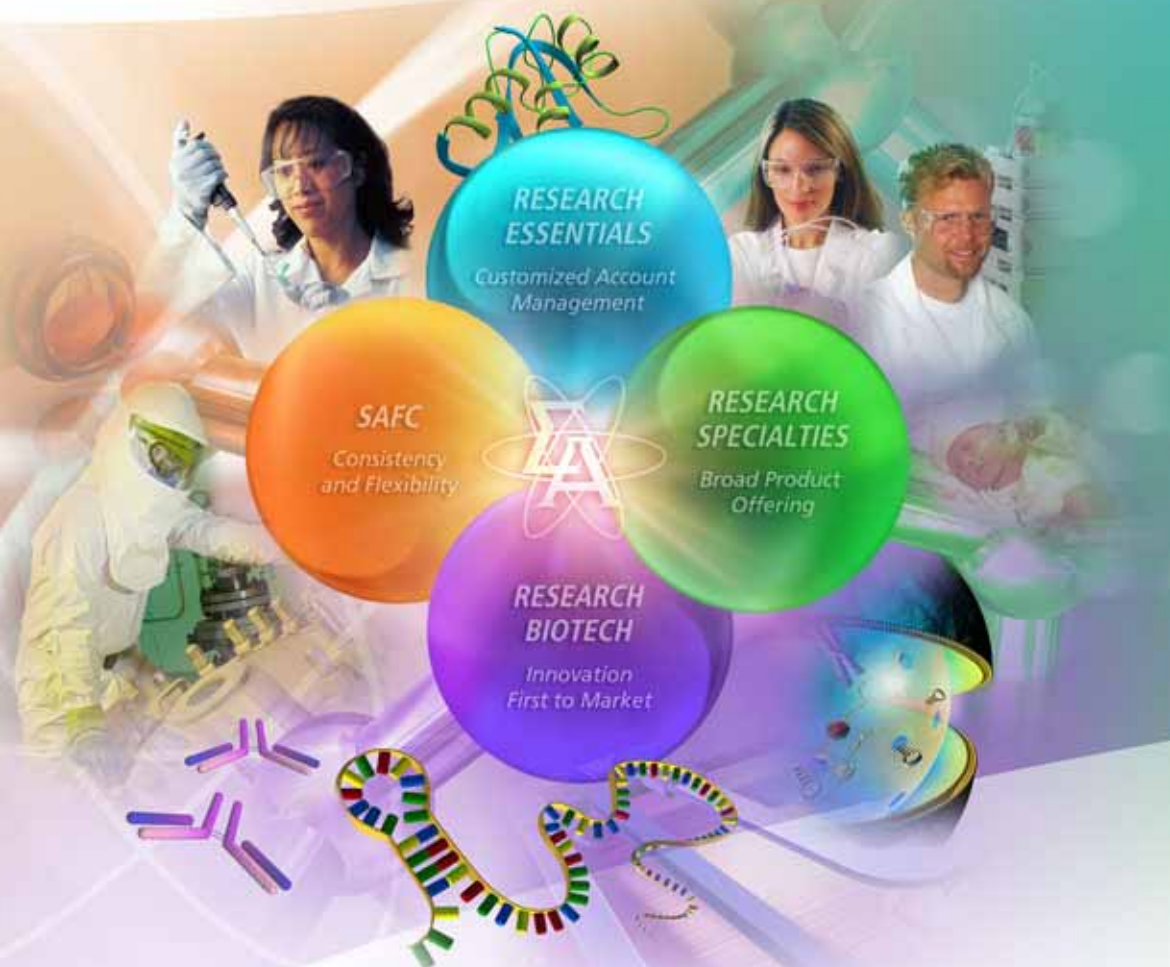


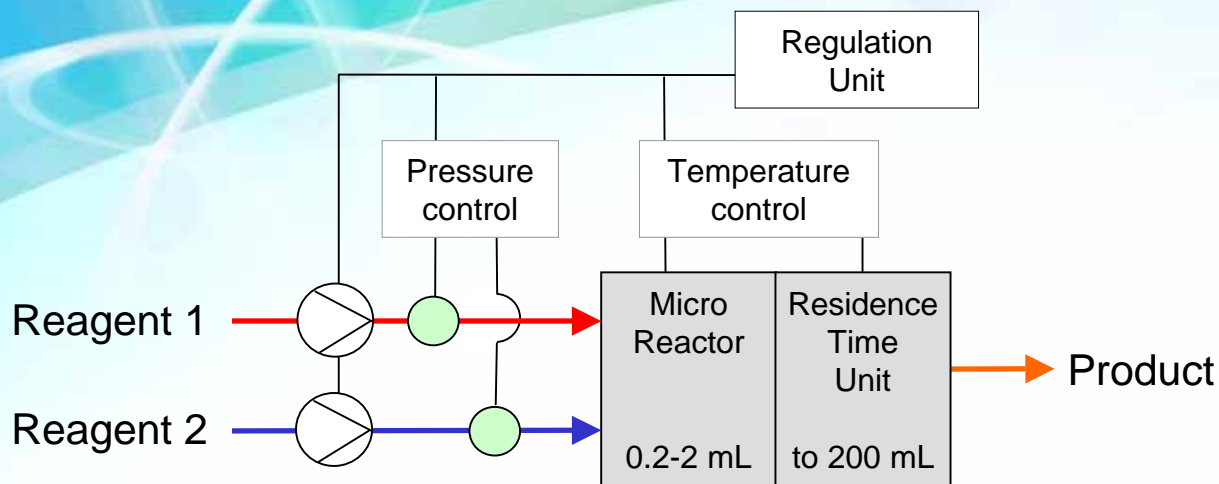
# Industrial Production of Chemicals in Microstructured Reactors



By Gregor Wille  
[gwille@sial.com](mailto:gwille@sial.com)

Workshop with EPFL on MRT. November 22, 2007 in Buchs.

# Concept of Microreaction Technology



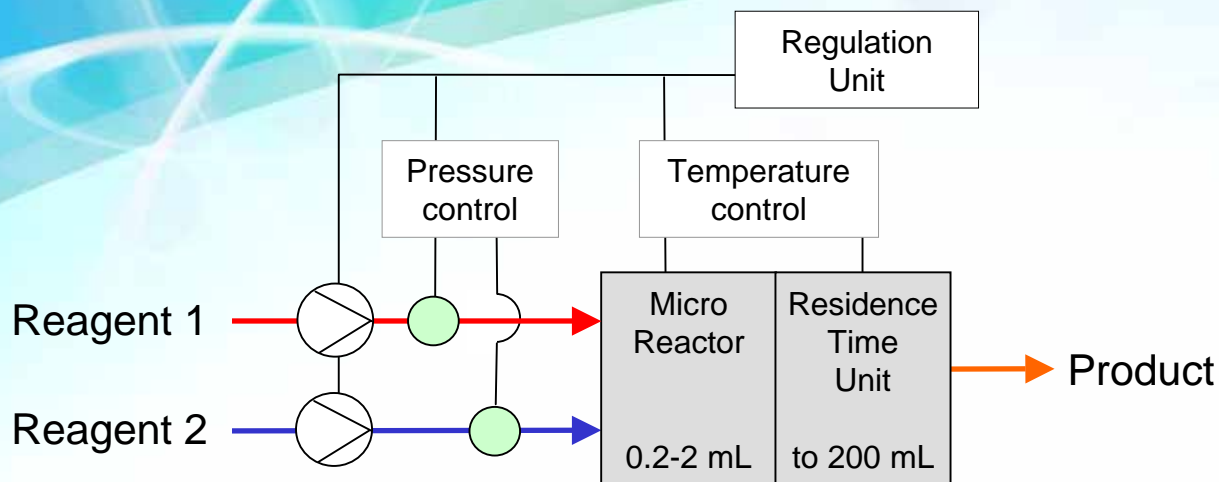
## Typical parameters

Pressure (bar)	0.2 - 4
Temp. accuracy (K)	+/- 2 (MR)
Flow (mL/min/line)	1-15

- Residence time  $\tau$  stands for reaction time:  
 $\tau = \text{Reaction volume [mL]} / \text{Total flow rate [mL/min]}$
- Output is dictated by operation time rather than batch-scale
- Operation at net reaction temperature & net reaction time

