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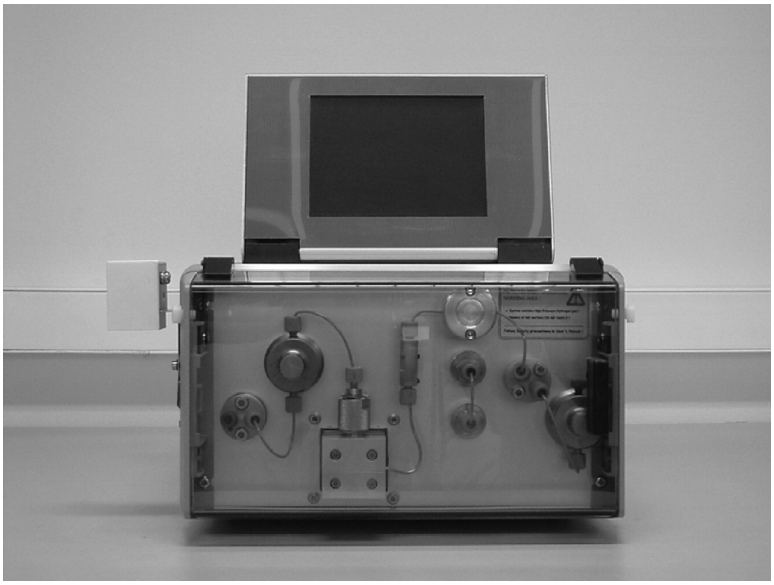

Continuous-Flow High Pressure Hydrogenation Reactor for Optimization and High-Throughput Synthesis

Richard V. Jones,*,† Lajos Godorhazy,† Norbert Varga,† Daniel Szalay,† Laszlo Urge,‡ and Ferenc Darvas†,‡

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This paper reports on a novel continuous-flow hydrogenation reactor and its integration with a liquid handler to generate a fully automated high-throughput hydrogenation system for library synthesis. The reactor, named the H-Cube, combines endogenous hydrogen generation from the electrolysis of water with a continuous flow-through system. The system makes significant advances over current batch hydrogenation reactors in terms of safety, reaction validation efficiency, and rates of reaction. The hydrogenation process is described along with a detailed description of the device's main parts. The reduction of a series of functional groups, varying in difficulty up to 70 °C and 70 bar are also described. The paper concludes with the integration of the device into an automated liquid handler followed by the reduction of a nitro compound in a high throughput manner. The system is fully automated and can conduct 5 reactions in the time it takes to perform and workup one reaction manually on a standard batch reactor.

Introduction

Catalytic heterogeneous hydrogenation is one of the most important and widespread techniques in the reduction of functional groups.[1−5] Even with the development of homogeneous catalysis, the use of heterogeneous catalysts is still preferable and holds many advantages over their homogeneous counterparts. These include stability of the catalyst, ease of separating the catalyst from the product, the wide range of reaction conditions available, and the ability to reduce highly unreactive functional groups.[6] The impact of genomics and proteomics and the subsequent generation of large numbers of drug targets has forced the chemical industry to refine and speed up chemical and biological screening.[7,8] As yet, hydrogenation, although highly prevalent in organic synthesis, has yet to be developed as a high-throughput tool because of the limitations of the manner in which hydrogenation is performed.

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.[9] The use of hydrogen cylinders as a hydrogen source has restricted hydrogenation to specially built facilities. 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.

A new wave of hydrogenation microreactors have been developed to overcome these disadvantages by utilizing flow-through of solvent and gas into a immobilized-Pd catalyst containing microchannels.[10] The microreactors are designed to increase the efficiency of the mixing of the gas phase, the liquid substrate phase, and the solid catalyst phase. The use of continuous flow-through reactors is an important development in making high-throughput hydrogenation a possibility. However, the technology currently available uses substrate flow rates of 0.1 mL/h, and therefore, the amount of product, although high in yield, is low in scale. The pressure of the reaction is also atmospheric, limiting the capability of the device to reduce substrates such as aromatic heterocycles.

