

Chemical Synthesis and Efficient Scale-Up in Flow Reactors

Paul Watts

^aDepartment of Chemistry, The University of Hull, Hull, HU6 7RX.

^bChemtrix BV, Burgemeester Lemmensstraat 358, Geleen, The Netherlands.

RSC Speciality Chemicals Symposium 2011: Continuous Flow Technology
Geneva, 15-16 June 2011



CHEMTRIX

Visit Chemtrix at booth FC8 in the Flow Chemistry Pavilion

Benefits of Micro Reactor Technology

- Increased reaction control
 - Efficient mixing
 - Accurate control of reaction time, temperature and pressure
 - Improved atom efficiency, product selectivity, yield and purity
 - Increased run-to-run and reactor-to-reactor reproducibility
 - Increased catalyst turnover and lifetimes

Benefits of Micro Reactor Technology

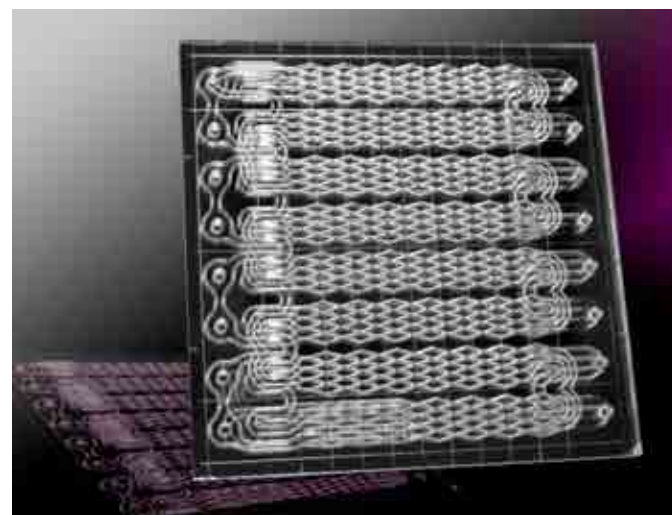
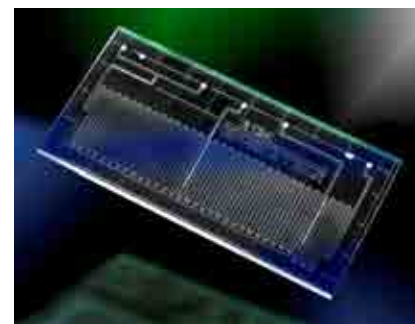
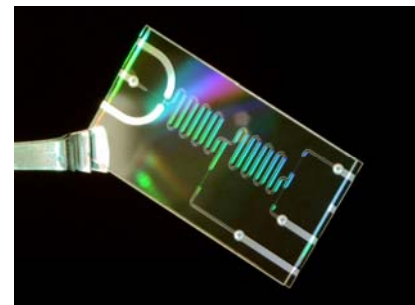
- Increased reaction control
 - Efficient mixing
 - Accurate control of reaction time, temperature and pressure
 - Improved atom efficiency, product selectivity, yield and purity
 - Increased run-to-run and reactor-to-reactor reproducibility
 - Increased catalyst turnover and lifetimes
- Increased process safety
 - Due to rapid dissipation of heat of reaction
 - Low reactant hold-up
 - Real-time *in-situ* analytical evaluation of reactions

Benefits of Micro Reactor Technology

- Increased reaction control
 - Efficient mixing
 - Accurate control of reaction time, temperature and pressure
 - Improved atom efficiency, product selectivity, yield and purity
 - Increased run-to-run and reactor-to-reactor reproducibility
 - Increased catalyst turnover and lifetimes
- Increased process safety
 - Due to rapid dissipation of heat of reaction
 - Low reactant hold-up
 - Real-time *in-situ* analytical evaluation of reactions
- Lower cost and shorter development cycles
 - Higher chemical selectivity leading to higher yield
 - Reducing the amount of reagents and catalyst
 - Reducing the size of the plant
 - Faster scale-up from lab to plant scale

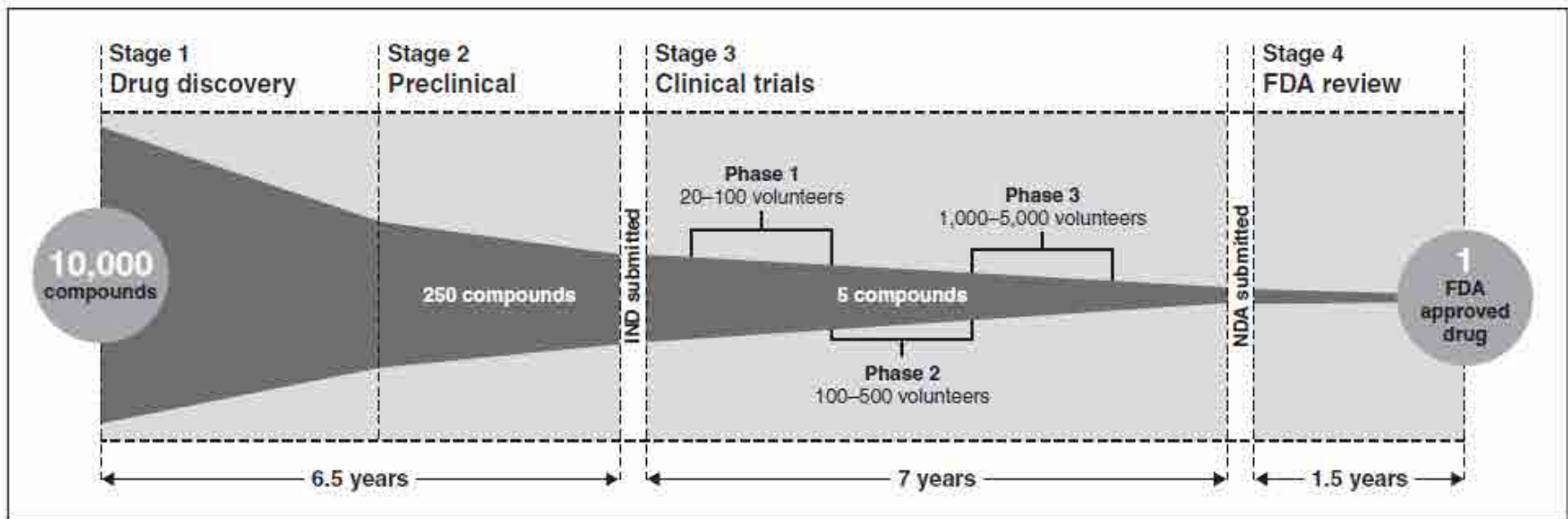
Better definition of a 'Micro' Reactor

- 'Micro' reactors
 - Defined as a series of interconnecting channels formed in a planar surface
 - Channel dimensions of 10-300 μm
 - Very small dimensions result in very fast diffusive mixing
 - Rapid heat transfer
 - High throughput experimentation
- 'Flow' (or meso) reactors
 - Dimensions $> 300 \mu\text{m}$ (up to 5 mm)
 - Mixing much slower
 - Incorporate mixers
 - Throughput higher
- Reactors fabricated from polymers, metals, quartz, silicon or glass
- Why glass?
 - Mechanically strong
 - Chemically resistant
 - Optically transparent



Where is MRT being used?

- Industry generally introduces MRT where safety is a major concern
 - Xian Chemicals (China) - 30 tonne/annum nitroglycerine manufacture
 - DSM - Ritter reaction (1700 tonnes manufactured to date)
 - DSM - Nitration to form Naproxen intermediate (190 tonnes conc. HNO₃ in 7 weeks)
- Case studies published showing financial savings of using MRT in production
- Drug discovery



Continuous Flow Concept: Facile Up-Scaling

- Rapid scale-up is a '*strategic competitive advantage*'
 - Process chemists require methodology that increases reactor throughput without lengthy re-optimisation steps

Method Development



Scale-up



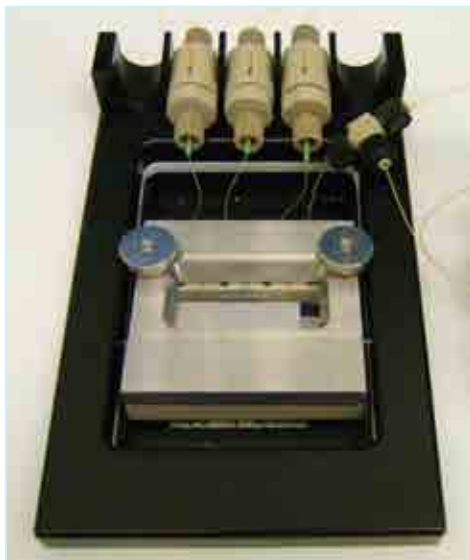
Production



- Furthermore ideally want to optimise the process:
 - Fast
 - Using minimal material

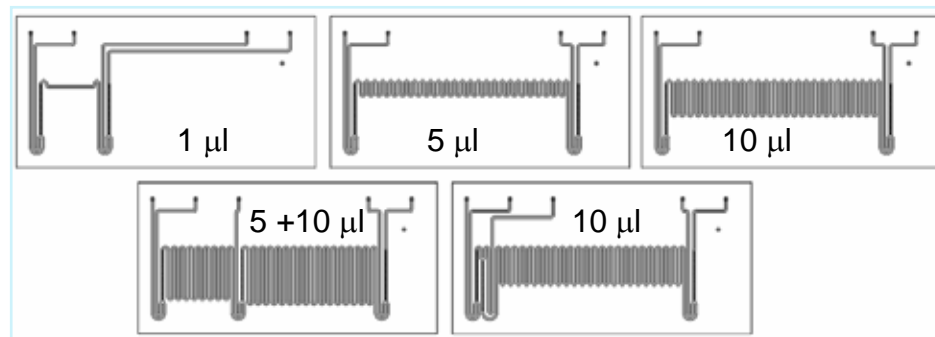
Labtrix

- Reaction optimisation

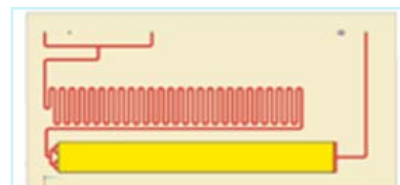


Features

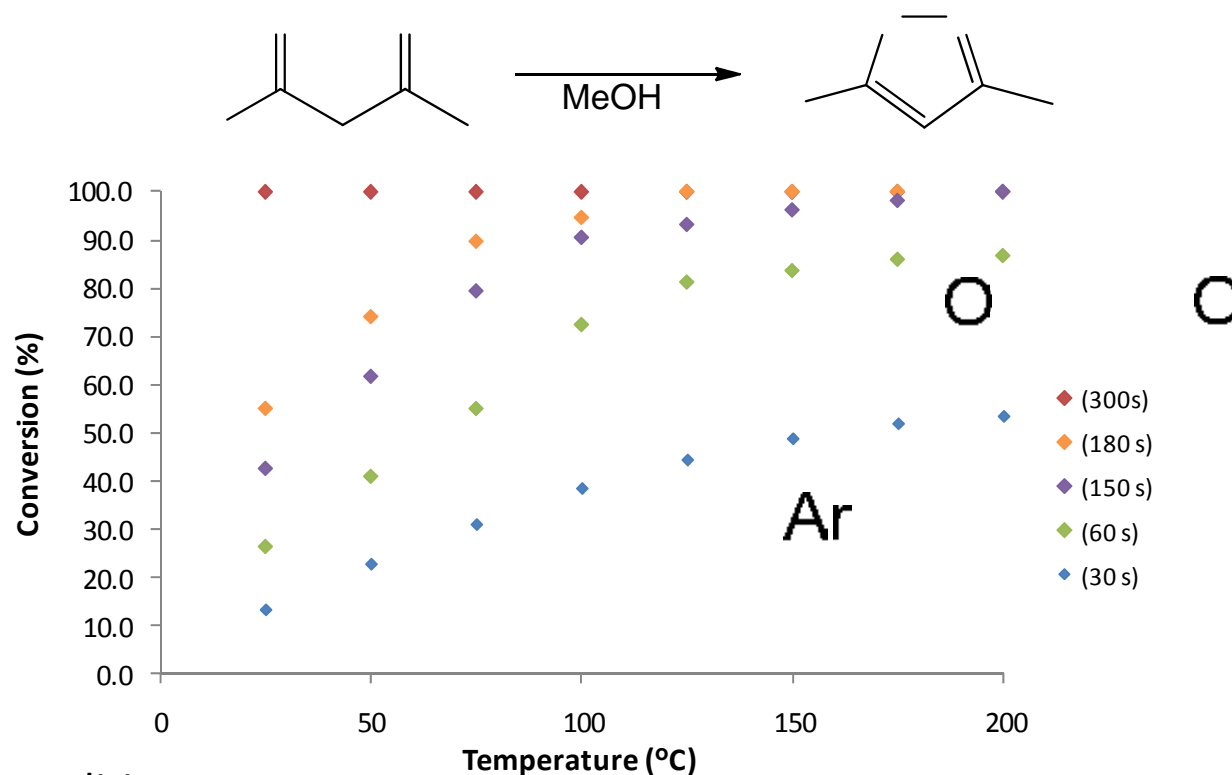
- Syringe pumps
- Automated sample collection and control
- Tests at pressures of 25 bar and temperatures of -15 to 195°C
- Standard interchangeable reactors:



- Catalyst reactor.



