Advantages of continuous synthesis

- **Safety** - Small scale, no headspace, no accumulation of reactive/toxic intermediates
- **Expansion of reaction space/toolbox/feasibility** - Many “Forbidden Reactions” become feasible
- **Robustness, stability, QbD** - Steady-state, continuous processes
- **Scalability** – scale-up faster and reliable
- **Versatility and flexibility** - customizable and adjustable equipment
- **Leverage and efficiency** - increase in throughput, with a dramatically reduced equipment footprint
Elements needed to realize continuous synthesis

- Chemically compatible, easily integrated continuous flow reactors with operation conditions that can be scaled from research to production
- Knowledge based design, in-line monitoring and optimization approaches of synthesis, workup, and purification steps
- Ability to scale predictably over several orders of magnitude of production for homogeneous as well as multiphase processes
- Immobilization and/or recycling of catalysts
- Development of workup techniques for integration with reaction sequences and when economically advantageous, recycle of regents
- Methods for handling (addition, formation, separation,...) of solids in continuous flow reactors

Components of a microreactor system

- Reagents
- Reactor: microstructured metal, Si, glass, ceramic, or stainless steel, polymer tubing
- Pump: syringe, HPLC, gear, pressure driven ...
- Mixer: active (stirring), passive (diffusion)
- Temperature control
- Thermal quench
- In-line Monitoring: UV-vis, FTIR, Raman, HPLC
Microstructured Systems

Tube Flow Systems

www.imvt.kit.edu

http://www.vapourtec.co.uk/

www.imm-mainz.de

www.chemtrix.com

www.thalesnano.com

Production Systems

Lonza/Ehrfeld/BTS
www.ehrfeld.com

ESK
www.esk.com

Corning
S. Braune et al., Chemistry Today 2008 26 (5) Sep-Oct
www.corning.com
When is a premixing necessary?

- Diffusion time $\tau_m = \frac{L^2}{D}$ alone is not sufficient.
- The Damköhler number is the appropriate scaling of reaction and transport effects:
  \[ Da = \frac{kC_0^{n-1}d_i^2}{4D} = \frac{\text{rate of reaction}}{\text{rate of transport}} \]
- 1st order reaction 95% conversion after $k\tau = 3$
  \[ \Rightarrow Da = \frac{3d_i^2}{4\tau D} \]
- Similar numbers can be derived for other reaction expressions or experimental data.

---

Dispersion effects

Bodenstein number (Bo) enables estimate of deviation from plug flow:

\[ Bo = \frac{uL}{D} \]

Plug flow:

Laminar flow:

\[ D = D + \frac{u^2 d_i^2}{4\beta D} \]

$\beta = 48$ tube
$\beta = 30$ square channel

Application to a glycosylation reaction

Improvement of mixing: 3x throughput
Elimination of dispersion: identical behavior across tubes, no byproduct


Rapid reaction optimization using inline analysis and feedback

Automated system with feedback capabilities for optimization
Plug-and-play
Different in-line analysis methods, e.g., HPLC, FTIR
Self calibrating
Customizable, experimental optimization algorithms
‘Black-box’ approaches
Model based methods

Multi-variable reaction optimization

Yield = 80%

T = 88°C  R_t = 50s

- Nelder-Mead Simplex algorithm for online optimization
- 46 automated experiments to move from benzaldehyde yield of 21% to 80%
- Achieved 1 experiment per 10 minute throughput rate


Online optimization with ReactIR flow cell

- Black box optimization is feasible with a variety of optimization techniques.
- The choice of methods significantly influences the number of experiments

Microreactors can produce chemical kinetics in relatively few experiments

- Benefits of using integrated microreactors for kinetic studies:
  - Rate law (mechanism formulation)
  - Rate parameters

- With the appropriate approach, microreactors yield:
  - Study reactions at unconventional conditions
  - Better control of residence time and temperature
  - Investigate fast reactions
  - No temperature gradient
  - No mixing gradient
  - No head space
  - Accurate sampling