We have developed a device, the H-Cube, to overcome these disadvantages and offer the possibility of performing high-pressure hydrogenations as a high-throughput library step. The following is a description of the components and processes involved in the hydrogenation process followed by the integration of the reactor with a liquid handler for automated high-throughput synthesis.

Method and Reactor Description

The H-Cube continuous-flow reactor was developed in-house at Thales Nanotechnology.

The H−Cube system, Figure 1, is composed of three major components: (1) a touch-screen operator system, (2) a substrate delivery system, and (3) a reactor.

1. Touch-Screen Operator System. This user interface is a graphic touch screen (Figure 2) which displays operational parameters such as flow rate, temperature, and

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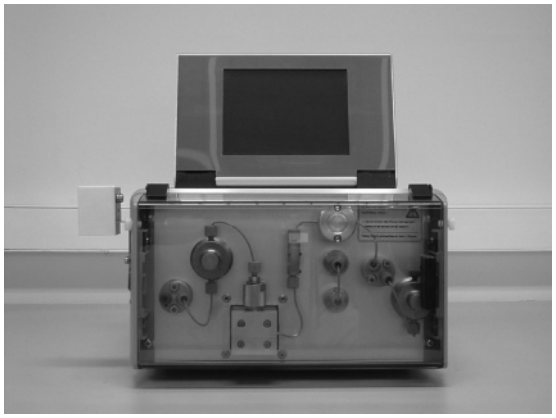


Figure 1. H-Cube continuous-flow reactor.

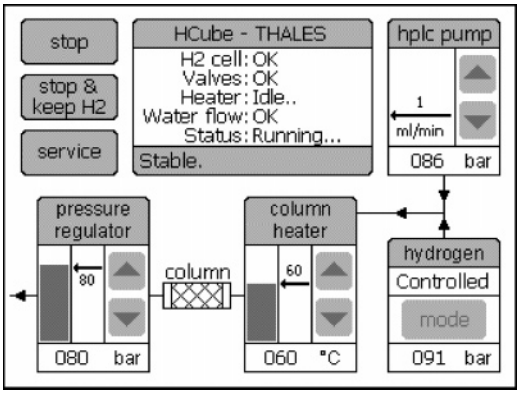


Figure 2. Touch screen panel for reaction control.

pressure. The different parameters can be set to specific reaction conditions by pressing on the arrows. Flow rate can be set from 0.1 to 3 mL/min, while temperatures and pressures can be set to a maximum of 100 °C and 100 bar, respectively.

2. Substrate Delivery System. Substrates can be introduced into the device via two methods. The starting material is dissolved in the reaction solvent and delivered to the H-Cube through an HPLC pump.[11] This method of delivery has been used to reduce substrates up to a scale of 100 g. In another method, smaller substrate quantities, dissolved in a volume of solvent up to 20 mL, may be injected into a 6-port injection valve placed between the HPLC pump and the H-Cube. The substrates are fed into the reactor using a reservoir of solvent.

3. Reactor. (i) Generation of Hydrogen. Hydrogen is produced through the electrolysis of deionized water. The anode side of an electrolytic cell is charged with water, and the protons migrate to the cathode under the effect of an applied current where they are reduced to produce hydrogen gas. The oxygen, formed by the discharge of hydroxide ions at the anode, is removed from the cell with the recycled water. The use of deionized water as hydrogen source offers obvious safety benefits compared to the use of a high-pressure hydrogen cylinder. All hydrogen generated for the reaction is used in situ.

The newly generated hydrogen gas enters a motorized valve. This valve controls the amount of hydrogen released into the reaction system through the hydrogen/substrate mixer (Figure 3). The substrate/hydrogen mixer contains a porous

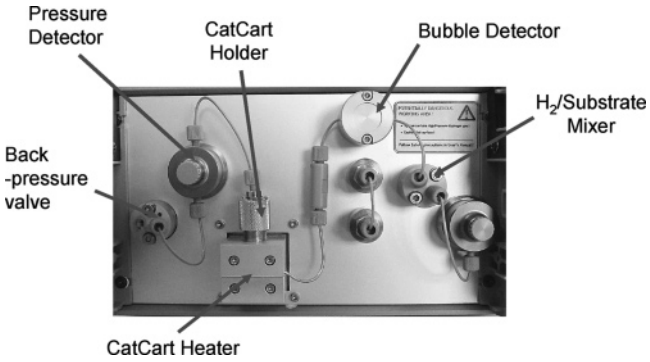


Figure 3. The H-Cube reaction line.

titanium frit where the hydrogen is pushed through to reduce the size of the hydrogen bubbles. The hydrogen bubbles feed into the stream of substrate passing across the surface. The diffusion of bubbles into the solvent stream ensures efficient mixing of the two phases.

