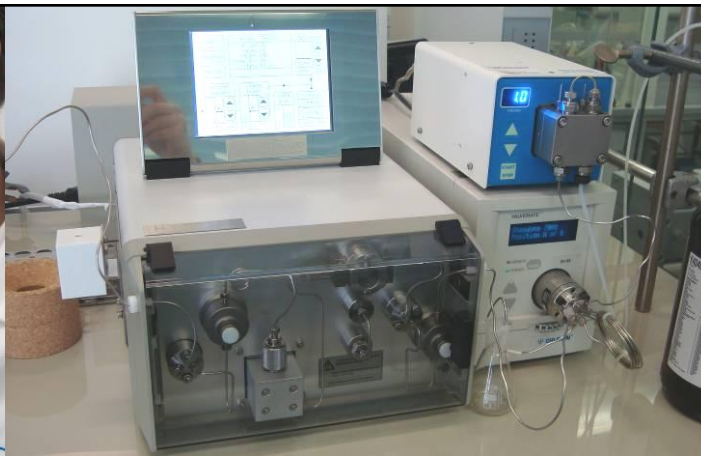


Continuous Flow Hydrogenation with the H-Cube at Roche Basel & Nutley

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):

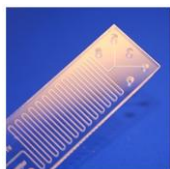
$$\frac{A_s}{V_s} = 225m^{-1}$$



meso reactor (cylindrical reactor)

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

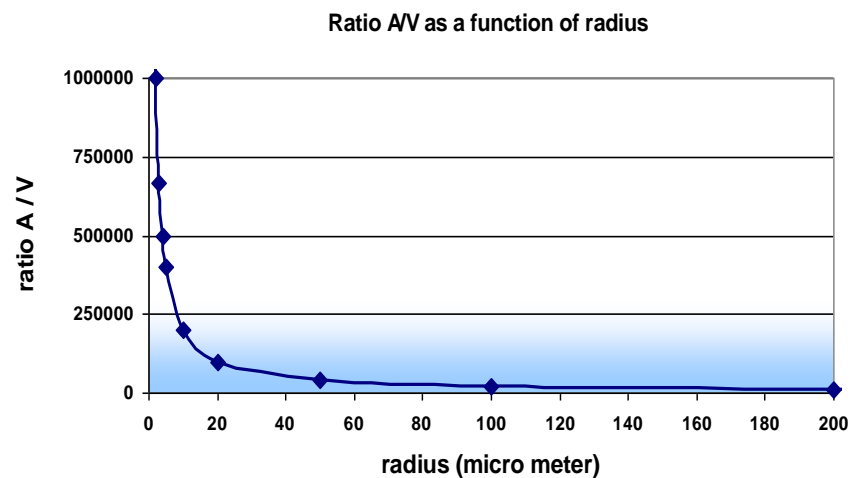
$$\frac{A_c}{V_c} = 4000m^{-1}$$



micro reactor (cylindrical reactor)

$r = 150$ μ m:

