

# Learnings from Flow Chemistry for API Synthesis

A Chemists View

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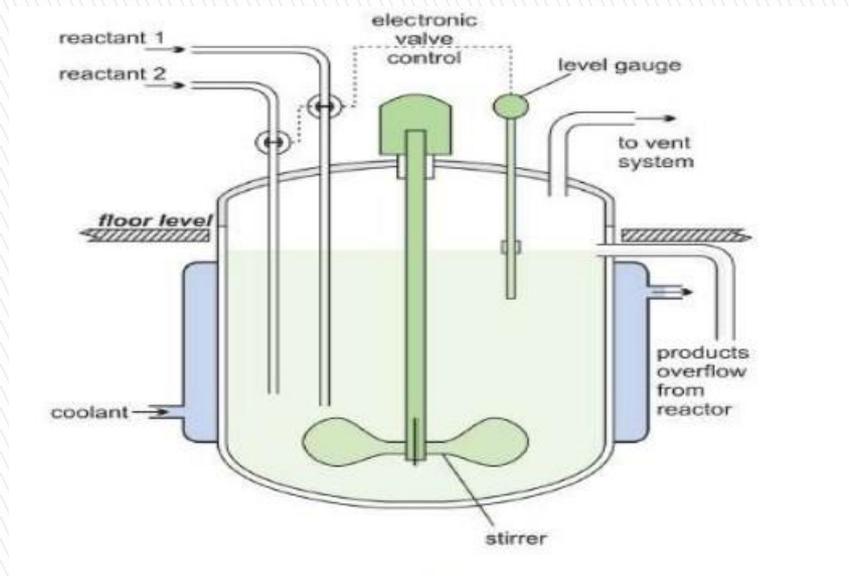
# Why Flow

- ▶ Enables difficult to scale processes.
- ▶ Process control can be very stable.
- ▶ Amenable to real time monitoring.
- ▶ Process velocity: less inventory in warehouses.
- ▶ Equipment footprint.

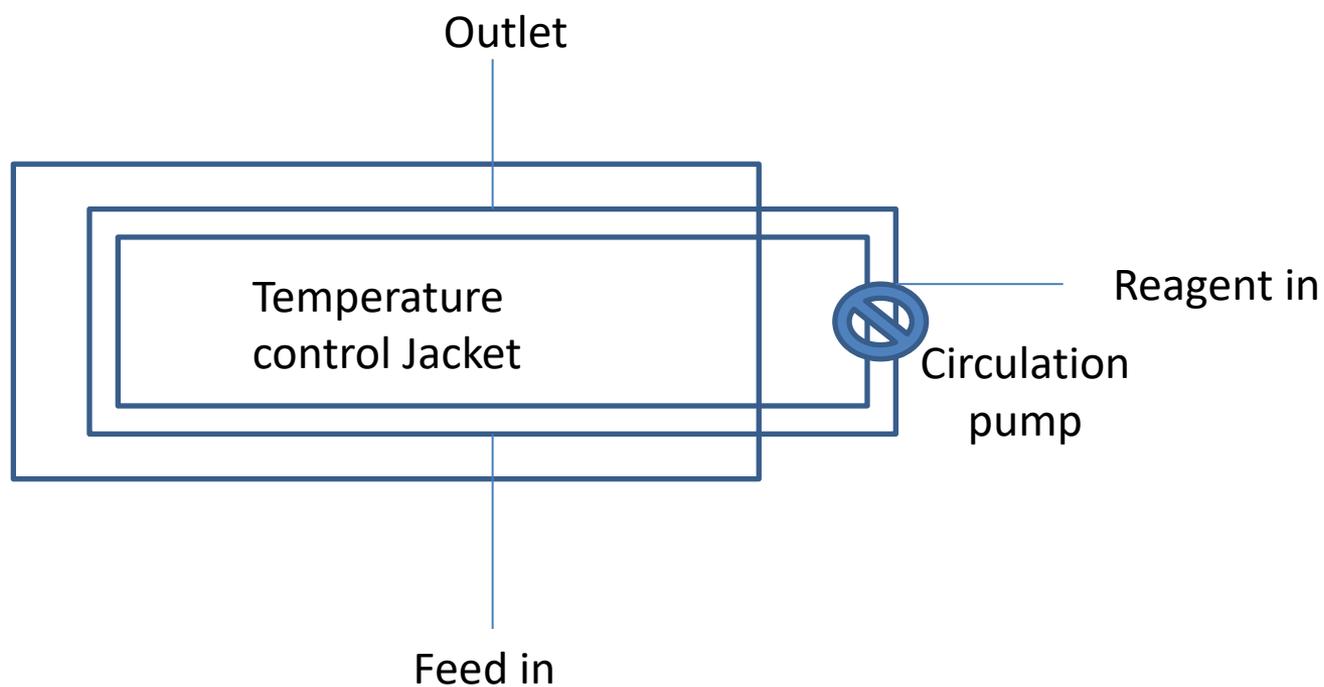
# Chemical Unit Operations Amenable to Flow

- ▶ Reactive chemistry.
- ▶ Biphasic extractions and separations.
- ▶ Distillation/ solvent exchange.
- ▶ Membrane filtration.
- ▶ Crystallisation
- ▶ Filtration
- ▶ Drying
- ▶ Chromatography