(ii) Reaction Line (Figure 3). The reaction line is made up of orange PEEK tubing and a stainless steel line (0.5 mm internal diameter) attached via Fingertight connectors. Once the substrate enters the reaction line it is combined with the hydrogen in the substrate/hydrogen mixer. The gas/solvent mixture passes through a bubble detector, which determines if there is hydrogen in the reaction line, and then into a heater unit.

The CatCart heater unit is a coiled stainless steel reaction line running through a heater block. The heating is controlled via a Peltier system which heats the reaction block, hence the reaction line, up to a maximum of 100 °C. The temperature of the heater block is monitored via a digital thermometer which in turn controls the heating to and maintaining of the set temperature. The small diameter of the reaction line means that the heating of reaction mixture to temperature is efficient and quick. The constant flow of solvent means that the system is cooled efficiently when not heating. It is well documented that the temperature of a hydrogenation reaction is difficult to regulate in a batch reactor leading to hotspot formation, which in turn can generate side products or deactivate the catalyst.[12] On the flow reactor, any increase in temperature caused by hydrogenation is quickly detected and the heating ceases. Cooler substrate entering the heater and catalyst cools the catalyst system to the set temperature; therefore, the system maintains an exact temperature throughout the experiment.

A catalyst cartridge is embedded in the heater block. The standard catalyst cartridge is a stainless steel tube 30 mm in length with an internal diameter of 4 mm, which allows approximately 140 mg of catalyst to be contained (Figure 4). The main types of catalyst which can be used are Pd/C, Pt/C, Pearlman's catalyst, Rh/C, Raney nickel, and Raney cobalt. The catalyst particle size is kept between 30 and 40 μm to allow uniform flow and pressure through the catalyst column. There are filters placed at either end of the cartridge to prevent leaching of the catalyst into the reaction line. The catalyst cartridges offer a number of advantages over batch reactor systems.

The catalyst cartridge reduces human exposure to the catalyst significantly, which in turn reduces the risks involved

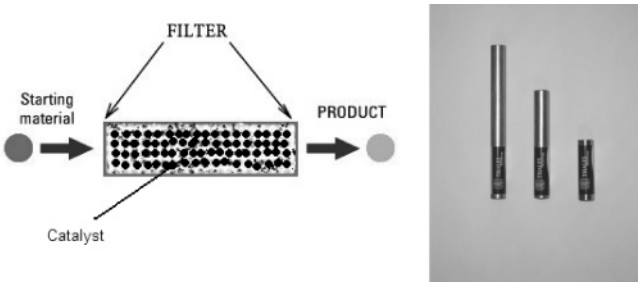


Figure 4. Schematic of the catalyst cartridge and the three different sizes.

with the handling of pyrophoric catalysts. The installation of the cartridge involves a quick placement into the reaction line. The filter system means that no filtering is required at the end of the experiment making the process more efficient and safer. It also means the catalyst can be reused for a different substrate; this has significant relevance to the automated section described later.

The hydrogenation process takes place solely inside the cartridge. The substrate/hydrogen mixture flows through microchannels formed by the packed catalyst. The active area ratio of catalyst to hydrogen and substrate is therefore very high leading to increased reaction rates. The reaction mixture flows out of the cartridge and through a back-pressure regulator, which can restrict the flow of reaction mixture through the system generating an increase in system and hydrogen pressure in the process. The pressure of the system can be increased up to 100 bar (1450 psi). Once the reaction mixture has passed out of the system, it is collected in a sample vial. The time taken to pass through the system into the reaction vial is 2.5 min at a flow-rate of 1 mL/min. After this time, TLC or LCMS samples may be taken to see if product conversion is satisfactory. Removal of the solvent directly yields the product.