Rapid Reaction Evaluation



Optimal conditions:

- Micro reactor: 180 sec, 125 °C, 100% conversion
- Batch stirred reactor 1 h, 125 °C *cf.* 93.6 % conversion

Investigation:

- Number of reactions: 200
- Time taken to generate samples: 27 h
- Volume of reactants employed: 5.97 ml (94.3 mg 1,3-diketone)

Azide Synthesis

- Synthetically useful route to primary amines, triazoles and isocyanates

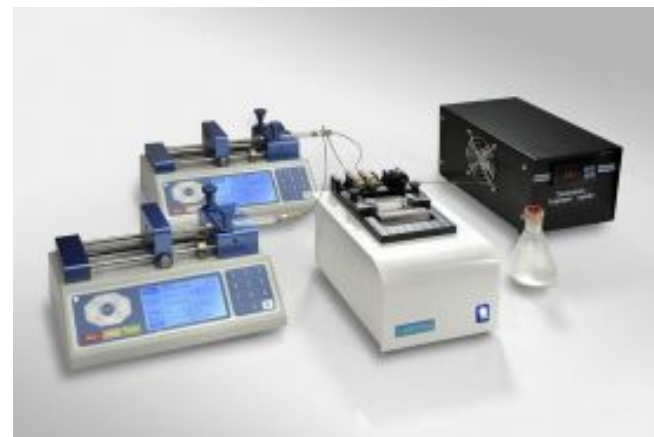


Disadvantages:

- Exothermic reaction
- Products are often hazardous substrates
- Generation/build-up of explosive intermediates
 - Diazidomethane and hydrazoic acid

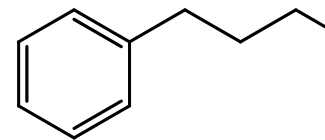
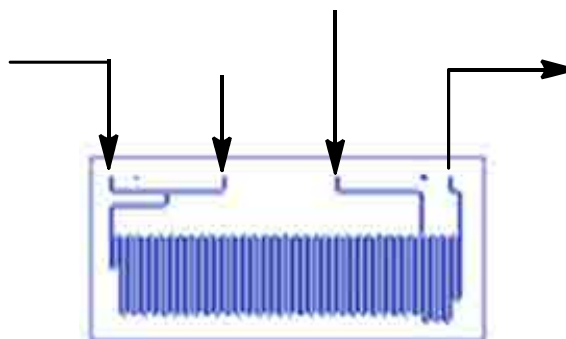
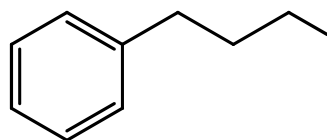
Why investigate under continuous flow?

- Increase reactor safety
 - No headspace therefore reduced risk of HN₃ build-up
 - Efficient dissipation of heat generated
- Increase productivity as a function of wider operating temperatures
- Increase economic feasibility
- Provide a generic method for the production of these versatile intermediates



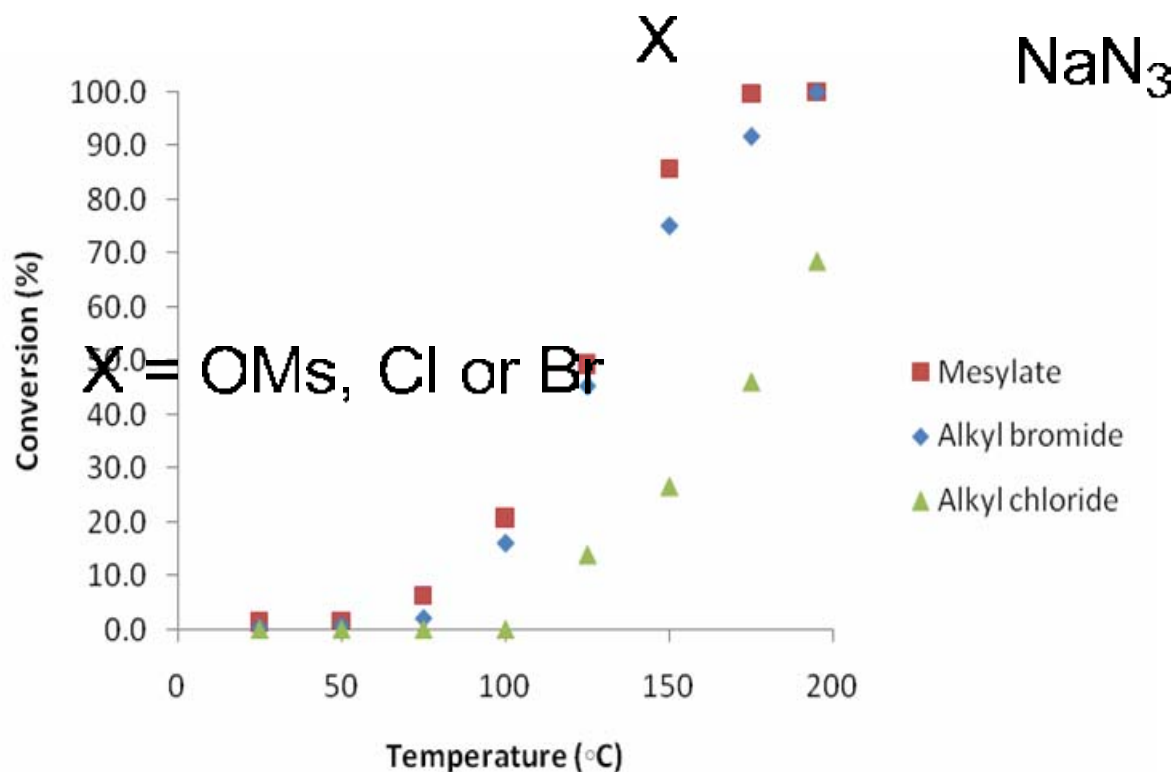
○

Azide Synthesis



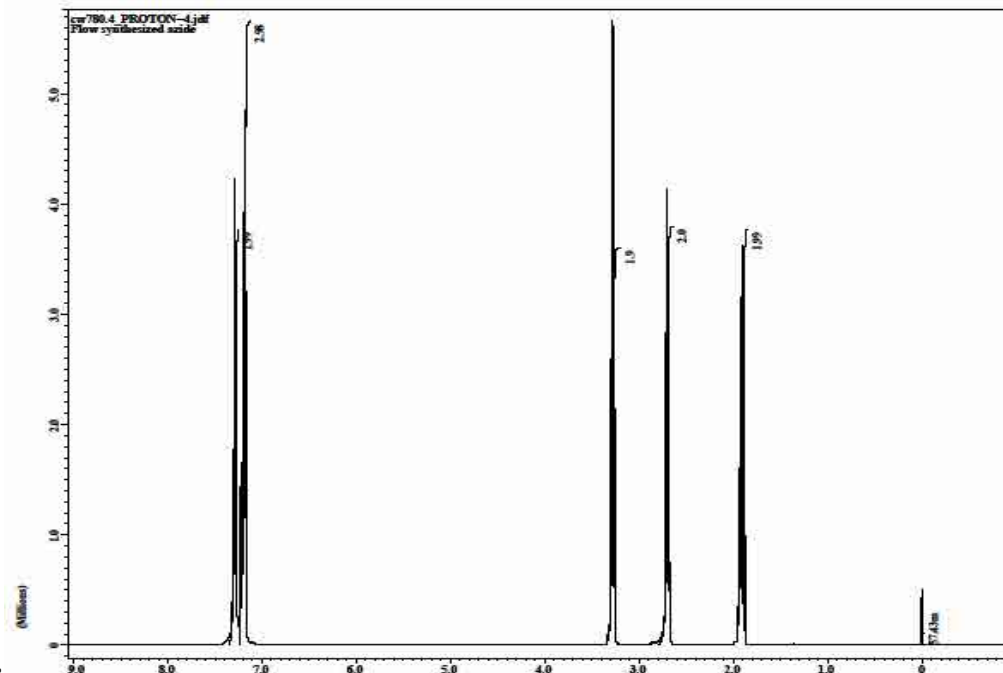
Operating Conditions:

- Pressure-driven flow
- 0.66 M reagents
- 25 to 195 °C
- 25 Bar pressure
- Optimised conditions
- 30 sec residence time
- 99 % conversion



Azide Synthesis

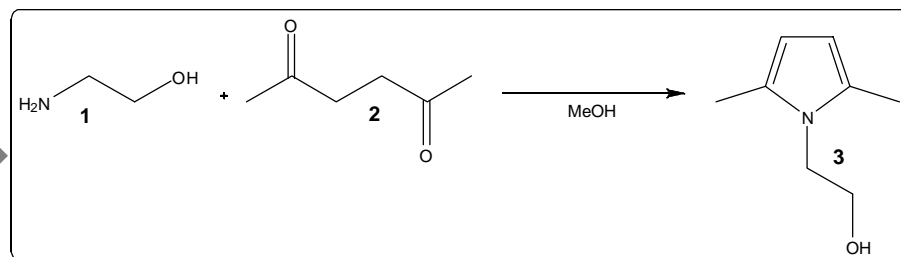
- Employing 0.66 M (EtOH) alkyl precursor and 0.66 M (50:50 aq. EtOH) NaN_3



Order of reactivity was observed to be $\text{OMIS} > \text{DI} \gg \text{Cl}$

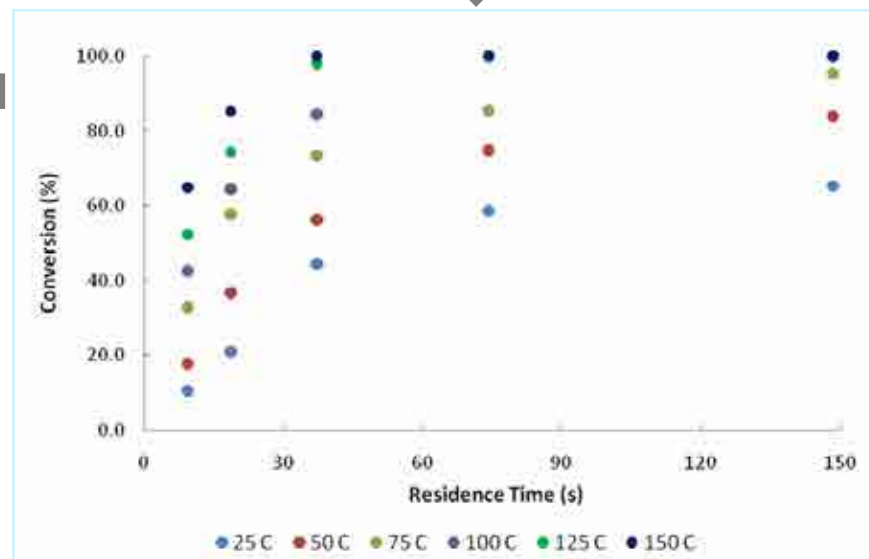
- Using OM derivative, the azide obtained at a throughput of 79 mg h^{-1} @ $195 \text{ }^\circ\text{C}$
 - Analytically pure after an aqueous extraction
- Cl derivative gave 70% conversion under these conditions
 - Potentially offers economic advantages overall

