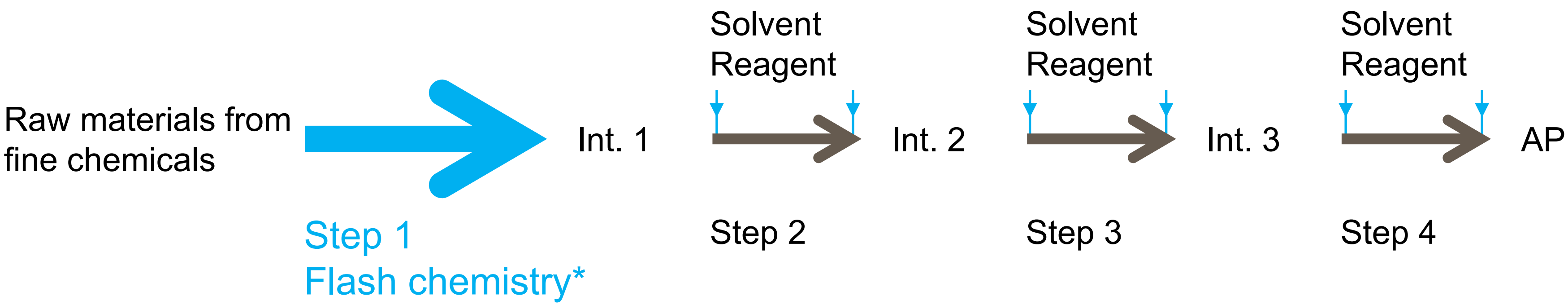
Pharma&Biotech

Lonza 'Factory of Tomorrow' for Flow Processes and MicroReactors

Practical Continuous Flow Technology, Munich, Germany

Dominique Roberge / Lonza Ltd, 3930 Visp / 5 June 2013© Lonza

Re-design the Chemical Routes with the Concept of Flash Chemistry in Flow



- Flow Processes / Microreactors lead to drastic improvements
  - Excellent heat transfer & mixing
  - Exact control of residence time
  - Segregation of feeds, small volume, robust (pressure) etc.
- **Inherently Safer Design** from the high level of confinement

= Intensified Mini-Plant Concept

* Flash chemistry concept see: Yoshida, J.-I. et al., *Chemistry – A European Journal* **2008** (14) 7450

Reaction Classification & Advantages

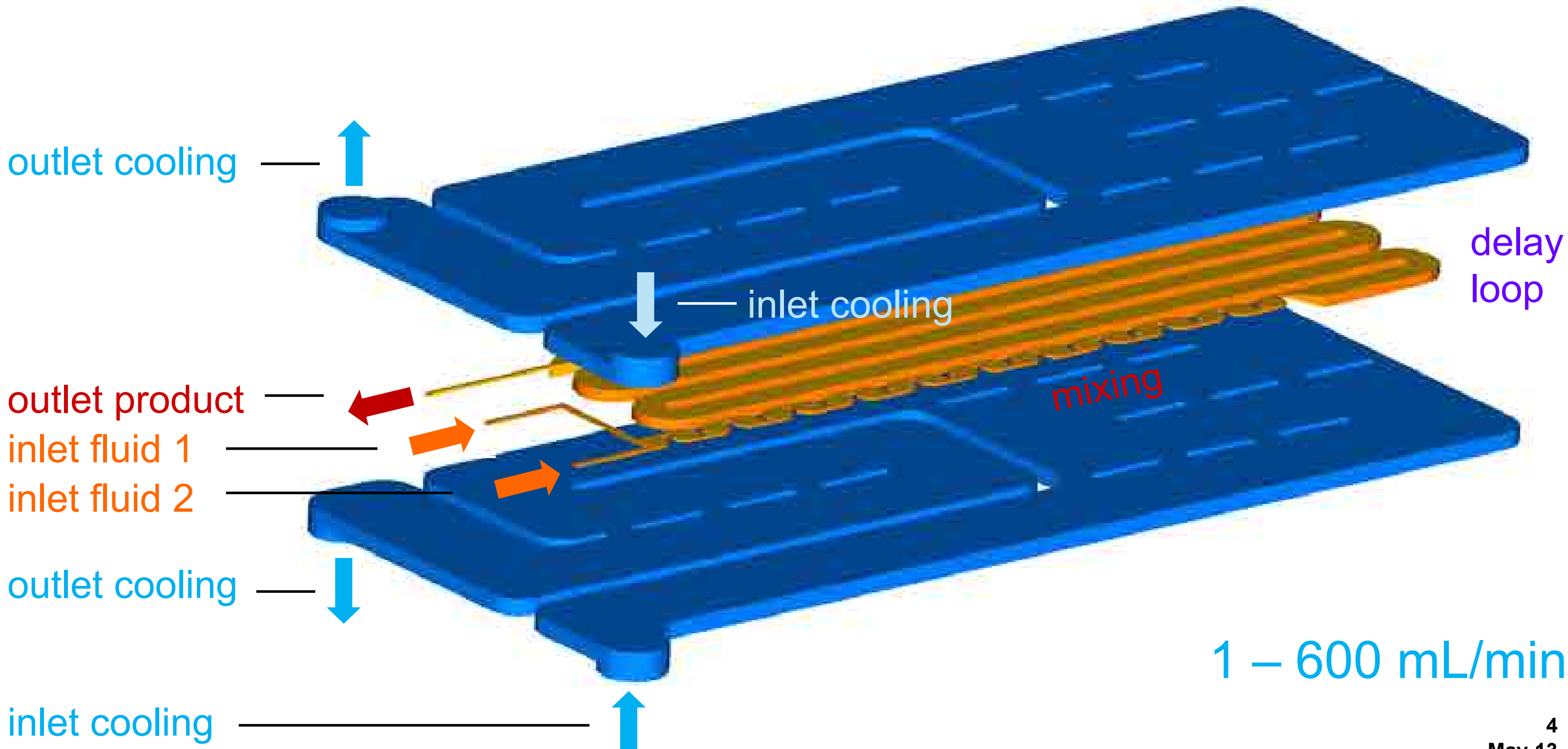
Type A reactions
- Very fast (< 1 s)
- Controlled by the mixing process
- Increase yield through better mixing/heat exchange

