# CONTINUOUS PROCESSES, FLOW CHEMISTRY

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# CONTINUOUS PROCESSES

BATCH PRODUCTION

CONTINUOUS PRODUCTION

# CONTINUOUS PROCESSES

**Typical Signals of Potential Problems on Scale-up**

- **Change of mixing speed changes product yield;**
- **Different mode of addition changes product yield;**
- **The position of a feed stream changes product yield;**
- **Scale up to a vessel with different geometry;**
- **Different holding time before work up;**
- **Poor heat transfer;**
- **Stability of intermediates;**
- **Different stirring**

# CONTINUOUS PROCESSES

**Pros/Cons of Continuous Processing in Pharma Manufacturing**

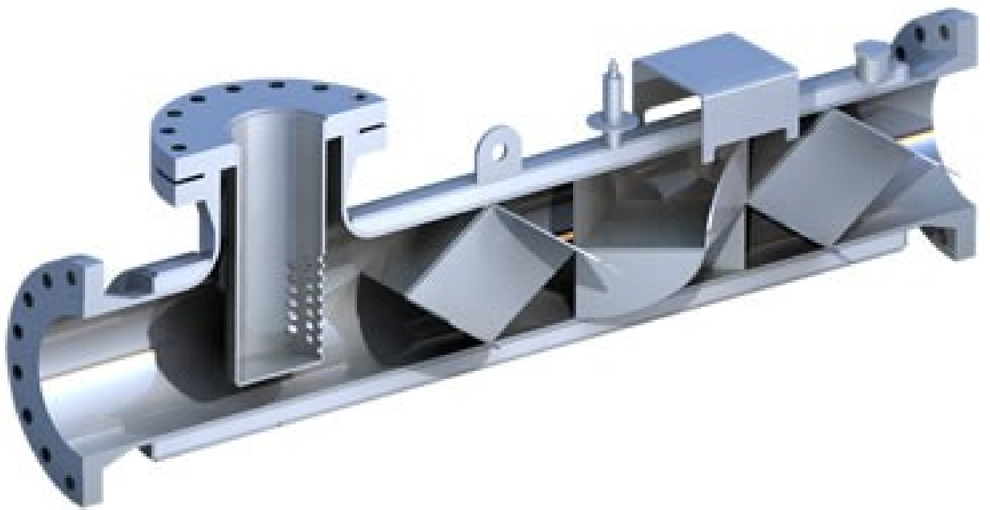
| Factor | Pros | Cons |
|---|---|---|
| Processing | Increased knowledge of the process due to the data rich environment, which includes in-line, real-time process monitoring (known as "PAT" - Process Automation Technology) | Many processes are validated and licensed by the FDA, therefore modification from batch to continuous processing in existing operations requires a significant investment of money and time |
| Operating Cost | Operating costs are lower due to less handling of product throughout the process | None |
| Capital Cost | Less overall facility cost | New technology brings high cost for new equipment |
| Facility Integration | Vertical integrated with a small building footprint required | Most existing facilities are not vertical, so retrofitting is a challenge |
| Quality | Improved quality as process is monitored in real-time and product data collected | Increased data collection also means increased need for analysis, storage, etc. |
| Scale Up | Ability to scale up production by running continuous equipment longer; do not necessarily need to add production "lines" | Most developers do not have experience with the technology, need to find specialists to design and program the equipment |
| Other Factors | | • Current excess capacity in batch processing pharma facilities<br>• Resistance to change from a traditional method<br>• New skills required to support process technology<br>• Current FDA regulations do not account for continuous processing implications just yet; will require interpretation of long-standing rules; most in "wait and see" mode |

# CONTINUOUS PROCESSES

## Typical Elements of a Continuous process:

- Efficient mixing enables fine control of reaction temperature within the whole reactor

Static mixers



High Surface area / Volume Ratio

# CONTINUOUS PROCESSES

**Typical Elements of a Continuous process:**

- Continuous operations can be applied for both cryogenic and high temperature processes;
- Much broader range of temperatures;
- Effective with respect to energy;

# CONTINUOUS PROCESSES

**Typical Elements of a Continuous process:**

- Reactive species can be separated thus minimizing side products (and raising yields);

# CONTINUOUS PROCESSES

**Typical Elements of a Continuous process:**

- Utilization of nontraditional techniques (photochemistry, sonochemical reactions, passing through a bed of a catalyst or immobilized enzyme)

# CONTINUOUS PROCESSES

**Typical Elements of a Continuous process:**

- Enables much safer processes;
- Only tiny portion of the reaction mixture is exposed to high temperature or exothermic reaction occurs only with very small amount of reactants;
- Advantage working with highly toxic compounds (cyanides, phosgene, diazomethane, ozone)

# CONTINUOUS PROCESSES

**Typical Elements of a Continuous process:**

- Opportunity in the field of intellectual property;
- Relatively easy monitoring in real time (PAT);
- Variability according to a purpose;
- Supported by authorities;
- Fitting well into Quality by Design concept;
- Sometimes untypically milder reaction conditions;
- Increasing of productivity (scaling out, numbering up);

# CONTINUOUS PROCESSES

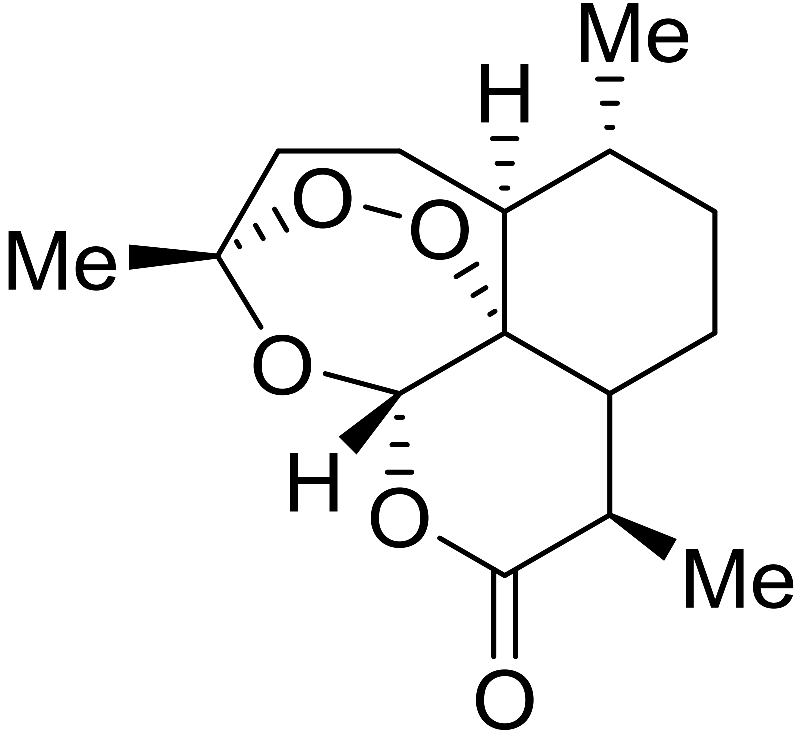
**Typical Elements of a Continuous process:**