Physical-Organic Chemistry - Kinetics



Plot kinetic curves

Determine reaction order
and rate constant



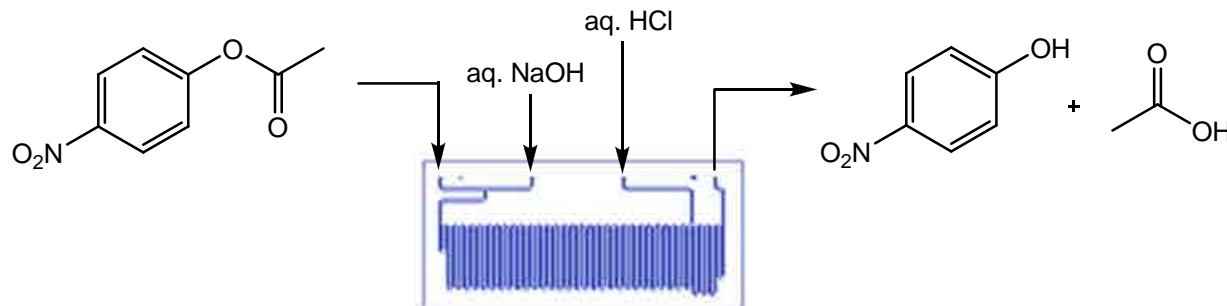
Paal-Knorr reaction:

- Second order reaction
- Rate constant @ 75 °C = $5.4 \times 10^{-3} \text{ L mol}^{-1} \text{ s}^{-1}$

Optimal conditions: 2.5 M reagents, 37 s @ 150 °C affords the pyrrole **3** at a throughput of 418 mg h⁻¹

Hydrolysis of *p*-Nitrophenyl Acetate

Reaction manifold:



Reaction Conditions:

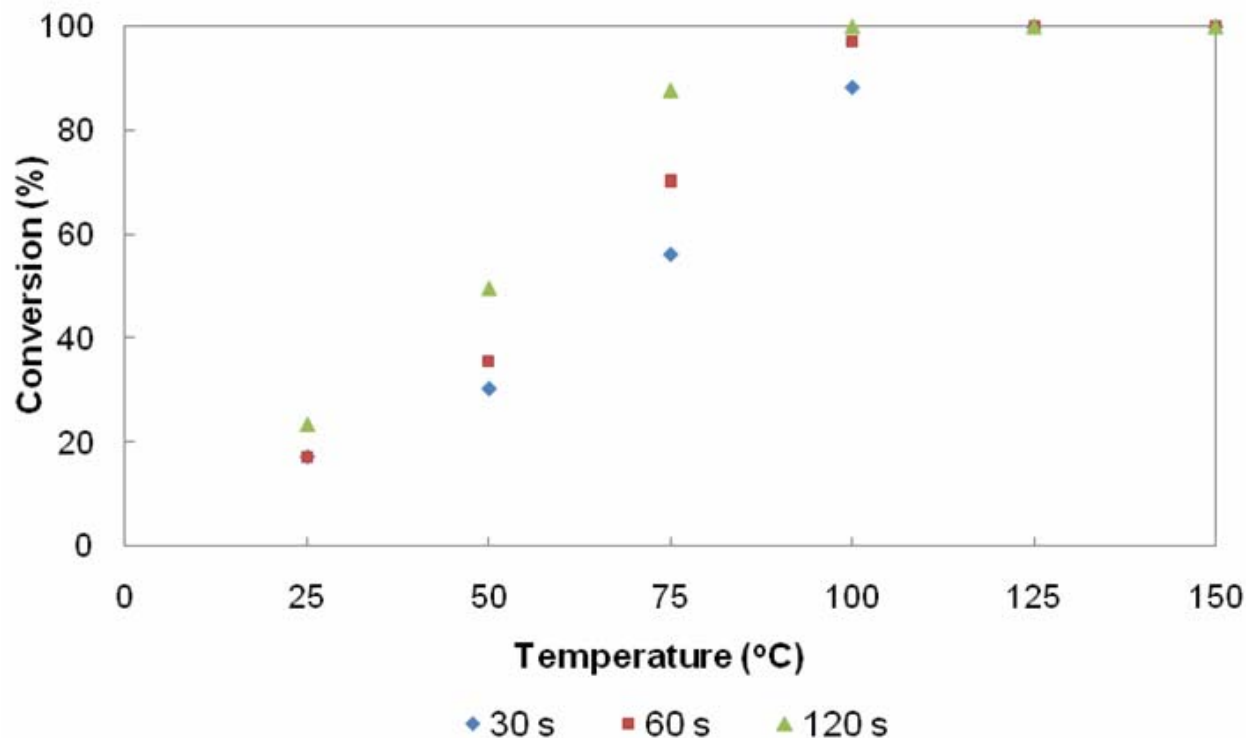
- *p*-Nitrophenyl acetate in toluene (0.05 M) and NaOH in DI H₂O (0.5 M)
- Total flow rate = 2 to 20 $\mu\text{l min}^{-1}$, Temperatures = 25 to 150 $^{\circ}\text{C}$

Biphasic System:

- Immiscibility of reactants affords segmented flow



Hydrolysis of *p*-Nitrophenyl Acetate



Optimal conditions:

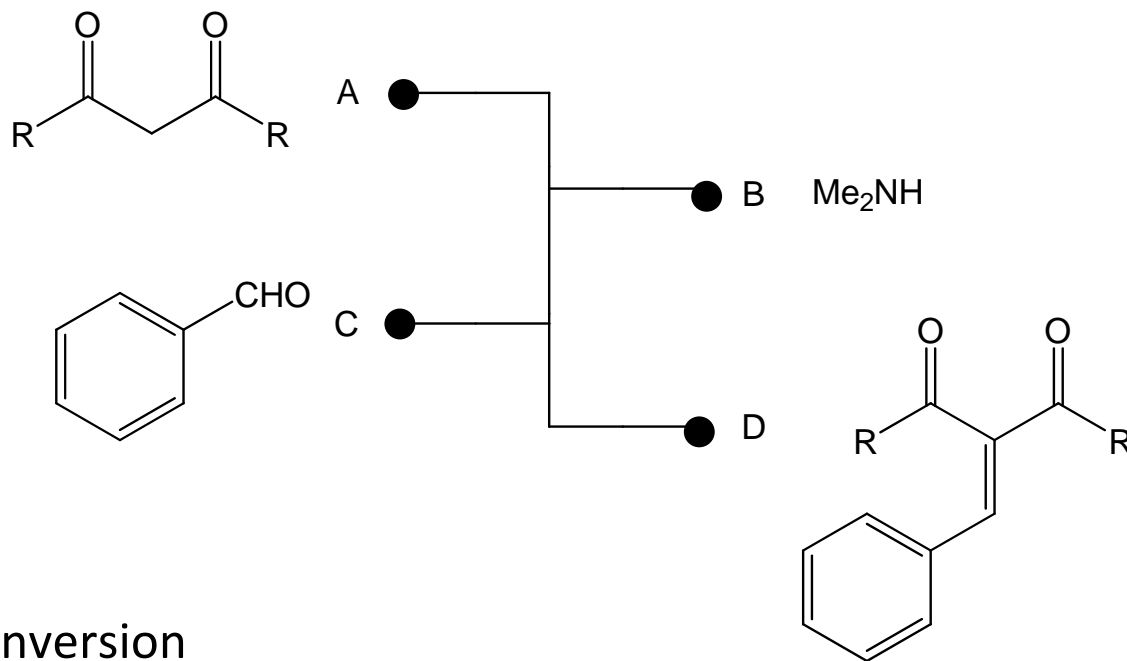
- 60 sec, 125 °C affording 100% conversion

Extraction of kinetic information:

- Performing flow experiments at several reaction times enables the k_{obs} to be readily extracted from the data generated
 - *i.e.* @ 75 °C, $k_{\text{obs}} = 0.0143 \text{ s}^{-1}$ for *p*-nitrophenyl acetate hydrolysis

Knoevenagel Reaction

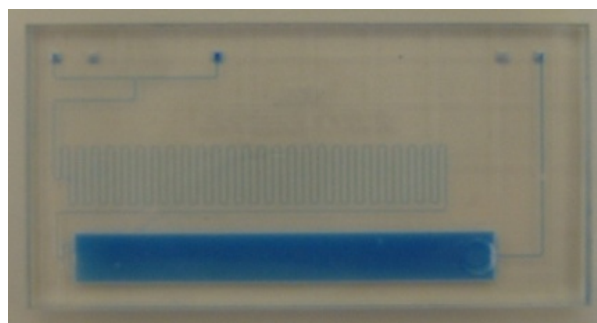
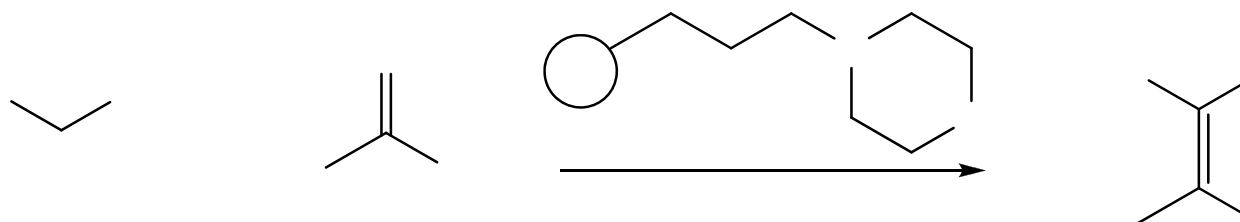
- Solution phase Knoevenagel reaction
- 1:1 Ratio of reagents (0.5 M) in MeCN
- Important to use appropriate reagent concentrations



- 100 % conversion
- Reaction very '*atom efficient*'
- BUT product contaminated with base!!
 - Traditional solvent extraction needed
 - This clearly reduces the advantages of flow reactors

Functionalised Reactors

- Fabricate micro reactors which enable catalysts and/or supported reagents to be spatially positioned

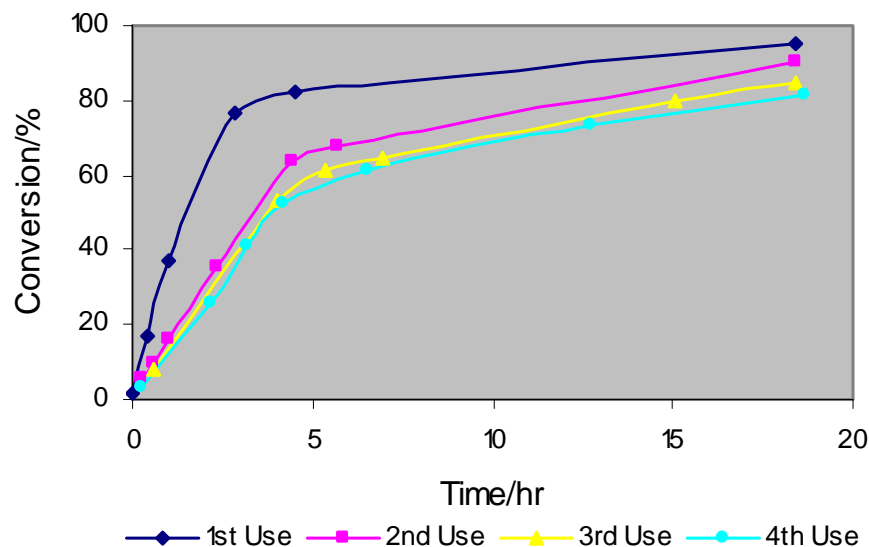


- Quantitative conversion to analytically pure product

 R_2
 H
 O
 Si
 $R \text{ and } R_2 = COOCH_3, COCH_3, CN$

Key Results of Heterogeneous Catalysis in Flow

- Supported reagents deteriorate with time in batch reactions as a result of physical damage and/or loss

