Process Intensification in Small Scale Pharmaceutical Production

Aleksandar Mitic

Prof. Krist V. Gernaey (PROCESS-CAPEC, DTU Chemical Engineering)

Prof. Kim-Dam Johansen (CHEC, DTU Chemical Engineering)

MS Tommy Skovby (H. Lundbeck A/S)

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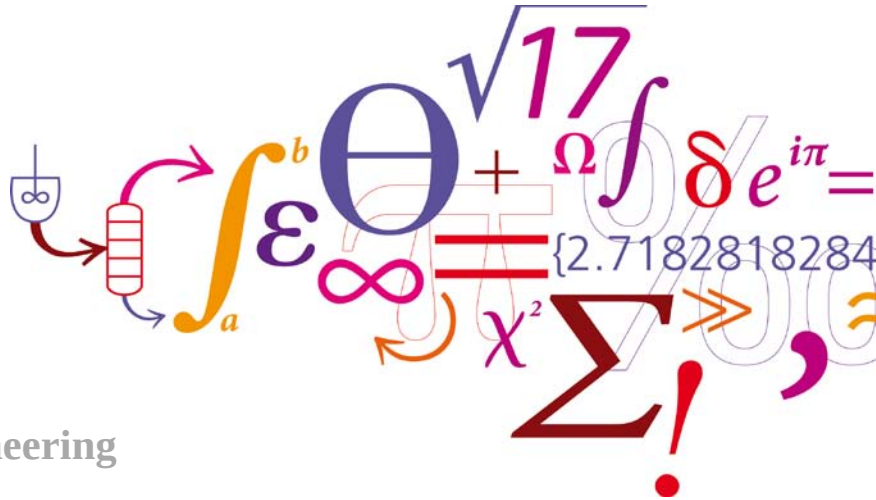
NL GUTS & PIN-NL
Separation and Process Intensification
Bronswerk Heat Transfer Nijkerk
The Netherlands



DTU Chemical Engineering

Department of Chemical and Biochemical Engineering

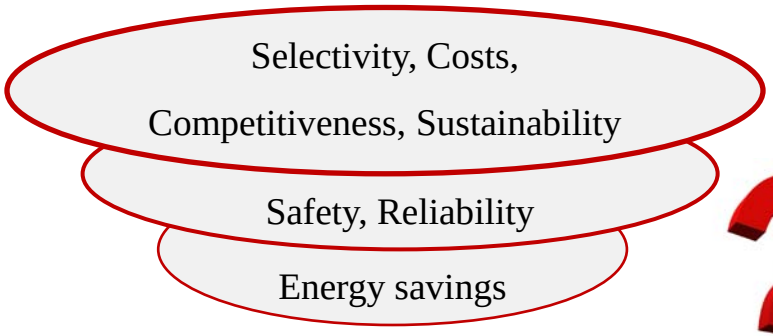
Outline

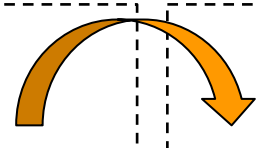
- Process intensification
- Example process
- Synthetic route towards Clopenthixol
- Manufacturing route towards Clopenthixol
  - Grignard alkylation
  - Hydrolysis and separation L-L
  - Dehydration reaction
  - Hydroamination reactions
- Conclusions and future perspectives

Process intensification

- Definition:
  - "PI provides radically innovative principles ('paradigm shift') in process and equipment design which can benefit (often with more than a factor two) process and chain efficiency, capital and operating expenses, quality, wastes, process safety and more" (*EFCE in European Roadmap for Process Intensification*)

Major drivers





Goals

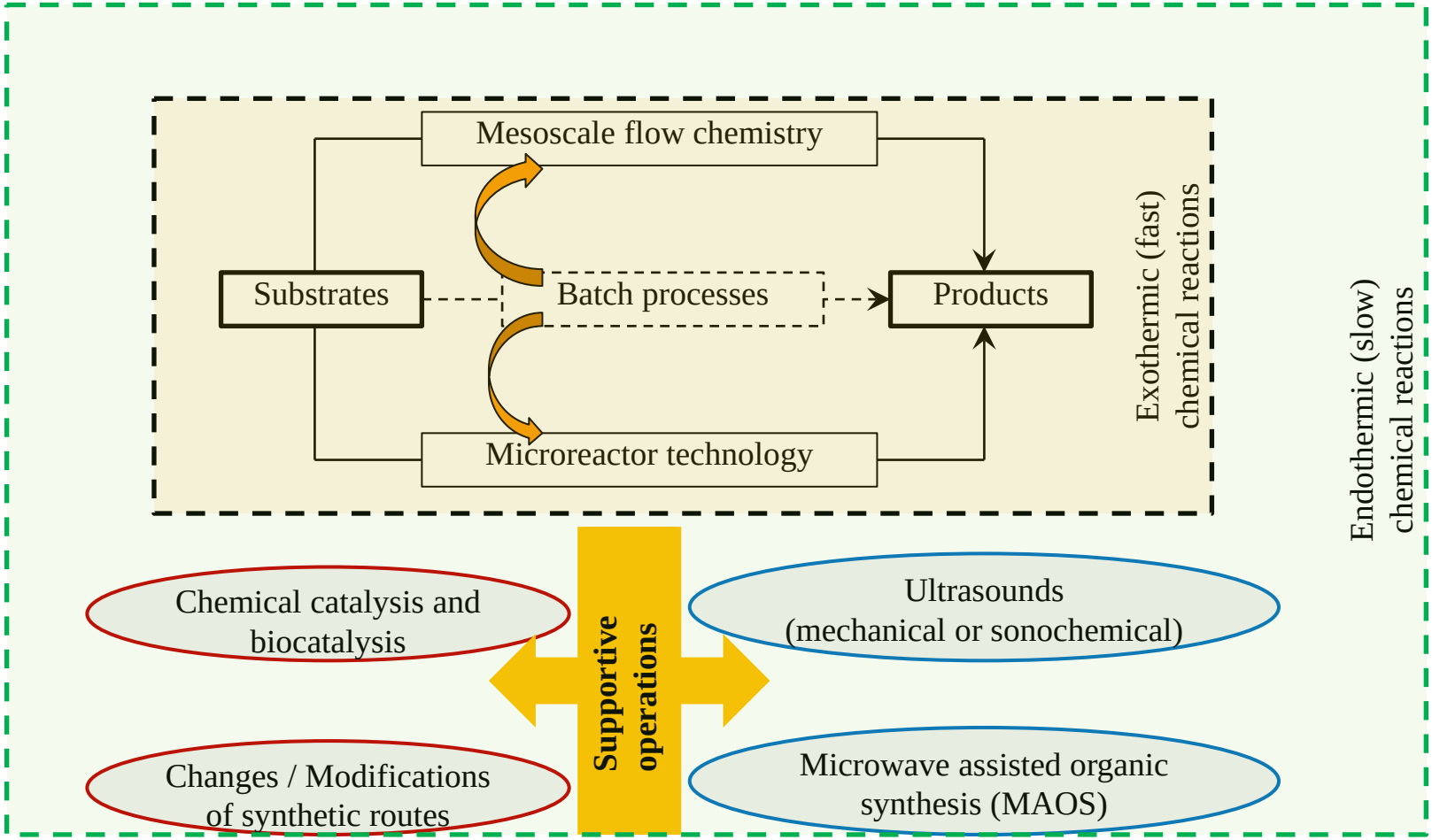
- ✓ cheaper processes
- ✓ smaller equipment/plants
- ✓ safer processes
- ✓ less energy consumption
- ✓ shorter time to market
- ✓ less waste/by-products
- ✓ better company image

Dechema. *European Roadmap for Process Intensification. Creative Energy - Energy Transition.*

Moulijn, J. A.; Stankiewicz, A. I. *Re-engineering the chemical processing plant: process intensification.* Marcel Dekker, Inc.: New York, USA, Vol. 982003.

Process intensification

- Small scale pharmaceutical production



Process intensification

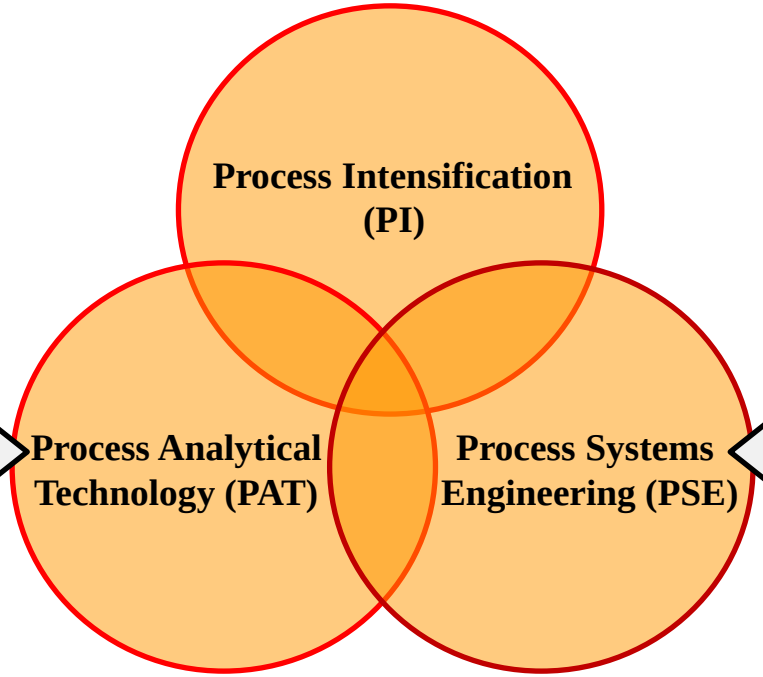
- Cooperation with other disciplines important for the pharmaceutical industry

Goals:

- ✓ Deeper understanding of process
- ✓ Higher production quality
- ✓ Lower production costs
- ✓ Self-adjusting production processes
- ✓ ...

Tools:

- ✓ Process analyzers
- ✓ Process chemometrics
- ✓ Real time process monitoring and control
- ✓ Automation



Goals:

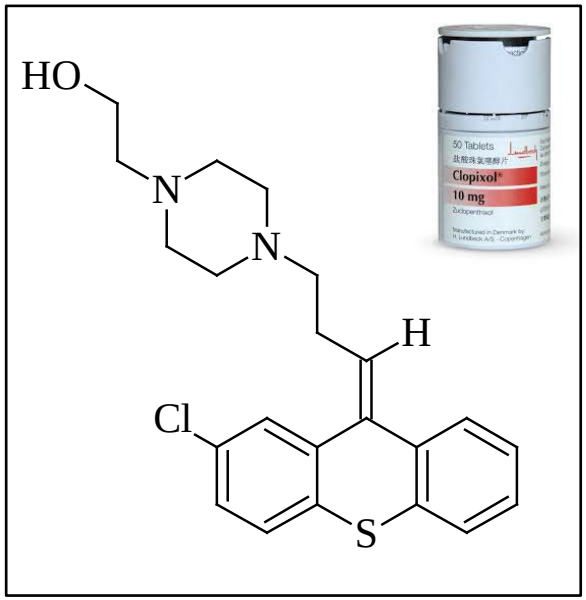
- ✓ Efficient usage of resources
- ✓ New simulation methods and decision making tools
- ✓ Functional, integrated design of product and processes
- ✓ Optimization of performance
- ✓ ...

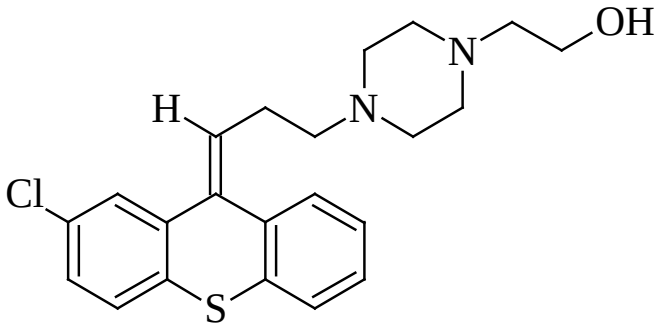
Tools:

- ✓ Numerical analyses, optimization methods
- ✓ Informatics and intelligent systems
- ✓ ...

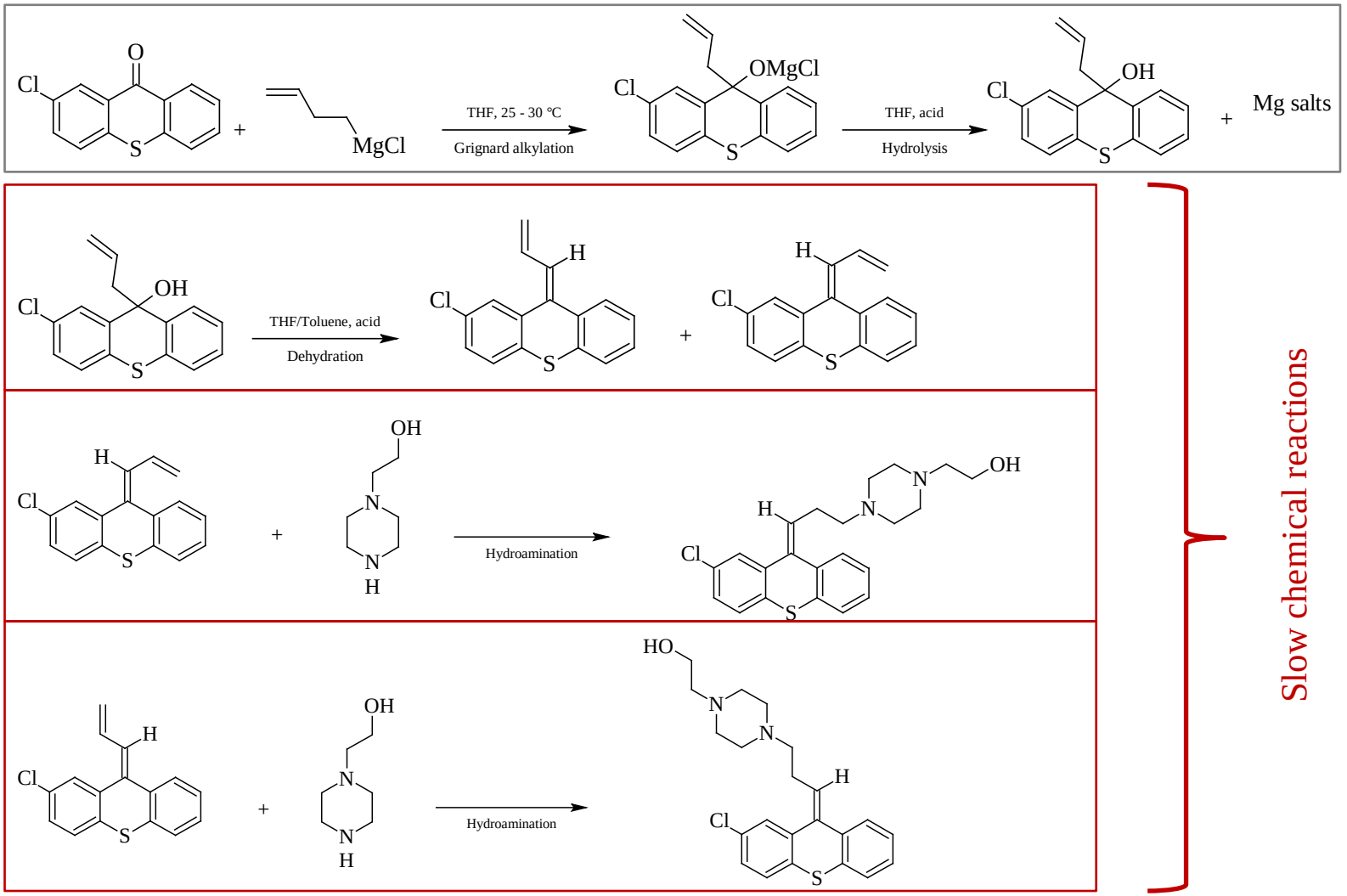
Example process

- Clopenthixol
  - a product of H. Lundbeck A/S
  - thioxanthene compound as a mixture of two geometrical isomers
  - cis-isomer (API) – Zuclopenthixol
  - treating schizophrenia and mania