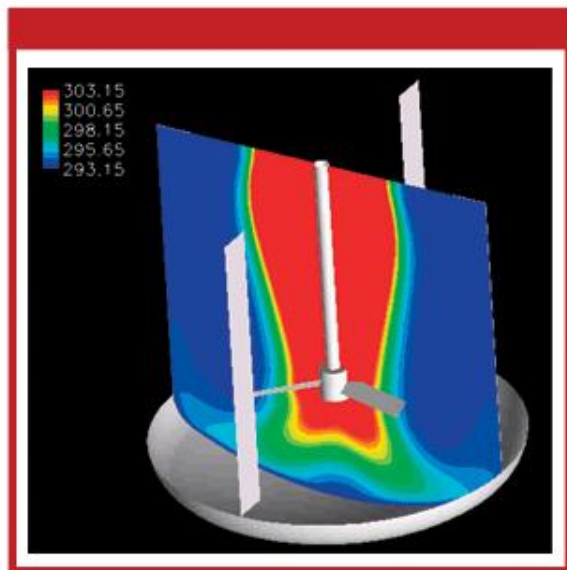
$$\frac{A_c}{V_c} = 13333m^{-1}$$



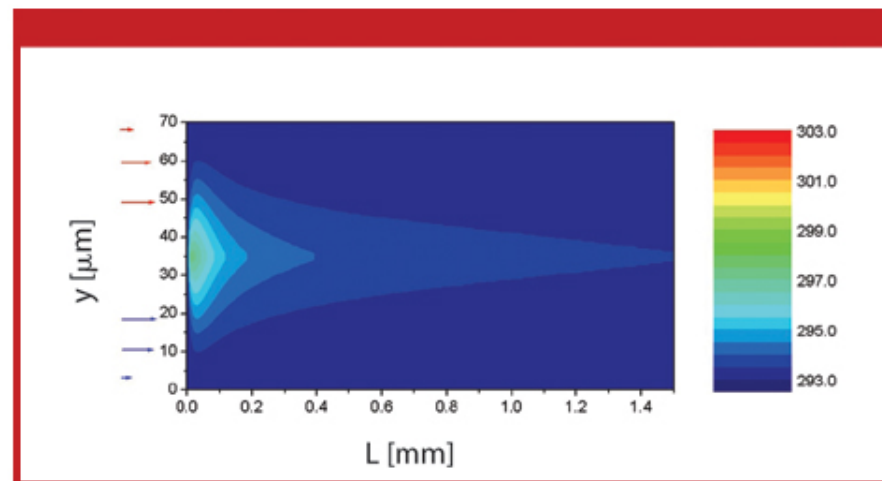
- Dramatic increase of surface-to-volume ratio from meso to micro reactors (and compared with batch)
- Superior capacity for heat and mass transfer
- Exact temperature control possible / avoidance of hot spots

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

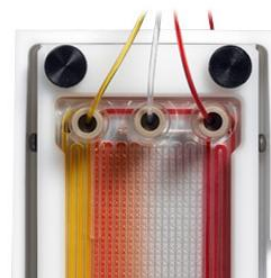
FlowSyn from



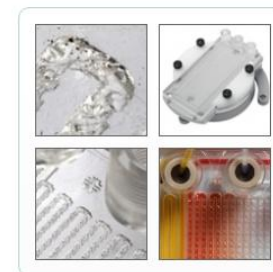
- Compact continuous flow reactor
- Reactions can be heated up to 260°C (Hastelloy reactor)
- Back pressure regulators of up to 70 bar (1000 psi) for superheating of solvents
- Easy to use interface
- 1 system installed



coil reactor



glass chip reactor



<http://www.uniqsis.com>

Flow Chemistry Equipment Basel

In-house working station



- Glass static mixer for turbulent mixing through 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