Type B reactions
- Rapid reaction (10 s to 30 min)
- Predominantly kinetically controlled
- Avoid overcooking and increase yield

Type C reactions
- Slow reaction (> 30 min)
- Batch processes with thermal hazard
- Enhance safety
- Need intensification

Microreactors Are at the Heart of a Dramatic Shift in API Production

It enables continuous processes based on plug flow reactors with minimal volume of reagents, rapid dynamic responses and robustness, good temperature control, efficient mixing, etc.



1 – 600 mL/min

Video of a Gas-liquid Type A Reaction in the FlowPlate® MicroReactor

Agenda

- Reactor design for scale-up
  - Parallelization / Numbering-up illusion

Process intensification

- Impact on production unit >> Factory of Tomorrow
  - Example 1. Organometallic reaction
  - Example 2. Azide chemistry

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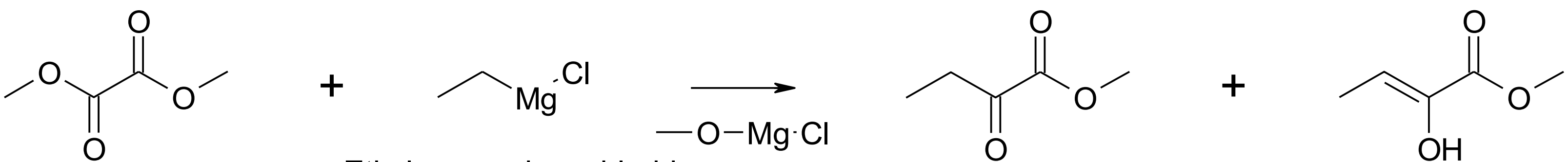
Grignard Reaction as a Test Reaction for Manifold & Heat Exchange Performances



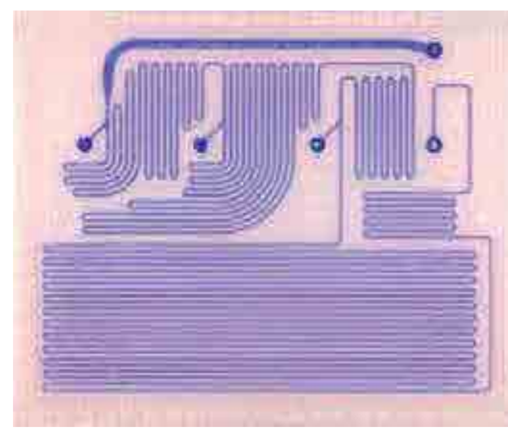
Dimethyl oxalate
CN 16543
MW 118.09

Ethylmagnesium chloride
CN 38038
MW 88.82

2-MOB
CN 32182
MW 116.12

2-MOB_enol
CN 32759
MW 116.12
RRT 1.17

Feed-1:	Dimethyloxalate (15 wt%), rest DME
Feed-2:	Grignard (19 wt%), rest THF
Temperature:	-15°C, all feeds pre-cooled
Stoichiometry:	Grignard / Dimethyloxalate = 1.15
Flow rate:	40 g/min in total with
	1 or 4 injection points (Grignard)



