Specializing in Flow Chemistry for:

- Reaction Optimization
- Process Development, Including new Synthetic Routes
- Producing Quality Compounds
- Process Equipment

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What is Continuous-Flow Chemistry?

- Replace batch methods with innovative fluidic solutions that enable the use of reaction conditions that are not easily achieved by conventional methods.
- Increases the “chemical space” available for process development.
- Flow systems consist of pumps, mixers, reactors, separators and detectors.

Traditional Batch
Fine Chemicals and Pharmaceuticals

Continuous-Flow
Commodity and Petrochemicals

Small-scale Continuous-Flow
Why use Continuous-Flow Chemistry?

Advantages of continuous-flow systems:
- Controlled mixing and quenching
- 100 fold increase in heat and mass transfer
- Ability to handle highly reactive systems
- Access conditions not easily achieved by conventional methods
- Continuous operation
- Scalable
- On-line optimization and monitoring reaction output

Desired result:
- Faster reactions, higher selectivities, better yields and lower costs
Fundamentals of Flow Chemistry

Mixers:
- Very rapid mixing – near “instantaneous”
- Provides excellent control of reagent concentrations (homogeneity)
- Establishes a well defined beginning and end points for the reaction

Reactors:
- Designed to provide excellent heat and mass transfer
- Engineered to cause proper fluid dynamics resulting in narrow residence time distributions
Changing Reaction Parameters

\[
\frac{\text{Reactor Volume}}{\text{Flow Rate}} = \text{Reaction Time}
\]

For a given reactor:
\[
\uparrow \text{ in flow rate} = \downarrow \text{ in reaction time}
\]
\[
\frac{1 \text{ mL}}{0.25 \text{ mL/min}} = 4 \text{ min}
\]

For a given flow rate:
\[
\uparrow \text{ in reactor volume} = \uparrow \text{ in reaction time}
\]
\[
\frac{2 \text{ mL}}{0.25 \text{ mL/min}} = 8 \text{ min}
\]

Scale:
throughput = total flow rate \times product concentration \times molecular weight of product
\[
1.0 \text{ mL/min} \times 0.5 \text{ mol/L} \times 240 \text{ g/mol} = 7.2 \text{ g/hr}
\]

Increases in throughput can be achieved by:
1) increasing flow rate (with proportional increase in reactor volume)
2) parallelization
Fundamentals of Flow Technology

Flow Rate

1 μL/min  10 μL/min  100 μL/min  1 mL/min  10 mL/min  100 mL/min  1 L/min
Flow Technology - Mixers

Low Flow Rates

Mixing:
- Mixing occurs via DIFFUSION
- Fast mixing is achieved by decreasing the diffusion path length
- Best executed by combining streams in very small channels
- Interdigitated micromixers

Jensen Group
MIT
Flow Technology - Mixers

Higher Flow Rates

Mixing:
- Mixing occurs via CONVECTION
- Fast mixing is achieved by inducing some secondary flow within the fluid
- Best executed by introducing stationary obstacles within the channels
- Static mixers are an effective way to induce secondary flow

Advanced-Flow Reactor
Corning
Flow Technology - Reactors

Residence Time Distribution

Reactors:

- Residence time distribution is affected by dispersion along the length of the flow reactor.
- In critical applications, "plug-like" flow can be induced either by creating secondary flow within the circulating fluid, or via segmented flow using a second phase.

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convective mixing
Flow Technology - Reactors

**Silicon based microreactor**
- Channels are etched out of the Si wafer, which is then capped by a Pyrex wafer to form the fluidic channel
- Small reactor volumes (50 – 150 μL)

**Tubular reactors**
- Comprised of a length of open tubing
- Infinitely variable:
  - total volume
  - internal and external diameter
  - material of construction

**Packed-bed reactors**
- Also Infinitely variable:
  - volume, diameter, particle size, material of construction
  - can be adapted for heterogeneous catalysis
Flow Technology - Separators

Two-Phase Flow

- Aqueous Phase
- Organic Phase

- Continuous liquid-liquid separation is easily achievable with membrane separators.
- The “wetted” layer is driven through the porous membrane due to a difference in pressure.