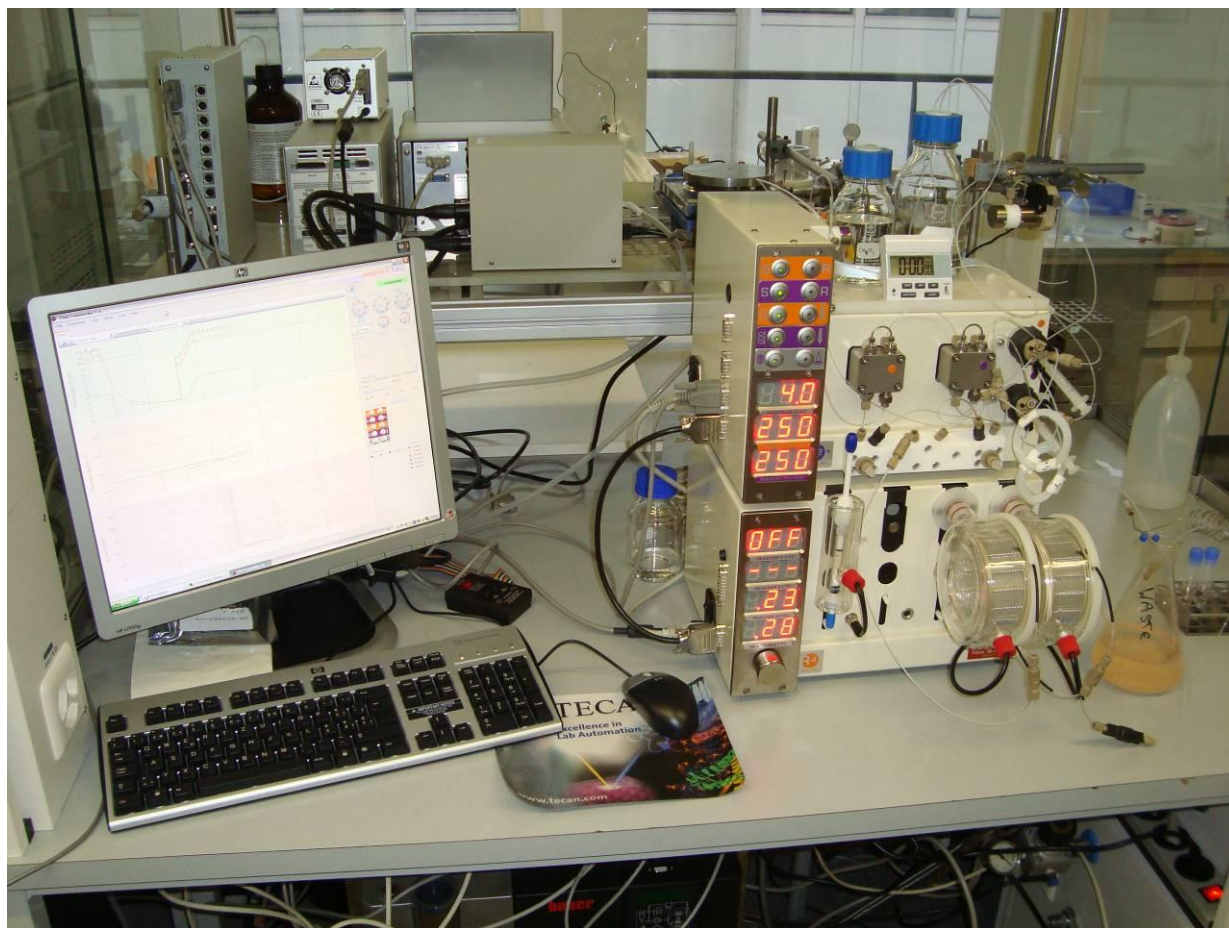
- Modular continuous flow reactor
- Temperature range from ambient to 250°C
- 4 Independently heated reactor zones (2 x up to 250°C)
- Easily expandable to realize more complex reaction scenarios
- 3 Systems installed (1 acid resistance)



<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

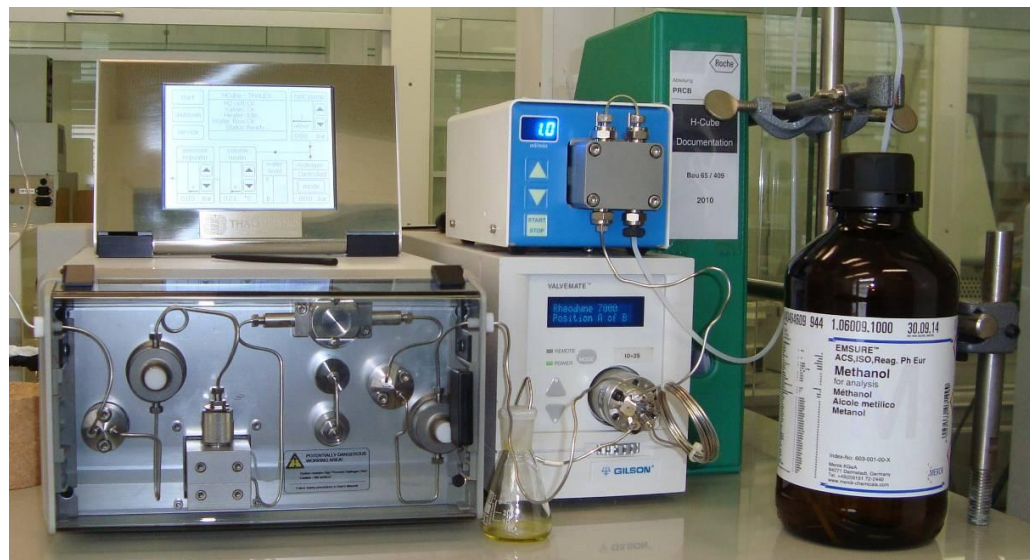
Supervised Open-Access: H-Cube™ from ThalesNano

