Synthesis Design Through the Lens of Flow Chemistry – When, How, and Why

Ischia Advanced School of Organic Chemistry
Ischia, Italy

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26 September 2016

Tim Jamison
MIT

Outline

A. Definitions

B. 3-Minute Synthesis

C. Continuous Pharmaceutical Manufacturing

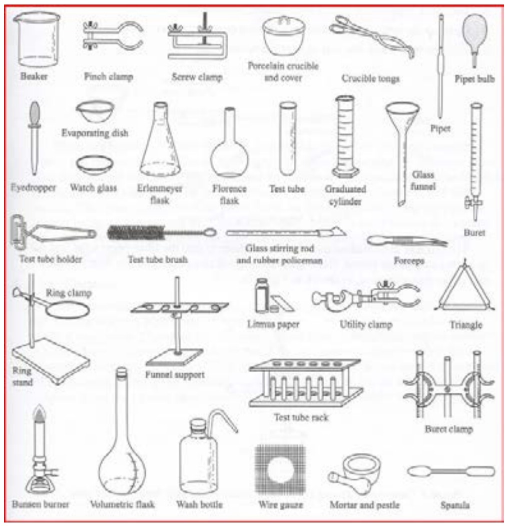
D. When should I use flow chemistry?

E. How do I do flow chemistry?

F. Why should I use flow chemistry?

Batch Synthesis ("Batch Chemistry")

- From **Day 1**, we teach and conduct chemistry in **batch.**

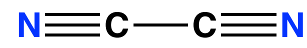


- To do so, we use **test tubes, beakers, flasks, separatory funnels, etc.**

- When we scale up, we generally use **larger batch** equipment.

Batch Synthesis (“Batch Chemistry”)

- **Batch** synthesis has been very successful – and for >200 years. **Chemists “think in batch”.**



Cyanogen
(Gay-Lussac, 1815)

- However, **batch** is not without limitations, e.g., scaling, safety, efficiency, cost (CapEx/OpEx). Nearly all manufacturing industries are **continuous** – automobiles, planes (!), electronics, food, chemicals (petro, bulk, et al.) – but **pharma** tends to use **batch**.

- **Continuous flow synthesis** offers not only practical advantages, but also an **expanded conceptual framework.** **What happens when chemists “think in flow”?**

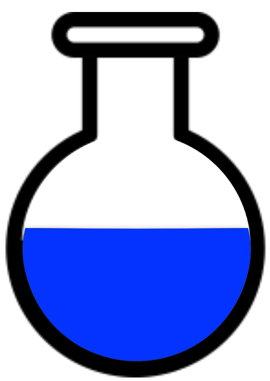
Batch and Flow Reactions

Consider the following chemical reaction:

$$A \longrightarrow B$$

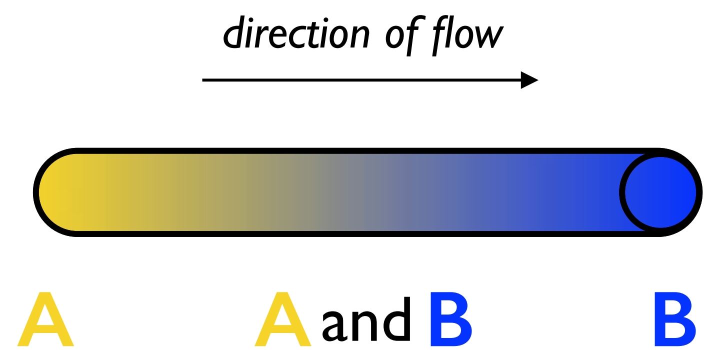
starting material — product

Batch



System **changes** with time

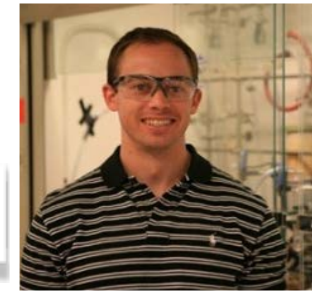
Flow

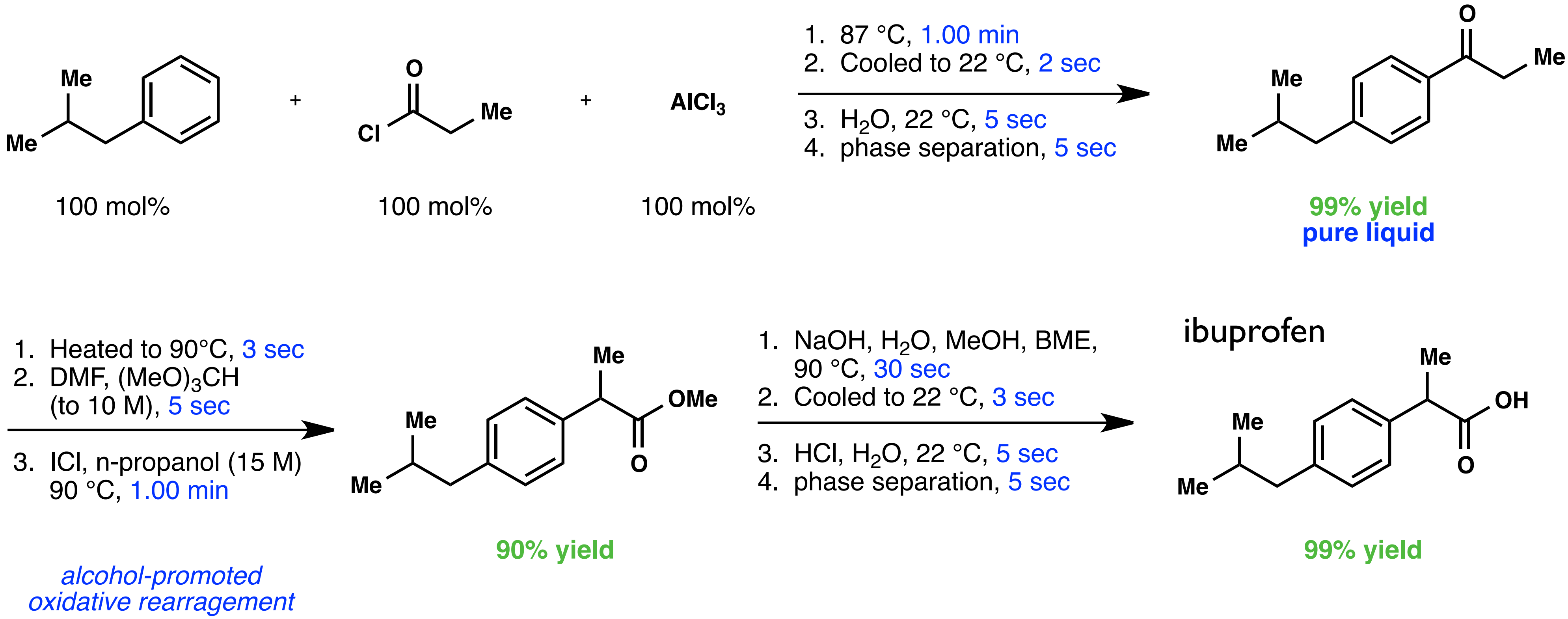


System is at **steady state**

A 3-Minute Synthesis

Dr. David Snead





- 3 C–C, C–O bond-forming steps
- 2 workup steps
- 2 separations
- 4 heating/cooling operations
- 89% overall yield
- total elapsed time: 3:03

- 3.67 g prepared in 3 minutes
- total internal volume of all equipment used: 30 mL

- 1.2 g/min
- 72 g/h
- 1.7 kg/d
- 12 kg/week
- **630 kg/year**

A 3-Minute Synthesis

Questions and Concerns

neat Friedel-Crafts acylation?
heat Friedel-Crafts acylation?? — very dangerous

heat/cool in **2-3 sec**? — nearly impossible

workup + separation
in **< 10 sec**? — very challenging

- $AlCl_3$ in propionyl chloride
- **ICl** + DMF, TMM, *n*PrOH
~5 M, 90 °C — very corrosive

11 operations in a total time
of 3 min 3 seconds? — preposterous

If conducted in
flasks, separatory funnels

batch

A 3-Minute Synthesis

neat Frie
heat Frie

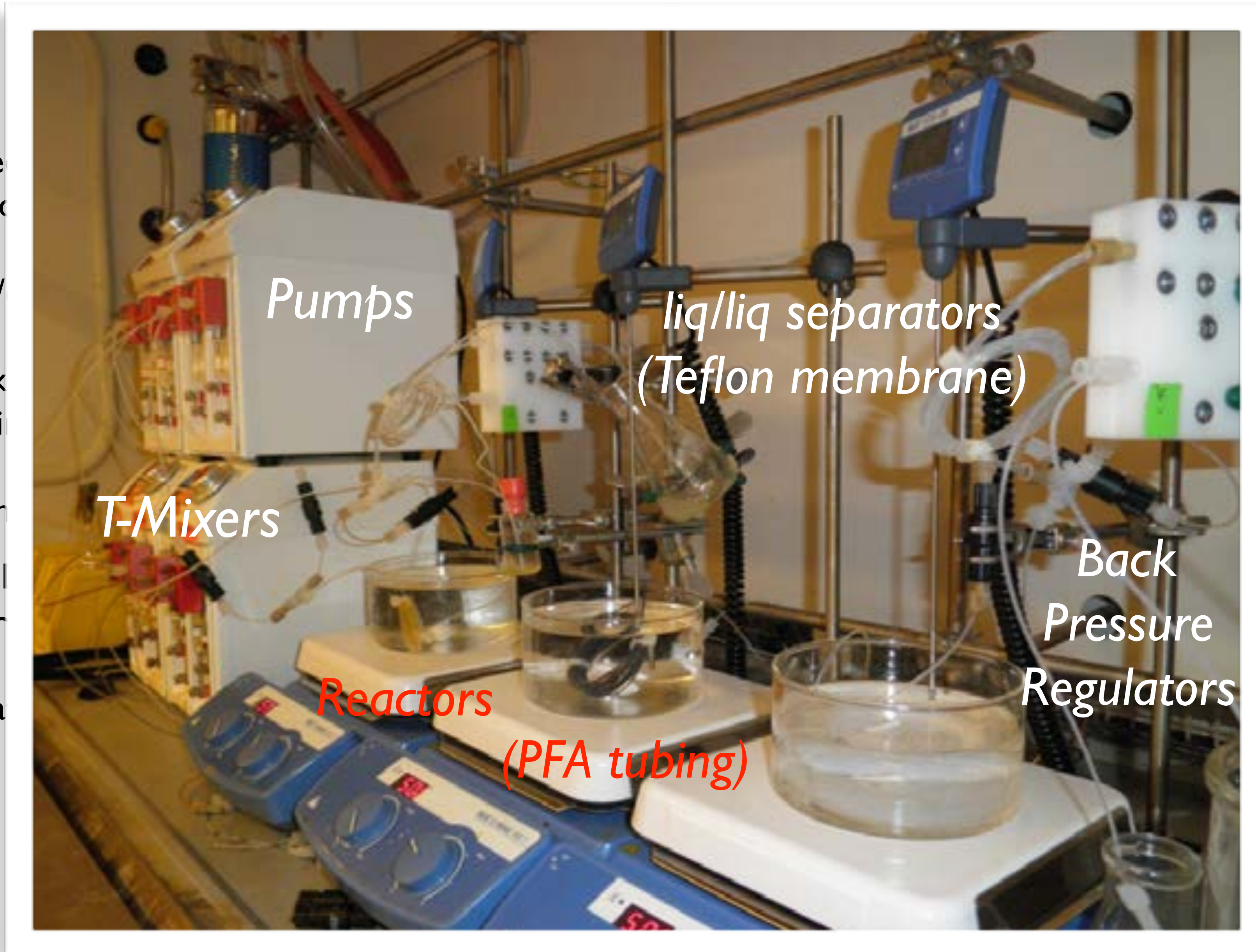
heat/

work
i

• $AlCl_3$ ir

• **ICl +** I

11 opera
of 3



A 3-Minute Synthesis

Features and Opportunities

neat Friedel-Crafts acylation?
heat Friedel-Crafts acylation?? — very rapid heat transfer

heat/cool in **2-3 sec**? — very rapid heat transfer

workup + separation in **< 10 sec**? — in-line separation (teflon membrane)