Roberge et al., Chem. Eng. Technol. **2008** (31) 1155

Barthe et al., *Chem. Eng. Technol.* **2008** (31) 1146

Limitation of Pressure Driven Systems – Avoid Manifold / Parallelization

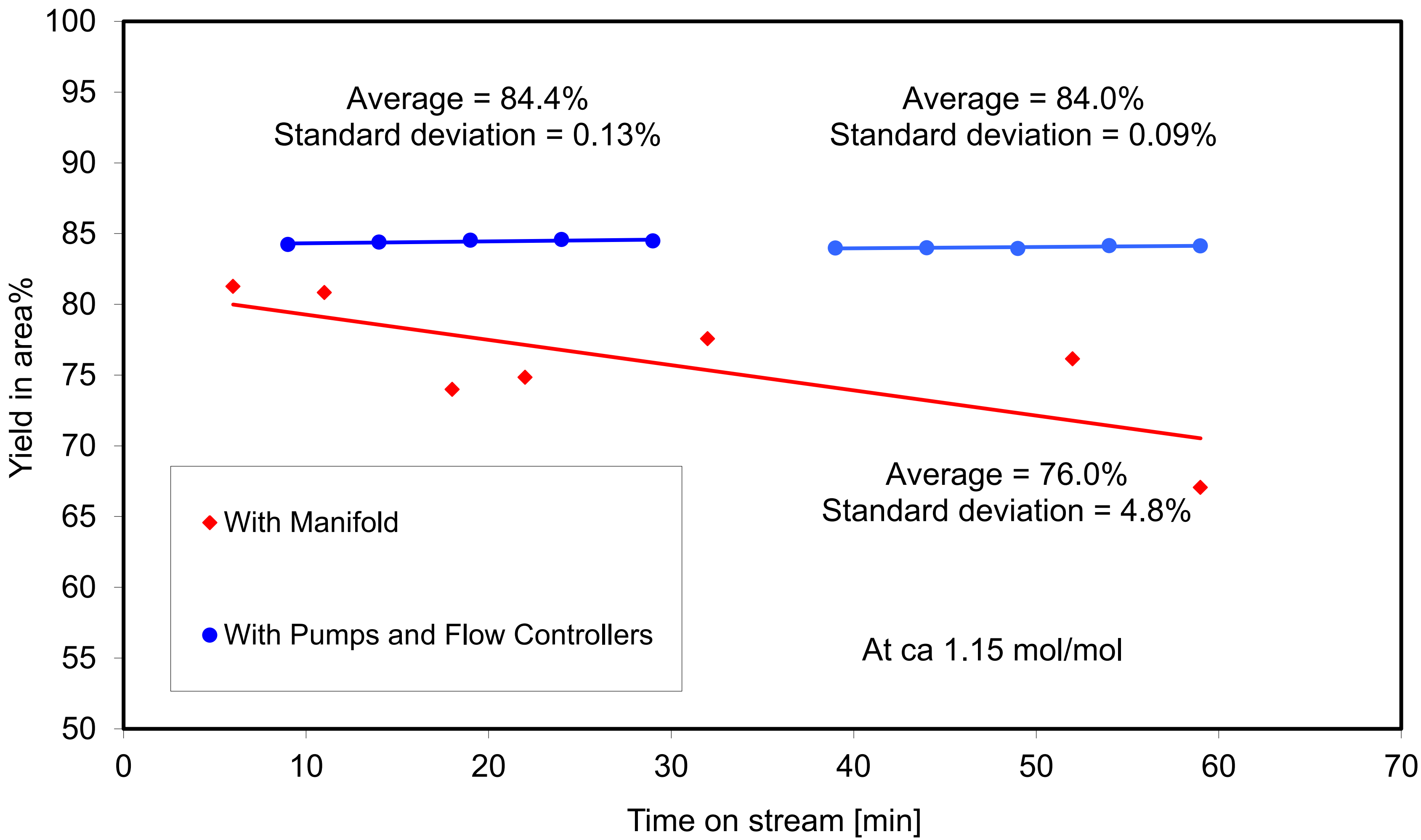


Plate Size to Drive Scale-up: FlowPlate® MicroReactors

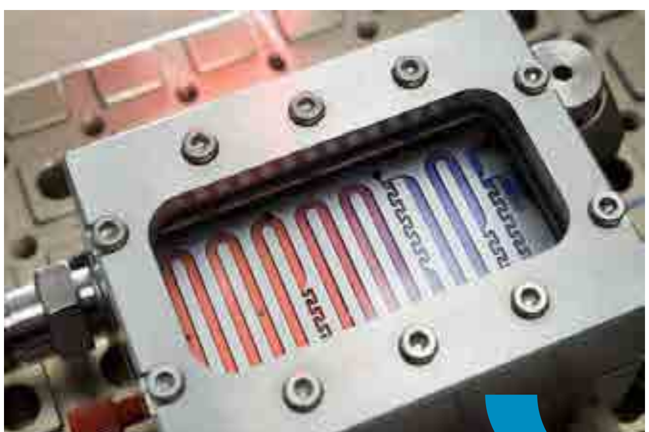
Development Reactor

- View the chemistry
  - Chemical systems are metastable!
- Test different structures
  - Ensure stoichiometry

