Roche

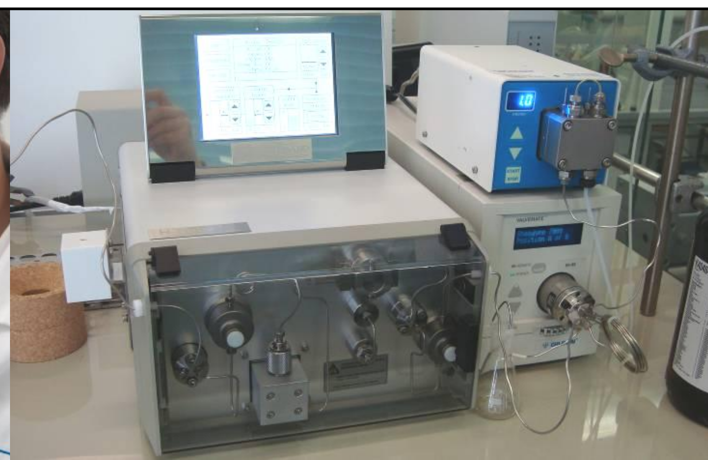
Pharmaceuticals

Continuous Flow Hydrogenation with the H-Cube

at Roche Basel & Nutley

Rainer E. MARTIN

ThalesNano User Group Meeting Oct 21 & 22, 2010, Budapest



- Why Using Flow Chemistry ?

- Why Using Flow Chemistry ?
- Basel Flow Chemistry Equipment
- Selected Hydrogenation Examples
- Knowledge Sharing
- Conclusions and Key Learnings

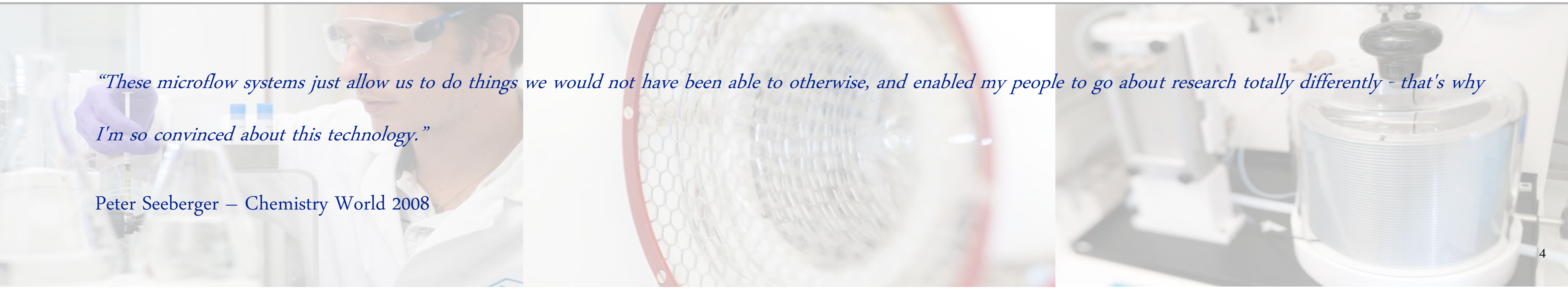
Why Using Flow Chemistry ?

Advantages of conducting reactions in flow

- Very fast mixing
- Increased reactivity
- Superheated reactions
- Pressurized reactions
- Use of hazardous reagents
- Generation of unstable intermediates
- Telescoped reaction sequences

- Reduction in synthesis time
- Increased efficiency
- Suitable for automation
- Integration of biological in vitro screening
- Real time in-line diagnostics
- Easy scale-up from g ⇨ kg

- Lower solvent usage
- Less waste
- 24/7 operation possible



"These microflow systems just allow us to do things we would not have been able to otherwise, and enabled my people to go about research totally differently - that's why I'm so convinced about this technology."

Peter Seeberger – Chemistry World 2008

Advantages of Flow Chemistry

A few theoretical considerations…

round bottom flask (spherical reactor)

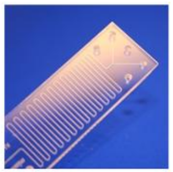
10 mL Volume (r = 0.0134 m):

$$\frac{A_s}{V_s} = 225m^{-1}$$

meso reactor (cylindrical reactor)

10 mL Volume (r = 0.5 mm, l = 12.73 m):

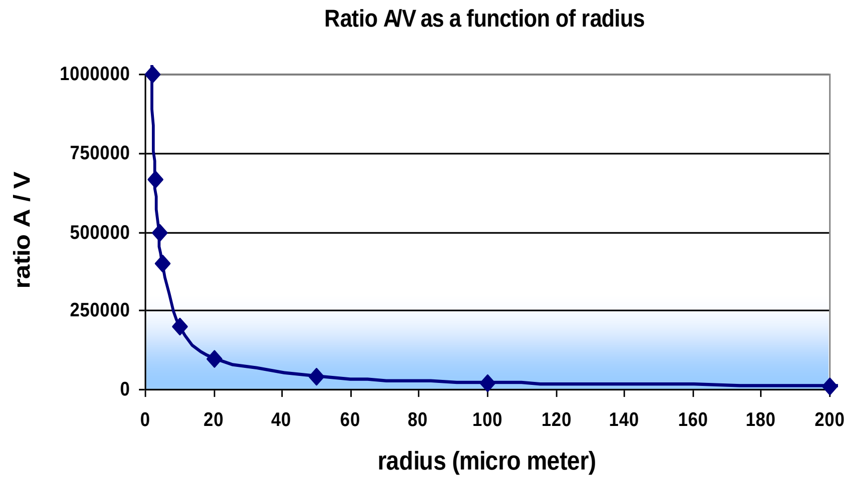
$$\frac{A_c}{V_c} = 4000m^{-1}$$



micro reactor (cylindrical reactor)

r = 150 µm:

