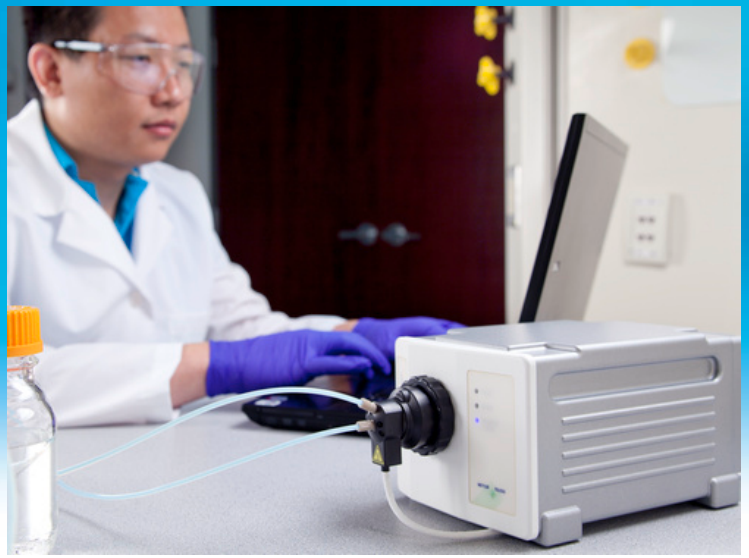
Enhanced Development and Control of Continuous Processes



METTLER TOLEDO

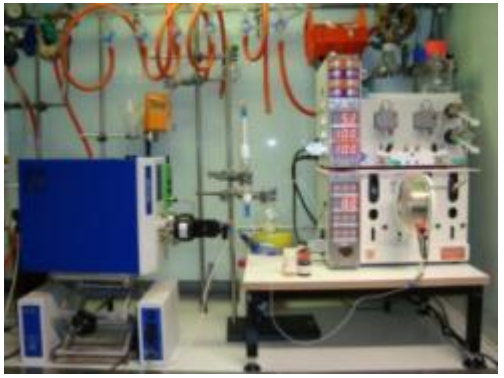
Agenda

Continuous Flow Chemistry - Analysis Challenges

- FlowIR™ for Continuous Flow Chemistry
- Application One - Oxazole Formation
- Application Two - Fluorination Reaction
- Application Three - Accurate Control of Reagent Addition in Multi-step Segmented Flow Processes Using Inline Infra-red Monitoring
- Summary

Continuous Chemistry - Analysis Challenges

One of the main analytical challenges is real-time inline monitoring for enhanced understanding and control of reactions, especially when dealing with multistep sequences



- Chemical
  - Information concerning reaction monitoring is highly desirable, as this normally requires taking a sample offline for TLC, LCMS, UV, etc.
  - Inline monitoring would greatly assist with rapid optimization procedures
- Chemical
  - Information concerning the stability of reactive intermediates is highly desirable, as these cannot always be detected by other methods
- Technical
  - Information concerning dispersion and diffusion is highly desirable as these are unavoidable side effects of continuous flow - very important to characterize these parameters for multistep reaction sequences

Photo courtesy of Professor Steven V. Ley

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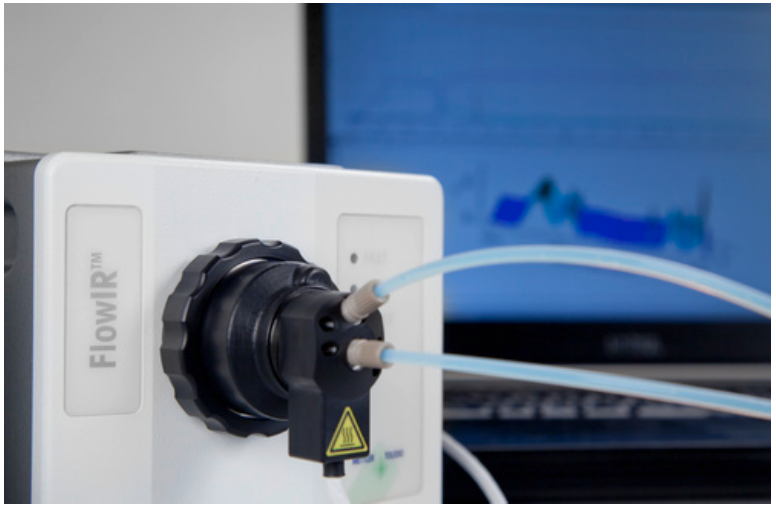
FlowIR™ for Flow Chemistry