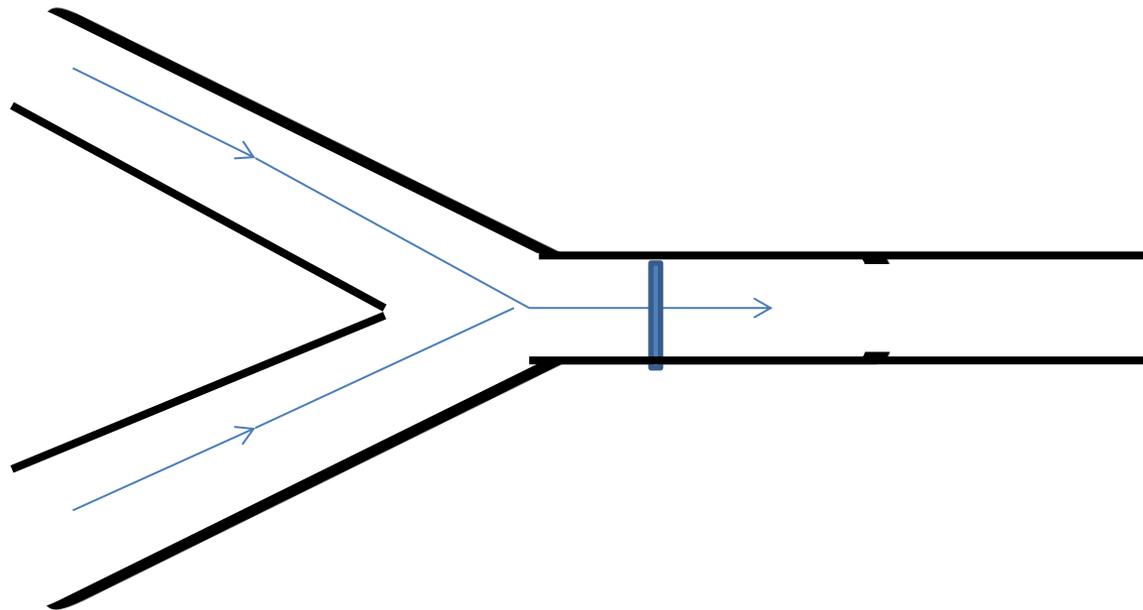
# Continuous Stirred Tank Reactor CSTR



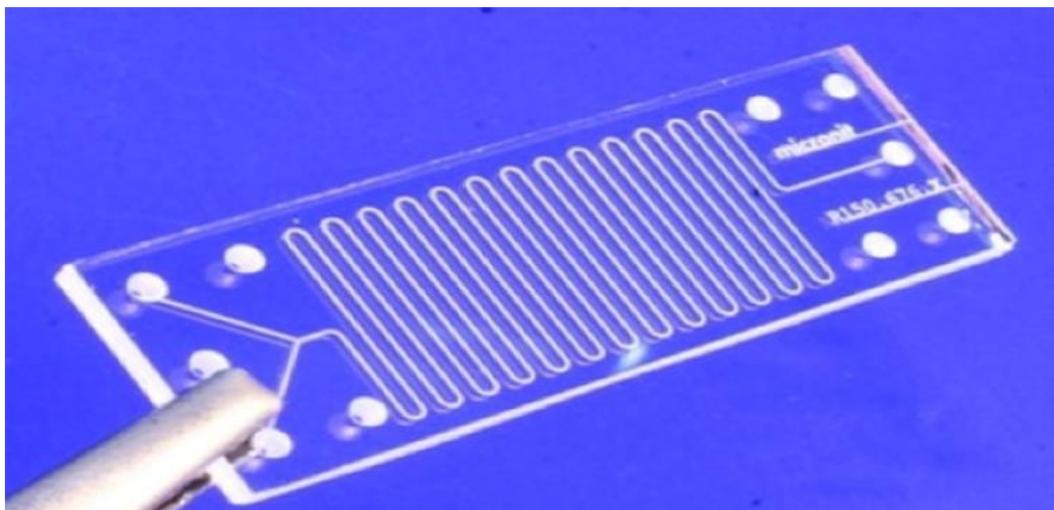
# Pumped Loop Reactor



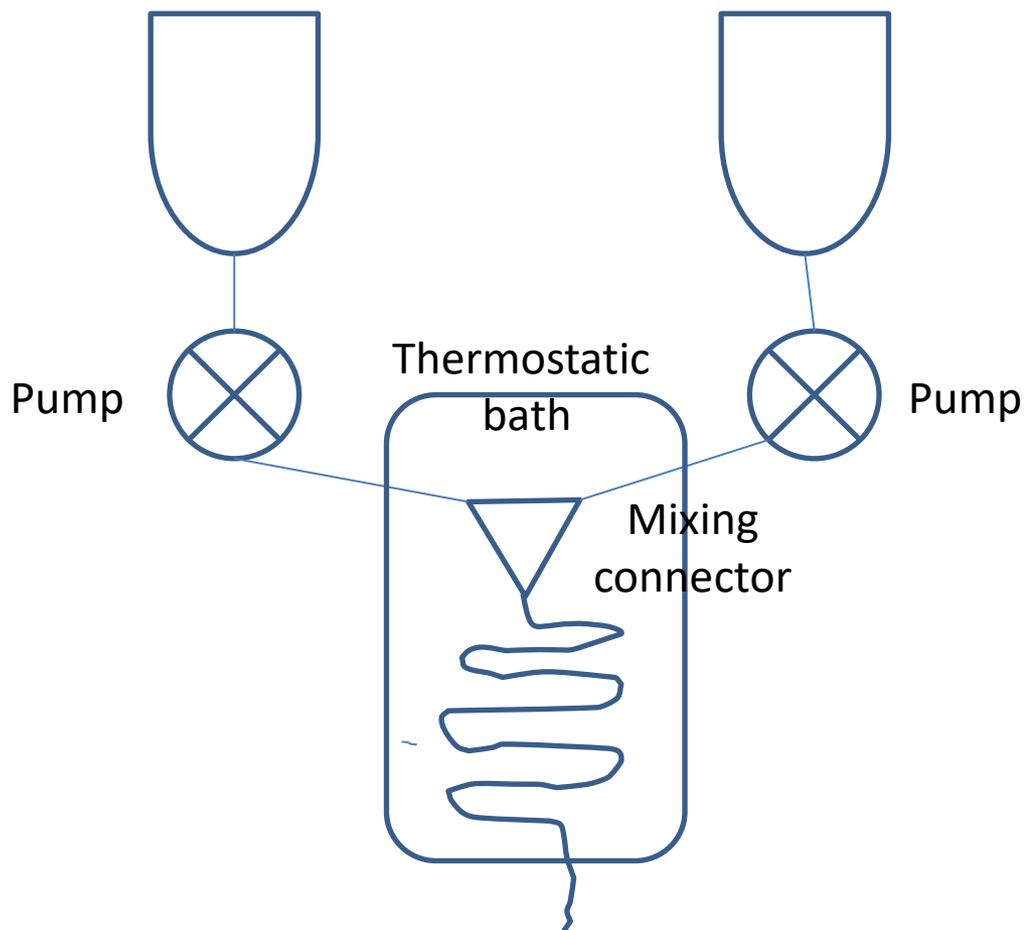
