SNAPDRAGON
CHEMISTRY

ENABLING REACTIVE AND HAZARDOUS PROCESSES WITH CONTINUOUS FLOW TECHNOLOGIES

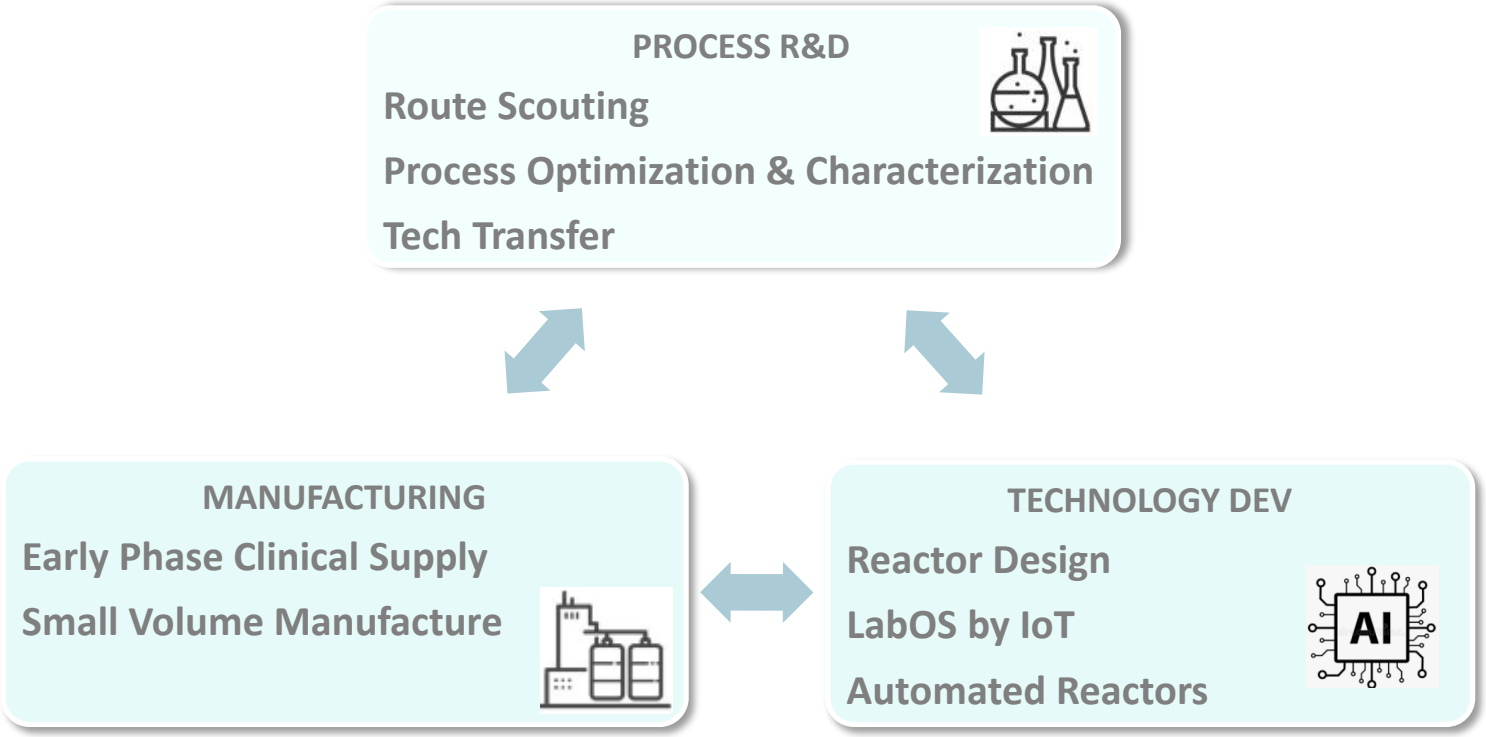
LI-JEN PING

P2SAC FALL CONFERENCE 2022

DECEMBER 15TH, 2022

Snapdragon Chemistry

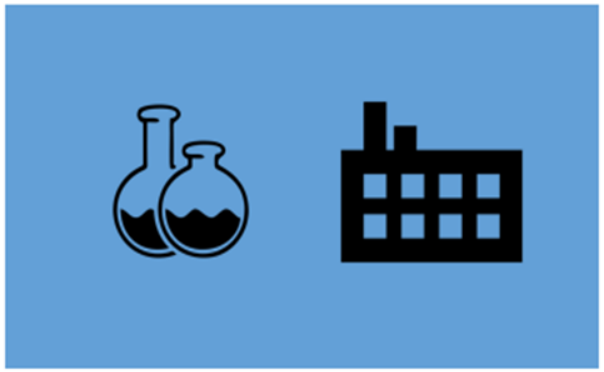
Our Mission: To help our clients harness the significant, lasting advantages of continuous flow technology and autonomous reaction platforms to transform their entire discovery, development & manufacturing value chain.



Providing solutions to clients with advanced manufacturing technology

Snapdragon Chemistry

SNAPDRAGON FACILITIES



R&D Center

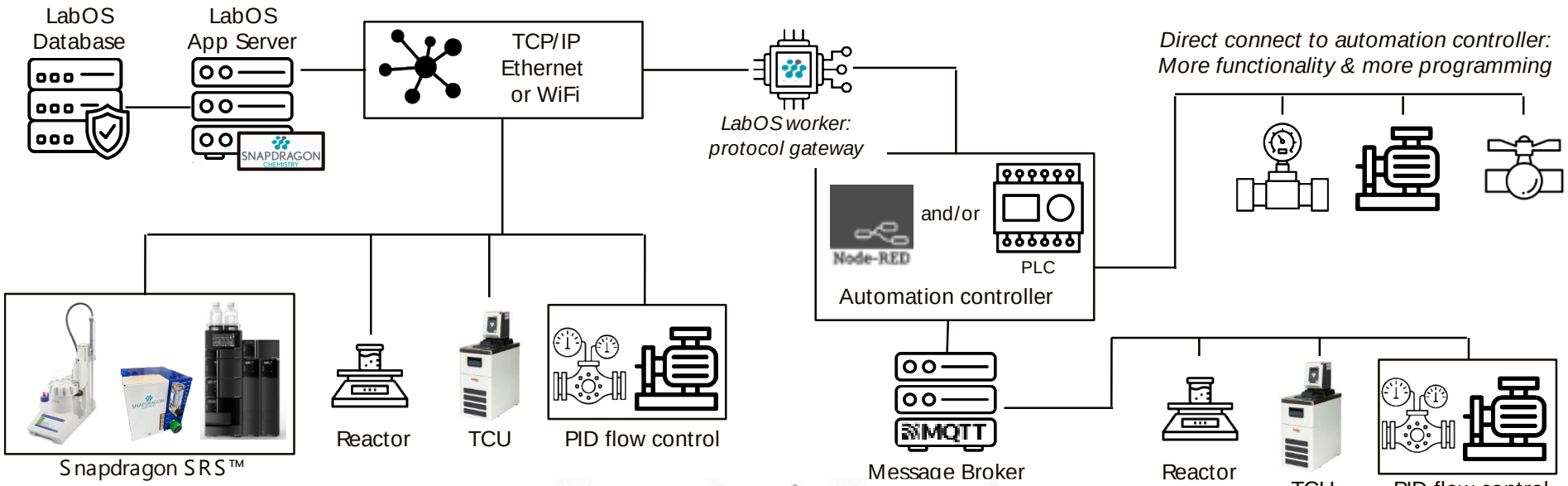
New Facility

Location : Waltham, MA (12 miles west of Boston)