FlowIR™

- Designed specifically for flow chemistry
- High performance with no utility requirement (except power)
- Universal (fits with any flow system)

- Determination of dispersion effects
  - Used for stoichiometric control
- Multi-step/stage reaction control
- Faster structural information in real time
- Immediate determination of steady-state conditions
- Immediate detection of reaction start/end point
- Information on reaction mechanism/pathway
- Detection of transient intermediates
- Information without the need to sample



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- Continuous Flow Chemistry - Analysis Challenges
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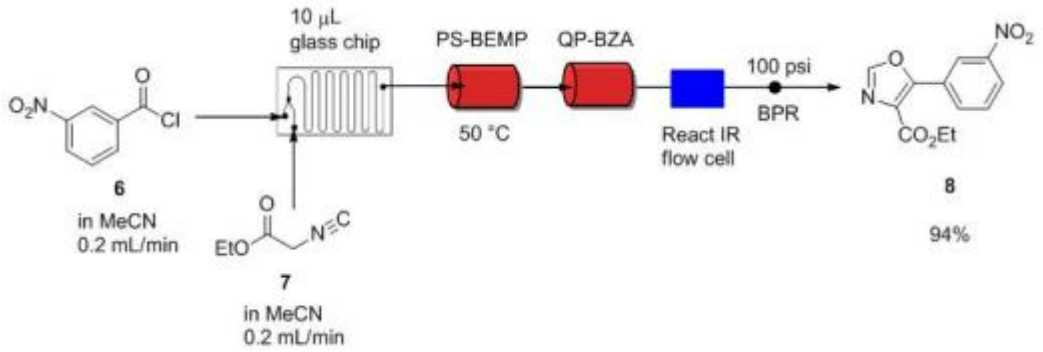
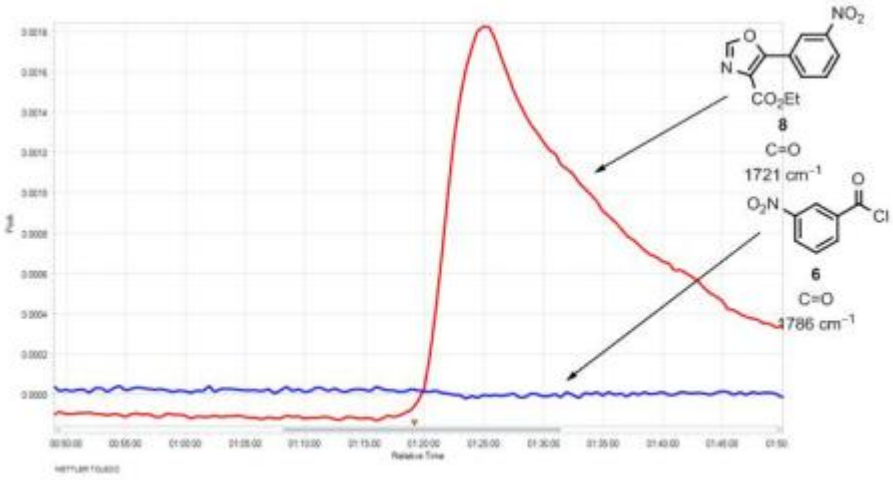
Oxazole Formation

Monitoring a continuous oxazole formation within a microfluidic device (10µL)



- Oxazole formation is monitored by following its unique carbonyl absorbance at 1721cm^{-1}
- Benzylamine column shown to be an effective scavenger of excess acid chloride (used to drive reaction to completion)
- Dispersion effect caused by columns clearly shown in product trend curve



Baumann, M.; Baxendale, I. R.; Ley, S. V.; Smith, C. D.; Tranmer, G. K. *Org. Lett.* **2006**, *8*, 5231-5234.
C.F. Carter, H. Lange, I.P. Baxendale, S.V. Ley, J. Goode, N. Gaunt, B. Wittkamp, Org. Proc. Res. Dev., 2010, 14, 393-404.