A continuous-flow standalone hydrogenation reactor

H-Cube from



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 D₂O possible (via electrochemical D₂ 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

Continuous Flow Hydrogenation with the H-Cube™



Christoph Kurat, Stepha H. Ohmura H., Rainer S. Martin*

* Hoffmann-La Roche Ltd, Pharmaceutical Division, P400
 Flg 887 402, 4070 Basel, Switzerland

Advanced-flow standalone hydrogenation reactor



Key features

- In-line generation of hydrogen from molecular sieves
- Heating up to 100 °C and pressure up to 10 bar (10 MPa)
- Dedicated hydrogen gas (Co-Cat[®])
- Continuous hydrogenation (on-line or batch)
- Full automation possible
- Small footprint

Advantages over conventional batch process

- Reaction scale (in terms of reaction pressure and temperature)
- Improved safety
- High pressure (up to 10 bar) and high temperature (up to 100 °C)
- Large number of samples (Co-Cat[®]) can be easily installed
- Dedicated possible (Co-Cat[®]) generation for the synthesis of Co-Cat



Supervised open-access H-Cube



- Easy use thanks to the presence of the H-Cube
- Application Note: User Manual and Co-Cat generation manual provided (green book)

Reaction setup



- Easy setting of flow, pressure and temperature for each reaction
- H-Cube pump (flow and pressure) and Co-Cat inlet
- Hydrogen is mixed with reagent, heated and passed through a mixing coil
- Hydrogen gas is generated continuously from molecular sieves

Selected compounds synthesizable with the H-Cube

 Reduction of ketone Co-Cat, 100 bar, 100 °C, 10 min, 10 MPa	 Reduction of ketone Co-Cat, 100 bar, 100 °C, 10 min, 10 MPa	 Reduction of ketone Co-Cat, 100 bar, 100 °C, 10 min, 10 MPa
 Reduction of ketone Co-Cat, 100 bar, 100 °C, 10 min, 10 MPa	 Reduction of ketone Co-Cat, 100 bar, 100 °C, 10 min, 10 MPa	 Reduction of ketone Co-Cat, 100 bar, 100 °C, 10 min, 10 MPa

Supervised open-access H-Cube

How and how to use?

3. How to use ...

- Selection of all flow parameters
- Applied amount in the 100 mg range (depending on the reaction)
- Co-Cat typically used for an amount of 0.1 g of material
- Percentage of reagent (e.g., Co-Cat, NiCl₂·DME) can be varied directly and can be kept individual when (using H-Cube)
- After use, the reactor is flushed with 10 min of clean air system
- H-Cube can be used for the synthesis of the product

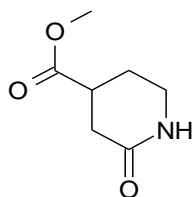
Where?

- Hoffmann-La Roche, Flg 887 402 (phone 7000)