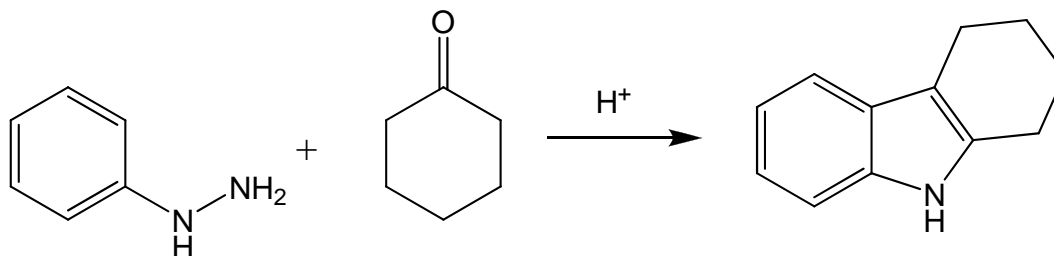


- Reagents last longer in micro reactions as they suffer less damage in flow reactors
- Higher effective catalyst concentration
- Throughput *ca.* 10 mg/hr/channel

Run No.	Conversion (%)
1	98.3
2	98.5
3	98.3
4	98.3
5	98.4
6	99.2
7	99.1
8	99.1
9	100.0
10	99.6
11	99.3
12	100.0
13	100.0
14	99.2
Mean = 99.1 %, % RSD = 0.65	

Indole Synthesis

- Core structure of many pharmaceuticals
- Reaction conditions:
- 0.1M Phenylhydrazine, cyclohexanone, methanesulphonic acid in DMF
- Heat

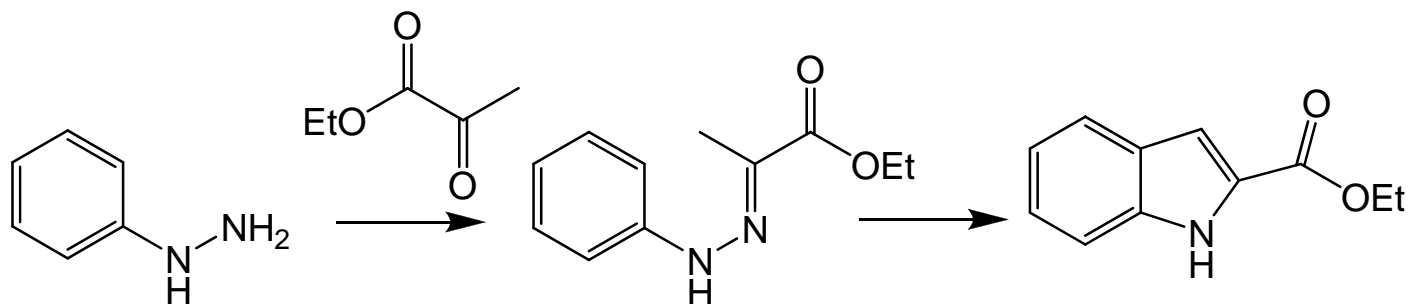


Temperature (°C)	Flow Rate (μLmin ⁻¹)	Indole (%)
90	1	60.7
95	1	81.3
105	1	85.7
105	0.5	93.3
115	0.5	98.9

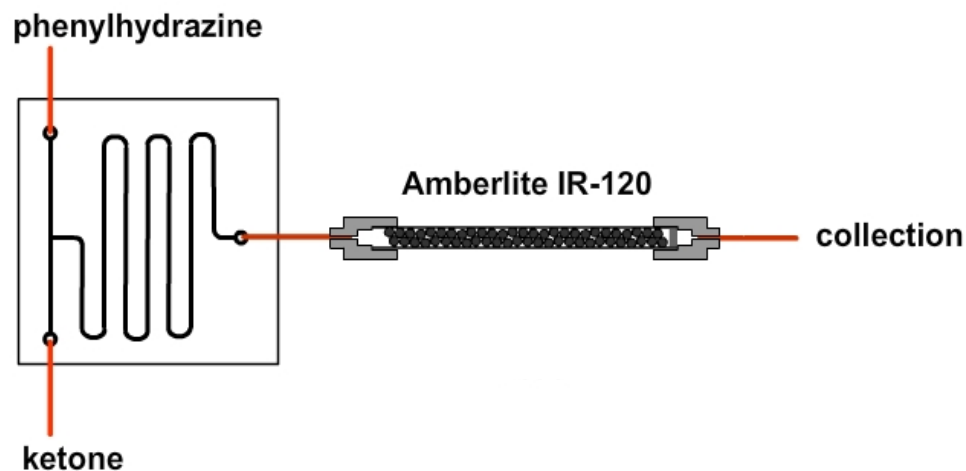
- Note that excess reagents were not necessary
- Similar results for other unfunctionalised ketones *Tetrahedron*, 2010, **66**, 3861

Indole Synthesis

- Reaction of ethyl pyruvate
- Acid caused product degradation - very low yields of product



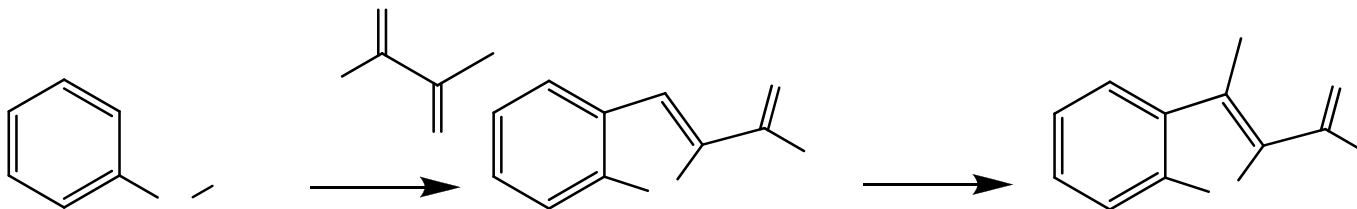
- Reactor incorporating a solid supported acid: Amberlite IR-120



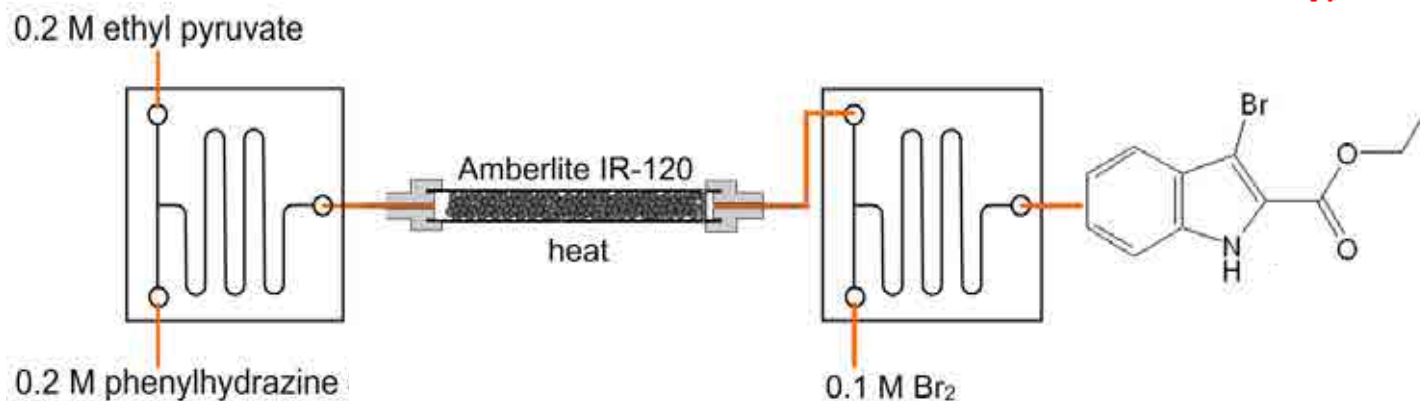
- 56% isolated yield at 70 °C in EtOH
- Easier product isolation

Multi-Step Indole Synthesis

- Aim to incorporate radiolabel



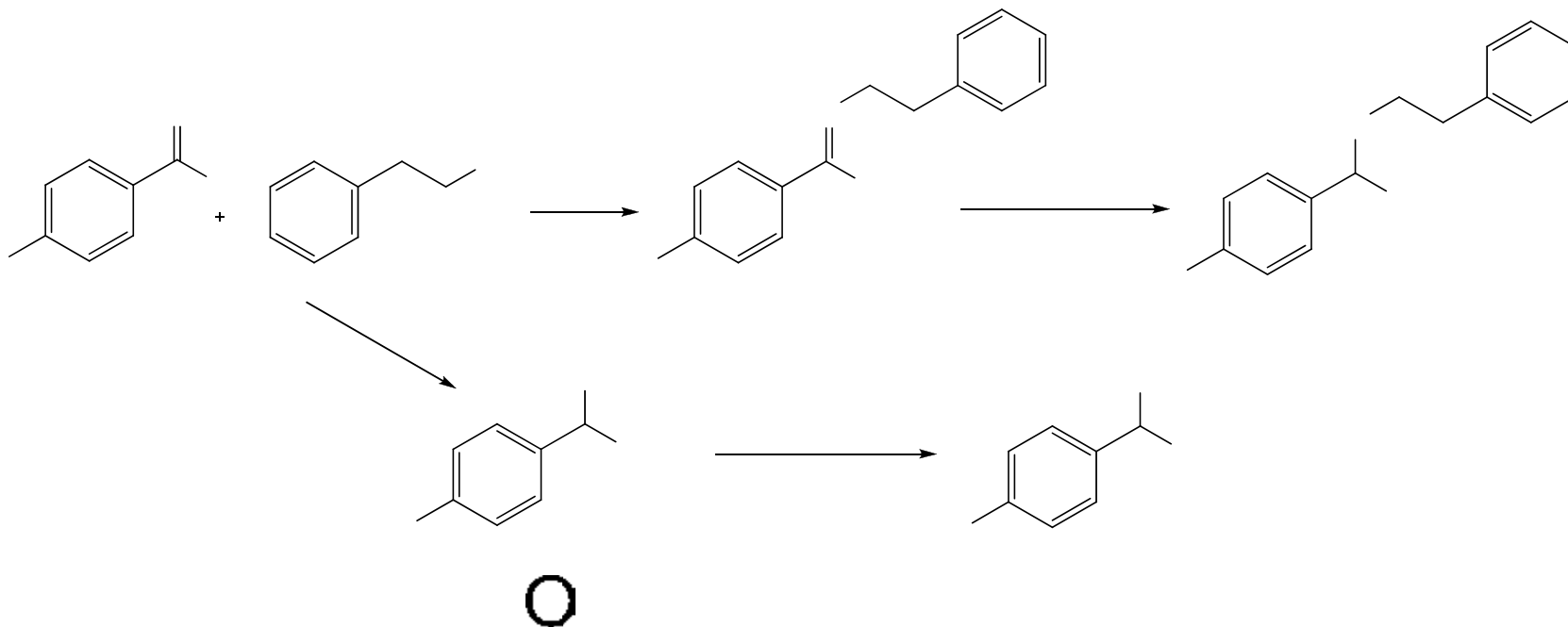
- Challenge for continuous flow reactors:
 - Solvent compatibility between reaction steps
- Screening study found MeCN to be the best compromise for both reactions



- 46% overall yield at 75 °C in MeCN

Synthesis of α -Aminonitriles: Increased Control

Strecker Reaction:



- Low yields, complex reaction mixtures \longrightarrow laborious purification required
 - Problematic with aromatic aldehydes due to slow imine formation

