The Limitations of Batch Processing and the Benefits of Continuous Processing for APIs

Oliver Maurer, Peter Poechlauer
DSM Fine Chemicals Nfg. GmbH & Co KG
Austria

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Continuous processing

..small structured reactors

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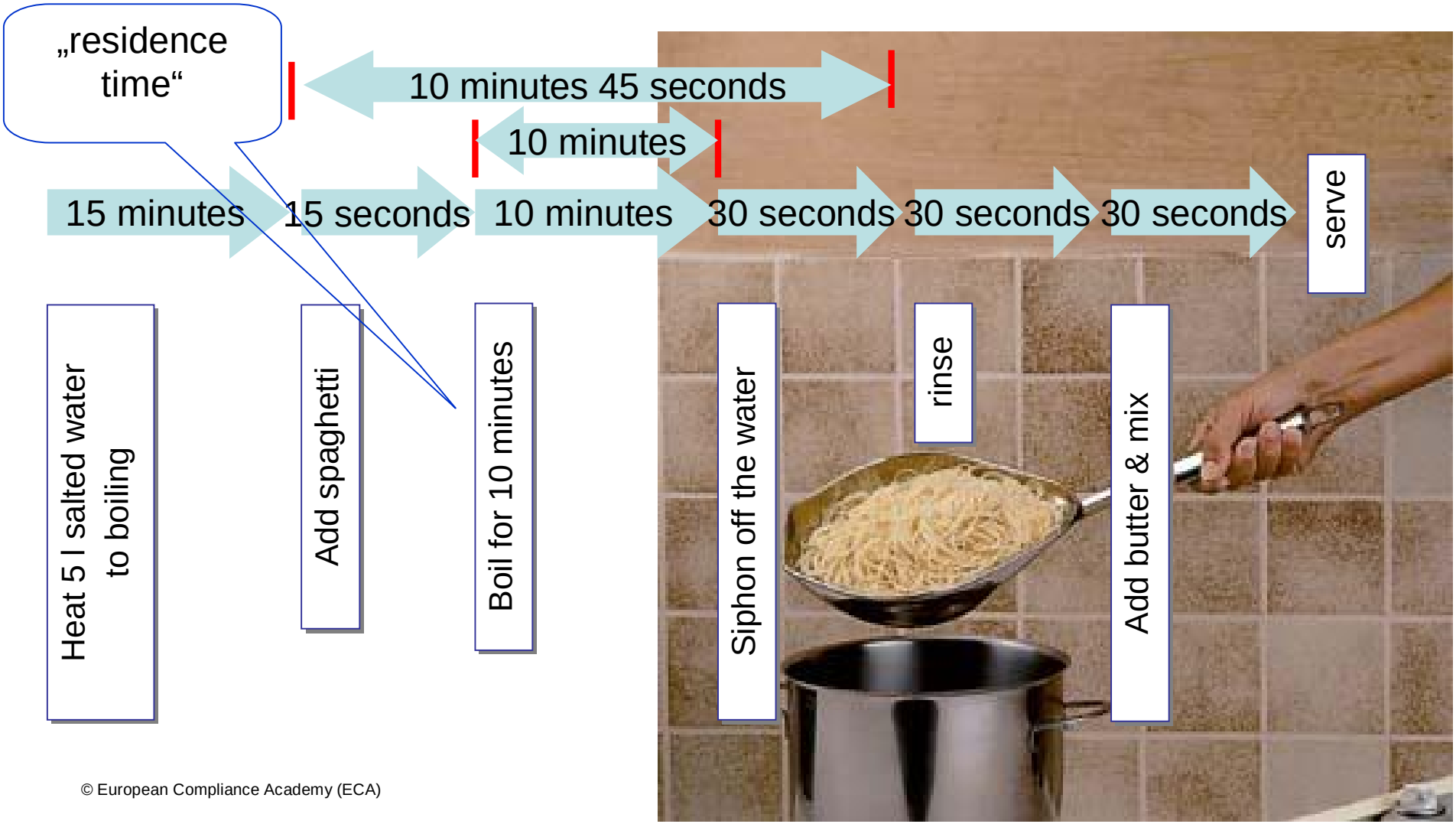
The limitations of batch processing

SERIOUS example: boil 500g spaghetti



The limitations of batch processing

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NOW: boil 500 kg spaghetti

17-25 minutes

10 minutes

30 minutes | 2-5 minutes | 10 minutes | 5-10 minutes | 5-10 minutes

„residence time“

15 minutes | 15 seconds | 10 minutes | 30 seco

Heat 5000 l salted water t

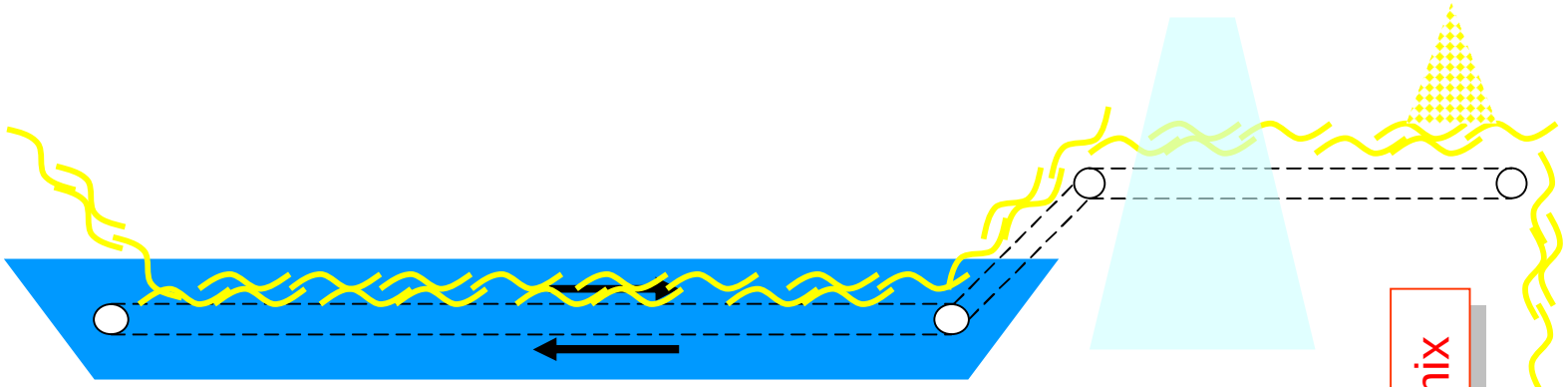
Add ti…(?)

Boil fo

Siphon o ater

THIS IS CALLED A „SCALE-UP PROBLEM

The „CONTINUOUS spaghetti boiler“



RESIDENCE TIME

add

boil

Siphon off

rinse

Add butter & mix

- „Scale-up“ much easier
- Wide parametre space
- Omit unnecessary operations
- Steady state
- „Quality by design“

The „CONTINUOUS spaghetti boiler“

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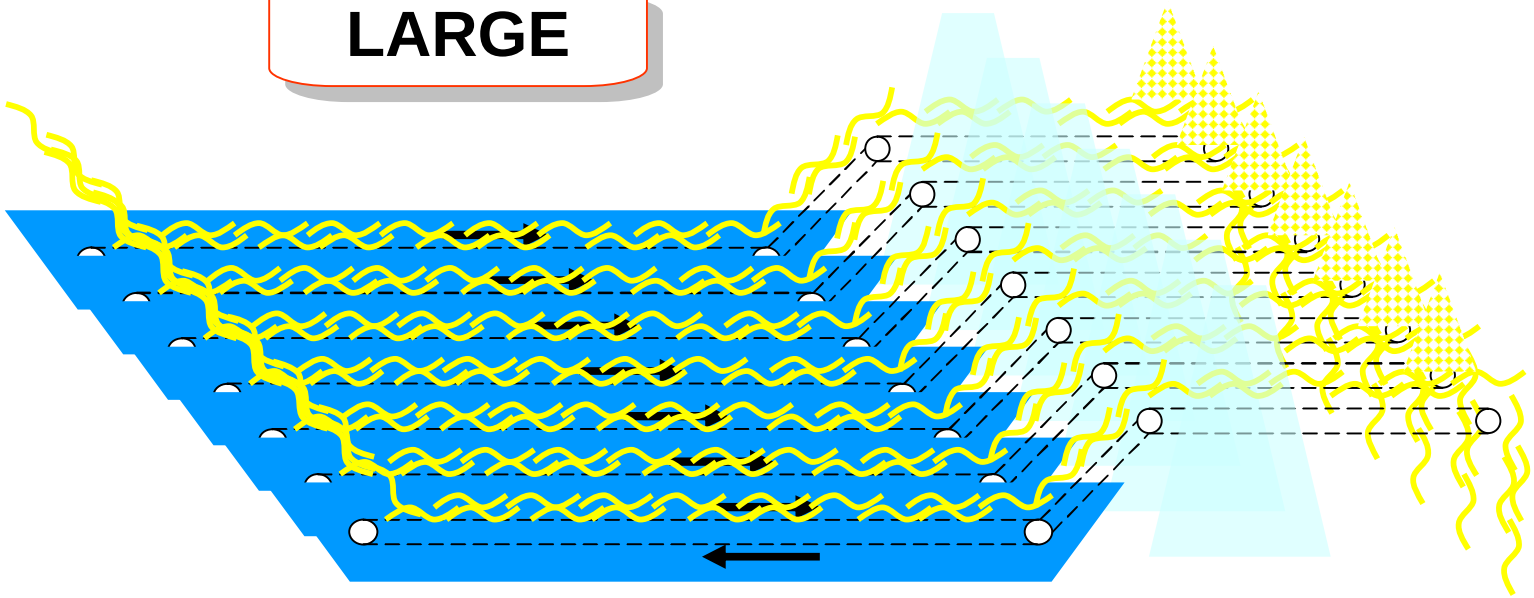
LARGE



To increase capacity, we do not „scale up“, but „number up“.
The machine **characteristics do not change with size**.

