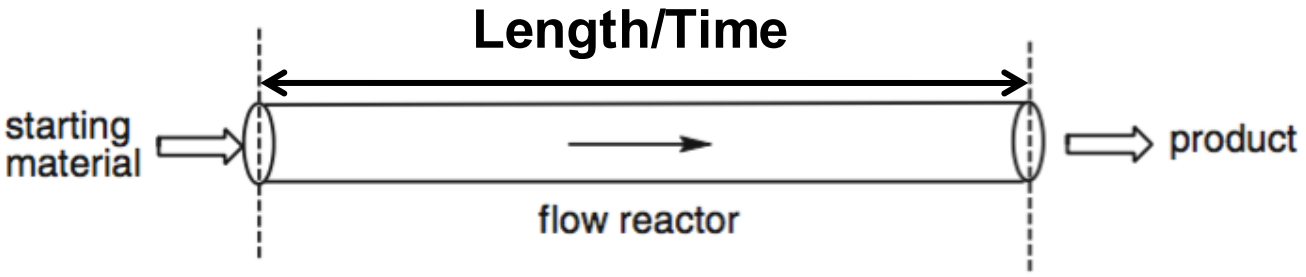
Continuous Process Intensification

L2: Continuous Flow Processes/Tools/Practices

Anil Kumar

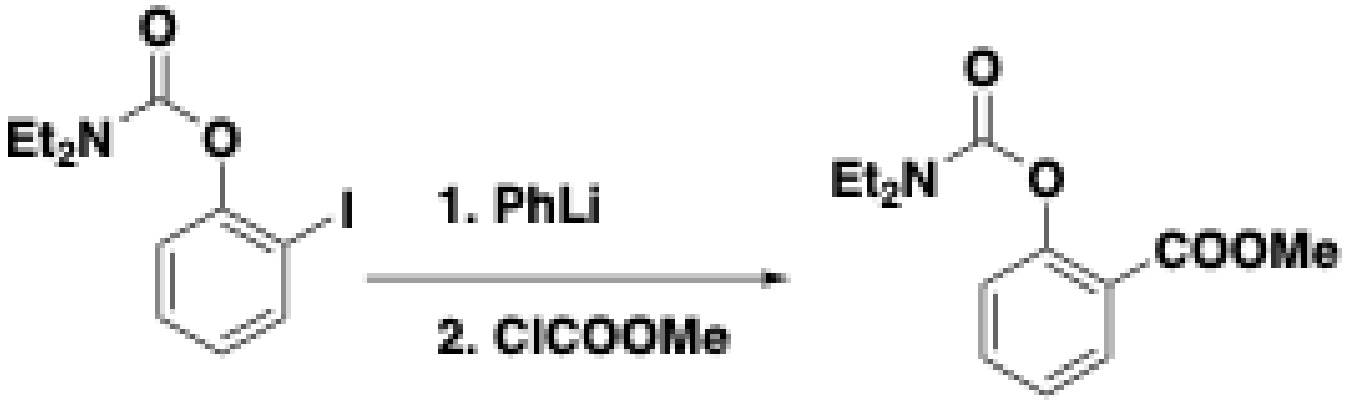
Flow Processes



- Each molecule passing through the device experiencing the same reaction times, temperatures, pressures and surroundings.
- Excellent batch-to-batch reproducibility
- No Head-Space (excellent for G-L-S/L-L/L-S/G-L reactions)
- No secondary nucleation or side reactions
- Ease scale-up without much re-optimization & redesign
- Controlled Reactivity/Selectivity

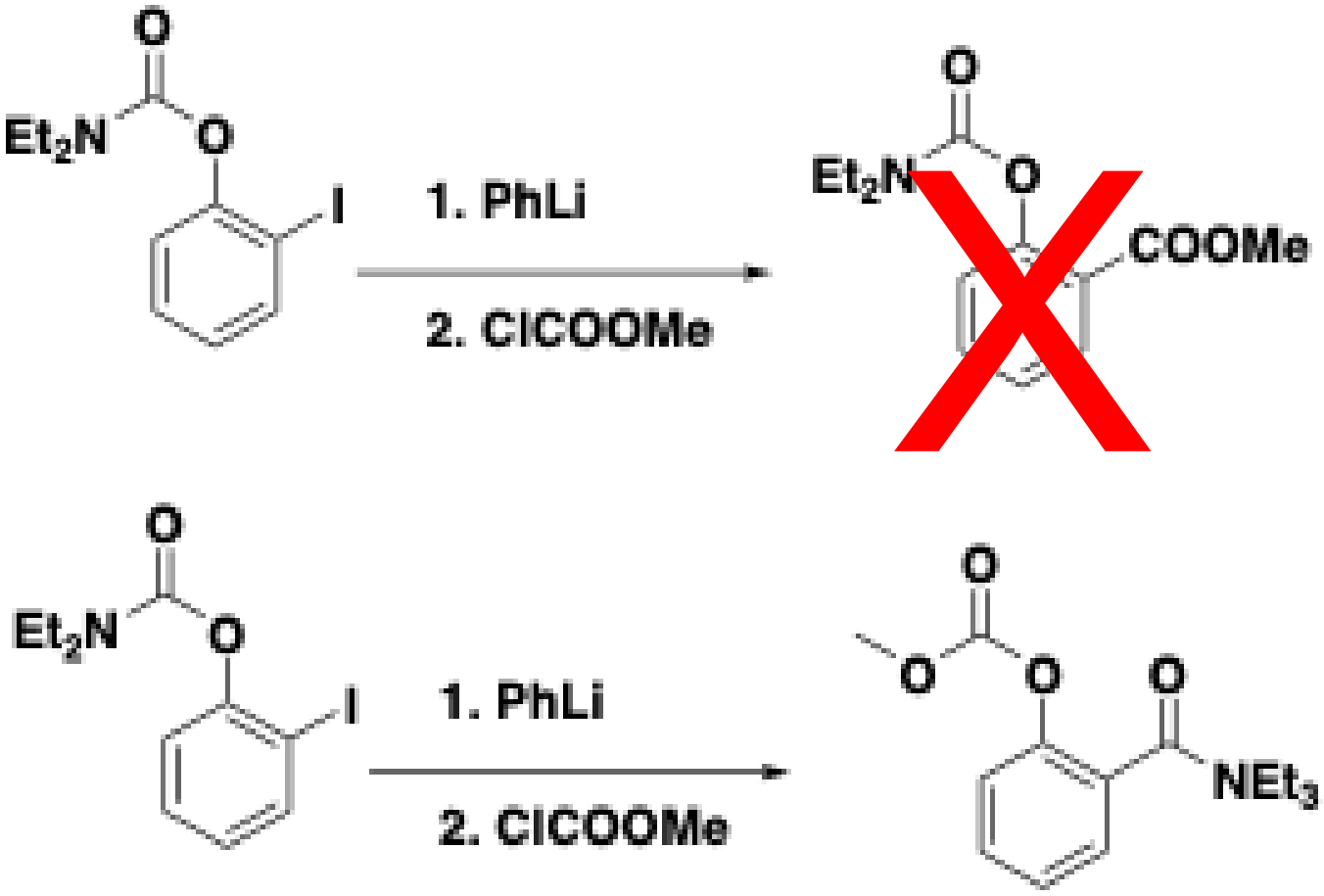
Micro Reaction Technology in Organic Synthesis, C Wiles and P Watts, 2011, CRC

Time Resolved Synthesis



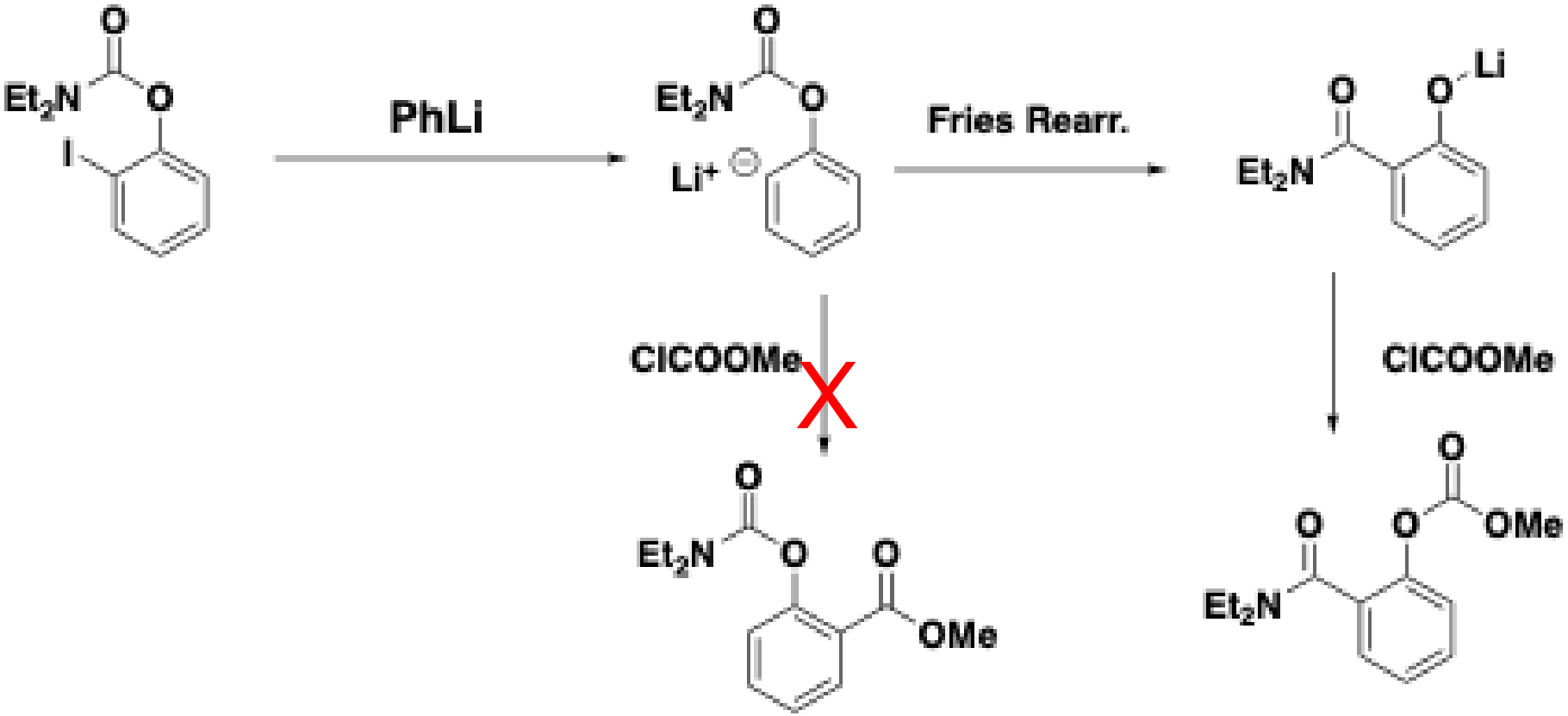
Kim et al. Science, 2016, 352,6286, 691

Time Resolved Synthesis



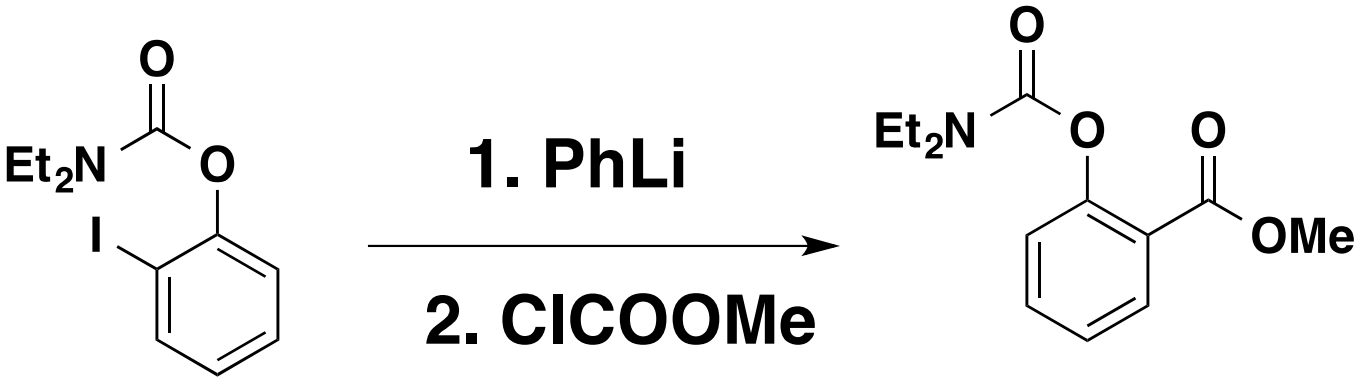
Kim et al. Science, 2016, 352,6286, 691

Time Resolved Synthesis

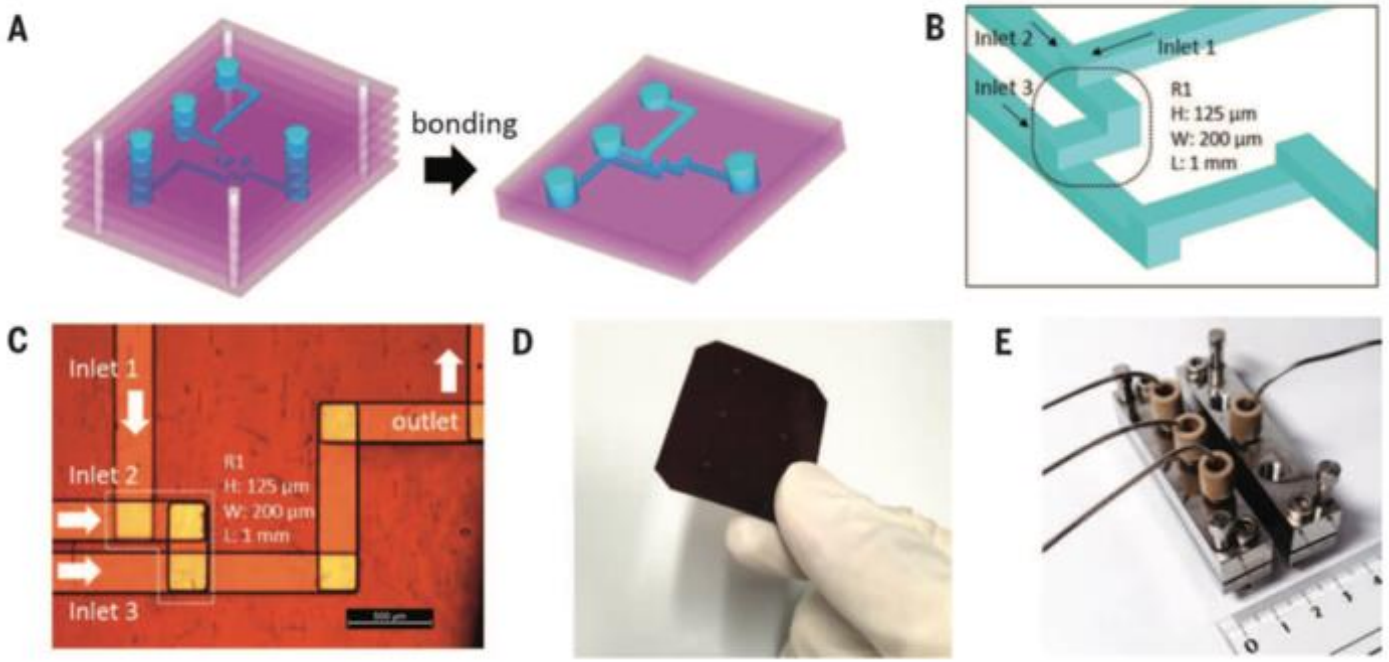


Kim et al. Science, 2016, 352,6286, 691

Time Resolved Synthesis

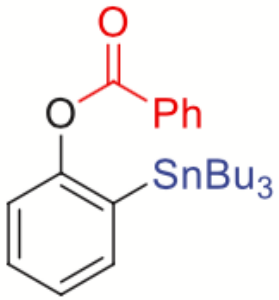


Continuous Flow of 25 nL; 0.33 ms; 91%



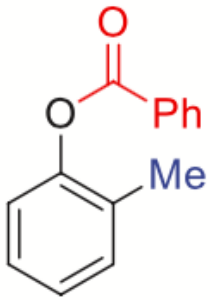
Kim et al. Science, 2016, 352,6286, 691

Time Resolved Synthesis

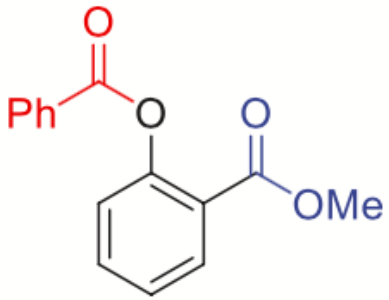


5a, 86%*

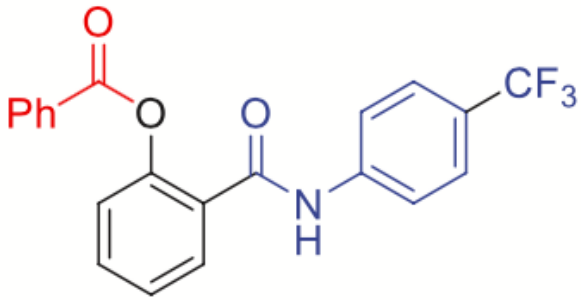
5b, 94%



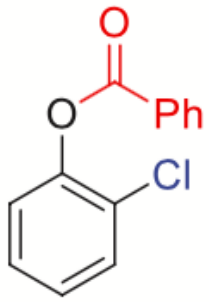
5c, 98%



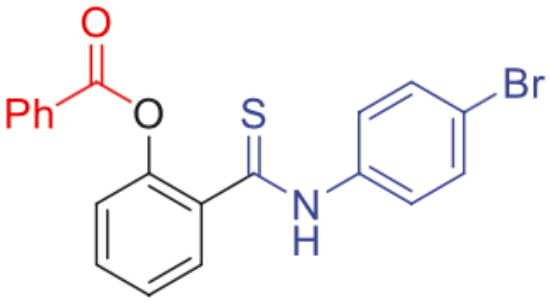
5d, 88%



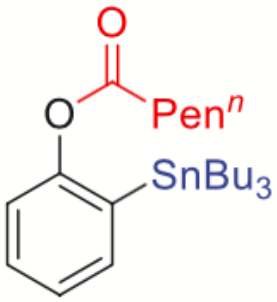
5e, 79%



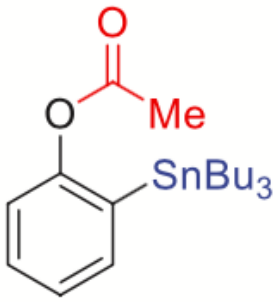
5f, 62%*



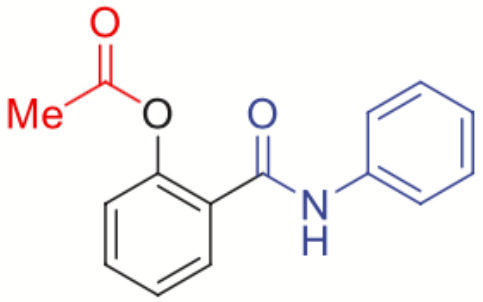
5g, 61%



5h, 91%*



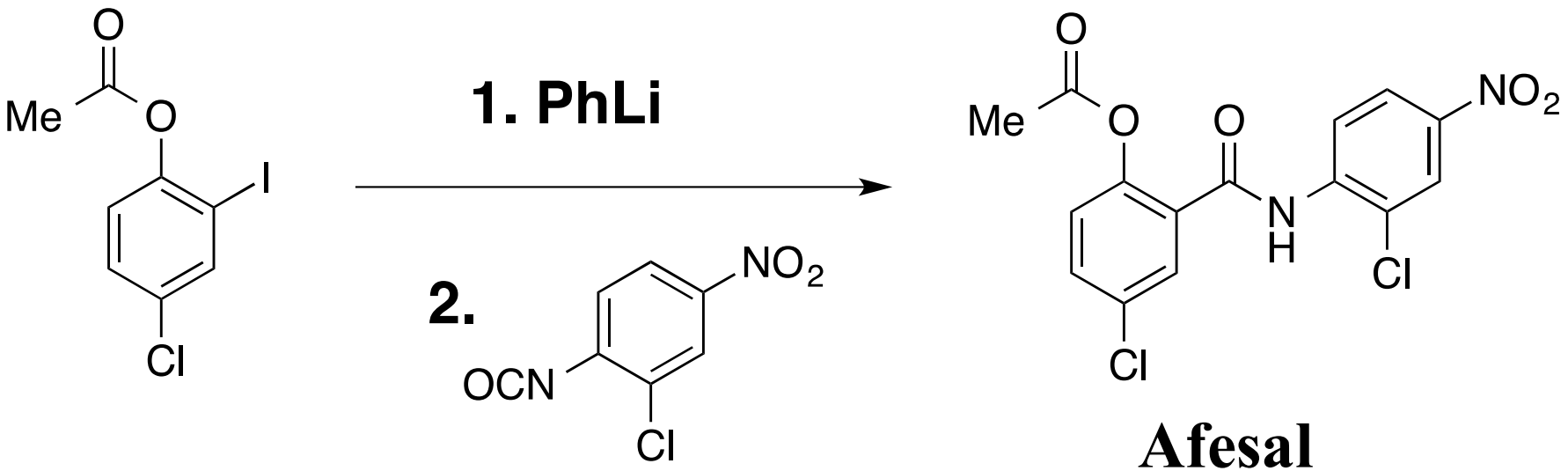
5i, 72%



5j, 75%†

Kim et al. Science, 2016, 352,6286, 691

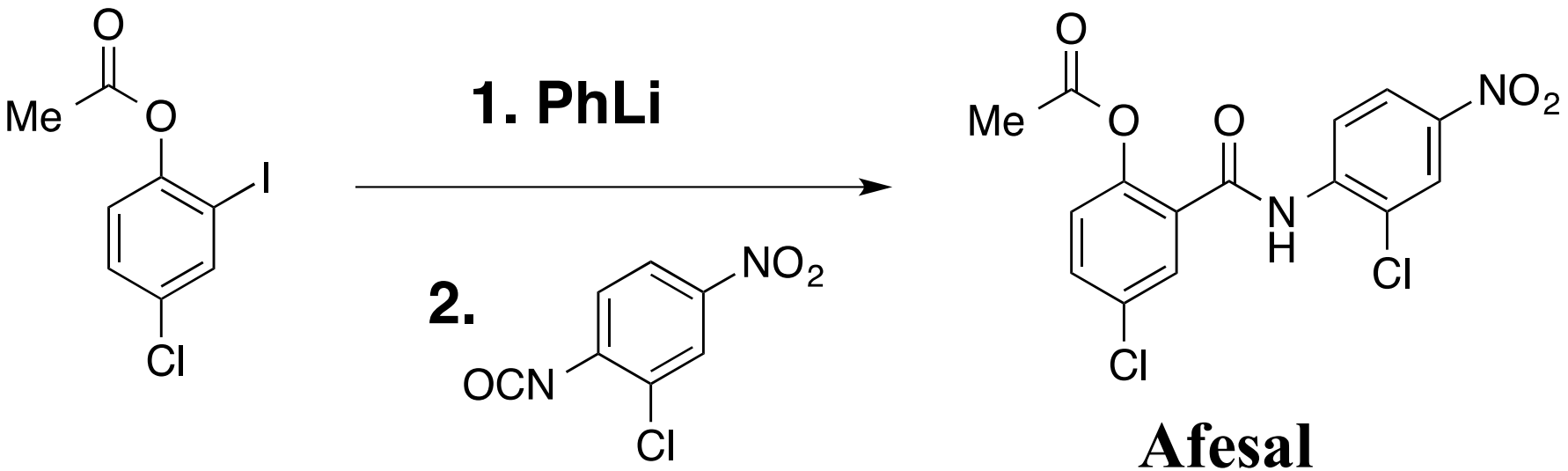
Time Resolved Synthesis



Afesal
(anthelmintic activity)
67%

Kim and Yoshida et al. Science, 2016, 352,6286, 691

Time Resolved Synthesis

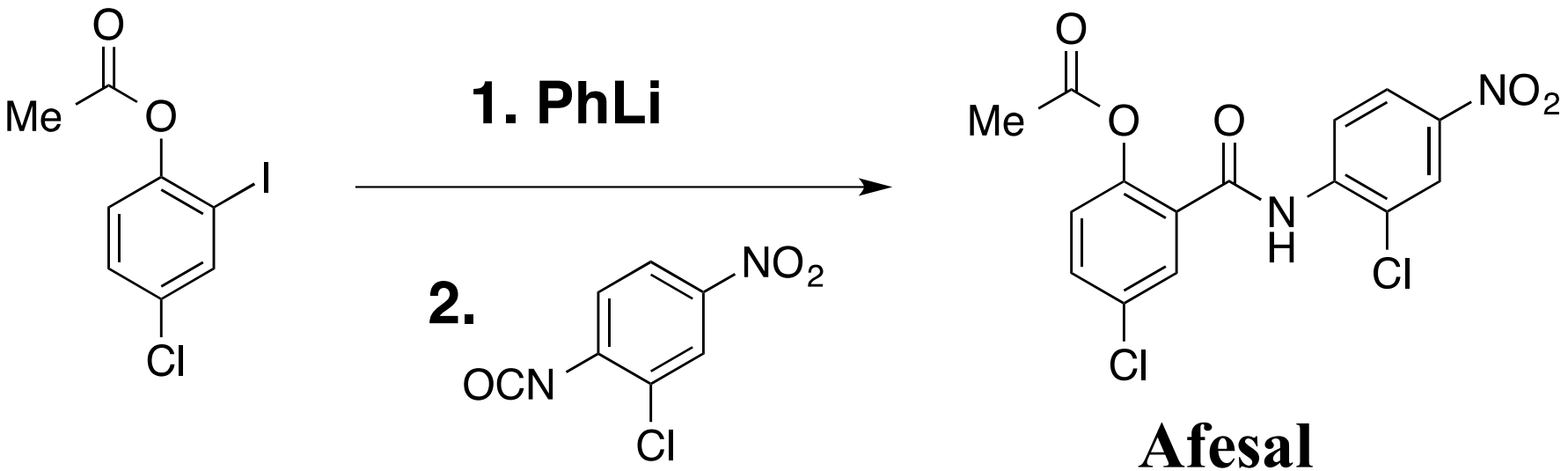


Afesal
(anthelmintic activity)
67%

25 nl @ 67%

Kim and Yoshida et al. Science, 2016, 352,6286, 691

Time Resolved Synthesis

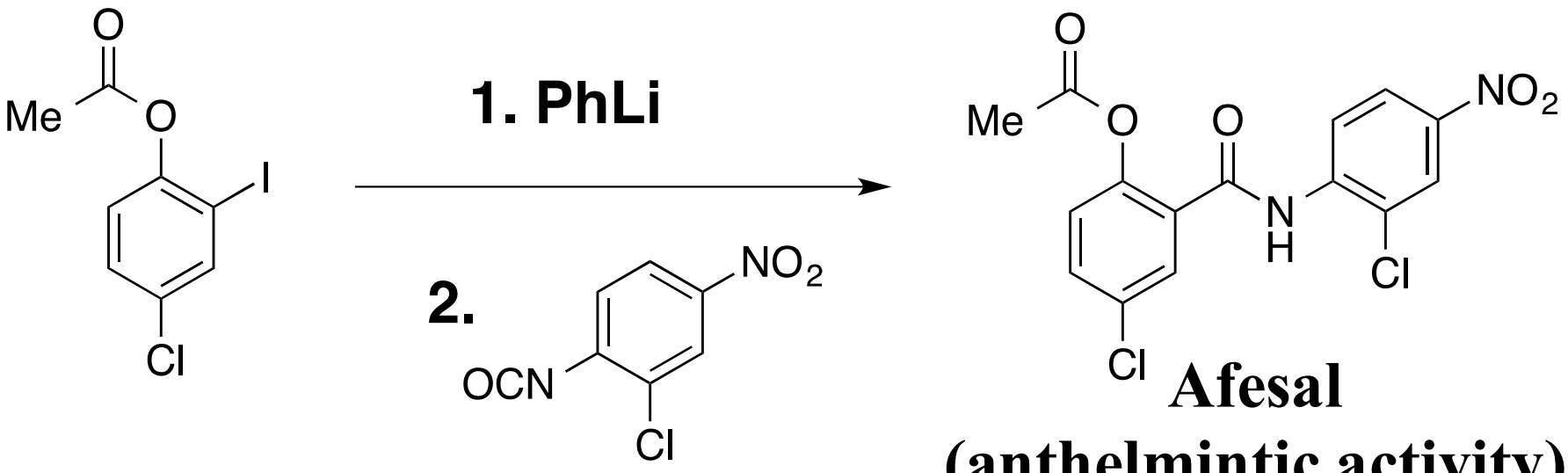


Afesal
(anthelmintic activity)
67%

25 nl @ 67% = 5.3g/h

Kim and Yoshida et al. Science, 2016, 352,6286, 691

Time Resolved Synthesis



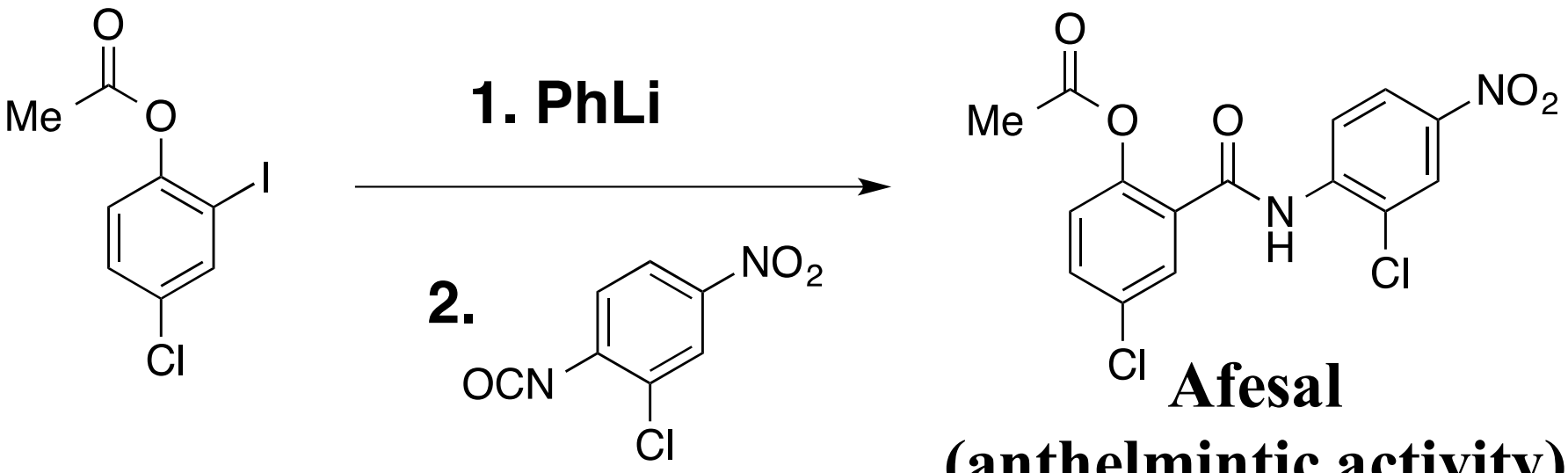
Afesal
(anthelmintic activity)
67%, 5.3g/h

25 nl @ 67% = 5.3g/h

10 ml: ??

