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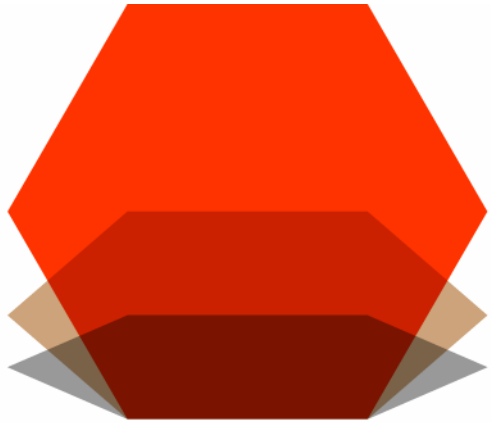
Your Specialist for Hazardous Reactions.

Royal Society of Chemistry Symposium
Elements of Success, Lithium and Boron Session 2

Lithiation from Lab to Commercial Scale – In the Field of Hazardous Chemistry

June 10, 2010 Messe Berlin, Germany



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SYNTHESIS

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Content

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Your Specialist for Hazardous Reactions.

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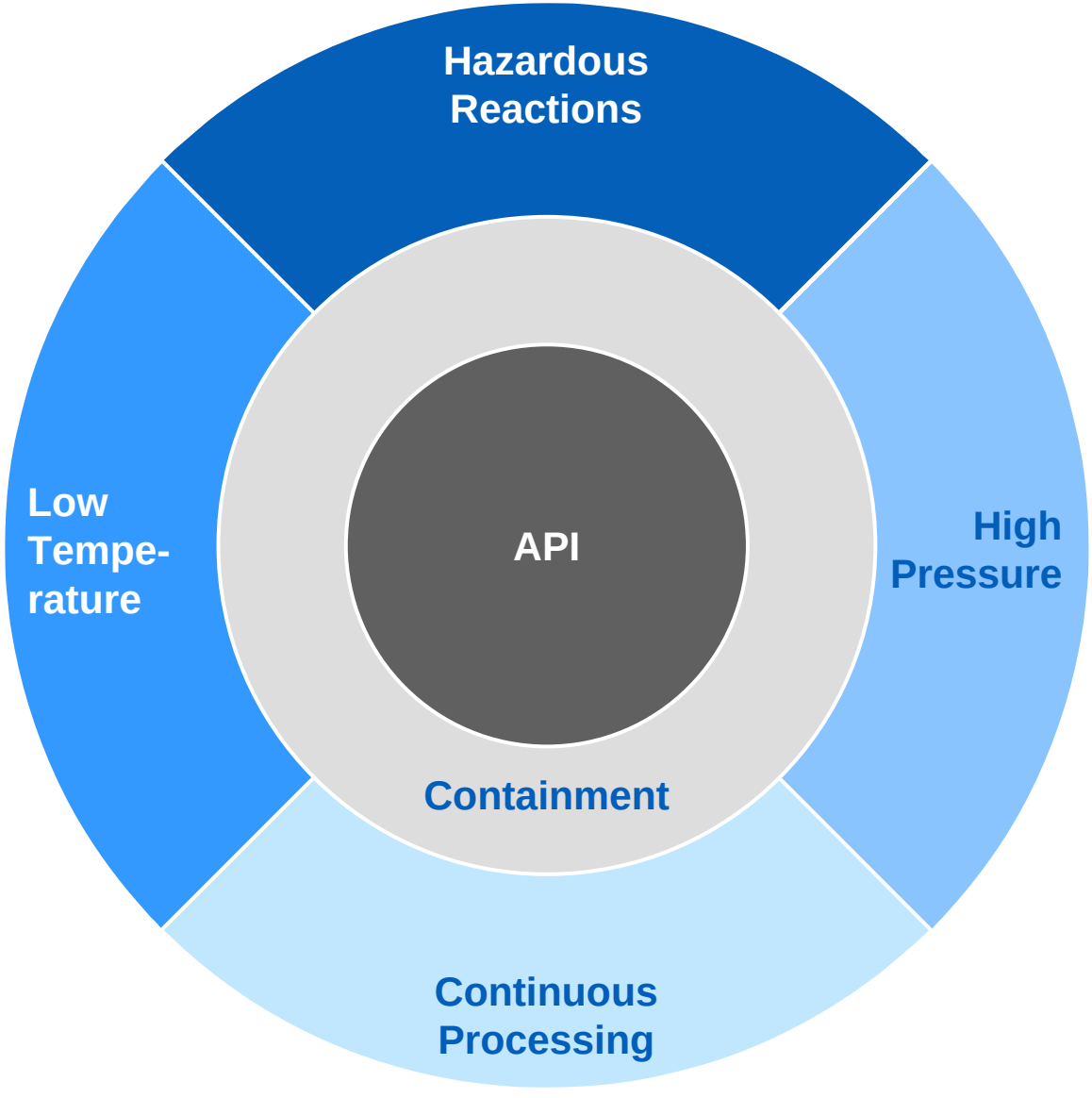
DOTTIKON ES' Technology Platform



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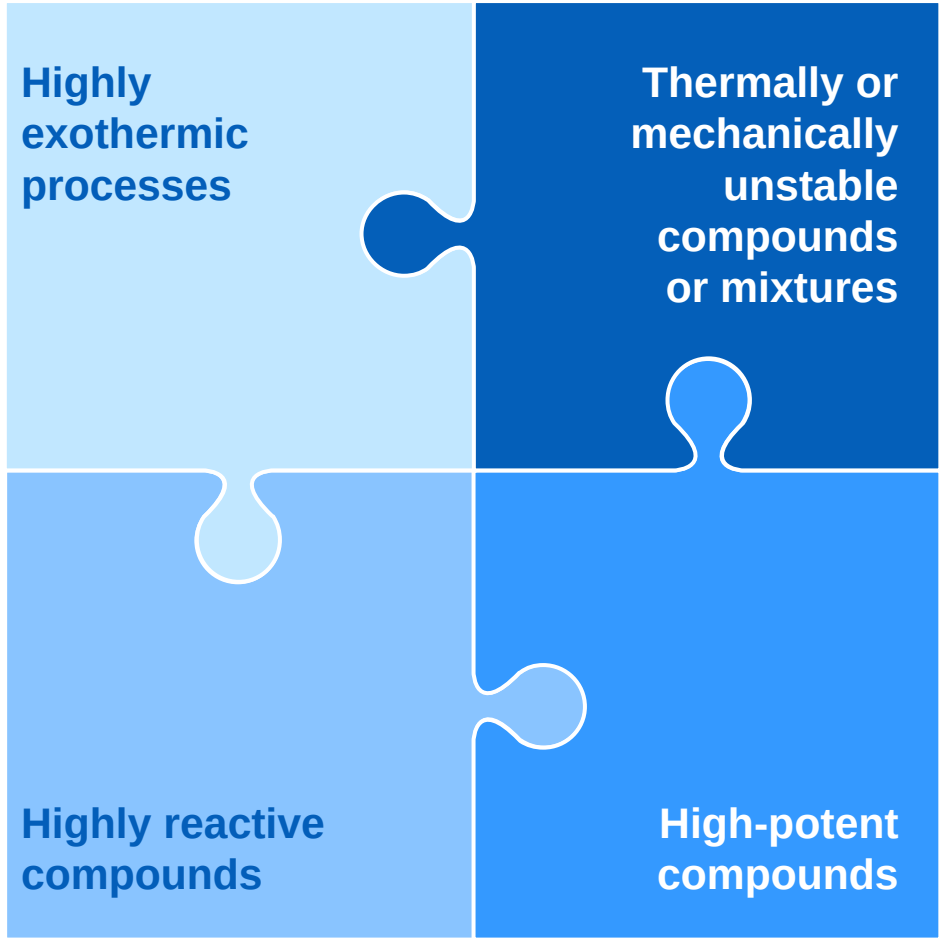
Hazardous Reactions at DOTTIKON ES