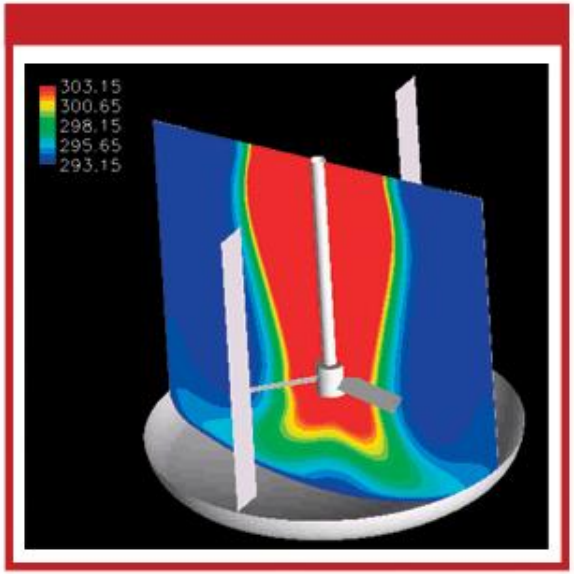
$$\frac{A_c}{V_c} = 13333m^{-1}$$



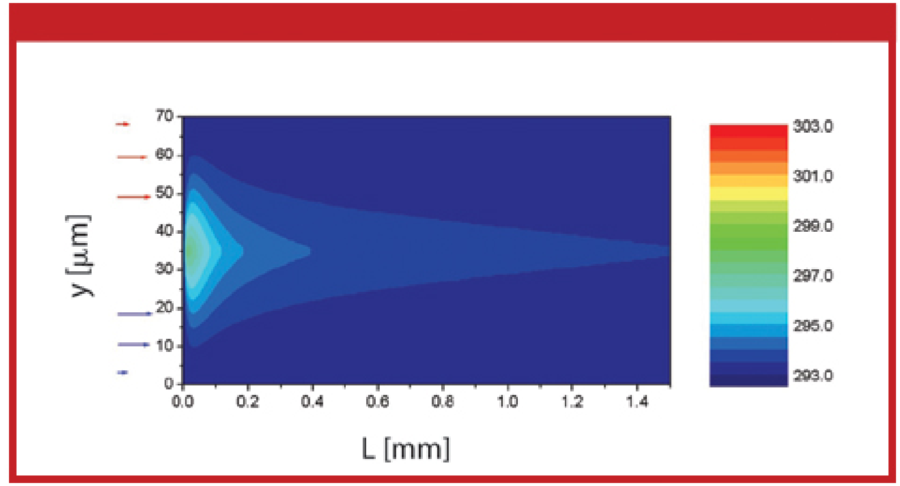
- Dramatic increase of surface-to-volume ratio from meso to micro reactors (and compared with batch)
- Superior capacity for heat and mass transfer
- Exact temperature control possible / avoidance of hot spots

Efficient Heat Transfer in Microreactors

Comparison batch vs. flow reactor



Heat distribution in a batch-synthesis reactor



Heat distribution in a microreactor.

Using microreactors in chemical synthesis. Batch Process vs Continuous flow.

Weiler, Andreas; Junkers, Matthias. SAFC Pharma, Buchs, Switz.

Pharmaceutical Technology **2009**, *Suppl. S6*, S10-S11

- Exothermic neutralization reaction in simulated batch reactor
- Cooling only takes place at the surface of the reactor –> strong temperature gradient of about 10 °C
- In a microreactor, the heat created by mixing the two reagents is also detectable, but much smaller heat gradient of < 3 °C
- It only takes a few millimeters of path length for the reagent stream to cool down
- Less formation of hot spots

- Basel Flow Chemistry Equipment

Flow Chemistry Equipment Basel

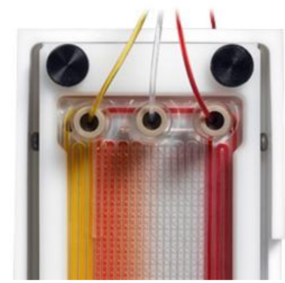
Uniqsis

FlowSyn from

http://www.uniqsis.com

- Compact continuous flow reactor
- Reactions can be heated up to 260°C (Hastelloy reactor)
- Back pressure regulators of up to 70 bar (1000 psi) for superheating of solvents
- Easy to use interface
- 1 system installed

coil reactor



glass chip reactor

Flow Chemistry Equipment Basel

In-house working station

- Glass static mixer for turbulent mixing throught chip volume
- UV detector for in-line analysis
- Fraction collector with multi-experiment package for automated reaction optimization