-
- **Selected Hydrogenation Examples**
-

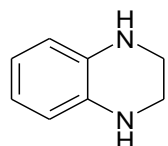
Transformations using the H-Cube

Various Compounds



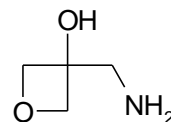
Ring reduction of
2-OH pyridine

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



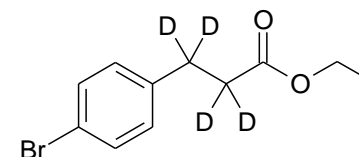
Reduction quinoxaline

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



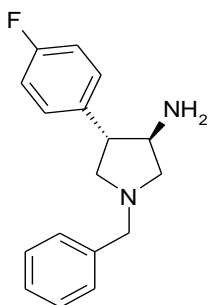
Reduction nitro group

10% Pd(OH)₂/C, 70°C, 90 bar
0.4 ml/min, 83 %



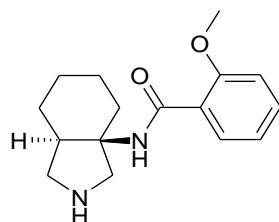
Reduction of acetylene

RaNi, 70°C, 80 bar, 0.5 ml/min, 85 %



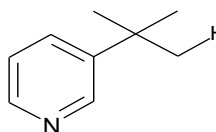
Reduction nitro group

RaNi, 60°C, 60 bar, 1.0 ml/min, 65 %



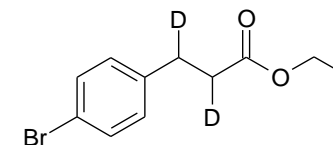
Removal benzyl group

10% Pd/C, 100°C, full H₂, 2.0 ml/min, 90 %



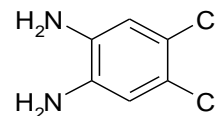
Reduction of iodine

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



Reduction of alkene

RaNi, 70°C, 80 bar
0.5 ml/min, 99 %



Reduction nitro group

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

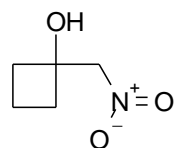
1 l D₂O = ca. 440.- USD

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

Hydrogenations using the H-Cube

Support Project A

H-cube reduction: Slow NO₂ reduction speed-up

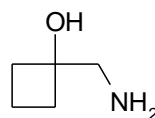


literature

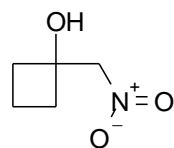
Pd(OH)₂/C, EtOH

2.8 bar, **11 days**

quant.



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



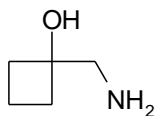
H-cube

Pd(OH)₂/C MeOH (50 mg/ml)

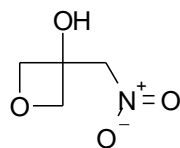
90 bar, 70°C, 0.4 ml/min

3 cycles (45 min)

58%



250 mg



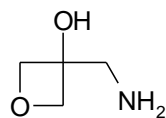
H-cube

Pd(OH)₂/C MeOH (50 mg/ml)

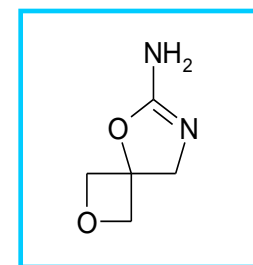
90 bar, 70°C, 0.4 ml/min

3 cycles (45 min)

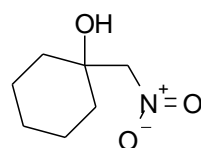
83%



Building block:



250 mg



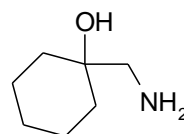
H-cube

Pd(OH)₂/C MeOH (50 mg/ml)

90 bar, 60°C, 0.4 ml/min

4 cycles (1h)

70%

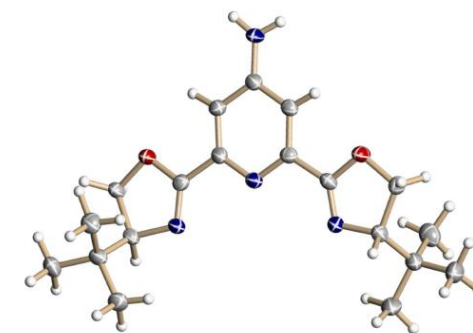
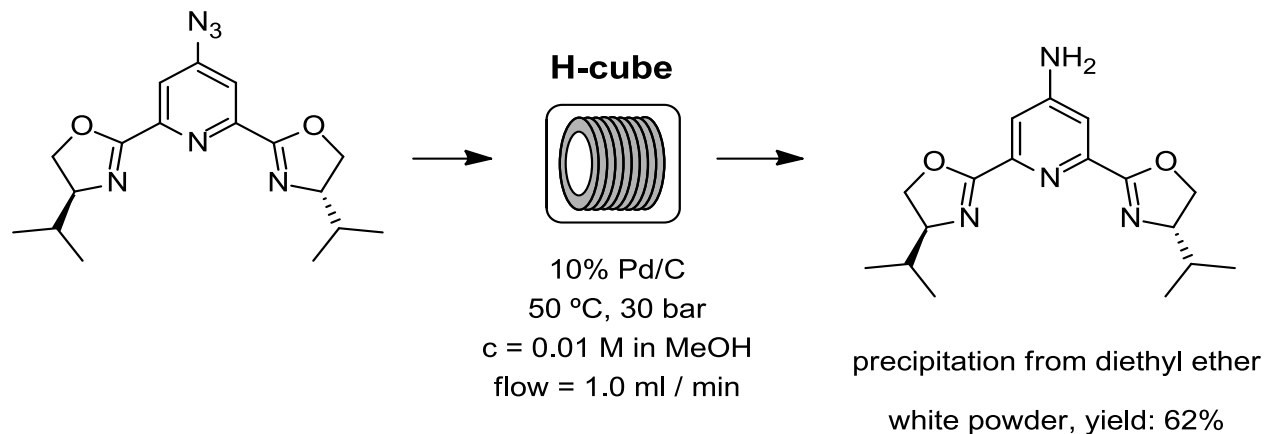