✓ Materials need to stay into solution

# Concept of Microreaction Technology



## Typical parameters

Pressure (bar)	0.2 - 4
Temp. accuracy (K)	+/- 2 (MR)
Flow (mL/min/line)	1-15

- Residence time  $\tau$  stands for reaction time:

$$\tau = \frac{\text{Reaction volume}}{\text{Total flow rate}}$$

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↑ **+++ Output**

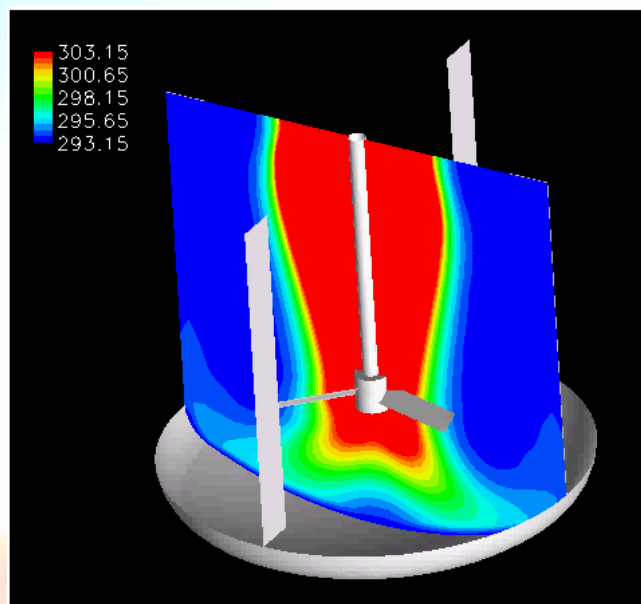
$$\tau = \frac{\text{Reaction volume}}{\text{Total flow rate}}$$

↑ **+++ Output**

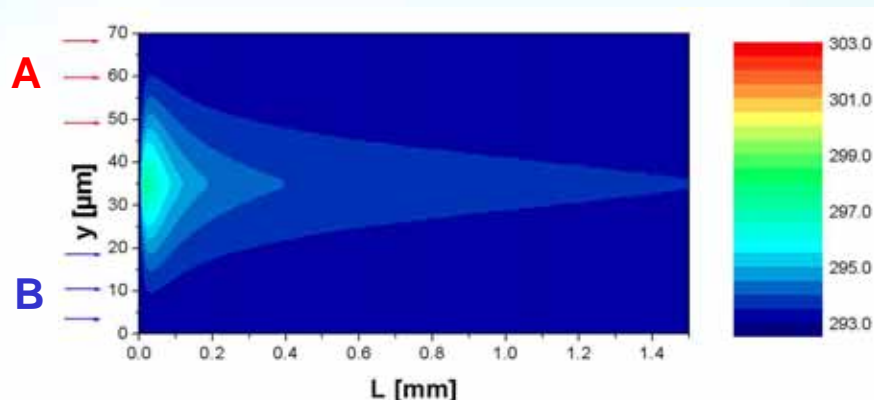
# Heat transfer in liquid-/liquid

## Vessel

- 500 RPM, 1 m<sup>3</sup> vessel
- Cooling from outside
- Heat release 55kJ/mol
- Mixing by turbulence



## Microreactor



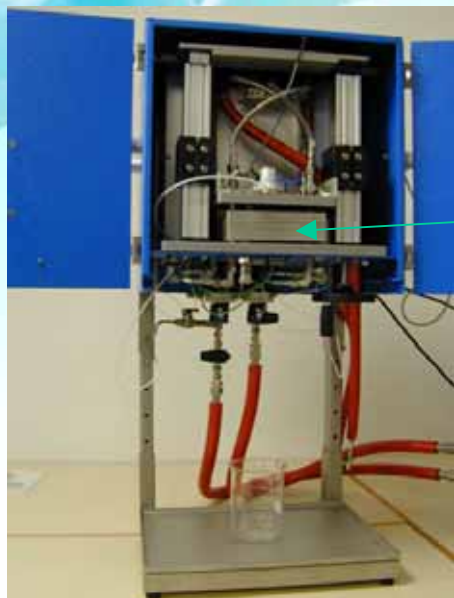
Reactor type	Surface/Volume [cm <sup>2</sup> /cm <sup>3</sup> ]
Flat microchannel width approx. 100 μm	<b>200</b>
100 ml flask	1
50 galon reactor	0.08
1 m <sup>3</sup> reactor	0.06

Similar considerations apply for mixing

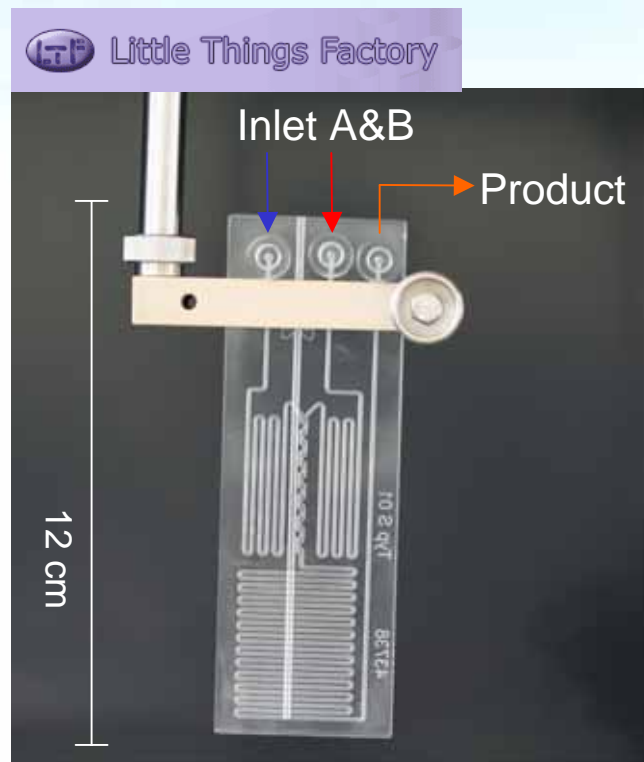
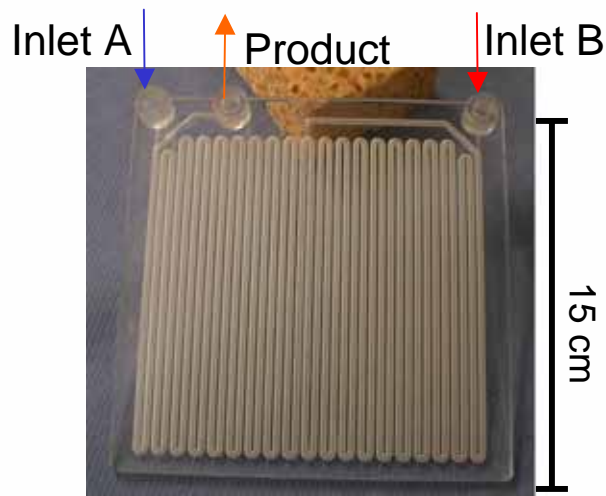
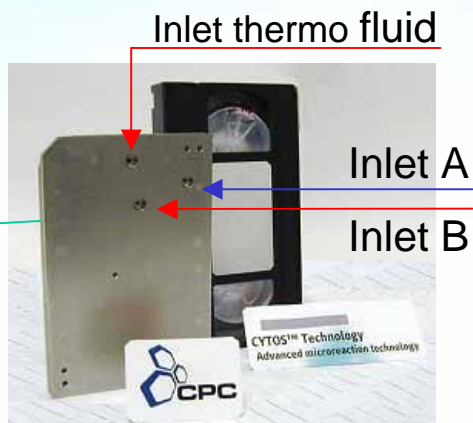
→ 1:1 mixture realised in MR systems extremely fast