Flow Chemistry Equipment Basel

Vapourtec

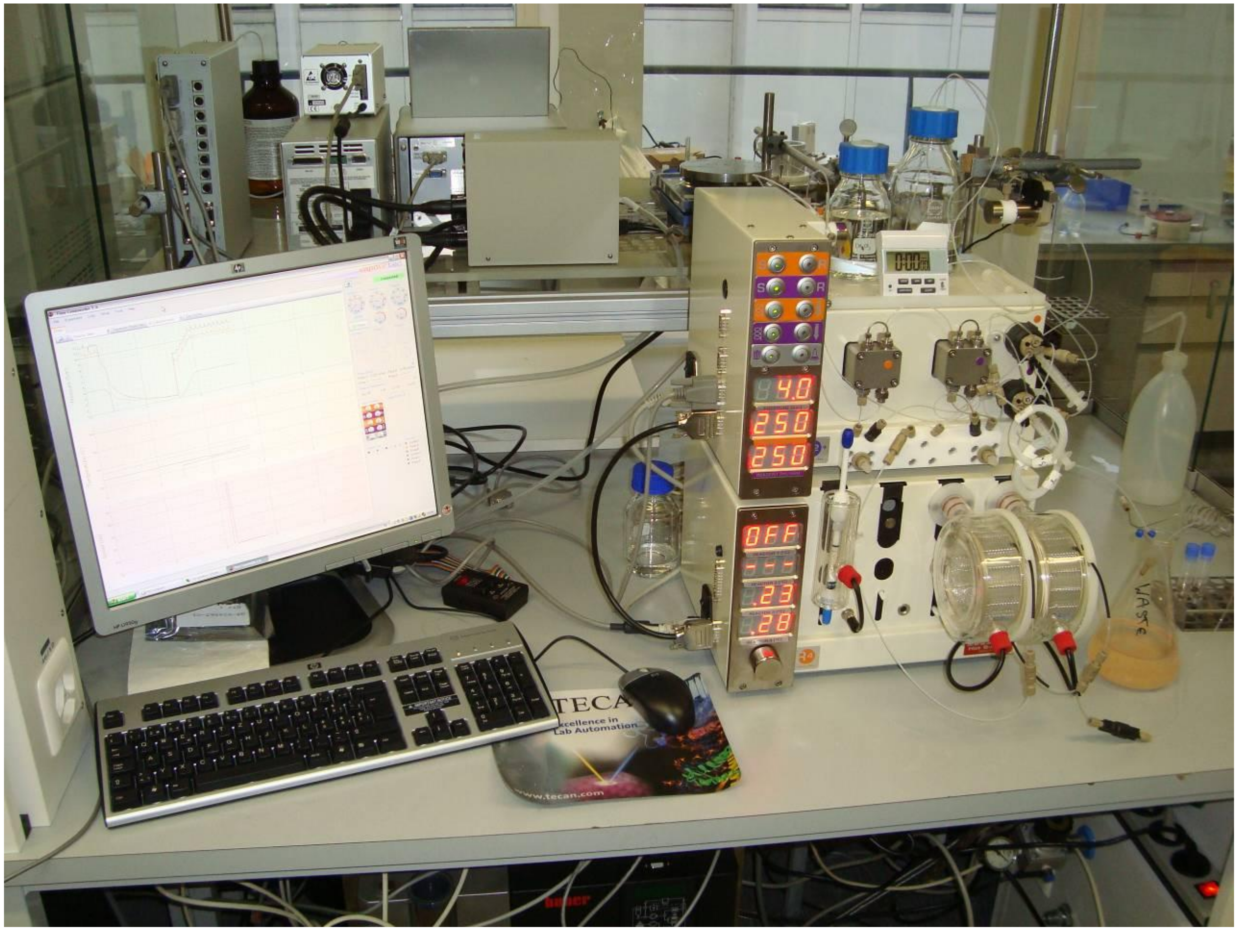
R2+R4 from vapourtec

- Modular continuous flow reactor
- Temperature range from ambient to 250°C
- 4 Independently heated reactor zones (2 x up to 250°C)
- Easily expandable to realize more complex reaction scenarios
- 3 Systems installed (1 acid resistance)

http://www.vapourtec.co.uk

Flow Chemistry Equipment Basel

In-house working station



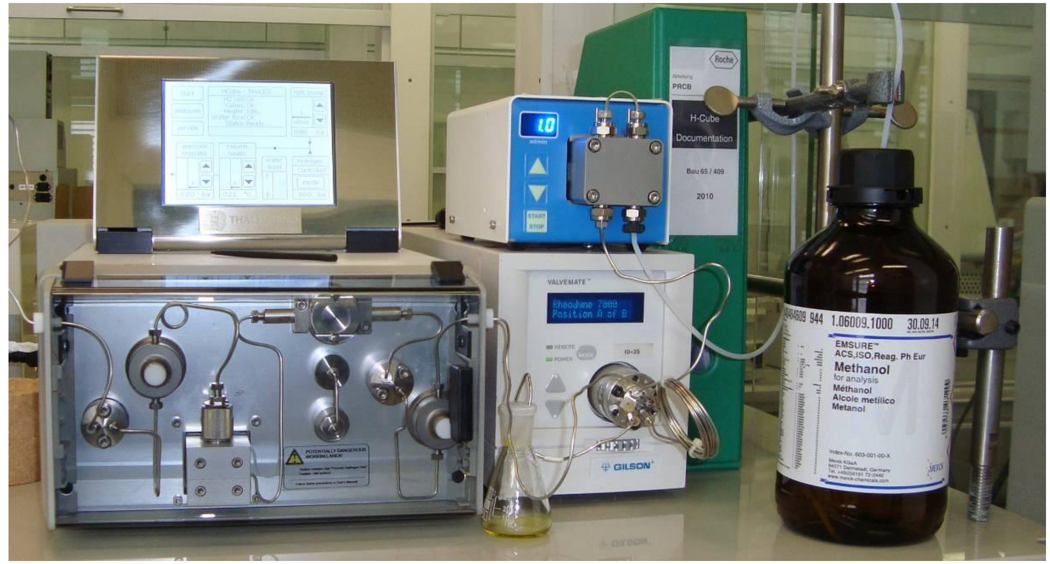
- High temp. coil up to 250°C / 50 bar
- UV detector for in-line analysis
- Fraction collector for automated multi-experiments