Expensive Catalyst

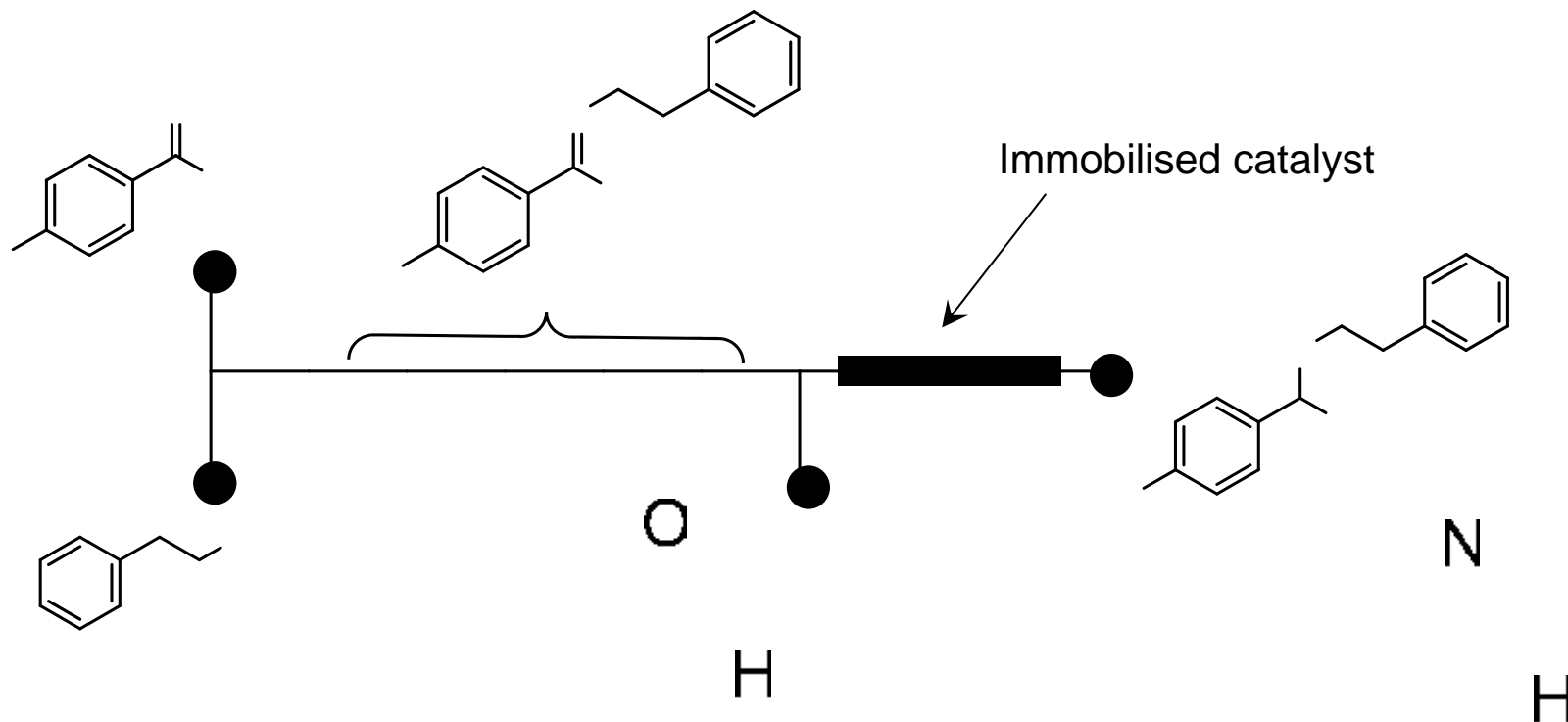
- Difficult to recover and recycle
- Generation of acidic waste

Br

TMSCN

Br

Continuous Flow Synthesis



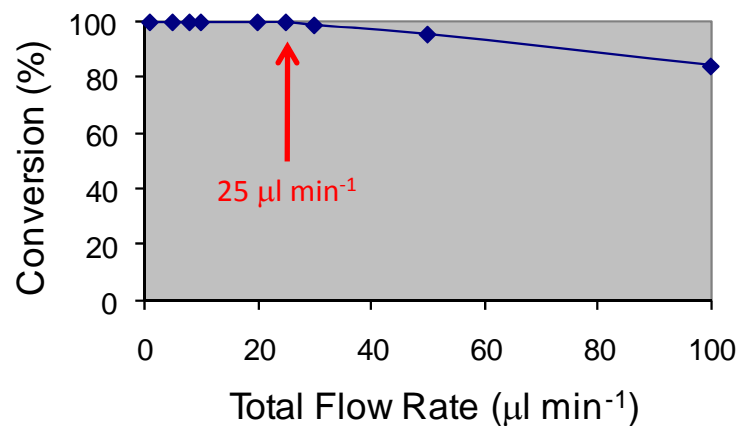
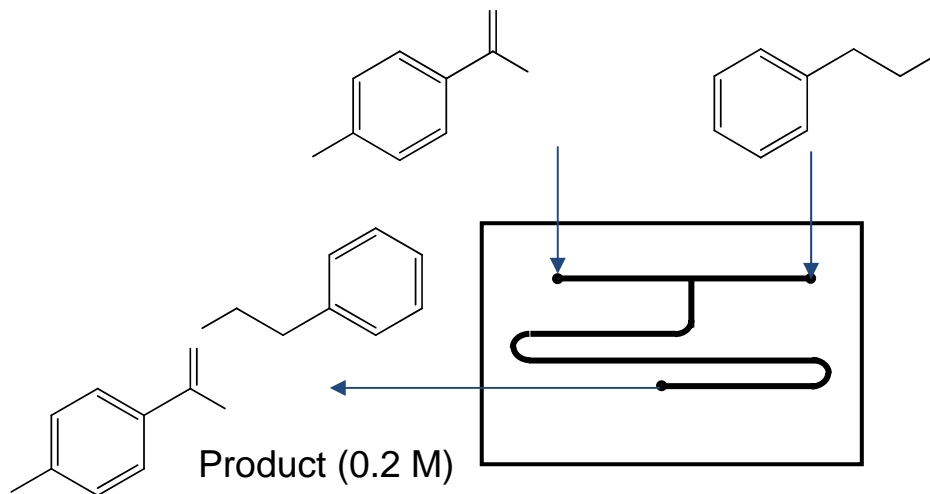
Aims of Flow Reaction

- Enable optimisation of imine formation
 - To minimise or prevent cyanohydrin formation
- Employ a stoichiometric quantity of TMS-CN and amine
- Recycle catalyst efficiently
 - Reduce degradation due to absence of stirring

Flow Synthesis of Imines

Reaction Conditions

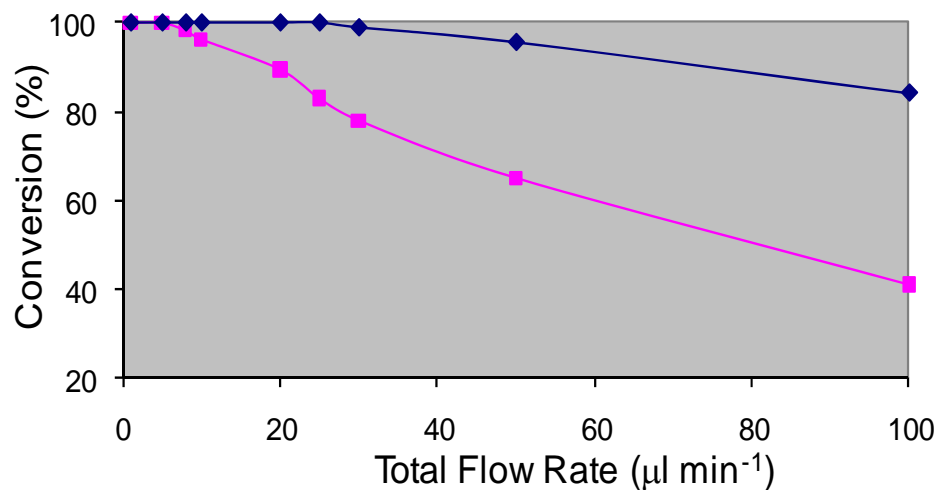
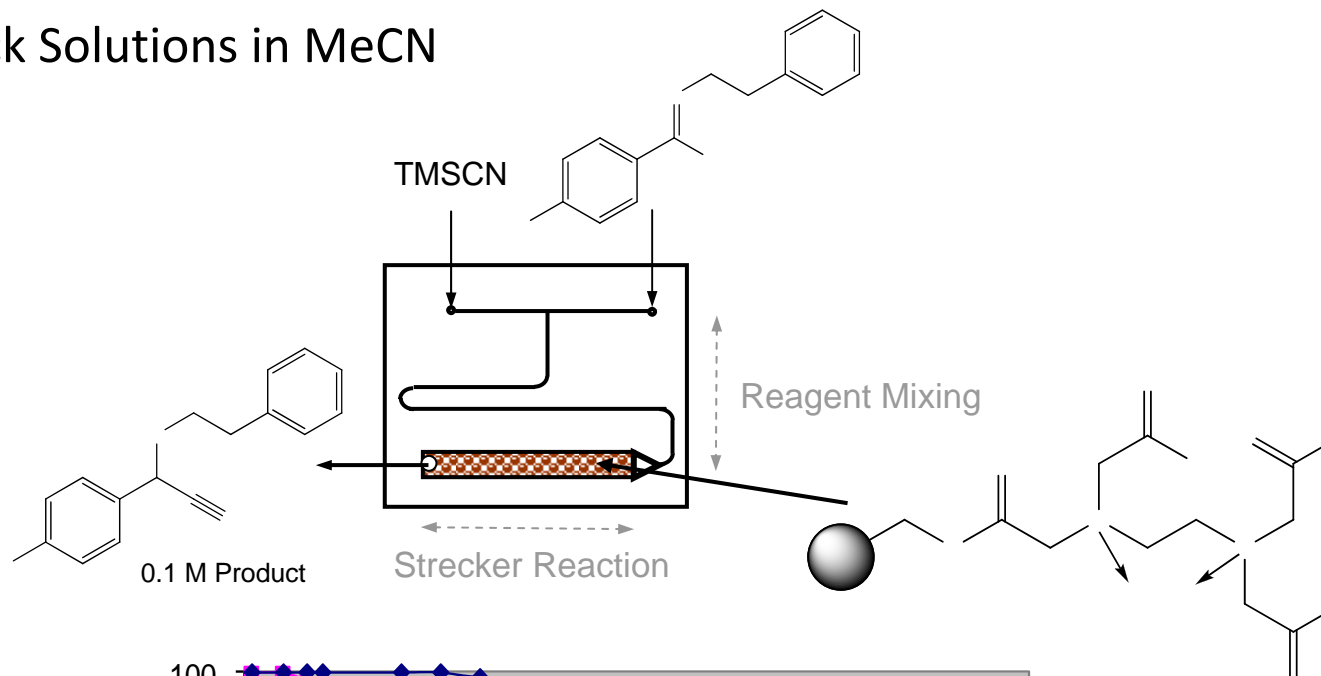
- 0.4 M Stock Solutions in MeCN
- Micro Channel Dimensions = 150 μm (wide) x 50 μm (deep)



- Reaction products analysed, off-line, by GC-MS
 - Identify optimal conditions for imine formation