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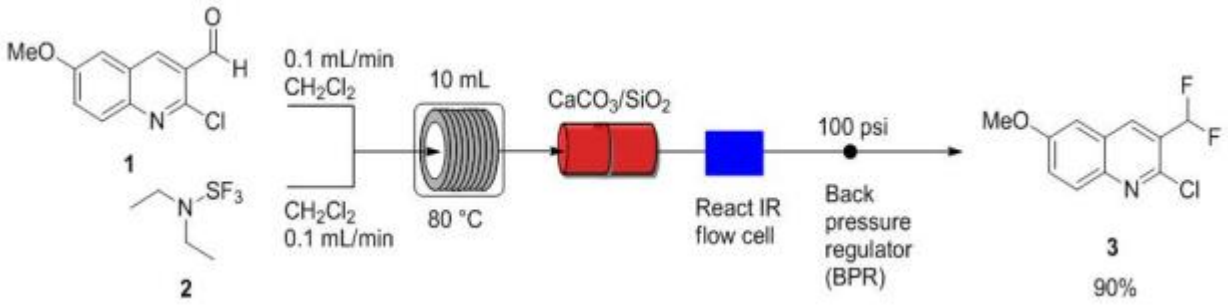
Fluorination Reaction Using DAST

Experimental setup



$CaCO_3$ and SiO_2 column provides an inline quench and cleanup

Vapourtec R2+/R4 system

ReactIR™ 45m

Convection Flow Coil (CFC) reactor

DS Micro Flow cell

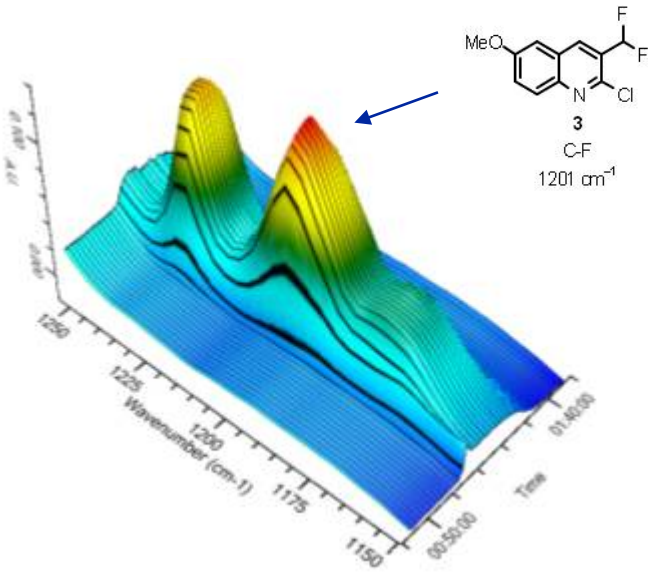
Reaction output

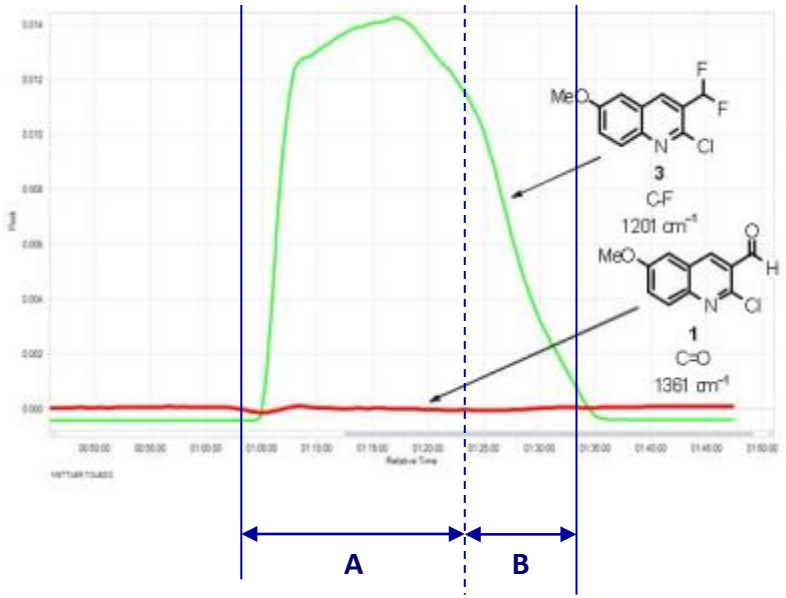
Baumann, M.; Baxendale, I. R.; Martin, L. J.; Ley, S. V. *Tetrahedron* **2009**, *65*, 6611–6625

Baumann, M.; Baxendale, I. R.; Ley, S. V. *Synlett* **2008**, 2111–2114.

