Microreactors and Microfluidic Cells in Organic Synthesis

MacMillan Group Meeting
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Microreactors and Microfluidic Cells in Organic Synthesis

Presentation Outline

- Introduction
- Microreactor Design Fabrication and Operation
- Advantages of Microreactors
  - Increased Yields and Selectivity
  - Increased Safety
  - Increased Efficiency
- Organic Reactions in Microreactors
  - Stoichiometric Reactions
  - Catalytic Reactions
- Conclusions

Lead References:

Why use microreactors instead of more traditional reaction vessels?
Microreactors and Microfluidic Cells in Organic Synthesis

Introduction

- Each stage of scale-up usually requires re-optimization of the process.

- The process does not change.
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Microreactor Design

- Consist of a series of small channels (10–1000µm)
- Common materials include: Silicone, glass, stainless steel, and plastics
- Simple "home-made" devices can still give good results
- Usually attached to auxiliary pumps and fluid delivery lines
- Fluids introduced via hydrodynamic pumping or electroosmotic flow
Microreactors and Microfluidic Cells in Organic Synthesis

Microreactor Design

- Syringe pumps and peristaltic pumps are the most popular means to provide hydrodynamic flow.

- Advantages include: Pumps are relatively inexpensive, they can be used with any solvent and microreactor material, pump does not contact fluid (peristaltic).

- Disadvantages include: Only slow flow rates for small channel reactors, pulsing of flow, and susceptible to parabolic flow profiles.
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Microreactor Design

Electroosmotic or electrokinetic flow results when a potential bias is applied between the channel inlet and outlet.

Advantages include: Very precise fluid handling with computerized automation, velocity profile is nearly flat greatly reducing reagent dispersion.

Disadvantages include: Usually more expensive than hydrodynamic pumping devices, limited to materials that develop surface charge (glass, silicone), limited solvent compatibility.
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Microreactor Design

Channel junctions can be simple Y or T-type junctions

More complex configurations and channel shapes are possible

Mixing times are usually on the microsecond time-scale
Microreactors and Microfluidic Cells in Organic Synthesis
Advantages of Microreactors

Microreactors can lead to increased yields and selectivities through rapid mixing and better thermal management.

Typical stirred reactions mix by convection. Inhomogeneities in the fluid and small changes in the reaction vessel can produce convective dead zones that lead to concentration gradients, poor heat transfer "hot spots", and ultimately inefficient chemistry.

Small dimension microreactors can effect mixing in microseconds, classical reactors mix on the order of seconds or longer. Rapid mixing and superior temperature control occur due to high surface-to-volume ratios 30,000 m²·m⁻³ vs. 100 m²·m⁻³.


Microreactors and Microfluidic Cells in Organic Synthesis
Advantages of Microreactors

- Watt's aldol reaction is one example where the rate increase is dramatic

\[
\begin{align*}
\text{OSiMe}_3 + \text{H} & \xrightarrow{TBAF} \text{OH} \\
\text{Time Needed to Reach 100\% Conversion} \\
\text{Flow: 20 minutes} & \quad \text{Batch: 24 hours}
\end{align*}
\]

- Taghavi-Moghadam obtained excellent Grignard addition selectivity

\[
\begin{align*}
\text{Optimized Flow Conditions: 78\% Yield, 95:5 A:B} \\
\text{Batch Conditions: 49\% Yield, 65:35 A:B}
\end{align*}
\]

Microreactors and Microfluidic Cells in Organic Synthesis

Advantages of Microreactors

- Microreactors allow access to exothermic or possible runaway reactions

\[
\text{C}_6\text{H}_5\text{OH} \xrightarrow{\text{HNO}_3} \text{C}_6\text{H}_5\text{NO}_2\text{OH} \quad \text{C}_6\text{H}_5\text{NO}_2
\]

Yield of mononitrate mixture increased from 55% to 75%.
Purity increased from 56% to 78%.
Polymeric byproducts reduced by a factor of 5.