The continuous-flow process, combined with a short residence time in the reactor, means that reaction optimization can be performed rapidly on novel substrates. After 3 min, the user can analyze the reaction mixture to detect whether the first set of reaction conditions yield 100% product. If not, temperature or pressure may be increased using the touch screen control. The reactor will then take a short period of time to reach the new set of parameters and elute the reaction mixture at these conditions. Another analytical sample can then be taken to monitor how the new parameters have affected product conversion. This process can be repeated until a maximum conversion is found. Catalyst cartridges may also be exchanged quickly to determine the effect of differing catalyst types on yield and conversion. This way, optimization for the reduction of novel substrates is simple, more efficient, and less invasive than with batch reactor methods.

All lines and valves are standard commercially purchased HPLC equipment. The orange PEEK tubing and the finger-tight fittings are built to withstand pressures of 350 bar, while the green PEEK tubing can withstand pressures of 240 bar.[13]

4. Hydrogenation Reactions Validated Using the Continuous-Flow Reactor. The device was tested on a wide range of functional groups using different catalysts, temperatures, and pressures. All parameters were assessed against % product conversion and yield.

Using the optimal conditions stated in Table 1, compounds **1**, **2**, and **3** were all reduced to achieve quantitative yields. The reductions were performed in minutes with 0.1 mmol quantities. Benzyl-protected phenethylamine **5** and naphthol **4** plus carbobenzyloxy-protected tryptamine **6** were all subjected to hydrogenolysis using our device giving 100% conversion and high yields. Reducing 1 mmol of *trans*,*trans*-1,4-diphenyl-1,3-butadiene **7** on the H-Cube took 20 min using 10% Pd/C at room temperature and 1 bar resulting in an 82% yield and a 96% conversion by NMR. Alkyne **8** was also reduced in a quantitative yield.

Alkenes can also be reduced selectively to alkanes in the presence of ketone functionalities. To demonstrate this, we decided to reduce 1 mmol of cyclohexa-2-enone **9** on the H-Cube. Ethanol was used as the solvent, and 10% Pd/C was used as the catalyst; the temperature and pressure parameters were set to room temperature and 1 bar, respectively. Reduction to cyclohexanone was achieved with an 85% yield in less than 5 min.

Reactions can also be performed under an inert gas atmosphere. Oxime **10** and nitrile **11** were reduced under argon using dry 2 M ammonia in methanol as a solvent, which enhanced the conversion to the primary amine resulting in a quantitative yield. The reactions were carried out using Raney Nickel as catalyst and at high temperature and pressure to obtain high yield and conversion.

The above reactions were scaled up to between 1 and 10 g with similar results. All results are highlighted in Table 1.

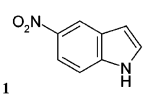
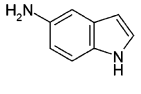
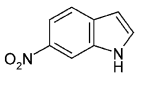
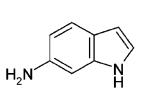
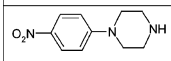
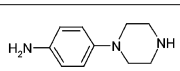
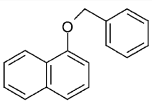
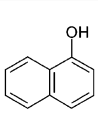
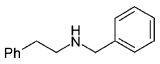
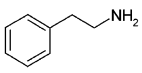
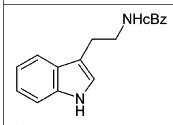
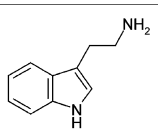
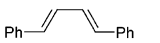
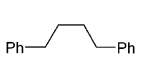
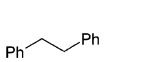
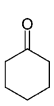
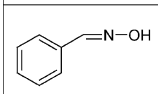
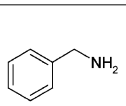
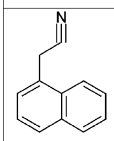
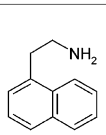
All reductions detailed in Table 1 were reduced 100% after only one flow through the system. Previous studies have demonstrated the higher rates of reaction achieved on the H-Cube compared to batch reactor technology and why high conversion is obtained after only a short residence time on the catalyst.[14] This can be attributed to the high mass transfer rates generated from such a high catalyst to substrate−hydrogen ratio compared to the batch process where a suspension of substrate and catalyst are stirred under an atmosphere of hydrogen. The mixing of the three phases is poor, and therefore, the hydrogen uptake and reaction rates are also poor.