Fluorination Reaction

Dispersion effects are clearly monitored





- Expected time for product to come out of the reaction line: 20 mins (**A**), [4mL total volume at 0.2mL/min = 20 mins]
- Actual 36 mins (**A+B**)
- Additional time **B** is required due to dispersion, diffusion and chromatographic effects caused by polymer-supported reagents

C.F. Carter, H. Lange, I.P. Baxendale, S.V. Ley, J. Goode, N. Gaunt, B. Wittkamp, Org. Proc. Res. Dev., 2010, 14, 393-404.

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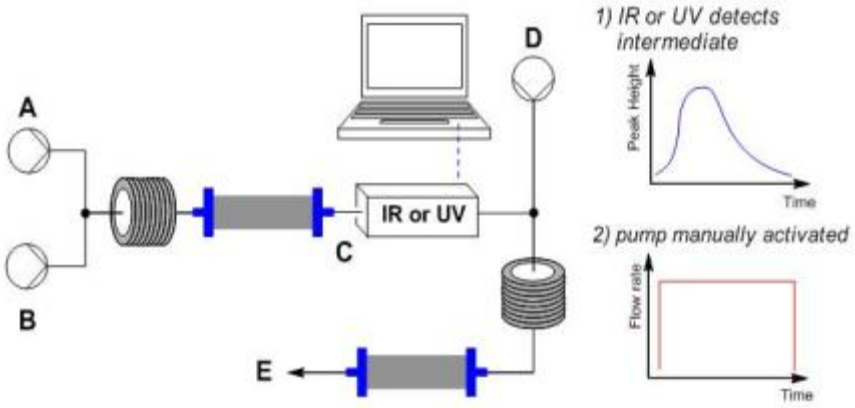
Accurate Control of Reagent Addition in a Multi-step Process

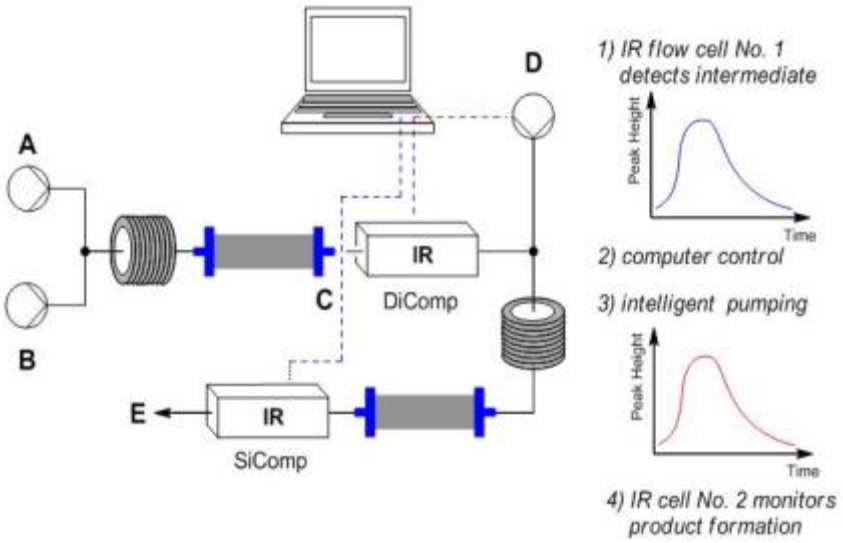
- The unavoidable dispersion of the reaction “plug” is a significant issue when performing multi-step sequences in flow
- The controlled addition of exact stoichiometries of reagents to a product stream is therefore challenging with the current commercially available flow equipment
- Poor control is wasteful on small scale (chiral/expensive/toxic material used in excess) and requires additional purification.