Continuous processing…

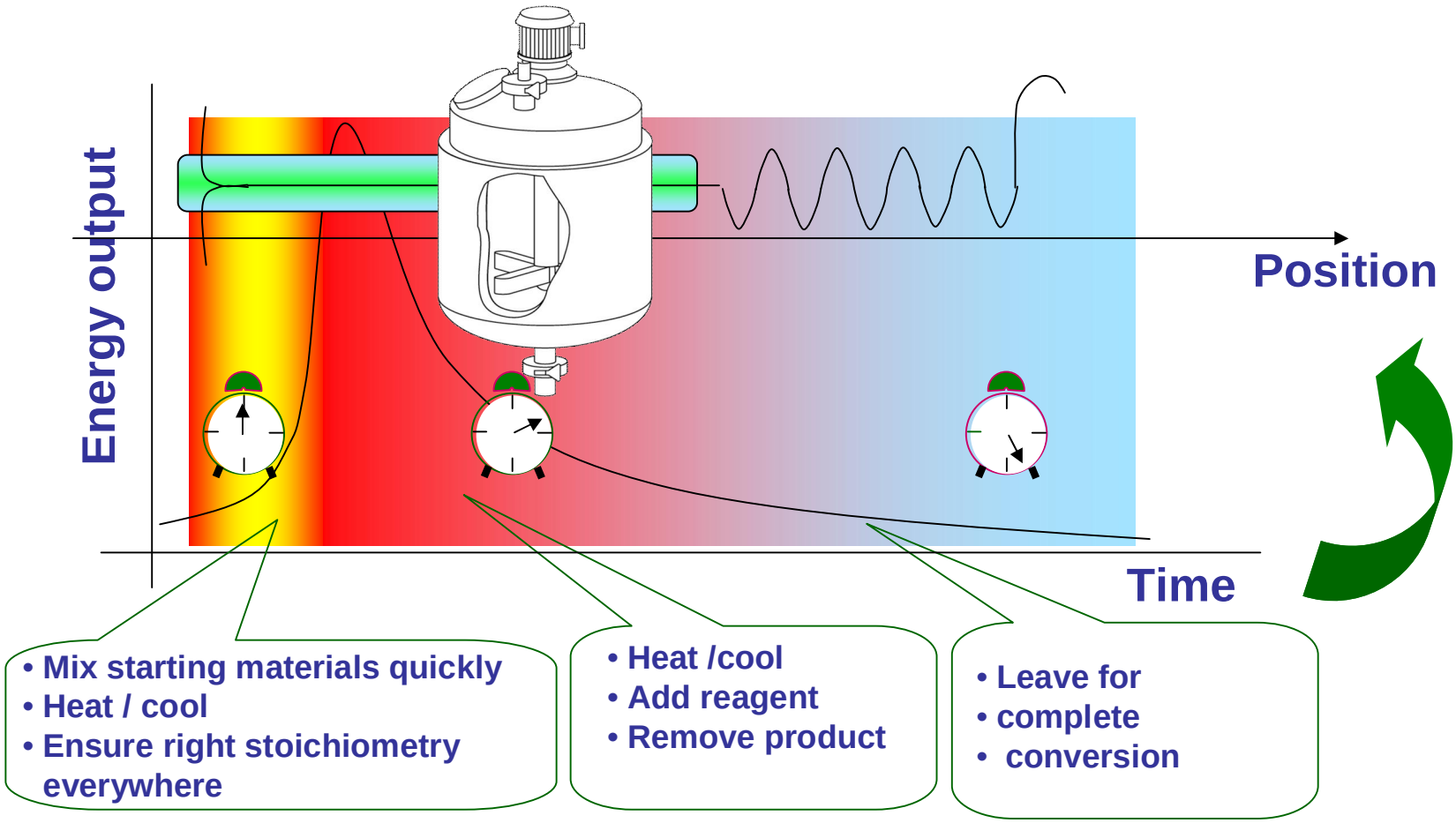
- is standard in base chemicals and in polymers
- is standard in food processing
- is entering pharmaceutical synthesis.

- allows to run processes
  - •that are „safe by design“ (not „safe by control“)
  - •that deliver „quality by design“

FDA actively supports the industry to develop such processes

The ideal reactor…

Quickly provides ideal conditions for every phase of the reaction:



Compare: process control…

Batch recipe:

Start stirrer

Heat jacket to..°C

Add …kg of A

Add in total ..kg of B

at a rate to keep

the temperaure below…°C

Stir at ..°C for ..more hours until IPC ok.

Continuous flow recipe:

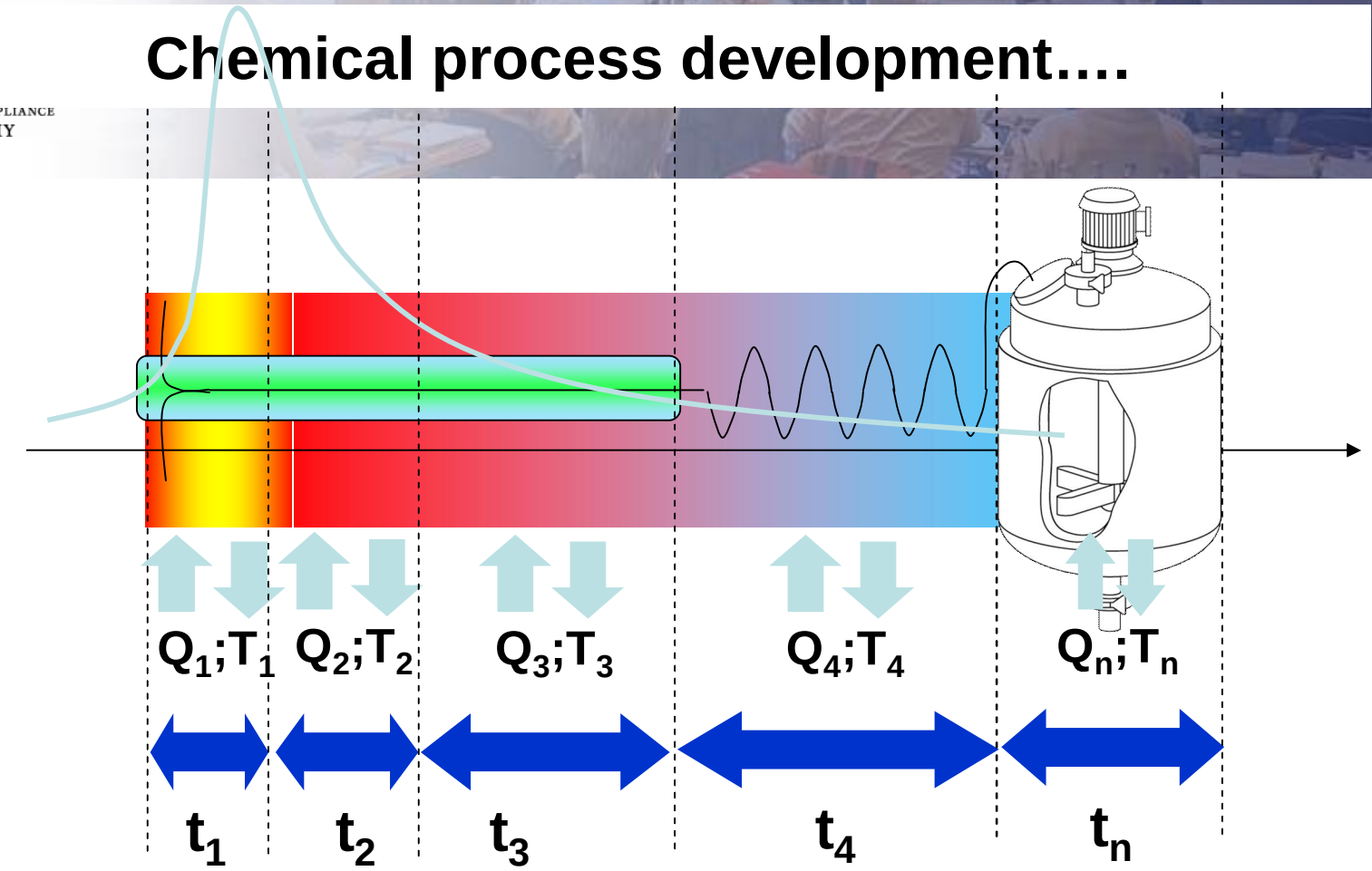
Heat system to..°C

Add A at a rate of…kg/h

Add B at a rate of…kg/h

(..until batch has desired size.)

Chemical process development….



…is “identifying the ideal environment” for every phase of a reaction

…and providing this environment to optimize it for

- process throughput figures
- product quality attributes

Basics: reaction enthalpy vs. heat transfer

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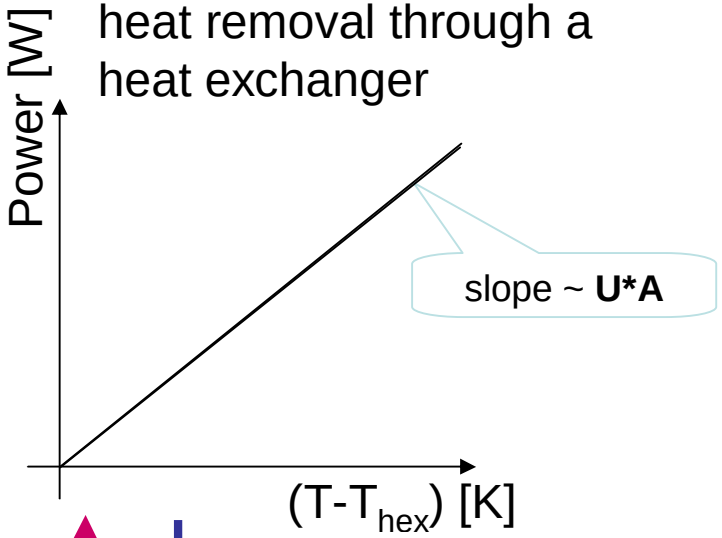
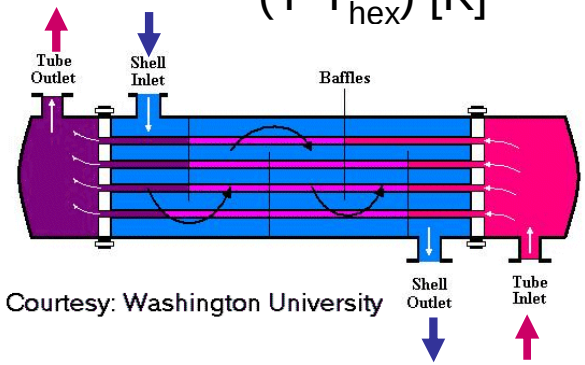
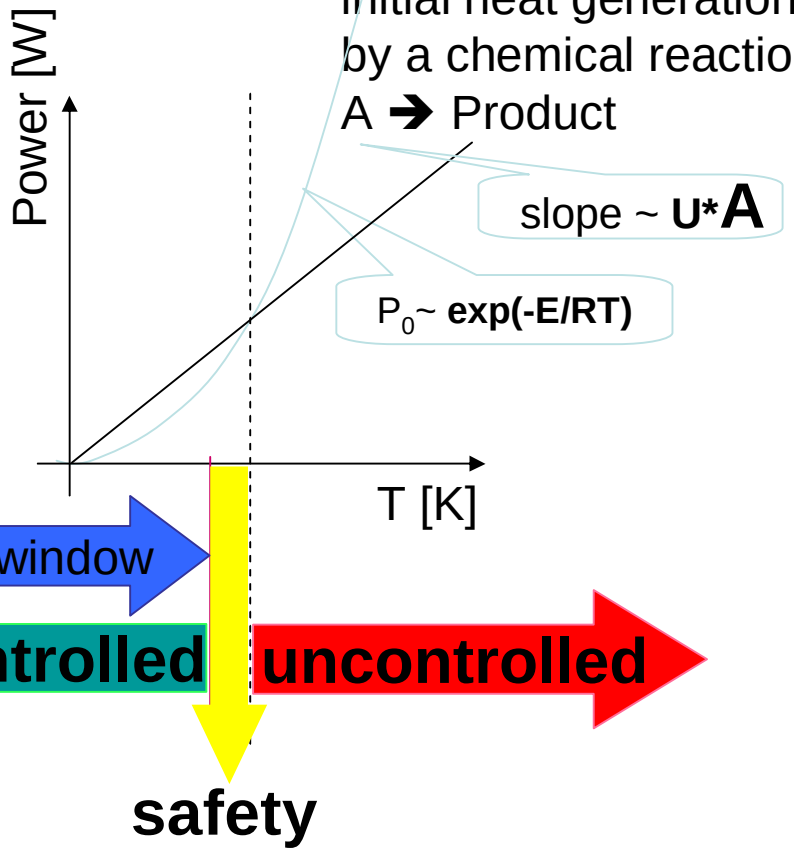
heat removal through a heat exchanger





