U.S. ARMY COMBAT CAPABILITIES DEVELOPMENT COMMAND – ARMAMENTS CENTER

Continuous Reactors for Energetic Materials Synthesis

Joseph Rheinhardt, PhD

Research Scientist III

CS Squared, LLC

AGENDA

- **Answering the "When" of Flow**
  - Advantages of Flow Chemistry: The Three C's
    - **C**hemistry
    - **C**ontrol
    - **C**ost
  - Screening Reactions for Continuous
    - Calabrese and Pissavini Screening Framework
    - Roberge Reaction Classification Scheme
    - Reaction/Reactor Selection Matrix

- **Answering the "What" of Flow**
  - Transformers and Generators
  - Survey of Commercial Off-The-Shelf Apparatus
    - Continuous Reactors
    - Continuous Crystallizers and Filters
    - Ancillary Equipment
      - Spectroscopic Tools
      - Pumps
      - Separators

- **Summary and Additional Resources**

Answering the “When” of Flow

ADVANTAGES OF FLOW: THE THREE C's

- **Chemistry**
  - Safety: Smaller scale; No headspace; No accumulation of reactive or toxic intermediates
  - Expansion of the Reaction Space: "Forbidden" reactions are feasible in flow; Reactions in Novel Process Windows (high temperature, high pressure, increased concentration/solvent-free, explosive or thermal runaway regimes)

- **Control**
  - Seamless Scale Up: Scale up (numbering up) is faster and more reliable
  - Versatility and Flexibility: Customizable and adjustable equipment; Ease of switching products; Flexibility to turn throughput up or down
  - Increased space–time yield (increased throughput in smaller footprint)
  - Steady-state, continuous process feedback
  - Quality by Design (QbD)/Quality by Control (QbC)

- **Cost**
  - Less energy, water, and raw material costs (solvents, cleaning fluid)
  - Lower labor cost
  - Less capital depreciation
  - Increased product yield and quality

Jensen, K. *Microreactors in Discovery and Development*, *PoaC Symposium,* ***2013***.
Calabrese, G. S.; Pissavini, S. *AIChE Journal,* **2011**, *57(4)*, 828-834.

SCREENING REACTIONS FOR CONTINUOUS

Pressures exceed reactor capability? Temperatures exceed reactor capability? Chemistry not compatible with reactor? Equilibrium reactions?	Likely no benefit and/or not possible	Increasing applicability
Solid precipitates? Very slow kinetics? Solid reactants or catalysts? Gaseous reactants? Homogeneous catalysts?	Possible benefits, but with technical challenges	
Gas evolution? Reaction benefits from pressure > 120 Pa Unstable intermediates? Fast kinetics? Highly toxic reactants or byproducts? Reactions requires or benefits from T < -10 °C? Rapid mixing required? Highly exothermic? Over-reaction possible? Requires precise stoichiometric control?	Likely to benefit	

Calabrese, G. S.; Pissavini, S. *AIChE Journal,* **2011**, *57(4)*, 828-834.

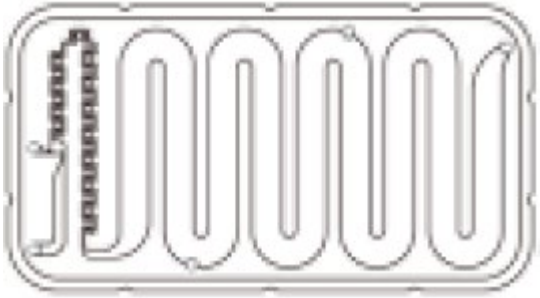
ROBERGE REACTION CLASSIFICATION SCHEME

- **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

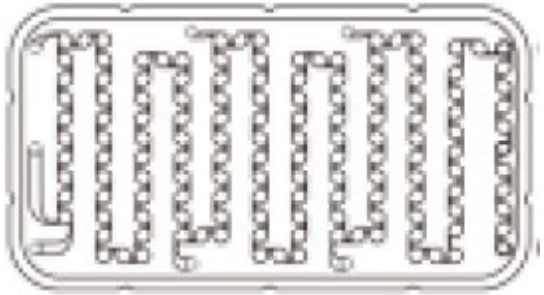
Plouffe, P.; Macchi, A .; Roberge, D. M. *Org. Proc. Res. Dev.,* **2014**, *18*, 1286-1294.

