



Continuous-flow chemistry: an emerging technology for organic synthesis

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1. Continuous-flow chemistry: a promising tool for organic synthesis

- Synthesis in continuous-flow: new equipment
- Flow chemistry vs. traditional batch method
- Types of flow chemistry: advantages and drawbacks

2. Overview of some applications of flow chemistry in organic synthesis

- Handling highly reactive species in flow
- Natural products and drug syntheses in flow
- Synthetic flow photochemistry

General readings

REVIEWS:

Machine-Assisted Organic Synthesis, S. V. Ley et al. *Angew. Chem. Int. Ed.* **2015**, *54*, 10122 (open access)

The integration of flow reactors into synthetic organic chemistry, I. R. Baxendale *J. Chem. Technol. Biotechnol* **2013**, *88*, 519 (open access)

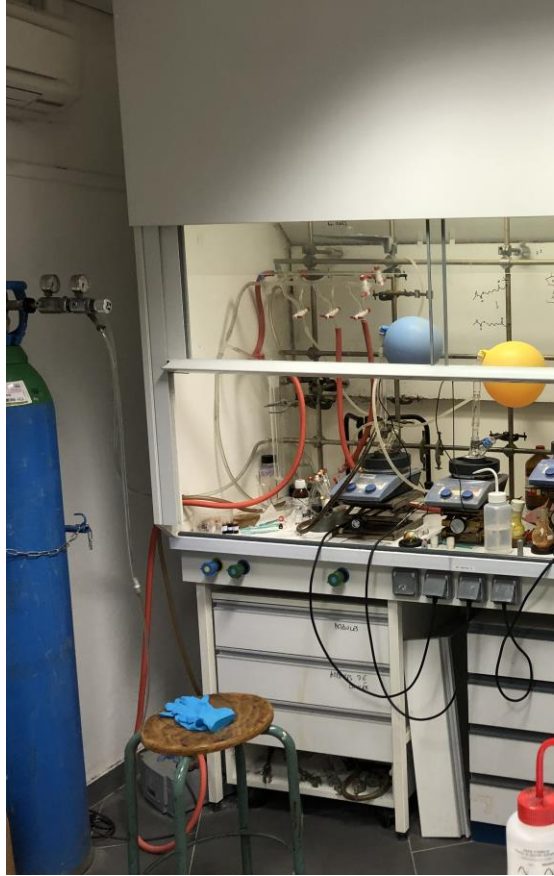
Continuous flow multi-step organic synthesis, D. Webb and T. F. Jamison *Chem. Sci.* **2010**, *1*, 675 (open access)

Flow 'Fine' Synthesis: High Yielding and Selective Organic Synthesis by Flow Methods, S. Kobayashi **2015**, *11*, 425 (open access)

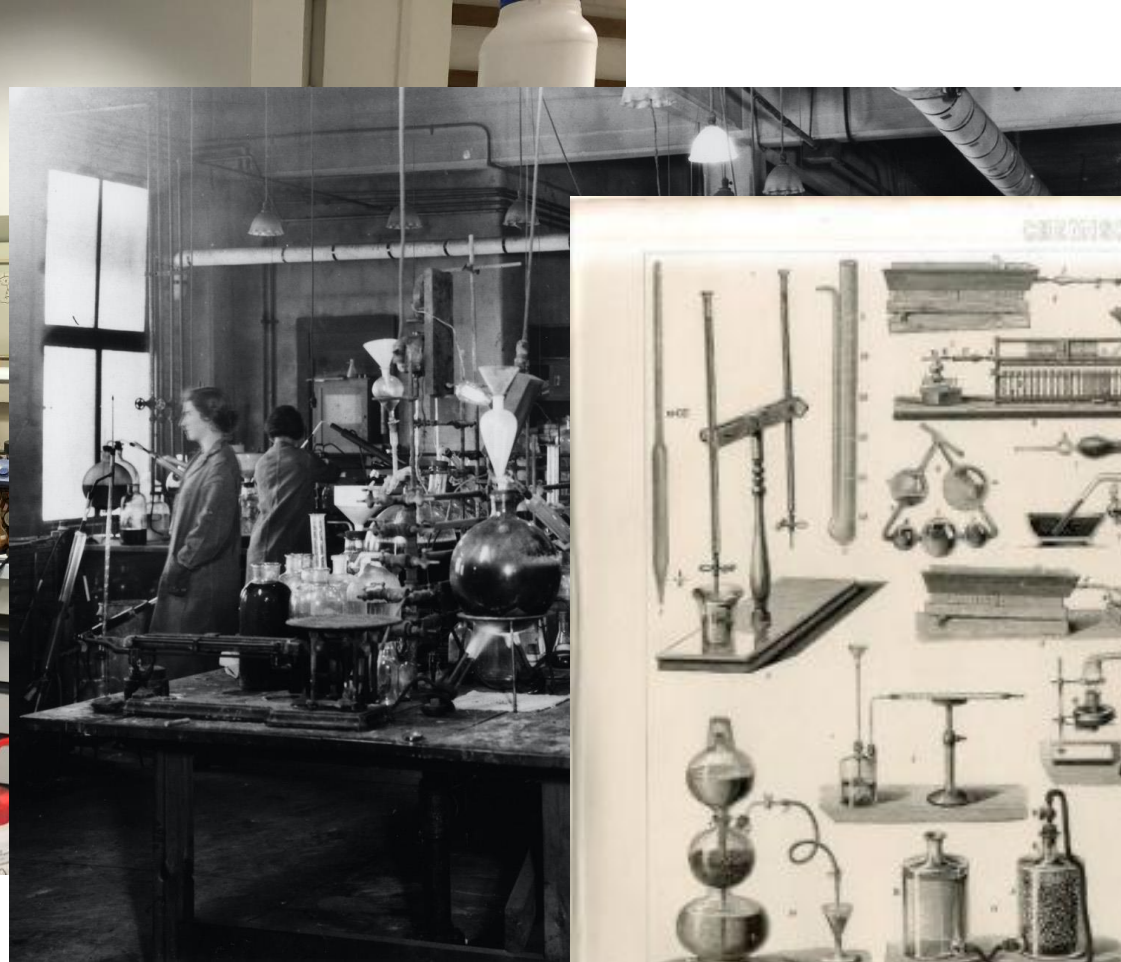
Continuous-flow chemistry: a promising tool for organic synthesis

Synthesis in flow: new equipment

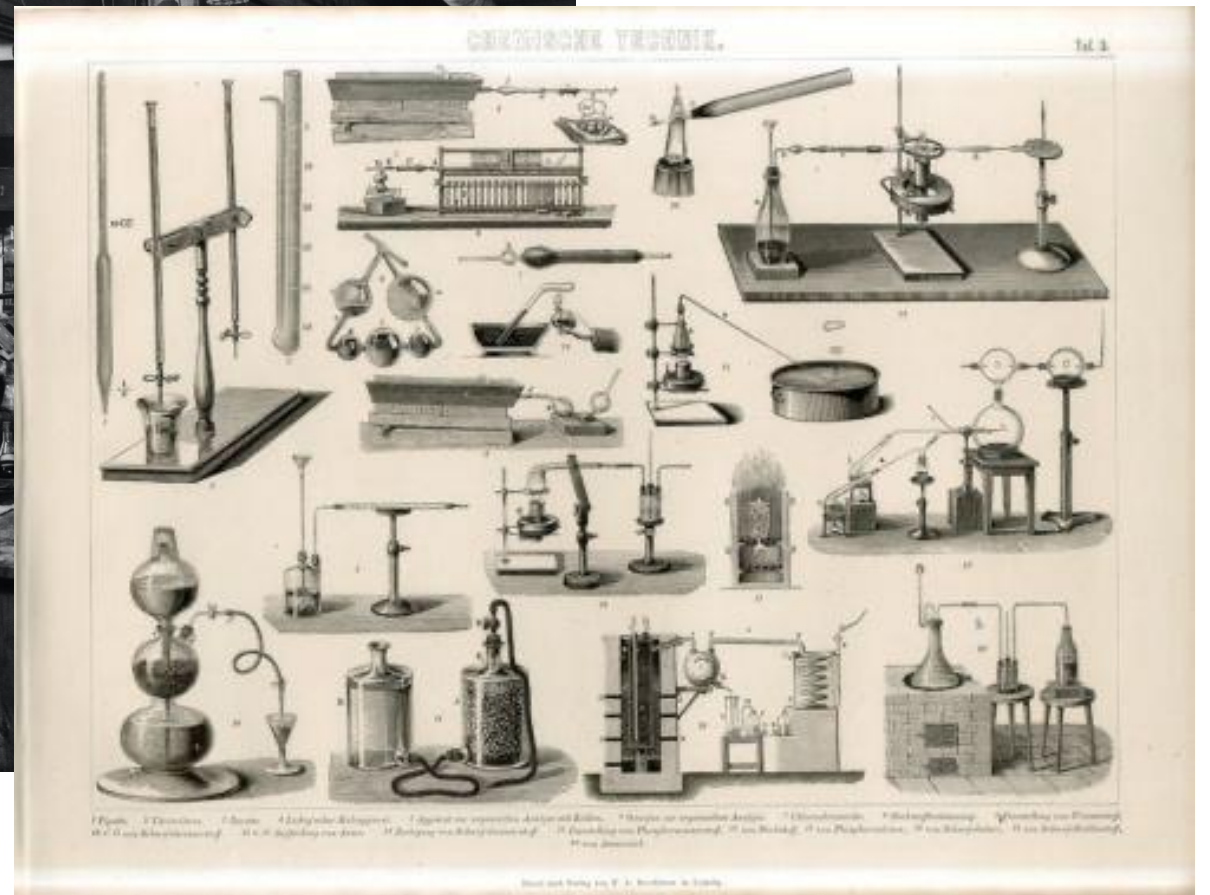
The familiar chemistry laboratory



2025



1920



1850

Traditional synthesis in « batch »



