



Project:

H-Cube Midi™ Product Update

„From mg to kg in one day”

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Executive Summary

The difficulties involved with scaling up reactions from laboratory to process scale are well known.¹ Reaction pathways are often designed in laboratories on a small scale. Laboratory experiments carried out in test tubes or small flasks produce the required chemical or product, but may not indicate the side effects of the reaction. 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 catalyst and inhibition effects. The time taken for the reaction to take place is often extended significantly with scale up. This change in thermochemistry can lead to formation of other products. Reagents or solvents used on a small scale may carry too much of a health risk when used in larger amounts. The above side effects may lead to disastrous consequences if not evaluated fully. These include fire and explosion hazards. Indeed, methods and technologies are missing that allow rapid transfer from the research level to process development without time-consuming adaptation and optimization of methods from the laboratory scale to production plant scale.

The advent of flow technology can overcome these restrictions and allow rapid preparation of compounds with minimum workup. Reactions are carried out on a small scale but can be scaled up by performing the reactions in parallel. This has a number of advantages. The thermochemistry of the reaction doesn't change, so the reaction result will be constant. The heat production is highly controllable meaning many hazardous reagents that were prohibited previously may now be used in a safe controlled manner. Furthermore, reagents or compounds only undergo short reaction times and are then eluted into a collection vial, so further reaction with starting materials or thermal decomposition is unlikely. Since ThalesNano's reactors utilize

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continuous flow any amount of material can be produced by leaving the reaction running until the required product is produced.

The main advantages of the flow-through approach, such as facile automation, reproducibility, safety and process reliability, are yet to be fully exploited for scale up.²

The H-Cube® was a break-through for flow-reactor technology as well as a significant advancement on current hydrogenation technology³. The H-Cube® has led the way for flow-reactor technology by being the first commercially successful micro-flowreactor that has become quickly adopted as the preferred method for hydrogenation. A flow process coupled with high pressure endogenous production of hydrogen from water electrolysis and proprietary catalyst cartridges has meant that hydrogenation is now safer and reaction times decreased significantly. The only limit, so far, has been scale with a maximum potential output of 100 g per day.

The H-Cube Midi™ represents the first step in the ThalesNano, Inc.'s development towards process scale flow hydrogenation. Utilizing current H-Cube® technology, the H-Cube Midi™ seeks to increase the capacity of the present H-Cube® to 500 g per day without compromising efficiency and safety. The H-Cube Midi™ will allow users of the H-Cube® to scale up reactions and achieve the same result.

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H-Cube Midi™ Overview



- Capable of producing from 150-500 g per day in a standard laboratory - no special precautions regarding explosion proof rooms required
- The maximum flow rate is 25 mL/min at elevated temperature and pressure up to 150°C and 100 bars
- High-quality, robust design, easy to handle and operate
- On-demand internal hydrogen generation, requiring only a source of distilled water
- Single/repeat-use, replaceable, MidiCart™ catalyst column module, conveniently located at the front of the device, enabling rapid and easy operator access
- A number of safety features including hydrogen leak detector
- Smallest possible footprint, maximising available bench space
- Full system Touch Screen control and monitoring

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Ease of Operation

The H-Cube Midi™ uses a Touch-Screen interface. All of the parameters that control and monitor **the H-Cube Midi™** functions are input and displayed using this touch screen. To monitor the the system using a computer interface (requires additional software) is possible.

The H-Cube Midi™ may be used safely in any fumehood environment, while its minimal footprint maximizes available fume hood space. **The H-Cube Midi™** employs a number of high pressure liquid chromatography (HPLC) connections, pumps and delivery systems. The maintenance of the instrument is therefore simple for those users already experienced with HPLC technology and easy to teach to those users who have no such experience.