- Small volumes also enable the safe use of toxic or explosive reagents

\[
\text{C}_6\text{H}_{13} \xrightarrow{\text{Rose Bengal, O}_2, \text{h}} \text{C}_6\text{H}_{13}\text{O}
\]

Yield of ascaridole increased:
67% batch to 85% in microreactor
89% Yield, 1.8 minute residence time
91 g/hour throughput

Microreactors and Microfluidic Cells in Organic Synthesis
Stoichiometric Reactions

A variety of carbon–carbon bond forming reactions have been carried out in flow

\[
\text{Me} \xrightarrow{1. \text{NaHMDS, THF, } -100^\circ C} \xrightarrow{2. \text{PhCBr}} \text{Me} + \text{PhMe} + \text{PhMe} \\
\text{Flow: 41\% Yield, 91:9 d.r., only s.m. present} \\
\text{Batch: 31\% ield 85:15 d.r., >10\% byproduct} \\
\text{Increased temp in batch gave >50\% byproduct}
\]


\[
\text{MeO} \xrightarrow{\text{NaOCH}_3} \xrightarrow{\text{MeOH}} \text{MeO} + \text{MeO} \\
\text{Flow: Tunable } E:Z\text{ ratio from 1:2 to 5:1} \\
\text{Batch: 3:1 } E:Z
\]

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Stoichiometric Reactions

- Oxidations and reductions in flow often show marked improvement over batch conditions due in part to precise fluid handling capabilities.

\[
\begin{align*}
\text{OH} & \quad \xrightarrow{1. \text{DMSO/TFAA}} \quad \text{K} + \text{S} + \text{O} \\
& \quad \xrightarrow{2. \text{Et}_3\text{N}} \\
\text{At } -20 \text{ °C:} & \\
\text{Microreactor gives 88% desired product} \\
\text{Batch gives 19% product, 72% side products}
\end{align*}
\]


- Reinhoudt observed a dramatic rate increase for Fisher esterification at identical concentrations for the flow and batch reactions.

\[
\begin{align*}
\text{\[\text{OH} \quad \xrightarrow{\text{H}_2\text{SO}_4, \text{EtOH}} \quad \text{\[OEt} \\
& \quad \xrightarrow{50 \text{ °C}} \\
\text{For 40 minute reaction time:} & \\
\text{Microreactor Yield: 83%} \\
\text{Batch Yield: 15%}
\end{align*}
\]

Microreactors and Microfluidic Cells in Organic Synthesis
Stoichiometric Reactions

Watts and Haswell have demonstrated the use of microreactors in peptide synthesis as an alternative to solid-phase synthesis.

\[
\text{Cl}\text{FmocCHN}^{-}\text{C}^{-}\text{O}\text{H} \xrightarrow{\text{EDCI, CH}_2\text{Cl}_2} \text{Cl}\text{FmocCHN}^{-}\text{C}^{-}\text{OPFP}
\]

\[
\text{H}_2\text{N}\text{C}^{-}\text{O}\text{Dmab} \xrightarrow{\text{DMF}} \text{Cl}\text{FmocCHN}^{-}\text{C}^{-}\text{N}\text{C}^{-}\text{O}\text{Dmab}
\]

Multiple syringe pumps sequentially added the reagent mixtures.


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Stoichiometric Reactions

- Photochemistry has also found application in flow, including high-throughput synthesis

[2+2] Cycloaddition

\[ \text{Haloacetylene} + \text{CH}_3\text{CN} \rightarrow \text{Product} \]

83-88% Yield, >25 g/hour
>600 g in 24 hours

[5+2] Cycloaddition

80% Yield, >7 g/hour
>150 g in 24 hours

Hook, D. B. A.; Dohle, W.; Hirst, P. R.; Pickworth, M.; Berry, M. B.; Booker-Milburn, K. I. 
Microreactors and Microfluidic Cells in Organic Synthesis
Catalytic Reactions