• $AlCl_3$ in propionyl chloride

• **ICl** + DMF, TMM, *n*PrOH ~5 M, 90 °C — small amounts of hazardous reagents

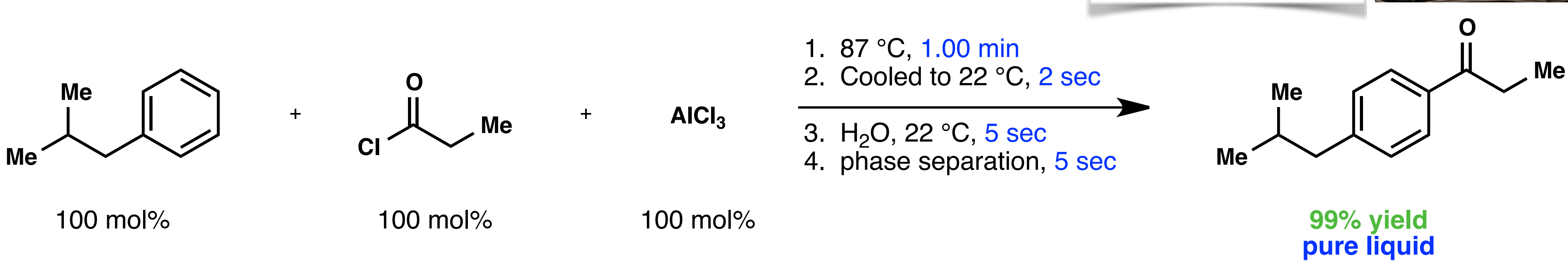
11 operations in a total time of 3 min 3 seconds? — feasible

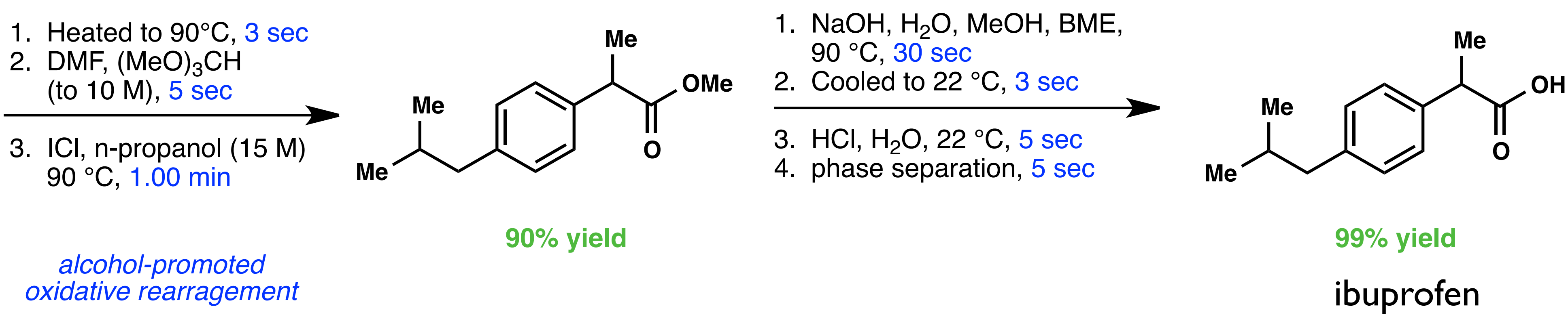
Snead, D. R.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2015**, *54*, 983-987.

See also: Bogdan, A. R.; Poe, S. L.; Kubis, D. C.; Broadwater, S. J.; McQuade, D. T. *Angew. Chem. Int. Ed.* **2009**, *48*, 8547-8550.

Process Intensification: Throughput

Dr. David Snead



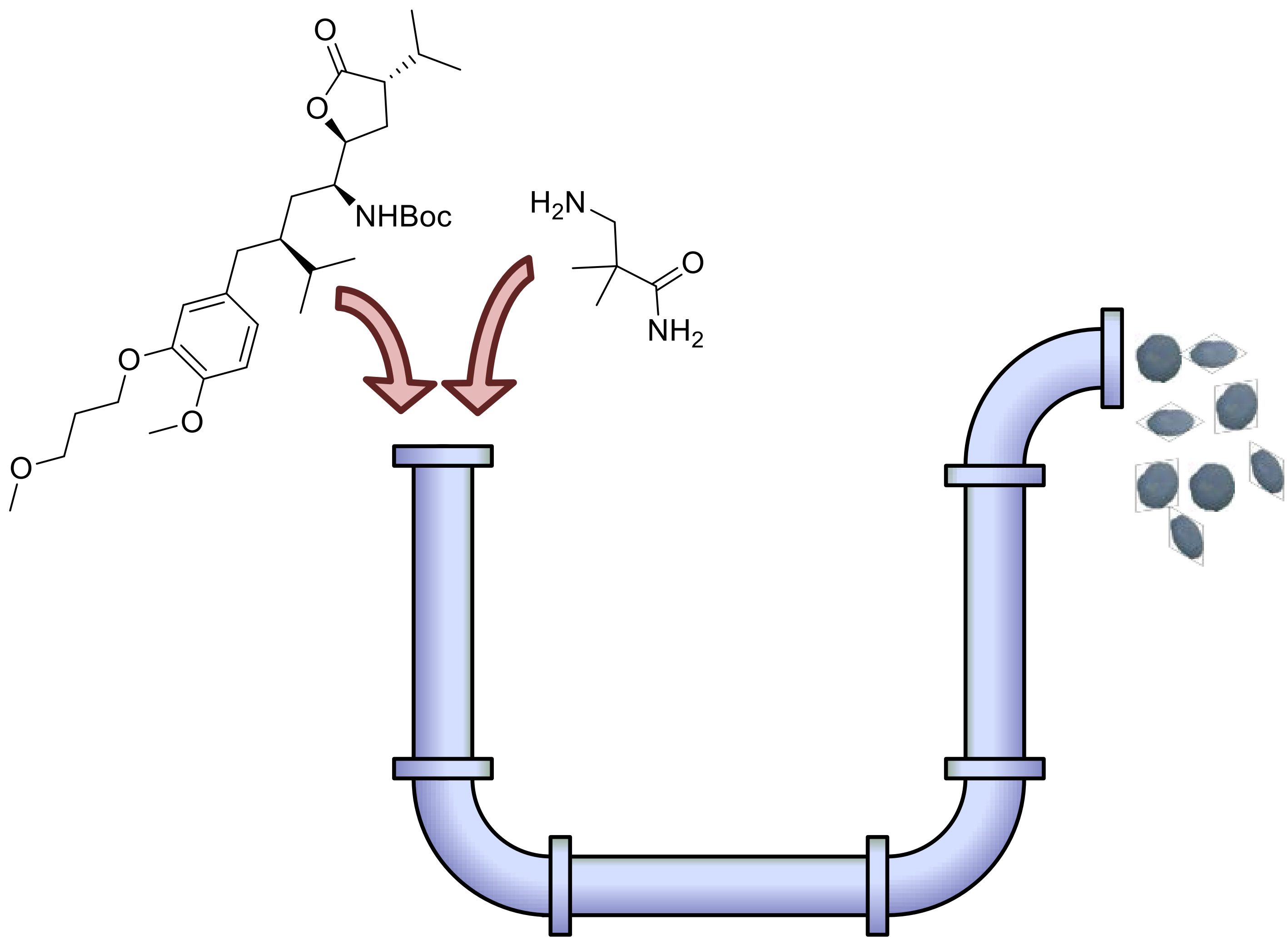


- **1.2** g/min
- **72** g/h
- **1.7** kg/d
- **12** kg/week
- **630 kg/year**

Many anticipated impacts upon synthesis of Active Pharmaceutical Ingredients

Snead, D. R.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2015**, *54*, 983-987.

First End-to-End Continuous Pharmaceutical Manufacturing



Angew. Chem. Int. Ed. **2013**, *52*, 12359-12363.

Org. Proc. Res. Dev. **2014**, *18*, 402-409.

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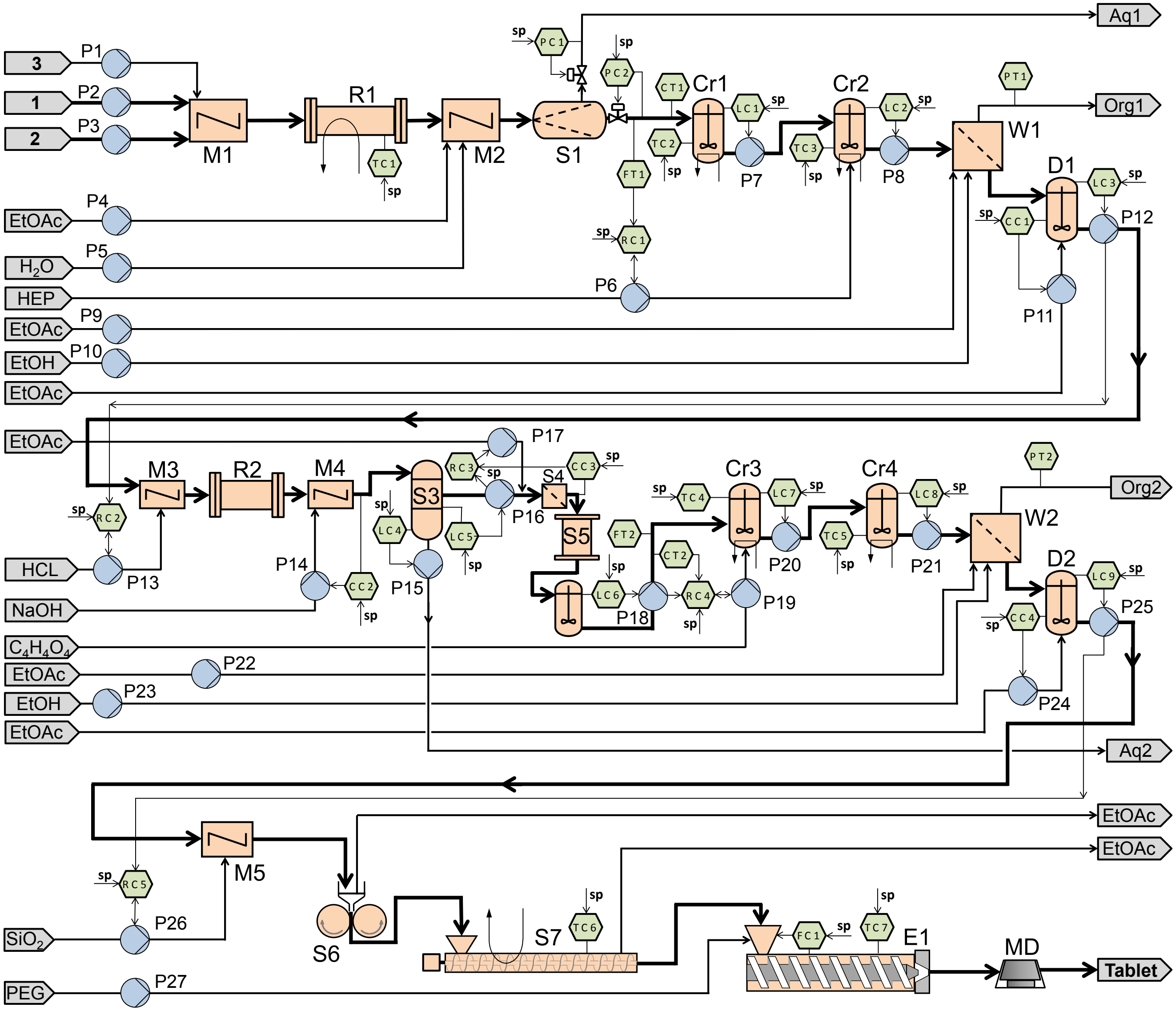


• 2 years, Team of 30 (7 graduate students, 10 postdocs, 8 technicians, 5 faculty)

• 8500 tablets/day (>3,000,000/year), met USP standards and passed uniformity and stability tests

• 25 m^2, 21 unit operations (batch) reduced to 14, 300 h reduced to 48 h.