# Plug Flow Reactor PFR



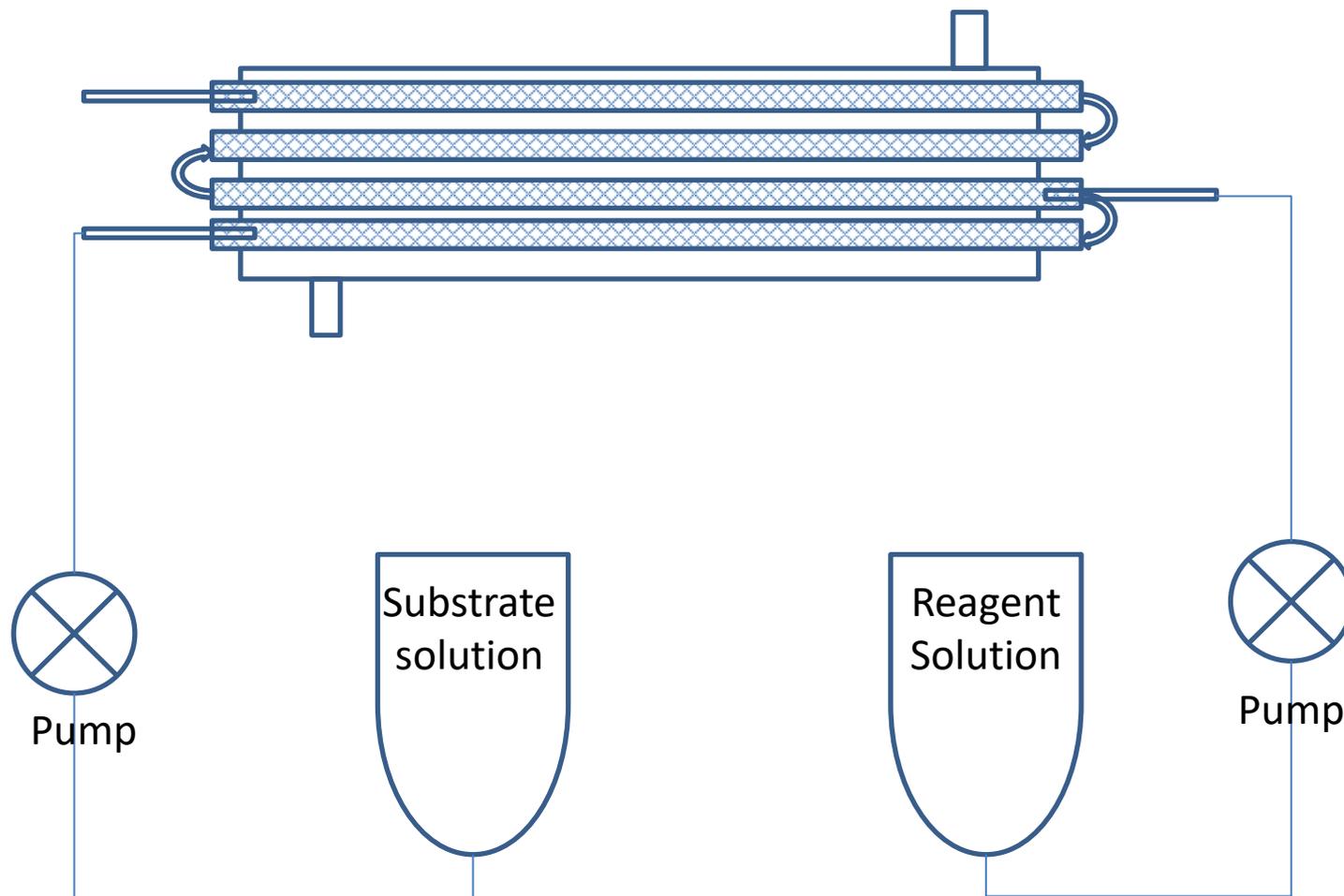
# Micro Channel Reactor



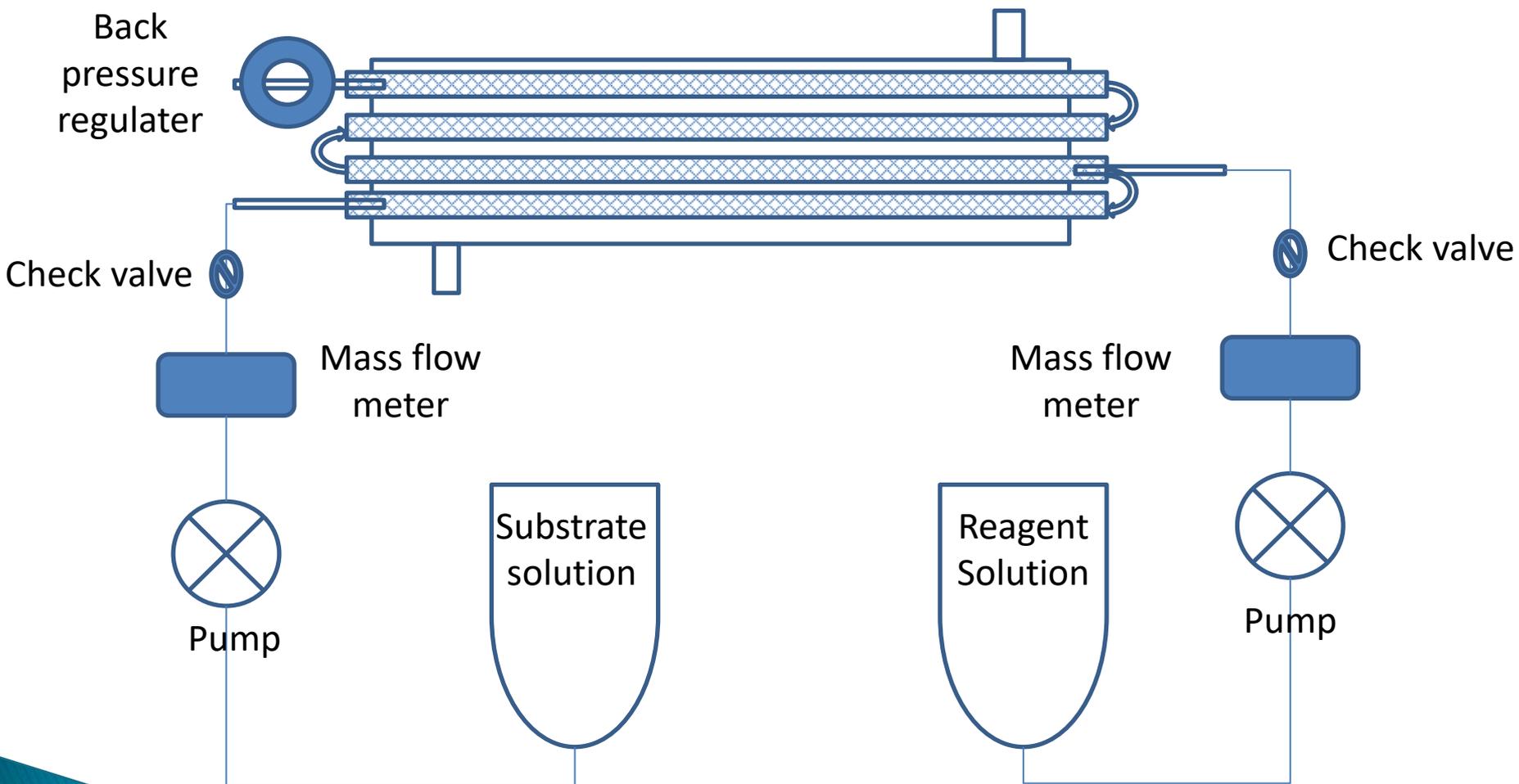
# Narrow Tube Reactor



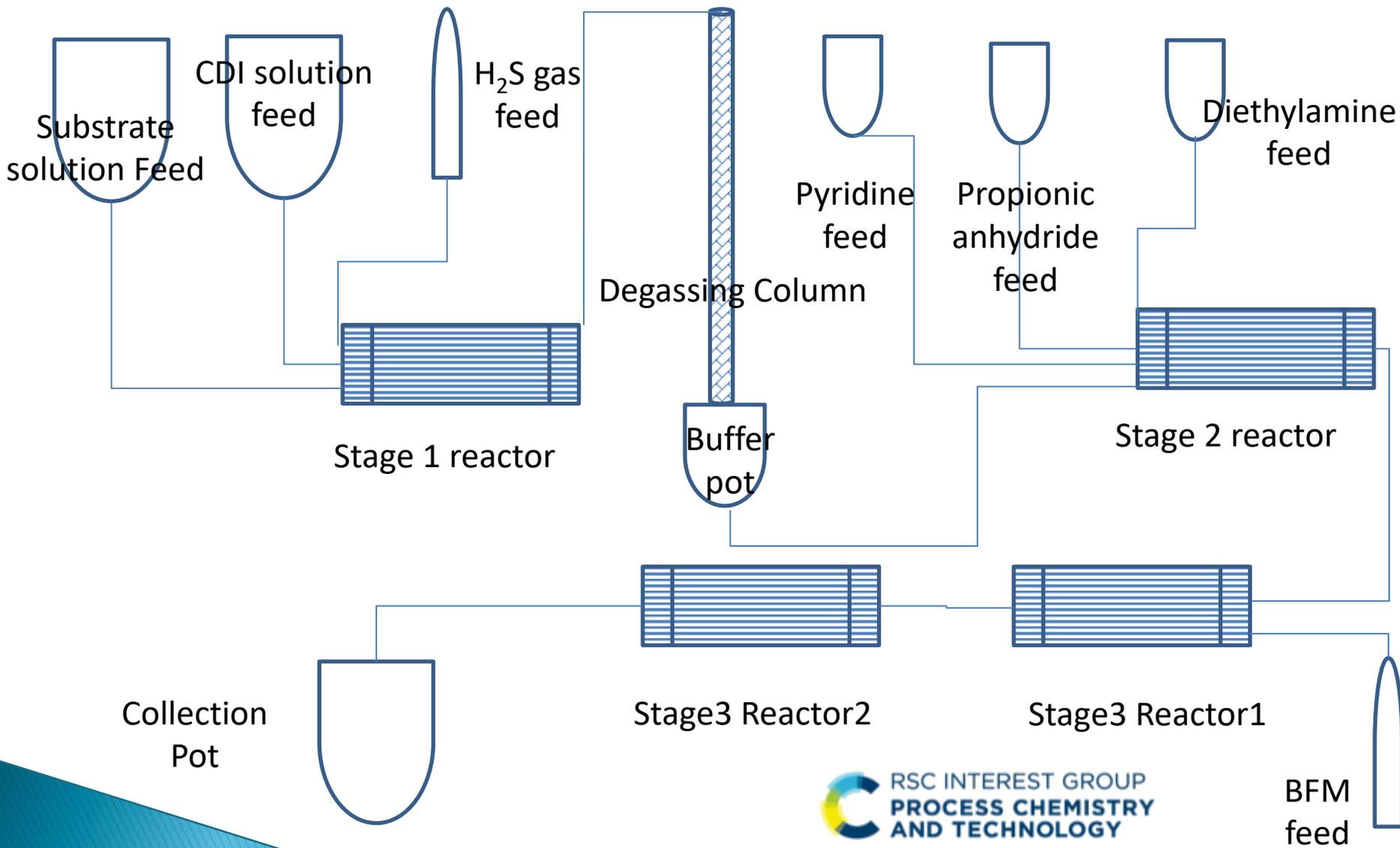
