Maxime Dousset

Bibliographic seminar

May 17th 2016

1960s

Rachel Carson wrote , *Silent Spring.* It outlined the devastation that certain chemicals had on local ecosystems. The book served as a wake-up call for the public and scientists alike.

1969s

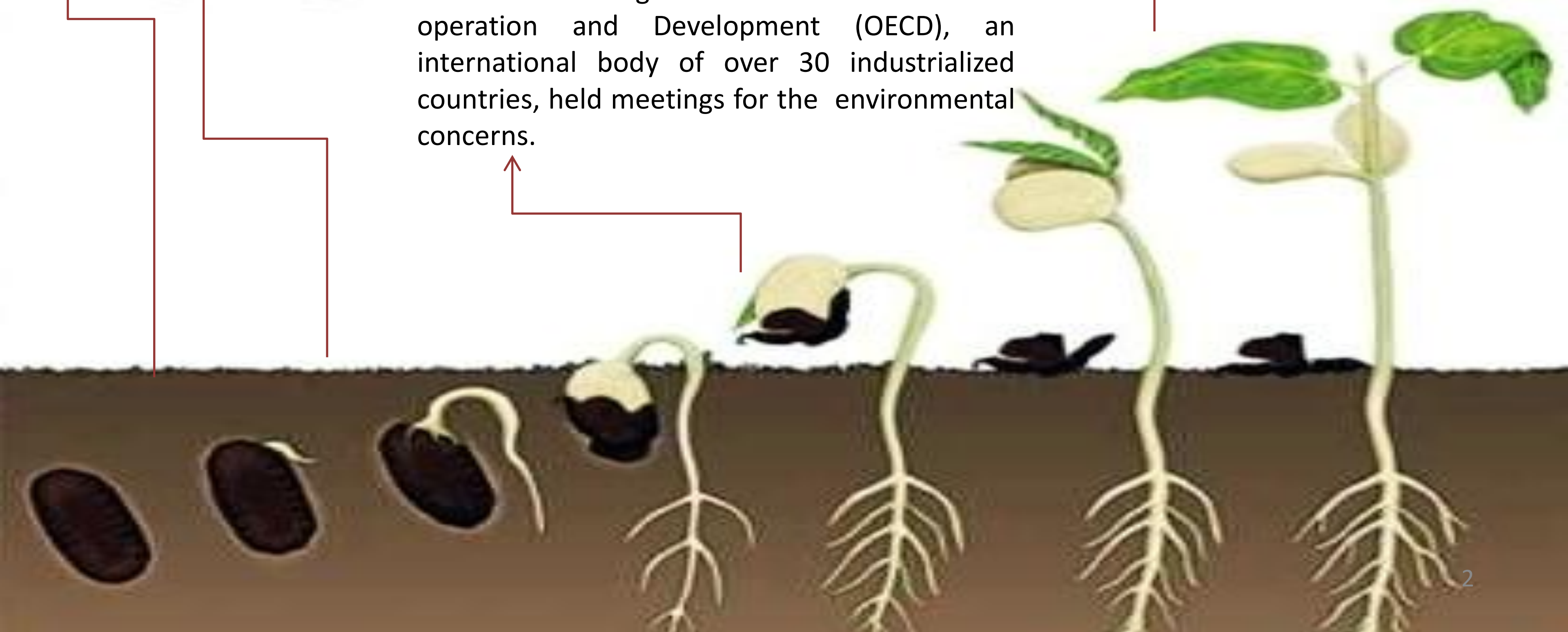
Congress passed the National Environmental Policy Act (NEPA). The law's goal was to "create and maintain conditions under which man and nature can exist in productive harmony“

1980s

Creation of Organization for Economic Co-operation and Development (OECD), an international body of over 30 industrialized countries, held meetings for the environmental concerns.

1998s

Paul Anastas and John Warner wrote the ground breaking book, *Green Chemistry Theory and Practice* with the 12 Principles of Green Chemistry



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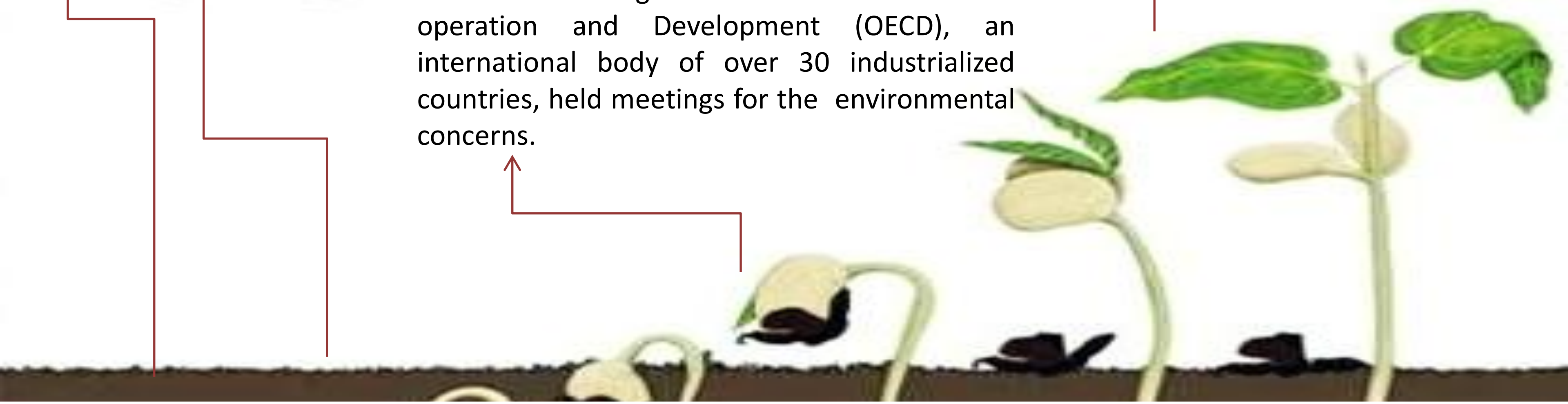
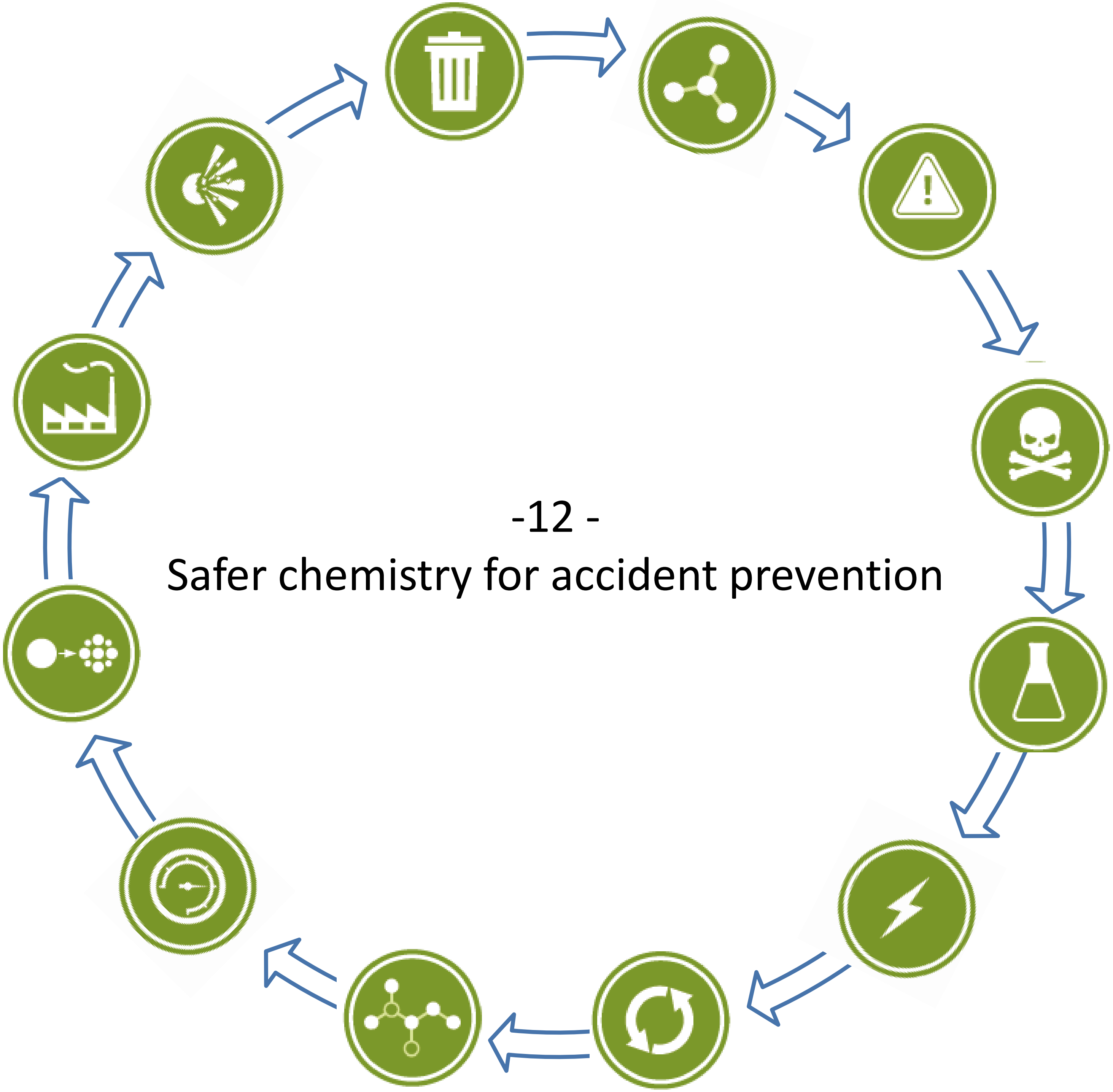


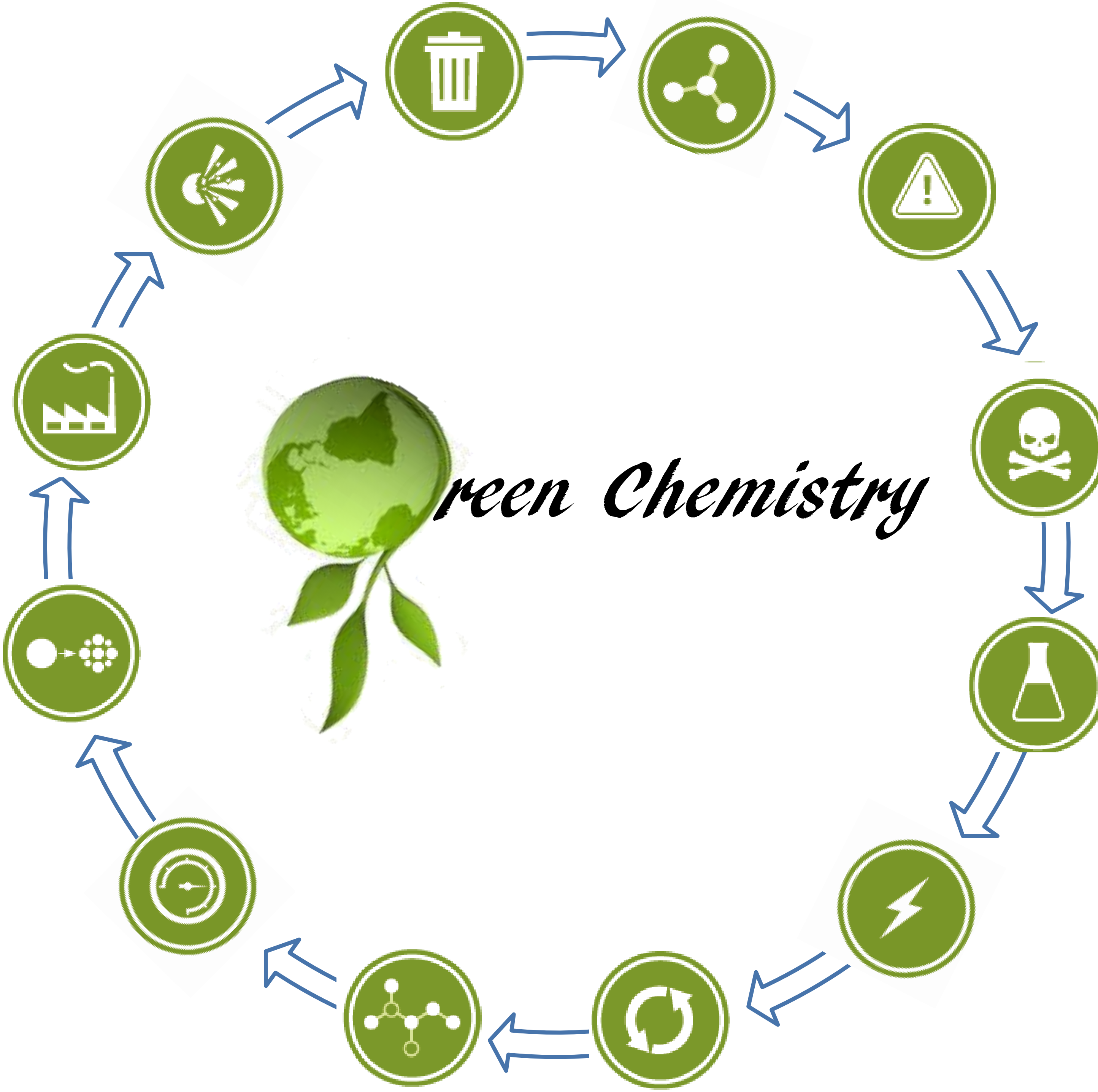
Today and the future

Today, more than 98% of all organic chemicals are still derived from petroleum. Much remains to be done …



-12 -

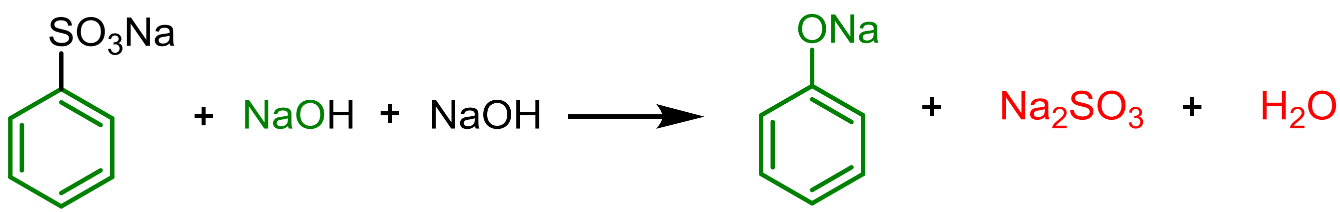
Safer chemistry for accident prevention


reen Chemistry

2 - Atom Economic

❖ Trost proposed this concept in 1991

Atomic Utilisation (AU) = MW final product / ∑ MW starting materials



MW	180	40	40	116	126	18

AU = 116 / (180 + 40 + 40) = 0.44 atoms constitued the final product
0.56 lost atoms