Kim and Yoshida et al. Science, 2016, 352,6286, 691

Time Resolved Synthesis



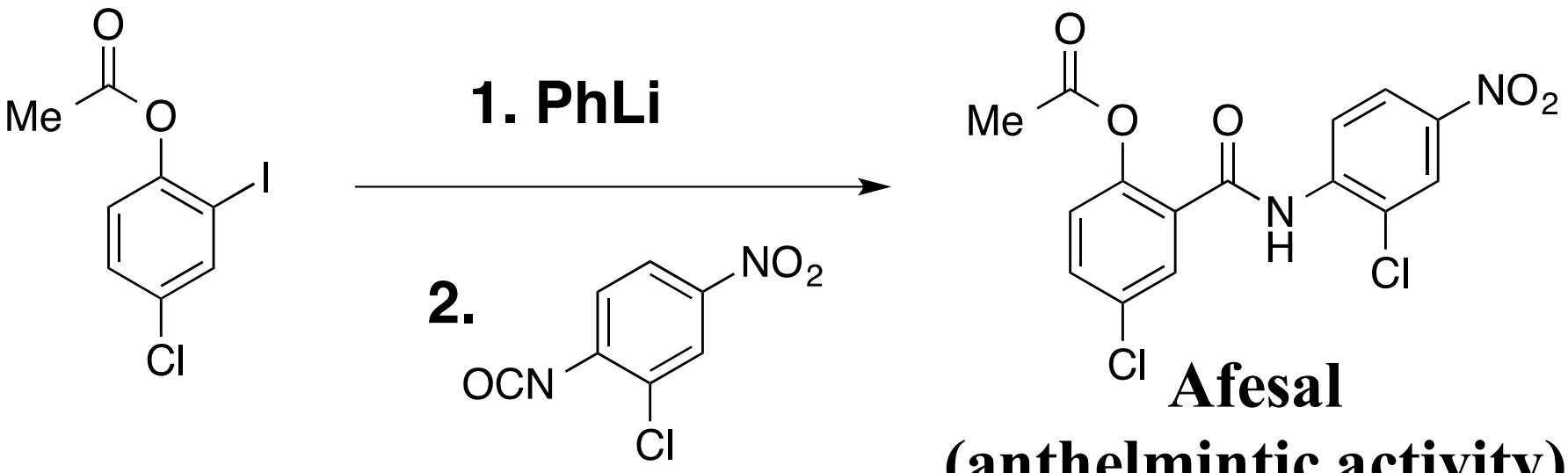
Afesal
(anthelmintic activity)
67%, 5.3g/h

25 nl @ 67% = 5.3g/h

10 ml ($1:4x10^5$)

Kim and Yoshida et al. Science, 2016, 352,6286, 691

Time Resolved Synthesis



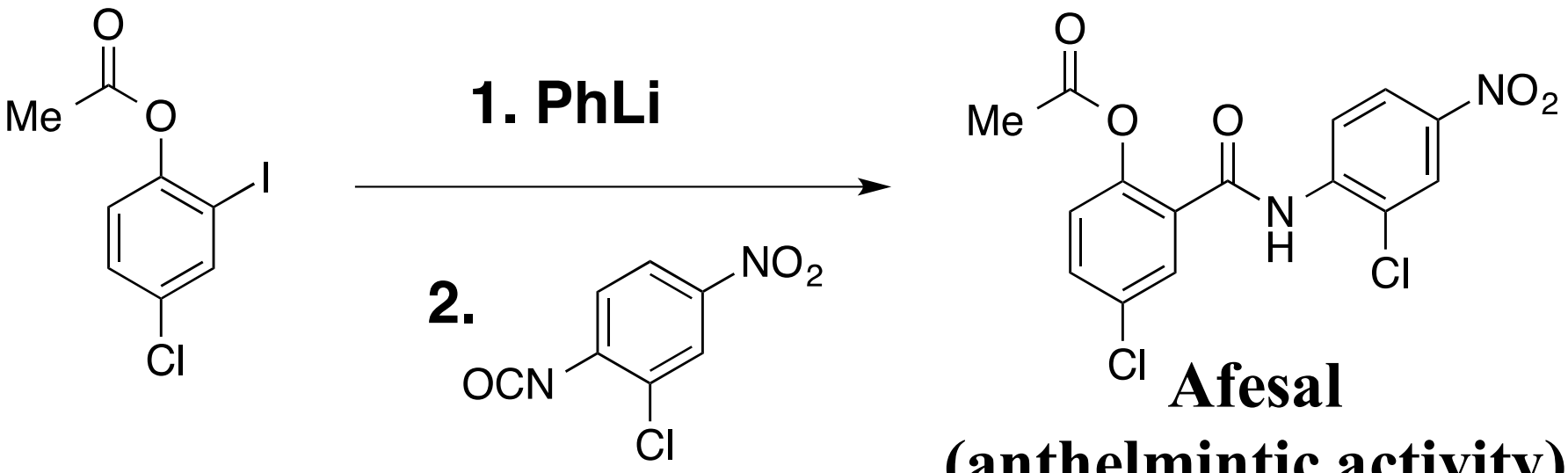
Afesal
(anthelmintic activity)
67%, 5.3g/h

25 nl @ 67% = 5.3g/h

10 ml ($1:4x10^5$)
5.3g/h = 2.1 ton/h

Kim and Yoshida et al. Science, 2016, 352,6286, 691

Time Resolved Synthesis



Afesal
(anthelmintic activity)
67%, 5.3g/h

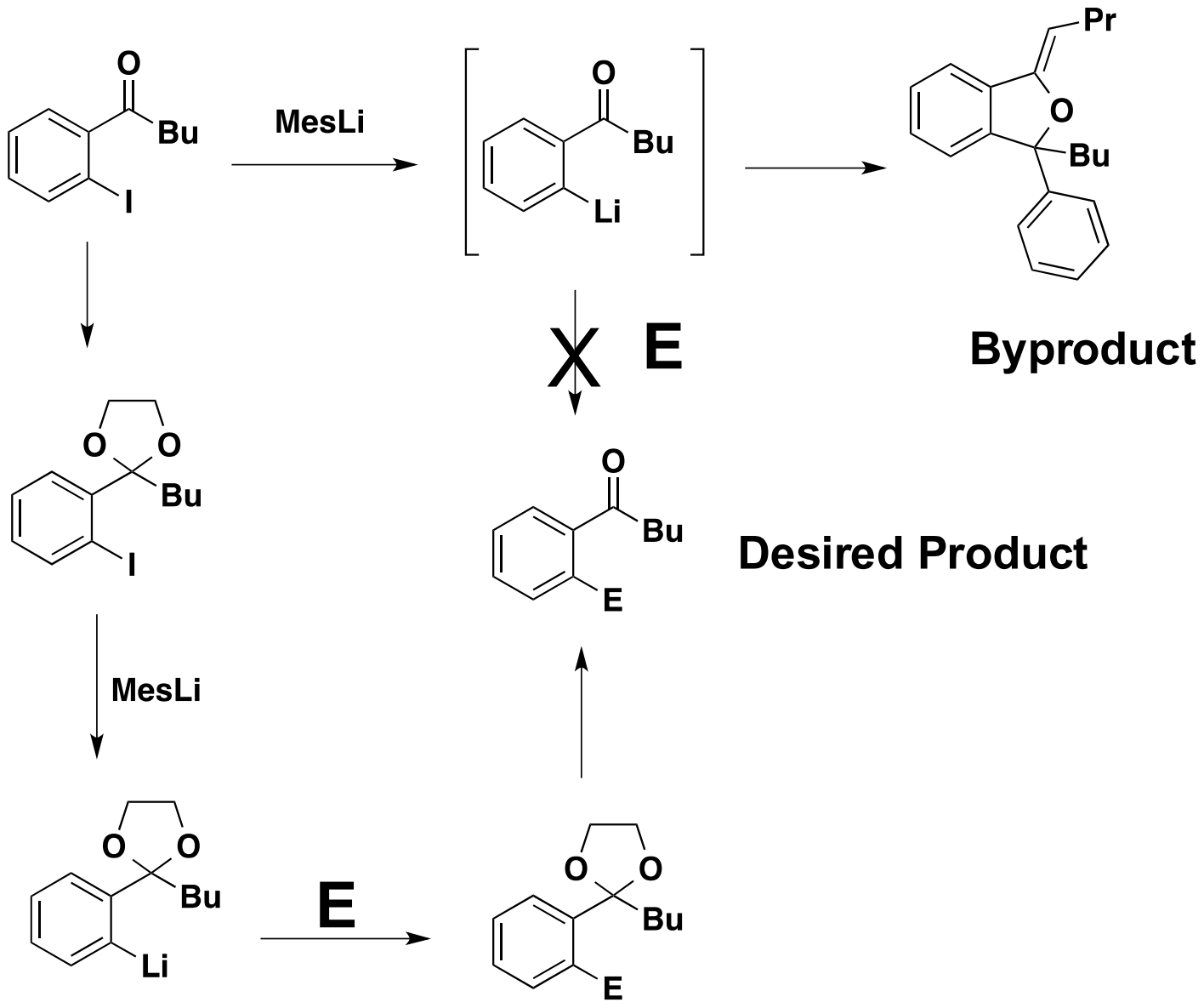
25 nl @ 67% = 5.3g/h

10 ml ($1:4x10^5$)
5.3g/h = 2.1 ton/h

Throughput: Vol x time

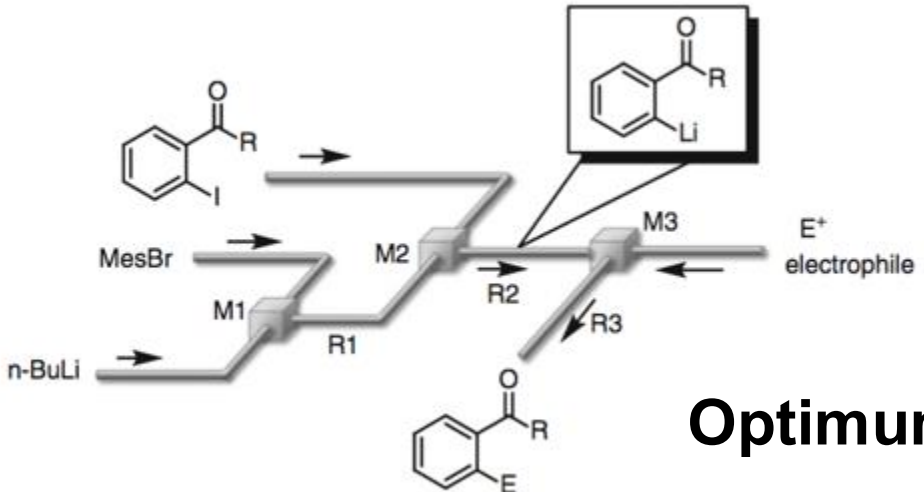
Kim and Yoshida et al. Science, 2016, 352,6286, 691

Time Resolved Synthesis

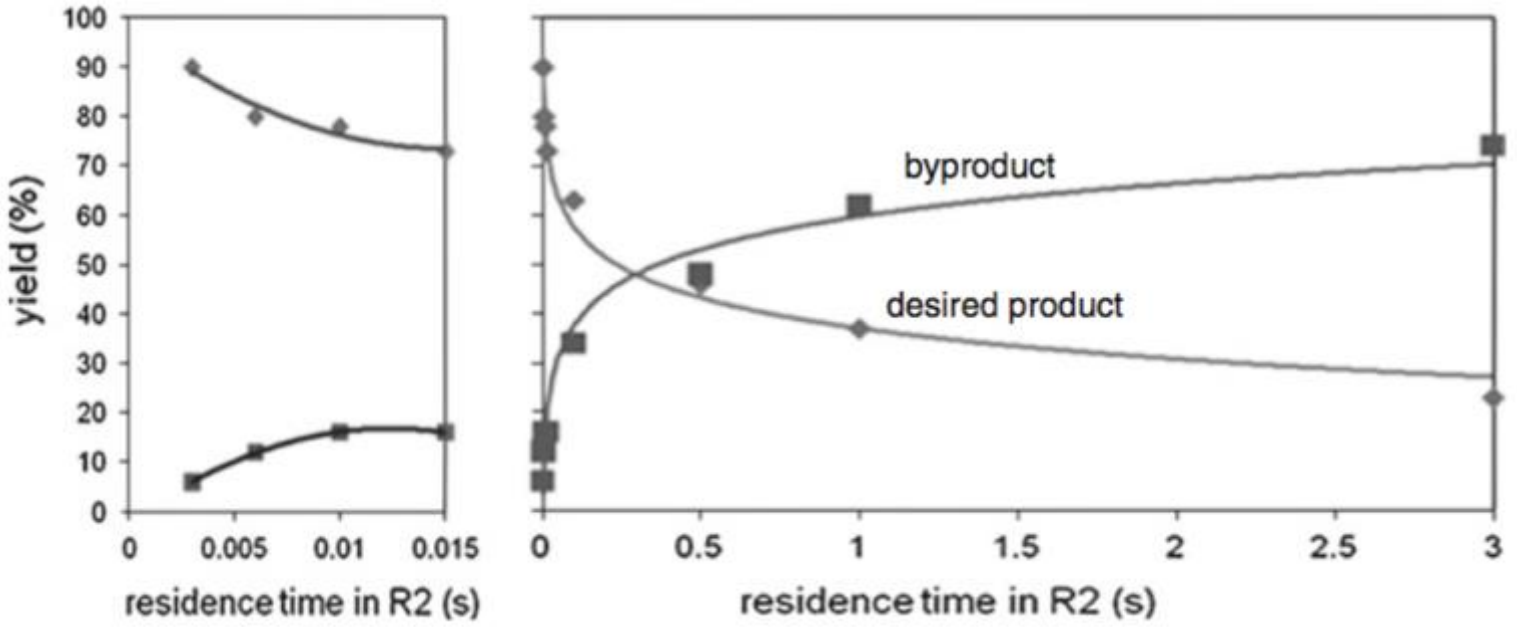


"Basics of Flow Microreactor Synthesis", J. Yoshida, Springer Briefs in Molecular Science, 2015

Time Resolved Synthesis

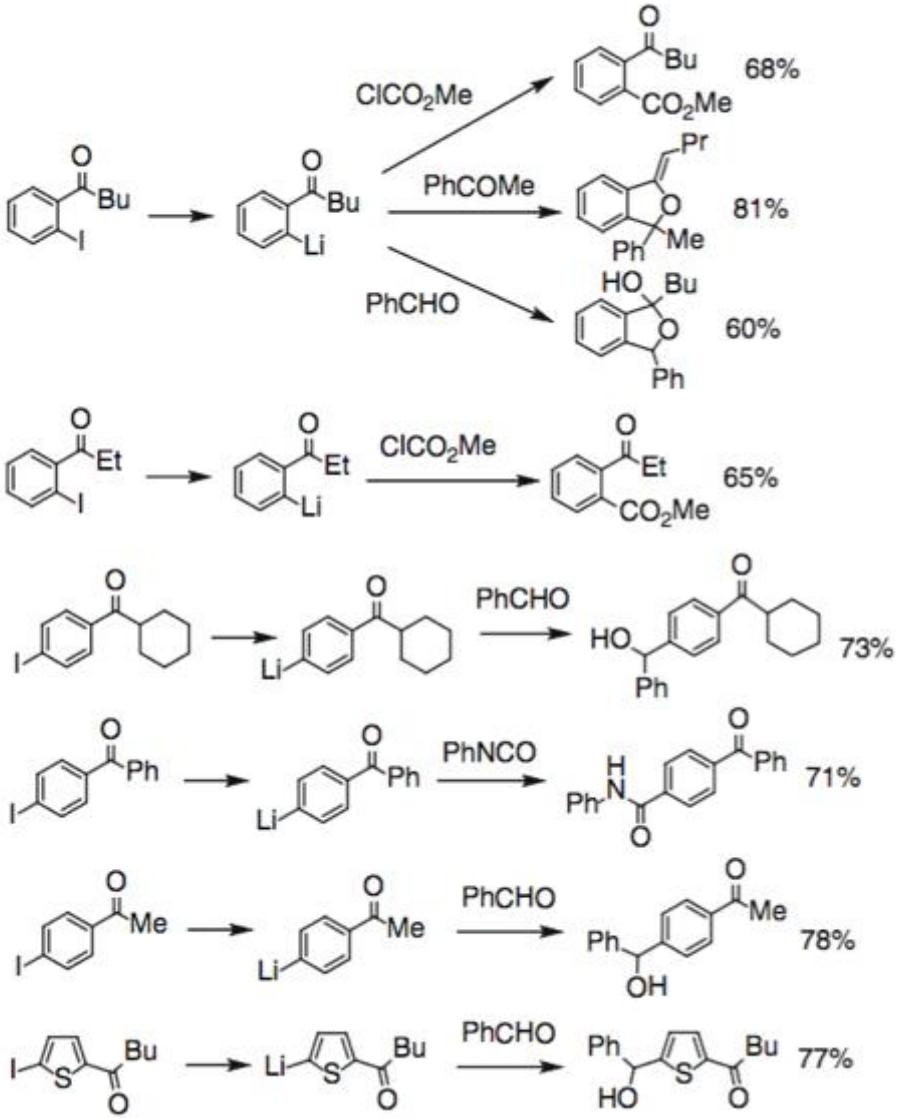


Optimum Resident Time of 3ms



"Basics of Flow Microreactor Synthesis", J. Yoshida, Springer Briefs in Molecular Science, 2015

Time Resolved Synthesis



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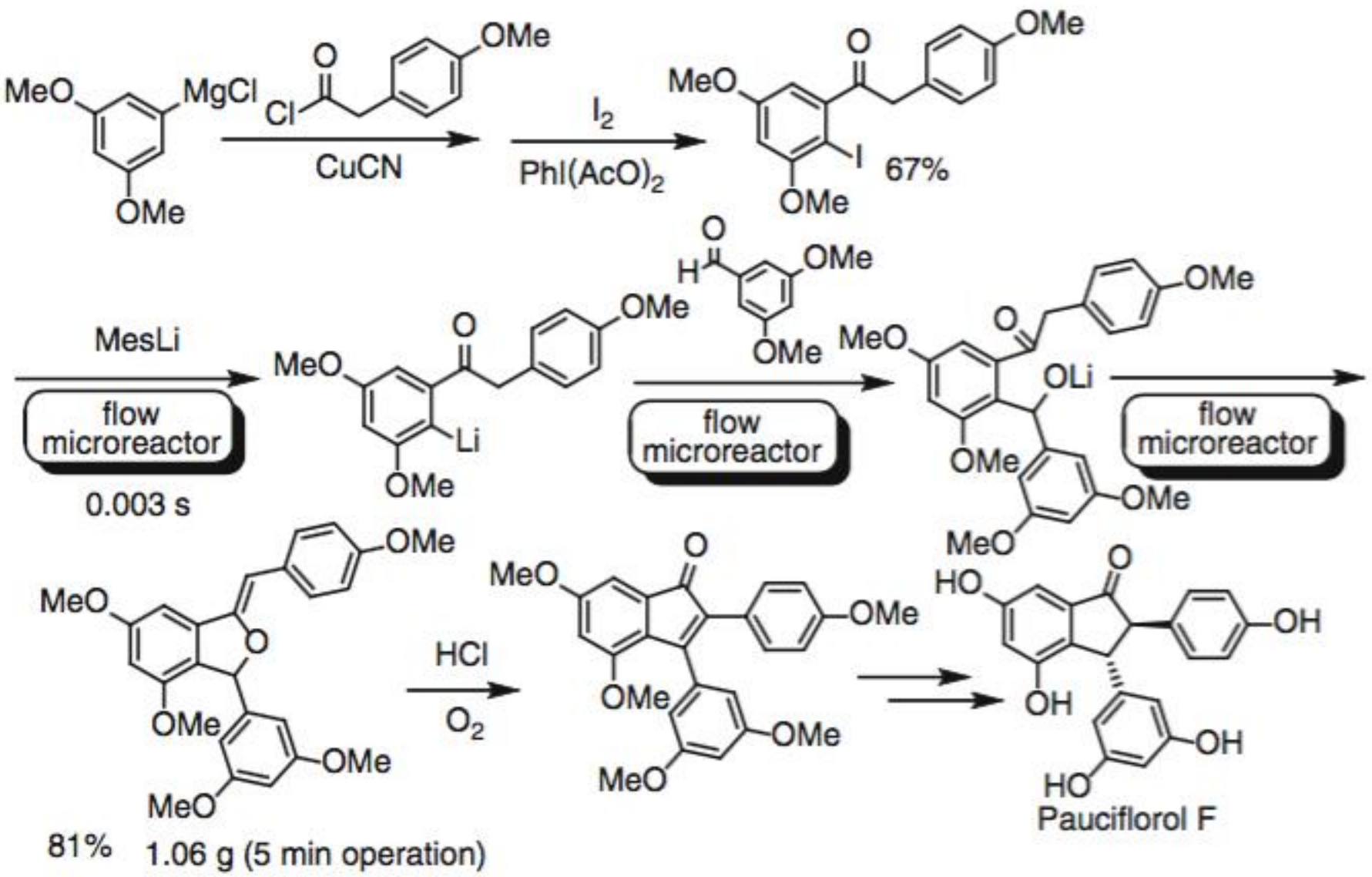
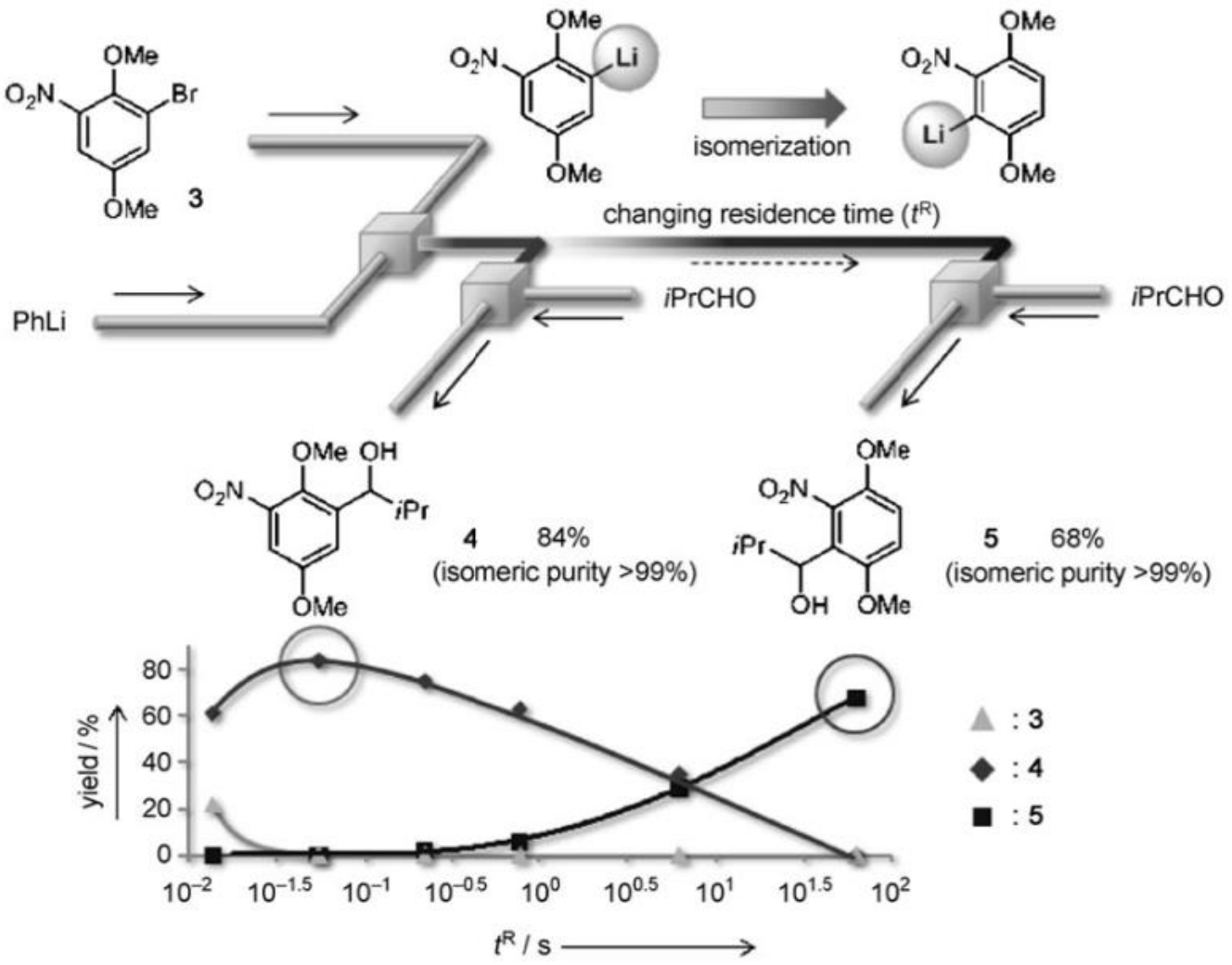


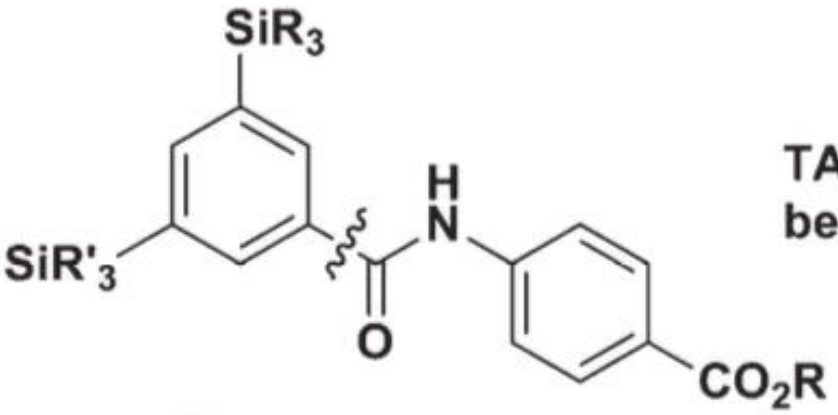
"Basics of Flow Microreactor Synthesis", J. Yoshida, Springer Briefs in Molecular Science, 2015

Kinetic vs Thermodynamic Control

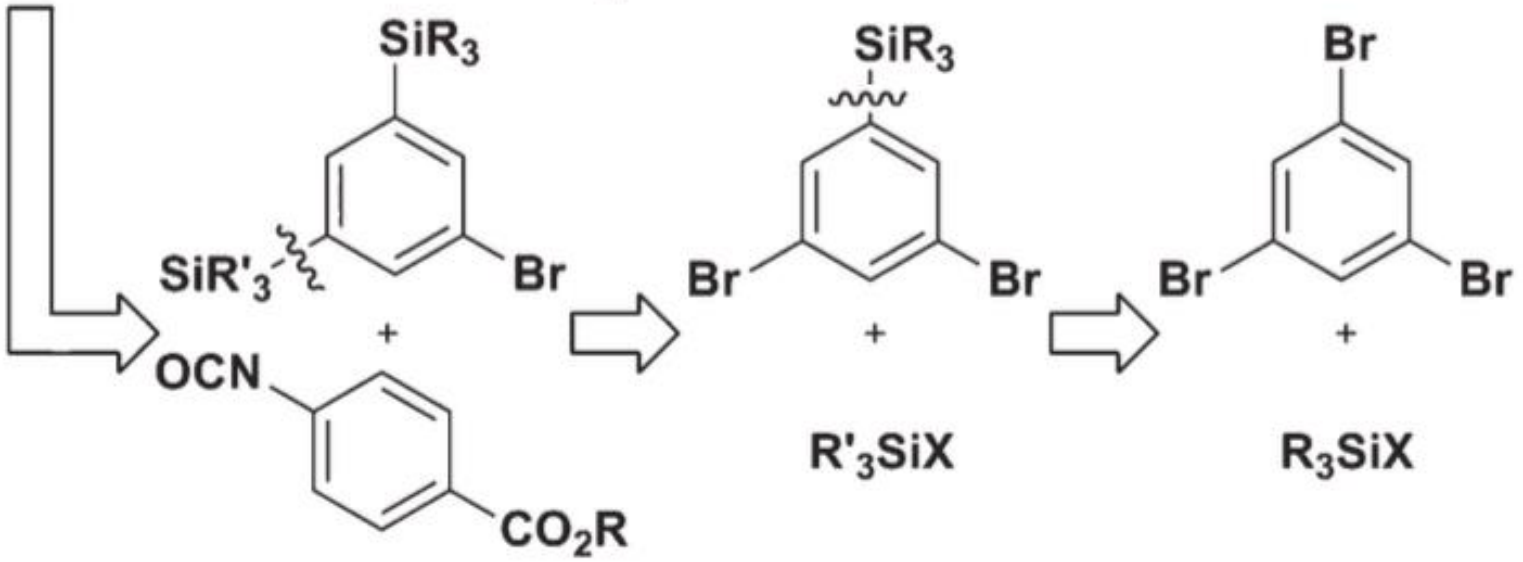


Angew. Chem. Int. Ed. 2009, 48, 8063 –8065

Fast Library Generation

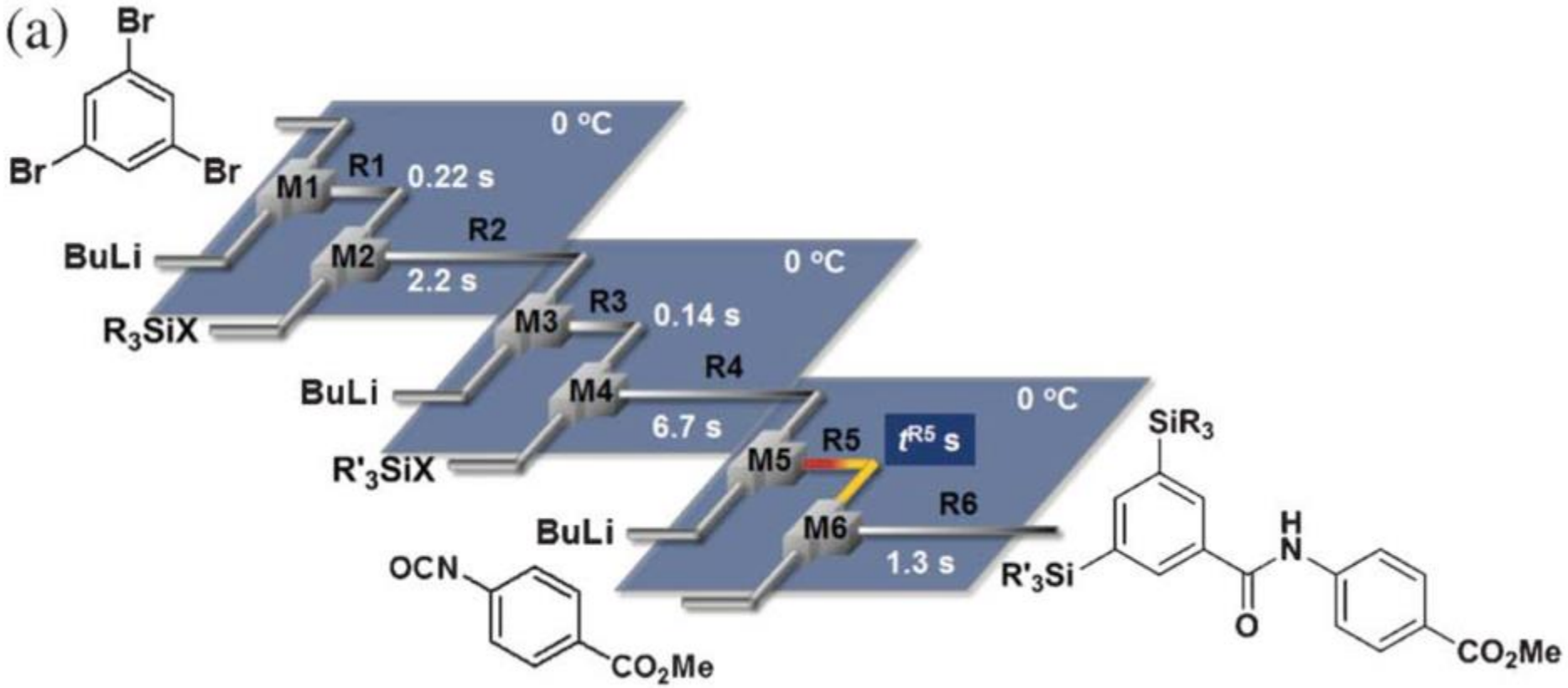


TAC-101(4-[3,5-bis(trimethylsilyl)benzamido] benzoic acid) analogues



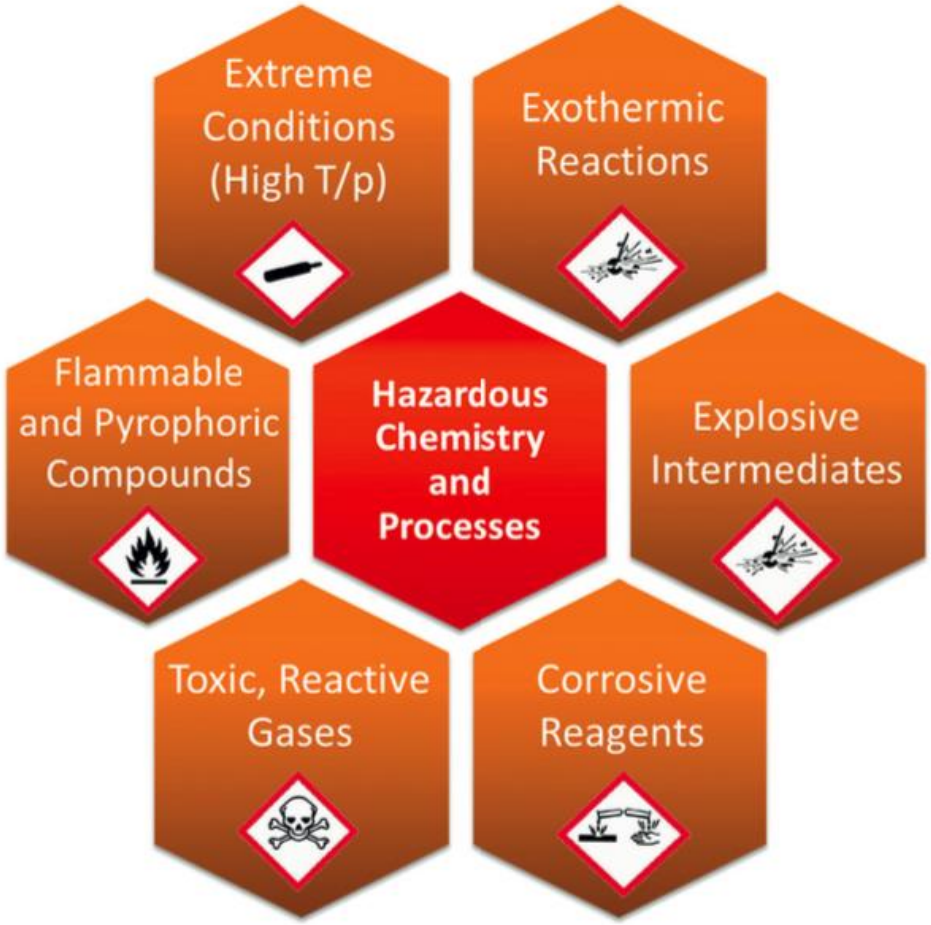
RSC Adv., 2011, 1, 758–760

Fast Library Generation



RSC Adv., 2011, 1, 758–760

Hazardous Chemistry

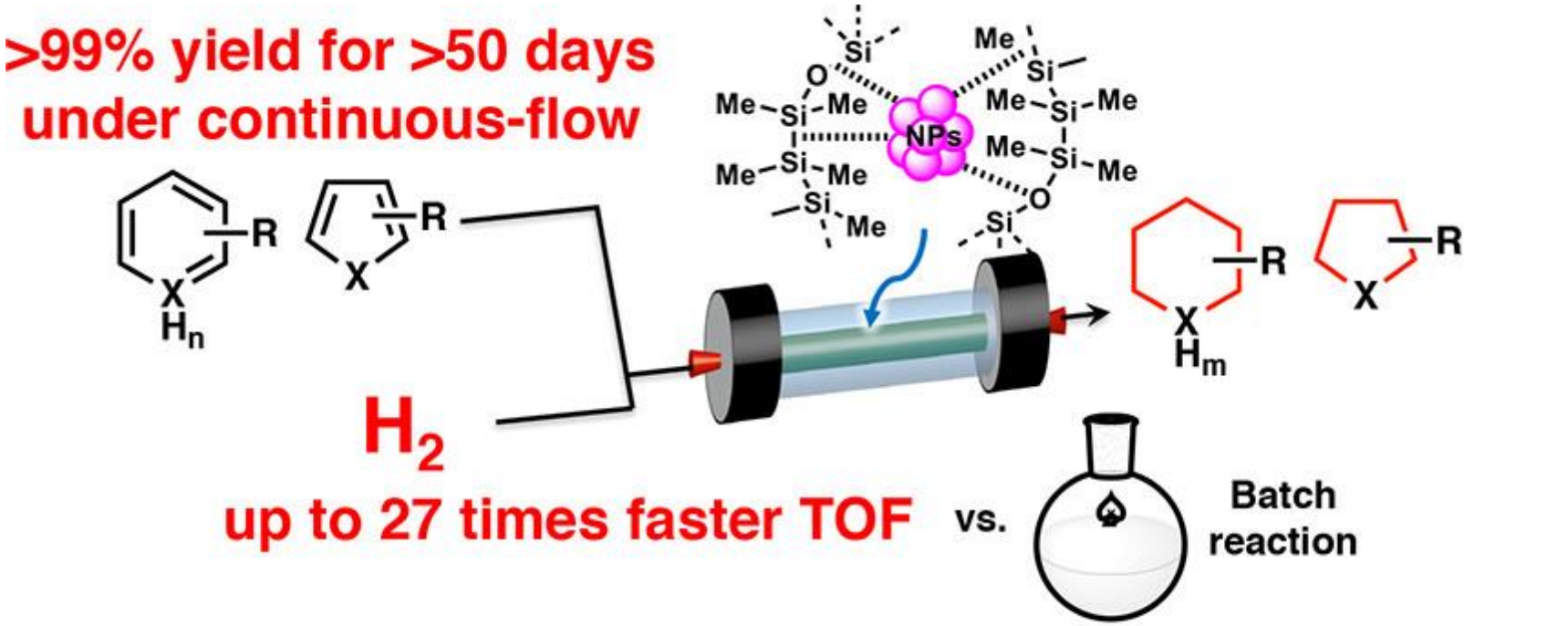


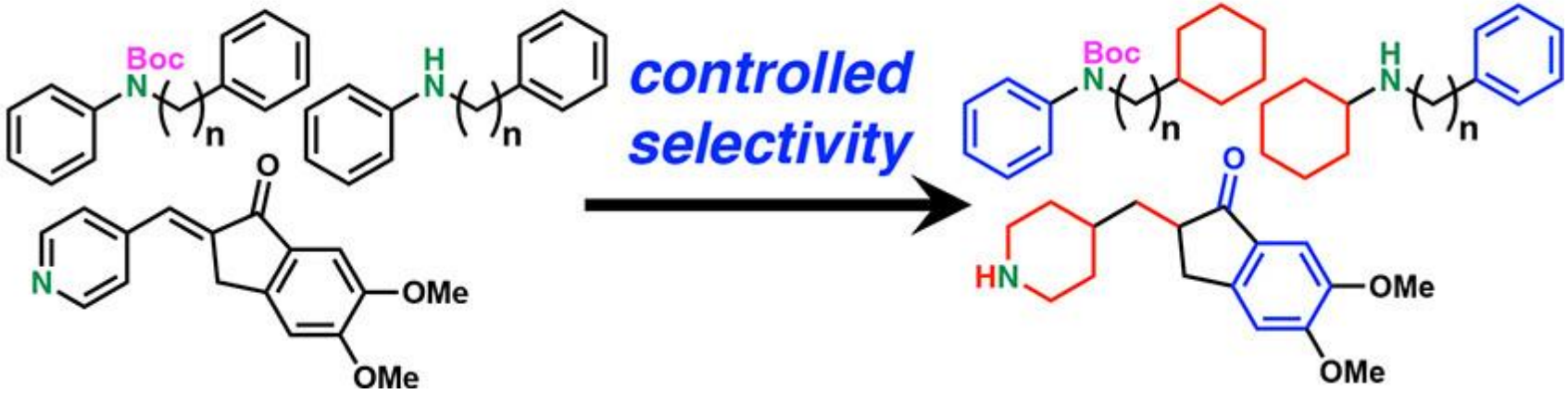
- Diazomethane
- Hydrazoic Acid
- Isocyanides
- Phosgene
- Fluorination
- Chlorination
- Peracids