Micro-scale

Meso-scale (>10 ml/min)

Gas-liquid separation

Jensen Group, MIT
Flow Technology – In-line Monitoring

A → Pump → Mixer → Reactor → Mixer → Detector → C

- UV Absorption
- Ocean Optics

- FTIR
- Mettler-Toledo

- 6-way sample valve
- “In-line” HPLC
Reaction Optimization

Small-scale:

- Flow systems can be used to perform a very large number of experiments without utilizing a lot of compound.

Precise control:

- Very good control over reagent concentration, reaction time and reaction temperature is easily achieved due to efficient mixing and heat transfer.
- Can easily find the optimal reaction conditions.

Increased “chemical space”:

- Flow systems can allow for easy access to reaction conditions that are not accessible using traditional batch equipment.
- Reactions run at higher temperatures and pressures can display much faster reaction rates and greater selectivity.
Reaction Optimization - Glycosylation

Glycosyl Donor 2 + Glycosyl Acceptor 1 → Desired Product 3 + Orthoester 4

Fast mixing:
Very small channels (50 μm)

Small-scale:
Small reactor volume (70 μL)

5-port silicon-based microreactor

Reaction Optimization - Glycosylation

Glycosyl Donor 2 + Glycosyl Acceptor 1 \xrightarrow{TMSOTf, CH2Cl2} Desired Product 3 + Orthoester 4

- Product is formed at temperatures of -60 °C and higher
- Orthoester side-product is completely avoided when reaction is performed under optimal reaction conditions:
  
  \[ \text{Time} = 27 \text{ sec} \]
  
  \[ \text{Temp} = -40 \degree \text{C} \]

Seeberger, P. H., et. al.  
*Chem. Comm.* 2005, 24, 578
Reaction Optimization – N-Alkylation

- Increasing the reaction temperature from 50 to 90 °C increases the reaction rate by a factor of more than 5
Reaction Optimization - Oxidation

20 experiments successfully performed in ~40 minutes
Process Development – Efficient Synthesis

**Optimum conditions:**
- Operation of continuous-flow systems under optimal reaction conditions maximizes yields and throughput, while minimizing waste

**Increased “chemical space”:**
- Performing reactions under “extreme” conditions provides access to new chemical reactions, possibly eliminating the need for some synthetic steps
- Shorter syntheses, better selectivities, and faster reaction

**Continuous multi-step synthesis:**
- Performing multiple flow reactions, in series, continuously eliminates the need for intermediate isolation and handling
- Reduces waste
- Reduces the need for intermediate inventory
- Minimizes the safety hazards associated with reactive intermediates
Process Development – High Temperatures

Pd-Catalyzed Aminocarbonylation

- Chemical outcome of the reaction (selectivity) is affected by multiple factors (catalyst, solvent, base, substrate, gas pressure, etc...)
- Reaction is difficult to optimize in small-scale batch experiments.
- Limited in terms of reaction temperature and pressure

Process Development - Aminocarbonylation

- Up to 36 reaction samples per day
- 4-7 minute residence time for 100% conversion
- Controlled selectivity between two products
- Continuous flow alternative to microwave chemistry
- Gas-liquid segmented flow with 10-fold increase in contact area

Process Development – High Pressure

120 µL silicon µreactor compressed in an aluminum chuck

- 250 or 500 psi back pressure regulator
- High pressure syringes and syringe pumps
- Cooled mixing zone