---

**Reaction example**

\[
\begin{align*}
\text{Isoprene Concentration} & \quad \text{Probability Distribution} \\
0.45 & \quad 0.50 & \quad 0.55 & \quad 0.60 & \quad 0.65 & \quad 0.70 & \quad 0.75 & \quad 0.80 & \quad 0.85 & \quad 0.90 & \quad 0.95 & \quad 1.00 & \quad 1.05 & \quad 1.10 & \quad 1.15 & \quad 1.20 \\
\end{align*}
\]

\[r_I = -k_1 C_1 C_2\]

Parameter | After 8 experiments
---|---
\(E_A\) (kJ/mol) | 50.7 ± 0.9 (1.8%)
\(A \times 10^5\) (M\(^{-1}\) s\(^{-1}\)) | 1.71 ± 0.6 (35.5%)

Determine rate parameters
Optimize conditions
Scale-up

Scale-up based on kinetics and reactor models

- Use chemistry information with reactor flow and heat transfer models to predict performance of scaled up system
  - Example: incorporating kinetics from microreactor to scale up by a factor of 500 using a Corning Advanced Flow Reactor System
  - Predicted performance agrees with experimental data

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (min)</th>
<th>Temp. (°C)</th>
<th>Experimental</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>110</td>
<td>78.1 ± 0.4</td>
<td>79.3</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>100</td>
<td>82.6 ± 0.1</td>
<td>83.7</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>110</td>
<td>85.2 ± 1.0</td>
<td>86.5</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>126</td>
<td>83.5 ± 3.1</td>
<td>83.9</td>
</tr>
</tbody>
</table>


Using high pressure and temperature to accelerate reactions - Aminolysis of epoxides

Flow reactor yields similar to microwave batch yields without headspace issues, shorter reaction times, reduced bis-alkylation, and scalable performance – performance scales to larger reactors

Kinetics and scaling of Aminolysis of epoxides

- Single preparation of two reagent solutions, 0.5 to 2 g of each reagent to scan up to 35 sets of conditions with samples in triplicate, generating over 100 data points within one 8-h period.
- Scale from 0.12 mL to 12 mL with accurate prediction of yield
- Dean flow off-sets increased dispersion


Continuous flow systems for manufacturing

- Production scale systems can be achieved by scale-out or scale-up
  - **Scale-out** – parallelization of microreactors
    - Retain heat and mass transfer benefits
    - Large challenges in fluidic connections and control
  - **Scale-up** – increasing size of reactor
    - Realize higher production rates
    - Retain heat transfer advantages
    - Reduce micro-scale concerns (i.e. clogging)
    - Use knowledge of chemistry and process to scale
- **Example:**
  - Corning/DSM - 5 weeks of operation - 40 metric tons processed (Chemistry Today, Vol 26, Sep-Oct 2008)
Examples of reactor scaling

Lonza/Ehrfeld/BTS
www.ehrfeld.com

Corning
www.corning.com

Scaling multiphase reactions

\[-r_A = \frac{dC_A}{dt} = k_A \alpha (C_A^* - C_A)\]

- Gas-liquid flow: spiral design (silicon nitride) and Corning AFR
- Liquid-liquid flow: spiral design, Corning LFR & AFR

Spiral design
Corning LFR
Corning AFR

Volume: 220μL
450μL
8.7mL

Length: 400μm
700μm
1 mm
Mass transfer in gas-liquid flow: pH-measurements by laser induced fluorescence (LIF) and velocities by particle image velocimetry (PIV)

Regions of high mass transfer correspond to regions with increased flow


Mass transfer in gas-liquid flow

- Microreactors:
  - Mass transfer is connected to internal recirculation
  - Interfacial slip governs the strength of this recirculation
  - Mass transfer is dominated by the bubble cap

S. Kuhn, M.J. Nieves Remacha
Gas-liquid flow in Corning AFR

- Periodic merging and break-up of the bubbles
- Constant renewal of the gas-liquid interface
- Interfacial area is more efficiently used (entire gas bubble vs. bubble caps)

Butanol-water: mass transfer in Corning AFR and LFR modules

- Splitting and combining droplets provide effective mass transfer over different length scales
Flow patterns of liquid/liquid flow:

