

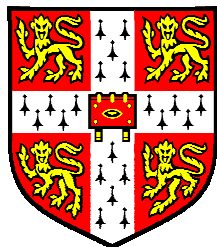


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Agenda and Introduction

Dr. Jason Tierney, Biofocus DPI

*ThalesNano 1st UK Flow Chemistry Seminar.
University of Cambridge. 17th February 2009.*



Housekeeping



ThalesNano 1st UK Seminar on Flow Chemistry

Venue : Unilever Lecture Theatre.

Speaker Programme

Morning Session Chair : Dr. Jason Tierney, Biofocus DPI.

- 10:00 AM Registration.

- 10:30 AM Opening remarks.
Dr. Jason Tierney, Biofocus DPI.

- 10:45 AM “Flow Chemistry – A ThalesNano perspective”
Mr. Richard Jones, Director of Product Development, ThalesNano ZRt.

- 11:15 AM “Experiences with H Cubes at Novartis, Horsham”
Mr. Andy Dunstan, Novartis, Horsham

- 11:30 AM “Continuous Flow Processing Utilizing High temperature/Pressure Conditions”
Guest speaker: Dr Toma Glasnov, Karl Franzens University, Graz, Austria.

- 12:00 AM Lunch (Buffet served in atrium outside Unilever theatre)



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Venue : Unilever Lecture Theatre.

Speaker Programme

Afternoon Session Chair : Dr. Robert Wheeler, GlaxoSmithKline, Stevenage.

- 12:30 PM “Overview of Catalyst Research for Scale-up Hydrogenation.”
Attila Wootsch. Ph.D., ThalesNano.
- 12:50 PM “H-Cube Automator, Do Flow and Automation Mix?”
Amanda Campbell. Ph.D., GlaxoSmithKline, Stevenage.
- 1:05 PM “High-Speed Reaction Optimisation using an Automated H-Cube.”
Mr. Gavin Bluck, Syngenta, Bracknell.
- 1:20 PM Any further questions / discussion.

Workshop Programme

Venue : Whiffen ITC Laboratory.

- 1.40 PM – 3.10 PM “Practical Demonstration / Questions – H-Cube, H-Cube Midi and X-Cube Flash.”
3 Groups of 30 Minutes.



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What is Flow Chemistry?

- Reactions take place in microchannels ranging in size from a few microns up to 1mm inner diameter - **Meso Flow Chemistry**.
- **Efficient mass transfer** (fast, controlled mixing).
- **Laminar flow** is observed which leads to **excellent reproducibility** compared to turbulent flow.
- **Efficient heat transfer** (accurate reaction temperature control) enabling exothermic and endothermic reactions to be conducted without issue.
- Reactions performed in such a small volume are intrinsically **safer** than traditional synthesis methods.
- Allows in-situ generation and use of hazardous reagents / intermediates.
- **Solvent superheating** - reaction temperature can be far above the solvent's boiling point boiling, due to ability to contain pressure leading to faster reactions (Cf Microwave chemistry).
- **Generation of new chemistries** and **access to new entities** not accessible by batch processes (eg Better selectivity and higher reaction yields)
- **Scalability** is achieved by simply pumping continuously the reagents.
 - Whole reaction mixture experiences the same set of conditions.
- Possible to couple work-up / purification / analysis in-line with flow chemistry reaction. Examples:
 - Supported scavenging / catch and release.
 - Liquid/Liquid Extraction.
 - Chromatographic separation.
 - LC-MS analysis – Potential for rapid reaction optimisation.



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Flow Chemistry - Factors To Consider

➤ **Reactors**

- Coils (PFA Tubing, Stainless Steel / Hastelloy – eg, 4ml, 8ml, 16ml volume).
- Omnifit Columns / CatCarts (eg Reagents / Scavengers)
- Possible to link reactors to increase reactor volume (Scaling up).

➤ **Temperature / Pressure**

- Higher temperatures and pressures now achievable (Cf – Microwave chemistry).
 - 200°C / 150bar (ThalesNano X-Cube) and 350°C / 200bar (ThalesNano X-Cube Flash).

➤ **Residence Time**

- The residence time of the reagents in the reactor (i.e. the amount of time that the reaction is heated or cooled) is calculated from the volume of the reactor and the flow rate through it.
- Residence time = Reactor Volume / Flow Rate.
- *Scaling-up – Maintain same Residence Time by increasing reactor volume and flow rate.*

➤ **Stoichiometry**

- Controlled by concentration and ratio of reagents mixed together.

➤ **Solubility / Solvents**

- Critical that reagents are soluble in reaction solvent.
- Large range of solvents compatible with flow chemistry (including DCM, MeCN, DMF, THF etc).
- Initially run reactions at 0.05M / 0.1M overall concentration.
- Immobilise catalysts / supported reagents (eg CatCarts).
- Possible to utilise or generate organically soluble salts (Eg Tetramethyl / tetraalkyl ammonium salts) to improve solubility of reagents.



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ITC – Innovative Technology Centre, University of Cambridge.

- Innovative Technology Centre for Advanced Chemical Synthesis.
- Prof. Steve V. Ley Group. Director: Dr. Ian Baxendale.
- Established in 2005.
- Concentrates expertise in advanced chemical synthesis tools and methodologies.
- Tasks:
 - Use polymer-supported reagents and polymer-supported scavengers in order to facilitate synthesis.
 - Transfer chemical reactions into flow.
 - Develop new polymer-supported reagents or polymeric reagents.
 - Develop new flow apparatuses in collaboration with chemical engineers.
- So far: 104 publications, covering both methodologies and natural product syntheses.
- Consult : <http://leyitc.ch.cam.ac.uk> for information, equipment, projects and ITC publications on flow chemistry.



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