Production Reactors

- Design as a key ingredient to scale-up
  - Avoid parallelization
- Enable Clean in Place
  - Multi-purpose & ready for cGMP

FlowPlate® Lab



Channel structure

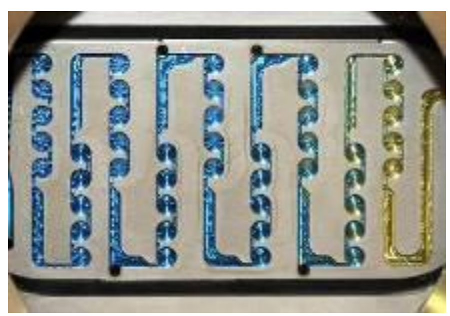


Plate Size: A6 Plate Size: A5

Roberge et al., *Chemistry Today* **2009** (27) 8

As Small as Needed and Use "Micro" Where Useful

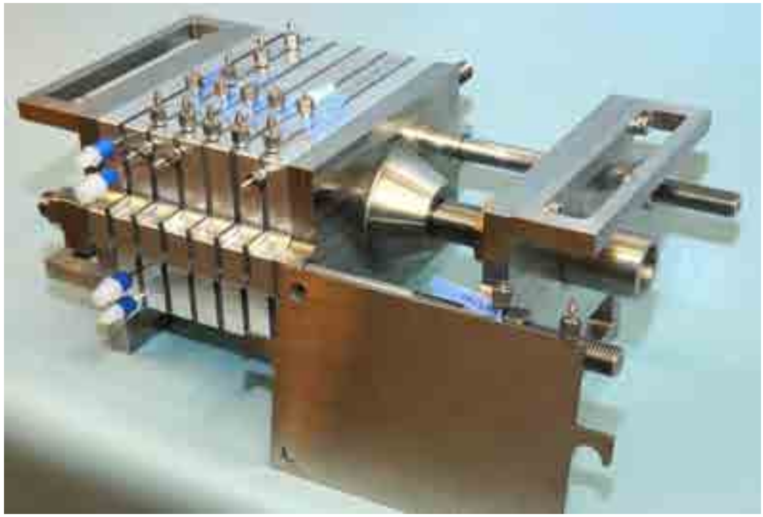
Multi-scale design to maximize heat transfer and optimize mixing

but allowing variable residence time modules > gain volume

- Up to several hundreds of mL
  - seconds to minutes
- Variable channel depth
  - to limit pressure drop

Can be coupled with residence time modules

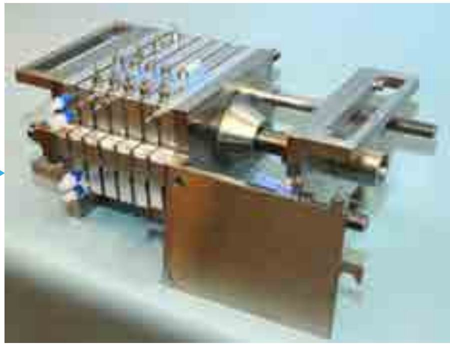
- Several liters
  - up to 30 minutes



Flow rate from 15 to 600 mL/min
No internal parallelization
Micro dimension = 500 µm
Larger dimension = 2 mm

Scale-up Strategy
Conventional Technology versus MRT

MMRS
Interface
Modules



MMRS

Production Scale
Modules

Apparatuses used at the early stage of process development need to have the potential for further scale-up.

Typical Projects in our Pipeline

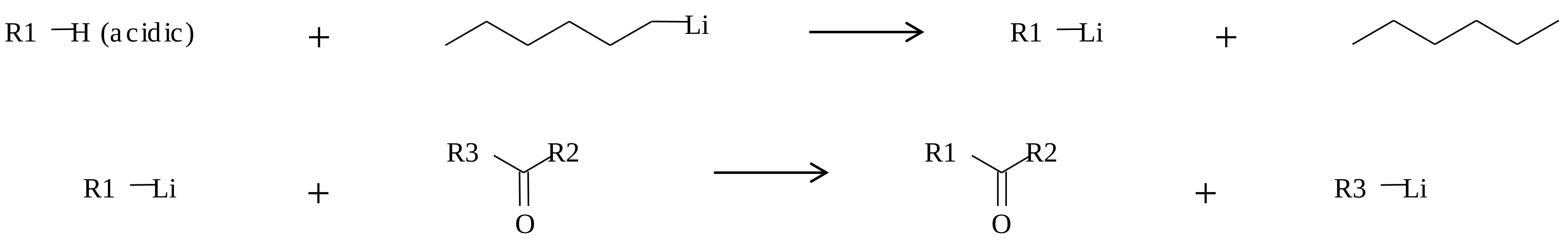
Projects	Formula	P [bar]	T [°C]
Project 1	Aggressive chemistry (corrosion!)	85	250
Project 2	Organo-lithium reactions	Normal	-30
Project 3	Fischer-Indole synthesis	20	170
Project 4	Acid-catalyzed cyclization	Normal	-40
Project 5	Nucleophilic substitution (Cl)	20	220