# MR Systems at Buchs: Multipurpose mandatory

**Stainless microreactor** with integrated thermo circuit



CYTOS® Lab System



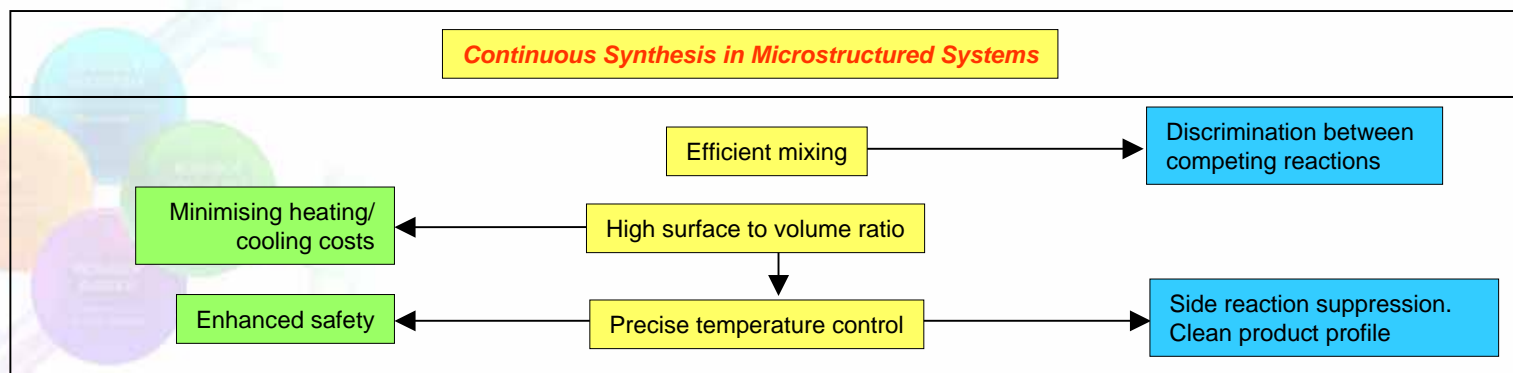
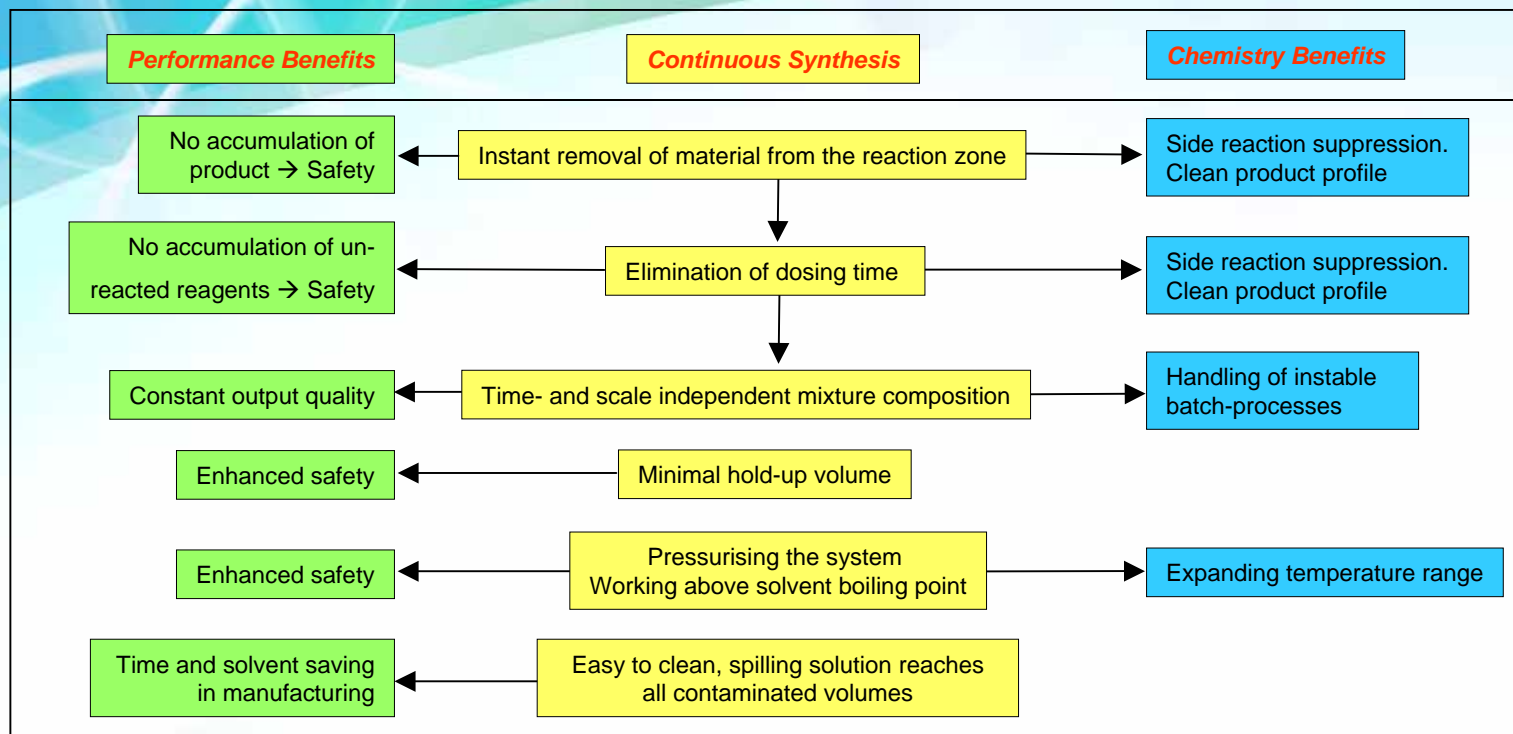
**Glass microreactor** S01 type.  
Part of the Sigma-Aldrich  
Microreactor Explorer Kit  
#19979



SIGMA-ALDRICH

**Glass microreactor** XXL type, with integrated RTU of 15 mL.

# Microreaction Technology Benefits



# How can the advantages be used?

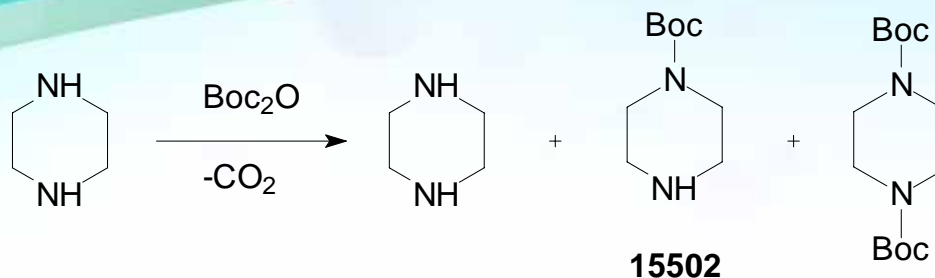
- **General process development**
  - **Continuous mono-Boc-protection of diamines**
- High exothermic/hazardous reactions  
(scale-up difficult due to safety reasons)
- Products which are instable under reaction conditions
- Product profile improvement



**SIGMA-ALDRICH**

# Continuous mono-Boc-protection of diamines

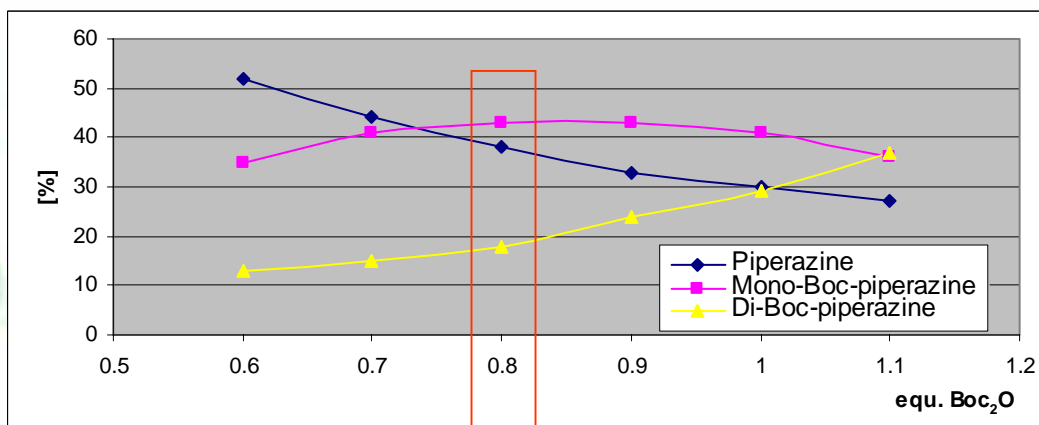
- Example reaction:



- **Step 1:** Finding the best solvent

Methanol showed best solubility. THF, toluene, DCM caused blocking

- **Step 2:** Equivalent optimisation



conditions of choice

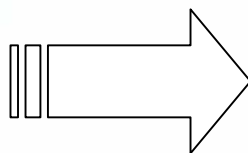


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# Continuous mono-Boc-protection of diamines

- **Step 3:** Production optimisation, rising concentration and flow rate

Concentration optimisation	
$C_{(\text{piperazine})}$ [M]	Production [g/d]
0.5	115
1.3	299
1.6	MR blocked



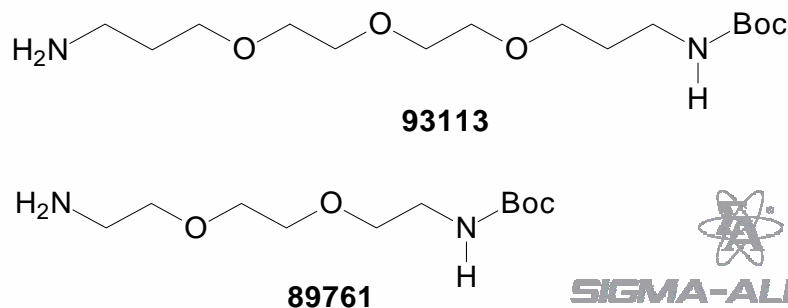
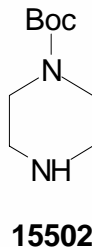
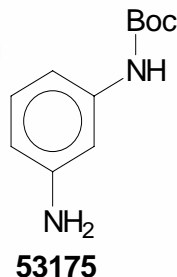
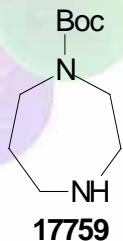
Throughput optimisation	
Feed A, B [ml/min]	Production [g/d]
2	299
2.7	404
4	597
6	Boc2O uncomplete

Residence volume fixed at 75 mL

- **Summary**

- Production of 600 g/d, residence time 18.8 min
- 20 experiments
- Standard protocol enables manufacturing of similar products spending minimal development efforts (1-2 days)  
→ production of a few 100-gram during the subsequent night

- **Sigma-Aldrich catalogue products**



SIGMA-ALDRICH

# How can the advantages be used?

- General process development
- **High exothermic/hazardous reactions**  
(scale-up difficult or impossible due to safety reasons)
  - **Ionic liquids**
  - **Diketene chemistry**
  - **Epoxidations**
- Products which are instable under reaction conditions
- Product profile improvement



# Production of ionic liquids with MRT

04367 (normal quality)

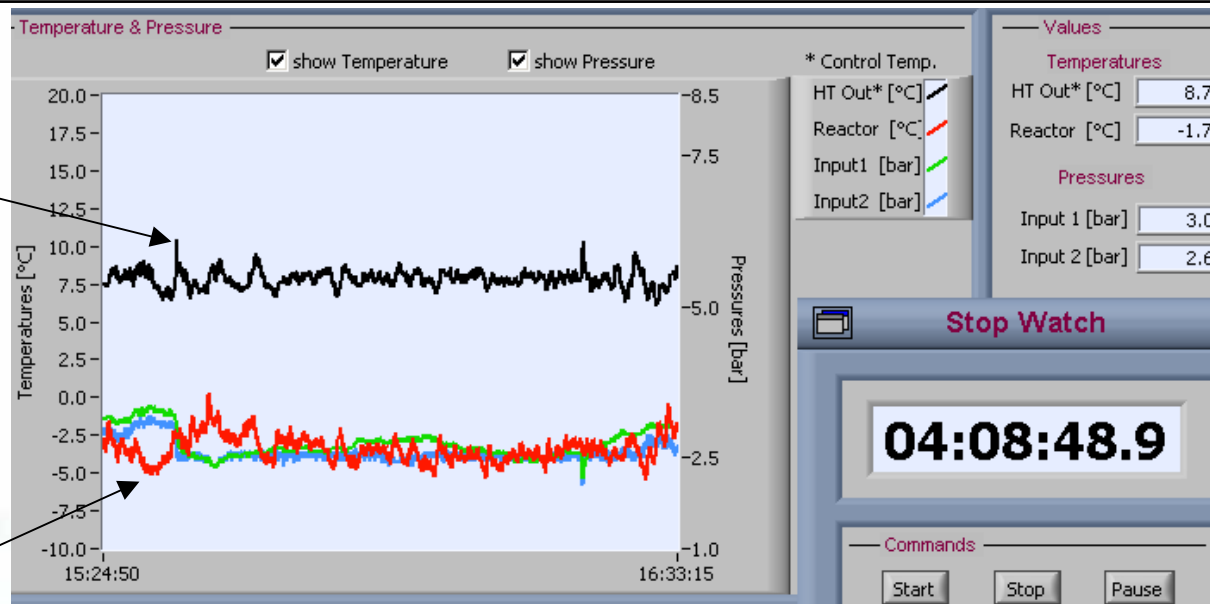
00738 (grade for catalysis)



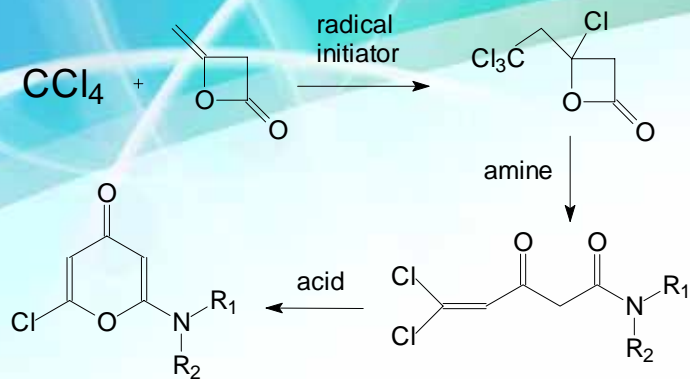
- External chillier operates 11°C (red line) below reaction temperature of 8°C (black line)
- The mixtures colour turns to dark upon  $T > 20^{\circ}\text{C}$
- Synthesis using neat materials  $\rightarrow$  output  $> 1.5$  kg/h

Reaction temp.

External chillier



# MR system with extras: Diketene chemistry



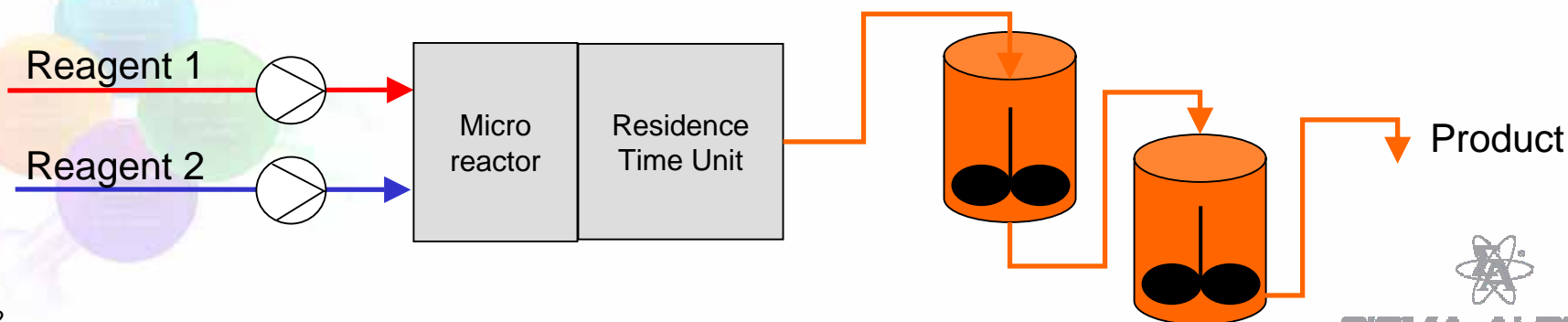
## • Crucial points

- Diketene is highly explosive,  $\text{CCl}_4$  is carcinogen
- $\beta$ -lactone is instable (step 1)
- 5 kg of final product required, synthesised in 240 h
- Potential output optimization 1.4 kg/d