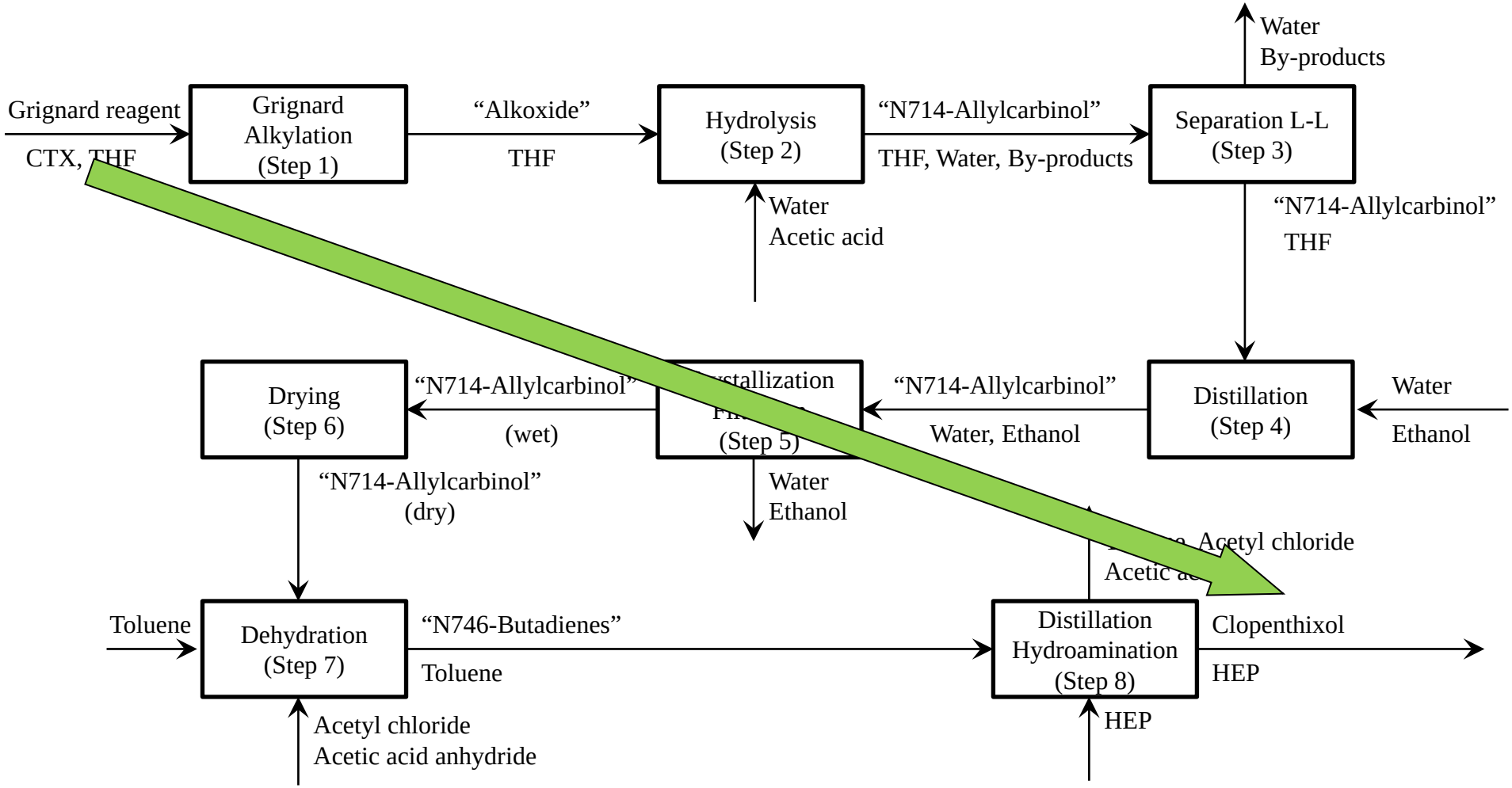




Synthetic route towards Clopenthixol



Manufacturing route towards Clopenthixol



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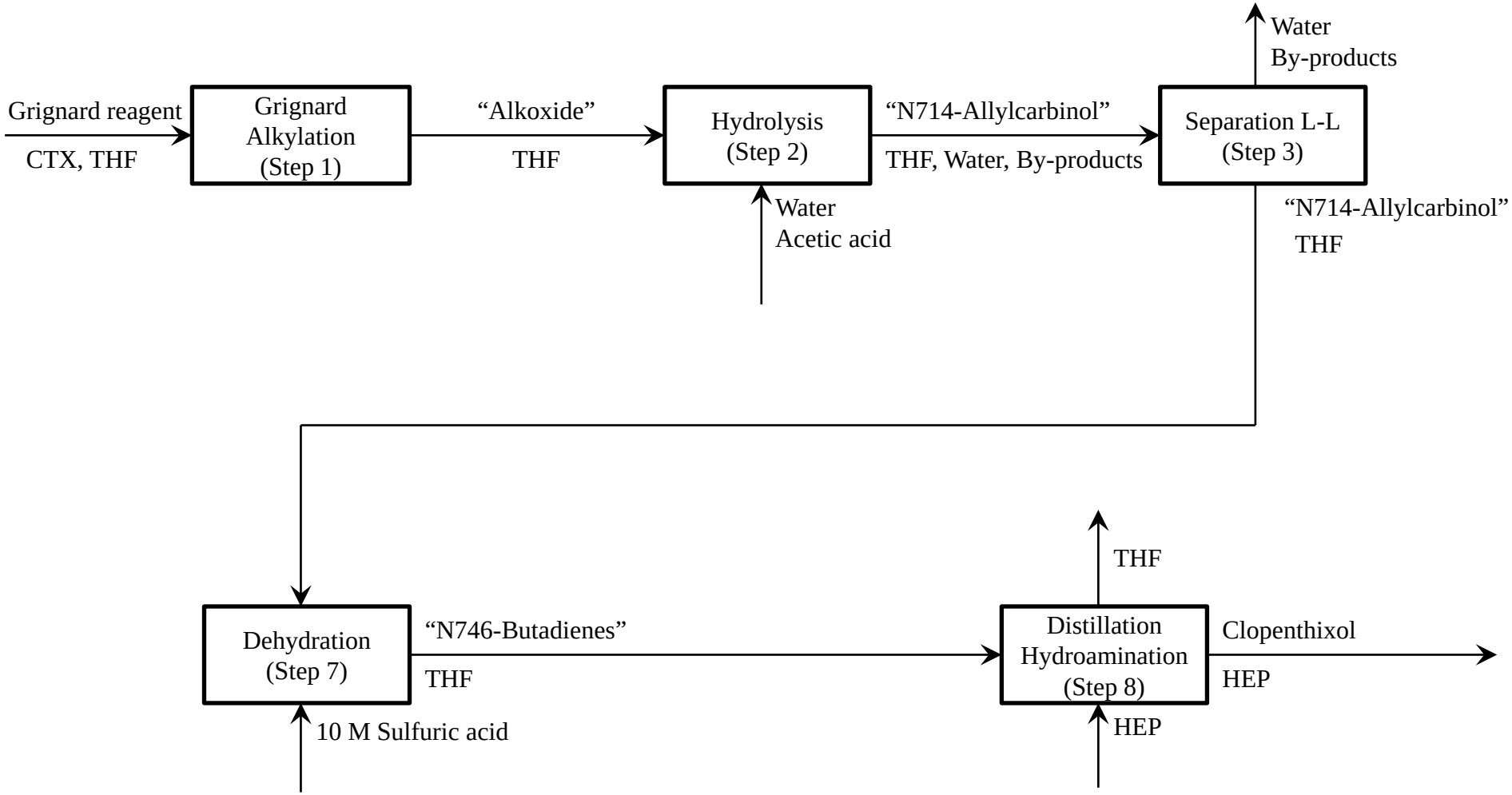
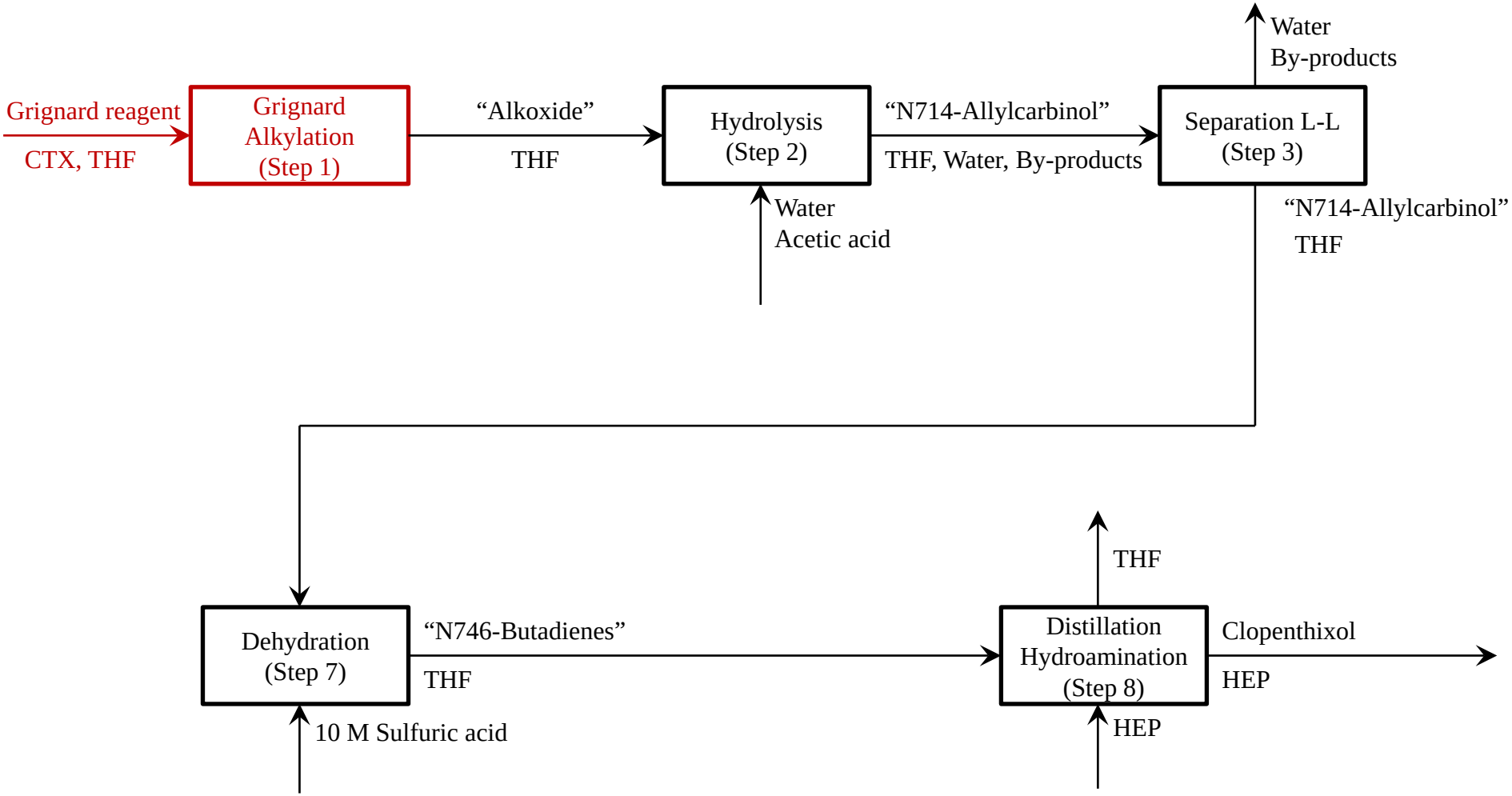


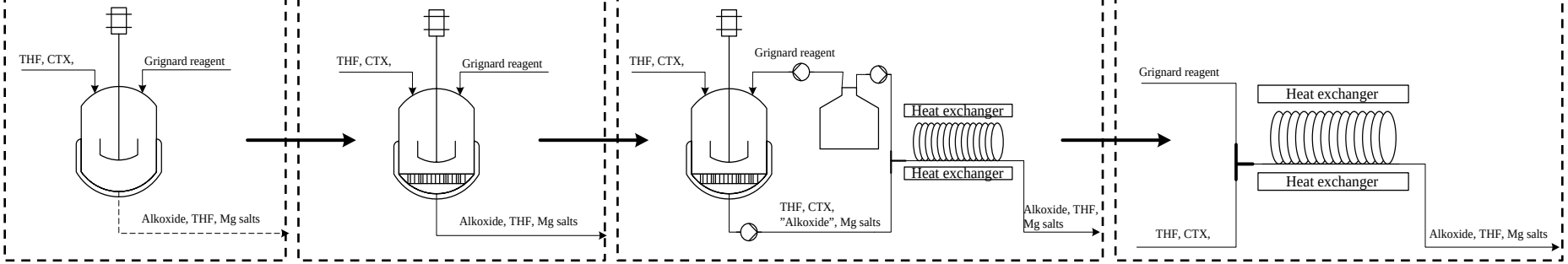
Manufacturing route towards Clopenthixol