Hexane/Water

Hexane always dispersed phase due to hydrophilicity of glass walls

- $Q_w = 10 \text{ mL/min}$, $Q_h = 10 \text{ mL/min}$
- $Q_w = 40 \text{ mL/min}$, $Q_h = 40 \text{ mL/min}$

- $Q_h, Q_w = 10 - 80 \text{ mL/min}$
- $d_p$ decreases from inlet towards outlet
- $d_p = 0.3 - 1.4 \text{ mm}$
- $a = 1000 - 10000 \text{ m}^{-1}$
- $k_L a = 0.9 - 41 \text{ s}^{-1}$
- $\Delta P = 2.5 - 120 \text{ kPa}$

CFD will ultimately allow prediction of mass transfer performance

- $Q_w = 20 \text{ ml/min}$, $Q_h = 20 \text{ ml/min}$
- $Q_w = 40 \text{ ml/min}$, $Q_h = 10 \text{ ml/min}$
Example of mass transfer effects

With increasing volumetric aqueous-to-organic phase ratio, the rate of catalyst transfer across the aqueous slug-cap interface increases.

Corning LFR behaves better due to higher mass transfer rate.

Y. Zhan, S Born

Multi-step synthesis using solvent switch

- Preparation of aryl triflate in first reaction step
- Extract base and residual reagent by liq-liq extraction
- Solvent switch by single stage microfluidic distillation
- Carry out subsequent reaction step via Heck reaction

Liquid-Liquid Extraction enables multistep synthesis

DPPA on-demand

- Biphasic conditions solve NaN₃ solubility.
- Outlet 0.2 M excess NaN₃ pH = 9.5 (pKa HN₃ = 4.75).
- Membrane separation removes water and salts.
- In-line FTIR allows product stream to be immediately quenched/used

Scaling-up: Continuous run

- Corning Low Flow Reactor
- 9-12 mL/min $t_{res} = 1-1.3$ min
- $v_f = 12$ mL/min, $F_{DPPA} = 1$ mol/hr, 6 kg/day
- Use in downstream chemistry (Curtius,...)
Multistep synthesis of amides directly from alcohols and amines

Oxidation with $O_2$:
- Lower cost
- Simplify workup
- Catalyst of choice: $Ru/Al_2O_3$ - 5wt%

Continuous microreactor synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>$T$ (°C)</th>
<th>Conversion $^\circ$ (%)</th>
<th>Yield $^\circ$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ethyl benzyl alcohol</td>
<td>100</td>
<td>95</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>benzyl alcohol</td>
<td>110</td>
<td>86</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>4-tert-butyphenyl alcohol</td>
<td>100</td>
<td>&gt;99</td>
<td>90$^\circ$</td>
</tr>
<tr>
<td>4</td>
<td>benzyl 2-Chlorobenzyl alcohol</td>
<td>120</td>
<td>&gt;99</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>benzyl 2-Bromo-4-chlorobenzyl alcohol</td>
<td>130</td>
<td>97</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>benzyl 2-Bromo alcohol</td>
<td>110</td>
<td>&gt;99</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>benzyl alcohol</td>
<td>130</td>
<td>97</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>4-tert-butyphenyl alcohol</td>
<td>130</td>
<td>&gt;99</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>4-tert-butyphenyl alcohol</td>
<td>110</td>
<td>96</td>
<td>69</td>
</tr>
<tr>
<td>10</td>
<td>benzyl alcohol</td>
<td>120</td>
<td>&gt;99</td>
<td>97</td>
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<td>11</td>
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<tr>
<td>12</td>
<td>benzyl alcohol</td>
<td>120</td>
<td>&gt;99</td>
<td>81</td>
</tr>
</tbody>
</table>
Catalyst immobilization and recycle

- Packed beds – high surface area supports
  - Potential for high catalyst loading
  - Physical (e.g., fluorous) and chemical (covalent) attachment to catalyst surface
- Biphasic systems
  - Homogeneous catalysis - catalyst in one phase, substrates in another
  - Integration of separators and pumps for continuous operations and recycling
- Nano filtration
  Low molecular weight cut-off solvent stable membranes


Challenges
- Retain activity of immobilized catalyst
- Leaching of catalyst, especially metal centers, requiring the use of downstream metal capture beds
- Solvent selection
- Sufficiently low and sharp molecular cut-off and solvent stability of membranes