- Current situation - use the IR to generate a dispersion curve of the intermediate and manually switch the pump on

Accurate Control of Reagent Addition in a Multi-step Process

- Alternative: use real-time concentration of a product specific band from the ReactIR™ and convert it into a flow rate that allows the third stream to be dispensed proportional to the concentration of the intermediate via LabVIEW



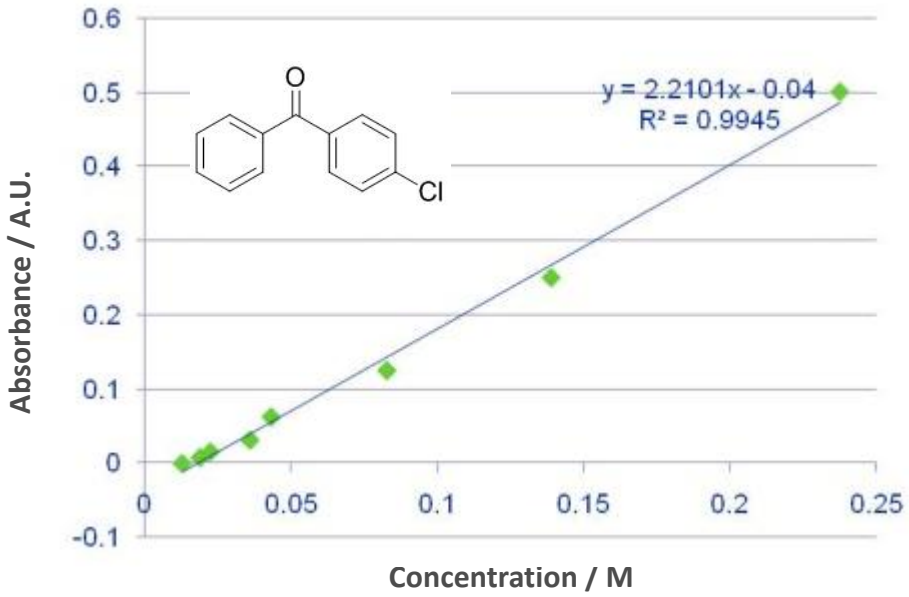
H. Lange, C. F. Carter, M. D. Hopkin, A. Burke, J. G. Goode, I. R. Baxendale and S. V. Ley, *Chem Sci, 2011, 2, 765-769*

Can We Add a Third Stream with Accurate 1:1 Stoichiometry?

X = stoichiometry between the two components
F = flow rate of output process
[D] = conc of third stream component
A = peak height value measured by IR
k = conversion factor

$$\text{Flow rate of third stream} = \frac{XFk}{[D]} \cdot A$$

- K determined from a concentration screen of the intermediate
- Test system: two inert compounds (4-chlorobenzophenone & 3-methyl-4-nitroanisole)



FR = ((1× 0.25 × 2210)/0.0833) × A
= 6630 × A

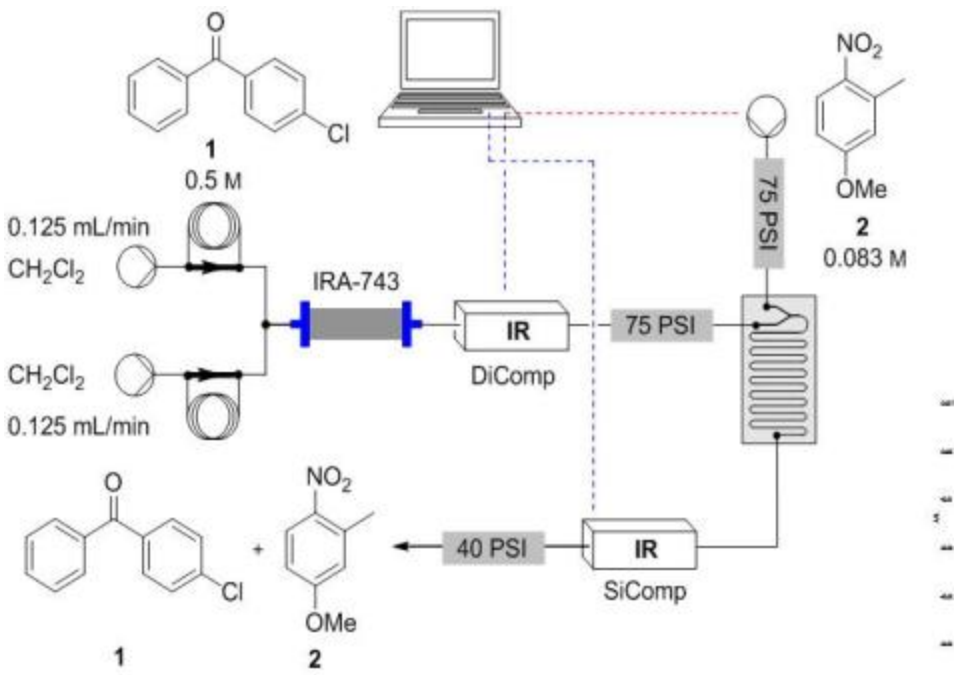
Therefore labview will multiply the live peak height value of 4-chlorobenzophenone by 6630 to generate a concentration dependent flow rate in μL/min