- Need for efficient and robust pumps, inert tubings, vessels to collect products and store starting components, fittings, pressure gauges, pressure relief valves, static mixers, heat exchangers, separators
- Residence time (average time needed for a molecule to pass through a reactor);
- Flow rate (ml per min.);

# FLOW CHEMISTRY

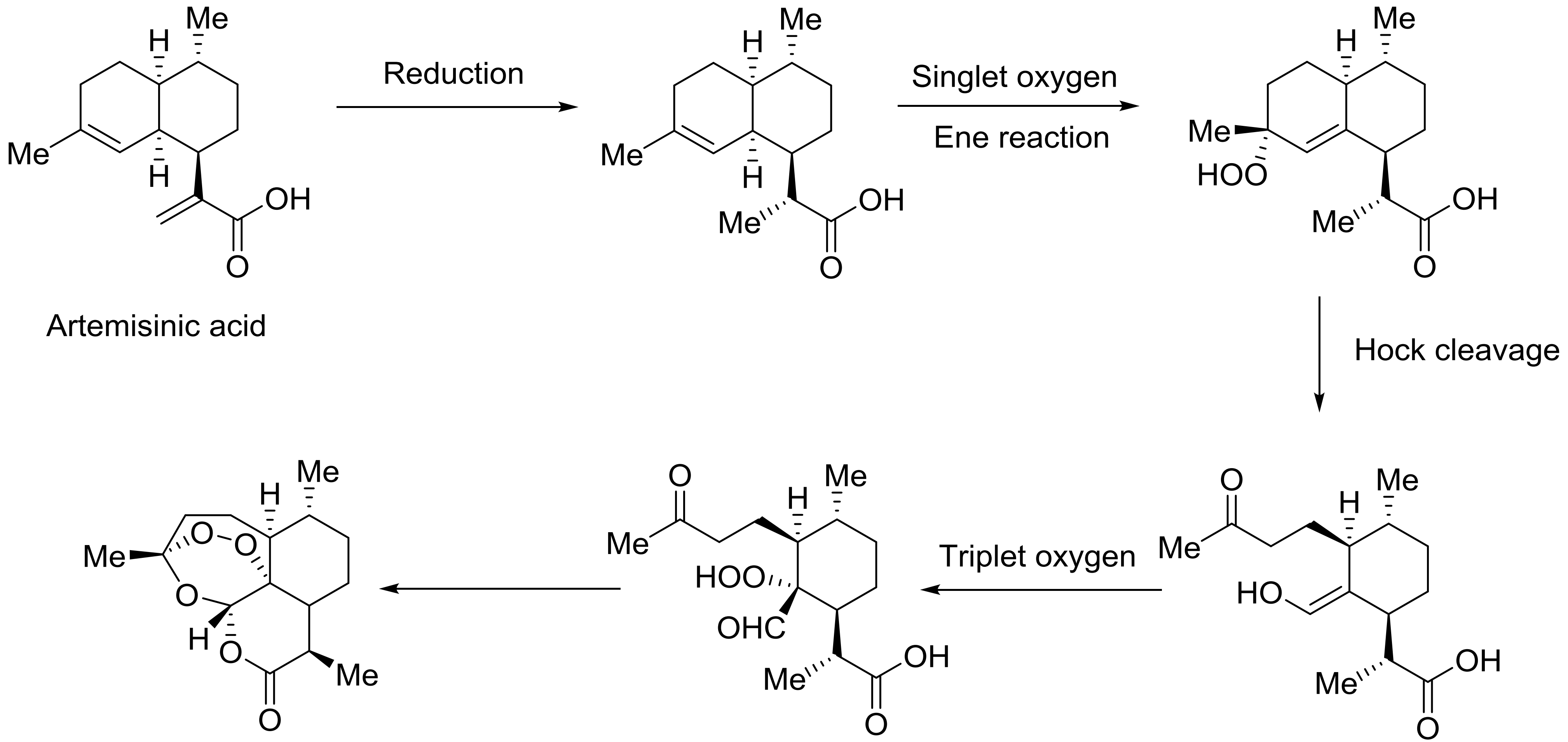
## Artemisinin continuous production

Used in the treatment of malaria
2015 – Nobel prize for its discovery (1972)
Extracted from plant *Artemisia annua*
(sweet wormwood)



