AVT-340 Research Workshop on Preparation and Characterization of Energetic Materials

Continuous Reactor Technology for Energetic Materials Synthesis

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2-4 & 9-11 February 2021

AGENDA

- **Introduction to Flow Chemistry**
  - Flow Regimes
  - Relevant Parameters
  - Reaction Classification
  - Reaction/Reactor Selection Matrix
- **Commercial-off-the-shelf Reactors for Continuous Synthesis**
- **Continuous Crystallization and Filtration**
  - Crystallization Fundamentals
  - Discovery Tools
  - Continuous Crystallizers and Filters
- **Process Analytics Tools and Ancillary Equipment**
  - Spectroscopic Instruments
  - Pumps
  - Separators
  - Hydrogen Gas Generators
- **Summary and Additional Resources**

Continuous Reactor Technology for Energetic Materials Synthesis

Introduction to Flow Chemistry

ADVANTAGES OF CONTINUOUS SYNTHESIS

- **Safety**
  - Small scale; no headspace; no accumulation of reactive or toxic intermediates
- **Expansion of reaction space**
  - “Forbidden” or difficult reactions are feasible in flow
  - Opens novel process windows (high temperature, high pressure, increased concentration/solvent-free, conditions in the explosive or thermal runaway regimes)
- **Scalability**
  - Scale-up (numbering-up) is faster and more reliable
- **Versatility and flexibility**
  - Customizable and adjustable equipment
- **Leverage and efficiency**
  - Increase in throughput with a dramatically reduced equipment footprint
  - Increase space-time yield by process intensification (smaller, cleaner, safer, more energy efficient)
- **Robustness and stability**
  - Quality by Design (QbD) or Quality by Control (QbC)
  - Steady-state, continuous process feedback

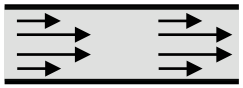
INTRODUCTION TO FLOW CHEMISTRY

Reynolds number (Re)

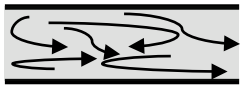
$$\mathrm{Re} = \frac{\text{inertial forces}}{\text{viscous forces}} = \frac{\rho v L}{\mu}$$

Laminar – Re < 2,300
Transient – 2,300 < Re < 4,000
Turbulent – 4,000 < Re

Laminar flow



Turbulent flow



Prandtl number (Pr)

$$\mathrm{Pr} = \frac{\text{momentum diffusivity}}{\text{thermal diffusivity}} = \frac{c_p \mu}{k}$$

Liquid metals – 0.004 < Pr < 0.030
Gasses – 0.7 < Pr < 1.0
Water –1.7 < Pr < 13.7
Light Organics – 5 < Pr < 50
Oils – 50 < Pr < 100,000

$$\beta = \frac{\text{heat generated}}{\text{heat removed}} = \frac{-r \Delta H_{rxn} d_F^2}{4 \Delta T_{ad} \kappa}$$

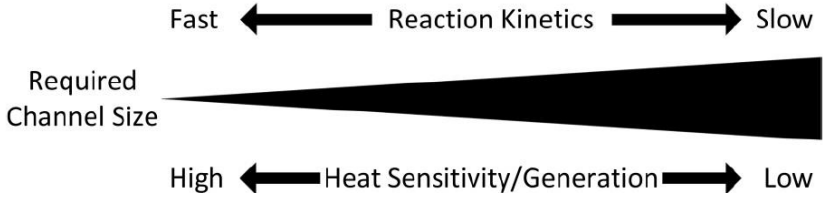
Damköhler numbers (Da)

$$\mathrm{Da_I} = \frac{k_r c^{m-1} L}{v} = \frac{\text{residence time}}{\text{reaction time}} >> 1$$

$$\mathrm{Da_{II}} = 17.4 k_r c^{m-1} \left(\frac{\nu}{\varepsilon}\right)^{1/2} = \frac{\text{mixing time}}{\text{reaction time}} << 1$$

$$\mathrm{Da_{III}} = \frac{k_r c^m \Delta H_r L}{c_p \Delta T v} = \frac{\text{reaction heat}}{\text{temperature increase}}$$

$$\mathrm{Da_{IV}} = k_r c^m \Delta H_r \frac{4 \rho d_h}{U \Delta T} = \frac{\text{rate of heat generation}}{\text{rate of heat removal}} < 0.2 \text{ to avoid hot spots}$$



Péclet Number (Pe)

$$\mathrm{Pe} = \frac{\text{advective transport}}{\text{diffusive transport}} = \frac{vL}{D}$$

Bodenstein number (Bo)

$$\mathrm{Bo} = \frac{\text{advective transport}}{\text{axial dispersion}} = \frac{vL}{D_{ax}}$$

Kockmann, N. *Chem. Eng. Technol.*, **2008**, *31*, 1188-1195
Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem. Int. Ed.*, **2011**, *50*, 7502-7519
Plouffe, P.; Macchi, A .; Roberge, D. M. *Org. Proc. Res. Dev.*, **2014**, *18*, 1286-1294.

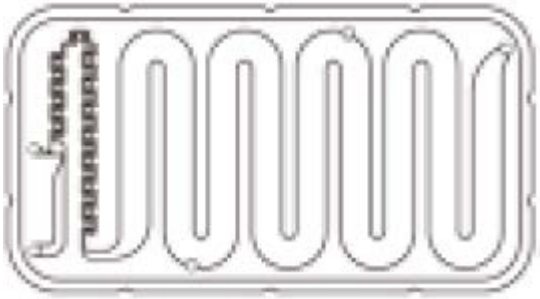
ROBERGE REACTION CLASSIFICATION SCHEME

- **Type A reactions**
  - Very fast, typically < 1 s
  - Controlled by diffusion and mixing
  - Improved mixing/heat exchange may increase yield
- **Type B reactions**
  - Rapid reactions, typically 10 s to 30 min
  - Kinetically controlled – rate may be accelerated by increased temperature, pressure, or concentration
- **Type C reactions**
  - Slow reactions, > 30 min to hours
  - Involve potential hazards such as autocatalysis or thermal accumulation
  - Kinetics make reactions suitable for batch, but continuous offers improved safety or product quality
- **Type D reactions**
  - Reactions that are not A, B, or C
  - Should be intensified to at least Type C to be done in flow

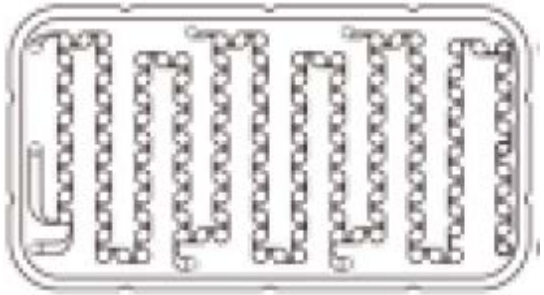
Plouffe, P.; Macchi, A .; Roberge, D. M. *Org. Proc. Res. Dev.,* **2014**, *18*, 1286-1294.

REACTION/REACTOR MATRIX

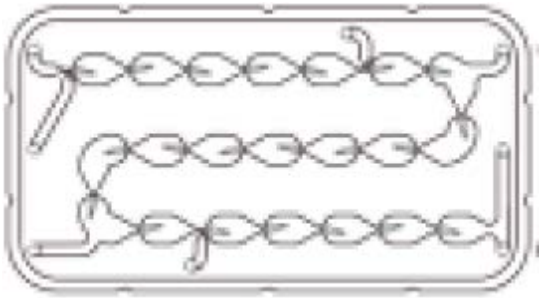
Rates/Phases	Homogeneous	Liquid-Liquid	Gas-Liquid	Solid-Liquid
Type A	Plate SZ/TG	Plate LL	Plate LL	CSTR/ Packed Bed
Type B	Plate SZ/TG Coil	Plate LL Coil pulsated	Plate LL Coil pressure	CSTR/ Packed Bed
Type C	Static mixer Coil	State mixer Coil pulsated	Static mixer Coil pressure	Coil pulsated



SZ (serpentine)



TG (tangential)



LL (liquid-liquid)

Plouffe, P.; Macchi, A .; Roberge, D. M. *Org. Proc. Res. Dev.,* **2014**, *18*, 1286-1294.

Continuous Reactor Technology for Energetic Materials Synthesis

Commercial-Off-The-Shelf Reactors

LABORATORY REACTORS

Uniqsis FlowSyn

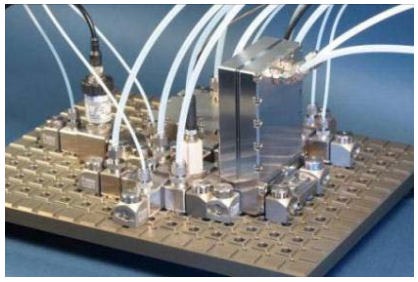
www.uniqsis.com

- All PTFE or PTFE–Hastelloy construction available
  - Temperature: –70 to +260 °C; Pressure: 100 bar
- Data Logger and FlowControl™ Software
  - Plan experiments; Monitor and log temperature, pressure, and flow rate
  - Wireless or remote control over LAN
- Up to 3 temperature zones and 3 reagent inputs available
- Available LED Photoreactor

Vapourtec RS-400

- PFA or Hastelloy construction available
  - Temperature: –70 to +250 °C; Pressure: 50 bar
- Flow Commander™ Software
  - Plan experiments; Monitor and log temperature, pressure, and flow rate
  - API Package can be driven by .NET Software Framework
- Up to 4 reactors and 4 reagent inputs available
- Available Photoreactor (Hg lamp or LED) and Electrochemical reactor

Ehrfeld Modular MicroReaction System (MMRS)



- Hastelloy construction available
  - Temperature: –20 to +200 °C (–100 to +600 °C); Pressure: 100 bar
- Integrates with LabManager® automation system from HiTec Zang
  - Consists of a control unit and LabVision® visualization and automation software
- More than 60 different microreaction modules
- Available Photoreactor (UV lamp or LED)

LABORATORY REACTORS

Uniqsis FlowSyn

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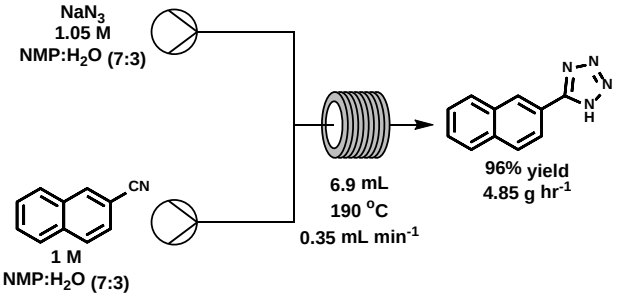
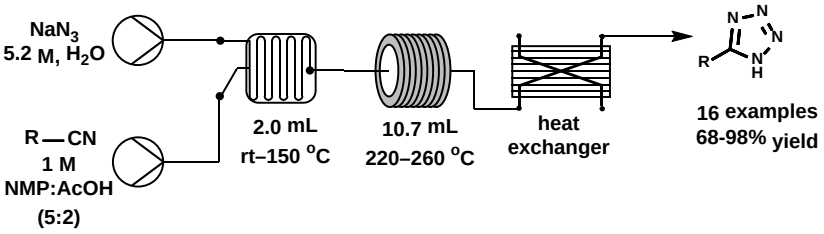
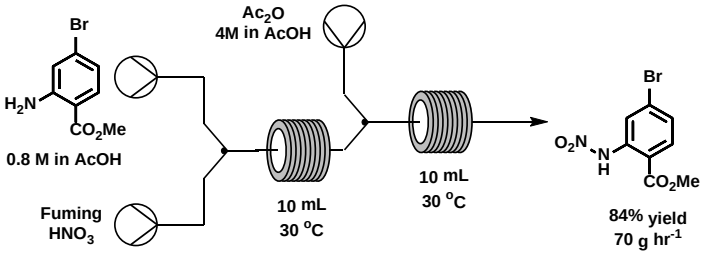


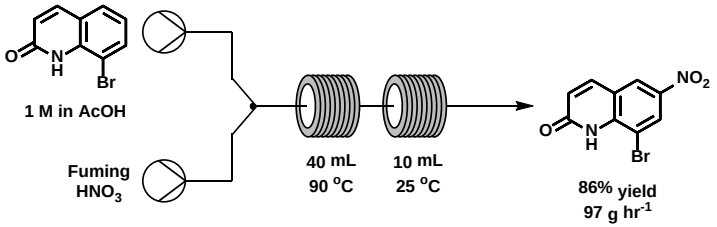
Palde, P. B.; Jamison, T. F. Angew. Chem. Int. Ed., **2011**, *50*, 3525-3528.



