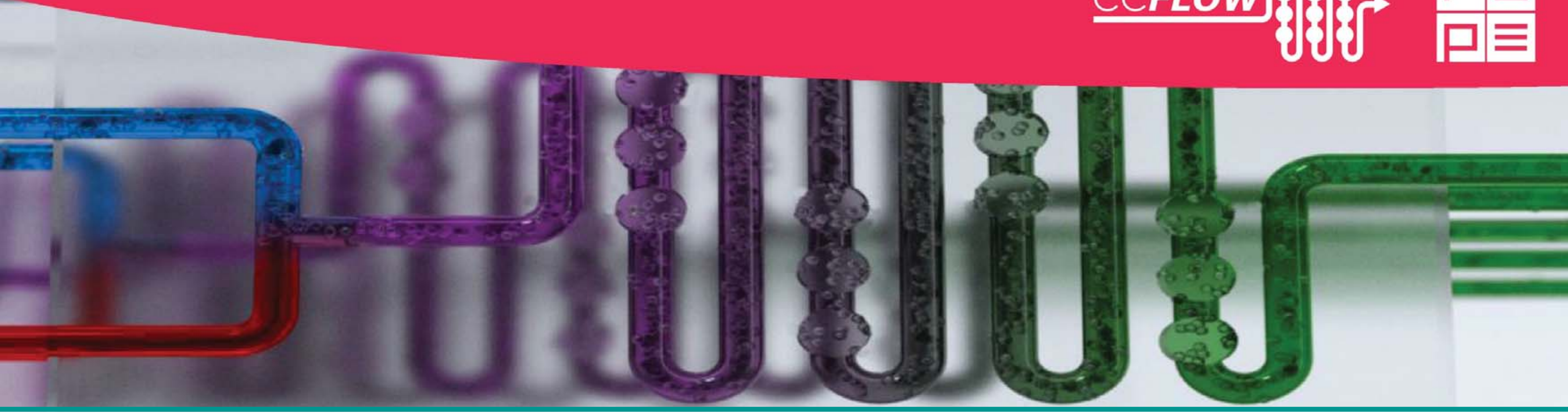
From Flow Chemistry in the Lab towards Industrial Implementation on Scale - Case Studies on Continuous API Synthesis

C. Oliver Kappe

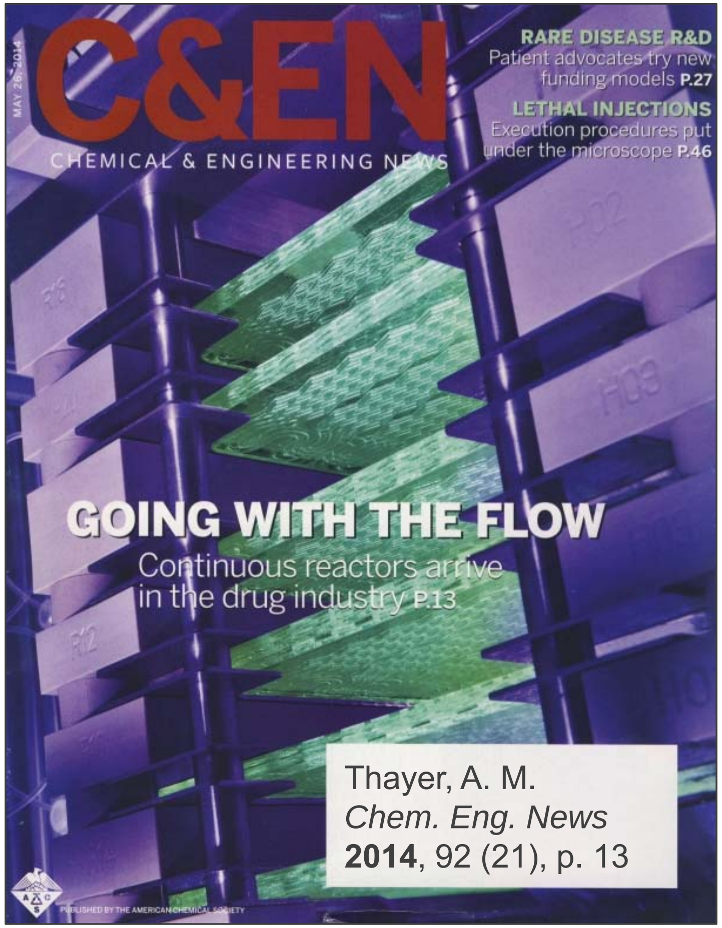
Center for Continuous Flow Synthesis and Processing (CCFLOW), RCPE GmbH and Institute of Chemistry, University of Graz, Austria

oliver.kappe@uni-graz.at http://ccflow.at



TU Graz / UNI GRAZ / JOANNEUM RESEARCH / Federal Ministry Republic of Austria Climate Action, Environmen Energy, Mobility, Innovation and Technology / Federal Ministry Republic of Austria Labour and Economy / FFG Promoting Innovation. / Das Land Steiermark Wirtschaft, Tourismus, Regionen, Wissenschaft und Forschung / SFG NEUES DENKEN. NEUES FÖRDERN.

Continuous Processing – A Hot Topic in the Pharmaceutical Industry



Thayer, A. M.
Chem. Eng. News
2014, 92 (21), p. 13

PROS AND CONS

Continuous processes have advantages over batch methods, but they have challenges as well.

Advantages

- Low capital investment
- Less space required
- Safer with hazardous reactions
- Shorter processing times
- Possible novel chemistries
- Straightforward scale-up
- Need for less inventory
- Potential cost savings
- Better product quality
- Improved environmental impact

Challenges

- Competes with existing investments
- Mind-set change needed to shift
- Perception of higher risk
- New engineering/operating skills
- Lack of adequately trained people
- Equipment availability at all scales
- Up-front development demands
- Limitations with solids
- Mastery of start-up and shutdown
- Relatively untested regulatory path

Mullin, R.
Chem. Eng. News
2019, 97 (17), p. 28

FDA Calls on Manufacturers to Begin Switch to Continuous Production

in-Pharma Technologist.com

News & Analysis on Pharmaceutical Technology & Manufacturing

By Zachary Brennan

30-Apr-2015 - Last updated on 01-May-2015 at 19:49 GMT

Subscribe

Though making the switch from batch to continuous manufacturing may be difficult, costly and time consuming, pharma manufacturers and CMOs should begin to consider the switch as in the long-run it will end up saving companies time, money and space, FDA's CDER Director Janet Woodcock told congressmen in a hearing Thursday.

Woodcock's answers on continuous processing come as a new draft House bill calls on the Commissioner of the FDA to "*award grants to institutions of higher education and nonprofit organizations for the purpose of studying and recommending improvements to the process of continuous manufacturing of drugs and biological products and similar innovative monitoring and control techniques.*"

Woodcock received a few questions asking to compare the differences between batch and continuous manufacturing and after explaining the fundamentals, said, "*I don't know why it's not more widely used*" as "*this is the future.*"

Lee, S. L. et al.
J. Pharm. Innov. **2015**, *10*, 191
Fisher, A. C. et al.
Int. J. Pharm. **2022**, *622*, 121778

March 2023: ICH Guideline Q13 "Continuous Manufacturing of Drug Substances & Drug Products"

Key Green Engineering Research Areas for Sustainable Manufacturing: A Perspective from Pharmaceutical and Fine Chemicals Manufacturers

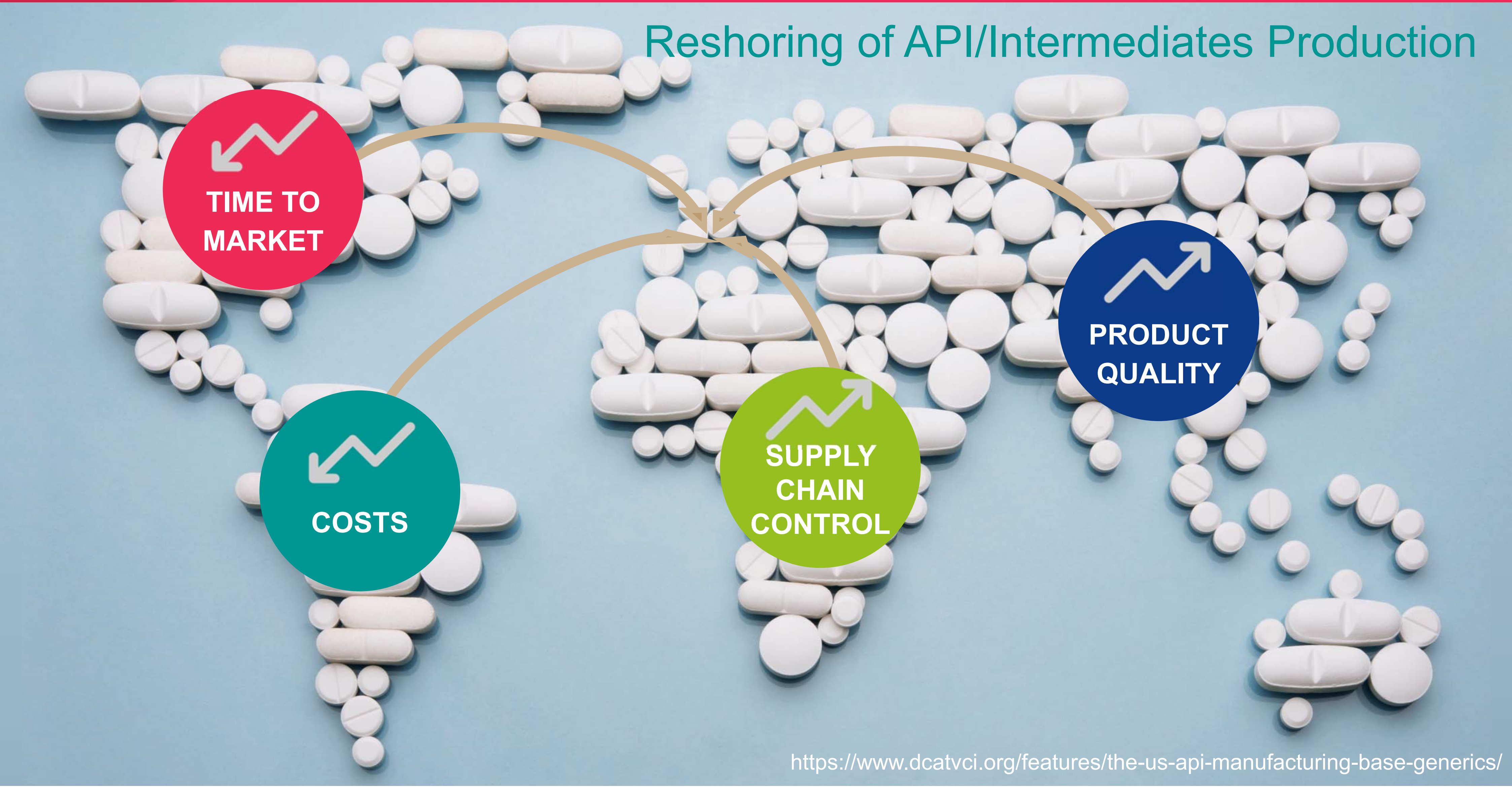
Jimenez-Gonzales, C. et al. *Org. Process Res. Dev.* **2011**, *15*, 900

ABSTRACT: In 2005, the American Chemical Society (ACS) Green Chemistry Institute (GCI) and global pharmaceutical companies established the ACS GCI Pharmaceutical Roundtable to encourage the integration of green chemistry and engineering into the pharmaceutical industry. The Roundtable developed a list of key research areas in green chemistry in 2007, which has served as a guide for focusing green chemistry research. Following that publication, the Roundtable companies have identified a list of the key green engineering research areas that is intended to be the required companion of the first list. This publication summarizes the process used to identify and agree on the top key green engineering research areas and describes these areas, highlighting their research challenges and opportunities for improvements from the perspective of the pharmaceutical industry.

Table 1. Key green engineering research areas: results of the brainstorming and prioritization exercises

Rank	Main Key Areas	Sub-areas/aspects	Votes
1	Continuous Processing	Primary, Secondary, Semi-continuous, etc.	12
2	Bioprocesses	Biotechnology, Fermentations, Biocatalysis, GMOs,	11
3	Separation and Reaction Technologies	Membranes, crystallizations, etc.	11
4	Solvent Selection, Recycle and Optimization	Property modeling, volume optimization, recycling technologies, in process recycle, regulatory aspects etc.	10
5	Process Intensification	Technology, process, hybrid systems, etc	9

Reshoring of API/Intermediates Production

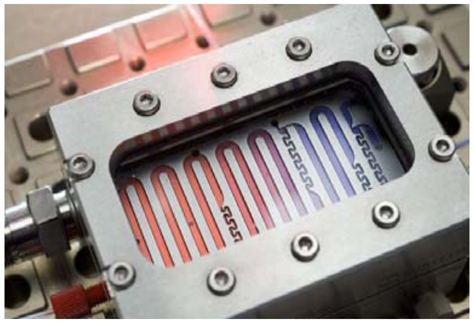


https://www.dcatvci.org/features/the-us-api-manufacturing-base-generics/

Advantages of Microreactor/Continuous Flow Chemistry

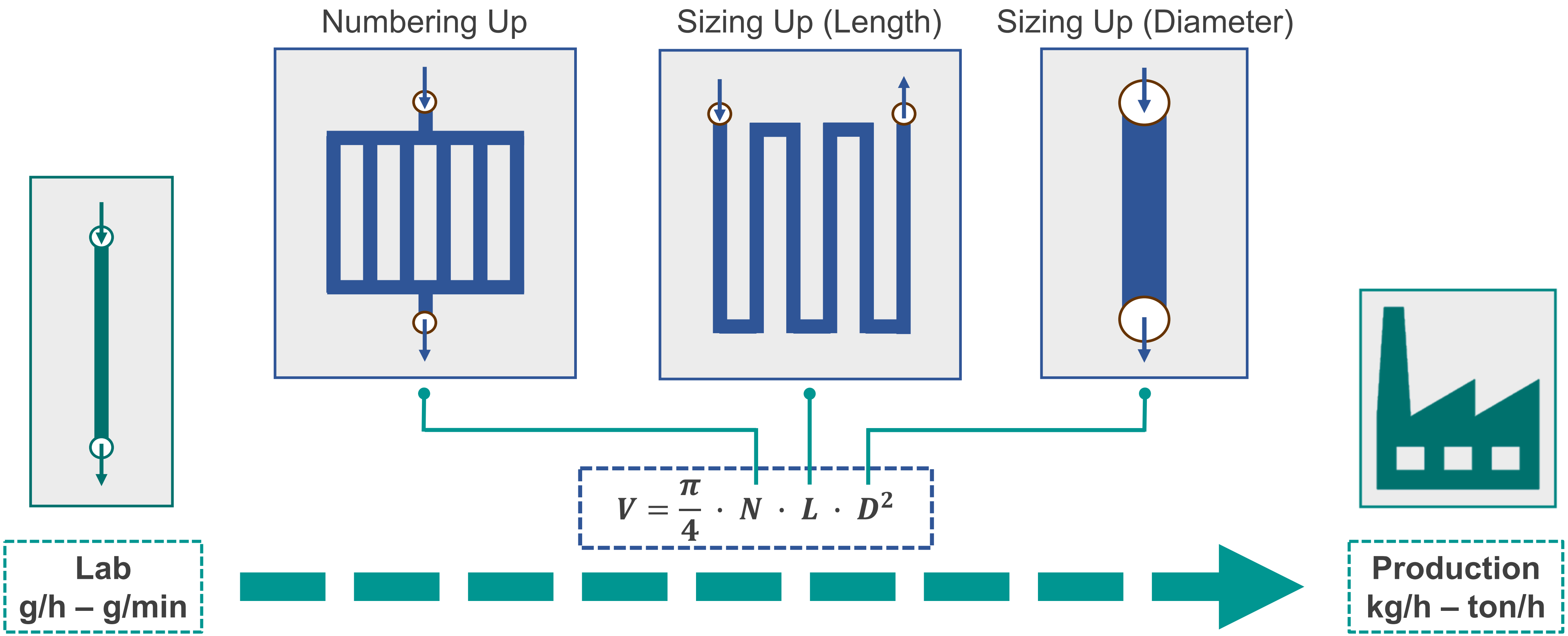
- Very efficient mixing of the reactants (micromixing)
- Rapid heat transfer and temperature control (high surface-to-volume ratio)
- Enhanced mass transfer for multi-phasic reactions (e.g. gas/liquid)
- Control of residence/reaction times
- Hazardous reagents/conditions
- Multi step reactions in a continuous sequence
- Continuous in-line purification possible by:
  - liquid/liquid extraction
  - membrane technology
  - solvent evaporation/swap
- Integrated real-time analytics (PAT)
- Easy scale-up of a proven reaction by:
  - increase of time
  - numbering up (internal, external)
  - sizing up (geometry, length)

Microreactor for Flow Processing



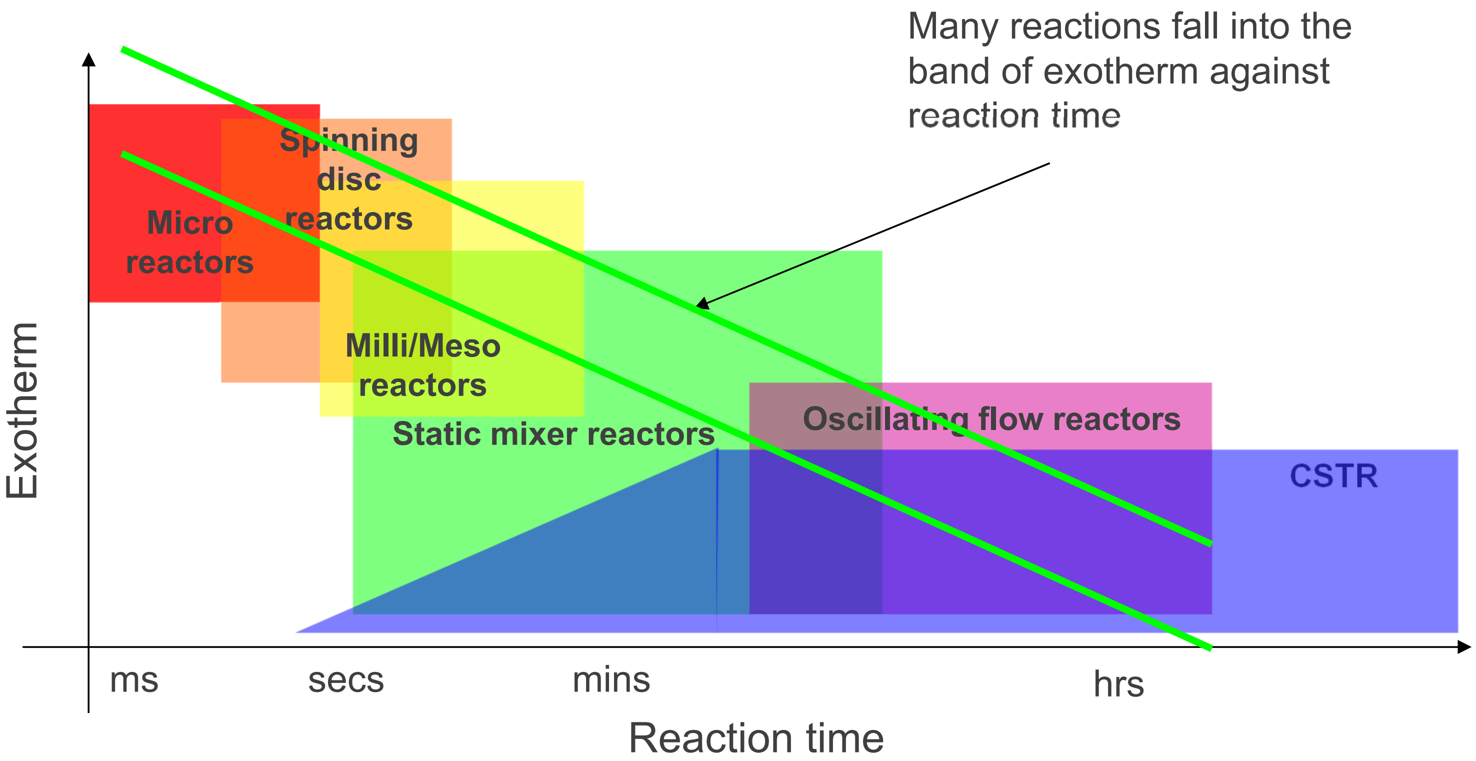
Scale-Up by Smart Dimensioning

Scalability Concept: Scale-Out and Scale-Up (Smart Dimensioning)



Dong, Z. et al. (Kuhn/Noel) *Chem. Eng. Sci.* **2021**, 100097
Zhang, J. et al. (MIT) *Annu. Rev. Chem. Biomol. Eng.* **2017**, *8*, 285; *Micro Process Engineering*, Wiley-VCH, Weinheim, **2009**

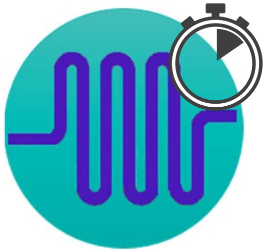
Equipment Selection – Reactor Technology



Huw Thomas, Foster Wheeler Energy Ltd (2002-2013)

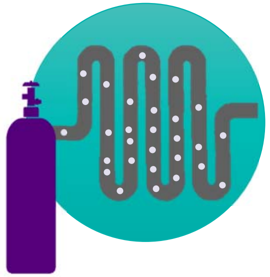
Flow Chemistry at CCFLOW –
Scalability and Manufacturability (CoG/Sustainability)

Flash Chemistry



High-T/p

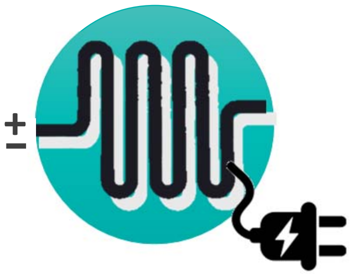
Gas-Liquid



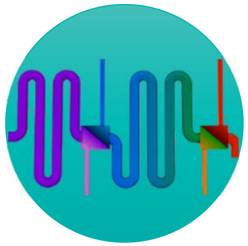
Hazardous Chemistry

Photochemistry

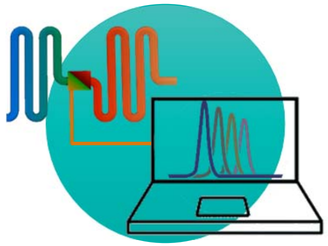
Electrochemistry



Multi-step/APIs



PAT/Process Control

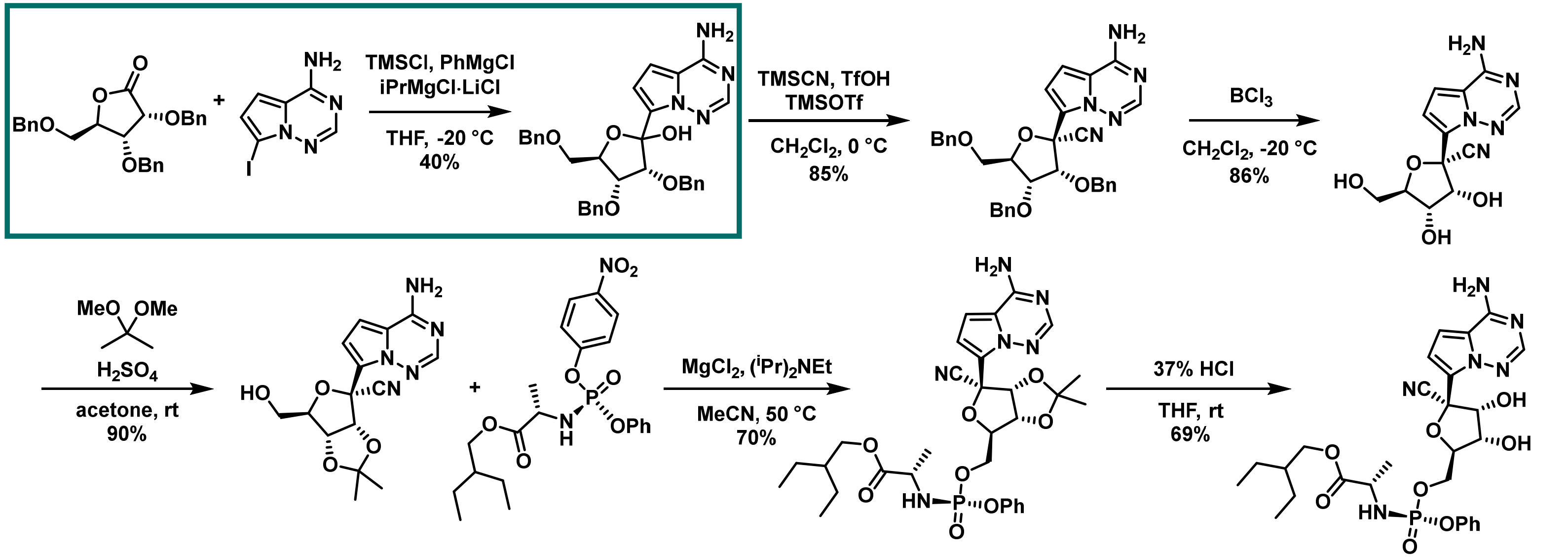


Organo-/Biocatalysis

3D-Printed Reactors/Calorimetry

Reactive Extrusion

Manufacturing Route to Remdesivir (COVID-19)