# FLOW CHEMISTRY

## Artemisinin continuous production



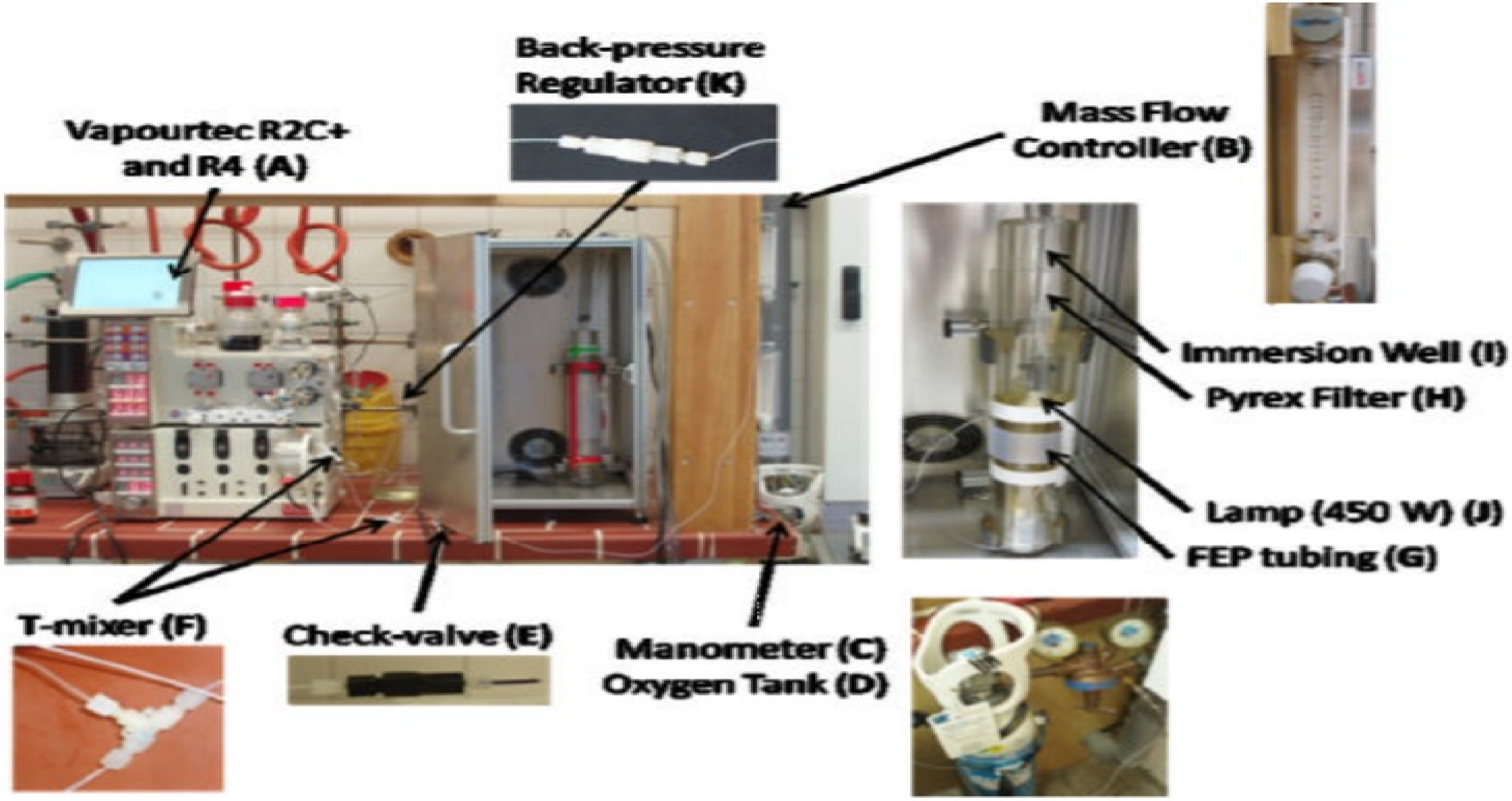

Artemisinic acid

Artemisinin

Lévesque, F.; Seeberger, P.H. *Angew.Chem. Int. Ed.* *51*, 1706 (**2012**)

# FLOW CHEMISTRY

## Artemisinin continuous production




Lévesque, F.; Seeberger, P.H. *Angew.Chem. Int. Ed. 51*, 1706 (**2012**)