5. Integration of the Reactor into an Automated Liquid Handler. The reactor can be easily integrated into an automated RSP 9000 Cavro liquid handler through a Valco Vici 6-port injection valve to produce an automated high-throughput hydrogenation setup.[15]

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 (Figure 5) switches the flow of solvent from the reactor to the injection loop, pushing the injected substrate out of the loop into the reactor.

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

Table 1. Experimental Conditions and Yields of Experiments Carried out on the H-Cube

Substrate	Product[a]	Conditions	Yield[b]
 1		10% Pd/C or Raney-Ni, EtOAc/EtOH (1:1), Flow rate:1mL/min, Pressure: 1 bar, Temp.:25°C	95-97%
 2		10% Pd/C or Raney-Ni, EtOAc/EtOH (1:1), Flow rate:1mL/min, Pressure: 1 bar, Temp.:25°C	96%
 3		Raney Nickel EtOAc/EtOH (1:1), Flow rate:1mL/min, Pressure: 1 bar, Temp.:25°C	99%
 4		10% Pd/C, EtOAc/EtOH (1:1), Flow rate:1mL/min, Pressure: 1 bar, Temp.:60°C	85-97%
 5		10% Pd/C, EtOAc/EtOH (1:1), Flow rate:1mL/min, Pressure: 1 bar, Temp.:80°C	89%
 6		10% Pd/C, EtOAc/EtOH (1:1), Flow rate:1mL/min, Pressure: 1 bar, Temp.:50°C	81-85%
 7		10% Pd/C, EtOH, Flow rate:1mL/min, Pressure: 1 bar, Temp.:25°C	82%
8		10% Pd/C, EtOH, Flow rate:1mL/min, Pressure: 1 bar, Temp.:25°C	94%
 9		10% Pd/C, EtOH, Flow rate:1mL/min, Pressure: 1 bar, Temp.:25°C	85%
 10		Raney Ni, 2M NH_3 in MeOH, Flow rate:1mL/min, Pressure: 70 bar, Temp.:70°C	88%
 11		Raney Ni, 2M NH_3 in MeOH, Flow rate:1mL/min, Pressure: 70 bar, Temp.:70°C	99%

[a] All products exhibited spectral data (^{1}H NMR and MS) consistent with their structures. [b] Yields refer to isolated pure products.

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 schematic of the system and a picture of the system are shown in Figure 6.

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. Twenty-five samples of 5-nitroindole (0.1 mmol, 16.2 mg) were injected automatically into a continuous flow of ethyl acetate/ethanol (1:1) solvent at 6 min intervals. The reductions were carried out at room temperature and atmospheric pressure with a 1 mL/min flow rate. On hundred forty milligrams of 10% palladium on charcoal was used as the catalyst in the column. Each sample was analyzed by LCMS and then NMR. A graph of the results is in Figure 7.

The first twenty injections proceeded favorably, all maintaining a high conversion rate of >90% and a quantitative yield. The remaining 5 injections deteriorated to a conversion rate of <70% which is attributed to the deactivation of the catalyst caused by poisoning from the amine product. It is anticipated that the use of longer catalyst cartridges or the insertion of an automated catalyst changer into the system would increase the number of compounds reducible in a single run without catalyst deactivation to 50−100 reactions. The same nitro reductions performed on a batch reactor[16] required over 30 min per reduction, including catalyst addition, purging of air, pressurization, 15 min 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 the 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.

The barrier to performing a hydrogenation as a last step in a library synthesis because of the practical limitations of manually reducing 2000 small scale compounds can now be removed. The system can be used to remove benzyl groups, providing a useful alternative to BOC and FMOC protecting groups which employ harsh acidic deprotection conditions.