Grignard alkylation

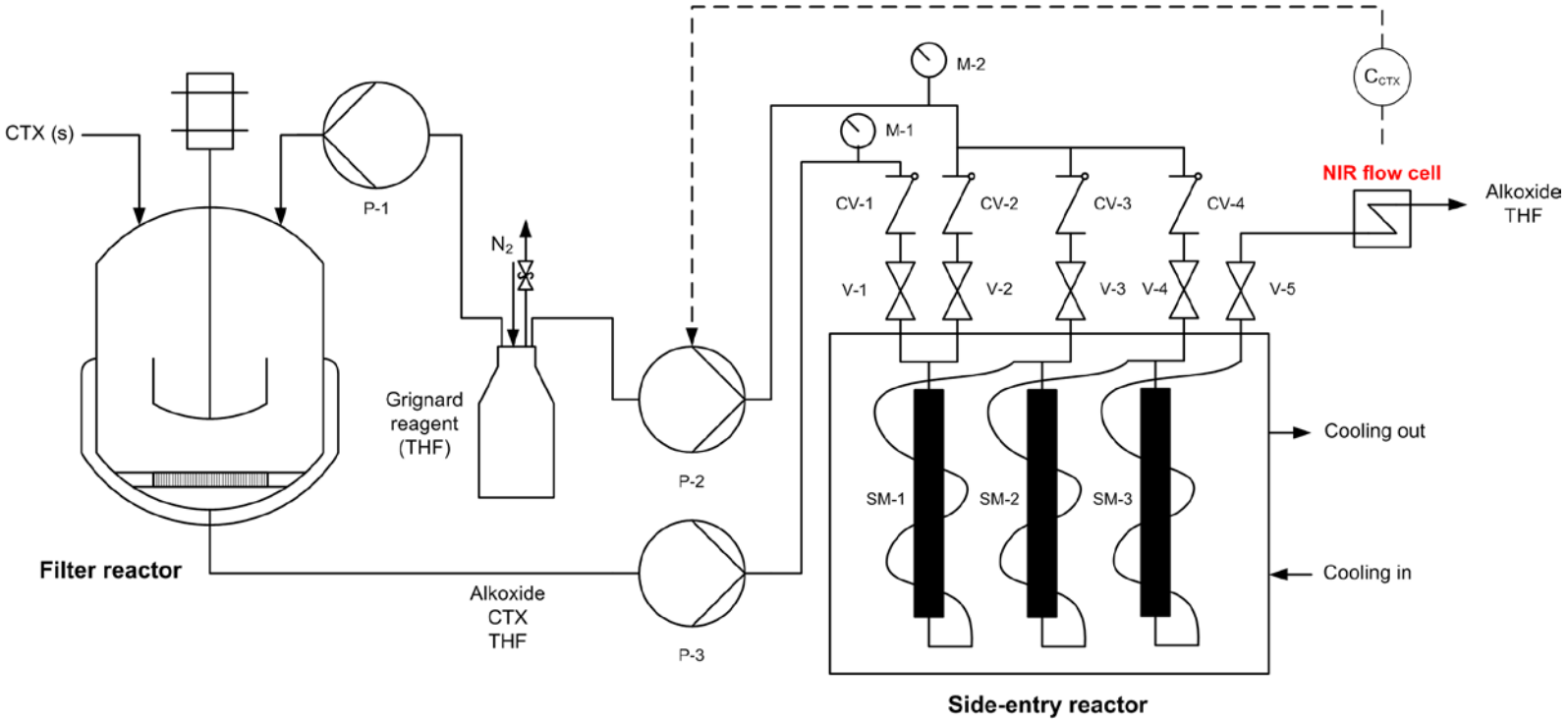
- Action plan

• Batch mode	• Filter reactor	• Filter reactor and mesoscale tubular reactor	• Mesoscale tubular reactor
• Room temperature	• Room temperature	• Room temperature	• Room temperature
• Solubility of CTX in THF	• Solubility of CTX in THF	• Solubility of CTX in THF regulated with a filter	• Solubility of CTX in THF is issue again
• Inadequate dosage of Grignard reag.	• Inadequate dosage of Grignard reag.	• Good dosage of Grignard reag.	• Inadequate dosage of Grignard reagent



Grignard alkylation

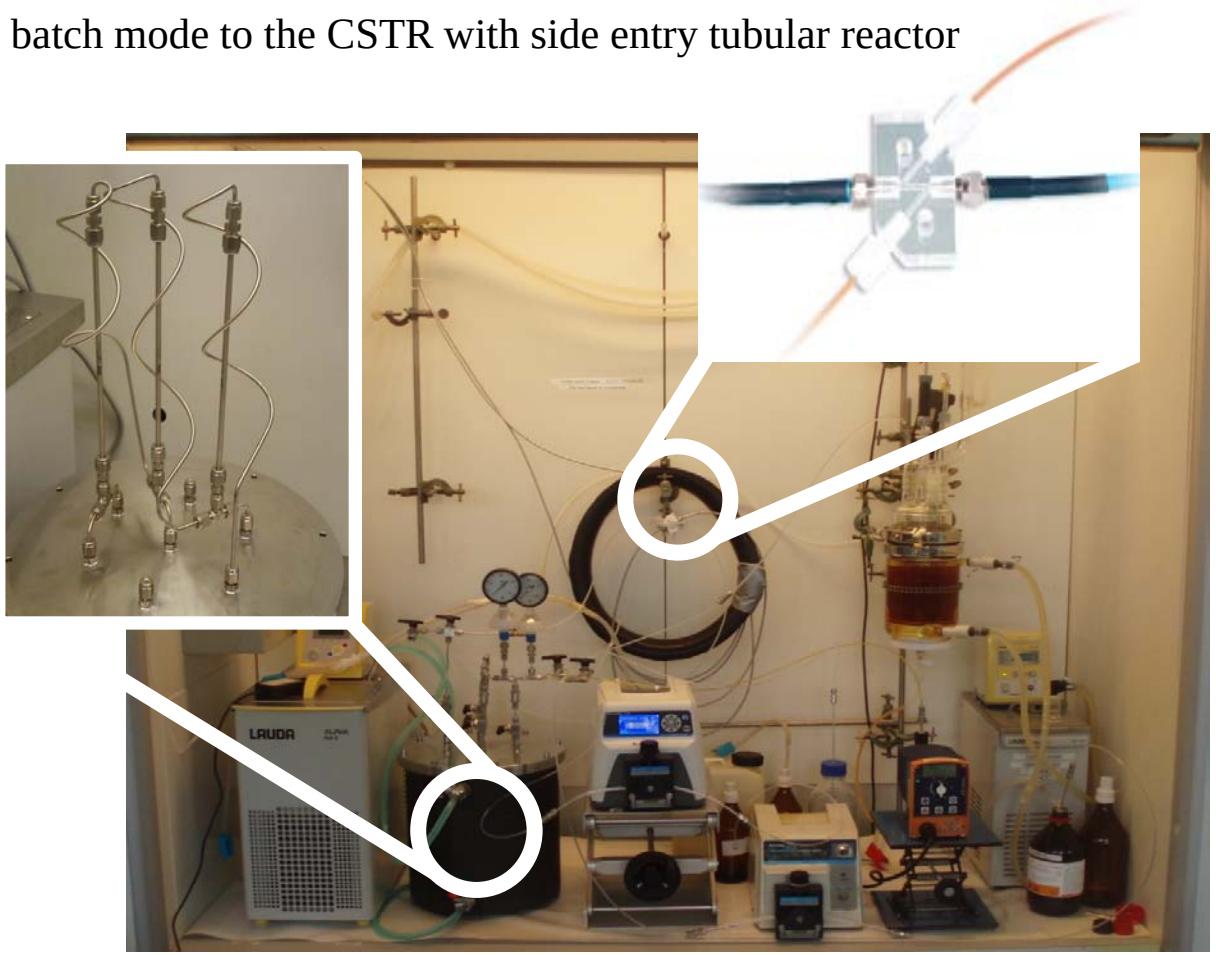
- Switch from batch mode to the CSTR with side entry tubular reactor



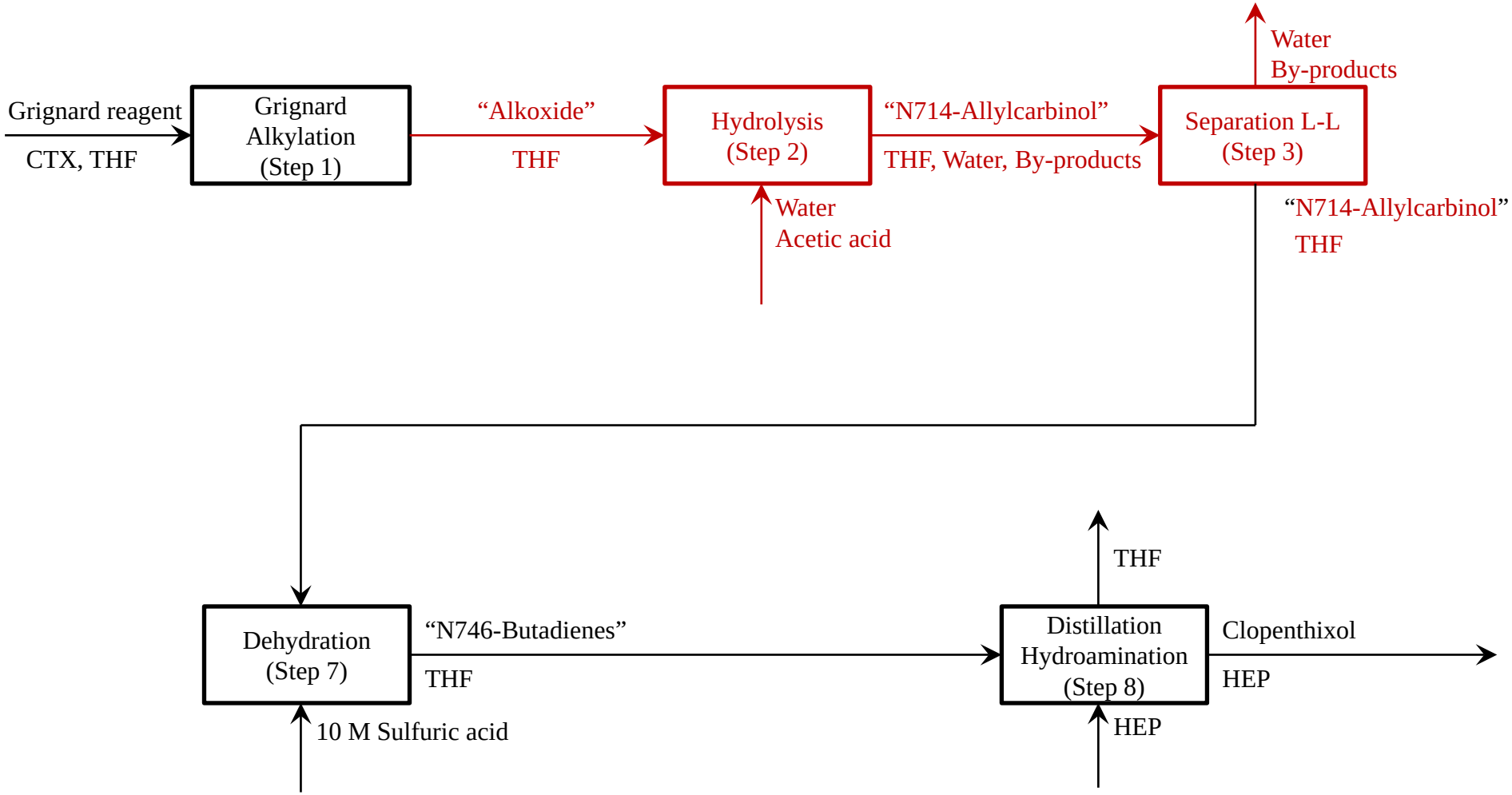
Cervera-Padrell, A. E.; Nielsen, J. P.; Jønch Pedersen, M.; Müller Christensen, K.; Mortensen, A. R.; Skovby, T.; Dam-Johansen, K.; Kiil, S.; Gernaey, K. V. *Monitoring and Control of a Continuous Grignard Reaction for the Synthesis of an Active Pharmaceutical Ingredient Intermediate Using Inline NIR spectroscopy*. Organic Process Research & Development **2012**, 16 (5), 901-914

Grignard alkylation

- Switch from batch mode to the CSTR with side entry tubular reactor

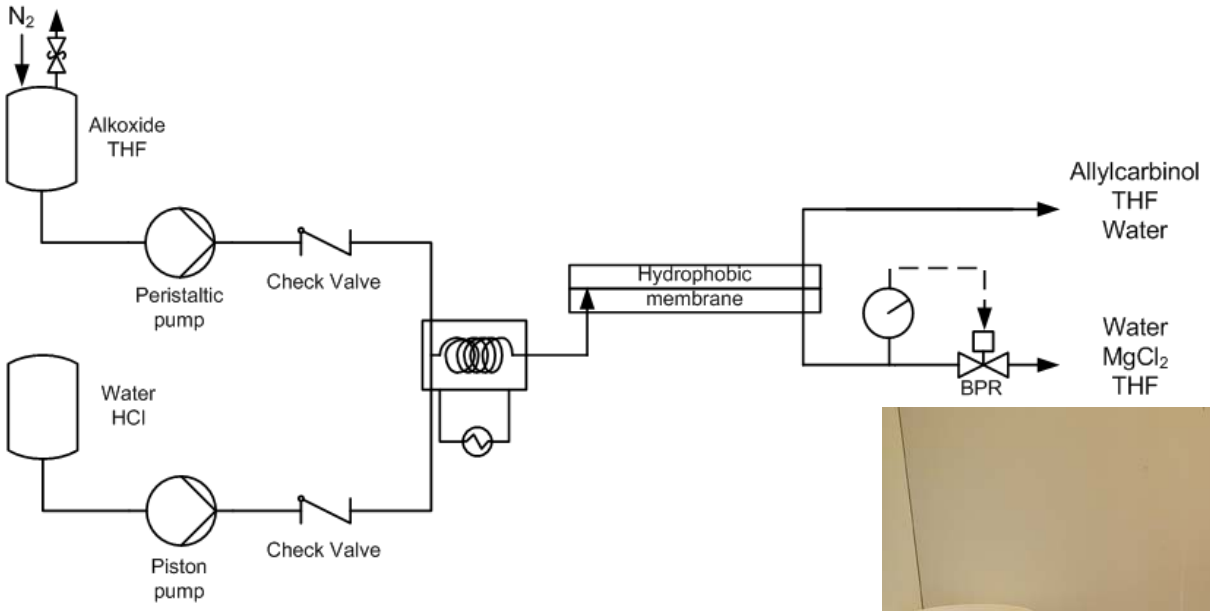


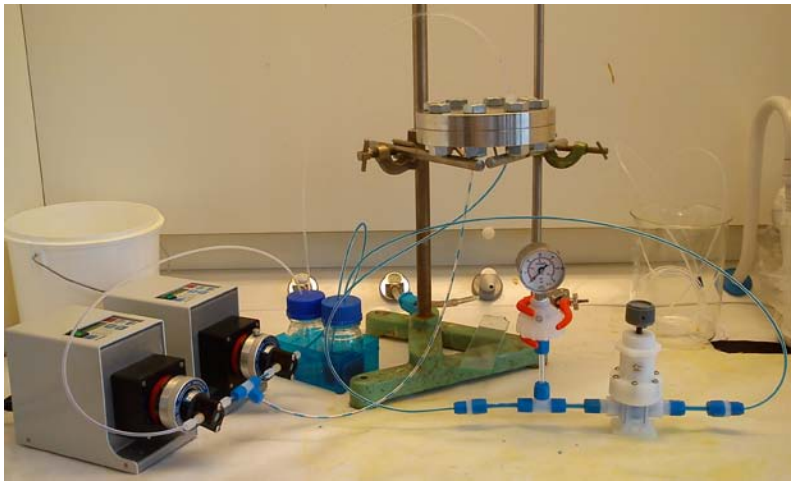
Manufacturing route towards Clopenthixol