- Nitrations
- Grignard reactions
- Hydrogenations
- Oxidations



- Nitro compounds
- Azides
- Nitrate esters
- Peroxides
- Diazo compounds

- Hydrides
- Dimethyl sulfate
- Nitric acid
- $POCl_3$, PCl_5, $POBr_3$, PBr_3
- $SOCl_2$, SO_2Cl_2

- HAPIs
  - 20–100 µg/m^3
  - 1–20 µg/m^3
  - <1 µg/m^3

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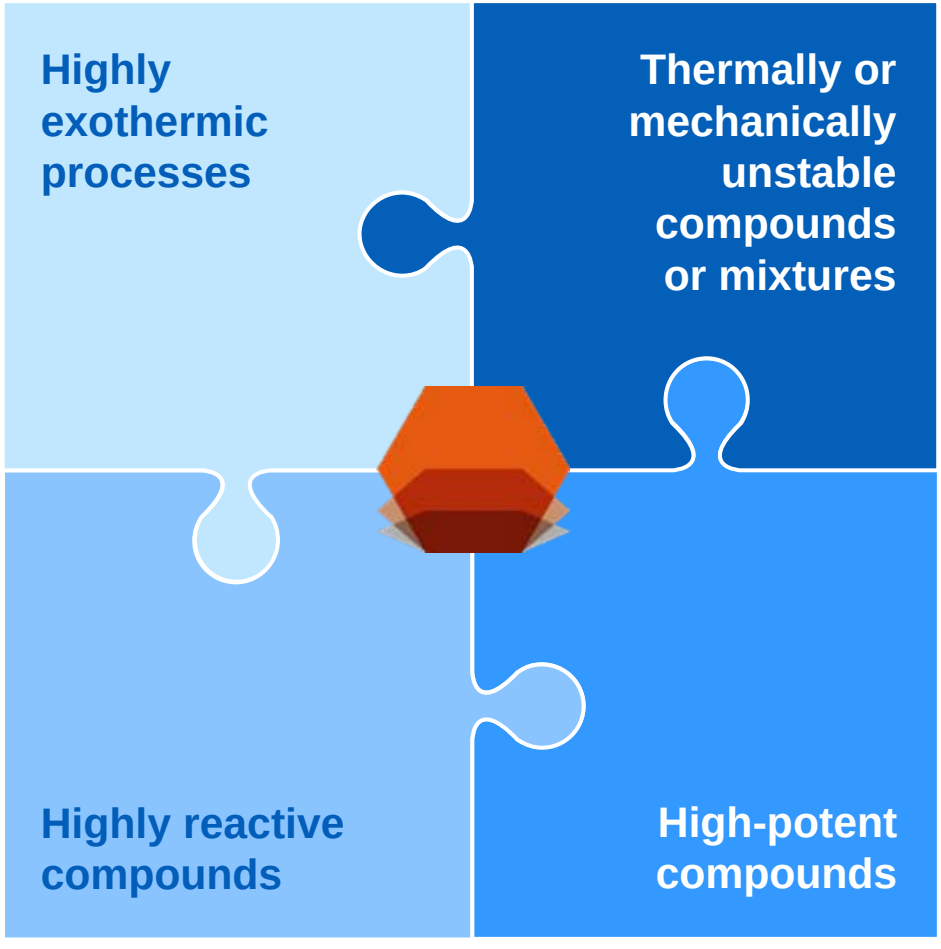
Hazardous Reactions at DOTTIKON ES

Prerequisites for development and production



- Profound knowledge of critical process and engineering parameters
- Dedicated equipment on all scales
- Strongly developed safety culture

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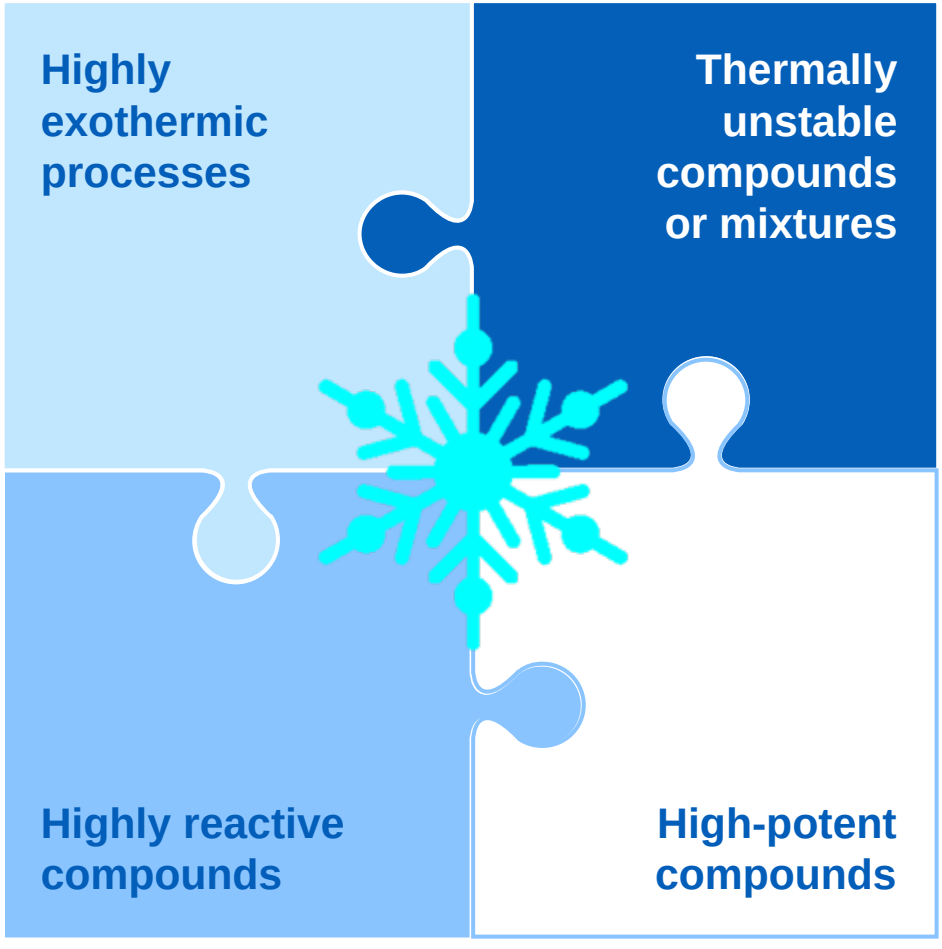
Low Temperature Chemistry at DOTTIKON ES