# Tube reactor with Static Mixing



# Typical Single Stage Reactor



# Process Schematic



# Batch vs Flow

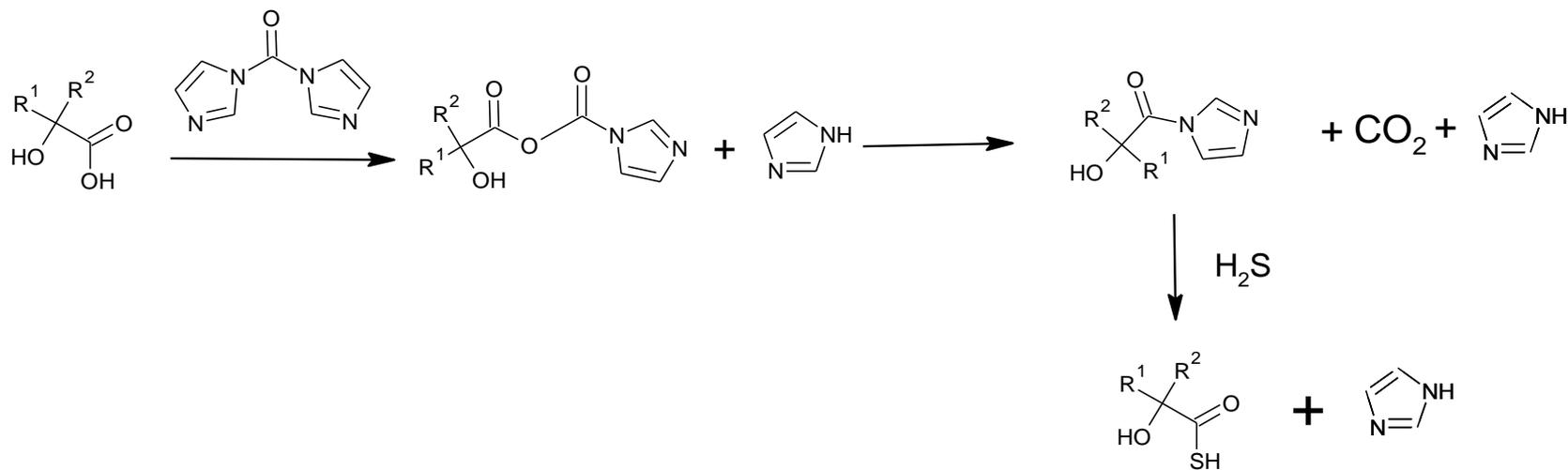
## Batch:

- ▶ Reagents and solvents charged by mass.