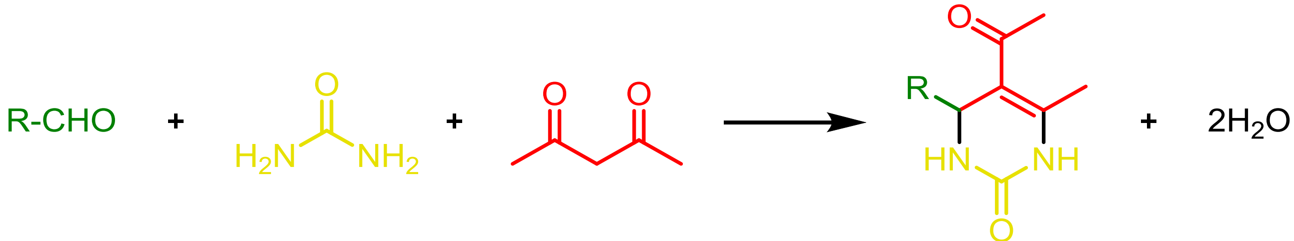
B. M. Trost, *Science*, **1991**, *254*, 1471

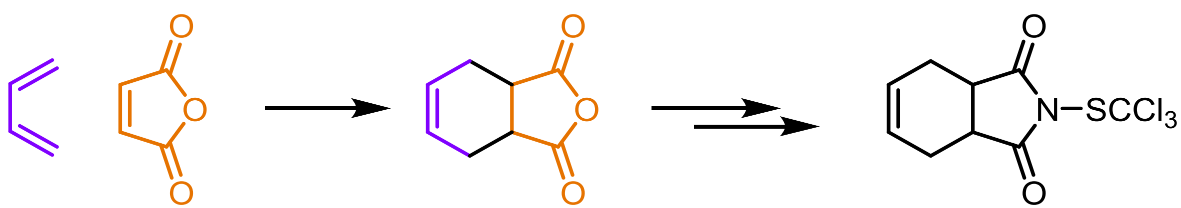
2 - Atom Economic

❖ Trost proposed this concept in 1991

Atomic Utilisation (AU) = MW final product / ∑ MW starting materials

✓ Ugi
✓ Biginelli
✓ Diels-Alder
✓ Morita-Baylis-Hillman
✓ Rearrangement : Claisen , Cope…





Captan (Antifungal)

B. M. Trost, *Science*, **1991**, *254*, 1471

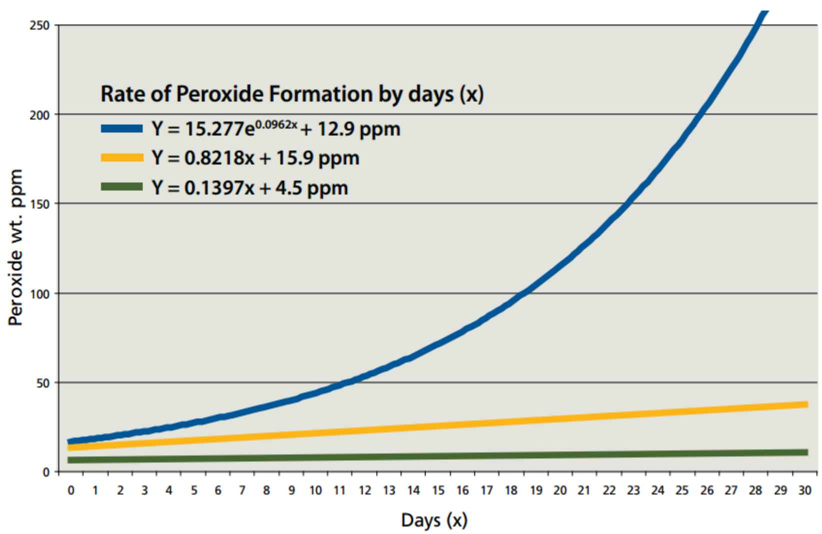
3 - Less Hazardous Chemical Synthesis

❖ Your solvents could be substituted

DCM, THF: 2-MeTHF renewable resources such as corn cobs and bagasse

MTBE, THF, 1-4 Dioxane: Cyclopentyl methyl ether (CPME) no peroxyde formation

Peroxide Formation of Ether Solvent



THF 19 days to reach 100 ppm

THF Stabilized 102 days to reach 100 ppm

CPME Stabilized 683 days to reach 100 ppm

Conditions

- 20 mL of each sample in a brown bottle (capacity of 65 mL)
- Stored at room temperature, in a dark place and in the presence of air

CPME is a product of Zeon Corporation with approval by Toxic Substances Control Act (TSCA) and European List of Notified Chemical Substances (ELINCS).

Price
1L ± 100 - 150 €

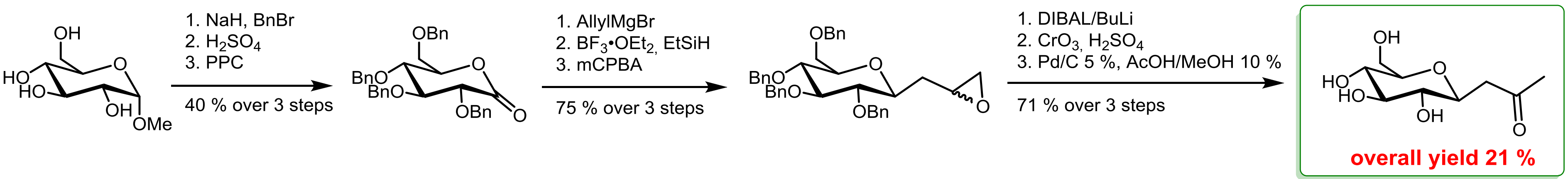
✓ Reaction with PEGs (polyethylen glycol) or Water

Source: Sigma-Aldrich

8 - Reduce derivatives

[...] the ability to synthesize ketone with the α -anomeric configuration [...] opens up the possibility of using this approach with R-glycosidases

J. Am. Chem. Soc. **1998**



2 years later

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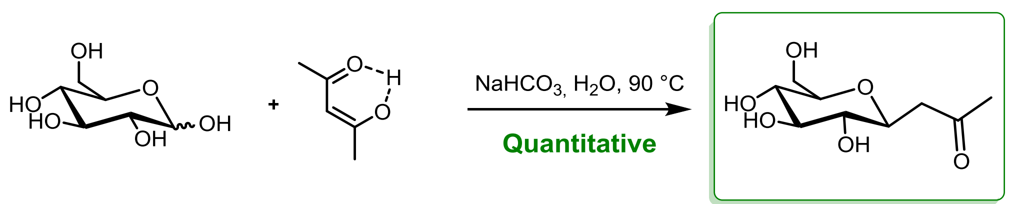


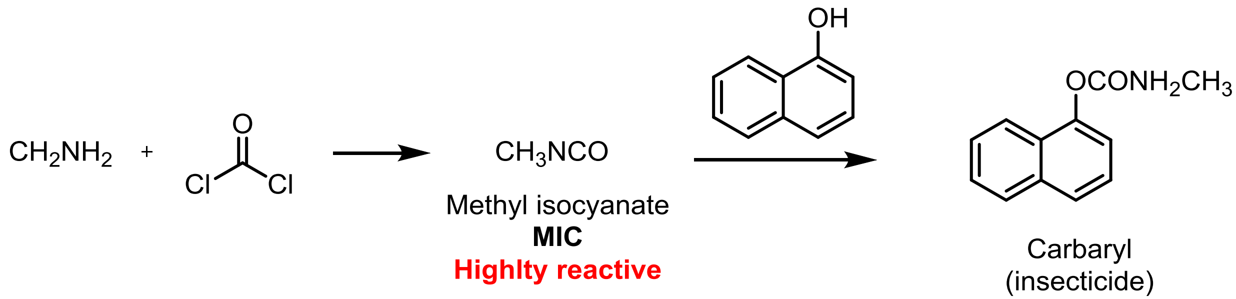
(a). S. Howard, S. G. Withers. *J. Am. Chem. Soc*. **1998**, *120*, 10326, (b) F. Rodrigues, Y. Canac, A. Lubineau. *Chem. Commun*, **2000**, 2049.

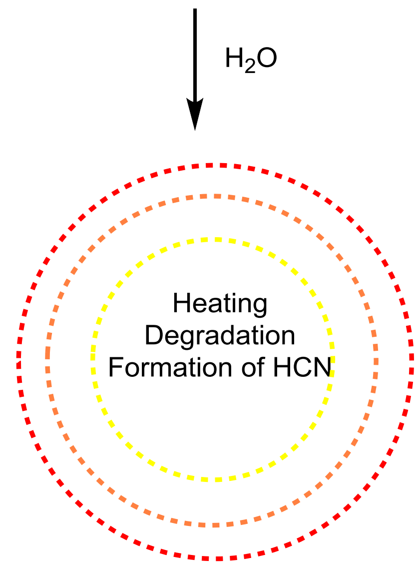
Choose and develop chemical procedures that are safer and inherently minimize the risk of accidents.
Know the possible risks and assess them beforehand

WHY ?

Bhopal Catastrophe 3^{th} December 1984

12 - Safer Chemistry for Accident Prenvention



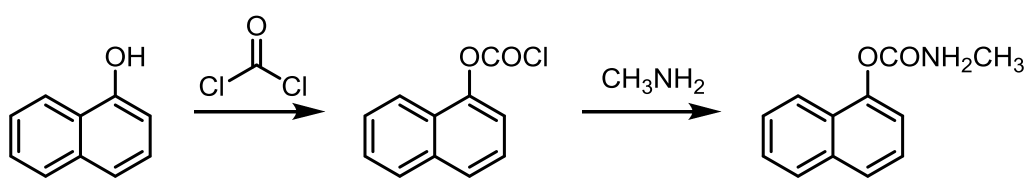


42 000 Kg of MIC

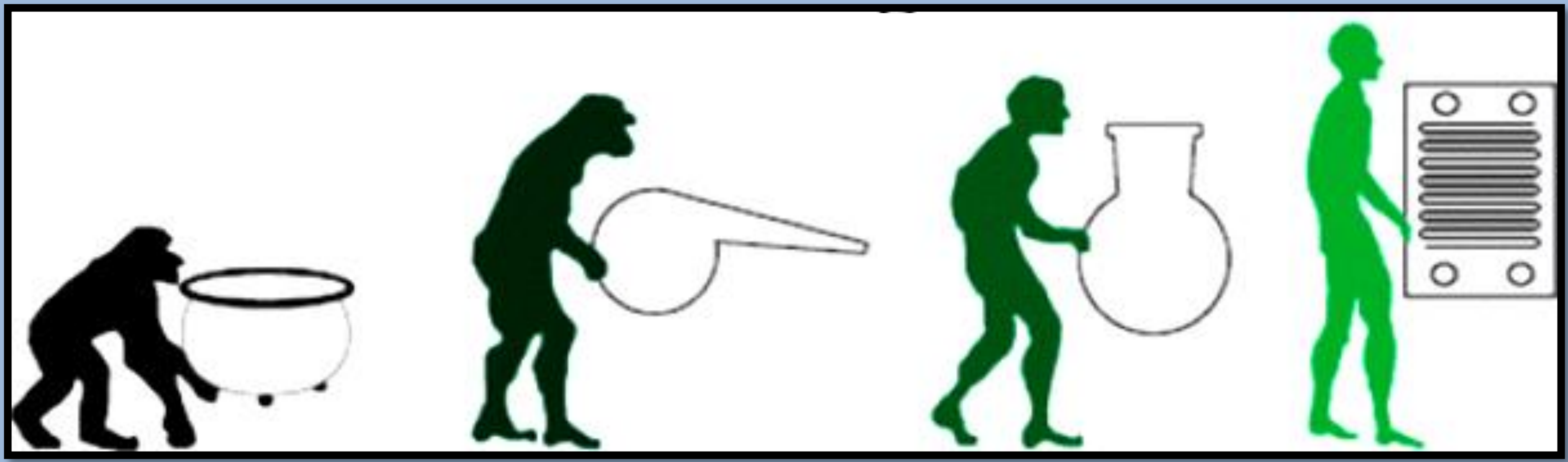
11 000 people dead

500 000 people infected

Alternative ?