Courtesy: Washington University

initial heat generation by a chemical reaction
A ➔ Product



slow down the reaction or adapt the plant

slowing down a reaction...

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“tricks”:

dilute with solvent

dose reagents slowly

run at (very) low temperature

reflux cooling

avoid fast reactions

use “mild” equivalents

of reagents

cost:

larger plant

additional unit operations

costly infrastructure

limited solvent choice

safety cost

longer synthetic routes

reagent costs

...requires additional process control

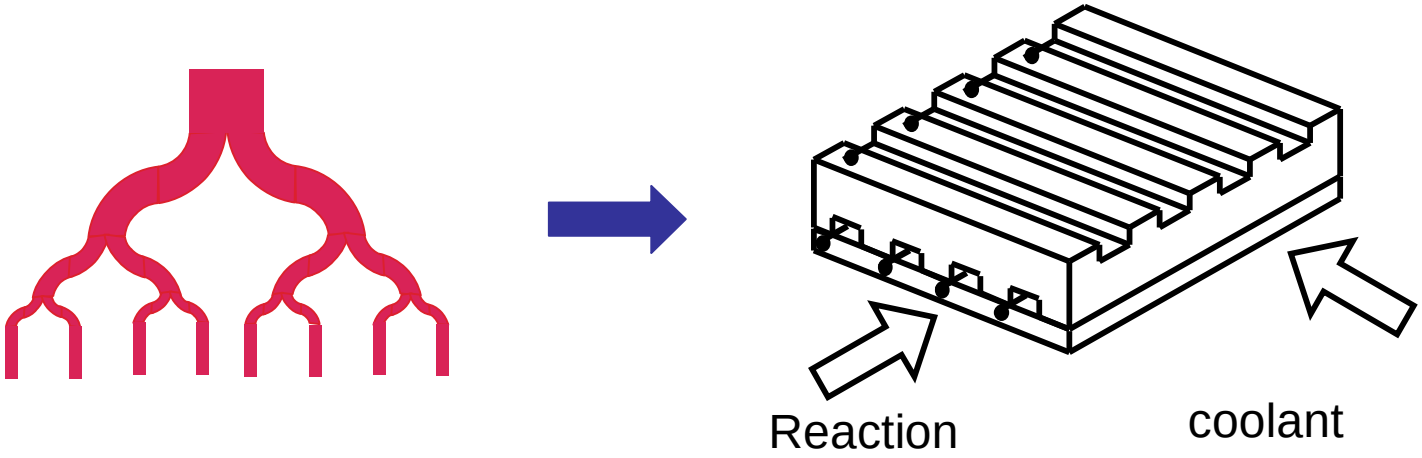
...creates a larger environmental footprint

Micro Reactors...

Micro reactors are continuously operated machines that allow strict control of (phases of) reactions that

- **are very fast**
- **are exothermic**
- **use hazardous materials.**

Their interior is divided into small compartments with large heat exchange areas.

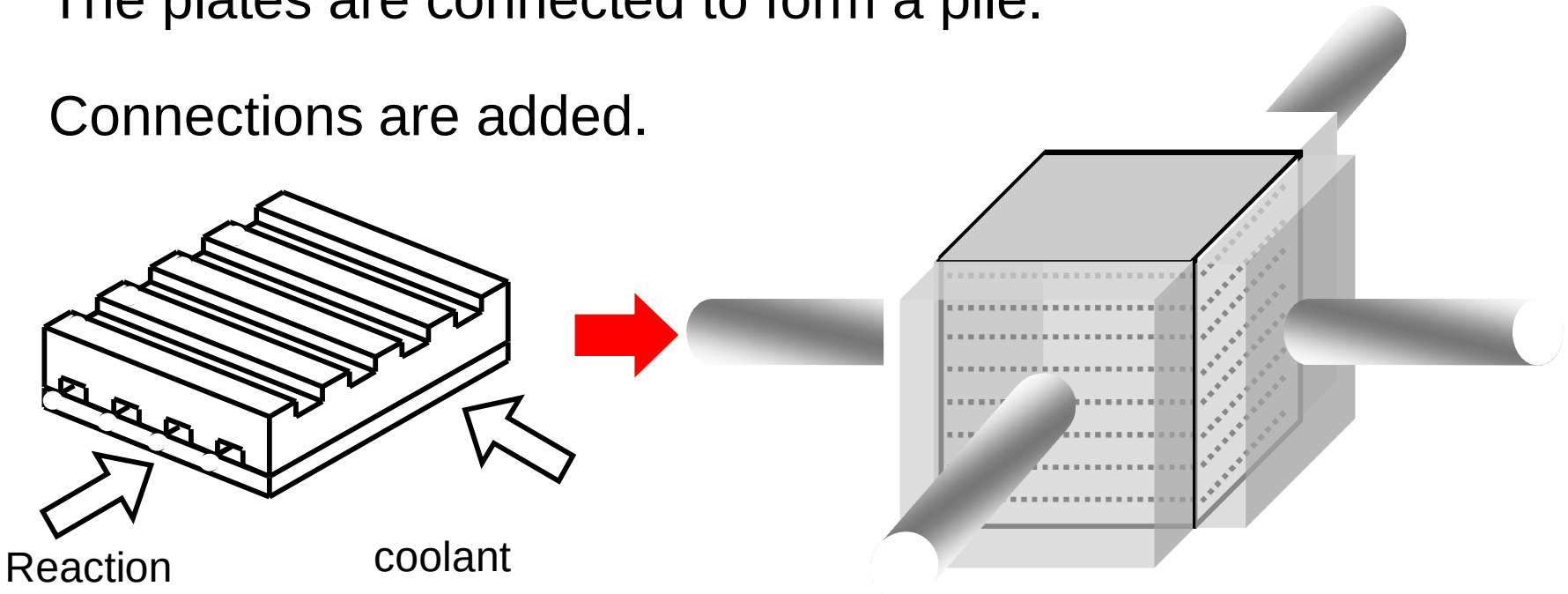


How to build such a device?

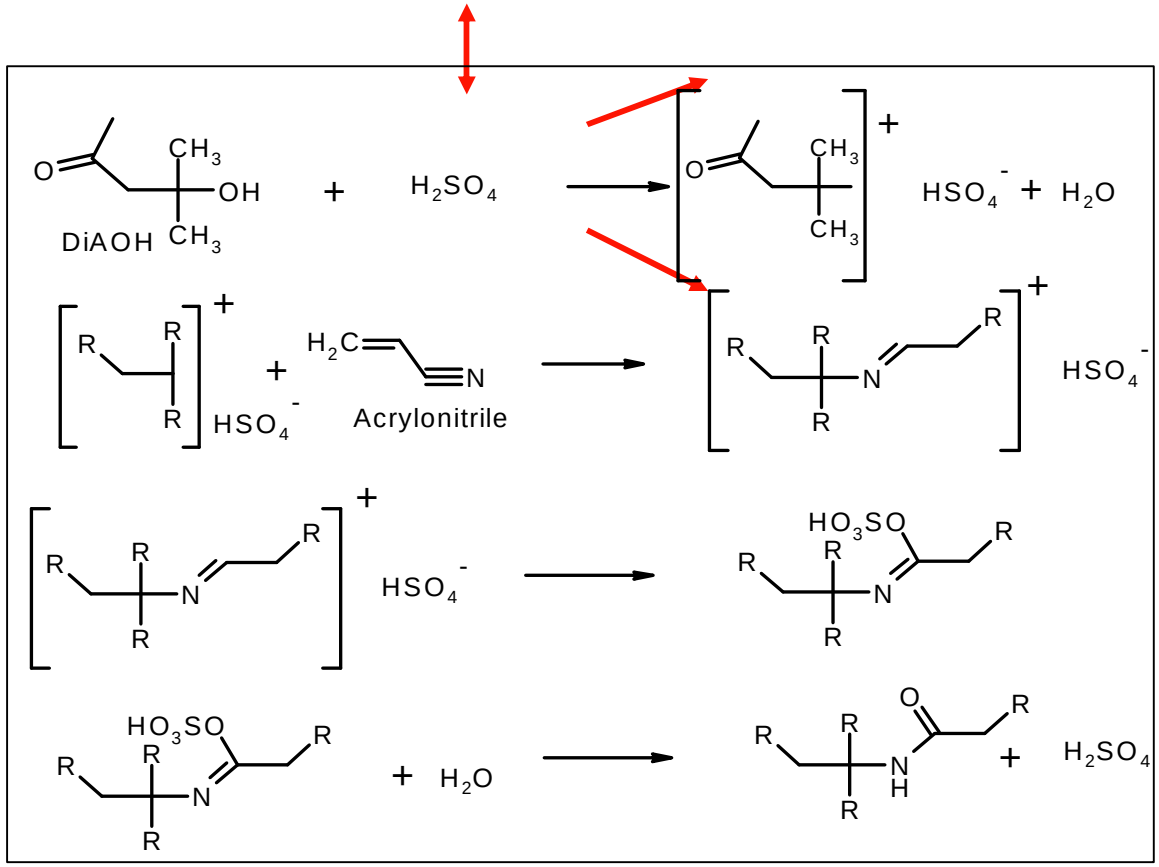
Pipes, tubes, mixers are built as surface structures on plates.

