalyst cartridge system, which minimizes contact with pyrophoric catalysts and removes the need for a potentially hazardous catalyst filtration step.
3. The conversion of a batch process to a flow process reduces the size of reaction area to less than 1 mL significantly reducing the probability of an exothermic runway reaction. The removal of batch reactor headspace from the reactor also contributes to improved safety.

The H-Cube® was tested on numerous test reactions from room temperature and pressure to 150°C and 100 bar. The types of reactions ranged from simple double bond reductions, nitrile

reductions, oxime reductions, benzyl group hydrogenolysis, to aromatic heterocycle saturations. Most reactions progressed in quantitative yield and conversion.

A comparison was made with batch in terms of reaction rate. In a typical batch reactor, a stirred suspension of substrate and catalyst is reacted under an atmosphere of hydrogen. The mass transfer between the gas-liquid and liquid-solid phases in a batch reactor is, therefore, very low since there is a low interfacial area between the three phases. This was represented in the results where the batch reactions showed 11 and 20% conversion compared to the H-Cube®'s quantitative conversion.

The H-Cube® 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.

The H-Cube® was connected to Mettler Toledo's ReactIR™ FTIR system. The ReactIR™ allows analysis of reaction mixtures "on the fly". 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. All literature studies indicate this is the first time that flow hydrogenation reactions had been optimized in this way.

A series of reactions were run on a larger scale H-Cube®, called the H-Cube Midi™ 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. A longer catalyst lifetime can be attributed to the flow process. Any product formed that can deactivate the catalyst, such as a primary amine, continuously flows out of the reactor. The deactivating product does not remain on the catalyst long enough to poison the catalyst leading to increased catalyst longevity and the possibility of catalyst recycling.

The H-Cube® was incorporated into an automated liquid handler to conduct fully automated hydrogenation as part of a library production for the first time.

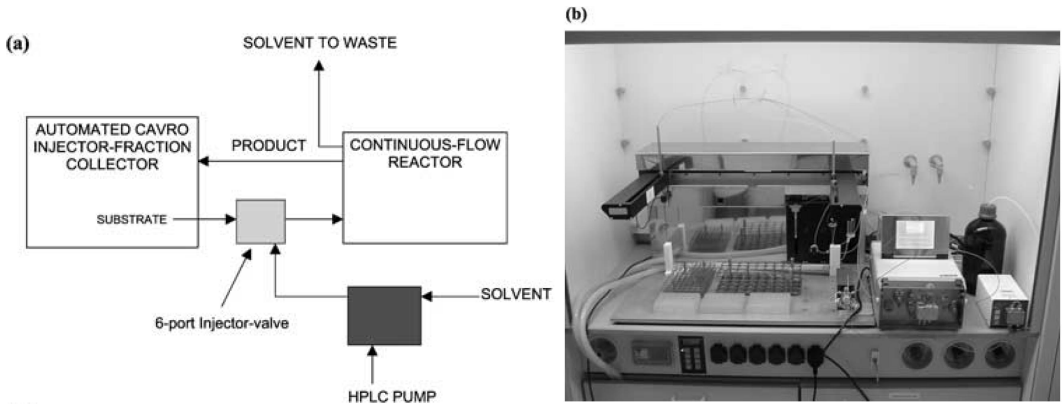


Figure 49. A continuous-flow reactor set-up for high throughput hydrogenation.

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. The same number of reactions in batch would take a minimum of 12.5 reactions.

In summary, the H-Cube® was successfully developed and tested on a number of different reactions with favourable comparisons to batch. The H-Cube® was developed to be fully automated and, therefore, could significantly extend the technical repertoire of combinatorial and high-throughput synthesis leading to enhanced diversity and allowing performance of transformations that were previously neglected because of practicality or safety concerns.

Finally, 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.

7 Publication List

Below is a list of all my publications:

1) Jones, R.; Godorhazy, L.; Szalay, D.; Gerencsér, J.; Dormán, Gy.; Urge, L.; Darvas, F. A novel method for high-throughput reduction of compounds through automated sequential injection into a continuous-flow microfluidic reactor. *QSAR Comb. Sci.* **2005**, *24*(6), 722-727.
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9 Appendix

All products exhibited spectral data (1H.NMR and MS) consistent with their structures.

9.1 Data for the selective reduction of 4-nitro-bromo-benzene

The sample was collected and analyzed with HPLC-MS (Agilent 1100 Series, Waters Micromass ZQ) or GC-MS (Agilent 6850 Series II). The products received under the optimal conditions were isolated by evaporation of the solvent and then analyzed by GC-MS and 1H-NMR (Bruker Avance II 400 MHz). For optimizing the reaction conditions, the pressure, temperature and the flow rate were varied.

The reaction on the H-Cube® was described as above.
In order to avoid a high pressure drop on the catalyst cartridge (typically observed above a flow rate of 4 mL/min) and to shorten the residence time, the 30 mm long catalyst bed was filled to occupy a catalyst bed length of 15 mm (1/2 the length of the cartridge) or 7 mm (1/4 the length of the cartridge) with the active material, and the remaining empty space was filled with quartz sand.
To determine the precise residence time, the dead volume of the catalyst cartridge (CatCart®) was measured. The residence time was adjusted by changing the flow rate of the system during the reaction and was calculated using the formula of (dead volume) / (flow rate). The dead volume of the CatCart® is 0.14 mL.

General procedure for batch hydrogenation reactions:
The batch reactions were performed in a flask or in an autoclave system (MT-07281) using the same solvent as the experiments performed using flow hydrogenation. .
In the flask experiment, a mixture of 1 mmole starting material and 3 mmoles ammonium formate was dissolved in 20 mL solvent. Then the catalyst- the same amount as in a CatCart® - was placed into the flask. The reaction was carried out with constant stirring at the same temperature as the H-Cube® experiment and at atmospheric pressure. At regular intervals 2 mL samples of reaction mixture were collected using a sampling tube and after the filtration

it was analyzed with HPLC-MS (Agilent 1100 Series, Waters Micromass ZQ) or GC-MS (Agilent 6850 Series II).