Hydrolysis and separation L-L

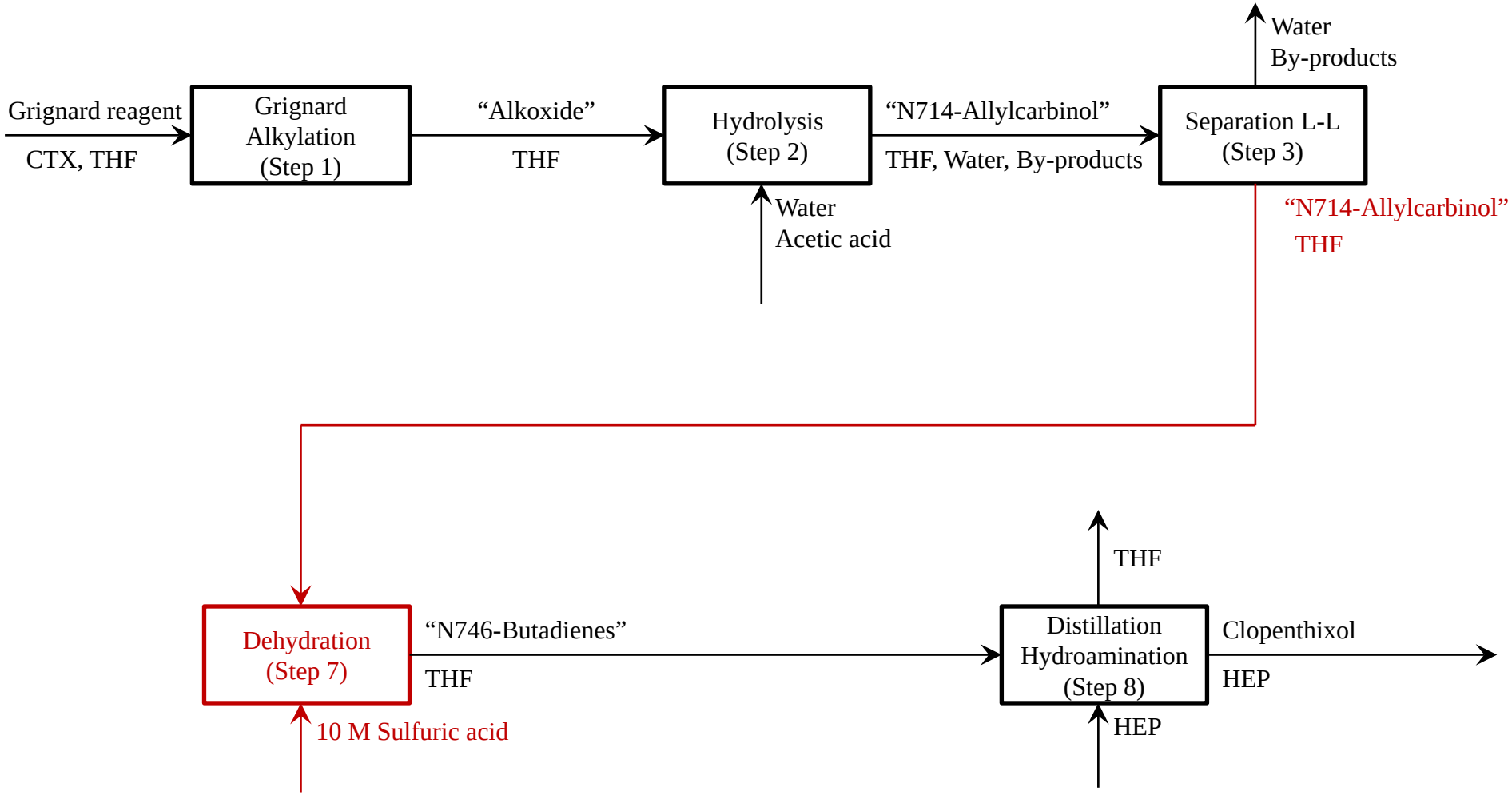
- Switch from batch mode to tubular laminar reactor with consequent L-L sepration with miniscale hydrophobic PTFE membrane separator





Cervera-Padrell, A. E.; Morthensen, S. T.; Lewandowski, D. J.; Skovby, T.; Kiil, S.; Gernaey, K. V. *Continuous Hydrolysis and Liquid–Liquid Phase Separation of an Active Pharmaceutical Ingredient Intermediate Using a Miniscale Hydrophobic Membrane Separator*. Organic Process Research & Development **2012**, 16 (5), 888-900

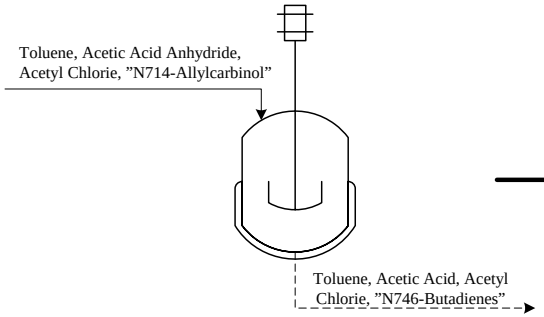
Manufacturing route towards Clopenthixol



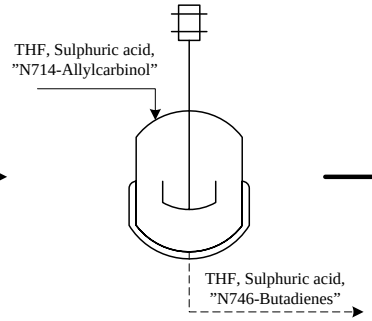
Dehydration reaction

- Action plan

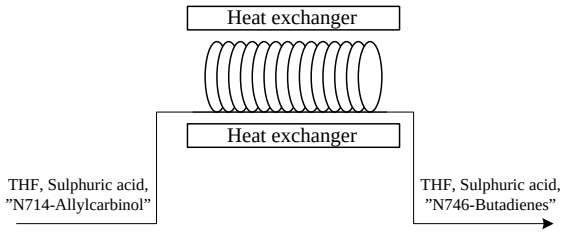
- 2 h for complete conversion
- Reflux conditions in batch mode
- Acetic acid anhydride and acetyl chloride – catalytic system
- Toluene as a solvent



- 3 h for complete conversion
- Reflux conditions in batch mode
- Sulphuric acid used as a chemical catalyst
- THF used as a solvent

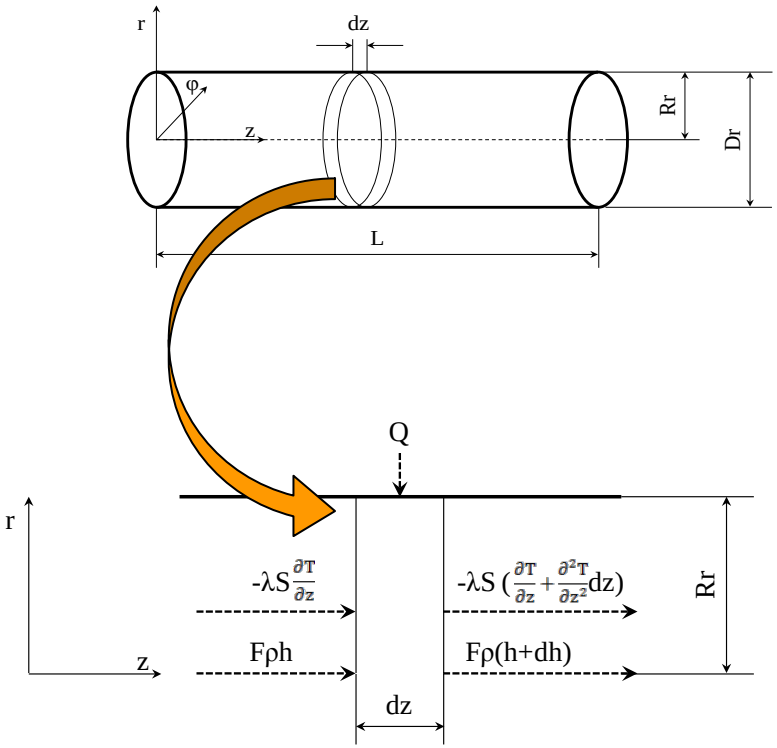


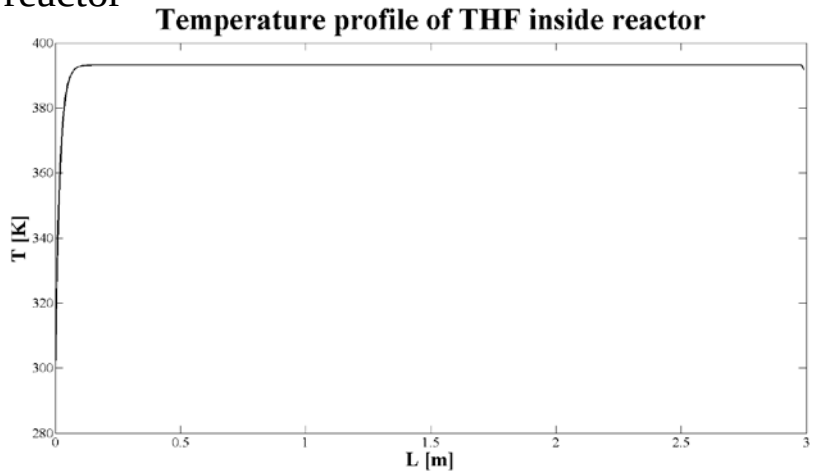
- 3 min for complete conversion
- Increased pressure in the system
- Sulphuric acid used as a chemical catalyst
- THF used as a solvent

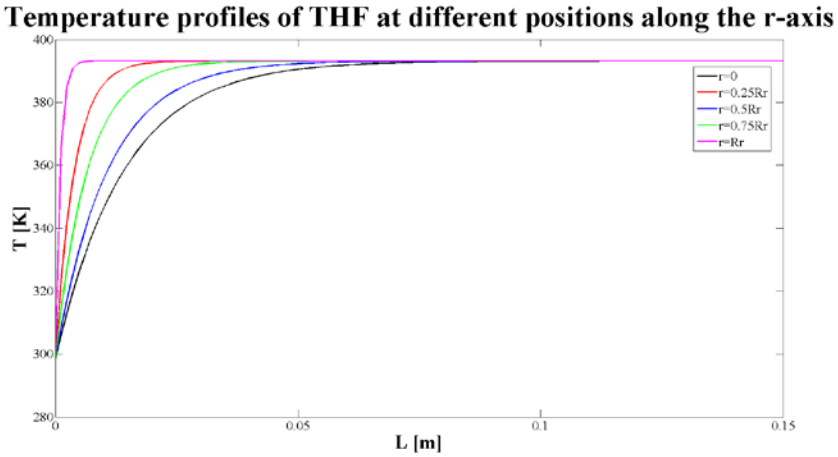


Dehydration reaction

- Switch from batch towards mesoscale tubular reactor



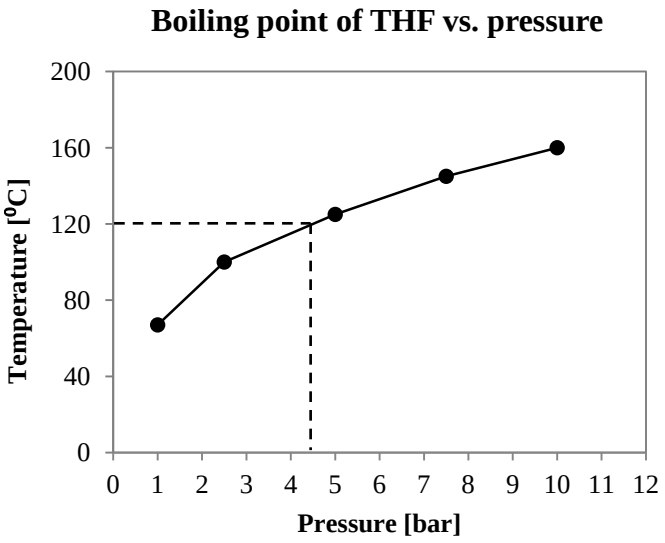




Dehydration reaction

- Constraints:

1. Low boiling point of THF



✓

2. High molar concentration of sulphuric acid cause formation of impurities

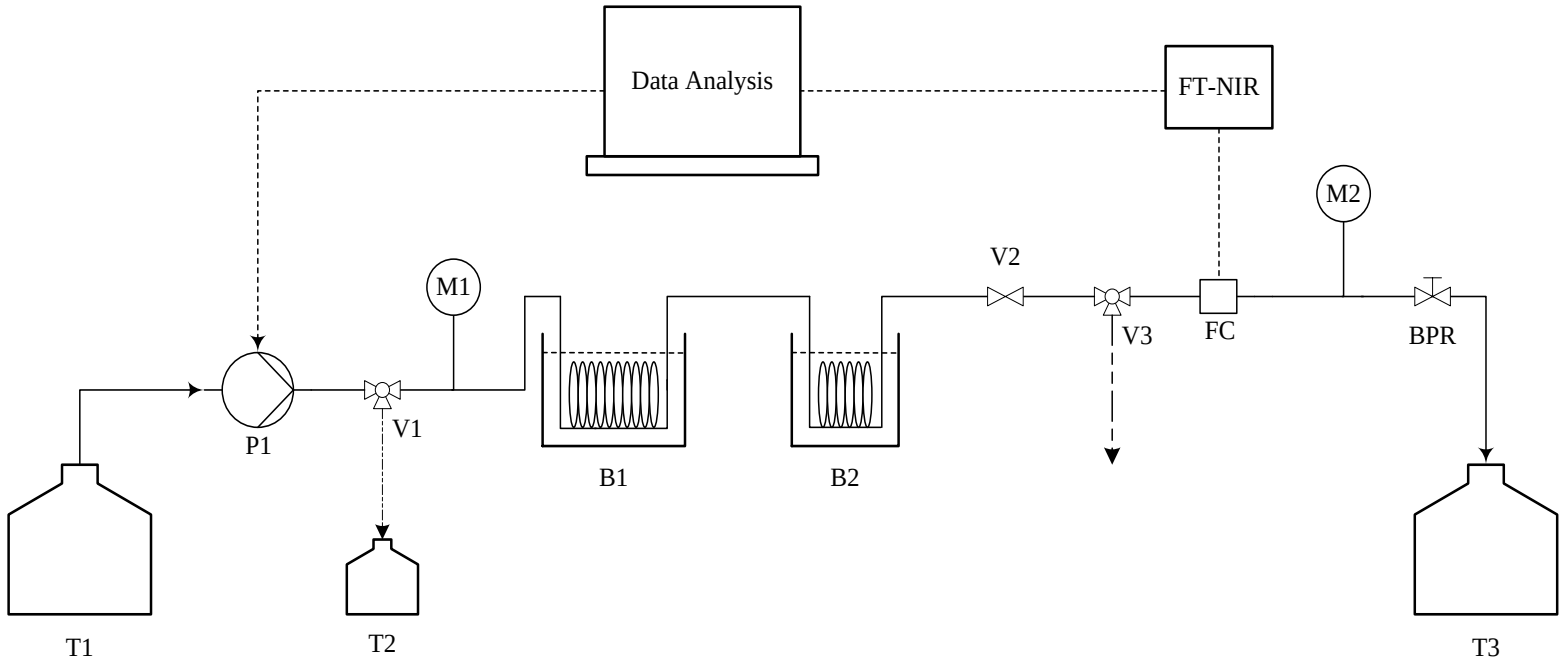
Below 12 M of H_2SO_4 ✓

3. Limited solubility of water in THF

Below 1.4 M of H_2O ✓

Dehydration reaction

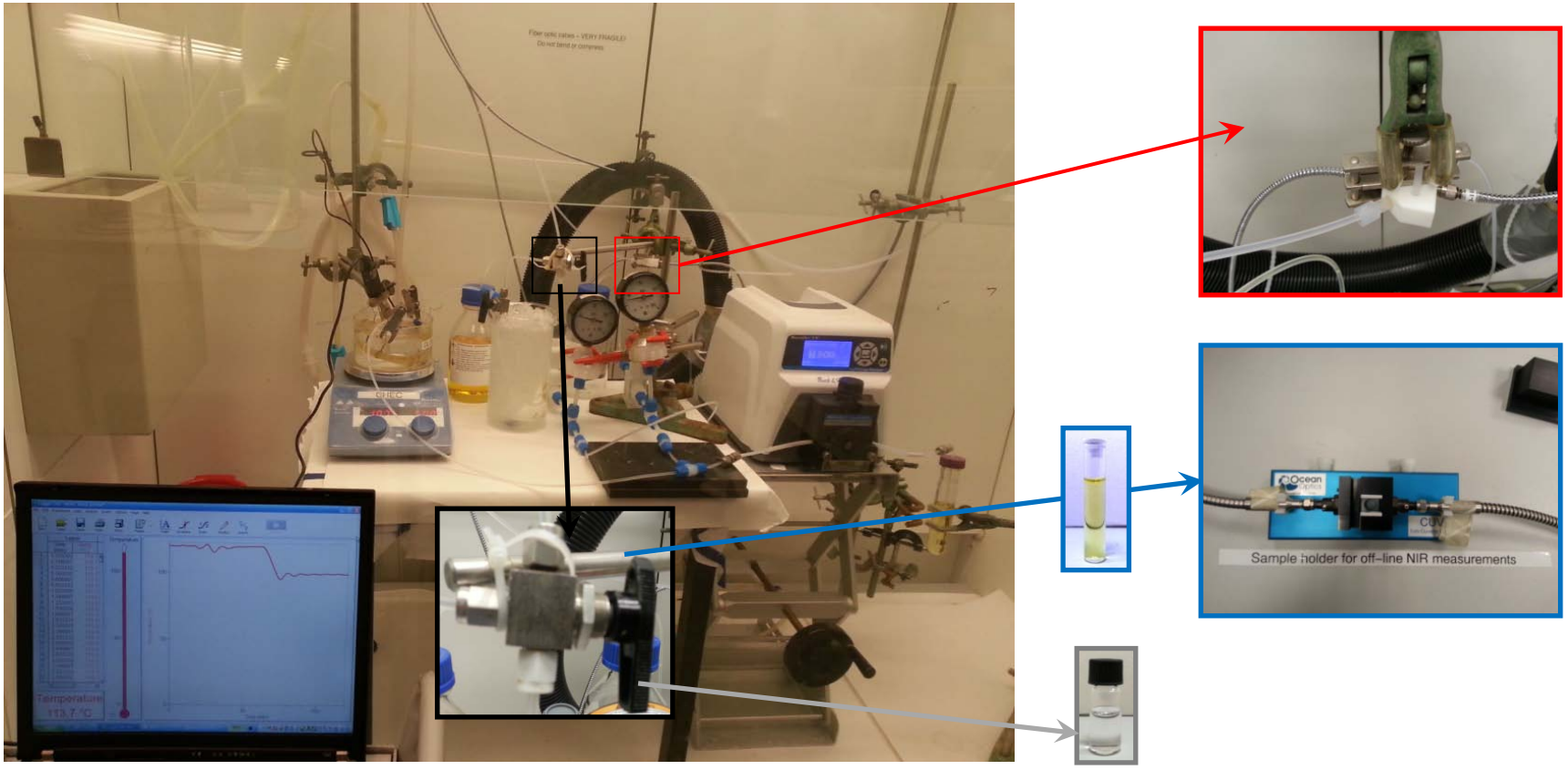
- Switch from batch towards mesoscale tubular reactor



Mitic, A.; Cervera-Padrell, A., E.; Mortensen, A., R.; Skovby, T.; Dam-Johansen, K.; Javakhishvili, I.; Gernaey, K. V. *Application of a Mesoscale Laminar Tubular Reactor in the Manufacturing of an Active Pharmaceutical Ingredient (API) Intermediate*. Organic Process Research & Development (in preparation)

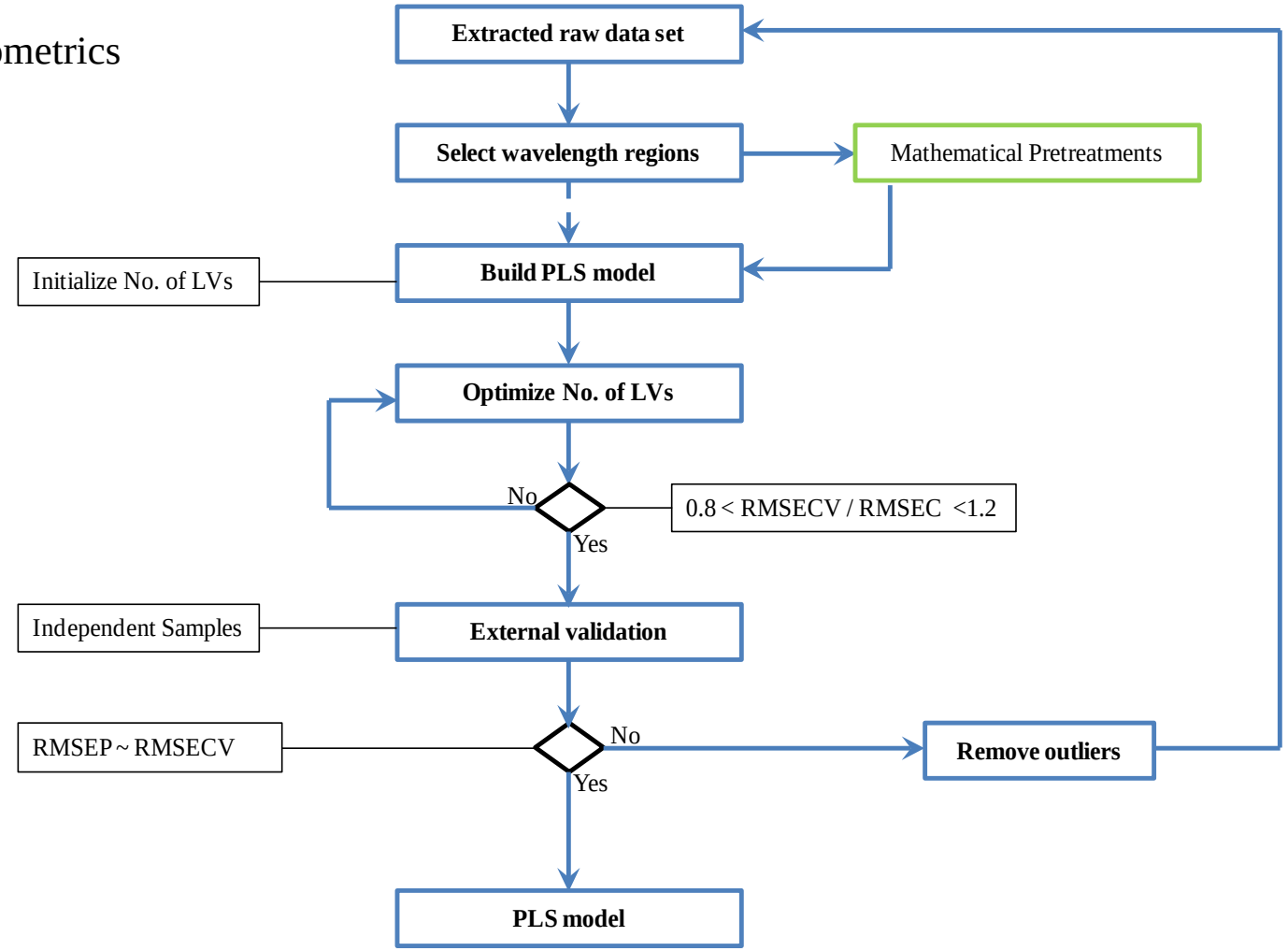
Dehydration reaction

- Switch from batch towards mesoscale tubular reactor



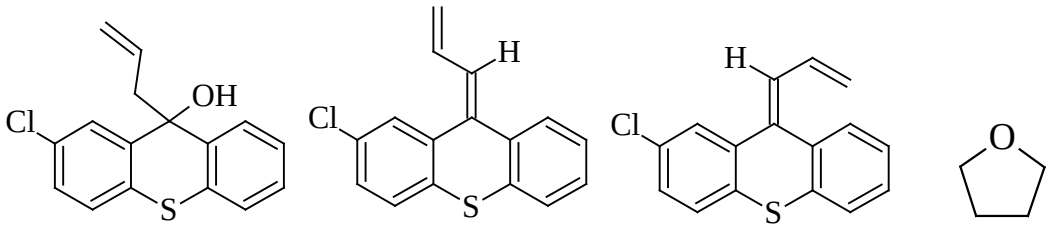
Dehydration reaction

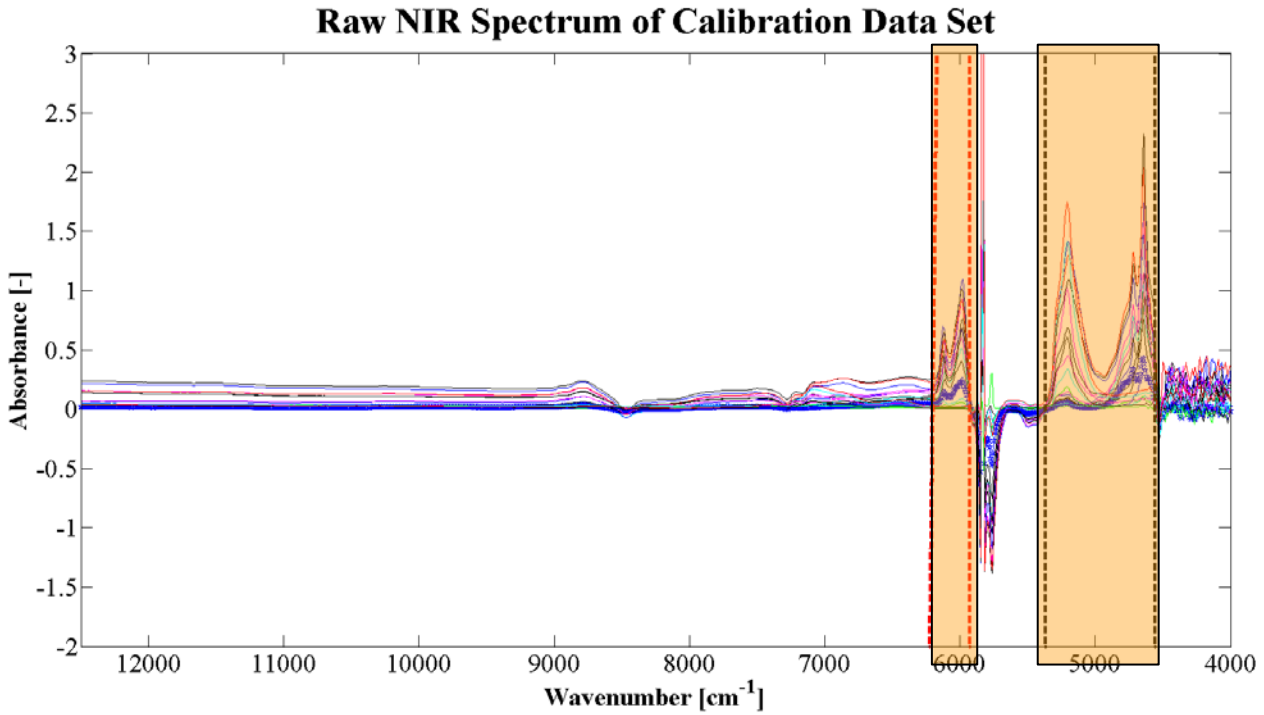
- Process Chemometrics



Dehydration reaction

- Constituents
  1. THF
  2. H_2O
  3. “N714-Allylcabinol”
  4. “N746-Butadienes”





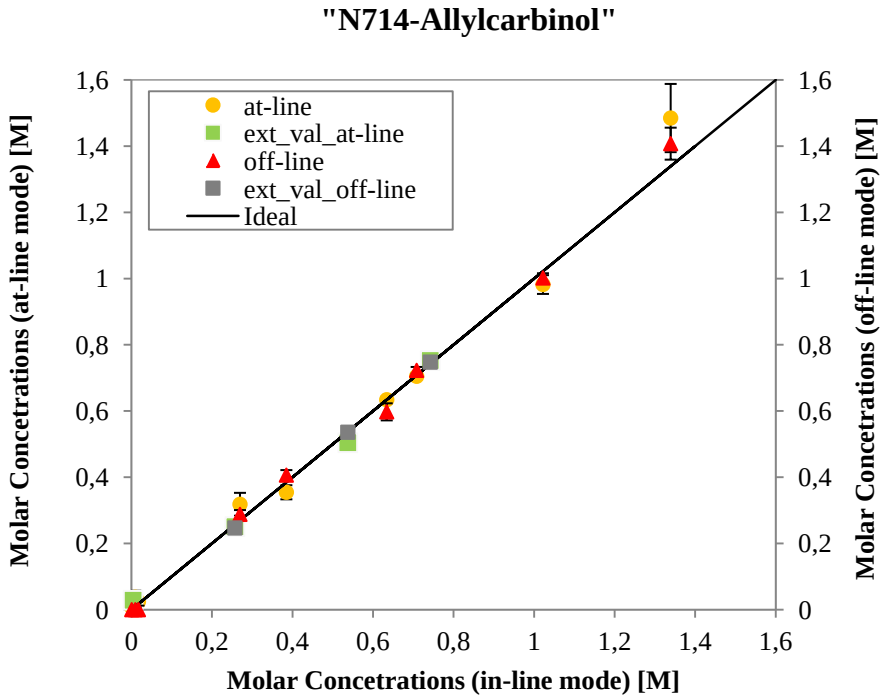
Dehydration reaction

- Choice of the best pre-treatment for “N714-Allylcarbinol”

No.	Pre-treatment	At-Line				In-Line			
		f	RMSECV	RMSEC	RMSEP	f	RMSECV	RMSEC	RMSEP
1.	-	4	0.0250	0.0237	0.0430	4	0.0196	0.0198	0.0161
2.	BLC	4	0.0370	0.0345	0.0340	4	0.0197	0.0199	0.0154
3.	MC	4	0.0253	0.0225	0.0409	4	0.0206	0.0197	0.0159
4.	SG1+7p	2	0.0967	0.0950	0.0785	3	0.0620	0.0634	0.0696
5.	SG1+11p	3	0.0571	0.0667	0.0697	3	0.0924	0.0668	0.0920
6.	SG1+15p	4	0.0552	0.0667	0.0697	5	0.0438	0.0668	0.0920
7.	SG2+7p	2	0.0664	0.0760	0.0944	4	0.0245	0.0228	0.0226
8.	SG2+11p	4	0.0572	0.0477	0.0426	5	0.0272	0.0211	0.0377
9.	SG2+15p	4	0.0381	0.034	0.0148	7	0.0770	0.0313	0.0755
10.	MC+SG1+15p	3	0.0473	0.0508	0.0411	7	0.0235	0.0134	0.0351
11.	MC+SG2+15p	3	0.0892	0.0921	0.0895	7	0.0865	0.0308	0.0873
12.	MC+BLC	3	0.0385	0.0392	0.0312	3	0.0239	0.0244	0.0085