Test new technological approaches

- Hydrogenation, Electro-dialysis, membranes, ozonolysis…

Example 1: FlowPlate® MicroReactor to Control Reaction Heat

2-Step Synthesis: Lithiation and Coupling



Some Disadvantages

- Plugging = Lonza patent applied Ultrasonic De-plugging System

First reaction: Type A, highly exothermic (ΔTad > 75°C)

- Microreactor

Second reaction: Type B, exothermic (ΔTad < 25°C)

- Static mixer under adiabatic conditions

Ultrasonic De-Plugging System

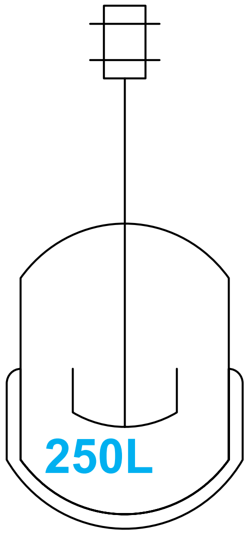
- Optimize to use with the FlowPlate® MicroReactors
- Ultrasonic System to enable stable operations over days / weeks
- Ultrasound is generated in the liquid > to create true cavitation
- Optimal for spot plugging like in the mixing zone or exit
  - Imperative for organometallic reactions with BuLi

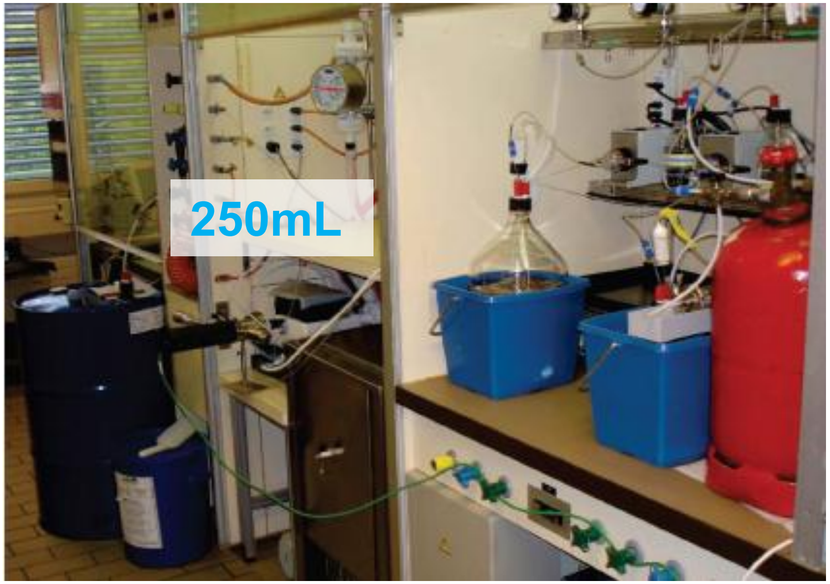
Microreactor Technology Leads to Dramatic Process Intensifications

Process intensification to enable inherently safer processes leading to a production paradigm

- Lower reactor investment
- Less manpower
- Higher flexibility
- Enhance safety
- Faster change-over

“Factory of tomorrow”