Supervised Open-Access: H-Cube™ from ThalesNano

A continuous-flow standalone hydrogenation reactor

H-Cube from ThalesNano

CatCart® Cartridges



http://www.thalesnano.com

Key features & advantages over conventional batch process

- In-situ generation of hydrogen and thus improved safety
- Faster optimization (variation of reaction parameters during operation; max 100°C and 100 bar; screening catalysts)
- Heterogeneous (no filtration required, CatCart) & homogeneous catalysis
- Deuterations with D_2O possible (via electrochemical D_2 generation)
- 1 System installed

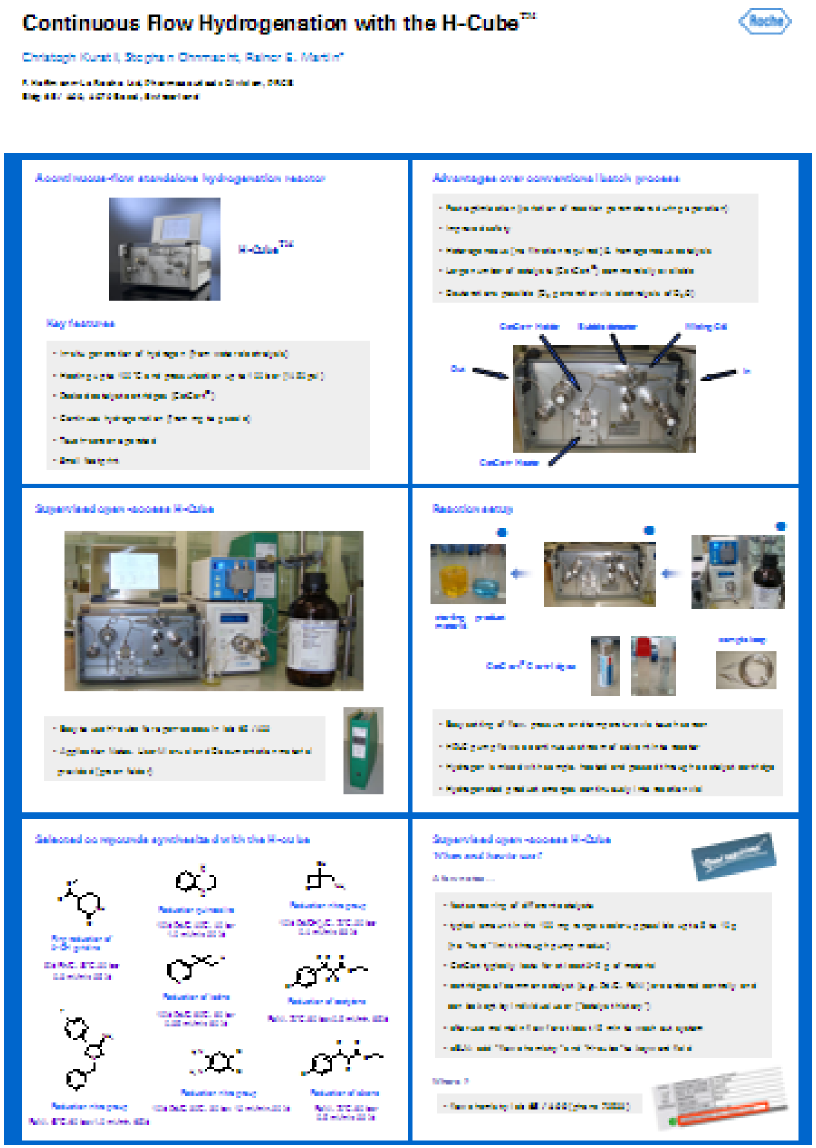
Supervised Open-Access: H-Cube™ from ThalesNano

A continuous-flow standalone hydrogenation reactor

Application Notes, User Manual, List of available Catalysts and Documentation provided

Continuous Flow Hydrogenation with the H-Cube™

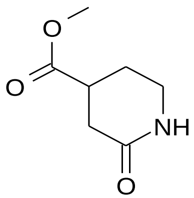
Instructional poster for supervised open access