For the autoclave experiments, 3 mmoles of starting material were dissolved in 60 mL solvent. The mixture and the catalyst were placed into the autoclave. After sealing the reactor, the air content was purged by flushing three times with 10 bar of nitrogen. Next, the autoclave was heated up to a temperature comparable with the H-Cube® and finally pressurized with hydrogen. During the experiment, the pressure consumption in each reaction was continuously monitored and the stirring rate was fixed at 500 r.p.m (magnetic stirring). At regular intervals a 2 mL sample of product was collected using a sampling tube and after filtration analyzed with HPLC-MS (Agilent 1100 Series, Waters Micromass ZQ) or GC-MS (Agilent 6850 Series II). The experiment was stopped at a selected time and the reactor flushed two times with nitrogen again before opening.

Substrate	**Conc. (mol/dm^3)**	**Applied catalyst**	**Supplier of catalyst**	**Amount of the catalyst in the CatCart® (g)**	**Applied solvent**
1-Bromo-4-nitrobenzene	0.05	Au/TiO_2 RuO_2 10% Pd/C: quartz sand (1:3) 1% Pd/C: quartz sand (1:3) 1% Pt(V)/C: quartz sand (1:3)	World Gold Council Aesar Johnson Matthey Aldrich Strem Chemical	0.25 0.06 0.03 0.03 0.03	Ethanol Methanol

Table A1: Reaction conditions and catalysts applied during continuous hydrogenation reactions on the H-Cube®

* The MicroCatCart™ contains a one-third of the usual amount of catalyst found in a CatCart® 30 cartridge.

Substrate	Method	Pressure (bar)	Catalyst	Applied solvent
1-Bromo-4-nitrobenzene	flask	1	1 % Pd/C	Ethanol
	autoclave	25	1 % Pt/C	
	autoclave	25	Au/TiO_2	
	autoclave	25	RuO_2	

Table A2: Catalyst and solvents applied in the batch hydrogenation experiments

9.2 Synthesis of 5-aminoindole using automated sequential injection

16.2 mg (0.1 mmoles) of 5-nitroindole was dissolved in 2 mL of 1:1 ethyl acetate:ethanol. Twenty-five samples were made up in total. A VICI Valco 6-port valve with a 2 mL injection loop was connected between the HPLC pump and the microfluidic reactor. A 30 mm length column of 10% Pd/C was inserted into the microfluidic reactor.

The valve was switched to position A. The HPLC pump was set to a flow of 1 mL/min and started, commencing a flow of 1:1 ethyl acetate/ethanol solvent mixture through the system. The temperature on the reactor was set to room temperature and the pressure to 1 bar. A 2 mL sample of 5-nitroindole was injected into the 2 mL size loop. After the system had reached the required temperature the valve was switched to Position B, flushing the nitro sample into the reaction line. The hydrogen was then allowed to flow into the reactor. After one minute the valve position was changed back to Position A. Another sample was manually injected into the sample loop. After a period of 7 minutes in total, the new nitro sample was released into the system and the collection vial was changed for a new one. This procedure was repeated for the remaining samples. Evaporation of the solvent gave the product in 98% yield. m/z 132.00 [M+]. All LCMS results are displayed below in Table A3.

5-nitroindole Injection Number	Product MW	HPLC Result (%) at 254 nm
1	132	100
2	132	100
3	132	100
4	132	100
5	132	100
6	132	100
7	132	100
8	132	97
9	132	90
10	132	97
11	132	100
12	132	100
13	132	100
14	132	100
15	132	100
16	132	100
17	132	94
18	132	97
19	132	96
20	132	97
21	132	81
22	132	93
23	132	87
24	132	68
25	132	87

Table A3: Results for sequential injection of 5-nitroindole

9.3 Automated production of nitro compound library

The twenty-five fractions were collected and LCMS samples were taken for analysis, the results are shown in Table A4. The samples were each reduced to dryness using a constant stream of nitrogen. The samples were then analyzed by NMR.

Run	Product	LCMS Analysis
first run	5-aminoindole	96
first run	2-aminonaphthalene	85
first run	7-aminoindole	98
first run	4-aminoanisol	96
first run	1-(4-aminophenyl)piperazine	98
second run	5-aminoindole	96
second run	2-aminonaphthalene	89
second run	7-aminoindole	99
second run	4-aminoanisol	97
second run	1-(4-aminophenyl)piperazine	100
third run	5-aminoindole	100
third run	2-aminonaphthalene	89
third run	7-aminoindole	100
third run	4-aminoanisol	97
third run	1-(4-aminophenyl)piperazine	100
fourth run	5-aminoindole	100
fourth run	2-aminonaphthalene	90
fourth run	7-aminoindole	98
fourth run	4-aminoanisol	87
fourth run	1-(4-aminophenyl)piperazine	99
fifth run	5-aminoindole	100
fifth run	2-aminonaphthalene	83
fifth run	7-aminoindole	98
fifth run	4-aminoanisol	96
fifth run	1-(4-aminophenyl)piperazine	100

Table A4: LCMS results for twenty-five hydrogenation reaction runs with H-Cube® combined with a liquid handler.

NMR Data

5-Aminoindole: The spectral data were in full accordance with the literature.[75]

2-Aminonaphthalene: The spectral data were in full accordance with the literature.[76]

7-Aminoindole: ^{1}H NMR (400 MHz, dimethyl sulfoxide DMSO, 25°C): δ=6.62 – 7.12 (m, 5 H), 10.31 (s, 2 H).

4-Aminoanisol: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ= 3.75 (s, 3 H), 6.64 (d, *J*=8.8 Hz, 2H), 6.76 (d, 2 H, *J*=8.8 Hz, 2 H).

1-(4-Aminophenyl)piperazine: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ=2.90 – 3.03 (m, 8 H), 6.58 (d, *J*=8.3 Hz, 2 H), 6.73 (d, *J*=8.3 Hz, 2 H).

The above comparison was repeated several times with identical results.