Prerequisites for development and production



- Profound knowledge of critical process and engineering parameters
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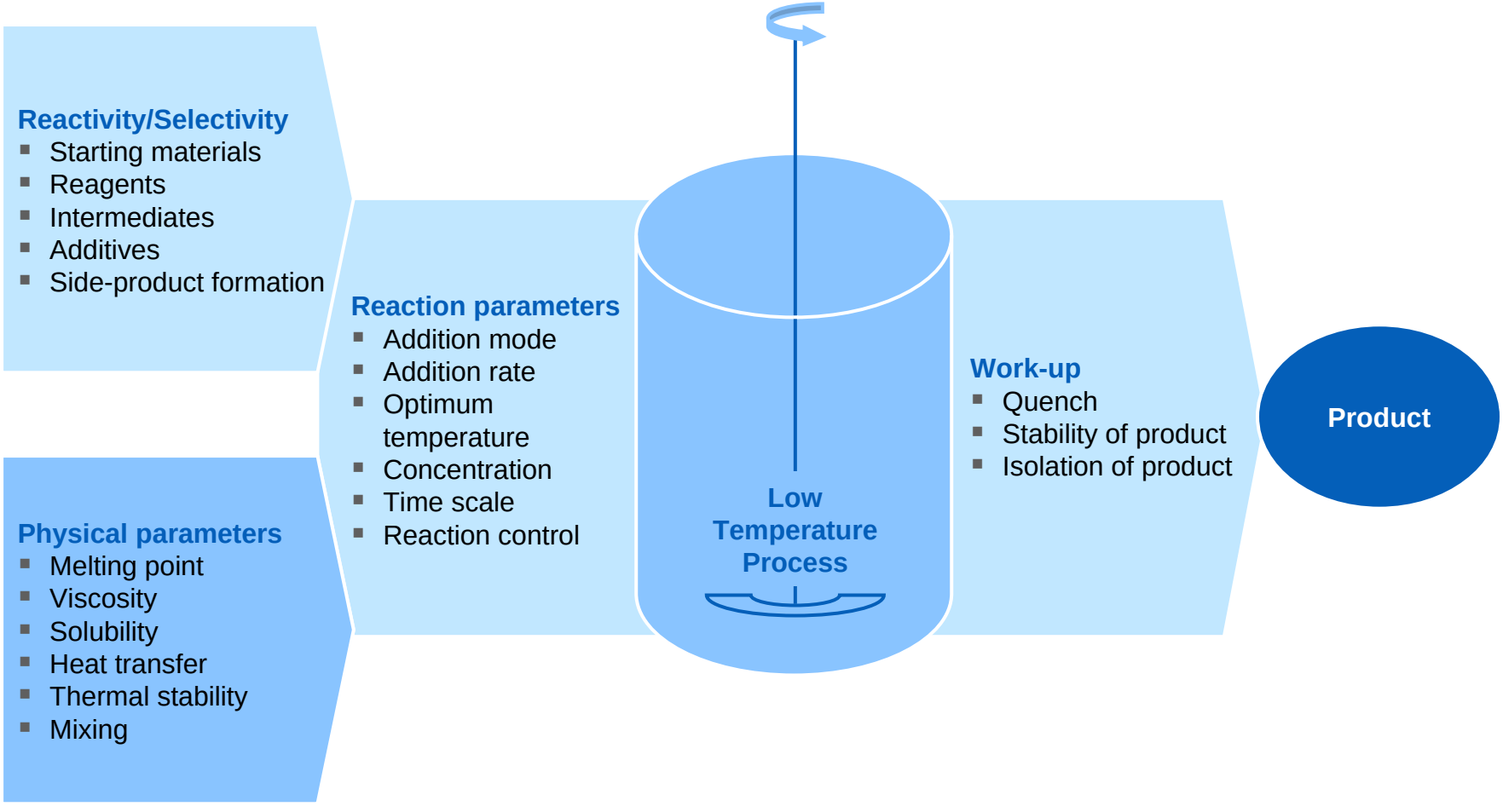
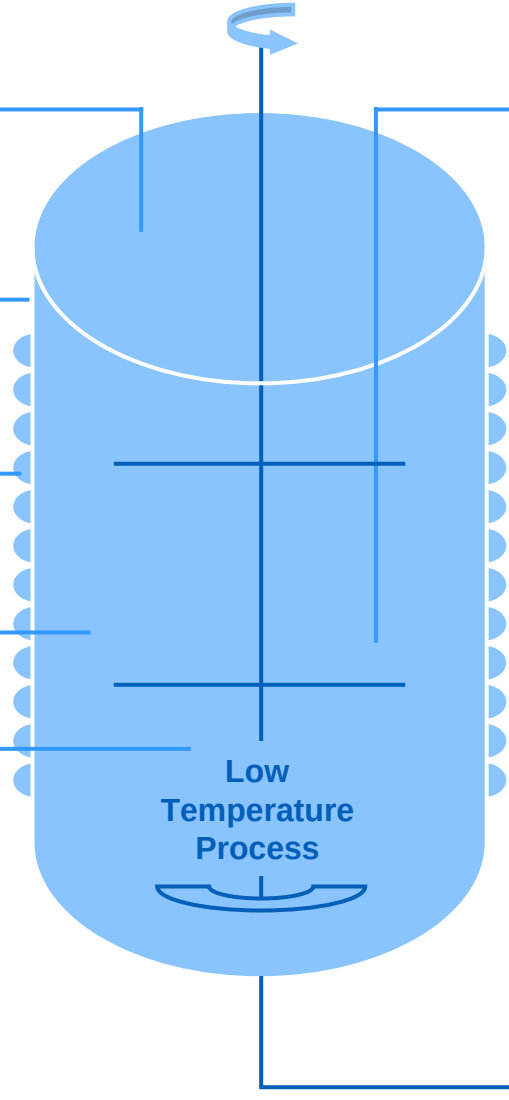
Critical Process Parameters

Low Temperature Process



Critical Engineering Parameters

Low Temperature Process



Dosage
- Precooling
- Feed location

Reactor
- Type of construction
  area-volume-ratio

Efficient cooling system (ΔT)

Material of construction

Efficient stirrer
- Heat transfer
- Low minimum stirrable volume

Reaction control
- Temperature
- Pressure
- PAT

Temperature controlled transfer pipes

Others
- Seals
- Welding seams
- Isolation of cooling system

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Low Temperature Equipment on all Scales

	Research & Development	Small Scale and Pilot Plant	Production
			
			
Reactor Temperature	▪ 0.1–0.5 L ▪ Adjustable −80°C	▪ 100–160 L ▪ Adjustable −80°C	▪ 1'600 L ▪ Adjustable −100°C
Essential equipment	▪ Efficient cooling system ▪ Temperature controlled transfer pipes ▪ All in one place		

