

The automation of a novel continuous-flow hydrogenation reactor as a tool to facilitate high-throughput compound synthesis.

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- The pharmaceutical and chemical industry is continuously searching for technologies that make synthesis easier, faster, and safer to perform. The advance of micro-flow technology is helping to realize these goals.

- Microflow technology has many advantages. The reactors are low-volume, so temperature and pressure control are easier and more precise, making reactions safer to perform. The flow of material through the reactors is only a matter of minutes, so results can be achieved in a very short space of time. Automation of the reactors is generally easier to perform on flow instruments than on batch reactors, therefore with the advent of new flow reactors, some processes may be automated, which may not have been possible before.

- At ThalesNano, we have developed a series continuous-flow reactors for organic synthesis. Below is a description of the automation of the H-Cube™, a hydrogenation reactor, and how this may be applied to other flow reactors.



Continuous-flow Hydrogenation

The hydrogenation reactor, H-Cube™, is a compact continuous-flow reactor which performs high pressure hydrogenations through the use of a microfluidic reaction line, in-situ hydrogen generation and a catalyst cartridge system (CatCart™).

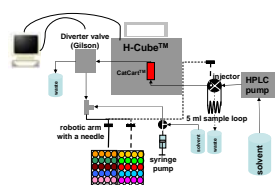


- A flow of substrate is pumped into the reactor where it is combined with hydrogen, produced by the electrolysis of water

- The substrate/hydrogen mixture is heated and/or pressurized, up to 100°C and 100 bar (1450 psi) respectively, and then passed through a catalyst cartridge (CatCart™)

- The reaction takes place on the catalyst and the generated product elutes continuously into a collection vial.

Automated High-throughput Hydrogenation^{1,2}



The H-Cube was incorporated into a Gilson 271 automated liquid handling system. This allows a large number of small-scale compounds (up to 10ml) to be automatically injected sequentially into the device at timed intervals and the hydrogenated products collected in different fractions. By reusing the catalyst, removing the filtration step, avoiding pressurizing and depressurizing between samples, the whole process can be fully automated and produce a higher throughput. Evaporation of solvent yields the product.



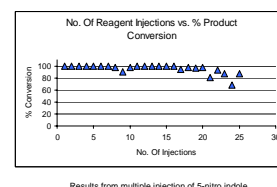
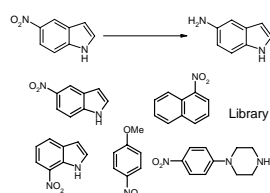
A multi-channel catalyst changer can also be incorporated into the H-Cube Autosampler system, so that the reactor has 6 different reaction zones. A multi-channel valve system controls the direction of the flow into either zone. Six different catalysts may be used in each zone. A compound or series of compounds may be automatically injected into each different catalyst under different temperatures and pressures and a fraction collected for each set of conditions.

Summary

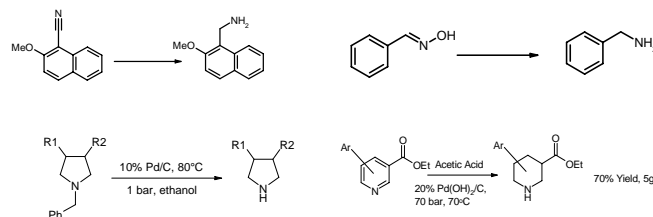
We have developed a hydrogenation system, H-Cube™, which was successfully integrated into an automated liquid handling system. Validation reactions were performed on the system. The validation reactions demonstrated that it is possible to reduce a library on the automated system as part of a final library step. The system's high throughput capability was demonstrated when 50 compounds were reduced in less than 6 hours in complete conversion. Lastly, a summary of the work conducted on the automated system by the University of Cambridge was presented.

References: (1) Jones R., Godorhazy L., Varga N., Szalay D., Urge L., and Darvas F., *J. Comb. Chem.*, **2006**, *8*(1), 110-116 (2) Jones R., Godorhazy L., Szalay D., Urge L., Darvas F., *QSAR Comb. Sci.*, **2005**, *24*(6), 722-727. (3) Knudsen, K., Holden, J., Ley, S., Ladlow, M., *Automated Synthesis and Catalysis.*, 2007, Paper available in the March edition.

Pilot-testing of automated high-throughput system using 3 different libraries



In order to validate that a compound could be repeatedly injected and converted using the H-Cube automated system, 5-nitro indole (16.2 mg per substrate) was injected sequentially on a single CatCart (145 mg of 10% Pd/C) every 6 minutes. The first twenty injections produced total product conversion, while the last five showed the catalyst started to deactivate. A small library of 5 simple aromatic nitro compounds, Library 1, was then used to assess the minimum time between sample injections. Tests showed that restricting the time between injections to 7 minutes and above gave no cross-contamination, but by decreasing the interval to less than 6 minutes led to contamination. The same library was then used to test the capacity of the columns to produce 100% product conversion in high yield. Varying the solvent or time between injections gave 100% reduction on over 50 compounds on the same CatCart™. The experiment took less than 6 hours to reduce 50 compounds. Other examples which have been tested on the H-Cube system are given below:



Automated deprotection³

Work carried out under Prof. Steven Ley's group in collaboration with GSK at the University of Cambridge has yielded significant results in utilizing the system for benzyl and cbz protecting group removal. A small library of 8 N-cbz protected compounds was selected and each compound subjected to sequential injection through the automated

system. Each compound (3.5ml, 0.05M) was reacted under 80°C, 1 bar, and 1ml/min flow rate. In all cases, the deprotected derivatives were isolated in high yield and purity. In particular, both protecting groups (cbz and O-benzyl) were simultaneously removed from Z-(OBn)-Tyr-OMe. Results are displayed in Table 1.

Substrate	Conversion [%] ^(a)	Yield [%] ^(b)
Cbz-Pro-OMe	99	99 ^(b)
Cbz-Piperazine	99	80 ^(b)
Cbz-(Arg(OMe)-OMe)	99	77
Cbz-(OBn)Tyr-OMe	97	83 ^(b)
Cbz-Ser-OMe	98	82
Boc-(N-Cbz)-Lys O(Naph)	95	86
Cbz-Thr-Tyr(OBn)-O ^t Bu	99	96
Cbz-Pro-tryptazole	99 ^(a)	99

References: (1) Jones R., Godorhazy L., Varga N., Szalay D., Urge L., and Darvas F., *J. Comb. Chem.*, **2006**, *8*(1), 110-116 (2) Jones R., Godorhazy L., Szalay D., Urge L., Darvas F., *QSAR Comb. Sci.*, **2005**, *24*(6), 722-727. (3) Knudsen, K., Holden, J., Ley, S., Ladlow, M., *Automated Synthesis and Catalysis.*, 2007, Paper available in the March edition.