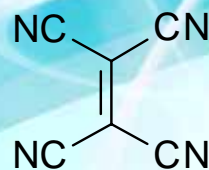


Experimental set-up in the lab

Attached cascade reactors extended residence time

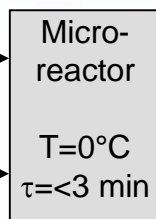


# Epoxidation

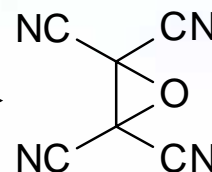


Fluka product 87120  
1.16 M in AcCN

H<sub>2</sub>O<sub>2</sub>  
35% in Wasser



Product



Fluka product 87121  
Yield 47% (Batch 23%)

Quench on  
ice-water

- Reaction is exothermic
- Temperature in batch controlled by dosing rate
- Product may decompose upon extended contact  
→ Instant work-up required (mismatch with temp. control by dosing rate)
- Reaction mixture changes colour when completed from pink to yellow → Conversion detectable visually (photo right)
- Material collected from MR outlet was white.

Working up the completely converted batch gave yellow material.



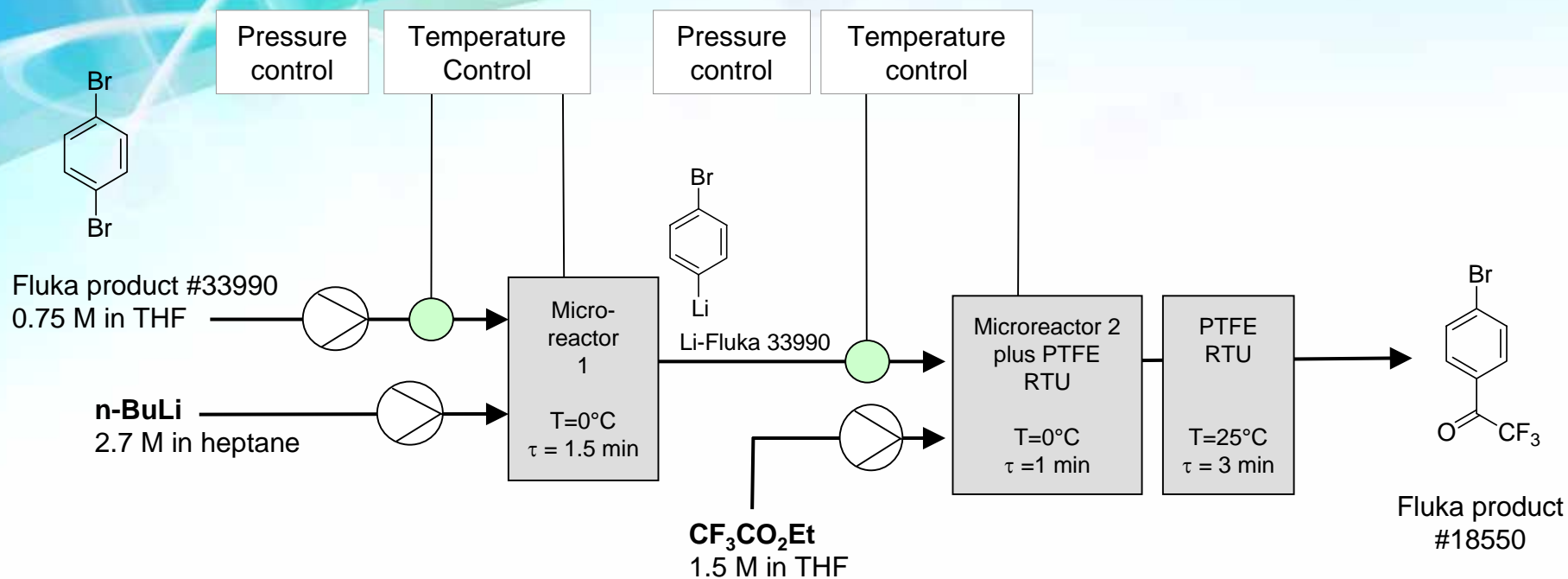
SIGMA-ALDRICH

# How can the advantages be used?

- General process development
- High exothermic/hazardous reactions  
(scale-up difficult due to safety reasons)
- **Interception of instable intermediates/products**
  - **Lithium organic chemistry, systems with 2-3 stage**
  - **Cleaving a sensitive ester**
- Product profile improvement

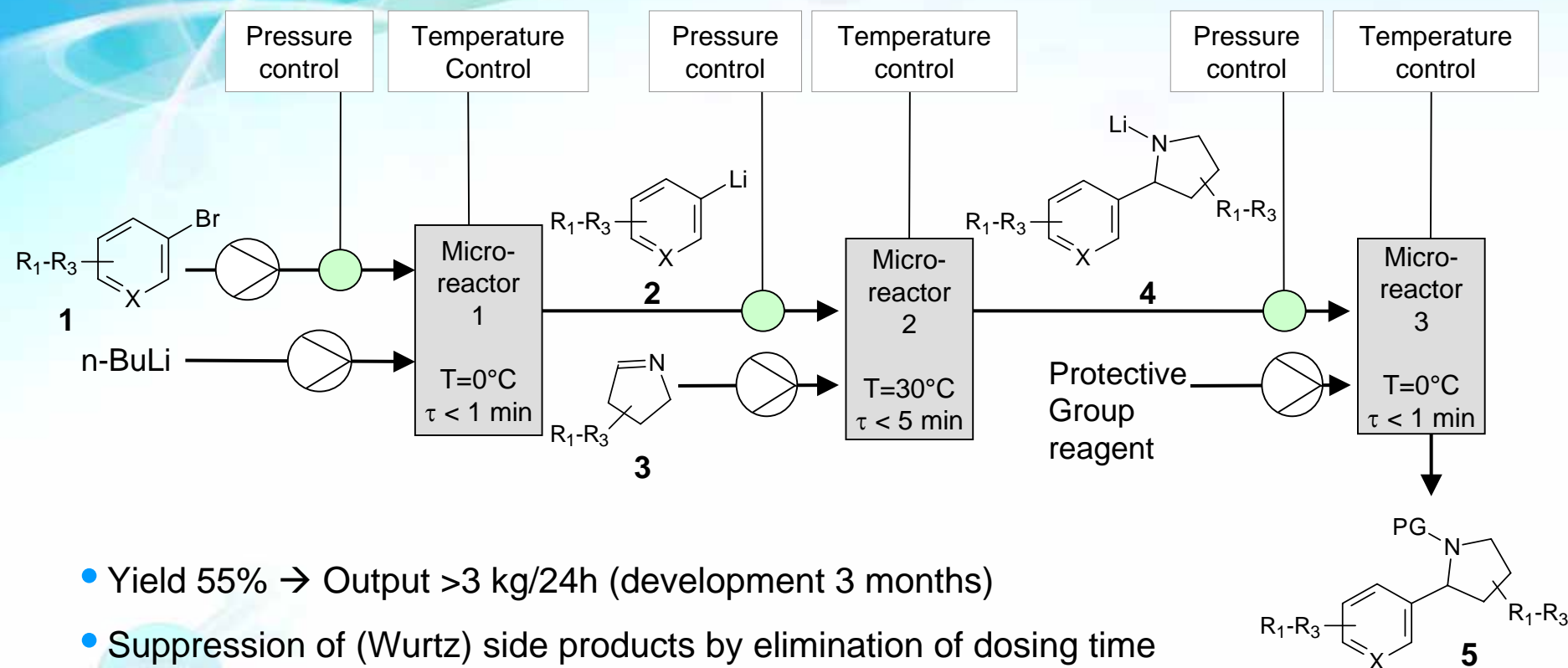


# Interception of instable intermediates in 2-stage assembly

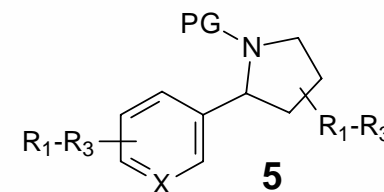


- No need for cryogenic vessels
- Product comes in constant quality (batch yields are changing)
- Synthesis in batch is limited by size
- Side-products (Wurtz-coupling, double lithiation etc.) reduced to a minimum