Dehydration reaction

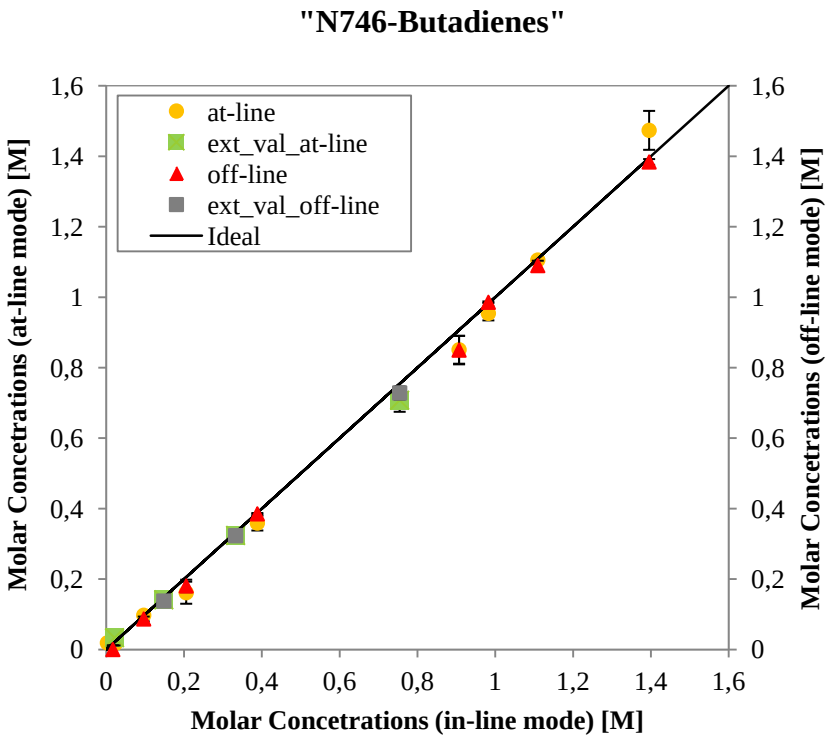
- Validation of the calibration model for “N714-Allylcarbinol”

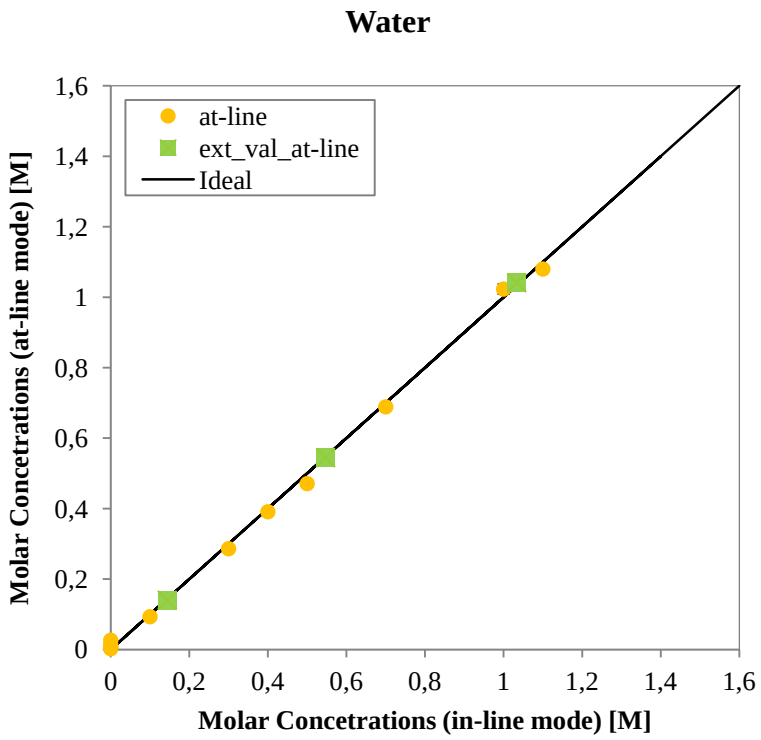


- ✓ High accuracy of experimental data ($R^2 > 0.992$)
- ✓ Robust calibration model for FT-NIR
- ✓ Issue with high molar concentrations (1.4 M and above)

Dehydration reaction

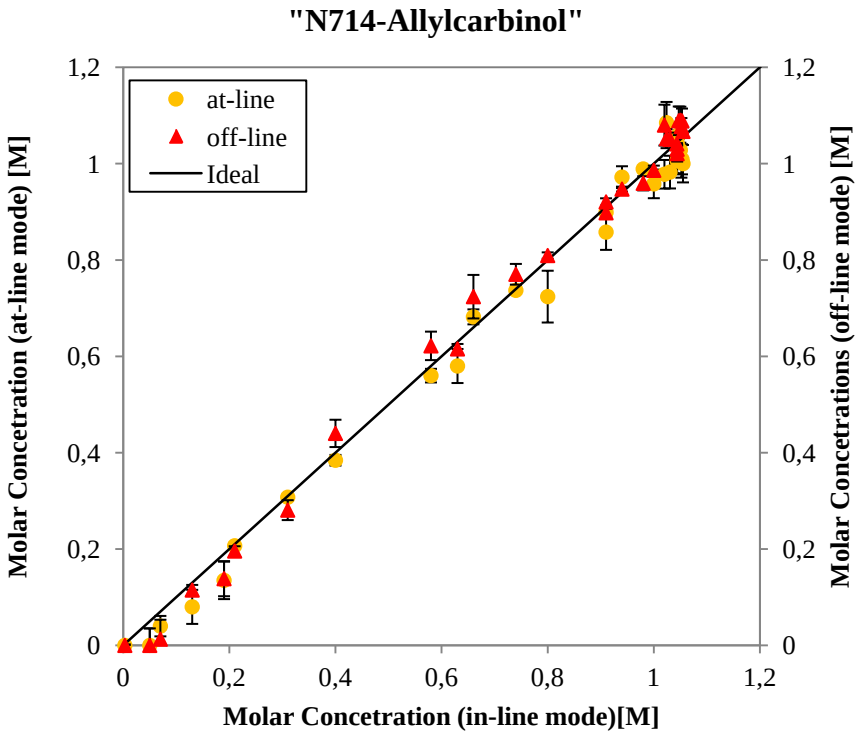
- Validation of the calibration model for “N746-Butadienes” and water





Dehydration reaction

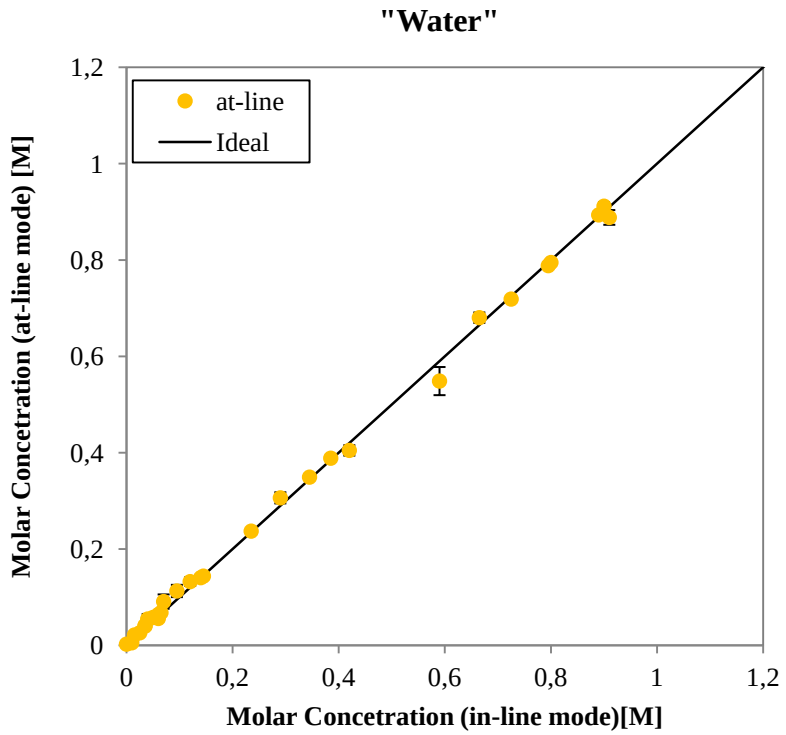
- Real-time process monitoring of “N714-Allylcarbinol”



- ✓ High accuracy of experimental data ($R^2 > 0.993$)
- ✓ Precise data for kinetic model development
- ✓ Easier process control and automation

Dehydration reaction

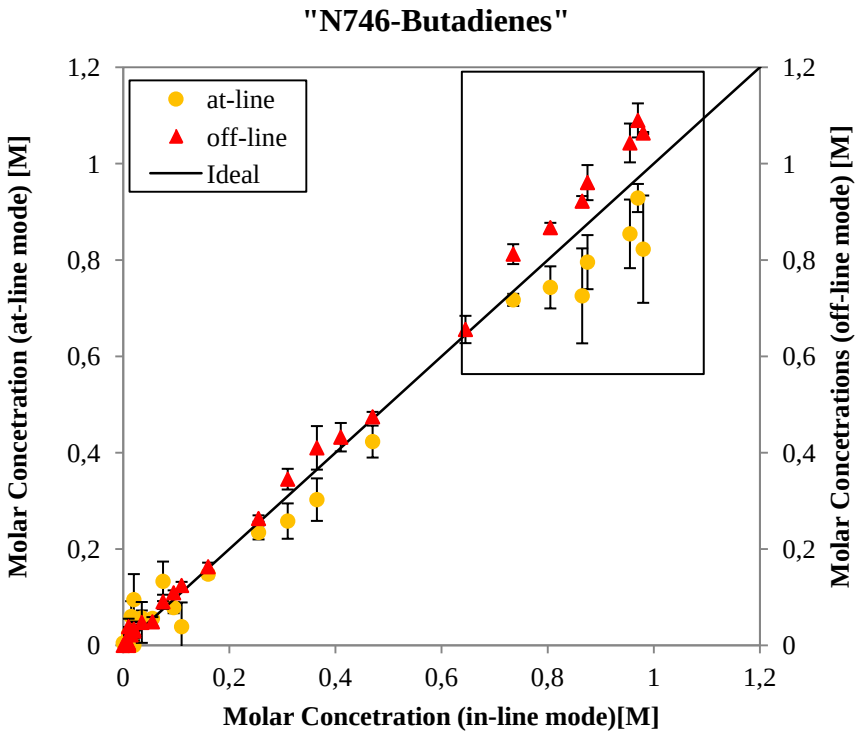
- Real-time process monitoring of water



- ✓ High accuracy of experimental data ($R^2 > 0.998$)
- ✓ Operational window is respected
- ✓ Robust calibration model for FT-NIR

Dehydration reaction

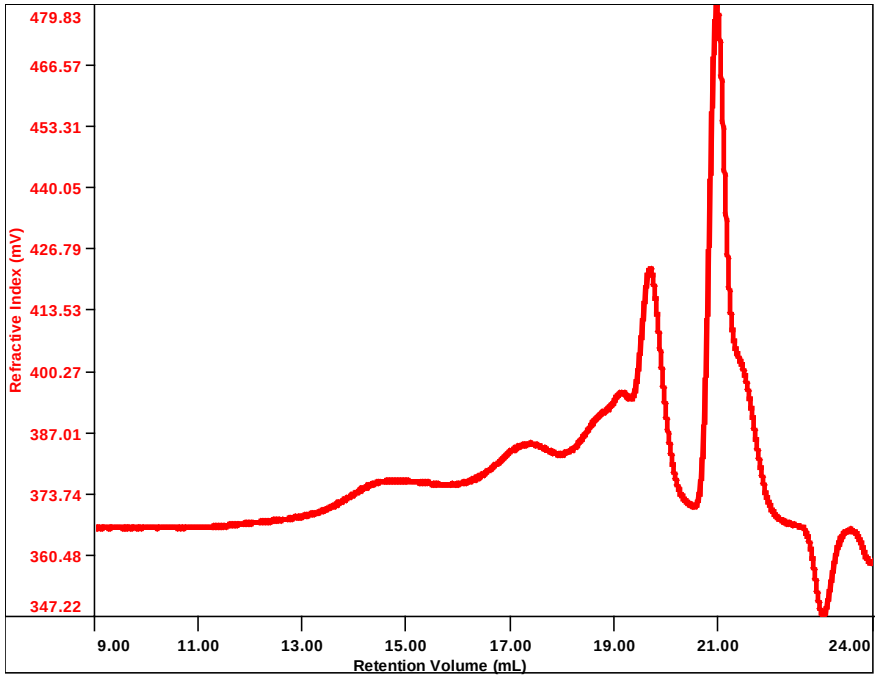
- Real-time process monitoring of “N746-Butadienes”



- ✓ High accuracy of experimental data if the molar concentration is lower than 0.8 M
- ✓ Issues with side chemical reactions
- ✓ Issues with real-time process monitoring