- Catalysts can be introduced as solutions or be immobilized on solid support

![Chemical reactions and yields](image)

Suzuki coupling

Sonogashira coupling

Mizoroki-Heck coupling


Microreactors and Microfluidic Cells in Organic Synthesis

Catalytic Reactions

Catalytic oxidations and reductions in microreactors have been studied extensively.

\[
\begin{align*}
\text{HOCN} & \xrightarrow{\text{Pd/C, MeOH, H}_2, 25 \degree C} \text{HOOCN} & \text{72\% flow} \\
\text{Pd/C, MeOH, H}_2, 90 \degree C & \rightarrow \text{HOOCN} & \text{71\% Yield} \\
\text{51\% batch} & \text{<2 min.}
\end{align*}
\]


\[
\begin{align*}
\text{NHCbz} & \xrightarrow{\text{Pd/C (10\%), H}_2, \text{EtOAc}/\text{AcOH}/\text{EtOH}} \text{NHCbz} \\
\text{Flow: 98\% conversion in 3.5 hours} & \text{Batch: Complete conversion took 3 days}
\end{align*}
\]


\[
\begin{align*}
\text{O} & \xrightarrow{\text{Sc}[\text{N(SO}_2\text{C}_8\text{F}_{17})_2]_3, 30\% \text{H}_2\text{O}_2, \text{PhCF}_3} \text{O} + \text{O} \\
\text{Flow: 100\% Yield, 97:3 ratio of regioisomers} & \text{Batch: 53\% Yield, 67:33 ratio}
\end{align*}
\]

Microreactors and Microfluidic Cells in Organic Synthesis

Catalytic Reactions

Organocatalytic reactions are also known to take place in microreactors.

Watts has generated several amine bases suspended on silica to catalyze the Knoevenagel condensation.


For: Temp < −70°C, rxn. time <1 min favors B
at −40°C, time > 4 min exclusively A

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Catalytic Reactions

Reaction details for Seeberger's glycosylation in a microreactor

Mixing Zone: 200 μm
Retention/Reaction Zone: 400 μm
Retention times from less than 1 min to over 1 hour
In situ Et₃N quench/dilution/standard injection for HPLC product analysis
100 mg s.m. enabled analysis of 40 rxn. conditions in <24 hours

Microreactors and Microfluidic Cells in Organic Synthesis
High-Throughput Synthesis

Researchers at Johnson and Johnson utilized the CYTOS benchtop microreactor to access large quantities of synthetically useful intermediates synthesized through potentially hazardous reaction conditions.

Microreactors and Microfluidic Cells in Organic Synthesis
High-Throughput Synthesis

- Highly exothermic reactions that are problematic in batch-type reactors are easily controlled

\[
\begin{align*}
\text{L-tert-leucine} & \quad \xrightarrow{\text{aq. NaOH, THF, r.t. \(-40^\circ C\)}} \quad \text{amide product} \\
\text{91\% Yield, 7 min residence time} & \quad 1 \text{ kg/12 hours}
\end{align*}
\]

- The CYTOS microreactor system can handle temperatures from \(-65^\circ C\) to over \(200^\circ C\)

\[
\begin{align*}
\text{Newman-Kwart rearrangement} & \quad \xrightarrow{\text{170^\circ C}} \quad \text{amide product} \\
\text{100\% Yield, 14 min residence time} & \quad 34 \text{ g/hour}
\end{align*}
\]

Microreactors and Microfluidic Cells in Organic Synthesis

High-Throughput Synthesis

- Reactive/unstable intermediates can be generated *in situ* and used in subsequent reactions

\[
\text{OMe} \quad \text{Mg, THF, or} \quad \text{MgBr, Li} \quad \text{OMe} \quad \begin{array}{c}
\text{BR} \quad \text{M} = \text{MgBr, Li} \\
\text{M} = \text{MgBr, Li}
\end{array}
\]