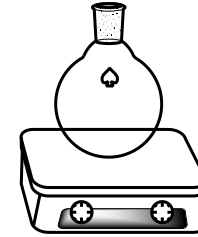
2025

1



Beaker
Erlenmeyer
Weighting, pouring

2



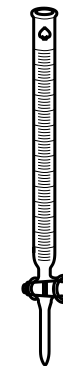
Round bottom flask
Magnetic stirrer
Mixing, reacting

3



Separating funnel
Quenching, extracting

4



Column chromatography
Purifying

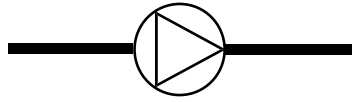
Synthesis in continuous flow: new equipment

1



Beaker
Erlenmeyer

Weighting, pouring



Pumps

Pouring, pumping mixtures



Syringe pumps



Peristaltic pumps



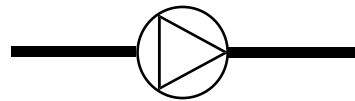
HPLC pumps

Synthesis in continuous flow: new equipment

1

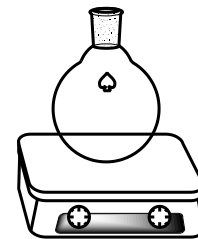


Beaker
Erlenmeyer
Weighting, pouring



Pumps
Pouring, pumping mixtures

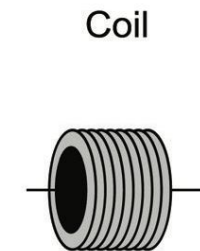
2



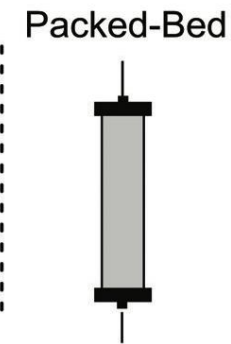
Round bottom flask
Magnetic stirrer
Mixing, reacting



Chip



Coil



Packed-Bed



Micromixers
microscale



Coil reactors
milliscale



Packed bed
*Heterogeneous catalysis,
scavengers*

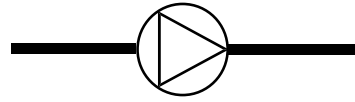
Synthesis in continuous flow: new equipment

1



Beaker
Erlenmeyer

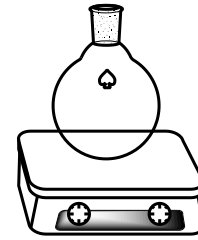
Weighting, pouring



Pumps

Pouring, pumping mixtures

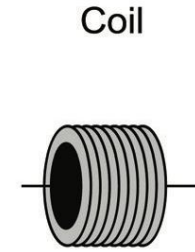
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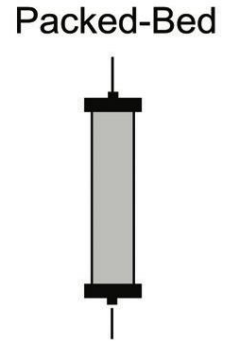
Round bottom flask
Magnetic stirrer
Mixing, reacting



Chip



Coil



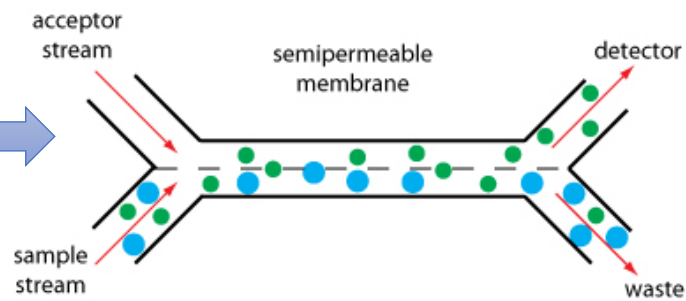
Packed-Bed

3



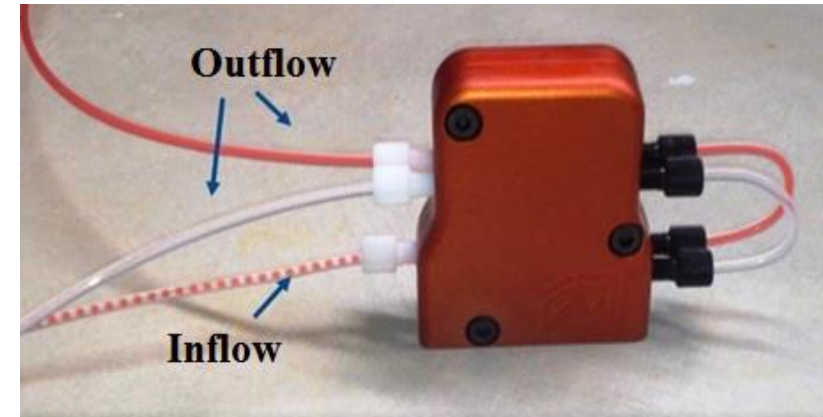
Separating funnel

Quenching, extracting



Membrane separator

Extracting



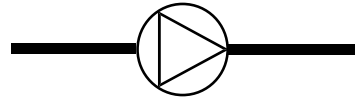
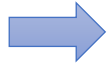
Zaiput Tech.