Chemical Generator: Make and use in Flow

O. Kappe and coworkers, Angew. Chem. Int. Ed. 2015, 54, 6688 – 6728

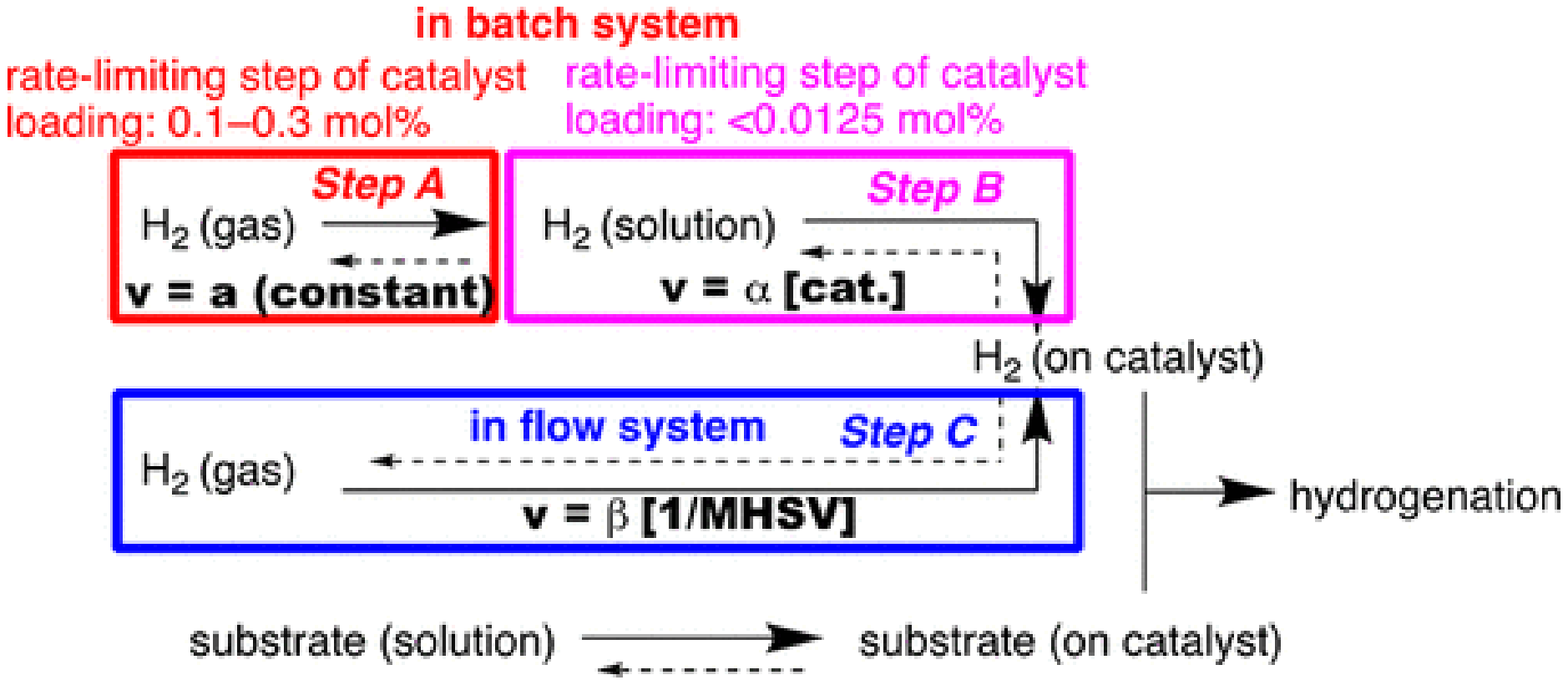
Hydrogenation





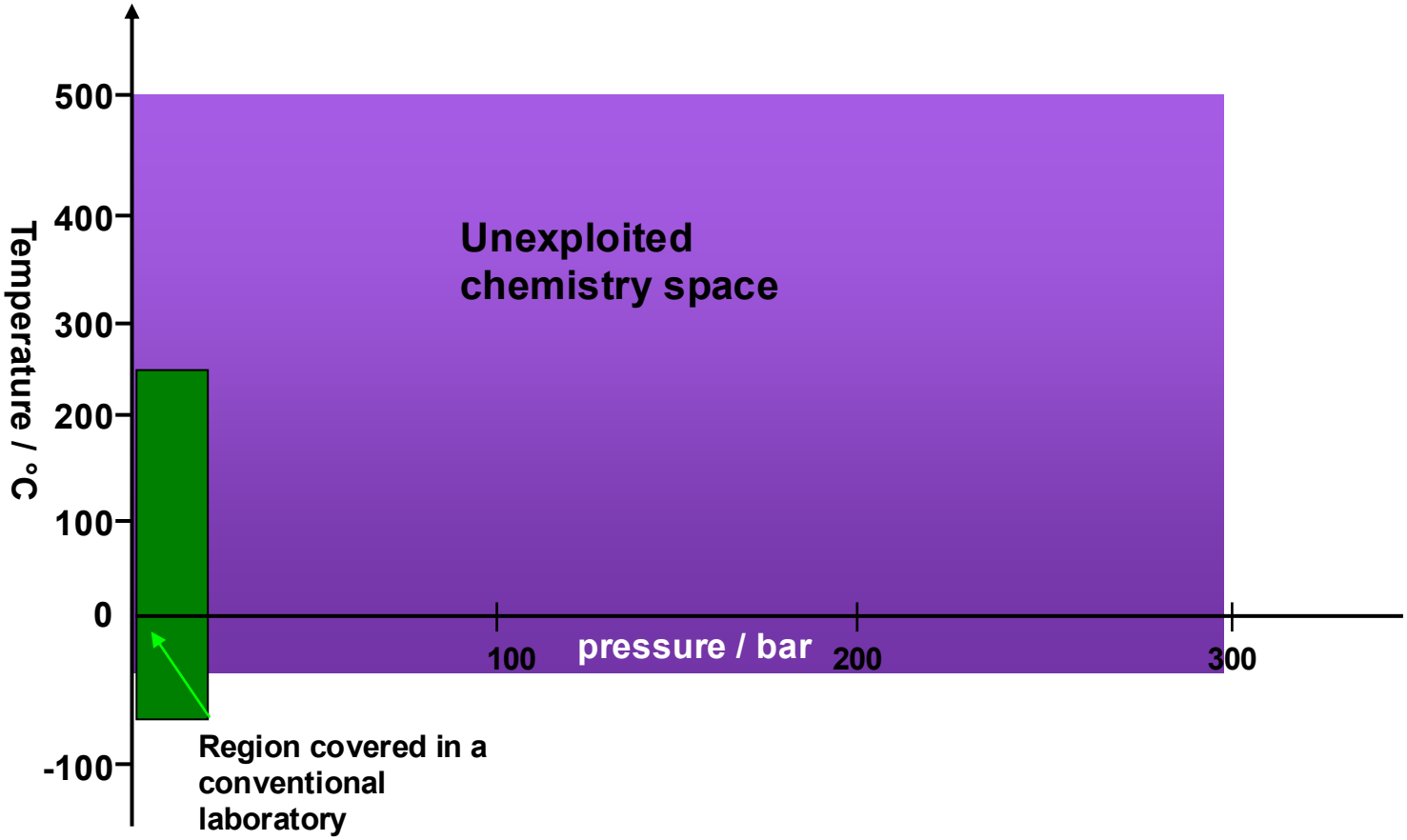
J. Am. Chem. Soc. 2018, 140, 36, 11325–11334

Hydrogenation

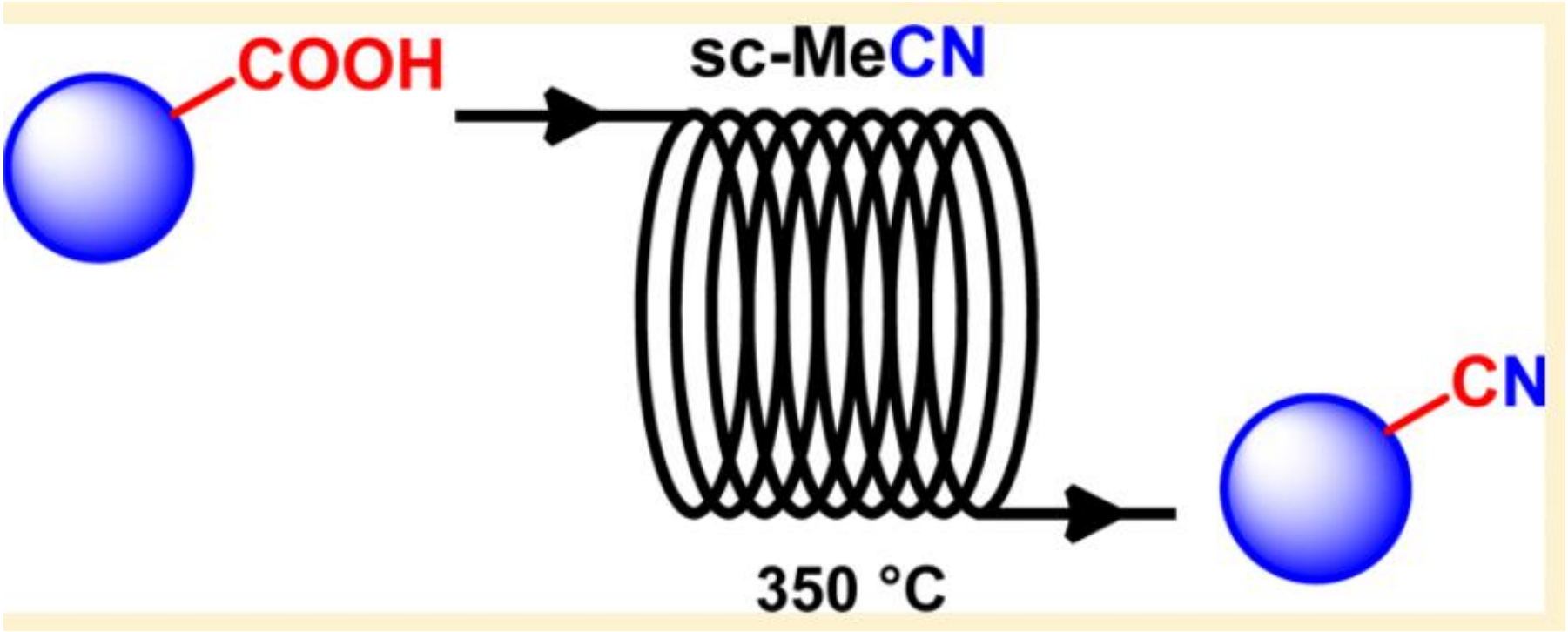


J. Am. Chem. Soc. 2018, 140, 36, 11325–11334

What is the issue with chemical space?

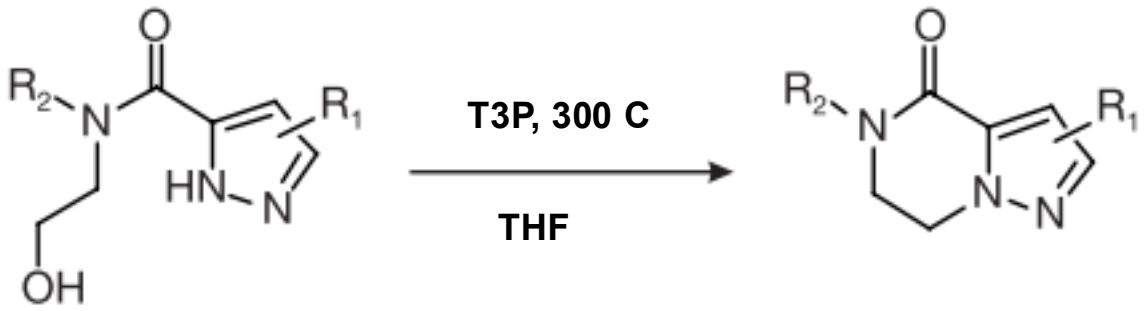


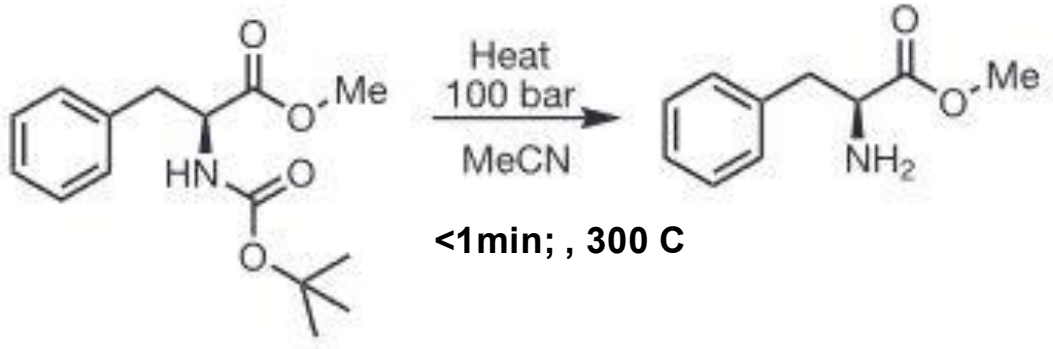
Acetonitrile as Nitrile Source



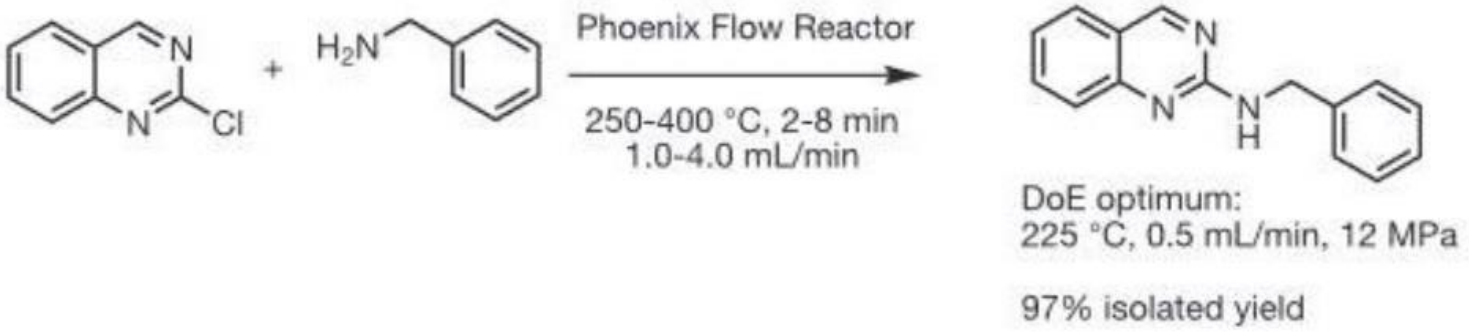
Kappe and Coworkers, J. Org. Chem. 2013, 78, 10567−10571

Mitsunobu Without DEAD





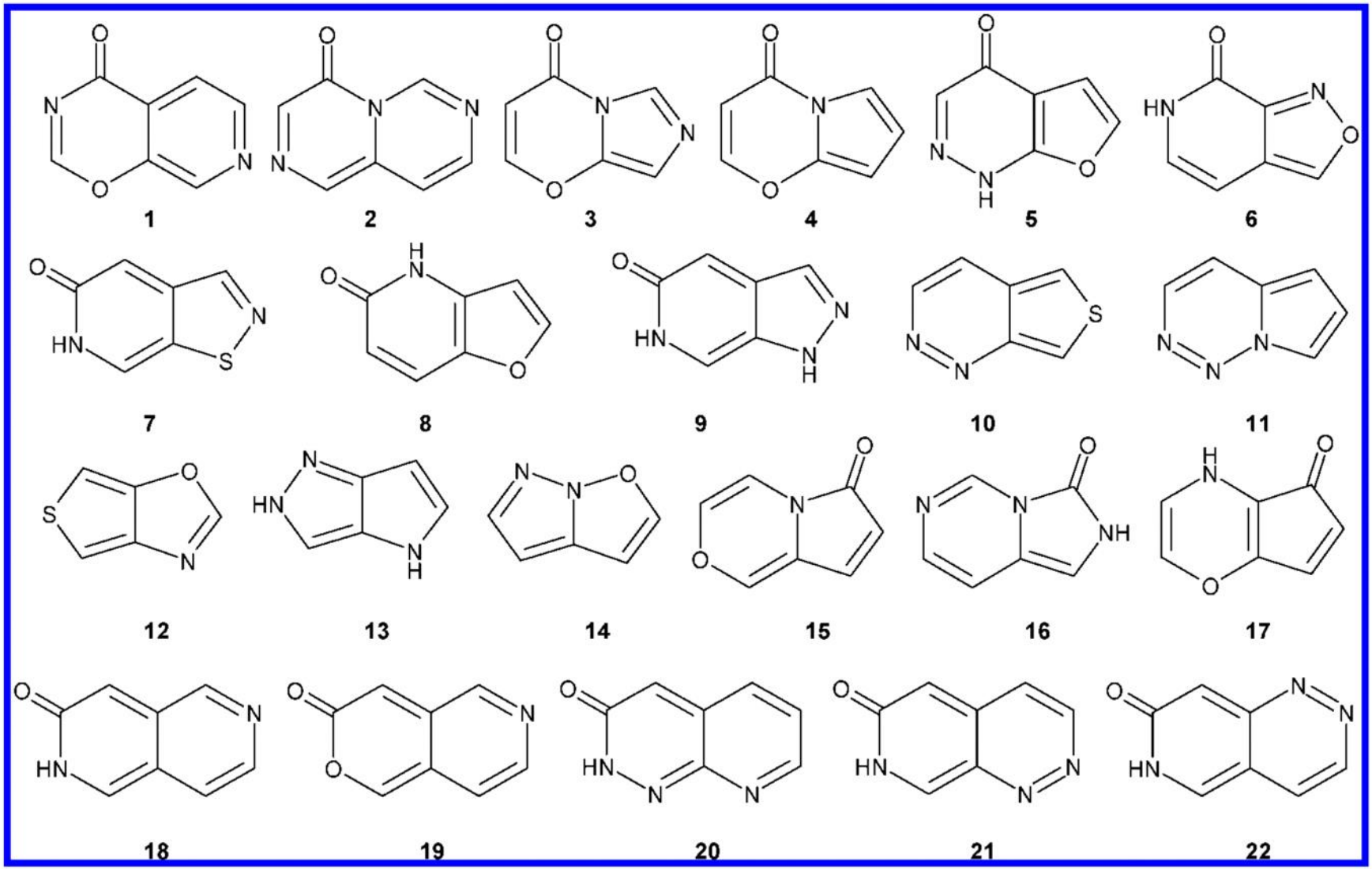
<1min; , 300 C



DoE optimum:
225 °C, 0.5 mL/min, 12 MPa

97% isolated yield

NCE: Heterocycles



J. Med. Chem. 2009, *52*, 2952–2963

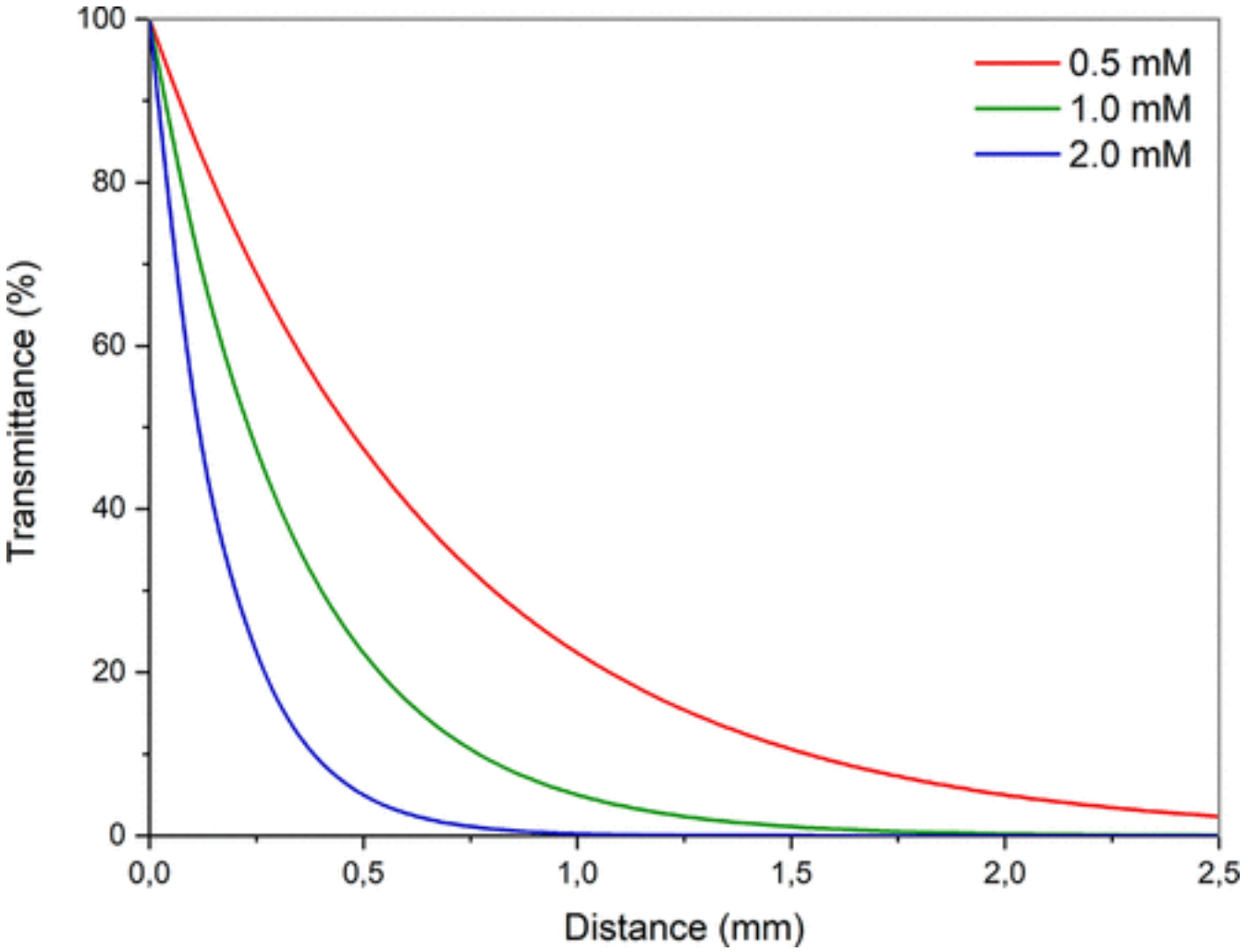
We believe there are a lot of "forbidden" and "forgotten" chemistries, working with highly efficient but highly energetic small molecules, that would allow us to make APIs much more efficiently than is currently possible working in batch

Oliver Kappe *University of Graz, Austria*

Flow Process Benefits

Photochemistry…

Flow Photochemistry

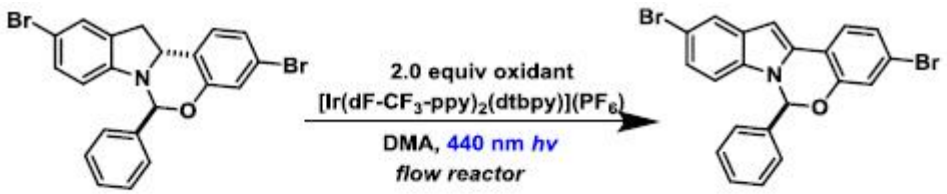


Chem. Rev. 2022, 122, 2, 2752–2906

Industrial Flow Reactors:
Merck - Photochemistry

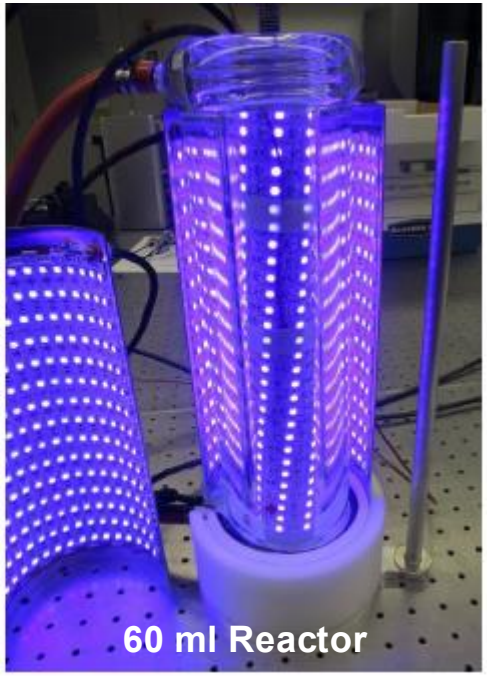
Over the years Merck have succeeded with anion formations, diazomethane reactions, ketamine additions and aerobic oxidations, more recently photochemistry has featured;

Photoredox-catalysed Indoline Dehydrogenation:



[M]	Loading	Oxidant	τ (min)	Temp °C[a]	Yield[b]	% ee[c]
0.2	0.5 mol %	tBPB	60	25	84	96.7
0.2	0.2 mol %	tBPA	120	25	88	95.0
0.4	0.2 mol %	tBPA	90	0	89	99.1
0.4	0.2 mol %	tBPB	45	0	90	99.5
0.4	0.2 mol %	tBPB	45	-10	86	99.8
0.5	0.1 mol %	tBPB	60	-10	94	99.7
0.5	0.1 mol %	tBPB	30	0	93	99.9

[a] Reactor jacket temperature, [b] Assay yield determined by HPLC, [c] Determined by chiral HPLC



- Flow conditions drastically increased yield & shortened the reaction time
- Catalyst loadings ~ 0.1 mol% → 100 g demonstration (5 h)

Process Intensification

Increase Rate of a Reaction

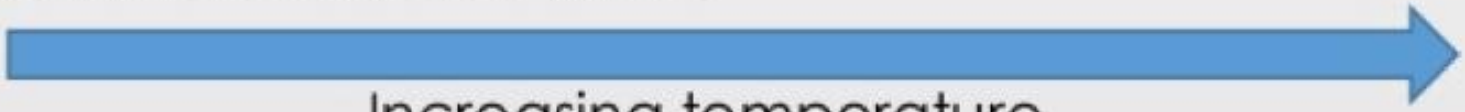
Improving Heat-Transfer:

- **More molecules can react per unit time**
  - **Increase Concentration**
  - **Increase Temperature**

Rate of a Reaction

$$k = A * e^{-E_a/RT}$$

Rule of Thumb: for every 10°C increase in temperature the rate of reaction becomes twice



Increasing temperature

80 °C	90 °C	100 °C	110 °C	120 °C	130 °C	140 °C	150 °C	160 °C
8 hr	4 h	2 hr	1 hr	30 min	15 min	8 min	4 min	2 min

Decreasing reaction time

Rate of a Reaction

Clausius-Clapeyron Equation

$$\ln \frac{P_1}{P_2} = \frac{\Delta H_{vap}}{R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right)$$

Rate of a Reaction

	TEMPERATURE (°C)															
	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250
1 Butanol	0.5	0.8	1.1	1.5	2.1	2.8	3.7	4.7	6.1	7.7	9.5	11.7	14.2	17.1	20.4	24.1
1 Propanol	1.2	1.6	2.3	3.2	4.1	5.4	7.0	9.0	11.3	14.0	17.2	20.9	25.2	30.0	35.5	41.7
Acetic Acid	0.6	0.8	1.1	1.4	1.9	2.5	3.2	4.1	5.1	6.3	7.8	9.5	11.4	13.7	16.3	19.2
Acetone	3.7	4.8	6.1	7.6	9.5	11.6	14.1	16.9	20.1	23.8	27.9	32.5	37.6	43.2	49.4	56.2
Acetonitrile	2.0	2.7	3.7	4.8	6.3	8.1	10.3	13.0	16.3	20.2	24.8	30.2	36.6	44.0	52.5	62.3
Benzene	1.8	2.5	3.1	3.9	4.9	5.9	7.2	8.6	10.3	12.2	14.4	16.9	19.6	22.7	26.1	29.9
Carbon tetrachloride	1.9	2.5	3.2	4.0	5.0	6.1	7.4	8.9	10.5	12.4	14.6	16.9	19.6	22.4	25.6	29.0
Chloroform	3.1	4.0	5.0	6.3	7.8	9.6	11.7	14.1	16.8	19.9	23.4	27.3	31.7	36.6	42.0	47.9
Cyclohexane	1.7	2.2	2.9	3.6	4.5	5.5	6.7	8.1	9.7	11.5	13.5	15.7	18.3	21.0	24.1	27.5
DCM	5.9	7.5	9.4	11.7	14.3	17.4	20.9	24.9	29.4	34.5	40.2	46.5	53.5	61.2	69.6	78.7
Di ethyl ether	6.1	7.6	9.4	11.5	14.0	16.8	20.0	23.6	27.7	32.2	37.3	42.9	49.0	55.7	63.1	71.0
Diglyme	0.1	0.2	0.3	0.4	0.6	0.8	1.0	1.3	1.7	2.2	2.8	3.6	4.4	5.5	6.7	8.1
Dioxane	1.0	1.3	1.7	2.3	2.9	3.7	4.7	5.9	7.2	8.8	10.6	12.7	15.2	17.9	21.0	24.4
DME	1.2	1.6	2.0	2.5	3.0	3.7	4.5	5.4	6.4	7.5	8.8	10.2	11.8	13.5	15.4	17.5
DMF	0.2	0.3	0.4	0.6	0.8	1.0	1.3	1.7	2.1	2.6	3.2	3.9	4.7	5.6	6.6	7.8
DMSO	0.1	0.1	0.1	0.2	0.2	0.3	0.4	0.7	0.9	1.2	1.5	2.0	2.5	3.2	4.0	5.0
Ethanol	2.1	2.9	4.0	5.3	7.0	9.1	11.6	14.7	18.3	22.6	27.6	33.4	40.1	47.7	56.3	65.9
Ether	6.1	7.6	9.4	11.5	14.0	16.8	20.0	23.6	27.7	32.2	37.3	42.9	49.0	55.7	63.1	71.0
Ethyl Acetate	2.0	2.7	3.5	4.4	5.6	6.9	8.5	10.4	12.5	14.9	17.6	20.7	24.1	27.9	32.1	36.8
Formic Acid	1.0	1.3	1.7	2.2	2.9	3.6	4.5	5.6	6.9	8.3	10.0	11.9	14.1	16.6	19.4	22.5
Heptane	1.2	1.7	2.2	2.9	3.8	4.8	6.1	7.6	9.5	11.6	14.1	16.9	20.2	24.0	28.2	33.0
Hexane	2.5	3.1	4.0	5.0	6.1	7.4	9.0	10.7	12.7	14.9	17.4	20.2	23.2	26.5	30.1	34.1
IPA	2.0	2.8	3.8	5.1	6.7	8.7	11.0	13.9	17.2	21.2	25.7	30.9	36.8	43.5	51.0	59.4
MEK	1.9	2.4	3.1	4.0	4.9	6.1	7.5	9.0	10.8	12.8	15.1	17.6	20.4	23.4	26.8	30.5
MeOH	3.3	4.5	6.0	7.9	10.2	13.0	16.5	20.6	25.4	31.1	37.7	45.3	54.0	63.9	75.1	87.7
NMP	0.0	0.0	0.1	0.1	0.1	0.2	0.3	0.4	0.5	0.7	1.0	1.2	1.6	2.0	2.5	3.1
Pentane	5.9	7.3	9.0	10.9	13.0	15.5	18.3	21.4	24.8	28.5	32.7	37.2	42.0	47.3	52.9	59.0
p-Xylene	0.3	0.4	0.6	0.8	1.1	1.4	1.7	2.2	2.7	3.4	4.1	5.0	6.0	7.1	8.4	9.9
t Butyl Alcohol	1.9	2.7	3.6	4.8	6.3	8.1	10.2	12.7	15.6	19.0	22.9	27.3	32.3	37.8	44.0	50.8
THF	2.7	3.5	4.4	5.5	6.9	8.4	10.1	12.2	14.4	17.0	19.9	23.1	26.6	30.5	34.7	39.4
Toluene	0.7	1.0	1.3	1.7	2.2	2.7	3.4	4.2	5.1	6.2	7.5	8.9	10.5	12.3	14.4	16.7
Water	1.0	1.2	1.8	2.6	3.7	5.0	6.6	8.5	10.8	13.5	16.5	20.0	23.8	28.1	32.8	37.9

Rate of a Reaction

$$\ln \frac{P_1}{P_2} = \frac{\Delta H_{vap}}{R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right)$$

Is there a limit to how high Temp one can attain

Rate of a Reaction

$$\ln \frac{P_1}{P_2} = \frac{\Delta H_{vap}}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right)$$

Is there a limit to how high Temp one can attain

Yes, up to Supercritical Temperature of a Solvent

Rate of a Reaction

$$k = A\, e^{-Ea/RT}$$

What else can be done to increase Rate of Reaction

Rate of a Reaction

$$k = A\, e^{-Ea/RT}$$

Improving Mixing:

- **More molecules can react per unit time**
  - **Increase A**

FUMI Reactor

1. Line Contacting

Formation of thin flowing films of reagents

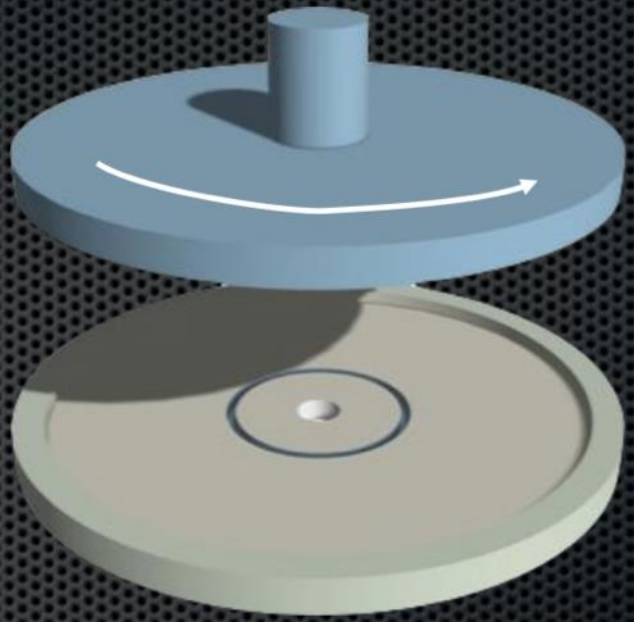
2. FUMI

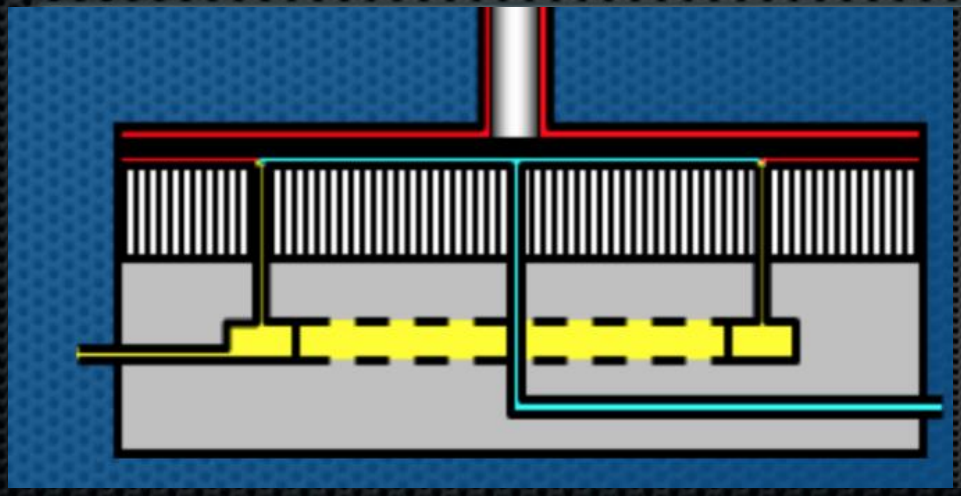
Forced Uniform Molecular Interdiffusion

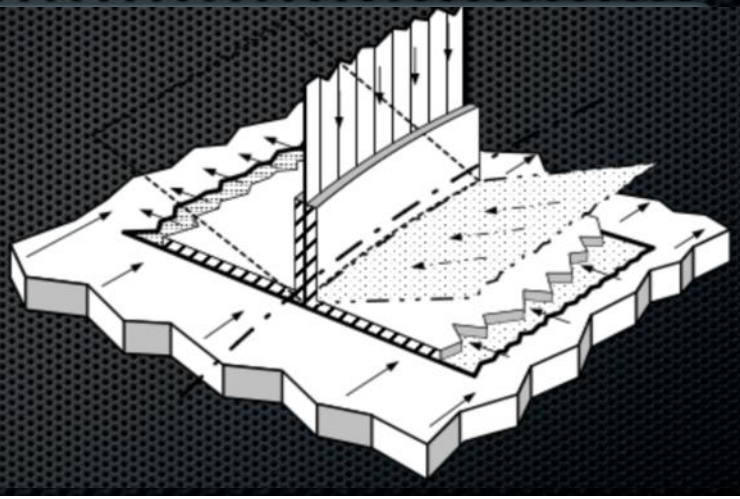
The Synthetron incorporates two innovations

2. FUMI

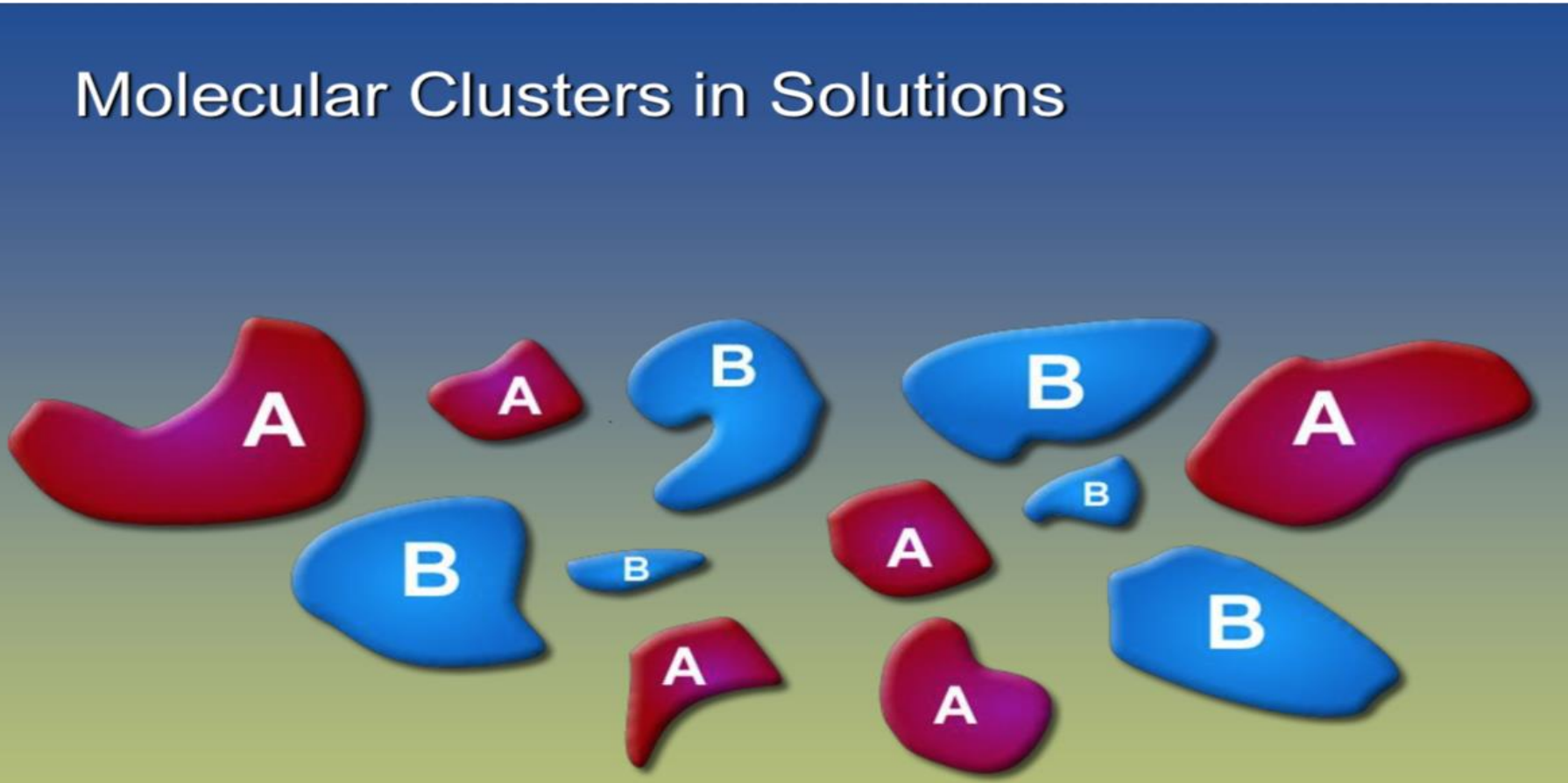
Forced Uniform
Molecular
Interdiffusion





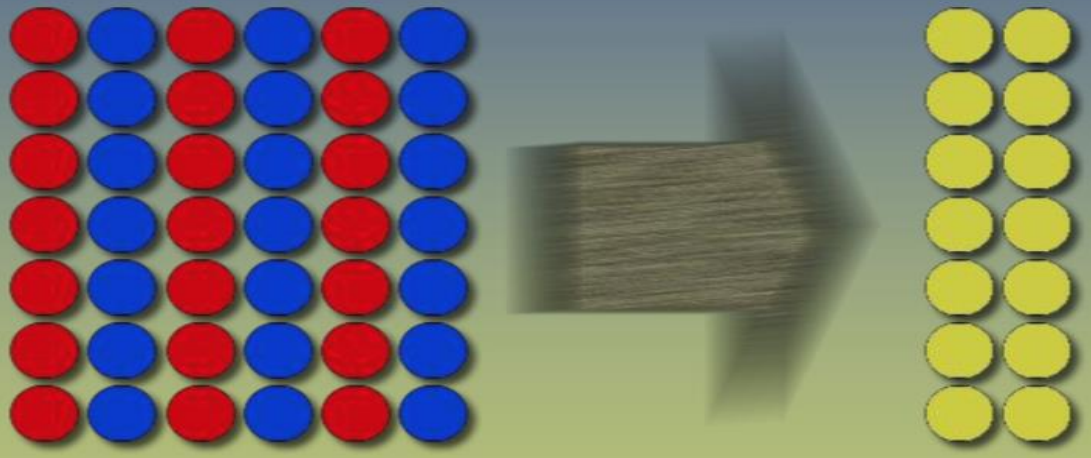


FUMI Reactor

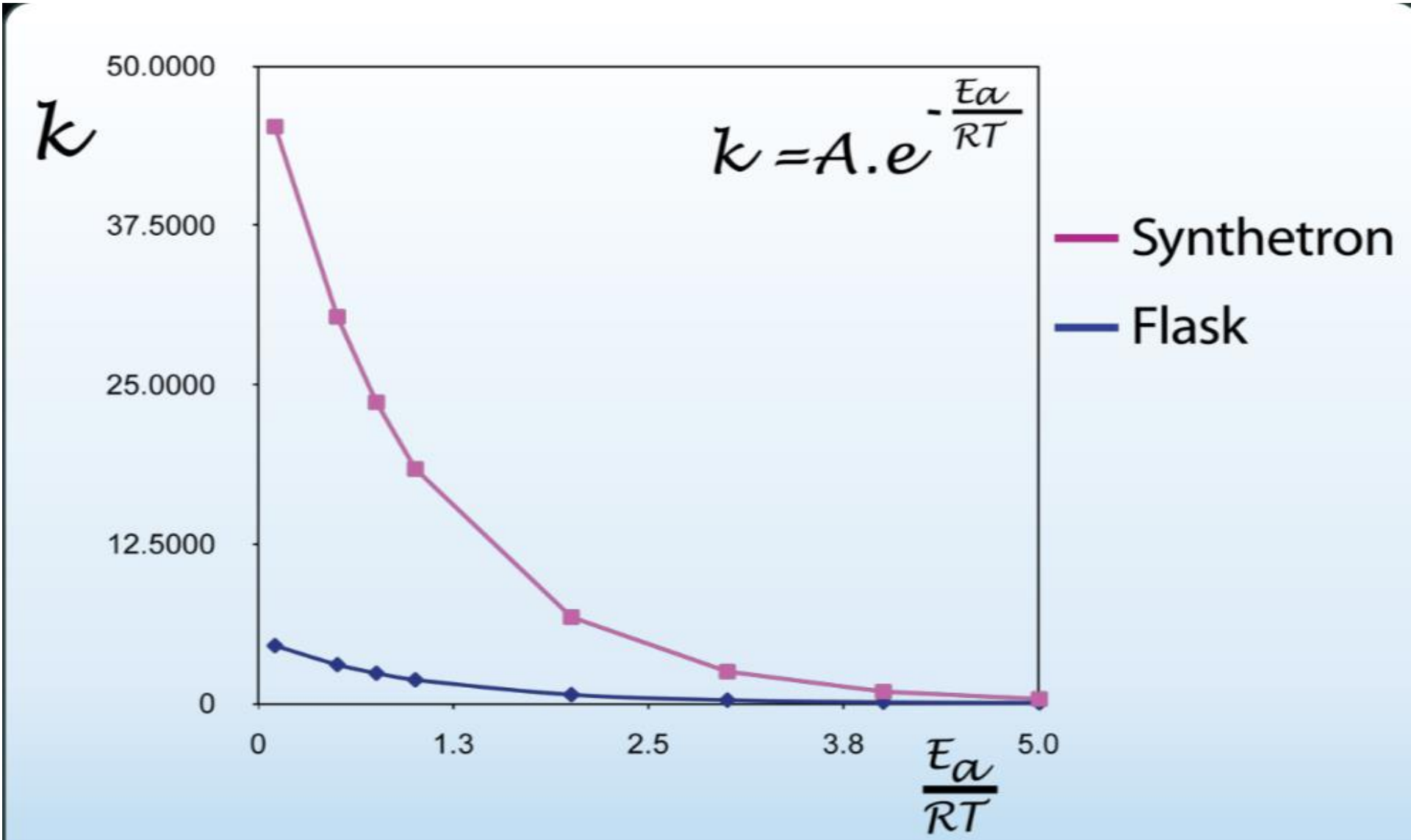


FUMI Reactor

Ideal flow reaction



FUMI Reactor



FUMI Reactor

- **Enhanced mixing leading to large increase in rate of reaction**
- **Very high surface area to volume ratio (up to 180k m^2/m^3)**
- **High throughput (up to 400 ml/min)**

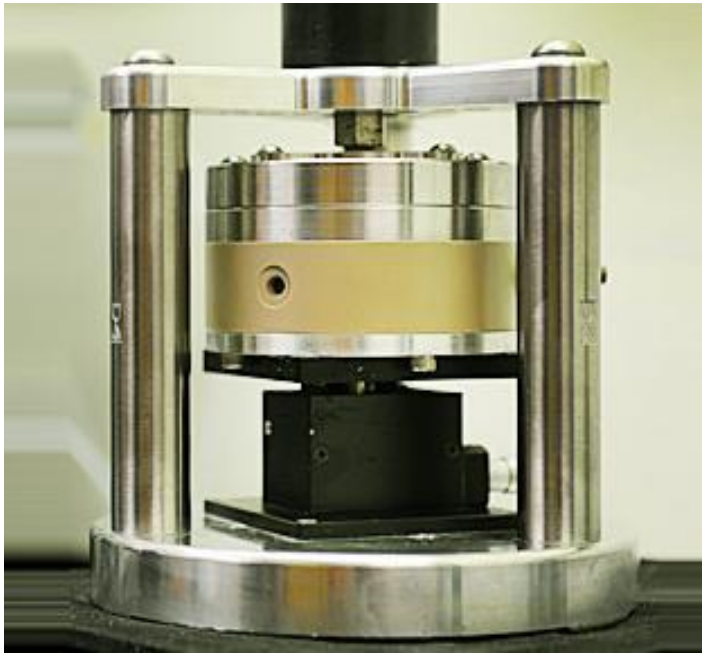
Spinning Disc Technology

No More Limits in Chemical Industry

Continuous Flow Chemistry Lab

Spinning Disc Technology

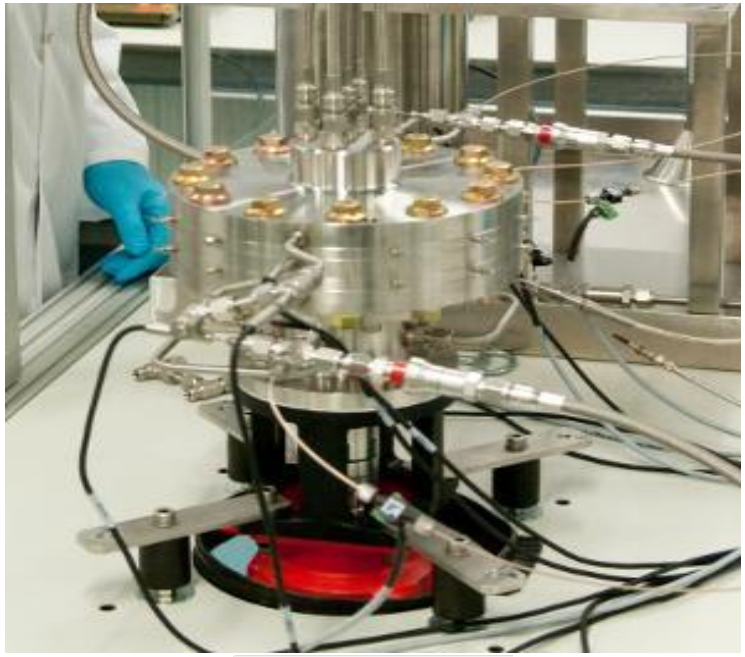
FUMI Spin Disk



KinetiChem, Inc.

Reactions : **0.03 sec**
Volume : **0.2 ml**
Product : **2 - 3 µ**
Output : Kilos / hour

Spinning Disk Reactor

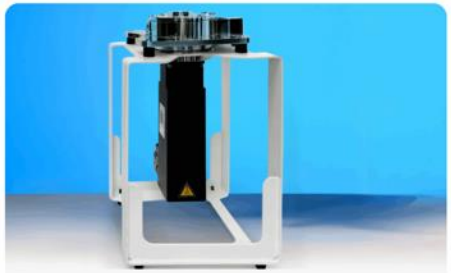


SPINID

SpinPro-300
Volume : 300 ml
Output : 10 T / day +

Continuous Flow Chemistry Lab

Spinning Disc Technology



SpinPro R1

Volume: 5 mL
Stages: 1
Disc speed: 6000 rpm
Max. pressure: 10 barg
Max. temperature: 140 °C
Material: Hastelloy

SpinPro R2

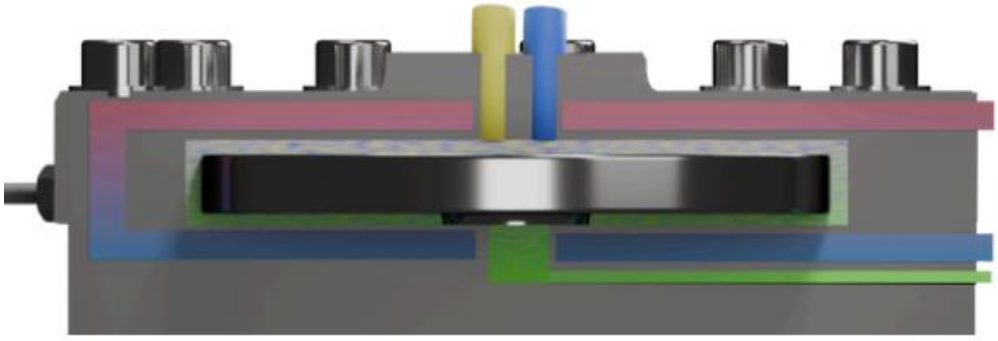
Volume: 15 mL
Stages: 3
Disc speed: 6000 rpm
Max. pressure: 10 barg
Max. temperature: 140 °C
Material: Hastelloy

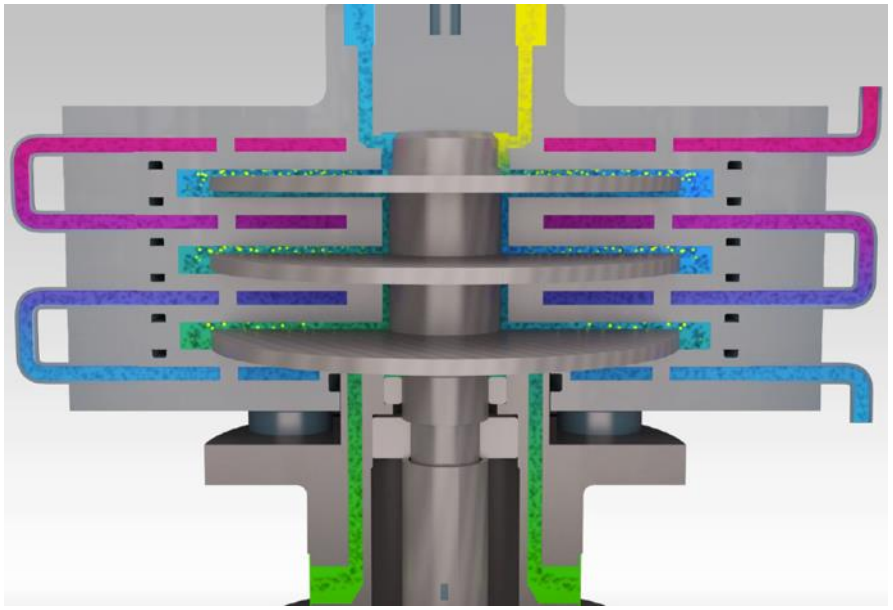
SpinPro R3

Volume: 135 mL / 230 mL
Stages: 3
Disc speed: 3000 rpm
Max. pressure: 10 barg
Max. temperature: 160 °C
Material: SS316, Hastelloy

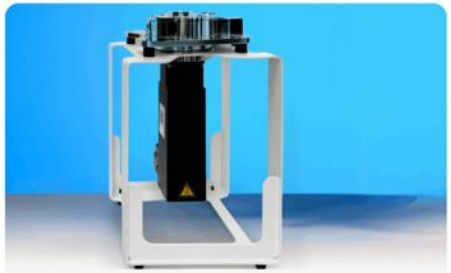
SpinPro R4

Volume: up to 2 L
Stages: 3
Disc speed: 1000 rpm
Max. pressure: 10 barg
Max. temperature: 160 °C
Material: SS316, Hastelloy





Spinning Disc Technology



SpinPro R1

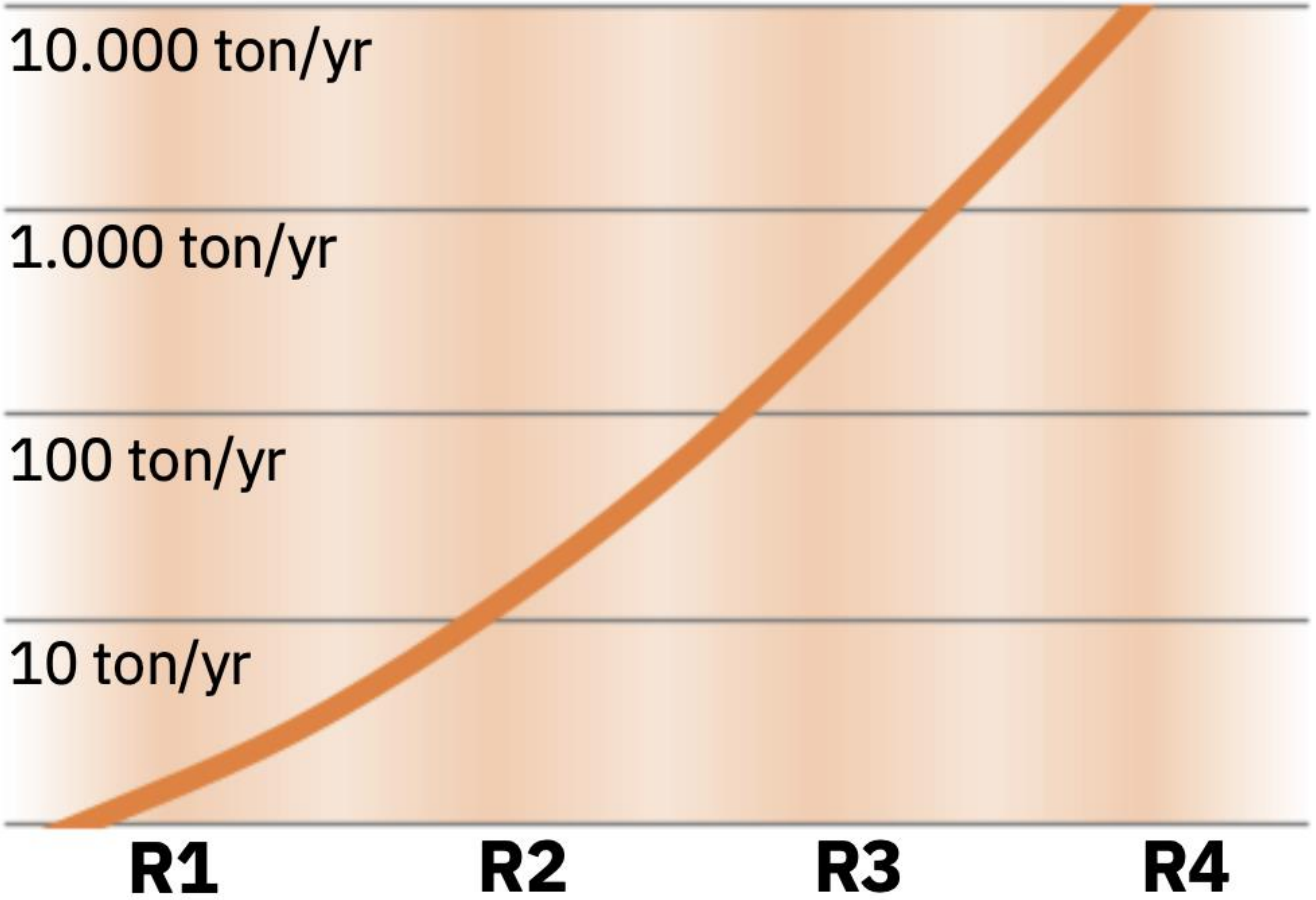
Volume: 5 mL
Stages: 1
Disc speed: 6000 rpm
Max. pressure: 10 ba
Max. temperature: 1
Material: Hastelloy

SpinPro R2

SpinPro R3

SpinPro R4

› 2 L
000 rpm
e: 10 barg
ature: 160 °C
16, Hastelloy

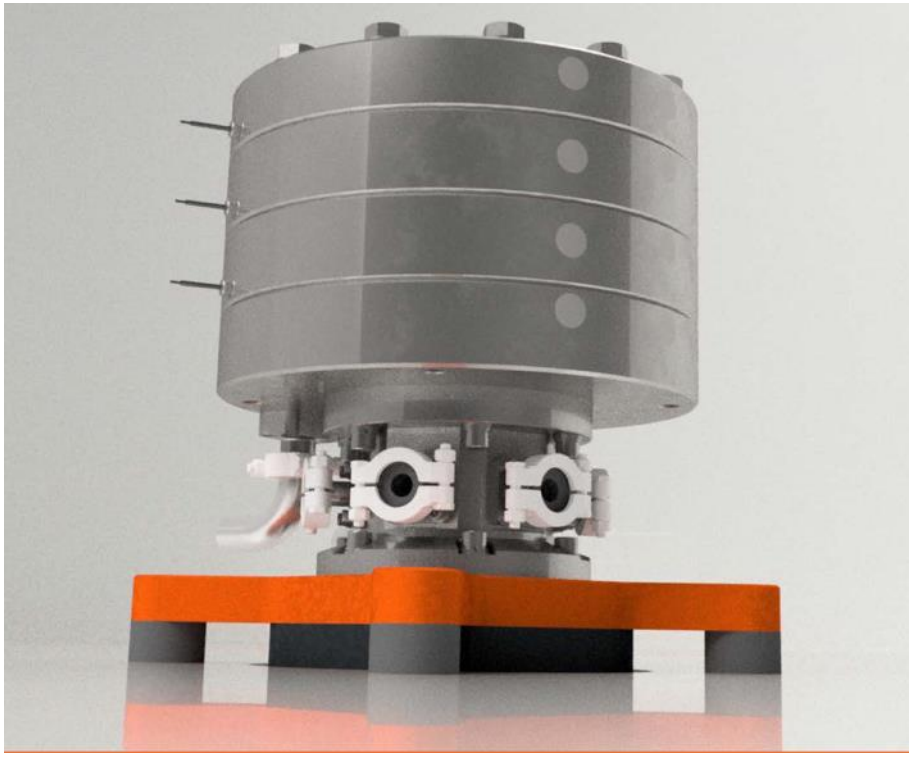


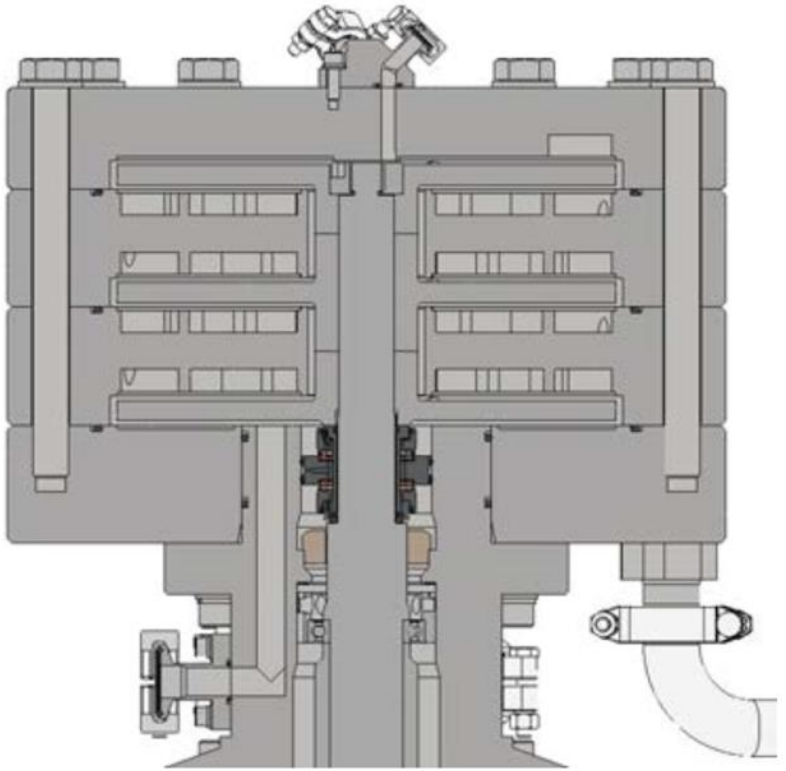
Continuous Flow Chemistry Lab

Spinning Disc Technology

Continuous Flow Chemistry Lab

Spinning Disc Technology

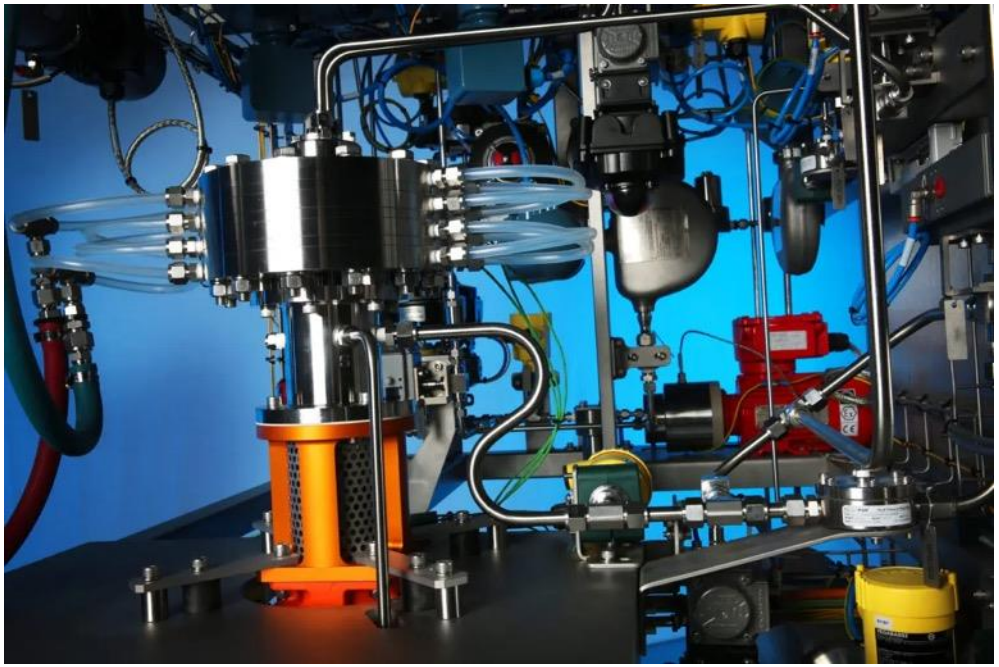




FlowID R4

Continuous Flow Chemistry Lab

Spinning Disc Technology



R3 Skid

Continuous Flow Chemistry Lab

Spinning Disc Technology

R4 Skid

Continuous Flow Chemistry Lab

Spinning Disc Technology

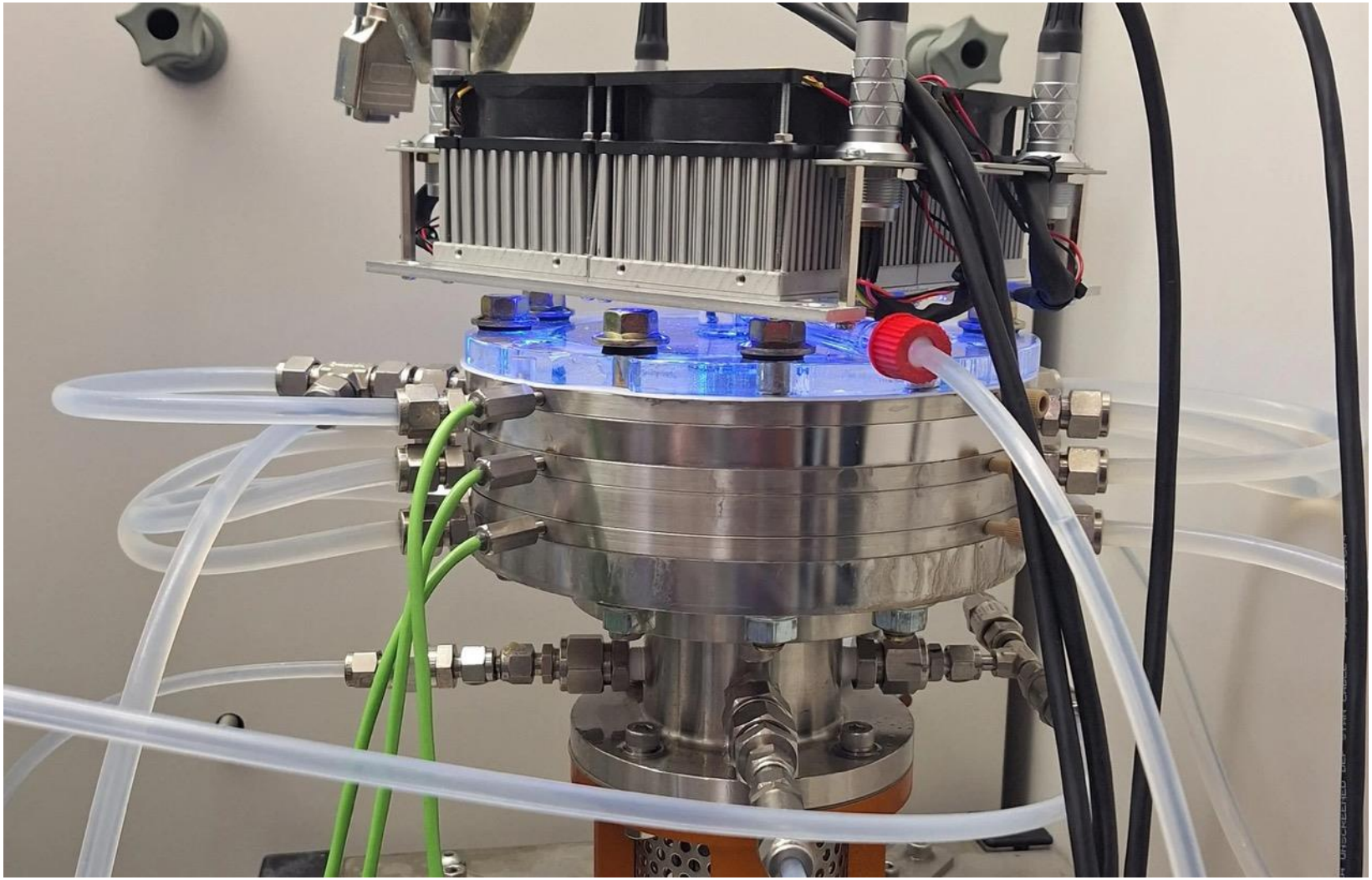


Photo Flow Spinning Disc

Continuous Flow Chemistry Lab

Spinning Disc Technology

Modular Plant

Spinning Disc Technology

API – Final Step NITRATION

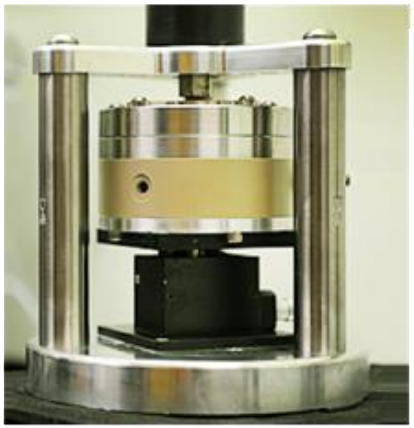
INDIA

Aromatic NITRATION (L/L)

in Spinning Disk Reactor (SpinPro)