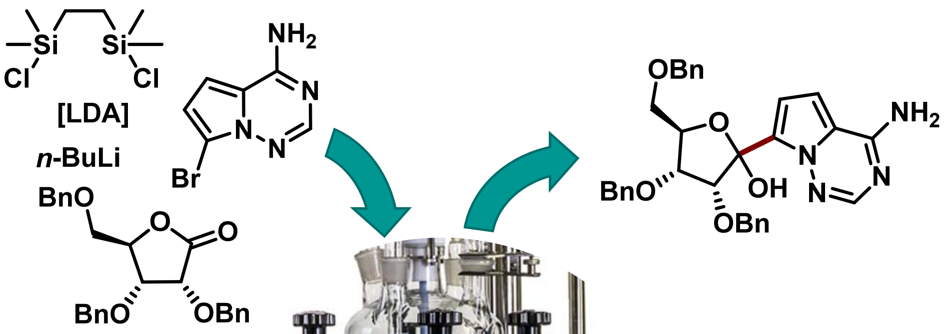
Warran, T. K. et al. *Nature* **2016**, *531*, 381
cf. organolithium method: Siegel, D. et al. *J. Med. Chem.* **2017**, *60*, 1648 (~20% yield)
cf. flow *C*-glycosylation (Mg): von Keutz, T. et al. *Org. Process Res. Dev.* **2020**, *24*, 2362

“The production of remdesivir is a long, linear chemical synthesis process that must be completed sequentially and includes several specialized chemistry steps and novel substances with limited global availability. The process is both resource- and time-intensive, with some individual manufacturing steps taking weeks to complete………..The typical ***timeline for manufacturing a drug like remdesivir at scale is nine to 12 months****; we have reduced that period to six to eight months.”*

https://www.gilead.com/purpose/advancing-global-health/covid-19/working-to-supply-remdesivir-for-covid-19 (June 24, 2020)
cf. Jarvis, L. M. Scaling up remdesivir amid the coronavirus crisis, *Chem. Eng. News* **2020** (April 20)

Key *C*-Glycosylation Step – Batch Process (0.2 M, -78 °C)

Xue, F. et al. *Org. Process Res. Dev.* **2020**, *24*, 1772



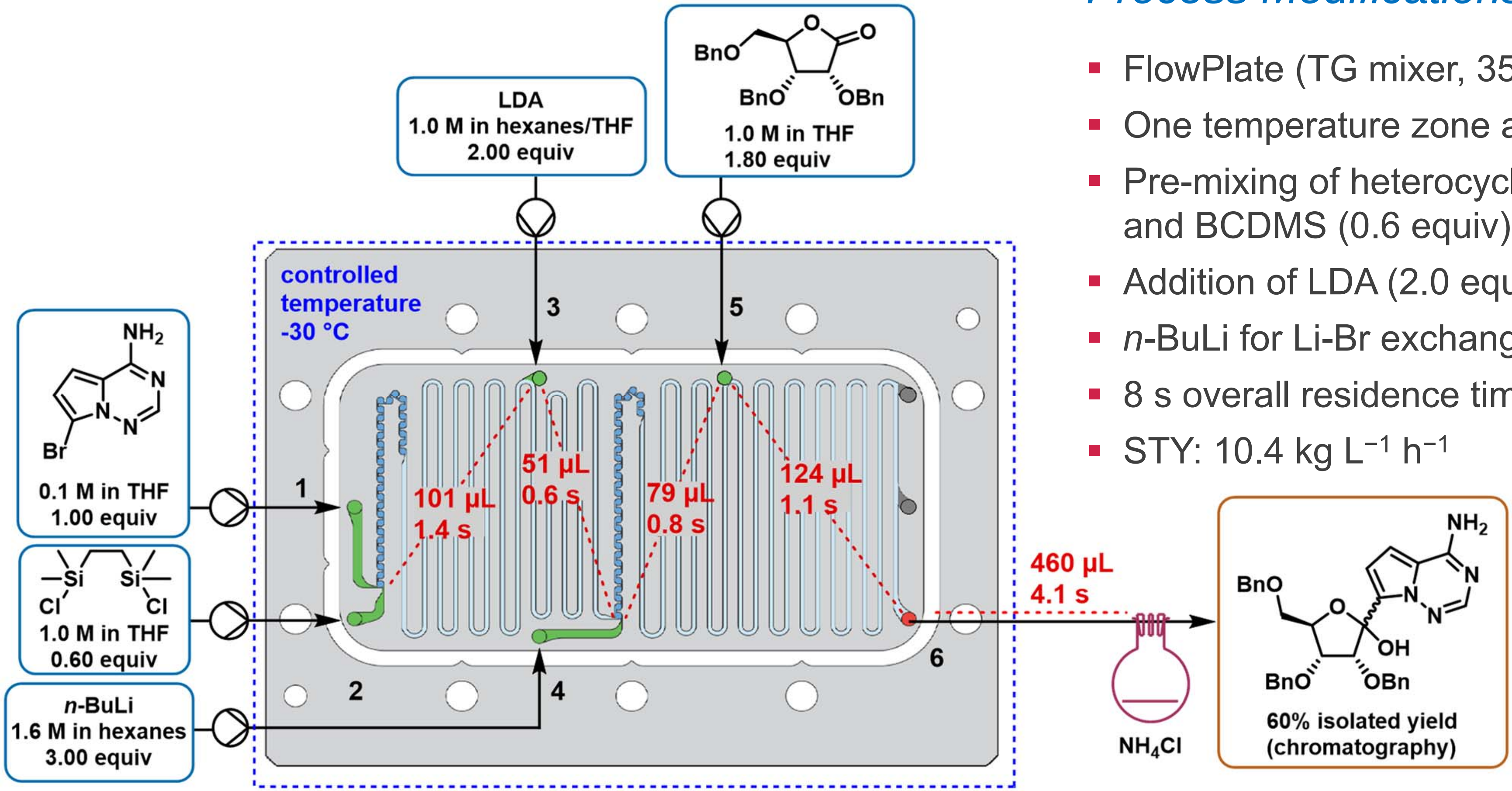
180 g scale
20 L vessel

1. charge heterocycle (0.845 mol) and anhydrous THF (1.44 L) to oven-dried reactor under N_2 at 20 °C
2. stir for **10 min**
3. charge BCDMS (1.1 equiv) in THF (360 mL)
4. stir for **15 min**
5. charge diisopropylamine (1.1 equiv)
6. cool to -85 °C to -78 °C (**?? 1 h ??**)
7. charge *n*-BuLi (2.5 M in hexane, 1.45 L, 4.3 equiv) within **4 h** (-78 °C)
8. react for **30 min** (-85 °C to -78 °C)
9. charge lactone (2.0 equiv) in anhydrous THF (0.9 L) within **3 h** (-85 °C to -78 °C)
10. react for **2 h** (-85 °C to -78 °C)
11. gradually warm to 0 to 10 °C (**?? 1 h ??**)
12. quench by addition of 1 M citric acid (3.6 L) at <25 °C (**10 min**)
13. work-up (62% yield by crystallization)

>12 h (full working day)

Key *C*-Glycosylation Step – Five Stream Flow Procedure (-30 °C)

von Keutz, T. et al.
Org. Process Res. Dev. **2021**, *25*, 1015



Process Modifications

- FlowPlate (TG mixer, 350 µL)
- One temperature zone at -30 °C
- Pre-mixing of heterocycle (0.1 M) and BCDMS (0.6 equiv)
- Addition of LDA (2.0 equiv) for deprotonation
- *n*-BuLi for Li-Br exchange (3.0 vs 4.3 equiv)
- 8 s overall residence time (8.5 g h^{-1})
- STY: 10.4 kg L^{-1} h^{-1}

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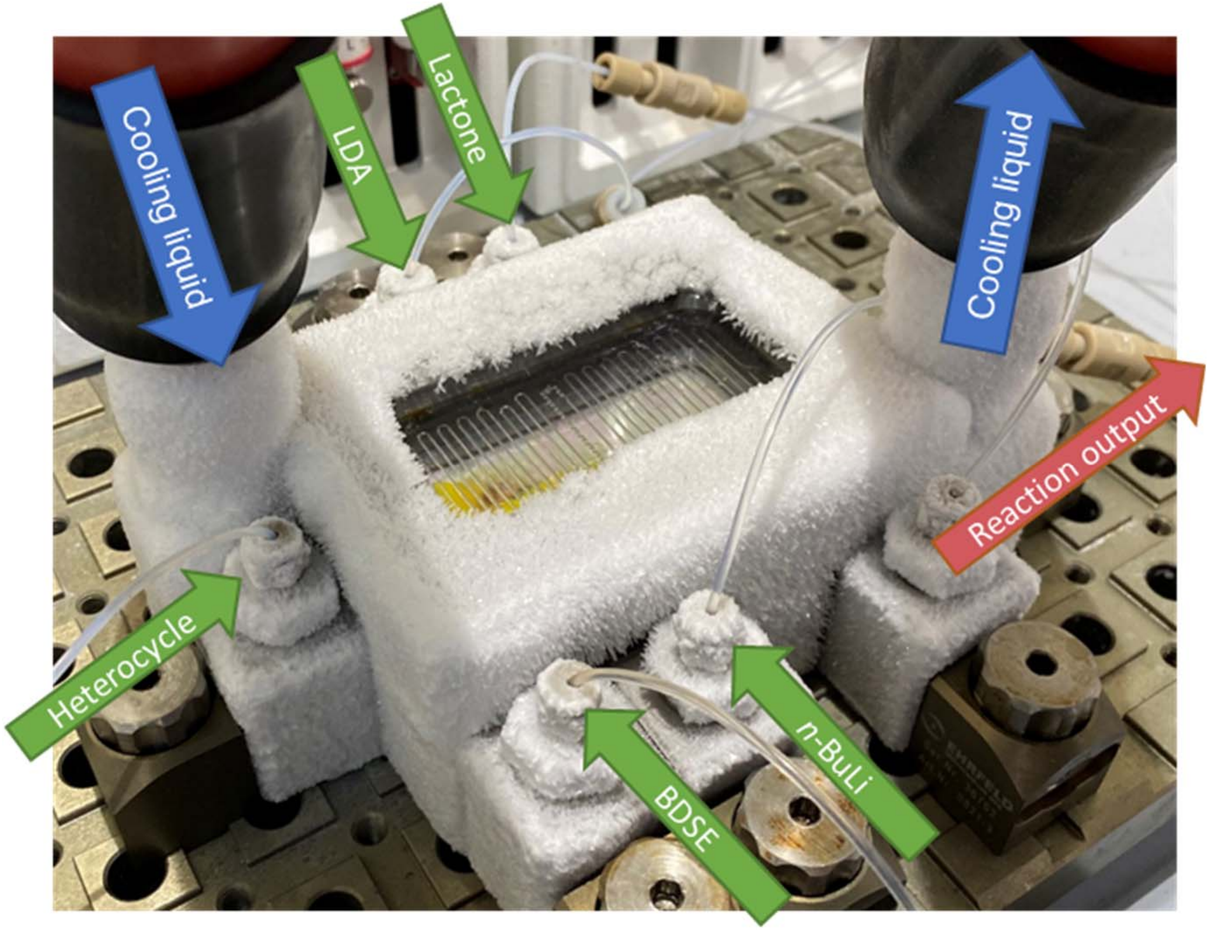
von Keutz, T. et al.
Org. Process Res. Dev. **2021**, *25*, 1015



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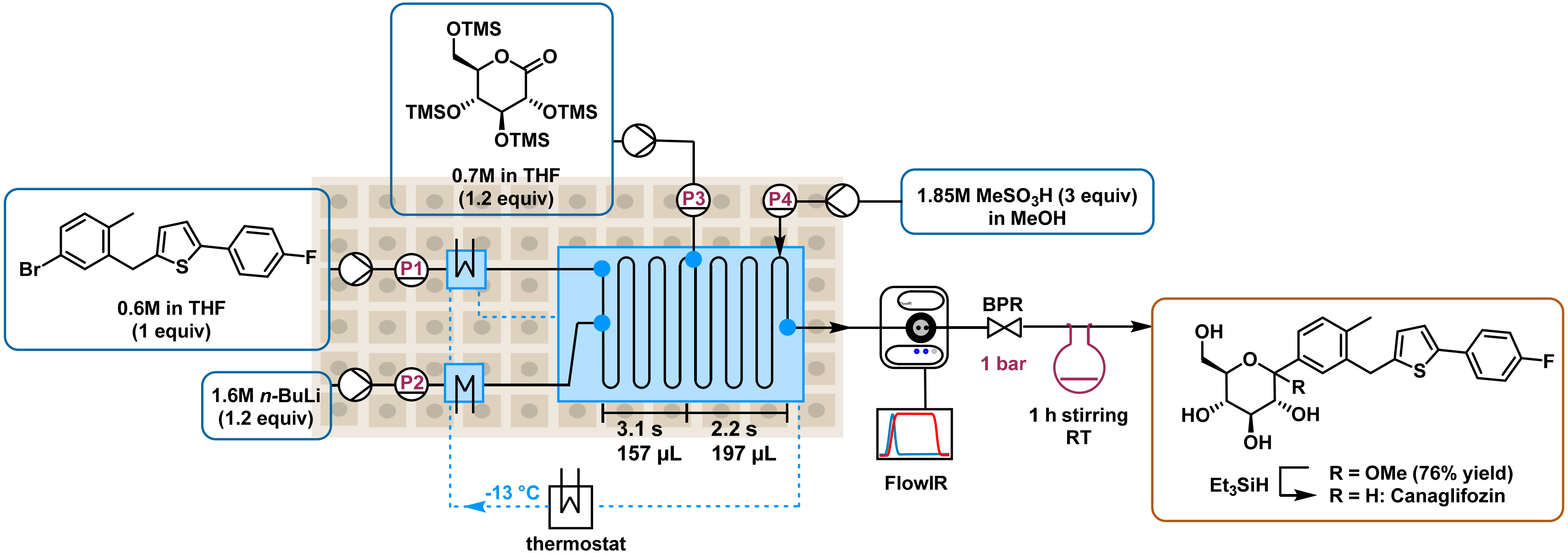
EHRFELD Mikrotechnik

Telescoped Process toward the Synthesis of Canagliflozin

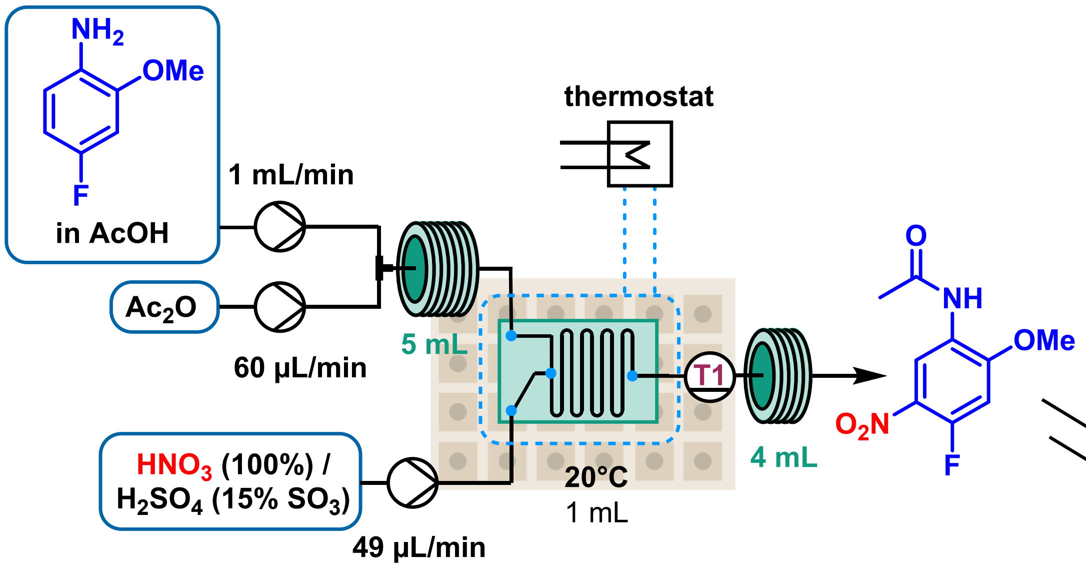


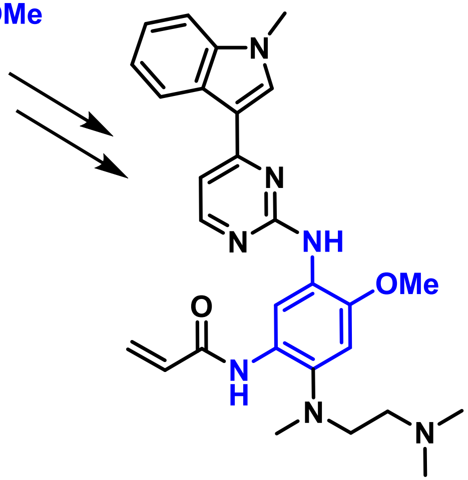
- 350 µL micromixer (TG mixer)
- −13 °C vs cryogenic (−78 to −50 °C) in batch
- 5 s vs >2 h reaction time (step 1 and 2)

Polterauer, D. et al. *Tetrahedron Lett*. **2021**, *83*, 153351
cf. biaryl building block: Cantillo, D. et al. *Chem. Eur. J.* **2015**, *21*, 12849

Continuous Nitration Towards Osimertinib Intermediate (Lab Scale)

- 5.6 g/h throughput
- 130 g/day

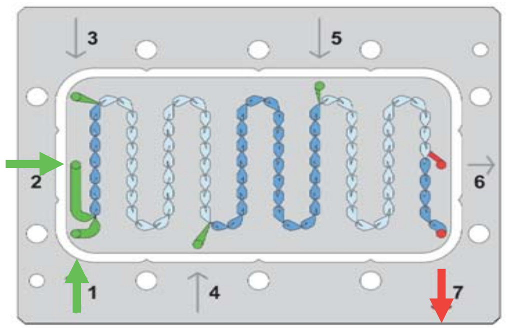




Osimertinib

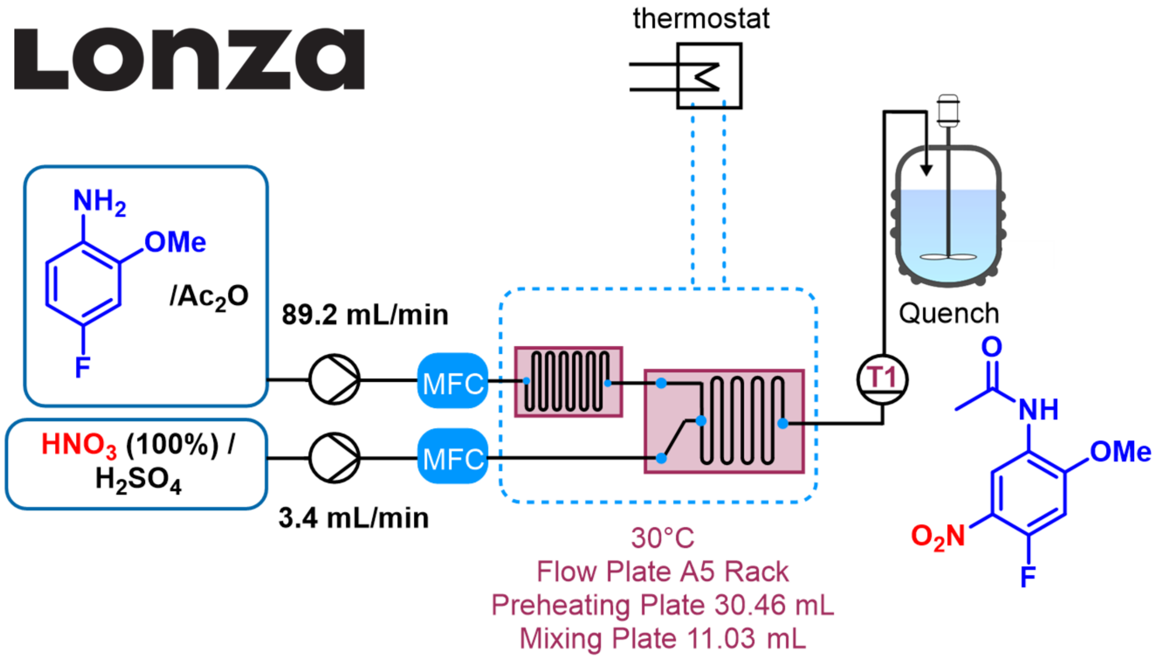
AstraZeneca

LL-Mixer (0.24 mL)
Channel width 0.2 mm
Channel depth 0.5 mm



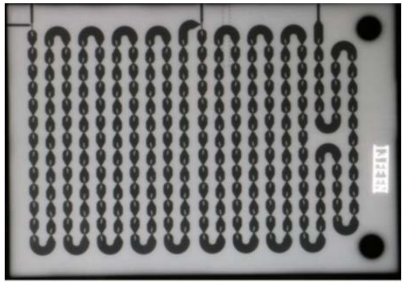
- reaction needs to be absolutely water free
- arene/Ac_2O/H_2SO_4/HNO_3 = 1/1.2/1.15/1.15 (mol)
- residence time in plate mixer ~13 s
- 82% isolated yield (7.5 g)

Continuous Nitration Towards Osimertinib Intermediate (Pilot Scale)



- 0.45 kg/h
- ~11 kg/day

LL-Mixer A5 (11 mL)
Channel width 0.5 mm
Channel depth 1.25 mm

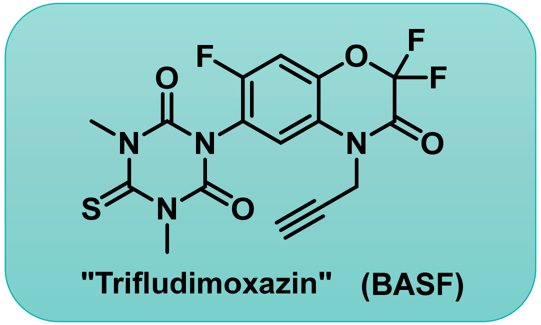


larger structure of A5 LL-Mixers (~25 mL)
width 0.7 mm × depth 1.75 mm
(4 × A5 plates in series, ~100 mL)

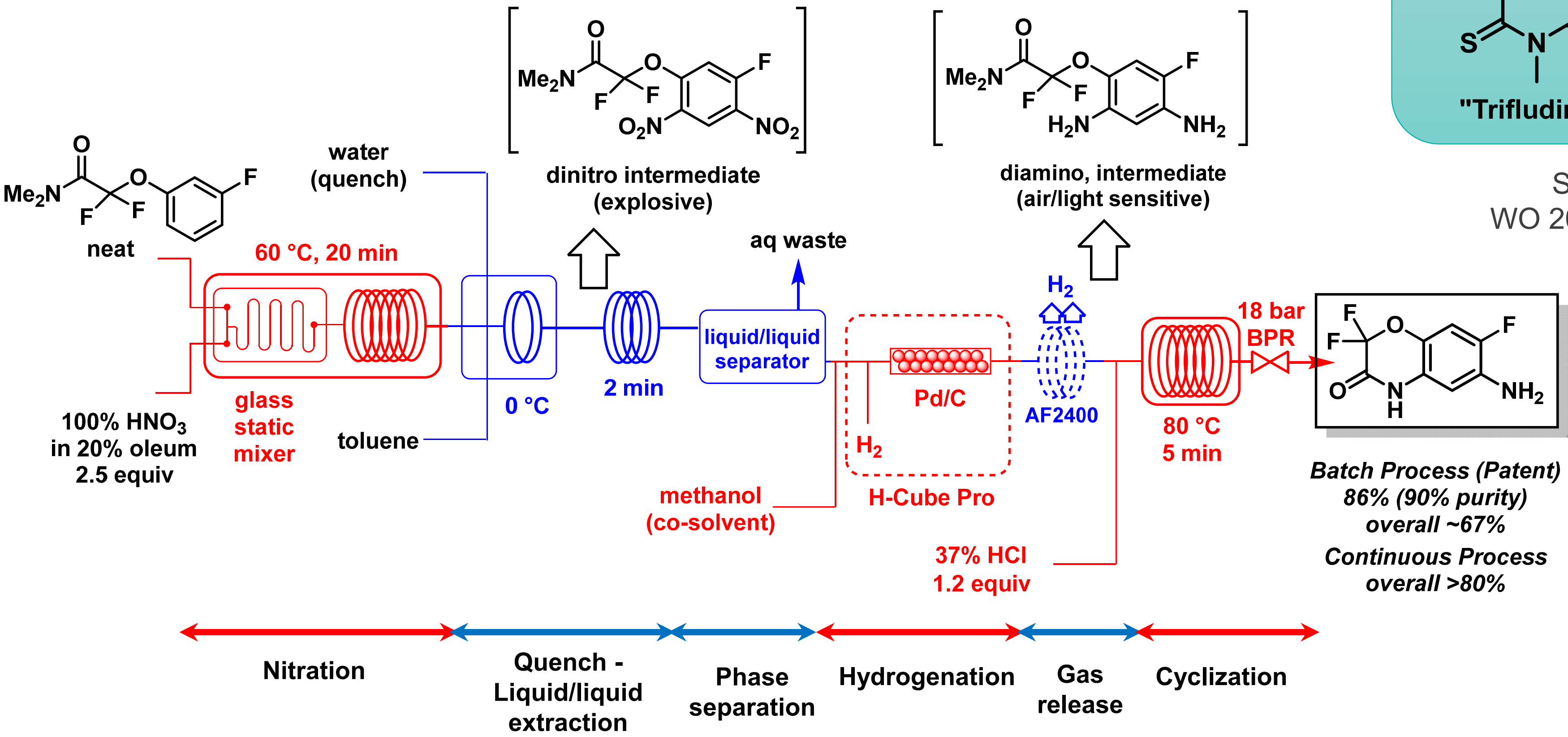
- arene/Ac_2O/H_2SO_4/HNO_3 = 1/1.2/1.1/1.1 (mol)
- residence time ~7 s (full mass transfer limited)
- 83% isolated yield (HPLC assay >99%)