The Flow Chemistry



Definition

Materials

Workup – Purification
Analysis – Reactors

FLOW CHEMISTRY

Micro reactor

VS

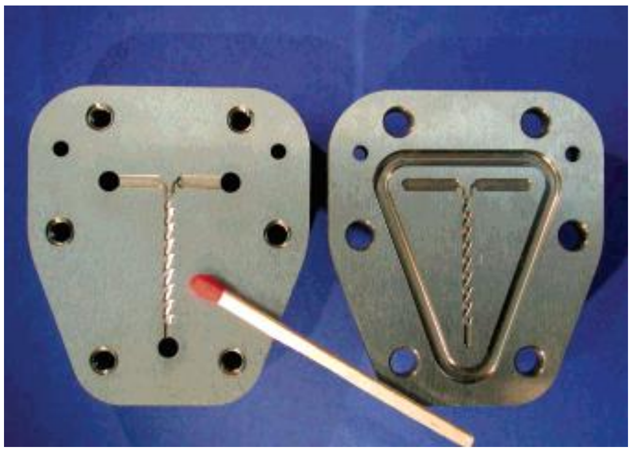
Batch reactor

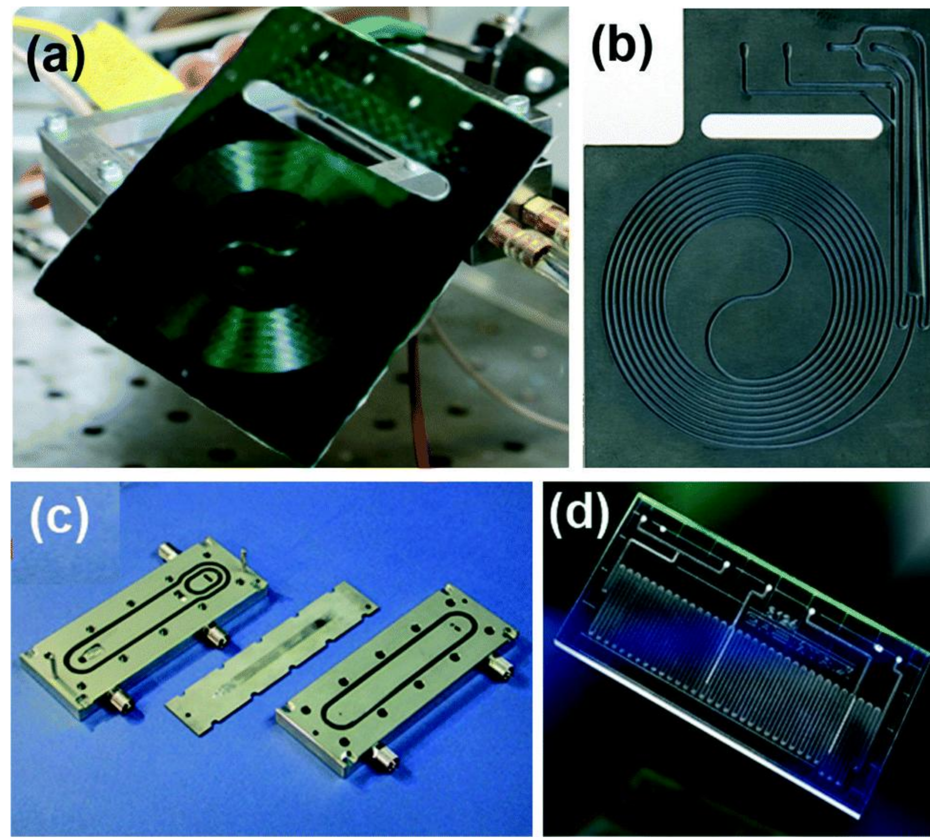
Bilan

Outlook

Definition of a Micro reactor

A microreactor is a reactor with characteristic dimensions in the range of micrometers and reactions volumes from nanoliters to microliters.



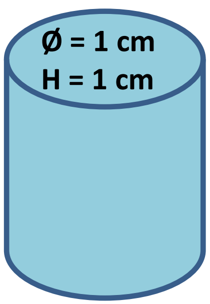


(a) A. R. Bogdan, D. T. McQuade. *Chem. Rev.* **2007**, *107*, 2300 (b) K. F. Jensen, B. J. Reizman, *Lab. Chip*, **2014**, *14,* 3206

Definition of a Micro reactor

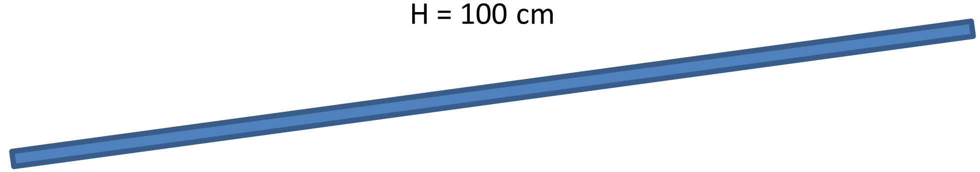
Advantages :

- ✓ Using solvent under pression beyond their boiling point
- ✓ In some cases the rate of reaction is better
- ✓ homogeneous heating and cooling faster
- ✓ Unstable intermediate easier to using
- ✓ Small volume is safer
- ✓ Automatisation
- ✓ …



$V = 0.78\ cm^3$
$S = 4.7\ cm^2$

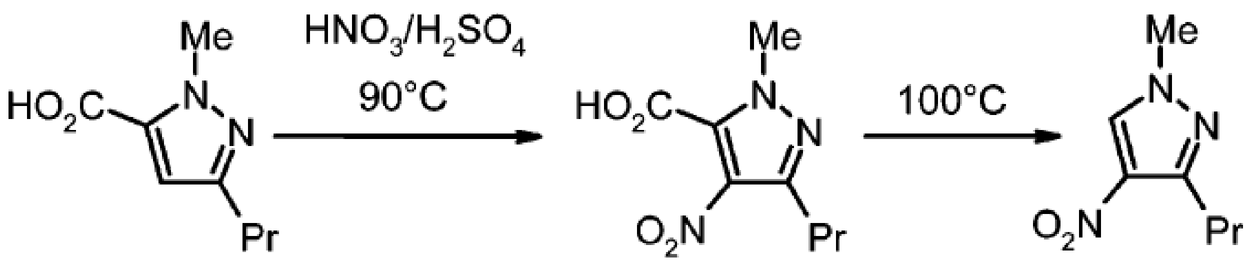
Ø = 0.1 cm
H = 100 cm



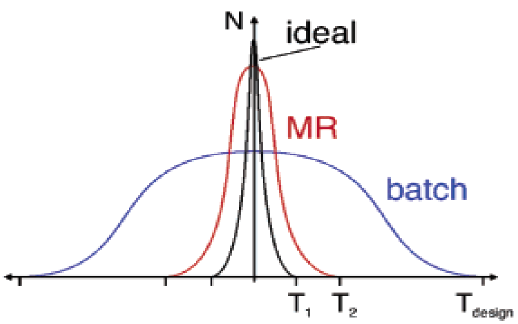
$V = 0.78\ cm^3$
$S = 31.4\ cm^2$

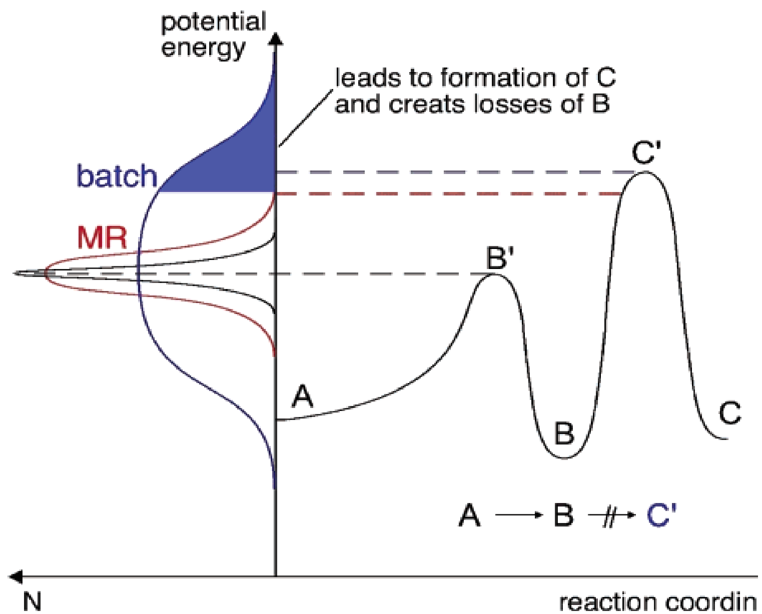
Definition of a Micro reactor

Exemple with homogeneous heating and cooling faster



A **B** **C**





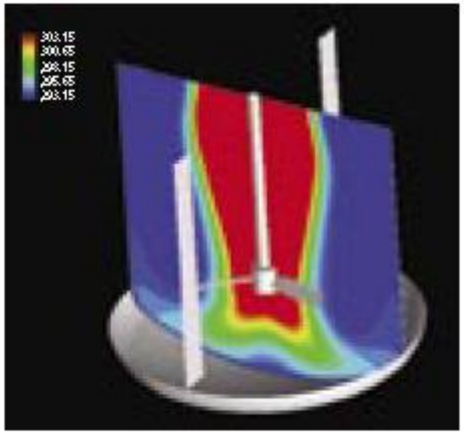
(a) A. R. Bogdan, D. T. McQuade. *Chem. Rev.* **2007**, *107*, 2300, (b) M. Hohmann, W. Stirner. *Org. Process. Res. Dev.* **2004**, *8*, 440

Definition of a Micro reactor

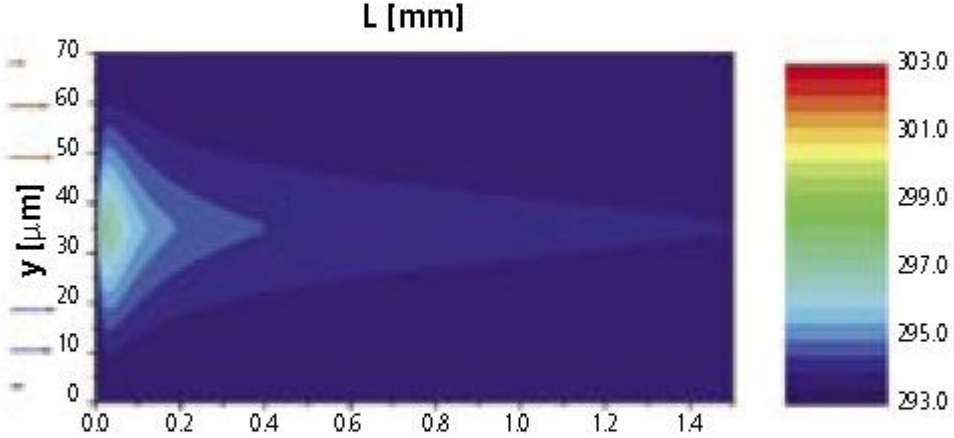
Exemple with homogeneous heating and cooling faster

Typical Flow Reactor	$= 200 cm^2 cm^{-3}$	10C=5 seconds
100ml Round Bottom Flask	$= 1 cm^2 cm^{-3}$	10C=2 minutes
$1 m^3$ Plant Vessel	$= 0.06 cm^2 cm^{-3}$	10C=1 hours

Batch



Flow



Source: Pfizer

Definition

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Workup – Purification
Analysis – Reactors

FLOW
CHEMISTRY

Micro reactor

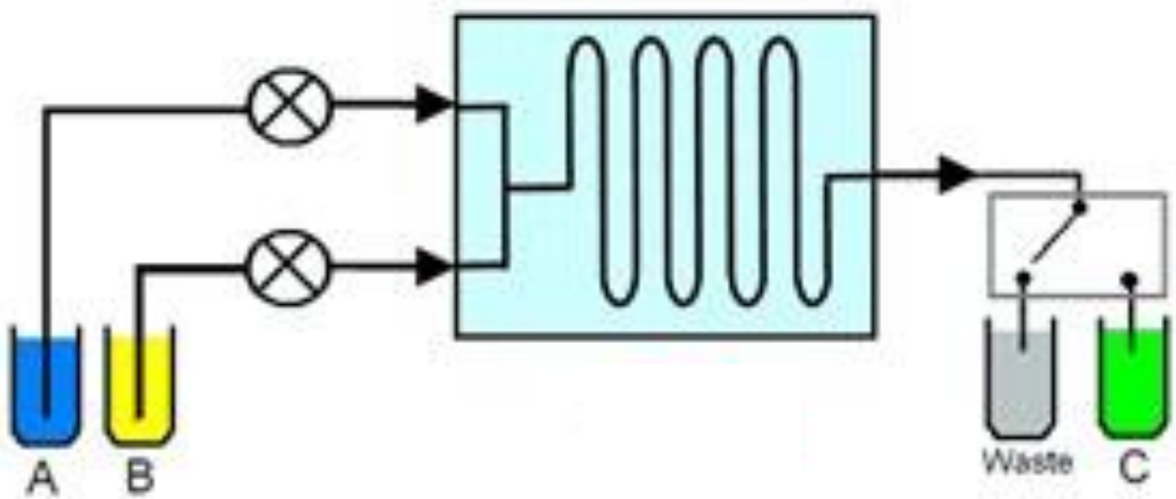
VS

Batch reactor

Bilan

Outlook

•Materials

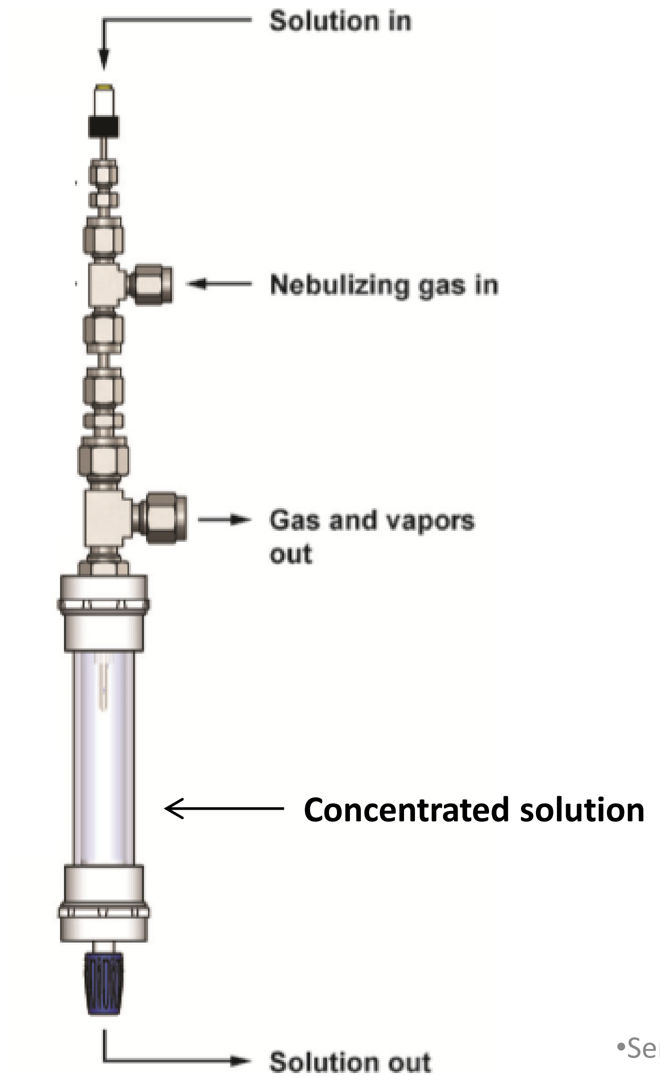


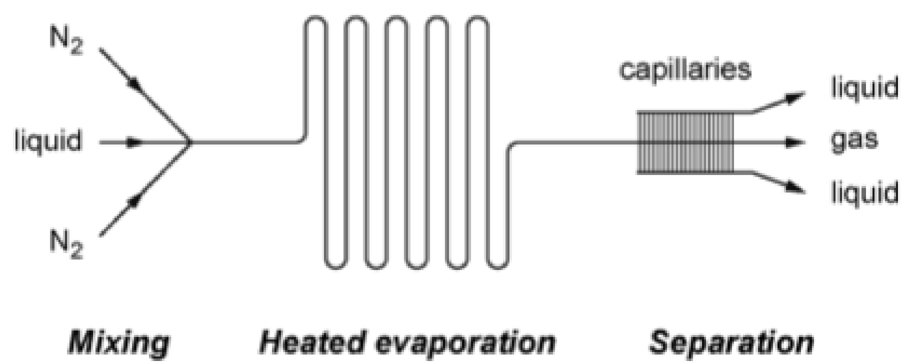
- ✓ Pumps
- ✓ Microreactor
- ✓ Heater or cooler system
- ✓ Collector

Mixer
Extractor
Distillation
Concentrator
Chromatography
Photo or MW reactor
....