The plates are connected to form a pile.

Connections are added.



Example 1: synthesis of diacetone acrylamide



Fast !
exothermic

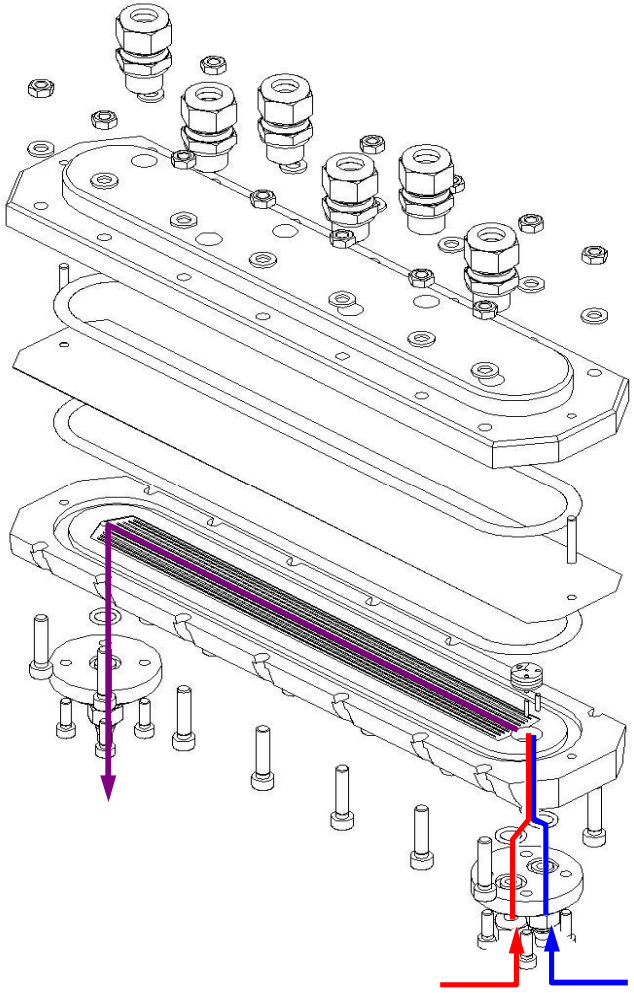
Selective?

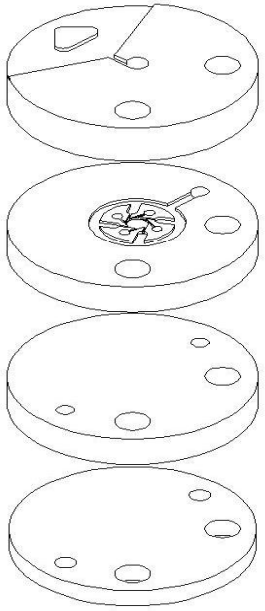
…multi step:
Exothermy is
not parallel to
„conversion“

Experience: what did we do?

We used a micro reactor custom designed by IMVT to develop a scalable lab synthesis of our product.

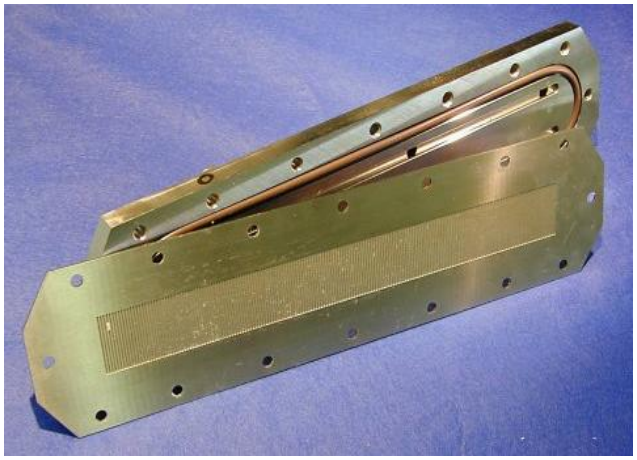
IMVT designed a production scale reactor based on the DSM lab data

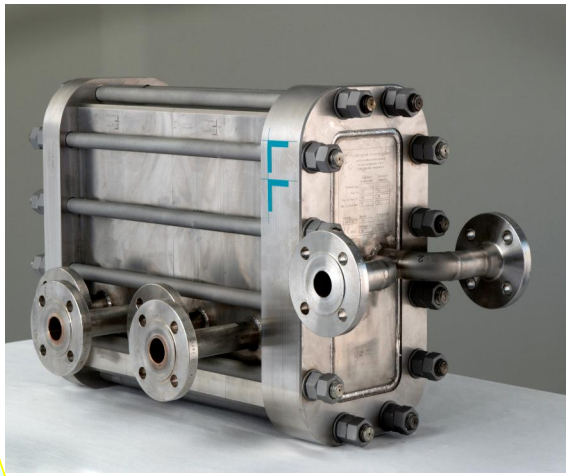




Production Reactor: Design & Development

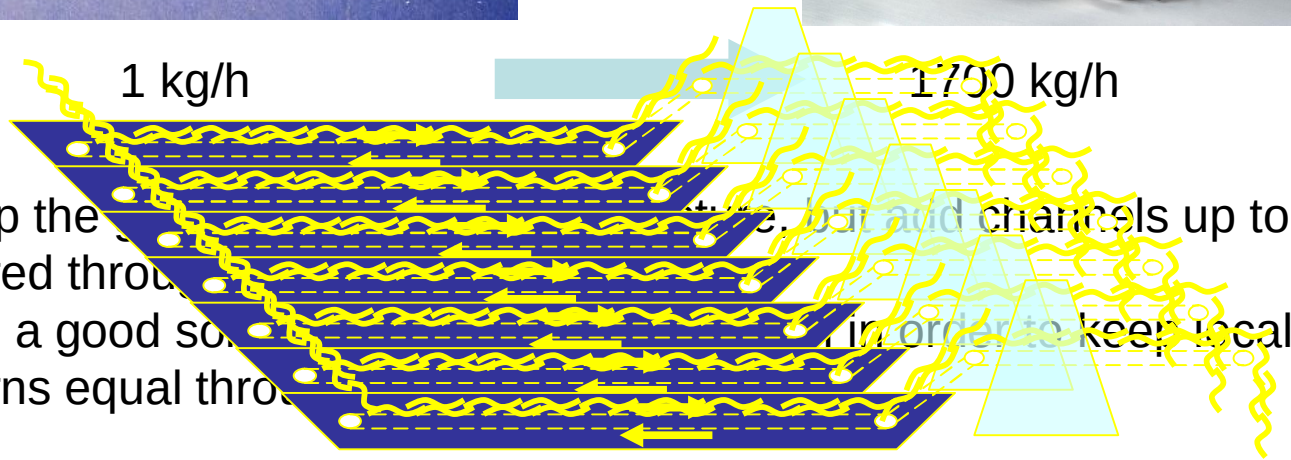
Scaling up a microreactor





1 kg/h

1700 kg/h



• Keep the [illegible] channels up to the required throu[illegible]

• Find a good so[illegible] in order to keep local flow patterns equal thro[illegible]

Results of production

- Production reactor was operated during several months in 6 production campaigns
- >1500 tons of product
- Same improvement of chemical yield as in lab – saving raw materials and waste costs.
- Still improvements possible…

Key success factors of implementation

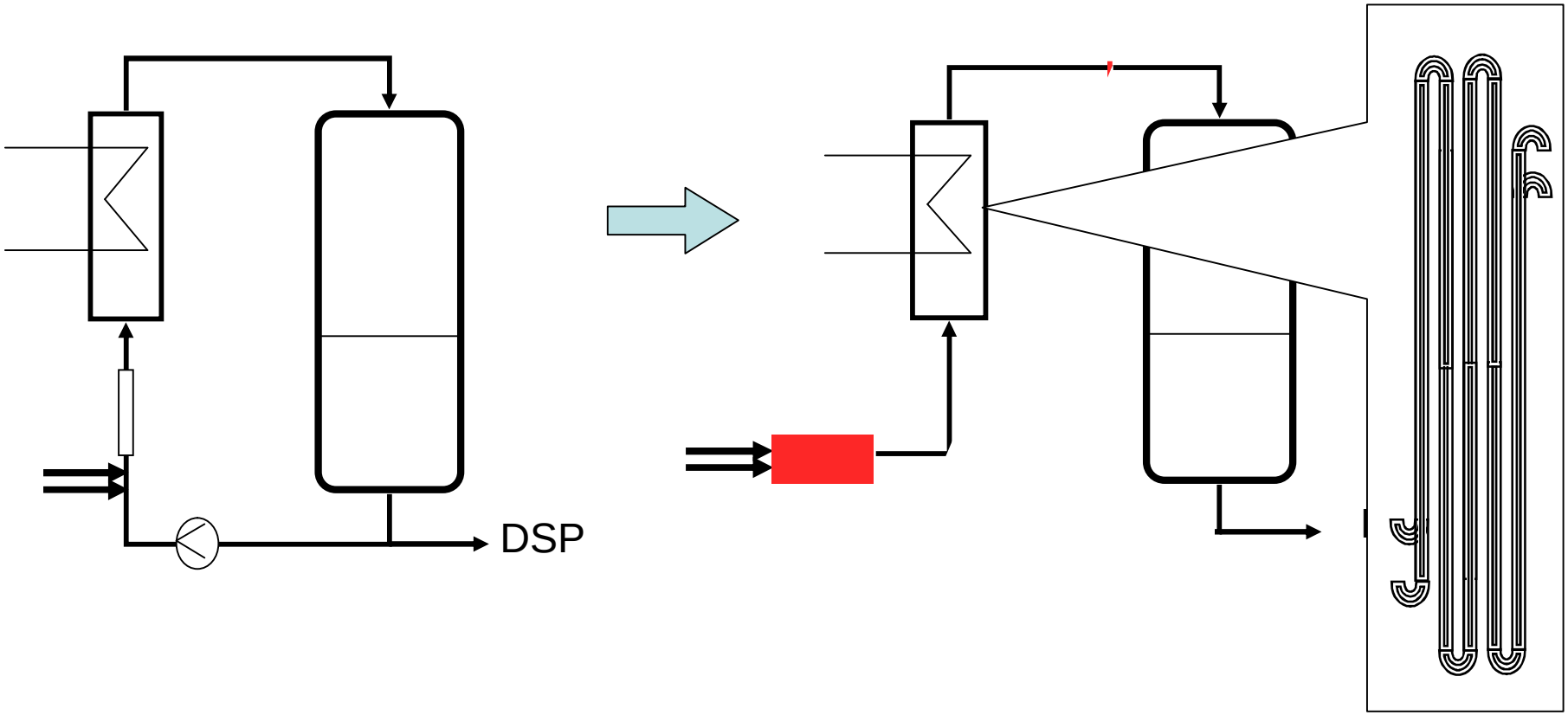
As a first step of implementation, the micro-reactor did not *replace* an existing installation, but was *added* to increase selectivity.