Kinetichem, Inc

FLOWID NETH



Synthetron
Volume : 0.14 ml
Reaction time : 6 s

Lab

x2300

Throughput : 1550 t/yr

Product : **600 t/yr**

in a **270 ml** Reactor

Highly exothermic,
Fast & Biphasic reaction

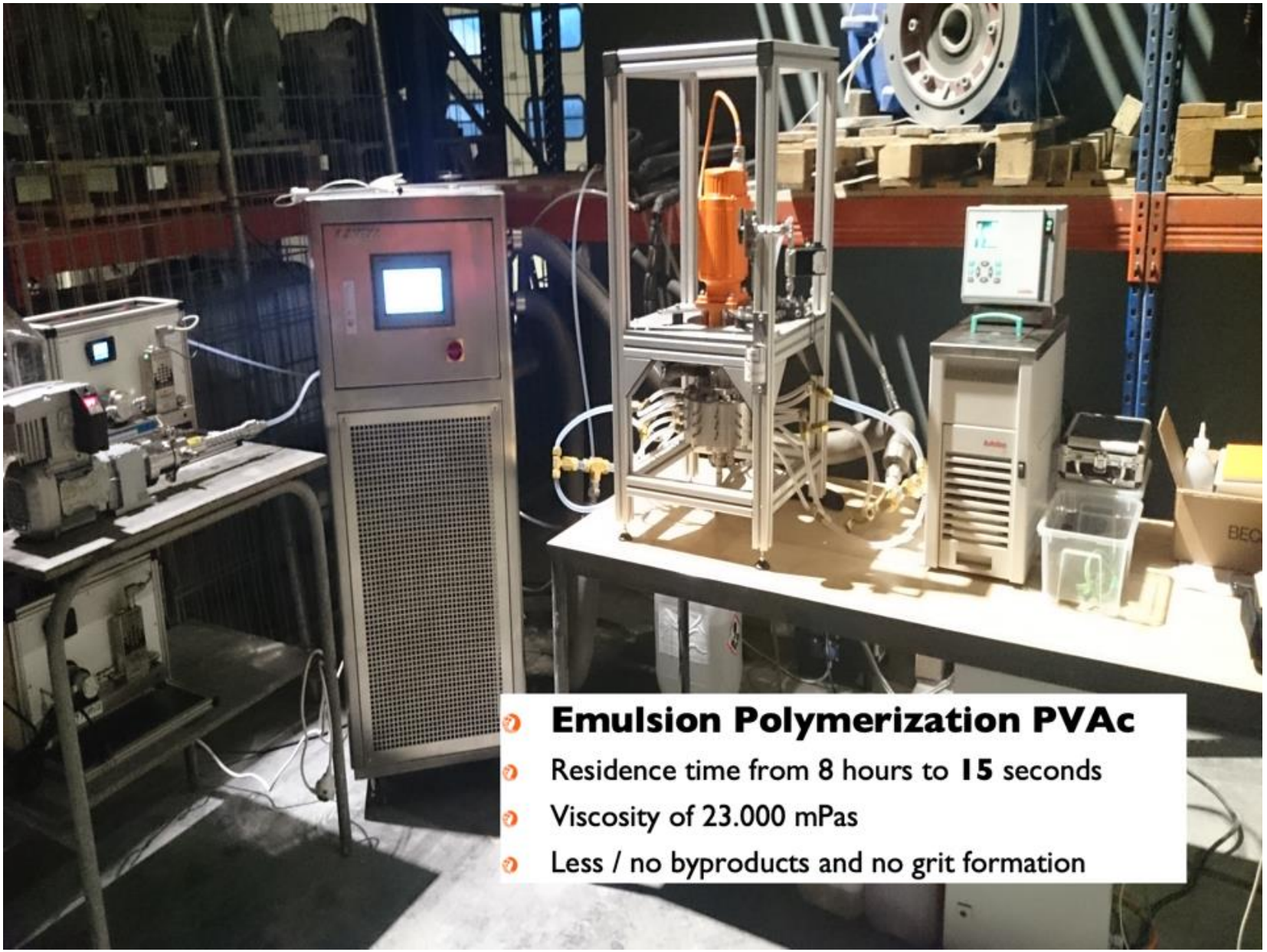
SpinPro-300
Volume : 270 ml
Reaction time : 5 s
Throughput : 194 kg/h

Industrial

Spinning Disc Technology

- **Super Glue production**
- 4 process steps: reaction, separation, reaction, extraction
- Residence time from 10 minutes to 9 sec (50kg/h)
- In-process analytics using SpinSolve NMR

Spinning Disc Technology



BuLi Scaleup: FLOWID

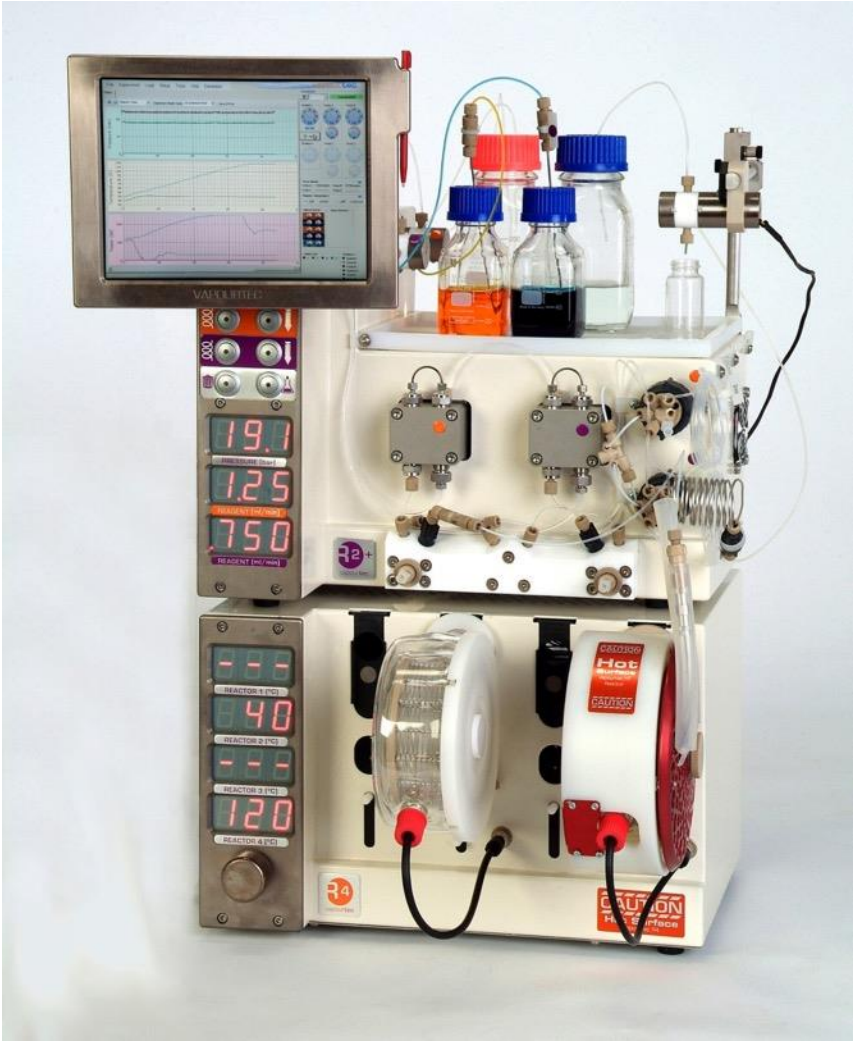
Even at throughputs of almost 100 kg/hr and a reactor temperature of +15 degrees Celsius, the synthesis was performed without difficulty.

The reactor footprint of 1 m^2 allows the unit to be installed virtually anywhere where service lines can be connected, such as between existing fixed equipment. Start-to-finish sensor communications for process monitoring and data logging are built into the reactor and can be customized depending on chemistry

Lab Module: Vapourtec

R Series System

Best Selling Flow Reactor



vapourtec

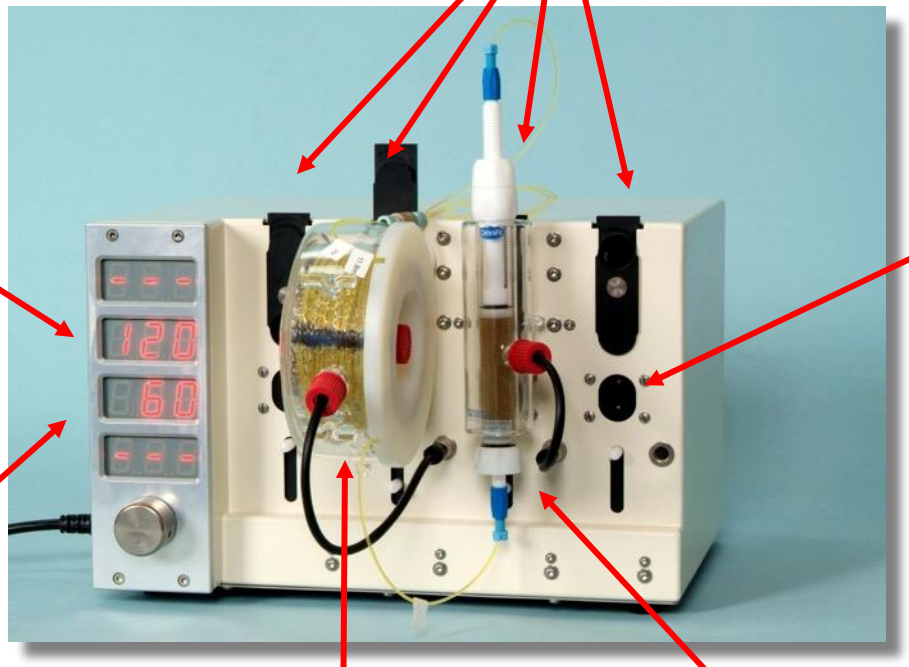
Lab Module: Vapourtec

Vapourtec E-Series

Lab Module: Vapourtec

R4 Reactor station

4 independently temperature controlled reactor positions



Temperature control from -70°C to +250°C

Reactors click into place in seconds for easy setup

Simple UI for stand alone operation. Large parameter display, visible from the other side of the lab

Each position can accept a tube reactor….

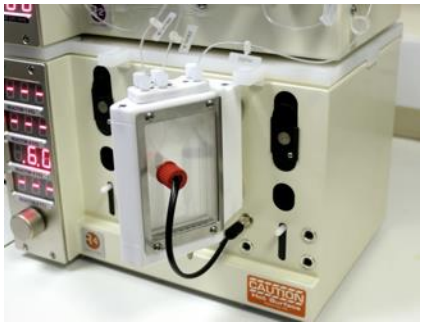
…or a packed column reactor

Lab Module: Vapourtec

Standard PFA coil
Ambient to 150°C

High Temp SS coil
Ambient to 250°C

Cooled PFA coil
Ambient to -70°C



CHIP Reactor

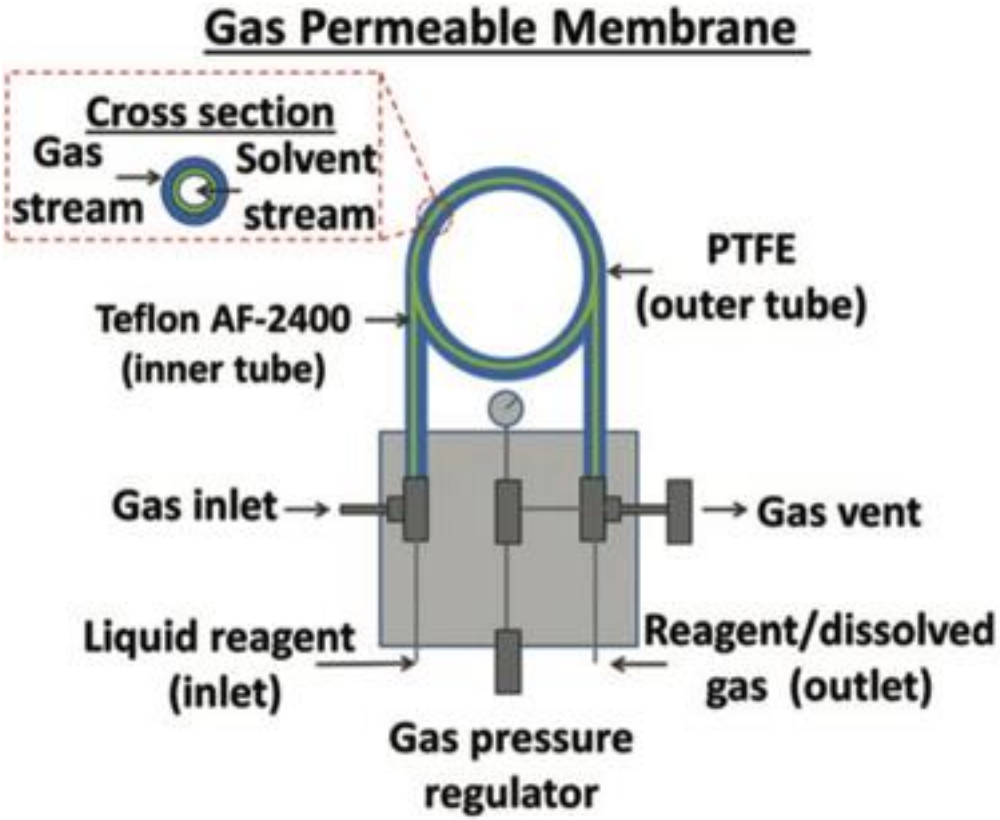
Standard Column
Ambient to 150°C

Cooled column
Ambient to -60°C

Gas/Liquid reactor
Ambient to 150°C

Large Volume
Reactor

Tube in Tube Reactor



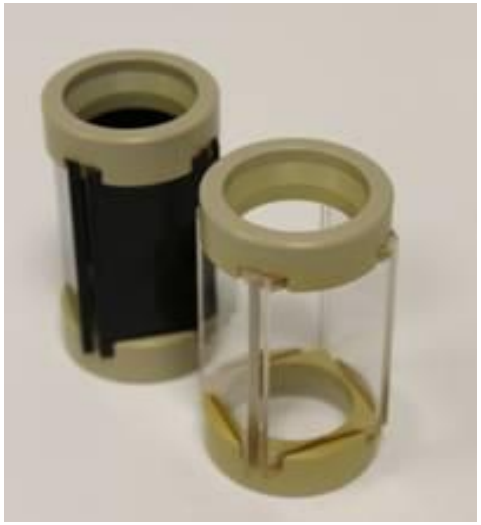
Lab Module: Vapourtec

The New Vapourtec UV-150 Photochemical Reactor

Features of the UV-150

- Fits both E and R-Series systems
- Multiple gram / hour scale-up
- High intensity UV light source
- User selectable UV power
- Light source wavelength filtering
- Temperature control -5^{0}C to 80^{0}C
- Easily changed reactors
- Space saving compact design
- Interlocks ensure safe operation
- Optional spectrometer for real time monitoring of transmission spectra

Lab Module: Vapourtec



To ensure the best possible reaction selectivity the UV-150 is provided with a temperature controlled environment for the duration of the reactant's passage through the reactor. Within the UV-150, the reactor region is separated and sealed from the lamp region.

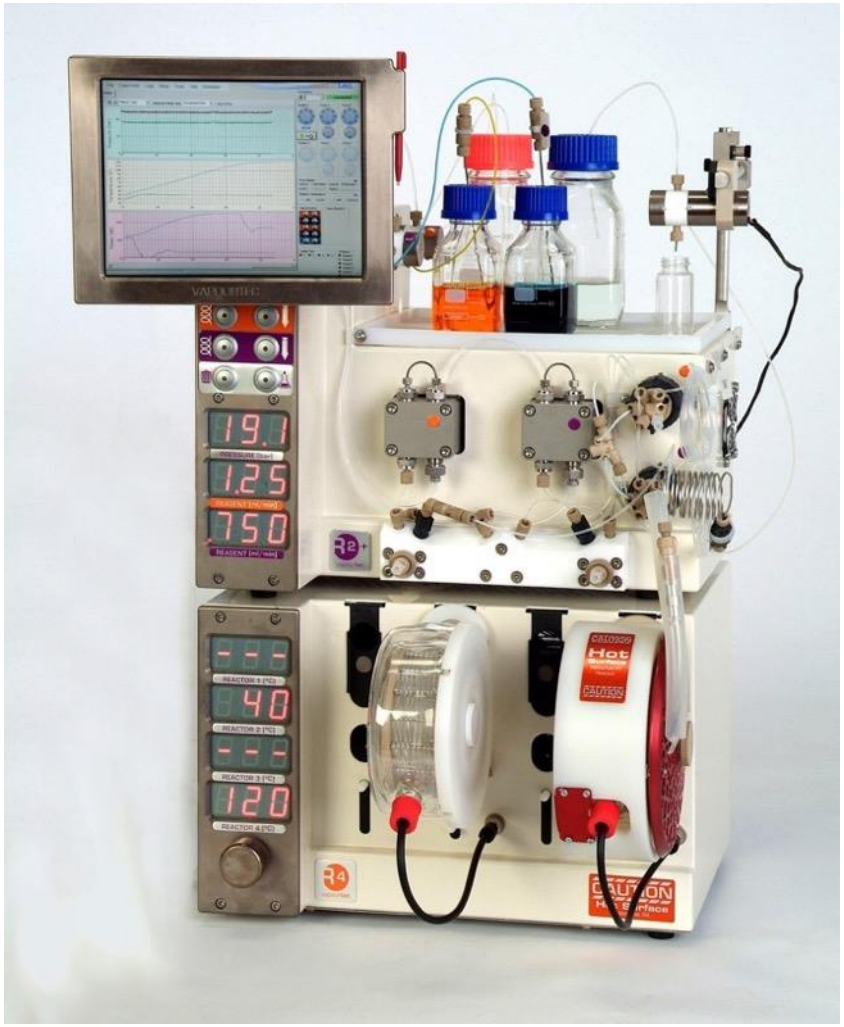
Lab Module: Vapourtec

Lab Module: Vapourtec

Vapourtec E-Series

Vaptec Peptide Module

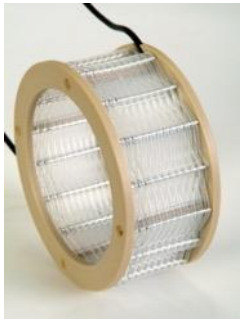
Lab Module: Vapourtec

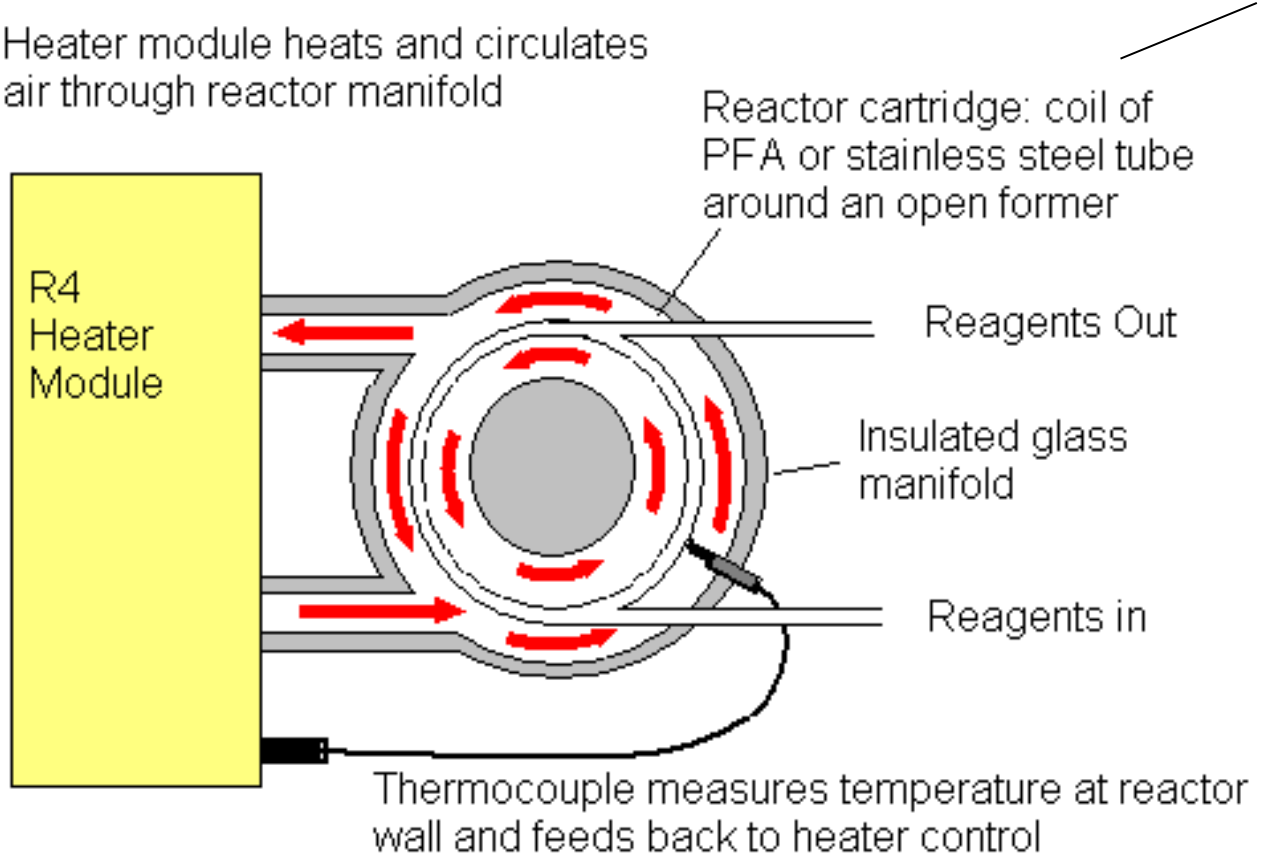


vapourtec

Lab Module: Vapourtec

Unique reactor heating / cooling system





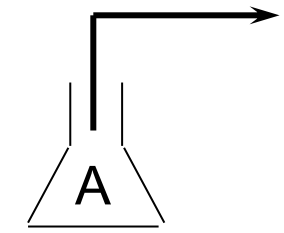
Lab Module: Vapourtec

Where does Vapourtec fit in ?

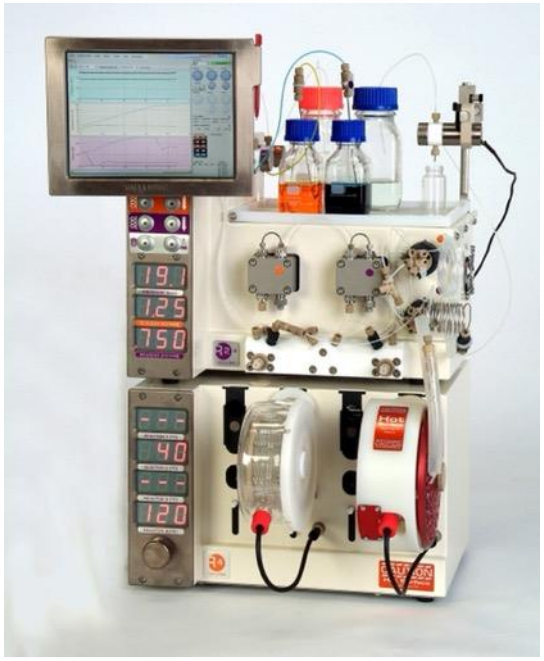
Flow principles can be applied to >14 orders of magnitude in scale, from earliest chemistry to late manufacturing

nano	micro	meso	kilo lab	pilot plant	manufacturing

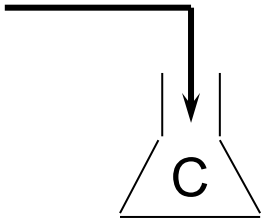
ng → *μg* → *mg* → *g* → *kg* → *10 kg* → *100 kg* → *multi-ton*



Vapourtec R4



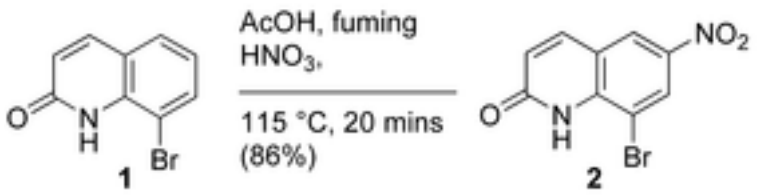
Scale translation?



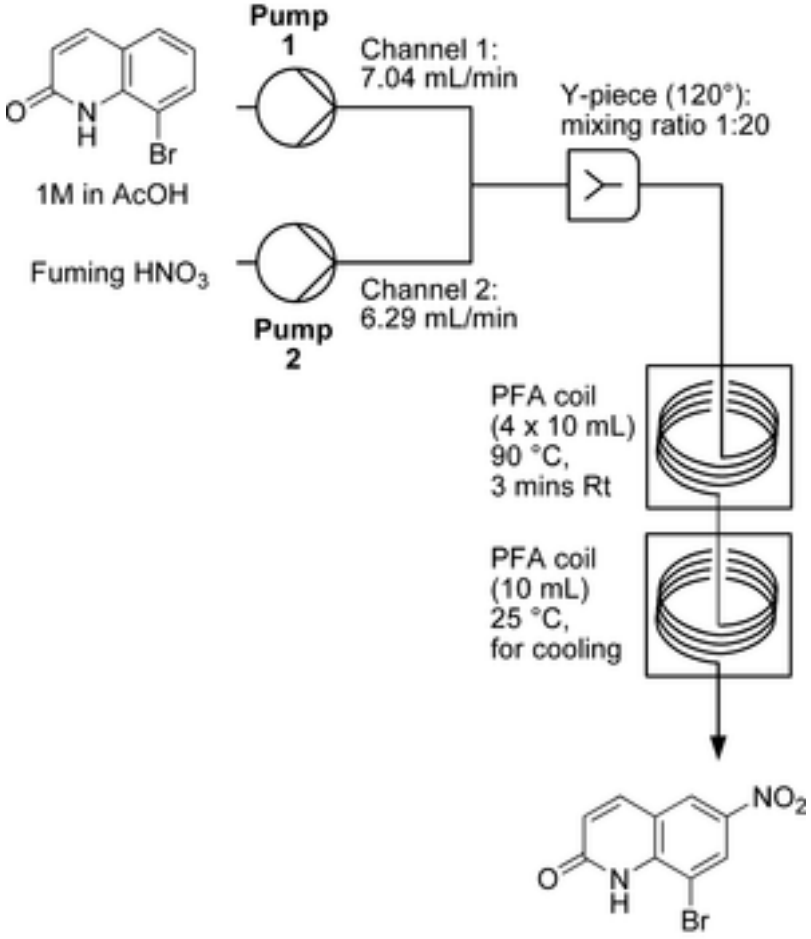
50 mg (convenience)
to 1000 g / day (“real chemistry”)

Nitration

Batch: only allowed on < 0.1 mol scale



Flow: 97 g/hr (86% yield)



Novartis

Vapourtec R Series

97g/hr
> 670g

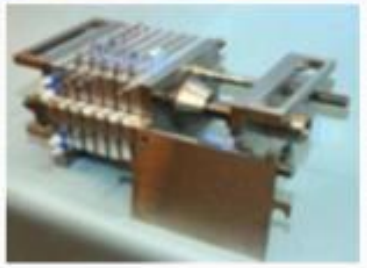
OPRD, 2011, 15, 1447

Lab to Production Modules

EHRFELD

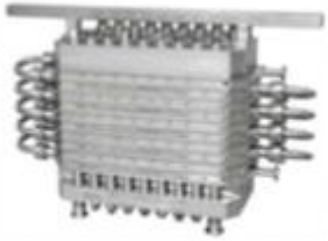
Scale-up Strategy

FlowPlate®

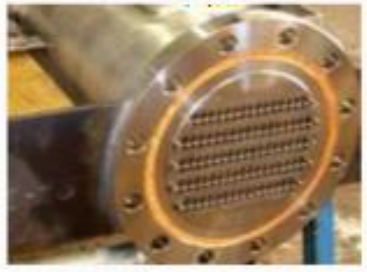


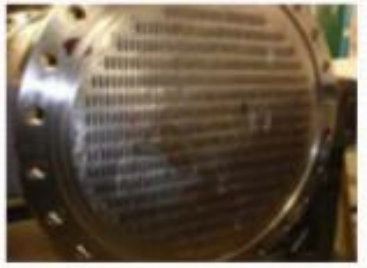
MMRS

ART®



Miprowa®

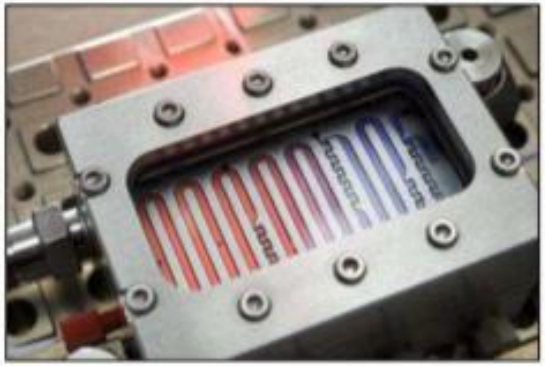




R&D → Interface → Pilot → Production

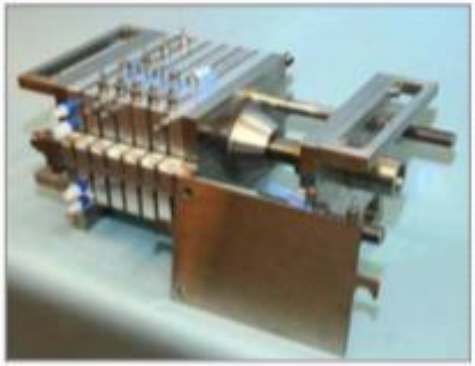
Lonza FlowPlate™ MicroReactors

EHRFELD
Mikrotechnik BTS



- Laboratory System:
- **1** – 50 mL/min
- Integrated in MMRS
- Process R&D
- Pre-clinical phase

- Small-scale Production:
- A6: **30** – 150 mL/min
- A5: 100 – **300 mL/min**
- Clinical phase 1, 2, 3

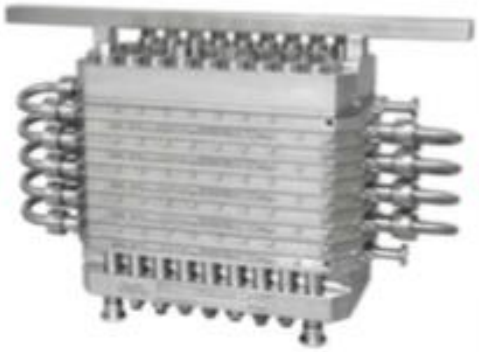


- Large-scale production:
- 200 – **600 mL/min**
- Production of commercial products

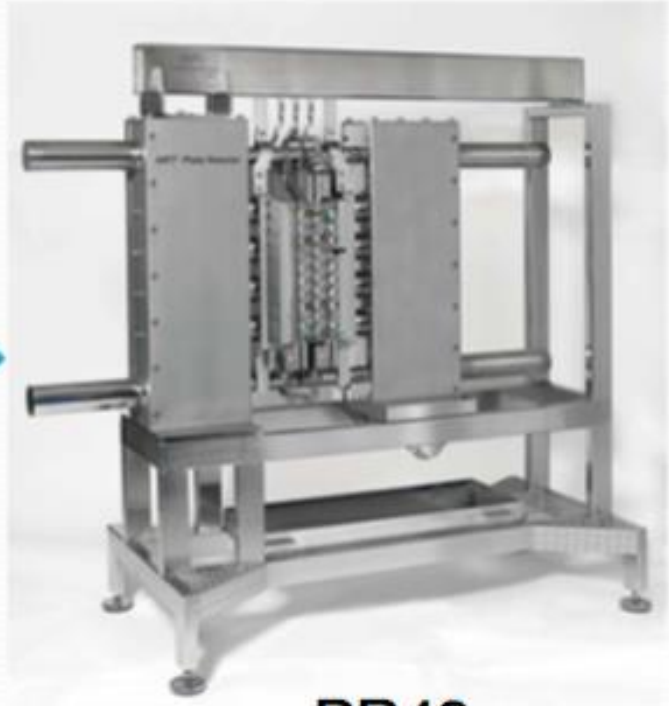
Lonza FlowPlate™ Lab → **Lonza FlowPlate™ A6 & A5** → **Lonza FlowPlate™ A4**

Scale-up Strategy III:
ART®

LabPlate®



PR37



PR49

Channel equaling-up

R&D and kilo lab	Pilot scale	Production Scale
0.1 – 2 L/h	0,5 L/h – 40 L/h	25 L/h – 1500 L/h

Miprowa® Reactors: From Lab to Production

EHRFELD Mikrotechnik BTS

- 1 – 10 L/h
- For use with MMRS
- Process development & intensification
- Small-scale production
- 2...8 channels

Miprowa® Lab

- 10 – 100 L/h
- Process development & intensification
- Small-scale production
- 1...3 channels

Miprowa® Matrix

- 100 – 10.000 L/h
- Quick scale-up
- Robust & easy to maintain
- Production
- 5...1000 channels

Miprowa® Production

MIPROWA

Ehrfeld Mikrotechnik BTS designed, manufactured and supplied a MIPROWA production reactor for Shaoxing Eastlake Biochemical (China) for a production capacity of up to 10,000 t/a. The MIPROWA millireactor with a throughput of about 1m³/h has a nominal width of 400 mm and a length of 7 m and contains about 150 rectangular reaction channels with exchangeable static mixers.

