Rapid Reaction Optimization and Scale-Up: Continuous Flow Reactors for Applications in Green Chemistry

Paul Watts

Department of Chemistry, The University of Hull, Hull, HU6 7RX.
Chemtrix BV, Burgemeester Lemmensstraat 358, Geleen, The Netherlands.

CPAC Summer Institute 2010, 20-22 July 2010
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
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

What is a Flow 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 μm (up to 5 mm)
  – Mixing much slower
    – Incorporate mixers
  – Throughput higher
  – More useful when packed with catalysts

• Reactors fabricated from polymers, metals, quartz, silicon or glass

• Why glass?
  – Mechanically strong
  – Chemically resistant
  – Optically transparent
PET - Rapid Reaction Optimisation

• Reaction of 3-(3-pyridinyl)propionic acid

\[
\begin{array}{c}
\text{Pyrene} \\
\text{CH}_2\text{COOH}
\end{array}
\xrightarrow{R'\rightarrow X}
\begin{array}{c}
\text{Pyrene} \\
\text{CH}_2\text{COO}R'
\end{array}
\]

\(\text{Bu}_4\text{NOH, DMF}\)

\(\text{CH}_3\text{I} \text{or} \, ^{11}\text{CH}_3\text{I}\)  
\(\text{FCH}_2\text{CH}_2\text{OTs} \text{or} \, ^{18}\text{FCH}_2\text{CH}_2\text{OTs}\)

• Reaction optimised with one equivalent of \(\text{^{12}CH}_3\text{I}\) (10 mM concentration) at RT

• Hydrodynamic flow (syringe pump)

• Reaction with \(^{11}\text{CH}_3\text{I}\)
  – At 0.5 µl/min flow rate RCY 88%

• Reaction of \(^{18}\text{FCH}_2\text{CH}_2\text{OTs}\) at 80 °C
  – At 0.5 µl/min flow rate RCY 10%

• Purify by HPLC

*Lab Chip, 2004, 4, 523*  
Total Synthesis of PET agents

- Micro reactors generally used for synthesis steps only
- Other steps often performed using traditional approaches
- Need to develop better integration of all steps
- EU FP7 project: Radiochemistry on a Chip (ROC)
- 4M Euro project

Also on-line measurement/detection technology would add value

http://www.roc-project.eu
Indole Synthesis: Rapid Optimisation

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

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Flow Rate (μLmin⁻¹)</th>
<th>Indole (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>1</td>
<td>60.7</td>
</tr>
<tr>
<td>95</td>
<td>1</td>
<td>81.3</td>
</tr>
<tr>
<td>105</td>
<td>1</td>
<td>85.7</td>
</tr>
<tr>
<td>105</td>
<td>0.5</td>
<td>93.3</td>
</tr>
<tr>
<td>115</td>
<td>0.5</td>
<td>98.9</td>
</tr>
</tbody>
</table>

- Note that excess reagents were not necessary
- Similar results for other unfunctionalised ketones

_Tetrahedron_, 2010, in press
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

* Tetrahedron, 2010, in press*
Multi-Step Indole Synthesis

- Aim to incorporate radiolabel

![Chemical structure](image)

- 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

_Tetrahedron_, 2010, in press
Epoxidation of Alkenes

- 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 \textit{in situ}

**Experimental set-up:**
- Reactor packed with Novozyme 435
- Alkene 0.1 M and $\text{H}_2\text{O}_2$ 0.2 M in EtOAc

![Epoxidation reaction diagram]

Epoxidation of Alkenes: Rapid Evaluation

- Evaluation of optimum reaction conditions
- Alkene 0.1 M and H$_2$O$_2$ 0.2 M in EtOAc

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

Epoxidation of Alkenes: Catalyst Lifetime

- Reactor continually used for 25 hours to evaluate performance at optimum experimental conditions

- No loss in activity observed
- RSD 0.08%
- Library synthesis

(+)–γ-Lactamase Enzymes

- Hydrolysis of amides

\[
\begin{align*}
  &\text{R} \quad \text{NH}_2 \\
\text{\longrightarrow} & \text{R} \quad \text{OH}
\end{align*}
\]

- Resolutions

\[
\begin{align*}
  \text{(+) \, \gamma-lactam} & \quad \text{\longrightarrow} & \quad \text{(-) \, \gamma-lactam} \\
  & & \quad \text{+ \quad (+) \, Amino Acid}
\end{align*}
\]

- CLEA from a cloned thermophilic enzyme packed into reactor
  - \textit{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 μl/min

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

*Biotechnology J.*, 2009, 4(4), 510-516
Synthesis of $\alpha$-Aminonitriles: Increased Control

Strecker Reaction:

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

Expensive Catalyst

- Difficult to recover and recycle
- Generation of acidic waste
Continuous Flow Synthesis

Aims of Flow Reaction

• Enable optimisation of imine formation
  – To minimise or prevent cyanohydrin formation
• Employ a stoichiometric quantity of TMSCN 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

0.1 M Product

Strecker Reaction

Reagent Mixing

Conversion (%)