250 mg

Hydrogenations using the H-Cube

Support Project B

Azide Reduction with H-cube



**X-ray crystal structure
tert-butyl pybox ligand**



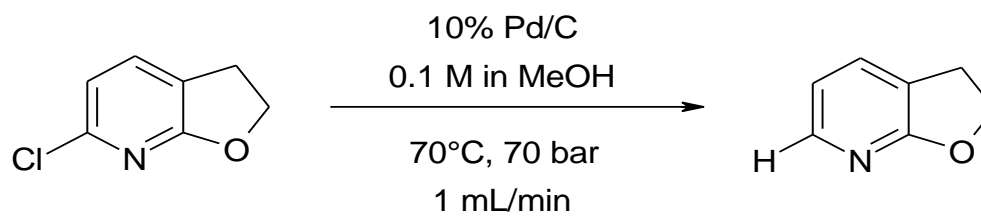
5.0 g isopropyl ligand prepared

- 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

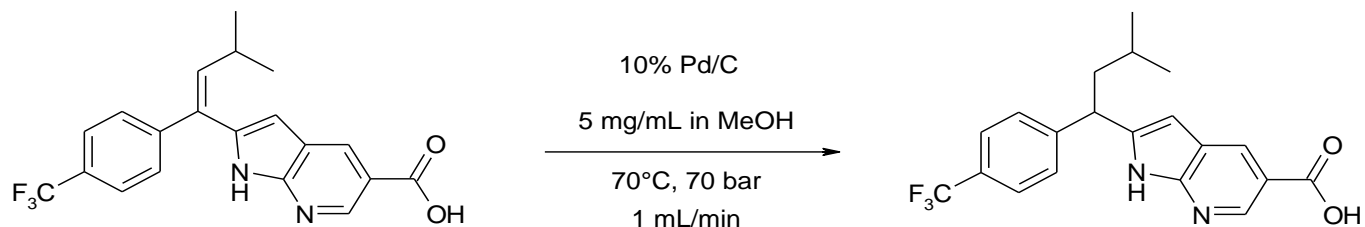
Support Project C

De-chlorination



Hydrogenations using the H-Cube

Support Project D (Nutley)