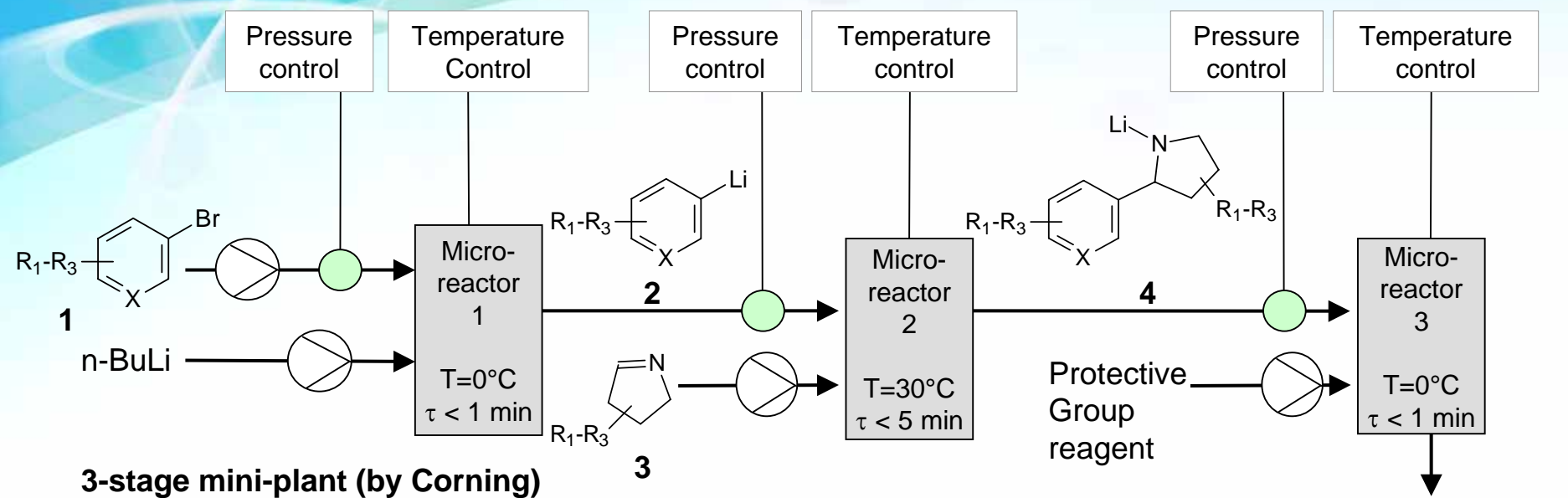
# Intercepting instable intermediates



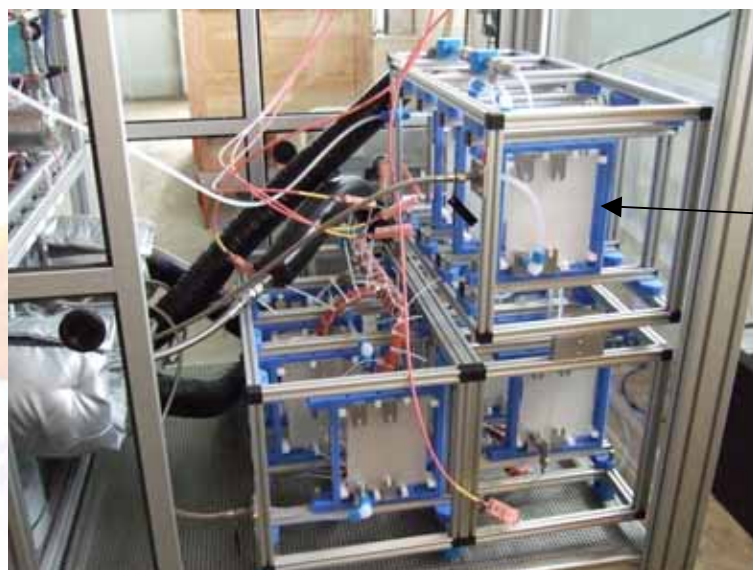
- Yield 55% → Output >3 kg/24h (development 3 months)
- Suppression of (Wurtz) side products by elimination of dosing time
- Li-intermediate unstable upon  $T > -30^{\circ}\text{C}$  → safe handling at 0 to  $+30^{\circ}\text{C}$  in MR  
→ Short contact time prevents degradation
- Impurity profile improved (compared to batch)
- Batch yields changing → Mixture from MR comes in constant quality



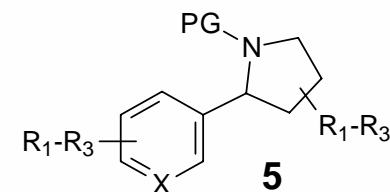
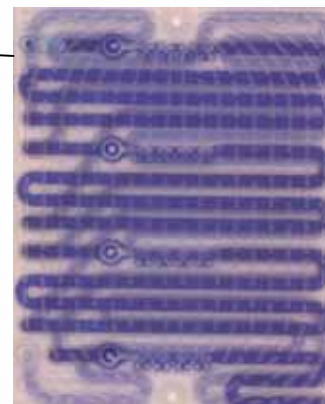
# Intercepting instable intermediates



3-stage mini-plant (by Corning)



Glass microreactor (active temp.-control)