Batch \(-10 \, ^\circ \text{C}: 32\%\) Yield (M = Li)
Batch \(-65 \, ^\circ \text{C}: 80\%\) Yield (M = Li)
Flow \(-14 \, ^\circ \text{C} \, (17\, \text{sec})\) then \(-40\, ^\circ \text{C}\)
87% Yield, 54g/h (M = Li)

- Ring expansion with ethyl diazoacetate exhibits an initiation period resulting in a violent exotherm and gas evolution when 60% reagent addition has occurred

\[
\begin{array}{c}
\text{Pyrrolidinone} + \text{N}_2 \quad \text{BF}_3\text{Et}_2\text{O} \\
\text{Boc} \quad \text{Boc}
\end{array}
\]

89% Yield, 1.8 minute residence time
91 g/hour throughput

Microreactors and Microfluidic Cells in Organic Synthesis

Enantioselective Reactions

- Reek's asymmetric transfer hydrogenation reaction

\[
\text{Me} \quad \text{Me} \quad \text{OH} \quad \text{OH} \quad \text{Me} \quad \text{O} \\
\text{Ph} \quad \text{Me} \quad \text{OH} \quad \text{OH} \quad \text{Ph} \quad \text{Me}
\]

\[
\text{[RuCl}_2(p\text{-cymene})]_2 \quad \text{KOT-Bu} \quad \text{95% Yield, 90% ee}
\]


- Salvadori's glyoxylate–ene reaction with polystyrene–bound bis(oxazoline)

\[
\text{Me} \quad \text{Me} \quad \text{H} \quad \text{CO}_2\text{Et} \quad \text{OH} \quad \text{H} \quad \text{CO}_2\text{Et}
\]

\[
\text{Ph} \quad \text{Ph} \quad \text{CH}_2\text{Cl}_2, 0 \degree \text{C} \quad \text{Batch: 99% Yield, 89% ee, 6 h} \quad \text{Flow: 78% Yield, 88% ee, <5 min}
\]

**Microreactors and Microfluidic Cells in Organic Synthesis**

**Enantioselective Reactions**

Dialkyl zinc addition gave good yields and ee's initially but showed erosion over time.

![Chemical structure and reaction](image)

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<th>Aldehyde</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<td>X = H</td>
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Microreactors and Microfluidic Cells in Organic Synthesis

Enantioselective Reactions

Reetz et al. used integrated microchip electrophoresis to analyze enzymatic reactions

![Enzymatic Reaction Diagram](image)

<table>
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<th>Method</th>
<th>Conv (%)</th>
<th>ee (%)</th>
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Schwalbe's synthesis of Ciprofloxacin and analogs is an excellent example of the utility of microreactors.

Microreactors and Microfluidic Cells in Organic Synthesis
Multi-Step Reactions

- Schwalbe's microreactor schematic for the synthesis of Ciprofloxacin analogs

Reagent pulses were separated by solvent plugs enabling continuous library synthesis

Ley's synthesis of oxomaritidine was accomplished exclusively in flow.

PIFA = (ditrifluoroacetoxyiodo)benzene

Microreactors and Microfluidic Cells in Organic Synthesis
Multi-Step Reactions

Ley's synthesis of oxomaritidine was accomplished exclusively in flow.

Product obtained with >90% purity by $^1$H NMR
40% isolated yield overall (phenolic oxidation gave 50% yield)
Natural product can be obtained in less than 1 day
Only obtained 20 mg of (+)-oxomaritidine

Conclusions

- Microreactor technology is still a relatively new and unexplored tool for organic chemists.
- Microreactors have the potential to increase reaction efficiency and safety while reducing environmental impact.
- Continuous flow reactors can allow access to large quantities of synthetically useful intermediates.
- Asymmetric catalysis is possible but there are few examples in the literature.
- Multiple reactors in tandem can be used to rapidly build molecular complexity.