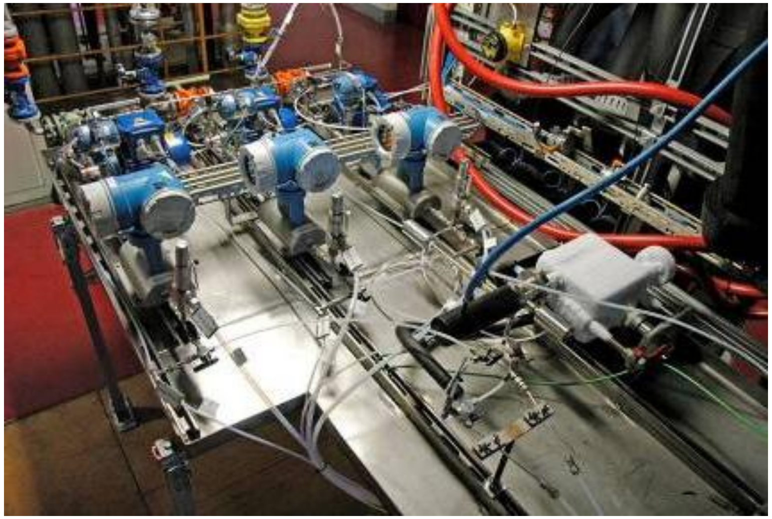




Earlier Pilot Plant using Microreactor Technology

Key Features

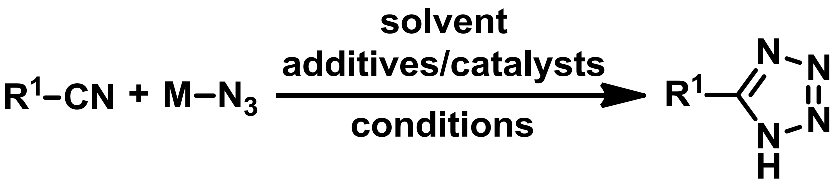
- Multi-purpose system
  - Modular
  - Hastelloy
  - T = -80 to +180°C
- ATEX standards
- Qualifiable for cGMP production
- 3 dosage lines
  - 1 - 8 bar
  - 5 - 500 g/min (per line)



Track record
2 tons of isolated product
20 m^3 processed fluid

Example 2: Azide Chemistry in Microreactors

Azide-Nitrile Addition to make Tetrazole Derivatives



a) M = H, b) M = Na, c) M = $Si(R^2)_3$, $Sn(R^2)_3$, $Al(R^2)_3$

Typical Type C reaction requiring several hours

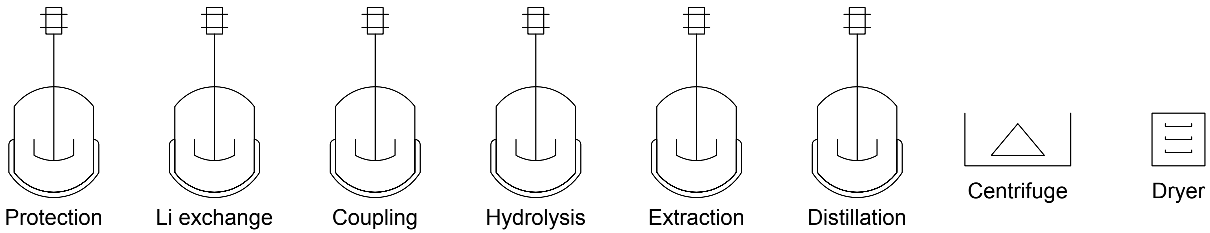
The mixture was heated under a N2 atmosphere at 100-105°C for 50 h

- **Segregation of Feeds**: NaN_3 prepared in a special containment and precisely mixed in the reactor avoiding batch bulk handling
- **Volume Minimization & Robustness**: Reaction in flow performed in 10 min at 220°C

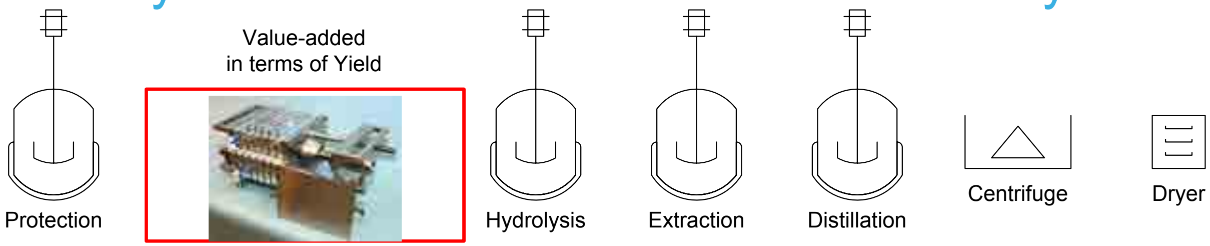
Gutmann et al., Angewandte Chemie International Edition **2010**, DOI:10.1002

The Future of Flow Processes:
Full Integration of MRT in Production Units

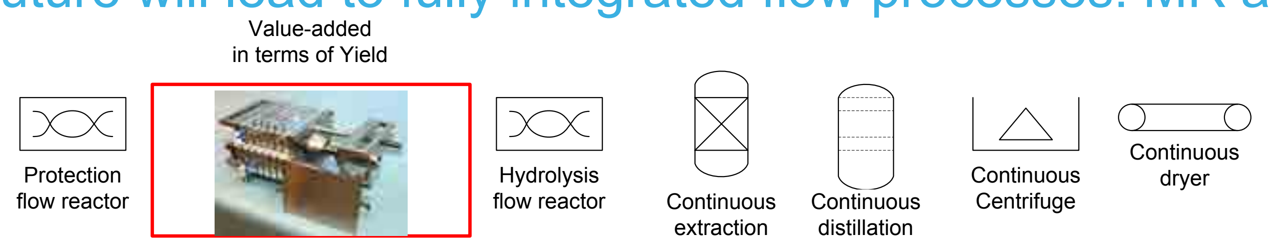
In the past conventional means all batch processes