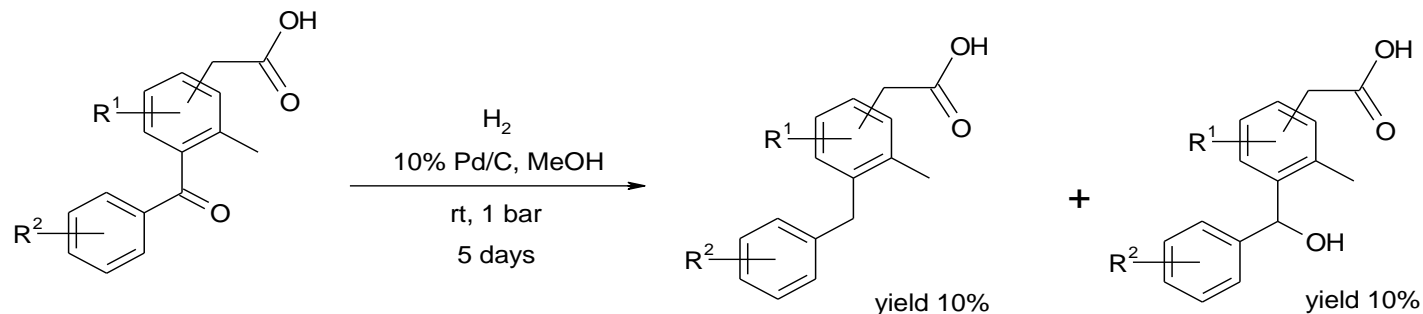


- Parr shaker failed to give desired reaction product

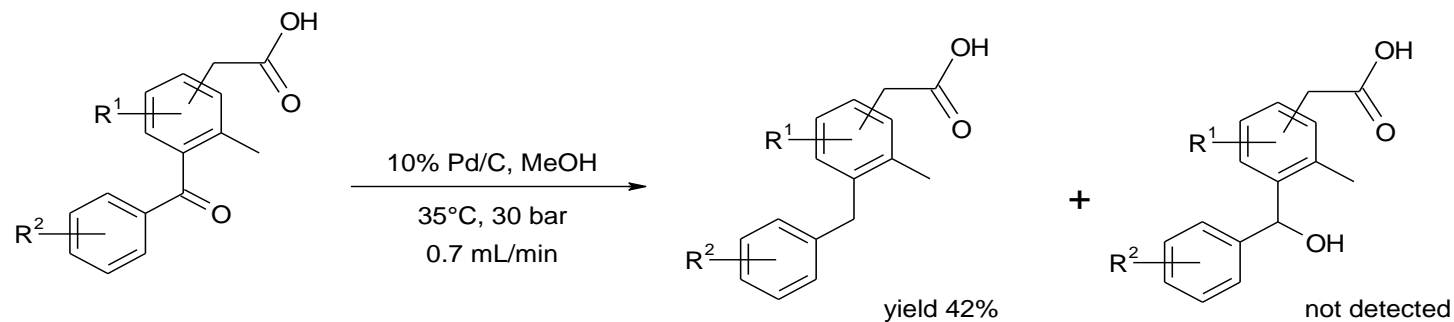
Hydrogenations using the H-Cube

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



Project Workspace:
FlowChemistry

Martin, Rainer E (martir30)
Tuesday, 24.08.2010 13:30 Basel Server Time

ASTA
EMEA

Search ShareWeb for

Project Personal Enterprise Tools Help

Announcing Two New ShareWeb Features!

ShareWeb Collaborative Wo... > Pharma Research > Research Project Teams > **FlowChemistry**

Home [Project Information](#) [What's New ?](#) [Participants](#)

FlowChemistry

[People & Purpose \(FlowChemistry\)](#) [Meetings & Calendars \(FlowChemistry\)](#) [Strategies & Timelines \(FlowChemistry\)](#) [Target Information \(FlowChemistry\)](#)

[Links \(FlowChemistry\)](#) [Compound Data \(FlowChemistry\)](#) [FlowChemistry Archive](#) [Training Playground \(FlowChemistry\)](#)

[An Automated Microfluidic System for Online Optimization in Chemical Synthesis](#)
Jonathan P. McMullen and Klavs F. Jensen
Department of Chemical Engineering, Novartis-MIT Center for Continuous Manufacturing, Massachusetts Institute of Technology, Cambridge (Publication of the Month, August 2010)

[Literature Alerts](#)

Browse (All item types)

<input type="checkbox"/>	Type	Name	Size	Modified
<input type="checkbox"/>	Document	An Automated Microfluidic System for Online Optimization in Chemical Synthesis Jonathan P. McMullen and Klavs F. Jensen Department of Chemical Engineering, Novartis-MIT Center for Continuous Manufacturing, Massachusetts Institute of Technology, Cambridge (Publication of the Month, August 2010)		24.08.2010 12:56
<input type="checkbox"/>	Folder	Application Notes	3 Items	07.01.2010 11:10
<input type="checkbox"/>	Folder	Equipment	9 Items	02.06.2010 16:08
<input type="checkbox"/>	Folder	FlowChem	2 Items	13.01.2010 12:44
<input type="checkbox"/>	Folder	Literature Alerts		22.12.2009 11:14