Gutman, B. et al. Angew. Chem. Int. Ed., **2010**, *49*, 7101-7105.

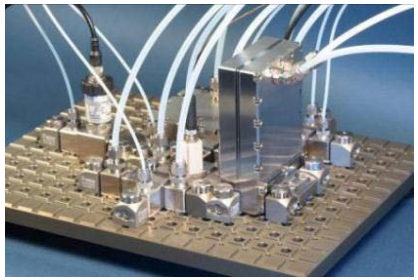
Vapourtec RS-400

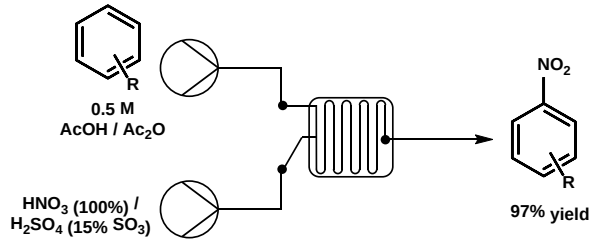


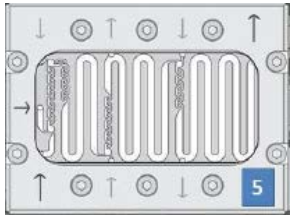


Brocklehurst, C. E.; Lehmann, H.; La Vecchia, L. *Org. Process Res. Dev.*, **2011**, *15*, 1447-1453.

Ehrfeld Modular MicroReaction System (MMRS)







LL-Mixer 0.24 mL internal volume

Köckinger, M. et al. *Org. Process Res. Dev.*, **2020**, *24*, 2217-2227.
Sagmeister, P. et al., *React. Chem. Eng.*, **2020**, *5*, 677-684.

SCALABLE REACTORS

Corning Advanced-Flow™ Reactors

- Borosilicate glass or SiC (G1 and larger) construction available
  - Temperature: –60 to +200 °C; Pressure: 18 barg
  - Metal-free system for high chemical durability
- Integrated thermostat; plug and play system with data monitoring
- Lab Photo Reactor Option
  - Tunable LED source with 6 different wavelengths; wireless control

Chemtrix Labtrix® S1 and Protrix®

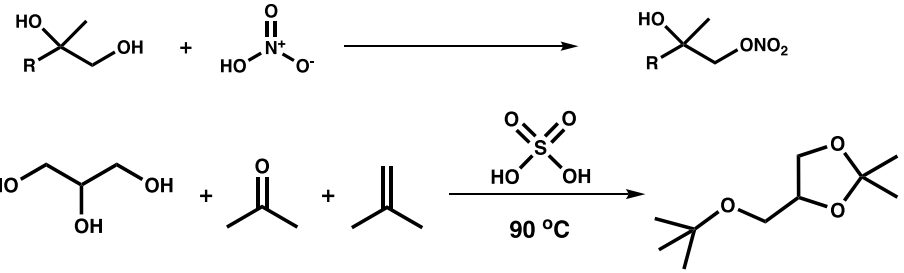
- Inert wetted materials:
  - Labtrix® S1: PTFE, ETFE, FFKM, Glass
  - Protrix®: PTFE, FFKM, SiC
  - Temperature: –20 to +195 °C; Pressure: 20 bar
  - Volume: 1 to 19.5 µL (Labtrix® S1); 1 to 13.5 mL (Protrix®)
- Dedicated software for automated data logging and sample collection
- Protrix® processes can be directly scaled to production (Plantrix®)

AM Technology Coflore® ACR

- Hastelloy reactor block; Hastelloy or ceramic agitators
  - Temperature: –40 to +140 °C; Pressure: 10 bar
- ACR cell block has 10 reaction cells connected via interstage channels
  - Sample points, addition points, & temp measurement can be added to any reaction cell
- Agitating platform provides horizontal agitation to reactor block for mixing
- Temperature data & agitation rates can be accessed by USB or LAN

SCALABLE REACTORS

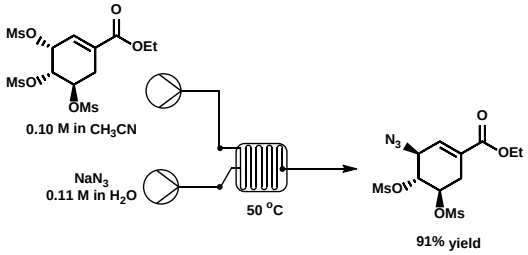
Corning Advanced-Flow™ Reactors



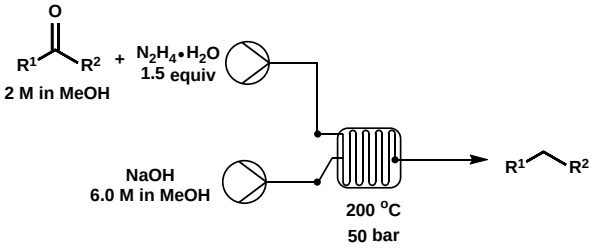
85% yield
>99% by GC

Braune, S. *et al. Chemistry Today*, **2008**, *26(5)*, 1-4.
Monbaliu, J-C. M. *et al*. *Bioresource Technology*, **2011**, *102*, 9304-9307.

Chemtrix Labtrix® S1 and Protrix®

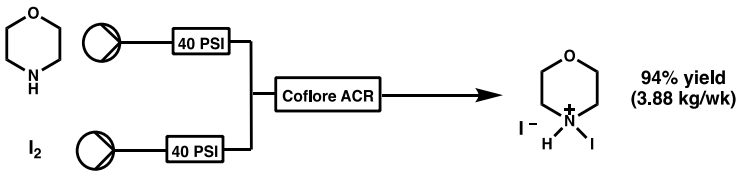


Sagandira, C. R.; Watts, P. *Beilstein J. Org. Chem.*, **2019**, *15*, 2577-2589.

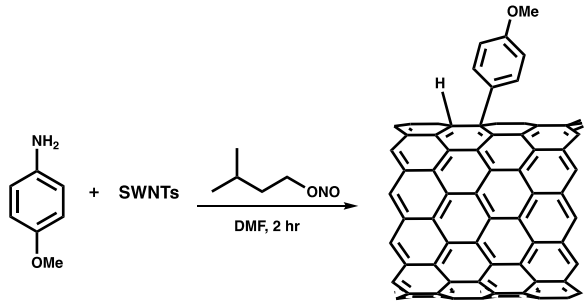


Znidar, D. *et al. Org. Process Res. Dev.*, **2019**, *23*, 2445-2455.

AM Technology Coflore® ACR



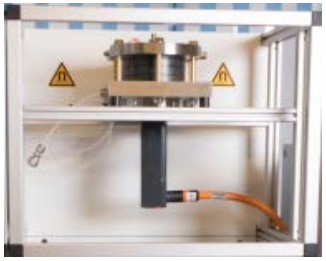
Browne, D. L.; Deadman, B. J.; Ashe, R.; Baxendale, I. R.; Ley, S. V. *Org. Process Res. Dev.*, **2011**, *15*, 693-697.



Oger, N.; Le Grognec, E.; Felpin, F-X. *Org. Chem. Front.*, **2015**, *2*, 590-614.

SPINNING DISC REACTORS

Flowid SpinPro R10



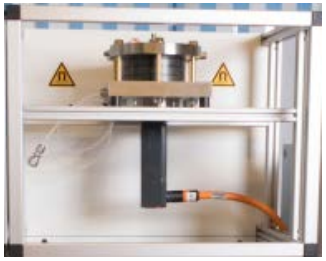
- SiC Spinning Disc Reactor
  - Three-stage reactor; 19 mL total volume
  - Temperature: –20 to +160 ºC; Pressure: 10 bar
- Discs can be mechanically or chemically modified
- Suitable for precipitations and for controlled emulsification
- Pilot (R300) and production (R1000) scale units available

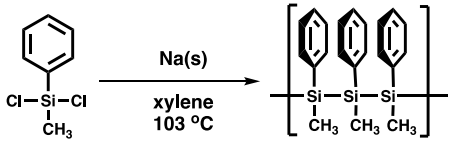
KinetiChem Synthetron™

- Hastelloy C-22 surfaces; inert fluoropolymer seals
  - 10 µL to 1.3 mL lab scale spinning disc reactor
  - Temperature: –40 to +150 ºC; Pressure: 10 bar
- 1,000 W motor; speed up to 14,000 RPM
- TouchScreen Allen Bradley Micro800 series controller/data logger
  - 4 x K-type thermocouple collection ports
  - 2 x 4-20 mA pressure transmitters

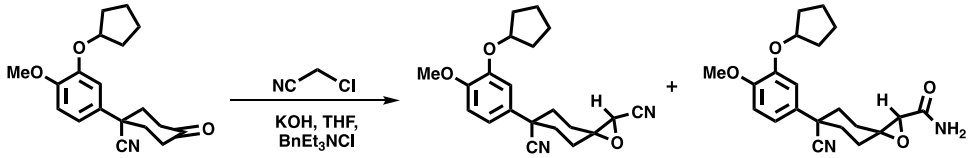
SPINNING DISC REACTORS

Flowid SpinPro R10



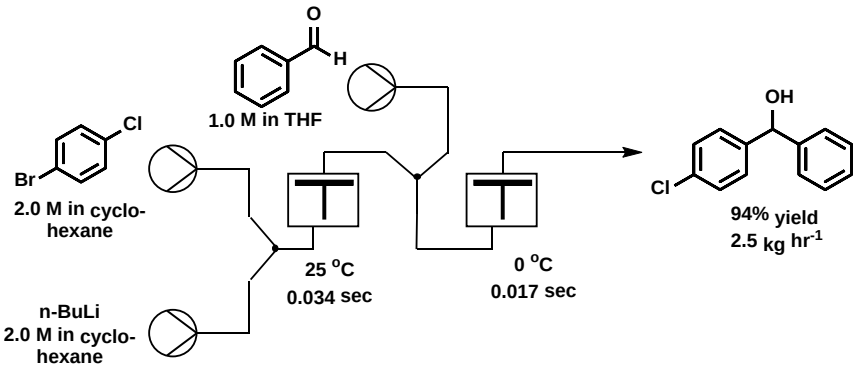


Hees, M.; Georgi, U.; Bachus, H.; Muller, K-S. US Patent Office US 2018/0346655, December 6, 2018