R&D Center: 16,000 SF, >20 hoods, 2 kilolabs, analytical suite, machine shop, electronics shop. Team of ~75 including chemists, chemical engineers, mechanical engineers, software engineers

New facility (across the street): 51,000 SF, additional R&D labs, GMP kilo labs, QC, TechOps, Warehouse, Admin, Meeting center (opened in May 2022)

TECHNOLOGY DEVELOPMENT – LABOS

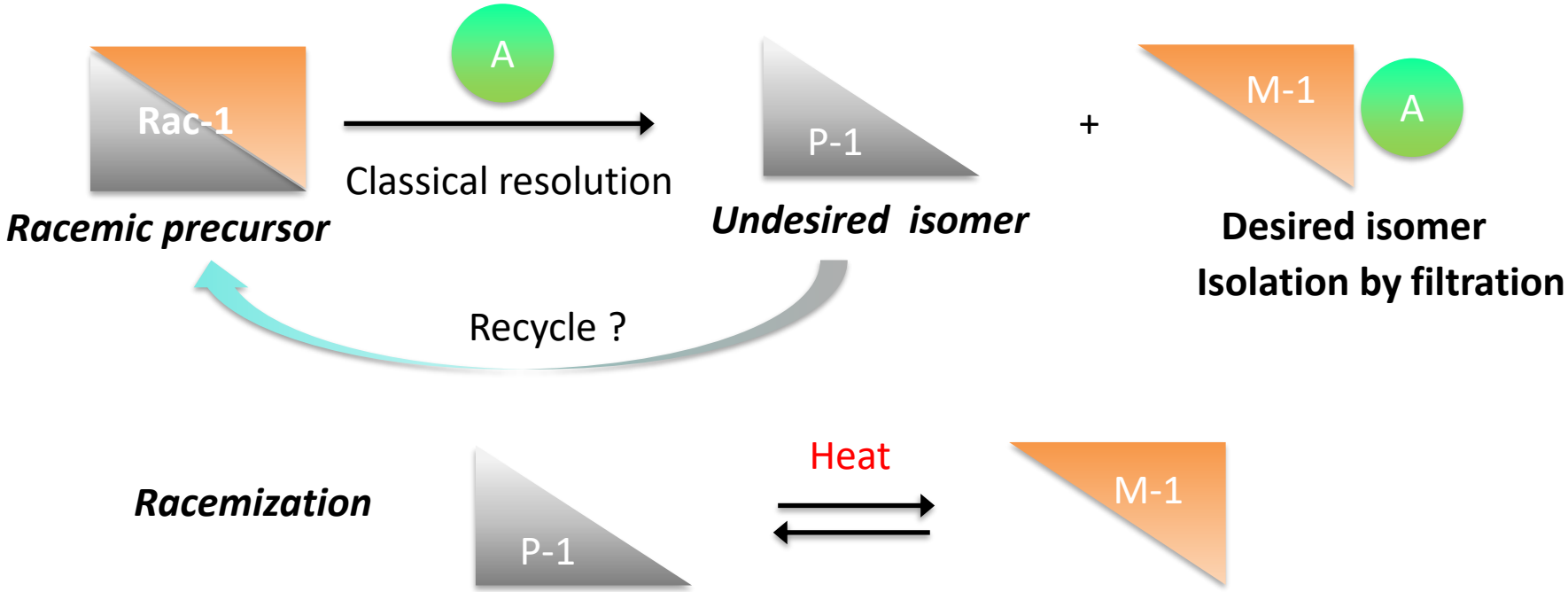


LabOS allows high confidence, control, data collection and safety of reactions and reactor systems

CASE-1
HIGH TEMPERATURE AND PRESSURE CONTINUOUS PROCESS

Org. Process Res. Dev. **2022**, *26*, 2636−2645

High Temperature Racemization

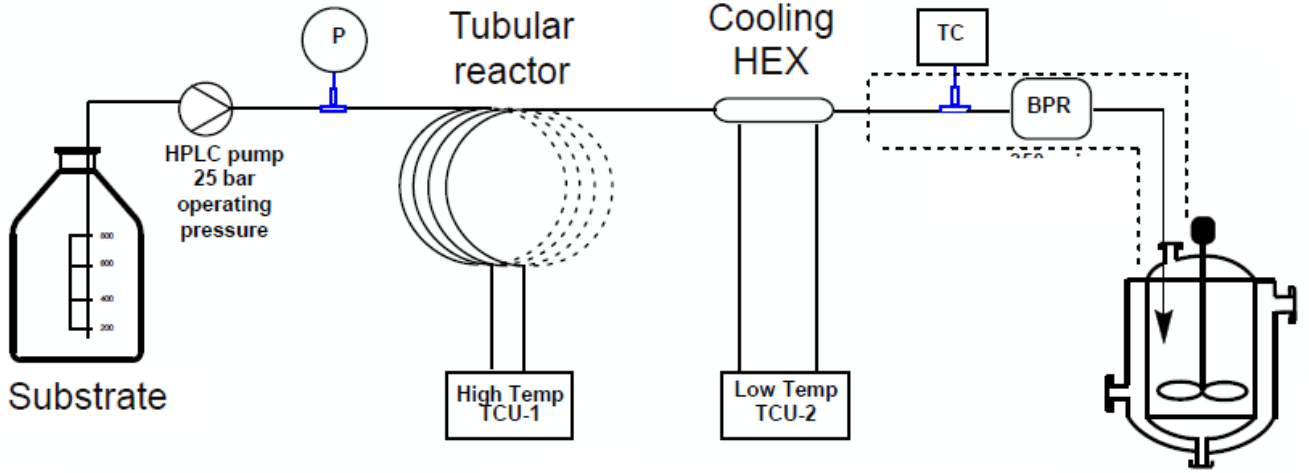


- The half-life for atropisomer interconversion is 26 min at 280°C
- To achieve full conversion at scale, it needs extreme operation temperature (> 300°C)
- Solvent of choice: superior solubility of P-1, high boiling point
- Not feasible to deliver a scalable and efficient process in batch reactors