9.4 Analytical data and spectra

Analytical data for selective reduction of 4-bromo-nitrobenzene (Table 4)

5%Rh/C

Mode: flow

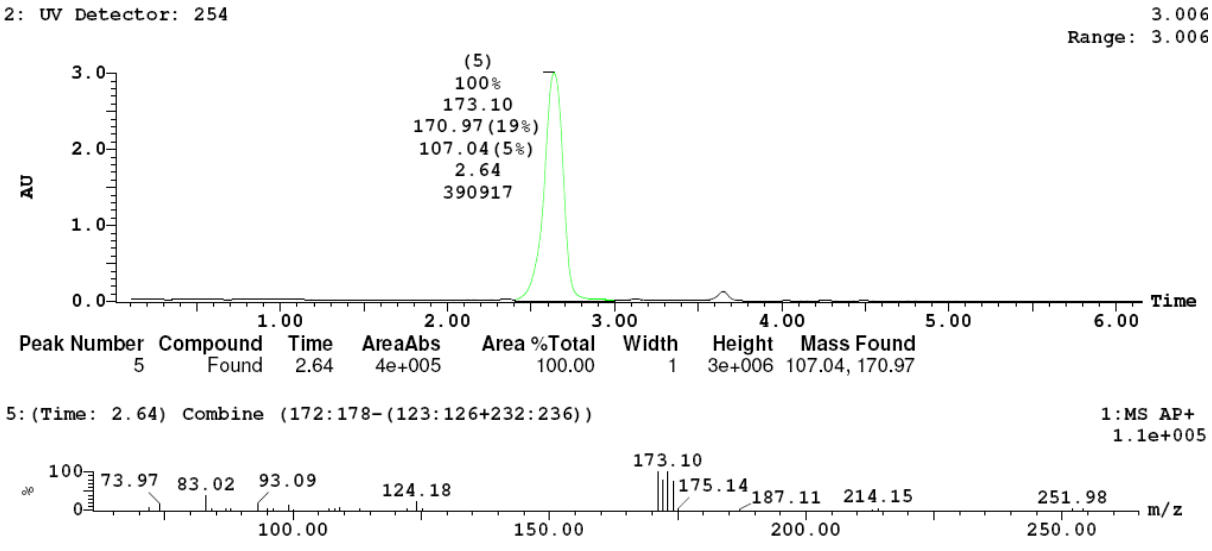
Res. time: 0.6 s

Product: 1D

Conversion: 100%

Selectivity 99. %

LC-MS:



5%Rh/C

Mode: flow

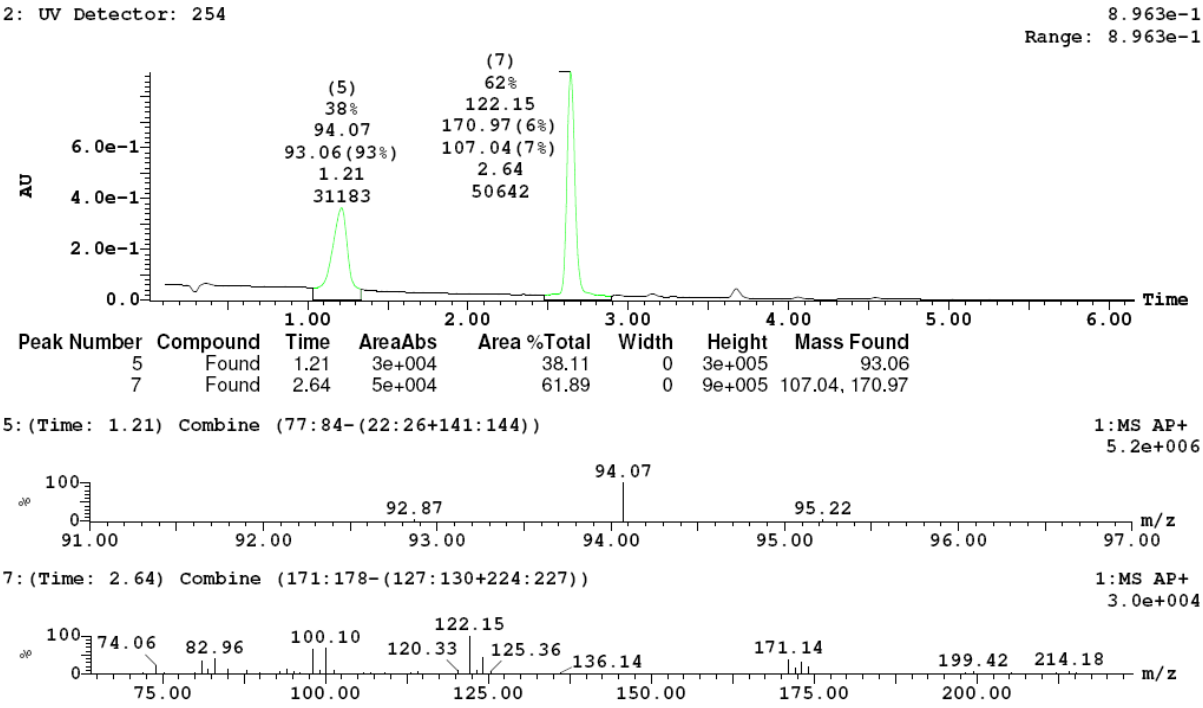
Res. time: 24 s

Product: 1D, 1E

Conversion: 100%

Selectivity: 38% (1D), 62% (1E)

LC-MS:



5%Rh/C

Mode: batch

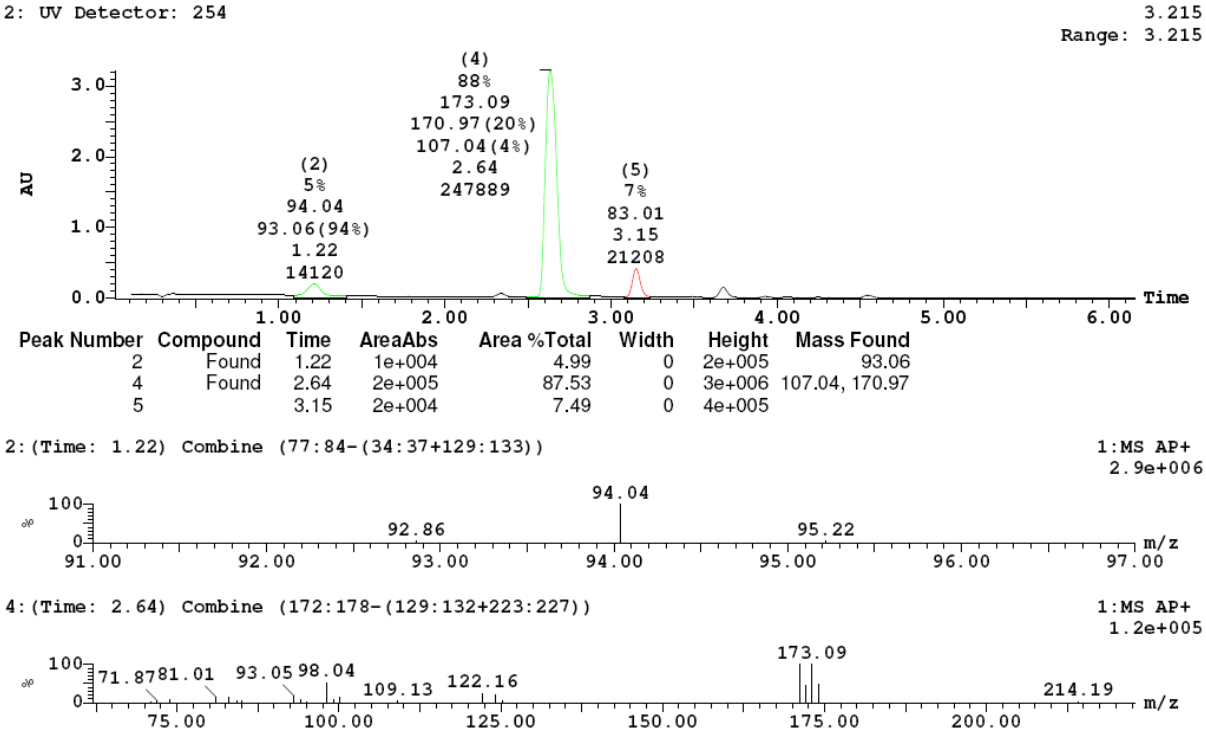
Res. time: 3600 s

Product: 1D, 1E

Conversion: 100%

Selectivity: 88% (1D), 5% (1E)

LC-MS:



RuO_2

Mode: flow

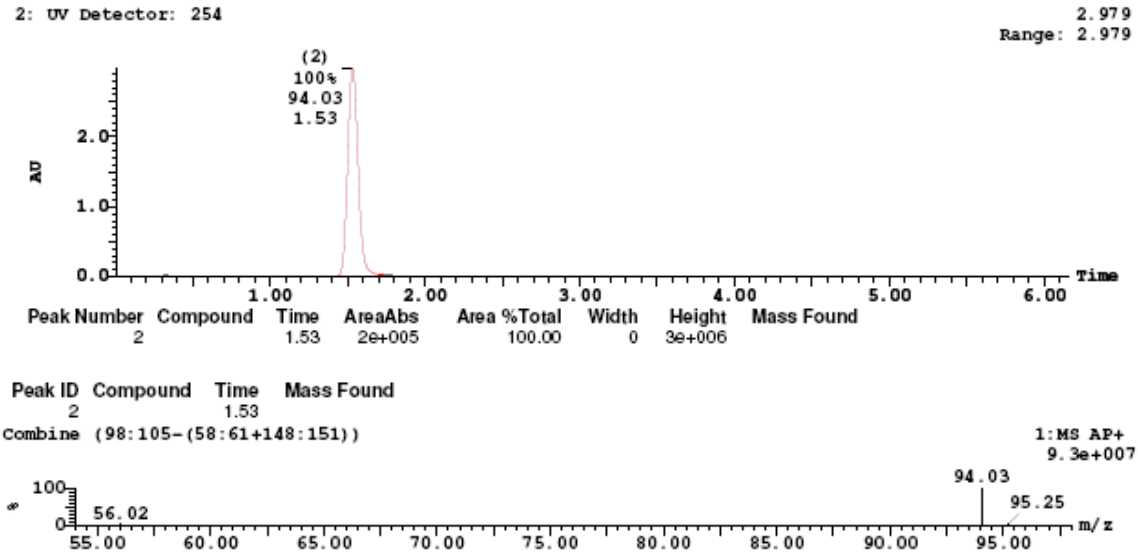
Res. time: 17 s

Product: 1D

Conversion: 100%

Selectivity: 100% (1D)

LC-MS:



RuO_2

Mode: flow

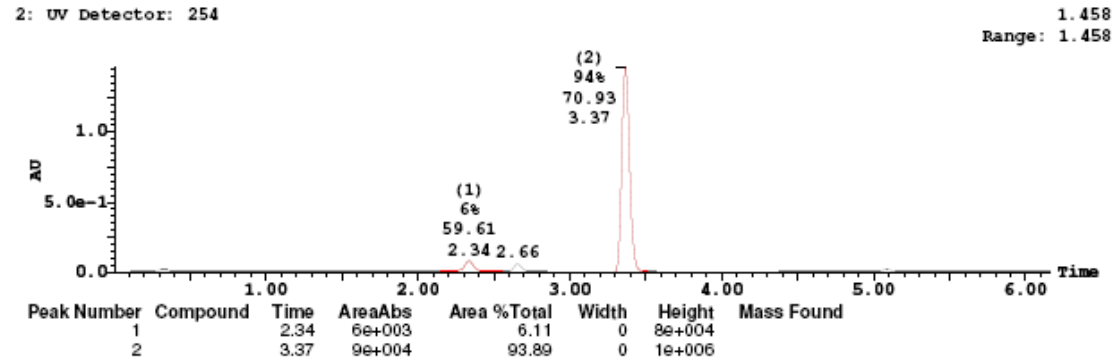
Res. time: 17 s

Product: 1B

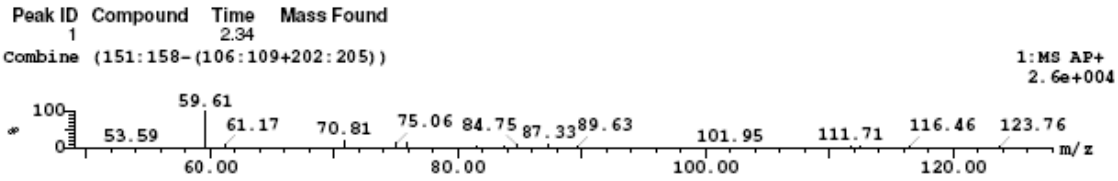
Conversion: 6%

Selectivity: 100% (1B)

LC-MS:



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		2.34	6e+003	6.11	0	8e+004	
2		3.37	9e+004	93.89	0	1e+006	