REACTION/REACTOR MATRIX

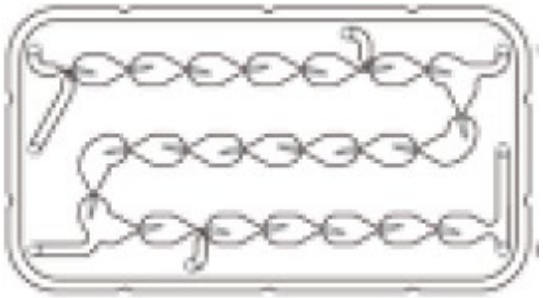
Rates/Phases	Homogeneous	Liquid-Liquid	Gas-Liquid	Solid-Liquid
Type A	Plate SZ/TG	Plate LL	Plate LL	CSTR/ Packed Bed
Type B	Plate SZ/TG Coil	Plate LL Coil pulsated	Plate LL Coil pressure	CSTR/ Packed Bed
Type C	Static mixer Coil	State mixer Coil pulsated	Static mixer Coil pressure	Coil pulsated



SZ (serpentine)



TG (tangential)



LL (liquid-liquid)

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

Answering the “What” of Flow

TRANSFORMERS AND GENERATORS

Transformers

Oxidation Modules
- O_2 via two-feed approach
- Tube in tube reactor
- Homogeneous oxidant & T-mixer

Reduction Modules
- H_2 via tube in tube combined with catalyst
- *In situ* H_2 generation—pressurized gas-liquid mixer & packed bed reactor
- Homogenous reductions (DIBALH)

Nitrations
- Mixed acid nitrations
- Nitration using acetyl nitrate (HNO_3-Ac_2O-AcOH)
- Alternative Nitration Condition (N_2O_5 + TFE; NH_4NO_3–H_2SO_4)

Olefinations
- Polymer-assisted HWE olefination using packed bed reactor
- Wittig reaction using SS coil at 210 ºC

Generators

In situ Hazardous Materials
- Stable Reagents
  - Cl_2, Br_2, BrCN, HCN, NOCl, N_2H_4, SO_2, $COCl_2$, $ClCH_2OCH_3$, R-NC
- Limited Stability Reagents
  - H_2O_2, RCO_3H, N_2CHCO_2Et, R-N_3, LDA
- Unstable Reagents
  - O_3, CH_2N_2, CF_3CHN_2, HN_3, BrN_3, ClN_3 $^1O_2$

Reactive Intermediates
- Iminium cations
- Benzyne
- R-MgX
- Aryllithium
- Carbon-centered radicals
- Alkyl diazo compounds
- Benzyl diazo compounds

Guidi, M.; Seeberger, P. H.; Gilmore, K. *Chem. Soc. Rev.*, **2020**, *49*, 8919-8932.
Dallinger, D.; Gutmann, B.; Kappe, C. O. *Acc. Chem. Res.*, **2020**, 53, 1330-1341.

Continuous Reactors for Energetic Materials Synthesis

Commercial-Off-The-Shelf Apparatus

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

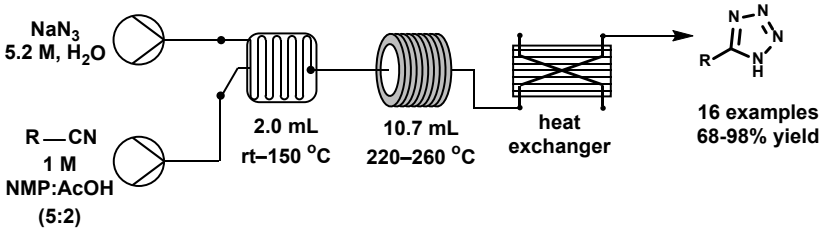
Ehrfeld Modular MicroReaction System (MMRS)