- **exothermic alkoxylation**
- **Replaces 20 Batch Reactors**

Fastest Transition from Lab to Production

http://www.chemanager-online.com/en/topics/thermal-processes/millireactor-production

Lab to Production: CHEMTRIX

Innovative Technology:

Scalability & System Flexibility at all Stages

CHEMTRIX

DISCOVERY

Labtrix® (µg to mg's)

-20 to 195 °C

- Rapid reactions
- Efficient evaluation
- mg consumption
- Parameter accuracy
- New chemical entities

DEVELOPMENT

KiloFlow® (g to kg's)

-15 to 150 °C

- Rapid up-scaling
- Process validation
- kg Production in a lab
- New process windows
- Flexible production

PRODUCTION

Plantrix® (kg to ton's)

-30 to 200 °C

- Facile up-scaling
- Forbidden chemistry
- Safe production
- High quality products
- Cost effective

Lab to Production: CHEMTRIX

Labtrix®:

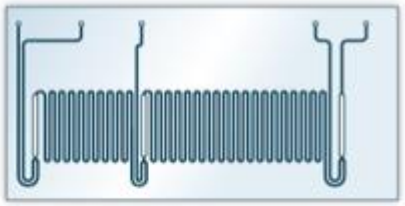
Flow Chemistry Method Development

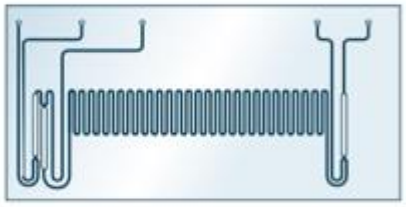
CHEMTRIX

- Increased safety
- Generate reliable & reproducible data
- Access to new chemical possibilities
- Fast method development
- Minimal use of raw materials
- High flexibility
- Easy to use
- Scalable flow chemistry methods

Lab to Production: CHEMTRIX

Labtrix

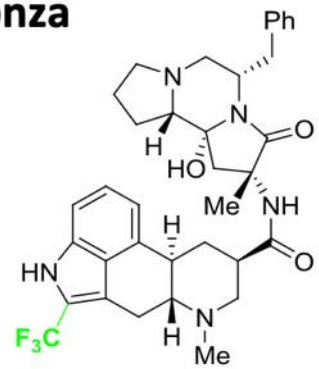




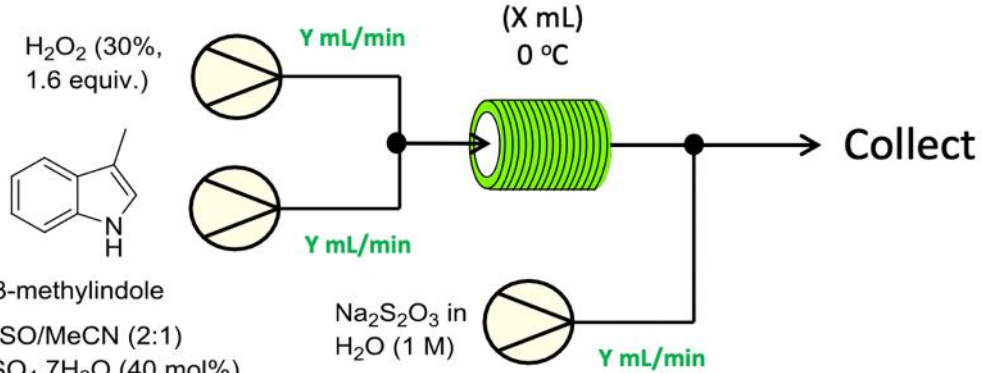
Minisci Trifluoromethylation

Chem. Eur. J. **2017**, *23*, 176-186.

Lonza



DHE Model substrate



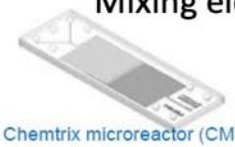
3-methylindole

DMSO/MeCN (2:1)
$FeSO_4.7H_2O$ (40 mol%)
H_2SO_4 (0.8 equiv)
CF_3I (1.2-1.6 equiv.)

Y-connector (0.5 mm thru hole, 1.7 µL) and tubing (PFA, 0.4 mm i.d.)

Uniqsis microreactor (UMR) (1.800 µL internal volume)

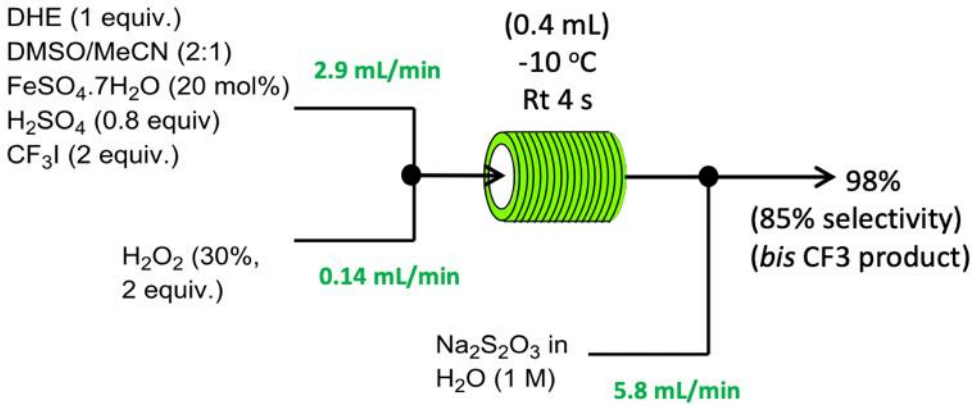
Mixing element



Chemtrix microreactor (CMR) (19 µL internal volume)

Reactor		Rt (s)	Conv.
Tubing	(87 µL)	1	94
Tubing	(8 µL)	0.1	61
Tubing	(4 µL)	0.05	51
Uniqsis	(1.8 mL)	11	94
Chemtrix	(19 µL)	0.3	95

Modular MicroReaction System From Ehrfeld Microtechnik BTS with a Lonza FlowPlate SZ reactor



Slide: Ian R. Baxendale

Plantrix® made of EKasic® Silicon Carbide
Efficient Industrial Production & Superior Chemical Flexibility

CHEMTRIX

- High productivity
- High chemical flexibility
- Less scale-up risk
- Handling of solids
- Increased safety
- Environmental friendly production
- Small footprint

Plantrix® Industrial Flow Reactor:
Specifications

CHEMTRIX

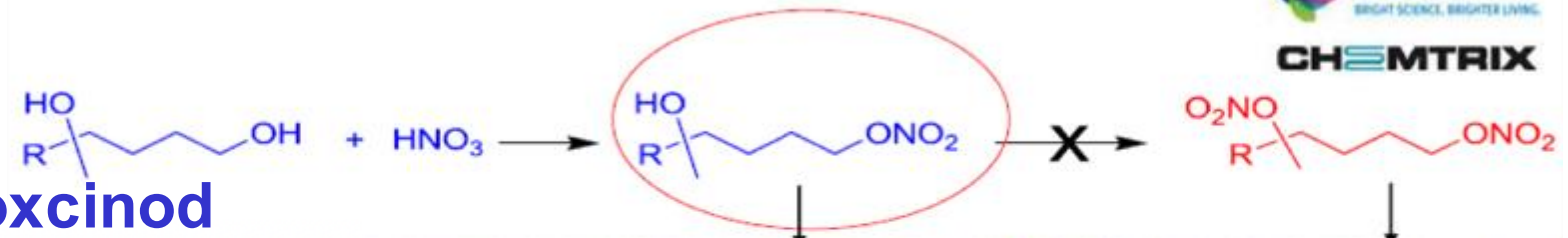
Plantrix® MR260

Plantrix® MR500

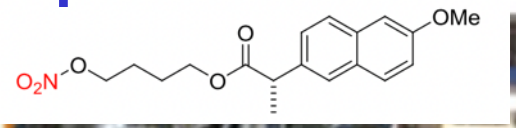
Specification	Plantrix® MR260	Plantrix® MR500
Channel Dimensions (mm)	2.0 x 2.0	3.5 x 3.5
Temperature Range (°C)	-30 to 200	-30 to 200
ΔT (Service - Process) (°C)	< 70	< 70
Maximum Operating Pressure - Service Fluid (bar)	6	6
Maximum Operating Pressure - Process Fluid (bar)	25 (< 100 °C) 16 (≤ 200 °C)	25 (< 100 °C) 16 (≤ 200 °C)
Module Dimensions (mm)	110 x 260	200 x 500

Industrial Aliphatic Nitration (L-L)

DSM
CHEMTRIX



Naproxcinod



Lab Scale	Industrial Scale TRIALS	Final PLANT Production
GLASS AFRs	96 Glass AFRs for Trials only	>100 Tonnes (EKasic) SiC

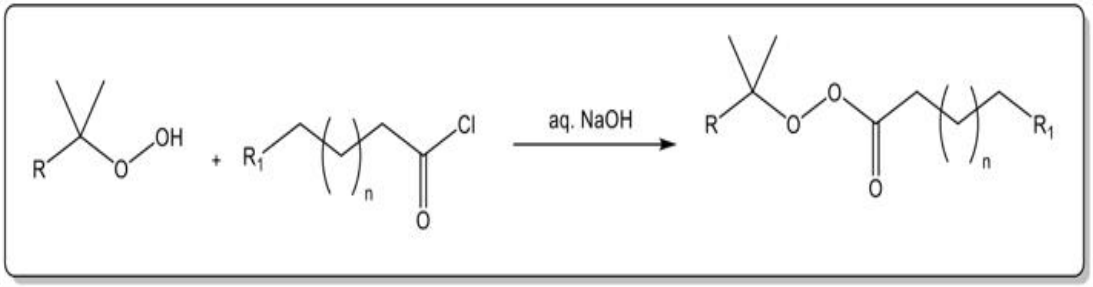
DSM selected ChemtriX v/s Corning. Reasons: very few and "secure" connections, "non-leachable" & "diffusion-bonded" SiC (ChemtriX) v/s Glass or "brazed" SiC (Corning)

Drivers: Control reaction exotherm (runaway, **explosive**) for process **safety**
High **"mono- nitro" selectivity**, high-productivity & GMP production

Case Study – Peracid Acylation (L/L)

10,000 tonne/year

CHEMTRIX



Challenges in Batch:

- Corrosive reagents & unstable product
- Highly exothermic reaction
- High dilution employed & long reaction time

Flow Process Conditions:

- Reaction temperature **< 30 °C**
- MR260 Throughput = **5.7 l/h**
- MR555 Annual Production = **10,000 tonne**

Advantages:

- Thermal control
- Metal & glass-free reactors
- Increased product purity
- Stepwise reagent addition minimises peroxide decomposition

Plantrix® Industrial Flow Reactor:
OmniChem – Why Flow Chemistry?

(L-L)

Customer process involved:

- Three exothermic steps requiring slow addition (8 h) → Thermolabile intermediate
  → **Two most exothermic** (400 J/g) in Plantrix®
- **Potent product, OEB-5** (occupational exposure band 0.1-1 µg/m^3)

Developing a multi-stage continuous process therefore allowed OmniChem to achieve;

- **Increased process safety due to improved thermal control & minimised exposure**
- **Higher productivity** *cf.* batch (x2)

Technical Advantages:

- Small, mobile equipment tested in lab & moved to production
- Reduced material inventory
  → Transfer to bunker for batch conversion
- Process robustness enhanced *via* automation

Results with Plantrix

- FDA approved materials of construction
- Excellent thermal control
- Modularity

CHEMTRIX

Next Steps: 25x scale-up (multi-tonne/week)

Plantrix@

Commercial continuous manufacturing @ > 500 MT per year

Doubling of annual throughput cf. dedicated batch unit

Reduction in the overall carbon footprint by 30%

Target price manufacturing

NITRATION (L-L) CHINA

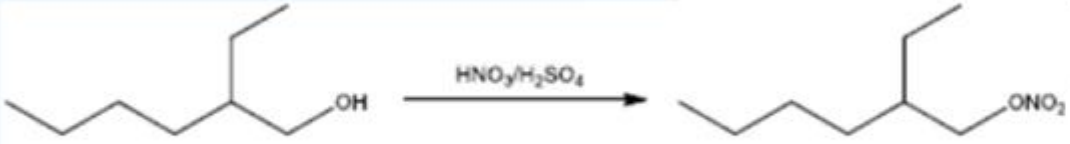
Continuous Nitration of Alcohols Plantrix®: 70 % Nitric Acid

The synthesis of energetic materials *via* nitration reactions can be problematic owing;

- Inefficient heat & mass transfer

→ Strong exotherms lead to by-product formation & product decomposition

CETANE Improver



2-Ethyl-1-hexanol → **2-EthylHexyl Nitrate**

10,000 tonnes / annum : CHINA

$HNO_3:H_2SO_4$	HNO_3:hexanol (eq.)	Product	By-product
1:0	3.1	×	×
1:0.286	2.5	×	✓
1:0.767	1.5	Minimal	✓
1:1.130	1.25	✓	✓
1:1.726	1.0	✓	×

✓ No by-product formation observed under optimal conditions

Optimal Conditions in Plantrix®:

12 s reaction time @ 18 °C (99.6 % purity by GC)
→ production 10,000 tonnes/annum

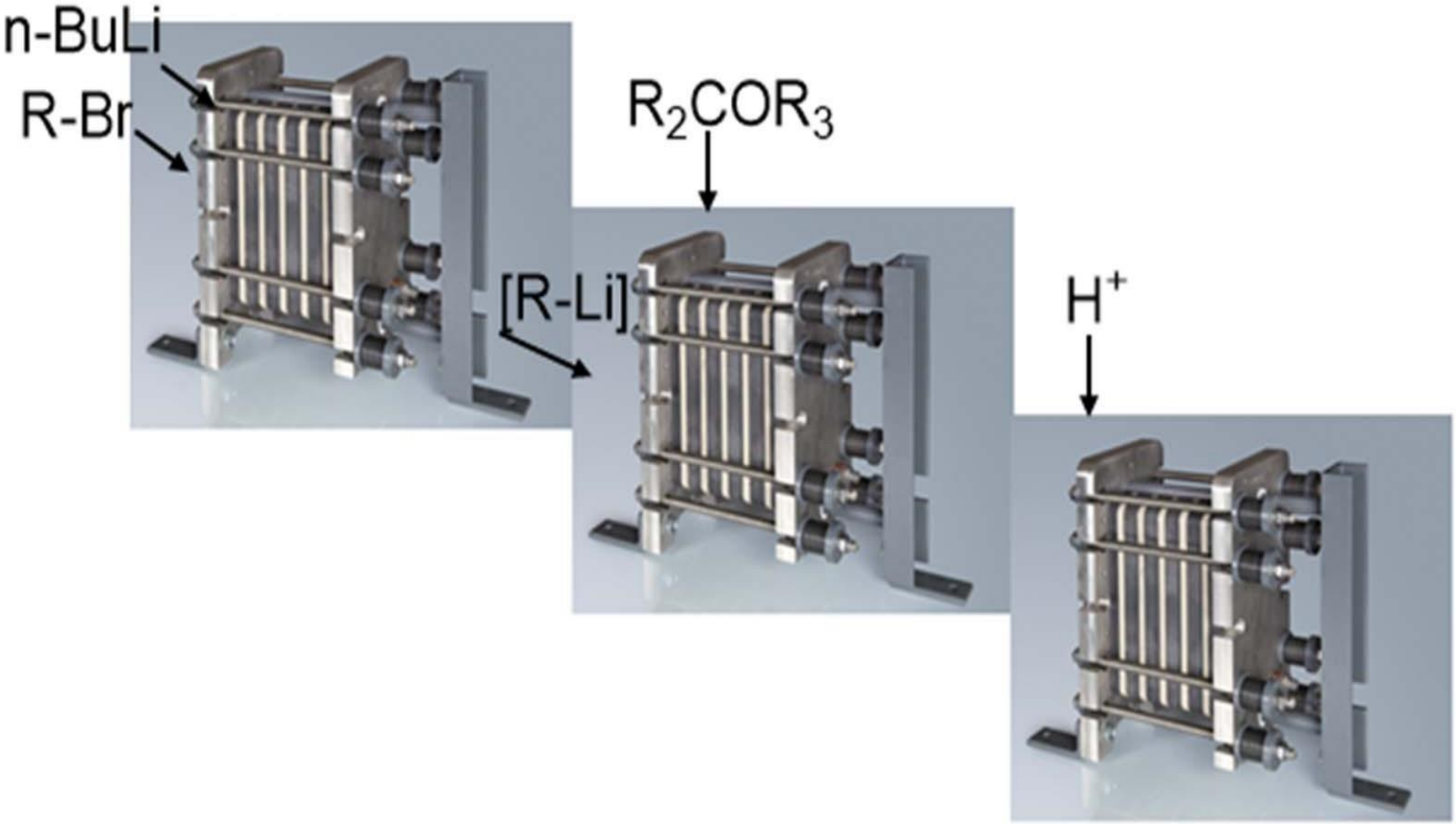
Plantrix® MR555

Advantages:

- Small hold-up volume
- Rapid mixing & efficient heat transfer allows intensified process
- Solvent-free production technique
- Metal-free modules facilitate use of highly corrosive reagents

courtesy CHEMTRIX

Lab to Production: CHEMTRIX



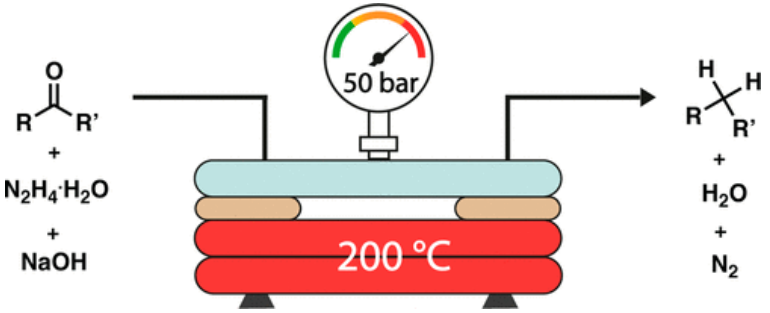
Chemtrix Protrix

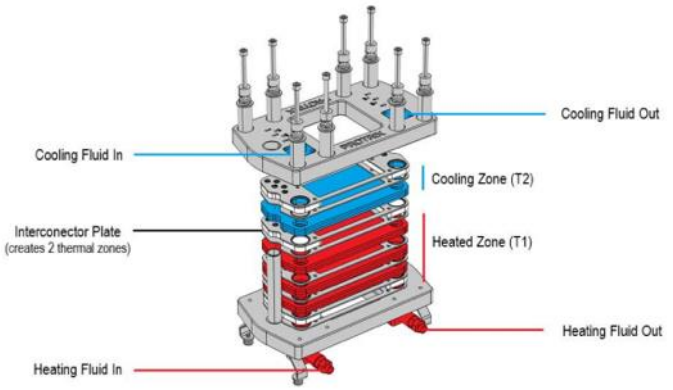
Vol: 1-13.5 ml

FR: 0.2 to 20 ml/min

Size: 350 (W) x 200 (D) x 250 mm (H)

Wolff–Kishner Reduction





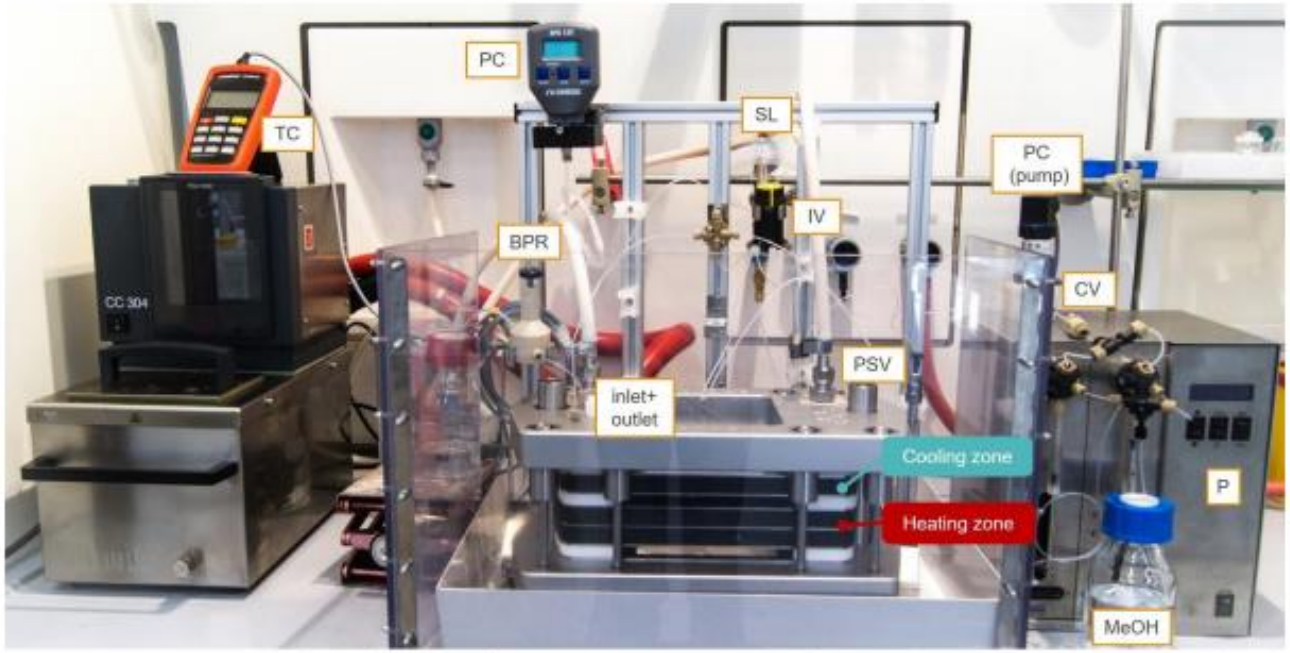


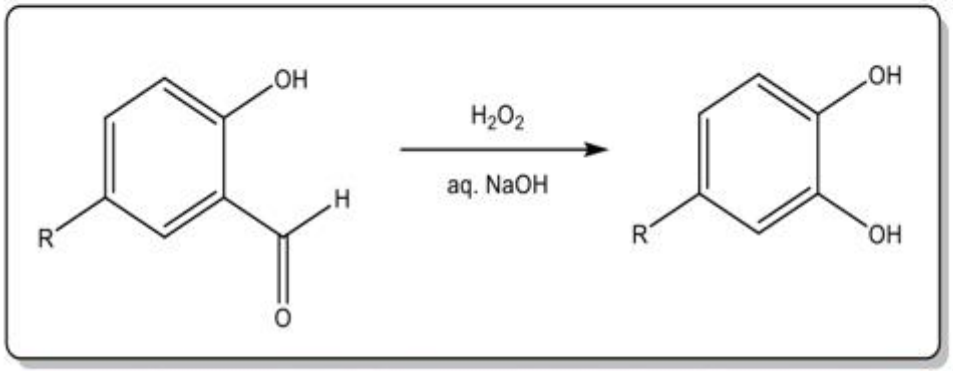
Figure S3. Image of continuous flow set-up. BPR: **B**ack **P**ressure **R**egularor; CV: **C**heck **V**alve; IV: **I**njection **V**alve, P: **P**ump; PC: **P**ressure **C**ontrol, PSV: **P**ressure **S**afety **V**alve; TC: **T**emperature **C**ontrol; The cooling zone of the reactor was cooled by water using an aquarium pump.

Org. Process Res. Dev. 2019, 23, 11, 2445−2455

Case Study – Dakin Oxidation (L/L)

4.32 tonne/year in a fume-hood

CHEMTRIX



Reasons for Flow:

- Safety risk H_2O_2 at scale
- Shorter synthetic route
- Reduced reagent use (1.05 eq.)
- Increased throughput

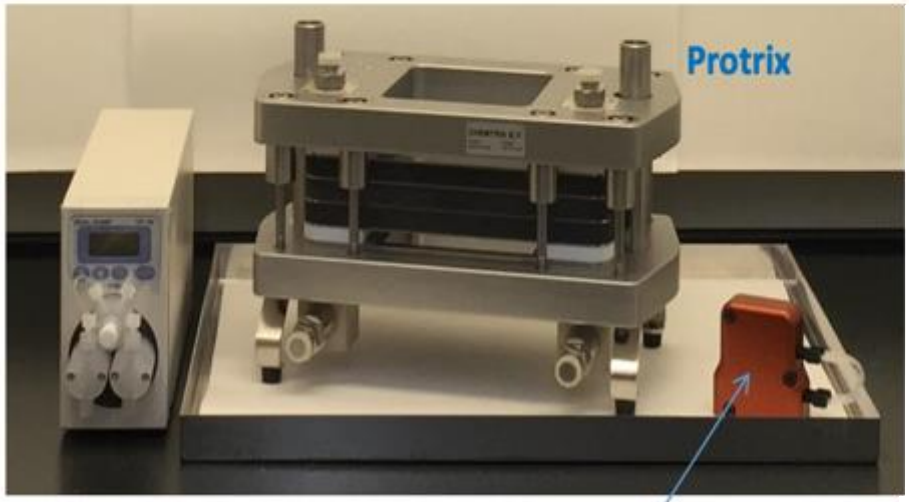
Protrix® for development:

- Metal & glass-free reactor
- Integrated thermal control

→ 30 s reaction *cf.* 6 h in batch

→ Quant. catechol (14.4 kg 24 h^{-1})

= 4.32 tonne yr^{-1}



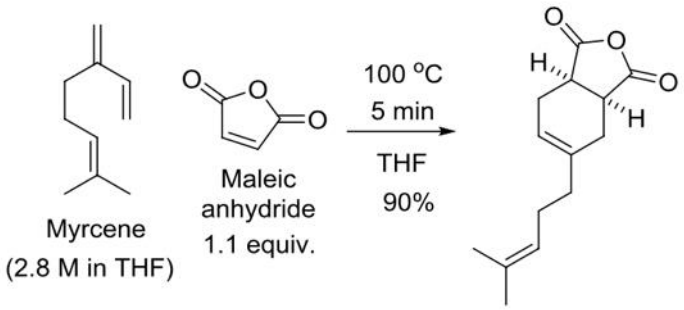
Continuous phase separation performed in the lab & batch extraction

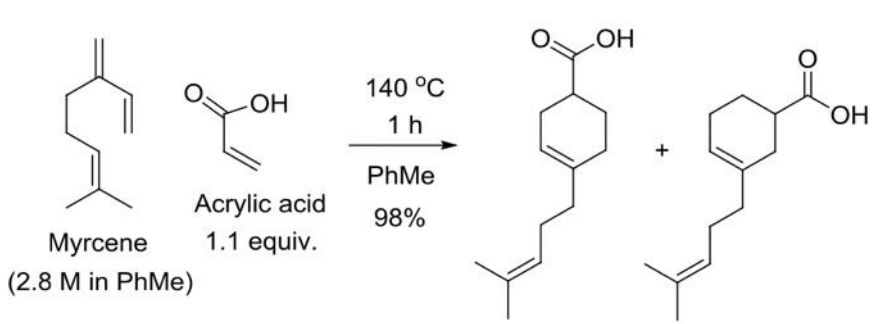
- Continuous **extraction** at scale using Zaiput extractor / separator set-up

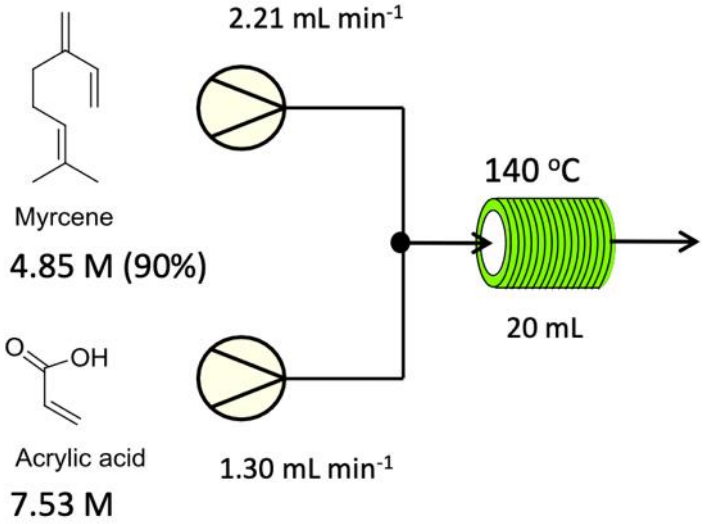
Diels–Alder Reactions of Myrcene

Beilstein J. Org. Chem. **2017**, *13*, 120–126

Interest in surfactant properties for Fragrance materials







tubular flow reactor
(Vapourtec R-series)

X 7.5

plate flow reactor
(Chemtrix MR260)

Teledyne Isco D-series dual syringe pumps
(100 DX, with Hastelloy™ syringes)

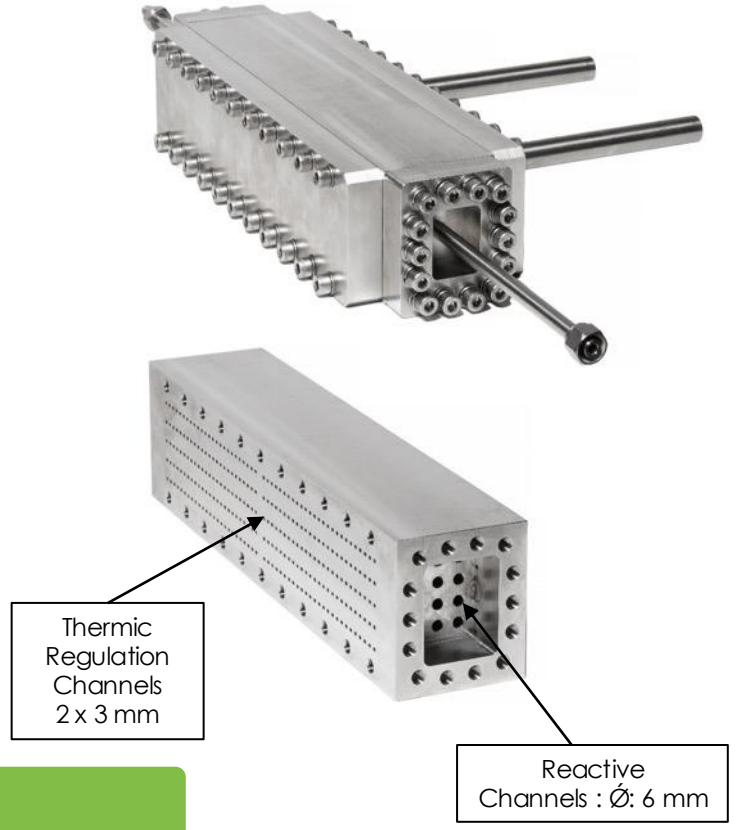
40 min Rt
20 mL volume (2 x 10 mL)
140 °C 99% conversion
= 1.29 mmol min^{-1} = 269 mg min^{-1}
STY = 0.40 kg L^{-1} h^{-1}

30 min Rt
105 mL volume (2 x 10 mL)
140 °C 100% conversion
= 9.65 mmol min^{-1} = 2 g min^{-1}
STY = 1.14 kg L^{-1} h^{-1}

Slide: Ian R. Baxendale

What makes KHIMOD reactors unique?

- **Large scope of alloys**
  - Stainless Steel, Inconel, Hastelloy, Monel, Zirconium ...
  - Making KHIMOD HERs compatible with highly corrosive reagents
- **Outstanding heat exchange capacity**
  - 16 thermic regulation channels per reactive channel
  - Heat exchange capacity from 600 to 1 400 KW/m3/K
- **Extreme resistance to pressure & temperature**
  - Standard model : up to 93 bars and 550°C
  - Customized model : up to 200 bars and 800°C
- **High flexibility of design**
  - Adjustable reactive channel length
  - Opportunity to heat or cool the reagents before the reaction
- **Opportunity to use fixed bed catalysts**
  - Wide range of catalysts available at our partners
  - Option to use catalytic static mixers from Precision Catalysts



With KHIMOD,
unlock your chemical potential

AM Technology

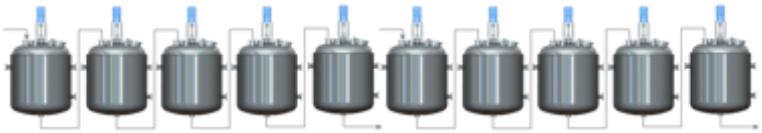
ACR (Agitated Cell Reactor)

Shaken not Stirred

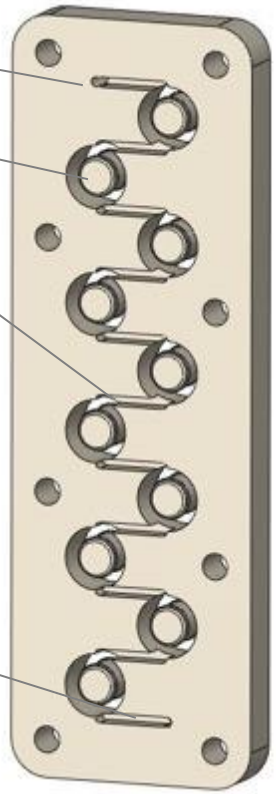
AM Technology

Coflore: Equivalent to a series of CSTRs

- The series of 10 small CSTRs in one block



45 cm

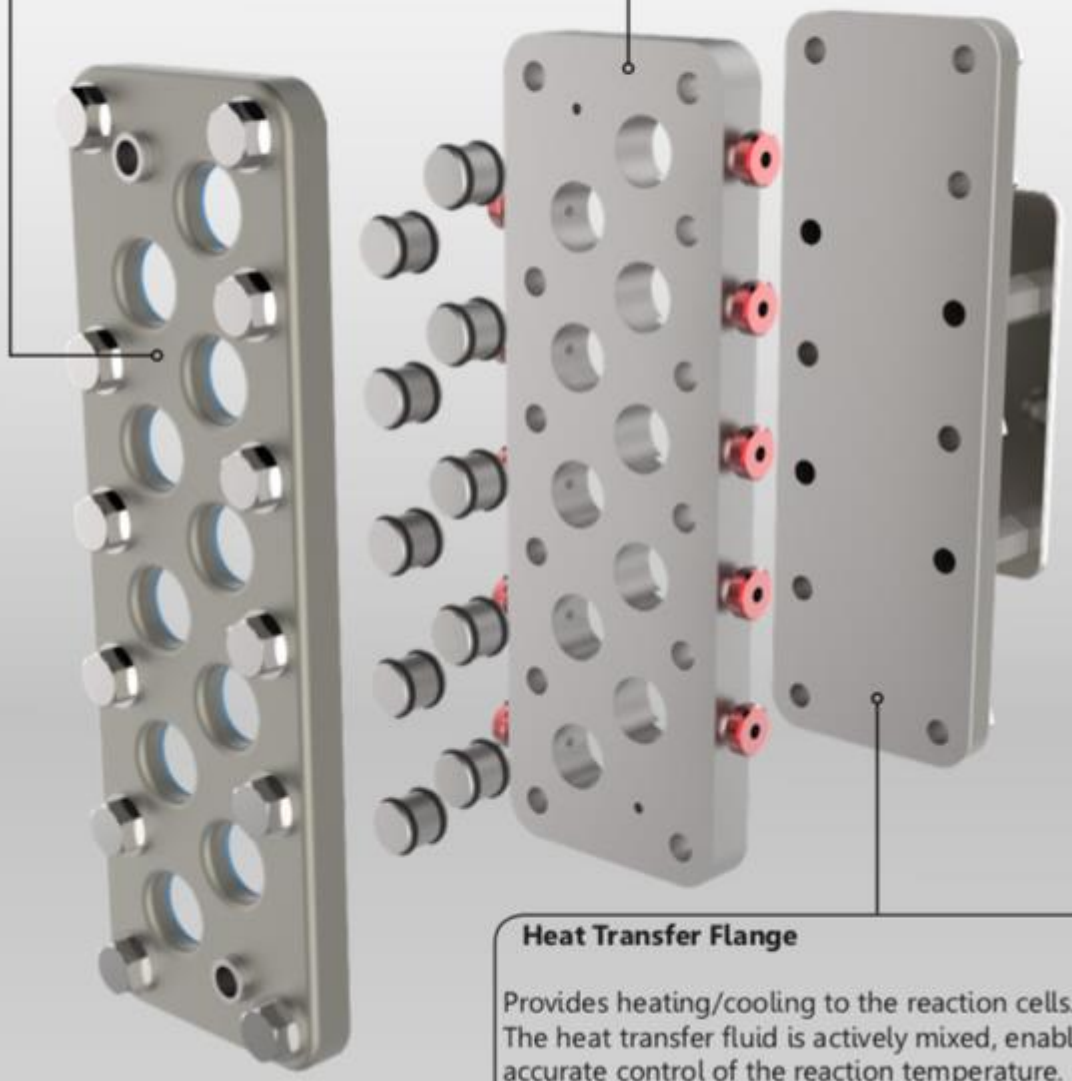


Process Flange

The Process flange incorporates the Process connections, for the reactor inlet/outlet and glass windows for viewing inside.