Synthesis in continuous flow: new equipment

1

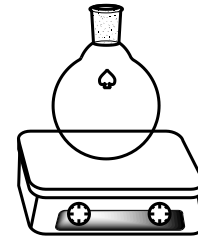


Beaker
Erlenmeyer
Weighting, pouring



Pumps
Pouring, pumping mixtures

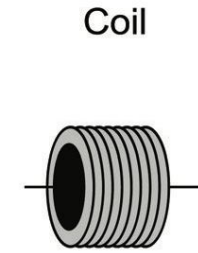
2



Round bottom flask
Magnetic stirrer
Mixing, reacting

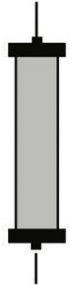


Chip



Coil

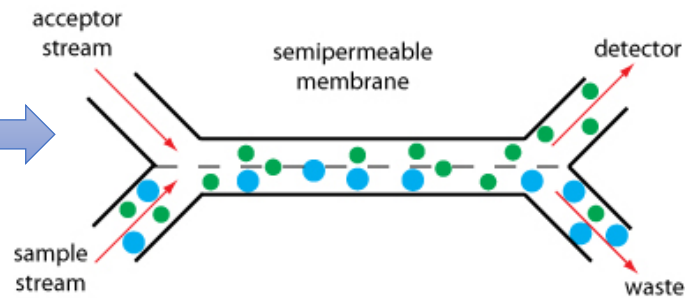
Packed-Bed



3

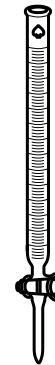


Separating funnel
Quenching, extracting



Membrane separator
Extracting

4



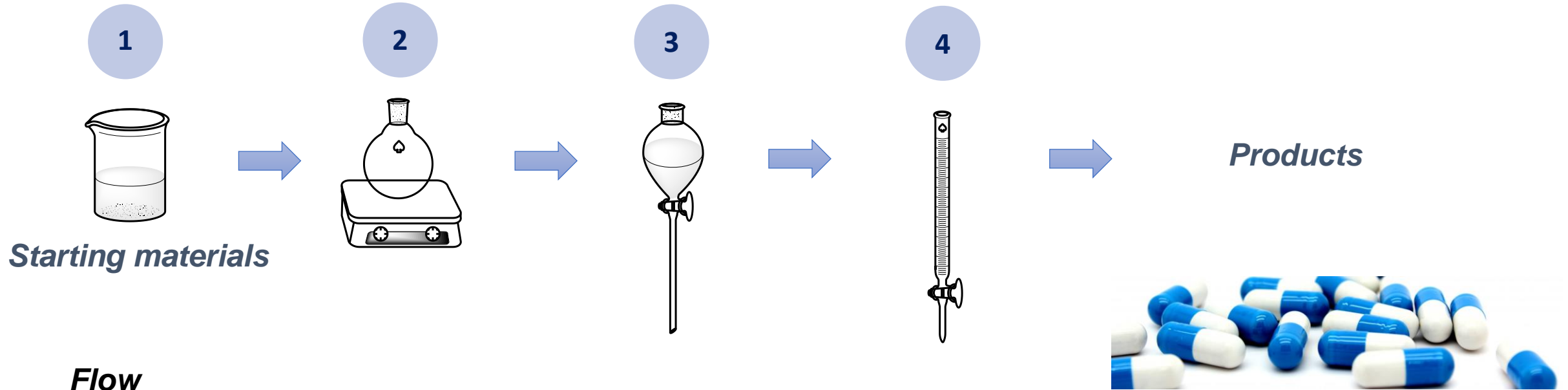
Column chromatography
Purifying



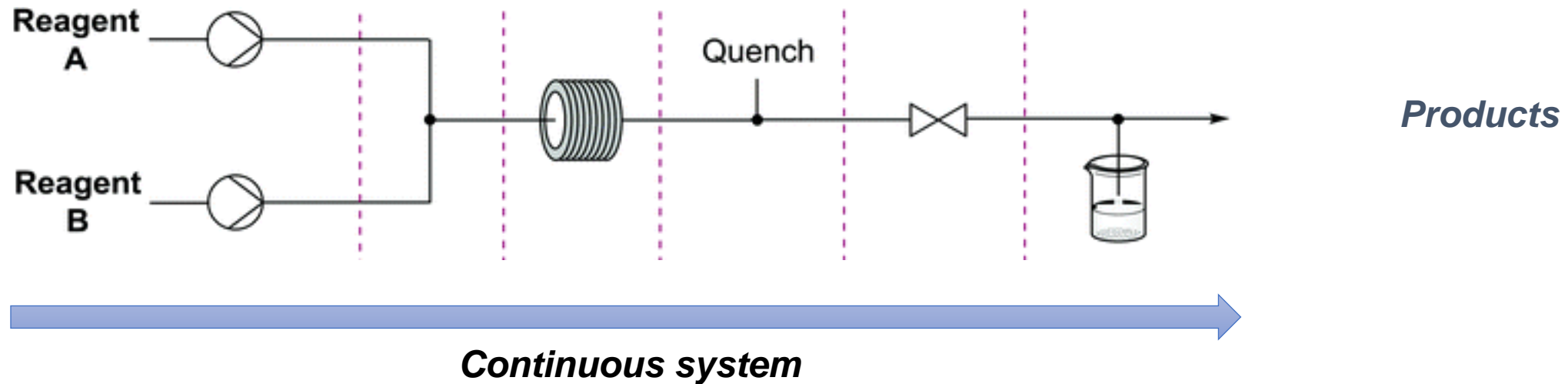
Scavenging column
Purifying

Synthesis in continuous flow: new equipment

Batch



Flow



Synthesis in continuous flow: new equipment



Vapourtec flow reactor



Syrris flow reactor

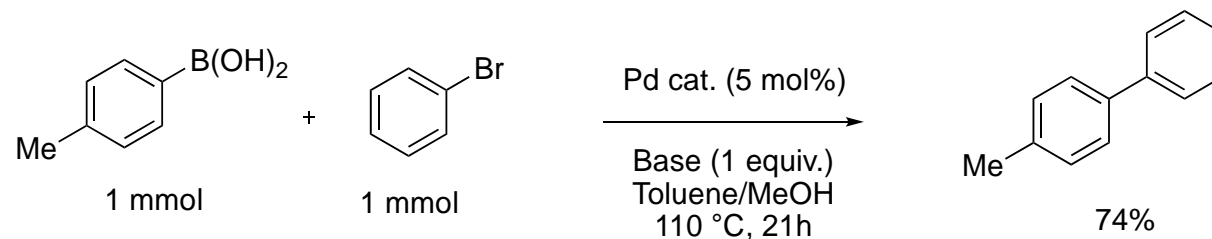
Continuous-flow chemistry: a promising tool for organic synthesis

Batch vs. flow chemistry

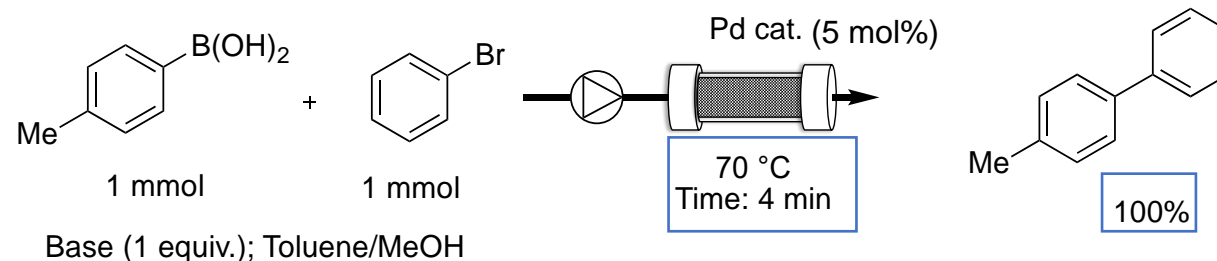
Batch vs. flow chemistry

- **Flow chemistry is a synthetic technique:** the chemistry and mechanisms remain the same

Batch procedure:



Flow procedure:

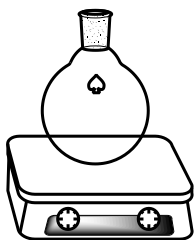


S. Ley *et al*, *Chem. Comm.* **2005**, 2175.

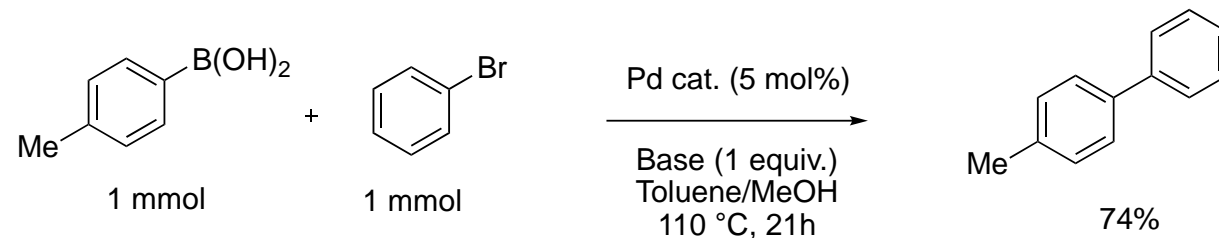
- **Flow chemistry is a tool** for increasing the control of the key reaction parameters to selectively control reactions pathways (temperature, pressure, mixing and stoichiometric ratios)

Batch vs. flow chemistry

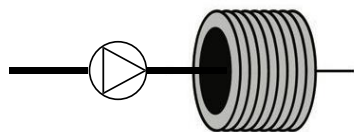
- Reactions parameters in batch



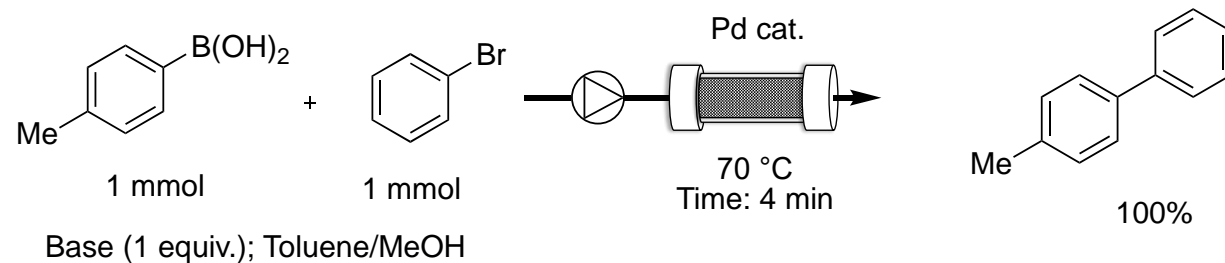
- Reaction time
- Concentration
- Temperature
- Mixing



- Reactions parameters in flow



- Residence time (flow rates)
- Molarity (flow rate ratios)
- Temperature
- Pressure **new!**

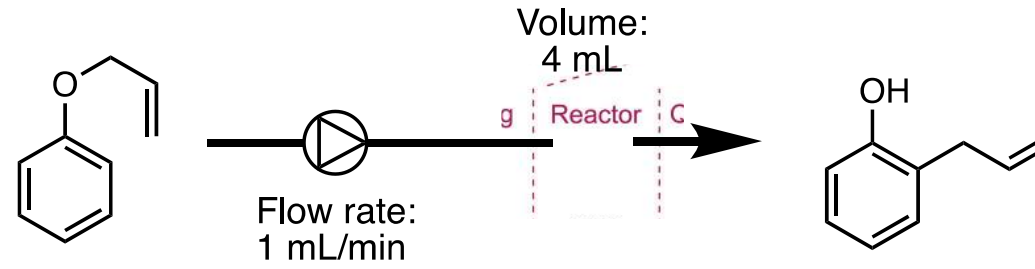


Batch vs. flow chemistry

- Flow rates influence:

1

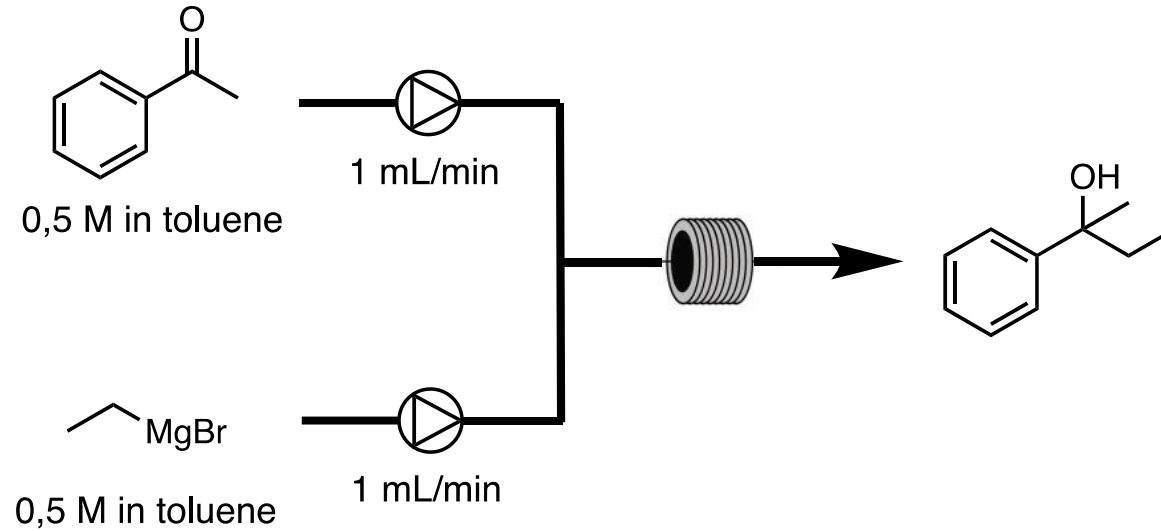
Residence time:



Residence time:

2

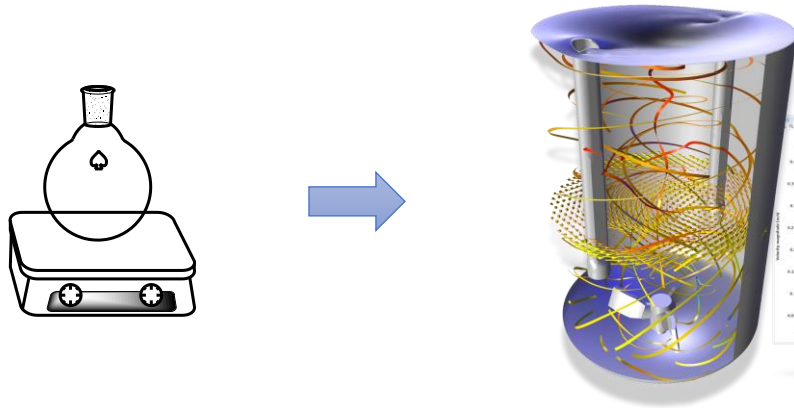
Stoichiometry:



Max concentration:

Batch vs. flow chemistry

- **Mixing in batch**



Turbulent / chaotic:

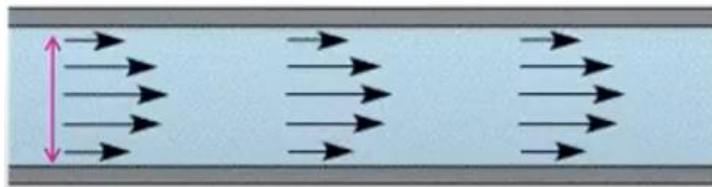
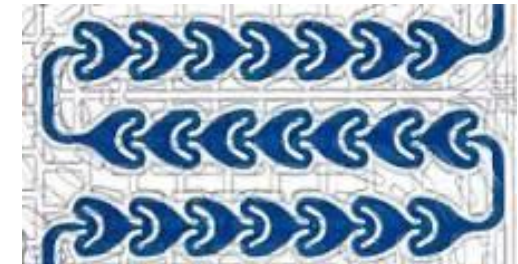
- lack of reproducibility
- Heat and mass transfer not optimal

- **Mixing in flow**



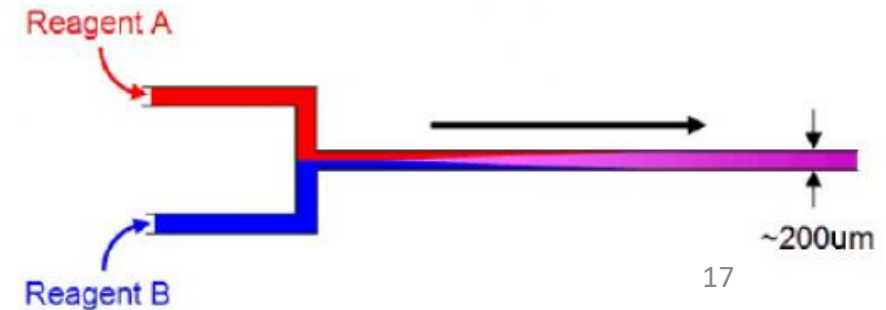
Turbulent / chaotic

- Big scale
- Possible to use static mixer to increase mass transfer



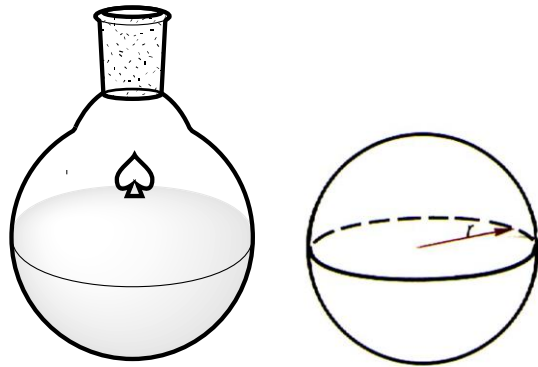
Laminar (diffusion)

- Small diameters
- Fast and reproducible



Batch vs. flow chemistry

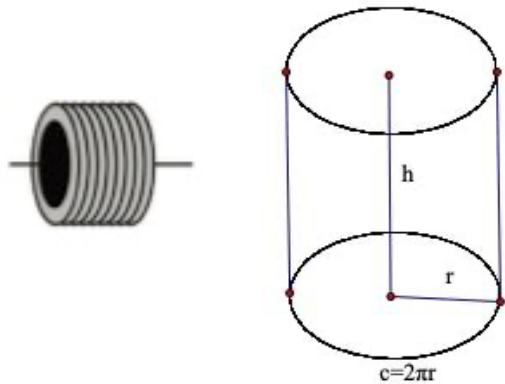
- **Temperature:** flow chemistry reactors have a much greater surface area to volume ratio



Batch reactor:

- Volume: $\frac{4}{3}\pi r^3$
- Surface area: $4\pi r^2$

Volume: 1 cm^3
Surface area: 4.8 cm^2



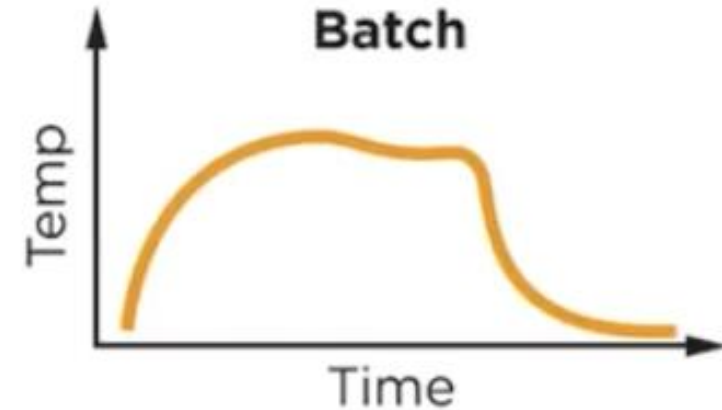
Flow reactor:

- Volume: $\pi r^2 h$
- Surface: $2\pi r h$

Volume: 1 cm^3 ($d = 1 \text{ mm}$)
Surface area: 40 cm^2

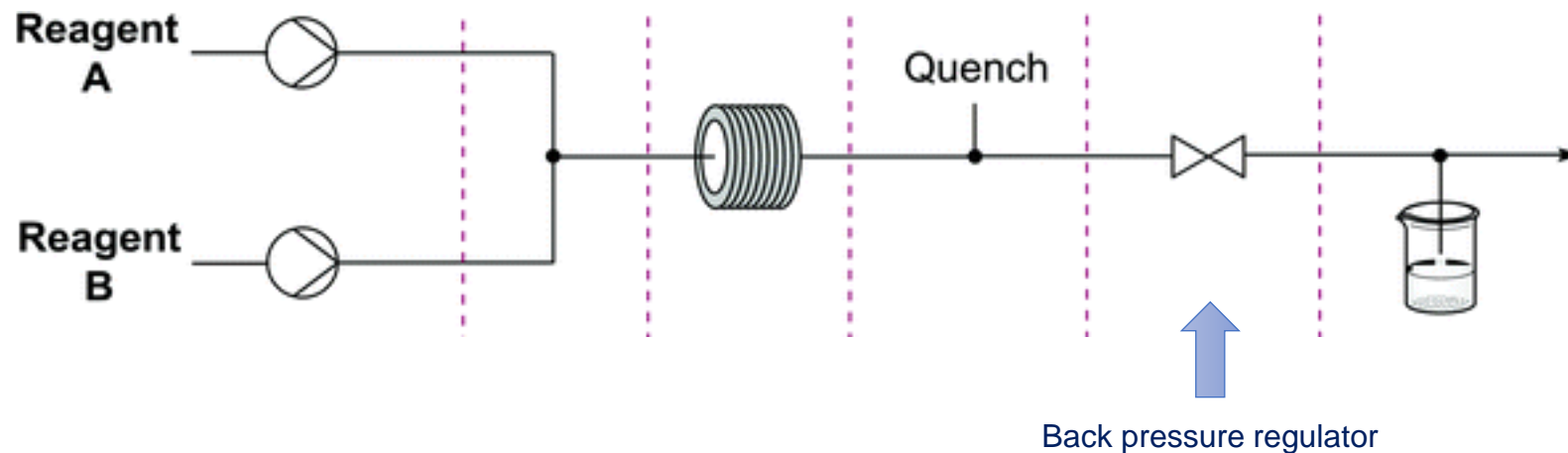
Volume: 1 cm^3 ($d = 0,5 \text{ mm}$)
Surface area: 80 cm^2