• Selected Hydrogenation Examples

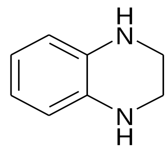
Transformations using the H-Cube

Various Compounds



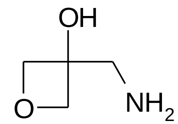
Ring reduction of
2-OH pyridine

5% Rh/C, 30°C, 20 bar
0.2 ml/min, 95 %



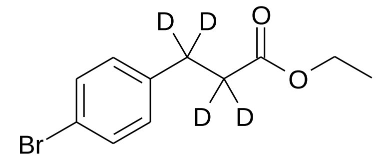
Reduction quinoxaline

10% Pd/C, 40°C, 40 bar
1.0 ml/min, 90 %



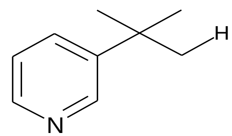
Reduction nitro group

10% $Pd/OH)_2/C$, 70°C, 90 bar
0.4 ml/min, 83 %



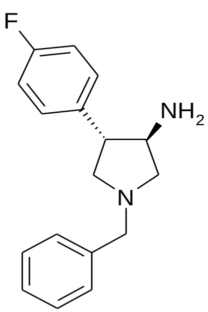
Reduction of acetylene

RaNi, 70°C, 80 bar, 0.5 ml/min, 85 %



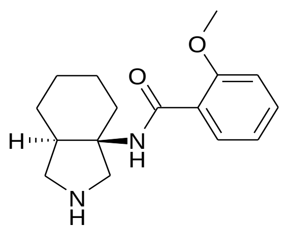
Reduction of iodine

10% Pd/C, 80°C, 80 bar
0.25 ml/min, 80 %



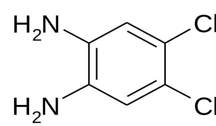
Reduction nitro group

RaNi, 60°C, 60 bar, 1.0 ml/min, 65 %



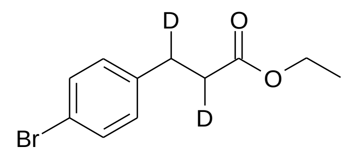
Removal benzyl group

10% Pd/C, 100°C, full H_2, 2.0 ml/min, 90 %



Reduction nitro group

10% Pd/C, 30°C, 30 bar, 1.0 ml/min, 90 %



Reduction of alkene

RaNi, 70°C, 80 bar
0.5 ml/min, 99 %

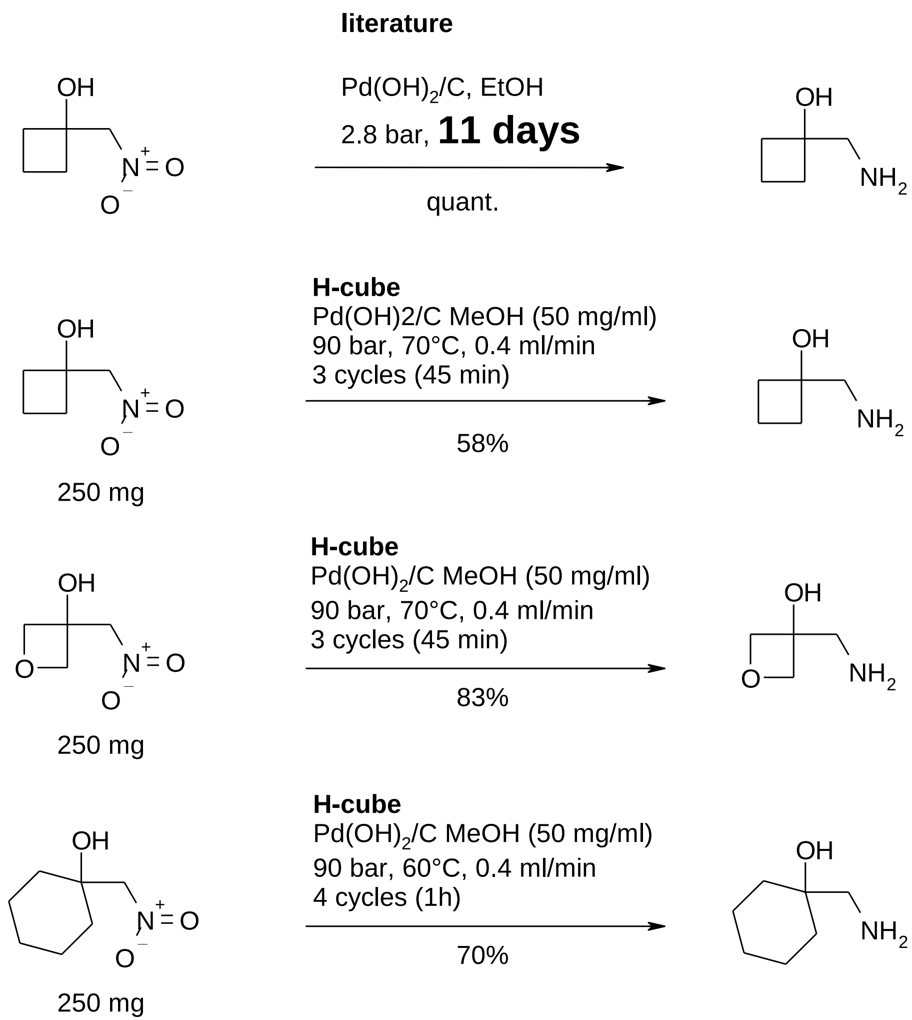
1 l D_2O = ca. 440.- USD

- H-Cube in "non-hydrogene" mode: reduction with formic acid using Pd/C cartridge as a catalyst ?
- Use of Pd catlyst cartridges for other reaction types possible (e.g., Suzuki, Buchwald,...)

Hydrogenations using the H-Cube

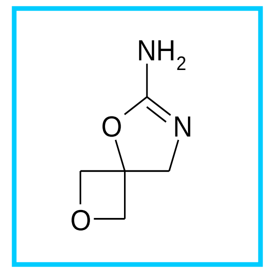
Support Project A

H-cube reduction: Slow NO_2 reduction speed-up



H-cube allows easy access to high pressure conditions for small amounts of material