Köckinger, M. et al. *Org. Process Res. Dev.* **2020**, *24*, 2217

Telescoped Synthesis of Agrochemical Intermediate

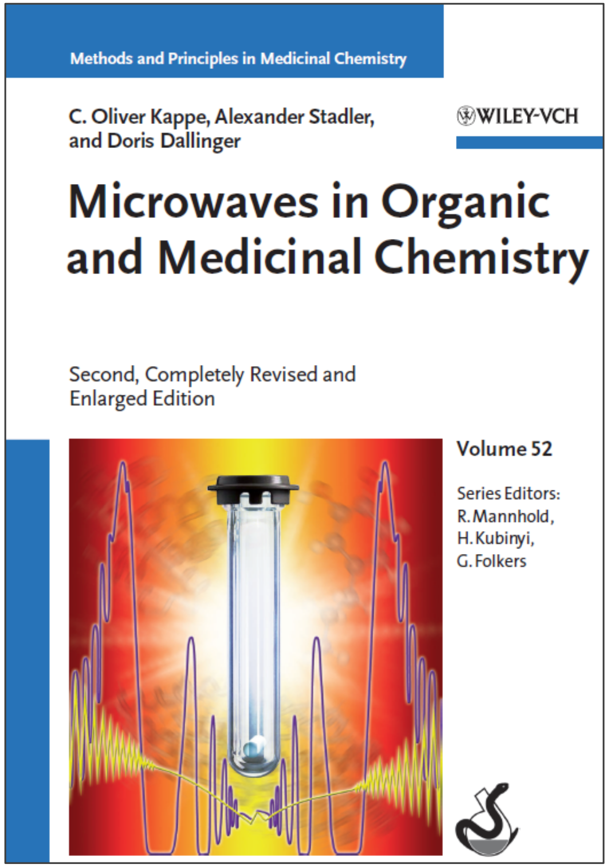


Steinbrenner, U. et al.
WO 2015071087 A1, **2015**



EP 15201920.4
Cantillo, D. et al. *Org. Process Res. Dev.* **2017**, *21*, 125

Process Intensification - Translating Microwave Batch to Flow

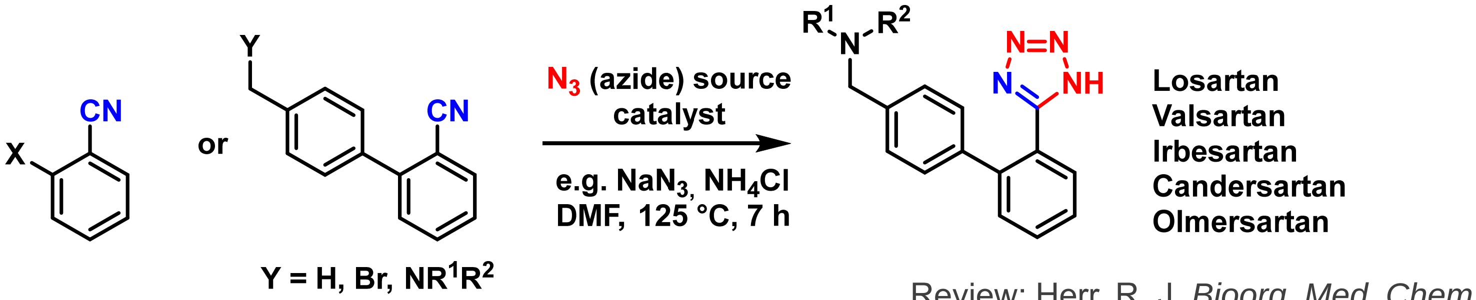


- transition metal catalyzed C-X bond formation
- other metal-mediated processes
- metathesis, CH-bond activation
- cycloaddition reactions
- rearrangements
- enantioselective reactions
- organocatalysis, biocatalysis
- radical reactions
- oxidations, reductions
- heterocycle synthesis
- total synthesis
- solid- /fluorous phase synthesis
- immobilized reagents, scavengers and catalysts
- solid phase peptide synthesis

Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250 (~3300 citations)
Kappe, C. O.; Stadler, A.; Dallinger, D. "*Microwaves in Organic and Medicinal Chemistry*" Wiley-VCH, **2005** (2nd Ed **2012)**
Glasnov, T.; Kappe, C. O. "*Microwave-to-Flow Paradigm*" *Chem. Eur. J.* **2011**, *17*, 11956

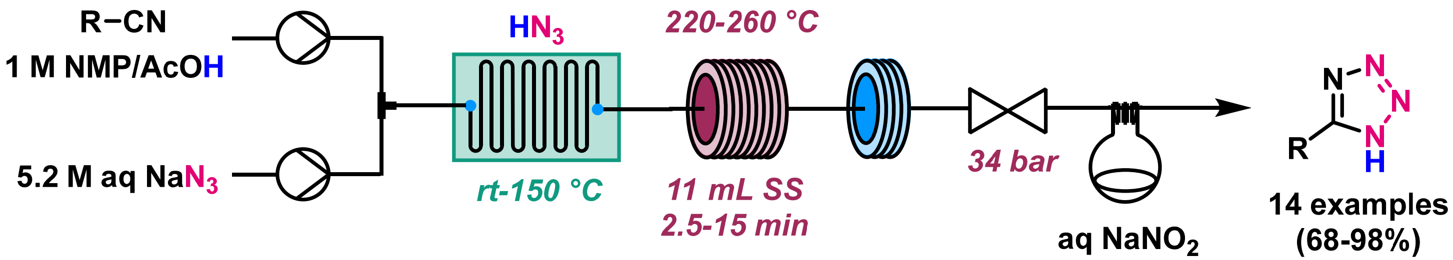
Tetrazole Synthesis in Flow under High-T/p Conditions

Sartans (Angiotensin II Receptor Antagonists)



Review: Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379

Two-Feed Continuous Flow Approach (In Situ HN_3)



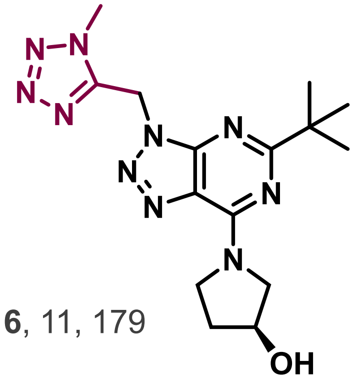
Lonza

Gutmann, B. et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 7101; *J. Flow Chem.* **2012**, *2*, 8
Mechanism: Cantilo, D. et al. *J. Org. Chem.* **2012**, *77,* 10882; *J. Am. Chem. Soc.* **2011**, *133,* 4465

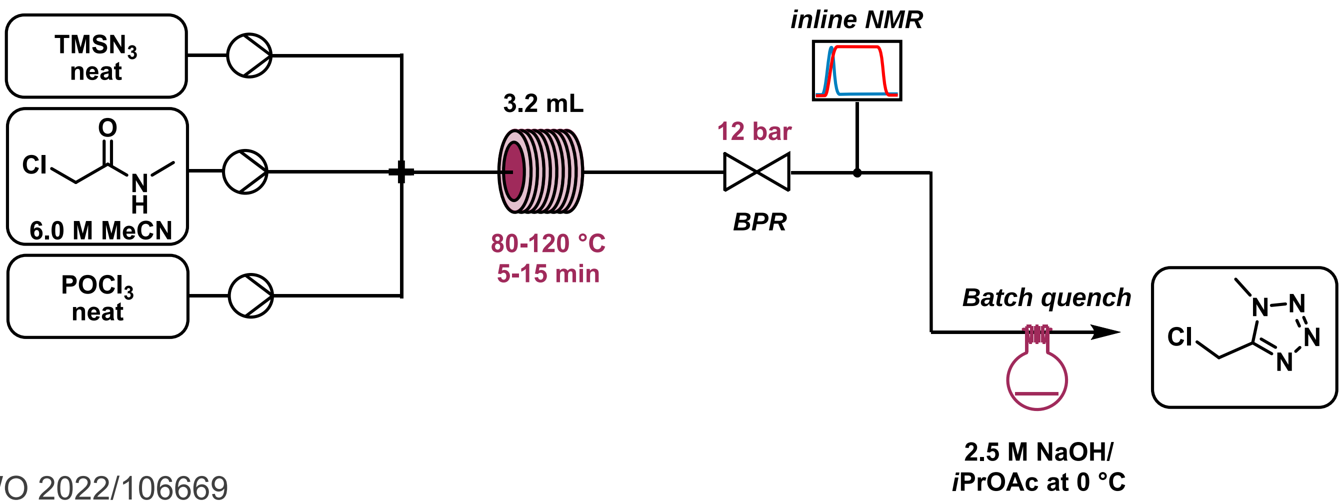
Tetrazole Synthesis in Flow under High-T/p Conditions

Cannabinoid Receptor 2 (CB2) Agonist (Vicasinabin)

- Microwave batch to flow translation
- Process analytics in real time (NMR/FT-IR)
- Continuous flow synthesis and workup strategy (~80% yield after crystallization, 10 g/h productivity)



Nettekoven, M. et al.
ChemMedChem **2016**, 11, 179



WO 2022/106669
Sagmeister, P. et al. *Org. Process Res. Dev.* **2021**, 25, 1206
cf. microwave batch procedure: Chandgude, A. L.; Dömling, A. *Eur. J. Org. Chem.* **2016**, 2383

Tetrazole Synthesis in Flow under High-T/p Conditions

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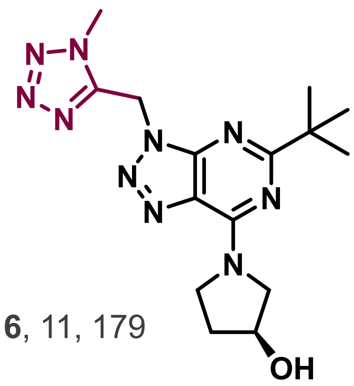
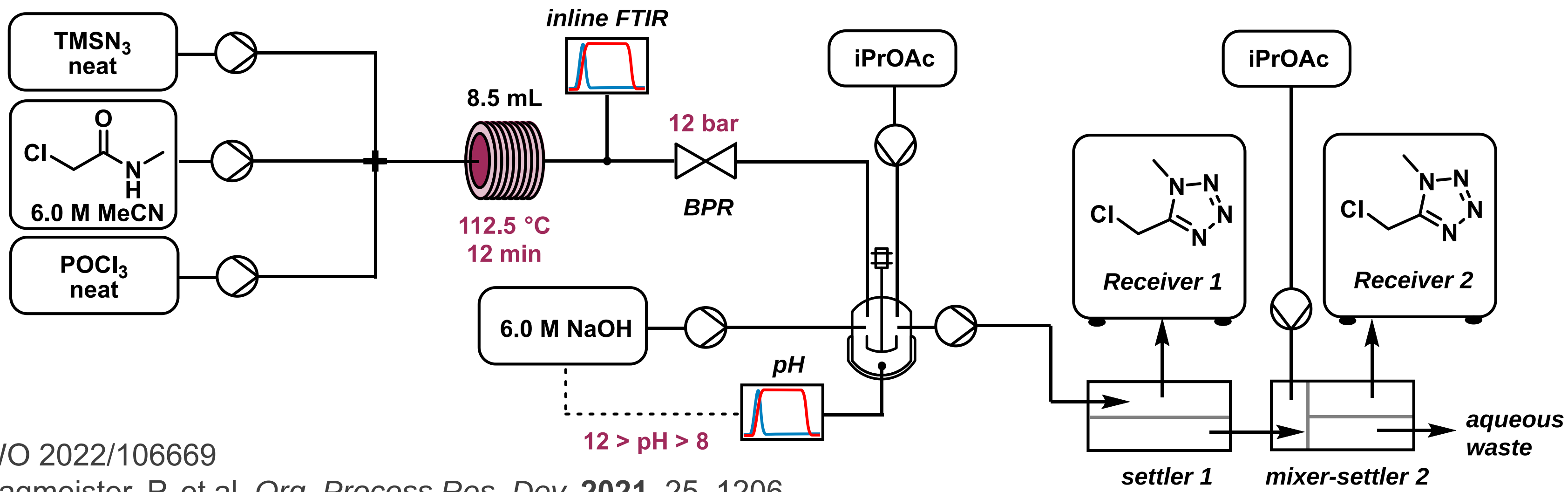
Roche



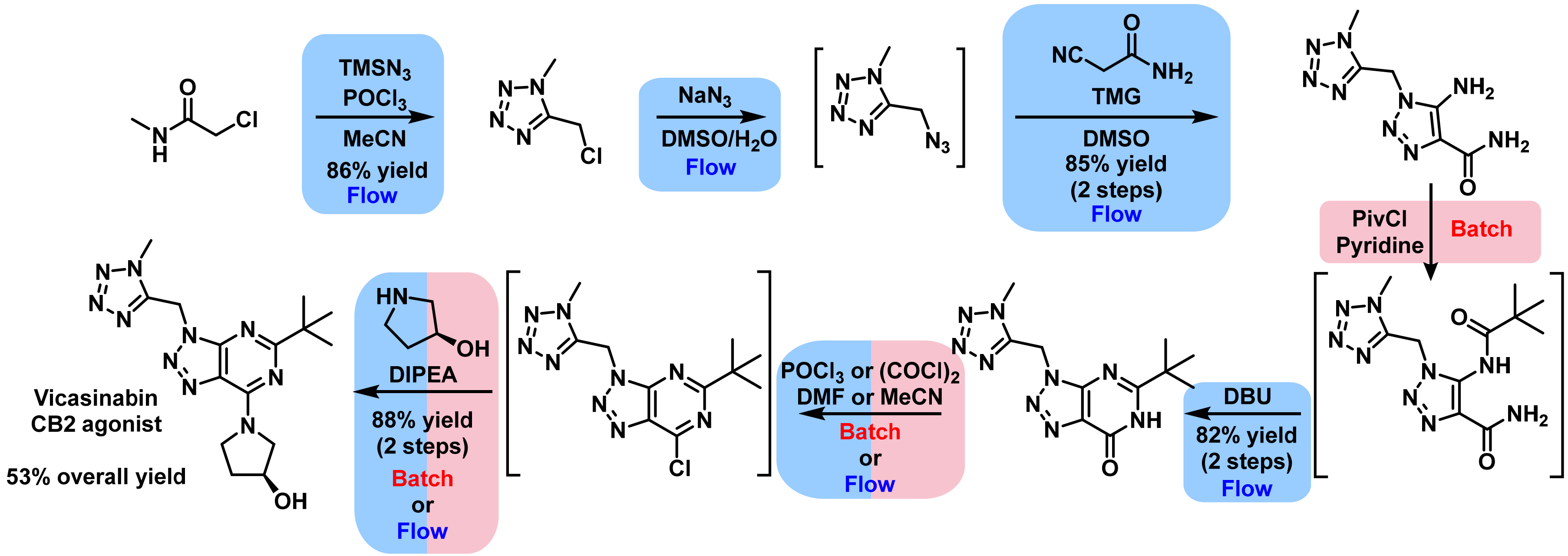
Nettekoven, M. et al. *ChemMedChem* **2016**, 11, 179



WO 2022/106669
Sagmeister, P. et al. *Org. Process Res. Dev.* **2021**, 25, 1206
cf. microwave batch procedure: Chandgude, A. L.; Dömling, A. *Eur. J. Org. Chem.* **2016**, 2383

End-to-end Synthesis of Vicasinabin Enabled by Flow Chemistry

Hybrid Flow and Batch Approach



WO 2022/106669 and patent pending

Sagmeister, P. et al. *Org. Process Res. Dev.* **2021**, 25, 1206 (step 1)

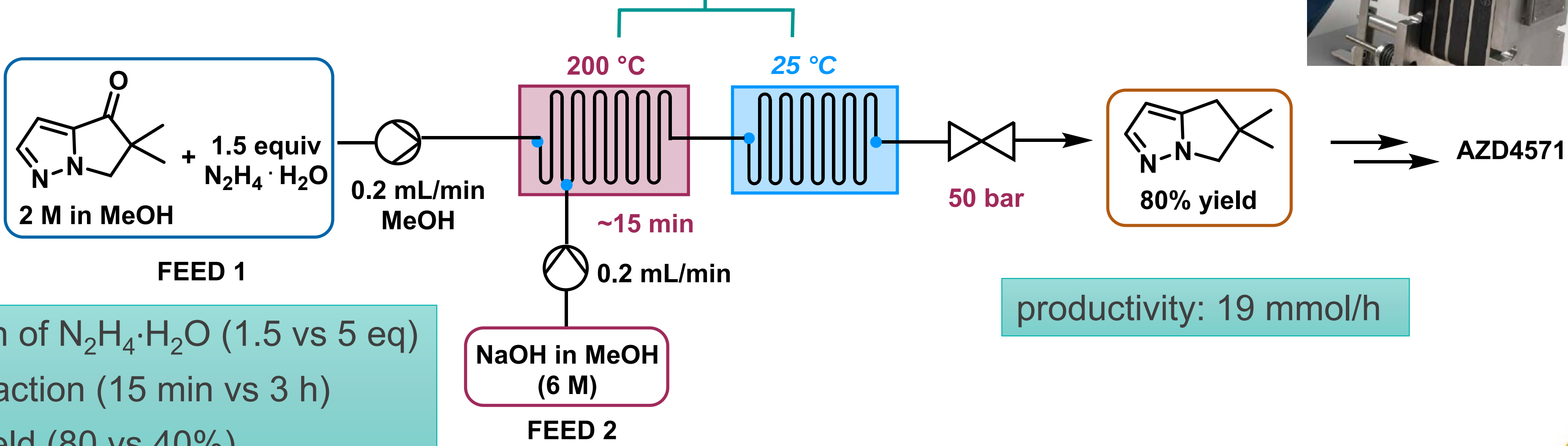
Sagmeister, P. et al. *Org. Process Res. Dev.* **2023**, 27, 592; Prieschl, M. et al. *Org. Process Res. Dev.* **2023**, 27, 601

Continuous-Flow Synthesis of an AZD4571 Building Block

Protrix SiC Reactor
2 reactor plates (6.91 mL)
1 cooling plate (3.61 mL)
CHEMTRIX

Scale-Up

Plantrix SiC Reactor
(100 mL – 4 L)
Patheon part of Thermo Fisher Scientific



productivity: 19 mmol/h

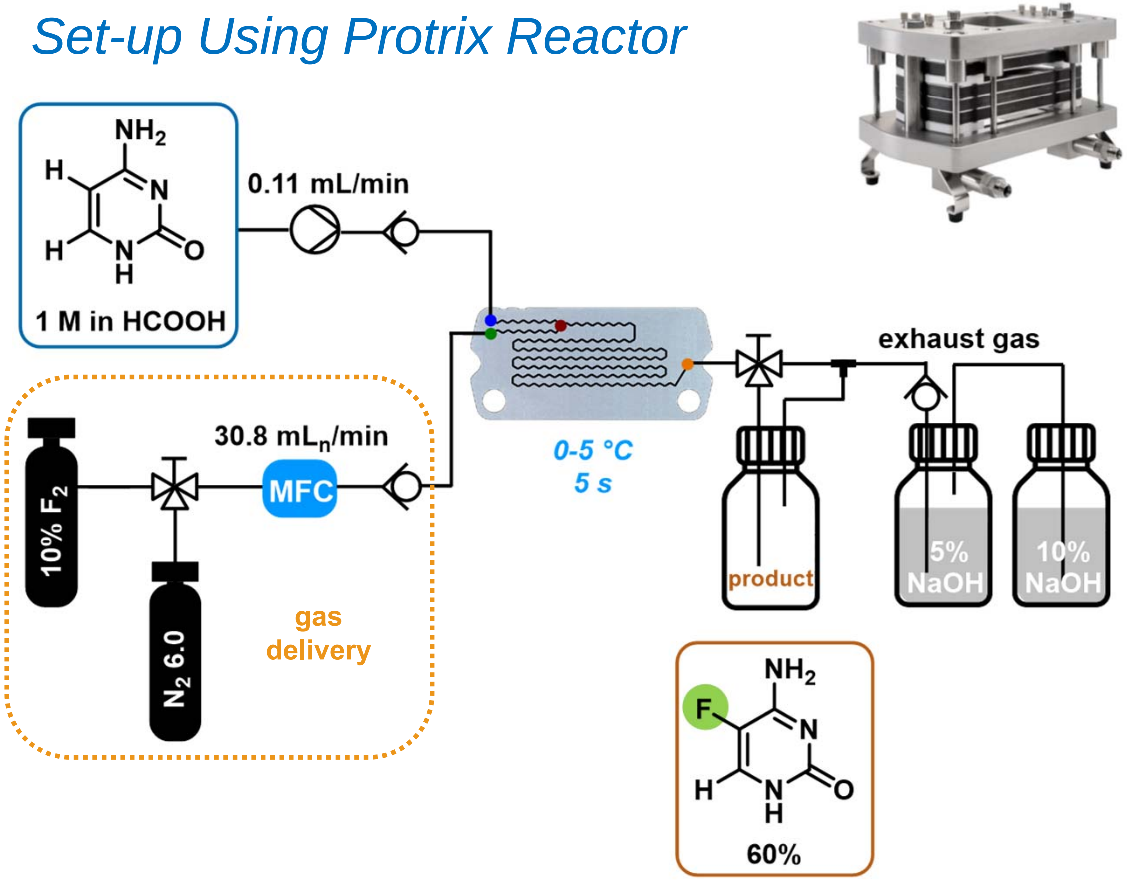
- Reduction of $N_2H_4{\cdot}H_2O$ (1.5 vs 5 eq)
- Faster reaction (15 min vs 3 h)
- Higher yield (80 vs 40%)

AstraZeneca

Znidar, D. et al., *Org. Process. Res. Dev.* **2019**, 23, 2445
cf. Newman, C. G. et. al. (MIT) *Green Chem.* **2014**, *16*, 176 (~0.5 mL SiC microreactor)

Direct Fluorinations using 10% F_2/N_2 in a SiC Reactor

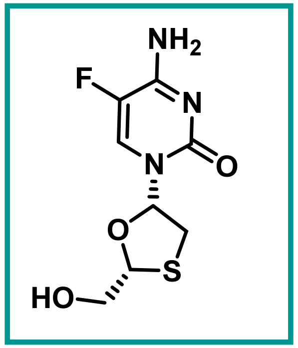
Set-up Using Protrix Reactor



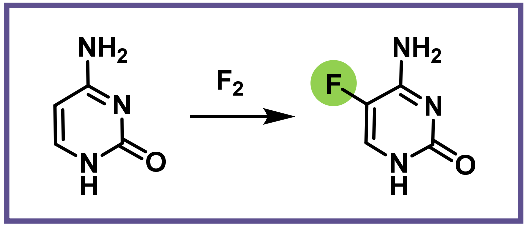
Znidar, D. et al. *ACS Chem. Health Saf.* **2022**, *29*, 165
cf. Harsanyi, A. et al. (Sanofi) *Org. Process Res. Dev.* **2017**, *21*, 273

Emtricitabine (FTC)

- antiretroviral agent
- treatment of HIV/AIDS
- commonly used in combination therapy with Tenofovir and Efavirenz (Truvada, Atripla)
- Atripla: \$2.8 billion in sales