Reaction profiles:



Batch vs. flow chemistry

- **Pressure:** flow chemistry reactors have typically smaller volumes and can be pressurized (much easier than a batch reaction)



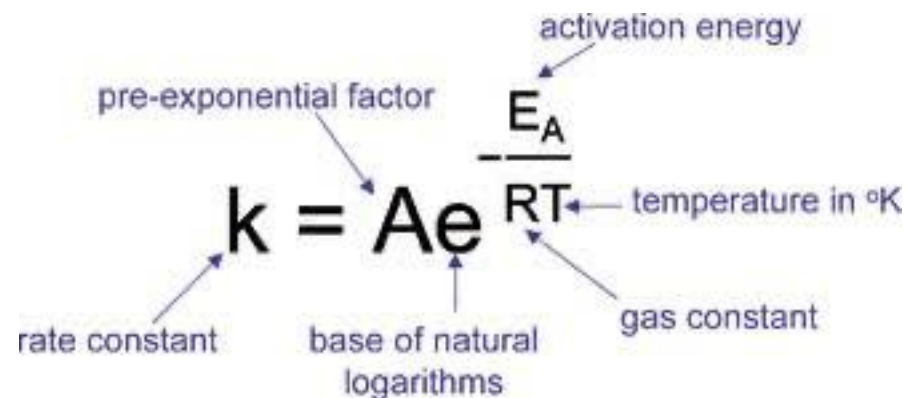
- By pressurizing, flow reactors can operate at **temperatures above the typical boiling** point of reactions
- **Easy superheating** of reactions above reflux temperatures at atmospheric pressure
- Useful for reactions with gas (either adding or evolving)
- Avoid cavitation (volatile material boiling)

Batch vs. flow chemistry

- **Pressure:** example of solvent superheating amenable to flow chemistry

Solvent	1 bar	7 bar	17 bar
dichloromethane	41 °C	109 °C	153 °C
methanol	65 °C	138 °C	185 °C
water	100 °C	181 °C	231 °C

- Arrhenius rate law:



- Reactions are 2x faster for every 10 °C rise
- 100 °C rise > 1000 time faster

- To sum up the range of applications and benefits

Better mixing, temperature and pressure control



- Faster reactions
- Reaction conditions not possible in batch
- Better reproducibility, easier scale-up
- Reactions are usually more selective

Equipment advantages



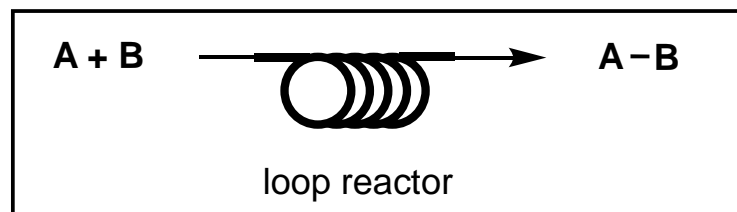
- Safer reactions
- Simpler work-up
- Easy integration of inline analysis
- Space !
- Faster reaction optimisation

Continuous-flow chemistry: a promising tool for organic synthesis

Types of flow chemistry: advantages and drawbacks

Types of flow chemistry: advantages and drawbacks

- **Type 1: no catalyst**

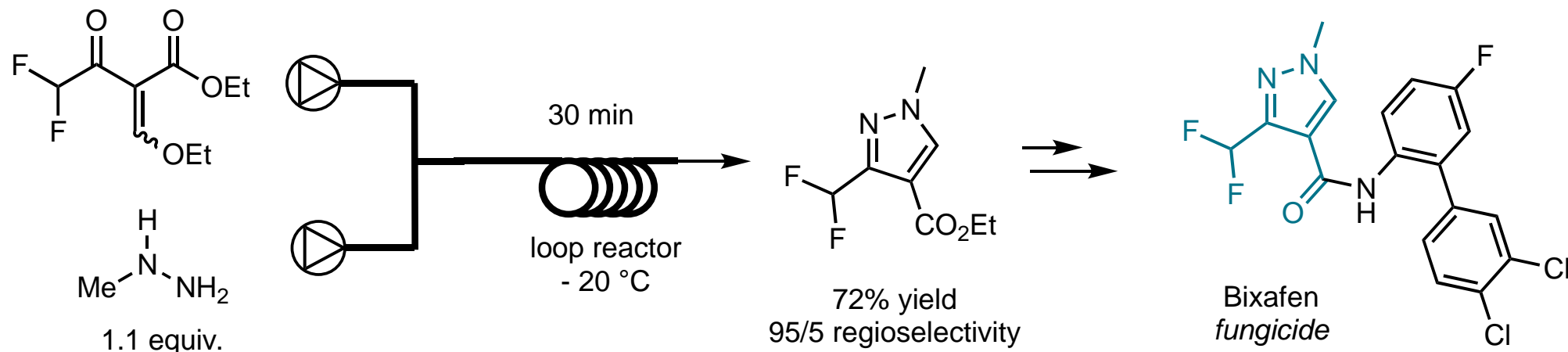


Advantage: product generated continuously (efficiency)

Drawbacks: remaining A or B and by-product eluted (waste)

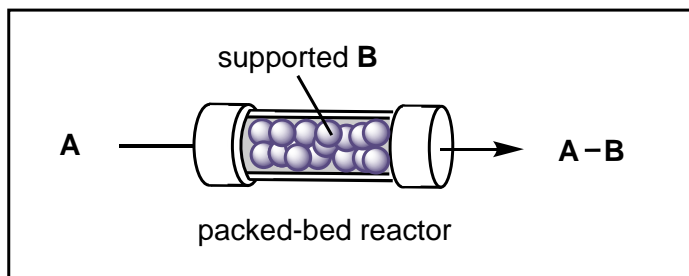
S. Kobayashi, *Chem. Asian J.* **2016**, 11, 425.

Example: pyrazole flow synthesis



Types of flow chemistry: advantages and drawbacks

- **Type 2: supported reagents**

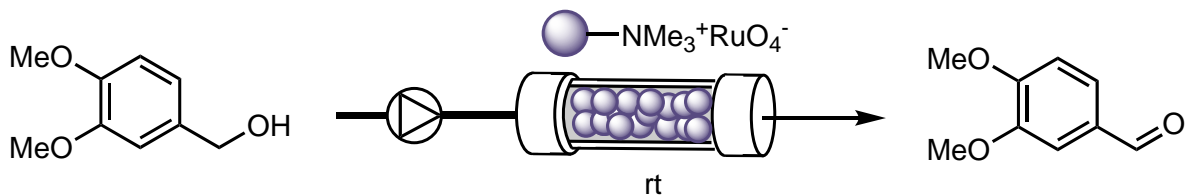
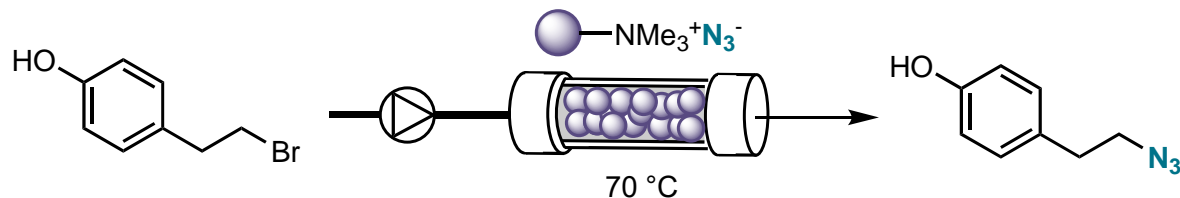


Advantage: product generated continuously (efficiency)
contamination with unreacted **A** might be avoided

Drawbacks: over-reaction may occur (excess of **B**)
B is consumed and must be replaced (uncontinuous)

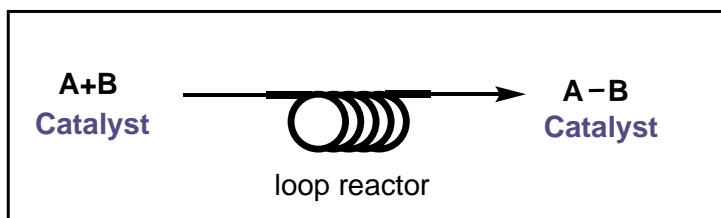
S. Kobayashi, *Chem. Asian J.* **2016**, *11*, 425.