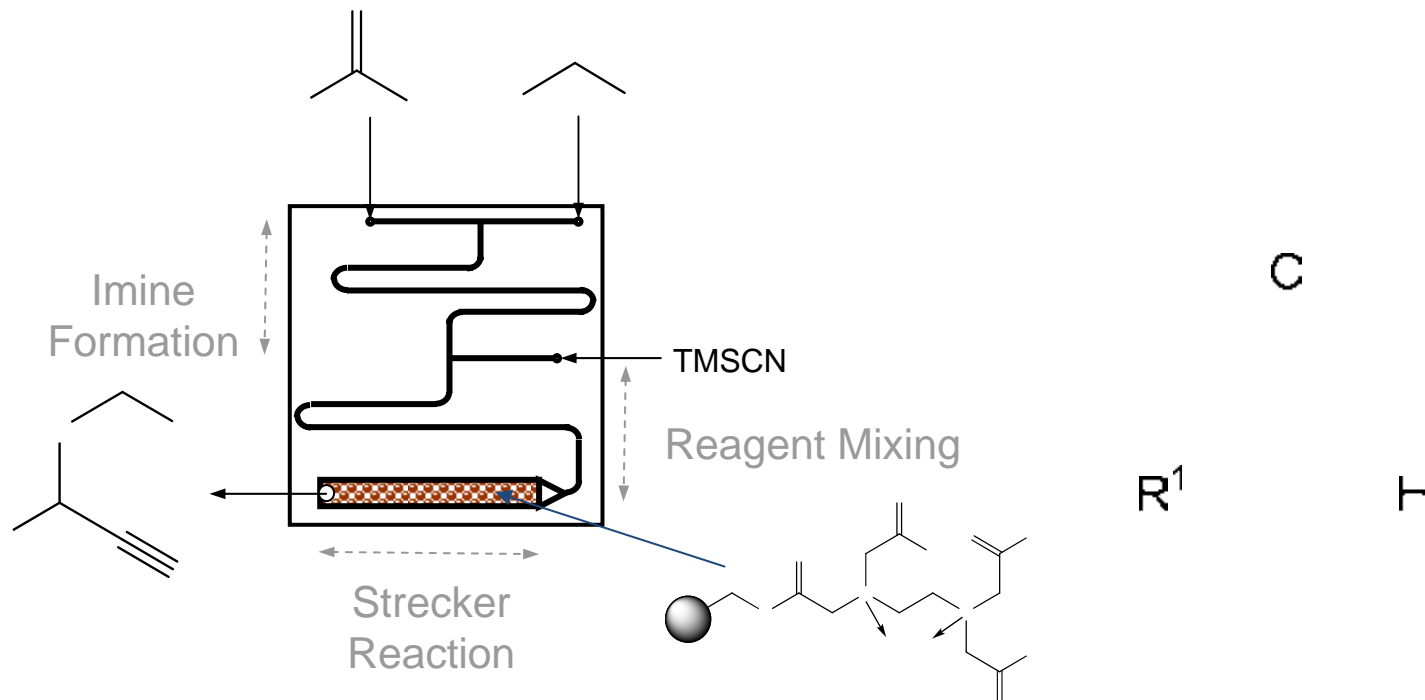
Continuous Flow Addition to Imine

0.2 M Stock Solutions in MeCN



Br

Multi-Step Reaction



Flow: Quantitative Conversion (by NMR), 9.45 mg hr⁻¹ (5.0 μl min⁻¹)

Batch: 64 % Conversion, stirred for 24 hr (1.5 eq. TMSCN)

ICP-MS Analysis:

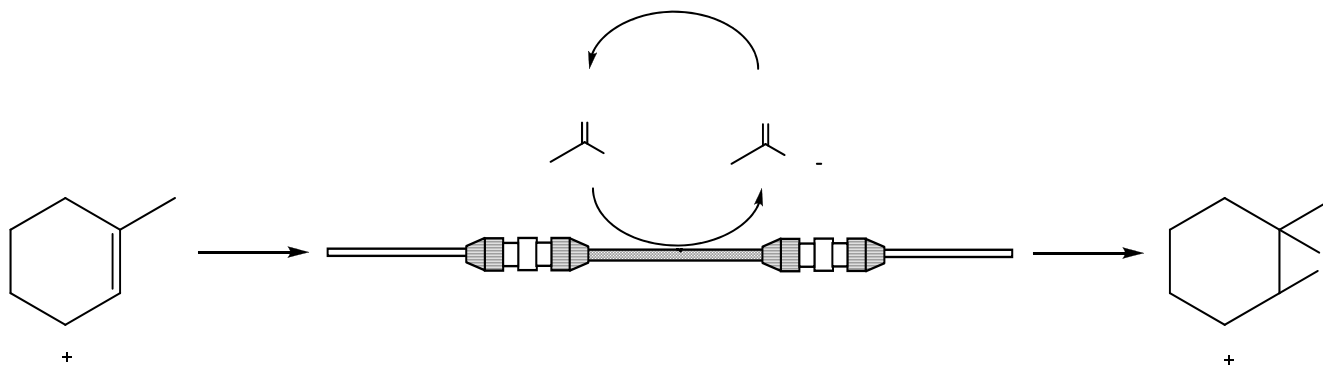
- Stirred Batch Reaction: 440 ppm Ru
- Micro Reaction: No observable difference from the blank (MeCN)
- Library of 51 compounds prepared

Epoxidation of Alkenes: Improved Safety

- Epoxides are very useful reaction intermediates
- Traditionally prepared using organic peracids
 - Hazardous on a large scale
- Enzyme 'greener' but usually denatured by the reaction conditions
- Avoided using a flow reactor where peracid generated *in situ*

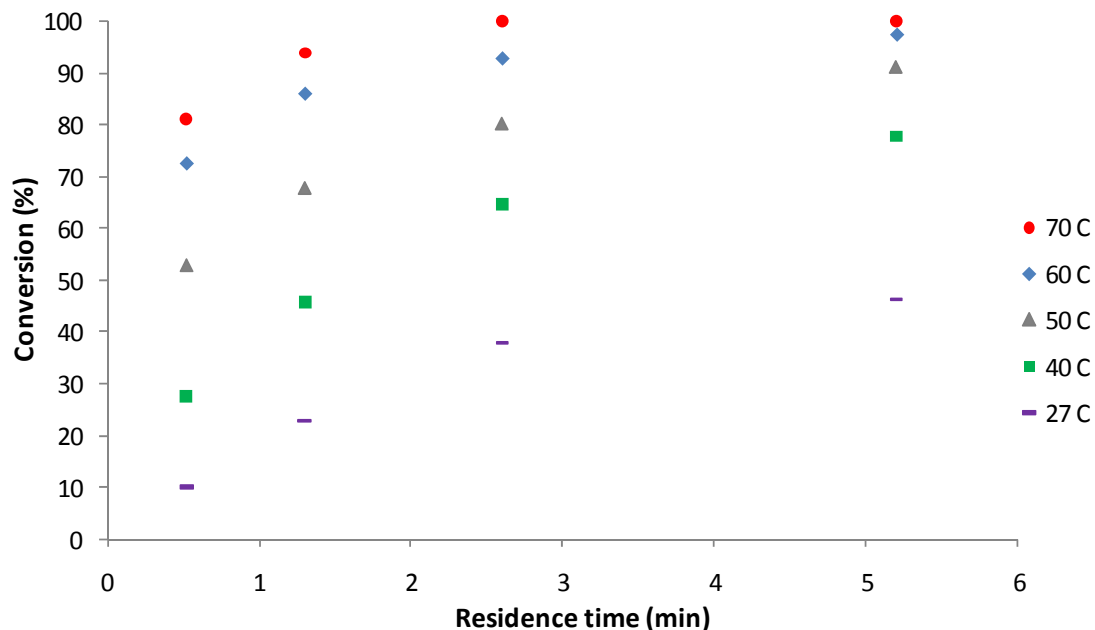
Experimental set-up:

- Reactor packed with Novozyme 435
- Alkene 0.1 M and H₂O₂ 0.2 M in EtOAc



Epoxidation of Alkenes: Rapid Evaluation

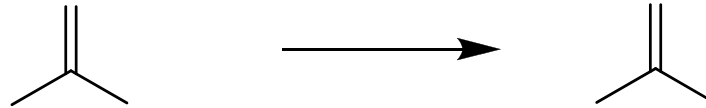
- Evaluation of optimum reaction conditions
- Alkene 0.1 M and H₂O₂ 0.2 M in EtOAc



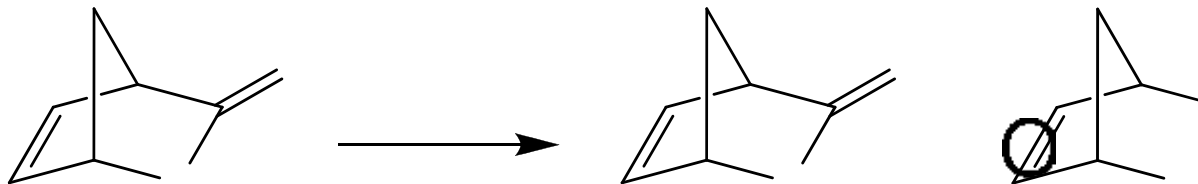
- Optimum conditions:
 - Temperature 70 °C
 - Residence time 2.6 minutes
- Higher temperatures denatured the enzyme

(+)- γ -Lactamase Enzymes

- Hydrolysis of amides



- Resolutions



- CLEA from a cloned thermophilic enzyme packed into reactor R NH_2
 - Comomonas acidovorans*
- Enzyme found to be stable at 80 °C

Substrate Screening

- Experimental conditions
 - Optimum temperature 80 °C
 - Substrate 10 mmol/L concentration in phosphate buffer pH 7
 - Flow rate 1 ml/min

Substrate	Substrate conversion (%)
racemic- γ -lactam (+/-)	50.0
(<i>R</i>)-(+)-lactamide	100.0
acetamide	0
propionamide	16.0
butyramide	33.4
isobutyramide	58.7
acrylamide	39.4
Benzamide	100.0
<i>m</i> -toluamide	100.0
<i>p</i> -toluamide	100.0
<i>m</i> -aminobenzamide	24.3
<i>p</i> -aminobenzamide	11.0
Nicotinamide	0

Grignard Reaction

- C-C bond forming → versatile reaction for the synthesis of alcohols, carboxylic acids, alkanes and ketones



Problems Large-scale Grignard Reactions:

- **Highly exothermic**
 - Performed at low temperatures
- Instantaneous, **mixing** controlled reaction
 - Careful dosing required to avoid hot spot formation
 - Competing side reactions and **product decomposition**

Manipulation of Grignard Reagents using MRT:

- Rapid **dissipation of heat** of formation ensures minimal thermal gradient
- Perception that inorganic reagents cannot be handled within micro channel reactors

O

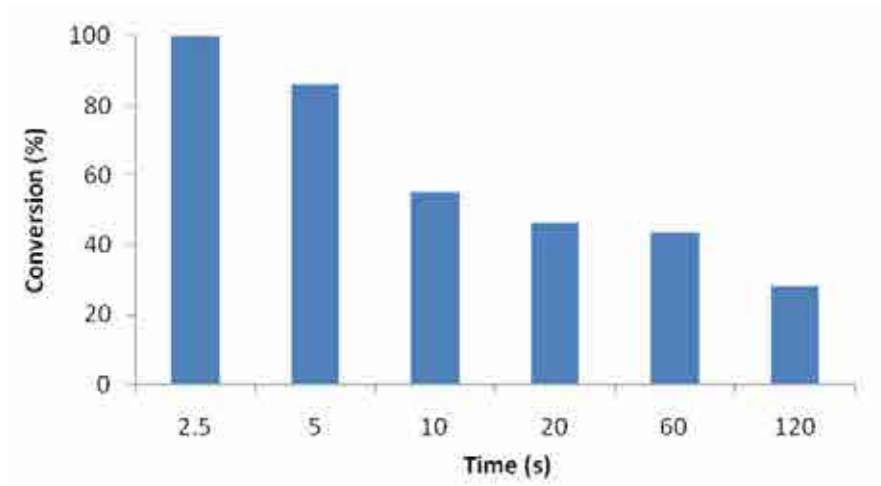
H

R¹M

-78 to -20

Grignard Reaction

Effect of Reaction Time @ -15 °C:



Optimal Conditions for 1-Phenylpropan-1-ol:

- Reactant concentration 0.5 M, stoichiometry 1:1, reaction time 2.5 s and reactor temperature -15 °C
- SOR reactor essential for rapid mixing:



Translation of Microwave Methodology

- Whilst microwaves have found widespread use in medicinal chemistry labs for the rapid screening of thermally activated reactions, scaling is challenging