Currently the MR is used to increase reaction yield & safety



Future will lead to fully integrated flow processes: MR and more…



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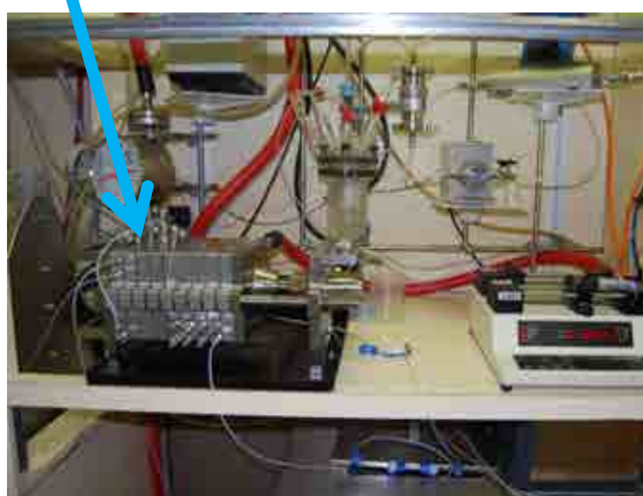
Reaction and Work Up Integrated in One Flow Unit

Mini-Plant concept to enable **New Processes** and extend the design space of how we perform chemistry

Key Features

- Microreactor for a **flash reaction**
- CSTR for precipitation
- High pressure valve
- Filter to removal salt
- Wiped film evaporator
- Fraction collector



Throughput

- More than 1 kg/day of product;
  distillation is limiting

Lonza "Factory of Tomorrow" for Continuous Flow / MRT

Aim: huge process intensification via flow

Cabin concept to enable high flexibility

- Use of various equipment: microreactors, static mixers, extraction column, distillation (thin-wiped film, etc.)
- Various flow rates, high pressures & temperature
  - Up to several tons
  - 100 bar – 300°C > hydrogenation

Faster Scale-up and change-over

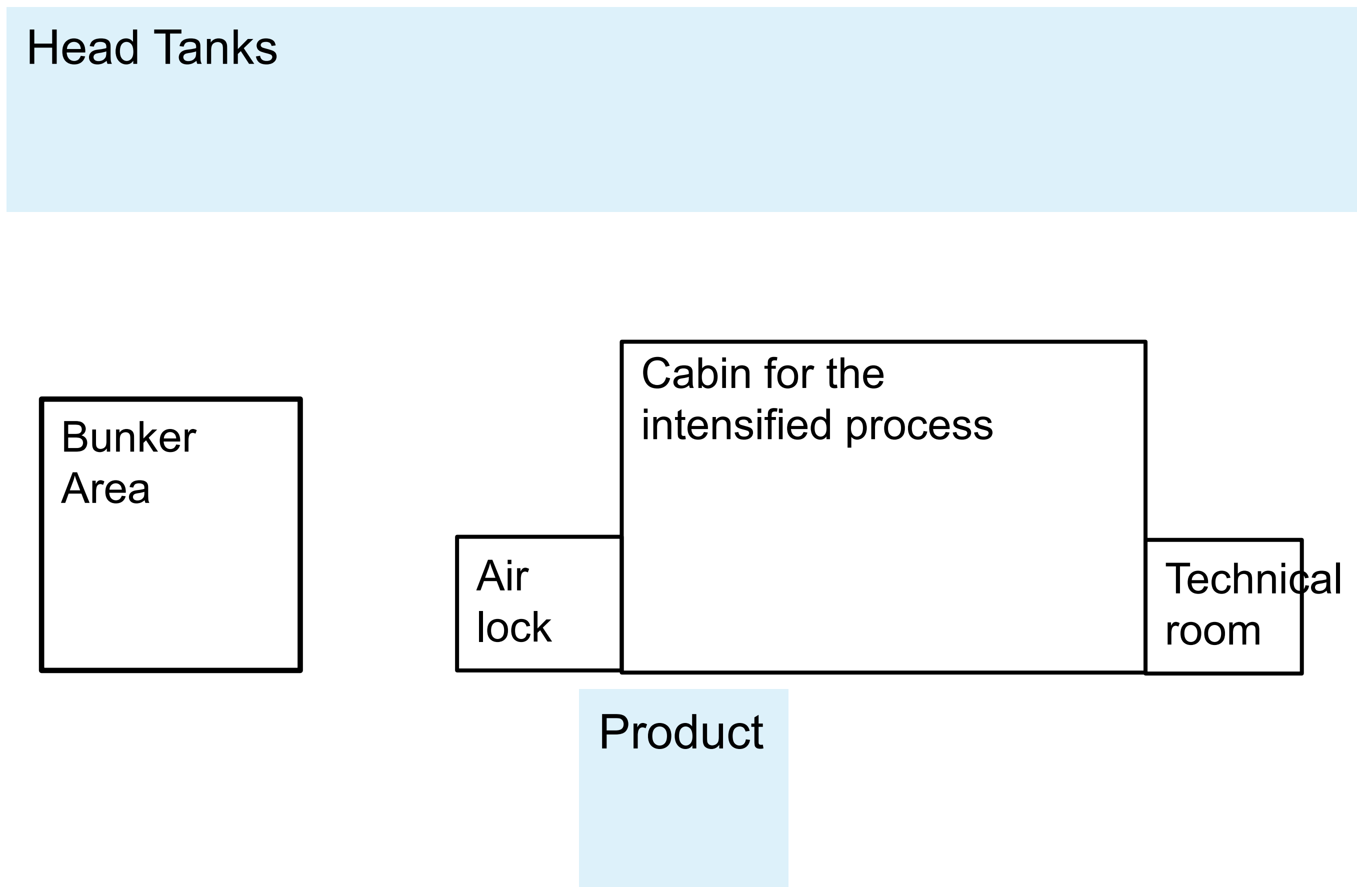
- Non ATEX
- New concept for cGMP qualification