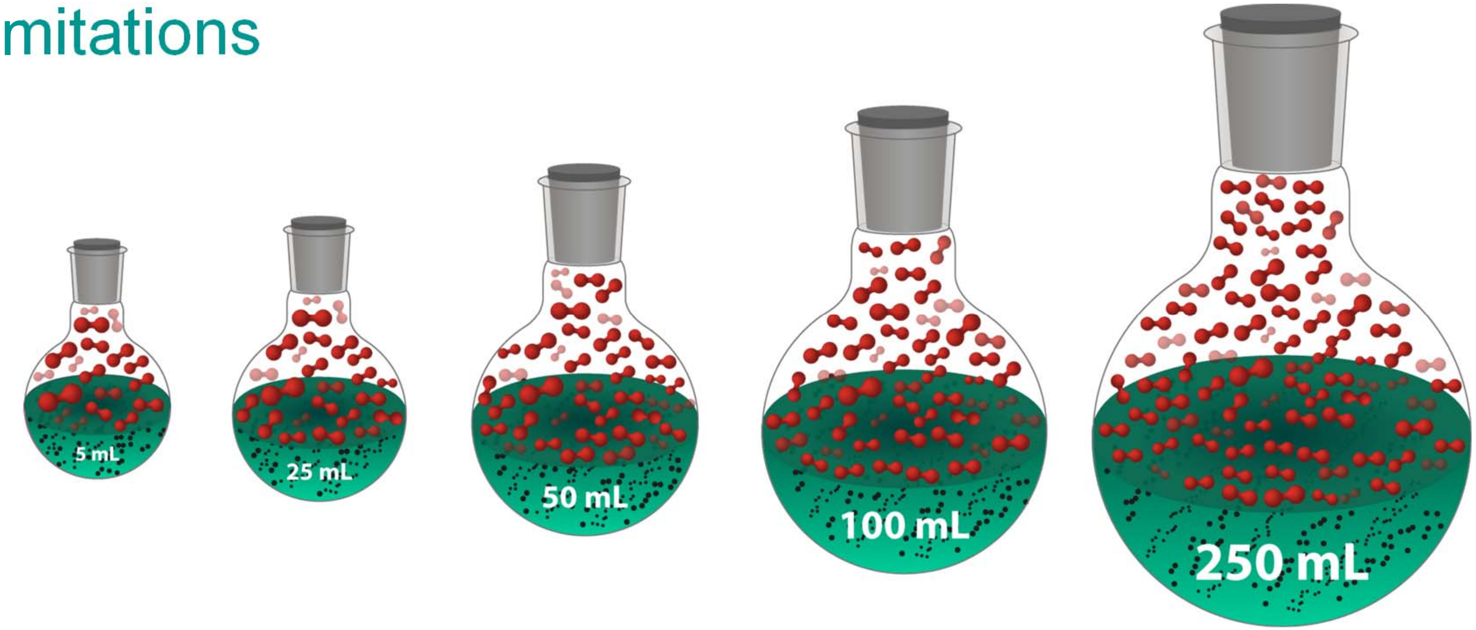


COST REDUCTION VIA DIRECT FLUORINATION



US8748604, **2011**

Scaling-up Gas-liquid Reactions in Batch – Mass Transfer Limitations



Volume (mL)	5	25	50	100	250
Radius r (m)	0.014	0.021	0.025	0.033	0.043
Interfacial area a ($m^2\ m^{-3}$)	107	71	60	46	35

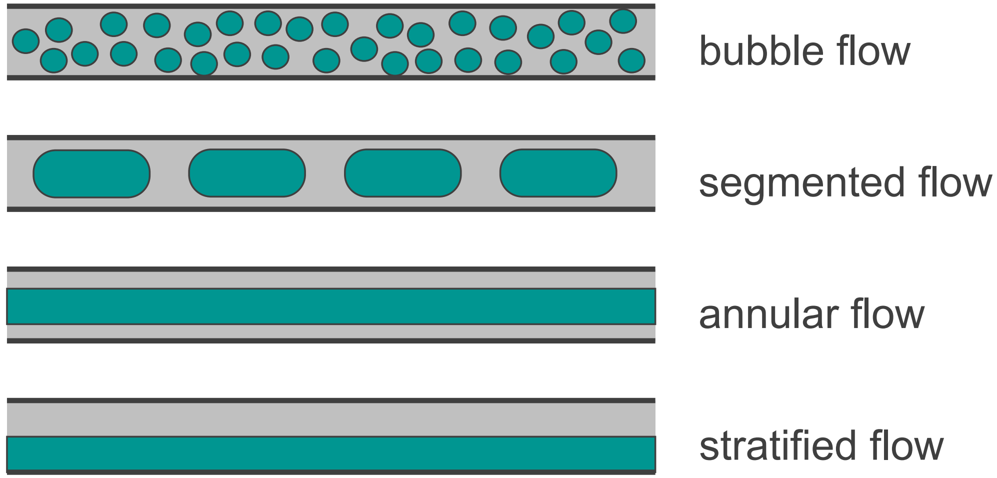
Review: Mallia, C. J.; Baxendale, I. R. *Org. Process Res. Dev.* **2016**, *20*, 327

Mass Transport Intensification in Flow

Gas-Liquid Flow Regimes - Interfacial Areas

- interfacial area in coil reactors is 50 to 700 m^2m^{-3}
- interfacial area in micoreactors up to 18.000 m^2m^{-3}

Mallia, C. J.; Baxendale, I. R. *Org. Process Res. Dev.* **2016**, *20*, 327
Yue, J. et al. *Chem. Eng. Sci*. **2007**, *62*, 2096



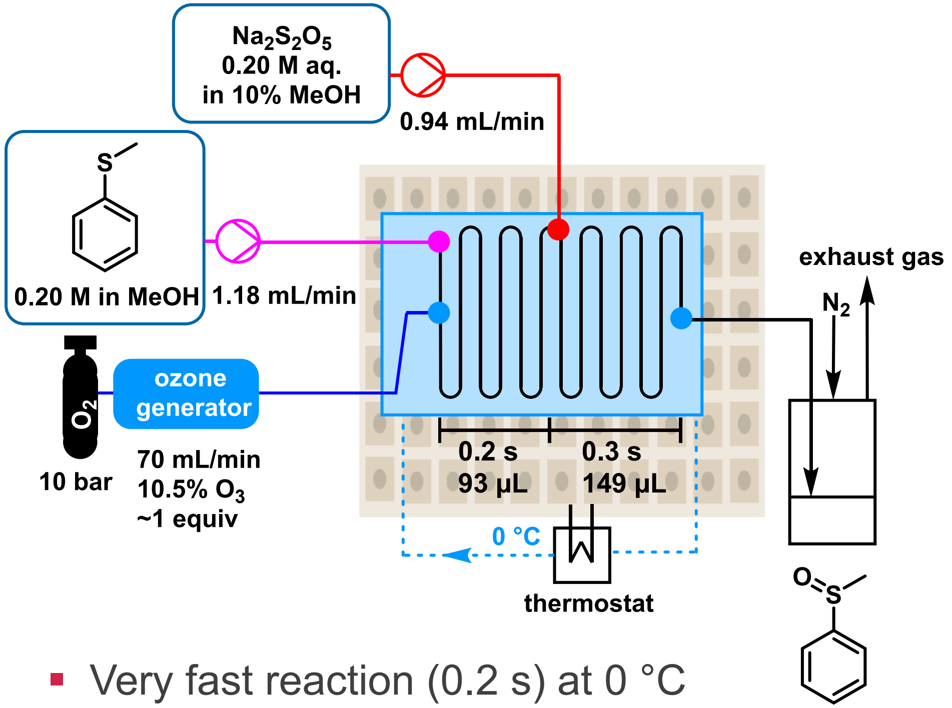
Other Factors

- higher solubility of gases in pressurized reactors (Henry's law)
- exact dosing using mass flow controllers, use of large stoichiometric excess (headspace) avoided
- safety aspects

Gavriilidis, A. et al. *React. Chem. Eng.* **2016**, *1*, 595; Pieber, B.; Kappe, C. O. *Top. Organomet. Chem*. **2016**, *57*, 97
Hone, C. A.; Kappe, C. O. *Top. Curr. Chem.* **2019**, *377*, 2; Kockmann, N. et al. *React. Chem. Eng.* **2017**, *2*, 258

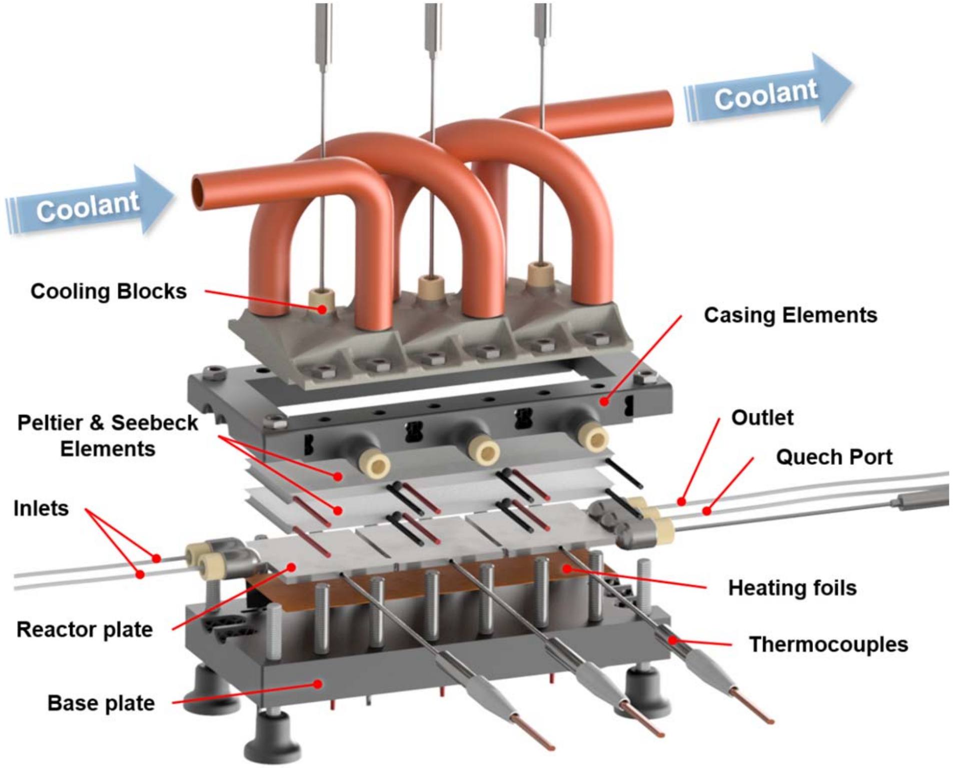
Ozone Chemistry in Microreactors

Selective Sulfide Oxidation



- Very fast reaction (0.2 s) at 0 °C
- Intensive gas-liquid mixing

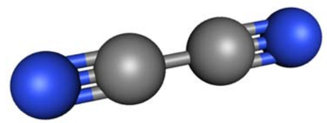
Polterauer, D. et. al. *React. Chem. Eng*. **2021**, *6*, 2253
cf. flow ozonolysis in tubing (22 s): Irfan, M. et al. *Org. Lett.* **2011**, *14,* 984



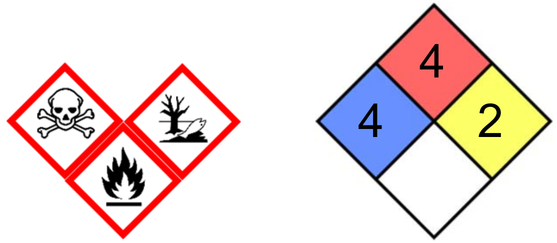
reaction enthalpy: dH_R = ca. - 190 kJ/mol

Maier, M. C. et al. *React. Chem. Eng.* **2020**, *5*, 1410
cf. flash chemistry: Fu, G. *React. Chem. Eng.* **2023**, *8*, 577

Cyanogen $(CN)_2$ – A “Forgotten” Reagent

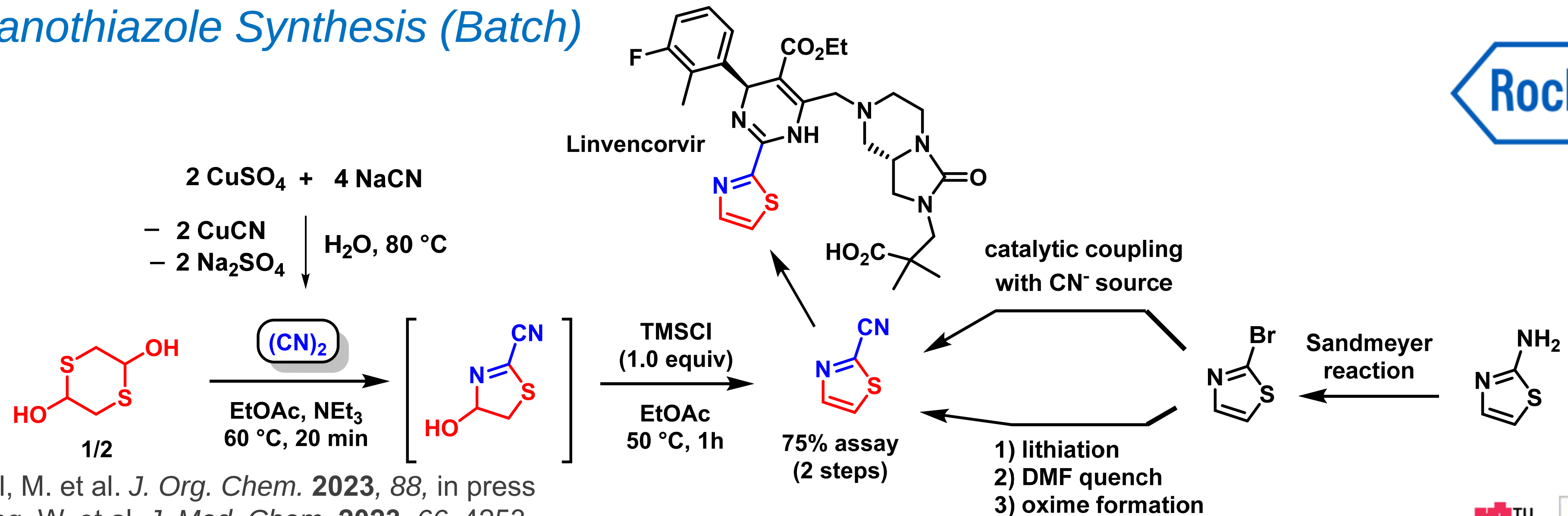


- Highly reactive and toxic gas (bp. -21 °C)
- Discovered in 1816, scarce reports in organic synthesis since 1950
- Cheaply available on large scale as grain fumigant (20-30 USD per kg)



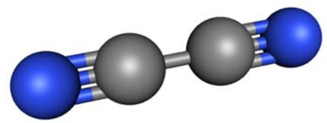
Gay-Lussac, G. *Ann. Phys.* **1816**, 1372; Hooper, J. L. et al. *Pest Manag. Sci.* **2003**, 353

2-Cyanothiazole Synthesis (Batch)



Prieschl, M. et al. *J. Org. Chem.* **2023**, *88,* in press
cf. Zhang, W. et al. *J. Med. Chem.* **2023,** *66,* 4253

Cyanogen $(CN)_2$ – A “Forgotten” Reagent



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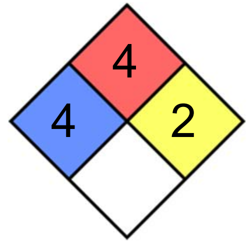
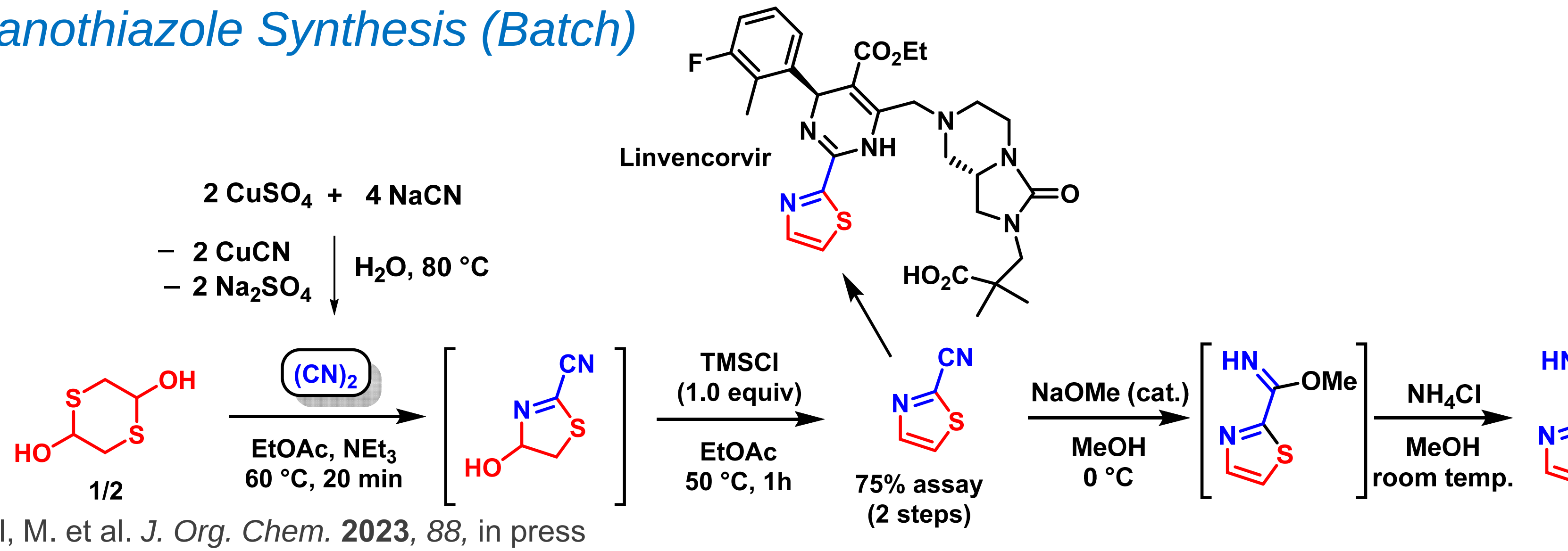


Gay-Lussac, G. *Ann. Phys.* **1816**, 1372; Hooper, J. L. et al. *Pest Manag. Sci.* **2003**, 353

2-Cyanothiazole Synthesis (Batch)

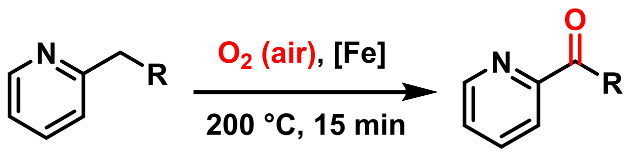


Prieschl, M. et al. *J. Org. Chem.* **2023**, *88,* in press
cf. Zhang, W. et al. *J. Med. Chem.* **2023,** *66,* 4253

Multiphase Flow Chemistry Examples (O_2, CO, CO/O_2, CO/H_2)

Lonza

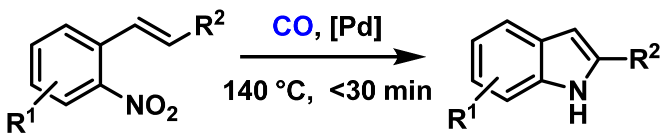
Benzylic Oxidations



Green Chem. **2013**, *15*, 320
ACS Catal. **2013**, *3*, 2669

Lonza

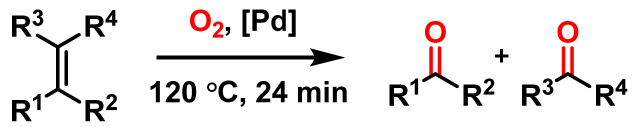
Reductive Cyclization



RSC Adv. **2017**, *7*, 10469

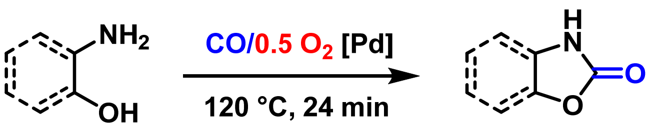
AstraZeneca

Alkene Cleavage



ChemCatChem **2017**, *9*, 3298

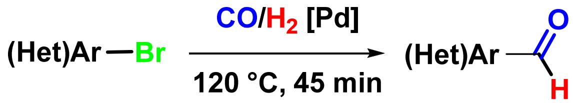
Oxidative Carbonylation



Org. Process Res. Dev. **2017**, *21*, 1080

AstraZeneca

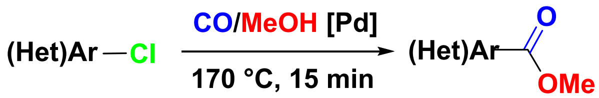
Reductive Carbonylation



ChemSusChem **2019**, *12*, 326

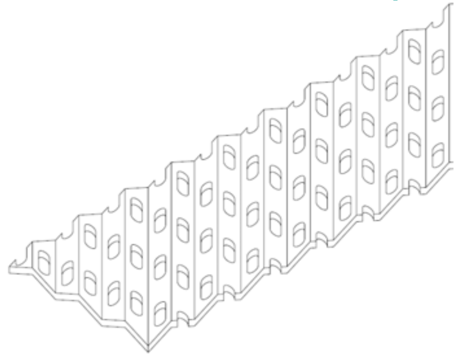
Janssen

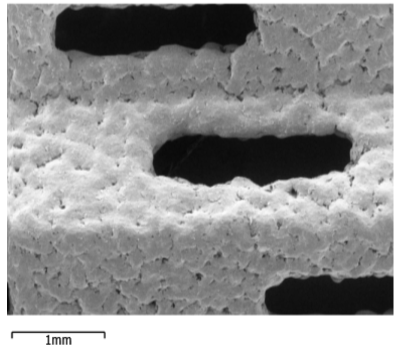
Methoxycarbonylation

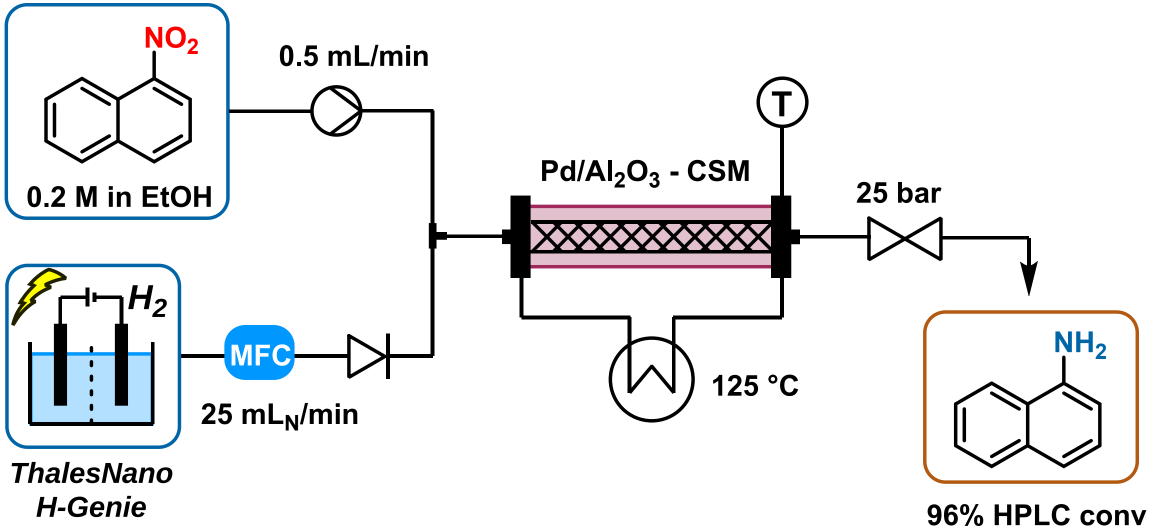


ChemCatChem **2019**, *11*, 997

Continuous Hydrogenation using Catalytic Static Mixers (CSM)

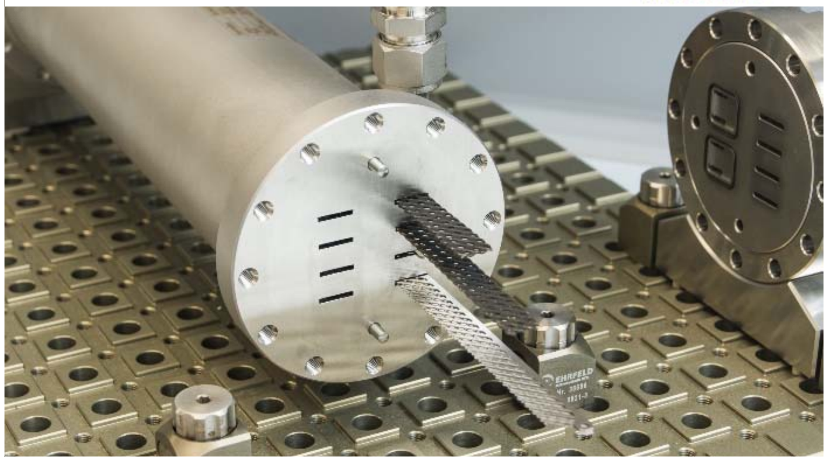






cf. catalytic static mixers: Avril A. et al. (CSIRO) *React. Chem. Eng.* **2017**, *2*, 180
Hornung, C. H. et al. *Org. Process Res. Dev.* **2017**, *21*, 1359
Gardiner, J. et al. *Org. Process Res. Dev.* **2018**, *22*, 1448
Comparison with packed bed technology: Zhu, Y. et al. *J. Flow Chem.* **2021**, *11*, 515