Recycling of homogeneous catalysts

- Continuous recycling of unmodified homogeneous palladium catalysts via liquid-liquid phase separation

\[
\begin{align*}
\text{Br} & \quad \text{OMe} \\
\text{toluene, 2M KOH, TBAB 5 mol%} & \quad 100^\circ \text{C} \\
\text{MeO} & \quad \text{L3} \\
\text{OMe} & \quad \text{HO} \\
\text{P(} & \quad \text{i-Pr)} \\
\text{i-Pr} & \quad \text{i-Pr} \\
\text{i-Pr} & \quad \text{i-Pr} \\
\text{L3} & \quad \text{L3}
\end{align*}
\]

- Continuous catalyst recycling in palladium catalyzed hydroxylation of aryl halides. 5 runs with nearly constant yield of ~80%, but then slow degradation of the catalyst.

Li, P. et al. ChemCatChem 2013
Continuous nano-filtration and recycle of a metathesis catalyst in a micro flow system

Evonik Puramem® 280 membrane retains catalyst in the system
• Low co-fee of catalyst to make up for deactivated catalyst
• Continuous ethylene removal to reduce catalyst deactivation

• TOF ~ 750 h⁻¹ at the start of the experiment
• 10 minute residence time with > 94% product at the reactor outlet
• Total TON of 935 was obtained using this system.
Exploring the origins of clogging

- Handling of solid reagents and products raise challenges for microreactors


Teflon reactor with integrated ultrasound

- Continuous operation without plugging
- Piezo @ 50kHz, 30 Watt

Kuhn, S. et al., Lab Chip 11 2488-92 (2011)
Batch synthesis has numerous challenges and limits realization of novel nanostructures

- Optical properties and average size depend on factors difficult to control: injection, local temperature and concentration fluctuations, mixing and cooling rates
- Controlled growth of heterostructures difficult to realize, specifically core/shells and graded alloys

Precursors

Optical properties and average size depend on factors difficult to control: injection, local temperature and concentration fluctuations, mixing and cooling rates. Controlled growth of heterostructures difficult to realize, specifically core/shells and graded alloys.

Two stage system: Separate investigations of mixing and aging processes

Aging temperature is significant

- Residence time: 4 min (fixed)
- Solvent, octane at 65 Bar

Reactor design for gradual addition

- Consideration
  - Distribution of each side flows
  - Viscosity and flowrate changes
  - Residence time after each injection
  - Reactor size restriction
  - Prevent back flows

Sequential addition of molecular precursors increase InP QD size

**InP / ZnS Core-Shell QD Synthesis**

**InP Growth Investigation**

1. Mixing
2. Aging
3. Seq-Growth
4. Shell Formation

**Synthesis of InP/ZnS core shell structures**

- **In(MA)₃**: Indium myristate
- **(TMS)₃P**: tris(Trimethylsilyl) phosphine
- **MA**: Myristic acid
- **Zn(OA)₂**: Zinc oleate
- **(TMS)₂S**: Bistrimethylsilyl sulfur
Hierarchical assembly nanostructures for catalysis: nanoparticle synthesis

S.K. Lee, et al., Lab Chip, 2012, 12, 4080 - 4084
Hierarchical assembly nanostructures for catalysis: self assembly

S.K. Lee, et al., Lab Chip, 2012, 12, 4080 - 4084

Hierarchical assembly nanostructures for catalysis: Microreactor application

Oxidation of 4-isopropyl benzaldehyde

S.K. Lee, et al., Lab Chip, 2012, 12, 4080 - 4084
Summary

• Microreactors are coming of age
• Understanding of reaction and mass transfer enables implementation and scaling of flow processes
• Automated tools for extraction of chemical kinetics by using statistical techniques
• Automated optimization based on black box approaches, or better, models with chemical kinetics
• Scaling of homogeneous systems can be accomplished with classical reaction engineering concepts
• Quantitative understanding of heat and mass transfer needed for scaling of multiple phase systems
• Emerging techniques for handling of solids, including the synthesis of nanoparticles
• Ability to synthesize complex micro-nano structures

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Questions?