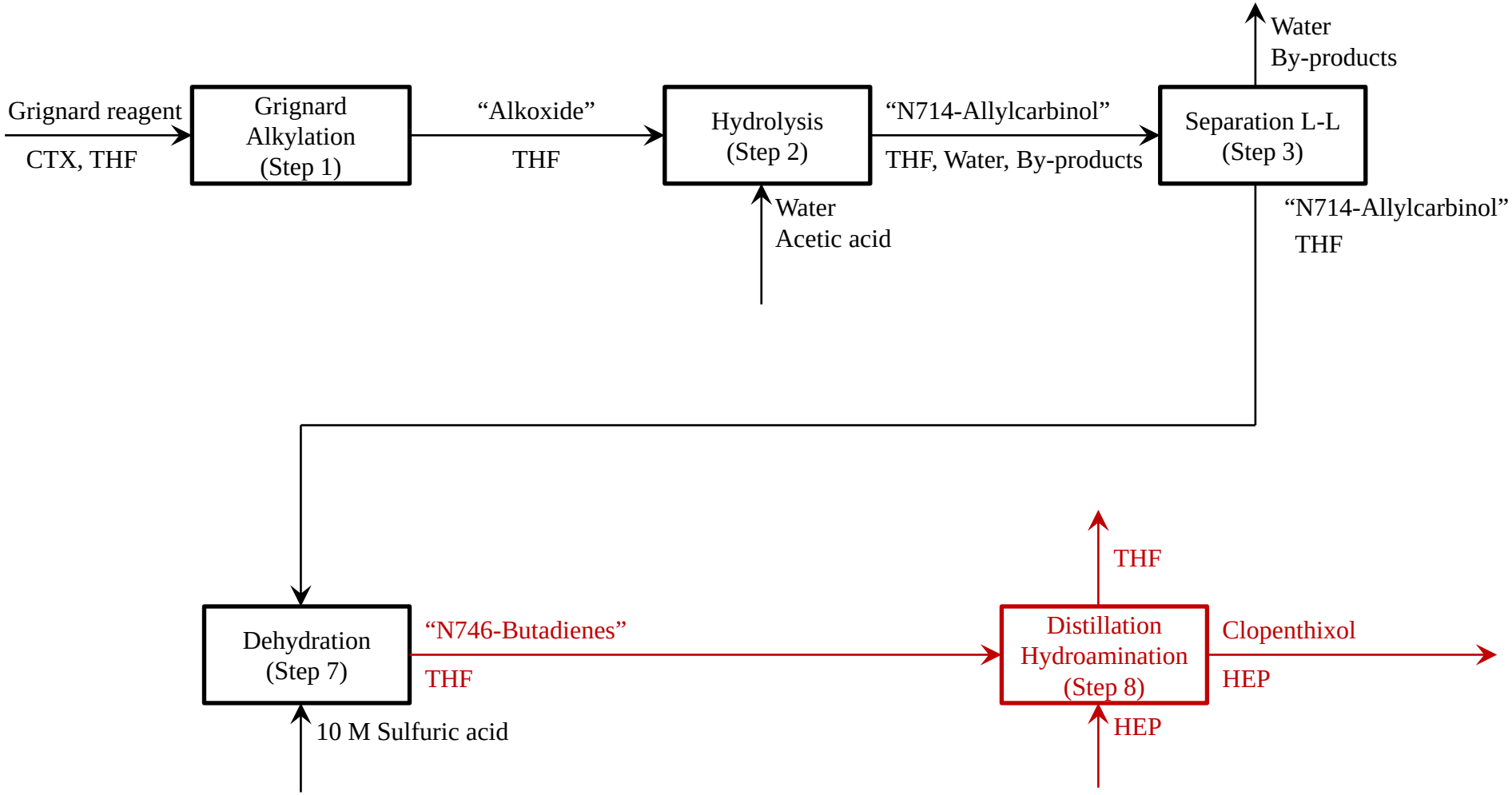
Dehydration reaction

- Analysis of side reactions



- ✓ Hydronium ions break THF ring
- ✓ Polymerization of THF
- ✓ Chemical reactions of open THF rings with carboctaion intermediate
- ✓ Impurities with high Mw

Manufacturing route towards Clopenthixol



Hydroamination reaction

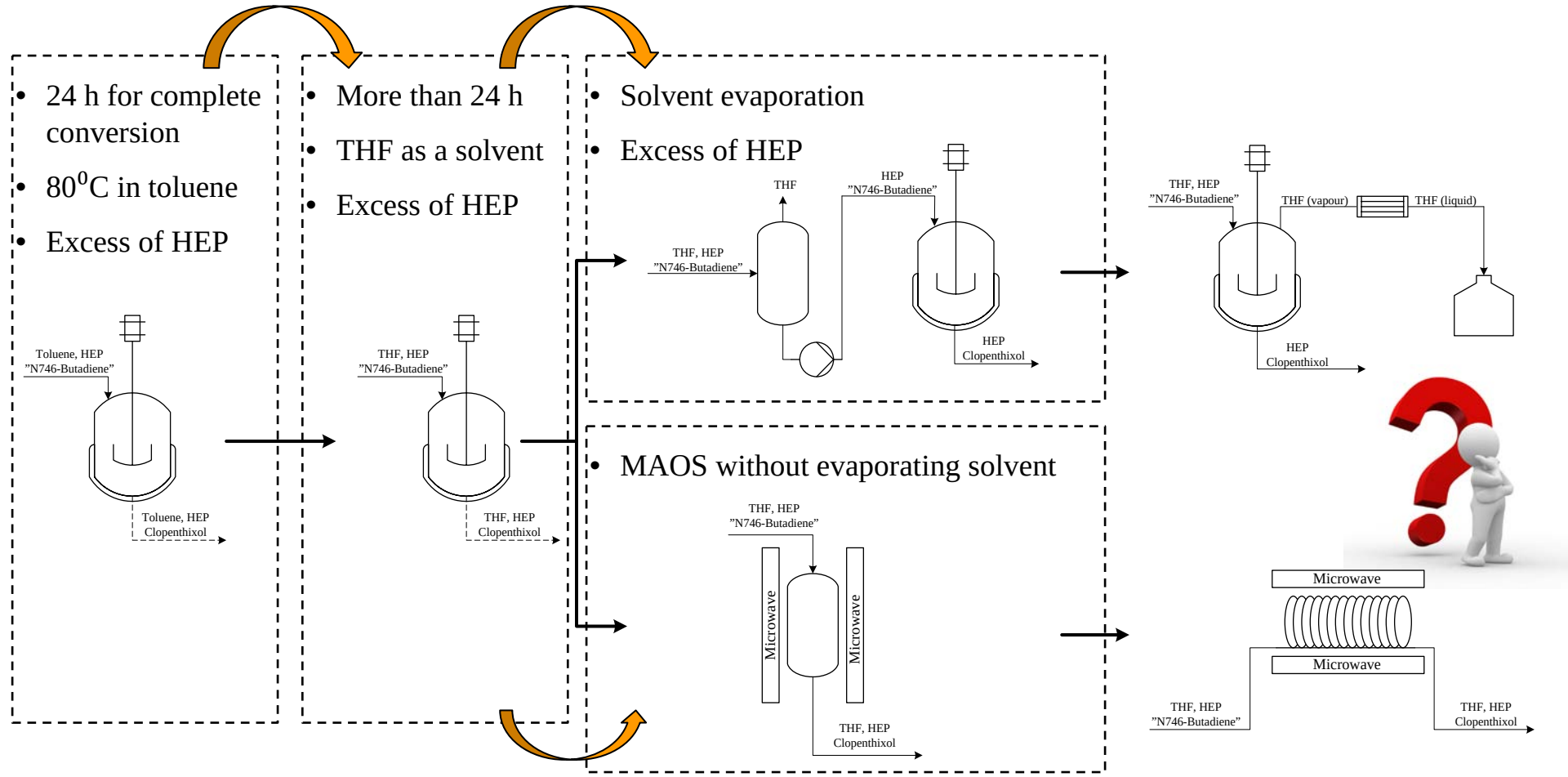
- Action plan

- 24 h for complete conversion
- 80^0C in toluene
- Excess of HEP

- More than 24 h
- THF as a solvent
- Excess of HEP

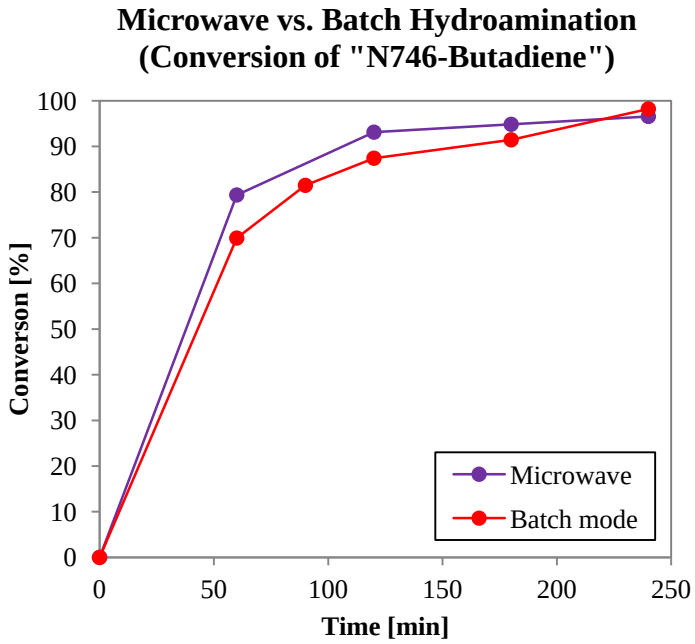
- Solvent evaporation
- Excess of HEP

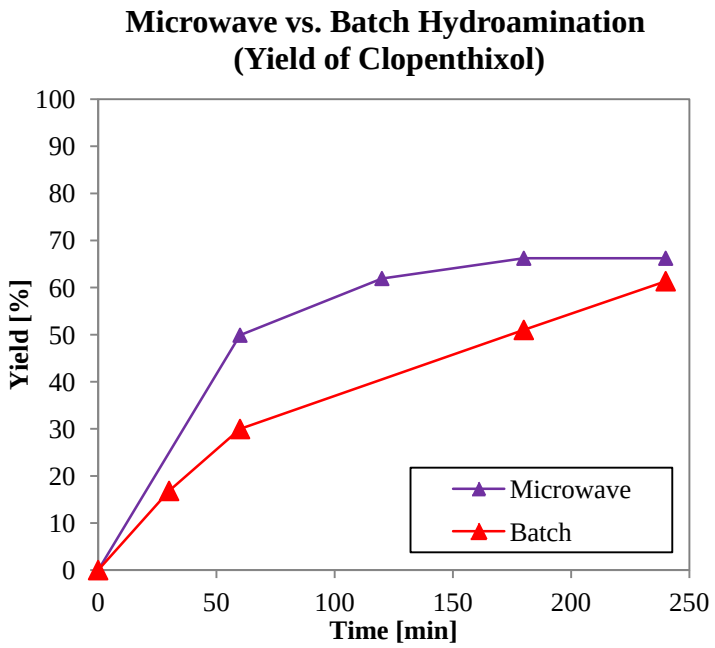
- MAOS without evaporating solvent



Hydroamination reaction

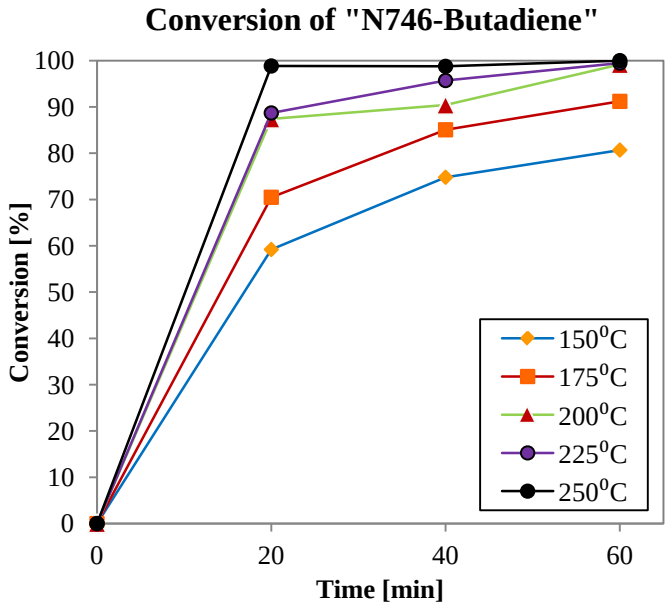
- Comparison between MAOS and solvent-free batch approaches

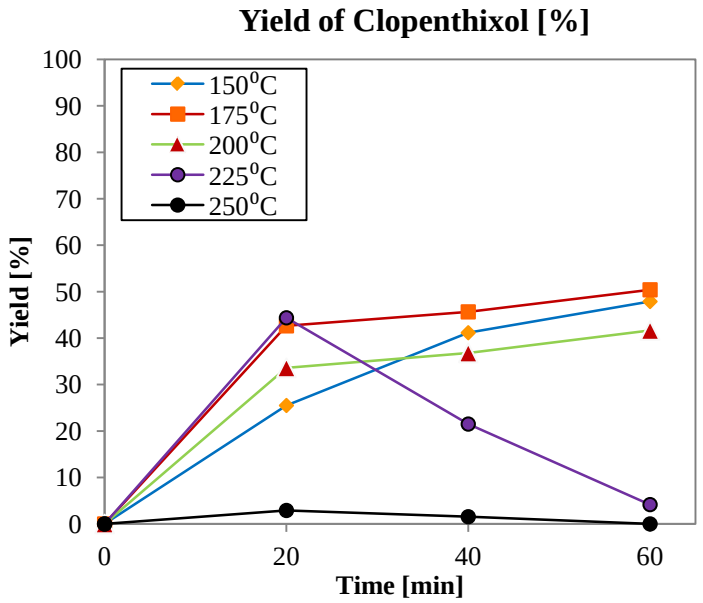




Hydroamination reaction

- Influence of the temperature increase on conversion of “N746-Butadienes” and yield of Clopenthixol





Hydroamination reaction

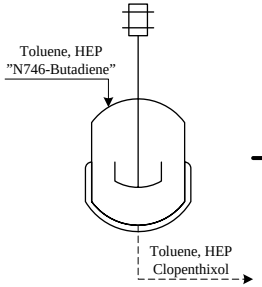
- Action plan

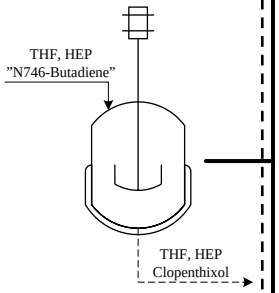
- 24 h for complete conversion
- 80^0C in toluene
- Excess of HEP

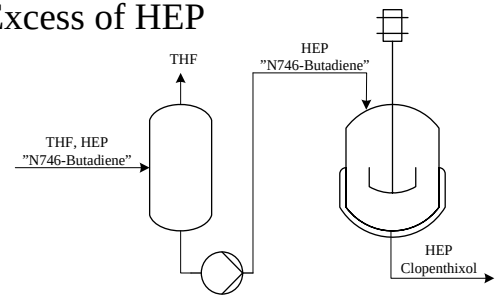
- More than 24 h
- THF as a solvent
- Excess of HEP

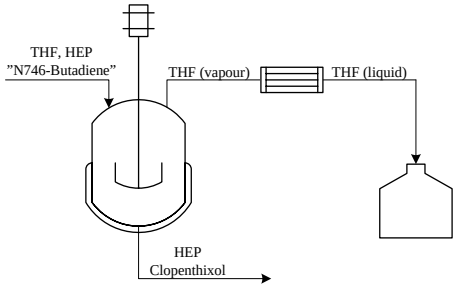
- Solvent evaporation
- Excess of HEP

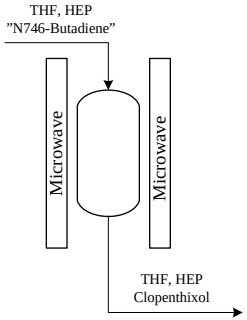
- MAOS without evaporating solvent

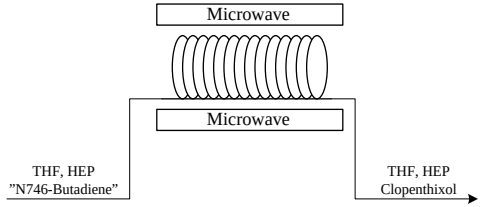








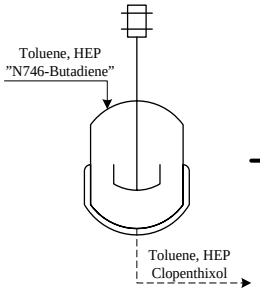




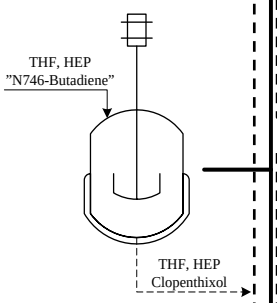
Hydroamination reaction

- Comparison between MAOS and solvent-free batch approaches

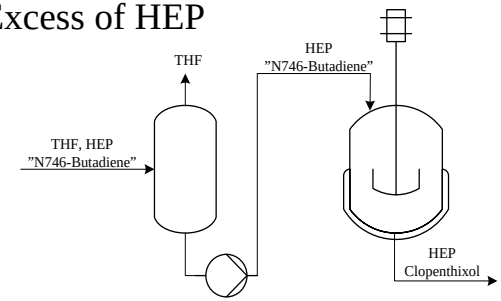
- 24 h for complete conversion
- 80^0C in toluene
- Excess of HEP