- ▶ Contents temperature controlled by addition rate.
- ▶ Solid charging routine
- ▶ Reaction time an independent variable

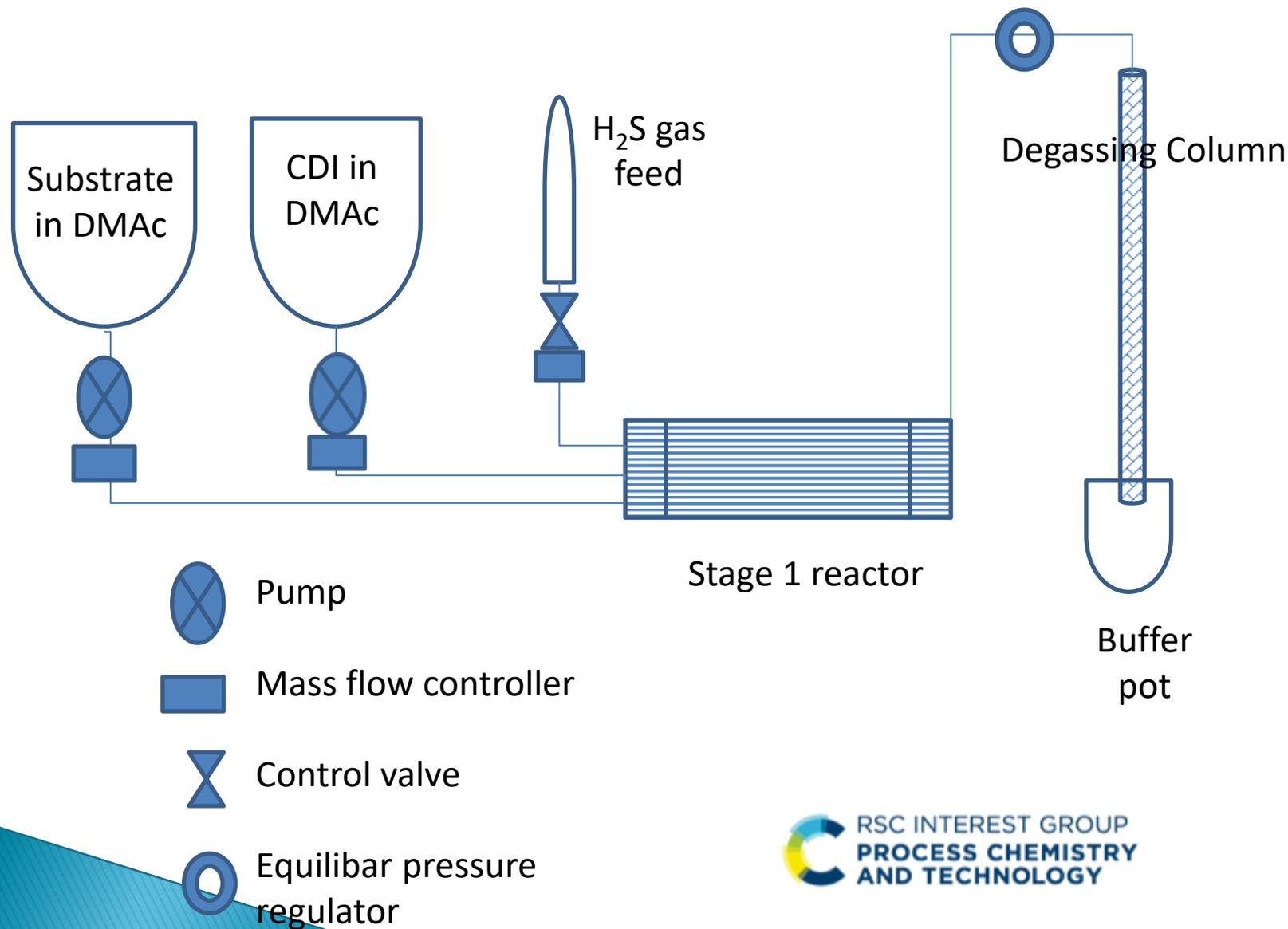
## • Flow:

- Feeds prepared by mass
- Stoichiometry and reaction time determined by flow rates.
- Contents temperature function of equipment and jacket
- Reaction at full stoichiometry at mixing point

# Stage 1 Chemistry



# Process Schematic Stage 1

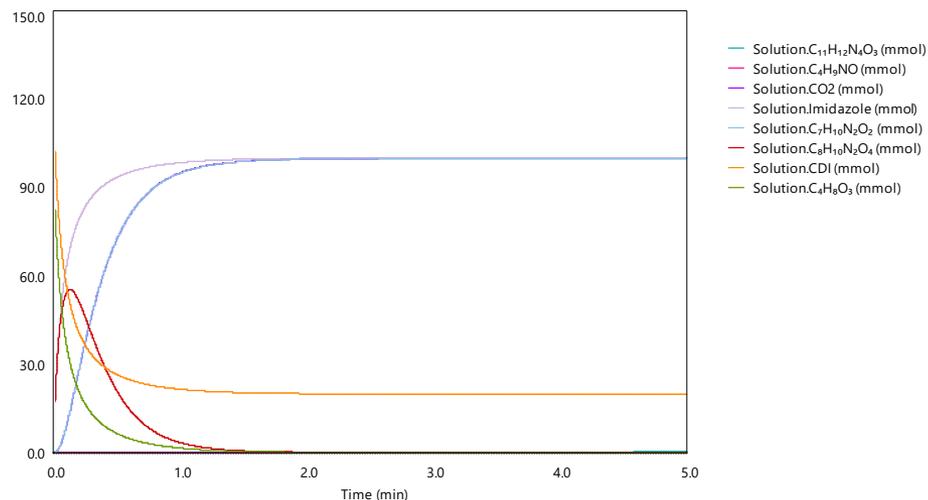


# CDI Reaction Profile

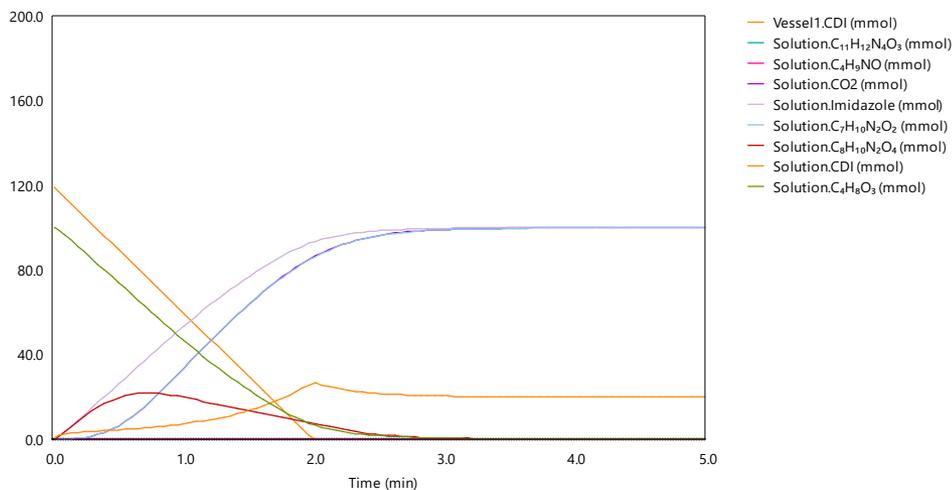