Angew. Chem. Int. Ed. **2013**, *52*, 12359-12363.

Org. Proc. Res. Dev. **2014**, *18*, 402-409.

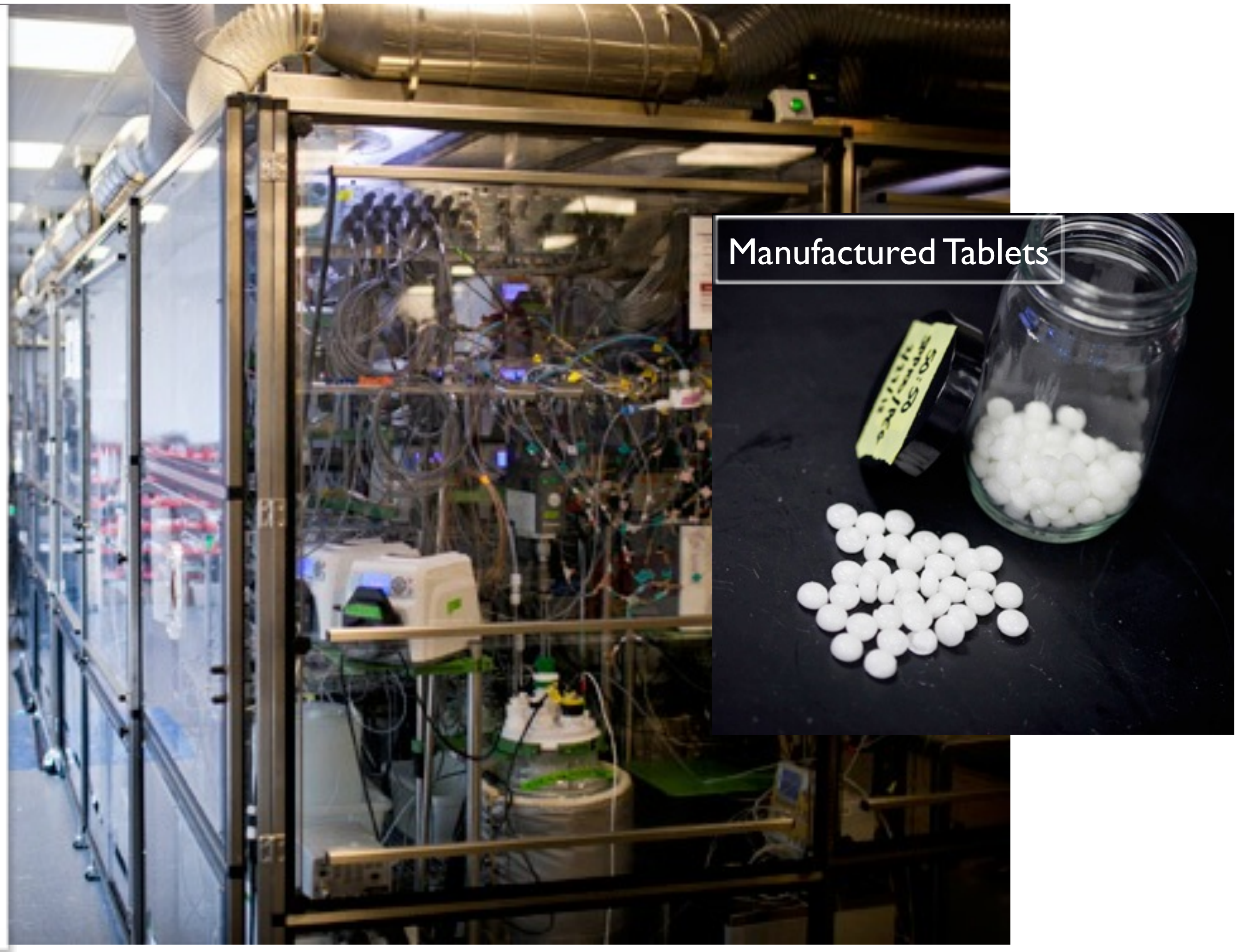
First End-to-End Continuous Pharmaceutical Manufacturing

"The Redline"

- Everything shown in process diagram enclosed herein

- Large fraction of equipment and tech off-the-shelf

- Run at steady-state for >240 hours



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"Pharmacy on Demand"

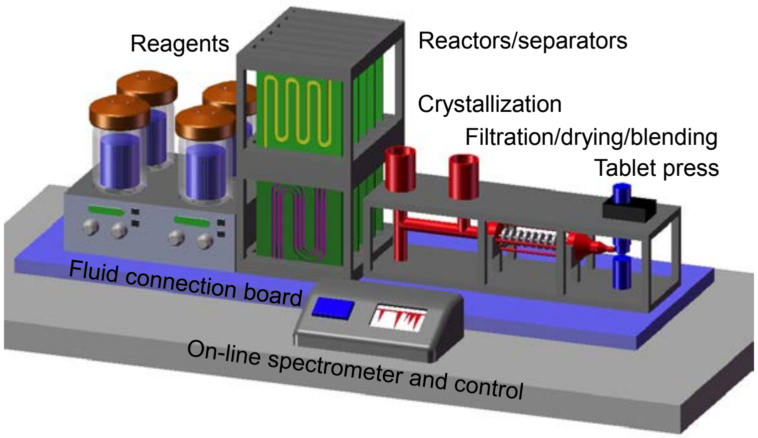
One Device – **7 Different Medicines** (and then 7 more)

Collaborators (MIT Chem Eng)
Prof. Klavs Jensen
Prof. Allan Myerson

NOVARTIS — MIT Center for Continuous Manufacturing — DARPA

	Redline	PoD RFA
Timeline (years)	2	1.5 (+3)
Targets	1	7 (+7)
End-to-End? (synth + form)	yes	yes
Doses (per day)	8500	1000
Talent (each year)	20	6 (2 per PI)
Footprint	25 m^2	"tabletop" (+ handheld)

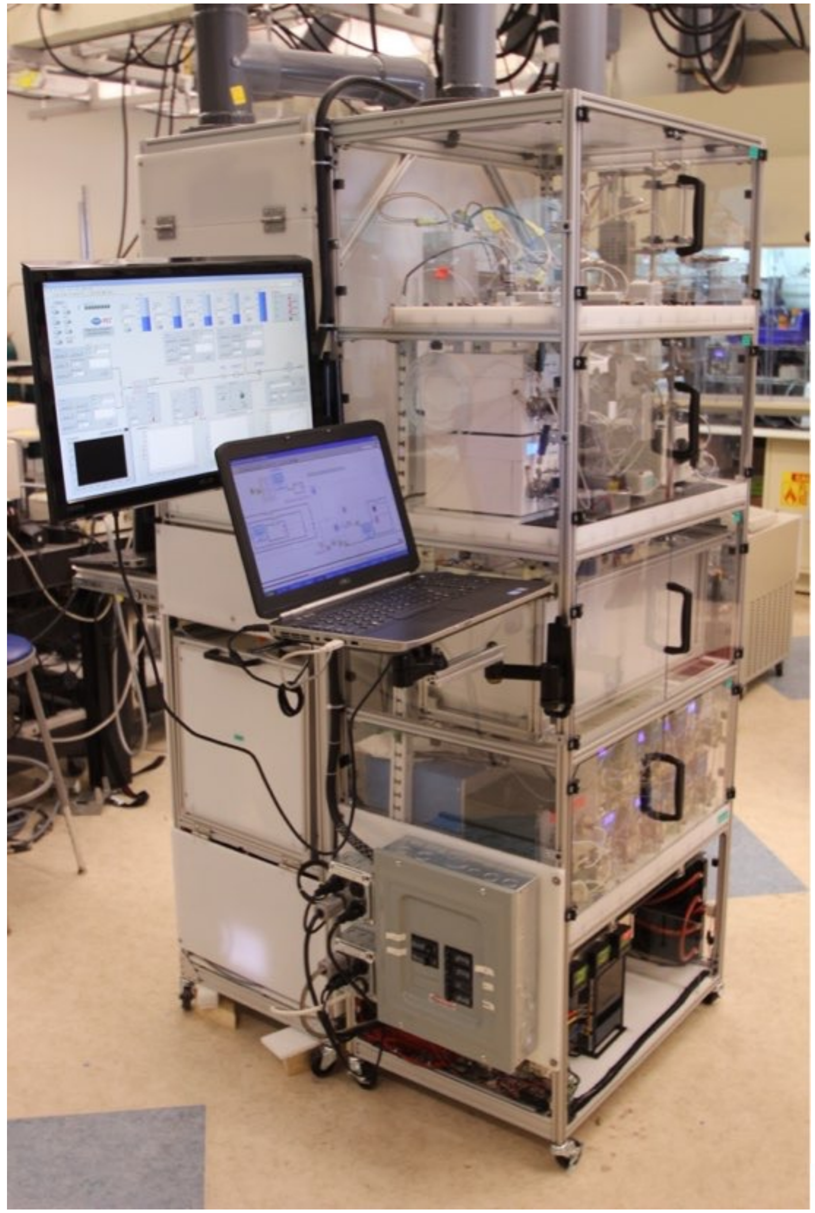
PoD



3 research groups
(2 PD per group)

18 months

Science **2016**, *352*, 61-67.



- refrigerator-sized
- compact, reconfigurable
- API synthesis and formulation
- 1,000-1,000,000 doses per day