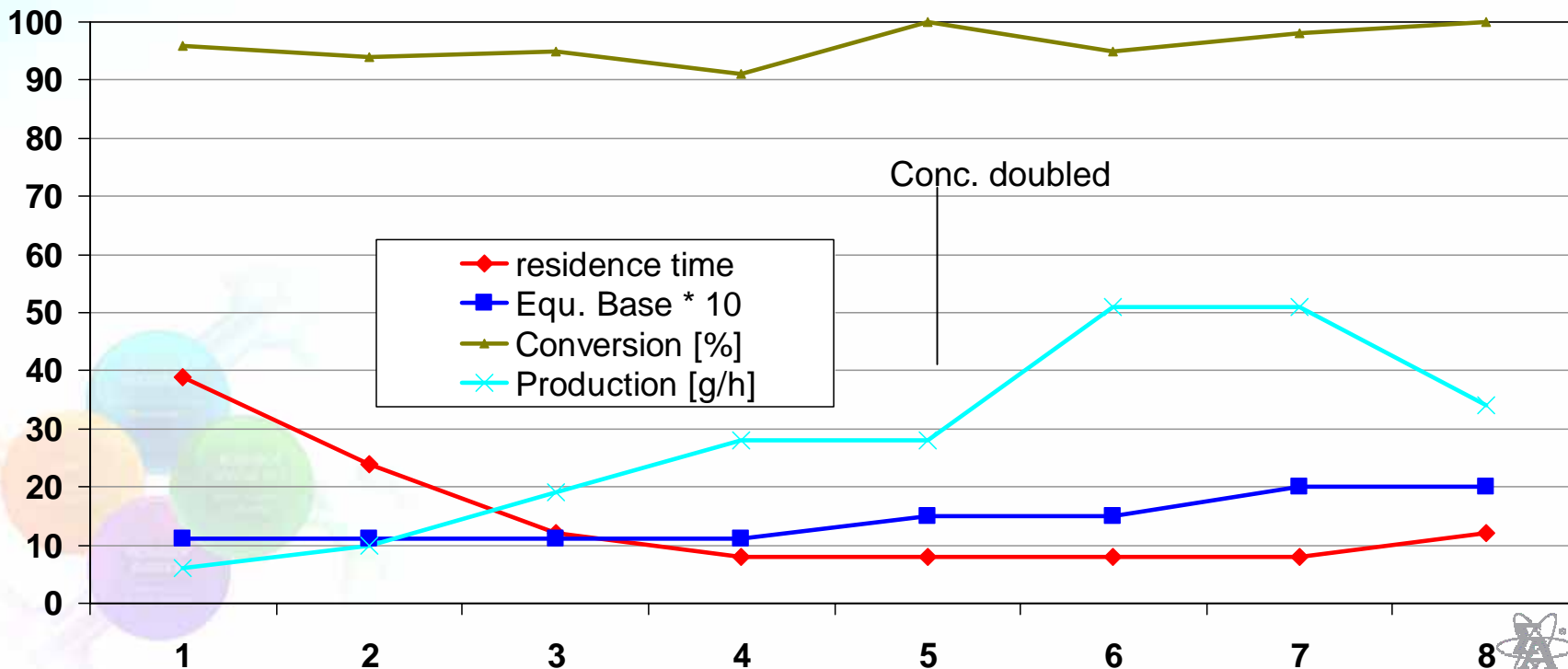


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# Ester cleavage of vitamin A derivative



- Cleavage conditions: Acetate X in THF, KOH in Ethanol: Water, temperature 60°C
- Product is sensitive to air, temperature, light → instant quench essential
- Final production capacity: 800 g/d
- Optimisation process is given below

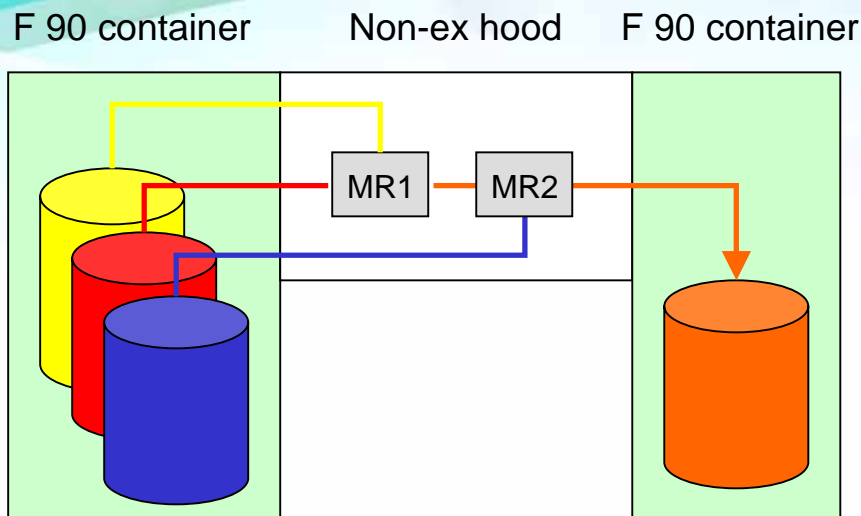


# Comparison batch process/microreactor process for vitamin A derivative synthesis

<b>Production of 500 g</b>		
	<b>Batch process</b>	<b>Microreactor process</b>
<b>Reactor</b>	20 lt Vessel	Microreactor (1.5 ml + RTU)
<b>Reaction conditions</b>	KOH in Methanol/Water	Feed 1: 1 M Acetate X in THF Feed 2: 2 M KOH
<b>Reaction time</b>	16 h	39 min
<b>Reactor time</b>	16 h	15 h
<b>Hours of work</b>	26 h	10 h
<b>Reliability</b>	low	high
<b>Upscale</b>	no	unrestricted
<b>Yield</b>	40%	68%

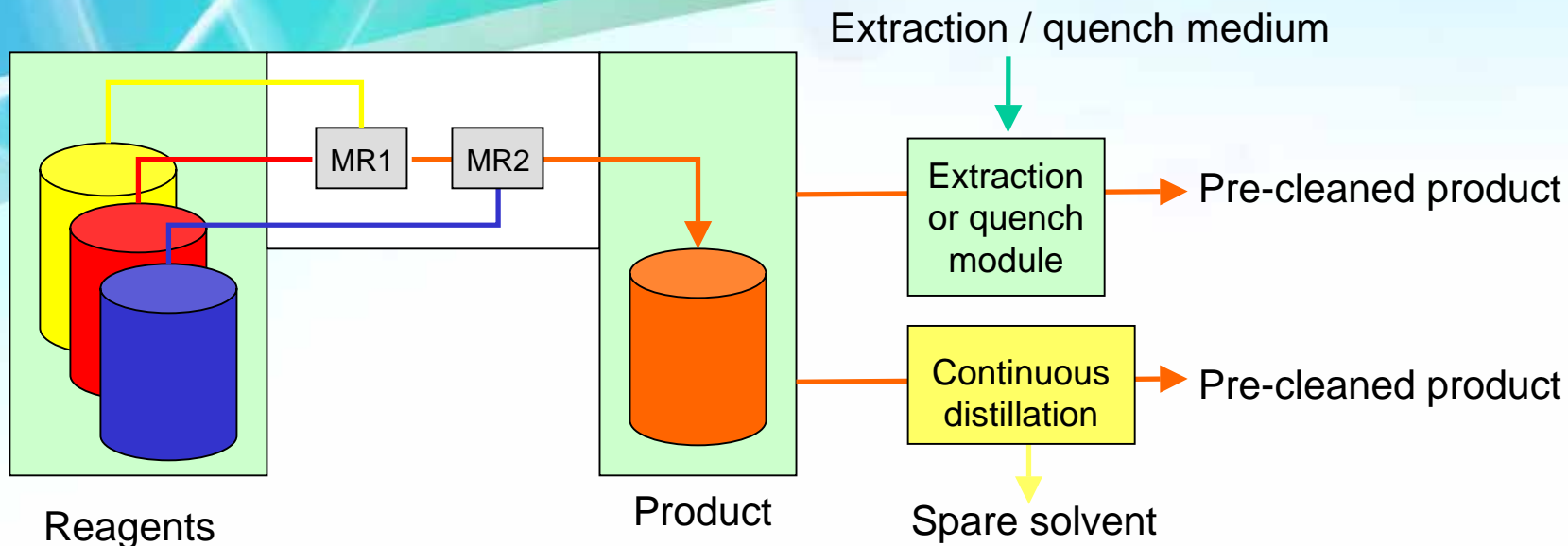


# Cost saving expectations for installations



- Storage vessel in Ex-protected area (each m<sup>2</sup> costs money!)
- Footprint for storage also contributes to installation costs.
- Time/space/yield for the reaction zone does not give a full picture
- Universal MR facilitate use as dedicated plants & cleaning

# Handling multi-kg campaigns



- Unquenched product stays in the container until **all** reagent passed the MR  
→ Degradation possible
- Product stability tests needed for long-term campaigns
- Continuous work-up is useful

## Output calculation

$$\text{Output (g/h)} = \text{Flow rate (mL/min)} \times \text{Conc (mmol/mL)} \times \text{MW (g/mol)} \times \text{Yield (\%)} \times 0.0006$$
$$153 \text{ g/h} = 10 \text{ mL/min} \times 1 \text{ ml/min} \times 300 \text{ g/mol} \times 85 \% \times 0.0006$$

→ 2.1 kg / 14 h



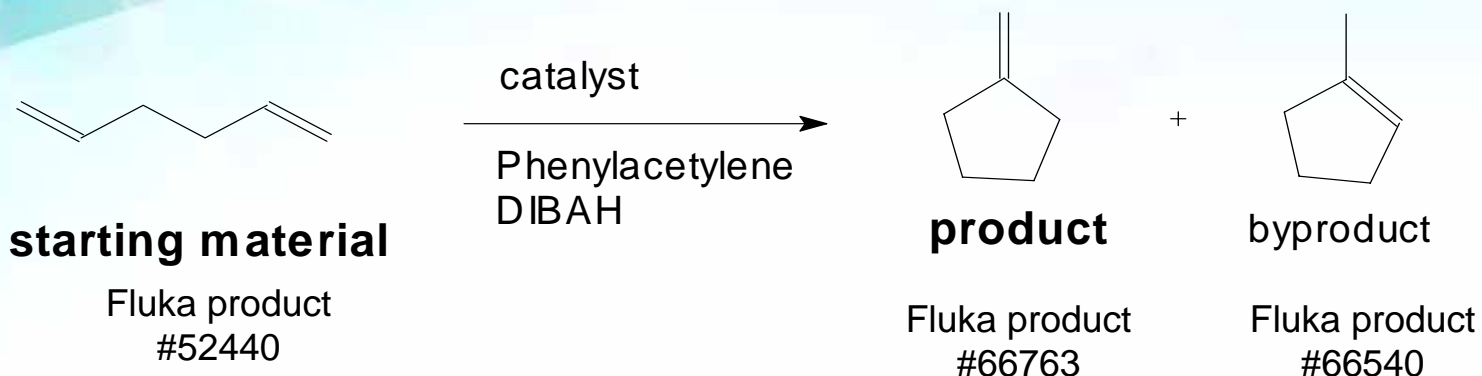
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# How can the advantages be used?