Conclusion

We have described the technical specifications of H-Cube, a novel continuous-flow high-pressure hydrogenation device for use in high-throughput library synthesis. The device conducted reactions on a variety of substrates at pressures up to 70 bar and temperatures of up to 70 °C in high yield. The reactions could be monitored during operation, and the reaction parameters could be rapidly modified to achieve conditions for 100% conversion. No filtration was required after completion of the reaction, making the hydrogenation

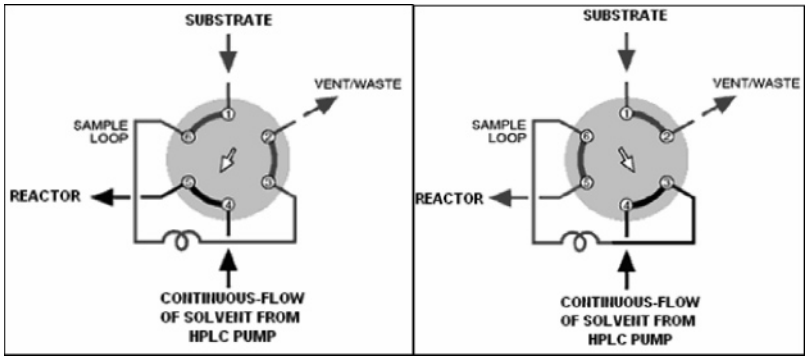


Figure 5. Flow of solvent through valve at position A and position B.

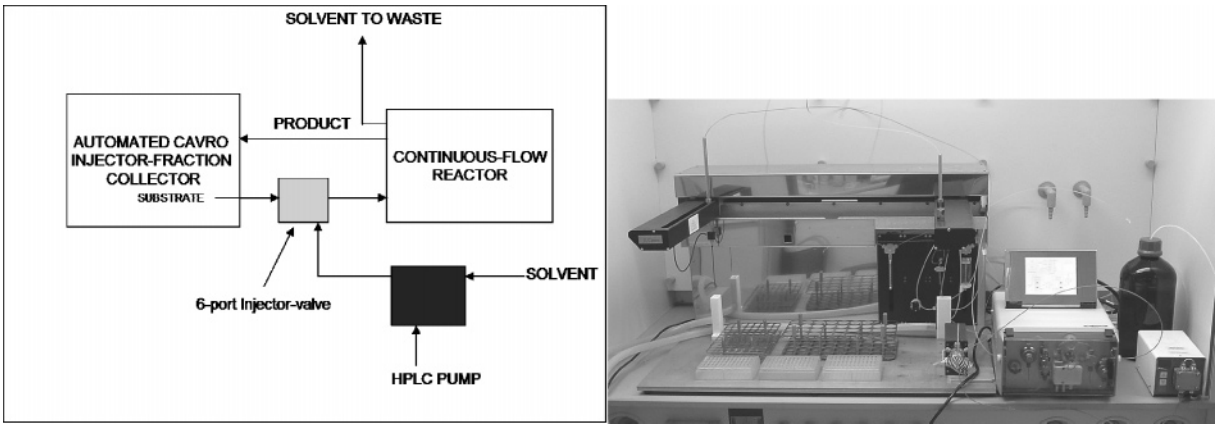


Figure 6. A schematic (a) and picture of the H-Cube (b) integrated into a Cavro automated liquid handler.

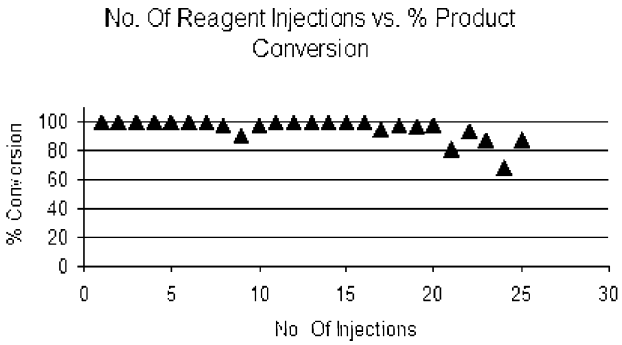


Figure 7. Graph of the multiple injection results.

process safer and efficient, and the solvent was reduced to dryness to yield the product in a pure form. The H-Cube can also be integrated into an automated liquid sampler system to form a high-throughput hydrogenation station. Work is underway to utilize this system for the reduction of large numbers of compounds as part of drug-discovery library generation practice. This device 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. This fact is justified with three recent papers where the instrument was used successfully to reduce a simple aromatic nitro compound library, selectively reduce imines, and deprotect compounds produced via a 3-component Biginelli reaction in a microwave.[17,18]

Experimental Section

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 was a Purospher STAR RP-18 endcapped, 3 μm, 30 $\times$ 4 mm. The detection wavelengths were 220 or 254 nm.

