Organic Synthesis in Micro Reactors

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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 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 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
Indole Synthesis: Rapid Optimisation

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

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

<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>

_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

- 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
## Multi-Step Synthesis: Incompatible Reagents

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Conversion (%)</th>
<th>Actual Yield (g)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldehyde</td>
<td>99.99</td>
<td>0.0150</td>
<td>99.4</td>
</tr>
<tr>
<td>4-Bromobenzaldehyde</td>
<td>99.99</td>
<td>0.0338</td>
<td>99.8</td>
</tr>
<tr>
<td>4-Cyanobenzaldehyde</td>
<td>99.99</td>
<td>0.0284</td>
<td>99.7</td>
</tr>
<tr>
<td>2-Naphthaldehyde</td>
<td>99.99</td>
<td>0.0298</td>
<td>99.8</td>
</tr>
<tr>
<td>Methyl-4-formyl benzoate</td>
<td>100.0</td>
<td>0.0253</td>
<td>99.7</td>
</tr>
<tr>
<td>4-Benzyloxybenzaldehyde</td>
<td>99.99</td>
<td>0.0219</td>
<td>99.1</td>
</tr>
<tr>
<td>Nitrothiophenecarboxaldehyde</td>
<td>99.99</td>
<td>0.0238</td>
<td>99.7</td>
</tr>
<tr>
<td>3,5-Dimethoxybenzaldehyde</td>
<td>99.99</td>
<td>0.0213</td>
<td>99.5</td>
</tr>
<tr>
<td>4-Methylbenzaldehyde</td>
<td>99.99</td>
<td>0.0284</td>
<td>99.3</td>
</tr>
</tbody>
</table>

*Lab Chip, 2007, 7, 322*
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 *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 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

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%

Epoxidation of Alkenes: Library Synthesis

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Temperature (°C)</th>
<th>Residence Time (min)</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>70</td>
<td>2.6</td>
<td>100.0</td>
<td>99.1</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>5.2</td>
<td>57.2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>2.6</td>
<td>100.0</td>
<td>99.2</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>5.2</td>
<td>31.9</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>2.6</td>
<td>32.1</td>
<td>-</td>
</tr>
</tbody>
</table>


(+)–γ-Lactamase Enzymes

- Hydrolysis of amides

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{CONH}_2 & \quad \text{COOH}
\end{align*}
\]

- Resolutions

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

- CLEA from a cloned thermophilic enzyme
  - *Comomonas acidovorans*
Temperature Dependance of CLEAs

• Experimental conditions
  • Flow rate 1µl/min
  • Substrate 10 mmol/L benzamide in phosphate buffer pH 7

![Graph showing substrate conversion vs. reaction temperature. The graph peaks at a reaction temperature of 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 α-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
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

![Diagram showing the synthesis of imines](image)

Graph showing conversion (%): 25 μl min\(^{-1}\)
Continuous Flow Addition to Imine

0.2 M Stock Solutions in MeCN

Strecker Reaction

Reagent Mixing

Conversion (%)

Total Flow Rate (µl min⁻¹)
Multi-Step Reactor Design

Reaction Conditions: Total flow rate 5.0 μl min⁻¹, 0.4 M aldehyde and amine, 0.2 M TMSCN
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

Reaction of Bifunctional Compounds

- Would ketones react under these conditions?

- No trace of reaction of ketone

  Chemoselective for aldehydes, no reaction of the ketone moiety!!

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

- Residence time $ca.$ 1 min
- ICP-MS analysis of reaction products
  - $< 1$ ppm Ga detected

<table>
<thead>
<tr>
<th>Flow Rate ($\mu l$ min$^{-1}$)</th>
<th>Temperature ($^\circ$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>
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<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>

Increasing purity
Decreasing productivity

Increasing purity
Increasing productivity
### Reaction Array of Ketones

![Reaction Array of Ketones](image)

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Product</th>
<th>Flow Rate ($\mu$L min$^{-1}$)</th>
<th>Temperature ($^\circ$C)</th>
<th>Yield (%)</th>
<th>Throughput (mg h$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>40</td>
<td>99 (78)$^a$</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>40</td>
<td>100 (98)</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>40</td>
<td>99 (95)</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>40</td>
<td>99 (85)</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>40</td>
<td>100 (85)</td>
<td>48</td>
</tr>
</tbody>
</table>

- Products isolated in high yield and purity
- Throughput $>$ 50 mg hr$^{-1}$
- Library of 10 compounds prepared
- Catalytic turnover $>$ 850
- Ga also a better catalyst for the aldehydic Strecker reaction
  - cf. PS-RuCl$_3$

$^a$ The number in parentheses represents the isolated yield obtained by Olah
Conclusions

• Micro reactors allow the rapid optimisation of reactions
  – 5 minute reactions (followed by analysis)
  – High surface to volume ratio ideal for solution phase chemistry
  – High-throughput library synthesis

• Immobilised catalysts allow the synthesis of highly pure compounds
  – Longer lifetime of catalysts
  – Less leaching

• With regard to the Strecker reaction the micro reactor system generated products in:
  – Higher purity
  – Higher conversion
  – Higher selectivity

*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

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