- novel chemistry
- novel technology

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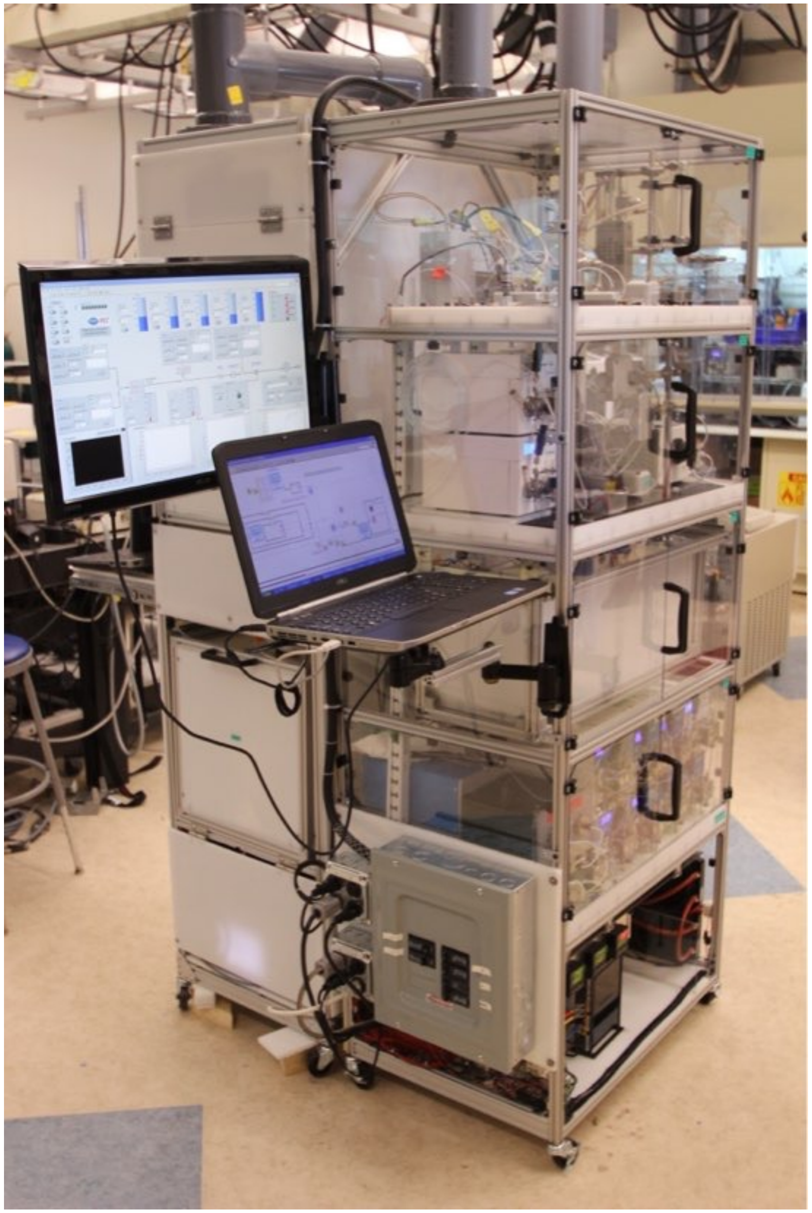
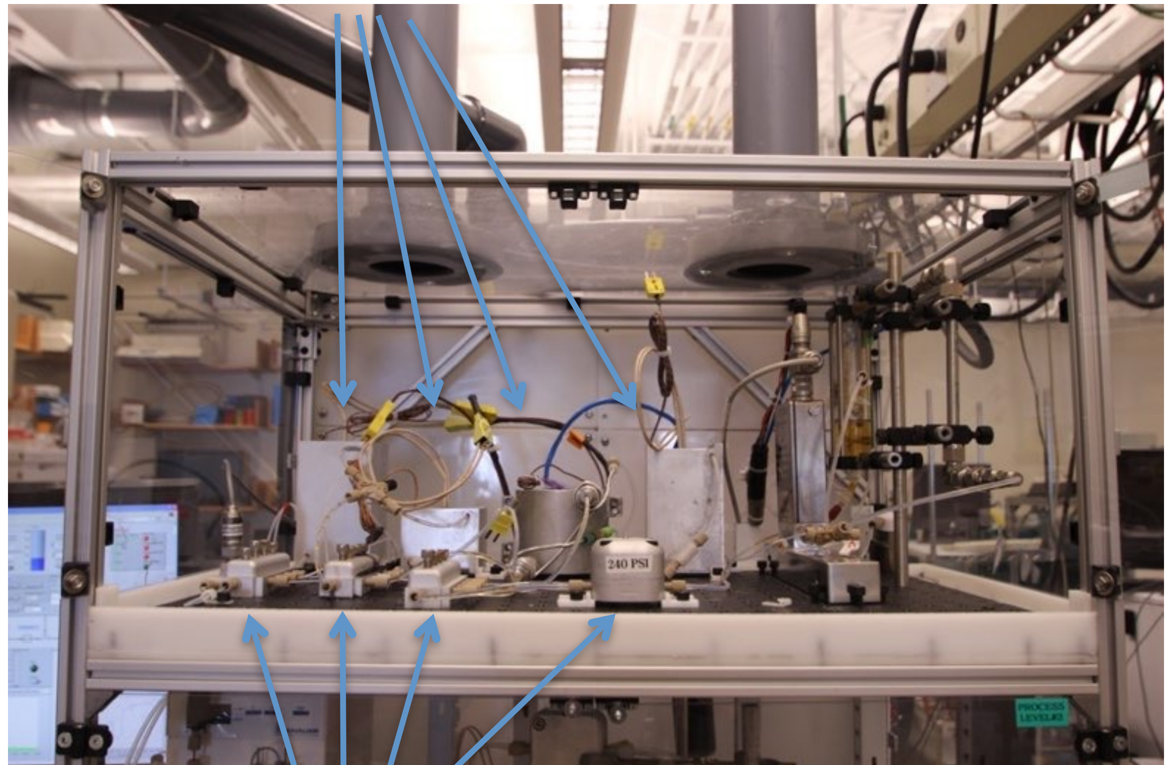


Encased,
spiral PFA tubing
reactors
(novel)



Backpressure regulators
(novel, now commercial)

- **Total volume < 2 m³**

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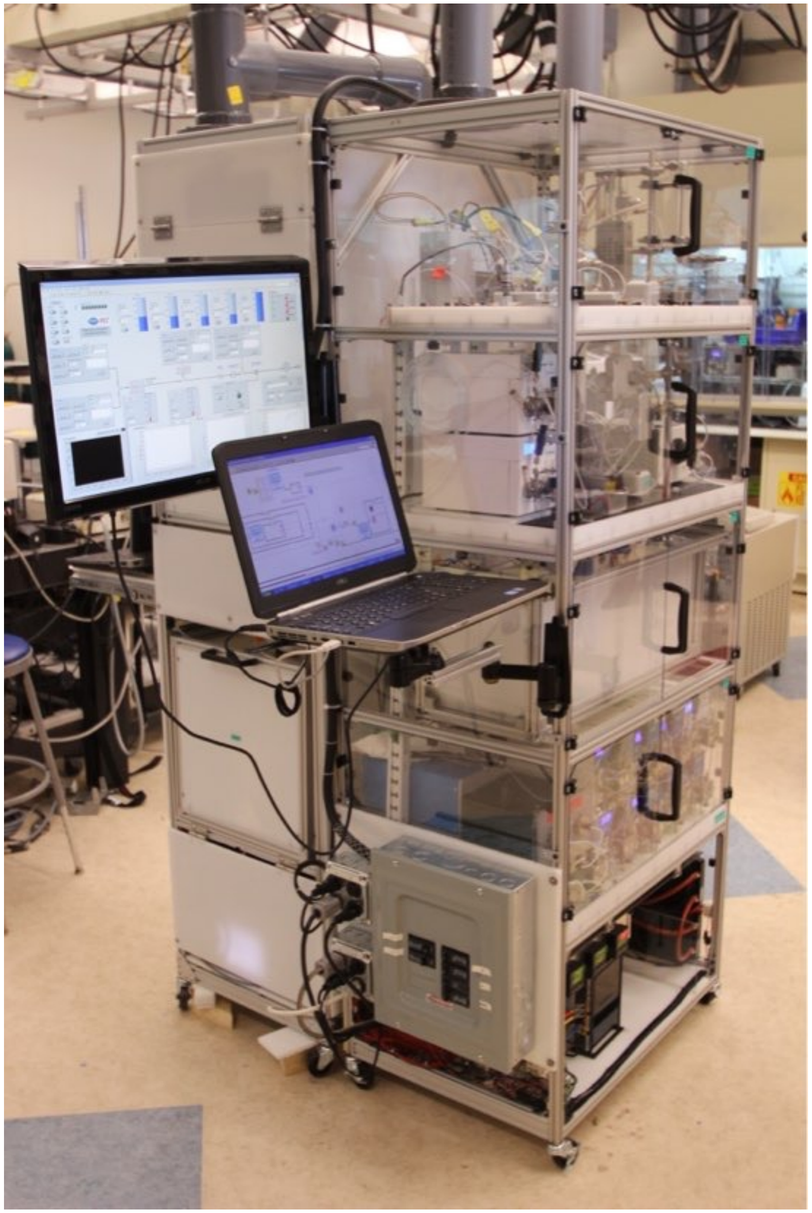
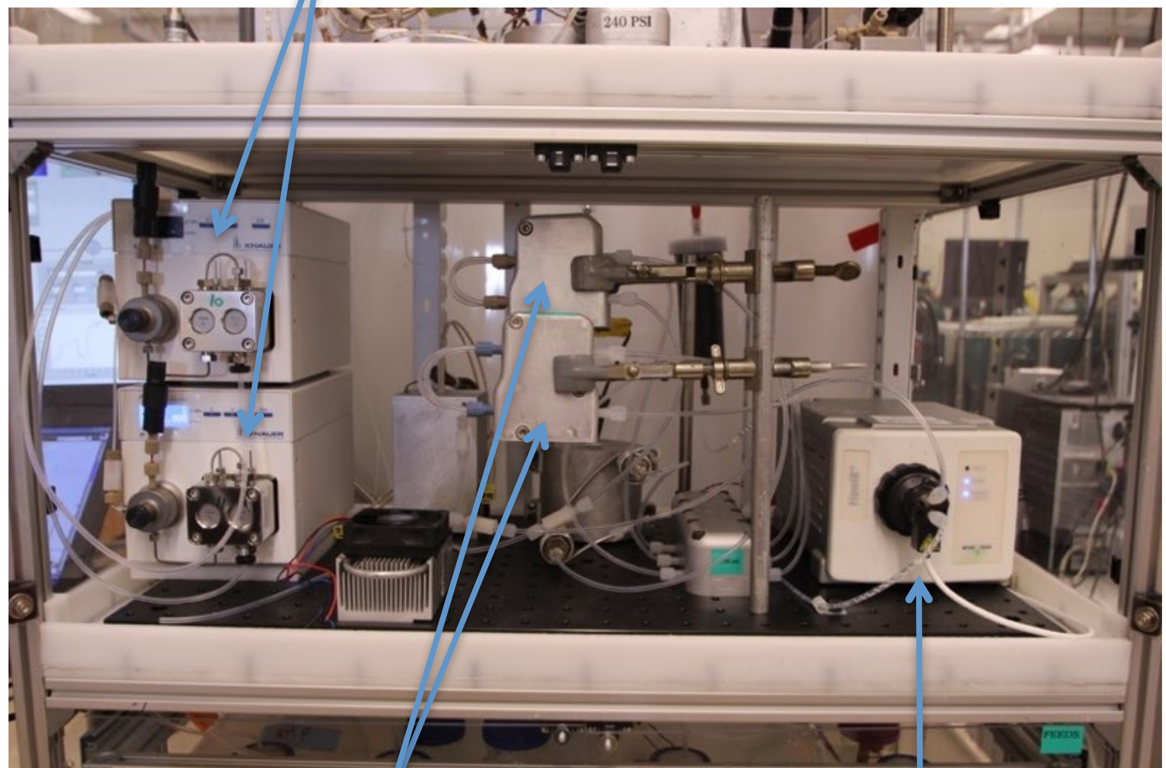


Knauer
pumps
(existing commercial)

Zaiput Flow Technologies
Groundbreaking Innovations in Flow Chemistry
www.zaiput.com



Liquid-liquid separators
(novel, now commercial)

In-line IR
(existing commercial)