-
- **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

Matthias Nettekoven

Jean-Michel Adam

Technical Support

Daniel Zimmerli

David Wechsler

Sponsors

Alex Alanine

René Wyler

Torsten Hoffmann

Jochen Böhm

External Partners

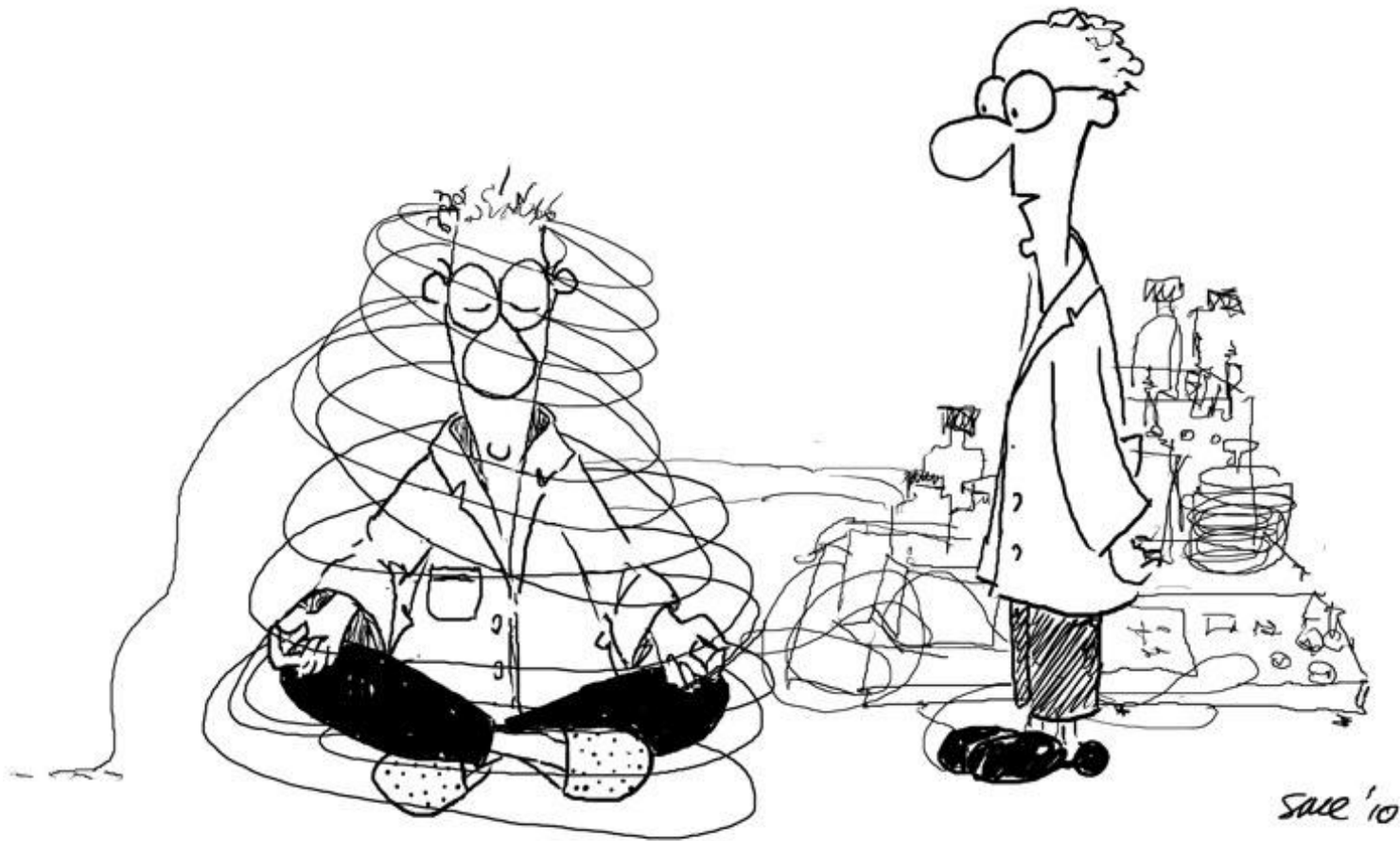
Prof Steven Ley

Dr Ian Baxendale

ITC members

Microreactors do not provide new chemistry.

However, they open up the opportunity for better chemistry!



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



RoSearch

Journal of Plasma Research and Early Development Basel (pRED)

Chemie im Fluss
Stresshormonblockade
Blökatalyse

August 2010



We Innovate Healthcare