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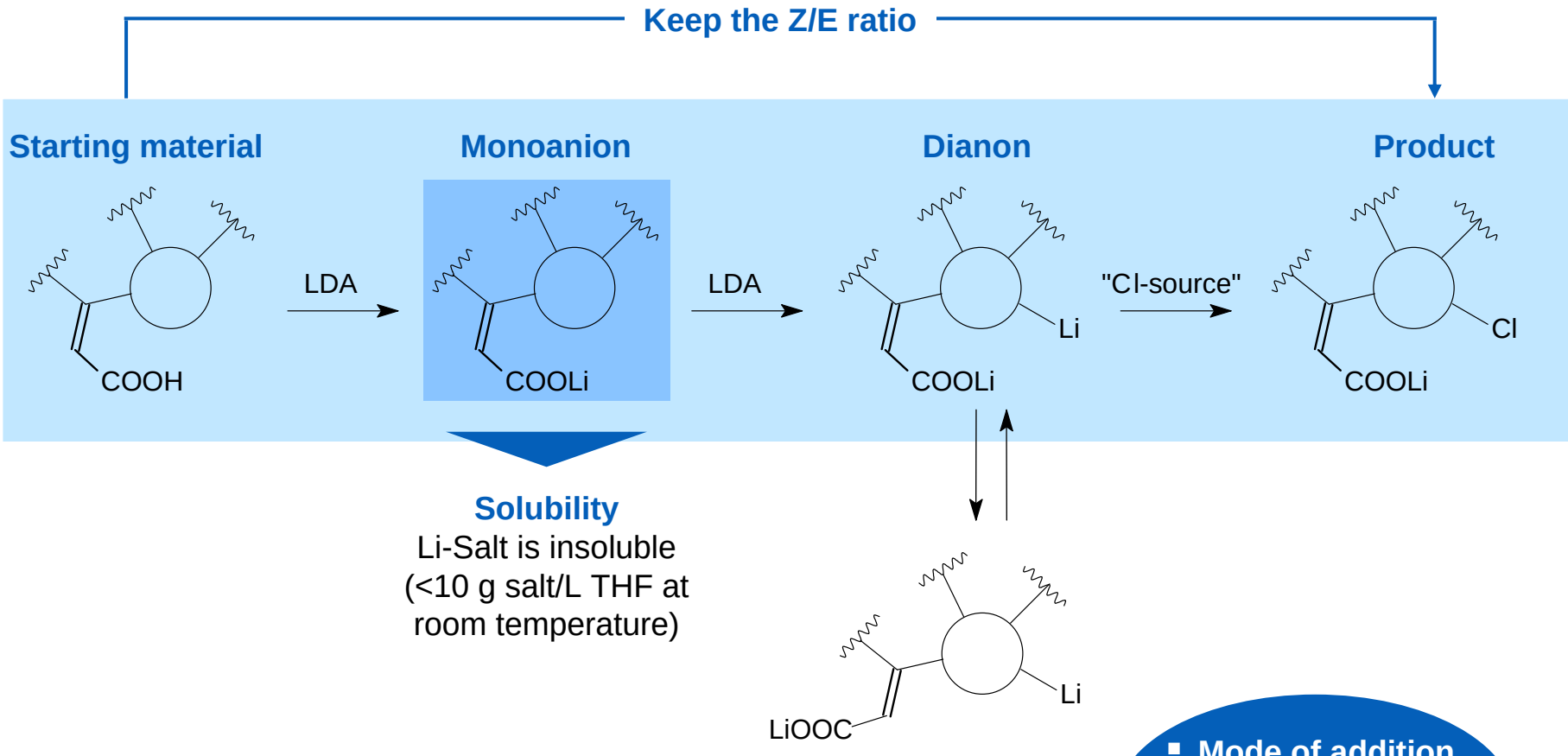
Content

Case Study

Batch Process – Solubility Monoanion



- **Mode of addition must be inverse**
- **Starting material to LDA**

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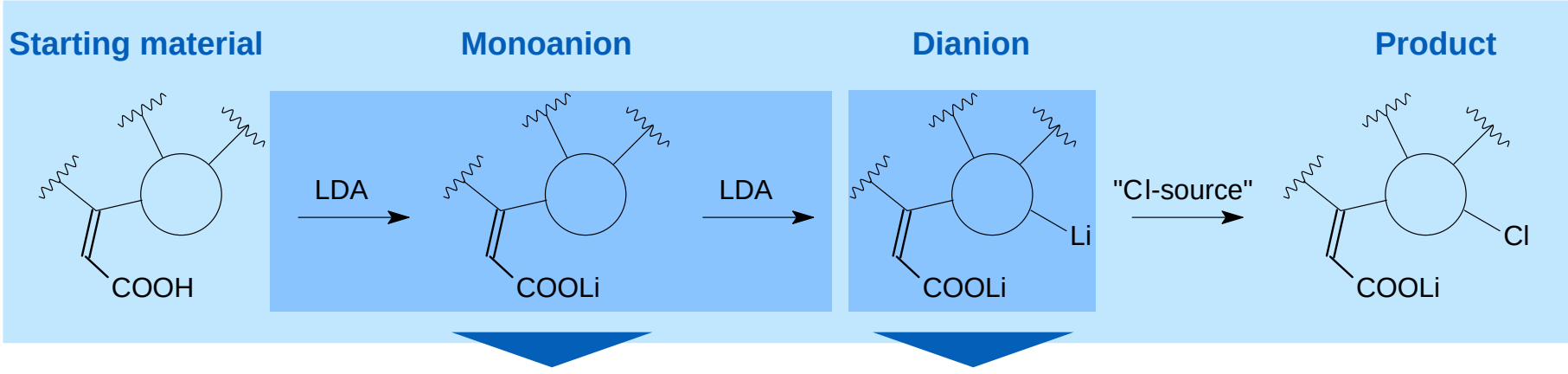
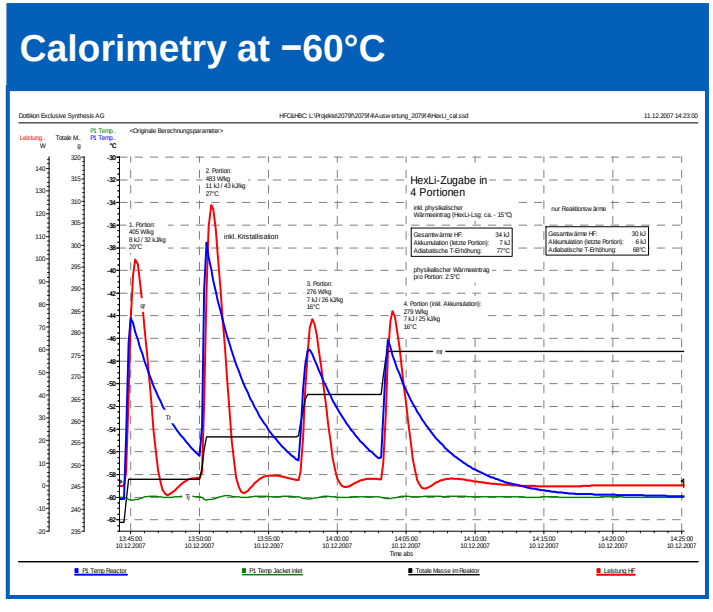
Case Study

Batch Process – Stability of Dianion



Exotherm

Calorimetry at −60°C



Stability

Dianion is T-sensitiv

- **Efficient cooling system**
- **Cooled transfer of dianion to electrophile necessary**

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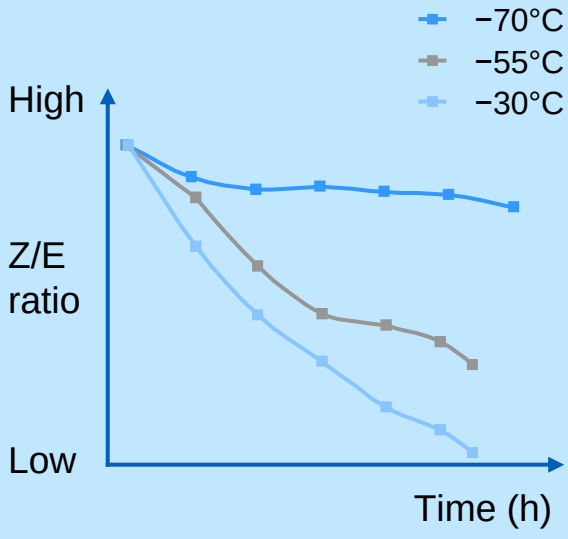
Case Study