Org. Process Res. Dev. **2022**, *26*, 2636−2645

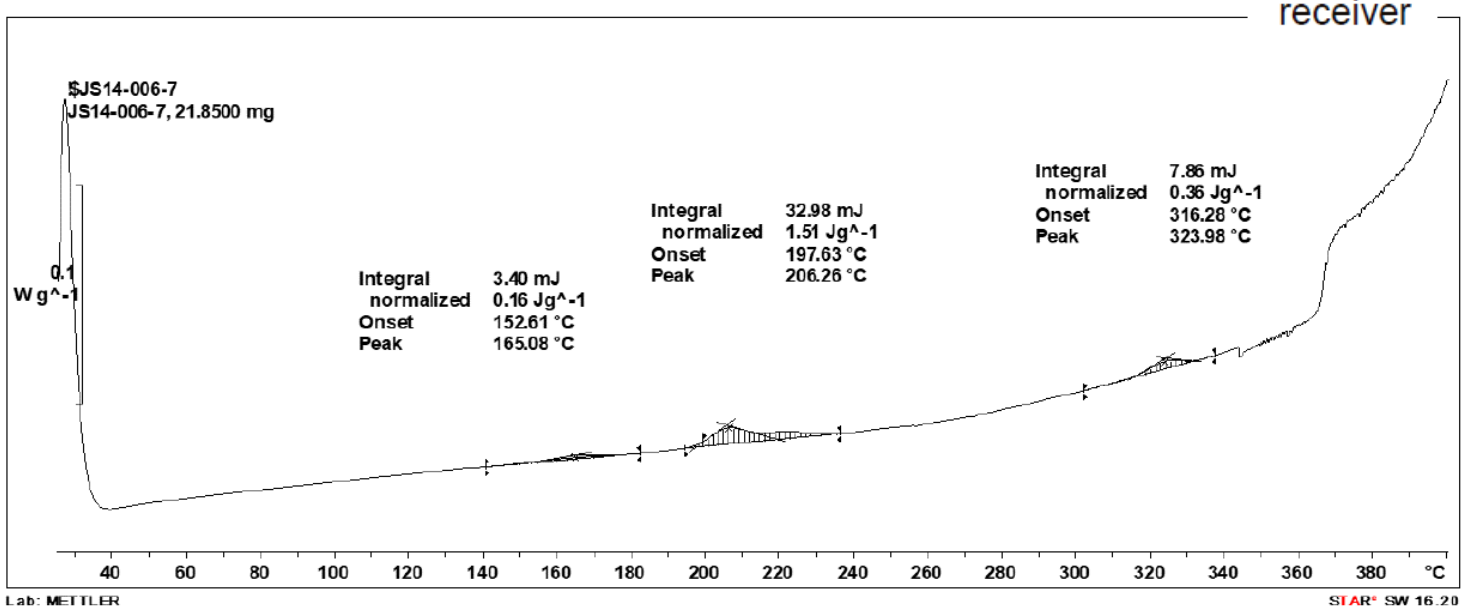
Ultra-high Temperature

- Racemization reaction at > 300 °C
- Super heated solvent system (P_{vap} > 20 bar)
- Decomposition reaction at ~ 340-360 °C
- Product crystallized below 100 °C



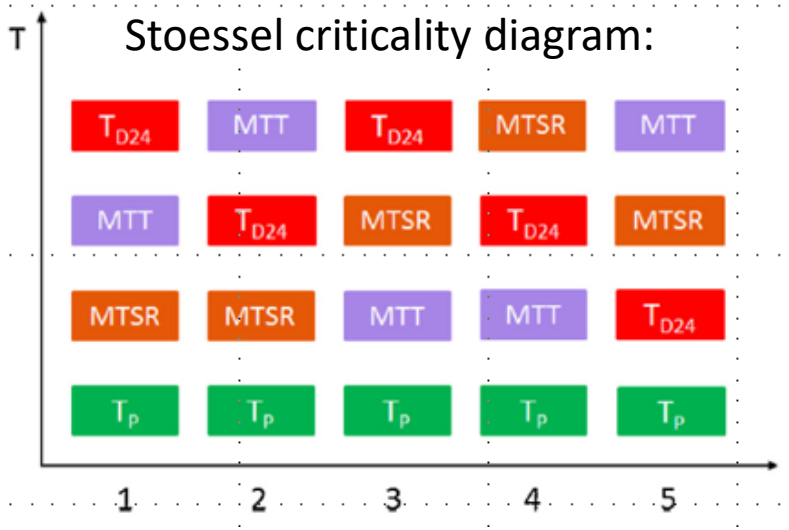
Key hazards:

- High temperature and back pressure
- Energetic decomposition reaction
- Clogging and over pressurization

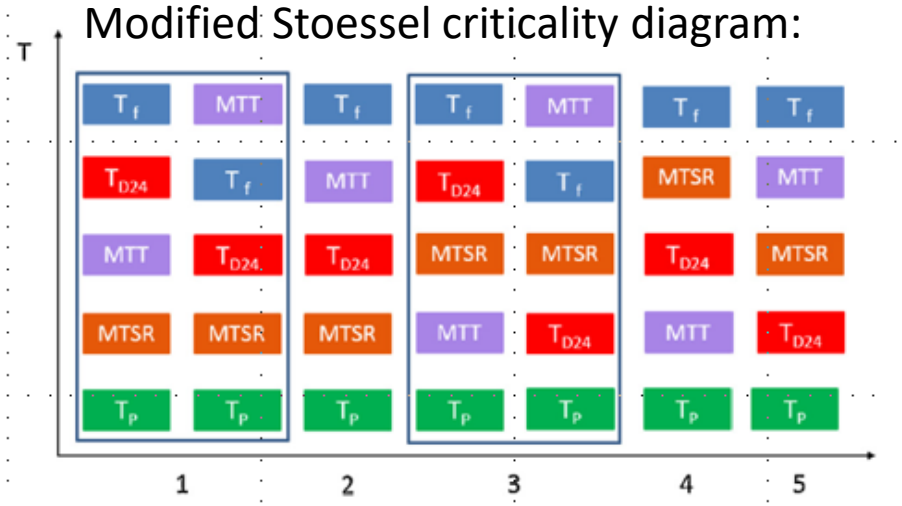


Thermal Hazard Assessment

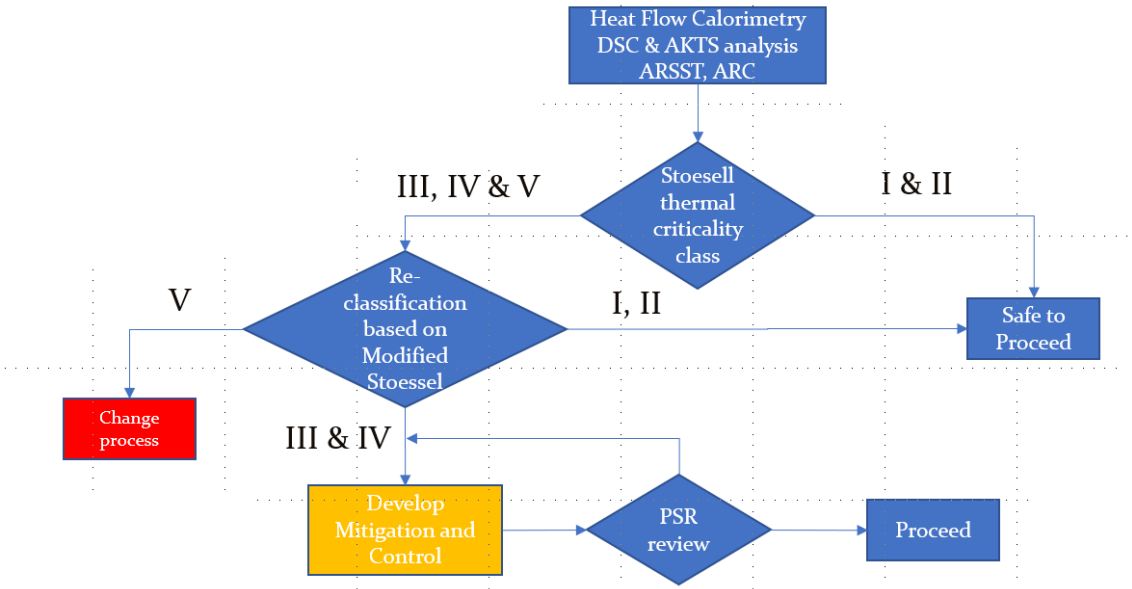
Stoessel criticality diagram:



Modified Stoessel criticality diagram:



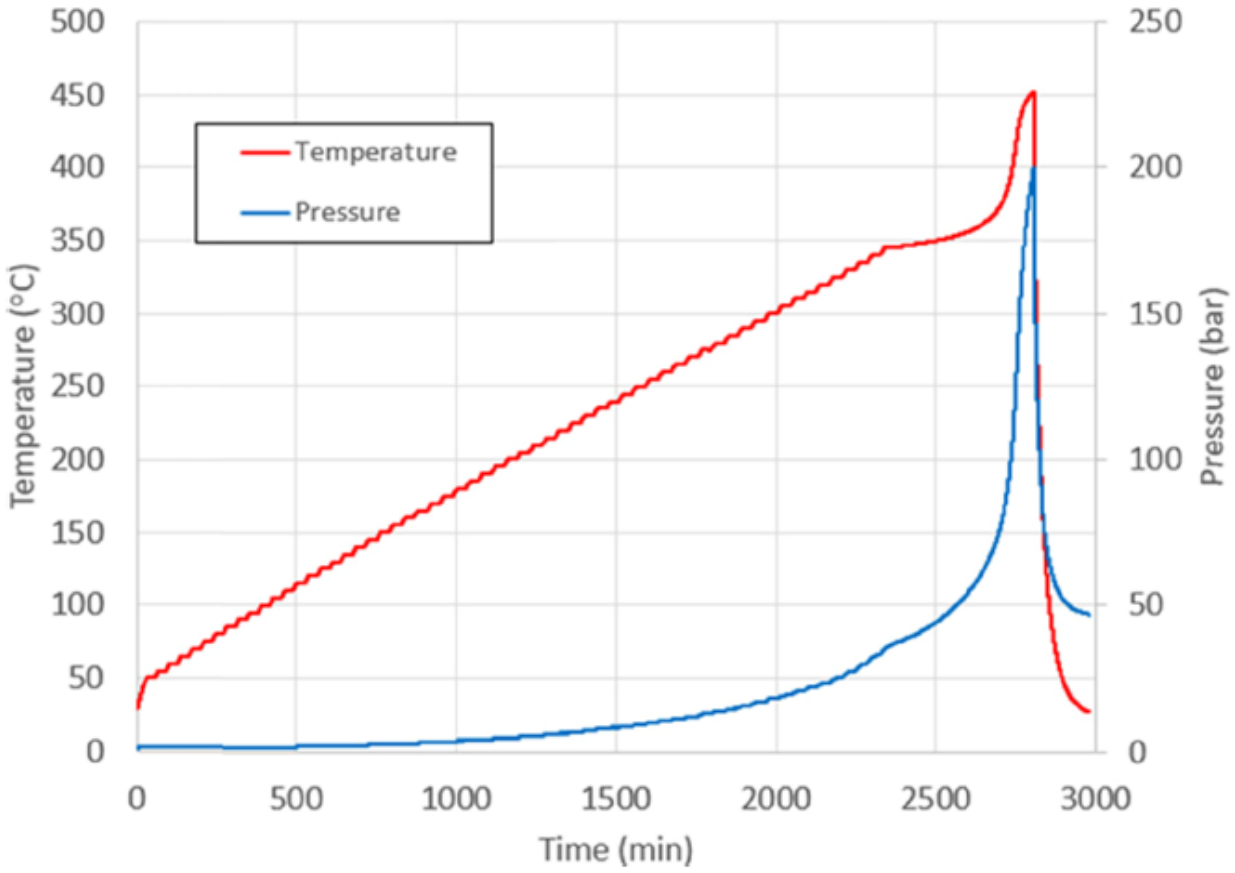
Process Safety and Environ. Protec., **2019**, 129, 112-118



Temperature	Description
T_p	Process temperature
MTSR	Max temperature of synthetic reaction
MTT	Max temperature of technical reasons
T_{D24}	Temperature at which the TMR_{ad} is 24 hours
T_f	Final temperature under adiabatic conditions $T_f = T_p + \Delta T_{ad,r} + \Delta T_{ad,d}$, if MTSR ≥ T_{D24} $T_f = T_p + \Delta T_{ad,r}$, if MTSR < T_{D24}

Adiabatic Reaction Calorimetry

- 10% solution of P-1 in anisole
- T_{onset} around 347 °C
- T_{D24} was regressed to be 330 °C
- Criticality classification
  - T_p : ca. 310 °C (=MTSR)
  - T_{D24} : 330 °C
  - MTT: ca. 370 °C (based on back pressure)
  - T_p =MTSR < T_{D24} < MTT : **Criticality Class 2 process**



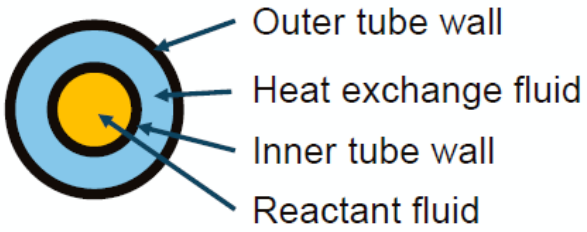
Org. Process Res. Dev. **2022**, *26*, 2636−2645

Safety Aspects of Tubular Reactor

Parameter	Batch (50-L glass)	Flow (tube-in-tube SS reactor)	Benefits in flow
Pressure and temperature rating	< 1 barg -6- - 200 °C	up to 300 barg > 400 °C	Higher failure points
Ratio of surface area / volume (cm^2 / cm^3)	~ 0.1	~ 10	Higher area for heat transfer
Heat transfer coefficient (W/m^2 K)	~ 10-100	> 500	More efficient heat transfer
ϕ-factor	~ 2	~ 40	Larger intrinsic heat sink in the case of cooling failure

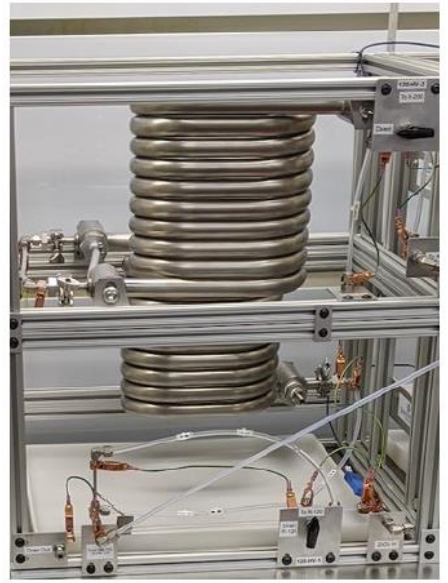
Reactor ϕ-factor

$$\emptyset = 1 + \frac{m_{vessel}C_{p,vessel} + m_{coolant}C_{p,coolant}}{m_{rxn}C_{p,rxn}}$$