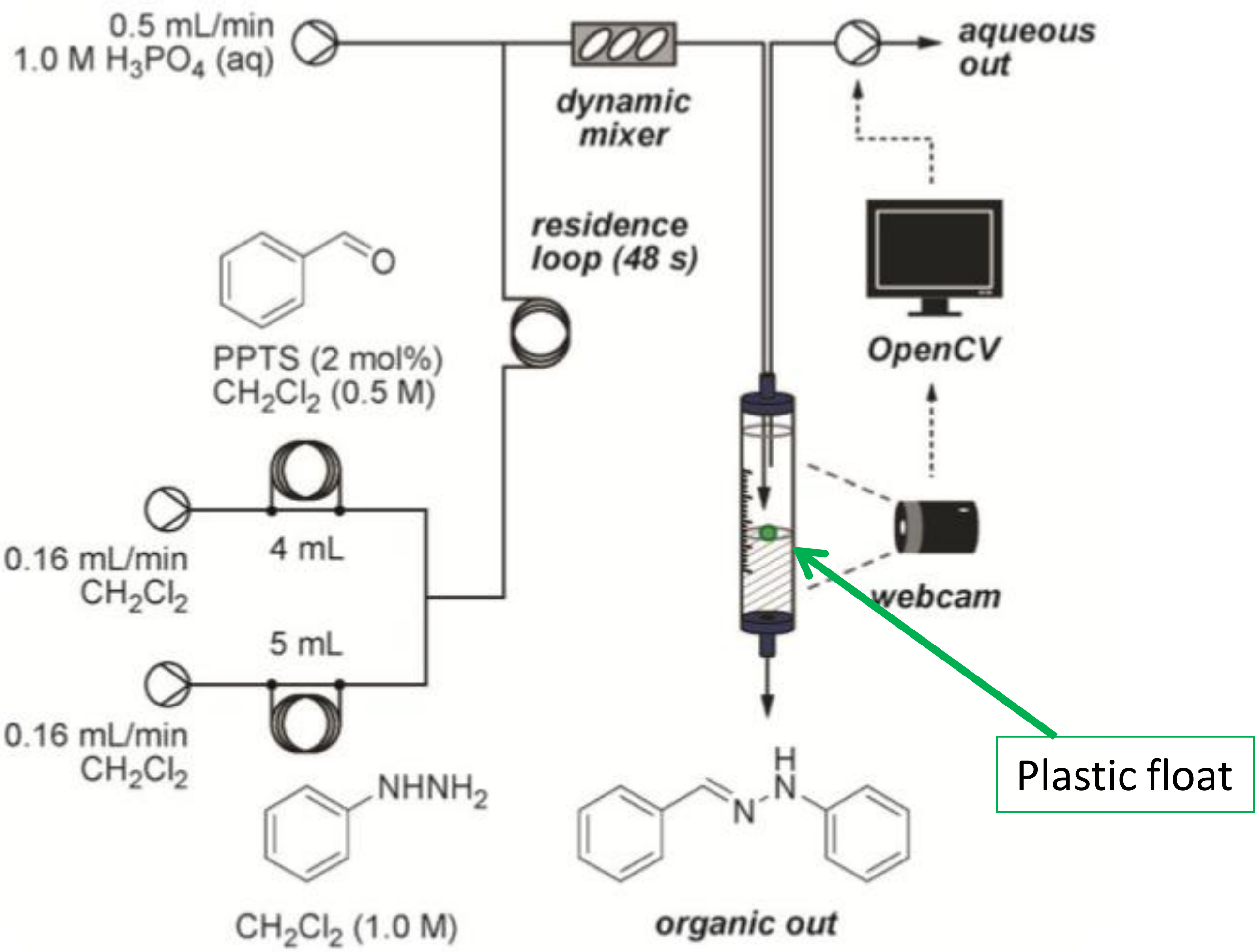
D. E. Fitzpatrick, S. V. Ley, *Angew. Chem. Int. Ed.* **2015**, *54*, 3449