Scale-up of Process

Stability of dianion



Tempera-ture and time strongly de-termine Z/E ratio

Limitation of scale-up in batch

- Dosage time will be longer
- Heat transfer decreases

- Achieve minimum hold time for dianion
- Efficient heat transfer

Continuous mode for large scale

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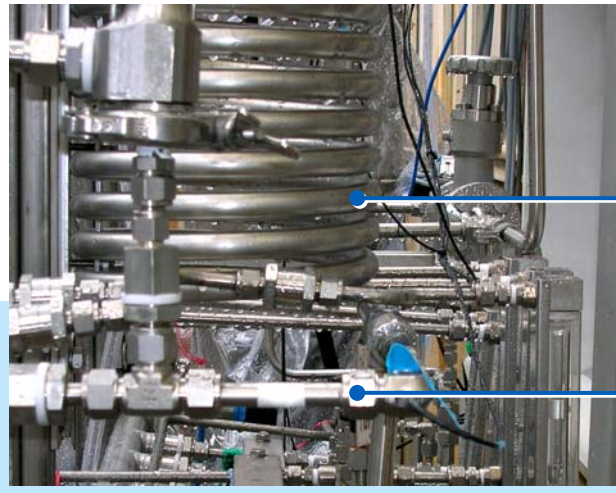
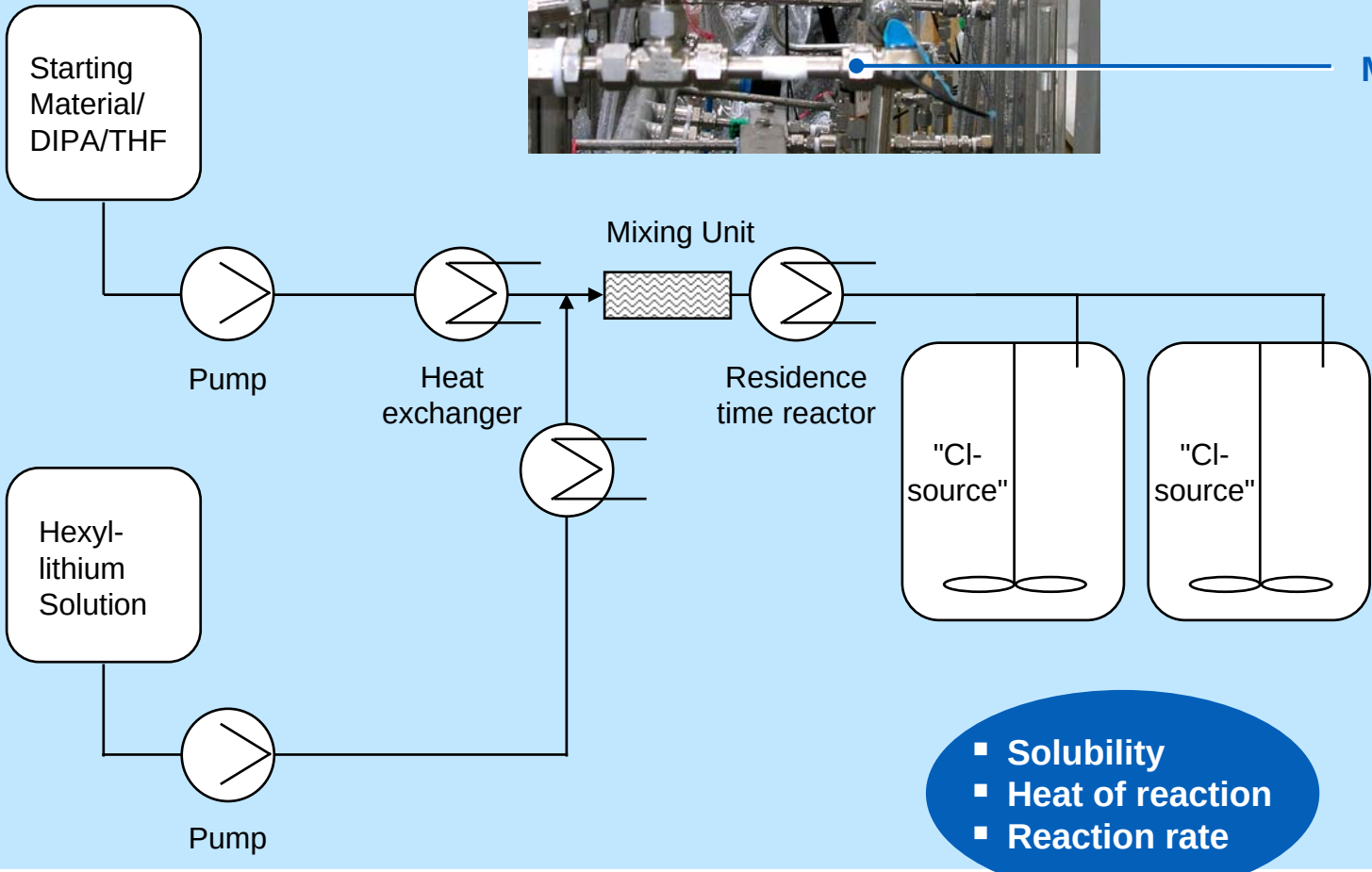
Case Study

Layout of Continuous System





- Solubility
- Heat of reaction
- Reaction rate

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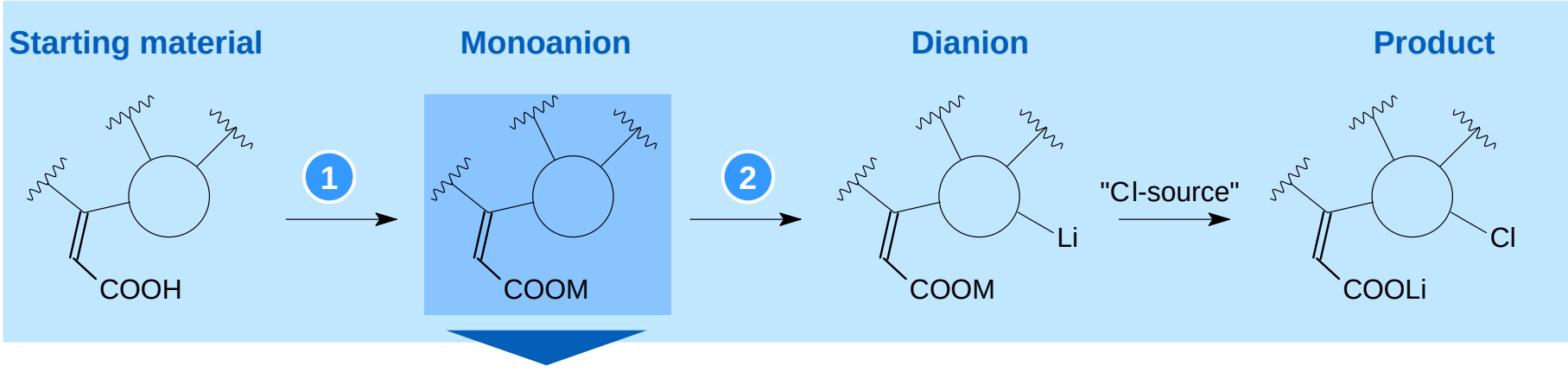
Case Study

Continuous Mode – Solubility and Heat of the Reaction



Solubility M = Na
Sodium salt is soluble
(300 g salt/L THF at −60°C)