RuO_2

Mode: batch

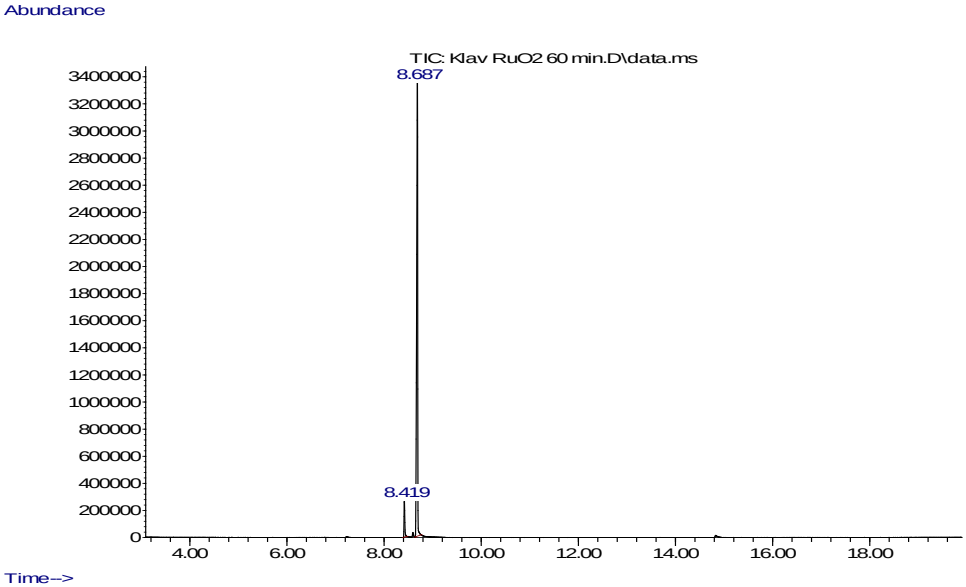
Res. time: 3600 s

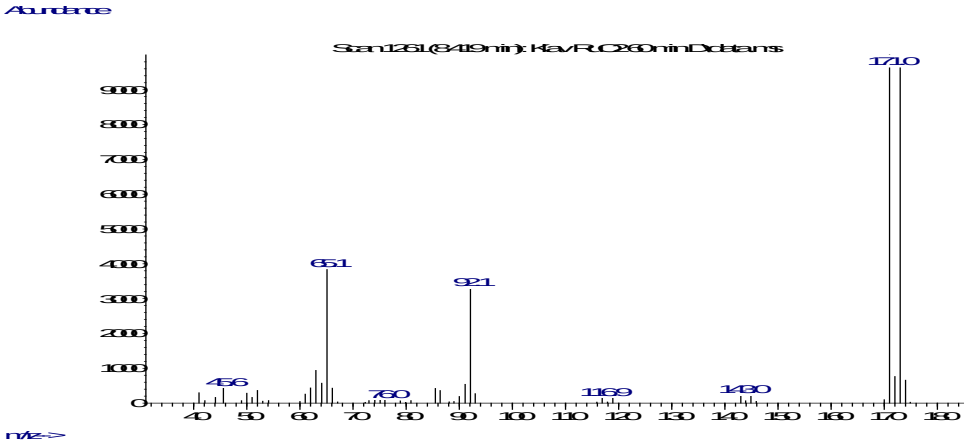
Product: 1D

Conversion: 6%

Selectivity: 100% (1D)

GC-MS:





8,687 min is the starting material

Au/TiO_2

Mode: flow

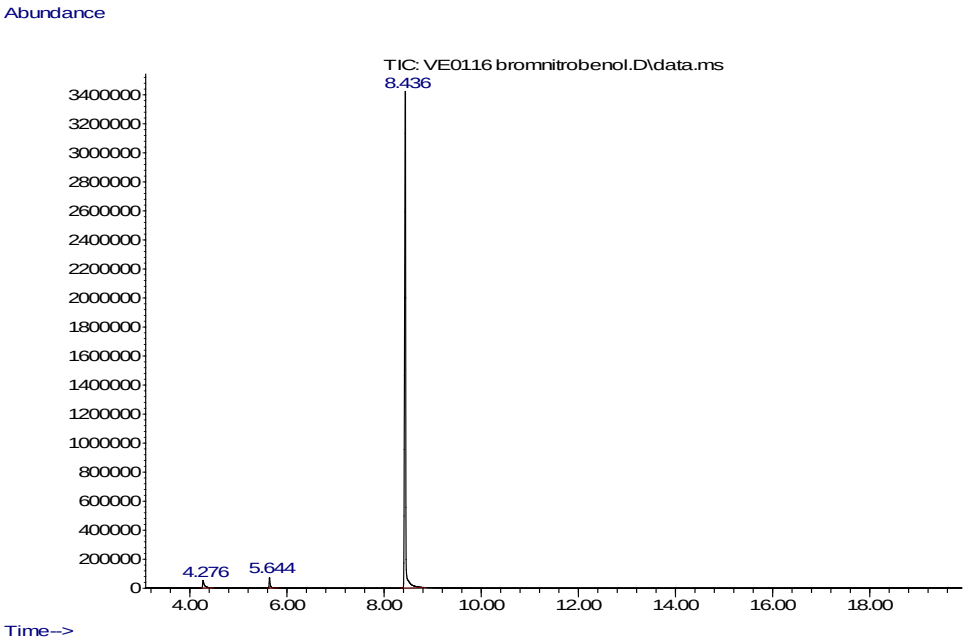
Res. time: 17 s

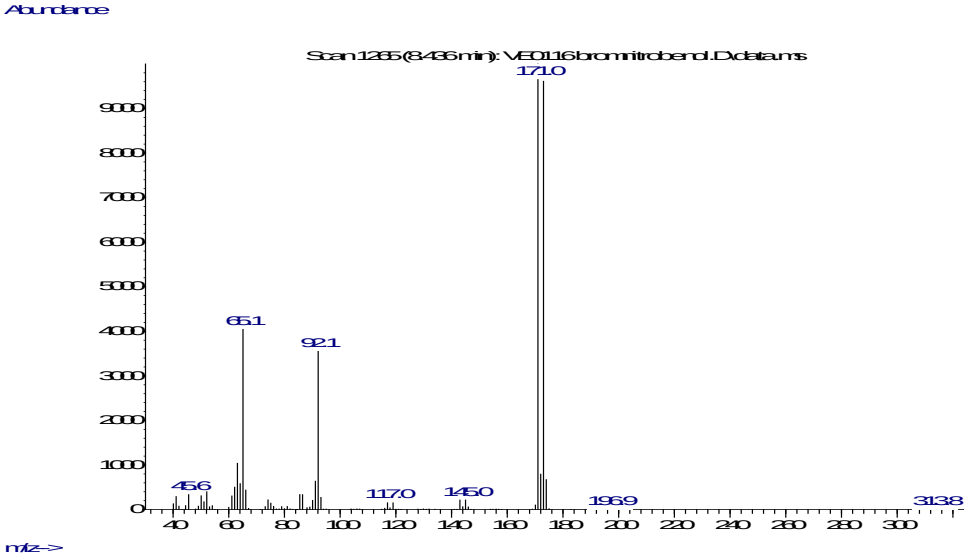
Product: 1D

Conversion: 94%

Selectivity: 100% (1D)