Brechtelsbauer, C. M. H.; Oxley, P. Process for epoxidising substituted cyclohexanones. European Patent Office EP 1 206 640 B1, February 4, 2003

KinetiChem Synthetron™

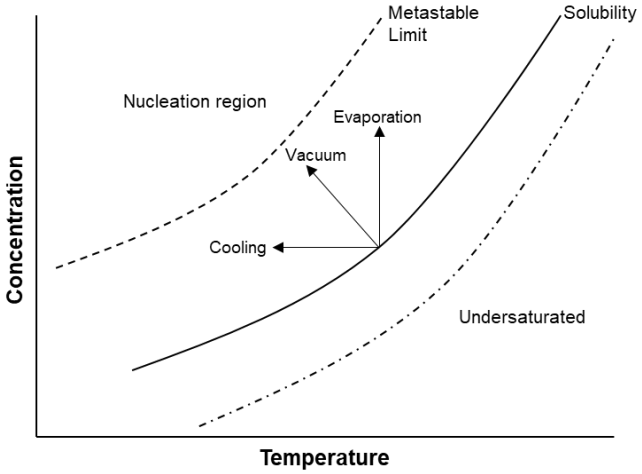


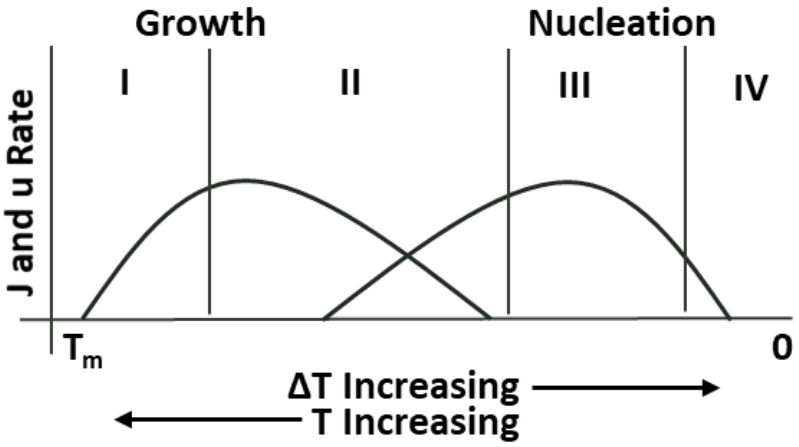
Slocum, D. W. *et al., Tetrahedron Lett.*, **2010**, *51*, 4793-4796.

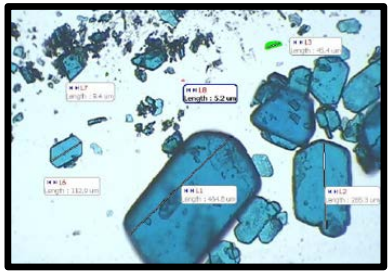
Continuous Reactor Technology for Energetic Materials Synthesis

Continuous Crystallization

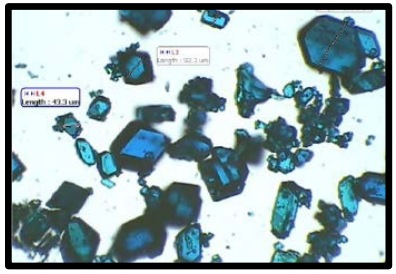
CRYSTALLIZATION FUNDAMENTALS







Stirred Tank



COBC

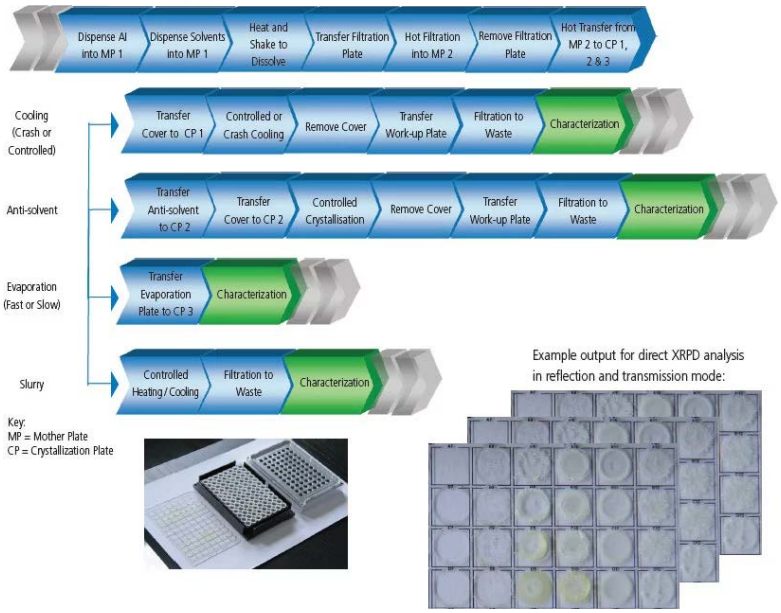
- **Flow crystallizers enable locating the operating curve to optimize**
  - Crystal size distribution
  - Shape
  - Polymorph
  - Purity

Ni, X.; Liao, A. *Crystal Growth & Design*, **2008**, *8*, 2875-2881.

CHEMSPEED SWING CRYSTAL

SWING CRYSTAL will perform crystallization, salt, polymorph, and solubility screening workflows

- **Crystallization MTP**
  - 24, 48, 96 well plate
  - Detachable glass bottom
  - Glass plate can be placed directly on XRPD
- **Filtration Plate**
  - 24, 48, 96 tips with semi-disposable filters
  - Heated filtration of process fluid
  - Simultaneous filtration of 24, 48, 96 wells
- **Evaporation Plate**
  - 24, 48, 96 tips
  - Tips standing above liquid level for controlled evaporation of solvent
- **Work-up Plate**
  - 24, 48, 96 tips
  - For filtration to waste after crystallization

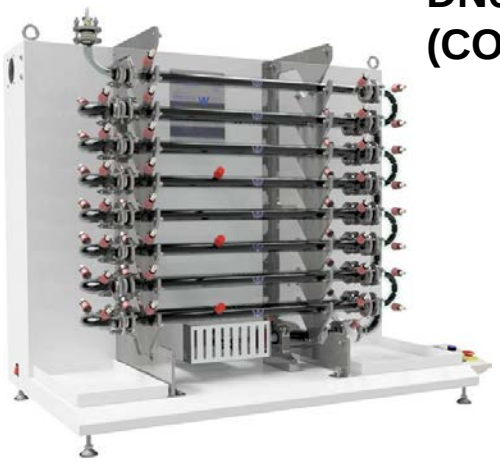


Cui, P., McMahon, D. P., Spackman, P. R., Alston, B. M., Little, M. A., Day, G. M., Cooper, A. I.,, *Chem.Sci.*, 2019, *10,* 9988-9997.

NITECH® SOLUTIONS

DN25 Oscillatory Baffled Reactor (OBR)

- Borosilicate glass vessel; 25 mm diameter; 110 mL internal volume
- Temperature: –20 to +120 ºC; Pressure: ambient
- Oscillator Frequency: 0.1 to 3 Hz in 0.1 Hz increments
- Oscillator Stroke: 5 to 40 mm in 1 mm increments
- May be configured for batch, semi continuous, or continuous operation
- Optimized OBR parameters may be used for COBC

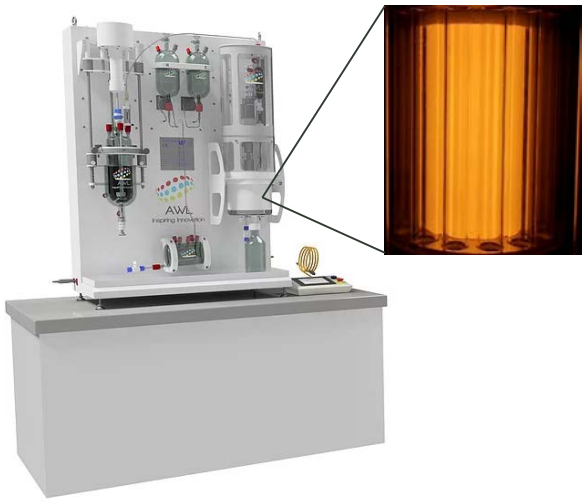


DN6/DN15 Continuous Oscillatory Baffled Crystallizer/Reactor (COBC/R)

- Glass (DN6/DN15) or Hastelloy (DN15); 200 mL (DN6)/1.25 L to 4.5 L (DN15) internal volume
- Temperature: 0 to +100 ºC (DN6); –20 to +150 ºC (DN15)
- Pressure: 0 to 3 bar (DN6); 0 to 10 bar (DN15)
- Oscillator Frequency: 0.1 to 6 Hz (DN6); 0.1 to 3 Hz (DN15)
- Oscillator Stroke: 2 to 25 mm (DN6); 11 to 68 mm (DN15)
- ATEX compliant DN15 models available

Peña, R.; Olivia, J. A.; Burcham, C. L.; Jarmer, D. J.; Nagy, Z. K. *Cryst. Growth Des.*, **2017**, *17*, 4776-4784.
Kacker, R.; Maaβ, S.; Emmerich, J.; Kramer, H. AIchE J., **2018**, *64*, 2450-2461.

ALCONBURY WESTON CCF50 AND CCF20-LITE CONTINUOUS CAROUSEL FILTER



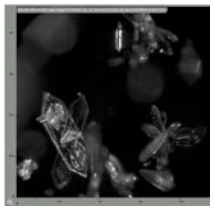
- **CCF50 For Hazardous Locations:**
  - Meets DOE Standard 1212 for Energetic Materials
  - No/Minimal particle shear
  - Up to three wash solvent reservoirs
  - 1 moving part
  - 50 mm ports – 40 g of material per port
  - Entry-to-exit time typically 10 to 15 minutes
  - Cake wetted to set parameters before discharge
  - Optional dryer
    - Dry gas fed to mass spec to monitor solvent content

- **CCF20-Lite Features:**
  - New product provides CCF20 functionality w/o ancillaries
  - Auto transfer function from external reactor/crystallizer
  - Automated filtration and wash cycle
  - Optional N_2 blanket system
  - Optional cooling vessel for wash solvent

Continuous Reactor Technology for Energetic Materials Synthesis

Process Analytics Tools and Ancillary Equipment

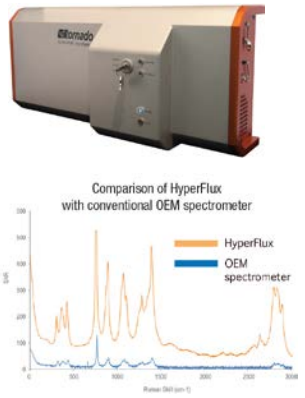
BLAZE METRICS™ AND TORNADO SPECTRAL SYSTEMS



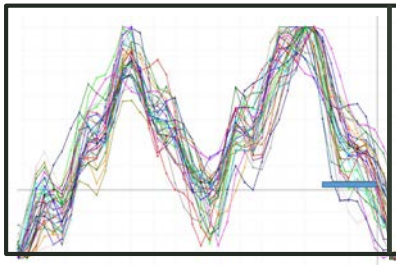
One Probe with Multiple Integrated Technologies – Simultaneous Acquisition:

- **Microscopy:** high contrast, high resolution, highest dynamic range for understanding single dispersed phase and multiple phase, multiple component particle systems
- **High Dynamic Range Turbidity (HDR):** dynamic range measuring from low to extremely high dispersed phase concentrations; can track change at nano or micron scale, measure optical transitions in liquid and/or solid phase, operate in translucent to black solutions
- **Advanced Chord Length (A-CLD):** removes flow speed artifacts and reduces multiple other artifacts of scanning tools; track changes in particle size, count, and shape
- **Particle Focused Raman (PFR):** can dramatically increase Raman signal captured from dispersed phase particles; find and track polymorphs, solvates, hydrates, impurities; differentiate multiple component systems.
- **Immersed Probe Tip Material:** Hastelloy 22, 276, SS, or custom
- **Window Materials:** Sapphire, Kalrez, Nickel, and Gold plate
- **Temp:** -10 to 100 ^{o}C (-10 ^{o}C requires N_2 purge)
- **Pressure:** 6 bar (standard); 22 bar (optional)

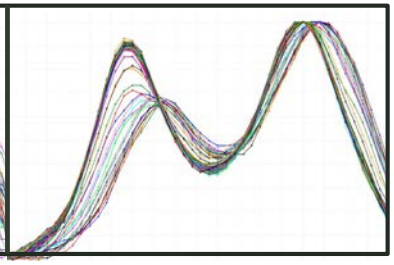
- **HyperFlux™ Pro Plus Raman**
  - 200–3300 cm^{-1} optical range
  - Laser Power: 20 mW to 495 mW (ATEX compliant)
  - Excitation wavelength: 785 nm



Ball Probe w/Tornado (pre-processed)



Blaze PFR Probe w/Tornado (raw data)



MAGRITEK BENCHTOP NMR

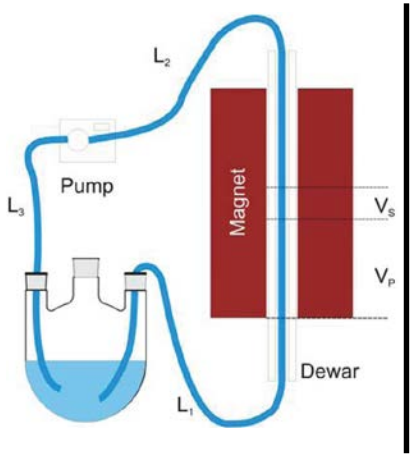
- **Available Pulse Sequences**

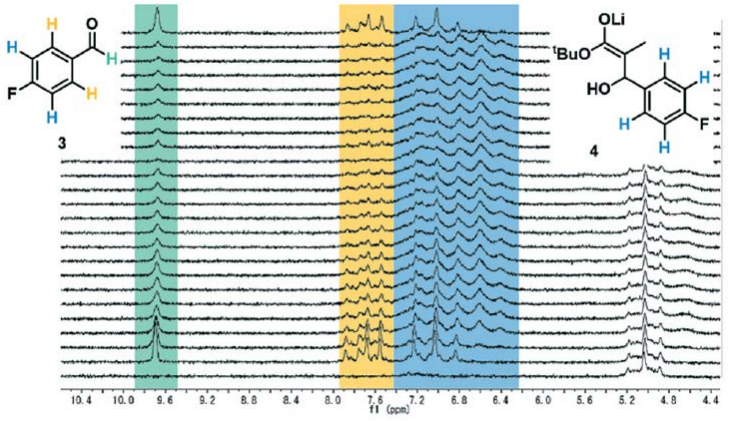
- Proton
  - 1D
  - Paramagnetic
  - 2D COSY
  - 2D TOCSY
  - 2D JRES
  - T_1, T_2
  - Reaction Monitoring

- Carbon
  - 1D
  - DEPT
  - HETCOR
  - HMBC
  - HMQC
  - HSQC
  - HSQC-ME

- **Specifications**
  - 43, 60, or 80 MHz (^{1}H)
  - 23” x 17” x 16”
  - 120 lbs
  - 110–240 AC, 60 Hz
  - Operating Temp: 20 to 25 ^{o}C
  - 2 G line completely inside spectrometer

- Optional third nuclei: ^{7}Li, ^{11}B, ^{15}N, ^{23}Na, ^{29}Si, ^{19}F, and ^{31}P





Sagmeister, P.; Willimas, J. D.; Hone, C. A.; Kappe, C. O. *React. Chem. Eng.*, **2019**, *DOI: 10.1039/c9re00087a*

PUMPS

Vapourtec SF-10

- Self-priming
- Flow rate: 0.02 to 10 mL min^{-1}
- Max pressure: 10 bar
- Pumps solutions, suspensions, light slurries, and gasses
- Versatile options for external control

- Operating Modes:
  - Constant flow rate or ramped flow rate
  - Volume dosing
  - Gas delivery
  - Pressure controller

Fuji Techno SMP

www.fuji-techno.co.jp/english

- Super Metering Pump is pulse-free; metal-free version available
- Able to feed liquid at ± 0.1% of specified flow range
- Max flow rate: 15.3 to 108.6 mL min^{-1}
- Max discharge pressure: 20 bar

- Applications
  - Additive feed into extruder
  - High precision dosing
  - Line mixing
  - Emulsification

Teledyne ISCO

- Seven D-series pumps
  - Flow rates: < 1 µl min^{-1} to 400 mL min^{-1}
  - Max pressure: > 2000 bar
  - HLf-series pumps conform to UL Class I, Div 2, Groups A, B,C, & D, T4 environments
- Air and electric valve continuous flow systems
  - Max Temp: 160 °C (air); 200 °C (electric)
  - Flow rates: 1 µl min^{-1} to 133 mL min^{-1}
  - Max Pressure: > 1300 bar

SEPARATORS

Zaiput Flow Technologies

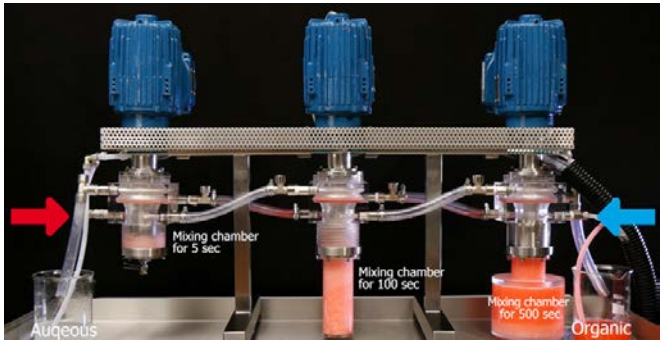
Liquid–Liquid/Gas–Liquid Separators

- Provide continuous separation of immiscible phases by exploiting differences in wettability of a porous membrane
- Max Temperature: 130 °C; Max Pressure: 20 bar
- Wetted parts: ETFE, PFA, FEP, PTFE
- 0.5 mL internal volume; 0 – 10 ml min^{-1} total flow rate

Multi-Stage Extraction Platform

- Bench-scale tool for countercurrent liquid-liquid extraction
- Max Temperature: 80 °C
- Wetted parts: ETFE, PFA, FEP, PTFE, FFMK, PVDF
- ~3 mL per stage internal volume, 0 – 10 ml min^{-1} total flow rate

CINC Centrifugal Extractors



- Continuous mixing / extraction / separation in one step
- Device can be retrofitted to increase the mixing time in a larger mixing volume
- Lab scale results easily scaled up to production
- Hastelloy C22 construction available; ATEX compliant
- Temperature –30 to +130 °C; Pressure: 20 bar
- 0 – 1000 ml min^{-1} total flow rate

HYDROGEN GAS GENERATORS

ThalesNano H-Cube™ Series

- Hydrogenation without cylinders
- Electrolytic cells generate H_2 up to 60 NmL/min and 100 bar
- Temperature range: 10 to 150 ^oC
- Flow rates: 0.3 to 3 mL/min

ThalesNano H-Genie™ High Pressure H_2 Generator

- Generates ≥ 99.99% purity H_2
- Gas flow range: 0.1 to 1 NL
- Pressure range: 1 to 100 bar
- Temperature range: 10 to 150 ^oC
- Suitable for batch, continuous, and balloon fill operation
- Monitors and records H_2 consumption
- Uses < 1 μS cm^{-1} water
- Requires ion filter for H_2O reservoir (consumable)

SUMMARY AND ADDITIONAL RESOURCES

- **Advantages of flow chemistry**
  - Safety
  - Expansion of reaction space to include “forbidden” reactions
  - Lower CAPEX and OPEX
  - Reduced footprint
  - Ease of scale-up

- **Advances in continuous reactor technology have expanded the equipment capability envelope to accommodate an increasing number of process demands**

Additional Resources

- *Flow Chemistry*, Volumes 1 & 2 by F. Darvas, G. Dormán, and V. Hessel (Eds.)

- *The Hitchhikers Guide to Flow Chemistry, Chem. Rev.*, **2017**, *117*, 11796–11893.

- *The Concept of Chemical Generators: On-Site On-Demand Production of Hazardous Reagents in Continuous Flow, Acc. Chem. Res.*, **2020**, *53*, 1330-1341.

- *How to approach flow chemistry*, *Chem. Soc. Rev.*, **2020**, *49*, 8910.

- joseph.rheinhardt@cssquaredllc.com

Supplementary Slides

SPECIALTY REACTORS

CEM Discover SP Microwave System

- 0-300 W power
- 10 mL or 80 mL Flow Cell Accessory
  - Temperature: 0 to +300 °C (10 mL); 0 to +200 °C (80 mL)
  - Pressure: 17 bar
- Integrated camera available
- Gas addition kit available

ElectroCell Micro Flow Cell®

- Electrode area: 10 cm^2
- Max current density: 400 mA cm^{-2}
- Standard electrode gap: 4 mm
- Internal volume: 10 mL
- Max temperature dependent upon choice of frame, sealing, electrode materials
- Flow rate: 0.18 – 1.5 L min^{-1}
- Pilot and production scale units available

ThalesNano PhotoCube™ Pro

- Available wavelengths: 365, 395, 457, 500, 523, 595, 623 nm and white
- Batch: 4 mL and 20 mL glass vials
- Continuous: 2–20 mL loop volume
- Temperature: 20 to 100 °C
- Max power: 128 W