- 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

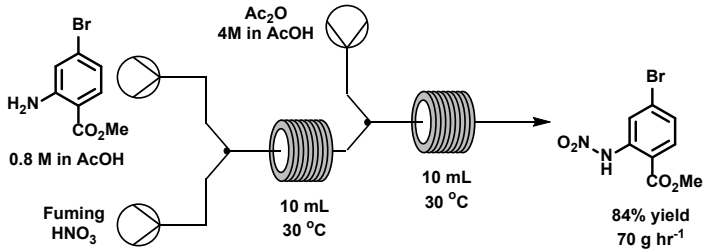
Uniqsis FlowSyn

www.uniqsis.com



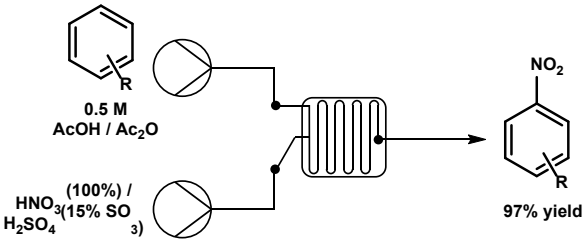
Gutman, B. et al. Angew. Chem. Int. Ed., **2010**, *49*, 7101-7105.

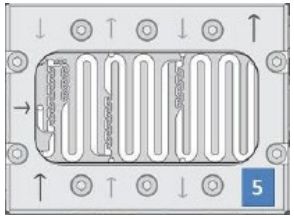
Vapourtec RS-400



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

Ehrfeld Modular MicroReaction System (MMRS)



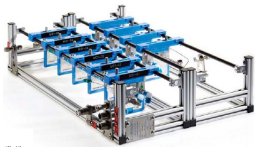


LL-Mixer 0.24 mL internal volume

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®

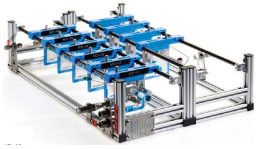
- Inert wetted materials:
  - Labtrix® S1: PTFE, ETFE, FFKM, Glass
  - Protrix®: PTFE, FFKM, SiC
  - Temperature: –20 to +195 °C; Pressure: 20 bar
  - Volume: 1 to 19.5 µL (Labtrix® S1); 1 to 13.5 mL (Protrix®)
- Dedicated software for automated data logging and sample collection
- Protrix® processes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

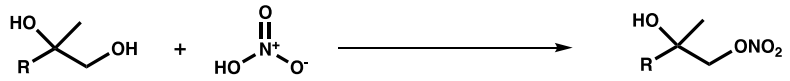
AM Technology Coflore® ACR

- 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

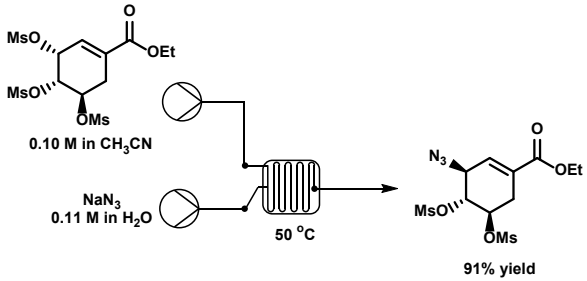
Corning Advanced-Flow™ Reactors





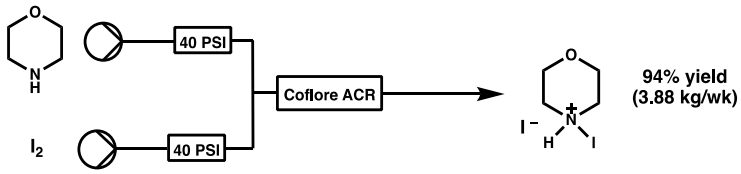
Braune, S. *et al. Chemistry Today*, **2008**, *26(5)*, 1-4.