Plug flow Reactor



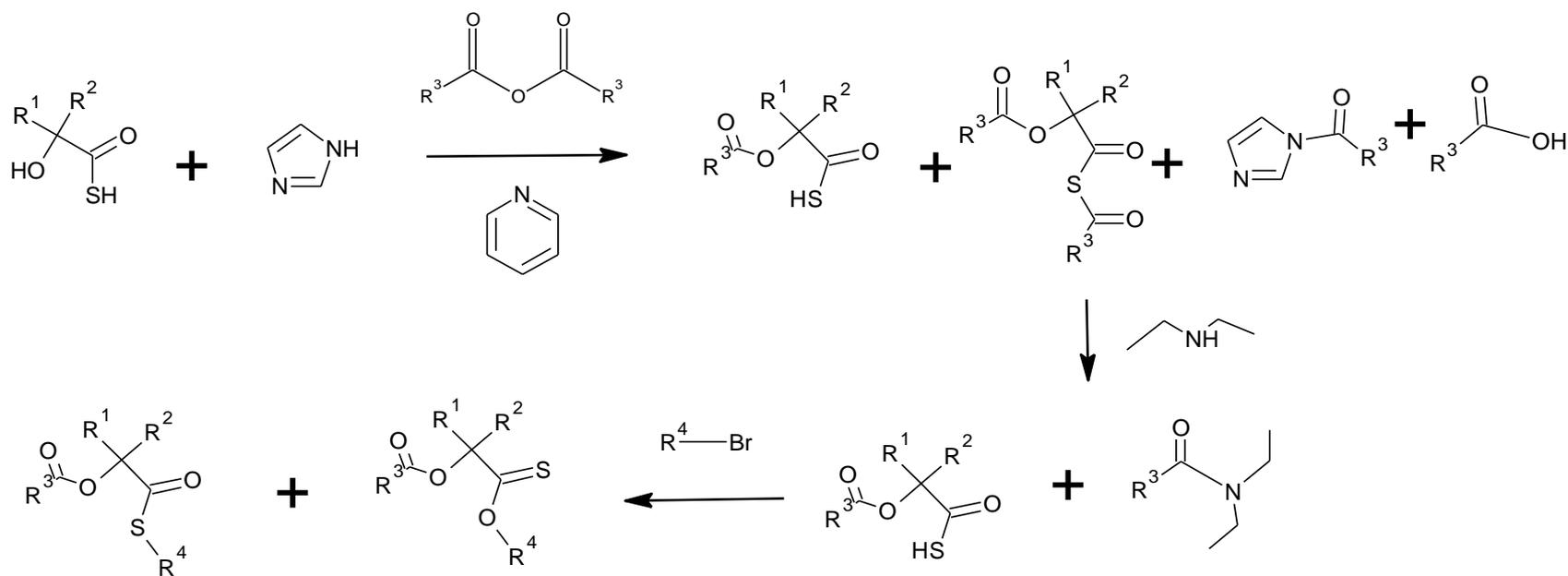
Batch Reactor  
2minute Dosing



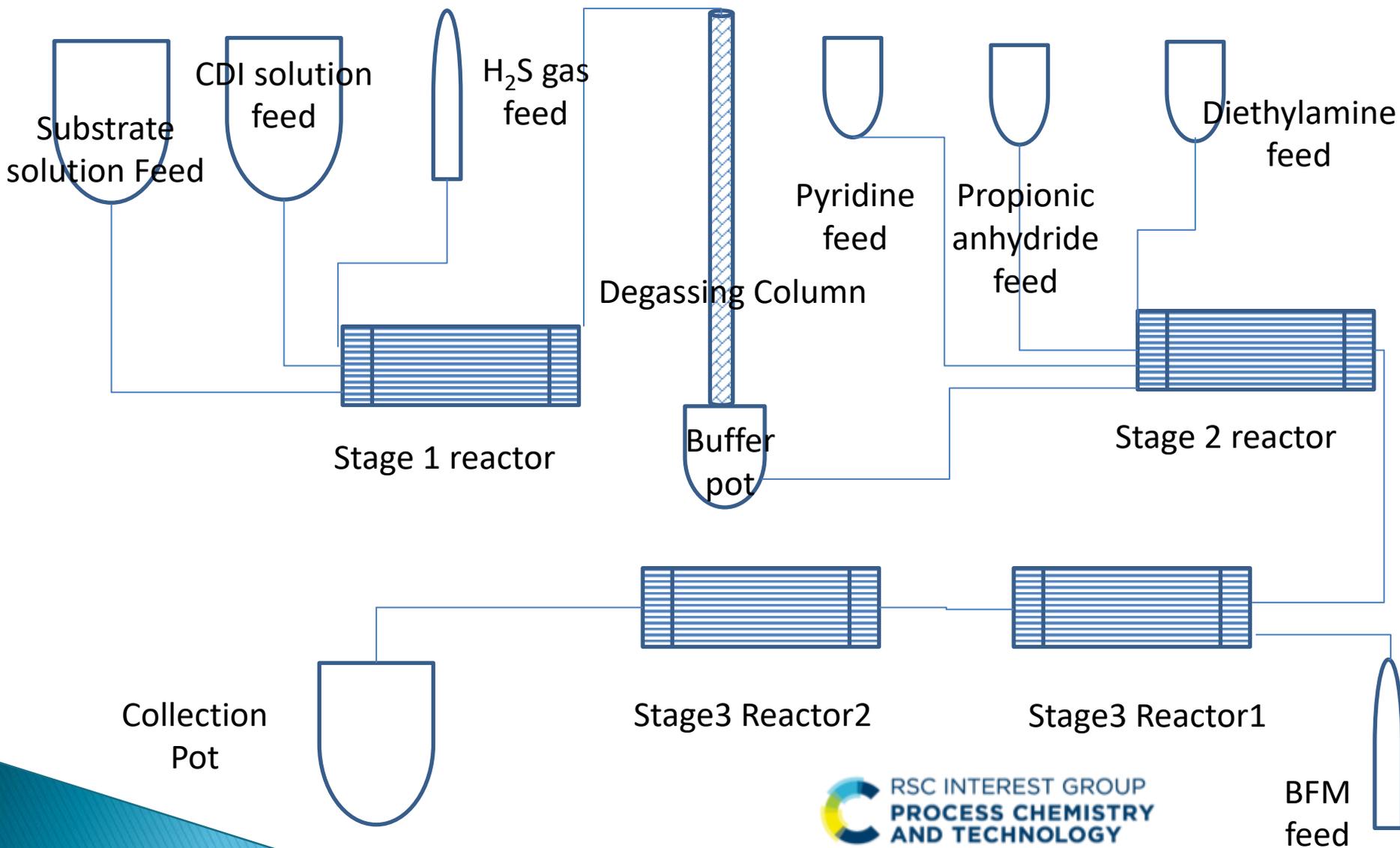
Var 1 of Base Case



# Stages 2 and 3



# Process Schematic



# Telescoped Processes

## For

- Reduced number of vessels used.
- Reasonable process velocity.