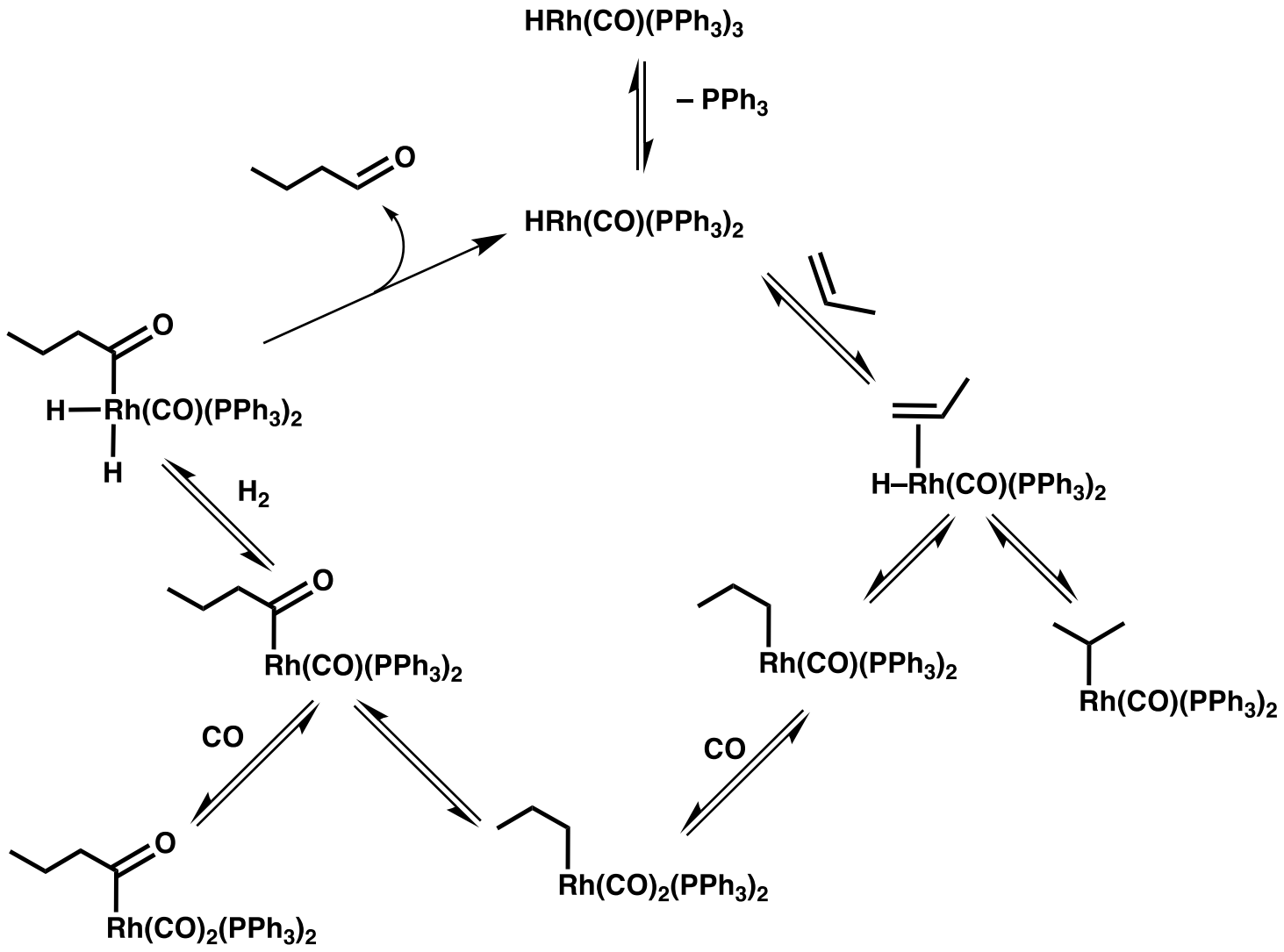
ThalesNano IceCube™

- Temperature: –70 or –50 to +80 °C
- Max pressure: 6 bar
- Main reactor volume: 8 mL
- Functions with Peltier plate technology; uses only tap water and electric power
- PTFE reaction line
- Modular system with software control
- Two reaction zones for multi-step syntheses
- Can be configured for 2, 3, or 4 reactants in one sequence
- Ozone Module generates up to 14% O_3 (at 20 NmL min^{-1} O_2 flow rate)

ThalesNano Phoenix Flow Reactor™

- Temperature: 10 to 450 °C
- Max pressure: 200 bar
- 30 min warmup time
- Stainless steel, Hastelloy, and PTFE sample loops available in 4, 8, and 16 mL volumes
- 40 mL loops available in stainless steel or PTFE
- Fully automated w/ remote control
- Capable of handling gaseous reagents with optional Gas Module™

CHEMICAL REACTIONS: A CHEMIST'S PERSPECTIVE



CHEMICAL REACTIONS: A CHEMICAL ENGINEER'S PERSPECTIVE

CHEMICAL REACTIONS: THE RULE OF 4

Choice of Reaction Time

1 hour	4 hours
12 – 16 hours	72 hours

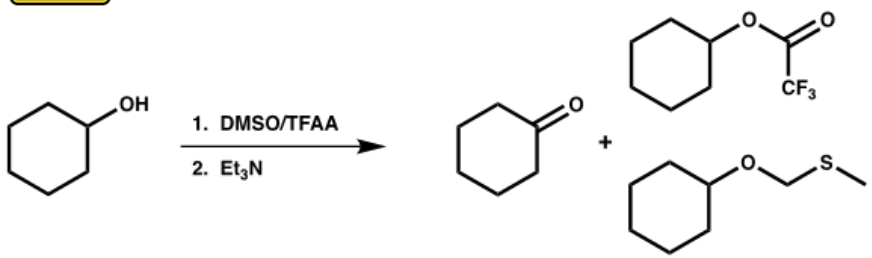
Choice of Reaction Temp

– 78 ^{o}C	0 ^{o}C
25 ^{o}C	Reflux

Choice of Solvent

Closest to me	Freshly distilled
It’s my favorite	Used in reference

LITERATURE EXAMPLES



Kawaguchi, T.; Miyata, H.; Ataka, K.; Mae, K.; Yoshida, J. *Angew. Chem. Int. Ed,* **2005**, *44*, 2413-2416.

Swern Oxidation: Batch 19% yield at –20 °C
Flow 88% yield at 20 °C

Short residence time ensures fast transfer of unstable intermediate before decomposition

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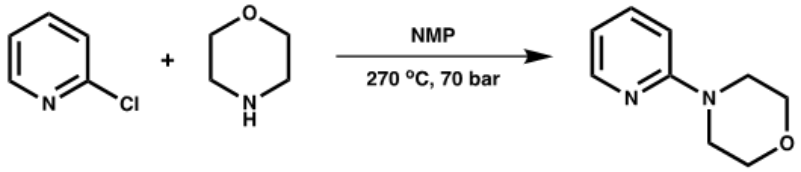

Razzaq, T.; Glasnov, T. N.; Kappe, C. O. *Eur. J. Org, Chem.,* **2009**, 1321-1325.

SN_{Ar} Reaction: Batch 3–24 hrs; 50–110 °C
Flow 8 min; 270 °C

High temperature and pressure in flow reactor dramatically reduces reaction time

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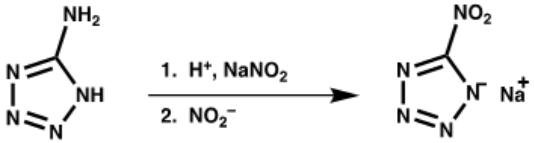

Zaborenko, N.; Murphy, E. R.; Kralj, J. G.; Jensen, K. F. *Ind. Eng. Chem. Res,* **2010**, *49*, 4132-4139.

Sandmeyer Reaction: N_2 evolved in the batch process can lead to potentially explosive conditions. Reaction exotherm (elevated temperature) can cause product loss

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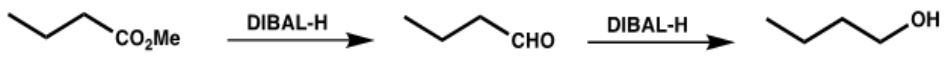
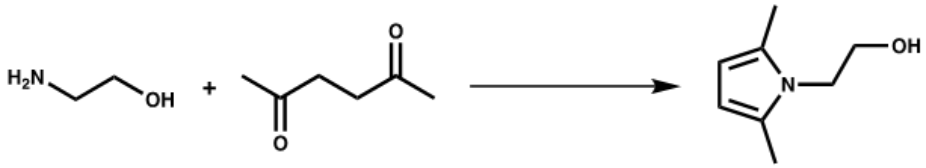


Ducry, L.; Roberge, D. M. *Org. Proc. Res. Dev.,* **2008**, *12*, 163-167.

DIBAL-H reduction:

Batch 83% butyraldehyde yield at –65 °C
Flow 82% butyraldehyde yield at –20 °C

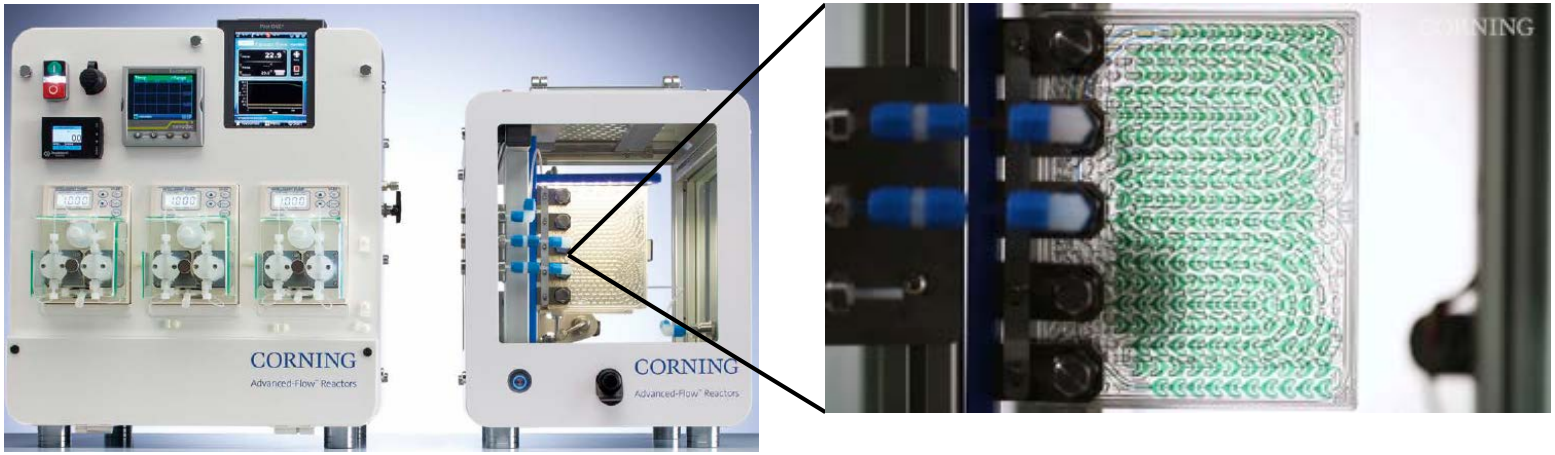


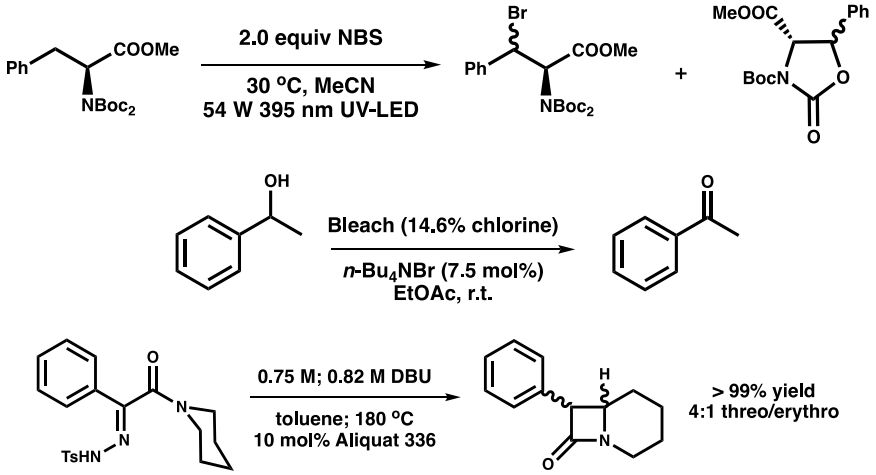
Taghavi-Moghadam, S.; Kleemann, A.; Golbig, K. G. *Org. Proc. Res. Dev.,* **2001**, *5*, 652-658.