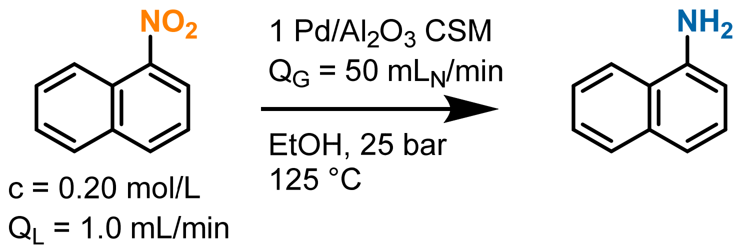
Miprowa Lab Reactor



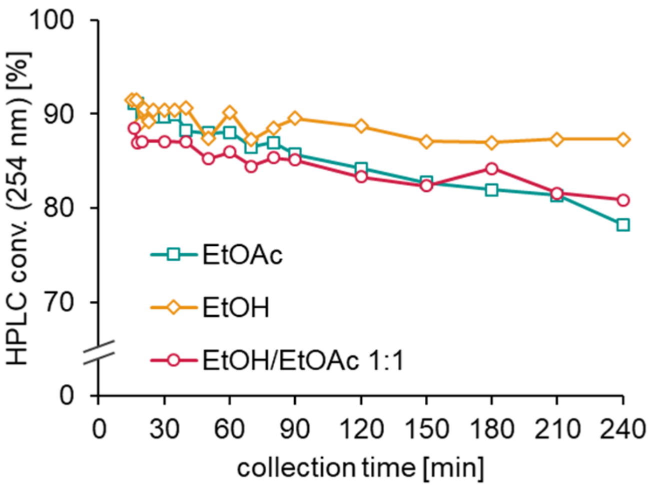
Biessey, P. et al. *Chem. Eng. Technol.* **2015**, *38*, 602

Reaction Parameters: Pd/Al_2O_3

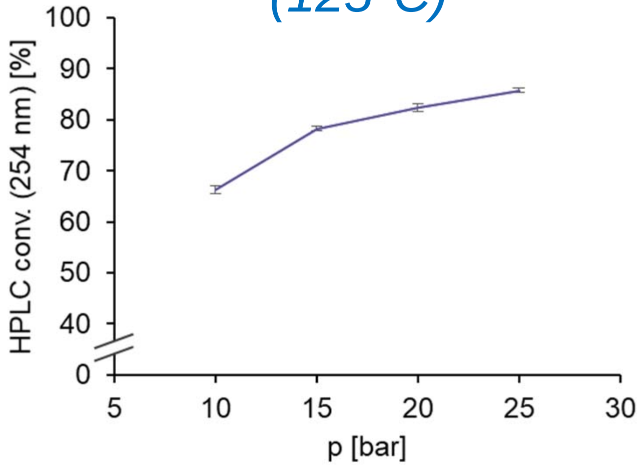
- Solvent selection:
  - Solubility tests
  - CHEM21 recommendations
  - Preliminary hydrogenation test runs



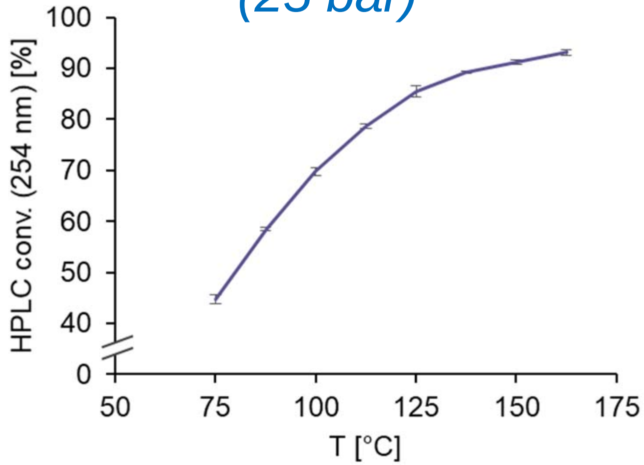
Solvent Dependent Stability



Pressure Influence (125°C)



Temperature Influence (25 bar)



Pd/Al_2O_3 CSM Stability

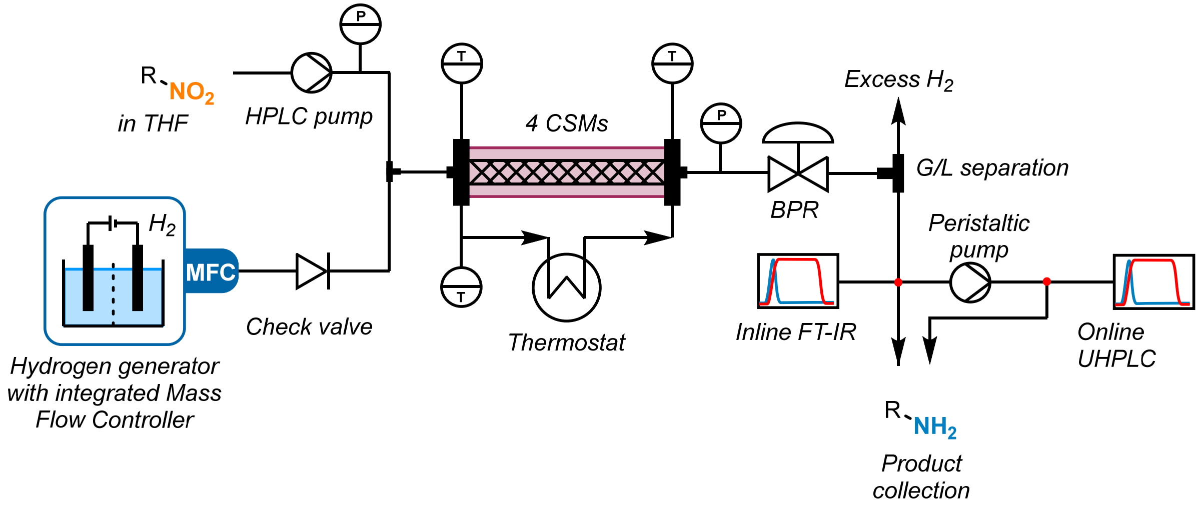
- Same CSM for all initial optimizations: stable
- Constant weight: 7.458 g vs. 7.462 g after 2 months (ca. 12 mg Pd per CSM)
- ICP-MS analysis:
  - a) 1 CSM EtOH/H_2 purge at 125 °C
  - b) 1 CSM hydrogenation reaction in EtOH at 125 °C
  - c) 1 CSM hydrogenation reaction in EtOH at 175 °C
  - d) 4 new CSMs hydrogenation reaction in EtOH at 125 °C

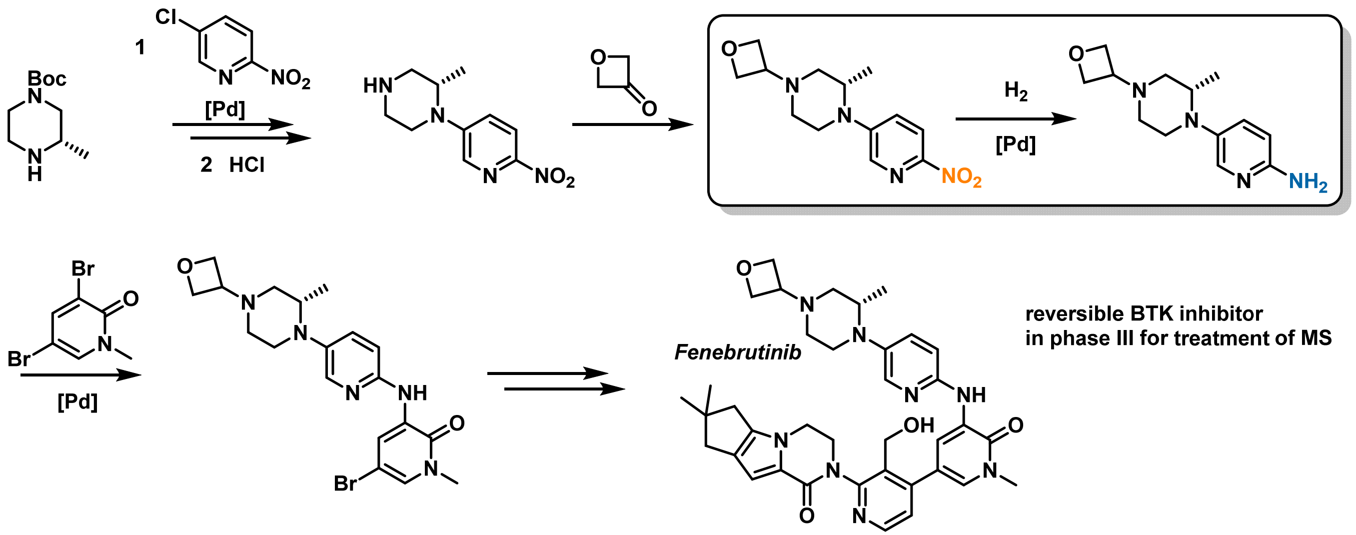
entry	Al [ppm]	Cr [ppm]	Fe [ppm]	Ni [ppm]	Cu [ppm]	Mo [ppm]	Pd [ppm]
a)	< 0.05	< 0.001	< 0.01	< 0.005	< 0.0005	< 0.005	< 0.0005
b)	< 0.05	< 0.001	< 0.01	0.019 ± 0.002	< 0.0005	0.0050 ± 0.0006	< 0.0005
c)	< 0.05	< 0.001	< 0.01	< 0.005	< 0.0005	0.0063 ± 0.0002	< 0.0005
d)	< 0.05	< 0.001	< 0.01	< 0.005	< 0.0005	< 0.005	< 0.0005

Lebl, R. et al. *Catal. Today* **2022**, *338*, 55

Hydrogenation/PAT Setup

- Reactor
  - Ehrfeld Miprowa Lab (4 Channels)
- Liquid handling
  - Knauer P 4.1 S (HPLC)
  - Vapourtec SF-10 (peristaltic)
- H_2 feed
  - ThalesNano H-Genie
- Thermostat
  - Huber CC 304
- Back Pressure Regulator (BPR)
  - Equilibar Zero Flow
  - Bronkhorst EL-PRESS (controller)

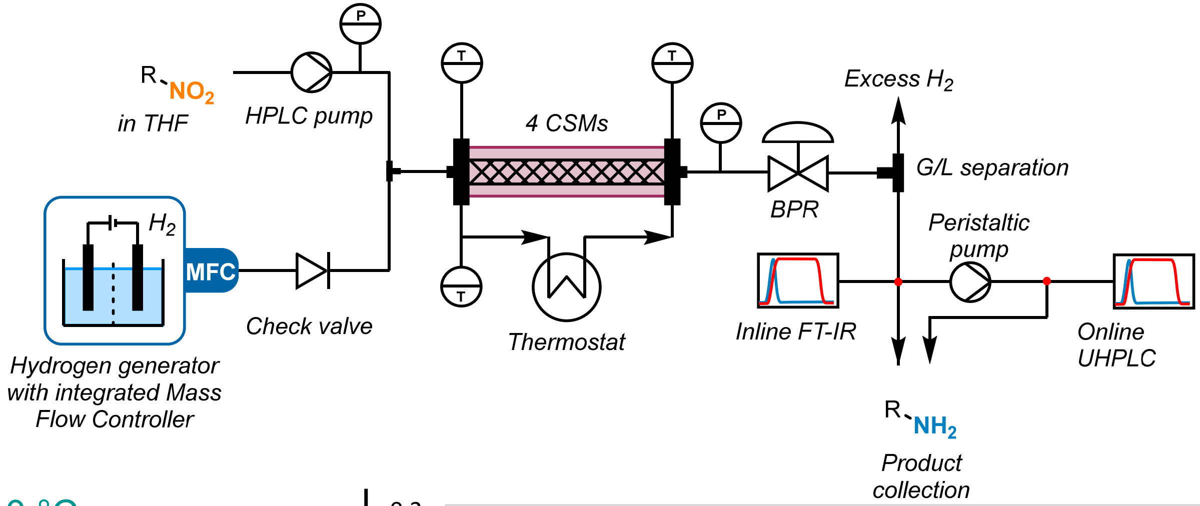


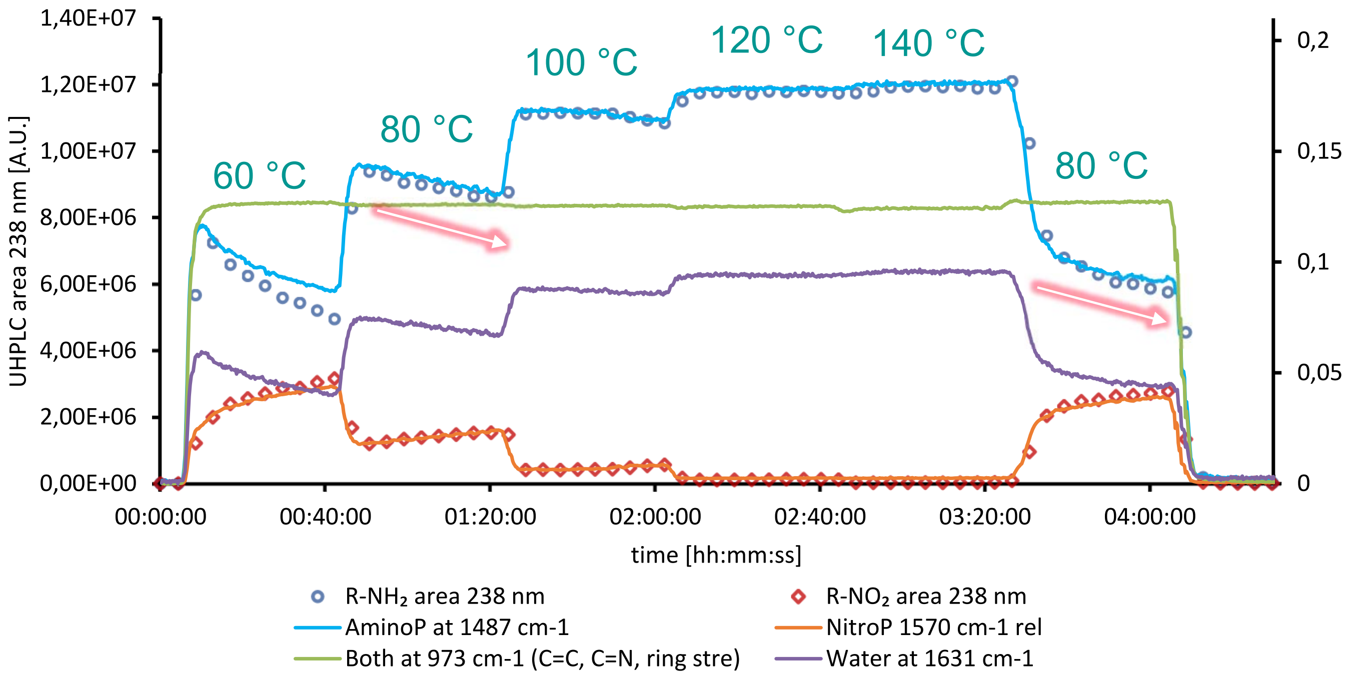


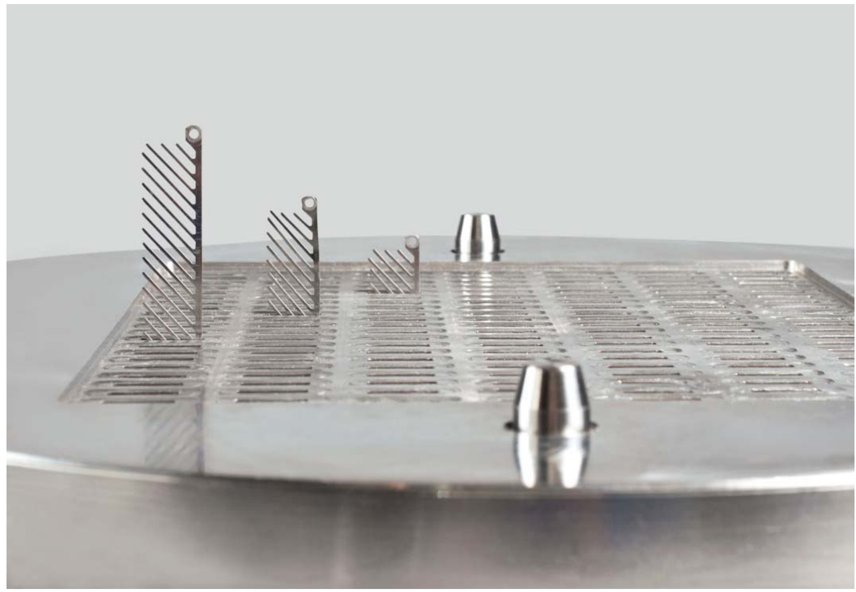
Hydrogenation/PAT Setup

Roche

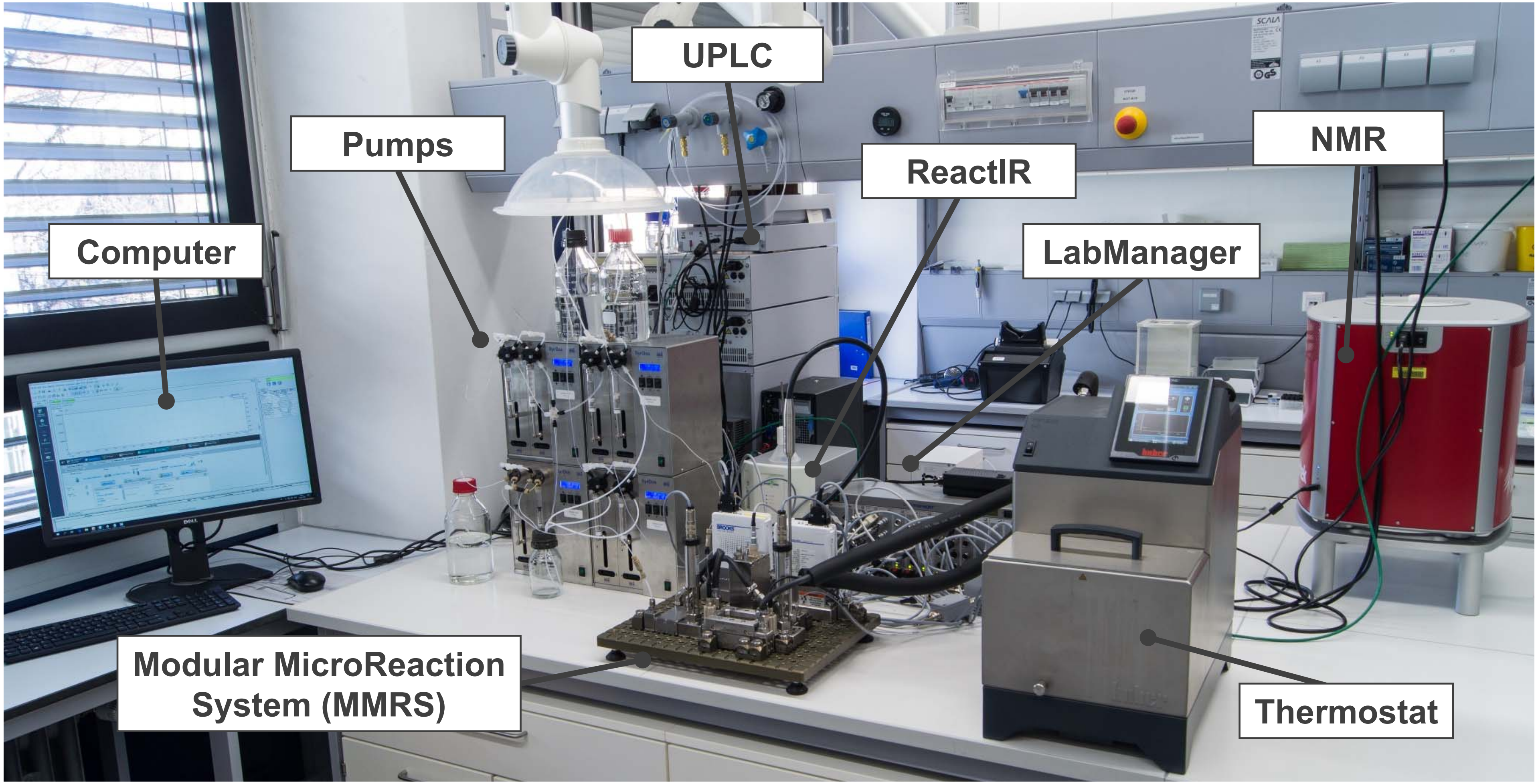
- Temperature was increased in 40 min intervals





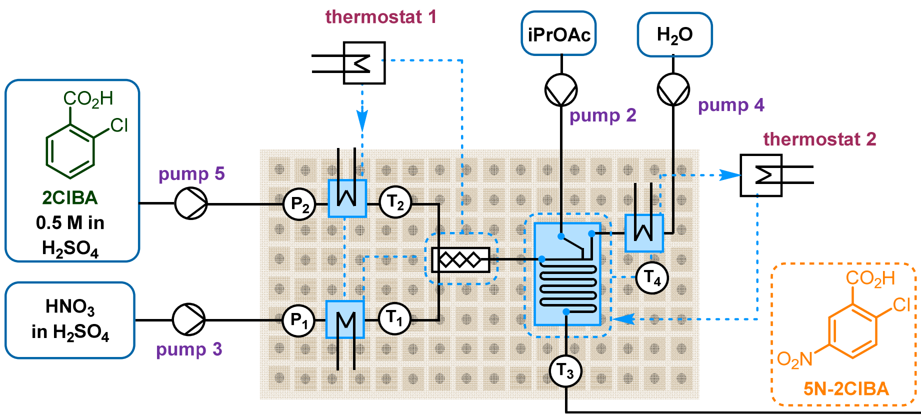


Lab of the Future: Integration of Multiple Types of PAT Tools to a Single Platform



Sagmeister, P. et al. *React. Chem. Eng.* **2019**, *3*, 1571

Model-based Strategies for Real-time Control of API Synthesis

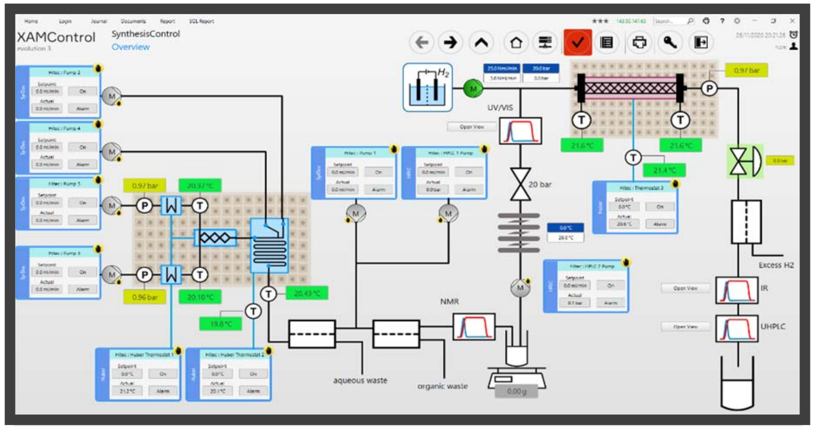


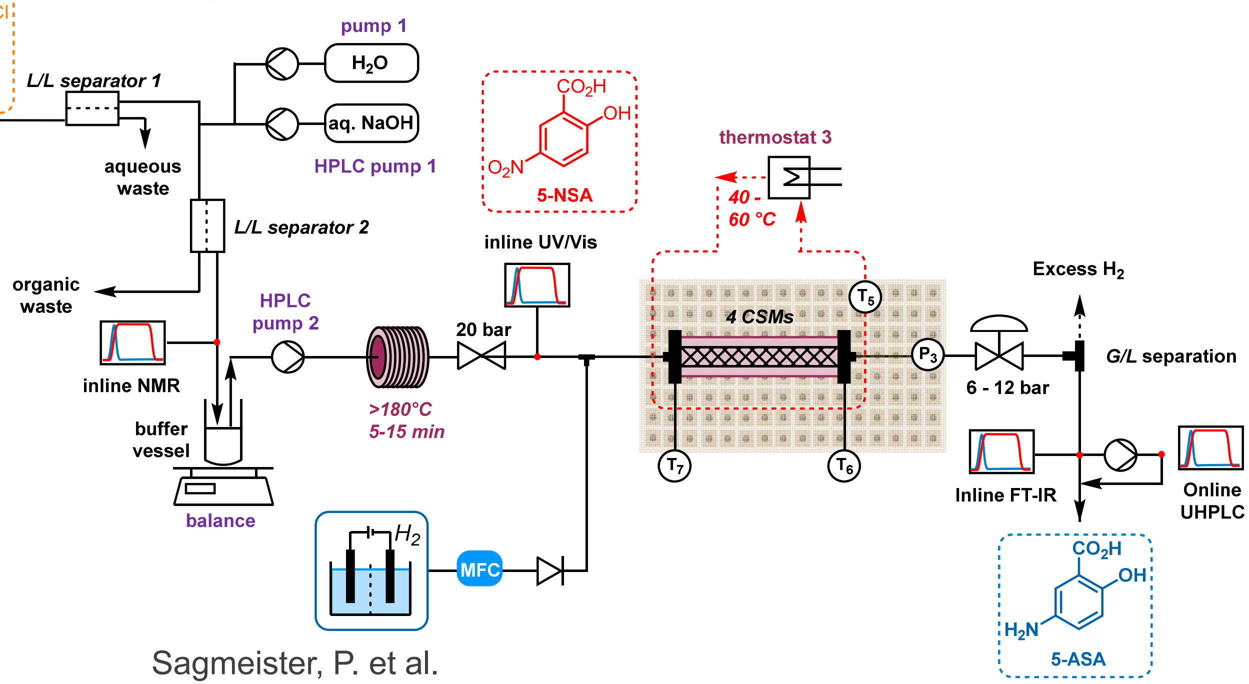
PAT Tools

- 4 thermostats
- 8 pumps
- 2 liquid/liquid separations
- 14 p/T sensors

- NMR (Magritek)
- UV/Vis (Avantes)
- IR (Mettler Toledo)
- UPLC (Shimadzu)