Examples:



Types of flow chemistry: advantages and drawbacks

- **Type 3: homogeneous catalysis**

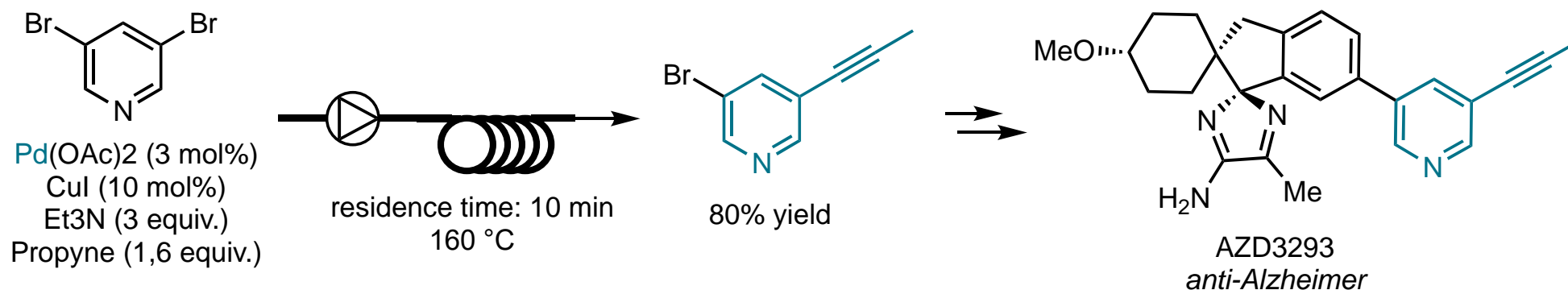


Advantage: product generated continuously (efficiency)
homogeneous catalysis proceeds smoothly

Drawbacks: homogeneous catalyst cannot be separated/recycled

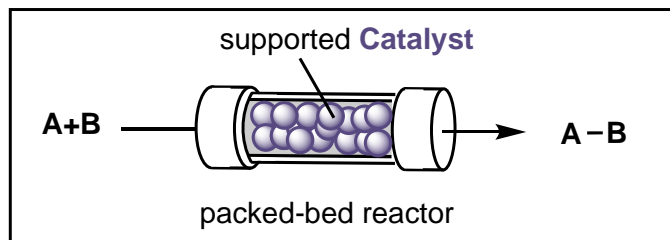
S. Kobayashi, *Chem. Asian J.* **2016**, *11*, 425.

Example:



Types of flow chemistry: advantages and drawbacks

- **Type 4: heterogeneous catalysis**

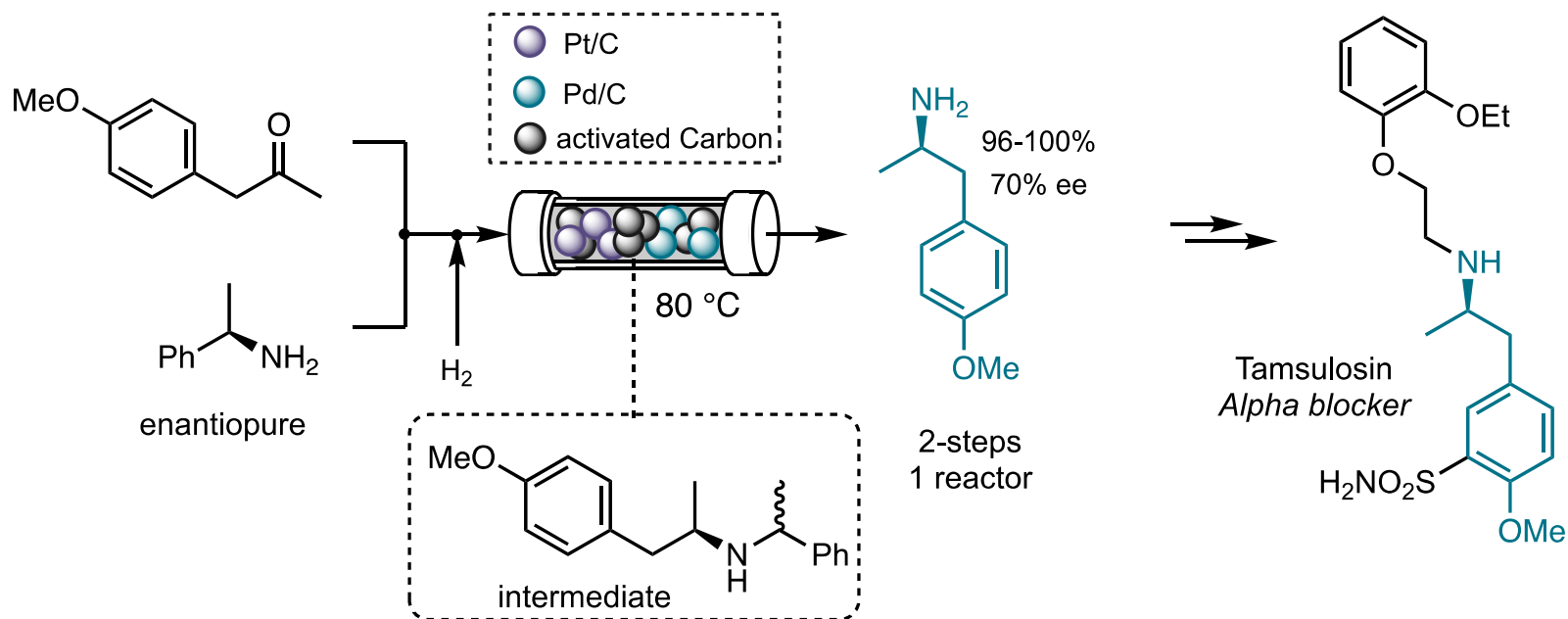


Advantage: product generated continuously (efficiency)
heterogeneous catalyst reusable and recycled
allows for multistep continuous sequences

Drawbacks: usually less reactive vs. homogeneous

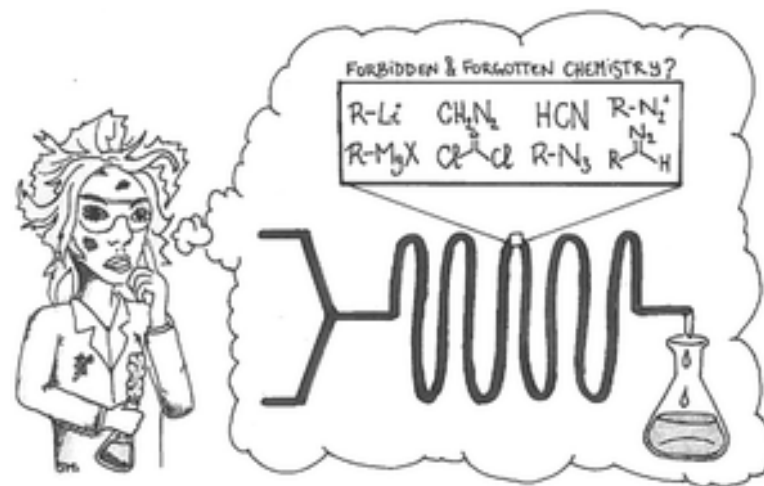
S. Kobayashi, *Chem. Asian J.* **2016**, *11*, 425.

Example:



Applications of flow chemistry in organic synthesis

Handling highly reactive species in flow



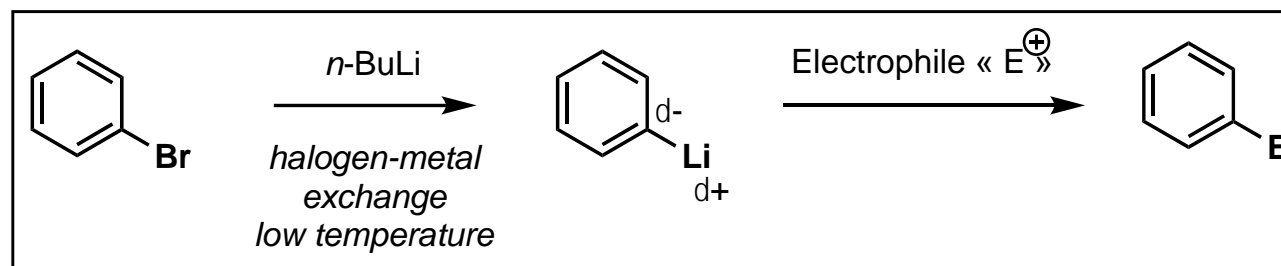
Handling reactive species in flow

- **Case study: organometallic reagents**

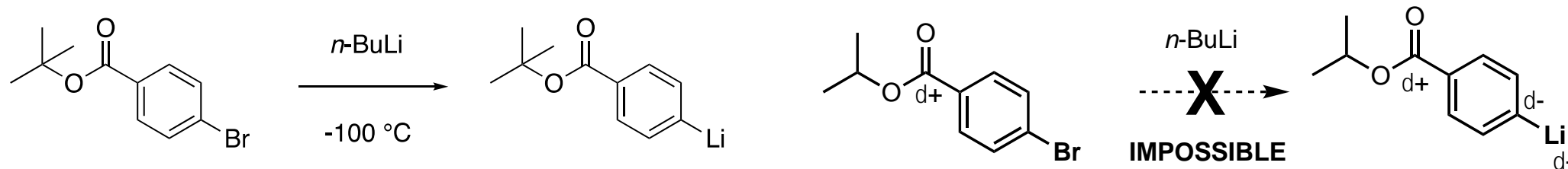
- Fast and often exothermic
- Low temperature required (-78 °C): decreases the reaction rate but enhance selectivity
- Slow addition, dilution are also essential to reduce by-product formation and safety hazard
- **In batch: heat dissipation is challenging on scale**
- **In flow: high surface area-to-volume ratio, improve heat dissipation and accurate temperature control**