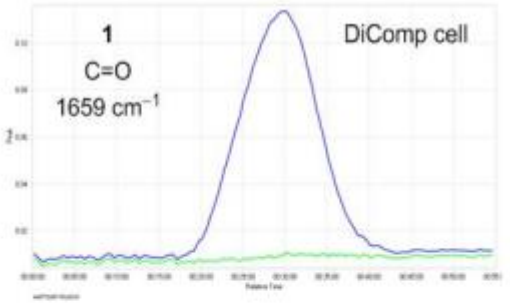
H. Lange, C. F. Carter, M. D. Hopkin, A. Burke, J. G. Goode, I. R. Baxendale and S. V. Ley, *Chem Sci, 2011, 2, 765-769*

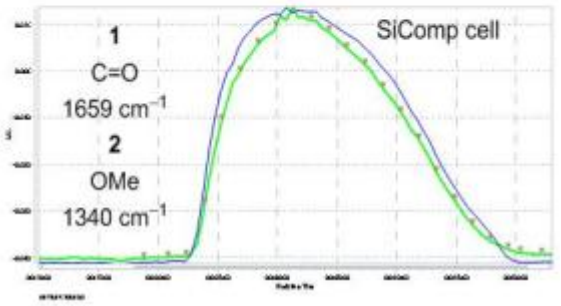
Can We Add a Third Stream with Accurate 1:1 Stoichiometry?