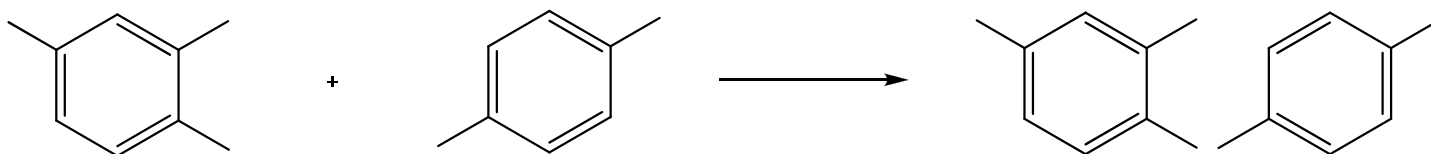
Advantages of Flow:

Reactions can be readily pressurised and 'super-heated' like microwaves, but;

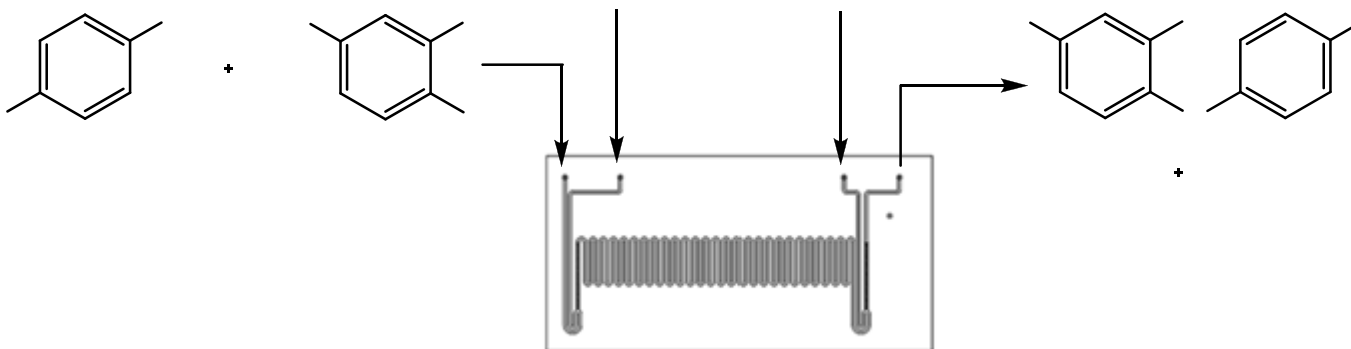
- No solvent dependency on the actual reaction temperature
- Efficient heating and accurate control of reaction time
- Reactions can be scaled

Model Reaction:

- To demonstrate this, the following etherification reaction was performed using Labtrix[®] S1 and the data obtained compared with the literature¹



Translation of Microwave Methodology



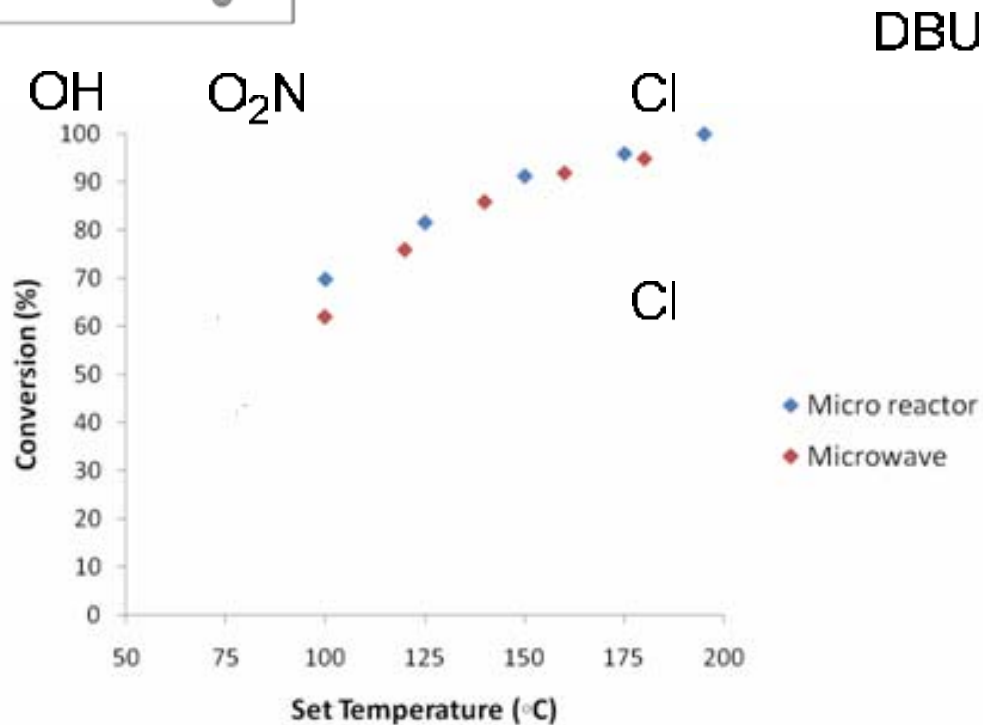
Reaction Conditions:

- Residence time 10 mins
- 1.30 M Phenol and DCNB in DMA

MeCN



- Performing the reaction in MeCN
 - Equivalent conversions obtained



Facile Up-Scaling

- Rapid scale-up is a 'strategic competitive advantage'
 - Process chemists require methodology that increases reactor throughput without lengthy re-optimisation steps

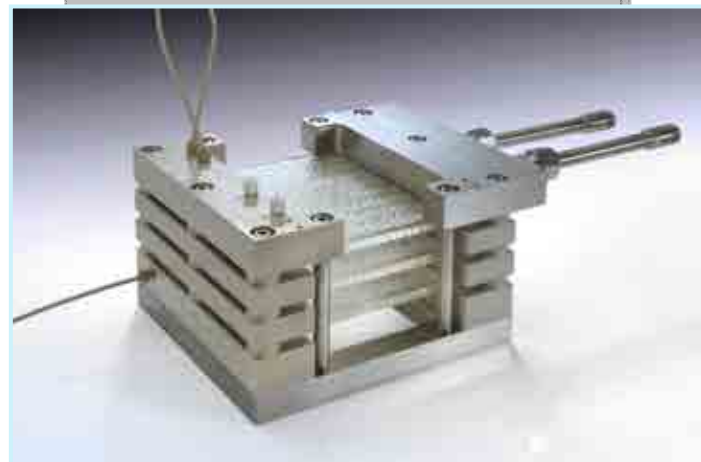
Method Development



Scale-up



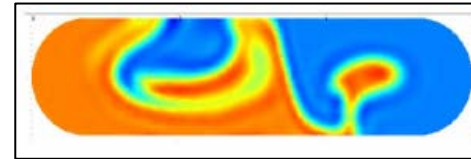
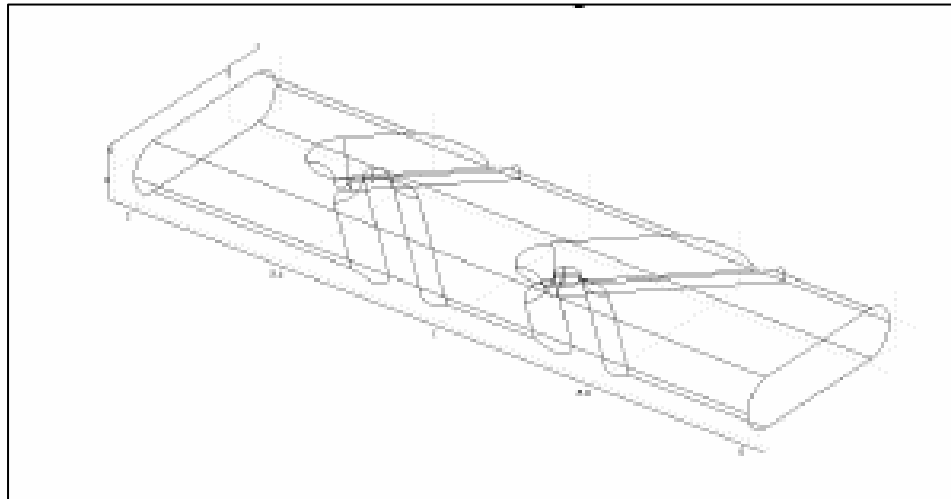
Production



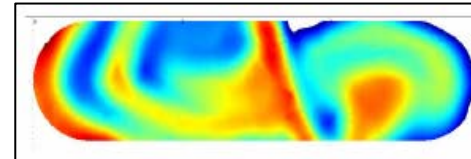
- Reaction channel dimensions increased
 - 'micro' 300 μm x 120 μm to 'meso' 1.4 mm x 1.0 mm

Efficient Scale Up - Mixing Technology

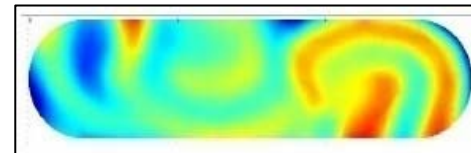
- Need to ensure that the mixing is the same in all reactor designs
- Staggered Oriented Ridges (SOR) fabricated in the channels



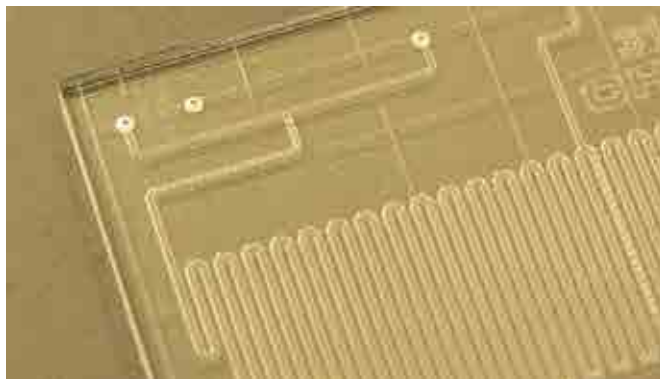
1 Unit



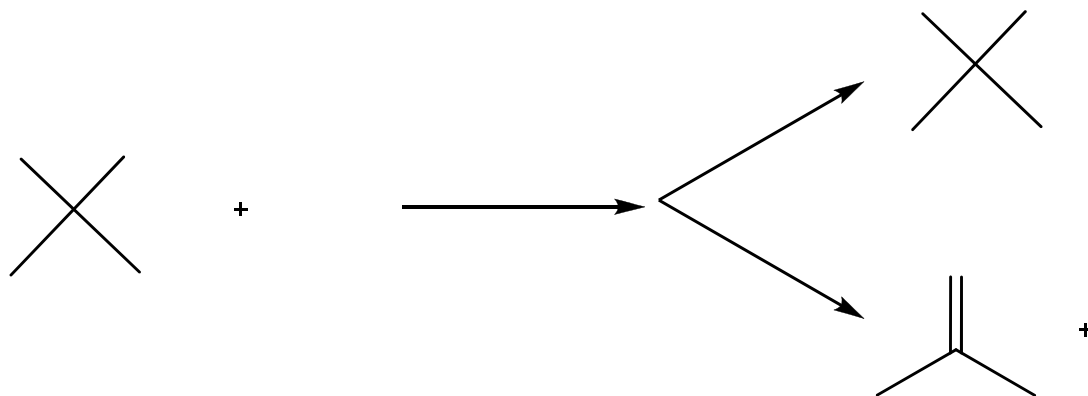
2 Units



3 Units



Mixing Efficiency using Fourth Bourne Reaction



[DMP] (M) ^a	Mixing Time (ms)
0.05	31.7
2.5×10^{-2}	63.5
1.25×10^{-2}	127.0
6.25×10^{-3}	254.0

^a After mixing but before reaction (50 % Stock)