GC-MS:




Abundance
Scan 1285 (8.436 min): VE0116bromnitrobenol.D\data.ms
171.0
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
65.1
92.1
45.6
117.0
145.0
196.9
313.8
40
60
80
100
120
140
160
180
200
220
240
260
280
300
m/z-->

<u>Au/TiO$_2$</u>

Mode: flow

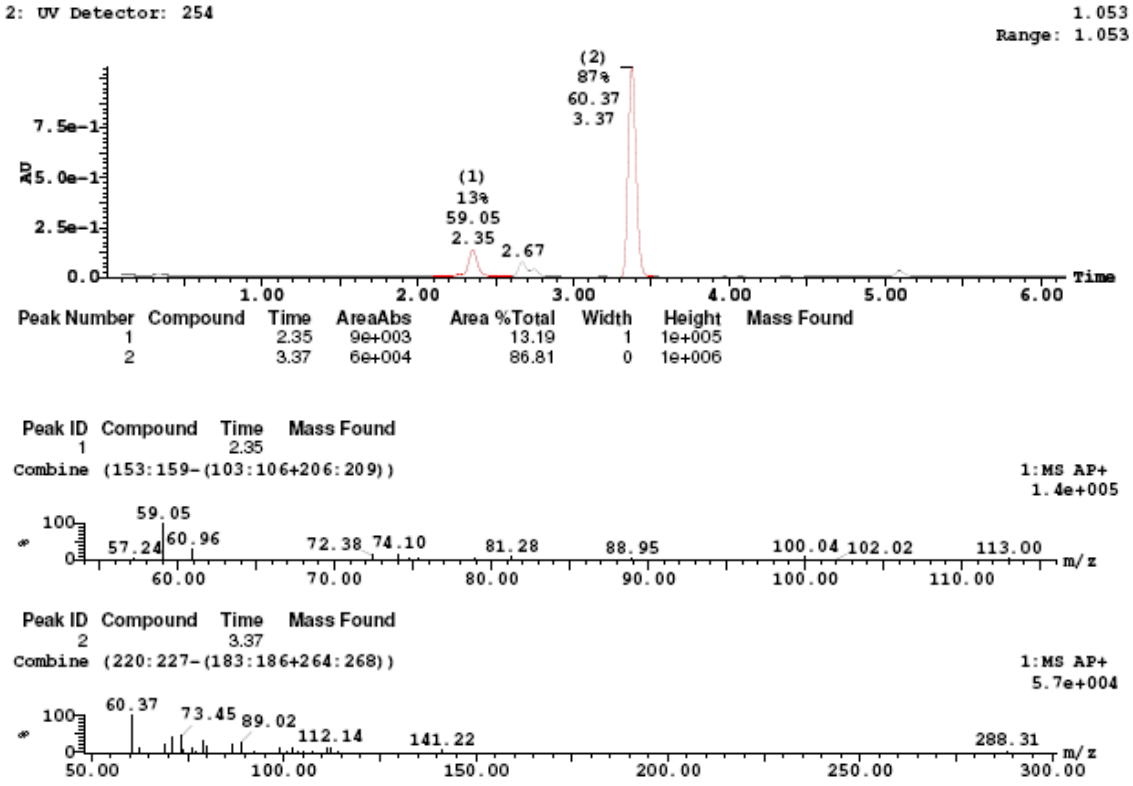
Res. time: 2.1 s

Product: 1B

Conversion: 13%

Selectivity: 100% (1B)

LC-MS:



Au/TiO_2

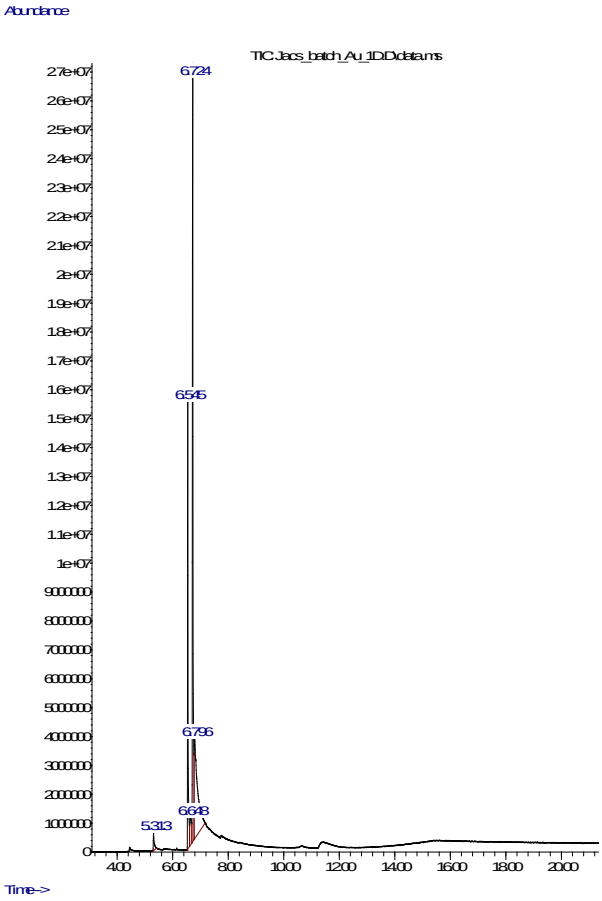
Mode: batch

Res. time: 2.1 s

Product: 1D, 1E

Conversion: 23%

Selectivity: 85% (1D), 2% (1E)