Chemtrix Labtrix® S1 and Protrix®



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

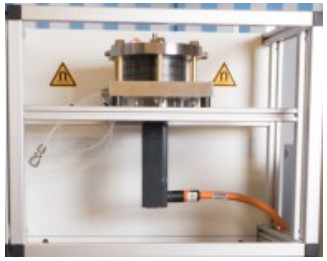
AM Technology Coflore® ACR



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

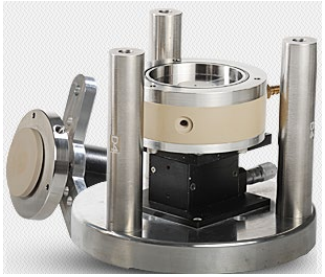
SPINNING DISC REACTORS

Flowid SpinPro R10



- SiC Spinning Disc Reactor
  - Three-stage reactor; 19 mL total volume
  - Temperature: –20 to +160 °C; 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

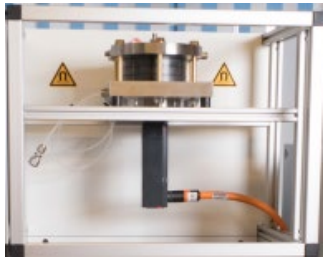
KinetiChem Synthetron™

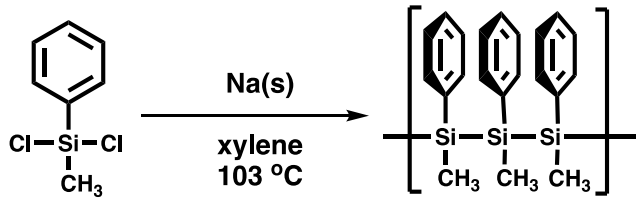


- Hastelloy C-22 surfaces; inert fluoropolymer seals
  - 10 µL to 1.3 mL lab scale spinning disc reactor
  - Temperature: –40 to +150 °C; Pressure: 10 bar
- 1,000 W motor; speed up to 14,000 RPM
- TouchScreen Allen Bradley Micro800 series controller/data logger
  - 4 x K-type thermocouple collection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

SPINNING DISC REACTORS

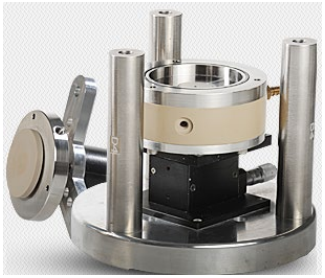
Flowid SpinPro R10

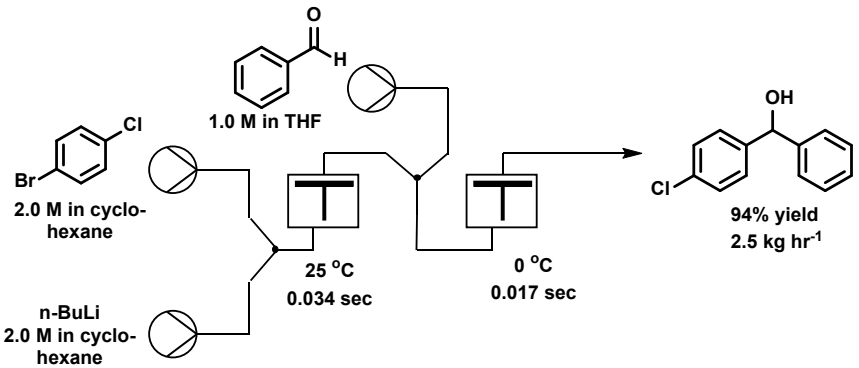




Hees, M.; Georgi, U.; Bachus, H.; Muller, K-S. US Patent Office US 2018/0346655, December 6, 2018

KinetiChem Synthetron™



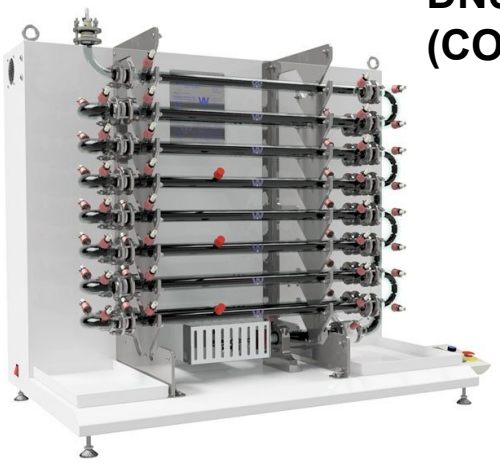


Slocum, D. W. *et al., Tetrahedron Lett.*, **2010**, *51*, 4793-4796.