MS data were collected on a ZQ Singlequad (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 measured on a Nicolet FTIR MAGNA 750 spectrophotometer.

For parallel synthesis, the RoboSynthon cascading reactor family (ComGenex International, So. San Francisco) was employed.

Starting materials were purchased from commercial sources. Silica gel 60 F_{254} (Merck) plates were used for TLC. Solvents were dried and purified according to the well-established methods.[12] Evaporations were carried out under reduced pressure.

All products exhibited spectral data (^{1}H NMR and MS) consistent with their structures. Please refer to Table 1 for details of experimental conditions.

5-Aminoindole. A typical experimental procedure for the hydrogenation of 5-nitroindole is as follows.

The stock solution was prepared by dissolving 5-nitroindole (0.162 g, 0.001 mol) 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. The pressure was set to 1 bar, the flow rate of the system to 1 mL/min, and the temperature to 30 °C using the touch screen control. The "Full Hydrogen" mode was selected. The reaction was started by pressing the "start" button on the touch screen control. After passing through the instrument, the total reaction mixture was collected (20 mL in 20 min), and the column was washed with the solvent mixture (10 mL in 10 min) 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).

6-Aminoindole. The experiment was performed in the same manner as that for 5-aminoindole.

4-Piperazino aniline. The experiment was performed in the same manner as that for 5-aminoindole.

Naphthalene-1-ol. The experiment was performed in the same manner as that for 5-aminoindole except the temperature was set to 60 °C.

Phenethylamine. The experiment was performed in the same manner as that for 5-aminoindole except the temperature was set to 80 °C.

2-Indol-3-yl-ethylamine. The experiment was performed in the same manner as that for 5-aminoindole except the temperature was set to 80 °C.

1,4-Diphenylbutane. The experiment was performed in the same manner as that for 5-aminoindole.

1,2-Diphenylethane. The experiment was performed in the same manner as that for 5-aminoindole.

Cyclohexanone. The experiment was performed in the same manner as that for 5-aminoindole.

Phenylmethylamine. The experiment was performed in the same manner as that described above except the temperature and pressure were set to 70 °C and 70 bar, respectively. Solvent was 1 M NH_3 in methanol and the catalyst was Raney nickel.

2-[1]-Naphylethylamine. The experiment was performed in the same manner as that described above except the temperature and pressure were set to 70 °C and 70 bar, respectively. Solvent was 1 M NH_3 in methanol and the catalyst was Raney nickel.

Repeated Sequential Injection of 5-Aminoindole. 5-Nitroindole (16.2 mg, 0.1 mmol) was dissolved in 2 mL of 1:1 ethyl acetate/ethanol. Twenty-five samples were made 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 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 was resturned to position A. Another sample was manually injected into the sample loop. After a period of 7 min, 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 in Table 2, located in the Supporting Information section.[19]

Batch Reactor Comparison Study. 5-Nitroindole (16.2 mg, 0.1 mmol) was dissolved in methanol (2 mL) and placed in a 10 mL round-bottomed flask with a stir bar. The flask was placed in an ice bath and a slow stream of nitrogen was flowed over the top of the flask. One hundred forty-five milligrams 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 atm pressure. The reaction was stirred vigorously for 3 min before the hydrogen was released. Initial TLC results showed poor conversion. NMR analysis showed a 2% conversion. The reaction was again put under hydrogen at the same pressure and left for a further 12 min. Analysis of the reaction mixture showed complete conversion. The total time for catalyst addition, reaction, and filtration took approximately 30 min.

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Supporting Information Available. Table 2 detailing the results of the sequential injection of 5-nitroindole. This material is available free of charge via the Internet at http://pubs.acs.org.

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