# FLOW CHEMISTRY

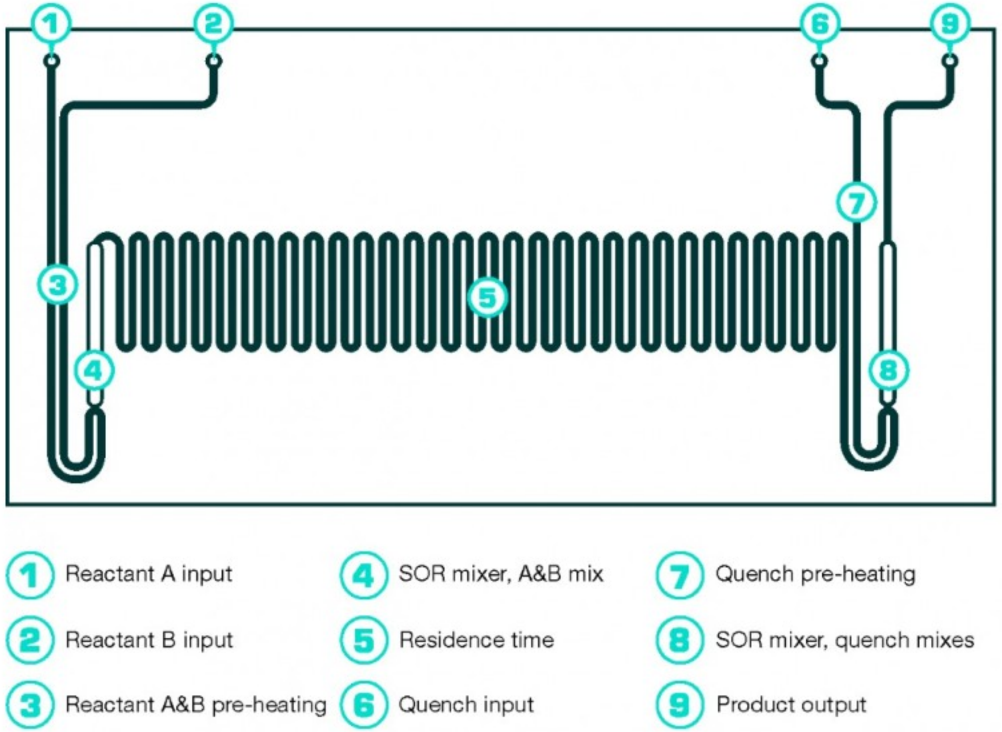
**Artemisinin continuous production**

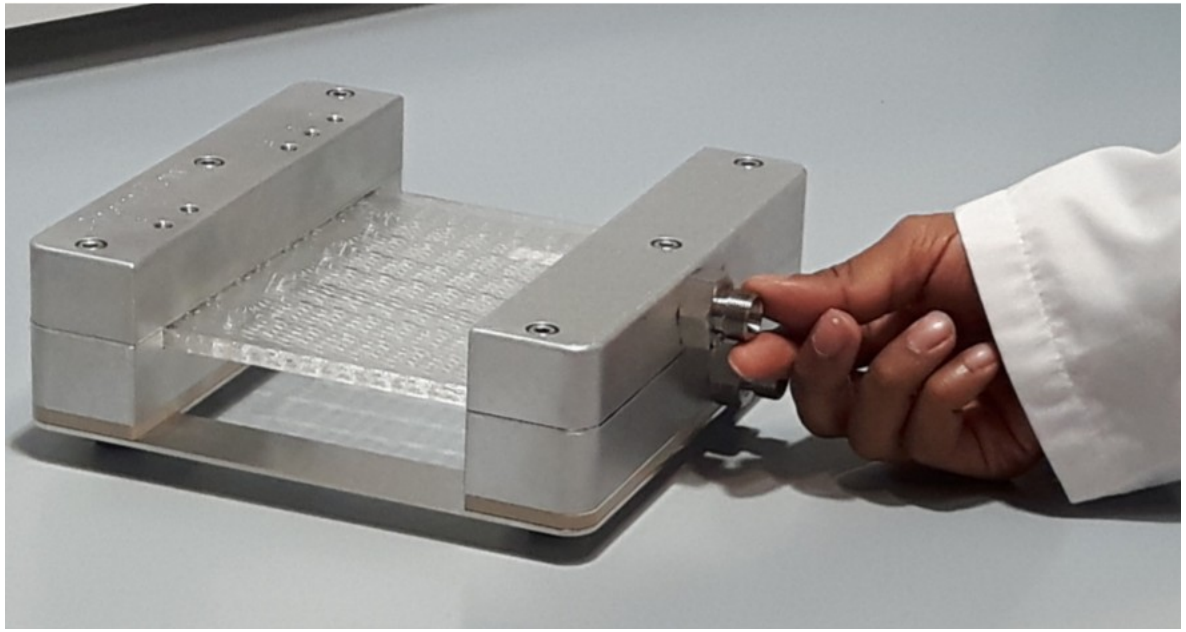
**1500 simple photoreactors (each 200 g of artemisinin a day) would be sufficient to cover demand for roughly 225 million doses necessary for the malaria treatment (2009 WHO estimate)**

Lévesque, F.; Seeberger, P.H. *Angew.Chem. Int. Ed. 51*, 1706 (**2012**)

# FLOW CHEMISTRY

## Microreactors

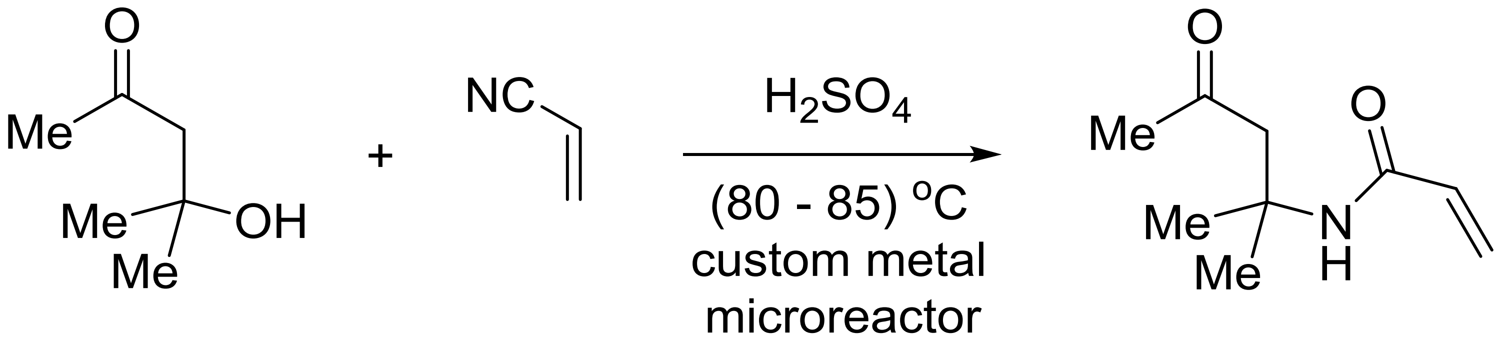


Chemtrix company microreactor

# FLOW CHEMISTRY

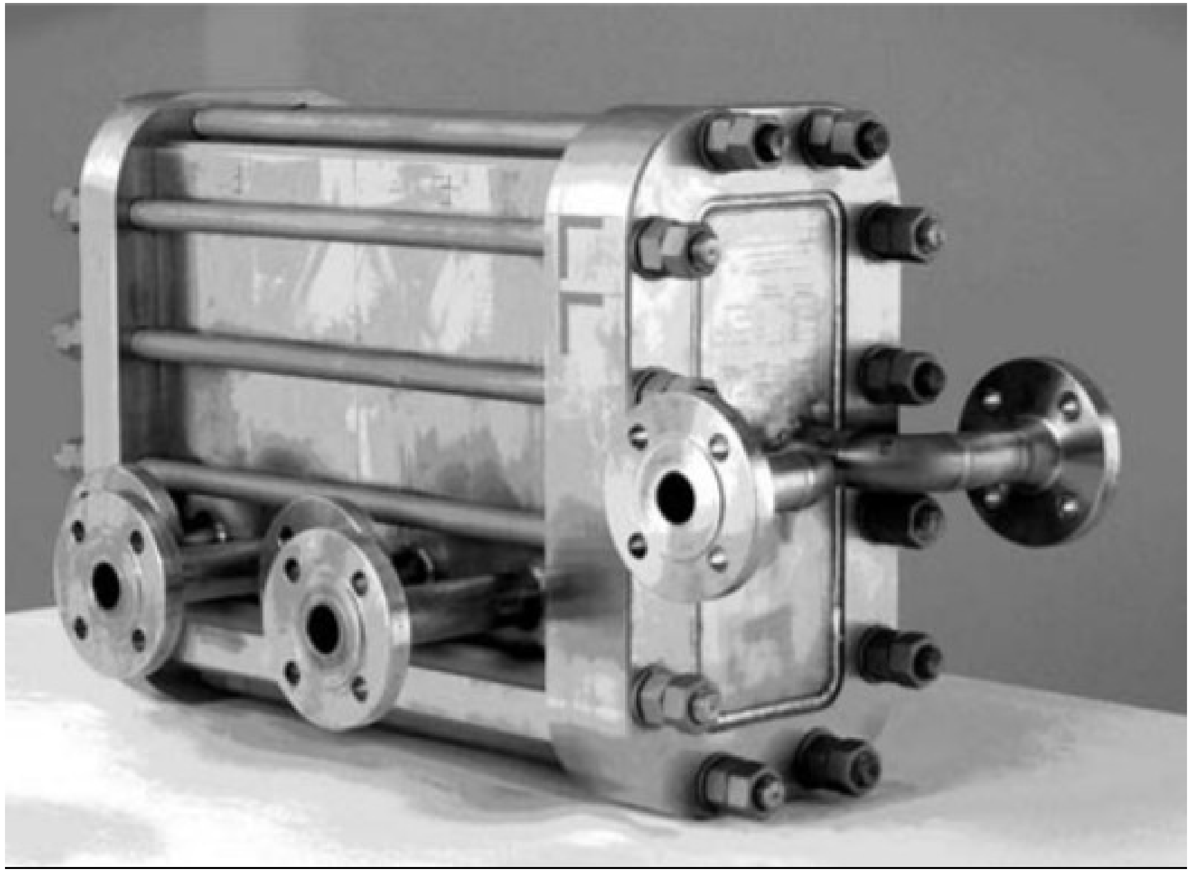
## Microreactors




DSM company, control of the exothermic Ritter reaction on very large scale (40 tons a day);
Decreased decomposition
Yield was increased by 15%
Waste was decreased by 15%
Ondrey, G. *Chem. Eng. 118*, 17 (**2011**)