	Heat of the reaction	Maximum heat output
1 + 2	ΔT_{ad} = 77°C	483 W/kg
2	ΔT_{ad} = 60°C	365 W/kg

- Solubility of monoanion as Na Salt very good
- Na salt as starting material
  - ΔT_{ad} smaller
  - Max heat output lower

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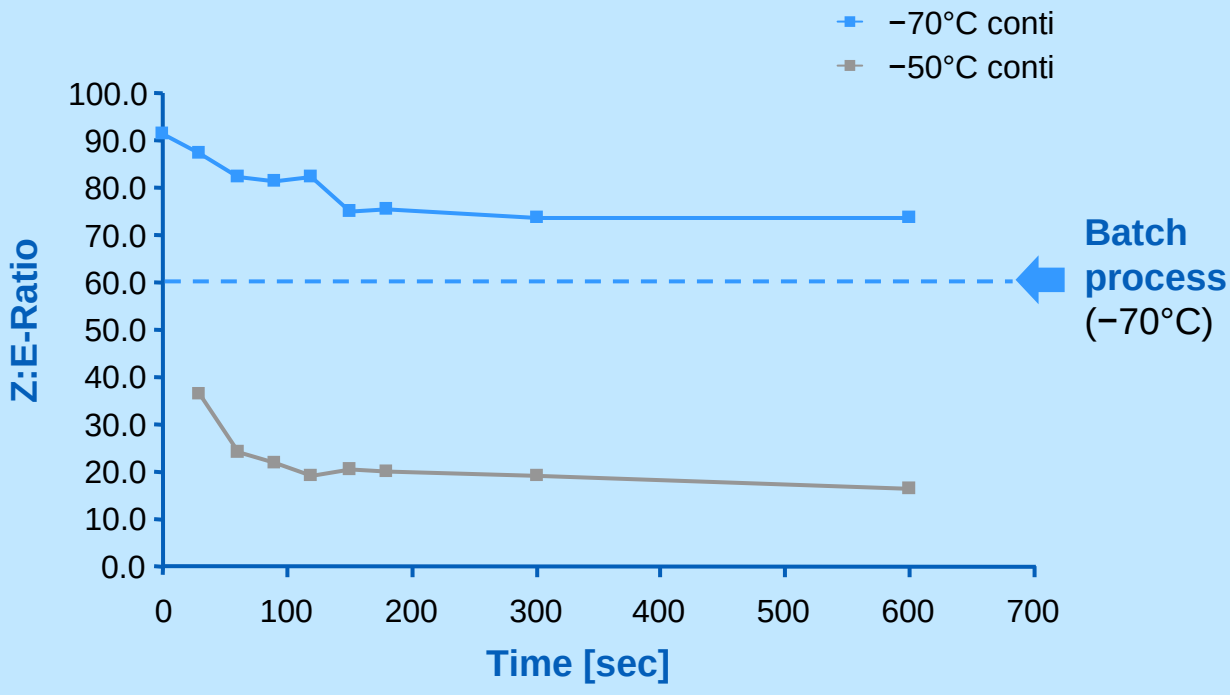
Case Study

Continuous Mode – Reaction Rate

Influence of temperature



- Reaction extremely fast (both steps)
- Selectivity higher than batch mode
- The lower the temperature the better

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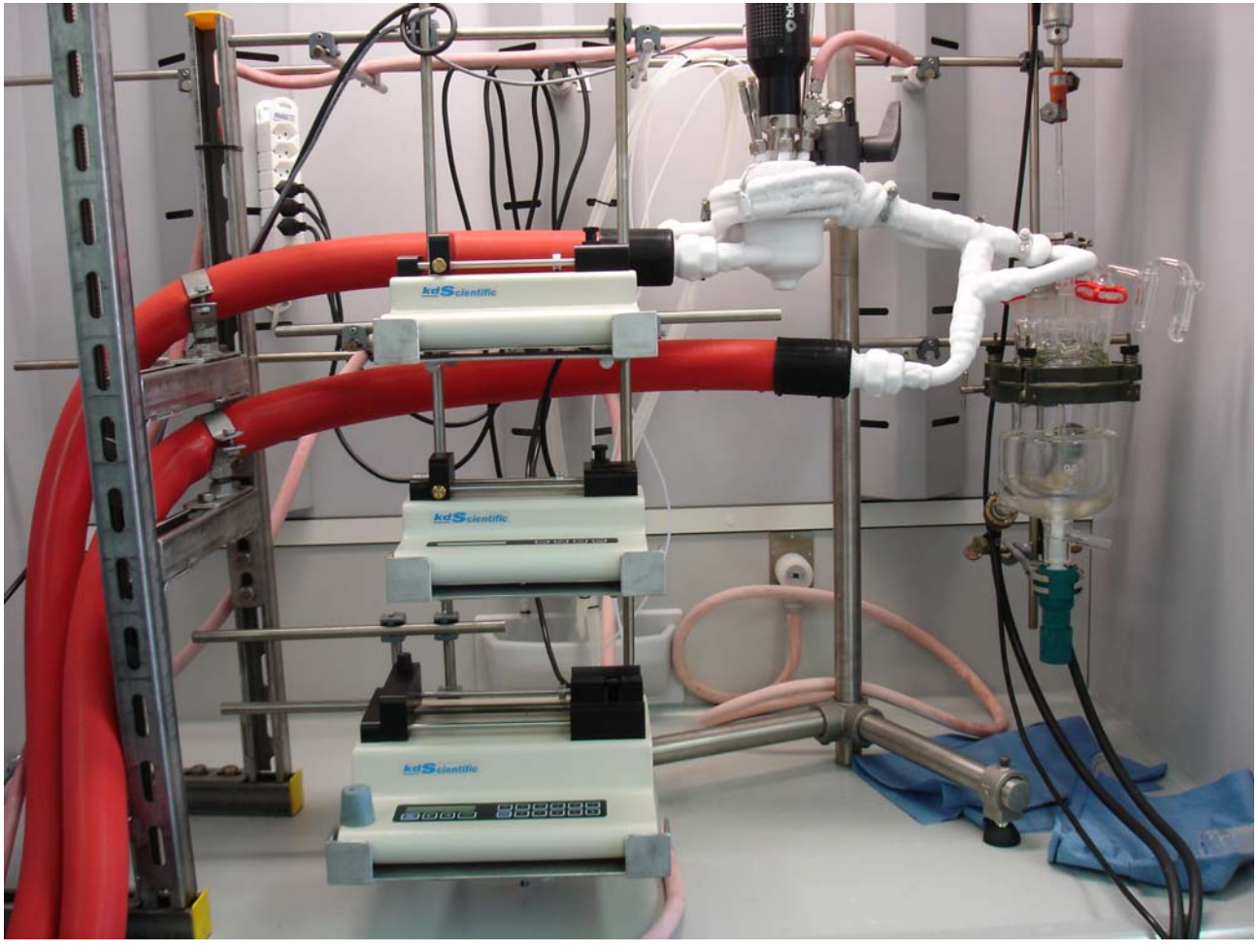
Case Study