4-chlorobenzophenone

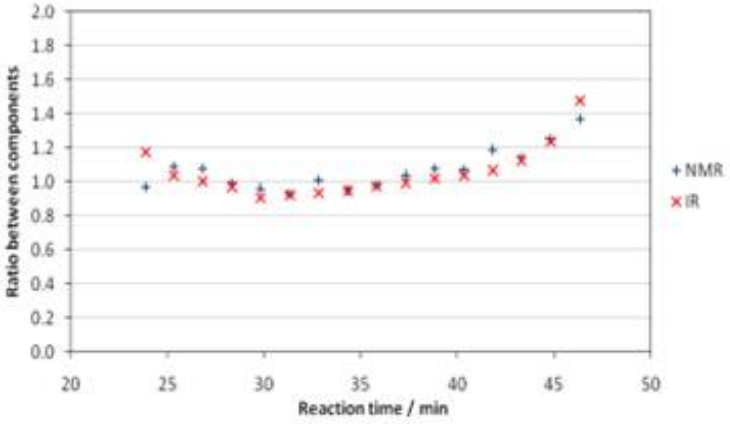
3-methyl-4-nitroanisole





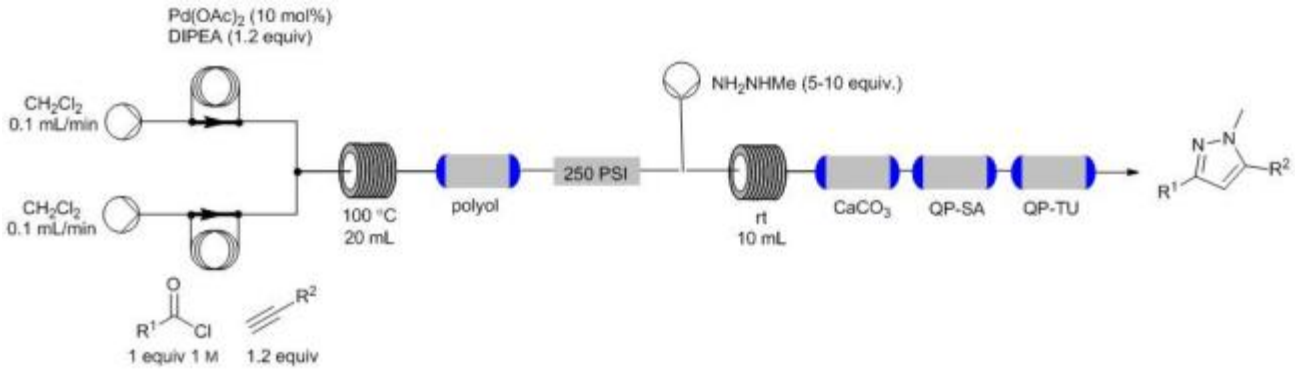


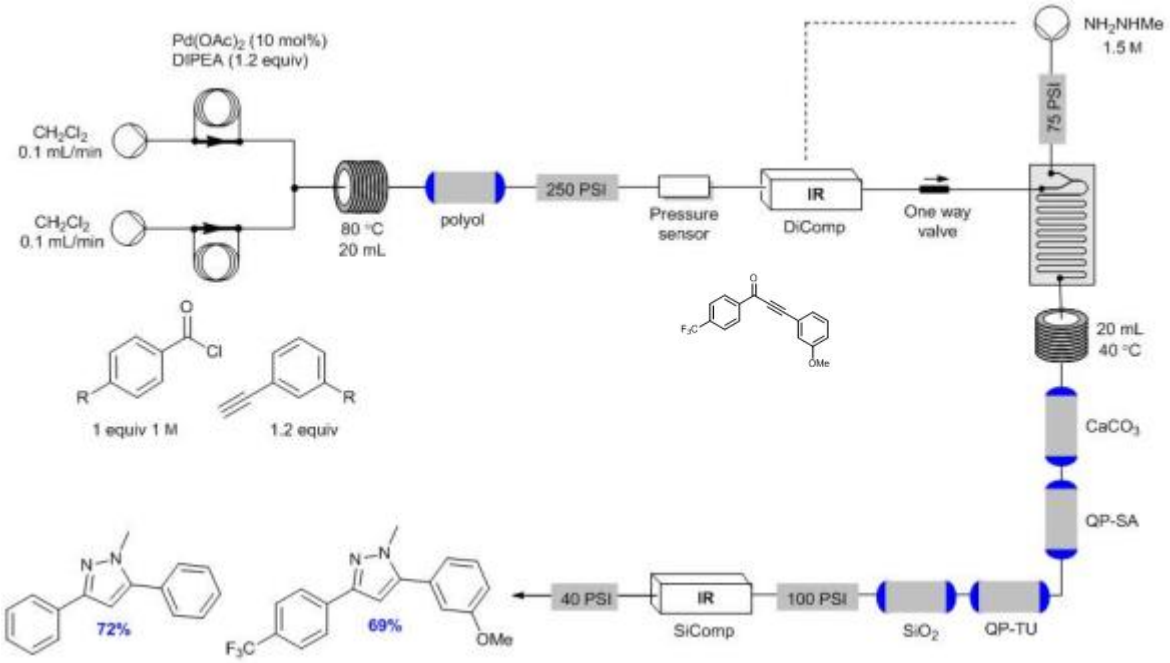
- Third stream successfully added with 1:1 stoichiometry for >97% of the material
- Limitation at the ends of the dispersion curves arises from inaccuracy of piston pumps at very low flow rates
- Absolute ratios determined using 1H NMR spectroscopy to confirm results



H. Lange, C. F. Carter, M. D. Hopkin, A. Burke, J. G. Goode, I. R. Baxendale and S. V. Ley, *Chem Sci, 2011, 2, 765-769*

Application to yne-one Project





No IR control

- 10 equiv toxic hydrazine used
- Visual observation used to manually switch the third pump
- Extensive purification required

With IR control

- Amount of toxic hydrazine pumped reduced to 3 equiv.
- Reduced reaction temperature to avoid polymerisation of terminal acetylene
- Plug of silica gel allows chromatographic separation with IR detection
- Crystalline material obtained from both processes