Thermal dilution factor of the reaction mass by the reactor and coolant

Thermal mass (mCp, kJ/K)	Flow (90 mL tube/tube SS)	Flow (1.1 L tube/tube SS)	Batch (50L glass)
Reactor (%)	29	43	13
Coolant (%)	68	44	29
Reaction (%)	3	13	58
ϕ-factor	33	8	1.7



The higher phi factor and heat transfer rate in the tube/tube flow reactor means that, in the case of cooling failure, the adiabatic temperature rise is significantly reduced

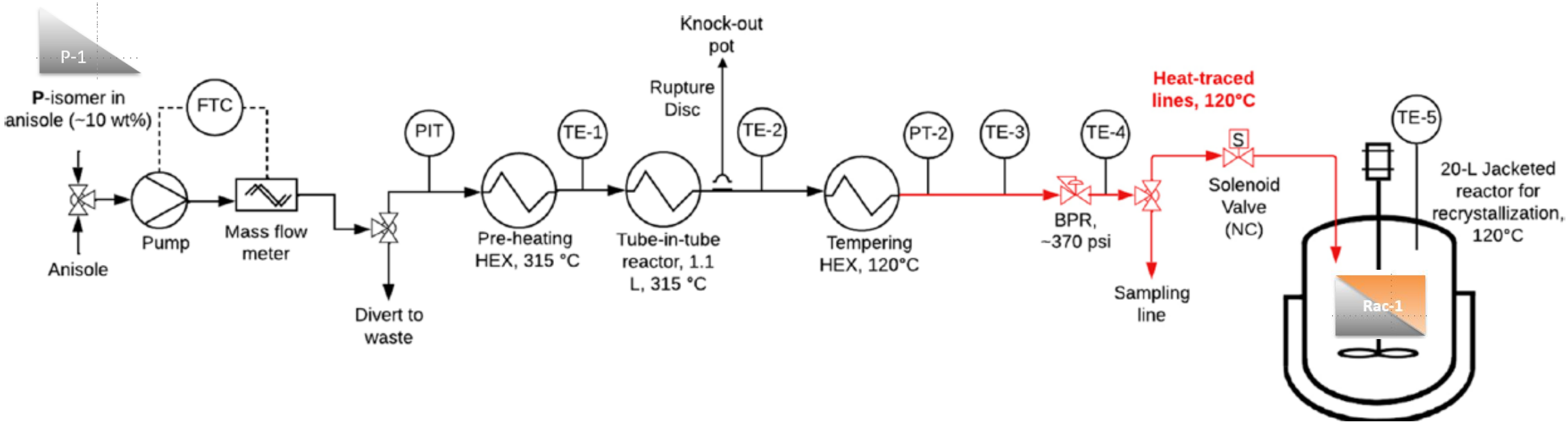
Hazardous Conditions and Mitigations

API 521 methodology and internal PHA process to identify hazardous conditions

Hazardous conditions	Worst case scenario	Mitigation strategy
Plugged outlet	Max pressure of pump	Rupture disk, interlock and knockout pot
Cooling water failure	Process fluid exit BPR at reaction temperature and flashes as vapor	Attended operation; interlock on shutdown
Abnormal process heat input	Decomposition reaction starts at 360 °C	Interlock on temperature control unit
Inadvertent valve opening	BPR goes to a higher set pressure and effectively closes, same as the plugged reactor	Rupture disk, interlock and knockout pot
Chemical reaction	Reaction starts to occur at 360 °C	Interlock on temperature control unit
Failed BPR	Flashing of solvent into hood	NC solenoid valve wired to e-stop

Vent sizing calculations performed by Fauske indicated rupture disk was approx. the same size as the reactor tube

Successful Demonstration Run



- 1.1 L tube-in-tube reactor with ~ 100 mL pre-heater and tempering cooler
- Process > 15 kg of solution at ~ 80 g /min over 3 hours, resident time of 13 min
- Maxed out 6 kW heater with internal temperature of ~ 295˚C