Continuous Reaction Equipment

Laboratory Equipment

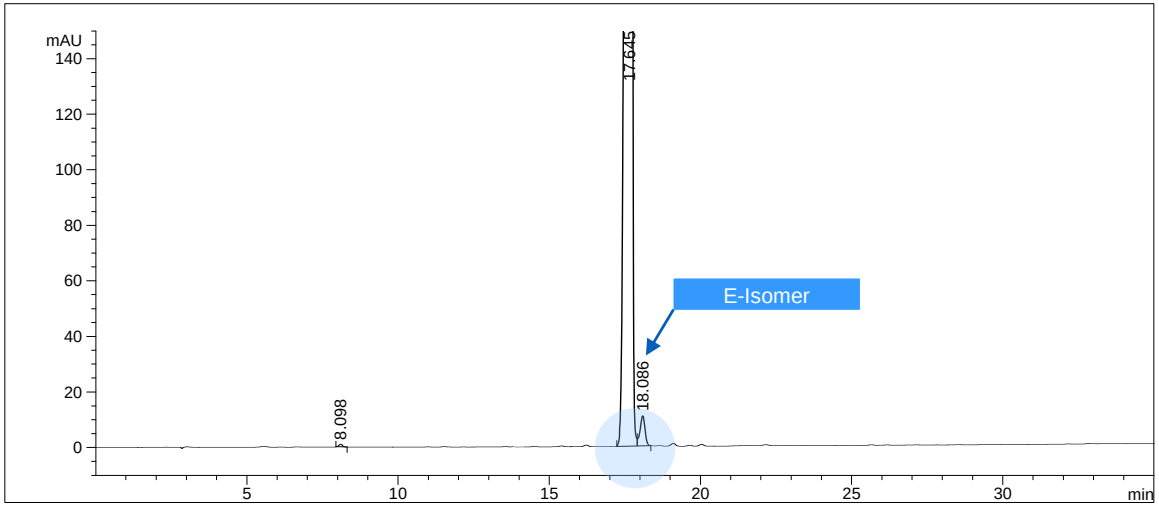


Case Study

Proof of Concept/Results

Impurity profile – reference standard from batch mode (purified by recryst)

Impurity profile – material from continuous process crude



- Combination low temperature and continuous technology
- Higher Selectivity
- Cleaner reaction/improved impurity profile
- Constant quality over time
- Minimum of risk
  - Only small amounts material in production

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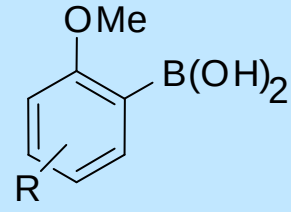
Content

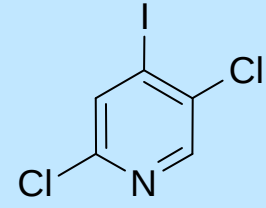
Lithiation to new Intermediates for C-C Coupling Process

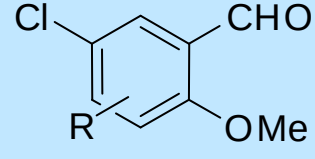
Lithiated inter-mediates

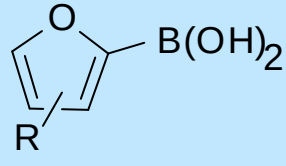
- Alkylation
- Formylation
- Halogenation
- Metallation
- Formation of boronic acid

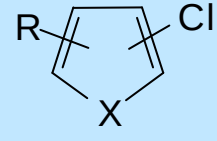
Intermediates for C-C Coupling











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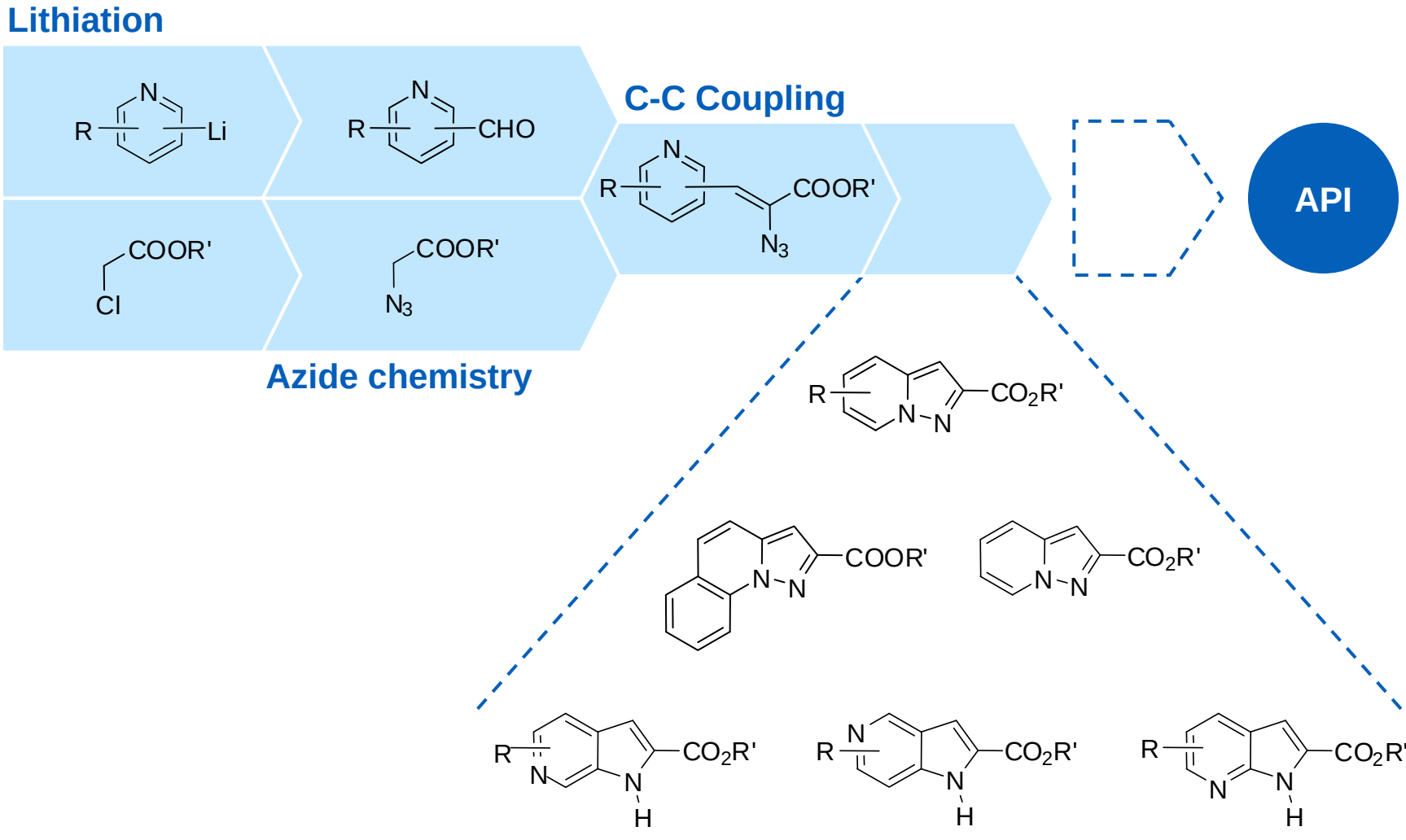
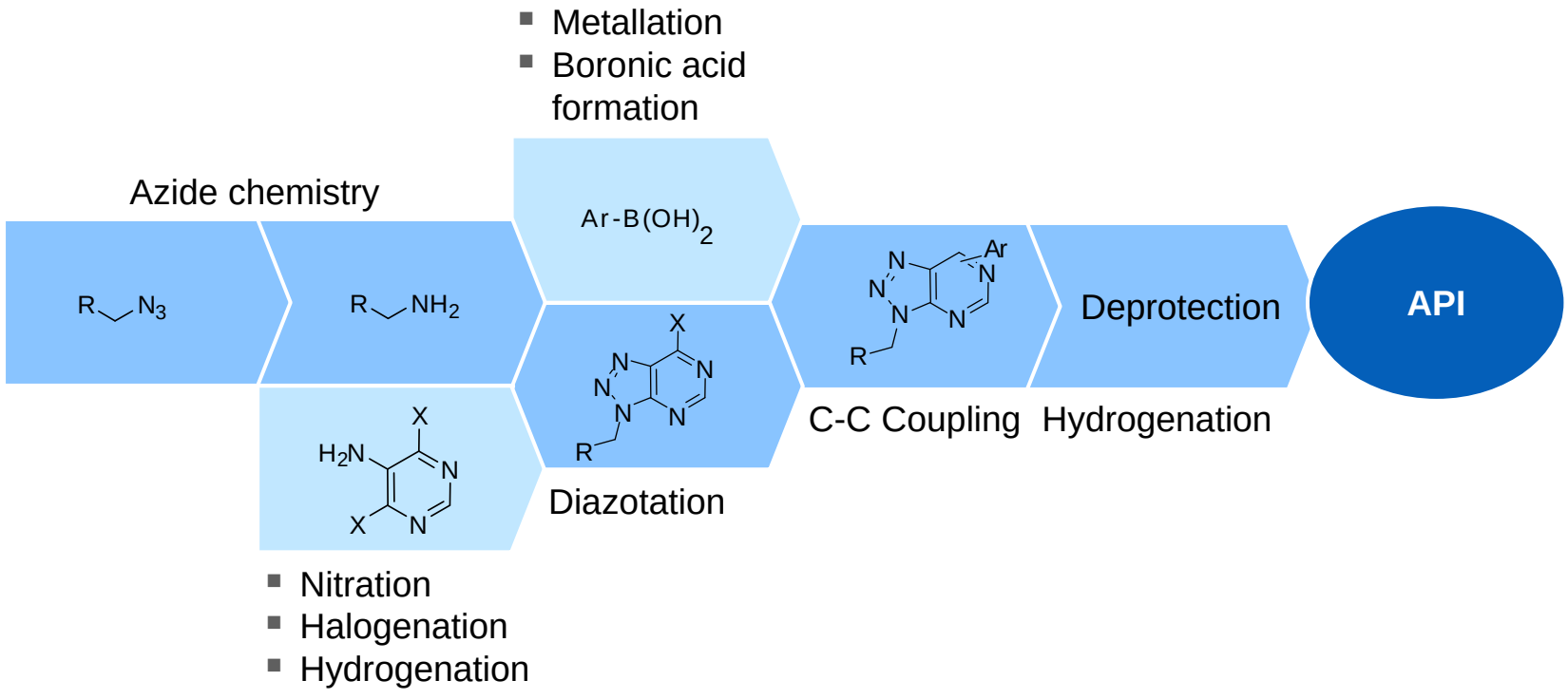
Lithiation to new Building Blocks