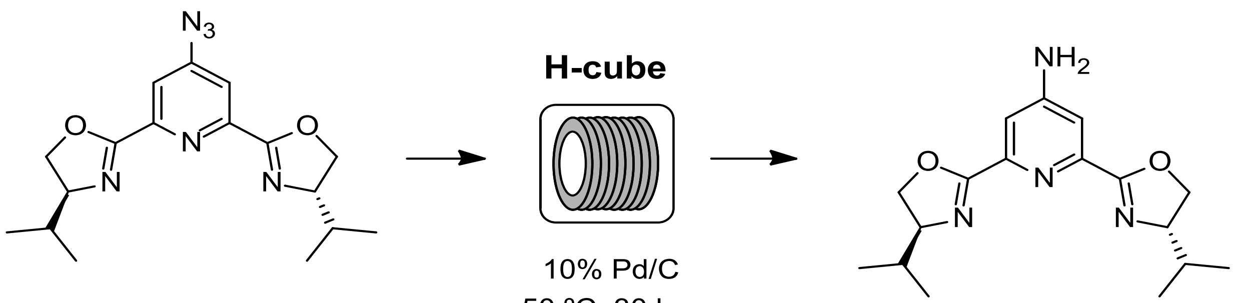
Building block:



Hydrogenations using the H-Cube

Support Project B

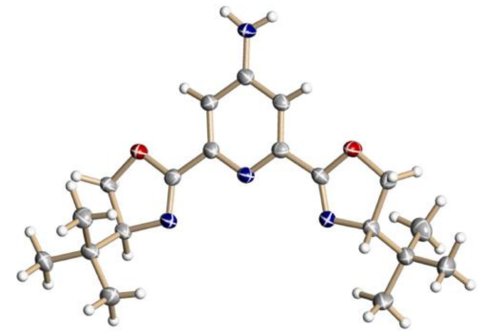
Azide Reduction with H-cube



10% Pd/C
50 °C, 30 bar
c = 0.01 M in MeOH
flow = 1.0 ml / min

precipitation from diethyl ether

white powder, yield: 62%



X-ray crystal structure

***tert*-butyl pybox ligand**

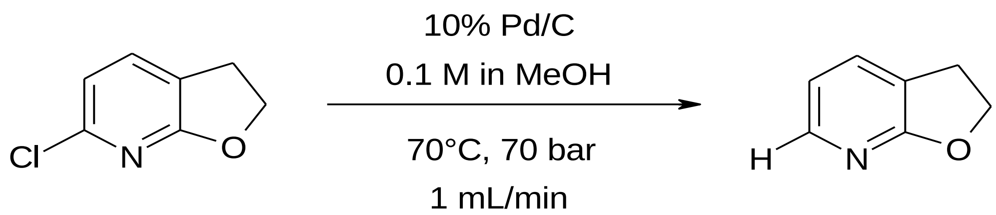
5.0 g isopropyl ligand prepared

- Two pybox ligands synthesized in flow (3 steps) in good yields (for immobilization on solid support)
- No chromatography required / telescoping of step 2 and 3 possible

Hydrogenations using the H-Cube

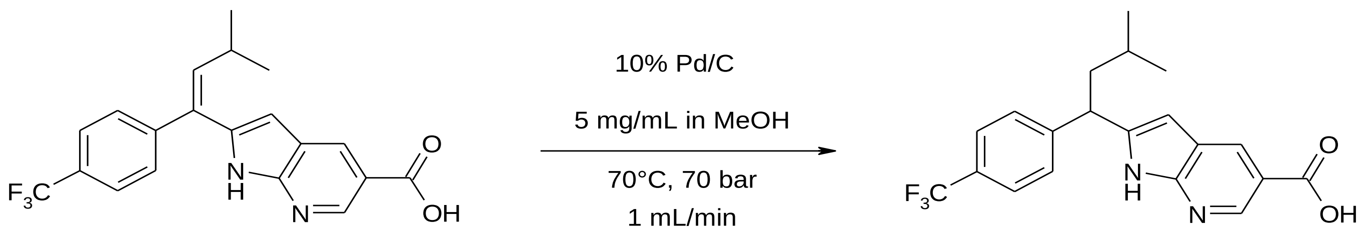
Support Project C

De-chlorination



Hydrogenations using the H-Cube

Support Project D (Nutley)