- **Total volume < 2 m^3**

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MIT DARPA

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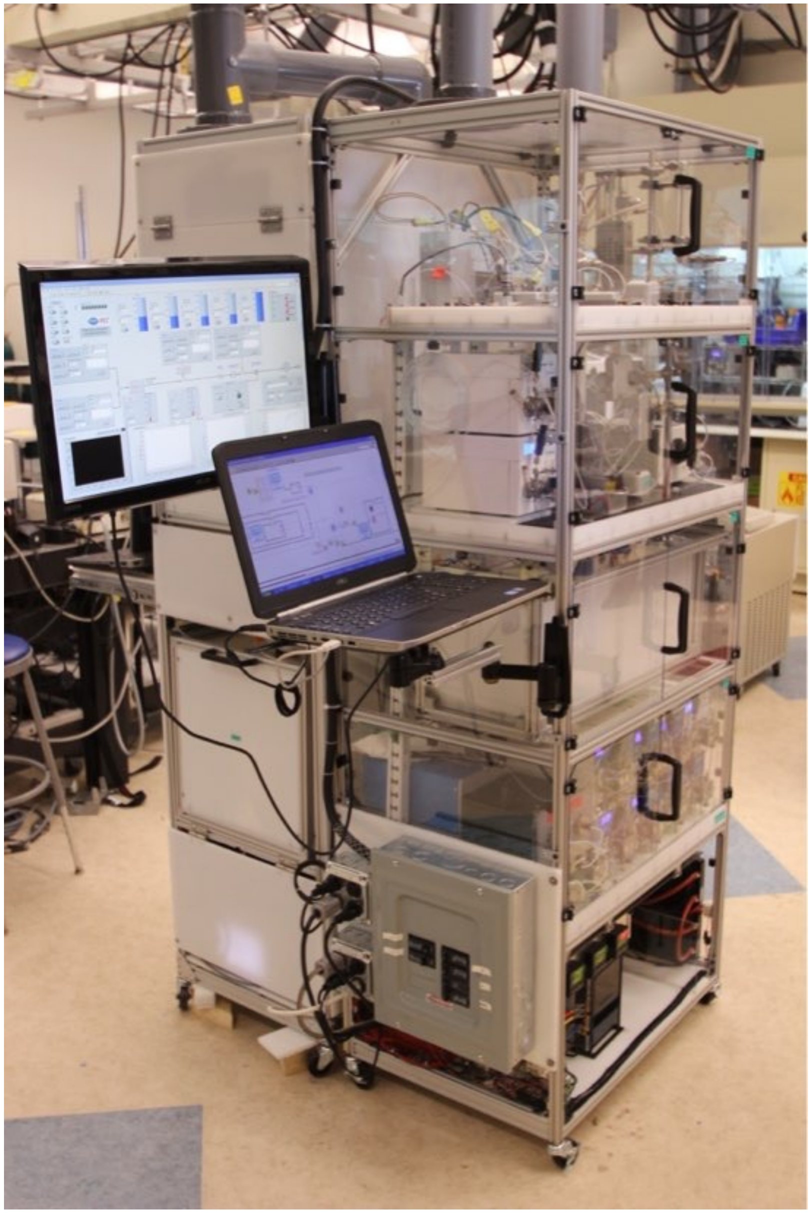
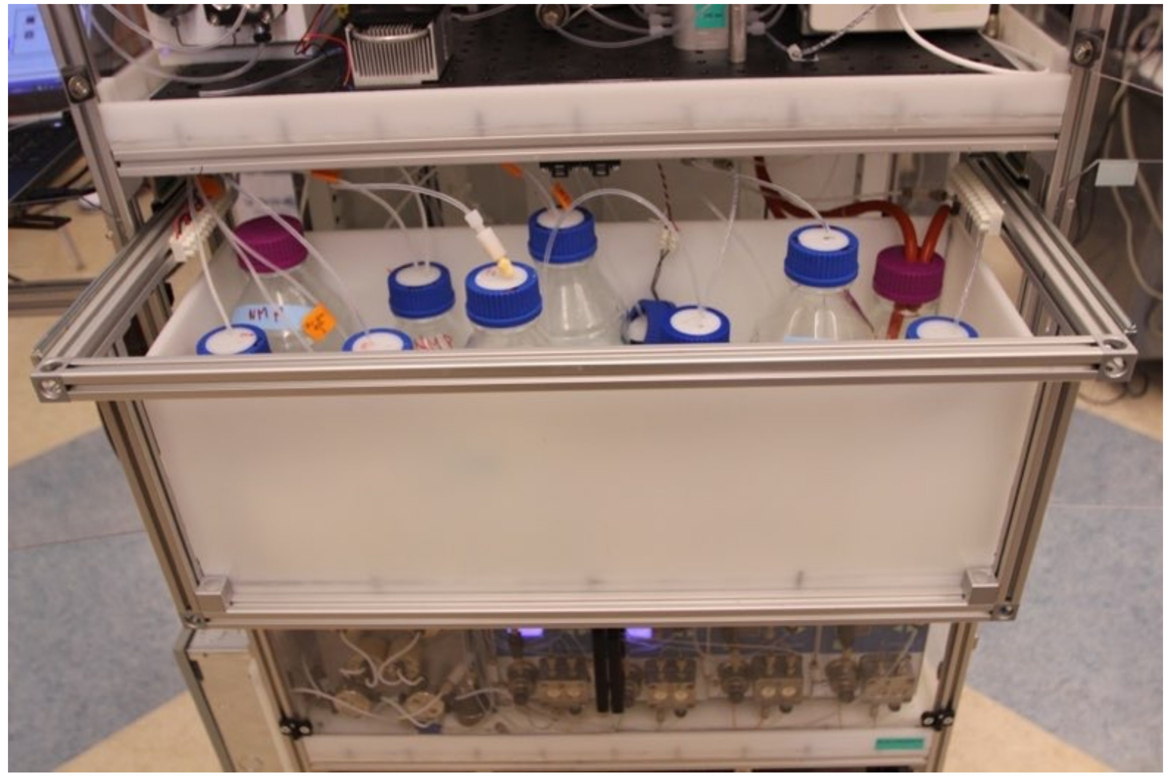


reagents and **solvents**



- **Total volume < 2 m^3**

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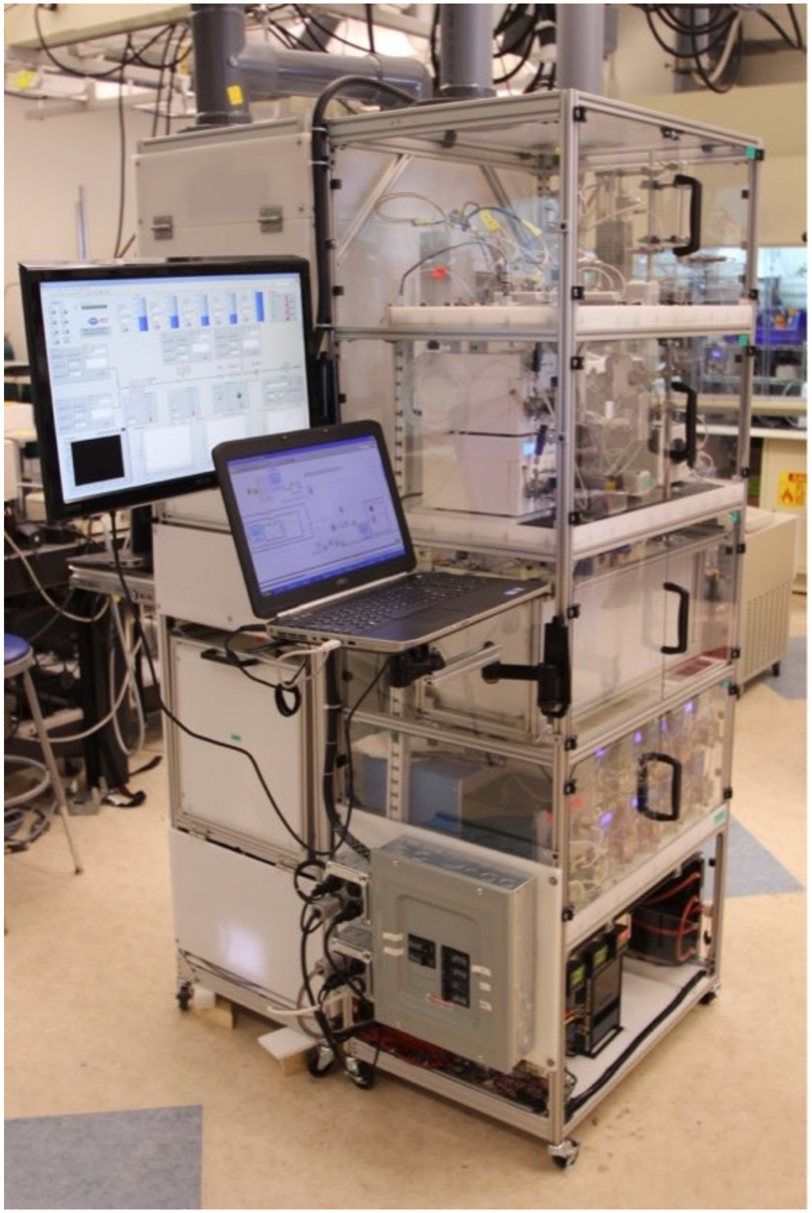
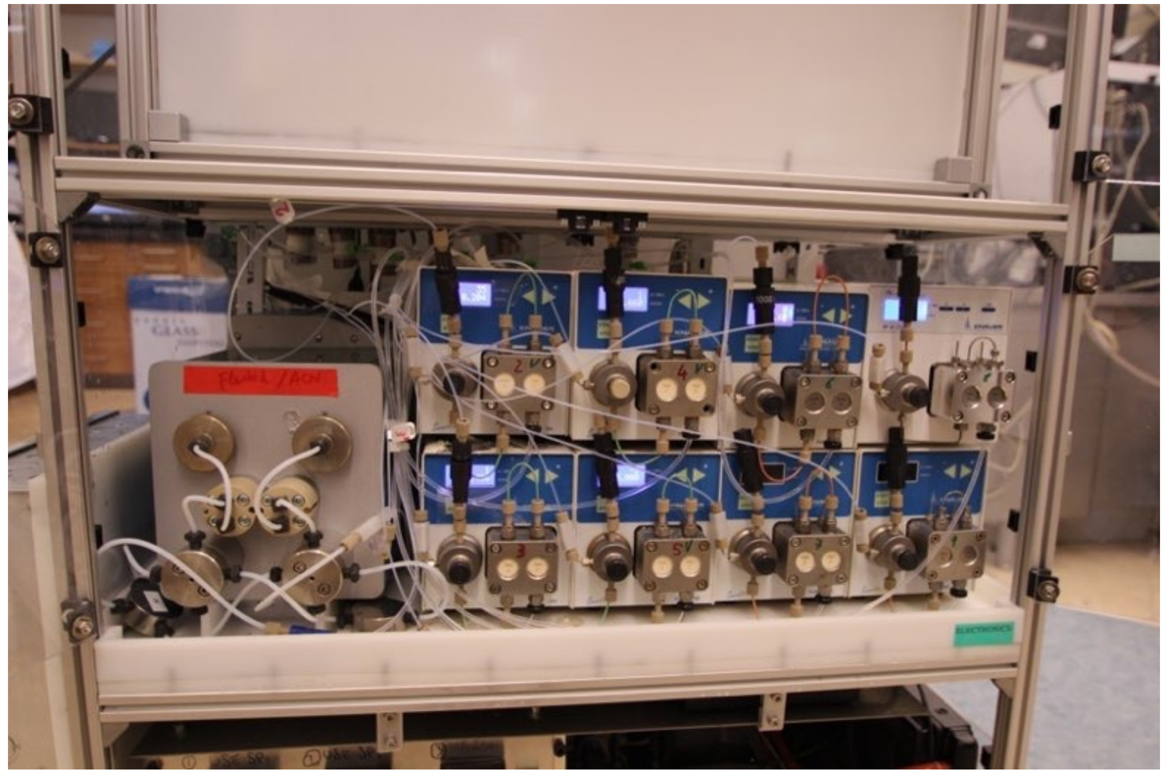


pumps



- **Total volume < 2 m^3**

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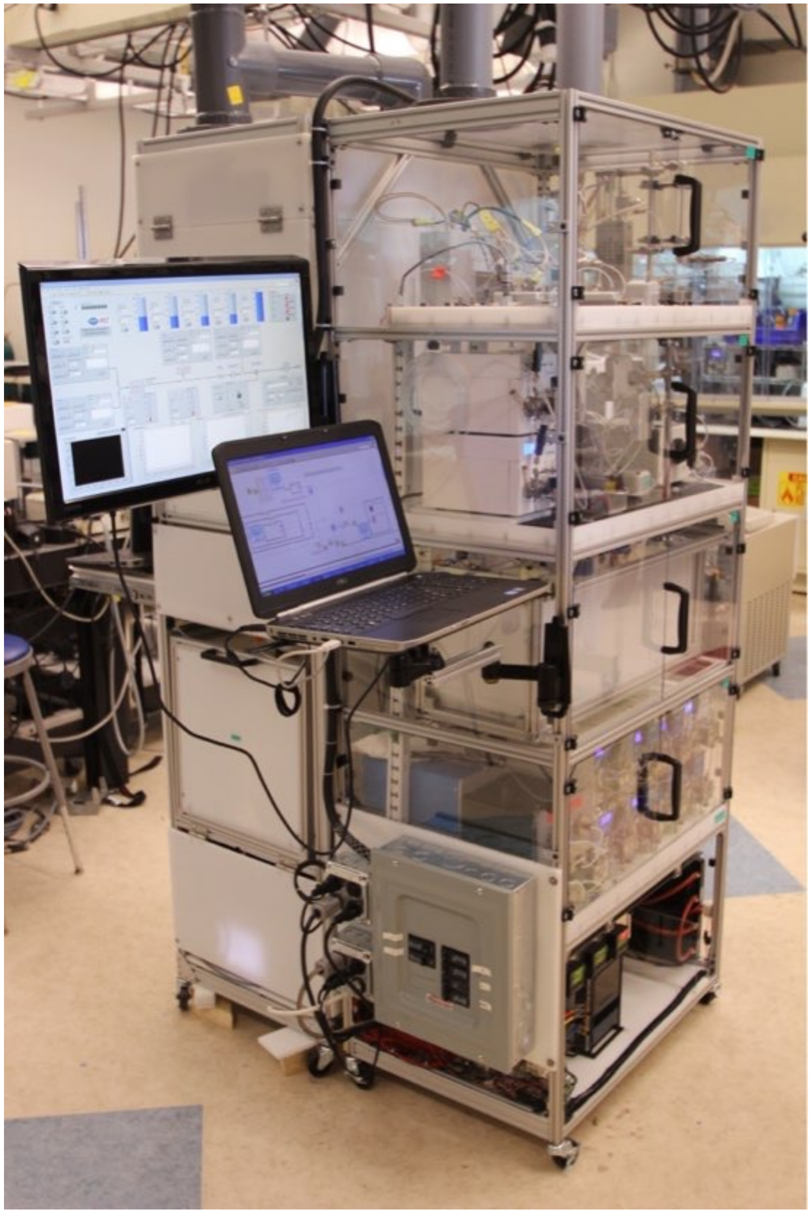