Control Software (XAMControl)





Sagmeister, P. et al.
Angew. Chem. Int. Ed. **2021**, *60*, 8139

Autonomous Continuous Flow Chemistry Platform

Self-Optimization

Sagmeister, P. et al.
Adv. Sci. **2022**, *9*, 2105547

Dynamic Experiments

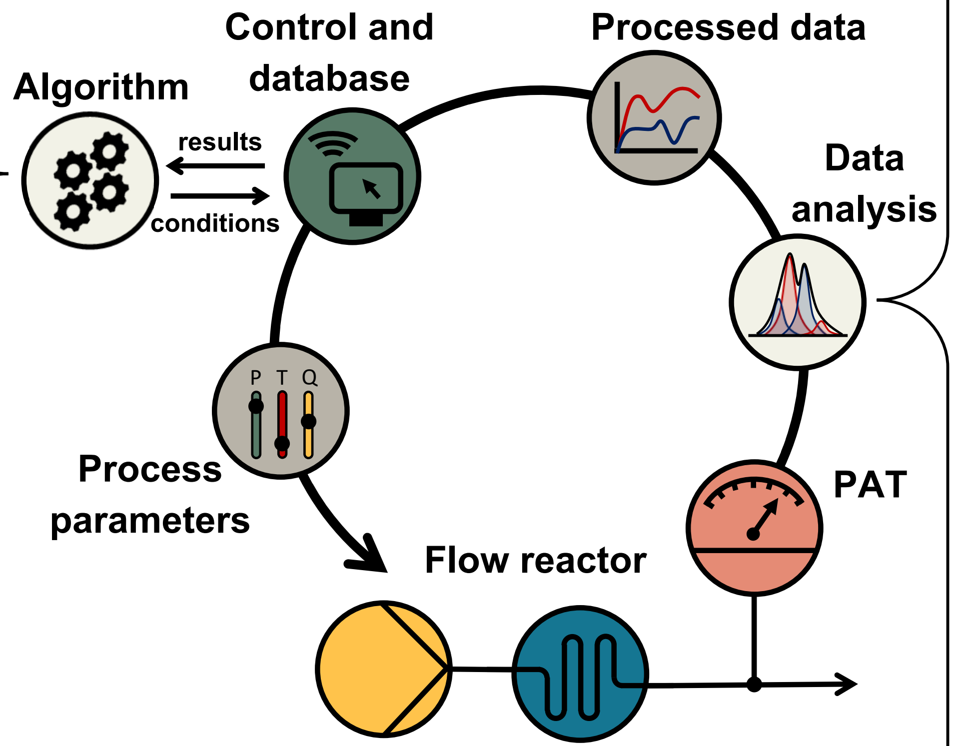
Sagmeister, P. et al.
manuscript in preparation

Iterative Model Building

Knoll, S. et al.
React. Chem. Eng. **2022**, *7*, 2375

Model Predictive Control (MPC)

Sacher, S. et al. *Chem. Eng. Res. Des.* **2022**, *177*, 493
J. Process Control **2023**, *152*, 59



Integration

Sagmeister, P. et al.
React. Chem. Eng. **2019**, *4*, 1571

Partial Least Squares (PLS)

Sagmeister, P. et al.
React. Chem. Eng. **2020**, *5*, 677

Indirect Hard Modeling (IHM)

Sagmeister, P. et al.
Angew. Chem. Int. Ed. **2021**, *60*, 8139

Artificial Neural Network (ANN)

Sagmeister, P. et al.
Digital Discov. **2022**, *1*, 405

Flow Photochemistry

- Enables new transformations and improves old ones
- LED light sources bring improved efficiency, selectivity and durability
  - Versus “classical” Hg vapor lamps
  - High power LEDs available λ ≥ 365 nm
- High throughput achievable in a small reactor
- Proven solution for scaling up photochemistry
  - Optimize reactor dimensions and reaction/catalyst concentrations using Beer-Lambert law
- Use of “photon equivalents” for straightforward batch to flow transfer or scale-up

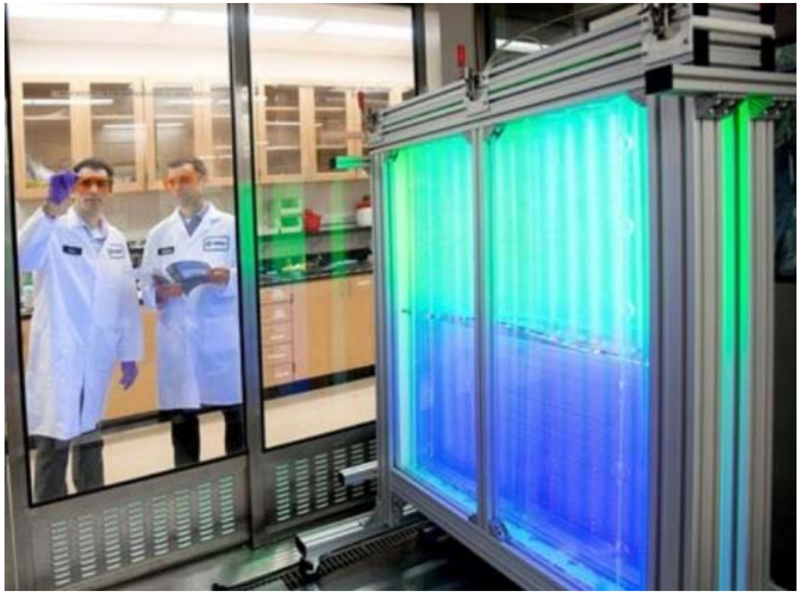
Corcoran, E. B. et al. *Angew. Chem. Int. Ed.* **2020**, *59*, 11964

COMMENT

https://doi.org/10.1038/s41467-019-13988-4 *Nat. Comm.* **2020**,*11*, 804

Photons as a 21st century reagent

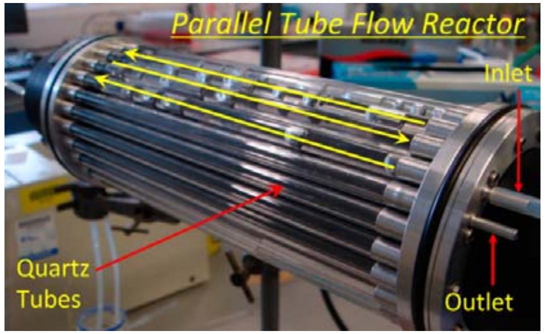
Holly E. Bonfield [1,2], Thomas Knauber [3], François Lévesque [4], Eric G. Moschetta [5], Flavien Susanne [1] & Lee J. Edwards [1*]



Cambie, D. et al. *Chem. Rev.* **2016**, *116*, 10276; Buglioni, L. *Chem. Rev.* **2022**, *122*, 2752

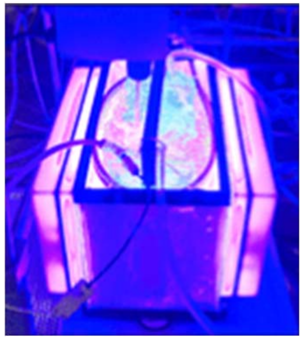
Large Scale Flow Photochemical Reactors – Recent Examples

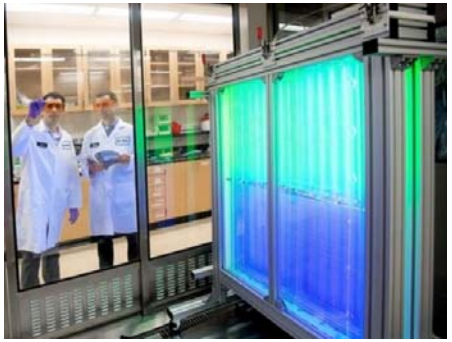
GSK/Booker-Milburn "Firefly"



Booker-Milburn, K. I. et al.
Org. Process Res. Dev. **2016**, *20*, 1806

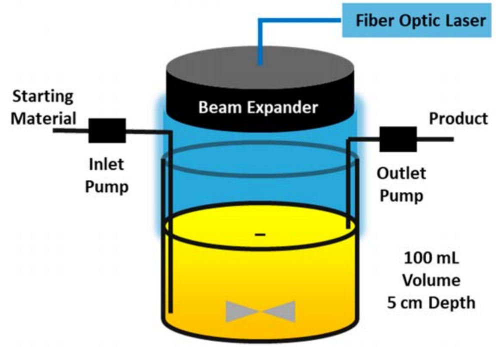
Merck "Fishtank"





Lévasque, F. et al. *Org. Process Res. Dev.* **2020**, 24, 2935

Abbvie Laser CSTR



Harper, K. C. et al.
ACS Cent. Sci. **2019**, *5*, 109

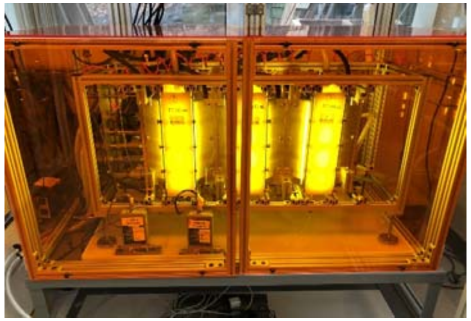
Heraeus (Numbering Up)

Werner, S. et al. EP 2065387A2 (**2008**)

Asymchem/Amgen (Tubing)

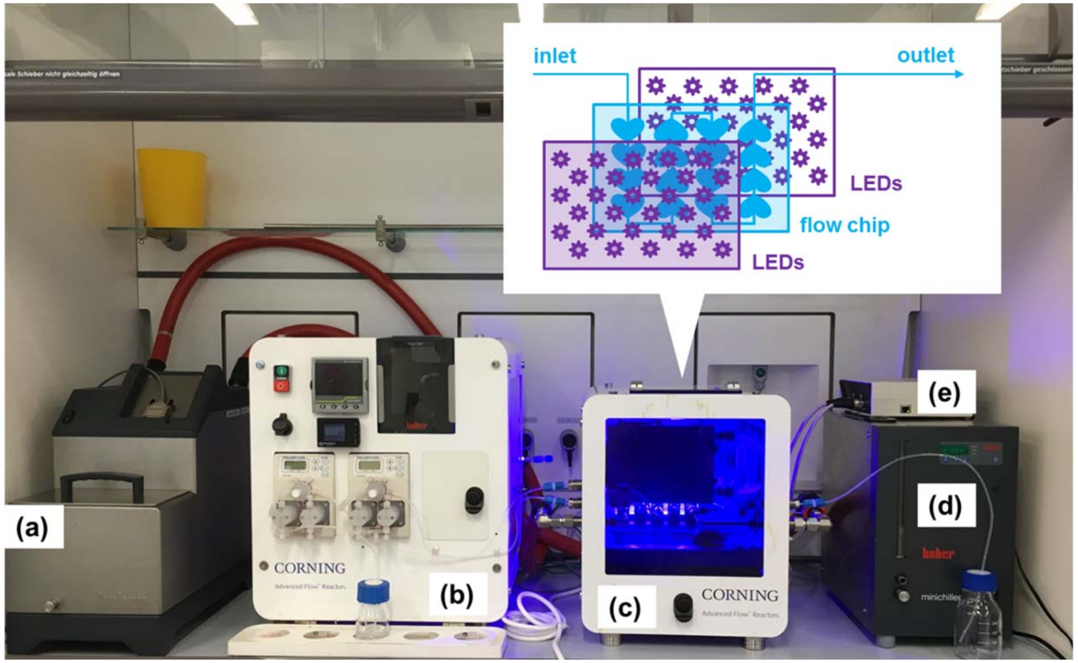
Beaver, M. G. et al.
Org. Process Res. Dev. **2020**, *24*, 2139

Snapdragon (Tubing)



@SnapdragonChem

Corning® Advanced-Flow™ Photo Reactor – Lab Scale



a) Huber thermostat (reactor plate temp. control)

b) Control module
- HPLC pumps
- mass flow controller (gases)
- thermostat control
- system parameter monitor

c) Reactor (2.8 mL) and LED housing

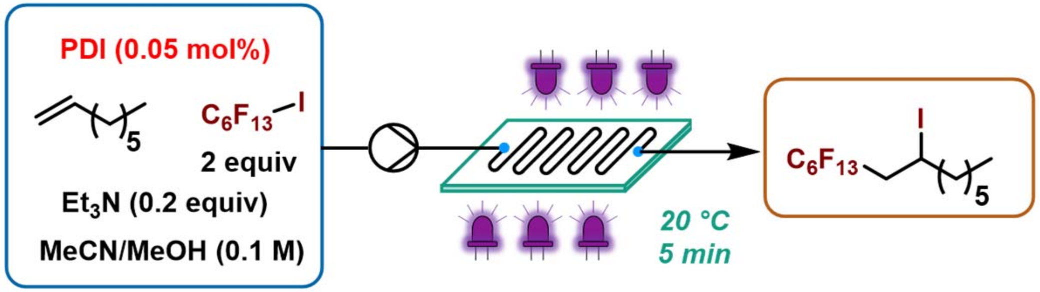
d) Thermostat (LED plate temp. control)

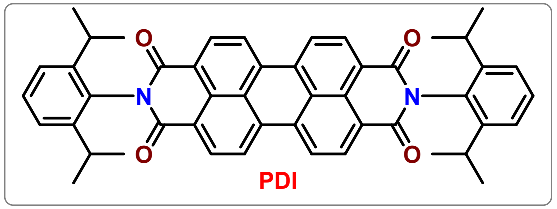
e) Lamp control module

- Small channel depth for effective irradiation
- Mixing structure for multiphasic reactions
- Improved temperature control
- Tuneable wavelength and intensity

NBS Benzylic Bromination Chen, Y. et al. *ChemPhotoChem* **2018**, *2*, 906
Ethylene [2+2] Williams, J. D. et al. *Org. Process Res. Dev.* **2019**, *23*, 78
Nitrosyl Chloride Lebl, R. et al. *React. Chem. Eng.* **2019**, *4,* 738
Catalyst-free ATRA Rosso, C. et al. *Org. Lett.* **2019**, *21*, 5341
Reduction of Ar-X Steiner, A. et al. *Eur. J. Org. Chem.* **2019**, 5807
ATRA Steiner, A. et al. *React. Chem. Eng.* **2021**, *6*, 2434

Iodoperfluoroalkylation of Alkenes (ATRA)

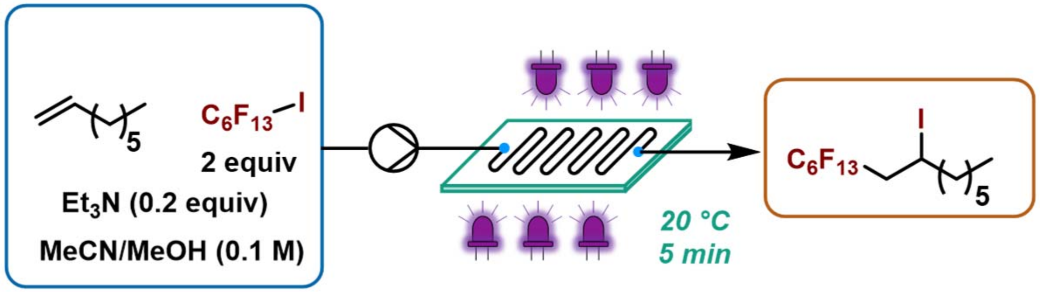


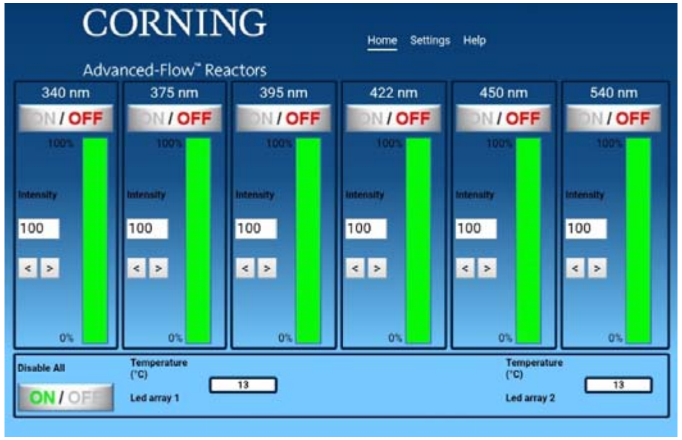


Wavelength	Yield [%]
365 nm	95
385 nm	97
405 nm	97
422 nm	95
450 nm	95
540 nm	88
610 nm	0

cf. batch reference: Rosso, C.; Prato, M. et al. *ChemPhotoChem* **2019**, *3*, 193 (4 h reaction time)

Iodoperfluoroalkylation of Alkenes





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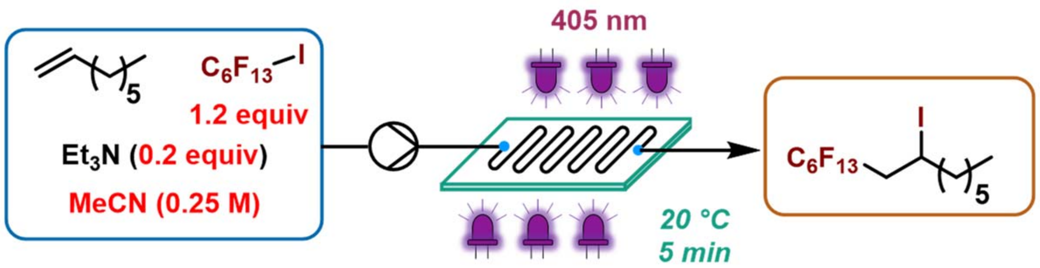
422 nm	95
450 nm	95
540 nm	88
610 nm	0

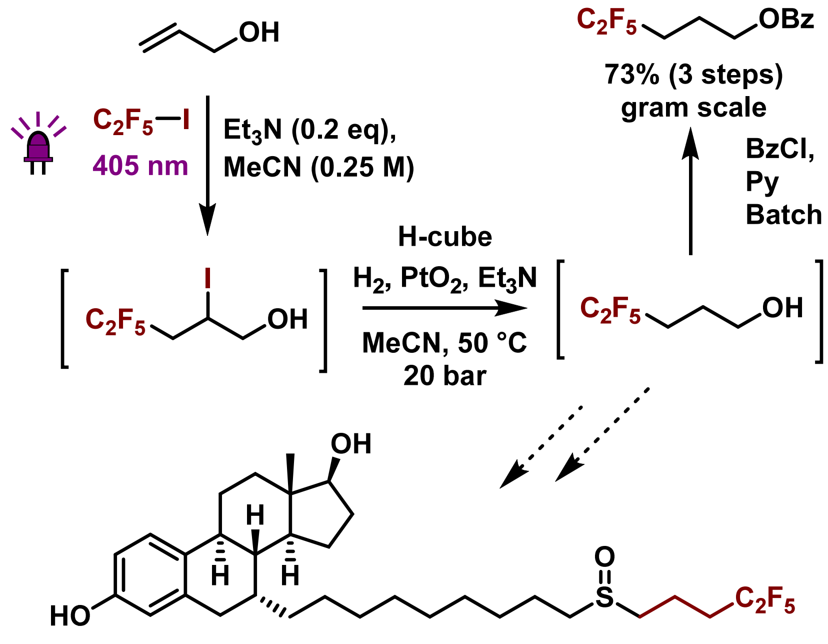
Wavelength	Yield [%]
365 nm	94
385 nm	94
405 nm	94
422 nm	34
450 nm	0
540 nm	0
610 nm	0

cf. batch reference: Rosso, C.; Prato, M. et al. *ChemPhotoChem* **2019**, *3*, 193 (4 h reaction time)

Iodoperfluoroalkylation of Alkenes



- C−I bond activated by halogen bonding with Et_3N
- substrate scope explored in alkenes and perfluoroalkyl iodides
- applied in synthesis of Fulvestrant fluorinated side chain

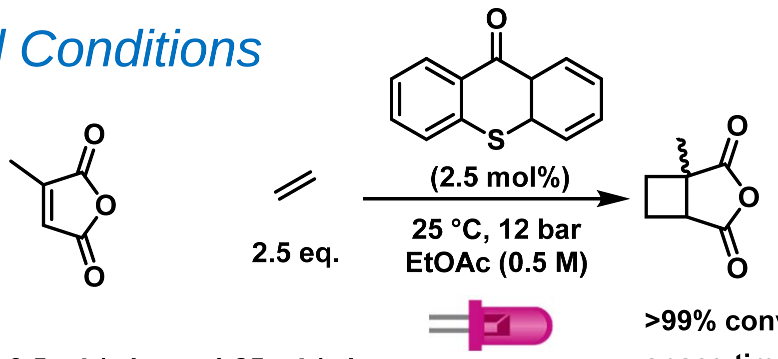


Fulvestrant (anticancer)

Rosso, C. et al. *Org. Lett.* **2019**, *21*, 5341

Sensitized Photochemical [2+2] Reactions

Optimized Conditions



Flow rate: 0.5 mL/min 1.25 mL/min

375 nm LEDs

>99% conversion
space-time yield = 759 g L^{-1} h^{-1}
residence time approx. 5 min 12 sec

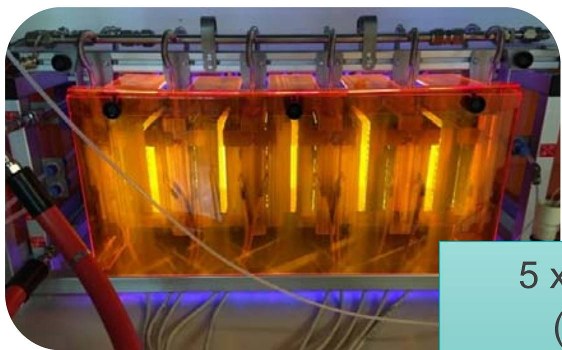
G3 Photoreactor

5 x **G3** plate
(**250 mL**)
55 mL/min

"Lab" Photoreactor

1 x "low flow" plate
(**2.8 mL**)
0.5 mL/min

G1 Photoreactor



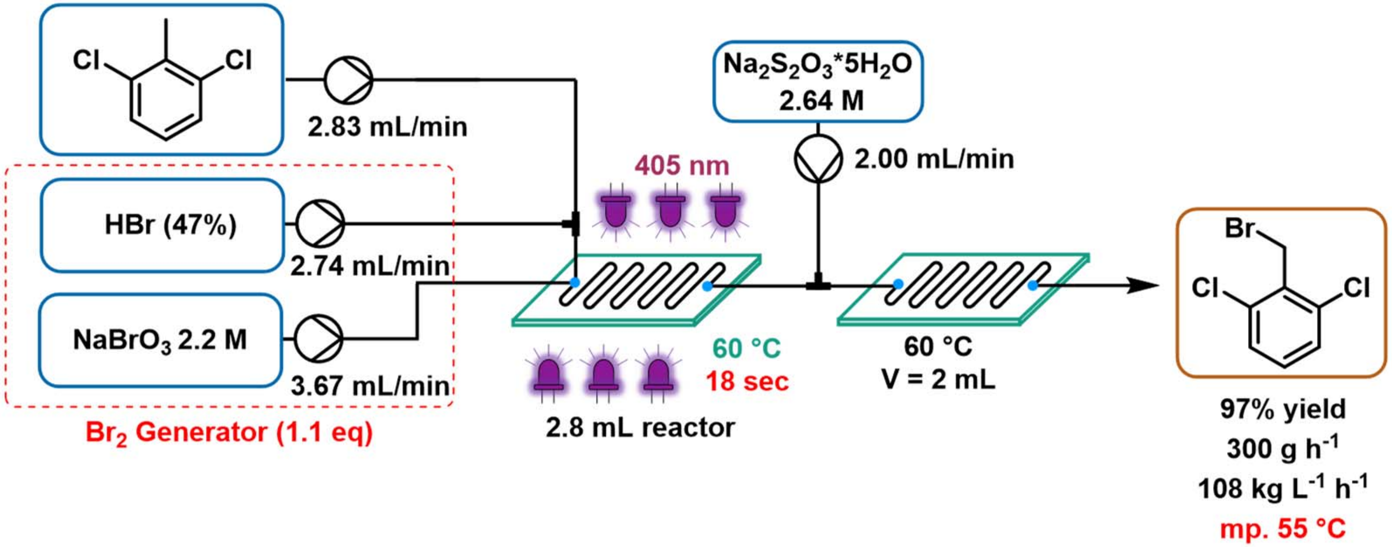
5 x G1 plate
(**41 mL**)
7.6 mL/min

- linear scale-up by multiple reactor plates in series
- >100 g material processed in 10 h
- consistent reaction behavior throughout

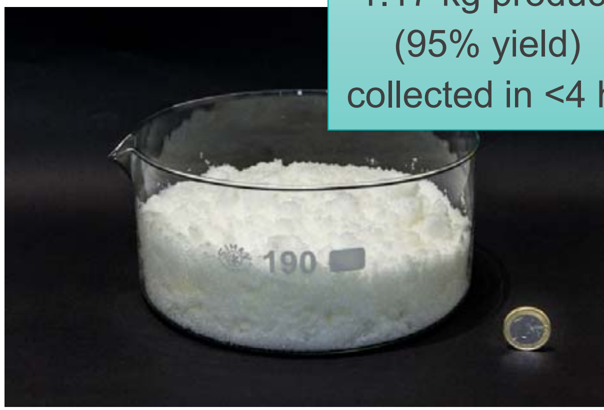
Williams, J. D. et al. *Org. Process Res. Dev.* **2019**, *23*, 78

Continuous Benzylic Bromination – Lab Scale with Quench in Flow

2,6-Dichlorobenzylbromide (API Intermediate)



1 x “low flow” plate
(**2.8 mL**)
9.24 mL/min

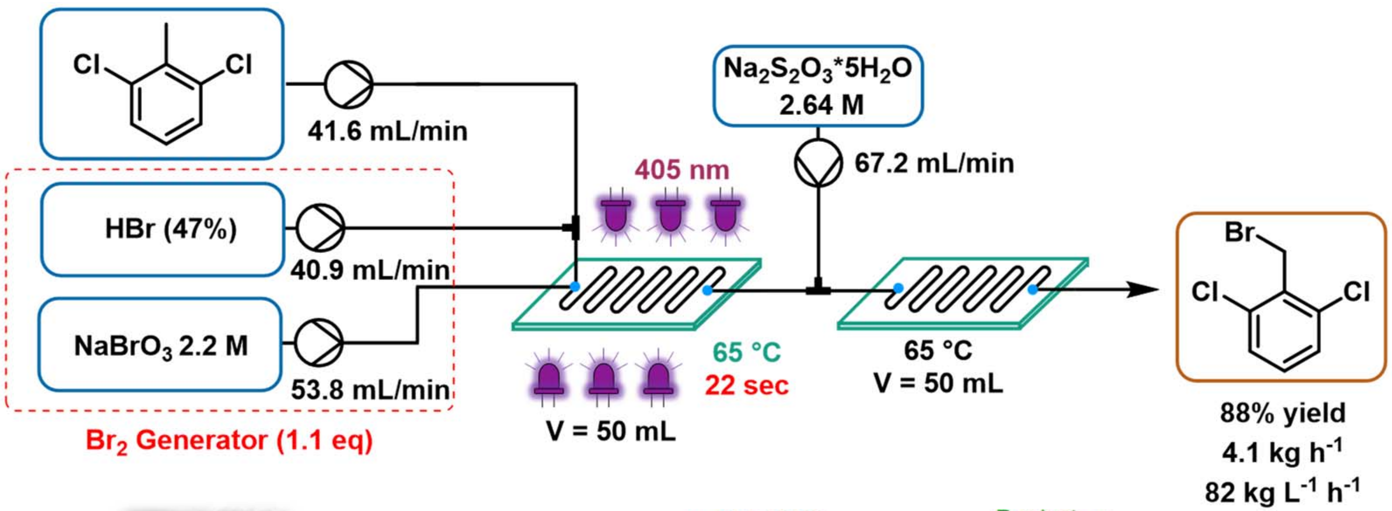


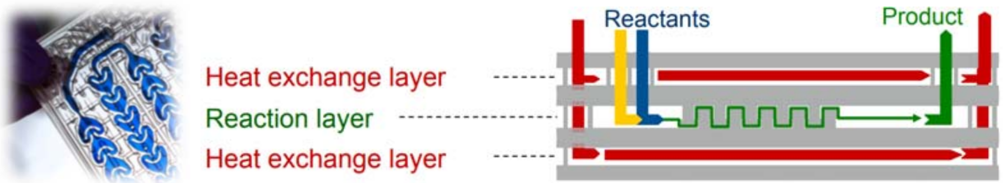
1.17 kg product
(95% yield)
collected in <4 h!