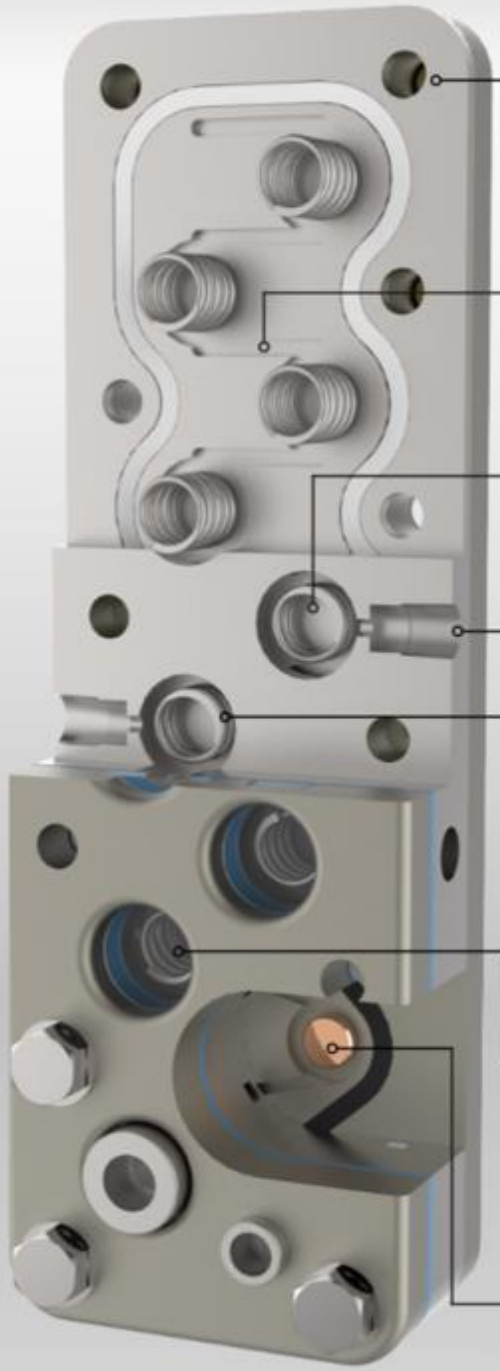
ACR Cell Block

The ACR Cell block has 10 reaction cells connected together via interstage channels. Cell blocks are interchangeable.



Heat Transfer Flange

Provides heating/cooling to the reaction cells. The heat transfer fluid is actively mixed, enabling accurate control of the reaction temperature.



ACR Cell Block

Operating Range:
Pressure: Up to 10 Bar
Temperature: -40 to +140°C
Cell blocks are interchangable.

Interstage Channel

Interstage channels connect the cells together, giving the performance of 10 CSTR's

Reaction cell

10ml Volume per cell, working volume can be tailored using different agitator sizes.

Side ports

The side ports in the reactor block can be used for inlet/sample points or temperature probes without dismantling the reactor block.

Agitators

Agitators generate active mixing inside the cell. Active mixing decouples mixing and plug flow from residence time.
Agitators are interchangeable with different designs.

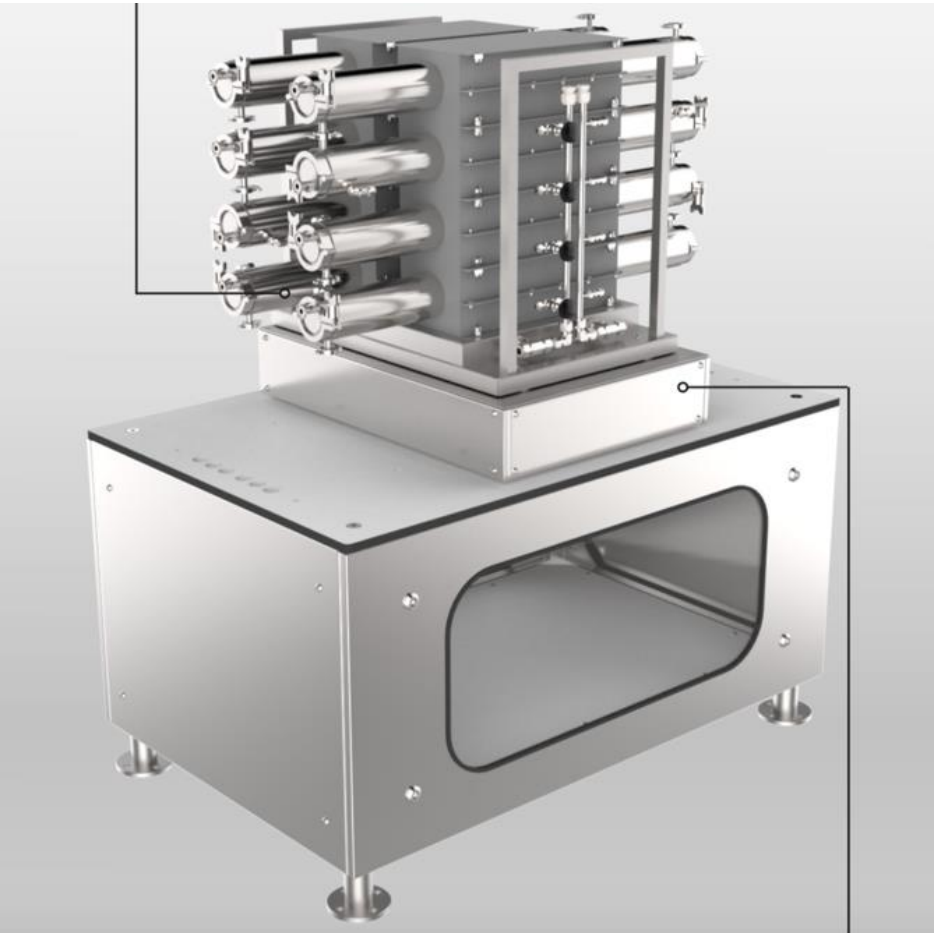
Glass Windows

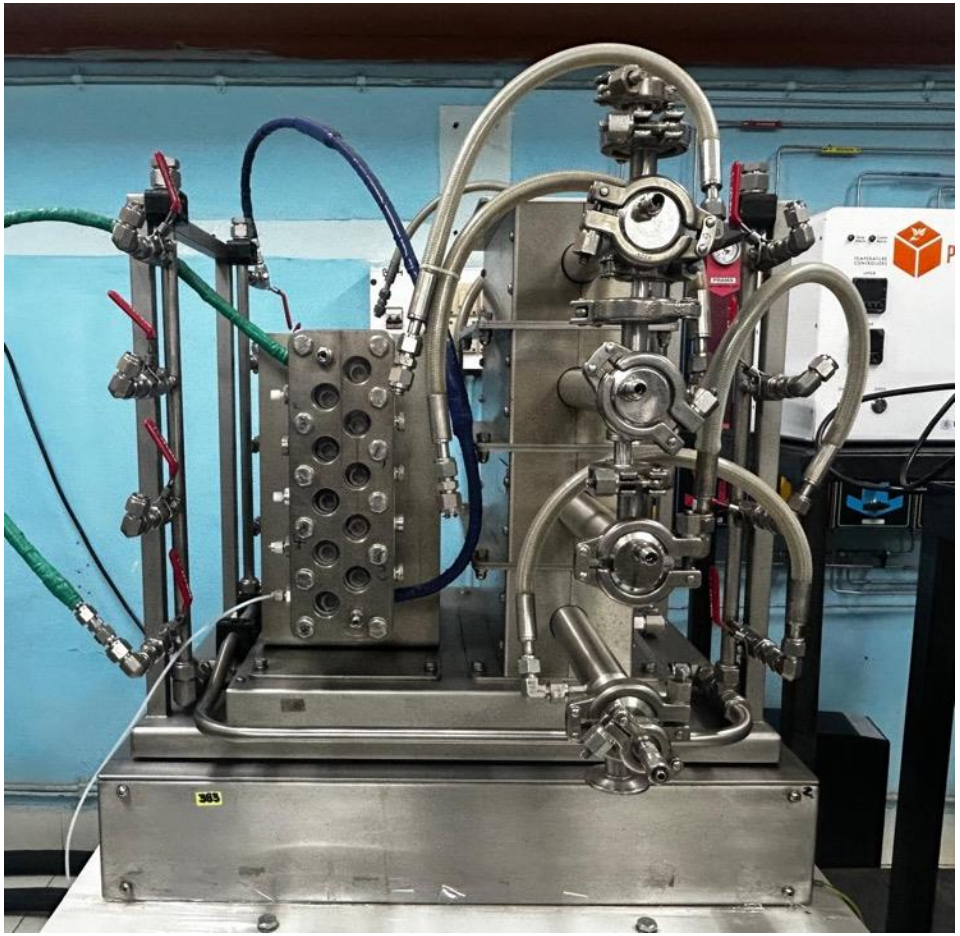
Borosilicate glass windows enable viewing inside the reactor.

Heat transfer

Agitators generate active mixing inside the heat transfer flange. Active mixing enables accurate control of the reaction temperature.

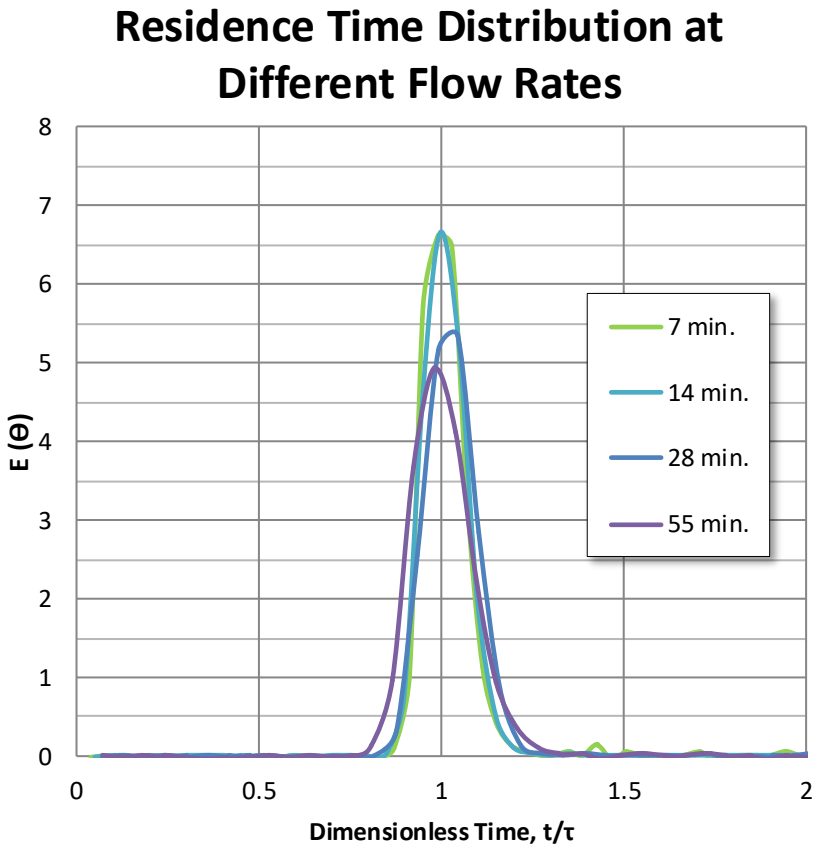
ATR: Agitated Tube Reactor





30-100 ml, 700 ml-10.0 L

Undisturbed Plug Flow even at Longer Residence Times



- Standard 10 tube system
- Total length 3.2m
- Dynamic mixing ensure narrow residence time distribution at all flow rates

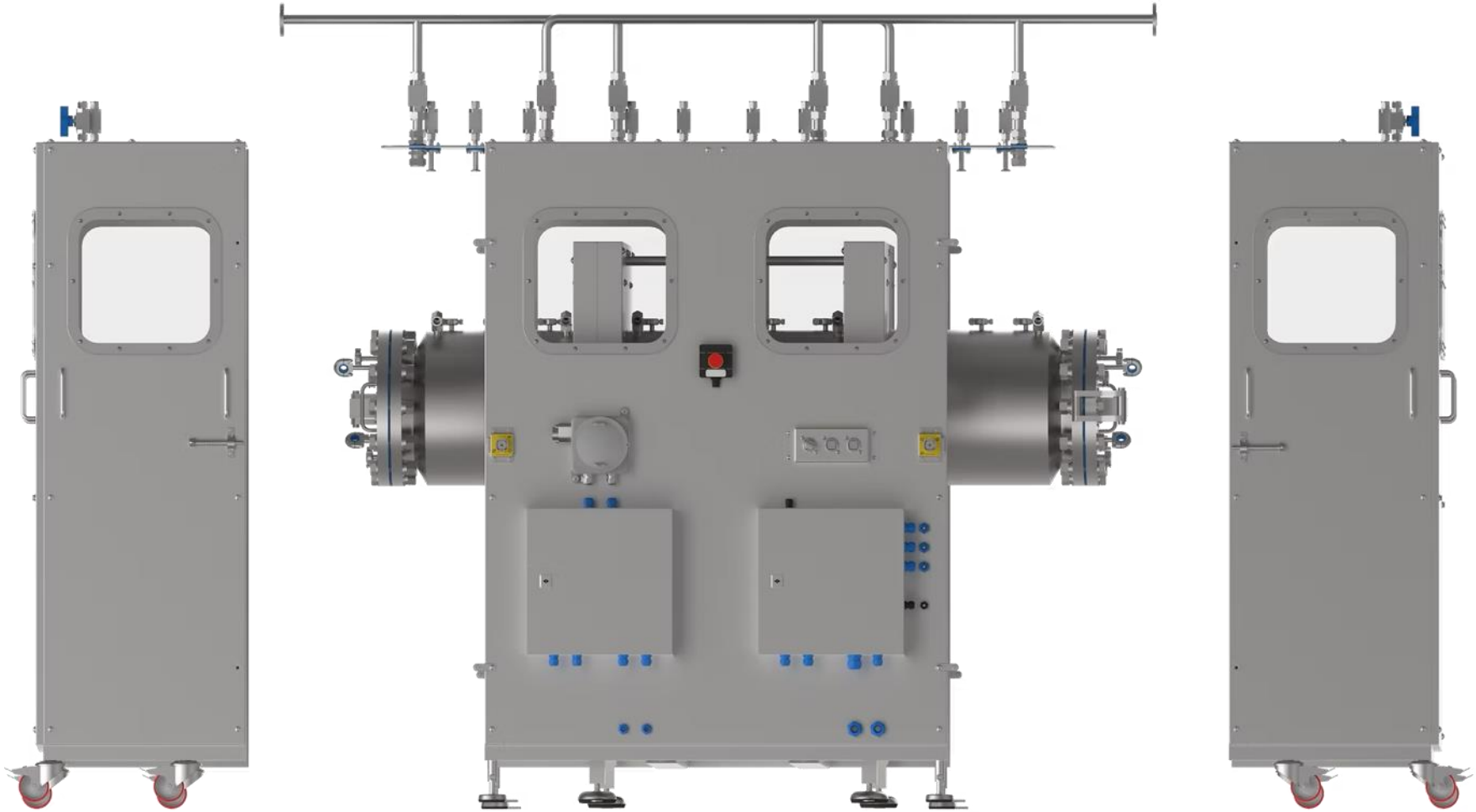
Residence Time (min)	Equivalent CSTRs
7	870
14	302
28	216
55	158

RTR: Rotating Tube Reactor

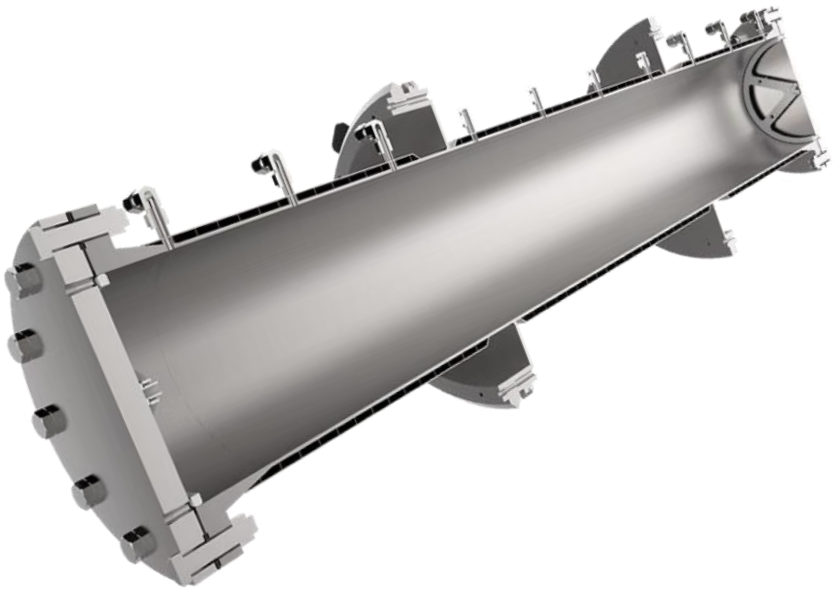
2250 (W) x 1200 (L) x 1940 (H)

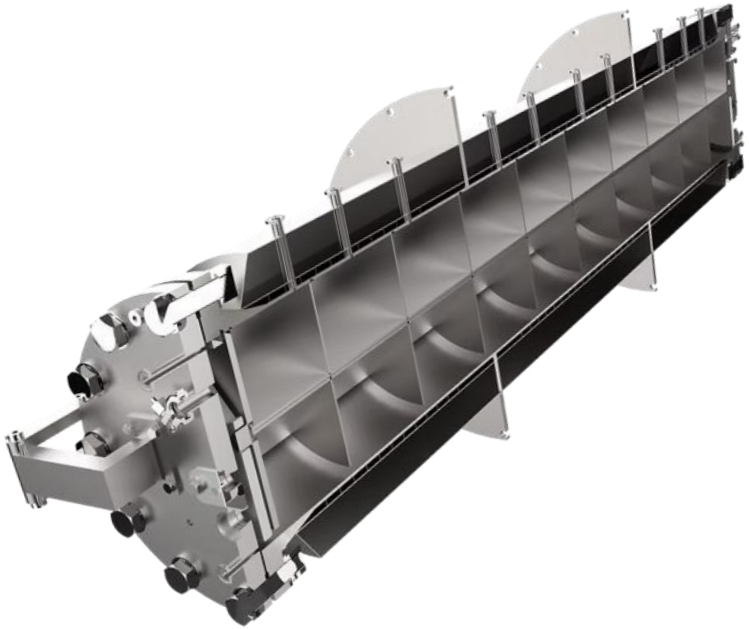
5m RT: >28 kL Volume in 24hr

RTR: Rotating Tube Reactor

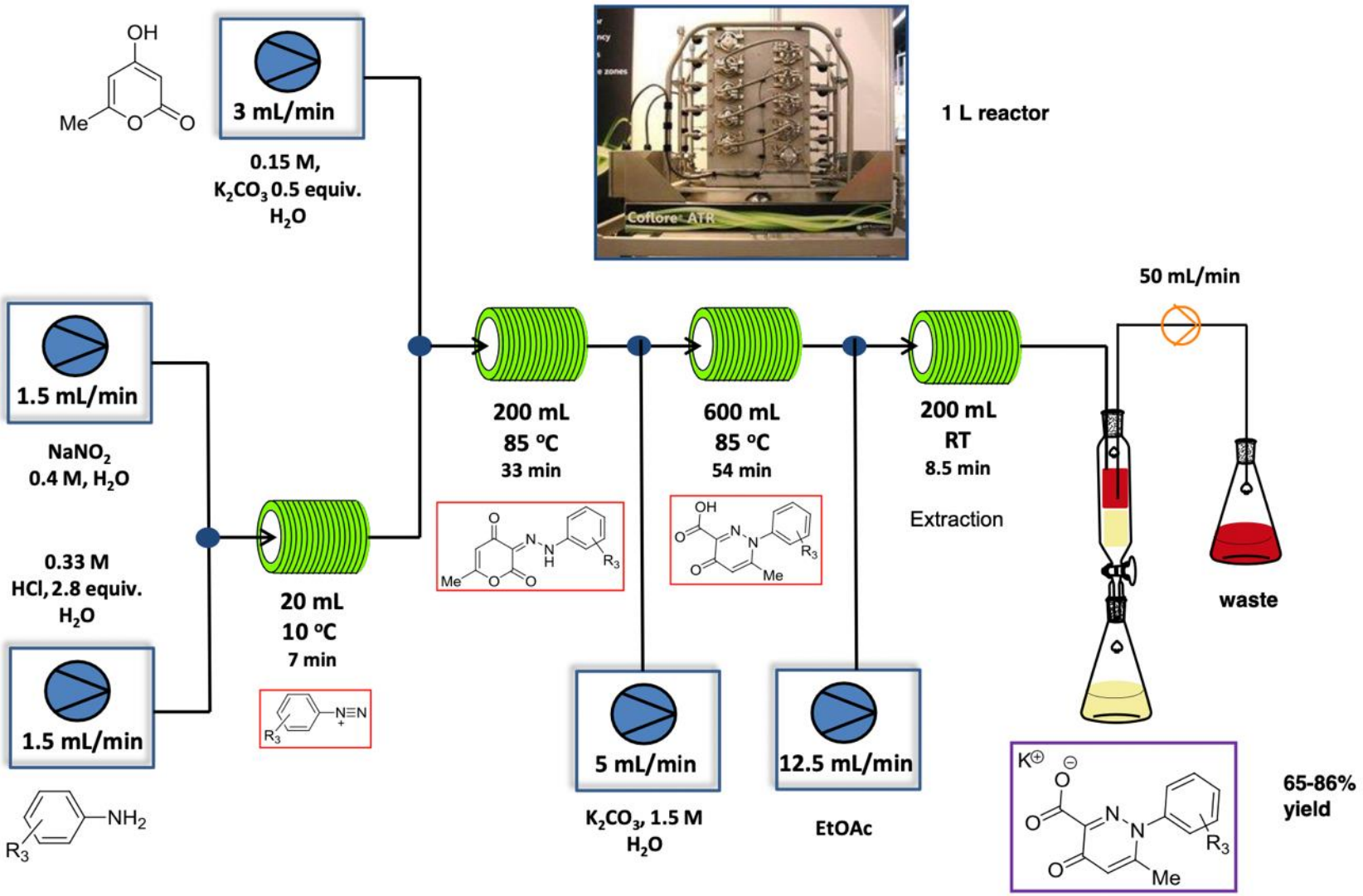


RTR: Rotating Tube Reactor





Synthesis of Pyridazine



4 step process in 1 L reactor output: 8.2 g/h (80% isolated)

Start-up (Steady state – 3RV): 5.15 h and 3.2 h shut down.

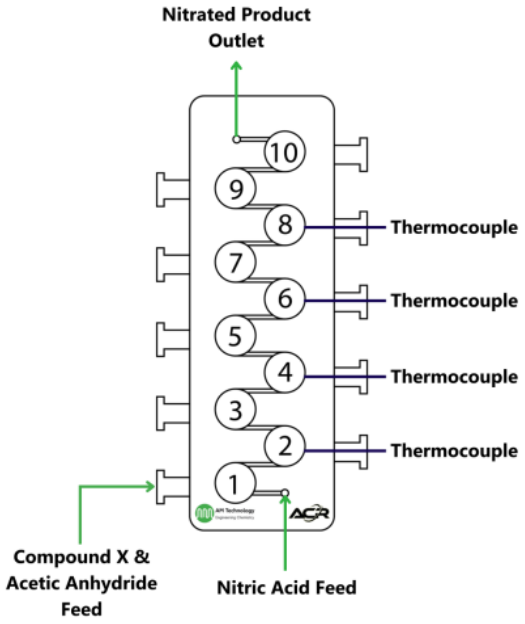
Slide: Ian R. Baxendale

Org. Process Res. Dev. **2016**, *20*, 371-375.

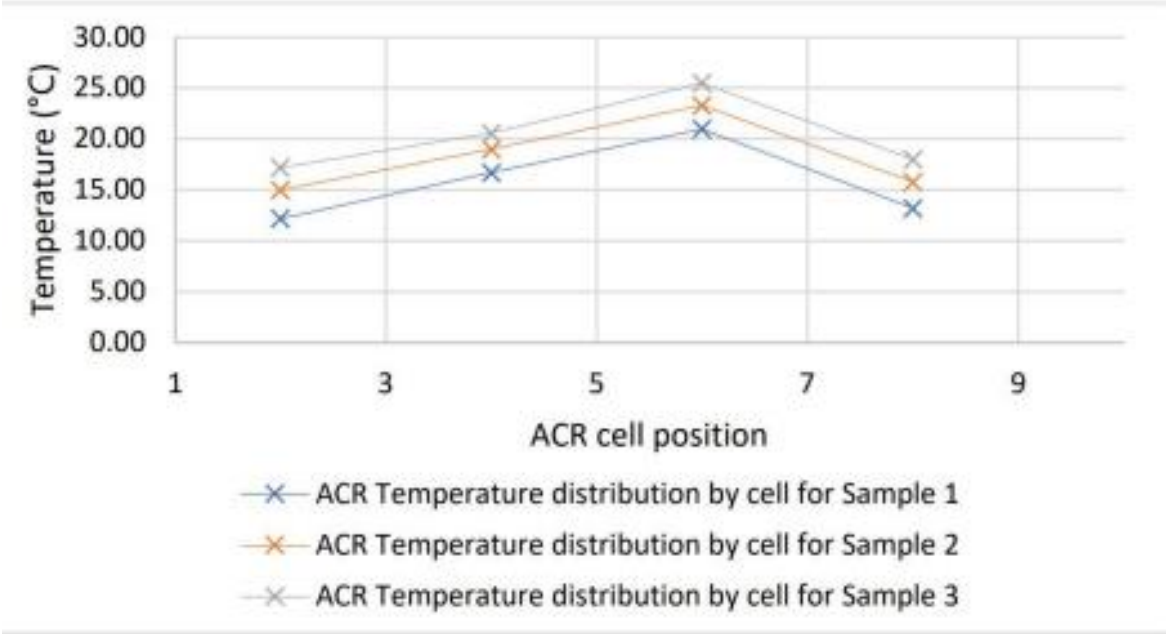
During production

AM Technology
Engineering Chemistry

Exothermic control in the Coflore® ACR



batch methods takes 6-12 hours with dropwise addition accounting for 3 hours, and at temperatures up to 80°C → **ACR 11 min RT at 25 °C**



- Calorimetric data showed the enthalpy of reaction to be -3250 J/g.
- The nitrated product is formed as a precipitate within the reactor

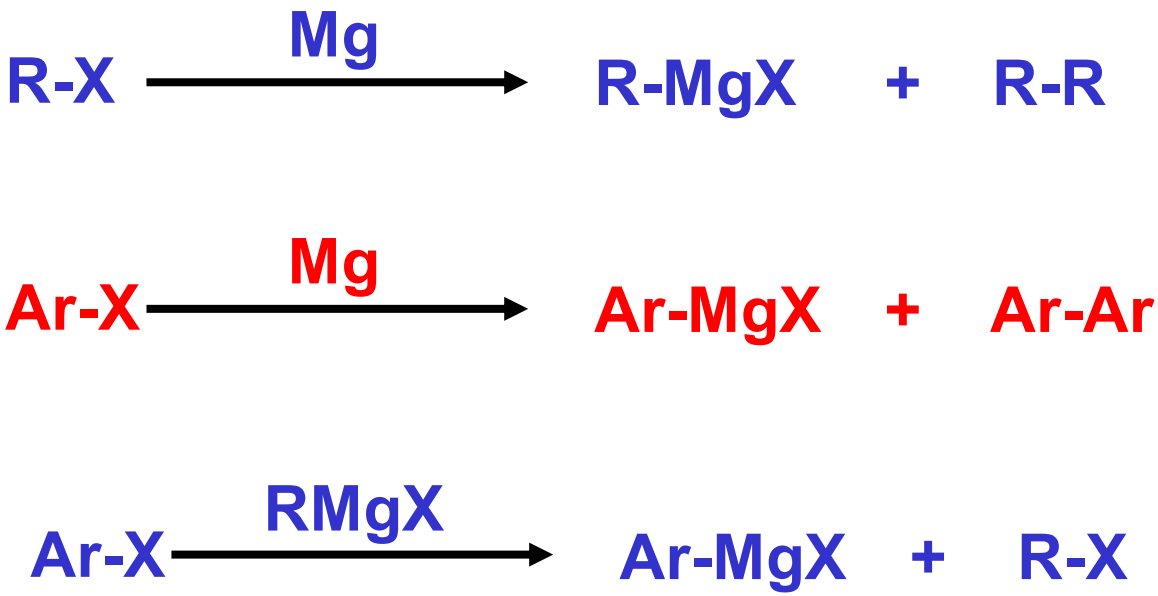
Magnesium Solids Handling in the Coflore® ATR

Figure 2: The Coflore ATR experimental set up.

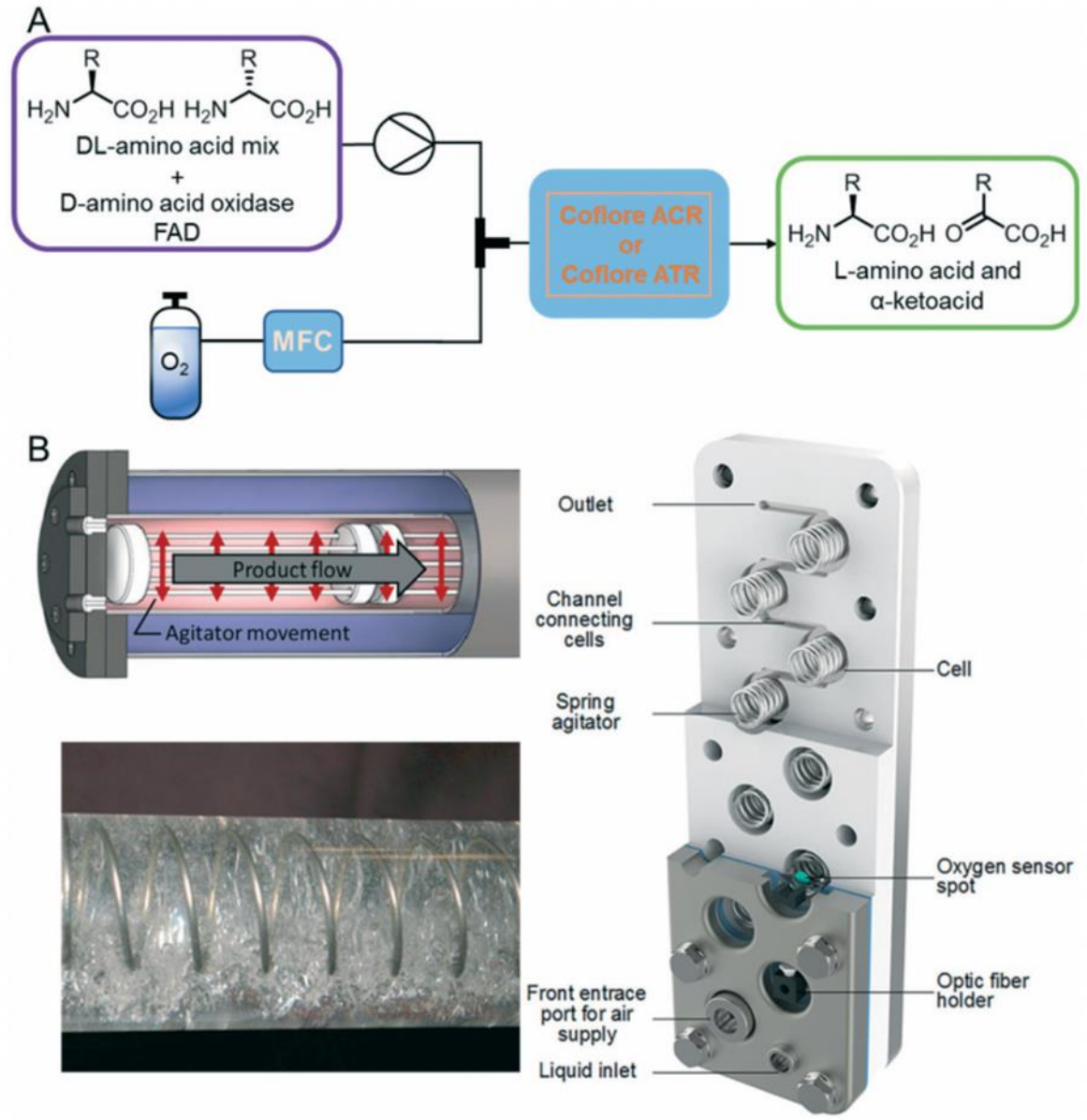
- Coflore ATR and a peristaltic pump with a 10 wt% magnesium powder in petroleum ether
- feed vessel stirrer RPM was set to 300, and the ATR agitation set to 4 Hz. The slurry flow was "top-down"
- determined the mass of magnesium at petroleum ether in the sample collection (outlet slurry weight %).