Concentration



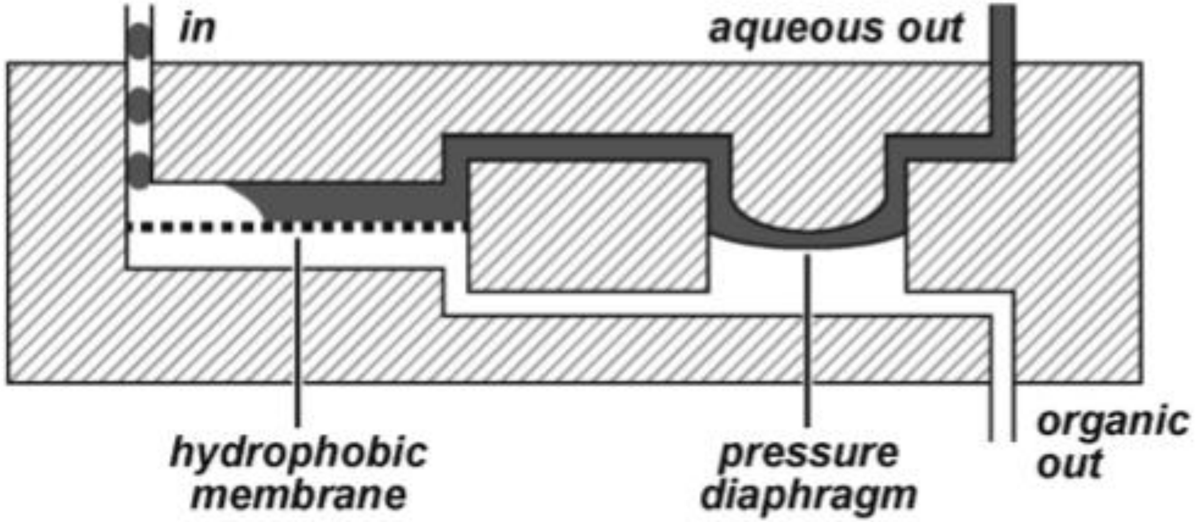


Liquid-Liquid separation

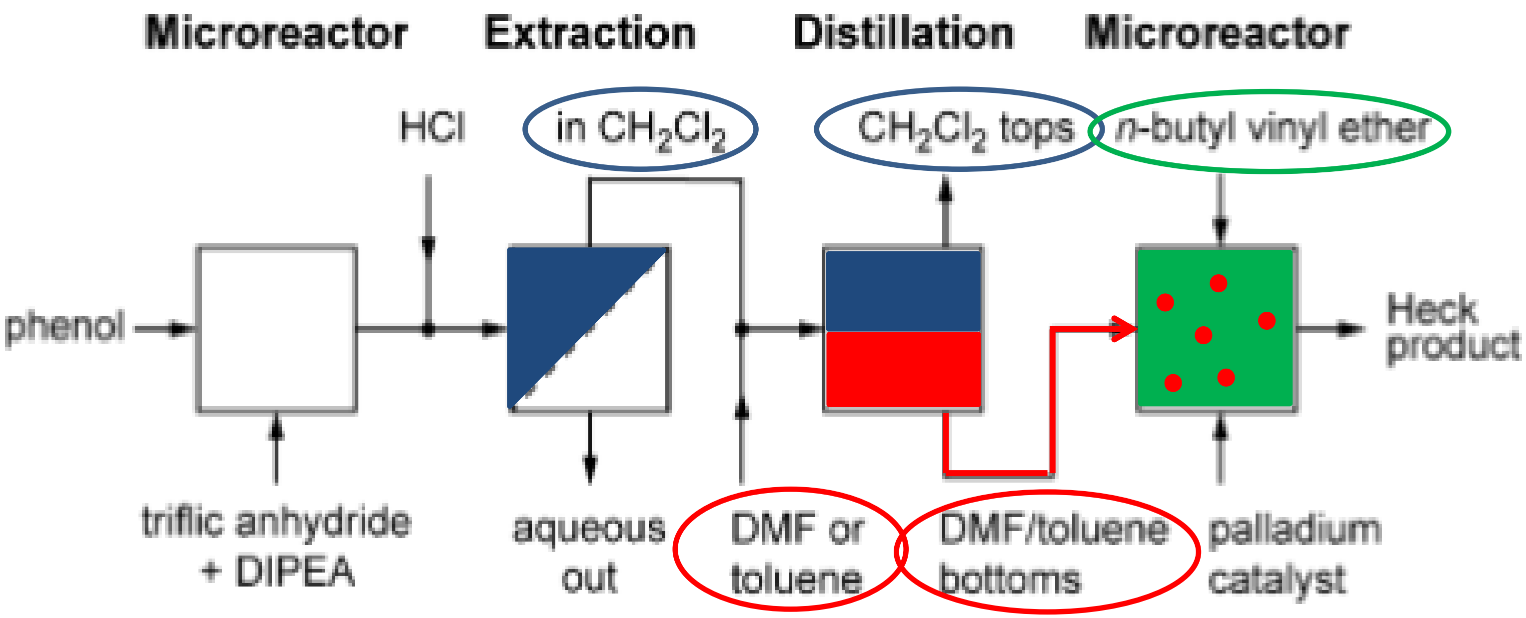


Liquid-Liquid separation

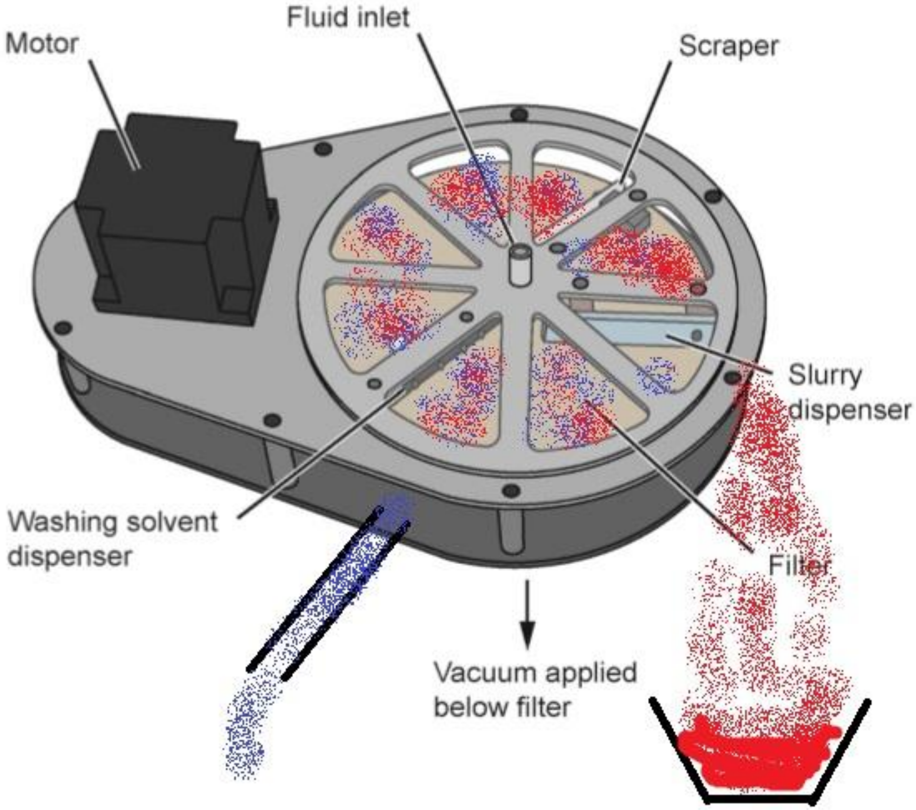
Biphasic solution

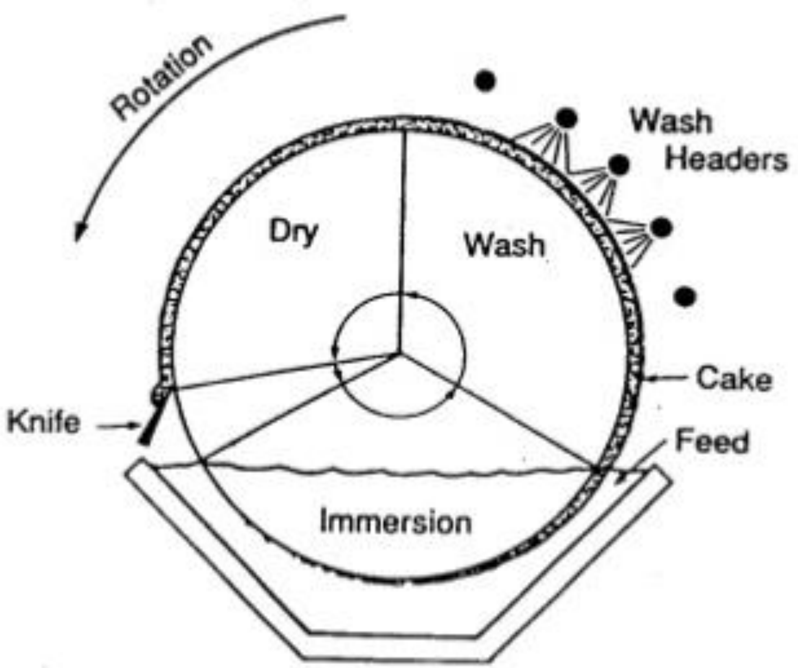


Solvent Switching

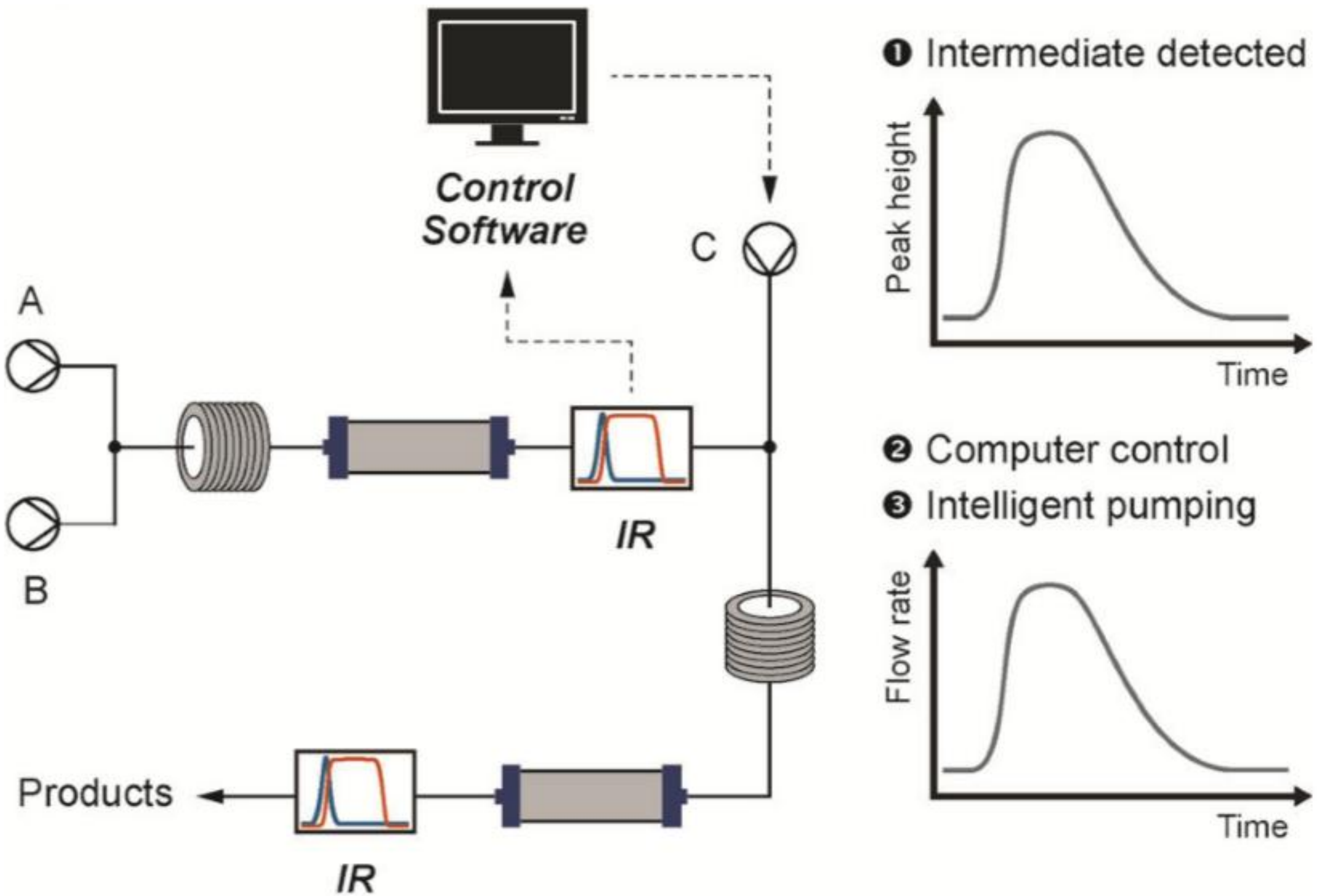


Filtration: Rotating sintered glass disk



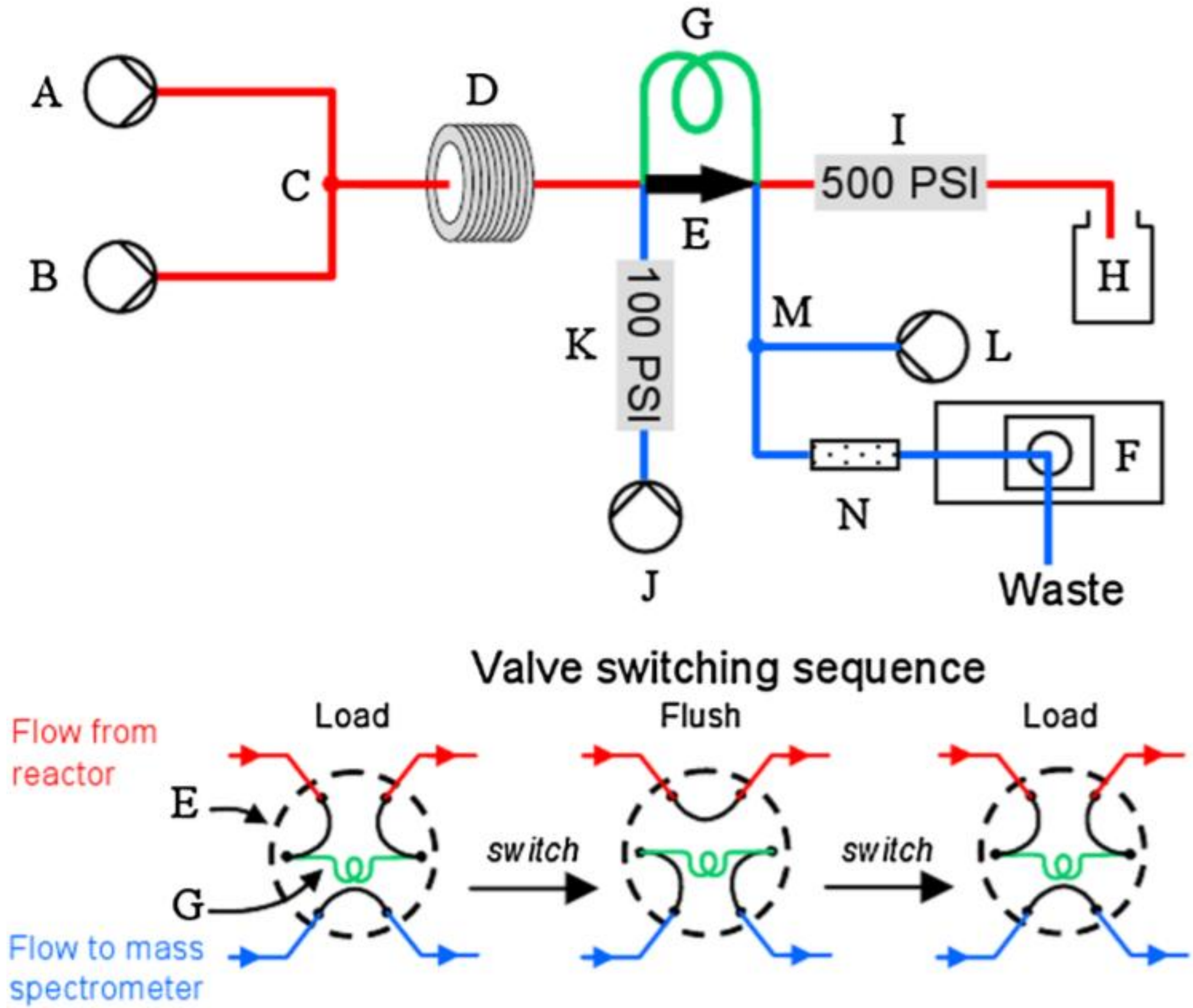


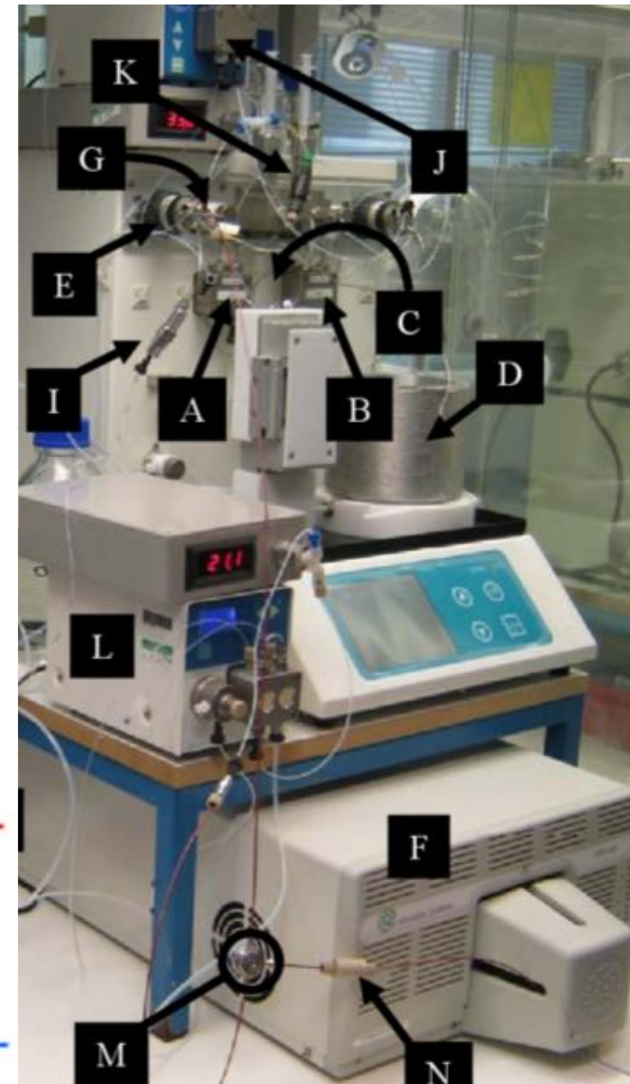
Infrared Spectroscopy



•Materials / Analysis

Mass Spectrometry

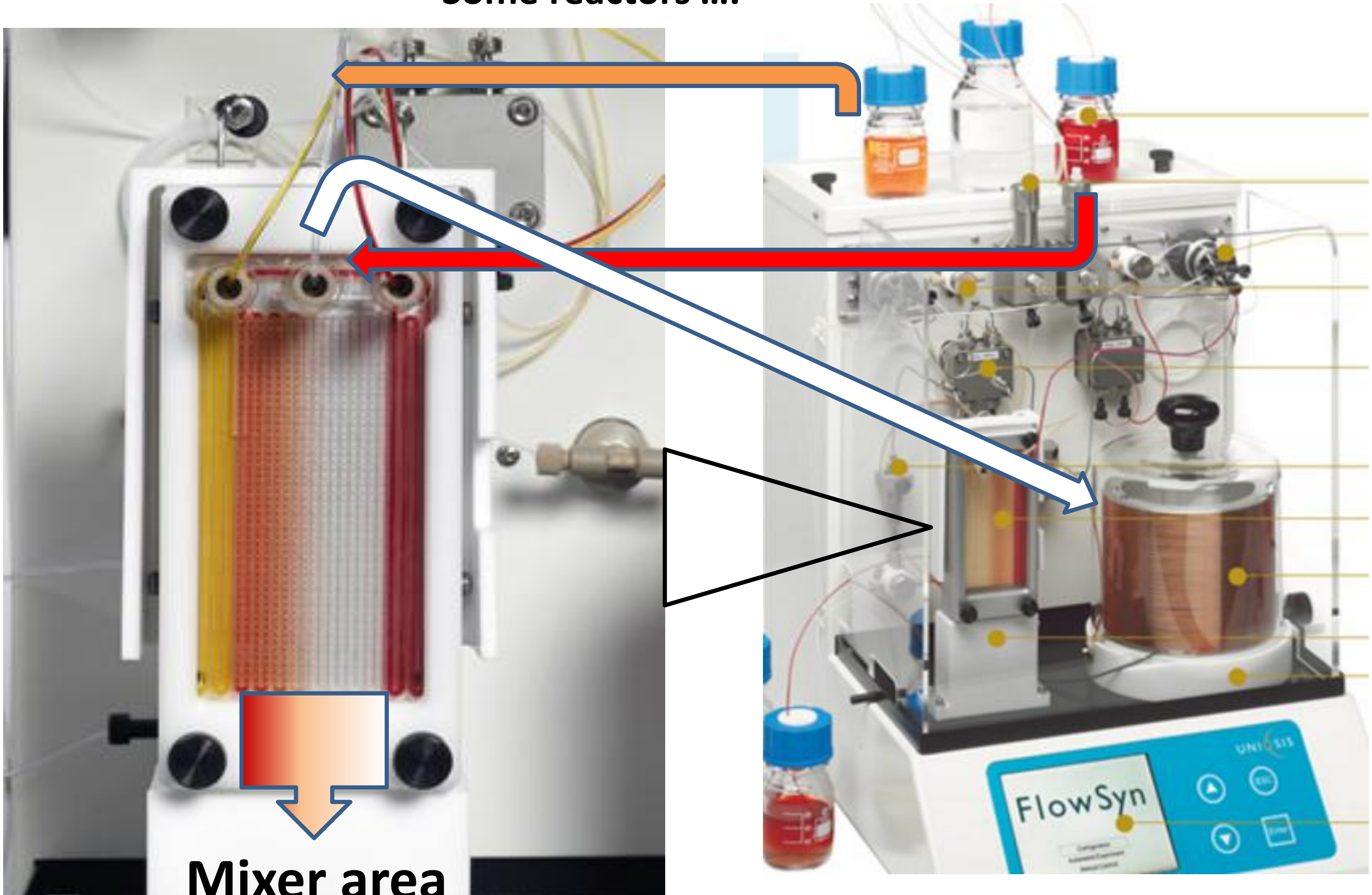




R. M. Turner, S. V. Ley, *Rapid. Commun. Mass. Spectrom*. **2012**, *26*, 1999.

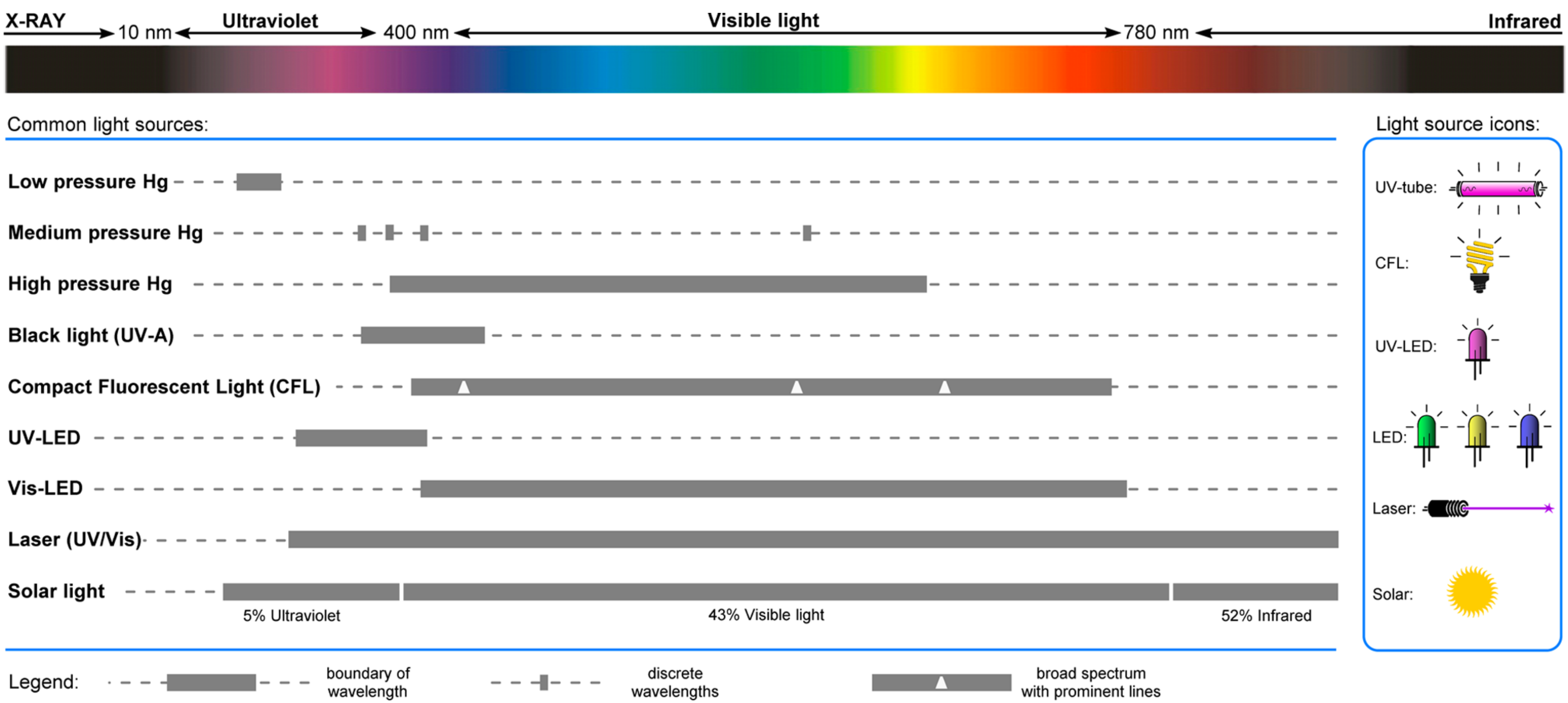
•Materials / Reactors

Some reactors ….



D. Roberge,C. O. Kappe. *Angew. Chem. Int. Ed.* **2010**, *49*, 7101