➔ The change to the production plant was *minimally invasive.*

The transition from fed batch to continuous operation was simplified by using the initial reaction vessel as buffer tank.

➔ The operation of the micro reactor was, within limits, decoupled from the work-up.

„minimally invasive“ plant reconfiguration

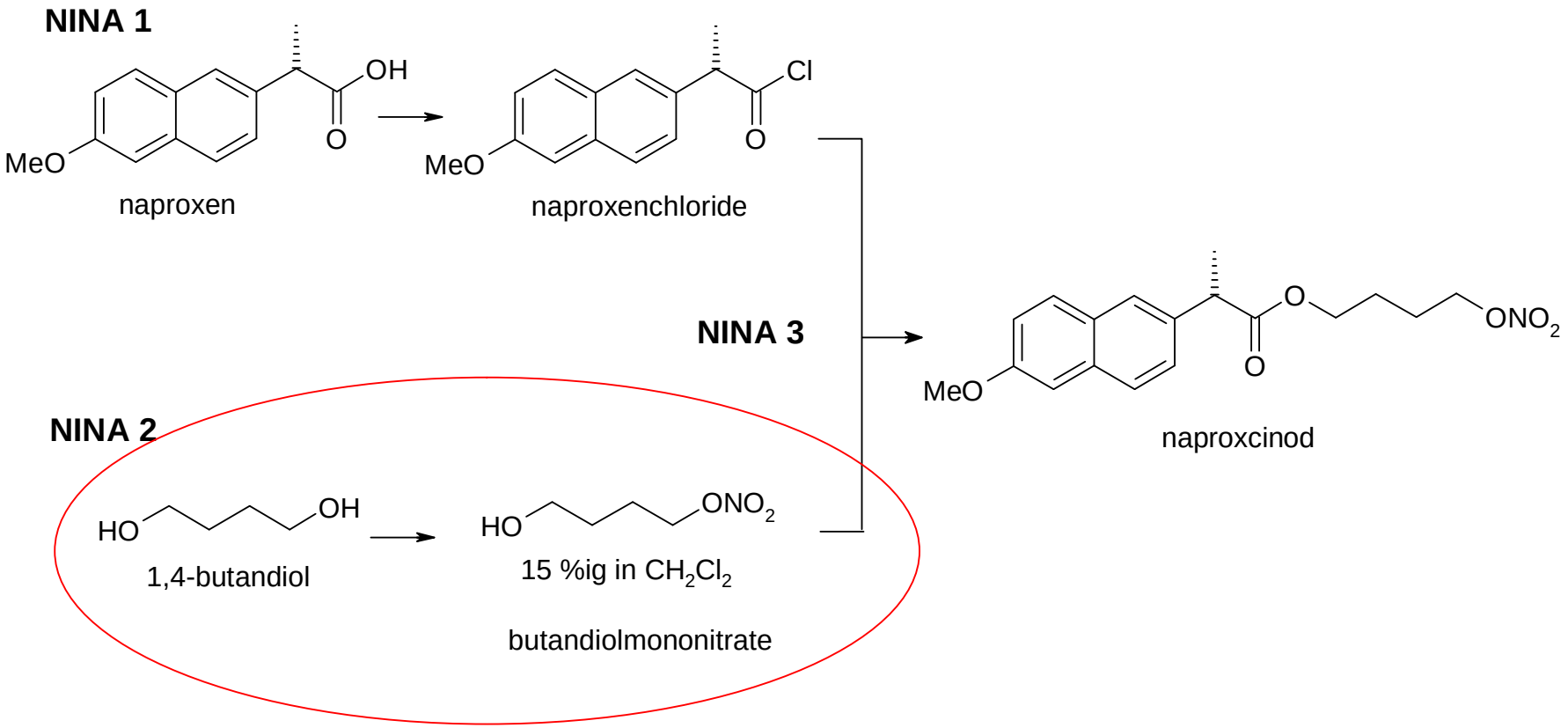


Pinning down further applications

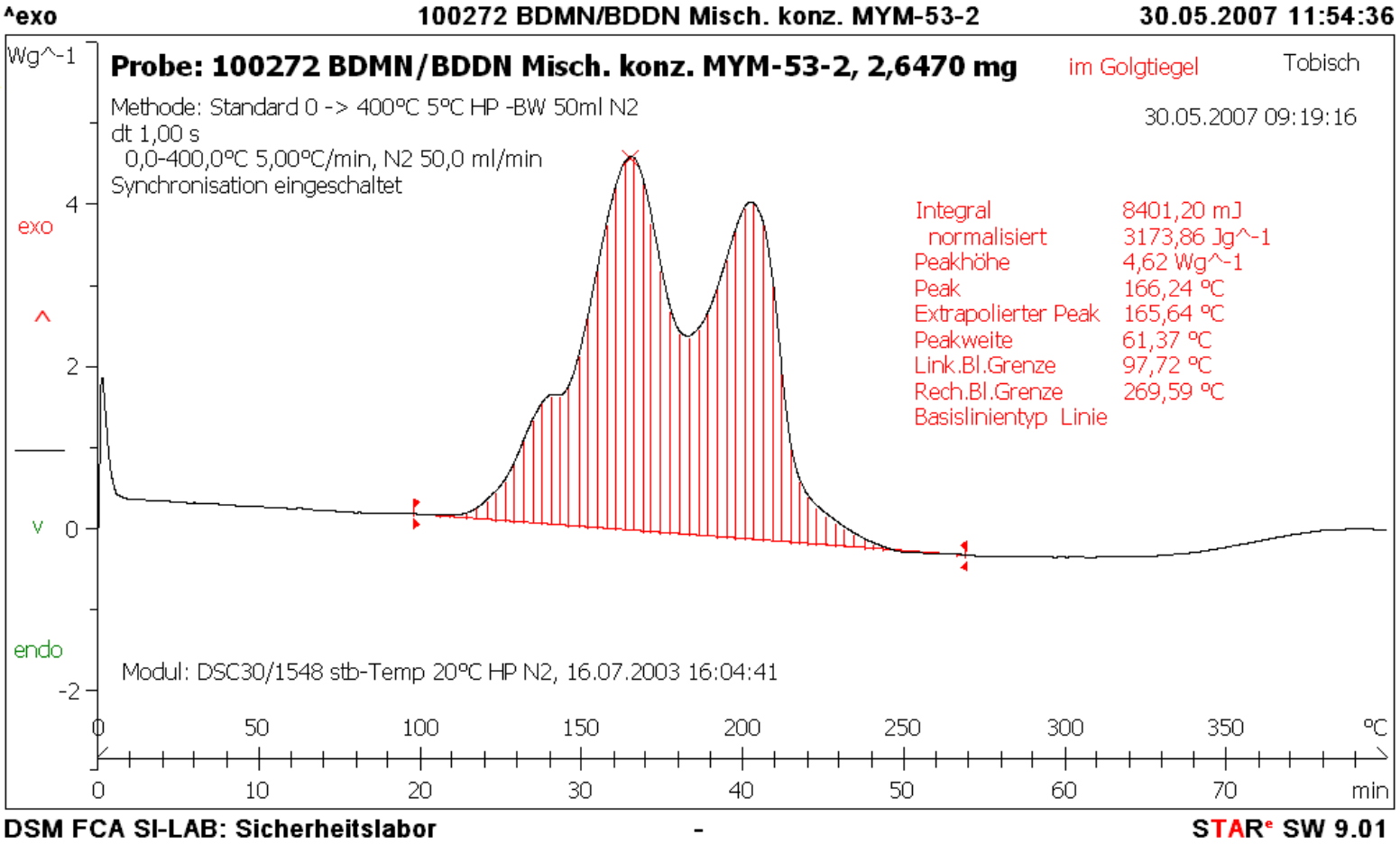
Look for „fed batch“ applications in the plant („reaction mass is circulated through a heat exchanger and reagent is added to the loop at a rate to keep the temperature below xx°C“)

Look for time consuming operations or reactions: (“reagents are mixed at 40-50°C and after 2 hours the mixture is gradually heated to 90°C and kept there for 2 more hours to complete the conversion”)