power, I/O, electronics

- **Total volume < 2 m^3**

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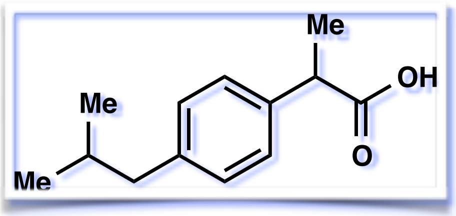
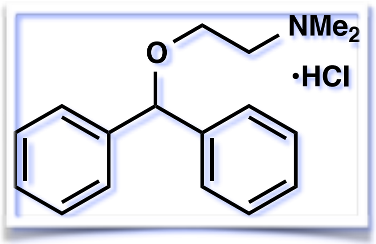
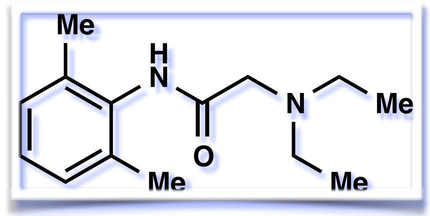


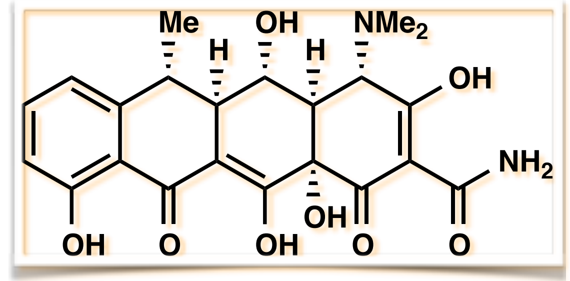
ibuprofen



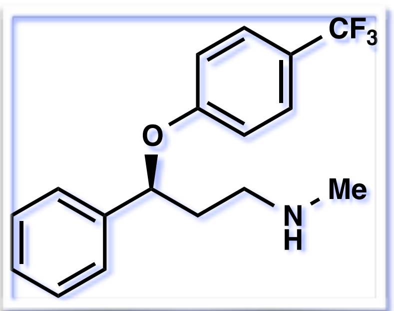
diphenhydramine (Benadryl)



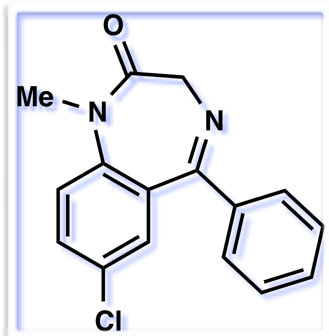
lidocaine



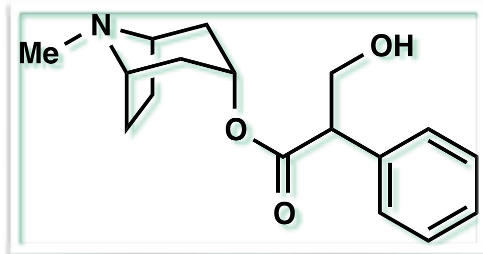
doxycycline



fluoxetine (Prozac)



diazepam (Valium)



atropine

Phase I Targets

- **family-refrigerator-sized**
- **upstream continuous, downstream batch**
- **liquid formulations**

David Snead | **Ping Zhang** | **Christina Dai**

Zhi He | Liam Kelly | Grace Russell

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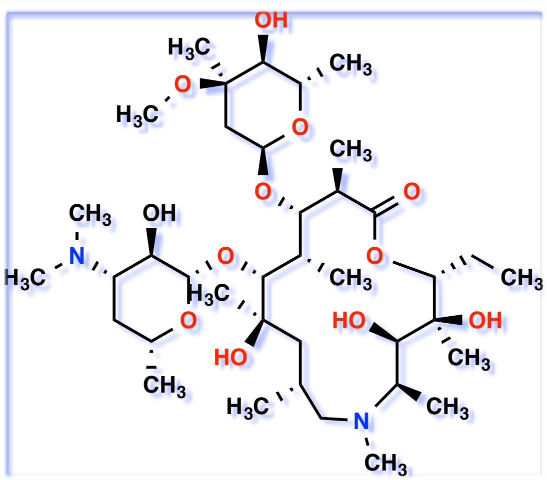
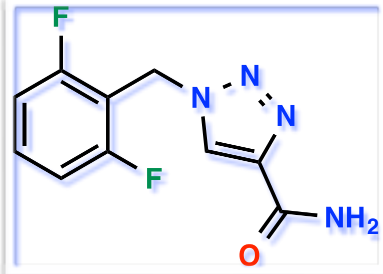
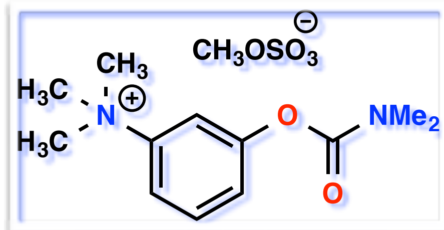


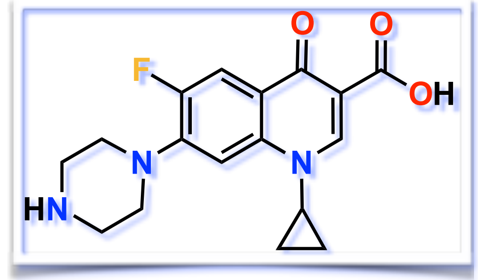
azithromycin



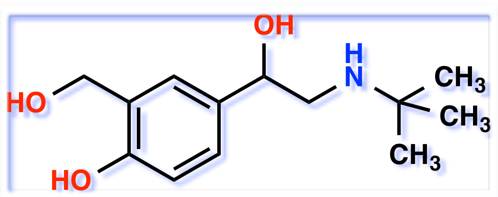
rufinamide



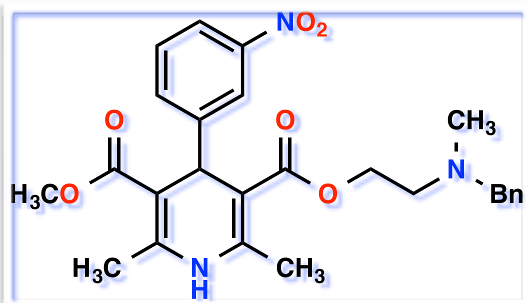
neostigmine



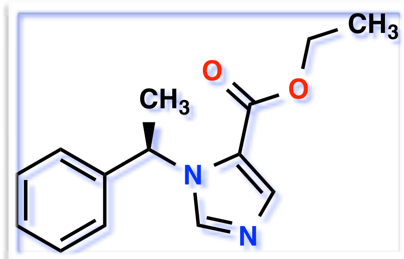
ciprofloxacin



salbutamol



nicardipine



etomidate

Phase 2 Targets

- dorm-room-refrigerator-sized
- end-to-end continuous
- “solids module” (tablets)

David Snead | Ping Zhang | **Christina Dai**

Zhi He | **Liam Kelly** | **Grace Russell**

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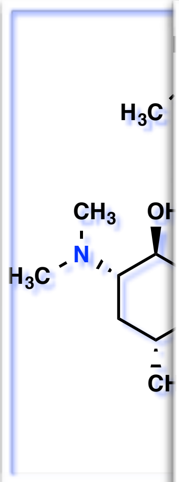
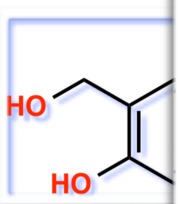


az



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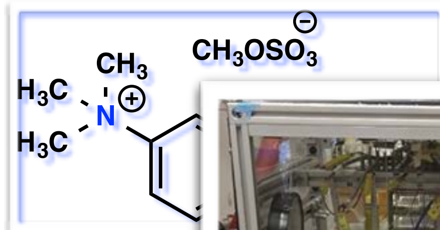
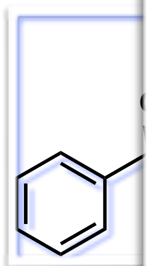


neos



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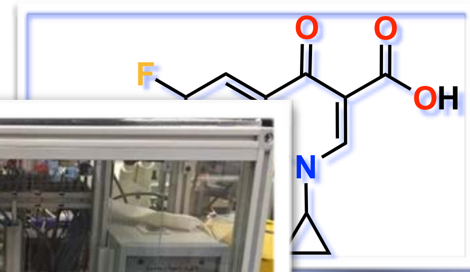
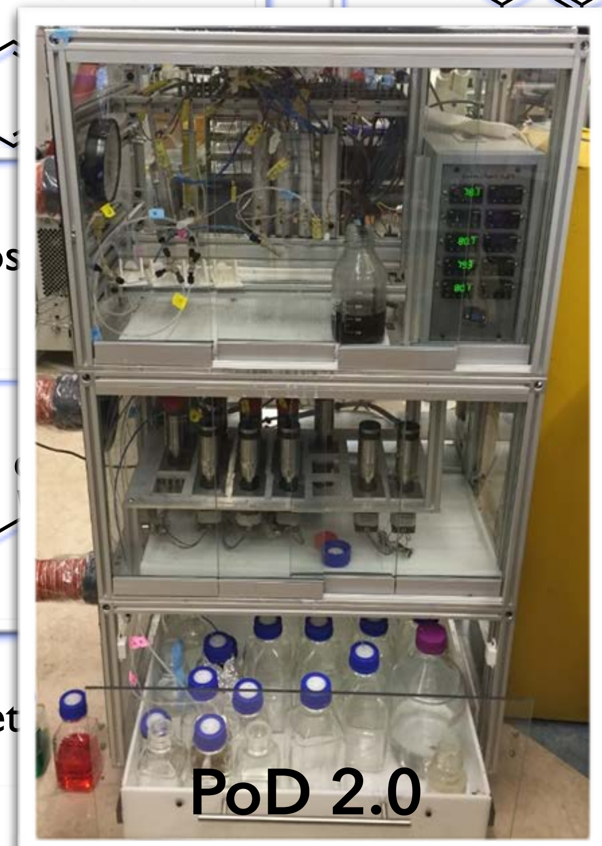


acin



Targets

efrigerator-

Christina Du

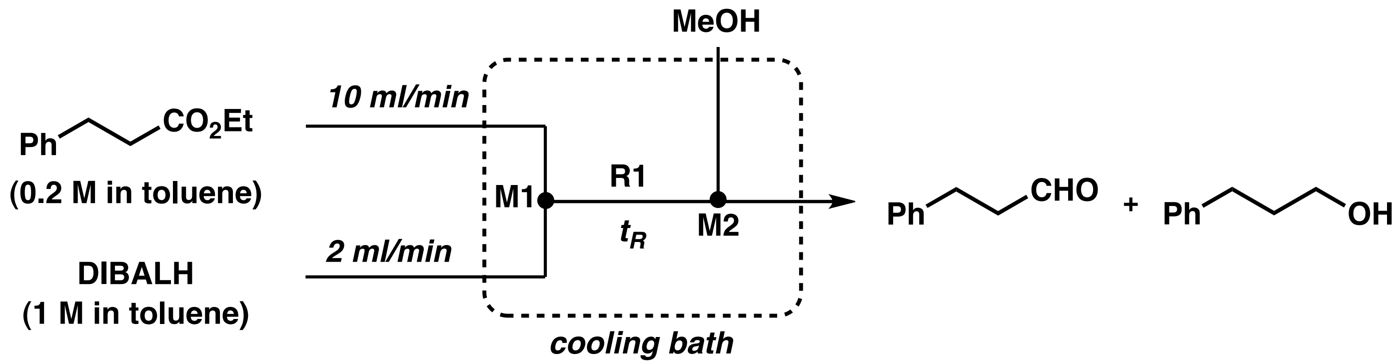
ntinuous

• “solids module” (tablets)