- General process development
- High exothermic/hazardous reactions  
(scale-up difficult due to safety reasons)
- Products which are instable under reaction conditions
- **Product profile improvement**
  - **Synthesis of methylenecyclopentane**



# Continuous synthesis of methylenecyclopentane



## • Crucial points

- High exothermic reaction
- Isomerisation observed upon extended contact time product/catalyst
- Specification 66763: Purity > 99%
- Batch process provided byproduct with similar b.p.  
→ Separation problems upon contamination

# Continuous synthesis of methylenecyclopentane

Exp.	Temp.	Product (%) 66763	By-product (%)
1	45°C	0.2	0.06
2	50°C	2.5	0.03
3	55°C	57	0.01
4	60°C	58.5	0.02

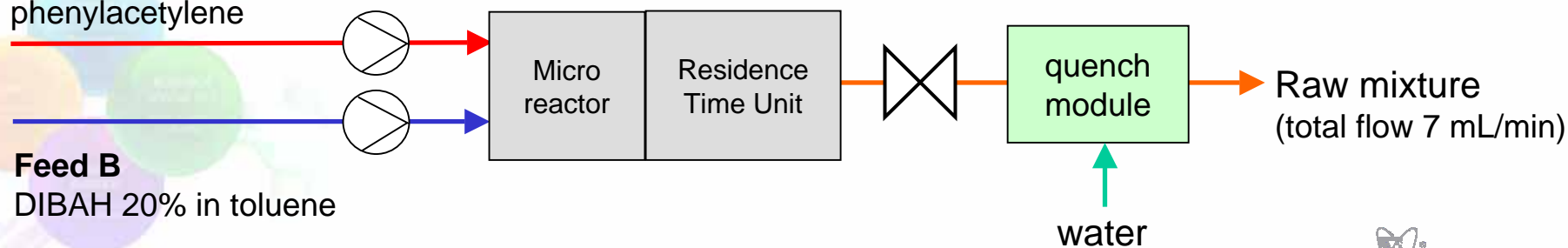
- Residence time: ca. 7 min
- Activation temp. of catalyst cloth to reagent boiling point → valve
- Synthesis using neat materials → output > 4 kg/24h

## Feed A

diene  
catalyst  
phenylacetylene

## Feed B

DIBAH 20% in toluene



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# Technology pushes innovation

- 2004**
- Purchase of integrated MRT-System as **enabling technology** for problematic batch synthesis (exothermic, side product formation)
  - Corporate production of retinol (Vitamin A alcohol, 180 k\$)
  - Further technology development (glass reactors)
  - Established knowledge network with manufacturers and users  
→ Identification of a “MRT starter kit“ as a market gap



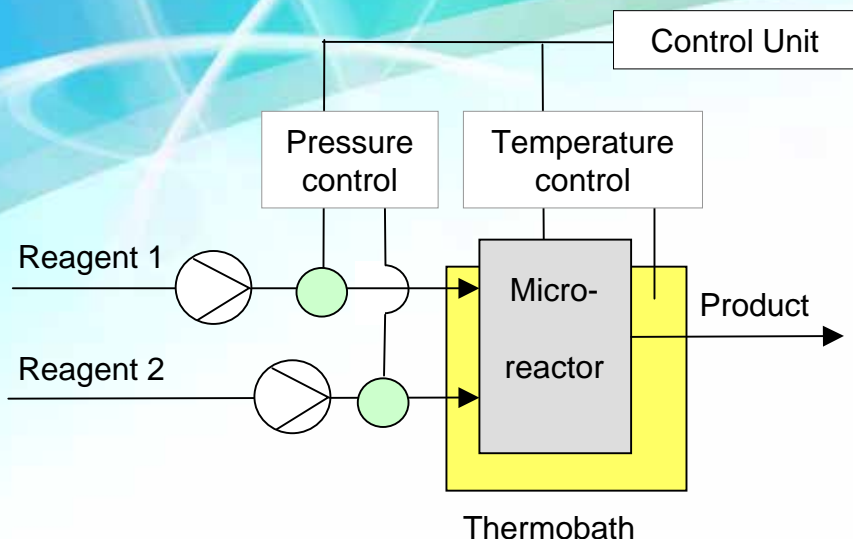
- today**
- Production of 40 catalog products
  - Several SAFC CS projects
  - Launch MEK #19979
  - Tech Transfer to prod., SAFC

...



19979

# Sigma-Aldrich Microreactor Explorer Kit 19979



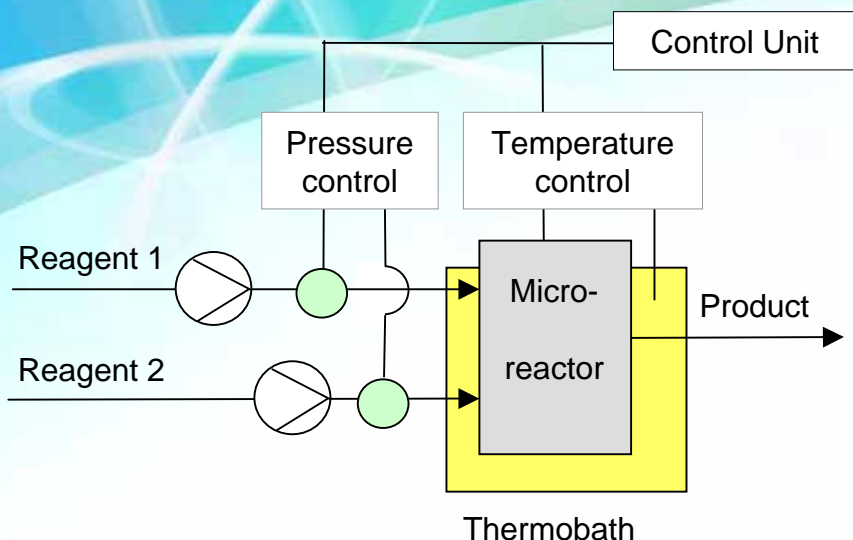
Sigma-Aldrich product #19979  
Market launch in April 2007

## Specifications

Flow rates:	0.2 to 15 mL/min/pump (full temp. range)
Volume microreactor:	0.85 mL
Volume residence time unit:	25 mL (PTFE tube, adjustable and expandable)
Reagent touching materials:	PTFE, borosilicate glass, ceramics
Temp. range:	-70 to 150°C
Max. inner pressure:	6.5 bar



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# Summary of industrial MRT aspects

- Handling benefits are strong arguments for MR application (2-stage set-up)
- Multipurpose MRs cover a wide range of synthesis demands
- Running synthesis simply in continuous manner offers broad spectrum of advantages. Sophisticated flow regime not always essential
- Besides classical measures (yield) product appearance and reliability count
  
- High flow rates preferred due to higher output
- Time/space/yield has to focus on the entire set-up incl. periphery
- Parameter control (flow/consumption!) is a must
  
- Future working field: (partial) continuous work-up