Photo-reactors



V. Hessel, T. Noel, *Chem. Rev.*, **DOI:** 10.1021/acs.chemrev.5b00707

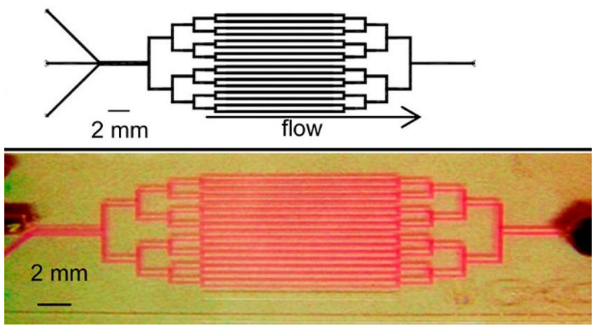
•Materials / Reactors

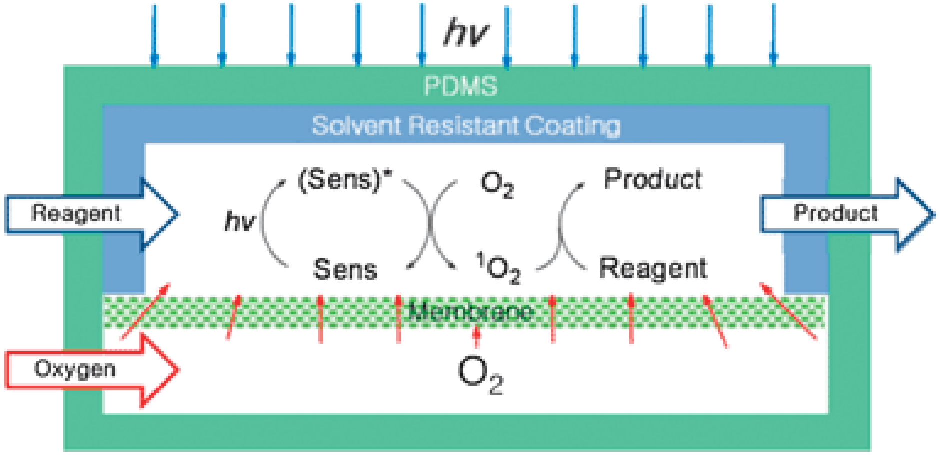
Photo-reactors

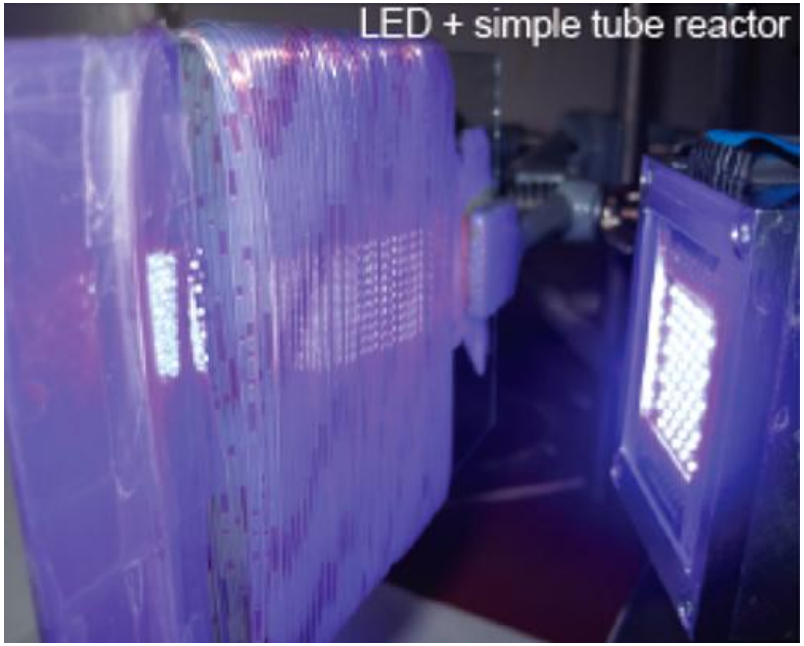
V. Hessel, T. Noel, *Chem. Rev.*, **DOI:** 10.1021/acs.chemrev.5b00707

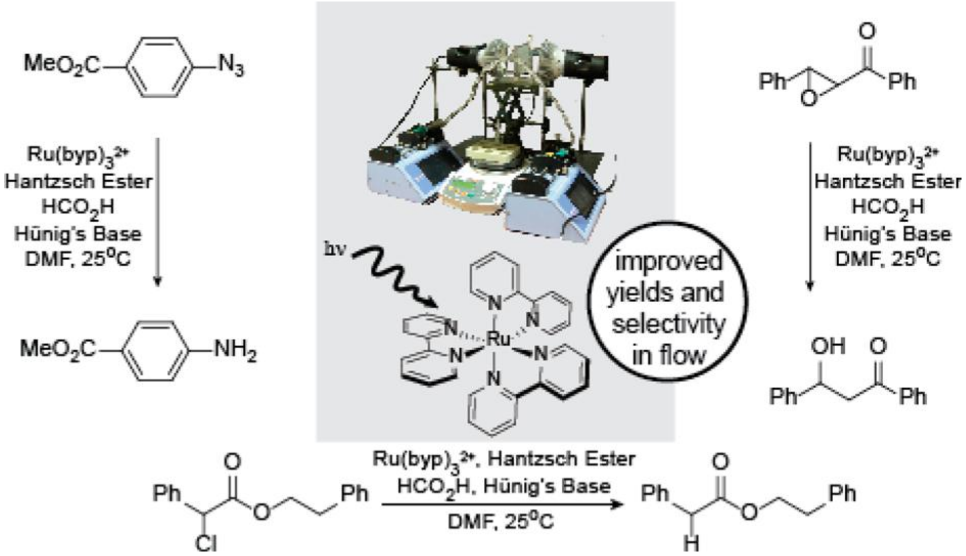
•Materials / Reactors

Photo-reactors



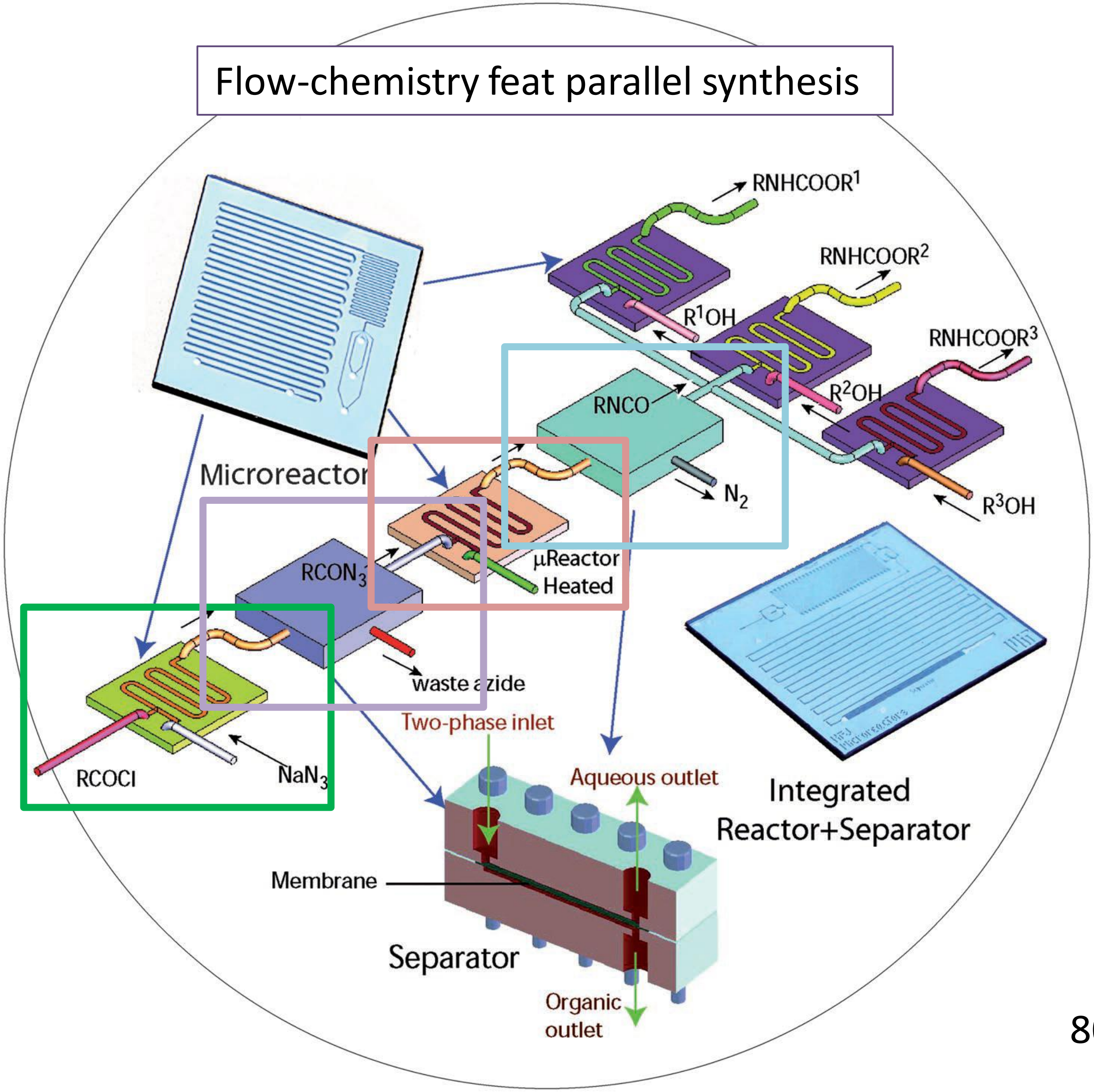


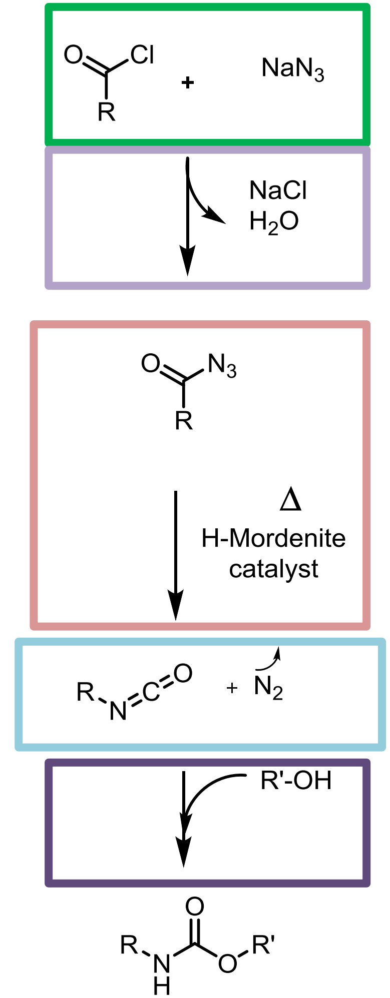




D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384

•Materials / Reactors





80-120 mg by day

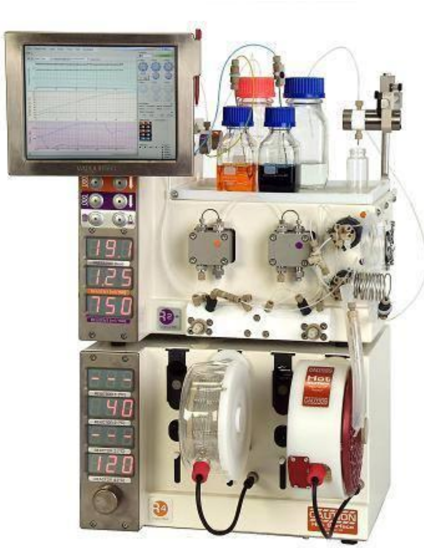
J. G. Kralj, K. F. Jensen, *Angew. Chem. Int. Ed.* **2007**, *46*, 5704

•Materials

Few prices ….