Pt(V)/C

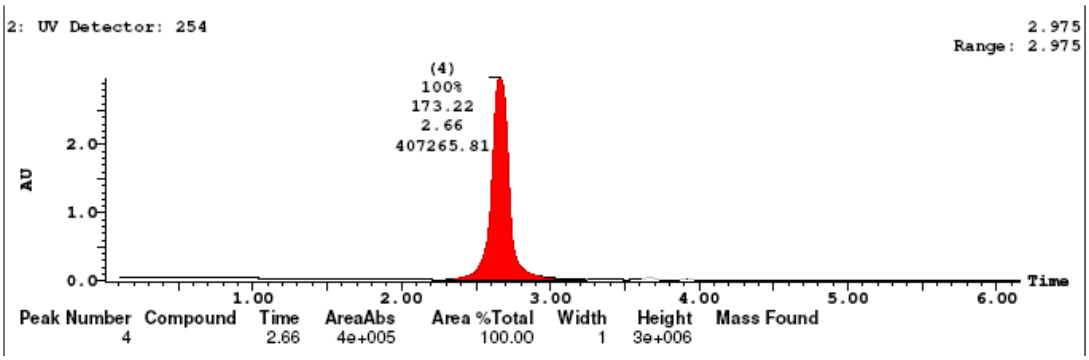
Mode: flow

Res. time: 11.8 s

Product: 1D

Conversion: 100%

Selectivity: 100% (1D)



Pt(V)/C

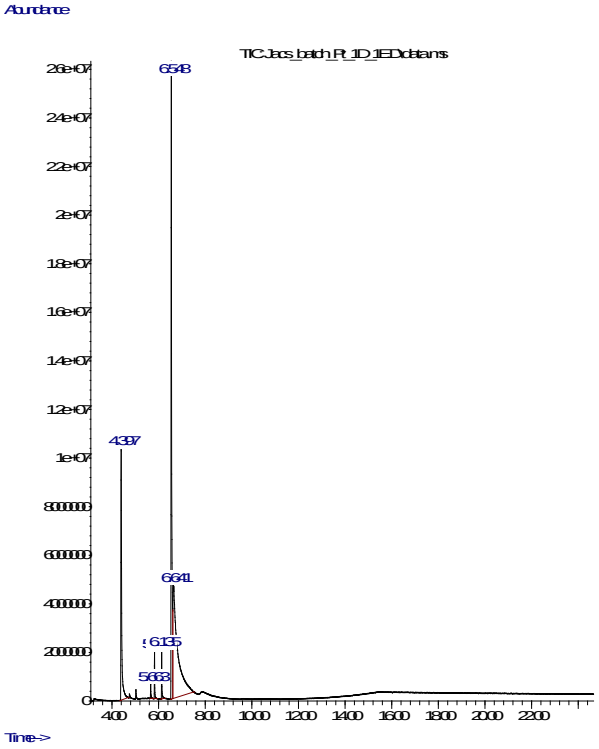
Mode: batch

Res. time: 1800 s

Product: 1C, 1D, 1F, 1E

Conversion: 100%

Selectivity: 4% (1C), 77% (1D), 2% (1F), 1% (1E)



Pd/C

Mode: flow

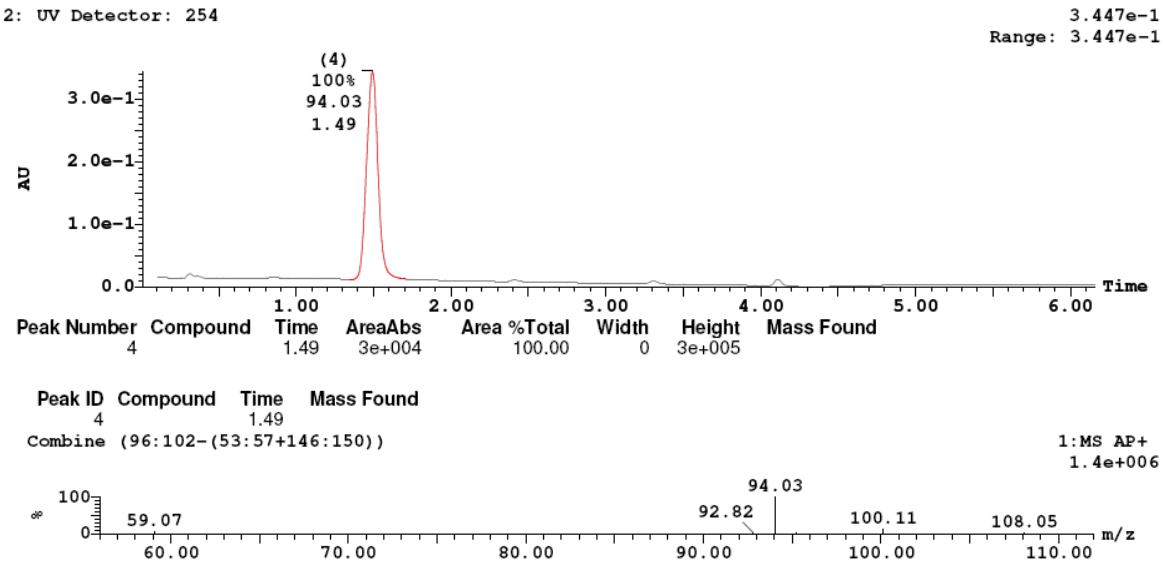
Res. time: >1s

Product: 1E

Conversion: 100%

Selectivity: 100% (1E)

LC-MS:



Pd/C

Mode: flow

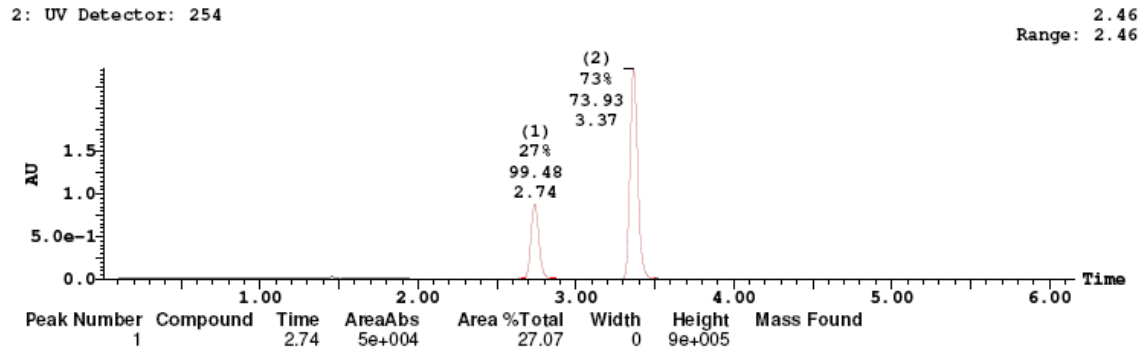
Res. time: 0.43 s

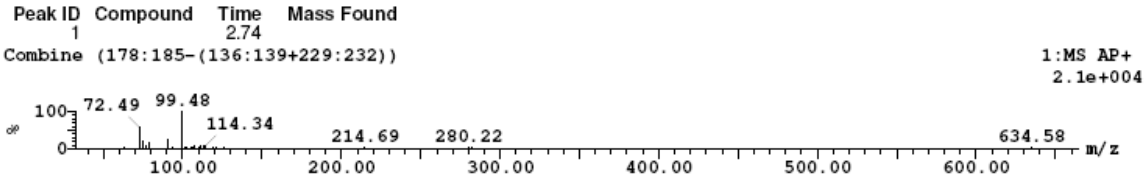
Product: 1F

Conversion: 27%

Selectivity: 100% (1F)

LC-MS:





Pd/C

Mode: batch

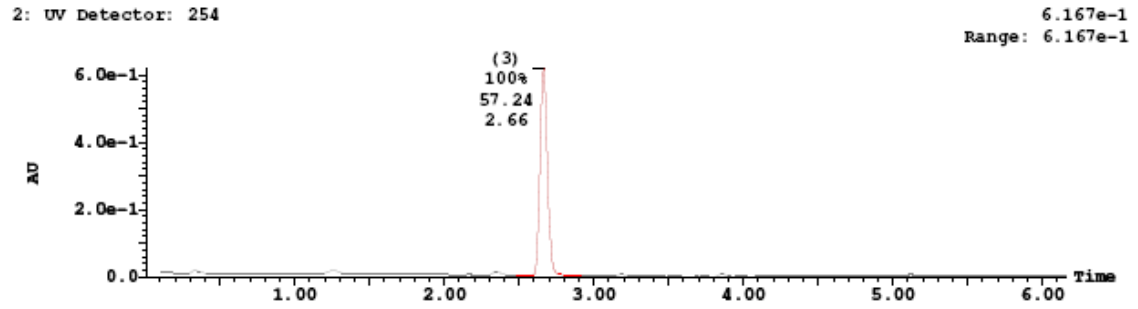
Res. time: 900 s

Product: 1E

Conversion: 100%

Selectivity: 100% (1E)

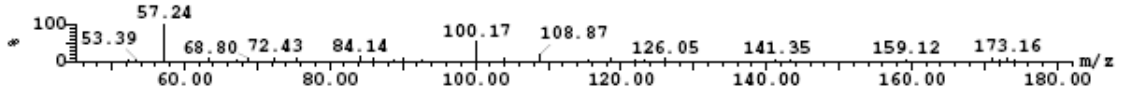
LC-MS:



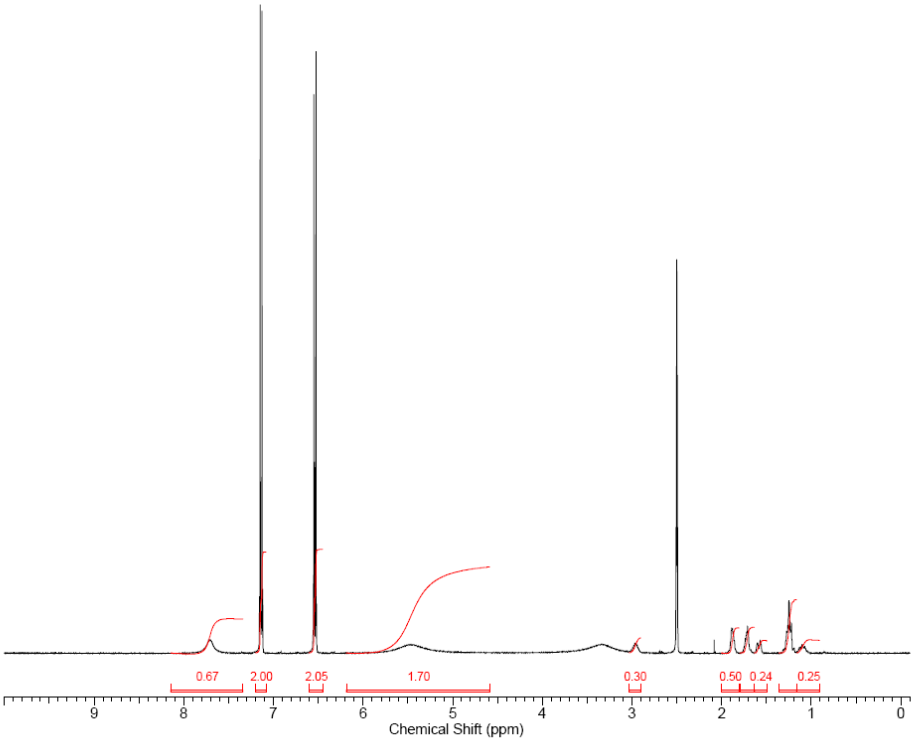
Peak ID	Compound	Time	Mass Found
3		2.66	

Combine (173:180-(129:132+227:230))

1:MS AP+
2.1e+004



NMR of product 1D:



Comment	0116-1Y;kj23894
Date	19 Jan 2009 15:23:44
Nucleus	1H
Frequency (MHz)	400.13
Number of Transients	32
Solvent	DMSO-d6
Acquisition Time (sec)	3.9846
Pulse Sequence	zg30
Points Count	32768
Receiver Gain	406.00
Sweep Width (Hz)	8223.43
Spectrum Offset (Hz)	3203.6973
Temperature (degree C)	29.600

No.	(ppm)	Value
1	[0.91 .. 1.16]	0.25
2	[1.16 .. 1.36]	1.06
3	[1.49 .. 1.64]	0.24
4	[1.64 .. 1.79]	0.51
5	[1.81 .. 2.00]	0.50
6	[2.90 .. 3.03]	0.30
7	[4.59 .. 6.19]	1.70
8	[6.45 .. 6.60]	2.05
9	[7.08 .. 7.20]	2.00
10	[7.34 .. 8.14]	0.67

Acknowledgements

For my sons, Aidan and Benjamin, my reason for being.

For my parents, who have always been there for me.

And for Ferenc and Csaba, because without them and their continual encouragement and perseverance this work would not have been possible.