# FLOW CHEMISTRY

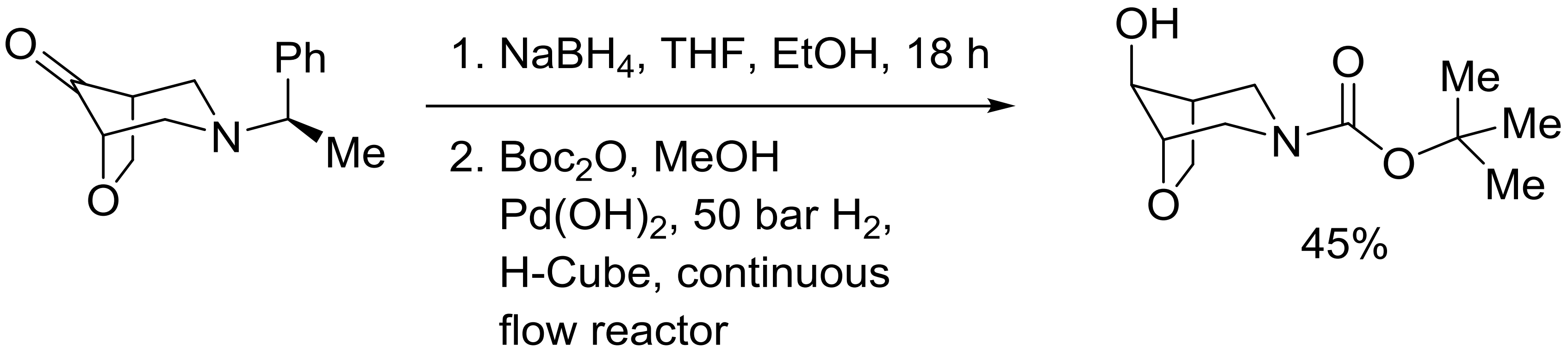
- **DSM company**



The microstructured flow reactor for throughput at 1700 kg per hour

# FLOW CHEMISTRY

## Microreactors



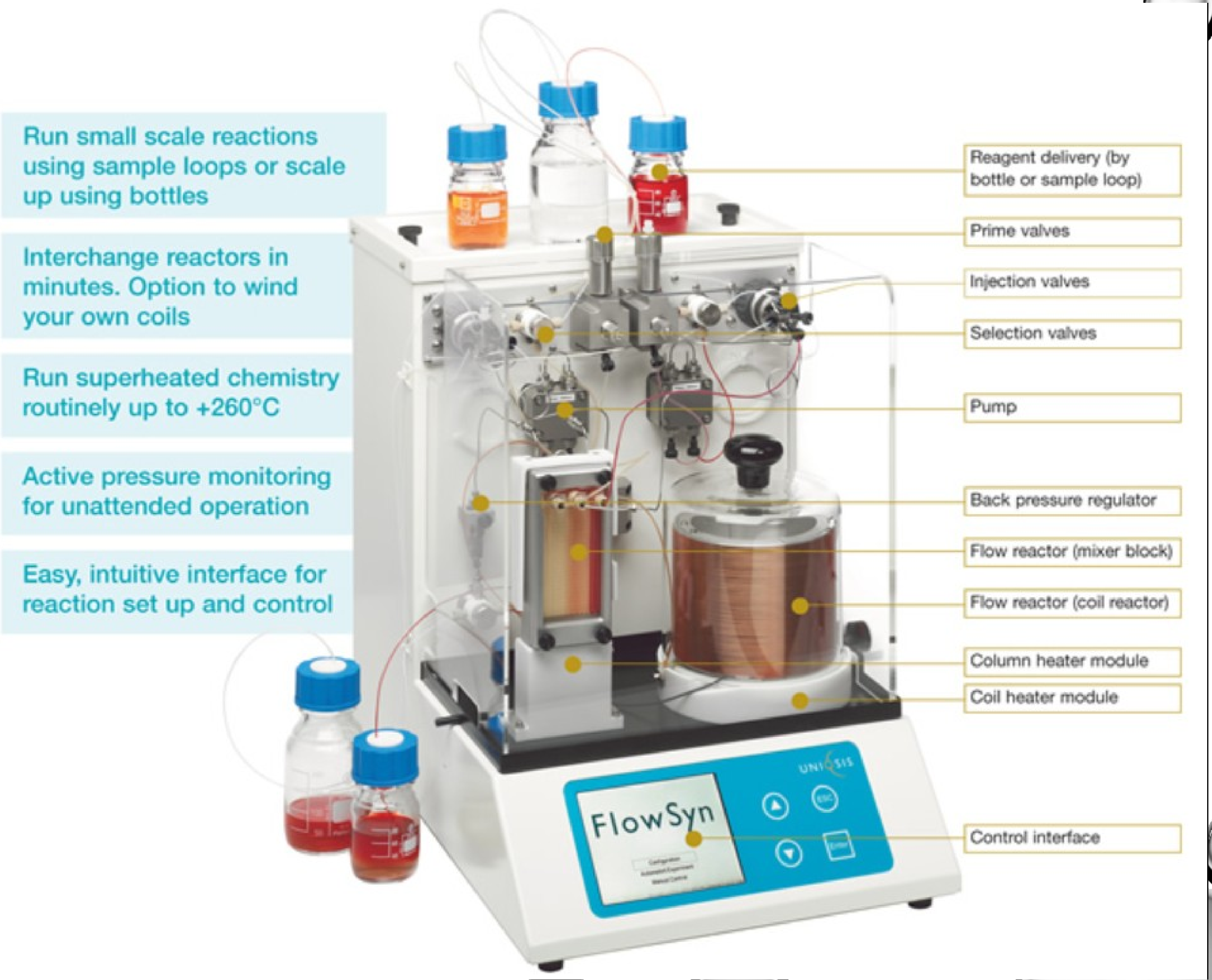

ThalesNano company

Spadoni, C. *et al Chim. Oggi* 38 (**2006**)