NITECH® SOLUTIONS

DN25 Oscillatory Baffled Reactor (OBR)

- Borosilicate glass vessel; 25 mm diameter; 110 mL internal volume
- Temperature: –20 to +120 °C; 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

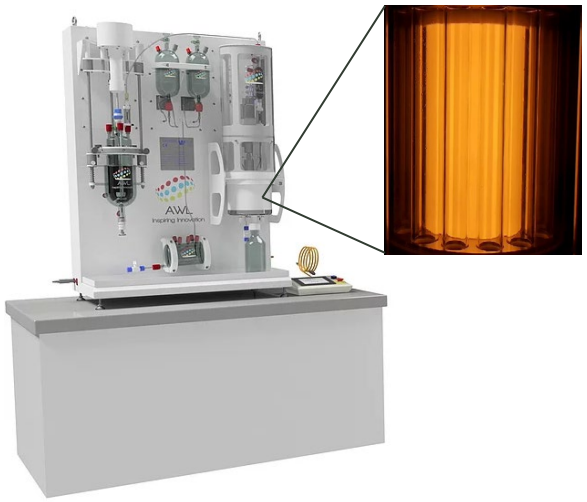


DN6/DN15 Continuous Oscillatory Baffled Crystallizer/Reactor (COBC/R)

- Glass (DN6/DN15) or Hastelloy (DN15); 200 mL (DN6)/1.25 L to 4.5 L (DN15) internal volume
- Temperature: 0 to +100 °C (DN6); –20 to +150 °C (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.

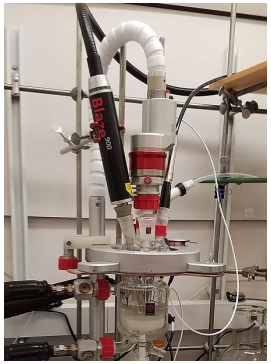
ALCONBURY WESTON CCF50 AND CCF20-LITE CONTINUOUS CAROUSEL FILTER

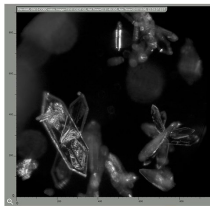


- **CCF50 For Hazardous Locations:**
  - Meets DOE Standard 1212 for Energetic Materials
  - No/Minimal particle shear
  - Up to three wash solvent reservoirs
  - 1 moving part
  - 50 mm ports – 40 g of material per port
  - Entry-to-exit time typically 10 to 15 minutes
  - Cake wetted to set parameters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

BLAZE METRICS™ AND TORNADO SPECTRAL SYSTEMS

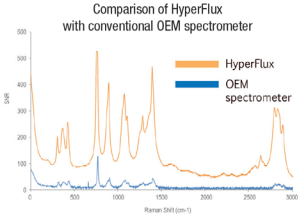




One Probe with Multiple Integrated Technologies – Simultaneous Acquisition:

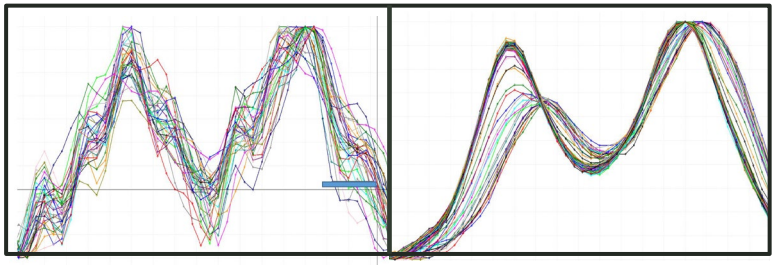
- **Microscopy:** high contrast, high resolution, highest dynamic range for understanding single dispersed phase and multiple phase, multiple component particle systems
- **High Dynamic Range Turbidity (HDR):** dynamic range measuring from low to extremely high dispersed phase concentrations; can track 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 °C (-10 °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