Jensen, K. F.; Jamison, T. et al. 
Process Development – Epoxide Ring Opening

![Chemical Structures](Image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Pressure (psi)</th>
<th>Equiv. Amine</th>
<th>Temp. (°C)</th>
<th>Time</th>
<th>Product (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Bis (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% Conversion</th>
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<td>1</td>
<td>Batch (μW)</td>
<td>~100</td>
<td>1.2</td>
<td>150</td>
<td>30 min</td>
<td>65</td>
<td>31</td>
<td>100</td>
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<tr>
<td>2</td>
<td>Batch (μW)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>1.2</td>
<td>150</td>
<td>30 min</td>
<td>69</td>
<td>28</td>
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<td>3</td>
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<td>30 min</td>
<td>72</td>
<td>27</td>
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<tr>
<td>4</td>
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<td>500</td>
<td>1.2</td>
<td>240</td>
<td>15 s</td>
<td>61</td>
<td>14</td>
<td>76 (80)&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>1.2</td>
<td>240</td>
<td>30 s</td>
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<td>21</td>
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<td>240</td>
<td>1 min</td>
<td>72</td>
<td>24</td>
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<td>15 s</td>
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<td>240</td>
<td>30 s</td>
<td>92</td>
<td>6</td>
<td>100</td>
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</table>

<sup>a</sup> 2x scale (2 mL in a 5 mL vial)<br>
<sup>b</sup> Yield based on HPLC (~1% of Regioisomer isolated)<br>
<sup>c</sup> Product yield based on recovered starting material

- Microreactor enables superheating (240 °C) at high pressure
- Very short reaction time ($t_{1/2} = 2-3$ seconds)<br>
- Product stream output = 7 g/h (60 kg/y) using a single microreactor

Process Development – Multi-Step Synthesis

- Integration of work-up techniques for multiple step synthesis
- In-line liquid-liquid and gas-liquid separation
- Unique membrane separation technology for fluid handling
- Library synthesis

Process Development – Multi-Step Synthesis

**Triflation**

\[
\text{ArOH} \quad \xrightarrow{\text{DIEA}} \quad \text{ArOTf}
\]

- Tf\(_2\)O
- DCM
- 20°C

**Heck Coupling**

\[
\text{ArOTf} \quad \xrightarrow{\text{Pd(OAc)}_2, \text{DPPP}} \quad \text{Ar} + \text{OR}^1
\]

- Base/ Toluene (or DMF)
- \(\Delta\)

**Operation of 4 elementary steps continuously**

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

Process Development – Multi-Step Synthesis

Producing Compounds – Scale-up Strategies

**Optimal Conditions:**
- After reaction optimization or development of new reactions, the optimal conditions can be used to produce compounds

**Scale:**
- Even small continuous-flow systems can produce large quantities of compounds
- Small footprint for production facilities

**Quality:**
- On-line analytical instrumentation can ensure that the chemical outcome of the reaction is exactly as expected
Producning Compounds - Pharmaceuticals

Rimonabant

- Central cannabinoid receptor antagonist - anti-obesity drug (Sanofi -Aventis - approved in Europe)
- Three separate chemical transformations performed under continuous-flow
- Lithiation at ambient temperature instead under cryogenic conditions
- Aluminum mediated coupling developed for scale up
- throughput = 100 g/day

Producing Compounds - Energetic Materials

Continuous-flow simplifies synthesis, removes reaction heat and evolved gas, making the process safer and efficient

- ~90% yield of final product
- Highly efficient Si-based micromixer - “instantaneous” mixing
- Production of 2.8 g/hr

i2Chem Founders

Klavs Jensen
- Professor MIT, microreactor inventor and internationally recognized chemical reaction engineer

James Little - President, CEO, i2Chem
- Serial entrepreneur executive (Waters, Zymark, Cetek)

Peter Seeberger
- Director - Max Planck Institute of Colloids and Interfaces
- Worldwide recognized organic chemist, microreactor and med-chem specialist

Martin Schmidt
- Professor - MIT, microreactor inventor and international leader in microfabrication and MEMS

Joe Caruso
- Advisor, investor, and board member for a number of early stage companies
i2Chem Scientific Advisory Board

Technical Founders (Jensen, Seeberger, Schmidt)

Stephen L. Buchwald
• Camille Dreyfus Professor of Chemistry - MIT
• Worldwide recognized leader in organic chemistry

Chris Cimarusti
• Former Senior VP of Development at BMS

Paul Reider
• Former VP of Process Chemistry at Merck
• Former VP of Chemistry at Amgen
• Professor of Chemistry - Princeton University
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