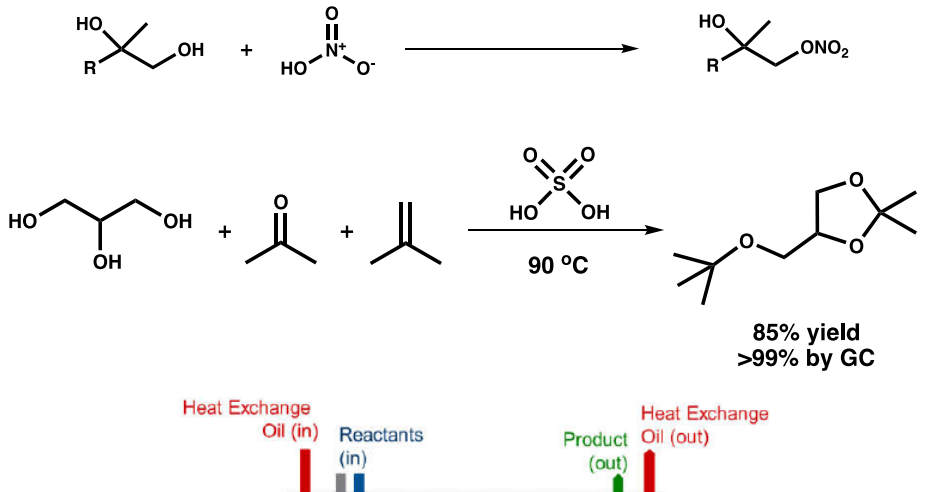
Paal–Knorr pyrrole synthesis: Solvent free

Batch 86% yield
Flow 98% yield

CORNING ADVANCED-FLOW REACTORS







Chen, Y. *et al. ChemPhotoChem*, **2018**, *2*, 906-912. i
Zhang, Y.; Born, S. C.; Jensen, K. F. *Org. Process Res. Dev.*, **2014**, *18*, 1476-1481.
Gerardy, R.; Winter, M.; Vizza, A.; Monbaliu, J-C. M. *Reac. Chem. Eng.*, **2017**, *2*, 149-158.
Braune, S. *et al. Chemistry Today*, **2008**, *26(5)*, 1-4.
Monbaliu, J-C. M. *et al. Bioresource Technology*, **2011**, *102*, 9304-9307.

CORNING ADVANCED-FLOW REACTORS

Low-Flow Reactor

Laboratory scouting glass reactor

FLOW RATE: 2 to 10 ml/min

G3 Reactor

Pilot and production glass reactor

FLOW RATE: 400 to 2000 ml/min

G1 Reactor

Process development and small production glass reactor

FLOW RATE: 30 to 200 ml/min

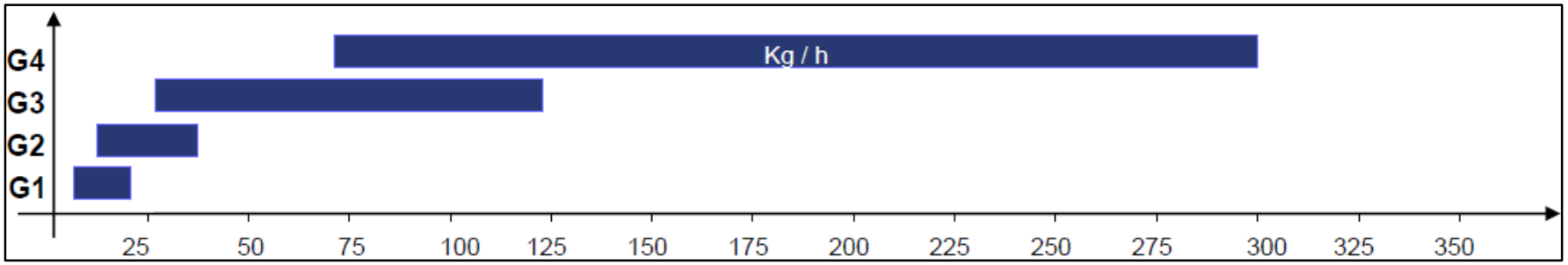
G4 SiC Reactor

Production silicon carbide reactor

FLOW RATE: 1000 to 8000 ml/min

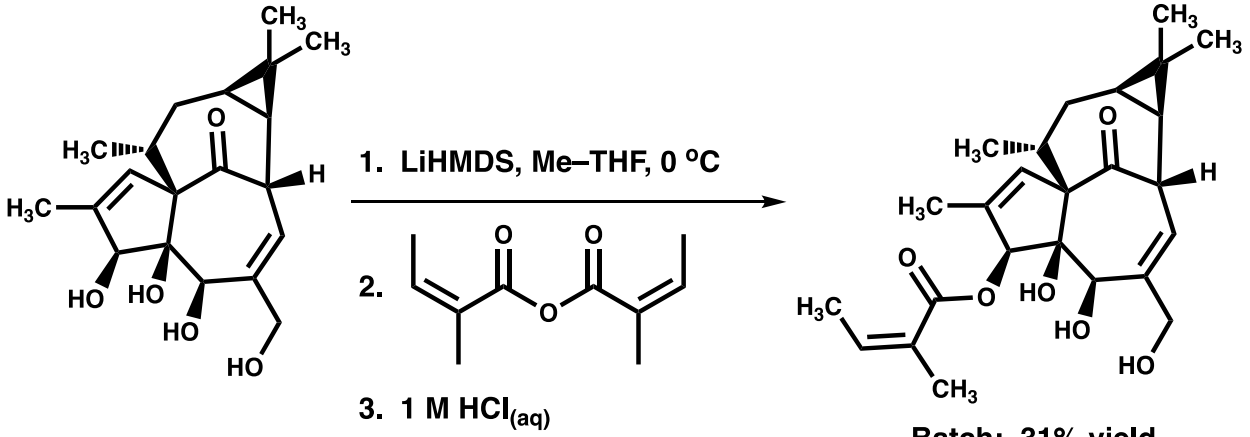
Boundary Conditions

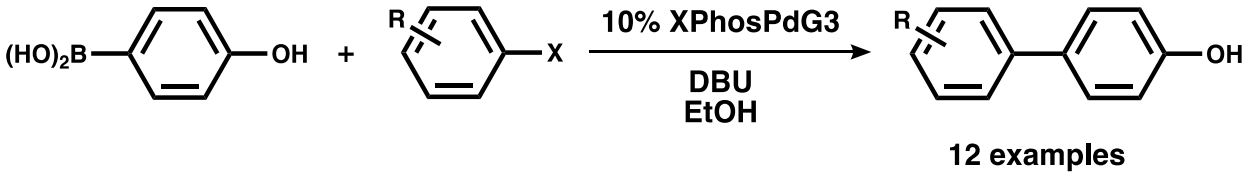
Temperature (°C)	- 60 to 200
Pressure (barg)	0 to 18

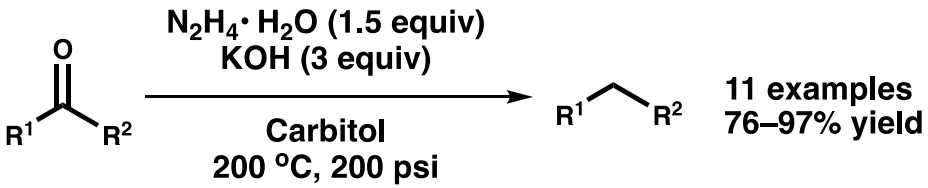


Corning: The future flows through Corning® Advance-Flow™ Reactors, **2016**, Corning Incorporated. www.corning.com/reactors Accessed February 15, 2019.

CHEMTRIX PLANTRIX SiC REACTOR



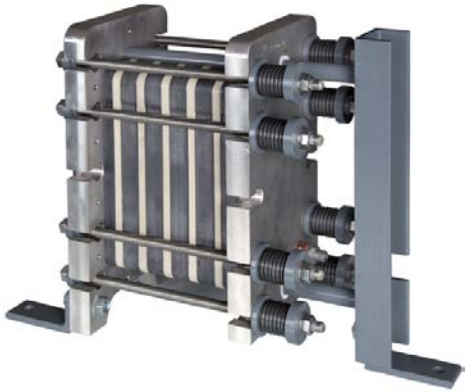




Jordan, R. W.; Dixon, C.; Gorin, B. A Continuous Flow Process for the Preparation of Ingenol-3-mebutate. World Intellectual Property Organization WO2015/176175 A1, November 26, 2015.
Jaman, Z.; Mufti, A.; Sah, S.; Avramova, L.; Thompson, D. H. *Chem. Eur. J.*, ***2018***, *24*, 9546-9554.
Newman, S. G.; Gu, L.; Lesniak, C.; Victor, G.; Meschke, F.; Abahmane, L.; Jensen, K. F. *Green Chemistry*, **2014**, *16*, 176-180.

CHEMTRIX SiC CONTINUOUS FLOW REACTORS

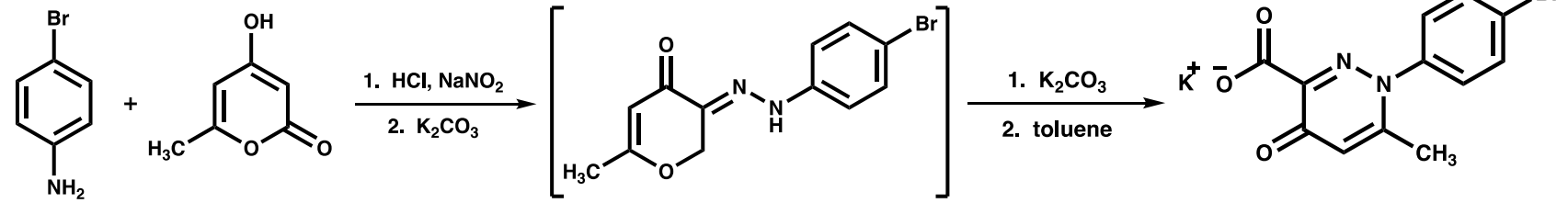
- **Protrix® (lab)**
  - Throughput: 0.12 to 1.2 L/hr
  - Flexible Reaction Volume: 1.0 – 13.5 mL
  - Maximum Pressure: 25 bar
  - Dimensions (W x D x H): 14 x 8 x 10 in

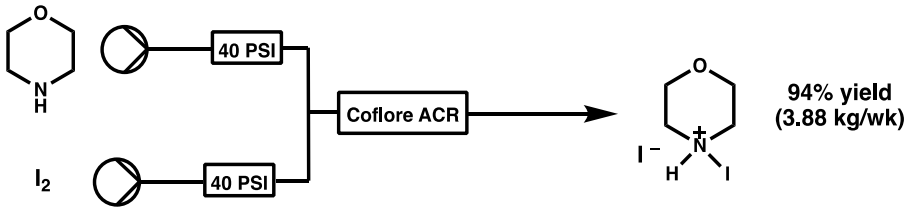


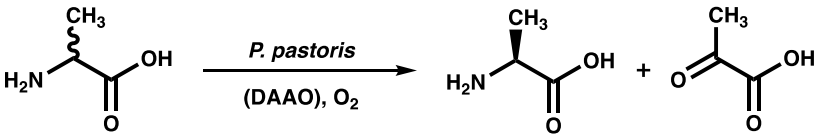
- **Plantrix® MR260 (pilot)**
  - Throughput: 1 to 36 L/hr
  - Flexible Reaction Volume: 2.7 – 170 mL
  - Maximum Pressure: 25 bar
  - Dimensions (W x D x H): 8 x 17 x 28 in