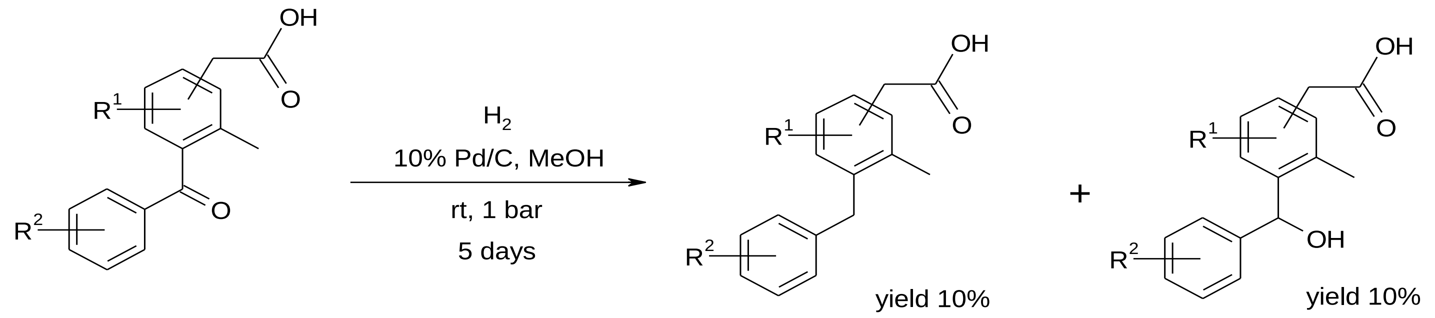


- Parr shaker failed to give desired reaction product

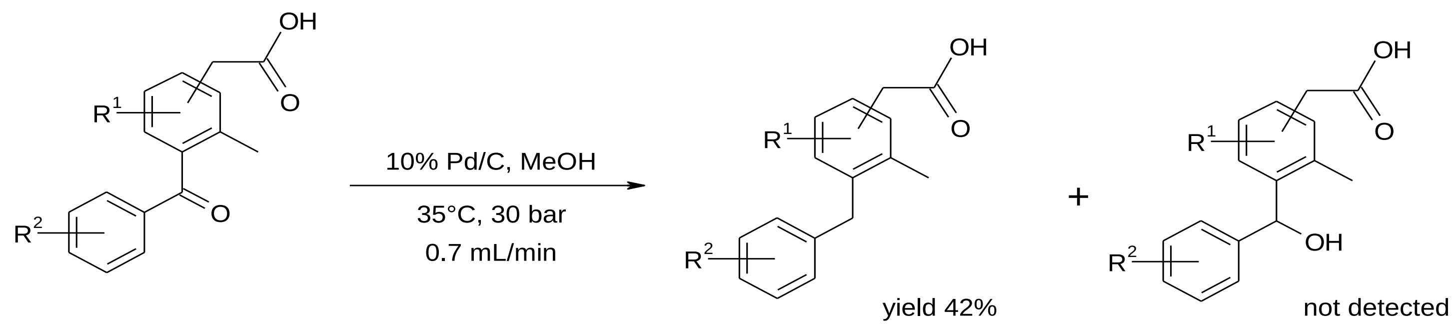
Hydrogenations using the H-Cube

Support Project E (Nutley)

batch



flow

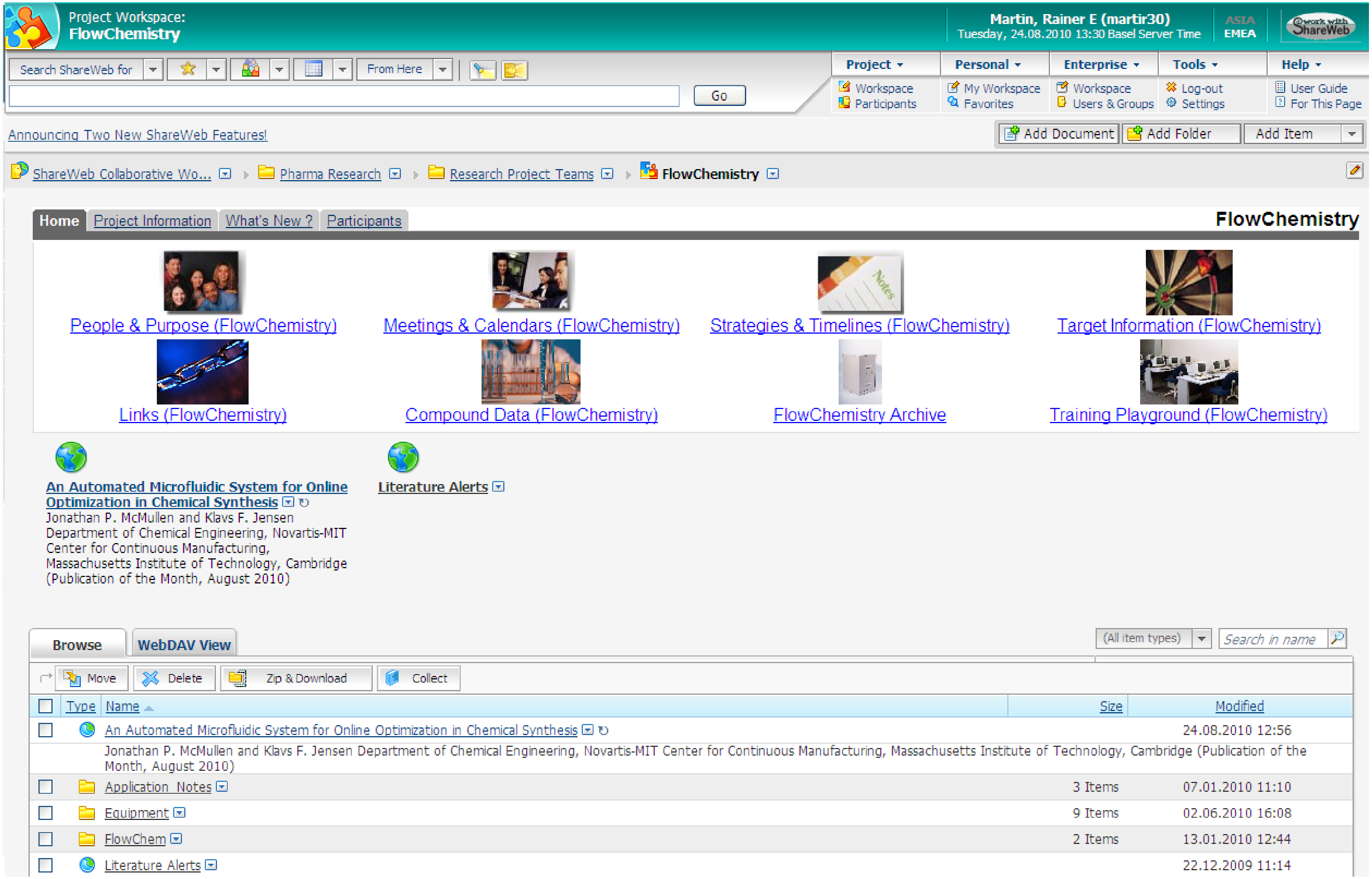


- batch process: mainly starting material remained after 5 days at atmospheric pressure
- Parr shaker failed to give desired reaction product as well