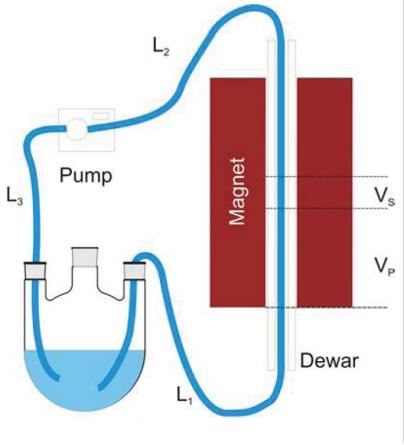
- **Available Pulse Sequences**

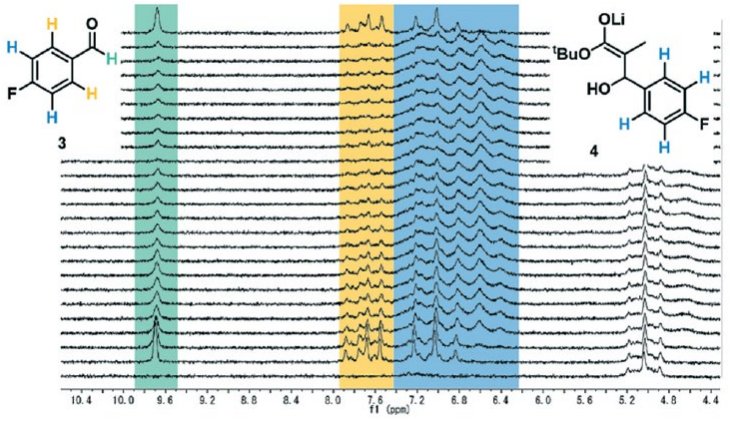
- Proton
  - 1D
  - Paramagnetic
  - 2D COSY
  - 2D TOCSY
  - 2D JRES
  - T_1, T_2
  - Reaction Monitoring

- 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

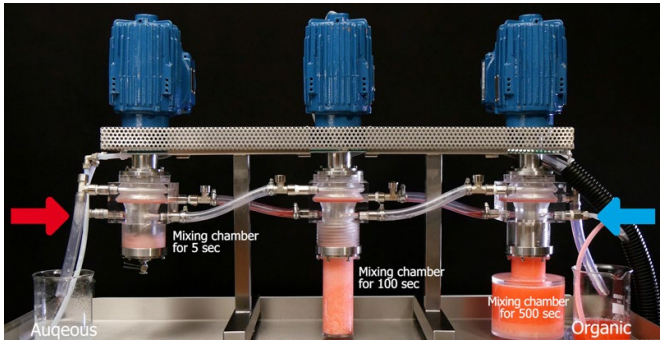
Liquid–Liquid/Gas–Liquid Separators

- 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

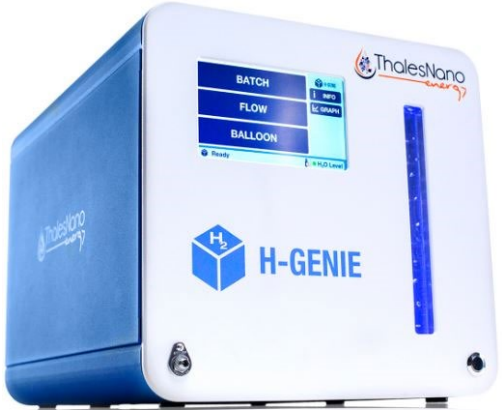


- Continuous mixing / extraction / separation in one step
- Device can be retrofitted to increase the mixing time in a larger mixing volume
- Lab scale results easily scaled up to production
- Hastelloy C22 construction available; ATEX compliant
- Temperature –30 to +130 °C; Pressure: 20 bar
- 0 – 1000 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 °C
- 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 °C
- 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.
- Flow Chemistry and Continuous Processing Conference (virtual) 10 – 12 May, 2021
- Flow Chemistry Congress 2021, Boston, MA (Dates to be confirmed)
- **Questions?**
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