>> Overall goal is to reduce drastically the costs of goods

Throughput

- 900 mL → 10 kg/day
- 3600 mL → 40 kg/day

“Factory of Tomorrow”



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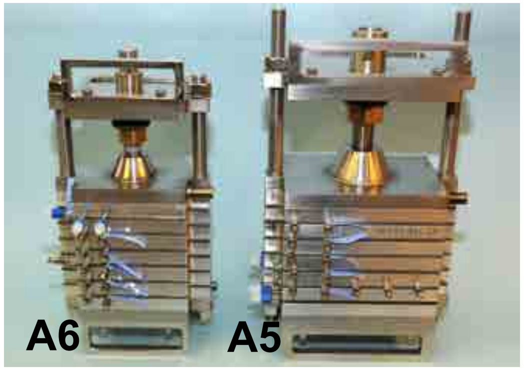
Economical Gain: Batch Versus Flow

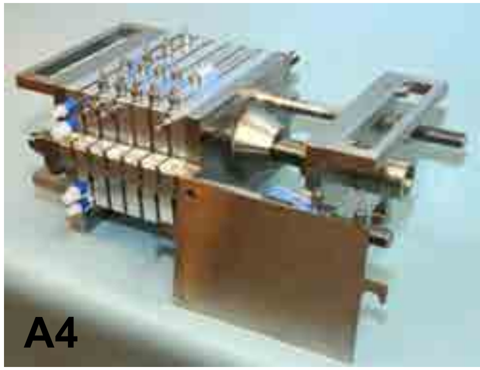
Example 1: Process development in clinical trials / kg scale	
Batch Process	**Flow Process**
Reactor volume = 250 L	Reactor volume = **250 mL**
	Faster change over & cleaning
	Manufacturing gain = **up to 30%**

Example 2: Commercial manufacturing / ton scale	
Batch Process	**Flow Process**
Reaction time = **10 - 14 h**	Reaction time = **0.2 h**
Reactor volume = **10 m^3**	Reactor volume = **0.03 m^3**
Cycle time = 21 h	Cycle time = 16 h
Productivity = **764 kg/d**	Productivity = **977 kg/d**
Need bunker to cover the 10 m^3 Investment = 4 MCHF for a bunker infrastructure	Lower assets usage; special confinement

Infrastructure Overview

FlowPlate®





A++

Portable skid mounted units anywhere

- Visp FCC
- Nansha, China
- Our customers

Laboratory System	Factory of Tomorrow	Commercial Manufacturing
Flow labs fully integrated with kg-Labs	Piloting at lower costs	Modular, flexible on skid mounted units
1-150 g/min Few g to tens of kg	**150-600 g/min** 0.1–5 tons campaigns	**0.6- 5 kg/min** 5–80 tons campaigns
- Your green and sustainable process of tomorrow	- Plugging issues solved - Fully automated - Scale-up concept tested	- Fit for any scale - Streamlined and simplified processes - Drastic reduction in costs of goods

Conclusions

Flow technologies are the heart of a quantum leap in pharmaceutical manufacturing leading to greener processes at lower costs

- Design new chemical routes

Lonza is a leading manufacturer of chemicals using flow processes and advanced technologies

- The central part of the lab development is the microreactor

Acknowledgments & Contacts

- N. Kockmann, R. Forbert, and O. Kappe (external)

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