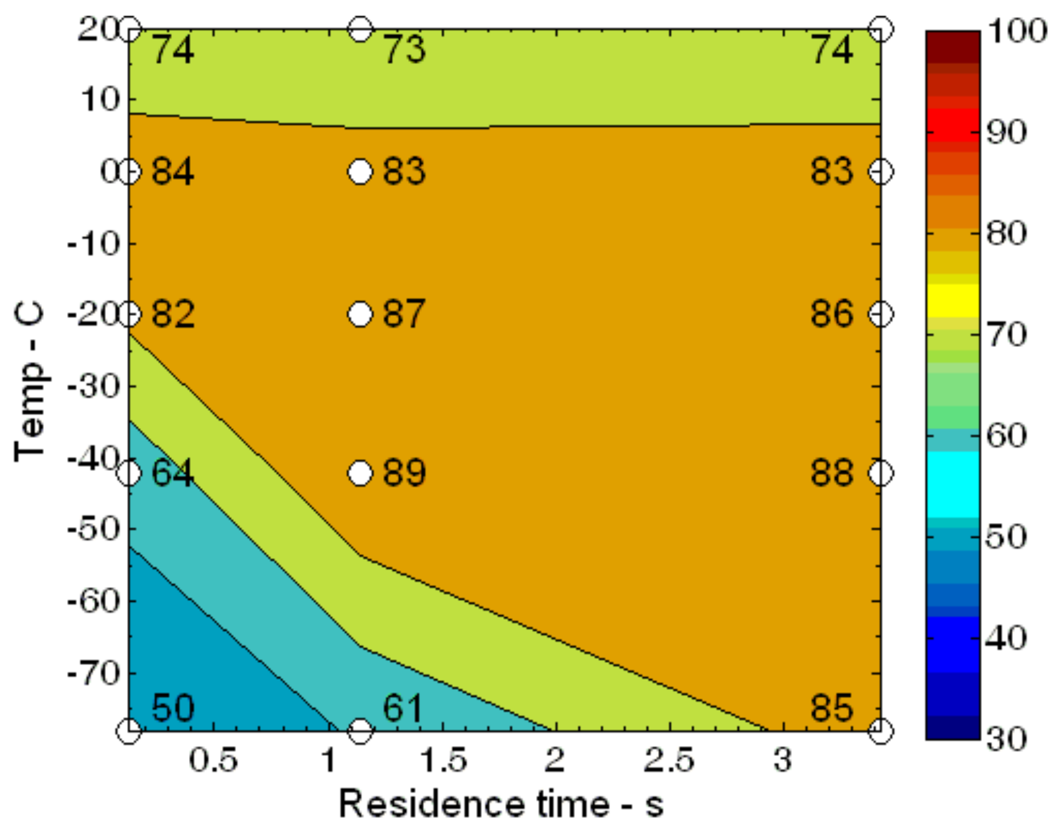
ce Russell

Continuous DIBAL-H reduction of ethyl hydrocinnamate

effect of temperature and t_R at constant flow-rate (12 ml/min)



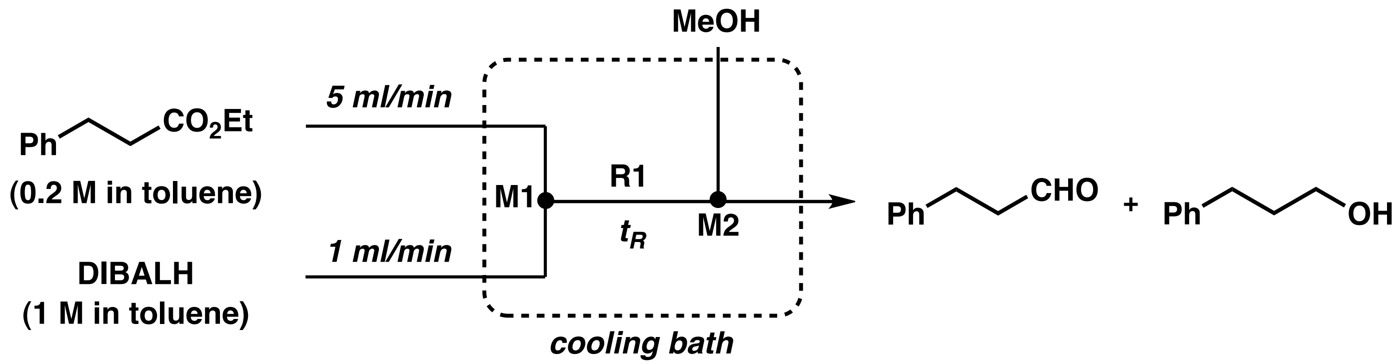
yield



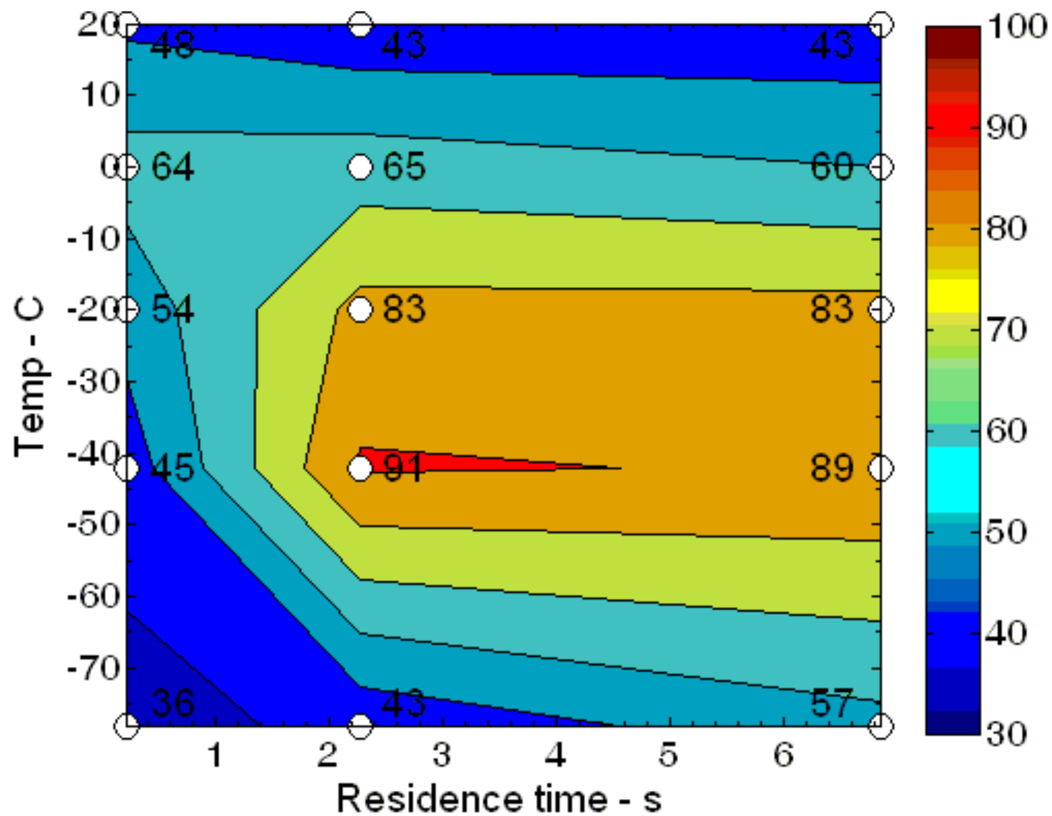
- No yield over 90%
- Lower yield at lowest temperature and shortest residence times (remainder primary alcohol byproduct)

Continuous DIBAL-H reduction of ethyl hydrocinnamate

effect of temperature and t_R at constant flow-rate (6 ml/min)



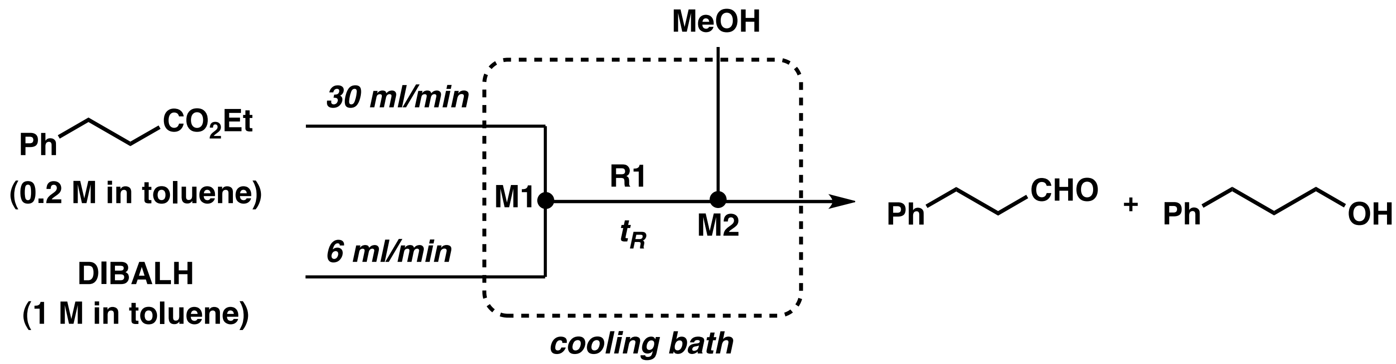
yield



- >90% yield under only very specific conditions, that is:
- **Strong dependence** of yield on
  - **temperature**
  - **residence time**

Continuous DIBAL-H reduction of ethyl hydrocinnamate

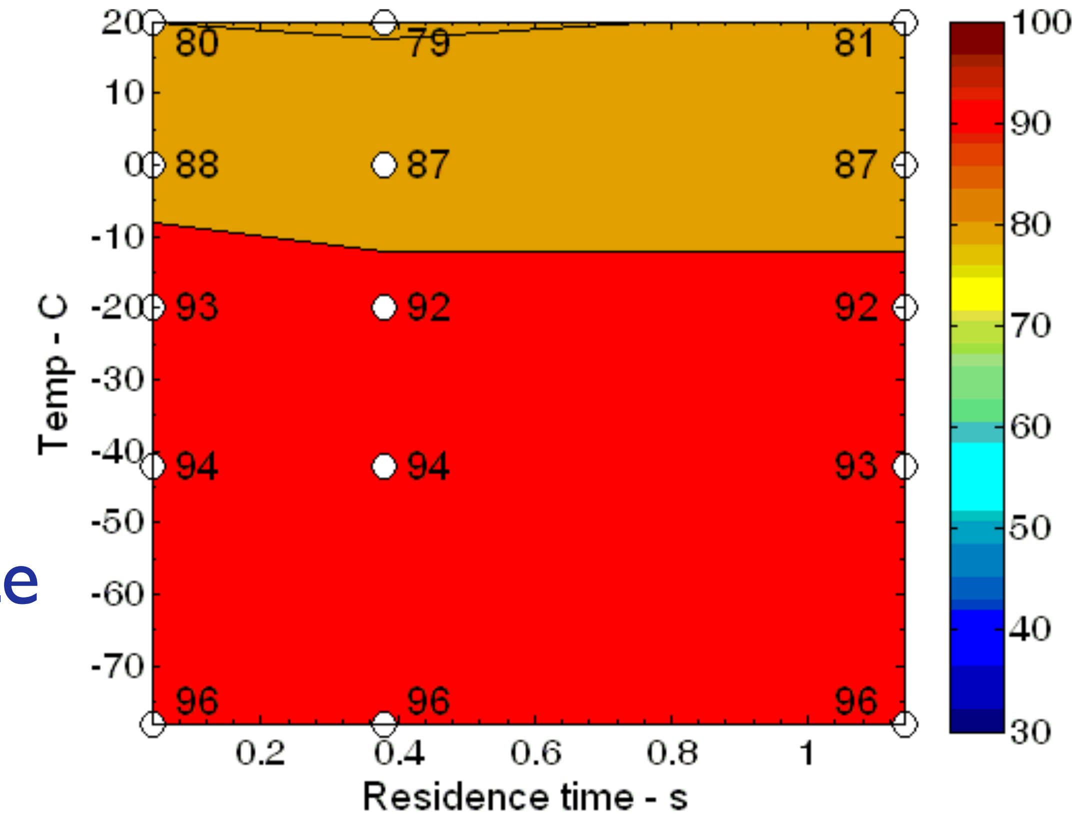
*effect of temperature and t_R at constant flow-rate (**36** ml/min)*



- **Minimal dependence** of yield on temperature
- **Negligible** residence time dependence!