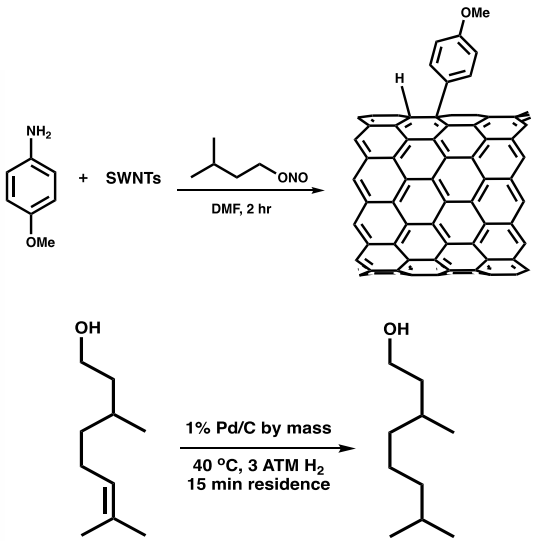
- **Plantrix® MR555 (production)**
  - Throughput: 5 to 400 L/hr
  - Flexible Reaction Volume: 100 – 4,000 mL
  - Maximum Pressure: 25 bar
  - Dimensions (W x D x H): 14 x 32 x 56 in

AM TECHNOLOGY COFLORE AGITATED CELL REACTOR









AM Technology; Hydrogenation: Technical Note https://docs.wixstatic.com/ugd/62b9f0_a51fb78855414be2a5b9fab26dee5358.pdf. Accessed February 21, 2018.
Oger, N.; Le Grognec, E.; Felpin, F-X. *Org. Chem. Front.*, **2015**, *2*, 590-614.
Browne, D. L.; Deadman, B. J.; Ashe, R.; Baxendale, I. R.; Ley, S. V. *Org. Process Res. Dev.*, **2011**, *15*, 693-697.
Filipponi, P.; Gioiello, A.; Baxendale, I. R. *Org. Process Res. Dev.*, **2016**, *20*, 371-375.
Jones, E.; McClean, K.; Housden, S.; Gasparini, G.; Archer, I. *Chem. Eng. Res. Des.*, **2012**, *90*, 726-731.

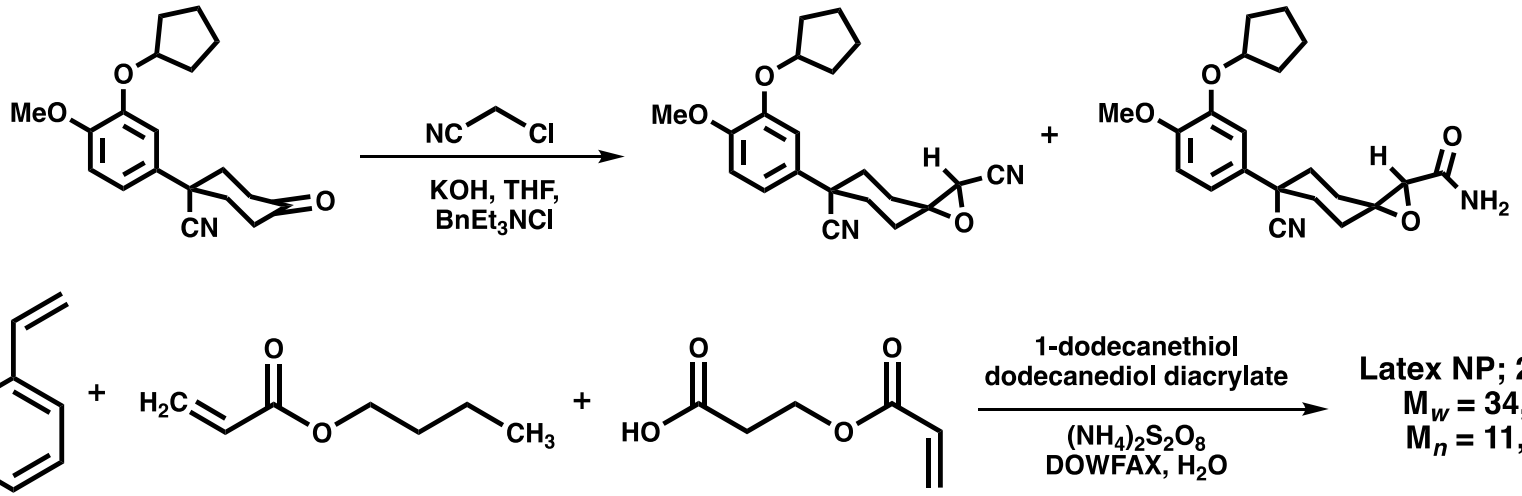
AM TECHNOLOGY COFLORE AGITATED CELL REACTOR

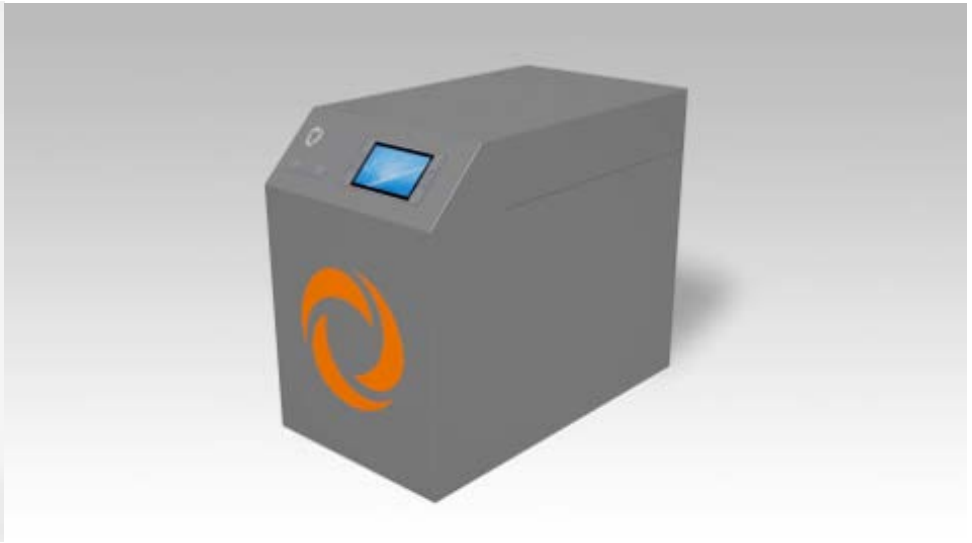
- **Coflore ACR (lab)**
  - Throughput: 0.1 to 300 mL/min
  - Reactor Volume: 30, 50, 70, & 100 mL available
  - Maximum Pressure: up to 20 bar
  - Agitation Speed: 2 – 9 Hz

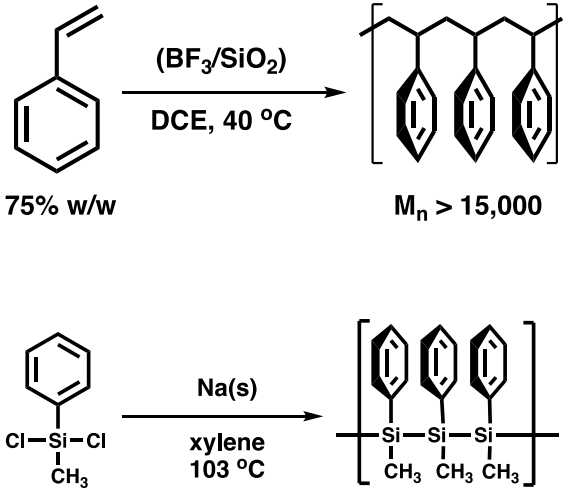
- **Coflore ATR (pilot)**
  - Throughput: up to 600 L/hr
  - Reactor Volume: 0.35 & 1.25 L tubes (up to 8)
  - Maximum Pressure: up to 80 bar
  - Agitation Speed: 2 – 9 Hz

- **Coflore RTR (production)**
  - Throughput: 290 L/hr (20 min residence time)
  - Reactor Volume: 100 L
  - Design Pressure: FV/10 bar

FLOWID SPINPRO R300 SPINNING DISC REACTOR







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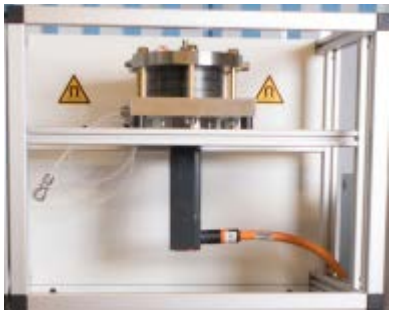
Lai, Z.; Cheng, C-M.; Wolfe, C. M.; Jackson, M. A. Latex emulsion polymerizations in spinning disc reactors or rotating tubular reactors. US Patent Office US 7,683,142 B2, March 23, 2010.
Boodhoo, K. V. K *et al. J. Appl. Polym. Sci.* **2006**, *101*, 8-19.
Hees, M.; Georgi, U.; Bachus, H.; Muller, K-S. Continuous method for reactions with fine-particulate alkali metal dispersions. US Patent Office US 20188/0346655, December 6, 2018.

FLOWID SPINPRO SPINNING DISC REACTORS



- **SpinPro R10 (lab)**
  - Flow Rate: up to 70 L/hr
  - Reactor Volume: 8 - 20 mL (3 stages)
  - Maximum Pressure: up to 10 bar
  - Rotation: 8,000 rpm

- **SpinPro R300 (pilot)**
  - Flow Rate: up to 600 L/hr
  - Reactor Volume: 135 – 230 mL (3 stages)
  - Maximum Pressure: up to 10 bar
  - Rotation: 3,000 rpm

- **SpinPro R1000 (production)**
  - Flow Rate: up to 3,600 L/hr
  - Reactor Volume: 430 mL (7 stages)
  - Maximum Pressure: up to 10 bar
  - Rotation: 4,500 rpm

THALESNANO FLOW REACTORS

H-Cube™ Series

- Hydrogenation without cylinders
- Electrolytic cells generate H_2 up to 60 NmL/min and 100 bar
- Temperature range: 10 to 150 ^oC
- Flow rates: 0.3 to 3 mL/min

IceCube™ Flow Reactor

- Cools by Peltier plate technology using only tap water and electricity
- Temperature range: -70 or -50 ^oC to 80 ^oC
- Pressure capability: 6 bar
- Flow rates: 0.2 to 4 mL/min

Phoenix Flow Reactor™

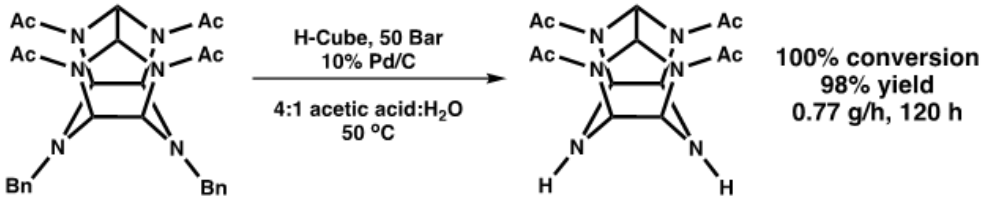
- Temperature up to 450 ^oC
- 10 minute warm up time (30 ^oC to 450 ^oC)
- Pressure capability: 200 bar maximium

Gas Module™

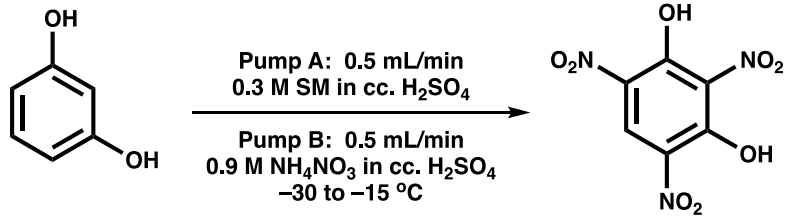
- Cylinder fed—works seamlessly with H-Cube and Phoenix Reactors
- Pressure capability: 100 bar maximum
- 14 different gasses: compressed air, O_2, CO, ethylene, SynGas for hydroformylations, CH_4, C_2H_6, He, H_2, N_2, N_2O, NO, Ar, CO_2 (after preheating) Other gases can be introduced