Safety Features

The Touch Screen displays and controls essential reaction parameters, while in-built detectors safely monitor every aspect of **the H-Cube Midi™** function:

- A detector shuts down the device in the event of a hydrogen leak or blockage.
- No external hydrogen storage such as gas cylinders necessary.
- No direct catalyst handling, pre- or post-reaction
- Minimum exposure to hazardous reactants, such as radio-labelled or mutagenic intermediates

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Method Description

The H-cube Midi™ system works through the hydrogenation of a continuous flow of substrate. The substrate is flowed through the system using an automatically controlled piston-pump at flow-rates up to 50 mL/min. Once entering the H-Cube Midi™ reaction line, the flow of substrate is mixed with a continuous flow of hydrogen. The hydrogen is created by the electrolysis of water within an electrolytic cell. The electrolytic cell is based on the original H-Cube® cell, but has been modified for a larger output of hydrogen. The hydrogen gas and a solution of the reactant are mixed, pre-heated and transferred to a disposable catalyst cartridge (MidiCart™) that is preloaded with the required heterogeneous catalysts.

The MidiCart™ is a stainless steel tube packed with a heterogeneous catalyst and a filter at either end. The filter prevents any of the catalyst from leaking and allows the catalyst to be recycled at the end of each experiment. The substrate-hydrogen mixture reacts on the catalyst, converts to product and then flows out of the cartridge. The high ratios of catalyst compared to the substrate-hydrogen mixture ensure high mass transfer rates and therefore high rates of reaction. The MidiCart™ design has been enlarged to cope with higher flow rates and concentrations. 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.

The continuous flow of reaction mixture out of the device allows the operator to carry out on-the-spot analysis of the resulting reaction mixture. Reaction parameters can be easily adjusted using a touch-screen interface in order to achieve a better product yield. The ability to continuously monitor production is vital to ensure that the purity of product is maintained throughout the scale up process. Fractions of product may be collected to ensure that contamination of product through starting material doesn't transpire because of catalyst deactivation or poisoning.

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Reaction Examples

The following is a series of validation reactions to test the applicability and the capacity of the system.

Materials and General Methods

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, 3 μ m, 30x4 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.

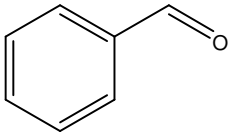
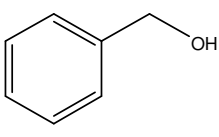
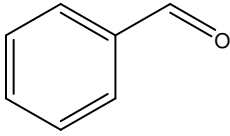
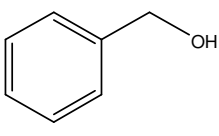
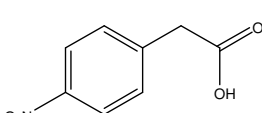
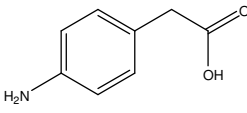
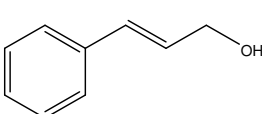
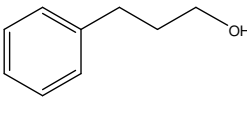
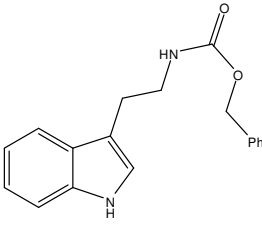
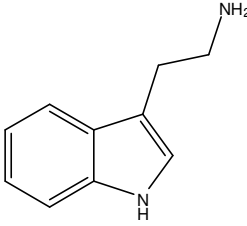
General Experimental

Hydrogenation of benzaldehyde to form benzyl alcohol

Benzaldehyde (71g, 0.67 moles) was dissolved in methanol (1911 mL, 0.35M). A MidiCart™ containing 10% Pd/C was loaded into the H-Cube Midi™. Pure methanol was pumped through the H-Cube Midi™ at a flow-rate of 10 mL/min. The temperature and pressure were set to 40°C and 70 bar respectively. Once the H-Cube Midi™ was producing hydrogen at the set temperature and pressure, the inlet line was switched from the solvent to the benzaldehyde solution. After 3 hours pure solvent was run through the system for 10 minutes to wash any residual compound off the catalyst. Evaporation of the solvent yielded the product (52 g, 72% yield).