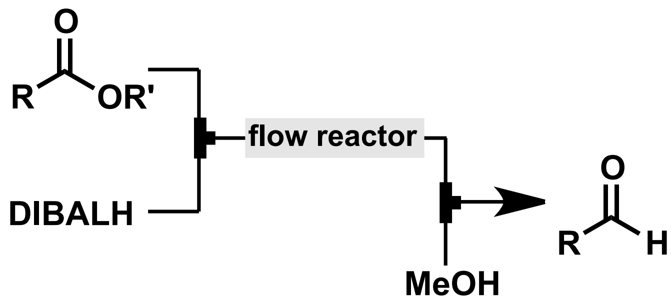
Hypothesis: High flow rate enhances mixing.

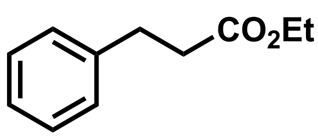
yield



For a review on micromixing see: Hessel, V, Löwe, H, Schönfeld, F. *Chem. Eng. Sci.* **2005**, 2479.

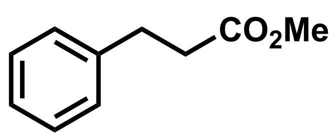
DIBAL-H Resurrected!
Applications to Other Common and Useful Aldehydes





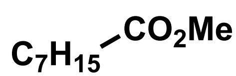
> 95%

t_R = 0.4 s, T = –78 °C,
A_1 = 30 mL·min^{-1},
1.0 equiv. DIBALH



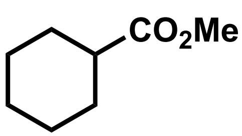
> 95%

t_R = 6.6 s, T = –42 °C,
A_1 = 5 mL·min^{-1},
1.2 equiv. DIBALH



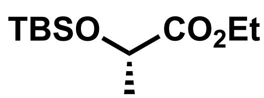
> 95%

t_R = 15.2 s, T = –78 °C,
A_1 = 5 mL·min^{-1},
1.2 equiv. DIBALH



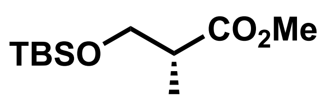
> 95%

t_R = 8.0 s, T = –78 °C,
A_1 = 10 mL·min^{-1},
1.1 equiv. DIBALH



> 95%

t_R = 15.0 s, T = –42 °C,
A_1 = 5 mL·min^{-1},
1.6 equiv. DIBALH



> 95%

t_R = 15.0 s, T = –78 °C,
A_1 = 5 mL·min^{-1},
1.5 equiv. DIBALH

- **Highly reproducible**
- **Very high throughput (up to 1 kg RCHO per day with < 1 mL microreactor)**
- **Robust**
- **Scalable**
- **Flow platform allowed for the rapid identification of the optimum reaction parameters.**
- **Mixing is critical for selectivity.**
- **Nearly impossible to emulate in batch.**

Webb, D.; Jamison, T. F., *Org. Lett.* **2012**, *14*, 568.

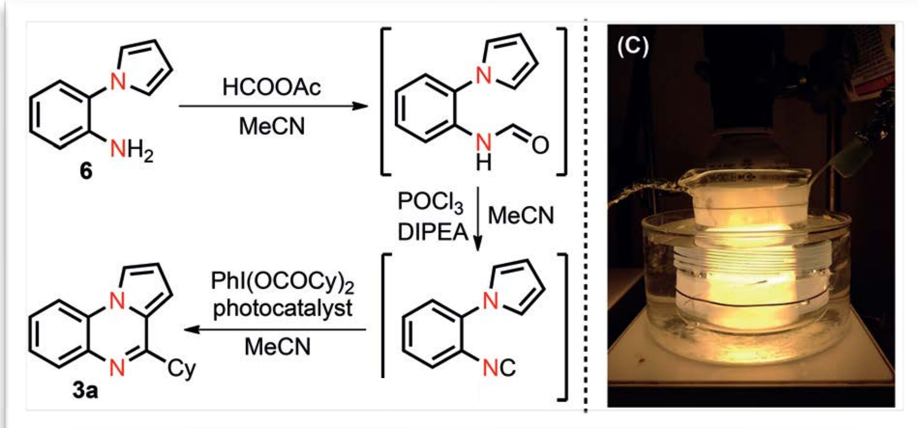
Webb, D.; Jamison, T. F., *Org. Lett.* **2012**, *14*, 2465.

When Should I Use Flow? General Considerations:

• Attribute	• Reaction Types that Benefit
• Heat Transfer • Temperature Control	• Fast (< 1 min) and/or Exothermic • Competing Mechanisms/Pathways
• Superb Mixing	• Mixing- or Transport-Dependent • Multi-Phase, e.g., Gas-Liquid
• Minimal Reaction Volumes	• Hazardous or Unstable Intermediates • Fast (< 1 min) and/or Exothermic
• Surface Area : Volume	• Pathlength-Dependent Efficiency • Photochemistry, Electrochemistry
• Access to "Extremes" (Temperature, Pressure, [A])	• Slow under "typical" conditions • Second-Order RLS

Other Examples of Chemistry Enabled or Enhanced by Flow

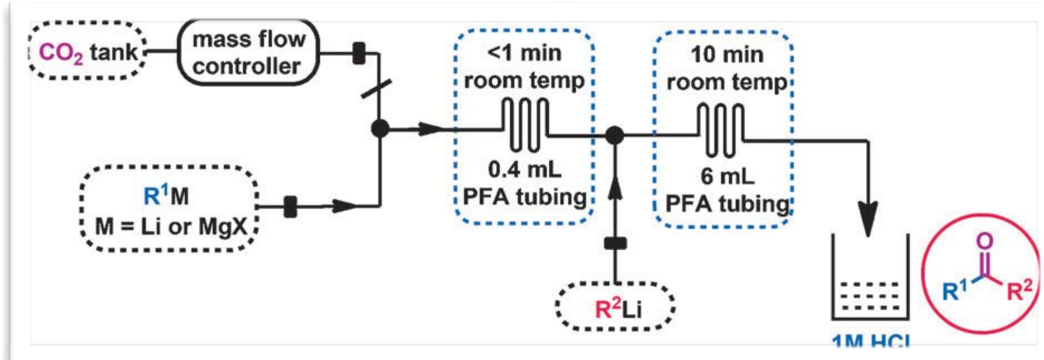
Photochemistry, Photoredox Catalysis



• Beer-Lambert Law

Angew. Chem. Int. Ed. **2014**, *53*, 14451-14455.

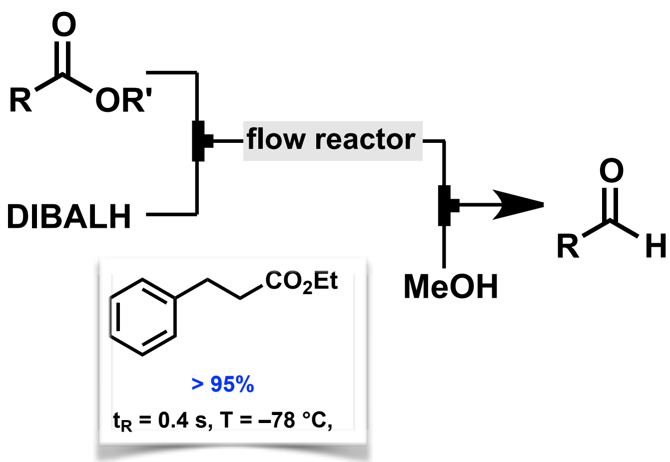
Synthesis using Gases



• Multistep (different gases), Gas/Liquid separators

Angew. Chem. Int. Ed. **2014**, *53*, 8416-8420.

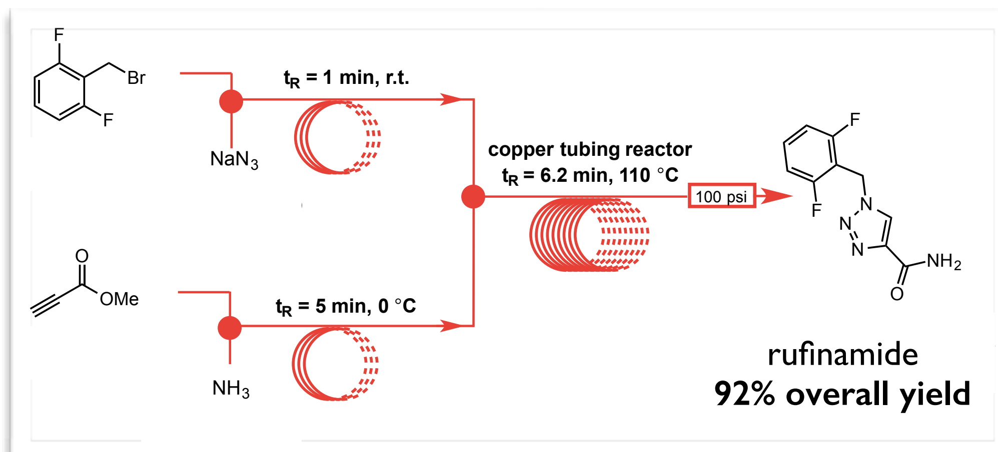
Very Fast Reactions (< 1 s)



• Precise temperature and t_R control

Org Lett. **2012**, *14*, 568-571.

On-Demand Synth/Use of Unstable



• RN_3 (as above), HN_3, O_2, and many others

Org. Proc. Res. Dev. **2014**, *18*, 1567-1570.

How – Equipment Modularity Comparison

	• Batch		• Flow	
Reagent Addition		Syringe Pumps		Syringe Pumps
Reactors		Flasks		Tubing
Mixers		Stirbars		T-Mixers
Compart-mentalization		Rubber Septa		Back Pressure Regulators
Separations		Separatory Funnels		Membrane Separators

Prediction: Flow will soon enjoy the same degree of **modularity** that has been a feature of organic synthesis for 200 years. Soon to be released: *rotovap*

Why Go with the Flow?

I. Technical: **Unlimited exciting transformations** that are challenging or next-to-impossible in batch are **straightforward** in flow.

II. Tactical: **This expanded platform** provides **many more ways** to make molecules and the ability to make **novel molecules.**

III. Strategic: **Continuous Flow Synthesis** offers a powerful, unique, and conceptually novel approach to **synthesis design** in all chemistry contexts.

Reviews: Webb, D.; Jamison T. F. "Continuous Flow Multi-Step Organic Synthesis," *Chem. Sci.* **2010**, *1*, 675-680.

McQuade, D. T.; Seeberger, P. H. "Applying Flow Chemistry: Materials, Methods, and Multi-Step Synthesis," *J. Org. Chem.* **2013**, *78*, 6384-6389.

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