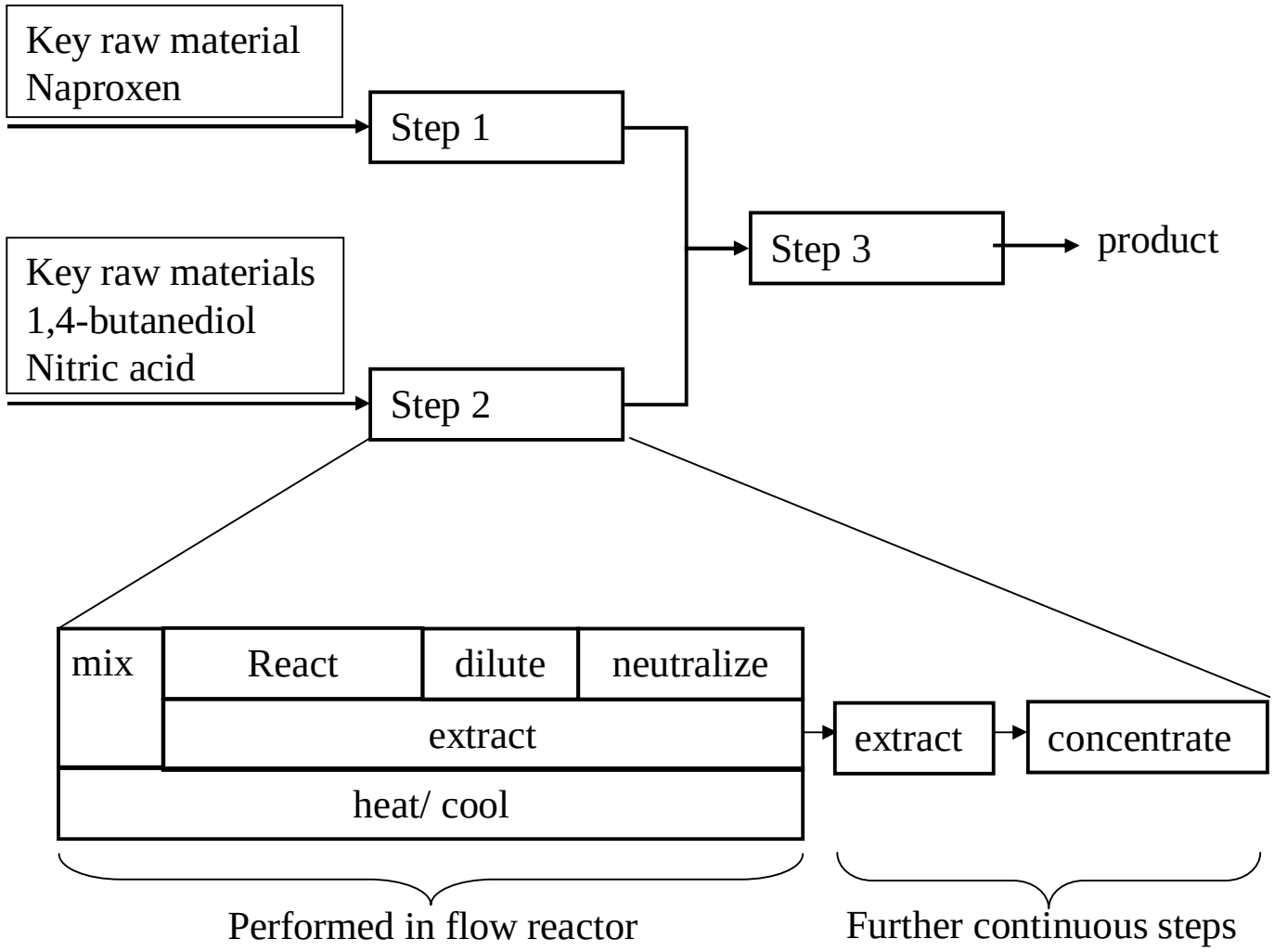
Example 2: pharma intermediate



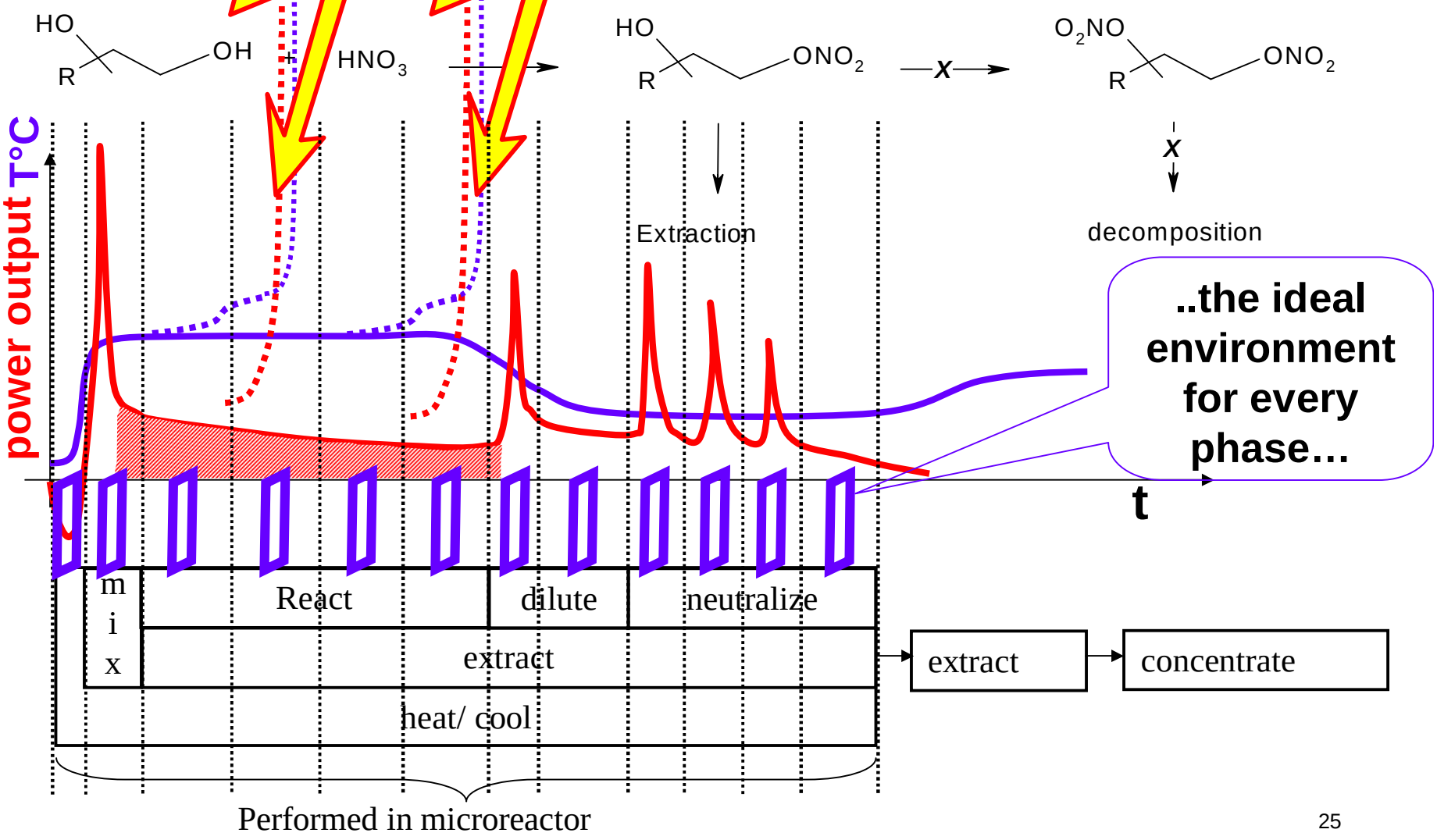
Vigorous decomposition..



Process – unit operations



Process chemistry of a nitration



A micro reactor in production

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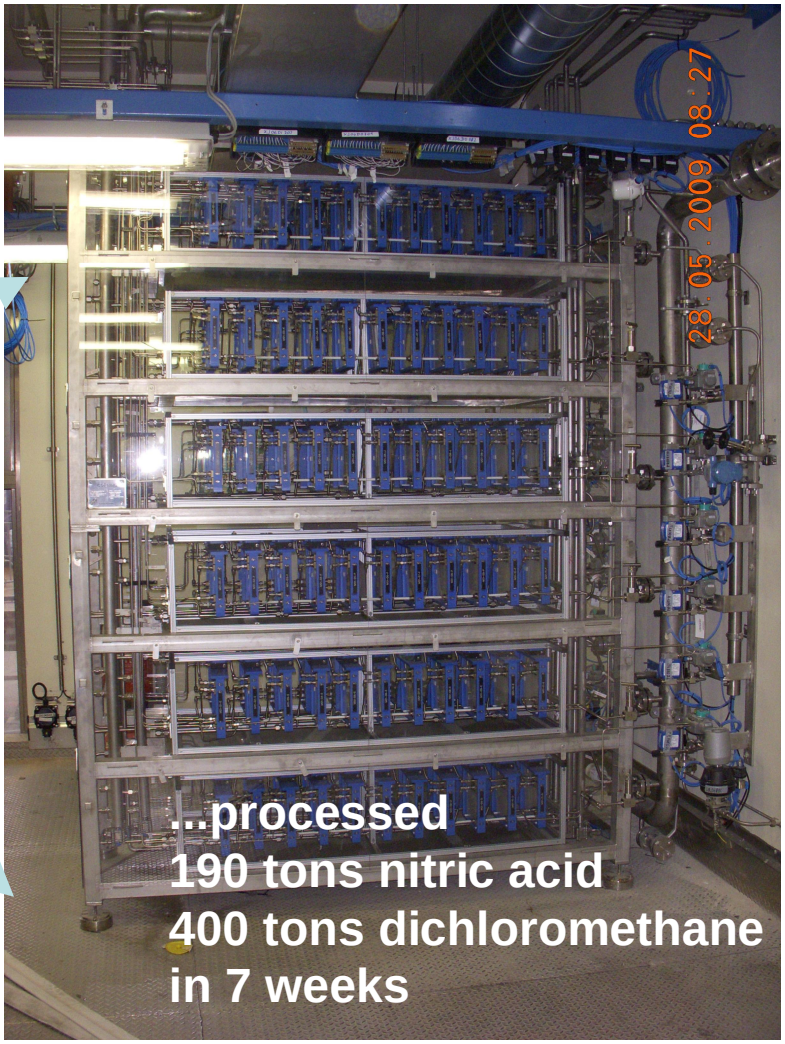
we parallelized a “modular lab reactor” to reach desired productivity

…under cGMP !

large-scale micro reactor in B700

x20



micro reactor in B700 – next generation

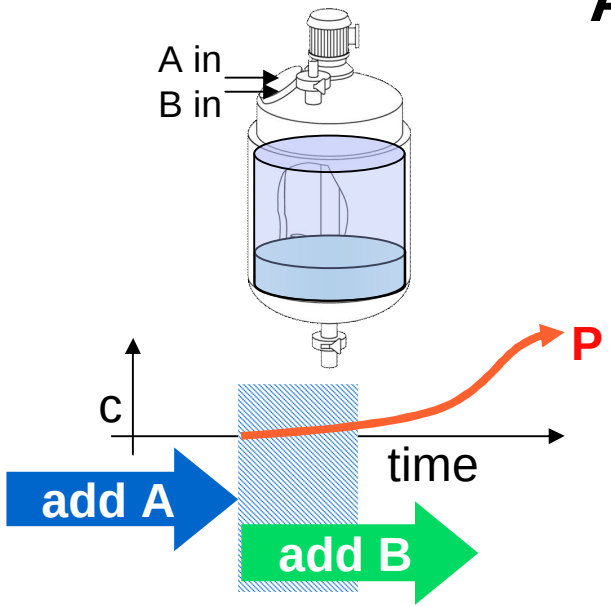
…a break…

Translate a batch process into a flow process:

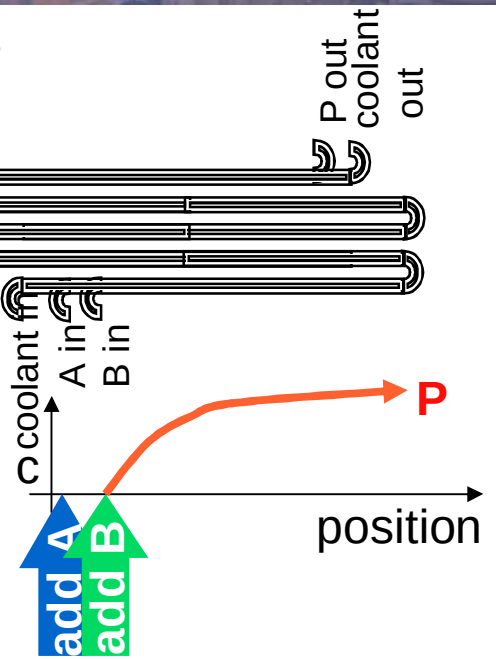
- Consider the “processing history” of a volume element of a reaction mixture
- Differences, equivalencies.
- Reactor dimensions
- Exercises

Differences in processing history

A + B ➔ P



large excess
of A over B



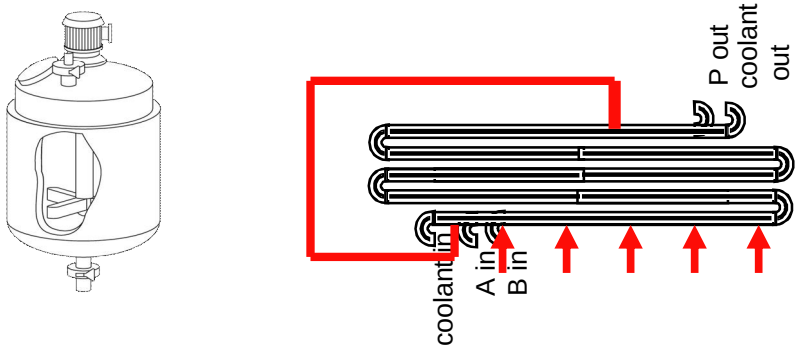
constant ratio
of A and B

“feed A and B”

“to A add B”
“co-feed A and B”

Ratio of A and B changes constantly
Volume & stirring change constantly
What else ?

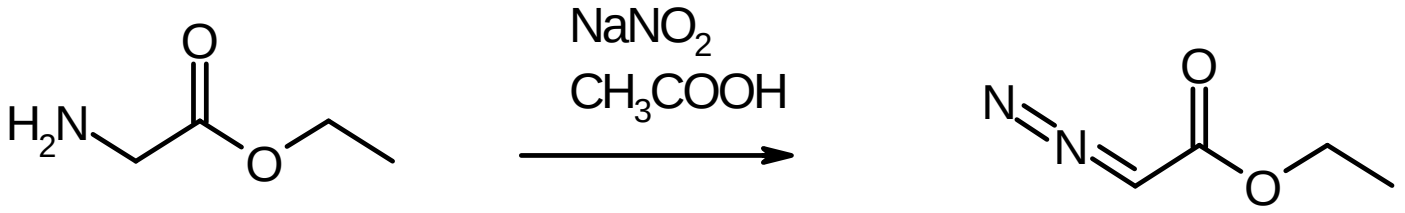
relation: stirred tank / tube reactor



Feeding regime	equivalent	comment
Add A; add B slowly to keep [B] small	Constant inflow of A multiple addition of B	Equivalent; better T-control of reactor
Co-feed A and B into reactor until final volume is reached	constant inflow of A and B into product recycle loop	mixing behaviour / heat removal in vessel is constantly changing
A+B➔P➔Decomp.:lower temp to avoid formation of Decomp.	tune length of pipe. quench at exit	pipe allows quick reaction while minimizing formation of Decomp. **NO** recycling
P1⬅A➔P2 with E1>E2 (E=act.energy) To get P2 decrease the temp	To get P2 decrease the temp.	no difference

In-house example: Ethyl diazoacetate

The synthesis of ethyl diazoacetate is seemingly simple:



ethyl aminoacetate *HCl
(glycine ethyl ester *HCl)
103.12
C4H9NO2 * HCl

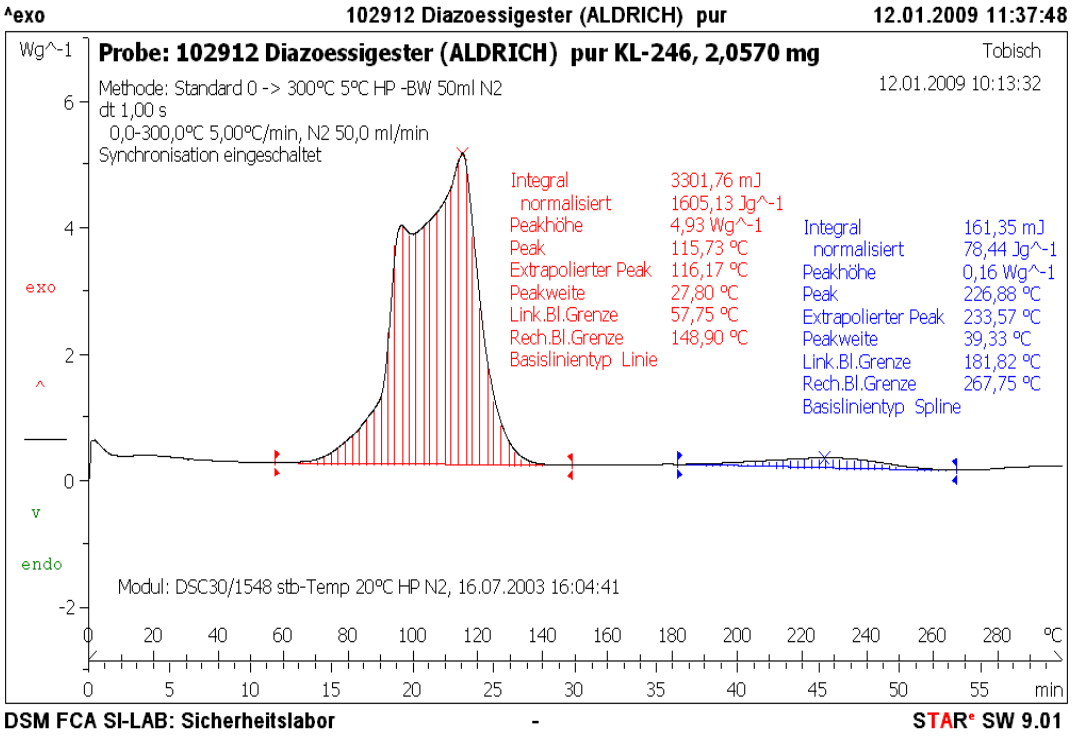
ethyl diazoacetate
114.12
C4H6N2O2

"To a cooled acidic solution of glycine ethyl ester hydrochloride add sodium nitrite solution and extract the product with an organic solvent".

Ethyl diazoacetate (EDA)

Pure EDA is dangerous:

- Start of decomposition at 65˚C
- Energy of decomposition 1605 J/g
- Positive result in „falling hammer" test" at 29,4 J



Do not transport
Do not store
No mineral acids
No metal ions

Pure product removed from supplier catalogue

How to produce it safely?

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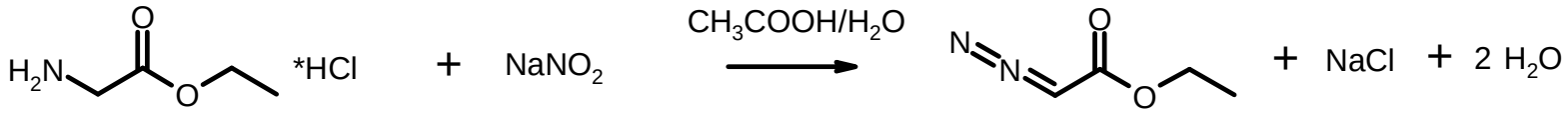
"To a cooled acidic solution of glycine ethyl ester hydrochloride add sodium nitrite solution and extract the product with an organic solvent".



ethyl aminoacetate *HCl
(glycine ethyl ester *HCl)
103.12
$C_4H_9NO_2 * HCl$

A + **B**

sodium nitrite
69.00

P

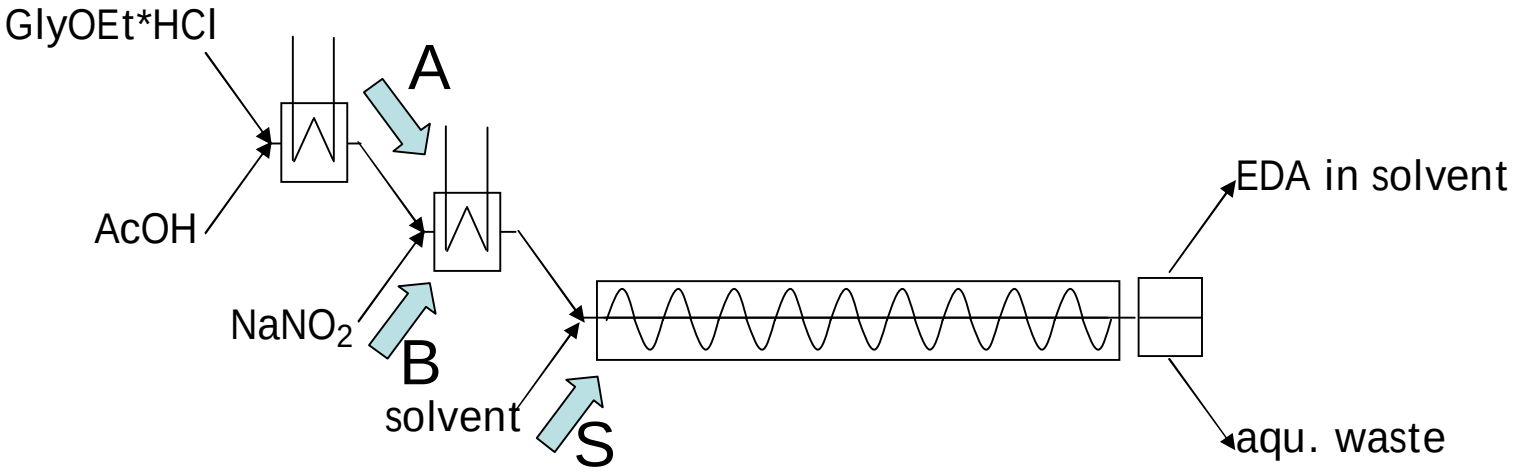
ethyl diazoacetate
114.12
$C_4H_6N_2O_2$ soluble in org. solvent

P $\xrightarrow{1605J/g}$ $\mathbf{P_{dec} + N_2}$

Let us take the following **fictitious or simplified figures**

- use 2mol/l solutions of A and B each, Density =: 1kg/l
- cp of aq. solution =: 4 kJ/kg*K; cp of org. solution =: 2kJ/kg*K
- Use an aqueous / organic phase ratio =: 1
- assume 1 min in total for reaction plus extraction yields approx. 100% P
- installation is in operation for 8000h/yr

Ethyl diazoacetate: flow equivalent of lab recipe:



"To a cooled acidic solution of glycine ethyl ester hydrochloride =:A
add sodium nitrite solution =:B
and extract the product with an organic solvent" =:S.