- Knowledge Sharing

Sharing Knowledge & Experience

Literature alert & share web



- Conclusions and Key Learnings

Conclusions and Key Learnings

- setup of dedicated flow chemistry lab
- H-cube run as supervised open access platform
- for new users short introduction mandatory
- 3 different loops for up-scaling available (0.5 ml, 5 ml, 10 ml)
- electronic lab journal: "**H-Cube**" and "**flow chemistry**" keywords used

- useful technology for rapid search of reaction conditions (catalyst, temperature, pressure, flow)
- suitable for processing of material up to 2-5 g
- telescoping time-consuming; upfront investment of time required to get process established
- FC not necessarily a first option for „standard chemistry“ that provides good results in batch

Flow Chemistry Basel

Acknowledgments

Contributors

Kin-Chun Luk (Nutley)

Christoph Kuratli

Stephan Ohnmacht (3 month)

Falk Morawitz (student)

Internal Partners

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Technical Support

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Sponsors

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René Wyler

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External Partners

Prof Steven Ley

Dr Ian Baxendale

ITC members

Microreactors do not provide new chemistry.

However, they open up the opportunity for better chemistry!

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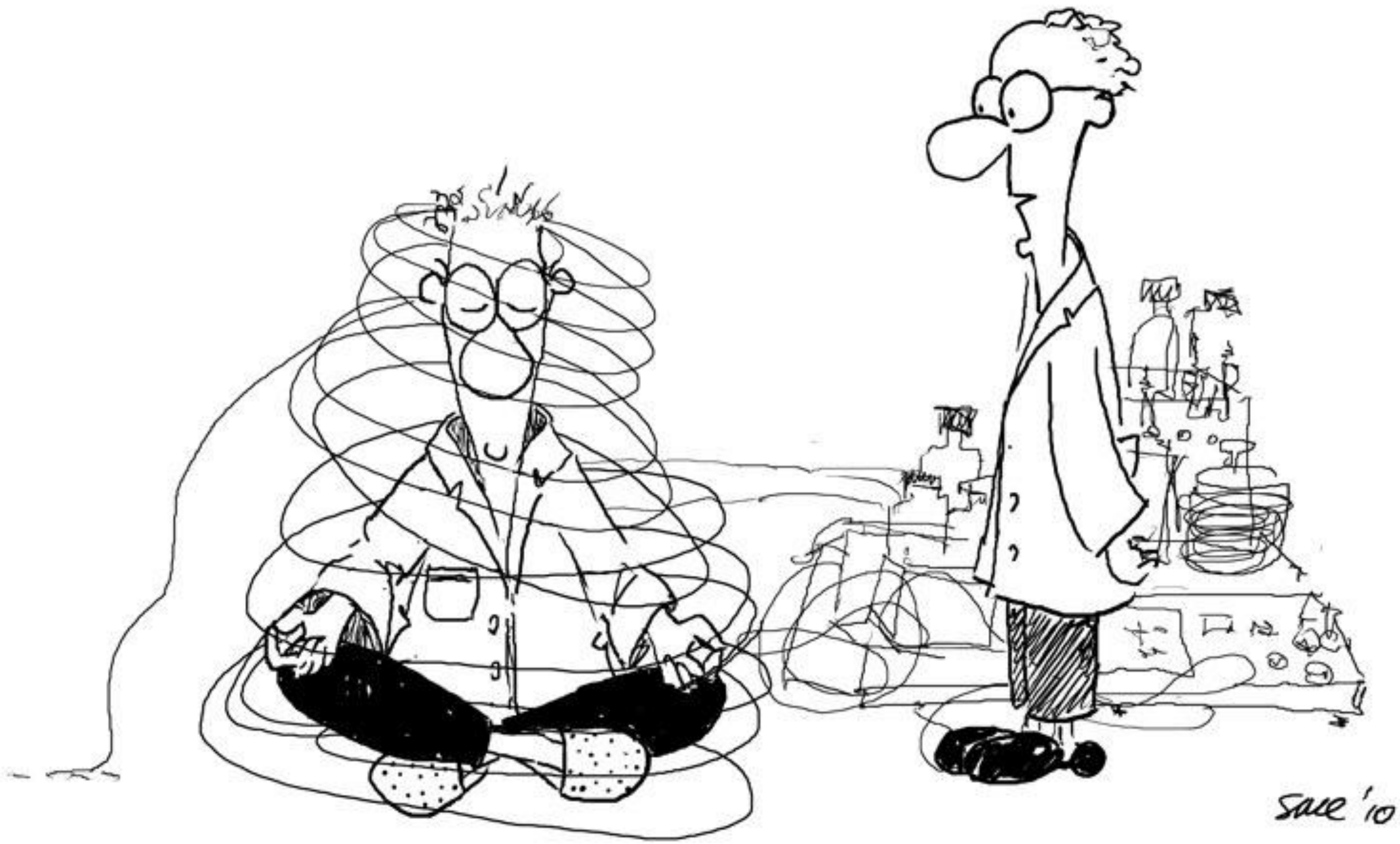

- SO ?.... CAN YOU FEEL THE FLOW ?.. -

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RoSearch
Chemie im Fluss
Stresshormonblockade
Biokatalyse
August 2010

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