## Against

- ▶ Complex from process instructions and operator point of view.
- ▶ Increased risk of maloperation.
- ▶ Probably require in process checks.
- ▶ Cause of process failure difficult to identify
- ▶ Need cleaning verification between batches

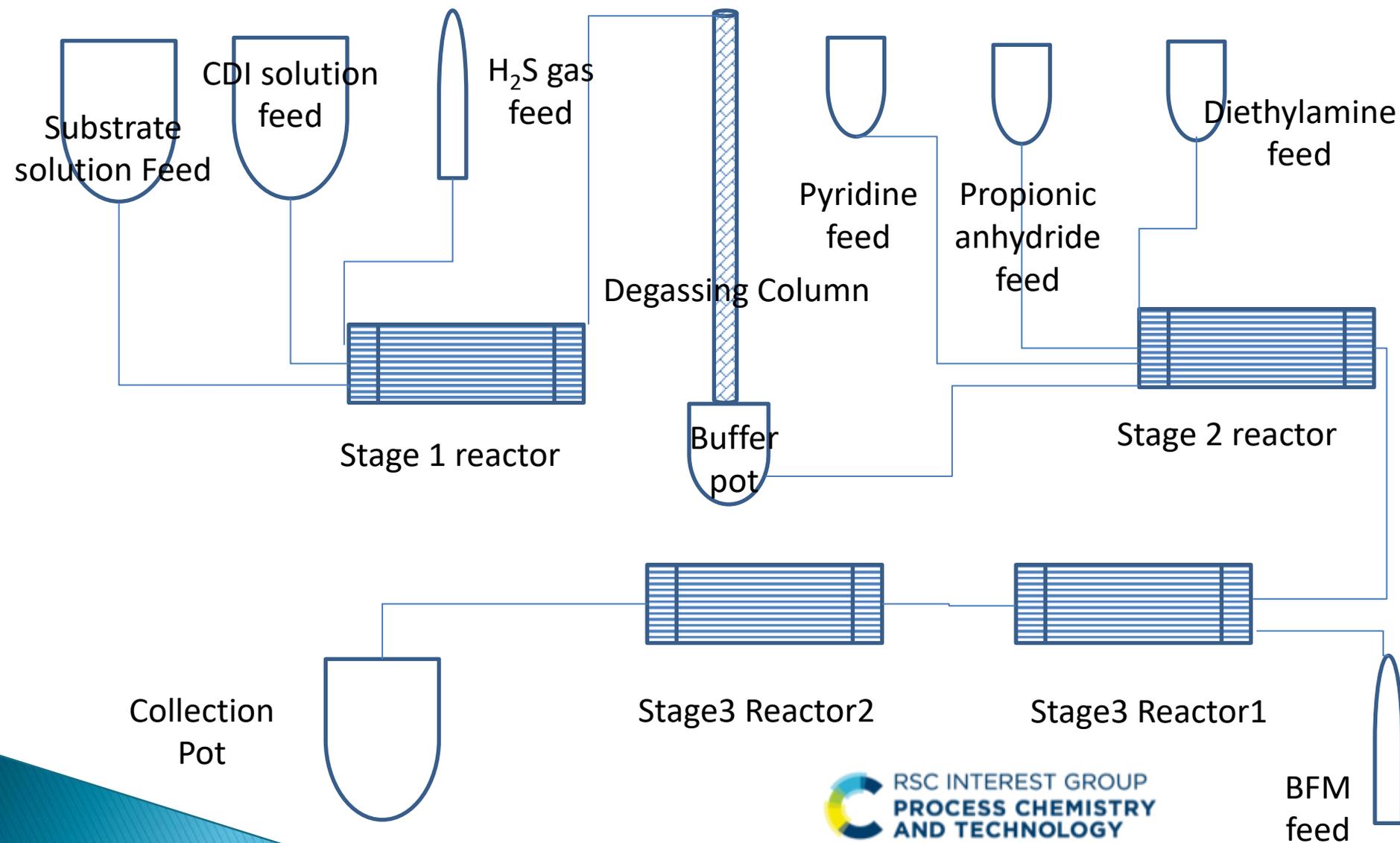
# Telescoped vs multistage flow

- ▶ Able to run in process checks and take corrective action eg stir for longer add more reagent prior to moving to next step.
- ▶ Process can be monitored continuously but unable to correct material that has already moved on. Each step is segregated stage 1 reactor never sees stage 3 so less risk of contamination

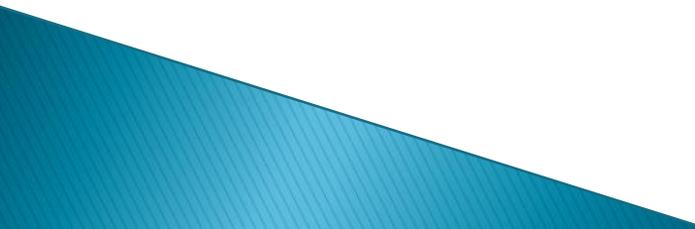
Telescoped

Multi stage flow

# Process Schematic



# Process Optimisation and Design Space Definition

- ▶ Both multistage flow processes and telescoped batch processes suffer from too many variables.
  - ▶ This process has 9 flow rates 4 reactor temperature, 2 solution feed concentrations and a buffer pot fill level 16 parameters in all.
  - ▶ A large part of this must be reduced by process understanding as the experimental demand is just too large to explore the whole design surface.
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# Summary

- ▶ Avoiding solids will make your process easier but be prepared to see them at unexpected moments.
- ▶ In developing a flow process you will have to change your mindset on what constitutes an independent variable.
- ▶ A good understanding of the reaction kinetics and impurity profile over the whole process is essential.
- ▶ Incomplete earlier steps are going to be your main route to failure. Design with this in mind! Ensure your analytical methods can cope with this.

# Acknowledgements

- ▶ All my colleagues “Chemists, Analysts and Engineers” over the years who delivered this process.
- ▶ Scale up systems whose software and support underpinned the kinetic understanding of this process

# Q and A