# FLOW CHEMISTRY

## Microreactors

Uniqsys (GB)



# FLOW CHEMISTRY

## Microreactors


Chemtrix

# FLOW CHEMISTRY

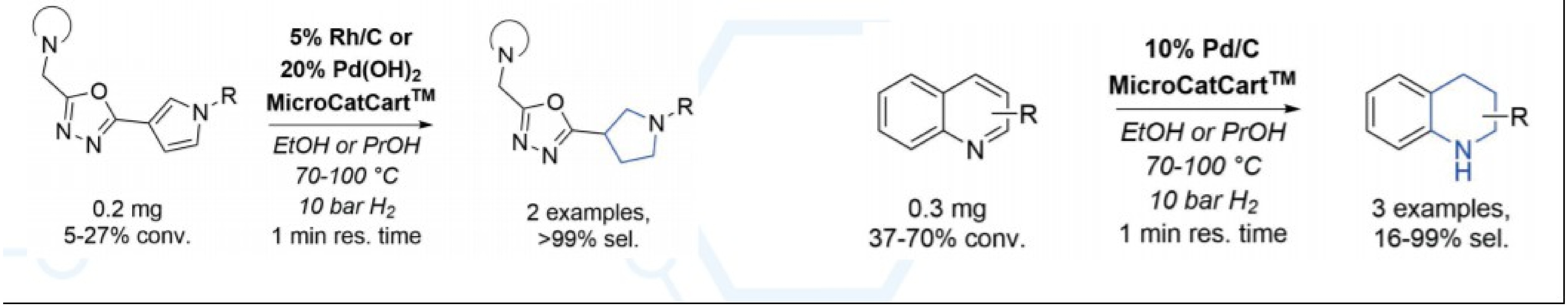
## Microreactors


ThalesNano
1.Q 2020

**MicroCube$^{TM}$**

# FLOW CHEMISTRY

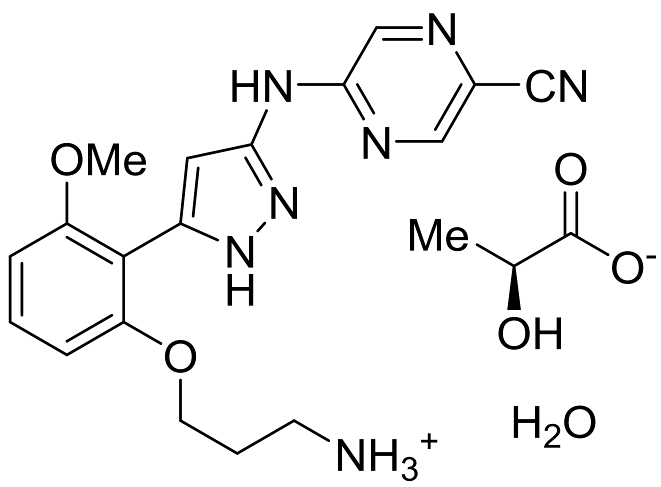
## Microreactors




ThalesNano product brochure

# CONTINUOUS PROCESSING

- Eli Lilly, new production unit utilizing continuous processes in Kinsale, Ireland;
  Prexasertib monolactate monohydrate




8 continuous process step, including using hydrazine;
Designated production unit, the product is cytotoxic → extensive cleaning measures, only 24 kg needed;
Small flow set up could be after each lot discarded;

Halford, B. *C&EN Global Enterprise 95*, 23 (**2017**)

# CONTINUOUS PROCESSING

**Continuous Operations Using Larger Reactors**

**Spinning Disk Reactor**

- Thin films of reactant solution permitting rapid heat exchange;
- Solutions applied to the center of a spinning disk are driven to the edges by centrifugal forces;
- The contact time with the disk is inversly proportional to the angular velocity;
- Preferred for fast reactions;

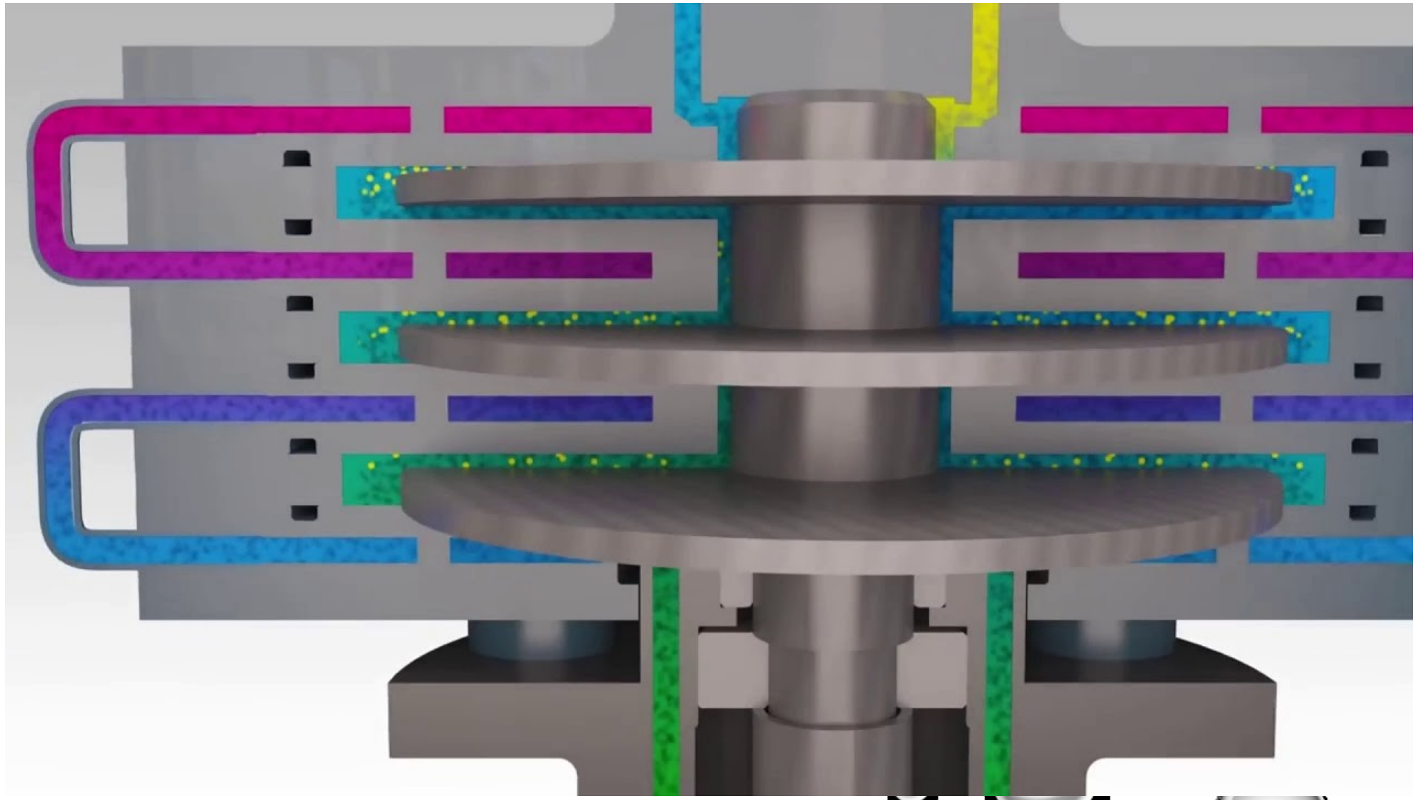
*Org. Process Res. Dev. 15*, 997 (**2011**)