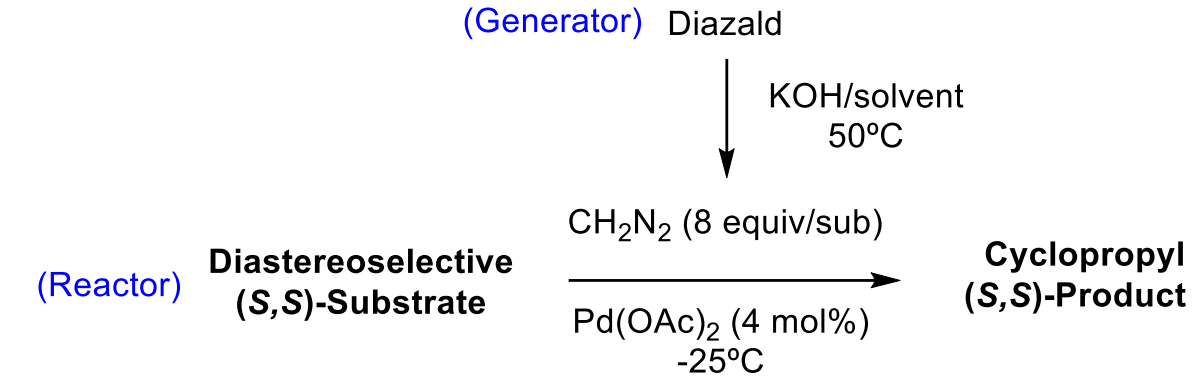
CASE-2
CONTINUOUS PROCESS FOR HIGH HAZARD AND REACTIVE CHEMICALS

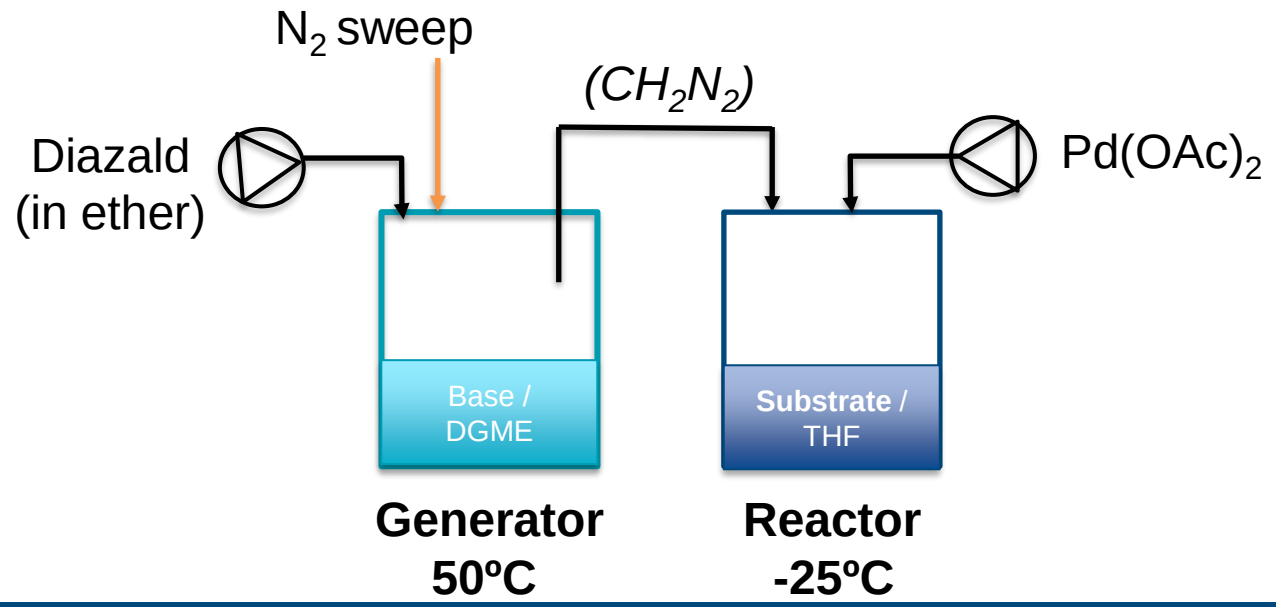
Org. Process Res. Dev. **2021**, *25*, 522−528

Background

- **Client's process:**
  - About:
    - Pd-catalyzed
    - Diastereoselective reaction
    - Cyclopropanation
  - Limitations
    - Prepared diazomethane in batch in ether solvent
    - Portion-wise additions of Diazald into generator during CH_2N_2 reaction
    - Portion-wise additions of $Pd(OAc)_2$ into reactor while CH_2N_2 was being carried over
    - Requires specialized equipment
    - Scalability issues

- **Goal**: Develop a method of delivering purified diazomethane in a safe, scalable continuous flow reactor to use in sensitive metal-catalyzed reactions.





Properties of Diazomethane

Chemical Identification	
CAS#	334-88-3
Formula	CH_2N_2
Physical Properties	
Physical description	Yellow gas with musty odor
Molecular weight	42.1
Freezing point	-229°F (-145°C)
Boiling point	-9°F (-23°C)
Vapor pressure	>1 atm
Vapor density	1.45

Exposure Limits	
OSHA PEL (8-hr TWA)	0.2 ppm
Explosion Hazards	
LEL in air	3.9% (v/v)[1]
LEL in N2	14.7% (v/v)[1]
Decom. temperature	< 120°C

Possible triggers of explosion[2]

- Ground joints and sharp surfaces of glassware
- Vibration or heavy shaking
- Expose to direct sun light or placed near a strong artificial light
- Impurities or contaminants

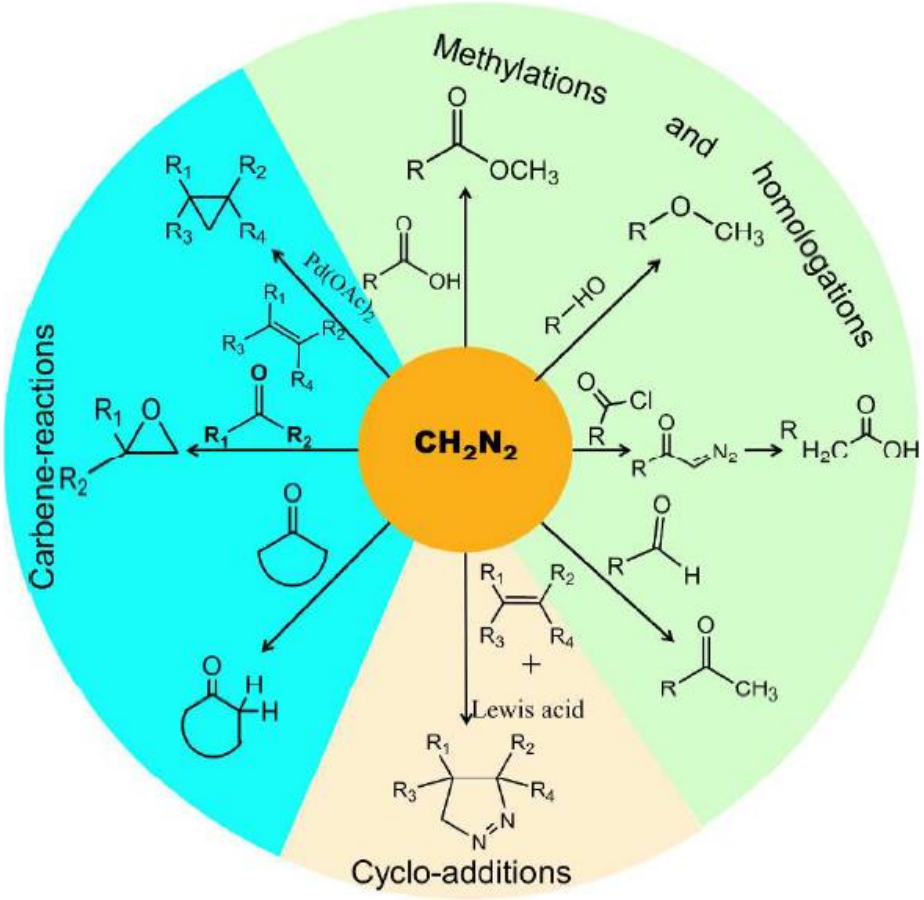
1. Org. Process Res. & Dev. **2002**, *6*, 884–892

2. Reed, Donald E.; James A. Moore (1961). "DIAZOMETHANE". *Organic Syntheses*. **41**: 16

Usage of Diazomethane

Advantages	Disadvantages
Versatility for different chemical transformations	Explosive
Selectivity	Toxic / Carcinogen
High reactivity	Not practical beyond laboratory scale
Easy to generate	Downstream purification

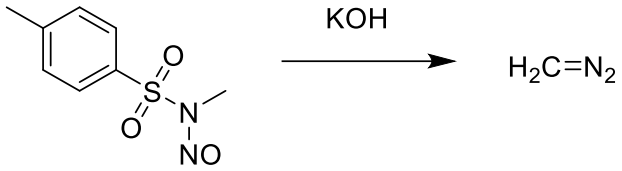
Synthetic applications of diazomethane



Org. Process Res. Dev. **2018**, *22*, 446−456

Generation of CH_2N_2

- Choice of precursor
  - *N*-methyl-*N*-nitroso-p-toluenesulfonamide (MNTS or Diazald®) : lower toxicity, cost and vapor pressure