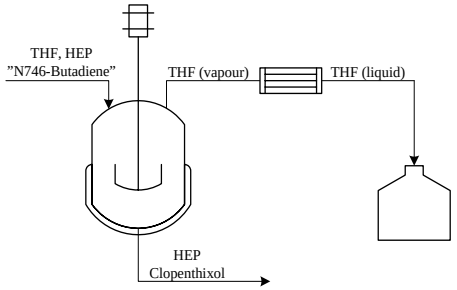


- More than 24 h
- THF as a solvent
- Excess of HEP

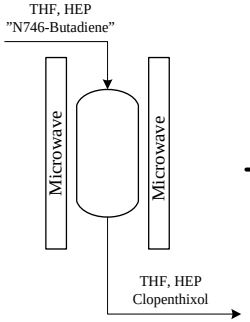


- Solvent evaporation
- Excess of HEP

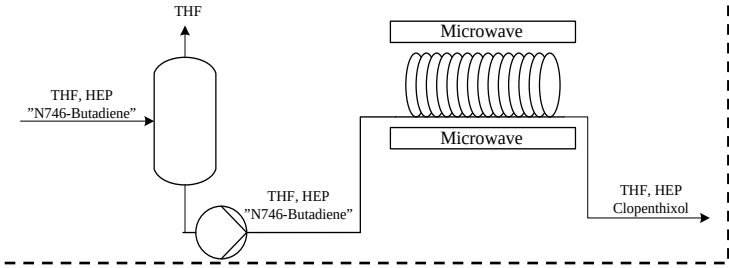




- MAOS

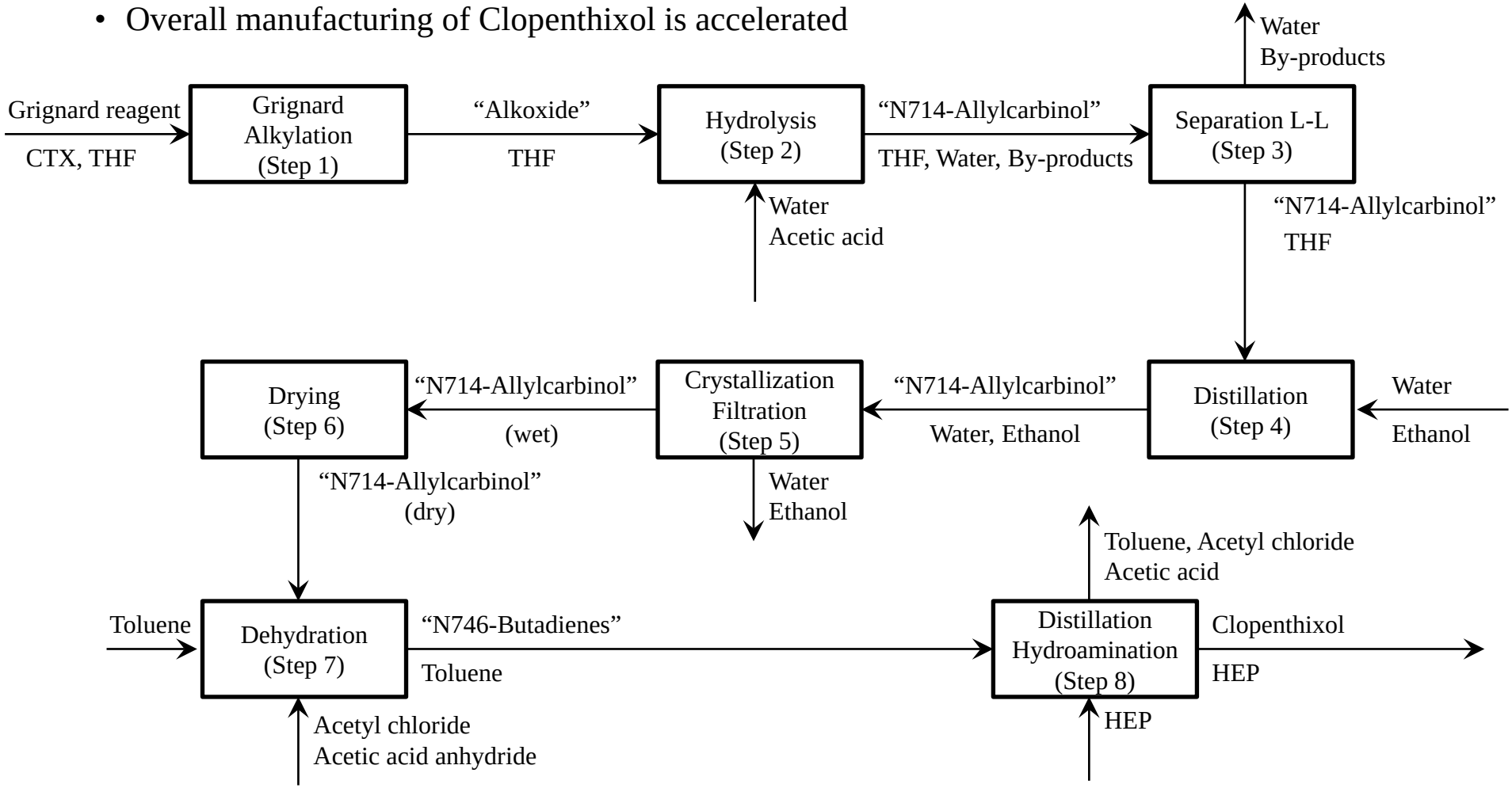


- MAOS with previously evaporated solvent



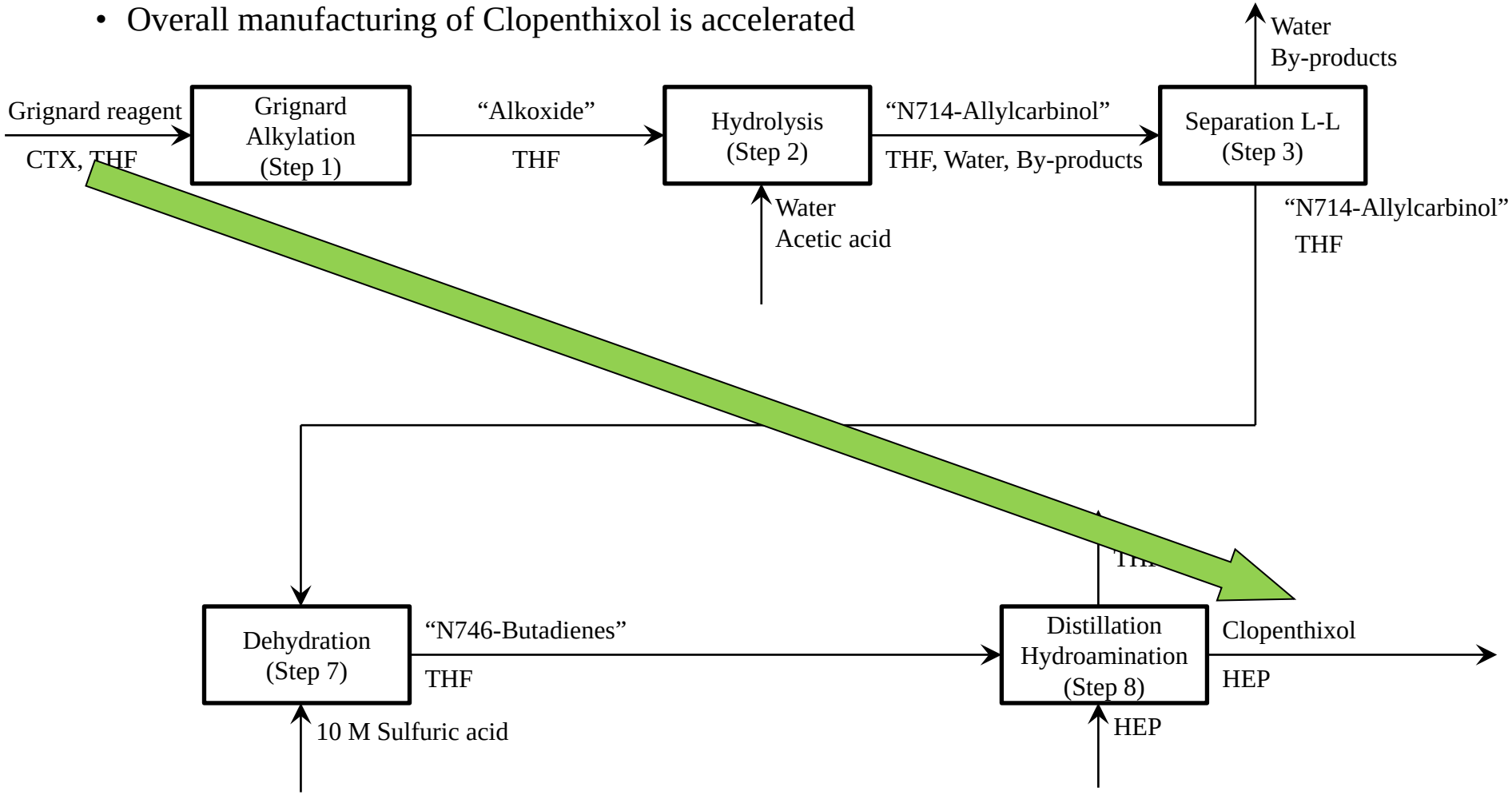
Conclusions and future perspectives

- Overall manufacturing of Clopenthixol is accelerated



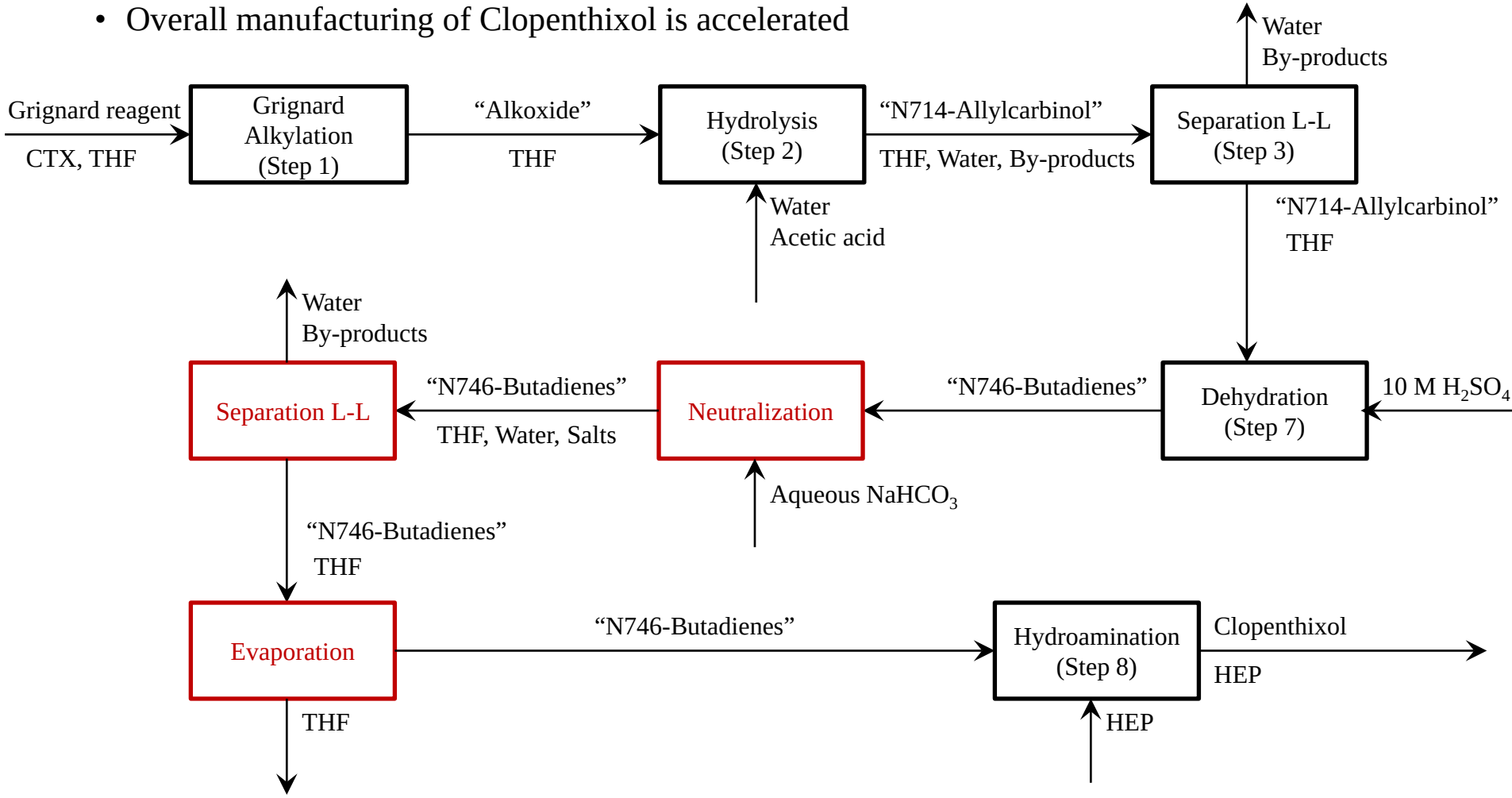
Conclusions and future perspectives

- Overall manufacturing of Clopenthixol is accelerated



Conclusions and future perspectives

- Overall manufacturing of Clopenthixol is accelerated



Conclusions and future perspectives

- Slow chemical reactions are accelerated without using transition metals as chemical catalysts
- Transfer from batch to continuous processes is done together with satisfying PAT requirements
- Faster route from initial substrate to Clopenthixol is established with decreased number of non-value added activities (intermediate storages, unnecessary purification steps)
- Change from sulphuric acid to another dehydration agent should be done in the dehydration step
- Change of solvent in the dehydration step should be also considered
- Combination of evaporation and MAOS should be performed as the most desired option for the hydroamination reaction

Thanks for your attention. ☺

??? Questions ???

Contact details

Department of Chemical and Biochemical Engineering
Technical University of Denmark
Building 229
DK-2800 Lyngby
Denmark

- **Krist V. Gernaey**

  Email: kvg@kt.dtu.dk
  Phone: +45 45 25 29 70

- **Aleksandar Mitic**

  Email: asmi@kt.dtu.dk
  Phone: +45 45 25 29 49