- **Organolithium chemistry: strong base (pka *n*-BuLi : 50), reacts violently with H₂O, exothermic reactions**

- Halogen-metal exchange in batch:

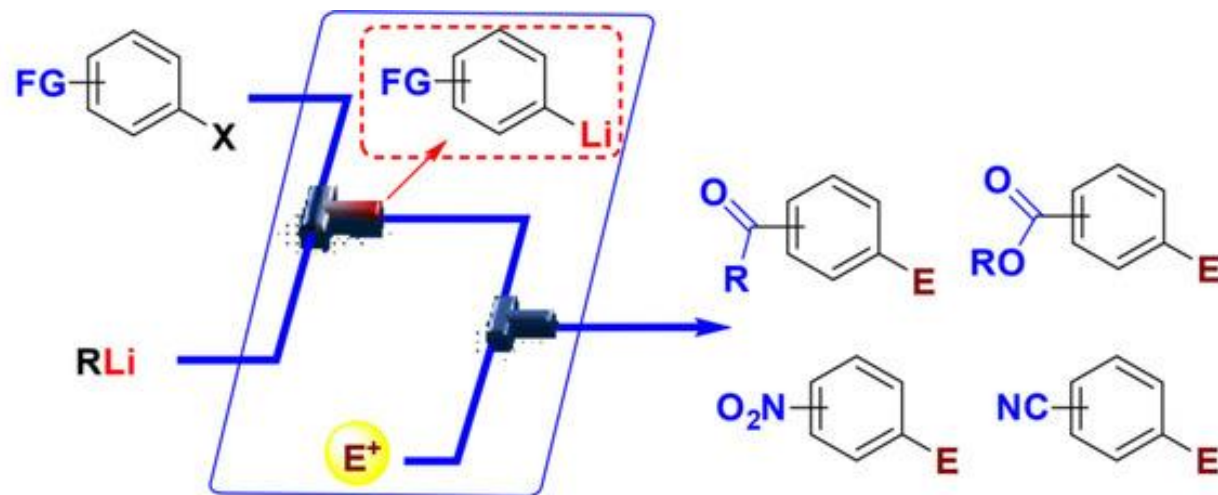


- Limitations:



Handling reactive species in flow

- **Flash chemistry:** playing with the flow rate to control selectivity



FG = RCO, COOR, CN, NO₂
 X = Br, I
 RLi = *s*-BuLi, *n*-BuLi, PhLi, MesLi

FG	Batch macro reactor			Flow microreactor		
	<i>o</i> -	<i>m</i> -	<i>p</i> -	<i>o</i> -	<i>m</i> -	<i>p</i> -
CO ₂ ^t Bu	-100 °C	-100 °C	-100 °C	0 °C	0 °C	0 °C
CO ₂ ⁱ Pr	-100 °C	<i>impossible</i>	<i>impossible</i>	-28 °C	-48 °C	-48 °C
CO ₂ Et	<i>impossible</i>	<i>impossible</i>	<i>impossible</i>	-48 °C	-58 °C	-58 °C
CO ₂ Me	<i>impossible</i>	<i>impossible</i>	<i>impossible</i>	-48 °C	-58 °C	-78 °C
NO ₂	-100 °C	<i>impossible</i>	<i>impossible</i>	0 °C	-28 °C	-28 °C
CN	-100 °C	-100 °C	-100 °C	0 °C	-28 °C	-28 °C

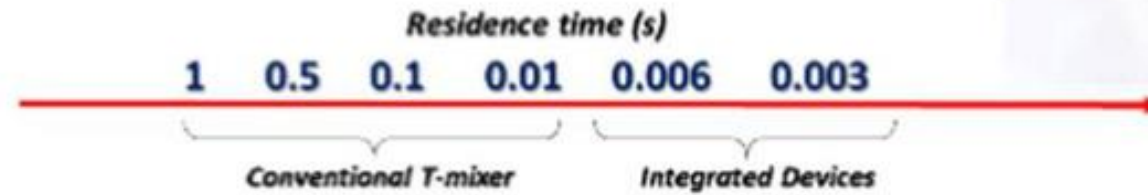
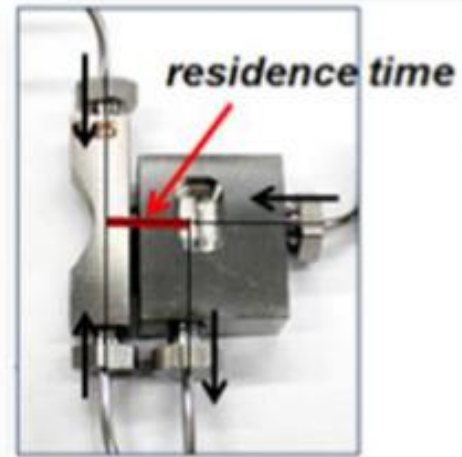
Handling reactive species in flow

- **Flash chemistry:** playing with the flow rate to control selectivity

Conventional T-mixer:
Two micromixers need to be
connected with microtube reactor

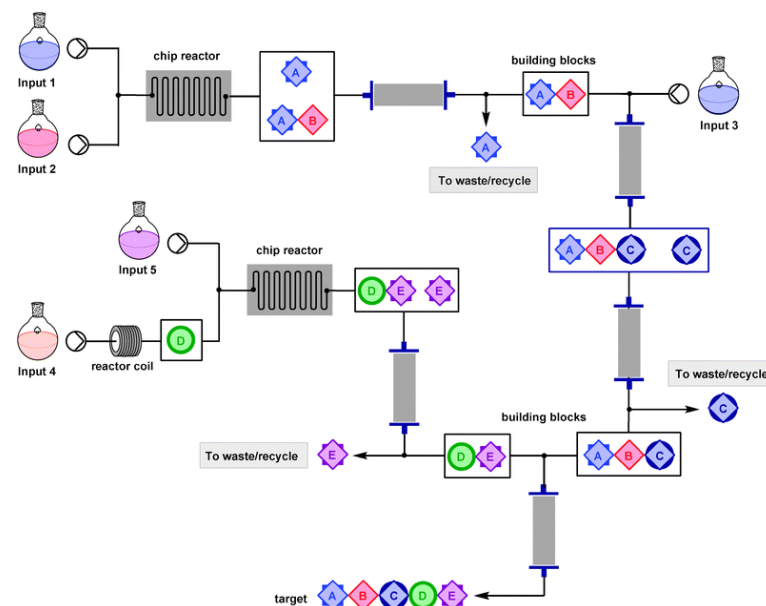


Integrated Devices:
Micromixer and microtube
reactor are combined



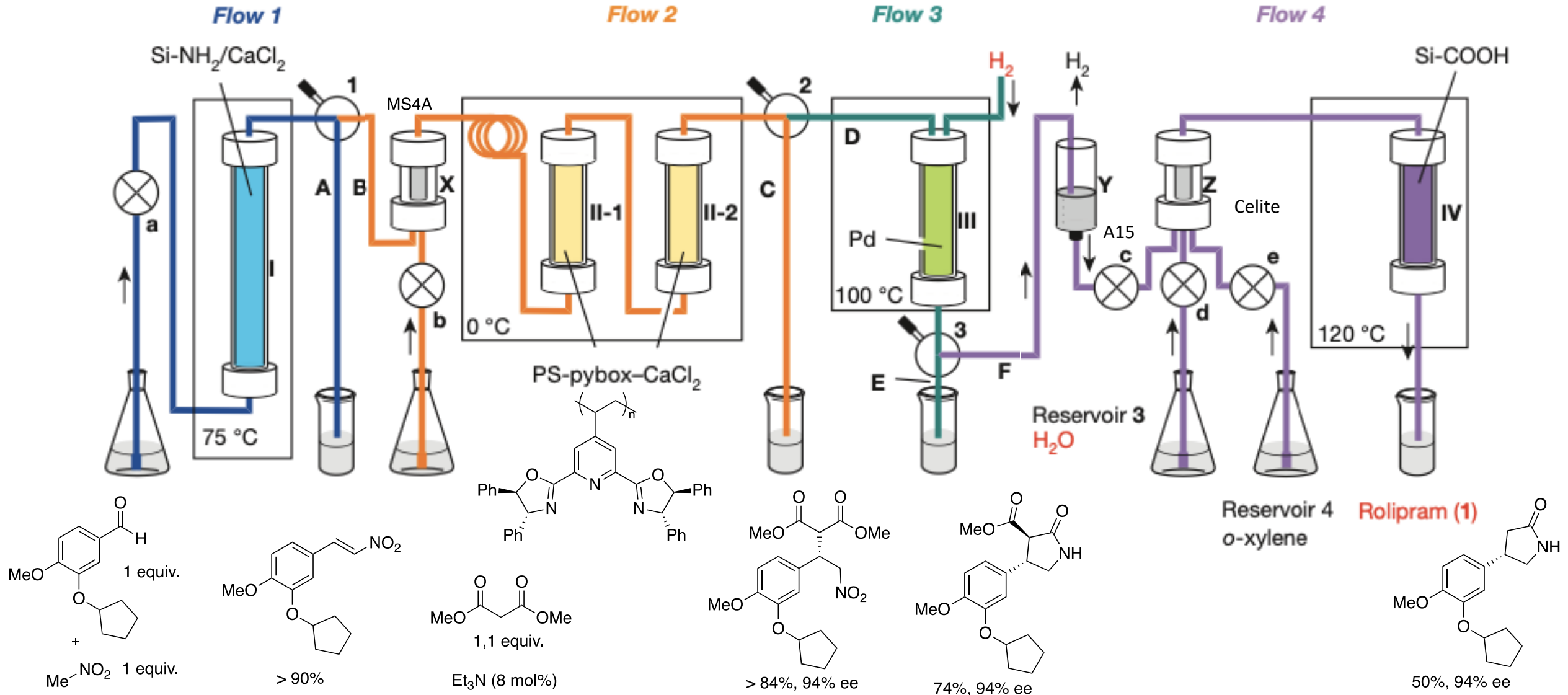
Applications of flow chemistry in organic synthesis