https://www.youtube.com/watch?v=p42pCoOJ5sc

# CONTINUOUS PROCESSING

## Continuous Operations Using Larger Reactors

### Spinning Disk Reactor



# CONTINUOUS PROCESSING

## Continuous Operations Using Larger Reactors

**Spinning Tube-in-Tube Reactor**

- Reactor of this type increases reaction rates by improving mixing through high shear rate, which is independent of the residence time and dependent upon the angular velocity and the gap between the spinning internal tube and the stationary external tube

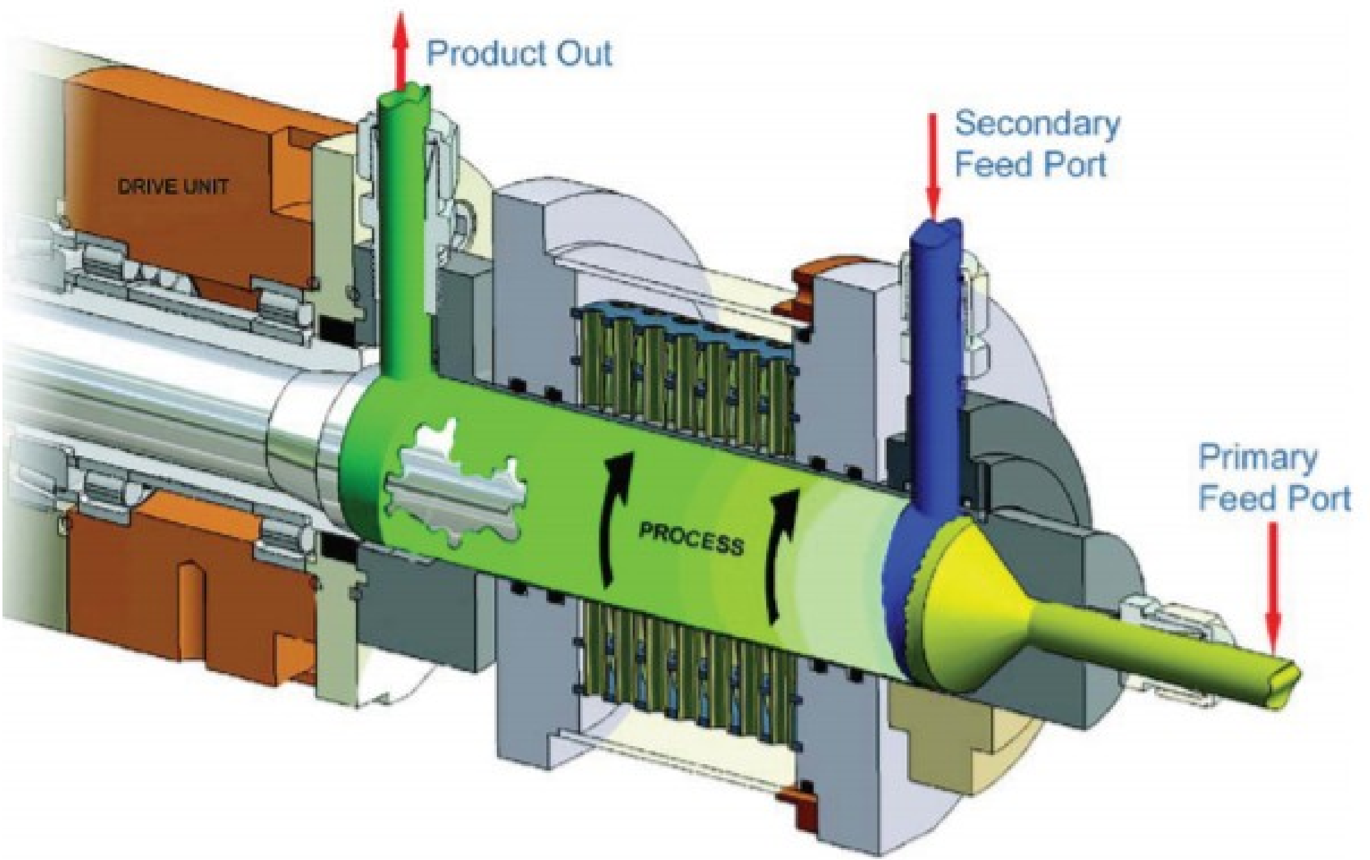
- Gonzales, M.A. *et al Org. Process Res. Dev. 13*, 64 (**2009**)

- OPRD 12, 946 (2008)