< 4 % hydrolysis = efficient mixing

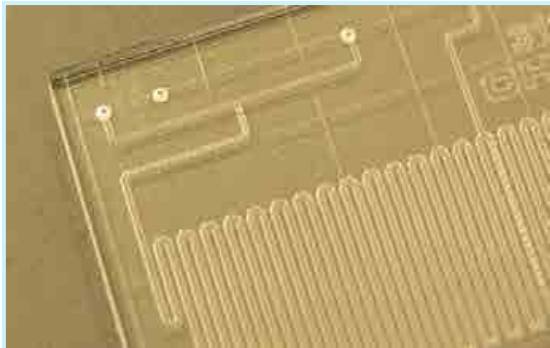
H

HCl
aq. EtOH

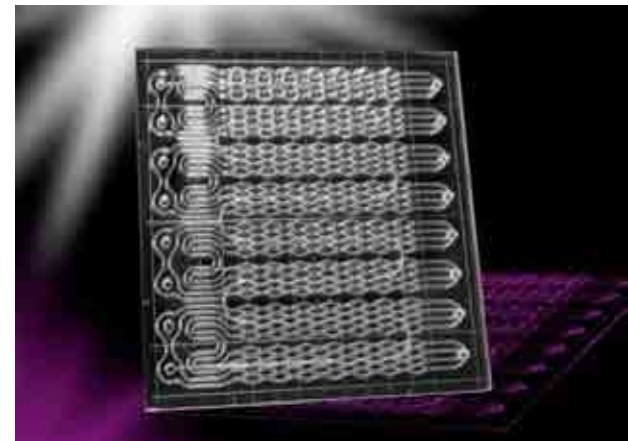
Mixing Efficiency using Fourth Bourne Reaction

Validate the Scaling Principle:

- The reaction was repeated in a 0.8 ml containing same SOR mixer as a micro reactor

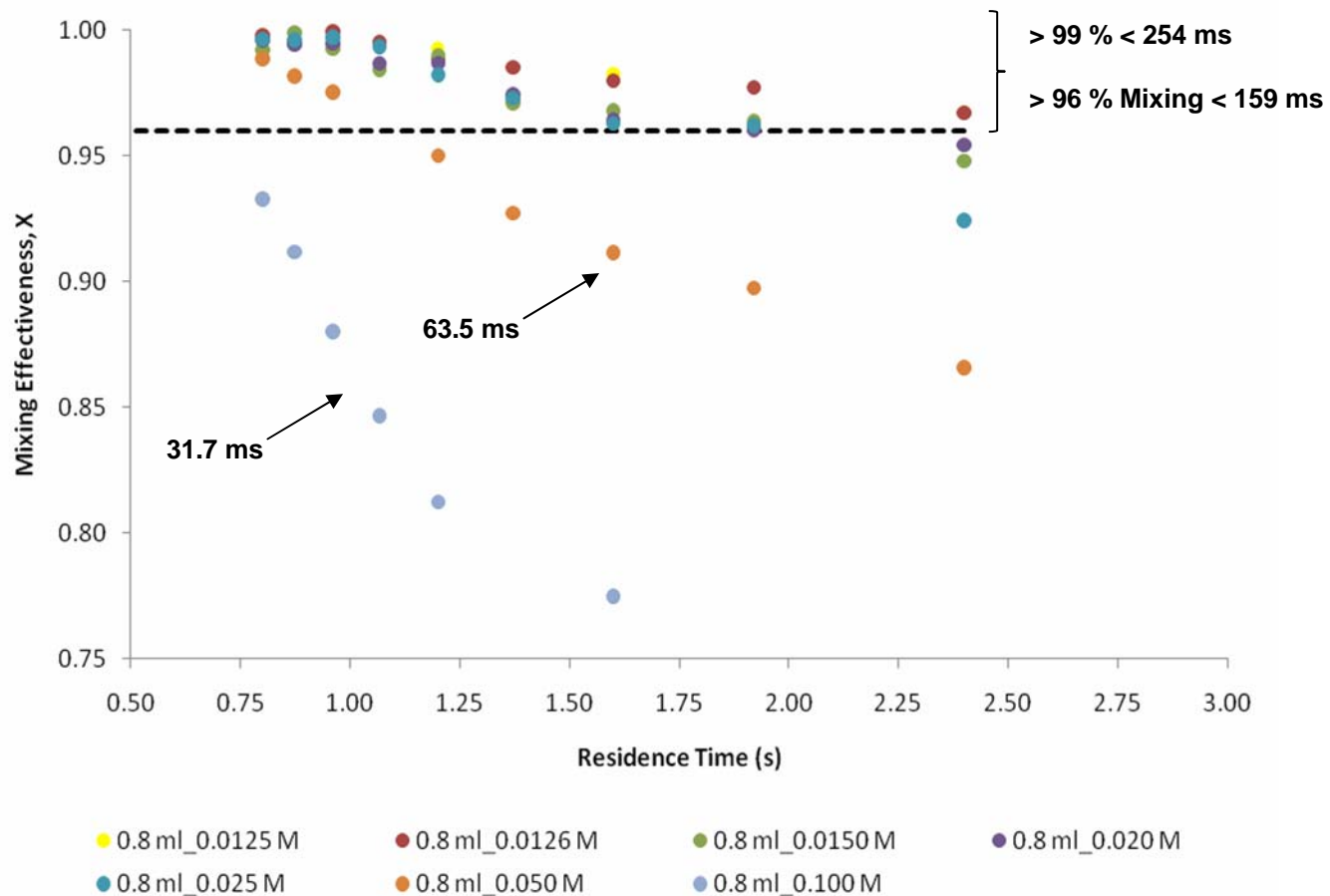


Reactor Volume = 1.0 μ l



Reactor Volume = 0.8 ml

Mixing Efficiency using Fourth Bourne Reaction

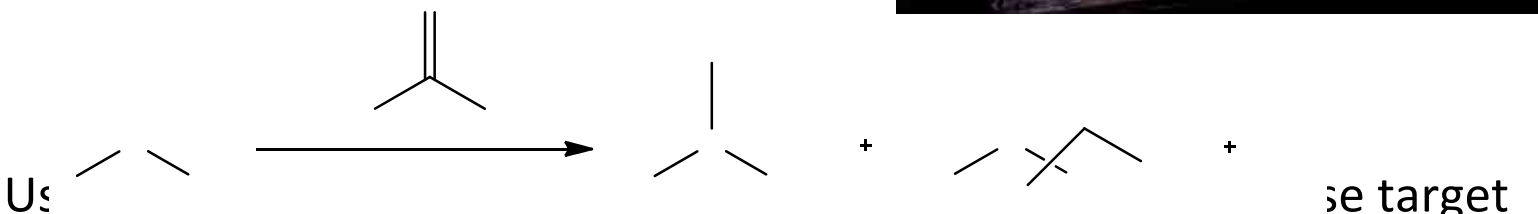


Chemical Appraisal of Plantrix by J&J

Chemical Appraisal:

- Plantrix chemically evaluated by J&J, a multi-national pharmaceutical company
 - Details of the process are confidential

Eschweiler Clarke Reaction:

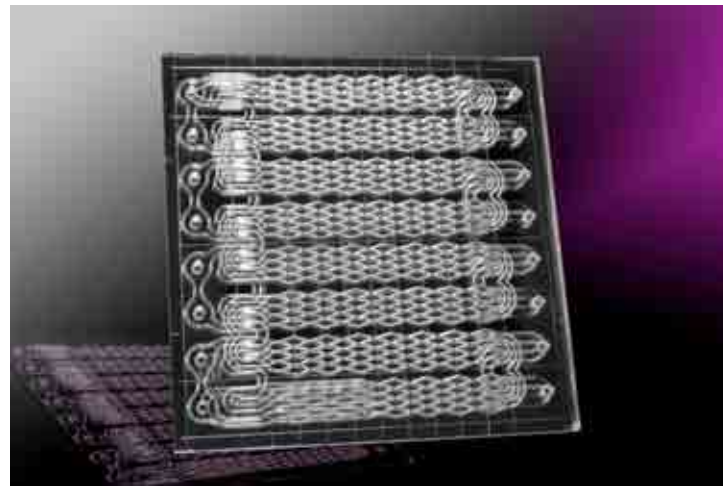
- 

intermediate (+ minimise by-product formation), were predicted based on 5 batch reactions

→ 56 s @ 122 °C

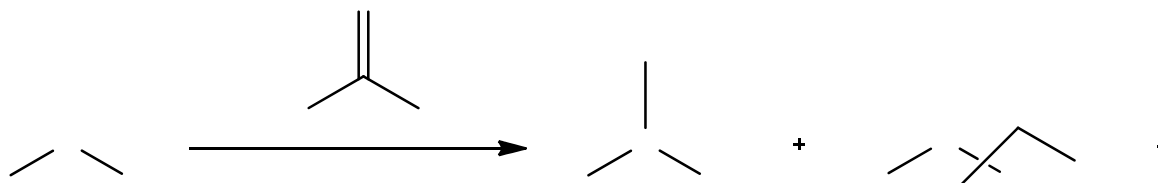
- Outside the operating conditions safely attainable in batch reactors, CO₂ ↑

Solution: Use a continuous flow reactor



Chemical Appraisal of Plantrix by J&J

Reaction Conditions Evaluated within Plantrix:



- Residence times = 15, 30 and 60 s
- Reactor temperatures = 120 to 145 °C → Analysis = Offline HPLC
 - 20 conditions screened in 3 h

Results:

	Batch	Predicted Optimal Conditions	Plantrix®
N-Methyl Derivative	87.0	93-93.5	93.5
By-product	10.0	1.7-2.5	2.1
Others	3.0	1.0-1.2	-

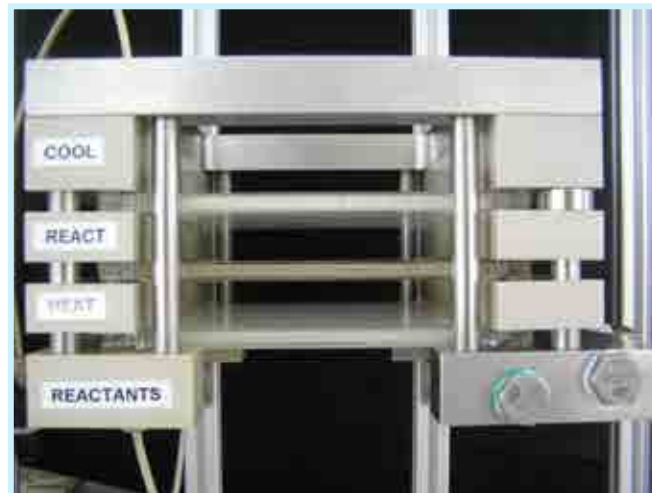
- Reaction translated to a 1 Litre PFA reactor for 100 kg production
- 3 Validation batches performed, results presented to the FDA who confirmed;

‘no additional analytical PAT tools were required for production’

Plantrix[®] Production Capacity

Chemical Appraisal:

- Plantrix chemically evaluated by J&J, a multi-national pharmaceutical company
 - Details of the process are confidential



Model System:

- 0.5 M Product concentration (MW = 200), 1 min reaction time

	Labtrix [®]		Plantrix [®]	
	Micro Reactor	1 Channel	8 Channel	8 Channel
Volume per Reactor Channel	10 μ l	0.8 ml	6.5 ml	6.5 ml
Micro Reactors	1	1	1	1
No. Reactors per Holder	1	1	1	10
Volume per Holder	10 μ l	0.8 ml	6.5 ml	65 ml
Throughput*	60 mg hr ⁻¹	4.8 g hr ⁻¹	39.0 g hr ⁻¹	390 g hr ⁻¹ (9.36 kg day ⁻¹)

- Using a range of product configurations, you can;
 - Minimise reagent use (0.8 ml), or tailor production rates

Conclusions

- Micro reactors allow the rapid optimisation of reactions
 - Rapid process development
- Increased reaction control
 - Higher purity
 - Higher conversion
 - Higher selectivity
- More reproducible synthetic procedures
 - Operator independent synthesis
- Increased catalyst turnovers and lifetimes
 - Easier purification/isolation
- Increased process safety
 - Due to rapid dissipation of heat of reaction
 - Low reactant hold-up
- Equipment for method development and production developed

Visit Chemtrix at booth FC8 in the Flow Chemistry Pavilion