Full AFRICA System (Syrris)
100 to 350 k€

Microreactor Kit 19979
Sigma-Aldrich : 17 k€



Vapourtec
50 k€

FlowSyn System
57 k€

Definition

Materials

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FLOW
CHEMISTRY

Micro reactor
VS
Batch reactor

Bilan

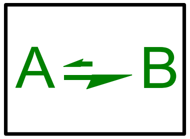
Outlook

•Micro reactor VS Batch reactor

The large contact area and small size of reactor pipe improved the mixer between reactants and in some cases increases

- the yield

- the selectivity

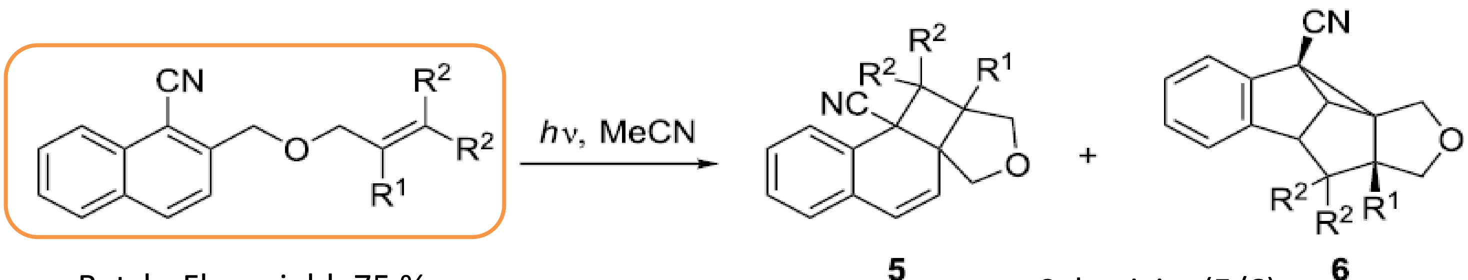


- reaction time

- safety

Micro reactor VS Batch reactor

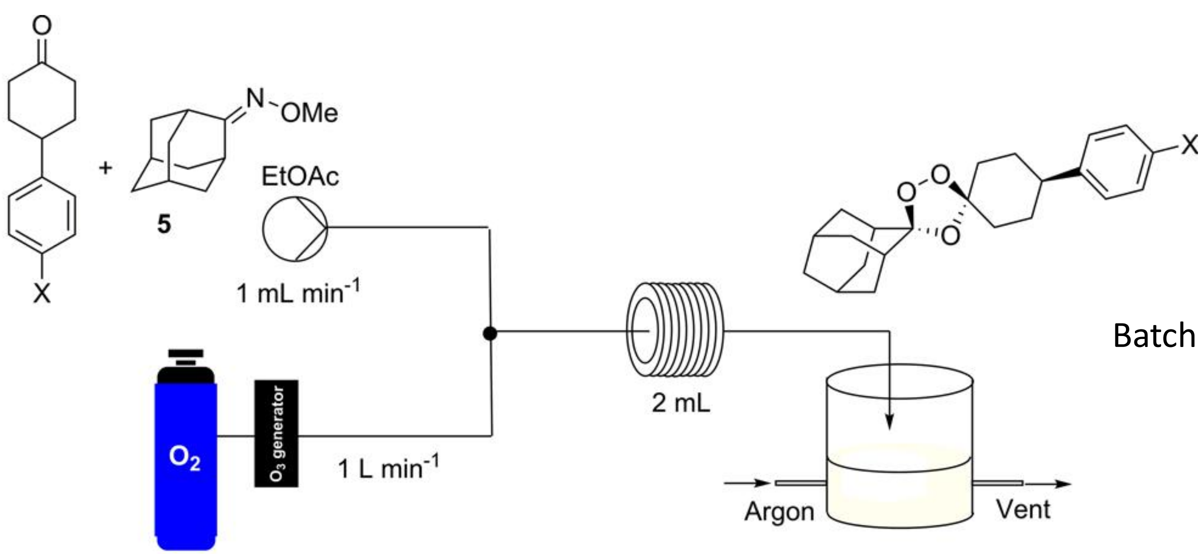
•Photocyclisation [2+2]



Batch -Flow yield: 75 %
Production: 0.01 mmol/h

Selectivity (**5**/**6**)
Batch : 55 / 45
Flow : 96 / 4

•Griesbaum Co-ozonolysis: New antimalaria candidate

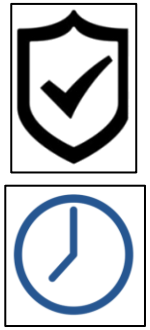


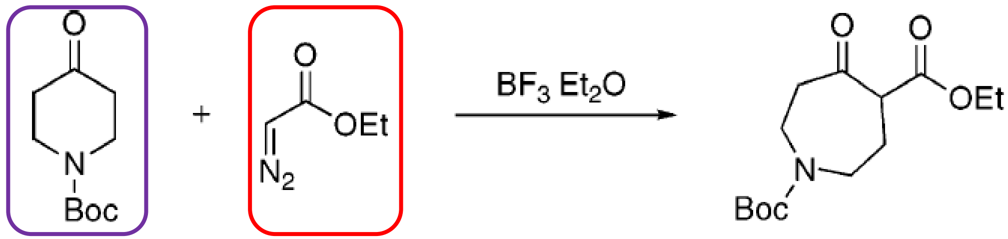
Batch -Flow yield: 70 %
1.9g / h

(a) J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn , *Beilstein J. Org. Chem*. **2012**, *8*, 2025, (b) M. B. Berry, S. V. Ley, *Org. Lett.* **2015**, *17*, 3218

Micro reactor VS Batch reactor

•Tiffeneau-Demjanow reaction

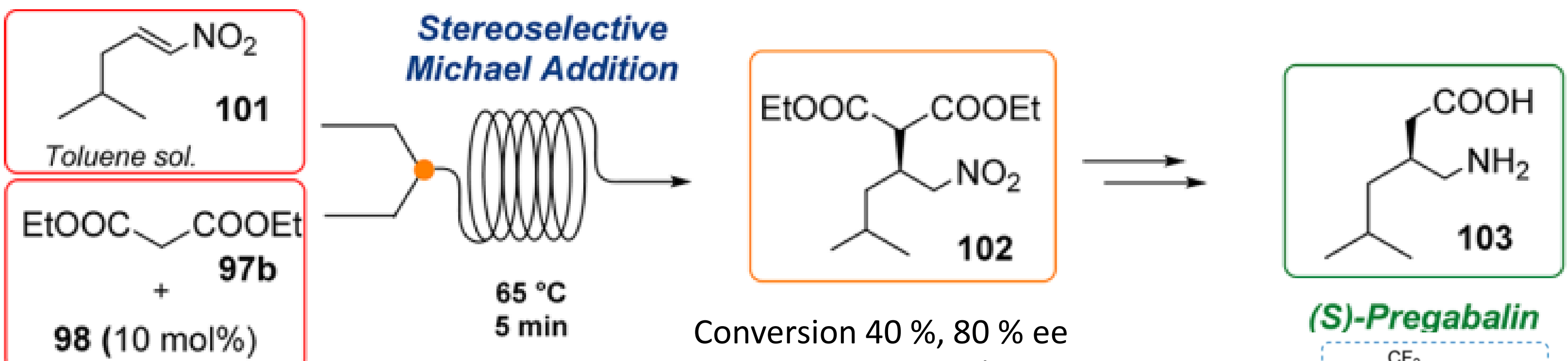




Batch -Flow yield: 90 %
Batch: at -25°C in 30 min
Flow : at 10 °C in 2 min

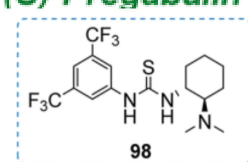
Production: 91 g/h

•Homogeneous stereoselective Organocatalysis: Michael Addition



Conversion 40 %, 80 % ee
Production: 1 g/ h

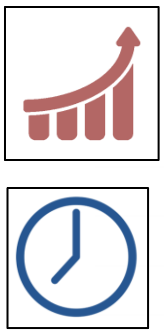
(S)-Pregabalin

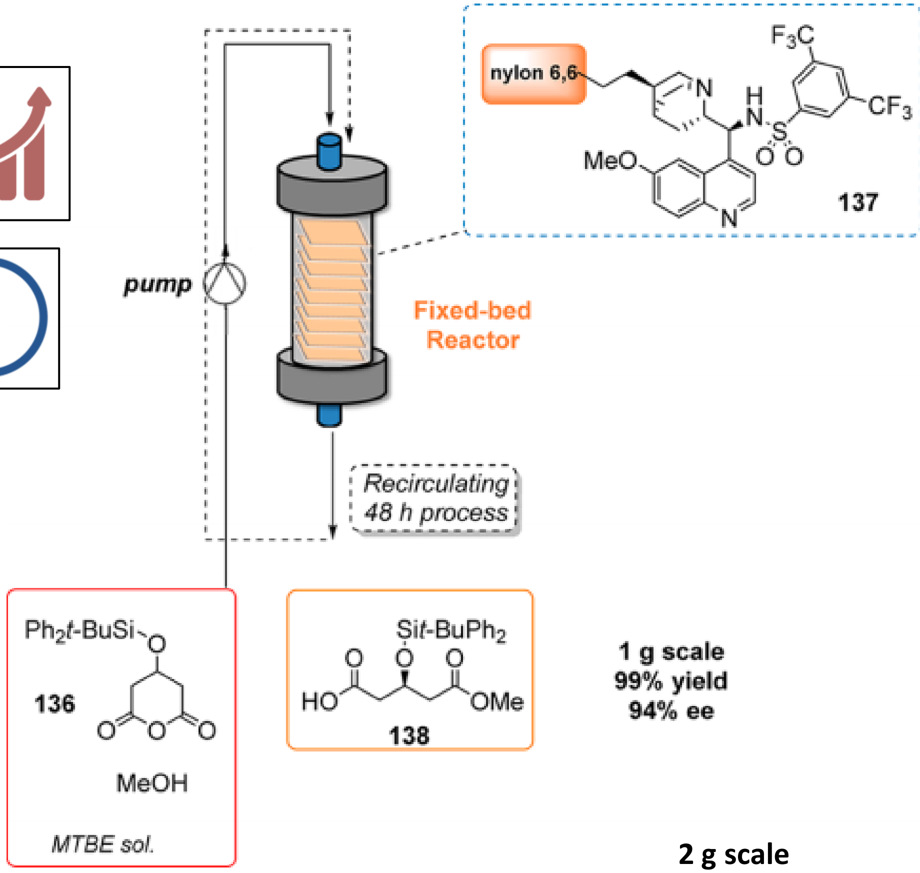


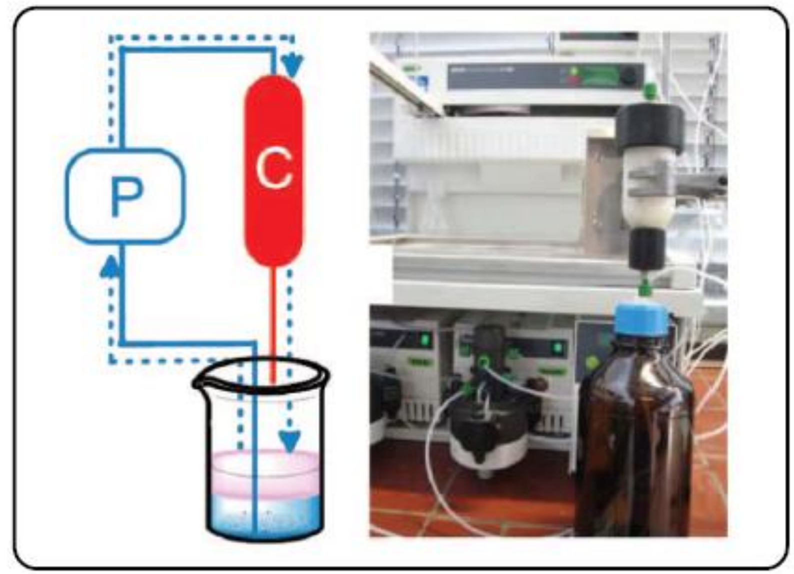
(a) X. Zhang, S. Stefanick, F. J. Villani, *Organic Process Research & Development,* **2004**, *8*, 455, (b) S. Rossi, A. Puglisi, *Symmetry,* **2015**, *7*, 1395.