How to produce it safely?

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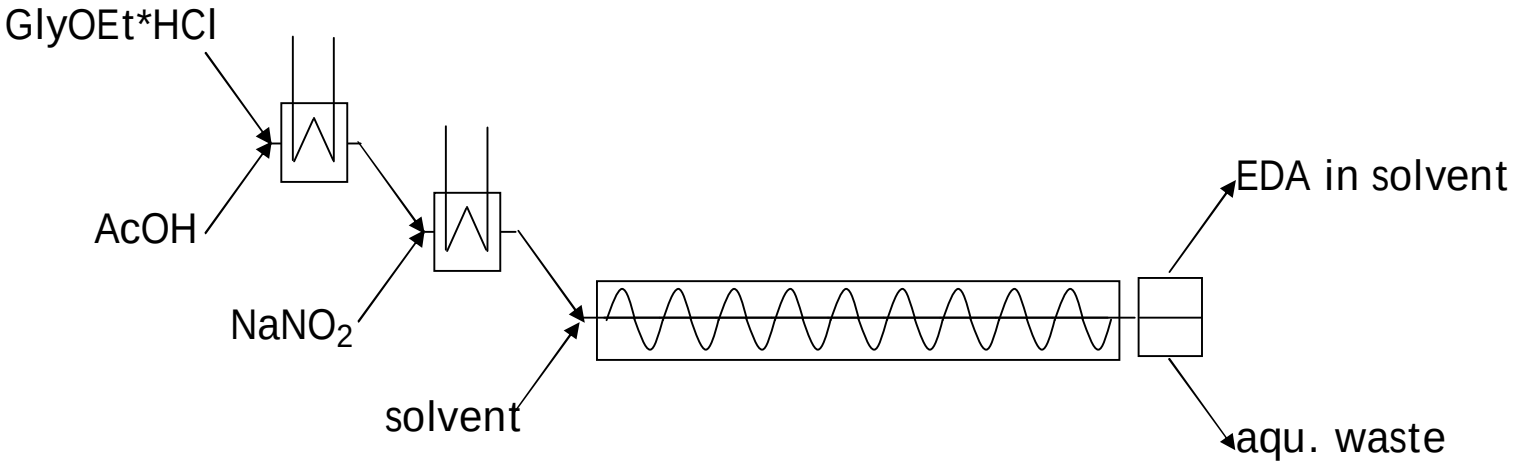
Questions:

1. Which annual demand will an installation producing 1 mol/min (=114g/min) meet ?
2. How big is the working volume of this installation ?
3. How much product does this installation contain (at most)?
4. If, for whatever reason, all product in the installation decomposes,
    1. How much gas will be evolved?
    2. **BONUS:** How much will the temperature rise (before / after phase separation)?
5. How would you store the product ?

Ethyl diazoacetate: flow equivalent of lab recipe:

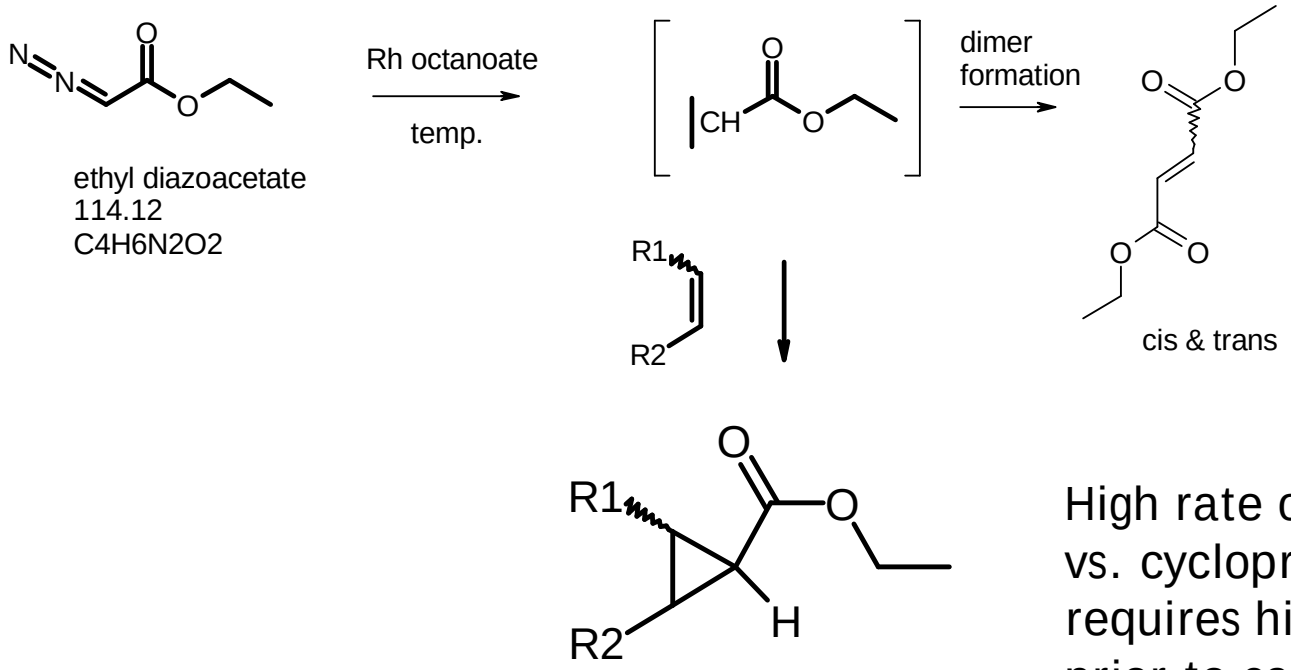


"To a cooled acidic solution of glycine ethyl ester hydrochloride
add sodium nitrite solution
and extract the product with an organic solvent".

... do not store the product...

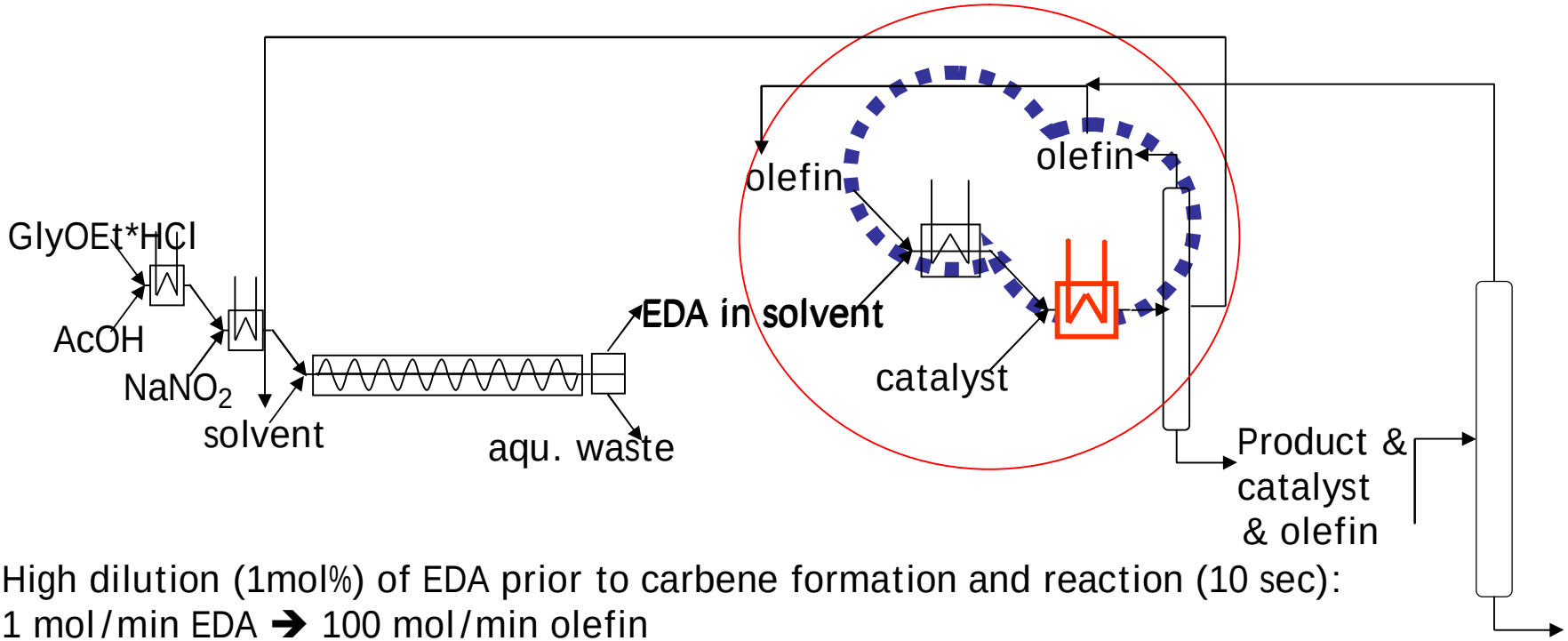
Further reaction of ethyl diazoacetate

Carbene formation & cyclopropanation of unreactive olefin:



High rate of dimer formation vs. cyclopropanation requires high excess of olefin prior to carbene formation

Combine plants…



High dilution (1mol%) of EDA prior to carbene formation and reaction (10 sec):
1 mol/min EDA ➔ 100 mol/min olefin
➔ ~ 500 kg/h distilled; reactor hold-up: <2kg

conclusions

- Continuous manufacturing is entering pharmaceutical synthesis
- It allows designing and operating processes that are
  - “safe by design”
  - deliver “quality by design”
- It increases the speed of development, process scale-up
- It reduces the (quality risk) of process scale-up
- It allows continuous process improvement to keep processes sustainable.
- It is a powerful tool for “cGMP for the 21st century”

Thank you

DSM Pharma Chemicals

Dr. Peter Poechlauer
Principal scientist

E-mail: peter.poechlauer@dsm.com

Internet: www.dsm.com
www.dsmpharmachemicals.com