Steiner, A. et al. *Green Chem*. **2020**, *22*, 448

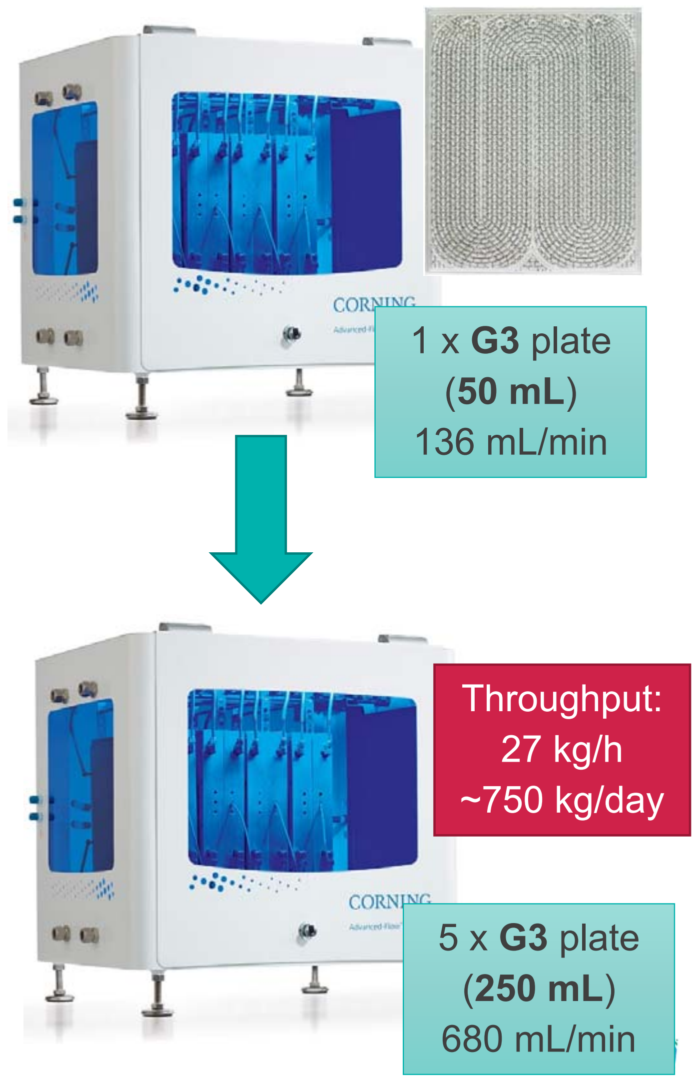
Continuous Benzylic Bromination – Production Scale

2,6-Dichlorobenzylbromide (API Intermediate)

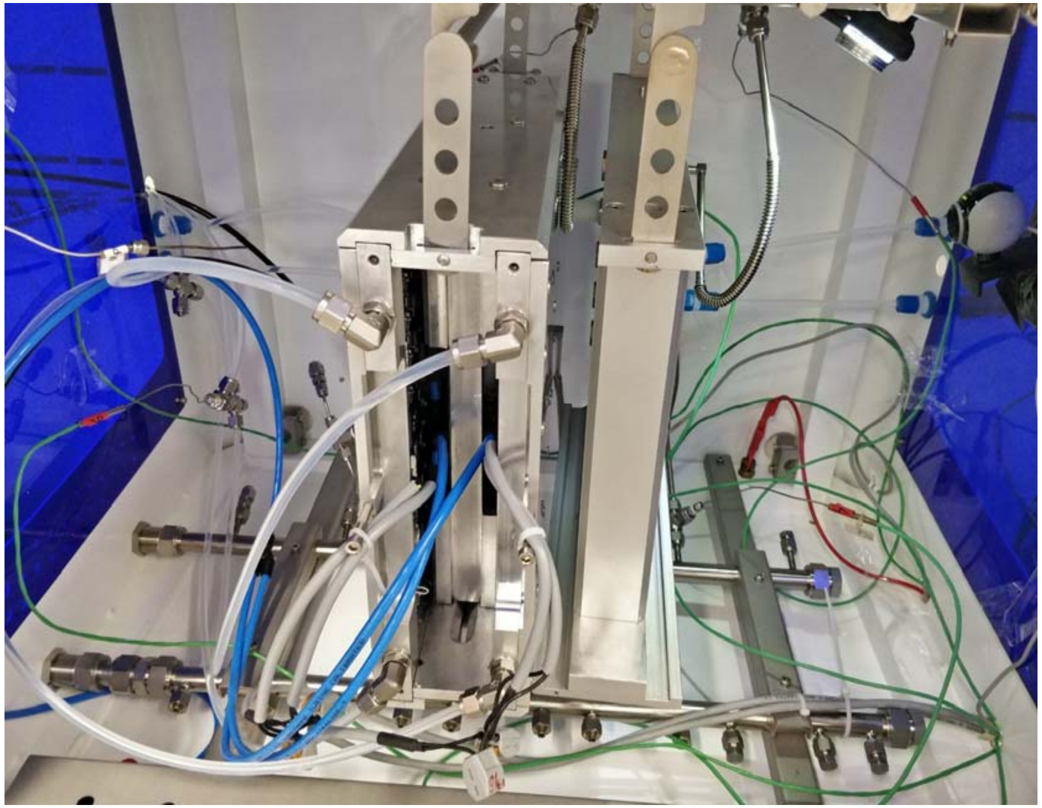




Steiner, A. et al. *Org. Process Res. Dev.* **2020**, *24*, 2208



Experimental Setup



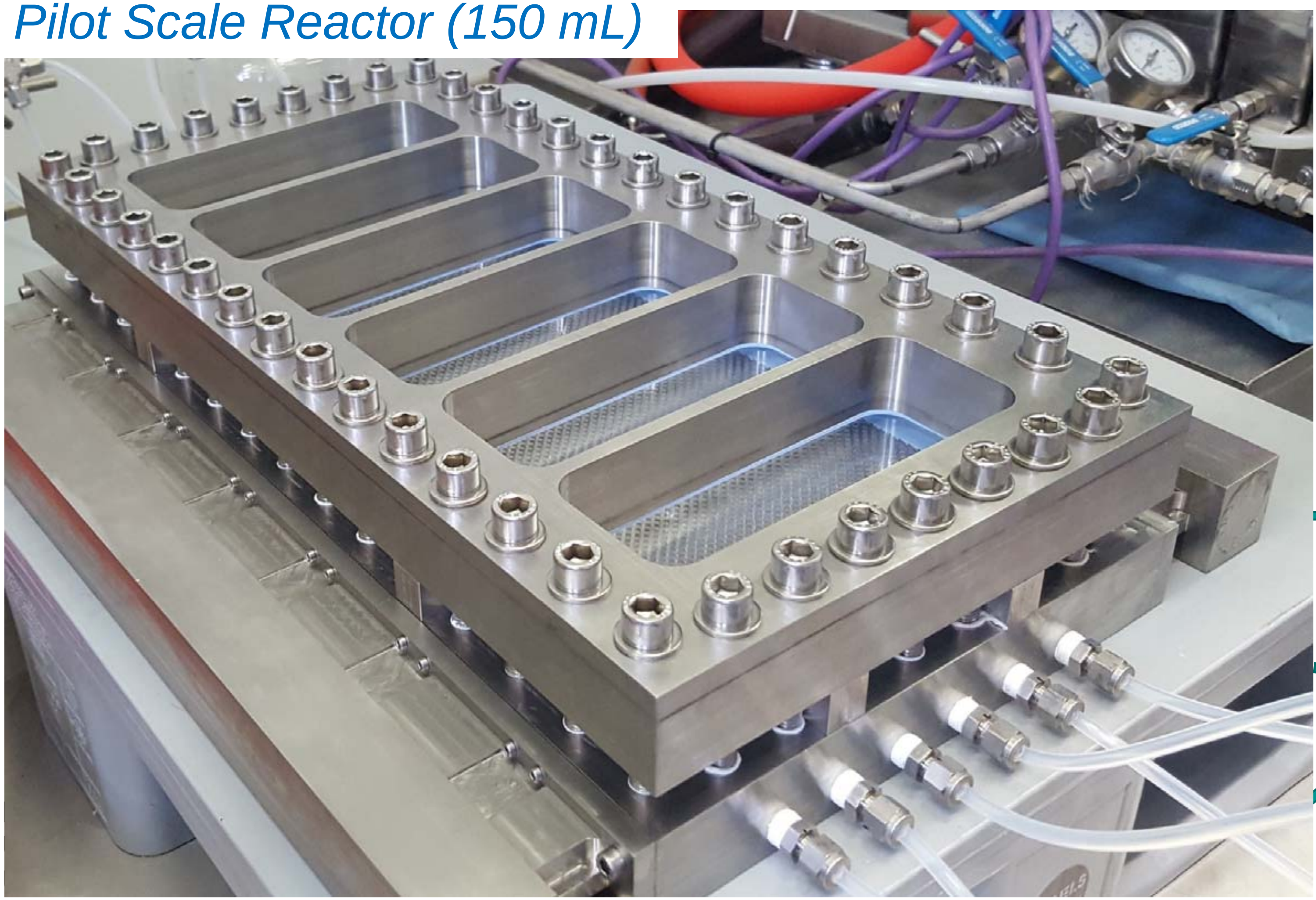
Steiner, A. et al. *Org. Process Res. Dev.* **2020**, *24*, 2208

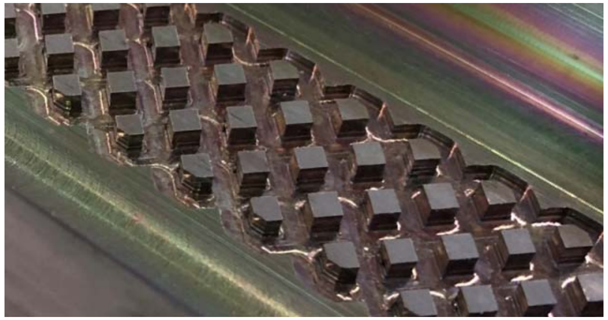
HANU Reactor – Handling Solids in Flow

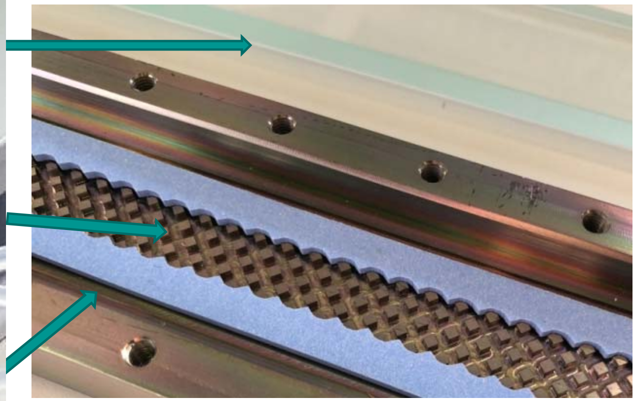
Pilot Scale Reactor (150 mL)

CREAFLOW

www.creaflow.be

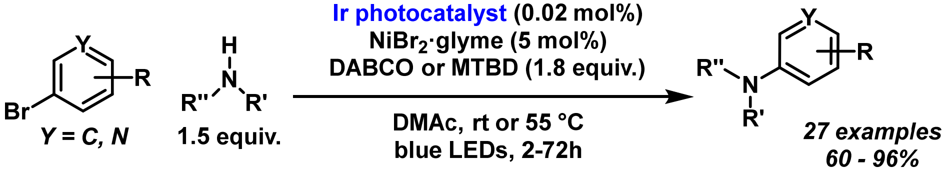


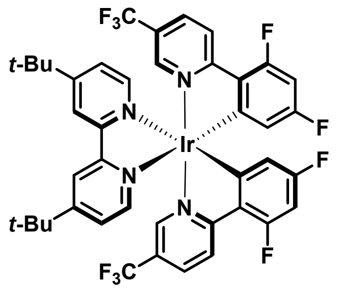




Dual Nickel/Photocatalytic C-N Cross-couplings

Iridium Complexes as Photocatalysts (Buchwald, MacMillan)

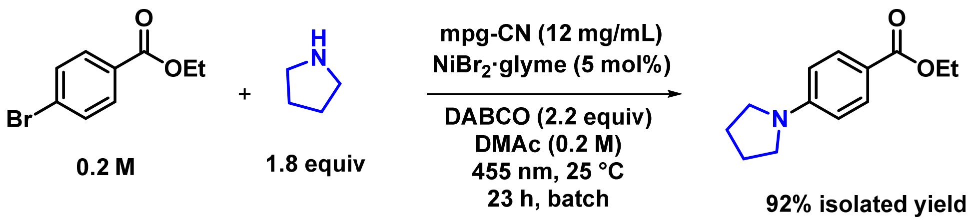


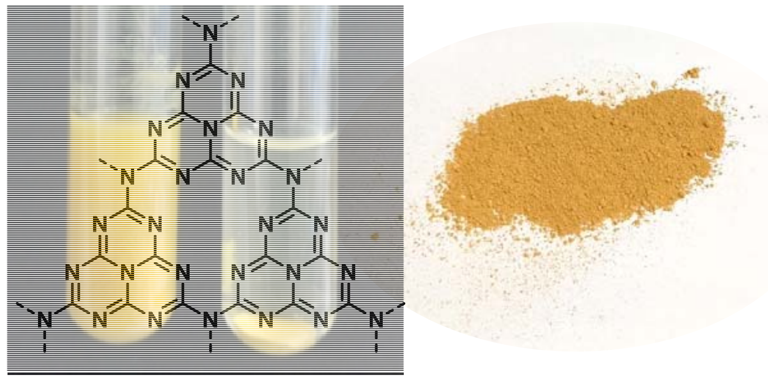


Iridium photocatalyst
Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6
800 €/g Sigma-Aldrich

Corcoran, E. B. et al. *Science* **2016**, *353*, 279

Carbon Nitrides as Photocatalysts (Antonietti, König, Pieber)

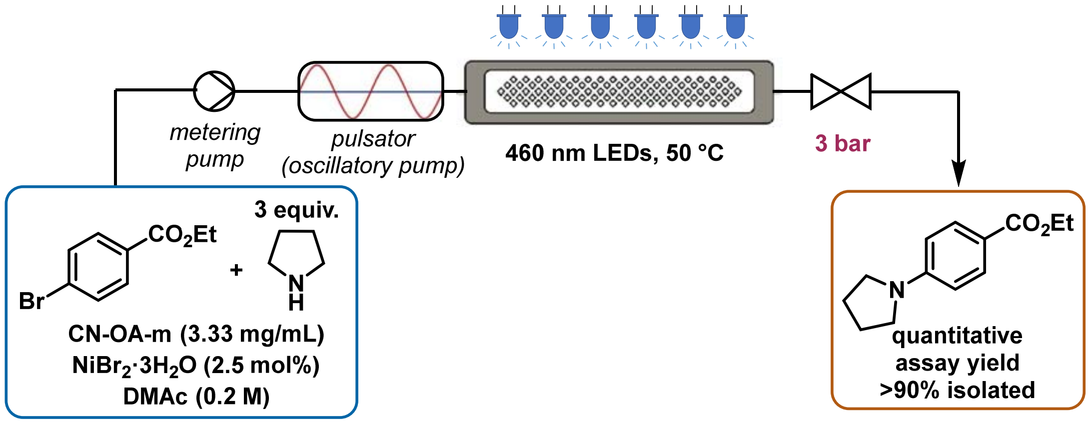


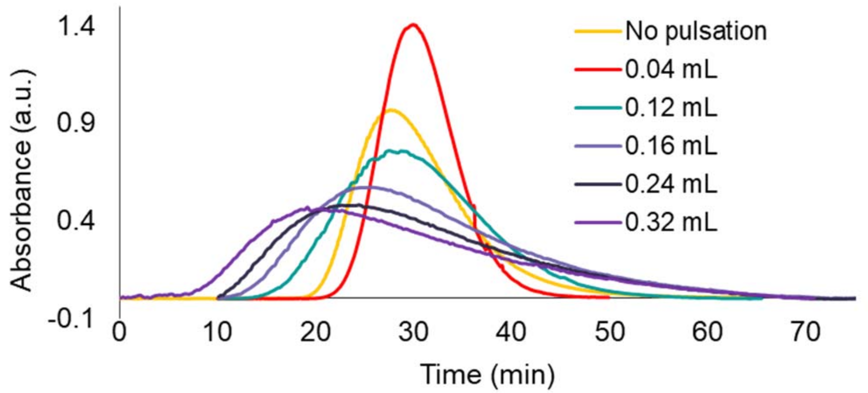


mpg-CN
inexpensive, solid, recyclable

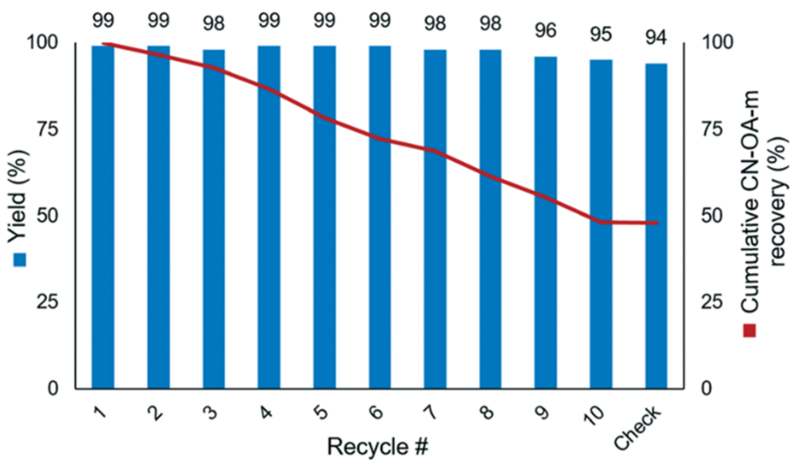
Gosh, I. et al. *Science* **2019**, *365*, 360
cf. Pieber, B. et al. *Nature Catal.* **2020**, *3*, 611; *Angew. Chem. Int. Ed.* **2019**, *58*, 9575

Semi-heterogeneous Photoredox Catalysis in the HANU Reactor



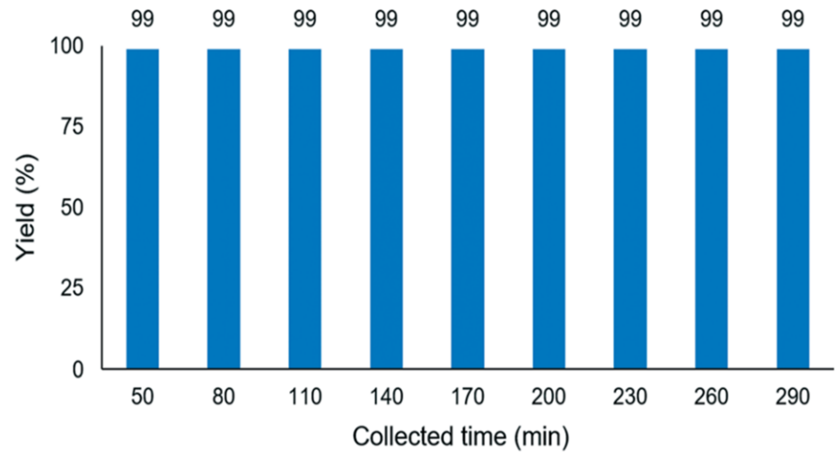


- Pulsation characteristics optimized for narrow RTD

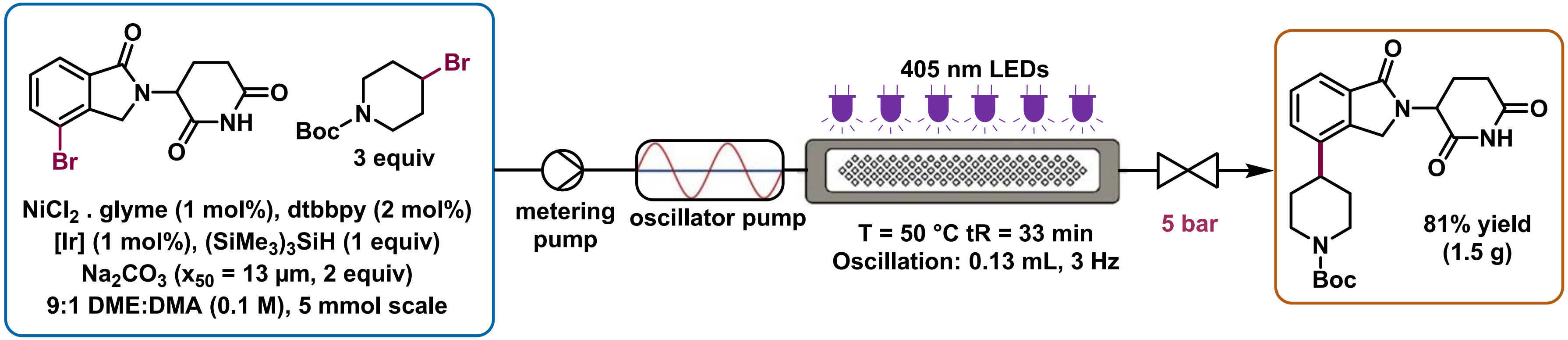


Rosso, C. et al. *React. Chem. Eng.* **2020**, *5*, 597

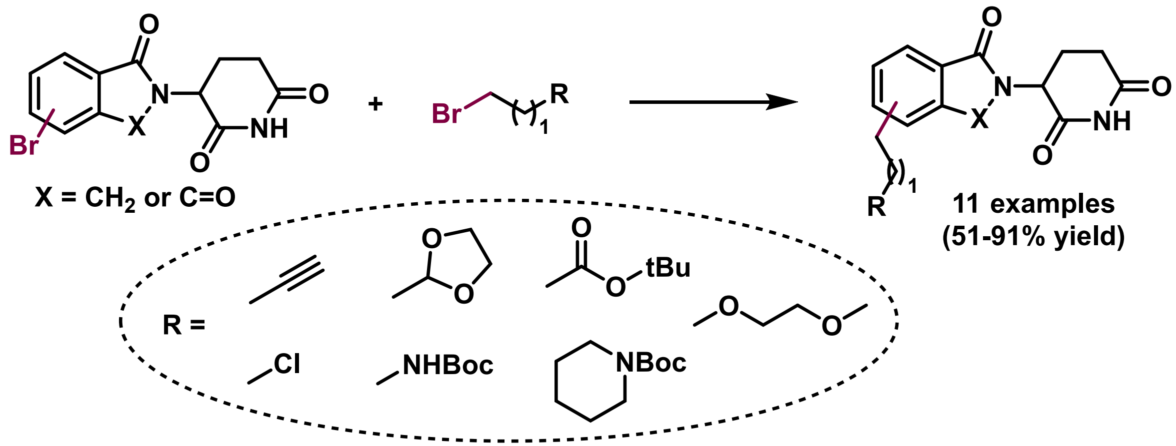
- Heterogeneous carbon nitride catalyst recycled 10 times with no loss of activity
- Stable operation for >5 hours, producing >12 g (2.7 g/h) aryl amine