THALESNANO FLOW REACTORS

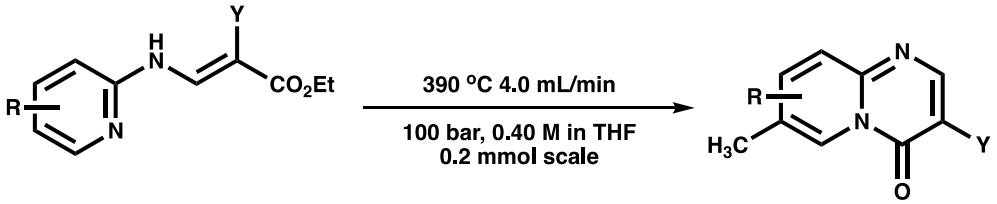
H-Cube™ Series



IceCube™ Flow Reactor



Phoenix Flow Reactor™



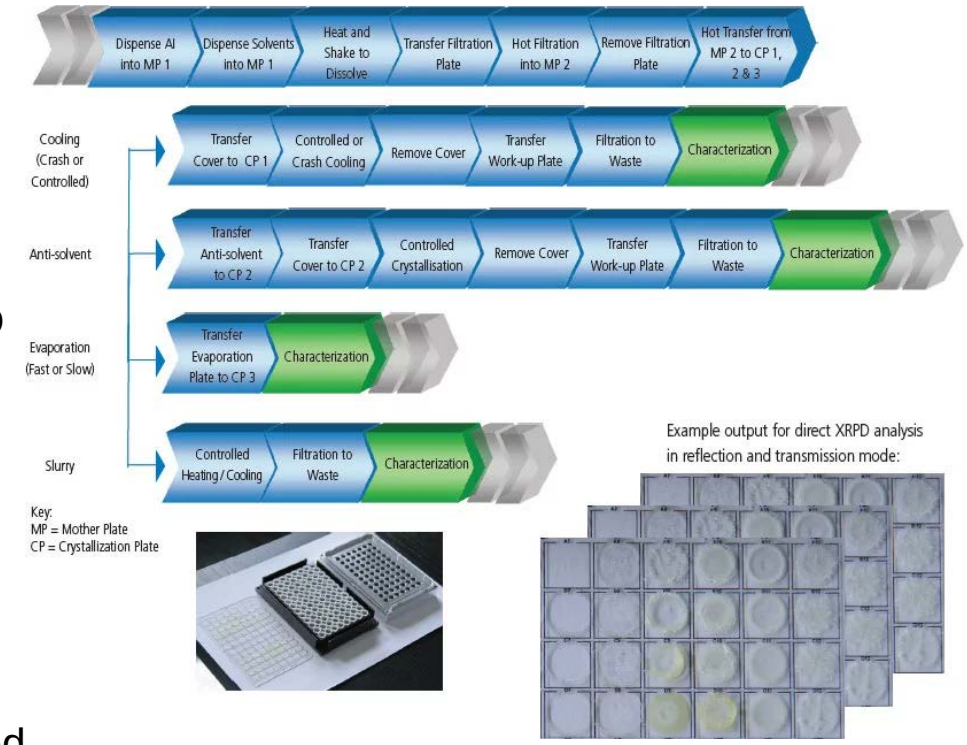
9 examples
77–96% yield

Dong, K.; Sun, C. H.; Song, J. W.; Wei, G. X.; Pang, S. P. *Org. Process Res. Dev.,* **2014**, *18*, 1321-1325.
Nitration: ThalesNano https://thalesnano.com/applications/high-energy-chemistry/nitration/ Accessed March 3, 2019.
Tsoung, J. *et al. J. Org. Chem*, **2017**, *82*, 1073-1084.

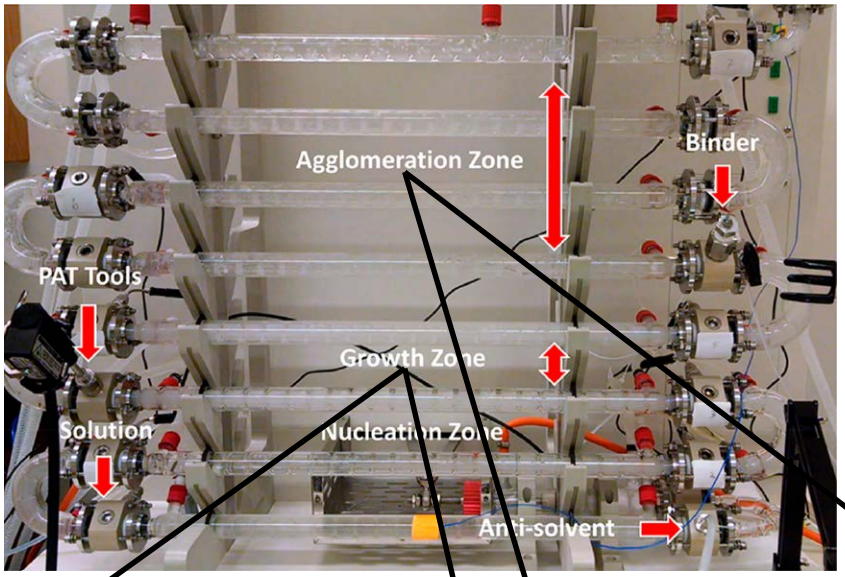
CHEMSPEED SWING CRYSTAL

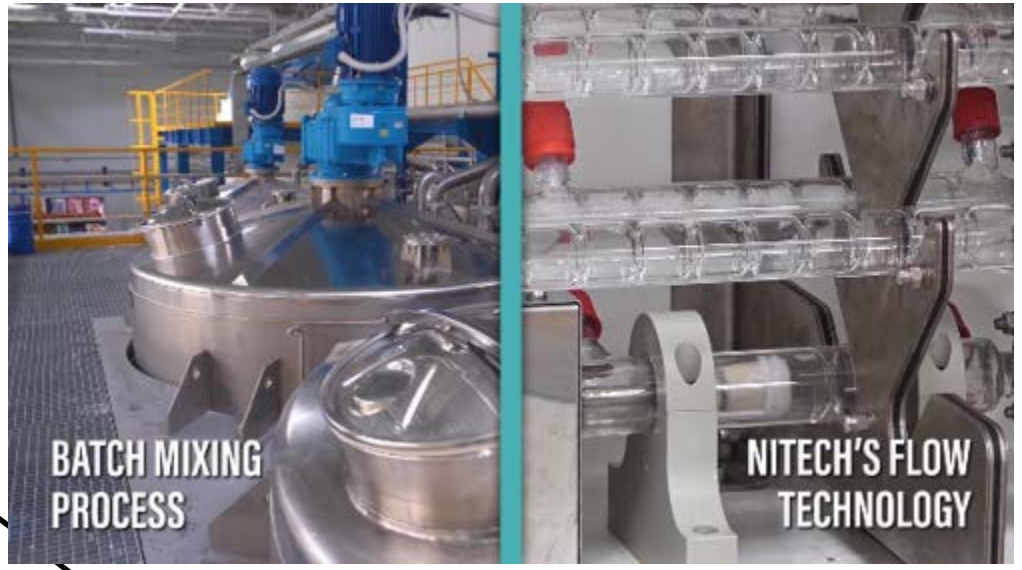
SWING CRYSTAL will perform crystallization, salt, polymorph, and solubility screening workflows

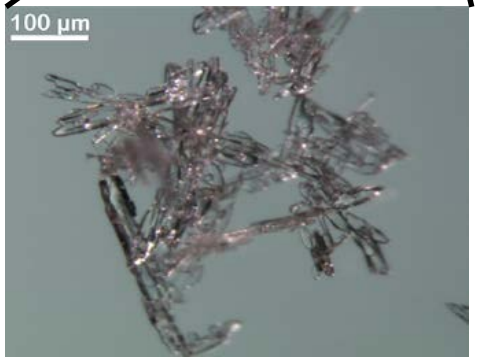
- **Crystallization MTP**
  - 24, 48, 96 well plate
  - Detachable glass bottom
  - Glass plate can be placed directly on XRPD
- **Filtration Plate**
  - 24, 48, 96 tips with semi-disposable filters
  - Heated filtration of process fluid
  - Simultaneous filtration of 24, 48, 96 wells
- **Evaporation Plate**
  - 24, 48, 96 tips
  - Tips standing above liquid level for controlled evaporation of solvent
- **Work-up Plate**
  - 24, 48, 96 tips
  - For filtration to waste after crystallization

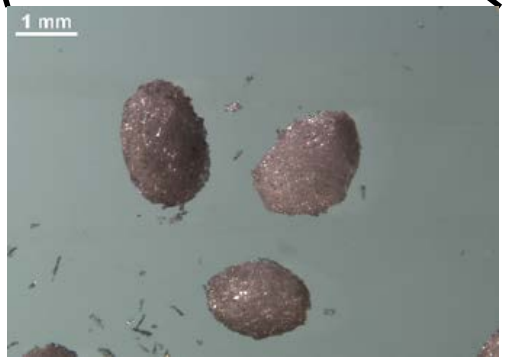


NITECH CONTINUOUS OSCILLATORY BAFFLED CRYSTALIZER





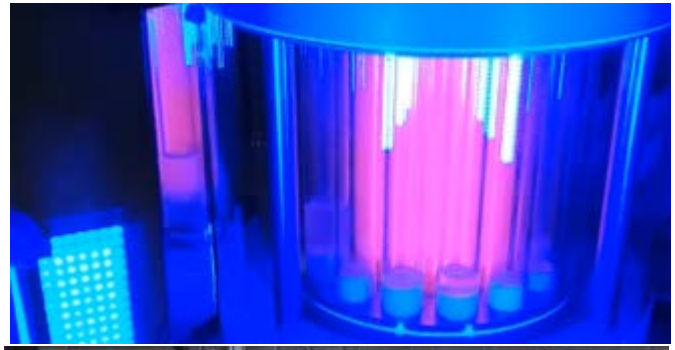




- **Integrable Process Analytics Tools**
  - FTIR and Raman
  - Focused Beam Reflectance Method
  - Laser Diffraction Methods (DLS)
  - Imaging techniques

Peña, R.; Olivia, J. A.; Burcham, C. L.; Jarmer, D. J.; Nagy, Z. K. *Cryst. Growth Des.*, **2017**, *17*, 4776-4784.
Kacker, R.; Maaβ, S.; Emmerich, J.; Kramer, H. AIchE J., **2018**, *64*, 2450-2461.

ALCONBURY WESTON AWL CFD 20 CONTINUOUS CAROUSEL FILTER AND DRYER



- **Carousel filtration and drying features**
  - 1 kg/hr capacity at pilot-scale; 12-24 kg/hr at production scale
  - Inert atmosphere and full vacuum capability
  - Two wash solvents selectable; wash solvent dispensed via atomization nozzles to prevent disturbing the filter cake
  - Post-filtration and washing the cake can be de-liquored to <15% moisture content with convection drying able to achieve <1% moisture in minutes
  - Buffer vessel allows for batch, semi-continuous, and continuous operation
  - Automatic CIP mode washes carousel, ports, and ejection head without disassembly