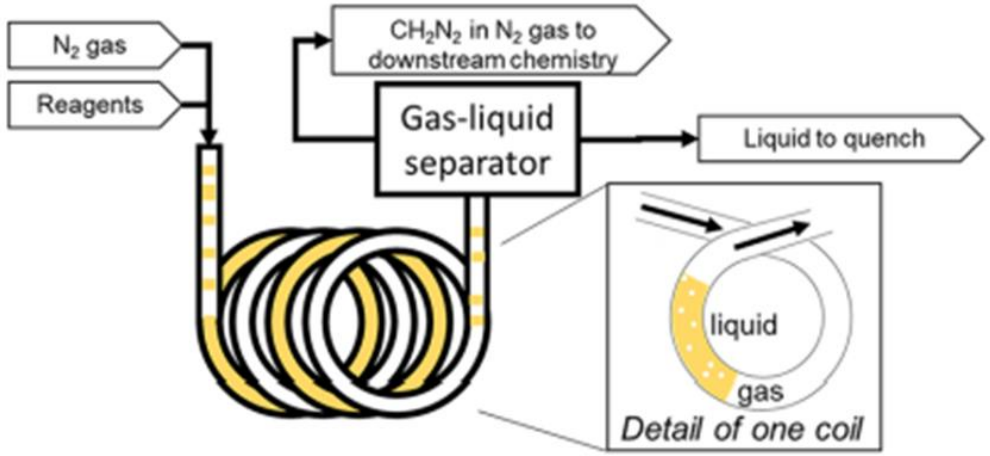
  - Desensitized as 15-20% wetted with water

Diazald®	
M.W.	214.24
m.p.	61-62 °C
Appearance	Yellow powder
Onset of decom.	~59 °C

- Choice of solvent
  - high-boiler solvent
    - 95:5 Sulfolane:water
- Composition of KOH solution
  - Varied the conc. of KOH to reduce water content, which leads to precipitation in-line
    - 25 w/w% KOH

Generation of Diazomethane

- SDC reactor design
  - Inspiration from Eli Lilly paper (Science, 2017)
    - Design kept coil filled with 50% gas, 50% liquid to keep accumulation low
    - Enabled gas residence time to be x3 faster than liquids
  - Plug flow reactor
    - Vertical orientation
    - Minimal headspace
  - Uses inline nitrogen sweep
    - Acts as carrier gas
    - Keeps CH_2N_2 below LEL (~15 v/v in N_2)
    - Prevents liquid from going backwards



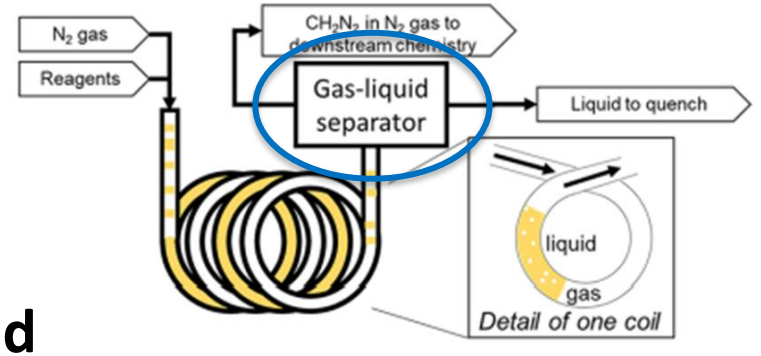
Plug flow reactor

Vertical orientation

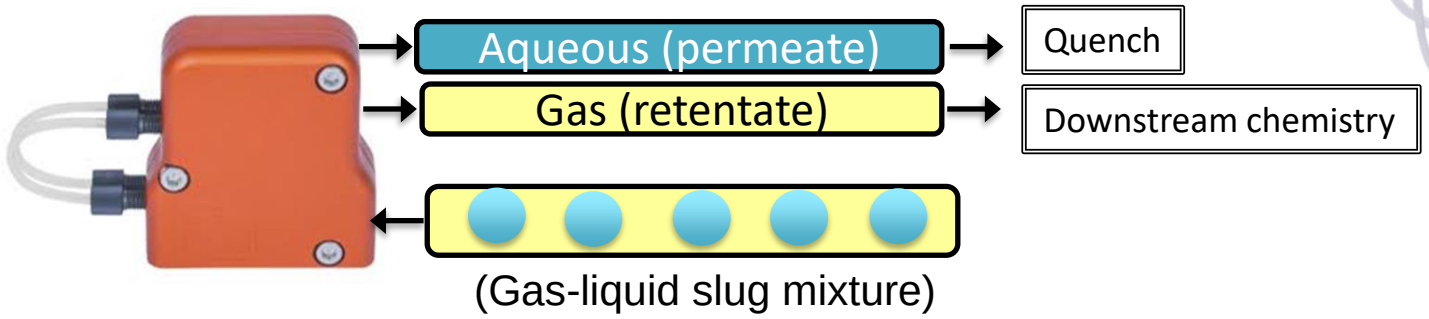
N_2 as carrier gas

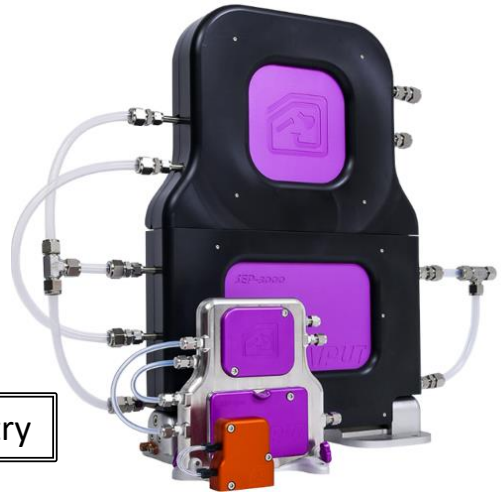
Cole et al., *Science* **356**, 1144–1150 (2017)

Purification of Diazomethane



- **Zaiput separator for gas/liquid**
  - SEP-200 handles up to 200 mL/min
  - Gas and liquid slugs enter separator
  - PTFE Hydrophilic membrane
    - CH_2N_2/N_2 is retained
    - Aqueous layer is the permeate





Minimal headspace / smaller volume

No moving parts

Designed for continuous flow processes

Verification

- Test reactor design for CH_2N_2 productivity
  - Establish throughput
  - Calculate yield for the generation of CH_2N_2

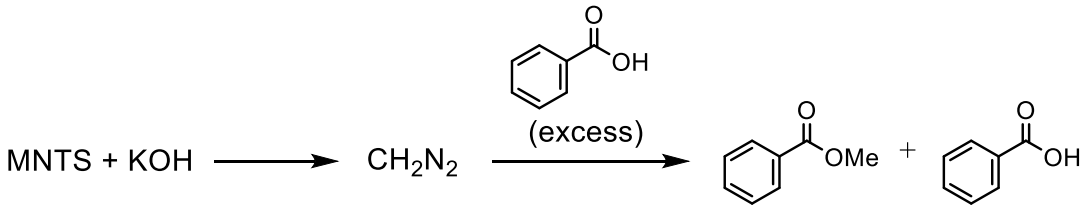


Table 1. Summarized Results from Diazomethane Generation System Using Zaiput SEP-200 with 1.52 equiv of KOH and 1.5 equiv of Benzoic Acid (0.5 M)

			flow rates in diazomethane generator		
entry	MNTS throughput (mmol/min)	solvent	liquid (g/min)	N_2 (slpm)	yield (%) of CH_2N_2
1	4.9	DMSO/DGME[a]/H_2O	7.4	0.685	75–80
2	4.9	sulfolane/H_2O	12.0	1.07	76–82
3	9.6	sulfolane/H_2O	24.0	2.13	77–79
4	13.7	sulfolane/H_2O	33.7	2.99	64
5	19.6	sulfolane/H_2O	47.7	4.27	incomplete gas–liquid separation

[a]DGME = diethylene glycol monoethyl ether.