Metallaphotoredox $C_{sp}{}^3$-$C_{sp}{}^2$ Cross-Coupling (PROTACs)



- Stable processing of suspension
  - Na_2CO_3 particle size
  - pulsation parameters
  - DMA as co-solvent
  - slightly decreased concentration

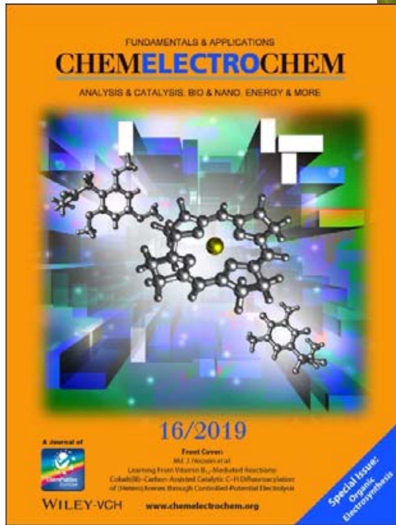


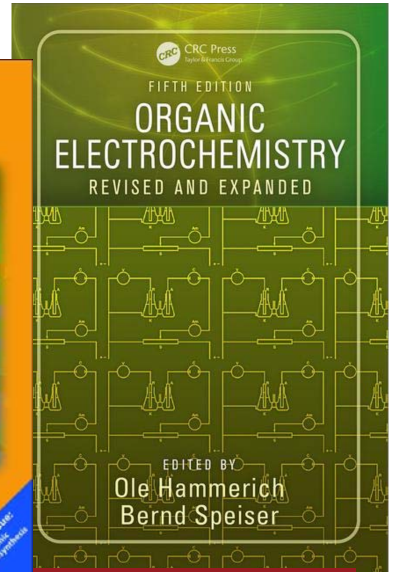
cf. Zhang, P. et al. *J. Am. Chem. Soc*. **2016,** *138*, 8084
Steiner, A. et al. *ChemCatChem* **2022**, *14*, e202201184

Electroorganic Synthesis – A Renaissance

Book

- Hammerich, O.; Speiser B. *Organic Electrochemistry: Fifth Edition*; CRC Press: Boca Raton, 2016

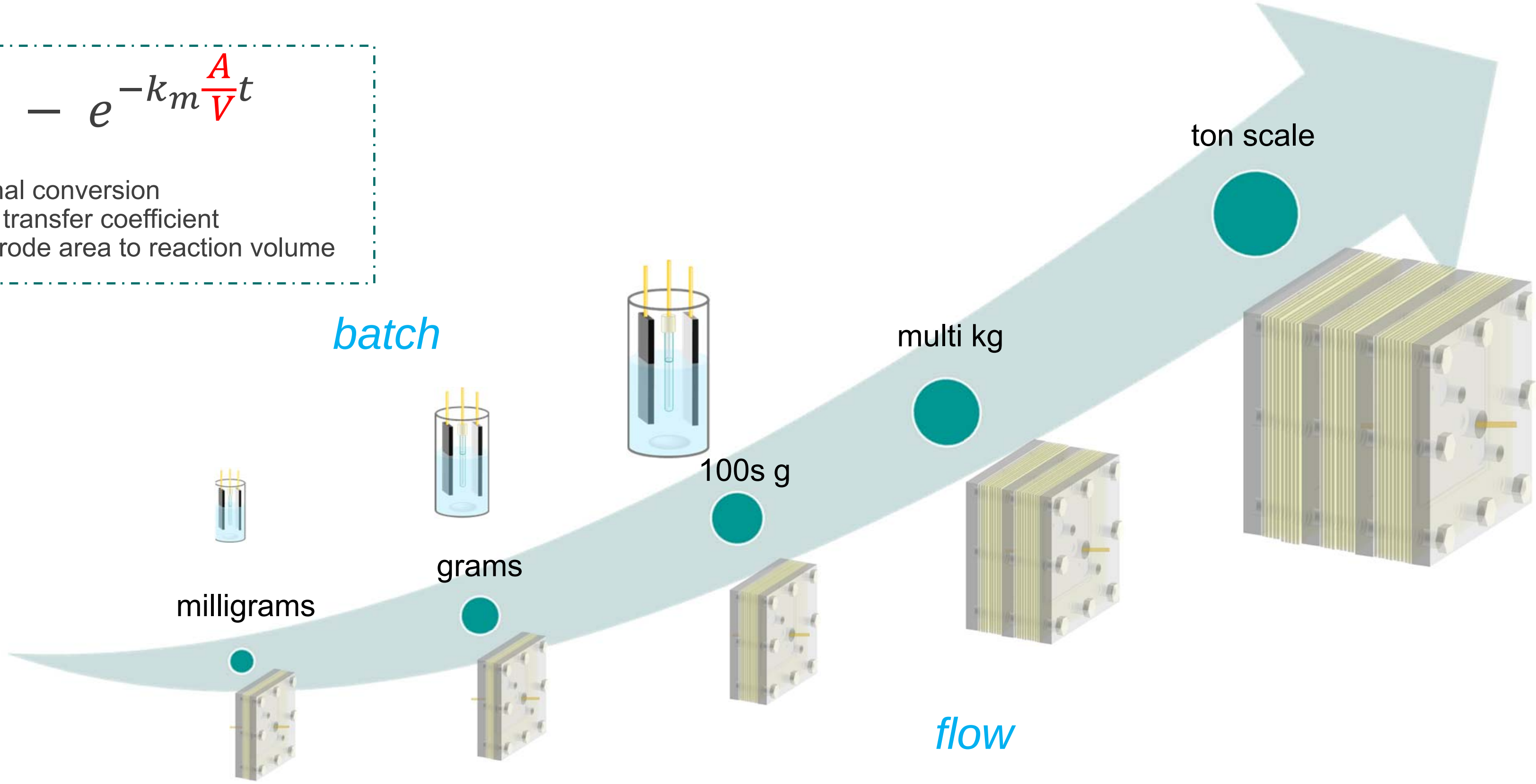




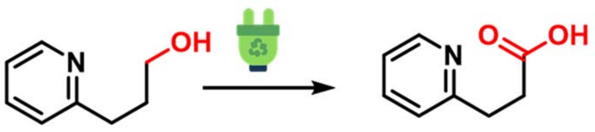
Flow Electrochemistry is the Scale-Up Strategy

$$X = 1 - e^{-k_m \frac{A}{V} t}$$

X = fractional conversion
K_m = mass transfer coefficient
A/V = electrode area to reaction volume

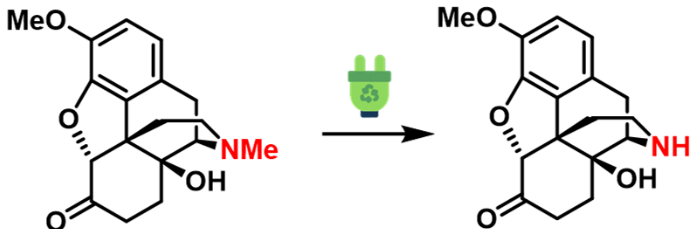


Electroorganic Synthesis at CCFLOW (2018-2023)

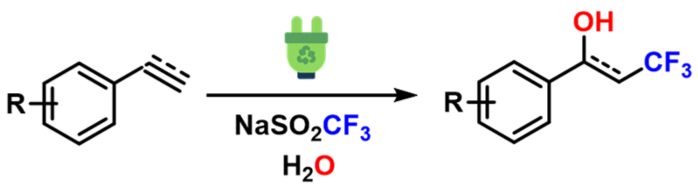


Org. Process Res. Dev. **2022**, *26*, 1486

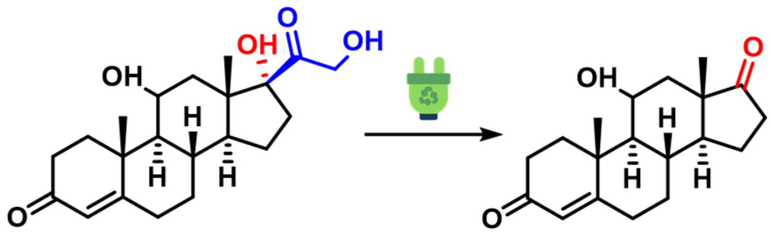
Green Chem. **2021**, *23*, 2382



ACS Sust. Chem. Eng. **2022**, *10*, 8988
Org. Lett. **2020**, *22,* 6891 (patent pending)



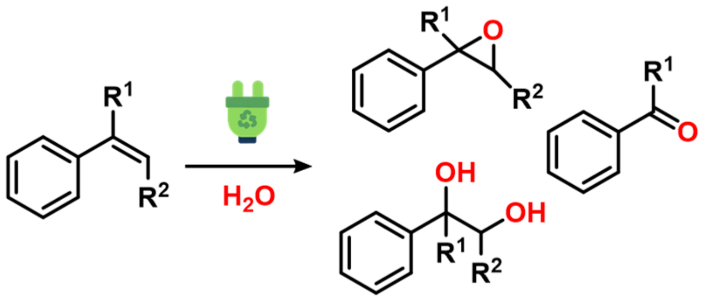
Org. Biomol. Chem. **2019**, *17*, 1384
Chem. Eur. J. **2018**, *24*, 17234



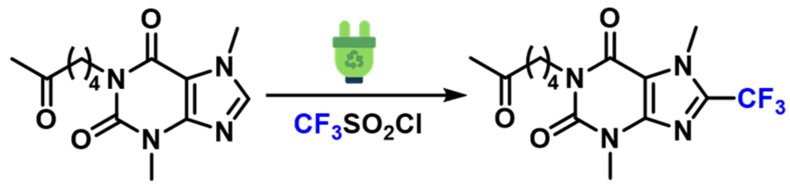
Chem. Eur. J. **2021**, *27*, 6044

J. Org. Chem. **2021**, *86* 16026

Synlett **2022**, *33*, 166



Electrochem. Sci. Adv. **2021**, *1,* e2100002



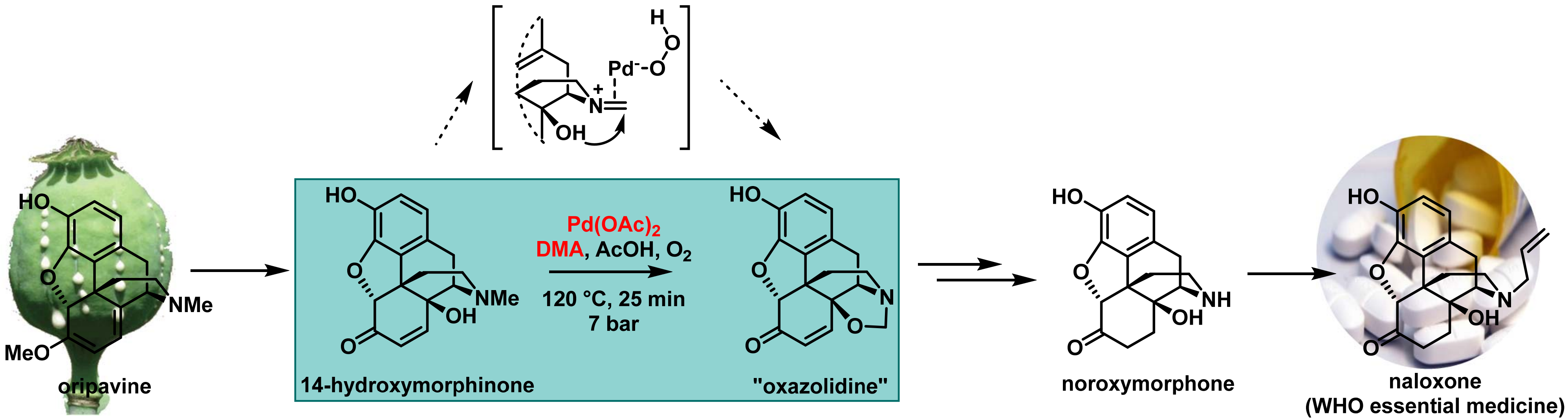
Org. Lett. **2019**, *21*, 7970

electrochemical technology focus:

Chem. Methods **2021**, *1*, 36
ChemElectroChem **2020**, *7*, 2777
J. Flow. Chem. **2020**, *10*, 181

Continuous Manufacturing of Opioid Derived APIs (2012-2016)

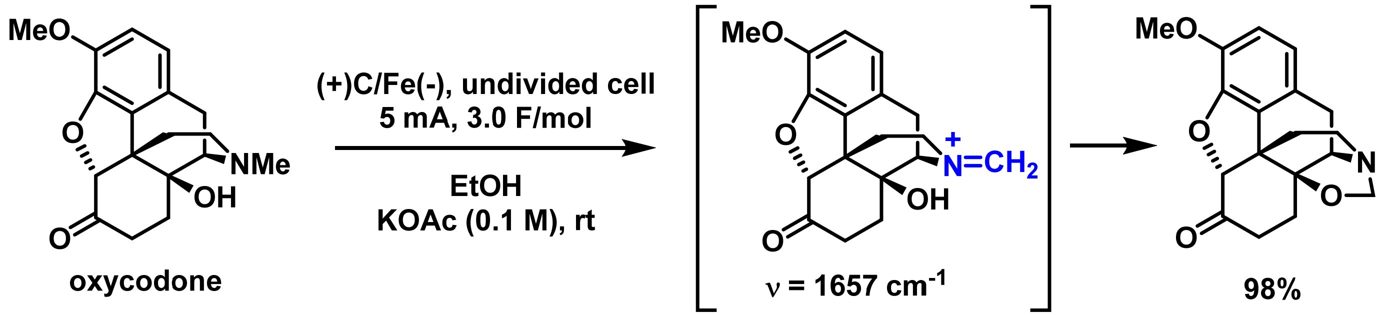
Pd-Catalyzed Aerobic N-Demethylation



WO 2017184979, WO 2017185004
Gutmann, B. et al. *Chem. Eur. J.* **2016**, *22*, 10393; *ACS Sust. Chem. Eng.* **2016**, *4*, 6048; *Eur. J. Org. Chem.* **2017**, 914
Eur. J. Org. Chem. **2017**, 6505

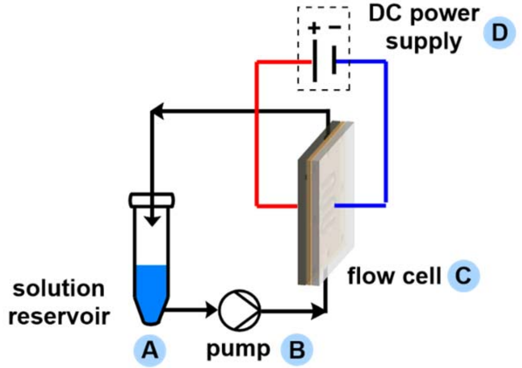
Electrochemical *N*-Demethylation of Oxycodone

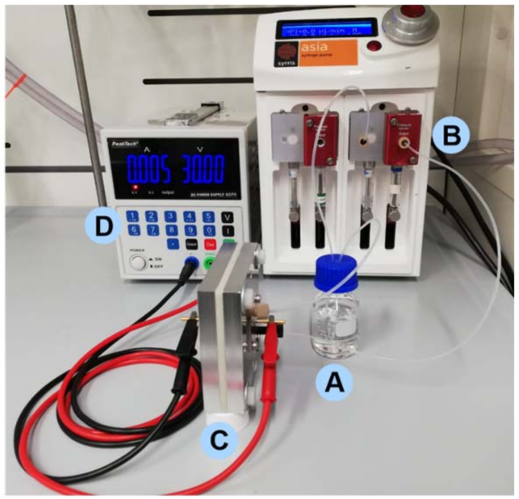
AZAD PHARMA AG

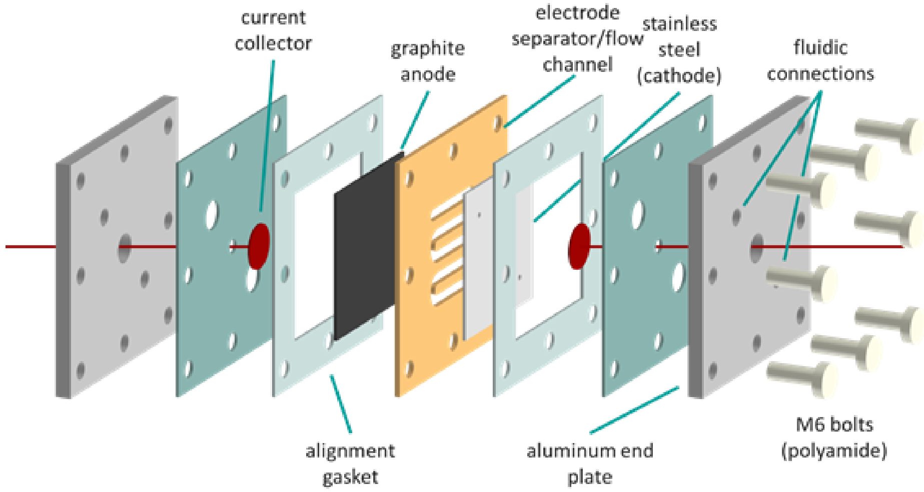


Sommer, F. et al. *ACS Sustain. Chem. Eng.* **2022**, *10*, 8988

Flow Set-Up



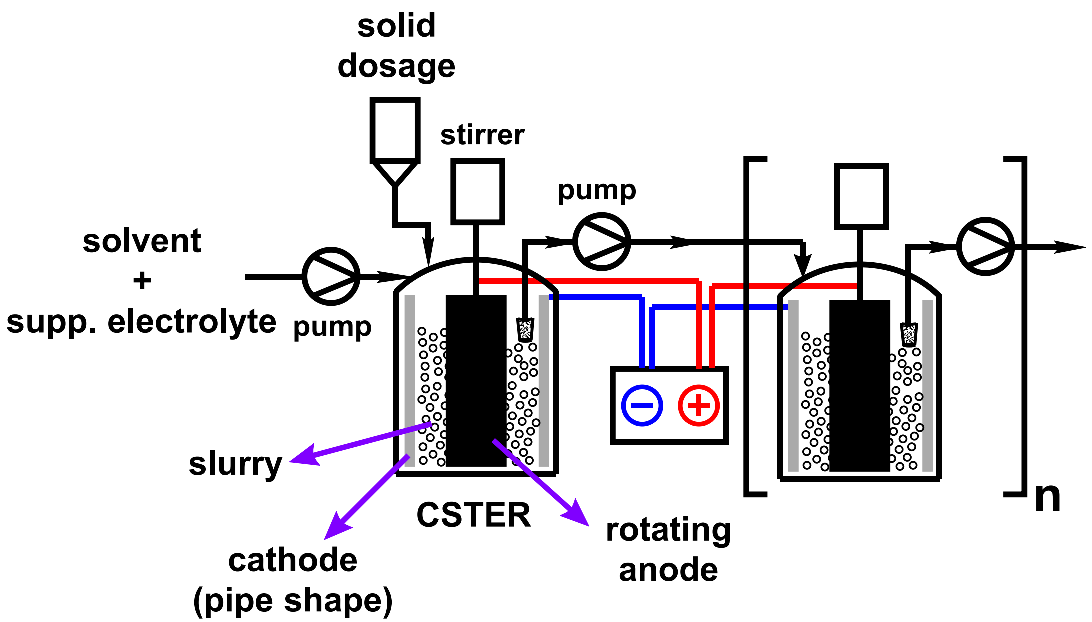


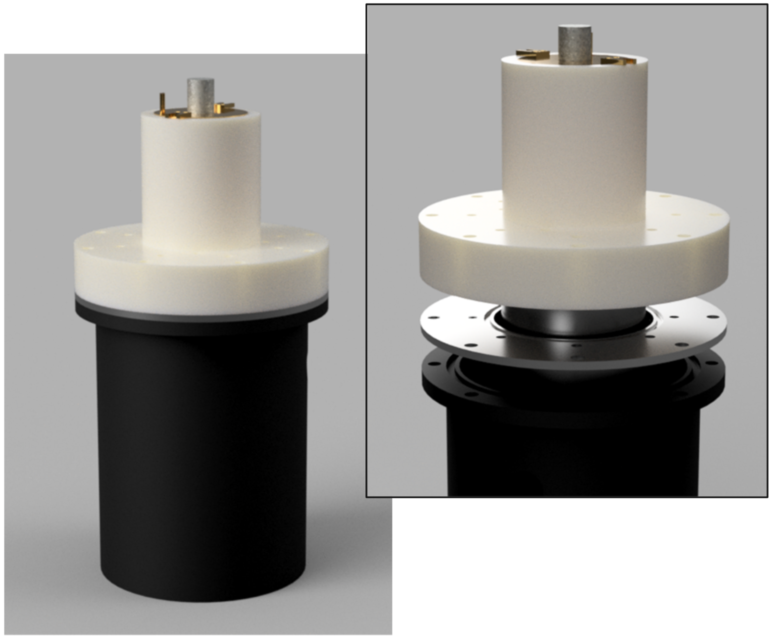


Jud, W. et al. *Chem. Methods* **2021**, *1*, 36
available from www.analytical-sales.com

Continuous Stirred Tank Electrochemical Reactor

austria wirtschaftsservice aws





- CSTER with rotating electrodes solves the issues associated with solids and gas formation
- Directly scales from ElectraSyn 2.0 as interelectrode distance is identical (5 mm)

AWS "Prototypenförderung" – 2021 (patent pending)

Conclusions – Continuous Processing and Flow Chemistry

- Safer, more robust (in-line PAT) and scalable processes
- New chemistries ("designer reagents") and processing windows in fit-for-purpose reactors
- Allows redesigning of APIs syntheses utilizing "forbidden" and "forgotten" chemistries
- Cheaper and more sustainable access to APIs and essential medicines (on-site, on-demand)

Novartis Continuous Manufacturing Lab (2018)

Flow Chemistry Projects/Publications with Industry 2010-2023

Pharma

Actinogen
Allergan
CEJ **2017** 176

AstraZeneca
OPRD **2015** 1062….
CST **2022** 1799 (11)

ASKAT
CEJ **2022** e202200741

AZAD PHARMA AG
ACSSCE **2022** 8988

BAYER
OPRD **2014** 1360

Boehringer Ingelheim
AS **2022** 2105547

Janssen PHARMACEUTICAL COMPANIES OF Johnson&Johnson
CEJ **2016** 10393….
CC **2020** 14621 (6)

Lilly
JOC **2014** 8486….
RCE **2021** 2434 (10)

MERCK
CCC **2022** e202201184
MSD

NORAMCO INC
OPRD **2016** 376….
EJOC **2017** 914 (4)

Pfizer
OPRD **2022** 1486

SERVIER
ASC **2023** 1660

Roche
OPRD **2021** 1206…
JOC **2023** xxxx (5)

sanofi

SANOCHEMIA DEVELOP.PRODUCE.SUPPLY
ucb
willow
Takeda

Agro/Fine Chemicals

allnex The Coating Resins Company
ACSSCE **2021** 8980
OPRD **2021** 2367

BASF The Chemical Company
ASC **2010** 323
OPRD **2017** 125

CLARIANT
GPS **2012** 281

HOS

syngenta

umicore materials for a better life

CMO/CDMO

Cominnex
EJOC **2020** 7051
GC **2021** 5626

Lonza
ACIE **2010** 7101….
RCE **2022** 2582 (20)

mi micro innova efficient processing
OPRD **2011** 858….
JPC **2023** 59 (5)

Patheon part of Thermo Fisher Scientific
JFC **2016** 211….
CEJ **2022** e202200741 (5)

SEQENS
OPRD **2023** 323

Acknowledgements: CCFLOW Team and Funding Agencies

Center for Continuous Flow Synthesis and Processing (http://ccflow.at)

ZUKUNFTSFONDS STEIERMARK

FFG Forschung wirkt.

SFG NEUES DENKEN. NEUES FÖRDERN.

FWF Der Wissenschaftsfonds.

Das Land Steiermark

Bill & Melinda Gates foundation

austria wirtschaftsservice aws

ACS Green Chemistry Institute Pharmaceutical Roundtable