Natural product and drug syntheses



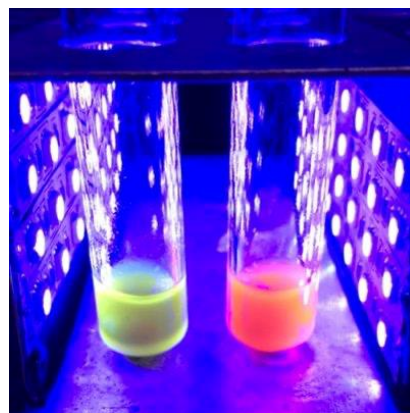
Natural products and drug syntheses

- (R) and (S)-Rolipram (Alzheimer disease)



Applications of flow chemistry in organic synthesis

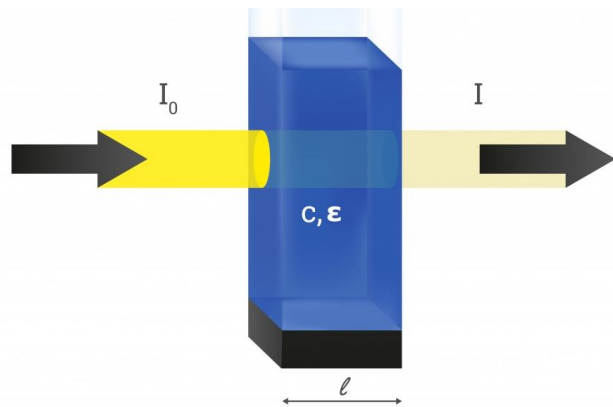
Photochemistry in flow



- **Photochemistry and flow: a perfect match**

- **Beer-Lambert law:** light transmittance decreases exponentially with the distance from the light source

$$A = -\log T = -\log\left(\frac{I}{I_0}\right) = \epsilon.l.c$$



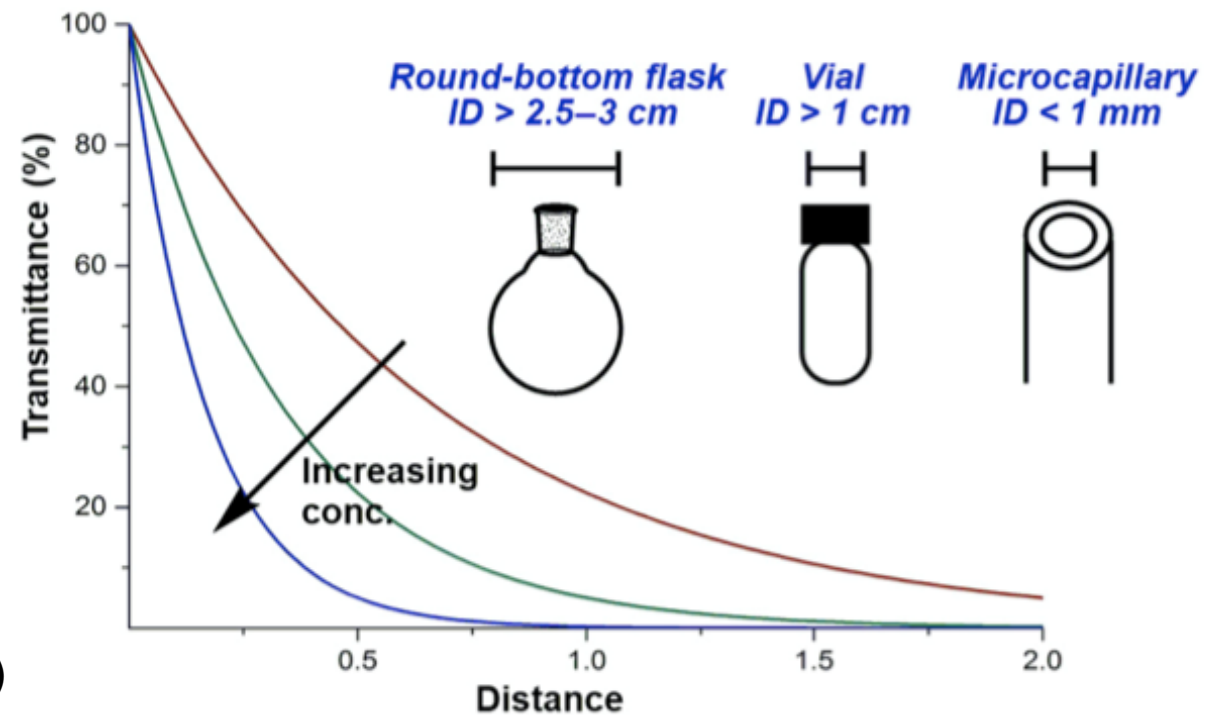
A: Absorbance

T: Transmittance

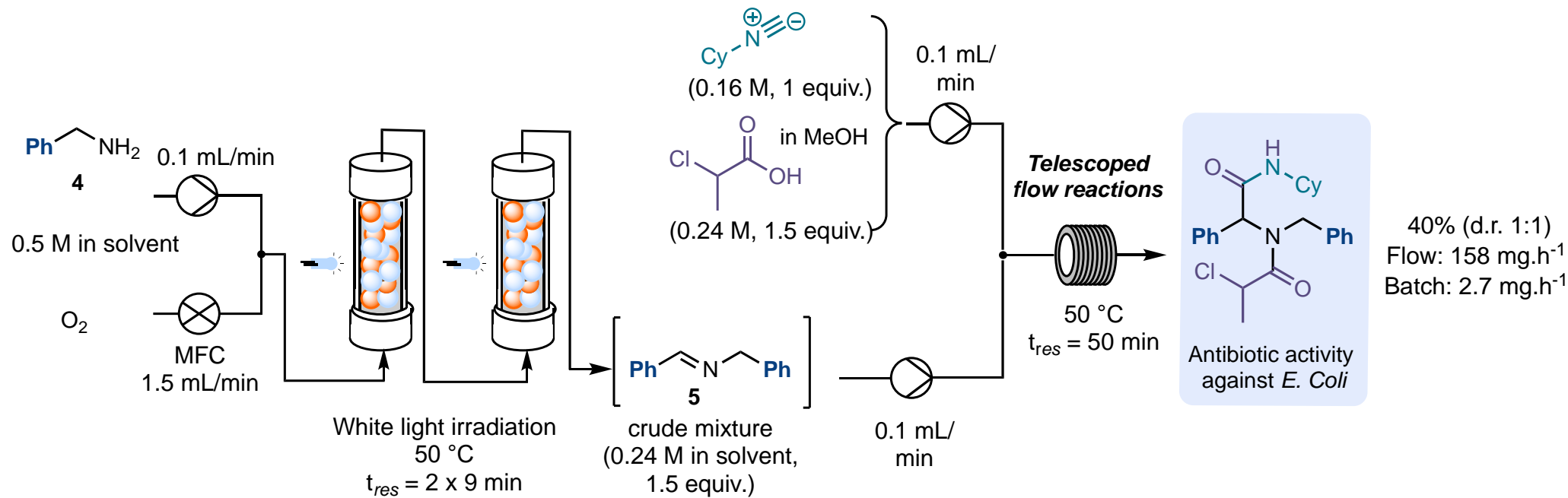
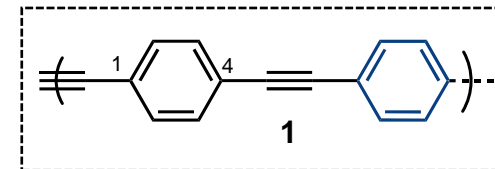
ϵ : molar extinction coefficient ($\text{L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$)

l: length of cuve (cm)

C: sample concentration ($\text{mol}\cdot\text{L}^{-1}$)



Heterogenous photocatalysis and telescoped synthesis



Global warming: the central role of chemistry

Chemistry is everywhere: pharma, materials, oils, gasoline ...

« **Green chemistry** »: 12 principles

1 Prevent waste

2 Atom economy

3 Safer synthesis

4 Design benign chemicals

5 Benign solvents & auxiliaries

6 Design for energy efficiency

7 Use of renewable feedstocks

8 Reduce derivatives

9 Catalysis (vs. Stoichiometric)

10 Design for degradation

11 Real-time analysis

12 Less hazardous chemistry

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