Flow Rate (mL/min)	Residence Time in the Experimental Setup (min)	Average Slurry Con-centration (wt%)	Residence Time in a 10 L ATR (min)
1000	1.6	10.7	10
700	2.3	10.9	14.4

Magnesium Solids Handling in the Coflore® ATR



Continuous Biocatalytic Resolution of DL-alanine



React. Chem. Eng., 2022, 7, 490–550

DRL

ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

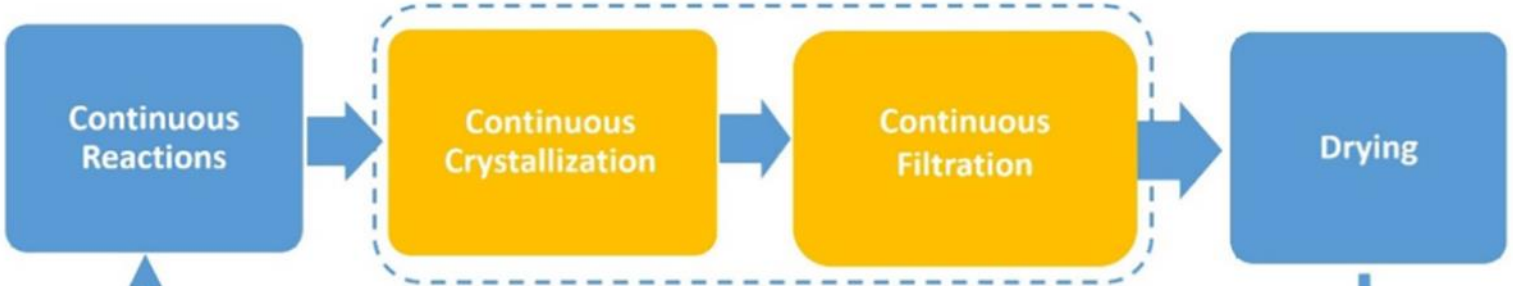
pubs.acs.org/OPRD

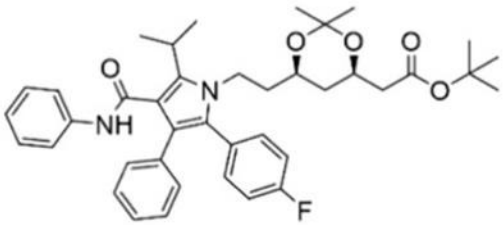
Article

Continuous Crystallization of Atorvastatin Calcium at a Multitonnage Scale Using Dynamically Mixed Flow Reactors for Target Polymorph Control

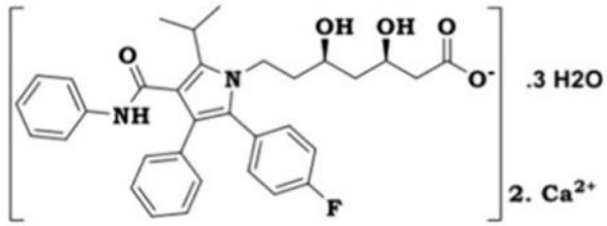
Naga Lakshmi Ramana Susarla, Dharma Jaganadha Rao Velaga, Mohammed Yakoob Sardar, Anirban Ghosh, Ravi Kumar Gorle, Suhas Jawlekar, Rajeev Rehani Budhdev, and Srividya Ramakrishnan*

DRL





Atorvastatin Related Compound –I (2)



Atorvastatin Calcium Trihydrate (1)

DRL

Agitated Cell Reactor

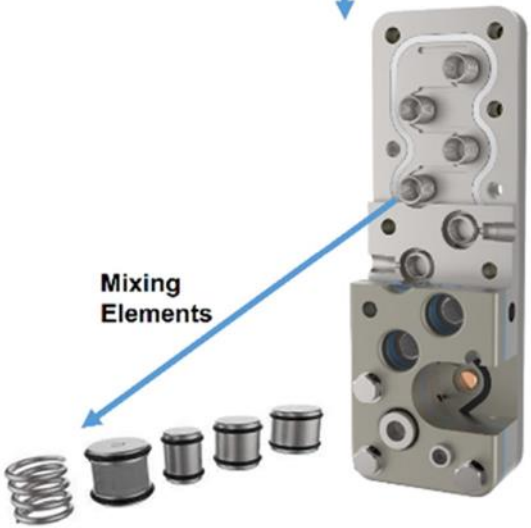
Scaleup

Agitated Tube reactor

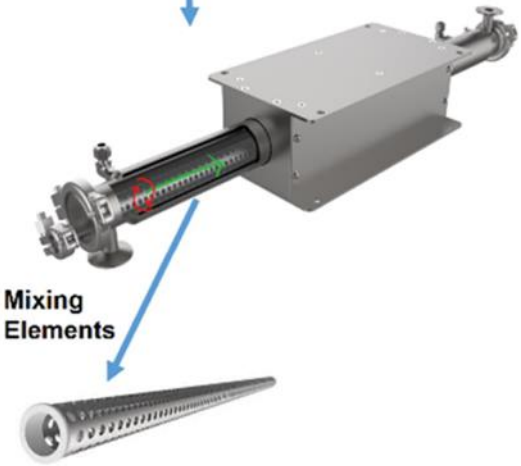
Scaleup

Rotating Tube reactor

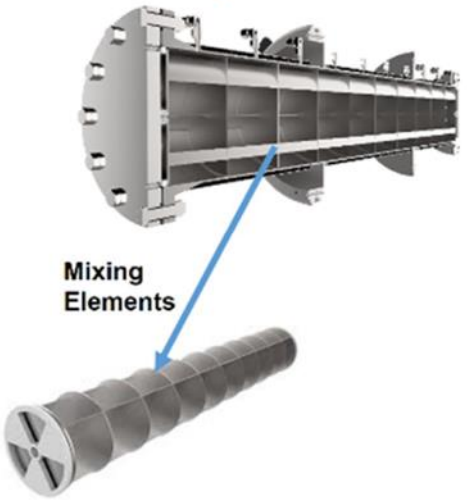
Interior View



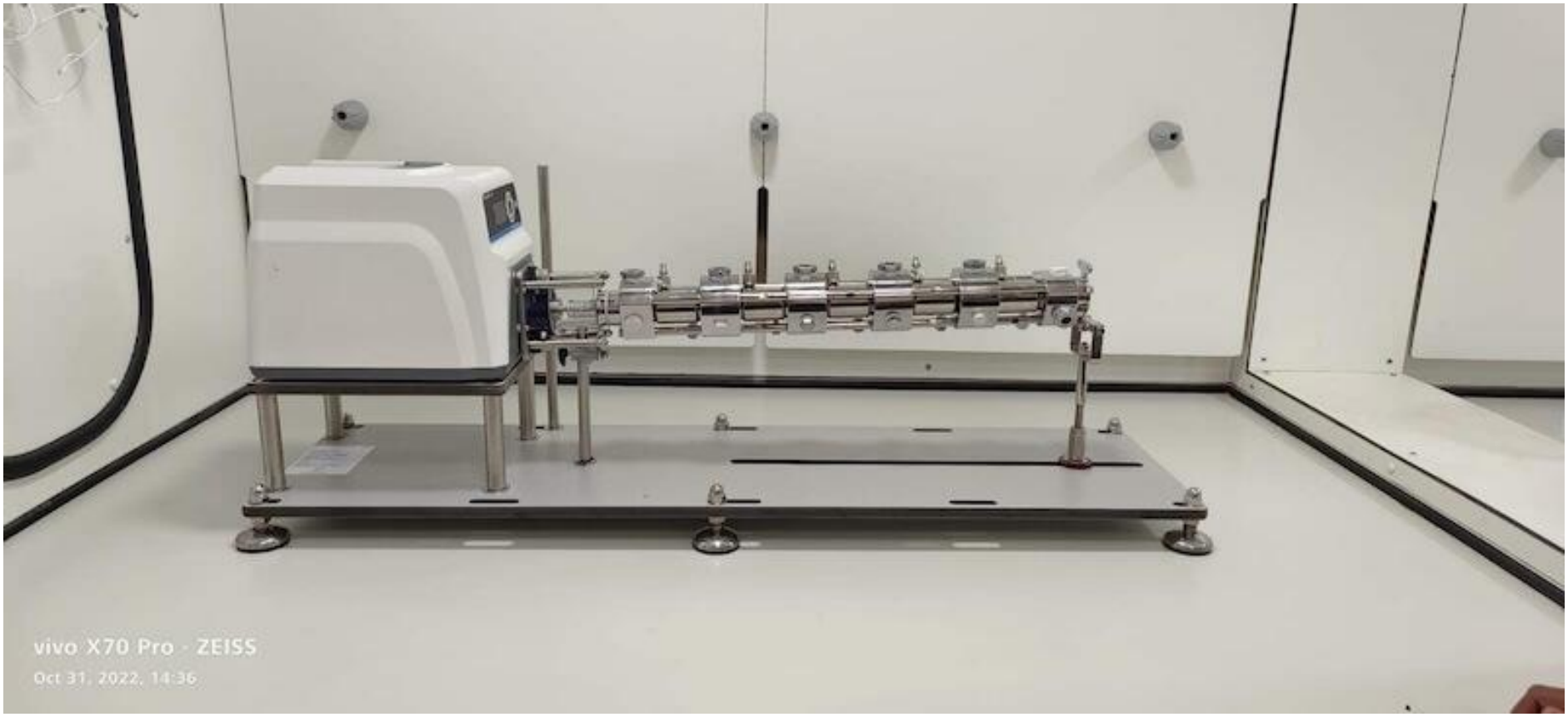
Interior View



Interior View



Autichem DART-DM



Most Economic Slurry reactor
Lab to Production

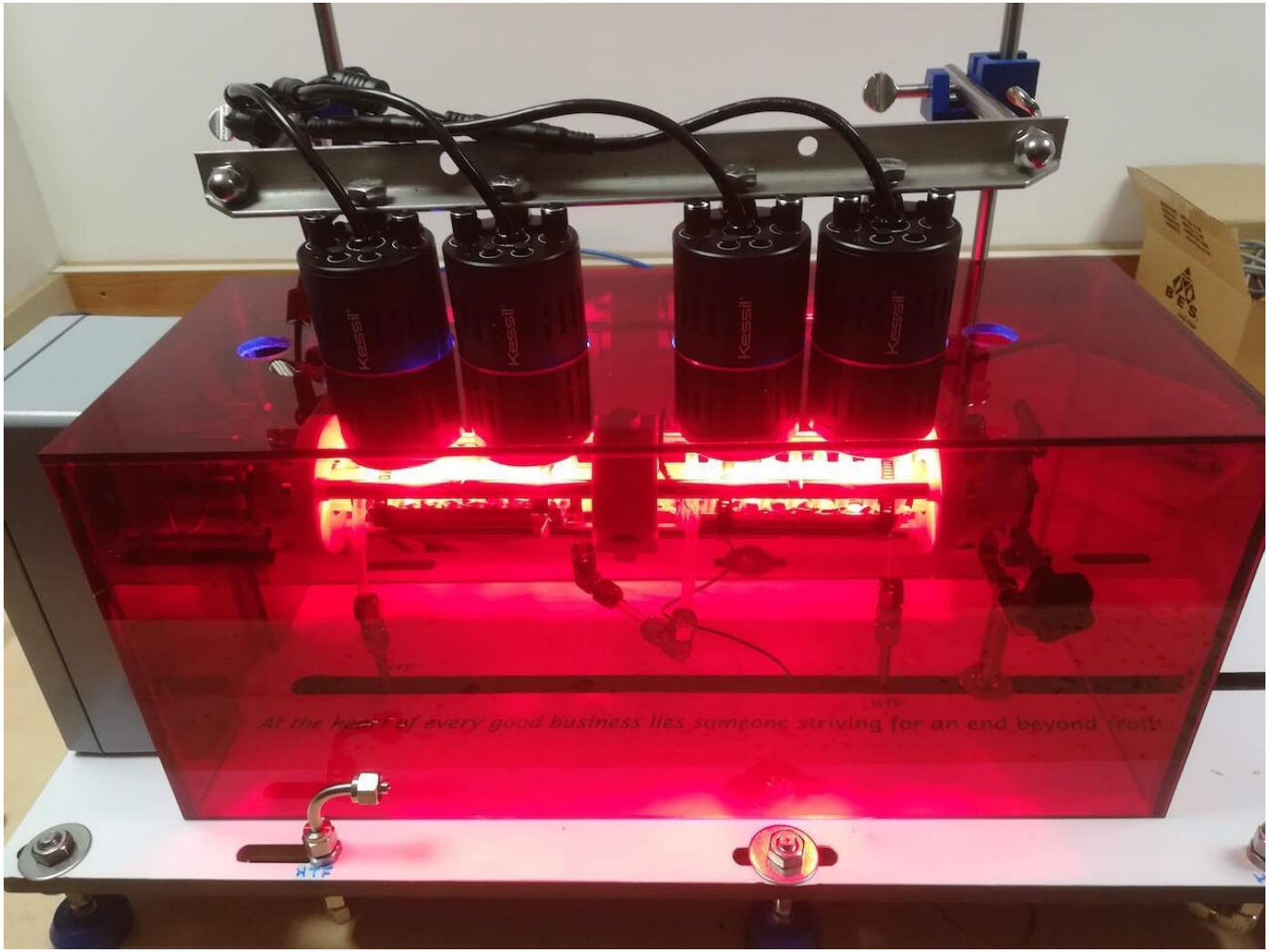
https://autichem.co.uk/

Autichem DART-DM

50 Liter

https://autichem.co.uk/

Autichem DART-DM

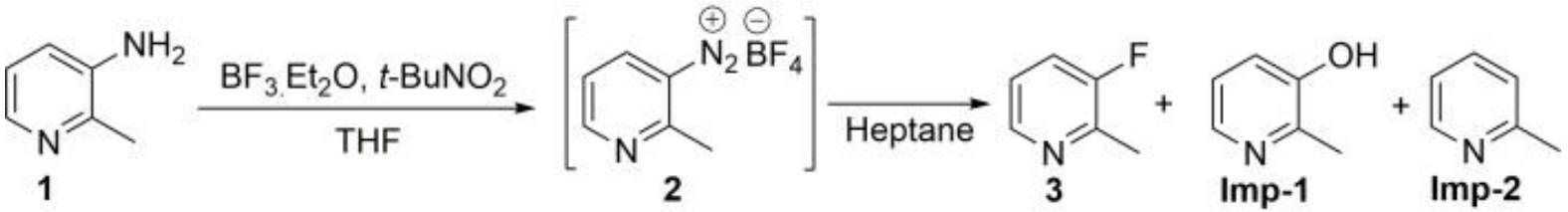


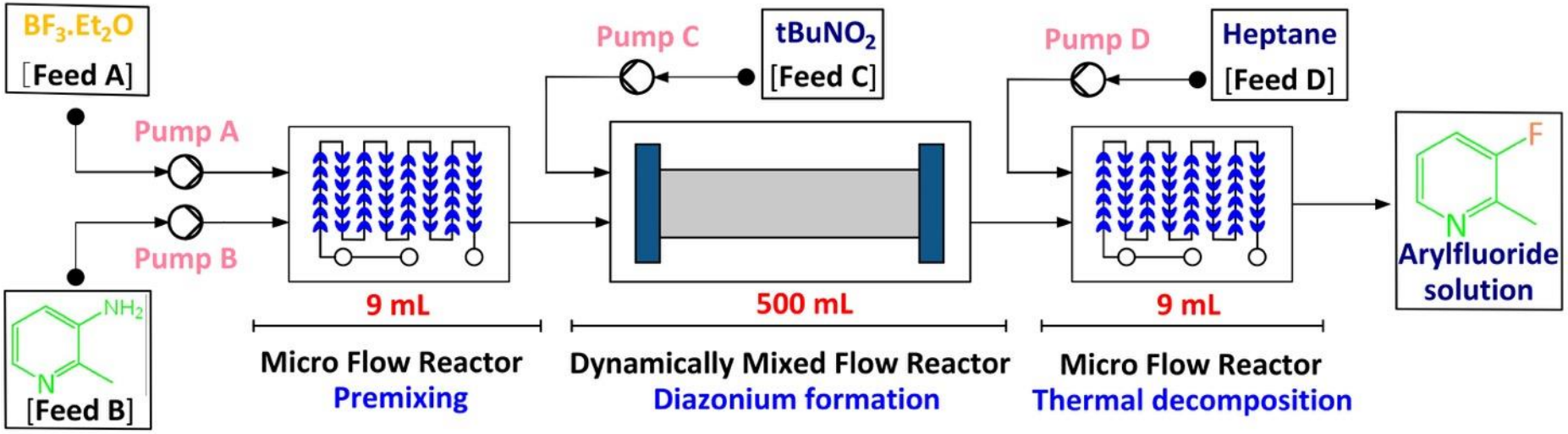
Slurry in Photo Flow

MOC: Metal, PEEK, Glass…

Autichem DART-DM

A Scalable Balz-Schiemann Reaction





Shenzhen Hwagen Pharmaceutical; Guangdong Raffles Pharmaceutical Technology

DOI:10.3791/64937

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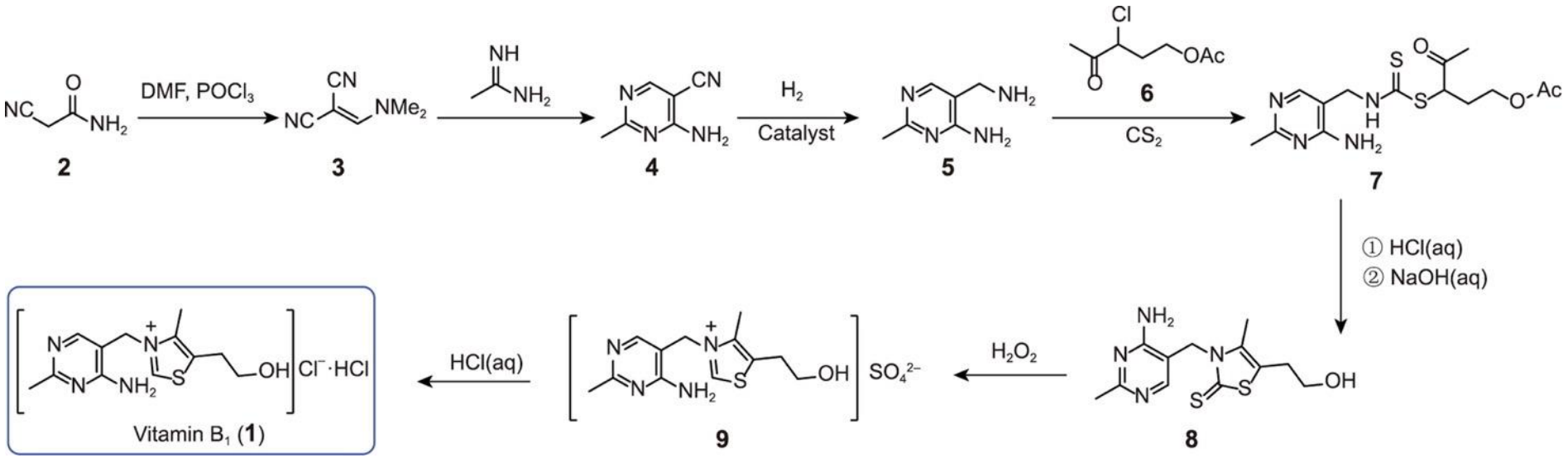
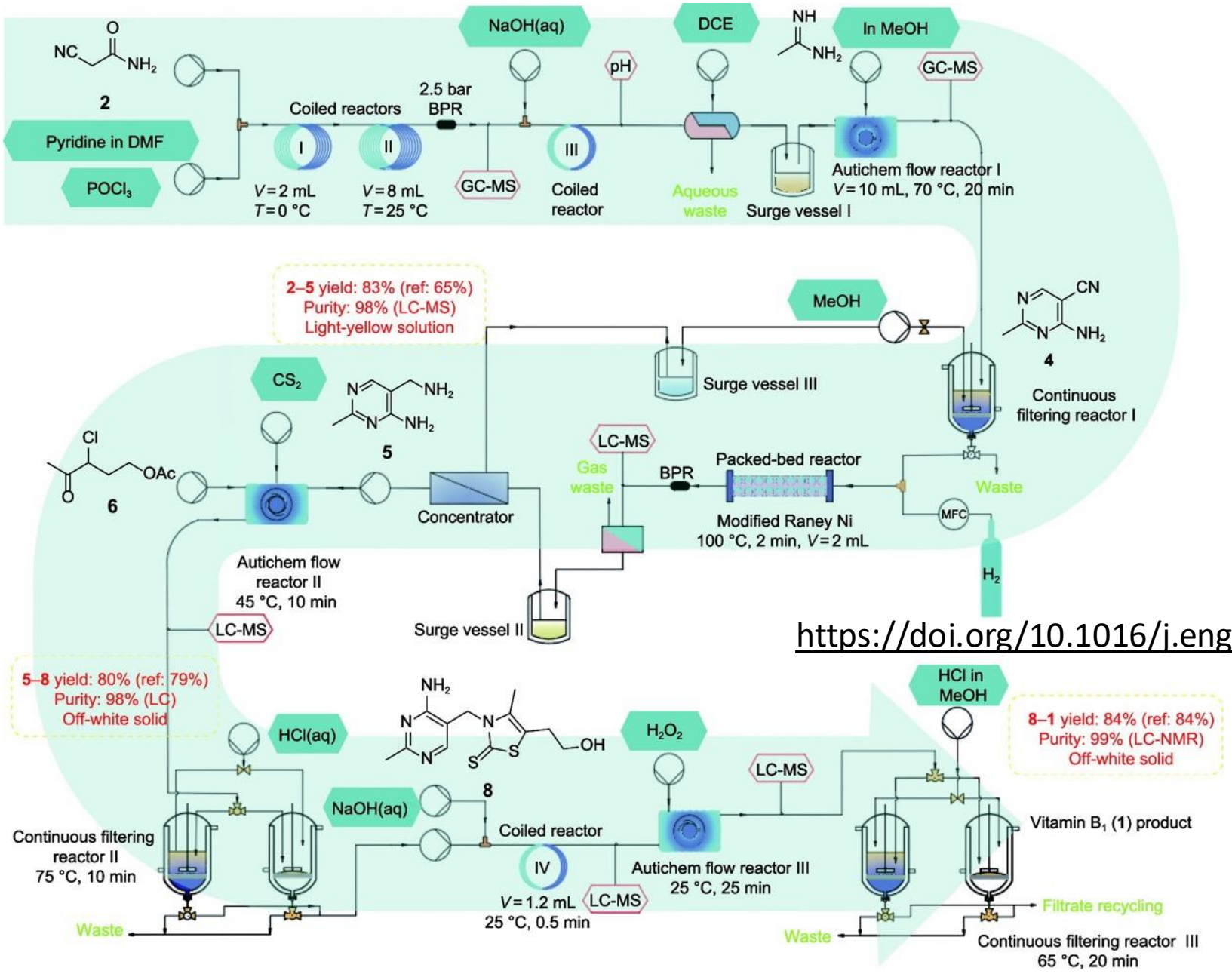
Vitamin B1: 8 Step telescopic



47.7% in 3.5 hr

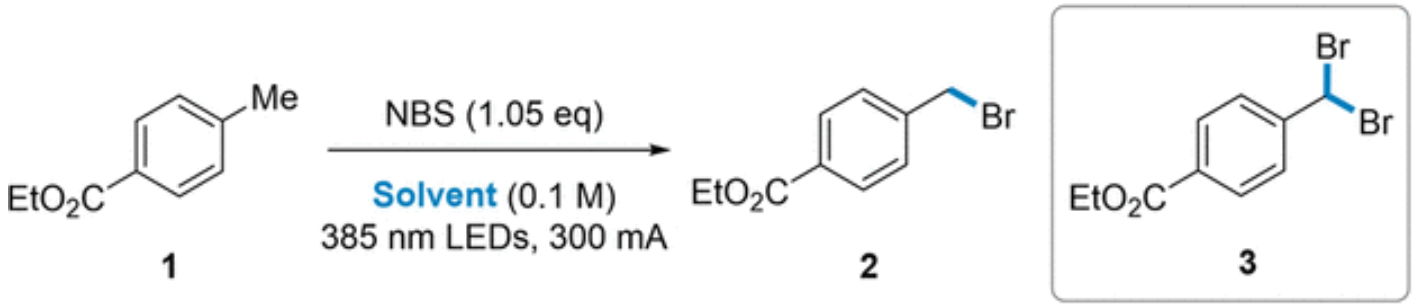
https://doi.org/10.1016/j.eng.2023.01.016

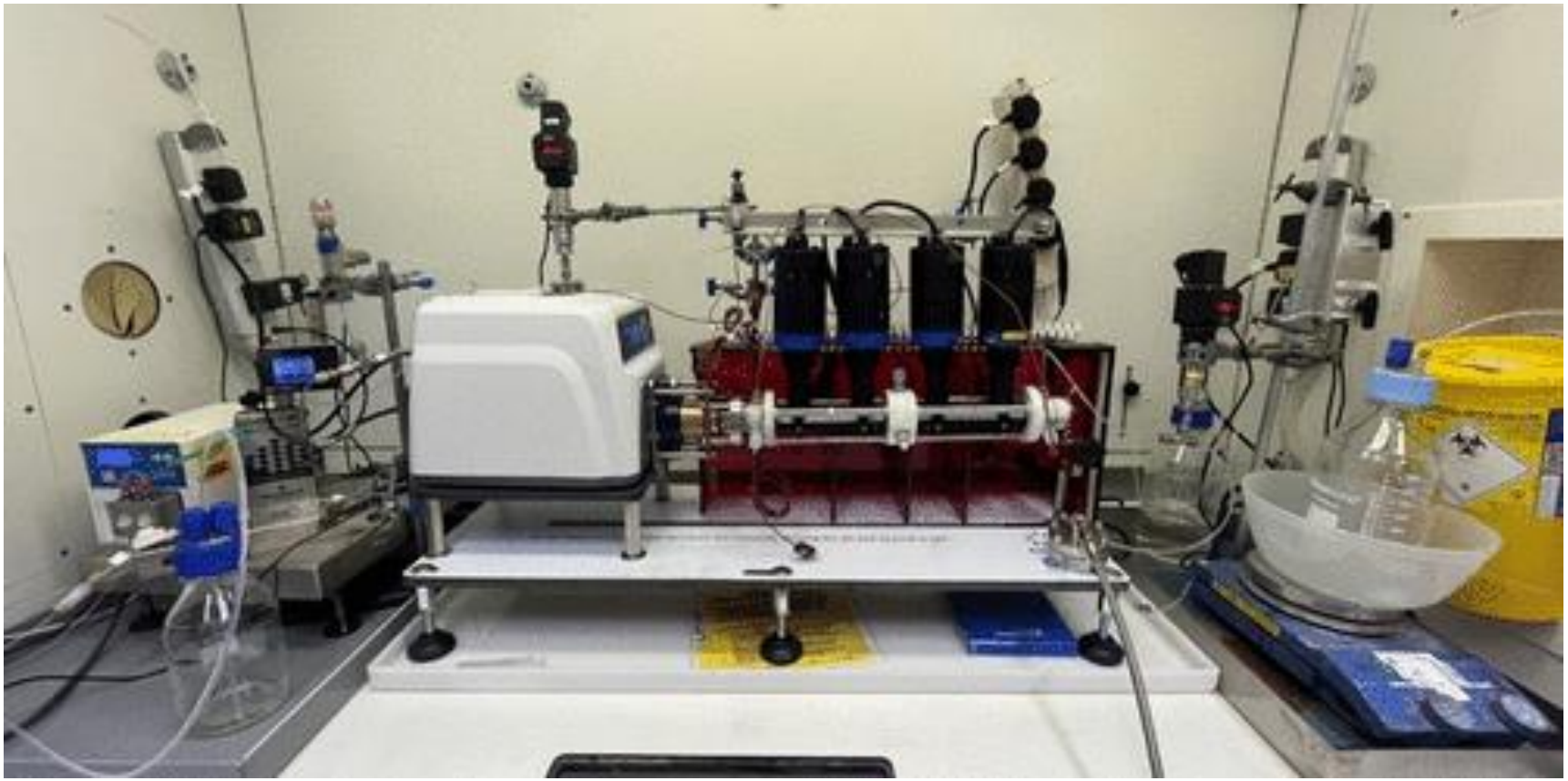
Autichem DART-DM



https://doi.org/10.1016/j.eng.2023.01.016

Autichem DART-DM





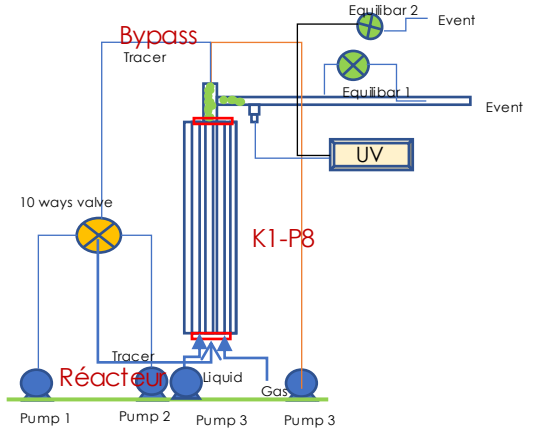
Org. Process Res. Dev. 2024, 28, 5, 1725–1733

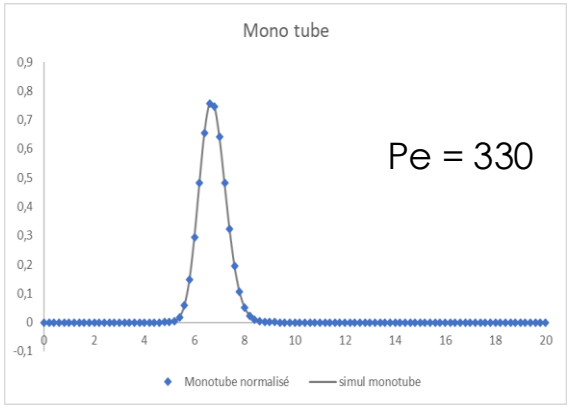
Size and capacities of KHIMOD Heat Exchanger Reactors

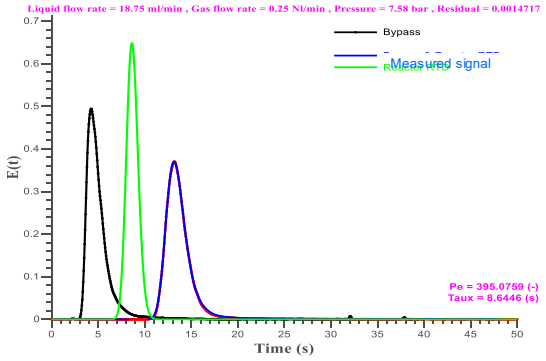
	K1	K2	K3	K4	K5
Application	Kilolab scale	Pilot & Industrial scale	Industrial scale	Industrial scale	Industrial scale
Capacity / HER *	2 to 30 t/y 0,3 to 4 kg/hour	150 t/y 18 kg/hour	350 t/y 44 k g/hour	620 t/y 78 kg/hour	1 900 t/y 240 kg/hour
Capacity for a 10 HER rack*	/	1,5 kt/y	3,5 kt/y	6,2 kt/y	19 kt/y
Inner volume / HER	0,008 to 0,1 l	0,5 l	1,2 l	2,2 l	7 l
Channel length	0,3 to 3,6 m	0,3 to 18 m	0,3 to 36 m	0,3 to 75 m	0,3 to 235 m
Number of channels	12	64	144	250	784

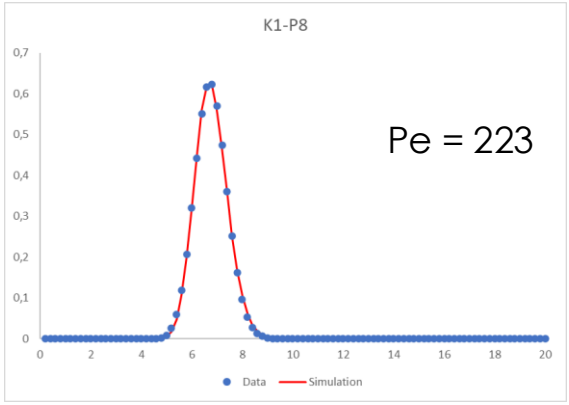
** Capacity based on a 20 s residence time, a 20% weight concentration and OEE at 90 %*

Plug flow behaviors' of a single channel vs a 8 channels reactors









$$Pe = \frac{u \cdot L}{D}$$

K2 in operation

Successful Commissioning of Multi-Product, Multi-step Flow Chemistry Plant for API's & Intermediates at CIPLA Ltd.

Project Scope: The multi-product, multi-step flow chemistry production plant was engineered to be **flexible** in terms of **products, number of process steps & process types.** The compact, small footprint system was designed to be retrofitted into an existing asset base. This results in additional flexible production capabilities within an existing facility.

Compared to the use of existing technologies, **fast process scale-up** from R&D to production drove the innovation within this project & was realised by **combining Plantrix® silicon carbide (SiC) reactors from Chemtrix BV & a Hastelloy Coflore® Agitated Tube Reactor (ATR) reactor/extractor from AM Technology.** Smooth operation of the continuous flow system was ensured by using super metering **pulse-free precise pumps from Fuji Techno.**

Why Combine Technologies?

- **Process flexibility & safety**
- **Speed of scale-up**
- **Enhanced process control *via* automation**
- **Higher production output from same facility**
- **Reduced inventory of hazardous reagents**

Cipla
Caring for Life

"This project demonstrates that multi-step flow processes can be successfully implemented within a matter of months .The system employs a small number of hardware elements which can be configured to suit a wide range of chemistries. The inherent benefits of this approach over batch methods are substantial in terms of greater safety, emissions reduction, performance, reduced plant footprint & energy costs".

Central to the success of a multi-purpose system is to combine static & active flow reactors, facilitating the performance of a series of challenging steps that often involve highly exothermic transformations, short-lived intermediates, corrosive reagents & extraction steps".

Partners: This project was a success through Partnership!

processintensification AMTechnology Fuji Techno CHEMTRIX Scalable Flow Chemistry

Anthem Biosciences

Flow Plant

Modular plant set up wherein we can set up reaction modules based on requirement

>100X scale up from lab to plant

Anthem Biosciences

Case study summary - Projects converted to Flow

Nitration
10 projects
Upto 10 ton scale

Oxidation
H_2O_2 oxidation, air oxidation, swern oxidation
5 projects
Upto 200 kg

Hydrogenation
Palladium on carbon (Reduction, Reductive amination, CBZ cleavage)
5 projects
Upto 300 kg

Acid amine coupling
3 projects
Upto 50 kg scale

Butyl lithium
2 projects (2 & 4 steps)
Upto 30 kg

Diazotization
Using t-butyl nitrite
2 projects
Upto 1 ton

Selective O-THP protection
1 project
50 kg/day

HBr/H_2O_2
1 project
30 kg/day

Isomerization
Using Palladium on Carbon
100 kg/day

Hydrolysis
3 projects
Upto 50 kg scale

Cyclisation
2 projects
Upto 30 kg

Halogenations
Proof of concept – Iodination, Bromination
2 projects
Upto 1 kg