The rest of the examples are carried out as above. A summary of their results are given in the Table below. The reactions were carried out on a MidiCart™ either with internal measurements of 9.5 mm x 90 mm or 20 mm * 86 mm

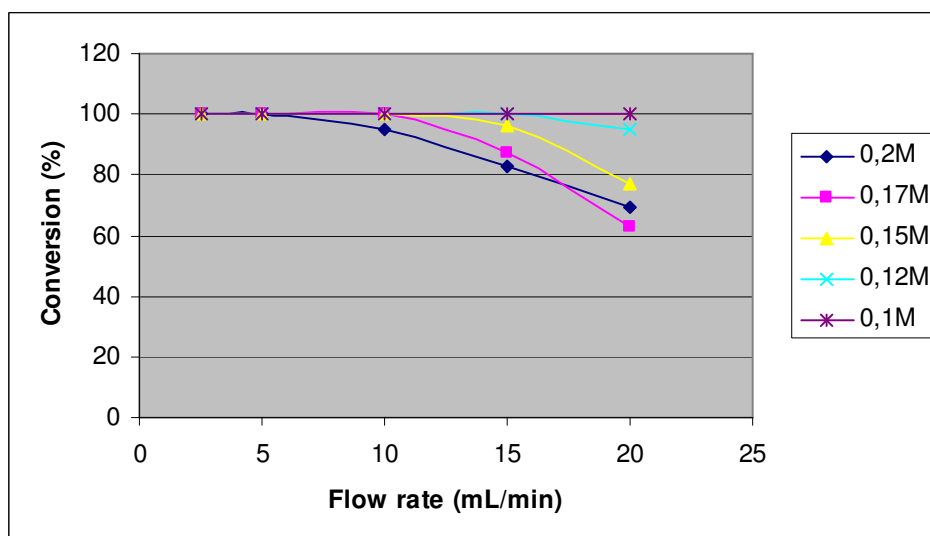
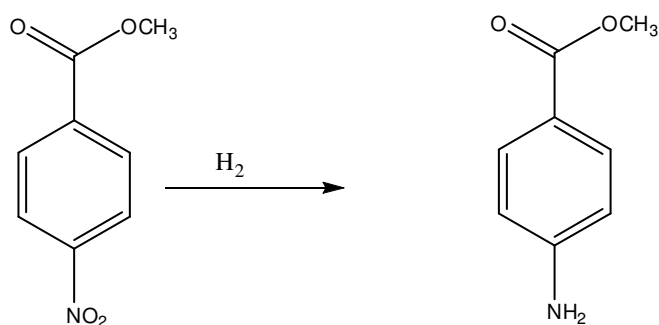
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Starting Material	Product	Reaction Conditions	Amount Processed/ Time	Calc. Amount for 8 hours	Yield
		Flow-rate: 10 mL/min Temperature: 40°C Pressure: 70 bar Solvent: methanol Catalyst: 10% Pd/C (2,9 g) Concentration: 0.35 M	71 g in 3 hours	190 g	72%
		Flow-rate: 25 mL/min Temperature: 40°C Pressure: 70 bar Solvent: methanol Catalyst: 10% Pd/C (10,84 g) Concentration: 0.35 M	74,2 g in 80 min	445,2 g	74%
		Flow-rate: 30 mL/min Temperature: 30°C Pressure: 30 bar Solvent: methanol Catalyst: 10% Pd/C (2,81 g) Concentration: 0.05 M	46,2 g in 3 hours	123 g	90%
		Flow-rate: 10 mL/min Temperature: 90°C Pressure: 10 bar Solvent: ethanol Catalyst: Raney Cu (17,4 g) Concentration: 0.2 M	92 g in 6 hours	122.66 g	82%
		Flow-rate: 10 mL/min Temperature: 60°C Pressure: 50 bar Solvent: ethanol Catalyst: 10% Pd/C (3,1 g) Concentration: 0.05 M	13.9 g in 1.5 hours	74 g	95%

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Optimisation of the conditions with H-Cube Midi™ can be carried out very quickly and effectively.

The optimisation of the reduction of methyl-4-nitrobenzoate was completed within a few hours by scanning the concentration and the flow rate at a set temperature.



Parameters: 5% Pd/C, P: 70 bar, T: 70°C, Flow rate: 20-2,5 mL/min, C: 0,2-0,1 M

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Summary

The H-Cube Midi™ has managed to increase the throughput of the original H-Cube significantly while maintaining the safety benefits. High yield and conversion were maintained in every example despite the increase in flow-rate. Preliminary experiments with larger columns gave throughputs up to 500 g/day. Once the H-Cube Midi™ is released it will represent a bench mark in flow scale-up technology.

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