# CONTINUOUS PROCESSING

## Continuous Operations Using Larger Reactors

## Spinning Tube-in-Tube Reactor



# CONTINUOUS PROCESSING

## Continuous Operations Using Larger Reactors

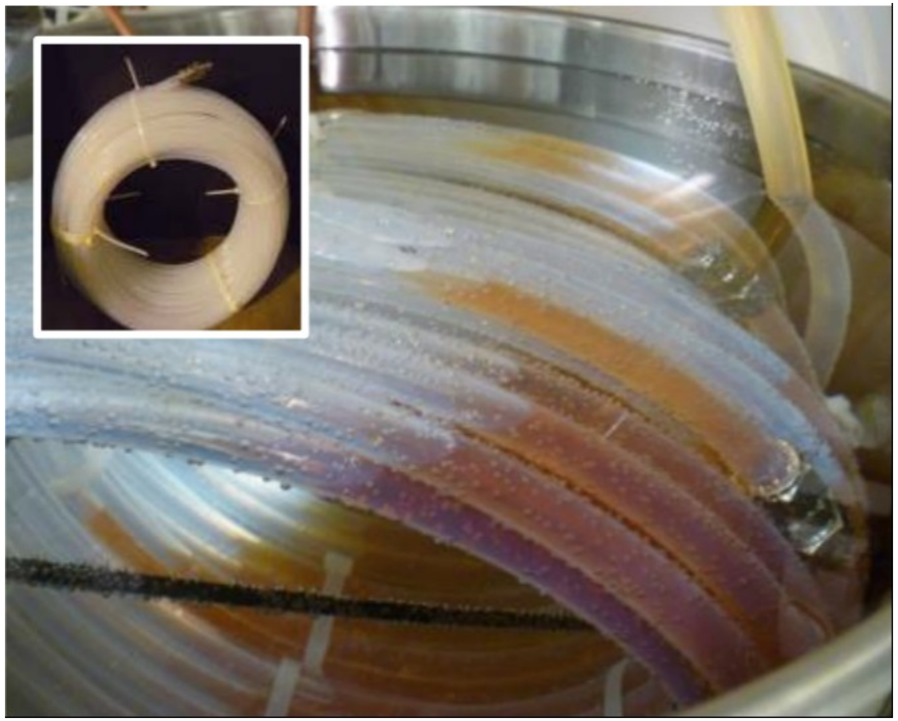
**Plug Flow Reactors**

- Reactants mix in thin discs (plugs) moving away from the entry point (theoretical assumption);
- Mixing in radial direction, no mixing in axial direction;
- The composition changes until a plug of product emerges from the reactor;
- Turbulence can be amplified by the presence of static mixers

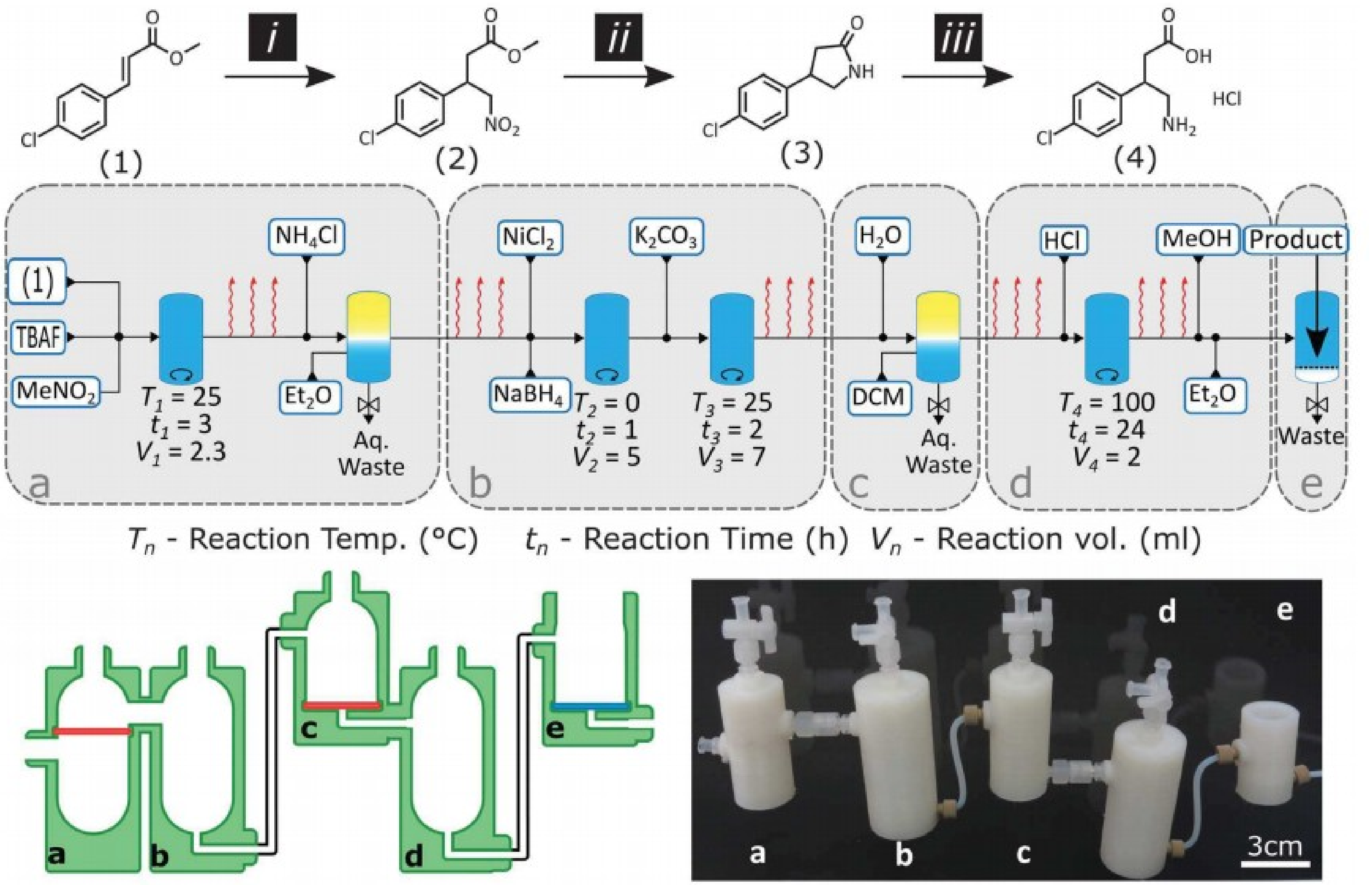
# CONTINUOUS PROCESSING

- Continuous Operations Using Larger Reactors

## Plug Flow Reactors



# CONTINUOUS PROCESSING




Kitson, P.J. *et al Science 359*, 314 (**2018**)

# CONTINUOUS PROCESSING AND FLOW CHEMISTRY

## Summary

- Used for decades in petrochemical and food industry;
- Start to attract attention even in conservative pharmaceutical industry;
- Going commercial – new already established companies offering service, expertise, solutions and products;
- Boom of new materials – microreactors (glass, ceramic, metal), pumps, tubings, mixers, fittings, valves, prepacked columns);
- Disadvantage – clogging, corrosion,
- Lack of common experience and expertise;
- Continuous processes are not suitable for all reactions