Micro reactor VS Batch reactor

•Heterogeneous anhydride desymmetrization



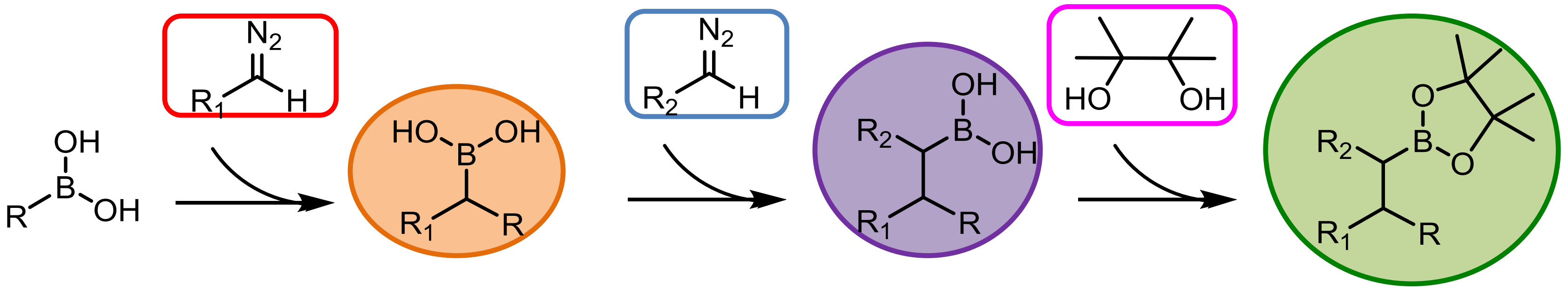


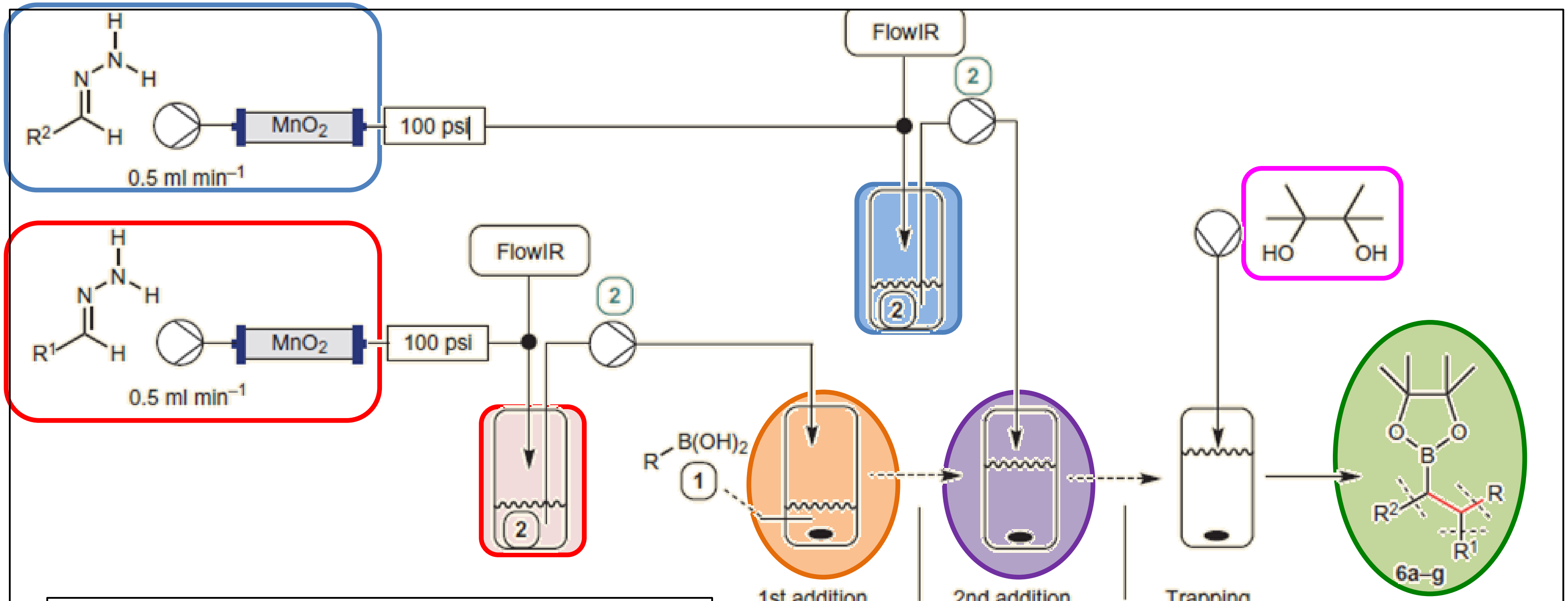


2 g scale
Batch : conv. 25 %, 71 % ee
Flow : conv. 73 %, 87 % ee

(a) M. Benaglia, F. Coccia, F. Cozzi, A. Puglisi, *Adv. Synth. Catal.* **2015**, *357*, 377. (b) C. E. Song, J. S. Gutmann, B. List, *Science,* **2013**, *341*, 1225

Micro reactor VS Batch reactor



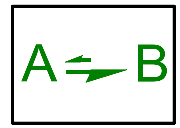


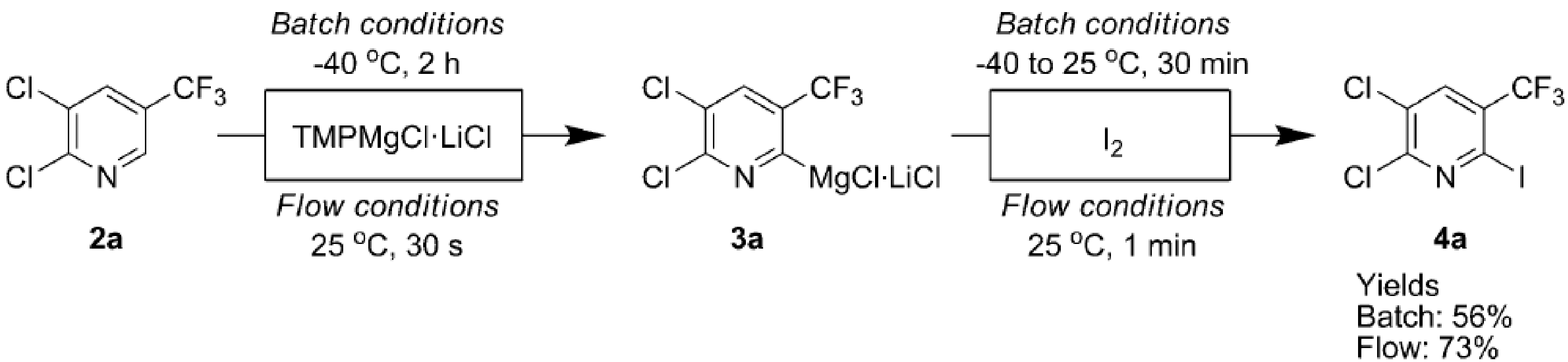
mg scale
Substrats with three differents R group
40 - 90 %

(a) D. C. Blakemore, S. V. Ley, *Nature Chemistry*, **2016**, *8*, 360. (b) J. M. Hawkinsb, S. V. Ley, *Chem. Sci*, **2015**, *6*, 1120

Micro reactor VS Batch reactor

- Heterocycles functionalization





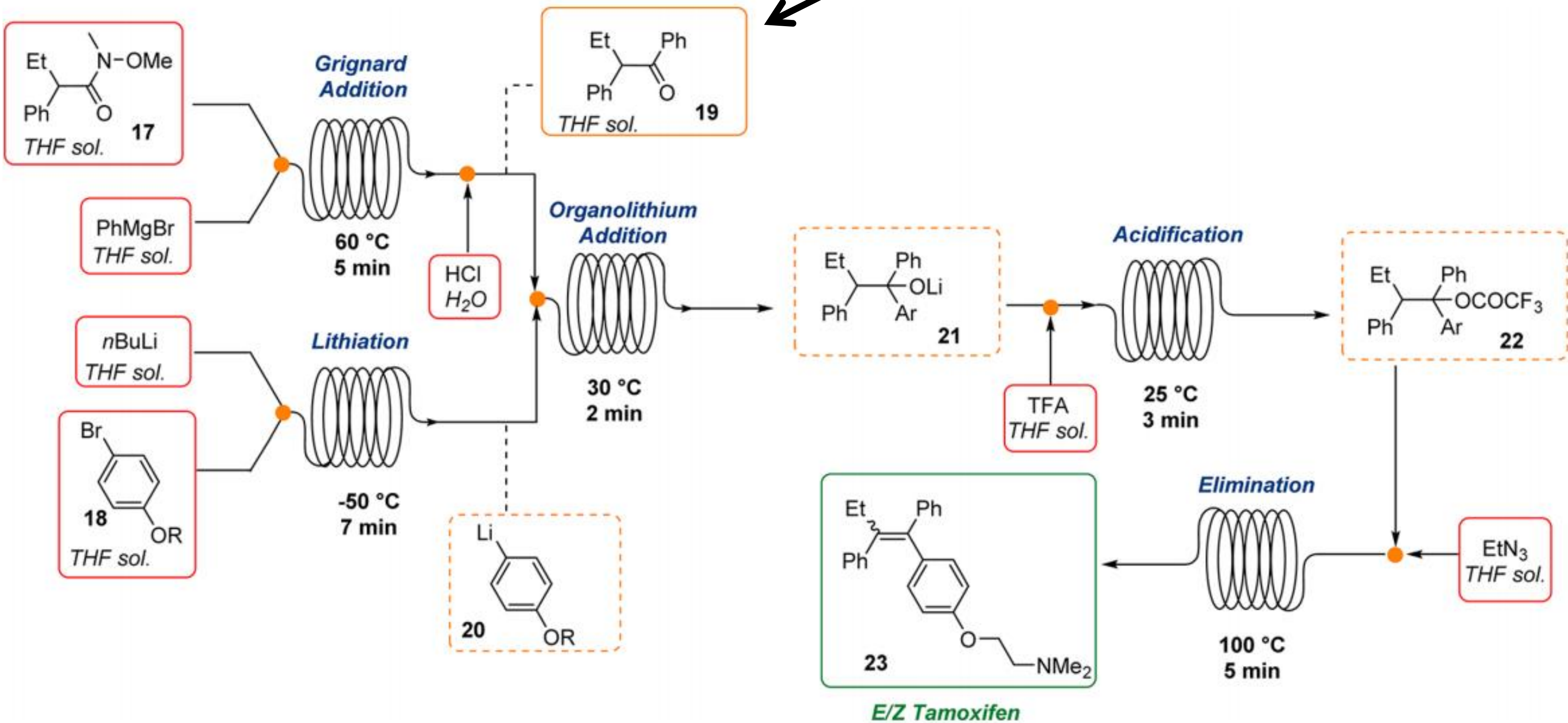
Up to 45 mmol scale in flow
< 10 mmol scale in batch: oligomerisation

T. P. Petersen, M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7933

Micro reactor VS Batch reactor

- Tamoxifen synthesis

97 % yield, 40 g get in 6h



84 % (E/Z) = 25:75
80 min to get 12.43 g

(a) D. Guthrie, S. V. Ley, *Org. Process. Res. Dev.*, **2013**, *17*, 1192, (b) R. Porta, M. Benaglia, A. Puglisi, *Org. Process. Res. Dev.*, **2016**, *20*, 2

Micro reactor VS Batch reactor

- Tamoxifen synthesis

(a) D. Guthrie, S. V. Ley, *Org. Process. Res. Dev.*, **2013**, *17*, 1192, (b) R. Porta, M. Benaglia, A. Puglisi, *Org. Process. Res. Dev.,* **2016**, *20*, 2

Bilan

Outlook

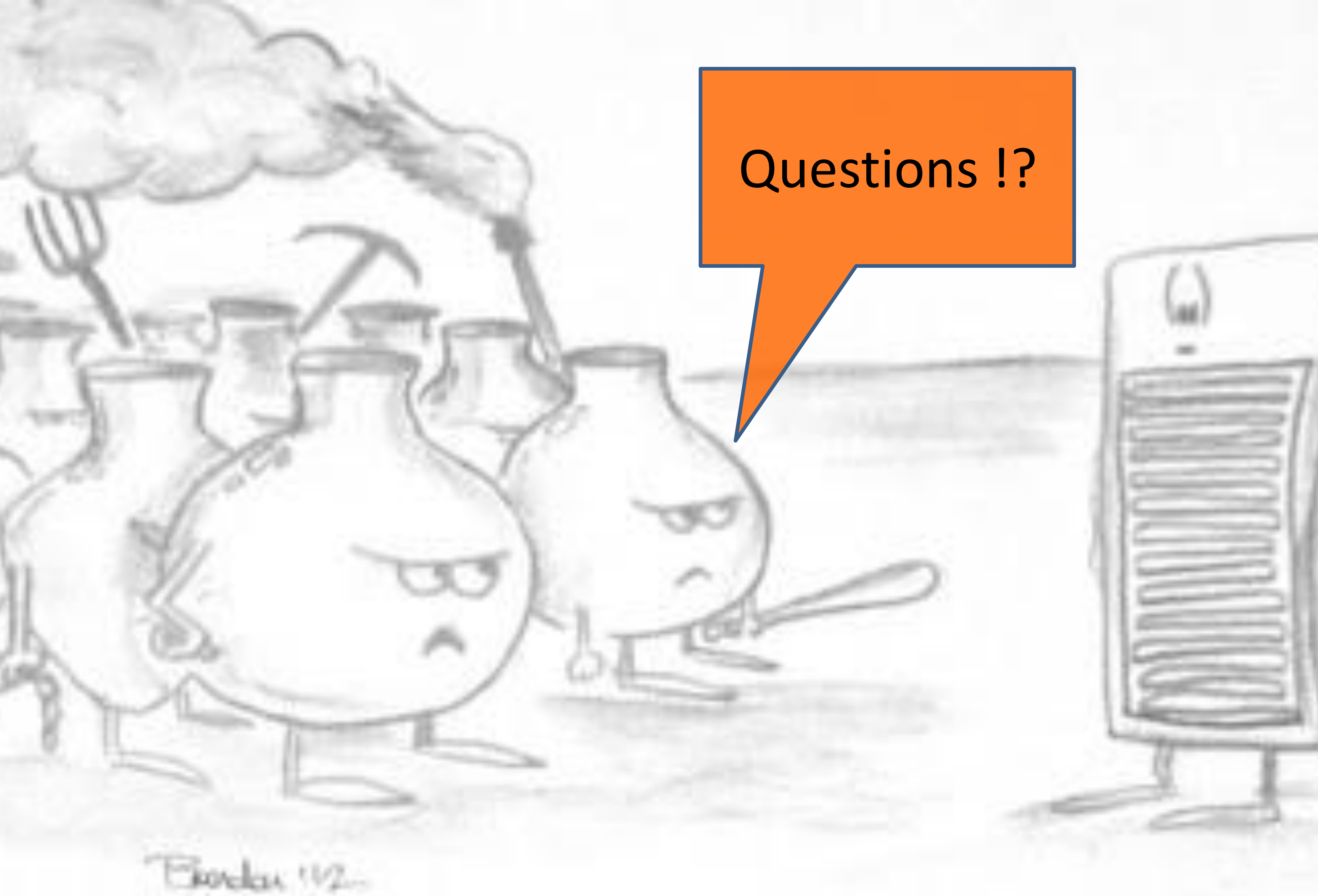
The transformations developed in flow display many advantages over the corresponding batch reactions, such as:

- respect many Green Chemistry principles
- a higher yield and/or selectivity (reaction time, less degradation…)
- safety profile (diazo, ozone…)
- faster and more efficient process (temperature, pressure…)
- direct transfer from development to manufacturing and highly flexible modules to perform on demand synthesis

The flow technologies requires:

- complex physicals and flow's mechanical studies
- complex materials which are not always available
- some techniques asks a lot of optimization
- to improve the enantiomeric process

The flow technologies continue to be developed and become more accessible
to accomplish efficient and more complex
syntheses.


Questions !?