Combination of Low Temperature with Hazardous Chemistry



Combination of all Elements of DOTTIKON Technology Platform Makes API Manufacturing Efficient

ILLUSTRATIVE



Straight forward and efficient APIs process includes

- Hazardous Reactions
- Use of low temperature technology
- Continuous process
- High pressure technology

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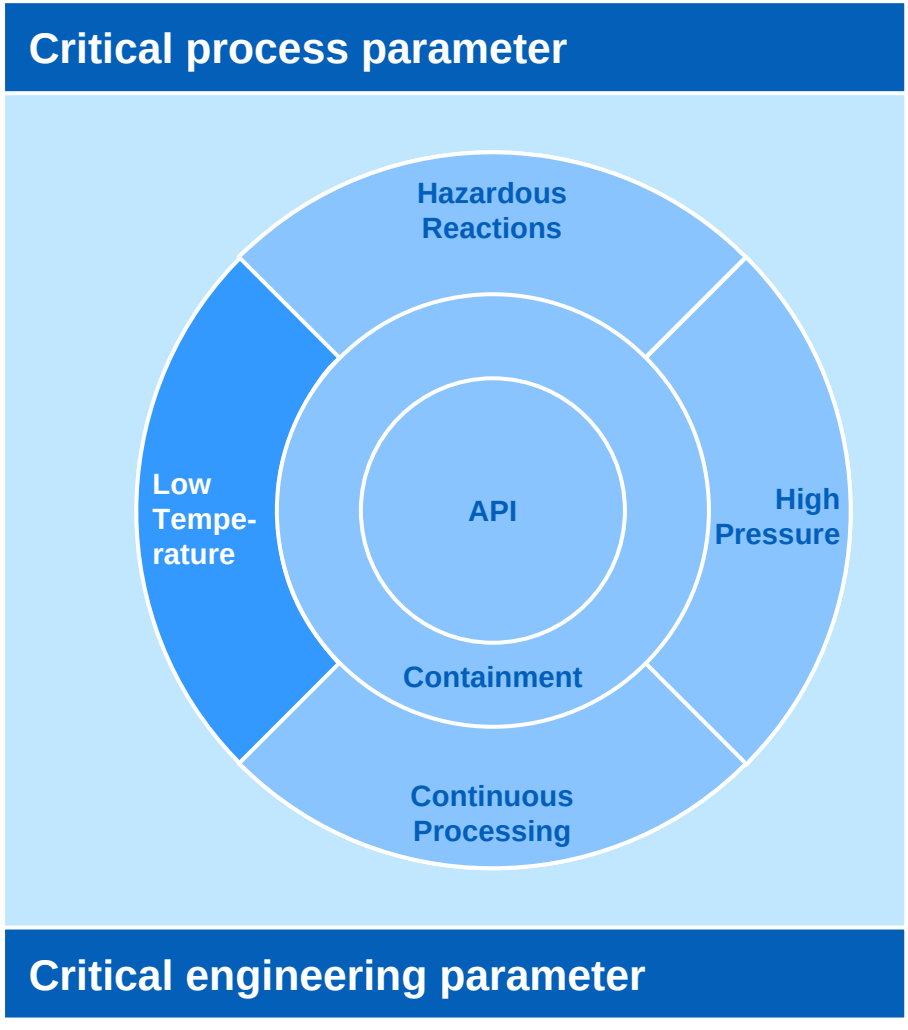
Summary



Combination of low temperature chemistry with other core technologies of DOTTIKON results in the key benefits

- Processes with higher selectivity, higher yield and improved impurity profiles
- Access to a broad variety of advanced intermediates and APIs

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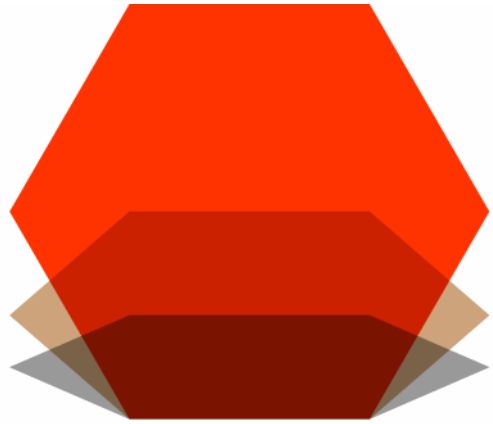
Team



Visit us at booth no A5

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