Application to yne-one project

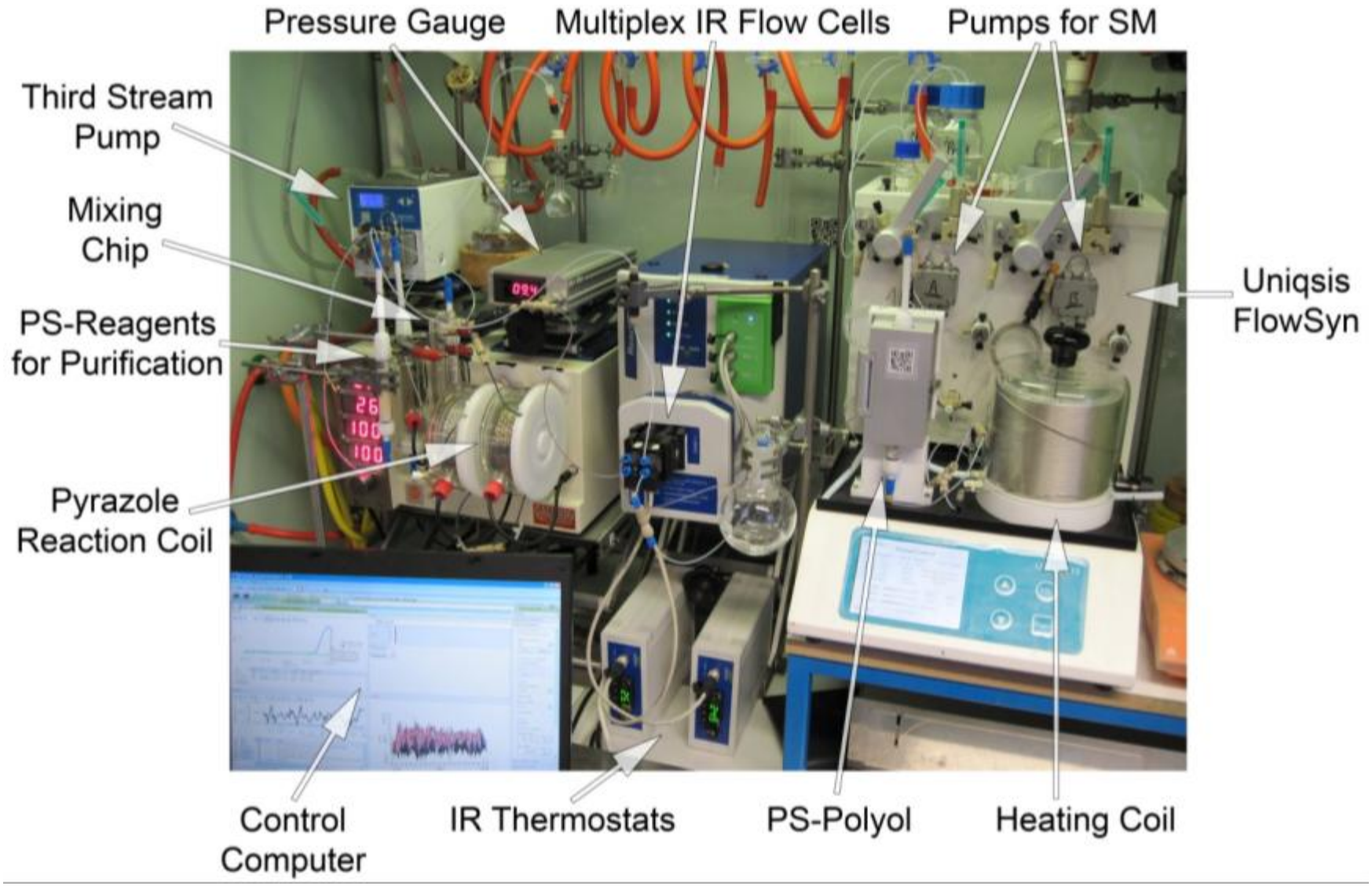


Photo courtesy of Professor Steven V. Ley

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Summary

Summary

- ReactIR™ DS Micro Flow Cell (FlowIR™) has been shown to instantaneously obtain highly molecular-specific chemical information. This can provide a unique insight into continuous flow chemistry

- The case studies demonstrate that FlowIR™ can be used with a range of different scale flow reactors:
  - Microscale - 10μL (Future Chemistry)
  - Meso scale flow reactors (Uniqsis, Vapourtec)
  - Large kilo lab flow reactors (Alfa Laval)

- The ability to track dispersion curves now makes it feasible to accurately apply a third stream via a feedback controlled flow that exactly matches the required amount of reagent to the output of the first flow reactor. This leads to improved product yield and reduced purification steps.