Flow Reactor Design

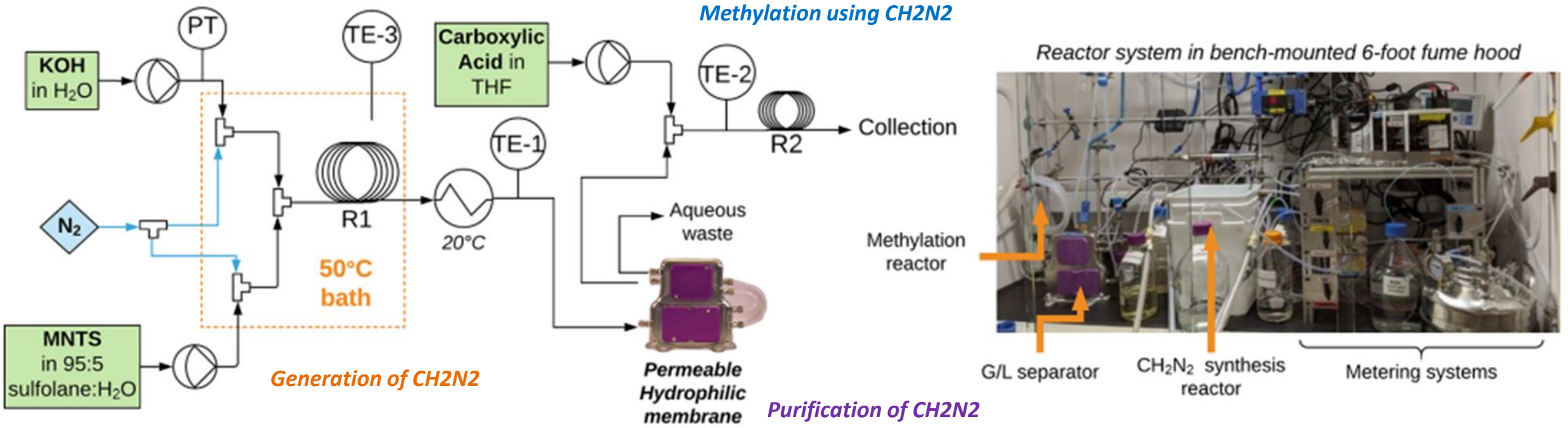


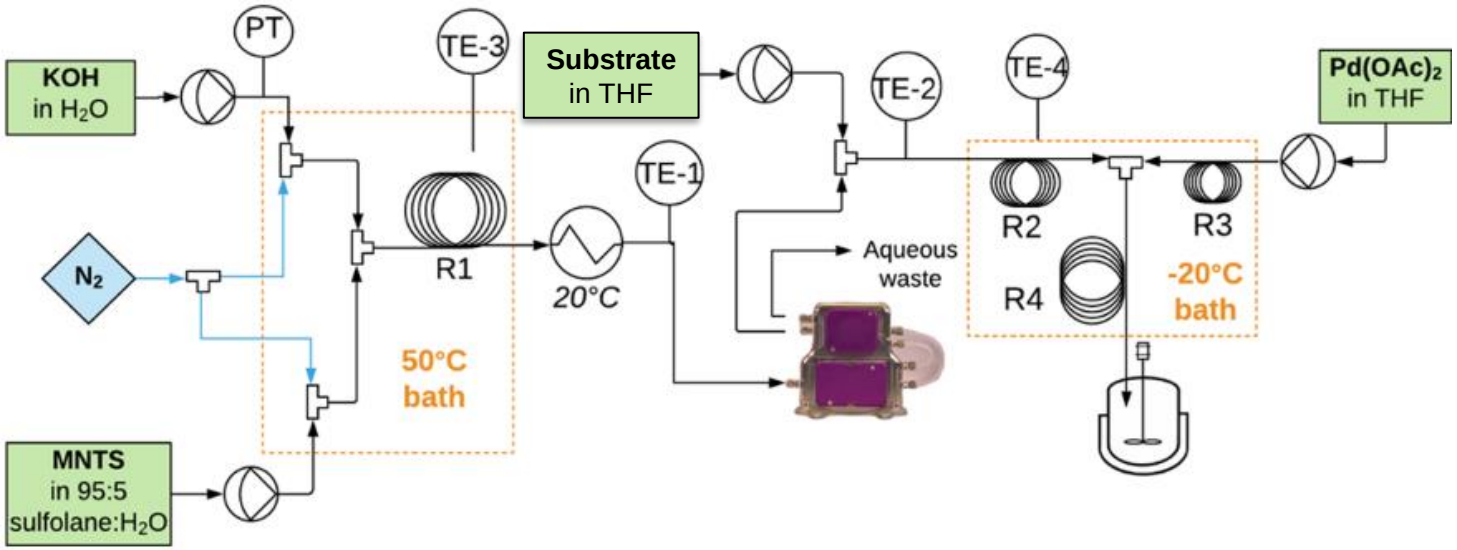
Figure 2. Process flow diagram of diazomethane synthesis reactor and downstream carboxylic acid methylation. *R1* = 240 mL, *R2* = 120 mL. Feed rates: KOH in H_2O (13.7% w/w), 4.11 g/min; MNTS in 95:5 sulfolane/H_2O (12.3% w/w), 14.6 g/min; N_2, 1.02 slpm per feed (2.04 slpm total); carboxylic acid in THF (0.5 mmol/g solution), 8.34 g/min.

Overall volume of CH_2N_2 in the system (incl. methylation reactor) : < 53 mg

Downstream Processing

- Pd-catalyzed cyclopropanation

MNTS solution mass flow rate (g/min)	18.3
MNTS solution composition	11.6 wt% **MNTS** 95/5 w/w% Sulfolane/H_2O
KOH stoichiometry	1.52 equiv
Total N_2 Flow Rate (L/min)	3038 (50% LEL at 100% yield)
Diazald Equivalents	7.5 (~ 6 equiv CH_2N_2)
CH_2N_2 Generation Temp	50 ° C
Substrate Mass Flow Rate (g/min)	10.62
Substrate Throughput (mmol/min)	1.31
$Pd(OAc)_2$ Catalyst loading	2 mol %
LCAP Conversion	97%



- **Takeaway**: purified CH_2N_2 was successful in the cyclopropanation of **substrate** to **product** in high conversion at the production rate of 20 g/h with <50 mg of CH_2N_2 inventory in system

Acknowledgement

High temperature racemization

- Snapdragon Chemistry: Eric Fang, David D. Ford, Kiersten Campbell, Kevin D. Nagy, Jillian W. Sheeran, Reem Telmesani,
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- Fauske and Associates

Diazomethane process

- Snapdragon Chemistry: Grace Russell, David D. Ford, Eric Fang, Matthew Bio, Kiersten Campbell; Jillian W. Sheeran, Gerald Hummel, Christopher P. Breen, Anamika Datta, Changfeng Huang
- Qpex Biopharma: Serge H. Boyer, Scott J. Hecker
- Zaiput Technologies

Questions?