Total Flow Rate (μl min⁻¹)
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

Ketonic Reaction: Novel Processing Conditions

- Novel immobilised Ga(OTf)$_3$ catalyst derivative prepared in-house

Reaction Conditions
- Packed-bed containing 10 mg of PS-Ga(OTf)$_2$
  - $1.1 \times 10^{-2}$ mmol of Ga
- 0.4 M in DCM stock solutions of all reagents
  - Pressure-driven flow
  - Temperatures 25-50 °C
Evaluation of PS-Ga(OTf)$_2$ by Continuous Flow

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Flow Rate ($\mu$l min$^{-1}$)</th>
<th>Temperature (°C)</th>
<th>Conversion (%)</th>
<th>Theoretical Throughput (mg h$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>RT</td>
<td>25.6</td>
<td>13.6</td>
</tr>
<tr>
<td>10</td>
<td>RT</td>
<td>40.8</td>
<td>10.8</td>
</tr>
<tr>
<td>5</td>
<td>RT</td>
<td>52.3</td>
<td>7.0</td>
</tr>
<tr>
<td>1</td>
<td>RT</td>
<td>89.1</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Increasing purity
Decreasing productivity
Evaluation of PS-Ga(OTf)$_2$ by Continuous Flow

![Chemical Reaction](image)

<table>
<thead>
<tr>
<th>Flow Rate ($\mu$L min$^{-1}$)</th>
<th>Temperature (°C)</th>
<th>Conversion (%)</th>
<th>Theoretical Throughput (mg h$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>RT</td>
<td>25.6</td>
<td>13.6</td>
</tr>
<tr>
<td>10</td>
<td>RT</td>
<td>40.8</td>
<td>10.8</td>
</tr>
<tr>
<td>5</td>
<td>RT</td>
<td>52.3</td>
<td>7.0</td>
</tr>
<tr>
<td>1</td>
<td>RT</td>
<td>89.1</td>
<td>2.4</td>
</tr>
<tr>
<td>20</td>
<td>RT</td>
<td>25.6</td>
<td>14.5</td>
</tr>
<tr>
<td>20</td>
<td>30</td>
<td>76.2</td>
<td>43.1</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
<td>100.0</td>
<td>56.6</td>
</tr>
<tr>
<td>20</td>
<td>50</td>
<td>100.0</td>
<td>56.6</td>
</tr>
</tbody>
</table>

- Residence time *ca.* 1 min
- ICP-MS analysis of reaction products
  - < 1 ppm Ga detected
- Library prepared
Production Technology

Scale-up:
- Re-optimised at each stage
- Costly and time consuming

Scale-out:
- Numbering-up/replication
- Cost effective and flexible
- Requires reproducibility within single reactors

Chem. Commun., 2007, 443
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:

- 1μl
- 5μl
- 10μl
- 10μl
- 10μl

• Catalyst reactors:
Rapid Reaction Evaluation: 1,2-Azole Synthesis

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 (n = 5)
• Time taken to generate samples: 27 h
• Volume of reactants employed: 5.97 ml (94.3 mg 1,3-diketone)
• Limiting factor: Analytical evaluation of the samples and data processing (4 days)
Plantrix Meso Reactors

- Glass reactors 15 cm x 15 cm:
  - Contain six layers (2 reactor layers, 2 heat transfer layers and a top/bottom plate)
  - Reaction channels of 1 mm (wide) x 0.7 mm (deep) x 10.5 m (long)

- Reactor can be used for multi-input and operated at 10 bar
  - Temperatures of -40 to 200°C (depending on tubing material)
- Pre-heater and cooler modules are also available to increase/decrease reactant temperature ahead of reaction zone or upon collection
- Customizable reactors available to maximize productivity
Plantrix Scale Up

• Holder is constructed from stainless steel and PEEK
  – All wetted parts are chemically resistant and metal-free

• Separate inputs for reactants and heating fluid
  – Remove contamination risk when exchanging reactors
• Reactors can be stacked to increase productivity (x 10)
  – Scale a process from 0.13 kg h⁻¹ to 1.3 kg h⁻¹ with no change of operating conditions
• Further increases can be made by employing multiple holders
  – *i.e.* Ten holders = 13.0 kg h⁻¹ (11.4 tonne annum⁻¹)
Plantrix System
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
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
  – Suitable for library synthesis
• Increased catalyst turnovers and lifetimes
  – Easier purification/isolation
• Increased process safety
  – Due to rapid dissipation of heat of reaction
  – Low reactant hold-up

Chem. Commun., 2007, 443
Chem. Rev., 2007, 107, 2300
Research Workers and Collaborators

• Researchers
  • Dr. Charlotte Wiles
  • Dr. Bongkot Ngamsom
  • Dr. Joe Dragavon
  • Dr. Vicki Hammond
  • Dr. Gareth Wild
  • Dr. Tamsila Nayyar
  • Dr. Julian Hooper
  • Dr. Linda Woodcock
  • Dr. Haider Al-Lawati
  • Dr. Nikzad Nikbin
  • Dr. Ping He
  • Dr. Victoria Ryabova
  • Dr. Vinod George
  • Dr. Leanne Marle
  • Mairead Kelly
  • Ben Wahab
  • Francesco de Leonardis

• Collaborators
  • Hull colleagues
  • Prof. J. A. Littlechild
  • TNO
  • TUe

• Funding
  • EPSRC
  • Sanofi-Aventis
  • LioniX
  • AstraZeneca
  • EU FP6
  • EU FP7
  • Yorkshire Concept